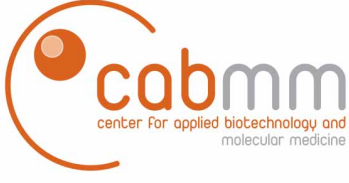




University of
Zurich^{UZH}



Translational Research in Zurich

The Zurich Model - Prepared for Clinical Translation from GLP to GMP and GCP

Historically, Switzerland – and Zurich in particular – hold an internationally well-recognised and leading position in basic and applied biomedical research. The strong networking of the Swiss Federal Institute of Technology Zurich (ETH), the University of Zurich (UZH), and the University Hospital Zurich (USZ) forms a powerful scientific and translational cluster in the life sciences sector. It catalyses a high level of expertise in broad interdisciplinary areas, which is a fundamental prerequisite for leading edge biomedical research and prospective developments of innovative clinical applications. Engineers, scientists, and clinicians at ETH, UZH and USZ work together to investigate basic mechanisms and underlying principles of

numerous diseases to collaboratively develop new diagnostic and therapeutic interventions.

Biomedical research has been conventionally separated into two fundamental clusters: basic and applied research, where applied research can be further subdivided into preclinical and clinical research. Basic research is necessary to feed the understanding of normal states in comparison with disease states, but does not necessarily directly translate into clinically significant applications. Applied research enables and fosters the development and improvement of new diagnostics and biomedical applications for patients based on the clinical understanding of disease development and progression.

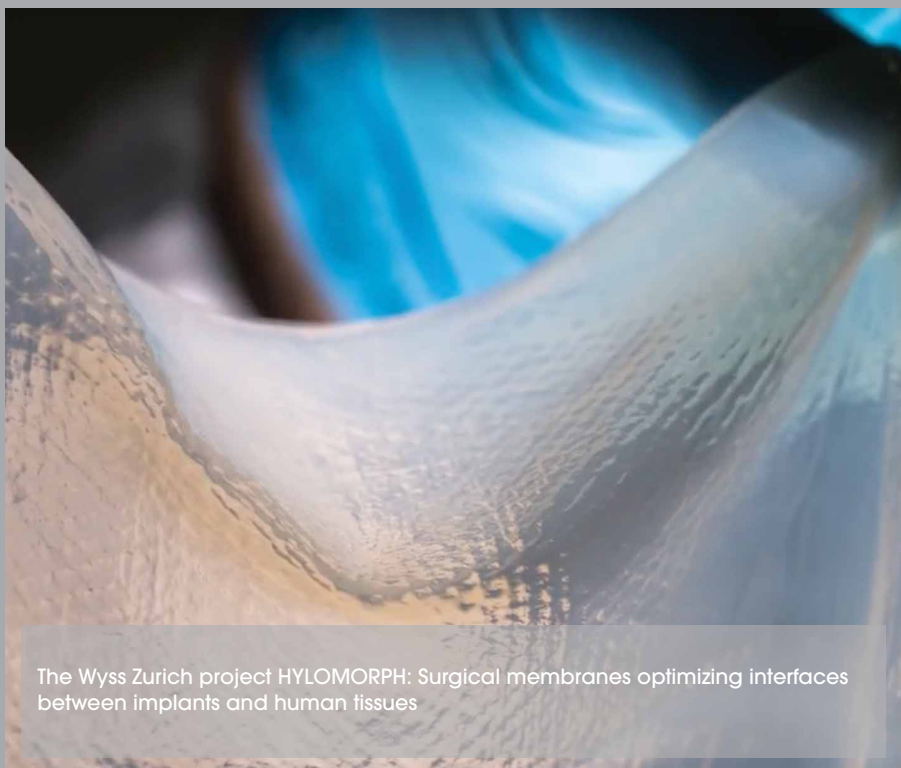
The principal goal of translational research is to integrate and translate improvements in basic biology and physiology towards clinical trials, finally taking research from the bench to the bedside. Bolstered by discoveries in the fields of molecular and cell biology, regenerative medicine technologies in particular are expected to provide new strategies for therapeutic treatment modalities by replacement of tissue through transplantation; regeneration of tissue by stem cell or gene editing applications; and rejuvenation of resident regenerative capacities (for example, resident stem cells) with the ultimate goal of 'restitutio ad integrum' (restoration to the original condition). The Institute for Regenerative Medicine (IREM) of UZH aims to advance molecular life sciences into next-generation bio-inspired therapies at the interface of degeneration and regeneration; with a focus on the most relevant human diseases, including neurodegeneration and cardiovascular diseases.

It is well known that there is a long latency period between any scientific discovery and its widespread application within a clinical setting. Many scientific discoveries do not achieve clinical translation because results are often not scalable; or because industry and investors typically prefer to invest in more mature, clinically advanced technologies. For the very important preclinical phase, the Musculoskeletal Research Unit (MSRU) and the Vetsuisse Faculty Zurich at UZH provide in-depth expertise in the fields of musculoskeletal (bone and cartilage, tendon, spine, disc) research as well as soft tissue (cardiovascular, wound healing) research. In order to translate preclinical results into a clinical

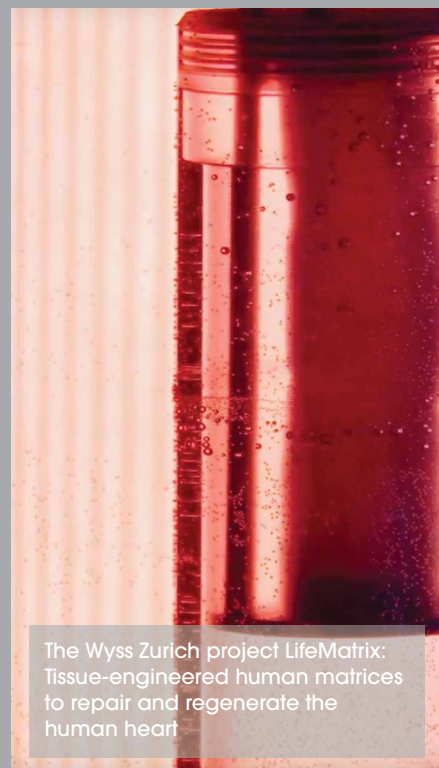
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The Wyss Zurich project HYLOMORPH: Surgical membranes optimizing interfaces between implants and human tissues



The Wyss Zurich project LifeMatrix: Tissue-engineered human matrices to repair and regenerate the human heart

setting, the MSRU facility is part of the Good Laboratory Practice (GLP) monitoring programme accredited by Swissmedic, which has greatly facilitated clinical translation and implant registration processes. The MSRU also provides GLP accredited histological processing and analyses (see also page 5 within this document).

MSRU is well connected to other core facilities such as the Functional Genomics Center Zurich (FGCZ), a state-of-the-art research and training facility jointly operated by the ETH and UZH, which provides key expertise for 'Omics' research. In close scientific proximity, the Competence Center for Applied Biotechnology and Molecular Medicine (CABMM) is dedicated to fostering advances in clinically oriented research in the fields of regenerative medicine, experimental medicine and surgery, applied biotechnology; and molecular medicine. CABMM is embedded within both the Vetsuisse and Medical Faculty of UZH; and provides an interdisciplinary research platform on which basic scientists and clinicians are able to exchange scientific information and create collaborations for the purpose of developing novel therapeutic approaches for the treatment of dysfunctional and diseased tissues. With the substantial infrastructure and knowhow necessary to build collaborations within the life sciences research community in Zurich, these achievements provide a solid ground for prospective clinical investigations in humans.

The majority of registered clinical studies currently following the Advanced Therapy Medicinal Products (ATMPs) track are driven by academic institutions. However, due to general lack of cleanroom infrastructure, quality management staff with a background in regulatory affairs and substantial funding at academic institutions, early clinical phase developments are stuck in what is often called the 'Valley of Death'. Swiss entrepreneur, philanthropist and three time honorary doctor, Hansjörg Wyss wanted to change this, saying in 2014: "Breakthrough discoveries in medical and technological fields have to be made available as soon as possible for the benefit of mankind. I want to help accelerate the translation process and build a bridge between basic research and application."

To attain this goal, Hansjörg Wyss asked ETH and UZH to join forces to launch the joint endeavour Wyss Zurich. This accelerator was funded by Hansjörg Wyss with an initial investment of \$120m (€106.58m) and began operations in March 2015. The paramount objective of Wyss Zurich is commercialisation and clinical application through spinoffs, licensing deals and trade sales. For the efficient translation of new findings into first clinical settings, Wyss Zurich provides all necessary expertise and infrastructure for the manufacture of clinical grade products following the regulatory standards of Good

Manufacturing Practice (GMP; see also page 4 within this document).

However, within the field of life sciences, translational research is by its very nature deeply complex; and so it requires support from multiple disciplines. Consequently, in addition to implementing basic funding of the production of clinical-grade material, it was imperative to establish a tight link between the Clinical Trials Center Zurich (CTC), UZH and USZ. The CTC is ISO 9001:2015 certified and provides planning and realisation of clinical trial projects in compliance with the ordinances of the Swiss Human Research Act, local regulations and the international Good Clinical Practice Standards (ICH-GCP); which emphasises the 'from bench to bedside' approach (see also page 6 within this document).

With a world leading biomedical research community at ETH, UZH and USZ; a tight circle of key stakeholders in the fields of GLP, GMP and GCP; and close collaborations within the Vetsuisse Faculty, the CTC and the Wyss Zurich, Zurich appears well prepared to tackle the translational hurdles for the implementation of prospective biomedical interventions – particularly in highly complex and interdisciplinary fields such as regenerative medicine.

GMP, GLP and GCP at the Zurich Location

The Zurich location offers the complete quality chain of Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP); and Good Clinical Practice (GCP). Hence, patients benefit from the development of a medical product or treatment manufactured under GMP, preclinically tested under GLP; and clinically evaluated according to GCP.

Dealing with GMP requirements at academic institutions in Zurich

The Good Manufacturing Practice (GMP) requirements for academic institutions in Zurich are covered by the GMP Core Facility at Wyss Zurich. Wyss Zurich is a joint accelerator of the University of Zurich and ETH Zurich (Swiss Federal Institute of Technology Zurich), which was made possible by a generous donation from Swiss entrepreneur and philanthropist Dr. h.c. mult. Hansjörg Wyss.

The Regenerative Medicine Platform of Wyss Zurich is dedicated to manufacturing clinical-grade products which meet the required regulatory standards. The platform is a certified cleanroom facility for Good Manufacturing Practice (GMP), which covers GMP specialists, expert advisors and GMP qualified infrastructure.

The Regenerative Medicine Platform provides the expertise, guidance and infrastructure required to respond to the diverse regulatory and technical challenges of bringing treatment to a clinical setting. It aims to support academic projects in the efficient translation of preclinical biomedical research to applied regenerative therapies; and to accelerate the entry of innovative scientific discoveries into clinical trials. In particular, it addresses the increasing existing demand for the clinical application of newly developed drugs and transplant products (also called Advanced Therapy Medicinal Products, or ATMPs).

Support is provided through the following departments, infrastructure and services:

Manufacturing

- Manufacturing of products under GMP conditions for clinical supply;
- 800m² facility (GMP grade A, B, C, D);
- Five separate GMP grade B and C cleanrooms for handling different manufacturing processes; and
- Qualified equipment for the production of drugs and ATMPs.

Quality Management

- Swissmedic manufacturing licence and Certificate of GMP Compliance for drugs and cell therapy products;
- Certified Quality Management System (Master Standard Operating Procedures, Deviation Management, Change Control Management, Risk Management, etc.);
- Review and approval of all GMP-relevant documents in order to guarantee compliance with GMP regulations; and
- Advice for project teams on scientific compliance from senior GMP experts (project-specific strategies).

Quality Control

- QC laboratories with qualified equipment for the analytical testing of drugs and ATMPs;
- Analytical batch release and in-process control for clinical supply, stability studies, transport studies, process validation runs, etc.; and
- Environmental monitoring of the GMP facility (testing for airborne particles, airborne microorganisms and surface microorganisms).

Biobank

- Qualified cryo infrastructure for controlled freezing and storage of therapy-relevant cell and tissue samples (e.g. master and working cell bank) in the vapour phase of liquid nitrogen.

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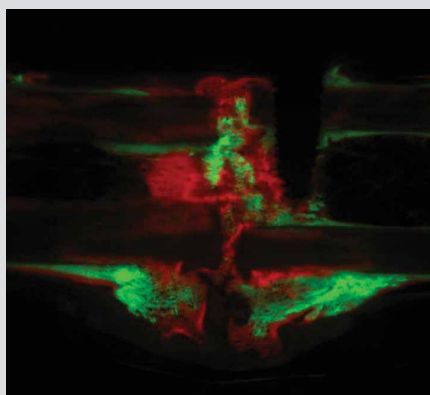
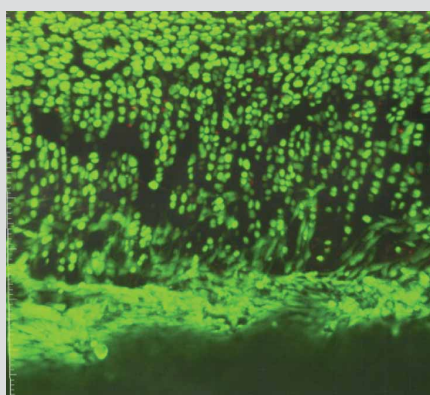
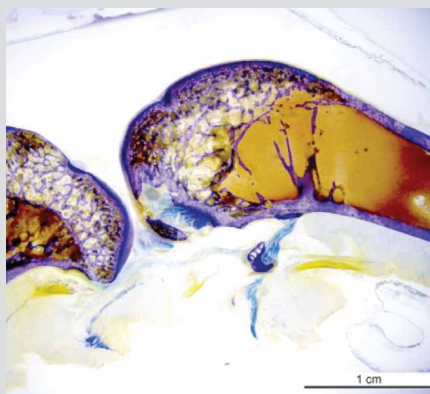
GLP at the Musculoskeletal Research Unit, Vetsuisse Faculty, University of Zurich

The future lies in translational medicine: this interdisciplinary 'bench-to-bedside' approach promotes collaborations among researchers in different fields, thereby creating a network between universities, clinics and the companies developing their ideas. Zurich's startup scene is an ideal site to combine academic backgrounds with industrial and scientific knowhow. For years, the Musculoskeletal Research Unit (MSRU) at the University of Zurich has been performing nonclinical studies in the fields of musculoskeletal as well as soft tissue research. As the demand from the industry to conduct testing in accordance with internationally accepted guidelines became prominent, it was the vision of Prof. Dr. Brigitte von Rechenberg that MSRU as a university group should perform studies in compliance with the Swiss Ordinance relating to Good Laboratory Practice (SR 813.112.1).

MSRU's GLP certification, combined with years of expertise in the field of veterinary research, offers a substantial advantage to internationally oriented partners aiming to save costs, material, time and animals; the latter in accordance with the animal protection demands of the three Rs (replace, reduce, refine).

The challenge of GLP implementation at a university is the integration of different laboratories into a single test facility. Although some working groups at our test facility are independent and spatially separated, they are still subject to MSRU's GLP policy. Even though working under GLP conditions demands time and additional expenses, the understanding of its importance is crucial to guarantee the traceability and safety of generated data. This poses a constant challenge in regard of personnel training in GLP compliance, Standard Operating Procedures and monitoring. Due to interdisciplinary collaborations, a pool of highly qualified personnel is available; resulting in outstanding product testing.

We endeavour to maintain our high standard and act as a reliable link to high quality treatment in favour of the patients. We offer:



Technical Expertise:

- Musculoskeletal research (bone & cartilage, tendon, spine & disc); and
- Soft tissue research (cardiovascular, wound healing).

Imaging:

- Radiology;
- MRI/CT; and
- MicroCT.

Histology laboratory:

- Decalcified, paraffin-embedded histology (different stainings, immunohistochemistry);
- Non decalcified, plastic-embedded histology (different stainings);
- Ground sections (quantitative histology, e.g. histomorphometry);
- Thin sections (qualitative histology); and
- Cryosections.

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GCP at the Clinical Trials Center, University Hospital Zurich

All clinical research projects must be conducted in compliance with the Guidelines for Good Clinical Practice (GCP). GCP is an international ethical and scientific quality standard for the design, conducting, recording and reporting of trials which involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and wellbeing of trial subjects are protected, consistent with the principles which have their origin in the Declaration of Helsinki; and that the clinical trial data is credible (Ref. ICH-GCP(R1)).

The Clinical Trials Center (CTC) Zurich is part of the Research and Education Office of the University Hospital Zurich and was established in 2006; supported by the University of Zurich, the Swiss National Science Foundation (SNSF) and the Swiss State Secretariat for Education, Research and Innovation (SERI).

The CTC is an ISO 9001:2015 certified institute with the necessary broad expertise to support academic projects in the field of translational and clinical research across all disease and topic areas, including projects with the focus on further usage of clinical data and samples.

Professional medical and paramedical CTC personnel provide research teams with consultations and support during all stages of a clinical project. This support includes:

Concept and Planning

- Consultations on methodological design and statistical planning;
- Budgeting;
- Feasibility checks; and
- Medical writing and preparation of essential documents.

Preparation and Set-up

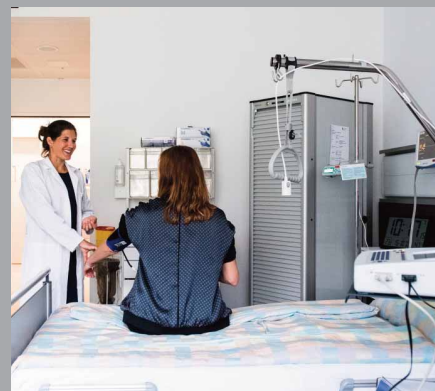
- Document review in order to guarantee compliance with national and international law and GCP guidelines/ISO14155;
- Submission to the Cantonal Ethics Committee and Regulatory Authorities (Swissmedic, FOPH);
- Set-up support for quality management systems (QMS); and
- Contracts and agreements.

Conduct and Control

- ISO certified Infrastructure with qualified equipment, Phase I Facilities;
- Qualified staff for GCP/ISO14155 compliant study conduct and management;
- Data management and software complying with all regulatory requirements in the areas of quality management, software development, FDA (21 CFR Part 11)/GCP and data privacy;
- Safeguarded monitoring to control the quality of generated data and to assure the patients' rights and safety; and
- Audits (including system audits, site audits, GCP/GMP/GVP) and inspection preparation.

Termination and Results

- Scientific data evaluation; and
- Archiving.



The comprehensive educational program of the CTC places emphasis on the theoretical and practical training of persons involved in the planning and conduct of clinical research projects. All courses are accredited by the Swiss Institute of Medical Education (SIME/SIWF/ISFM), Swissmedic, swissethics, SGPM/SAPM and SwAPP; and are open to medical and paramedical personnel engaged or interested in clinical research. In addition to GCP courses, University Certificates of Advanced Studies (CAS) are provided in Clinical Trial Management, Clinical Data Management and Clinical Monitoring, which can be attended separately or be combined into a Diploma of Advanced Studies (DAS). Since 2011, the CTC is an FMH-SIME-approved Postgraduate Education Training Site in Pharmaceutical Medicine.

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Good laboratory practice is also a question of ethics and animal protection

The official regulations for medical devices changed in January 2018 to state that preclinical studies involving medical devices must now be conducted under Good Laboratory Practice (GLP) conditions. GLP is a quality system which regulates both the organisational process and the circumstances under which preclinical safety studies are planned, conducted, monitored, documented, archived and reported. This new regulation can be seen as the consequence of several implant scandals, including the use of silicone breast implants of nonmedical quality in reconstructive or cosmetic surgery. These scandals affected the entire industry, which had to adapt to more restrictive laws and greater responsibilities for conducting their preclinical studies.

What appears to be only an administrative burden and complication on a first glance is a fundamental benefit for the use of experimental animals at second glance. GLP regulations require a detailed study plan which must be signed by all parties before any activity can be undertaken – so each singular step, including housing, acclimatisation, support measures during the experiment and anaesthesia; as well as surgical procedures and full evaluation protocols – have to be clearly outlined in advance. Standard Operating Procedures (SOPs) have to be established for each activity, as well as for equipment and use of infrastructure. Score sheets to document the health state of the experimental animals must be completed in full. Personnel have to be regularly trained. Once the preclinical studies begin,



detailed documentation of each activity is required; guaranteeing that the SOPs are strictly followed.

Regular inspections by an internal or external quality officer (QA) are required and changes outlined in their written reports must be adapted immediately. Finally, a very detailed report including files with all raw data of each individual animal has to be composed. Evaluations for biocompatibility must be conducted according to ISONORMS dictated by the regulatory authorities. Depending on the country, either each individual study or the entire laboratory must be audited and accredited by the relevant regulatory bodies.

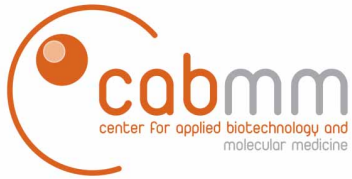
This entire procedure clearly improves the overall quality of preclinical studies and, by extension, the responsible use of experimental animals. Researchers and industrial partners are well advised to incorporate GLP principles early in their studies: if this recommendation is followed, repetition of preclinical studies in order to comply with regulatory issues can be avoided and the lives of many animals can therefore be saved. This keeps the three Rs (reduce, refine and replace) alive – involving GLP fulfils not only regulatory compliance, but in the long term also respects the ethical use of animals and their welfare.

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