CellCAN
Regenerative Medicine and Cell Therapy Network

New developments in Cancer Immunotherapy

Lymphoma Canada, Montreal
September 16, 2017

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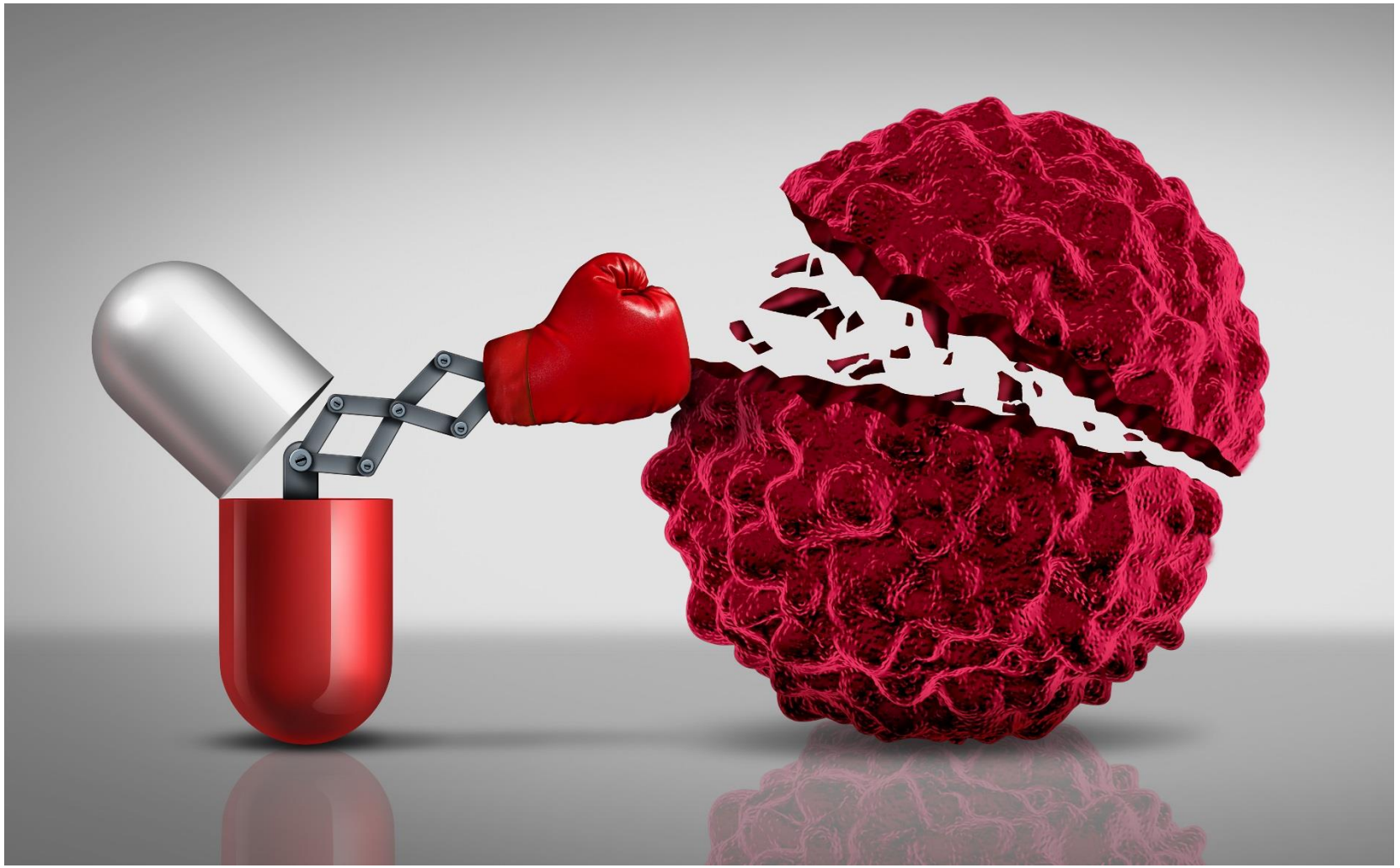
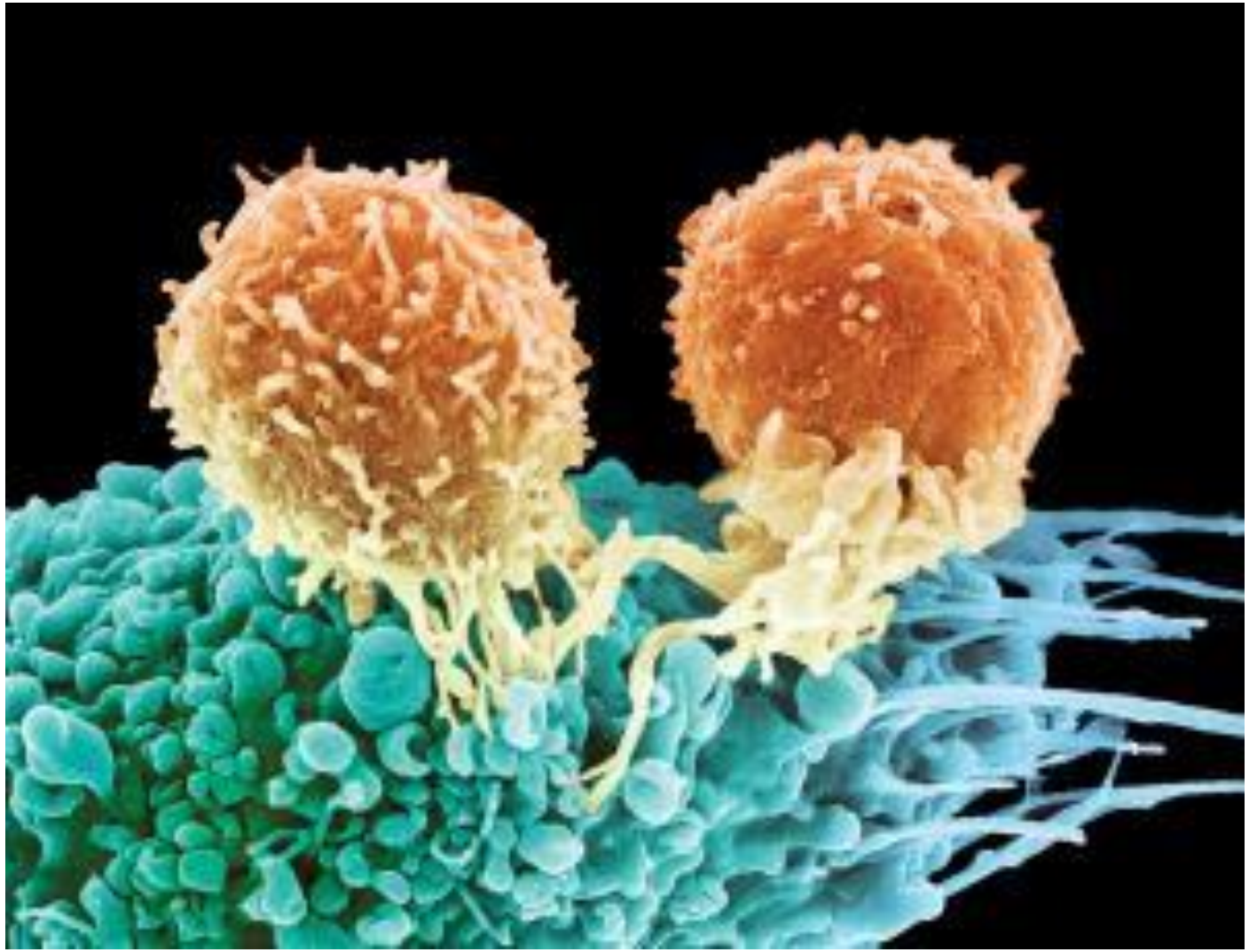
Prof. Medicine, Université de Montréal

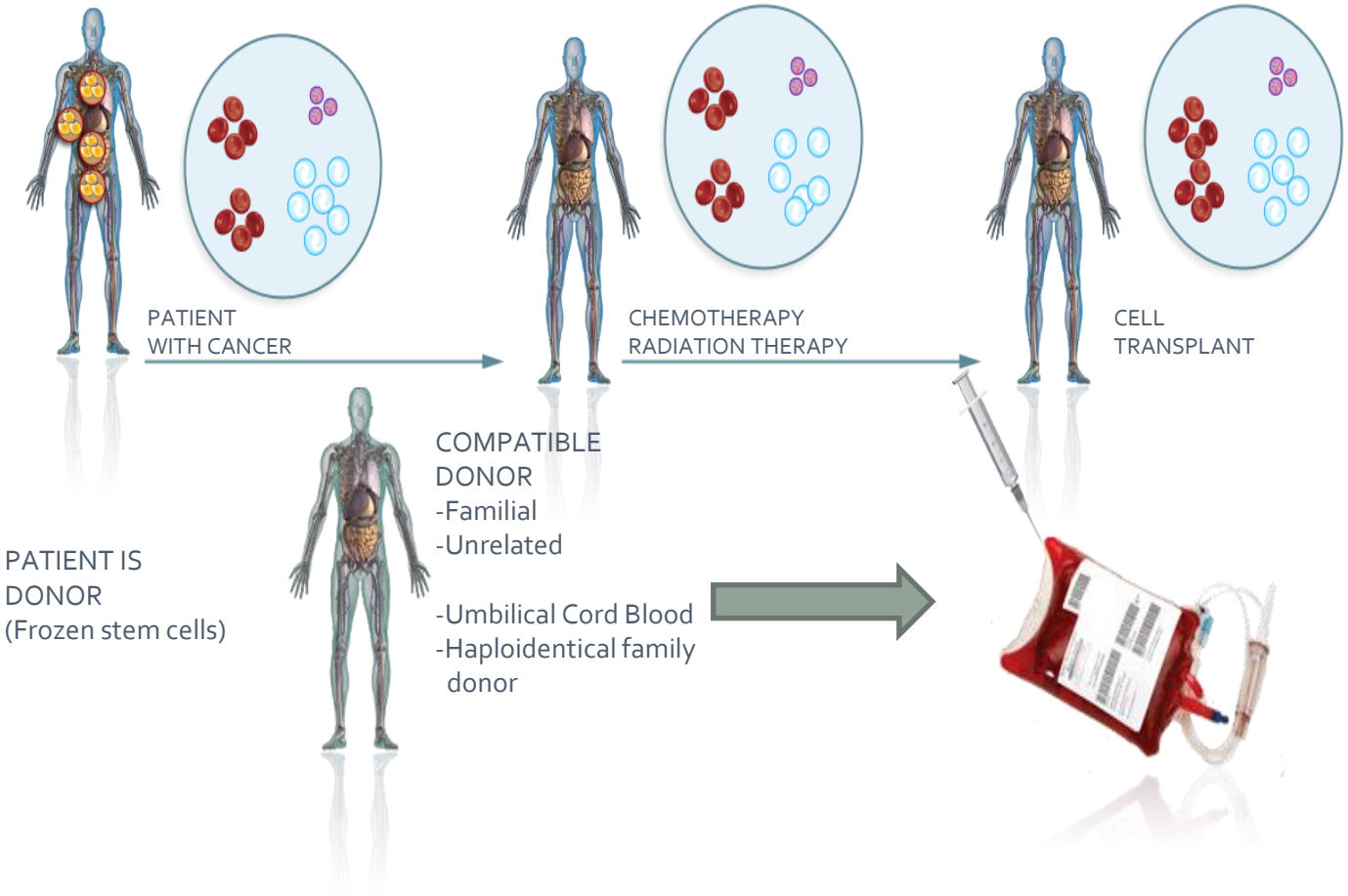
Drug therapy for cancer



CELL therapy for cancer



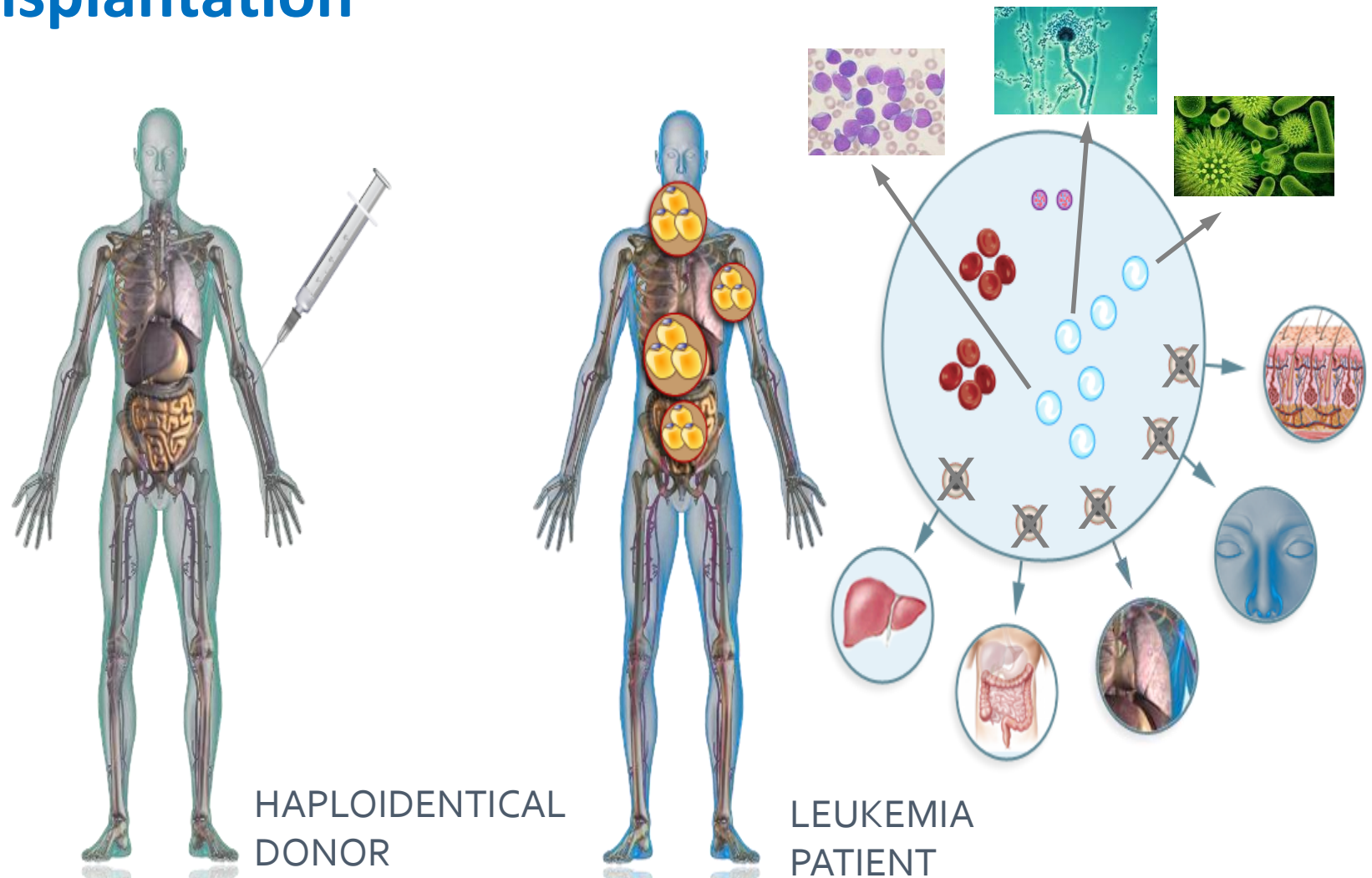
STEM CELL TRANSPLANTATION



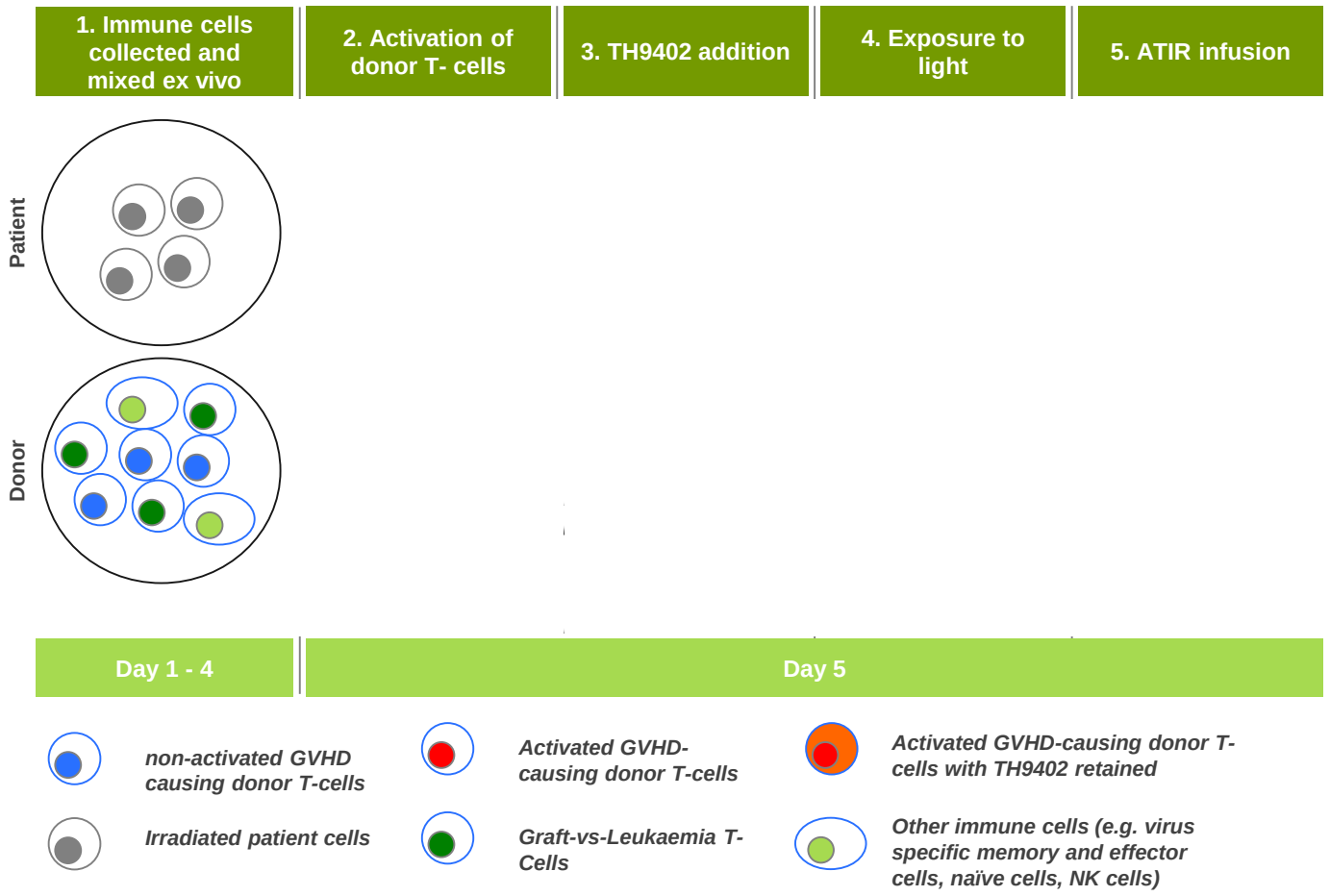
Allogeneic Hematopoietic Cell Transplantation (AHCT)

- One of the most important medical breakthrough of the last 50 years
- Can cure ~50% of refractory HCs
- By far the most effective form of cancer immunotherapy
- Cure by AHCT (the GVTE effect) is mediated by donor T cells that react against minor histocompatibility antigens (MiHAs) present on cancer cells – GVTE strength is sub-optimal

Challenge in Haploidentical Donor Transplantation



ATIR: Selective removal of GVHD-causing T-cells while retaining key innate and adaptive components of immune system



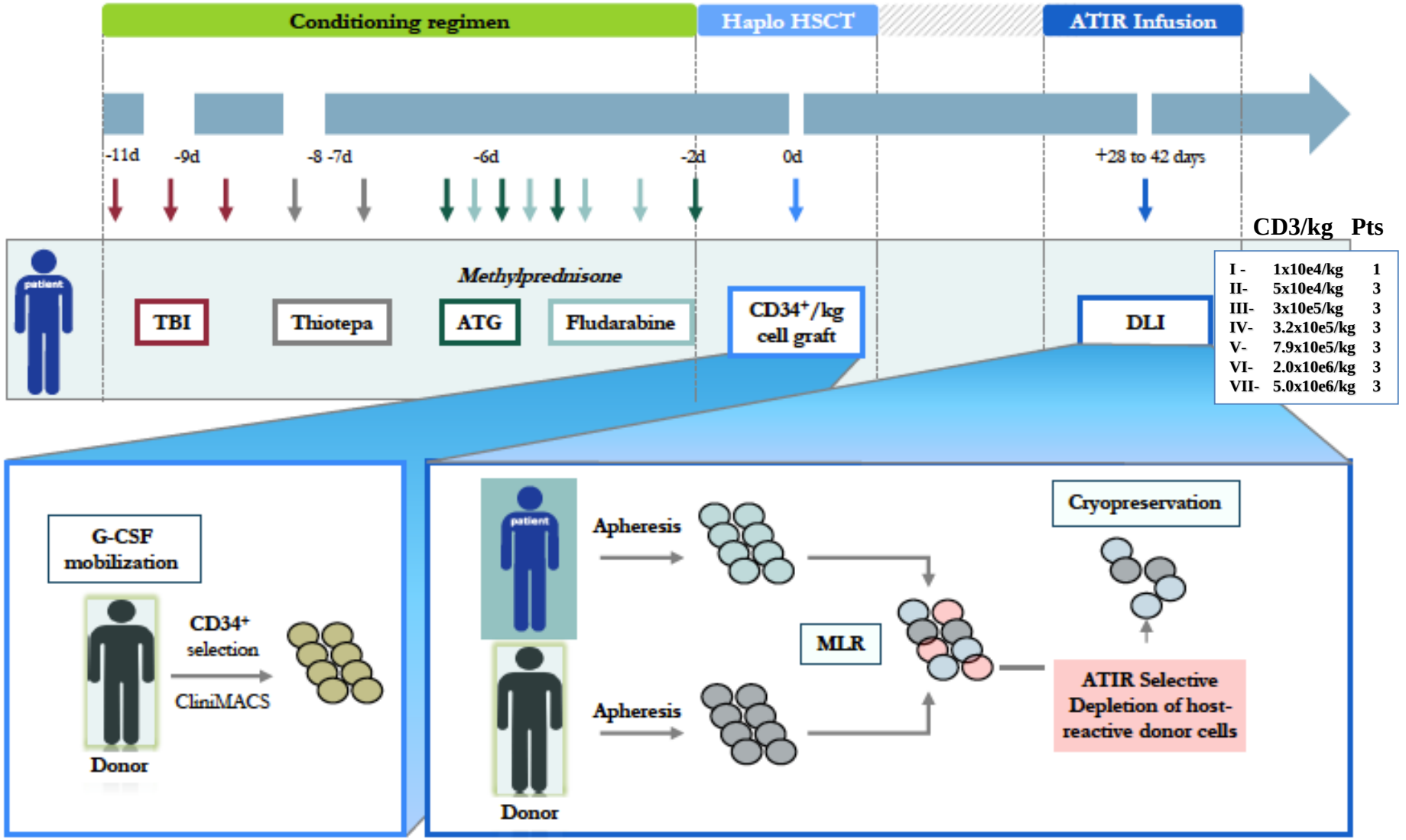
ATIR characteristics

- Selective removal of GVHD-causing T-cells
- Key immune cells are retained to protect against infections
- T-cells directed against leukaemic cells are retained

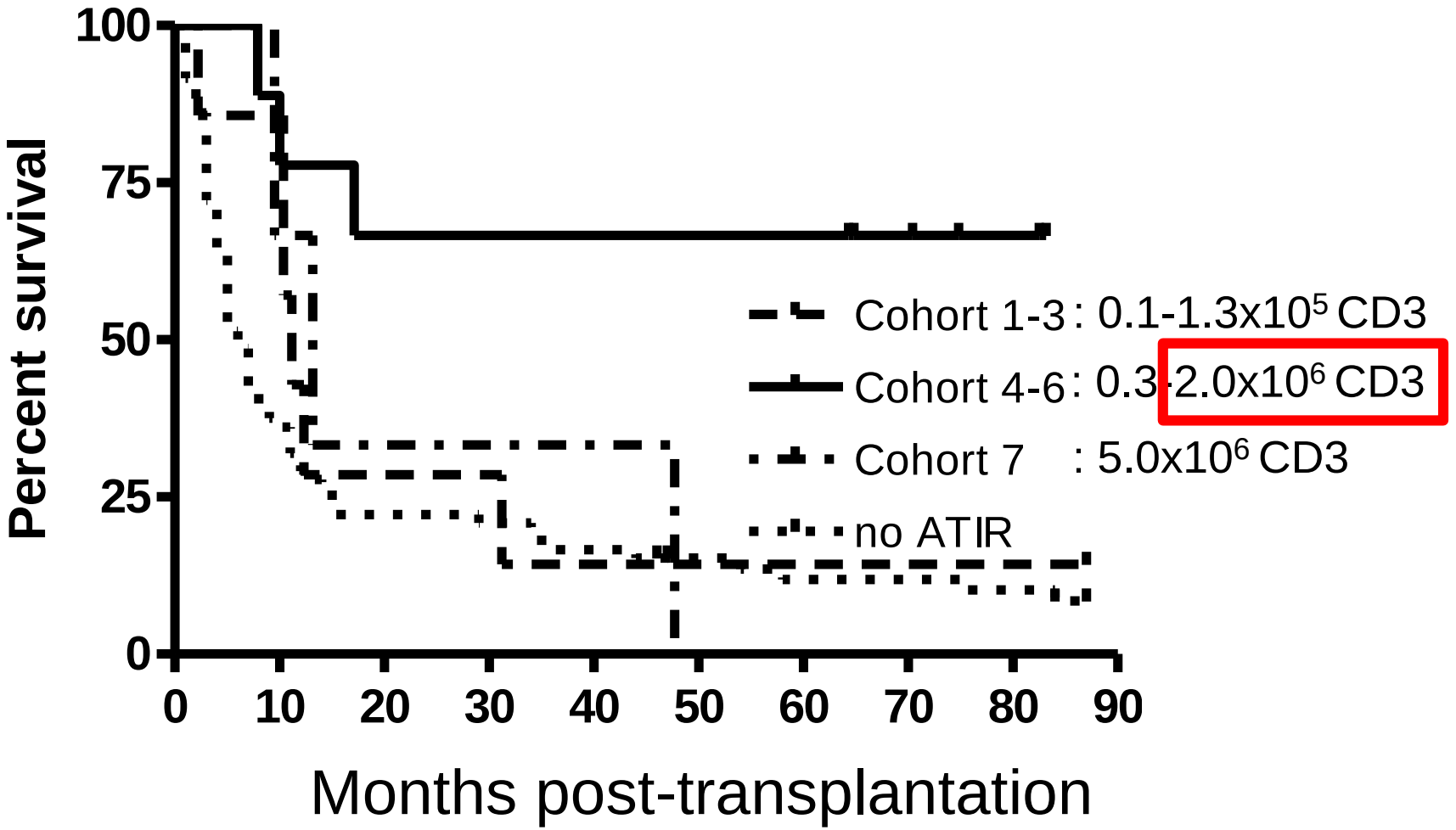
Potential clinical benefits

- Improved donor availability
- Minimal risk of life threatening GVHD
- No prophylactic immune suppression needed
- Less cancer relapse
- Reduced TRM; improved OS

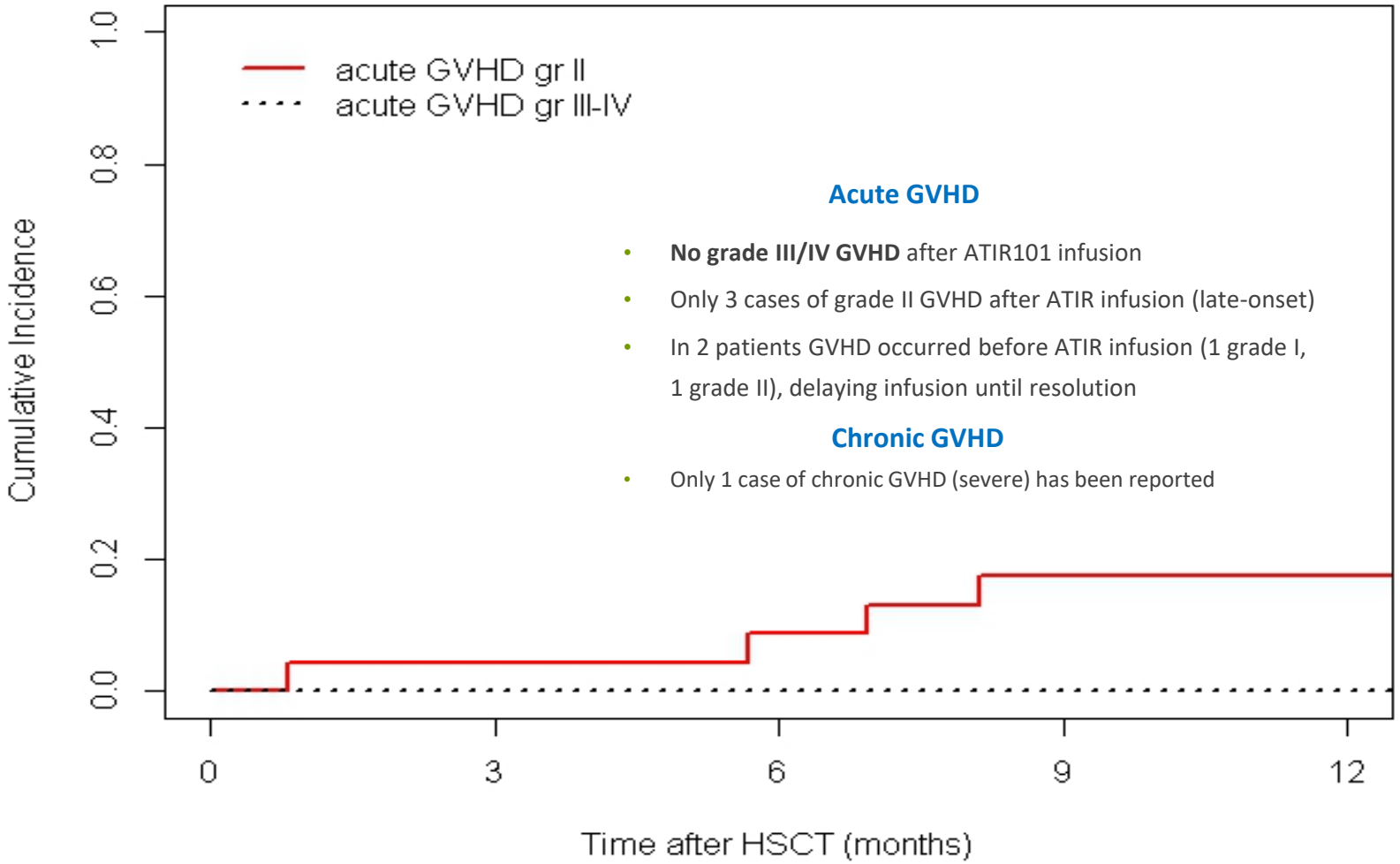
Haploidentical HSCT + ATIR: high-risk hematologic malignancies



Phase I clinical trial: Defining ATIR cell dose



Phase II international clinical trial: 23 patients



Acute GVHD

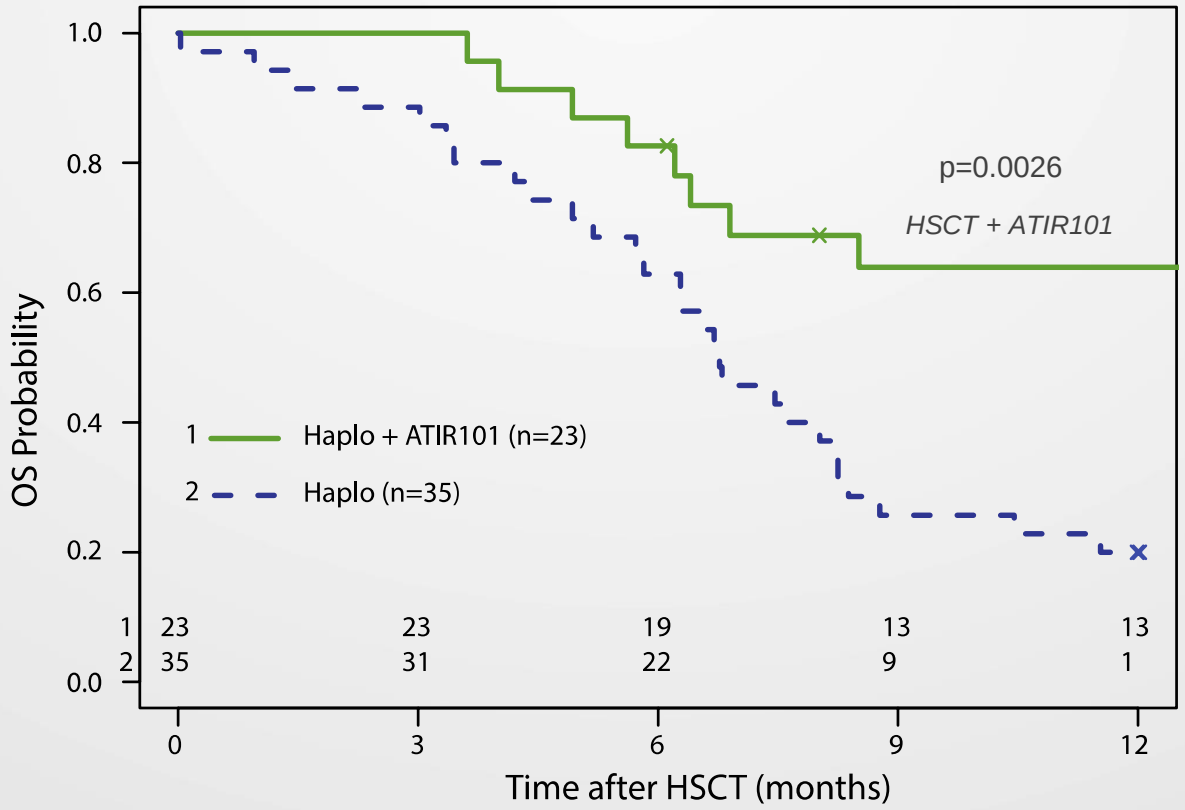
- **No grade III/IV GVHD** after ATIR101 infusion
- Only 3 cases of grade II GVHD after ATIR infusion (late-onset)
- In 2 patients GVHD occurred before ATIR infusion (1 grade I, 1 grade II), delaying infusion until resolution

Chronic GVHD

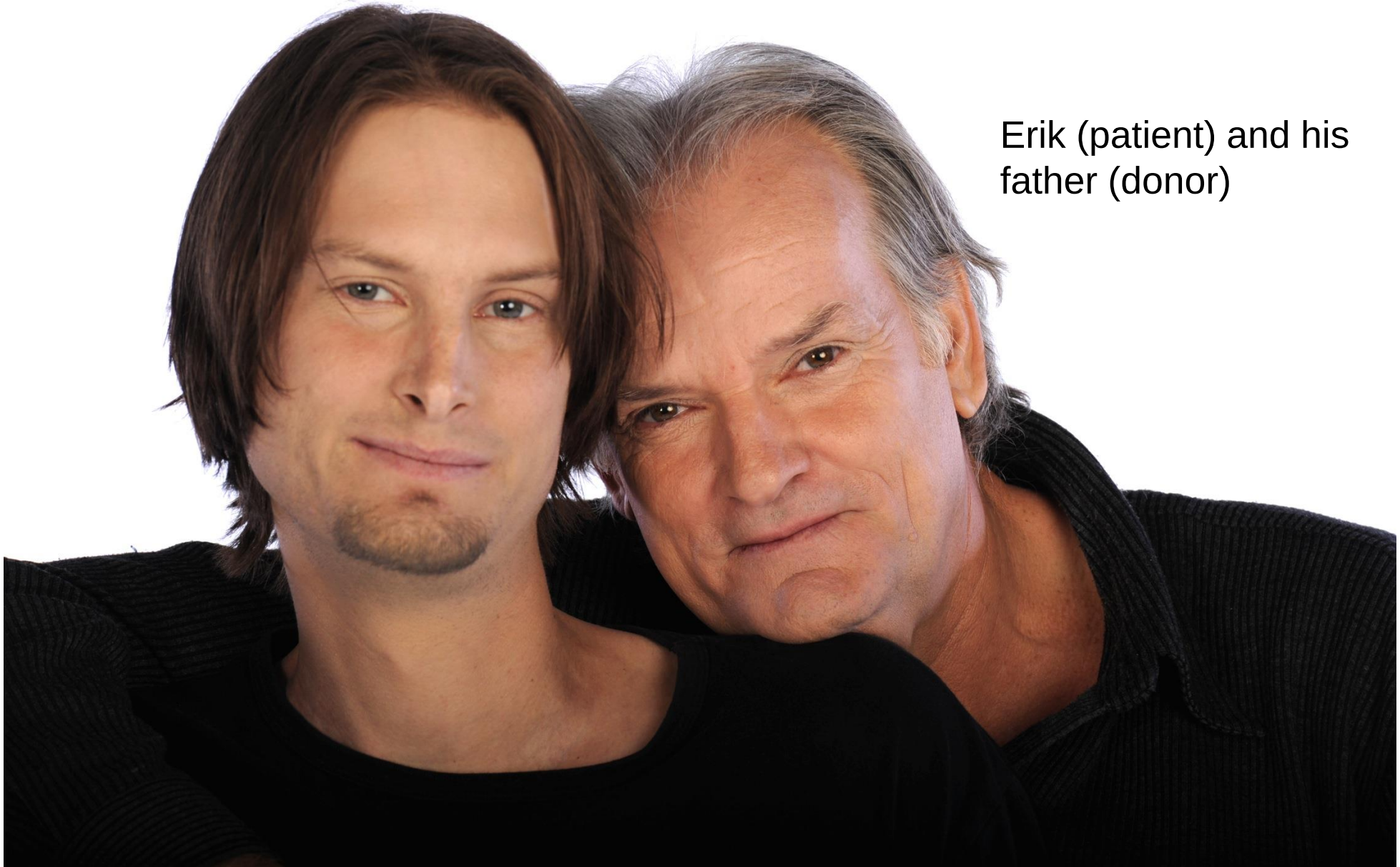
- Only 1 case of chronic GVHD (severe) has been reported

- Comparison with control data from an observational cohort study[1]

Overall survival



ATIR101 significantly reduces TRM and improves OS compared to CD34+ haplo-transplants



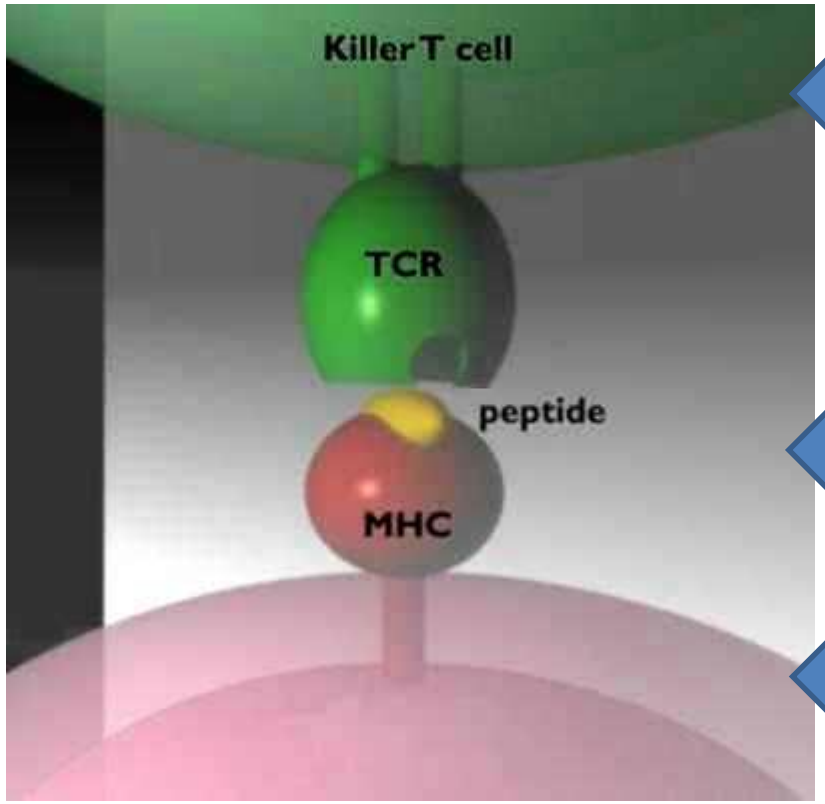
Erik (patient) and his father (donor)

From AHCT to MiHA-targeted Rx

- Despite its success, conventional AHCT is a rudimentary and toxic form of Tx based on injection of unselected T cells

- Selected→Can we select cells that will react toward cancer cells in a selective fashion?

Immune cells react against MiHA non-self peptides (protein fragments) on the surface of cancer cells

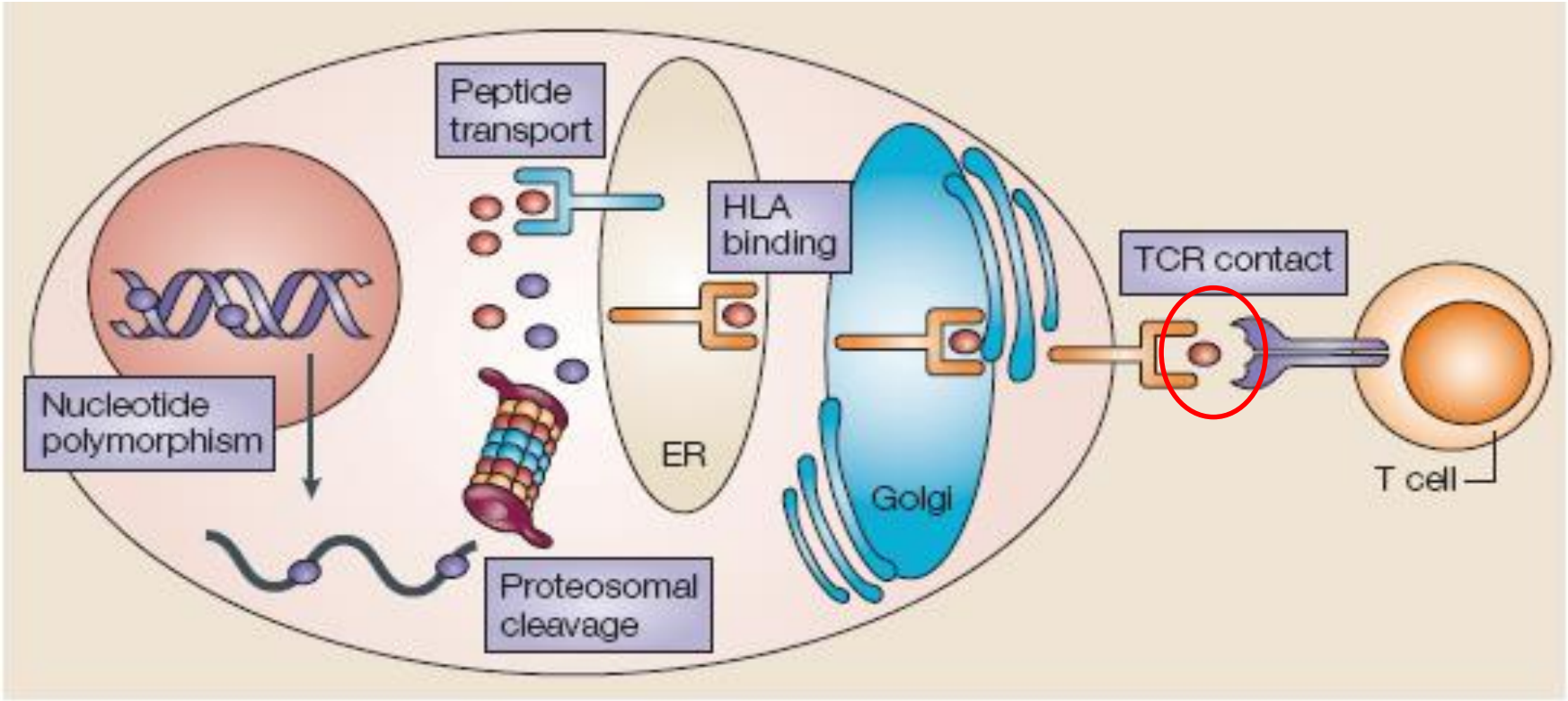


Donor cells of the immune system able to recognize non-self (leukemia)

Target: MiHA

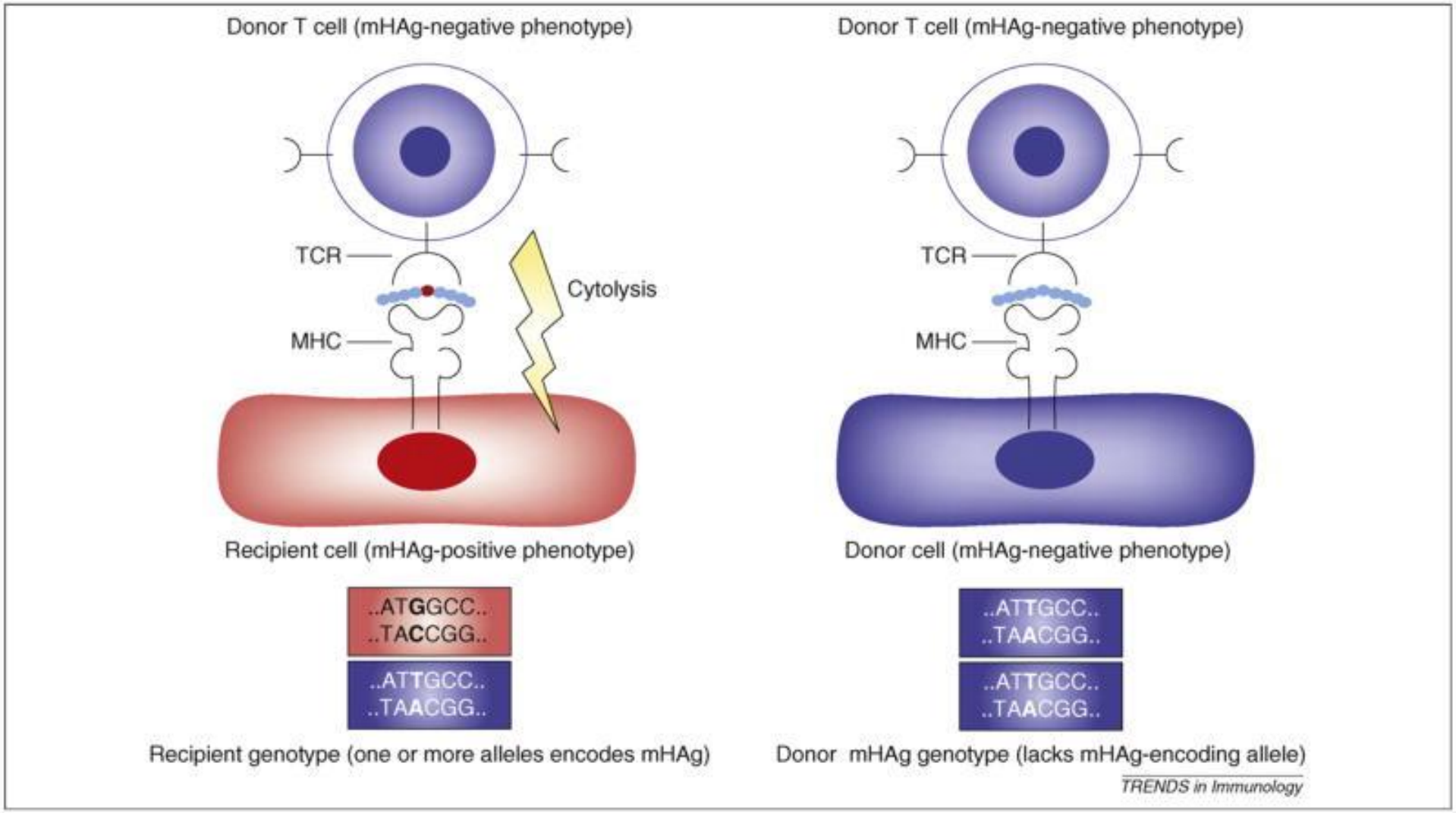
Patient cancer cells harboring peptide (MiHA)

What is a Minor Histocompatibility Antigen (MiHA) ?



Leukemia cell

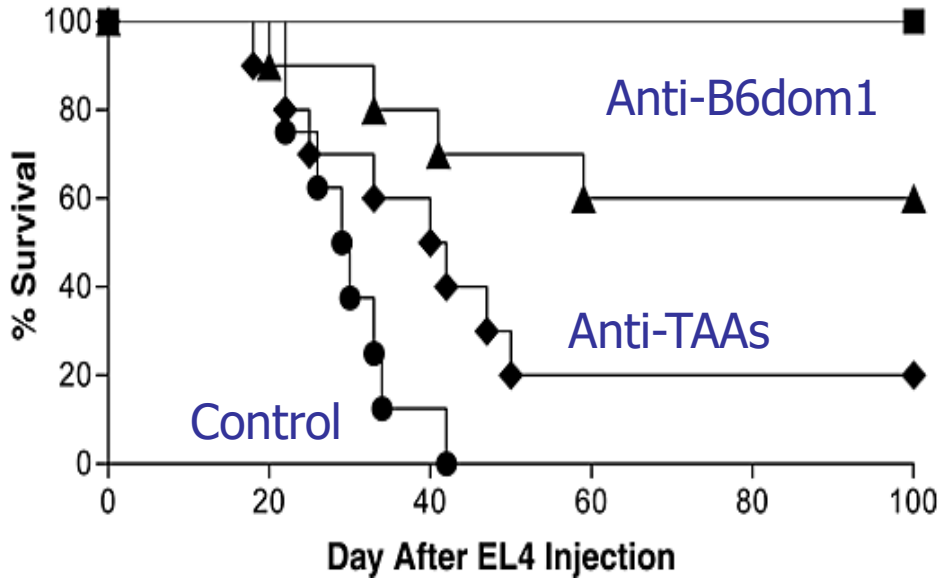
Graft-vs-Tumor Effect is mediated by donor immune cells that recognize MiHAs on leukemic cells

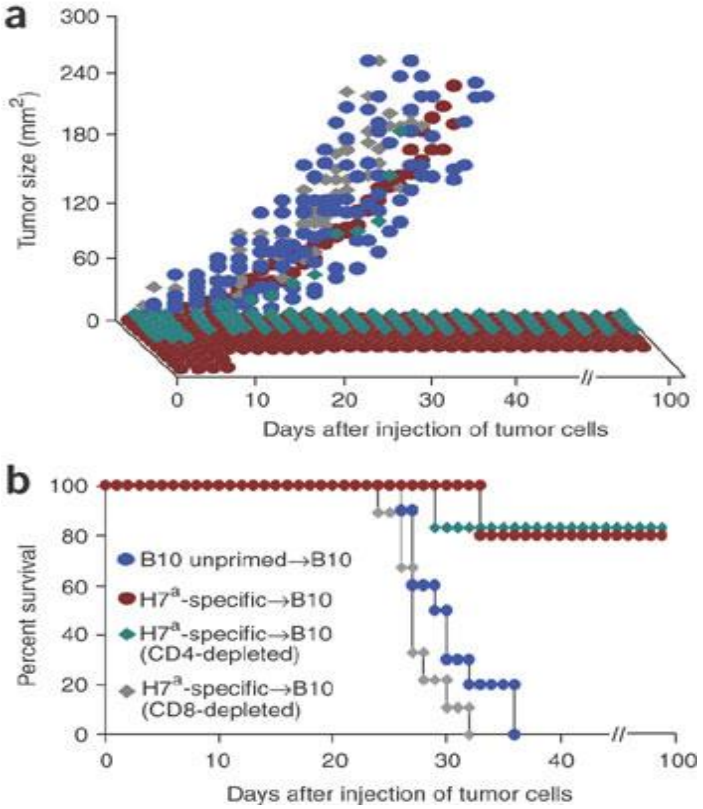


Cancer Immunotherapy with H7^a-specific T cells

- Leukemia (**Nat Med 2001; 7:789-794**)

Melanoma (Nat Med 2005;11:1222-1229)





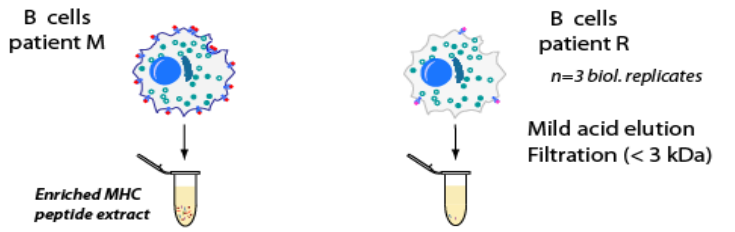
Using Proteogenomics For MiHA Discovery

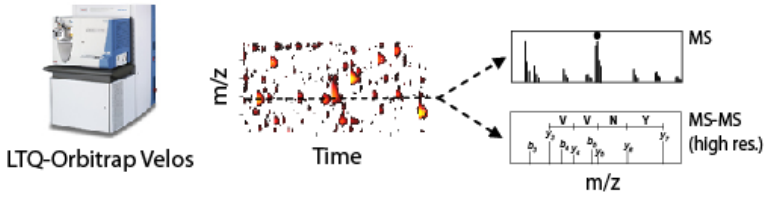
MHC I peptide isolation

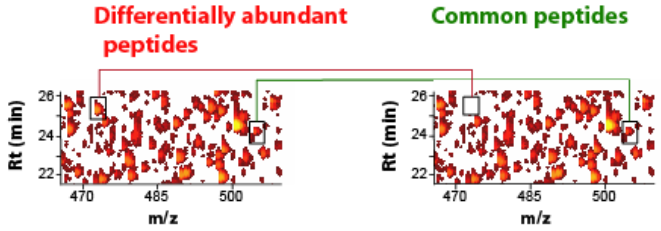
LC-MS/MS

Hierarchical clustering

IHA selection
nd profiling







Personalized translated transcriptome

Ion profiling

Protein identification
Mascot (know sequences)
Peaks (*de novo* sequencing)

ProteoProfile
Peptide maps and clustering of peptide ions across conditions and replicates

Candidate selection

- Novel MiHA
- Binding motifs
- Allelic frequency (SNPs)
- Immunogenicity

Expression of MiHA coding genes in leukemic cell

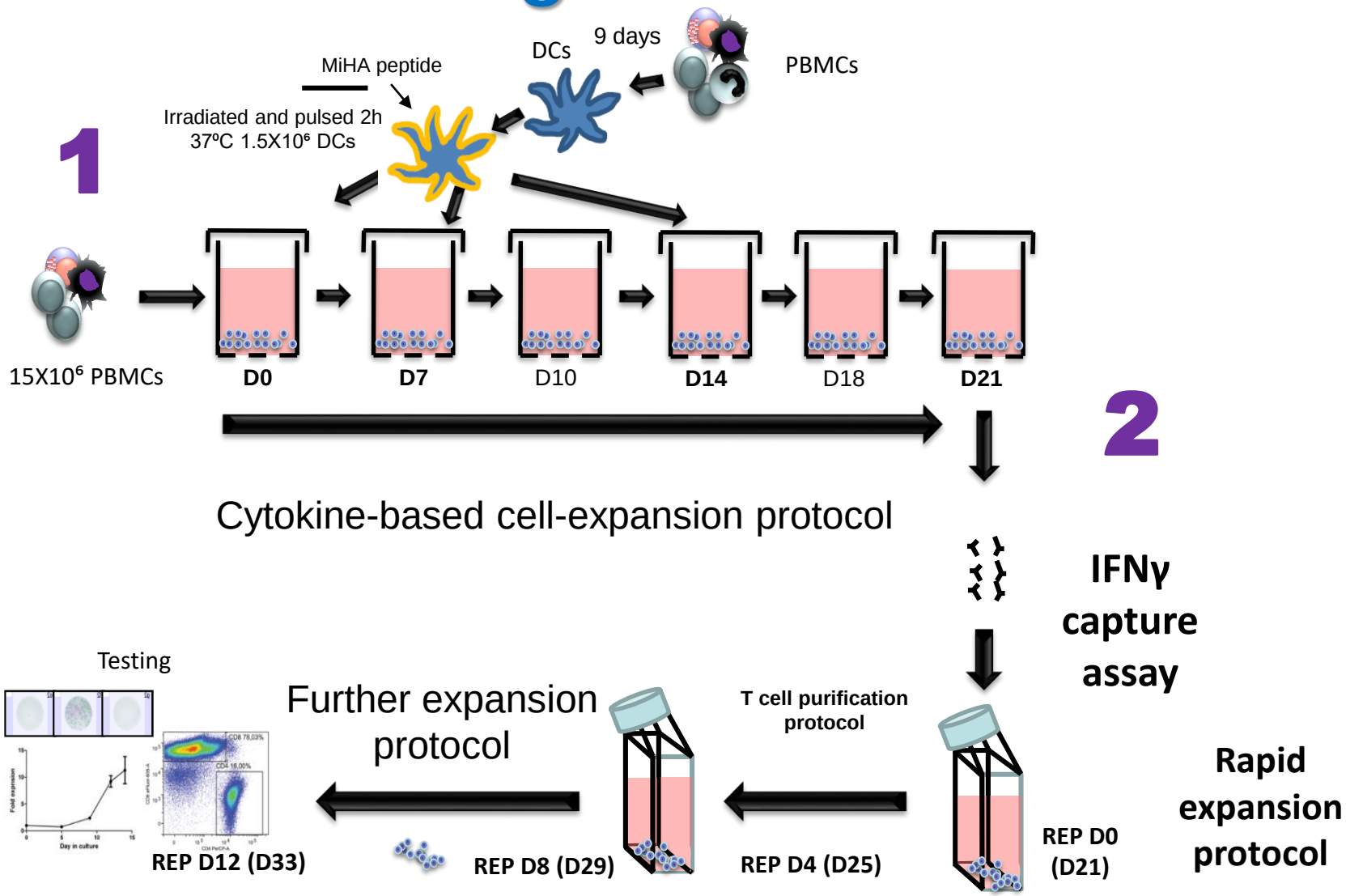
Number of peptides selected

~15,000 MiHA Candidates

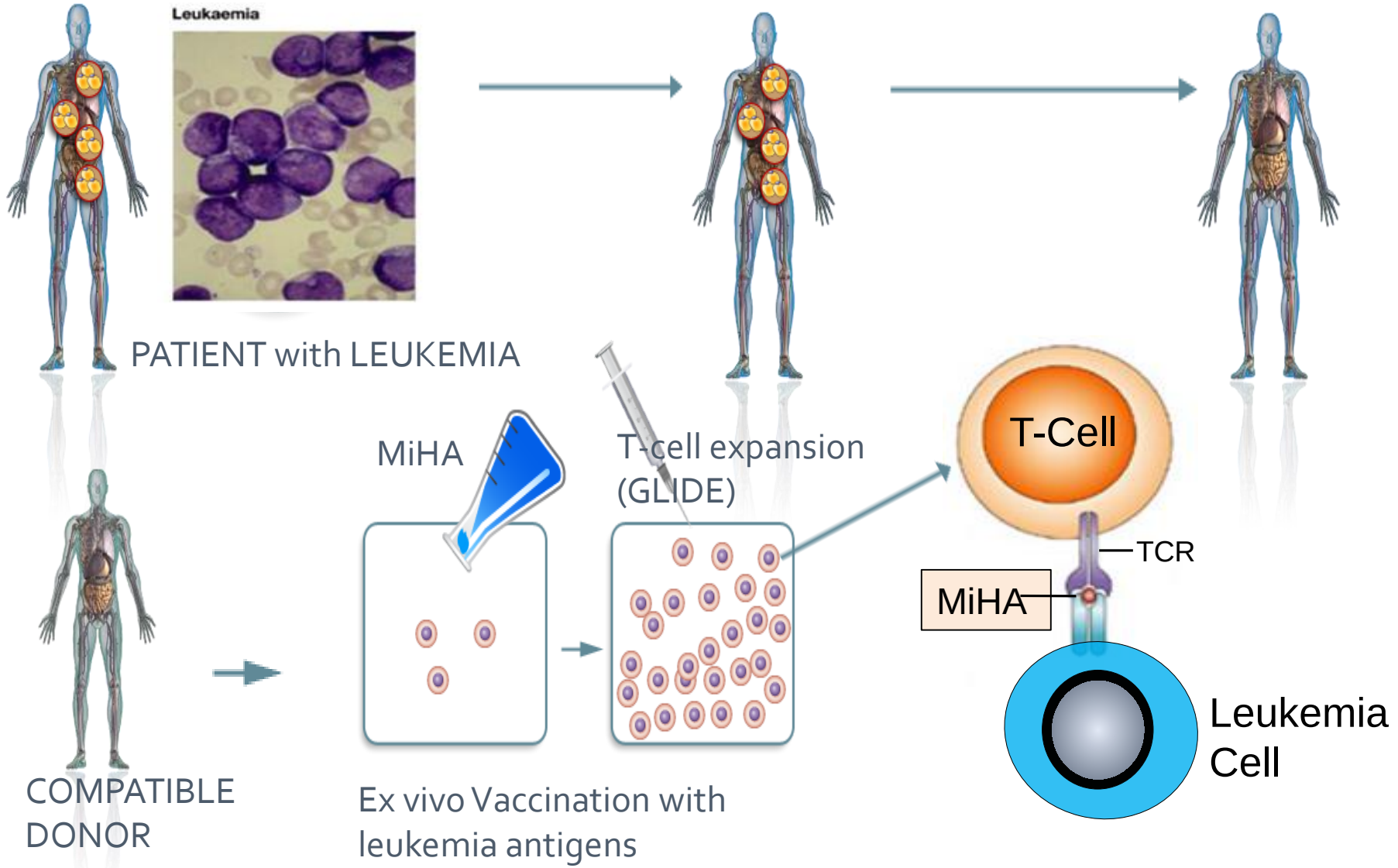
467 MiHA Candidates expressed at high frequency

98 neo-MiHAs appropriate for immunotherapy

Manufacturing Anti-Cancer Cells



MiHA anti-leukemia therapy (GLIDE)
(Genome Québec/Génome Canada/Amorchem/BioCanRx)

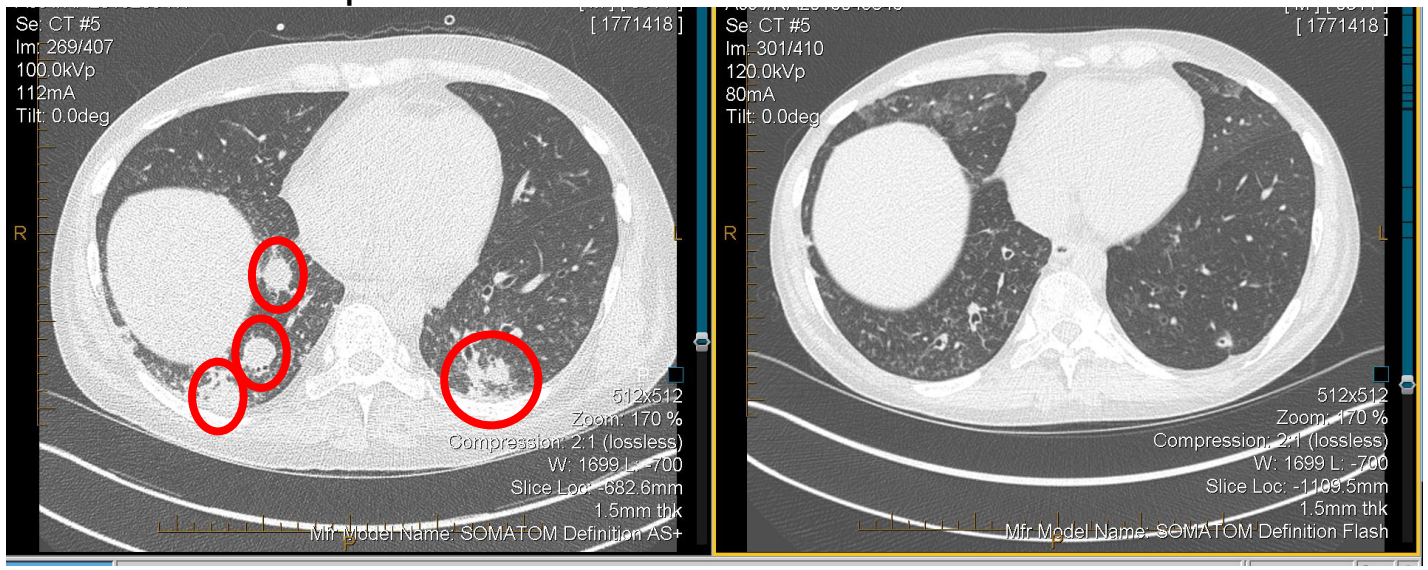


Antigen-specific T cells against refractory Epstein-Barr Virus infection and lymphoma

EBV-TCL-01
(NCT02580539 - JS Delisle)

2 weeks post infusion

3.5 months post infusion



ELISPOT – persistance of response (EBNA1 et LMP2)

Can Cellular Therapy be Industrialized ?

Manual

- ✓ Translation
- × Regulatory
- × Scalable
- × Economical

Robotic Duplication

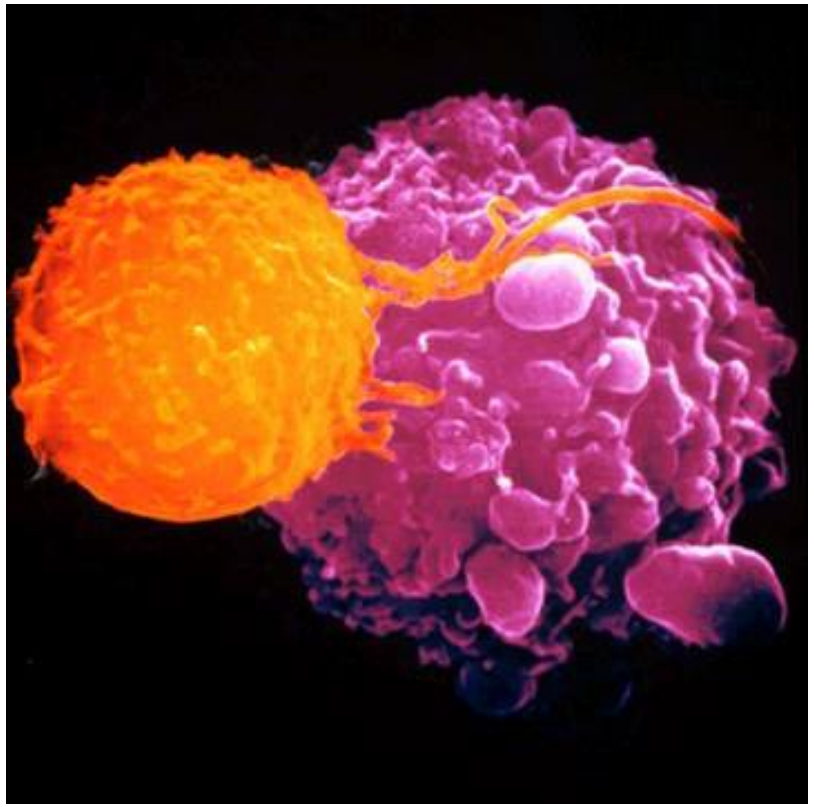
- × Translation
- ✓ Regulatory
- × Scalable
- × Economical

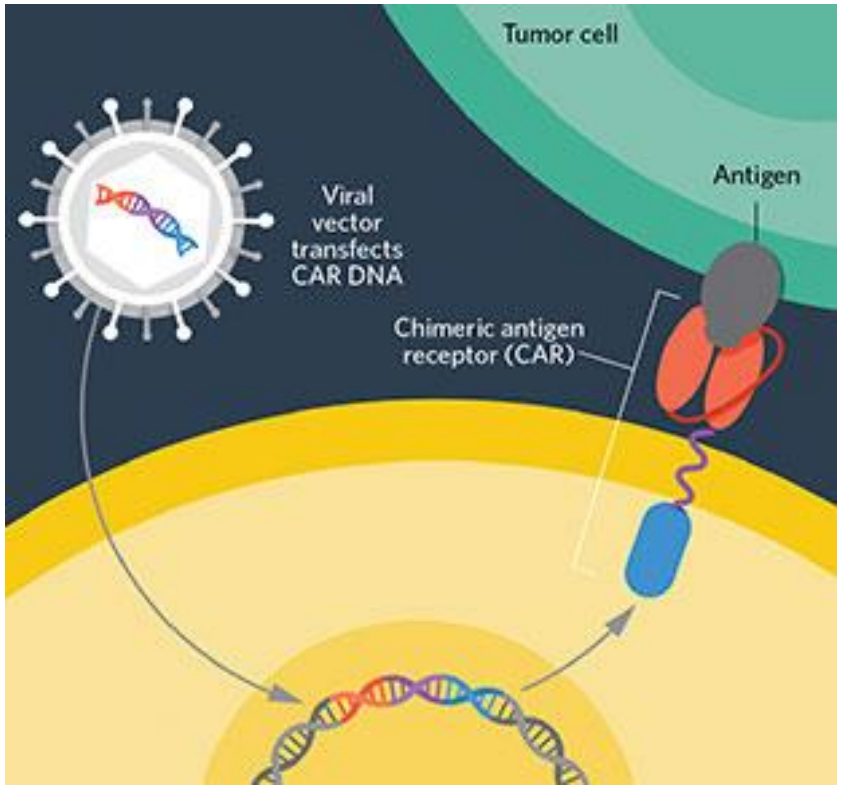
Automated Bioreactors

- ✓ Translation
- ✓ Regulatory
- ✓ Scalable
- ✓ Economical

Real time – quality monitoring

Chimeric Antigen Receptor (CAR) Technology

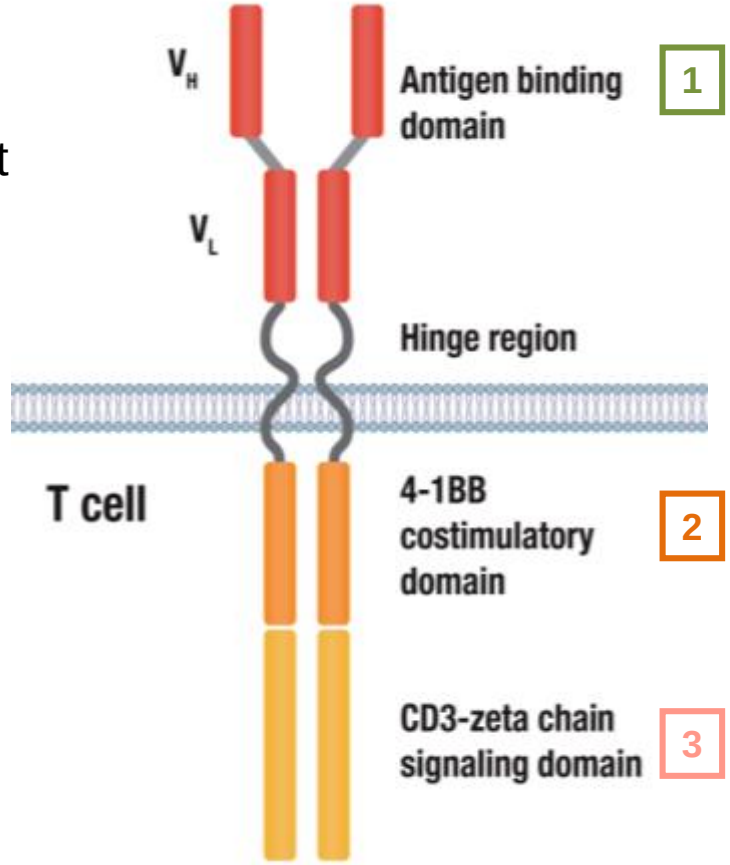




Brower V, The Scientist, April 1, 2015

Design of CD19-targeted CTL019

- On July 1, 2014, the FDA granted "breakthrough therapy" designation to CTL019, the anti-CD19 CAR T-cell therapy developed at the University of Pennsylvania (UPenn)
- Gene transfer technology using a lentiviral vector is used to transduce T cells to CTL019 cells
- The CTL019 CAR consists of T-cell activation domains coupled to an anti-CD19 single-chain variable fragment[1-3]
  - 1 Antigen-binding domain
    - Recognizes CD19 antigen on B cells
  - 2 4-1BB costimulatory domain
    - Increases T-cell activation and enhances cytolytic function of T cells
  - 3 CD3-zeta chain signaling domain
    - Induces T-cell activation



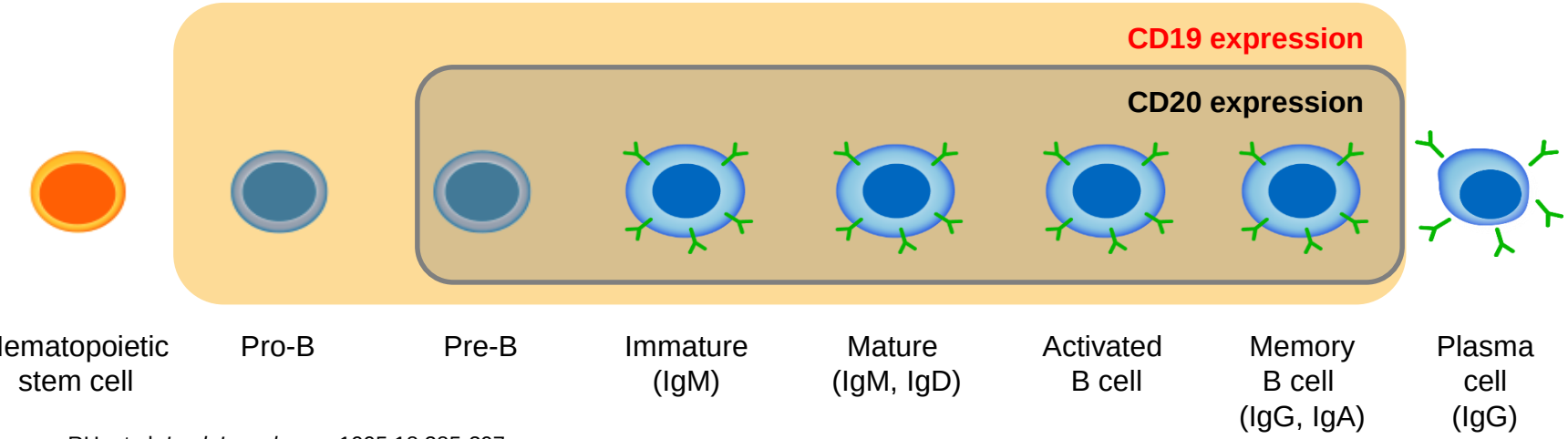
UPenn construct scFv-41BB-CD3ζ

1. Milone MC, et al. *Mol Ther.* 2009;17:1453-1464; 2. Zhang H, et al. *J Immunol.* 2007;179:4910-4918; 3. Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73.

CD19 is an Ideal Tumor Target in B-Cell Malignancies

CD19 expression is generally restricted to B cells and B cell precursors[1]	• CD19 is not expressed on hematopoietic stem cells[1]
CD19 is expressed by most B-cell malignancies	• CLL, B-ALL, DLBLC, FL, MCL[1]

Antibodies against CD19 inhibit tumor cell growth



1. Scheuermann RH, et al. *Leuk Lymphoma*. 1995;18:385-397
Image adapted from Janeway CA, Travers P, Walport M, et al. *Immunobiology*. 5th ed. New York, NY: Garland Science; 2001:221-293; Scheuermann RH, et al. *Leuk Lymphoma*. 1995;18:385-397; and Feldman M, Marini JC. Cell cooperation in the antibody response. In: Roitt I, Brostoff J, Male D, eds. *Immunology*. 6th ed. Maryland Heights, Missouri: Mosby;2001:131-146.

CTL019 in ALL: Efficacy

Response	n/n	%
Complete response	27/30	90
Negative minimal residual disease	22/30	73
Duration of response (7 mo median follow-up)	19/27[a]	70

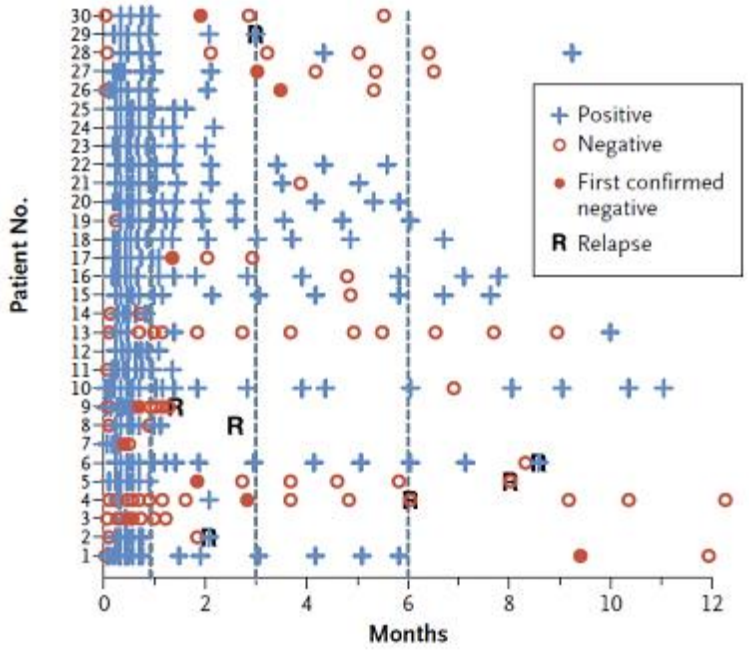
[a] 15 patients received no further therapy, and 4 patients withdrew from the study to receive other therapy.

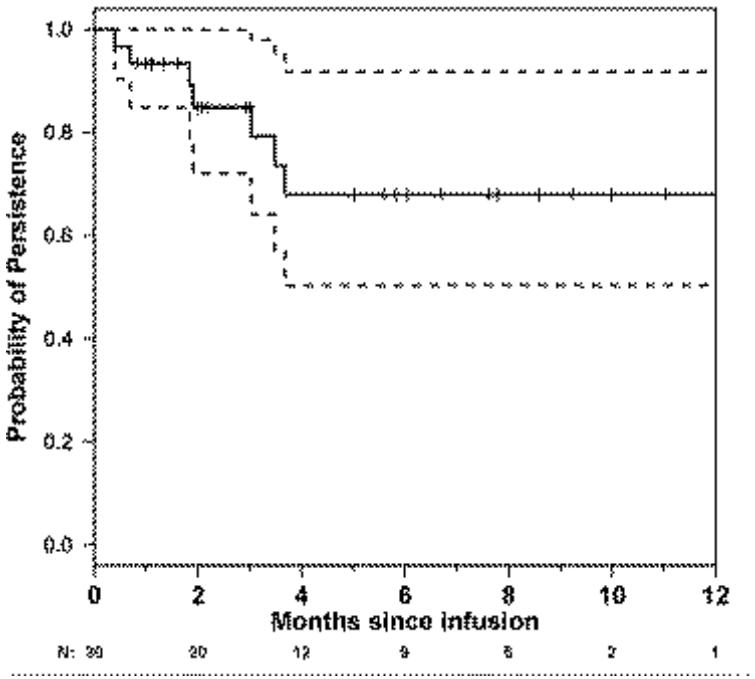
- 7 patients who had achieved a CR subsequently relapsed (time to relapse ranged from 6 weeks to 8.5 months)
  - 3 patients with $CD19^-$ ALL experienced relapses
  - 3 relapses developed after early loss of CTL019-modified T cells at 2 weeks to 3 months and were $CD19^+$
- CTL019-modified T cells were detected in the CSF of 17 of 19 patients with evaluable specimens, which may have implications for successful disease surveillance in that compartment
  - The 2 patients with CSF blasts at infusion had no detectable CNS leukemia with a follow-up of 6 months, and no CNS relapses were observed

NOVARTIS

Maude SL, et al. *N Engl J Med*. 2014;371(16):1507-1517.

CTL019 in ALL:
In Vivo Expansion and Long-Term Persistence





- CTL019-modified T cells were detectable in the blood by flow cytometry for up to 11 months (left)
- The probability of 6-month CTL019 persistence was 68% (95% CI, 50%-92%; right)
- CTL019 cells were observed to traffic to the CNS in pediatric patients with ALL

Maude SL, et al. *N Engl J Med*. 2014;371(16):1507-1517.

CTL019 in ALL: Updated Results (Pediatric)

- Data reported from 48 pediatric pts with r/r ALL, as presented at ASPHO 2015[1]
- 45 of 48 pts (94%) in complete remission
- The 6-month overall survival was 81% (95% CI, 70,94; figure)

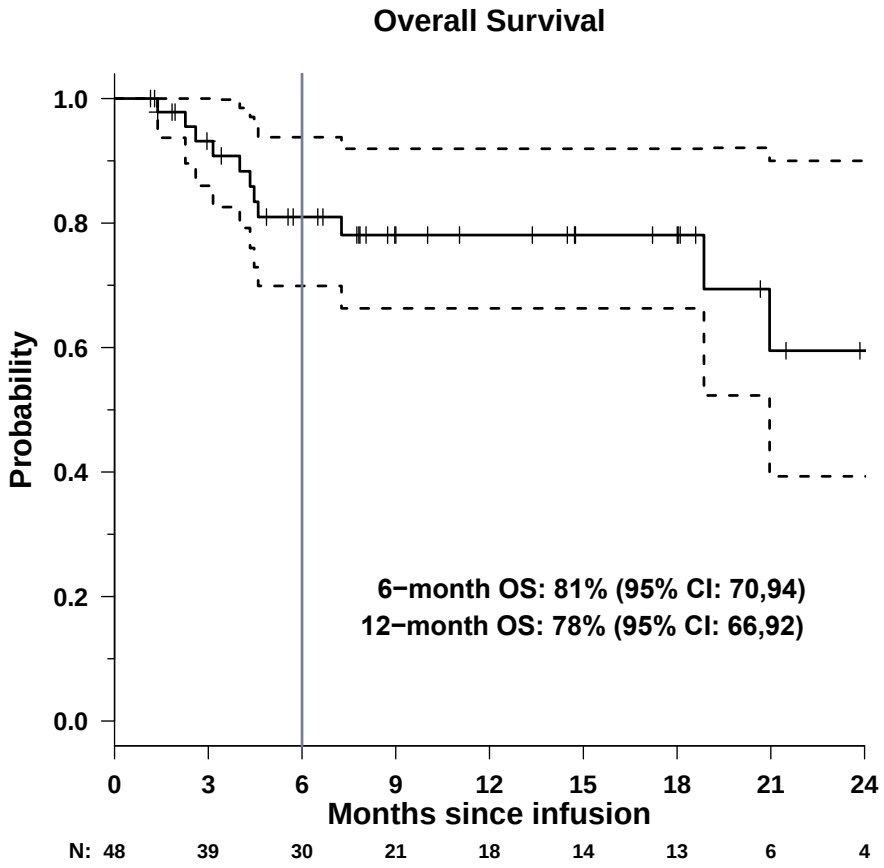
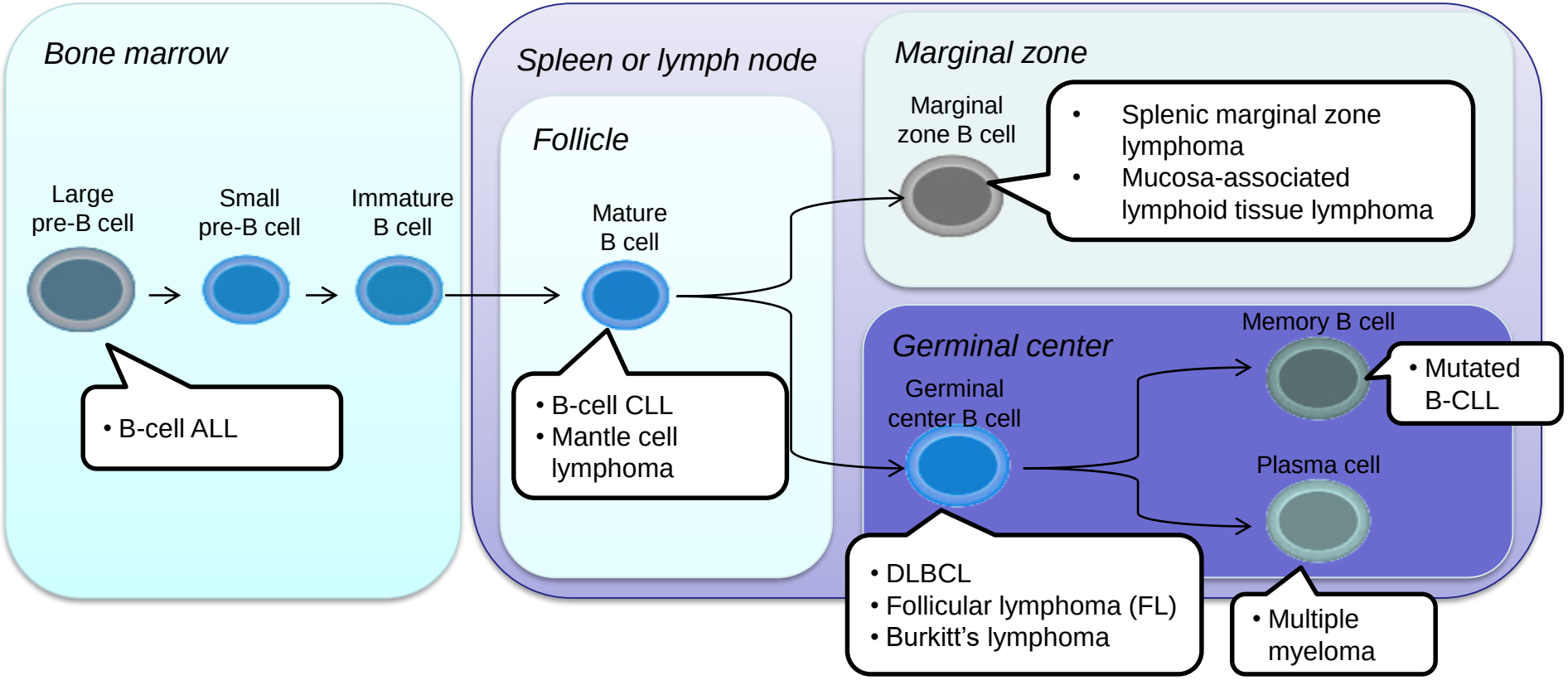


Figure: Kaplan-Meier survival curve of overall survival with number (N) of patients at each time point indicated below x axis.

1. Maude SL, et al. In: The American Society of Pediatric/Hematology/Oncology Conference. May 6–9, 2015, Phoenix, AZ . Abstract 4003.

NOVARTIS

A Variety of Neoplasms Arise at Different Stages of B-cell Differentiation

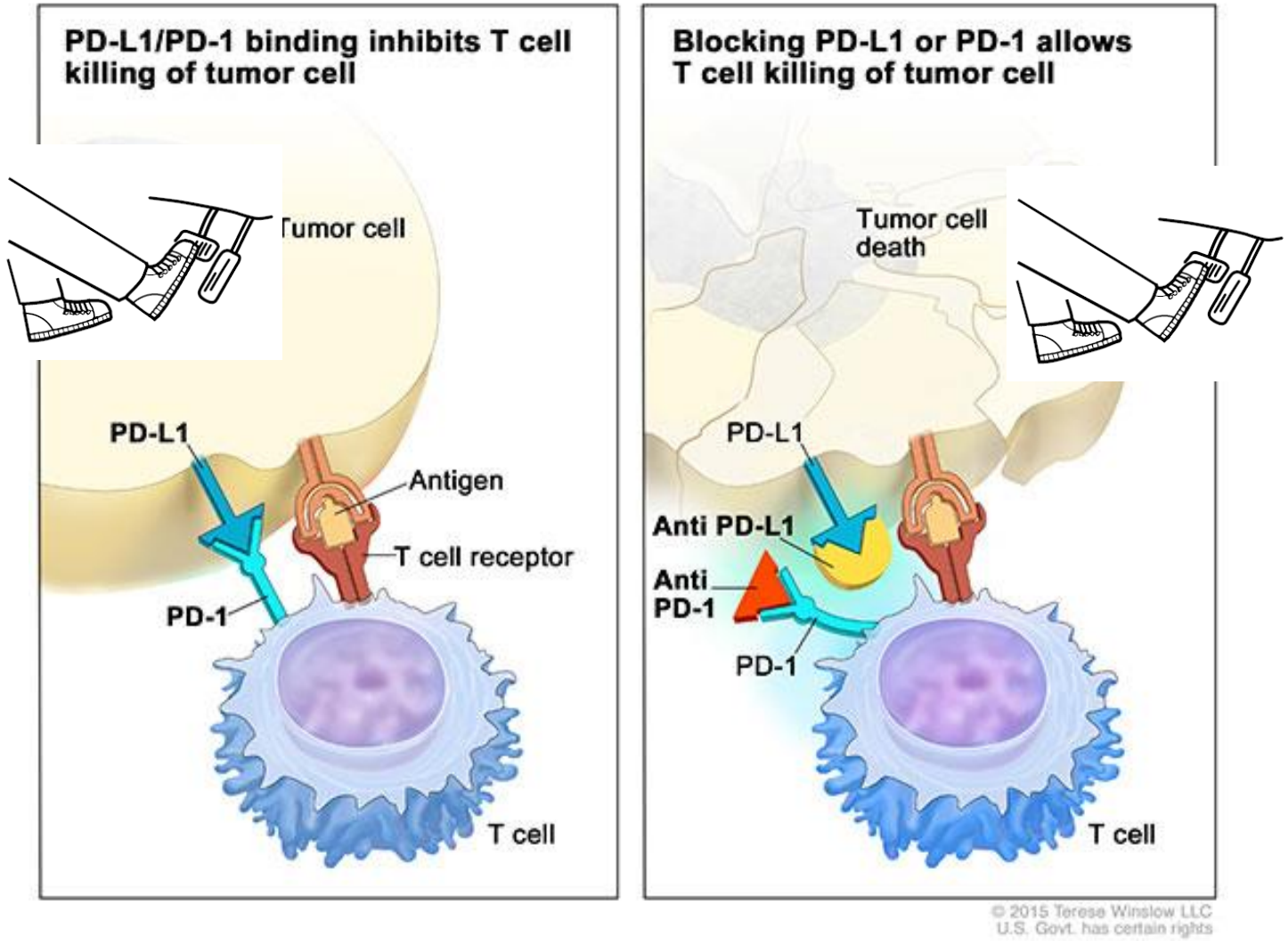


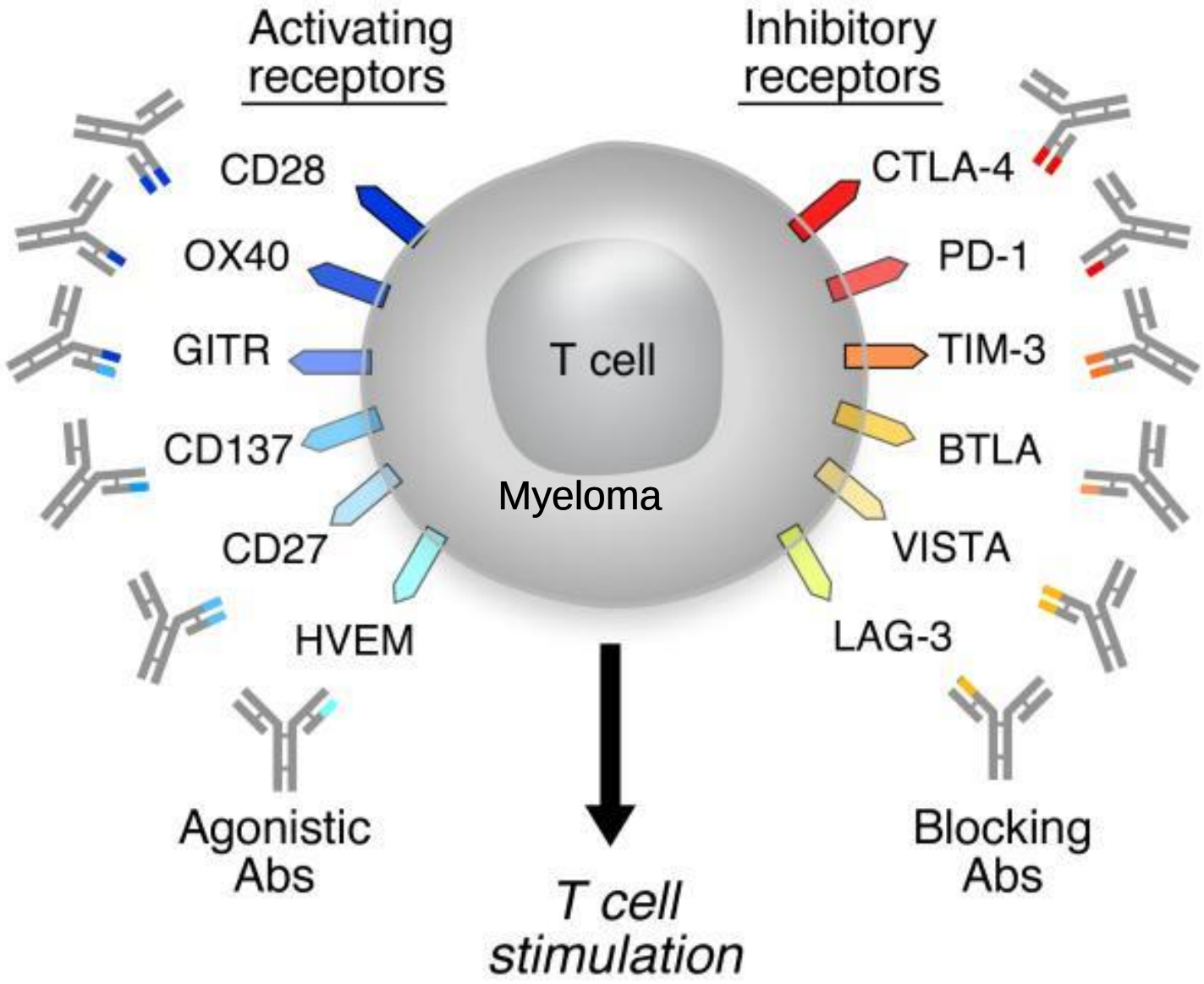
- CD19 expression is generally restricted to B cells and B cell precursors and, importantly, is expressed by most B-cell malignancies and is therefore an ideal target[1,2]
- Accordingly, a number of trials are planned investigating the use of CTL019 in a range of B-cell malignancies

NOVARTIS

1. Scheuermann RH, et al. *Leuk Lymphoma*. 1995;18:385-397; 2. Ghetie MA et al. *Blood*. 1994;83:1329-36.

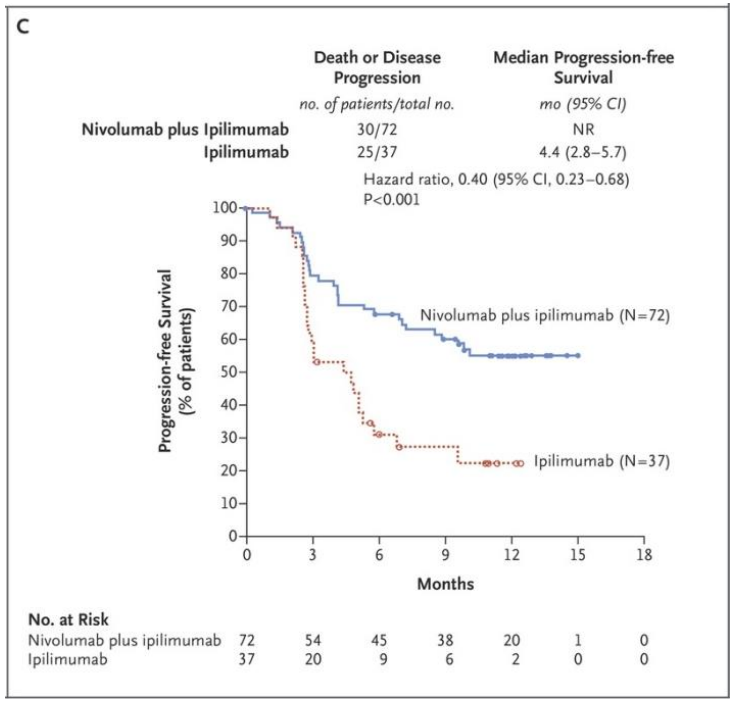
Checkpoint blockade




Activating receptors
Inhibitory receptors
CD28
OX40
GITR
CD137
CD27
HVEM
CTLA-4
PD-1
TIM-3
BTLA
VISTA
LAG-3
T cell
Myeloma
Agonistic Abs
Blocking Abs
T cell stimulation

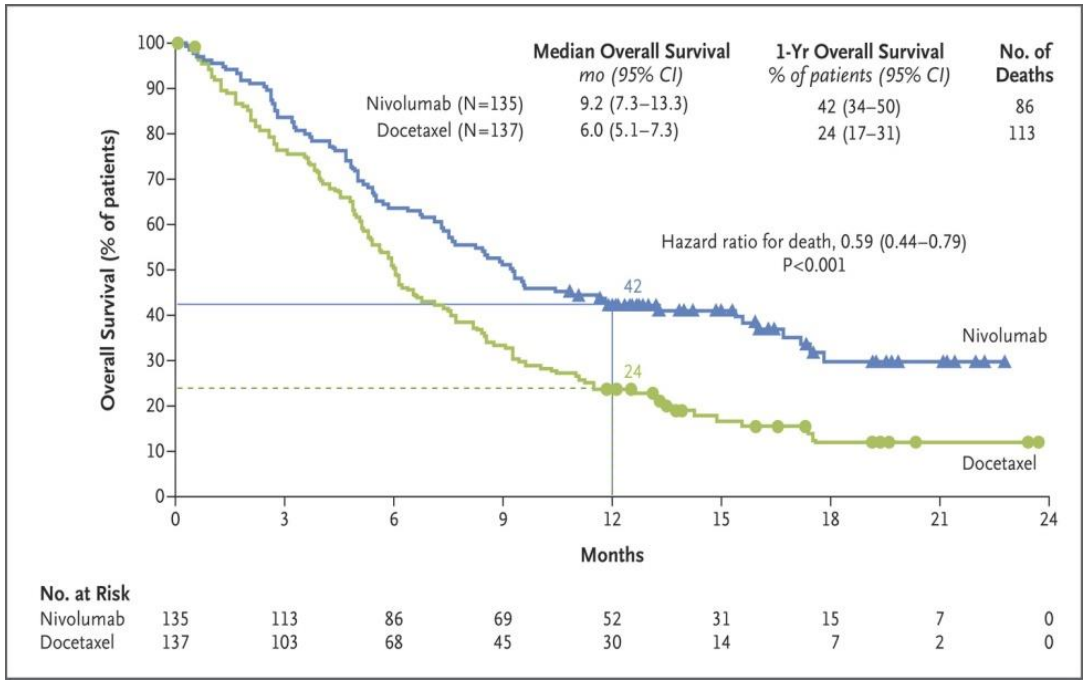
Checkpoint inhibition: a game changer

Metastatic melanoma



Postow MA et al. N Engl J Med 2015;372:2006-2017.

Advanced lung cancer



Brahmer J et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1504627

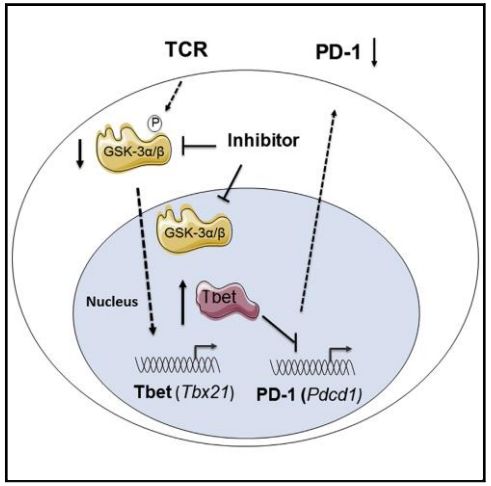
The NEW ENGLAND JOURNAL of MEDICINE

Article

Immunity

Glycogen Synthase Kinase 3 Inactivation Drives T-bet-Mediated Downregulation of Co-receptor PD-1 to Enhance CD8+ Cytolytic T Cell Responses

Graphical Abstract



Authors

Alison Taylor, James A. Harker, Kittiphat Chanthong, Philip G. Stevenson, Elina I. Zuniga, Christopher E. Rudd

Correspondence

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In Brief

The upstream pathway regulating PD-1 expression is not clear. Rudd and colleagues show that inhibition of the serine/threonine kinase GSK-3 upregulates T-bet expression, which decreases PD-1 expression and enhances CTL function. They demonstrate that the use of GSK-3 inhibitors in vivo inhibits PD-1 and enhances T cell clearance of viral infections.

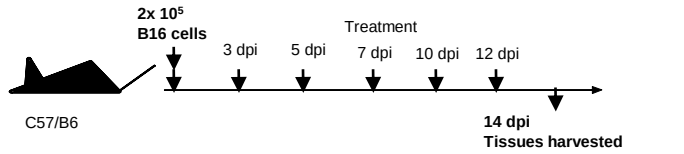
Highlights

- GSK-3 is a key upstream kinase that contributes to inhibition of PD-1 transcription
- GSK-3 siRNAs or inhibitors block PD-1 transcription to thereby enhance CTL function
- GSK-3 inhibition enhances *Tbx21* transcription, which represses PD-1 transcription
- Use of GSK-3 inhibitors in vivo downregulates PD-1 and enhances viral clearance

Taylor et al., 2016, Immunity *44*, 274–286
February 16, 2016 ©2016 The Authors
http://dx.doi.org/10.1016/j.immuni.2016.01.018

CellPress

Small molecule down-regulation of PD-1 reduces B16 metastatic melanoma



Healthy Control | B16 no treatment | Plus XL334 | Plus Anti-PD1 | Plus XL334 and anti-PD1

Christopher E Rudd

Centre d’excellence en thérapie cellulaire
(CETC)
Centre of Excellence in Cellular Therapy
Hopital Maisonneuve-Rosemont

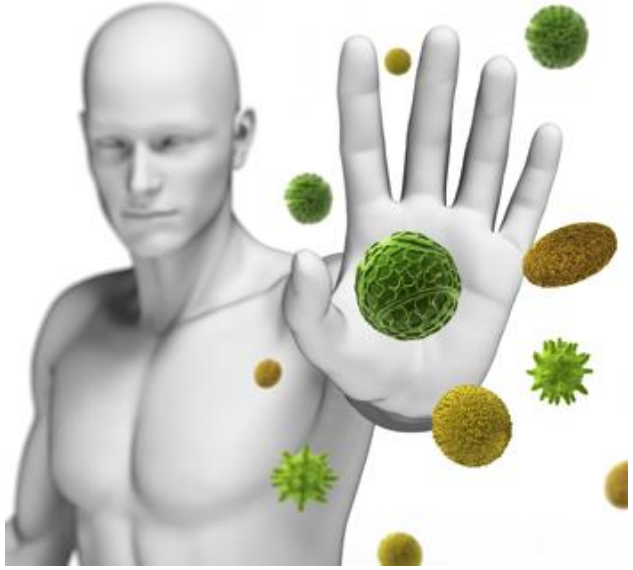
L’Assomption

CETC building

NIVEAU RDC
LABS CETC

Centre for Commercialization of Cancer IMMUNOTHERAPY

Accelerating market access of **breakthrough innovations** to fight cancer



Vision & Mission

- Vision: C3i will be Canada's catalyst for cancer immunotherapy business development

- Mission: Accelerate the discovery, commercialization and access to cancer immunotherapy

C3i's One-Stop-Shop Model

C3i Structure in 4 Business Units with Unique Combination of Key Assets

Biomarker & Diagnostic Unit

Focussing on Immunomonitoring and Precision Medicine

cGMP Manufacturing Unit

Only GMP cell production facility in Canada

Clinical Research Unit

Strong focus on Cancer Immunotherapy

Innovation & Commercialisation Unit

Investing in Innovative Cancer Immunotherapies, asset development & commercialization.

- Translation from bench to clinic
- Large Network of Investigators
- Regulatory Expertise
- In-house development of biomarkers
- On Site cGMP facility
- Efficient Clinical Trial Implementation
- Business Oriented Team
- Venture Capital Investment

STATE-OF-THE-ART
FACILITIES

State-of-the-art cleanrooms to accommodate clinical grade production of human cell products.

WORLD-RENOWNED
EXPERTISE

Key Canadian investigators and highly specialized personnel come together in the field of stem cell therapy to assist you with your research needs.

EXPLORE OUR
SERVICES

THERAPEUTIC AREAS »

TISSUE TYPES »

CELL TYPES »

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Pascal | Accueil 13

Page | Activité 2 | Paramètres | Développer l'audience | Aide

CellCAN

Santé/médecine/produits pharmaceutiques

Page communautaire sur Hôpital Maisonneuve-Rosemont

J'aime | S'abonner | Message | •••

Journal | À propos | Photos | Avis | Plus

PERSONNES

9 mentions J'aime

Eloi Courchesne, **Mario Proulx** et **5 autres personnes** aiment ça.

+2

Ciblez **1 600 000** personnes à proximité **Montréal**.

Promouvoir la Page

Invitez vos amis à aimer CellCAN

Statut | Photo / Vidéo | Évènement/moment-clé +

Quoi de neuf ?

CellCAN a partagé un lien.
Publié par Pascal Mailhot [?] · il y a 6 heures

Dans le cas du cancer du sein, la recherche sur les cellules souches cancéreuses, « mères » des cellules tumorales, est une voie particulièrement originale et innovante, porteuse de grands espoirs pour l'avenir.

H

CETTE SEMAINE

2 Mentions J'aime une Page

NON LU(S)

2 Notifications

0 Messages

Récent
2014

Votre publicité

CellCAN
Mobilizing knowledge and promoting advances in regenerative medicine and cell therapy.

Aimer la Page · 9 personnes aiment cette Page

Promouvoir la Page

Jean Robert Faucher a commenté la photo de Stéphan Gravel.

Stéphane Ethier et Justin Cadiou sont désormais amis.

Roch F. Gamache Bon courage à tous mes anciens collègues et amis de la colline...

Audrey Ruel-Manseau Pro et Audrey Jacques sont désormais amies.

Greg Rochon aime le lien de Anne Celano Frohna.

Claudia Larochelle aime Le Pharmachien.

Pierre Diotte Prevost aime la photo de Isabelle Ferrandez Deshêtres.

Louis-Félix Binette aime

Mathieu Bock-Côté Web
Karine Gaucher Web
Stephanie St-Onge Web
Thaïs Dubé Mobile
Geof St-Laurent Web
Martin Constant
Maria Eva

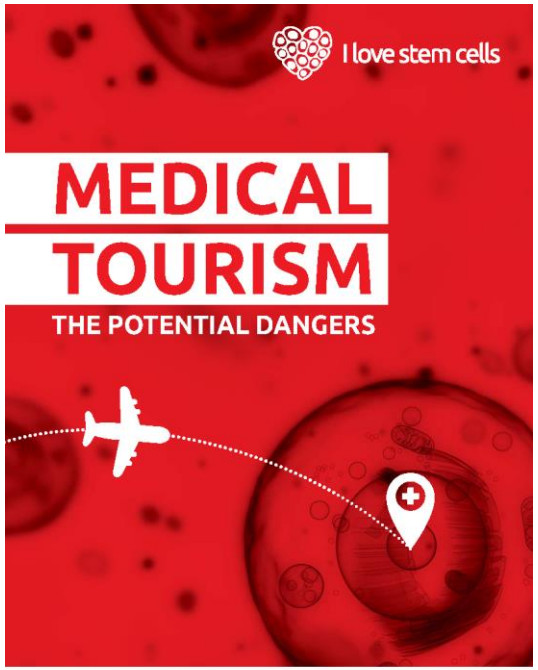
PLUS D'AMIS (22)

Akli Ait Abdallah Mobile

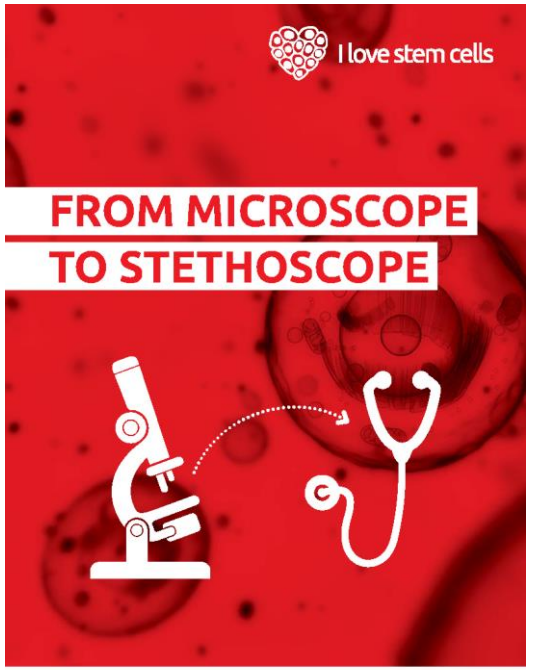
Recherche

Customized tools for knowledge dissemination – Information booklets

CellCAN
Regenerative Medicine and Cell Therapy Network



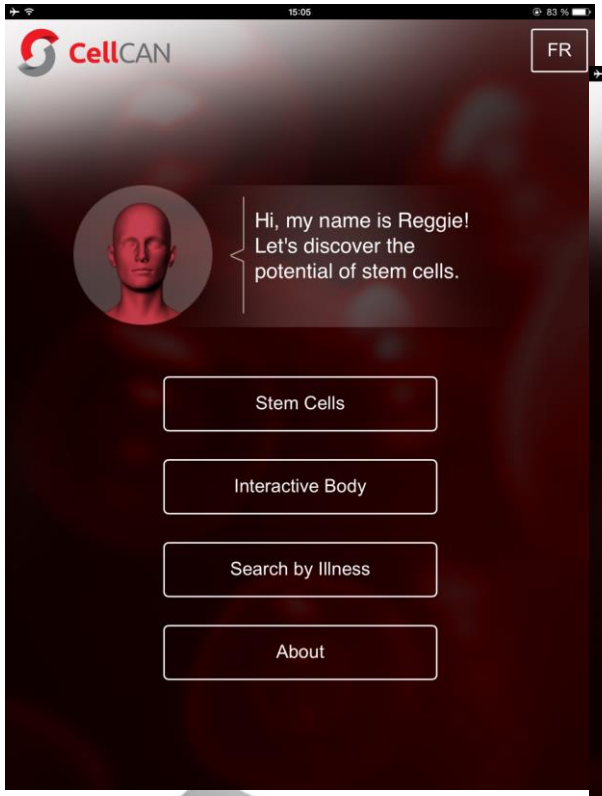
CellCAN
Regenerative Medicine and Cell Therapy Network

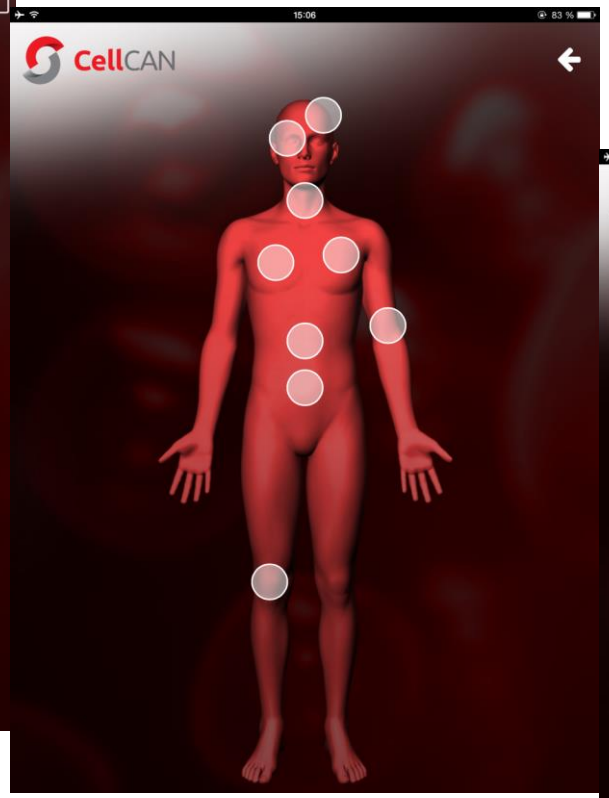


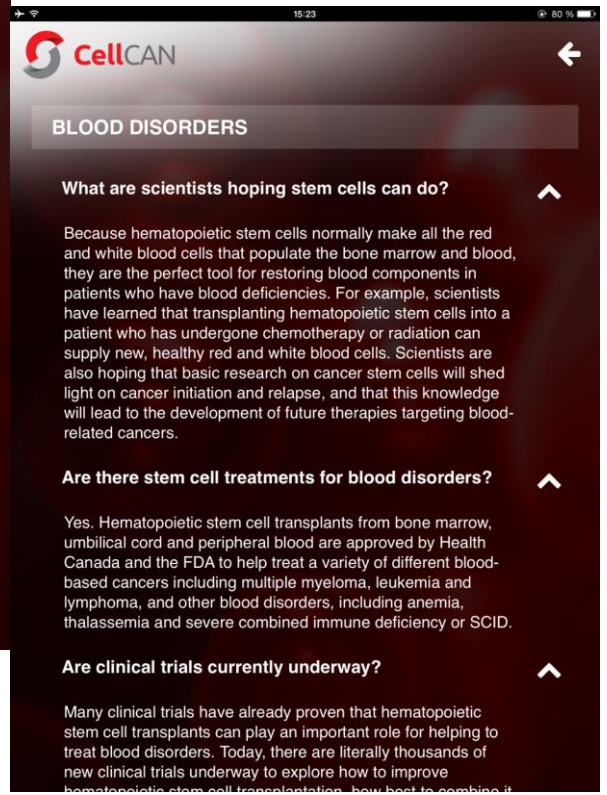
CellCAN
Regenerative Medicine and Cell Therapy Network

For general practitionners & health care professionnals

Customized tools for knowledge dissemination – Mobile App







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- <u>Clinical transplant teams</u>
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- H Bonig (Frankfurt, Germany)

<u>DC Roy laboratory</u>

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