www.schirinkretschmann.de/You-may-have-a-Pink-Cadillac

Breathing life into an artwork by Schirin Kretschmann, "You may have a Pink Cadillac, 2011," a permanent installation at the Center for Biomedical Research, Ulm.

The Team:
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PhD Students: V. Emmerling, R. Kratzer, L. Krutzke, J.-M. Prill
Study Programme Experimental Medicine Student:
M. Scheitenberger
Additional Members of Thesis Advisory Committees:
H.J. Fehling (Ulm), H. Geiger (Ulm), M. Hörer (Laupheim), M. Ogris (Munich), P. Ng (Houston), R. Schirmbeck (Ulm), K. Ulbrich (Prague)

Department of Gene Therapy

Viral Vectors for Therapeutic Applications

Head: Stefan Kochanek

We are strongly interested in the development of new therapeutic procedures for diseases, for which there is currently no treatment. We use viral and non-viral gene transfer to introduce genes into cells, cell culture and also in vivo. Vectors loaded with specific genes may either help to treat certain diseases (somatic gene therapy) or, in the case of infectious diseases, to prevent them (genetic vaccination). Complex hurdles must be overcome before safe and successful gene therapy can be possible. This can only be achieved by means of a close cooperation of various scientific and medical disciplines. A strong scientific focus is on the development of gene transfer vector technology by genetic and chemical engineering and the use of improved vectors for selected inborn or acquired disorders as well as new vaccine strategies in preclinical models.

Viruses as a Delivery Vehicle for Genes

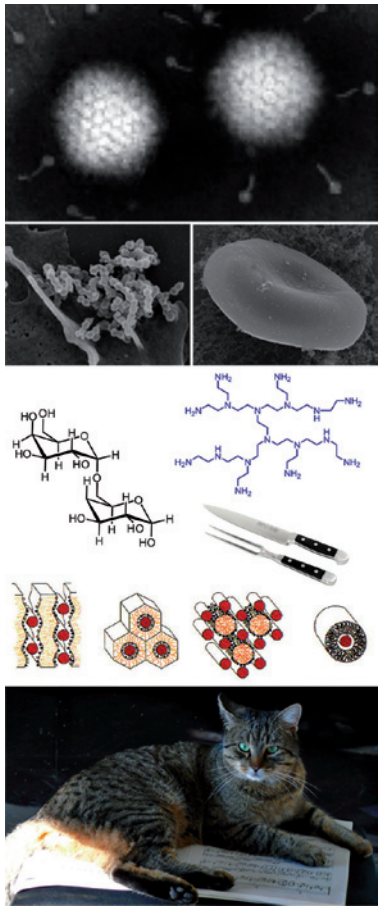
Since viruses have evolved together with their host, they are by nature very efficient delivery vehicles for their genes. By removing one or several essential genes, they can then be used for efficient gene transfer in vitro and in vivo to specific cell types. Adenoviruses have been studied for many years and are very well understood from a molecular point of view. Several projects in our laboratory thus relate either to the improvement of adenovirus vectors or to their use in different genetic and non-genetic diseases.

Overcoming Barriers in Gene Therapy

So far, in vivo gene therapy has only been successful in a few cases. The main reason for this is the lack of efficient gene transfer in vivo due to the interaction of vector particles with barriers in the blood and in tissues. In two separate PhD projects, Jan-Michael Prill and Lea Krutzke use chemical and genetic modification of adenovirus vectors to identify and overcome barriers imposed by human blood in order to achieve targeted gene delivery to specific tissues.

Vectors for Genetic Vaccination

Genetic vaccination shows considerable promise as a solution to overcome the limitations of classical vaccines. However, neither the mechanisms of induction nor the persistence of adaptive immune responses, when the antigen is expressed following gene transfer, are completely understood. In the past, we have observed that the immunogenicity of adenovirus vectors limits the multispecificity of T cell



Some of our tools for gene transfer: we are flexible... and we also like arts and music.

responses raised against vector-encoded antigens and we design experiments with the aim of better understanding basic mechanisms. Such studies will likely open avenues for an improved vector design based on a better understanding of the basic principles of the induction of immune responses in the context of gene transfer. In her PhD project, Ramona Kratzer, uses adenovirus as a vaccine vector and attempts to improve the immunogenicity of encoded antigens by optimizing the coding sequence, with a special focus on antigen glycosylation.

Oncolytic Vectors for Tumor Therapy

A new focus of the laboratory is the development of oncolytic viruses for the treatment of solid cancers and the testing of these vectors in improved models of pancreatic cancer. These studies take into account the complex composition of solid tumors that, in addition to neoplastic cells, contain many other cell types, such as stromal cells and endothelial cells, and also an extracellular matrix.

Primary Cell Immortalization and Vector Production

One of our long-standing interests is also the immortalization and characterization of primary human cells from amniotic fluid (MD project of Marina Scheitenberger) with the aim of generating cell lines that are suitable for industrial production of viral vectors.

Industrial Production of Adeno-Associated Virus (AAV) Vectors

In her PhD project conducted at Rentschler Biotechnology GmbH, Laupheim, and supervised by Dr. Markus Hörer, Director Virus-based Biologics, Verena Emmerling will generate improved production cell lines for a high titer production of AAV vectors.

Neurodegenerative Diseases

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder that is caused by the expansion of a CAG triplet repeat in exon 1 of huntingtin, a very large protein that is located in the cytoplasm of many, including neuronal, cell types. In our work we try to improve our understanding of the function of normal and mutant huntingtin either by recombinant production of full-length huntingtin or by using adenovirus vectors as a tool for functional studies with the long-term goal of contributing to the development of a treatment for HD.

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Selected Publications:

- *Kreppel F, Kochanek S (2008): Modification of adenovirus gene transfer vectors with synthetic polymers: a scientific review and technical guide, Mol Ther 16, 16-29.*
- *Kron MW, Engler T, Schmidt E, Schirmbeck R, Kochanek S, Kreppel F (2011): High-capacity adenoviral vectors circumvent the limitations of ΔE1 and ΔE1/ΔE3 adenovirus vectors to induce multispecific transgene product-directed CD8 T-cell responses. J Gene Med. 13(12):648-57.*
- *Prill JM, Espenlaub S, Samen U, Engler T, Schmidt E, Vetrini F, Rosewell A, Grove N, Palmer D, Ng P, Kochanek S, Kreppel F (2011): Modifications of adenovirus hexon allow for either hepatocyte detar-geting or targeting with potential evasion from Kupffer cells. Mol Ther. 19:83-92.*
- *Zong S, Kron MW, Epp C, Engler T, Bujard H, Kochanek S, Kreppel F (2011): ΔE1 and high-capacity adenoviral vectors expressing full-length codon-opti-mized Merozoite surface protein 1 for vaccination against Plasmodium falciparum. J Gene Med. 13:670-9.*
- *Dong X, Zong S, Witting A, Lindenberg KS, Kochanek S, Huang B (2012): Adenovirus vector-based in vitro neuronal cell model for Huntington's disease with Human disease-like differential aggregation and degeneration. J Gene Med. 14, 468-81.*
- *Laakkonen JP, Engler T, Romero IA, Weksler B, Couraud PO, Kreppel F, Kochanek S (2012): Transcellular targeting of fiber- and hexon-modified adenovirus vectors across the brain microvascular endothelial cells in vitro. PLoS One. 7(9):e45977.*