Development of HCT/Ps at CBCT

GMP for HCT/Ps within academic facilities by commercial partnership

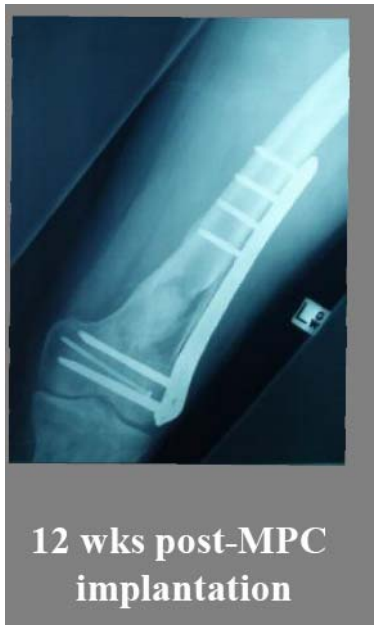
Dominic Wall

Operations Director-Centre for Blood Cell Therapies
Peter MacCallum Cancer Centre
University of Melbourne, Australia
&
Chief Scientific Officer
Cell Therapies Ltd

www.celltherapies.com.au

What is happening with cell based therapies?

9 months non-union
Large defect



12 wks post-MPC implantation

Table 1. Key Industry Parameters: Tissue Engineering, Regenerative Medicine, and Stem Cell Therapeutics

Worldwide estimates for 2007 (rounded totals; $ [millions])	
Total private sector activity	$2400
Total commercial sales	$1500
Total development-stage spending	$860
Number of FTEs	6100
Number of firms or business units	171
Number of firms or business units in commercial stage	47
Number of firms or business units with products in clinical trials	57
Percent of companies that are U.S. based	55%
Cumulative patients treated with regenerative medicine products*	1,200,000
Capital value of listed firms (50)	$4700

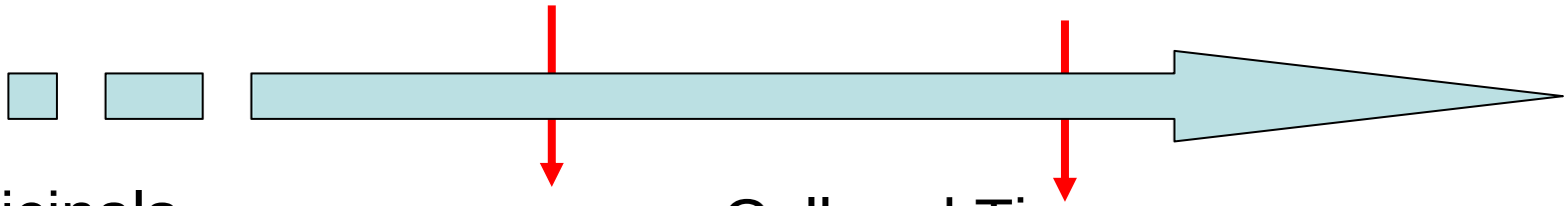
*Excludes cord cell banks.

Lysaght et al, Tissue Engineering 14:2 2008

	M	patient (k)
• Biological active bone grafts	$700*	170
• Regenerative biomaterials	$240	750
• Cord Banking	$270	
• Skin replacement, ACI	$90^	250

*rhBMP-2
^living, bi-layered skin using neonatal foreskin keratinocytes and fibroblasts with bovine Type I collagen

2 models of therapy
Autologous directed treatments…presumed to be harder?
Allogeneic cell banks…presumed to be easier?
Except when it come to persistence, immunity & function



Medicinals

- No collections/donors
- large batches
- high throughput
- open system, term sterile
- control of starting materiel
- complex processes , real PD, TT, validation
- Stable complex protocol
- unknown recipient
- short expiry / storage
- No fresh release

Cell and Tissue

- Donors and collections & opportunity costs
- single product high value batches
- low throughput
- Partial closed system, no term sterile
- labour intensive
- limited control of starting materiel
- Evolving research based protocols, ? PD, validation?, efficacy?, dose?
- Known recipients
- Banking
- Fresh product release…testing?

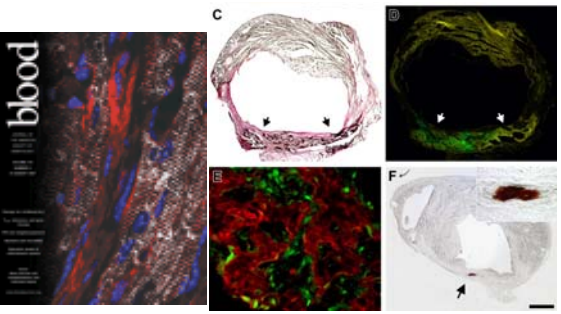
What are the real risks, if any, for Cell Therapy in regenerative medicine?

Inappropriate differentiation?

Malignant transformation?

Biomaterials?

Potential risks of bone marrow cell transplantation into infarcted hearts
Martin Breitbach et al
Blood 2007 110: 4 1362-9



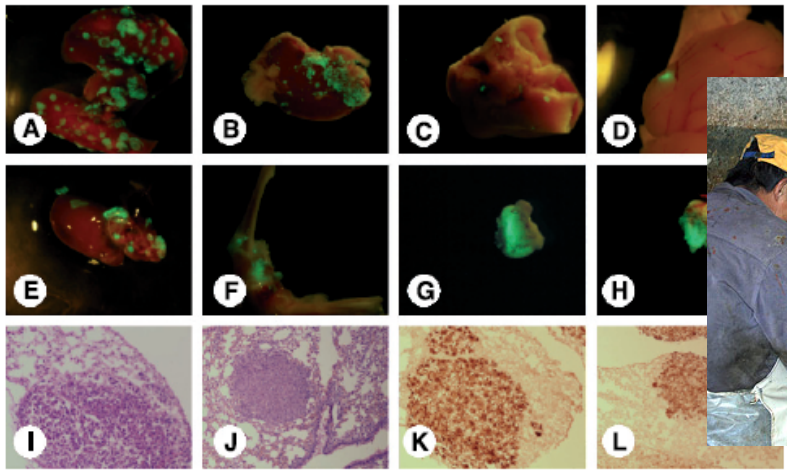
Diabetes. 1997 Jul;46(7):1120-3. Improved human islet isolation using a new enzyme blend, liberase.
Linetsky E, Bottino R, Lehmann R, Alejandro R, Inverardi L, Ricordi C.

[*Cancer Research* 65, 3035-3039, April 15, 2005]

Priority Reports

Spontaneous Human Adult Stem Cell Transformation

Daniel Rubio[1], Javier Garcia-Castro[1,2], Maria C. Martin[3], Ricardo de la Fuente[1], Juan C. Cigudosa[3], Alison C. Lloyd[4] and Antonio Bernad[1]



Any issues like Heparin?

Or is the risk elsewhere?

The healthcare context

"Last spring, doctors at Mercy Medical Center on Long Island gave a patient the news she had feared: Cancer had been detected in her left breast…. On May 25, she had a double mastectomy. The next day, she died of complications from the surgery. As it turned out, the woman did not have cancer. According to the State Department of Health, the pathology report from the woman's surgery had found no tumors in her breasts. The hospital's lab had mixed up her test with another woman's."

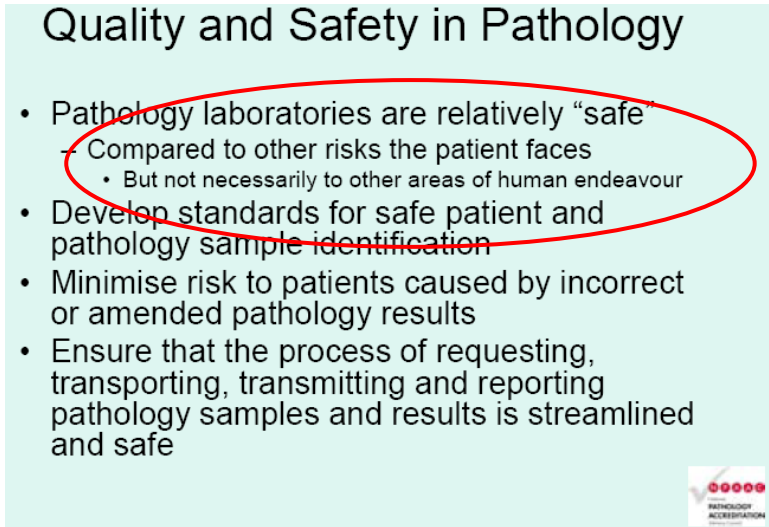
The state report said "the most likely source of the error" was the technician engaging in a practice called "batching," which involves handling more than one specimen at a time.

New York Times Feb 11th 2008

Pathology errors

- F .33-.61% of tests, .05-.11% patients
- Almost always pre-analytical (up to 75%)
- Australian data
  - Data with surgical biopsies
  - Incorrect transcription of Patient ID
  - Median of 1% of all requests
- Local experience

  0.006% wrong blood/correct tube detected



Tissue & cell harvesting

Better controlled than usual healthcare processes?

Average Fatal Accident Frequency Rates (deaths per 100 million hours of exposure) for Various Activities

Being pregnant	1
Travelling by train	5
Working at home	8
Working in agriculture	10
Having a unit of donated blood and becoming HIV positive	10
Being in traffic (overall, in any capacity)	50
Working in the construction industry	67
Flying in a commercial aircraft	100
Being a patient in an Australian hospital	**2,000**
Being anaesthetized	2,000
Parachute jumping	20,000
Having elective abdominal aortic surgery	200,000

Adapted from IATROGENIC INJURY IN AUSTRALIA- A report prepared by the Australian Patient Safety Foundation 2001

The solution is to control the process – from harvesting through to reimplantation

The process is controllable…

Source material…

Incidence of HIV, HBV, HCV, HTLV among tissue and blood donors

Incidence per 100,000 person	Australian		United States of America	
	Musculoskeletal Tissue Donor	First time blood donor	Musculoskeletal Tissue Donor	First time blood donor
Anti-HIV	12.97	1.03	30.12	3.23
HBsAg	4.43	1.48	18.32	6.15
Anti-HCV	10.04	4.04	12.38	3.45
Anti-HTLV	6.06	0.17	5.59	0.81

Yao & Zheng et al Annals Internal Medicine 148:792, 2008

Is a quality system only there for regulatory compliance?
Does it have any role in cell therapy?
"Force majeure" or misadventure in clinical care

Unintentional allogeneic treatments and labelling issues ✓ *USA, AU*
Thawed or heated doses, lost products or lost labels ✓ *All*
Micro & Viral Contamination ✓ *HBV transmission in banked product*
"Unexpected" outcomes ✓ *USA, elsewhere?*
Is healthcare manufacturing uniformly safe and well governed…

Quality and Safety in Pathology

- Pathology laboratories are relatively "safe"
  - Compared to other risks the patient faces
    - But not necessarily to other areas of human endeavour
- Develop standards for safe patient and pathology sample identification
- Minimise risk to patients caused by incorrect or amended pathology results
- Ensure that the process of requesting, transporting, transmitting and reporting pathology samples and results is streamlined and safe

STEM-CELL TRANSPLANTS GO AWRY | Lawsuits allege fraud and negligence

Some cancer patients died after time-saving change

The leaders of a Kansas City treatment program say they provide "excellent" care to their patients, but lawsuits allege that a period of failings led to suffering and death.

By ALAN BAVLEY and JULIUS A. KARASH

http://www.kansascity.com/mld/kansascity/news/local/15705281.htm (2 of 13)17/10/2006 9:33:44 AM

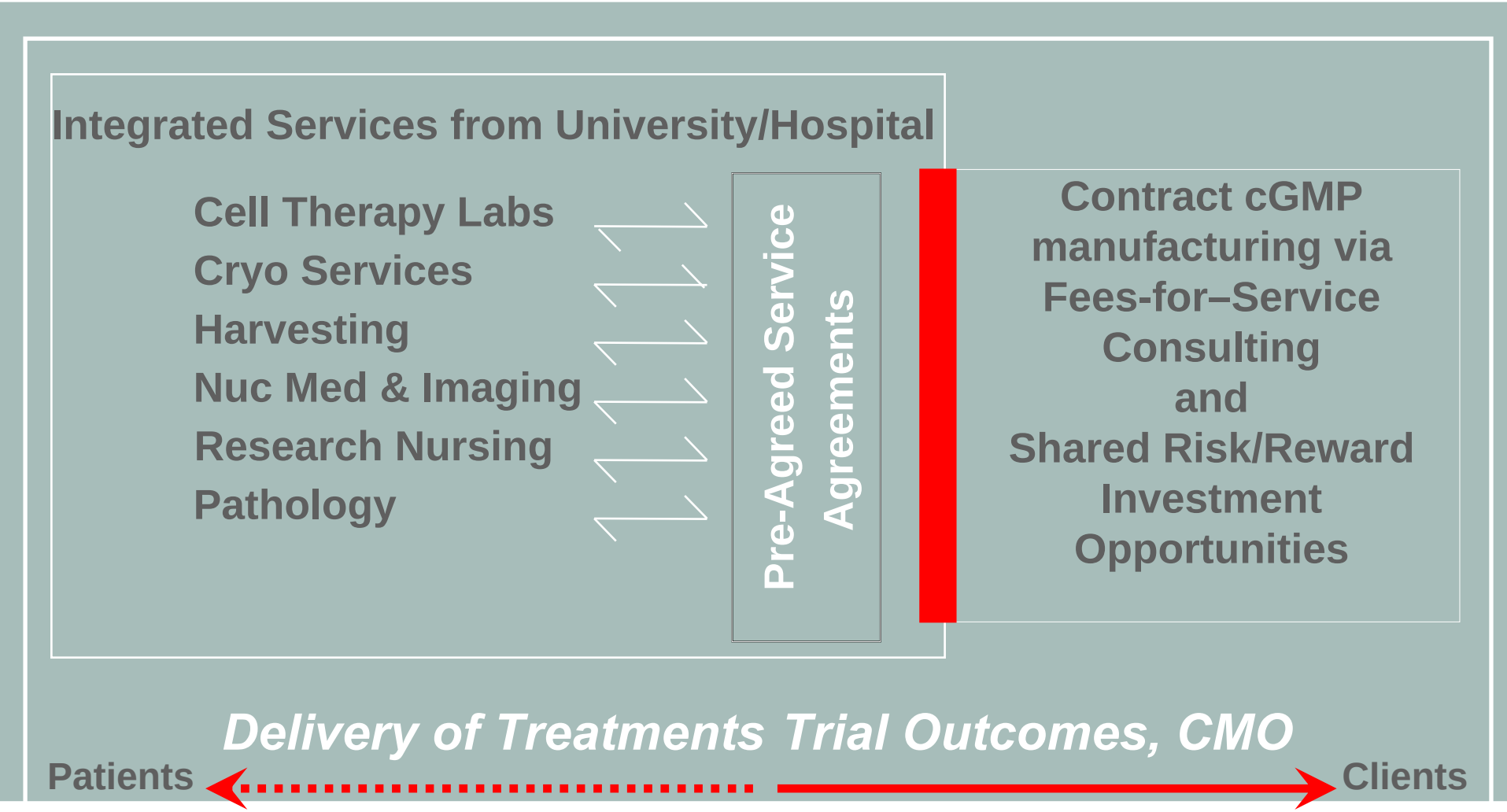
Kansas City Star | 10/08/2006 | Some cancer patients died after time-saving change

"…To save time
.. a lab director …ordered a quicker freeze
… The stem cells died.
From August 1998 to June 1999, the program treated 40 adult patients -.
About a fourth of these patients died within 100 days of their transplant from complications such as hemorrhages…"

How to provide real GMP within academic facilities

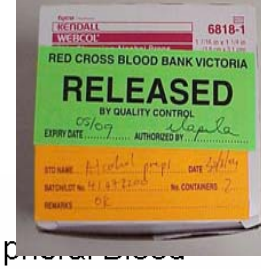
- Wholly supported by academic/hospital institution- substantial cost, financial viability, GMP credibility, governance?
- Wholly commercial- support of basic research, maintenance of clinical linkages, academic/investigator priorities?
- A hybrid approach…using a special purpose company…

Commercial Model



Peter Mac and Cell Therapies

- Academic & Clinical service
- Underpinned by quality agreements- external QM and quality services (doc control, audit, QSO)
- 2 x cGMP TGA licences
  - 149827 PBSC -Apheresis (harvesting), Cryopreservation and banking
  - 162398 Chondrocytes- Cell culture, Manufacturing Cleanrooms
- Agreements for TGA licensed, (BP/EP or USP) mycoplasma testing, endotoxin, sterility, NAT and mandatory serology as well as microbial contamination testing
- Quality Manager and Production Manager for each trial
- Trial manufacturing issues- excluded but compliant
  - Constituents and specification
  - Essential processes
  - Product specification
  - Containers/shelf life & storage precautions
  - Arrangements for Quality Control
  - In process specs and methods for QC
  - Test methods

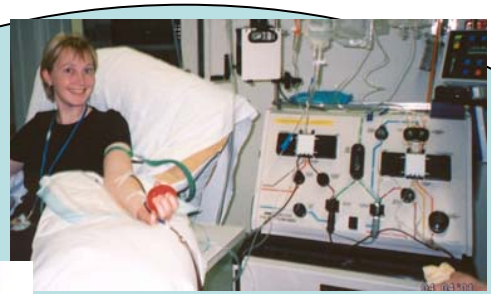


It is possible to control autologous treatments…

#^DCs & artificial APCs
^Macrophages
#T cells (GM)
*PBSC (HPC-A)
^Expansion cultures
#Peptides
*Matrix associated Chondrocytes
^MSCs
MCBs & others (islets etc)

*cGMP licensed
#CTX
^CTN

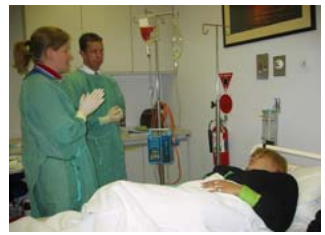
- CBCT is a product of formal collaboration between Peter Mac and external partners
- Compliance by initially electing to **decline** available exemptions
- Uniformity of compliance for **all** products
- Focus on highest volume activity
- Gap analysis to determine support requirements for each activity
- Focussed on therapeutics- std of care, CMO, trials
- Scope of quality:



Clinical Referral

Pre- treatment...

Donor evaluation, Harvesting, processing, storage, testing, shipping and release...



Infusion, subsequent treatment

Cell Therapies

And regulators are finally starting to provide more regulatory certainty…

Australia

This is to inform you that the Australian Government has recently agreed to proceed with the establishment and implementation of the regulatory framework for human cell and tissue therapies (HCT) excluding assisted reproductive tissues and solid organs. The issue of possible regulatory arrangements for solid organs has been referred to the new national organ donation and transplantation authority.

Europe

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL no 1394/2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

Pre clinical data and regulators

FDA questions…

- Which kind of cell (s) will be used?
- What is the source of the cells?
- How many cells are needed to achieve the desired response?
- Are the cells injected/implanted alone?...with other cells/agents?…with a scaffold?...encapsulated?
- Are the cells modified?...now a ‘gene therapy’?
- What is the optimal method/route to deliver the cells?
- What is the optimal timing of cell injection/implantation relative to the onset of the disease/injury?
- What happens to the cells *in vivo* following delivery?
- What is the risk/benefit ratio for the intended patient population?

EMEA questions…

- origin (autologous - allogeneic);
- ability to proliferate and differentiate;
- ability to initiate an immune response (as target or effector);
- level of cell manipulation (in vitro/ex vivo expansion /
- activation / genetic manipulation);
- mode of administration (ex vivo perfusion, local, systemic);
- duration of exposure (short to permanent);
- combination product (cells + bioactive molecules or structural materials)
- availability of clinical data on or experience with similar products.

Pre clinical design

FDA

- ‘Clinical’ product (human cells)

  Immune competent animals given immunosuppressive drugs

Or Genetically immunodeficient strains

Or Immune privileged implantation sites

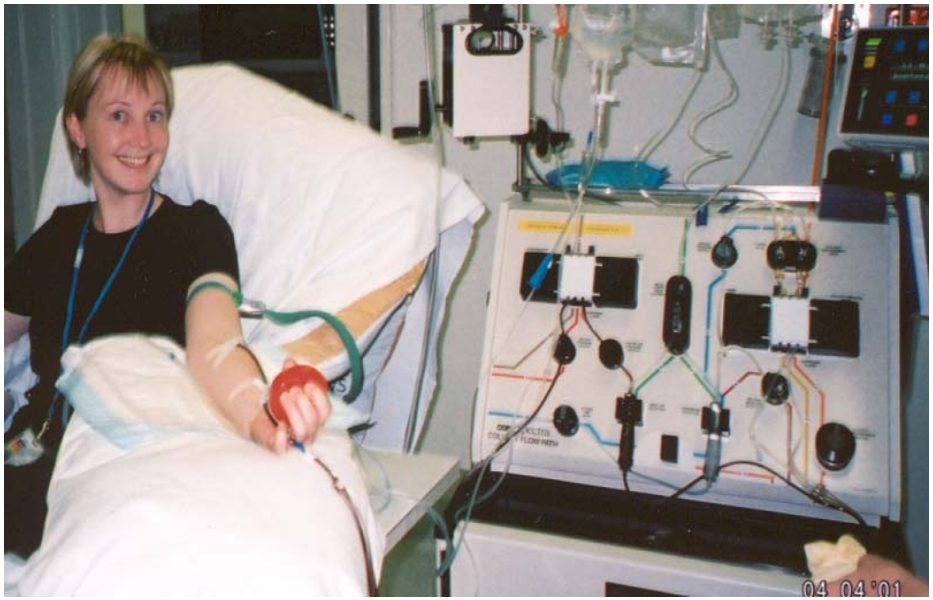
Or Immune privileged’ cells

- Use of analogous cell product in an animal model

EMEA

- Human cells in immunosuppressed animals
- Homologous cells in animal studies
- Human ex vivo /invitro studies

Cell & Tissue harvesting



- Most challenging for GMP
- Tracking, labelling
- Training and validation
- Coping with a significant staff overhead for GMP compliance
- Reporting lines- production v professional issues
- Fundamental for GMP compliance
- Micro contamination issues
- Logistics of shipping viable tissue
- Always Controllable? Yes...

Guidelines on Good Professional Practice

for the Procurement of Human Tissue and Cells for Drug Production

Christoph Gaissmaier

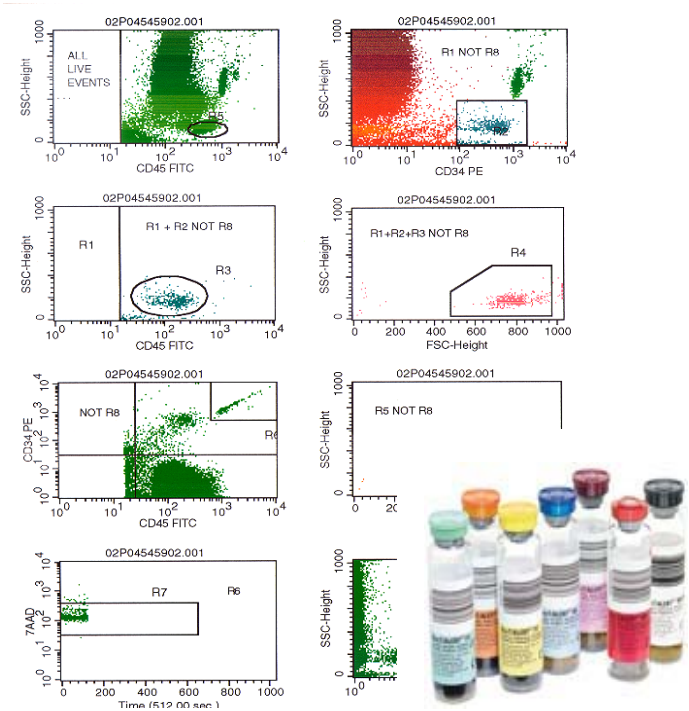
Associate Members of the German Society of Surgery:

German Society for Endovascular and Vascular Surgery (DGG), German Association of Paediatric Surgery (DGKCH), German Society for Orthopaedics and Orthopaedic Surgery (DGOOC), German Society of Plastic, Reconstructive and Aesthetic Surgery (DGPRÄC), German Society for Thoracic and Cardiovascular Surgery (DGT), German Society of Thoracic, Heart and Vascular Surgery (DGTHG), German Society for Traumatology (DGU), German Society of Visceral Surgery (DGVC), German Society of Neurosurgery (DGNC).

Cell and Tissue Manufacturing

Facilities are not always the most important challenge
Cleanrooms ≠ GMP

- Always in a cleanroom?
- Functionally closed systems to support automation
- Process validation & data to support manufacturing environments
- Challenges – legacy products, third party collections and storage,
- Fresh product testing & release
- Which methods, which regulator, who is licensed?



Testing

- *viability*
- *Cell counts*
- *Microbiology vs Sterility*
- *Serology*
  - *HIV1-2, HTLV, HCV, HBV, syphilis*
- *NAT if applicable*
- *Mycoplasma*
- *Identity & characterisation*
- *In process vs release testing*

- *Which require licences?*
- *False positives*
- *Real risk v regulatory risk*

Hospital services essential for cGMP cell therapy

- Engineering
- Supply
- Cleaning
- IT
- Other clinical units

What can you influence (by formal agreement), or what will you duplicate?

Surviving manufacturing audits

- TGA- by manufacturing regulators, as opposed to product regulators
  - Agreements
  - NCR and QS, Doc Control
  - QC, manufacturing, testing etc

- 9 TGA audits over 6 years for two licences (one in 01, other in 03)
- How many academic facilities have been audited by ‘real’ manufacturing auditors?
- How many facilities remain operational when actually compliant for GMP?
- GxP? Credible, actual?

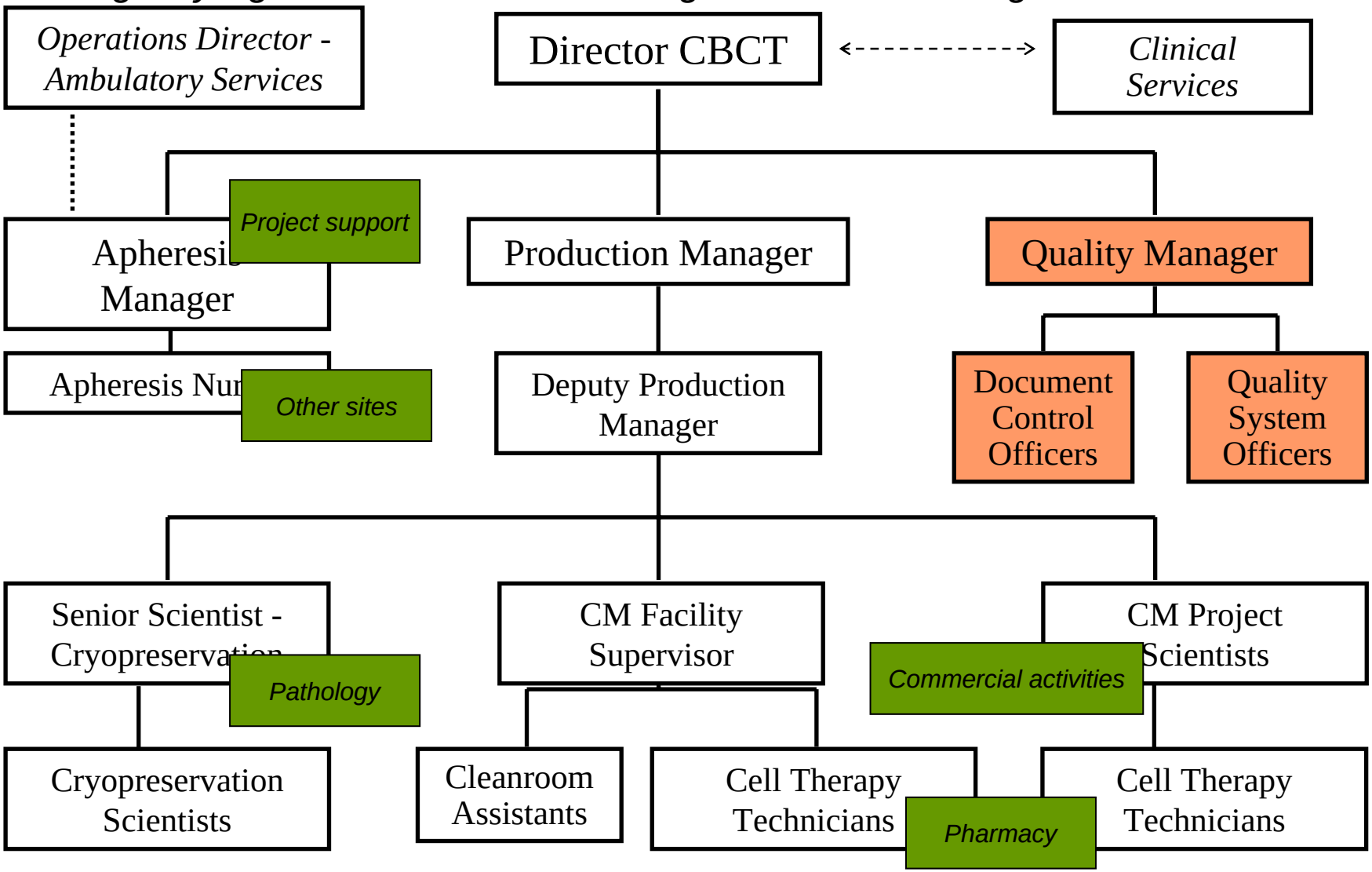
First steps

- Alliances, collaborations, partnerships
- Governance arrangements, nominees
- Gap analysis, a quality policy & manual
- Process- for now, or for Phase III and beyond
- A business model for life after commissioning
- Credentialling…FACT, AABB or others
- How to survive vendor / sponsor qualifications/manufacturing or trial audits?
- How should one manage regulatory and business risk?
- Training, documentation etc…

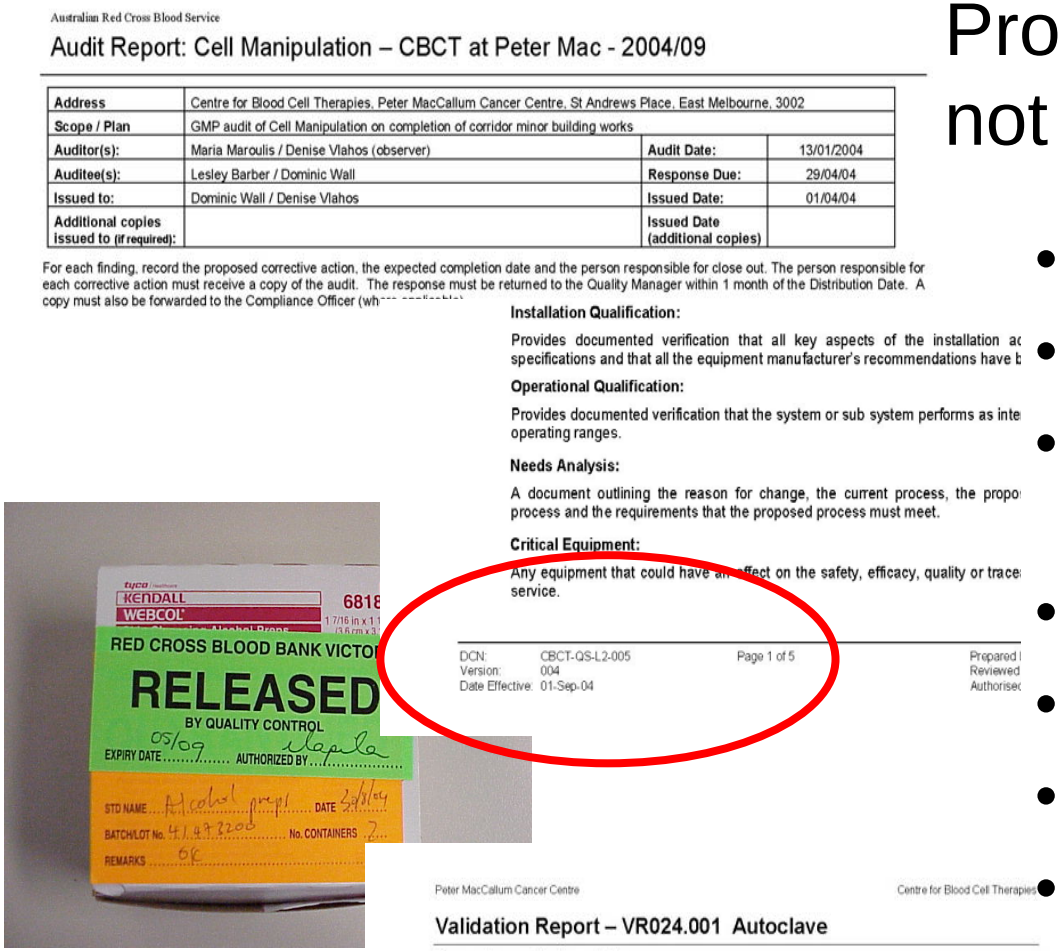
Organisations often have multiple participants, but ***there can only be one leader with regards to accountability for the operations of the quality system***

Defensibility, credibility, management review

Inter-agency Agreements are the first target for audit challenge…



Progressive development- not everything is perfect



Australian Red Cross Blood Service

Audit Report: Cell Manipulation – CBCT at Peter Mac - 2004/09

Address	Centre for Blood Cell Therapies, Peter MacCallum Cancer Centre, St Andrews Place, East Melbourne, 3002		
Scope / Plan	GMP audit of Cell Manipulation on completion of corridor minor building works		
Auditor(s):	Maria Maroulis / Denise Vlahos (observer)	Audit Date:	13/01/2004
Auditee(s):	Lesley Barber / Dominic Wall	Response Due:	29/04/04
Issued to:	Dominic Wall / Denise Vlahos	Issued Date:	01/04/04
Additional copies issued to (if required):		Issued Date (additional copies)	

For each finding, record the proposed corrective action, the expected completion date and the person responsible for close out. The person responsible for each corrective action must receive a copy of the audit. The response must be returned to the Quality Manager within 1 month of the Distribution Date. A copy must also be forwarded to the Compliance Officer (wh

Installation Qualification:

Provides documented verification that all key aspects of the installation ac specifications and that all the equipment manufacturer's recommendations have b

Operational Qualification:

Provides documented verification that the system or sub system performs as inte operating ranges.

Needs Analysis:

A document outlining the reason for change, the current process, the propo process and the requirements that the proposed process must meet.

Critical Equipment:

Any equipment that could have an effect on the safety, efficacy, quality or trace service.

DCN: CBCT-QS-L2-005 Page 1 of 5
Version: 004
Date Effective: 01-Sep-04

Peter MacCallum Cancer Centre — Centre for Blood Cell Therapies

Validation Report – VR024.001 Autoclave

Keywords: Autoclave, sterile

	Name	Signature	Date
Prepared By:	L. Barber		
Reviewed By:	J. Coverdale		
Authorised By:	D. Vlahos		

1.0 Introduction

The new 35L bench-top steam sterilizer (autoclave) will be used by the Cell Manipulation Facility to sterilise re-usable instruments, rotor parts and containers by steam under pressure.

- A Quality Manual
- Document Control
- Non-conformance reporting, deviations
- Auditing
- Validation
- Training
- Process Change Management
- Other activities

Allogeneic vs Autologous product

- EMEA…**identity is linked to the process**
- At what stage should automation be anticipated? Impact of later process changes, impact on value of preclin data and Phase 1-2 data?
- What impact will this have on total costs of the auto v allo approaches?

What should be the minimum manufacturing standards for manufacturing cells?

What are the principal risks to a GMP manufacturer dependent upon external tissue & cells?

What is better – auto or allo?

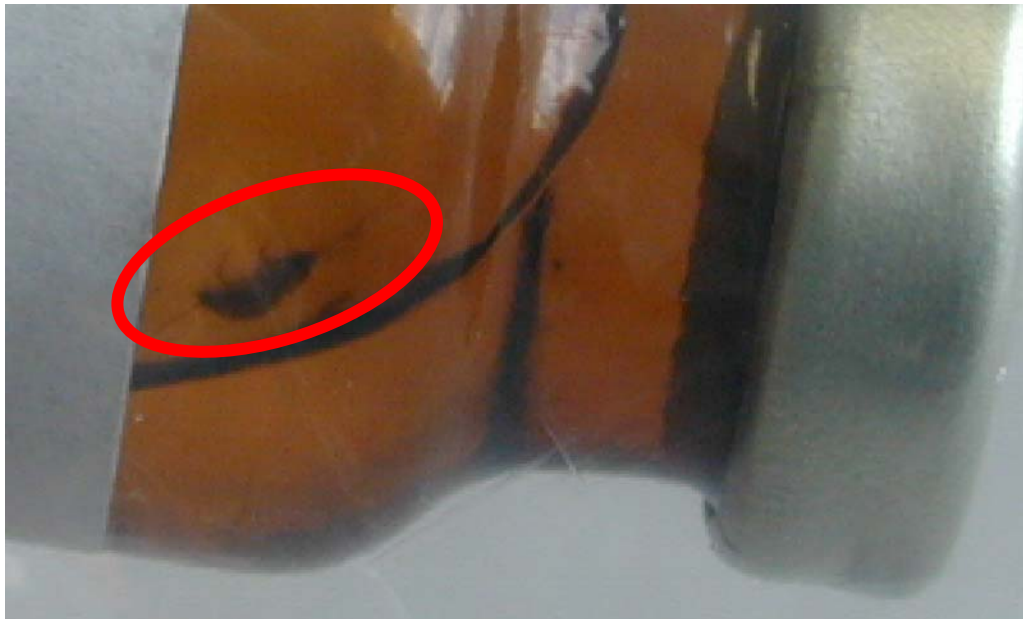
Product is the process?

What business model, or funding?

How to avoid a ‘failed facility’

Are there other residual business risks?

•Suppliers- clinical grade, “for further manufacturing”, testing services



Autologous regenerative treatments can be safely managed and they can be a commercially viable business within an academic program…

Good data, better documentation

Follow up, traceability, QA data

Defensibility, safety, less risk

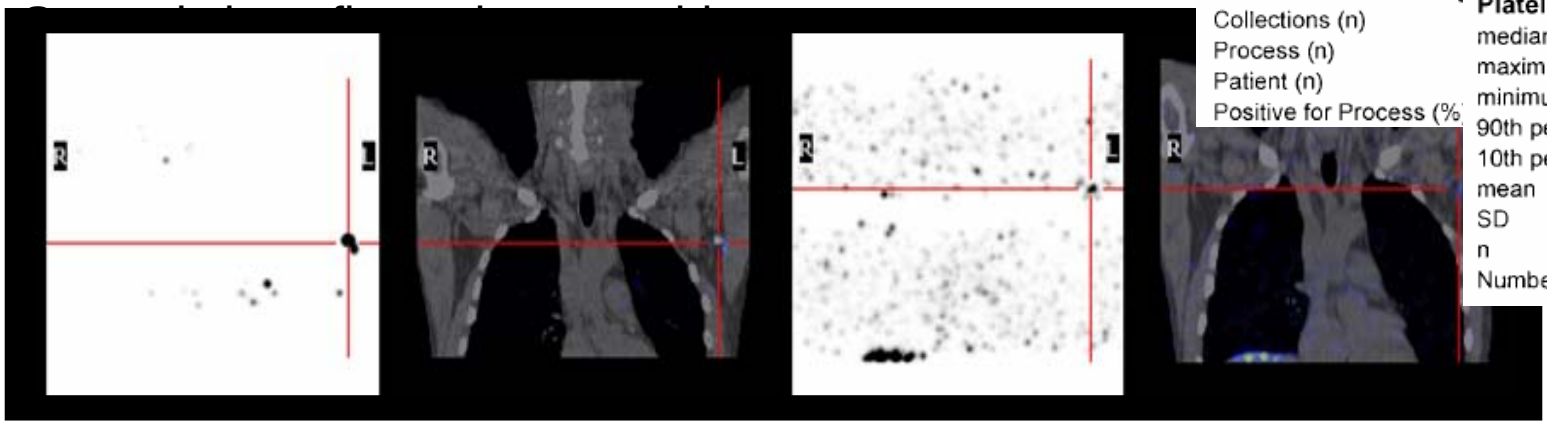
Processing Data	Jul-07
WBC Yield (%) Limit > 75%	
median	88
maximum	104
minimum	74
90th percentile	98
10th percentile	77
mean	88
SD	7
n	
Number outside limit	

CD34+ x10^6/kg (no lim
median
maximum
minimum
90th percentile
10th percentile
mean
SD
n

Positive Microbiolo
Collections (n)
Process (n)
Patient (n)
Positive for Process (%

Infusion Data
Neutrophil Recovery (Limit < 14 da
median
maximum
minimum
90th percentile
10th percentile
mean
SD
n
Number outside limit

Platelet Recovery (Limit < 21 days)
median
maximum
minimum
90th percentile
10th percentile
mean
SD
n
Number outside limit



Coronal PET/CT images showing presence of activity within axillary lymph node at 2 hours (left) and 20 hours (right) after ID injection into volar aspect of left forearm. Images were considered positive evidence for cell migration

Centre for Blood Cell Therapies

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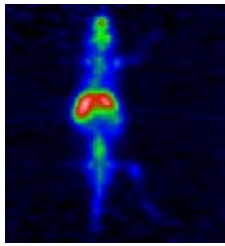
Jude Moloney
Garth Cameron
Angela Morgan
Lucy Kravets
Maja Wilkie
Javier Haurat
Peter Gambell
Kerrie Stokes
Gill Treloar
Tanya Pisanelli
Marijana Vanevski
Dayna Jackson
Prof Patrick Coghlan
Denise Vlahos
Rachael Kelly
Irene Lazzarini

IV



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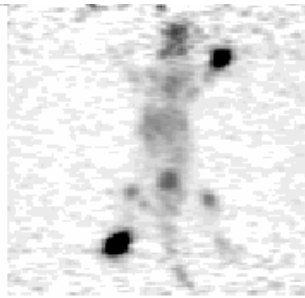

Cell Therapies
ACN 100 285 918

Managing Director
Ray Wood

www.celltherapies.com.au