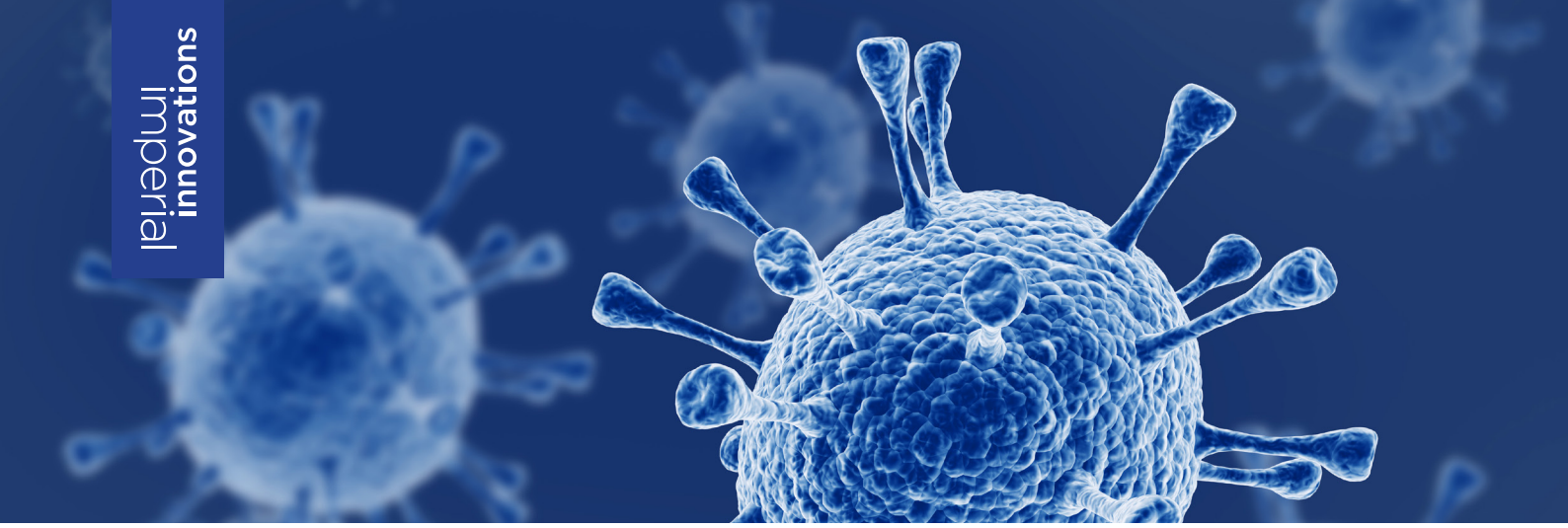

Novel large-scale method of production of AAVs

And other viral delivery vectors

Summary

The present invention relates to a novel viral delivery vector with scope for more cost-effective commercial production over existing technologies. The platform comprises a phagemid hybrid with recombinant adeno-associated virus (AAV) components.

Background

Clinical translation of adeno-associated virus (AAV) and recombinant AAV (rAAV)-mediated gene therapy has been held back by a vector production bottleneck. AAVs are non-enveloped viruses with a 4.7Kb wild type genome flanked by inverted terminal repeats (ITRs). AAV production into icosahedral virions relies on two genes, rep and cap, which provide the proteins necessary for replication and encapsidation of the viral genome, in addition to adeno-helper proteins usually provided by an external source.

At present, laboratory scale production of rAAV uses DNA transfection to introduce the required genetic elements in to human embryonic kidney HEK293 cells. However, transfection methods are not appropriate for large-scale production due to major limitations in efficiency, yields and costs. Additionally, live viruses such as adenovirus or herpes simplex virus are often used to supply the adeno-helper functions, which present significant health and safety concerns for in vivo use.

Alternative methods such as baculovirus expression vectors (BEVS) with Sf9 insect cell system are possible but face similar issues in terms of costs and safety.

Technology

The present invention provides a hybrid vector system comprising a phagemid/AAV (PAAV) particle. The novel genome construct is a phagemid, in this case a hybrid of a phage-derived genome and rAAV transgenes. Two origins of replication are present, one phage and one bacterial. This hybrid differentiates from conventional phagemids in that viral transgenes, rather than generic non-viral components, are incorporated into the phagemid under the influence of the bacterial promotor.

This novel hybrid contains no structural bacteriophage genes, which comprise over 50% of a conventional phage genome. Thus,

Quick Info

Benefits

- Novel viral delivery platform scalable to large-scale commercial production.
- Increased efficiency of production, efficacy, yield, purity and safety over existing technologies.
- Reduced size of phagemid allowing scope for incorporating many or large transgenes into one phagemid particle.

Monika Kraszewska-Hamilton
Healthcare Licensing Executive
e: monika.hamilton@imperialinnovations.co.uk
t: +44 (0)20 3053 8823

Technology reference number: 6794

this phagemid particle is dramatically smaller in size than previously developed hybrid constructs. This smaller genome allows for increased efficiency of vector production, flexibility of the vector system and increased efficacy in gene transduction.

As the phagemid advantageously does not include any structural elements, a “helper” vector is required for capsid formation. The bacteriophage promotor (e.g. F1 ori) of the phagemid is upstream of a packaging signal, which enables replication of the vector into ssDNA while persisting inside a prokaryotic culturing host. A separate “helper” vector encoding phage structural proteins extrudes the phagemid from the prokaryotic host. Thus, a chimera of a replication-deficient viral genome packaged inside a bacteriophage is formed. Alternatively, the “helper” vector may encode viral vector structural proteins.

This system provides further advantages in enhanced gene transfer, production yield, biodistribution and evasion from eukaryotic cellular barriers over existing technologies. Another significant consequence of using the smaller phagemid particles of the invention is that they have the ability to accommodate extremely large and numerous transgene cassettes or gene inserts, such as all the genes for recombinant virus (e.g. rAAV). Hence, by combining the genetic components for viral production into a single or multiple phagemid vector(s), an efficient commercial-scale virus-producing gene delivery system has been designed.

Applications

The present invention finds use in commercial-scale production of viral delivery vectors suitable for gene therapy.

Value proposition

The global viral vector and plasmid DNA manufacturing market accounted for $261 million in 2016 and is expected to reach $1090 million by 2023, registering a CAGR of 22.6% from 2017 to 2023 (Allied Market Research).

Team

Professor Amin Hajitou is a Reader in Neuroinflammation and Neurodegeneration in the Faculty of Medicine of Imperial College London.

Paladd Asavarut is a doctoral researcher in Prof Hajitou’s group in the Faculty of Medicine of Imperial College London.

Teerapong Yata was a postgraduate researcher in Prof Hajitou’s group in the Faculty of Medicine of Imperial College London.

Intellectual Property

This technology is subject of international patent application WO2017077275.

IMPERIAL INNOVATIONS

London Office
52 Princes Gate,
Exhibition Road,
London, SW7 2PG

Tel: +44 (0)20 3053 8850

Email: info@imperialinnovations.co.uk

Web: www.imperialinnovations.co.uk