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Cover Story

Small molecule inhibitors to manipulate adenovirus gene transfer

The ultimate success of gene therapy relies on suitable delivery systems. In a time when gene therapy is being implemented with promising results in the clinic, efforts to improve the safety and efficacy of the vectors are imperative. Due to the safety concerns associated with using viral vectors, many non-viral gene delivery systems have been developed with acceptable efficacy. The non-viral delivery systems, however, are still not able to match the capability of viral vectors. Advances in vector design and novel strategies to improve therapeutic outcomes are closely linked to our growing knowledge of virus biology. Adenoviruses (Ad) in particular are of great interest in the gene therapy setting. Naturally, the flurry of studies aimed at understanding their complex *in vivo* infectivity profile has resulted in some major developments in the field. Coagulation factor X (FX) has been at the center of several of these studies and has been found to be a key factor in determining Ad tropism, immune recognition and evasion [1–4].

In this issue, Duffy and co-workers present their work focusing on the development of a high throughput screening assay and its use to identify small molecules capable of interfering with Ad transduction [5]. Realizing the important role of FX, they hypothesized that finding an inhibitor of Ad gene transfer in the presence of the coagulation factor would be of significant value in the *in vivo* setting—in particular to reduce or limit the profound liver gene transfer observed when adenovirus vectors are injected into the bloodstream. To test this, a robust fluorescent cell-based screen of a diverse array of pharmacological compounds was designed and effectively implemented. The development of the screen itself may be a valuable research tool. It is flexible to manipulate the general virus infection processes which consist of a complex range of distinct biological steps. After multiple rounds of *in vitro* screening, several small molecules were successfully identified that blocked Ad-mediated transduction; both *via* the classical CAR-mediated and critical FX-mediated infection pathways. It was interesting to note that the three most promising small molecule "hits" blocking Ad transduction shared similar chemical characteristics. Such information led the team to develop a pharmacophore model and investigate the most important chemical features of the hits. The subsequent testing of related compound libraries identified more potent hits. The properties of the small molecules can be improved through this iteration process.

The mechanism of action of the compounds was found to block efficient intracellular virus transport, and the data indicated that the compounds act independently of FX. While more studies are required to provide further insight into the precise mode of action, the study clearly demonstrated that small molecules are capable of preventing Ad transduction. The presence of two hit compounds substantially reduced transgene expression after subjecting mice to a high dose of virus *via* intravenous injection. The work by Duffy et al. offers an important proof-of-concept study and a tool that underpins future endeavors utilizing small molecules to manipulate Ad biology in gene therapy applications. If Ad vectors, and any viral vectors, can be used with enhanced safety without unexpected side effects, it will certainly make gene therapy safer and more practical. We look forward to the days when gene therapy becomes a routine process for clinical applications.

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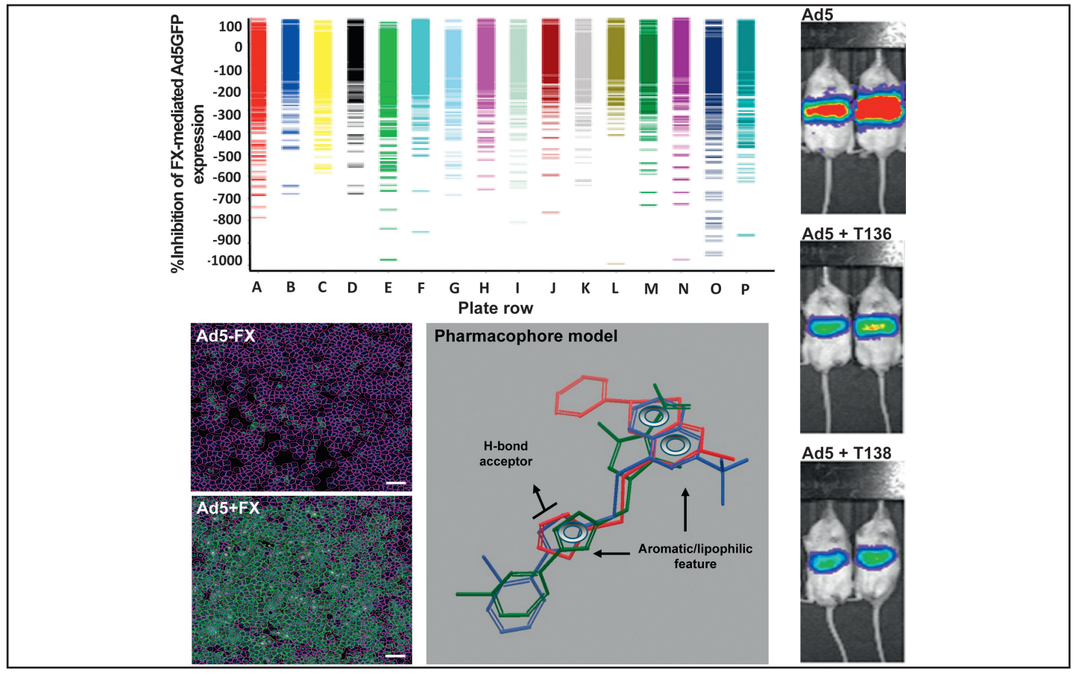

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