HEVAR

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Final activity report

HEVAR – Herpesvirus based vaccines against rotavirus infections	
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Hevar

HErpesvirus-based Vaccines Against Rotavirus infections

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1. PROJECT SUMMARY

HEVAR is a collaborative project involving four academic laboratories from four European countries (France, Switzerland, Germany, Italy) and four academic laboratories belonging to three South American countries (2 x Argentine, Brazil, Uruguay). The overall scientific goal of HEVAR was to contribute to a better understanding of the immune biology of rotavirus infections using a novel generation of gene transfer vectors derived from herpes virus simplex type 1 (HSV-1), as a first step towards the development of innovative genetic vaccines to fight against these pathogens, which are the most common and important cause of severe dehydrating diarrhoea in young children of developing countries.

In addition to contributing to a better understanding of the immune biology of rotavirus infection and of evaluating the feasibility of using HSV-1 vectors as anti-rotavirus vaccines, the main deliverables of HEVAR are a set of toolboxes containing a large collection of HSV-1-based and DNA-based vectors expressing mouse, monkey and human rotavirus antigens, that we have immunologically evaluated and rendered accessible to any academic team wishing to use them for vaccine development or fundamental research on rotaviruses.

A last set of deliverables consisted in a series of scientific meetings and events required to implement the transfer of knowledge and complex technology that is necessary to generate, produce, and evaluate, HSV-1-based gene transfer vectors in South America (including the implementation of a local platform for viral vector production and distribution), therefore improving the human capital and the technological competence of these countries, as well as the reciprocal transfer to European teams of knowledge on the biology of rotavirus and other endemic viruses with high social cost in South America, as a way to strengthen the awareness to, and the understanding of, these neglected diseases.

2. WORK PLANNED, PERFORMED, RESULTS ACHIEVED

The overall objectives of HEVAR were therefore (i) to generate a battery of HSV-1-based vectors expressing antigens from different rotavirus strains, either individually or in combination, (ii) to evaluate the ability of these vectors to elicit humoral and cellular immune responses, and particularly neutralizing and protective responses, in model animals (mice) and (iii) to implement the transfer of knowledge and technologies required to generate and produce the viral vectors in South-America. To achieve these major tasks, the HEVAR project was divided into 3 scientific work-packages (WP): Vector construction (WP1), Evaluation of immune responses (WP2) and Transfer of knowledge and technology (WP3).

For **WP1**, the first major task was to individually clone into different types of plasmids the genes encoding the 4 structural proteins (VP2, VP4, VP6 and VP7) and one non-structural protein (NSP4) from 4 different rotavirus strains: mice EC, monkey RRV, and human Wa and DS-1 strains, and to validate the identity of these genes through sequencing. This task was fully achieved, and the 20 rotavirus genes were cloned and validated. A second major task of WP1 was to generate HSV-1 vector backbones able to simultaneously express or display one or more rotavirus antigens from different loci and under the control of various types of regulatory sequences. This task was also fully achieved. Furthermore, we have generated more vector backbones than planned. A third major task was to use the backbones and the cloned rotavirus genes to generate HSV-1-based vectors expressing rotavirus proteins (both amplicon and recombinant vectors). As planned, the rotavirus genes were used to generate a large battery of HSV-1 vectors expressing single or combined rotavirus antigens. The expression profiles of these vectors, and the localization and properties of the expressed rotavirus proteins, have been characterized in infected cells, both by Western blotting and by immune-fluorescence studies. Importantly, in the last part of HEVAR we demonstrated that vectors simultaneously expressing 3 different rotavirus proteins (RRV VP2/VP6/VP7) were able to induce the *in situ* assembly of empty rotavirus-like particles, which is a major achievement of our project. Lastly, these vectors were sent to our immunology partners for immune-evaluation in

mice. We consider therefore that all major tasks of WP1 were successfully accomplished and the WP1 deliverables were satisfactorily achieved.
For **WP2**, the main tasks were to evaluate the toxicity and the immune responses elicited in model animals (mice) by the different vectors produced in WP1. Towards this end, during the first year of the period, WP2 partners had set up the experimental conditions and developed the tools and approaches required to perform the immune-evaluation. In the second and third years of the project this evaluation took place. The most important aspects of the immune evaluation were to study whether the vectors were able to elicit both humoral and cellular specific responses, to compare the relative efficacy of different routes of immunization, to characterize the nature of the humoral responses (type of immunoglobulins, neutralizing antibodies), and to explore if the vectors were able to induce protection to rotavirus challenge. Several different vectors, expressing mouse and monkey rotavirus antigens have been already immunologically evaluated in this way. Our results indicate that most of these vectors, but particularly amplicon vectors, elicited significant levels of humoral and/or cellular responses. Furthermore, some of the antibodies, raised by vectors expressing VP4 or VP7 antigens, displayed neutralizing activity and we also observed a significant level of protection against high-dose challenge with live rotavirus when using vectors expressing three different rotavirus proteins. These results are quite encouraging in the perspective of generating novel genetic vaccines. As above quoted, the number of HSV-1 vectors generated in WP1 is large, and immune-evaluation of other vectors is still ongoing.

In addition, as we have described in the second intermediary report, we had accumulated some delay in WP1 as some rotavirus genes were strikingly difficult to be cloned and, furthermore, when introduced into HSV-1 vectors, some unexpected toxic effect resulted in low-level production of the vectors, particularly in the case of recombinant vectors. Although most of these difficulties were later resolved, the delay accumulated in vector production resulted in a concomitant delay in vector evaluation, which explains why some vectors are still being evaluated now. This task will therefore be continued after the end of the project.

Regarding **WP3**, the main goals of the project were (i) to establish a technological vector platform in South-America, able to locally generate and produce viral vectors for South American partners, (ii) to implement the transfer of knowledge and methodologies between partners, based on trainings and exchanges between HEVAR laboratories and on the implement a PhD programme that allowed several South-American PhD students to accomplish part of their work in European laboratories, and (iii) to organize courses, conferences, and seminars, at the time of our general meetings. All these tasks have been satisfactorily accomplished. It is important to stress that the quality of the links established between South-American and European teams was very good and that in most cases the scientific collaborations and the training of young researchers will continue after the end of the present project.

In conclusion, virtually all tasks and deliverables planned at the beginning of the project have been successfully achieved, in spite of some difficulties described in the first and second intermediary reports. As a result, we feel that the work and results achieved by HEVAR constitute a significant advance in the comprehension of many aspects of the immune biology of rotavirus infection. The large set of available DNA-based and HSV-1 based vaccines that we have developed and are available to any academic laboratory willing to use them for their research will certainly boost further experimentation and novel approaches in the domain of rotavirus immune biology. The neutralizing and protective antibodies elicited, as well as the cellular responses we observed, demonstrate the feasibility and the interest of exploring innovative ways to immunize against rotaviruses, and represents a first significant step in the development of HSV-1-based vector vaccines to fight against these agents. Lastly, the implementation of a local platform for HSV-1 vector production in South America, as well as the training of many young South American researchers and technicians, who have learnt how to develop and to apply these vectors, will certainly contribute to further developments and collaborations in the field of viral vectors for gene transfer and as vector vaccines.

To finish, we would like to stress that the collaborations and links established between European and South American partners were both delightful in social terms and fruitful in scientific terms, and will, without any doubt and funded by other means, be continued in the future.

3. DISSEMINATION

The main dissemination events during the project were the three HEVAR Conference days, held in Buenos Aires, Rio de Janeiro, and Quilmes, as well as the theoretical and practical HEVAR-Midterm course held in Montevideo. All these conferences were highly successful, having attracted a large number of students and researchers. In addition, the goals, strategies, and results of the HEVAR project were disseminated and are still being disseminated essentially through talks and lectures, both in European and South American countries, as well as through oral presentations and posters communicated to scientific meetings. Two papers were already published (1, 2), a third manuscript has been recently submitted for publication and is now under revision (3), and two further articles are currently being prepared.

We would like to stress, however, that results and approaches, such as those produced or carried out by the HEVAR project, require not only the cloning of genes and the generation of vectors, but also the immunological evaluation of these vectors, and cannot therefore be published in good quality journals before the ending of the immune evaluation process which, in many cases, is still ongoing. Other manuscript will thus be submitted for publication as soon as this evaluation will be achieved.

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(2) Dresh C, Edelmann SL, Marconi P, Brocker T. Lentiviral-mediated transcriptional targeting of dendritic cells for induction of T cell tolerance in vivo. J Immunol 2008 Oct 1; 181(7): 4495-506

(3) D'Antuono A, Laimbacher AS, La Torre J, Tribulatti, V, Romanutti C, Zamorano P, Quattrocchi V, Schraner EM, Ackerman M, Fraefel C, Mattion N. HSV-1 amplicon vectors that direct the in situ production of heterologous antigens in mammalian cells may eventually be used for genetic immunization. Submitted (2010).

4. CONTRACTORS INVOLVED

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Universita degli Studi di Ferrara

University of Zurich

Ludwig-Maximilians-Universitaet Muenchen

Universidad de la Republica

Instituto Oswaldo Cruz

Universidad Nacional de Quilmes

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PROJECT OBJECTIVES AND MAJOR ACHIEVEMENTS DURING THE WHOLE PROJECT

1. PROJECT OBJECTIVES

Diarrhoea caused approximately 2 million deaths per year worldwide in the last decade and was responsible for an estimated 20% of mortality in children aged less than 4 years in developing countries. Rotaviruses are the most common cause of severe dehydrating diarrhoea in young children in these countries, accounting for 20% to 60% of hospitalized cases. Rotavirus infection and disease cannot be controlled by hygiene and sanitation measures and almost all children will be infected with rotavirus in the first years of life. An estimated 140 million diarrhoeal episodes, and a minimum of 450,000-600,000 deaths per year, with immense medical/societal costs, mainly in developing countries, highlights the urgent need for the development and deployment of an effective prophylactic anti-rotavirus vaccine, that would have universal application as part of childhood immunization programs.

The overall scientific goal of HEVAR was to contribute to a better understanding of the immune biology of rotavirus infections using a novel generation of gene transfer vectors, as a first step towards the development of innovative genetic vaccines to fight against these pathogens. To this end, HEVAR partners have developed a large battery of herpes simplex virus type 1 (HSV-1)-based vectors for the generation and analysis of rotavirus-specific expression and display model vaccines. Our approach was based on the possibility of engineering HSV-1-based vectors expressing and/or displaying rotavirus antigens, either individually or in combination, alone or together with immune-modulator genes. Our goal was to evaluate the ability of these vectors to elicit protective immune responses against rotavirus infection in mice, therefore helping to elucidate the contribution of individual rotavirus antigens, and of different components of the immune system, to the architecture of the immune response and to protection upon rotavirus challenge in this animal model. This project entailed therefore a truly innovative procedure that was expected to generate knowledge and technologies relevant for the ultimate development of a novel generation of prophylactic vector vaccines, rationally designed to prevent human rotavirus infections. We have the feeling that this was actually the case.

At the biotechnological level, the main deliverables of HEVAR are a set of toolboxes containing a large collection of HSV-1-based and DNA-based vectors expressing mouse and monkey rotavirus antigens that have been or are being evaluated in mice. These toolboxes also contain a set of vectors expressing human rotavirus antigens from strains with epidemiological significance in South America (Wa and DS-1 strains). These tools are currently available and accessible to any academic team wishing to use them for vaccine development or fundamental research on rotaviruses.

A last set of deliverables consisted in transfer of knowledge and technology. This included, on one hand, the transfer from European groups to South American partners, of the knowledge and complex technologies required to locally generate, produce, distribute, and evaluate, the HSV-1-based gene transfer vectors, therefore, improving the human capital and the technological competence of these countries. On the other hand, the South American partners have transmitted to European teams their knowledge on the biology of rotavirus and other endemic viruses with high social cost in South America, therefore strengthening the awareness to, and the understanding of, these neglected diseases. The collaborations and links established between European and South American partners have been delightful in social terms, and fruitful in scientific terms, and will, without any doubt, be continued in the future.

1. WORKPACKAGE 1 – VECTORS CONSTRUCTION (UZH)

1.1 Partners involved

	Organisation	Scientist names (team leader)	Country
WP leader	UZH	C. Fraefel	CH
Contributors involved in the reported work	UdelaR	J.Arbiza	UY
	IOC	J.P.Gagliardi Leite	BR
	UNIZH	C.Fraefel	CH
	UCBL	A. Epstein	FR
	UFRA	R.Manservigi, P.Marconi	IT
	UNL	J.D.Claus	AR

1.2 List of deliverables

Deliverable No	Deliverable title	Planned delivery date	Actual delivery date
D-1.1	Novel HSV-1 BACs	M8	M8
D-1.2	Cloned rotavirus genes	M8	M28
D-1.3	HSV-1 vector vaccines	M30	M36
D-1.4	Kits of evaluated HSV-1 vectors	M36	M42

D-1.1 Several HSV-1-containing bacterial artificial chromosomes (BACs) have been done. In addition, amplicon genomes containing one, two, or more IRES sequences, therefore allowing simultaneous expression of three proteins from polycistronic mRNA, were also achieved and were used for expressing two or three different rotavirus antigens. Furthermore, although not initially planned, we have adapted the Gateway cloning system (Invitrogen) to the amplicon vector system, therefore allowing the construction of vectors simultaneously carrying up to four different transcription units in the same genome. Therefore, this deliverable was achieved.

D-1.2 All planned rotavirus genes, belonging to four rotavirus strains have been amplified by RT-PCR and individually cloned into basic plasmids, expression plasmids, amplicon plasmids, and recombination plasmids. Their identity was confirmed by sequencing in all cases. Therefore, this deliverable also has been satisfactorily achieved.

D-1.3. As it will be described below, many different vectors have already been generated and many others are currently in the process of being achieved. We should note in this context that each rotavirus antigen can be used to generate different types of vectors (for example, amplicon vectors and recombinant vectors) and that each of these vectors can express one or more rotavirus antigens, or be under the control of different regulatory sequences. Therefore, the number of vectors that can be generated is huge, by far much larger than the number of rotavirus genes cloned (20 genes). In this way, more than thirty HSV-1 vectors have been already achieved, some of them expressing only one rotavirus antigen, some expressing two or more antigens, while others are being generated. We would like to stress that we have been successful in generating vectors that simultaneously express 3 different rotavirus antigens from the same strain and induce the assembly of empty rotavirus-like particles in the infected cells, which represents a major achievement in the field. Therefore, we consider that this deliverable also is achieved.

D-1.4. Several kits of evaluated vectors are already available. However, as stated in the precedent paragraph, the number of vector kits that can be generated and evaluated is very large. Therefore, while this deliverable can be considered as formally achieved, we would like to stress that several other vector kits already generated are currently being evaluated, and that the evaluations will continue after the end of the project.

1.3 Summary of activities

WP leader	C. Fraefel

Summary of activities done during the whole project

The overall aim of work package 1 (WP1) was to generate a full set of HSV-1 vector vaccines expressing human, rhesus and mouse rotavirus-specific antigens. Several partners contributed to this aim by cloning specific cDNAs of rotavirus genes from different strains, by constructing and characterizing viral vectors, by improving vector production, and by generating stocks of vector vaccines for WP2. The specific contributions of the different partners are summarized below:

UdelaR
UdelaR has sucessfully cloned genes (cDNA) from murine rotavirus EDIM-Cambridge strain (EC) and from the Rhesus monkey rotavirus strain (RRV), including VP6, VP7, VP4, VP2 and NSP4. The identity of all these genes was validated by sequencing.
UdelaR also constructed and produced HSV-1 amplicon vectors expressing rotavirus EC-VP6 or EC-VP7 genes. Expression of the individual genes was confirmed by Western blots and immune-fluorescence analysis.

IOC
The role of IOC was to clone and validate the cDNAs of VP2, VP4, VP6, VP7 and NSP4 genes from two human rotavirus strains, Wa and DS-1, from rotavirus infected cells. In addition, IOC has constructed and partially characterized HSV-1 amplicon vectors expressing the VP4, VP6 and VP7 genes from the Wa strain, and VP4 and VP7 from the DS-1 strain.

UNIZH
The goal of UNIZH was to (i) generate HSV-1 amplicon vectors expressing individual or combined rotavirus structural proteins, (ii) to characterize gene expression in vector transduced cells, and (iii) to prepare vaccine vector stocks for WP2. These objectives have been successfully completed. Moreover, the generation of rotavirus empty like particles (VLPs) by amplicons expressing two (VP2/VP6) or three (VP2/VP6/VP7) different rotavirus proteins was recently achieved, as demonstrated by electron microscopy and immunogold labelling. UNIZH has also developed new bacterial artificial chromosomes (BACs) for the future construction of HSV-1 vaccine vectors that display and express individual rotavirus genes fused to the HSV-1 glycoprotein C (gC) transmembrane domain. The BACs are functional in terms of encoding an infectious HSV-1 genome, but rotavirus genes have not yet been fused to gC.

UCBL
In addition to be the general coordinator of HEVAR, the main role of UCBL in WP1 was to generate amplicon plasmid backbones and helper viruses to produce amplicon vectors, using the Cre/loxP system generated in UCBL some years ago. UCBL was largely involved in the transfer of materials and technology to UNL, allowing this group to establish the technological platform for vector production in South America. In addition UCBL has adapted the Gateway cloning system (Invitrogen) to be used for the generation of amplicon vectors simultaneously expressing several transcription units. To this end, UCBL created one amplicon-gateway DEST plasmid, as well as several intermediary ENTRY plasmids for simultaneously cloning 2, 3 or 4 transcription units into the DEST amplicon plasmid. Some human rotavirus genes belonging to the human DS-1 strain are already cloned into different ENTRY plasmids.

UFRA
The main goal of UFRA was to generate defective recombinant HSV-1 vector vaccines that express one or more rotavirus antigens. Towards this end, UFRA has used both the standard homologous recombination approach in

mammalian cells, and later the engineering galK system for cloning rotavirus genes in the context of HSV-1-BACs. In this way, structural rotavirus genes (VP2, VP4, VP6, VP7) from human, murine and monkey strains have been individually introduced in different loci of the HSV-1 genome, and placed under the control of different regulatory sequences. Some of these vectors also express immune-modulator factors such as GM-CSF. We would like to note, however, that UFRA found that many of these vectors were very difficult to produce in large amount, as compared to control vectors, suggesting that some rotavirus proteins could be toxic for the infected cells. This is the first time we observe such a phenomenon.

UNL

The main task of UNL in WP1 was to optimise vector production in the vector platform in South America. More precisely, UNL contributed to this WP by (i) optimizing the culture and infection parameters in order to improve the production of replication-incompetent HSV-1 in Vero 7b cell cultures, (ii) determining the kinetics of production of replication-incompetent HSV-1 vectors in Vero 7b cell cultures infected at very low multiplicity of infection, (iii) optimizing the culture and infection parameters in order to improve the production of replication-incompetent HSV-1 vectors expressing rotavirus proteins in 7b cell cultures, (iv) evaluating the influence of temperature on the production of replication-incompetent recombinant HSV-1 expressing rotavirus genes, (v) evaluating the effect of cell passage on the production of replication-incompetent recombinant HSV-1 vectors expressing rotavirus proteins in Vero 7b cell cultures, (vi) evaluating the stability of rotavirus genes in replication-incompetent recombinant HSV-1 vectors, (vii) evaluating the ability of replication-incompetent recombinant HSV-1 vectors harbouring rotavirus genes to express recombinant products in non-permissive cells, and (viii) evaluating the effect of virus (replication-incompetent HSV-1 expressing GFP and rotavirus proteins) passage on the expression of GFP.

Main achievements and results

1. Cloning rotavirus genes.

All planned rotavirus genes were cloned and sequenced, thus validating their identities. We have cloned 20 rotavirus genes, encoding the 4 structural proteins (VP2, VP4, VP6, VP7) and one non-structural protein (NSP4) from 4 different rotavirus strains: rodent EC, monkey RRV, and human Wa and DS-1 strains.

2. Generation of vector backbones.

We have cloned several HSV-1 genomes into BACs, thus creating a very useful set of recombinant HSV-1 vector backbones to clone rotavirus genes in bacteria. These HSV-1 BACs can be used to express rotavirus genes or to display rotavirus antigens.

We constructed amplicon plasmids carrying one or two IRES sequences, thus allowing to express one, two or three rotavirus proteins from polycistronic mRNAs.

We adapted the Gateway cloning system (Invitrogen) to the amplicon vectors, thus creating both DEST plasmids and different ENTRY plasmids that allow the simultaneous cloning of several rotavirus genes into the same plasmid, but as individual transcription cassettes.

3. Generation of HSV-1 vectors expressing rotavirus antigens.

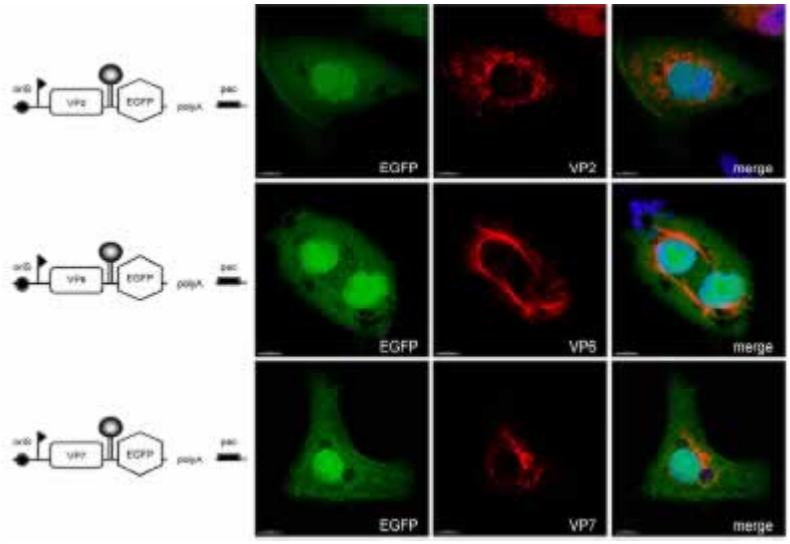
We have cloned the 20 rotavirus genes in standard amplicon and in recombinant backbone genomes, as well as in the novel backbone genomes (described in paragraph 2), therefore generating vector genomes that were then packaged into amplicon and recombinant vector particles. We have created many more than 20 vectors, each expressing one rotavirus proteins, since each rotavirus gene was introduced into different vectors, both amplicon vector and recombinant vectors, either alone or in combination, and placed under the control of different regulatory sequences, or even under the control of IRES sequences. Actually, we have constructed more than 30 vectors and several others are currently being achieved. Some of these vectors were produced as master and working stocks, while others exist only as master stocks. These vectors have been used to study molecular and cellular properties of the rotavirus proteins and were sent to partners in WP2 for immune-evaluation. A surprising observation was that while the amplicon vectors could be produced quite well, the recombinant vectors expressing rotavirus proteins were very difficult to be produced in large amounts.

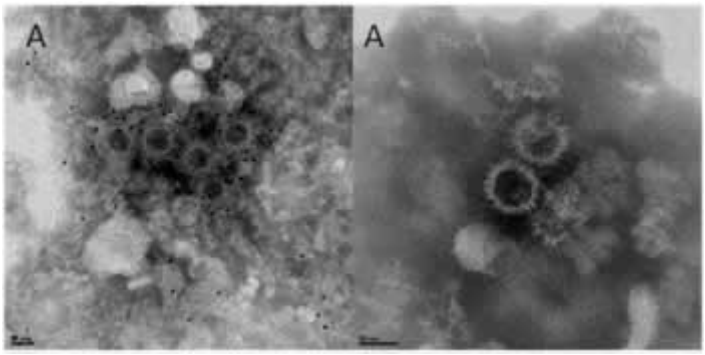
4. Properties of the vectors and of the rotavirus proteins expressed alone or in combination.

Many of the vectors described in the precedent paragraph were used to infect cultured cells, in order to study the toxicity of the vectors, the strength and kinetics of transgene expression, the localization and nature of the

rotavirus structural antigens (punctuated, fiber-like, diffuse), as well as the impact on each of them of the presence of other rotavirus proteins. These properties have been studied by indirect immune-fluorescence, using both optic and confocal microscopy, by Western blots, and in some cases by electron microscopy. Using well-characterized antibodies and antisera, we have in this way confirmed that the vectors expressed rotavirus proteins that had the expected molecular weight and formed structures already described in the literature. We observed that the structure formed by a particular protein when expressed alone was often profoundly modified by the concomitant presence of a second rotavirus protein, thus suggesting interactions between them. We observed, when using vectors that express three different proteins from a polycistronic mRNA that the second or third proteins were synthesized in much lesser amounts than the first, which has an impact in then kinetics of expression of the downstream proteins. In particular, when cells were infected with an amplicon vector expressing either two (VP2/VP6) or three (VP2/VP6/VP7) rotavirus proteins, we observed the assembly of empty rotavirus-like particles (VLP) at 48 hours pi, when the level of expression of the third protein was high enough. The identity of the VLPs was confirmed using immunogold under electron microscopy. This is a major achievement, since VLPs are particularly interesting as immunogenic structures. The future study of the immune responses of animals inoculated with vectors inducing the assembly of VLPs in vivo, could reveal the signification of these vectors as vector vaccines. To conclude, this approach allowed us to confirm that the different vectors expressed the expected rotavirus proteins in the infected cells. The vectors were then produced in large amounts and sent to partners in WP2, for immunological evaluation.

The details of the experiments and the results described in the above paragraphs were already presented in the intermediary reports. Just to illustrate some of our results, we are presenting here two pictures. The first one shows the intracellular distribution of RRV VP2, VP6 and VP7, individually expressed from different amplicon vectors (upper image), while the second shows electron microscopy images of RRV VLPs assembled in cultured Vero 2.2 cells infected with a polycistronic amplicon expressing RRV VP2, VP6 and VP7 and labelled with immunogold (bottom).





1.4 Dissemination

no	WP	Planned / actual Dates	Communication type	Type of audience	Targeted countries	Size of audience	Partner(s) responsible, involved	Report. period
1	ALL	25th March, 2007	Newspaper article - PERFIL	General public	Argentina, Uruguay, Chile, Brasil, Paraguay, España, EEUU	The newspaper distributes around 86,500 copies.	Graciela Glikmann, UNQ - Alberto Epstein, UCBL	1
2	WP1	28th March 2007	Oral	Researchers, PhD students, University students	Argentina	50	Peggy Marconi (UFRA)	1
3	WP1	28th March 2007	Oral	Researchers, PhD students, University students	Argentina	50	Roberto Manservigi (UFRA)	1
4	WP1	28th March 2007	Oral	Researchers, PhD students, University students	Argentina	50	Corinne Potel (UCBL)	1
5	WP1	28th March 2007	Oral	Researchers, PhD students, University students	Argentina	50	Cornel Fraefel (UZH)	1
6	WP1	28th March 2007	Oral	Researchers, PhD students, University students	Argentina	50	Mabel Berois (UdelaR)	1
7	WP1	28th March 2007	Oral	Researchers, PhD students, University students	Argentina	50	Alejandro Castello (UNQ) and Jose Paulo Leite (FioCruz)	1
10	WP1	39185	Oral	Biology and biochemistry students.	Uruguay	60	UdelaR	1
14	WP1	August to November, 2007	Oral	University students, Facultad de Bioquímica y Ciencias Biológicas, UNL	Argentina	26	UNL	1
15	WP1	14 September 2007	Oral	Italian Virologists	Italy	40	UFRA	1
16	WP1	39335	Oral	Researchers, PhD students, University students	Brazil	20	IOC	1
17	WP1	39345	Oral	Researchers, PhD students, University students	Uruguay	120	UdelaR	1
18	WP1	11-12/10/2007	Oral	Swiss Virologists	Switzerland	40	UZH	1
19	WP1	39377	Oral	Lecture	Brazil	20	IOC	1
20	WP1	29/11-21/12/2007	Oral	Biology students, University of Zurich	Switzerland	20	UZH	1
21	WP1	27 and 30 of November 2007	Oral	Master students, University of Ferrara	Italy	32	UFRA	1
22	WP1	39722	Oral	Researchers, PhD students, University students	Brazil	120	IOC	1
23	WP1	39722	Poster	Researchers, PhD students, University students	Brazil	120	IOC	1
25	WP1	6th May 2008	Invited Lecture	University of Giessen, Germany	Germany	40	UZH	2
26	WP1	30th May 2008	Training course	Undergraduate, MSc, PhD and Posdoc students	Uruguay	20	UdelaR	2

no	WP	Planned / actual Dates	Communication type	Type of audience	Targeted countries	Size of audience	Partner(s) responsible, involved	Report. period
28	WP1	12th June 2008	Invited Lecture	Microbiologists	International	250	UZH	2
29	WP1	20-21st June 2008	Lecture	Italian Microbiologists (SIMIF)	Turin - Italy	50	UFRA	2
32	WP1	August to November 2008	Lectures	Students of the course « Biology of the Viruses », career of Biotechnology, Facultad de Bioquímica y Ciencias Biológicas, UNL	Argentina	35	UNL	2
33	WP1	1st-15th September 2008	Theoretical-practical seminar:	Students of the course “General Biology”, career on Biology and career on Biochemistry.	Uruguay	10	UdelaR	2
35	WP1	22-23rd September 2008	Lecture	Italian Virologists (SIV)	Orvieto- Italy	100	UFRA	2
36	WP1	22nd September 2008	Lecture	Graduate and post-graduate	Switzerland	20	UZH	2
37	WP1	22-25th September 2008	Communication to the IX Argentine Congress of Virology*	Scientists	Argentina, Uruguay,	450	UNL	2
38	WP1 - WP2	22-25th September 2008	Communication to the IX Argentine Congress of Virology**	Scientists	Argentina, Uruguay,	450	UNL – UNQ	2
41	WP1	26th September 2008	Lecture	Post-graduate	Switzerland	25	UZH	2
42	WP1	October 2008	Communication at "XIX National Meeting of Virology and III Mercosul Meeting of Virology"	Researchers, PhD students, University students	Brazil	120	IOC	2
43	WP1	October 2008	Communication at "XIX National Meeting of Virology and III Mercosul Meeting of Virology"	Researchers, PhD students, University students	Brazil	120	IOC	2
44	WP1	13-15th October 2008	Lecture	Italian Microbiologists (SIM)	Rome - Italy	100	UFRA	2
45	WP1	27th November - 19th December 2008	Student’s course and lectures	Biology students, University of Zurich	Switzerland	20	UZH	2
46	WP1	22 and 29th of November 2008	Student’s course and lectures	Master students, University of Ferrara	Ferrara - Italy	32	UFRA	2
48	WP1 - WP2		Mid-term Hevar Conference - Montevideo, Uruguay					2
49	WP1	7-8th April 2008	Lecture	Students and young researchers	South American countries	100	UFRA	2

no	WP	Planned / actual Dates	Communication type	Type of audience	Targeted countries	Size of audience	Partner(s) responsible, involved	Report. period
50	WP1	7-8th April 2008	Lecture	Students and young researchers	South American countries	100	UZH	2
51	WP1	7-8th April 2008	Lecture	Students and young researchers	South American countries	100	UZH	2
52	WP1	7-8th April 2008	Lecture	Students and young researchers	South American countries	100	UFRA	2
54	WP1	9th-14th April 2008	Practical course	Selected students and young researchers	South American countries	20	UFRA / UCBL / UZH	2
55	WP1	9th-14th April 2008	Practical course	Selected students and young researchers	South American countries	20	UFRA / UCBL / UZH	2
56	WP1	9th-14th April 2008	Practical course	Selected students and young researchers	South American countries	20	UFRA / UCBL / UZH	2
57	WP1	9th-14th April 2008	Practical course	Selected students and young researchers	South American countries	20	UFRA / UCBL / UZH	2
58	WP1	9th-14th April 2008	Practical course	Selected students and young researchers	South American countries	20	UFRA / UCBL / UZH	2
63	WP1	May 28, 2010	Oral communication to the XIII Meeting of the Uruguayan Society for Bioscience:" HSV-1 amplicon vectors: a versatile tool for gene delivery in eukaryotic cells"	Scientists	Uruguay, Argentina	150	UdelaR	3
64	WP1	August to November, 2009	Lectures	Students of the course « Biology of the Viruses », career of Biotechnology, Facultad de Bioquímica y Ciencias Biológicas, UNL	Argentina	35	UNL	3
67	WP1	Sept 7-18, 2009	Theoretical-practical seminar: "The use of Herpes Simplex 1 as expression-vector and genetic therapy (amplicon system)"	Students of the course "General Biology", careers of Biology and Biochemistry.	Uruguay	10	UdelaR	3
68	WP1	October 2009	Communication to the XVII Young Researches Conference of the AUGM.*	Young scientists, students	Argentina, Uruguay, Brazil	500	UNL	3
69	WP1	Oct 15/16, 2009	Presentation Meeting of Virology PhD students	PhD students and supervisors	Switzerland	50	UniZH	3
70	WP1	October 28 2009	Lecture	PhD students and young scientists	France	50	UCBL	3

no	WP	Planned / actual Dates	Communication type	Type of audience	Targeted countries	Size of audience	Partner(s) responsible, involved	Report. period
74	WP1	December 2009	Communication to the XXIX Annual Meeting of the Argentine Society for Virology**	Scientists	Argentina, Uruguay, Brazil	120	UNL - UNIZH	3
76	WP1	Feb 4/5, 2010	Presentation Virology retreat	Members of Institute of Virology	Switzerland	30	UniZH	3
78	WP1	May 25, 2010	Presentation Course scientific presentations	PhD students	Switzerland	25	UniZH	3
79	WP1	June 3, 2010	Poster session workshop	PhD students	Switzerland	25	UniZH	3

1.5 Exploitable knowledge and its use

#	Exploitable Knowledge (description)	Category A, B or C	WP	Sector(s) of application	Timetable for commercial use	Patents or other IPR protection	Owner & Other Partner(s) involved
1	Novel vectors generation	A	WP 1	Research purposes	N/A	To be determined	UCBL, UFRA, UZH, UdelaR
2	Clones and sequences of all the structural genes from 4 rotavirus strains (2 human, one monkey and one mice)	A	WP 1	Research purposes	N/A	N/A	UdelaR, IOC,
3	Vectors inducing in situ assembly of empty rotavirus-like particles (VLPs)	A	WP 1	Research and/or commercial purposes	To be determined	To be determined	UZH
4	Different sets of DNA plasmids carrying the whole set of structured rotavirus genes either alone or in various combinations (around 50 plasmids)	A	WP 1	Research purposes	N/A	N/A - Available for the scientific community for research purposes	UCBL, UZH, UFRA, UdelaR, UNL, IOC
5	HSV-1-based vector genomes expressing the whole set of rotavirus structured genes both alone or in combination (around 30)	A	WP 1	Research purposes	N/A	N/A - Available for the scientific community for research purposes	UCBL, UZH, UFRA, UdelaR, IOC

2. WORKPACKAGE 2 – EVALUATION OF THE IMMUNE RESPONSES (LMU)

2.1 Partners involved

	Organisation name	Scientist name (team leader)	Country
WP leader	LMU	T. Brocker	DE
Contributors involved	LMU	T. Brocker	DE
	UNQ	G. Glikmann, A. Castello	AR

2.2 List of deliverables

Deliverable No	Deliverable title	Planned delivery date	Actual / Forecast delivery date
D-2.1	Evaluated rotavirus based vaccines (report)	M8	M10
D-2.2	Evaluated HSV-1-based vaccines (report)	M36	M43
D-2.3	Human rotavirus immuno-dominant epitopes identified	M36	Ongoing
D-2.4	Best combined HSV-1 vaccines identified	M36	M43

D-2.1. This deliverable was achieved in time.

D-2.2 and D-2.4. As already stated in the precedent chapter (WP1), we have constructed a very large battery of recombinant and amplicon vectors, which express different rotavirus antigens, both alone and in combination, and under the control of different regulatory sequences. Using those vectors we have infected animals (mice) in order to evaluate the immunological properties of these vectors. As described below many, but not all, vectors induced quite high levels of cellular and humoral responses. Furthermore, we have characterized which vector configurations are the best and which rotavirus antigens induce neutralizing and protective responses when inoculated via the intramuscular route with HSV-1 vectors. We thus consider therefore that D-2.2 and D-2.4 are achieved, even if other vectors are still being evaluated.

D-2.3. Due to the relatively low T-cell immunogenicity of the vectors and the difficulty to produce them in high amounts, it was not possible to initiate epitope mapping in HLA.A2-transgenic mice in due time. In order to perform epitope mapping and testing in HLA.A2 mice we need higher amounts of vector particles. This was not foreseeable in the beginning but it is now possible and the epitope mapping is now ongoing. This deliverable is therefore not yet achieved.

2.3 Summary of activities:

WP leader	Thomas Brocker (LMU)

Summary of activities done during the whole project	

The overall objective of WP2 was to evaluate the immune responses elicited in mice inoculated with vectors produced in WP1. The main tasks of this WP were to explore if the vectors elicited both humoral and cellular responses, to compare different inoculation routes, to analyse which type of vector configuration and which type of antigen behaved the best as a vector vaccine, to characterize the type of antibodies eventually induced, both in terms of immunoglobulin type and neutralizing activity, and to evaluate protection against rotavirus challenge. Two partners, LMU and UNQ, contributed to WP2. During the first year of HEVAR, while vectors were still not available, both partners set up the conditions to evaluate the humoral and cellular immune responses and

developed the required tools and approaches that have been used during the second and third year, once the vectors started to arrive for evaluation. UNQ worked in part with vectors produced in Europe (UNIZH and UFRA) and in part with vectors produced by UNL. Partner LMU worked only with vectors produced in the European laboratories. While UNQ focused in humoral responses and on protection against challenge, LMU focused mainly in cellular responses, though this partner also analysed in some cases the induction of antibodies.

LMU

Development of detection systems for HSV-based vaccine responses

In order to be able to monitor vaccine-induced immune responses, we set out to develop ELISA-based and flow-cytometry-based (FACS) methods for analysis of sera and lymphocyte population of immune mice. To this end we performed several pilot experiments for optimization with recombinant HSV-1-vectors produced by UFRA. More precisely, and as it was described in detail in the intermediary reports, the methods that have been set up by LMU were mainly (i) immunization, (ii) antibody detection, tetramer staining and flow cytometry, (iii) single-cell suspensions from lymph nodes and spleen, (iv) flow cytometric detection of intracellular cytokines after in vitro re-stimulation, (v) in vivo cyto-toxicity assay, (vi) HSV-1-ELISA, (vii) monitoring of expansion of antigen-specific CD8 T cells from peripheral blood of HSV-1 immunized mice, (viii) intracellular cytokine staining (ICCS), and (ix) evaluation of humoral responses

Evaluation of immune responses against HSV-1-based rotavirus vaccines

All vaccines, which we received, were tested immediately in the planned assays, testing immune responses against amplicon and recombinant vectors expressing mainly the VP6 protein from EC strain, although some vectors expressing EC-VP2 and EC-VP7 were also evaluated. Although first evaluations were negative, as new vectors became available in higher amounts, new assays were performed using stimulating peptides from these proteins as described in bibliography or predicted by special programs. Also, a different route (intramuscular, im) was tested for immunization and adopted for further assays because comparable responses were observed with the control HSV-1 peptide. Immune responses elicited by several recombinant and amplicon based vaccines were evaluated by ex-vivo stimulation of splenocytes with appropriate peptides. As described below, positive humoral and cellular responses against VP2, VP6 and VP7 were observed and quantified.

UNQ

Development of tools and detection systems for HSV-1 based vaccine responses

The main tasks developed by partner UNQ during the whole project were: (i) importation of the EDIM Cambridge (EC) murine rotavirus strains (G3P[17]) from Dr. Harry Greenberg Laboratory, Stanford University, California, USA (ii) setting up the conditions for propagating RRV and EC (culture adapted) rotavirus strains in roller bottles in order to obtain stocks of even quality for the assays to be performed through the complete project, (iii) production of immunological reagents and setting up of procedures (ELISA assays for murine IgG, IgA and IgM specific to rotavirus, antigen detection, production and storage as reference material of murine hyperimmune sera against rotavirus (RV), inactivated RV particles and splenocytes of RV hyperimmunized mice, setting up conditions for ELISA methods for detection of different isotypes of murine immunogobulins in sera and intestinal content, development of Fluorescent Focus Assay), (iv) development of a murine model of rotavirus infection (Strain ECwt), (v) development of ELISA methods to detect mouse IgG, IgA and IgM anti bGal, (vi) determination of efficacy and immunogenicity of different routes of inoculation using bGal expressing vectors (inoculation routes tested: subcutaneous, intraperitoneal, intragastric, oral (gelatin pellets), intranasal, intramuscular), and (vii) setting up of a positive control vaccine model.

Evaluation of immune responses against HSV-based rotavirus vaccines

Vectors tested:

- **1st set of experiments:** Recombinant vector: T0ZGFP-VP6 RRV (one dose and two doses). Amplicon vectors: pHSV-VP6 EC-EGFP, pHSV-VP2 EC-EGFP. Route of immunization: Subcutaneous.
- **2nd set of experiments:** Recombinant vector: T0 RRV VP6. Routes of immunization: intramuscular and intranasal. Amplicon vectors: pHSV-RRVVP7, pHSV-RRVVP4. Route of immunization: intramuscular.
- **3rd set of experiments:** Amplicon vectors: ZH1: expressing VP6 from EC strain, ZH2: expressing VP6 and VP2 from EC strain, ZH3: expressing VP6, VP2 and NSP4 from EC strain. Route of immunization: intramuscular.
- **4th set of experiments:** Amplicon vector: ZH4: expressing VP6, VP2 and VP7 from RRV strain. Route of immunization: intramuscular.

Main achievements and results

1. Humoral responses

We have observed medium to high levels of IgGs in sera of animals inoculated with amplicon vectors individually expressing EC-VP2, EC-VP6, RRV-VP4, RRV-VP7, as well as with amplicons simultaneously expressing EC-VP6/VP2 and RRV-VP6/VP2/VP7. In the case of amplicons expressing RRV VP4 and RRV VP7 we detected neutralizing antibodies. Furthermore, significant levels of protection were seen in animals inoculated with amplicons simultaneously expressing VP6, VP2 and VP7 from RRV strain. In contrast, we observed no IgA in the faeces of animals inoculated with amplicons, nor IgG in the sera of animals inoculated with recombinant vectors expressing RRV VP6.

These experiment demonstrate the ability of the amplicon vectors to induce high levels of antibodies when the vectors express a single protein and lesser levels when the amplicon expresses multiple genes. However, in two series of experiments with amplicons expressing surface proteins, even low-intermediate levels of antibodies demonstrate to have detectable neutralizing activity, and the response resulted protective in particular cases. This uneven protection might be due to suboptimal dose, so it would be worthy to increase the dose to confirm this hypothesis.

2. Immunization routes.

UNQ developed ELIZA methods to detect mouse IgA, IgM and IgG anti bGal and to determine the efficacy and immunogenicity of different routes of inoculation using bGal expressing vectors. The inoculation routes tested were subcutaneous, intraperitoneal, intragastric, oral, intranasal, and intramuscular. The intramuscular administration was the most effective route in terms of antibody production. In a 2-dose schedule, it was as effective as the subcutaneous and intraperitoneal routes, but antigen-specific IgG levels were detected after a single dose only by intramuscular administration.

3. Cellular responses

Different series of experiments were done, using both amplicon and recombinant vectors expressing EC-VP6 protein. Some tests were done also with amplicon vectors simultaneously expressing EC VP6/VP2/NSP4 or RRV VP6/VP7. The immunization route was intramuscular.

In a first series of experiments, we observed a clear cellular response (expansion of CD8 T cells) to EC-VP6 antigen expressed from amplicons, but not with recombinant vectors. In a second series of experiments, cellular responses were evaluated in terms of percentage of gamma-IFN producing CD8 T cells. In this case a positive response was again observed with amplicons expressing EC-VP6, but not with amplicons expressing more than one antigen. Again, the recombinant vectors resulted ineffective in inducing immune responses. In a third series of experiments, responses against EC-VP6 were again clearly detected. Notably, a slight increase in dose of the amplicon expressing EC-VP6 caused a much higher response. Low-level responses against EC-VP2 and RRV-VP7 specific peptides were also detected in mice immunized with the relevant amplicons.

To conclude, the immunological evaluations clearly show that HSV-1 amplicon vectors expressing rotavirus antigens are able to induce both humoral and cellular responses in mice, and that at least with some of the antigens (VP4, VP7) the vectors induce neutralizing antibodies. Furthermore, with amplicons expressing three rotavirus proteins (VP2/VP6/VP7), we also observed significant protective responses, which is perhaps related to the ability of these vectors to induce assembly of empty VLPs. Surprisingly, the recombinant vectors were negative, inducing no immune responses. It is not clear why, but this is probably related with the observation, detailed in the WP1 report, that recombinant HSV-1 do not grow well when carrying rotavirus antigens, which suggests that in the context of the recombinant-infected cells, the rotavirus proteins are probably too much toxic. But this is only a speculation for the moment. Our observation also indicate that HSV-1 amplicons expressing individual rotavirus antigens are able to induce the highest positive humoral and cellular responses when introduced via the intramuscular route, while the subcutaneous and intraperitoneal routes also induce immunization but with lower intensities. Amplicons simultaneously expressing more that one rotavirus proteins elicit positive responses mainly against the protein that is directly downstream the promoter, this is, the protein that is synthesized in greater amounts, as compared to the cistrons placed downstream IRES sequences. Although the difficulty already described in producing large amounts of vectors have somewhat limited the immunological evaluation, the results obtained so far are quite encouraging. The evaluations will thus continue after the end of HEVAR, particularly using the vectors expressing human rotavirus proteins, both alone and together, as independent transcription units.

2.4 Dissemination

no	WP	Planned/actual Dates	Communication type	Type of audience	Targeted countries	Size of audience	Partner(s) responsible, involved	Report. period
1	ALL	25th March, 2007	Newspaper article - PERFIL	General public	Argentina, Uruguay, Chile, Brasil, Paraguay, España, EEUU	The newspaper distributes around 86,500 copies.	Graciela Glikmann, UNQ - Alberto Epstein, UCBL	1
8	WP2	28th March 2007	Oral	Researchers, PhD students, University students	Argentina	50	Thomas Brocker (LMU)	1
9	WP2	28th March 2007	Oral	Researchers, PhD students, University students	Argentina	50	Graciela Glikmann, UNQ	1
11	WP2	6th July, 2007	Oral	Researchers, PhD students, University students	Argentina	30	Graciela Glikmann, UNQ	1
12	WP2	13th July, 2007	Seminar	Researchers, PhD students, University students	Argentina	20	Alejandro Castello, UNQ Laura Esteban, UNQ	1
13	WP2	13th July, 2007	Seminar	Researchers, PhD students, University students	Argentina	20	Romina Sian, UNQ	1
24	WP2	28th March 2008	Graduate Thesis.	Students, researchers and professors. Department of Science and Technology. UNQ	National	50	UNQ	2
27	WP2	5th June 2008	Intern Seminar.	Students and researchers. Department of Science and Technology. UNQ	Argentina	50	UNQ	2
30	WP2	12-16th July 2008	Poster presentation.	Virology Congress. 27th Meeting of the American Society for Virology. Cornell University, Ithaca, NY, USA	International		UNQ	2
31	WP2	12-16th July 2008	Poster presentation.	Virology Congress. 27th Meeting of the American Society for Virology. Cornell University, Ithaca, NY, USA	International		UNQ	2
34	WP2	2nd September 2008	Intern Seminar.	Students and researchers. Department of Science and Technology. UNQ	Argentina	50	UNQ	2
38	WP1 - WP2	22-25th September 2008	Communication to the IX Argentine Congress of Virology**	Scientists	Argentina, Uruguay,	450	UNL – UNQ	2
39	WP2	22-25th September 2008	Poster presentation.	IXth Argentine Virology Congress. Buenos Aires, Argentina	National		UNQ	2
40	WP2	22-25th September 2008	Poster presentation.	IXth Argentine Virology Congress. Buenos Aires, Argentina	National		UNQ	2

no	WP	Planned/actual Dates	Communication type	Type of audience	Targeted countries	Size of audience	Partner(s) responsible, involved	Report. period
47	WP2	2008 (in press)	Journal (Current Topics in Virology). Review article.	Virology researchers.	International		UNQ	2
48	WP1 - WP2		Mid-term Hevar Conference - Montevideo, Uruguay					2
53	WP2	7-8th April 2008	Lecture	Students and young researchers	South American countries	100	LMU	2
59	WP2	9th-14th April 2008	Practical course	Selected students and young researchers	South American countries	20	LMU	2
60	WP2	9th-14th April 2008	Practical course	Selected students and young researchers	South American countries	20	LMU	2
61	WP2	October 2008	Paper - J Immunol. 2008 Oct 1;181(7):4495-506	Scientists	International	NA	LMU	2
62	WP2	April 14th, 2009	Conference	Researchers and students	Brazil	100	IOC	3
65	WP2	11th August, 2009	Seminar “Immune response to amplicon vectors: Animal Mouse Model”. Centro de Virología Animal	Researchers, PhD students, University students	Argentina	20	UNQ	3
72	WP2	10th November 2009	Conference “Epidemiological Aspects of Rotavirus Infections in Latinoamerica” - Universidad Nacional de Quilmes	Researchers, PhD students, University students	Argentina	100	UNQ	3
73	WP2	November 10th, 2009	Conference	Researchers and students	Argentina	70	UNQ	3
77	WP2	29.3. – 2.4.2010	Conference, Poster	Researchers and students	International	100	LMU	3

2.5 Exploitable knowledge and its use

#	Exploitable Knowledge (description)	Category A, B or C	WP	Sector(s) of application	Timetable for commercial use	Patents or other IPR protection	Owner & Other Partner(s) involved
6	Evaluation of the immunologic potential of several HSV-1 based vector vaccines expressing different rotavirus antigens	A	WP2	Research and/or commercial purposes	To be determined	To be determined	LMU, UNQ, UZH
7	Immunization protocol	B	WP2	‘Immunization	n.a.	n.a.	n.a.
8	Read out of cellular immune response	B	WP2	vaccinology	n.a.	n.a.	n.a.
9	Read out of humoral immune response	B	WP2	Vaccinology	n.a.	n.a.	n.a.

3. WORKPACKAGE 3 – TRANSFER OF KNOWLEDGE AND TECHNOLOGY (UCBL)

3.1 Partners involved

	Organisation	Scientist names (team leader)	Country
WP leader	UCBL	A. Epstein	FR
Contributors involved in the reported work	UCBL	A. Epstein	FR
	IOC	J. P. Gagliardi Leite	BR
	UNIZH	C. Fraefel	CH
	UFRA	R. Manservigi, P. Marconi	IT
	UNL	J. D. Claus	AR
	UDELAR	J. Arbiza	UY
	LMU	T. Brocker	DE
	UNQ	G. Glikmann, A. Castello	AR

3.2 List of deliverables

Deliverable No	Deliverable title	Planned delivery date	Actual / Forecast delivery date
D-3.1	Annual lectures and seminars	M36	Several
D-3.2	Courses	M6	Several
D-3.3	Mid-term HEVAR conference	M18	M18
D-3.4	PhD programme	M36	M43
D-3.5	HEVAR vector production platform	M12	M24

D-3.1 and D-3.2. We have organized several lectures, seminars and courses during the HEVAR project. The most significant were the 3 HEVAR-Conference days, which took place in Buenos Aires (2007), Rio de Janeiro (2009) and Quilmes (Argentine) (2009).
D-3.3. The Mid-term HEVAR Conference took place in Montevideo, Uruguay, in April 2008, i.e., at the expected time. It was a very successful scientific meeting.
D-3.4. Several Master degrees and PhDs were developed during this project. Some PhD degrees will be obtained after the ending of the project.
D-3.5. The HEVAR production platform is achieved. All the biological elements required to produce high quality vectors are already in the laboratories of partner UNL and thanks to their participation to courses, conferences and individual trainings, UNL is able to produce optimized batches of the different vectors. Furthermore, several batches of HSV-1 vectors have been already prepared in UNL and sent to other partners.

3.3 Summary of activities

WP leader	A. Epstein

Summary of activities done during the whole project

The main goals of WP3 were (i) to establish a vector platform in South-America, able to locally generate and produce viral vectors for the South American partners, (ii) to organize courses and lectures, including three HEVAR-conference days and the Mid-term HEVAR Conference, at the time of our general meetings, (iii) to put

into practice the transfer of knowledge and methodologies between partners, based on exchanges between HEVAR laboratories, and particularly in supporting South-American PhD students of the network to accomplish part of their PhD work in Europe. All these tasks have been satisfactorily achieved. All partners contributed to this WP. We would like to stress that thanks to the high quality of the links established between South American and European partners, in many cases the collaborations and the training of young researchers will continue after the end of HEVAR.

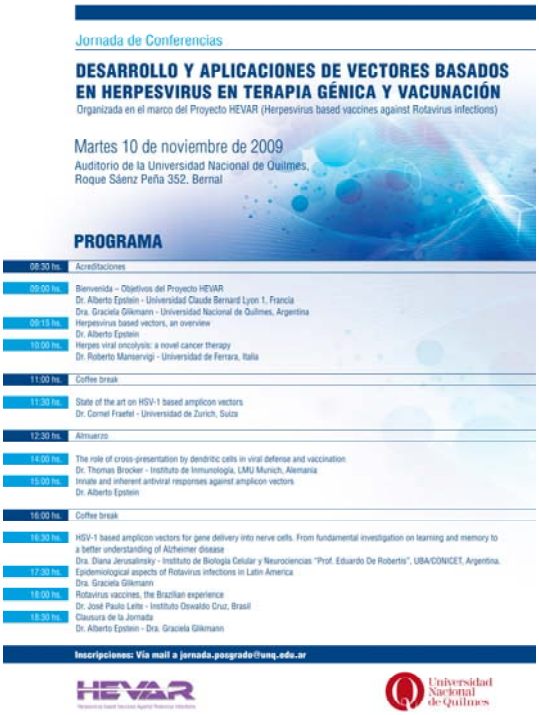
Main achievements and results

1. Establishment of a technological platform in Argentine.

Partners UFRA, UNIZH, UCBL and UNL were more particularly involved in this task. The European groups have transferred to UNL all the biological materials (essentially plasmids, cell lines, vector genomes and HSV-1 genomes) required for production and titration of both recombinant and amplicon HSV-1 vectors, while young students and researchers from UNL came to the European laboratories to learn vector technology. On the other hand, partner UNL optimized most of the parameters required for wild type HSV-1 and HSV-1-based vectors, it has produced working and master stocks of most of these materials, and several batches of HSV-1 vectors were produced and sent to partners UNQ for immune-evaluation, as described in more detail in the third intermediary report. Therefore, this technological platform is already functioning as a common service for the South American HEVAR partners, and we would like to stress that this platform is also collaborating with other teams in Argentina wishing to use HSV-1 vectors, even if they do not belong to the HEVAR network.

2a. HEVAR Conference days.

During the project we have organized 4 important courses: three HEVAR-Conference days and one Mid-term HEVAR Conference, always at the time of our general meetings in South America. The first HEVAR Conference day took place during the kickoff meeting in Buenos Aires (Argentine) in April 2007. The second was in Rio de Janeiro (Brazil) in April 2009, and the third was held in Quilmes (Argentina), in November 2009. These Conference days consisted in a series of 8 to10 talks, generally given by HEVAR partners, although both in the Rio de Janeiro and Quilmes conferences some talks were given by invited researchers. In all cases, the main topics of the Conference days were the development and applications of HSV-1 based vectors for gene therapy and vaccine development, but we included also topics on immunology and on epidemiology and pathogenesis of neglected diseases. The three Conference days were highly successful scientific events, which attracted many students and young researchers. We estimate that more that 200 people in total attended these conferences. In particular, the Rio Conference day Conference was homologated by the Rio de Janeiro University as part of the doctoral background of PhD students. The announcements of the Rio and Quilmes HEVAR Conference days are shown below.



2b. The Midterm HEVAR Conference on viral vectors as genetic vaccines against pathogens.

However, the most important activity of HEVAR in this respect was the organization of the Mid-term HEVAR conference. This conference was held in the city of Montevideo (Uruguay) from 7 to 14 April 2008. Due both to the number and high-level quality of the professors, and to the fact that all students were carefully selected amongst a long list of candidates, the Conference had a high international standard and was a very successful event, both from the scientific and social points of view, allowing that more than 50 researchers from different countries and continents spent together one week discussing on vector vaccines and tropical diseases. Furthermore, due to the validation of the Conference as a postgraduate course by the University of the Republic of Uruguay and to the agreements between most South American academies, all students received credits for their PhD curricula, meaning that this Conference was considered as a significant element of their PhD programmes.

The Conference started with a two-days series of lectures and seminars, extensively covering the fields of viral and bacterial vectors for gene transfer, applications of vectors as genetic vaccines to fight against viruses, bacteria and parasites, innate and immune responses of the hosts to vector infections and, lastly, molecular and immune biology of rotavirus infections (see annexed programme of the Conference). These lectures were held in English. The last session of the theoretical part of the Conference consisted in four presentations, followed by a round-table, on ethical, industrial, patenting, and other practical issues related to the use of biotechnologies. This round-table, to which participated four South American experts, was held in Spanish to facilitate the exchanges between lecturers and students. The second part of the Conference was a 6-days practical training on the generation and production of the different types of HSV-1-derived vectors, the assessment of transgene expression by molecular and immunological approaches, and the study of the immune responses elicited by these vectors in mice. In addition, the students red and discussed with the teachers several scientific papers related to the techniques they were learning. The last day of the Conference was devoted to the evaluation of the students. All of them succeeded and obtained rather high notes.

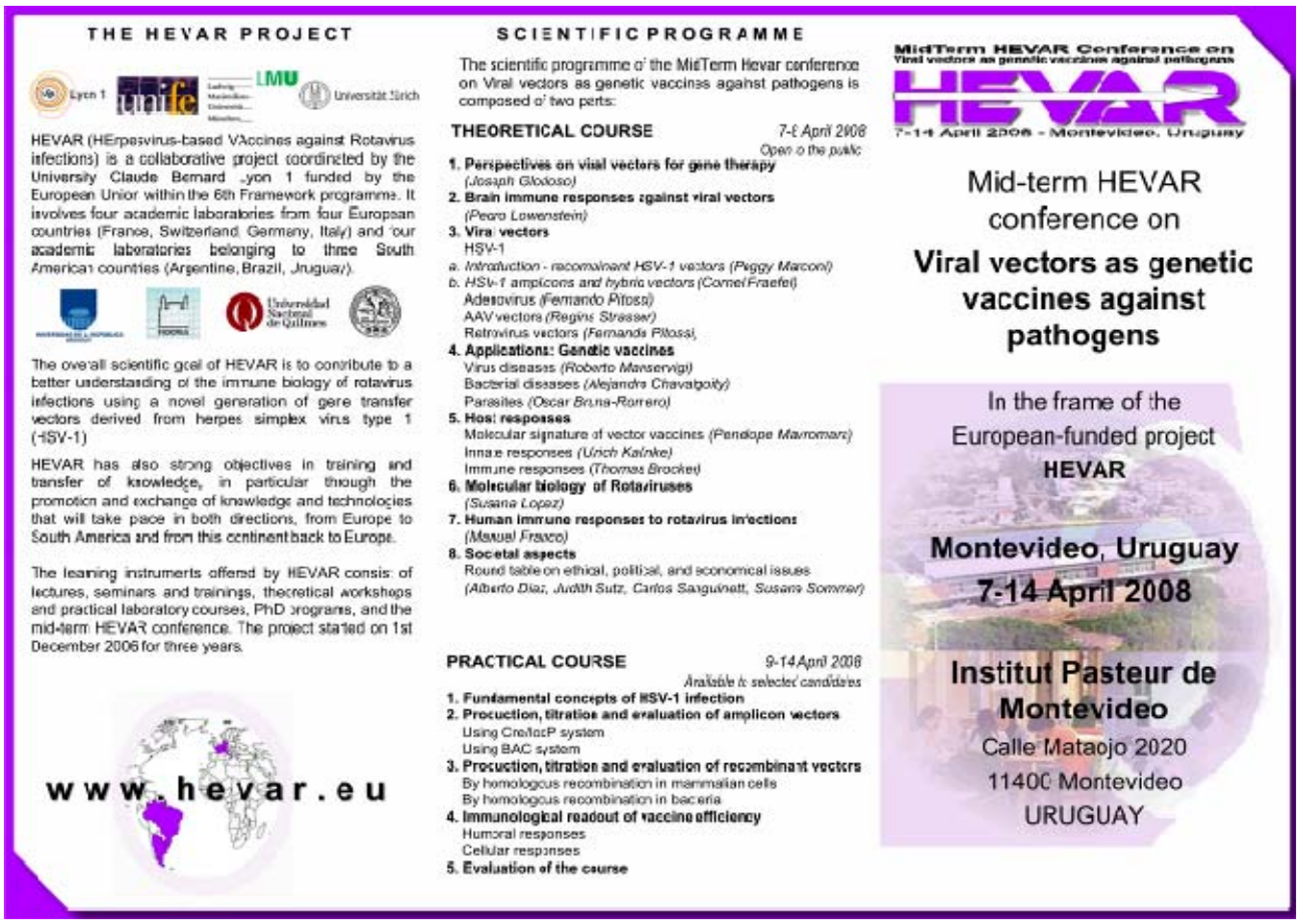
In addition to the HEVAR partners that participated as teachers, we invited a group of 12 professors, from Europe, USA and different South American countries. We covered their travels and other expenses. All of them, including several internationally recognized researchers, accepted to generously participate to the Conference without asking any fees. Several European technicians, researchers, and PhD students, belonging to the four HEVAR laboratories, took part to these trainings.

Since the theoretical lectures were open to the public, many students and researchers, mainly from Uruguay but also from Argentine, who did not received fellowships to participate to the Conference, attended nevertheless the lectures. We estimate the mean number of attendants to be close to a hundred people. Twenty-two students received fellowships covering travels and other expenses to participate to the Conference, including lectures and trainings. Actually we received more that 40 candidatures and decided to create a HEVAR Committee to select 22 students, based firstly on the excellence of their CV or of the laboratory where they are conducting their studies. In addition, we decided to keep a equilibrium between countries and universities in order to avoid as much as possible the participation of more that two students belonging to the same university or institute. The students that received fellowships belong to 6 different South American countries (Uruguay, Argentina, Brazil, Chili, Colombia,Venezuela) and represent more that 15 universities or research centres.

The main sponsor of the Conference was, of course, the European Commission, as most of the funds required for the fulfilment of the conference had been already budgeted in the HEVAR project. The second main sponsor was the Institute Pasteur of Montevido (IPMon), who accepted generously and without any restraint to give us the installations and scientific instruments of the IPMon for the practical trainings. Several biotechnology companies (Biriden, ProImmune, BD), both from Europe and South America, accepted to support the conference, generously providing us with reagents for the trainings and material for the courses.

To conclude, our feeling is that the HEVAR midterm Conference was a very successful event. The students and the teachers (both from HEVAR or not belonging to the network) agreed in that the lectures were of high level and presented the state-of the-art of the different vector systems and their possible applications as vector vaccines. The three conferences on the innate and adaptive immune responses to virus/vector infection were particularly appreciated, as was also the conference on the molecular biology of rotavirus infections. The practical trainings were achieved in time and the 22 selected students could participate to the construction of at least one class of vectors and to the assessment of their transgenic expression and their immunological impact in mice. According to their own declarations: this course was of paramount importance in their conceptual and practical training as researchers.

The announcement and the programme of the Mid-term HEVAR Conference are shown below.



Many other lectures and seminars were also given by individual partners of HEVAR as is described in detail in the Dissemination chapters.

3. Trainings and PhD programme

The last chapter of WP3 was to contribute to the transfer of knowledge and technologies required to locally generate, produce, and evaluate the HSV-1-based gene transfer vectors, therefore, improving the human capital and the technological competence of these countries. On the other hand, the South American partners have transmitted to European teams their knowledge on the biology of rotavirus and other endemic viruses with high social cost in South America, therefore strengthening the awareness to, and the understanding of, these neglected diseases. Concretely, this chapter consisted in trainings and in the implementation of a PhD programme that allowed many students, both from Europe and South America, to accomplish part of their PhD work in the laboratories of other HEVAR partners, as shown in Table 1 and Table 2.

Table 1. Trainings and exchanges accomplished during the whole duration of the project.

Name (Partner)	Destination (partner)	From	To
1. Verónica Gioria (UNL)	UDELAR	Dec 2006	Dec 2006 (two weeks)
2. Verónica Gioria (UNL)	UDELAR	Feb 2007	Feb 2007 (one week)
3. Lorena Tome (UDELAR)	UNIZH	Nov 2007	Nov 2007 (one week)
4. Andrea Blanc (UDELAR)	UNL	March 2007	March 2007 (ten days)
5. Matias Melendez	UNIZH	March 2008	April 2008 (one month)
6. Andrea Blanc (UDELAR)	UCBL	Sept 2008	Oct 2008 (two weeks)
7. Carlos Palacios (UNL)	UDELAR	March 2009	March 2009 (one month)
8. Karine Thoinet (UCBL)	UNIZH	JuLY 2009	July 2009 (two weeks)
9. Carlos Palacios (UNL)	UNIZH	Aug 2009	Sept 2009 (one month)

10. Rosana P. Rota (UNQ)	UNIZH	Aug 2009	Aug 2009 (one month)
11. Laura Esteban (UNQ)	UFRA	Sept 2009	Oct 2009 (two weeks)
12. Andrea Laimbacher (UNIZH)	UNL	Sept 2009	Sept 2009 (two weeks)
13. Laura Esteban (UNQ)	LMU	Oct 2009	Oct 2009 (three weeks)
14. Andrea Laimbacher (UNIZH)	UNL	Nov 2009	Nov 2009 (10 days)
15. Andrea Blanc (UDELAR)	UNQ	May 2010	May 2010 (one week)
16. Alejandro Castello (UNQ)	LMU	Jan 2010	June 2010 (6 months)
17. Carlos Palacios (UNL)	UNIZH	Sept 2010	May 2011 (nine months, funded by UNIZH)

Table 2. Diplomas obtained thanks to the implementation of HEVAR.

Name	Degree (Master or PhD)	Date (or expected date)
1. Andrea Blanc (UDELAR)	Master	November 2009
2. Fernando Lopez Tort (IOC)	Master	June 2010
3. María Florencia Rossetti (UNL)	Master	July 2010
4. Andrea Laimbacher (UNIZH)	PhD	December 2010
5. Rosana Rota (UNQ)	PhD	August 2011
6. Carlos Palacios (UNL)	PhD	December 2011
7. Laura Esteban (UNQ)	PhD	December 2011

4. CONSORTIUM MANAGEMENT

4.1 Involved partners

Workpackage number	**4**	**Start date or starting event:**				***M1***		
Workpackage title	**Management, Dissemination, Exploitation**							
Participant id	**P1**	P2	P3	P4	P5	P6	P7	P8
Person-months per participant:	**13**	1	1	1	1	1	1	1

4.2 List of deliverables

Deliverable No	**Deliverable title**	**Planned delivery date**	**Actual / Forecast delivery date**
D-4.1	*Project handbook*	*M2*	*M4*
D-4.2	*Collaborative website*	*M2*	*M4*
D-4.3	*Periodic activity reports – Year 1*	*M14*	*M14*
D-4.3	*Periodic activity reports – Year 2*	*M25*	*M25*
D4.4	Final activity reports, final management reports and audit certificates	M45	M45

The deliverables planned for the three project periods were delivered in due time.

4.3 List of milestones

- Final assessment review (completion of the project objectives, exploitation plan).

The final review took place on 10th June 2010 in Lyon, France.

4.4 Major change in the deadline, partners involved, resources

No major changes to comment.

4.5 Comments on main technical changes and impact on next activities

No major changes to comment.

4.6 Comments in regard to the partners' contribution

Part of the funds included in the Other costs budget for the training activities, as planned in Annex 1 under the item "Mid-term Hevar Conference" were transferred from UCBL to partner 5, Universidad de la Republica, since the consortium had not decided of the place where the Conference would take place when the proposal was submitted and negotiated, and had hence included the corresponding budget in the Coordinator's share of the funds. Montevideo, Uruguay, and the local Pasteur Institute have later been defined as the most suitable place to host the Conference, therefore the funds have been transferred to the local partner so as to make the organisation of the even easier from a practical and financial point of view. A transfer of 25 000 € has been formalised through the accepted first request of amendment.

4.7 Work description (starting point, progress towards objectives, summary of activities, difficulties and proposed solutions, deviations and corrective actions if applicable)

- **Task 1. Monitoring of the scientific aspects of the project**

The scientific coordination of the project relies mainly on intensive contacts between the coordinator and the workpackage leaders, as well on reports submitted regularly by each scientific manager on the collaborative website.

- **Project meetings**

Consortium meetings and conference days						
Place	**Date**	**Participants**	**Related WP**	**Main object**	**Conclusions**	**Report. Period**
Buenos Aires, Argentina	27th March 2007	All	WP3	First Hevar training course	-	1
Buenos Aires, Argentina	29th to 30th March 2007	All	All	Kick-off Meeting,	Main deliverables for 1st year and work implementation	1
Ferrara, Italy	5th October 2007	All	All	HEVAR – General assembly meeting	Discussion of results obtained during the first 6 months of the project and work implementation.	1
Montevideo, Uruguay	10/04/2008	All	ALL	General assembly meeting	Presentation of work done and results, scientific discussions, workplan for the next 6 months	2
Montevideo, Uruguay	7-14th April 2008	All	ALL	Mid-term Hevar Conference	All partners + external students	2
Munich, Germany	13/10/2008	All	ALL	Mid-term assessment review of the project results	Assessment of the obtained results, workplan for the coming period, scientific discussions.	2
IOC, Rio de Janeiro, Brazil	14th April 2009	All	WP3	Hevar Conference day	-	3
IOC, Rio de Janeiro, Brazil	15-16th April 2009	All	ALL	HEVAR - General assembly meeting	Assessment of the progress of the project, workplan for the coming 6 months	3
University of Quilmes, Buenos Aires, Argentina	10th November 2009	All	WP3	Hevar Conference day	-	3
Buenos Aires, Argentina	11th-12th November, 2009	All	ALL	HEVAR - Consortium Meeting	Discussion of results obtained and work implementation.	3
Université Claude Bernard, Lyon, France	10th June 2010	All	ALL	HEVAR – Final Assessment Review meeting	Discussion of results obtained during the whole project.	3

Technical meetings (internal partners meetings)				
Place	**Date**	**Participants**	**Related WP**	**Main object**
UDELAR – Montevideo (Uruguay)	December 2006 (two weeks)	Verónica Gioria – Andrea Blanc – Juan Arbiza	WP1-WP3	Training
UDELAR – Montevideo (uruguay)	February 2007 (two days)	Verónica Gioria – Andrea Blanc – Juan Arbiza	WP1-WP3	Obtention of cell lines.
UNL – Santa Fe (Argentina)	March 2007 (two weeks)	Andrea Blanc – Verónica Gioria – Carlos Palacios	WP1-WP3	Training and technology transfer
UDELAR – Montevideo (Argentina)	July 2007 (one day)	Juan Arbiza . Mabel Berois – Juan Claus	WP1-WP3	Exchange of information regarding vector production.
Buenos Aires	10th August, 2007	Juan Claus, Nora Mattion and Graciela Glikmann	WP2 and WP1	Meeting of members of Production Platform Group and LIV team at Universidad Nacional de Quilmes.
UNIFE (Ferrara, Italia)	October 2007 (one day)	Peggy Marconi – Juan Claus	WP1-WP3	Exchange of information regarding vector production – Arrangements for vector transfer from Italy to Argentina.
UNIZH_ Zurich	November 2007 (one week)	Lorena Tome	WP1-WP3	Training and technology transfer
Buenos Aires, Argentina	December 2007	Alberto Epstein, Graciela Glikmann	WP2 - WP3	Preparation of the Hevar mid-term Conference
Montevideo, Uruguay	December 2007	Alberto Epstein, Juan Arbiza	WP1 - WP3	Preparation of the Hevar mid-term Conference, meeting with the Pasteur Institute representatives
Zurich, Switzerland	March 3- 27, 2008	Matias Melendez	WP1	training
UDELAR – IP-Mon, Montevideo (Uruguay)	April 2008	Graciela Glikmann – Nora Mattión – Carlos Palacios – Juan Claus	WP1-WP2	Arrangements for vector transfer from UNL to UNQ.
Zurich	June 2- Sept. 29, 2008	Alejandra d'Antuono	WP1	training
Madrid, Spain	2-4 July 2008	Alberto Epstein, Cornell Fraefel	WP1	Technical meeting
UNQ, Buenos Aires (Argentina)	July 2008	Marcelo Argüelles – Carlos Palacios	WP3	Transfer of vectors for immunological evaluation
SAV 2008 Buenos Aires, Argentina	September 22-25	Andrea Blanc – Lorena Tome - Alejandro Castello	WP1	Congress. Transfer of EC rotavirus strain samples.
Lyon, France	September 28 – October 11	Andrea Blanc – Juan Arbiza	WP1	Training, technology transfer and discussion of preliminary results.

Place	Date	Participants	Related WP	Main object
UdelaR Montevideo (Uruguay)	November 13 2008	Juan Arbiza - Mabel Berois – Alberto Epstein	WP1	Exchange of information and planning on vector production.
UNQ – Buenos Aires (Argentina	November 2008	Marcelo Argüelles – Carlos Palacios	WP3	Transfer of vectors for immunological evaluation
UdelaR-Faculty of Sciences, Montevideo (Uruguay)	March 15-25, 2009	UdelaR - UNL (Lorena Tomé- Carlos Palacios)	WP1	Training, technology transfer and production.
UdelaR-Faculty of Sciences, Montevideo (Uruguay)	June 2009	UdelaR - UNL (Juan Arbiza – Mabel Berois - Juan Claus)	WP1	Optimization of production of amplicon vectors.
Buenos Aires, Argentina	28 June 2009	UNQ - UNL (A. Castello, R. Rota, M. Argüelles, L. Esteban, J. C. Abdusetir, N. Mattion, C.Palacios, G. Glikmann)	WP2 and WP3	Internal Meeting
UdelaR-Faculty of Sciences, Montevideo (Uruguay)	June 2009	UdelaR - UNL (Juan Arbiza – Mabel Berois - Juan Claus)	WP1	Optimization of production of amplicon vectors.
Buenos Aires, Argentina	2 June 2009	UCBL - UNL (Alberto Epstein - Nora Mattion - Alejandra d'Antuono)	WP1-WP3	Technical meeting with UNL regarding dissemination actions
UZH, Zürich, Switzerland	July 2009	UZH - UCBL (Andrea Laimbacher - Karine Thoinet)	WP1	Technical training
International Herpes Virus workshop 2009, Ithaca, USA	July 2009	UCBL - UFRA - UZH (Alberto Epstein - Roberto Manservigi - Peggy Marconi - Cornel Fraefel)	WP1	Technical meeting with UZH and UFRA (International Herpes Virus workshop 2009)
UdelaR-Faculty of Sciences, Montevideo (Uruguay)	August 8-25, 2009	UdelaR - IOC (Andrea Blanc- Fernando Lopez Tort)	WP1	Training and technology transfer.
UZH, Zürich, Switzerland	August 2009	UNL - UNIZH (Carlos Palacios – Andrea Laimbacher – Cornel Fraefel)	WP1 - WP3	Training and technology transfer.
University of Quilmes, Buenos Aires, Argentina	01/11/2009	UNQ - UNL (G. Glikmann–A. Castello – M. Argüelles – C. Palacios – N. Mattión – Juan Claus)	WP1	Transfer of vectors for immunological evaluation
University of Quilmes, Buenos Aires, Argentina	November 2009	UCBL - UNL (Alberto Epstein – Nora Mattión – Carlos Palacios – Juan Claus)	WP1 - WP3	Technology transfer
University of Quilmes, Buenos Aires, Argentina	November 2009	UNQ - UNL (Graciela Glikmann – Alejandro Castello – Marcelo Argüelles – Carlos Palacios – Nora Mattión – Juan Claus)	WP1 - WP2	Transfer of vectors for immunological evaluation
Buenos Aires, Argentina	December 2009	UCBL - UNL (Alberto Epstein - Nora Mattion - Carlos Palacios)	WP1-WP3	Technical meeting with UNL regarding dissemination actions

Place	Date	Participants	Related WP	Main object
University of Quilmes, Buenos Aires, Argentina	March 2010	UNQ - UNL (G. Glikmann – Marcelo Argüelles - Juan Claus)	WP1	Transfer of vectors for immunological evaluation.
University of Quilmes, Buenos Aires, Argentina	March, 2010	UNQ - UNL (Graciela Glikmann – Marcelo Argüelles - Juan Claus)	WP1 - WP2	Transfer of vectors for immunological evaluation.
UdelaR-Faculty of Sciences, Montevideo (Uruguay)	April 5-23, 2010	UdelaR - IOC (Andrea Blanc- Fernando Lopez Tort)	WP1	Training, technology transfer and production.
University of Quilmes, Buenos Aires, Argentina	May 7-11, 2010	UdelaR - UNQ (Andrea Blanc- Laura Esteban- Juan Carlos Abducetir)	WP1	ELISA with serum samples from mice immunized with amplicons expressing VP6 and VP7 EC
UZH, Zürich, Switzerland	May 16-22, 2010	UFRA - UZH (Sabrina Facchiolo, Andrea Laimbacher)	WP1	Technical Training
Buenos Aires, Argentina	17-20 May, 2010	UdelaR - UNQ (G. Glikmann, M. Argüelles, L. Esteban, J.C. Abdusetir A. Blanc)	WP1, WP2	Internal Meeting

- **Involved workforce**

Partner	Name	Position	Sex	Date of entry into the project team	Date of exit from the project team
UCBL	Alberto Epstein	Group leader	Male	01/12/2006	30/06/2010
UCBL	Aldo Pourchet	PhD student	Male	01/02/2008	30/09/2008
UNQ	Alejandro A. Castello	Researcher	Male	01/12/2006	30/06/2010
LMU	Andela Kozar	Lab-aid	Female	01/04/2007	31/07/2008
UdelaR	Andrea Blanc	PhD student	Female	01/12/2006	30/06/2010
LMU	Andrea Bol	Animal care taker	Female	01/08/2007	30/11/2008
UZH	Andrea Laimbacher	PhD student	Female	01/12/2006	30/06/2010
UZH	Anna Paula de Oliveira	PhD student	Female	01/12/2007	30/06/2010
LMU	Anna Wähe	PhD-Student	Female	15/10/2008	14/10/2009
LMU	Bettina Kellersch	Scientist	Female	01/01/2009	31/03/2010
UNL	Carlos Palacios	PhD student	Male	01/12/2006	30/06/2010
LIP	Carole Hugon	Other	Female	01/12/2006	30/03/2010
LIP	Cédric Henry	Other	Male	01/12/2008	30/06/2010
LIP	Christelle Missonnier	Financial controller	Female	01/12/2006	30/06/2010
LMU	Christian Barthels	PhD-student	Male	15/03/2010	30/04/2010
LMU	Christiane Dresch	PhD-Student	Female	01/01/2007	Dec 2007
LMU	Christine Federle	Technician	Female	March 07	01/09/2008
LMU	Christine Ried	Technician	Female	01/02/2006	30/04/2010
LMU	Christine Rothenaigner	Other	Female	01/01/2007	31/12/2008
UCBL	Colline Biollay	Technician	Female	01/12/2007	28/02/2009
UZH	Cornel Fraefel	WP1 leader	Male	01/12/2006	30/06/2010
UFRA	Elena Berto	Research Scientist	Female	01/12/2006	30/09/2009
LIP	Florence Coutarel	Other	Female	01/12/2006	30/06/2010

Partner	Name	Position	Sex	Date of entry into the project team	Date of exit from the project team
LMU	Gisela Mair	Administration	Female	01/03/2007	30/06/2010
UNQ	Graciela Glikmann	Professor	Female	01/12/2006	30/06/2010
LMU	Hartmut Engelmann	Staff-scientist	Male	Feb 2007	01/10/2007
LIP	Hongxia Chanal	Other	Female	01/04/2008	30/06/2010
UFRA	Ilaria Volpi	PhD student	Female	Nov. 1, 2007	30/06/2010
LIP	Javier Olaiz	Other	Male	01/12/2006	30/06/2010
UCBL	Joëlle Thomas	Assistant Professor	Female	01/12/2006	30/06/2010
IOC	José Paulo Gagliardi Leite	Group leader	Male	01/12/2006	30/06/2010
UdelaR	Juan Arbiza	Group leader	Male	01/12/2006	30/06/2010
UNQ	Juan Carlos Abdusetir Cerfoglio	MSc	Male	01/08/2008	30/06/2010
UNL	Juan Daniel Claus	Researcher	Male	01/12/2006	30/06/2010
UCBL	Karine Thoinet	Technician	Female	01/12/2006	30/06/2010
LMU	Katharina Breit	Technician	Female	01/02/2010	15/02/2010
UNQ	Laura E. Esteban	PhD student	Female	07/01/2007	30/06/2010
UNQ	Liliana Rudak	Technician	Female	01/07/2008	30/06/2010
UdelaR	Lorena Tome	PhD student	Female	01/12/2006	30/06/2010
IOC	Luis Fernando López Tort	Post-doctoral student	Male	01/12/2006	30/06/2010
UdelaR	Mabel Berois	Researcher	Female	01/12/2006	30/06/2010
UNQ	Marcelo H. Argüelles	Researcher	Male	01/12/2006	30/06/2010
FioCruz	Marcos Lima de Mendonça	Post-doc student	Male	01/04/2007	30/06/2010
UNL	María Florencia Rossetti	Pre-graduate student	Female	01/12/2006	30/06/2010
UFRA	Maria Giovanna Foschini	PhD student	Female	01/03/2008	30/06/2010
LMU	Marianne Scheuerecker	Technician	Female	01/02/2009	31/12/2009
LIP	Marta Esteban	Project manager	Female	01/12/2006	30/06/2010
UZH	Mathias Ackermann	Co-investigator	Male	01/12/2006	30/06/2010
UCBL	Matias Melendez	PhD student	Male	01/01/2009	30/06/2010
LMU	Milka Grdic	Animal caretaker	Female	01/07/2009	31/03/2010
UNL	Nora Mattion	Researcher	Female	01/12/2006	30/06/2010
UCBL	Pascale Texier	Technician	Female	01/12/2006	30/06/2010
LIP	Patricia Odet	Other	Female	01/12/2006	30/06/2010
UFRA	Peggy Marconi	Co-Investigator	Female	01/12/2006	30/06/2010
LMU	Reinhard Obst	Staff-scientist	Male	01/01/2007	30/06/2010
UFRA	Roberto Manservigi	Leader group	Male	01/12/2006	30/06/2010
UNQ	Romina Scian	M.Sc.	Female	07/01/2007	30/04/2008
UNQ	Rosana P. Rota	PhD student	Female	01/12/2006	30/06/2010
UFRA	Sabrina Facciolo	PhD student	Female	01/01/2007	30/06/2010
LIP	Simone Cruset	Other	Female	01/12/2006	30/06/2010
LIP	Sylvain Roussy	Other	Male	01/12/2006	30/06/2010
LMU	Thomas Brocker	Professor	Male	01/12/2006	30/06/2010
UNL	Veronicia Gioria	Technician	Female	01/12/2006	30/06/2010
LMU	Wolfgang Mertl	Animal care taker	Male	01/02/2007	30/11/2008

- **Task 2: Monitoring of the administrative and financial aspects**

- **Administrative management**

The overall management and information workflow between partners is based both on physical meetings and on the collaborative website. The following consortium meetings took place during the performance of the project:

- the kick-off meeting in Buenos Aires, from 29th to 30th March 2007, which was organised by partners UCBL and UNQ with the support of the management team,
- a General assembly meeting in Ferrara, Italy, on 5th October 2007, which was organised by partner UFRA, with the support of the management team.

- a General assembly meeting in Montevideo, Uruguay, in parallel with the Mid-term Hevar Conference, from 7th to 14th April 2008, which was organised by partner UdelaR, with the support of the management team,
- the internal Mid-term assessment meeting in Munich, Germany, on 13th October 2008, which was organised by partner LMU, with the support of the management team,
- a General assembly meeting in Rio, Brazil, associated to one day of Conference, from 14th to 16th April 2009, which was organised by partner IOC, with the support of the management team,
- a General assembly meeting in Buenos Aires, associated to one day of Conference, from 10th to 12th November 2009, which was organised by partner UNQ, with the support of the management team,
- the Final assessment meeting in Lyon, France, on 10th June 2010, which was organised by partner UCBL, with the support of the management team.

For each meeting, the partners' presentations as well as the minutes are available on the collaborative website. Attendance sheets were signed by all attendants, and attendance certificates were made available on request of the participants.

The main tools that are provided by Lyon Ingénierie Projets (LIP) for the management of the project are:

- the project handbook and the collaborative website, delivered during the first reporting period,
- the public website (for which LIP collected from all partners a list of the required elements such as partner presentation, authorisation to publish the logos, pictures…), implemented during the first period, and updated since then in particular to advertise the Mid-term Hevar Conference and the Conference days.

The internal reporting is based on the preparation by all partners of an activity report which presents a summary of the activities, the main results, the encountered difficulties and proposed solutions as well as the outside dissemination actions. Suggestions concerning the implementation of project, the student exchanges or external collaborations are also collected thanks to these reports.

The reports are published on the collaborative website, so as to be available for all project members and assessed by the workpackage leaders and the project coordinator.

- **Financial management:**

The distribution of payments was implemented as follows:

		Maximum EC contribution (global project duration)	**First payment distribution**	**Second payment distribution 26/11/2008**	**Third payment 09/06/2009**
1	UCBL	215 762,40	**48 980,90**	50 136,58	25 600,71
	EZUS	*5 975,64*	5 975,64	-	-
	LIP	*88 018,96*	34 024,36	21 841,47	11 152,67
2	UFRA SMDMS	164 070,00	67 068,00	38 124,85	19 467,28
3	UNIZH	170 220,00	67 488,00	39 553,92	20 197,00
4	UNI MUENCHEN	216 800,00	85 919,20	50 377,68	25 723,82
5	RAU	189 025,00	**115 896,70**	43 923,62	22 428,25
6	IOC	183 026,00	77 129,60	42 529,64	21 716,46
7	UNQ	182 980,00	71 112,00	42 518,95	21 711,00
8	UNL	124 120,00	50 159,60	28 841,69	14 727,12
TOTAL		**1 539 998,00**	**623 754,00**	**357 848,40**	**182 724,32**

4.8 Task 3 - Knowledge management

The knowledge includes two communication levels:

- the documents available to the public, in particular project activities, news, press releases, homepage, invitations to public parts of meetings… These documents will be available on the public project website. The consortium is not yet ready to publish any exploitable current results. The IPR protection measures and publications are expected to take place mainly during the second and third periods of the project.
- the documents available only inside the consortium for working purposes. These documents are published on the restricted access area of the project collaborative website.

▪ Public website

Beside the collaborative website which objectives are to facilitate the exchange of information in a secure way between partners, to simplify the monitoring of the project and to consolidate the partners' data for the administrative and scientific reporting, a public web site has also been developed.

The address of the public project web site is www.hevar.eu. The web site describes the project from a general point of view. It is an information system for different audiences in order to let them know how the project is doing. On the other hand from the consortium point of view, it is a way to get a feedback from the public and to promote the projects outputs and results.

Its main parts are project presentation, partners presentations, public documents and useful links. It also involves the necessary contact and legal information in accordance with the French legislation.

The public website was updated during the second reporting period, in particular to advertise the Mid-term Hevar Conference, and to make available the Application forms for the students who wish to attend this event, and during the third period, to advertise the Hevar Conference days.

▪ Collaborative website

A collaborative website is available since April 2007. Its objective is to facilitate the exchange of information in a secure way between partners, to simplify the monitoring of the project and to consolidate the partners' data for the administrative and scientific reporting.

After the availability of the collaborative website, the main tasks were: implementation and general maintenance of the collaborative website, creation and updating of the administrative documents, updating of the news, creation and updating of the partners' data…

4.9 Legal management, dissemination and exploitation of results

All the legal documents concerning the European contract (i.e. Technical annex, Annex II – General conditions, Forms A) have been made available to the Partners through the Documents centre part of the collaborative website.

The consortium agreement has been finalised and signed by the participants during the first reporting period. The final version is available on the collaborative website.

No need for amendments related to this agreement has been identified during the project duration.

HEVAR is a collaborative project involving four academic laboratories from four European countries (France, Switzerland, Germany, Italy) and four academic laboratories belonging to three South American countries (Argentine, Brazil, Uruguay). The overall scientific goal of HEVAR is to contribute to a better understanding of the immune biology of rotavirus infections using a novel generation of gene transfer vectors derived from herpes virus simplex type 1 (HSV-1), as a first step towards the development of innovative genetic vaccines to fight against these pathogens, which are the most common and important cause of severe dehydrating diarrhoea in young children of developing countries.
In addition to contributing to a better understanding of the immune biology of rotavirus infection and of evaluating the feasibility of using HSV-1 vectors as anti-rotavirus vaccines, the main deliverables of HEVAR will be a set of toolboxes containing a large collection of HSV-1-based and DNA-based vectors expressing human and mouse rotavirus antigens that will be evaluated in mice, which will be rendered accessible to any academic team wishing to use them for vaccine development or fundamental research on rotaviruses.
A last set of deliverables will consist in a series of scientific meetings and events required to achieve the transfer of knowledge and complex technology required to generate, produce, and evaluate, the HSV-1-based gene transfer vectors in South America, therefore, improving the human capital and the technological competence of these countries, as well as the reciprocal transfer to European teams of knowledge on the biology of rotavirus and other endemic viruses with high social cost in South America, as a way to strengthen the awareness to, and the understanding of, these neglected diseases..

5. EXPLOITABLE KNOWLEDGE AND ITS USE

#	Exploitable Knowledge (description)	Catego -ry A, B or C	WP	Sector(s) of application	Timetable for commercial use	Patents or other IPR protection	Owner & Other Partner(s) involved
1	Novel vectors generation	A	WP1	Research purposes	N/A	To be determined	UCBL, UFRA, UZH, UdelaR
2	Clones and sequences of all the structural genes from 4 rotavirus strains (2 human, one monkey and one mice)	A	WP1	Research purposes	N/A	N/A	UdelaR, IOC,
3	Vectors inducing in situ assembly of empty rotavirus-like particles (VLPs)	A	WP1	Research and/or commercial purposes	To be determined	To be determined	UZH
4	Different sets of DNA plasmids carrying the whole set of structured rotavirus genes either alone or in various combinations (around 50 plasmids)	A	WP1	Research purposes	N/A	N/A - Available for the scientific community for research purposes	UCBL, UZH, UFRA, UdelaR, UNL, IOC
5	HSV-1-based vector genomes expressing the whole set of rotavirus structured genes both alone or in combination (around 30)	A	WP1	Research purposes	N/A	N/A - Available for the scientific community for research purposes	UCBL, UZH, UFRA, UdelaR, IOC
6	Evaluation of the immunologic potential of several HSV-1 based vector vaccines expressing different rotavirus antigens	A	WP2	Research and/or commercial purposes	To be determined	To be determined	LMU, UNQ, UZH
7	Immunization protocol	B	WP2	'Immunization	n.a.	n.a.	n.a.
8	Read out of cellular immune response	B	WP2	vaccinology	n.a.	n.a.	n.a.
9	Read out of humoral immune response	B	WP2	Vaccinology	n.a.	n.a.	n.a.

*(A: results usable outside the consortium / B: results usable within the consortium / C: non usable results)

6. DISSEMINATION OF KNOWLEDGE

6.1 Dissemination activities during the whole project duration

no	WP	Planned/actual Dates	Communication type	Type of audience	Targeted countries	Size of audience	Partner(s) responsible, involved	Reporting period
1	ALL	25th March, 2007	Newspaper article - PERFIL	General public	Argentina, Uruguay, Chile, Brasil, Paraguay, España, EEUU	The newspaper distributes around 86,500 copies.	Graciela Glikmann, UNQ - Alberto Epstein, UCBL	1
2	WP1	28th March 2007	Oral	Researchers, PhD students, University students	Argentina	50	Peggy Marconi (UFRA)	1
3	WP1	28th March 2007	Oral	Researchers, PhD students, University students	Argentina	50	Roberto Manservigi (UFRA)	1
4	WP1	28th March 2007	Oral	Researchers, PhD students, University students	Argentina	50	Corinne Potel (UCBL)	1
5	WP1	28th March 2007	Oral	Researchers, PhD students, University students	Argentina	50	Cornel Fraefel (UZH)	1
6	WP1	28th March 2007	Oral	Researchers, PhD students, University students	Argentina	50	Mabel Berois (UdelaR)	1
7	WP1	28th March 2007	Oral	Researchers, PhD students, University students	Argentina	50	Alejandro Castello (UNQ) and Jose Paulo Leite (FioCruz)	1
8	WP2	28th March 2007	Oral	Researchers, PhD students, University students	Argentina	50	Thomas Brocker (LMU)	1
9	WP2	28th March 2007	Oral	Researchers, PhD students, University students	Argentina	50	Graciela Glikmann, UNQ	1
10	WP1	39185	Oral	Biology and biochemistry students.	Uruguay	60	UdelaR	1
11	WP2	6th July, 2007	Oral	Researchers, PhD students, University students	Argentina	30	Graciela Glikmann, UNQ	1
12	WP2	13th July, 2007	Seminar	Researchers, PhD students, University students	Argentina	20	Alejandro Castello, UNQ Laura Esteban, UNQ	1
13	WP2	13th July, 2007	Seminar	Researchers, PhD students, University students	Argentina	20	Romina Sian, UNQ	1

no	WP	Planned/actual Dates	Communication type	Type of audience	Targeted countries	Size of audience	Partner(s) responsible, involved	Reporting period
14	WP1	August to November, 2007	Oral	University students, Facultad de Bioquímica y Ciencias Biológicas, UNL	Argentina	26	UNL	1
15	WP1	14 September 2007	Oral	Italian Virologists	Italy	40	UFRA	1
16	WP1	39335	Oral	Researchers, PhD students, University students	Brazil	20	IOC	1
17	WP1	39345	Oral	Researchers, PhD students, University students	Uruguay	120	UdelaR	1
18	WP1	11-12/10/2007	Oral	Swiss Virologists	Switzerland	40	UZH	1
19	WP1	39377	Oral	Lecture	Brazil	20	IOC	1
20	WP1	29/11-21/12/2007	Oral	Biology students, University of Zurich	Switzerland	20	UZH	1
21	WP1	27 and 30 of November 2007	Oral	Master students, University of Ferrara	Italy	32	UFRA	1
22	WP1	39722	Oral	Researchers, PhD students, University students	Brazil	120	IOC	1
23	WP1	39722	Poster	Researchers, PhD students, University students	Brazil	120	IOC	1
24	WP2	28th March 2008	Graduate Thesis.	Students, researchers and professors. Department of Science and Technology. UNQ	National	50	UNQ	2
25	WP1	6th May 2008	Invited Lecture	University of Giessen, Germany	Germany	40	UZH	2
26	WP1	30th May 2008	Training course	Undergraduate, MSc, PhD and Posdoc students	Uruguay	20	UdelaR	2
27	WP2	5th June 2008	Intern Seminar.	Students and researchers. Department of Science and Technology. UNQ	Argentina	50	UNQ	2
28	WP1	12th June 2008	Invited Lecture	Microbiologists	International	250	UZH	2
29	WP1	20-21st June 2008	Lecture	Italian Microbiologists (SIMIF)	Turin - Italy	50	UFRA	2

no	WP	Planned/actual Dates	Communication type	Type of audience	Targeted countries	Size of audience	Partner(s) responsible, involved	Reporting period
30	WP2	12-16th July 2008	Poster presentation.	Virology Congress. 27th Meeting of the American Society for Virology. Cornell University, Ithaca, NY, USA	International		UNQ	2
31	WP2	12-16th July 2008	Poster presentation.	Virology Congress. 27th Meeting of the American Society for Virology. Cornell University, Ithaca, NY, USA	International		UNQ	2
32	WP1	August to November 2008	Lectures	Students of the course « Biology of the Viruses », career of Biotechnology, Facultad de Bioquímica y Ciencias Biológicas, UNL	Argentina	35	UNL	2
33	WP1	1st-15th September 2008	Theoretical-practical seminar:	Students of the course “General Biology”, career on Biology and career on Biochemistry.	Uruguay	10	UdelaR	2
34	WP2	2nd September 2008	Intern Seminar.	Students and researchers. Department of Science and Technology. UNQ	Argentina	50	UNQ	2
35	WP1	22-23rd September 2008	Lecture	Italian Virologists (SIV)	Orvieto- Italy	100	UFRA	2
36	WP1	22nd September 2008	Lecture	Graduate and post-graduate	Switzerland	20	UZH	2
37	WP1	22-25th September 2008	Communication to the IX Argentine Congress of Virology*	Scientists	Argentina, Uruguay,	450	UNL	2
38	WP1 - WP2	22-25th September 2008	Communication to the IX Argentine Congress of Virology**	Scientists	Argentina, Uruguay,	450	UNL – UNQ	2
39	WP2	22-25th September 2008	Poster presentation.	IXth Argentine Virology Congress. Buenos Aires, Argentina	National		UNQ	2

no	WP	Planned/actual Dates	Communication type	Type of audience	Targeted countries	Size of audience	Partner(s) responsible, involved	Reporting period
40	WP2	22-25th September 2008	Poster presentation.	IXth Argentine Virology Congress. Buenos Aires, Argentina	National		UNQ	2
41	WP1	26th September 2008	Lecture	Post-graduate	Switzerland	25	UZH	2
42	WP1	October 2008	Communication at "XIX National Meeting of Virology and III Mercosul Meeting of Virology"	Researchers, PhD students, University students	Brazil	120	IOC	2
43	WP1	October 2008	Communication at "XIX National Meeting of Virology and III Mercosul Meeting of Virology"	Researchers, PhD students, University students	Brazil	120	IOC	2
44	WP1	13-15th October 2008	Lecture	Italian Microbiologists (SIM)	Rome - Italy	100	UFRA	2
45	WP1	27th November - 19th December 2008	Student's course and lectures	Biology students, University of Zurich	Switzerland	20	UZH	2
46	WP1	22 and 29th of November 2008	Student's course and lectures	Master students, University of Ferrara	Ferrara - Italy	32	UFRA	2
47	WP2	2008 (in press)	Journal (Current Topics in Virology). Review article.	Virology researchers.	International		UNQ	2
48	WP1 - WP2		Mid-term Hevar Conference - Montevideo, Uruguay					2
49	WP1	7-8th April 2008	Lecture	Students and young researchers	South American countries	100	UFRA	2
50	WP1	7-8th April 2008	Lecture	Students and young researchers	South American countries	100	UZH	2
51	WP1	7-8th April 2008	Lecture	Students and young researchers	South American countries	100	UZH	2
52	WP1	7-8th April 2008	Lecture	Students and young researchers	South American countries	100	UFRA	2

no	WP	Planned/actual Dates	Communication type	Type of audience	Targeted countries	Size of audience	Partner(s) responsible, involved	Reporting period
53	WP2	7-8th April 2008	Lecture	Students and young researchers	South American countries	100	LMU	2
54	WP1	9th-14th April 2008	Practical course	Selected students and young researchers	South American countries	20	UFRA / UCBL / UZH	2
55	WP1	9th-14th April 2008	Practical course	Selected students and young researchers	South American countries	20	UFRA / UCBL / UZH	2
56	WP1	9th-14th April 2008	Practical course	Selected students and young researchers	South American countries	20	UFRA / UCBL / UZH	2
57	WP1	9th-14th April 2008	Practical course	Selected students and young researchers	South American countries	20	UFRA / UCBL / UZH	2
58	WP1	9th-14th April 2008	Practical course	Selected students and young researchers	South American countries	20	UFRA / UCBL / UZH	2
59	WP2	9th-14th April 2008	Practical course	Selected students and young researchers	South American countries	20	LMU	2
60	WP2	9th-14th April 2008	Practical course	Selected students and young researchers	South American countries	20	LMU	2
61	WP2	October 2008	Paper - J Immunol. 2008 Oct 1;181(7):4495-506	Scientists	International	NA	LMU	2
62	WP2	April 14th, 2009	Conference	Researchers and students	Brazil	100	IOC	3
63	WP1	May 28, 2010	Oral communication to the XIII Meeting of the Uruguayan Society for Bioscience:" HSV-1 amplicon vectors: a versatile tool for gene delivery in eukaryotic cells"	Scientists	Uruguay, Argentina	150	UdelaR	3
64	WP1	August to November, 2009	Lectures	Students of the course « Biology of the Viruses », career of Biotechnology, Facultad de Bioquímica y Ciencias Biológicas, UNL	Argentina	35	UNL	3
65	WP2	11th August, 2009	Seminar "Immune response to amplicon vectors: Animal Mouse Model". Centro de Virología Animal	Researchers, PhD students, University students	Argentina	20	UNQ	3

no	WP	Planned/actual Dates	Communication type	Type of audience	Targeted countries	Size of audience	Partner(s) responsible, involved	Reporting period
66	WP3	Aug - Nov, 2009	Lectures	Students of the course « Biology of the Viruses ». Facultad de Bioquímica y Ciencias Biológicas, UNL	Argentina	35	UNL	3
67	WP1	Sept 7-18, 2009	Theoretical-practical seminar: “The use of Herpes Simplex 1 as expression-vector and genetic therapy (amplicon system)”	Students of the course “General Biology”, careers of Biology and Biochemistry.	Uruguay	10	UdelaR	3
68	WP1	October 2009	Communication to the XVII Young Researches Conference of the AUGM.*	Young scientists, students	Argentina, Uruguay, Brazil	500	UNL	3
69	WP1	Oct 15/16, 2009	Presentation Meeting of Virology PhD students	PhD students and supervisors	Switzerland	50	UniZH	3
70	WP1	October 28 2009	Lecture	PhD students and young scientists	France	50	UCBL	3
71	WP3	oct-09	Communication to the XVII Young Researches Conference of the AUGM.*	Young scientists, students	Argentina, Uruguay, Brazil	500	UNL	3
72	WP2	10th November 2009	Conference “Epidemiological Aspects of Rotavirus Infections in Latinoamerica” - Universidad Nacional de Quilmes	Researchers, PhD students, University students	Argentina	100	UNQ	3
73	WP2	November 10th, 2009	Conference	Researchers and students	Argentina	70	UNQ	3
74	WP1	December 2009	Communication to the XXIX Annual Meeting of the Argentine Society for Virology**	Scientists	Argentina, Uruguay, Brazil	120	UNL - UNIZH	3

no	WP	Planned/actual Dates	Communication type	Type of audience	Targeted countries	Size of audience	Partner(s) responsible, involved	Reporting period
75	WP3	Dec 2009	Communication to the XXIX Annual Meeting of the Argentine Society for Virology**	Scientists	Argentina, Uruguay, Brazil	120	UNL, UNIZH	3
76	WP1	Feb 4/5, 2010	Presentation Virology retreat	Members of Institute of Virology	Switzerland	30	UniZH	3
77	WP2	29.3. – 2.4.2010	Conference, Poster	Researchers and students	International	100	LMU	3
78	WP1	May 25, 2010	Presentation Course scientific presentations	PhD students	Switzerland	25	UniZH	3
79	WP1	June 3, 2010	Poster session workshop	PhD students	Switzerland	25	UniZH	3

6.2 Project webpage

Beside the collaborative web site which objectives are to facilitate the exchange of information in a secure way between partners, to simplify the monitoring of the project and to consolidate the partners' data for the administrative and scientific reporting, a public web site was also developed.

The address of the public project web site is www.hevar.eu. The web site describes the project from a general point of view. It is an information system for different audiences in order to let them know how the project is doing. On the other hand from the consortium point of view, it is a way to get a feedback from the public and to promote the projects outputs and results.

Its main parts are project presentation, partners presentations, public documents and useful links. It also involves the necessary contact and legal information in accordance with the French legislation.

From a technical point of view, it is based on html language, and was created with the aim of applying the best practices defined by the W3C.

The public website was updated during the second reporting period, in particular to advertise the Mid-term Hevar Conference, to make available the Application forms for the students who wish to attend this event, and to advertise the Hevar Conference days.

7. PUBLISHABLE RESULTS

(1) A.A. Castello, M.H. Argüelles, R.P. Rota, L.E. Esteban, R. Scian, G. Glikmann. Rotavirus Immune Response and Vaccine Update. Current Topics in Virology 2008, 7 (1): 1-20

(2) Dresh C, Edelmann SL, Marconi P, Brocker T. Lentiviral-mediated transcriptional targeting of dendritic cells for induction of T cell tolerance in vivo. J Immunol 2008 Oct 1; 181(7): 4495-506

(3) D'Antuono A, Laimbacher AS, La Torre J, Tribulatti, V, Romanutti C, Zamorano P, Quattrocchi V, Schraner EM, Ackerman M, Fraefel C, Mattion N. HSV-1 amplicon vectors that direct the in situ production of heterologous antigens in mammalian cells may eventually be used for genetic immunization. Submitted (2010).