COST

Domain Committee "BMBS"

COST Action BM0803

Start Date 29/01/2009

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A European network of the HLA diversity for histocompatibility, clinical transplantation epidemiology and population genetics (HLA-NET)

MONITORING PROGRESS REPORT

Reporting Period: from April 2011 to April 2012

This Report is presented to the relevant Domain Committee.
It contains three parts:

I. Management Report *prepared by the COST Office/Grant Holder*
II. Scientific Report *prepared by the Chair of the Management Committee of the Action*
III. Previous versions of the Scientific Report*; i.e., part II of past reporting periods*

The report is a "cumulative" report, i.e. it is updated annually and covers the entire period of the Action.

Confidentiality: the documents will be made available to the public via the COST Action web page except for chapter *II.D. Self evaluation*.

Based on the monitoring results, the COST Office will decide on the following year's budget allocation.

Executive summary (max.250 words): The Action made significant achievements during the last period, i.e. by completing and making available the *HLA-NET Population questionnaire* and the *Guidelines for reporting HLA typings*, by typing samples to resolve specific ambiguities, by generating a first set of statistical results on the HLA data of several national donor registries, by setting up a common schema for databases to be networked, and by putting together more information on national and institutional ethical rules. A key article was published in the *International Journal of Immunogenetics* with HLA-NET methodological recommendations, and several other papers are in preparation. Inter-disciplinarity was promoted through the organisation of a joint HLA-NET/AHPD meeting to perform data analysis and to which several ESR participated as trainers, and through STSM. A new partnership was initiated within the frame of a new funded European FP7 research grant involving 4 HLA-NET laboratories and integrating HLA-NET activities, a project which is expected to have a high impact in public health (organ transplantation). HLA-NET members have also been preparing work for the Joint 16th International HLA and Immunogenetics Conference/26th European Immunogenetics and Histocompatibility Conference/23rd British Society of Histocompatibilty and Immunogenetics Conference (Liverpool, May-June 2012). Three new countries joined the Action which currently counts 21 COST countries and 1 non-COST country. Although very few STSM have been organised in 2011, HLA-NET participants have been encouraged to participate and up to 12 STSM have been planned for next year.

I. Management Report *prepared by the COST Office/Grant Holder*

I.A. COST Action Fact Sheet

COST Action BM0803 - A European network of the HLA diversity for histocompatibility, clinical transplantation, epidemiology and population genetics (HLA-NET)

- **Domain** *BMBS*

- **Action details:**

CSO Approval: 8/06/2008 **End date:** 28/01/2013
Entry into force: 22/09/2008 **Extension:** *NA*

Objectives The molecular characterization of the HLA (Human Leucocyte Antigen) polymorphism in human populations represents a crucial step in several disciplines concerned by public health (histocompatibility/transplantation and epidemiology) and also constitutes a main research focus in human molecular evolution (molecular population genetics). While needing similar requirements at the different levels of their analysis (good quality of sampling, high resolution HLA typing, powerful biostatistic analyses adapted to complex HLA data, easy access to specific population databases and understandable computer tools), the investigators working in these different fields are currently limited in their interactions. HLA-NET offers an innovative framework by which those scientists will put their expertise in laboratory work, clinical work, ethical issues, population genetics, biostatistics and/or computer science into contribution to elaborate consensual standards, define common procedures and share high quality data and tools. Highly significant scientific, technological and societal benefits are expected through the Action with immediate applications in donor-recipient matching,case-control studies and population genetics research. The network will expand and disseminate its results through an electronic platform starting with more than 15 laboratories throughout Europe. The workshops supported by this Action will permit essential transfers of knowledge and expertise at the European scale and will foster collaboration throughout Europe and beyond.

Keywords: HLA, histocompatibility/transplantation, epidemiology, population genetics, European network

- **Parties:**

Austria (10/06/2009)	Greece (03/03/2009)	Poland (11/06/2009)
Belgium (22/09/2008)	*Hungary (26/04/2012)**	Portugal (22/09/2008)
Bulgaria (04/04/2011)		
Croatia (13/07/2010)		
Cyprus (10/09/2011)		
	Italy (07/01/2009)	Slovenia (05/02/2009)
Denmark (16/01/2009)	Latvia (03/11/2008)	Spain (22/09/2008)
Finland (13/01/2009)		Switzerland (22/09/2008)
France (01/10/2008)	Netherlands (13/07/2010)	United Kingdom (22/09/2008)
Germany (16/01/2009)	Norway (13/07/2010)	

* Most recent nomination

- **Intentions to accept:**
- **Other participants:** Albania (non COST)
- **See participants at http://hla-net.eu/wiki_spa/doku.php?id=action:facts**

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- **Action Web site:** *http://hla-net.eu*

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- **Working Groups** *(list of WGs and names and affiliations of participants)*

WG1, Populations:

- **Alicia Sanchez-Mazas**, University of Geneva, Switzerland (Leader)
- **Benedicte Lie**, Rikshospitalet, Oslo University Hospital, Norway
- **Berta Martins da Silva**, ICBAS, Porto, Portugal
- **Dário Ligeiro**, Centro de Histocompatibilidade do Sul, Lisbon, Portugal
- **Marja-Liisa Lokki**, University of Helsinki, Finland
- **Stéphane Buhler**, University of Geneva, Switzerland
- **Michel Toungouz Nevessignsky**, Erasme Hospital, Brussels, Belgium
- **Valérie Dubois**, EFS Rhone Alpes, Lyon, France
- **Chryssa Papasteriades**, Evangelismos General Hospital, Athens, Greece
- **Genc Sulcebe**, University Hospital Center Mother Teresa, Tirana, Albania
- **Frans Claas**, Leiden University Medical Center, Leiden, The Netherlands
- **María Eugenia Riccio**, University of Geneva, Switzerland
- **Jean-François Eliaou**, University Hospital Montpellier, France

WG2, Typing:

- **Jean-Marie Tiercy**, University Hospital Geneva, Switzerland (Co-leader)
- **Blanka Vidan-Jeras**, Blood Transfusion Ctr, Ljubljana, Slovenia (Co-leader)
- **Milena Ivanova-Shivarova**, University Hospital Alexandrovska, Sofia, Bulgaria
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- **Constantia Voniatis Papaioannou**, Makarios III Hospital, Nicosia, Cyprus
- **Stéphane Buhler**, University of Geneva, Switzerland
- **Maria Spyropoulou-Vlachou**, General University Hospital of Athens, Greece

WG3, Bioinformatics:

- **José Manuel Nunes**, University of Geneva, Switzerland (Leader)
- **Christelle Vangenot**, University of geneva, Switzerland
- **Carlheinz Muller**, ZKRD Helmholtzstr., Ulm, Germany
- **Hans-Peter Eberhard**, ZKRD Helmholtzstr., Ulm, Germany
- **Faviel Gongalez-Galarza**, University of Liverpool, UK
- **Soreen Buus**, University of Copenhagen, Denmark
- **Hazael Maldonado Torres**, Anthony Nolan Research Institute, London, UK
- **Jaime Martorell**, H. Clinic de Barcelona Servei Immunologia, Barcelona, Spain
- **Steven G Marsh**, Anthony Nolan Research Institute, London, UK

WG4, ethics:

- **Gottfried Fischer**, Medical University of Vienna, Austria (Co-leader)
- **Ann-Margaret Little**, Histocompatibility & Immunogenetics Service, Glasgow, UK (Co-leader)
- **Anne-Marie van Walraven**, Leiden University Medical Centre, The Netherlands
- **Susan Tonks**, University of Oxford, UK

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I.C. Overview activities and expenditure

Meetings

Meeting Type	Date	Place	Paid part	Cost	Status	Total
CORE1	19-Jan-2011	Geneva (CH)	2	1391.22	Paid	
MC/WG	17-18-Mar-2011	Athens (EL)	29	22743.39	Paid	
Workshop	06-May-2011	Prague (CZ)	9	4956.70	Paid	
Workshop	07-Nov-2011	Geneva (CH)	25	15173.72	Paid	
CORE2	08-Nov-2011	Geneva (CH)	4	959.41	Paid	
						45'224.44

STSM

Beneficiary	Date	From	To	Cost	Status	Total
Ms Maria Eugenia Riccio	21-Nov-2011 – 03-Dec-2011	Geneva (CH)	Marseille (FR)	800	Paid	
Dr Cláudia Carvalho	01-Feb-2011 – 22-May-2011	Porto (PT)	London (UK)	2500	Paid	
						3'300

Other

Title	Date	Place		Cost	Status	Total
TS	21-24-Feb-2011	Porto (PT)		13181.33	Paid	
Dissemination				3000	Paid	
FSAC				7,394.95	Paid	**23'576.28**

Action Total **72'100.72**

II. Scientific Report

II.A. Innovative networking

MC and WG members of the Action met in Athens in March 2011 (5th MC/WG meeting) and in Leiden in March 2012 (6th MC/WG meeting) to work on the four main aspects of the project: 1) population data, 2) molecular data and typing techniques, 3) statistical and computer tools, and 4) ethical issues.

1) **Population data**

As a result of the 5th and 6th MC/WG meetings, the list of labs susceptible to submit population/registry data to HLA-NET was increased to 35, among which European, North African and West Asian laboratories. The *HLA-NET population questionnaire* to send to those labs was completed, and an electronic version was uploaded on the hla-net.eu website, in collaboration with WG3. The group discussed on the WG1 chapter of the paper to publish in the *International Journal of Immunogenetics* (Sanchez-Mazas et al. 2012b, see below), making a report of its activities and suggesting to avoid an outdated terminology for ethnic groups (for example terms like "Caucasian", "Black" and "Mongoloid"). This issue was also discussed in relation to the "ethnic groups" category defined in allelefrequencies.net database (AFND) for which WG1 proposed new recommendations (e.g. eliminate the category and define populations only on the basis of geographical and linguistic characteristics). Strategies were discussed to contact laboratories in 2012 (e.g. using EFI facilities like mailing lists and Newsletter) and the objectives of a symposium on anthropological aspects of registry data were discussed with WG2 (see below).

2) **Molecular data and typing techniques**

The document *Guidelines for reporting HLA typing results* was finalized and uploaded on the hla-net.eu website. Participants agreed to type population samples in order to resolve DRB1*14:01/14:54 and DQB1*03:01/03:19 ambiguities, and joint results on the resolution of HLA-DRB1*14:01:01G, DQB1*03:01:01G and B*44:02:01G ambiguities in 6 European population groups (French, Portuguese, Swiss, Croatian, Italian, Slovenian) were presented at the 6th MC/WG meeting in Leiden. Preliminary data have been prepared to be presented as a poster at the Joint 16th International HLA and Immunogenetics Conference/26th European Immunogenetics and Histocompatibility Conference/23rd British Society of Histocompatibilty and Immunogenetics Conference (Liverpool, May-June 2012) and a full paper is also in preparation. Rare alleles have continued to be submitted to allelefrequencies.net database (AFND). In the Leiden meeting, some preliminary (French, Slovenian, Quebec, Belgian) and final (Swiss) results on the available registry data were presented by Stéphane Buhler and the objectives of a symposium to be organized on this topic was discussed with WG1 (see above).

3) **Statistical and computer tools**

WG3 updated an electronic form of the *HLA-NET population questionnaire* prepared by WG1 (see above) and worked on a database structure allowing to network the AFND and Geneva databases thanks to a common schema compatible with other WGs' recommendations. A paper on this topic is in preparation. Suggestions were made by WG3 on file formats for data upload (compatible with HML, proposing dialog boxes and allowing instant validation), on statistical analyses for dataset validation (mandatory HWE estimation, neutrality testing, haplotype estimation), on reporting frequencies (indicating sample size and 95% significant frequency threshold, method or software used with version number or date, and graphic representation), and on comparing samples in simple situations (t-tests, Wilcoxon-Mann-Whitney, Kolmogorov-Smirnov, Chi^2, exact, …, with multiple test corrections when necessary). All the data input

forms, distributions maps, programs, tools and databases will be the public part of HLA-NET.

4) **Ethical issues**

The ethical part of the *HLA-NET population questionnaire* has been completed and integrated. The questionnaire on ethical issues completed in the previous MC/WG meeting was sent to individuals in 26 European countries, and the 18 responses received were reviewed and presented in Leiden. The individuals interrogated are generally aware that either national or institutional guidelines/legislation exist in their country, formal ethical approval for collection of both new samples and previously stored samples have most often to be applied, informed consent has to be signed by the subjects sampled, most samples are linked anonymised, regulatory bodies monitor research in their country, and national law does not allow commercial exploitation of research samples / data. More people will be interrogated to get more representative results.

WG4 has also been updating its bibliography on ethics literature related to genetic testing, population analysis, biobanking, as well as a list of Websites with relevant information.

Scientific talks at MC/WG meetings

The Action has been active in stimulating research interest among its members through numerous talks:

- During the 5th MC/WG meeting in Athens, 2 conferences were presented by local speakers Katerina Tarassi on *«Genetic diversity in the Greek population»* and Chryssa Papasteriades on *«HLA and Disease: Interesting findings, peculiar association in Greek population»,* and 2 conferences were presented by invited speaker Gurvinder Kaur (All India Institute of Medical Sciences, New Dehli) on *«Genetic Diversity of HLA in the Indian subcontinent and implications in Transplantation and Disease»* and MC member Frans Claas on *«Towards a European acceptable mismatch program for highly sensitized patients».*
- During the 6th MC/WG meeting in Leiden, 3 conferences were presented by local speakers Monique Jöris on *«Frequent HLA haplotypes in unrelated hematopoietic stem cell transplantation»,* Anne-Marie van Walraven on *«Searching donors for Dutch patients»* and Frans Claas on *«Immunological challenges during pregnancy». Prof Jon J van Rood* was also invited as a keynote speaker to talk on *«IPA-NIMA».*
- All conference drafts are available at:

  http://hla-net.eu/wiki_spa/doku.php?id=action:invitees.

Other meetings:

The Action has also organized several meetings to promote collaboration and inter-disciplinarity:

- EFI meeting in Prague, Czech Republic, 4-7 May 2011: Oral session VII «HLA-NET» chaired by MC chair A. Sanchez-Mazas A and MC member G. Fischer, **«**COST-Europe and beyond**»** at the 25th European Immunogenetics and Histocompatibility Conference (EFI) 4-7 May 2011, Prague (Czech Republic). HLA-NET invited for an oral presentation some of the researchers who submitted an abstract to EFI but were not presenting a talk (Chuanfu Z, Toropovskiy A, Bishara A, Papasteriades C, Sulcebe G, Masson D, Voorter C). This event encouraged more people to collaborate with HLA-net members.
- HLA-NET/AHPD meeting in the Jura, France, 7 November 2012: a «satellite meeting» to the Action core meeting held in Geneva (see below) was organized in order to coordinate the work done by HLA-NET with the project «Analysis of HLA Population Data» (AHPD) of the 16th International Histocompatibility Workshop

held in Liverpool in May-June 2012. This meeting welcomed a total of 26 participants from 14 countries, who worked on the data that they submitted to the project. The computer tools developed within the framework of HLA-NET were used for this purpose. A report was posted on the wiki at https://hla-net.eu/wiki_spa/doku.php?id=events:jura-meeting.

- Core group meeting, Geneva, 8 November 2011 (Gottfried Fischer, Blanka Vidan-Jeras, Jean-Marie Tiercy, Michel Toungouz Nevessignsky, José Nunes, Alicia Sanchez-Mazas, Derek Middleton). This meeting allowed preparing all HLA-NET activities (work plan) for 2012.

II.B. Inter-disciplinary networking

As in previous years, the Action has continued to promote and develop inter-disciplinary work, e.g. through the organisation of a «data analysis» satellite workshop («Jura meeting», November 2011, see above) during which many Action members usually working at the wet-lab could analyze their data on specific computer programs (i.e. Gene[rate] developed within the frame of the Action) with the help of other Action participants (researchers and PhD students from the University of Geneva), and through STSM (mostly wet-lab analyses performed by ME Riccio in Marseilles, fall 2011). The publication of a common paper reporting the results of the Action (Sanchez-Mazas et al. 2012b) also demonstrates the potential of the Action for integrating the results of laboratory, biostatistical and computer work. A further outcome is the networking of databases taking into account both anthropological and genetic data, and for which a common schema has been elaborated and a paper prepared (Vangenot et al. *An integrated database schema to represent genetic, geographical and linguistic diversity for the study of human populations*, In prep).

In addition, the work done during the Action has been crucial for setting up a new partnership resulting in obtaining an important grant for a new European FP7 research project (FP7-health-2012-innovation, proposal 305385, title « A Europe-wide strategy to enhance Transplantation of highly sensitized patients on basis of Acceptable HLA Mismatches », acronym EUROSTAM). This project is coordinated by MC member F. Claas from the Leiden University Medical Center (LUMC), and includes, among other partners, Eurotransplant International (NL) and the National Health Services Blood and Transplantation (UK) as Foundations for organ allocation, in addition to several European Universities and private companies. Four among the 11 EUROSTAM partners are laboratories involved in HLA-NET with complementary expertise. Two of them are specialists in immunogenetics of solid organ transplantation (F. Claas and J. Martorell's labs) and the other two lead bioinformatics projects such as the allelefrequencies.net database (D. Middleton's lab) and the Geneva/Gene[rate] databases, biostatistical and computer tools (A. Sanchez-Mazas' lab). This new project is expected to provide a highly significant impact in public health (clinical transplantation).

Interdisciplinary networking is now also considered as a main asset of COST Action BM0803 in the context of the EFI Society, where Action members have been invited many times to contribute their expertise through teaching sessions and special HLA-NET sessions at EFI annual conferences. The possibility of a more formal and long-term participation of HLA-NET partners in EFI is currently under discussion.

II.C. New networking

New countries and participants In 2011, two new countries entered the Action: Bulgaria and Cyprus, and in 2012 one additional country, Hungaria (Attila Torday), raising to 21 the number of participating COST countries (plus one non-COST country, Albania). The total number of participants directly involved in the Action raised to 47 (including 4 non-active members), among which 24 females and 7 ESR.

ESR: Cláudia Carvalho moved as a STSM from Porto to London from February to April

2011 to work on «Identification of KIR polymorphism by sequence-based typing», and María Eugenia Riccio moved as a STSM from Geneva to Marseilles in November 2011 to work on «Resolution of ambiguities at HLA-DRB1 in several populations from Afghanistan». The reports are available on the wiki at https://hla-net.eu/wiki_spa/doku.php?id=action:stsm.

The number of **STSM** was low in 2011 but the number announced for 2012 (12 STSM) increased very much thanks to repeated calls by the MC chair to all Action members. In addition, several ESR from Geneva (María Eugenia Riccio, Christelle Vangenot, Da Di, Mathias Currat, Stéphane Buhler, and Stephan Weber) participated to the «Jura meeting» to train immunogeneticists and other researchers working in the web-lab to data analysis with appropriate computer programs. Also, one master student ESR from Geneva (Mélanie Cuénod) attended the Jura meeting as a trainee.

Promotion

- **Meetings/conferences**: HLA-NET was promoted in several meetings and through connections to several scientific programs (see references in the List of conferences below): as mentioned above, A HLA-NET session was organized in the EFI meeting in Prague (4-7 May 2011) (Conference Sanchez-Mazas et al. 2011). HLA-NET was also presented at the 15èmes Journées Educationnelles de l'EFI, 27-28 September 2011 (Conference Buhler 2011) and at the EFI REGION 8 Histocompatibility & Immunogenetics Laboratories Meeting, Athens (Conference Sanchez-Mazas 2011). The chair was invited to present a talk on her research at a discussion meeting on *Human evolution, migration and history revealed by genetics, immunity and infection* organized in June 2011 at the Royal Society of London (Conference Sanchez-Mazas 2011). Most member of the Action will participate as leaders or participants of research projects in the next Joint 16th International HLA and Immunogenetics Conference/26th European Immunogenetics and Histocompatibility Conference/23rd British Society of Histocompatibilty and Immunogenetics Conference held in Liverpool in May-June 2012. In this conference, a special «HLA-NET open meeting» has been scheduled in the Conference programme. The chair has also been invited to organize a teaching session on «Handling Immunogenetics data» at this Conference (http://ihiwefibshi.org/conference-programme.asp). During the workshop, HLA-NET members from Geneva will also coordinate 3 AHPD project sessions (with training to data analysis like in the «Jura meeting»).

- **Funded European research project**: as described above in ***II.B. Inter-disciplinary networking,*** a FP7 grant (FP7-health-2012-innovation, proposal 305385, acronym EUROSTAM) was obtained by HLA-NET MC member F. Claas (NL) with 3 other HLA-NET MC members as partners (the Action chair A.Sanchez-Mazas from CH, D.Middleton from UK, and J. Martorell from SP). In this project, HLA-NET is specifically mentioned as an essential consortium for the analysis of HLA data in European populations.

- **Project of the Swiss National Foundation**: a new research project «Early human settlements in contrasting environments: HLA molecular variation and its link to population expansions and immune adaptation» has been submitted for funding in April 2012 to the Swiss FNS. Many collaborations for HLA molecular typings are planned in this project thanks to the work done by HLA-NET in HLA data analysis. The project will also use the data gathered and computed tools developed within the frame of HLA-NET.

- **Database networking**: thanks to several discussions between A.Sanchez-Mazas, J.M. Nunes, D. Middleton and F. Galarza-Gonzalez, the last one occurring in Liverpool in April 2012, an agreement has been found to use the public database allelefrequencies.net (AFND) as the central database of the HLA-NET bioinformatics platform. Population data will be filtered in this database according to HLA-NET recommendations and computer programs (Gene[rate]) and used for statistical analyses through an automated pipeline.

Publications The studies announced in the previous report on HLA variation in India (Riccio et al., 2011), on HLA DNA sequence variation among human populations (Buhler & Sanchez-Mazas 2011) and on a new resampling schema to validate frequency estimation and selective neutrality (Nunes et al. 2011) have been published. In addition, we published a critical view of genetic studies in East Asia (Sanchez-Mazas et al. 2011a, after a talk presented at an international meeting in Cornell, USA), a review paper on immunogenetics studies (Sanchez-Mazas et al. 2011b), and, as mentioned above, the mid-term HLA-NET methodological recommendations (Sanchez-Mazas et al. 2012b). The talk given by the Action chair at the Royal Society of London in June 2011 was published in the Philosophical Transactions in April 2012 (Sanchez-Mazas et al. 2012a). Other publications acknowledging HLA-NET include a study of linkage disequilibrium between HLA-G and HLA-E (Di Cristofaro et al. 2011) and a paper on HLA diversity in pathogen-rich environments (Sanchez-Mazas et al. 2012a). A study of HLA molecular variation in the Swiss national registry in currently under review (Buhler et al. Under review).

Annex: List of articles published in 2011 or prepared in 2011 and published in 2012, with acknowledgments to HLA-NET (ESR are in bold)

1. **Buhler S**, Sanchez-Mazas A (2011). HLA DNA sequence variation among human populations: molecular signatures of demographic and selective events. PLoS ONE 6(2): e14643.
2. **Di Cristofaro J**, **Buhler S**, **Frassati C**, Basire A, Galicher V, Baier C, Essautier A, Regnier A, Granier T, Dzia Lepfoundzou A, Chiaroni J and Picard C (2011). Linkage disequilibrium between HLA-G*0104 and HLA-E*0103 alleles in Tswa Pygmies. Tissue Antigens 77, 193-200.
3. **Nunes, J.M.; Riccio, M.E.**; Tiercy, J-M., Sanchez-Mazas, A. (2011) Allele frequency estimation from ambiguous data: using resampling schema in validating frequency estimates and in selective neutrality testing. Human Biology. Human Biology 83:437-47.
4. **Riccio, M.E.; Nunes, J.M.**; Rahal, M.; Kervaire, B.; Sagart, L.; Tiercy, J-M.; Sanchez-Mazas, A. (2011) The Austro-Asiatic Munda population from India and its enigmatic origin: a HLA diversity study. Human Biology 83:405-35.
5. Sanchez-Mazas, A.; **Di, D.; Riccio, M.E.** (2011a) A genetic focus on the peopling history of East Asia: critical views. Rice 4:159-169
6. Sanchez-Mazas A, Fernandez-Viña M, Middleton D, Hollenbach JA, **Buhler S**, **Di D**, **Rajalingam R**, Dugoujon J-M, Mack SJ, Thorsby E (2011b) Immunogenetics as a tool in anthropological studies. Immunology, first published online 11 APR 2011. |
7. Sanchez-Mazas A, **Lemaître J-F, Currat M** (2012a) Distinct evolutionary strategies of human leucocyte antigen loci in pathogen-rich environments. Philosophical Transactions of the Royal Society B: Biological Sciences 367 (1590) 830-839
8. Sanchez-Mazas A, Vidan-Jeras B, **Nunes JM**, Fischer G, Little A-M, Bekmane U, **Buhler S**, Buus S, Claas F, Dormoy A, Dubois V, Eglite E, Eliaou J-F, **Gonzalez-Galarza F**, Grubic Z, Ivanova M, Lie B, Ligeiro D, Lokki ML, Martins da Silva B, Martorell J, Mendonça D, Middleton D, Papaioannous Voniatis D, Papasteriades C, Poli F, **Riccio ME**, Spyropoulou Vlachou M, Sulcebe G, Tonks S, Toungouz Nevessignsky M, **Vangenot C**, van Walraven A-M & Tiercy J-M (2012b) Strategies to work with HLA data in human populations for histocompatibility, clinical transplantation, epidemiology and population genetics: HLA-NET methodological recommendations. International Journal of Immunogenetics, Article first published online: 25 APR 2012 | DOI: 10.1111/j.1744-313X.2012.01113.x

Currently under review:

9. **Buhler S, Nunes JM**, Nicoloso G, Tiercy JM and Sanchez-Mazas A. The heterogeneous HLA genetic makeup of the Swiss population. PLoS One (under review).

Currently in preparation:

10. **Vangenot C, Galarza-Gonzalez F**, Sanchez-Mazas A, Middleton D, **Nunes JM** (in preparation) An integrated database schema to represent genetic, geographical and linguistic diversity for the study of human populations.

List of conferences given by Action members in 2011 and related to HLA-NET:

1. Buhler, S. (27.09.2011) **Projet HLA-NET et peuplement humain**, talk presented at the 15èmes Journées Educationnelles de l'EFI, 27-28 September 2011, Tours (France).

2. Sanchez-Mazas, A. (06.06.2011) **Role of migration, demography and natural selection in the molecular evolution of the HLA polymorphism in human populations**, talk presented at the London Royal Society meeting Human evolution, migration and history revealed by genetics, immunity and infection, 6-7 June 2011 (invited speaker). Available audio recording at http://royalsociety.org/events/2011/human-evolution/.

3. Sanchez-Mazas A, Fischer G, Chuanfu Z, Toropovskiy A, Bishara A, Papasteriades C, Sulcebe G, Masson D, Voorter C (2011). **COST-Europe and beyond**. 25th European Immunogenetics and Histocompatibility Conference (EFI) 4-7 May 2011, Prague (Czech Republic). Oral session VII.

4. Sanchez-Mazas, A. (22.01.2011) **HLA population genetics**, talk presented at the EFI REGION 8 Histocompatibility & Immunogenetics Laboratories Meeting, Athens.

Posters and reports published in 2011 and directly related to HLA-NET:

1. **Burt C** (2011) HLA-NET Training School – Population Analyses for HLA and other Immunogenetic Systems – Porto 21st Feb-24th Feb 2011. EFI Newsletter 64 (April 2011), p.23-25.
2. **Population data questionnaire** published in Sanchez-Mazas et al. (2012b) and online at http://hla-net.eu/population_questionnaire.
3. **Guidelines for reporting HLA typings** published in Sanchez-Mazas et al. (2012b) and online at http://hla-net.eu/reporting_HLA_typings_guidelines.

III. Previous scientific report(s)

Reporting Period: January 2010 – January 2011

Innovative networking

MC and WG members of the Action met in Helsinki in June 2010 to work on the four main aspects of the project: 1) population data, 2) molecular data and typing techniques, 3) statistical and computer tools, and 4) ethical issues.

1) **Population data** The number of laboratories declaring their interest to provide population or registry data for the project increased to 30, and the list was completed on the wiki. The proposed data include samples from Europe, Middle-East, India and West Asia.

The population questionnaire was updated a) to specify the loci analysed and the DNA technologies used for typing and add a link to the *Guidelines for reporting HLA typings*, b) to include information on data submission, and c) to include questions on ethical considerations, according to suggestions made by WG2, WG3 and WG4, respectively. The group is now ready to contact all laboratories to fill the questionnaire and send the data, which will be validated in the next period.

2) **Molecular data and typing techniques** Ambiguities outside exons 2 and 3 (class I) and exon 2 (class II) were defined for each locus based on frequencies reported in published population studies, on www.allelefrequencies.net, and on the common and well-defined allele list published by Cano et al. 2007 (Hum.Immunol. 68: 392-417). Alleles that might have an impact on population data analysis were defined. The *Guidelines for reporting ambiguities* were rediscussed and emphasis was put on the importance of reporting all possible genotype pairs instead of NMDP or allele groups. Rare alleles (a total of 193 distinct alleles) were defined and included in the database allelefrequencies.net.

3) **Statistical and computer tools** The basic schema for the HLA-NET database was completed and a publication is currently in preparation. WG3 has also been working a) to set up computer programs in order to validate data through a set of mandatory steps before their implementation into the database, and b) to include geographic information (maps). The group also prepared the *Training School on Population Analyses for HLA and other Immunogenetic Systems* that was organised in Porto in February 2011 (see report by Claire Burt in the publication list, Burt 2011) and that received 30 attendees.

4) **Ethical issues** A first draft of a questionnaire ("checklist") on ethical issues to address for research on population genetics was completed and loaded on the wifi. It was also distributed to EFI Commissioners for comments and feedback, and the responses are currently being reviewed. WG4 has also been setting up a bibliography on ethics literature related to genetic testing, population analysis, biobanking, as well as a list of Websites with relevant information.

Conferences During the MC/WG meeting, 3 conferences on epidemiological issues were presented: by Riitta Paakkanen (University of Helsinki, Finland) and MC member Una Bekmane (Riga Stradins University, Latvia), on HLA and disease associations, and by Dr Samuli Ripatti (Institute for Molecular Medicine Finland FIMM), on modeling aspects.

Inter-disciplinary networking

Inter-disciplinary networking in Action BM0803 involves laboratory work, biostatistics, bioinformatics, ethics, anthropology, population genetics, epidemiology, immunogenetics, organ and stem cell transplantation and molecular evolution. Such a high level of inter-disciplinarity is unique and provides research groups and clinicians with a high potential to work fast and efficiently, allowing them to run their analyses from data production to data analysis and interpretation. Additional knowledge obtained from working with several disciplines also provides a significant impact in public health (clinical transplantation, epidemiological studies). This crucial aspect of the Action attracts many students and young researchers, as shown by the success of the *Training School on Population Analyses for HLA and Other Immunogenetic Systems* held in Porto in February 2011 (about 60 applications and 30 funded participants).

The near availability of huge sets of European HLA data reported with the same standards is attracting the interest of other research groups and networks and raising some discussions about possible uses of these data besides those presented in the MoU. The possible cooperations relate mainly to applications of clinical or epidemiological relevance, further discussions and concrete results are expected in the next period.

New networking

New countries and participants In 2010, 3 new countries entered the Action: Croatia, Norway and The Netherlands, raising to 18 the number of participating COST countries. A non-COST country, Albania, also joined the Action. The total number of participants directly involved in the Action raised to 45 (including 4 non-active members), among which 23 females and 7 ESR.

ESR: Daniele Catanzaro moved from Brussels to Geneva to work on new models for genetic association studies. A paper was published thanks to the ideas developed during this STSM (Catanzaro et al. 2010). A second STSM from Porto to London was prepared end 2010 for Cláudia Carvalho but could finally only start early in 2011. The number of STSM is quite low in the Action because most laboratories belong to hospitals and other clinical institutions rather than to universities, and the number of students eligible for STSM is low. On the other hand, year 2010 was particularly productive in publications, several of them involving ESR (see list of publications where ESR are indicated in bold). Several ESR (Nunes, Buhler, Vangenot) also actively participated in the preparation of the Training School that was held in February 2011 in Porto.

Promotion HLA-NET was promoted in several meetings and through connections to several scientific programs: A HLA-NET session was organized in the EFI meeting in Florence (15-18 May 2010) (Sanchez-Mazas et al. 2010a) where a poster was presented (Sanchez-Mazas et al. 2010b) and a report was published (Ligeiro 2010). A joint meeting with members of the Igdawg project also took place there to discuss on the 16th IHWG workshop projects *AHPD: Analysis of HLA Population Data* (A. Sanchez-Mazas, http://16ihiw.org/projects/sanchezmazas_ahpd.html**),** whose report was published in 2010 (Nunes et al. 2010) and *Immunogenomic Data Management Methods* (S. Mack & J. Hollenbach, http://16ihiw.org/projects/mack_idawg.html)**.** HLA-NET sent data to the 16th IHWG workshop project on *Frequency of rare alleles* (F. Gonzalez, M. Fernandez-Viña & D. Middleton). The HLA-NET Chair also presented the Action in the *5th East-West Immunogenetics Conference in Pilsen (4-5 March 2010)* to representatives of Eastern countries in order to encourage participation of these countries to the Action (Sanchez-Mazas 2010a), in the annual conference of SFHI (French-speaking society of histocompatibility and immunogenetics) in Paris (*26 November 2010)* (Sanchez-Mazas 2010b), and in the EFI REGION 8 Histocompatibility & Immunogenetics Laboratories Meeting, Balkan External Proficiency Testing (B EPT) Evaluation – Athens - 22 January 2011 (Sanchez-Mazas 2011).

Publications A common publication was prepared in 2010 with Igdawg group members and past EFI president E. Thorsby on *Immunogenetics as a tool in anthropological studies* (Sanchez-Mazas et al. 2011, published online 11 April 2011). Thank to this work, the Chair was invited to present a talk at the Royal Society of London in June 2011 (http://royalsociety.org/human-evolution/). Other publications acknowledging HLA-NET included: two studies of HLA variation in North Africa (Fadhlaoui-Zid et al. 2010) and India (Riccio et al., in press); an analysis of HLA DNA sequence variation among human populations (Buhler & Sanchez-Mazas 2011); a linkage disequilibrium study between HLA-G and -E in Tswa Pygmies (Di Cristofaro et al. 2010); and a new resampling schema to validate frequency estimation and selective neutrality (Nunes et al. In press).

Several national or international funded projects involving COST colleagues have been running in 2010. Among the most significant, we will mention the Swiss COST project funded at the Swiss National level on The HLA genetic structure of Switzerland through the analysis of more than 20,000 individuals from 15 regions (applicants *A.Sanchez-Mazas & J-M Tiercy*), and several projects of the 16th International HLA and Immunogenetics Workshop (chairs *SGE Marsh & D. Middleton*, workshop to be held in Liverpool in June 2012): AHPD: Analysis of HLA Population Data (*A. Sanchez Mazas),* Frequencies of Rare Alleles (*F. Gonzalez, D. Middleton**),*** Population global distribution of KIR and ligand (*D. Middleton), and* IHIWS Registry Diversity Project (*C. Müller & SGE Marsh).*

Annex: List of articles published in 2010 or prepared in 2010 and published in 2011,

with acknowledgments to HLA-NET (ESR are in bold)

1. **Nunes JM**, **Riccio, ME**, **Buhler S**, **Di D**, **Currat M**, **Ries F**, Almada AJ, Benhamamouch S, Benitez O, Canossi A, Fadhlaoui-Zid K, Fischer G, Kervaire B, Loiseau P, de Oliveira DCM, Papasteriades C, Piancatelli D, **Rahal M**, Richard L, Romero M, Rousseau J, Spiroski M, Sulcebe G, Middleton D, Tiercy JM, Sanchez-Mazas A (2010) Analysis of the HLA population data (AHPD) submitted to the 15th International Histocompatibility/Immunogenetics Workshop by using the GENE[RATE] computer tools accommodating ambiguous data (ahpd project report). Tissue Antigens 76:18-30.
2. Fadhlaoui-Zid K, **Buhler S**, Dridi A, Benammar El Gaaied A, Sanchez-Mazas A (2010). Polymorphism of HLA Class II genes in Berbers from Southern Tunisia. Tissue Antigens 76:416-420.
3. **Catanzaro D**, Andrien M, Labbé M, Toungouz-Nevessignsky M (2010) Computer-aided human leukocyte antigen association studies: a case study for psoriasis and severe alopecia areata. Hum Immunol. 2010 Aug;71(8):783-8.
4. **Buhler S**, Sanchez-Mazas A (2011). HLA DNA sequence variation among human populations: molecular signatures of demographic and selective events. PLoS ONE 6(2): e14643.
5. **Di Cristofaro J**, **Buhler S**, **Frassati C**, Basire A, Galicher V, Baier C, Essautier A, Regnier A, Granier T, Dzia Lepfoundzou A, Chiaroni J and Picard C (2011). Linkage disequilibrium between HLA-G*0104 and HLA-E*0103 alleles in Tswa Pygmies. Tissue Antigens 77, 193-200.
6. Sanchez-Mazas A, Fernandez-Viña M, Middleton D, Hollenbach JA, **Buhler S**, **Di D**, **Rajalingam R**, Dugoujon J-M, Mack SJ, Thorsby E (2011) Immunogenetics as a tool in anthropological studies. Immunology, first published online 11 APR 2011. |
7. **Riccio ME**, **Nunes JM**, Rahal M, Kervaire, Sagart L, Tiercy JM, Sanchez-Mazas A (in press). The Austro-Asiatic Munda population from India and its enigmatic origin: a HLA diversity study. Human Biology.
8. **Nunes JM**, **Riccio ME**, Tiercy J-M, Sanchez-Mazas A (in press) Allele frequency estimation from ambiguous data: using resampling schema in validating frequency estimates and in selective neutrality testing. Human Biology.

Conferences:

5. Sanchez-Mazas A (2010a) Haematopoietic stem cell transplantation in Europe: Population aspects. 5th East-West Immunogenetics Conference, 4th-5th March, 2010, Pilsen (Czech Republic).
6. Sanchez-Mazas A, Vidan-Jeras B, **Nunes JM**, Fischer G (2010a) HLA-NET, an EU-funded Network of research on HLA Diversity: Connections to EFI. 24rd Immunogenetics and Histocompatibility Conference (EFI) 15-18 May 2010, Florence (Italy). Special session.
7. Sanchez-Mazas A (2010b) Projet HLA-NET et peuplement humain. Journées de la Société Francophone d'Histocompatibilité et d'Immunogénétique (SFHI), Paris (France), 25-26 novembre 2010.
8. Sanchez-Mazas A (2011) HLA in population genetics . EFI Region 8 Histocompatibility & Immunogenetics Laboratories Meeting, Athens (Greece), 22 January 2011.

Posters and Published reports:

4. Sanchez-Mazas A, **Nunes JM**, Vidan-Jeras B, Fischer G, Little AM, Bekmane U,

Buhler S, Buus S, Dormoy A, Dubois V, **Eberhard HP**, Eglite E, **Gonzalez-Galarza F**, Grubic Z, Ivanova M, **Lie B**, **Ligeiro D**, Lokki ML, **Maldonado Torres H**, Marsh SGE, Martins da Silva B, Martorell J, Mendonça D, Middleton D, Muller C, Papasteriades C, Poli F, Sulcebe G, Tonks S, Toungouz Nevessignsky M, van Walraven AM, Tiercy JM (2010b) HLA-NET, EU-funded network for research on HLA diversity. Poster presented at the 24rd Immunogenetics and Histocompatibility Conference (EFI) 15-18 May 2010, Florence (Italy).

5. **Ligeiro D** (2010) HLA-NET – An EU-funded network on research on HLA diversity. EFI Newsletter 62 (August 2010), p.34-35.
6. **Burt C** (2011) HLA-NET Training School – Population Analyses for HLA and other Immunogenetic Systems – Porto 21st Feb-24th Feb 2011. EFI Newsletter 64 (April 2011), p.23-25.

Reporting Period: January 2009 – January 2010 (January 15th, 2010*)*

Innovative networking

MC and WG members of the Action met twice (Porto, May 2009 and Vienna, December 2009) after the kick off meeting to work on the four main aspects of the project: 1) population data, 2) molecular data and typing techniques, 3) statistical and computer tools, and 4) ethical issues. The following results were obtained:

Population data

The working group decided to focus on the collection of several sets of data with the following priorities: a) European populations, b) populations from surrounding countries (e.g. North Africa, West Asia,..), and c) populations from other regions but related to Europe (e.g. local minorities of European countries such as Congolese in Belgium, etc). Population samples are to be defined on specific criteria based on anthropological studies (see below); however, for statistical reasons related to the number of available samples and individuals per sample, bone marrow registry data will also be used under clear-cut conditions.

A preliminary list of labs contributing population samples was created on the HLA-NET website through a wiki for continuous updating. Currently, a total of 15 European population samples provided by the laboratories participating to the Action are available for the project: French, Belgian, Italian, Bulgarian, Bulgarian Gipsy, Croatian, Norwegian, Sami, Finish, Portuguese, Slovenian, Swiss, Greek, Latvian and Albanian. The group got the agreement from the European Federation of Immunogenetics (EFI) to collaborate in the collection of data by using its services (mailing list, EFI newsletter) and presenting HLA-NET in a special session of its next annual conference (Florence, May 2010).

In order to standardize the collection of population data, a specific questionnaire on the characterization of the sampled populations was created and is available on the website for interested participants. An important issue was the definition of populations from an anthropological point of view. The group decided to avoid *a priori* classifications of ethnic groups in both questionnaires and databases, and to consider instead several levels of description related to geographic origin, language(s) spoken and any other relevant information on the ancestry of each studied population. As a perspective, specific recommendations will be established to replace outdated ethnic definitions (e.g. Caucasian, ..) with ethically acceptable alternative names. Another project is to encourage online publications of population data with HLA-NET “accreditation” resulting from the work of the Action.

Molecular data and typing techniques

The working group worked on the characterization, at the molecular level, of the population data to implement, taking into account that different techniques (e.g. direct or reverse SSO, SSP, SBT) and levels of resolution (e.g. 2 and 4-digit) were used in the last 10 years. Guidelines were defined for a) using specific typing techniques, b) handling ambiguities and c) reporting results at each level of resolution. A first version of this *Guidelines* document is available on the HLA-NET wiki. Specific recommendations will further be defined for data that cannot be easily processed to the recommended format. Two other important issues were the definition of ambiguities outside HLA exons 2 and 3 that might have an impact on population data analysis and the definition of alleles that could have been mistyped in the past. These tasks are currently in progress. The group also developed a preliminary strategy to analyze complex HLA data from BMD registries (Nunes and Buhler 2009).

Statistical and computer tools

The working group discussed on the HLA-NET database infrastructure integrating both population information and HLA typing data and chose to go for an abstraction of a database that will act as a gateway. Preliminary schemas of that database as an interchange layer for HLA-related population data were designed during a STSM (Gonzalez and Nunes 2009) and discussed in relation to the recommendations done for population and molecular data definitions (see above points 1 and 2). An important issue was the implementation of geographic information, either from scratch as personal vectors or raster maps, or from Google maps. Electronic formats for data implementation and modalities of data transfer are still to be defined. The creation of a computer program repository for data analysis, with links to available programs and comments on strengths and weaknesses of each program is in progress. This platform will also include pages to discuss on minimal standard statistics to use for data analysis, on the feasibility of web interfaces to software programs and other relevant topics. The idea to publish the implemented data (with restrictions for registry data) through an open access journal has been retained as an attractive objective allowing independent confirmation of results, data aggregation, open approach and possibility to re-analyze data at other levels.

II.B. Inter-disciplinary networking

Ethical issues

The working group defined three sets of situations (i.e. prospective studies, retrospective studies, and both kinds) in which ethical issues were to be addressed in relation to the objectives of HLANET, taking into account the balance between risks for the subjects and/or populations and benefits for the researchers and/or scientific community. A list of questions (e.g. ethical approval, informed consent, details on information provided, traceability vs anonymity, validation of typing / reliability) was put forward in each case. Specific problems linked either to electronic data sharing or sharing of biological samples (with UK legislation as an example) were also presented. The development of a specific questionnaire aiming at defining the ethical requirements of each European country regarding the questions addressed by the Action is currently in progress. Improvements of the questionnaire for the implementation of population data (see point 1) have also been done accordingly.

II.C. New networking

The group invited several scientific experts to help working on different issues of the Action: on ethical issues (Porto, May 2009) with André Herchuelz (ULB, Brussels), Alex Mauron (University of Geneva), and Peter Murray-Rost (University of Cambridge, UK); and on anthropological issues (Wien, December 2009), with Sir Walter Bodmer

(John Radcliffe Hospital, Oxford). The next meeting will welcome experts in epidemiological issues.

Transfer of competences through STSM

A PhD student in bio-informatics from Liverpool (F. Gonzalez) improved his experience in the design of population databases in a population genetics lab in Geneva, with direct applications to the Action (see point 3). A PhD student (E. Riccio, female) from a population genetics lab in Geneva was trained for HLA-A, -B and –DRB1 molecular typing of about 100 samples from Lombardy and Trento in a transplantation lab (Milano). The publication of the results is in progress.

Connection with other projects

In addition to its connection to EFI and POSEIDON in Europe (e.g. see Sanchez-Mazas 2009), the group started to work on possible connections between HLA-NET and several components of the International Histocompatibility and Immunogenetics Workshop (IHIW), namely the ahpd component (actually, already connected to HLA-NET, see Nunes et al. in press and http://geneva.unige.ch/generate/), the rare allele component (http://allelefrequencies.net, consideration has been given of using the website in collaboration with HLA-NET), and the Igdawg project (http://www.igdawg.org/).

Presentations and Publications (2009)

Nunes J (2009-) HLA-NET website: http://hla-net.eu

Nunes J and Buhler S (2009) Working with ambiguous HLA data in BMD registries. COST MC/WG Meeting, Vienna (Austria), December 10-11, 2009.

Gonzalez F and Nunes JM (2009) Population databases: schemas and data abstraction. COST MC/WG Meeting, Vienna (Austria), December 10-11, 2009.

Sanchez-Mazas A (2009) Europe and its Minorities in the context of the new HLA-NET European Network**,** in *Minority issues in HSC procurement*, 23rd EFI Conference, Ulm (Germany), May 9-12, 2009.

Nunes JM, Riccio ME, Buhler S, Di D, Currat M, Ries F, Almada AJ, Benhamamouch S, Benitez O, Canossi A, Fadhlaoui-Zid K, Fischer G, Kervaire B, Loiseau P, Muniz de Oliveira DC, Papasteriades C, Piancatelli D, Rahal M, Richard L, Romero M, Rousseau J, Spiroski M, Sulcebe G, Middleton D, Tiercy JM, and Sanchez-Mazas A (in press) Analysis of the HLA population data submitted to the 15th International Histocompatibility/Immunogenetics Workshop by using the GENE[RATE] computer tools accommodating ambiguous data (*AHPD* project report). Tissue Antigens.