EAVI2020 Year 2 Publications Summary

1. Summary for publication

The European AIDS Vaccine Initiative 2020 (EAVI2020) funded by the EU under the Horizon 2020 program aims to accelerate the identification and development of an effective HIV vaccine that may have utility both to prevent infection and contribute to the establishment of long term remission in those infected with the virus. HIV-1 is responsible for a global pandemic of 35 million people and continues to spread at a rate of >2 million new infections/year. It is widely acknowledged that a protective vaccine would be the most effective means to reduce HIV-1 spread and ultimately eliminate the pandemic, while a therapeutic vaccine may help mitigate the clinical course of disease and lead to strategies of viral eradication. However, despite 30 years of research, we do not have a vaccine capable of protecting from HIV-1 infection or impacting on disease progression. This in part represents the challenge of identifying immunogens and vaccine modalities with reduced risk of failure in late stage development. To overcome this bottleneck some of the most competitive research groups in vaccine discovery from 22 European public institutions and biotechs from 9 EU countries together with top Australian and Canadian groups and US collaborators, have agreed to join forces in the EAVI2020 project, providing a pool of international expertise at the highest level. EAVI2020 is providing a platform for the discovery and selection of several new, diverse and novel preventive and/or therapeutic vaccine candidates for HIV/AIDS. Emphasis is being placed on early rapid, iterative, small vaccine studies to select and refine the best vaccine candidates and determine the impact of factors such as gender and genetics. Animal models are being used to complement human studies, and to select novel vaccine technologies to be advanced for clinical testing. This work is helping us to develop innovative prediction models increasing the chance of discovery of an HIV effective vaccine.

1.2 Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far

The work of EAVI2020 has been targeted across 8 interlinked objectives designed to meet the main aims of the project detailed above. The first object has been to design HIV envelope proteins - the primary target of protective antibodies that show high stability and native conformation, a challenging task given the fragile architecture and wide diversity of this protein. The main aim of this objective is to design a minimum of 8 new vaccine candidates to move forward for manufacture and clinical testing. During the first two years of the project we have developed two novel envelope vaccine candidates based on a consensus sequences of all circulating strains of HIV. These are known as ConM and ConS.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 681137. The sole responsibility for the content of this project lies with the authors. It does not necessarily reflect the opinion of the European Union. The European Commission is not responsible for any use that may be made of the information contained therein.

These have been designed and optimised at the molecular level, expressed as recombinant proteins and have undergone a battery of test to determine that they have the right structure, that is highly stable and appropriate for manufacture. The selection of two different design strategies will allow us to compare and contrast their potential to induce protective antibodies in animal models and human trials. We have also developed an additional process to provide further chemical stabilisation of the proteins by process known as chemical cross-linkage. These have now been transferred for clinical manufacture and process optimization. Additional work has been performed to develop and select a second generation of vaccine candidates. These are based on the molecular stabilization developed for the first candidates but use a cocktail of three glycoproteins that have been generated by computer modelling to cover the diversity of HIV strains that are in current global circulation. Known as B cell mosaic immunogens, these have been characterised for structure, stability and binding of protective antibodies (antigenicity). All of these products are under assessment in animal models. Work has also been initiated to generate a third wave of candidates for manufacture and clinical testing. Here we have identified potential HIV envelope sequences from HIV infected individuals that naturally make protective (neutralising antibodies) early infection. Work to develop these targets will continue to progress through the next year of the project.

In parallel to working on antibody-based approaches for vaccine design, we have also been pursuing candidate vaccines that evoke specific white blood cells (T cells) able to kill cells infected with HIV – these cells may help to clear infection before it is established and might be useful for treatment of HIV. This work has focused on two main T cell vaccine candidates using alternative approaches, a) the conserved beneficial sequences known as the HTI vaccine and b) the conserved mosaic vaccine known as tHIVconsvX immunogen. Both of these immunogens have to date been inserted into a range of vaccine platforms known as DNA, MVA, adenovirus vectors. Additional work has been undertaken to transfer these sequences or “immunogens” into RNA, BCG and lentiviral platforms. Work on a further T cell candidate, a "designer Gag" (dGag) sequence has been completed on time. dGag contains the most common escape mutations that the virus uses to evade the immune response – focus on these will prevent viral escape and help the immune system to control viral replication. These approaches are being assessed in comparative analysis in preclinical models. The inclusion in RNA is highly innovative and it is anticipated that this work is showing promise in animal models. A further objective has been to assess the breadth of presentation in a context of a wide-range of MHC class I molecules (cell surface proteins that present small sequences of the virus to immune cells that are then able to kill the infected cell). This is an important objective as T cell breadth is one of the key targets of the immunogen design strategy. The objective of ongoing evaluations are to select the best vaccine combinations and schedule (so called “prime-boost” approached) for down-stream development through animals and human studies.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 681137. The sole responsibility for the content of this project lies with the authors. It does not necessarily reflect the opinion of the European Union. The European Commission is not responsible for any use that may be made of the information contained therein.

The main third objective in year 2 of this program has been the production and formulation of vaccine components (adjuvants, vectors, proteins) to be advanced for human clinical trials. Critical to this is the manufacture of Envelope vaccine constructs, monoclonal antibodies for their purification and the generation of high producing cell lines. To meet these objectives our first vaccine candidates: ConM and ConS designs have progressed from the establishment of producer cells (year 1) to full GMP manufacture (year 2). An additional objective for year 2 has been the GMP production of monoclonal PGT145 for vaccine purification. A further objective has been the successful transfer and development of research grade process to generate cross-linked envelope candidates to full manufacture. This has been successfully completed in year 2. We have also established a process for GMP production of the selected MLPA-liposomal adjuvant and this has been generated as an engineering run providing material to support the preclinical program. All these are under ongoing testing in animal models as a prelude to clinical testing. An additional objective of the manufacturing program in year 2 has been the selection of three mosaic constructs to support the second wave of clinical studies. These constructs have been moved forward to establish stable producer cells for GMP production. To support the T cell vaccine candidates we have manufacture 2 MVA constructs expressing tHIVconsvX and HTI immunogens.

A fourth objective of the project has been the development of Advanced Animal Models to define predictive correlates (measures) of protective immune responses. To meet this objective, we have been testing a range of vaccines in small animal models with promising results. This has aided the vaccine candidates selected for manufacture above. Our advanced products (ConM and ConS) are under evaluation in animal infectious challenge models. We have generated a globally unique dataset on the B cell repertoire within the challenge animal model to help facilitate immune analysis, this will be made available to the wider scientific community. A further objective of year 2 has been the selection of adjuvant for manufacture and use in the planned clinical trials. Advanced studies of candidate protein adjuvants has been performed in advanced animal studies. This has led to the selection of MPLA-liposomes administered by the intramuscular route for our clinical program. GMP manufacture of the liposomes has competed process development.

A fifth objective of the project is to assess a range of novel immunogens in human clinical trials to determine safety of the approach and the ability to induce protective immune responses prior to selection for large efficacy trials (subsequent to this project). The first clinical trials have yet to be initiated. Nevertheless, work has been initiated to develop trial designs and ensure the development of an appropriate regulatory pathway to progress immunogens towards clinical study. This has been realised through meetings with the relevant governmental agencies to discuss our preclinical toxicology plans and product specifications.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 681137. The sole responsibility for the content of this project lies with the authors. It does not necessarily reflect the opinion of the European Union. The European Commission is not responsible for any use that may be made of the information contained therein.

A sixth objective has been development of advanced immunological analysis to facilitate prioritisation of novel protective and/or therapeutic HIV-1 vaccines. Work during the second year to meet this objective has focused on further development of the immunological assays needed for animal and human studies – this is a process of continual refinement. Progress has been driven by our algorithm for sample prioritisation using core and specialised technology developed in year 1. A major objective of work in year 2 has been the immunological assessment of animal studies designed to evaluate and select immunogens and adjuvant for progression through GMP manufacture and subsequent clinical investigation. This has led to lead candidate selection of ConM and ConS envelope immunogens, with mosaic envelope immunogens selected for the second clinical wave. On-going work is optimising advanced antibody functional assays for use in human and animal models. Core (ELISpot, ICS) and specialised (VIA, viral inhibition assay) assays have been established for T cell based programs and a process of laboratory validation has been initiated. Work is ongoing to meet our objective of optimising the VIA assay for assessment of therapeutic vaccines in HIV positive subjects. A wide range of novel reagents have been generated to facilitate immunological analysis.

The seventh objective is to develop new molecular tools to study the evolution of antibody sequences and gene expression studies. A major effort in meeting these objectives within year 2 has been made to rapidly define the repertoire of antibody genes in advanced animal models. Specifically, we have developed a novel computational approach, IgDiscover, which identifies gene sequences from such expressed antibody repertoires. We have been developing blood cell analysis using novel cytof-technology to facilitate our objective of developing greater depth in understanding of vaccine elicited immune response. In relation to our objectives in determining better marker of prediction we have identified a novel and important biomarker (IL-27) able to differentiate HIV infected individuals with high or low levels of HIV in the blood, providing a direct correlation with the size of the latent viral reservoir. This will prove a critical tool in our planned clinical trials to assess the potential therapeutic impact of our HTI and tHIVConsvX vaccines.

Our final and eighth objective is the generation and selection of a novel and diverse portfolio of promising HIV-1 prophylactic and therapeutic vaccine candidates for further clinical development by the end of the program in the context of the European and Developing Countries Clinical Trials Partnership (EDCTP) and other allied Partners. Work in the second year of the project has been tightly focused on meeting this objective by the end of the project. Particular highlights have been the generation of a pipeline of novel B and T cell immunogens and their incorporation into a wide range of vaccine delivery technologies: adjuvanted recombinant proteins, nucleic acid vectors (DNA RNA), viral (MVA, ChAd, IDLV) and bacterial (BCG) vectors that are under evaluation in preclinical models and progressing towards early clinical testing. Informal discussions are ongoing with potential funding agencies over the status or our vaccine portfolio and further funding of an

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 681137. The sole responsibility for the content of this project lies with the authors. It does not necessarily reflect the opinion of the European Union. The European Commission is not responsible for any use that may be made of the information contained therein.

expanded clinical program. This has already led to external funding and partnership on different aspects of the tHIVconsvX and HTI immunogen program.

1.3 Progress beyond the state of the art and expected potential impact (including the socio-economic impact and the wider societal implications of the project so far)

The work of EAVI2020 over the past 2 years has already moved the field beyond the state of the art with respect to the molecular design of stabilised native-like viral envelope glycoproteins. The design strategies have reached their eighth iteration (ConMv8) and the mutations (including the introduction of inter and intra-protomer disulphide bonds) can now be applied to most envelope sequences. This is an advance from the beginning of the project where most envelope sequences could not be expressed as stabilised immunogens with native like structure. The development of a novel process to provide further chemical stabilisation of the proteins (cross-linking) and translation of this approach from a research setting to a manufacturable process provides and additional advance – this process can be applied to multiple vaccine targets for a range of viral infections and not just HIV. The innovations achieved in process manufacture and antibody affinity purification of these immunogens places Europe in a highly competitive position. The development of B cell mosaic immunogens as stabilised recombinant proteins also represents a world-first. The identification of potential HIV envelope sequences from HIV infected individuals that naturally make protective (neutralising antibodies) early infection is highly novel and the IgDiscover platform is a key new tool for international scientists to better interpret the evolution of antibody responses in animal models. The development and refinement of the Viral Inhibition Assay is allowing scientists for the first time to determine the functional activity of vaccine induced T cells to kill cells infected with HIV. The identification of IL-27 as a novel biomarker in blood capable of predicting the size of the latent viral reservoir in infected individuals may prove vital to the development and testing of potential cure strategies. In year 2 of the project a number of publications have been generated (11). In summary, the work of the EAVI2020 project is on track to increase the number of candidate vaccines which can be tested in human clinical trials. It is also developing a tool box of assays to select and reject vaccine candidates based on sound scientific evidence, thus increasing the chance of discovery of an effective preventative and/or therapeutic vaccine.

In this respect it is widely acknowledged that development of a protective vaccine would be the most effective means to reduce HIV-1 spread and ultimately eliminate the pandemic, while a therapeutic vaccine may help mitigate the clinical course of disease and may contribute to virus eradication strategies. This remains a priority with 2M new infections occurring every year with rates still growing in specific populations and regions. Furthermore, population growth could lead to a net increase in new infections in spite of the current decline, at least in some countries, regions or areas. Access to available prevention and treatment will remain a challenging for specific populations and regions. For every person starting antiretroviral treatment one to two people are newly infected,

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 681137. The sole responsibility for the content of this project lies with the authors. It does not necessarily reflect the opinion of the European Union. The European Commission is not responsible for any use that may be made of the information contained therein.

with 20 million more people predicted to acquire HIV by 2031 increasing potential treatment costs from $22 billion up to $35 billion a year. Ultimately the development of an effective vaccine may be critical to ensuring access to treatment, which can also keep pace with the number of new infections. With the use of vaccines in therapy this may provide a critical tool in ensuring the health of the 37million people living with HIV.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 681137. The sole responsibility for the content of this project lies with the authors. It does not necessarily reflect the opinion of the European Union. The European Commission is not responsible for any use that may be made of the information contained therein.