

ABOUT PER.C6[®] TECHNOLOGY

July 2009

Manufacturing of biopharmaceuticals is subject to many changes, such as rising volume demands and more stringent safety requirements. These conditions challenge conventional manufacturing platforms, which have not adapted sufficiently to address these changes. Crucell's PER.C6[®] production cell line is designed to meet these demands. It is an established production technology ideally suited for the development and large-scale manufacturing of a wide range of biologics including vaccines, antibodies, therapeutic proteins and gene therapy products.

**What is PER.C6[®]?**

PER.C6[®] is a human designer cell line for the development and large-scale manufacturing of biopharma products. In areas where Crucell does not aim to develop its own products, we license the technology to the biopharmaceutical industry. Currently over 75 companies and organizations have selected our PER.C6[®] technology to develop their own products across a wide range of therapeutic areas.

PER.C6[®] adaptable

Manufacturing of biopharmaceuticals has to take account of rapidly changing factors, such as rising volume demands and more stringent safety requirements. These shifts are a major challenge to conventional manufacturing platforms that have not adapted or become sufficiently flexible to cope with such changes. Our PER.C6[®] production cell line, however, is designed to meet these demands.

PER.C6[®] well protected

Our PER.C6[®] technology is protected by numerous patents. In addition, in order to benefit from our proprietary technology, potential customers not only need our know-how, but also our PER.C6[®] cells, which are only available from us under agreement. These agreements put certain restrictions on further dissemination and use of the PER.C6[®] cells. This combination of protections – patented know-how and the need to have access to the actual PER.C6[®] cells results in the PER.C6[®] technology being the best protected human cell technology in the world.

PER.C6[®] for protein and antibody production

We have collaboration with DSM Biologics for the application of PER.C6[®] for proteins and antibodies. Together with DSM we license PER.C6[®] for proteins and antibodies as well as invest in further innovation of PER.C6[®].

Working alongside DSM Biologics on the PER.C6[®] manufacturing platform, we believe that there is tremendous potential to reduce the production costs of monoclonal antibodies, whilst increasing yield resulting in more affordable treatments for patients.

In June 2008, we jointly announced that we had achieved a record-level titer of 27 grams per liter at harvest for an antibody product using PER.C6[®] at our PERCIVIA joint venture development center in Massachusetts, the USA.

Applications

Vaccine Production

Many of today's vaccines are produced on animal-derived substrates, including fertilized chicken eggs and mouse brains. To overcome limitations in production capacity, processing time, and safety risks associated with the use of animal-derived substrates, Crucell's PER.C6[®] technology is an attractive alternative production technology. PER.C6[®] technology supports the growth of a wide variety of human disease-causing viruses that can subsequently be processed into vaccines. It can be used for the manufacturing of inactivated whole virus, live-attenuated, live-vector, split and subunit vaccines. PER.C6[®] technology also allows for efficient production of recombinant vaccines.

Antibody and Therapeutic Protein Production

Crucell's PER.C6[®] technology is a reliable, safe and scalable technology for the production of monoclonal antibodies and recombinant proteins. In December 2002, Crucell formed an alliance with DSM Biologics to expand manufacturing services for therapeutic proteins and monoclonal antibodies. This alliance offers the total package in bio-manufacturing from cell line generation and the establishment of cell banks to large-scale manufacturing.

Gene Therapy Production

Gene therapy is one of the most promising technologies of modern medicine. The most commonly used vector in gene therapy is the adenoviral vector, but its clinical use has thus far been hampered by the potential generation of unwanted replication-competent adenoviruses (RCA) during the production process. PER.C6[®] technology eliminates this problem, as it does not produce RCA due to homologous recombination, making it the platform of choice for the large-scale production of clinical-grade adenoviral vectors. The two companies have since formed a PERCIVIA Development Center in Cambridge Massachusetts specializing in further development of the cell line for the expression of recombinant pharmaceutical products.

Product Pipeline

Many of Crucell's pipeline products are based on its PER.C6[®] technology. These include:

- Ebola vaccine
- Influenza vaccine
- Malaria vaccine
- Tuberculosis vaccine
- Rabies antibody combination

Licensees

In areas where Crucell does not aim to develop its own products, the company licenses its PER.C6[®] technology to the biopharmaceutical industry. Numerous biopharmaceutical companies and organizations have selected Crucell's PER.C6[®] technology to develop their own products across a wide range of therapeutic areas. Several of these products are in various stages of clinical development.

Licensees include:

Vaccines

Vaxin
Merck & Co.
sanofi pasteur
Tibotec (J&J)
Harvard School of Medicine
Okairos
Novartis
Transgene

Proteins/Antibodies

GSK
MorphoSys
Talecris Biotherapeutics
Medarex
Daiichi Sankyo
MedImmune
CSL
Invitrogen Corporation

Gene Therapy

Ark Therapeutics
Merck & Co.
Transgene
TapImmune
Vascular Biogenics
Elm Biotech
NeoTropix