

Commercializing Cell Based Therapies within or alongside an Academic Institution

Ray Wood
Managing Director
Cell Therapies Pty Ltd
www.celltherapies.com.au

Cell Therapies P/L is an independent CMO specialising in translational medicine where cGMP skills are required.

We would appear to have achieved a novel position in that we are a successful commercial venture running inside/alongside an academic institution

Peter MacCallum Cancer Centre and the formation of Cell Therapies Pty Ltd



Peter Mac



- Australia's foremost specialist cancer centre
- Integrated cancer research programs and laboratories.
- Multidisciplinary holistic care – experts from all fields work together, providing the best care at all stages of illness
- Manages 40% of cancer patients in Victoria, 160+ Beds; 9000 new patients each year
- 400+ researchers with an emphasis on translational medicine
- Oncologists and haematologists sub-specialise in both common and rare types of cancer.
- Specialised equipment and technology enabling highly complex treatments to be administered safely.
- Last year we offered 200,000 outpatient and 20,000 inpatient treatments.
- Large Clinical trials program >175 concurrent trials in 2010

We have been “in business” for 12 yrs
(1999)

&

Financially independent for 8+

Delivering autologous cell therapies for a
mix of early Phase trials and one
standard of care regenerative medicine

We are a multidisciplinary resource with a track record of translating research protocols into successful clinical trials.

Our clients are organisations that need to manage their risk profile and have embraced an outsourcing policy.

Cell Therapies P/L is:

- A commercial therapeutics manufacturer
- Majority owned by Peter Mac
- **3 x TGA Manufacturing licences**
 - 149827 Stem Cells -2001
 - 162398 Orthogen Australia- chondrocytes- 2003
 - MI-2009-LI-05411-3 Mesoblast- Mesenchymal Precursor Cells-- July 2010
- Trial CMO and other commercial & academic activity
- Consulting, trial and product approvals
- Product and process development
- A J.V. in Japan & affiliates in Malaysia, Indonesia

ute – Centre for Blood Cell Therapies

on and Release of Peripheral Blood SC) – Learning Module

Patient-Identificati
Generated-by:Peter..... 1
admission-or-reqe:
versions)¶ 2
Placed-onto:¶
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• -> Packs-(large
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• -> BacT/Alert:(l

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STEP 8

001)¶
• -> Product-Packs¶
• -> Sample-Tubes¶
• -> BacT/Alert¶

TGA THERAPEUTIC GOODS ADMINISTRATION

Licence to Manufacture
Therapeutic Goods

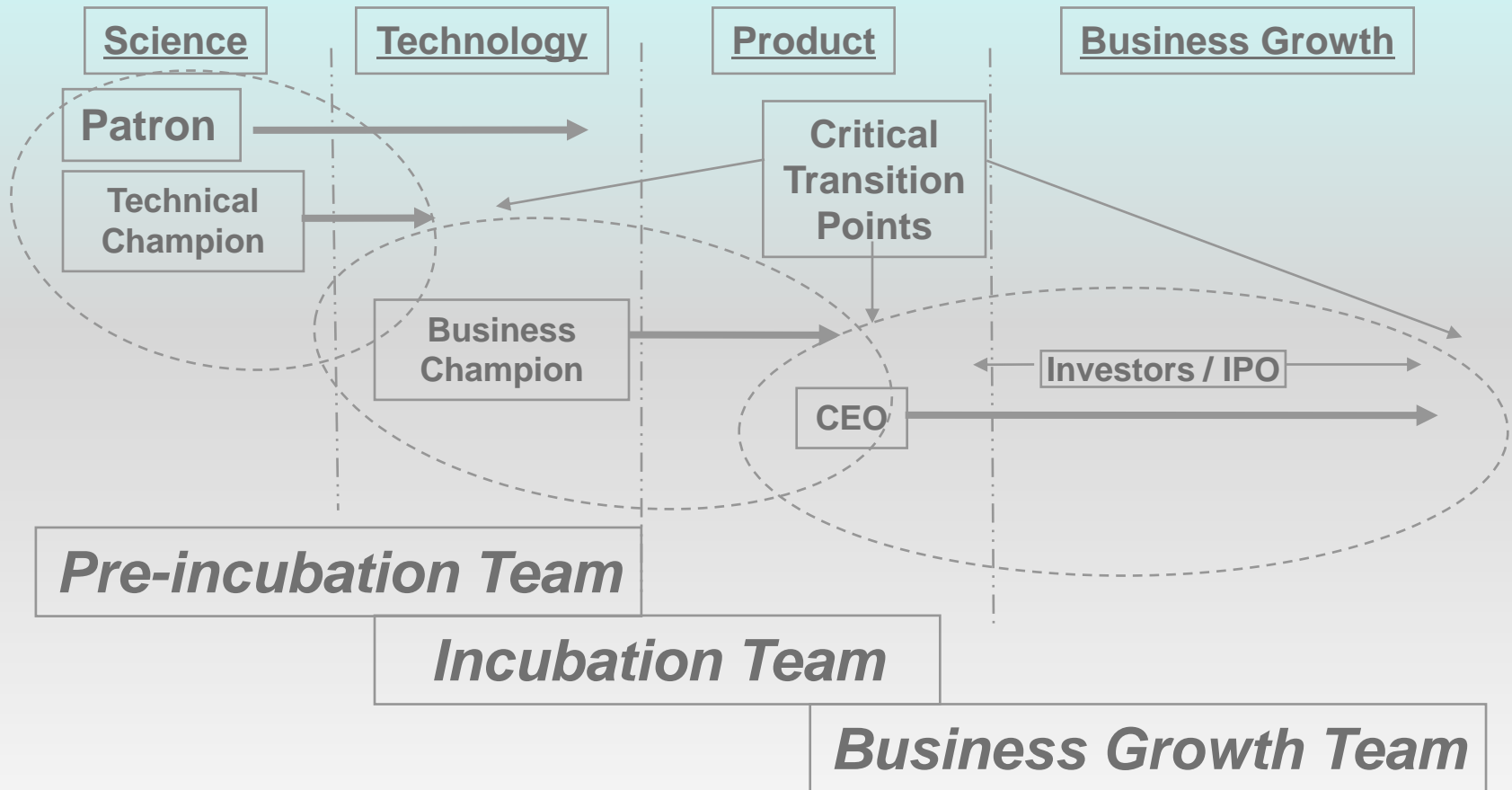
LICENCE NO: 149827

Manufacturer:
CENTRE FOR BLOOD CELL THERAPIES

Manufacturing site for which the licence applies:
PETER MACCALLUM CANCER INST.
ST ANDREW'S PLACE
EAST MELBOURNE VIC 3002

Health and Ageing

Spin-off / Startup Stages



Why set up a commercial venture?

and

What can an academic centre offer

vs..

a commercial CMO?

Why Cellular Therapeutics ?

- Hot topic with strong market interest
- Scarce global resources for cGMP cell manipulation and delivery of treatments
- Experience with TGA/FDA/EMA
- Fully Integrated Clinical trial capability including SOP and processing protocol development available.

- Translational capabilities
- +
• Multidisciplinary Resources
- +
• GMP compliance
- =
• A path to market?

- But.....

- Path for Who and Why?
- Who is the client/recipient/customer ?
- What is the targeted outcome ?
 - Revenue
 - Profit
 - Publications
 - Credibility
 - Delivery of novel std. of care therapies
 - Survival

Basis for a commercial operation:

- Initially a service based business
- Incremental growth & positive cash flow
- Scalable opportunity with controlled risk
- Vehicle for sponsor's research outcomes
- Early mover and Gate Keeping opportunity
- 'Blue sky' can be x% of the outcome

Cell Therapies Pty. Ltd

- Independent subsidiary responsible for and in control of all commercial aspects of cGMP cell and tissue processing at Peter MacCallum Cancer Centre
- Operates under a management contract that includes obligations to achieve and maintain financial independence and full cost recovery for all resources utilised

Obligations

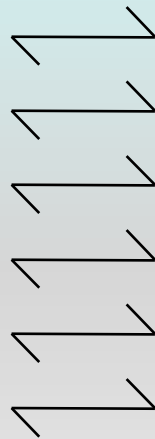
- Requirement to provide cGMP infrastructure to Peter Mac researchers alongside external clients.
- Fee paying requirement for all users
- Royalties and shareholder dividends

Our USP = One stop shop:

Established Arrangements

Integrated Services from Peter Mac's CBCT

Cell Lab (CBCT)
Cryo-Services
Apheresis
Nuc Med & Imaging
Research Nursing
Pathology



Pre-Agreed Service
Agreements

Contract cGMP
manufacturing via
Fees-for-Service
Consulting
and
Shared Risk/Reward
Investment Opportunities



Delivery of Treatments

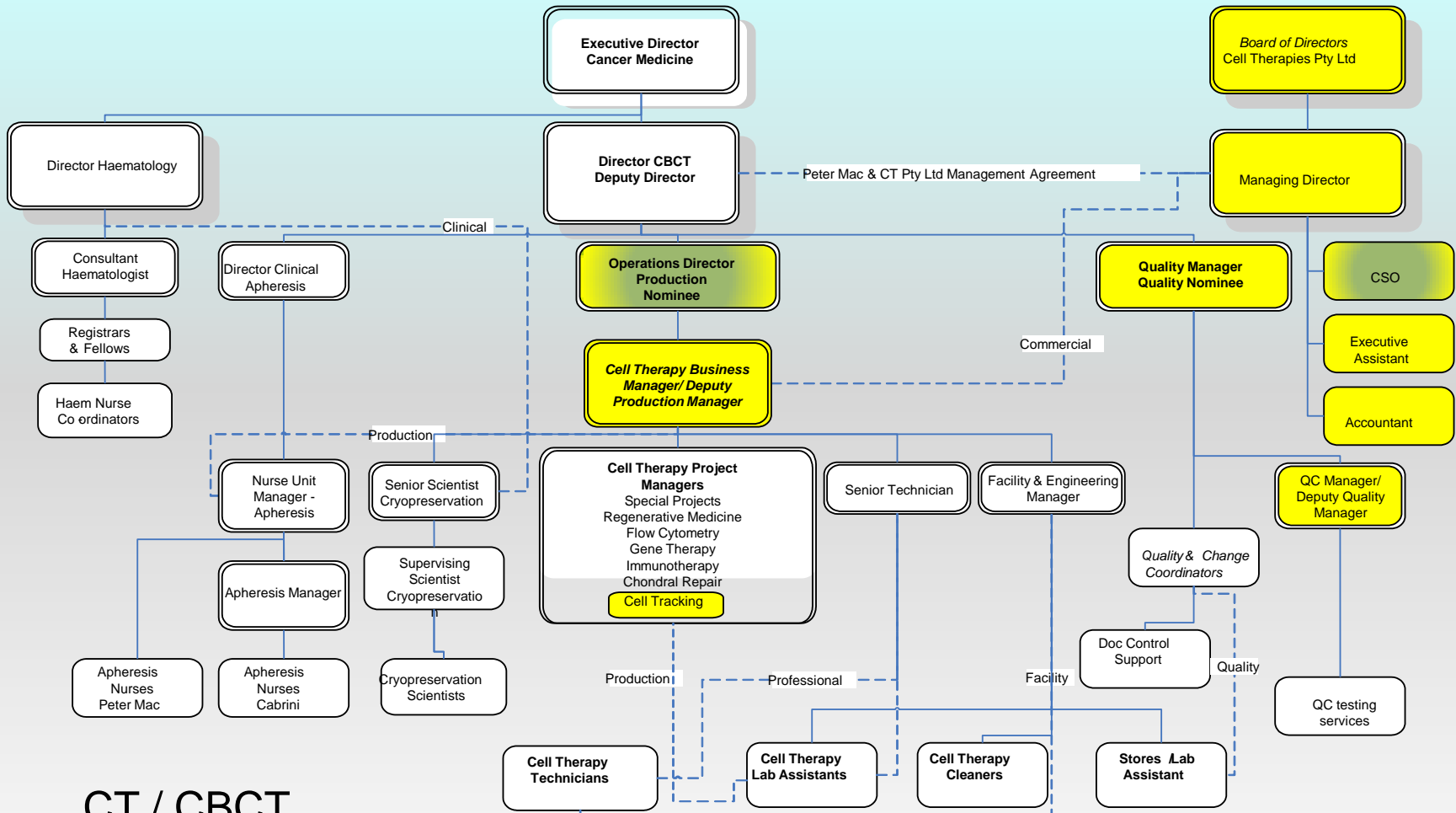
Clinical Trial Outcomes

Patients



Clients

Internal Organisation of CT & Centre for Blood Cell Therapies



CT / CBCT Organisational Chart

- Primary reporting relationship
- - - Secondary reporting relationship
- - - clinical
- - - Nature of reporting relationship
- Director or manager position
- Cell Therapies Staff

Outcomes

- Self sustaining
- Expanded capabilities & skills
- Undertaken broader range of cell processing. (DC's, MSC's, T-cells, Chondrocytes, auto logistics, allo banking, process validation)
- Better positioned to capture value

Activity and Capacity

- Five PC2/3 clean rooms staffed with a team of 15 scientists and technicians plus peripheral support and senior management for oversight of clinical, scientific and commercial activities.
- 5 to 8 projects running at any one time.
- Evolving Mix of Phase I, II & III trials
- Work load originally dominated by SOP development and process improvement is shifting .
- Only one standard of care product with insurance reimbursable status after 8 years!

Lessons Learned:

Competing objectives
and
Pragmatic decisions

Structure(s) required to resolve internal
vs. external requirements

Lessons Learned cont'd:

- Researchers
- SOP's
- Release criteria
- The “regulator”
&
- Project Management !

A key question for the stakeholders:

Service provider or a researcher?

Key characteristics required:

- Independence
- Speed in decision making
- Contract engagement
- Commitment to completion
- Predictability

Manage relationships with:

- The regulator(s)
- Principal Investigators
- Ethics committee(s)
- The Sponsor

Staffing:

Skill, expertise and experience

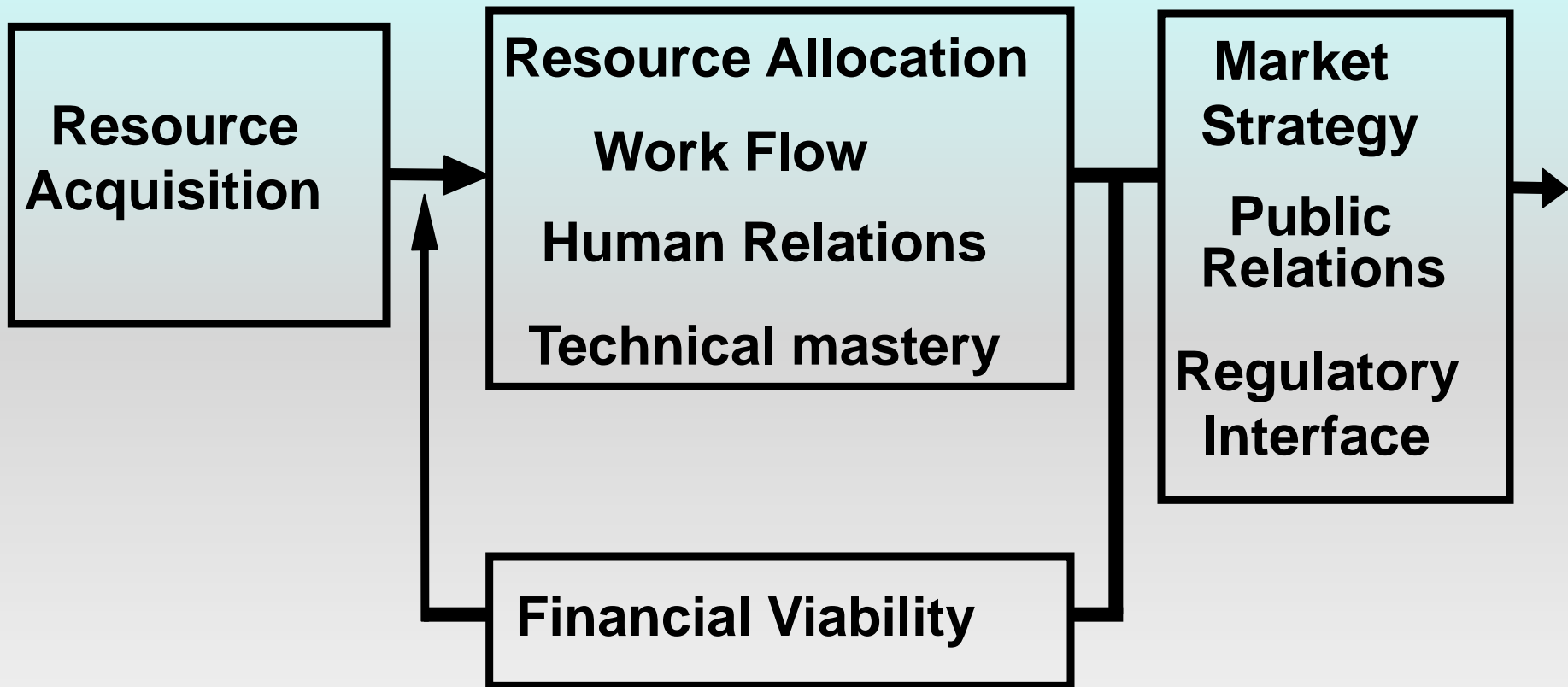
How much is desirable?

vs.

What is mandatory?

Staff profiles

What is Important to Manage?



Source: DSP Dr Bruce Johnston 1998

What's next?

- Automation
- A requirement to validate needle to needle
- COGS
- Staff profiles to match evolving market requirements
- Slow but demonstrable Regulatory harmonisation
- Availability and pricing of Consumables
- An expectation of an accelerated approval process

Feedback to Early-phase trials

Research:

- Pure
- Applied
- Cross disciplinary

Scientific + Commercial Questions:

Safety:

- Foreseeable adverse events
- Unexpected adverse events

Feasibility:

- Cost
- Timing
- Practicalities of production
- Practicalities of product release
- Practicalities of administration
- Regulatory compliance

Preclinical data

Clinical data

Market:

- Clinical demand
- Payment
- New discoveries

Changing Roles

Trial coordinating centre

site, facility or clinical research organisation
appointed by sponsor
responsible for **data management, database management, liaison with participating institutions participating, randomisation services, statistical analysis.**

Trial Manager

supervises overall conduct and data management of the Trial at the TCC.
Liaison between the Trial Chairperson, the Trial Management Committee, the Institution(s), HRECs (when required).

Sponsor

An individual, company, institution or organisation which takes responsibility for the **initiation, management, and/or financing of a clinical trial.**

Principal Investigator

Responsible for **conduct** of trial

Study Coordinator

- Data manager
- Or
- Research Nurse:

Production Manager

Responsible for setting up, overseeing and **managing production** of therapeutic product according to GxP and regulatory requirements

Quality Manager

Responsible for ensuring and reporting on **Quality issues** around therapeutic product

Trial Monitor

Responsible for **monitoring and reporting** on **conduct** of trial

Responsible for the **day to day activities** of a clinical trial at a Trial Site including:
recruitment and **screening** of patients
upkeep of **source data** documentation
completion of **Case Report Forms**
maintenance of **regulatory documents**

Other risks...

Biomaterials?

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.

Animal derived materials... Enzymes? Serum?



毛利君
Mao Li Jun

董事经理
Managing Director

... bare-handed workers at Yuan Intestine & Casing Factory, untangle and flush pig intestines that will be used to make heparin...

"The supplier to Baxter ... was Changzhou SPL plant in Changzhou City, China.

STREET JOURNAL

2008

Newspaper My Online Journal Multimedia & Online Extra

Blocked Advertisement

Legislators Review Inspection Policy Amid Heparin Fallout

BY JON KAMP

Word Count: 663 | Companies Featured in This Article: Baxter International

In the wake of hundreds of reactions in patients who took Baxter International Inc.'s blood thinner heparin, two U.S. lawmakers said they are considering changes in law to guard against the marketing of drugs made at plants that haven't been inspected by regulators.

It isn't yet known what factors are behind 350 bad reactions and four fatalities among U.S. patients who took Baxter-made heparin, as tallied by the Food and Drug Administration last week, when Baxter temporarily halted heparin production. Questions have been raised, though, about how the FDA failed to inspect a Chinese plant that supplies much of the ...

Why are we in this space ?

- Results but.....Inclusion, exclusion- how applicable to patients?



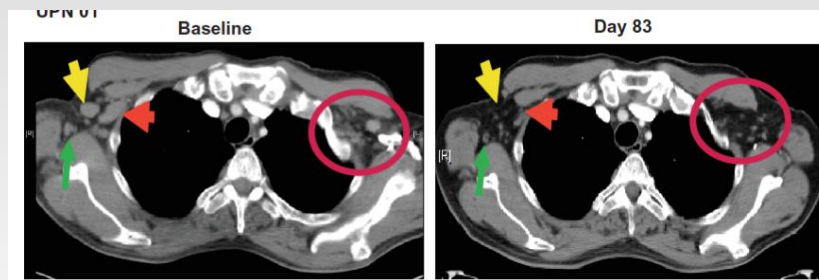
No. of patients	Treatment	Objective responses
270	IL-2	16% (6% CR)
85	LAK cells + IL-2	24% (7% CR)
86	TIL + IL-2	34% (6% CR)
35	TIL + NMA + IL-2	51% (9% CR)
25	TIL + MA + IL-2	72%

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

Because3 years later

- Compelling benefit vs risk
- Leading to ...?

However: Single patient report



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