

Research Thrust

1. Macromolecular crowding and its applications

a. Matrix enhancement

Macromolecular crowding is an established biophysical principle that governs macromolecular association in all biological systems *in vivo* and *in vitro*. Hence we are interested in applying this principle to realize an *in vivo*-like environment in our *in vitro* cell culture models. Synthesizing extracellular matrix is a major challenge in current tissue engineering. The advantages of such an ECM are manifold. Not only will such a matrix provide structural support for the cells to grow by attaching themselves to the ECM as *in vivo*, but also the ECM can direct the differentiation of the cells into a definite lineage. Developing this technology entails devising the tool box to set up the platform. Such a tool box would have to cater to identifying the different ECM proteins, exemplified by collagen, the oldest known biomaterial so far.

b. Stem cell differentiation

Modeling the stem cell niche to control aspects of stem cell properties *in vitro*. A “stem cell niche” is a 3D environment of cell subsets and extracellular matrix (ECM) that can indefinitely house stem cells and direct their self renewal and production of progeny. We want to focus on the isolated effects of the ECM on adult human stem cells. To achieve our objectives we will use biological ECMs derived from different cell types and use their deposited ECM and apply biophysical principles to 1) control niche specific stem cell properties (niche effect) and 2) direct differentiation into niche specific cell types particularly of CNS lineages (niche-specific differentiation). Phenotypic changes of progenitor cells from bone marrow and cord blood will be monitored by screening for cell surface markers, secreted molecules and gene expression patterns.

2. Scar wars

Fibrosis and scar formation, locally or systemically, represent an imbalance between deposition of collagen and its breakdown, resulting in unwanted accumulation of collagen. This leads to a broad spectrum of tissue disturbances ranging from local scarring to completely shutting down internal organs. In plastic and eye surgery it hampers the therapeutic outcomes, in tissue engineering it currently prevents progress f. e. in peripheral nerve repair. We therefore aim to implement antifibrotic substances in surgical procedures, wound healing and tissue engineering. Basically we evaluate drugs that down regulate collagen deposition and thus scar formation and fibrosis. The drugs we use are basically enzyme inhibitors that exert specific actions on collagen biosynthesis at transcriptional, posttranslational and extracellular level. Since abnormal scarring is frequent in SE Asia, this project has a major regional impact.

3. Neovascularization in Tissue Engineering

A major hitherto unmet need in tissue engineering is the promotion of vascularization of and into biomaterials to render implanted tissue viable. Some of the antifibrotic compounds mentioned below have the potential to modulate angiogenesis. These compounds shall facilitate the design of antifibrotic biomaterials for tissue engineering that become rapidly vascularized and thus enhance the outcome of tissue repair procedures. In contrast, a combination of antifibrotic and antiangiogenic effects is sought for the treatment of fibroproliferative disorders which are most often coupled with hypervascularization. Since keloid formation and an fibroproliferative eye disorder, pterygium, are frequent in SE Asia this project has a major regional impact.

4. Tissue Modulation and Cross linking

Transglutaminases as biological cross-linkers: Transglutaminases (TGases) represent enzymes that create isodipeptide cross-links between proteins (gamma-glutamyl-epsilon lysyl) in the extracellular space. We have recently shown that TGase 2 stabilizes the dermo-epidermal junction of skin, zonule fibers of the eye lens, basement membrane of the cornea, as well as elastic microfibrils in tissue and cultures. We also have previously devised a screening assay to monitor the epidermal TGase activity in patients with inherited cornification disorders. Goals: (1) to identify further TGase crosslinking sites in various human tissues (2) to test recombinant TGase2 and microbial TGases for their ability to cross-link supramolecular structures in a variety of human tissues (3) to identify peptide sequences that serve as artificial substrates for TGases (3) polymerize biomatrices or biomimetic synthetic matrices with engineered cross-linking sites derived from the identified substrate sequences.