NRC·CNRC

INCREASED VIRAL PRODUCTION

Licensing opportunity L-12392

HIGHLIGHTS

Viruses are often used with mammalian cell culture systems as live factories for the production of biologics such as recombinant proteins and vaccines. A common example is the use of human embryonic kidney (HEK293) cells to produce adenovirus that expresses the gene of interest. The use of expression systems provides flexibility in determining the conditions under which virus production can be optimized.

The NRC has developed a simple, cost-effective and scalable method suitable for both research and commercial scale production that enhances adenovirus production by applying osmotic stress to host HEK293 cells.

TECHNOLOGY TRANSFER

- A commercial exploitation licence for the technology
- Development of this technology through a joint collaboration or service

MARKET APPLICATIONS

The technology can increase production of:

- Adenoviruses
- Non-budding viruses (e.g. adeno-associated virus, reovirus)
- Budding viruses (e.g. retrovirus, lentivirus, baculovirus)
- It can be used with the following expression systems:
- Human embryonic kidney 293 (HEK293) cells
- Other mammalian cells (e.g. A549, CHO, Hela)
- Insect cells (Sf9)

HOW IT WORKS

Since virus production in cell culture systems occurs in two sequential phases, the growth and production phases, the NRC examined the effect of hyperosmotic stress on cellular physiology and adenovirus production in HEK293 cells during each phase. The selective effects of hyperosmotic stress on cells at different stages of the *in vitro* viral production process were identified, and a simple and effective method was developed to increase viral yields.

Adenovirus productivity in HEK293 cells can be increased 2-3 fold and as high as 11 fold by inducing hyperosmotic stress during the growth phase and subsequently infecting the cells under less stressful osmotic conditions. Hyperosmotic stress can be achieved simply by addition of low-cost media supplements such as salts (e.g. NaCl, KCl, KNO^3), sugars (e.g. sucrose, glucose, fructose) or other chemicals. Optimal conditioning of the cells during the growth phase can be achieved rapidly (within 3 passages, 1 week).

Subsequent dilution or changing the media back to lower osmolarities results in enhanced virus yields. Priming of the cultures in the growth phase can be reversed by switching back to standard media, which allows for maximum flexibility. The method has been tested in bioreactor production runs of up to 20L. When coupled with NRC proprietary HEK293 expression systems, this technology can be a cost-efficient way of further enhancing virus production.

BENEFITS

- Increase viral yields from mammalian cell expression systems by 2-3 fold, up to 11 fold
- Rapid, simple, and flexible method compatible with several commercially available media formulations (5 media tested)
- Application of hyperosmotic stress is reversable, providing flexibility during different cycles
- Scalable for use in bioreactors for commercial production purposes

Please note: In the 1970s, Dr. Frank Graham developed the HEK293 cell line, which is now widely used for academic research and in the pharmaceutical and biotechnology industries around the world. The NRC has developed proprietary versions of the HEK293 cell line, referred to as HEK293SF-3F6 and HEK293-6E.

PATENTS

NRC file 12392: Patent issued in the United States; pending in Canada.

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