

NEWSLETTER

JANUARY 2012 - ISSUE 66

.....FROM THE EFI PRESIDENT

DEAR EFI MEMBERS,

Time flies! From the 1st of January until the 31st of December, in total 365 days, EFI as a society serves its members. What have been achieved since the beginning of the year and what do we expect from the next one? At first EFI has changed its view in terms of focusing not only to the Annual Meeting or EFI Conferences. The focus goes now additionally to the regional meetings to the basemen of our Society. We had several regional meetings this year from Armenia, Balkan, France, Saudi Arabia, Russia, The Netherlands and many others where the EFI spirit was transmitted. The Executive Committee of EFI tries also to make bursaries available for participants and financially supports the organizers. It is the idea of "*giving to the membership what the membership deserves*". From the Annual Conference we obtain enough financial means so that we can support regional meetings. Furthermore, EFI plays a leading role in the summer school held this year in Puerto Rico and organized by our ASHI friends. In two years we will host the meeting in Europe and already now the respective Committee is putting the needed things together to have an excellent meeting for all the newcomers in our field. EFI supports also conferences and congresses within Europe, as the International Histocompatibility Workshop in Liverpool, and the NK meeting in the US. Bursaries are available to visit other laboratories, too, to learn new methods or ideas. In other words, EFI has reached the age of a full grown Society and is proud for that.

There are so many points to be acknowledged here, and therefore I have to apologize immediately for those I will surely forget. Thinking about EFI is thinking in dimensions as Education,

Accreditation/Certification, and Science. All these three pillars are making EFI to the Society we all know, need and are proud of. I will not forget the words of one of the leading scientist in Immunogenetics, who expressed the hope that EFI remains a scientific Society and will not drift to a business Society. Indeed, EFI is a scientific Society proven by its Annual Conferences but EFI is an educational society as well as has been shown in the Annual Conference and the regional meetings but also a business Society as has been demonstrated by its excellent accreditation/certification program.

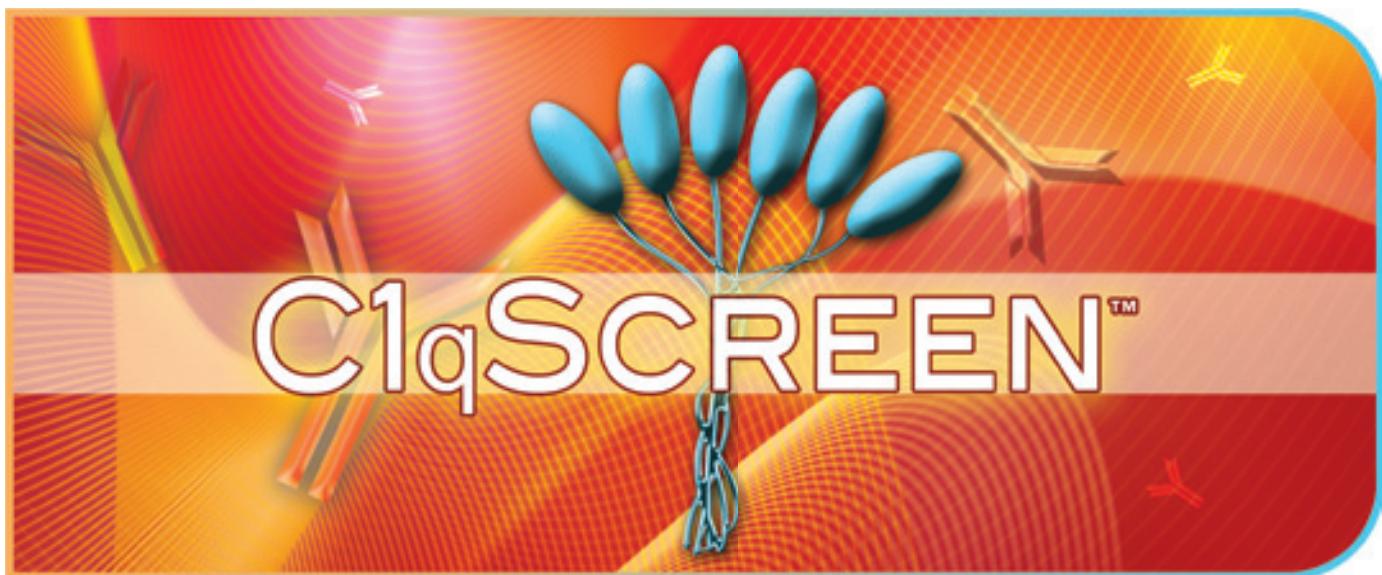


At present EFI has 986 members and 258 laboratories with an Accreditation. These are really milestones and a burden for the future. The Education Committee together with the European Society of Organ Transplantation is building up a program for certification of individuals in Transplantation Immunology. It will start from the 'Laboratory Directors' and continuing for all members of the laboratories. It will be Europe-wide.

The real spirit of Europe lives in EFI and personally I am proud of it. For the first time to my knowledge we have an 'Executive Committee' with members from different countries only, with the needed exception of the treasurers who must be from France. It is Europe in a smaller scale with a better understanding of the different mentalities.

The Scientific Committee is performing excellent as usual, and we should make use of the expertise in this Committee more than that we are doing now. The Accreditation Committee has a very difficult task to discuss and sometimes to reject applications for Accreditation. Here we will have some crucial changes in the near future because of the EU directive for Accreditation. The Committee will provide information about this topic presumably during the General Assembly. The 'Standards Committee' is working perfectly making our daily life a bit more difficult but for the sake of a better life for our patients. 'Standardization' is indeed the word of the year in EFI to my opinion. I have to admit that we need it with a bit of flexibility. We have also to make sure that the individuals who have to use them understand the standards. It is not easy. I indeed hope that we can remain as we are with a certain degree of flexibility and that we do not have to introduce an explanation for every formulated Standard as done for the laws in every of our countries. Finally, the Committee for 'Proficiency Testing' has managed to move the heaviest rock ever, by introducing Standards for EPT providers and participants. They are ready, need only to be finally approved, and there we go.

A big thank to all the members of EFI who took the challenge to serve the



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....FROM THE EDITOR'S DESK

This Newsletter clearly shows that the EFI community is very active all over Europe. You will find many reports on meetings in different places including several in the Eastern part of Europe. It is nice to see that the H & I activities in Eastern Europe are increasing, which is also the case for the number of accredited laboratories over there. As you will see, many of the reports in this Newsletter have been written by bursary recipients. It is good to notice that EFI is spending its money to support the members in order to enable them to visit these educational meetings.

In this issue Tony Slavcev gives a beautiful extended report on the activities during last years' EFI meeting in Prague, which was attended by more than 800 participants. The meeting was a great success and it is certainly a challenge for Derek Middleton and Steve Marsh to reach a similar level during the upcoming meetings in Liverpool. I assume that many of you are involved in projects related to the 16th International HLA and Immunogenetics Workshop (IHIW), which takes place just before the combined EFI/BSHI /IHIW conference. Don't forget to identify suitable candidates for the Julia Bodmer young scientist award, which will be delivered during the opening session of this conference.

Furthermore, in this issue a little bit of HLA history reflected in the contribution by Rene Duquesnoy. It is clear that the road to the HLAMatchmaker algorithm was an interesting and fascinating one.

After the successful International Summer school on Immunogenetics in Puerto Rico last year, it is now the turn of APHIA to host this prestigious teaching event. A first announcement is included in this issue. I am sure that the attractive environment and the excellent local wines might be good reasons to attend but, of course, the main reason to participate is the high level of teaching provided by tutors from EFI, ASHI and APHIA.

Hopefully the many contributions to this Newsletter are interesting and useful for you and I am looking forward to your contributions to the next one.

Frans Claas

Deadline for contributions to EFI Newsletter 67 is April 20, 2012.
Please send your contributions in Word format by e-mail to fhjclaas@lumc.nl

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.....FROM THE EFI PRESIDENT (CONTINUED)

Society in Committees, to be inspectors or to organize annual and regional meetings. Without their help we would have never be there where we are. Last not least many thanks to the two fairies in our EFI office: Ingrid Abelman, for the EFI business, and Sonja Geelhoed for the Accreditation. They are helping to move this ship EFI to the good direction.

So EFI is doing well and we have no concerns? I would be very happy if it would have been like this. I have to admit that this is not the case. We indeed have a

successor problem, namely a translational problem in our field. Looking to the different meetings one can observe that too few younger colleagues are there. We need fresh blood in EFI, we need the discussion between the generations, and we need the new ideas, the challenge, and the motivation. We need the questioning and the search for new solutions for the challenges of the future. Be assured the problem will be tackled.

Keep the words in mind I stated above: "on one side EFI is a scientific society

translating results from the laboratory to clinical applications". We have done that in the past and we **MUST** do this in the future.

From here I wish you and all of your laboratory coworkers and family all the best for a healthy and prosperous 2012.

C u in Liverpool, the city of the International Histocompatibility Workshop, our Annual EFI meeting 2012, and the Beatles! Good Luck Derek and Steve!

Ilias Doxiadis,

SUMMARY REPORT OF THE EFI EXECUTIVE COMMITTEE MEETINGS HELD 29-30 OCTOBER, LEIDEN, THE NETHERLANDS

The Executive Committee held a very productive meeting in Leiden.

The meeting was held in central Leiden and we thank Ingrid Abelman and Sonja Geelhoed for the excellent organisation.

The Executive Committee meeting, chaired by the EFI President Ilias Doxiadis, was the first meeting for the four new councillors, Martin Petrek, Michel Toungouz, Blanka Vidan-Jeras and Carlos Vilches. Future and past organisers of EFI conferences, Junior Lardy, Derek Middleton, Marie Schaffer, Tony Slavcev and the Meetings Liaison, Marcel Tilanus, were invited to join the meeting to make their presentations.

At the beginning of the meeting, the action points from the minutes from the previous meeting held in Prague were reviewed and the minutes were accepted.

The President Ilias Doxiadis made several announcements which were discussed by the committee:

EFI website

An EFI website working group has been formed, consisting of volunteers from the EFI membership. The aim of this group is to review the current website and to make a proposal for its future development. The group is being chaired by the President Elect, Gottfried Fisher.

EFI session at ESOT

EFI hosted a very successful satellite session during the ESOT meeting held in Glasgow in September. The theme of the session was the clinical relevance of HLA antibodies as defined by differ-

ent methods. A review of this and other ESOT sessions was published in the last EFI newsletter.

Meetings Liaison

Marcel Tilanus wishes to step down as Meetings Liaison at the Liverpool Conference in order to focus on the organisation of EFI 2012 in Maastricht. The committee discussed the role of Meetings Liaison and whether this could be taken on by a member of the Executive Committee. No decision on a successor to Marcel has yet been made.

Wikipedia

The President, President Elect and Secretary aim to update the Wikipedia content for EFI

Corporate Membership

EFI currently does not have Corporate Members, however ASHI does. The Executive Committee will consider this further during the Liverpool meeting

POSEIDON

The President and Treasurer were working on completing the financial summaries for the activities undertaken by EFI.

The EFI Secretary, Ann-Margaret Little updated the committee on the secretarial activities:

Elections

There will be no planned vacancies on the Executive Committee and therefore no elections will take place in 2012. This gives time for the updated website to be implemented which should

have the capability to handle electronic voting.

Proposal to change voting system

A request has been received from an EFI member who wishes the Executive Committee to change the current voting system.

Currently our voting system for electing councillors (when we have three vacancies, which is the 'normal' situation, and more than three candidates) requires each person to vote for three different candidates. The requester is concerned that this system is not democratic because if a member does not vote for three candidates, the vote is not counted. Therefore voters may end up voting for someone they do not want to vote for. The options that were suggested are, we allow members to give three votes to the same person or that all members have one vote only.

This request promoted much discussion amongst the Executive Committee. The system in place works in favour of promoting successful election outcomes for EFI members from smaller countries where there are fewer EFI members voting. The pros and cons of various proposals for changing the current voting system were discussed. Eventually, the Executive Committee agreed that as this issue has only been raised by one EFI member (and supported by a second), there was no immediate need to take action. It was also highlighted that the current Execu-

tive Committee members were all representatives from different countries with the exception of the Treasurer and Deputy Treasurer who both must come from France. This has not been the situation for some time.

Bursaries

The Deputy Secretary, Mats Bengtsson compiled a report from the twenty-two meeting reports prepared by EFI members who received bursaries to attend the Prague meeting. This was published in the last EFI newsletter.

EFI Logo

Former EFI Secretary, Ieke Schreuder has informed the Executive Committee via Past President Steven Marsh, that the EFI logo was created by Past President Julia Bodmer. We will now explore how to officially ‘trademark’ this logo.

The EFI Treasurer, Valerie Dubois, presented the current EFI financial statement.

Income

The EFI budget remains with a positive balance due to income from previous conferences

Future Expenditure

The Executive Committee approved financial support for the ‘Educational Meeting in Armenia’ to be held November 2011 and the East – West meeting to be held in Olomouc, Czech Republic to be held March 2012.

In addition bursaries were approved for members to attend the Educational Meeting in Armenia; the Updates in Histocompatibility and Immunogenetics meeting in Bucharest and the Society for Natural Immunity (NK cell) meeting in California, USA.

The Executive Committee approved to add a 500 euro bench fee to the current Education Bursary. It was also approved that the provision of Education Bursaries should not be restricted to EFI members with greater than one year membership as long as the hosting laboratory director is an EFI member.

EFI meetings being planned Liverpool, May 27th to June 3rd 2012, Chairs: Steven Marsh and Derek Middleton

Derek Middleton updated the plans for the 2012 EFI conference which will be held in conjunction with the British Society for Histocompatibility and Immunogenetics and the 16th International HLA and Immunogenetics Workshop.

The Workshop takes place on Monday, Tuesday and Wednesday and the Joint Conference will take place on Friday, Saturday and Sunday. The EFI committee meetings planned for Thursday will be held in the nearby Hilton hotel.

All chairs and speakers for the teaching sessions are confirmed. All plenary speakers and an additional guest speaker are confirmed.

All social events are organised with the exception of the Speakers Dinner and Ceppellini Dinner which need to be confirmed.

On the Friday evening the Olympic torch will be passing through Liverpool Sponsorship has been confirmed by many companies but there are still more possibilities to be followed up on.

Maastricht, the Netherlands, May 11-14 2013, Organisers: Marcel Tilanus and Junior Lardy

Junior Lardy presented an update for this meeting. The organisation has made significant progress and this meeting will make full use of media applications such as Facebook, Twitter and LinkedIn.

Stockholm, Sweden, June 25-28 2014, Organisers: Mats Bengtsson, Marie Schaffer, Ann-Charlotte Wikstrom

Marie Schaffer presented the proposal to host the EFI meeting in Stockholm which will be held in the new “Stockholm Waterfront Conference Centre”.

Previous EFI meeting

Prague, Czech Republic, May 4-7 2011, Chairs: Gottfried Fischer and Tony Slavcev

Tony Slavcev presented the closing statement for the very successful Prague EFI Conference with a profit of ~ € 95,000. There were 851 participants attending the meeting from many different countries. The Executive Committee shared a glass of champagne with Gottfried and Tony to congratulate their success

The Meeting Liaison, Marcel Tilanus updated the Executive Committee on his activities

Marcel has liaised with the organisers of the Prague meeting to produce their final report. He has also been involved in providing advice to the organisers of future EFI meetings.

There was discussion over the use of Professional Conference Organisers (PCO) that are members of the World Leading Congress Organisers (WLCO), as this allows exchange of data and experience. Another option is to have a single PCO committed to EFI for 3-5 years, which would be good for continuity for both EFI and our sponsors. The PCO’s used in Germany (Lentzsch) and the Czech Republic (Guarant) have made enquiries to Marcel about this possibility.

Marcel has been collating information from meetings held since Toulouse and he now has very good data regarding activities at each conference. He will add the information from Liverpool and Maastricht as soon as these conferences have been organised. With this information a template can be made for future organisers and if this is successful the need for an identified “Meetings Liaison” may not be necessary.

Proposal for EFI 2015

Three applications were received from members wishing to host the EFI Conference in 2015. The proposed host locations are Geneva, Kos and Prague. After discussion, (during which committee members with potential conflicts of interest left the room), it was decided that despite the success of the Prague meeting in 2011, we would not consider this application further. Both Geneva and Kos will be considered and a decision will be made during our Liverpool meeting.

Overall we had a very busy day with much productive discussion.

Ann-Margaret Little, EFI Secretary.

ELECTION OF NEW MEMBERS TO THE EFI EXECUTIVE COMMITTEE 2012

There will not be an election for new members to join the EFI Executive Committee in 2012 as there are no vacancies. The next election will be in 2013.

Ann-Margaret Little, EFI Secretary and Mats Bengtsson, EFI Deputy Secretary.

THE JULIA BODMER AWARD AND EFI ANNUAL CONFERENCE BURSARIES

Applications are invited for the prestigious Julia Bodmer Award, to be delivered during the opening session at the next EFI conference in Liverpool, United Kingdom. The Julia Bodmer Award is given to a young scientist in recognition of their outstanding work within the Immunogenetics field. The award also acknowledges the laboratory in which the scientist has performed their research. Any member of EFI can propose a candidate for the Julia Bodmer Award. The application must include the candidate's CV with publications and a letter of support from the head of the candidate's laboratory. Candidates must be an EFI member and be under 35 years of age. All applications will be reviewed by the Scientific Committee who will make the final decision on who will receive the award. The winner of the award will deliver a presentation describing their work at the EFI conference and will receive 1000 euros to cover travel and hotel expenses. The

registration fee for the meeting will also be provided by EFI.

All proposals must be sent in writing to the EFI Secretary via Ingrid Abelman at the EFI Central Office, (I.L.Abelman@lumc.nl) before 19th March 2012.

EFI Annual Conference Bursaries

A number of bursaries will be awarded to EFI members who have been selected to present an abstract at the EFI conference (either oral or poster presentation). Only one bursary per laboratory will be awarded. There is no age limit for applicants. Priority will be given to individuals who have not received a bursary previously. Members are eligible to receive a maximum of two bursaries. The EFI Executive Committee will evaluate the applications. The bursaries will be paid to the applicant by direct bank transfer or cash during the conference. All bursaries will be awarded on the strict condition that the

recipient submits a report of ~2 pages on any scientific session of the conference, which will be published in the EFI newsletter, following the conference. These reports must be sent to the EFI Secretary via Ingrid Abelman at the EFI Central Office, (I.L.Abelman@lumc.nl) by July 1st 2012.

Applications for bursaries for the EFI conference in Liverpool, United Kingdom must be received by Monday March 19th, 2012 and should include a short CV, a supporting letter from the laboratory director and a copy of the abstract that has been submitted. Applications must be sent to Ingrid Abelman at the EFI Central Office, (I.L.Abelman@lumc.nl). Applications after the deadline will not be considered. The applicants will be contacted by the EFI Secretary by Wednesday April 11th, 2012 to inform them if their application has been successful.

Ann-Margaret Little, EFI Secretary.

EFI STANDARDS COMMITTEE REPORT

The EFI Standards version 5.6.2 became active from 1st October 2011. A copy v5.6.2 and a tracking document detailing the changes has been posted on the EFI website. In October, two new members were elected to our Committee, Ingrid Fae (Vienna) and Junior Lardy (Amsterdam). They will join us for their first meeting in Liverpool next year and we are all looking forward to working with them.

It was agreed at our meeting in Prague that the EFI Autumn meeting would become the main meeting of the Standards Committee, to allow sufficient time for discussion. This meeting took place in Leiden in October, when we completed revisions which will become v5.7. There are several proposed changes for this new version. The main differences are:

1. There are new standards for HPA and HNA testing in Section J.
2. Section M has been updated and is now arranged in a more logical order which separates Luminex-

based standards from those for Flow Cytometry.

3. In order to facilitate the move towards joint EFI/ISO accreditation inspections, some of the standards in Section C have been modified or re-located elsewhere in the standards.
4. Perhaps one of our most significant proposed changes for this version will be to standards L2.3400 and L3.2560 which refer to the need to report all potential ambiguities for molecular typing results. It has long been acknowledged that this will become impractical as the number of known alleles increases. Now that we have more than 7000 recognised HLA alleles, we felt a need to relax this standard, and have agreed that ambiguities must be documented, but that if all ambiguities are not included on the report, a comment that additional data are available in the laboratory must be added.
5. We have also responded to comments from our Commissioners

and Inspectors and other members who have asked for clarification in various problem standards.

These proposed changes which will eventually become v5.7 (and a tracking document for you to follow) will be circulated to you all by email early in the New Year for your comments. Please look carefully at the new standards, and write to me with any concerns. If you would rather not write to me in English, do feel free to write in your own language and we will arrange a translation.

Finally, we are also still working on the new format of the EFI Standards which will be equivalent to this new version 5.7. This has been an extensive piece of work led by Thibaut Gervais, which is almost complete now, and will hopefully be circulated for comments sometime next year.

Kay Poulton (Manchester, UK)
Chair, EFI Standards Committee

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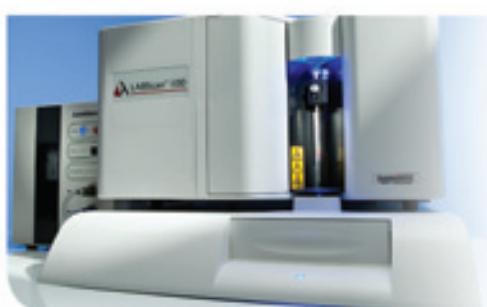
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Programme of the 16th International HLA and Immunogenetics Workshop and the combined EFI/BSHI/IHIW conference in Liverpool

Monday 28th May 2012

0800-1800 hours	Registration
0900-1800 hours	International Histocompatibility Working Group in Haematopoietic Cell Transplantation - Effie Petersdorf and Mari Malkki
1900-2300 hours	Welcome Reception, Merseyside Maritime Museum

Tuesday 29th May 2012

0800-0900 hours	Registration
0900-1930 hours	International Histocompatibility Working Group in Haematopoietic Cell Transplantation - Effie Petersdorf and Mari Malkki
0830-1230 hours	IHIWS Registry Diversity Project - Martin Maiers, Carlheinz Müller, Steven Marsh
1600-1930 hours	
0830-1230 hours	Population global distribution of KIR and ligand - Jill Hollenbach, Raja Rajalingam, Derek Middleton
0830-1230 hours	Improving Prediction of Chronic Rejection by Donor Specific Antibody and Serum Creatinine - Paul Terasaki and Mikki Ozawa
0830-1230 hours	The Role of Natural Killer Cells in Solid Organ Transplantation - Jeroen van Bergen and Ilias Doxiadis
0830-1230 hours	Development of an HLA Epitope Database - Rene Duquesnoy
1230-1600 hours	Immunogenetics of Aging - Elissaveta Naumova, Graham Pawelec and Milena Ivanova
1230-1930 hours	AHPD: Analysis of HLA Population Data - Alicia Sanchez Mazas
1230-1600 hours	Towards Standardization of Microparticle-based, Solid Phase, HLA Antibody Identification Assay - Robert Bray and Howard Gebel
1230-1600 hours	Prevalence of IgA anti-HLA antibodies and previous graft survival in kidney re-transplant candidates - Bernd Spriewald, Marie-Luise Arnold and Ilias Doxiadis
1230-1600 hours	Pharmacogenomics - Clara Gorodezky and Susie Leffell
1600-1930 hours	Global Distribution of Extended HLA Haplotypes - Medhat Askar and Marcelo Fernandez-Vina
1600-1930 hours	MICA-MICB Project - Peter Stasny and Yizhou Zou

Wednesday 30th May 2012

0830-0900 hours	Registration
0900-1800 hours	KIR Open to presentation of abstracts from anyone
0830-1230 hours	IHIWS Registry Diversity Project - Martin Maiers, Carlheinz Müller, Steven Marsh
1600-1930 hours	
0830-1230 hours	The Analysis of HLA Class I Non-coding Regions - Linda Smith
1600-1930 hours	Immunogenomic Data Management Methods - Steve Mack and Jill Hollenbach
1230-1600 hours	Frequencies of Rare Alleles - Favian Gonzalez, Marcelo Fernandez-Vina, Derek Middleton
1230-1600 hours	Evaluation of Antibody Frequencies and Solid Phase Assays - Andrea Zachary and John Hart
1230-1600 hours	AHPD: Analysis of HLA Population Data - Alicia Sanchez Mazas
1600-1930 hours	Next Generation HLA sequencing Diane de Santis and Richard Allcock
1930-0100 hours	Workshop Party at Circo, Albert Dock

Thursday 31st May 2012

0900-1800 hours	Optional excursion to the Lake District
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Conference Programme

Thursday 31st May 2012

1500-1800 hours	Registration
1900-2200 hours	Welcome Reception, St George's Hall

Friday 1st June 2012

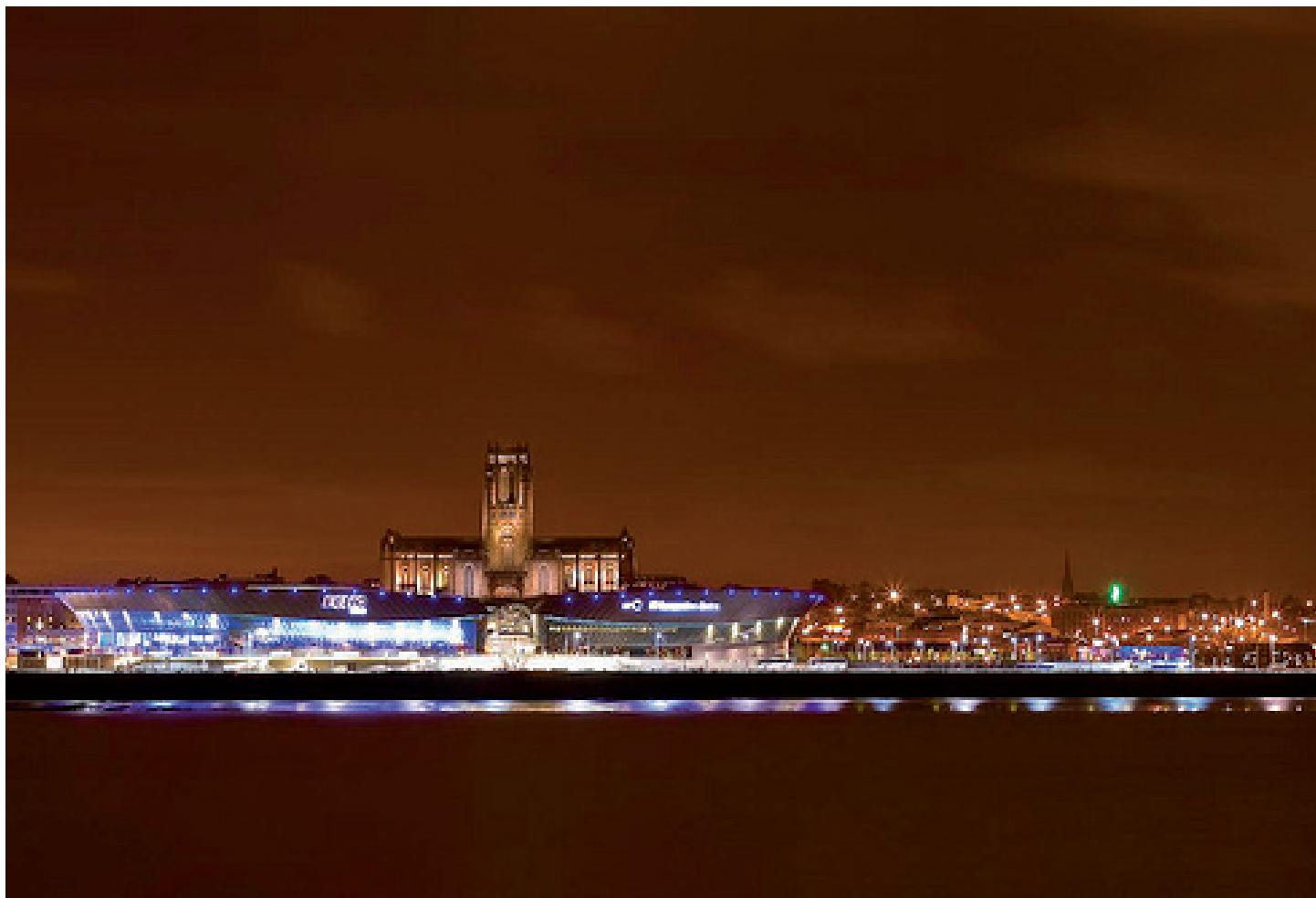
0830-0900 hours	Registration
0900-0915 hours	Welcome
0915-1030 hours	Plenary Lectures Cappellini Lecture Professor Gerhard Opelz, Institute of Immunology, University of Heidelberg, Germany
1030-1100 hours	Break Parallel Sessions Workshop Reports, Oral Presentations Teaching Session: Second Generation Sequencing Professor Neil Hall, University of Liverpool, UK Professor Dimitri Monos, University of Pennsylvania, USA
1100-1300 hours	Lunch Satellite Symposia BSHI AGM Plenary Session: Structure & Binding Professor Jamie Rossjohn, Monash University, Australia Professor James McCluskey, The University of Melbourne, Australia Professor Munir Pirmohamed, University of Liverpool, Liverpool
1300-1445 hours	Break
1315-1415 hours	Exhibition & Posters

Saturday 2nd June

0830-0900 hours	Registration
0900-1030 hours	Plenary Session: Evolution and Impact on Infectious Disease Professor Peter Parham, Stanford University School of Medicine, USA Professor Ronald Bontrop, Biomedical Primate Research Centre, The Netherlands Dr Mary N. Carrington, National Cancer Institute at Frederick, USA
1030-1100 hours	Break Parallel Sessions Workshop Reports, Oral Presentations Teaching session: Virtual Crossmatching versus Solid Phase and Standard Crossmatch Procedures Dr Caner Süsal, University of Heidelberg, Germany Professor Robert Bray, Emory University Hospital, Atlanta, USA
1100-1300 hours	Lunch Satellite Symposia Best Abstract Session Break EFI General Assembly
1300-1445 hours	
1315-1415 hours	
1445-1645 hours	
1645-1715 hours	
1715-1845 hours	

Sunday 3rd June

0830-0900 hours	Registration
0900-1030 hours	Plenary Session: Workshop Highlights Professor Effie Petersdorf, Fred Hutchinson Cancer Research Center, Seattle, USA Professor Frans Claas, Leiden University Medical Centre, The Netherlands
1030-1100 hours	Break
1100-1300 hours	Parallel Sessions Workshop Reports, Oral Presentations Teaching session: Handling Immunogenetics Data Professor Alicia Sanchez-Mazas, University of Geneva, Switzerland Dr Steven Mack, Oakland Research Institute, USA
1300-1445 hours	Lunch
1315-1415 hours	Satellite Symposia
1445-1615 hours	Plenary Session: Hilliard Festenstein Lecture Professor John Trowsdale, University of Cambridge, UK Terasaki Lecture Dr GJ Pettigrew, Cambridge Transplant Unit, UK
1615-1645 hours	Break
1645-1730 hours	Plenary Session Professor Kevin Warwick, Professor of Cybernetics, University of Reading, UK
1730 hours	Closing Ceremony
1930-0100 hours	Gala Dinner, Aintree Race Course



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25th European Immunogenetics
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Prague | Czech Republic
May 4–7 | 2011



EVENT REPORT:

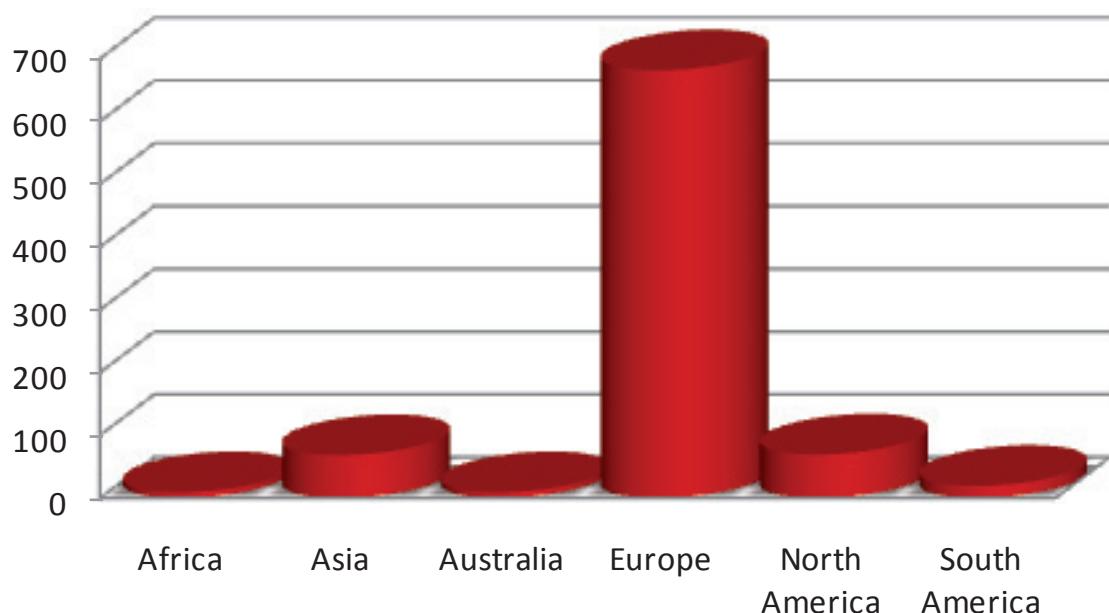
25th European Immunogenetics and Histocompatibility Conference
Prague, Czech Republic, May 4–7, 2011

REGISTRATION

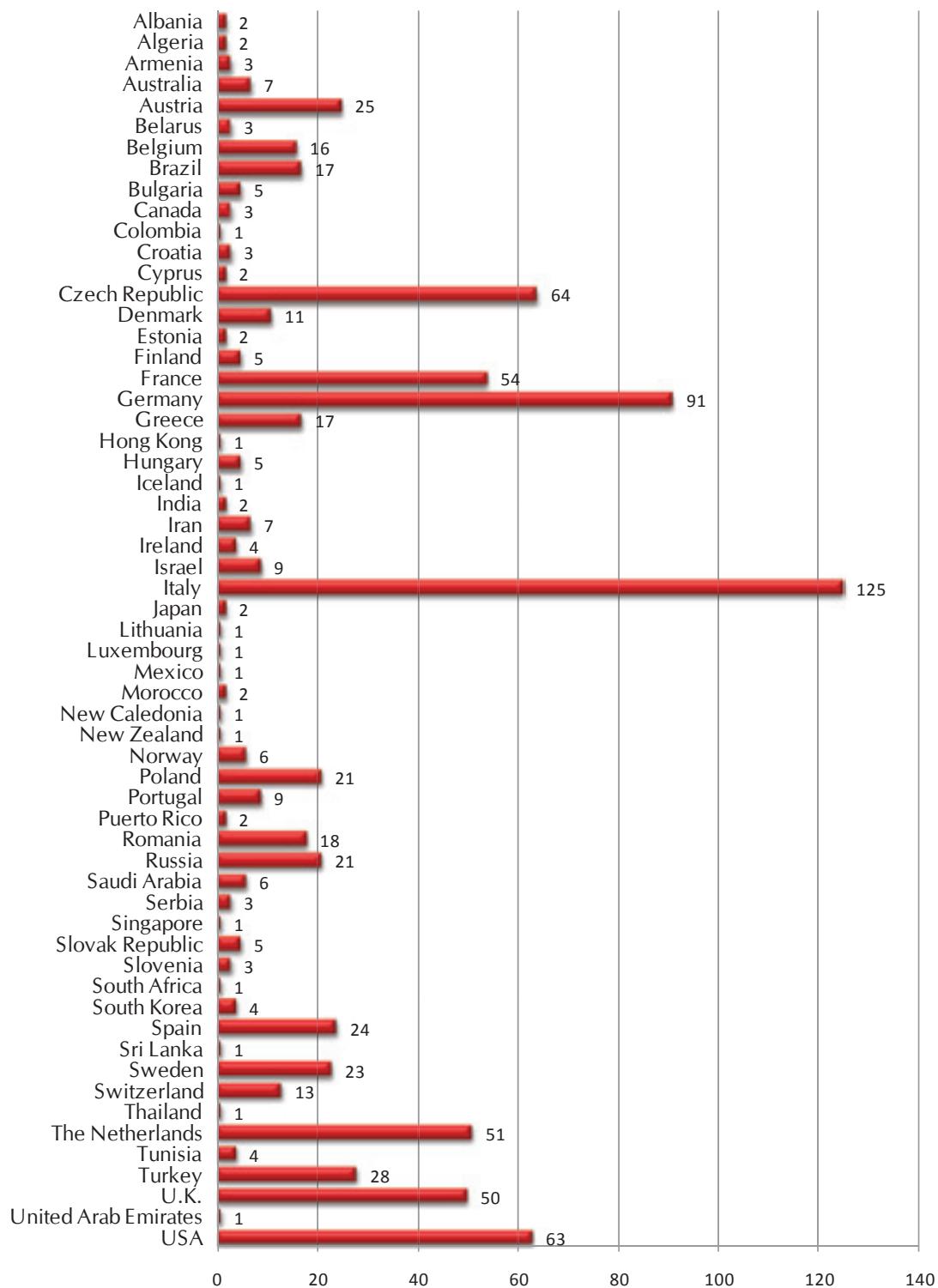
The 25th European Immunogenetics and Histocompatibility Conference **was attended by 805 participants** out of **833 totally registered persons**. There were slightly more women than men registered to the conference – 56% women and 44% men.

Number of participants according to the Continents

The participants arrived from all over the world. The highest number of participants arrived from Europe. The lowest number of participants arrived from Africa and Australia.



Number of participants according to the Countries



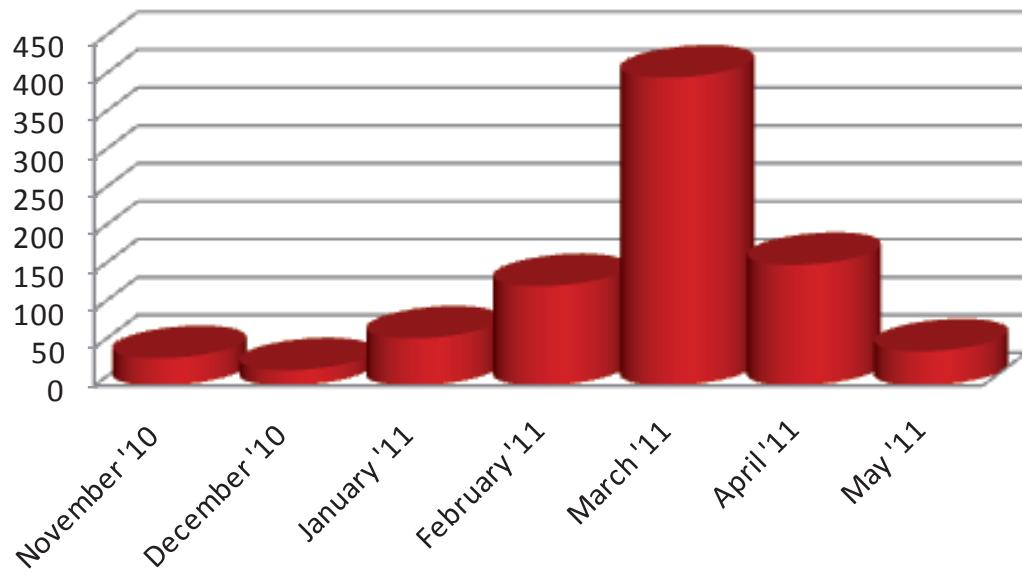


25th European Immunogenetics
and Histocompatibility Conference

Prague | Czech Republic
May 4–7 | 2011



More than one half of the total number of participants registered before the Early registration deadline – 31 March 2011.



Agenda

The motto of the congress “Immunogenetics 2011: From Basic Science to Clinical Applications and Beyond” emphasizes immunogenetics as a science with multiple interfaces with clinical practice which most certainly has led to the increased recognition of the importance of this field during the last decade.

More than 360 abstracts from all continents were evaluated.

Plenary Sessions

Opening Ceremony

Julia Bodmer Award
Ceppellini Lecture

Plenary Session I

Genetics-Epigenetics-Gene Interactions of the HLA Complex



25th European Immunogenetics
and Histocompatibility Conference

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Plenary Session II

From Peptide Motifs to Vaccines

Plenary Session III

NK Cells: First or Second Line of Defence

Plenary Session IV

Antibodies Revisited

Plenary Session V

Alloreactivity and Tolerance in Transplantation

Social Events

EFI Inspectors' Dinner on Tuesday, May 3

Rio's Restaurant Vyšehrad



Welcome Reception on Wednesday, May 4

The Welcome Cocktail was held on the first conference day – on Wednesday, 4 May 2011, starting right after the end of the Opening Ceremony at Prague Congress Centre.

Music was performed by the student orchestra "Three Weeks After".





25th European Immunogenetics
and Histocompatibility Conference

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Thursday, May 5, 19:30

On Thursday the social programme started with the Concert at the Church U Salvátora. The concert was free for all registered participants.

The Ceppellini Dinner - Villa Richter Restaurant and Speakers' Dinner – Café Imperial Restaurant followed the concert.

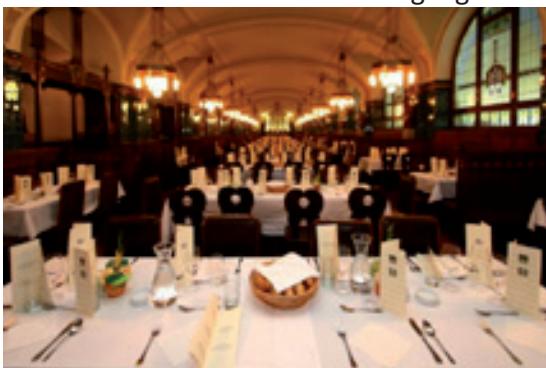
From 22:00 the One Lambda Party was held.



Friday, May 6, 20:00

Gala Dinner in the Municipal House

The Gala Dinner was the social highlight of the congress. Czech specialities were served.





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REPORT ON AN EDUCATIONAL VISIT TO MILAN

Nina Lauterbach

Maastricht University Medical Center, Maastricht, the Netherlands

Host-institute: Unit of Molecular and Functional Immunogenetics, Milan, Italy

Period: March -July 2011

I would like to thank the EFI education committee for the bursary that gave me the opportunity to visit the Unit of Molecular and Functional Immunogenetics in Milan in Italy. September 2008 I started my PhD project which focuses on HLA polymorphism and functionality which I perform at Transplantation Immunology, Laboratory Tissue Typing in Maastricht in the Netherlands. In our study we identified HLA-DPB1 full length polymorphism in 148 samples using an RNA based approach. Our results showed various DPB1 alleles with, in addition to the polymorphism in exon 2, polymorphic positions in exon 1, 3, 4 and 5. Interestingly, alleles with identical exon 2 sequences but differences in other exons were found and based on these differences outside exon 2 one new allele has been identified. Taken in consideration these results and the fact that DPB1 functionality is not clear based on exon 2 polymorphism our aim is to determine if this newly identified polymor-

polymorphism beyond exon 2 is relevant for T cell recognition and a collaborative study with their lab gave me the opportunity to learn the strategy for obtaining DPB1 specific T cell clones. Such functional assays are crucial in our future research topics to unravel the functional role of HLA polymorphism.

In the first period of my stay I got familiar with the lab and was involved in the transduction procedures for several cell lines as we wanted to transduce cell lines with the DPB1 alleles of our interest. I also brought cell lines along to Italy which were typed as the DPB1 alleles possessing the substitutions beyond exon 2. I used these cell lines together with the transduced cell lines as targets in the functional assays. I would like to thank Pietro Crivello for



tional assays in order to accomplish my research aim and to collect knowledge on the procedures to perform mixed-lymphocyte-reactions and to obtain DPB1 specific T cell clones. I would like to thank Laura Zito for obtaining the MLRs and T cell clones relevant for my project and for her support in getting familiar with the procedures regarding the functional assays and DPB1 specific T cell clones.

I performed many functional assays to study the activation status of the DPB1 specific CD4 T cells against our targets of interest. Thereby, I got familiar with many aspects on the functional assays to study the relevance of HLA-DPB1 polymorphism.

Next to the hours I spend in the lab I have also spent some wonderful days enjoying Milan and the places surrounding this energetic city. I loved living in the center of Milan as it is a city that never sleeps. I want to thank Pietro Crivello for introducing me to some great people and the Italian life style, of which I got really fond of.

I would like to thank Katharina Fleischhauer for giving me the opportunity to work in her laboratory and to deepen my research project and for sharing her views and knowledge with me in her well established laboratory.

Last, but definitely not least I would like to thank my wonderful colleagues from Milan; Laura Zito, Federico Sizzano, Cinzia Pultrone and Pietro Crivello. I never felt so welcome and you were not only wonderful colleagues but became also great friends. I will never forget the Italian lessons! Hopefully we can meet in Holland some time soon.



From left to right: Cinzia Pultrone, me (Nina Lauterbach), Laura Zito, Federico Sizzano, Christina Toffalori, Pietro Crivello

phism outside exon 2 is important in CD4 T cell functionality. The group of Katharina Fleischhauer in Milan is well known for their studies regarding T cell functionality with DPB1 specific T cell clones. We were interested to explore if

instructing me and for his knowledge in retroviral transduction protocols. This was an excellent opportunity for me to get familiar with this method. After finishing transduction of the cell lines I focused on the performance of func-

FIRST EFI EDUCATIONAL AND TRAINING MEETING IN ARMENIA



The Armenian Bone Marrow Donor Registry (ABMDR) hosted the first-ever European Federation of Immunogenetics (EFI) Training and Educational Meeting to be held in Armenia.

The meeting took place in Yerevan during November 18-19 at the Ani Plaza Hotel. Featuring world-renowned speakers from Europe and elsewhere, it brought together close to 150 doctors and experts in the fields of immunogenetics and bone marrow transplantation. The meeting was attended by participants representing more than 15 countries from Europe, the region and the CIS including Armenia, Iran, Georgia, Kazakhstan, Russia, Ukraine and others.

With sessions dedicated to recent advances in HLA, immunogenetics, stem cell and organ transplantation, and HLA-disease associations, the conference functioned as a global forum for sharing scientific expertise and expanding the knowledge base of participants. As importantly, the event fostered international medical cooperation and helped pave the way for the advancement of immunogenetics in various countries. The conference was organized by ABMDR, under the auspices and major sponsorship of EFI.

The selection of Armenia as the host country of the EFI meeting was made in January of this year. As announced by the EFI leadership, the main factors in selecting Armenia were the scope and quality of ABMDR's work. Specifically, the federation cited ABMDR's HLA

tissue typing laboratory in Yerevan as the only, and EFI-accredited, facility of its kind in the entire region.

At the opening ceremony of the conference, welcome remarks were delivered by Deputy Health Minister, Dr. Sergay Khachaturian, Dr. Ara Babloyan, chairman of the National Assembly's Committee on Social Affairs, Healthcare, and Environmental Protection; Dr. Ilias Doxiadis, president of EFI; Dr. Bella Kocharyan, honorary chair of ABMDR; Dr. Frieda Jordan, president of ABMDR; and Dr. Sevak Avagyan, executive director of ABMDR.

As Dr. Avagyan spoke of ABMDR's accomplishments and goals, he stated: "Our tissue typing operation has had the challenge of responding to a tremendous influx in prospective bone marrow stem cell donors due to the great success of our efforts, both in the U.S. and throughout the diaspora. Last year, which marked our registry's tenth anniversary, recruitment teams registered an astounding 5,000 donors within a short span. This is, of course, a good challenge to have, as we currently have over 1,500 patient families seeking a donor match from our registry."

Dr. Avagyan's aim of reaching out to larger numbers of patients struck by life-threaten-

ing blood-related diseases was echoed by Dr. Bella Kocharyan. "We view the EFI meeting in Yerevan as a stepping stone toward the establishment of a bone marrow transplantation center in Armenia," she said.

As Dr. Frieda Jordan addressed conference participants, she underscored the significance of the EFI meeting in Armenia. "Six years ago," she said, "we welcomed our first EFI colleagues to Yerevan, when they came to inspect our laboratory operations. A few months after their visit, we learned that ABMDR was granted EFI accreditation — ours was the first laboratory of its kind in the CIS to receive it. Now we experience another first for the registry, and for Armenia: hosting an international scientific symposium of this caliber is an honor, and — we hope — an opportunity to continue to 'surprise' our colleagues with the quality of our work and the progress we have made." ...



"We owe much of our success to plain hard work and the dedication of the ABMDR staff and volunteers," Dr. Jordan continued. "But we also owe it to colleagues such as yourselves who, for many years before us, have created the models for success and set the standards for our work. And now, perhaps, we are in a position to 'give back' to our colleagues. ABMDR has not only built a foundation for its own success, but can also be a source of information for other registries getting started. Each of our registries is a beacon of hope for all who suffer from life-threatening blood-related diseases. At this EFI meeting, we are gathered to share our knowledge with each other as we all work toward giving the greatest gift imaginable: life itself."

Speaking on behalf of EFI, Dr. Ilias Doxiadis had high praise for ABMDR as he addressed the attendees. Citing

ABMDR's global efforts in the past several months to launch the EFI meeting in Yerevan, Dr. Doxiadis applauded the registry's success in helping provide an international platform where foremost immunogenetics specialists could share their expertise with colleagues from a diversity of countries. Dr. Doxiadis expressed hope that the meeting would lead to new avenues of cooperation between current EFI members such as ABMDR and other conference participants.

Following the conclusion of the meeting, EFI Region 8 chair and commissioner Dr. Chryssa Papasteriades congratulated ABMDR for hosting the unprecedented event. "This has been a fantastic symposium," she said. "The top-notch scientific program, the excellent coordination, the memorable social events that complemented the various sessions, and, above all, the

wonderful diversity of participants as well as the friendly, infinitely supportive atmosphere resulted in an extraordinary success."

The conference received extensive news coverage, both locally and internationally. At the end of the conference new members were joined EFI from the regional countries and expressed great interest to apply for EFI accreditation.

About the Armenian Bone Marrow Donor Registry: Established in 1999, ABMDR, a nonprofit organization, helps provide matched donors for patients worldwide who are suffering from life-threatening blood-related illnesses whose last hope of survival is to have a bone marrow stem cell transplantation. To date, the registry has recruited over 22,000 donors.

For more information, visit abmdr.am.

FIRST EFI TRAINING AND EDUCATIONAL MEETING" IN ARMENIA

Reactions of two bursary recipients

Dmitry Klyuchnikov

The first EFI educational meeting in Armenia was very interesting and fruitful for me. I learned a lot thing about HLA and disease association, establishing a bone marrow donor registry and population genetic of HLA.

I was very impressed the report about population genetics of HLA by Dr. Carlheinz Müller. In their report he observed the largest registries in Europe and showed us the differences in haplotype frequency between different registries. And he demonstrated that known haplotypes can help with resolving ambiguities and it can be useful for donor search . The most similar were registry in Germany and France. European registries extremely differ from Asian registries in haplotype presentation. That is why development of national registries is very important for each country. The report was very demonstrative.

Also the report about establishing of donor registry in Armenia by Frieda Jordan was very interesting. She told us about constitution, structure and achievements of ABMDR. The experience of other countries is extremely

important for Russia, because there it just begins to gain momentum at the present time.

Sarah Palmer

Herewith I would like to give a review of Professor Bornhäuser's lecture entitled 'Chimerism analysis post stem cell transplant – technical aspects and new methods' .

Professor Bornhäuser provided a brief historical overview of the techniques employed to study chimerism, ranging from Southern blotting and Fluorescence In Situ Hybridisation (FISH) through to more modern PCR-based techniques used to amplify variable number tandem repeat (VNTR) or short tandem repeat (STR) markers. Advances since the 1990's in PCR-based methods have seen a move towards more quantitative analyses, capable of calculating the percentage donor DNA in a given sample using a combination of peak height and area beneath the peak generated by fluorochrome signals. Professor Bornhäuser touched upon the sample requirements for chimerism analysis, as well as the difficulties of obtaining a pre-trans-

plant recipient derived sample post-transplant. Solutions for which include isolating DNA obtained from buccal swabs, nail clippings or hair strands. After addressing the technical aspects of chimerism analysis, Professor Bornhäuser focussed on the clinical application of the technique, which is employed to diagnose loss of graft function associated with a loss of chimerism in patients undergoing reduced intensity conditioning, haplo-identical stem cell transplantation, and cord blood transplantation. Emphasis was placed upon a two-stage diagnostic system in which a more crude assay can be employed in the early stages post-transplant where a mixture of both donor and recipient derived cells coincide, followed by the need for increased sensitivity during follow-up investigations to enable early detection and treatment of minimal residual disease.

Finally, the audience were introduced to the future of chimerism analysis, which aims to improve upon the current standards using immuno-magnetic isolation or flow-cytometric sorting to pre-enrich samples with target cell populations prior to chimerism analysis.

EFI'S BURSARY FOR ARMENIA MEETING:

A WELCOME HUG TO NEWEST ACCREDITED LAB

Since Histocompatibility Department of 'Laiko' Hospital is the last EFI accredited laboratory of 2011, I decided to make a report, based on sessions of First EFI training and Educational meeting in Armenia that commented EFI standards (Dr. G. Fischer) and accreditation program on region 8 (Dr. C. Papasteriades). Before anything else, I would like to thank EFI for the opportunity offered to me, to attend this meeting with a bursary.

Our laboratory belongs to the 8th region (Balkans +Israel), with commissioner in our area Dr. C. Papasteriades. Balkan EPT is coordinated and organized for this region by Prof. E. Naumova (Bulgaria) and Prof. Oguz (Turkey), and is one of the two quality control schemes we participate in order to help us evaluate our results on a regular basis. Our lab also participates to UK Neqas for H&I Scheme 4A1.

Our first step was to contact Ms. Sonja Geelhoed from EFI Accreditation Office and receive from her information and guidance as well as Application packet A, which is designed for first application of EFI accreditation and first round inspection. Our team started to prepare the lab according to EFI standards and when we felt ready, we sent a filled

packet A back to Accreditation Office and asked from our Commissioner Dr. Papasteriades to arrange the inspection team and an appropriate date. Exposing ourselves and our every day routine tactics to the inspection team, proved a 'profitable' thing to do, since reported mistakes and deficiencies became our source and guide map for future development. As commented from Dr. G. Fischer in the related session in Armenia's meeting, hiding or making things up in a laboratory just to look good before and during an inspection is nothing more than a quality 'discount', amateurism among professionals.

At the end of the first round we managed to accredit our laboratory, for Class I and Class II HLA-typing using molecular 2 digit typing techniques, for donor registry typing and disease association studies. At this point I would like to thank EFI community for the encouragement, support and guidance, in our effort to improve the quality of our work and finally certify our lab as accredited. Although we are the last accredited EFI laboratory, it seems that we will be the first Histocompatibility lab that will be also accredited for ISO 15189 from EA (European Cooperation for Accredita-

tion).

Armenia – host country of this meeting- is a part of this region, and was really impressive as well as inspiring, the quality and quantity of the work done, on a relatively limited time from a dedicated lab team and insightful leaders. Finally I would like to mention the huge potential that comes from region 5, a future opportunity for EFI family to grow and for all of us to gain even more experience and friends.

An Arabic proverb saying: blessed he who can give to his children **roots** and **wings**.

Rephrasing this for HLA people, it seems that working in this area gives both,

Our roots: the genetics of our ethnic populations

Our wings: the opportunity to study other people's roots, exchange experience and learn from each other

Eleni Lekka

Chemist /Technical Supervisor, B.Sc., M.Phil., Ph.D.,
Department of Immunology & Histocompatibility,
'Laiko' General Hospital, University of Athens,
Greece

REQUEST FOR INFORMATION ON HLA AND KIR DATA

MANAGEMENT

The Immunogenomics Data Analysis Working Group (IDAWG) is collaborating with ASHI to survey the Laboratory Directors in the Histocompatibility and Immunogenetics community on their current HLA and KIR data management and analysis practices. We hope that the participation of EFI Laboratories in this survey will provide a comprehensive overview of current practices in the community. The results of the survey will be presented at the 16th IHW meeting in Liverpool next year.

We would like to extend the offer for your lab to participate in the survey. The survey should take approximately 15 minutes to complete and can be accessed at [\[We realize that each laboratory manages data differently, and that many laboratories do not perform data analyses; however, we value your expertise as an EFI Accredited Laboratory Director, and hope that you will be able to share some of what your laboratory does in terms of generating, managing and transmitting HLA and KIR data. It is not necessary that you as Director complete the survey if you would rather designate an individual from your group that routinely manages and/or analyzes data.\]\(http://key.com/s>IDAWG.</p></div><div data-bbox=\)](http://www.surveymon-</p></div><div data-bbox=)

The survey can be submitted anonymously, and although survey participants are invited to take part in the

larger IDAWG 16th International Workshop project, information specific to individual laboratories will be kept confidential; individual laboratories will not be identified without providing consent.

More information about this project can be found at: <http://immunogenomics.org/workshop.html>.

Please direct any questions or comments about the survey to: survey@immunogenomics.org.

Cheers,

Steve Mack and Jill Hollenbach
Immunogenomics Data Analysis Working Group

My Life with HLA

Rene Duquesnoy



When my children were very young they often asked me for a bedtime story: "HLA and Antibodies". In each story, my early life would be full with adventures like being an astronaut

walking on the moon or, a lion hunter in Africa or, a World War II spy dropped beyond enemy lines, etc. However, something always went wrong, like my space suit started to leak, or a big lion was going to jump on me and my rifle did not work, or the Nazis were closing in on me and there was no escape possible. In other words, each story ended with a cliffhanger and then in a panic I would ask myself: "What am I doing here... ???" ... and at that moment I decided to go into "HLA and Antibodies". My children always responded with "Oh Dad" but at subsequent bedtimes, they always wanted to hear about a new adventure.

Well, how did my life with HLA really begin? I was born in The Hague, The Netherlands. As a son of a cobbler I was lucky enough to go to high school and then the Technological University of Delft, where I obtained an Ingenieur degree (equivalent to a US degree between MS and PhD) in chemical engineering with a minor in organic chemistry. In 1963 I emigrated to the United States where I joined the Department of Pathology at the University of Tennessee in Memphis as a Research Associate working on a breast cancer project. I knew almost nothing about medicine but fortunately I was allowed to enter graduate school and in 1967 I received a PhD degree in Pathology. My dissertation was "Effect of Immunization with Estrone-Protein Conjugates on 9,10-Dimethyl 1,2-Benzanthrazine-Induced Mammary Carcinogenesis".

In 1968 I was married to Betty and we moved to the Minneapolis where I did a post-doctoral fellowship with the world-famous immunologist Robert A Good at the University of Minnesota. My research interests were endocrine influences on immune function and I studied an interesting model of an immunodeficient pituitary dwarf mouse (1).

In 1970, I went to Milwaukee to become Assistant Professor of Microbiology at the Medical College of Wisconsin and at the same time, I was hired by The Milwaukee Blood Center as a part-time director of their developing HLA laboratory. I learned about HLA in the laboratory of Edmond Yunis at the University of Minnesota and Harriet Noreen taught me the Amos method of serological typing.

About two years later, Glenn Rodey became the full-time director of the MBC HLA laboratory, but in 1973 I joined again following my disassociation from the Microbiology Department at MCW. Dick Aster, Director of MBC, and I played racquetball, and he offered me a position to work on a project on HLA matching in platelet transfusion for which he and Glenn Rodey had been awarded a 5-year NIH contract. Glenn had developed an excellent HLA laboratory but because of his interest in clinical immunology, he moved to the Department of Pathology at the Medical College of Wisconsin. I continued to work on his cross-reactive HLA matching algorithm, the so-called BU and BX mismatches to identify suitable platelet donors for highly sensitized patients. These activities led to many presentations at meetings and publications; some are listed below (2-6). This HLA matching scheme is still being used by many platelet transfusion services worldwide.

In 1974, I became director of an HLA laboratory which under Glenn Rodey's initiatives, had developed an outstanding serum screening program to identify HLA-specific antibodies in multiparous female blood donors. My studies focused initially on the splits of HLA-A10 called 10.1(now A25) and 10.2 (now A26). We had identified "monospecific" sera for these splits (7) but several HLA experts, including Rose Payne, were skeptical at that time. I sent some small aliquots to Rose Payne for her evaluation and she responded with a request for larger volumes; that was such good news!. These sera were submitted to the 6th International HLA Workshop and became reference reagents for A25 and A26. I became interested in the structural relationship between the cross-reactive A25 and A26 and why some antibodies

reacted with A25+A32 and others with A26+A11.

At the 6th International HLA Workshop Conference in Aarhus, Denmark, I gave a presentation about a possible structural explanation of HLA antigen crossreactivity. We must consider the fact that in 1975 there was no information about HLA molecular structure and amino acid sequences which would come many years later. I gave this talk at a plenary session and all of a sudden, the chairman interrupted me by saying "Mr. Duquesnoy, stop all this nonsense..." Someone in the audience stood up and stated "I completely agree, we are wasting our time....". There was quite a discussion by the audience whether or not I could continue. While watching this it came to my mind that for a newcomer like myself this experience is not so bad, people will remember my name. I was allowed to continue my presentation. During the coffee break, Jean Dausset (who became a Nobel laureate) asked me to explain my ideas and we had a most cordial discussion for about 10



Figure 1 Definition of MB with 7th Workshop serum clusters

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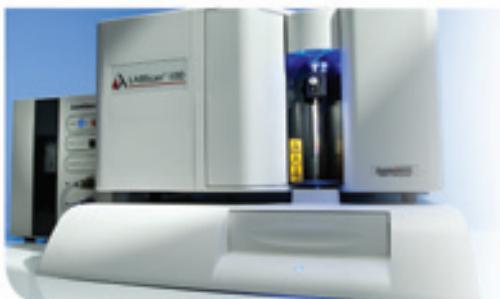
* Donor Specific Antibody based on reference HLA typing information from the donor.

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minutes. A report entitled "Approach to a Molecular Model for HL-A Antigenicity" was published in the Proceedings of the 6th Workshop (8). This was the beginning of my interest in the structural basis of HLA epitopes, which was not surprising because of my academic training in organic chemistry.

Participants in the 7th International HLA Workshop (Oxford, UK) were organized into regions worldwide and I joined Bo Dupont (Sloan-Kettering, New York) and Edmond Yunis (who had moved to Harvard, Boston) in US Region 7. A major topic was the serological identification of HLA-D, and among the 150 sera submitted worldwide there were 35 reference reagents, including two from Milwaukee that defined the DRw1-7 specificities. My task was to analyze the reactivity of all 150 sera with the US Region 7 cell panel that included many African-Americans (9). We discovered three serum clusters that reacted very differently than the DRw clusters. Being at the Milwaukee Blood Center, I called these specificities MB1, MB2 and MB3, and a Hardy-Weinberg equilibrium analysis suggested that they belonged to a separate HLA-D locus (10). Marilyn Marrari, who started to work with me in 1976, made the serograph shown in Figure 1.

A collaborative study with the transplant surgeon Myron Kaufman showed a beneficial effect of MB matching on survivals of 21 kidney transplants from one-haplotype mismatched related donors. In 1980, a publication appeared in the New England Journal of Medicine (11) and received national nationwide attention, including newspaper articles and TV interviews on major networks.

In those days, increasing numbers of investigators were searching for a second class II locus, including Paul Terasaki who defined the MT system and Stephen Shaw at the National Cancer Institute who discovered the "Secondary B-cell" system (SB) with primed alloreactive lymphocytes. We did a population study with him (12). Lysostrip experiments (13) and sequential immunoprecipitation studies with our sera (14-16) clearly demonstrated that DR and MB were separate molecules. Moreover, Adriana Zeevi, who had joined me as a post-doctoral fellow, had cultured alloreactive T cell clones specific for MB and MT (17).

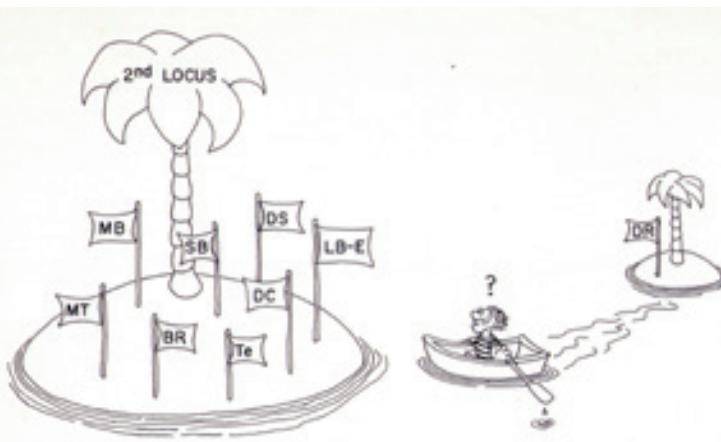


Figure 2 Discovery of the 2nd HLA-D locus

Multiple DR-associated systems were proposed. There was considerable confusion as illustrated in Figure 2 and there was much skepticism about MB. In 1981 I was asked to give a seminar at Saint Louis Hospital in Paris trying to convince Jean Dausset. After a 2½ hour session, he said that he had to think more about MB and members of his group were excited about such a positive reaction. I participated actively in the lively discussions at the 8th International Workshop Conference (Los Angeles) in 1980. During a brief break, Jon van Rood, who I admire so much, stood next to me in the men's bathroom and he said "Rene, don't push MB so much, let people figure it out themselves". This was such good advice and I thanked him. At the 9th International Workshop (Munich) in 1984, the MB system was officially recognized as HLA-DQ, whereas MT2 and MT3 were called DR52 (HLA-DRB3) and DR53 (HLA-DRB4), respectively, and the SB system became HLA-DP.

During the early 1980s, the bone marrow transplantation field was rapidly expanding. The shortage of HLA identical sibling donors was a significant problem, and there were many discussions about using unrelated donors especially after a successful transplant case at the Fred Hutchinson in Seattle. At a large meeting in Minneapolis, I recall the general consensus was one of not being ready for such approach. The Milwaukee Blood Center had a file of 12,000 HLA-A,B-typed platelet donors and it turned out that at Children's Hospital there was a 4-year old boy with aplastic anemia in need of a bone marrow transplant from an unrelated donor. While so far the transplant failure rate for aplastics had been 100%, we searched our platelet donor file for HLA-A,B identical donors who then also had to be matched serologi-

cally for HLA-C, DR, MB and MT. No molecular methods were available, but we performed cellular testing in large 30x30 checkerboard Mixed Leukocyte Cultures and SB typing with primed lymphocytes. This led to the identification of a suit-

able donor (a 48-year old grandmother, not related) and hematologist Bruce Camitta performed the bone marrow transplant in 1982. Engraftment was excellent and although there was severe graft-versus-host disease, the patient survived. A subsequent publication (18) received widespread attention with newspaper articles and TV interviews on national networks. As far I know, the individual is still alive and might be considered the world's longest surviving aplastic anemia patient with an unrelated bone marrow transplant. This successful case was helpful in establishing the National Marrow Donor Program where I served on their HLA committee.

The efforts of Sue Hackbarth and Marilyn Marrari in serum screening of multiparous blood donors permitted the Blood Center to develop a most comprehensive inventory of serological typing reagents. We contributed the largest number of sera to the 8th Workshop (Los Angeles, 1980) and we provided many sera to the American, Latin-American and Brazilian Histocompatibility Workshops. We also discovered a new class II determinant, MC1, which is associated with DR1 and DR4, and has a high frequency in rheumatoid arthritis patients (19). Several companies began to pursue the commercial distribution of serological typing trays. I arranged for David Dubell, President of PelFreez, to develop a relationship whereby the Blood Center would provide all sera for the typing trays manufactured by PelFreez. Bill Cannady managed their Clinical Division in New Jersey and they needed more space. I convinced him to move their facilities to Milwaukee. Because of this new business relationship, the Blood Center administration decided to create a separate commercially oriented division for the serum screening program. Shortly thereafter in 1983, I accepted an offer from the University of Pitts-

burgh to direct tissue typing activities for their large transplant program.

I was very fortunate that Marilyn Marrai joined me in the move to Pittsburgh. She became supervisor of the HLA laboratory at the Central Blood Bank and began to play a key role in the Proficiency Testing program, a joint effort of ASHI and the College of American Pathologists (CAP). This program had its first survey in 1980. I was a member of the Proficiency Testing committee at the time and a commercial company (that exists no more) had a contract to distribute the specimens. Unfortunately, the first two shipments had poor quality whereby samples could not be HLA-typed, and the survey subscribers started to demand refunds. During that moment of crisis, I remarked to the committee that it should not be so difficult to distribute viable cells. After a successful mock survey, we proposed and were awarded a contract that was cheaper to produce and generated a nice annual income for ASHI because the subscription fees stayed the same. The surveys expanded markedly after the transfer of the contract to Pittsburgh, growing to seven different surveys to evaluate serological and molecular HLA typing, serological and flow cytometry screening for class I and class II HLA antibodies, HLA-B27 detection and engraftment monitoring. The computer facilities at CAP collected and collated the survey data whereas Marilyn and I did the analyses and prepared the reports. We also published the survey experiences (20-22). This fruitful partnership between ASHI and CAP continued until 2002 when ASHI decided to conduct surveys on its own. In 2003, CAP became a competitor with its own surveys, and ASHI awarded us a contract for proficiency testing that included specimen distribution and a website-based computer component for data collection, analysis and reporting. In 2007, we withdrew from the survey program and Marilyn continues working with me on HLA epitopes.

Overall, my experience with proficiency testing was most rewarding as were my other activities with ASHI, including serving as treasurer (1978-1980), vice-president of ABHI (1982-1984), ASHI president (1986-1987) and on numerous committees. I must admit my feelings of nostalgia for the good times at the early annual ASHI meetings when nobody minded my singing about HLA. But let's go back to research...

Adriana Zeevi had received her Ph.D. from Bar Ilan University in Israel and her dissertation was on soft agar colonies of phytohemagglutinin-activated lymphocytes. In 1979, she became a post-doctoral fellow in my laboratory in Milwaukee, expecting to be trained in serology and blood banking. But instead, she studied the cloning of MLC activated lymphocytes from soft agar cultures. This resulted in many publications about T-cell allorecognition of class I and class II cellular determinants (17, 19, 23-28). Also in Milwaukee, Afzal Nikaein was a post-doctoral fellow from Iran; she worked on the cloning of autoreactive T-cells (29) and learned the elements of HLA typing.

I was also most fortunate that Adriana moved with me to Pittsburgh in 1984, where she joined the faculty of the University of Pittsburgh. She applied her cloning methods to the propagation of graft-infiltrating lymphocytes from human heart transplants and bronchioalveolar lavages (BAL) of lung transplant patients. We had a productive relationship with cardiothoracic transplant surgeon Bartley Griffith and his team, and later on with liver transplant pioneer Thomas Starzl. New transplant monitoring methods were developed such as the biopsy growth assay (30-33) and the BAL lymphocyte test (34-36). Many studies addressed the characterization of graft-infiltrating lymphocytes (31, 37-40).

Three students wrote their PhD dissertations under my direction. Susan Saidman studied the characterization of lymphocytes infiltrating liver transplants (41-43). She also analyzed the effect of pre-existing HLA antibodies on combined liver-kidney transplants (44). Yolanda Colson studied the adherence of alloreactive lymphocytes to vascular endothelium (45-47). Christina Kaufman worked on the propagation and characterization of graft-infiltrating alloreactive lymphocytes in relation to acute and chronic rejection of heart transplants (48-50).

Several fellows under Thomas Starzl also worked in my laboratory. John Fung, a most intelligent young researcher, studied liver and cardiothoracic allograft-infiltrating cells (38, 40, 51-52) and humoral sensitization of liver-kidney transplant patients (44, 53). Bernd Markus from Germany, another bright and productive young investigator, did in vitro studies on liver allograft propagated lymphocytes and HLA on

endothelium (45, 54). His clinical studies demonstrated for the first time the dualistic effect of HLA matching on liver transplantation: it reduces rejection but on the other hand, it augments HLA-restricted immune mechanisms of allograft damage (55-56). Other investigators have supported this concept, and my studies with Rafael Manez showed that HLA matching is associated with an increased incidence and severity of viral disease of transplanted livers (57-58). Thomas Weber, also from Germany, worked on graft-infiltrating cells (31-32). His clinical studies demonstrated that highly sensitized liver transplant recipients require intra-operatively more platelet and red cell transfusions but nevertheless remain at high risk for bleeding problems, although the liver transplant itself is quite resistant to antibody-mediated injury (59). In one unpublished case, we found that a HLA-matched platelet transfusion was most effective.

My interest in MB (now called HLA-DQ) expanded with a collaboration with Massimo Trucco, who was at the Wistar Institute in Philadelphia. He had developed molecular (RFLP) methods for DQA and DQB typing, and his findings were compared with our serological data and cellular determinations with primed alloreactive T-cell clones. These studies led to several publications summarized in two reviews (60-61). My laboratory was also doing serological HLA typing for a large diabetes program at our institution (62). Since they needed a molecular biologist and Massimo was going to relocate, I arranged for his move to Pittsburgh. Soon afterwards, Massimo went on his own and he has done very well here.

In 1987, Thomas Starzl brought from a Japanese company a compound called FR-900506 for which he had high expectations as a immunosuppressive drug. He gave us 5 mg for in vitro studies and the other 5 mg were used for animal transplant models. This drug was more potent than cyclosporine (63-66) and has now widespread clinical use as tacrolimus.

Following my arrival in Pittsburgh in 1984, I had become increasingly involved with research and I was fortunate enough to receive several RO1 grants from NIH. To relieve my clinical responsibilities, Thomas Starzl hired Yui Iwaki, who had been with Terasaki for many years, as the director of tissue typing. After almost two years, Mas-

simo Trucco assumed this position. In 1997, I became, surprisingly enough, co-director with Adriana Zeevi. This lasted until 2006 when I became a clinical consultant for another five years.

During the early 1990s, my research interests began to add a new dimension. The cloning experiments of transplant biopsy-propagated lymphocytes showed that only very small proportions were HLA-specific alloreactive T-cells. What were the properties of the other cells? Moreover, we found that lymphocytes cultured from coronary arteries of transplanted hearts had many CD4-negative, CD8-negative $\gamma\delta$ cells; such cells are often involved with chronic inflammation (67). The direction of my research changed to heat shock proteins (HSP) and stress responses in transplantation. Ricardo Moliterno from Brazil performed his PhD dissertation work on HSP-induced propagation of lymphocytes from human heart transplant biopsies and the HSP reactivity of graft-infiltrating lymphocytes with a rat heart allograft model provided by Luis Valdivia (68-70). Kaihong Liu, a post-doctoral fellow from China, identified HSP-dependent autoreactive lymphocytes in rat heart grafts (71). Our studies were well received as indicated by several invited reviews (72-75). NIH funding was a different situation and after several unsuccessful applications, I gave up on this project and went fully back to HLA.

My return to HLA meant again HSP but in this case, the acronym stood for the Highly Sensitized Patient. I have always been interested in humoral sensitization and in 1990, I published a paper on antibodies against private and public determinants and their roles in defining mismatch acceptability (76). It was quite easy to get a three-year NIH grant for these studies. So 25 years after the paper on the molecular model of HLA antigenicity (8), I began

to focus on structurally based HLA epitope matching and this led to HLAMatchmaker (77-78). The algorithm considered initially the concept that HLA epitopes can be defined by amino acid triplets. Indeed, triplet matching has a beneficial effect on kidney and corneal transplants (79-80) and increases the availability of suitably matched donors (81). Frans Claas and his group in Leiden observed in transplantation and pregnancy induced sensitization that numbers of mismatched triplets predict antibody responses to HLA-A,B antigen mismatches (82). This concept of epitope load has also been verified for other HLA mismatches (83-84). The Eurotransplant program has included HLAMatchmaker as a useful tool to find acceptable mismatches for highly sensitized patients (85-87). Over a period of three years, I spent a most enjoyable and productive six-month sabbatical with Frans Claas and he was so kind to arrange the prestigious Boerhave Visiting Professorship award for me. HLAMatchmaker has also been used to find platelet donors for refractory thrombocytopenic donors (88) and matching at the epitope level seems better than the cross-reactivity system described in 1977 (2, 89).

Although this research was supported by another five year NIH grant, I concluded that triplets were insufficient descriptions of HLA epitopes. After studying the literature on protein epitopes and how they interact with antibodies, I applied the term "eplet" to describe a patch of residues within a 3 Ångstrom radius on the molecular surface (90). Medhat Askar, a post-doctoral fellow from Egypt, studied class II eplets (91). Recent progress with HLAMatchmaker has been summarized in several reviews (92-95) and increasing numbers of clinical laboratories are using the program. A dedicated website www.HLAMatchmaker.net has downloadable pro-

grams, articles and other information.

Although eplets might be considered key elements of HLA epitopes, it is necessary to validate them with specific antibodies tested with informative HLA panels. Human monoclonal antibodies generated by Arend Mulder in Frans Claas' group have particularly been useful for these types of studies. Many of them are specific for eplets whereas other detect epitopes defined by eplet pairs with one of them being a self-eplet present on an HLA antigen of the antibody producer (96-97). These findings suggested an autoreactive component of the HLA antibody response and further investigations have led to the so-called nonself-self paradigm of HLA epitope immunogenicity (98). Accordingly, a mismatched eplet on an immunizing antigen elicits an antibody response if the other surface residues in the vicinity of that eplet are the same or very similar as those in the same area of an allele of the antibody producer (99-100). This paradigm may be clinically relevant and future studies are planned to explain why sensitized patients have restricted antibody specificity patterns although they have been exposed to multiple mismatched epitopes. Under auspices of the 16th Histocompatibility Workshop and in collaboration with an international working group, I plan to develop a website-based database of antibody-defined HLA epitopes and a suitable epitope annotation useful in the clinical setting. My ultimate goal is the implementation of acceptable and permissible HLA epitope matching in clinical transplantation.

Although I am now officially retired as Professor Emeritus of Pathology at the University of Pittsburgh, my life with HLA will continue as long as I am able. This means more studies, papers and presentations, and I am so grateful that HLA has been good to me. Finally, I want to thank the people cited above and many others not mentioned for interacting with me in so many beneficial ways. My life with HLA would have been very different without them.

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REPORT OF THE 15TH FRANCOPHONE EDUCATIONAL MEETING AT TOURS

By Mireille Drouet

The 15TH francophone educational meeting took place at Tours on 23 and 24 of September 2011 organized by Marie Denise Boulanger and her team. The meeting assembled over 200 participants, who enjoyed two sunny days, and was divided into four sessions.

The topic of the first session was **Polymorphism: Myriam Labalette (Lille)** had to answer the philosophical question "Is a polymorphism a necessity or a constraint?" She brilliantly demonstrated that polymorphism was a necessity in the fight against pathogens organisms due to its role in the peptide presentation but also its contribution in the reproduction of humans via the function of pheromone of HLA peptides, the expression of HLA-G on trophoblast. **Anne Cesbron (Nantes)** told the history of techniques to analyses HLA polymorphism from serology to DNA. The HLA-NET project (**Stéphane Buhler, Genève**) aimed to standardize the analysis of the polymorphism, to elaborate recommendations for HLA clinical analysis and provide a database to understand the history of human population. The HLA system is not the only polymorphic system which impacts the outcome of transplantation: **Pascale Loiseau (Paris)** reviewed the influence of other polymorphic genes such as cytokines, genes involved in drugs metabolisms or innate anti-infection immunity. **Anne Dormoy** informed the participants on the creation of a database to record rare alleles. This data can be accessed on the SFHI site (www.sphi.eu).

The second session was dedicated to quality insurance: our commission-

ers (**Anne Cesbron, Dominique Masson and Pascale Perrier**) provided information on modifications of EFL standards, recommendations for fulfilling the EFL packages. Direct connection between Luminex and the laboratory computer is not only time saving but improves the

agency and the HLA laboratories. **Matthias Buchler (Tours)** explained the specific difficulties of renal transplantation with living donors. The use of Rituximab in the treatment and prevention of humoral rejection was exposed by Yvon Lebranchu (Tours). **Jean Luc**



security (M Bujan, Geneva) After a comparison of the EFL standards and the norm ISO V15189, **Mireille Drouet** presented the twelve working groups who are establishing protocols for methods validation. Two examples of their work were exposed by **Lena Absi** (HLA antibodies screening by lymphocytotoxicity) and **Hélène Ansart-Pirenne** (HLA typing by luminex PCR SSO).

The third session, Organ transplantation, was opened by **Emmanuelle Prada Bordenave**, director of the Agence of Biomedecine, who underlines the collaboration between this national

Between sessions we were allowed a relaxing break at Chenonceau Chateau, over the Cher river.

Taupin (Bordeaux) led us in the search of the frontier between "nasty" and "kind" HLA antibodies; a delicate task. The fourth session was a teaching session animated by **Guillaume Dautin (Besançon)** and **Virginie Renac (Rennes)** about the role of HLA antibodies in inefficient platelet transfusion and TRALI

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STANDARDISATION OF THE EPT SCHEME ON MONITORING OF HEMOPOIETIC CELL CHIMERISM

Allogeneic hemopoietic cell transplantation (HCT) is a successful modality of therapy for many patients with haematological disorders, and successful outcome has been associated with a state of stable chimerism. However, establishing whether hematopoietic stem cells are of donor or recipient origin can be a difficult task, even when blood group or karyotypic differences between donor and recipient are known. Several approaches have been published for the detection of chimerism. In sex-mismatched transplantation settings, information on the ratio between donor and recipient can be obtained efficiently and rapidly by using fluorescent in situ hybridization (FISH) with probes specific for X- and Y-chromosome. Recent methods, based on DNA studies using restriction fragment length polymorphisms (RFLPs) and Southern blotting techniques, can be used to distinguish between donor and recipient cells after HCT. Using RFLP analysis, chimerism can be detected at levels approaching 10%. However, DNA analysis by Southern blot is not always possible when DNA is provided in limited quantities. The PCR method overcomes

this problem by allowing detection of mixed chimerism on very small samples and moreover, at levels below 1%. The use of these markers has the additional advantage of being independent from sex mismatch. This technology is now recognized as a highly sensitive measurement of degrees of chimerism.

Many Italian immunological and haematological laboratories are performing a chimerism analysis after HCT, following different methods and protocols. With the support of a grant of the Italian Ministry of Health and the collaboration of the participating laboratories, the Istituto Superiore di Sanità had set up in 2009 an experimental EPT scheme on chimerism monitoring, in order to standardise this analysis on the national territory. To organize a scheme that could have been compatible with all the other EPT schemes run by the Istituto Superiore di Sanità on commission by the National Centre for Transplantation, two existing international protocols have been analysed. The ASHI protocol soon appeared to be more feasible than the one adopted by UKNEQAS, and it has been implemented from the beginning. The scheme

included twelve participants in the first year and fifteen in the following years. Two shipments are provided per year, each one includes two blood samples from buffy-coat donors with the same blood group and five mixtures of different percentages of the two specimens. Results must be returned within 20 days and the correct ones are defined by the mean of the percentages reported by the laboratories after removing the outlier values, except for cases in which only one component is present. Assessment of the quality of the performances is made considering the ranges defined by the mean + standard deviation (SD) (very good performance) and the mean +2SD (good performance). Fourteen laboratories perform STR analysis using either commercial kits or home made products. The remaining laboratory analyses chimerism with two different approaches: by HLA-PCR SSO and by Real Time PCR for a more accurate quantification. All the participants achieved good results in the last years. The table reports those relative to the analysis of the first specimens sent in 2011.

The EPT on chimerism monitoring has

Laboratories	Method	N. of fragments	M1		M2		M3		M4		M5	
			%R	%D	%R	%D	%R	%D	%R	%D	%R	%D
Mean ± SD			97.7± 1.8	2.3± 1.8	66.4± 7.3	33.6± 7.3	28± 5.7	71.9± 5.7	8.7± 2	91.3± 2	1.2± 1.3	98.8± 1.3
Range			95.9-99.5	0.5-5.1	58.6-73.7	26.3-40.9	22.3-33.7	66.2-77.6	6.7-10.7	89.1-93.3	0-2.5	97.5-100
Mean ±2SD			97.7± 3.6	2.3± 3.6	66.4± 14.6	33.6± 14.6	28± 11.4	71.9± 11.4	8.7± 4	91.3± 4	1.2± 2.6	98.8± 2.6
Range			94.1-100	0-5.9	51.8-81	19-48.2	16.6-39.4	60.5-83.3	4.7-12.7	87.3-95.3	0-3.8	96.2-100
1	PCR-STR	16+amelogenin	97	3	64	36	27	73	8	92	2	98
2	PCR-STR	16	100	0	65	35	26	74	6	94	0	100
3	PCR-STR	15+amelogenin	98	2	64	36	28	72	8	92	0	100
4	PCR-STR	10	95	5	65	35	26	74	10	90	3	97
5	PCR-STR	15+amelogenin	100	0	65	35	28	72	8	92	2	98
6	PCR-STR	16	97	3	66	34	28	72	9	91	3	97
7	PCR-STR	10	97	3	63	37	30	70	13	87	0	100
8	real-time PCR	6	100	0	65	35	27	73	6.5	93.5	1.2	98.8
9	PCR-STR	10	100	0	56	44	22	78	7	93	0	100
10	PCR-STR	7+amelogenin	96	4	90	10	47	53	12	88	0	100
11	PCR-STR	16	97	3	67	33	25	75	7	93	2	98
12	PCR-STR	15+amelogenin	99.8	0.2	66	34	30	70	6	94	0.5	99.5
13	PCR-STR	9+amelogenin	99	1	64	36	28	72	9	91	1	99
14	PCR-STR	15+amelogenin	97	3	65	35	27	73	9	91	3	97
15	PCR-STR	6	95	5	60	40	25	75	7	93	0	100
8	PCR-SSO	loci HLA-B,-C, DRB, DQB1	99-95	1-5	30-70	70-30	10-30	90-70	5-10	95-90	1-5	99-95

recently been included in the National EPT programme funded by the Italian Ministry of Health. The EPI rules for EPT providers will be applied, even if it has not yet been included among the categories. EPI standards, version 5.6.2, include haemopoietic chimerism and engraftment monitoring (I4.000), and it is to be expected that laborato-

ries performing this assay routinely will be asked to be accredited in the next future, which means that they have to participate in a proper EPT scheme like the one presented here.

We are grateful to all the participants for collaboration and support, in particular to Dr. Benedetta Mazzi for expert assistance.

Francesca Quintieri, Doriana Campagnile and Maria Paola Perrone*

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REPORT BY BURSARY RECIPIENTS, WHO ATTENDED THE 8TH INTERNATIONAL SUMMER SCHOOL

Emilia Jaskula

The 8th International Summer School on Immunogenetics was held in Puerto Rico, USA, on September 19–22, 2011, under the auspices of the American Society for Histocompatibility and Immunogenetics with the support of the Asia-Pacific Histocompatibility and Immunogenetics Association and the European Federation for Immunogenetics. The meeting and the 6 invited speakers: Marcelo Fernández-Viña, Rhonda Holdsworth, Marilyn Pollack, Narinder Mehra, Derek Middleton, and

in HLA from Turkey, Ireland, Brazil, Poland, Canada, USA, Romania, the Czech Republic and Switzerland and provided a perfect forum for discussion to young scientists. The program included lectures on Immunogenetics of HLA, Population HLA genetics, NK cells and KIR genes, Immunogenetic Factors in Disease, Serologic HLA Epitopes and Allo-immunogenicity in Transplantation, Molecular Methods in HLA, Histocompatibility in Hematopoietic Stem Cell Transplantation, Methods for Antibody Detection, HLA in Transfusion, the Contribution of Histocompatibility and Immunogenetics including the Role of the HLA Laboratory in Solid Organ Transplantation as well as 17 participants' research oral presentations.

On the first day, one of the sessions was about NK cells and KIR genes lectured by Derek Middleton. The speaker characterized natural killer (NK) cells and KIR receptors and their role in autoimmune diseases, in hematopoietic stem cell transplantations (HSCT), tumors as well as virus-infected cell elimination. NK cells are known for their ability to kill infected and tumor cells without prior sensitization of the host. They usually

express the surface CD16 (Fc RIII) and CD56 markers. There are 2 subsets of NK cells. Most of the circulating NK cells are CD56dim and CD16bright associated with intrinsic cytotoxicity. CD56bright NK cells are enriched in secondary lymphoid tissues and produce immunoregulatory cytokines including IFN, TNF and GM-CSF. CD56dim NK cells represent a more mature population derived from CD56bright NK cells. NK cell functions are regulated by inhibitory and activating receptors recognizing ligands on the cell surface including the killer cell immunoglobulin-like receptor (KIR) family and C-type lectin-like inhibitory receptor CD94/NKG2A, which recognizes HLA-E and leukocyte inhibitory receptors. Moreover, NK cells also express pattern recognition receptors like the TLRs and NOD proteins. KIR receptors are encoded by the polymorphic leukocyte gene family in the leucocyte receptor complex located on chromosome 19. KIR receptors are characterized by the presence of two (KIR2D) or three (KIR3D) extracellular immunoglobulin domains and intracytoplasmic short (S) or long (L) tails transducing activating or inhibitory signals, respectively. Inhibitory KIR receptors have four ligands in HLA class I molecules: HLA-C is recognized by KIR2DL1, KIR2DL2 and KIR2DL3; HLA-B by KIR3DL1 and HLA-A by KIR3DL2, while HLA-G is a ligand for KIR2DL4. Until April 2011 KIR receptors were represented by 614 alleles and 321 proteins. There are two groups of KIR haplotypes – A and B. The B haplotype is defined by the presence of one or more of the activating KIR genes: KIR2DS1/2/3/5, KIR3DS1 and the inhibitory genes KIR2DL5A/B and KIR2DL2. Group A haplotypes are characterized by the absence of all these genes and utilizing up to eight genes: those of the framework as well as KIR2DL1, KIR2DL3, KIR2DS4 and KIR3DL1. MHC class I are negative regulators of NK KIR activity. One of the viral strategies to evade detection



David Turner attracted 17 delegates – postgraduate fellows, tissue tyers or PhD students with some experience

express the surface CD16 (Fc RIII) and CD56 markers. There are 2 subsets of NK cells. Most of the circulating NK

elimination by the immune system is a decreased MHC class I gene expression on infected cells which leads to the reduced response of CD8 T cells. To avoid triggering an NK cell response to infected cells, viruses preferentially downregulate class I allotypes that are not predominant ligands of NK receptors. HIV decreased expression of HLA-A and -B but not -C and -E, HCMV reduces the expression of class I HLA but not HLA-E. Moreover, viruses express viral equivalents of MHC I, which block NK activation and may acquire changes in epitopes that increase the binding of MHC class I ligands to inhibitory KIRs.

Human reproduction is influenced by polymorphic HLA-C ligands of KIR receptors. About 5–10% of pregnancies are affected by preeclampsia, which is a significant cause of pregnancy-associated mortality. Preeclampsia is associated with uterine AA genotype KIR and the presence of HLA-C2 on the surface of extravillous trophoblast cells. The HLA-C2 molecule interacting with the inhibitory receptor KIR2DL1 causes the remodeling of maternal blood vessels to prematurely cease, increasing the probability of preeclampsia in the absence of compensating activating KIR (Parham P J Exp Med. 2004).

Many studies have been performed to determine the role of KIR receptors and their HLA class I ligands polymorphisms as potential genetical immune system regulators influencing susceptibility to human disease. HLA-Cw*0602 genes have been associated with Psoriasis. Moreover, the KIR2DS1 activating gene, one of the HLA-C ligands, may play a role in the susceptibility to psoriatic arthritis (PsA) (Williams F, Hum Immunol. 2005). Individuals carrying KIR2DL3 or KIR2DL1 have suffered more frequently from a tuberculosis infection (Méndez A Tissue Antigens. 2006), while homozygous HLA-C1 genotype is associated with idiopathic bronchiectasis. Individuals carrying a KIR2DS5 genotype have more frequently diabetes (Middleton D, Hum Immunol. 2006) and bladder tumors is associated with the presence 2DS4/3DL1 genotypes (Middleton D, Tissue Antigens. 2007). Natural killer cells also play a major role in tumor surveillance. KIR2DL and/or KIR2DS2, with the presence of the HLA-C1 ligand, is a protective genotype in CML. Individuals being HLA-Bw4 homozygous (i.e. do not have HLA-Bw6) are more susceptible to developing CML (Middleton D, Tissue Antigens. 2009). Missing KIR ligands and KIR ligand incompatibility models are the

source of NK cell alloreactivity in hematopoietic stem cell transplantations. KIR ligand incompatibility leads to NK alloreactivity in graft-vs-host disease (GvHD) direction and is not relevant in transplantations where donors and recipients are matched. The situation where hematopoietic stem cell transplant recipients are lacking one or more of the KIR motifs present in the donor has resulted in the emergence of an alloreactive NK-cell repertoire in HLA-identical settings, which can trigger graft-vs-leukemia (GVL) effects. Unfortunately, conflicting results have been reported regarding the genetic control of NK alloreactivity in haematopoietic stem cell transplantations. KIR ligand incompatibility has possible benefits in haploidentical transplants, but there is no consensus considering the influence of the KIR ligand incompatibility model in MUD transplantations. Most studies suggested that the missing KIR ligand model is associated with better HSCT patient outcome and may be relevant in SIB transplantations. A Donor KIR gene repertoire and the total number of KIR activatory and inhibitory genes and donor B haplotypes have also been reported to be variable. The previously reported different effects of KIR ligand incompatibility or missing KIR ligands in HSCT are probably the result of a heterogeneous disease group in studies, the presence of T cells (cohorts with depleted and non-depleted T cells), different condition and GvHD prophylaxis, donor –recipient matching or the type of donor and dissimilar statistical test power.

Maria Eugenia Ricco

The second lecture was given by Prof. Narinder Merha. He introduced the HLA system, with an historical perspective of pioneers in this research field, and gave a detailed description of HLA genes: class I and II allele's expression, structure, function and diversity. He discussed the biological and clinical implications of HLA allelic and haplotypic diversity and the evolutionary mechanisms acting on the MHC system.

After the coffee break, Prof. Fernandez-Viñas gave a presentation on human population migrations, as evidenced by the analysis of HLA alleles, lineages and haplotypes distribution. His talk mainly focused on the HLA polymorphism and diversity observed in different populations, particularly in major regions such as Africa and the Middle East, as well as in specific populations such as Israeli and Native Americans.

Prof. Fernandez-Viñas highlighted the necessity of increasing the amount of data from minorities in bone marrow donor registries. He also presented convergent evolution as a mechanism explaining part of the currently observed HLA diversity.

After lunch, Prof. Mehra presented his talk on immunogenic factors in diseases. He showed that the importance of studying HLA and disease association is not only crucial for learning the biological function of HLA and understanding the disease origin and development, but also for determining MHC-based vaccination strategies. He described the approach leading to the identification of a disease associated to one or several MHC genes, as well as its limitations, and detailed the evidence of the association between HLA and some diseases like Narcolepsy and Type 1 Diabetes, among others.

A part of the afternoon was dedicated to formal discussions with tutors in a relaxed ambiance. The goal of this activity was to talk about the topics presented by the tutors during the day and to establish a list of questions that were going to be discussed the following day in a plenary session.

The last presentations of the day were made by the trainees. Six participants presented their own personal work on a wide range of topics from population genetics to disease association studies.

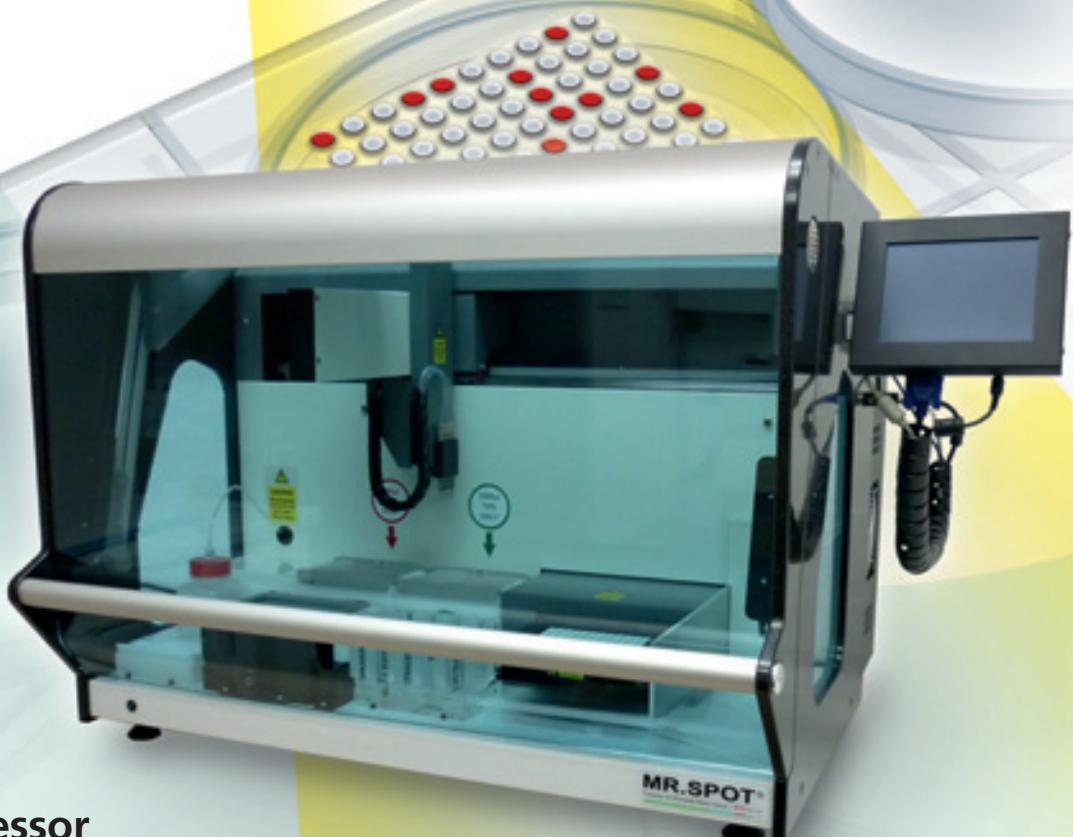
The second day began with the plenary discussion of working group questions prepared on Tuesday, allowing a fluent interaction between speakers. This was followed by Prof. Rhonda Holdsworth lecture on histocompatibility in hematopoietic stem cell transplantation (HSCT). She described the different kinds of mismatches and sources of donors, and, after detailing assorted strategies for matching, she pinpointed the complexity of finding a suitable matched donor while minimizing in the same time adverse outcomes (i.e. GVHD and no engraftment).

Prof. Fernandez-Viña's last lecture was centered on HLA allo-immunogenicity in transplantation. He detailed different factors affecting engraftment, the immunogenicity of B and T cells epitopes and supertypic epitopes in HLA C molecules. He ended his talk by discussing the comprehensive list of HLA factors for prioritization of donors, while minimizing the number of mismatches, in order to find the best donor selection trade-off.

The final presentation of the morning

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was given by David Turner, focusing on the molecular methods employed for HLA analysis. He gave an exhaustive description of the various molecular methods used for HLA analysis and how they evolved from those developed before PCR invention to the next generation sequencing and microarrays techniques that are currently available. After a succulent lunch taken over tutor's company at the conference hotel, afternoon presentations were made by students. Four participants presented their own research related to the day topics. Their presentations were followed by friendly discussion with tutors around a cup of coffee. The day finished with a lovely sightseeing tour of Puerto Rico, where the narrow colonial streets bring us into the discovery not only of the fascinating history of the city, but also the delectable local food!

Yalcin Seyhun

Topics of the last day were programmed to make presentations of HLA antibodies and renal transplantation. Serologic epitopes, CREG's, clinical relevance of eplets, HLA Matchmaker algorithm and detection of antibodies using Luminex technique were presented by Rhonda Holdsworth.

Afterwards, two presentations were presented by Marilyn Pollack as Methods of XM/Antibody Detection and Role of the HLA Laboratory in Solid Organ Transplantation. In this presentation, properties of different methods were compared and discussed in detailed. The reasons of weak correlation between positive DSA and negative XM were listed according to antigen concentrations on beads, disadvantages of SAB and inhibitory factors. Finally, it was concluded that use of sensitive screening and XM methods can avoid hyperacute antibody mediated rejection. Prof. Pollack described that role of antibody typing and identification as well as HLA typing and matching in solid organ transplantation. Methods

of XM and PRA, molecular and serological typing methods were given. Also, the importance of standardizing of tests and labs was emphasized. Pre-transplant desensitization protocols for patients with DSA and/or high PRA were introduced. The rules of UNOS and KAS, paired living donor exchange and AM program were listed as possible options of transplantation.

In the presentation by David Turner, the clinical significance of HLA, HPA (Human Platelet Antigens) and HNA (Human Neutrophil Antigens) highlighted in transfusion. Also, mechanism of platelet destruction and managing patients with platelet refractoriness were discussed. The clinical side effects of transfusions were classified as hemolytic/nonhemolytic and related/unrelated with HLA Abs. The presentation was ended by the clinical features of acute GVHD and post-transfusional GVHD.

The tutors' presentations were opened by Derek Middleton's presentation and finally closed by his Renal Tx in Europe and the Contribution of Histocompatibility and Immunogenetics presentation on the last day of the course. The dramatic gap between the number of kidney transplant and waiting list was shown via graphics and to solve the problems were discussed. The relevance of cold ischemia time, HLA matching and donor relationship in kidney transplantation was explained by graphics and figures. Reasons for a patient not receiving a graft and ways of increasing the chances of a transplant were listed. The presentation ended with highlighting the important features of the virtual XM and matching strategies.

During the summer school period, the students presented their own research studies in the afternoon sessions. Many various topics include MICA, population genetics, HLA Abs, techniques, viral infections, signal transduction, complement factors, disease related molecules and pathological findings

were presented by the students and discussed with tutors.

Karel Medek

I would like to express my thanks for providing me an interesting possibility to participate in 8th International Summer School on Immunogenetics, hosted this year by ASHI in close collaboration with EFI and APHIA, and took place from September 19 until September 22 in San Juan, Puerto Rico.

The city of San Juan, guarding the gateway to the Caribbean Sea, creates a remarkable connection between history and present time and is an ideal place for informal interactions in a wonderful environment. The Summer School was held on Sheraton Old San Juan, a nice hotel in the heart of Old San Juan. Well-appointed meeting room was filled with natural light and provides unique views of Old San Juan Bay as well as stimulating atmosphere for discussion of different aspect of Immunogenetics. Well done lectures and very interesting presentations of my colleagues extended my knowledge of modern researches in the fields of Hematopoietic Stem Cell Transplantation, Antigen Presentation, Immunological Tolerance, Solid Organ Transplantation and many others. I was very interested in lecture *NK and KIR*, presented by Derek Middleton, because I have not came into deeper contact with this theme before and e.g. information about higher risk of pre-eclampsia in connection with some KIR genotypes was brand new for me.

I have had an opportunity to present the research work of our department called *IκBα in Relation to Type 2 Diabetes and Its Microvascular Complications* and hope that it fits into the wide range of Immunogenetics at least partially.

The social interactions were not forgotten too. Excellent meals in combination with social events like excursion in the old city provided entertainment for all participants.

Report on the 8th International Summer School on Immunogenetics September 19 - 22, 2011 San Juan, Puerto Rico

Aftenie Loredana

The 8th International Summer School on Immunogenetics was hosted by the American Society for Histocompatibility and Immunogenetics (ASHI) together with Asia Pacific Histocompatibility and Immunogenetics Association (APHIA) and the European Federation for Immunogenetics (EFI). The summer school took place at the Sheraton hotel in Old San Juan Puerto Rico. San Juan, the capital of Puerto Rico is the oldest city on US territory founded in 1521 by Juan Ponce de León . The 465-year-old city was originally conceived as a military stronghold which has evolved into a charming residential and commercial district with narrow steep streets paved with cobbles of adoquine, a blue stone brought on Spanish ships. The city includes more than 400 carefully restored 16th- and 17th-century Spanish colonial buildings and two of the largest defenses forts ever built in the Americas, San Felipe del Morro Fortress(1540) and San Cristóbal Fort(1634).

This year the Immunogenetics Summer School was attended by post-graduate students, PhD students, young researchers from universities and laboratories from countries world-wide: FRANCE , TURKEY , IRELAND, BRAZIL , POLAND , USA, CANADA, ROMANIA, CZECH REPUBLIC, SWITZERLAND and distinguished lecturers from USA (Marcelo Fernández-Viña, Stanford University), AUSTRALIA (Rhonda Holdsworth, Australia Red Cross Blood Services), INDIA (Narinder Mehra, All India Institute of Medical SciencesTrpl Immun & Immunogenetics), ENGLAND (Derek Middleton, Royal Liverpool University Hospital Prescott St, Transplant), USA (Marilyn Pollack, University of Texas Health Science Center), UNITED KINGDOM (David Turner, Scottish National Blood Tranfusion).

The program began in the evening of Monday, September 19 with a Welcome Reception and tutor group assignments and ends on Thursday, September 22 with a farewell dinner. Each applicant show an interest to present his work in a 15 minutes presentation, based on the abstract submitted in the application. All the speakers delivered high-quality lectures for inspiring discussions, informal exchange of ideas, and socializing most of the time in tutor groups assigned (each tutor pair guide 5-6 students). All the students appreciated a week of concentrated study and direct contact with the tutors. Furthermore, the school provided a good opportunity to get to know other people working in the field, to meet distinguished scholars, and to establish contacts that may lead to research collaborations in the future. On Wednesday the students spent a captivating afternoon at the sightseeing tour of Puerto Rico. The tour included fully narrated historic guided walking tour in English with full dinner with appetizer, alcoholic drinks, and dessert progressively eaten over the course of four restaurant stops. Apart from this excursion, the schedule included some leisure time for socializing.

Generous financial support provided by the European Federation for Immunogenetics (EFI) helped students with bursaries and I owe a deep debt of gratitude for making this possible. This summer school gave me an opportunity to explore the new horizon of Immunogenetics and there was enough opportunity for extensive exchange and discussion in the field.

We are most grateful to Nadège Toth, the meeting organizer (ASHI's Associate Meeting Manager) that created a really friendly atmosphere and make a big contribution to the success this year Immunogenetics Summer School.

I must admit this summer school has added a lot to my knowledge the program was very interesting and helpful. Overall, the summer school can be considered very successful there is a clear need for such summer school events.





THE 9TH INTERNATIONAL SUMMER SCHOOL ON IMMUNOGENETICS

VICTOR HARBOR - SOUTH AUSTRALIA



11th - 13th November 2012
Whaler's Inn Resort



UPDATES IN IMMUNOGENETICS & HISTOCOMPATIBILITY AND ANNUAL BALKAN EPT REGION 8 MEETING, BUCHAREST

Reports by 4 bursary recipients

Claudia Lehman

The two days in Bucharest at the EFI workshop in December 2011 provided an interesting program on antibody screening and identification, HLA typing strategies and aspects about stem cell transplantation. Another focus of the workshop was quality aspects in H & I laboratories and the EPT in the Balkan region.

The first session was on antibody screening with the different methods currently used in HLA labs. Here the first speaker, Ilias Doxiadis talked about epitopes, relevant and non-relevant antibodies, prozone effect, advantage and disadvantage of the Luminex technology. The magic solution is acceptable mismatch search. In summary the laboratories should not forget "old" methods like CDC and combine them with new technologies for clinical applications

Dario Merlo

The second talk of the session, was presented by Mahmut Carin (Istanbul, Turkey) and its names was "Single Antigen FlowCytometry"; he underlined too the problems in finding an HLA specificity, such as the time, the strength, the complement-binding, the Ig class and he presented the impressive flow-PRA technique using single antigen beads, and the utility to consider also DP and DQ specificities.

The next and last presentation of the session was performed by Antonij Slavcev from Prague, Czech Republic. His talk's title was "EFI standards for antibody screening and crossmatching - an update" and he presented the updates of the EFI standards valid from October, 1st 2011. The changing referred to the laboratory-dependent choose of the other technique in addition to CDC; the minimum number in the PRA panel, sufficient to cover more HLA specificities possible; the choose of a screening method that gives less "surprises" at the crossmatch; the need to have all the informations about the sensitising situation of every patient joining in the awaiting list; the need to distinguish between HLA antibodies and non-HLA or autoantibodies.

Tsvetelin Lukyanov

Murielle Verboom talked about the SBT

technique and its use for HLA high resolution typing. She shared the experience of the Hanover Medical School in HLA typing, hemizygote sequencing and automation of the process. Some problems of the technique, like allele drop-out, peak shift and ambiguities, were also discussed. The talk ended with the advantages of the Next Generation Sequencing, as this state of art approach gives clonal sequencing results and thus the cis-phase of allelic variations.

Next speaker, Joannis Mytilineos have talked about "HLA matching in Stem Cell Transplantation – what to search and match for". He has drawn the audience's attention to hematopoietic stem cell transplants and some factors related to patients' survival. Since the first HSCT, the number of transplants is constantly growing. While the number of transplants from related donors is relevantly constant in the past few years, the number of unrelated transplants is rapidly growing. The most frequently transplanted patients in Germany are those with AML, followed by patients with MDS, ALL, CML, NHL and etc. One of the slides represented a drawing showing the organization of donor-selection process in Germany – many donor centers all over the country, separated search units, and the interaction between them and transplant centers. In related HSCT, a 6/6 HLA-A, -B, -DRB1 match is preferred, while in unrelated – 10/10 HLA-A, -B, -C, -DRB1, -DQB1 is strongly recommended. Age, sex, CMV status, ABO, KIR-ligands and HLA-DP are additional criteria taken into consideration in a process of donor selection. HLA matching is important for post-transplant survival, but it does not affect the engraftment and relapse. Contrary, HLA-DP mismatching isn't relevant to survival, but increases the risk of GVHD, and decreases the risk of relapse. Additionally, disease stage is also important for the overall survival.

The last lecturer, Elissaveta Naumova, have talked about the monitoring of chimerism in transplanted patients and the importance of this analysis for the early detection of post-HSCT complications like GVHD, relapse, graft rejec-

tion and graft failure. Almost two thirds of patients with malignant disease achieved complete donor chimerism, whereas persistent mixed donor chimerism is more likely to be observed in non-malignant patients. Pre-transplantation conditioning highly affects the short term levels of chimerism, but not the long term, whereas HLA matching was not found to be relevant to chimerism level. Graft failure and graft rejection events were more frequent in non-malignant cases and they could be predicted by chimerism analysis quite early than by other clinical evidences. In some cases GVHD could also be predicted by this analysis.

Pinar Ata

My purpose to join this event was because of the opportunity to discuss quality issues at Tissue Typing field. Quality as a whole is a symphony that needs all the instruments acting in harmony. From the point of Tissue Typing Laboratory view it is proper working of substructure, the crew, maintenance with all of it in a continuous well-being in good performance. So as the external proficiency testing, internal quality and continuous development is the most important issue. For this to be achieved technician education credits, internal testing of the system and the lab techs, biologists should be taken into consideration. The Quality Assurance procedures must state the frequency of actions or assessments and the mechanisms for documenting them. These procedures must be targeting continuous quality improvement. Quality Assurance targets has to be reached for preanalytical, analytical and postanalytical processes. A well designed and documented QC program minimizes laboratory costs by maximizing efficiency and guarantees the clinically acceptable accuracy and reproducibility.

In my opinion as a person at the very beginning of this field, for all the QA targets to be reached there may be some important steps EFI and BEPT could be organising for the future.

One of them could be examinations for both the directors and the technical staff. There might be educational credits that technical staff should have

annually to be able to be considered as qualified for that particular technique. This may be also important for the staff when they are first starting to work at an accredited Lab setting.

Second is to have councils checking all the labs without discriminating the

accreditation status for their preanalytical, analytical and postanalytical processes by external proficiency testing as at the present and also may be to visit the labs to inspect the analysis on-site additionally.

Third may be the councils that may

check new techniques when optimized at different labs whether the technique is further developed or could be used for diagnostic purposes. These may be discussed at a different session at the annual congresses.

ACCREDITATION OF TWO LABORATORIES IN RUSSIA



In 2010/11 the EFI accreditation region 5 welcomed the first two laboratories from Russia to achieve EFI accreditation. These are the laboratories of Dr Ludmilla Bubnova in St Petersburg and Dr Larisa Trusova in Samara. The Commissioner for region 5 Dr Blank Vidan-Jeras also received many enquiries for information about and help with the EFI accreditation process from other laboratories in Russia. To help provide this information and assistance to the labs a workshop on EFI accreditation was organised by the Commissioner and the director and staff from the laboratory in St Petersburg.

The EFI Accreditation Workshop took place in the beautiful venue of Pushkin, close to St Petersburg, on 27-28 June 2011. The EFI President Elect Prof Gottfried Fischer, Dr Andrea Harmer (Chair Accreditation Committee) and Dr Luca Mascaretti (General Secretary Accreditation Committee) took part in the workshop together with Blanka Vidan-Jeras.

The Workshop was very well attended with representatives from 24 laboratories in Russia taking part. A representative from the Ministry of Health also joined the workshop which was welcomed by the members of the Accreditation Committee. The aim of

the workshop was to provide detailed information about the Accreditation Programme and to explain the application process including how to complete the necessary papers for packet A.

The workshop opened with overviews of the EFI accreditation programme and of the situation in region 5. This was followed by several presentations on the different sections of the standards and inspection checklist. The final presentation of the first day was an introduction to the EFI application Packet A and this was followed by round table sessions where the EFI experts could work with small groups of participants. This presented an opportunity to show individual labs how to complete specific sections of packet A.

After a long and productive first day it was a pleasure for the EFI representatives to attend a gala dinner and have the opportunity to talk in a more informal setting with the participants from across Russia. This was also a chance to experience excellent Russian hospitality with a wonderful dinner and typical musical entertainment.

The second day of the workshop started with very informative presentations from the two accredited Russian labs. Dr Bubnova spoke about the experience and benefits of the accredi-

tation process for the Russian Center of Tissue Typing in St Petersburg and Dr Trusova gave a presentation on the recent experience of the laboratory of the Clinical Center of Cellular Technologies in Samara. These presentations provided useful insights for the other labs into the preparation that needs to take place before an inspection and what the experience of the actual inspection is like. The final session of the workshop was again a round table discussion allowing the representatives from the different labs to ask further questions on the application process or to work through some sections of the EFI standards with explanations about what is required to achieve compliance for some of these. Throughout both days there was plenty of opportunity for the participants to ask questions and this was facilitated by the excellent simultaneous translation service which had been arranged by the local organisers.

Overall the workshop provided an excellent opportunity for EFI to present and explain the accreditation process to a large number of potential aspirant labs. This proved to be an effective way of providing this essential support for an exciting new area of growth for EFI. It also helped highlight some issues for the labs in Russia and to discuss possible solutions to problems. In particular the lack of formal External Proficiency Testing programmes within the country was recognised and the difficulties of accessing other programmes for labs that are widely spread across the great distances that are found in Russia was acknowledged. The Commissioner for region 5 had some constructive discussions with some of the laboratory directors on how issues with EPT may be approached and work will continue to try to solve these.

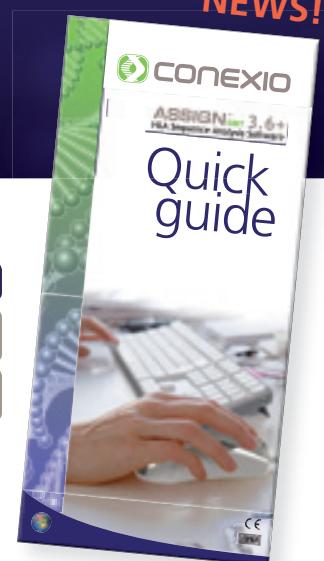
This was a successful workshop for the EFI Accreditation programme and the members of the Accreditation Committee particularly acknowledged the excellent organisation of the event by Dr Bubnova and her colleagues.

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Plenary session I: Genetics-Epigenetics-Gene Interactions of the HLA complex

In this plenary session, three expert speakers presented the current state of the art concerning the control of HLA expression by genomic, epigenetic and transcriptional mechanisms, and their importance for tumor immunotherapy

The first speaker was Professor S. Beck from the UCL Cancer Institute University College London. He focused his presentation on epigenetic variation analysis as a tool to better characterize physiological and pathological phenotypes. A recent Epigenome-Wide Association Study (EWAS) on 14.000 cases of several common diseases, with 3.000 shared controls, revealed that epigenomic alterations were frequently present at the MHC locus in these complex diseases. Moreover, supporting the relevance of EWAS studies, the journal Nature Biotechnology has dedicated the entire issue of October 2010 on this topic. These articles point out that in contrast to GWAS, Genome-Wide Association Studies (GWAS) can explain only a small fraction of phenotypic variation, underscoring the complexity of health and disease and the resulting need for new approaches to study them

Professor Beck's laboratory studies epigenetic variations such as DNA methylation, histone modifications and microRNAs and how they modulate genome function. They developed a method capable of analysing the cytosine methylation status by discriminating between 5-methyl-cytosine (5mC) and 5-hydroxymethyl-cytosine (5hmC), using two different techniques: 1) the methylated DNA immunoprecipitation or MeDIP assay, a whole genome approach which involves the use of an antibody against 5-MeC to isolate the methylated fraction of the genome; 2) the Infinium Illumina assay, which permits to interrogate >450,000 methylation sites per sample at single-nucleotide resolution. Alterations in the methylation status can thereby be classified into MVPs - "methylation-variable positions"; DMRs - "differentially methylated regions"; VMRs - "variably methylated region"; ASM - "allele-specific DNA methylation"; HSM - "haplotype-specific methylation". EWAS studies have a more complex design than GWAS: 1) the material used in the study is critical since the epigenetic pattern is different from tissue to tissue, and even more complex is the selection of the correct control; 2) the difficulties in clarifying if the epigenetic alteration is a cause or a consequence of the phenotype observed, raising the necessity to study large cohorts. By whole genome screening of the genomic methylation status, Professor Beck's laboratory has identified several differentially methylated regions (DMR) between benign and malignant neurofibroma, which are potential prognostic disease markers. These data were also confirmed by the expression analysis of the genes identified. Integration of GWAS and EWAS is also used in his laboratory to gain a more complete picture of the aetiology of common diseases, in particular of type I and type II diabetes and the inflammatory bowel disease (IBD)

The second speaker was P.J. van den Elsen, Associate Professor at the University Medical Center of Leiden in The Netherlands. He focused his presentation on the transcriptional control of HLA molecules, starting with a brief introduction on HLA expression by different tissue types. Classical HLA class I and the non-classical HLA-F gene products are expressed in almost all nucleated cells, while the expression of other non-classical class I molecules is restricted. HLA-G is confined primarily to fetal trophoblast cells and thymic epithelium, whereas HLA-F is mainly expressed in lymphoid cells. Constitutive expression of MHC class II proteins is confined to antigen-presenting cells, which include dendritic cells, macrophages, B lymphocytes and thymic epithelial cells. On the other cell types, expression of MHC class II molecules can be induced in an environment rich in inflammatory cytokines (of which IFN- γ is the most potent) or upon T cell activation. The control of these genes relies both on *cis*-acting promoter elements, some of which are shared between HLA class I and II genes, and on epigenetic modifications, such as methylation and acetylation of the DNA histonic tails

Useful techniques study and identify the promoter region of a gene include the chromatin immuno-precipitation assay (CHIP) and the bisulphite sequencing of the identified regions of interest. Taking advantage of these techniques, the control elements of MHC class I and II were identified

Activation of MHC class I (with the exception of HLA-G) and β 2-microglobulin gene promoters are mediated by three major elements: enhancer A, IFN-stimulated response element (ISRE) and the SXY module, which contain the binding site for nuclear transcription factor B (NF- B), interferon regulatory factor (IRF) family members and the MHC enhanceosome, respectively. In the upstream regulatory promoter elements the binding site of Sp1 and E boxes could

also be found, the latter interacting with upstream stimulatory factor 1 (USF-1) and USF-2. Not only the type but also the sequence variation of the promoter affects the level of the gene activation and expressivity among the various MHC class I genes, explaining the presence of differential cell-type specific basal and inducible expression levels

The SXY module is shared between HLA class I and II and accessory gene (invariant chain, HLA-DM and HLA-DQ) promoters that is cooperatively bound by a multi-protein complex containing regulatory factor X (RFX) and CIITA, complex termed as MHC enhanceosome

These two elements are essential for MHC class II regulation as illustrated by studies with cell lines established from patients with a severe immunodeficiency where *null* mutations in one of the RFX subunits or CIITA lead to the lack of MHC class II expression and to reduced the levels of MHC class I transcription. This suggests that CIITA is essential for MHC class II expression, but not for class I. Interestingly, the group of van den Elsen has identified NLRC5 as the specific transcriptional regulator necessary and sufficient for the expression of critical components in the MHC class I pathway (Meissner *et al.*, 2010). Like CTIIA, NLRC5 is upregulated upon INF- γ stimulation and interacts with the conserved module WXY

In the second part of his presentation, Professor van den Elsen focused the attention on the epigenetic modifications of the four promoters controlling the expressivity of CTIIA. He reported on studies performed in uveal melanoma cell lines, showing that the trimethylation of histone H3-lysine 27 (3Me-K27-H3) in the CIITA promoter contribute to strongly reduce CIITA expression levels upon IFN- γ induction, suggesting an explanation to the lack of MHCII molecule expression at the cell surface level (Hollings *et al.*, 2007). Finally, he showed the results of a paper under submission concerning how methylation and acetylation of the histone tails of CTIIA promoters affects its expressivity in normal CD4+ T-cells and in malignant Tcells

Both the epigenetic modifications are associated with the control of MHC2TA gene in normal and neoplastic T-cells, involving the entire 14-kb CIITA multipromoter region

Differences between normal unstimulated CD4+ T-cells and malignant MHC-II negative Tleukemia consist in the presence on histinic tails of the repressive markers, 3Me-K27-H3 and 3ME-K20-H3, suggesting a role of this modification in leukemia transformation

The last speaker was Professor F. Garrido from the University of Granada in Spain. He introduced the topic of the sophisticated mechanisms of immune evasion by tumor cells. In particular, his talk focused on alterations in the expression of MHC-I molecules that lead to the escape from the immune surveillance by T-lymphocytes. From the study of different HLA class I negative melanoma cell lines, they evidenced that some of these lines could revert the phenotype upon exposure to IFN- γ or other cytokines, while other could not. Methodologies capable of defining altered HLA class I expression by cancer cells. include the combined use of immuno-histochemistry with tissue micro-dissection, PCR, comparative genomic hybridisation, fluorescent *in situ* hybridization and LOH analysis with specific markers spanning the chromosomal region of the MHC and the β 2-microglobulin locus. Using these techniques, they documented that MHC class I loss is a frequent phenomenon in solid tumors: 88% of breast carcinomas, 90% of cervical cancer, 74% of colorectal cancer. The mechanism underlying the alterations in MHC class I expression vary and can occur at any step required for MHC synthesis, assembly, transport or expression on the cell surface. These defects can occur at the genetic, epigenetic, transcriptional and post-transcriptional level and present either regulatory abnormalities that can be recovered by cytokine treatment or structural defects that cannot be reversed. Thus, MHC class I deficiency could be subdivided into two main groups: reversible defects (regulatory, or “soft”) and irreversible defects (structural or “hard”)

Interestingly, they were able to demonstrate *in vivo* that the downregulation of MHC class I molecules by tumor cells leads to the escape from the control of immune system. In two case reports of cancer patients treated by autologous vaccination and immunotherapy (IFN α -2b and autologous vaccination plus BCG as adjuvant) they described that remission or progression of different metastatic lesions correlates with lower or higher expression levels of HLA class I molecules, respectively

On the basis of these observations, Professor Garrido concluded by stressing the importance of monitoring HLA class I antigen expression as prognostic marker, especially in the setting of vaccination trials. The prevalence of “soft” or “hard” lesions in the tumor cells could be a key factor determining their susceptibility to immune attack, and should therefore be taken into consideration in the choice of the best therapeutic option to adopt

All talks of the plenary session were in line with the topic of my project. They gave me interesting suggestions on how to proceed with my experiments, in particular concerning potential molecular mechanisms used by tumor cells to avoid immune responses

Finally, I want to express my gratitude to EFI enabling me to take part, also actively by presenting my data in an “oral communication”, in this scientific and social meeting

FIRST EFI EDUCATIONAL AND TRAINING MEETING IN ARMENIA

The Armenian Bone Marrow Donor Registry (ABMDR) hosted the first-ever European Federation of Immunogenetics (EFI) Training and

The meeting took place in Yerevan



during November 18-19 at the Ani Plaza Hotel. Featuring world-renowned speakers from Europe and elsewhere, it brought together close to 150 doctors and experts in the fields of immunogenetics and bone marrow transplantation. The meeting was attended by participants representing more than 15 countries from Europe, the region and the CIS including Armenia, Iran, Georgia, Kazakhstan, Russia, Ukraine and others.

With sessions dedicated to recent advances in HLA, immunogenetics, stem cell and organ transplantation, and HLA-disease associations, the conference functioned as a global forum for sharing scientific expertise and expanding the knowledge base of participants. As importantly, the event fostered international medical cooperation and helped pave the way for the advancement of immunogenetics in various countries. The conference was organized by ABMDR, under the auspices and major sponsorship of EFI.

The selection of Armenia as the host country of the EFI meeting was made in January of this year. As announced by the EFI leadership, the main factors in selecting Armenia were the scope and quality of ABMDR's work. Specifically, the federation cited ABMDR's HLA tissue typing laboratory in Yerevan as the only, and EFI-accredited, facility of its kind in the entire region.

At the opening ceremony of the conference, welcome remarks were delivered by Deputy Health Minister, Dr. Sergay Khachaturian, Dr. Ara Babloyan, chairman of the National Assembly's Committee on Social Affairs, Healthcare, and Environmental Protection; Dr. Ilias Doxiadis, president of EFI; Dr. Bella Kocharyan, honorary chair of ABMDR; Dr. Frieda Jordan, president of ABMDR; and Dr. Sevak Avagyan, executive director of ABMDR.

As Dr. Avagyan spoke of ABMDR's accomplishments and goals, he stated: "Our tissue typing operation has had the challenge of responding to a tremendous influx in prospective bone marrow stem cell donors due to the great success of our efforts, both in the U.S. and throughout the diaspora. Last year, which marked our registry's tenth anniversary, recruitment teams registered an astounding 5,000 donors within a short span. This is, of course, a good challenge to have, as we currently have over 1,500 patient families seeking a donor match from our registry."

Dr. Avagyan's aim of reaching out to larger numbers of patients struck by life-threatening blood-related diseases was echoed by Dr. Bella

Kocharyan. "We view the EFI meeting in Yerevan as a step toward the establishment of a bone marrow transplant center in Armenia," she said.

As Dr. Frieda Jordan addressed conference participants, she scored the significance of the EFI meeting in Armenia. "When we came to inspect our laboratory operations. A few months ago, we learned that ABMDR was granted EFI accreditation, making it the first laboratory of its kind in the CIS to receive it. Making another first for the registry, and for Armenia: hosting a scientific symposium of this caliber is an honor, and a wonderful opportunity to continue to 'surprise' our colleagues with our work and the progress we have made." ...

We owe much of our success to plain hard work and the dedication of the



ABMDR staff and volunteers," Dr. Jordan continued. "We are grateful to colleagues such as yourselves who, for many years, have created the models for success and set the standards. And now, perhaps, we are in a position to 'give back' to you. ABMDR has not only built a foundation for its own success, but can also be a source of information for other registries getting started. Our registries is a beacon of hope for all who suffer from blood-related diseases. At this EFI meeting, we are sharing our knowledge with each other as we all work toward the most unimaginable: life itself."