Department of Biochemistry

THESIS DEFENSE

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“Development of an Adenoviral Gene Vector with Designed Shield and Adapter for Paracrine Delivery of Therapeutics”

A major limitation of strategies utilizing biologics for the treatment of cancer is achieving high local concentrations within the tumor microenvironment. Furthermore, off-target toxicity often narrows the therapeutic window during repeated high bolus injections of the therapeutics. An alternative would be the production and secretion of therapeutic agents in a paracrine manner directly within the tumor. Viral gene delivery offers a powerful platform for the generation of such a ‘biofactory’. The viral gene vector would require (a) the ability to specifically infect target cells in the tumor or tumor microenvironment, (b) shielding from the neutralization by the immune system and (c) the capacity to harbor multiple genes in order to produce a therapeutic cocktail.

Here I describe the development of such a targeted stealth adenovirus suitable for the generation of such a ‘biofactory’. Our recently developed bispecific DARPin adapters enable the viral targeting of the adenovirus to different tumor surface biomarkers. Genetic modifications of the viral genome allow the generation of tailored viral capsid which escapes the interaction with specific host proteins. Furthermore, we have engineered a high-affinity protein coat to protect the virus from the immune system. We have shown that the combination of shield and adapter increases viral gene delivery to xenografted tumors in vivo and reduces liver off-targeting and immune neutralization.

This study highlights the power of protein engineering for viral vectors overcoming the challenges of local and systemic viral gene therapies. Further, I will discuss the potential application of this novel gene vector for high and continuous intratumoral activity of biologics. This approach of paracrine delivery of therapeutics could fulfil the enormous potential of biologically active therapeutics that are currently limited by high systemic toxicities.

Date & time: Wednesday, March 28, 2018 at 04:00 pm
Location: Lecture Hall Y03-G-95, UZH Irchel

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