Publications and Impact Factor (weighted average) of the EOC in the last 5 years

Absolute numerical values of the EOC publications sorted according to Impact Factor ranges

EOC Citations in Each Year

Timespan: 2012-2016
h-index: 44

Timespan: 2006-2016
h-index: 85
EOC Clinical Trial Unit (CTU-EOC)

CTU-EOC Services 2016
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Preface
Preface

This year the EOC Scientific Report has a new layout. Each chapter is developed in a new structured, organised way. This allows the reader not only to gain an overview of the research carried out at the EOC, but also to appreciate in detail the research activities of each EOC clinical service, department or laboratory.

Considering the above, I would like to highlight that many of the finest hospitals not only provide health services, but also perform medical research. The quality of service in hospitals is evaluated in several ways, for example using a Quality Improvement (QI) implementation approach. Research impact is also an achievement of a good hospital and can be measured by citations indices (e.g. Impact Factor, h-index).

In this connection, in 2016, the scientific productivity of the EOC proceeded with its upward pattern in terms of quantity of its publications (+52% compared to peer-reviewed publications in 2012) and was almost comparable to 2015 in terms of quality (see the analysis of the total Impact Factor, shown in the charts in chapter 8).

The citation frequency of the EOC publications was also analysed by Thomson Reuters Web of Science platform and has constantly increased in the last 5 years. In particular, the EOC h-index was 44 in this timespan, and this value indicates an achievement of a good institution as it measures the research impact and, therefore, the quality of services.

Also in 2016, the research laboratories (IDR/IDS for oncology and LBN/NSI for neurosciences) and all the EOC clinical services significantly contributed to producing top-level research and obtaining high acknowledgement at national and international levels.

Furthermore, the institutional Clinical Trial Unit (CTU-EOC) has increased its activity by building fruitful collaborations with new departments and services, since it started in 2012. It has undertaken the full development and conduct of projects and has provided more complex services (see also chapter 4).

In 2016, the EOC was accepted as an associate member of the Swiss Clinical Trial Organisation (SCTO), and a representative of the EOC can participate in the SCTO Steering Board as an observer without voting rights.

Through the Clinical Trial Unit, the EOC participates in some of the SCTO projects and is a member of the EUPATI Advisory Board of Switzerland. EUPATI is the European Patients’ Academy on Therapeutic Innovation, which provides education and training tools for representatives of patient organisations.

This positive development in quality of clinical and translational research activities, conducted within the EOC hospitals, institutes and laboratories, is certainly crucial for the newly-established Human Medicine Master of the Faculty of Biomedical Sciences of the Università della Svizzera Italiana (USI).

The different sections included in this Scientific Report, provide a detailed description of the
research lines currently developed by the EOC laboratories and all the clinical services or departments to convey the profound significance of their value.

Clinical and translational research projects covering all the main areas of medicine and biology are actively promoted and developed.

To this end, an Official Registry of the EOC studies was created, with the support of the EOC Information and Communication Technology (ICT) Department, whose research activity is detailed in the new chapter 7.

The Registry of the EOC studies started on 7th April 2014 and was included in the www.eoc.ch website as a web-based resource in July 2016. It contains information on clinical and translational trials carried out in the EOC hospitals, publicly and privately funded or not supported by sponsors (see also chapter 6).

The Registry is a tool of great importance for ensuring and improving the quality of the trials, promoting information exchange and facilitating collaborations within the scientific community.

Therefore, research now has become a fundamental part of hospital activities in order to guarantee the quality and safety of the services provided to our patients.

Indeed, it is impossible to carry out research without keeping completely up-to-date, otherwise there would be no hope of receiving funding for the research projects. We are all fully aware of the fact that constantly keeping up-to-date in our different fields and activities is an essential prerequisite to ensure that our patients receive the most innovative therapies available and the correct treatment in an efficient and effective manner.

Finally, I wish to thank all those people who through their hard and silent work and passion for their different fields, contribute, day after day, to ensuring the availability of the most suitable diagnostic, therapeutic and healthcare approaches, based on state-of-the-art scientific evidence, while supporting scientific progress in the medical-health field, despite the difficulties sometimes found therein.

I would like to end by pointing out that patient care based on the best scientific evidence remains and will always be our foremost concern.

**Fabrizio Barazzoni MD MPH**

FMH Prevention and Public Health

Head of the Medical Area of the EOC Head Office

Head of the EOC Academic Education, Research and Innovation Area (AFRI)

Chair of the Scientific Research Advisory Board

Bellinzona, 3rd July, 2017
Oncology Institute of Southern Switzerland (IOSI)
1. **Oncology Institute of Southern Switzerland**

The IOSI includes all the specialisations dealing with oncology within the EOC in a single organisational structure. The IOSI is devised according to the North American model of "comprehensive cancer centres", but has its own particular structure, as it has a horizontal structure throughout the EOC.

Therefore, the IOSI is intended to be an all-inclusive structure, containing all the specialisations that deal with the diagnosis, treatment and research in the field of tumour diseases.

The IOSI has six services: medical oncology, radio-oncology, haematology, nuclear medicine, palliative care and research. Each service has its own research program coordinated by the IOSI Scientific Board that decides on common research guidelines. The research laboratories at the Institute for Research in Biomedicine (IRB) are part of the Institute of Oncology Research (IOR) and are run by the "Fondazione ticinese per la ricerca e la cura dei linfomi" (Ticino Foundation for research and treatment of lymphomas), although functionally, they are part of the IOSI's Research Division.
1.1. Medical Oncology Service

Prof. Michele Ghielmini MD
Medical Director of the IOSI and Head Doctor

It is well known, but worthwhile being constantly repeated, that patients are treated much better in health structures where research is carried out. Indeed, physicians, who spend some of their working time (and very often also of their free time!) dealing with clinical studies and research are obliged not only to be very updated but also to predict future developments in their field. Research is absolutely necessary to become a specialist in a specific disease within oncology.

At the IOSI, there are always more organised disease-oriented structures, where physicians, who are particularly interested in one neoplastic disease, try - very often in a multidisciplinary way - to ensure the highest possible treatment quality to their patients. This entails collaborations in national and international studies and close co-operation with the research activities developed by our colleagues who work in the laboratory field (IOR). A continuous and fruitful collaboration between clinicians as well as basic and translational researchers, has always been one of the focuses of the activities of the IOSI. This has increasingly become more apparent every year, considering also the establishment of the Human Medicine Master of the Faculty of Biomedical sciences.

Peer reviewed publications in 2016

Fontanella S, Bongiovanni M, Nobile A, Uccella S, Mazzucchelli L, Espeli V, Giovanella L.


Main areas of research


Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), white blood cell count, and platelet count are inflammatory-based prognostic parameters predicting survival in colorectal cancer. NLR is involved in almost every stage of colorectal cancer and is associated with reduced efficacy of systemic therapy or radiotherapy. Also, NLR is associated with worse outcomes and PLR is also gaining attention as a prognostic marker. The purpose of this retrospective analysis is to correlate the inflammatory-based prognostic parameters with outcomes in patients with potentially resectable liver metastases from colorectal cancer, treated with perioperative systemic therapy.


The objectives of the trial are to determine the recommended phase-2 dose of the MEK-Inhibitor binimetinib in combination with pemetrexed and cisplatin and to show that the combination is feasible and has preliminary activity in previously untreated patients with advanced non-small cell lung cancer with KRAS mutations. The primary endpoint is the dose-limiting toxicities (DLTs) resulting from the combination of binimetinib with pemetrexed and cisplatin. Secondary endpoints are objective response, progression-free survival, overall survival, adverse events. Blood samples for translational research will be collected at baseline and at progression. The multicenter single-arm, open-label phase IB trial consists of two parts: part 1: dose escalation with 2 doses of binimetinib; part 2: expansion cohort at the recommended MTD level of binimetinib. Binimetinib will be given during induction therapy in combination with chemotherapy and the maintenance phase until progression. The inclusion of patients will stop after the inclusion of 18 patients (a maximum of 12 evaluable patients for part 1 – dose escalation and reaching a total of 18 patients after completion of part 2 – expansion cohort).


We performed a retrospective analysis of 281 patients, >80 years old, with newly diagnosed DLBCL treated in 4 referral institutions in Switzerland and Northern Italy. The primary endpoints were overall survival (OS), progression-free survival (PFS) and cause-specific survival (CSS). Systemic chemotherapy was administered to 239 patients, and 119 of them received rituximab in their initial treatment. At a median follow-up of 5.5 years, 5-year PFS was 26% (95% CI, 20-32%), 5-year OS was 31% (95% CI, 25-37%), and 5-year CSS was 48% (95% CI, 41-55%) for the entire cohort. Rituximab and/or anthracyclines as part of the initial treatment were associated with improved outcome. CSS in patients receiving both agents approximated 60% at 5 years. At multivariate analysis, rituximab use maintained a significant prognostic impact after controlling for age, performance status, stage, haemoglobin and LDH levels. The International Prognostic Index (IPI), as well as the more recently proposed indices, could discriminate patients with significantly different outcomes.


The current standard of care for advanced stage Hodgkin lymphoma consists of 6 cycles of BEACOPPesc, which is the control arm in this
study. BEACOPPesc is a very effective regimen, but it is frequently associated with acute and long-term toxicity. By implementing brentuximab vedotin into the BEACOPP backbone, a new chemotherapy regimen, BrECADD, was designed to reduce the toxicity of first line treatment while maintaining equally high efficacy as with the current standard of care, escalated BEACOPP. Due to its unique combination of efficacy and tolerability, it is a highly interesting candidate for the improvement of established chemotherapy regimens. In this prospective, multicenter, randomised and open-label trial, patients in the standard group are treated with 6 cycles of escalated BEACOPP. Patients in the experimental group receive 6 cycles of the BrECADD chemotherapy regimen.

Analisi dell’espressione genica di ROR1 nei carcinomi polmonari: un nuovo marcatore nell’ottica di nuove terapie bersaglio-specifiche (Gene expression analysis of ROR1 in lung carcinomas: a new marker in view of new target-specific therapies).

Lead investigator: L. Wannesson.

The study is ongoing.

Main funding

Swiss Group for Clinical Cancer Research (SAKK); ABREOC (internal competitive grant); our own scientific foundation; scientific foundations of the departments we perform the trials with.
1.2. Radiation Oncology Service

Antonella Richetti MD
Head Doctor

Main areas of research

The scientific activities of the Radiation-Oncology Service, with the contribution of the physicians and a research nurse/data manager, are aimed at participating in multicentric Swiss and international clinical studies, in the following clinical fields:

Breast cancer

IRMA: breast cancer with low risk of local recurrence: partial and accelerated irradiation with three-dimensional conformal radiotherapy (3DCRT) vs. standard radiotherapy after conserving surgery (phase III study).

Lead investigator IOSI: MC. Valli.
Sub-investigators: A. Richetti, S. Cima.

Conservative surgery (including large breast resection and lumpectomy + biopsy of the sentinel lymph node and/or axillary dissection) followed by post-op RT: Trial arm 38.5 Gy total in 10 fractions (3.85 Gy per fraction), twice a day with an interval of at least 6 hours between the two fractions, for five consecutive working days. Control arm 45 Gy/18 fractions, or 50 Gy/25 fractions, or 50.4 Gy/28 fractions, or isoeffective fraction schemes, once a day for 5 days a week. A 10 - 15 Gy boost is allowed in centres where it is part of the standard treatment. Primary objectives: the main aim of this study is to evaluate whether partial hypofractionated and accelerated irradiation of the sole surgical cavity, in patients suffering from

Peer reviewed publications in 2016


breast cancer with low risk of local recurrence and undergoing conservative surgery, is not inferior to postoperative irradiation with conventional fractionation of the entire breast as regards local control, measured in terms of incidence of ipsilateral recurrences as first event. Total number of randomised pts: 2437; IOSI/RT pts: 100.

IBCSG 38-10 / BIG 3-07 / TROG 07.01: a randomized phase III study of radiation doses and fractionation schedules for ductal carcinoma in situ (DCIS) of the breast.

Lead investigator: IOSI: A. Richetti.
Sub-investigators: MC. Valli, S. Cima.

Women with completely excised non-low risk ductal carcinoma in situ (DCIS) treated by breast conserving surgery suitable for adjuvant whole breast radiation therapy (RT) are eligible for the study. Women will be randomised to receive one of the following two treatments: Arm 1: Whole breast RT alone using standard fractionation (50 Gy/25 fractions, 5 per week) Arm 3: Whole breast RT using standard fractionation (50 Gy/25 fractions, 5 per week) plus tumour bed boost (16 Gy/8 fractions, 5 per week). Primary objective: to individualise treatment selection for women with DCIS following breast conserving surgery to achieve long-term disease control with minimal toxicity. Total number of randomised pts: 1608; IOSI/RT: 5 pts.

Study closed for accrual on 22nd June 2014, follow-up still ongoing.

TOXMAB: observational cohort study, aimed at evaluating the skin and pulmonary late toxicity after conservative surgery and postoperative radiotherapy in patients with bilateral synchronous breast cancer.

Lead investigator: IOSI: MC. Valli.
Sub-investigators: S. Cima.

Patients with bilateral synchronous breast cancer treated with conservative surgery and postoperative radiotherapy (RT) of both breasts with volumetric modulated arc therapy (VMAT) technique and simultaneous integrated boost (SIB), are included. Total number of patients to be included: 20.

Patients included to date: 18.

MEPITEL: use of mepitel film dressing compared to standard treatment in order to prevent skin toxicity during postoperative radiotherapy after conservative surgery for breast cancer.

Lead investigators: MC. Valli, D. Valcarenghi.

Comparison between mepitel film and standard treatment to prevent skin reactions due to radiotherapy (>/- grade 2, according to RTOG score).

Primary endpoint: reduction in moist desquamation (RTOG score =2) in the experimental arm.

Neuro-Oncology cancer

IOSI-RTO-001: stereotactic hypofractionated radiotherapy or radiosurgery of the resection cavity after surgical removal of solid tumour brain metastases.

Lead investigator and Trial chair: GF. Pesce.
Sub-investigator: NC. Azinwi.

Patients with brain metastases from solid tumours (lung, breast, kidney, melanoma, colorectal) in good general condition and controlled systemic disease will be irradiated to the resection cavity with 18 Gy in a single fraction or 5-7 Gy with 5 consecutive daily fractions. The aim of the study is to investigate the role of focused high-dose irradiation to reduce the risk of local relapse after resection of brain metastases while avoiding whole brain radiotherapy and the related toxicity. Total number of randomised IOSI/RT pts: 8.

ABBVIE M13-813, RTOG 3508: a randomized, placebo controlled phase 2b/3 study of ABT-414 with concurrent chemoradiation and adjuvant temozolomide in subjects with newly diagnosed glioblastoma (GBM) with Epidermal Growth Factor Receptor (EGFR) amplification (Intellance 1).

Lead investigator: IOSI: GF. Pesce.
Sub-investigator: NC. Azinwi.

60 Gy in 30 fractions over 42 days (up to 49 days) + temozolomide (TMZ): daily for 42 days (up to 49 days) + blinded ABT-414 (an antibody drug conjugate) or placebo: D1 of Weeks 1, 3 and 5. 28 days
(+/-3 days) after completion of chemo-radiation, TMZ: D1-5 q28 days x 6 cycles + blinded ABT-414 or placebo: D1 and D15 q28 days x 12 cycles. The aim of the study is to determine whether the addition of ABT-414 to concomitant radiotherapy and TMZ plus adjuvant TMZ extends Progression Free Survival (PFS) and Overall Survival (OS) among subjects with newly diagnosed GBM harbouring EGFR amplification. The study opened for accrual in February 2016, but unfortunately it has already been closed due to low accrual.


Patients will be treated with radiotherapy 50.4 Gy in 28 fractions x 1.8 Gy or temozolomide 75 mg/m² daily x 21 days, q28 days until progression or for max. 12 cycles. The aim of the study is to demonstrate a difference in progression-free survival for primary treatment. Total number of randomised pts: 700; IOSI/RT: 4 pts. Study closed for accrual, follow-up still ongoing.

EORTC 26082-22081: radiation therapy and concurrent plus adjuvant temsirolimus (CCI-779) versus chemo-irradiation with temozolomide in newly diagnosed glioblastoma without methylation of the MGMT gene promoter – a randomized multicenter, open-label, Phase II study. Lead investigator IOSI and Trial chair: GF. Pesce.

Recent data have shown a higher survival rate in patients treated for glioblastoma with standard radiotherapy and temozolomide, if they have the methylated MGMT promoter gene. The current trial aim is to explore a new treatment option for patients with unfavourable glioblastoma subpopulation with unmethylated MGMT promoter methylation. Total number of randomised pts: 257. Study closed for accrual in 2013, follow-up still ongoing. To date no survival benefit in the experimental arm. Study was published in 2016 (see page 14 for list of publications).

Urogenital cancer

EORTC 22043-30041: immediate or early salvage post-operative external radiotherapy combined with concomitant and adjuvant hormonal treatment versus immediate or early salvage post-operative external radiotherapy alone in pT3a-b R0-1 cN0M0 / pT2 R1 cN0M0, Gleason score 5-10 prostatic carcinoma. A phase III study. Lead investigator IOSI: GF. Pesce. Sub-investigator: NC. Azinwi.

Patients will receive a single dose of 20 Gy for lesions with a diameter <3 cm, or 5 x 5-10 Gy (total of 25-30 Gy) for lesions with a diameter of ≥3 cm. The main objective is to assess the probability and duration of the biochemical response after IGRT. The study has been open for accrual since January 2017.

SAKK 01/10: carboplatin chemotherapy and involved node radiotherapy in stage IIA/B seminoma. Lead investigator IOSI: GF. Pesce. Sub-investigator: NC. Azinwi.

Within 13 weeks after orchiectomy, the patients will receive one infusion of carboplatin AUC 7 on day 1 of trial treatment, followed, 3 weeks later, by 15 x 2 Gy (stage IIA) or 18 x 2 Gy (stage IIB) small volume, involved node radiation therapy. The primary objective of this trial is to test the efficacy and safety of carboplatin chemotherapy and involved node radiotherapy in patients with stage IIA/B seminoma. Total number of randomised IOSI/RT pts: 1.

Megavoltage equipment with nominal photon energies ≥ 6 MV is required. Rotational techniques such as Tomotherapy®, Rapidarc®, intensity-modulated arc technique and volumetric-modulated arc therapy will also be eligible. The patient will be treated in an isocentric setting and all fields will be applied for 5 days per week for the total RT duration. RT in the standard arm A will be administered to a total dose of 64 Gy in 32 fractions of 2 Gy over 6.4 weeks. RT in the experimental arm B will be administered to a total dose of 70 Gy in 35 fractions of 2 Gy over 7 weeks. Primary objective: assessment of tumour control, toxicity and quality of life (QoL) after dose intensified salvage radiotherapy (RT).

Total number of randomised pts: 350, IOSI/RT: 12 pts. Study closed for accrual on 1st April 2014, follow-up still ongoing.

**Lung cancer**

EORTC 22055-08053: phase III study comparing post-operative conformal radiotherapy to no post-operative radiotherapy with completely resected non-small cell lung cancer and mediastinal N2 involvement.

*Lead investigator IOSI: A. Richetti.*

*Sub-investigator: F. Martucci.*

All eligible patients will be randomised between thoracic adjuvant conformal radiotherapy at the dose of 54 Gy/27 to 30 fractions and no thoracic adjuvant radiotherapy. Primary objective: improvement of Disease-Free Survival (DFS) by conformal thoracic radiotherapy compared to no radiotherapy.

Total number of randomised pts: 351, IOSI/RT: 0 pts.

SAKK 15/12: early prophylactic cranial irradiation with hippocampal avoidance in patients with limited disease small-cell lung cancer: a multicenter phase II trial.

*Lead investigator IOSI: GF. Pesce.*

*Sub-investigator: F. Martucci.*

Trial treatment consists of HA-PCI concomitant to the second cycle of chemotherapy and radiotherapy. The HA-PCI regimen consists of a total dose of 25 Gy (2.5 Gy/fraction/5XW) for 2 weeks. Cisplatin or carboplatin and etoposide will be administered for 4 to 6 cycles according to local standards. Radiotherapy consists either of 45 Gy (1.5 Gy/fraction/2D/5XW) for 3 weeks or 60 Gy (2 Gy/fraction/5XW) for 6 weeks according to local standards. Primary objective: assessment of neurocognitive function after early hippocampal avoidance prophylactic cranial irradiation.

Total number of randomised pts: 10, IOSI/RT: 0 pts.

**Head and neck cancer**

INT 48/14, HEO: health and economic outcomes of two different follow-up strategies in effectively cured advanced head and neck cancer. A phase II trial.

*Lead investigator IOSI: A. Richetti.*

*Sub-investigator: F. Martucci.*

Patients deemed to be in complete remission at month 6 (+/-1 month) after curative treatment will be randomised to two follow-up arms: Arm A, non-intensive, follow-up according to NCCN guidelines with CT scan or MRI only on the occurrence of new signs or symptoms versus Arm B, intensive, as arm A, but with CT scans, MRI or PET scans at fixed time points according to the type of tumour, smoking history and age. QoL forms and socio-economic questionnaires will be administered in both arms.

Total number of randomised pts: 80, IOSI/RT: 0 pts.

**Collaboration with the EOC Medical Physics Service**

The clinical and scientific progress in our Radiation Oncology Service is also largely the result of a significant intellectual and technological exchange with the Service of Medical Physics. From 2015 to 2016, the above-mentioned service underwent many important changes, with a complete renewal of the staff and the setting. For that reason, the focus of the physical team, led by Dr. Stefano Presilla, was to maintain a high level of efficiency in the clinical activity. Nevertheless, the contribution to several scientific works and some publications was invaluable.

The other colleagues from the Medical Physics staff are the following:

Dr. P. Colleoni, Dr. D. Gaudino, Dr. F. Pupillo, Dr. L. Bellesi and Dr. M. Carrara.
Main funding

Swiss Group for Clinical Cancer Research, SAKK (SAKK 01/10, SAKK 09/10, SAKK 15/12, IBC-SG 38-10); ABREOC (internal competitive grant) (IOSI-RTO-001; IOSI-RTO-002); European Organisation for Research and Treatment of Cancer (EORTC). INT 48/14 and IRMA study, no funding.
1.3. Nuclear Medicine Service and PET/CT Center

Prof. Luca Giovanella MD
Head Doctor

Nuclear medicine uses substances emitting low radiation level (radiopharmaceuticals) and technologically very advanced equipment (gamma cameras, SPET/CT and PET/CT tomographs) to carry out diagnostic tests (scintigraphy, tomoscintigraphy, SPECT/CT and PET/CT) in every medical branch. Moreover, some radiopharmaceuticals are used for the treatment of hyperthyroidism and goitre, thyroid carcinomas, bone metastases, some lymphomas and inflammatory arthropathy.

The Service is based at the Regional Hospital of Bellinzona and Valli (San Giovanni) and the Regional Hospital of Lugano (Civico). In both hospitals, all nuclear medicine diagnostic tests, including PET/CT, iodine-131 treatments (outpatients), intra-articular radiosynoviorthesis and treatments for bone metastases are carried out. The centre for in-patient iodine-131 treatments and other radioisotopic therapies is based at San Giovanni Hospital (3 dedicated rooms). The Service includes the EOC Integrated Center for Thyroid Diseases: “one-stop-shop” specialised consultations, including diagnostic procedures (US, scintigraphy, fine-needle and core-needle biopsy) and non-surgical therapies (drugs, radioiodine, US-guided alcohol injection and HIFU), are provided and the EOC Multidisciplinary Thyroid Board is coordinated.

Peer reviewed publications in 2016


Main areas of research

Thyroid diseases

A new high-sensitive thyroglobulin assay in the follow-up of differentiated thyroid carcinoma.
*Lead investigator:* L. Giovanella.

Molecular markers on fine needle aspiration biopsy in the differential diagnosis of thyroid nodules with indeterminate cytology.
*Lead investigators:* L. Giovanella, P. Trimboli.

Elastosonography in the assessment of thyroid nodules.
*Lead investigators:* L. Giovanella, P. Trimboli.

Role of FDG-PET/CT in the differential diagnosis of thyroid nodules with indeterminate cytology.
*Lead investigator:* L. Giovanella.

Treatment of benign thyroid nodules by high intensity focused ultrasound (HIFU).
*Lead investigators:* L. Giovanella, P. Trimboli.

Quantitative ultrasonography analysis of thyroid nodules and surrounding gland tissues.
*Lead investigators:* L. Giovanella, P. Trimboli.

Oncology

IELSG 37 study.
*Lead investigators:* L. Ceriani, E. Zucca.

A multicenter randomised phase 3 comparative study assessing the role of involved mediastinal radiotherapy after rituximab-containing chemotherapy regimens to patients with Primary Mediastinal Large B-Cell Lymphoma.

GHSG HD17.
*Lead investigators:* L. Ceriani, E. Zucca.

A trial designed to determine whether radiotherapy may be omitted in low-risk patients after chemotherapy.

GHSG HD18.
*Lead investigators:* L. Ceriani, E. Zucca.

A study designed to individualise treatment according to early response to chemotherapy.

SAKK 35/14: rituximab with or without ibrutinib for untreated patients with advanced follicular lymphoma in need of therapy.
*Lead investigators:* L. Ceriani, E. Zucca.

A randomised, double-blinded, SAKK and NLG collaborative Phase II trial.

BELLE-CBKM120F2302.
*Lead investigators:* O. Pagani, L. Ceriani.

A phase 3 randomised double-blind clinical trial with BKM120 or placebo combined with fulvestrant in postmenopausal patients with breast carcinoma and positive hormonal receptor HER2-negative, locally advanced or metastatic cancer, in progression after treatment with aromatase inhibitors.

BAYER B8-223/16298.
*Lead investigators:* O. Pagani, G. Paone.

A phase 2 randomised double-blind placebo-controlled trial of radium-223 dichloride vs. placebo when administered to metastatic HER2 negative hormone receptor positive breast cancer with bone metastases treated with hormonal treatment.

BAYER B8-223/17096.
*Lead investigators:* O. Pagani, G. Paone.

A phase 2 randomised double-blind placebo-controlled trial of radium-223 dichloride vs. placebo when administered to metastatic HER2 negative hormone receptor positive breast cancer with bone metastases treated with the standard treatment exemestane and everolimus.

Health and economic outcomes of two different follow-up strategies in effectively cured advanced head and neck cancer.

Swiss Extended PET Registry (SEPR).
*Lead investigator:* G. Treglia.

Meta-analysis on PET/CT.
*Lead investigator:* G. Treglia.
**Cardiology**

**ANMCO (Associazione nazionale medici cardiologi ospedalieri - Italian Association of Hospital Cardiologists) ISCHEMIA.**

*Lead investigators: T. Moccetti, L. Ceriani.*

A multinational, randomised clinical trial with the aim of comparing the optimal medical treatment versus an interventional strategy added to the optimal medical treatment in patients with mild-severe ischaemia.

**Neurology**

**Biogen 221AD302.**

*Lead investigators: L. Sacco, G. Treglia.*

A Phase 3 multicenter, randomised, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of aducanumab (BIIB037) in individuals with early Alzheimer’s disease.

**Main funding**

ABREOC (internal competitive grant); Medeo Diagnostics; Mallinkrodt-Covidien; Sanofi-Genzyme; Roche Diagnostics; Brahms-Termofisher; GE diagnostics, Ibsen AB; Covance Clinical and Periapproval Services Ltd; Oncosuisse; Bioclinica; Biogen; Swiss Group for Clinical Cancer Research (SAKK); International Extranodal Lymphoma Study Group (IELSG); Therac tion.
1.4. Palliative Care Service

Claudia Gamondi MD, MSc
Clinical Director

Palliative care involves looking after a patient and his family adopting a global approach aimed at maintaining or re-establishing the best possible quality of life through an interdisciplinary approach, involving doctors, nurses, psychologists and social workers, all with highly specialised skills.

The Palliative and Supportive Care Clinic IOSI-EOC (CCPS), which can be found in all the EOC hospitals, has the mission to promote this philosophy and disseminate the specific know-how of palliative care to hospital teams through specialist consultation at the patient’s bedside, by developing the necessary training programmes.

The Palliative Care Unit (UCP - Unità di Cure Palliative) is equipped with seven beds and a specialist team as part of the IOSI inpatient units at San Giovanni Hospital in Bellinzona. The Unit is designed to offer relief from suffering in unstable, complex situations.

The CCPS of the IOSI is a highly advanced model, labelled “Designated Center of Integrated Oncology and Palliative Care (ESMO 2004-2016). The Palliative Care Unit was awarded with the “Quality in Palliative Care” (Qualité Palliative 2016) label.

The research Unit includes Claudia Gamondi, MSc (responsible physician), Tanja Fusi, MD, MSc and Yves Franzosi (part-time research coordinator) and boasts national and international collaborations. Its main partners are: IOSI Oncology Service, SUPSI, Haute École Santé Lausanne, Service de Soins Palliatifs (CHUV, Lausanne), Onkologische Palliativmedizin in St. Gallen and the International Observatory for End of Life Care (Lancaster, UK), Istituto Nazionale dei Tumori, INT (Milano, Italy).

Peer reviewed publications in 2016


Survey of Palliative CH members’ attitudes to assisted dying.

Lead investigator: C. Gamondi.

This project seeks to describe Swiss Palliative CH members’ perspectives on assisted suicide, considering that this is a highly controversial issue, debated in the literature and by public opinion. The primary aim of this study is the prevalence of various viewpoints within palliative CH and the ways in which views are similar or different not only across locations, language groups, levels of experience and practice contexts, but also across the various professions involved in palliative care. It is a mixed method study, using semi-structured interviews to 20 palliative care nurse specialists and social workers recruited from the three different linguistic regions. It will be an 18 months project.

Currently, the study is in progress.

Interaction between clinical and genetic factors in modulation of opioid analgesia and side effects in cancer pain.

Sponsor-investigator: A. Caraceni.

Lead investigator for IOSI: C. Gamondi.

This is a one-year observational prospective study aimed at defining the interaction between longitudinal response to opioids and a set of genetic predictors, discovered in previous studies and identifying genetic variants that are more sensitive to nausea and vomiting induced by opioids. During the 28 days, follow-up patients will be visited and interviewed to determine the opioid that is most suited to patients’ needs.

Currently, the study is in progress.

The development of collaborative palliative care integration in respiratory medicine consultations for adult outpatients with advanced chronic obstructive pulmonary disease (COPD): An action research study.

Lead investigator: T. Fusi.

Chronic obstructive pulmonary disease (COPD) is a leading cause of worldwide morbidity and mortality. Although the recognition of COPD, as a life-limiting condition with palliative care (PC) needs, is increasing, PC provision in COPD remains difficult. The disease unpredictability and the misconception that a PC approach is exclusively relevant in the last few days of life prevent a timely integrated care plan for patients with advanced COPD. The aim of this study is to understand how to integrate PC provision for adult outpatients with severe COPD. A participatory action research study conducted in a respiratory service in Southern Switzerland will engage healthcare professionals in generating new knowledge on PC approaches in this field, while collaboratively reviewing and changing current practices.


Lead investigator: C. Gamondi.

This is a one-year observational prospective study with the following purposes: (a) describe how adult patients die in public hospitals in Ticino and, in particular, how they are assisted as they approach death; (b) identify any differences in the treatment of patients whose death is expected, compared to those whose death is not expected; (c) assess the perception of doctors and nurses as regards the quality of care provided before death.

Currently, the study is completed and the publication is ongoing.

Main funding

FIT (Fine Vita Ticino – “End of life Ticino”) study. Epidemiology of death in Ticino’s public hospitals: ABREOC (internal competitive grant).
The major aim of 2016 for the haematology Service was the development of the translational aspects in the haematology research. This was mainly possible due to the arrival of Dr. Davide Rossi, who joined the haematology team in late 2015 and became head of the research activity. In 2016, several junior physicians were integrated into the translational research program giving the possibility to pursue a career both in clinical and experimental haematology. Moreover, in 2016 a comprehensive database for all patients with chronic lymphatic leukaemia was created, and a prospective biobanking of liquid biopsies for lymphatic malignancies was initiated.

In 2016, Dr. Bernhard Gerber initiated a research program for plasma cell disorders, which was funded by ABREOC. He developed a database of all patients with plasma cell disorders treated at the IOSI and started and carried out in collaboration with Dr. Rossi and Prof. A. Neri, Milan, the first experiments using liquid biopsies in plasma cell myelomas. The Haematology Service continues to offer clinical studies for all the main entities of haematological malignancies. In 2016, after a longer period without clinical study in ALL patients, the GRAALL 2014 protocol was opened offering treatment for younger patients with first-line disease. The second important trial, opened in 2016, is HOVON 135 for elderly AML patients unfit for intensive chemotherapy. The opening of this trial has an important strategic impact since it is the first trial that the HOVON/SAKK consortium performs in this patient population. Since the majority of patients with AML are elderly and often unfit for intensive chemotherapy, it is very likely that this trial will have a good accrual and its pick-a-winner design foresees future studies based on the same trial design.

Peer reviewed publications in 2016


Main areas of research

Clinical research into acute myeloid leukemia in elderly patients - HOVON 103.
Lead investigators: G. Ossenkoppele, B. Löwenberg, G. Stüssi.

The HOVON 103 trial was activated in 2011 introducing a novel trial design to SAKK studies. It is a randomised phase II study in elderly AML patients with multiple parallel experimental arms, which are all compared to a common standard arm. The first arm of the study with lenalidomide was finished and is currently analysed. The publication is ongoing. The second study drug is tosedostat, a metalloproteinase inhibitor and the accrual to the study was finished in 2016. Currently, the data analysis is ongoing. The third drug is selinexor, a first-in-class substance, which was accepted by Swiss authorities. Currently, we are waiting for the study to be opened.

AML in elderly non fit patients - HOVON 135.
Lead investigators: G. Huls, S. Blum, G. Stüssi.

In 2015, together with the HOVON group we developed a clinical study for elderly AML patients unfit for intensive therapy. In this difficult-to-treat group of patients, new therapies are highly needed, but, unfortunately, these patients are rarely included in clinical trials. The study is also designed as a pick-a-winner trial; the first study drug is ibrutinib in combination with decitabine. The study was opened at the end of 2016 and had a very positive accrual in the first few months.

Prospective, observational, multicenter, non-interventional study on the identification of biomarkers that are predictive of early ibrutinib treatment failure in high-risk TP53 mutated chronic lymphocytic leukemia.
Lead investigator: D. Rossi.

The general aim of the project is the identification of dynamic molecular markers that can help the early and real-time prediction of sustained benefit or no benefit from ibrutinib treatment in CLL harbouring TP53 mutations. Specific aims of the project include assessing whether clearance of TP53 mutated clones translates into a predictive biomarker of long-term benefit from ibrutinib treatment in CLL and determining whether plasma cell-free DNA represents a sensitive tool that can early and dynamically inform on the development of ibrutinib resistant mutations in CLL.

Main funding

Swiss Group for Clinical Cancer Research (SAKK); Stichting Hemato-Oncologie voor Volwassenen Nederland (HOVON); Swiss Cancer League/Krebsliga (KLS).
The Research Division operationally encompasses both the different units carrying out clinical investigations within the IOSI as well as the experimental laboratories at IOR (Institute of Oncology Research). The collaboration and the coordination among all scientists and physicians involved in research is guaranteed by the Scientific Board of the IOSI, where all the six services of the IOSI as well as IOR are represented. The last year was positive, not only because important research papers were published in journals with a very high impact factor, but also because we were able to solve the logistic problems at IOR. In the previous years, I regularly reported the tough logistic situation of our researchers, who were really “packed” in the locations which were available to us. Since the new research building in Bellinzona will be ready only at the beginning of 2021, in the meantime we decided to move 3 of our 5 research groups outside the IRB premises. We were able to find a location (Via Pometta 1), which is very close to IRB bis, where we have the mouse facilities. The place on Via Pometta 1 has now more than 600 m$^2$ of space for the labs of the three groups (Catapano, Alimonti, Theurillat), while on the first floor, an almost equal area is reserved for offices, meeting rooms and other rooms which are necessary to carry out studies in the lab. We intended to move already in December 2016, but because of some legal problems, we were in the end forced to postpone the date we could start working in the new premises, to January 2017. We have now an ideal situation for our 60 researchers. This will certainly increase their productivity.

In last year’s report, I introduced the new Group Leader (Dr. Davide Rossi), who joined the haemo-oncological research, partly led by Francesco Bertoni. Davide Rossi’s group of has already expanded very well during 2016 and has already produced some outstanding abstracts and publications. The same can also be said for the other groups, among which Dr. Jean Philippe Theurillat’s group has now consolidated and become very productive.

In November, we had the good news that Dr. Andrea Alimonti, who was selected as the director of a biomedical research institute at the University of Geneva, decided to remain in Bellinzona, also because he was appointed as first Professor of molecular oncology in the new biomedical faculty of USI, “Università della Svizzera Italiana”. Again, although the decision was already taken in the last two months of 2016, the title was officially announced in a nice public ceremony only on January 23rd 2017. This development is also due to the fact that in April 2016, IOR was officially recognised as affiliated to USI by Ticino’s Regional Parliament, although the decision of the University had already been taken one year earlier. This legal and political recognition is crucial, not only from a financial point of view, but also because it opens up many possibilities of new cooperation with other universities in Switzerland and abroad.

From an operational point of view, the IOSI clinical research is mainly divided into five units:

- New Drug Development Unit, under the direction of Prof. Cristiano Sessa MD
- Lymphoma Unit, coordinated by Emanuele Zucca MD, PD
- Breast Unit, coordinated by Olivia Pagani MD
- Gastrointestinal Cancer Group, coordinated by Piercarlo Saletti MD
- Prostate Cancer Unit, coordinated by Enrico Roggero MD.

As can be seen in the following pages, particularly the Lymphoma Unit played a very active role last year, because it not only carried out many national and international studies, but was also featured in high impact factor journals.
1.6.1. New Drug Development Unit

Prof. Cristiana Sessa MD
Deputy Head Doctor

Peer reviewed publications in 2016


Main areas of research

Studies completed in 2016


A Phase I, open-label, non-randomized dose escalating safety, tolerability and pharmacokinetic study of TAS-114 in combination with S-1 in patients with advanced solid tumors. Lead investigator: C. Sessa. Sponsor: TAIHO.

Phase I multicenter, open-label, clinical and pharmacokinetic study of lurbinectedin (PM01183) in combination with weekly paclitaxel, with or without bevacizumab, in patients with selected advanced solid tumors.

Lead investigator: C. Sessa.
Sponsor: Pharmamar.

An open-label pilot study of the Novo TTF-100L (O) system (Novo TTF therapy) concomitant with weekly paclitaxel for recurrent ovarian carcinoma.

Lead investigator: C. Sessa.
Sponsor: Novocure.

A dose-finding study of OTX105/MK-8628 in adults with selected advanced solid tumors (MK-8628-003).

Lead investigator: A. Stathis.
Sponsor: Oncoethix GmbH.

Studies ongoing

All the current Phase I studies have a very extensive translational component with repeated pharmacokinetic and pharmacodynamic assessment (tumour tissues, peripheral blood).

Dose-finding study of PF 05212384 with paclitaxel and carboplatin (Phase I study) (IOSI-N-DU-001).

Investigator initiated trial/Lead investigator: A. Stathis.

A Phase I dose finding study of oral LTT462 in adult patients with advanced solid tumors harbouring MAPK pathway alterations.

Lead investigator: C. Sessa.
Sponsor: Novartis.

This is a multicentric international first in human study to define a recommended dose and regimen future studies of LTT 462. The study consists of 2 parts, part 1 (dose escalation) for patients with all solid tumours provided they have the requested molecular alterations, and part 2 (dose expansion) with multiple groups, according to histological diagnosis (KRAS/BRAF mut non small cell lung cancer; KRAS/BRAF mut ovarian cancer; BRAF mut melanoma with relapse on prior BRAF inhibitors; solid tumors other than those in the previous groups). The interest of the study resides in the availability of a unique compound with a very selective target of inhibition (ERK1/ERK2) downstream of MEK1/MEK2. This is the second ERK inhibitor brought into clinics.

The main expectations of antitumour activity are in ovarian cancer (in patients with low-grade serous or endometrioid) and in melanoma relapsing after BRAF.

We entered the study when it was still in its escalation part in which only 4 centres in Europe participate.

An open-label – phase I/IIA study of BAL101 553 administered as a 48-hour intravenous infusion in adult patients with advanced solid tumors.

Lead investigator: C. Sessa.
Sponsor: Basilea Pharmaceutica.

A multicentric Swiss study to determine the maximum tolerated dose (MTD) of this new microtubule-targeting agent (MTA), when given as a 48-hour infusion by an elastomeric pump. This compound was brought into clinics because of the good antitumour profile in vitro and in vivo experimental models, also in taxol-resistant ovarian cell lines. In the initial Phase I study BAL 101553 was given as a 2-hour infusion which was associated with hypertension and muscle pain. The administration of a longer infusion should overcome these toxicities by providing prolonged therapeutic plasma levels without peak levels responsible for toxicities. The study is ongoing in 3 Swiss centres, with the coordination of the SAKK (Swiss Group for Clinical Cancer Research).

A phase Ib/III multicenter, randomized, open-label trial of Talimogene Laherparepvec (TVEC) in combination with pembrolizumab for the treatment of subjects with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN).

Lead investigator: V. Espeli.
Sponsor: Amgen.

The objective of this study is to assess the safety (Phase I part) and efficacy (Phase III) of TVEC in combination with the anti PD1 pembrolizumab in patients with SCCHN relapsing after platinum. TVEC is a virally-based oncolytic immunotherapy consisting of an immune-enhanced herpes simplex virus type-1 which selectively replicates in solid tumours. TVEC is injected in the target lesions...
(skin, soft tissue or lymph node) while pembrolizumab is administered intravenously.

In the Phase Ib part (40 patients) TVEC and pembrolizumab are given in combination in all patients to define the recommended dose for Phase III where patients are randomised to receive pembrolizumab with/without TVEC.

Phase I part was completed and Phase III part (450 patients) will start in April. The primary end-points of the Phase III are Progression Free Survival and Overall Survival.

A phase III double blinded, placebo controlled study of Xilonix™ for improving survival in metastatic colorectal cancer.

*Lead investigator: P. Saletti.*

*Sponsor: XBiotech.*

The objective of the study is to assess the efficacy in terms of Overall Survival of the human monoclonal antibody, MABp1 (Xilonix™), specific for human interleukin 1α in patients with metastatic colorectal cancer that is refractory to standard therapy. The interesting features of the new molecule are the multiple targets controlling angiogenesis, invasiveness and leucocyte infiltration of the microenvironment.

The study completed the planned accrual of 600 patients rapidly.

Phase III multicenter, randomized open label study of avelumab (MSB 0010718C) alone or in combination with pegylated liposomal doxorubicin versus pegylated liposomal doxorubicin alone in patients with platinum-resistant/refractory ovarian cancer.

*Lead investigator: C. Sessa.*

*Sponsor: Pfizer.*

This is a multicentric international study for which the IOSI is the coordinating centre for Switzerland. The interest of the study resides in the possibility of getting the anti PD-L1 avelumab. Hints of antitumour activity have already been reported in this unfavourable patients setting with similar compounds. The objective of the study is to demonstrate that avelumab given alone or in combination with doxyl is inferior to doxyl in extending Overall Survival in patients with platinum-resistant/refractory ovarian cancer.

The planned sample size is from 550 randomised patients over a 16-month period.

All the above-reported studies had a separate financial agreement to define the payments of the sponsor to cover the cost of the patient’s exams due to the participation in the study and the work of the health personnel involved.
In 2016, the primary activities of the Lymphoma Unit were dedicated to the development of clinical studies and the increasing and continuing collaborations with the genomic research activities conducted in the laboratory of Dr. Francesco Bertoni.

In 2016, the International Extranodal Lymphoma Study Group (IELSG) successfully published the results of some studies.

**Peer reviewed publications in 2016**


Main areas of research

Phase I studies

**OSI-LND-001**: a phase I study of inotuzumab ozogamicin (CMC-544) in combination with temsirolimus (CCI-779) in patients with relapsed or refractory CD22-positive B-cell Non Hodgkin’s Lymphomas.

*Lead investigator: A. Stathis.*

Phase I study for patients with lymphoma. Besides the IOSI, the study is open in other two Swiss centres (St. Gallen and Bern).

**A Phase I, multicenter, open-label study of IMGN529 administered intravenously in adult patients with relapsed or refractory NHL.**

*Lead investigator: A. Stathis.*

**A Phase IB trial with MK-8628, a small molecule inhibitor of the Bromodomain and Extra-Terminal (BET) proteins, in subjects with selected hematologic malignancies.**

*Lead investigator: A. Stathis.*

**Phase I study of oral PQR309 in patients with relapsed or refractory lymphomas.**

*Lead investigator: A. Stathis.*

Retrospective study

Retrospective analysis of patients on single agent therapeutics for relapsed lymphoma.

*Lead investigators (Study Chairs): A. Younes, C. Batlevi, A. Copeland, A. Dogan.*

*Local lead investigator: A. Stathis.*

IELSG - Prospective Studies

**IELSG 30**: A phase II study of R-CHOP with intensive CNS prophylaxis and scrotal irradiation in patients with primary testicular diffuse large B-cell lymphoma.


**IELSG 37**: A randomized, open-label, multicenter, two-arm phase III comparative study assessing the role of involved mediastinal radiotherapy after rituximab-containing chemotherapy regimens to patients with newly diagnosed Primary Mediastinal Large B-Cell Lymphoma (PMLBCL).

*Lead investigators: M. Martelli, A.J. Davies, M. Gospodarowicz, E. Zucca.*


**IELSG 38**: A phase II study of chlorambucil in combination with subcutaneous rituximab followed by maintenance therapy with subcutaneous rituximab in patients with extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT Lymphoma).


The enrollment of 112 patients was completed in March 2016. End of trial expected for Q4: 2019.

**IELSG 42**: An international phase II trial assessing tolerability and efficacy of sequential methotrexate-aracytin-based combination and R-ICE combination, followed by high-dose chemotherapy supported by autologous stem cell transplant, in patients with systemic B-cell lymphoma with central nervous system involvement at diagnosis or relapse (MARIETTA regimen).

*Lead investigators (Study Chairs): G. Illerhaus, A. Ferreri.*

*Local lead investigator: A. Moccia.*

IELSG 43 - High-dose chemotherapy and autologous stem cell transplant or consolidating conventional chemotherapy in primary CNS lymphoma - randomized phase III trial (MATRix).


Local lead investigator: E. Zucca.

On 31.12.2016: 100 patients enrolled in 20 centres in 3 countries.

Main funding

IELSG 37 - A randomised, open-label, multicenter, two-arm phase III comparative study assessing the role of involved mediastinal radiotherapy after rituximab-containing chemotherapy regimens to patients with newly diagnosed Primary Mediastinal Large B-Cell Lymphoma (PMLBCL):

- Swiss National Science Foundation (SNSF, from 2013 to 2016 - 3 years) CHF 440,920
- Oncosuisse: Performance Agreement (from Q3 2014 until Q4 2016 - 2.5 years) - CHF 600,000.00.

1.6.3. Breast Unit

Olivia Pagani MD
Deputy Head Doctor and Clinical Director of the Breast Unit

The Breast Clinical Research Unit (1 head oncologist, 1 junior oncologist, 1 chemist, 2 data managers) is involved in clinical studies in patients with early and advanced breast cancer. The most significant collaborations are set up with national (Swiss Group for Clinical Cancer Research – SAKK) and international (International Breast Cancer Study Group – IBCSG, Breast International Group – BIG) cooperative groups. The Unit also runs sponsored clinical trials, in particular with new drugs. Dr. Pagani is also the clinical research coordinator of the Senology Center of Southern Switzerland (CSSI), Swiss and European certified.

During 2016 the Unit carried out 12 clinical studies in early and advanced breast cancer. In 2016 the Unit published 7 papers in peer-reviewed journals.

Dr. Pagani is actively involved in the major international collaborations mentioned below:

- European School of Oncology (ESO) – European Society of Medical Oncology (ESMO) Metastatic Breast Cancer Task Force, the organiser of the biannual advanced breast cancer consensus conference
(ABC), whose guidelines are now a landmark for the multidisciplinary treatment of metastatic breast cancer
— European School of Oncology (ESO) - European Society of Medical Oncology (ESMO) - Breast Cancer in Young Women Task Force, the organizer of the biannual young women breast cancer consensus conference (BCY), whose guidelines are becoming a reference tool for the complex treatment of young patients with early and advanced breast cancer.

Dr. Pagani was the chair of the 3rd conference, held in Lugano in November 2016 and she is a panel member of the St. Gallen International Breast Cancer Conference, which sets the recommendations for the management of early breast cancer every 2 years.

Main areas of research

One clinical study in women with early breast cancer, coordinated by IBCSG

IBCSG 48-14/BIG 8-13, POSITIVE (Pregnancy Outcome and Safety of Interrupting Therapy for women with endocrine-responsive breast cancer).

The study assesses the risk of breast cancer relapse associated with temporary interruption of endocrine therapy (ET) to permit pregnancy.
Eight clinical studies in women with advanced breast cancer

Three studies coordinated by SAKK:

SAKK 96-12: prevention of symptomatic skeletal events with denosumab administered every 4 weeks versus every 12 weeks – A non-inferiority phase III trial (REDUSE).

SAKK 21/12: a phase I and stratified, multicenter phase II trial of transdermal CR1447 (4-OH-testosterone) in endocrine responsive-HER2 negative and triple negative-androgen receptor positive metastatic or locally advanced breast cancer.

SAKK 25/14: eribulin as 1st line treatment in elderly patients (≥70 years) with advanced breast cancer: a multicenter phase II trial.

Two studies sponsored by Novartis:

A phase Ib/II, multicenter, study of the combination of LEE011 and BYL719 with letrozole in adult patients with advanced ER+ breast cancer (CLE-E011X2107).

A Phase III randomized, double-blind, placebo-controlled study of LEE011 or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with hormone receptor-positive, HER2-negative, advanced breast cancer (MONALEESA-7).

Two studies sponsored by Bayer in collaboration with the IOSI Nuclear Medicine Service:

A phase II randomized, double-blind, placebo-controlled trial of radium-223 dichloride versus placebo when administered to metastatic HER2 negative hormone receptor positive breast cancer subjects with bone metastases treated with hormonal treatment background therapy.

A phase II randomized, double-blind, placebo-controlled trial of radium-223 dichloride in combination with exemestane and everolimus versus placebo in combination with exemestane and everolimus when administered to metastatic HER2 negative hormone receptor positive breast cancer subjects with bone metastases.

One study sponsored by MERCK in women with triple negative breast cancer (KEYNOTE-119):

A randomized open-label phase III study of single agent pembrolizumab (PD-1 checkpoint inhibitor) versus single agent chemotherapy per physician’s choice for metastatic triple negative breast cancer.

One qualitative study in collaboration with the Institute for Public Communication of the University of Southern Switzerland (USI)

myTAMINO: Examining Determinants of Therapy Preference of Oncology Patients: to explore patients’ preferences for iv or oral administration of chemotherapy.

One study in male breast cancer

EORTC 10085 – Clinical and biological characterization of male breast cancer:

An international EORTC, BIG, TBCRC and NABCG intergroup study: establishment of a prospective database including patients’ characteristics, disease features, treatments received and clinical outcomes for 30 months in several centres in Europe, the US and third countries. Based on the results of this study, specific clinical trials will be designed in male breast cancer patients.

A surgical study coordinated by SAKK


A research project financed by EOC (ABREOC)

Impact of diet and fasting in breast cancer patients: improvement in treatment-related toxicity and overall quality of life and possible impact on prevention of relapse and/or progressive disease (Project ALISA).

Lead investigator: O. Pagani.

In collaboration with the Department of Predictive...
Main funding

SAKK; IBCSG; European Organisation for Research and Treatment of Cancer (EORTC); ABREOC (internal competitive grant); Novartis; Bayer; MERCK and other competitive and non-competitive external funding.

1.6.4. Gastrointestinal Cancer Group

Piercarlo Saletti MD
Deputy Head Doctor of Medical Oncology Service

Peer reviewed publications in 2016


Sorafenib with or without everolimus in patients with advanced hepatocellular carcinoma (HCC): a randomized multicenter, multinational phase II trial (SAKK 77/08 and SASL 29).

Main areas of research

The scientific activity in GI cancers developed trials conducted by Swiss Group for Clinical Cancer Research (SAKK) and companies. More specifically, we participated in the following studies:

SAKK 41/13 trial – Aspirin: adjuvant aspirin treatment in PIK3CA mutated colon cancer patients.

A randomized, double-blinded, placebo-controlled, phase III trial.

Coordinating Investigator: U. Güller.
Local lead investigator: P. Saletti.
Sponsor: SAKK.
Some studies show that patients with colorectal cancer who regularly take low-dose aspirin, experience a more favourable disease progression than patients who do not. This applies in particular to patients with a modified PI3K gene (PIK3CA mutation) in their tumour cells. In such patients, aspirin is believed to reduce the risk of a recurrence after treatment for colorectal cancer. However, the results of current investigations into the role played by aspirin were compiled retrospectively and are somewhat equivocal. In the SAKK 41/13 trial, patients who were curatively resected for stage II/III colon cancer and who are known to have a PIK3CA mutation are randomly assigned to receive daily low-dose aspirin or placebo for three years (randomisation 2:1). The study is currently recruiting.

ALLIANCE/SAKK prospect trial (N1048): Phase II/III trial of neoadjuvant FOLFOX with selective use of combined modality chemoradiation versus preoperative combined modality chemoradiation for locally advanced rectal cancer patients undergoing low anterior resection with total mesorectal excision (PROSPECT).

Lead investigator: D. Schrag.
Local lead investigator: P. Saletti.
Sponsor: Swiss sponsor representative: SAKK; Overall sponsor: Alliance.

Patients with rectal cancer are usually treated with combined radiotherapy and chemotherapy, followed by surgical removal of the tumour and subsequent chemotherapy. In the randomised prospective phase III PROSPECT trial, patients with only a few affected lymph nodes, a tumour (stages T2 and T3) that has not infiltrated other organs yet and can be removed with safe margins, are eligible to enrol. The aim of the PROSPECT study is to evaluate whether radiotherapy can be safely omitted in some patients without impairing chances of a cure. If this treatment strategy proved to be correct, omitting radiotherapy could simplify treatment and reduce side effects. The study is currently recruiting.

INCB 18424-363 (The JANUS 2 Study): a randomized, double-blind, phase 3 study of the JAK1/2 inhibitor ruxolitinib or placebo in combination with capecitabine in subjects with advanced or metastatic adenocarcinoma of the pancreas who have failed or are intolerant to first-line chemotherapy (The JANUS 2 Study).

Study Director: F. Dawkins, Incyte Corporation.
Local lead investigator: P. Saletti.
Sponsor: Incyte Corporation.

There is no standard treatment for patients with advanced or metastatic pancreatic cancer refractory to first-line chemotherapy. Systemic inflammation is a potential therapeutic target in solid tumours. The hypothesis to evaluate the efficacy of JAK inhibition in patients with solid tumours and high levels of systemic inflammation was initially supported by a subgroup analysis of the randomised, double-blind Phase 2 RECAP study, which suggested a survival benefit in patients with high levels of C-reactive protein. In the randomised, double-blind, phase 3 JANUS 1, the primary objective was to compare the overall survival of ruxolitinib, a JAK1/2 inhibitor, in combination with capecitabine versus capecitabine alone as second line in patients with advanced or metastatic pancreatic cancer. Unfortunately, the decision to stop the study was made after a planned interim analysis of JANUS 1 demonstrated that ruxolitinib plus capecitabine did not show a sufficient level of efficacy to warrant continuation.

Ruolo predittivo di EGFR, PIK3CA e PTEN nella risposta a trattamento radio-chemioterapico pre-operatorio in pazienti affetti da carcinoma rettale localmente avanzato (Predictive role of EGFR, PIK3CA and PTEN in the response to preoperative radio-chemotherapy in patients with locally advanced rectal carcinoma).

Lead investigator: P. Saletti.

The study is ongoing.

Main funding

SAKK; ABREOC (internal competitive grant) and other competitive and non-competitive external funding.
1.6.5. Prostate Cancer Unit

Enrico Roggero MD
Adjunct Physician of the Medical Oncology Service

Peer reviewed publications in 2016


Main areas of research

The Prostate Cancer Database.
Lead investigator: E. Roggero.
Collaborators: B. Marongiu, MR. Pascale.

A collection of clinical and histopathological information of patients with prostate cancer (PCa) diagnosed and treated at the IOSI and the Urology Service of Regional Hospital of Bellinzona and Valli (San Giovanni). Data were recorded retrospectively from 2002 to 2011 (cases are now collected prospectively). The primary objective of the PCa database is the collection of clinical-pathological data of PCa patients that are diagnosed and treated at our Institution. Secondly, it is a tool to find out new prognostic/predictive factors and to support clinical and translational research. A recent analysis of our database showed that in non-metastatic PCa patients treated with curative intent, the site of the first metastasis is an independent prognostic factor for specific PCa survival. Moreover, the time after metastatic progression strongly impacts on patients’ outcome. Finally, preliminary analyses of markers of proliferation and disease aggressivity were carried out in a similar PCa series.

Pilot study comparing genomic and metabolomic profiling of patients’ prostate cancer at diagnosis and during disease progression to find specific intra-individual genetic and metabolic alterations.
Lead investigator: E. Roggero.
Collaborator: MR. Pascale.

This is a retrospective pilot study with the aim to characterise PCa at diagnosis and at disease recurrence and/or metastasis by using an integrated approach based on genomics and metabolomics. In addition to testing technical feasibility, the main objectives of the study are to investigate the intra-tumour heterogeneity and identify a specific molecular signature associated with different steps of cancer evolution. Currently, using our PCa database, we have selected 6 cases of patients whose diagnostic biopsies or prostatecto-
mies at the time of diagnosis and biopsy specimens at disease progression are available. Now, these samples are under investigation.

Comparative study to assess the impact of a multidisciplinary evaluation in the treatment of patients with prostate cancer - The MAP CAT (Multidisciplinary Approach to Prostate Cancer Treatment) study.

Lead investigator: E. Roggero.
Collaborators: F. Stoffel, GF. Pesce, B. Marongiu, MR. Pascale.

This study is the first IOSI clinical study in the urogenital area and aims at assessing the impact of the multidisciplinary discussion on the choice of the treatment of patients with PCa by comparing one historical control group, whose therapeutic decisions were taken by individual medical specialists, to one experimental group, enrolled in the study, whose therapeutic strategy is jointly formulated by multidisciplinary discussion. In December 2016, the actual recruitment rate was lower than the estimated one. Thus, a series of corrective measures were implemented, including an electronic patient’s announcement form with an automatic transmission, weekly urogenital multidisciplinary board, clinical study promotion to improve the recruitment. In December 2017, the accrual rate is expected to be successfully increased compared to the last year.

The study is conducted with the support of the Clinical Trial Unit (CTU-EOC).

Pilot epidemiological study on the prevalence of Human Papilloma Virus (HPV) in patients with prostate cancer in Ticino.

Lead investigator: E. Roggero.
Collaborators: L. Mazzucchelli, J. Barizzi, MR. Pascale, B. Marongiu.

The role of HPV in the oncogenesis of PCa is controversial. In a retrospective study conducted in collaboration with the University of Trieste, we showed a high prevalence of HPV and reduced survival in patients with HPV-positive primary cancer in a cohort of the North-Eastern area of Italy. These data, together with those in the literature, support the necessity for a prospective study to assess the etiological role of HPV in PCa. The primary objective is to estimate the prevalence of HPV in PCa in Ticino; this information is currently unavailable. The secondary objectives are the preliminary assessment of HPV association with the marker of malignant transformation induced by the virus (p16), with clinicopathological data and the prevailing virus subtype identification. The study was approved by the Ethics Committee (EC) in March 2015. The final results are expected by the second half of 2017.

Clinical Urogenital SAKK Trials

SAKK 96/12.

Treatment of patients with bone metastases using Xgeva® - Prevention of symptomatic skeletal complications with denosumab administered every 4 weeks versus every 12 weeks.

STAMPEDE.

Systemic therapy for progressive or metastatic cancer of the prostate. A multi-arm multi-stage randomised controlled trial.

SAKK 01/10.

Novel combination treatment of radiotherapy and chemotherapy in attenuated form for patients with stage IIA/B seminoma.

SAKK 08/14 IMPROVE.

Metformin combined with enzalutamide.

Main funding

ABREOC (internal competitive grant); Fondazione Ticinese per la ricerca sul cancro (Ticino’s Foundation for Cancer Research) (external competitive grant).
The program in Tumour Biology and Experimental Therapeutics includes the research teams that work on Experimental Therapeutics and Prostate cancer biology (Prof. Carlo Catapano, MD, PhD), Molecular Oncology (Prof. Andrea Alimonti MD) and Prostate Cancer Functional Genomics (Dr. Jean-Philippe Theurillat).

The main objective of the program is to integrate the activity of the various IOR research teams on common themes, such as the study of prostate cancer and other solid tumours and the investigation of novel therapeutic approaches. Research projects include the study of the biological, molecular and genetic mechanisms along with preclinical and translational studies on new forms of cancer treatment. These studies involve numerous collaborations within IOR teams and with the clinical research units of the IOSI and other research centres worldwide.

Experimental therapeutics and prostate cancer biology
Prof. Carlo Catapano MD, PhD
Group Leader

The research activity in the Experimental Therapeutics group is focused on the development of new anticancer therapies exploring the molecular mechanisms of epigenetic regulation, that are at the basis of cancer progression.

During 2016, considerable progress was made in the study of new drugs targeting transcription factors (STAT3, NF-kB) and epigenetic regulators (BRD4, LSD1, EZH2). These compounds are now under pre-clinical and clinical investigation for the treatment of various types of cancer. In 2016, these projects received funding from various research agencies (KLS, SNSF, FTRC) and pharmaceutical companies (Otsuka, Incyte, E2DG). In the framework of SNSF project on the role of noncoding RNA, epigenetic regulators and new therapeutic targets in human cancers, two important studies have now been completed and are in publication. Significant progress was also made in the evaluation of experimental therapies capable of targeting the cancer stem cell component in human tumours, particularly in prostate cancer. These studies led to the identification of key epigenetic and metabolic processes that sustain the maintenance and expansion of cancer stem cells and to the experimental validation of specific molecular targets for discovery of new anticancer drugs. In addition to the ongoing funding from KLS and FTRC, a new project that explores the molecular details of metabolic reprogramming in cancer stem cells, was funded by SNSF in 2016 in the framework of an international collaboration with research teams in Germany, Switzerland, Italy and the United States.

Research activity in the Prostate cancer biology group was focused on the role of the transcription factors ETS (ERG and EHF) in prostate cancer progression and on their interactions with the mechanisms of epigenetic regulation and phenotypic reprogramming. An important study published in 2016 in the Journal of Clinical Investigation, demonstrated a new oncogenic mechanism that involves EHF, STAT3 and a microRNA (miR-424). This mechanism is active in highly aggressive prostate tumours and its identification will allow designing new approaches for the personalised treatment of high-risk patients. Research undertaken by the group also showed the important role of EHF in cell differentiation, phenotypic
reprogramming and expansion of cancer stem cells in prostate tumours. In 2016, the project exploring the role of the transcription factor EHF received further funding by SNSF to study the mechanisms linking EHF to the acquisition of cancer stem cell properties in prostate cancer using newly developed cellular and transgenic mouse models.

The study of the interactions of the ETS factors with epigenetic regulators is another important aspect of group research with high translational potential in clinical application for the treatment of prostate cancer. Molecular interactions that involve new partners and new mechanisms were identified. New projects that will explore the role in cancer pathogenesis and the therapeutic implications of these interactions granted funding by KLS and SNSF in 2016. SNSF will explore, in collaboration with the International Centre for Genetic Engineering and Biotechnology (ICGEB, Cape Town, SA) and the University of Bern, the network of molecular interactions that cooperate with the transcription factor ERG and contribute to prostate cancer progression and, on the basis of this knowledge, they will design and test new therapeutic strategies.

**Peer reviewed publications in 2016**


Main funding

Epigenetic cross-talks and novel therapeutic strategies to prevent disease progression in ERG fusion-positive prostate cancer: Swiss National Science Foundation (SNSF) (Catapano, Carbone, Zerbini; 2016-2020).

Targeting metabolic reprogramming and plasticity of cancer stem cells to impact on tumor progression and treatment resistance: SNSF (Catapano; 2016-2019).

The ETS transcription factor ESE3/EHF as a regulator of prostate epithelial cell differentiation and stem cell properties: SNSF (Carbone; 2016-2019).


The ETS transcription factor ESE3/EHF as a regulator of prostate epithelial cell differentiation and stem cell properties: SNSF (Carbone; 2013-2016).


Structural basis for the inhibition of STAT3 transcription factor by small molecules: KLS (Catapano-Cavalli; 2016-2018).


Promoter-proximal long noncoding RNAs and transcriptional regulatory mechanisms in human cancer: Novartis Foundation (Catapano; 2015-2016).

Preclinical and clinical development of novel STAT3 inhibitors: Otsuka, Japan (Catapano; 2015-2016).


BRD inhibitors for prostate cancer: Oncoethyx, France (Catapano; 2015-2016).

Molecular Oncology
Group Leader: Prof. Andrea Alimonti MD

The molecular oncology laboratory directed by Prof. A. Alimonti focuses on the identification of novel experimental therapies based on senescence enhancement for cancer, in particular for prostate cancer therapy. In a recent paper published in ‘Nature Communications’, we described a novel therapeutic approach based on the targeting of NOTCH in prostate cancer. Our results provide evidence that PTEN loss in prostate tumours upregulates the expression of ADAM17, thereby activating NOTCH signalling. Using prostate conditional inactivation of both Pten and Notch1 along with preclinical trials carried out in Pten-null prostate conditional mouse models, we demonstrate that Pten-deficient prostate tumours are addicted to NOTCH signalling. Importantly, we find that pharmacological inhibition of γ-secretase promotes growth arrest in both Pten-null and Pten/Trp53-null prostate tumours by triggering cellular senescence. These findings also have clinical relevance since in human prostate tumour samples we found that NOTCH signalling is frequently upregulated in PTEN deficient tumours and NOTCH activation correlates with treatment resistance and decreases overall survival. These findings describe a novel pro-tumourigenic network that links PTEN loss to ADAM17 and NOTCH signalling, thus providing the rationale for the use of γ-secretase in prostate cancer therapy.

Our research group continued to expand the Pre-clinical Core Facility of transgenic mouse models for prostate cancer, including new mouse models for the study of cancer immunology and started the characterisation of the immunophenotype of prostate tumours of different genetic backgrounds in parallel with the polysome profile analysis of secreted factors released by these tumour cells. Our objective is to identify factors that contribute to the intra-tumour recruitment of myeloid cells or promote the skewing of these cells in M2 TAMs. The genetically modified mouse models generated so far, include different prostate conditional and prostate specific transgenic mice including: Ptenpc-/-, ERG+, Trp53-/-, NOTCH-1-/-, TIMP-1-/-, CXCR2ko, TNFaR-/-, PDH1-/-, DUSP16 and CDCP1+ and their respective crosses with the Ptenpc-/- . The advantage of using these models is to study the genes involved in the metabolism of prostate tumour (PDH), the process of metastatization (TIMP-1, CDCP1) and the contribution of the tumour immune response to prostate cancer development and therapy. The team has also recently strengthened the clinical implications of previous findings in the field of cancer immunology, setting up methods to detect circulating myeloid cells in the blood of patients affected by prostate cancer and obtained financial support for two new clinical trials in prostate cancer patients. The molecular oncology laboratory is supported by several grants including the prestigious European Research Council (ERC CoG). The laboratory has a stable collaboration with the ETH and Universitätssspital in Zurich, the University of Lausanne and Harvard University.

Peer reviewed publications in 2016

Di Mitri D, Alimonti A.
Non-Cell-Autonomous Regulation of Cellular Senescence in Cancer.

Identification of Salvia haenkei as gerosuppressant agent by using an integrated senescence-screening assay.

Inhibition of Notch pathway arrests PTEN-deficient advanced prostate cancer by triggering p27-driven cellular senescence.
Main funding

Several research fundings, including: European Research Council (ERC CoG; competitive grant); Cardio-Oncology grant (competitive grant); Josef Steiner Foundation (competitive grant); Swiss Cancer League (competitive grant); Prostate Cancer UK (competitive grant); Novartis IIT grant; Dakio Sankio grant.

Prostate Cancer Functional Genomics
Jean-Philippe Theurillat MD
Group Leader

Cancer is driven by cardinal genetic alterations that activate driver genes. Driver mutations are not only essential to initiate tumourigenesis, but are also required for tumour growth and maintenance. This raises the possibility of targeting these mutations, opening more specific, therapeutic opportunities to treat cancer patients.

Our research group focuses on new drivers of prostate cancer with emphasis on advanced, castration-resistant disease. We aim at exploring the roles of these genes in tumourigenesis with the ultimate goal to develop new therapeutic avenues for patients suffering from prostate cancer (exemplified in Fig. 1).

Fig. 1. TRIM24 is a druggable coactivator of the androgen receptor (AR) and a driver of castration-resistant prostate cancer.

Also, our group develops new strategies to tailor cancer therapy in the clinic empirically. Patient-derived tumour cells will be used to test drug responses prior to treating the patient. This approach may guide decision-making in the clinic in an individualised manner (Fig. 2).

Fig. 2. Patient-derived cancer and normal cell lines may allow empirical testing of drug responses in culture prior treating the patient.


Main funding

Genetically-induced aberrant chromatin states in prostate cancer – Biology and Therapy: Swiss National Science Foundation (SNSF) (Professorship Grant; amount: CHF 1,600,000; duration: 09/2014-08/2018).

Role of TRIM24 in prostate cancer initiation and progression: Schweizer Krebsliga/Swiss Cancer League (competitive grant for a salary of a research scientist and consumables; amount: CHF 247,000; duration: 09/2015-08/2017).

Generation and characterisation of new prostate cancer cell lines: Swiss Life Jubiläumsstiftung (grant for consumables; amount: CHF 30,000; 05/2015).

Start-up funding for mouse experiments and postdoc salary 1 year: IDR Fondazione Linfomi Ticino (Foundation for the Research and Cure of Lymphoma in Ticino) (amount: CHF 150,000; 08/2015).

Herstellung und onkogenomische Charakterisierung von Prostatakrebszelllinien: Vontobel-Stiftung (grant for ½ technician salary; amount: CHF 30,000; 02/2016).

Pharmacological inhibition of TRIM24 in castration-resistant prostate cancer: An Effective Tool Towards the Cure of Advanced Prostate Cancer?: Movember Foundation (grant for postdoc salary for 2 years; amount: CHF 200,000; 04/2016).

Oncogenic Aversion: a concept towards new therapeutic avenues in prostate cancer: San Salvatore Foundation (grant for postdoc and consumables; amount: CHF 170,000; 12/2016).
Non-Hodgkin’s lymphomas are neoplasms derived from lymphoid cells at various stages of development and represent the fifth most frequent cancer. The development of novel treatment strategies based on targeted drugs and the identification of the biological and genetic features, that may allow a rational application of tailored therapies, hold the potential of increasing curability for poor risk lymphoma patients and spare toxicity for the good risk-ones. During 2016, we published some paper describing the anti-tumour activity of novel compounds as single agents or in combination. The addition of the MEK inhibitor pimasertib to the BTK inhibitor ibrutinib or the PI3K-delta inhibitor idelalisib improves the activity of the two latter compounds both in diffuse large B-cell lymphoma and in mantle cell lymphoma. Similarly, we saw that the addition of an epigenetic agent, the BET Bromodomain inhibitor OTX015 (MK-8628), can increase the efficacy of the BTK inhibitor ibrutinib, of the anti-CD20 monoclonal antibody rituximab, of the HDAC inhibitor vorinostat, and of the mTOR inhibitor everolimus in diffuse large B-cell lymphoma. Moreover, other 2016 papers from our group also showed that OTX015 is active also in ALK-positive anaplastic large cell lymphoma and non-small cell and small cell lung cancer models. During 2016, we contributed to other published papers, coordinated by other investigators, both from IOR (Alimonti, Rossi) and from other centres. In the last publication, the application of an algorithm, optimised at IOR, led to identify a new subgroup of ALK-negative anaplastic large cell lymphoma, characterised by the expression of ERBB4, a potential therapeutic target. During the year, we also worked on the characterisation of a series of additional novel compounds and performed DNA profiling on the clinical specimens collected within a large phase III trial for patients with mantle cell lymphoma (preliminary data presented at the ASH, AACR and EORTC-NCI-AACR meetings).

Peer reviewed publications in 2016


Novel small molecule targets FLI1 in lymphoma and T-ALL: Leukemia & Lymphoma Society (Bertoni - main applicant; amount: USD 600,000).

Analysis of circulating tumor DNA to inform lymphoma management: Oncosuisse (Bertoni - co-applicant; amount: CHF 330,800).

Targeted agents in splenic marginal zone lymphoma: mechanisms of resistance and new combinations: Swiss National Science Foundation (SNSF) (Bertoni - main applicant; amount: CHF 429,800).

Characterization of FLI1 as an oncogene and therapeutic target in diffuse large B-cell lymphomas: Oncosuisse (Bertoni - main applicant; amount: CHF 359,800).

An international phase III multicenter, randomised study with lenalidomide maintenance versus observation after intensified induction regimen containing rituximab followed by high-dose chemotherapy and autologous stem cell transplantation as first-line treatment in adult patients with advanced mantle cell lymphoma: Identification of DNA and methylation changes associated with the clinical outcome: Oncosuisse (Rinaldi - main applicant, Bertoni - co-applicant; amount: CHF 115,800).

Identificazione di nuovi meccanismi patogenetici e nuove terapie in linfomi aggressivi pediatrici (Identification of novel pathogenic mechanisms and new therapies in paediatric aggressive lymphomas): Fondazione Gelu (Bertoni - main applicant).

Functional analysis of altered transcriptional pathways in diffuse large B-cell lymphoma of the ABC subtype: SNSF Sinergia (Bertoni - co-applicant).

Steiner Trees for Functional Analysis in Cancer System Biology: SNSF (Kwee - main applicant, Bertoni - co-applicant; amount: CHF 153,900).
Main areas of research

Analysis of circulating tumor DNA to inform lymphoma management.

**Lead investigator:** D. Rossi.


A highly sensitive ultra-deep NGS approach was developed to track the genetic profile of B-cell tumours by using plasma as a source of tumour DNA. In diffuse large B-cell lymphoma, genotyping of plasma cell-free DNA correctly identifies almost all biopsy confirmed mutations and informs on the spatial heterogeneity of tumour clonal composition. Longitudinal analysis of plasma samples under treatment tracks clonal evolution and the emergence of resistance mutations. In classical Hodgkin lymphoma, a hard-to-genotype tumour on the tissue
biopsy because of the scarce representation of the Reed-Sternberg tumour cells, plasma cell-free DNA genotyping efficiently recovers mutations of tumour origin. Overall, these results provide the proof-of-principle that cell-free DNA genotyping allows a real-time and non-invasive way to track clonal evolution and emergence of treatment resistant clones in lymphoid tumours, including situations of low tumour burden (i.e. classical Hodgkin lymphoma) and mutations hidden in non-accessible tumour compartments.

**Molecular prediction of long term benefit from ibrutinib in high risk chronic lymphocytic leukemia.**

**Lead investigator:** D. Rossi.


The IOSI-EMA-001 study (NCT02827617) is an observational, non-intervention, multicenter study consisting of the prospective and longitudinal collection of peripheral blood samples and clinical data from high-risk CLL patients treated with ibrutinib monotherapy. The study aims at monitoring the dynamics of cell signalling and clonal evolution in CLL under ibrutinib. The objectives of the project include: i) identify dynamic molecular markers that can help the early and real-time prediction of sustained benefit from ibrutinib treatment vs imminent progression; and ii) refine the current approach for treatment tailoring in CLL patients by allowing the identification of patients who, though being in clinical response under ibrutinib, need immediate switch to alternative options. Preliminary data coming from the sequencing of the first 10 patients enrolled in the IOSI-EMA-011 study are showing clues of clonal evolution already after 2 weeks of ibrutinib treatment in 20% of cases. Preliminary pathway analysis suggests by-pass signalling activation in patients with persistent metabolically active disease at the imaging studies.

**Integrated molecular and clinical profiling to optimize outcome prediction in splenic marginal zone lymphoma — IELSG 46.**

**Lead investigator:** D. Rossi.

**Collaborators:** C. Thieblemont, F. Bertoni, G. Gaidano, C. Montalbán, E. Zucca, L. Arcaini.

Splenic marginal zone lymphoma (SMZL) is a rare, orphan, B-cell malignancy. Although the majority of SMZL displays an indolent course, a significant proportion of patients (~25-30%) experience a poor outcome and survive <5 years. The accurate identification of high-risk cases represents an unmet medical need in SMZL and can help future clinical trial design and rationale and cost-effective development of treatments based on novel agents. Currently, the prognosis of SMZL can be stratified on the clinical ground by two scores, namely the IIL and the HPLL scores, though they are neither 100% sensitive nor 100% specific in the identification of high-risk patients. Because molecular aspects of SMZL (i.e. immunoglobulin gene mutations, 7q deletion, and NOTCH2, KLF2 and TP53 mutations) represent promising prognostic biomarkers, their incorporation into the clinical prognostic models currently available for SMZL, might improve risk stratification of patients. The IELSG46 study aims at developing an integrated clinico-molecular prognostic model for survival prediction in SMZL.

**Main funding**

Molecular prediction of long-term benefit from ibrutinib in high-risk chronic lymphocytic leukemia (ID: 320030_169670): Swiss National Science Foundation (SNSF) (external competitive grant; year of activation: 2017; duration: 3 years; amount: CHF 429,000).

Analysis of circulating tumour DNA to inform lymphoma management (ID: KFS-3746-08-2015): Swiss Cancer League (external competitive grant; year of activation: 2016; duration: 3 years; amount: CHF 330,800).

Unrestricted research grant: Gilead (external non-competitive grant; year of activation: 2016; duration: NA; amount: CHF 50,000).

Unrestricted research grant: Abbvie (external non-competitive grant; year of activation: 2016; duration: NA; amount: CHF: 30,000).
In recent years, nurses at the IOSI, as well as throughout the EOC, have been developing additional knowledge and skills to be able to offer their patients high-quality professional services. Their approach refers to the “Relationship-based care” model that is based on the quality of the relationship between nurses and patients. This model requires responsibility, accountability and investment in training and research as essential conditions to respond to the many health needs of patients more effectively and to contribute to their well-being.

Within an ever-changing healthcare system, the development of expertise in care is an essential element to ensure competent and individualised care and to promote a real multidisciplinary collaboration. To facilitate these processes, research in the field of nursing is developing. The main purpose of investigation in this area is to contribute to the development of knowledge in all areas where nurses must take their decisions for the sake of patients and their families. Nursing research has specific purposes and contents, but is not different in methods compared to other fields of research.

On this basis, a Nursing Research and Development Office was set up within the IOSI Nursing Service, under the responsibility of Dario Valcarenghi (PhD).

**Peer reviewed publications in 2016**

*How to maintain equity and objectivity in assessing the communication skills in a large group of student nurses during a long examination session, using the Objective Structured Clinical Examination (OSCE).* Nurse Educ Today. 2016;38:54-60. doi: 10.1016/j.nedt.2015.11.034. Epub 2016 Jan 7.


Bressan V, Tolotti A, Barisone M, Bagnasco A, Sasso L, Aleo G, Timmins F. 

Cadorin L, Bagnasco A, Tolotti A, Pagnucci N, Sasso L. 

Valcarenghi D, Pedrazzani C, Di Giulio P, Moser L, Bianchi M. 
*La gestione del dolore nei pazienti di un Istituto Oncologico Svizzero e il ruolo degli infermieri: dai programmi alla realtà.* PROFESSIONI INFERMIERISTICHE (online). 2016; 69(3).
Main areas of research

Fatigue in cancer patients at the IOSI.
Lead investigator: D. Valcarenghi.

The purpose of the study is to estimate the prevalence and intensity of the symptom fatigue in cancer patients hospitalised at the IOSI and how nurses manage it. The study has a mixed, quantitative and qualitative, design. Fatigue in patients admitted to the IOSI, in the reference period, will be assessed by administering the Brief Fatigue Inventory (BFI - Italian version) and doing in-depth interviews. Nursing will be evaluated using focus groups and analysis of the documentation of care provided. The data collection started in June 2016, and the study is still ongoing.

Information search of the patient with cancer along its path of disease - INFO-SEEK.
(project in partnership with USI)
Lead investigator: E. Germeni (USI).
Collaborators: M. Bianchi, C. Pedrazzani, D. Valcarenghi, P. Schultz (USI).

The study aims at understanding and learning the various methods used by cancer patients to search for information in the different stages of their disease. It is a longitudinal qualitative study that consists of in-depth interviews with cancer patients followed at the IOSI. All consenting patients will be interviewed in three different moments of their path of disease: after diagnosis, after the start of the scheduled treatment and after about six months from the first treatment. The study will be conducted following the theories and methods of qualitative research (Grounded Theory approach). During 2016, the study was amended with the approval of the Ethics Committee, by reducing the number of interviews for each patient (avoiding the interview close to the diagnosis). At the end of 2016, only 12 patients were surveyed compared to 30 expected. The study is still ongoing.

Look Good - Feel Better workshops: an opportunity for cancer patients at the IOSI?
Lead investigator: C. Pedrazzani.
Collaborators: S. Tosi, M. Zanon, D. Valcarenghi.

The study started in January 2012. Its purpose is to assess the effects of Look Good - Feel Better workshops attendance on patients. In the workshops, patients learn, from expert beauticians, how to enhance their body image further to cancer and cancer treatments. Patients are asked to fill in the Body Image Scale (BIS), an international validated tool, about 8 weeks before and after attending the workshop. At the end of 2016, 31 workshops were carried out with 220 participants, and 66 women agreed to participate in the study, which ended in Summer 2016.

The relationship between nursing decision-making and patient outcomes in two European Cancer Centers (research project in partnership with the University of Genoa).
Lead investigator: D. Valcarenghi.
Supervisor: F. Carnevale (McGill University, Montreal, CA), L. Sasso & A. Bagnasco (Unige - Genoa - Italy).
The purpose of the study is to understand how nurses working in two different cancer centres (IOSI and San Martino Hospital, Genoa) take healthcare decisions and evaluate the pertaining outcomes on the patients. The constructivist grounded theory approach is used to analyse and provide a theoretical explanation of the process under investigation. Data are collected using semi-structured interviews and on-site observations. Data collection and analysis process are circular and structured into two phases. Analysis is performed through (open, axial, and selective) coding. The phenomenon observed in this study is interpreted according to an explicative theory called ‘dynamic decisional adaptation’. The first interview was conducted in May 2015. The study was completed in 2016.

Mepitel film toward standard treatments for the prevention and treatment of skin toxicity from radiation therapy in the postoperative treatment of breast cancer.


The purpose of the study is to compare the effectiveness of mepitel film in preventing the onset of radiotherapy skin toxicity (> / = grade 2, according to RTOG score) compared to standard treatment (SASRO Protocol) in women undergoing radiation treatment after conservative surgery for breast cancer at the IOSI. It is a randomised controlled, open-label, phase III trial and 164 patients will be recruited in two years (82 in each arm). The protocol was approved by the Ethics Committee and Swissmedic in 2015. The recruitment of patients started in January 2016 and is still ongoing.

Utilization and complications of the vascular devices used at IOSI (AVI, CVC, PICC).


The purpose of the study is to describe how the three vascular principles are used with patients treated at the IOSI (which patients will be involved, how long it will take, what and how many complications it will have, patient satisfaction), in order to improve their appropriateness of use. From the study start time, three cohorts of cancer patients will be progressively set up according to the type of vascular device implanted in them (n. 50 per cohort). The cohort of patients with a central venous catheter (CVC), the cohort of patients with peripheral inserted central catheter (PICC) and the cohort with a central venous catheter implanted (AVI). The data collected at the local level will then be verified and compared with the literature data, particularly with respect to the incidence of the detected complications. The study will start in 2017.

Main funding

Fatigue in cancer patients at IOSI: ABREOC in 2014 (internal competitive grant). It started in June 2016 and is still ongoing.

Information search of the patient with cancer along its path of disease - INFO-SEEK: project self-funded, in partnership with USI. It started in December 2014 and is still ongoing.

The use of the Peripherally Inserted Central Catheters (PICC) at Ente Ospedaliero Cantonale (EOC): evaluation of the effects: project self-funded. It started in January 2016 and is still ongoing.

Look Good – Feel Better workshops: an opportunity for cancer patients at the IOSI?: self-funded project. It started in January 2012 and ended in Summer 2016.

The relationship between nursing decision-making and patient outcomes in two European Cancer Centers: ABREOC in 2015, in partnership with the University of Genoa. It started in 2015 and ended in 2016.

Mepitel film toward standard treatments for the prevention and treatment of skin toxicity from radiation therapy in the postoperative treatment of breast cancer: project funded by Mölnlycke Healthcare. It started in January 2016 and is still ongoing.

Neurocenter of Southern Switzerland (NSI)
2. Neurocenter of Southern Switzerland

Prof. Alain Kaelin MD, PhD
Head of Department and Scientific Director of NSI and Neurosciences

The Neurocenter of Southern Switzerland (NSI) hosts the services of neurology, neurosurgery, neuroradiology, neuroanaesthesia as well as the neuroscience research unit. The goal of the NSI is to confer the highest quality of treatment to the patient with the application and promotion of an inter- and multidisciplinary approach. To ensure a continuous excellence of care, the implementation of basic and clinical research, as well as educational duties, is an important priority for the NSI.

Academic collaboration with local, national and international universities and hospitals including regular teaching activities at the level of the Master of Medicine at the University of Bern and Basel, as well as active participation in PhD programs in neurosciences at the University of Bern, Basel and Zurich are contributing to the success of the NSI. The main focus of scientific activities at the NSI currently relies on multiple sclerosis, sleep disorders, movement disorders and stroke, even though, active research is also carried out in other fields of clinical neuroscience.

For clinical research, one of the two seats of the Clinical Trial Unit of the Ente Ospedaliero Cantonale (CTU-EOC) is located at the NSI. The Clinical Trial Unit supported the investigators of the NSI for investigator-initiated and sponsor-initiated studies and participated in several studies described below. The pertaining projects in basic and clinical research carried out or still ongoing in 2016, are summarised in the following sections.
The Multiple Sclerosis Center aims at offering an optimal care for patients with multiple sclerosis (MS) mainly living in the Ticino area. A dedicated team of two senior neurologists, one neuroradiologist, three assistants, one neuropsychologist, and three MS nurses specialised in multiple sclerosis, run the outpatient care service and concomitantly performs research activities. Research contributes to offering alternative and innovative treatments to patients and advancing knowledge in the MS field.

Peer reviewed publications in 2016


Main areas of research

The Multiple Sclerosis Center focuses on three long-term research topics

**MS epidemiology** is endorsed by the participation in the Swiss Cohort of MS patients (SMSC), an innovative project to establish a clinical database and a biological sample collection available for current and future research. Our Multiple Sclerosis Center achieved the goal for inclusion of patients, as 107 patients have already been enrolled. It participates in a sub-study to validate multimodal evoked potentials for prognosis and monitoring the MS disease course in different stages of the disease.

**Upcoming MS treatments** can be provided to our patients with primary and/or secondary relapsing-remitting MS through our participation in several international trials. Some of them evaluate suitable MS therapeutic compounds such as ocrelizumab (NCT01247324) and siponimod (NCT01665144). Observational trials focus on new drug administration methods (TERIFL06965, NCT02076841, NCT02247310) or gather safety and efficacy data on marketed drugs (fingolimod (CTFY720D2406), natalizumab (NCT02386568), di-methylfumarate (NCT02047097)). Industry-sponsored research is also performed in migraine indication (NCT02483585).

**Investigator-initiated trials** focus on the diagnosis and on the understanding of MS symptoms aiming at improving the patients’ quality of life.

**Ongoing studies**

**Serum neurofilament light chain levels: a biomarker for prediction of neurological disability in multiple sclerosis.**

Lead investigator: C. Zecca. **Collaborators:** C. Gobbi, G. Disanto and J. Kuhle (Department of Neurology, University of Basel).

Neurofilaments (NF) are structural elements of neurones composed of three NF chains (light (NFL), medium and heavy (NFH)) and α-internexin in the central nervous system (CNS) or peripheral nervous system. NF are released into the extracellular space following neuronal death and are therefore considered as a candidate biomarker of ongoing neurodegeneration. Levels of neurofilaments are abnormally high in cerebrospinal fluid in patients with MS and correlate with measures of disease severity. Obtaining CSF is a relatively invasive procedure which limits the potential use of NF as biomarkers in MS in clinical trials. A sensitive electrochemiluminescence (ECL)-based immunoassay for the quantification of NFL in serum was recently developed and showed a close correlation between serum and CSF NFL levels. We investigate the potential role of serum and CSF NFL levels in the prediction of future neurological disability and the correlation between serum and CSF NFL levels in MS patients of the Ticino cohort and their association with different clinical phenotypes. This is a retrospective analysis of biosamples of 200 MS patients and 254 healthy controls. Cox regression models will be used to test the association between baseline serum and CSF NFL with time to reach disability milestones as measured by the EDSS and time to develop new clinical relapses.

**Pain network and neuropsychological profile in multiple sclerosis and migraine patients – a clinical and Magnetic Resonance Imaging study (EDC. NSIMS.14.01).**

Lead investigator: C. Zecca. **Collaborators:** G. Riccitelli, E. Pravatà, A. Cianfoni, C. Gobbi.

This is a prospective, observational, cross-sectional, case-control, three-arm, single-center research project aiming at investigating brain functional and structural substrates of pain network in patients with multiple sclerosis (MS) and migraine and at defining the relationship between brain functional activity, the severity of brain tissue damage and specific neuropsychological profile in MS patients with migraine. Assessments include Magnetic Resonance Imaging data acquisition running 6 different sequences, EDSS score and neuropsychological tests assessing executive functions, attention, memory, and visuospatial abilities. The intrinsic brain functional connectivity from MRI BOLD data obtained at rest will be estimated. The microstructural and
Macrostructural brain damage using high field T1 and DTI MRI techniques will be quantified. A correlation between MRI findings and clinical and neuropsychological measures in MS patients with and without migraine and patients with migraine alone will be established.

At present, 84 out of 100 planned patients were enrolled and concluded the assessments.

**Multidimensional assessment of fatigue in multiple sclerosis – observational study – Ticino (EOC. NSI.13.02).**

*Lead investigator:* C. Gobbi.


This cross-sectional, prospective, observational, instrumental investigation seeks to: 1) provide a detailed characterisation of fatigue in a cohort of selected MS patients, including a definition of the boundaries and the overlaps between fatigue, somnolence, mood disorders and attention dysfunction; 2) see how the prevalence and the overlaps between fatigue, somnolence, depression and attention dysfunction are influenced by the method of assessment; 3) better characterise sleep structure in MS patients with fatigue under both the macro- and microstructural point of view.

Inclusion criteria are a definite diagnosis of MS (or clinically isolated syndromes according to the current criteria, Expanded Disability Status Scale (EDSS) score < 7.0 and last magnetic resonance imaging (MRI) within previous 12 months. Fatigue, sleep, psychiatric and cognitive assessments will be performed using appropriate questionnaires.

At present, 84 out of 100 planned patients were enrolled and concluded the assessments.

**Clinical trials in collaboration with the pharmaceutical industry**

**EMR200136_597 (NCT02949908):** a phase IV, prospective, multicenter, open-label, uncontrolled, non-interventional, single arm study to measure treatment satisfaction of multiple sclerosis (MS) patients on Rebif® after discontinuing initial first-line treatment.

*Sponsor:* Merck.

**CHE-TYS-12-10341 (NCT02386556):** a prospective, multicenter, single-arm phase IV study to assess the correlation of EDSS with quality of life in MS patients treated with natalizumab.

*Sponsor:* Biogen.

109MS421 (NCT02776072): a multicenter, global, retrospective, observational study to characterize real-world clinical outcomes in patients with relapsing-remitting multiple sclerosis treated with disease-modifying therapies (Tecfidera®, Copaxone®, Aubagio®, or Gilenya®).

*Sponsor:* Biogen.

105MS401 (NCT02230969): Plegridy™ (peginterferon r-1a) Real World Effectiveness and Safety Observational Program (POP).

*Sponsor:* Biogen.

109MS401 (NCT02047097): a multicenter, global, observational study to collect information on safety and to document the drug utilization of Tecfidera™ (dimethyl fumarate) when used in routine medical practice in the treatment of multiple sclerosis.

*Sponsor:* Biogen.

**CBAF312A2304 (NCT01665144):** exploring the efficacy and safety of siponimod in patients with secondary progressive multiple sclerosis (EXPAND).

*Sponsor:* Novartis.

**CFTY7200D2406:** long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.

*Sponsor:* Novartis.

**COMB157G2302 (NCT02792231):** a randomized, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of ofatumumab versus teriflunomide in patients with relapsing multiple sclerosis.

*Sponsor:* Novartis.

**WA21092/93 (NCT01247324):** a study of ocrelizumab in comparison with interferon beta-1a (Rebif®) in patients with relapsing multiple sclerosis.

*Sponsor:* Roche.

**TERIFL06965:** teriflunomide in RRMS patients assessing clinical benefit and patient...
reported outcomes in real-life medical practice. 
Sponsor: Sanofi-Aventis.

20120297 (NCT02483585): a phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of AMG 334 in migraine prevention. 
Sponsor: Amgen.

CHE-AVX-12-10348 (NCT02076841): tolerability and quality of life in patients with multiple sclerosis switched to intramuscular interferon beta-1a autoinjector (Avonex® PenTM). 
Sponsor: Biogen.

The study closed in 2016.

Sponsor: Bayer.

The study closed in 2016.

Active internal collaborations

M. Manconi, NSI 
Multidimensional assessment of fatigue in multiple sclerosis – observational study 
1 ongoing research project.

A. Cianfoni, NSI 
Pain network and neuropsychological profile in multiple sclerosis and migraine patients 
1 ongoing research project, 1 publication (case report).

A. Reinert, NSI 
1 publication (case report).

Active external collaborations

L. Kappos and J. Kuhle, Department of Neurology, University of Basel 
Validation of multimodal evoked potentials; Swiss Multiple Sclerosis Cohort-Study; Serum neurofilament light chain levels 
1 publication, 1 publication submitted (Annals of Neurology journal).

V. Martinelli, Department of Neurology, San Raffaele Scientific Institute, Milan, Italy 
MS treatment with fingolimod 
1 publication submitted (Multiple Sclerosis Journal, MSJ).

R. Mantegazza, Neuroimmunology and Neuromuscular Diseases Unit, IRCCS Foundation, “Carlo Besta” Neurological Institute, Milan, Italy 
1 publication (case report).

M. Filippi, Neuroimaging Research Unit, San Raffaele Hospital, Milan, Italy 
2 publications (original papers).

Main funding

C. Zecca: 
Serum neurofilament light chain levels: a biomarker for prediction of neurological disability in multiple sclerosis: ABREOC (internal competitive grant).

Pain network and neuropsychological profile in multiple sclerosis and migraine patients - a clinical and Magnetic Resonance Imaging study (EOC. NSIMS.14.01): Swiss MS Society (external competitive grant; amount obtained in 2015: CHF 42,000; year of activation: 2015; duration: 2 years).

G. Disanto: 
Pre-diagnostic presentations of multiple sclerosis in primary care: a case-control study: Swiss MS Society (external competitive grant; amount obtained in 2016: CHF 20,000; year of activation: 2016; duration: 1 year).

C. Gobbi: 
Effects of repetitive transcranial magnetic stimulation and cognitive rehabilitation on cognitive functions in patients with multiple sclerosis: an explorative study with structural and functional MRI: Swiss MS Society (external competitive grant; amount obtained in 2016: CHF 35,000; year of activation: 2016; duration: 1 year).

Number of trainees

Two Masterclass medical students (cand. Med) from the University Hospital of Basel (September 2016).
2.2. Neuromuscular Unit, Myosuisse Ticino Center

Claudio Gobbi MD, PD
Head Doctor of the Neurology Service - Coordinator of Center (Neurology)

Prof. Gian Paolo Ramelli MD
Head Doctor of the Paediatrics Service - Coordinator of Center (Neuropaediatrics)

Collaborators: Giorgia Melli MD PhD, Paolo Ripellino MD, Massimiliano Tiberti MD, Anna Maria Sury
Case Manager

The Neuromuscular Unit is housed in the Myosuisse Ticino Center, which belongs to a network of other Swiss centres specialised in neuromuscular diseases. It provides interdisciplinary and specialised consultancy to patients with neuromuscular diseases, including clinical neurological and instrumental evaluations for accurate diagnosis. The Neuromuscular Unit participates in the Swiss Register of Neuromuscular Disorders (Duchenne dystrophy and other myopathies, myotonic dystrophy, ALS and other rare diseases). Its main research collaborations are established with: the EOC Microbiology Laboratory, “Centre Hospitalier Universitaire Vaudois (CHUV) – (CHUV University Hospital)” of Lausanne, the University Hospital of Basel, the Institute for Research in Biomedicine (IRB) of Bellinzona and several referral centres for neuralgic amyotrophy in England and in the Netherlands collecting European data on neuralgic amyotrophy.

In 2015 we started a prospective pilot study on neurological complications related to hepatitis E in Switzerland.

Main areas of research

Neurological Complications of Acute Virus E infection (NeuroCAVE) (EOC.NSI.MS.1502).

Lead investigator: C. Gobbi.
Collaborator: P. Ripellino.

For the first time, neurological complications related to hepatitis E are studied prospectively. An outbreak in Ticino (due to contaminated meat ingestion) allowed us to follow up 52 acute HEV cases in 2 years (IgM+ and IgG+; PCR+/−). The majority of patients were hospitalised. HEV PCR was positive in 15 cases, and genotype 3 was identified. Overall, 14 patients had Neuralgic Amyotrophy (NA), 19 myalgias and 1 transverse myelitis. NA was bilateral in 9 cases and more common in males, whereas myalgias occurred more frequently in females. 8 cases of NA were confirmed with EMG, showing a predominant upper trunk (C5-C6) involvement. The common findings of CSF analysis, MRI and US in NA patients, and their response to oral Prednisone or IVlg were investigated. The neurological complications of acute HEV genotype 3 infection are frequent (60%) among patients, even with mild hepatitis, and consist mainly in NA and myalgias.

Main funding

ABREOC (internal competitive grant).
2.3. Sleep and Epilepsy Center

Prof. Mauro Manconi MD
Head of the Neurology Service - Chief of Center

The sleep and epilepsy laboratory’s scientific mission is to explore brain function during sleep and sleep-related disorders to achieve important pieces of knowledge in the new, intriguing and extremely growing field of sleep research. Our group is internationally recognised for its results in the area of sleep related movement disorders such as restless legs syndrome, periodic limb movement disorders, sleep disorders during pregnancy and the relationship between sleep and stroke.

Two important goals were achieved by the Sleep Center in 2016:

- The official recognition by the Swiss Sleep Society (SSSSC) as a training centre of category A for the sleep medicine expert certificate
- The recognition by the International RLS Foundation as a centre of excellence for the diagnosis and treatment of restless legs syndrome (unique in Switzerland and second in Europe).

In the last five years, thanks to consolidated local and external collaborations, we obtained large competitive grants from the Swiss National Foundation, two of them focused on the impact of sleep disorders on the stroke outcome, one on the effects of sleep related movement disorders on cardiovascular system, one on infraslow oscillation in sleep and the last on sleep disorders and perinatal depression. A further large competitive grant was obtained in 2014 by the Italian Ministry of University to study the efficacy of light therapy on perinatal depression, and the study started in 2015. Other fields of interest, supported by starting competitive local and national grants, include: sleep disorders in Parkinson Disease, sleep disorders in attention deficit hyperactive disorder and infraslow oscillating process in sleeping brain; innovative tools like High-Density EEG will be used in both cases. Educational initiatives such as university masters, European level master courses in sleep medicine, exchanging scholar and fellowship programs and periodic meeting with general population are a further basic pillar of our group’s mission.

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Peer reviewed publications in 2016


World Association of Sleep Medicine (WASM) 2016 standards for recording and scoring leg movements in polysomnograms developed by a joint task force from the International and the European Restless Legs Syndrome Study Groups (IRLSSG and EURLSSG).


Diagnostic accuracy of the standard and alternative periodic leg movement during sleep indices for restless legs syndrome.


Main areas of research

Sleep-related movement disorders: Restless Legs Syndrome (RLS) and Periodic Limb Movements (PLM).
*Lead investigators: M. Manconi, S. Fulda.*

The impact of RLS/PLM on cardiovascular function. RLS/PLM as a risk factor for perinatal depression. Respiratory-related limb movements. Time structure of PLM in RLS and other sleep disorders. RLS/PLM in multiple sclerosis and their relationship with fatigue. Treatment and management of long-term complication in RLS, in particular, the augmentation phenomena. Time-structure and dopaminergic response of periodic limb movements during sleep in the spinal lesion.

Sleep and stroke.

The impact of sleep disorders on stroke outcome. Efficacy of early CPAP treatment in stroke patients with sleep apnea in improving the stroke outcome.

Infra-slow oscillations.
*Investigators: S. Fulda, M. Manconi, C. Prosperetti.*

Computation analysis of periodic limb movements during sleep and another infraslow-oscillating process during sleep.

Sleep disorders in pediatrics, hyperactive attention deficit disorder.
*Investigators: S. Miano, M. Manconi, V. Pezzoli, GP. Ramelli.*

Cycling alternating pattern as a diagnostic marker of hyperactive attention deficit disorder.

Sleep disorders during pregnancy and its relationship with perinatal depression.

The main aim is to identify early sleep-related markers of perinatal depression, to test the efficacy and safety of light treatment as a preventive and therapeutic strategy for perinatal depression, and to identify possible genetic risk factors for perinatal depression and RLS during pregnancy.

Nocturnal eating disorder.
*Lead investigators: M. Manconi, P. Vinai.*

Differential diagnosis, polysomnographic and neuropsychological features of sleep-related eating disorder and nocturnal eating disorders.

Sleep and Parkinson Disease.

Characterisation of the so-called “sleep benefit” (SB) phenomenon, i.e. the spontaneous improvement in motor function referred by some patients with Parkinson’s Disease at awakening.

Active Local Collaborations

A. Auricchio, Cardiocenter TI
RLS/PLM and cardiovascular risk
1 SNSF (Swiss National Science Foundation) grant.
P. Schulz, Science Communication University, USI
Judisky study - Effective empowerment in insomnia
1 SNSF grant.

C. Gobbi, NSI
Sleep/Fatigue in MS
1 paper (review), 1 ongoing study.

S. Galati, NSI
Sleep and Parkinson disease (PD)
1 ongoing study, (ABREOC grant).

C. Cereda, NSI
Sleep-related risk factors for CVD
3 papers.

A. Kaelin, NSI
Sleep and Parkinson disease (PD).

M. Pons, A. Riglietti, Pneumology Service, Regional Hospital of Lugano
Central control of breathing during sleep
2 papers in the process of being printed.

T. Gyr, Gynaecology and Obstetrics Service, Regional Hospital of Lugano
Iron infusion in RLS during pregnancy
1 paper.

M. Preve, Cantonal Psychiatric Clinic of Mendrisio
Life-ON project
1 paper.

Active External Collaborations

S. Clemens, East Carolina University, Greenville, USA
Basic Science (spinal dopaminergic network)
2 papers.

J. Winkelmann, Harvard University, Boston, USA
Sleep-related movement disorders (PLM hypoxia)
2 papers.

R. Ferri, IRCCS Oasi Institute, Italy
Sleep-related movement disorders (PLM/RLS)
36 papers.

C. Bassetti, Bern University, Inselspital, Switzerland
Sleep stroke, pregnancy related RLS
10 papers.

L. Ferini-Strambi, IRCCS San Raffaele, Italy
Sleep/Epilepsy disorders
48 papers.

O. Polo, University of Tampere, Finland
Spinal lesioned model of PLM/RLS
1 paper.

S. Happe, University of Münster, Germany
Computer analysis (LM during sleep)
1 travel grant (ESRS – 2014).

I. Gorayeb, University of Bordeaux, France
Sleep microstructure and PLM in monkeys
2 papers.

F. Fanfulla
Sleep and Stroke
2 papers.

Main funding

M. Manconi (co-applicant), L. Ratti, G. Chiaro:

M. Manconi (lead investigator), S. Fulda, A. Auricchio:

M. Manconi (lead investigator), T. Gyr, C. Garbazza:
Restless Legs Syndrome and Sleep Disorders During Pregnancy and Sleep Related; Risk Factor for Perinatal Depression: MIUR (Italian Department of University Research) Finalised Research, Italian Ministry of University (Italian competitive national grant) (global amount: Euro 901,000; duration: 2015-2019).

S. Fulda (co-applicant):
Sleep Disorder Research. Infra-Slow-Oscillation during Sleep; M. Manconi (Lead investigator): EOC/IBM (funding amount CHF 175,000; started in December 2014; duration 2 years).
The Life-ON Project: Light-Therapy in Perinatal Depression; M. Manconi (lead investigator); SNSF (amount: CHF 525,000; duration: 2015-2018).

S. Fulda (lead investigator), C. Prosperetti: ISO Study: Infra-slow oscillations I: ABREOC (internal competitive grant; duration: 2015-2016).


S. Miano, M. Manconi: A1DHD Study: Markers polisonnografici del disturbo dell’attenzione ed iperattività in età pediatrica e disturbi del sonno (Polysomnographic markers of attention deficit and hyperactivity disorder in paediatric age and sleep disorders): ABREOC (internal competitive grant; duration: 2015-2016).


Awards 2016
Manconi M.
Best Poster Award at The 6th Giornata della Ricerca Clinica della Svizzera Italiana 2016 (The 6th Clinical Research Day of Southern Switzerland 2016), Lugano, 18th March 2016
An open-label study of the efficacy and safety of Intravenous Ferric Carboxymaltose in pregnant women with Restless Legs Syndrome.
2.4. Movement Disorders Center

Claudio Staedler MD
Head Doctor of the Neurology Service - Chief of Center

Collaborators: Prof. Alain Kaelin MD PhD, Salvatore Galati MD PhD

Research on movement disorders represents one important recent research interest at the Neurocenter of Southern Switzerland. In January 2014, Prof. A. Kaelin joined the movement disorders research group and activities were consolidated in 2015 and 2016. Currently, the priority of the translational research efforts relies on the pathogenesis and potential treatment of dyskinesias, involuntary movements that develop in the course of the long-term levodopa treatment of patients with Parkinson’s disease (PD). Both clinical research and basic research are carried out. All basic research is performed in the “Laboratory for Biomedical Neurosciences” (see paragraph 2.10: Laboratory for Biomedical Neurosciences - LBN). Other collaborative projects are underway, mainly in collaboration with the University of Bern. In particular, a neurophysiological project financed by the Swiss National Science Foundation and investigating motor system recovery in children after stroke continued in 2016.

In addition, a database of more than 200 patients of Ticino with movement disorders, in particularly PD, was set up and will be useful for the performance of epidemiological and clinical studies and an ambitious translational research project using skin biopsy to diagnose Parkinson’s Disease was funded by the Swiss Parkinson Association and is ongoing.

Peer reviewed publications in 2016

Cubo E, Ramos-Arroyo MA, Martinez-Horta S, Martínez-Descalls A, Calvo S, Gil-Polo C; European HD Network (Kaelin A).

Clinical manifestations of intermediate allele carriers in Huntington disease.


Strategies for treatment of dystonia.


T2-relaxometry predicts outcome of DBS in idiopathic Parkinson’s disease.


Distinct roles of cortical and pallidal β and γ frequencies in hemiparkinsonian and dyskinetic rats.


Enkephalin and dynorphin neuropeptides are differently correlated with locomotor hyper-sensitivity and levodopa-induced dyskinesia in parkinsonian rats.
Main areas of research

Role of sleep homeostasis in the development of levodopa-induced dyskinesias in PD patients.

Lead investigator: S. Galati.
Collaborators: A. Kaelin, C. Staedler, A. Salvadè, N. Amato, S. Sarasso (University of Milan).

Levodopa is the most effective treatment for PD, but its therapeutic window becomes narrower in the course of the disease, mainly because of the development of levodopa-induced dyskinesia. Although evidence from animal models of PD suggested a striatal hyper-plasticity underlying the development of dyskinetic movements, their pathogenesis remains not entirely understood. In recent years, slow homeostatic tuning of intrinsic excitability occurring during sleep has been considered fundamental for network stabilisation by sliding plasticity thresholds. Hypothesising an association between these sleep process and dyskinesia, we evaluated the synaptic downscaling during sleep by using high-density EEG, and we are conducting a cross-sectional polysomnographic study in different stages of the disease. All patients were recruited and the data are now analysed.

Electrophysiological effects of an acute block of the nigrostriatal pathway with respect to the cortico-striatal and cortico-thalamic interplay.

Lead investigator: S. Galati.
Collaborators: A. Kaelin, A. Stefani (University of Rome).

Spreading of slow cortical rhythms into the basal ganglia is a well-demonstrated phenomenon in PD. Accordingly, striatal dopamine depletion drives cortical-basal ganglia slow wave coherences in urethane-anesthetised rats. The neuronal basis of this pathological synchronisation was the subject of several investigations, and its behavioural relevance is widely debated. The acute pharmacological inactivation of the SNc-striatal pathway led to a fast developing coherence between cortex and basal ganglia time locked with a significant contralateral akinesia. This procedure offers the advantage of detecting electrophysiological changes irrespectively of chronically developing compensatory mechanisms. This study started in 2015.

Time course of the development of beta ad gamma-band oscillations in the basal ganglia of Parkinsonian rats with and without levodopa-induced dyskinesia.

Lead investigator: S. Galati.
Collaborators: JC. Möller, A. Kaelin, A. Stefani, (University of Rome), A. Salvadè, V. D’Angelo (University of Rome).

The relation between beta and gamma band oscillation and parkinsonian symptoms was based on their identification in local field potential recordings from cortex and basal ganglia of patients affected from PD. Indeed, a direct causative relation of beta band oscillations in PD was inferred by the subtle clinical worsening of akinesia given by stimulating the subthalamic nucleus with the beta band frequency. However, the dissociation of these oscillations and clinical symptoms is also apparent, since it is uncorrelated to the clinical state. To explain these conflicting results between beta band oscillations and clinical motor symptoms in PD we are conducting a closer monitoring of cortical and basal ganglia oscillation in the freely moving parkinsonian animal. The data collection and analysis have been recently completed and a first article has been published.

Role of lateral habenula in emerging of levodopa-induced dyskinesia.

Lead investigator: S. Galati.
Collaborators: G. Di Giovanni (University of Malta, University of Cardiff), A. Kaelin, A. Stefani, (University of Rome).

The lateral part of habenula (LHb) has been proposed to play a role in both the modulation of sleep and levodopa induced dyskinesia (LID). It is also notable that hyperactivation of the LHb might induce aggravation of LID and sleep disturbance with up-regulation of REM sleep. LHb represents a key structure between the motor and non-motor behaviour receiving inputs from basal ganglia nuclei such as an internal segment of globus pallidus/entopeduncular nucleus (GPi/EPN), and lateral hypothalamus (LH), and projects primarily to the brain stem nuclei. This project will investigate the effect of LHb lesion on sleep in parkinsonian animal showing LID.
Prevalence and genetics of movement disorders in Ticino - database and biobank.

Lead investigator: S. Galati.

This database was created to capture the spectrum of movement disorders in the population in Ticino. We are currently collecting clinical data as well as additional examinations. The ultimate scope is to capture the mutation frequency of genes involved in these diseases mainly the monogenic forms of PD.

Modulation of striatal gene expression changes in Parkinsonian rats with levodopa-induced dyskinesia.

Lead investigator: A. Kaelin.
Collaborator: S. Sgroi.

This is a PhD thesis of the “Graduate School for Cellular and Biomedical Sciences” of the University of Bern with S. Sgroi as a doctoral student until 2015 and postdoc in 2016 and Prof. A. Kaelin as the thesis supervisor. This project focuses on the role of the endogenous opioidergic neuropeptides in levodopa-induced dyskinesia. Please see “Laboratory for Biomedical Neurosciences” (par. 2.10).

Alpha-synuclein oligomers detection by skin biopsy: a novel early biomarker for Parkinson’s disease?

Lead investigator: A. Kaelin.
Collaborator: G. Melli.

This is a translational research project investigating the potential role of skin biopsies in the early diagnosis of Parkinson’s Disease and started in 2015. Please see “Laboratory for Biomedical Neurosciences” (par. 2.10).

Cortical Reorganisation of Cerebral Networks after Childhood Stroke: Impact on Outcome.

Lead investigator: M. Steinlin (University of Bern).
Co-investigator at the NSI: A. Kaelin.

This is an important multicenter project using fMRI and Transcranial Magnetic Stimulation for investigating motor recovery after stroke in children. The long-term goal is to develop therapeutic strategies better adapted to children through a better understanding of the mechanisms specifically involved in children. The whole study is performed within the context of the Swiss Neuropediatric Stroke Registry (SNPSR). The SNPSR is a population-based registry prospectively collecting data on childhood stroke and represents the unique possibility to study children suffering from an ischaemic arterial stroke on a nationwide basis. This multicenter project will strengthen this Swiss initiative and the data of this study will allow us to determine variables that influence the cortical reorganisation and outcome after childhood stroke. The Neurocenter of Southern Switzerland is collaborating on this project mainly thanks to its expertise in Transcranial Magnetic Stimulation of the motor system.

A first article was published.

Main funding

Role of sleep homoeostasis in the development of levodopa-induced dyskinesias in PD patients: ABREOC (internal competitive grant); Fondazione malattie neurodegenerative dell’adulto e dell’anziano Ticino (Foundation for the study of neurodegenerative diseases in adult and elderly people in Ticino).

Electrophysiological effects of an acute block of the nigrostriatal pathway with respect to the cortico-striatal and cortico-thalamic interplay: Fondazione malattie neurodegenerative dell’adulto e dell’anziano Ticino (Foundation for the study of neurodegenerative diseases in adult and elderly people in Ticino); Parkinson Schweiz.

Time course of the development of beta ad gamma-band oscillations in the basal ganglia of Parkinsonian rats with and without levodopa-induced dyskinesia: Fondazione malattie neurodegenerative dell’adulto e dell’anziano Ticino (Foundation for the study of neurodegenerative diseases in adult and elderly people in Ticino).

Role of lateral habenula in emerging of levodopa-induced dyskinesia: Fondazione malattie neurodegenerative dell’adulto e dell’anziano Ticino (Foundation for the study of neurodegenerative diseases in adult and elderly people in Ticino).

Prevalence and genetics of movement disorders in Ticino - database and biobank: Fondazione malattie neurodegenerative dell’adulto e dell’anziano Ticino.
Modulation of striatal gene expression changes in Parkinsonian rats with levodopa-induced dyskinesia: Fondazione Baasch Medicus (Baasch-Medicus Foundation) and Fondazione malattie neurodegenerative dell’adulto e dell’anziano Ticino (Foundation for the study of neurodegenerative diseases in adult and elderly people in Ticino).

Alpha-synuclein oligomers detection by skin biopsy: a novel early biomarker for Parkinson’s disease?: ABREOC (internal competitive grant); Swiss Parkinson Foundation.

Cortical Reorganisation of Cerebral Networks after Childhood Stroke: Impact on Outcome: Swiss National Science Foundation (SNSF).
2.5. Stroke Center

Claudio Städler MD
Head Doctor of the Neurology Service - Coordinator of Center

Carlo W. Cereda MD
Head of the Neurology Service - Coordinator of Center

Collaborators: Concetta Manno MD, Vesna Stojanova MD, Jane Frangi Study Nurse

The Stroke Unit EOC (SUN EOC) has been an accredited Comprehensive Stroke Center (since 2014) and therefore recognised as one of the Swiss centres of excellence for the treatment of patients with stroke. The Stroke Center provides optimal care for patients with cerebrovascular diseases. A dedicated and multidisciplinary stroke specialised team takes care of the patients in the acute phase (inpatient unit) and also in a specialised outpatient clinic. The group also performs research activities, mainly focused on 4 topics in clinical research: multimodal imaging and diagnosis of ischaemic cerebrovascular diseases, stroke prevention, stroke epidemiology, and stroke recovery in the acute phase.

Main areas of research

Investigator-driven projects

BIO-PREDISC-TIA SWISS cohort study - BIOmarkers and PREDISC diagnostic evaluation for patients with suspected Transient Ischaemic Attacks. 
Prospective multicenter observational cohort study.
Sponsor-investigator: CW. Cereda.
Collaborators: University of Lausanne (CHUV), University Hospital Inselspital, Bern, University of Basel, University of Zurich, Stanford Stroke Center (Stanford University, CA).

The clinical diagnosis of transient ischaemic attacks (TIAs) shows a significant variability among physicians. PREDISC score is a composite score (clinical and radiological) that has shown to improve inter-rate agreement for the diagnosis of TIA. We conduct a prospective multicenter observational
cohort study, in which we will recruit a total of 56 patients per centre, within 48 hours of onset of transient neurological symptoms (TIA) over a period of 1 year. On admission, the patient will undergo a complete diagnostic work-up, including a clinical neurological examination, determine the ABCD2 score and the Clinical part of the PREDISC SCORE (0-4). In addition, patients will be scanned with MRI as early as possible after symptom onset, but no later than 48 hours from admission. The results of MRI will give the PREDISC Imaging score and determine the final PREDISC Score (1-8). In addition, the serum will be obtained for the analysis of biomarkers (microRNA, Exosomes, PBP and others). The primary objective is to establish whether or not patients with suspected TIA classified by the PREDISC score to be “very likely” to have a true ischaemic event (score 4-8) will have a significantly higher level of a pre-specified biomarker compared to subjects with TIA events classified as “unlikely” to be related to an ischaemic event (PREDISC SCORE 0-1).

Rehabilitation combined with bihemispheric transcranial direct current stimulation in subacute ischemic stroke: a randomized, controlled, double-blind study - The Re.Com.Bi.Ne. (Rehabilitation Combined with Bihemispheric Neuromodulation) post-stroke study.

Randomised multicenter interventional trial - NCT 01644929.
Lead investigators: CW. Cereda, R. Müri.
Collaborators: Clinica Hildebrand Brissago (CH), University Hospital, Inselspital, Bern (CH), Helios Klinik Zihlschlacht (CH).
Sponsor: EOC.

Rehabilitation after stroke improves motor functions by promoting plastic changes and transcranial direct current stimulation (tDCS), a form of non-invasive brain neuromodulation, is a promising tool for improvement of motor function by either up-regulating excitability of the affected cortex or down-regulating excitability in the intact one. In this study, we hypothesise that combining bihemispheric tDCS (anodal tDCS excitatory of the ipsilesional motor cortex, and cathodal tDCS inhibitory of the contralesional motor cortex) with simultaneous physical/occupational therapy in the subacute phase of ischaemic stroke may improve upper limb motor recovery in humans. This study is a randomised, controlled, double-blind, cross-over, multicenter, clinical trial. Outcome measures are functional motor scores (Fugl-Meyer Assessment Upper Extremity, the extended Barthel Index, the Ashworth scale, the Test of Upper Limb Apraxia, the grip strength evaluated by the Jamar Hydraulic Hand dynamometer). This study is designed to provide a class I evidence of the possible adjunctive restorative effect of bihemispheric tDCS combined with physical/occupational therapy in the subacute phase after stroke.

SSR- Swiss Stroke Registry.
Prospective multicenter observational registry.
Lead investigator: L. Bonati; Steering Committee: CW. Cereda.
Collaborators: University Hospital of Lausanne (CHUV), University Hospital, Inselspital, Bern, University Hospital of Basel, University Hospital of Geneva (HUG), University Hospital of Zürich (USZ), CH. Sponsor: University of Basel (CH).

This project is the largest and more comprehensive Swiss nation-wide prospective stroke registry with data from the acute phase of stroke to long-term outcome measures.

Sleep deficiency and stroke outcome - Sleep deficiency and sleep fragmentation and their impact on the short- and long-term outcome of ischemic stroke and transient ischemic attacks.
Bicenter prospective observational cohort study - NCT 02559739.
Lead investigators: M. Manconi, C. Bassetti.
Sponsor: Inselspital Bern, CH.

The working hypotheses are that stroke survivors with sleep deficiency and sleep fragmentation due to insomnia, sleep-disordered breathing or restless legs syndrome will involve: (1) higher mortality from all causes and higher frequency of new cardio-/cerebrovascular events; and (2) a less favourable clinical outcome. Outcomes will be compared between patients with and without sleep deficiency and fragmentation.

The BIOSIGNAL-Study - Biomarker Signature of Stroke Aetiology Study.
Prospective multicenter observational study - NCT 02274727.
Lead investigators: M. Katan, CW. Cereda.
Sponsor: University Hospital of Zürich (USZ), CH. Collaborators: Columbia University, NY, USA; University Hospital of Lausanne (CHUV); University Hospital of Geneva (HUG); University Hospital of Zürich (USZ); University Hospital, Inselspital, Bern.

The three-year cumulative risk of a recurrent stroke, dependent on aetiology, is up to 25 percent. At present, preventing recurrence relies on a broad approach to reduce risk factors associated with atherosclerosis, heart disease and metabolic disorders. However, more specific interventions, such as anticoagulation and surgery or stenting, need aetiological information. BIOSIGNAL aims at determining where the most promising biomarkers can help identify stroke aetiology and also predict recurrent stroke. In addition, the insights gained into the processes underlying different stroke subtypes may lead to more targeted diagnostic tools.

PRESS - Predictive Swallowing Score. Prospective multicenter cohort study. 
Lead investigators: G. Kägi, CW. Cereda. 
Sponsor: G. Kägi, Cantonal Hospital St Gallen. Collaborators: Department of Neurology, Kantonsspital St. Gallen; Department of Neurology, Inselspital, Bern; Department of Otorhinolaryngology, Kantonsspital St. Gallen, Switzerland.

Guidelines recommend early tube feeding in stroke patients with impaired oral intake for ≥ 7 days. However, early tube feeding should start within 72 hours after stroke onset. Hence, clinicians need to anticipate the clinical evaluation of dysphagia in their stroke patients. Nevertheless, validated prognostic risk scores of the impairment of oral intake are not available. Predictive Swallowing Score (PRESS) is an easily applicable prognostic risk score of impaired oral intake after stroke. We will conduct a prospective multicenter cohort study in five Swiss stroke centers. The study duration will be 2 years. We will include acute stroke patients with a severe initial impairment of oral intake. They will receive a baseline visit with neurologic, logopedic and radiologic assessments, as well as two follow-up visits after 7 and 30 days. The main aim of this multicenter study is to internally and externally validate the PRESS score in five Swiss stroke centers. The secondary objective is to develop and validate a late prognostic risk score (Late-PRESS), which shall be assessed after 7 to 10 days in patients with persistent impairment of oral intake.


Randomised trials established the benefit of revascularisation by carotid endarterectomy (CEA) for moderate and severe carotid stenosis. However only patients with a high risk of stroke under medical therapy benefited from CEA. For a wide range of patients, there was neither clear benefit nor harm from CEA. Medical therapy for stroke prevention has improved since these original trials. Therefore CEA may not be beneficial in many patients with carotid stenosis treated by modern optimised medical therapy (OMT).

We hypothesise that in patients with carotid stenosis at low and intermediate risk for stroke, OMT alone is as effective in the long-term prevention of cerebral infarction and myocardial infarction (MI) as revascularisation and OMT combined. ECST-2 is a multicenter, randomised, controlled, open, prospective clinical trial with blinded outcome assessment. We will use a risk model based on clinical characteristics to calculate a 5-year Carotid Artery Risk (mCAR) score, which will stratify patients as at high risk (≥15%), intermediate risk (7.5-15%), or low risk (<7.5%) of future stroke. Patients with symptomatic or asymptomatic atherosclerotic carotid artery stenosis will be included (>50%, NASCET criteria), suitable for revascularisation with CAR score indicating low or intermediate risk. Patients will be randomly allocated in equal proportions to be treated by immediate carotid revascularisation with OMT or OMT alone. The planned duration of follow-up is a minimum of 5 years up to a maximum of 10 years. The primary outcome measure for the full trial is any stroke at any time, plus non-stroke death occurring within 30 days of revascularisation. For the safety MRI analysis: the combined 2-year rate of cerebral infarction, cerebral haemorrhage, MI or periprocedural death after randomisation as assessed by
follow-up MRI and screening for MI.

SWITCH - Decompressive hemicraniectomy in intracerebral hemorrhage.
*Randomised multicenter interventional trial - NCT 02258919.*
Sponsor-Investigators: CW. Cereda, V. Stojanova.
Local lead investigator: P. Scarone;
Collaborators: Neurosurgery Service, Regional Hospital of Lugano and University Hospital Inselspital, Bern.
Sponsor: University Hospital, Inselspital, Bern (CH).

The primary objective of this randomised controlled trial which started in 2015, is to determine whether decompressive surgery and best medical treatment in patients with spontaneous ICH will improve outcome compared to best medical treatment only. Secondary objectives are to analyse mortality, dependency and quality of life. Safety endpoints are to determine the cause of any mortality and the rate of medical and surgical complications after DC compared with the best medical treatment alone.

**Clinical trials in collaboration with the pharmaceutical industry**

**SOCRATES – Acute Stroke Or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes.**
*A randomised, double-blind, multinational study - NCT01994720.*
Local lead investigator: CW. Cereda;

The primary objective of the study is to compare the effect of 90-day treatment with ticagrelor vs. aspirin for the prevention of major vascular events (composite of stroke, myocardial infarction [MI], and death) in patients with acute ischaemic stroke or transient ischaemic attack (TIA).

**NAVIGATE ESUS – Rivaroxaban versus aspirin in secondary prevention of stroke and prevention of systemic embolism in patients with recent Embolic Stroke of Undetermined Source (ESUS).**
*A randomised, double-blind, multinational study - NCT02313909.*
Local lead investigator: CW. Cereda;

This is a study in patients who recently had an ischaemic stroke and in whom no clear cause of the stroke could be identified. These strokes are likely due to a proximal blood clot (from Heart or Aorta) and therefore, can be called embolic stroke of undetermined source. The abbreviation is ESUS. The study will compare 2 antithrombotic regimens. Patients will be randomly assigned to either rivaroxaban 15 mg or aspirin 100 mg and the study is intended to show if patients given rivaroxaban have fewer vascular events.

**RE-SPECT ESUS - Dabigatran etexilate for secondary stroke prevention in patients with Embolic Stroke of Undetermined Source.**
*A randomised, double-blind, multinational study - NCT022392120.*

The study addresses to patients who recently had a brain attack (stroke) “with embolic characteristics” with no clear cause of the stroke (ESUS). The study will compare 2 secondary prevention therapies. Patients will be randomly assigned to either dabigatran 150 mg bid or aspirin 100 mg and the study is intended to show the secondary prevention effect of dabigatran in preventing ischaemic and haemorrhagic strokes.

**Main funding**

**BIO-PREDISC-TIA SWISS cohort study - BIO-markers and PREDISC diagnostic evaluation for patients with suspected Transient Ischaemic Attacks: Fondazione Svizzera di Cardiologia (Swiss Foundation of Cardiology), Swissheart (external competitive grant; activation: 2016; amount: 70,000; duration: 2 years).**

**The Re.Com.Bi.Ne. (Rehabilitation Combined with Bihemispheric Neuromodulation) post-stroke study: ABREOC (internal competitive grant).**

**Number of trainees**

Five medical students (cand. med) from the universities of Basel, Zurich, Ulm (Germany), Berlin (Germany) and Varese (Italy).
2.6. Neuropsychology Service

Leonardo Sacco MD
Head of Service

The Neuropsychology and Behavioural Neurology Laboratory provides a comprehensive assessment of adult patients with cognitive or behavioural symptoms. Neuropsychological assessment involves a systematic evaluation of higher cognitive abilities: intelligence, executive functions, attention, memory, language and visuospatial functions. The case studies include suspected memory problems and dementia cognitive and behavioural deficit resulting in various neurological and neurological conditions, such as stroke, epilepsy, Parkinson’s disease, multiple sclerosis, brain tumours, traumatic brain injury, learning and developmental disorders. A dedicated team of a senior neurologist and six neuropsychologists run the outpatient Laboratory and concomitantly perform research activities. The topic of the research is the early diagnosis of dementia. The research activity involves local and national participations. We are participating in an international study to test the efficacy of a human antibody against amyloid in mild Alzheimer’s disease.

Peer reviewed publications in 2016


Main areas of research


This study is included into the metabolic and ageing cohort whose importance was acknowledged by the scientific board and external reviewers. The overall purpose of this investigation is to expand the current knowledge about HIV-associated neurocognitive disorders (HAND) in the HIV ageing population. The current proposal aims at clarifying the global
Neuropsychological markers of conversion from Mild Cognitive Impairment to Alzheimer’s disease: a 5 years follow-up study.  
Lead investigator: L. Sacco.  
Co-investigator: S. Rossi.

The aim of the study is to determine which neuropsychological markers (semantic memory, executive functions, memory-ecological test) better reflect the neurodegenerative damage in patients with mild cognitive impairment (MCI). The primary objective is to prove that some specific neuropsychological tests administered at T0 to MCI subjects are predictive of a probable conversion to AD, during the period of the study (5 years). The secondary objective of the study is to analyse the time of conversion and the influence of some sociodemographic variables in our sample. Patients are currently screened and involved in the research.

Neuropsychologic outcome after aneurysmal subarachnoid haemorrhage – a new implementation of the prospective multicenter Swiss SOS study.  

In the first step, we include all patients with aneurysmal subarachnoid haemorrhage (aSAH). The aim is the prospective implementation of a widely employed, standardised neuropsychological and (Health-related Quality of Life) HrQoL outcome battery of high quality. Such efforts may help identify subtle but important treatment effects, which may otherwise go unnoticed. The Swiss SOS-NPsych study was designed to: (a) improve the detection of neuropsychological deficits, depression, anxiety, and fatigue; (b) follow aSAH in Switzerland; (c) assess the HrQoL in aSAH patients in Switzerland; (d) develop and validate a neuropsychological testing battery, which may be used for future studies on this subject.

Clinical trial in collaboration with the pharmaceutical industry

Lead investigator: L. Sacco.  

Aducanumab is a human monoclonal antibody that recognises aggregated forms of β amyloid (A), including soluble Aβ oligomers and deposited fibrillar A β. Interim analyses of the ongoing multiple dose study (Study 221AD103) demonstrated target engagement, a pharmacodynamic effect on amyloid reduction, and an effect on the Clinical Dementia Rating (CDR)-Sum of Boxes (SB) and Mini-Mental State Examination (MMSE) suggestive of a reduction in the progression of clinical impairment for aducanumab treated subjects. This is a Phase 3 study (221AD301 and 221AD302), which will assess the efficacy and safety of aducanumab compared to placebo in subjects with early Alzheimer’s disease (AD), including mild cognitive impairment due to AD and a subset of mild AD.

Main funding

Neurocognitive assessment in the metabolic and ageing cohort “The NAMACO study”: Swiss HIV Cohort Study (SHCS) (external competitive grant; 2012).

Neuropsychological markers of conversion from Mild Cognitive Impairment to Alzheimer’s disease: a 5 years follow-up study: ABREOCD (internal competitive grant).

Neuropsychological outcome after aneurysmal subarachnoid haemorrhage – a new implementation of the prospective multicenter Swiss SOS study: Registre Suisse Hemorragie Sousarachnoidale (Swiss Registry of Subarachnoid Haemorrhage).

Engage and Emerge study: efficacy and safety Of Biib037 in subjects with early symptomatic Alzheimer’s Disease: Biogen (external grant).

Number of trainees

Two students in neuropsychology from the universities of Milano-Bicocca and Fribourg.
2.7. Neurosurgery vService

Prof. Michael Reinert MD
Head Surgeon

Research priorities of the Neurosurgery Service are in the field of neuro-oncology, neurovascular and spinal neurosurgery. Neuro-oncology is one of the key domains of the NSI and the collaboration with the IOSI has a longstanding tradition. In 2015 and 2016 we initiated the field of experimental research with cell cultures and animal models of glioblastoma. The scope is to improve the understanding of neuro-oncological biomolecular pathways to ameliorate patient outcome. Thereby, new innovative surgical techniques can be developed. Furthermore, by using new preoperative diagnostic non-invasive strategies (MR-spectroscopy study for IDH detection) focused tumor resection can be achieved. These findings can then be correlated with intraoperative findings (NSI Brain tumor Data Bank) and post-operative brain tumor processing (Laboratory for Biomedical Neurosciences, LBN and Cantonal Institute of Pathology, ICP Locarno).

Peer reviewed publications in 2016


Neuro-oncology

Brain Tumour Research Group
(see also paragraph 2.10: Laboratory for Biomedical Neurosciences - LBN)

Prof. Michael Reinert MD
Group Leader

Collaborators: M. Sarti, D. Piffaretti, F. Burgio, E. Pravatà, U. Pieles (FHNW, Basel), L. Mariani (University of Basel), E. Vassella (University of Bern), R. Wiest (University of Bern)

Neuro-oncology is one of the key domains at the NSI and the collaboration with the IOSI has a long-standing tradition. The scope of the research project is to improve the understanding of neuro-oncological biomolecular pathways to improve patient outcome. By using new preoperative diagnostic non-invasive strategies (MR-spectroscopy study for IDH detection), focused tumour resection can be achieved. These findings can then be correlated with intraoperative findings (NSI Brain Tumour Data Bank) and post-operative brain tumour processing (LBN and Cantonal Institute of Pathology, Locarno). RAMAN spectroscopy is used to develop a new intraoperative online tumour- and tumour stage recognition. By a collaboration with the FHNW and UNIBAS the necessary nanoparticles are specifically conceptualised and produced by our PhD students. Differences of RAMAN signal of tumour in cell culture and tumour exposed to nanoparticles are studied at the LBN. Furthermore, in an in vivo tumour model in mice, the effect of anti-brain tumour-coated nanoparticles is studied upon completion of tumour resection and online tumour cell recognition. In this last study, the long-term scope is to develop a new surgical microscope, which permits immediate intraoperative tumour recognition.

Main areas of research

RAMAN guided resection of glioma using nanoparticles targeted cell recognition in the mouse model.
Investigators: M. Reinert, F. Burgio and D. Piffaretti.

This project aims at using Raman technology to better recognise and differentiate brain tumour areas from normal, non-invaded areas during in vivo surgical resection. To increase Raman sensitivity, and to specifically target brain tumour cells, antibody-conjugated, surface enhanced Raman scattering (SERS) gold nanoparticles (GNPs) are used. A protocol for GNPs surface functionalisation was defined and optimised. It involves three main steps including the attachment of a Raman active molecule, a polyethene glycol shell to increase gold colloidal stability, and the conjugation with anti-EGFR antibodies. Successful GNPs surface functionalisation was confirmed, and currently the functionality of the conjugate is under investigation. GNPs selectivity for EGFR is analysed in vitro in cultured human brain tumour cell lines expressing different EGFR levels. As such, GNPs selection will be defined by testing their ability to cross an artificial Blood Brain Barrier before performing in vivo analysis in a xenograft mouse model.

Hydroxyglutarate detection in wild-type and mutant IDH glioma cells by Raman spectroscopy.

The new 2016 World Health Organisation Classification of Tumours of the Central Nervous System makes a revolution compared to its 2007 predecessor. In addition to the histology, for the first time, biomolecular parameters were included in order to help understand the real nature of SNC tumours better. Among the different molecular markers, we can find ATRX and TP53 mutations, 1p/19q co-deletion, WNT activation, EGFR amplification or EGFR variant III mutation and IDH mutations. Isocitrate dehydrogenase (IDH) is an enzyme that catalyses the conversion of isocitrate to α-ketoglutarate (α-KG). In eukaryotes, there
are three isozymes of IDH, the cytoplasmic/peroxisomal IDH1 and the mitochondrial IDH2 and IDH3. IDH1 and IDH2 mutations resulting in neomorphic enzymatic activity are found in certain cancers such as glioma and glioblastoma, acute myeloid leukaemia, and colon cancer. This neoactivity shows a change in the substrate specificity resulting in the conversion of a-ketoglutarate to 2-hydroxyglutarate (2-HG). Clinically, since the first paper on IDH was published, IDH mutant gliomas seem to have a better prognosis in particular regarding the overall survival. Moving from the possibility of detection of 2-Hydroxyglutarate with our RAMAN spectroscopy, the objective of our study is to differentiate IDH mutant and wild-type glioma. The final purpose of the project will be the intraoperative detection of IDH mutant and wild-type tumour cells, giving an extremely helpful information which can guide the surgeon during the resection of the tumour.

Swiss Gioma Network: patient data collection and analysis.  
Lead investigators: F. Marchi, M. Reinert.

The Swiss Gioma Network is a nationwide initiative launched to intensify the collaboration of specialties involved in the care and research of intrinsic brain tumours. The objective is to improve and foster care and research by coordinating joint activities of therapeutic disciplines - neurosurgery, neuro-oncology, including paediatric neuro-oncology, radiation oncology – as well as diagnostic disciplines - neuroradiology, nuclear medicine and neuropathology. The registry was developed in collaboration with the Institute of Social and Preventive Medicine (ISPM) of the University of Bern and is hosted on its MEMdoc portal.

Spinal Neurosurgery

Main areas of research

Studio AIRO: vertebral arthrodesis with pedicular screws: retrospective comparison between intraoperative CT and cone-beam CT associated with spinal navigation.  
Lead investigator: P. Scarone.

Collaborators: G. Vincenzo, D. Distefano, S. Presilla, M. Reinert.

This is a retrospective study on spinal navigation aiming at comparing two different spinal navigation techniques, one associated with a true intraoperative CT (AIRO system, available at our centre since October 2014) and the other with a Cone-beam CT (O-arm system, available at our centre since 2008). The primary objective is to evaluate the difference between the two groups in the number of misplaced pedicular screws, which is a measure of accuracy.

Triojection Study: post-marketing confrontation study between Triojection and microdiscectomy for the treatment of lumbar disc herniations (see below, neuroradiology).  
Lead investigator: A. Cianfoni.  
Collaborators: P. Scarone, P. Maino.

This a prospective randomised study that aims at comparing ozone injection (Triojection) to lumbar microdiscectomy to treat patients with lumbar disc herniations which do not respond to standard medical treatments and steroid injections. The primary objective of this study is to compare the early clinical outcomes following non-surgical treatment with Triojection® to surgical discectomy. Early is defined as less than or equal to 6 months. The primary outcome measure will be the amount of improvement in leg pain after treatment. This will be determined by taking the difference between the baseline score and the average of the post-treatment scores at 1 week, 1, 3 and 6 months. The secondary objective is the number of patients having a subsequent injection and/or surgeries. Other secondary objectives include the duration of surgery, the clinical results, the position of screws in different groups of patients, and the radiation exposure with different techniques. Our centre is actually one of the few neurosurgical services in the world, which has these two techniques available. The results of this study show a high accuracy with spinal navigation associated with intraoperative CT in pedicle screw positioning, confirming the results of previous studies. Moreover, we found a lower rate of intraoperative screw repositioning with iCT AIRO compared to O-arm.
Patient radiation-dose during spinal surgery with intraoperative CT.

Lead investigator: P. Scarone.
Collaborators: S. Presilla, D. Gaudino, G. Fumagalli ("Università degli Studi dell’Insubria" (University of Insubria) of Como and Varese, Como, Italy).

In this in-vitro study, we measured the effective doses to different organs using an anthropomorphic phantom in conjunction with thermoluminescent dosimeters.

Comparison between percutaneous versus open dorsal stabilization in spinal surgery.

Lead investigator: N. Porz.

A prospective study comparing two operation techniques for transpedicular screw placement and stabilisation in the lumbar and thoracic spine surgery.

Vascular Neurosurgery

Main areas of research

SWITCH - Decompressive hemicraniectomy in intracerebral hemorrhage.

Sponsor-Investigators: CW. Cereda, V. Stojanova.
Local lead investigator: P. Scarone;
Collaborators: D. Valsecchi, C. Cereda, M. Reinert.

In collaboration with the Stroke Center, see above.

The primary objective of this randomised controlled trial is to determine whether decompressive surgery and the best medical treatment in patients with spontaneous ICH will improve outcome compared to the best medical treatment only.

The secondary objectives are to analyse mortality, dependency and quality of life.

The safety endpoints are to determine the cause of any mortality and the rate of medical and surgical complications after decompressive craniectomy compared to the best medical treatment alone.

Thirty-six patients were randomised until now in more than 20 hospitals in Europe.

Our centre is one of the main contributors with 2 randomised patients (one randomised to decompressive craniectomy and the other randomised to the best medical treatment).

Modified WFNS study.


The "Modified WFNS" is a study that aims at demonstrating how the actual WFNS score (World Federation of Neurological Surgeons Grading System for Subarachnoid Hemorrhage) does not allow you to define, with adequate accuracy, the clinical status in those patients, affected by aneurysmal SAH, with poor GCS at the onset. Therefore, a retrospective study (carried out by the Neurosurgery of Inselspital of Bern), showed how the early signs of brain herniation, in addition to the WFNS score, seemed to be more effective to determine the clinical status and its prognostic value. In December 2015, this multicenter prospective, not randomised study began. The aim is to recruit 250 patients, throughout Switzerland, with SAH and poor grade of WFNS score, and to evaluate the correlation between their clinical outcome and the signs of brain herniation at the onset (hWFNS score).

Swiss SOS (subarachnoid haemorrhage).

Collaborators: A. Venier, M. Reinert.

The Swiss SOS is a nationwide, multicenter clinical study in patients with aneurysmal subarachnoid haemorrhage. Initiated in 2008, it evolved to be a prospective, institutional-review-board approved continuous database, currently containing anonymous information on > 1700 patients. The aims of the Swiss SOS are: (a) to serve as a tool for disease monitoring in Switzerland, (b) to measure and control the quality of aSAH treatment in Switzerland, (c) to foster clinical research and collaboration between eight Swiss neurovascular centers, d) to guide the future direction of aSAH management in Switzerland. Lugano joined the study in 2013 and in 2014, all the retrospective data about SAH treated in our Hospital from 2009 to 2013 were provided. The website (www.swiss-sos.ch) is currently online.

In February 2016, we hosted the “Swiss SOS” annual meeting.

Somatosensory evoked potentials during clipping of unruptured middle cerebral artery aneurysms: new signal processing techniques for prevention of brain ischemia.
Lead investigator: L. Valci.
Collaborators: F. Tecchio, F. Cecconi, E. Colamartino.

This is a prospective, observational, single-center research project, which aims at analysing the somatosensory evoked potential (SSEP) signal for the prevention of cerebral ischaemia during operations for intracranial aneurysms. The primary goal is the construction of a device capable of reading and interpreting the SSEP signal and of sending an alarm in visual form (light signal) directly into the eyepiece of the operating microscope, once ischaemia is suspected; the secondary endpoint is the search for an electrophysiological index, that is more sensitive than the SSEP amplitude, to detect cerebral ischaemia. The study will continue for three years and is intended to include 30 patients with unruptured middle cerebral artery aneurysm. This study is conducted by the Intra-operative electrophysiology group that consists of two medical doctors and four technicians. This research team for intraoperative electrophysiology was created in 2015 and collaborates with the CNR (National Research Council) of Rome.

Other clinical cohort studies in the field of vascular neurosurgery

Lead investigator: T. Robert.

- Anatomic and angiographic analyses of ophthalmic artery collaterals in Moyamoya disease
- Clinical outcome after an aneurysmal SAH without preventive treatment of cerebral vasospasm
- Clinical and angiographic improvement of cerebral vasospasm after intracisternal injection of papaverine during clipping surgery in an aneurysmal SAH population presenting with symptomatic vasospasm
- Using cisterns to minimise brain retraction: the example of a posterior oriented anterior communicating artery aneurysm. How I do it
- Thrombosis of Venous Outflows of the Cavernous Sinus: Possible Aetiology of the Cortical Venous Reflux in case of Indirect Carotid-Cavernous Fistulas
- Does the recanalisation of the inferior petrosal sinus during the endovascular treatment of a carotid-cavernous fistula represent an independent factor of sixth nerve palsy or worsening?
- Does tamoxifen treatment promote the occurrence of dural arteriovenous fistulas?
- A proposed grading system to evaluate the endovascular curability of deep-seated arteriovenous malformations.


Lead investigator: L. Valci.

Intra-operative electrophysiology allows safeguarding of the main functions of the central and peripheral nervous system during surgery by using the fundamental principle of the nervous system itself, i.e., the electrical current flow. At present, this group is composed of two medical doctors and four technicians. A research team for intraoperative electrophysiology was created in 2015. Its purpose is to understand the working mechanisms of the central nervous system and to study the techniques that allow the protection of nervous structures during neurosurgical operations. Currently, the group collaborates with the CNR (National Research Council) of Rome on the project “Somatosensory evoked potentials during clipping of unruptured middle cerebral artery aneurysms: new signal processing techniques for prevention of brain ischaemia”.

Main funding

M. Reinert (lead investigator):
Neuro-oncology projects: neurosurgical funds (amount: CHF 500,000; started: 2015 - duration: 2018; type of fund: non-competitive, two PhD student positions, fellowship in neuro-oncology).

Intra-Operative Neurophysiology Group (IONG): somatosensory evoked potentials during clipping of unruptured middle cerebral artery aneurysms: new signal processing techniques for prevention of brain ischaemia: ABREOC (internal competitive grant).
2.8. Neuroradiology Service

Alessandro Cianfoni MD, PD
Deputy-Head
Emanuele Pravatà MD
Research Coordinator

The Neuroradiology Service of the NSI provides a comprehensive array of state-of-the-art morphological and functional advanced diagnostic neuroimaging, advanced innovative image-guided minimally invasive spine interventions as well as endovascular diagnostic and therapeutic procedures.

During 2016, several ongoing research projects continued in both the diagnostic and interventional neuroradiology fields. In particular, data acquisition continued for the project “High-resolution post-contrast imaging at 3 Tesla: a comparison of three different techniques”, and other two projects regarding CT accuracy in the acute stroke setting and the accuracy comparison of two different spine surgery implant techniques were carried out in cooperation with the Stroke Center and the Neurosurgery department, respectively (see below). New interventional research projects in the field of spine minimally invasive procedures for vertebral stability also started, one of them with the external cooperation of the Polytechnic Institute of Milan and Ospedali Riuniti Hospital of Bergamo, Italy (see below). The Interventional Neuroradiology is also actively involved, along with Neurosurgery and the Pain Center, in the "Post-marketing non-inferiority study comparing Trijojection to Discotommy for Lumbar Disc Herniation" multicenter international clinical trial, comparing minimally-invasive disc herniation treatment with surgery. Finally, an fMRI research project, regarding MRI brain functional correlates of the Tako-Tsubo and X-syndrome cardiac diseases, in cooperation with Dr. Mattia Cattaneo and Prof. Augusto Gallino’s cardiology research team in Bellinzona, continued. Other active collaborations with the Inselspital of Bern and the San Raffaele Hospital in Milan through the Multiple Sclerosis Center continued in the field of advanced neuroimaging research in 2016.

Since 2016, the Neuroradiology Service has been a co-investigator site for MRI data acquisition in a multicenter phase 3 clinical trial testing the efficacy of Aducanumab monoclonal antibody sponsored by Biogen, for the treatment of AD-related MCI, locally coordinated by Dr. Sacco’s Neuropsychology team.

Peer reviewed publications in 2016

Pravatà E, Tavernier J, Parker R, Vavro H, Mintzer JE, Spampinato MV.
The neural correlates of anomia in the conversion from mild cognitive impairment to Alzheimer’s disease.

Pravatà E, Zecca C, Sestieri C, Caulo M, Riccitelli GC, Rocca MA, Filippi M, Cianfoni A, Gobbi C.
Hyperconnectivity of the dorsolateral prefrontal cortex following mental effort in multiple sclerosis patients with cognitive fatigue.

Prodi E, Grassi R, Iacobellis F, Cianfoni A.
Imaging in Spondylodiskitis.

Spampinato MV, Langdon BR, Patrick KE, Parker RO, Collins H, Pravata’ E;
Alzheimer’s Disease Neuroimaging Initiative.
Gender, apolipoprotein E genotype, and mesial temporal atrophy: 2-year follow-up in patients with stable mild cognitive impairment and with progression from mild cognitive impairment to Alzheimer’s disease.

Ventura E, Manno C, Gobbi C, Vitale VA, Cianfoni A.
MR neurography of a vagal neuropathy.
Main areas of research

High-resolution post-contrast imaging at 3 Tesla: a comparison of three different techniques.

Acquisition of gadolinium-enhanced magnetic resonance images (MRI) increases accuracy in detection and characterisation of neoplastic and multiple sclerosis (MS) brain lesions. We hypothesise that potentially relevant diagnostic differences exist between 3 available gadolinium-enhanced MRI techniques ("MPRAGE", "VIBE" and "SPACE"). Patients scheduled to undergo brain MRI for known or suspected tumours or MS. Test sequences consecutively and randomly acquired during a single examination per patient, after intravenous administration of 0.1mmol/Kg of gadobutrolum. Contrast-enhancing lesion (CELs) detectability, volume, conspicuity (a qualitative judgment of how clearly CELs appear), and artefacts were assessed by two independent neuroradiologists (E. P., D. D.) blind to clinical data.

Post-marketing non-inferiority study comparing Triojection to discectomy for lumbar disc herniation.
Lead Investigator: A. Cianfoni.
Co-investigators: P. Scarone, P. Maino, G. Bonaldi (Papa Giovanni XXIII Hospital of Bergamo, Italy).

Lumbar disc herniation can cause radicular pain. When conservative non-invasive treatment fails and pain persists, surgical discectomy is commonly performed. The use of ozone injection in the disc was reported in non-controlled series to be of benefit in such patients. Ozone intradiscal injection is a minimally invasive image-guided intervention, performed as an outpatient procedure.

This randomised controlled multicenter international trial (3 centres in Europe) aims at comparing surgical discectomy versus a single intradiscal ozone injection in patients with radicular pain without neurological impairment caused by a lumbar disc herniation, resistant to conservative treatment.

Stroke and stroke “mimics” in the acute setting: a one year experience in our centre.
Investigators: E. Prodi, L. Danieli, E. Pravatà, C. Manno, CW. Cereda, A. Cianfoni.

Stroke can be mimicked by non-vascular clinical syndromes that are sudden and focal.
In our centre, we aim at reviewing the prevalence of stroke-mimic conditions and investigating the ability of our diagnostic protocol (consisting in brain CT + angiography CT + perfusion CT) to discriminate ischaemic stroke from stroke-like conditions in the acute/hyperacute phase.
Patients with imaging studies performed from January to December 2016 for clinical suspicion of acute ischaemic stroke were included. We will compare the results of the first CT examination with the findings of the follow-up assessment (CT and/or MRI and/or angiography) and with the final clinical diagnosis at discharge.

Vertebral body stenting and cement augmentation to restore structural stability in extreme spinal osteolysis.

Vertebral augmentation can be used in neoplastic vertebreal lesions for pain palliation and/or stabilization of collapsed or at-risk-of-collapse vertebral bodies. Osteolysis widely involving cortical margins of the vertebreal body pose a risk of cement leakage and can ultimately limit the amount of bone cement that can be injected, resulting in insufficient stabilisation. We want to retrospectively assess technical feasibility, clinical effectiveness and complications of the cement augmentation of vertebreal bodies affected by extreme osteolysis by the use of implantable vertebral body stents, to provide stability and bone cement containment.
The procedures have been performed at NSI in the last 2B months. Follow-up has terminated. Amendment to an existing approved Ethical Committee authorisation is being requested for this retrospective assessment.
Pedicular screw-anchored vertebral body stenting and cement augmentation to restore structural stability in extreme spinal osteolysis.


Vertebral augmentation can be used in neoplastic vertebral lesions for pain palliation and/or stabilisation of collapsed or at-risk-of-collapse vertebral bodies. Osteolysis widely involving cortical margins of the vertebral body pose a risk of cement leakage and can ultimately limit the amount of bone cement that can be injected, resulting in insufficient stabilisation. We want to retrospectively assess technical feasibility, clinical effectiveness and complications of the cement augmentation of vertebral bodies affected by extreme osteolysis by the use of implantable vertebral body stents, to provide stability and bone cement containment. A novel technique, using percutaneous fenestrated pedicular screws to anchor the vertebral body stents to the posterior elements of the vertebra, ensures safer stabilisation of the implants, preventing hardware mobilisation, and should provide further 360-degree stabilisation of the vertebra. The procedures have been performed at NSI in the last 16 months. Amendment to an existing approved Ethical Committee authorisation is being requested for this retrospective assessment.

Studio biomeccanico a supporto dell’utilizzo di stent vertebrali, cemento e viti peduncolari nel trattamento di pazienti con metastasi spinali con lisi ossea estrema (Biomechanical study supporting the use of vertebral stents, cement and pedicular screws in the treatment of patients with spinal metastases with extreme osteolysis).


Spinal osteolytic metastatic lesions are often associated with a severe reduction in quality of life due to associated pain, instability risk, fractures and, in the most severe cases, neurological symptoms caused by compression of nerve structures. Vertebral soma lesions, which reduce the strength of the load bearing front column, are responsible for the highest risk of vertebral fracture and instability. Different therapeutic actions can be directed to preservation of neurological functions, pain relief and mechanical stabilisation. Posterior stabilisation surgery is a proven and effective method of restoring spinal stability: it can be carried out using different techniques, with open or percutaneous surgery, but should always be accompanied by front column stabilisation with partial or total corpectomy and placement of autologous bone, cage or bone cement grafts. However, stabilisation surgery operations, are not always feasible in neoplastic patients due to numerous factors, such as age, life expectancy, patient’s clinical status, frequent multilevel pathology or poor bone quality. In particular, the operation of corpectomy is particularly invasive and burdened by high rates of morbidity and long hospitalisation times, especially in this category of patients. This study aims at providing the biomechanical basis for the use of an innovative mini-invasive technique, based on the use of metal stents, bone cement and pedicular screws, not necessarily coupled with posterior fixation, in patients with metastatic spinal lesions with extreme osteolysis at risk of fracture of the vertebral soma. This technique is intended to provide mechanical support and stability, reduce hospitalisation and postoperative complications linked to the invasiveness of traditional surgical procedures, thus resulting in a significant improvement in life quality of the treated patients. To this end, comparative analysis of the finished elements, highlighting the biomechanical advantages deriving from the use of the new technique on the remaining parts of the backbone, will be performed.

This study is carried out by the biomechanical engineers of the Polytechnic Institute of Milan.

Minimally invasive spinal hardware rescue with cement augmentation.

Investigators: K. Huscher, L. Roccatagliata, A. Cianfoni.

Surgical spinal instrumentation used to treat traumatic and porotic fractures, instability and deformities, might be complicated at short- or long-term by insufficiency spinal fractures at treated or adjacent levels, bone resorption, painful mobilisation, or pull-out of screws. These complications often require major corrective surgical intervention. Minimally invasive percutaneous image-guided vertebral cement augmentation (cement rescue) might represent an alternative option in selected patients.
This study retrospectively reviews clinical, imaging and procedural charts of a consecutive series of patients who underwent a cement augmentation procedure for spinal hardware complications. Ethical committee authorisation is being requested for this retrospective assessment.

**Active Internal and External Collaborations**

P. Scarone (lead investigator), Neurosurgery Service (NSI)
Stabilizzazione vertebrale con viti peduncolari: studio retrospettivo comparativo tra due tecniche di neuronavigazione: tomografia computerizzata intraoperatoria e tomografia a fascio conico associata a navigazione spinale (Spinal stabilisation with pedicular screws: a retrospective comparative study between two neuronavigation techniques: intraoperative computed tomography and cone beam tomography associated with spinal navigation)
1 ongoing study.

T. Villa, Laboratory of Biological Structure Mechanics, Chemistry, Material and Chemical Engineering Department “Giulio Natta”, Polytechnic Institute of Milan
Studio biomeccanico a supporto dell’utilizzo di stent vertebrale, cemento e viti peduncolari nel trattamento di pazienti con metastasi spinali con lisi ossea estrema (Biomechanical study supporting the use of vertebral stents, cement and pedicular screws in the treatment of patients with spinal metastases with extreme osteolysis)
1 ongoing study.

**Main funding**

High-resolution post-contrast imaging at 3 Tesla: a comparison of three different techniques (EOC. NEURORAD.1501): ABREOC (internal competitive grant).

Studio biomeccanico a supporto dell’utilizzo di stent vertebrale, cemento e viti peduncolari nel trattamento di pazienti con metastasi spinali con lisi ossea estrema (Biomechanical study supporting the use of vertebral stents, cement and pedicular screws in the treatment of patients with spinal metastases with extreme osteolysis): fondazione scientifica FROM (FROM scientific foundation), Bergamo, Italy (duration: 12 months; amount: Euro 12,000).
The EOC Pain Management Center promotes the highest possible quality of life for patients with persistent pain, by offering accurate diagnosis and direct interventions to reduce, eradicate or manage the pain and provide support particularly around the management of pain problems of high medical and psychological complexity, and around the use of controlled drugs, minimal invasive interventions and neuromodulation. The outpatient Service which is present in all the EOC Hospitals has the mission of providing specialist consultations, evidence-based and the most up to date treatments to all chronic pain patients in Ticino.

Since 2015, academic cooperations with the University of Maastricht and the VUMC University Medical Center of Amsterdam have been formalised. The collaboration with Prof. Dr. Bert A. Joosten in Maastricht is related to research projects investigating the effects of dorsal root ganglion stimulation for treatment of diabetic neuropathy. The collaboration with Prof. Roberto Perez at the VUMC in Amsterdam is related to investigating technical aspects to improve safety and efficacy in pain therapy. New research collaboration also started with Prof. Marco Barbero from the Rehabilitation Research Laboratory of the University of Applied Sciences and Arts of Southern Switzerland.

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Peer reviewed publications in 2016

Zanini C, Maino P, Möller JC, Gobbi C, Raimondi M, Rubinelli S.

Main areas of research

The accuracy of the Ultrasound-guided versus the blind conventional Refill Technique of Intrathecal Pumps, a prospective comparison study. 
Investigators: P. Maino, RSGM. Perez, E. Koetsier.

The purpose of this study is to assess the accuracy and safety of the US-guided refill technique compared to the blind conventional refill technique in subjects undergoing regular refills of their Med-Stream programmable infusion systems for the treatment of chronic pain or spasticity. 19 patients were enrolled. Two pain physicians will complete the blind technique once and twice the US-guided technique each, within the same patient on consecutive refill procedures. The primary endpoint is the number of attempts to enter the RFP with the needle comparing the US-guided technique versus the blind technique. The secondary endpoints are the number of skin punctures, the time to enter the RFP with the needle and patient discomfort in order to assess user friendliness. 19 patients were enrolled from January to April 2015. The refills were performed over a period of 24 months. At the moment, we are analysing the results of this study.

Radiation dose exposure for lumbar Transforaminal Epidural Steroid Injections and facet joint blocks under CT versus fluoroscopic guidance: a retrospective comparison study. 
Investigators: P. Maino, S. Presilla, P. Colli, RSGM. Perez, E. Koetsier.

The purpose of this study is to compare patient radiation dose for lumbar TFESIs and facet joint blocks under CT fluoroscopic guidance versus guidance. The primary endpoint is the difference between the mean estimated effective dose (ED) of CT guidance and fluoroscopic guidance for TFESIs and facet joint blocks. We retrospectively reviewed a series of CT-guided and fluoroscopy-guided lumbar TFESIs and facet joint blocks on 42 patients (18 men, 24 women; mean age, 60 ± 14 years; range, 30 – 90 years). These patients collectively underwent a total of 100 procedures. At the moment, we are analysing the results of this study.

Dorsal Root Ganglion Stimulation for the management of intractable painful polyneuropathy: a prospective case series. 

A prospective, single-arm, single-center pilot study to obtain preliminary information on the ability of Dorsal Root Ganglion Stimulation (DRGS) in relieving the painful symptoms in patients with polyneuropathy. The primary outcome will be the change in pain intensity assessed by Numeric Rating Scale at baseline and 6 months post-DRGS implant. Secondary outcomes involve the assessment of: changes in neuropathic pain aspects, sensory perception improvement measured by Quantitative Sensory Testing, changes in health-related quality of life, changes in mood, global improvement of change, changes in the impact of pain on physical functioning, satisfaction with stimulation, evolution of the SFN assessed by repeated biopsies. At the moment, we are recruiting patients for this study.

A randomized, double-blind, placebo-controlled, multicenter efficacy study of the Gelstix™ device to treat chronic discogenic low back pain. 
Investigators: P. Maino, RSGM. Perez, A. Cianfani, E. Koetsier.

Double-blind, prospective, randomised, placebo-controlled, outcome study. The purpose of this study is to evaluate the efficacy of treatment with the GelStix™ device in a patient population that had no benefit from conservative care. The total expected number of patients to be randomised is 72. At the moment, we are recruiting patients for this study.


The goal of this study is to develop the technique of experimental DRG-SCS and gain a first insight into the effect of L5 DRG-SCS in female PDP
Sprague-Dawley rats. Diabetes was induced by intraperitoneal injection of streptozotocin. Animals are tested for mechanical hypersensitivity using Von Frey hindlimb withdrawal testing at baseline, and once a week for 4 weeks following streptozotocin injection, to select animals that develop PDP. Subsequently, animals are implanted with a DRG-SCS electrode at L5 and stimulated for 30 minutes at 2 and 3 days following implantation. Immediately before stimulation, 15 and 30 minutes during stimulation, and 15 and 30 minutes after stimulation, animals were tested for mechanical hypersensitivity. First data indicate a successful reduction in mechanical hypersensitivity upon DRG-SCS in PDP rats. Further analysis in more animals is following.

Main funding

Dorsal Root Ganglion Stimulation for the management of intractable painful polyneuropathy: a prospective case series: ABREOC (internal competitive grant).

Spinal cord stimulation of the L5 dorsal root ganglion for the treatment of experimental painful diabetic polyneuropathy: St. Jude Medical (non-competitive grant; amount: CHF 60,000).

P. Maino: Neuromodulation RELIEF STUDY (A7007), a global registry to evaluate long-term effectiveness of neurostimulation therapy for pain: Boston Scientific International SA (non-competitive grant; amount: CHF 37,000).
The Laboratory for Biomedical Neurosciences (LBN) is committed to discovering therapies and innovative diagnostics measures for patients affected by neurodegenerative diseases, a family of debilitating and irreversible disorders that significantly affect the life quality of patients and caregivers.

Basic, translational and clinical research are complementary disciplines of biomedical sciences. The integration of the LBN into the NSI offers the unique opportunity for translational research that is reciprocally fostered by clinicians and biologists. Our science aims at filling the traditional gap between discoveries in basic research and their applications in medicine. The vision of the LBN is to improve the understanding of neurodegenerative disorders at the functional and molecular levels. To do so, we established a research platform enabling a comprehensive approach based on cellular and animal models of disease coupled with innovative, functional analysis and state of the art molecular and genetic methodologies.

The studies focus on the elucidation of the molecular mechanisms involved in the initiation, progression and consequences of motor disorders such as Parkinson’s disease or other neurodegenerative disorders collectively defined as proteinopathies. To analyse cellular and animal models of disease, we offer a wide range of technologies such as electrophysiology, behavioural analysis, histology, flow cytofluorometry, confocal microscopy, as well as modern methods in cellular and molecular biology.

The team of Dr. Paolo Paganetti (see also page B7: Neurodegeneration Research Group) takes a molecular and cellular approach to investigate the causes of neurodegenerative diseases such as frontotemporal dementia, Parkinson’s disease, Alzheimer’s disease, and Huntington’s disease. The search for novel therapeutics is based on counteracting aberrant protein levels by targeting protein modification, misfolding and toxicity, which also define new diagnostic markers.

The research groups of Prof. Dr. Alain Kaelin and Dr. Salvatore Galati (see also paragraph 2.4: Movement Disorders Center) successfully created and implemented animal models for Parkinson’s disease, which are tailored to behavioural and histopathological investigations as well as electrophysiological studies. These research models were implemented to understand the pathological mechanisms underlying these brain disorders and as experimental models to test new therapeutic interventions. An additional project seeks markers of Parkinson’s disease in human skin.

The team led by Prof. Michael Reinert (see also paragraph 2.7: Neurosurgery) focuses research on brain tumours with particular emphasis on methods aimed at improving the surgical intervention.

Another important objective of the LBN is training and education of young scientists to foster their career in basic and clinical research. As part of the scientific community, the LBN advocates the exchange of know-how and data among national and international research teams and the dissemination of our rationale and results through specialised and general communication channels. Education and training at the LBN for young scientists, interested in a career in basic and translational research, is granted by a state of the art infrastructure and an excellent supervision which help achieve an academic degree (master student, PhD student) or by widening and deepening their scientific knowledge (postdoctoral and visiting fellows). With the envisaged integration into the Faculty of Biomedical Sciences and Master School of Human Medicine of the University of Southern Switzerland, the LBN will have the ability to assign a PhD degree. In the meantime, PhD and Master students hosted at the LBN participate in the corresponding
programs offered by national and international academic institutions, whilst absolving their practical work within the LBN research facilities as well as actively participating in lectures, seminars and courses organised by the LBN or by the LBN in collaboration with other research institutes located in Ticino. PhD and Master students pursue their research projects under the mentorship of experienced group leaders and learn modern research technologies and how to conduct a scientific research project independently.

The five PhD students hosted by the LBN in 2016 were affiliated with the University of Bern, the University of Zurich and the University of Basel.

Our Laboratory exists thanks to a substantial financial support received by competitive research grants, charitable organisations and donors. For the years 2015-2017, the support provided by the EOC was supplemented with a total amount of CHF 3.1 million that we received until the end of 2016, which has already covered 51% of the total LBN expenses. The competitive grants provide about 60% of the external support.

Neurodegeneration Research Group
Paolo Paganetti PhD
Group leader

Collaborators: C. Foglieni, S. Papin, G. Pedrioli, S. Pinton, A. Salvadé, G. Ulrich

The discovery of disease mutations in gene encoding for the proteins that build up brain deposits in patients affected by neurodegenerative disorders established a link between the sporadic and the hereditary disease forms. Most importantly, this demonstrates that these aberrant protein species initiate the neurodegenerative process and cause cell loss. The research group studies the molecular processes that regulate protein misfolding, deposition and toxicity in cellular models of disease. In particular, we are interested in characterising post-translational modifications and subcellular localisation of the proteins involved in the pathogenesis of neurodegenerative disorders.

In 2016 our work enabled us to win several prestigious and highly competitive national research grants, which will allow us to advance our sciences further as well as to establish alliances and collaborations with well-known research groups in Switzerland and Europe. Several research projects have already started or are about to start. Moreover, a major US-based translational research foundation has selected our group to validate a new diagnostic marker for Parkinson’s disease.

— **Project 1:** Modification of tau as function of subcellular distribution.
(Giorgio Ulrich, in collaboration with Prof. Paola Picotti, ETHZ)
We are studying the modification of the protein tau, which is associated with frontotemporal dementia, Parkinson’s and Alzheimer’s disease, when located in the nucleus and other subcellular sites. Protein mislocation and modification are assumed to be key determinants of tau-induced neuronal cell loss and represent disease biomarkers

— **Project 2:** Structural and cellular determinants regulating TDP-43 multimerization in health and disease.
(Chiara Foglieni, in collaboration with Prof. Magdalini Polymenidou, Uni ZH)
We are studying the formation of homo and hetero protein complexes composed of the protein TDP-43, which is associated with frontotemporal dementia and amyotrophic lateral sclerosis. At least three different forms of TDP-43 aggregates with very different activity, physiological oligomers involved in RNA and DNA metabolism, cytosolic granules forming during cellular stress and the pathological aggregates observed in the disease were described. The complementation technology we implemented to study TDP-43 biology is also used to study the protein tau as well as the huntingtin protein involved in Huntington’s disease.
— Project 3: **Extracellular vesicles involved in disease spreading and transmission in the brain.**
  (Giona Pedrioli, in collaboration with Prof. Anne Spang, Biocenter, Uni Basel)
  We are studying extracellular vesicles such as exosomes for their role in transporting proteins from neurone to neurone, in particular for proteins associated with neurodegenerative disorders. Transcellular transport of proteins may represent the key molecular process at the basis of disease progression. For this project that has recently started, we are establishing protocols and evaluating markers to study if and how an intracellular protein can reach the interior of a receiving cell

— Project 4: **Measuring pathological protein forms as markers of Parkinson’s disease.**
  (Dr. Stéphanie Papin, in collaboration with the Michael J Fox Foundation)
  We are implementing and validating a test to measure pathological forms of proteins associated with Parkinson’s disease. The aim of this study is to develop a test for the diagnosis, the analysis of progression and as a therapeutic read-out of disease

— Project 5: **Nuclear Tau in health and disease.**
  (Dr. Stéphanie Papin)
  The main function of the protein tau is in the regulation of microtubules. Nevertheless, tau was also found in the nucleus where it can bind and protect DNA. The main objective of our project is to investigate the function of nuclear tau further. In particular, we will assess the role of tau in the DNA damage response, in chromatin modification and epigenetic regulation of gene expression, and identify mechanisms mediating the nuclear translocation and function of tau.

**Peer reviewed publications in 2016**

Chopra V, Quinti L, Khanna P, Paganetti P, Kuhn R, Young AB, Kazantsev AG, Hersch S. 
**LBH589, A Hydroxamic Acid-Derived HDAC Inhibitor, is Neuroprotective in Mouse Models of Huntington’s Disease.**

**BACE-1 is expressed in the blood-brain barrier endothelium and is upregulated in a murine model of Alzheimer’s disease.**

**Synthesis and structure-activity relationship of 2,6-disubstituted pyridine derivatives as inhibitors of β-amyloid-42 aggregation.**
Main funding

Gelu Foundation
Lead investigator: P. Paganetti.
Amount: CHF 750,000. Started: 2015 - duration: 2019 (five years). Type of fund: competitive, one senior scientist position, five trainees.

Gabriele Charitable Foundation
Lead investigator: P. Paganetti.

NN
Lead investigator: P. Paganetti.

AILA/OIL
Lead investigator: P. Paganetti; Co-investigator: A. Salvadè.
Amount: CHF 100,000. Started: 2016 - duration: 2016 (single contribution). Type of fund: non-competitive, research equipment.

Swiss National Foundation (SNF)
Lead investigator: P. Paganetti.
Amount: CHF 210,000. Started: 2016 - duration: 2019 (three years). Type of fund: competitive, one PhD student, research consumables.

Swiss National Foundation (SNF Sinergia)
Co-investigator: P. Paganetti.
Lead investigators: B. Schuler and M. Polymenidou (Uni ZH), F. Allain and G. Jeschke (ETHZ).
Amount: CHF 2,600,000. Started: 2017 - duration: 2020 (four years). Type of fund: competitive, one PhD student, research consumables.

Michael J Fox Foundation
Co-investigators: P. Paganetti and G. Sancesario (Università di Roma Tor Vergata – University of Rome “Tor Vergata”).
Lead investigator: L. Petricca (IRBM Science Park Rome).

Synopsis Foundation
Lead investigator: P. Paganetti; Co-investigator: S. Papin.
EOC Multisite Departments and Services
3. EOC Multisite Departments and Services

The multisite Departments and Services are structures that are transversal to all EOC institutes and are an organisational model of clinical management. The Departments are, as a rule, the functional and organisational integration of operational units that are homogeneous, similar, or complementary to and mutually dependent on one another, sharing the same goals — which could not be achieved otherwise. They are, however, clinically independent, with their own separate professional responsibility. The Departments are made up of the relevant Services, Divisions and Units, grouped according to nosology, function and size. The needs for clinical governance are also taken into account in the organisation of the Departments.
3.1. EOC Department of Surgery

Prof. Raffaele Rosso MD, FACS, FRCS
Head of Department of Surgery, Head Surgeon - Regional Hospital of Lugano

The EOC Department of Surgery guarantees high-quality localised surgical assistance, either planned or in emergency situations, making use of the specific specialised skills of the Department and is intended to be the best solution to harmonise and rationalise the facilities for surgery in the Canton.
Main areas of research

Pilot study of a new prosthesis for transfemoral amputated patients. Clinical study protocol.  
**Lead investigator:** C. Candrian.  
**Collaborator:** M. Delcogliano.

The purpose of this study is to investigate a custom-made prosthesis for transfemoral amputated patients. It is a prospective, case series pilot study. The population involved consists of 5 patients, who underwent a transfemoral amputation and experienced several problems with the conventional socket prosthesis. The custom-made prosthesis was designed and the study protocol was submitted to the ethical committee.

The brace after arthroscopic suturing of the rotator cuff: Is it really mandatory or just a trend?  
**Lead Investigator:** C. Candrian.  
**Collaborator:** F. Marbach.

It is a prospective randomised multicenter study to assess whether applying the brace postoperatively affects the rate of re-rupture of the supraspinatus tendon sutured and the clinical outcome of patients in terms of pain, function and range of motion. 100 patients will be involved in the study, randomised in three different centres. The study protocol was submitted to the ethical committee.

Peer reviewed publications in 2016

**Acute patellofemoral instability in children and adolescents.**  

**Can a biomimetic osteochondral scaffold be a reliable alternative to prosthetic surgery in treating late-stage SPONK?**  

Hassink G, Testa EA, Leumann A, Hügle T, Rasch H, Hirschmann MT.  
**Intra- and inter-observer reliability of a new standardized diagnostic method using SPECT/CT in patients with osteochondral lesions of the ankle joint.**  

**Prosthetic Joint Infections Due to Coagulase-Negative Staphylococci.**  

Pauli W, Koch A, Testa E, Dopke K, Perry P, Honigmann P.  
**Fixation of the Proximal Metatarsal Crescentic Osteotomy Using a Head Locking X-Plate.**  
Anterior cruciate ligament reconstruction with three different surgical techniques. Comparison of the clinical outcome and CT study of the positioning of the femoral and tibial tunnels.

**Lead Investigator:** C. Candrian.

**Collaborators:** L. Deabate, M. Delcogliano.

The purpose of the study is to compare the positioning of the femoral and tibial tunnels using a low dose CT scan in 3 main surgical arthroscopic reconstruction techniques of the anterior cruciate ligament (anteromedial, ranstibial, out-in). The clinical results will be compared in the different tunnel positions. It is a prospective randomised study. 66 patients will be involved. The study protocol is under review.

Is fast-track for anterior surgical approach THA really possible and cost-effective?

**Lead investigators:** P. Gaffurini, C. Candrian.

**Collaborators:** L. Deabate, M. Delcogliano.

The study aims at understanding the feasibility and reliability of performing total hip arthroplasty in one-day surgery. A group of patients with a few comorbidities (ASA 1/2) will be chosen to undergo THA as outpatient surgical patients. We will evaluate the patient’s comfort, the patient’s clinical outcome, any kind of adverse event and the procedure cost-effectiveness. The study protocol is being finalised.

Positioning of sacroiliac screws using an intraoperative 3D CT-guided navigation system (O-Arm©) in posterior pelvic ring fractures.

**Lead investigator:** C. Candrian.

**Collaborator:** S. Ghisla.

The aim of this retrospective study is to evaluate our results of positioning percutaneous sacroiliac (SI) screws using an intraoperative 3D CT-guided navigation system (O-Arm©), by analysing the position of the screws with a CT scan as well as the clinical outcome of the patients, reporting neurological, vascular, gastrointestinal, urogenital, infectious or other type of complications. Moreover, we compared our results to those obtained with the traditional technique and available in literature.

The study was submitted to a peer-reviewed journal.

Fixation of ankle syndesmotic injuries: why wait after surgery for a 3D position control? A retrospective study.

**Lead investigator:** C. Candrian.

**Collaborators:** E. Testa, J. Muller.

Malpositioning of the fibula after fixation of the ankle syndesmosis is a frequent problem. The intraoperative CT Scan (O-arm™ system) enables intraoperative 3D image acquisition and has already been successfully used for other pathologies. We reviewed 21 patients, treated from February 2009 to September 2015, with ankle fractures and associated lesions of the syndesmosis. For the syndesmotic lesions, a tricortical upper-syndesmotic screw was placed in all cases. Ten surgeries were performed using the O-arm™ during the operation. Eleven patients were operated with conventional fluoroscopy, and a postoperative CT-scan was performed. In the control group, two cases of malpositioning of the tibiofibular joint have been detected in the postoperative CT-scan and have been revised successfully with the intraoperative use of the O-arm™. The study was submitted to a peer-reviewed journal.


**Lead investigator:** C. Candrian.

**Collaborators:** E. Testa, J. Muller.

The study aims at analysing the clinical outcome and radiological healing of two groups of patients treated with osteosynthesis of Weber B fractures followed by different rehabilitation protocols. In the first group, total weight bearing will be allowed from the day after surgery, while in the second group, only partial weight bearing will be allowed up to 6 weeks after surgery. The randomised prospective study will involve 60 patients. The study protocol is under review.

A prospective randomized control trial on posterior “Anti-glide” and lateral positioning of plate osteosynthesis in patients with lateral malleolar fractures (Type Weber B). Clinical study protocol.

**Lead investigator:** C. Candrian.

**Collaborator:** E. Testa.
In this study, we wish to analyse the problem related to the positioning of two different plates in the lateral malleolar osteosynthesis. We will randomise two groups of patients; in the first one the osteosynthesis will be carried out with an anti-glide posterior plate, in the second one the plate will be positioned laterally. The primary endpoint of this study is to compare the rate of material removal due to clinical problems. The secondary endpoint is to investigate the clinical and radiological rate of complications in the two groups. It is a prospective, case series study. The population involved consists of all the patients affected by lateral malleolar fracture type Weber B. The study protocol will be submitted to the ethical committee.

Open-book fractures of the pelvis: how to avoid missing the diagnosis?
Lead investigator: C. Candrian.
Collaborators: N. Habib.

Recent reports have shown that in patients with multiple injuries after trauma, delayed diagnoses and missed injuries following CT scans have an incidence of 1.3 to 47%. With the increasing numbers of pelvic binders used in polytraumatised patients, many pelvic injuries especially lesions of the symphysis pubis are missed by the anatomical reduction by the binder. Our study is aimed at answering the question: when should the pelvic binder be released prior to radiological imaging and when should repeat radiographs or CT scans be done? We answered this question by reviewing the literature and by analysing 4 cases we encountered of missed open book fractures. Moreover, we created an algorithm to help reduce the number of missed injuries, the number of late diagnoses and increase the patient’s survival rates. The study was submitted to a peer-review journal.

Mild brain injury and new anticoagulant drugs: risk of intracranial haemorrhage?
Retrospective study.
Lead investigator: C. Candrian.
Collaborator: L. Uccella.

The aim of this study is to assess the incidence of intracranial haemorrhage in patients with mild brain injury and a GCS of 15 on anticoagulant and long-term antiplatelet therapy. We will evaluate the need for head CT scans in these patients by retrospectively analysing the clinical data.

Direct anterior vs. posterolateral approach for bipolar hip hemiarthroplasty in femoral neck fractures: a prospective randomized study.
Lead investigator: C. Candrian.
Collaborator: P. Gaffurini, M. Molina, S. Verzellotti.

The aim of this prospective study is to compare two surgical approaches used for bipolar hip hemiarthroplasty (BHA) on elderly patients with femoral neck fractures with the primary endpoint of the early recovery. One hundred patients aged 75 years or older were randomised to surgery using either a direct anterior (DA-group) or posterolateral (PL-group) approach and were followed up for 6 months.

Pain perception at three days and one month after surgery was significantly higher in PL-group patients (p<0.0001). Functional recovery was comparable in the two groups (at 3 days, 1 and 3 months after surgery), but only in DA-group the ADL and CAS scores at 6 months did not show significant differences in the scores before the trauma (p=0.1864 and p=0.1012) and the patients recovered the previous degree of autonomy. The study is being printed in a peer-review journal.

Main funding

Different scientific projects: grant by Medacta International SA (Str. Regina, 6874 Castel S. Pietro, Switzerland; non-competitive external fund, CHF 150,000; it started on 1st January 2017).

Pilot study of a new prosthesis for transfemoral amputated patients. Clinical study protocol: ABREOC (internal competitive grant; it started on 1st September 2016).

Fracture Database: DePuy Synthes grant (non-competitive external fund, CHF 150,000; it started on 1st January 2016).

Regenerative Medicine Technologies Laboratory: EOC grant (non competitive internal fund, CHF 680,000; it started on 1st March 2016); Cardio-centro Ticino grant (non-competitive internal fund, CHF 320,000; it started on 1st March 2016).
The Regenerative Medicine Technologies Laboratory exploits an interdisciplinary approach combining bio-engineering and biology to engineer human 3D musculoskeletal tissues for developing advanced in vitro models to dissect pathophysiological processes and generating cell based orthopaedic implants.

Peer reviewed publications in 2016


Main areas of research

Advanced 3D in vitro models for the study of musculoskeletal patho-physiology.
**Lead investigators:** M. Moretti, C. Candrian.
**Collaborator:** C. Arrigoni.

Advanced microfluidic and mesoscale in vitro models can be used as platforms for the investigation of biological mechanisms or as potential substitutes of damaged tissues. In our laboratory, we studied the possibility to achieve mesoscale and microfluidic vascularised models of musculoskeletal tissues, based on hydrogels with embedded human endothelial and mesenchymal stromal cells. In particular, we combined a micro-fabrication strategy with the self-organisation of vascular cells to obtain a perfusable vascularisation of the construct. We then developed a model of vascularised bone tissue, based on the previous model and in addition to the cell-loaded fibrin hydrogel calcium phosphate nanoparticles, osteoblast and osteoclast precursors, to mimic the remodelling activity of the bone.
Regarding the regeneration of damaged tissues, we studied a protocol for the decellularisation of tendons, based on a custom bioreactor, for the subsequent re-cellularisation, in view of a potential strategy for tendon substitution.

**Study of the immunomodulatory and chondroprotective effect of mesenchymal stem cells through a microfluidic model of osteoarthritic joint.**

*Lead investigators: M. Moretti, C. Candrian.*

*Collaborator: C. Arrigoni.*

The inflammatory aspect of osteoarthritis gained increasing attention in the development of new therapies for this disease. In particular, mesenchymal stem cells, which have important immunomodulatory effects, were proposed as potential candidates for the treatment of osteoarthritis. In this project, started in September 2016, we aim at investigating the immunomodulatory potential of different types of mesenchymal stem cells in a microfluidic model of osteoarthritic joint. The microfluidic model involves the presence of a cartilage compartment in contact with a layer representing the synovial membrane, based on cells, derived from osteoarthritic patients, embedded in 3D hydrogels.

**Main funding**

Study of the immunomodulatory and chondroprotective effect of mesenchymal stem cells through a microfluidic model of osteoarthritic joint: ABREOC (internal competitive grant; it started on 1st September 2016.)
Main areas of research

Randomised controlled trials


**Lead investigator:** D. Christoforidis

**Co-investigators:** A. Ferrario, M. Hobil, S. Pozza, R. Rosso.

This is a local prospective randomised placebo-controlled cross-over study that examines the efficacy of ondansetron to treat defecatory dysfunction after low anterior resection for rectal cancer. Patients are given 4 weeks of ondansetron followed by 4 weeks of placebo, in a random sequence. Outcomes are measured with standardised questionnaires. Faecal and histological biomarkers are measured before and after treatment. The study started recruiting in October 2016.

Two surgical techniques for the treatment of pilonidal sinus: a randomized controlled study.

**Lead investigator:** D. Christoforidis

**Co-investigators:** B. Pravini, M. Schmalzbauer.

This is a local RCT that compares the modified Karydakis technique (excision and lateral primary closure) vs. simple fistulectomy for the treatment of symptomatic pilonidal disease. The primary endpoint is the percentage of patients healed at 3 weeks; the secondary endpoints are total healing time, infection rate, recurrence rate. The study accrual has reached approximately 70% of the total sample size.

**PROSPECT study:** Alliance Study N1048—N1048: A phase II/III trial of neoadjuvant FOLFOX with selective use of combined modality chemoradiation versus preoperative combined modality chemoradiation for locally advanced rectal cancer patients undergoing low anterior resection with total mesorectal excision.

Peer reviewed publications in 2016

International Surgical Outcomes Study group (Christoforidis D).

Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle- and high-income countries.


Mezzetto L, Veraldi GF, Engelberger S, Giovannacci L, van den Berg J, Rosso R.

Successful Endovascular Repair of a Penetrating Aortic Ulcer in Bacterial Aortitis.


Schmauss D, Machens HG, Harder Y.

Breast Reconstruction after Mastectomy.


van den Berg JC.

Drug-eluting balloons in below the knee treatment.


van den Berg JC.

The added benefits and efficacy of atherectomy in the lower limb.


Mezzetto L, Veraldi GF, Engelberger S, Giovannacci L, van den Berg J, Rosso R.

Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle- and high-income countries.

Local investigator (responsible surgeon): D. Christoforidis.

A multicenter international prospective randomised study, under the guidance of Swiss Group for Clinical Cancer Research (SAKK), on neoadjuvant therapy for cancer.

Translational research studies

Computational analysis of arterio-venous fistulas for hemodialysis.
Lead investigator: L. Giovannacci.

Computational models will be applied to study the complex haemodynamics found in the anastomotic segment of arterio-venous fistulas. These will offer a new opportunity to analyse the different types of anastomosis, and will suggest the best geometry and conformation to guarantee a lower rate of venous hyperplasia.

Isolation and characterisation of tumour stem cells in colorectal cancer.
Sponsor-investigator: G. Iezzi, University of Basel.
Local lead investigator: R. Rosso.

We are collaborating on this project carried out by the University of Basel as clinical consultants and providers of human tissue. This study aims at determining the phenotype and function of tumoural stem cells of colorectal cancer (CD133+) as well as their interaction with T lymphocytes infiltrating the tumour. In vitro and in vivo experiments are held at the University of Basel using cells extracted from patient blood samples, normal and neoplastic colorectal mucosa.

Cohort trials

The “OP-LA” study: Functional recovery of elderly patients undergoing surgery for colorectal neoplasia.
Sponsor-investigator: G. Ugolini.
Local lead investigator: D. Christoforidis.

A multicenter prospective observational study that assesses the functional recovery of over 70-year old patients by administering specific questionnaires before surgery, 1 month and 3 months after surgery. The study started at the University of Bologna. The other participating centres include Cleveland Clinic (Florida), Humanitas (Milan) and Niguarda Hospital (Milan). We aim at recruiting 30 patients over 2 years.

Analysis of risk factors for prolonged stay after colectomy within an Enhanced Recovery After Surgery (ERAS) protocol.
Lead investigator: D. Christoforidis.

A study within our prospective database of ERAS patients to assess the reasons for a prolonged stay after colectomy even when hospital discharge criteria are fulfilled.

Efficacy and safety of laparoscopy for revisional surgery.
Lead investigator: D. Christoforidis.
Co-investigators: S. Deretti.

A retrospective cohort study of patients treated in our hospital in the past 5 years that analyses the laparoscopic approach to re-operate patients shortly after an abdominal operation. Efficacy, safety, and potential advantages over laparotomy are explored.

Simple acute sigmoid diverticulitis.
Lead investigator: D. Christoforidis.
Co-investigators: A. Ferrario di Tor V, A. Colombo, M. Simonelli, S. Popeskou, A. Leoncini.

A retrospective cohort study of patients treated in our hospital in the past 5 years that analyses outcomes after acute simple diverticulitis. We compared outcomes of patients with a first episode of diverticulitis versus a recurrent episode and explored other risk factors that predict a complicated outcome. The aim is to establish criteria that safely allow ambulatory treatment of simple diverticulitis.

Post-operative peristomal morbidity.
Lead investigator: D. Christoforidis.
Co-investigators: B. Barberà Carbonell, G. Staccini, C. Treter.
A retrospective cohort study of patients treated in our hospital in the past 3 years that analyses outcomes after the surgical construction of intestinal stoma. We analysed morbidity around the stoma site based on photographs and medical charts. This retrospective study will form the basis of a prospective randomised trial protocol, that compares two different techniques to suture the intestinal mucosa to the skin.

**Bilateral implant-based breast reconstruction: Form-stability or ergonomy?**

*Lead investigator: Y. Harder.*
*Co-investigators: B. Scarsi, JC. Alfonso.*

Form-stable silicone gel-filled breast implants are associated with a sensation of coldness and foreign body as well as capsular contracture often resulting in reoperation. Due to new viscous and elastic properties of the silicone gel within the implant shell, these implants mimic round shape while lying and anatomical shape while standing. This prospective quality control study evaluates surgery-induced morbidity (haematoma, infection, skin necrosis, ...) and long-lasting tolerance (capsular contracture, “rippling”, ...) in bilateral skin-sparing mastectomy and immediate implant-based reconstruction to understand whether elasticity excels stiffness.

**Main funding**

Efficacy of ondansetron in the treatment of low anterior resection syndrome (LARS): a single-centre, randomized, double blind, placebo-controlled crossover study: ABREOC (internal competitive grant).

Two surgical techniques for the treatment of pilonidal sinus: a randomized controlled study: ABREOC and the Research Fund of the Department of Surgery (internal, non-competitive fund).

PROSPECT study: Alliance Study N1048 – N1048: A phase II/III trial of neoadjuvant FOLFOX with selective use of combined modality chemoradiation versus preoperative combined modality chemoradiation for locally advanced rectal cancer patients undergoing low anterior resection with total mesorectal excision: no local funding.

Computational analysis of arterio-venous fistulas for hemodialysis: ABREOC.

Isolation and characterization of tumour stem cells in colorectal cancer: University of Basel.

The “OP-LA” study: Functional recovery of elderly patients undergoing surgery for colorectal neoplasia: ABREOC.

Analysis of risk factors for prolonged stay after colectomy within an Enhanced Recovery After Surgery (ERAS) protocol: no funding.

Efficacy and safety of laparoscopy for revisional surgery: no funding.

Simple acute sigmoid diverticulitis: no funding.

Post-operative peristomal morbidity: no funding.

Bilateral implant-based breast reconstruction: Form-stability or ergonomy?: no funding.

**Awards 2016**


Presented at the 4th World ERAS Congress, Lisbon, Portugal, 27th-30th April 2016.

Selected for the “Best oral papers” session.
Main areas of research

The 2016 Thoracic Surgery research activity focused on thoracic oncology and surgical technique topics and new classification proposals for particular types of tumours such as thymomas. International prospective trials on stem cells, in collaboration with Cardiocentro Ticino and Harvard University (Boston, USA), are ongoing.
Peer reviewed publications in 2016


Main areas of research

Sonographic follow-up of patients with cubital tunnel syndrome (CTS) undergoing open neurolysis in situ or endoscopy: a prospective study.
Lead investigators: C. Fusetti; S. Lucchina.

The sonographic examination is a useful technique in the assessment of the follow-up of patients undergoing surgical treatment for cubital tunnel syndrome (CTS). Moreover, there is a direct correlation between the values of the cross section area (CSA) of the ulnar nerve determined by sonographic examination and the clinical pre- and post-operative state in patients undergoing ulnar nerve decompression at the elbow. The purpose of the study is to compare the clinical results of open release and endoscopically-assisted cubital tunnel release, which encounter decompression of the ulnar nerve at the elbow, using the differences found by sonographic examination of the cross section area (CSA) of the ulnar nerve, in order to look for an association between the clinical results and the CSA.
The study is ongoing.

Peer reviewed publications in 2016

Meinero P, Stazi A, Carbone A, Fasolini F, Regusci L, La Torre M.
Endoscopic pilonidal sinus treatment: a prospective multicentre trial.

Main areas of research

In collaboration with Policlinico Umberto I Hospital, Sapienza University of Rome

Endoscopic pilonidal sinus treatment: a prospective multicenter trial.
Lead investigators at Regional Hospital of Mendrisio: L. Regusci, F. Fasolini.

Pilonidal disease (PD) is a common inflammatory disease of the gluteal fold, resulting in recurrent acute/chronic infection at the level of the natal cleft. In this study, endoscopic pilonidal sinus treatment (EPsiT), a new endoscopic minimally invasive procedure, was evaluated for its effectiveness in treating PD.
250 prospective patients with chronic PD were enrolled in a prospective multicenter study conducted at a secondary and tertiary colorectal surgery centre. The primary end-point of this study was wound healing, and the short-/long-term outcomes such as healing time, morbidity rate and recurrence rate were analysed. The secondary end-point of this study was the quality of life (QoL).
The study was completed and published in 2016.
3.2. EOC Department of Internal Medicine

Prof. Luca Gabutti MD
Head of the Department of Internal Medicine, Head Doctor - Regional Hospital of Bellinzona and Valli (San Giovanni).

The EOC Department of Internal Medicine is a functional type of organisational structure, and is managed and coordinated by the Department Board. The rules adopted for its operation are based on the fundamental principles of shared clinical governance (accountability, participation, transparency and management), and it is organised using a multisite approach, offering a gateway to general internal medicine services. Moreover, it can advise and direct patients to the appropriate reference centres.

The EOC Department of Internal Medicine was set up to ensure high-quality localised internal medicine assistance, either planned or in emergency situations, making full use of its specific specialised skills, as the best way to harmonise and rationalise the facilities for this sector in the Canton.

Cardiology Service
Regional Hospital of Lugano

Giorgio Moschovitis MD
Head of Service

Main areas of research

In collaboration with the Cardiovascular Research Center of the Regional Hospital of Bellinzona and Valli (San Giovanni)

Tako-Tsubo Cardiomyopathy and Cardiac Syndrome X: new insights into the pathophysiology of two orphan cardiac diseases. (refer to the chapter of Cardiovascular Research Center of the Regional Hospital of Bellinzona and Valli, San Giovanni).

In collaboration with the Cardiology Department of the University Hospital of Basel and with the Cardiovascular Research Institute of Basel (CRIB), and with the support of the Clinical Trial Unit EOC

Swiss Cohort Atrial Fibrillation study “Swiss AF”. Lead investigator: D. Conen of the University Hospital of Basel.
Main Coordinator and responsible for Southern Switzerland: A. Gallino (refer to the chapter of Cardiovascular Research Center of the Regional Hospital of Bellinzona and Valli, San Giovanni).

In collaboration with the Cardiology Department of the University Hospital of Basel

Evidence-Based Treatment in Heart Failure (EVI-TA-HF), Analysis of Iron Deficiency in Heart Failure (RAID-HF).
Lead investigator in Switzerland: O. Pfister of the University Hospital of Basel.

Prospective Multicenter Registry conducted in Austria, Germany and Switzerland, which aims at collecting data on clinical characteristics of consecutive patients suffering from chronic heart failure (CHF) with ejection fraction (EF) < 40%, and at analysing medical and device therapy including ICD and CRT, mortality, non-fatal complications, in-hospital and follow-up and symptoms after one year, and re-hospitalisation (EVITA-HF Registry).

In the substudy, data about the ferric state and haemoglobin and their association with prognosis and quality of life of CHF patients are collected (RAID-HF).
Study closed for accrual on 31st December 2015; Last follow-up: 31st December 2016.
Clinical Trial Protocol CRLX030A3301: a multi-center, prospective, randomized, open-label study to assess the effect of serelaxin versus standard of care in acute heart failure (AHF) patients (RELAX-AHF-EU).

Lead investigator in Switzerland: Ph. Meyer of the University Hospital of Geneva.

Local lead investigator: T. Moccetti of the Cardiocentro Ticino of Lugano.

Local primary co-investigator: G. Moschovitis of the Regional Hospital of Lugano.

Sponsor and Clinical Phase: Novartis Switzerland, Phase IIIb.

The aim of this study is to assess the efficacy, safety and tolerability of intravenous infusion of 30 μg/kg/day serelaxin administered for 48 hours, when added to standard therapy in patients hospitalised with acute heart failure. Efficacy will be determined based on the combined primary endpoint of in-hospital worsening of heart failure requiring rescue therapy and all-cause deaths mortality through day 5. Patients will be followed-up for 30 days. The purpose of this study is to generate clinical evidence, especially in the short term period (in-hospital and at 30 days) that will complement existing and future serelaxin data sets in AHF. The study population will consist of male and female patients (≥18 years old) admitted to the hospital for AHF, with systolic BP ≥125 mmHg and mild-to-moderate renal impairment. This study is currently recruiting patients.
The Infectious Diseases Service (SMI) is a specialised day clinic that deals with patients with infectious diseases. The Service works in close collaboration with local GPs. The SMI is one of the seven reference centres for the Swiss HIV Cohort Study (SHCS), one of the world’s largest epidemiological and clinical studies in the HIV field with more than 19,000 participants. The intense scientific activity is reflected in the large number of publications available at the website www.shcs.ch.

Main areas of research

Impairment of CCR6+ and CXCR3+ Th cell migration in HIV-1 infection is rescued by modulating actin polymerization.

Investigators: V. Cecchinato, E. Bernasconi, RF. Speck, M. Proietti, U. Sauermann, G. D’Agostino, G. Danelon, T. Rezzonico Jost, F. Grassi, L. Raeli,
CD4+ T cell repopulation of the gut is rarely achieved in HIV-1-infected individuals who are receiving clinically effective antiretroviral therapy. Alterations in the integrity of the mucosal barrier have been indicated as a cause of chronic immune activation and disease progression. In this study, we present evidence that persistent immune activation causes impairment of lymphocytes to respond to chemotactic stimuli, thus preventing their trafficking from the bloodstream to peripheral organs. CCR6+ and CXCR3+ Th cells accumulate in the blood of aviremic HIV-1-infected patients on long-term antiretroviral therapy, and their frequency in the circulation positively correlates to levels of soluble CD14 in plasma, a marker of chronic immune activation. Th cells show an impaired response to chemotactic stimuli both in humans and in the pathogenic model of SIV infection, and this defect is due to hyperactivation of coflin and inefficient actin polymerisation. Taking advantage of a murine model of chronic immune activation, we demonstrate that cytoskeleton remodelling, induced by okadaic acid, restores lymphocyte migration in response to chemokines, both in vitro and in vivo. This study calls for novel pharmacological approaches in those pathological conditions characterised by persistent immune activation and loss of trafficking of T cell subsets to niches that sustain their maturation and activities. The study was completed in 2016.

The Swiss HCVree trial: impact of a test, treat and cure strategy on the hepatitis C prevalence in men having sex with men in the SHCS.


Background: the prevalence of hepatitis C infection (HCV) is increasing in HIV-positive men having sex with men (MSM) participating in the SHCS. MSM practising high-risk sexual behaviour are recognised to be the main drivers of the current HCV epidemic. Improvement of (i) HCV screening and (ii) subsequent universal treatment with the newest anti-HCV direct acting agents (DAAs) in this population could have a major impact on the prevalence of HCV infection in Switzerland.

Study Aims: to identify the prevalence of ongoing HCV infection in MSM participating in the SHCS, to evaluate HCV treatment uptake of the newest DAAs and finally to investigate the impact of an HCV test, treatment and cure strategy on the postintervention HCV prevalence in this population.

Study Design: all MSM underwent intensified HCV-screening by measuring HCV-RNA to assess the prevalence of ongoing HCV infection in this population (Period A: October 2015 to March 2016). After that, interferon-free HCV treatment with the newest DAAs was offered to all HCV-RNA positive MSM. The goal of universal HCV treatment is to rapidly reduce the pool of infectious MSM (Period B: April 2016 to December 2016). After this treatment period, the prevalence of ongoing HCV infection will be re-assessed in the same population (Period C: from March 2017). The change in prevalence of HCV infection and different parameters will be compared before and after the intervention. The study is ongoing.

The Swiss HIV Cohort Study Core Project Metabolism and Aging (M + A core project).

Lead investigator: P. Tarr (in Lugano: E. Bernasconi).

This ongoing study has already been described in the previous report. The aim is to assess morbidity of HIV-infected patients outside the classic opportunistic diseases. Indeed, premature ageing with cardiovascular and cerebrovascular disease, osteoporosis, neurocognitive dysfunction, diabetes mellitus, lipodystrophy, and other morbid conditions are increasingly important determinants of the long-term health of HIV-infected individuals.
cause for central apnoeas that are frequently observed in the acute phase of a cerebral ischaemic event. In particular, an alteration in the baroreflex and chemoreflex, expression of a state of activation of the sympathetic nervous system, could be a causal factor in the genesis of SDB, as well as an independent risk factor for cerebral ischaemic events. Their joint study will provide useful elements of pathophysiological clarification. After three years data collection is now finished, and data analysis is still ongoing.

Peer reviewed publications in 2016


Nephrology and Haemodialysis Service
Regional Hospital of Lugano

Carlo Schönholzer MD
Head Doctor

Main areas of research

NOSTONE TRIAL - Randomized double-blind placebo-controlled trial assessing the efficacy of standard and low dose hydrochlorothiazide treatment in the prevention of recurrent nephrolithiasis.
Sponsor-Investigator: D. Fuster, Inselspital.
Lead investigators: at CHUV, USZ, USB, HUG, KSSG, KSA and Regional Hospital of Lugano (C. Schönholzer).

Assessment of the efficacy of standard and low dose HCTZ treatment in the recurrence prevention of calcium-containing kidney stones. More specifically, assessment of the dose-response relationship for three different dosages of HCTZ.
Primary outcome: Incidence of stone recurrence (a composite of symptomatic or radiologic recurrence) during study treatment and dose group.

InterACTIVE-HD - Interregional Automatically Controlled Therapy to ImproVE HemoDialysis.
Sponsor-Investigator: ML. Costantino, Politecnico of Milan.
Lead investigators: at Lecco, Como, Varese, Sondrio Hospitals and Regional Hospital of Lugano (C. Schönholzer), in collaboration with the Nephrology Service of St. Gallen Cantonal Hospital (KSSG) and Chur Canton Hospital.
Id project: 240590; reference number: A1.2016.0099367;
date protocol sent: 30.09.2016.
Ex-novo development of automatic data generation during haemodialysis treatment. Optimisation of models and algorithms for the management of haemodialysis sessions. The possible use of these systems in telemedicine, also related to home treatments.

Main funding

NOSTONE TRIAL - Randomised double-blind placebo-controlled trial assessing the efficacy of standard and low dose hydrochlorothiazide treatment in the prevention of recurrent nephrolithiasis: SNSF (#33IC30_166785/1, external competitive grant, budget: CHF 2,500,000).

InterACTIVE-HD - Interregional Automatically Controlled Therapy to ImproVE HemoDialysis: INTERREG Italy – Switzerland (Programma Operatorio di Cooperazione Transfrontaliera Italia-Svizzera/Cooperazione Territoriale Europea) (“Surgical Cross-Border Cooperation Programme Italy-Switzerland/European Territorial Cooperation” - external competitive grant, submitted on 30.09.2016 and final decision in Spring 2017, budget required: 1,800,000 euros).

Peer reviewed publications in 2016

Patient-specific modeling of multicompartmental fluid and mass exchange during dialysis.

Violo L, De Francesco M, Schoenholzer C.
Risk of cancer in patients with polycystic kidney disease.
Clinical Pharmacology and Toxicology Service
Regional Hospital of Lugano

Alessandro Ceschi MD, PD, FEAPCCT
Deputy-Head

The Service of clinical pharmacology and toxicology of the EOC was established in June 2015, and one of its main tasks is to advise other departments and physicians in safe drug therapy use and to promote the rational use of medicines. The Service also performs clinical research designed to improve drug safety, partly in co-operation with other clinical pharmacology and toxicology departments of Swiss university hospitals. Our ultimate goal is to personalise drug therapy by optimising beneficial effects while minimising adverse effects and costs.

Peer reviewed publications in 2016

Hypokalaemia in hospitalised patients.

Adverse Effects of Plant Food Supplements and Plants Consumed as Food: Results from the Poisons Centres-Based PlantLIBRA Study.

Adverse Effects of Plant Food Supplements Self-Reported by Consumers in the PlantLIBRA Survey Involving Six European Countries.

Main areas of research

Population-based nested case-control study on lifestyle factors, psychiatric and neurologic comorbidities, and drug use associated with incident seizures among adult patients with depression.
Lead investigator: M. Bloechliger, University of Basel.

Co-investigators: A. Ceschi, S Rüegg, SS Jick, CR. Meier, M. Bodmer.

This is a population-based nested case-control analysis in adult patients with newly diagnosed...
depression using data from the U.K.-based Clinical Practice Research Datalink (CPRD). It aims at investigating in detail the lifestyle factors, comorbidities, and co-medications are associated with seizures among adult patients with depression, as no observational study has explored risk factors for new-onset seizures among such patients yet. In cases with incident seizures and matched controls, as reported from the general population data, the potential risk factors for seizures, estimated using odds ratios with 95% confidence interval, are the following: underweight (body mass index <18.5 kg/m²), smoking, alcoholism, drug abuse, psychiatric or neurologic comorbidities, and concomitant use of drugs.

**Medication incidents in primary care medicine: a prospective study by the Swiss Federal Sentinel Reporting System.**

*Lead investigator: M. Gnädinger, University of Zurich.*

This is a prospective surveillance study to identify cases of medication incidents among primary care patients in Switzerland during the year 2015, to describe the type, frequency, seasonal and regional distribution of medication incidents in primary care and to elucidate possible risk factors for medication incidents. The rationale is that although most safety research was conducted in the inpatient setting, evidence indicates that medical errors and adverse events are a threat to patients in the primary care setting as well. Study participants are patients undergoing drug treatment by 167 general practitioners or paediatricians reporting to the Swiss Federal Sentinel Reporting System.

**Inflammatory markers in patients with Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome.**

*Lead investigator: AB. Taegtmeyer, University of Basel.*

This is a retrospective observational study looking at C-reactive protein (CRP), pro-calcitonin (PCT), leucocyte- and eosinophil counts in patients with DRESS syndrome reported to the pharmacovigilance centres in North-Western and Southern Switzerland and cases reported in the literature, as the extent of the elevation of inflammatory markers in patients with DRESS syndrome is currently not accurately known.

**Swiss Drug Emergency Network (Swiss-DEN): a multicenter analysis of acute recreational substance toxicity.**

*Lead investigators: A. Ceschi (Southern Switzerland centre), M. Liechti (Basel centre), E. Liakoni (Bern centre).*
*Co-investigator: L. Müller for the Southern Switzerland centre.*

The recreational use of psychoactive substances is common and novel psychoactive substances (NPS) with often unknown toxicological properties have emerged in the last few years in response to market trends and legislative control. In 2015, 98 NPS were reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) for the first time and more than 380 have been detected in the last 5 years. Despite this fact, there is only limited systematic collection of data on acute drug toxicity or hospital presentations. The European Drug Emergencies Network (Euro-DEN) project has set up a network of sentinel centres across Europe to systematically collect data on patients presenting to the emergency departments (EDs) with acute drug/NPS toxicity. Currently, the only ED participating from Switzerland is the University Hospital of Basel. This study sets up a network of sentinel centres across Switzerland (Basel with Prof. M. Liechti, Bern with Dr. E. Liakoni, and Ticino with PD Dr. A. Ceschi as main investigators) to collect systematic data on recreational drug toxicity within a Swiss-DEN and also to contribute to the Euro-DEN project as associated centres similarly to the co-beneficiary centres across the EU. With the systematic collection of data on acute drug toxicity from 3 different regions of Switzerland, we aim at providing a better picture of the current situation of toxicity associated with substance use in order to improve medical management and prevention. Data will also be provided to the Euro-DEN project, thus contributing to the European network with data collection and also facilitating additional research collaborations.
Development and validation of an electronic active real-time surveillance system of adverse drug reactions in hospitalized patients.

Lead investigator: A. Ceschi.
Master student of the University of Zurich: P. Hitz.

The underreporting of adverse drug reactions is one of the main limitations of pharmacovigilance systems worldwide. This study aims at developing and validate an electronic, non-complex, real-time surveillance system of adverse drug reactions in hospitalised patients due to the absence of such a system at Swiss national level and the considerable complexity of the few systems described in the literature.

Impact of medication reconciliation at admission to the hospital: prospective study in an internal medicine ward.

Lead investigator: N. Rizza.
Co-investigators: A. Ceschi, M. Pironi, O. Giannini, P. Borella.

This study aims at evaluating the impact of medication reconciliation at admission to an internal medicine ward by quantifying the number of medication discrepancies detected by performing a best possible medication history (BPMH) and evaluating their clinical relevance.

Main funding


Swiss Drug Emergency Network (Swiss-DEN): a multicenter analysis of acute recreational substance toxicity: Swiss Centre for Applied Human Toxicology (SCAHT), Basel (external competitive grant; only for the Basel Centre).
Main areas of research

Coagulation activation using different haemodialysis membranes.
*Sponsor-Investigator: L. Gabutti.*

In a randomised controlled cross-over study, the activation of the coagulation using 3 different dialysis membranes was analysed (study completed and publication).

Hypokalemia in hospitalised patients; an educational, multicentric, controlled, before and after study.
*Sponsor-Investigator: L. Gabutti.*

In a survey, the incidence and risk factors of Hypokalemia in EOC hospital inpatients were analysed (study completed and publication).

Swiss Salt Study: kidney function assessment.
*Sponsor-Investigator: M. Burnier.
Investigator for the subanalysis: L. Gabutti.*

Several secondary analyses of the data from the “Swiss Salt Study” are currently underway. The study is ongoing.

Temperature of the dialysate and haemodynamics: a randomised study.
*Sponsor-Investigator: L. Gabutti.*

In a randomised controlled cross-over study, the haemodynamic consequences of changing the temperature of the dialysate were analysed. The study is ongoing.

Therapeutic appropriateness; choosing wisely: improvement of medication prescription appropriateness upon discharge from internal medicine services of Swiss hospitals through continuous monitoring of prescription variability. The Swiss Network Prescription Monitoring Study "SWIMIT".
*Sponsor-Investigator: L. Gabutti.*

The study is ongoing.
Magnesium in the dialysate and haemodynamics. 
*Sponsor-Investigator:* L. Gabutti.

The study aims at analysing the haemodynamic consequences of changes in the concentration of magnesium in the dialysate (the cross-sectional phase is completed, the interventional phase is planned).

"Choosing Wisley": monitoring of drug prescriptions (Benzodiazepines, Proton Pump Inhibitors, Neuroleptics) and laboratory tests. 
*Sponsor-Investigator:* L. Gabutti.

The study is ongoing: the analysis is completed.

**Vascular ageing.**
*Sponsor-Investigator:* L. Gabutti.

A cohort study involving a sample of the population of Southern Switzerland is planned. The pulse wave velocity and the main risk factors for cardiovascular diseases will be monitored prospectively for 2 years. The study is ongoing.

**Hemodialysis membranes consequences: to assess the long-term impact on platelet count of HD-membranes of similar polysulfones in a cross-sectional retrospective study.** 
*Sponsor-Investigator:* L. Gabutti.

To explore the haemodynamic intradialytic consequences using different polysulfone membranes in a cross-sectional study. The results are published in abstract books.

**Dialysate Electrolites.**
*Sponsor-Investigator:* L. Gabutti.

Potassium: to assess the impact of potassium Gap on delta Blood Pressure during HD. Chloride: to assess the hemodynamic consequences of dialysate Chloride. Bicarbonate: dialysate bicarbonate; intradialytic blood pressure (BP) behaviour and risk of intradyalitic hypotension. The results are published in abstract books.

**Magnesium in the dialysate and haemodynamics.** 
*Sponsor-Investigator:* L. Gabutti.

The study aims at analysing the haemodynamic consequences of changes in the concentration of magnesium in the dialysate.

**Main funding**

All projects were funded by Balli and Gianella foundations, except the study Magnesium in the dialysate and haemodynamics that was funded by ABREOC (internal competitive grant).
Main areas of research

“In vivo” comparison in human carotid atherosclerosis: Plaque Neovascularization (PLAVASC) NCT02321410.

Lead investigators: A. Gallino, M. Cattaneo.

There is increasing evidence that neovascularisation of atherosclerotic plaque plays a major role in plaque instability resulting in acute vascular events. Contrast-enhanced Ultrasound (CEUS) is a bedside technique, which allows neovascularisation to be visualised. Dynamic contrast-enhanced plaque MRI (DCE-MRI) was also evaluated for in vivo quantification of plaque neovascularity.

The aim of the study is to assess and validate the value of CEUS, a bedside technique, in detecting plaque neovascularisation and to compare it with the quantitative assessment by DCE-MRI in carotid atherosclerosis.

A group of 30 patients with asymptomatic carotid atherosclerosis (> 50% stenosis on Doppler ultrasound) will undergo Carotid Duplex ultrasounds and CEUS. High-resolution plaque MRI and DCE-MRI will be performed in the same patients and will be analysed by two separate operators blinded to the results of the CEUS in order to detect the efficacy of CEUS when compared with in vivo DCE-MRI, as per the reference standard. The study was completed in 2016.

Tako-Tsubo Cardiomyopathy and Cardiac Syndrome X: new insights into the pathophysiology (ENDAUT) NCT02307214 or Tako-Tsubo Cardiomyopathy and Cardiac Syndrome X: new insights into the pathophysiology of two orphan cardiac Disease.

Investigators: A. Gallino, M. Cattaneo, AP. Porretta.

Tako-Tsubo Cardiomyopathy (TTC) and Cardiac Syndrome X (CSX) are respectively acute
and chronic cardiac conditions whose clinical presentation, mimicking the onset of acute myocardial ischaemia in the absence of epicardial coronary disease. Despite significant progress, their underlying pathophysiology, which seems to evoke some similarities, still remains elusive. Endothelial dysfunction and autonomic imbalance have both been individually implicated in their puzzling pathogenesis.

The investigators plan to conduct the study in a cohort of TTC patients, CSX patients and healthy volunteers with the following primary objective: to assess the response of endothelial function (through the Endopat score) to the autonomic tone activation induced by a 10-minute stress mental test. The assessment of autonomic tone during activation through the evaluation of Spontaneous Baroreflex Sensitivity (BRS) and its correlation with endothelial function (Endopat score) will represent the secondary objectives. The study was completed in 2016.

**Brain-heart interactions in Tako-Tsubo Cardiomyopathy and Cardiac Syndrome X (BRAINHEART)**

NCT02759341.

**Investigators:** M. Cattaneo, MM. Cattaneo, A. Gallino.

The Tako-Tsubo Cardiomyopathy (TTC) and the Cardiac Syndrome X (CSX) are respectively acute and chronic heart orphan diseases. There are indications that mental and psychosocial aspects may also contribute to these two diseases. The purpose of this study is to search for possible differences in mental activity, response to stressful events and function of specific areas of the brain deeply involved in relation to mind and heart. 45 subjects will be recruited and divided equally into: patients with CSX, patients with TTC (at least 6 months ago) and patients with previous acute myocardial infarction (at least 6 months ago). All participants will undergo a clinical interview and will complete several questionnaires that assess various mental functions, stress response and quality of life. In addition, in a separate visit, the participants will undergo a Magnetic Resonance Imaging without contrast medium that helps assess the function of specific areas of the brain. The study is currently recruiting patients.

**Swiss Cohort Atrial Fibrillation study “Swiss-AF”**

**Lead investigator:** D. Conen.

**Main Coordinator and responsible for Southern Switzerland:** A. Gallino.

**Collaborators:** M. Di Valentino, G. Moschovitis, A. Auricchio.

With the support of the EOC Clinical Trial Unit.

Swiss-AF increased the level of the overall inclusion of patients (>80 patients) in Switzerland as well in Ticino Canton. It should be pointed out that Ticino Canton included a higher level of patients compared to the initial scheduled expected number of patients. The contribution by Southern Switzerland undoubtedly helped make it possible to continue this study that is supported by a Swiss National Foundation (SNSF) large grant. The major hint in including patients was patients’ unwillingness to undergo MRI examinations (MRI follow-up from time zero to two years).

**Main funding**

“*In vivo*” comparison in human carotid atherosclerosis: Plaque Neovascularization (PLAVASC) NCT02321410: Swiss Heart Foundation (external competitive grant).

Tako-Tsubo Cardiomyopathy and Cardiac Syndrome X: new insights into the pathophysiology (ENDAUT) NCT02307214” or “Tako-Tsubo Cardiomyopathy and Cardiac Syndrome X: new insights into the pathophysiology of two orphan cardiac Disease: respectively: Swiss Heart Foundation (external competitive grant) and ABREOC (internal competitive grant).

**Brain-heart interactions in Tako-Tsubo Cardiomyopathy and Cardiac Syndrome X (BRAINHEART)**

NCT02759341: Swiss Heart Foundation (external competitive grant; CHF 7,000 obtained in 2015).

Swiss Cohort Atrial Fibrillation study, Swiss-AF: SNSF, Swiss Heart Foundation (Grant Number: 33CS30_148474/1).
Main areas of research

Influence of hemodialysis on physical activity and motor skills in patients with stage V chronic renal insufficiency (K/DOQI).

Investigators: O. Giannini, P. Quadri, D. Zemp.

This is a prospective multicenter observational study carried out among an outpatient population of at least 30-50 patients with chronic renal insufficiency (CKD 5, in line with K/DOQI) who were about to receive dialysis at the Haemodialysis and Nephrology Service day centres or private dialysis centres in Ticino. The purposes of the study are: to quantify the changes in the overall level of mobility and the postural and walking strategies that accompany entry into dialysis and to highlight factors linked to the fragility of the patients and/or dialysis, that are likely to affect the degree of mobility and independence in everyday life, the patients’ balance and walking control, as well as the danger of a fall. The study is currently recruiting patients.

Main funding

ABREOC (internal competitive grant).
3.3. EOC Department of Intensive Care Medicine

Prof. Paolo Merlani MD
Head of the Department of Intensive Care Medicine, Head Doctor - Regional Hospital of Lugano

The EOC Department of Intensive Care Medicine includes the relevant services in the Hospitals of Bellinzona, Lugano, Mendrisio and Locarno. The Department has a functional type of organisational structure and is managed and coordinated by the Department Board. The rules adopted for its functioning are based on the fundamental principles of shared clinical governance (accountability, participation, transparency and management), and is organised using a multisite approach. Here, too, the creation of the EOC Department of Intensive Care Medicine was aimed at providing the most suitable response to the need to harmonise and rationalise the services provided in this sector in our Canton.

Intensive Care Medicine Service
Regional Hospital of Bellinzona and Valli

Prof. Andreas Perren MD
Head Doctor

Main areas of research

Physical restraint in the ICU: psychological consequences.

This multicenter study was planned to depict the clinical scenario of physical restraint practice in adult ICUs and to analyse the relationship between its use and the occurrence of adverse events. A second purpose was to investigate the psychological outcome after physical restraint. While the first part of the study was published in 2015, the second part is under analysis.

Reliability of data from the Swiss ICU Minimal Data Set.
Investigators: A. Perren, B. Cerutti, M. Kaufmann, HU. Rothen.

Since 2008, each accredited Swiss ICU has committed to providing (on a yearly basis) structural and procedural data regarding each treated patient. One of the main objectives defined by our society to establish and maintain this Minimal Data set (MDSi) is to «promote epidemiologic research». However, little is known regarding the reliability of the different variables apart from the NEMS-/ and SAPS II scores. Their relative usefulness for scientific research and quality improvement, which are the main purposes of this ongoing research, remain, therefore, to be evaluated. A subsequent research topic will cover the distribution of resource use in Swiss ICUs, and respectively, the factors driving and influencing it (patient’s characteristics, type and level of ICU, regional differences in care protocols and other aspects not yet revealed).

Main funding

Physical restraint in the ICU: psychological consequences: ABREOC (internal competitive grant).

Reliability of data from the Swiss ICU Minimal Data Set: Swiss Society of Intensive Care Medicine grant.
Main areas of research

**Multicenter, observational screening survey for the detection of chronic thromboembolic pulmonary hypertension following pulmonary embolism.**


In a prospective, multicenter observational study, conducted between 2008 and 2015 we screened 1699 patients with an acute pulmonary embolism in 11 Swiss pulmonary hypertension centres in order to assess the cumulative incidence of chronic thromboembolic pulmonary hypertension.

**Epidemiology and long-term outcomes of traumatic brain injury in a Swiss trauma centre.**


This non-concurrent single-centre cohort study, conducted in a level 1 trauma centre aimed at analysing clinical features of patients with traumatic brain injury and identifying potential predictors of 6-month outcomes.

**Cerebrovascular responsiveness to carbon dioxide.**

*Investigators:* S. Klinzing, G. Brandi, A.

**Prevalence and severity of pulmonary hypertension in patients developing primary graft dysfunction following lung transplantation.**


Primary graft dysfunction (PGD) is a significant cause of early mortality after lung transplantation and is characterised by severe hypoxemia and infiltrates in the allograft. The pathogenesis of PGD is very complex and not fully understood. The aim of the present observational study is to assess the contribution of pre-existing pulmonary hypertension in the development of TBI.

**Pretransplant dyslipidaemia influences primary graft dysfunction after lung transplantation.**


**Impact of a communication strategy on family satisfaction in the intensive care unit.**

Main funding

Multicenter, observational screening survey for the detection of chronic thromboembolic pulmonary hypertension following pulmonary embolism: Swiss Society of Pulmonary Hypertension grant.

Epidemiology and long-term outcomes of traumatic brain injury in a Swiss trauma centre: this work was supported by the University Hospital of Zurich.

Prevalence and severity of pulmonary hypertension in patients developing primary graft dysfunction following lung transplantation: this work was supported by the University Hospital of Zurich.
3.4. Paediatric Department of Southern Switzerland

Prof. Gian Paolo Ramelli MD
Head of Department of Paediatrics, Head Doctor - Regional Hospital of Bellinzona and Valli

Surgical and medical paediatrics involves the health of neonates, infants, children, and adolescents, their growth and development and their opportunity to achieve full potential as adults. Paediatric care encompasses a broad spectrum of health services ranging from preventive healthcare to the diagnosis and management of acute and chronic (often malformative) diseases. Paediatrics deals with biological, social and environmental influences on the developing child and the impact of disease and dysfunction on development. Children differ from adults anatomically, metabolically, physiologically, immunologically, psychologically and developmentally.

Main areas of research

Pediatric Robotic Surgery Program.

Lead investigator: M. Mendoza-Sagaon.
In collaboration with “Groupe d’étude de coeliochirurgie infantile”.

Retrospective chart review research in clinical cases.

Lead investigator: M. Mendoza-Sagaon.

Appendix extraction after laparoscopic appendectomy in children: An easy, safe, and inexpensive technique.

Surgical Paediatrics Service

Mario Mendoza-Sagaon MD
Head Doctor - Chief of Research Unit

Vincenzo De Rosa MD
Deputy-Head - Chief of Research Unit

Retrospective chart review research in clinical cases.

Lead investigator: M. Mendoza-Sagaon.

Pediatric Robotic Surgery Program.

Lead investigator: M. Mendoza-Sagaon.
In collaboration with “Groupe d’étude de coeliochirurgie infantile”.

Minimally invasive surgical management of ureteropelvic junction obstruction in the murine mode.

Lead investigator: G. De Bernardis.
In collaboration with the Institute of Oncology Research, IOR.

Peer reviewed publications in 2016

Helbling R, Lava SA, Simonetti GD, Camozzi P, Bianchetti MG, Milani GP.

Lavagno C, Camozzi P, Renzi S, Lava SA, Simonetti GD, Bianchetti MG, Milani GP.
Breastfeeding-Associated Hypernatremia: A Systematic Review of the Literature.

Mendoza-Sagaon M, Hamitaga F, Hurni Y, Voumard N.

Saner C, Simonetti GD, Wühl E, Mullis PE, Janner M.
Circadian and ultradian cardiovascular rhythmicity in obese children.

Santi M, Lava SA, Simonetti GD, Stettbacher A, Bianchetti MG, Muggli F.

Minimally invasive surgical management of ureteropelvic junction obstruction in the murine mode.

Lead investigator: G. De Bernardis.
In collaboration with the Institute of Oncology Research, IOR.
Medical Paediatrics Service

Prof. Mario G. Bianchetti MD
Dean - Faculty of Biomedical Science, USI - Research Unit Coordinator

Prof. Gian Paolo Ramelli MD
Head Doctor - Chief of Research Unit

Prof. Giacomo D. Simonetti MD
Head Doctor - Chief of Research Unit

Pier Luigi Brazzola MD
Head of Service - Chief of oncologic projects

Alessandra Ferrarini MD
Head of Service - Chief of genetic projects

Barbara Goeggel Simonetti MD, PD
Head of Service - Chief of neuropaediatric projects

Federica Vanoni MD
Head of Service - Chief of rheumatologic projects

Main areas of research

Abnormal autoantibodies and epilepsy.
Lead investigator: GP. Ramelli.
In collaboration with the University Children’s Hospital of Geneve.

Arterial stiffness among children and adolescents with chronic diseases.
Lead investigator: GD. Simonetti.

Blood pressure in the acute phase of arterial ischemic stroke.
Local Investigator: B. Goeggel Simonetti.
In collaboration with the Neurozentrum, Bern.

Blood pressure in pediatric arterial ischemic stroke.
Lead investigator: B. Goeggel Simonetti.
In collaboration with the Swiss Neuropediatric Stroke Registry.

Blood pressure and heart rate rhythmicity in obese children.
Lead investigator: GD. Simonetti.

Cardiovascular health among Swiss-Italian men undergoing examination to assess fitness for recruitment into the army.
Lead investigator: GD. Simonetti.
In collaboration with the EOC Department of Internal Medicine, Regional Hospital of Bellinzona and Valli (San Giovanni) and the Federal Department of Defense.

Cardiovascular safety of propranolol in infantile hemangioma.
Lead investigator: MG. Bianchetti.
In collaboration with the University Children’s Hospital of Milan.

Development of a complex intervention to improve the management of procedural pain in neonates.
Lead investigators: C. Balice, GD. Simonetti.

Etio-pathogenesis, diagnosis and treatment of cervicocerebral artery dissection.
Local investigator: B. Goeggel Simonetti.
In collaboration with the Neurozentrum Bern.

Fever phobia.
Lead investigator: GD. Simonetti, MG. Bianchetti.

Haemorrhagic stroke in childhood, a population-based observational study.
Lead investigator: B. Goeggel Simonetti.
In collaboration with the Swiss Neuropediatric Stroke Registry.
Iatrogenic cerebrocervical artery dissection.  
Local investigator: B. Goeggel Simonetti.  
In collaboration with the Neurozentrum Inselspital, Bern.

International intracranial artery dissection.  
Co-leading investigator: B. Goeggel Simonetti.  
In collaboration with the Neurozentrum Inselspital, Bern.

International “Juvenile Inflammatory Rheumatism Cohort”.  
Local investigator: F. Vanoni.

Juvenile idiopathic arthritis.  
Local investigator: F. Vanoni.  
In collaboration with the Gaslini Hospital, Genoa.

Projects currently underway: a. Ultrasonographic findings; b. Wrist involvement.

Management of Goodpasture’s syndrome in childhood.  
Lead investigator: GD. Simonetti.

Metabolism of sodium in infants with a. acute pyelonephritis; b. acute bronchiolitis; and c. acute gastroenteritis.  
Local investigator: MG. Bianchetti.  
In collaboration with the University Children’s Hospital of Milan.

Oral ibuprofen for croup.  
Lead investigators: GD. Simonetti, MG. Bianchetti.  
In collaboration with the University Children’s Hospital of Milan.

Parental representations of their children’s illness: does “rare” make a difference? A qualitative research protocol.  
Lead investigator: MG. Bianchetti.  
In collaboration with the Department of Communication Sciences, Lugano.

Patterns and trends of pediatric bloodstream infections.  
Local investigator: L. Kottanattu.  
In collaboration with the Swiss Centre for Antibiotic resistance.

Pill size of brand-name drugs containing antihypertensive agents.  
Lead investigators: GD. Simonetti, MG. Bianchetti.  
In collaboration with the University Children’s Hospital of Milan.

Project for a Swiss Cerebral palsy register.  
Lead investigator: GP. Ramelli.  
In collaboration with the SACD Swiss Academy of Childhood Disability.

Regional differences in the prescription of vitamin D among Swiss pediatricians.  
Lead investigators: MG. Bianchetti, GD. Simonetti, GP. Ramelli.

Safety and efficacy of oral fingolimod in Rett Syndrome.  
Lead local investigator: GP. Ramelli.  
In collaboration with the University Children’s Hospital of Basel.

Sleep-Related Disorders in Children with Attention-Deficit Hyperactivity Disorder.  
Lead investigator: GP. Ramelli.  
In collaboration with the Neurocenter of Southern Switzerland.

Under-recognized and uncommon skin findings in Schönlein-Henoch purpura and related vasculitides.  
Lead investigators: GD. Simonetti, GP. Ramelli, MG. Bianchetti.

Case reports - Ongoing studies  
Investigators: GD. Simonetti, MG. Bianchetti, GP. Ramelli.

— Melkersson-Rosenthal syndrome  
— Microdeletion 17p13.2p13.1  
— Treatment of C3-glomerulopathy with eculizumab  
— Neonatal cardiomyopathy: a diagnostic chameleon.

Early detection and intervention for Swiss-Italian children with autism spectrum disorders - Ongoing studies  
Lead investigator: GP. Ramelli.  
In collaboration with A. Ferrarini.

— Clinical usefulness of the modified checklist for autism in toddlers  
— Outcome following early educational and behavioural interventions  
— Usefulness of chromosomal microarray.
Systematic (or narrative) reviews of the literature - Ongoing studies

Investigators: GD. Simonetti, MG. Bianchetti, GP. Ramelli.

- Acute nonspecific mesenteric lymphadenitis
- Acute benign myalgia cruris
- Biologics in paediatric rheumatology
- Central nervous system involvement in rotavirus infections
- Hyponatremia in children with acute respiratory infections
- Posterior cerebral oedema syndrome in children and adolescents
- Lobar nephronia in childhood
- Tubulointerstitial nephritis and uveitis
- Acute kidney injury in infectious mononucleosis
- Arrested hydrocephalus in children: personal experience and comprehensive review of the literature
- D-lactic acidosis
- Hyperammonemic encephalopathy complicating urinary tract infections; m. Evaluation of children with cutaneous lesions of vasculitis.

Paediatric Oncology

Participation in several phase II/III international, multicenter studies - Ongoing studies

Lead local investigator: PL. Brazzola.

- SIOPEL 6 (international multicenter clinical study uses chemotherapy combined with surgery for the treatment of standard-risk hepatoblastomas in young children and adolescents)
- AIEOP-BFM-ALL 2009 (international multicenter study for the treatment of acute lymphoblastic leukaemias in young children and adolescents)
- HIT-HGG 2007 (international cooperative phase II trial of the HIT-HGG study group for the treatment of high-grade glioma, diffuse intrinsic pontine glioma, and gliomatosis cerebri in children ≥ 3 years and adolescents < 18 years)
- CWS-2007-HR (this study proposes standard treatment following the guidelines of the CWS study group [CWS guidance] for paediatric soft tissue sarcomas)
- SIOP-CGT-II (prospective trial for the diagnosis and treatment of children, adolescents and young adults with Intracranial Germ Cell Tumours)
- SIOP-PNET-5 (prospective international study on clinically standard-risk medulloblastoma in children older than 3 to 5 years with a low-risk biological profile or an average-risk biological profile)
- Kraniopharyngeom 2007 (prospective international multicenter clinical study to assess the results of using radiotherapy in craniopharyngiomas that were not completely removed)
- HR-NBL-1.5 (open, randomised multicenter phase III trial; therapy optimisation study for high-risk neuroblastoma)
- End of Life (to evaluate the possibility to involve young patients in the decision process about the end of life treatment)
- Ewing 2008 (joint international protocol aimed at optimising management of Ewing sarcoma in individuals eligible for neoadjuvant chemotherapy).

Participation in international registries

Lead local investigator: PL. Brazzola.

- COSS Registry for bone tumours
- SoTISar Registry soft tissue tumours, which include sarcomas, gastrointestinal stromal tumours, very aggressive juvenile fibromatosi and hamartomas
- EuroNet-PHL-C1 Registry for Hodgkin lymphoma
- SIOP-LGG 2004 Registry for Low-Grade Glioma
- HIT 2000 Registry for cerebral tumours
- EU-RHAB multinational registry for rhabdoid tumours of any anatomical site
- GPOH-MET registry for rare malignant endocrinological tumours
- STEP Registry for rare tumours (e.g. carcinoma)
- PI Pathfinder 5 Study (phase III study of a new recombinant factor VIII for the prophylaxis and therapy for haemophilia A).

Main funding

Review sistematica sulla PRES (posterior reversible encephalopathy syndrome) in età pediatrica (Systematic review on PRES - posterior reversible encephalopathy syndrome - in paediatric age)
(Lead investigator: GD. Simonetti): ABREOC (internal competitive grant).

Inchiiesta sulla prescrizione della vitamina D da parte dei pediatri in Svizzera (Inquiry on the prescription of vitamin D by paediatricians in Switzerland) (Lead investigator: GD. Simonetti): ABREOC.

Blood pressure in pediatric arterial ischemic stroke: AstraZeneca Grant-in-aid of the Swiss Hypertension Society to B. Goeggel Simonetti (peer-reviewed project: CHF 10,000).

Grant of the Fondazione Balli to GD. Simonetti for nephrologic research: CHF 40,000.

**Awards 2016**

Goeggel Simonetti B.
Award for the Best Publication in Clinical Neurosciences 2015 by the Fondazione Neuroscienze Ticino, 28th April 2016.

**Promotion 2016**

Goeggel Simonetti B.
Venia Legendi for Paediatrics with subspecialty Neuropaediatrics from the Medical Faculty of the University of Bern.

Mendoza-Sagaon M.
Honorary Secretary of the European Society of Paediatric Endoscopic Society (ESPES) from 1st October 2014 to 1st October 2017.
3.5. EOC Department of Laboratory Medicine

Franco Keller PhD
Head of Department

The Department of Laboratory Medicine (EOLAB) was set up to meet the requirements of modern medicine as regards laboratory services, and also because of the need to minimise costs and make a more rational use of resources, including increasingly sophisticated and expensive equipment. Although operates in different parts of Ticino, it has a centralised location for its technical, scientific and administrative services, thus providing a unified image of the whole Department. This form of organisation also has greater potential for a rational development. The Department is the result of an innovative project, which also arouses interest outside the Canton, and can be considered one of the major public institutions of medical analysis in Switzerland.

Peer reviewed publications in 2016


Main areas of research

Improving the laboratory diagnosis of late-onset hypogonadism (LOH).

Late-onset hypogonadism (LOH) is a clinical and biochemical syndrome defined as the presence of three sexual symptoms (decreased frequency of morning erection, decreased frequency of sexual thoughts and erectile dysfunction) combined with a total testosterone (T) < 11 nmol/L.

The aim of this study was to provide age and method-specific normal ranges for total T in healthy men. We used a carefully selected group of 300 eugonadal men, with no known history of depression, diabetes, hypertension or erectile dysfunction, to measure total T. We compared reference intervals among four different assays platforms as well as the gold standard liquid chromatography/mass spectrometry. As expected, we found substantial differences in T level concentrations measured by various methods. Therefore, we provided method-specific reference values. Surprisingly, all the calculated reference ranges included the cut-off of 11 nmol/L, which is currently adopted for the diagnosis of hypogonadism, and the lower limit was far below this level.

**Studio di marcatori biochimici tiroidei** (Study of thyroid biochemical markers).
*Lead investigators*: M. Imperiali, L. Giovanna.

Thyroid carcinoma is the most recurrent endocrine tumour. 90% of thyroid carcinomas are represented by papillary and follicular carcinoma and are commonly defined as differentiated thyroid carcinomas (DTC).

Diagnosis of DTC includes TSH-measurement, thyroid ultrasound and thyroid scintigraphy as well as fine-needle-aspirate of the most suspicious nodules for cytology.

Treatment of these types of carcinoma includes total thyroidectomy as well as thyroid-residual ablation with I-131.

The prognosis is good, however, 20-30% of patients develop a local/metastasis relapse. It is, therefore, crucial to propose a long-term follow-up that includes monitoring of specific tumour markers such as the thyroglobulin molecule.

Today, new promising markers such as BRAF-mutations, Htshr, CYFRA-21, CA-19.9 and oncofoetal fibronectin seem to be more sensitive in the detection of relapsing disease.

The aim of this study is to evaluate the analytical superiority of these new markers in detecting relapsing disease compared to the classical approach.

Main funding

Improving the laboratory diagnosis of late-onset hypogonadism (LOH): several supplier companies are providing the diagnostic kits.

**Studio di marcatori biochimici tiroidei** (Study of thyroid biochemical markers): ABREOC internal competitive grant.

Awards 2016

Imperiali M.
Swiss MedLab Award 2016
Improving the laboratory diagnosis of late-onset hypogonadism (LOH).
3.6. Anaesthesiology Services

Anaesthesiology Service
Regional Hospital of Bellinzona and Valli

Luciano Anselmi MD
Head Doctor

Peer reviewed publications in 2016

Aguirre JA, Märzendorfer O, Brada M, Saporito A, Borgeat A, Bühler P.
Cerebral oxygenation in the beach chair position for shoulder surgery in regional anesthesia: impact on cerebral blood flow and neurobehavioral outcome.

Saporito A, Anselmi L, Borgeat A, Aguirre JA.
Can the choice of the local anesthetic have an impact on ambulatory surgery perioperative costs? Chloroprocaine for popliteal block in outpatient foot surgery.

Saporito A, Calciolari S, Ortiz LG, Anselmi L, Borgeat A, Aguirre J.
A cost analysis of orthopedic foot surgery: can outpatient continuous regional analgesia provide the same standard of care for postoperative pain control at home without shifting costs?

Main areas of research

Can the choice of the local anesthetic have an impact on ambulatory surgery perioperative costs? Chloroprocaine for popliteal block in outpatient foot surgery.
Investigators: A. Saporito, L. Anselmi, A. Borgeat, J. Aguirre.

Short-acting local anaesthetics can significantly reduce day-hospital clinic length of stay, reducing motor block duration after a peripheral nerve block and thus speeding up home discharge. In the context of a tailored perioperative protocol, this translates into a reduction in hospital fixed costs.

Protocolized care to reduce hypotension after spinal anesthesia (ProCRHYSA randomized trial).
Investigators: S. Ceruti, B. Minotti, S. De Vivo, L. Anselmi, A. Saporito.

Vena cava ultrasound has already been used for an indirect estimation of volemic status in critical care patients. The aim of this protocol is to apply this technique to an elective surgical patient undergoing spinal anaesthesia in order to guide a titrated volume repletion to reduce the incidence of post-spinal arterial hypotension.
3.7. Dermatology and Allergology-Clinical Immunology Services

Carlo Mainetti MD
Head Doctor of the Dermatology Service

Giovanni Ferrari MD
Head of the Allergology and Clinical Immunology Service

Peer reviewed publications in 2016

Swiss S1 Guidelines on the Systemic Treatment of Psoriasis Vulgaris.

Mainetti C, Guillod C, Leoni-Parvex S.
Successful Treatment of Relapsing Bowen’s Disease with Ingenol Mebutate: The Use of Dermoscopy to Monitor the Therapeutic Response.

Mainetti C, Scolari F, Lautenschlager S.
The clinical spectrum of syphilitic balanitis of Follmann: report of five cases and a review of the literature.

Genetic susceptibility to cutaneous melanoma in Southern Switzerland: role of CDKN2A, MC1R and MITF.

Romano C, Gaviria Morales E, Feci L, Trovato E, Fimiani M.
Six cases of tinea bullosa in Siena, Italy.

Main areas of research

Emergencies in dermatology outpatient clinics in a non-university hospital in Southern Switzerland (2016-01814).
Sponsor-Investigator: C. Mainetti.
Local lead investigator: L. Pelloni.

Urgent care in dermatology is in some cases very subjective and has a multi-factorial nature: on the one hand, there are medical emergencies, such as drug eruptions, severe infections and severe allergic reactions; on the other hand, there is what patients or general practitioners consider a deserving urgent care. Indeed, skin semiotics is much
more visible to the eyes of patients and those close to them. Therefore, urgent dermatological care may well create more anxiety for the patient than problems concerning other organs.

The objectives of our project are to evaluate the skin manifestations leading a patient to ask for an urgent consultation in our Dermatology Service and to establish how long symptoms have been present. We will also evaluate if there are substantial differences in the type of diagnosis made between patients treated under urgent care and those visited with regular appointments at our department.

Main funding

Fondo Scientifico Dermatologia EOC (EOC Dermatology Scientific Fund).

Awards 2016

Swiss Society of Dermatology and Venereology (SSDV) Award, 99th Annual Conference, 24th-26th August 2016, Geneva, for the best poster “case reports or case series” granted to:

Mainetti C, Scolari F, Lautenschlager S.
The clinical spectrum of syphilitic balanitis of Follmann: report of five cases and a review of the literature.

3.8. Geriatrics Service

Pierluigi Quadri MD
EOC Geriatrics Service Coordinator

The EOC Geriatrics Service, that is based at the Regional Hospitals of Lugano, Bellinzona and Välli, Mendrisio and Locarno, provides a multidisciplinary approach with specialist day clinics and wards to assess and intervene at an early stage or to prevent these geriatric problems. The Service also operates in a network together with other local dedicated geriatric structures.

Main areas of research

The following studies are currently underway; the first two are in collaboration with Mario Negri Pharmacological Research Institute in Milan, Department of Neurosciences, geriatric neuropsychiatry:

The feasibility of physiotherapy associated with the cognitive approach (imagery) for elderly patients with a fear of falling: observational pilot study.


The purpose of the study is to break the vicious circle of the fear of falling and to improve mobility (and subsequently the elderly patients’ functional capacity), considering cognitive interventions (imagery) alongside physiotherapy in elderly patients (with or without previous falls without serious consequences) who experience a fear of falling.

Study ended on 31<sup>st</sup> December 2014: Data processing is still in progress in 2017.

Maranesi E, Merlo A, Fioretti S, Zemp DD, Campanini I, Quadri P.

A statistical approach to discriminate between non-fallers, rare fallers and frequent fallers in older adults based on posturographic data.

Influence of haemodialysis on physical activity and motor skills in patients with chronic kidney disease, stage 5 (K/DOQI).


The purpose of this study is to assess the changes in the degree of autonomy and overall mobility that accompany the entry into dialysis and to highlight any risk factors associated with altered strategies of postural control and walking, the fragility of patients and/or dialysis treatment which are likely to affect the degree of mobility and autonomy in everyday life, control of balance and gait, as well as the risk of falling. The study is still in progress.

A longitudinal and observational registry of patients with memory disorders (Ticino Canton Study) in the Sottocenerino Geriatrics Service day clinics.

This is a database of patients with balance disorders and gait abnormalities and/or with a history of falls assessed anamnestically, functionally and using quantitative tools.

Main funding

ABREOC (internal competitive grant), Fondo per la Ricerca Geriatrica (Fund for Geriatric Research) of the Regional Hospital of Mendrisio.
3.9. Gynaecology and Obstetrics Services

The Services of Gynaecology and Obstetrics are a point of reference for women’s health and guarantee a service for women during pregnancy and childbirth. They also deal with urogenital dysfunctions and breast pathologies. The Breast Cancer Center of Southern Switzerland (CSSI), which is based at the Regional Hospitals of Bellinzona and Val di Sole, San Giovanni and Lugano, was specifically set up in 2004 to deal with breast pathologies.

Gynaecology and Obstetrics Service
Regional Hospital of Lugano

Thomas Gyr MD
Head Doctor

Main areas of research

The management of young women with breast cancer in Switzerland: a snapshot.

We plan to conduct a multicentric retrospective observational study on the management of young women with breast cancer (BC) in Switzerland. The aim of the project is to describe patterns of care of BC according to patient, tumour and care provider characteristics and to explore possible disparities among the three geographical/linguistic regions of Switzerland (Italian, French and German).

In particular, we would like to answer the following questions:
- Do Breast Units and BC specialists (i.e. BC care providers) in Switzerland follow the international expert recommendations and guidelines?
- Is there any under or overtreatment due to young age at BC diagnosis?
- Are there substantial treatment and outcome differences between the 3 linguistic regions?

Locally advanced and inoperable breast cancers.

To better understand demographic and psychosocial characteristics of women with LABC in our region and possibly identify factors which delayed medical advice, we interviewed all patients with T4 at diagnosis treated at our institution.

A manuscript entitled: “Can we make a portrait of women with inoperable locally advanced breast cancer?” was submitted to the Editor of ‘The Breast’ for peer review and publication in December 2016.

The Service is also actively participating in:

INSPIRE phase 4 trial, International Nipple Sparing Mastectomy Registry.
Local lead Investigator: F. Meani.

INSPIRE is a patient-centred phase IV trial, in which patients who undergo nipple sparing mastectomy and immediate reconstruction for breast cancer or risk-reducing intervention, are prospectively registered. The target is to collect all relevant outcomes, primarily oncological results, as well as patient satisfaction. The goal of the INSPIRE research project is to show the safety and effectiveness of nipple-sparing mastectomy - a procedure which is rapidly growing in popularity, despite the lack of scientific evidence to support its application. INSPIRE will allow patients to be offered a safe and reliable alternative to a mastectomy plus reconstruction for risk-reducing purposes, as well as for cancer treatment.

Main funding

Application for grant was submitted to Swiss Cancer League in December 2016.
Low-dose oral misoprostol for labour induction.

Lead investigator: B. Lipp von Wattenwyl.

Collaborators: A. Vanetti, C. Canonica.

Off-label use of oral misoprostol for labour induction is known for its effectiveness, its safety and low cost with different administration protocols. As suggested by the WHO, owing to concerns about the risk of uterine hyperstimulation with vaginal misoprostol, more recent trials have focused on the oral route of misoprostol administration. A reduced risk of caesarian births and a lower risk of Apgar score below 7 at 5 minutes of life were observed. Therefore, we switched from vaginal to oral application with a “low-dose” oral regimen. We examined a retrospective cohort of 121 induced deliveries considering the average time to labour, the average time to delivery, the induction failure rate and the labour dystocia as well as the overall rate of cesarian section.

The study was completed and published, as a poster, at the “SGGG-Kongress 2016”, 22nd–24th June 2016, Interlaken, Switzerland.
3.10. Radiology Services

Radiology Service
Regional Hospital of Lugano

Filippo Del Grande MD
Head Doctor

Peer reviewed publications in 2016

Chalian M, Del Grande F, Thakkar RS, Jalali SF, Chhabra A, Carrino JA.

High-Resolution 3-T Magnetic Resonance Imaging of the Shoulder in Nonsymptomatic Professional Baseball Pitcher Draft Picks.

Patellar instability: CT and MRI measurements and their correlation with internal derangement findings.

Ventura E, Manno C, Gabbi C, Vitale VA, Cianfoni A.
MR neurography of a vagal neuropathy.

Main areas of research

In collaboration with the University Hospital of Zürich, Switzerland

LSOS (lumbar stenosis outcome study): Multicentric imaging evaluation of spinal canal stenosis.
Lead investigator: G. Andreisek (USZ Zürich).

The purpose of this multicentric study (imaging part) is the correlation of MRI features in RX and MRI and the description of MRI findings of spinal canal stenosis in a large multicentric cohort of patients. The study is ongoing.

In collaboration with the University of Applied Sciences and Arts of Southern Switzerland (SUPSI)

Test-retest reliability of ultrasound echo intensity parameters in subjects with healthy Achilles tendons.
Lead investigators: M. Barbero, A. Schneebeli.

The purpose of the study is the evaluation of the test-retest reliability of ultrasound echo intensity parameters in subjects with healthy Achilles tendons. The study is ongoing.

In collaboration with Johns Hopkins Hospital, Baltimore, Maryland USA

— Evaluation of WIP sequences for the elbow compared to standard 2D sequences
— Evaluation of rotational misalignment with WIP MARS sequences in MRI
— Evaluation of WIP MARS sequences in patients after hip arthroplasty compared to standard slice-encoding for metal artifact correction (SEMAC) sequences.

— Evaluation of WIP MARS sequences in patients after knee arthroplasty compared to standard slice-encoding for metal artifact correction (SEMAC) sequences.

Lead investigators: J. Fritz, F. Del Grande.

The studies are ongoing.

The added value of contrast-enhanced MR sequences for the characterization of "indeterminate" soft tissue masses.

Lead investigator: LM. Fayad.

The purpose of the study is to define the added value of contrast-enhanced MR sequences for the characterisation of "indeterminate" soft tissue masses. The study is ongoing.

Spinal manifestation of genetically proven patients with Loeys Dietz syndrome compared to control group.

Lead investigators: A. Poretti, F. Del Grande.

The study is ongoing.
Main areas of research

The main topics of the ongoing clinical research projects are in the field of atherosclerosis imaging through 3 Tesla Nuclear Magnetic Resonance plaque imaging techniques. These studies are carried out in collaboration with Prof. Chung Yuan’s group, University of Seattle (WA), USA.

Plaque neovascularization: assessment by contrast ultrasonography and plaque magnetic resonance (HR-MRI): In vivo comparison in human carotid atherosclerosis.
Investigators: M. Cattaneo, R. Wyttenbach, A. Porretta, C. Yuan, D. Xu, A. Gallino et al.
Collaboration between Regional Hospital of Bellinzona and Valli and University of Seattle (WA), USA.

The study is ongoing.

Use of high-resolution MRI for planning of radiotherapy in patients with prostate cancer: a dosimetric study.
Investigators: NC. Azinwi, R. Wyttenbach et al.

The study is ongoing.

Computed tomography image quality phantom study using IMR, iDose and filtered back projection.
Investigators: S. Presilla, L. Bellesi, R. Wyttenbach.

The study is ongoing.

Main funding

3.11. Acupuncture and Traditional Chinese Medicine Studio

Acupuncture and Traditional Chinese Medicine Studio
Regional Hospital of Mendrisio

Giuseppe Peloni MD
Clinic Head of Surgery - Chief of Studio

Wilma Sanzeni-De Marco MD
Adjunct Physician - Chief of Studio

Main areas of research

Acupuncture in rehabilitation program for elderly at high risk of falling.

Gait and balance disorders belong to the most common causes of falls in older adults and often lead to injuries and disability, affecting independence and quality of life. Physical activity and in particular, balance and strength training of lower limbs are known to be effective in fall prevention programmes.

The aim of this study is to evaluate the integration of acupuncture in an outpatient rehabilitation programme for elderly with increased risk of falling.

From 2013 to 2016, 60 frail older patients underwent physiotherapy and occupational therapy for two months, twice a week. 45 participants completed the programme. 18 of them followed additional acupuncture sessions once a week. The fall risk assessment performed before and after treatment included Timed Up and Go test, Short Physical Performance Battery (SPPB), computerised posturography and gait analysis under single- and dual-task condition.

Mean age was 81 (62-94) years. Mini Mental State Examination was 26.6. Acupuncture did not differ from the no-acupuncture group either for baseline or follow-up assessments. The general functional ability in particular SPPB (p<0.05) was improved, some posturography parameters were improved but not significantly and no parameters of gait analysis were changed significantly.
Clinical Trial Unit EOC (CTU-EOC)
4. Clinical Trial Unit EOC (CTU-EOC)

The mission of CTU is to promote clinical research and education to provide services to implement and perform clinical and translational studies in compliance with the Good Clinical Practice (GCP) and national laws. Since it started in 2012, the CTU-EOC has increased its activity by building fruitful collaborations with new departments (Fig. 1), it has undertaken the full development and conduct of projects and has provided more complex services (Fig. 2).

Fig. 1

![Bar chart showing collaborations with new departments from 2012 to 2016]

Fig. 2

![Bar chart showing services provided from 2012 to 2016]

Quality Assurance

In order to promote quality, in 2016 the EOC Directorate for Internal Audit audited some clinical studies completed or ongoing at the EOC. The Clinical Trials Center (CTC) of Zurich was in charge of the audit
with the logistical support of CTU-EOC. As a result of this first assessment, the development of a future plan of regular audits is under discussion.

Quality control will be also an essential component of the two projects developed by CTU in 2016, which will be carried out in 2017 with the coordination of CTU. These include: the establishment of the EOC Biobank, in collaboration with EOLAB, that will be part of the Swiss biobanking platform and the introduction of the national general consent in all the EOC facilities.

Education and training

In 2016, 4 courses on Good Clinical Practice and ethics in research were organised (3 for Investigators, 1 for Sponsor-Investigator) with a total of 42 participants.

The program and the structure of the courses were modified to comply with Swissethics requirements.

In 2016, the online platform was implemented with the possibility of uploading the program, the course material, the evaluation form and the multiple choice exam (MCE).

The certificate of attendance, if the MCE is passed, can be downloaded as well.

Face to face activity and direct interaction between speakers and attendants are essential components of the learning process and are requested by Swissethics for the accreditation of the courses.

Events

CTU-EOC, together with Università della Svizzera Italiana (USI), organised the 6th Clinical Research Day of Southern Switzerland. The participation increased, compared to 2015, with 243 attendees, 123 abstracts and 90 posters exposed.

The 7th Clinical Research Day will be held on March 10th at the University of Lugano, again in collaboration with Università della Svizzera Italiana (USI).

Swiss Clinical Trial Organisation (SCTO)

Swiss Clinical Trial Organisation (SCTO) is a non-profit organisation acting as the central cooperation platform for patient-oriented clinical research in Switzerland. It contributes to creating a favourable environment for a high-quality clinical research in Switzerland by promoting:

— A nationally harmonised research culture, including continuing education needed for this purpose
— The establishment of national networks
— The integration of national clinical research in international networks
— The transfer of knowledge between basic research and therapeutic applications
— The dialogue between academia, industry and authorities, as well as trade organisations and professional associations
— Favourable conditions in the field of clinical research in general.

The SCTO founding members include the Swiss Academy of Medical Sciences (SAMS), the boards of directors of the University Hospitals of Basel, Bern, Geneva, Lausanne and Zurich, the board of directors of the Cantonal Hospital of St. Gallen, and the Collège des Doyens.

In 2016, the EOC was accepted as an associate member, and a representative of the EOC can participate in the SCTO Steering Board as an observer without voting rights.

Through the Clinical Trial Unit, the EOC participates in some of the SCTO projects and is a member of the EUPATI Advisory Board of Switzerland. EUPATI is the European Patients’ Academy on Therapeutic Innovation, which provides education and training tools for representatives of patient organisations. The national platform EUPATI Switzerland helps distribute these tools and serves as a point of contact for questions and information. SCTO and Swissmedic support the national platform.
Scientific Research Advisory Board (ABREOC)
5. Scientific Research Advisory Board (ABREOC)

The Scientific Research Advisory Board of the EOC (ABREOC) was set up as an advisory body in October 2007 and to coordinate the research in the EOC Hospitals. ABREOC aims at improving knowledge in the medical and nursing fields by:

- Fostering research within the EOC
- Promoting collaboration with both national and international research institutions
- Encouraging the creation of research centres in specific sectors
- Creating the appropriate conditions for the greatest possible integration between research and its clinical applications
- Encouraging interdisciplinary research.

ABREOC operates in accordance with the current legislation, taking into account the recommendations of the Swiss Academy of Medical Sciences and the Cantonal Ethics Committee. The EOC medical staff may submit to ABREOC research projects, requiring funding, to be carried out in the EOC Hospitals.

ABREOC has the following specific tasks:

- To propose the general guidelines for research to be carried out in the Hospitals, taking into account local interests, skills, initiatives and activities
- To identify the sectors or new areas in which to promote or continue research
- To create the general necessary conditions to foster research
- To provide an assessment of the scientific value of research projects for which the EOC funding is requested, paying particular attention to how the project fits with the EOC vision and mission
- To inform, in line with the available budget, about funding grants for research projects not covered by external funding
- To assess, when consulted by the EOC Head Office or local management, the scientific value of studies or scientific research not funded by the EOC and their consistency with the EOC vision and mission
- To regularly collect all necessary information regarding research authorised by and carried out within the EOC from the Cantonal Ethics Committee.
ABREOC Members

Fabrizio Barazzoni MD, MPH, Chief Medical Officer of the Medical Area - EOC Head Office, Head of the EOC Academic Education, Research and Innovation Area (AFRI), ABREOC Chairman
Manuela Sarti MD, Oncology Specialist, Head of Research Service of the EOC Academic Education, Research and Innovation Area (AFRI), coordinator of the ABREOC Secretariat.

Colette Balice, MSc, Specialist Nurse and Scientific Collaborator - EOC Nursing Area
Prof. Enos Bernasconi MD, Deputy-Head of Internal Medicine, Regional Hospital of Lugano
Prof. Franco Cavalli MD, IOSI Scientific Director, Bellinzona
Prof. Dimitri Christoforidis MD, Deputy-Head of Surgery - Regional Hospital of Lugano
Prof. Paola Di Giulio, member of the professional skill teaching staff (SUPSI) - Department of Health (DSAN)
Prof. Augusto Gallino MD, Consultant in Cardiology - Regional Hospital of Bellinzona and Valli
Prof. Alain Kaelin MD PhD, Head of Department, NSI - Regional Hospital of Lugano
Piergiorgio Mombelli MD, Consultant in Internal Medicine - Regional Hospital of Locarno
Alberto Pagnamenta MD, PD, MSc Head of Intensive Care Medicine Service - Regional Hospital of Mendrisio
Prof. Gian Paolo Ramelli MD, Head Doctor of Paediatrics - Regional Hospital of Bellinzona and Valli

ABREOC studies

From 2008 to 2016, 93 out of 159 clinical and translational studies submitted to the EOC Scientific Research Advisory Board were funded by the Scientific Fund.
The funds allocated by ABREOC since 2008, when the first funding was awarded, are specified below:

<table>
<thead>
<tr>
<th>ABREOC notices of competition</th>
<th>No. projects submitted</th>
<th>No. projects approved</th>
<th>No. projects rejected</th>
<th>Total amount requested by researchers</th>
<th>Amount awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008 – 2016</td>
<td>159</td>
<td>93</td>
<td>64</td>
<td>CHF 11,474,144.28</td>
<td>CHF 3,981,097.55</td>
</tr>
</tbody>
</table>

The tables linked to the “Report” (Appendices 1, 2, 3, 4, 5, 6, 7 and 8) list the projects that received funding with the state of progress indicated for each project: either concluded (with a publication or a final report) or underway:

www.eoc.ch/Area-Professionisti/Ricerca/Appendices-2016
Official Registry of the EOC studies
6. Official Registry of the EOC studies

In compliance with the Directive on the establishment of ABREOC, whose aim is to regulate and promote (clinical and translational) scientific research, and considering also the recommendations by the Swiss Academy of Medical Sciences (SAMS) and the Cantonal Ethics Committee, it was decided to create an Official Register of the EOC studies with the support of the EOC Information and Communication Technology (ICT) Department.

The Official Registry started on 7th April 2014 and was included in the www.eoc.ch website as a web-based resource in July 2016.

The Database of the EOC studies contains information on clinical (e.g. interventional, non-interventional) and translational trials carried out in the EOC hospitals, publicly and privately funded (competitive and non-competitive grants) or not supported by sponsors. It provides an open access to information on clinical studies on a wide range of diseases and conditions.

The studies are generally submitted to the Registry when they begin, and the information in the Registry is updated throughout the study (see also the flowchart below).

The data of the trials are entered into the Database (currently 300 studies) by the researchers themselves, supported by a data manager.

The CTU-EOC, together with the EOC Academic Education, Research and Innovation Area (AFRI) and the EOC Directorate for Internal Audit, supervises the correct conduct of the studies, in the specific instance, if the studies are carried out according to the “Good Clinical Practice” (GCP), as required by the “Federal Act on research involving humans” (HRA).

The Register allows for useful analysis of data from the studies and is a very important tool to promote information exchange, to facilitate collaborations within the scientific community and last but not least, to assure and improve the quality in clinical and translational research studies.
An example of study submission procedure:

1. Ethics committee approval
2. Opening a form
3. Automatic e-mail
4. Filling in the form
5. Annual update of status study
6. Scientific journal publication
EOC Information and Communications Technology Department (ICT)
7. EOC Information and Communications Technology Department (ICT)

The main objective of our ICT Department (ICT Area) is to supply all our Hospitals and Institutes with the more suitable technology tools and services for care, teaching and research activities. On the one hand, we ensure the technological know-how acquired after years of experience in the field and with the participation in national events, and on the other, we want to deliver the right tools following the economic sustainability criteria.

Innovation for us has a broad meaning: our service ranges from infrastructure (systems, clients and networks) to software-related aspects and focuses on the new trends of “business intelligence” and information management.

We deal, to some extent, with the typical “descriptive” activities in terms of statistics and dashboards, but especially for research, we are increasingly moving towards “Diagnostics” and “Predictive analysis”.

How? Our aim is to create a culture at people level and a framework platform at a technical level to be used by our researchers.

In other words, ICT Department is working in order to face the “BIG DATA” wave often mentioned in the media.

Several scientific research collaborations include:

Collaboration with Dalle Molle Institute for Artificial Intelligence (IDSIA)

We evaluated various partners to meet these new requirements, then we decided to work with one of the outstanding institutes of our region, the Institute for Artificial Intelligence in Ticino (IDSIA), affiliated with “Università della Svizzera Italiana” (USI) and the University of Applied Sciences and Arts of Southern Switzerland (SUPSI).

The first studied cases that were used to check methods and tools, were in oncology, and more precisely in nuclear medicine. In this area, we studied a dataset, managed by PD Dr. Luca Ceriani, Deputy-Head of Nuclear Medicine Service and PET/CT Center, together with Prof. Emanuele Zucca, Head of Lymphoma Unit (IELSG), on the mediastinal large B-cell lymphoma (IELSG 26 study).

The aim of this study was to verify the usefulness of 18F]fluorodeoxyglucose ([18F]FDG) positron emission tomography/computed tomography (PET/CT) to identify the patients with a potential risk for progression. The results were positive because the analysis helped us determine the early recognition of the patients with such risk. The study was published in Blood. 2015 Aug 20;126(8):950-6. doi: 10.1182/blood-2014-12-616474. Epub 2015 Jun 18.

Collaboration with the Sleep and Epilepsy Center, EOC Neurocenter of Southern Switzerland (NSI)

With Professor Mauro Manconi, a direct link was established with the IBM laboratory of neurosciences in Israel to have an exchange of expertise and statistical tools.
The scientific activity carried out by the EOC Services in 2016 resulted in 320 scientific publications.
Publications in 2016
The scientific activity carried out by the EOC Services in 2016 resulted in 320 scientific publications:

- 294 original articles published in peer-reviewed journals
- 9 original articles published in non-peer-reviewed journals
- 17 books or chapters in books.

The pie chart below shows the number of peer-reviewed articles published in 2016 for each EOC institution:

The list of publications is available on the EOC website by accessing the link below: 
www.eoc.ch/Area-Professionisti/Ricerca/Pubblicazioni-2016
At a glance:

In detail:

In 2016, the number of peer-reviewed publications continued to rise, compared to the data from the previous years (+52% compared to publications in 2012). The total impact factor (IF) (expressed as weighted average) was almost comparable to that of 2015 (Figure 1), in particular with regard to the publications in high and medium ranked scientific journals (Impact Factor 5 ≤ IF <10 and over 10) in terms of absolute numerical values (Figure 2).

Furthermore, our peer-reviewed publications and the total impact factor are comparable with the publication data of St. Gallen Cantonal Hospital (KSSG) (data taken from Wissenschaftliche Publikationen KSSG 2015) (Figure 3).

Figure 1. Publications and Impact Factor (weighted average) of the EOC in the last 5 years

Note: the institutional affiliation excluded 28 of 286 publications in 2015 and 20 of 294 publications in 2016 from researchers not yet affiliated to the EOC when the articles were published.


Figure 2. Absolute numerical values of the EOC publications sorted according to Impact Factor ranges

Figure 3. Comparison between the EOC and the KSSG peer-reviewed publications in the last 4 years (excluding 2016) with total Impact Factor
Impact of EOC research as a citation frequency measured by $h$-index

$H$-index is another popular citation index and was developed in 2005 by Hirsch to measure the academic impact of scientists. The application of this index has been extended to journals, countries, science funds and institutions\(^2\). The $h$-index of a hospital focuses on high-impact research papers published by its doctors or researchers and provides an interesting evaluation perspective on the research impact of top hospitals. Although there are numerous multidisciplinary databases providing information on publications and citations for computing the $h$-index, the ones that are commonly used include: Web of Science, Essential Science Indicators (ESI), Scopus and Google Scholar.

The citation frequency of the EOC publications was analysed by Thomson Reuters Web of Science platform on 29\(^{th}\) May 2017. The indices used by the platform were: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.

The citation frequency of our publications has constantly increased in the previous years (analysed time-span: 2012-2016 and 2006-2016), together with the total number of publications per year. The EOC $h$-index was 44 in 2012-2016 (Figure 4a) and 85 in 2006-2016 (Figure 4b) and these values indicate an achievement of a good institution as they measure the research impact and, therefore, the quality of services. A recent study based on ESI data collected from 1\(^{st}\) January 2000 to 31\(^{st}\) August 2010, highlighted that the top 50 high-impact hospitals in the world had a variable $h$-index ranging from 257 (Massachusetts Gen Hosp, the first one) to 21 (Taipei Vet Gen Hosp)\(^3\). In particular, two major hospitals, The Hospital for Sick Children (affiliated with the University of Toronto Faculty of Medicine, Canada) and Sahlgrenska University Hospital (a system of hospitals associated with the Sahlgrenska Academy at the University of Gothenburg, Sweden), had an $h$-index of 84 in the list mentioned above.

**Figure 4. EOC Citations in Each Year**

a. Timespan: 2012-2016

$h$-index: 44

b. Timespan: 2006-2016
h-index: 85

The h-index of our Institution in the timespan 2012-2016 is higher than that of another major cantonal hospital, Kantonsspital Graubünden of Chur (Figure 5, analysis performed on 8th June 2017) and higher than half of the h-index of a renowned university hospital, such as CHUV of Lausanne (Figure 6, analysis performed on 8th June 2017).

Figure 5. Chur Cantonal Hospital Citations in Each Year

Timespan: 2012-2016
h-index: 27
Although the h-index is only one measure and cannot cover all the achievements of a hospital or institution, it can provide a remarkable assessment of the research impact of a hospital or institution.

At the end of the day, all measurements of research quality should be taken with a grain of salt; it is certainly not possible to describe a scientist’s contribution to a given research field using simple numerical values.

As Albert Einstein (1879–1955) famously observed: “not everything that counts is countable, and not everything that’s countable counts”.

**Figure 6. CHUV Citations in Each Year**

Timespan: 2012-2016

*h*-index: 82

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**Corrigendum to**
Table 1 and Figure 5 (the h-index of EOC researchers, timespan 2012-2015) of the EOC Scientific Report 2015:

- Gaudio E. h-index: 9
- Martinetti G. h-index: 4
- Paone G. h-index: 3

(analysis performed on 29th May 2017)
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