Pre-clinical success for a universal flu vaccine offers hope for third generation approach

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Researchers from the University of Oxford's Department of Zoology have demonstrated pre-clinical success for a universal flu vaccine in a new paper published in *Nature Communications*.

Influenza is thought to be a highly variable virus, able to mutate and escape immunity built up in the population due to its circulation in previous seasons. However, influenza seasons tend to be dominated by a limited number of antigenically and genetically distinct influenza viruses. This creates a paradox as influenza is thought of as being highly variable while in reality influenza seasons are dominated by only a few strains.

Mathematical models produced in Professor Sunetra Gupta's group at the University of Oxford over the past 20 years have sought to find an answer to this paradox. Finally, through a collaborative approach across multiple departments, the group believes they have the answer.

Dr. Craig Thompson said: 'The integrated approach to vaccine design that we have applied to flu has to the potential to be applied to other previously intractable pathogens and could revolutionise the way we develop vaccines.'

Professor Sunetra Gupta said: 'I think this work serves a good example of how evolutionary models can have translational impact. We have gone from a prediction of a mathematical model to a blueprint for a universal influenza vaccine. The outstanding teamwork coordinated by Dr. Thompson is what made it all possible.'

The research team theorized that parts of the virus targeted by the immune system are, in fact, limited in variability and act as constraints on the evolution of the virus. Dr. Craig Thompson in Professor Gupta's group has now identified the location of these regions of limited variability. He has shown that such locations are targeted naturally by the immune system and through vaccination studies has shown that regions of influenza viruses that circulated in 2006 and 1977 were able to protect against infection with an influenza virus that last circulated in 1934.

Thirty mice were vaccinated with the epitopes identified in the study. Twelve mice were vaccinated with a control vaccine (a vaccine not containing the epitopes identified in the study but otherwise essentially the same as the vaccine containing the epitopes identified). Twelve mice were 'mock vaccinated' with no vaccine (just PBS/adjuvant without vaccine). Six mice were used as a normal control and were not vaccinated in any way.

The researchers identified regions of the virus which were limited in variability by mapping the historical variation of the influenza virus to the main target of the immune system—an influenza protein called 'haemagglutinin'. This allowed them to identify several regions of the protein which were previously thought of as highly variable as limited in variability. Further computational analysis showed that one of these regions cycled through a number of different states between 1918 and the present day. The researchers then showed that sera from children aged 6 to 12 cross-reacted to historical strains which they could not possibly have experienced. Mutagenesis of one of the regions identified in our bioinformatic/computational analysis from one state to another removed this cross reactivity. The research team then vaccinated mice with the individual versions of the region which induced periodic cross-reactivity to historical strain in mice—vaccination of mice with one of the versions reproduced exactly the cross reactivity produced by the sera from the children. They then showed that the versions of this region identified by our analysis and serology work that circulated in 1977 and 2006 were able to protect mice from a lethal challenge with an influenza virus that last circulated in 1934.

This experimental setup utilising a lot of controls allowed researchers to determine precisely that the epitopes they had identified were responsible for the cross-reactivity that researchers observed in the study.

The results of these studies can be exploited to create a novel type of 'universal' or broadly protective influenza vaccine, which once administered would provide lifelong protection against influenza. The team also hopes to apply the approach to other viruses such as HIV and HCV and believes that they can use it to produce a vaccine that protects against the common cold. The novel approach to vaccine design is outlined in the paper published in *Nature Communications*. Furthermore, such vaccines should be able to be produced in a low-cost manner, enabling healthcare providers such as the NHS to save money, unlike many new vaccines and drugs coming to the market.

This study also presents one of the first examples of where a mathematical model of the evolutionary dynamics of an infectious disease has led to the experimental identification of a novel vaccine target. The novel approach won an MRC Confidence in Concept Award in 2016, a Royal Society Translational Award in 2017 and an ERC Proof of Concept grant in 2018.

The WHO estimates that influenza kills 260,000-650,000 people and causes 3-5 million cases of severe illness each year. This burden typically falls on the elderly and young children, especially in developing countries. The best way to protect against influenza is through vaccination, although the problem with this is that the current influenza vaccine has to be administered each year and varies in its effectiveness.

More information: Craig P. Thompson et al, A naturally protective epitope of limited variability as an influenza vaccine target, *Nature Communications* (2018). DOI: 10.1038/s41467-018-06228-8

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