REGISTRIES 2013

1st International Workshop:

Challenges and Opportunities for the small and medium size bone marrow donor registries

3 - 5 October 2013, Paphos, Cyprus

Proceedings Book

REGISTRIES 2013

1st International Workshop:

Challenges and Opportunities for the small and medium size bone marrow donor registries

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October 3 – 5, 2013, Paphos, Cyprus

ORGANISERS

The Cyprus Bone Marrow Donor Registry (CYBMDR) - Karaiskakio Foundation

CYBMDR was the primary aim of the Karaiskakio Foundation, a non - profit organization created by a small group of people in 1996, for giving hope for life to people suffering from leukemia and other haematological malignancies in need of HSCT. With more than 120,000 Greek Cypriot and Turkish Cypriot registered volunteer donors, CYBMDR has the highest per capita ratio of donors in the world. In 2006 the first public cord blood registry was also established in Cyprus under the roof of CYBMDR.
Karaiskakio Foundation now operates a network of specialized biomedical laboratories designed to offer a comprehensive and integrated laboratory support to patients with haematological and other diseases. It is dynamically active in research and development, so as to ensure the continuous updating of its scientific base, the development of its services, the introduction of new technology and knowledge and secure financial resources for the development of its infrastructure and services.
www.karaiskakio.org.cy

Karaiskakio Foundation
Cyprus Bone Marrow Donor Registry

EEA and Norway Grants

The European Economic Area (EEA) was established on 1 January 1994 following the EEA Agreement which unites the member states of the European Union and the three EFTA States of Iceland, Liechtenstein and Norway into the Internal Market. The EEA is based on the same "4 freedoms" as the European Union: the free movement of goods, persons, capital and services among the EEA countries and aims at promoting strengthening of trade and economic relations among the EEA Member States. The grants provided through these Financial Mechanisms are contributing to reducing economic and social disparities in the EEA and strengthening of bilateral relations with the 15 beneficiary states. The donor countries share the responsibility to promote equality of opportunity, tolerance, security, environmental sustainability and a decent standard of living for all. The countries eligible for support under the EEA and Norway Grants are the 12 newest EU member states, and Spain, Portugal, Greece. The Norway Grants are financed by Norway alone and amount to €800 million for the period 2009-2014.
One of the beneficiary countries of the Norway Grants is Cyprus and a significant sector promoted is the improvement of public health and the reduction of health inequalities between the user groups. CYBMDR is funded to enhance its capacity to address the needs of patients with haematological malignancies without discrimination regarding age, gender and socioeconomic status. The implementation of this project, will improve its services and collaboration with other registries, including the Norwegian BMDR.
www.eeagrants.org

norway grants

COMMITTEES

SCIENTIFIC COMMITTEE

Dr Paul Costeas PhD,

- *Executive Director*
  Karaiskakio Foundation, Cyprus

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- *Medical Director*
  Head of the Norwegian BMDR, Norway

Machteld Oudshoorn, PhD,

- *Clinical Director of Europdonor Foundation*
  Chairman of BMDW Board, Chief Executive Officer of WMDA, The Netherlands

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WELCOME NOTE

Dear all,

It is with great pleasure that I welcome you on behalf of the organizing committee to the 1st International workshop on "Challenges and Opportunities for the Small and Medium Size Bone Marrow Donor Registries".

The venue of the workshop, the city of Paphos, has been selected as the European Capital of Culture for 2017 along with Aarhus in Denmark. The designation of an annual Capital of Culture was initiated by the Late Greek Minister of Culture, Melina Merkouri, and her French counterpart, aiming to bring Europeans closer together by highlighting the richness and diversity of European cultures and raising awareness of common history and values.

Similarly, by hosting a number of distinguished speakers and delegates from around the world, this workshop aims to help us share experiences on common challenges faced especially by the small and medium size registries and consequently to exchange ideas on how to create opportunities for sustainability through collaboration.
Paphos was also known as one of the most important pilgrimage centers in the ancient Greek world due to its famous Sanctuary of Aphrodite, the goddess of love and fertility.

The mythical birthplace of the Greek Goddess is near Palaepaphos (Old Paphos) at the seaside of "Petra tou Romiou" or the "Rock of Aphrodite".

The cult of Aphrodite may owe its origins to ancient Greek colonists, who adopted and hellenized the worship of a native fertility goddess named Astarte, the Greek name of the Mesopotamian Goddess Astort, or the Semitic Goddess Ashtar. So, even though Aphrodite appears to have originated from theeast, it was quickly identified with Cyprus as she was referred to by Homer and others as the "Cyprian" or the "Paphian" Goddess.

A significant part of the cult of Aphrodite at Palaepaphos was that of ritual prostitution. But, regardless of her promiscuous nature, Aphrodite held authority in many other areas besides sex: marriage, fertility, sailing, civic order, even war. The recurrent theme for her followers was her capacity to somehow create harmony and union.

And it is for this virtue of the Goddess, her capacity to create harmony and union, that she was selected as the symbol of this meeting, a meeting that seeks to promoteharmony and sustainability through collaboration and networking.

Before I close my welcoming remarks allow me to thank dearly the co-organizer of the meeting, Norway, the sole contributor of the Norway Grants. The EEA and Norway grants are provided through the contribution of three countries, the States of Iceland,

WELCOME NOTE

Liechtenstein and Norway, and aim to reduce economic and social disparities in the European Economic Area and to strengthenbilateral relations with the 15 beneficiary states.

The funding of the Norway granttowards the Karaiskakio Foundation aims to improve registry services through the upgrade of the overall infrastructure and the improvement of the operations of its registry regarding patients in need of haematopoetic stem cell transplantation.

This meeting was included in the activities of this project to promote sustainability of small, medium size registries through sharing experience and expertise and promoting further collaboration within the world's registries' community.
Of course, the organization of this workshop would not have been possible without the much appreciated support of our sponsors as well, whom we would like to thank for their generous contribution towards the success of our meeting.

I would also like to thank the conference management team from *Easy Conference* for their outstanding support. A special thank you goes to the distinguished speakers who agreed to travel from all over the world to share with us their experiences and expertise. Last but not least, I'd like to thank my colleague, Anita Koumouli, whose hard work made this workshop possible.

We hope that you will enjoy the workshop and have a taste of therenowned Cyprus hospitality. We also hope that the opportunities provided through this workshop for exchange of ideas and knowledge among associates from many different registries will help promote the growthandsustainability of our registries throughout the world.

Dr. Paul A Costeas
Executive Director
Karaiskakio Foundation

CONTENTS

SPEAKERS

Jon J. van Rood, Hononary Speaker (Netherlands)

- *Emeritus Prof. Intern Medicine, Leiden University Medical Center*

Torstein Egeland, Keynote Speaker (Norway)

- *Prof. of Immunology, Oslo University Hospital - Rikshospitalet, Head of Norwegian Bone Marrow Donor Registry*

Machteld Oudshoorn (Netherlands)

- *Associate professor at Leiden University Medical Center, Clinical Director at Europdonor Foundation, Chief Executive Officer of WMDA*

Carlheinz Muller (Germany)

- *CEO and Medical Director of ZKRD*

Michael Boo (USA)

- *Chief Strategy Officer, NMDP*

Michael Jones (USA)

- *Chief Information Officer, NMDP*

Ann O'Leary (UK)

- *Head of Register Development, ANBMT*

Joannis Mytilineos (Germany)

- *Director of Transplantation Immunology Institute for Clinical Transfusion Medicine and Immunogenetics, Ulm University*

Dimitri S Monos (USA)

- *Director, Immunogenetics Laboratory, Professor of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania*

Andreas Pavlou (Cyprus)

- Head of Digital at DELEMA McCANN Erickson

Alexander Schmidt (Germany)

- *Chief Scientific Officer of DKMS*

Martin McGre gor (UK)

- *Head of WBMDR, Welsh Blood Service, Wales*

Alexandros Spyridonides (Greece)

- *Head of BMT and Leukemia Program,Dept. of Internal Medicine, University Hospital of Patras*

Lydia Foeken (Netherlands)

- *Executive Director of WMDA*

David Steiner (Czech Republic)

- *Executive Manager of Steiner Company*

WORKSHOPS PROGRAM

THURSDAY, 3 OCTOBER 2013

Day 1: International Collaboration
Athenaeum Ballroom

10:00-14:00	*Registration*
14:00-15:30	**Opening:** Welcome Note - Paul Costeas Performer - Maria Poulli What Are Our Priorities? - Jon Van Rood GEMS: Sustainability through Collaboration – Torstein Egeland Question time
15:30-16:00	*Coffee Break* *Sponsored by Life Technologies*
16:00-18:00	**SESSION I: International Exchange - Chairs: T. Egeland, M. McGregor** International Exchange in Numbers - Lydia Foeken Exchange Across the Atlantic - Michael Boo WMDA Accreditation - Martin McGregor Future Collaboration Networks - Michael Jones Question time
18:30-20:30	*Welcome Reception* *Open bar sponsored by HistoGenetics*

WORKSHOPS PROGRAM

FRIDAY, 4 OCTOBER 2013

Day 2: Challenges and Opportunities
Athenaeum Ballroom

08:30-10:00	**SESSION II: Effective Donor Recruitment Strategies - Chairs: M. Korhonen, B. Soerensen** HLA Diversity: What is the Optimal Number of Donors - Calrlheinz Muller Registry Size vs. Registry Quality - Alexander Schmidt On-Line Recruitment: Does it really work - Ann O'Leary The Use of Social Media - Andreas Pavlou - Question time
10:00-10:30	*Coffee Break* *Sponsored by Illumina* illumina®
10:30-12:00	**SESSION III:Effective Search Strategies – Chairs: M. Oudshoorn, C. Muller** Selecting the Best Matched Donor - Machteld Oudshoorn The Impact of EMDIS on Donor Search - David Steiner When a Haploidentical Donor Becomes an Option - Alexandros Spyridonides - Question time
12:00-13:00	**SESSION IV: HLA Typing Options - Chairs: J. Mytilineos, P. Costeas** Current and Future HLA typing Methodologies - Joannis Mytilineos NGS, Coming of Age - Dimitri Monos - Question time
13:00-14:30	*Lunch*
14:30-16:30	***Sponsored Talks - Chairs: D. Monos, P. Costeas*** ***HistoGenetics- New Technologies in HLA Typing- N. Cereb*** ***Abbot Molecular- Transplant Genetics- C. Kalokyris*** ***Life Technologies- Options for Registry Workflows- P.Laird*** ***Illumina- Low Cost High Resolution HLA Typing by Next Generation Sequencing- V. Lange***
16:30-17:00	*Coffee Break*
17:00-18:30	**Session V: IT Training Workshop (By Registration Only)** Social Media Training - Andreas Pavlou BMDW: Advance Search Training - Machteld Oudshoorn Prometheus Training - David Steiner
19:30-22:00	*Conference Dinner*

WORKSHOPS PROGRAM

SATURDAY, 5 OCTOBER 2013

Day 3: The Next Step	
08:30-11:00	**SESSION VI: Sharing Experiences - Chairs: A. Koumouli, L. Foeken** **Athenaeum Ballroom** *Registry Abstract Presentations:* Current State of the Czech Stem Cells Registry and its Challenges- M. Kurikova Europdonor Foundation- M. Oudshoorn The Danish BMDR, Challenges- B. Soerensen Establishing International Registry, Challenges and Achievements- S. Avagyan The Norwegian BMDR- T. Egeland Irish Unrelated BMR- D. O'Donghaile I want Life! The Story of the Croatian BMDR- M. Mikulic The Welsh Experience- M. McGregor The Stefan Morsch Stiftung, Helping Leukemia and Tumor Patients since 1986- S. Morsch Finnish BMDR, Challenges- M. Korhonen Cyprus BMDR, The Work Behind the Mission Statement- A. Koumouli 25 Years SBSC, Looking Back and Looking Forward- L. Mader Discussion
11:00-11:30	*Coffee Break*
11:30-12:30	**Closing Session- Chair: P. Costeas** **Athenaeum Ballroom** *Closing remarks by chairs:* International Exchange- T. Egeland, M. McGregor Effective Donor Recruitment Strategies- M. Korhonen, B. Soerensen Effective Search Strategies- M. Oudshoorn, C. Muller HLA Typing Options- J. Mytilineos, P. Costeas Sharing Experiences- A. Koumouli, L. Foeken Discussion
12:30-13:30	*Lunch*
13:30-16:30	Closed Meetings **Mezzanine Level Suites** Group of European Medium Size Registries (GEMS)- T. Egeland Prometheus Users- D. Steiner

INTRODUCTION OF THE HONORARY SPEAKER

Dear all,

In this room there are people from different continents, with different backgrounds and from a variety of institutions including academic, medical, non-profit and non-governmental organizations. There are people from countries of various size and economic status, with one or more registries. Some of us represent registries with just few thousands of donors and some with several million. What brings us all together, however, is our willingness and commitment to help save the lives of peoplein need of bone marrow transplantation.

This diversity in our background is what makes us unique and distinctive. We collectively carry an enormous treasure of knowledge and experience. And this is the knowledge and experience that we are called to bring together and share during the next couple of daysin order to secure our registries' sustainability and oursuccess in helping others.

Throughout the workshop's sessions but also during our informal interactions we will have the opportunity to share our experiences in dealing with the challenges that we come across every day, to learn from each other and find ways to fine-tune our collaboration so we that can face successfully the upcoming threats and opportunities alike.

But before we look ahead we should not forget to look inthe past, and recognize the contribution of people who dared to dream and to see beyond the obvious and the convenient with courage, relentless determination and passion; people, who have dedicated their entire life working to serve the patients, science and humanity.

Such a unique person is Professor Jon Van Rood, one of the fathers of the world's marrow donor registries community.

Professor Van rood was born in Hague, Netherlands, in 1926 and received his medical degree in Leiden in 1952, "with pleasure" as he states in his modest biographical note. He trained in internal medicine and served as the director of the department of Immunohematology and blood transfusion. His discovery, in 1958, that pregnancy can induce anti-HLA antibodies was a milestone discovery that helped unravel the complexity of the HLA system andprove that matching the HLA-type of donor and recipient has a positive effect on the outcome of transplantation.

Since then he served in many posts and published more than 400 scientific articles that were cited thousands of times. His research was focused on the genetics of HLA, the study of minor histocompatibility antigens, platelet transfusion, organ and bone marrow transplantation, mechanisms of immune responses and tolerance.

In addition to his outstanding academic contribution, Professor van Rood played an instrumental role in building a scientific community around organ and stem cell transplantation through the establishment of the Eurotransplant Foundation, the

INTRODUCTION OF THE HONORARY SPEAKER

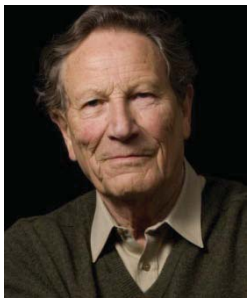
Europdonor Foundation, the Leiden Institute of Immunology, the European Foundation of Immunogenetics, the Bone Marrow Donors Worldwide, and the European Bone Marrow Transplantation Group.

We are very grateful and honored to have Professor Van Rood deliver a welcome note to our workshop, through a video recording.

HONORARY SPEAKER

JON J. VAN ROOD
EMERITUS PROF. INTERNAL MEDICINE, LEIDEN UNIVERSITY MEDICAL CENTER, THE NETHERLANDS

Biography



Johannes Joseph van Rood, born in Hague in 1926 started in Leiden his medical studies in 1944. After a three month interval as clinical clerk in the Presbyterian Hospital (head Prof R. Loeb) Columbia University New York in 1950 he received in 1952 his medical degree “with pleasure” in Leiden.
After a 6 month period as locum tenens of two general practitioners, he started his training as specialist in Internal Medicine in that same year in the Academic Hospital in Leiden (head Prof dr. J. Mulder) . During this period he was also responsible for running the Blood Bank of the hospital. He received his degree as Internist in 1957 and was promoted the same year as head of the department of Immunohematology and Blood Transfusion.
In 1958 he discovered that pregnancy can induce anti-HLA antibodies (Nature vol 181, pp173 (1958)), which enabled him to discover a statistical approach to unravel the genetic complexity of the HLA system (Thesis in Leiden (1962) cum laude, J.Clin Invest. (1963)). He returned to the USA in 1962 for a sabbatical in the Public Health Institute of the City of New York (head: Dr. F. Adler) closely associated with the New York University department of Immunology (head Prof B. Benaccereff), was promoted to Lector (associate professor) in 1965 and full professor in Internal Medicine1969.
His research centred on the genetics of HLA, the development of Class II serology (transplProc 1973), the recognition of minor histocompatibility antigens (Nature 1976, NEJM 1996), the relevance of HLA matching in platelet transfusions (Rev Belg Path 1965), organ transplantation (Lancet 1984, NEJM 1982), bone marrow transplantation (Lancet 1969), immune response genes (Lancet 1976, 1993, J Inf Dis 1983), and tolerance (Lancet 1978, Science 1988, NEJM 1989, Blood 2002).
Together with Prof.dr. E.A. Loeliger (section coagulation) and Prof. dr. P Lopes Cardozo (section cytology) he created the department of haematology in Leiden University Medical Center in 1976 of which he was the head until his retirement in 1991.He was furthermore founding president of the Eurotransplant Foundation (1967), the Europdonor Foundation (1972) the European Foundation of Immunogenetics (1985), BMDW (1988), the Leiden Institute for Immunology and the WMDA, an initiative of John Goldman, which was incorporated in 1994 and cofounder of the European Bone Marrow Transplantation Group (1979).

Abstract

Title: What Are Our Priorities?

Our first priority is and will remain the patient in need of an unrelated HSCT. However to be able to continue helping these patients, choices have to be made because in the last 10-15

years the world especially of the smaller registries has changed drastically. There are now over 25 million adult and CB donors available in BMDW. Two countries provide 70% of the donations and over 65% of the international donations come from one donor centre, due to very many well-typed, newly-recruited donors and an optimal IT infrastructure. As a result the smaller registries are confronted with a decrease of donations.

I assume that the first priority of the GEMS Registries is that their national organization can continue to exist, function and have a balanced budget. Let me first emphasize that each of the GEMS, should continue to have its own national office, which coordinates the requests, the contacts with the TCs, insurance companies and the local government and represents its country in meetings of the GEMS. This brings us to the question whether part of the registry tasks can be centralized. To give an example: can the BeNeLux (Belgium, Netherlands, Luxembourg) be served by one registry? I doubt whether this is a realistic option yet, but that might change if the number of stem cell donations in a country is low. If merging of two or more registries is not yet feasible, the GEMS Registries Cooperative (GRC) should strive to introduce top IT standard procedures to serve TCs in their country. This is an activity, which is already being realized as most of the 14 GEMS registries are already working to that end.

Another important task is to provide advice to the TCs when choosing a stem cell donor; such consultations can become an important source of income and deserve more emphasis in the WMDA accreditation requirements and in the operation of registries. In addition five registries have a close and efficient i.e. cost sparing collaboration with their national blood transfusion service. That saves money because you do not need two donor file administrations and part of the HLA typing costs can be earned back by both the stem cell donations and HLA matched platelet transfusions. Finally we should improve our service to TCs by introducing a 24-hour service if needed, just like the blood banks.

Big investments need to be made. The question is if the medium sized registries can do this on their own or whether active involvement and help from the two big registries and/or the European Community needs to be asked. In summary, if the medium-sized European registries want to survive and to continue to provide top medical service to our patients we must standardize our procedures and service on the highest quality level and work towards one integrated European operation. That will guarantee our patients in need of a transplant optimal care.

WHAT ARE OUR PRIORITIES?

GEMS PRIORITIES

1. Taking care of patients in need of a stem cell transplant.
2. Assuring the continuation of the National Registries and Cord Blood Banks.

1

WHY WILL A NATIONAL REGISTRY AND CBB REMAIN A NECESSITY?

1. As a window to the world to coordinate national and international requests for MUD.
2. To communicate with local and international government organisations, insurance companies, etc.
3. To provide immunogenetic advice to Transplant Centres.
4. To recruit stem cell donors with rare HLA phenotypes specific for its national patients.

2

AS A WINDOW TO THE WORLD TO COORDINATE NATIONAL AND INTERNATIONAL REQUESTS FOR MUD

1. BMDW is that window, but its governance and IT needs to be updated.
2. The GEMS have 3% of the world donors, 16% of the CBU and provide 3.5% of the stem cells globally,
3. But only to 12% of their national patients.

L. Foeken unpublished

3

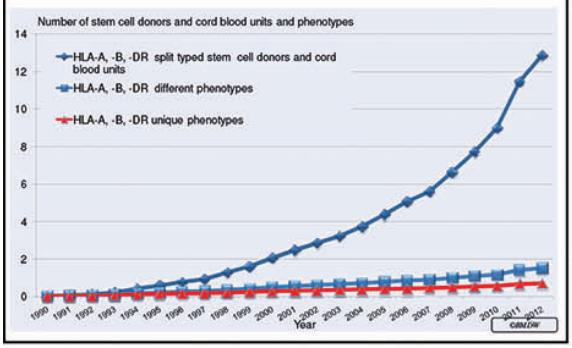
TO PROVIDE IMMUNOGENETIC ADVICE TO TRANSPLANT CENTRES

61% of 2,859 GEMS patients received an HSCT, which compares favourably with the 43% achieved globally.

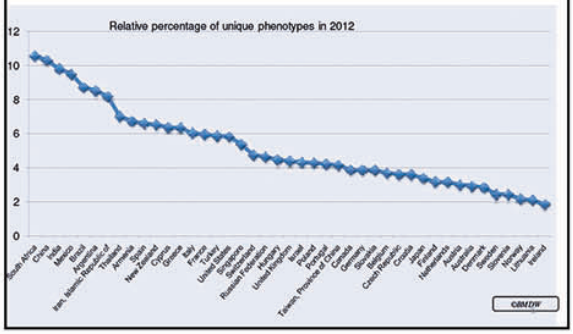
L. Foeken unpublished

4

TO RECRUIT STEM CELL DONORS WITH RARE HLA PHENOTYPES SPECIFIC FOR ITS PATIENTS



TO RECRUIT STEM CELL DONORS WITH RARE HLA PHENOTYPES SPECIFIC FOR ITS PATIENTS



WHAT ARE OUR PRIORITIES?

NON INHERITED MATERNAL ANTIGENS (NIMA) identify Acceptable Mismatches

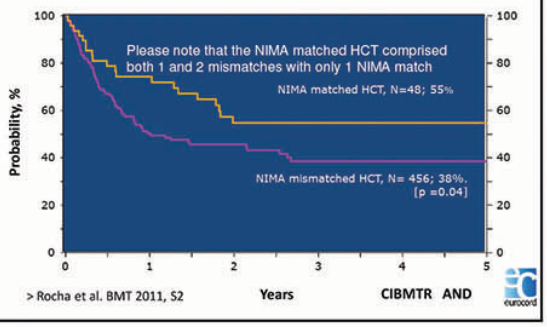
In vitro and epidemiological findings show that immune and regulator cells against NIMA IN CORD BLOOD:

- improve Neutrophil recovery,
- control relapse,
- diminish GVHD
- reduce TRM and improve survival.

Van Rood JJ and Oudshoorn M, Current opinion in Immunology 2009 vol. 21(5), p. 538: Van Rood et al PNAS 2009: Rocha et al. BBMT 2012.

7

OVERALL SURVIVAL



> Rocha et al. BMT 2011, 52 CIBMTR AND eurocord

CB VERSUS ADULT DONOR

- Survival similar
- Disadvantages
- 1 CBU costs € 1500 versus € 100 for Adult Donor
- CBU Transplant costs are higher than those of an Adult Donor.
- Treatment of relapse??
- Advantages
- Single HLA antigen mismatched but NIMA matched CBU have a faster take and might reduce relapse.
- 0,5 M CBU can help more patients than 25 M adult donors with a smaller investment: E 0,8 x 10/9 vs 2,5 x 10/9,
- Maternal typing increases the costs of a CBU harvest with € 25, but increases the number of phenotypes 14 fold.

9

COMPARING GLOBAL CORD BLOOD BANKS VERSUS REGISTRIES OUTPUT

Donations	Cord Blood National	Cord Blood International	Donor National	Donor International
19,264	71%	29%	54%	46%

10

CLOSING REMARKS

- Only 5 of the 14 GEMS registries shipped CB for their national patients in 2012?
  Could referral to experienced TC resolve this?
- By HLA typing the mother one can determine before birth whether it is worthwhile to harvest the CB or not.
- The DKMS, the EBMT and CIBMTR explore whether the NIMA effect is still present in adult donors.
- Think outside the box: more young well typed donors is not the only answer!

11

EXPECTED ADULT DONOR NIMA MATCHES

	Analysis on allele level	Analysis on split antigen level
Donors to be contacted	4,000	3,100
Responding mothers	1,800	1,400
Expected NIMA matches	120	133
• A	20	18
• B	8	4
• C	50	66
• DR(B1)	4	2
• DQ(B1)	38	43

All values are estimations

Expected NIMA matches are calculated from actual donor and patient phenotypes and allele/antigen frequencies of the German population

Main uncertainty factor: Percentage of patients with reliable follow-up information

Number of expected NIMA matches slightly higher than in the cord blood NIMA study (v. Rood et al., PNAS 2009), even if the DQ(B1) locus is not considered

KEYNOTE SPEAKER

TORSTEIN EGELAND

CHAIRMAN OF THE GEMS GROUP, PROF. OF IMMUNOLOGY, OSLO UNIVERSITY HOSPITAL, HEAD OF THE NORWEGIAN BONE MARROW DONOR REGISTRY, NORWAY

Abstract

Title: GEMS- Sustainability through Collaboration

The group of medium-sized European registries (GEMS) was established in Oslo, Norway, on September 28, 2011. GEMS, is one of two regional initiatives within WMDA that have been developed "to give stem cell donor registries the opportunity to share expertise and to update their colleagues about specific regional challenges". GEMS consists of European registries with approx. 20,000–100,000 donors each. Currently, 14 European registries participate:Barcelona (Spain),Leiden(TheNetherlands),Bern(Switzerland),Dublin(Ireland),Helsinki(Finland),Mechelen(Belgium),Nicosia(Cyprus),Oslo(Norway),Pontyclun(Wales),Prague(CzechRep.),Stockholm(Sweden),Vienna(Austria),Zagreb(Croatia), Århus(Denmark).

The main reason for representatives from these registries to get together was to discuss their emerging challenges. Firstly, their activity and donation rates are low in absolute figures with major impact on annual income. In the last years, this is more prominent with tendency to a reduction in donations, causing uncertain budgets and net balances negative. Thus, GEMS discuss possible means to improve income, reduce expenditures, and increase efficiency. Secondly, HLA typing of newly recruited donors to be done in large batches at reduced cost; an agreement with a HLA typing lab was made. Thirdly, GEMS focus on ways to exchange experience and/or join forces; to work smarter, cheaper and quicker in fields of donor recruitment, HLA typing, CT and work-up. Benchmarking will assess quality and efficiency, to identify weak points and bottlenecks. For registries with 20,000 -100,000 donors, it is still difficult to allocate resources, partly due to resource shortage and because many registries are integrated with daily hospital duties.

Biography

MD 1976; Dr. Med. (PhD) 1984; Specialist, Immunology and Transfusion Medicine 1990. Senior Consultant in Transplantation Immunology and Head, Section of Transplantation Immunology, Dept. of Immunology, Oslo University Hospital – Rikshospitalet.Professor in Medicine (Immunology), University of Oslo.Several national and international committees and boards, incl. President WMDA 2007-2008. More than 100 papers in international peer review journals in the field of immunology, stem cell biology, and unrelated stem cell donor and donation issues.

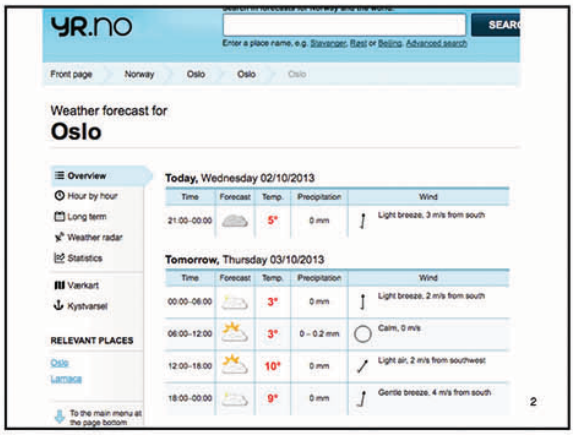
GEMS- SUSTAINABILITY THROUGH COLLABORATION

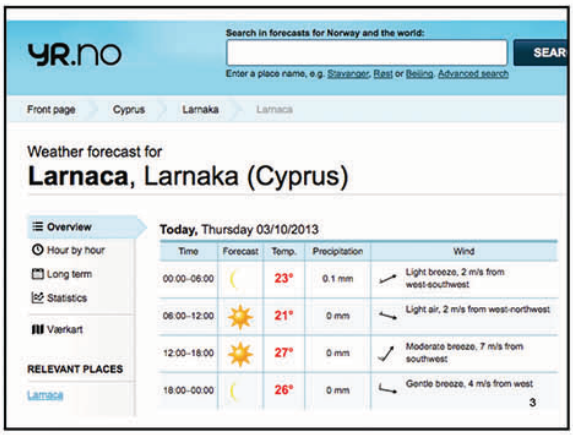
GEMS
Sustainability through Collaboration

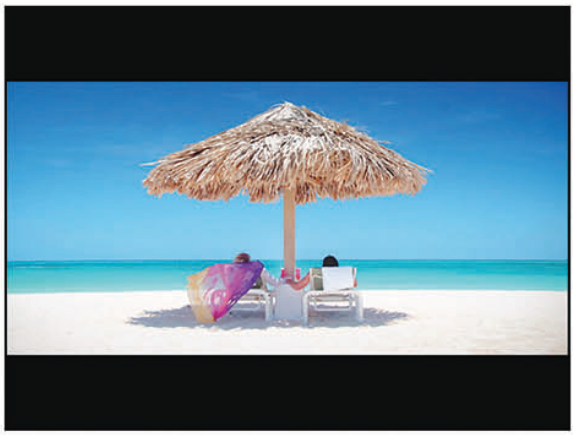
Group of European Medium Size Registries

Torstein Egeland
Norwegian Bone Marrow Donor Registry
NBMDR

1







GEMS
Background

- Challenges faced by medium size registries over the last few years:
  - a gradual *decrease* in number of donations → income challenges
  - a gradual increase in donation number *variability* → budget challenges
  - the donor pool is getting older every year, and more donors are reaching upper age limit → recruitment issues
- How can registries tackle these challenges?
  - learn from each other?
  - exchange ideas, material, procedures?
  - join forces, collaborate?
- Do medium size registries have a future?

5

GEMS
Background

GEMS was established on Sept. 28, 2011, in Oslo, Norway
European registries with 20,000 – 100,000 donors were invited to join
[common regional issues, reasonable number of donors (and donations)]
Established as a WMDA group (minutes on WMDA home page)

14 medium size European registries participate as of today

Austria	63,168	Ireland	21,154
Belgium	62,673	Netherlands	46,616
Croatia	35,145	Norway	30,255
Cyprus*	120,704	Spain**	120,414
Czech Republic (Prague)	22,020	Sweden	40,590
Denmark (Århus)	29,123	Switzerland	47,136
Finland	21,343	Wales	51,529

*Approx. 100,000 at establishment of GEMS
**Less than 100,000 at establishment of GEMS

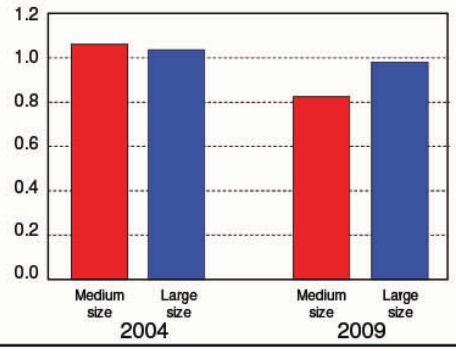
6

GEMS- SUSTAINABILITY THROUGH COLLABORATION

Donor pool size (Donation number)

7

Rel. number of donations per 1,000 A/B/DR-typed donors
Medium size European registries and large registries



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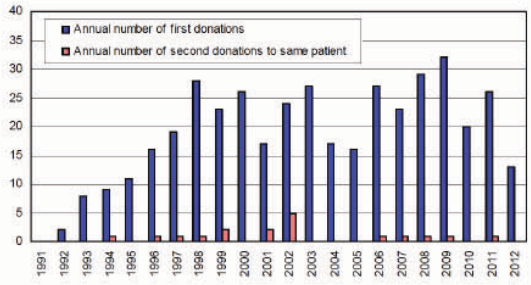
Annual number of donations
NBMDR experience



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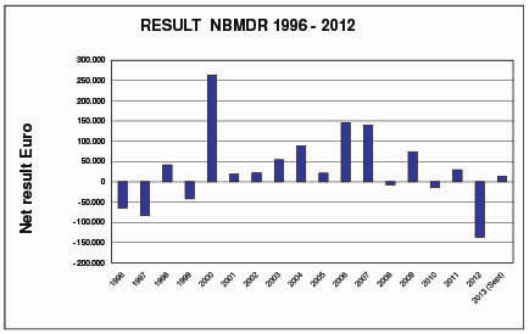
RESULT NBMDR 1996 - 2012



10

Relative number of donations to countries grouped according to donor pool size

WMDA Annual Report 2012

No. of regs. per cat.	Donating regs donor numbers	Receiving countries A	B	C & D	SUM
A (2)*	> 1 mill. *(13 mill.)*	37.4	16.5	11.8	65.7
B (19)	100,000 – 1 mill. *(4.3 mill.)*	3.2	24.9	2.4	30.5
C (22)	20,000 – 100,000 *(0.9 mill.)*	0.6	0.9	1.6	3.1
D (26)	< 20,000 (0.6 mill.)	0.2	0.1	0.4	0.7
SUM	*(18.8 mill.)*	41.5	42.4	16.2	100.0

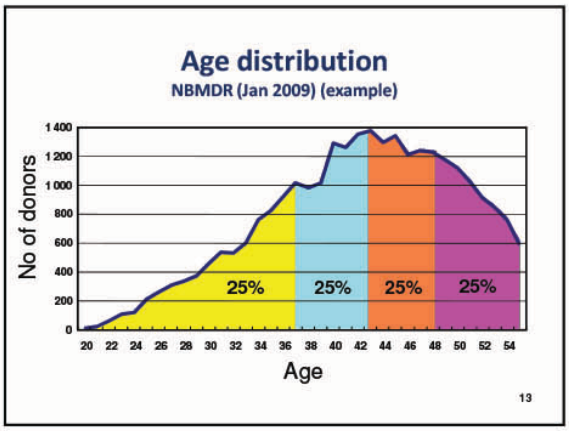
*A third registry is not included in this table

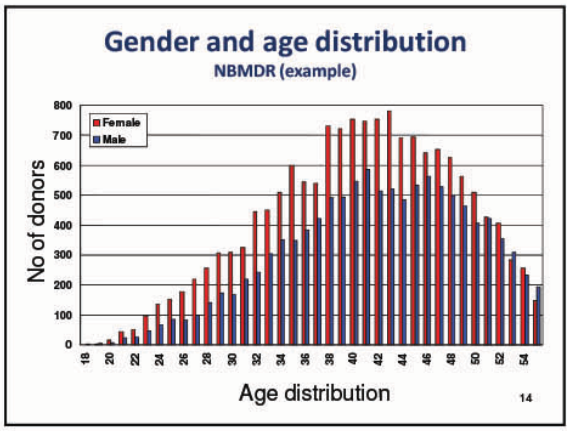
11

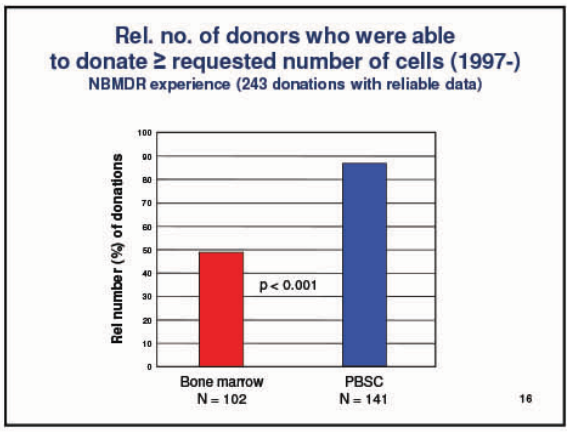
Donor age

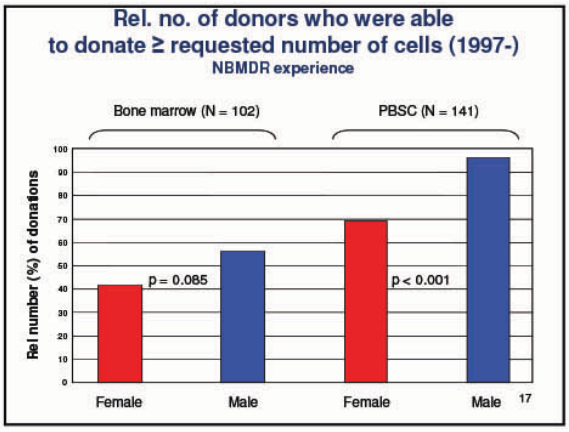
12

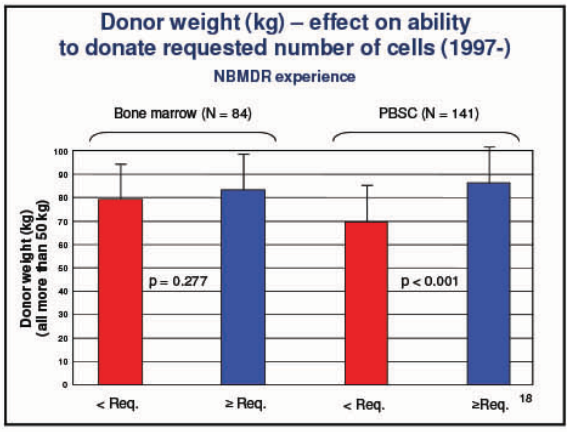
GEMS- SUSTAINABILITY THROUGH COLLABORATION



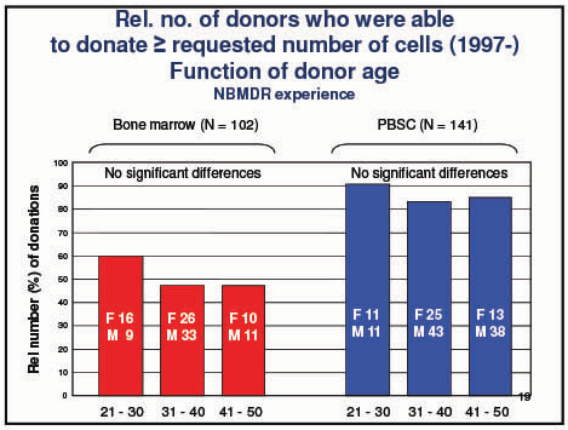








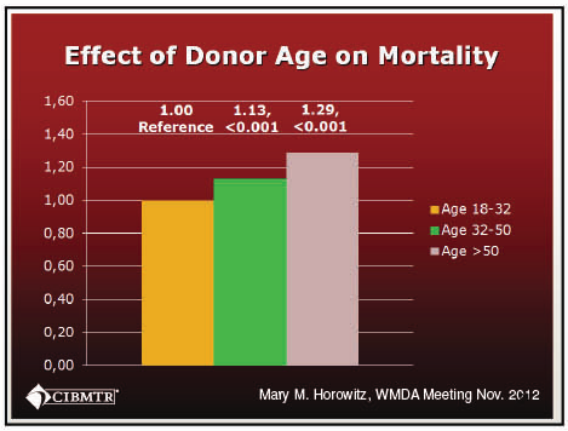
GEMS- SUSTAINABILITY THROUGH COLLABORATION

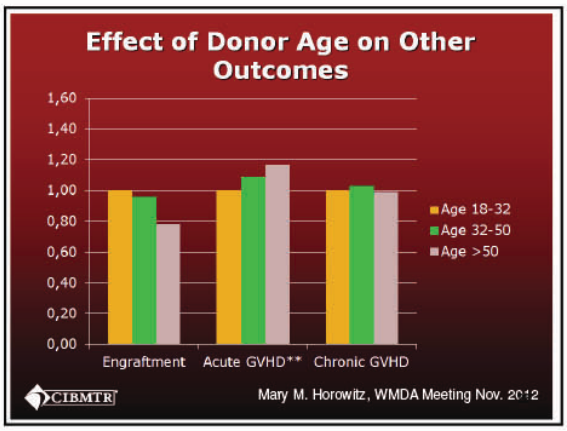


Conclusion

- It is more likely to get the requested number of cells (or more) after donation of PBSC than BM.
- When asking for donation of PBSC, it is more likely to get the requested number of cells (or more) from a male than from a female donor.
- When asking for donation of PBSC, it is more likely to get the requested number of cells (or more) from a large donor than a small donor.
- The age of the donor (< 50 years) has less impact of the number of collectable cells.

20





Conclusion

- Younger donors are preferable for the patients (patient mortality).
- Donor age has no significant effect on engraftment, AGVHD or CGVHD.

23

Critical review on a European medium size registry, exemplified by NBMDR

CONSEQUENCE OF REGISTRY SIZE

- Relative annual donation number is going down
- Annual number of donations varies – subject to income failure

CONSEQUENCE OF DONOR POOL COMPOSITION

- Too many donors are too old
- Too many donors are women
- Too many donors are insufficiently HLA-typed up-front (donors recruited many years ago)

24

GEMS- SUSTAINABILITY THROUGH COLLABORATION

GEMS
Initial issues discussed

- Overall presentation of common challenges for medium size registries
- Current status and development during the last five years of individual registries
- What are the strengths and weaknesses of medium size registries?
- Future strategy for recruitment (age and gender issues)
- Future strategy for HLA typing of new donors
- Future strategy for CT samples and workup
- How can we improve strengths and reduce weaknesses?
- How can we make ourselves more useful for international donations?
- Is time ripe for bilateral, regional or multilateral collaboration?

25

GEMS
Achievements

- GEMS members have got to know each other better, can share experience, can help and assist each other
- An agreement with a commercial HLA-laboratory for up-front HLA-typing of new donors is in place and use
- Benchmarking of GEMS registries to allow monitoring of quality indicators, e.g.
  - CT speed of response
  - CT donor cancellation rate
  - Donor work-up – donor unavailability / ineligibility
- Procedure for import from outside EU / WMDA accreditation (forms and procedure developed by Wales)

26

GEMS
Future issues to discuss

- Donor recruitment issues (age and gender)
- Combining and sharing resources (home page, documents, recruitment projects etc)
- Internet and social media utilization
- Donor safety issues
- Fund raising
- Marketing
- Reasonable registry size

27

PRESENTATION SUMMARIES

LYDIA FOEKEN – EXECUTIVE DIRECTOR OF WMDA, THE NETHERLANDS

Abstract

Title: International Exchange in Numbers

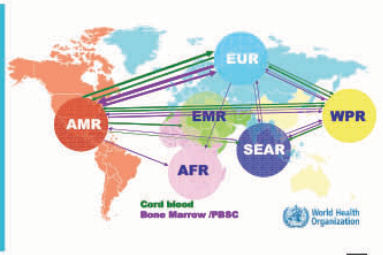
Living donors are increasingly requested for life-saving procedures for patients in need. Annually over 15000 unrelated HSCT are performed for patients with blood disorders worldwide. Because almost half of the haematopoietic progenitor cells (HPC) procured for unrelated transplantation cross international borders, optimal donor safety requires global strategies. To address this issue the World Marrow Donor Association (WMDA) has been founded in order to develop standards for the international exchange. Since 1997 WMDA is tracking the international exchange of HPC products. Over time the percentage of internationally exchanged HPC products increased from 30% to 46% in 2012. Europe is a continent where 9000 unrelated transplants are performed annually. How is the international exchange within Europe? Are there differences between the European countries? How many HPC products do European countries import from third countries? Interesting questions to be answered before plans can be developed about a possible European infrastructure for providing HPC products.

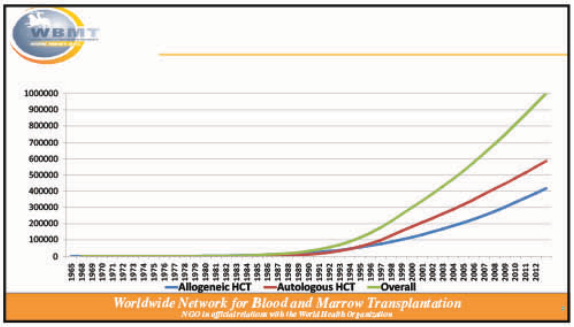
Biography

Lydia Foeken is the executive director of WMDA. WMDA is a well-recognized international non-profit association with members from 44 different countries. The association oversees the international exchange of stem cell products and promotes the interest of unrelated stem cell donors. As executive director she is responsible for the day-to-day management of the association and charged with implementing its strategic and operational plans under the direction of the board and membership of the association. Lydia is overseeing the different relations between the different WMDA Working Groups and (sub) committees and develops the PR, PA and fundraising activities of the Association and promotes the WMDA's role in the field of stem cell transplantation and cellular therapy.

INTERNATIONAL EXCHANGE IN NUMBERS

International exchange of hematopoietic progenitor cell products





A plan is born to start a registry and help patients with blood cancer in your country

Questions to start with…

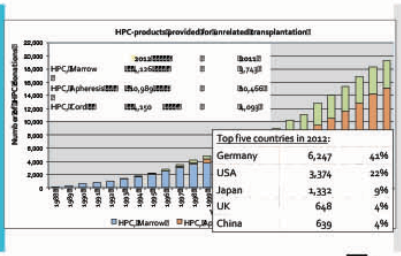
- What is the status of unrelated donor transplantation in your country?
- Are there already registries established in your country?
- Which country or registry is currently providing donor products for patients in your country?
- And the global status?

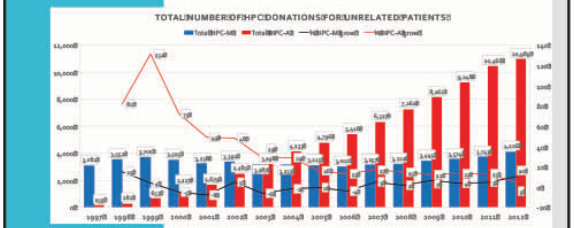
WMDA cares for donors who save patients' lives

Globally

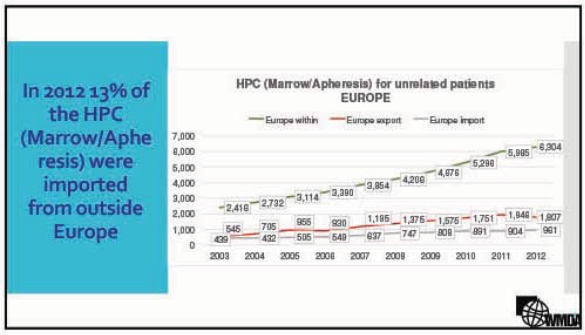
- WMDA is the principle organisation overseeing global standards for unrelated HPC donations and the international exchange of HPC products.
- WMDA accreditation is a highly prestigious status held by many registries (75% of the donors listed in *Bone Marrow Donors Worldwide* is listed in an accredited registry).
- And how many HPC donations are provided globally?

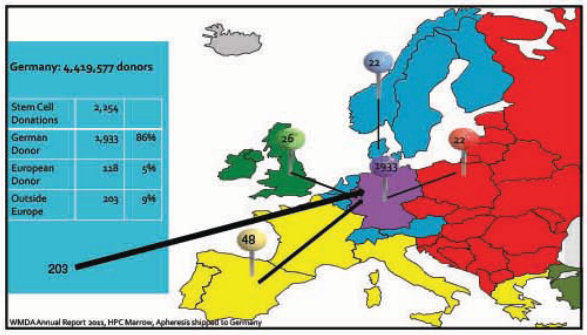
2012: 19,265 HPC donations to 56 different countries

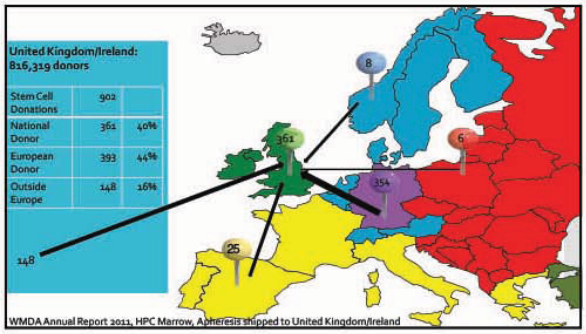


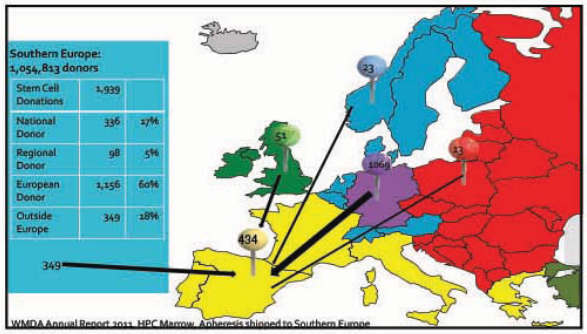


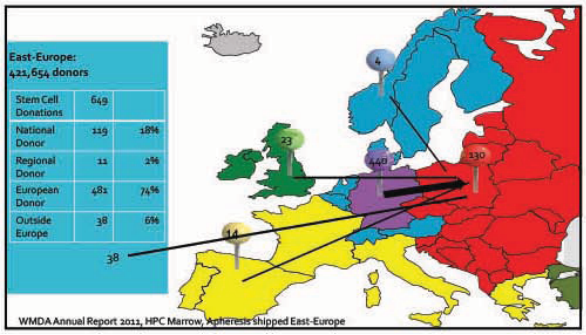
INTERNATIONAL EXCHANGE IN NUMBERS

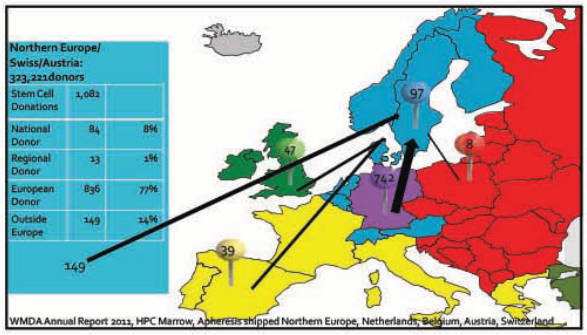






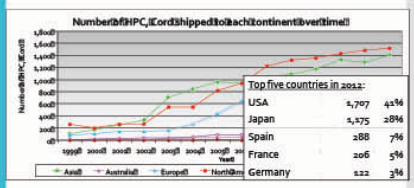






INTERNATIONAL EXCHANGE IN NUMBERS

In 2012 35% of the HPC (Cord) were imported from outside Europe



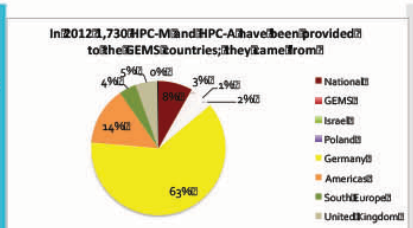
Seventy (70%) percent of the HPC Cord provided for unrelated European patients comes from France, Spain and North America.

Where do the cord blood units for European patients come from?

Region	No. CBU	Percentage (%)
Asia	13	1
Australia	24	3
North America	280	31
North Europe	47	5
South Europe	412	46
UK/Ireland	46	5
Germany	52	6
Eastern Europe	24	3
TOTAL	898	

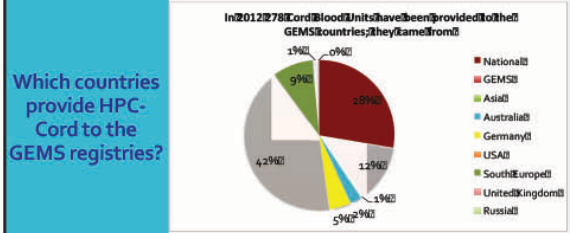
WMDA Annual Report 2012

Which countries provide HPC-M and HPC-A to the GEMS registries?



WMDA Annual Report 2012

Which countries provide HPC-Cord to the GEMS registries?



WMDA Annual Report 2012

Conclusions:

- Germany is providing over 60% of the HPC-Marrow/Apheresis products for European patients.
- United States is providing over 40% of the HPC-Cord products for European patients.

What is next? Twenty-one years after the publication of the first WMDA paper

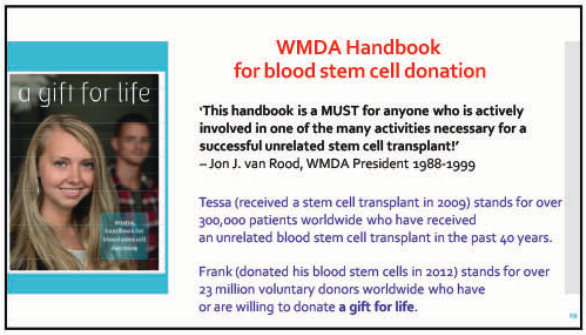
Bone Marrow Transplantation 1992, 10: 287–291 © Macmillan Press Ltd, 1992

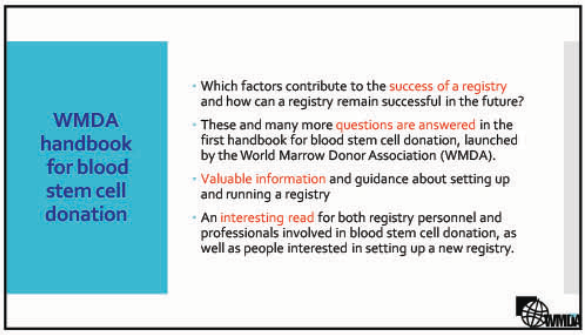
Special report

Bone marrow transplants using volunteer donors — recommendations and requirements for a standardized practice throughout the world

from the Executive Committee of the World Marrow Donor Association

INTERNATIONAL EXCHANGE IN NUMBERS





PRESENTATION SUMMARIES

MICHAEL BOO, J.D. – CHIEF STRATEGY OFFICER, NMDP, USA

Abstract

Title: Exchange across the Atlantic

Patients Served by Larger Registries would benefit from Efforts to Increase the Operational Efficiency and Effectiveness of small and medium size registries. NMDP pursues to serve all patients in the US in need of a transplant; thus must be able to provide the best available cell source regardless of location. Hence, NMDP has 41 international cooperative registry contracts. This year, almost 30% of the NMDP transplants will be with donors and more that 13% with CBUs from outside the US. Factors contributing to the use of international cell products include: diverse population in the US, improvement in IT systems, and improved information available on international donors. International search and facilitation is not optimized; limited information is available in search reports, and may be provided hours or days after the request. To address timelines, NMDP conceives a strategy to provide virtually all cell sources ranked by criteria established by the TC via an integrated search report at the finger tips of the TC at time of initial search. This service is supported by the HapLogic predictive algorithm. Better connectivity among small and medium size registries to establish the mechanisms to exchange information in the most efficient way possible may be limited due to lack of resources. Even if the resources exist, the larger registries prioritize efforts to connect with larger registries. Efforts of these registries to work together to standardize activities and take advantage of greater buying power, will increase access to their cell products by larger registries and help them to be more effective in serving their patients.

Biography

Michael Boo acts as Chief Strategy Officer of NMDP since October, 2001. He is responsible for strategic planning and guides public policy matters. He also manages international relationship development and leads business development activities, to include cord blood related matters. He earned a Juris Doctor at the William Mitchell College of Law in St. Paul, Minn., and a BA from the U. of Minn,, Duluth. He is the former vice president of strategic and corporate development for Allina Health System, an integrated healthcare system in Minneapolis. Prior to a 17-year career at Allina, he worked as counsel in real estate and as an attorney for a specialty law firm.

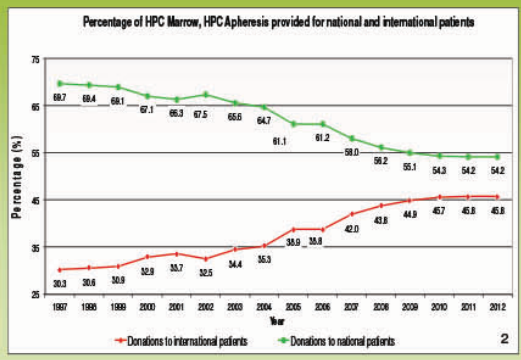
EXCHANGE ACROSS THE ATLANTIC

NMDP Engagement with International Registries

Michael Boo, Chief Strategy Officer
National Marrow Donor Program

BE THE MATCH

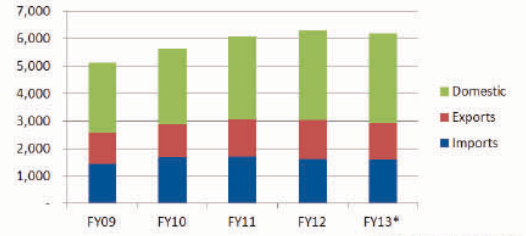
The Present



2

International Exchange

Procurements Facilitated by NMDP



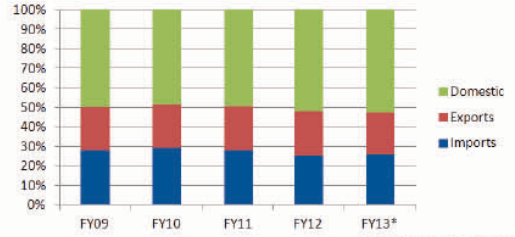
*FY13 through August 31, 2013

BE THE MATCH

3

International Exchange (cont.)

Procurements as % of Total

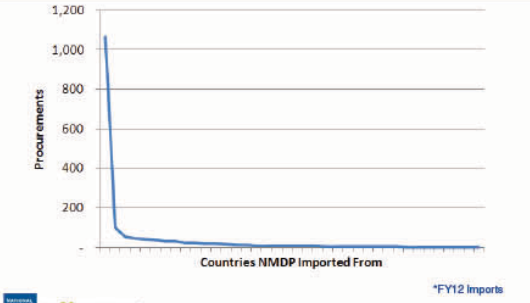


*FY13 through August 31, 2013

BE THE MATCH

4

NMDP Countries Importation

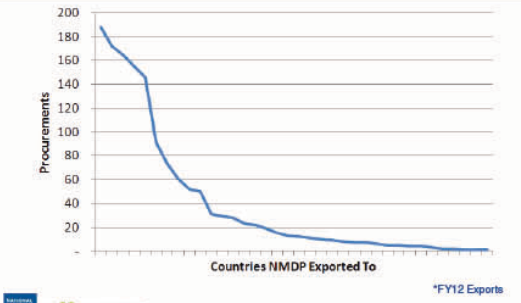


*FY12 Imports

BE THE MATCH

5

NMDP Countries Exportation



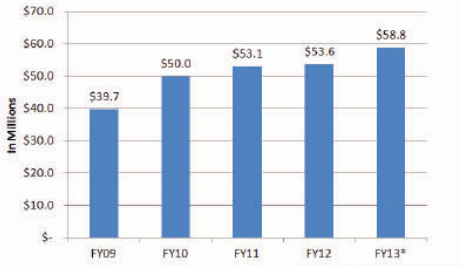
*FY12 Exports

BE THE MATCH

6

EXCHANGE ACROSS THE ATLANTIC

Revenue to External Countries



*FY13 as of September 25, 2013.

BE THE MATCH

7

Small and Medium Registries

- Small and medium registries play a critical role in the international registry landscape
- Individually, volume is small in relation to a products supplied by large registries
- As a group, small and medium registries play a significant role in the international exchange
- Relative to a local registry's domestic activity, procurement by the larger registries may be an important part of the local registry's activity

BE THE MATCH

8

NMDP Service Strategy

- Deliver a single search to the transplant center
- Provide the most comprehensive of possible matches
- Fully integrated search report
- Predictable, transparent and timely service

BE THE MATCH

9

Perception of Int'l Registries by US Transplant Centers

- Unique requirements for each registry
- Unpredictable performance
- Lack of transparency
- Off hours delivery

BE THE MATCH

10

Challenges: Forms

- *Use of unique, registry-specific forms for standard patient requests such as Preliminary Search, CT request and HLA typing or Work-up*
  - *Some forms don't contain enough information*
- Use WMDA forms where possible
  - Much effort has been spent to create WMDA forms that meet the needs of most registries

BE THE MATCH

11

Challenges: Timely Responses

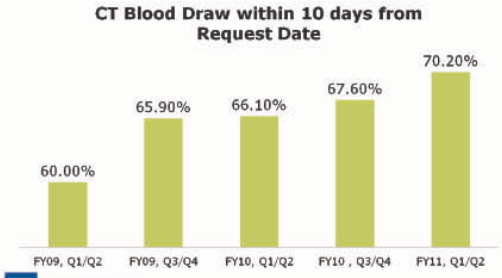
- *Lack of timely response to requests. For example – requesting registry sends a CT or HLA typing request, but days or weeks elapse before receiving registry responds with a blood draw date, test date or donor withdrawal*
- Establish a service standard (service level agreement) for each step of the process
  - E.g. Provide CT status updates within 7 days of request

BE THE MATCH

12

EXCHANGE ACROSS THE ATLANTIC

Tiered Donor Management: US Donor Centers



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Challenges: Timely Responses

- *Requesting registry sends requests for updates on the status of a request because the receiving registry has not provided an update on a request*
- Send updates to the requesting registry on a weekly basis for CT and HR requests. Respond to requesting registry ASAP if donor can not proceed
- When appointment or test date is established, inform requesting registry of anticipated shipping date or HLA results received date

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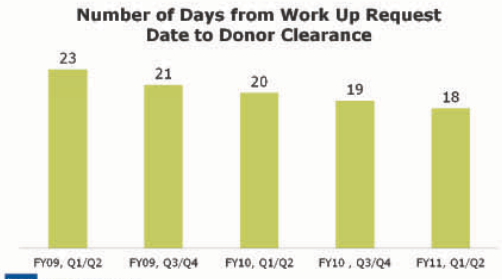
14

Tiered Donor Management: Donor Centers



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15

Challenges: Communications

- *Communication via fax is least desirable—all pages may not be numbered; difficult to read; difficult to track and reference*
- Avoid hand-written forms
- Use EMDIS for searches, CTs and typing requests
- Use email (and attach scanned documents) for other correspondence

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Challenges: Staff Changes

- *High staff turnover*
  - *without informing other registries*
- *Requesting multiple people be informed for each communication*
- *Difficulty contacting the registry in case of emergency (cancellations, product delivery changes)*
- Establish a group e-mail account
- Establish an emergency contact phone number 242/7 that will not change even if staff change

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Challenges: Blood Draw Requests

- *Some registries/countries do not routinely stock certain types of blood draw tubes requested by the transplant center*
- Identify these issues early (not day of draw) to allow time to negotiate and resolve. Registry staff must be able to understand the clinical implications of the request and determine if there will be issues.

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Challenges: Policy and Practice Issues

- *Some registries require that a CT be performed before HR testing can be requested---or require a stepwise progression of testing (certain loci or resolution)*
- Consider discussions with HLA labs, explain necessity/rationale of the TC. TC is looking for speed and economy.

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Challenges: Lab Turnaround Times

- *Limited/slow turnaround time for HLA typing requests*
- Establish Service Level agreements or incentive payments with labs
- Establish minimum and maximum (14 days) turnaround times

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Challenges: Courier Instructions

- *Courier drop-off and/or pick-up instructions lack sufficient detail*
- Establish a standard set of instructions for each pick-up or drop-off location that can be easily attached to an email – in a language known to the courier
- Verify accuracy with the center at least annually
- Ensure the location will be staffed in evening/overnight and that staff will be expecting courier
- Provide taxi instructions in native language

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Challenges: Financial

- *Delayed invoices*
- Institute a monthly statement to summarize outstanding invoices. Many registries refuse payment if the invoice is > 6 months old.

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Issues with Large Registries

- The problems go both ways
  - Large number of staff, many names to know
  - Large staff = specialization of duties: who do you contact for a non-case-related issue?
  - Staff turnover
  - NMDP's assigned case manager may change often: difficult to build good relationships when there is a low volume of activity

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Conclusions

- Want to improve awareness of potential donors
  - As close to upfront search as possible
- Reduce variation in activity
  - Same processes wherever possible
- Reduce burden of interaction
  - Minimize manual processes
  - Standardize electronic connections
- It's a two way street
  - We want our donors more widely available as well
  - We have to meet your performance expectations

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24

PRESENTATION SUMMARIES

MARTIN MCGREGOR – HEAD OF THE WBMDR, UK

Abstract

Title: WMDA Accreditation

Data from the WMDA Annual Report 2013 show that 15,115 HPSC products were provided for transplantation in 2012. Over 45% of these products involved a transplant from a donor in a country different to the patient's with shipment to 56 different countries. The increasing regulatory environment we work in created a complex international situation with no agreed single set of standards. The international standards that exist to-date: FACT-JACIE Standards - the principal accreditation for TCs and CCs and WMDA Standards – only accreditation specifically designed to the functions undertaken by a registry.
Currently 20 registries are WMDA accredited or qualified, accounting for 75% of the donors available in BMDW. The WMDA standards are recently revised (major re-organization to aid clarity and remove duplication) to be in effect on 1st January 2014. The concerns (resources required, interpretation of standards, preparation of application, required information, availability of reviewers) and benefits (confidence of peers, a mechanism for justification for import from outside EU, preparation for National inspections, training of a reviewer i.e. understand requirements, relate standards to operation of registry, inspectors perspective) of achieving WMDA accreditation will be discussed. Procedure: ensure you have staff familiar with the standards and how they apply to your registry, enroll a lead member of staff as key reviewer, don't delay, start today - have your Quality Management System (document control etc.) operational for at least a year, submit a letter of intent.

Biography

Martin has been involved with Registry activity since 1995 and was responsible for the design and implementation of the operational structure, documentation and systems of the WBMDR. In 2001 became Head of the WBMDR and in 2004 the WBMDR was the first registry to achieve WMDA accreditation. Currently a member of the WMDA Accreditation Steering Committee, he also acted as the 'Lead' for the WMDA Accreditation Committee sub group on 'Accreditation site visits. Previously he worked in various labs of the UK Blood Transfusion Service for 17 years until he became the Welsh Blood Service QA manager in 1990. In that role he designed and implemented the WBS QA system and in 1994 the WBS became the first UK Transfusion Centre to achieve ISO9000 registration.

WMDA ACCREDITATION

WMDA Accreditation

M. McGregor

Paphos Oct. 2013

M. McGregor Oct 2013

Interesting Fact ? - 1

- 68 current WMDA members
  - If they inspected each other:
    - Each would undertake 67 inspections
  - For the whole community this would result in a total of

4,556 inspections

M. McGregor Oct 2013

Introduction

- WMDA Annual Report 2012
  - 15,115 HPC Marrow, & HPC Apheresis provided for transplantation in 2012
  - 45% crossed national boundaries
  - 56 different countries

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Interesting fact ? - 2

- If a single Registry had to inspect all 20 accredited Registries and their associated collection centres, it would take more than....

17 years to inspect them all

(based on 1 inspection per week)

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- EU Directive 2004/23/EC
  - requires that imported tissues and cells can be traced from the donor to the recipient and vice versa. It also requires that the member states and establishments receiving such imports shall ensure that the product meets the standards of quality and safety equivalent to those laid down in the Directive
- National Regulators
  - National Regulators are responsible for the quality and safety of products produced in their country.
- Imports
  - You are responsible for the quality and safety of imported products that you facilitate.

M. McGregor Oct 2013

The future ?

The best way to predict the future is to invent it.

Alan Kay 1971

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WMDA ACCREDITATION

WMDA Accreditation

- Started in 2003.
- 20 registries currently WMDA qualified or accredited.
- 75% of the donors available on BMDW are listed in a WMDA qualified or accredited Registry.

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WMDA Accreditation

- Revised standard due to come into effect 1st January 2014
  - Major re-organisation of standard
    - aid clarity & remove duplication
  - See WMDA website
    www.worldmarrow.org/fileadmin/Committees/STDC/20140101-STDC-WMDA_Standards.pdf

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Standards

- No internationally agreed single set of standards
- 2 internationally recognised standards
  - FACT-JACIE
    - Principal for Transplant & Collection Centres
  - WMDA
    - Only one specifically designed for Registry functions

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Concerns

- Resources available
- Interpretation of the standards
- Preparation of application
- Providing required information
- Availability of staff to act as reviewer

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WMDA Accreditation

- Peer review of standards and accreditation process.
- Continued development and clarification of standards.
- Advisory documents available.
- Feedback from members to develop systems to reduce the workload in the submission and review of applications.

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Remember

- For a Registry to operate safely and effectively they should use a system that:
  - Does the right thing
    - Works to appropriate professional standards
  - Is consistent
    - Has an appropriate system of audits/inspection
  - Has controlled flexibility
    - Can deal with unexpected events in a controlled, safe and effective manner

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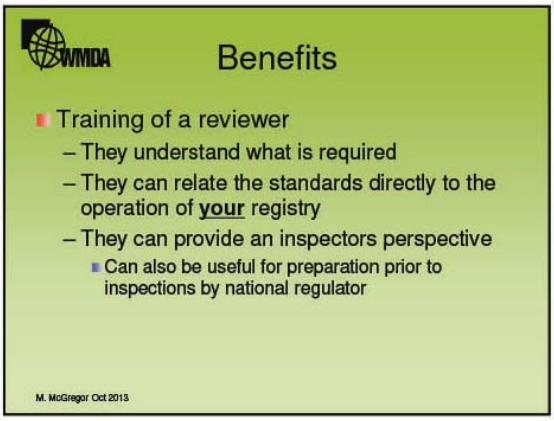
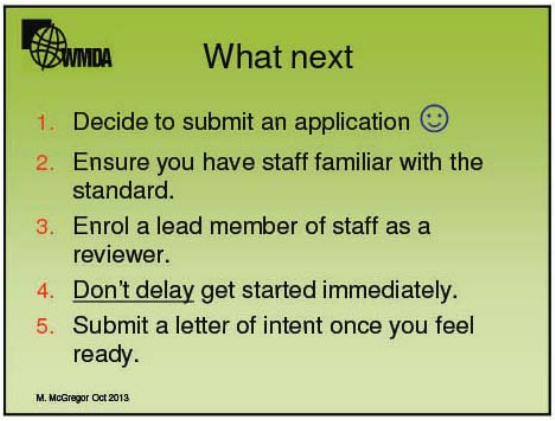
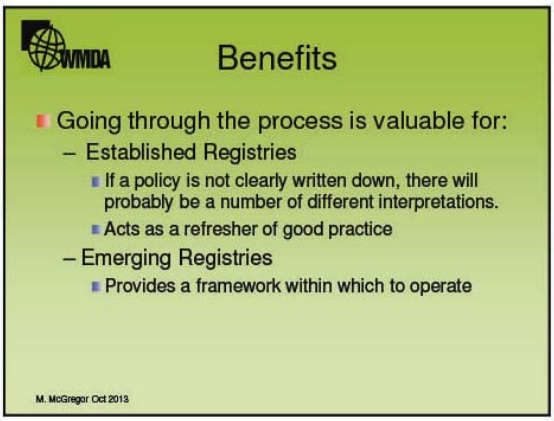
WMDA ACCREDITATION







PRESENTATION SUMMARIES

MICHAEL JONES – CHIEF INFORMATION OFFICER, NMDP, USA

Abstract

Title: Future Collaboration Networks

In this session, Michael Jones, CIO of the National Marrow Donor Program, will discuss why business collaboration is an important element to the success and survival of all registries, especially small and medium-sized registries. During this session, Michael will present some potential models for business collaboration, and discuss a real world example of how a collaborative effort is underway with the host registry, Cyprus.
Lastly, Michael will provide guidance on how others can pursue business collaboration that could potentially mitigate a registry's current challenges, as well as promote the successful facilitation of opportunities in the market place.

Biography

Michael Jones joined the National Marrow Donor Program (NMDP) in April 2007 as their first ever Chief Information Officer. Jones leads the Information Technology department responsible for all the organization's technology and information systems that support NMDP's unique and ever-expanding business. His department is responsible for delivering services in the following areas: Business Engagement, Project Management Office, Enterprise Architecture, Application Solutions and Infrastructure. He delivers many strategic initiatives for the NMDP and is the driving force behind deploying a Service Oriented Architecture (SOA) that facilitates efficient, optimal systems He is also one of the key leaders in the development and launch of the Phoenix Initiative, the NMDP's business transformation initiative designed to better serve patients and donors through the network. He currently serves as the Executive Sponsor. Lastly, he works closely on International Business collaboration where he partners with international registries to cultivate strong partnerships and devise solutions that support the registry's needs.

FUTURE COLLABORATION NETWORKS

Future Business Collaboration Networks

Michael Jones, CIO
National Marrow Donor Program
October 4, 2013
Paphos, Cyprus

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Opening

Transplant Centers are the ultimate customers!!!

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Why is Business Collaboration Important?

- Increase access to cell sources
- Meet the diverse needs of patients everywhere
- Promote knowledge sharing, idea generation and leverage capabilities
- Recognize that our success is dependent on others throughout the world

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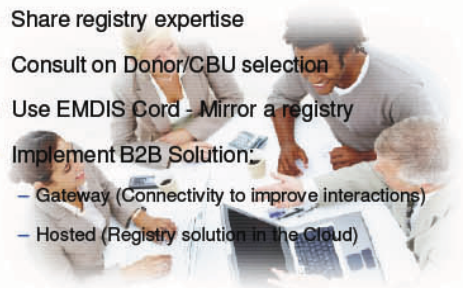
What Does Collaboration Look Like?

- Share registry expertise
- Consult on Donor/CBU selection
- Use EMDIS Cord - Mirror a registry
- Implement B2B Solution:
  - Gateway (Connectivity to improve interactions)
  - Hosted (Registry solution in the Cloud)



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EMDIS Cord: Mirror A Registry

- Originated from the EMDIS concept
- Accelerate searching and facilitation
- Faster process as a result of having the entire cord inventory of the partner registry
- NMDP mirroring with France Greffe de Moelle
  - Increase in typing activity and improved visibility of business activities (matches)

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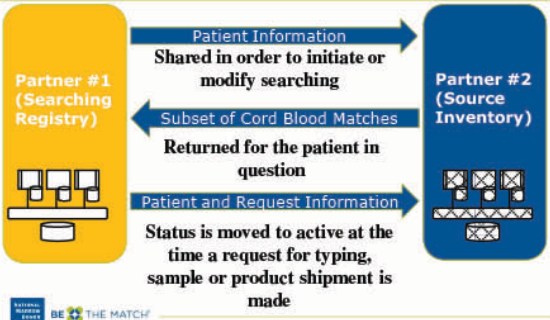
Traditional EMDIS (Classic)



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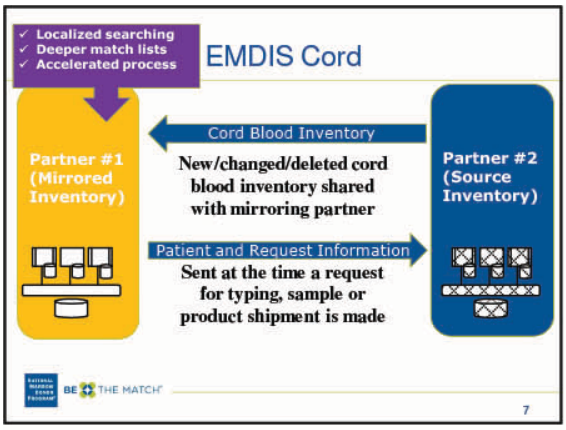
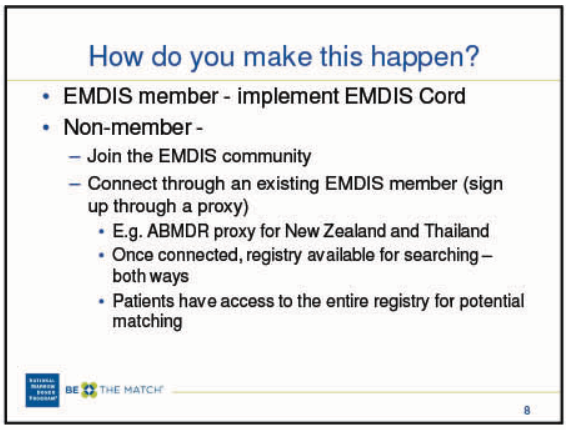
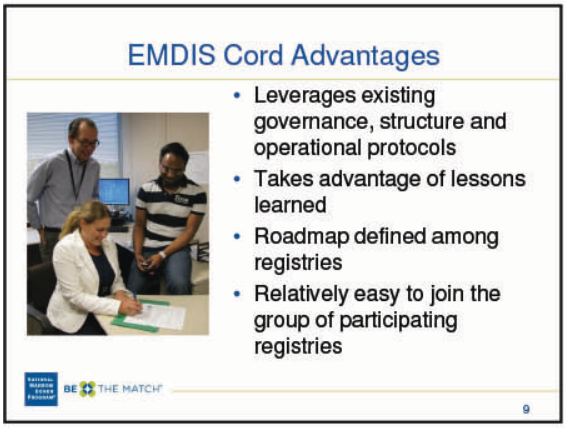
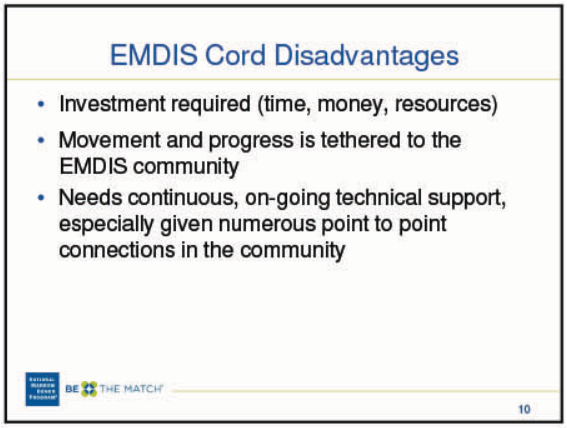
6

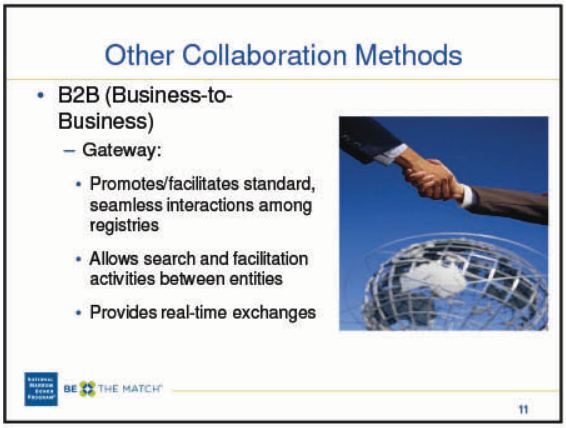
FUTURE COLLABORATION NETWORKS

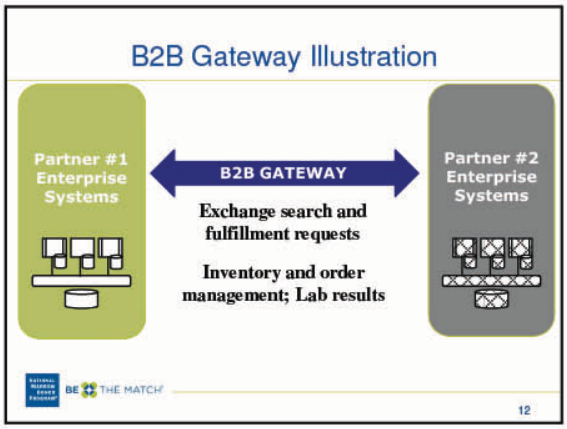












FUTURE COLLABORATION NETWORKS

Other Collaboration Methods (cont)

- B2B (Business-to-Business)
  - Hosted: registry in the cloud
    - Extends registry capabilities thereby extending the reach to local customers
    - Provides rapid deployment of registry capabilities
    - Becomes "Hosted" as a result of having their inventory integrated
    - Still preserves the multi-step search process -- local inventory search first

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B2B Hosted Illustration

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Closing Thoughts

- Small, mid-size and emerging registries face unique opportunities
  - Many options to address patient needs in their country
  - Ability to pool resources and efforts to achieve results
  - Availability of diverse cell sources (potential key to unique patient needs)

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Closing Thoughts

- Small, mid-size and emerging registries have unique challenges
  - How to address patient needs in their country
  - Limited resources to accomplish goals
  - Resources are stretched already (wear multiple hats)
  - Limited ability (financial) to capitalize on current advances

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16

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17

PRESENTATION SUMMARIES

CARLHEINZ MULLER – CEO AND MEDICAL DIRECTOR OF ZKRD, GERMANY

Abstract

Title: HLA Diversity, What is the Optimal Number of Donors

This seems to be the most frequently asked question in the world of donor registries. It typically occurs when a registry is established or grants are applied for and targets should be underpinned with a good rationale. Strangely enough, registries approaching a reasonable size tend to stop asking this question. A scientifically sound analysis of this question would require a rigorous definition of the term “optimal” by specifying the underlying function for which a maximum is to be sought depending on certain parameters. Albeit not easy, the monetary cost side of this function – recruiting new donor and operating a registry – can be seriously calculated. The more difficult part however is to quantify the benefit, i.e. to translate into money additional life years adjusted by quality (QALY) and certain medical and socio-psychological effects (e. g. compassion, hope, care minus the burden put on donors). In fact, the situation is even more complex since in many regions there are several (competing) registries and a substantial part of the patients has a choice of many donor candidates at any stage of the search including the final transplant.
This talk will focus on quantitative aspects of population genetics relevant for identifying suitable donors depending on polymorphism within the population, the typing resolution and the registry size. Similarities and differences of the populations represented in registries around the world as well as other relevant factors of influence and their continuous change will be discussed.
Apparently there is no simple and conclusive answer to the title question.

Biography

Carlheinz Mueller holds an MSc in mathematics from the U. of Munich and an MD, PhD in molecular bioinformatics from U. of Ulm. He is specialist in Transfusion Medicine and certified expert in Immunogenetics. In the 1980s he has been mainly working as a developer for medical software with a focus on tissue typing and immunohematology and co-founded an IT company. He later joined the University and Red Cross Blood Bank in Ulm as a resident in transfusion medicine. Since its foundation in 1992, he was Medical Director of ZKRD and since 1997 also its CEO. His main research interests are in bioinformatics and population genetics applied to the field of HLA and stem cell transplantation.

HLA DIVERSITY, WHAT IS THE OPTIMAL NUMBER OF DONORS

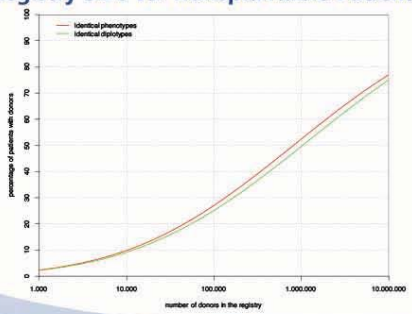
HLA Diversity: What is the Optimal Number of Donors ?

Carlheinz R. Müller

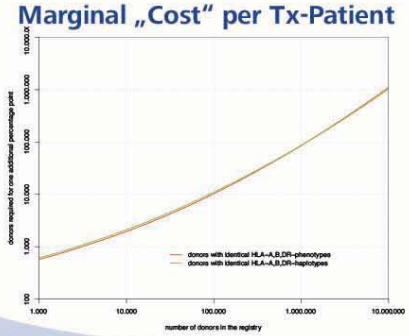
ZKDR – Zentrales Knochenmarkspender-Register Deutschland
(German National Stem Cell Donor Registry)
Ulm, Germany

www.zkrd.de

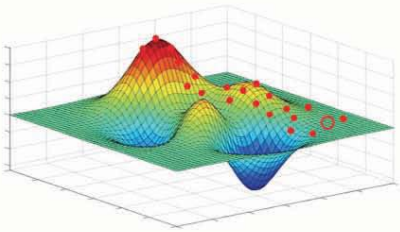
Registry Size vs. Transplantable Patients



Marginal „Cost" per Tx-Patient



What is Optimal?



Unpleasant Surprise

Any model that allows to calculate an Optimal number of donors for a registry has to put a price tag on the benefit ☹:

quality adjusted life years (QALY) gained

×

price / value of a gained QALY.

Parameters

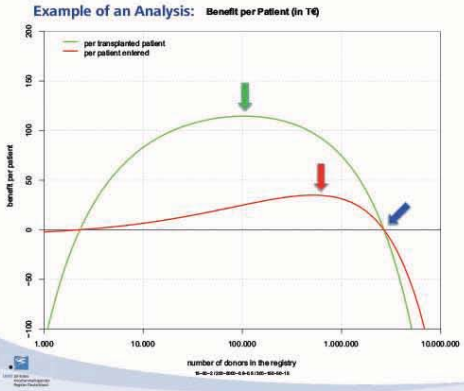
donor "life" time on the registry	l
donor recruitment cost	T
donor retention cost per year	R
patients per year	n_P
average cost of a search	D
fraction of patients (with donors) actually transplanted	t
survival rate	s
cost of a successful transplant	S
cost of an unsuccessful transplant	F
benefit QALY	Q
QALY per survivor	y

HLA DIVERSITY, WHAT IS THE OPTIMAL NUMBER OF DONORS

Input and Output Variables

number of donors	n_D	
cost of the registry	C_R	$n_D \times (T/l+R)$
% patients with donors	m	
number of transplants	n_T	$n_P \times m \times t$
cost without transplant	C_N	$(n_P - n_T) \times D$
cost of succ. transplants	C_S	$n_T \times s \times (D+S)$
cost of unsucc. transplants	C_U	$n_T \times (1-s) \times (D+U)$
survival benefit	P	$n_T \times s \times Q \times y$
balance	B	$P - C_N - C_S - C_U - C_R$
balance per patient / transplant	B_P, B_T	B/n_P, B/n_T

Example of an Analysis: Benefit per Patient (in T€)



Lesson Learned so Far

- Even in a simplistic model, the optimal number of donors depends on a lot of co-variables.
- The number of patients („market size“) and the cost of recruitment and typing are the major registry-linked influence factors.
- The cost of transplants and value of a QALY are the most critical co-variables.
- The major missing elements in those calculations are quality issues and external influences leading to complex interactions.

Critical Factors for Success

- Quantity
- Quality
- Efficiency
- Service
- Psychology

Thanks to

The ZKRD-team, in particular
Werner Bochtler, Hans-Peter Eberhard,
Ulrike Feldmann and Markus Beth.

Cornelie Haag (Dresden)

Jon van Rood, Matchteld Oudshoorn,
Jack Bakker, Angelo Melis
http://www.bmdw.org

Steven G. E. Marsh and James Robinson
http://hla.alleles.org/wmda/index.html

Send questions to

carlheinz.mueller@zkrd.de

PRESENTATION SUMMARIES

ALEXANDER SCHMIDT– CHIEF SCIENTIFIC OFFICER OF DKMS, GERMANY

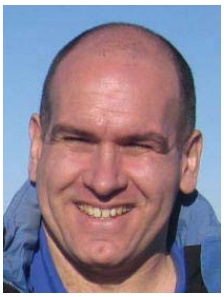
Abstract

Title: Registry Size vs Registry Quality

A population-specific shortage of registered donors is the most obvious reason for low probabilities to find matching donors for patients in need of a transplant. In practice, however, donor search is also complicated by the heterogeneous nature of HLA information in donor registries. Donor HLA information may differ by the number of loci typed, typing resolution and typing methods applied.
Related issues that will be addressed in this talk include:

- How does the completeness of HLA information affect the donation probability of registered donors?
- How does the completeness of HLA information of registered donors affect the chance that the optimal donor is identified?
- Which other factors do affect the donation probability and what does it mean for donor recruitment?
- Should one recruit more donors or rather invest in the typing quality of already registered donors?
- What is an appropriate typing profile for newly registered donors?

Biography



Alexander Schmidt studied medicine, mathematics, physics and economics in Giessen and Heidelberg. After working as a physician at the Neurology department of the University hospital in Heidelberg (1997-1998), he joined the Frankfurt office of the Boston Consulting Group where he focused on customers from the health care sector (1998-2002). Since 2002, he has worked for DKMS German Bone Marrow Donor Center in various positions. Currently, he is Chief Scientific Officer of DKMS and Chief Executive Officer of the affiliates DKMS Life Science Lab and DKMS Cord Blood Bank.

REGISTRY SIZE VS REGISTRY QUALITY

Registry size versus registry quality

Alexander Schmidt
Paphos / Cyprus
October 4, 2013

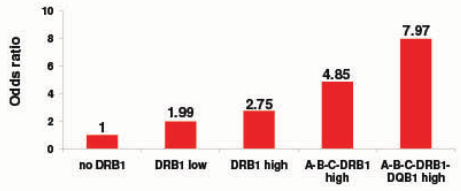
DELETE BLOOD CANCER

Agenda

- Effect of HLA typing level on donation probabilities
- Effect of HLA typing level on donor search success
- Effects of other factors
- Donor recruitment versus Re-typing of registered donors
- Appropriate typing profile

ZKRD results

Donation probability by typing level

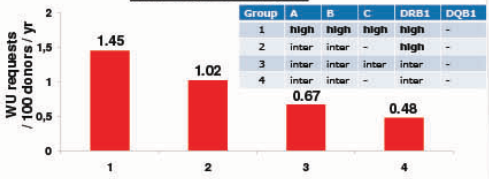


Very strong effect of typing level enhancements on donation probability!

3

Early DKMS results

Work-up probability by typing level (male donors ≤ 25 yrs)



Group	A	B	C	DRB1	DQB1
1	high	high	high	high	-
2	inter	inter	-	high	-
3	inter	inter	inter	inter	-
4	inter	inter	-	inter	-

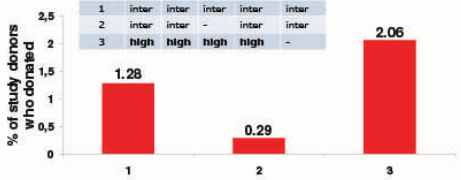
Again, strong typing level effects observable
Absolute figures higher than today!

4

FGM results

Donation probability by typing level

Group	A	B	C	DRB1	DQB1
1	inter	inter	inter	inter	inter
2	inter	inter	-	inter	inter
3	high	high	high	high	-



Strong effects of high-res typing and of HLA-C
Prospective study based on small numbers (only 5 donations in Group 2)

5

What follows from these analyses? (I)

There is a strong impact of completeness of HLA information on donation probabilities

Actual registry-specific donation probabilities depend on

- Population-specific HLA genotypes
- Donor availability
- Other registry quality parameters

For each typing level, probabilities decrease substantially over time

- This fact is, however, no argument against complete HLA typing

REGISTRY SIZE VS REGISTRY QUALITY

What follows from these analyses? (II)

Each registry can calculate the economic impact of enhancements of their donor typing profile, based on several registry-specific parameters

- Additional costs for typing profile enhancements
- Impact on donation probabilities (or, in general: request probabilities)
- Income from additional donations (and other requests, e.g., CT)

DKMS-internal analyses always showed positive economic effects of typing profile enhancements (data for HLA-DPB1 are vague)

- Positive impact will increase in the future due to significant typing cost reductions (-> NGS)

Agenda

Effect of HLA typing level on donation probabilities

Effect of HLA typing level on donor search success

Effects of other factors

Donor recruitment versus Re-typing of registered donors

Appropriate typing profile

8

How does incomplete HLA information affect donor search success?

Incomplete donor HLA information can cause problems

- Increase donor search times
- Fully HLA-matched donors may remain unidentified

Question: Is non-identification of completely matching donors due to incomplete HLA information a problem of practical relevance?

- We used a simulation approach to analyze this question

Simulation overview

Step 1 — Generation of a virtual donor registry

Step 2 — Generation of virtual patients

Step 3 — Execution of donor searches

Virtual donor registry

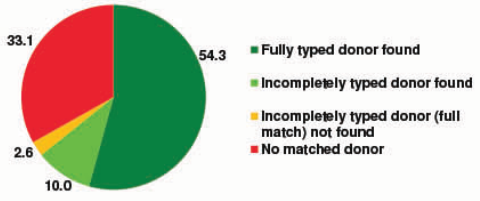
Simplified model of the DKMS Germany donor file

- 2,600,000 donors
- Based on German haplotype frequencies
  - Derived from a large sample of *n*>370,000 donors
- Each virtual donor was randomly assigned to one of 5 typing levels (i.e., HLA phenotype information was hidden accordingly)

	Loci					
Level	A	B	C	DRB1	DQB1	% of donor file
1	H	H	H	H	H	28
2	H	H	H	H	-	30
3	L	L	-	H	-	7
4	L	L	-	L	-	18
5	L	L	-	-	-	17

Simulation results (I)

Search for 10/10 match – 3 typing requests allowed



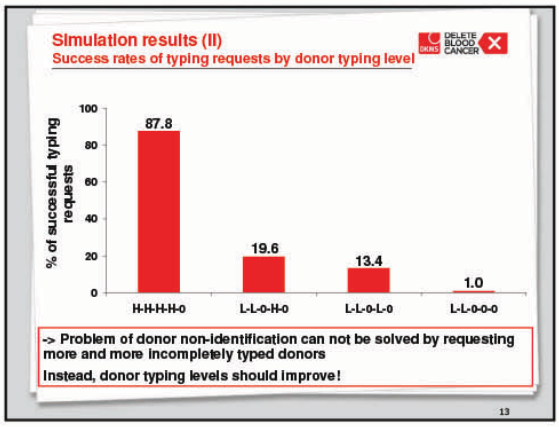
In most cases (87.4%), the search strategy has no impact on donor search success

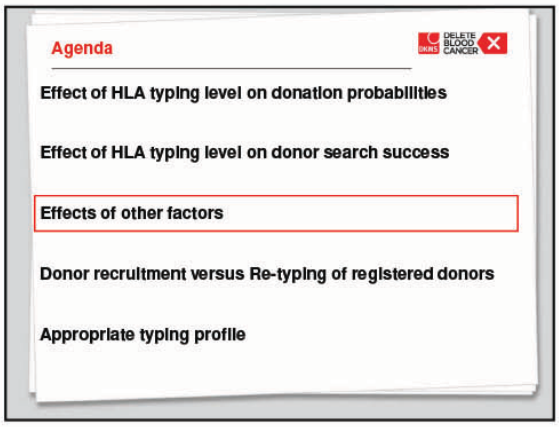
Of the remaining 12.6% of patients, 21.0% will not find a fully matching donor though at least one such donor is registered

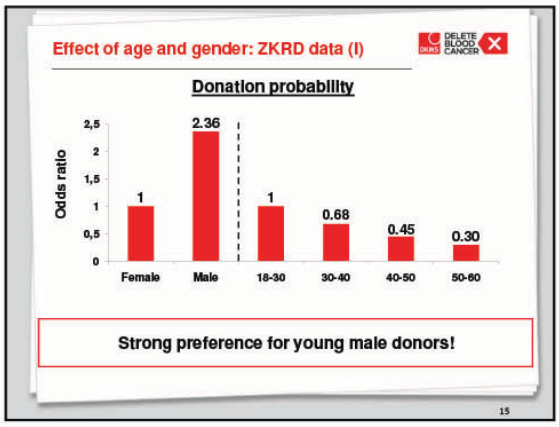
In total, this unfavorable outcome occurs for 2.6% of all patients

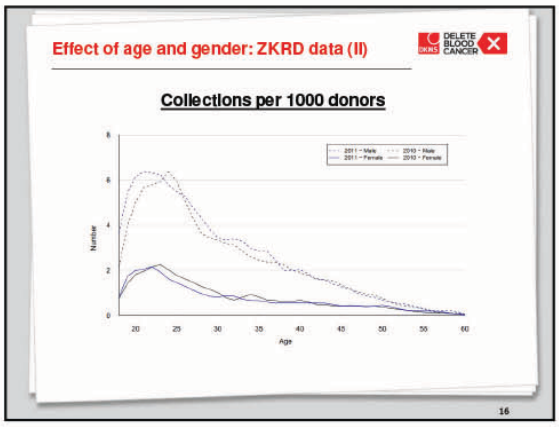
12

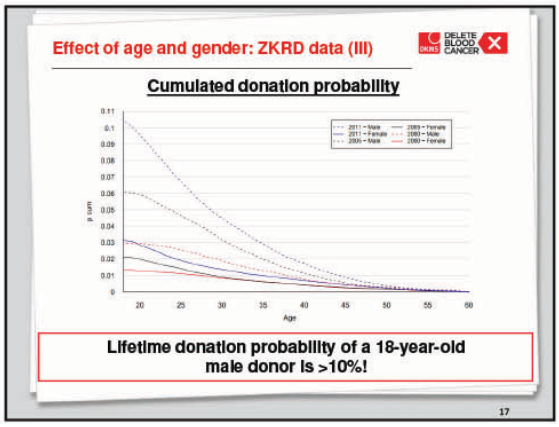
REGISTRY SIZE VS REGISTRY QUALITY

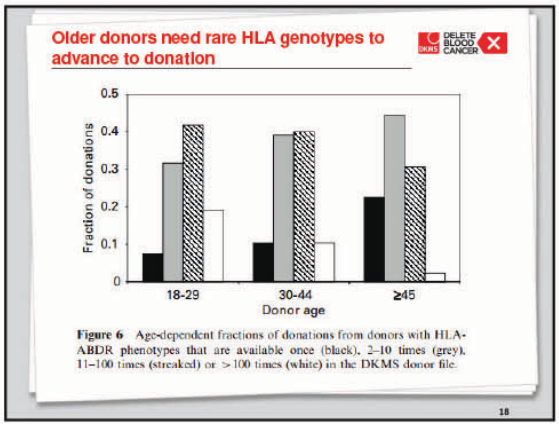












REGISTRY SIZE VS REGISTRY QUALITY

What follows from these analyses? (I)

Need for a strong recruitment focus on young male donors is obvious

Question: Should there be an age limit for donor recruitment that is stricter than donor safety considerations require?

Answer from patient perspective: No

- Older / female donors will be requested for donation if they share a patient's rare HLA genotype
- Age and gender are less important factors in donor selection than optimal HLA match

What follows from these analyses? (II)

Answer from an economic registry perspective: Difficult

"Amortization" of registration costs of older / female donors may indeed be doubtful

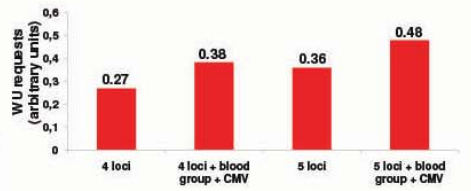
- Quantification based on registry-specific parameters possible
- Things will improve due to NGS-related cost reductions

Mothers may be important communicators in their families and thus contribute to the recruitment and availability of young (male) donors

In case that new donors are asked to contribute financially to their registration costs

- DKMS experience shows that older donors contribute significantly more than younger donors

Effect of blood group (AB0, Rh) and CMV status on work-up probability

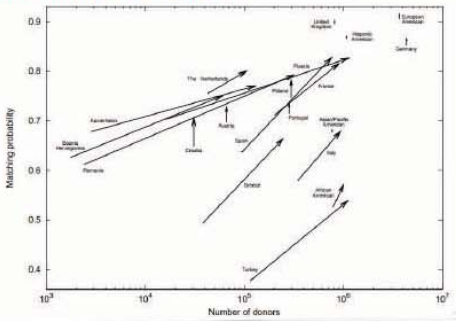


Effect of blood group + CMV slightly higher than of DQB1

Cave! Results of small prospective study

21

Model calculation results: Optimal recruitment of 5,000,000 donors



22

Agenda

Effect of HLA typing level on donation probabilities

Effect of HLA typing level on donor search success

Effects of other factors

Donor recruitment versus Re-typing of registered donors

Appropriate typing profile

Arguments for re-typing of registered donors

Complete HLA typing of registered donors increases patient benefits and registry income

Investments in donor re-typing normally pay off

Creating awareness for stem cell donation and convincing potential donors to register is more challenging than performing HLA typing

As donation probabilities decline with time, donors with insufficient HLA typing become increasingly "invisible"

- This fact also raises ethical questions

REGISTRY SIZE VS REGISTRY QUALITY

Arguments for ongoing donor recruitment

Donor file aging!

There are not enough donors in the global registry

- With significant differences between countries / populations
- In most countries there are some minorities that are severely underrepresented in the global registry

Each registry should follow both paths: Without ongoing recruitment it will fade away, without optimizing typing quality of registered donors it does not use donor commitment properly

Regarding the trade-off between donor file quantity and quality in the light of limited resources, there is no simple solution

- Each registry should carry out analyses based on their registry-specific parameters
- These analyses will probably provide some guidance but no definite solutions

Agenda

Effect of HLA typing level on donation probabilities

Effect of HLA typing level on donor search success

Effects of other factors

Donor recruitment versus Re-typing of registered donors

Appropriate typing profile

Appropriate typing profile

Upfront donor HLA typing should not fall behind the current standard for donor-recipient matching

- At least 4 loci (HLA-A, -B, -C, -DRB1) at high resolution
- DQB1 is definitely recommendable (ZKRD data), DPB1 optional

NGS has entered lab routine for HLA registry typing (e.g., DKMS Life Science Lab processes currently 40,000 samples per month)

- Higher resolution than Sanger
- Lower costs than Sanger
- Additional parameters induce no relevant additional costs

New DKMS NGS standard typing profile (starting in Oct / Nov 2013)

6 HLA loci at high resolution

- No ambiguities within the relevant exons
- Exclusion of the most frequent null alleles
- Exon phasing in preparation

Blood group (AB0, Rh)

CCR5Δ32

Related cost savings are used to add the CMV status to the typing profile (only donors with blood samples)

KIR in next extension stage (Spring 2014)

DKMS
Deutsche Knochenmarkspenderdatei
gemeinnützige Gesellschaft mbH
Schäfflerstraße 64-65 50933 Köln
T 0 70 71 9 43 - 0 F 0 70 71 9 43 - 1499
post@dkms.de

www.dkms.de

DKMS DELETE BLOOD CANCER

29

PRESENTATION SUMMARIES

ANN O'LEARY–HEAD OF REGISTER DEVELOPMENT AT ANBMT, UK

Abstract

Title: On-Line Recruitment: Does it really work

Online donor recruitment can offer a convenient, simple way for potential new donors to join bone marrow registries. However there are benefits and challenges to be considered. ANBMT has offered an online donor recruitment option since July 2010, at the same time that the charity moved to tissue-typing via saliva sample.

Over the past 3 years, online donor recruitment has proved a valuable recruitment channel which has grown significantly and now accounts for 40% of those joining. Significant benefits include: an immediate opportunity for interested potential donors; an effective option for smaller patient appeals; more accurate data capture (in comparison with paper applications); flexibility of data capture; reporting capabilities. It has been instrumental in achieving increase in donor numbers since 2010. However, in analyzing the effectiveness of this recruitment channel, we must also look at the challenges: controlling the numbers (dealing with increased volume); application form issues (data validity, non-mandatory fields); drop outs mid-application; return rate of kits (wastage rates); technical issues; ability to target effectively (male/female, ethnic minorities); cost-effectiveness.

Anthony Nolan's experience of online donor recruitment has been varied and has provided valuable lessons about our campaigns and insights into our target audience. These lessons will shape not only how online recruitment builds in the future, but also how Anthony Nolan expands its face to face donor recruitment program.

Biography

Ann O'Leary is Head of Register Development at Anthony Nolan and is responsible for ensuring the optimum size and composition of Anthony Nolan's Register of potential bone marrow donors. This involves managing all areas of recruitment, education and retention of donors.

She has been working in the area of altruistic donor recruitment for 7 years, having spent 4 years with the Irish Blood Transfusion Service before moving to Anthony Nolan in 2010.

ON-LINE RECRUITMENT: DOES IT REALLY WORK

Online donor recruitment - does it really work?

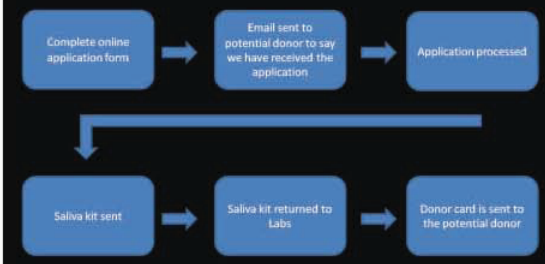
Ann O'Leary

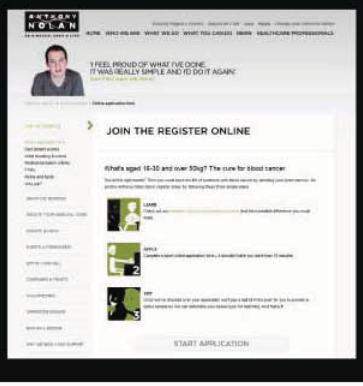
Head of Register Development

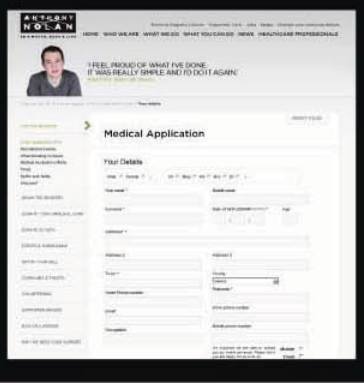
Background

- Began online recruitment in 2010
- In conjunction with:
  - new recruitment method
  - new brand
  - new website

Online recruitment journey







Benefit of online recruitment

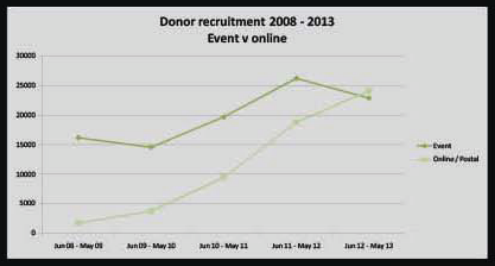
- An immediate call to action
- An affective option for patient appeals
- More accurate data capture
- Flexibility of data capture
- Reporting capabilities
- Opportunity for interaction

ON-LINE RECRUITMENT: DOES IT REALLY WORK

Social media

ANTHONY NOLAN

Growth of online recruitment



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Challenges of online

- "Perfecting" the process
- Drop-outs mid-application
- Technical issues
- Wastage rate
- Controlling the numbers
- Targeting

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Challenges of online

- **"Perfecting" the process**
- Drop-outs mid-application
- Technical issues
- Wastage rate
- Controlling the numbers
- Targeting

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"Perfecting" the process

- Online journey
- Fulfilment
- Packaging

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"Perfecting" the process

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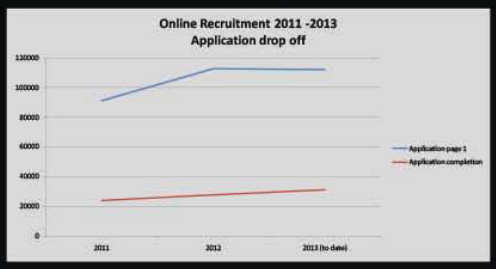
ON-LINE RECRUITMENT: DOES IT REALLY WORK

"Perfecting" the process

Challenges of online

- "Perfecting" the process
- **Drop-outs mid-application**
- Technical issues
- Wastage rate
- Controlling the numbers
- Targeting

Drop outs mid application



Challenges of online

- "Perfecting" the process
- Drop-outs mid-application
- **Technical issues**
- Wastage rate
- Controlling the numbers
- Targeting

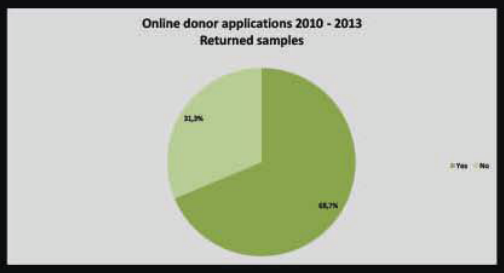
Technical issues

Challenges of online

- "Perfecting" the process
- Drop-outs mid-application
- Technical issues
- **Wastage rate**
- Controlling the numbers
- Targeting

ON-LINE RECRUITMENT: DOES IT REALLY WORK

Wastage of saliva kits



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Challenges of online

- "Perfecting" the process
- Drop-outs mid-application
- Technical issues
- Wastage rate
- **Controlling the numbers**
- Targeting

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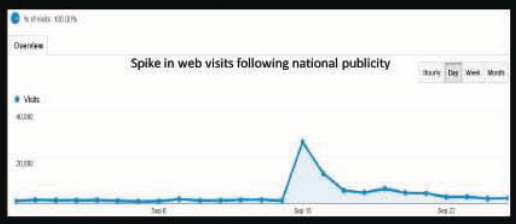
Controlling the numbers



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Controlling the numbers

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Challenges of online

- "Perfecting" the process
- Drop-outs mid-application
- Technical issues
- Wastage rate
- Controlling the numbers
- **Targeting**

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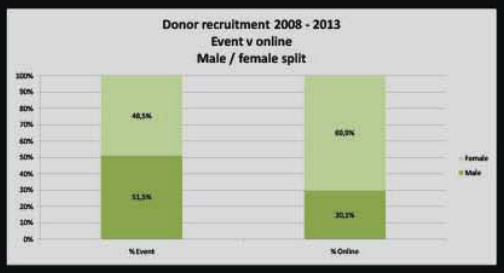
Targeting



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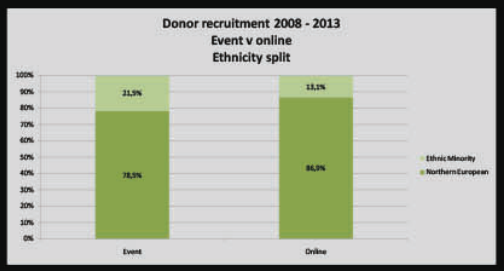
ON-LINE RECRUITMENT: DOES IT REALLY WORK

Targeting



ANTHONY NOLAN
BE A MATCH, SAVE A LIFE

Lessons for the future

- Improving online application form
- Introduction of a confirmation email
- New team position – online recruitment programme lead
- Exploration of online campaigns to improve targeting
- Examining face-to-face recruitment data collection options

ANTHONY NOLAN
BE A MATCH, SAVE A LIFE

Thank you

Questions

ANTHONY NOLAN
BE A MATCH, SAVE A LIFE

PRESENTATION SUMMARIES

ANDREAS PAVLOU– DELEMA MCCANN ADVERTISING AGENCY, CYPRUS

Abstract

Title: The Use of Social Media

Shout out how important it is for organizations that serve a holy cause to exist!
How can social media spread the word? How can we bring more people aboard?
How can we 'baptize' and turn real everyday people as our ambassadors?
Saving Lives is what makes a superhero!
We will explore the paths that social media open up for us.
How can NGOs benefit from the social media while maintaining a serious and responsible image?
How can we benefit from the existence of social media and why should we consider them in our media mix?

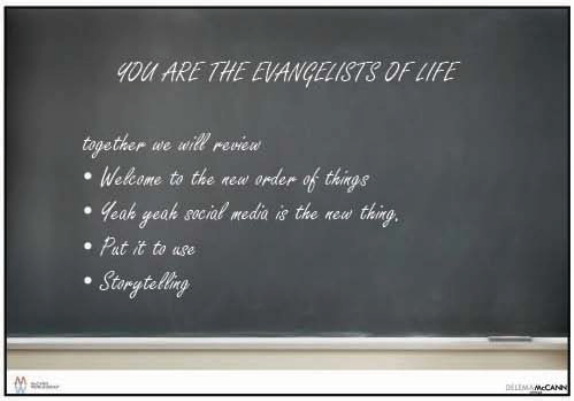
Biography

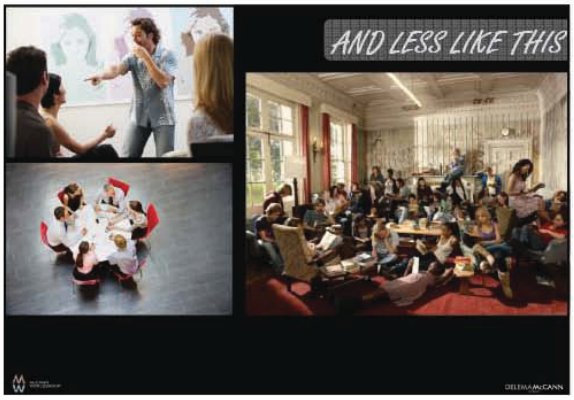
Andreas has been in the advertising sector and at DELEMA MCCANN CYPRUS since 2005. The need to create digital and interactive solutions for clients led him to initiate and lead the company's Digital Unit in 2009.

Andreas and his team are responsible for providing strategic and complete solutions in the digital environment, for both local and global brands active in Cyprus.

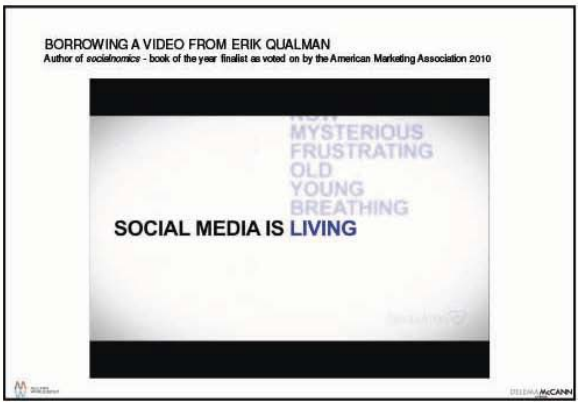
Andreas spent 6 years studying in New York and currently holds a BSc in Computer Science and an MBA in Marketing.

THE USE OF SOCIAL MEDIA





THE USE OF SOCIAL MEDIA



THE USE OF SOCIAL MEDIA

FACTS FROM EMARKETER

% of population

Social Network User Penetration Worldwide, by Region, 2011-2017
% of population in each group

	2011	2012	2013	2014	2015	2016	2017
North America	47.3%	50.0%	51.6%	53.1%	54.4%	55.3%	56.3%
Western Europe	34.5%	38.5%	41.9%	44.5%	46.6%	48.1%	49.4%
Central & Eastern Europe	30.0%	36.1%	40.6%	44.2%	47.1%	49.5%	51.8%
Latin America	25.8%	30.8%	36.2%	40.8%	45.9%	49.1%	52.1%
Asia-Pacific	13.0%	16.2%	19.7%	22.8%	25.4%	27.9%	30.2%
Middle East & Africa	9.5%	12.4%	15.5%	18.0%	20.2%	22.5%	24.2%
Worldwide	**17.6%**	**20.9%**	**24.4%**	**27.4%**	**30.0%**	**32.4%**	**34.5%**

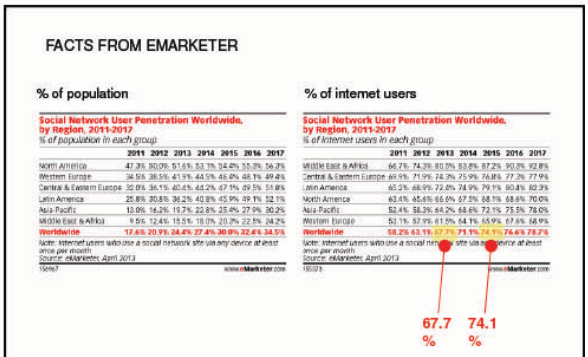
Note: Internet users who use a social network site via any device at least once per month
Source: eMarketer, April 2013

% of internet users

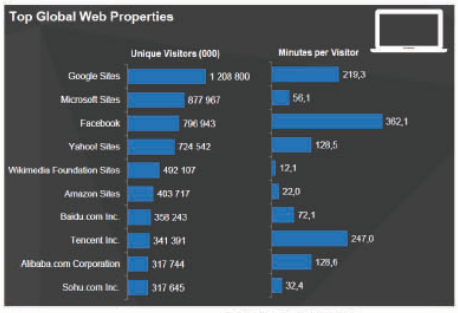
Social Network User Penetration Worldwide, by Region, 2011-2017
% of Internet users in each group

	2011	2012	2013	2014	2015	2016	2017
Middle East & Africa	66.7%	74.3%	80.0%	83.8%	87.2%	90.3%	92.8%
Central & Eastern Europe	69.9%	71.9%	74.3%	75.9%	76.8%	77.3%	77.9%
Latin America	65.2%	68.9%	72.8%	74.9%	79.1%	80.8%	82.3%
North America	62.4%	65.6%	66.6%	67.5%	68.1%	68.6%	70.0%
Asia-Pacific	52.4%	58.3%	64.2%	68.6%	72.1%	75.5%	78.0%
Western Europe	52.1%	57.9%	61.5%	64.1%	65.9%	67.6%	68.9%
Worldwide	**58.2%**	**63.1%**	**67.7%**	**71.1%**	**74.1%**	**76.6%**	**78.7%**

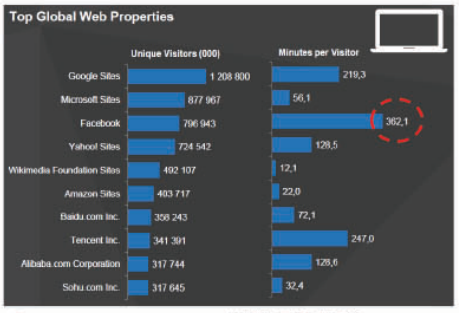
Note: Internet users who use a social network site via any device at least once per month
Source: eMarketer, April 2013



COMSCORE TELLS US

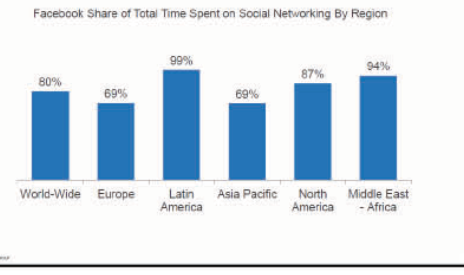


COMSCORE TELLS US

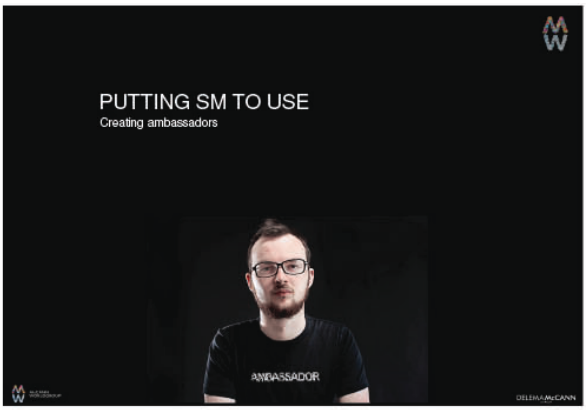


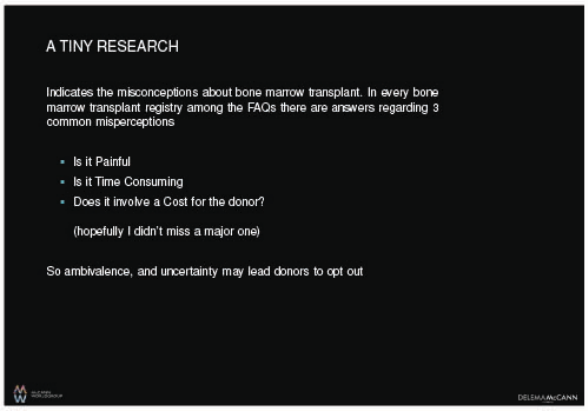
COMSCORE TELLS US

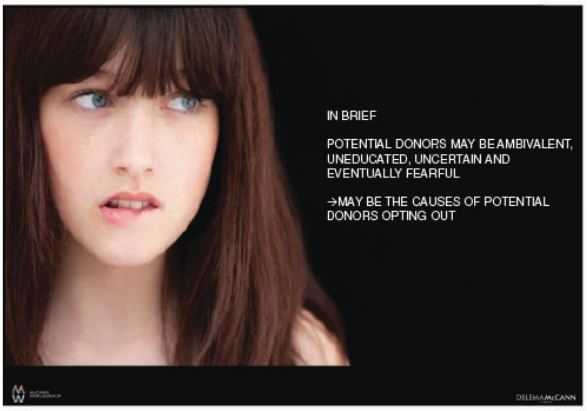
Virtually All Time Spent on Social Networking in Latin America is on Facebook



THE USE OF SOCIAL MEDIA







THE USE OF SOCIAL MEDIA

PUTTING SOCIAL MEDIA TO USE

We want to:

- Shout out how important it is for organizations such as yours to exist!
  We must keep serving this holy cause
- Build awareness and influence.
  Educate and Spread the word about donating bone marrow
- Bring aboard "ambassadors" and expand your reach.
  Ambassadors will continue to "evangelize" and broaden your audience
  (people tend to trust friends more than they trust an ad)

Heroes are those who choose to save a life even if their efforts fail to do so.
Give life a chance!

DELEMA/McCANN

STRATEGY

DELEMA/McCANN

SETTING UP YOUR STRATEGY

When our core target audience we want is aged 18-44 (best chances of a successful transplant),

SM is a must.

So before setting up accounts and starting to experiment we need to setup our strategy and our goals.

STEPS Strategy Formation:

Step1:

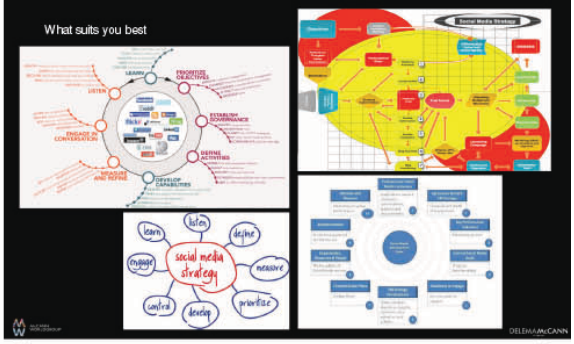
Step2:

...hmmm

DELEMA/McCANN

MODELS FOR EVERYONE

What suits you best



DELEMA/McCANN

SETTING UP YOUR STRATEGY

Your organization setup is key to how you will setup your strategy

How you are setup – strategies need to fit into organizations – NOT THE OTHER WAY AROUND

In brief:

STEPS Strategy Formation:

Step1: Define your vision.
Step2: Define your goals
Step3: Set your tactics
Step4-5: Execute, Listen, Measure & re-evaluate

DELEMA/McCANN

SETTING UP YOUR STRATEGY

STEPS Strategy Formation:

Step1: Define your vision.
The first step to successfully working social is to define your goals. What do you and your team want to accomplish? Where do you want to go, what is your vision

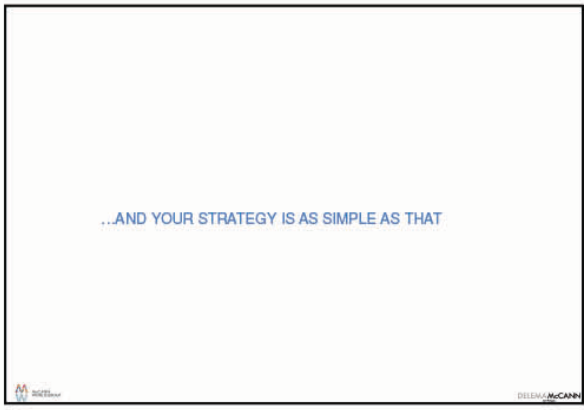
Step2: Define your goals

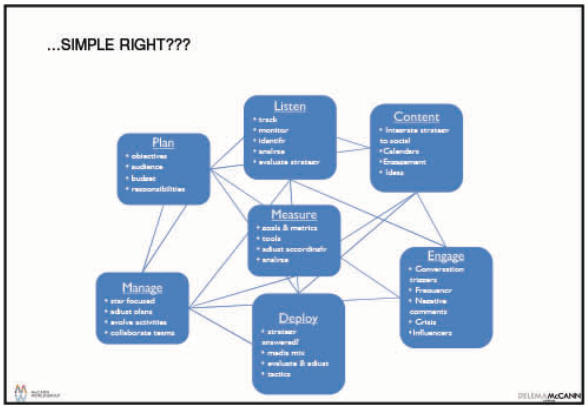
Step3: Set your tactics

Step4-5: Execute, Listen, Measure & re-evaluate

DELEMA/McCANN

THE USE OF SOCIAL MEDIA





THE USE OF SOCIAL MEDIA

WHAT EACH CHANNEL IS BEST USED FOR

FACEBOOK	TWITTER	YOUTUBE	GOOGLE+
This is the **dominant** Social Media used with approx 70% account ownership and around 50% the world's active internet users	Twitter is best used for short information 'shots'. Best in terms of response time. Consider it as your short news channel	YouTube is the second largest search base in the world.	Has a large number o f visits with activities generated from google services (such as gmail)
Best used for social engagement!	Tweet to update. (140 chars)	Build your own video library and group it in a channel.	Best used for sharing photos, videos
Tell a Story!	Quickly update	Centralized attraction	...linkedin., pinterest etc

In General usage of social networks by older users is increasing!

Age profiles of 35-44 , 45-54 and 55-64
all three have above 120% increase in facebook, twitter, g+

FACEBOOK - STORYTELLING

Use Facebook to tell a story

This is the place were your biggest engagement will occur. This is the social media were users are most likely to interact with you by liking, commenting, sharing or even simply reading.

Facebook will let you BOND with users and this should be your primary weapon to engage users, expand your reach, educate ignorance

→ establish emotional connection

How:

- Stories
- Examples
- Testimonials
- Videos

TWITTER – NEWS/UPDATE "SHOTS"

Use Twitter to quickly update and communicate news.

39% of Twitter users said most of the news they got on twitter was material they wouldn't have read elsewhere (Pew Research Center's Project for Excellence in Journalism)

Use influential people (held high) to talk about your cause.

Give updates from ongoing efforts (inform your audience about real results)

- An example could be to focus on how you could make a difference.

(or even engage by shocking – if you have approximately 100 followers on twitter probably 3 of them will get cancer! Join now!)

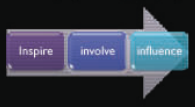
- Or even give a simple update – #Madeline, age 3 is looking for a bone marrow donor. Donate today @donateRgistry! with an update Madeline

YOUTUBE – THE POWER OF VIDEO

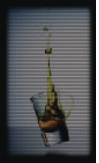
Create your channels and setup your own library.

Dedicated content to your cause (centralized)

Build a YouTube campaign and help people get inspired and more sensitive



- Example
  Video activity that focuses on a real case study of life saving through donation (modern days hero's).
- Ask people to share cases they know that may not be that known.

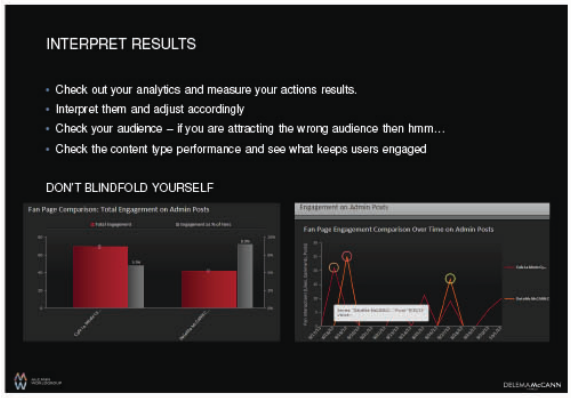


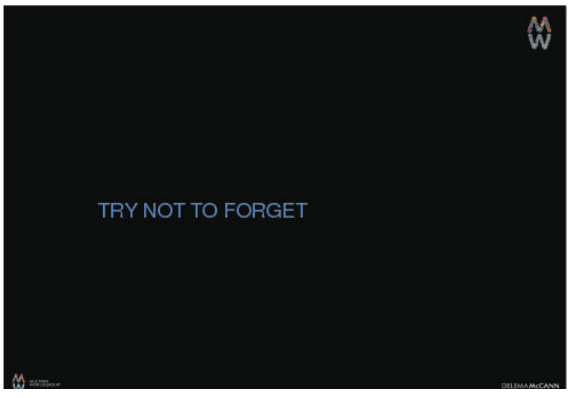
WHATEVER YOU DO... REMEMBER

Link them together | **Actions Need to be Integrated**

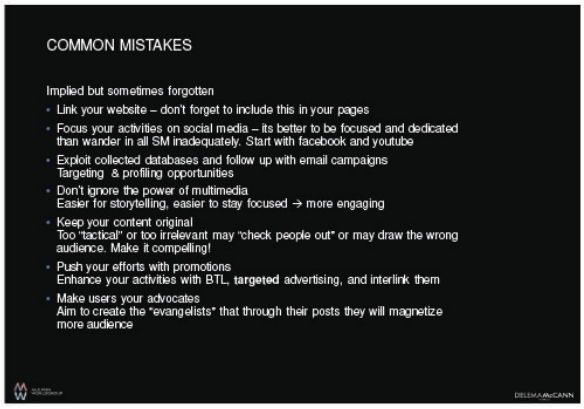
AHA ...THEN

THE USE OF SOCIAL MEDIA





THE USE OF SOCIAL MEDIA



PRESENTATION SUMMARIES

MACHTELD OUDSHOORN– CLINICAL DIRECTOR AT EUROPDONOR, CHAIR OF BMDW, CHIEF EXECUTIVE OFFICER OF WMDA, THE NEHERLANDS

Abstract

Title: Selecting the Best Matched Donor

Allogeneic HSCT is a curative procedure for patients with a variety of fatal blood diseases. To provide the best chance for an optimal outcome to a transplant, the patient and the donor must express the same histocompatibility molecules on their cell surfaces. Because of the extensive allelic diversity in the human population, patients are most likely to find a match among their siblings. However, most patients do not have a matched sibling thus require a search for a matched unrelated donor. Many countries have established registries of volunteer donors. These donors are listed in BMDW. BMDW provides tools to perform an initial search in order to assess the likelihood of identifying a matched donor and to determine which registries to approach for further testing of donors.

Selecting donors requires extensive knowledge at HLA. A donor search strategy starts with evaluating whether the patient's HLA assignments are complete. For potential 8/8 matches the typing must include HLA-A, -B, -C and –DRB1. In case of 10/10 matches the HLA-DQB1 loci also needs to be determined. The typing level of the patients needs to be adequate this means at least a high resolution typing assignment (exon 2 and 3 for HLA class I and exon 2 for HLA class II). One has to identify any uncommon or unexpected HLA assignments and have them confirmed either by family typing or by repeating the typing with a different typing technique. The frequency of the HLA alleles and HLA haplotypes has to be established and determined in which ethnic populations they occur with highest frequency. Once this has been done a donor search can be started. When the BMDW search report does not yield donors who potentially match the patient a strategy to locate the best potential mismatch needs to be implemented. In order to select donors one needs to know the answers to the following questions:

- Are some loci more important to match for than others?
- How do antigen mismatches compare to allele mismatches?
- What is the effect of multiple mismatches?
- Is the direction of mismatch important?

Biography

Machteld Oudshoorn received her M.Sc. in Chemistry at the State University, Leiden, The Netherlands, in April 1981, and her Bachelor in Medicine at the same university in September 1981. She completed her Ph.D. at the Department of Clinical Science and Immunology, Faculty of Medicine, University of Cape Town, South Africa, in June 1989. The title of her thesis was "Investigations into the complexity and polymorphism of HLA-D loci in South Africa".

Machteld Oudshoorn is an associate professor at the Department of Immunohematology and Blood Transfusion at the Leiden University Medical Center as well as Clinical Director of the Europdonor Foundation which is the Dutch Hematopoietic Stem Cell Donor Registry. She is the Chairman of the

PRESENTATION SUMMARIES

Board of Bone Marrow Donors Worldwide (BMDW), the worldwide file of unrelated donors and cord blood units, and the Chief Executive Officer of the World Marrow Donor Association (WMDA).

She is a member of the Immunobiology Working Party of the European Group for Blood and Marrow Transplantation (EBMT), a Member of the Immunobiology Working Committee of the CIBMTR and a member of the bioinformatics research advisory group of the National Marrow Donor Program. Machteld Oudshoorn is also a member of the Haemato Oncology Foundation for adults and a member of the HLA working group, both in the Netherlands.
In addition she is a HLA Search Advice Consultant for the South African Bone Marrow Donor Registry, located in Cape Town, South Africa.

SELECTING THE BEST MATCHED DONOR

SELECTING THE BEST MATCHED DONOR

COLLECT INFORMATION ON PATIENT

- HLA typing data
- Patient's HLA haplotypes if possible
- Data of birth
- Diagnosis and date
- Ethnicity
- Gender
- Weight
- CMV status
- ABO

CRITERIA TRANSPLANT CENTER PROTOCOL

- PBSC / BM
- CB single / double
- Urgency of search
- Specific HLA loci to be considered 4 or 5?
- Are mismatches acceptable?

EVALUATE THE PATIENT HLA TYPING. IS HLA TYPING SUFFICIENT TO START SEARCH?

Patient typing:
A*02:05, 68:04; B*35:DSGG, 53:01; C*04:01, 07:01
DRB1*03:01, 13:03; DQB1*02:01, 03:01

- search for a 10/10 match need 5 loci tested (HLA-A, -B, -C, -DRB1, -DQB1)
- search for a 8/8 match need 4 loci tested (HLA-A, -B, -C, -DRB1)

EVALUATE THE PATIENT HLA TYPING. IS RESOLUTION OF TESTING SUFFICIENT?

Patient typing:
A*02:05, 68:04; B*35:DSGG, 53:01; C*04:01, 07:01
DRB1*03:01, 13:03; DQB1*02:01, 03:01

- B*35:DSGG = B*35:01 / B*35:42/ B*35:57 / B*35:94. Multiple allele code can be found using DNA Type Look-up Tool (http://Bioinformatics.nmdp.org)
- All possible B*35:DSGG alleles share the sequence of exon 2 and 3 = Same Antigen Recognition Site (ARS)

EVALUATE THE PATIENT'S HLA TYPING. EVALUATE THE FREQUENCY OF ALLELES.

Patient typing:
A*02:05, 68:04; B*35:01, 53:01; C*04:01, 07:01
DRB1*03:01, 13:03; DQB1*02:01, 03:01

A*68:04 is uncommon.

- See rare allele list on http://Bioinformatics.nmdp.org or www.allelefrequency.net.
- Found once in African American, three times in Caucasian and one in other population.
- Has A*68:04 been confirmed in family? If not repeat HLA typing with different typing method.

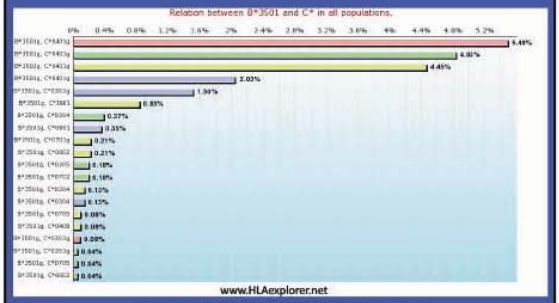
SELECTING THE BEST MATCHED DONOR

EVALUATE THE PATIENT'S HLA TYPING. EVALUATE HLA ASSOCIATIONS.

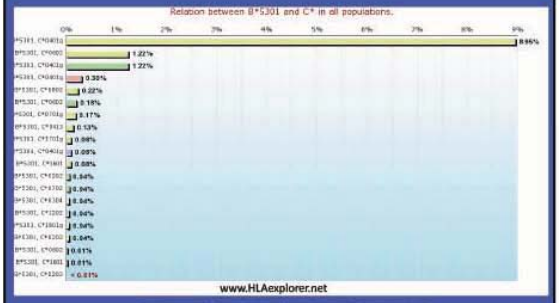
Patient typing:
A*02:05, 68:04; B*35:01, 53:01; C*04:01, 07:01
DRB1*03:01, 13:03; DQB1*02:01, 03:01

- B-C;
  Concordant with family typing?
  Common or uncommon?

B*35:01



B*53:01



EVALUATE THE PATIENT HLA TYPING. EVALUATE FREQUENCY OF PATIENT'S HAPLOTYPES.

Patient typing:
A*02:05, 68:04; B*35:01, 53:01; C*04:01, 07:01
DRB1*03:01, 13:03; DQB1*02:01, 03:01

- Use www.Haplostats.org or www.hlaexplorer.net
- A*02:05, B*53:01, C*04:01, DRB1*03:01
  HF = 0.0300 in African American
- A*68:04, B*35:01, C*07:01, DRB1*13:03 unknown

DONOR SELECTION IN STEM CELL TRANSPLANTATION QUESTIONS TO ANSWER

- Which loci should be evaluated for HLA matching?
- Are some loci more important than others?
- How do antigen mismatches compare to allele mismatches?
- What is the effect of multiple mismatches?
- Is the direction of mismatch important?

HLA AND OUTCOME STUDIES FROM THE CENTER FOR INTERNATIONAL BLOOD AND MARROW TRANSPLANT RESEARCH (CIBMTR)

I. Lee et al. 2007, Blood 110: 4576
   - N = 3,857
   - Leukemia and MDS
   - 92% BM; 8% PBSC
   - 100% Myeloablative conditioning regimen
   - Period: 1988-2003

II. Woolfrey et al. 2011, Biol. Blood marrow Transplant 17:885
   - Leukemia and MDS
   - N = 1,933
   - 100% PBSC
   - 65% myeloablative; 35% RIC/NM
   - Period: 1990-2006

SELECTING THE BEST MATCHED DONOR

EFFECT OF SINGLE HLA LOCUS MISMATCH ON SURVIVAL

	CIBMTR (BM)			CIBMTR (PBSC)		
	n	RR	p value	n	RR	p value
8/8	1840	1.00	-	1243	1.00	-
A mm	274	1.36	< 0.001	136	1.17	0.19
B mm	116	1.16	0.20	73	1.22	0.19
C mm	478	1.19	0.006	Allele 61 Antigen 189	0.82 1.41	0.30 0.0005
DRB1 mm	117	1.48	0.001	39	1.30	0.20

IMPACT OF SINGLE ALLELE AND ANTIGEN MISMATCHES ON MORTALITY

Low-risk Disease with a Single Mismatch
- allele HR 2.44, 1.41 – 4.22
- antigen HR 2.15, 1.28 – 3.60

Higher Risk Disease with a Single Mismatch
- allele HR 1.02, 0.70 – 1.48
- antigen HR 1.12, 0.86 – 1.47

Petersdorf et al Blood, 104: 2976, 2004

SINGLE ANTIGEN VS ALLELE MISMATCH

Lee et al. Blood 2007

No statistical difference if mismatched at antigen or allele level except for HLA-C where an antigen mismatch is worse than allele mismatch

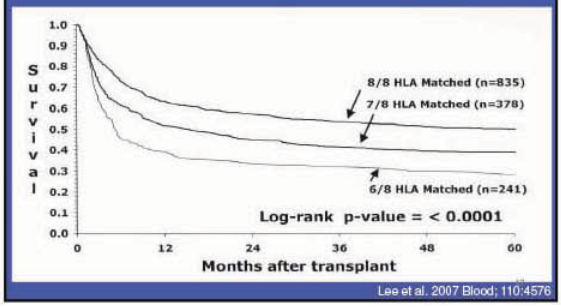
Woolfrey et al. Biol. Blood Marrow Transplant 2011.

HLA-C antigen mismatch is associated with worse outcome.

No statistical difference in outcome for HLA-C allele.

WHAT IS THE EFFECT OF MULTIPLE MISMATCHES?

SURVIVAL OF PATIENTS WITH EARLY STAGE DISEASE DEPENDING ON DEGREE OF HLA MATCHING FOR HLA-A, -B, -C, -DRB1



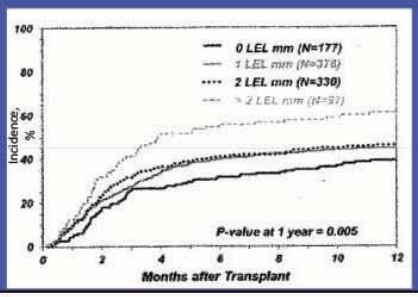
Lee et al. 2007 Blood; 110:4576

WHAT IS THE IMPACT OF MISMATCHES AT LOW EXPRESSION HLA LOCI –DP, -DQ AND –DRB3/4/5 ON TRANSPLANT OUTCOME?

FERNANDEZ-VIÑA ET AL. 2013, BLOOD 121: 4603

SELECTING THE BEST MATCHED DONOR

INCIDENCE OF TRM AS A FUNCTION OF DEGREE OF MISMATCHING AT HLA-DRB3/4/5, -DQ AND –DP (LEL) LOCI IN TRANSPLANTS MATCHED IN 7/8 ALLELES OF HLA-A, -B, -C AND –DRB1 LOCI



WHAT IS THE IMPACT OF HLA UNIDIRECTIONAL MISMATCHES ON THE OUTCOME OF MYELOABLATIVE HSCT?

HURLEY ET AL. 2013, BLOOD; 6: 4800

DIRECTION OF HLA MISMATCH AND TRANSPLANT OUTCOME

Outcome	7/8 HvG	7/8 GvH	7/8 Bidirectional
Overall survival	1.37 (1.04 – 1.81), p=0.03	1.67 (1.27 – 2.18), p=0.0002	1.29 (1.15 – 1.46), p<0.0001
TRM	1.44 (1.05 – 1.97), p=0.025	1.82 (1.37 – 2.42), p<0.0001	1.56 (1.36 – 1.79), p<0.0001
Relapse	1.38 (0.97 – 1.95), p=0.07	1.11 (0.76 – 1.63), p=0.60	0.98 (0.84 – 1.16), p=0.83
Acute GvHD III	0.83 (0.55 – 1.27), p=0.39	1.92 (1.40 – 2.62), p<0.0001	1.61 (1.38 – 1.88), p<0.0001
Graft failure	1.21 (0.43 – 3.40), p=0.71	1.97 (0.88 – 4.41), p=0.10	1.66 (1.12 – 2.45), p=0.011

(8/8 matched = Reference value): P< 0.01 threshold for statistical significance.
HR (95% CI), p value.

Hurley et al. 2013, Blood, 121: 4800

CONCLUSIONS I

- Invest time to critically look at patient's HLA typing.
- Pay attention to HLA allele frequencies and HLA associations.
- Select the "best" mismatched donors if no matched donors are available:
  - BM: mismatch HLA-B or –C
  - PBSC: avoid HLA-C antigen mismatches.

CONCLUSIONS II

- Try to match for HLA-DPB1, -DQB1 and HLA-DRB3/4/5 in case of 7/8 mismatched donor.
- For recipients HLA homozygous at a locus a single HvG mismatch is preferred over bi-directional mismatch.
- Avoid mismatches to which the patient is sensitized.
- Do not continue searching endlessly.
  Consider alternative cell source (cord, haplo-identical) or non-transplant option

QUESTIONS?

SELECTING THE BEST MATCHED DONOR

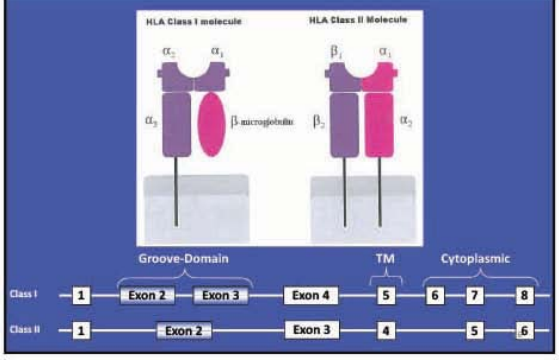
THE IMPORTANCE OF HLA-DPB1 IN UNRELATED DONOR HSCT

SHAW ET AL. 2007, BLOOD, 110: 4560

	Grades II-IV Acute GvHD	Relapse	Overall Mortality
Matched at HLA-DPB1	1	1	1
Mismatched at HLA-DPB1	1.33 (1.18-1.51, p<0.0001)	0.78 (0.67-0.92, p=0.002)	1.09 (0.99-1.19, p=0.07)
1 allele mismatched	1.31 (1.14-1.49, p=0.0001)	0.79 (0.67-0.93, p=0.005)	1.08 (0.98-1.19, p=0.13)
2 alleles mismatched	1.36 (1.18-1.58, p<0.0001)	0.76 (0.64-0.91), p=0.003)	1.09 (0.98-1.21, p=0.11)

Adjusted for: severity of diseases, patient age, number of mismatched HLA alleles, patient/donor gender and CMV, stem cell source, use of T-cells depletion.

HLA CLASS I AND II



PRESENTATION SUMMARIES

DAVID STEINER– MANAGER OF STEINER, LTD, CZECH REPUBLIC

Abstract

Title: The Impact of EMDIS on Donor Search

Reliable communications and data transfer of donor, patient records between all partners is one of the most important success factors in HSCT. The internet gives us great opportunities in registry to registry connections, including the software support of the whole process - from the preliminary search to transplant.
EMDIS (European Marrow Donor Information System) is an open computer network for data exchange among donor registries. Today, it covers 75% of all potential unrelated donors and CBUs registered in BMDW. The EMDIS community provides documentation, status information, software tools, support and a project management platform. The decrypted content of an EMDIS message is a text in special format, called the Flexible Message Language (FML). EMDIS emails are not read by humans, but computer systems that parse the FML text into elemental attributes and data fields that are further processed. The most advanced feature in EMDIS is the donor search process. When a national registry initiates an international donor search for a specific patient, its data is broadcasted to other EMDIS registries. Every recipient makes a donor search in the local database using its own algorithm and technology and replies with a set of potential donors. Then the requesting registry composes these partial results into one global EMDIS search result. In praxis, these results are received within several hours. The speech will describe the EMDIS network structure (theoretical vs. real connectivity), how effective it is, how important it is for effective searches and what are the main challenges.

Biography

David Steiner graduated in Computer Science from the Charles U. in Prague (2005). Then he studied IT at the ISAIP School in Angers, France. He graduated in Software Engineering from Czech Technical University in Prague. He finished his study by the diploma thesis: “Search for Unrelated Bone Marrow Donors” (2007). He complted MBA study at the U. of Lyon, France (2010) currently finishing PhD. at CTU. His doctoral thesis is “Probabilistic Matching in Search for Unrelated Stem Cell Donors”. He is member of the Biomedical Data Processing Group at the Department of Cybernetics of CTU. Since 2008, he is the manager of Steiner, Ltd. His team develops, maintains and supports software systems for stem cell donor registries, HLA laboratories and harvesting centers in more than 30 countries.

THE IMPACT OF EMDIS ON DONOR SEARCH

Impact of EMDIS on Donor Search

David Steiner

Cyprus

4th October 2013

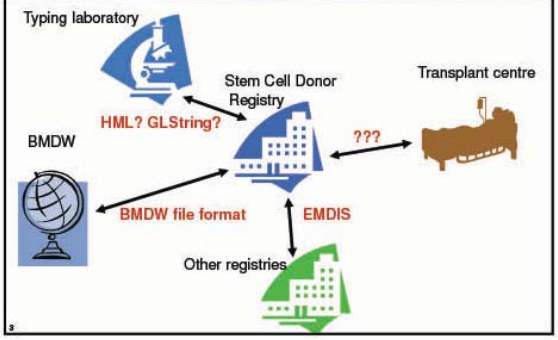
1

Content

- What is EMDIS?
- EMDIS search
- Challenges
- GEMS
- Future

2

Communication overview

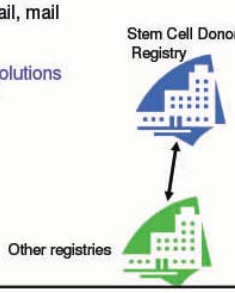


3

Communication overview

Classic solutions
• fax, email, mail

On-line solutions
• EMDIS



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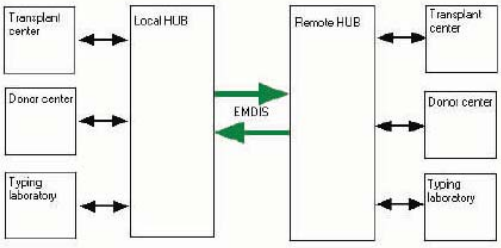
Communication overview



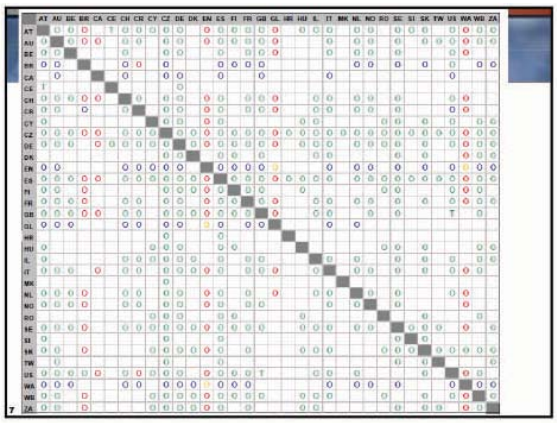
5

EMDIS

- Idea: single virtual international registry
- 85 % of the donors worldwide
- Whole process from preliminary search to donor workup
- It doesn't replace BMDW, search coordinators use both
- New features, development and maintenance (User Group and Technical Group)
- Only rules and communication protocol between registries

6

THE IMPACT OF EMDIS ON DONOR SEARCH



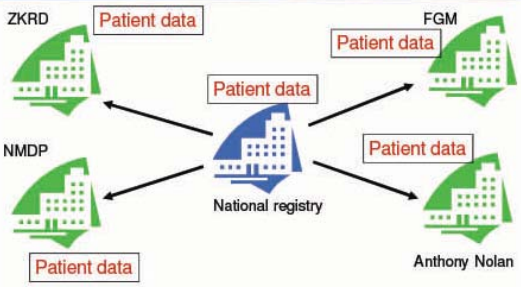
EMDIS Messages (1/2)

Message	Description
PAT_UPD	New patient registration
PAT_STAT	Patient status change
PAT_ALTPH	Patient alternative phenotype registration (not used)
DONOR_CB	List item of convenient donors for patient (one donor or cord blood)
PHEN_LIST	List item of convenient phenotypes for patient (one phenotype).
MATCH_SUM	Summary of search result for patient.
TYP_REQ	Request of further donor type testing.
TYP_RES	Result of further donor type testing
SMP_REQ	Request of sending of donor blood sample.
SMP_ARR	Supposed date of delivery of donor blood sample.
SMP_RES	Sample test result.
IDM_REQ	Request of sending of infectious illness sample.
IDM_RES	Result of request of sending of infectious illness sample.

EMDIS Messages (2/2)

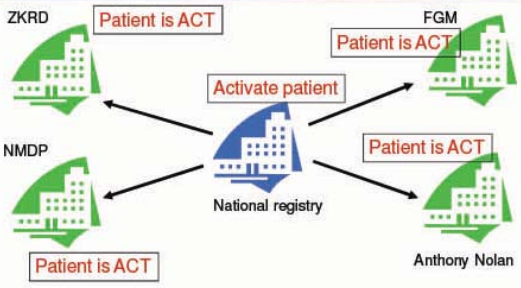
Message	Description
RSV_REQ	Request of donor reservation for transplantation purpose.
RSV_RES	Result of reservation.
REQ_CAN	Request cancel.
WOR_REQ	Request of starting work on transplantation.
MARR_STAT	State of „work" with donor.
NEW_ADD	Register data update.
MSG_DEN	Request rejection.
WARNING	Warning message.
TXT_MSG	Text message.
DON_UPD	Donor downloading. (not used)
SEA_RES	Search result. (not used)
NO_RES	No result. Service cannot be settled.
MSG_ACK	Received messaged confirmation.
RES_REM	Unsettled request remind.
ALM_REQ	Donor alternative phenotype reservation.
ALM_RES	Same as DONOR_CB, but it is used as answer to ALM_REQ
CBR_REQ	Request of supplemental information about Cord blood unit

EMDIS – preliminary request

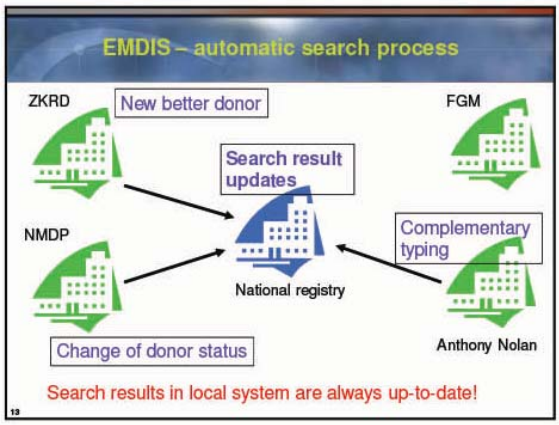


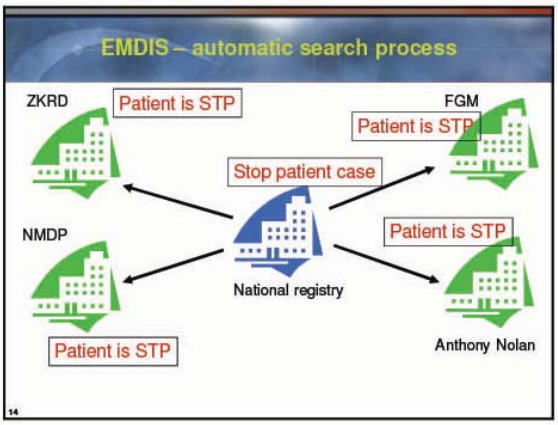
EMDIS – automatic search results

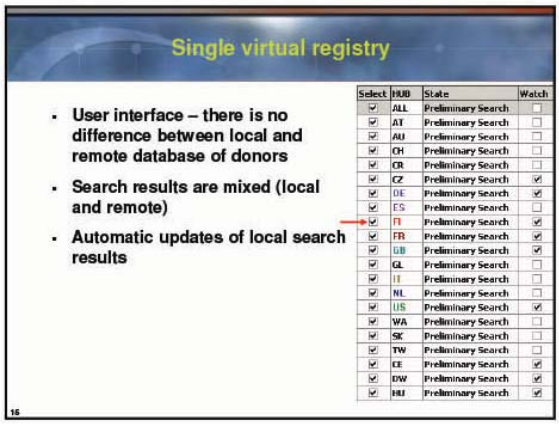
EMDIS – automatic search process

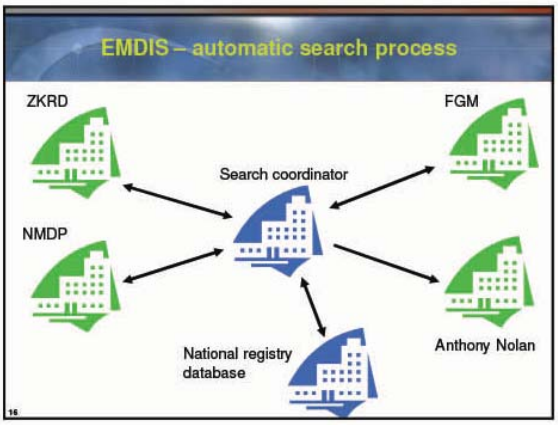


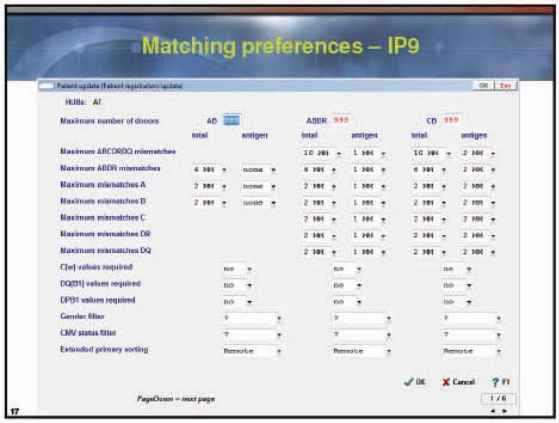
THE IMPACT OF EMDIS ON DONOR SEARCH

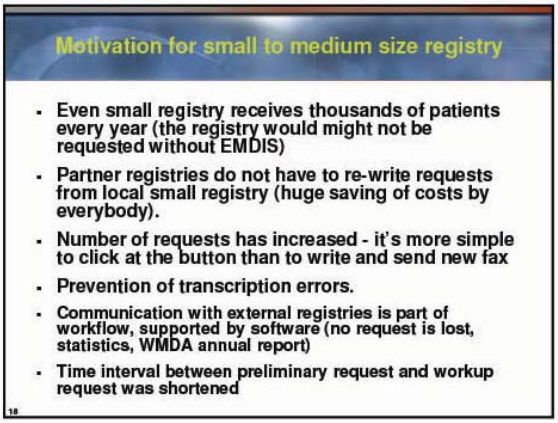












THE IMPACT OF EMDIS ON DONOR SEARCH

NMDP – Cooperation with international registries (Michael Boo, 3rd October 2013)

Issues

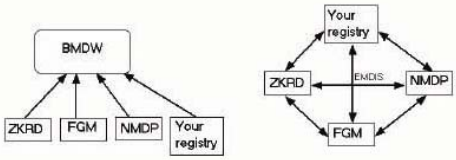
- Unique requirements for each registry
- Unpredictable performance
- Lack of transparency
- Off hours delivery

Needs

- As close to upfront search as possible
- Same processes wherever possible
- Standardise electronic connections

19

BMDW and EMDIS models



20

Multiple systems, different implementations

BMDW, EMDIS, Netcord, Traxis, etc.

- How do I get one integrated report?
- Why I don't see donor that I see in BMDW?
- How to get MM donors?
- Why I get donor that doesn't fit to matching preferences?

WMDA Matching Validation Project

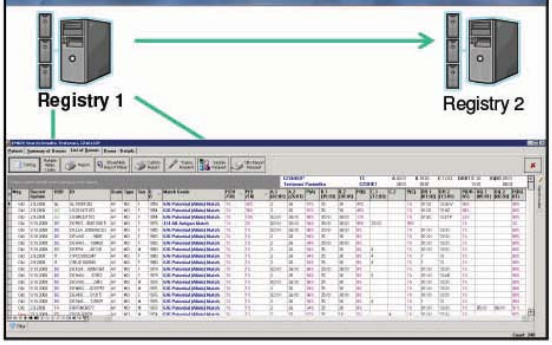
21

EMDIScord

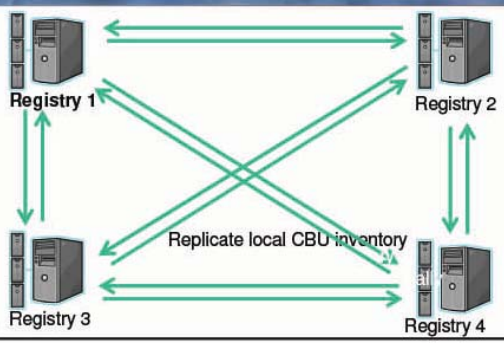
- **The goal of EMDIS-cord, based on the sharing of Cord Blood Unit (CBU) data, is to provide global CBU searching that is:**
  - **Current** (up to date inventory),
  - **Comprehensive** (all relevant fields → increase in EFFICIENCY),
  - **Real-time** (updating of data available everyday on line → increase in SPEED).
  - **Integrated results** (data from all participating registries in one list)

22

EMDIS – CBU search



EMDIScord – CBU search



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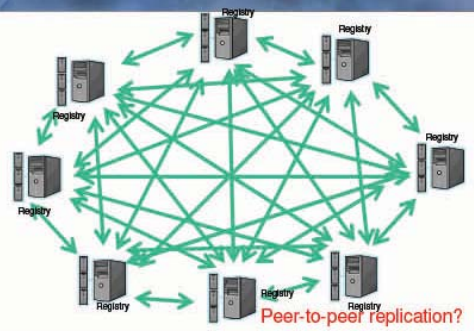
THE IMPACT OF EMDIS ON DONOR SEARCH

EMDIScord mirroring



25

NMDP – Michael Jones: Future Business Collaboration Networks

- Use EMDIS Cord – Mirror a registry
- Implement B2B Solution
  - Gateway
  - Hosted
- US-FR cord mirroring … increased activity

26

Current and future development

- Real-time and consistent search – option to run the search by remote or local algorithm
- EMDIScord
- EMDISdonor?

27

Current and future development

- Real-time and consistent search – option to run the search by remote or local algorithm
- EMDIScord
- EMDISdonor?
- Proxy model? – AU, DE, US
- Gateway model? – Prometheus
- Comprehensive – data model:
  - Cords: EMDIScord dataset
  - Donors: Gender will be required (IP10)

28

- Thank you for your attention!

29

PRESENTATION SUMMARIES

ALEXANDROS SPYRIDONIDIS– HEAD OF THE BMT AND LEUKEMIA PROGRAM, UNIVERSITY HOSPITAL OF PATRAS, GREECE

Abstract

Title: When a Haploidentical Donor Becomes an Option

Over 25.000 allogeneic HSCT are performed yearly worldwide. For approximately 70% of patients who lack an HLA matched sibling, the alternate sources are either, from unrelated volunteer donors, stored CBUs or haploidentical relatives. The expanding volunteer donor pool with the improved outcomes due to the better (HR) HLA matching of donor and patient resulted to the establishment of the well-matched unrelated HSCT as the standard and equal alternative for these patients. To date, unrelated donor transplant activity has surpassed the number of sibling donor transplants. However, despite the remarkable increase in the donor pool, the improvement in the speed of the search process and of graft transport to the TC, ethnic minority background and urgency of transplantation still remain obstacles that hinder 30% of patients to undergo unrelated HSCT. The goal is to close the gap in donor availability and to be able to treat all patients in need of HSCT in a timely manner. Practically, this can only be achieved using a haploidentical family member (sibling, children, or parents) as the donor. Based on the encouraging safety and efficacy data of this protocol one can ask if in the future the unmanipulated haploidentical transplantation with post-transplant cyclophosphamide will become the standard option not only for patients who lack a suitable unrelated donor but also for the ones who lack a sibling matched donor, replacing this way the need for an unrelated donor search. Donor registries should face this challenge by improving the unrelated donor search procedure.

Biography

Dr. Spyridonidis is Associate Professor of Hematology in Med. School of U. of Patras and Clinical Program Director of BMT and Leukemia Program at Patras University Hospital, Greece. He is certified in Internal Medicine, Hematology and Oncology. After completing his medical studies in Greece, he moved (1995-2005) to the Dept. of Hematology/Oncology of Freiburg U., where he completed his PhD. He received the *VeniaLegendi* (Assistant Professorship) of the U. of Freiburg in 2004. In 2006, he was appointed Assistant Professor at the U. of Patras where he established a full accredited Allogeneic HSCT Program, performing all types of transplants (related, unrelated, haploidentical). He established the BMT Lab and BMT Research Group. He founded the non-profit, non-governmental "Centre to Advance Public Awareness and Recruitment of Bone Marrow Donor Volunteers U. of Patras (CBMDP) registered in BMDW.

WHEN A HAPLOIDENTICAL DONOR BECOMES AN OPTION

1st International Workshop
Challenges and Opportunities for the small and medium size bone marrow donor registries
Paphos, Cyprus 2013

When a Haploidentical Donor Becomes an Option

Alexandros Spyridonidis, MD, PhD
Associate Professor
Head of the Bone Marrow Transplantation and Leukemia Program
Scientific Director of CBMDP (GR-2)
University of Patras, Greece

1

No disclosures

2

Overview

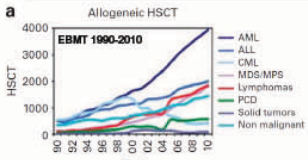
- ❑ HSCT Activity with focus on donor sources
- ❑ Alternative Donor sources:
  - ❑ Is there a consensus?
  - ❑ Focus on haplo option

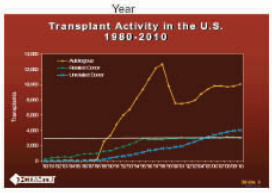
3

HSCT Activity

4

Allo- HSCT Activity is increasing





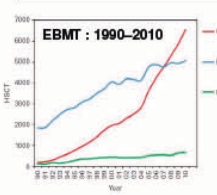
EBMT 1990-2010
❑Allo- HSCT: 135.179
BMT: 43%, PBSCT: 55% CB:2%

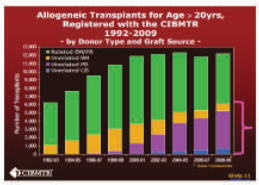
EBMT 2010 (390 allo- centers)
❑Allo-HCT:13.345
BMT: 22%, PBSCT: 71% CB:6%

Worldwide 2010:
approx . 30.0000 allo HCT

5

HSCT Activity / Donor source





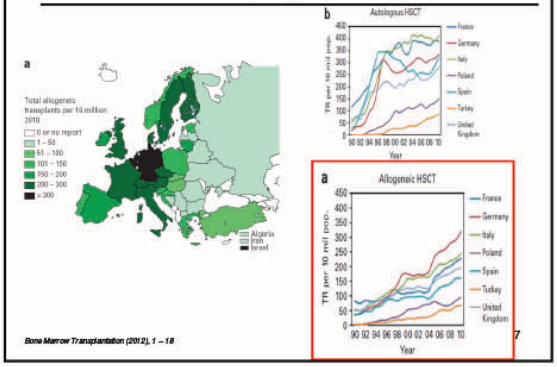
Improved Survival with Unrelated HSCT

Report	Period	1-Year OS
2010	2004-2008	57.9%
2009	2003-2007	56.3%
2008	2002-2006	54.0%
2007	2001-2005	51.5%
2006	2000-2004	48.5%
2003	1998-2001	42.2%

6

When a Haploidentical Donor Becomes an Option

HSCT Activity / country

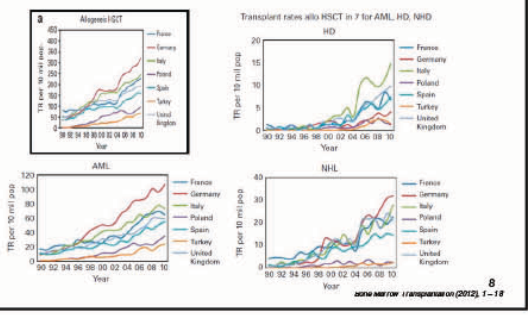


Bone Marrow Transplantation (2012), 1 – 18

7

HSCT Activity / country: Indication

The EBMT activity survey: 1990–2010
(In seven countries with a population >20 million)



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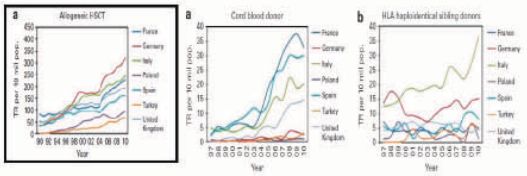
Bone Marrow Transplantation (2012), 1 – 18

HSCT Activity / country: Donor source

The EBMT activity survey: 1990–2010
(In seven countries with a population >20 million)



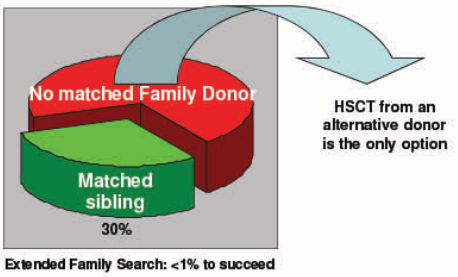
Bone Marrow Transplantation (2012), 1 – 18

Alternative transplant donor sources:

is there Consensus?

10

Donor sources for allogeneic HSCT

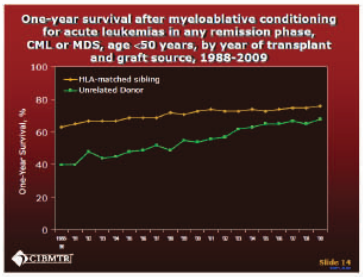


Extended Family Search: <1% to succeed

11

Transplant Outcomes

Sibling Donor =
Well Matched Unrelated Donor (8/8 or 9/9)



12

WHEN A HAPLOIDENTICAL DONOR BECOMES AN OPTION

The „real world" data

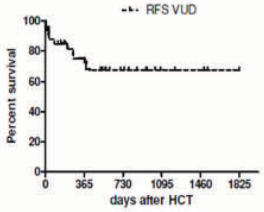
Pharmacokinetics and clinical activity of very low-dose alemtuzumab in transplantation for acute leukemia

A Spyridonidis, M Liga, E Triantafyllou, M Themeli, M Marangos, M Karakantza and N Zoumbos

Department of Internal Medicine, Hematology Division, BMT Unit, University Hospital of Patras, Rio/Patras, Greece

Alemtuzumab: 10-20 mg

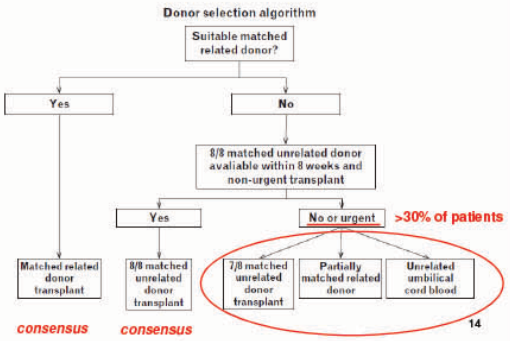
Type of transplant	Total (n= 66)
Matched sibling	30
Unrelated Donor	36
Mismacthed UD (7/8) HLA A/ B/ C/ DRB1	20 (6/4/10/-)



Bone Marrow Transplantation (2011) 46, 1363–1368

13

Donor selection algorithms: Is there a consensus?



14

Choice of Alternative Donor Source: Factors influencing decisions

- ❑THE SOURCE WITH THE BEST OUTCOME
  - ❑No randomized studies
- ❑Diagnosis
- ❑Urgency of transplant
- ❑Age
- ❑MMUD: locus? (DPB1, anti-HLA)
- ❑CB: cell dose, HLA mismtaches, (anti-HLA)
- ❑Haplo: NK alloreactivity, technical expertise,(anti-HLA)
- ❑Registry
- ❑Center Preference / Experience
- ❑Costs

15

Clinical Case (U Patras)

- ❑ 34 y old patient
- ❑2010: AML, inv 16 → CR-1
- ❑2012: Relapse → CR2-2
- ❑Referred for HSCT to Patras
  - ❑No siblings
  - ❑Unrelated donor search: No 8/8 matched donor
  - ❑**Alternative Donor Source**
    - ❑Mismatched Unrelated Donor (7/8)
    - ❑Cord Blood
    - ❑Haploidentical

16

Benefits and Risks of Each Graft Source at 2010

	Umbilical Cord Blood	Mismatched Unrelated Donor	Haploidentical Transplant
Benefit	Low Relapse	Low Relapse for High Risk Patients	Ready Availability
Benefit	Low Severe GVHD	Donor Lymphocyte Available	
Risk	Cost	GVHD	Relapse (esp RIC)
Risk	Infection	Transplant Related Mortality	Infection

17

Progress in MMUD HSCT

18

When a Haploidentical Donor Becomes an Option

Progress in MMUD HSCT: Use of proprietary in vivo T cell depletion

HLA-mismatched unrelated donors are a viable alternate graft source for allogeneic transplantation following alemtuzumab-based reduced-intensity conditioning

[1]Department of Haematology, University College London (UCL) Medical School, London, United Kingdom

Alemtuzumab: 50-100 mg

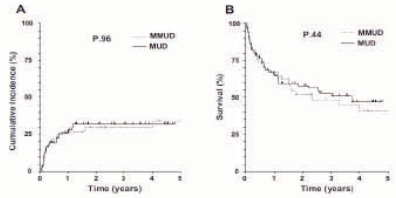


Figure 2. Survival of patients stratified according to 10/10 HLA match (MUD) or 6 to 9/10 HLA match (MMUD). (A) CI curves of TRM. (B) Kaplan-Meier curves for OS.

19

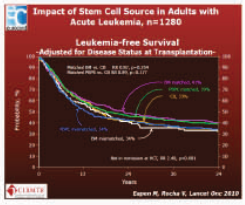
BLOOD, 24 JUNE 2010 • VOLUME 115, NUMBER 25

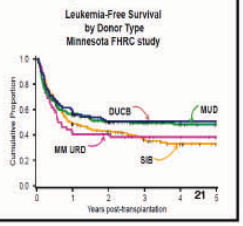
Progress in Cord Blood- HSCT

20

Progress in cord blood transplant

- By 2011 over 25.000 UCBT have been performed
- Both HLA match and cell dose are important for outcomes
- **No randomized studies** have compared UCB to other graft sources
- Results are better in children than adults
- Retrospective studies (MUD vs CB vs Haplo): **similar LFS, different outcomes**
  - **CBT: TRM higher, Low risk of GVHD and relapse**





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Future in cord blood transplant

- Ex vivo expansion to improve engraftment and immune recovery
- Direct intrabone marrow injection may speed engraftment
- Prostaglandin E2 for improvement of cord blood homing

22

Clinical Case

- 34 y old patient
- 2010: AML, inv 16 → CR
- 2012: Relapse
  - No siblings
  - Unrelated donor search: No well matched donor (8/8)
  - **Alternative Donor Source**
    - Mismatched Unrelated Donor (7/8): NOT FOUND
    - Cord Blood:
      - 2 UCB
      - 4/6 HLA matched, 4x10e7/kg TNC, 2x10e5/ kg CD34
      - Costs: 67.000 Dollars
    - Haploidentical: mother, 4/8 matched, KIR mismatched

23

Status of Haplo – HSCT 2011

24

WHEN A HAPLOIDENTICAL DONOR BECOMES AN OPTION

Problems with haplo-transplants

- Cost and technology
- Delayed immune recovery
- High rate of infections
- High transplant related mortality
- Leukemic relapse

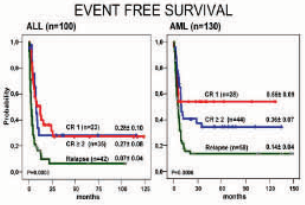
Platforms for haplo

25

Perugia Program: MEGA CD34 DOSE

1993-2005
(n=230)

EVENT FREE SURVIVAL

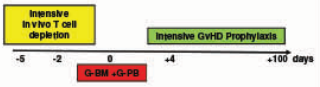


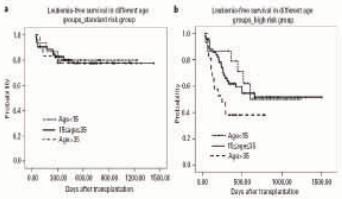
- ❑technical expertise
- ❑Cost for ex vivo T cell depletion
- ❑infections, TRM
- ❑High risk of relapse

26

Peking Program: MEGA IMS DOSE

2000-2005
(n=171)





- ❑Advantages
  - ❑No expertise
  - ❑No costs for ex vivo T cell depletion
- ❑Disadvantages
  - ❑Infections, TRM
  - ❑High risk of relapse

27

Haplo Transplant : The EBMT Experience (N=266)

A survey of fully haploidentical hematopoietic stem cell transplantation in adults with high-risk acute leukemia: a risk factor analysis of outcomes for patients in remission at transplantation

Two-year cumulative incidence

	TRM (%)		RI (%)		LFS (%)	
	AML	ALL	AML	ALL	AML	ALL
CR1	36 ± 10	61 ± 10	16 ± 10	26 ± 9	48 ± 10	13 ± 7
CR2	54 ± 5	44 ± 9	23 ± 5	27 ± 8	21 ± 5	30 ± 8
Advanced	66 ± 4	44 ± 9	32 ± 1	49 ± 9	1 ± 1	7 ± 5

Issues	Outcomes
Rejection	Minimal
GvHD	Minimal / acceptable
infections	HIGH
Relapse	HIGH *especially in ALL and in advanced disease*

28

BLOOD, 1 NOVEMBER 2006 • VOLUME 112, NUMBER 9

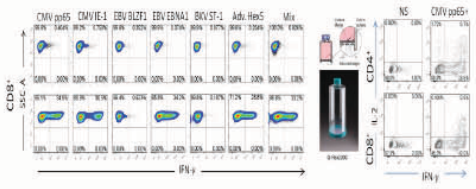
Future in haplo transplant

- Add back of suicide T cells (C Bordignon)
- Antigen specific T cell clones (H Heslop H Einsele A Velardi)
- Addition of Treg (M Martelli)
- CD19 BCD + alfa/beta TCD (R Handgretinger)

29

TRANSCELL: Univ. Patras / NIH Collaboration

❑Transfer of (multi) virus specific T cells to treat infections



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WHEN A HAPLOIDENTICAL DONOR BECOMES AN OPTION

Clinical Case

- 34 y old patient
- 2010: AML, inv 16 → CR
- 2012: Relapse
  - No siblings
  - Unrelated donor search: No well matched donor (8/8)
  - **Alternative Donor Source**
    - Mismatched Unrelated Donor (7/8): NOT FOUND
    - Cord Blood:
      - 2 UCB
      - 4/6 HLA matched, 4x10e7/kg TNC, 2x10e5/ kg CD34
      - Costs: 67.000 Dollars
  - Haploidentical: mother, 4/8 matched, KIR mismatched
    - In big and experienced centers with innovative cellular therapies

31

Progress in haplo transplant

32

The Immunobiology Working Party

Educational Event

28-29 September 2013, Perugia, Italy

Faculty of Medicine, University of Perugia

Session 1: Improving GvL while attenuating GvH reactions across HLA barriers

Chairs: Massimo F Martelli (Perugia), Maurizio Caniglia (Perugia)

- Pediatric haploidentical transplantation with TcR alpha/beta depleted hematopoietic grafts in Tübingen — *Rupert Handgretinger (Tübingen)*
- Discussion
- Pediatric haploidentical transplantation with TcR alpha/beta depleted hematopoietic grafts in Roma — *Franco Locatelli (Rome)*
- Discussion
- Haploidentical transplantation with unmanipulated G-CSF primed bone marrow and intensified immune suppression — *Willem Arcese (Rome)*
- Discussion
- Haploidentical transplantation with unmanipulated grafts and post-transplant rapamycin or cyclophosphamide — *Fabio Ciceri (Milan)*
- Discussion

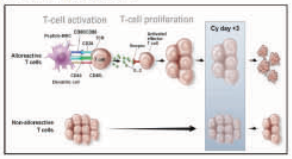
Session 1: Improving GvL while attenuating GvH reactions across HLA barriers (cont'd)

- Haploidentical unmanipulated bone marrow transplantation and post-transplantation cyclophosphamide — *Andrea Bacigalupo, Alida Dominietto (Genoa)*
- Discussion
- Haploidentical transplantation with TcR alpha/beta depleted hematopoietic grafts in adults — *Franco Aversa (Parma)*
- Discussion
- Transferring natural and adaptive immunity to improve outcomes of haploidentical hematopoietic transplants — *Andrea Velardi (Perugia)*
- Discussion
- *Coffee Break*

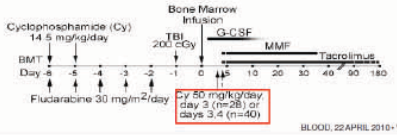
33

Progress in haplo transplant: Baltimore / Seattle

High-dose cyclophosphamide as single-agent, short-course prophylaxis of graft-versus-host disease



- Advantages
  - No expertise
  - No costs for T cell depletion
- Disadvantages
  - relapse

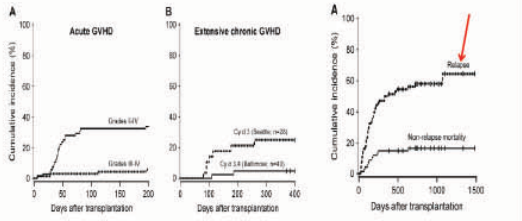


34

BLOOD, 22 APRIL 2010 • VOLUME 115, NUMBER 16

Progress in haplo transplant: Baltimore / Seattle

High-dose cyclophosphamide as single-agent, short-course prophylaxis of graft-versus-host disease



35

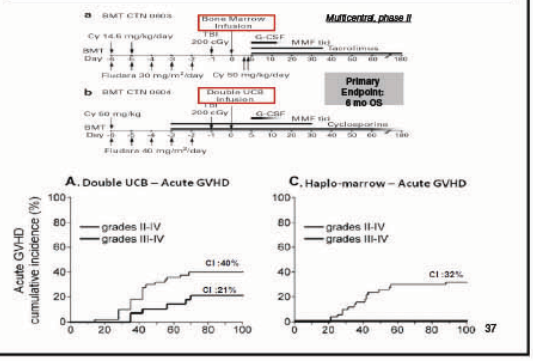
BLOOD, 22 APRIL 2010 • VOLUME 115, NUMBER 16

Is post Cyclo Haplo better than Cord Blood?

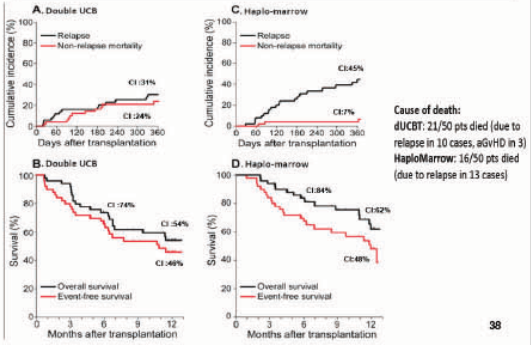
36

When a Haploidentical Donor Becomes an Option

Phase II, dUCBT vs Haplo Marrow



Phase II, dUCBT vs Haplo Marrow



Is post Cyclo Haplo better than MUD *or even MRD*?

39

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

T-Cell–Replete HLA-Haploidentical Hematopoietic Transplantation for Hematologic Malignancies Using Post-Transplantation Cyclophosphamide Results in Outcomes Equivalent to Those of Contemporaneous HLA-Matched Related and Unrelated Donor Transplantation

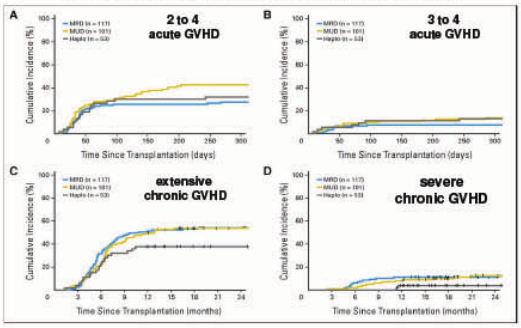
Asad Bashey, Xu Zhang, Connie A. Sizemore, Karen Manion, Stacey Brown, H. Kent Holland, Lawrence E. Morris, and Scott R. Solomon

- ❑retrospective comparison
- ❑All consecutive patients between 2005 and 2010
- ❑MRDs (n = 117),
- ❑ MUDs (n = 101)
- ❑haploidentical donors (n = 53) (If no MRD or MUD or urgent)

J Clin Oncol. 2013 Apr 1;31(10):1310-6.

40

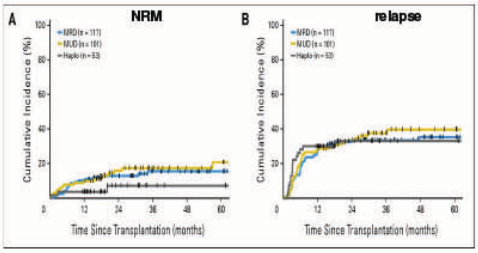
Cumulative incidence of graft-versus-host disease (GVHD) by donor type



Bashey A et al. JCO 2013;31:1310-1316

41

Cumulative incidence of nonrelapse mortality (NRM) and relapse of malignancy by donor type

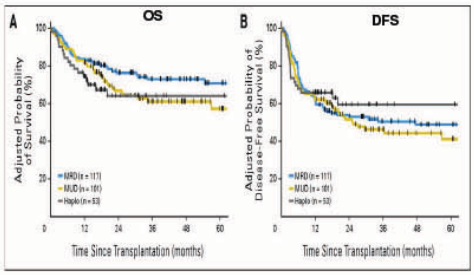


Bashey A et al. JCO 2013;31:1310-1316

42

WHEN A HAPLOIDENTICAL DONOR BECOMES AN OPTION

Adjusted estimated probabilities of (A) overall and (B) disease-free survival by donor type.



Bashey A et al. JCO 2013;31:1310-1316

43

Conclusion

Haploidentical transplantation performed using T-cell–replete grafts and post-transplantation cyclophosphamide

achieves outcomes equivalent

to those of contemporaneous transplantation performed using MRDs and MUDs.

44

Clinical Case

- 34 y old patient
- 2010: AML, inv 16 → CR
- 2012: Relapse
  - No siblings
  - Unrelated donor search: No well matched donor (8/8)

- **Alternative Donor Source**
  - Mismatched Unrelated Donor (7/8): NOT FOUND
  - Cord Blood:
    - 2 UCB
    - 4/6 HLA matched, 4x10e7/kg TNC, 2x10e5/ kg CD34
    - Costs: 67.000 Dollars
  - Haploidentical: mother, 4/8 matched, KIR mismatched
    - ~~In big and experienced centers with innovative cellular therapies~~
    - Also in small centers (the "real" world)

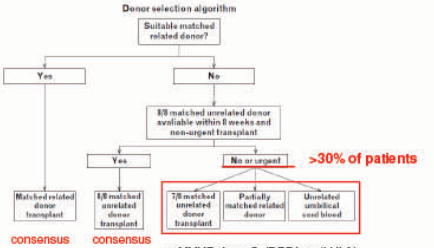
45

Clinical Case

- Conditioning: Busilvex 9.6 mg/kg, Thiotepa 20 mg/kg, Fludarabine 150 mg/m2
- GvHD Proph: Cyclophosphamide 50 mg/kg d+3, +4, CyA from d+5, MMF from d+5
- Graft: PBSC, CD34+ 3.6x10e6cells/kg bw
- Patient/ Donor: BG: B+ / B-, CMV: + /+
- Complications: **d+3, cytokine syndrome**, (38.7, CRP 8.1, erythema)
- Engraftment: WBC≥1000: d+33, PLT ≥20.000: nr
- acute GvHD: No
- CMV reactivation: 1x d+85, no other infections
- 09/2013, d+300: CR, Karnofsky 100%, no GvHD, PB/BM: Complete Chimera

46

Donor selection algorithms: Is there a consensus?



- MMUD: locus? (DPB1, anti-HLA)
- CB: cell dose, HLA mismtaches, (anti-HLA)
- Haplo: NK alloreactivity, technical expertise,(anti-HLA)
- **expertise**
- **Costs**

47

Many Thanks

BMT and Leukemia Unit
- S. Chondropoulos
- A. Delastic
- E. Kefala (Data Manager)

Collection / Processing Unit:
- **E. Triantafyllou**

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- D. Kokkinou
- A. Vittoraki

CBMDP
- Rector U Patras
- **V. Anastassopoulos**
- L. Oikonomopoulou

Karaiskakeio / CSHM
- P. Costeas
- A. Kournouli

Freiburg, Germany
- J. Finke

NIH, Washington, USA
- J. Barrett

48

PRESENTATION SUMMARIES

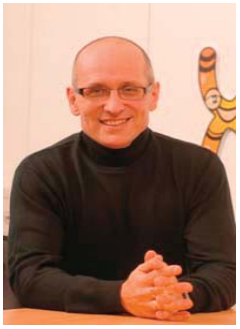
JOANNIS MYTILINEOS–DIRECTOR OF DEPARTMENT OF TRANSPLANTATION IMMUNOLOGY AT THE IKT/ULM UNIVERSITY, GERMANY

Abstract

Title: Current and Future HLA typing Methodologies

HLA is extremely polymorphic. Different HLA typing techniques are currently in place with different typing resolution. Serology and Mixed Lymphocyte Culture (MLC) have been replaced by molecular assays. Sequence specific oligonucleotide probing (SSOP), sequence specific priming (SSP), sequencing and many more will be discussed. With the fast pace by which technology is changing HLA typing laboratories serving registries need to keep up with the latest methodologies. This talk will also discuss the future methods and trends in HLA typing.

Biography



Joannis Mytilineos was born in Athens/Greece. He graduated from Heidelberg Medical School in 1986, and received his PhD and Adjunct Professor's degree in Immunology (1986-2004). After 15 years as head of the HLA Laboratory at the University of Heidelberg he took the lead of the Department of Transplantation Immunology at the IKT/Ulm University in 2004 where he is still employed.

Dr. Mytilineos has been co-chairing the Cytokine Components of the last three International Histocompatibility Workshops, as well as the 2009 annual EFI conference in Ulm. He was appointed as a councillor of the IHWG in 2004. He has been recently serving in both, the ASHI and the EFI executive boards. In his function as Chairman of the EFI Education committee he is also involved in the organisation of regional educational and scientific events, as well as of the EFI/APHIA/ASHI summer schools.

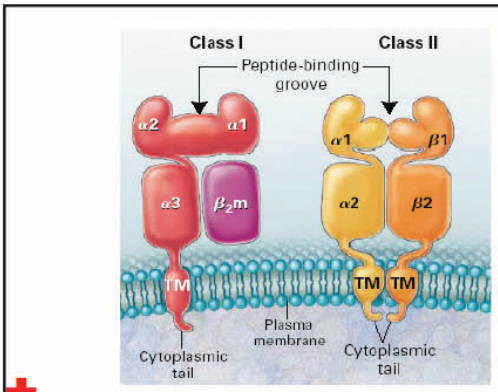
CURRENT AND FUTURE HLA TYPING METHODOLOGIES

Current and Future HLA-Typing Methodologies

Paphos, 4.10.2013

Joannis Mytilineos MD, PhD
Department of Transplantation Immunology
Institute for Clinical Transfusion Medicine and Immunogenetics
German Red Cross Blood Transfusion Service, and
Department of Transfusion Medicine - University Clinic Ulm
Ulm, Germany

1



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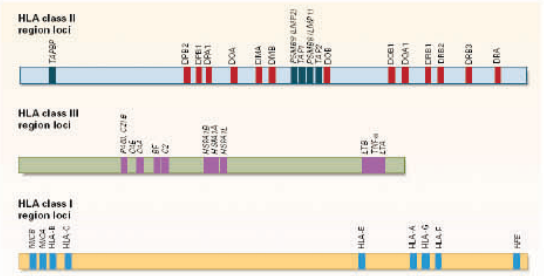
Human MHC



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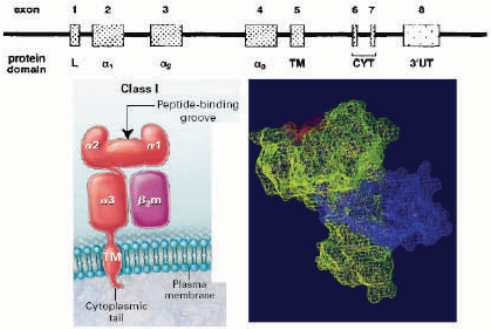

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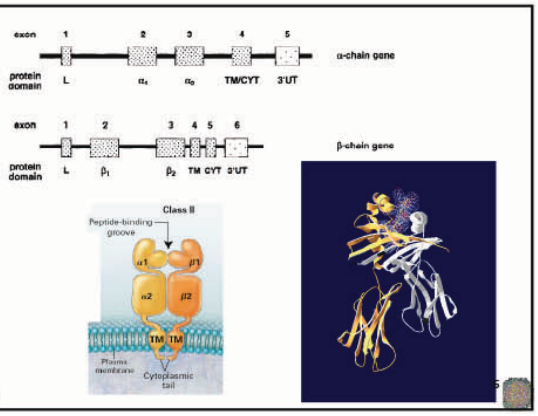

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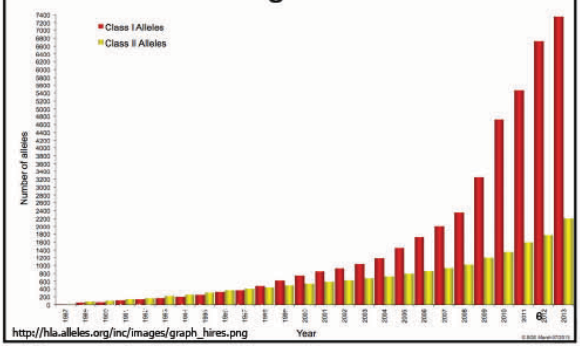
Annual Increase of the Number of HLA Antigens/Alleles



6

CURRENT AND FUTURE HLA TYPING METHODOLOGIES

Current Number of existing Alleles per HLA Locus

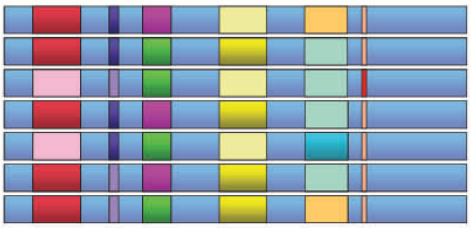
(Sep 2013/(Dec. 2008) / www.ebi.ac.uk/imgt/hla/stats.html)

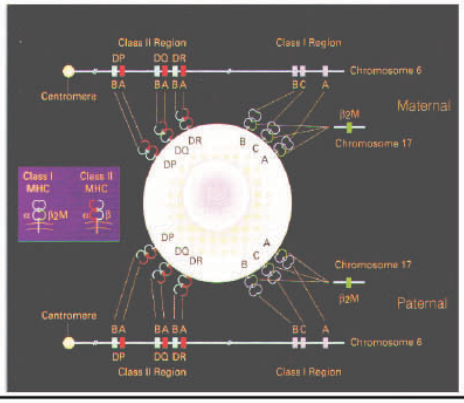
A	2.365 (733)
B	3.015 (1.115)
Cw	1.848 (392)
DRB	1.456 (697)
DQB1	416 (95)
DPB1	190 (132)

A total of 9.555 HLA Alleles as of Sep. 2013

7

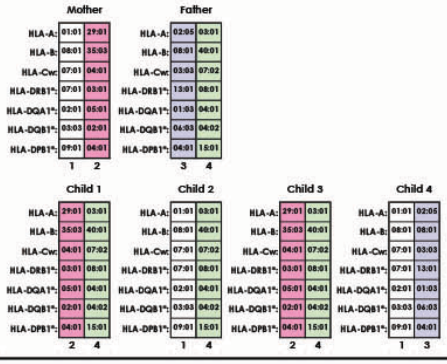
HLA alleles possess a "patchwork" pattern of polymorphism





9

Inheritence of HLA



10

Why do we type for HLA

- Transplantation
  - Solid Organs
    - Kidney
    - Pancreas
    - Heart
    - Cornea
  - Bone Marrow + HSC
  - HLA-A, B for platelet transfusions
- Disease association
  - B27 with AS
  - DR4 with RA
  - DR3, 4 & DQ2, 8 with Diabetes and coeliac disease
- Recurrent foetal loss
- Paternity testing

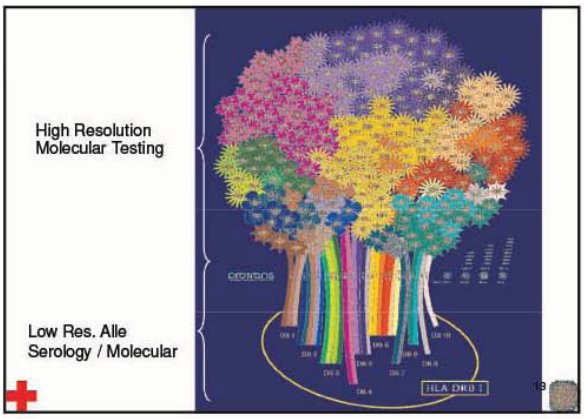
11

Methods for HLA-Typing

- Resolution degree
  - High Resolution = 2 fields: e.g. A*02:01
  - Low Resolution = 1 field: e.g. A*02
- Method
  - Serological
  - Molecular
  - Cellular
  - Biochemical

12

CURRENT AND FUTURE HLA TYPING METHODOLOGIES



Classical Methods

- Serological Typing (CDC)
  - NIH-Test, LCT, Micro-lympho-cytotoxicity test
- Cellular Tests
  - MLC (Mixed Lymphocyte Culture)
  - PLT (Primed Lymphocyte Typing)
- Biochemical Typing
  - One-dimensional, isoelectric focussing
  - Two-dimensional, isoelectric focussing

14

Serology

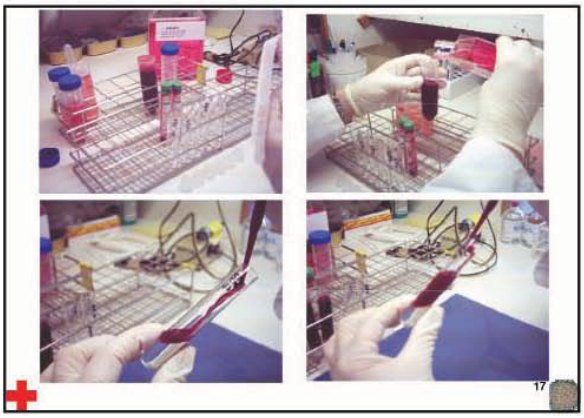
- Principle: Microlymphocytotoxicity
- Resolution: Low
- Genes: HLA-A, -B, (-Cw), DR, DQ
- Pro: Cheap and quick
- Con:
  - Low Resolution
  - Fresh material required!
  - Insufficient quality for HLA-class II Typing

15

Microlymphocytotoxicity Test

	+ve Reaction	-ve Reaction
HLA antiserum (Ab) + lymphocyte suspension (Ag) (Ag - Ab reaction)		
Complement dependent cell lysis		
Staining with AO/EB/Hb (as seen through microscope)		

16



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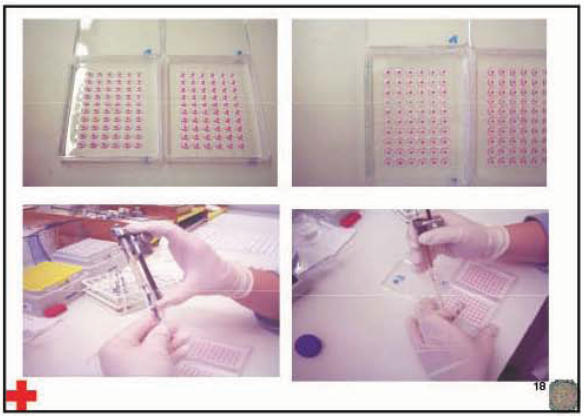


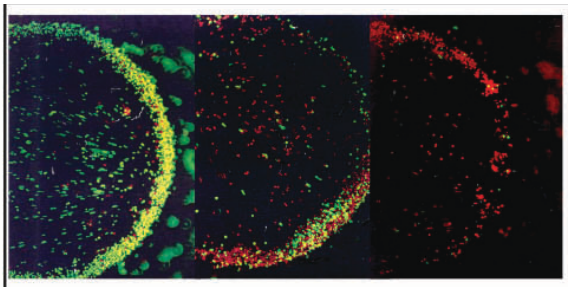
18

CURRENT AND FUTURE HLA TYPING METHODOLOGIES

SCORING

Percent dead cells	Score	Interpretation
0 - 10%	1	negative
11 - 20%	2	possibly negative
21 - 50%	4	weakly positive
51 - 80%	6	positive
81 - 100%	8	strongly positive
	0	not interpretable

19



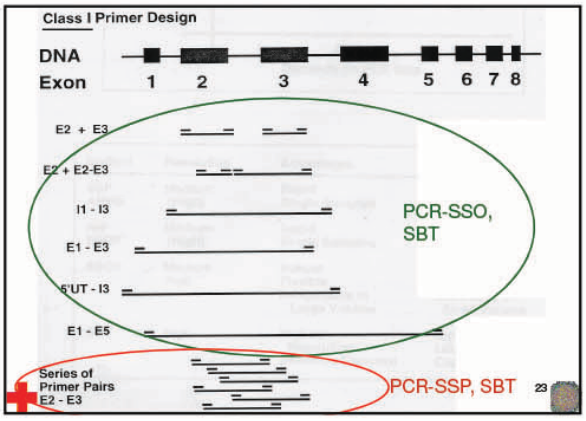
20

21

Molecular Methods for HLA-Typing

- **PCR-SSP**
- **PCR-SSO**
  - Classical
  - RDB
  - **Beads**
  - ELPHA
  - Chips-Arrays
- **SBT**
- **Next Generation Sequencing (NGS)**
- RFLP
- PCR-RFLP
- RSCA
- SSCP
- others

22



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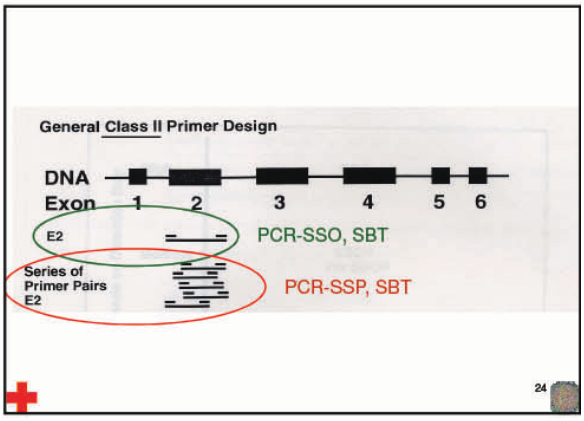


24

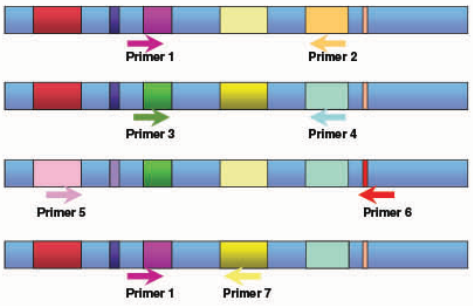
CURRENT AND FUTURE HLA TYPING METHODOLOGIES

PCR-SSP

- Principle: PCR with a series of Sequence Specific Primers
- Resolution: Low, intermediate and high
- Genes: HLA-A, -B, -Cw, -DRB1, -DQB1, -DQA1, DPB1

25

Sequence Specific Primer Design



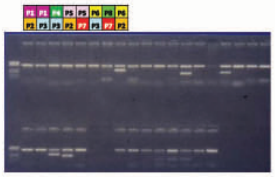
PCR-SSP

DNA-Isolation

PCR with sequence specific Oligos

Electrophoresis

Reading and Interpretation



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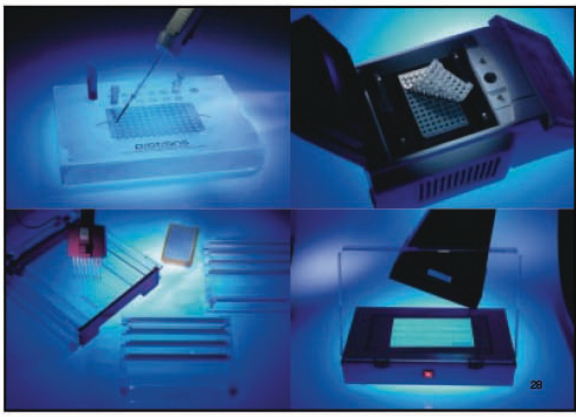
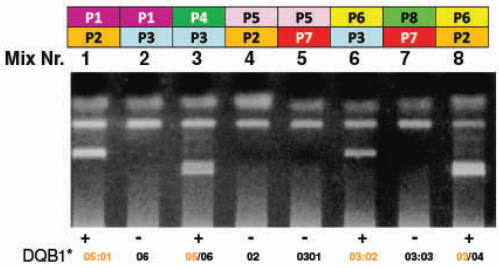


28

Example of a simple PCR-SSP-Typing



Typing Result: DQB1*03:02, 05:01

29

PCR-SSP

- Pros:
  - Low implementation costs (no expensive equipment)
  - Straight forward interpretation of results
  - Quickest molecular method (3 hours)
- Cons:
  - High consumption of DNA (in particular for high res)
  - Limited resolution in view of the increas. number of alleles
  - Constant need for primer updating – too cumbersome
  - Only low throughput possible

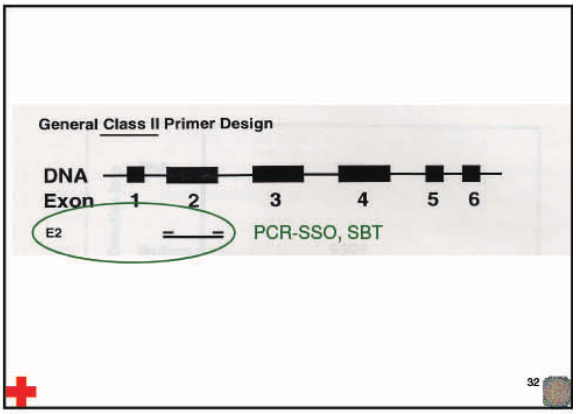
30

CURRENT AND FUTURE HLA TYPING METHODOLOGIES

PCR-SSO (Luminex)

- Principle: PCR & subsequent hybridization with Sequence Specific Oligonucleotides, which are coupled to the surface of fluorescently stained beads. Analysis is being performed in a specially designed FACS-machine (Luminex)
- Resolution: Intermediate to High
- Genes: HLA-A, -B, -C, -DRB1, -DQB1, -DQA1, -DPB1

31



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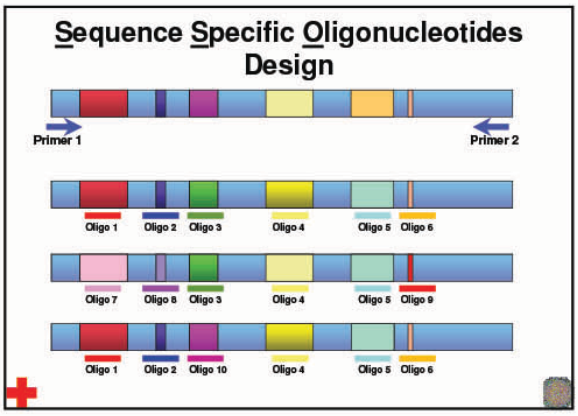
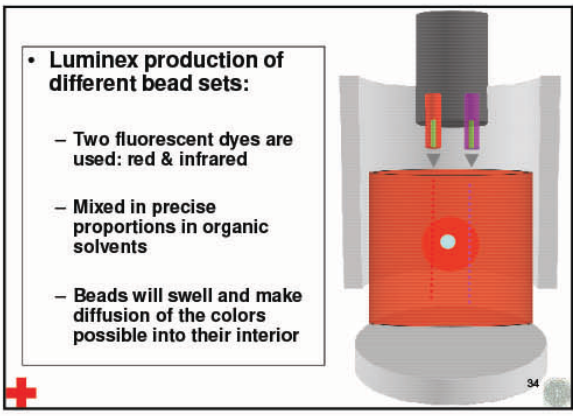
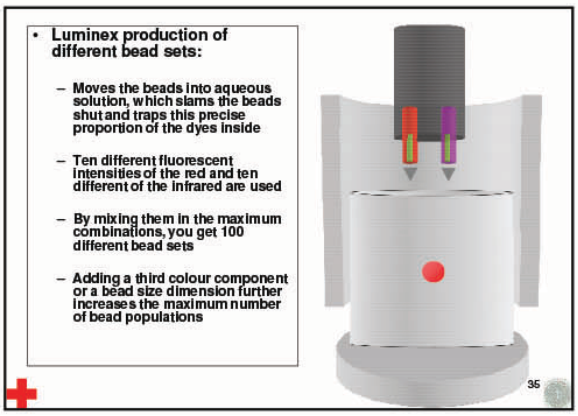
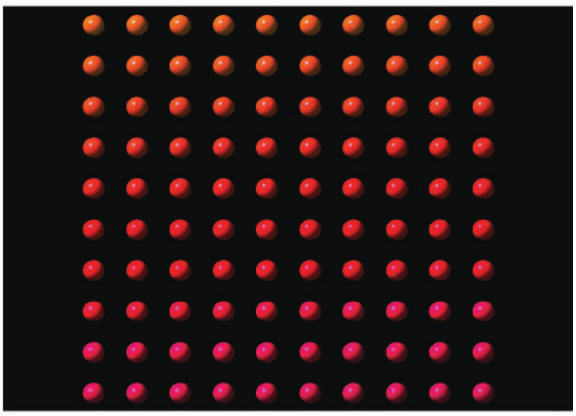
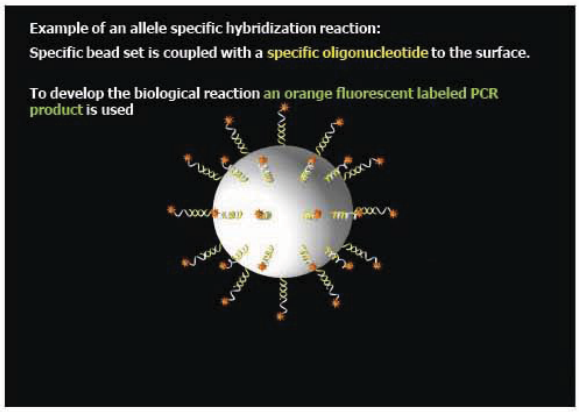


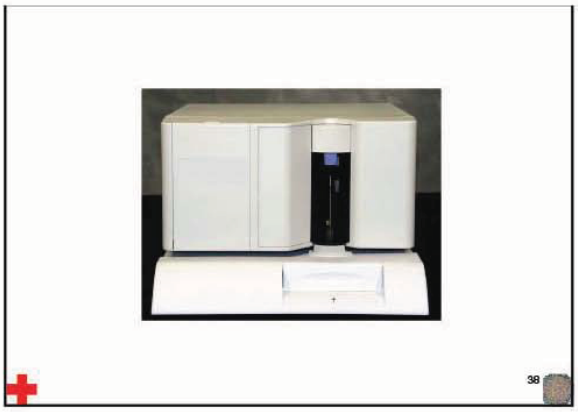


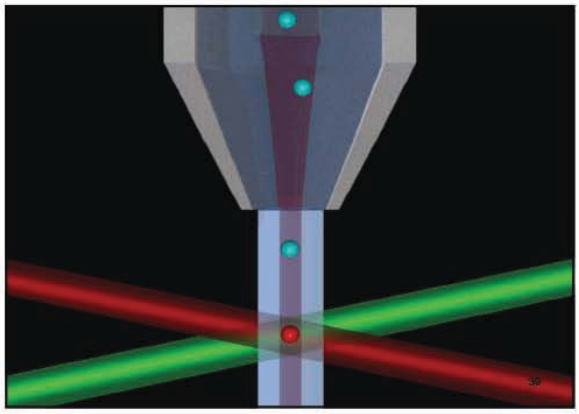


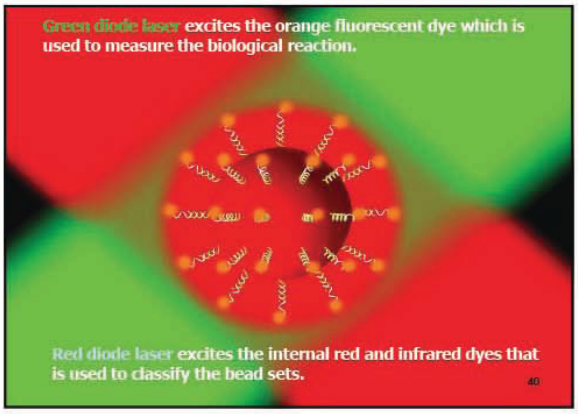


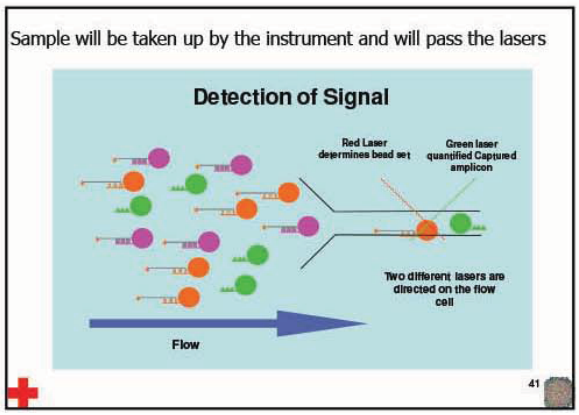
CURRENT AND FUTURE HLA TYPING METHODOLOGIES

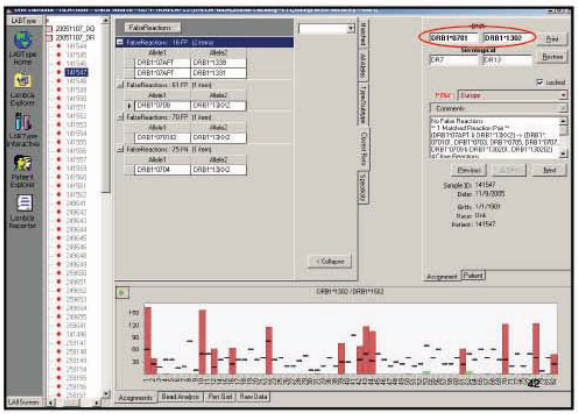












CURRENT AND FUTURE HLA TYPING METHODOLOGIES

PCR-SSO (Luminex)

- Pros:
  - Simultaneous Hybridisation of one PCR product with >100 oligonucleotides in one single tube (liquid chip)
  - High throughput with minimal staff requirments
  - Very few DNA material required
- Cons:
  - Reagent costs
  - Constant need for probe updating – too cumbersome
  - Limited resolution in view of the increas. number of alleles

43

SBT

- Principle: Direct Sequencing of a PCR Product (Sanger)
- Resolution: High
- Genes: HLA-A, -B, -Cw, -DRB1, -DQB1, -DQA1, -DPB1

44

High Resolution Typing Techniques

```
A*0101: AACGCCGATCCGTTACGCTAG
  SSO:  ???CGC????????????TAG
  SSP:  ???CGC????????????TAG
  SBT:  AACGCCGATCCGTTACGCTAG
```

45

High Resolution Typing Techniques

```
A*0101:  AACGCCGATCCGTTACGCTAG
```

Some years, months ore even days later....

```
A*0140:  AACGCCGACAGGTTACGCTAG
```

46

High Resolution Typing Techniques

```
A*01:001:  AACGCCGATCCGTTACGCTAG
  SSO:      ???GCC??????????????TAG
  SSP:      ???GCC??????????????TAG
  SBT:      AACGCCGATCCGTTACGCTAG
```

Some years later....

```
A*01:040:  AACGCCGACAGGTTACGCTAG
```

47

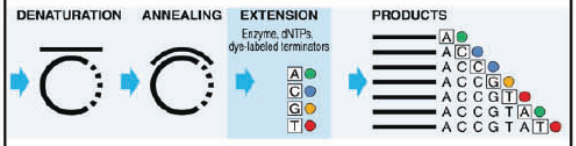
SBT Steps

1. DNA-Isolation
2. Locus-specific Amplification (PCR)
3. PCR Monitoring
4. Purification of Amplification product
5. Cycle Sequencing
6. Purification of the „Cycle Seq" products
7. Separation of the „Cycle Seq" fragments in an automatic Sequencer
8. Interpretation and evaluation of the raw data

48

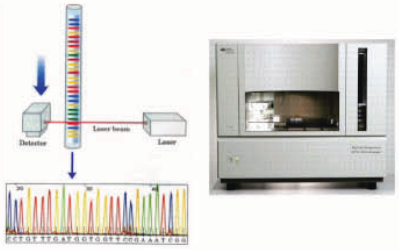
CURRENT AND FUTURE HLA TYPING METHODOLOGIES

5. SBT – Cycle Seq Step



49

7. SBT – Separation of the Cycle Seq fragments



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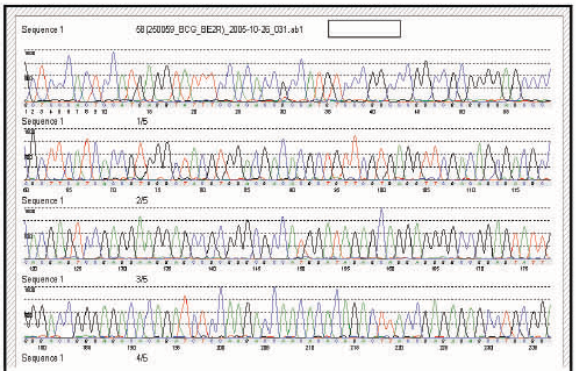


51

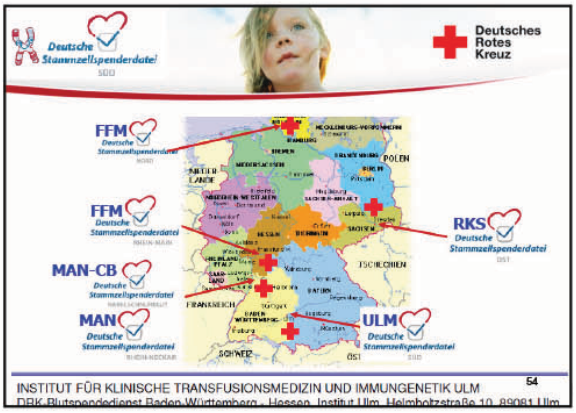
SBT

- Pros:
  - Highest Resolution possible
  - Results are valid indefinitely, because of direct reading of sequence information
  - Very few DNA material required
- Cons:
  - Costs for reagents and equipment
  - Rather time consuming in terms of pipetting steps & interpretation

52

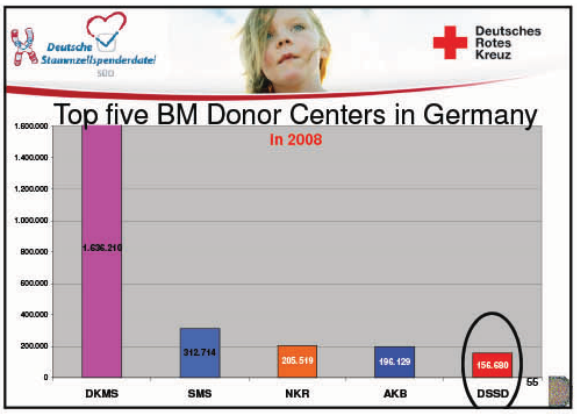
Why do we bother about all this?

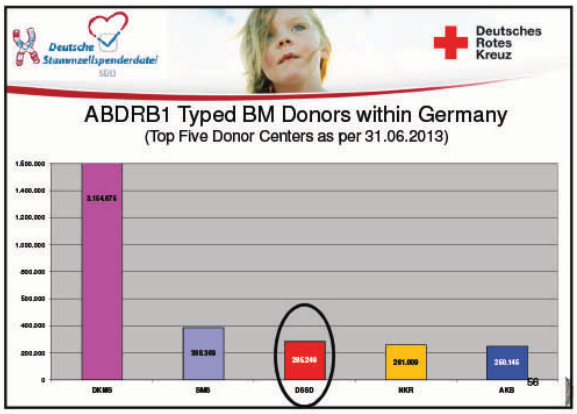
53

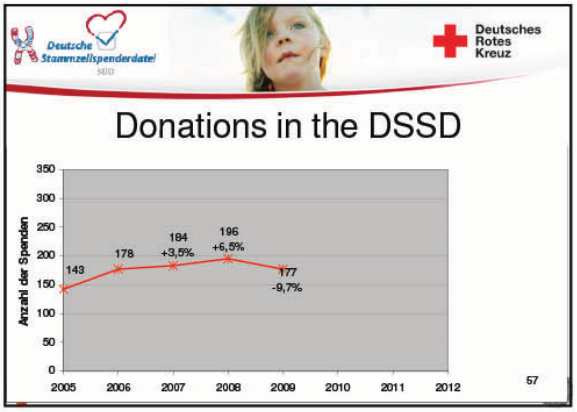


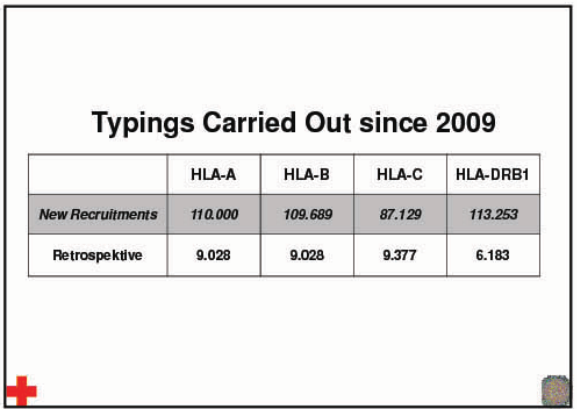
54

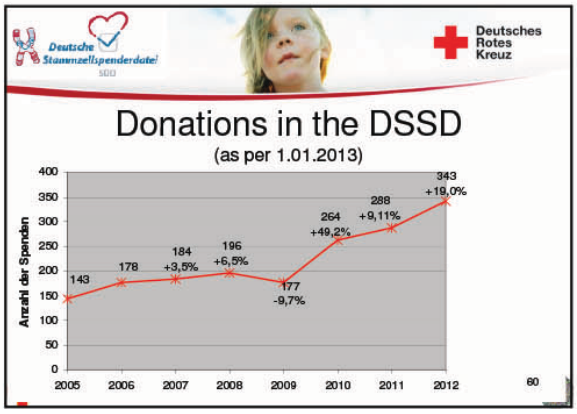
CURRENT AND FUTURE HLA TYPING METHODOLOGIES



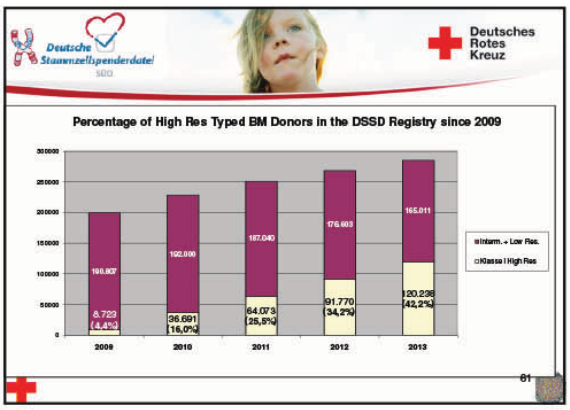


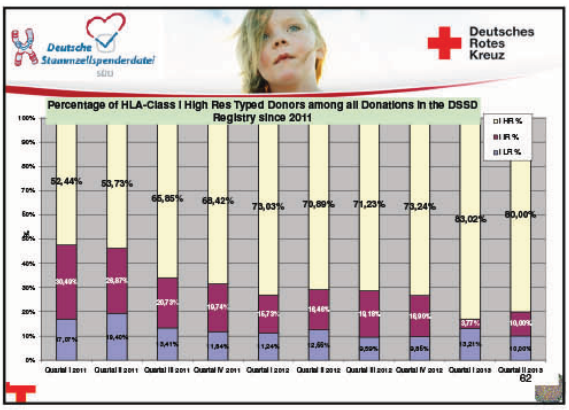


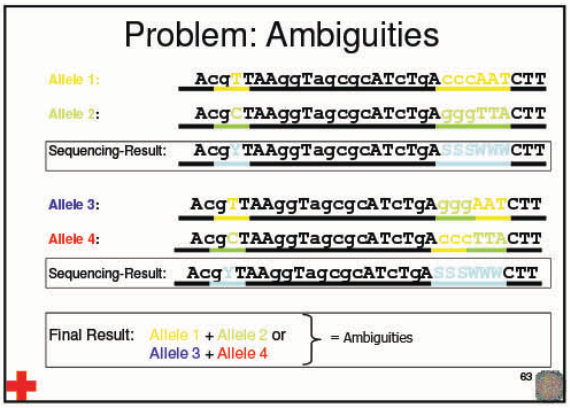


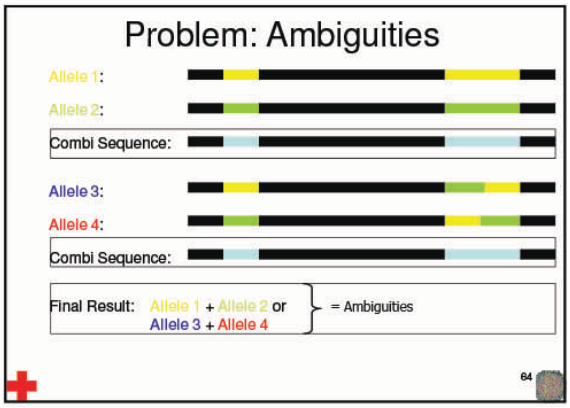


CURRENT AND FUTURE HLA TYPING METHODOLOGIES









Ambiguities – Relevance:

Allele/Antigen – Exon2/3

- Example:
  A*23:01, 02:05 or A*23:07N, 02:05 or
  A*23:17, 02:05 or 23:18, 02:05
  (Ambiguity outside exons 2/3)
- Clinical/Functional Consequence:
  - Possibility of a Mistyping
  - Risc for GvHD or Rejection currently not known – considered though to be of minor importance
- Standard Requirements:
  - ASHI/EFI Standards require resolution of ambiguities only if they are due to **nucleotide differences within exons 2/3 for Class I Alleles or exon 2 for Class II Alleles!**

65

Ambiguities – Relevance:

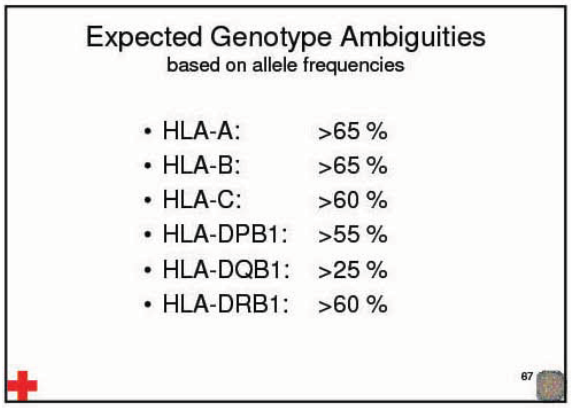
Allele/Antigen – NULL-Alleles

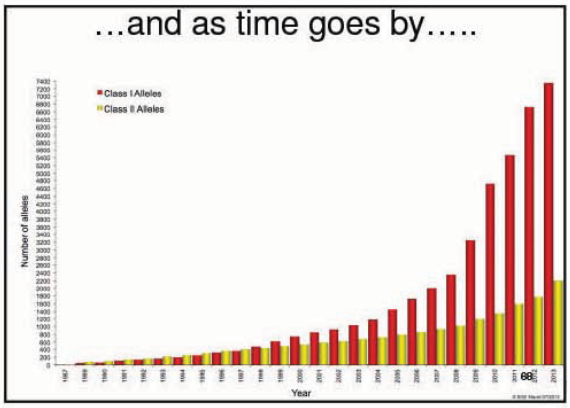
- NULL Alleles are identifiable by DNA Typing, however, they are not expressed on the surface of cells!

  Example:
  DNA-Typing: A*02:01, *24:02 or *24:09N
  Serology: A2,-
- There are currently >300 identified HLA NULL Alleles
- Their overall cumulative frequency is <0,1%
- Their functional/clinical Relevance is currently not examined, however, they may be associated with an increased risc for GvH if unrecogised
- According to the EFI/ASHI Standards Ambiguities involving NULL Alleles must be resolved –> Technical and financial implications!!!???

66

CURRENT AND FUTURE HLA TYPING METHODOLOGIES





PRESENTATION SUMMARIES

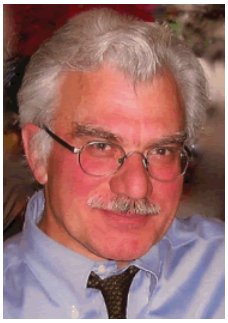
DIMITRI S. MONOS– DIRECTOR OF IMMUNOGENETICS LABORATORY AT CHILDREN'S HOSPITAL OF PHILADELPHIA, PROFESSOR OF PATHOLOGY AND LAB MEDICINE AT PERELMAN SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, USA

Abstract

Title: NGS, Coming of Age

High throughput sequencing technologies (cumulatively called Next Generation Sequencing-NGS) can be used to address the challenging problem of accurate, informative and cost effective characterization of HLA genetic polymorphisms. More recently, specific protocols that have been developed for this purpose on different NGS platforms, suggest that the seemingly complicated technology can be properly managed to allow HLA typing by NGS in a clinical diagnostic lab. One area that will be particularly affected is the bone marrow registries and the labs that support them.When donors are typed at the HR level, registries benefit as an increased number of transplants is facilitated per unit time, donors are selected more frequently and the time for identifying the proper donor is significantly reduced. These positive attributes can be enhanced with the introduction of NGS in our labs as this technology can provide informative HLA typing (allele level) at a reduced cost. A combination of platforms, protocols and analysis software have been validated and can deliver high quality HLA typing information. Beyond HLA typing, this technology can be used for the characterization of the whole MHC, impacting not only HLA typing but also our understanding of fundamental immunological mechanisms and therefore of autoimmunity and transplantation.

Biography



Dr. Monos is the Director of Immunogenetics Lab at The Children's Hospital of Philadelphia and Professor of Pathology and Lab Medicine at Perelman School of Medicine, University of Pennsylvania, USA. He earned his B.S. (Biology) at U. of Patras, Greece, and his Ph.D. (Biochemistry/Immunology) at Georgetown University, Washington, DC. Dr. Monos research interests cover a wide spectrum of HLA-related topics; DNA-based methodologies for HLA typing, structure/function relationships of HLAs, associations of HLAs with several diseases. His work has contributed on the development of the very key concept that genes within the MHC in coordination or independently of particular HLA alleles generate the disease phenotype.

NGS, COMING OF AGE

NGS, Coming of Age?

Dimitri Monos Ph.D.

Immunogenetics Laboratory, The Children's Hospital of Philadelphia
Department of Pathology and Lab Medicine
University of Pennsylvania, School of Medicine

Paphos, Cyprus, 3-5 October, 2013

Therefore due to current limitations of existing methods and the increasing rate of new alleles, there is strong demand for a new method for HLA genotyping.

Next-Generation Sequencing (NGS) is a method that can provide a complete solution to the HLA typing problem.

NGS Features Important for HLA Typing:

- **Provides sequencing information for a single DNA molecule - secures phase**
- **High throughput: large sequencing capacity allowing thorough evaluation of a genomic region and of many loci**

Strategies for HLA Typing by NGS

Exon-based typing (selected exonic/intronic sequences)

cDNA-based typing (selected exons can be included)

Full genomic typing

Full length Amplification (5'UTR to 3'UTR) of : HLA-A, HLA-B, HLA-C (3.3kb)
HLA-DQA1 (~7kb)
HLA-DQB1 (~7kb)

Partial Amplification of: HLA-DRB1 amplicon ~4 kb (gene ~15kb)
HLA-DPB1 amplicon ~7kb (gene ~12kb)

NGS Platform Characteristics

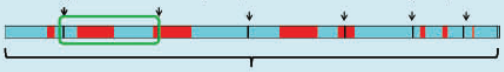
Characteristics	Spec/ CHOP	454 GS FLX (Titanium)	Illumina MiSeq (Paired-end 150 bp)	Ion Torrent PGM (Sept-2012)	Pacific Biosciences RS (C2 Chemistry)
Output	Spec	360-560 Mb (2 region) 240-440 Mb(8 region)	1 Gb last summer, 7Gb currently	20 Mb (314 Chip) 200 Mb (316 Chip)	60-140 Mb/SMRT Cell
	CHOP	200-250 Mb (8 region)	921 Mb last summer 6Gb currently	23-97 Mb (314 Chip) 132-158 Mb (316 Chip)	61-141 Mb/SMRT Cell
Read Length (bases)	Spec	~700 bases	2x 150 and 250 bases	~400 bases	~3,000 bases
	CHOP	300-380 bases (Avg) 758 bases (Max)	2x 150 and 250 bases	130-217 bases (Avg) 398 bases (Max)	1,907-2,244 (Avg) 14,159 bp(Max)
Total Error (indels, substitutions (%)	CHOP	1.20%	0.19% (2x150) 0.33% (2x250)	1.72%	14.1%
Flexibility (config, # samples)		+++ multiple region config	+++ Read length choices, nano /micro	+++ Different chips	+++ Addt'l SMRT Cells
Pre-Sequencing Time (Library Prep -> Seq)		3 Hrs (Library Prep) 6-8 Hrs (emPCR->Enrich) 2-3 Hrs (Run prep)	2 - 4 Hrs (Library Prep)	2-4 Hrs (Library Prep) 4-8 Hrs (emPCR->Enrich) 2 Hrs (Run prep)	2-3 Hrs (Library Prep)
Sequencer Run Time		10 Hrs	27 Hrs (2x150 bp) 40 Hrs (2x250bp)	2.5 - 4.5 Hours	1 ½ Hrs
Equipment Cost		$500,000 (GS FLX) $100,000 (GS Junior)	$125,000	$66,000 (PGM & Server) $15,000 (OneTouch)	$700,000
Automation & Peripheral Equip		+ REM e System	+++ Cluster Generation	++ OneTouch & ES	++ Mag Loader

Illumina MiSeq

WxDxH: 68.6cm x 56.5cm x 52.3cm

Library Preparation for Shotgun Sequencing

Fragmentation of DNA template (Nebulization/Sonication/Enzymatic)

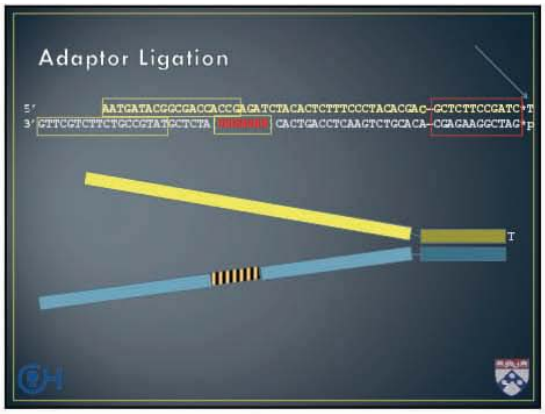


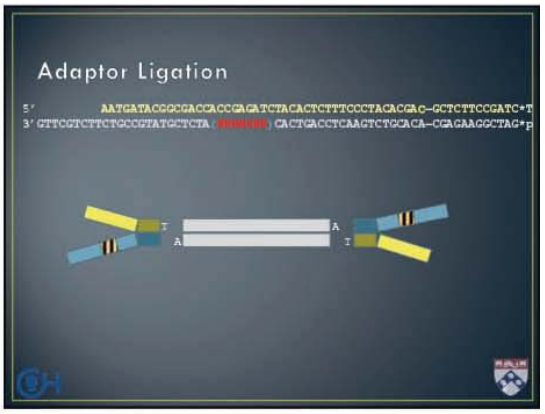
HLA Class I ~3.3 kb

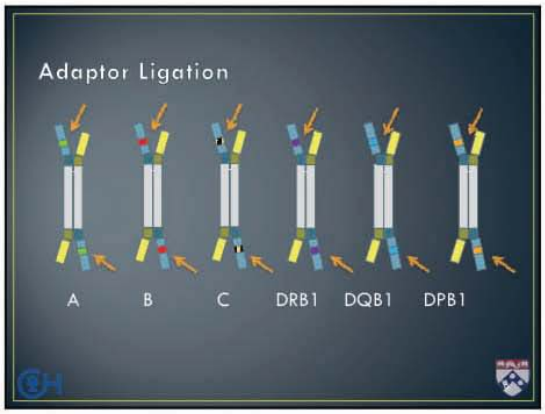
- Regions of interest are large PCR amplicons
- These amplicons are too long to sequence from a single DNA fragment
- These large amplicons must first be randomly fragmented to a size of 300-1000 bp prior to adaptor ligation

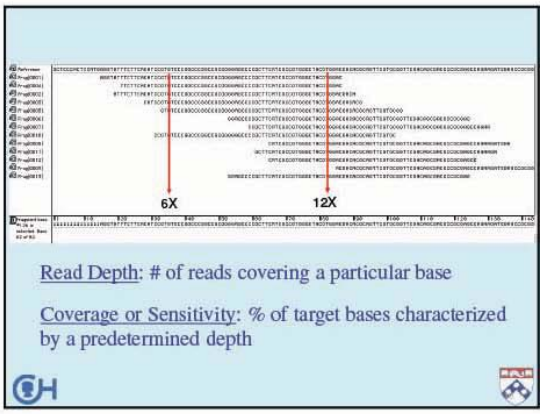
Adaptor Ligation

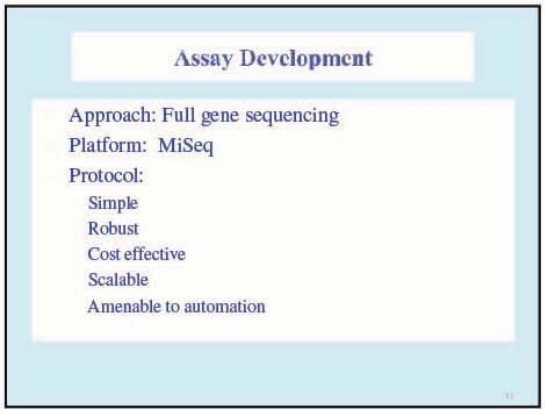
NGS, COMING OF AGE

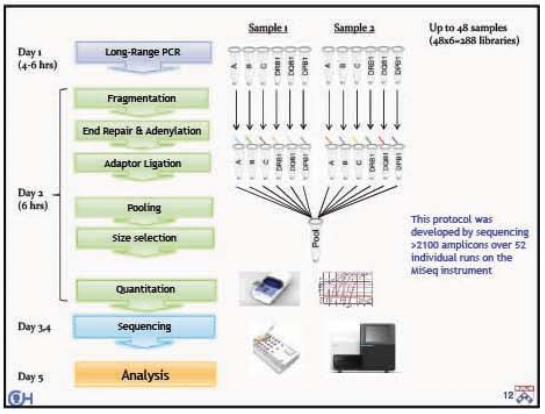












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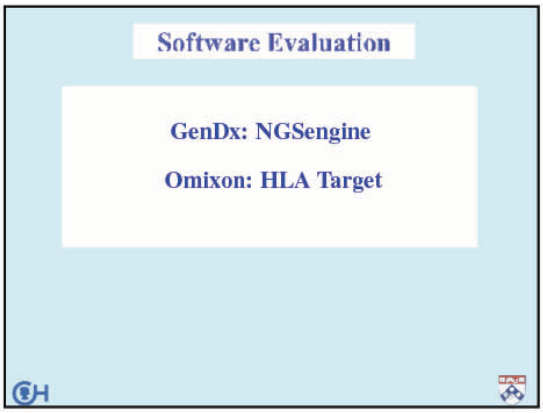

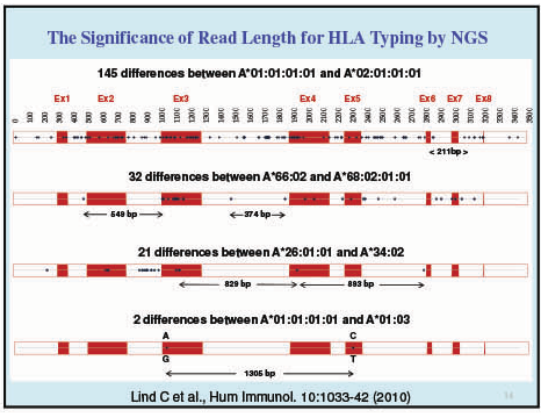

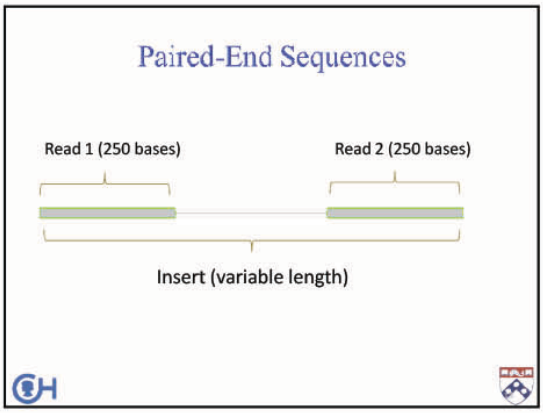

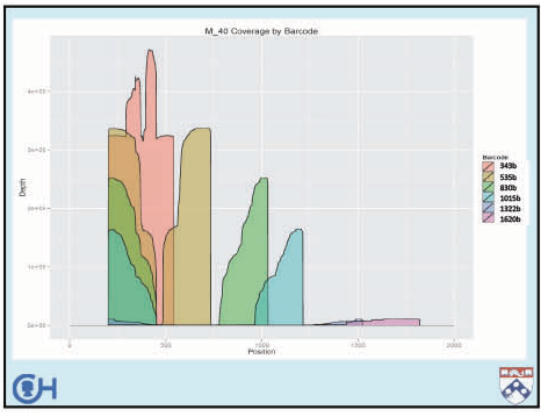

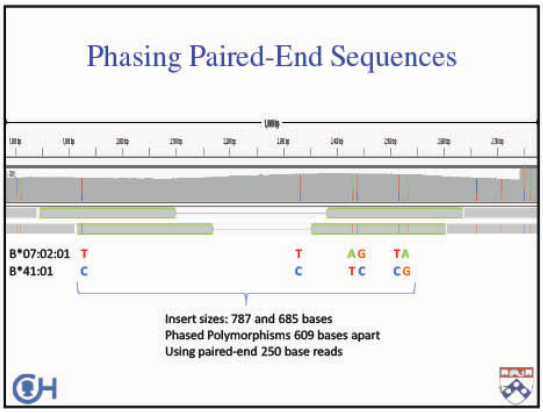

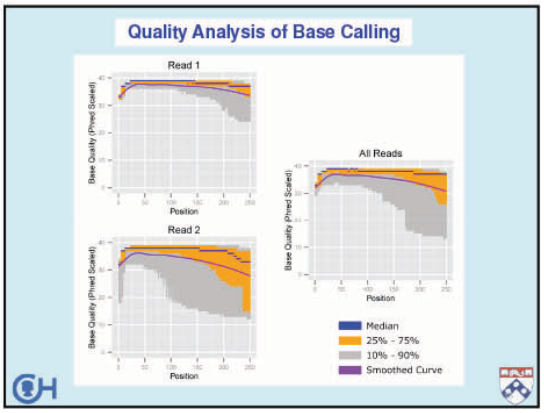

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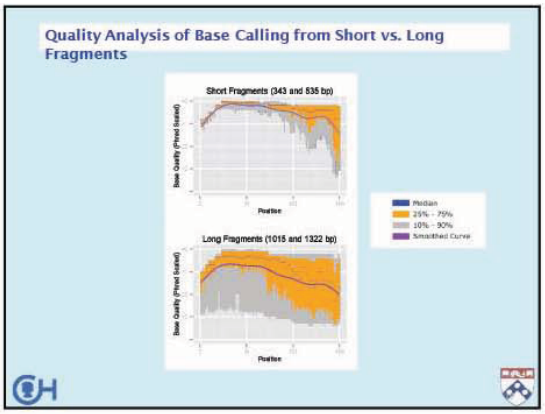
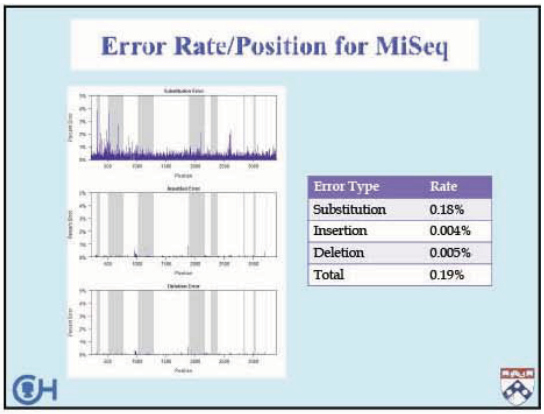
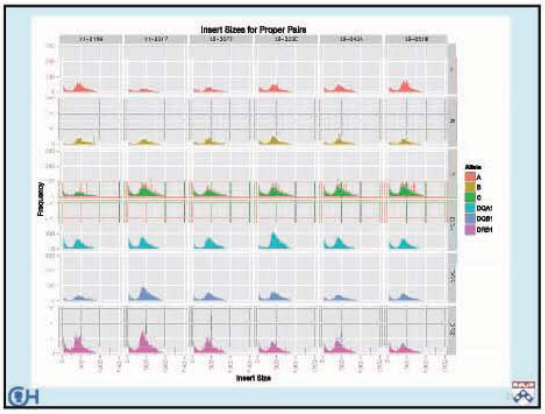
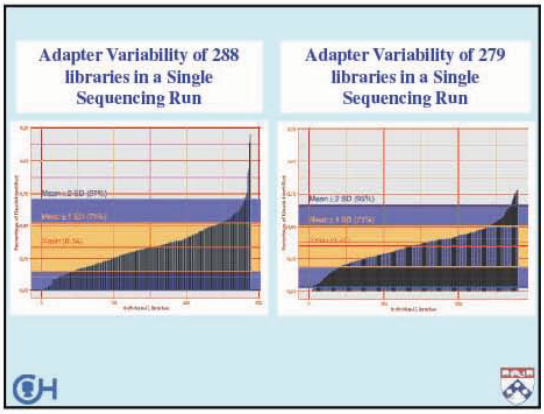
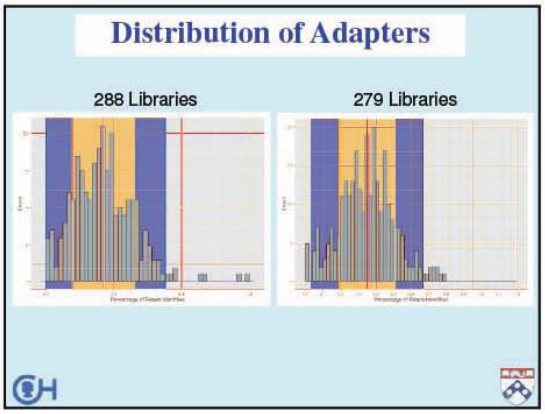
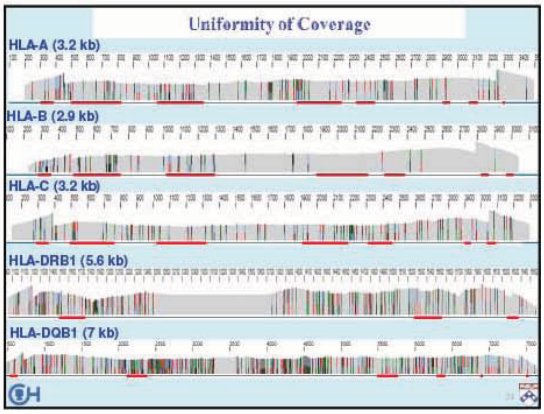




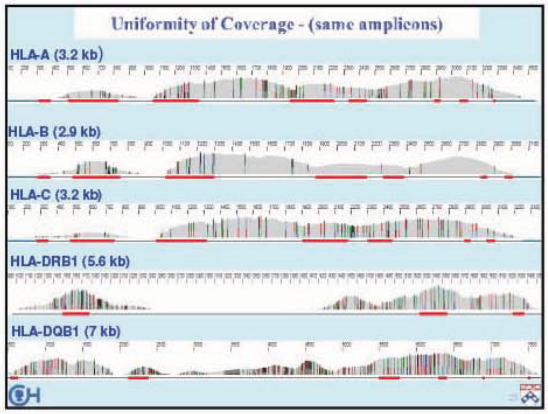








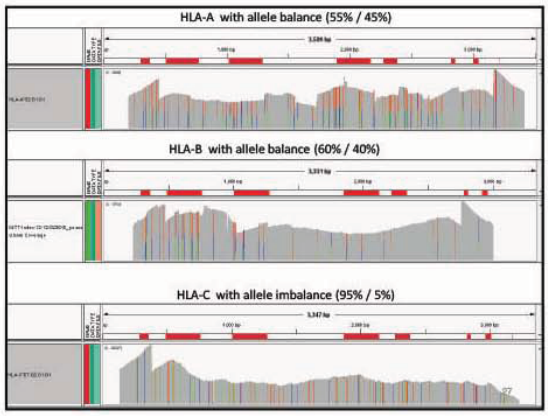
NGS, COMING OF AGE



Specificity of Mapping

$$\text{Specificity} = \frac{Reads\ Mapped}{Total\ Reads}$$

Locus	Specificity (from GenDX)
A	85.9%
B	87.0%
C	86.7%
DQB1	89.0%
Cumulative	87.2% (SD = 0.06)



Flow Cell	Average Output/Run	Average # Reads/Run	Samples*/Run
Nano	500 Mb	1.1 M	1-16 (6 loci x 16 samples = 96 amplicons on one 96-well tray)
Full size v2	6.6 Gb	13.1 M	16-96+ (up to six 96-well trays)

* 1 Sample: 6 loci (HLA-A, B, C, DRB1, DQA1, DQB1)

As of September 2013 (2 x 250 bp sequencing)

Accuracy of Genotype per Locus

	Omixon		GenDX	
	Fraction of Correct Allele Calls	% Accuracy	Fraction of Correct Allele Calls	% Accuracy
A	236/238	99.2%	237/238	99.6%
B	238/238	100.0%	238/238	100.0%
C	236/238	99.2%	233/238	97.9%
DRB1	234/238	98.3%	NA	NA
DQB1	237/238	99.6%	223/238	93.7%
Total	1181/1190	99.2%	931/952	97.8%

The two software tools combined resulted in 1184/1190 correct assignments; % Accuracy:99.5%

* Note: This accuracy is independent of sequencing depth

Genotyping Accuracy

The two genotyping programs for samples with sufficient depth (400x) at all 5 loci, called the correct genotypes for both alleles for 88/105 samples (84%).

Samples where Omixon was incorrect and there was no allelic imbalance: 6 (5.7%)

Samples where GenDX was incorrect and there was no allelic imbalance: 7 (6.7%)

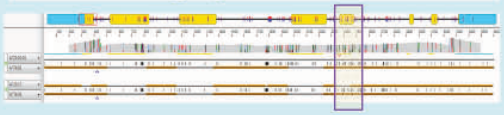
Samples with Imbalanced Alleles: 5 (4.7%). All 5 were flagged by Omixon and upon manual analysis were correctly called. They were all DQ alleles.

NGS, COMING OF AGE

Power of Full Gene Sequencing by NGS

More Accurate Genotyping:

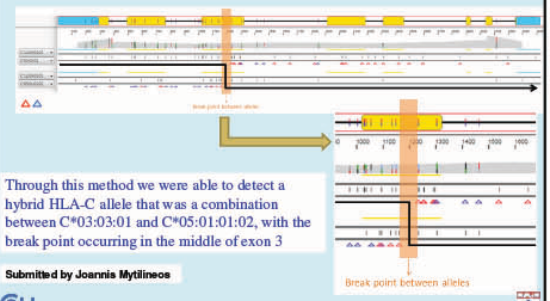
- Sample below is an HLA-A allele, expected to be a combination of A*23:01 and A*74:03 as typed by Sanger sequencing
- NGS results showed A*23:17 instead of A*23:01.
- A difference at the beginning of exon 5



… And Completion of Sequences

- Both alleles in this sample only have exon sequence reported in the IMGT/HLA database.
- All heterozygous positions are able to be physically phased and could be submitted to complete the sequencing of these alleles

Power of Full Gene Sequencing: Hybrid Alleles



Through this method we were able to detect a hybrid HLA-C allele that was a combination between C*03:03:01 and C*05:01:01:02, with the break point occurring in the middle of exon 3

Break point between alleles

Submitted by Joannis Mytilineos

Conclusions

- NGS can be used for the development of an HLA genotyping system with many advantages over current systems.
- We have developed a protocol for HLA typing on the MiSeq platform that characterizes the complete genes for HLA-A, B, C, DQA1, DQB1 and partially characterizes DRB1 and DPB1.
- To accommodate the maximum number of samples possible on the flow cell and obtain the best quality data, a number of metrics need to be accounted and balanced such as: optimal fragmentation and ligation conditions, size selection of the prepared library, appropriate amount placed on the flow cell, the reads generated by the different loci need to be of comparable amounts and depth needs to be relatively uniform across the length of the targeted genomic region.

Conclusions

- The design and thorough evaluation of amplification primers of each of these loci is absolutely necessary to avoid allele dropouts, preferential amplification or co-amplification. The software analysis and genotyping tools can be optimized to partially protect against these pitfalls.
- The process takes 3-4 days for a single run.
- The capacity of the system is from a single sample to about 100 samples and possibly more.

Acknowledgements

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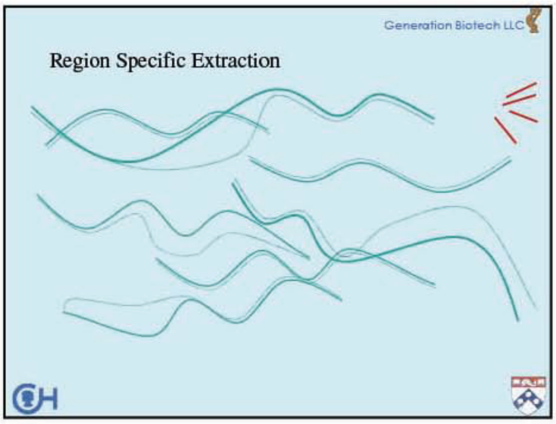
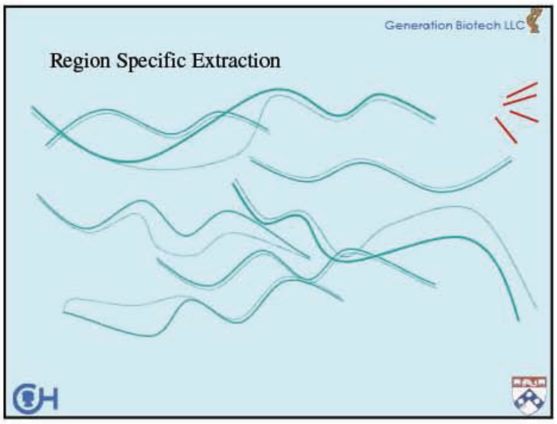
Rita Walker
Laura McLaughlin
Larisa Slavich
Marianne Rogers
Anh Huynh

Thank you

ΕΥΧΑΡΙΣΤΩ


Generation Biotech LLC
Region Specific Extraction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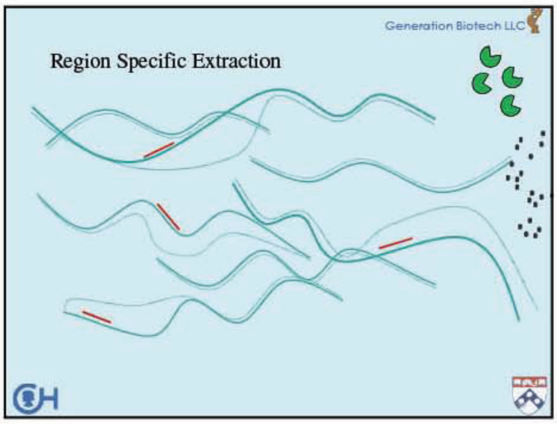
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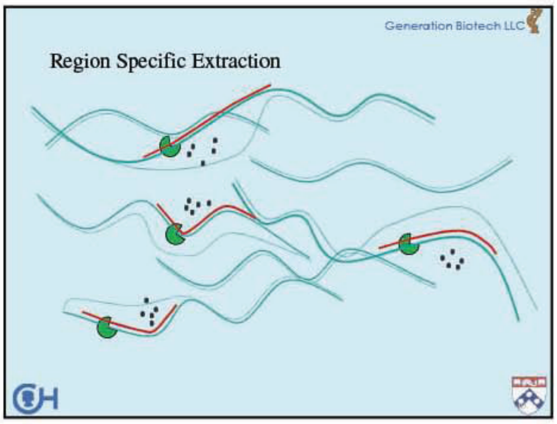
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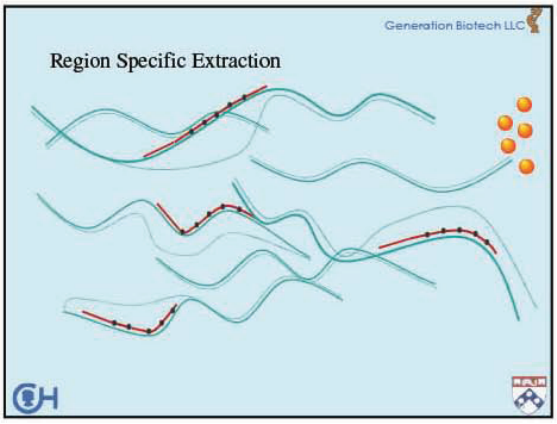
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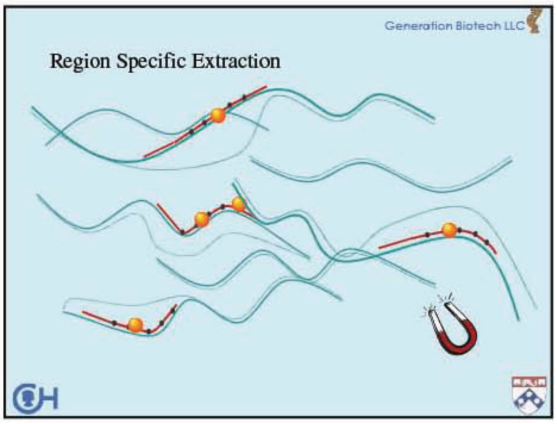
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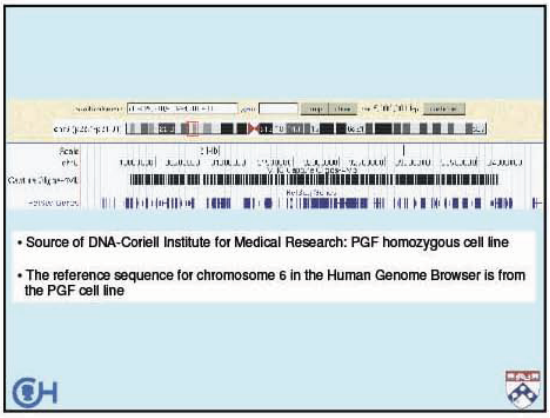
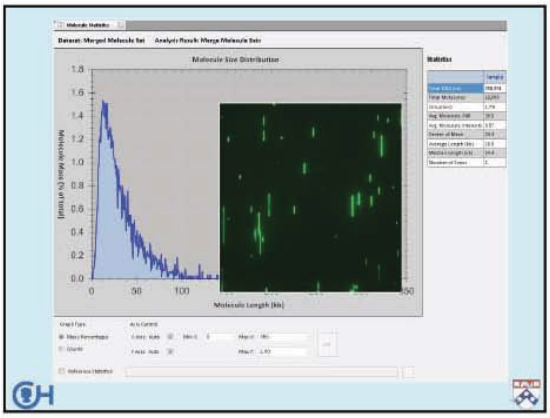
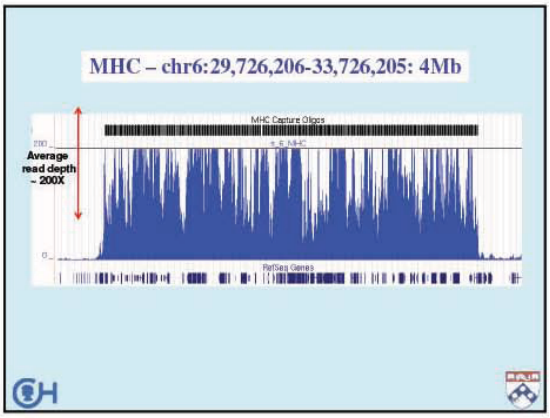
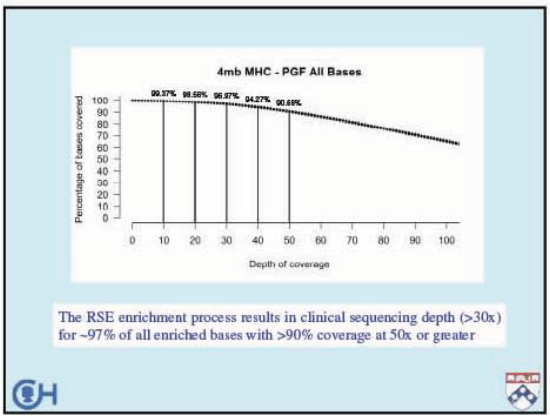
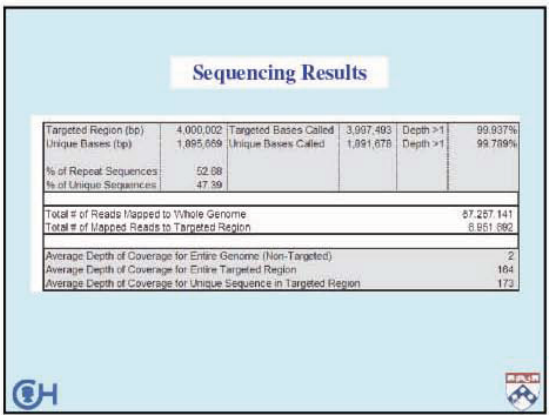
NGS, COMING OF AGE









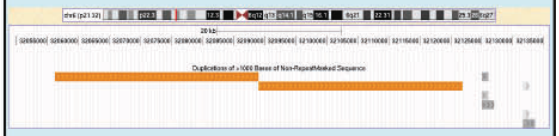


NGS, COMING OF AGE

Discrepancies between the reference sequence and our data

		Type of variants		Sanger agrees with NGS	Sanger agrees with reference	Total
Gene Regions	61 Sanger Validated Variants	Exon	Mismatches	4	4	8
		Intron	Mismatches	28	22	50
		Insertions/deletions		3		3
Intergenic	25 Sanger Validated Variants	Mismatches		15	10	25
				50	36	

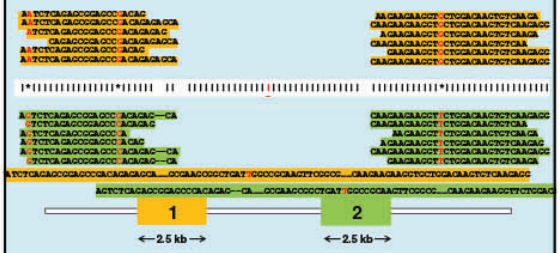
Segmental Duplications



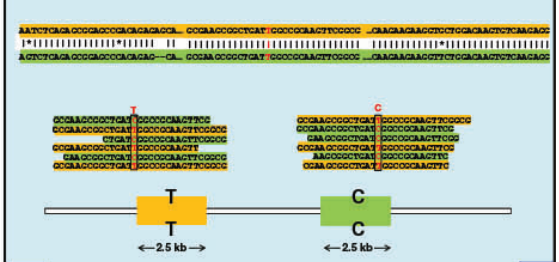
> 1Kb

> 90% sequence identity

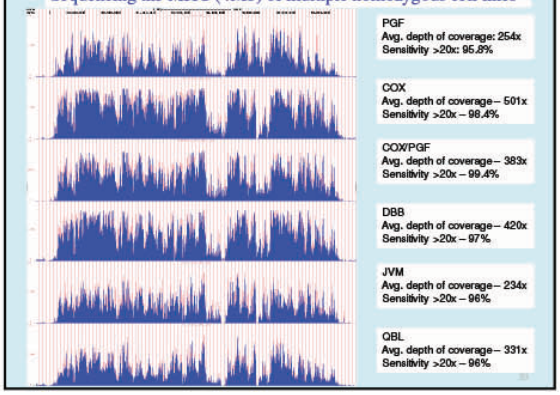
Resolving a Discrepancy Related to a Segmental Duplication



Resolving a Discrepancy Related to a Segmental Duplication



Sequencing the MHC (4Mb) of multiple homozygous cell lines



Acknowledgements

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Deborah Ferriola
Jamie Duke
Curt Lind

Steve Heron
Rita Walker
Laura McLaughlin
Larisa Slavich
Marianne Rogers
Anh Huynh

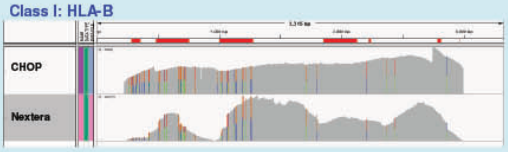
NGS, COMING OF AGE

Thank you

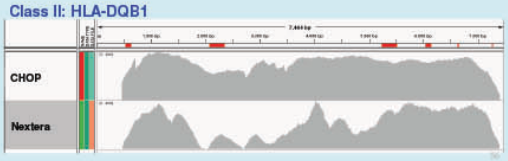
ΕΥΧΑΡΙΣΤΩ

Uniformity of Coverage

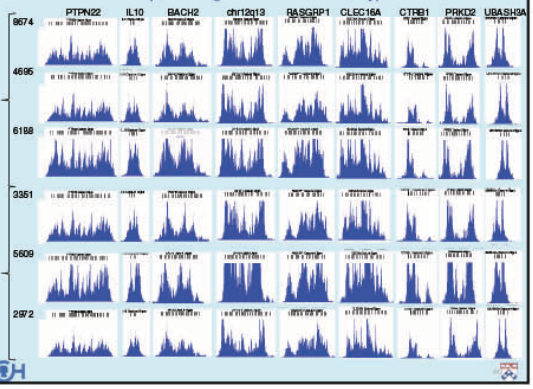
Class I: HLA-B



Class II: HLA-DQB1



Profiles of Captured Regions Associated with Type I Diabetes



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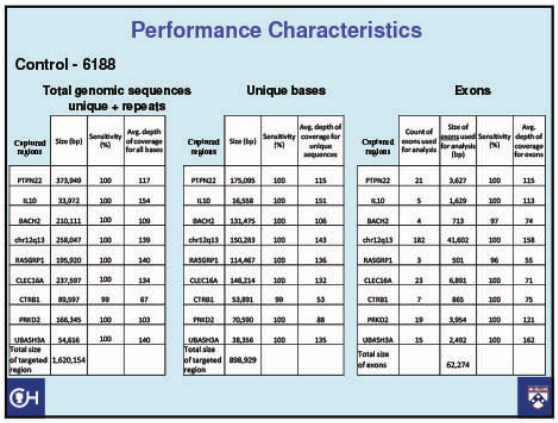

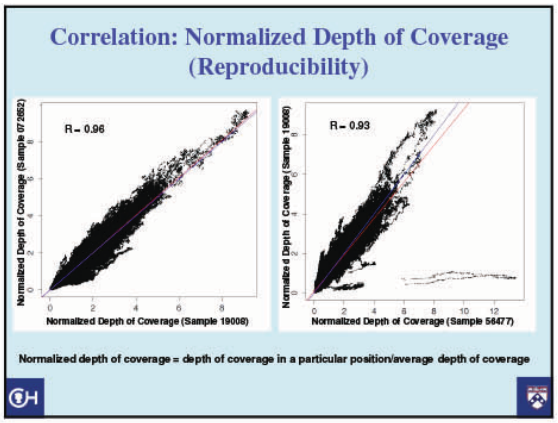

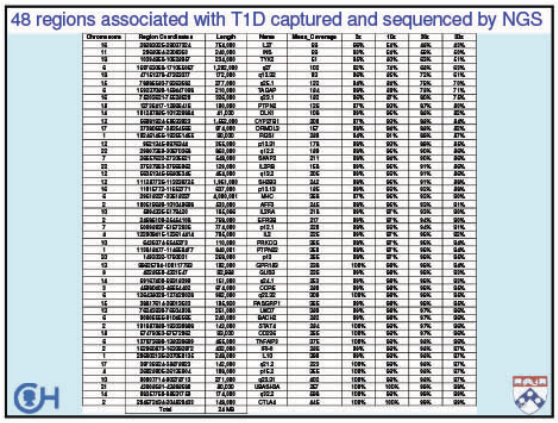

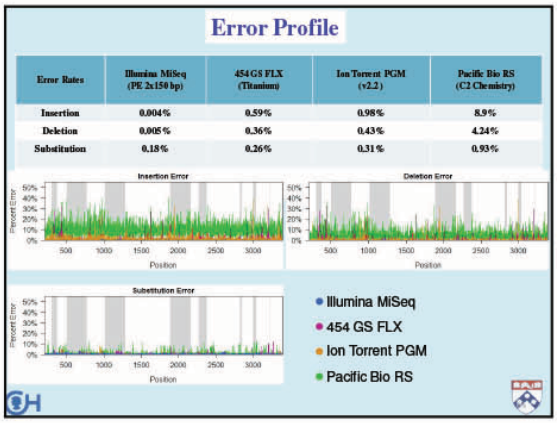

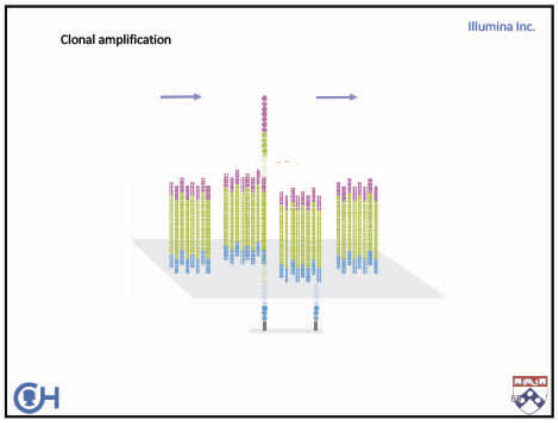

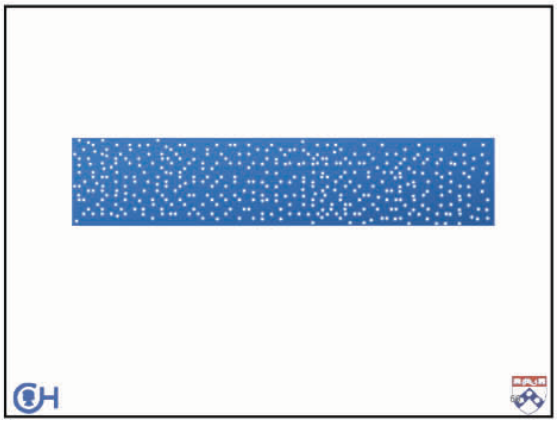

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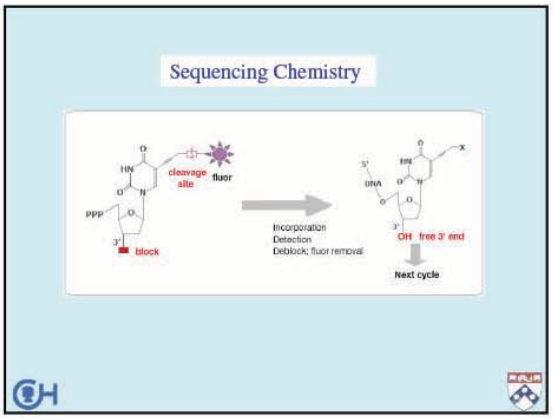

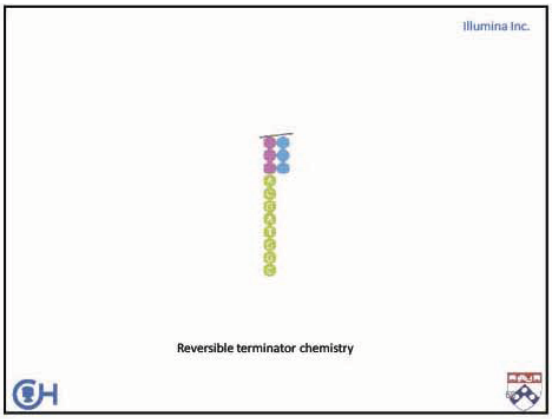

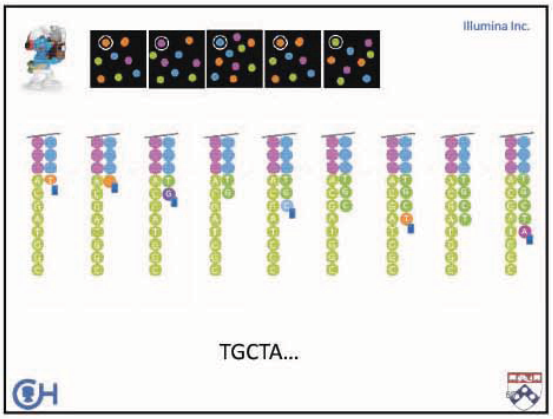

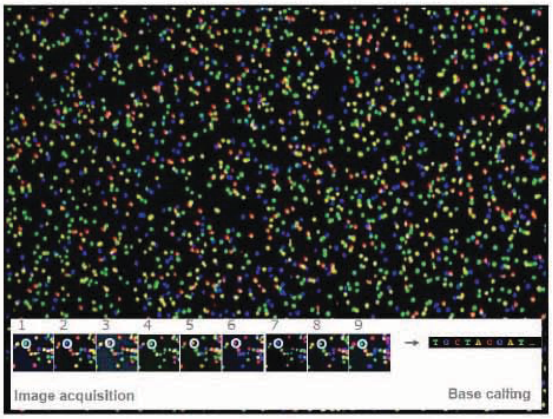

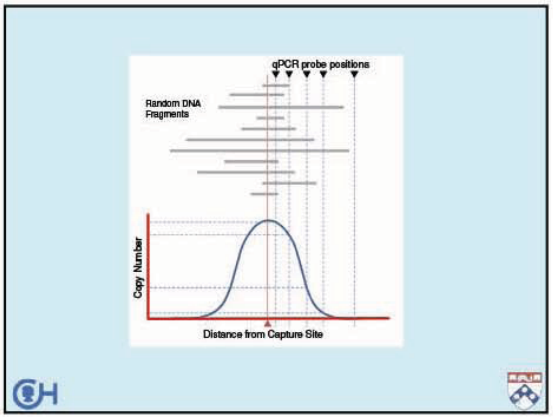

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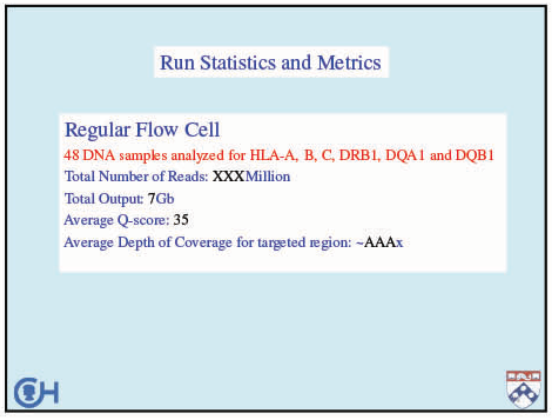

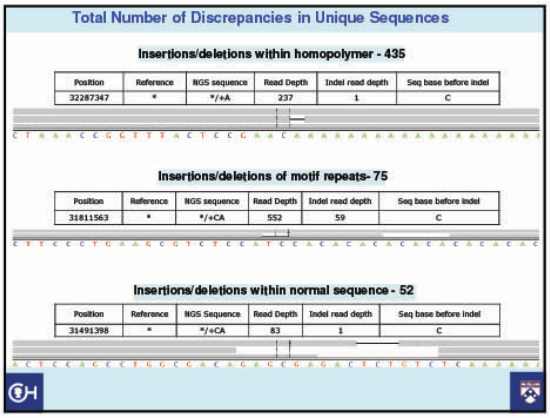

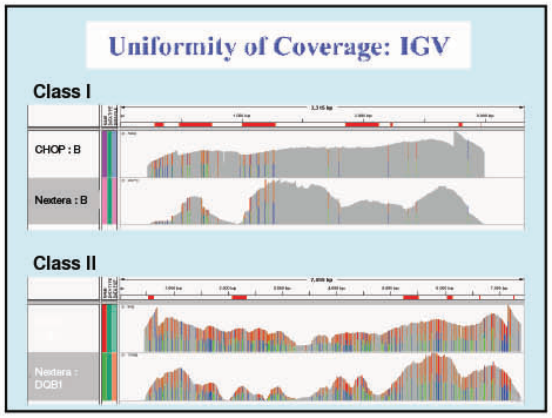

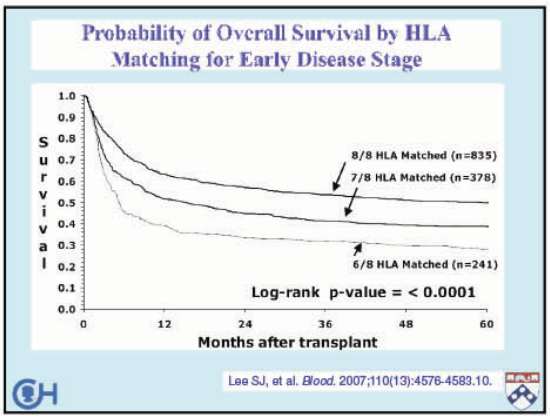

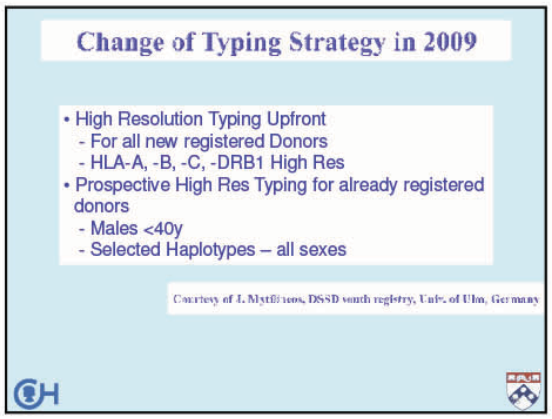

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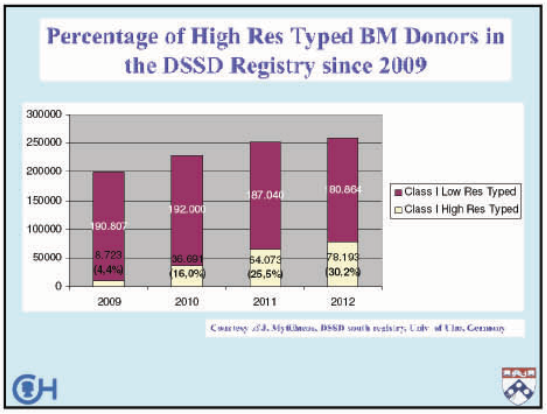
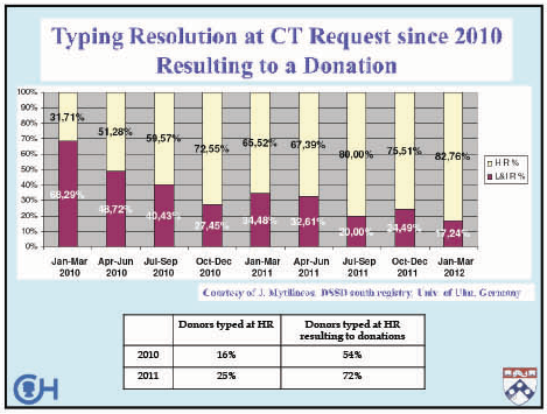
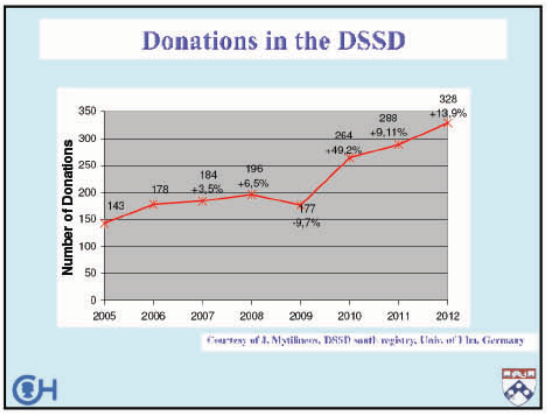
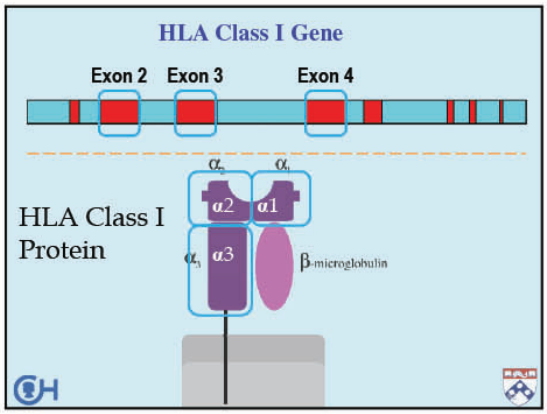
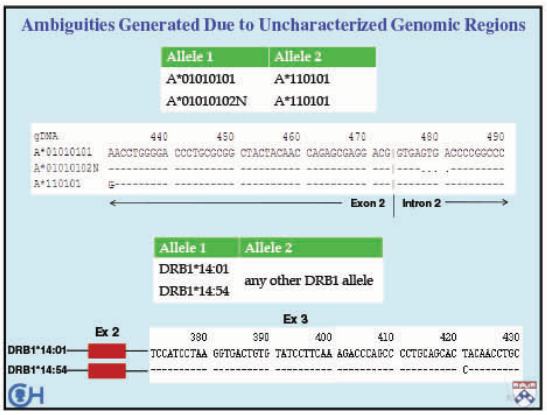


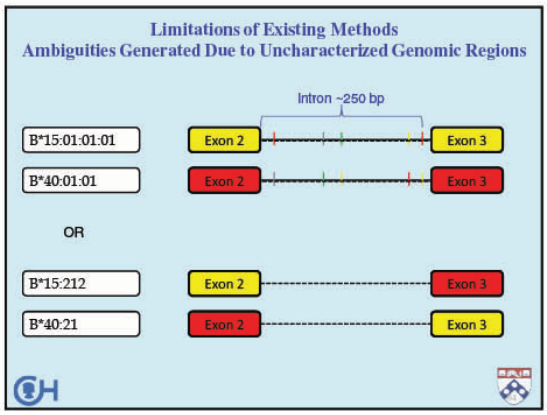


	Donors typed at HR	Donors typed at HR resulting to donations
2010	16%	54%
2011	25%	72%









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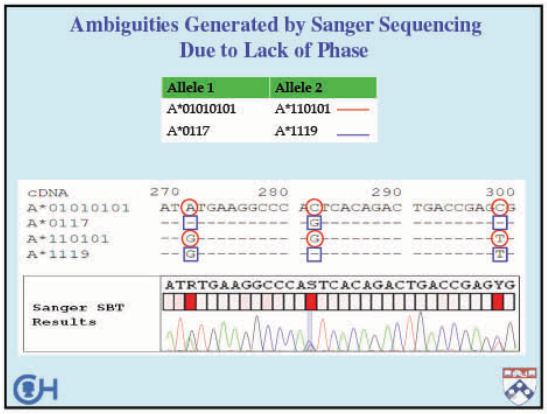
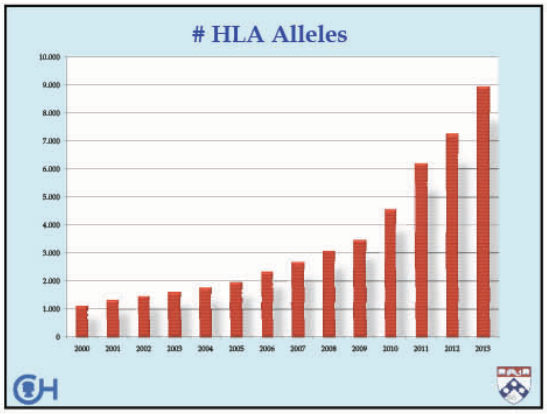
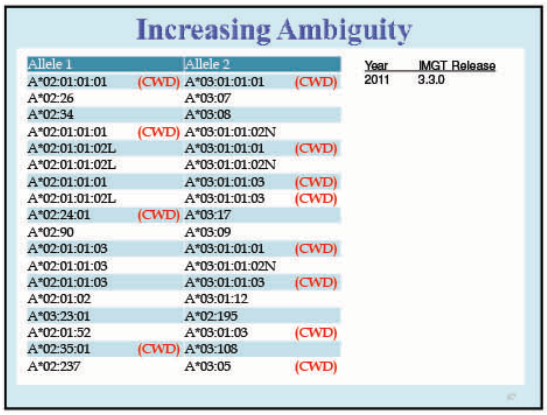
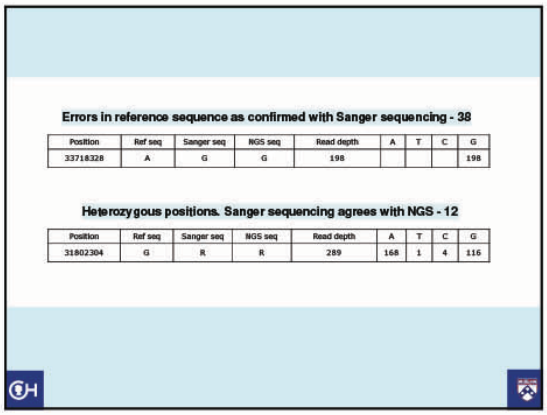
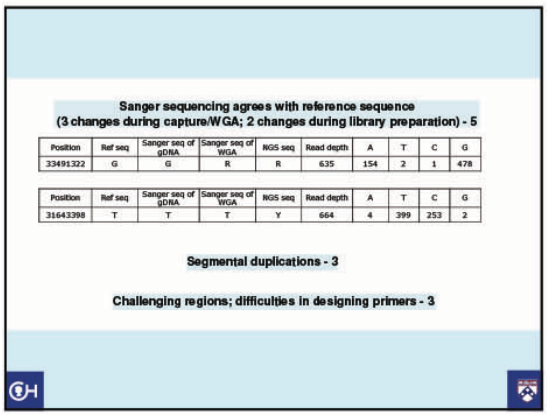










ABSTRACTS

One of the main objectives of this workshop was to share ideas and experiences that will help us face the challenges and seek the opportunities that will make the small and medium size registries better, more effective, financially and operationally more sustainable.

Therefore the closing session concentrated on sharing and understanding experiences and challenges of other registries:

Sharing Work Diversity Experiences - Many Small Registries are involved with more than just unrelated bone marrow donor searches. Your experiences may help other registries to expand their activities, which in turn, will make them more sustainable.

Sharing Recruitment Experiences - Each one of us operates in a different environment but we all try to recruit the best donors for our patients. Your recruitment strategy may help others improve their donor pool.

Sharing Marketing and Fundraising Experiences - Raising awareness and raising funds are both equally important factors for the sustainability of our operations.

Sharing Donor Search Experiences - Smaller registries have to be resourceful in order to be effective in their quest to find donors for their patients. You can share the tools and strategies you use and present interesting cases.

Sharing Donor Typing Strategies - The cost and the methodology for HLA typing of the new donors is one of the greatest concerns of a small registry. The level of typing and the method used can determine the quality of the registry and its financial survival.

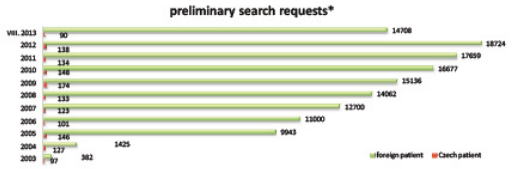
Current State of the Czech Stem Cells Registry and its Challenges

Marie Kurikova
Czech Stem Cells Registry
Institute for Clinical and Experimental Medicine

CSCR activities – patient focused I.

Searches of suitable donors and CBUs for Czech and foreign patients

- In 2012 we processed – 88 typing and 277 blood sample rqst. from Czech TC for Czech and foreign donors

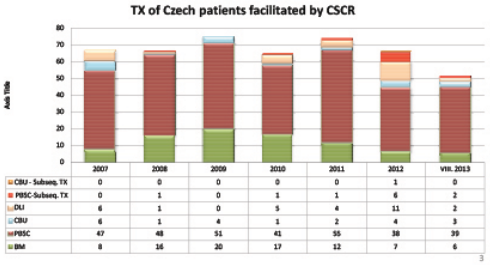


*EMDIS connection increases number of foreign requests

CSCR activities – patient focused II.

Arrangement of the transport of the grafts to the TCs (donors+CBU)

- registry is required to hold Tissue establisment certification as per Tissues and Cells Law – audited by State Institute for Drug Control
- Prepare documents, approve travel itineraries, etc.



	2007	2008	2009	2010	2011	2012	VIII. 2013
CBU - Subseq. TX	0	0	0	0	0	1	0
PBSC-Subseq. TX	0	1	0	1	1	6	2
DLI	6	1	0	5	4	11	2
CBU	6	1	4	1	2	4	3
PBSC	47	48	51	41	55	38	39
BM	8	16	20	17	12	7	6

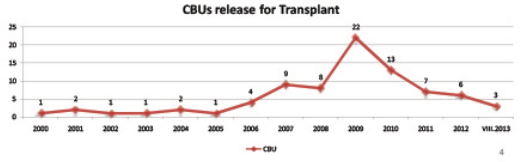
CSCR activities – Cord blood

Responsible for data maintenance for

- **Czech CBB** in BMDW and EMDIS
- **Eurocord Slovakia** in EMDIS

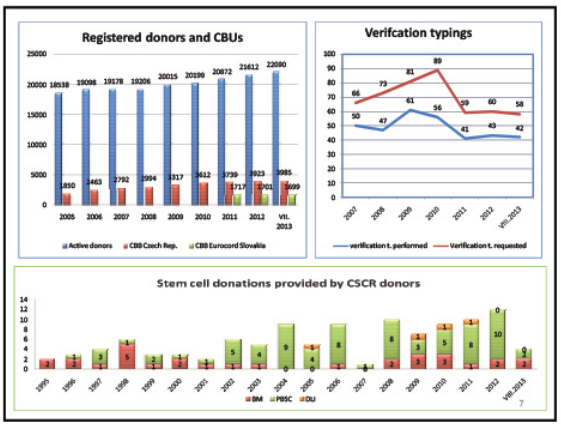
We handle yearly about - 100 additional information requests (CBU report)
100 **extended** typing rqst.
10 **verification** typing rqst.

CBU shipment – usually urgent matter – 3 days from rqst to transport



CSCR activities – Donor Centre

- Recruitment of new donors
  - Dept. of Immunogenetics, IKEM perfoms
    - initial donors' HLA typing - A,B,(C),DRB1* LR/IR – partly
    - extended typing
    - verification typing for 1 TC and CBUs upon request
- Updating of the donors' data and records in database at time of extended typing
  - DC contact all donors before their stored sample is typed (158 rqsts in 2012)
- Verification typing blood sample procurement and counselling of the donor
- Regular consultation with Collection c. on donors' health condition
- Coordination of PBSC and BM harvests with CC – apheresis dept. or orthopaedic clinic and harvesting haematologists
- Donor Follow Up

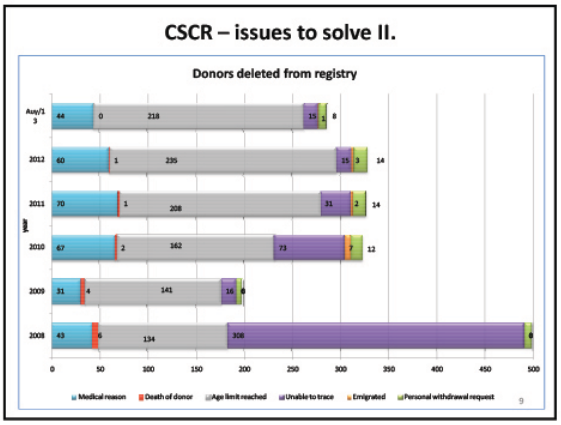


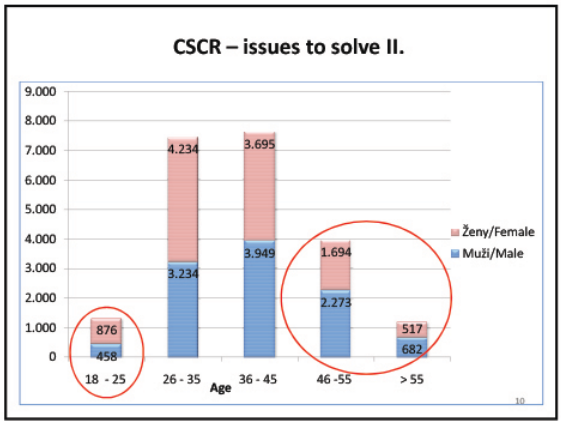
CSCR – issues to solve I.

Money !!!???

- Payments from health insurance limited / decreasing
- Donations (sponsors) – limited – registry is part of the governmental hospital

8





Recruitment and retention of donors - renewed effort

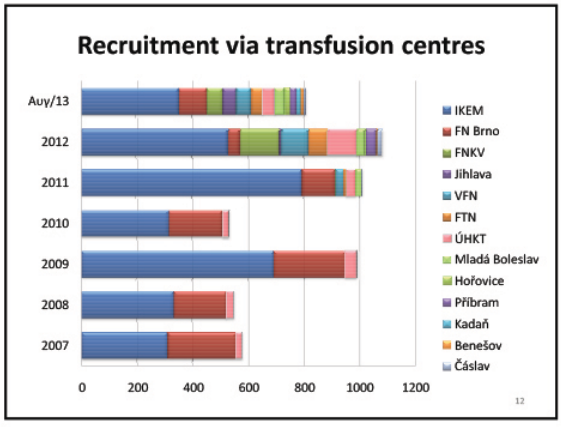
Year 2012-2013

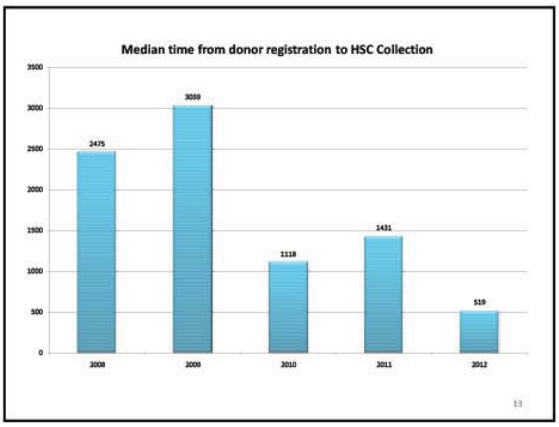
Intensified effort to inform general public of stem cells donation → register more donors

„Low-cost" recruitment

- Lectures for students, companies, groups
  - Technical University Liberec - patient focused drive,
  - Charles University Prague
- cooperation with several blood transfusion centers started
- total makeover of website www.darujzivot.cz was introduced with re-arranged and comprehensible information for public and both new and registered donors – connection to FB
- Cooperation with famous Ice-hockey team(s)
- Radio/TV news
  - 4 x/year „Donate with Czech Radio" (public broadcasting service)

11




Median time from donor registration to HSC Collection
3500
3000
2500
2000
1500
1000
500
0
2475
3039
1118
1431
519
2008
2009
2010
2011
2012
13


IKEM
PRAGUE
CSCR
Thank you for your attention
14

MACHTELD OUDSHOORN – EUROPDONOR FOUNDATION

europ donor

1st International Meeting Cyprus

3 - 5 October 2013

Machteld Oudshoorn

Clinical Director Europdonor

1

europ donor

Celebrating 25th Anniversary!

2

europ donor

Europdonor, facts and figures

- Founded in 1988 by Prof. Jon van Rood, celebrating 25th anniversary this year!
- Dutch donor Registry with more than 43.000 donors and CBU's
- Donor centres: Europdonor, Sanquin bloodbank and Nijmegen
- Collection centres: University Medical Centres in Leiden en Nijmegen
- In 2012: 35 stem cell donations and 12 CBUs delivered for national and international patients.
- Transplant Center search support and coordination for 453 Dutch patients (2012) in need of unrelated donor/CBU.
- Resulting in 376 transplants for Dutch patients performed in 2012.

3

europ donor

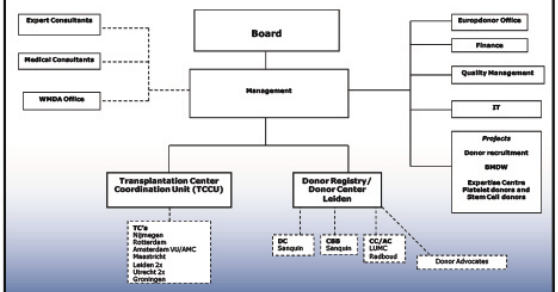
Europdonor, facts and figures

- 23,3 FTE, 30 people
- BMDW office and providing technical maintenance and user support
- WMDA office
- Not-for-profit organization with annual budget € 2 mln, (no government funding)

4

europ donor

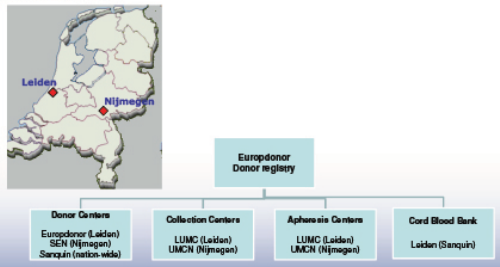
Organizational structure



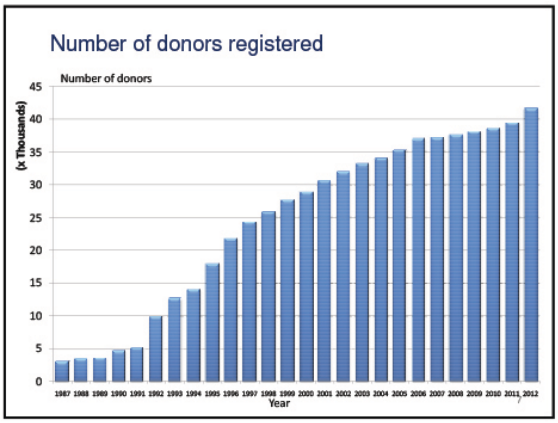
5

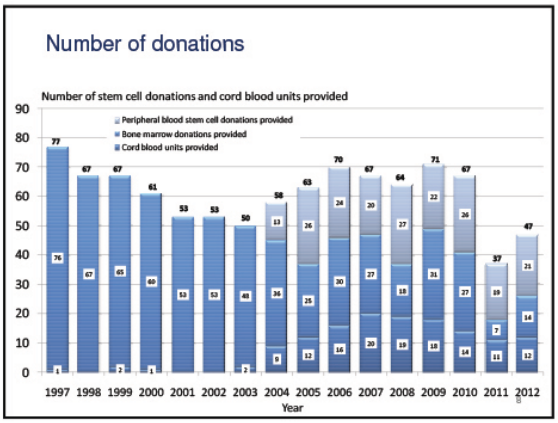
europ donor

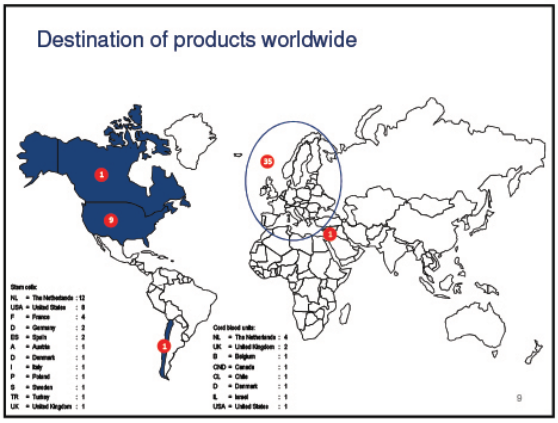
Organizational structure in the Netherlands

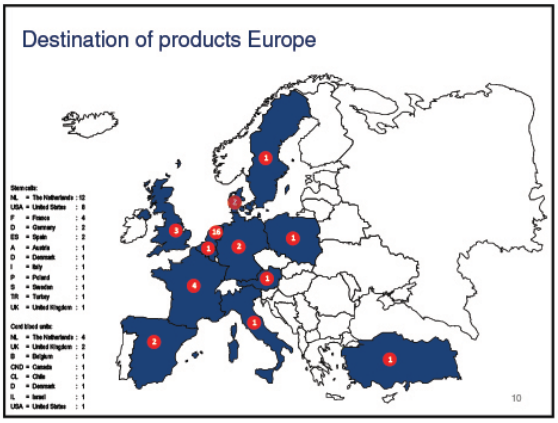


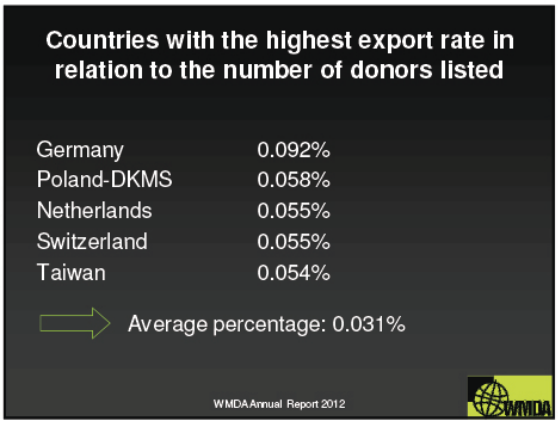
6

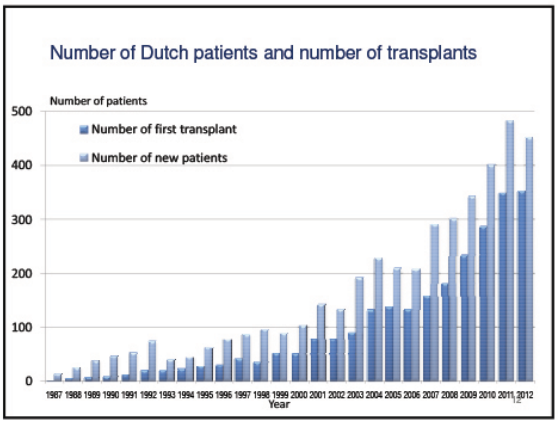

Number of donors registered
Number of donors
(x Thousands)
Year


Number of donations
Number of stem cell donations and cord blood units provided
Peripheral blood stem cell donations provided
Bone marrow donations provided
Cord blood units provided
Year

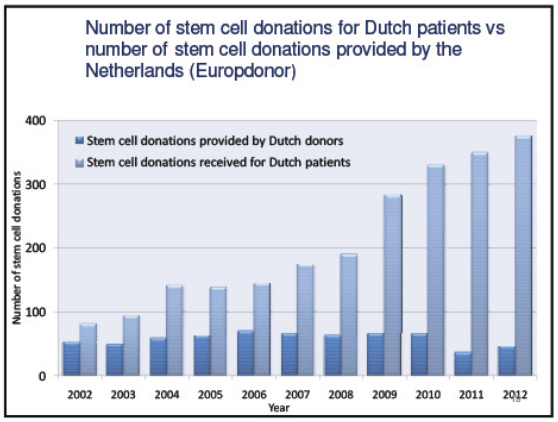

Destination of products worldwide


Destination of products Europe


Countries with the highest export rate in relation to the number of donors listed
Germany 0.092%
Poland-DKMS 0.058%
Netherlands 0.055%
Switzerland 0.055%
Taiwan 0.054%
Average percentage: 0.031%
WMDA Annual Report 2012


Number of Dutch patients and number of transplants
Number of patients
Number of first transplant
Number of new patients
Year

MACHTELD OUDSHOORN – EUROPDONOR FOUNDATION



In conclusion

- Europdonor may be 'small' but is a very active registry
- This is visible both in import as well as in export
- High number of transplants
- Active role in donor search and selection
- This provides opportunities for the future
  - Growing donor pool will bring more balance in patients/donations
  - Authority on donor search and selection within the Netherlands, useful for GEMS?
  - Good partnerships with TC's is crucial!
  - Seamless IT systems a requirement

14

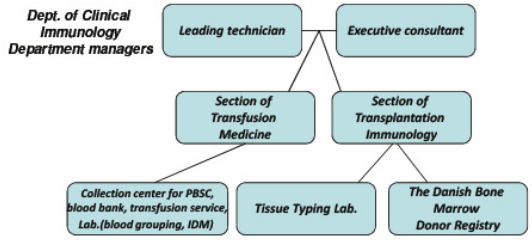
The Danish Bone
Marrow Donor Registry

Betina Sorensen M.D.
October 2013

The Danish Bone Marrow Donor Registry

- ***Organization:***
  - 1 hub (Aarhus)
    - PBSC collection center, donor center
  - 2 donor centers (Odense, Aalborg)
  - 1 marrow collection center (Aarhus)
  - 2 transplantation Units (Aarhus, Copenhagen)
  - Part of a tax-funded public health care system
  - Geographical location of patients/donors

The Danish Bone Marrow Donor Registry

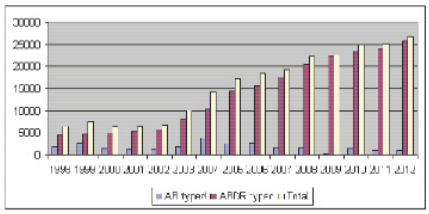


The Danish Bone Marrow Donor Registry

- ***Registry was established in 1990 among blood banks***
  - Decision to only recruit blood donors

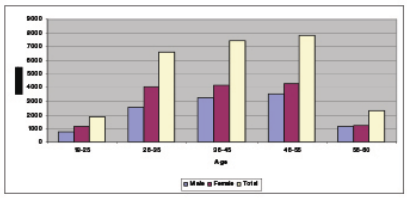
The Danish Bone Marrow Donor Registry

- ***Number of donors:***



The Danish Bone Marrow Donor Registry

- ***Age and gender of donors:***



The Danish Bone Marrow Donor Registry

- ***Benefits/challenges:***
- Part of a public hospital – follow their rules
- Many functions in one place
- Old, established registry – many traditions
- Valuable sharing experience and challenges
- Collaboration (GEMS)

The Danish Bone Marrow Donor Registry

- ***Where to begin?***
- Things that are "easy to implement"
  - Better HLA typing upfront
  - Better IT system
    - EMDIS
  - Better dialog with the transplant centers

The Danish Bone Marrow Donor Registry

- ***Next step - Things that are not so easy:***
- Recruitment:
  - Blood donors - Non-blood donors?

The Danish Bone Marrow Donor Registry

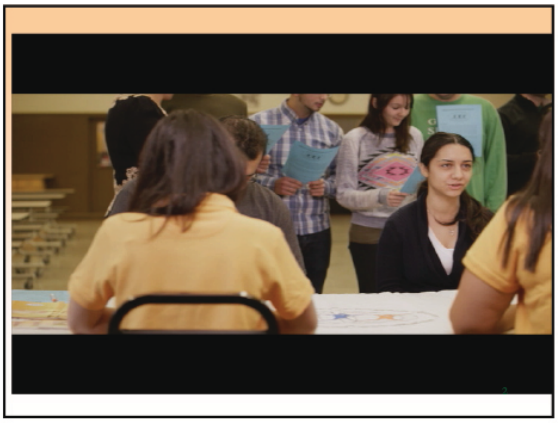
- ***Conclusion:***
- Meetings are valuable
- Be inspired
- Do what is possible

Establishing an International Bone Marrow Donor Registry

Challenges and Achievements

Dr. Frieda Jordan
Co-founder and President, ABMDR

1



Getting to know ABMDR

Our Mission

To save lives by recruiting and providing matched unrelated donors for bone marrow or stem cell transplantation to all Armenian & non-Armenian patients worldwide who are suffering from leukemia and other life-threatening blood related illnesses

Getting to know ABMDR

Brief history / major landmarks

- **1999** ABMDR is founded as an independent, non-governmental, not-for-profit organization
- **2001** State of the art laboratory is established in Yerevan, registry is started, first donor is recruited
- **2003** first transplant is facilitated
- **2005** Los Angeles office opens
- **2009** Stem Cell Harvesting Center begins operation

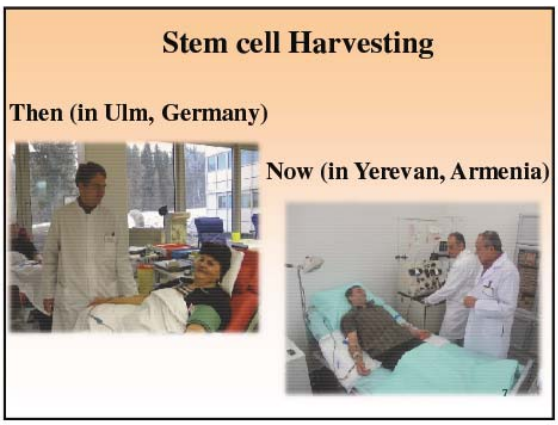
Getting to know ABMDR

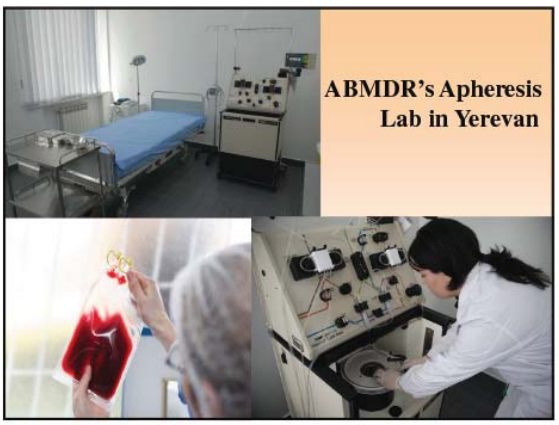
Special Challenges demanding Special Approaches

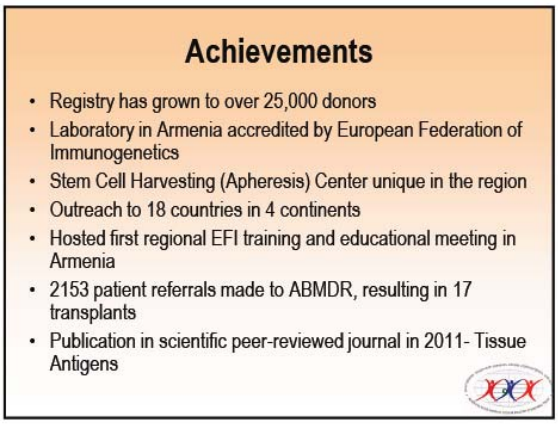
- Very unique genetic pool
- Very large and widespread diaspora
- No governmental financial support

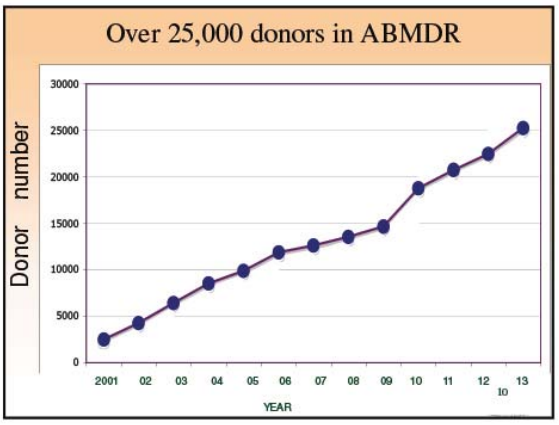
ABMDR's Molecular Tissue Typing Laboratory

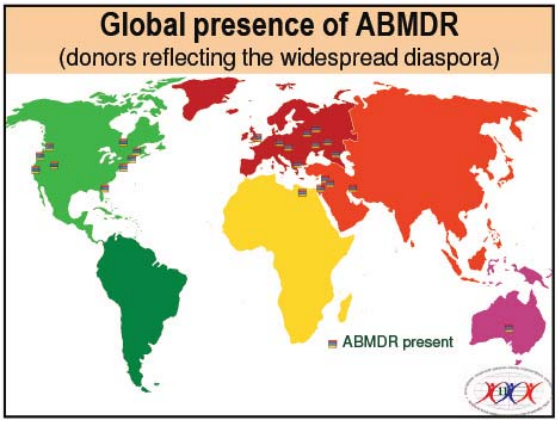
- State of the art equipment
- Cutting edge DNA technology
- Highly trained staff of physicians and technicians
- Accredited by European Federation of Immunogenetics (EFI)

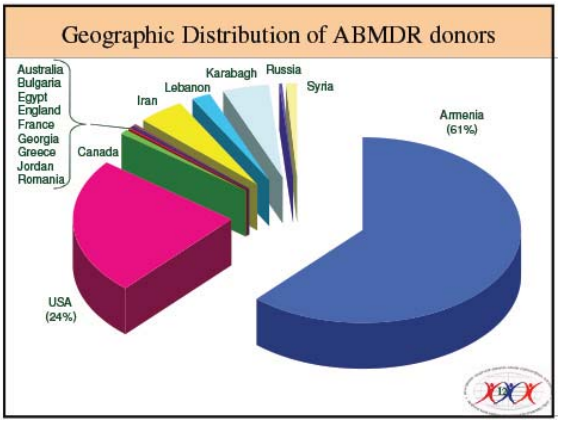

Stem cell Harvesting
Then (in Ulm, Germany)
Now (in Yerevan, Armenia)


ABMDR's Apheresis Lab in Yerevan

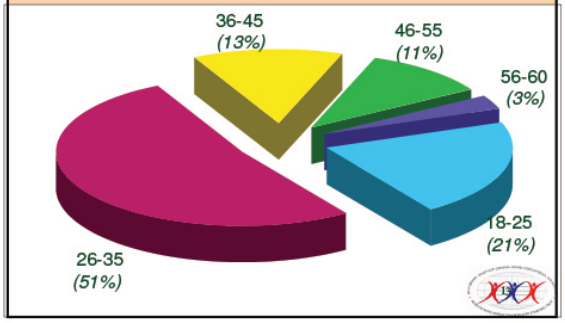

Achievements
• Registry has grown to over 25,000 donors
• Laboratory in Armenia accredited by European Federation of Immunogenetics
• Stem Cell Harvesting (Apheresis) Center unique in the region
• Outreach to 18 countries in 4 continents
• Hosted first regional EFI training and educational meeting in Armenia
• 2153 patient referrals made to ABMDR, resulting in 17 transplants
• Publication in scientific peer-reviewed journal in 2011- Tissue Antigens


Over 25,000 donors in ABMDR
Donor number
30000
25000
20000
15000
10000
5000
0
2001 02 03 04 05 06 07 08 09 10 11 12 13
YEAR

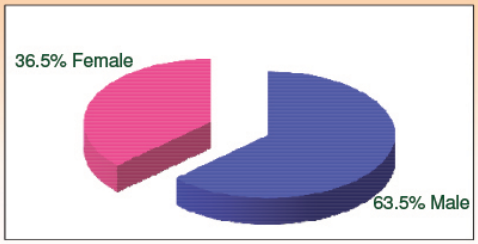

Global presence of ABMDR
(donors reflecting the widespread diaspora)
ABMDR present


Geographic Distribution of ABMDR donors
Australia
Bulgaria
Egypt
England
France
Georgia
Greece
Jordan
Romania
Canada
Iran
Lebanon
Karabagh
Russia
Syria
Armenia (61%)
USA (24%)

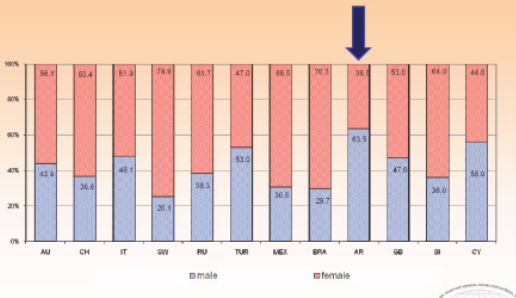
Very young donor base: 72% younger than 35 yrs old



High percentage of male donors



ABMDR has the highest male/female donor ratio



Operational networks

- USA
  - Dana Farber Cancer Center in Boston, MA
  - City of Hope in Duarte, CA
  - Children's Hospital in LA, CA
  - Glendale Memorial Hospital in LA, CA
  - Glendale Adventist Hospital in CA
- Europe
  - England: Anthony Nolan Institute
  - Germany: Institute for Clinical Transfusion Medicine and Immunogenetics Ulm
  - Cyprus: The Cyprus Bone Marrow Donor Registry
  - Greece: Evangelismos Hospital
  - Russia: Moscow and St. Petersburg Hospitals
- Middle East
  - Iran: Shariat Hospital in Tehran
  - Lebanon

Memberships/International networks

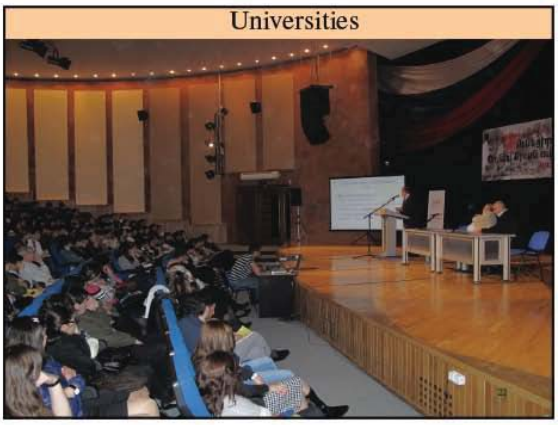
- World Marrow Donor Association (WMDA)
- Bone Marrow Donors Worldwide (BMDW)
- European Federation of Immunogenetics (EFI)
- American Society for Histocompatibility and Immunogenetics (ASHI)
- National Marrow Donor Program co-op member (NMDP)

Structure of ABMDR

- Armenia
  - Registry
  - Laboratory
- US
  - Operational office in Los Angeles
  - Recruitment centers in East Coast and West Coast
- Worldwide
  - Offices/representatives in
    - Karabagh
    - Iran
    - Lebanon
    - Russia
    - Germany


Bases of operation
• Churches/clergy
• Schools/colleges/universities
• Cultural and Political organizations
• Military
• Corporations
• Armenian Embassies


Churches


Universities


24


Schools


Military


Corporations
VIVACell


Bank of America


Embassies


Bulgaria

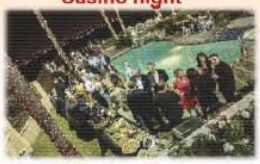
How do we publicize?

- Both in US and Armenia
  - Lectures
  - Articles in press
  - TV/Radio
  - Website
  - Newsletter
  - Other leaflets and publications
  - Fundraisers
    - Comedy night
    - Walkathon
    - Wine tasting
    - Casino night
    - Banquet/luncheons

Fundraising Events

Casino night

Gala



Wine tasting

Comedy Night

33

Where do we go from here?

- Increase ABMDR donor pool to 30,000
- Auto transplantation
- Comprehensive molecular diagnostic services to patients in Armenia
- Expand stem cell research and harvesting services in Armenia and in the region
- Help the Ministry of Health of Armenia establish a transplant center

34

ARMENIA OPERATIONS

ABMDR Board Members and Volunteers

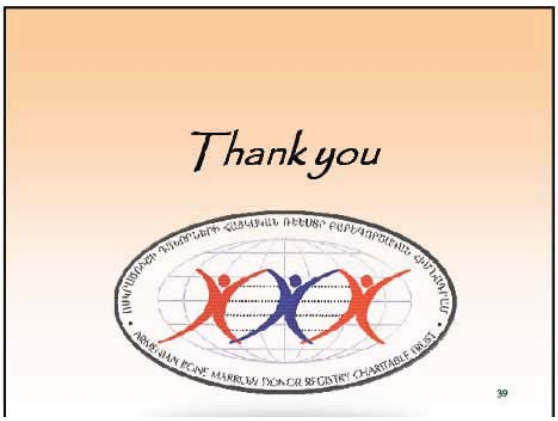
36

Dr. Bella Kocharian,
former First Lady of Armenia
and Honorary Chair of ABMDR

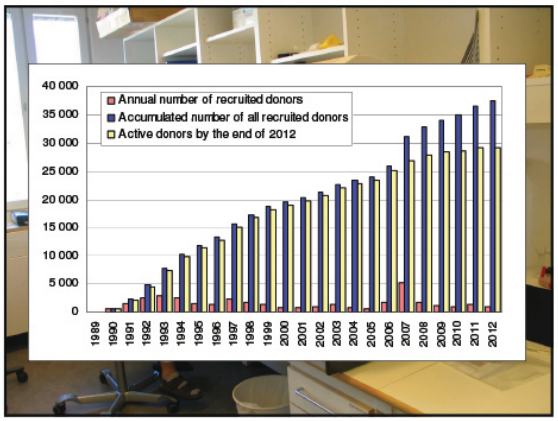
Mark Geragos Esq. Chairman
Dr. Frieda Jordan President
Dr. Sevak Avagyan Executive Director - Armenia

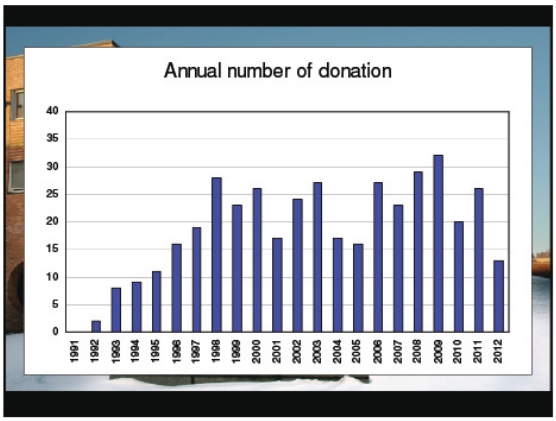
37

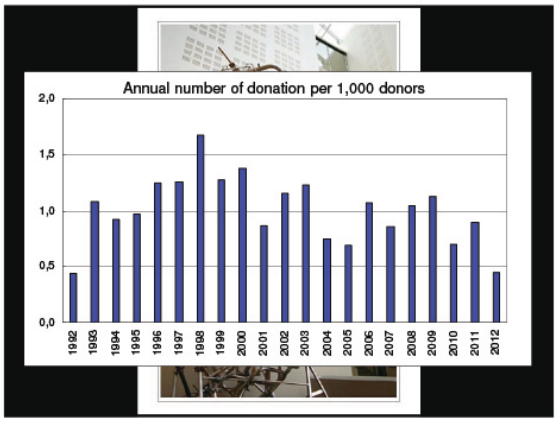
ABMDR
laboratory and harvesting center staff

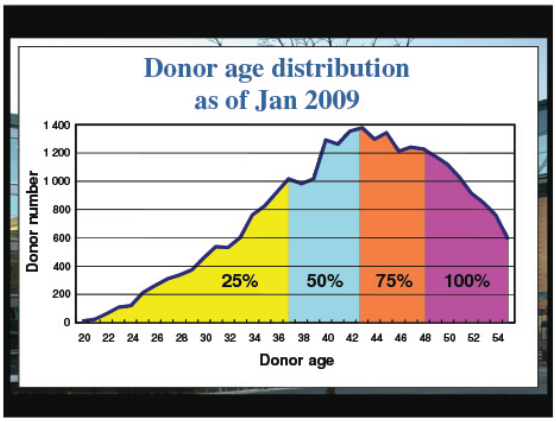


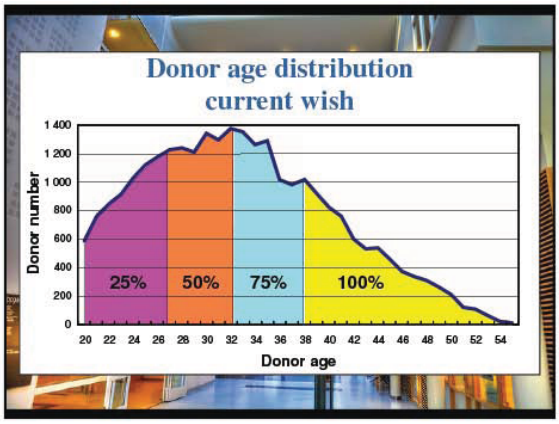
TORSTEIN EGELAND – THE NORWEGIAN BMDR

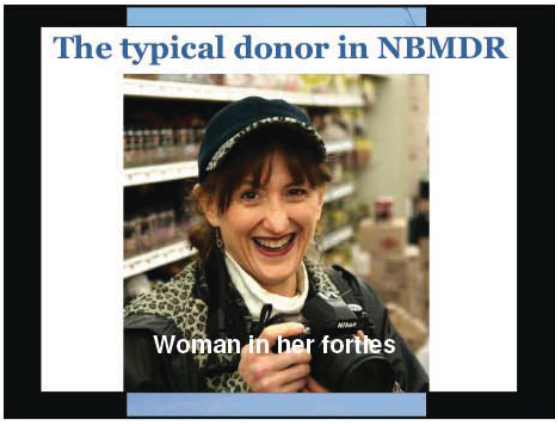


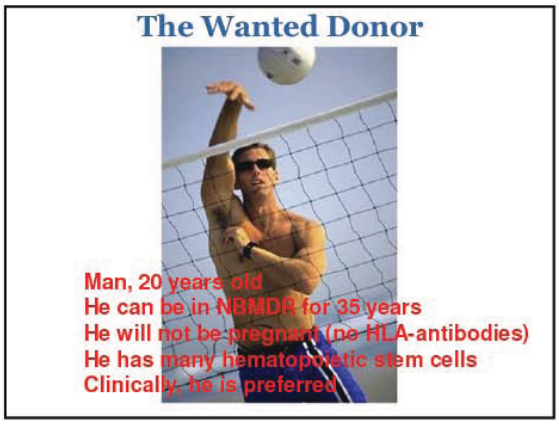







Donor age distribution
current wish
Donor number
1 400
1 200
1 000
800
600
400
200
0
25%
50%
75%
100%
20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54
Donor age


The typical donor in NBMDR
Woman in her forties


The Wanted Donor
Man, 20 years old
He can be in NBMDR for 35 years
He will not be pregnant (no HLA-antibodies)
He has many hematopoietic stem cells
Clinically he is preferred

IUBMR
Ireland

Diarmaid Ó Donghaile,
Sinéad Horgan

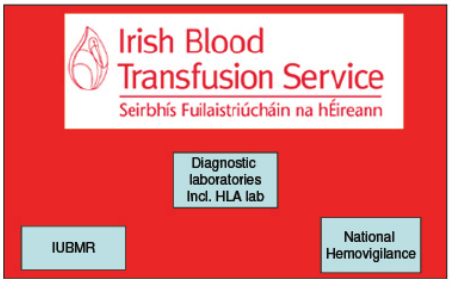
1

History

- The registry was established in 1989 within the Irish Blood Transfusion Service
- Full WMDA Accreditation in 2012
- On site Tissue Establishment inspection biannually by competent authority(IMB)
- Currently has 21,154 donors of which 21,031 are AB DRB1 typed.
- 14,234 are Class I DNA typed
- 14,825 are Class II DNA typed

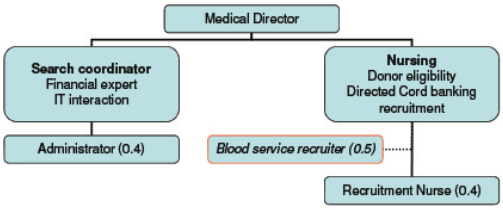
2

Structure



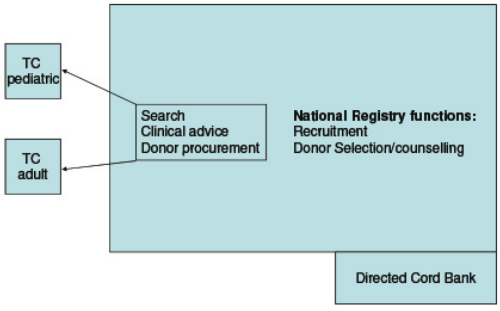
3

Structure: IUBMR



4

IUBMR: activities



5

IUBMR: Strengths

- Small groups can be efficient
  - Easy communication
  - Common expertise from necessity
- Knowledge base and expertise of a Blood Establishment
- Close relationship with transplant centers

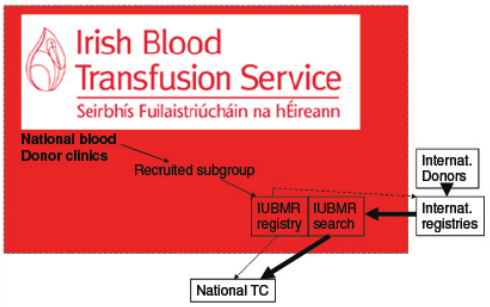
6

IUBMR: weaknesses

- Blood establishment dependency
  - Competing functions
  - *Irish financial strife*
- Funding limitation
  - Cannot fundraise independently
- IT support limited
- Staffing numbers has the potential to compromise function
- Small registry size

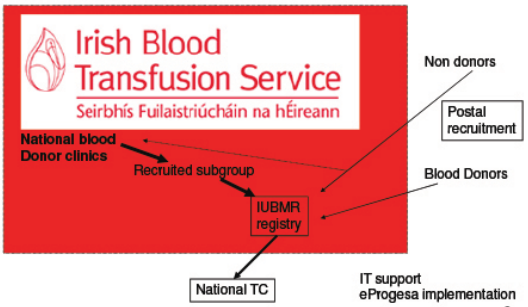
7

IUBMR: activity



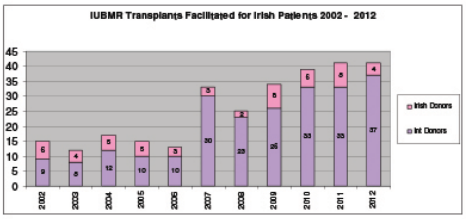
8

IUBMR: *desired* activity



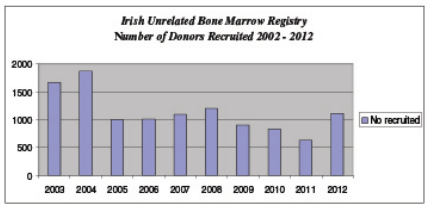
9

IUBMR: Number Of Transplants Facilitated



10

IUBMR Recruitment



11

Goals

- Enhance profile within blood service
- Better IT support
- Enhance donor recruitment

12

"I want life" – The story of the Croatian Bone Marrow Donor Registry

Mirta Mikulić

CBMDR – UHC Zagreb

1

"I want life" – The story of the Croatian Bone Marrow Donor Registry

Mirta Mikulić

CBMDR – UHC Zagreb

2

"I want life" – The story of the Croatian Bone Marrow Donor Registry

Mirta Mikulić

CBMDR – UHC Zagreb

3

"I want life" – The story of the Croatian Bone Marrow Donor Registry

Mirta Mikulić

CBMDR – UHC Zagreb

4

"I want life" – The story of the Croatian Bone Marrow Donor Registry

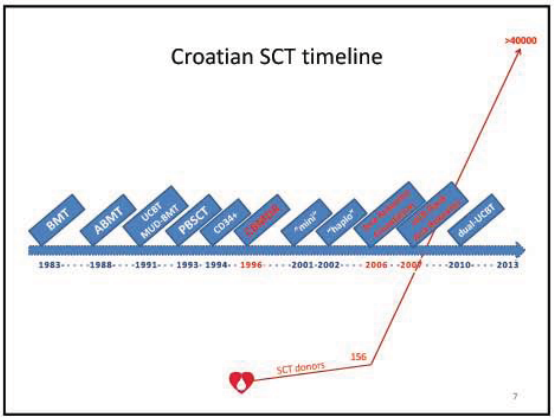
Mirta Mikulić

CBMDR – UHC Zagreb

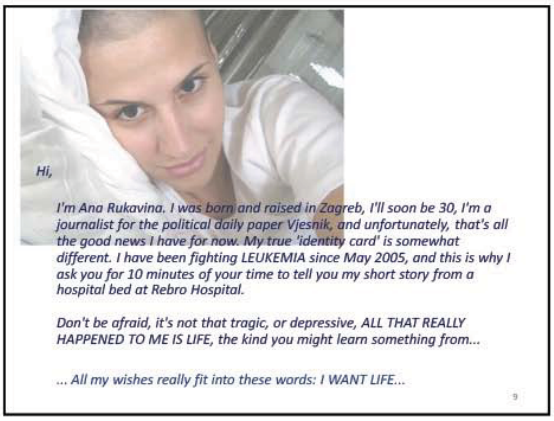
5

Croatian SCT timeline

6


Croatian SCT timeline
>40000
RMT
ABMT
UCBT
MUD-BMT
PBSCT
CD34+
"mini"
"haplo"
dkat-UCBT
1983
1988
1991
1993
1994
1996
2001
2002
2006
2010
2013
SCT donors
156

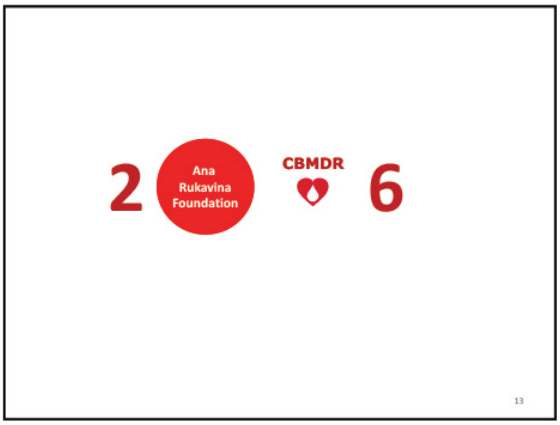

Ana Rukavina Foundation
Ana Rukavina Erceg (1977-2006)

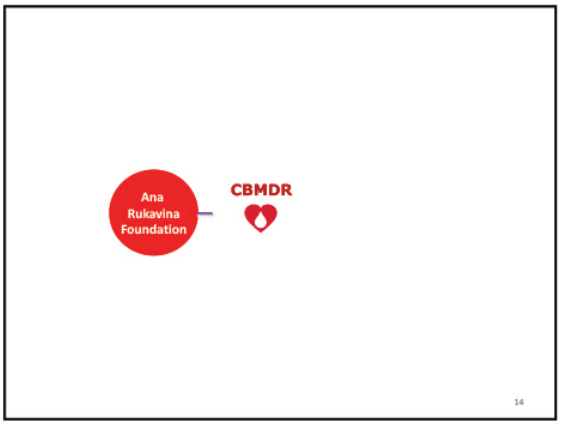

Hi,
I'm Ana Rukavina. I was born and raised in Zagreb, I'll soon be 30, I'm a journalist for the political daily paper Vjesnik, and unfortunately, that's all the good news I have for now. My true 'identity card' is somewhat different. I have been fighting LEUKEMIA since May 2005, and this is why I ask you for 10 minutes of your time to tell you my short story from a hospital bed at Rebro Hospital.
Don't be afraid, it's not that tragic, or depressive, ALL THAT REALLY HAPPENED TO ME IS LIFE, the kind you might learn something from...
... All my wishes really fit into these words: I WANT LIFE...

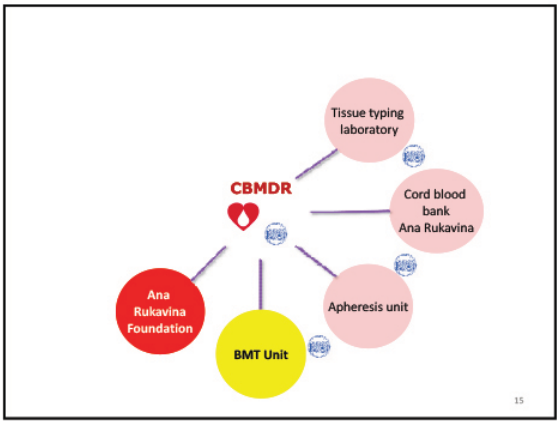

ZAKLADA ANA RUKAVINA
Ana Rukavina Foundation – since 2006
220 donor drives - 39 000 donors recruited
Umbilical Cord Blood Bank Ana Rukavina
17 concerts
3.000.000,00 Eur in donations
Projects:
I want life!
The cure is in us
New life for new life
One kuna for one drop of life

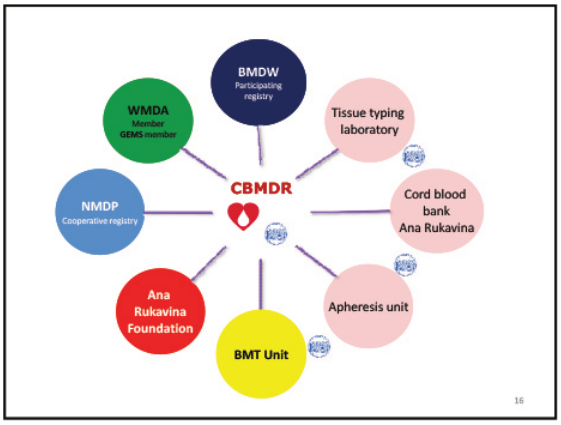

ZAKLADA ANA RUKAVINA
220 donor drives in 100 Croatian towns


ZAKLADA ANA RUKAVINA
17
Big concerts for the Foundation
30|11







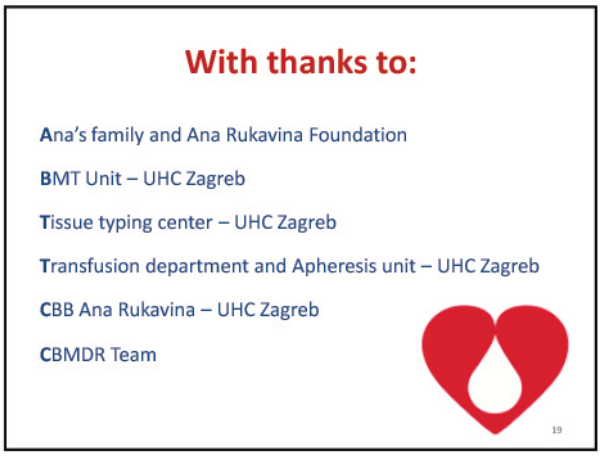


CBMDR in numbers

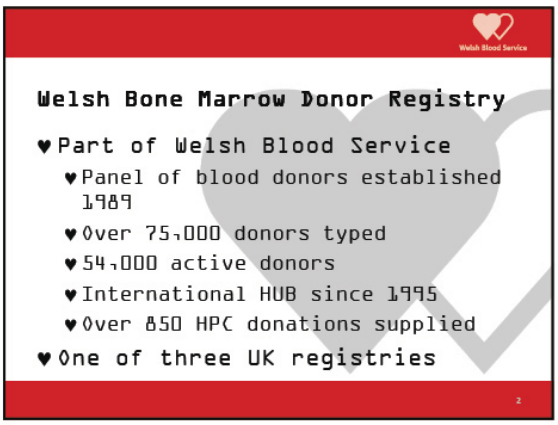
- **Donor recruitment**
  UHC Zagreb + 9 regional transfusion medicine centers
  + Ana Rukavina Foundation donor drives
- **35,145 BMDW registered** and 33,791 ABDR typed (96%) adult donors
- **2,379 registered CBUs** – 100% typed
- **First PBSC donation – 2009**
- **33 adult donor donations + 3 CBUs**
  20 Croatian patients + 16 international patients
- **30-40 searches** for our patients per year
- **80 imported** stem cell products

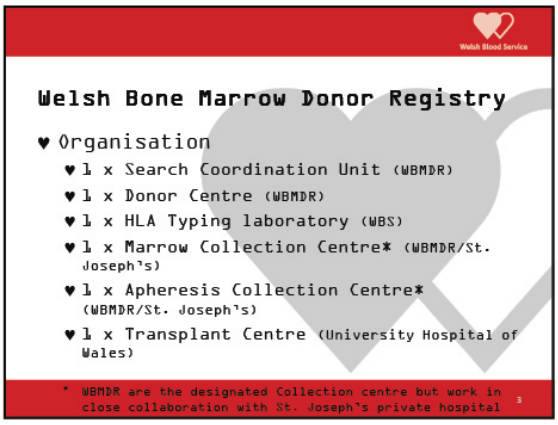
CBMDR – planning for the future

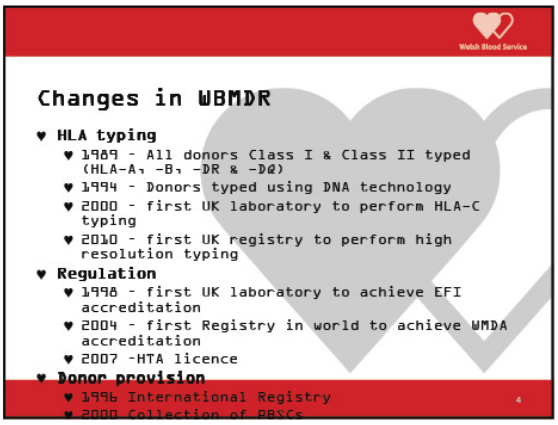
- **Continuous promotion and raising awareness about stem cell donation with support of the Ana Rukavina Foundation**
- Optimal size? Annual recruitment rate?
- Extended typing... consider upfront HR?
- Web and social media
- Prometheus / EMDIS
- Implementing new legislation into practice
  - "Law on human organ transplantation" – Dec 2012 – in accordance with EU directives 2010/53/EU and 2012/25/EU
- Application for WMDA qualification planned for 2014

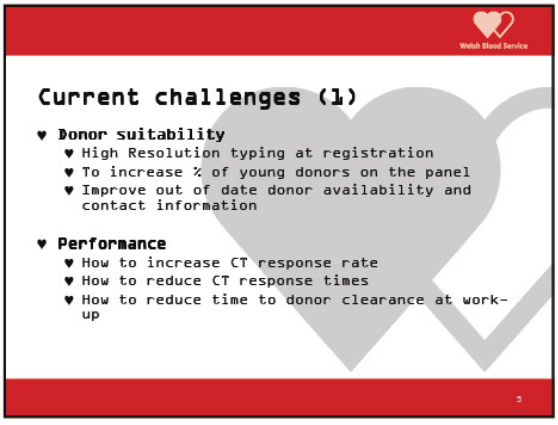

With thanks to:
Ana's family and Ana Rukavina Foundation
BMT Unit – UHC Zagreb
Tissue typing center – UHC Zagreb
Transfusion department and Apheresis unit – UHC Zagreb
CBB Ana Rukavina – UHC Zagreb
CBMDR Team
19

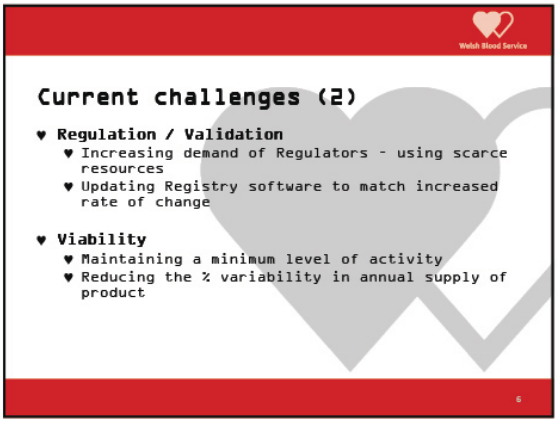
MARTIN MCGREGOR – WELSH BMDR



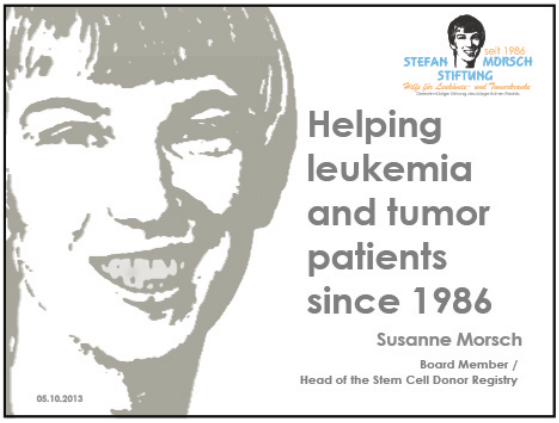


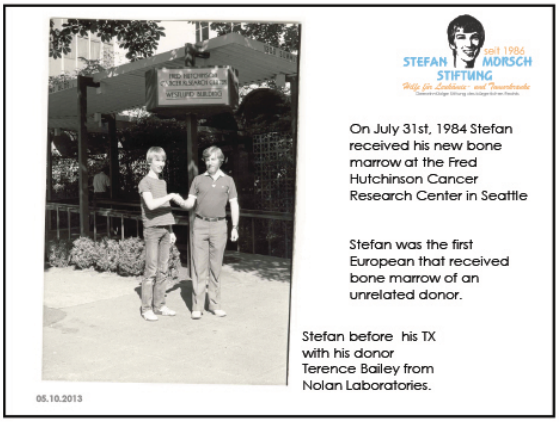


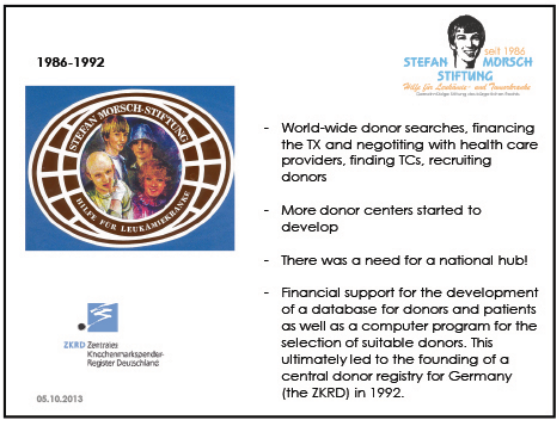




SUSANNE MORSCH – THE STEFAN MORSCH STIFTUNG, HELPING LEUKEMIA AND TUMOR PATIENTS SINCE 1986

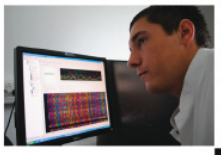






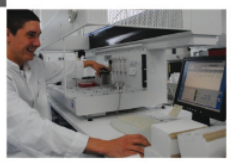
SUSANNE MORSCH – THE STEFAN MORSCH STIFTUNG, HELPING LEUKEMIA AND TUMOR PATIENTS SINCE 1986

HLA-Lab



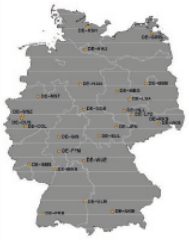
The HLA –Laboratory of the Stefan-Morsch-Stiftung under the Direction of Dr. Marco Schäfer was established in 1997.

Accredited by EFI and ASHI



05.10.2013

Bone Marrow and Stem Cell Foundation Germany



- Non-profit foundation, established in 1999.
- A national network of 26 cooperating German bone marrow donor centers. All donor centers are in fact ZKRD-independent registries, "donor center" is used to avoid misunderstandings.
- Strong advocacy group for donors, patients and volunteers. Negotiations with public and private health care providers
- Cooperation and support with blood drives, HLA-typing, stem cell collections, annual workshop, German Standards…
- Almost 2 million volunteer donors

05.10.2013

International Activities / Unrelated Donor Search Center

Since 2003 Donor Search Center for patients of the TCs in Moscow, St. Petersburg and Amman

Since 2013 German Search Center for the TCs in Flensburg and Lübeck.

Upon request: Support in the establishment of TCs and Registries in countries without a donor registry (f.e. Russia, Luxembourg).

HLA-typing support, sharing experience, providing information.

05.10.2013

Apheresis Center

2005: Opening of the adult stem cell collection center of the Stefan-Morsch-Stiftung in Birkenfeld.

05.10.2013

Financial support in the establishment of BMT Units

1999 - Campus Benjamin-Franklin, Charité in Berlin

2012 - Malteser Krankenhaus St. Franziskus-Hospital in Flensburg

05.10.2013

Our mission: Saving lives!

-Recruiting volunteers that join the registry to become potential bone marrow and stem cell donors

-Identifying matching donors

-Accompanying and supporting the unrelated donors from the time of registration until the time of donation and providing comprehensive information, education and advice.

-Supporting patients and their families, f. e. financial support for costs related to the treatment of the disease that lead to a financial distress (child care, travel costs, living costs of accompanying person,…).

-Funding of research / clinical trials / transplant centers

05.10.2013

SUSANNE MORSCH – THE STEFAN MORSCH STIFTUNG, HELPING LEUKEMIA AND TUMOR PATIENTS SINCE 1986

Donor recruitment

-Homepage – online registration

-Patient related drives

-Company drives

-Schools, Universities, Military

-YouTube / Social Networks

05.10.2013

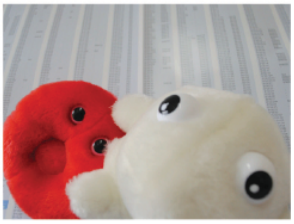
Additional criteria for registration in DE-SMS

- Ages 18-40
- Not more than two pregnancies

05.10.2013

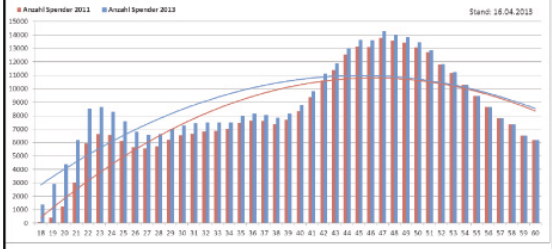
HLA-testing at registration

- Ages 18-30:
  - HLA-
    A*
    B*
    C*
    DRB1*
    DQB1*
  - high resolution level
- Ages 30+:
  - HLA-
    A*
    B*
    DRB1*
  - high resolution level

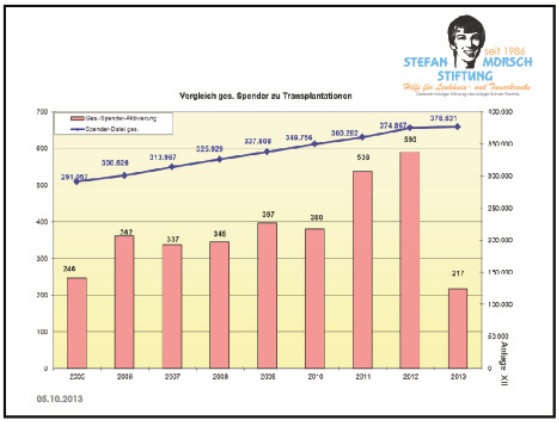


05.10.2013

Altersstruktur der Spenderdatei der SMS



05.10.2013



05.10.2013

Teamwork!

05.10.2013

SUSANNE MORSCH – THE STEFAN MORSCH STIFTUNG, HELPING LEUKEMIA AND TUMOR PATIENTS SINCE 1986

MATTI KORHONEN – WHY DO WE NEED A FINNISH BMDR?

Finnish Red Cross Blood Service

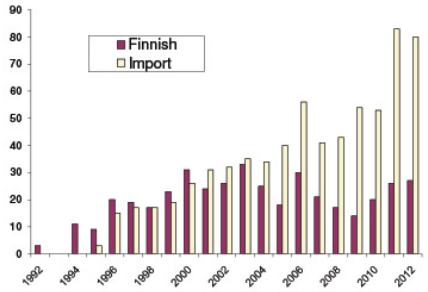
Why do we need a Finnish BMDR?

Tiina Linjama, MD
Matti Korhonen, MD
FBMDR
3.10.2013

www.veripalvelu.fi 1

Graft sources for Finnish patients

Finnish Red Cross Blood Service



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Finnish Red Cross Blood Service

Original article

HLA antigen, allele and haplotype frequencies and their use in virtual panel reactive antigen calculations in the Finnish population

K. Hamila, J. Pentsaari, T. Linjama, S. Koskela, T. Saarinen, J. Lauronen, M.-K. Auvinen, T. Jaatinen

Article first published online: 6 DEC 2012
DOI: 10.1111/tan.12035
© 2012 John Wiley & Sons A/S

Issue

Tissue Antigens
Volume 81, Issue 1, pages 35–43, January 2013

"The HLA antigen, allele and haplotype frequencies of the Finnish population are quite unique because of [illegible] gene pool. The study shows that there are few [illegible] population compared to mixed populations, and [illegible] more frequent."

Tiina Linjama, MD

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Sources of data

Finnish Red Cross Blood Service

- Analyses for the Prometheus probability matching project (Finnish BMDR donors/patients)
- NMDP data
- BMDW data

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Homogeneity of the Finnish Population

Finnish Red Cross Blood Service

Finland:

- <50 most common haplotypes constitute >50% of all haplotypes
- There are 34 haplotypes with a frequency of >0,5%

US caucasians:

- More than 100 most common haplotypes constitute >50% of all haplotypes
- There are 25 haplotypes with a frequency of >0,5%

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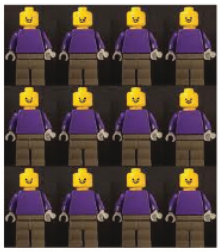
Finnish Red Cross Blood Service

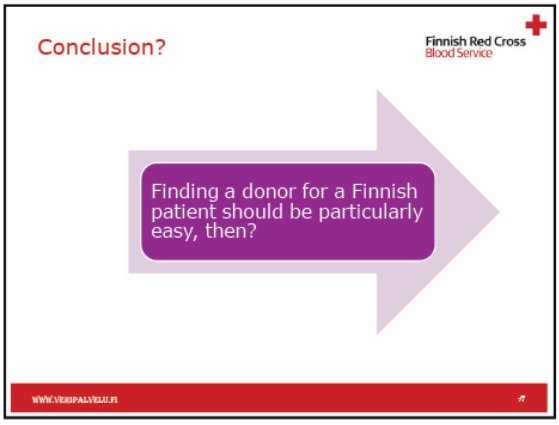


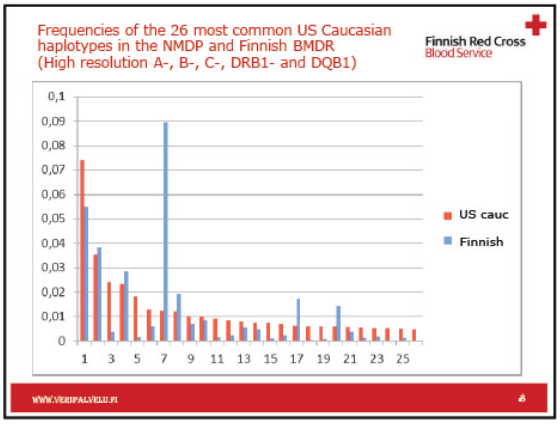
David Steiner/Prometheus:

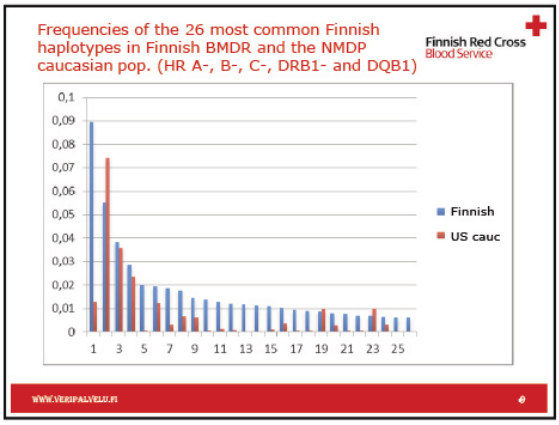
"I agree, the Finnish population is very homogeneous. The most homogeneous population I have seen in my analyses. "

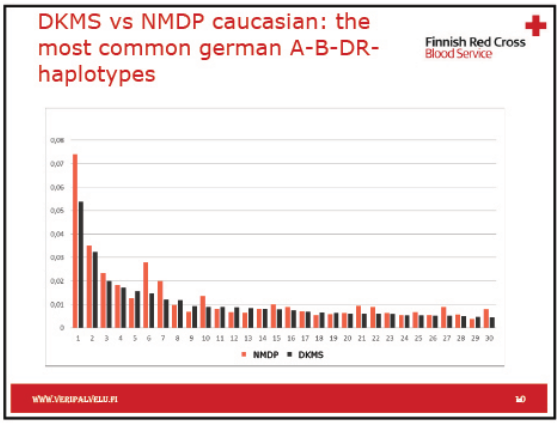
WWW.VERIPALVELU.FI 6

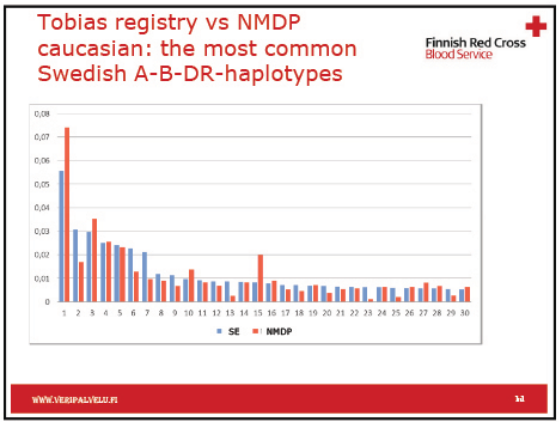
MATTI KORHONEN – WHY DO WE NEED A FINNISH BMDR?

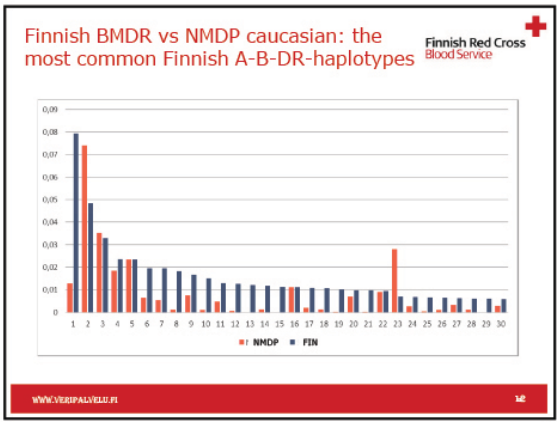








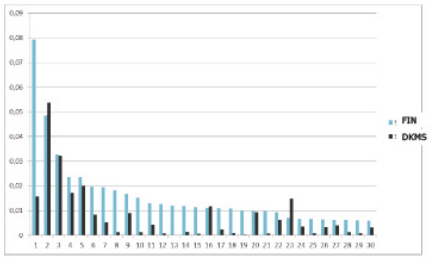




MATTI KORHONEN – WHY DO WE NEED A FINNISH BMDR?

Finnish BMDR vs DKMS : the most common Finnish A-B-DR-haplotypes

Finnish Red Cross Blood Service



WWW.VERIPALVELU.FI 13

The Finns are not average …

Finnish Red Cross Blood Service

- Six (15%) of the 40 most common Finnish haplotypes are not found in the NMDP at all
- Two of these have a frequency of > 1% (13. and 14. commonest)
- 15 (38%) of the 40 most common Finnish haplotypes are are >20x more frequent in the Finnish than among the US Caucasoid population.

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The impact of frequent HLA haplotypes in high linkage disequilibrium on donor search and clinical outcome after unrelated haematopoietic SCT

Finnish Red Cross Blood Service

- Jöris et al., Bone Marrow Transpl (2013) 48, 483-490
- Patients with one or two frequent haplotypes have a decreased risk of ≥grade II acute GVHD without increased risk of relapse compared to patients without FH (HR /95% CI: 0,53 /0,31-0,91).
- → non-HLA-allele coding regions have a significant impact on development of ≥ grade II aGVHD. There is more to successful HSCT than matching for HLA genes.

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Conclusions

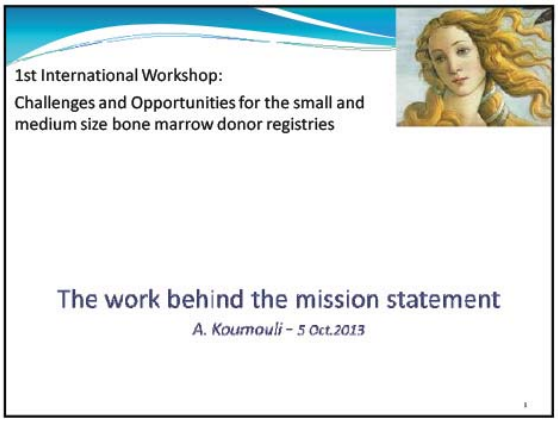
Finnish Red Cross Blood Service

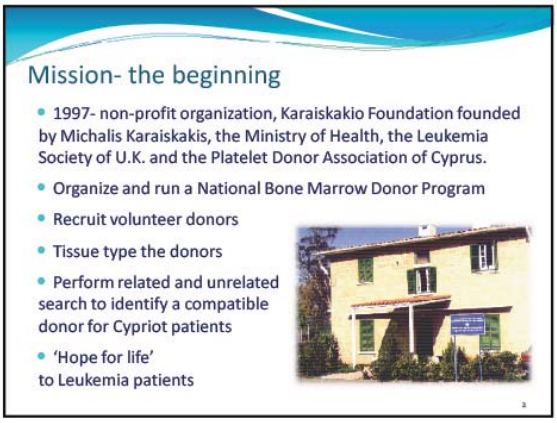
We (the BMDW) often s
we should recruit from
minorities …

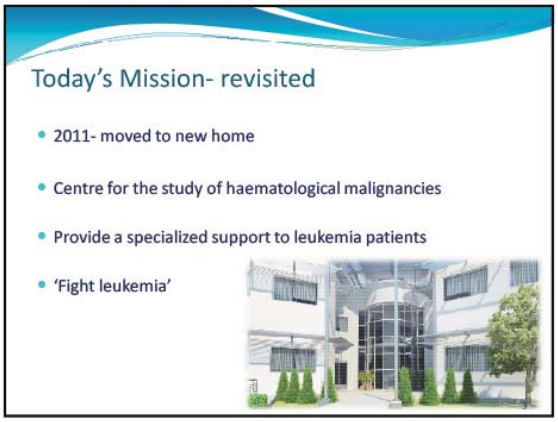
The Finns are one!

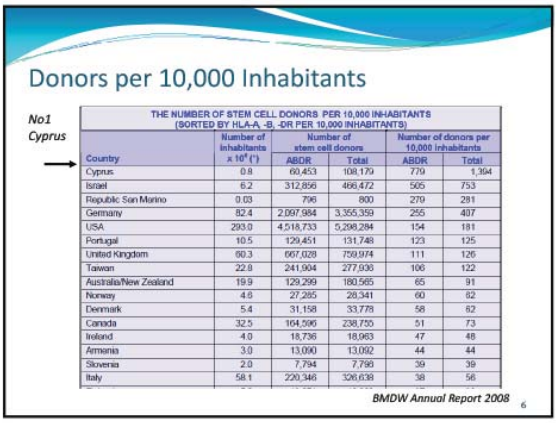
Even considerable enlargement of the large international registries (NMDP, DKMS, BBMDR) would likely not result in finding more donors for patients that have unique 'Finnish type' haplotypes

WWW.VERIPALVELU.FI 16









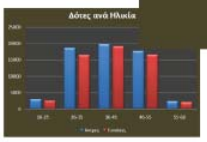
THE NUMBER OF STEM CELL DONORS PER 10,000 INHABITANTS
(SORTED BY HLA-A, -B, -DR PER 10,000 INHABITANTS)

Country	Number of inhabitants x 10^6 (*)	Number of stem cell donors ABDR	Number of stem cell donors Total	Number of donors per 10,000 inhabitants ABDR	Number of donors per 10,000 inhabitants Total
Cyprus	0.8	60,453	108,179	779	1,394
Israel	6.2	312,856	466,472	505	753
Republic San Marino	0.03	796	800	279	281
Germany	82.4	2,097,984	3,355,359	255	407
USA	293.0	4,518,733	5,298,284	154	181
Portugal	10.5	129,451	131,748	123	125
United Kingdom	60.3	667,028	759,974	111	126
Taiwan	22.8	241,904	277,936	106	122
Australia/New Zealand	19.9	129,299	180,565	65	91
Norway	4.6	27,285	28,341	60	62
Denmark	5.4	31,158	33,778	58	62
Canada	32.5	164,596	238,755	51	73
Ireland	4.0	18,736	18,963	47	48
Armenia	3.0	13,090	13,092	44	44
Slovenia	2.0	7,794	7,798	39	39
Italy	58.1	220,346	326,638	38	56

Gender and Ethnic Distribution of Donors

52% Males
48% Females

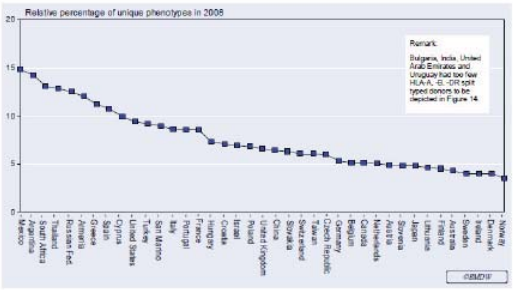
99,336 Greek Cypriots
19,824 Turkish Cypriots



CYBMDR December 2011

7

Genetic Heterogeneity of CYBMDR



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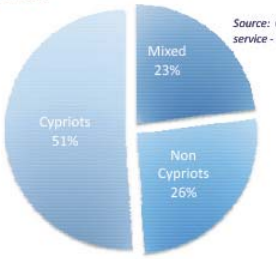
Future trends



Source: Cyprus statistical service - 2009

Marriage of Cypriot residents by nationality

9

Failure to identify a matched donor

More than 20% of patients from Cyprus fail to find a matched donor due to:

- Very high ***genetic heterogeneity*** of the Cypriot population – many unique phenotypes
- The very ***small number of sibling*** in the families of young patients
- The high percentage of ***mixed marriages*** (>50%) expected to increase the genetic diversity and the failure rate in the search process

10

The Cyprus Rotary Cord Blood Registry

CYPRUS ROTARY CORD BLOOD REGISTRY
ΚΥΠΡΙΑΚΟ ΡΟΤΑΡΙΑΝΟ ΑΡΧΕΙΟ ΟΜΦΑΛΟΠΛΑΚΟΥΝΤΙΑΚΩΝ ΜΟΣΧΕΥΜΑΤΩΝ

- 2005- establishment of public cord blood registry
- 1977 units stored
- Immunologic immaturity of lymphocyte - Lower risk of GVHD
- Degree of matching not as stringent
- Cryopreserved- 'off-the-shelf' substitute for blood or marrow units for transplantation
- High concentration of HSC
- Can use more than one unit in adults

11

HLA Typing Lab

- 2004-EFI accredited
- Sample Archiving
- Outsource: First time donors
- Further typing, Patient and Family donors, disease association

Methods:

- SSOP
- SSP
- SBT

- Quality Control

12

Diversification

2008-The Center for the Study of Haematological Malignancies (CSHM)

Morphology | Cytogenetics | Immunophenotyping

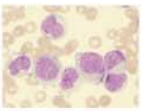
Cytochemistry | FISH | Molecular Biology

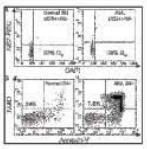
T. Haferlach MD, Chief, Grosshadern Leukemia Clinic, Munich

13

Haematology and Immunology Laboratory

- Sample reception and processing
- Archive of research material
- Morphology
- Cytochemistry
- Immunophenotype
- Workflow management

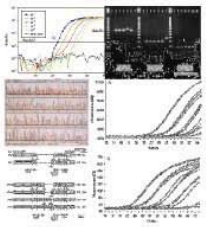




14

Molecular Haematology Laboratory

- Recurrent chromosomal aberrations – RT-PCR
- B and T cell Clonality Testing
- Mutational Analysis
  NPM1, FLT3, JAK2
- Sequencing analysis
  CEBPA, KIT, KRAS
- Prognostic Gene Expression
  WT1, BAALC, CLLU1
- MRD monitoring



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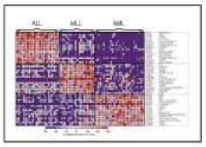
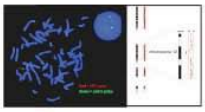
Genomics and Bioinformatics laboratory

- Gene Expression Profiling
- Virtual Karyotyping
- Loss of Heterozygosity
- Epigenetic Modification
- FISH analysis
- Bioinformatics training and support - Sanger Institute





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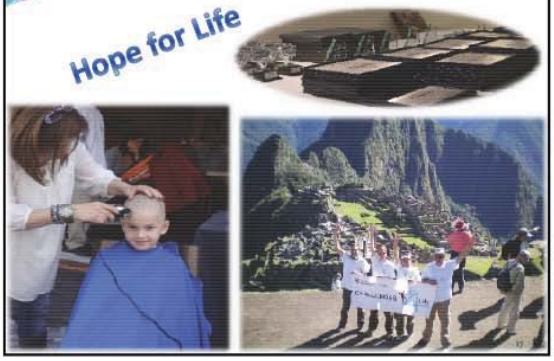
Hope for Life



17

Fight Leukemia

18

LILIANE MADER – 25 YEARS SBSC; LOOKING BACK AND LOOKING FORWARD

25 Years SBSC
Looking back & Looking forward

1st International Workshop: Challenges and Opportunities for the small and medium size bone marrow donor registries

Liliane Mäder, Head of Donor Center SBSC, Swiss Registry

Organisation and History of the Swiss Registry

- ✓ 1988 – Establishment of the «Swiss Bone Marrow Donor Registry»
- ✓ 2004 – Renaming into «Foundation Swiss Blood Stem Cells»
- ✓ 2011 – Merger of «Blood Transfusion SRC» and «Foundation Swiss Blood Stem Cells» to today's «Swiss Transfusion SRC»

| 2

The 3 operational businesses of the Swiss Registry

Donor Center

- ✓ Recruitment of unrelated blood stem cell donors
- ✓ Registration of CBUs
- ✓ Donor Relation Management
- ✓ Fundraising

S&T Coordination

- ✓ Unrelated donor search for Swiss patients
- ✓ Process search requests for international patients
- ✓ WorkUp for Swiss and international patients

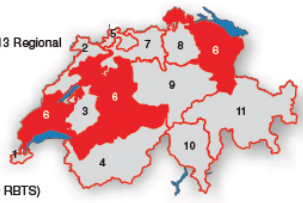
Donor FollowUp

- ✓ Lifelong follow-up of related and unrelated Swiss donors
- ✓ Harmonization of global donor follow-up processes

| 3

Development of Donor Centers in Switzerland

- ✓ until 2009…
  Donor recruitment was done by the 13 Regional Blood Transfusion Services (RBTS)
- ✓ 2009…
  Foundation of the 14th Swiss Donor Center SBSC located in Bern.
  Start of active donor recruitment.
- ✓ Today..
  11 Donor Centers (DC SBSC and 10 RBTS)



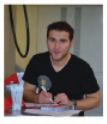
| 4

Recuitment Drives by SBSC Donor Center

Typing Events | Information Events | Media | Engagement Flyer

- ✓ Universities, companies, hospitals etc.
- ✓ Initiated by private persons, companies or by the Donor Center SBSC

Soccer tournament and typing event in Winterthur



| 5

Recuitment Drives by SBSC Donor Center

Typing Events | **Information Events** | Media | Engagement Flyer

- ✓ Information about the need of blood stem cell donors, the donation, registration process etc.
- ✓ Hospitals, companies, congresses, schools etc.

| 6

LILIANE MADER – 25 YEARS SBSC; LOOKING BACK AND LOOKING FORWARD

Recuitment Drives by SBSC Donor Center

Typing Events | Information Events | **Media** | Engagement Flyer

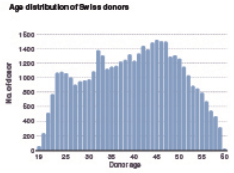
- ✓ Articles in print media, discussions in talk shows etc. are very effective recruitment drives
- ✓ Information and Motivation videos

Eine Mutter kämpft den Kampf ihres Lebens

Recuitment Drives by SBSC Donor Center

Typing Events | Information Events | Media | **Engagement Flyer**

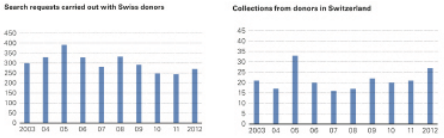
Unrelated Blood Stem Cell Donors in Switzerland



- ✓ About 40% of the donors have been recruited by the Donor Center SBSC
- ✓ Most donors register online (Buccal Swab)
- ✓ Average age of donors is 39 years
- ✓ We recruit donors at the age between 18 and 55
- ✓ Donors stay in the registry until their 60th birthday

Challenges of the SBSC Donor Center

❖ Increase quality of the Swiss donor pool



- ✓ Typing 6 Loci at «intermediate to high» resolution at timepoint of registration
- ✓ Increase the number of donors (publicity, new homepage, recruitment drives)
- ✓ Lower the age of Swiss donor pool (directed recruitment at universities etc.)
- ✓ Increase availability of Swiss Donors (new brochures and videos)

New Brochure

Donating blood stem cells: what you should know

New Video

1:0 Against Leukemia

Challenges of the SBSC Donor Center

- Establish a substantial Donor Relation Management
  - ✓ Newsletter to inform donors about SBSC activities (increase donor availability)
  - ✓ Donor Mailing (Birthday etc.)

- Manage Donor – Patient Contact (allowed in Switzerland since April 2013)
  - ✓ Establish a way to handle donor – patient correspondence

| 13

Challenges of the SBSC Donor Center

- Having only one Swiss Donor Center
  - ✓ Convince the remaining Regional Blood Transfusion Services to transfer their donors to the Swiss Registry

| 14

Thank you.

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info@sbsc.ch, www.sbsc.ch

ACTIVITIES OF THE BULGARIAN BONE MARROW DONOR REGISTRY (BBMDR)

L.Quin, M.Ivanova, T. Lukanov, A.Georgieva, S. Kandilarova, A.Nedialkova, E. Naumova

Bulgarian Bone Marrow Donors Registry (BBMDR) has been established in the Department of the Clinical immunology at the University Hospital "Alexandrovska", Sofia, Bulgaria, and since 2005 BBMDR is a member of the BMDW. At present the total number of the registered donors in BMDW is 685. As for the gender of our donors 49 % are females and 51%-males as prevailing age group is 26 – 35 years. Over 2005 – 2013 the Transplant Centers in Bulgaria have applied for HLA –matched related donor (MRD) and matched unrelated donor (MUD) in more than 385 patients with blood cancer. Suitable MRD has been found in 26 % of them and MUD in 46 %. Total number of BMT so far in Bulgaria is 105. For 28% of our patients no 10/10 HLA matched donor was found.

Therefore we decided to assess the probability of finding match donors in our population by analyzing HLA profiles defined by PCR-SBT in the BBMDR. Rare for South Europeans alleles such as A*02:11, *02:17, *02:141, *30:04; B*18:03, *27:07, *35:08; *44:05; *44:06, *47:01:01, *56:01:01; DRB1*04:10, *13:15 were identified in Bulgarians as well. Additionally alleles such as B*44:27 (37% of B*44:02G) and DRB1*14:54 (49% of DRB1*14:01G) were observed with frequencies comparable to that of common alleles B*44:02 and DRB1*14:01. HLA-B*44:27 was associated mainly with A*02:01, C*07:04, DRB1*16:01, DQB1*05:02, while B*44:02 was found in the following haplotypes: A*24:02, C*05:01, DRB1*15:01, DQB1*06:02, DRB1*11:01, DQB1*03:01. The Roma minority were quite different compared to the general Bulgarian population. Commonly observed were alleles: A*02:06, *02:12; *33:03, B*27:04, *39:06, B*40:06, *52:01; DRB1*11:03, *12:02; 14:04, *15:02. With highest frequencies was found haplotype A*01:01-B*40:06-DRB1*14:04.

Based on this HLA distribution a strategy for search of compatible donor was established.

Macedonian Bone Marrow Donor Registry (MKBMDR)

Authors: Meri Kirijas, Olivija Efinska Mladenovska, Aleksandar Petlichkovski, Mirko Spiroski

Institute of Immunobiology and Human Genetics, Faculty of Medicine, Ss Cyril and Methodius University - Skopje, Republic of Macedonia

The Macedonian Bone Marrow Donor Registry (MKBMDR) started its activity in 2010. The goal is to establish, maintain and improve the system of carrying out bone marrow and peripheral hematopoietic stem cell transplantations for patients with blood cancer and life-threatening diseases, from voluntary unrelated donors in the Republic of Macedonia. Since 2012 it has improved and multiplied its work. MKBMDR is member of Bone Marrow Donors Worldwide (BMDW) and EMDIS.

The Macedonian Bone Marrow Donor Registry has around 800 donors signed in the Registry. The majority of the donors are family members of the patients with leukemias and medical students. At the moment only around 300 samples are typed for HLA-A, -B, -C and –DRB1 and those results are available in BMDW for search.

Choosing the typing method was big chalenge for us. We started using RLS (Reverse Line Strip) 12 years ago for our first typings of patients with different types of leukemias and their families. The ambiguus results were resolved with SSP and sequencieng. We used the SSP for class 1 and sequencing for HLA class 2 ambiguities.

At the end of 2012, we obtained Luminex machine and started to type our donors with Luminex xMAP technology.

All the results from the typings were entered in the Prometeus software. This software eased our work, helped us organize better our Register and connected us with other European Registries.

We still have a lot of allele ambiguities, but we are trying to improve our typings and try to introduce sequenting as a method for typing of all donor. As we are small country, all these things need a lot of time, but we hope that in near future we will have better typed donors for the patients.

HLA-TYPING STRATEGY IN BONE MARROW DONOR REGISTRY, RUSSIA

D.Klyuchnikov[1], S.Volchkov[1], L.Trusova[2], O.Tyumina[2]

[1]Non-commercial partnership «Human Progenitor Cell Registry», [2]State-financed health institution of Samara region «Clinical Centre of Cell Technologies», Samara, Russia

Allogenic HSC transplantation showed the efficiency for the treatment of many hematological diseases. But more that in 2/3 cases suitable donor cannot be found among the siblings. The case is the very high HLA polymorphism rate. And to provide an efficient matched donor search the registries have been established around the world. Registries have been around more than 30 years and total number of worldwide available donors and cord blood units is more than 22 mln.

There is no national registry in Russia, and there are about 10 independent registries which are not connected in one network. The total number of donors is no more than 100 thousands.

Donors are typed for a several HLA loci and resolution levels depending on the typing strategy. The goal of the development of typing strategy is to increase the efficiency of donor search in the conditions of finance capabilities of the registry. In the most cases strategy depends on 3 main factors: finance, meeting the needs for search, definite donor characteristics (age, sex, and ethnicity). The first and the key factor is the funding, it determines almost all the typing strategy.

HPC registry is affiliated with donor centers and cord blood banks which are responsible for initial typing. And all the donor centers and cord blood banks have the different financial possibilities. That is why HPC registry does not set stiff requirements to follow the recommended typing strategy, and afford the ground for the donor centers and cord blood banks to develop their own typing strategies.

HPC registry recommends to perform typing at A-B-DRB1 loci at high resolution. Typing at 3 loci at initial stage, and absence the other criteria (sex, age, and ethnicity) are based on very little number of donors in the registry (5422 typed CBUs and 2091 donors) and in Russian Federation. And to gain the HLA diversity the recruitment of the ethnic groups recommended. To evaluate the efficiency of the typing strategy the advisory committee was organized.

In the current context of the bone marrow donorship in Russia and because of the large ethnic variety the criteria for the donor selection are much lower than in Europe.

NEXT-GENERATION SEQUENCING IN A CLINICAL LABORATORY SUPPORTING HSC REGISTRY

Sendi Montanic , Irena Kemperle, Andrijana Mendez , Blanka Vidan-Jeras

Till year 2010 the initial phase of the donor search in the Slovenian Hematopoietic Stem Cell Transplantation Program considered high resolution typing for DRB1, DQB1 and low resolution typing for HLA-A, B groups of alleles, while HLA-C typing was not taken into account at all. Eventually, patients and unrelated donors were matched on the basis of HLA-A, B, C, DRB1 and DQB1 at the allelic level (10/10). On the basis of our study on an impact of the typing strategy on finding an HLA-matched unrelated donor taking into account the role of HLA-C we changed initial phase of the donor search, so that HLA-C was immediately included. Moreover, we started to consider HLA-DQ locus at the same time as well. This strategy gives optimal results when donors are typed for all 5 loci at the highest possible level of resolution.

Recently, we tried to figure out whether next generation sequencing (NGS) with commercially available reagents could offer an appropriate approach for donor typing. In our clinical laboratory that supports HSC registry we mainly use Sanger sequencing (SBT) to obtain high resolution typings. We compared utility value of SBT with NGS using 50 samples. All were typed for HLA-A, B, C, DRB1, DQB1 with both methods. Comparable typing resolution, time consuming, availability on the market and prices were criteria for choosing AlleleSEQR Kits (Celera) with Assign 3.5+ (Conexio) software for SBT and GS GType HLA MR Primer Set, Roche 454 Sequencing System with Assign ATF 454 (Conexio) for NGS. Only results for exons 2 and 3 for class I and exon 2 for class II alleles were considered for analysis. Except one allele dropout that was observed by SBT and didn't occur in NGS, we didn’t observe any discrepancies between typing results obtained with both methods. Presence of null alleles didn’t significantly differ. Ambiguities that had to be resolved for SBT versus (vs) NGS per locus were as follows: A 62 vs 0%, B 90 vs 92%, C 74 vs 46%, DRB1 94 vs 36%, DQB1 20 vs 44%. While in HLA-A, C and DRB1 NGS had advantage, it was the opposite in HLA-B and DQB1. Average number of allele pair combinations (apc) obtained as a result of each typing shows the same pattern: A 11 vs 1apc, B 8 vs 12apc, C 6 vs 3apc, DRB1 13 vs 1apc, DQB1 2 vs 3apc.

Validated commercial kits and software for NGS and Sanger sequencing can give similar quality and resolution of results. In both cases for allele level HR results additional typings and expenses should be expected. For typing of donor/recipient pairs SBT remains more suitable in our laboratory. In high-throughput typing of registry donors NGS can have an advantage on SBT because of less workload, providing all necessary equipment and automation is introduced. We expect future development of cheaper and more user friendly high-throughput methods that will provide high resolution typings appropriate for HSC registries.

The Center for the Study of Haematological Malignancies

V. Nicolaidou, M. Kleopa, K. Nicolaou, C. Pierides, M. Manoloukos

Small and medium size bone marrow registries can face many challenges and competition from larger registries that have more resources. The key to sustainability for the small and medium size registries lays in the diversification of their services; indeed the nature of smaller registries offers an opportunity for development and diversification with the ultimate goal of providing the best possible services to their patients. One such example is the Center for the Study of Haematological Malignancies (CSHM) founded in 2008 as the main research pillar of Karaiskakio Foundation. Its purpose is to be established as a multidisciplinary, integrated and thematically focused centre that will combine state-of-the-art diagnostic methodology with cutting edge technology to fulfil the clinical needs of patients affected by haematological malignancies. At the same time, CSHM aims to create research and academic opportunities in the fields of haemato-oncology and immunology through collaborations with world-leading international institutions.

The Center is organized in three core laboratories; the Flow Cytometry Laboratory, the Molecular Haematology Laboratory and the Cytogenetics and Genomics Laboratory. The laboratories are furnished with state-of-the-art equipment including an 8 colour flow cytometer, teaching microscope, PCR, real-time PCR, a 24 capillary sequencer, liquid handling, cell culture, array scanner, fluorescent microscope and software for SKY FISH analysis. This structure and the fact that all laboratories act in concert allow them to offer an integrated approach for the diagnosis of haematological malignancies based on current state-of-the-art. In addition, a highly qualified, multidisciplinary team of scientists was established that provides scientific support for the continuing development of the diagnostic methodologies thus ensuring the best possible services for the patients. Using these valuable resources the Centre aims to expand its activities from the specialized diagnostic investigation to scientific research in the area of haemato-oncology and immunology. A number of research projects are currently underway in collaboration with the Wellcome Trust Sanger Institute in Cambridge, the University of Patras and the University of Cyprus.

The impact of the Center on the patients with haematological malignancies is greater than expected at this point. The network of integrated core laboratories offers high quality services while research activity contributes to the continuing development of these services. Importantly, further growth in the research arena paves the way for securing research grants thus contributing to the long-term sustainability of the Center. Such approaches for the small and medium registries can prove successful in offering the chance for attaining sustainability whilst serving the needs of their patients.

PHOTO GALLERY

PHOTO GALLERY















DELEGATES LIST

Surname	Name	Organisation	Country
Anastasiou	Nicos	Karaiskakio Foundation	Cyprus
Arvola	Anne	Finnish Red Cross Blood Service	Finland
Avagyan	Sevak	Armenian Bone Marrow Donor Registry Charitable Trust	Armenia
Barges	Stephane	Life Technologies	France
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