Nanobridges for targeted virus/host interaction and optimized gene transfer

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Objective: The goal of our integrated research project is to improve the efficiency and the selectivity of viral gene transfer via tailored peptide nanofibrils. These nanofibrils form bridges between viral vectors and their target cells, thus enhancing transduction rates and allowing to target specific cell types in gene transfer and therapy settings.

Background: Application of retroviral vectors in gene transfer or therapy approaches is often hampered by low transduction rates and/or the lack of specific cell targeting systems. We have shown that peptide nanofibrils derived from human semen potently increase retroviral infection (1-8). In collaboration with the group of T. Weil, we identified, characterized and patented a novel nanofibril-forming peptide termed Envitra (Fig. 1c) (9, 10). This 12-mer peptide forms fibrils (Fig. 1b, c), which act as a cationic bridge between virions and cells thereby increasing viral attachment (Fig. 1d). The peptidic nature of Envitra and other self-assembling peptides offers attractive new opportunities to further improve viral gene transfer by introducing novel functional entities to increase attachment rates and/or to target specific cell types.

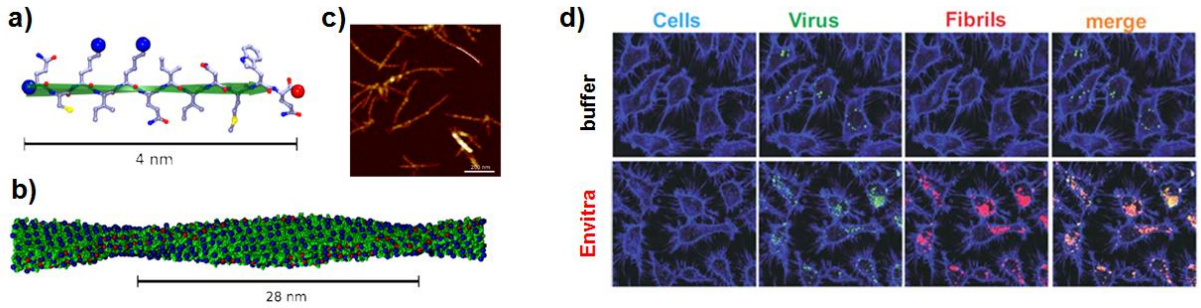

Figure 1. Envitra nanobridges for improved and targeted retroviral gene transfer. a) Molecular model of EF-C fibrils; b) Refined molecular model of a fibril exhibiting a helical pitch of 28 nm. (C: grey, N: blue, O: red, S: yellow, hydrogen atoms are omitted for clarity). C) Atomic force microscopy images of Envitra fibrils. d) Envitra nanobridges increase viral attachment rates to the cell membrane. Complex formation of nanofibrils (red) and virions (green) with target cells (blue).

Workplan: Oligopeptides (Envitra, others) with new functional entities like cell targeting moieties will be synthesized and nanobridge formation characterized by the Weil group (see separate project proposal). We will then study complex formation between nanobridges and virions and quantify their interaction with cells and the resulting transduction enhancing properties. We will use state-of-the-art retroviral vectors currently applied in gene therapy approaches and transduce primary cells of mouse or human origin. Targeted gene transfer into specific cell types will be analyzed using established FACS-based techniques. Together with our partner, we will establish a structure-activity-relationship to further optimize specific properties (transduction efficiency, cell targeting) of the nanobridges. The most promising nanobridges will then be analyzed for the efficacy to transduce clinically relevant primary cell types using mouse models as described (10).

Own references:

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