Molecular Clamp: a novel protein vaccine for influenza, RSV, Ebola and other viruses

KEY FEATURES

- Molecular Clamp technology is the basis of a novel subunit vaccine for class I and III enveloped viruses
- Stabilizes the pre-fusion form of viral fusion proteins to mimic the protein conformation found on live virus, exposing highly neutralizing epitopes
- Shown to stimulate efficacious immune responses in animal models of influenza;
  - ~4-fold more potent neutralizing immune response and ~80-fold more cross-reactive compared to an on-market influenza vaccine
  - Stable pre-fusion antigen for antibody drug discovery

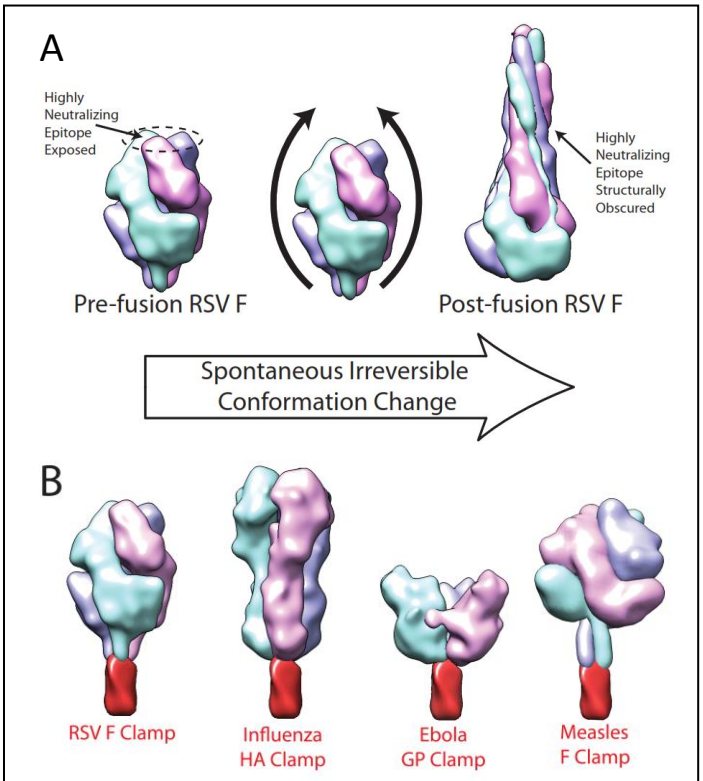
Background

All enveloped viruses, such as influenza virus and respiratory syncytial virus (RSV), require fusion of viral and host cell membranes to enter and infect the host cell. Viral fusion proteins facilitate this by undergoing structural rearrangements from a metastable 'pre-fusion' conformation to a highly stable 'post-fusion' conformation.

Viral fusion proteins are excellent subunit vaccine candidates for many medically important enveloped viruses as they are the primary targets of protective neutralizing antibody responses. However the intrinsic unstable nature of fusion proteins is a major obstacle for effective subunit vaccine design.

For vaccines, the pre-fusion form of the viral fusion protein is more desirable. Studies have shown the pre-fusion form of viral envelope fusion proteins contain important epitopes (not present on the post-fusion form) that produce broadly cross-reactive and potently neutralizing antibodies as part of a strong immune response.

Traditional approaches to recombinant expression of viral fusion proteins typically result in premature triggering and a conformational shift to the structurally more stable post-fusion form.



Molecular Clamp stabilization of viral fusion proteins
A. Irreversible conformational transition of viral fusion proteins occurs spontaneously in non-stabilized subunit vaccines. Broadly reactive immunological sites found predominantly in the pre-fusion form are not available in the post-fusion form.
B. Structural model of the RSV F, influenza HA, Ebola GP and Measles F stabilized in their native configuration by the molecular clamp technology.

Technology

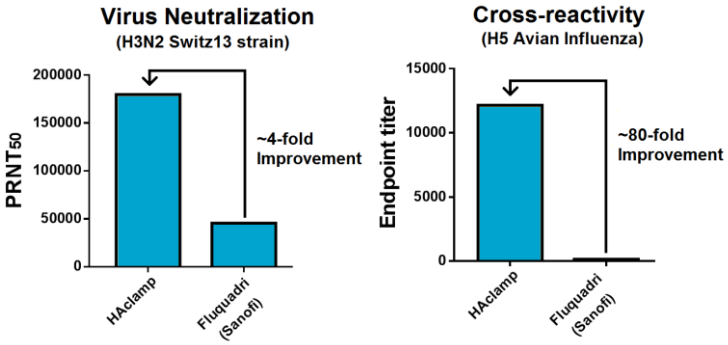
Molecular Clamp technology addresses the industry need to produce stabilized recombinant fusion proteins that remain substantially in their pre-fusion form. It uses a polypeptide moiety as a molecular clamp and has been shown to have increased stability over alternate stabilizing trimerization domains such as Foldon and GCN4.

Used as the basis of a novel protein vaccine, the molecular clamp technology is designed to elicit a protective immune responses against class I and III enveloped viruses of human and veterinary importance.

The clamped pre-fusion protein can also be used as an antigen in an antibody drug discovery program.

The Molecular Clamp approach is a platform technology. Researchers at The University of Queensland have already used it to produce chimeric polypeptides that mimic the pre-fusion conformations of influenza, RSV, HIV, measles virus and Ebola virus.

Data has shown the Influenza HA Clamp has strong reactivity with known protective monoclonal antibodies (C05, CR8043, FI6V3). It induced a more potent neutralizing immune response compared with current vaccine FluQuadri® (Sanofi Pasteur) and was found to be ~80-fold more cross-reactive antibody to heterologous strains (including avian H5N1).



Data with other viruses includes Ebola which induced a potent neutralizing immune response comparable with rVSV-ZEBOV (Merck). Further, the Molecular Clamp protein vaccine was shown to be heat stable with no loss in antigenicity after two weeks at 37°C.

Market Potential

In 2014, the value of the world market for vaccines was estimated at US$33 billion with the HIV market valued at US$14 billion and influenza market at US$4 billion.

As well as these and other applicable viruses of human importance, such as herpes virus, mumps and measles, the technology can also be applied to veterinary applications including bovine ephemeral fever virus (BEFV), bovine RSV, Hendra virus, Newcastle Disease virus and canine distemper virus.

Intellectual Property

The invention is the subject of an Australian provisional patent application covering chimeric polypeptide approaches to mimic the pre-fusion forms of class I and III viruses and its use.

Commercialisation Opportunity

UniQuest is seeking licensing, collaborative or investment partners to commercialise the technology.

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Professor Paul Young is Professor of Virology and Head of the School of Chemistry and Molecular Biosciences in the Faculty of Science at The University of Queensland. He has more than 35 years' experience developing viral diagnostics, vaccines and antiviral agents.

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