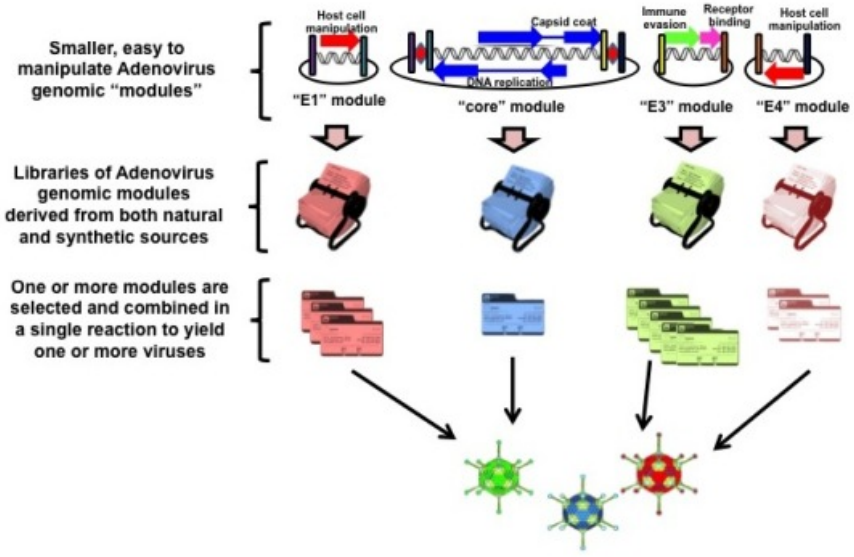
Modular Adenovirus Assembly Platform

INVENTION: Adenoviral vectors are regularly used for the delivery of exogenous DNA to mammalian cells for foundational research, vaccines, and gene therapy. Unfortunately, the potential of these vectors in these applications is hampered by the inability to manipulate the viral genome in a rapid and systematic manner, and limited by which serotypes can be used which in turn limits the type of host cell and systemic applications of same. In reality, there are hundreds of adenoviruses, each with unique and specialized capabilities allowing for the infection and replication in different host environments.

Researchers at Salk have developed a novel platform for the rapid assembly of adenoviral vectors from libraries of component parts. The adenoviral genome also has a natural modular structure that can be exploited for synthetic biology as it can be divided into four modules based on evolutionary conserved sequences and functions. Different combinations of the genomic modules derived from both synthetic and natural sources can be created using multi-site in vitro recombination, resulting in recombinant viruses with desired properties, including targeting specific cell types or tissue, evasion of the host immune system or triggering a particular immune response, and expression of exogenous proteins, such as pro-drug converting enzymes. In addition, multiple protein complexes and entire pathways can be assembled, delivered, and co-expressed via adenoviral infection. This technology overcomes many of the challenges associated with the generation of novel adenoviral genomes, and is a promising new tool for the development of novel research reagents, diagnostics, and therapeutics.



APPLICATIONS:

- Functional virology
- Vaccine development
- Development of targeted therapies
- Development of oncolytic and gene delivery therapies
- In vivo and in vitro expression in cell types and tissues that are usually difficult to transduce

ADVANTAGES:

- Ability to manipulate the 36 kb viral genome rapidly and systematically
- Library-based
- Can target nearly any cell or tissue type
- Ability to combine parts of viral genomes from various serotype
- Can generate human/mouse chimeras for use in genetically engineered mouse models of cancer

- Can generate novel adenoviruses that can evade neutralizing antibodies
- Efficient expression and delivery of multi-protein complexes and entire pathways
- Allows for generation of replication-defective or replication-competent viruses

STAGE OF DEVELOPMENT: Salk researchers have generated viruses that specifically target cancer cells defective for p53 or Rb. These viruses were able to infect, replicate, and kill cancer cells without deleterious effects on normal cells.

BACKGROUND: There are well over fifty human adenoviruses and hundreds that infect other species from fish to humans. Each of these viruses has unique capabilities for tissue targeting and replication, immune evasion, and host cell manipulation. As DNA viruses, they do not integrate into host DNA, can be produced to high titers using established GMP protocols, and have demonstrated safety in human gene therapy and oncolytic virus therapy. This new platform technology unlocks the natural power of thousands of years of evolution by creating a modular, rapid and systematic assembly method, thus allowing for the creation of thousands of novel recombinant adenoviral vectors for a myriad of uses.

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PATENT STATUS: U.S. Patent 9,217,160 and PCT application WO2014/153204 is pending

PUBLICATIONS: Ou, et al. 2012. A structural basis for the assembly and functions of a viral polymer that inactivates multiple tumor suppressors. Cell, 151:304-19.

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