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Abstract

The Long Road to a Universal Influenza Virus Vaccine †

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Abstract: Seasonal and pandemic influenza virus infections can cause significant disease worldwide. Current vaccines only provide limited, short-lived protection, and antigenic drift/shift in the hemagglutinin (HA) surface glycoprotein necessitates their annual reformulation and re-administration. To overcome these limitations, universal influenza virus vaccine strategies aim at eliciting broadly protective antibodies to conserved epitopes of the HA. We have developed two approaches. (1) The first is based on "chimeric" HA constructs that retain the conserved stalk domain of the HA and have exotic HA heads. Vaccination and boosting with such constructs successfully redirects the immune system in animals and in humans towards the conserved immune sub-dominant domains of the HA stalks; this results in an antigenic silencing of the HA heads and a protective immune response facilitated by the conserved HA stalks. In mice and ferrets, such a strategy protects the animals against homo-subtypic and hetero-subtypic challenge with influenza A strains as well as against influenza B variants. It is hoped that vaccine constructs expressing three components (i.e., conserved group 1 HA stalks, conserved group 2 HA stalks, and conserved influenza B HA stalks) will be protective against all future seasonal and pandemic strains. (2) The "mosaic" HA approach is based on antigenic silencing of the major immunodominant antigenic sites of the HA heads by only replacing those epitopes with corresponding sequences of exotic avian HAs, yielding "mosaic" HAs. In mice, a prime-boost vaccination regime with inactivated viruses expressing "mosaic" HAs elicited highly cross-reactive antibodies against the stalk domain of the HAs that were capable of eliciting Fc-mediated effector functions in vitro. Extensive trials will be necessary in the future in order to identify the optimal vaccination regime ("chimeric" HA-based versus "mosaic" HA-based) in humans.

Keywords: chimeric hemagglutinin; mosaic hemagglutin; neuraminidase; protection against influenza virus variants; influenza A, B and C viruses; immunodominance; immuno-subdominance