Publishable executive summary

General Aims of the project

As partial exception to the rule that untreated HIV-1 infection leads to the development of the acquired immunodeficiency syndrome (AIDS) and death within 8-10 years, a minority (<5%) of infected individuals maintain exceptionally prolonged survival in good healthy conditions without administration of antiretroviral therapy. These individuals have been variably defined, and are here referred to as "HIV-1 long-term nonprogressors (LTNP)". Since their first description in 1995, several cohorts of LTNP have been identified in USA and Europe. Given their paucity, national networks of clinical and research centres have been formed firstly in France (ALT Cohort) and then in Italy (ELVIS Cohort) to better study their particular features. GISHEAL, however, represents the first collaborative European consortium formed with the specific goal of creating a common database containing all the relevant information of European (France, Italy and London, UK) and African (Ugandan) LTNP. This database will be instrumental for investigating the host genetic background and the related gene expression profiles as well as the adaptive and innate immunological responses of LTNP in comparison with control cohorts of infected individuals with chronic progressive (CP) disease. A genome-wide approach based on screening of >100,000 single-nucleotide polymorphisms (SNPs) followed by proper validation steps is on the verge of describing novel genetic polymorphisms tightly associated with the LTNP condition in addition to validating those already described. The adaptive T lymphocyte (CD4, CD8) immune responses as well as the NK cell and γδ T cell responses to HIV have been studied in LTNP and CP and they will be linked, when possible, to their genomic and post-genomic profiles. The integration of all the gathered genetic, post-genomic and immunological information is currently being analysed by appropriate statistical programs in order to identify natural correlates of non-progression that could be of relevance to the general population of HIV-infected individuals, and to vaccine design.

Table 1. The Consortium

Role*	No.	Name	Short Name	Country	Date enter project	Date exit project
CO	1	Fondazione Centro San Raffaele del Monte Tabor	FCSR_AIP	Italy	Month 1	Month 30
CR	2	Universite Pierre et Marie Curie	UPMC	France	Month 1	Month 30
CR	3	Institut National de la Santé et de la Recherche Médicale Unit 720	INSERM-720	France	Month 1	Month 30
		Imperial College , London at Chelsea and				

CR	4	Westminister Hospital Medical Research Council – Uganda Virus Research Institute	IC MRC_UVRI	United Kingdom Uganda	Month 1 Month 6	Month 30 Month 30
CR	5	State University of Milano	UNIMI	Italy	Month 1	Month 30
CR	6	National Institute for Infectious Diseases "Lazzaro Spallanzani"	INMILS	Italy	Month 1	Month 30

*CO = Coordinator ; CR = Contractor;

The Project structure

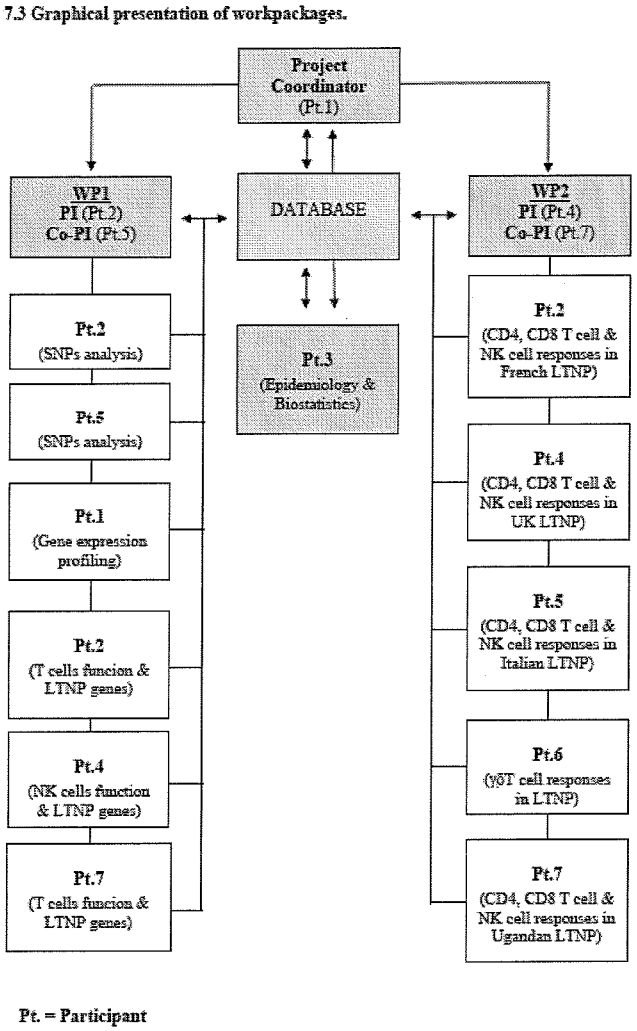
The project ha been structured in two distinct WPs (WP-1: Genetics & Post-Genomic; WP-2: Immunology) and by a central "core" represented by the Database implemented and updated under the direct responsibility of Partner 3 (Pt. 3) as well as of the Project Coordinator (Pt. 1), as illustrated in **Figure 1.**

The two WP principal investigators (PI) and their co-PIs have guaranteed that all the planned activities were developed smoothly and have provided a first line response to unexpected hurdles that, however, have been minimal and always solved without conflicts. At the same time, they have promptly communicated with the Project Coordinator and discussed variations from the planned development whenever required.

The general philosophy of GISHEAL has been inspired by two lines of work: on the one hand, each group has maintained its individual research on specific aspects of the LTNP condition. On the other hand, forces have been joined to maximise effort and to allow integration among scientists of different institutes and countries. This has allowed the construction of a **common European database** on HIV-1^+ LTNP that has been also the basis for performing genomic studies. All key investigators from Italy and the UK have met in Paris to perform the genomic analysis with the Illumina® HapMap550 platform under the expert supervision of Ioannis Theodoroou (Pt. 2). On the immunological side, the teams of Patrice Debre (Pt. 2) and Federico Martini (Pt. 6) have exchanged protocols and results in order to characterise the innate cell-mediated immune response of LTNP vs. control populations, particularly concerning the role of NK and γδ T cells. A Ugandan research assistant has received in depth training at the IC in London, UK (Pt. 4) and has exported then technology and immunological expertise to the associated MRC Centre in Entebbe, Uganda (Pt. 7).

As later described in detail, the close contact among the key scientists and physicians involved in GISHEAL has been instrumental to the overall efficiency of the consortium as it will be demonstrated soon in terms of scientific publications and related dissemination activities.

Figure 1. The Structure of GISHEAL



Main achievements of the 2nd Reporting Period

The second year of GISHEAL has been characterized by the consolidation of the different activities started during the first year. In particular, the the Database has been consolidated in terms of documents submitted using the software program "Access" (included in the PC version of Microsoft Office) that has been used for data supplements after their initial collection either in Excel or other software or directly on paper documents; a network of dedicated personnel from the individuals centres has been implemented in order to channel the codified information to the coordinator and responsible for the Database (Pt. 3, Dominique Costagliola, DC, INSERM 720, Paris, France). After a critical review of this preliminary filing has been satisfactory with an overall acceptance rate of ca. 80% (more precisely: the data relative to 213 patients out of 270, 79%, submitted were found eligible for inclusion in the database as of June 2008) the original Centres have verified and resubmitted their files achieving a global 90% of candidate LTNP fitting the defined inclusion criteria.

The second major activity of the second year has been the execution of a genome-wide association study (GWAS) on 144 validated Caucasian LTNP using the Illumina® HapMap550 platform, as later discussed in detail under the supervision of Pt. 2 (Ioannis Theodorou) and Pt. 5 (Agostino Riva). A population of 605 Caucasian HIV-1 seroconverters (belonging to the French "PRIMO" Cohort, in which Pt. 2 is involved) served as control for LTNP. Different single nucleotide polymorphisms (SNPs) in the Major Histocompatibility Complex (MHC) region were found strongly associated to the LTNP condition. In particular, these SNPs encompassed both Class I and Class III genes. Six out of the 10 SNPs showing the highest statistical association with the LTNP condition were found in the HLA-B region, confirming previous studies on so-called "elite controllers" (i.e. individuals who maintain their viremia levels undetectable in the absence of anti-retroviral therapy) indicating that Class I genes are indeed strongly correlated to the natural control of disease progression. Furthermore, we observed that ca. 65% of our LTNP naturally resist to HIV disease progression independently of HLA-B27 or B57. In this regard, quite strikingly, in our LTNP cohort 3 out of 32 SNPs with a Q-value <0.05 were located in the MHC Class III region supporting the concept that different MHC loci significantly contribute to long-term natural control of HIV disease progression in the absence of ART. Therefore, GISHEAL will provide novel evidence of a seminal role of MHC class III gene polymorphisms in determining the LTNP condition, at least in Caucasians.

Concerning the immunological activities, several parallel and cooperative efforts have been made in terms of exchange of SOPs for T cell functional assays, as well as in defining the panels of phenotypic markers and functional assays to be used for identification of immune response profiles of LTNP vs. control populations. In particular, first line testing of cellular samples by Elispot has been accomplished while the role of $CD4^+$ and $CD8^+$ T cells directed against the dominant epitopes of HIV-1 Gag and of the regulatory and accessory Nef and Tat proteins with specific regard to the magnitude, cell differentiation and functional characteristics is currently being defined by Pt. 2 and 4. Furthermore, the correlates of protection against disease progression mediated by HIV-1 specific helper T-cells, with particular regard to their proliferation and cytokine secretion, are being defined by Pt. 2 and 4. 2nd line testing on fresh samples of CD4 and CD8 T cells by multi-parametric phenotypic analysis including CFSE staining and the production of IFN-γ and IL-2 is currently being performed by use of an 8-colour LSRII flow cytometer by Pt. 2, 4 and 5. Concerning innate immunity, a significant modulation of Natural Killer Receptors (NKR) expression on the surface of γδ T cells has been found in LTNP in comparison to control patients with progressive disease and ongoing studies are verifying the role of these NKR expression on γδ T cell effector function by Pt. 2 and 6.

The exchange of information with prominent European scientists not belonging to the GISHEAL consortium, but sharing a common interest in LTNP and in correlates of natural protection from HIV disease progression, have been further consolidated. These scientists include Jose Alcami, Majadahonda, Spain, Hanneke Schuitemaker, Amsterdam, The Netherlands, Christine Rouzioux, Olivier Lambotte, Laurent Abel from Paris, France.

Recent scientific publications relevant to GISHEAL published by the Consortium (*GISHEAL members are indicated in bold)*

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