molecular pharmaceutics

editorial

Viruses in Pharmaceutical Research: Swiss Army Knives for the Prevention and Treatment of Disease

Viruses encompass a broad category of infectious agents and are able to infect all organisms on earth. The biomedical research community has capitalized on this versatility, using viruses for a wide range of pharmaceutical applications. Their use as vaccines is probably most widely known and certainly has the longest therapeutic history, but these days virus-based technology provides the foundation for a diverse number of scientific applications: ranging from gene therapy vectors to the building blocks of novel nanomaterials. This special issue aims to highlight the current state of the art of several pharmaceutical applications of viruses.

Traditionally, noninfectious "weakened" viruses have been used to prevent a variety of infectious diseases by eliciting an immune response that could immediately clear the "real" disease-causing virus upon infection. Matthews reviews a different take on this paradigm: she describes how one could use adenovirus to present antigens (of any virus, or nonvirus for that matter) to the immune system, by incorporating these antigens on the surface of the adenoviral capsid. This strategy results in the production of high levels of neutralizing antibodies, which are not always induced upon vaccination with the "original" pathogenic virus. This expands the number of infectious diseases that can be prevented using vaccination, including diseases for which there currently are no vaccines available.

In addition to using vaccines for the prevention of infectious diseases, one could envision activation of the immune system to clear tumor cells for the treatment of cancer. To make this a success, one would have to ensure a sufficient immune response against nonimmunogenic antigens. This is usually achieved by a "prime-boost" strategy, where the immune system is first "primed" to recognize an antigen, followed by a secondary "boost" to ramp up the immune response. Daemen et al. investigated a "heterologous" prime-boost immunization strategy, where different platforms are used for the prime and boost, to increase the cellular immune responses observed with single immunization or "homologous" prime-boost protocols. To that end, they used Semliki Forest virus genetically encoding the antigen, followed by influenza virus-derived virosomes loaded with the antigen protein. Interestingly, although antigen-specific lymphocytes were indeed present in larger numbers using the heterologous strategy, antitumor efficacy in a mouse model was not improved. This illustrates that we should not forget the ultimate therapeutic goal of immunizations—whether it is an antitumor effect or the prevention of an infectious disease—and not lose focus by only paying attention to surrogate markers of efficacy.

In addition to their use as vaccines, the lytic biology of some viruses lends itself toward particular therapeutic end points. This is most notable in the oncology arena. This issue highlights two different viruses that are rendered "conditionally replicative" for tumor cells, meaning they only infect and replicate in malignant cells. Since productive infection with these viruses results in cell lysis, tumor cells will be killed, leaving healthy tissue unharmed. Pesonen et al. review the development and use of oncolytic adenoviruses for the treatment of cancer. Much progress has been made in this area over the past decade or so, with many differently engineered variants of adenovirus currently in clinical trials. Of note, many cancer patients receive glucocorticoids to mitigate tumor-associated symptoms, leading to concerns about administering viruses in these immune-suppressed patients. Rajecki et al. authored an original article describing the safety of concomitant glucocorticoid treatment with oncolytic adenoviral vectors.

Another oncolytic virus currently being evaluated in the clinic is herpes simplex virus (HSV). Parker et al. describe methods to rapidly construct novel HSV1-based vectors

10.1021/mp100428c
Published on Web 02/07/2011

containing foreign genes that may aid in antitumor efficacy. If new therapeutic genes or combinations of genes can be tested more rapidly for their effect on HSV1's therapeutic potential, the most promising candidates can be advanced to human application at a more rapid pace.

In addition to their use as oncolytic agents, viruses are also being used in gene therapy schemas as carriers of genetic material that encode therapeutic proteins able to treat disease. Although less advanced clinically than oncolytic viruses, gene therapy remains an attractive and elegant therapeutic approach for many pathological conditions. As an example, Reynolds describes the use of adenovirus as a gene therapy vector for the treatment of pulmonary vascular disease by expressing bone morphogenetic protein receptor 2, since reduced expression of this protein is linked to initiation and progression of pulmonary arterial hypertension.

For both oncolytic and gene therapy applications of adenovirus, one of the main problems is the natural liver tropism of the virus upon administration into the bloodstream. Haisma and Bellu review the mechanisms of liver uptake, and describe several strategies to mitigate this phenomenon.

Another big hurdle for adenovirus-based therapies, in addition to its liver tropism, is its immunogenicity. Although this is capitalized on in the vaccination strategies described earlier, an immune response to either an oncolytic virus or a virus used a as a gene therapy vector will blunt the therapeutic efficacy of such viruses because they will be cleared by the immune system before having executed their therapeutic effect. One strategy to ameliorate this immune response is to attach polyethylene glycol (PEG) to the virus's surface, thereby reducing production of inflammatory mediators without affecting viral uptake in target cells. This same procedure also reduces toxicity of the vectors, at least in mice. However, little is known to what extent these effects would hold up in humans. Since nonhuman primates are the closest we can get to the human situation, Wonganan et al. examined the effects on PEGylation of adenovirus-based gene therapy vectors in baboons, compared to mice. There were some notable differences between the two species; this reiterates that translation from the mouse to the human is not a straightforward path.

Finally, a more recent application of viruses is in their use as templates for nanomaterials—their symmetry and reproducible size lend them to be excellent building blocks for these kinds of systems. Although there are several examples of such virus-based structures in electronics and engineering, their use as components of multifunctional systems for the imaging and treatment of disease is of particular interest to this special issue. Pokorski and Steinmetz review the approaches to building such multifunctional systems, by coupling targeting, imaging and therapeutic moieties to virus-based nanoparticles.

In the aggregate, there has been incredible progress in the use of viruses in pharmaceutical research in the last few decades; whether they are used for novel vaccine strategies, as oncolytic agents, gene delivery vehicles, or serve as the basis of new multifunctional systems, their use is endless. To paraphrase from Pokorski and Steinmetz's review: the potential applications of viruses are limited only by the imagination—they truly are the Swiss Army knives of disease prevention and treatment.

Maaike Everts

Guest Editor
Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama 35294, United States
E-mail: maaike@uab.edu

MP100428C