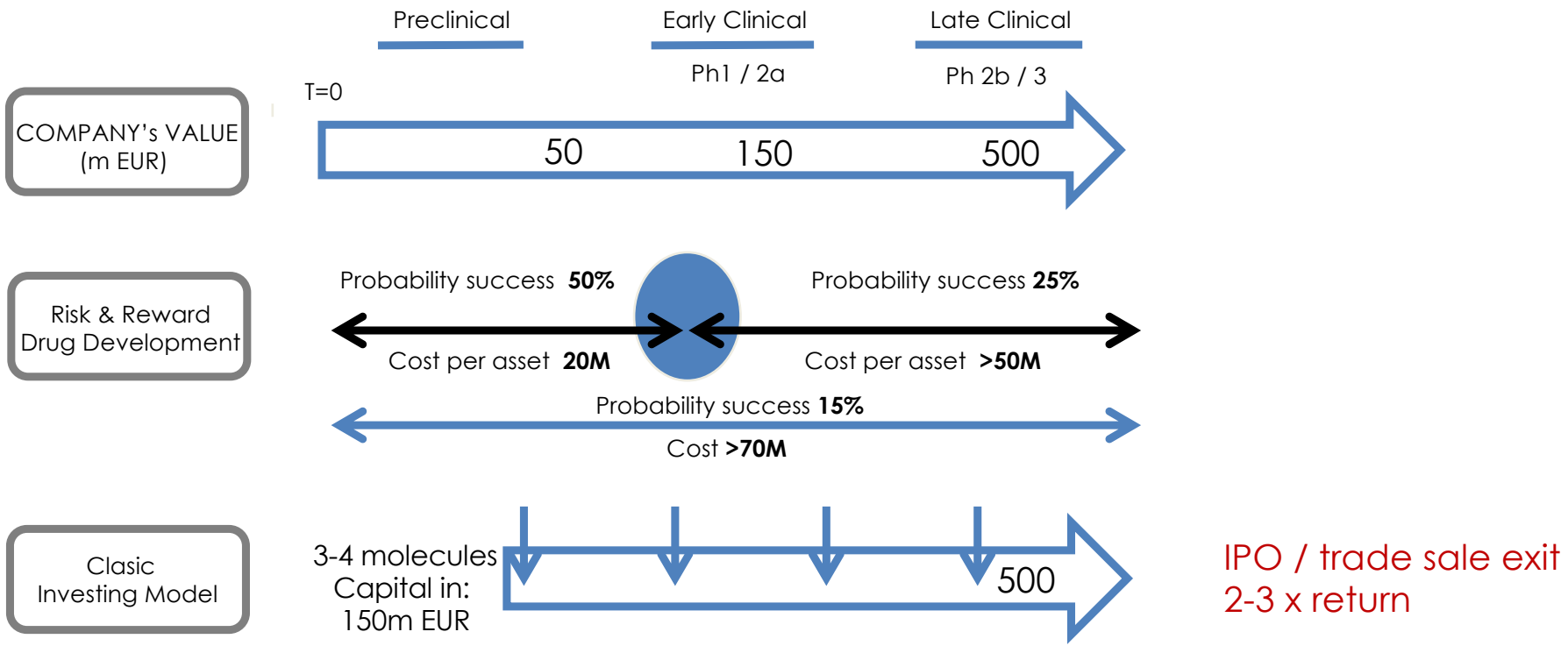
Medicxi

- Index Ventures life science ("**LS**") team spun out to form Medicxi Ventures in February 2016
- 4 partners and 15 executives together since 2004
- €326M invested in 67 heathcare companies to since 2000
- Backed by global pharmaceutical companies ("**Pharma**")
- Offices in Geneva, London, Cambridge (UK), Jersey

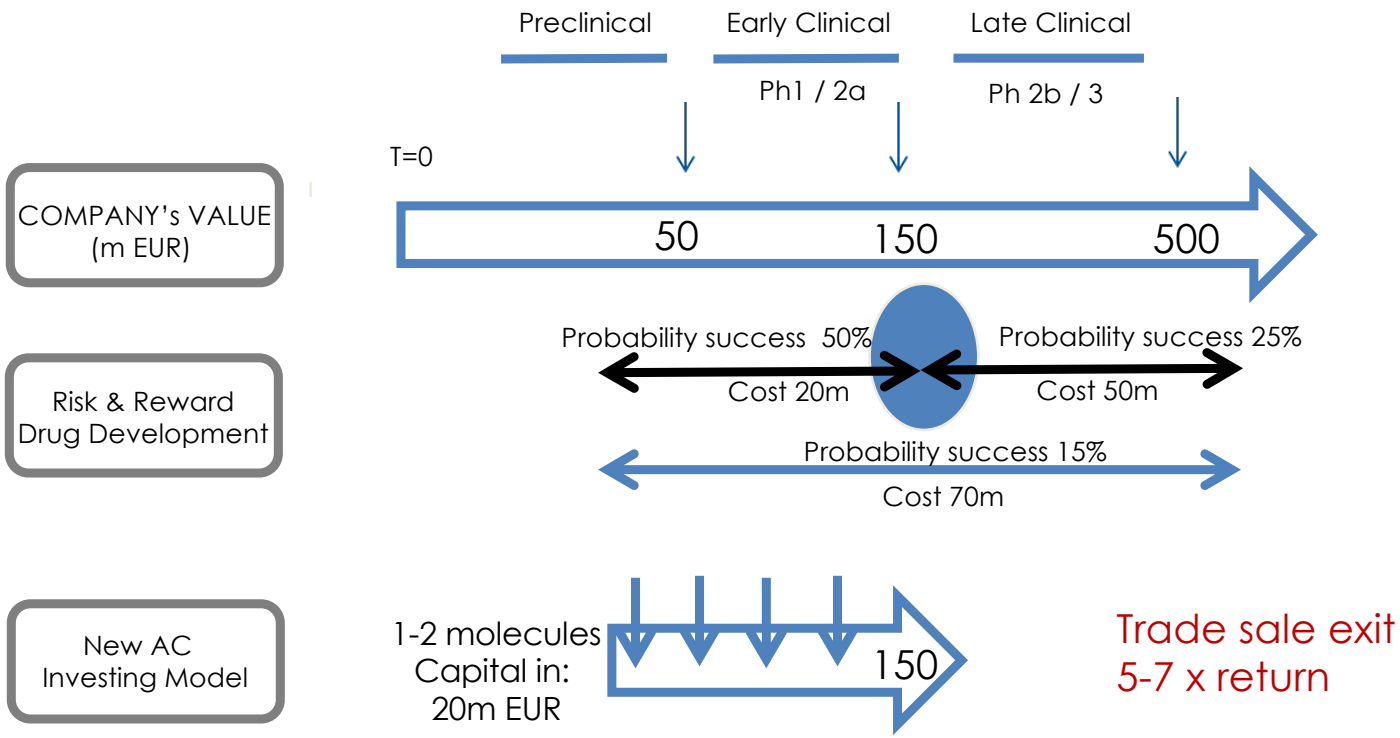
Clasical Investing Model:



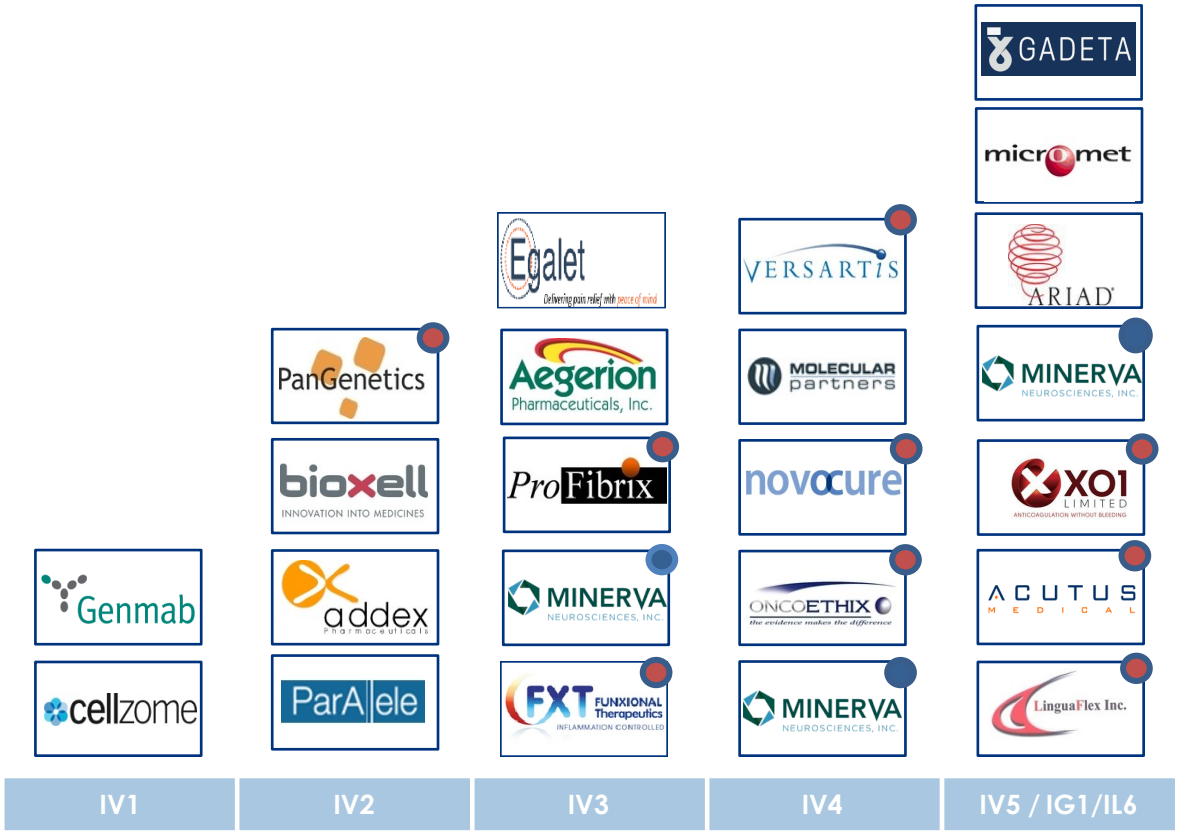
IPO / trade sale exit
2-3 x return

Asset Centric Investing Model:

Milestone-based, one molecule at a time



Selected historical (Index Ventures) investments



GADETA

Next generation cancer immunotherapy meets metabolomics

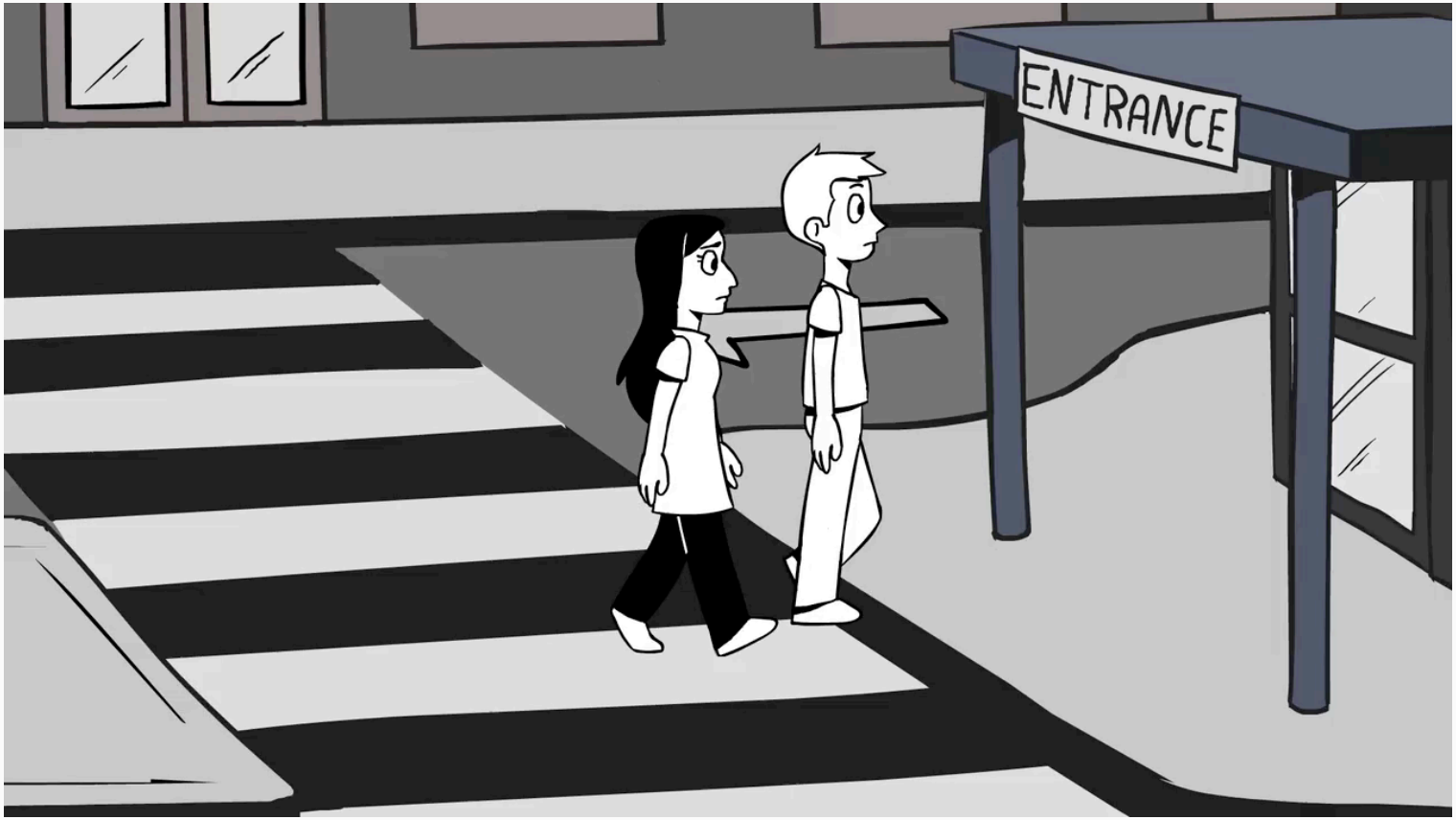
A UMCU spin-off company

Gadeta at a glance

- Developing proprietary Cellular Immunotherapy Platform to target hematological and solid tumors
  - Founded by Prof Jurgen Kuball from the Utrecht Medical Center Utrecht and Dr Mark de Boer, Venture Partner at Medicxi Ventures
- TEGs: T cells Engineered with Gamma delta ($\gamma\delta$) T-cell receptors
  - Unique approaches with clear advantages over existing technologies
    - Using current knowledge and manufacturing of $\alpha\beta$ T cells
    - Combined with unique $\gamma\delta$ T-cell receptors
    - Targeting novel and unique cancer cell targets
  - First program to enter clinic in Q1-2017
- Series A financing (EUR 7M) closed in January 2016
  - Medicxi Ventures
  - Baxalta Ventures
  - UMCU Holding, founders and management

Gadeta mission

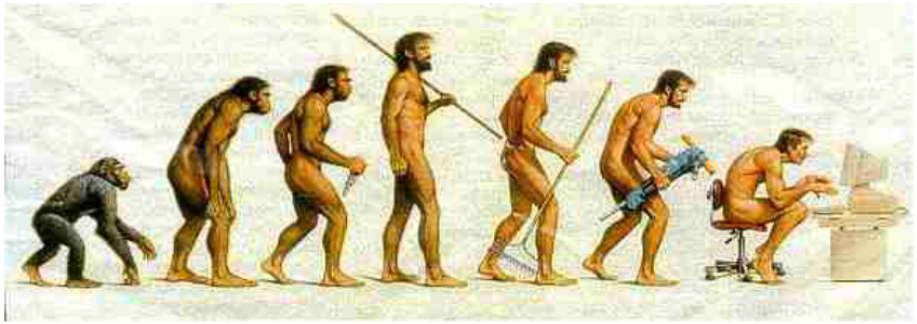
Cure more people with cancer



Visit www.gadeta.nl for video animation

γδ T-cells

survived > 500 M years of evolutionairy pressure

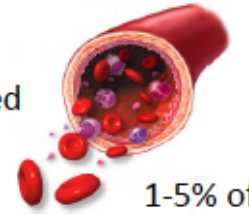


γδT cells must provide a substantial survival advantage

γδ T-cell share many features with NK cells and bridge the gap between innate and adaptive immunity

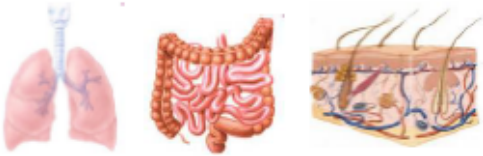
Vδ2+ γδT cells

Best characterized



1-5% of peripheral CD3+ T cells

Vδ2- γδT cells



Up to 50% of tissue CD3+ T cells

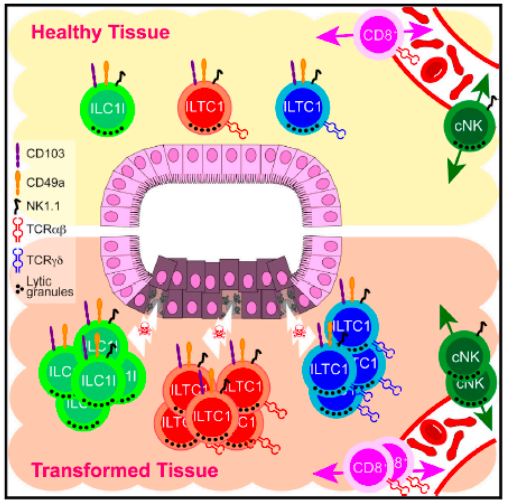
Functional evidence of cancer immune surveillance by γδT cells

Article

Cell

Cancer Immunosurveillance by Tissue-Resident Innate Lymphoid Cells and Innate-like T Cells

Graphical Abstract



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In Brief

Cell transformation triggers a cancer immunosurveillance mechanism that engages tissue-resident lymphocytes derived from innate, TCRαβ, and TCRγδ lineages.

Cancer Cell
Article

CellPress

Targeted Activation of Human Vγ9Vδ2-T Cells Controls Epstein-Barr Virus-Induced B Cell Lymphoproliferative Disease

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http://dx.doi.org/10.1016/j.ccr.2014.07.026

SUMMARY

Epstein-Barr virus-induced lymphoproliferative disease (EBV-LPD) after transplantation remains a serious and life-threatening complication. Herein we showed that the aminobisphosphonate pamidronate-expanded human Vγ9Vδ2-T cells efficiently killed EBV-transformed autologous lymphoblastoid B cell lines (EBV-LCL) through γ/δ-TCR and NKG2D receptor triggering and Fas and TRAIL engagement. By inoculation of EBV-LCL in Rag2$^{-/-}$γc$^{-/-}$ mice and humanized mice, we established lethal EBV-LPD with characteristics close to those of the human disease. Adoptive transfer of pamidronate-expanded Vγ9Vδ2-T cells alone effectively prevented EBV-LPD in Rag2$^{-/-}$γc$^{-/-}$ mice and induced EBV-LPD regression in EBV^{+} tumor-bearing Rag2$^{-/-}$γc$^{-/-}$ mice. Pamidronate treatment inhibited EBV-LPD development in humanized mice through selective activation and expansion of Vγ9Vδ2-T cells. This study provides proof-of-principle for a therapeutic approach using pamidronate to control EBV-LPD through Vγ9Vδ2-T cell targeting.

In humans: The “favorable” prognostic landscape …. is dominated by γδT cells

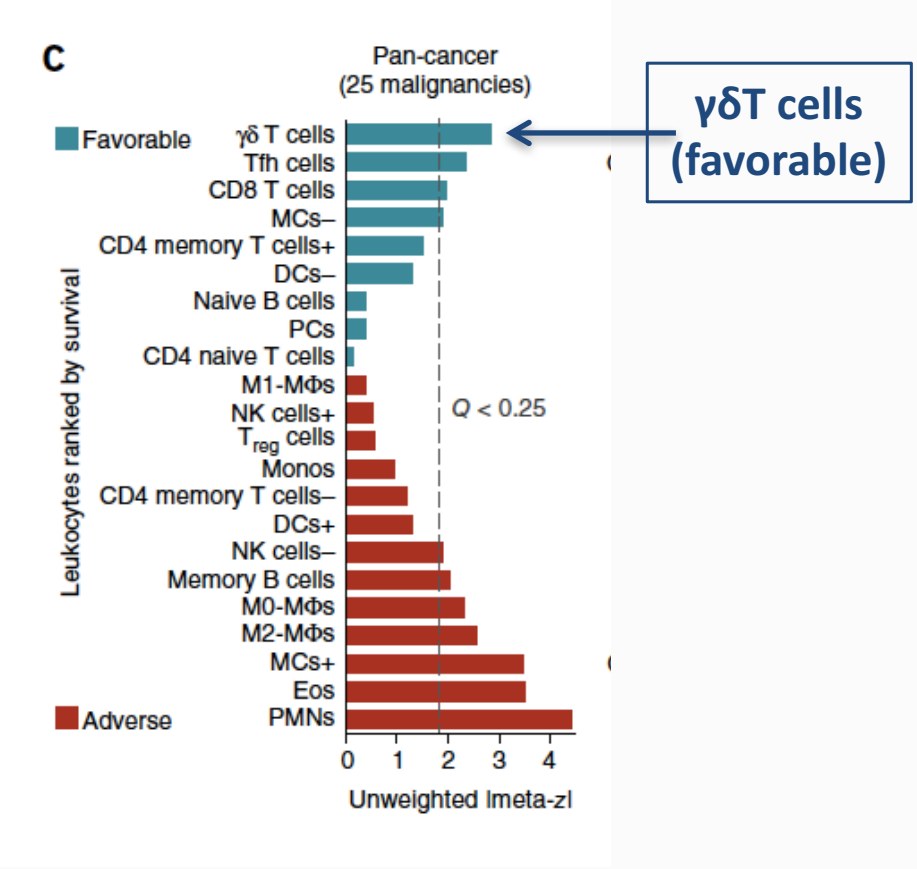
The prognostic landscape of genes and infiltrating immune cells across human cancers

Andrew J Gentles,, Aaron M Newman,, Chih Long Liu,, Scott V Bratman,, Weiguo Feng,, Dongkyoon Kim,, Viswam S Nair,, Yue Xu,, Amanda Khuong,, Chuong D Hoang,, Maximilian Diehn,, Robert B West,, Sylvia K Plevritis & & Ash A Alizadeh

Nature Medicine **21**, 938–945 (2015) doi:10.1038/nm.3909
Received 19 January 2015 Accepted 19 June 2015 Published online 20 July 2015

Abstract

Molecular profiles of tumors and tumor-associated cells hold great promise as biomarkers of clinical outcomes. However, existing data sets are fragmented and difficult to analyze systematically. Here we present a pan-cancer resource and meta-analysis of expression signatures from ~18,000 human tumors with overall survival outcomes across 39 malignancies. By using this resource, we identified a forkhead box MI (*FOXM1*) regulatory network as a major predictor of adverse outcomes, and we found that expression of favorably prognostic genes, including *KLRB1* (encoding CD161), largely reflect tumor-associated leukocytes. By applying CIBERSORT, a computational approach for inferring leukocyte representation in bulk tumor transcriptomes, we identified complex associations between 22 distinct leukocyte subsets and cancer survival. For example, tumor-associated neutrophil and plasma cell signatures emerged as significant but opposite predictors of survival for diverse solid tumors, including breast and lung adenocarcinomas. This resource and associated analytical tools (http://precog.stanford.edu) may help delineate prognostic genes and leukocyte subsets within and across cancers, shed light on the impact of tumor heterogeneity on cancer outcomes, and facilitate the discovery of biomarkers and therapeutic targets.



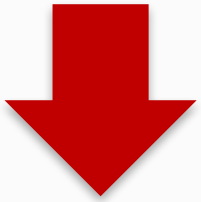
Why did clinical trials with γδT-cells fail so far?

- Homing properties of γδT-cells might be different
- Proliferation deficiency of conventional γδT-cells in many cancer patients is observed
- γδT-cells are sensitive to cancer cell expressed check point inhibitors
- Diversity of γδT-cells in NK-receptors & γδ-TCRs is unfortunately widely underestimated
- Frequently γδT-cells are absent in advanced stage cancer patients

Key success factors of Gadeta

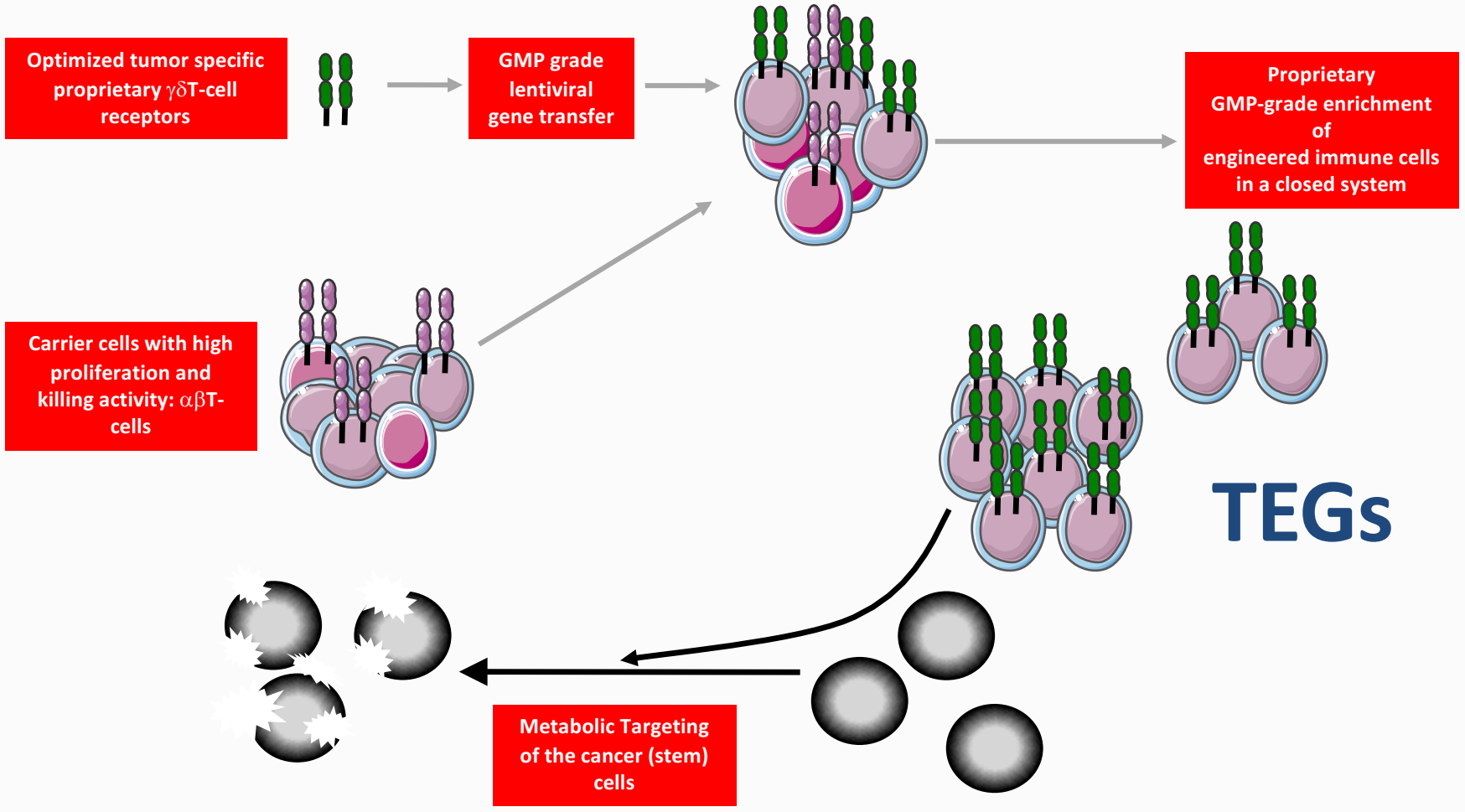
- Appreciating pitfalls and the unique strength of γδT cells during cancer immune surveillance for our therapeutic strategy

- Learning lessons from clinical trials with unmodified γδT cells



TEGs

T Cells Engineered To Express a Defined Gamma Delta TCR



Gadeta TEGs: γδ TCRs in αβ T-cells

- γδ TCR have interesting specificities
  - Sensing metabolic dis-regulation in cancer cells
  - Highly tumor-reactive receptors with the potential to target the cancer stem cells

- Overcoming limitations of γδ T-cells
  - Overcome tolerance induction of γδ T-cells
  - Taking advantage of one defined innate receptor with strong anti-tumor-reactivity

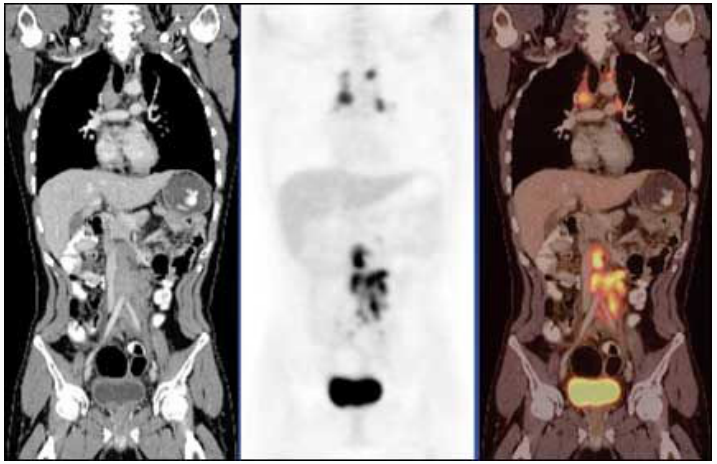
TEG Pipeline

Compound	Target	Indication	Research	Pre-clinical	Phase 1	Phase 2
TEG-1001	CD277	Hematologic cancers				
TEG-1002	CD277	Solid tumors				
TEG-2001	CD277	Solid tumors				
TEG-3001	Undisclosed					
TEG-4001	Undisclosed					

TEG-1001

Cancer is a metabolic disease

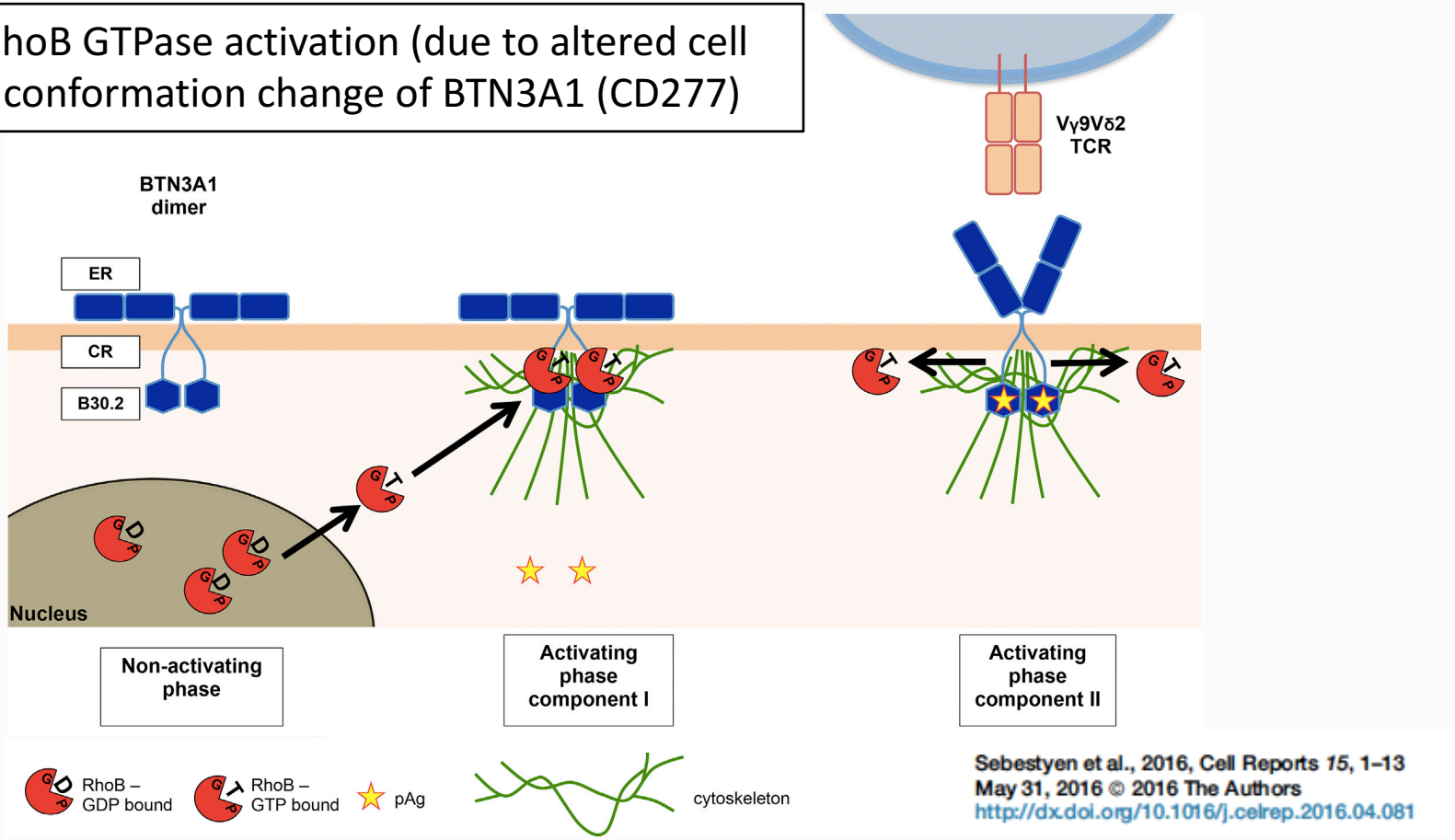
Daily practice: detecting cancer cells based on their metabolic state with PET CT



Utilizing a highly tumor reactive γ9δ2TCR for metabolic cancer targeting

TEG-1001 can sense metabolic state of cancer cells

IPP accumulation and RhoB GTPase activation (due to altered cell metabolism) result in a conformation change of BTN3A1 (CD277)



Sebestyen et al., 2016, Cell Reports *15*, 1–13
May 31, 2016 © 2016 The Authors
http://dx.doi.org/10.1016/j.celrep.2016.04.081

Conclusion

- **Gadeta: Cancer Immunotherapy meets Metabolomics**
- **TEGs** (αβT cells engineered with γδTCRs) allow an efficient targeting of cancer as metabolic disease
- Strong IP position
- Building strong pipeline
  - **First clinical trial with TEG-1001 in Q2/2017 in hematological malignancies**
  - **Second clinical trial with TEG-1002 in solid cancer in planning**
  - **Broadening the pipeline with other γδTCR lead structures**

GADETA

Contact: Mark de Boer (acting CEO)
mark@gadeta.nl