Project no.
511065

Project acronym
SARSVAC

Project title
Immunoprevention and immunotherapy of SARS infection

Instrument: **Specific Targeted Research Project**

Thematic Priority: **FP6-2003-SSP-2-SARS**

Title of report

Publishable final activity report

Period covered: **March 1st 2004- February 28th 2007**

Date of preparation: **October 10, 2007**

Start date of project: **March 1st 2004**

Duration: **36 months**

Project coordinator name: **Sergio Abrignani** (from March 1st 2004 to December 31st 2004)
Konrad Stadler (from January 1st 2005 to November 30th 2006)
Mariagrazia Pizza (since December 1st 2006)

Project coordinator organisation name: **Novartis Vaccines and Diagnostics S.r.l.** (ex Chiron S.r.l.)

1 Project execution

1.1. Summary of project objectives

The SARSVAC research project was aimed to three main objectives:

A. A killed virus vaccine that protects from SARS coronavirus infections

B. Recombinant vaccine based on SARS-CoVLPs

C. Human monoclonal antibodies against SARS-CoV for immunotherapy

1.2. Contractors involved

Partic. Role*	Partic. no.	Participant name	Participant short name	Country	Date enter project**	Date exit project**
CO	1	Novartis Vaccines and Diagnostics S.r.l.	NOVARTIS	Italy	Month 1 (start of project)	Month 36 (end of project)
CR	2	Philipps-Universität-Marburg	PUM	Germany	Month 1 (start of project)	Month 36 (end of project)
CR	3	Institute for Research in Biomedicine	IRB	Switzerland	Month 1 (start of project)	Month 36 (end of project)
CR	4	Fudan University	Fudan	People's Republic of China	Month 1 (start of project)	Month 36 (end of project)

1.3. Work performed and end results

- Preparation of an inactivated vaccine that protect from SARS coronavirus infections (Patent PCT, C12N7/00; Konrad Stadler, Anjeanette Roberts, Stephan Becker, Leatrice Vogel, Markus Eickmann, Larissa Kolesnikova, Hans-Dieter Klenk, Brian Murphy, Rino Rappuoli, Sergio Abrignani and Kanta Subbarao. SARS vaccine protective in mice. Emerging Infectious Diseases. 2005. 11-1312-1314).).
- Preparation of human monoclonal antibodies against SARS-CoV that can be used for passive immunotherapy (Traggiai E; Becker S, Subbarao K, Kolesnikova L, Uematsu Y, Gismondo MR, Murphy BR, Rappuoli R, Lanzavecchia A. An efficient method to make human monoclonal antibodies from memory B cells: potent neutralization of SARS coronavirus. *Nature Medicine*. 2004; 10:871-5; Lanzavecchia A, Bernasconi N, Traggiai E, Ruprecht CR, Corti D, Sallusto F. Understanding and making use of human memory B cells. 2006. *Immunol Rev* 211:303-309*)*. More than 400 mg of the three most interesting antibodies have been produced and stored with an efficient laboratory-scale production using EBV-B cell clones in high-density cell culture conditions free of any IgG contaminants of bovine or human origin. They are now suitable for structural and animal studies.
- Development of a recombinant vaccine based on SARS virus-like particles (VLP) which are non-infectious but will stimulate the production of antibodies and immune T-cells. For this part of the study a collaboration with NIH is still in course.

1.4.Impact of the project

The inactivated SARS-CoV vaccine, produced with a technology that has a safety record established by immunizing hundreds of millions of persons, protects mice from challenge with SARS-CoV. The vaccine adjuvanted with MF59 elicits neutralizing antibodies (titer 1:91) after only 2 doses. So, the vaccine vaccine obtained from SARSVAC project has desirable properties, and the results support further development and plans for clinical trials.
Another major impact that goes beyond the scientific achievement per se is related to the novel approach of producing monoclonal antibodies from human memory B cells (Patent: "Monoclonal antibody production by EBV transformation of B cells", Patent application No. PCT/IB2004/001071). Infact, Humabs LLC, a Delaware, USA limited liability company, was founded expressly to utilize and commercialize this technology and has obtained an exclusive license from the Institute for Research in Biomedicine. The SME Humabs SAGL, a Swiss subsidiary of Humabs, has been formed in Switzerland with the specific aim of strengthening Humabs' presence in Europe and of facilitating translation of the Humabs technology into therapeutic and diagnostic products for global markets.
The Humabs technology is now used for the production of highly potent neutralizing monoclonal antibodies to several serious human pathogens and toxins, including H5N1 influenza virus (Simmons CP et al, 2007, *PLoS Med*, in press), Malaria, Measles, Cytomegalovirus, Dengue virus, anthrax protective antigen, and diphtheria. All of these antibodies have been discovered in collaboration with leading non-profit institutions such as the US National Institute of Health, the University of Oxford and the Pediatric Dengue Vaccine Initiative, with support from The Wellcome Trust, the Bill and Melinda Gates Foundation and the EU HUMALMAB: *Human monoclonal antibodies for malaria research and therapy*).

1.5. Project web site

http://www.altaweb.eu/sarsavac

2. Dissemination and use

Section 1 - Exploitable knowledge and its Use

Overview table:

Exploitable Knowledge (description)	**Exploitable product(s) or measure(s)**	**Sector(s)** of application	Timetable for commercial use	Patents or other IPR protection	**Owner** & Other Partner(s) involved
Inactivated virus vaccine	A killed virus vaccine that protects from SARS coronavirus infections	Medical	2014	A patent has been filed in 2004 (PCT, C12N7/00).	Partner 1 (NOVARTIS
Human monoclonal antibodies	Human monoclonal antibodies against SARS-CoV for immunotherapy	Medical	2014	Patent	Partner 3 (IRB)

Section 2 – Dissemination of knowledge

Overview table

Planned/actual Dates	Type	Type of audience	Countries addressed	Size of audience	Partner responsible /involved
October 10th, 2004	*Kick-off meeting*	*SARS- VAC participants*	*EU*	*5*	*1, 3*
Overall period	*Direct e-mailing*	*Scientists*	*EU and China*	*All consortium*	*All participants*
June 6th, 2005	*Annual meeting*	*SARS- VAC participants*	EU	*All consortium*	*1*
December 2005	*Visit to Chinese partner*	*Coordinator and Chinese partner*	*EU and China*	*Students, researchers and local authorities*	*1,4*
May 9th, 2006	*Annual meeting*	*SARS-VAC participants*	*EU and China*	*All Consortium*	*1,4*
November 2006	*Visit to Chinese partner*	*Coordinator and Chinese partner*	*EU and China*	*Students, researchers and local authorities*	*1,4*
Overall period	*Publications*	*Scientists*	Worldwide		*All partners*

Meetings

The SARSVAC kick-off meeting was organized in Bellinzona (Switzerland) at the Institute for Research in Biomedicine (IRB) on October 10th, 2004. The second SARSVAC meeting was organized in Rome (Italy) at the Park Hotel AMARANTO Via Laurentina 5/F on June 6th, 2005, and the third annual meeting was been organised in China at the Fudan University, on May, 9th 2006.

Dissemination activities

The planned strategy for dissemination of SARSVAC results has been mostly focused on organizing meetings and seminaries in China to sensitize students, young and senior scientists and local authorities to SARSVAC project and describe the role played by the EU Commission. In addition, after the first meetings, a bilateral agreement between Italy and China has been finalized in 2006 to start collaborative studies on vaccines and related subjects.
A list of the above mentioned meetings is hereafter reported:

December 2005:
Meeting at the Shanghai Public Health Center (specifically created to study SARS and to cure patients). This meeting was done with the scope of starting collaborative links with China within research projects on human health issues.

May 2006:

- A first series of meetings at the Shanghai Medical College of Fudan University, Key Laboratory of Medical Molecular Virology, were devoted to the update of ongoing projects on vaccination strategies against SARS and to the planning of novel approaches for the prevention of pandemic flu. On behalf of the Shanghai Public Health Center was present the Vice Director (and Vice Dean of the Fudan Medical College) Prof. **Zhenghong Yuan**, Prof.

Di Qu (head of the Key Laboratory of Medical Molecular Virology), Prof. **Zhi-yi Xu** (the father of anti-hepatitis vaccination in China) and Dr. **Xuan-Yi Wang**. Informal presentation of 2 year-progress data of the EU project SARSVAC was given by Dr. Aldo Tagliabue from ALTA S.r.l. and the SARSVAC coordinator Dr. Konrad Stadler, and a long and informal discussion has followed, highlighting the difficulties of human sample handling along Chinese regulations and attempting to find suitable solutions that could foster effective collaboration and exchange. A specific discussion session was dedicated to initiatives of scientific collaboration:

1. Overview of the initiatives of bilateral collaboration between Italy and China in the field of scientific research, fostered by the national Ministries of Foreign Affairs, of particular relevance in the year 2006, which is the year of Italy in China;
2. Efforts of the EU Commission in fostering research collaboration with China, in particular in the field of public health threats such as viral diseases

The following discussion has established a series of issues of common interest in which both the Chinese and the Italian parties are strongly interested. These go from personnel exchange in research projects of immunology and vaccinology, to a better organized common use of unique blood samples from convalescent Chinese patients to detect the pathways of protective immunity against viral infections.

Finally a series of formal seminaries was given by Italian researchers at the Fudan Medical College.

Konrad Stadler (SARSVAC coordinator): **Vaccines against SARS**

Diana Boraschi (Institute of Biomedical Technologies of CNR, Pisa-Italy): **Role of innate immune mechanisms in the pathogenesis of autoimmunity**

Presentations were followed by intense discussion with students and University researchers.

- The meetings in China were concluded with the visit to the College of Traditional Chinese Pharmacy of the China Pharmaceutical University in Nanjing, the third Chinese partner of the exchange project. The visit to the College included two seminaries by Italian researchers:

Diana Boraschi (Institute of Biomedical Technologies of CNR, Pisa-Italy): **Role of innate immune mechanisms in the pathogenesis of autoimmunity**

Aldo Tagliabue (ALTA Srl): **MF59-adjuvanted vaccines for pandemic flu**

These were followed by a very lively and active discussion with the many students present to the seminaries

November 2006:

- Visit to the College of Traditional Chinese Pharmacy of the China Pharmaceutical University in Nanjing. Two seminaries have been held within the One-Day Course in Molecular Pharmacology organized for the students of the College:

Diana Boraschi (Institute of Biomedical Technologies of CNR, Pisa-Italy): **Macrophage innate responses in physiology and pathology**

Aldo Tagliabue (ALTA srl): **Progress in vaccines for emerging diseases**

Another visit was also done again

- Visit to the laboratories of the Shanghai Medical College of Fudan University whose agenda included a lot of meetings and discussions which have showed again the great will of Chinese researchers to start active collaborations outside China on research against pandemic viruses (SARS, bird flu) and to find together the solution to solve the actual bureaucracy obstacles of human samples handling.

On the whole the repeated visits to Shanghai and Nanjing have been very fruitful. Collaboration on scientific issues is not only possible but also bound to be of mutual interest and advantage. While the exchange project will foster collaboration on some specific research projects, a wider

collaboration is foreseen on global issues of public health, for which the bases have been already posed by ongoing EU-funded projects.

Section 3 - Publishable results

Publications.

Results obtained within the SARS-VAC project are already published or submitted for publication as reported below:

1. Daniel Voß, Anika Kern, Elisabetta Traggiai, Markus Eickmann, Konrad Stadler, Antonio Lanzavecchia, and Stephan Becker (2006). Characterization of severe acute respiratory syndrome coronavirus membrane protein. *FEBS Letters* 580(3):968-973
2. Stadler K. and Rappuoli R. (2005). SARS: Understanding the virus and development of rational therapy. *Curr. Mol. Med.* 5(7), 677-698
3. Wing-pui Kong, Ling Xu, Konrad Stadler, Jeffrey B. Ulmer, Sergio Abrignani, Rino Rappuoli and Gary J. Nabel (2005). Modulation of the immune response to the SARS spike glycoprotein by gene-based and inactivated virus immunization. *J Virol.* 79(22):13915-23
4. Stadler K., Roberts A., Becker S., Vogel L., Eickmann M., Kolesnikova L., Klenk HD., Murphy B., Rappuoli R., Abrignani S., and Subbarao K. (2005). SARS vaccine protective in mice. *Emerg. Inf. Dis.* 11(8):1312-14 [http://www.cdc.gov/ncidod/EID/vol11no08/04-1003.htm]
5. Stadler K., Masignani V., Eickmann M., Becker S., Abrignani S., Klenk H.D., Rappuoli R. (2003). SARS – Beginning to understand a new virus. *Nature Reviews Microbiology* 1, 209-218.