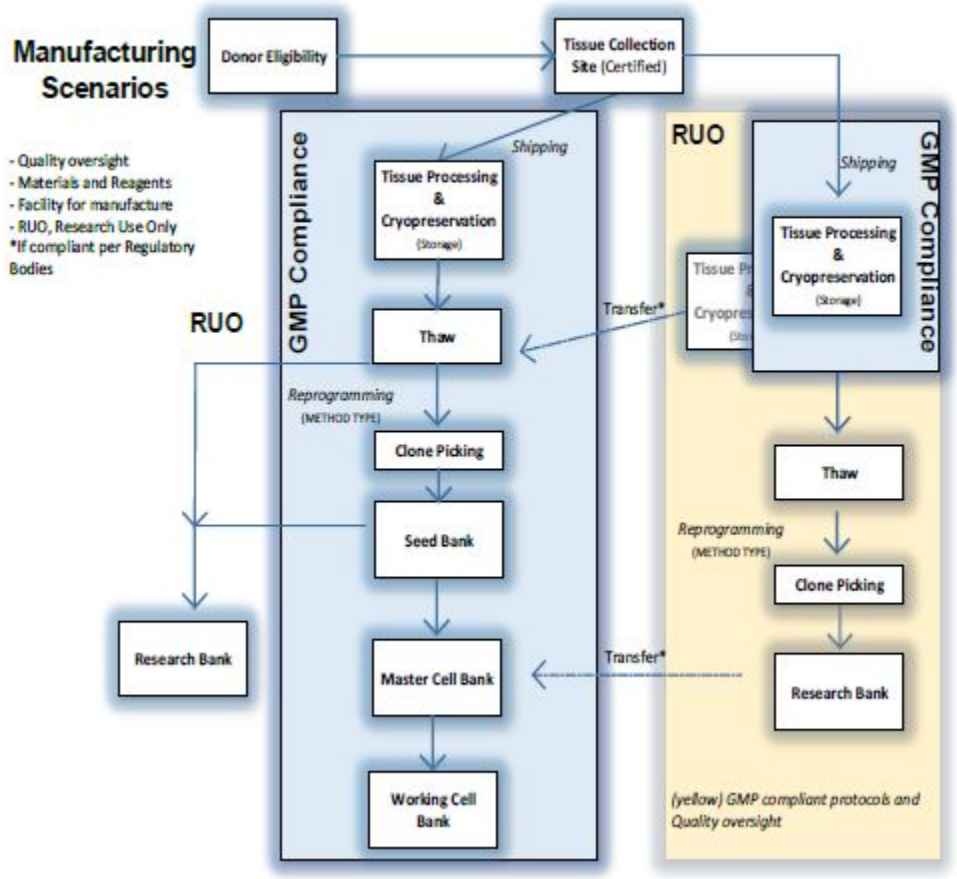
Registry Relationships

Virtual Roundtable

Tuesday, 30 JAN 2018

Generation of HLA-matched clinical grade induced pluripotent stem cell (iPSC) lines



Learning from the history of cell therapy manufacturing, HSC and MSC fields.

Smart people make new mistakes.

From Amanda Mack, Fujifilm CDI

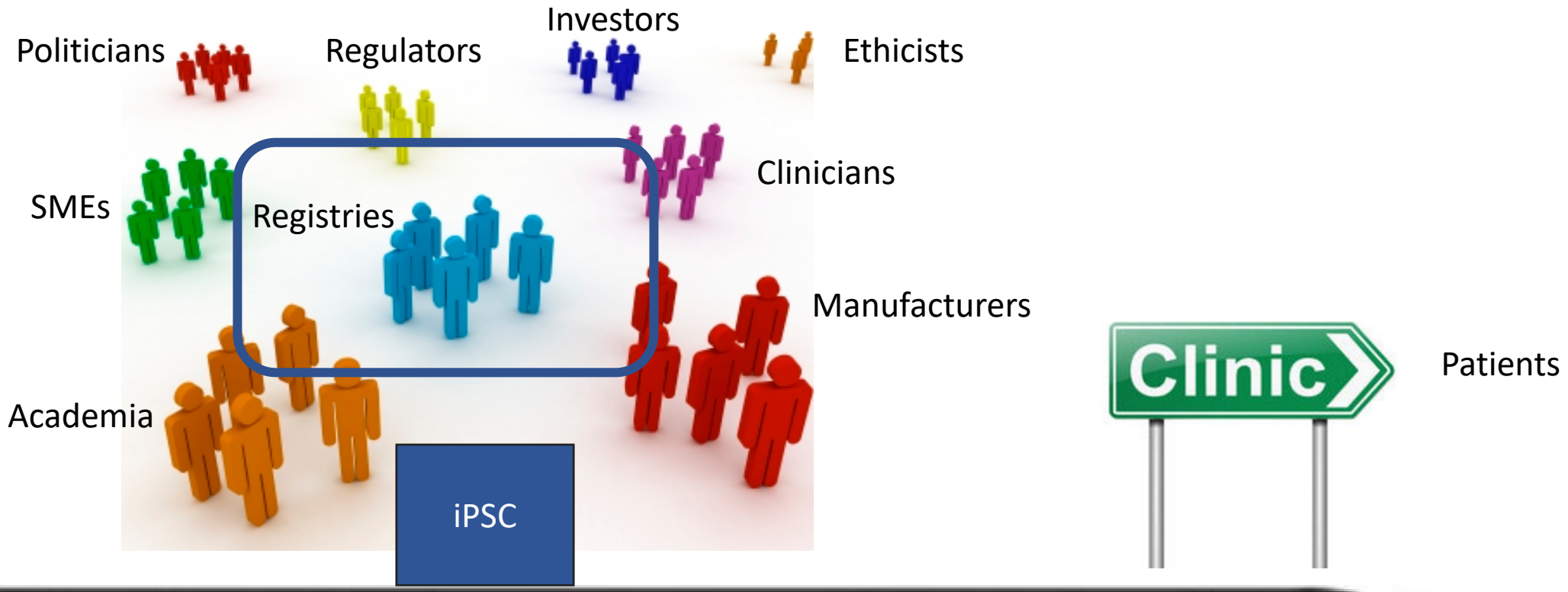
GAiT Progress

- Agreement on release criteria
- Development of searchable database for clinical grade iPSC
- Development of website to assist information pooling
- Organisation of Quality Round for Quality Tests not covered by Pharmacopeia
- ISSCR 2018 Melbourne

GAiT - breaching siloes to advance allogenic iPSC therapy development

Patients

GAiT - breaching siloes to advance allogenic iPSC therapy development



Chairs

Prof Steve Marsh
Anthony Nolan Research Institute

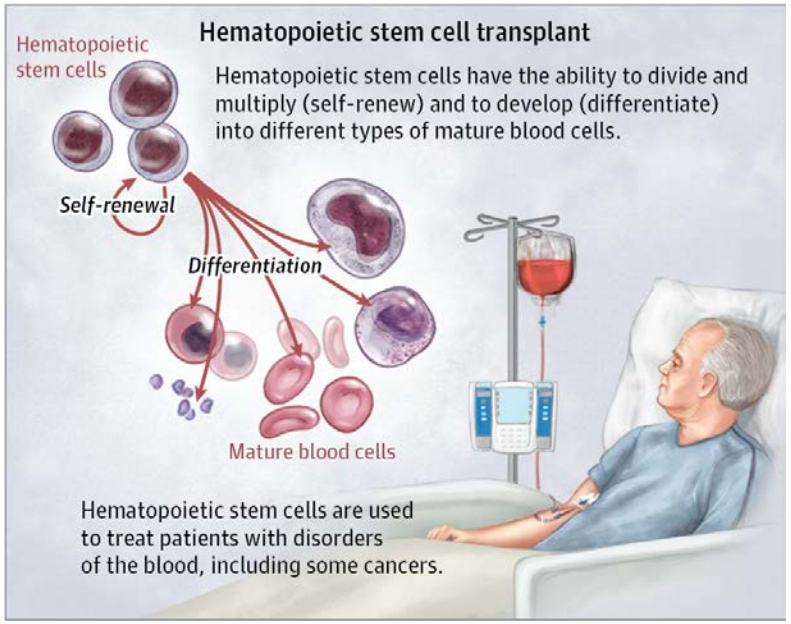
Dr Carlheinz Mueller
World Marrow Donor Association

Agenda

- Establishing relationships with blood and tissue registries – a key challenge for most in the GAiT community
- Understanding role of blood and tissue registries in the development of new therapies
- Understanding the risks registries face: reputation, data security, lack of trust dealing with third parties
- Understanding what are registries' missions and motivations: to serve donors and patients, assist front line services
- Who do registries want to engage with? Professionals as close to front line services as possible, with good reputation, who understand the risks and motivation of the registries

Haematopoietic Stem Cell Transplantation

- Patient HLA typed to high resolution
- In the absence of a related donor, national and international registries are searched for HLA matched donors
- Donors are selected to try and identify the optimum donor; young, male, CMV and HLA matched
- The patient hospital will receive donor sample(s) to confirm tests
- Patient clinicians will select final donor
- Donor consented to give stem cells by bone marrow aspirate or via apheresis for one patient

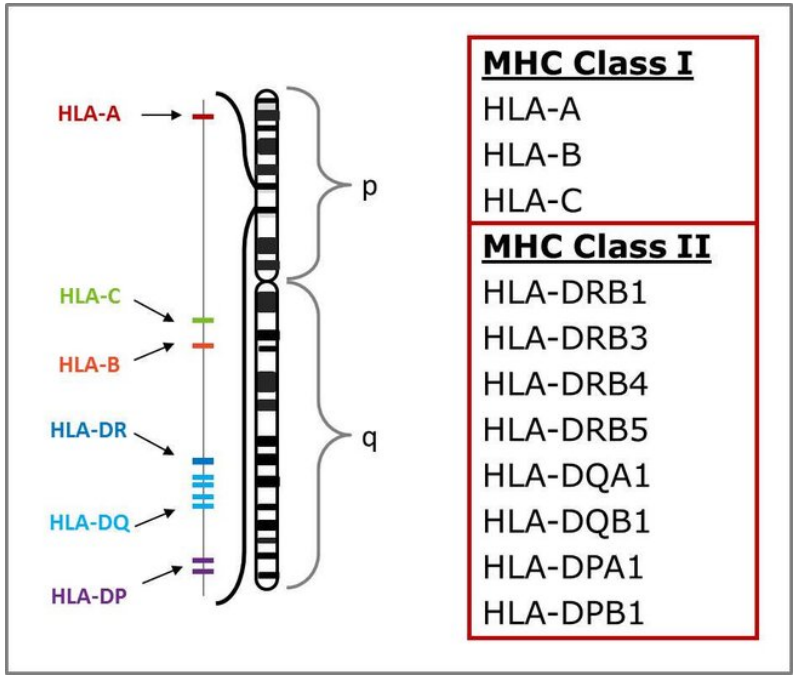


Donor selection for iPSC line derivation

- Identify frequent HLA haplotypes for a population/region/globally
- Search registries for donors homozygous for common haplotypes
- Donors also selected to be blood group O and ideally female
- Donors approached for confirmatory samples (consent?)
- The best donors are selected
- Donor consents to give an apheresis collection for iPSC derivation that could be used as therapy for multiple patients

Haplotype analysis

- Identification of common haplotypes at high resolution HLA type is important
- Requires large numbers of well typed donors
- Ideally collaboration with registries and/or BMDW will be able to facilitate this
- A formal request has been sent by GAiT to BMDW for access to global anonymised donor HLA types



Basic analysis using allelefrequencies.net

Haplotype	F in Cauc	F in Black	F in Hispanic	F in S Asian	F in NE Asian	F in Chinese
A*01:01-B*08:01-C*07:01-DRB1*03:01	6.57	1.2	1.86	0.3	0.25	0.3
A*03:01-B*07:02-C*07:02-DRB1*15:01	2.59	0.6	1.23	0.25	0.01	0.5
A*02-B*44-DRB1*04	2.4	0.5	0.4	0.02	0.01	0.1
A*29:02-B*44:03-C*16:01-DRB1*07:01-DQB1*02:01	2.2	0.6	2.94	0.04	0.04	0
A*02:01-B*07:02-C*07:02-DRB1*15:01	2.18	0.4	0.6	0.13	0.01	0.3
A*29-B*44-DRB1*07	2	0.6	1.8	0.04	0	0
A*01:01-B*57:01-C*06:02-DRB1*07:01-DQB1*03:03	1.1	0.2	0.4	2.16	0.01	0.6
A*30-B*13-DRB1*07	0.9	0.12	0.45	0.99	0.15	6.9
A*33:03-B*58:01-DRB1*13:02	0.2	0.01	0.05	0.64	3	1.9
A*01:01-B*37:01-C*06:02-DRB1*10:01-DQB1*05:01	0.2	0	0.12	1.4	0.23	1
A*02-B*35-DRB1*08:02	0.14	0.13	1.6	0.01	0.09	0.04
A*26:01-B*08:01-C*07:02-DRB1*03:01-DQB1*02:01	0.13	0	0	1.42	0	0.2
A*24:02-B*07:02-C*07:02-DRB1*01:01	0.09	0.01	0	0.53	3.72	0.23
A*33:03-B*53:01-C*04:01-DRB1*08:04-DQB1*03:01	0.05	0.85	0.18	0	0	0
A*33:03-B*58:01-C*03:02-DRB1*03:01-DQB1*02:01	0.04	0.15	0	1.06	0.11	2.5
A*33:03-B*44:03-C*07:01-DRB1*07:01-DQB1*02:01	0.04	0.13	0.01	2.8	0.06	0.7
A*34:02-B*44:03-C*04:01-DRB1*15:03-DQB1*06:02	0.04	0.83	0	0.01	0.01	0
A*30:01-B*42:01-C*17:01-DRB1*03:02-DQB1*04:02	0.04	1.6	0.54	0	0	0
A*02-B*46-DRB1*09	0.01	0	0	0.15	0.34	2.6
A*11-B*15-DRB1*12	0.01	0.01	0	0.25	0.02	1.5
A*24:02-B*52:01-C*12:02-DRB1*15:02	0.01	0	0	0.37	8.38	0.2
A*33:03-B*44:03-C*14:03-DRB1*13:02	0	0.01	0	0.15	4.6	1.4
A*24:02-B*54:01-C*01:02-DRB1*04:05	0	0	0	0.36	2.54	0.7
A*68:02-B*57:03-C*07:01-DRB1*03:02-DQB1*04:02	0	0.04	1.36	0	0	0
A*36:01-B*53:01-C*04:01-DRB1*11:01-DQB1*06:02	0	0.81	0.01	0	0	0
frequency of 25 haplotypes	20.94	8.8	13.55	13.08	23.58	21.67
percentage of patients with haplotype	**41.88**	**17.60**	**27.10**	**26.16**	**47.16**	**43.34**

Donor selection

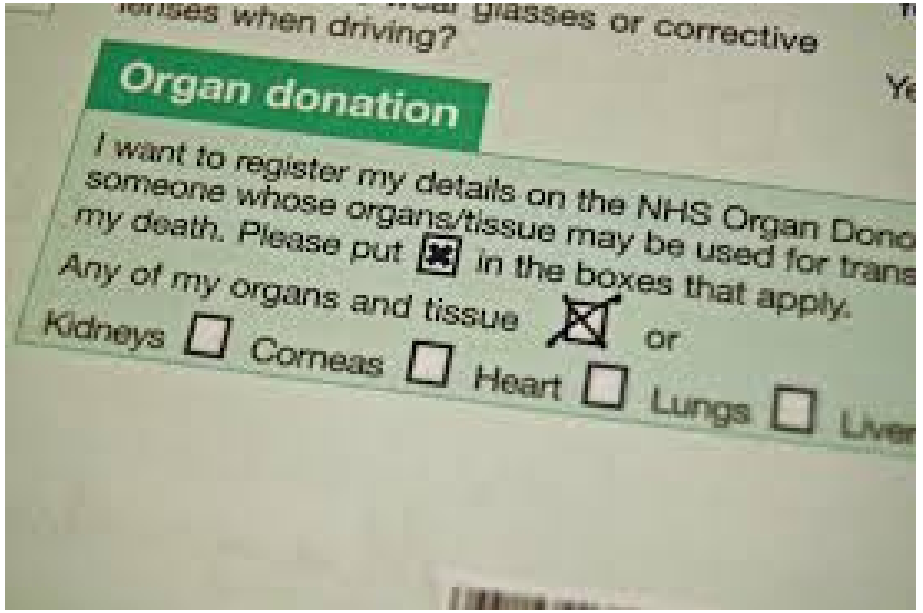
- iPS lines will need to be thoroughly evaluated and tested
- The more evaluation and testing of the donor that can be done early on in the selection phase will reduce effort on cells that will not meet GAiT requirements (see Appendix 1) e.g.
  - Nature of consent (re: global dissemination, commercial use, genetic analysis etc.)
  - Freedom to act (donor constraints, vector IP, institutional and regulatory constraints on use of lines)
  - Scientific suitability (safety [risk assessment, environmental/process control and testing] and characterisation)
- Legal considerations are complicated and should not be overlooked (see Appendix 2)

Will registries be able to provide material?

- Can registries be involved in this procurement?
- Is this beyond remit of registries?
- Which registries should be used; only those affiliated to WMDA?
- How will registries charge for service?
- What is different for cord banks?

What consent will be required?

- How will donors be approached?
- Example of how this has been achieved
  - Information and consent forms used for procurement of donor samples from New Zealand to UK
  - Material used to set up a GMP grade iPS line in UK, suitable for ~15% of UK population



Donor information and consent sheet

Donor Information and Consent Sheet

The generation of human iPS cells for therapy

Introduction

Why is this project being undertaken?

What are iPS Cells and how will they be used in this project?

Why do we want donors from New Zealand?

Why have I been chosen?

What does this involve for me?

What are the risks of taking part?

Will my confidentiality be protected?

Will I be re-contacted or receive any feedback on the programme?

Are there rules and regulations that determine how my cells will be used?

Do I have any rights to the cells or work in the project?

Will I receive any payment for taking part?

Who is funding the project?

Do I have to take part?

Can I change my mind about donating my cells?

Will my taking part be kept confidential?

Compensation

Who should I contact for further information?

DONOR CONSENT

The generation of human iPS cells for therapy

Date Information Sheet Given to Donor:	
Donor Identifier	

Please initial in the boxes below.

	Donor
I have read and understood the information sheet about this project. I have had the chance to consider the information and to discuss any concerns with individuals who are independent of this project.	
I agree to take part in the above study and understand that I am under no obligation to do so.	
I agree to donate samples of my blood to the New Zealand Blood Service and that these will be given to Roslin Cells Ltd to be used to make iPS cell lines as described above and to be used in the development of drugs and treatments for diseases. I understand that any iPS cell lines created will be owned by the UK Cell Therapy Catapult and may be distributed to laboratories in other countries for development of new therapies.	
I understand that I can withdraw my consent without giving any reason, until my cells have been used in to make iPS cells without my medical care or legal rights being affected.	
I understand that some of my donated samples and any stem cell lines made may be stored indefinitely for clinical and quality control purposes.	
I understand that my donation will be anonymised, but traceable and that full anonymity cannot be guaranteed.	
I agree that the New Zealand Blood Service and Roslin Cells may screen my donation and any subsequent stem cell lines derived for the presence of viruses or other diseases.	
I agree to provide a blood sample, which may be tested for infectious agents as required by NZ and International health authorities.	
I agree that genetic analysis may be performed on my donated samples and any subsequent stem cell lines which are derived. Data from cell lines may also be made available to others.	
I understand that if a stem cell line is made, that it will be stored in a stem cell bank and that it may be used in the development of drugs and treatments.	
I understand that cell lines or discoveries made using them may be valuable, but that I will not get any money from this.	
I understand that I may be re-contacted in the future if information of direct importance to my health, my family's health or public health becomes available.	
I understand that if new treatments are developed from stem cell lines, I cannot say who will get the treatment.	
I understand that stem cell lines may be used for commercial purposes.	
I agree that any tissue and blood donated may be disposed of, if unsuitable, in accordance with all relevant ethical and regulatory guidelines.	

Questions for panel from GAiT community

- Lygia V. Pereira, Ph.D. Laboratório Nacional de Células-Tronco Embrionárias, Depto. Genética e Biologia Evolutiva, Universidade de São Paulo, Brasil

    - What we've been trying to do is to cross our triple homozygotes (A-B-DR) with registries in different countries to determine (1) how much of each population they cover, and (2) which triple homoz cover the most - so that we will have a priority list to go after.

Questions for panel from GAiT community

- Keren Abberton, M.Rep.Sci., PhD, Scientific Project Officer, Cord Blood Bank Research Group, The Royal Childrens Hospital, Australia

  - using existing samples from established repositories such as cord blood banks, especially if the samples have been in storage for some time. Do we need to establish a framework for re-consenting donors and how much further information is required given that the samples would presumably have been collected under code compliant conditions for the registry?

  - What sort of follow up is required both in terms of donor health and any issues picked up through further screening required to ensure QA and QC? Benefits and risks of WGS in terms of donor/repository relationships?

  - I'm assuming that people won't be working with private banks which have varying levels of regulation?

  - Understanding the risks registries face: reputation, data security, lack of trust dealing with third parties also comes into this and ties into the question of ownership of a donated sample. How do we reconcile any commercial aspirations of 3rd parties with registry missions and where do we limit the ability to withdraw consent for use?

Thanks for your participation!

- Thanks to the Chairs Steve Marsh and CarlHeinz Mueller, GAiT Director and Histocompatibility & Immunogenetics working group co-lead Jihwan Song, Histocompatibility & Immunogenetics working group co-lead David Turner, Keren Abberton, Lygia da Veiga Pereira Carramaschi, Amanda Mack, Annelise Bennaceur.

- Please note GAiT will be co-hosting a session with ISCBI at ISSCR as we did last year.
- Updates on website, database, and QC manuscript to follow in the March newsletter. The website will have discussion board which will make an ongoing dialogue on important issues easier.
- Feel free to ask questions, give feedback, or offer assistance by emailing stephen.sullivan@gait.global

Appendix 1

Mandatory Donation, Procurement, and Testing Data Fields for clinical grade iPSCs in the GAiT's haplobank system

Donation, procurement and testing of cellular starting material	Permissiveness of donor consent	Consent form	Research use?	
			Genetic analysis?	
			Commercial use?	
		Attestation		
	Donor selection criteria	Immunotyping	Blood type	
			HLA Type I	
			HLA Type II	
			KIR	
	Regulatory compliance	Establishment type		
		GMP status	Compliant?	
		Licence/Registration status	2004/23/EC compliant? (EU)	
			2002/98/EC compliant? (EU)	
			Part 1271 compliant? (US)	
			CTO Regulation? (Canada)	
			CSA compliant? (Canada)	
			Category 1 Outsourcing Inst? (Japan)	
			Category 2 Outsourcing Inst? (Japan)	
			Category 3 Outsourcing Inst? (Japan)	
		Accreditation	AABB?	
			AATB?	
			FACT?	
			Other?	
	Donor health assessment and donor testing	General	Sex	
			Age	
			Geographic location	
			Year	
			Tissue type	
		Infectious disease	Screening according to local req'ts?	Travel history
				Tuberculosis
				Hepatitis
				HIV infection
				CJD or family history of prion disease
				EBV
				CMV
				Syphilis
				Herpes
				Toxoplasmosis
				Malignancy
				High risk behaviour for HIV, HBV, HCV
				Other
			Physical exam	unexplained lymphadenopathy mass or mucocutaneous lesions
				needle tracks or other signs of injection drug abuse
				active infections of clinical significance
			Testing	syphilis
				CMV
				EBV
				HTLV 1 & 2
				WNV
				HIV
				HBV
				HCV

Appendix 2

- Legislation protecting personally identifiable information is being developed in many jurisdictions worldwide, including for example, the recently amended Act on the Protection of Personal Information in Japan, or the newly signed Regulation on Data Protection in the EU. Such instruments give strict instruction on how data sourced from patients, or material biopsied from them can be taken and used (including whether or not these can be shared with third parties). If such data is shared with third parties, its use must frequently be monitored and managed. Adherence to statutes recording where data has gone, and who has used it, are potentially burdensome for cell therapy developers, particularly when personal information is being exported from other countries into the EU. An individual must frequently be nominated for managing compliance and such requirements do not reflect the usual access rules with which cell therapy developers work. For example, with the EU Regulation, individual donor consent does not overrule the specified information compliance requirements and pseudonymized or “coded link” data is not considered anonymized in the EU apparently.