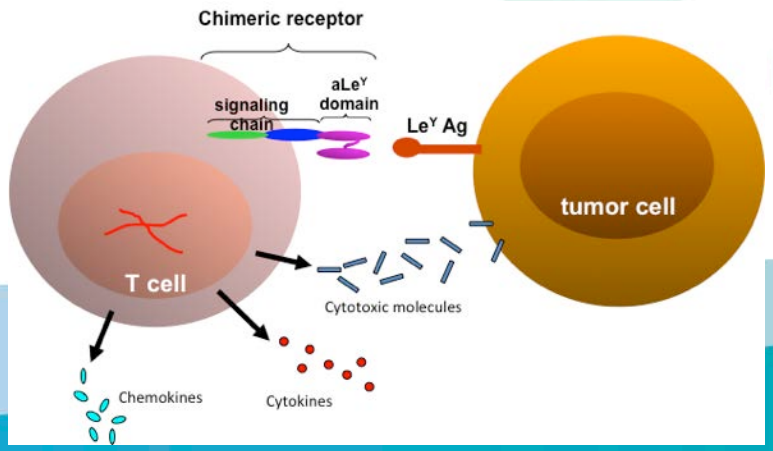
cell therapies

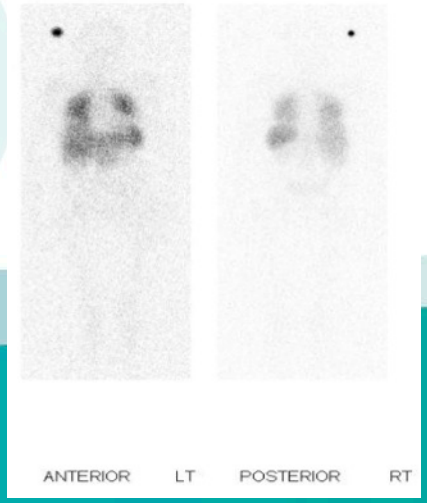
T-cells and cancer- new therapies…

Dominic Wall PhD FFSc (RCPA)
CSO
Cell Therapies Pty Ltd

Immunotherapy expertise

- Numerous immunotherapy trials since 2001- ranging from artificial APCs, cell banking of vaccine cell lines, DCs for cancer and infectious diseases through to gene modified T cells for patients locally, regionally and internationally
- Tech transfer of immunotherapy projects to EU and US and vice versa
- Secured CTX approval for HCV on behalf of academics centers including oversight of production of therapeutic peptides and proteins
- Approvals secured for 1st CAR-T cell CTX in Australia- 2006 onwards
- Currently supporting commercial and non-commercially sponsored CAR-T trials in solid cancers and haematology
- Specialist network support for cell harvesting & apheresis & cryopreservation in Australia and Rest of World (EU, Eastern Europe/ASEAN/Japan)
- Management of therapeutic NLRDs and DNIRs and TGA manufacturing approvals (when required)
- Additional modalities- advanced analytics/patient monitoring/in vivo cell tracking

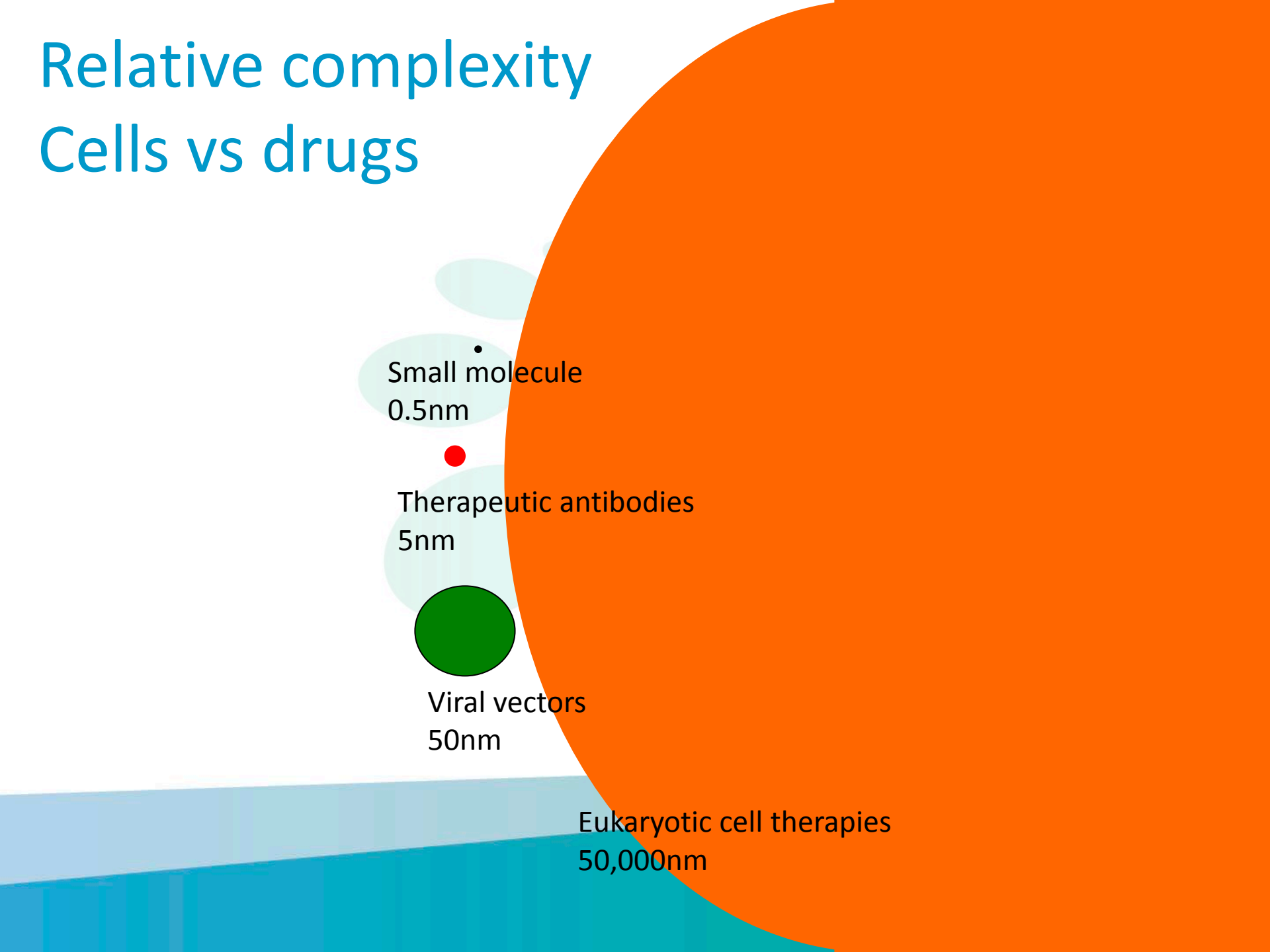




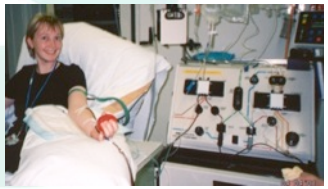
Human in vivo cell tracking of CAR-T cells, 22hrs post infusion

cell therapies

Relative complexity
Cells vs drugs

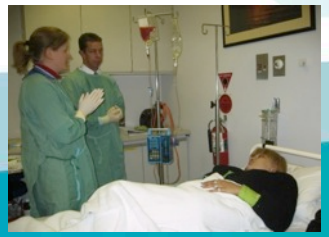


Inherent challenges for cell & tissue products



Medicinals

- No collections/donors
- Large lots
- high throughput
- Terminal sterilization
- Automated
- control of starting materiel
- Stable protocol
- unknown recipient
- Fixed volumes/inoculums
- Control of solutions

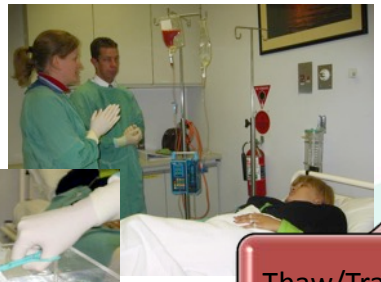


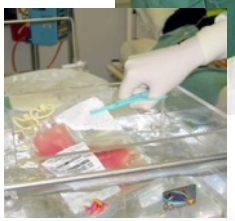
Cells and Tissue

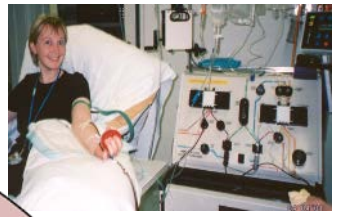
- Donors and collections
- single product lots, high value batches
- low throughput
- Partial closed system, no term sterile
- Traditionally labour intensive
- limited control of starting materiel
- Evolving research based protocols,
- Known recipients
- Variable volumes
- Often IV drugs/subclinical sepsis

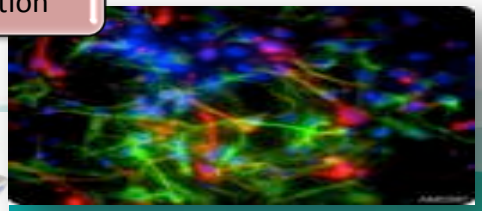
cell therapies

Cells need needle-to-needle control









Doctor

Collection

Isolation/ separation

Transformation/ differentiation

Expansion

Cryostorage

Scheduling/ logistics

Thaw/Transplant

- New technology paradigm
- Limited patients from each donor (sometimes just one)
- “Product is the process”
- Each process step impacts efficacy, safety
- Just in time, patient specific production in many cases
- Short (<48h) shelf-life

cell therapies

The immune system is powerful, and cells have risks…

Unexpected toxicity?

Malignant transformation?

Inappropriate differentiation?

Times Online March 15, 2006

Myfanwy Marshall outside Northwick Park hospital today. She said that her boyfriend was unrecognisable (Edmond Terakopian/PA)

Two fight for lives after drug trial poisoning

BY PHILIPPE NAUGHTON AND AGENCIES

The distraught girlfriend of one of two men fighting for their lives in a London hospital after being poisoned in a drug trial today said she had barely recognised him because his head was so swollen.

Myfanwy Marshall, 35, said that her boyfriend looked "like the Elephant Man" after being given a dose of the drug, TGN 1412.

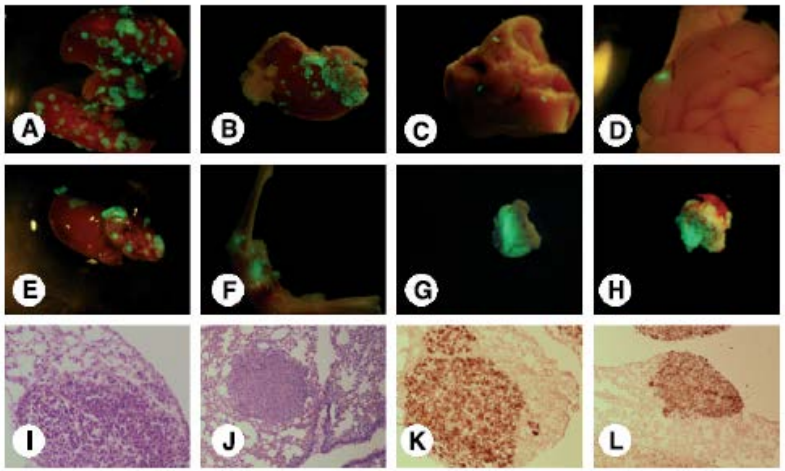
Her boyfriend is a 28-year-old landlord who had

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

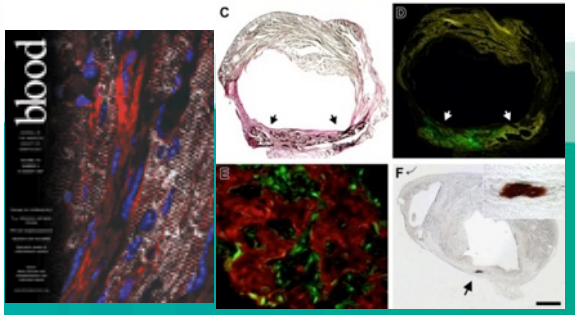
Priority Reports

Spontaneous Human Adult Stem Cell Transformation

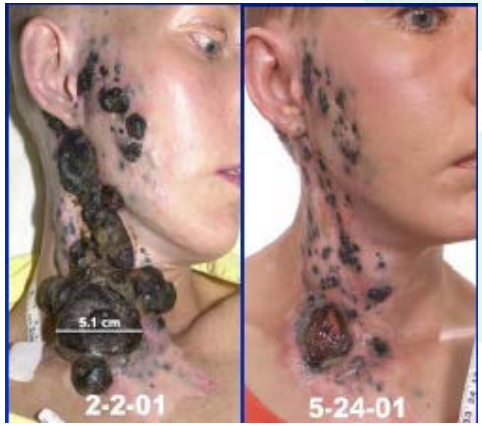
Daniel Rubio[1], Javier Garcia-Castro[1,2], Maria C. Martin[3], Ricardo de la Fuente[1], Juan C. Cigudosa[3], Alison C. Lloyd[4] and Antonio Bernad[1]



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



Cells as therapeutics
T-cell immunotherapy



No. of patients	Treatment	Objective responses
270	IL-2	16% (6% CR)
85	LAK cells + IL-2	24% (7% CR)
86	TIL + IL-2	34% (6% CR)
35	TIL + NMA + IL-2	51% (9% CR)
25	TIL + MA + IL-2	72%

Exciting data…but

- Truly representative melanoma patients?
- Is it scalable?

Rosenberg SA et al, Nature Reviews Cancer 2008 8:299-307

cell therapies

Redirecting a T cell

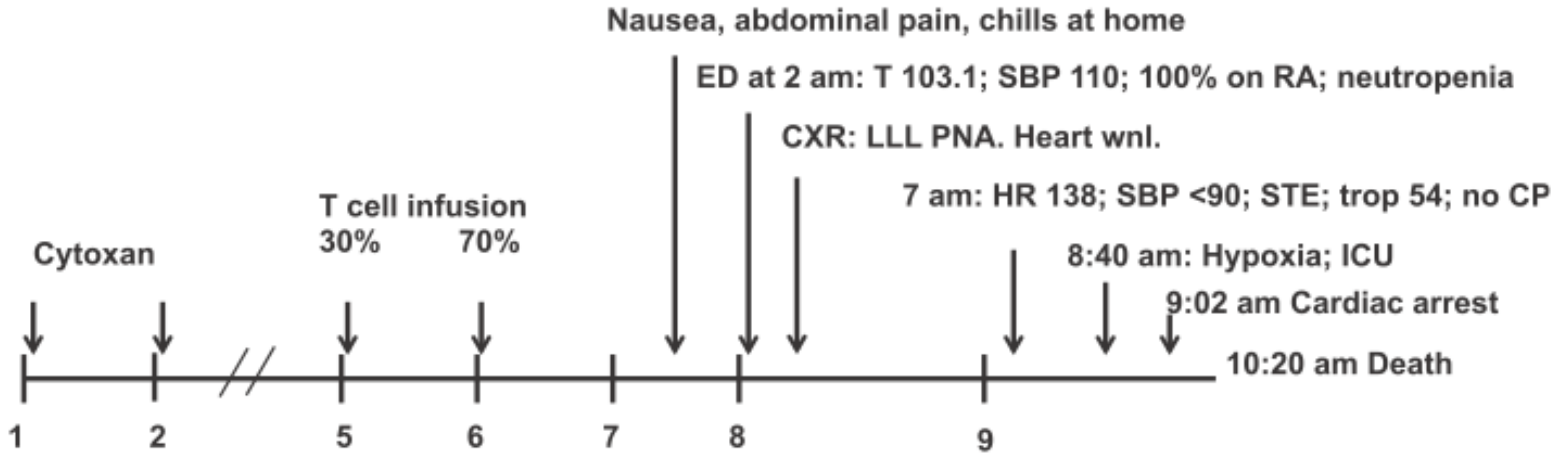
- How can we redirect a T cell to recognise a tumour antigen?
  - Prime T cells using an antigen presenting cell as the intermediary (Dendritic cell therapy)
  - Alter the T cell receptor (TCR) to recognise tumour antigens- would work with intracellular antigens, but is MHC restricted
  - Use synthetic constructs to activate T cells- not MHC restricted but only works with extracellular antigens
  - Intent is to create central memory T cells as well as effector (cytotoxic) T cells

Designing a new TCR for therapy

- Artificial TCR to HLA A*01 restricted antigen expression of MAGE-A3 peptide
- WT TCR has low affinity to self due to thymic deletion, so designed a high affinity TCR that would bind even with low HLA levels on tumour cells
- T cells expanded and use lentiviral vector 10 e9 infused (52% TE)
- 63yr old male with stage IIIB melanoma

Immunology can go wrong…

Patient 1



cell therapies

FDA clinical hold

Patient autopsy…

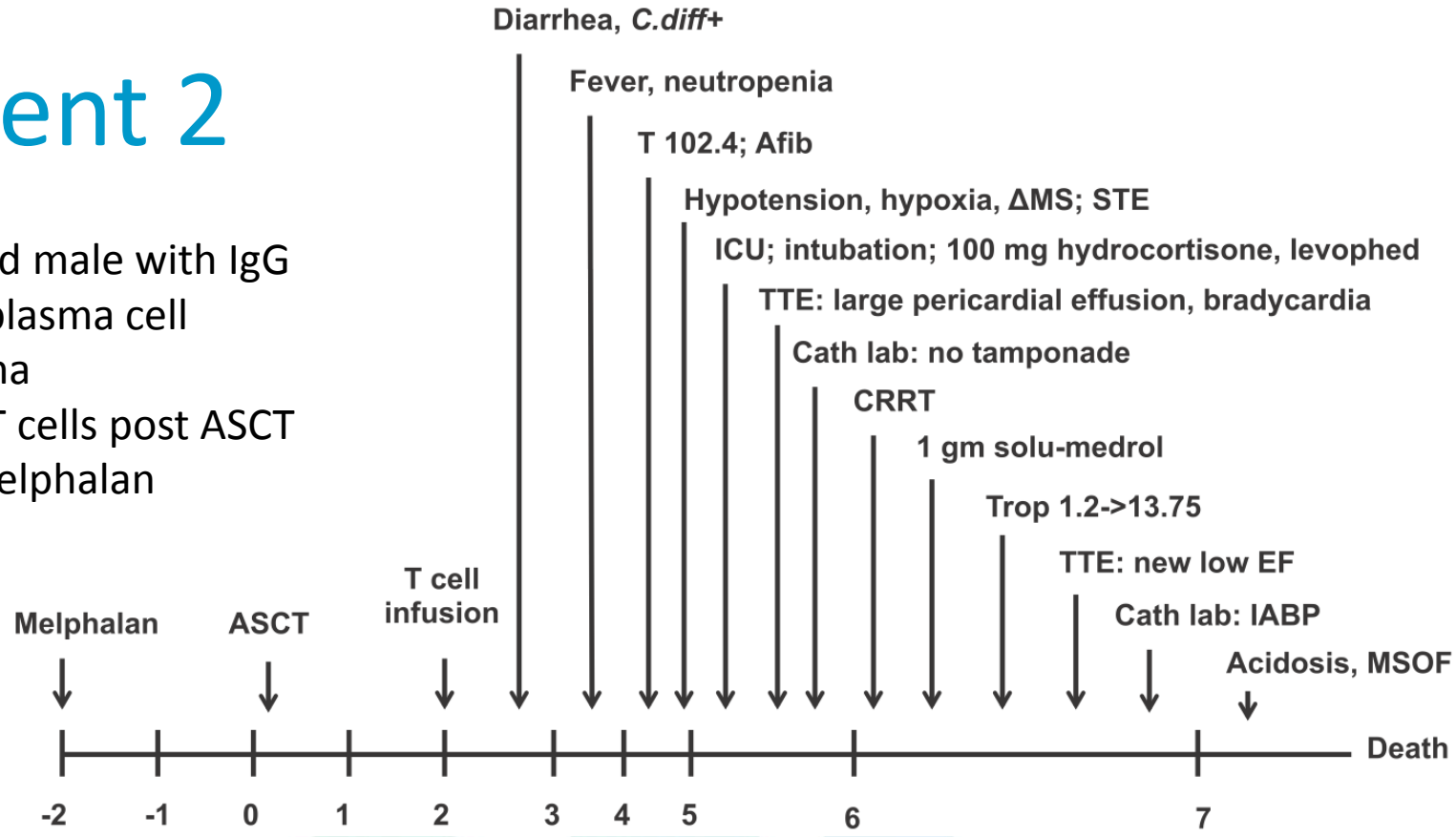
- Acute MI
- Severe atherosclerotic disease w 95% occlusion
- 2 scars in anterior ventricles- previous MI
- a history of silent MIs?

Assume….an MI followed by infarction

- Caused by? Metabolic demands from neutropenic fever, anemia and cytokine storm
- Protocol adds in cardiac stress test plus serial ECGs and tropT , consent updated
- study reopened

Patient 2

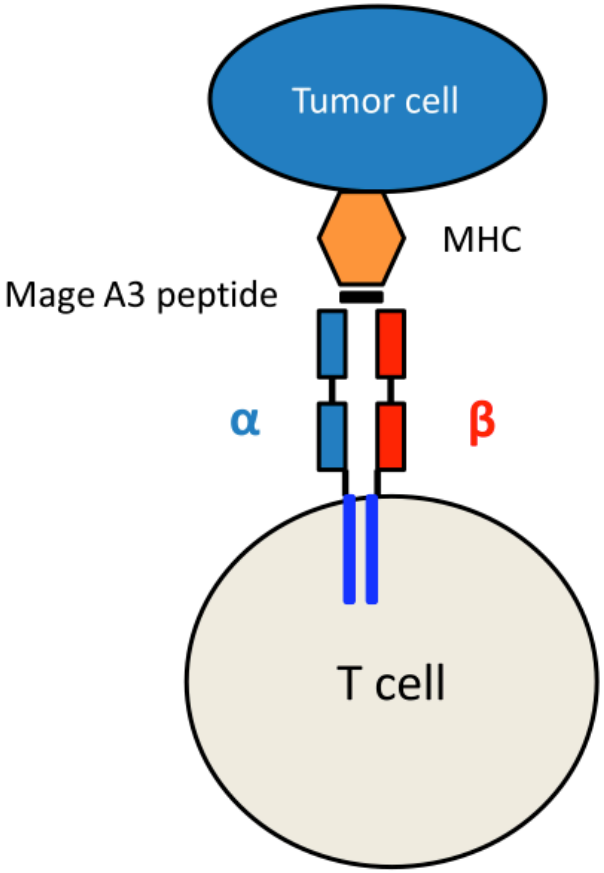
- 57 yr old male with IgG kappa plasma cell myeloma
- 2.4 e9 T cells post ASCT after melphalan



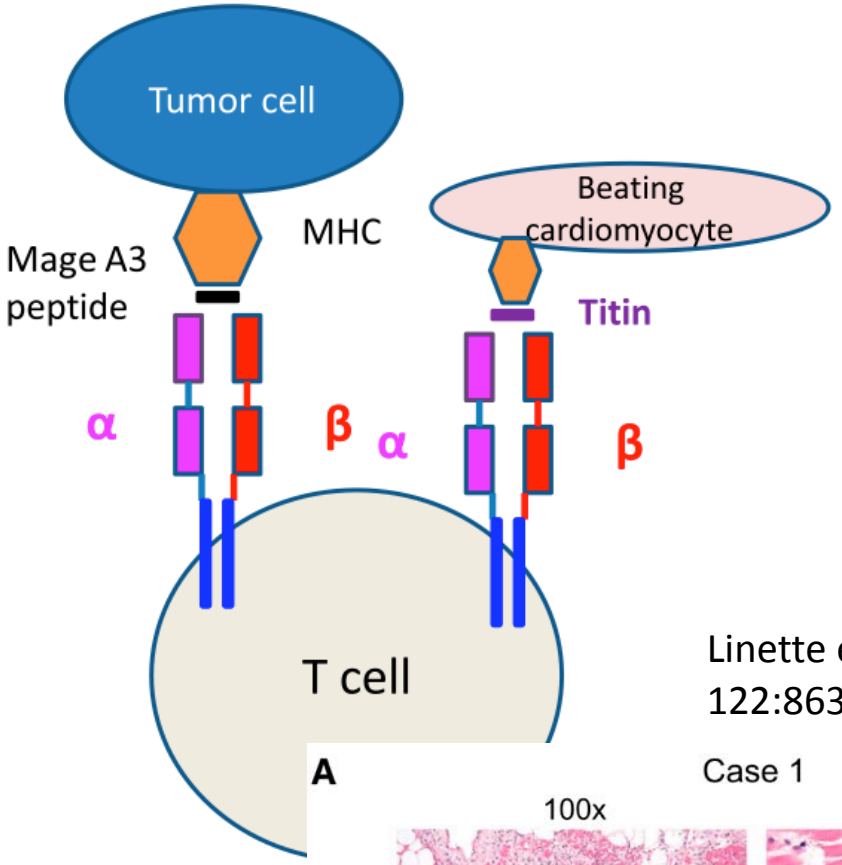
Died from cardiogenic shock

Myo-necrosis with +++ lymphoid infiltrate and no evidence of heart disease

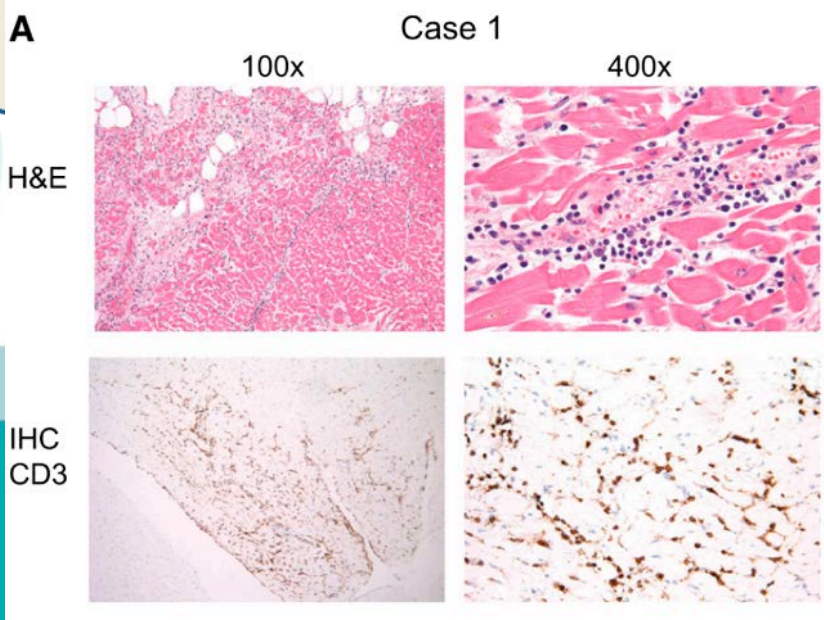
cell therapies



Heslop et al, 2013
122:854 Blood



Linette et al, 2013
122:863 Blood



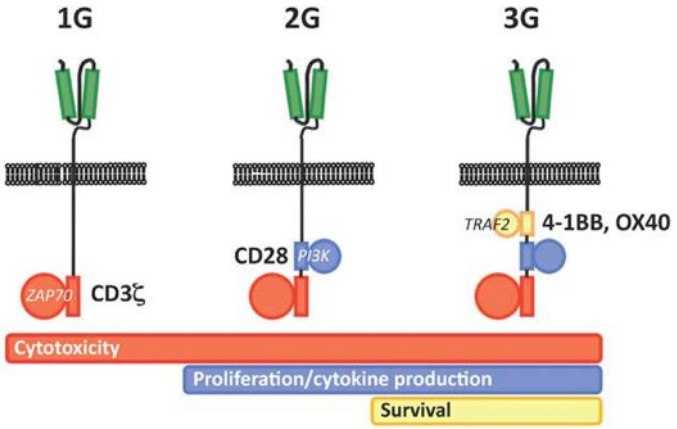
Accidental cross reactivity with a striated muscle protein- Titin

blood

2013 122: 863-871
Prepublished online June 14, 2013;
doi:10.1182/blood-2013-03-490565

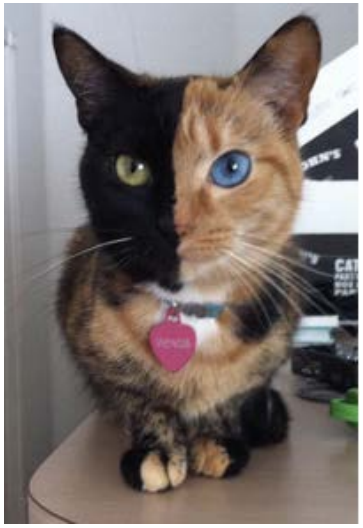
Cardiovascular toxicity and titin cross-reactivity of affinity-enhanced T cells in myeloma and melanoma

Gerald P. Linette, Edward A. Stadtmauer, Marcela V. Maus, Aaron P. Rapoport, Bruce L. Levine, Lyndsey Emery, Leslie Litzky, Adam Bagg, Beatriz M. Carreno, Patrick J. Cimino, Gwendolyn K. Binder-Scholl, Dominic P. Smethurst, Andrew B. Gerry, Nick J. Pumphrey, Alan D. Bennett, Joanna E. Brewer, Joseph Dukes, Jane Harper, Helen K. Tayton-Martin, Bent K. Jakobsen, Namir J. Hassan, Michael Kalos and Carl H. June



J Cancer 2011; 2:378-382

Chimeric Antigen Receptor



- Single chain variable fragments (scFv) derived from MoAbs recognizing particular antigen such as a cancer antigen
- scFv linked through trans-membrane domains to CD3 zeta signalling domains

Generation 1- scFv linked to CD3ξ= cytotoxicity

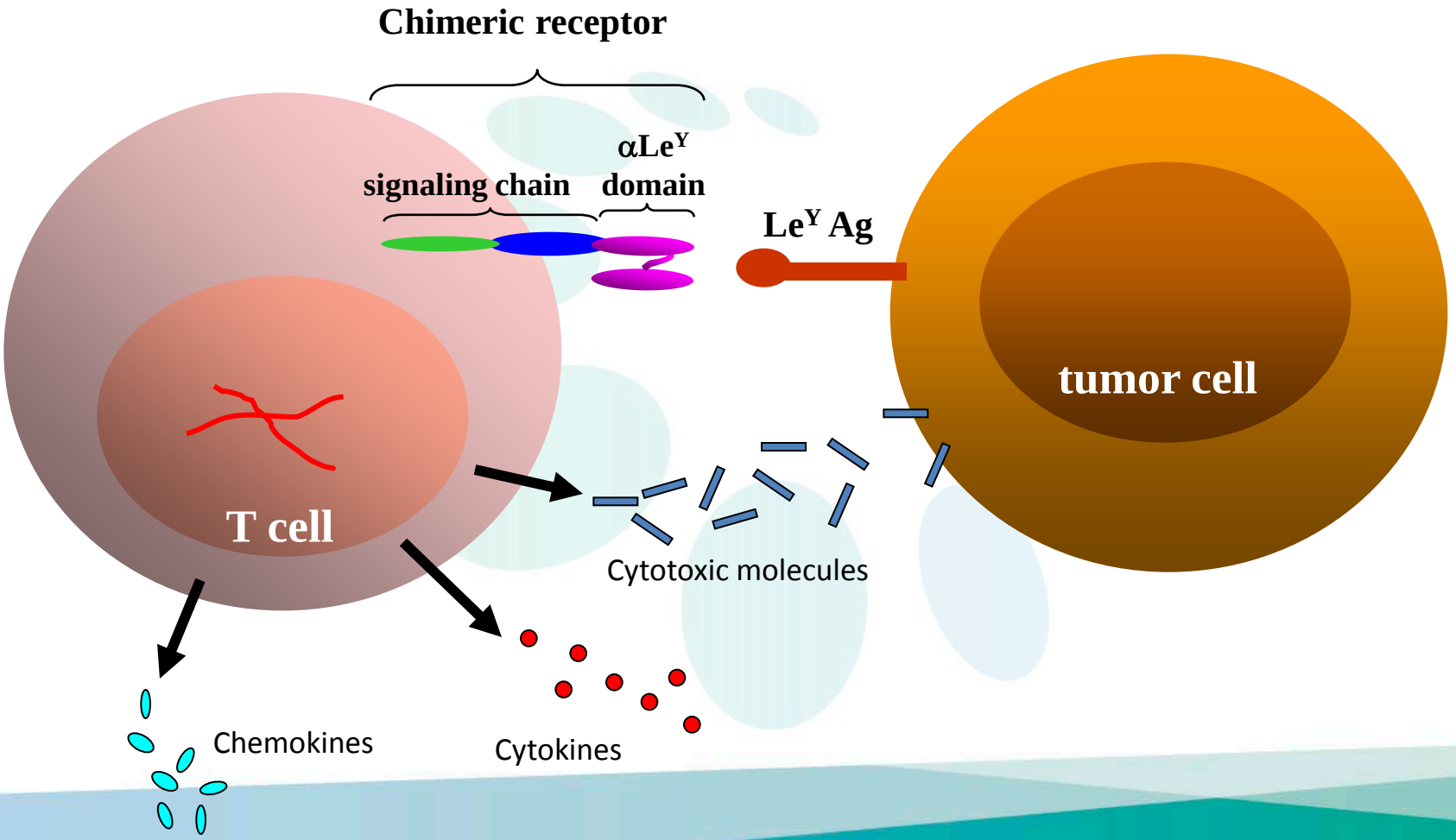
Generation 2- scFV + CD3ξ + CD28 = + proliferation

Generation 3- scFV + CD3ξ + CD28 + 4-1BB= + persistence

- Requires vector, growth factors & media

cell therapies

T cells gene modified to recognize an antigen



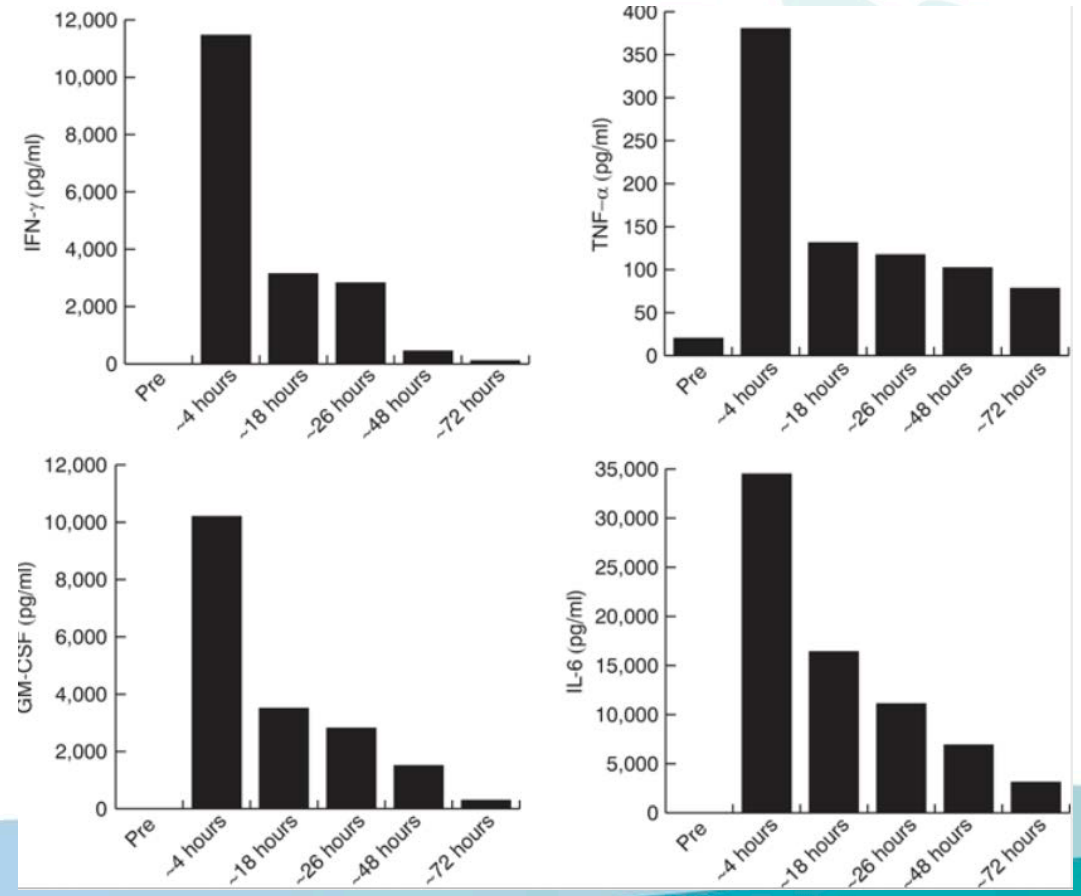
cell therapies

On Target Risks

- Proliferation of cells recognizing tumour antigens that can be expressed in normal tissue
- “Cytokine storm” cytokines, pulmonary tox and multi-organ failure
- Death 5 days post infusion in a CAR-T recognising ERBB2 (HER-2/neu) due to low level of expression in normal lung epithelia
- Safety systems with suicide genes?

Morgan, Richard; Yang, J. C. Kitano, M. Dudley, M. E. Laurencot, C. M. Rosenberg, S. A. (2010/02/25). "Case report of a serious adverse event following the administration of T cells transduced with a chimeric antigen receptor recognizing ERBB2". *Molecular therapy : the journal of the American Society of Gene Therapy* **28** (4): 843–51

Cytokine storm

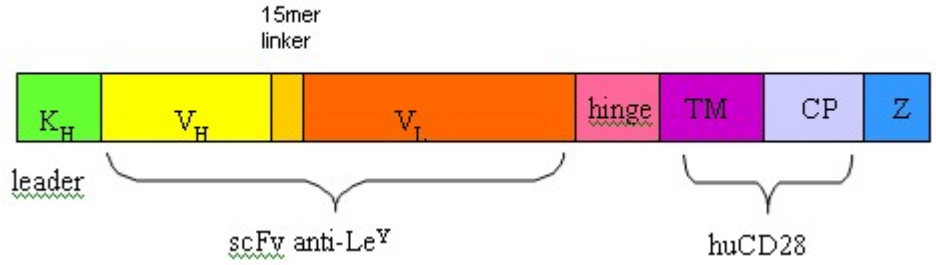


- Effects evident within 15 minutes
- Pulmonary infiltrates
- CD3ξ + 4-1BB
- 39 yr old patient with colon cancer at NCI

Morgan et al, 2011
28:4 Mol Therapy

cell therapies

Generation of modified T-cells



LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

- DNA coding for the humanized scFv derived from hu3S193

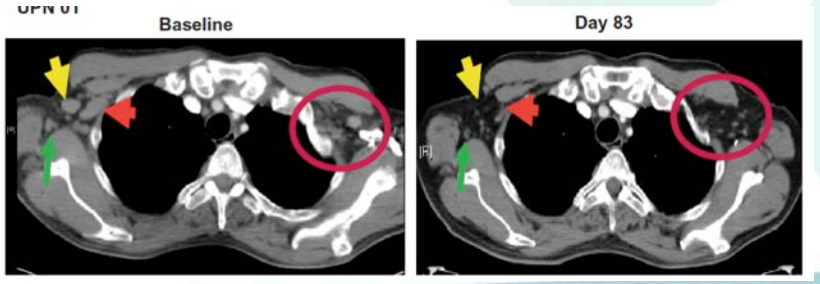
- Chimeric receptor consisting of the extracellular humanized scFv, recognizing the LeY Ag, linked to an extracellular CD8 hinge region, a transmembrane and cytoplasmic CD28 signaling domain, and zeta signaling chain
- A viral vector
  - Replication incompetent- single round of infectivity
  - High transduction efficiency even with non proliferating cells
  - Low risk of site-directed mutagenesis (X-SCID events…)
  - Typically either MLV (retroviral) or lentiviral
  - A major production challenge...

cell therapies

The breakthrough….

- A good antigen- CD19
- A good vector- lentivirus
- A good co-stimulator- 4-1BB
- Simple manufacturing

- The right patients



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.

SUMMARY

We designed a lentiviral vector expressing a chimeric antigen receptor with specificity for the B-cell antigen CD19, coupled with CD137 (a costimulatory receptor in T cells [4-1BB]) and CD3-zeta (a signal-transduction component of the T-cell antigen receptor) signaling domains. A low dose (approximately 1.5×10^5 cells per kilogram of body weight) of autologous chimeric antigen receptor–modified T cells reinfused into a patient with refractory chronic lymphocytic leukemia (CLL) expanded to a level that was more than 1000 times as high as the initial engraftment level in vivo, with delayed development of the tumor lysis syndrome and with complete remission. Apart from the tumor lysis syndrome, the only other grade 3/4 toxic effect related to chimeric antigen receptor T cells was lymphopenia. Engineered cells persisted at high levels for 6 months in the blood and bone marrow and continued to express the chimeric antigen receptor. A specific immune response was detected in the bone marrow, accompanied by loss of normal B cells and leukemia cells that express CD19. Remission was ongoing 10 months after treatment. Hypogammaglobulinemia was an expected chronic toxic effect.

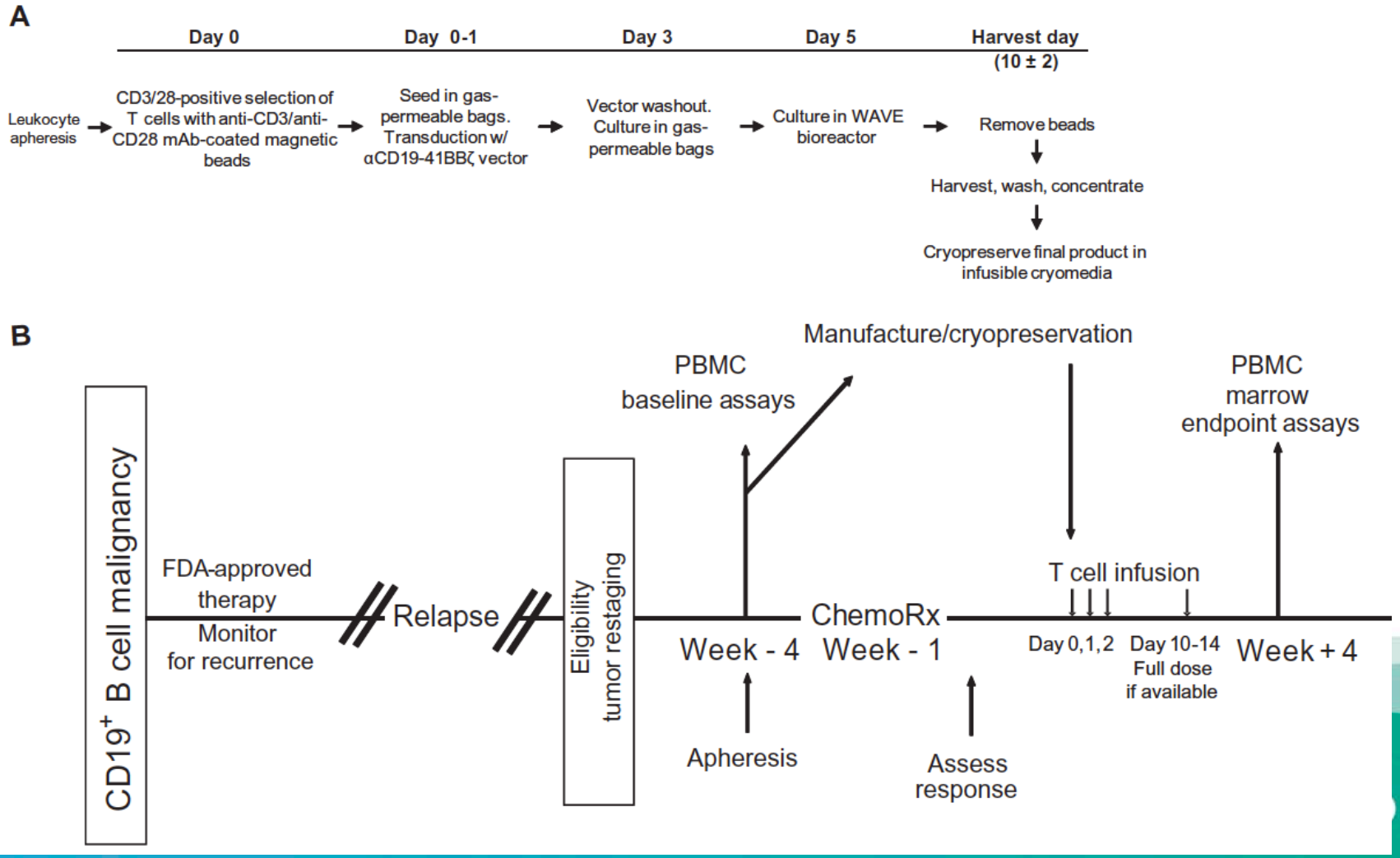
10.1056/NEJMoa1103849 August 10, 2011
N Engl J Med 2011

cell therapies

CD19 as a target

- B cell restricted
- Not on HSC
- Present in most B cell malignancies
  - CLL, B-ALL, DLBCL, FL, MCL
- Antibodies effect tumour growth

Manufacturing/Protocol



More CLL patients

- 3 patients plus 7 more
- 2 out of 3 original patients remain in remission 5 yrs later
- 1/3 received steroid at another treatment centre
- 1/3 received suboptimal dose

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NEWS RELEASE

DECEMBER 9, 2012

Leukemia Patients Remain in Remission More Than Two Years After Receiving Genetically Engineered T Cell Therapy

University of Pennsylvania Researchers Report on Results of Trial in 12 Patients, Including Two Children

ATLANTA — Nine of twelve leukemia patients who received infusions of their own T cells after the cells had been genetically engineered to attack the patients' tumors responded to the therapy, which was pioneered by scientists in the **Perelman School of Medicine at the University of Pennsylvania**. Penn Medicine researchers will present the latest results of the trial today at the American Society of Hematology's Annual Meeting and Exposition.

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215-349-5659

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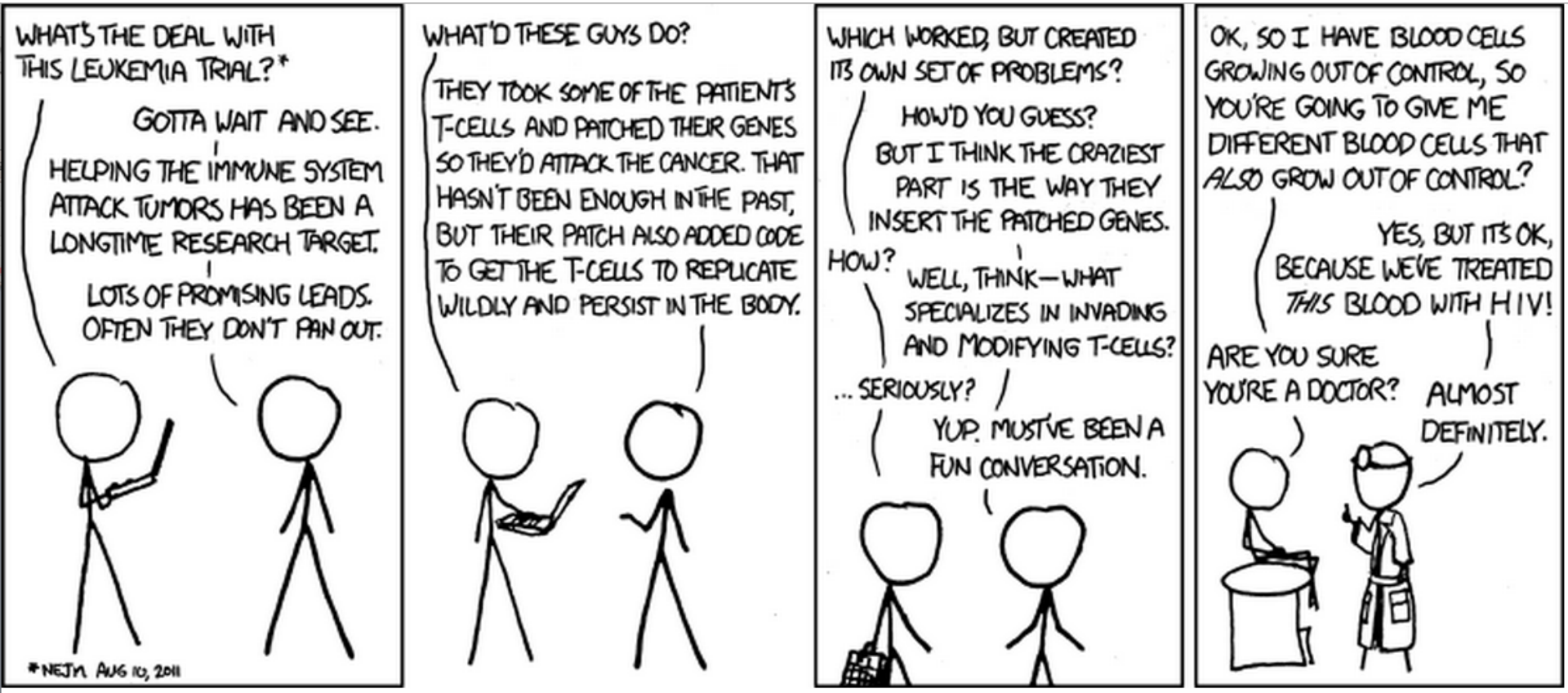
(Media Relations)
P: (215) 662-2560
F: (215) 349-8312

cell therapies

XKCD


WHAT'S THE DEAL WITH THIS LEUKEMIA TRIAL?*
GOTTA WAIT AND SEE.
HELPING THE IMMUNE SYSTEM ATTACK TUMORS HAS BEEN A LONGTIME RESEARCH TARGET.
LOTS OF PROMISING LEADS. OFTEN THEY DON'T PAN OUT.
*NEJM AUG 10, 2011
WHAT'D THESE GUYS DO?
THEY TOOK SOME OF THE PATIENT'S T-CELLS AND PATCHED THEIR GENES SO THEY'D ATTACK THE CANCER. THAT HASN'T BEEN ENOUGH IN THE PAST, BUT THEIR PATCH ALSO ADDED CODE TO GET THE T-CELLS TO REPLICATE WILDLY AND PERSIST IN THE BODY.
WHICH WORKED, BUT CREATED ITS OWN SET OF PROBLEMS?
HOW'D YOU GUESS?
BUT I THINK THE CRAZIEST PART IS THE WAY THEY INSERT THE PATCHED GENES.
HOW?
WELL, THINK—WHAT SPECIALIZES IN INVADING AND MODIFYING T-CELLS?
...SERIOUSLY?
YUP. MUST'VE BEEN A FUN CONVERSATION.
OK, SO I HAVE BLOOD CELLS GROWING OUT OF CONTROL, SO YOU'RE GOING TO GIVE ME DIFFERENT BLOOD CELLS THAT *ALSO* GROW OUT OF CONTROL?
YES, BUT IT'S OK, BECAUSE WE'VE TREATED *THIS* BLOOD WITH HIV!
ARE YOU SURE YOU'RE A DOCTOR?
ALMOST DEFINITELY.

Some points

- 1-10 e6/kg infused
- 1000 fold expansion of gene modified T-cells
- Persistence if beyond 6 months, for x years in BM, blood (& CSF)
- Some patients undergoes cytokine storm–like complication requiring ICU support- anti-IL6 mAb
- Persistent B-cell aplasia - ?lifelong Ig support
- 2kg plus of tumour lysed
- Molecular remission in patients

Salient points

- First patient had grossly sub-optimal dose
  - Still in complete molecular remission
  - With in-vivo 3 log expansion, how relevant is a cell dose?
  - One patient had delayed response- molecular analysis indicates a single cell was the source of the entire clinical response

ALL story

- Emily Whitehead- (Aged 5) May 2010 high risk ALL, relapsed Oct 2011, 2nd relapse Jan 2012
- April 2012 CAR-T cells
- ICU admission with CRS- IL6
- Now 3 years without cancer

Now with pediatric ALL…

- 60+ patients treated
- Cytokine-release syndrome + B-cell aplasia
- cytokine blockade with etanercept (TNF Amgen) and tocilizumab (IL6-R Roche)
- Antigen escape and T cell exhaustion -relapse with CD19 negative cells

Chimeric Antigen Receptor–Modified T Cells for Acute Lymphoid Leukemia

Stephan A. Grupp, M.D., Ph.D., Michael Kalos, Ph.D., David Barrett, M.D., Ph.D., Richard Aplenc, M.D., Ph.D., David L. Porter, M.D., Susan R. Rheingold, M.D., David T. Teachey, M.D., Anne Chew, Ph.D., Bernd Hauck, Ph.D., J. Fraser Wright, Ph.D., Michael C. Milone, M.D., Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.

N Engl J Med 2013; 368:1509-1518 | April 18, 2013 | DOI: 10.1056/NEJMoa1215134

Where are we now

- B-ALL 45 of 48 patients in CR
- Unaffected by allo, no GVHD, no tumour burden effects other than on CRS
- 8 months median follow up, OS 18 patients past 1yr, no events after 1 yr
- 15 relapses- 5CD19+ and 10 CD10-
- Promising results in DLBCL, FL

Extraordinary market activity in cell therapy- ALL, DLBCL, CLL and others

In Girl's Last Hope, Altered Immune Cells Beat Leukemia

Jeff Swensen for The New York Times

Total financings: 2014

$6.3 Billion Total Amount Raised in 2014

$3.0 Billion raised in 2013
YoY growth of 112%

$3.0 Billion Gene & Gene-Modified Cell Therapy

$491 Million raised in 2013
YoY growth of 510%

$687 Million Tissue Engineering

$708 Million raised in 2013
YoY growth of -3%

$2.6 Billion Cell Therapy

$2.0 Billion raised in 2013
YoY growth of 30%

Data provided by: informa

ALLIANCE for Regenerative Medicine

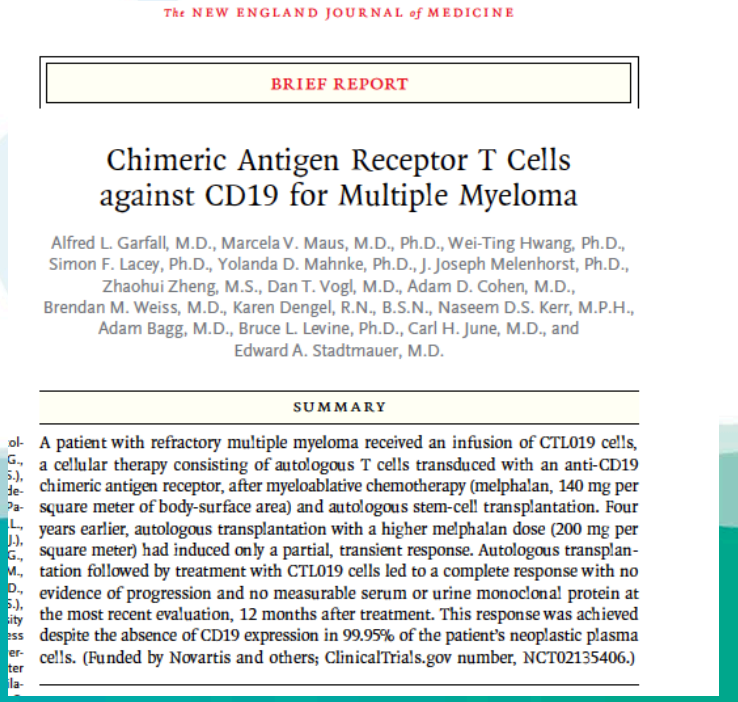
Jessica Kourkounis for The New York Times

Market activity

- IPOs
  - Kite (June 2014) $134m
  - Bellicum (Dec 2014) $160m
  - Juno (Dec 2014) $264m
  - Cellectis (March 2015) $228m
- Deals
  - U Penn and Novartis 2012
  - Celgene and Bluebird/Baylor 2013, 2015 $225m upfront
  - Servier/Pfizer & Cellectis $80m upfront, $185m per product
  - Kite & Amgen 2015 $60m upfront and $525m per product
  - Ziopharm/Intrexon & MD Anderson $100m stock/$20m/yr

CAR T outcomes

- Extraordinary response in B cells tumours
- Not all CAR-T are the same…persistence?
- Now myeloma…but how when it is CD19 negative?



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Chimeric Antigen Receptor T Cells against CD19 for Multiple Myeloma

Alfred L. Garfall, M.D., Marcela V. Maus, M.D., Ph.D., Wei-Ting Hwang, Ph.D., Simon F. Lacey, Ph.D., Yolanda D. Mahnke, Ph.D., J. Joseph Melenhorst, Ph.D., Zhaohui Zheng, M.S., Dan T. Vogl, M.D., Adam D. Cohen, M.D., Brendan M. Weiss, M.D., Karen Dengel, R.N., B.S.N., Naseem D.S. Kerr, M.P.H., Adam Bagg, M.D., Bruce L. Levine, Ph.D., Carl H. June, M.D., and Edward A. Stadtmauer, M.D.

SUMMARY

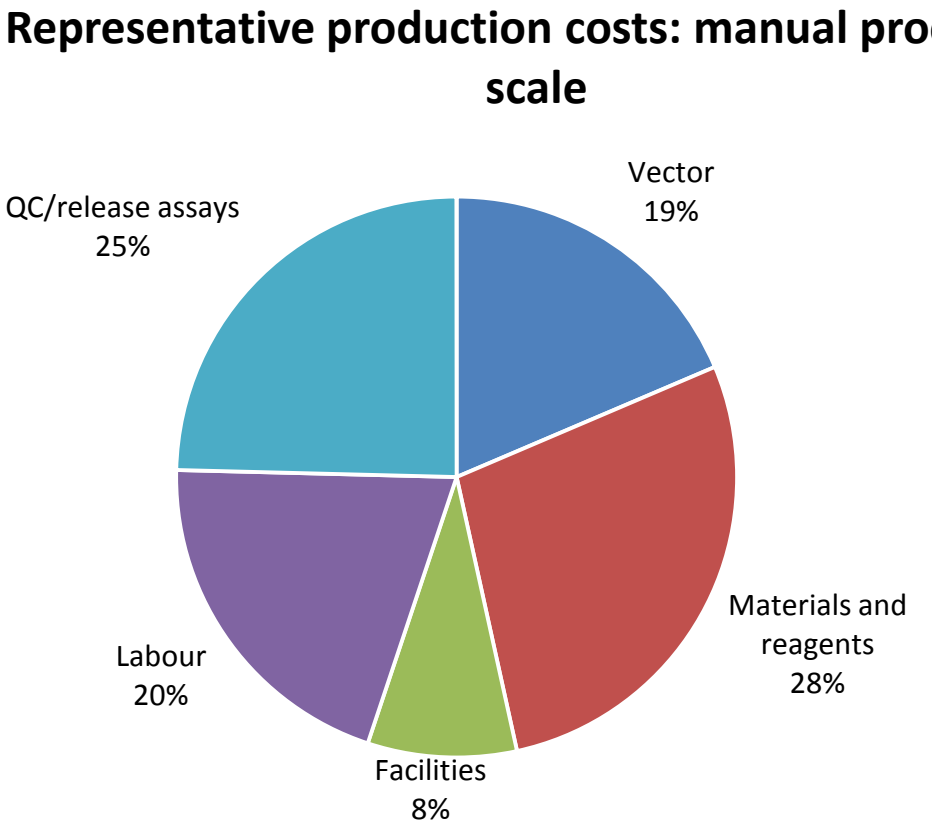
A patient with refractory multiple myeloma received an infusion of CTL019 cells, a cellular therapy consisting of autologous T cells transduced with an anti-CD19 chimeric antigen receptor, after myeloablative chemotherapy (melphalan, 140 mg per square meter of body-surface area) and autologous stem-cell transplantation. Four years earlier, autologous transplantation with a higher melphalan dose (200 mg per square meter) had induced only a partial, transient response. Autologous transplantation followed by treatment with CTL019 cells led to a complete response with no evidence of progression and no measurable serum or urine monoclonal protein at the most recent evaluation, 12 months after treatment. This response was achieved despite the absence of CD19 expression in 99.95% of the patient's neoplastic plasma cells. (Funded by Novartis and others; ClinicalTrials.gov number, NCT02135406.)

Cancer drug costs to patients

- **Provenge** (prostate cancer) $93,000 per three dose course of treatment
- **Cabazitaxel** (prostate cancer) $48,000 per course
- **Ipilimumab** (melanoma) $120,000 for four infusions
- **Vandenatinib** (Thyroid cancer) $10,400 per month
- **Brentuximab** (Hodgkin's lymphoma) $94,000 - $120,000 per course

- CAR T-cells? How much? How scalable for pharma – mediated manufacturing?

Internal COGS drivers for a manual process



cell therapies

Capacity scenarios: gene-modified cells

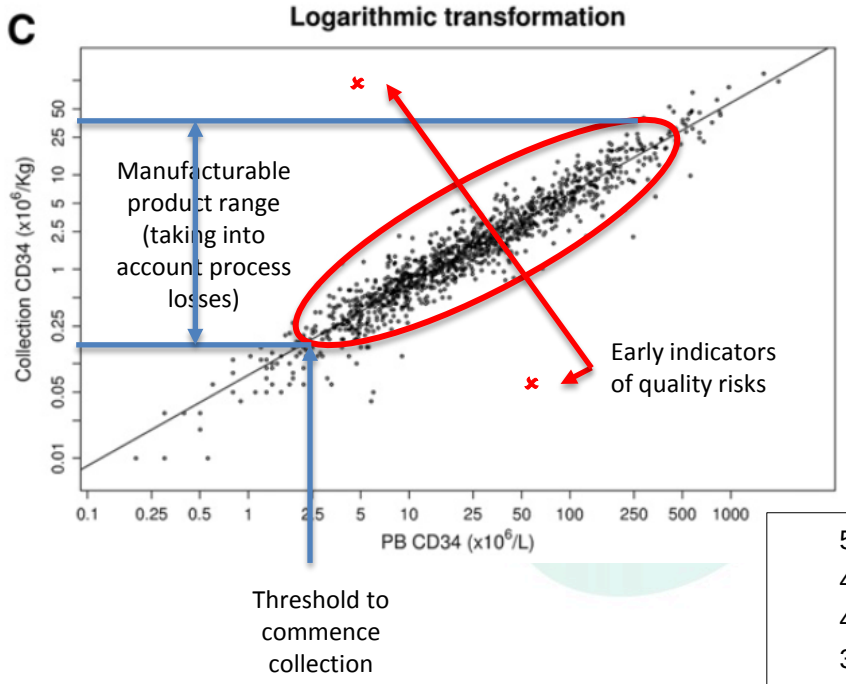
ILLUSTRATIVE

Scale up scenarios: gene modified/ immunotherapies	Clinical production	Commercial production	
	Current paradigm		"Autologous Production for the Future"
Demand (pax pa)	10's	1,000's	1,000's
Throughput/BSC/shift	40 pa	40 pa	150 pa
FTE/BSC (/100 pax)	4.5-6 (11-15)	3-4 (5-6)	1-2 (0.7-1)
BSC equivalents	1-2	100-200	30-50
FTE equivalents	9-12	300-800	30-80
COGS (ex consumable)	$60k	$40-50k	<$20k
COGS (all in)	>$100k	~$100k	$15-20k

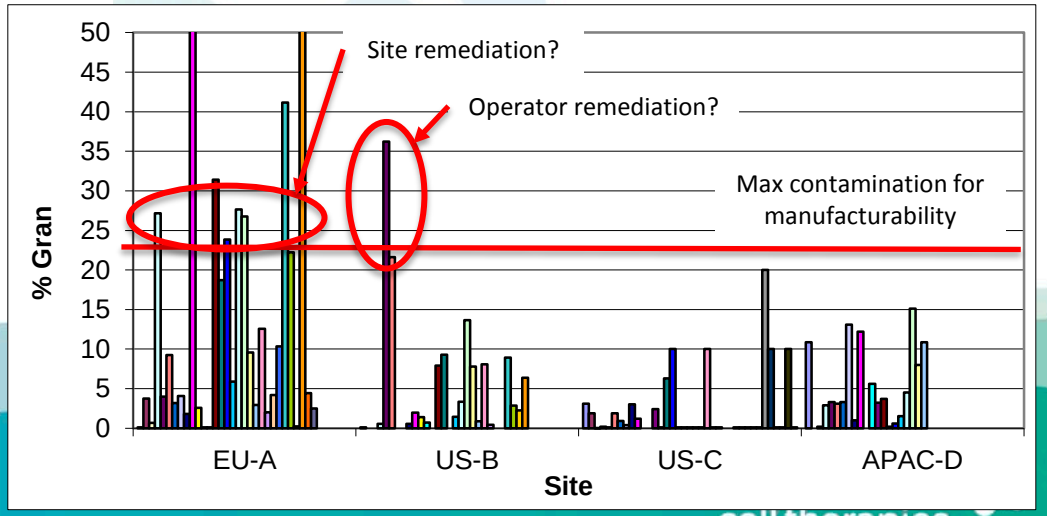
cell therapies

Specialist Apheresis process management toolkit

Collection algorithms



Site monitoring and benchmarking



cell therapies

Regional manufacturing and delivery network

Future - Malaysia
"Autologous Production for the Future" facility
- Commercial facility
- Multi-client user
- <10h flight from Dubai, Seoul, Melbourne

PharmaBio - Nagoya
Strategic Alliance

Research and translation - Adelaide
Nextcell at CRC for Cell Therapy Manufacturing

Home base - Melbourne
Peter Mac

Apheresis and tissue collection site management

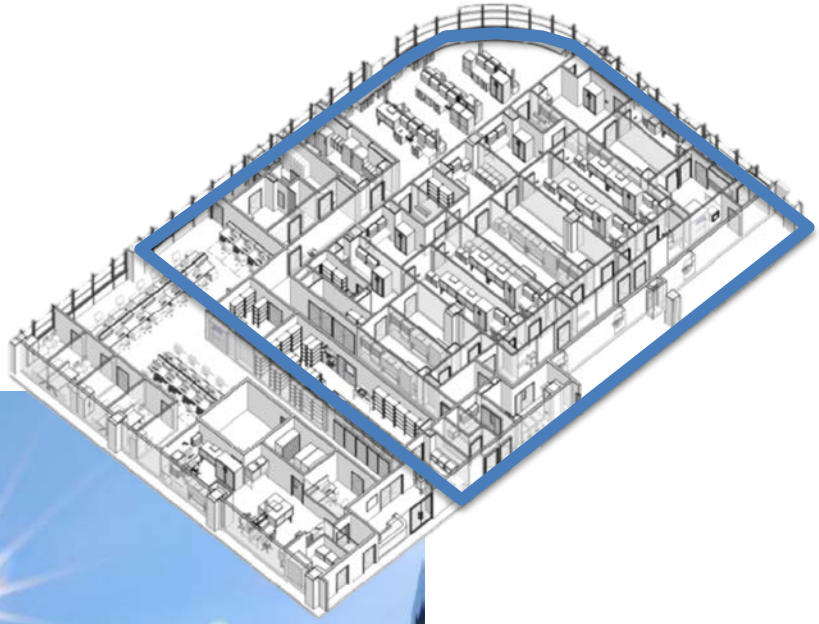
cell therapies

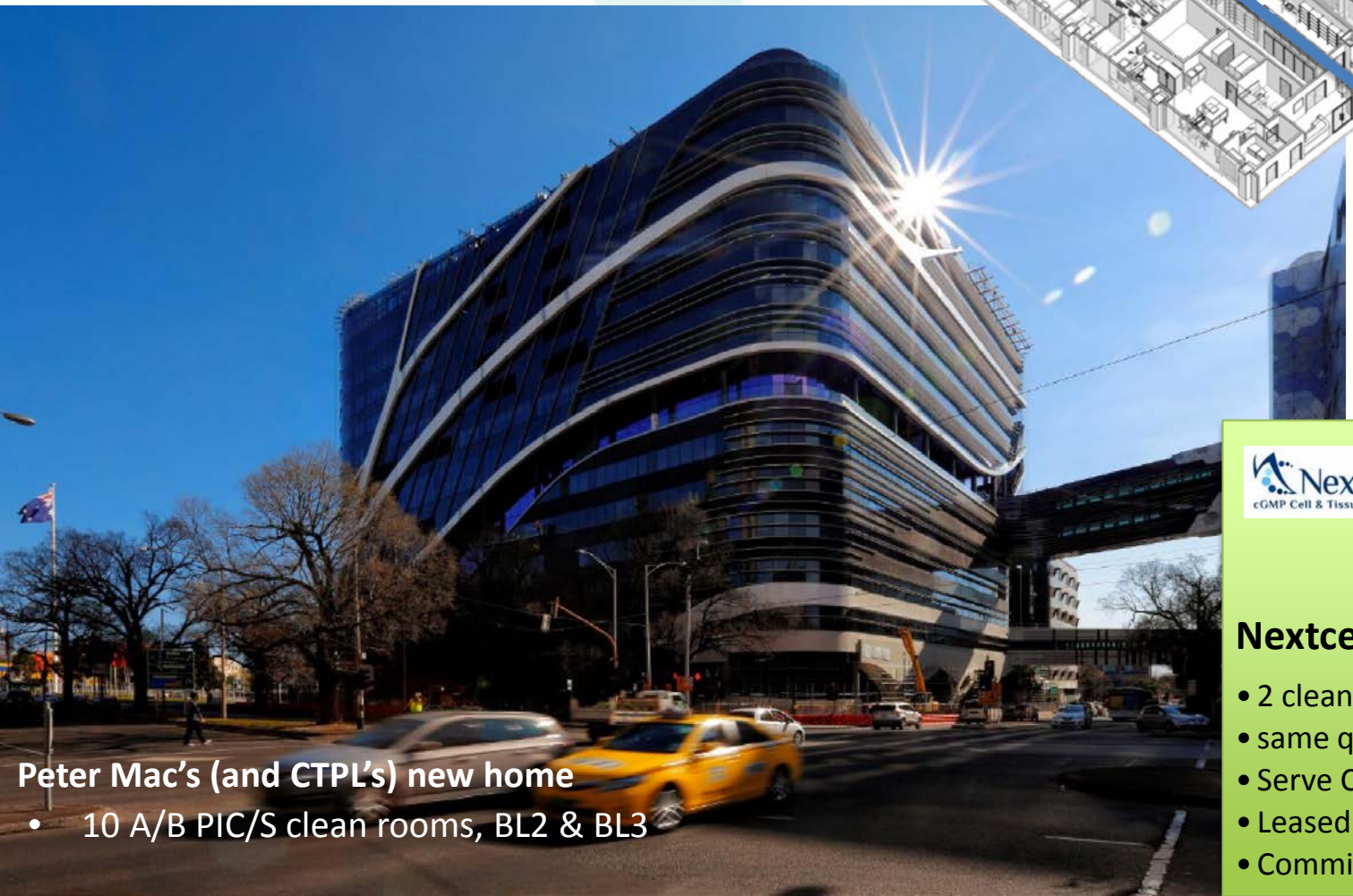
Conclusion

1. CAR-T are here, and the haematology treatment paradigm will change greatly…
2. CAR-T as therapy vs bridge to transplant
3. Biology is still unclear
4. Solid tumour targets unproven
5. Manufacturing is catching up, but patient diversity is challenging
6. How much will it cost?

New facilities Feb 2016

VICTORIAN COMPREHENSIVE CANCER CENTRE





Peter Mac's (and CTPL's) new home

- 10 A/B PIC/S clean rooms, BL2 & BL3

NextCell cGMP Cell & Tissue Therapies

Cell Therapy Manufacturing Cooperative Research Centre

Nextcell - Adelaide, SA

- 2 clean rooms
- same quality system
- Serve CTM@CRC
- Leased from UniSA
- Commissioned 2015

Further
enquiries…

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