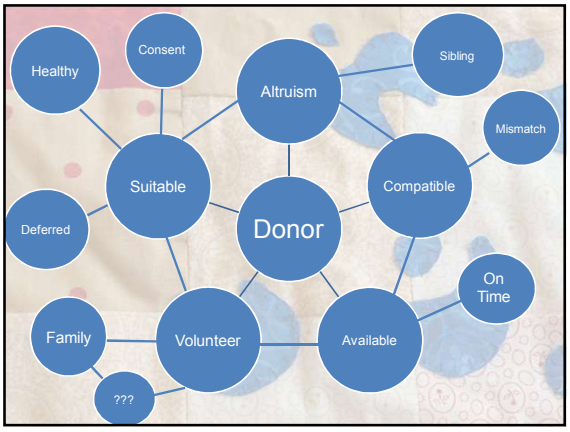
Focus on the donor

Anne-Marie van Walraven, PhD MPA

http://focusonthedonor.nl

A donor

What is the first word that comes to your mind?



Donation in historical perspective

Blood donation

- 1492 – Pope Innocentius VIII
- Three children as donor
- Each promised a ducat
- 'Transfusion' – through a tube in the stomach
- No survivors

Source: Stefano Infessura

First attempts

- 1939 Osgood et al.
  - F, 19 yr. hypoplastic marrow; infusion of 18 ml bone marrow; died of infection.
- 1940 Morrison & Samwick
  - M, 42 yr. aplastic anemia; infusion of 13 ml bone marrow; developed leukemia.

1950-60's

- McFarland et al.*
  - 37 patients: SAA
  - 20 bone marrow therapy, 17 controls
  - Conditioning: high dose prednisone (100-150 mg/daily)
  - Bone marrow procurement:

every effort was made to obtain marrow from a close relative; however, in 9 instances this was not possible, and professional donors had to be used.

*McFarland et al. Annals of Internal Medicine, 1961;108:91-101

Bone Marrow Therapy

The dose of bone marrow administered ranged between 1,000,000,000 and 40,000,000,000 nucleated cells. Some patients received multiple infusions from several donors, while others received only one infusion from a single donor. The marrow was generally administered intravenously, but in 7 cases it was injected directly into the medullary cavity (Table 2). The donor's blood was crossmatched with the recipient's in the usual manner.

*McFarland et al. Annals of Internal Medicine, 1961;108:91-101

Outcome

TABLE 2.—*Characteristics of Bone Marrow Therapy in 20 Patients*

Case	Total No. Marrow Cells Given (X10⁹)	No. of Donors	Relation of Donor to Recipient	Route Given	Outcome
1	30.0	12	None	I.V.*	Died
2	2.0	1	Uncle	I.V.	Living
3	5.5	1	Father	I.V.	Living
4	9.3	2	Father, Prof.	I.M. †	Died
5	6.2	1	Father	I.V.	Living
6	3.0	7	None	I.M.	Died
7	8.0	1	Father	I.V.	Living
8	13.4	2	None	I.V.	Died
9	2.0	2	Brother, Prof.	I.V.	Living
10	3.0	1	None	I.V.	Living
11	16.6	2	None	I.M., I.V.	Died
12	38.1	3	None	I.V.	Died
13	18.5	3	Sister, Uncle Cousins	I.V.	Died
14	15.7	2	None	I.V., I.M.	Living
15	15.6	4	Husband, Prof.	I.V., I.M.	Died
16	9.0	1	Brother	I.V.	Died
17	19.0	3	None	I.V.	Died
18	40.0	5	None	I.V.	Died
19	8.5	3	Sisters	I.M.	Living
20	3.0	2	Sister	I.M.	Living

* I.V. indicates intravenous.
† I.M. indicates intramedullary.

92 *Vol. 108, July, 1961*

*McFarland et al. Annals of Internal Medicine, 1961;108:91-101

Harvesting bone marrow

512 THOMAS AND STORB

Table 1.—Results of Human Marrow Aspirations

Donor	Age	Sex	Weight Kg.	Aspiration Site	Total Volume	Volume of Blood	Nucleated Cells × 10⁹	Peripheral Blood Cells × 10⁹	Marrow Cells × 10⁹
1	30	M	81.0	Sternum	50	25	1.68	0.18	1.50
				Anterior crests	212	137	4.76	0.95	3.81
				Posterior crests	634	534	16.67	3.74	12.93
				All	896	696	23.11	4.87	18.24
2	28	M	64.0	Sternum	142	112	3.23	0.67	2.56
				Anterior crests	243	188	7.05	1.12	5.93
				Posterior crests	610	465	17.81	2.79	15.02
				All	995	765	28.09	4.58	23.51
3	35	F	54.5	Sternum	64	24	3.36	0.14	3.22
				Anterior crests	101	61	4.24	0.35	3.89
				Posterior crests	211	151	11.37	0.88	10.49
				All	376	236	18.97	1.37	17.60
4	3	M	15.5	Tibia and anterior crests	60	35	3.1	0.3	2.8
				Posterior crests	83	58	6.0	0.5	5.5
				All	143	93	9.1	0.8	8.3

Thomas & Storb, Blood,1970;36:507-515

The start of bone marrow registries

What was the main reason?

In an atomic age, with reactor accidents not to mention stupidities with bombs, somebody is going to get more radiation than is good for him. If infusion of marrow can induce recovery in a mouse or monkey after lethal radiation, one had best be prepared with this form of treatment in man. The leukemic patient who needs radiation and bone marrow and the uremic patient who needs a spare kidney are people who deserve immediate consideration. From helping them one will be preparing for the atomic disaster of tomorrow and it is high time one did.

Bron: ED Thomas, Bone Marrow Grafting: "A Story of Man and Dog". http://www.washington.edu/research/pathbreakers/1955a.html

International collaboration

- 1989 – Start Bone Marrow Donors Worldwide
- MDP Belgium is one of the founding registries, together with
- United Kingdom, Netherlands, USA, France, Germany, Italy, Austria

Principles of Donor Care Management

- First do no harm: stem cell donation is not in the fysical interest of the donor
  - Donor information and examination by an independent physician[1]
  - Estimation of risk[2]
  - Sometimes: protect the donor for themselves
- The assumption that parents never refuse to donate is not a reason to use them as means to an end.[3]

1. Van Walraven et al., 2010,BMT;45:1269-1273
2. Shaw et al., 2010,BMT;45:832-838
3. Stelling 1 Focus on the Donor

Freedom of choice

- Respect for autonomy
- Information
  - Risk of the donation
  - Alternative treatments
- Informed consent

Safety

- Donation is accepted in society and must be a safe procedure
  - Severe events and adverse reactions registry
  - Short and long term effects
  - Follow up
    - Unrelated donors up till 10 years post donation

Shaw et al., 2010,BMT;45:832-838

Anonimity

- Legislation (local and international)
- Safeguard privacy donor/recipient
- Protect safety of donor/recipient

- Objective decision making donor
- Positive donation experience

The importance of donor care

- Donation is established in legislation
  - National level:
    - Organ legislation
  - European level: Tissues and Cells directive
  - International level : WHO guiding principles

Donor care – more specific

- Guidelines/Standards
  - JACIE (http://www.jacie.org/)
    - B6: allogeneic and autologous donor selection, evaluation, and management
  - FACT (http://www.factwebsite.org/)
  - WMDA (https://www.wmda.info/)

Donor vigilance

- Registry of
  - Severe reactions/events
  - Complications
- WMDA S(P)EAR registry[1]
  - Inventory
  - Analyse
  - Rapid alert
- A global registry for any donor's serious events and adverse reactions is the only way to prove safety of stem cell donation.[2]

1. http://www.wmda.info
2. Stelling 4 Focus on the Donor

What went wrong in 1492?

- Three children acting as donor
- Patient: Pope Innocentius VIII
- Remuneration: 1 ducat
- Transfusion – through tube into stomach
- No survivors

Issue 1: child as a donor

- Donors < 18 jaar
  - Donation is only allowed to sibling[1]
  - no alternative adult donor available[1,2]
  - donation is potentially 'life saving' [1,2]
  - Parents give proxy consent[1,2]
  - Donor gives assent for procedure[1]
  - Positive emotional relationship with recipient[2]
  - A risk (clinical, emotional, psychological) must be minimized[2]

1 – Convention on Human Rights and Biomedicin, art 19-20, Oviedo 1997
2 - AAP, 2010, Pediatrics;125:392-404

Issue 2: Voluntary and anonymous

- The family donor
  - 0-80 jr
  - Confrontation with donation: free choice?
  - Chance to help a loved one
  - Lifelong relationship (sometimes: broken)
- The onrelated donor
  - Aged 18 – 55 year (16-60 year)
  - No relationship recipient: anonymous donation
  - Altruism

Issue 3: Financial reward

- Donation is voluntary and unpaid
- Altruism as basic principle
  - WHO guiding principle 5[1]
  - WMDA Standard 3.03[2]
- Safety[3]
- Dignity[3]
- Donor altruism as motivation to donate must not be confused with 'carte blanche'.[3]

1.WHO Guiding principles, 2008
2. http://www.wmda.info
3. Boo et al. 2011, Blood;17:21-25
4. Stelling 8 Focus on the Donor

Issue 4: consent

- No informed consent
- No proxy consent
- Assent?

- Experimental treatment!

A lot happened since….

- Invention of the cardiovascular system (1628, Harvey)
- Invention of ABO bloodgroups (1901, Landsteiner)
- Start unravelling HLA system (1953, van Rood, Payne, Thomas, Dausset)

What do we know about donors?

- Donor research
  - Motivation[1]
  - Safety[2] (also retrospective studies)
  - Attrition[3]
  - Donation experiences:
    - (un)related donors (bone marrow/stem cells);
    - parents[4];
    - children[5]

1. Switzer et al. 1997
2. Shaw et al. 2010
3. Switzer et al. 2004
4. Van Walraven et al. 2012
5. Van Walraven et al. 2013

Advancing insight

- Worldwide Network for Blood and Marrow Transplantation
  - Donor Outcome Workshops
    - Bern (2009); Leiden (2011); Vienna (2013)
- European Group for Blood and Marrow Transplantation (EBMT)
  - Donor Outcome Committee
    - Establishment donor database

The missing link….

- Education

A European Master

- DoHeCa (http://www.donorhealthcare.org/)
  - European master in Donor Health Care
  - Funding Erasmusfund Life Long Learning
    - Blood, tissues, cells, organs
    - Physicians and nurses (BSN)
    - University of Amsterdam in collaboration with Sanquin
    - Start 2017??

Lifelong Learning Programme

Universiteit van Amsterdam

Donor Health Care

WMDA SCCP

- World Marrow Donor Association
- Search Coordinator Certification Program
  - Basic level (start 2015)
  - Advanced level (pilot phase, start 2016)
- Search coordinators of Registries and transplant centers
- http://www.worldmarrow.info

Conclusions I

- Donors deserve a respectful treatment
- Donor care management is presently getting more attention
- International collaboration helps to establish global donor safety
- Specific educational programs are being developed

Let's look at the other side

From experiment to regular treatment

- 1968 – 1st successful BMTs (1st child donor)
- 1987 – 1st unrelated bone marrow donation
- 1988 – 1st cord blood transplantation
- 1994 – G-CSF in family donors
- 1996 – G-CSF in unrelated donors
- 2006 – double cord blood
- 2014 – renewed interest in haplo-identical donors

Present facts

- Allogeneic haematopoietic stem cell transplantation (SCT) is an effective curative option for a variety of haematological disorders (leukaemia's and bone marrow failure syndromes)
- Approximately 70% of eligible patients lack an HLA identical sibling
- Stem cells provided by extended family members, unrelated donors or derived from cod blood are an acceptable alternative

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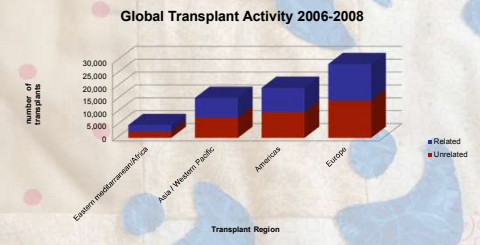
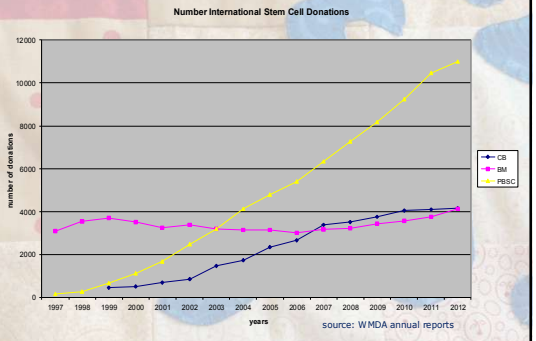
Transplant activity



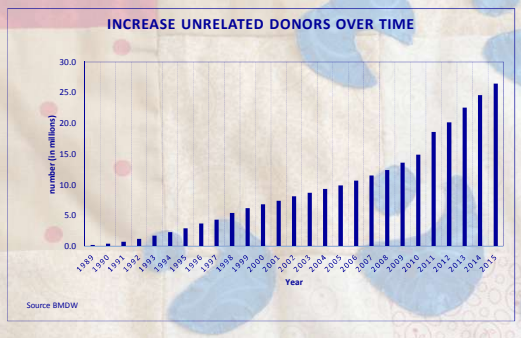
Source: Gratwohl et al. Haematologica,2013;98(8)1282-1290

Volunteer stem cell donations worldwide



source: WMDA annual reports

Global donor inventory



However…

- Mainstream of donors have North Western European background
- HLA diversity in donor pool is limited
- A number of patients does not reach transplantation
  - Range in Europe: 53% (range 7-78%)

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Faster is better than more?

- The Worldwide donor pool (Bone Marrow Donor Worldwide) increased from a few hundred thousand donors in the late eighties to 8 million in the year 2000 and now reached over 26 million.
- The answer to “How to increase the donor pool” is the answer to “how increase the chance on a successful unrelated donor search”*

*Heemskerk et al. Bone Marrow Transplantation,2005;35(7):645-652

Reasons for not reaching trx

Patient related
- Untimely start of donor search
- Clinical deterioration

Donor related
- HLA
- Donor availability
- Length of donor search

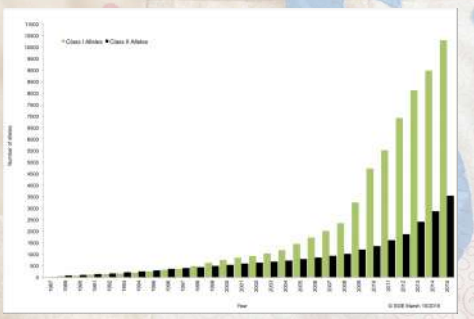
Patient related factors

- Start of search / HLA typing
  - At time of diagnosis?
  - At 1st remission?
- Clinical deterioration
  - Refractory disease
  - Early relapse
  - Refractory infections

HLA

- Polymorphism
  - 14,015 HLA alleles discovered

Increase of number of HLA- alleles



HLA

- Polymorphism
  - 14,015 HLA alleles discovered
  - Rare alleles -> negative predictor
- Associations
  - HLA-B/C, HLA-DRB1/DQB1
  - Unknown association?
- Haplotype frequency
  - A1-B8-DR3
  - Frequent haplotype -> positive predictor

Countless combinations?

- HLA-A*, -B*, DRB1* phenotypes
- The number of possible combinations?
  - >83,000,000,000,000,000,000
  - Estimation total number of humans ever lived: 100-115,000,000,000*

*Curtin, Scientific American, 2007;297(3):126

Keep in mind

- Rare HLA alleles and/or unknown HLA associations should ring a bell
- For a number of patients, a (partially) compatible donor or cord blood cannot be found.

The optimal donor pool

- Young – better outcome
  - 10% of all donors < 26 yr.
  - Recruiting younger donors: different approach
- Male – better grafts
  - Globally: 19% male & < 36 yr.
- Diverse – to serve as much patients
- Available – how to prevent attrition?
  - Information and motivation

Donor availability

- At verification typing stage
  - Donor temporary unavailable (TU)
  - Availability donors in EU MS: 74% (range 27-100%)
  - Ethnic minority donors
- At work up stage
  - Donor deferred for medical reason (8%)**
  - Donor no longer available for personal reason (2%)**
  - No show

*Lown, Bone Marrow Transpantation, 2014;49(4):525-531
**Van Walraven, Bone Marrow Transplantation, 2005;35(5):437-440

Effects of donor attrition*

- Patient
  - Perceptions about numbers of donors
  - Disappointment to loss of potential donors
- Donor
  - Guilt, negative self-perceptions
- Donor registries
  - Monetary costs
  - Loss of credibility
- Societal
  - Creation of 'non-volunteers'

NMDP:
An increase of 5% unavailability would offset 2 years of recruitment

Courtesy Prof. GE Switzer, IDRC 2014

Solutions?

- Recruitment strategies
  - Select the best candidates
  - 'Tailor-made' for different groups
  - Which factors are associated with commitment?
- Prevent donor retention
  - At recruitment: information
  - Analyse risks for opt-out at typing stage

Length of Donor Search

- Time from diagnose to transplantation
- Time needed to identify a donor
- How long does is take to identify a donor?

Factors of influence

- Urgency
- Level of knowledge and skills
  - HLA, search tools
  - International rules and regulations
- Efficient search strategy
  - Network
  - Back up donor
- Level of HLA typing of donors
  - 5 loci (HLA-A, -B, -C, -DRB1, -DQB1)
  - Low versus high resolution

Donor search: the Dutch experience

- 1987 – start unrelated donor searches
  - 3 transplant centers
- 2000 – 100 new Dutch searches per year
  - 6 transplant centers
- 2015 – appr. 600 searches per year
  - 10 transplant centers

Patient characteristics

adults	male/female (%)	Median age in yr (range)
1987-1995	65/35	27.4 (16.1-52.1)
1996-2000	60/40	33.2 (16.4-53.6)
2001-2006	64/36	43.5 (16.9-67.1)
2007-2012	59/41	52.3 (17.1-79-7)

children	Median age in yr (range)	% of all patients
1987-1995	5.6 (0.3-15.7)	49
1996-2000	6.5 (0.1-15.0)	51
2001-2006	6.9 (0.0-15.9)	30
2007-2012	6.3 (0.1-16.0)	17

Donor found vs reaching trx

Donor found	Patients (Caucasian descent)	Patients (non-Caucasian descent)
1987-1995	53%	29%
1996-2000	69%	42%
2001-2006	91%	65%
2007-2012	95%	82%

Reach trx	Patients (Caucasian descent)	Patients (non-Caucasian descent)
1987-1995	48%	23%
1996-2000	59%	32%
2001-2006	76%	52%
2007-2012	82%	69%

Stem cell source

	2001-2006		2007-2012	
	Patients (CAU)	Patients (non-CAU)	Patients (CAU)	Patients (non-CAU)
BM/PBSC	93.8	64.2	87.6	54.3
Cord blood	4.6	28.4	11.6	41.1
Alternative donor	1.6	7.4	0.8	4.6

Conclusions II

- HLA, length of search, donor availability, but also timely start of search are crucial for reaching transplantation
- Cord blood has become an important stem cell source
- Not all patients find a donor


Thank you for your attention!