RWTH AACHEN UNIVERSITY

Master Thesis

Computational analysis of pancreatic cancer treatment with gemcitabine

Developing and selecting drugs which are leading to tumor remission is a huge challenge because drug responses are patient- and tumor-specific. Functional precision oncology makes use of patient's cancer cells to directly evaluate whether a certain therapy is being effective. To gain translational data from in vitro drug testing the overall test conditions have to be as physiological as possible. The closer the in vivo conditions are being recapitulated in terms of the tumor microenvironment, dosing and drug concentrations used the higher the translational and predictive value. Parameters which are influencing are multifactorial depending on biological constraints but also pharmacokinetic is an important driver which needs to be aligned between the patient and the test system.

An important aspect to translate in vitro to in vivo response is the concentration and contact time of the drug. In collaboration with PreComb, a Swiss Biotechnology company, the variability in therapeutic outcomes will be investigated for the use case of gemcitabine treatment of pancreatic cancer. Physiologically-based pharmacokinetic (PBPK) models will be developed for mice and humans. Such PBPK models describe the physiology of an organism at a large level of detail and can be used amongst others to simulate time-concentration profiles in different tissues. Tumor drug exposure in the mouse PBPK model of gemcitabine will be linked to pharmacodynamic (PD) effect models of cancer growth to investigate tumor remission or relapse for different administration protocols. For the human situation, patient response data obtained from 3D tumor twins (3DTwin® Technology) will be analysed. The human PBPK model will be used for reverse dosimetry to compare in vitro drug concentration from automated testing with in vivo drug PK profiles in patients. The model-based analyses of drug responses in human tumor samples with the PBPK/PD of tumor progression in xenograft mice will support a mechanistic assessment of inter-individual variability in treatment outcomes. Also, the findings from this comparative analysis will provide important insights for in vitro to in vivo extrapolation.

Goals of the PhD thesis

- develop PBPK/PD models for gemcitabine in humans and mice;
- investigate in vivo drug responses in mice and humans for different dosing scenarios;

What do we expect from you?

We are looking for a highly motivated individual with an interest in computational biomedicine and physiology. The candidate should have a master in computational biology, natural sciences, pharmacology, engineering or informatics. She/he should furthermore be interested in PBPK modeling and have a quantitative mindset.

Contact

Prof. Dr. Lars Kuepfer
Institute for Systems Medicine with Focus on Organ Interaction
Email: lkuepfer@ukaachen.de
https://www.ukaachen.de/kuepfer

The work will be co-supervised by Dr. Jens Kelm, PreComb Therapeutics AG, Zurich.