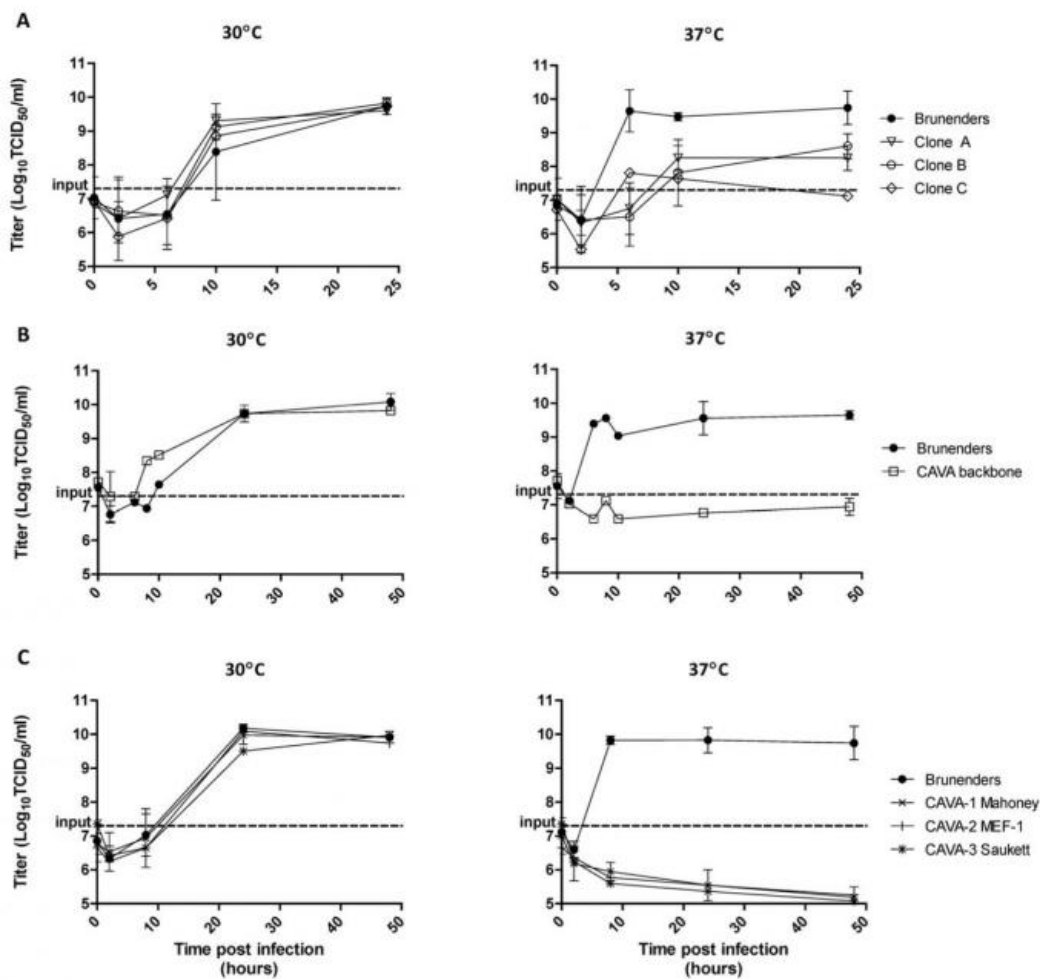


Using cold adaptation to produce safe inactivated polio vaccine candidates

August 24 2016, by Rashmi Gupta



Replication kinetics of different poliovirus strains at 30 and 37°C. From <http://dx.doi.org/10.1371/journal.ppat.1005483>.

Poliomyelitis, or polio, is a debilitating childhood disease caused by poliovirus. It has been eliminated from most parts of the world thanks to the extensive use of polio vaccines. However, there are concerns that current vaccines could lead to the reemergence of poliovirus in a polio-free world. It is important to safeguard this eradication by developing safer and more effective strains of polio for use in future vaccine preparations. Earlier this year, *PLOS Pathogens* published a study in which the authors used cold-adapted virus attenuation (CAVA) to develop temperature-sensitive poliovirus strains, which can be used to produce the next generation of vaccines. While CAVA has been used for other vaccines, it has not been used as a successful tool for poliovirus to date.

Why we need new polio vaccine options

The poliovirus has been mostly eliminated due to the efforts of the Global Polio Eradication Initiative (GPEI), a public-private partnership led by the World Health Organization (WHO). Since the formation and implementation of the GPEI in 1988, [polio case numbers have decreased by more than 99%](#). One of the important aspects of this initiative was to interrupt transmission of wild poliovirus by using a combination of routine immunization and surveillance of possible outbreaks. Two major types of vaccines are widely used internationally against polio: Orally administered, live attenuated Poliovirus Vaccine (OPV) and intramuscular (or subcutaneous) Inactivated Poliovirus Vaccine (IPV). In many countries, especially developing nations, OPV (a trivalent formulation of three live, attenuated strains) is the [vaccine](#) of choice as it is easy to administer, inexpensive, and provides greater intestinal immunity. Although OPV is very efficient and cheap, it has the potential to revert to neurovirulent forms that can cause [poliomyelitis](#). Therefore, [the WHO recommends](#) that an IPV made from attenuated strains would

be a safer choice in a world free of polio. Additionally, a recent [PLOS Pathogens paper](#) from a different group modeled the risks associated with OPV use and vaccine-derived polio emergence, with grim results indicating that the development of IPV options is more important than ever. However, current IPVs are made up of wild-type or virulent strains and carry a risk of possible re-emergence of poliovirus from vaccine production facilities. In order for IPV to be a realistic option for eradicating polio, new virus strains must be crafted.

What is CAVA and how can it help?

[In the PLOS pathogens paper](#), Dr. Barbara Sanders and her colleagues from the Netherlands, the USA, and the UK wanted to find novel strains for production of IPV, which are not only safe but also identical in their immunogenicity to the well-established IPV strains. For this, they used CAVA to make the virus unable to grow at the normal physiological temperature of the human body (37°C) but allow the virus to replicate effectively at low temperatures. The authors believe these temperature-sensitive strains would be safe to use for production of IPV as they would not be able to replicate at the normal physiological temperature in the natural host and thus would not be able to revert to neurovirulent forms.

CAVA has been used previously for the production of other viral vaccines, including influenza, and rubella viruses. In fact, Flu-mist, the nasal spray vaccine against influenza, contains cold-adapted, live-attenuated influenza virus. Scientists were able to generate cold-adapted, temperature-sensitive polioviruses as early as 1957. However, although these viruses showed increased replication at temperatures less than 37°C, they did not show complete loss of replication at 37°C, which is necessary for safe use of this technique in vaccine design.

Novel results on IPV strains using CAVA

Dr. Sanders' lab used serial passage at low temperature as well as genetic engineering to generate virus strains that not only showed increased replication at 30°C but also were incapable of replication at 37°C. The authors used Brunenders, a Type I partially-attenuated poliovirus to derive these highly temperature sensitive poliovirus strains. They performed in vitro serial passages of the virus, a process in which the virus is grown for a particular amount of time under specific conditions and then is transferred to new conditions and grown again for same amount of time, at low temperatures (26-30°C). After doing the serial passage for 34 times, they identified some clones that showed both increased growth at low temperature (30°C) and delayed growth at 37°C. The authors noted that those clones had some distinct nucleotide mutations. To ensure that there was a complete block in viral replication at 37°C, they introduced those mutations into the original Brunenders via cloning and transfection and generated CAVA backbone virus. This new virus showed no replication at 37°C.

Now, to generate CAVA-IPV vaccine strains, the authors replaced the capsid sequence, the nucleotide sequence that codes for the capsid or outer protein shell of the virus, of the CAVA backbone with the capsid sequences of each of the three viral strains, Mahoney, MEF-1 and Saukett that are present in the current IPV vaccine. This helped in mimicking the antigenic profiles of vaccine strains and led to the development of three new synthetically-derived viruses named CAVA-1 Mahoney, CAVA-2 MEF-1 and CAVA-3 Saukett. These three strains showed growth at 30°C and no growth at 37°C .

Then authors further performed in vivo and in vitro experiments on these three CAVA strains to determine their use as vaccine strains. First, they sought to confirm the attenuation of these strains by injecting them into lab mice. All three CAVA strains showed a highly attenuated

phenotype as none of the mice showed any paralysis. To determine if their attenuation was stable, they performed extended in vitro passages of these strains and then injected them into mice to check for neurovirulence. The results showed the same level of attenuation as parental strains, as none of the mice showed any symptoms of paralysis. To determine if these new strains are immunogenic in vivo (i.e. if they generate antibodies or not), they inoculated mice with a full IPV dose or different dilutions of the material from the new trivalent CAVA strains. These experiments showed that all three CAVA [vaccine strains](#) were immunogenic.

Looking ahead

The results of this study are promising and point towards a new way of generating polio vaccines. The authors indicate that the high-temperature sensitivity and in vivo neuroattenuation of these novel CAVA strains makes them non-infectious. Thus, they are safe to use to produce IPV and pose no threat in case of accidental leakage during vaccine manufacturing. The authors also note that although these strains are designed to be antigenically similar to conventional IPV strains, further work is needed to evaluate if their immunogenicity is also equivalent to IPV strains. These novel poliovirus [strains](#) have the potential to be used as vaccine candidates in future vaccine preparations.

More information: Sanders BP, de los Rios Oakes I, van Hoek V, Bockstal V, Kamphuis T, Uil TG, et al. (2016) Cold-Adapted Viral Attenuation (CAVA): Highly Temperature Sensitive Polioviruses as Novel Vaccine Strains for a Next Generation Inactivated Poliovirus Vaccine. *PLoS Pathog* 12(3): e1005483. [DOI: 10.1371/journal.ppat.1005483](#)

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