Tissue Engineering

Ivan Martin

Department of Biomedicine
Tissue Engineering
University of Basel and
University Hospital Basel

Group Members

PhD Students (med. fac.)
Majoska Berkelaar
Gordian Born
Andrea Mainardi
Andrea Mazzoleni
(phil.-nat. fac.)
Janhavi Apte
Mansoor Chaaban
Laura Dönges
Evrim Ceren Kabak
Jesil Kasamkattil

Postdocs
Dr. Maria Adelaide Asnaghi
Dr. Andres Garcia Garcia
Dr. Thibaut Klein,
Dr. Olga Krupkova
Dr. Sylvie Miot
Dr. Adrien Moya
Dr. Manuele Giuseppe Muraro
Dr. Karoliina Pelttari-Göritz
Dr. Sébastien Pigeot
Dr. Alessandro Pirosa
Dr. Laura Power

Research Associates
Prof. Dr. Andrea Barbero
PD Dr. Maria Filippova
Prof. Dr. Arnaud Scherberich

Surgical Research Associates
Dr. Chao Dong
PD Dr. Marcus Mumme

Technical Staff
Boris Dasen
Sandra Feliciano Barbosa
Dr. Morgane Hilpert
Francine Wolf

Undergraduate Students
Anna Amovilli
Anna Gryadunova
Wilson Idemudia
Federico Mariuzzo
Esma Tankus

Anke Wixmerten
(Administrative Staff)
Cecilia Palma, PhD Student
(External Collaborator)

List as of December 2020

From 3D culture models to regenerative surgery

The common denominator of the research projects in the group is related to the establishment of 3D cell culture systems, combining interdisciplinary efforts in cell biology, engineering technologies and materials science. These systems are used as models to investigate fundamental aspects of tissue development/pathologic changes, or as grafts to induce tissue regeneration. Our main focus is the development of cartilage and bone/bone marrow tissues, though the developed expertise has also been implemented in collaboration with other groups in different areas, including tumor modelling.

Cartilage tissue engineering and regeneration (Prof. A. Barbero)
Our goal is to repair cartilage defects of traumatic or degenerative nature using grafts engineered from autologous cells. We discovered that nasal chondrocytes (NC) have a larger and more reproducible capacity for cartilage regeneration as compared to other cell types, including articular chondrocytes. Moreover, NC display features of environmental plasticity and can thus genetically and functionally adapt to implantation in a joint. Our concept has been translated into a first-in-man study for the treatment of focal cartilage defects in the knee (Fig. 1). Based on the promising findings, we are now coordinating a multicenter phase II trial (BioChip) for the same indications, funded under the EU-Horizon2020 program. In parallel, with the goal to treat also degenerative cartilage diseases (e. g., osteoarthritis), we are currently investigating the capacity of NC to regulate the main pathological processes activated in a joint by inflammation and abnormal loading. In the framework of an ERC Synergy project (collab. with F. Rijli, FMI), we target understanding the molecular and epigenetic mechanisms endowing NC with their distinct functionalities.

Vascularized bone and bone marrow engineering (Prof. A. Scherberich)
One goal of the program is the controlled development of bone / bone marrow ossicles using human cells, as models for human hematopoiesis and as grafts for bone regeneration. We demonstrated that mesenchymal progenitors from human bone marrow or adipose tissue can recapitulate the developmental process of endochondral ossification. This involves the formation of cartilaginous intermediate tissues which robustly and efficiently remodel into functional ossicles upon implantation. The system was used to investigate interactions between stromal and hematopoietic cell components (collab. with T. Schroeder, D-BSSE) and to generate osteoinductive extracellular matrices (collab. with P. Bourgine, Univ. Lund).
An associated goal is the efficient vascularization of the implanted grafts to support scaled up bone regeneration. We found that axial vascularization of engineered implants with an arterio- venous (AV) bundle leads to a rapid formation of vascular networks (Fig. 2). This principle was used to reconstruct maxillary bone in a patient following carcinoma excision. The bone defect was satisfactorily restored by ectopic prefabrication of a vascularized bone graft using autologous fat-derived cells and an AV bundle, which was transferred into the defect site. Studies are ongoing to adapt and evolve the paradigm for use in the challenging clinical settings of infected bone.

Engineering platforms for 3D cell culture
Dynamic 3D cell culture under perfusion flow (Fig. 3A) has been introduced to model *in vitro* tissue development and physiological homeostatic processes (e. g., bone matrix deposition and resorption, stromal-vascular-hematopoietic cell interactions) as well as pathologic settings (e. g., cartilage degeneration, hematologic malignancies, solid tumor microenvironment) (collab with R. Skoda , C. Lengerke,

M. Bentires, G. Hutter). Generated systems have shown patterns of response to drugs or immunotherapy which cannot be mimicked by 2D cultures or by simple spheroids.

The bioreactor-based culture tools are being further developed (i) to introduce automation/control towards streamlined manufacturing of clinical grafts (Fig. 3B) or (ii) to increase throughput for larger scale tests in miniaturized compartments (Fig. 3C).

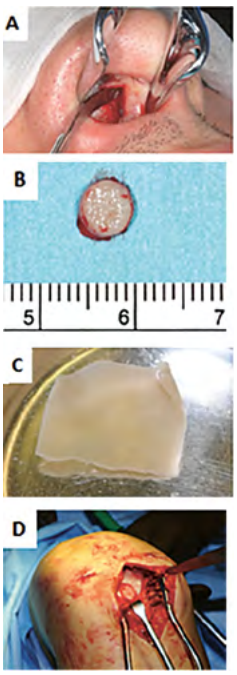

Fig. 1 Engineering of autologous nasal cartilage grafts. **(A)** Collection of a nasal cartilage biopsy from a patient, under local anesthesia and with minimal donor site morbidity. **(B)** Collected specimen of nasal cartilage septum, from which cells are isolated and expanded in culture. **(C)** Tissue engineered cartilage graft (macroscopic appearance) inserted in the knee cartilage defect of the patient following intraoperative shaping **(D)**. (See ref 5 for more details.)

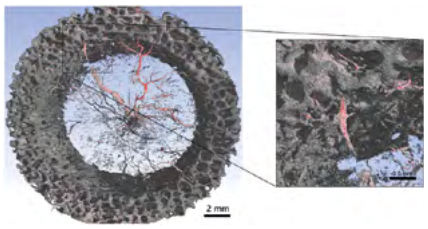

Fig. 2 Phosphotungstic acid-enhanced, three-dimensional micro-computed tomography reconstruction (left picture), showing ramified, radial vascularization (red staining) of an engineered osteogenic implant developing from an arterio-venous (AV) bundle (in the very center of the construct), after 8 weeks *in vivo.* The implant was initially inserted inside a hollow cylinder of devitalized bone (structure in grey) mimicking osteonecrosis. This dead material is also colonized by vascular structures (magnified picture in the right). (See ref 2 for more details)

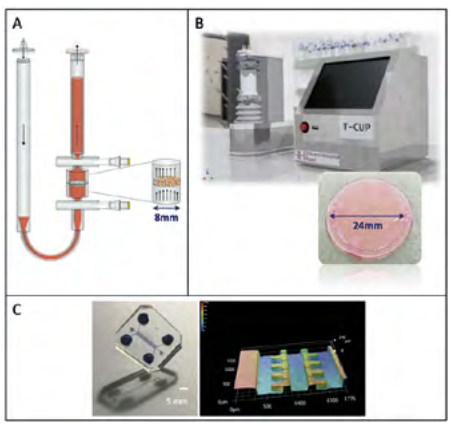

Fig. 2 (A) Direct perfusion system for efficient cell seeding and culture into 3D porous scaffolds to model *in vitro* tissue development and mimic physiological homeostatic processes or pathological settings. **(B)** Bioreactor-based system with automation and monitoring/control features for the clinical manufacturing of cartilage grafts. **(C)** Microfluidic-based system for dynamic loading of chondrocyte cultures, modelling traits of osteoarthritis, and testing possible therapeutic effects of soluble compounds. (See refs 1&3 for more details)

Selected Publications

Occhetta P, Mainardi A, Votta E, Vallmajo-Martin Q, Ehrbar M, Martin I, Barbero A, Rasponi M (2019). Hyper-physiological compression triggers osteoarthritic features in a cartilage-on-chip model. Nat Biomed Eng 3: 545–557.

Epple C, Haumer A, Ismail T, Lunger A, Scherberich A, Schaefer DJ, Martin I (2019). Prefabrication of a large pedicled bone graft by engineering the germ for de novo vascularization and osteoinduction. Biomaterials 192:118–127.

Bourgine PE, Klein T, Paczulla A, Shimizu T, Kunz L, Kokkaliaris K, Coutu D, Lengerke C, Skoda R, Schroeder T, Martin I (2018). *In vitro* biomimetic engineering of a human hematopoietic niche with functional properties. Proc Natl Acad Sci USA 115: E5688–E5695.

Occhetta P, Pigeot S, Rasponi M, Dasen B, Mehrkens A, Ullrich T, Kramerd I, Guth-Gundel S, Barbero A, Martin I (2018). Developmentally inspired programming of adult human mesenchymal stromal cells toward stable chondrogenesis. Proc Natl Acad Sci USA 115:4625–4630.

Mumme M, Barbero A, Miot S, Wixmerten A, Feliciano S, Wolf F, Asnaghi MA, Baumhoer D, Bieri O, Kretzschmar M, Pagenstert G, Haug M, Schaefer DJ, Martin I, Jakob M (2016). Nasal chondrocyte-based engineered autologous cartilage tissue for the repair of articular cartilage defects: an observational first-in-human trial. Lancet 388: 1985–1994.

Connection to Clinical Practice

Prof. C. Kunz, PD Dr. M. Mumme & Prof. A. M. Müller, Prof. D. J. Schaefer, Prof. S. Schaeren

Maxillofacial Surgery / Orthopaedics and Traumatology / Plastic, Reconstructive, Aesthetic and Hand Surgery / Spinal Surgery

Engineered cellular grafts for regenerative surgery

Facial and tracheal cartilage reconstruction

Engineered nasal cartilage grafts, previously successfully used for reconstruction of the alar lobule of the nose, are being investigated for the reconstruction of the nasal cartilage septum after perforation (M. Haug, B. G. Kaiser). Studies are ongoing to explore the use of epithelialized cartilage grafts for the management of empty nose syndromes (S. Negoias) and/or tracheal defects (D. Lardinois)

Articular cartilage and intervertebral disc repair.

Following the demonstration of feasibility and safety of nasal chondrocyte-based engineered cartilage for the treatment of knee cartilage injuries, a phase II study (total of 108 patients in 5 international centers) is ongoing to investigate efficacy (M. Mumme). Work is in progress to obtain regulatory approval (temporary authorization) and funding for the treatment of an extended set of orthopaedic indications using engineered nasal cartilage (M. Mumme). Pre-clinical studies are also exploring the use of nasal chondrocytes to engraft in intervertebral discs and block their degeneration (A. Mehrkens).

Bone repair

Treatment of humerus fractures in elderly individuals previously indicated the safety and biological functionality of stromal vascular fraction (SVF) cells intraoperatively derived from autologous adipose tissue. Grafts based on SVF cells are currently being investigated for axially-vascularized bone graft prefabrication in the reconstruction of the maxilla (C. Jaquiery, T. Ismail, A. Haumer, F. Thieringer), for congenital digit defects (A. Kämpfen) and for infected long bone defects (R. Osinga, M. Clauss, M. Morgenstern).