

# Programmable Vaccines

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## Technology description

The Curtiss Lab at Arizona State University has developed a next generation vaccine platform that uses bacteria to deliver protective antigens or DNA vaccines encoding protective antigens to prevent a variety of bacterial, viral, fungal and parasitic diseases. The bacterial carrier acts as a programmable and targeted 'guided missile', delivering the vaccine payload directly to the immune system of humans and animals.

### Next Generation Vaccines

An improvement over traditional vaccines uses a live bacterium to carry antigens (or DNA specifying antigens) directly to the immune system of a human or animal host. Needle-delivered vaccines are typically injected into muscle, where the antigens eventually make their way to the lymphoid system and hopefully present themselves in sufficient concentrations to elicit a strong immune response. These new vaccines are 'bacterially vectored' since they rely on a bacterial carrier as a vector or pathway into the body. By using bacteria as a carrier we stimulate the body's mucosal immunity, the first line of defense against pathogens that colonize on or invade through a mucosal surface. Orally (or mucosally) delivered *Salmonella* is the most superior bacterial vector in inducing long-lasting mucosal, systemic and cellular immunities, and a majority of our vaccines use *Salmonella* as the carrier.

*Salmonella*-vectored vaccines can be manufactured in a thermal stable freeze-dried state to be reconstituted at time of use, eliminating the "cold-chain" required by traditional vaccines where they are kept at the low temperature needed to preserve their function from point of manufacture to time of vaccination. *Salmonella*-vectored vaccines are also delivered orally by drops or delivered to animals in their drinking water or as a spray that is inhaled. Eliminating the needle eliminates the mild pain and discomfort of receiving a needle injection as well as the requirement of a trained health care worker or animal handler to deliver injections. In addition, many injectable vaccines do not induce long-lasting (cellular memory) immunity and thus require periodic re-immunization to sustain induction of protective immunity.

### Programmable Bacteria

This new generation of vaccines has another significant advantage over traditional vaccines; they employ bacteria that can be programmed to perform specific functions that improve the delivery of the vaccine, limit negative effects and ensure safety. This programming consists of removing or replacing genes that give the bacteria new characteristics. We can also control the expression of genes using a "genetic timer", a DNA switch that can activate or deactivate genes after a set amount of time has

elapsed. This timer is used for three separate systems of our vaccine. Our regulated delayed attenuation system allows for a fully invasive vaccine at time of immunization to avoid over-attenuation of the vaccine prior to it reaching immune induction sites. After a set number of bacterial strain divisions the vaccine becomes attenuated, thus striking an appropriate balance between attenuation and immunogenicity that previous live oral bacterial vaccines cannot match. Our regulated delayed antigen synthesis system uses the same timer mechanism to delay when antigens are synthesized by the vaccine. Unregulated expression of foreign antigens diverts precious energy and metabolic resources away from the metabolism of the vaccine and into synthesis of proteins from which the vaccine derives no selective advantage either in growth or replication. By delaying antigen synthesis we guarantee a robust initial entry of the vaccine into the host. Our third system is called regulated delayed lysis, and it rapidly degrades the *Salmonella* cell wall after entry into lymphoid tissues. This system releases synthesized antigens or DNA vaccines encoding antigens and also ensures that the *Salmonella* vaccine cannot establish a systemic persistence in vivo or survive if excreted into the environment by the host.

These systems can be used together or separately to provide a diversity of options for stimulating protective immunity against different pathogens. Antigens can be delivered by secretion or by lysis depending on need. We have one system that can induce better mucosal immunity, another that can induce better long-lasting cellular immunities than previous vectored vaccines, and another for much improved delivery of DNA vaccines by a bacterial vector.

Other important modifications are safety related. These include alterations that lessen or eliminate the traditional consequences of *Salmonella* infection such as diarrhea and stomach cramps, alterations that protect infants as well as pregnant, malnourished and immunocompromised individuals, and alterations that confer biological containment with no persistence of viable vaccine cells in vivo and no ability to survive if excreted. In addition all our vaccines are fully sensitive to all antibiotics that would typically be used to treat *Salmonella* infections.

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