Year 3 Impact Assessment

November 2014

BACKGROUND

In support of Deliverable 19.1, "*Impact assessment done through impact score card throughout the project",* a score card was drafted by a small Steering Committee subgroup with support of the project manager incorporating the key areas identified in Work Package 19. Feedback was sought from an external expert consultant and was incorporated. This draft, along with a set of definitional guidelines for each of the 34 identified data elements, was circulated to all consortium partners. During the first two years of the project, project impact was assessed and the reports were submitted.

INTRODUCTION

The science behind vaccines has become so sophisticated that no one laboratory can tackle modern vaccine science in isolation. Therefore some of the most competitive European research groups from public institutions and biotechs, together with top US groups on systems biology and adjuvants, have agreed to join forces in the Advanced Immunization Technologies ADITEC consortium. The ADITEC project is a 30M High Impact project funded by the European Commission. The scope of the project is to accelerate the development of novel and powerful immunization technologies for the next generation of human vaccines. This goal requires a multidisciplinary approach in which diverse but complementary scientific disciplines and technologies converge.

The research consortia participating in the ADITEC project consist of:

- large biopharmaceutical companies
- small- and medium-sized enterprises
- universities
- independent research institutes
- hospitals
- regulatory agencies

Several ADITEC scientists and institutions are part of the Sclavo Vaccine Association (SVA), the coordinating institution, which is dedicated to vaccine research and development.

The working concept of ADITEC is to use systems biology and advanced immune assays to elucidate, at a highly sophisticated level, to learn more about how effective vaccines stimulate the human immune system and then to apply this information to the rational design of novel and highly targeted immunization technologies against vaccine-resistant pathogens.

Over the five year duration of the ADITEC project, impact will be seen in the areas of innovation, knowledge, European competitiveness, public health in targeted sub population groups and in the structuring of the European Research Area (ERA) in the field of vaccine research. The first three project years are complete and impact is very evident. However, future years will bring an increased level of impact in all of these areas as the consortium and its research matures.

NEW BIOMEDICAL PRODUCTS, CLINICAL METHODS, VACCINATION DEVICES, ROUTES AND TIME SCHEMES FOR ADVANCED VACCINATION TECHNOLOGIES.

ADITEC is generating new knowledge on the human immune response to vaccines with a range of innovative vaccine technologies, to design new preventive or therapeutic immunisation strategies that will impact on prevention, alleviation or cure of disease.

The partners of ADITEC have begun to tackle the development of different prototype and innovative second generation adjuvants, modulators and delivery systems, innovative live antigen delivery vector systems and new vaccine formulation and delivery devices. ADITEC has begun the evaluation of different routes of immunization for a range of well-defined antigens, formulations and delivery devices or vectors to provide information on the magnitude and quality of the immune response in different anatomical sites. The evaluation of differing immunization schemes, in particular heterologous prime-boost approaches to provide information on the immune responses at different anatomical sites has also been initiated. Specific prime-boost approaches combined with specific immunization routes are being comparatively evaluated and will allow an informed decision on selection on their use for new preventive or therapeutic vaccines for specific diseases.

Impact

In this stage of the ADITEC project, four patents, one related to expression systems comprising polynucleotides encoding proteins and useful in the treatment of infections, by Partner 29 (Okairos), another by Partner 31, Vaccibody on stem reactive bodies the third by Partner 25 (Erasmus) for the immunocompromised ferret model and lastly, Partner 11 (University of Gotenberg), Cholera toxin A-like polypeptide useful as adjuvant component have been filed.

1. In addition to the successful patents Partners 31, and 21 (Vaccibody, and King's College London) have each identified , in Year 1 new adjuvants while Partner 5 (Institute Pasteur) has identified a new vector allowing the delivery of ESX antigens into airway dendritic cells In year two, Partner 24, CRNS, identified a new technology of using Nod ligands encapsulated in PLA particles to induce mucosal immunity through sub-cutaneous administration. Partner 38, Bioneedle TG has identified that the Bioneedle technology has an adjuvant effect and Partner 34, Crossbeta, has developed a booster protein containing Crossbeta domains. Year three has seen 2 new immunization technologies from Partner 47(Abera) ; 1) Outer membrane vesicles (OMVs) displaying at the surface a chimera consisting of all three H56 antigens fused to the autotransporter Hbp. Intrinsic adjuvant activity, safe (non-live), and compatible with nasal delivery. Intranasal immunization with the OMV/Hbp-H56 vaccine induced high levels of IL-17 and conferred protection against challenge with virulent M. tuberculosis and 2) Chlamydia vaccine candidate in the form of OMVs displaying fragments of MOMP fused to Hbp produced. Additionally Partner 2 (SSI) has identified one new immunological technology, re-directing a systemically induced immune responses to the mucosa, and Partner 5 (Institute Pasteur) , a new versatile vector allowing antigen delivery of ESX antigens into airway dendritic cells.

In total, **22 new immunization technologies** have been reported as identified to date.

Clinical trial work is well underway and will begin to produce significant results in the coming grant periods. The t**welve clinical trials** in the diagram below are planned..

Sponsor /Partner	Vaccine Population Objectives	Comments
UIBK	**Licensed Hepatitis B vaccine - alum** Elderly & young adults.	Ongoing recruitment. Completes 2015
OXF **UNIGE/NVD/** **EMORY**	**Licensed Influenza ± MF59 adjuvant** Infants Systems biology of adjuvanted vaccines in infants	Completed
SURREY **NVD/ICL /UIBK**	**Comparison of adjuvants in young and elderly with neoantigen (H5N1)**	On Hold – antigen supply
MPG	**Novel rBCG**	Trial outside of ADITEC Completed Analysis ongoing
SURREY	**Comparison of adjuvants prime-boost, matched neoantigens discordant adjuvants systems biology 36 young adults** **Licensed hepatitis B vaccines with alum (Engerix) or AS04** (MPL - Fendrix)	Ongoing recruitment. First samples shipped to Emory.
SURREY	**Heterologous route of immunisation prime-boost, breadth of CMI: IM TIV and nasal LAIV** Young adults	Start Q4 2014 or 2015
NVD	**Characterisation of adjuvants** **Novel influenza / menB + novel adjuvants** Healthy adults	Completed
SURREY	**Enhancing mucsal immune responses by targeted IM immunisation** 40 Adult women	Recruitment Complete LPLV Q4 2014. Interim data analysed
UGOT	**Licensed oral cholera / LAIV** Young adults: Sublingual immunisation with subunit / live vaccines versus intranasal and oral	Completed
UOXF **NVGH**	**Novel IM typhoid/paratyphoid; WT *S. typhi* challenge:** Young adults Systems biology of *S. typhil* oral challenge and vaccination	Model completed Conjugate vaccine approved
NVGH **SURREY**	**Novel GMMA *Shigella sonnei* vaccine** 52 Young adults Phase 1 trial comparing IM / ID / IN (using device) immunisation, dose escalation, novel antigen	Recruitment completed Last immunisation Oct 2014 LPLV Apr 2015
SURREY	Phase 1 Comparison of adjuvants with model antigen	Not yet selected
TBD	Novel technology developed in ADITEC	Not yet selected

BOOSTING EXCELLENCE OF EUROPEAN VACCINE RESEARCH LEADING TO MORE AND BETTER GENERIC KNOWLEDGE NEEDED TO SUPPORT VACCINE DEVELOPMENT

Broader impact in European vaccine research will be accomplished by stimulating interaction and cooperation among scientists by facilitating the exchange of information on the progress of current projects, participation in scientific meetings, and publication of scientific papers. Beyond the scientific research community, impact will be made through building awareness about the ADITEC project, objectives, the need for better optimized vaccine enabling technologies to fight infectious diseases and the scientific progress.

Specifically supporting vaccine development, generic knowledge in the areas of preclinical models which assess safety and efficacy, as well as age related effects will be shared and will provide preclinical proof of concept for selected new preventive and therapeutic vaccine strategies. These studies will allow informed decisions on the use of these selected strategies for further non-clinical and clinical studies.

Systems biology approaches will be employed to understand how effective vaccines stimulate the human immune system. By employment of advanced systems biology approaches combined with state-of-the-art imaging as well as immunological assays, ADITEC partners will identify molecular signatures that correlate

with, and predict, various key parameters of the innate and adaptive immune response. In addition, insights into the molecular mechanisms driving innate and adaptive responses to vaccination will be gained and shared with the vaccine development community.

Impact

Year 1 of the ADITEC project has produced and disseminated a surprising amount of knowledge for only the first year of the project. **One hundred eleven publications** have appeared in peer reviewed journals. Total Impact Factor of 840 with 32% of ADITEC publication having an Impact Factor higher than 9. Seventeen of these publications were authored jointly between two or more ADITEC partners. The articles were published in peer reviewed journals with impact factors ranging from 2.731 to 54.420. Sixteen publications have factors over 10 and 38 between 5-10. The partners have identified **33 exploitable results** from work completed to date. The number of publications and exploitable results will grow as the project progresses.

ADITEC Publications: Journal Impact Factors 2014	
New England J Medicine (2)	54,420
Nature Reviews Immunology	33,836
Nature Biotechnology (1)	23,268
Nature Reviews: Microbiology (1)	21,182
Immunity (2)	19,748
PLoS Medicine	15,250
Journal of Experimental Medicine (2)	13,850
J Clinical Investigation (2)	13,765
Cell Host Microbe	12,194
Trends in Immunology (2)	12,031
Nature Protocols (1)	11,740
PNAS (9)	9,681
Cold Spring Harbor Perspectives in Medicine (2)	9,630
PloS Pathogens (1)	9,127
Journal of Controlled Release (1)	8,078
Trends in Microbiology (1)	7,910
Current Opinion in Immunology (2)	7,867
Science Translational Medicine (5)	7,800
Current Opinion in Biotechnology (1)	7,711
Seminars in Immunology (1)	7,250
European Respiratory Society Monograph	7,125
Molecular Therapy	7,040
Mucosal Immunology (2)	6,963
AIDS	6,557
Seminars in Immunopathology	6,482
Retrovirology (1)	6,470
Arteriosclerosis, Thrombosis and Vascular Biology	6,338

J Internal Medicine (2)	5,785
J Infectious Disease (3)	5,778
J Virology (2)	5,076
European Journal of Immunology (1)	4,970
Journal of Biological Chemistry (1)	4,773
Biochimica et Biophys Acta	4,660
Annals of the New York Academy of Sciences (2)	4,375
J Leukocyte Biology	4,304
Expert Review of Vaccines (2)	4,217
PloS one (12)	4,092
Infection and Immunity (1)	4,074
Applied and Environmental Microbiology	3,952
Pharmaceutical Research	3,952
Microbial Cell Factories (1)	3,550
Tuberculosis (1)	3,474
Vaccine (7)	3,458
Immunobiology (2)	3,205
Molecular Immunology (1)	2,917
Cytometry	3,066
Current Opinion in Pulmonary Medicine	2,957
Journal of Biomedical Optics	2,945
Lancet Respiratory Medicine	2,917
Tuberculosis (Edinb) (2)	2,540
Sensors	2,457
Immunology Letters (2)	2,367
International Journal of Tuberculosis and Lung Diseases (2)	2,731
Frontiers of Immunology (6)	

Extensive active dissemination has occurred through the three years as the project as ADITEC partners were invited to **40 international conferences**, made **208 conference presentations** and attended well over **150 conferences**.

The ADITEC project kick-off meeting was organized and attended by **100 participants**. The Year 1 Annual meeting was held in Nice, France and was attended by 106 participants. Year 3Annual Meeting was held in Brussels Belgium and had 108 participants. Concurrent with the Annual Meeting, we held the Systems Biology for Vaccinology meeting attended by 78 participants. Several work package meetings were held through the three years, along with 19 Steering Committee meetings. All of these meetings focused on project status reporting, decision making and sharing of information among a wide variety of organizational representatives. The External Advisory Board met, and through a series of meetings, made a formal recommendation for the selection of the 3rd Model antigen. They also reviewed all of the applications for the 2 SME/Public Health Commissioned Research Support Calls and made support recommendations to the Steering Committee. During Year 3 we instituted an EAB update teleconference mid-year.

The project "kick-off" press release was carried by approximately **100 news sources** (print and websites). Additionally, ADITEC made entries in four blogs, sent out six news messages, created a new "laymens" flyer for distribution to non-scientific audiences, published **6 newsletters,** mailed to **over 750 people**, and published **3 general articles** in journals creating a broad awareness of the project and its goals.

Scientifically, **nine new animal models** have been developed by Partners 24, 23, 5 and 42 (CRNS, French Atomic Energy, Institute Pasteur, and Imperial College). Pre-clinical studies were conducted to identify correlates of protection comparing different routes of immunization, prime-boost strategies and the effect of age in response to vaccination. Animal models of challenge with influenza (ferrets), M. tuberculosis (mice and guinea pigs) and Chlamydia (mice) were established are ready to conduct protection studies with selected formulations.

In addition, Partners 9, 33, 35, 2, 31, 19, 21 and 32, (NVD, Duotol, Microbiotec, SSI, Vaccibody, IRB, King's College and Pevion) have reported the identification of **26 new immunological signatures**.

REINFORCE THE EUROPEAN COMPETIVENESS THROUGH KNOWLEDGE EXPLOITATION BY EUROPEAN INDUSTRIES ACTIVE IN THE DEVELOPMENT OF VACCINES OR SUPPORTING PRODUCTS SUCH AS ADJUVANTS, VECTORS OR VACCINATION DEVICES.

The ADITEC project represents a very important model in public private partnerships (PPP) that could become a model for future initiatives. This approach was created because the required technologies and expertise are so varied and sophisticated that it could only be carried out if many different laboratories with overlapping excellence join together. The programme integrates the work of 42 partners from 13 countries. The involvement of a substantial number of European SMEs (13) and vaccine companies (2) in this field will result in a strongly enhanced and integrated exploitation by European industries. Their involvement and commitment with R&D activities are among the most competitive in the EU.

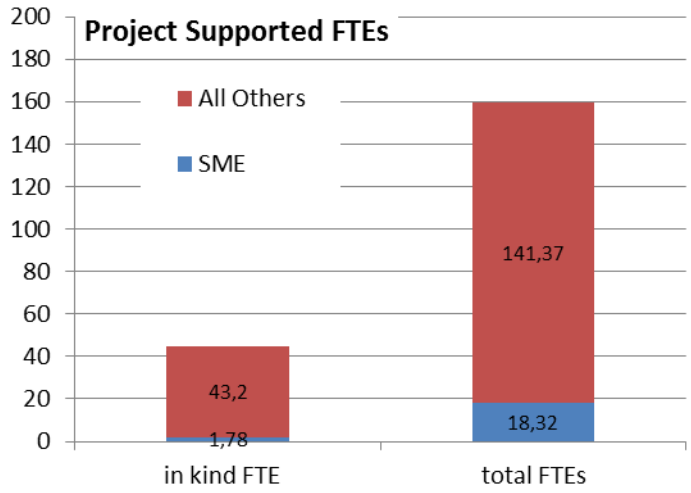
Internationally recognised training programmes cover targeted training in vaccinology at masters and professional levels, addressing both specific and broad aspects of translational immunology and vaccinology. The training will synergize with existing training schemes and support structures at Novartis Vaccines for Global Health and the University of Siena, the Advanced Course of Vaccinology (ADVAC) organized by University of Geneve and Fondation Merieux, translational vaccinology training at Surrey Clinical Research Cenetr, and training modules in adjuvant and vaccine formulation at WHO. These activities impact the European vaccine industry by mobilising these existing courses in a coordinated way and by promoting mobility and exchanges between participating EU countries and between academia and SME and industry institutions.

These joint training activities will provide another mechanism for bringing together the variety of project partners and also provide a vehicle to disseminate knowledge gained in the project. These approaches will facilitate the integration of research capacities, both public and private, across Europe and contribute to a wide dissemination of knowledge increasing European competitiveness.

Impact
ADITEC members participated in the development and teaching of both the ADVAC course, as well as the Masters Programme in Vaccinology and Pharmaceutical Clinical. For both Years 1 and 2, ADITEC sponsored **12 fellowships** for the Masters Programme**, 20 fellowships** in the ADVAC Course and will sponsor up to **12 fellowships** in the coming year. WHO in partnership with University of Lausanne developed and completed the theoretical and practical Adjuvant formulation courses. ADITEC sponsored **12 fellowships** for the theoretical course and **6 fellowship**s for the practical course and will do so again in the upcoming year. Training is also

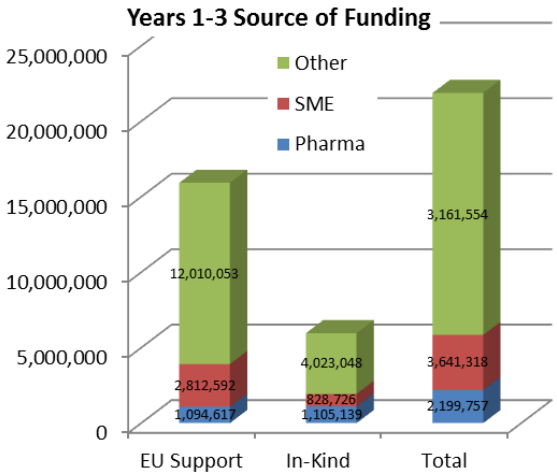
provided to Post docs/PhDs within the labs of partners. To date, **49.15 Post Doc/PHD FTEs** have been supported by ADITEC.

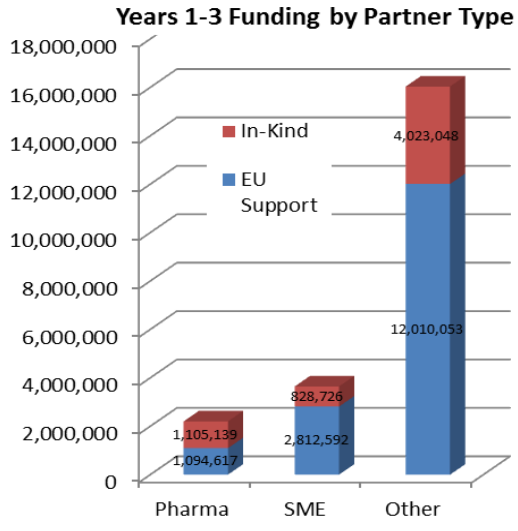
In total **159.69 FTEs** were reported receiving ADITEC support, with **18.32** located in SMEs. The project received **44.98 FTEs of in-kind support**, with 1.78 FTEs coming from SMEs.



In Euro, the first three years of the project was funded with a total of €21,874,176. Of this amount, €15,917,262 was European Commission support and €5,956,914 was in-kind donation. The expense distribution by type of organization is:

Total	Pharma € 2,199,757	SME € 3,641,318	Other € 16,033,102	Total € 21,874,176
EU Support	Pharma € 1,094,617	SME € 2,812,592	Other € 12,010,053	€ 15,917,262
In-Kind	Pharma € 1,105,139	SME € 828,726	Other € 4,023,048	€ 5,956,914





For Year 1,Partner 24 (CRNS) reported **€45.000 ERA funds leveraged** for vaccinology from the Euronanomed Research Program and Partner 23, (CEA) reported leveraging **330,000€. In Year 2, CRNS leveraged 35,000€ and CEA 450,000€. In Year 3, Kings College reported 100,000 € in additional funding and CRNS** again leveraged **30,000€** of additional funding.

PUBLIC HEALTH ISSUES IN TERMS OF DIRECTING RESEARCH TOWARD VACCINES FOR THE VERY YOUNG AND THE ELDERLY

As a most effective public health measure, vaccines are developed to meet the needs of the largest part of the target population, be it healthy children or adults. However, most of the disease burden in Europe affects individuals who are vulnerable because of their age (very young or elderly) or their co-morbidities. These vulnerable populations, routinely excluded from industry-sponsored clinical trials, are consequently deprived of evidence-based recommendations and/or efficient vaccines. This is demonstrated by the lack of influenza vaccines licensed for use prior to 6 months of age or by the most limited efficacy of split and subunit influenza vaccines in young children, in adults with chronic diseases affecting their immune competence, and in older adults. Similarly, gender issues have long been recognized as key determinants of immune responses, but key questions remain unanswered. Lastly, vaccines have long been considered as a "one size fits all" public health intervention, whereas genetic factors are now demonstrated as exerting a most critical influence on the predisposition to both infectious diseases and vaccine responses. These host factors affect both primary and memory vaccine responses, severely limiting the short-term and long-term benefit of current vaccines and immunization strategies.

Impact

Preclinical studies are actively underway in both elderly and neonatal mice. **Nine human studies**, have been initiated, **four** of which have been completed. and **five** are ongoing. **Two** remaining human studies are in the planning and development stage, while the final two are awaiting selection.

Mathematical models are currently being developed, and when data are available, will be used to assess age and gender related factors.

STRUCTURING THE EUROPEAN RESEARCH AREA IN THE FIELD OF VACCINE RESEARCH

In order to provide additional budget for innovative ideas and to advance promising candidate to the clinic and build other long term initiatives, an active dissemination, advocacy and resource mobilisation programme has begun. For this an extensive network of contacts with foundations, private funders, private industry, regional, national and European governments is being expanded to advocate for the impact on the economy, health, and competitiveness of the activities of this highly integrated programme, and to gain support for its co-funding and sustainability.

The Sclavo Vaccines Association is interfacing with other economic, industry and trade, health and developmental agencies of members and associated states national programmes. The association has developed links with other complementary partnerships and programmes in member states and associated members states in this area and has actively reached out to other stakeholders in the field of translational immunology and vaccinology.

Impact

Many collaborations among ADITEC supported researchers have been evident during the first year. The work of the ADITEC project is collaborative by nature with 42 partners involved over the 5 year period. During the first three years, **26 joint grant applications** were reported as submitted by our partners. **46 joint research projects** were initiated and **17 publications were co-authored** between two or more ADITEC partners. The work of 17 of the 19 work packages was designed having partners working across borders, which has promoted and will continue to facilitate extensive collaboration throughout the project. ADITEC partners have reported joining **17** international initiatives since the start of the project.

External partnerships have been solidified through **four Memoranda of Understanding** executed with, TBVI, European Vaccine Initiative and International Aides Vaccine Initiative (IAVI). Representatives from ADITEC met with high profile funders, regional and national governmental representatives advocating for the importance both from health and economic standpoints.

To date, the ADITEC coordinator has participated in the **submission of one concerted effort** to the European commission, one grant proposal, Innovation Partnership for a Roadmap on Vaccines in Europe (IPROVE) and . is currently working on a proposal in response to an IMI proposal call.

ADITEC has participated along with the University of Siena and Novartis, in the **creation of Master in Vaccinology and Pharmaceutical Clinical Development**, covering both specific and broad aspects of translational immunology and vaccinology. The training will integrate with existing training schemes and support structures . Six fellowship were awarded this past Year. The ADVAC Course of vaccinology organized by Partner 8 (Unige), 10 fellowships awarded. Two training modules, theoretical and practical, in adjuvant and vaccine formulation organized by Partner 22 (WHO) and University of Lausanne were completed in September 2013, 12 fellowships were awarded for the theoretical course and six for the practical course.. To date, ADITEC sponsored **12 fellowships** for the Masters Programme**, 20 fellowships** in the ADVAC Course and **16 fellowships** for the adjuvant formulation courses. These activities coordinate existing courses at a European level, thus promoting knowledge exchange among SME and industrial institutions in participating EU countries.

In just the first three years of the five year ADITEC project, impact is being made from new knowledge in the area of vaccines.. The extensive integration of universities, institutes, SMEs and industries built into the ADITEC project will help to close the gap between science and market, and will turn discovery into tangible vaccine products. This knowledge combined with the extensive dissemination plan and synergistic training activities will allow Europe's vaccine sector to keep pace as a leader in one of the quickest growing high tech segments of global business.