



International Histocompatibility Working Group in Hematopoietic Cell Transplantation

IHWG HCT Newsletter October, 2013

Dear Colleagues,

There is much progress to report on the Hematopoietic Cell Transplantation (HCT) Working Group activities since the 16th International HLA and Immunogenetics Workshop (IHIWS) in Liverpool. The Liverpool meeting was a great success thanks to our Chairmen, Dr. Derek Middleton and Dr. Steven Marsh. Our joint report was published in the *International Journal of Immunogenetics* (Petersdorf EW, Malkki M, Hsu K, Bardy P, Cesbron A, Dickinson A, Dubois V, Fleischhauer K, Kawase T, Madrigal A, Morishima Y, Shaw B, Spellman S, Spierings E, Stern M, Tiercy JM, Velardi A, Gooley T; International Histocompatibility Working Group in Hematopoietic Cell Transplantation. 16th IHIW: international histocompatibility working group in hematopoietic cell transplantation. *Int J Immunogenet* 40:2-10,2013) and details the highlights of the workshop studies. The 16th IHIWS studies for the HCT Working Group were supported by a data file of 25,963 transplants, a true milestone for which we should all be very proud! Our working group participants come from 18 countries and represent 59 laboratories, 435 transplant centers and 10 transplant and donor registries. The level of activity and commitment has continued in the year since the workshop. We would like to extend a warm welcome to the following new participants:

Noora Alakulppi, Advanced Therapies and Product Development, Finnish Red Cross Blood Service, Helsinki, Finland

Hélène Ansart-Pirenne, Laboratoire d'Histocompatibilité, AP-HP Créteil, France

Joseph Antin, Dana-Farber Cancer Institute, Boston, USA

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Agnès Batho, Laboratoire d'Histocompatibilité, EFS Caen, France

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Juliet Barker, Memorial Sloan-Kettering Cancer Center, New York, USA

Milka Bengochea, Instituto Nacional de Donación y Trasplante, University of the Republic, Ministry of Public Health Montevideo, Uruguay

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Jeremy Chapman, Sydney West Area Health Service of Australia, Sydney, Australia

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Brigitte Coeffic, Laboratoire d'Histocompatibilité, EFS Pays de la Loire, site d'Angers, France

Colleen Delaney, Fred Hutchinson Cancer Research Center, Seattle, USA

Florent Delbos, EFS Ile de France, Créteil, France

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Dominique Fizet, Laboratoire d'Histocompatibilité, EFS Bordeaux, France

Marylise Fort, Laboratoire d'Histocompatibilité, CHU Toulouse, France

Ephraim Fuchs, John Hopkins University School of Medicine, Baltimore, USA

Sabine Furst, Institut Paoli-Calmettes, Marseille, France

Eliane Gluckman, Eurocord, Hopital Saint Louis, Paris, France

Pierre Antoine Gouillard, Methodomics, Mortagne sur Sèvre, France

Marlies Groenendijk, The Haemato Oncology Foundation for Adults in the Netherlands (HOVON), Rotterdam, Netherlands

Nicholas Guillaume, Laboratoire d'Hématologie et d'Histocompatibilité, Centre Hospitalier Universitaire, Amiens, France

Daniel Hanau, Laboratoire d'Histocompatibilité, Etablissement Français du Sang Alsace, Strasbourg, France

Christian Harkensee, Institute of Cellular Medicine, University of Newcastle, Newcastle upon Tyne, UK

Irma Joosten, Department of Laboratory Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Anne Kennel, Laboratoire d'Histocompatibilité, CHU Nancy, France

Satu Koskela, Clinical Laboratory, Finnish Red Cross Blood Transfusion Service, Helsinki, Finland

Joanne Kurtzberg, Duke University, Durham, USA

Myriam Labalette, Laboratoire d'Histocompatibilité, CHU Lille, France

Xavier Lafarge, Laboratoire d'Histocompatibilité, EFS Bordeaux, France

Valerie Lapierre, Paris Gustave Roussy, France

Neubury Lardy, Sanquin Diagnostic Services, Amsterdam, Netherlands

Mary Laughlin, University of Virginia, Charlottesville, USA

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Kavita Raj, Guy's and St Thomas' Hospital, London, UK

Virginie Renac, Laboratoire d'Histocompatibilité, EFS Bretagne, Rennes, France

Kees Sintcolaas, Bloodbank Rotterdam, Rotterdam, Netherlands

Vanderson Rocha, Churchill Hospital, Oxford, UK

Nicoletta Sacchi and the Italian Bone Marrow Donor Registry, Italy

Peter Schlenke, Institut für Transfusionsmedizin und Transplantationsimmunologie, University Hospital Münster, Germany

Elizabeth J Shpall, MD Anderson Cancer Center, University of Texas at Austin, USA

Eric Spierings, Department of Immunology, University Medical Center Utrecht, Utrecht, Netherlands

Ioannis Theodorou, Laboratoire d'Histocompatibilité, AP-HP Pitié Salpêtrière, France

Marcel GJ Tilanus, Department of Transplantation Immunology, University Hospital, Maastricht, Netherlands

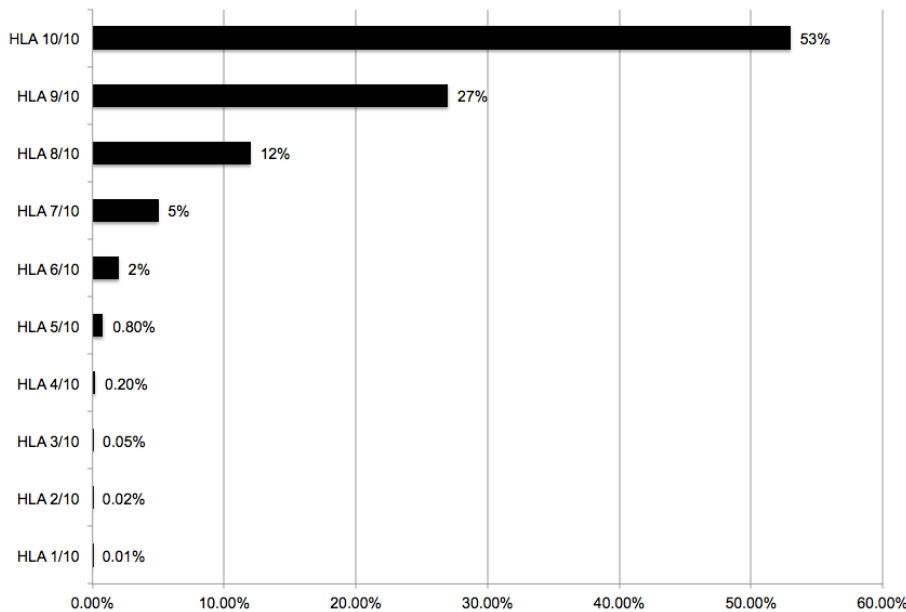
PREPARATIONS FOR THE 17TH IHIWS

The 17th IHIWS is chaired by Dr. Marcelo Fernandez-Vina and the members of the Steering Committee are Dr. Marcelo Fernandez-Vina, Dr. Dolly Tyan, Dr. Beth Trachtenberg, Dr. Steven Mack, Dr. Peter Parham and Dr. Effie Petersdorf. Ms. Susan Twietmeyer is the 17th IHIWS Project Manager. The committee is well underway in the organization and planning of the workshop and congress. The workshop will be held from *6-10 September 2017* in northern California to be followed by a joint meeting of the 17th IHIWS congress and 43rd annual meeting of the American Society for Histocompatibility and Immunogenetics from *11-15 September* in San Francisco. Dr. Steven Mack is developing the 17th IHIWS website, which will include this newsletter as well as important supporting materials for our working group in the future. As soon as the site is active, we will let you know so that you can obtain up-to-date information on components and the venue.

The broad theme of the 17th IHIWS is to define complete sequences and haplotypes for the MHC and KIR genetic regions. The workshop will utilize state-of-the-art next generation sequencing (NGS) and single nucleotide polymorphism (SNP) arrays to define full-length HLA and KIR genes, and will develop informatics and databases to support the analysis of sequence-level data. Expansion of reference cell panels for MHC region and KIR genes will be an important feature of the next workshop, serving as standards for the quality control of high-resolution sequencing and as reference sequences for comparative genetics. Please take a few minutes to complete and send in the questionnaire (found at the end of this Newsletter) which solicits feedback on your interest in actively using NGS and SNP arrays for the transplantation studies (described in more detail below).

IHWG TRANSPLANTATION DATABASE

The IHWG HCT Database has grown since the 16th IHIWS in Liverpool. As of October 2013, the working group's datafile includes data for a total of 30,161 transplants: 28,968 unrelated donor, 62 haploidentical and 1,131 single unit cord blood transplants. The composition of the unrelated donor cohort by HLA match grade is shown below:



Accrual of single locus mismatched unrelated donor-patient pairs continues to be an important group of patients to support the IHWG HCT studies of permissible HLA mismatches, as described below. High-resolution typing of HLA-DPB1 is strongly encouraged, as information at this locus will facilitate the analysis of risks stemming from mismatching at other class I and II genes. More information concerning HLA-DPB1 studies is provided below.

At the Liverpool workshop, discussion included new hypotheses to be tested in haploidentical related donor transplantation, and cord blood transplantation. The working group has had a great start to collecting typing and clinical data on both populations, and we encourage you to contact us if you have any questions or would like help in specific coordination of these data and samples. A total of 894 single cord blood transplant pairs have been collected thus far, and analysis of MHC region variation is underway. Participants interested in contributing data for these two populations should contact Effie Petersdorf (epetersd@fhcrc.org) and Mari Malkki (mmalkki@fhcrc.org) for any questions.

IHWG HEMATOPOIETIC CELL TRANSPLANTATION WORKING GROUP PROJECTS

17th IHIWS NGS

The 17th IHIWS will launch 2 new components focused on NGS for HLA and KIR. The component for NGS of HLA genes will be chaired by Dr. Marcelo Fernandez-Vina and Dr. Steven Mack and will generate full-length genomic sequences for HLA genes including HLA-A, B, C, DRB, DQA1, DQB1, DPA1, DPB1, and associated pseudogenes. The component for NGS for KIR genes will be chaired by Dr. Peter Parham and Dr. Beth

Trachtenberg and will generate complete genomic KIR sequences from reference cell lines and other materials contributed through working groups of the IHIWS. The HLA and KIR NGS components will each define the technological and instrumentation requirements, perform NGS in designated core laboratories, and develop software to support data analysis for HLA and KIR genes. NGS methods will be used to characterize *full-length* HLA and KIR gene sequences (i.e., 5' untranslated region, exons, introns, 3' untranslated region) where phase will be either definitively determined by family studies or established in homozygous reference samples. The specific NGS platforms include, but are not limited to, Illumina, Roche, PacBio, Ion Torrent methods.

Application of NGS for HCT Working Group Studies. The HCT working group has several options for contributing material and expertise to this important goal: 1) DNA from members of families who have unequivocal paternal and maternal segregation of haplotypes; 2) individuals who are homozygous for the same HLA allotype or allele by high-resolution typing. For laboratories who perform routine clinical testing of families or individuals, *informed consent must be in place* that permits the laboratory to contribute anonymized samples to the 17 IHIWS. Likewise, research samples that have appropriate consenting may be considered for NGS and SNP array genotyping.

Specific transplant-related studies of NGS for the IHWG HCT Working Group include the analysis of clinical outcome in patients and donors who are homozygous by NGS for single loci, or multiple loci. We anticipate that more information on the frequency of homozygosity defined by NGS for specific HLA and KIR loci, will be available once NGS is underway. These data will be used to define the scope and specific analyses that we will conduct for the 17th workshop.

Please contact Effie Petersdorf (epetersd@fhcrc.org) for more information and to discuss your specific interest and capacity for NGS. All HCT Working Group members are asked to complete the questionnaire at the end of this Newsletter for participation in NGS for transplant samples.

17th IHIWS SNP Arrays

A new 17th IHIWS SNP Component chaired by Dr. Beth Trachtenberg and Dr. Effie Petersdorf will generate SNP data for the MHC and KIR regions inclusive of the LCR, using dense arrays. In addition, the SNP component will apply ancestry informative markers to assess ancestry admixture. The component is actively investigating the specific methods for SNP genotyping, which include but are not limited to Affymetrix and Illumina platforms. The component will establish SNP-defined block structure within the MHC for the same HLA haplotypes as are being defined by NGS described above, and SNP block structure for the KIR genetic region.

Application of SNP Arrays and HCT Working Group Studies. The HCT working group's on-going analysis of MHC haplotypes will benefit from the SNP haplotype genotyping. The clinical outcomes analyses we have planned to undertake for HLA-A, C, B, DRB1, DQB1, DPB1-defined MHC haplotypes will also include HLA-E, F, G, MICA and MICB and SNPs that are typed on the arrays. More detailed information will be forthcoming once the platforms have been established and SNP content is known.

Active IHWG HCT Working Group Studies

HLA. The HCT working group database will serve as the resource for completion of outcomes analyses pertaining to permissive HLA mismatches (please see the figure above). Extension of 16th IHIWS studies of HLA-DPB1 T cell epitopes (Dr. Katharina Fleischhauer, Dr. Bronwen Shaw et al. *Lancet Oncology* 13:366-377, 2012) will also include hypotheses on HLA-DP epitope in the setting of other HLA disparities, and with minor histocompatibility antigen mismatching (Dr. Eric Spierings). Translation of IHWG data to clinical practice has been elegantly demonstrated by the development of an IMGT/HLA Database tool by Dr. Steve Marsh for classification of HLA-DPB1 T cell epitope determinants. We encourage working group members to visit EBML-EBI website at <http://www.ebi.ac.uk/ipd/imgt/hla/dpb.html> and gain experience with this tool. The importance of ethnicity on transplant outcome in HLA-matched patients was published this year (Dr. Yasuo Morishima et al. *Biology of Blood and Marrow Transplantation* 19:1197-1203, 2013) and will be extended to HLA-mismatched transplants.

Mapping MHC region variation has been completed for a discovery-validation cohort of HLA-matched unrelated donor transplants (Petersdorf et al *Science Translational Medicine* 4:144ra101) and a discovery cohort of HLA-mismatched pairs (Petersdorf et al *Blood* 121:1896-1905, 2013). Upon completion of genotyping

of a dense panel of SNPs for the new 17th IHIWS SNP component, MHC haplotype content will be analyzed for a comprehensive view of MHC variation and its organization in transplant recipients and donors.

The clinical significance of the TNF block is being examined in transplant pairs based on exciting information from Dr. Jean-Marie Tiercy's laboratory (Bettens et al. *Biology of Blood and Marrow Transplantation* 18:608-616, 2012). Currently, material from Dr. Tiercy's laboratory that have been defined for TNF d microsatellite alleles are being characterized in the Petersdorf laboratory for SNPs. Once this quality control has been completed, an IHWG HCT protocol for SNP genotyping will be made available to all interested laboratories who wish to participate in an analysis of the TNF block. All interested laboratories are asked to contact Effie Petersdorf (epetersd@fhcrc.org) for more information.

With the growth of our datafile for cord blood transplants, studies focused on HLA will be a starting point for 17th IHIWS analyses. Similarly, continued accrual of haploidentical related donor transplants will facilitate the analysis of NIMA and IPA on transplant outcomes.

Cytokines and Immune Response Genes. At the end of this Newsletter you will find a questionnaire pertaining to your laboratory's interest and capacity to genotyping specific polymorphisms of cytokine and immune response genes that have been previously reported in the literature to have clinical significance in transplantation. Our IHWG HCT working group datafile will serve as an independent validation of these polymorphisms. Interested laboratories are kindly asked to complete the questionnaire so that we may better define the scope of genotyping. If you are interested in additional genes that are not listed, please contact us to discuss.

KIR. Seventeen laboratories contributed KIR genotyping data from 2,237 hematopoietic stem cell transplant (HCT) donors and recipients for analysis at the 15th IHIW in Buzios. We continue to expand the database and were encouraged by the enthusiastic interest expressed at the 16th IHIWS in Liverpool.

Laboratories who are interested in the KIR-HLA working group or have previously submitted data to the working group will be able to access the HLA-KIR data submission form on-line at the 17th IHIWS website as soon as the website goes live. Laboratories who have not previously submitted data should refer to this document to begin the necessary steps for KIR genotype method validation and to familiarize themselves with the process of submitting KIR/HLA genotyping and clinical data to the working group. Laboratories who have previously submitted data are encouraged to update their data submission forms.

Please notify Dr. Katharine Hsu (hsuk@mskcc.org) with any questions about participating in the KIR-HLA working group studies. If you have additional proposals for analysis or are interested in participating on the Writing Committee for these projects, please let us know as soon as possible so that we may better plan these studies.

Goals of the IHWG HCT Working Group KIR Studies. The immediate priority of the working group is to expand the KIR-HLA transplant dataset to allow evaluation and comparison of different known mechanisms of donor NK reactivity in HCT. Driven by interactions between donor KIR, donor HLA and recipient HLA, these mechanisms of NK activity are assessed by the associations of different KIR-HLA genotype combinations with HCT outcomes of leukemic relapse, infection, graft-versus-host disease, and survival. Hierarchical effects of KIR-HLA gene combinations and effects of KIR and HLA allele combinations on transplant outcome will be assessed.

Proposed Ideas for Analysis. Initial KIR-HLA studies will focus on associations with HCT outcomes following myeloablative or non-myeloablative HCT for acute myelogenous leukemia. Subsequent studies will analyze KIR-HLA effects in different disease categories such as chronic myelogenous leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome, lymphoma, and non-malignant conditions. Additional studies will assess differences in KIR-HLA effects among specific ethnic groups, in HCT utilizing alternative stem cell donor sources (umbilical cord allografts, haploidentical donors), and in HCT with T-cell manipulated allografts.

From these studies, we hope to confirm previously described associations of KIR-HLA genotypes with HCT outcome, identify new associations, and understand in which disease category and transplant conditions are these associations most prominent. An evident practical application of this data will be to expand genetic criteria for stem cell donor selection to include KIR genotyping.

Contacting and Initiating the IHWG HCT Process. Interested laboratories should contact Dr. Katharine Hsu (hsuk@mskcc.org) or Dr. Effie Petersdorf (epetersd@fhcrc.org). Each laboratory should identify a contact person whose full contact information (name, title at institution, mailing address, phone number, fax number, email address) is included in the message. We will send the participant's information to the data management team to determine if the participant is already a member of the IHWG HCT component. If not, they will be assigned an IHWG lab code. Once assigned a lab code, the participating laboratory will receive an email explaining how to participate in the IHWG HCT component: data sharing agreements, instructions for clinical data, quality control, and a review of studies in which the laboratory's data will be included.

Data Requirements. All submitted data must be made available for IHWG HCT studies. *Data submitted for KIR studies must also include high-resolution typing of HLA-A, -B, -C, -DRB1, and -DQB1. We also request HLA-DRB3, -4, -5, DQA1, DPB1, and DPA1 if available.* KIR typing may be submitted after demonstration of successful typing of a KIR Reference Panel. Two reference DNA panels are available for quality control and can be purchased either from IHWG Cell and Gene Bank (<http://www.ihwg.org/reference/index.html>) or from UCLA (alocke@mednet.ucla.edu). Centers with limited ability to purchase either of these reference panels should contact Dr. Hsu (hsuk@mskcc.org) for DNA availability for reference testing.

KIR Quality Control Procedure. Participating laboratories must complete a KIR QC reference panel before data submission. Once quality control typing is complete, the participating laboratory will send the KIR quality control data to Drs. Hsu (hsuk@mskcc.org) and Malkki (mmalkki@fhcrc.org) for review. Review will be assessed within 1 week of submission. Successful demonstration of accurate gene typing of a QC reference panel using accepted KIR gene typing methods (PCR-SSP, SSOP, SBT) will permit acceptance of KIR gene typing data into the database. KIR allele typing is acceptable and welcomed if the allele typing method is first validated with the reference panel.

NEW PROPOSALS

As always, we welcome new proposals! Please contact Effie Petersdorf (epetersd@fhcrc.org) to discuss your ideas.

FUTURE IHWG HCT WORKING GROUP MEETINGS

We will convene interim meetings to discuss progress of the IHWG HCT studies before the October 2017 IHIWS. In addition, we will continue to use the established annual meetings that our working group members attend (clinical and basic) as convenient venues for our group to discuss on-going progress.

We look forward to our continued collaboration!

Best wishes,

Effie W. Petersdorf, MD, Project Leader, IHWG HCT Working Group, and Katharine Hsu, MD PhD, Chair, IHWG HCT Working Group KIR Studies