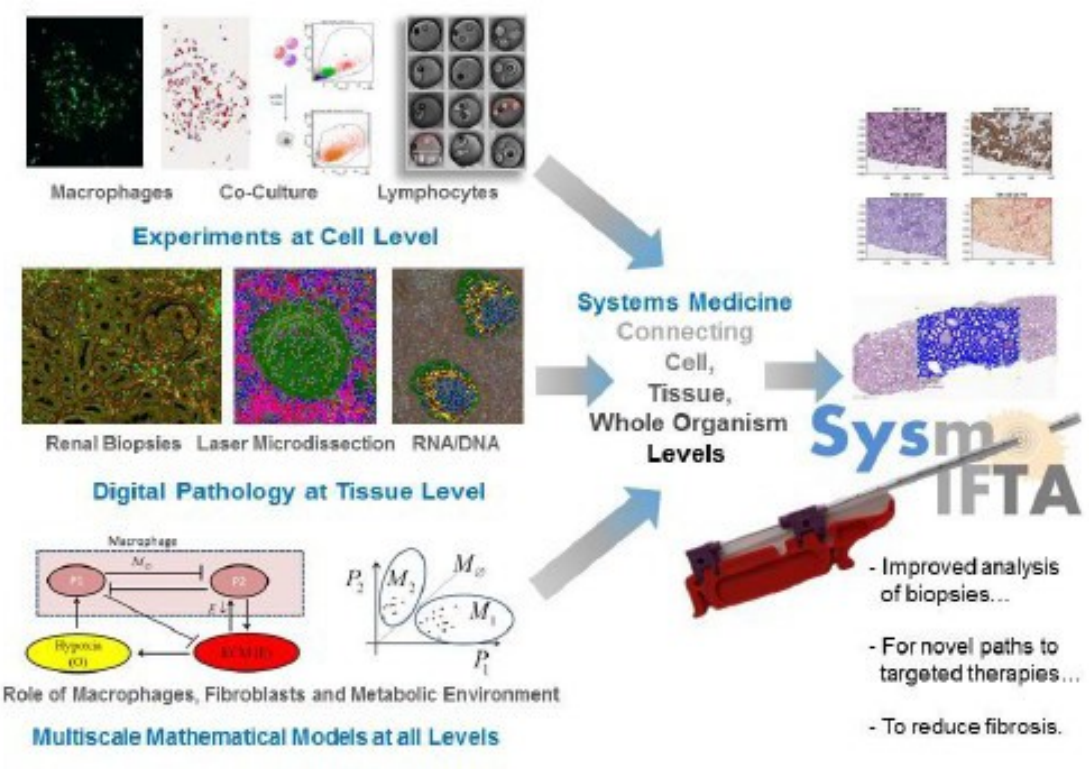
Sys-MIFTA: A systems medicine approach to minimize macrophage-associated interstitial fibrosis and tubular atrophy in renal allograft rejection

Transplantation medicine has been very successful in reducing the risk of acute rejection after kidney transplantation. A slowly progressing process referred to as “interstitial fibrosis and tubular atrophy" (IF/TA) is currently one of the main causes of declining renal function and has become a serious threat to transplanted kidneys.

The SysMIFTA project aims to explore the complex mechanisms that finally lead to kidney fibrosis, specifically targeting a particular subgroup of immune cells that can stimulate fibroblasts. These cells, named “alternatively activated macrophages" (AAM), are suspected to induce fibroblast activity to produce too many collagen fibers.

On the other hand, AAM can also have positive effects in transplanted organs, including immune regulation suppressing rejection. The aim of SysMIFTA is to better understand this role based on cell-based experiments, advanced image analysis of kidney tissue, and mathematical models that integrate the biological information from the molecular level all the way to the whole organism.



This understanding is important because many recent developments in immunotherapy open completely new paths towards targeting “bad” immune cells (e.g., pro-fibrotic AAM) without damage to “good” ones (e.g., regulatory immune cells suppressing rejection). The project supports new strategies to guide repositioning of such therapies that are primarily developed for autoimmune diseases or cancer in transplantation medicine.

The expected results include dynamic (agent-based) mathematical models reflecting essential mechanisms leading to IF/TA, their calibration and validation with biopsy-based, large-scale clinical data, and the clinical implementation of the systems medicine concept in knowledge-based, innovative workflows for biopsy evaluation guiding medical decisions. The project creates the scientific foundations for novel personalized therapeutic approaches, with the final goal to precisely target AAM and their interaction partners and reduce their negative effects on transplanted organs, while preserving the immunological balance required for long-term graft survival.

For patients, the loss of transplanted kidneys, the transparency and full computer-aided exploration of biopsy results will introduce advantages: more accurate and better reproducible results of biopsy-based diagnostics and improve outcome and thereby patients' lives.

In the sector of health care providers, the outcome of the project will help nephropathologists with novel technologies for biopsy evaluation, and clinical nephrologists whit better and more transparent therapeutic decisions. In touch with the international representative of the liver disease patient advocacy group.

The immediate economic impact is the benefit of faster, accurate, and reproducible results of biopsy-based diagnostics. This will lower the individual cost of treatment after complications.

PROJECT DURATION > 36 Months

Onset project: May 2016

Project ends: October 2019

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"*Fibrosis*" refers to the increased production of tissue fibres, mostly collagen, by specialized cells in the connective tissue called "fibroblasts". This process is necessary, for example in wound healing, and it is tightly regulated in the healthy body. In a transplanted kidney this regulation can be disturbed, and overshooting activity of fibroblasts can result in a thickened layer of connective tissue seriously reducing the capability of renal tubular cells to clean the blood.

Graft survival is an estimate of the probability of transplant functioning at a finite time after transplantation.

Model system is a representation of a process or a system that is used to describe and explain phenomena that cannot be experienced directly.

Click here to watch the Sys-MIFTA movie

ERACO SYSMED

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