Expert Opinion

Delivery of biologicals: the wish list is long...

Daan JA Crommelin
Faculty of Pharmaceutical Sciences, Utrecht University, Sorbonnelaan 16, 3584 CA Utrecht, The Netherlands

In this editorial, a wish list is drawn up for future research and development activities regarding biologicals.

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1. Delivery of biologicals: the wish list is long...

An increasing number of drugs are obtained through recombinant DNA technology or hybridoma technology. The market share of these 'so-called biologicals' is increasing steadily and rapidly [1,2]. Over the last few years the 'family' of mAbs has caused breakthroughs in the treatment of autoimmune diseases and cancer. In addition, IFNs form an essential part of the therapeutic arsenal used in multiple sclerosis patients and in fighting viral diseases. What binds these molecules, apart from the fact that they are proteins and produced by biotechnological means? This category of drugs is special; biologicals share a number of characteristics that need further attention from those of us who are involved in drug formulation research and development in academia and in the industry. This editorial discusses the challenges specifically related to the delivery of biologicals.

1.1 Route of administration

Traditionally, proteins are administered by the parenteral route. Oral administration results in unacceptably low bioavailabilities, because of protease and peptidase activity in the gastrointestinal tract and the intrinsically low cell membrane permeability of therapeutic proteins. Over the last 20 years many reports on efforts to break the 'stick to the needle' routine have been published. The dermal, nasal, pulmonary, oral and rectal routes have been tested. New excipients have been tried to enhance uptake; without much success. Only the pulmonary route may offer potential. However, at the present time, the bioavailability in pulmonary tests with the best studied protein, insulin, is ~ 10%. Therefore, there is still a lot of room to improve performance following pulmonary administration. Strategies to achieve that goal focus on perfecting inhaling technologies in combination with enhancing permeation characteristics of the protein by using effective and, above all, safe, permeation enhancers.

Interestingly, the fate of proteins following intramuscular or subcutaneous administration is rather obscure. At present, subcutaneous injection is the preferred route as the patients can administer the drug themselves. But what happens following injection? The bioavailability is lower after subcutaneous administration than after intravenous administration, and uptake is delayed. What protease activity causes loss of active protein? The lymphatic route plays an important role in transport of larger proteins away from the site of injection. What cells and tissues does the protein encounter and what is the effect of these interactions on the activity and safety profile of the protein drug? There are many questions, but few answers.

1.2 Formulation challenges

Pharmaceutical proteins are administered by the parenteral route. Traditionally, many of the injectables were available as (freeze) dried products. Today, however, one can observe a successful trend to bring aqueous protein solutions to the market. This means the introduction of new stabilising strategies with a rational choice of the excipients. Some proteins, such as IFNs, are dosed in µg doses. The chosen formulation should ensure full availability of the (expensive) protein to the patient. This implies the use of anti-adsorbents. On the other hand, some mAbs are dosed in hundreds of mg. In this case, solubility enhancing conditions may be required. New excipients for solubility enhancement, to avoid adsorption, or improve (freeze) drying processes and products, are in great need. The introduction of new excipients for parenterals requires major investments and takes time. For example, after years of study, the excipient trehalose was recently introduced in a mAb formulation as an alternative to presently used lyoprotectants such as sucrose. Our arsenal of accepted excipients, such as antioxidants, lyoprotectant, preservatives, solubilisers and antiadsorbents, is small and actually getting smaller as safety issues discourage the use of some of the 'old guard' excipients (e.g., mercury-containing preservatives). There is definitely a need for new excipients as experience teaches us: there is no such a thing as 'one size fits all'.

An area where industry has been quite active over the past few years is the need for improving patient friendliness of injectables. The pen-injectors are examples of successful efforts. State-of-the-art needle-free injection systems or injection systems based on microneedles for individual human use are now under investigation. Clearly, there is a need for such patient friendly injection systems.

1.3 Analytical toolbox

Proteins are complex molecules. Both during manufacturing, storage and handling, and *in vivo*, their behaviour depends on their primary, secondary, tertiary and, if applicable, quaternary structure. Our analytical toolbox with, for example, spectroscopic, chromatographic, electrophoretic and calorimetric approaches, and our bioassays, provide insight in the structure, some in great detail. However, at present, even a smart selection of analytical techniques from the toolbox will not be able to fully characterise larger protein molecules, as their specific structure is difficult to catch. Moreover, therapeutic proteins often are heterogeneous and occur in different isoforms, which makes full characterisation even more challenging. In conclusion, the analytical toolbox has changed over recent years. Mass spectrometry has developed into a powerful tool and developments in capillary electrophoresis, ultracentrifugation and field flow fractionation, just to mention a few, have also contributed to a better understanding of protein structures. However, the wish list is still long.

1.4 First/second generation/controlled release

More than 20 years ago insulin was introduced onto the market as the first recombinant human DNA protein. Most therapeutic proteins to follow were endogenous proteins produced via biotechnological means. Endogenous does not, however, mean safe and effective. The physiological action of endogenous proteins, such as insulin, tissue plasminogen activator and IFNs, is different from the injected 'therapeutic' versions of these molecules. For instance, insulin is secreted by the islands of Langerhans in the pancreas and passes the liver first on its way to the general circulation. This is not the case following intramuscular or subcutaneous injection and there is therefore dissimilarity between the action of insulin under physiological conditions and insulin as a 'replacement drug'.

Many therapeutic proteins have a short half-life, which causes short dosing intervals. Considering the inconvenience of frequent injecting to the patient, longer dosing intervals would be highly desirable. Second-generation therapeutic proteins have now been launched. In order to increase the dosing interval for IFN-α, the IFN glycoprotein chain is coupled to polyethylene glycol. Pegylated IFN-α has a strongly prolonged circulation half-life, allowing less frequent injections with at least similar therapeutic effects. For erythropoietin, a longer circulating version was developed by adding carbohydrate side chains to the original, endogenous erythropoietin. These are examples of a list that is growing rapidly. As changing the molecule usually affects the intrinsic activity of the protein, controlled-release systems are also now under development. Here the original, endogenous molecule is formulated in the delivery system. There is definitely a need for better delivery systems than the present generation of polylactic glycolic acid-based systems.

mAbs form a special group. The first therapeutic mAbs were murine antibodies. The induction of human antimouse antibodies during treatment limited the therapeutic potential of these antibodies. Later, chimeric, and subsequently humanised, antibodies entered the market. They showed a considerable advantage in being less immunogenic. The first fully human antibody, adalimumab (Humira®, Abbott Laboratories), has now entered the market. Another strategy is to reduce the size of the mAbs, using Fab′ fragments (going from 150 to 50 kDa) or even smaller molecules, creating single-chain antibodies (25 kDa). The full therapeutic potential of these new technologies is yet to be established.

1.5 Immunogenicity

Large molecules of protein nature tend to be immunogenic and antibodies are generated against the injected protein on prolonged administration. However, the mechanism behind this immune response is not well understood. Schellekens [3] mentions typical pharmaceutical issues, such as manufacturing, formulation and handling, as possible causes for induction of immune responses. This issue will definitely be a leading point in developing next generations of therapeutic proteins and formulations. Better insight into the mechanisms

behind immunogenicity and approaches to prevent immunogenicity of therapeutic proteins are essential for the successful further development of this field.

1.6 Handling

Proper handling of therapeutic proteins by the manufacturer, transporters, pharmaceutical and medical staff, and finally the patient, is a highly underestimated and underrated part of the sequence that must lead to the success of therapeutic proteins. Horror stories about heating protein formulations in magnetron ovens, or leaving the boxes on loading docks in the burning sun, are exemplary of the lack of understanding of handling these delicate (and expensive) molecules, from the production cell bank to the moment of injection [4]. Initiatives to fill this knowledge gap should have a high priority.

2. Expert opinion

Biologicals have become an increasingly important factor in our arsenal of drugs. One should realise that they are special as they are different from low-molecular-weight products in many ways. As previously mentioned, the wish list regarding the delivery of these products is long and in many cases basic insights are lacking. These need to be generated before substantial progress can be made. In other cases, basic handling knowledge is available and it is a question of dissemination of information and education.

I hope, and trust, that *'Expert Opinion on Drug Delivery'* will provide the proper platform for discussion and dissemination of knowledge to shorten my wish list on the delivery of biologicals.

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Affiliation

Prof. Dr Daan JA Crommelin[†1,2,3]
[†]Address for correspondence
[†1]Professor of Pharmaceutics, Dean of the Faculty of Pharmaceutical Sciences, Utrecht University, Sorbonnelaan 16, 3584 CA Utrecht, The Netherlands
Tel: +31 30 2536973/7306;
Fax: +31 30 2517839;
E-mail: d.j.a.crommelin@pharm.uu.nl
[2]PO Box 80.082, 3508 TB Utrecht, The Netherlands
[3]CSO of OctoPlus, Zernikedreef 12, 2333 CL Leiden, The Netherlands