Publishable Summary Report M12

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1. Summary of the Context and Overall Objective of the Project

Many HIV vaccine concepts and several efficacy trials have been conducted in the prophylactic and therapeutic fields with limited success. There is an urgent need to develop better vaccines and tools predictive of immunogenicity and of correlates of protection at early stage of vaccine development to mitigate the risks of failure. To address these complex and challenging scientific issues, the European HIV Vaccine Alliance (EHVA) program will develop a Multidisciplinary Vaccine Platform (MVP) in the fields of prophylactic and therapeutic HIV vaccines. The Specific Objectives of the MVP are to build up:

1) Discovery Platform with the goal of generating novel vaccine candidates inducing potent neutralizing and non-neutralizing antibody responses and T-cell responses;
2) Immune Profiling Platform with the goal of ranking novel and existing (benchmark) vaccine candidates on the basis of the immune profile;
3) Data Management/Integration/Down-Selection Platform, with the goal of providing statistical tools for the analysis and interpretation of complex data and algorithms for the efficient selection of vaccines; and
4) Clinical Trials Platform with the goal of accelerating the clinical development of novel vaccines and the early prediction of vaccine failure.

EHVA project has developed a global and innovative strategy which includes: a) the multidisciplinary expertise involving immunologists, virologists, structural biology experts, statisticians and computational scientists and clinicians; b) the most innovative technologies to profile immune response and virus reservoir; c) the access to large cohort studies bringing together top European clinical scientists/centres in the fields of prophylactic and therapeutic vaccines, d) the access to a panel of experimental HIV vaccines under clinical development that will be used as benchmark, and e) the liaison to a number of African leading scientists/programs which will foster the testing of future EHVA vaccines through EDCTP.

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

Significant progress has been made during the 1st year of the project towards the four objectives of the EHVA consortium. The main achievements are summarized as follows:

- **Discovery platform**. Our primary focus is to bring one RNA-based vaccine candidate and one envelop (Env) protein based vaccine candidate to clinical evaluation within the life span of the EHVA project.
    - For the RNA-based vaccine candidate, we have successfully completed the initial small animal experiments and down selected two candidates to be further evaluated in non-human primates. The initial NHP immunogenicity data will be available Spring 2017 and are expected to provide supportive data to make the go/no-go decision on which RNA vaccine candidate can be moved forward to clinical evaluation.

For the Env protein based vaccine, we have generated several promising novel candidates that aim at: 1) stabilizing existing Env trimers by structure guided molecularengineering; 2) immune focusing by immune silencing of immunodominant non-neutralizing surfaces using post-translational targeted glycan addition; 3) guiding B cell responses from germline B cells to mature bNAbs; 4) delivery of Env candidates through VLPs or DC-targeting with the goal to further improve Env immunogenicity. *In situ, in vitro*, and *in vivo* (small animals) characterization of these candidates are ongoing.

- **Immune profiling platform**. The main focus of this reporting period is the development and validation of novel assays, with special emphasis on assays to assess innate and antibody responses. This includes but not limited to: 1) validation of multiparamter flow cytometry, multiplex technology and CyTOF for innate immunity; 2) establishing a pseudovirus panel for the detection of neutralizing activity; 3) development of ADCC assay; 4) standardization of virus inhibition assay.
- **Data Management/Integration/Down-Selection Platform**. Main effort within this reporting period has been focused on building the EHVA Data Warehouse to be able to integrate different data and conduct meta analysis. The initial setup of the database is now completed.
- **Clinical Trials Platform**. The main activity of this reporting period is the development and preparation of Therapeutic Vaccine Trials platform with centres in multiple countries ready to evaluate the ability of combined innovative interventions to strenghten the control of HIV replication and reduce HIV reservoirs. The protocol is at the final stage of being finalized, incorporating some of the latest scientific findings in the field. EHVA will implement a novel adaptive trial design to this trial and will conduct the trials in patients who started antiretroviral treatment at either the primary or the chronic phase of HIV infection.

3. Progress beyond the state of the art and expected potential impact

EHVA program will lead to a number of innovation potentials:

- Large portfolio of vaccine candidates: EHVA aims to develop multiple vaccine approaches, including novel Env protein, RNA, replication competent vector, novel delivery system and adjuvants. Combination of these strategies increases the chance of a successful novel candidates. Innovation management combined with the robust screening platform (see below) will at the same time ensure early termination of less promising candidates and prioritizing to move the most promising candidate forward.
- Robust screening platform for early selection of vaccine candidates/regimens: Currently, more than 20 HIV candidate vaccines are in early clinical development, and the number of potential immunization strategies is much larger taking into consideration of the possible prime-boost combinations, number of injection and injection intervals. Efficient screening and early selection of the most promising candidate/regimen has been a challenge. The robust immunological and data integration platform of EHVA represents a strong tool to address this challenge not just for the HIV field but can be applied to other fields as well.
- Innovative clinical platform for the evaluation of vaccine candidates: EHVA promotes the Experimental Medicine and Adaptive Trial concept in the design of its trials. Combined with the comprehensive immunological profiling algorithm performed by centralized core labs with standardized/validated assays and centralized analysis with high dimensional data integration, these innovative designs will allow rapid evaluation and selection of the best-in-class vaccine candidates. Again such platform can be applied for the evaluation of other HIV or non-HIV vaccine candidates.

In summary, the powerful and highly innovative immunological, clinical and data integration platforms developed under EHVA will contribute to expediting the selection and development of promising vaccine candidates. This centralized and standardized pool of knowledge will enable new and less risky solutions for all public/private partnerships striving to develop HIV vaccines. The success of EHVA will contribute to reducing the cost of R&D programs, giving a higher visibility and credibility of the European research in the HIV vaccine field and be very adaptive to the evolution of the techniques and sciences. This will provide a basis for international standards that could be broader than HIV vaccines.