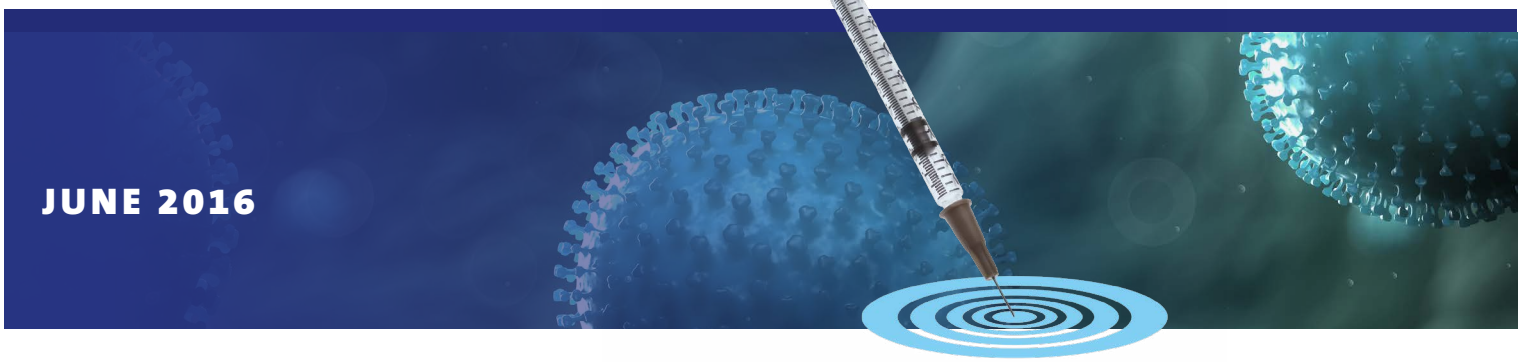
NEWSLETTER

FLUNIVAC



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FLUNIVAC: THE PROGRESS

A FLU VACCINE WOULD CERTAINLY BECOME MORE UNIVERSAL IF IT WERE TO ENTICE THE IMMUNE SYSTEM TO MAKE ANTIBODIES AND T-CELLS AGAINST PARTS OF THE VIRUS THAT ARE GENETICALLY CONSERVED, THUS AGAINST EPITOPES ON THE VIRUS THAT ARE COMMON IN ALL INFLUENZA VIRUSES.

Prof. Gerd Sutter explains: "From the start, the idea of the FLUNIVAC partners has been that - in order to induce robust immunity against as many flu viruses as possible - you need T-cell responses as well as antibody responses against conserved regions of the proteins. So our approach is to target several promising Influenza A virus proteins and to modify them in such a way that they induce an immune response that provides better and longer-lasting protection than the natural variants of the proteins. In 2014, FLUNIVAC'S first full year of operation, the consortium partners produced a number of recombinant MVAs, including a set of recombinants expressing the nucleoprotein (NP) of influenza virus. Since NP is a target for virus-specific T-cells, we had made a number of modifications to the protein in order to improve cross-reactive T-cell responses. Tests in mice have now demonstrated that the wild type NP already elicits T-cell production and the modified variant adds little to that, although the modifications resulted in improved T cell activation in vitro. Here our modification strategy seems not to be the right way forward. Another candidate antigen, however, is the M2e protein and here our work has yielded some very promising results."

Prof. Xavier Saelens, VIB-UGhent, continues: "Our research group in Ghent has been working with Prof. Sutter's group in Munich to come up with a new strategy to display M2e by MVA. Genetically, the coding information for the M2e leaves very little room for mutations in influenza A viruses, which makes it a potentially broadly protective antigen. A fusion protein comprising a vaccinia surface protein in which we inserted three copies of M2e (vvM2e), turned out to be a good strategy. We were glad to see that recombinant MVA with the vvM2e fusion protein express M2e very well and furthermore could induce a robust M2e-specific antibody response in mice. Moreover, vaccination with MVA-vvM2e protected the mice against challenge with influenza A virus. Our next aim is to make alterations in the M2e-sequences that are inserted as repeats in the fusion protein in order to cover as many influenza A subtypes as possible. A major challenge of the M2e-based vaccine approach, however, is to demonstrate correlates protection. We know that M2e-specific antibodies are essential to provide protection against influenza. However, to show in vitro that these antibodies have an impact on the virus is quite complicated. After all, they do not neutralize the virus directly (or they do so very exceptionally). But we are working on an in vitro system to show that the antibodies are indeed functional." →

FLUNIVAC: THE BASICS

THE QUEST FOR A UNIVERSAL INFLUENZA VACCINE

FLUNIVAC (InFLUenza virus UNIVersal VACcine development program) is a unique consortium of various European SMEs, universities and an industry partner, which is supported by the European Commission's Seventh Framework Program. FLUNIVAC's aim is to pave the way to the development of a universal influenza vaccine.

WHY IS A UNIVERSAL INFLUENZA VACCINE NEEDED?

Influenza viruses have a great capacity to mutate and change. Current flu vaccines are safe and effective, but they have to be updated annually to match the epidemic strains and occasionally there is a mismatch with the circulating virus strains. There is hence a great need for new vaccines that can induce broad immunity ideally against all manifestations of influenza in humans (seasonal, zoonotic and pandemic).

MVA: A CRUCIAL TOOL

A crucial element in FLUNIVAC's research is a vaccine delivery platform based on MVA (Modified Vaccinia virus Ankara). This replication deficient vaccinia-derived virus is unable to form new infectious particles in humans and thus is very safe to use. It allows the construction of recombinant MVAs that express influenza virus proteins in a way that favours recognition by our immune system.

“The second promising research line we are pursuing”, elaborates **Prof. Guus Rimmelzwaan**, FLUNIVAC’s project coordinator, “is the modification of the influenza virus hemagglutinin. Our group at the Erasmus MC in Rotterdam made quite a number of modifications to this protein to see if we could increase the antibody response against the stem region. Our constructs are all ready now and we will start vaccination experiments in mice in the very near future. We know the MVA is an excellent vector for the expression of the hemagglutinin, and this has been proven once again recently when we performed a clinical trial with an MVA recombinant vaccine expressing the hemagglutinin of an H5N1 influenza virus. We have demonstrated that this vaccine candidate is immunogenic in men, it provides good antibody responses and we boosted the vaccinated study subjects one year after the priming vaccination. This resulted in really strong antibody responses, not only against the homologous H5N1 strain, but also against strains of different clades of H5N1 viruses. We have shown that these antibodies even cross-react with the novel highly pathogenic avian influenza H5N8, which also emerged in The Netherlands. So, if this virus were to acquire the capacity to infect humans, our recombinant vaccine would already be a good candidate to be used against the H5N8 virus. In short: we have developed an intrasubtypic vaccine, protecting against various strains of H5 virus, and hence taken one of many small steps towards a universal flu vaccine.”

A MULTIDISCIPLINARY COLLABORATION

“One of FLUNIVAC’s major assets is the fact that we have forged a unique alliance of different partners with complementary top-level scientific expertise and knowledge”, says Prof. Rimmelzwaan. “Our non-academic partners indeed play a crucial part in the consortium. A nice example is the role of AmatsiQBiologicals in our study to compare the immunogenicity of MVA with a “gold standard”, in this case a subunit vaccine preparation with an adjuvant. AmatsiQBiologicals have produced some recombinant proteins, which are already being used by Novavax in their comparative studies. In 2016, we will run experiments in mice to see how immunogenic MVA is compared to the gold standard.”

THE FLUNIVAC CONSORTIUM

FLUNIVAC is a collaborative effort of three academic groups, four SME’s and an industry partner.

Department of Viroscience, Erasmus MC Rotterdam (coordinator)	Guus Rimmelzwaan
Artemis One Health Research	Ab Osterhaus
Institute for Infectious Diseases and Zoonoses, University of Munich (LMU)	Gerd Sutter
AIMM Therapeutics	Hergen Spits, Tim Beaumont
ProBioGen	Ingo Jordan, Volker Sandig
VIB-UGhent	Xavier Saelens
Novavax	Karin Lövgren Bengtsson, Linda Stertman
AmatsiQBiologicals	Annie Van Broekhoven, Fons Bosman

COOPERATION

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Publications 2015

Lidewij C.M. Wiersma, Joost H.C.M. Kreijtz, Stella E. Vogelzang-van Trierum, Geert van Amerongen, Peter van Run, Mechtild Ladwig, Stefanie Banneke, Hubert Schaefer, Ron A.M. Fouchier, Thijs Kuiken, Albert D.M.E. Osterhaus, Guus F. Rimmelzwaan **Virus replication kinetics and pathogenesis of infection with H7N9 influenza virus in isogenic guinea pigs upon intratracheal inoculation** doi:10.1016/j.vaccine.2015.08.050

Lidewij C.M. Wiersma, Stella E. Vogelzang-van Trierum, Joost H.C.M. Kreijtz, Geert van Amerongen, Peter van Run, Mechtild Ladwig, Stefanie Banneke, Hubert Schaefer, Ron A.M. Fouchier, Thijs Kuiken, Albert D.M.E. Osterhaus, Guus F. Rimmelzwaan **Heterosubtypic immunity to H7N9 influenza virus in isogenic guinea pigs after infection with pandemic H1N1 virus** doi:10.1016/j.vaccine.2015.08.038

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