

Progress in gene therapy

— are hospital pharmacies the next barrier?

By Julie Simpson, MRPharmS

As clinical trials of gene therapy products become more prevalent in the UK, hospital pharmacy staff are increasingly being asked to handle and aseptically manipulate the genetically modified viruses used to deliver therapeutic genes to cells — viral vectors. This, however, is proving to be something of a “stumbling block”, with many hospital pharmacy departments proving unable to rise to this challenge for a variety of reasons.

Facilities

A lack of facilities clearly impedes the ability of staff in hospital pharmacy departments to provide a gene therapy service. Current guidance for the handling of viral vectors in hospital pharmacies states that a negative pressure isolator or class 2 microbiological safety cabinet should be used to protect the operator and that the room should be positive in pressure to protect the product. Isolators, cabinets and rooms should be used only for the handling of gene therapy agents.¹ Even though gene therapy clinical trials are becoming more commonplace, dedicating facilities to gene therapy in this way is likely to mean that they are used less than if they were dedicated to, for example, chemotherapy production, or available for general aseptic (including clinical trial product) use. In an NHS environment where space (as well as time) is money, it is

not difficult to see why the provision of facilities for viral vector manipulation might not be greeted with a great deal of enthusiasm by, for example, trust accountants and board members.

Guidance

For those units that carry out a lot of gene therapy work, issues such as a lack of specific guidance predominate. Although guidelines for the handling of viral vectors for gene therapy in hospital pharmacies have been published,¹ they do not cover all of the issues that hospital pharmacists face when asked to participate in gene therapy trials. For example, how to manipulate different viral vectors in the same facility on a sessional basis has still to be addressed. This is a key issue for pharmacy staff at hospitals involved in more than one gene therapy clinical trial at a time.

Before any work involving gene therapy viral vectors is started, a risk assessment needs to be carried out to classify all activities into one of four classes (“class 1”, involving the least level of risk to human health and the environment, through to “class 4”, involving the most risk). It seems likely, but not clear, that with sufficient cleaning protocols in place, it might be deemed safe to handle a class 1 viral vector in the same facilities as a class 2 vector. (It is unlikely that class 3 or 4 vectors will be used in clinical trials and at present, there are no such clinical trials in the UK.)

What is particularly pressing is whether a viral vector (of whichever class) directed against cancer cells can be handled in the same facility as a viral vector directed at other diseases such as

those of the vascular system or nervous system. Should we follow the example of traditional aseptic hospital work and segregate vectors according to whether they are cytotoxic or non-cytotoxic? These are issues of increasing importance as more gene therapy clinical trials target diseases other than cancer.

As well as being classified by risk, viral vectors may be categorised as replication-deficient or replication-competent. Many ongoing gene therapy clinical trials directed against cancer are conducted with replication-deficient adenovirus vectors, but more recently oncolytic virotherapy with replication-competent viruses has emerged as an attractive therapeutic strategy. Tumour-selective oncolytic viruses are intended to replicate, propagate and spread exclusively in tumour cells, leading to their destruction, while not affecting normal cells. The use of such replication-competent vectors raises the further question of whether the aseptic processing of replication-competent viruses should be segregated from that of replication-deficient viruses.

Solutions

We have developed local guidance, incorporating official guidance where it is available. We have dispensed one viral vector at a time in a dedicated negative pressure isolator using a validated clean-down procedure between each viral vector. To minimise contamination and risk, if dispensed in the same working session, replication-deficient vectors are always prepared before replication-competent vectors, independent of their

safety classification, but generally class 1 vectors are dispensed before class 2 vectors. All dispensing procedures are subject to risk assessment for the individual viral vector. We have also been fortunate to have access to viral detection assays which are not readily available to most hospital pharmacy departments for validating, dispensing and clean-down procedures.

In the future, it may well be that clinical trial sponsors will develop gene therapy viral vectors in formulations that do not require aseptic manipulation — for example, prefilled syringes and lyophilised powders for reconstitution. Future gene therapy vectors might also be non-viral in nature, therefore avoiding the need for dedicated pharmacy facilities and compliance with genetically modified organism regulations. In the meantime, it is clear that the first licensed gene therapy products to the clinic are going to be viral vectors and that pharmacy departments will need to be prepared to handle such products.

Despite some successes, the efficient transfer of genes into the host remains the biggest challenge. It would be a shame if this barrier were to be overcome by scientific research and development, only for a lack of funds, facilities and know-how in hospital pharmacies to halt clinical trials and other progress in the gene therapy field.

References

1. Beaney AM. Quality assurance of aseptic preparation services. 4th edition. Appendix 6. Gene therapy. London: The Pharmaceutical Press; 2006.

Julie Simpson is gene therapy pharmacist at the Cancer Research UK Clinical Trials Unit, University of Birmingham