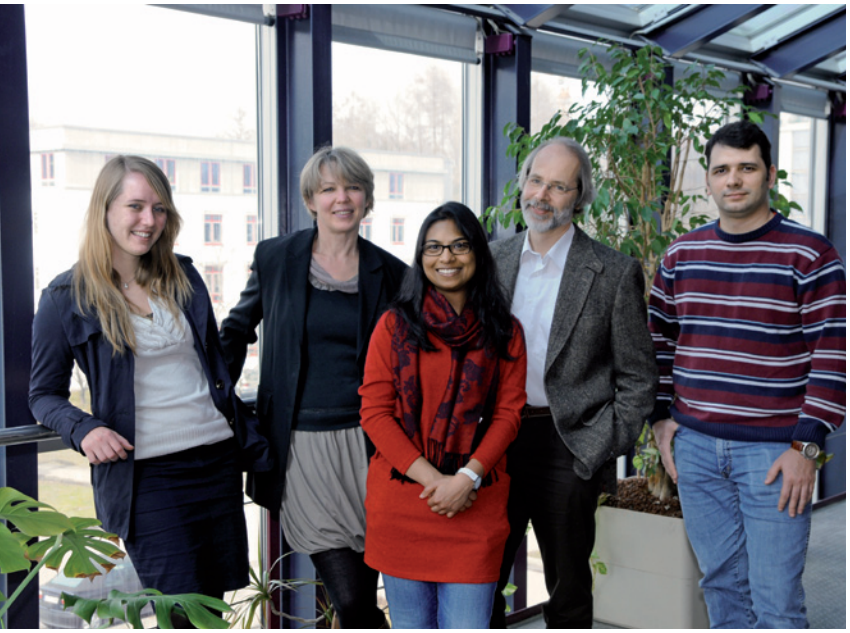


Institute of Pharmacology of Natural Products and Clinical Pharmacology

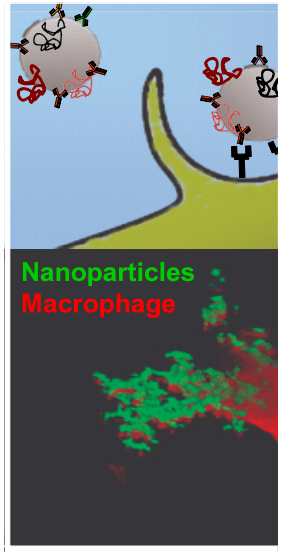
Work Group: Molecular Pharmacology and Biophysics

Head: Thomas Simmet

Modulation and Remote Control of Cell Function by Functionalized Nanosized Particles

Nanosized particles have a rapidly increasing number of industrial and medical applications. Macrophages are phagocytes that act as a first line of defense by internalizing particulate matter, including nanoparticles. Nanosized particles are capable of biasing relevant functions of immune cells, including those of macrophages. However, despite the frequent use of nanosized materials, the interactions of nanoparticles with phagocytosing immune cells remain poorly understood. Our goals are: i) to learn in greater detail how distinct surface properties and functionalizations of nanoparticles affect their interaction with cellular membranes; ii) to address cellular consequences that might be induced by distinct nanosized materials; and iii) to investigate how nanotechnology could be exploited for the remote control of cell functionality and eventually for therapeutic purposes. A wide variety of cell and molecular biological as well as biophysical methods and techniques, including advanced imaging, will be applied to address these questions.

This project is performed in collaboration with the Max Planck Institute for Polymer Chemistry (Prof. K. Landfester), Mainz, the Institute of Applied Physics (Prof. G.U. Nienhaus), KIT, Karlsruhe, and the Czech Academy of Sciences (Prof. A. Dejneka, Prof. V. Zablotskii).



Interaction between nanoparticles and macrophages

The Team:
Head of Institute: T. Simmet
Professors: J. Stingl, T. Syrovets
Group Leaders/Postdocs: O. Lunov, B. Büchele, C.Q. Schmidt, S. Hafner
PhD Students: M. El Gaafary, O. Efimkina, C. Loos, T. Paul, K. Stiebel, Z. Schmidt
Additional Members of Thesis Advisory Committees: V. Mailänder (Mainz), J. Brockmöller (Göttingen), T. Seufferlein (Ulm), H. McLeod (Chapel Hill), K. Scharffetter-Kochanek (Ulm)

Dr Oleg Lunof started his PhD in April 2009 and, having completed it successfully at the Institute of Pharmacology of Natural Products and Clinical Pharmacology in August 2011, he was awarded summa cum laude. Due to his outstanding performance, he also received the Doctoral Student Award in 2011.

Ulm University
Institute of Pharmacology of Natural Products and Clinical Pharmacology
Helmholtzstraße 20
D-89081 Ulm, Germany
Tel. +49 (0)731 500 65600
Fax +49 (0)731 500 65602
www.uni-ulm.de/klinik/nhk/

Work Group: Clinical Pharmacology

Head: Julia Stingl

Individual Mechanisms of Cytarabine Toxicity

Bone marrow suppression and hematological toxicity are frequent problems related to drug therapy with cytarabine (AraC). It would therefore be valuable to have predictive markers for the individual probability and severity of AraC-associated adverse effects. The aim of this project is to evaluate the role of genetic factors in individual drug toxicity to find predictive markers for the occurrence of AraC-related side-effects. As a model for the AraC toxicity, lymphocytes from healthy volunteers are used to examine the inter-individual differences in AraC toxicity and to correlate these findings with genetic factors.

Biomarkers for skin toxicity and response to EGFR inhibitors in keratinocytes and fibroblasts

For EGFR inhibitory anticancer drugs, it has been shown that the follicular epidermal growth signaling pathway is critical for both the frequently occurring skin toxicity mediated by effects of the EGFR-inhibitors on the keratinocytes as well as for the therapeutic response of tumor cells to the drug. Primary human keratinocytes serve as a model to understand individual genetic differences in the molecular drug action of the important new class of EGFR inhibitors.

Gene expression and activity of the EGFR signaling pathway will be characterized in keratinocytes and fibroblasts in order to study the genetic modulation of the EGFR inhibiton in these cells.

This project is performed in collaboration with the Institute for Pharmacogenomics and Individualized Therapy, University of North Carolina, Chapel Hill, NC, USA (Prof. H. McLeod). The PhD student T. Paul will spend about one year of his PhD studies in Chapel Hill and the remaining time in Ulm.

Selected Publications:

- *Lunov O, Syrovets T, Loos C, Nienhaus GU, Mailänder V, Landfester K, Rouis M, Simmet TH (2011): Amino functionalized polystyrene nanoparticles activate the NLRP3 inflammasome in human macrophages. ACS Nano 5:9648-9657.*
- *Lunov O, Syrovets T, Beil J, Delacher M, Tron K, Nienhaus GU, Musyanovych A, Mailänder V, Landfester K, Simmet TH (2011): Differential uptake of functionalized polystyrene nanoparticles by human macrophages and a monocytic cell line. ACS Nano 5:1657-1669.*
- *Lunov O, Zablotskii V, Syrovets T, Röcker C, Tron K, Nienhaus GU, Simmet Th (2011): Modeling receptor-mediated endocytosis of polymer-functionalized iron oxide nanoparticles by human macrophages. Biomaterials 32:547-55.*
- *Parmar S, Schuhmann C, Rüdiger S, Boeck S, Heinemann V, Kächele V, Seeringer A, Paul T, Seufferlein T, Stingl JC (2013): Pharmacogenetic predictors for EGFR-inhibitor-associated skin toxicity. Pharmaco-genomics, in press.*
- *Fuerst D, Parmar S, Schuhmann C, Rüdiger S, Boeck S, Heinemann V, Kaechele V, Stiebel K, Paul T, Seufferlein T, Mytilineos J, Stingl JC (2012): HLA polymorphisms influence the development of skin rash arising from treatment with EGF receptor inhibitors. Pharmacogenomics 13: 1469-76.*
- *Morag A, Pasmanik-Chor M, Oron-Karni V, Rehavi M, Stingl JC, Gurwitz D (2011): Genome-wide expression profiling of human lymphoblastoid cell lines identifies CHL1 as putative SSRI antidepressants response biomarker. Pharmacogenomics, 12:171-84.*