Adoptive T cell therapy

John Haanen, MD, PhD

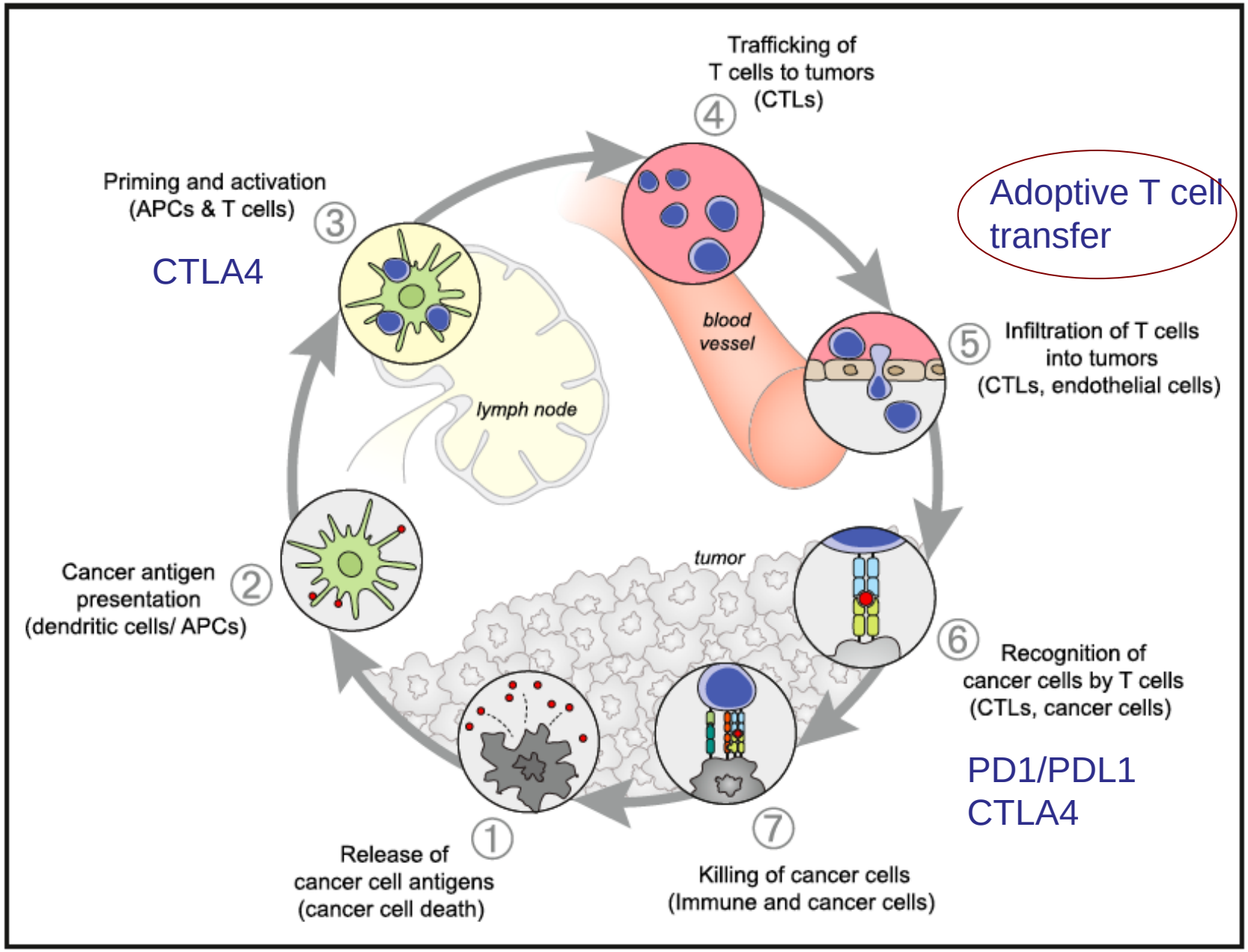
ESMO Asia 2015

Disclosures

Advisory role:	BMS, Pfizer, Roche, MSD, Novartis Neon Therapeutics
Research grant:	GSK, BMS, MSD

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

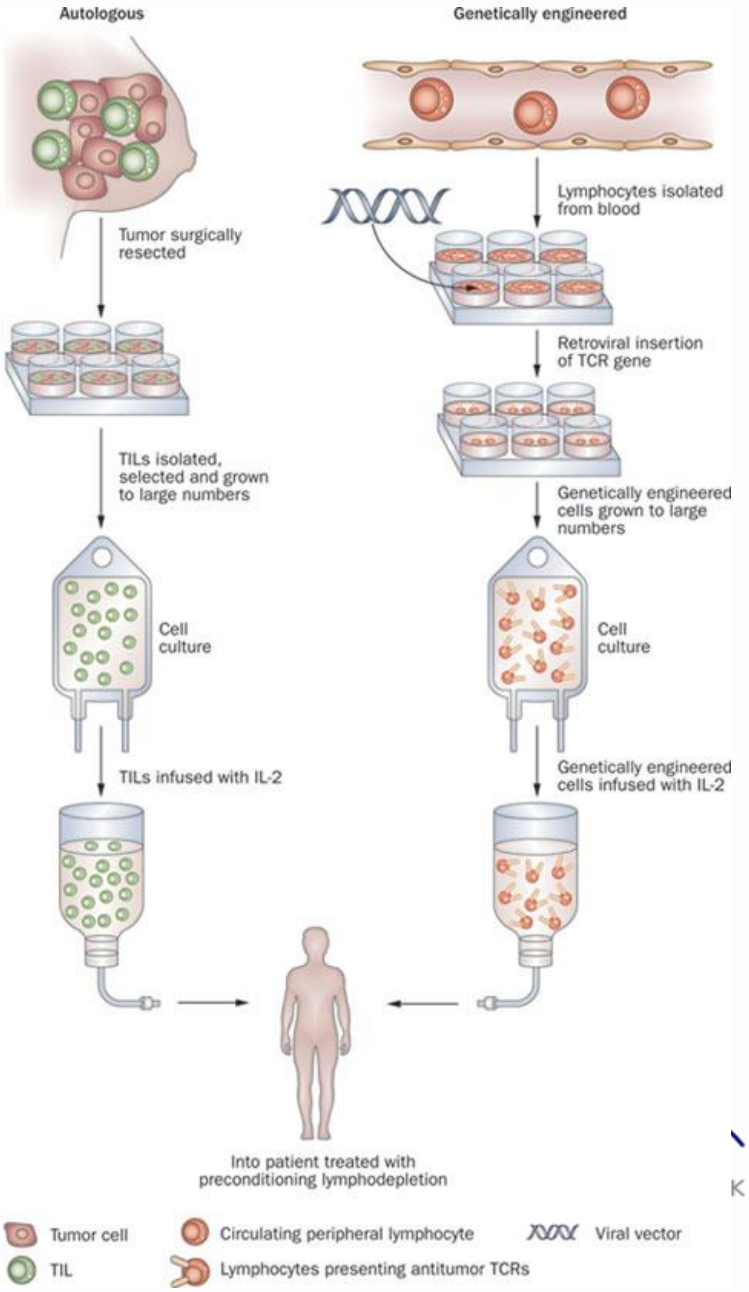
Cancer immunity cycle



Chen & Mellman Immunity 2013

Different strategies available for adoptive cell therapy

- Tumor infiltrating lymphocytes: TIL therapy
- Genetically modified peripheral blood lymphocytes
  - inserting a tumor-reactive TCR
  - inserting a tumor-reactive CAR
    - using retroviral insertion
    - using lentiviral insertion
    - using transposon-based insertion



Steven A. Rosenberg Nature Reviews Clinical Oncology (2011)

Role for T cells in cancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intratumoral T Cells, Recurrence, and Survival in Epithelial Ovarian Cancer

Lin Zhang, M.D., Jose R. Conejo-Garcia, M.D., Ph.D., Dionyssios Katsaros, M.D., Ph.D., Phyllis A. Gimotty, Ph.D., Marco Massobrio, M.D., Giorgia Regnani, M.D., Antonis Makrigiannakis, M.D., Ph.D., Heidi Gray, M.D., Katia Schlienger, M.D., Ph.D., Michael N. Liebman, Ph.D., Stephen C. Rubin, M.D., and George Coukos, M.D., Ph.D.

PERSPECTIVES

OPINION

The immune contexture in human tumours: impact on clinical outcome

Wolf Herman Fridman, Franck Pagès, Catherine Sautès-Fridman and Jérôme Galon

Science
AAAS

Type, Density, and Location of Immune Cells Within Human Colorectal Tumors Predict Clinical Outcome

Jérôme Galon, *et al.*

Science **313**, 1960 (2006);
DOI: 10.1126/science.1129139

AACR

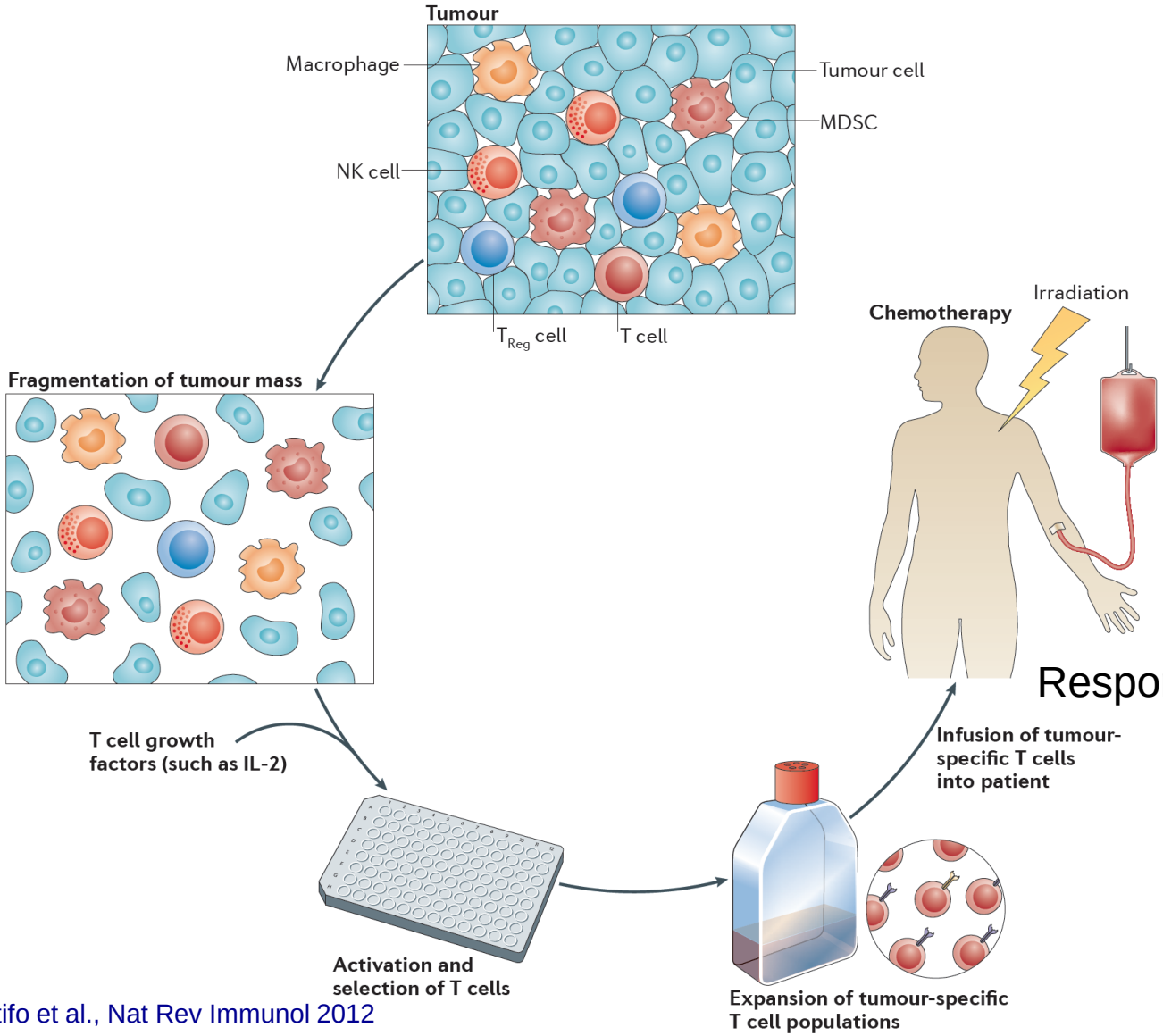
Cancer Research

Immunotype and Immunohistologic Characteristics of Tumor-Infiltrating Immune Cells Are Associated with Clinical Outcome in Metastatic Melanoma

Gulsun Erdag, Jochen T. Schaefer, Mark E. Smolkin, et al.

Cancer Res 2012;72:1070-1080. Published OnlineFirst January 19, 2012.

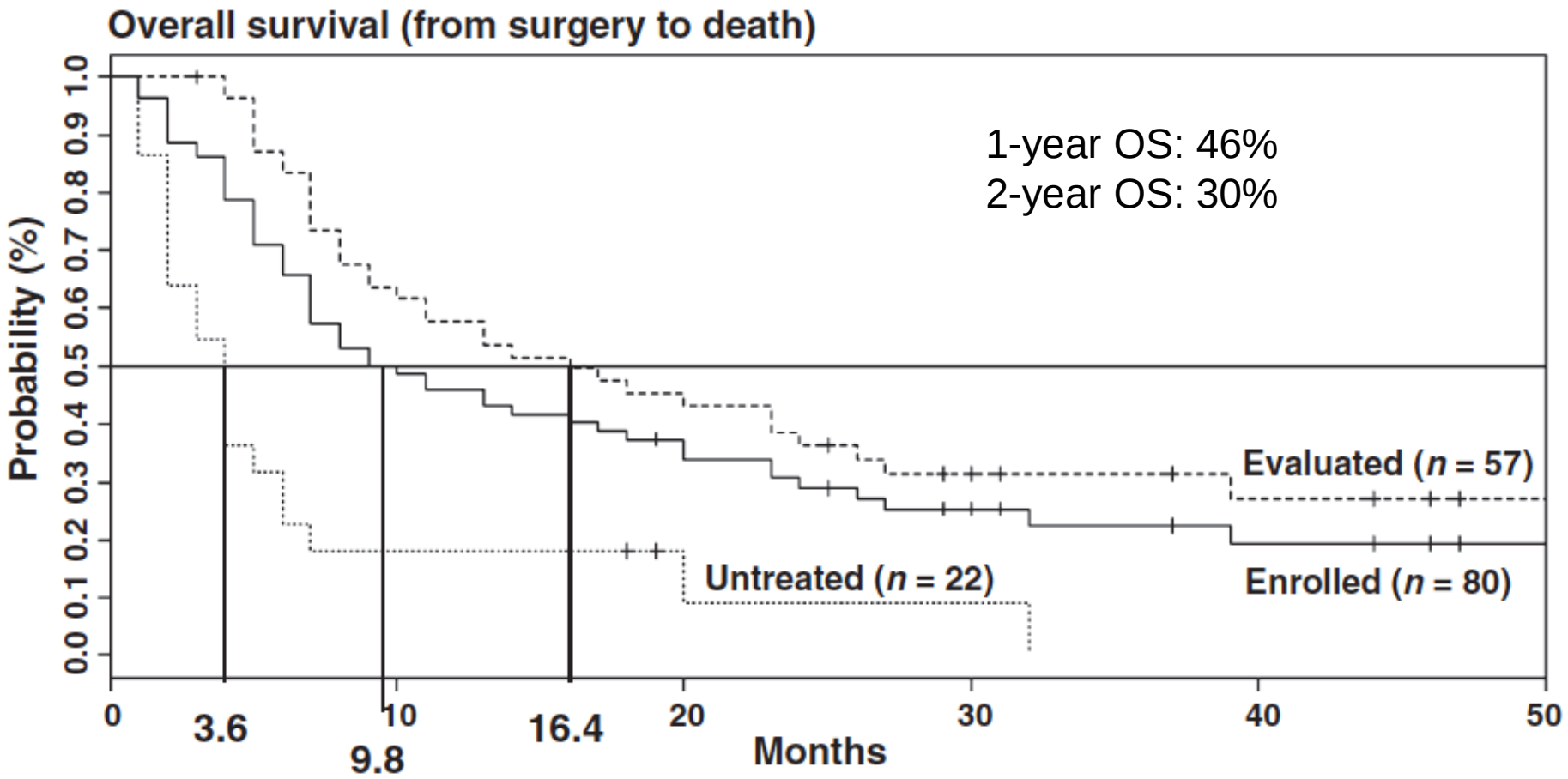
Tumor infiltrating lymphocytes: TIL therapy in melanoma



Response rate 40-70%

From: Restifo et al., Nat Rev Immunol 2012

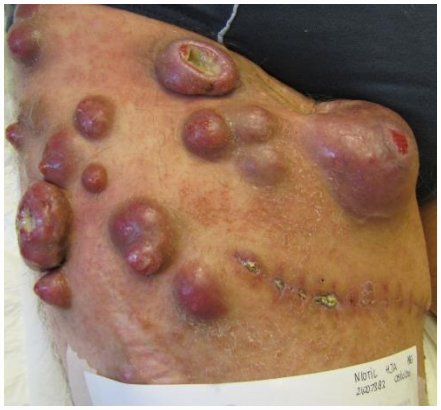
Overall survival of metastatic melanoma patients treated with TIL (ITT analysis)



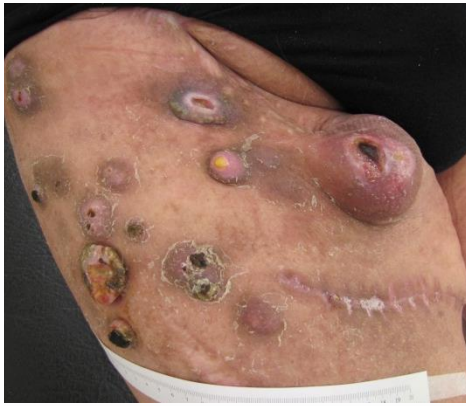
Besser et al., Clin Canc Res 2013

Clinical data N10TIL003: ongoing complete response 4 years

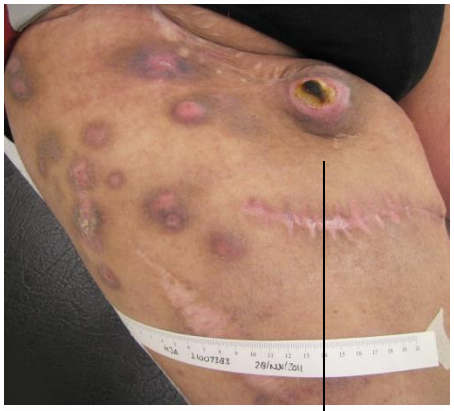
Prior to TIL



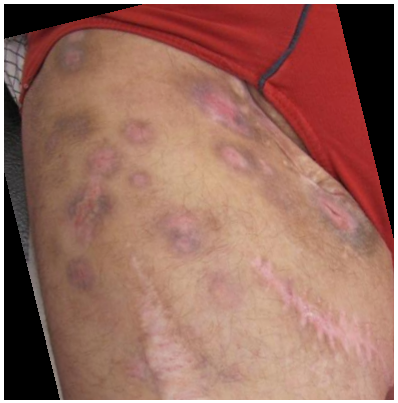
3 wks post TIL



8 wks post TIL



12 wks post TIL

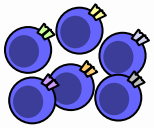


Biopsy at wk 7 showed no viable tumor cells

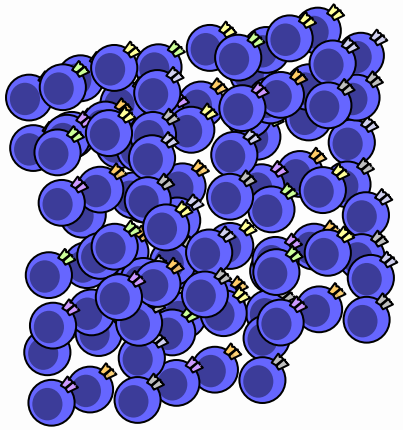
NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Immunotherapy of melanoma: TIL therapy

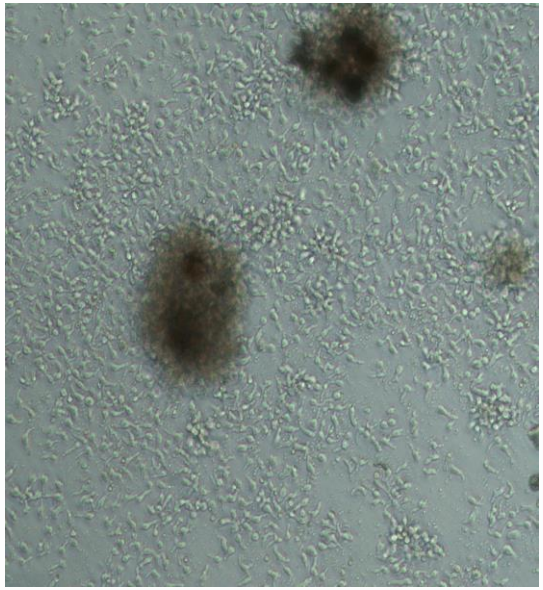
TIL are grown from melanoma tumors



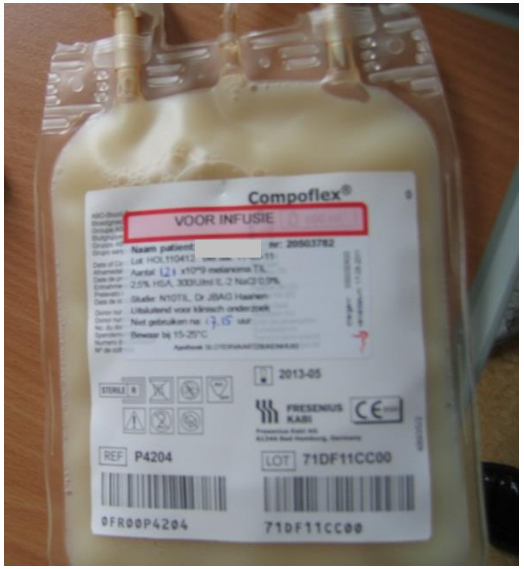
Rapid Expansion



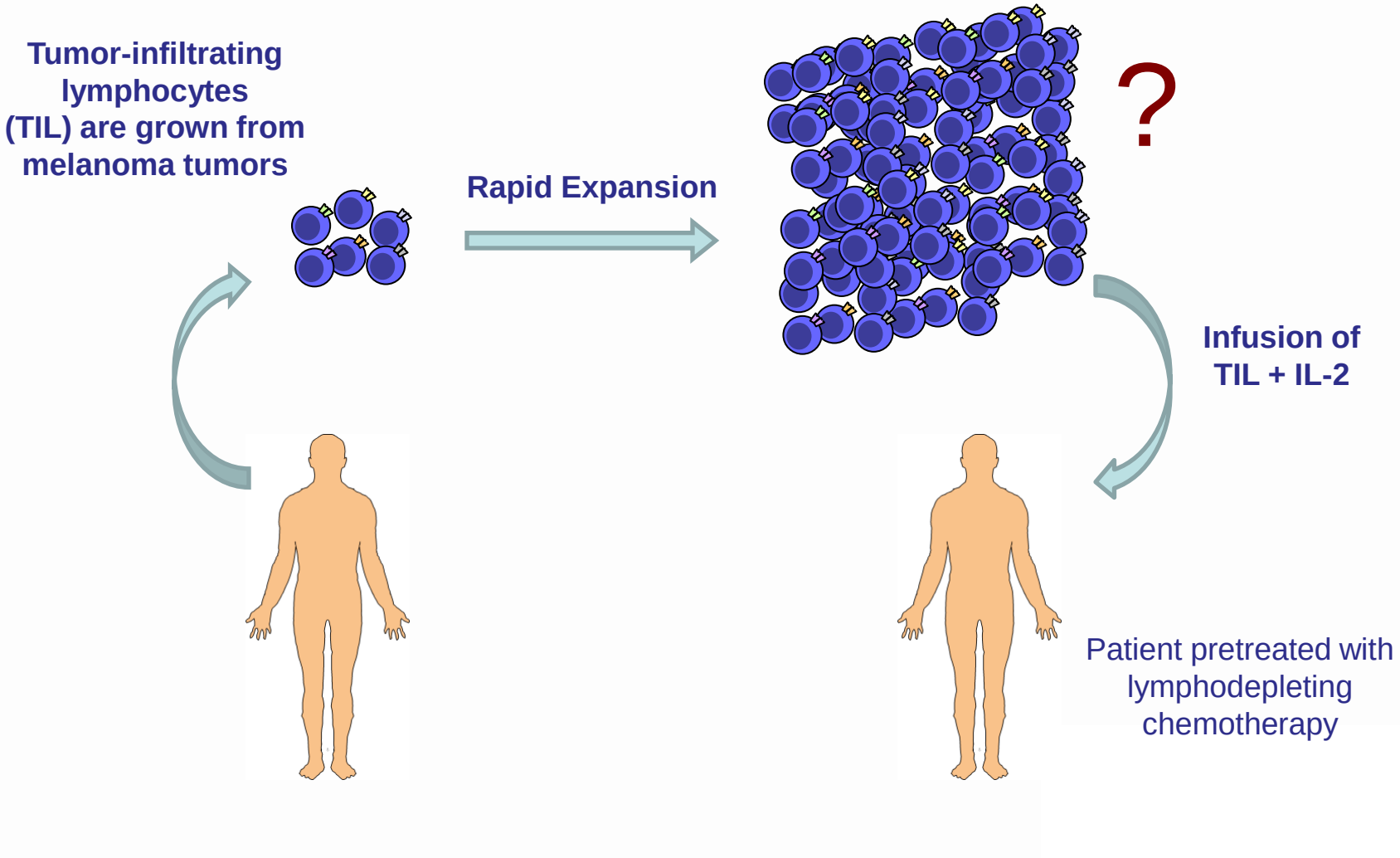
A few million T cells



$1x10^{11}$ T cells

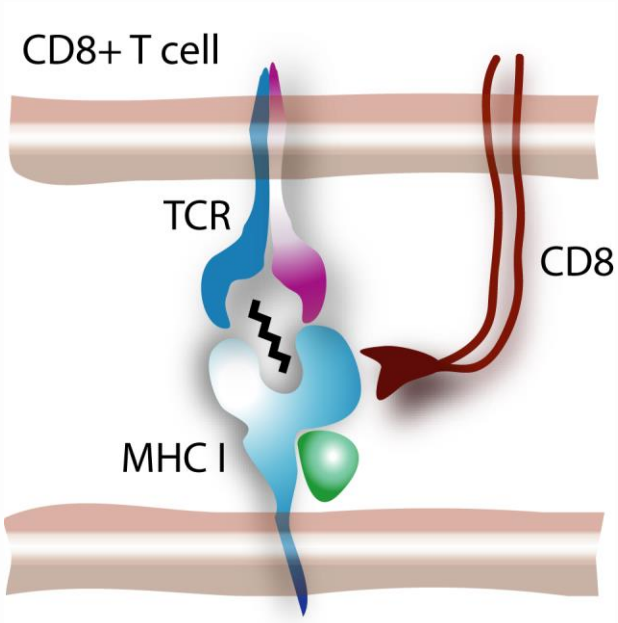


The big unknown



- Which cytotoxic T cells mediate cancer regression?
  - Could we specifically boost their numbers?

What could tumor-specific cytotoxic T cells detect on human cancer?

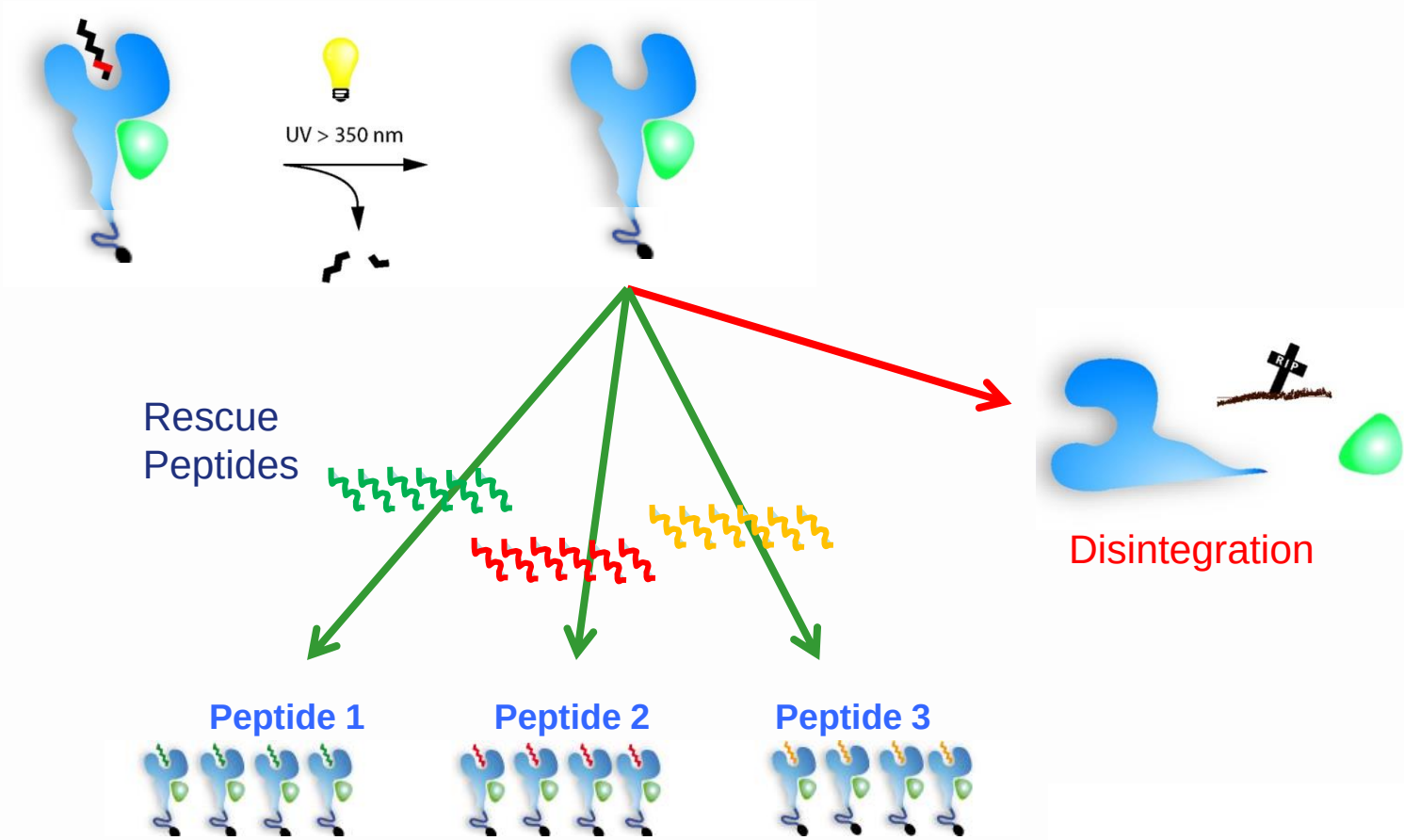


1. Self antigens (to which tolerance is incomplete)
   Shared between patients

2. 'Neo-antigens', epitopes that arise as a consequence of tumor-specific mutations
   In large part patient-specific, hence generally ignored

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

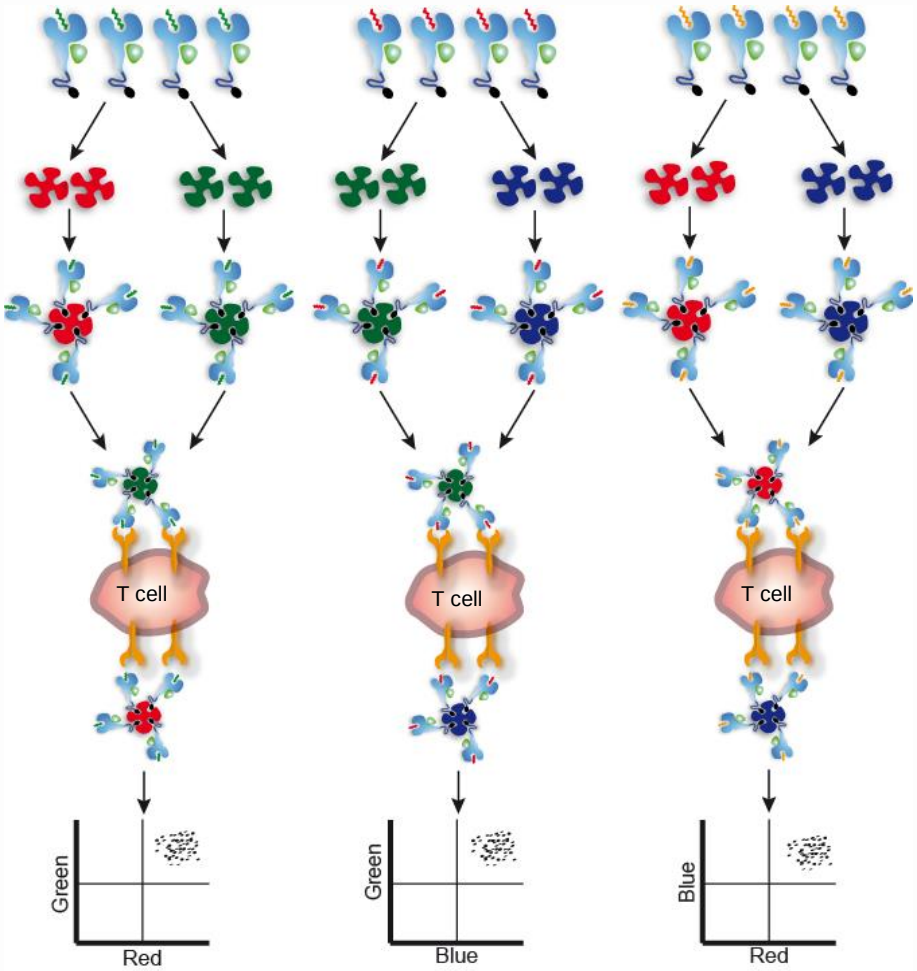
Generation of pMHC multimers by UV-induced peptide exchange



Allows generation of 1000s of pMHC in parallel

Toebes et al. *Nat. Med.* 2006
Bakker et al. *PNAS* 2008

Self-assembling molecular codes



Generate fluorochrome conjugated MHC multimers

Mix to create a collection of differentially encoded MHC multimers

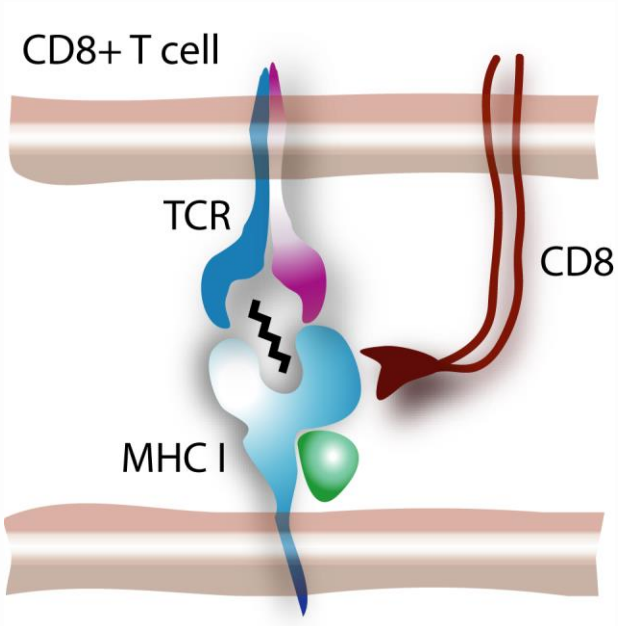
Assembly of combinatorial codes on T cell surfaces

Analysis by flow cytometry

Allows detection of 47 T cell responses in parallel

Hadrup et al, *Nat Methods* 2009, Andersen et al, *Nat Prot* 2012.

What could tumor-specific cytotoxic T cells detect on human cancer?



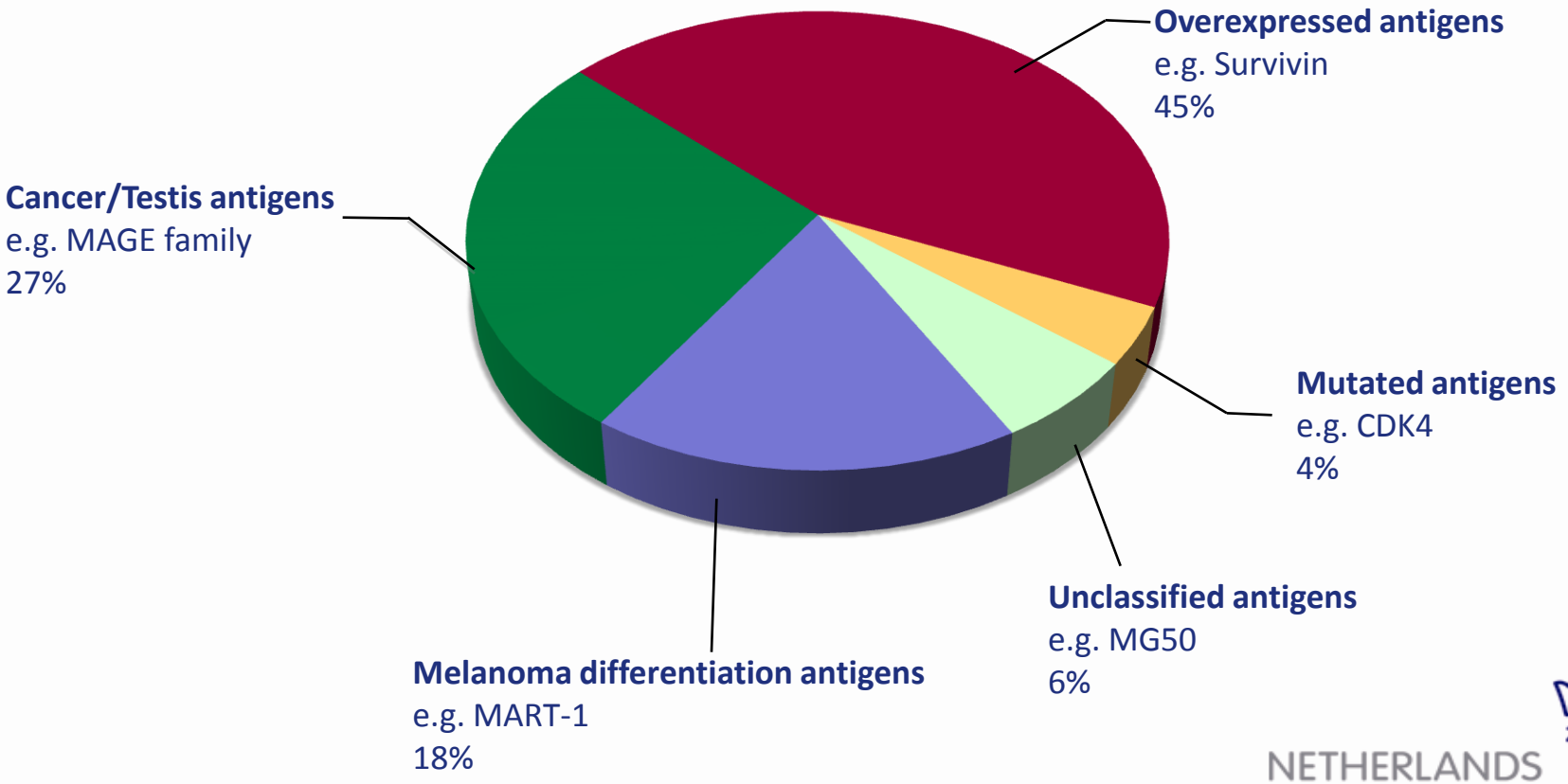
1. Self antigens (to which tolerance is incomplete)
   Shared between patients

2. 'Neo-antigens', epitopes that arise as a consequence of tumor-specific mutations
   In large part patient-specific, hence generally ignored

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Melanoma associated epitope panel

HLA-A2 restricted peptide panel includes 145 epitopes

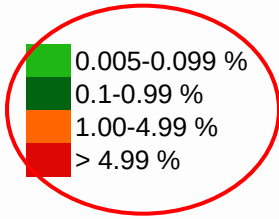


NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Kvistborg et al., Oncoimmunology 2012

Visualizing the composition of TIL

T cell responses are very low magnitude



		Young CD8 enriched TIL (NIH)																		Young TIL (Ella)						Selected TIL											
	Patient	LR	LN	KS	MV	CR	ER	MA	LD	SW	HE	AS	RE	OJ	AS	MG	NJ	BJ(f)*	SC*	57SV	63SM	51VS	60SD	41BA	52SD	14PA	09BY	31YR	PS	OM	BJ(m)	SM	ER	CR	BM	CJ	AD
MDA	Mart-1 ELA																																				
	gp100 IMD																																				
	gp100 YLE																																				
	gp100 VLY																																				
	gp100 AML																																				
	gp100 KTW																																				
	TRP2 VYD																																				
	TRP2 SVY																																				
	NY-MEL 1 VLH																																				
CT	CML28 AVL																																				
	Mage A4 GVY																																				
	MAGE A10 GLY																																				
	MageB1, B2 FLW																																				
	MAGE C2 LLF																																				
	MAGE C2 ALK																																				
	NY-ESO 1 SLL																																				
	HERV K mel MLA																																				
	SSX-2 KAS																																				
OE	GnTV VLP																																				
	GnT-V VLP10mer																																				
	Meloe-1 TLN																																				
	Telomerase RLF																																				
	Bing 4 CQW																																				
	Clinical response	NR	NR	NR	PR	PR	NR	NR	PR	PR	PR	NR	NR	NR	NR	PR	NR	NR	CR	PR	NR	PR	NR	NR	PR	CR	NR	NR	PR	PR	CR	PR	PR	NR	NR	CR	NR

Kvistborg et al., Oncoimmunology 2012

TILs against shared tumor antigens

- In the majority of TILs T cells specific for shared antigens can be found
  - Melanocyte differentiation Ags (Mart-1, gp100, etc)
  - Cancer/Testis gene products (NY-eso-1, MAGE, SSX-2, etc
  - Overexpressed Ags (Meloe etc.)
- Low frequency (mostly below 1%)
- No correlation with response

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

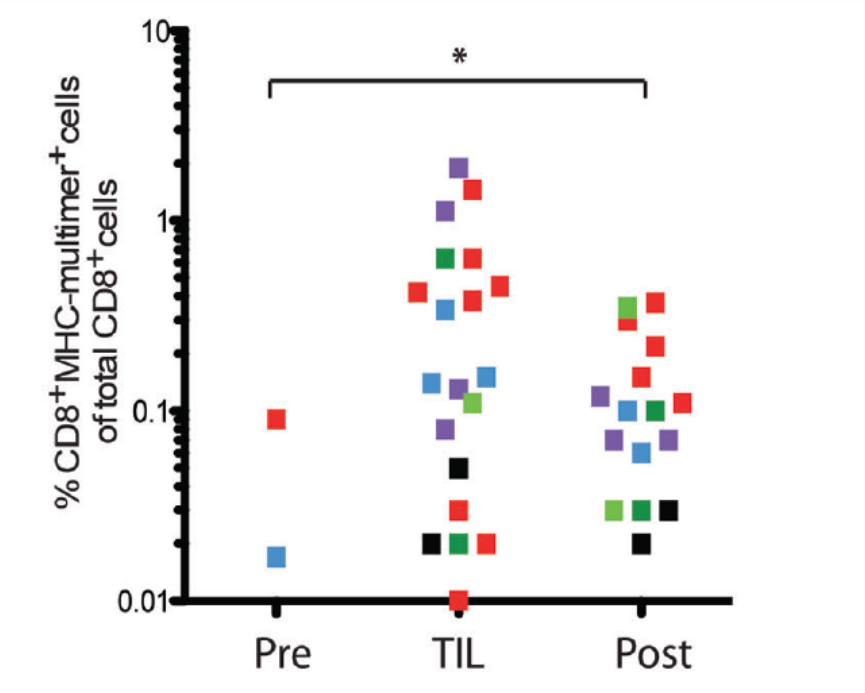
Kvistborg et al., Oncoimmunology 2012

RESEARCH PAPER

OncoImmunology 1:4, 409–418; July 2012; © 2012 Landes Bioscience

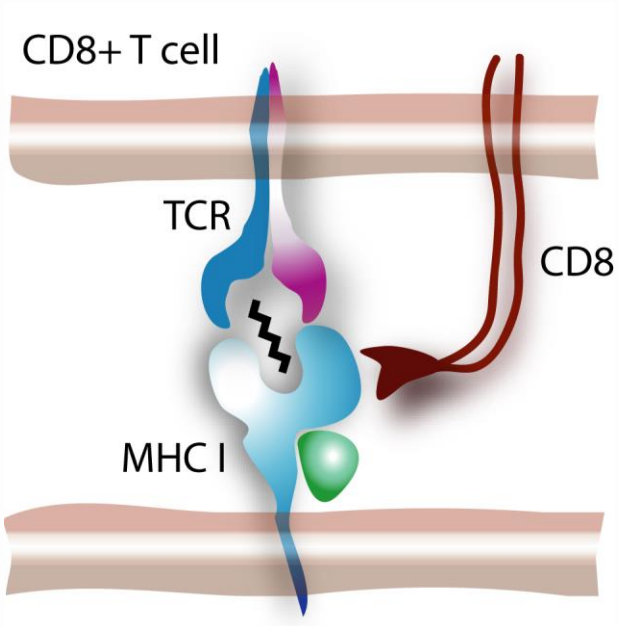
TIL therapy broadens the tumor-reactive CD8+ T cell compartment in melanoma patients

Pia Kvistborg,[1,†] Chengyi Jenny Shu,[1,†] Bianca Heemskerk,[1] Manuel Fankhauser,[1] Charlotte Albæk Thrue,[2] Mireille Toebes,[1] Nienke van Rooij,[1] Carsten Linnemann,[1] Marit M. van Buuren,[1] Jos H.M. Urbanus,[1] Joost B. Beltman,[3] Per thor Straten,[2] Yong F. Li,[4] Paul F. Robbins,[4] Michal J. Besser,[5,6] Jacob Schachter,[5] Gemma G. Kenter,[7] Mark E. Dudley,[4] Steven A. Rosenberg,[4] John B.A.G. Haanen,[1] Sine Reker Hadrup[2] and Ton N.M. Schumacher[1,*]



NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

What could tumor-specific cytotoxic T cells detect on human cancer?

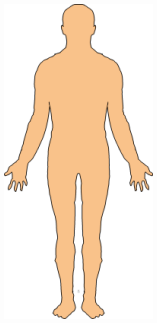


1. Self antigens (to which tolerance is incomplete)
   Shared between patients

2. ‘Neo-antigens’, epitopes that arise as a consequence of tumor-specific mutations
   In large part patient-specific, hence generally ignored

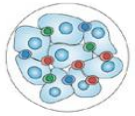
NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Pt 003: complete response upon TIL therapy



Resected tumor material

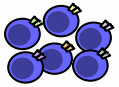
Isolate tumor cells



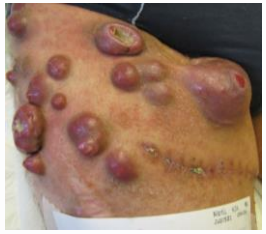
Identify tumor-specific mutations

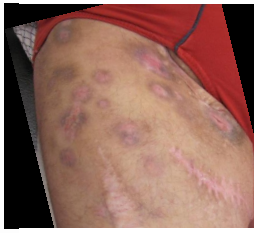
Predict potential epitopes

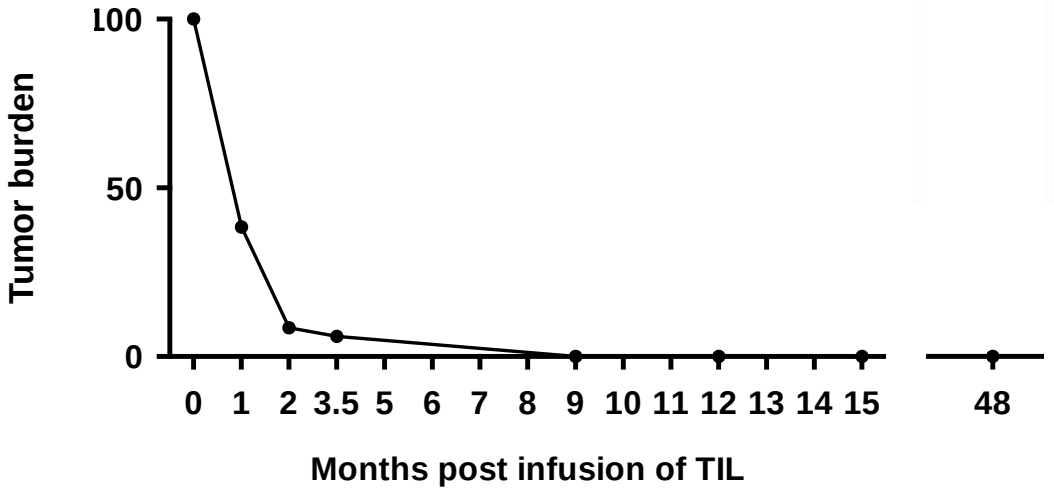
Isolate tumor-infiltrating T cells



Screen with MHC multimer technology

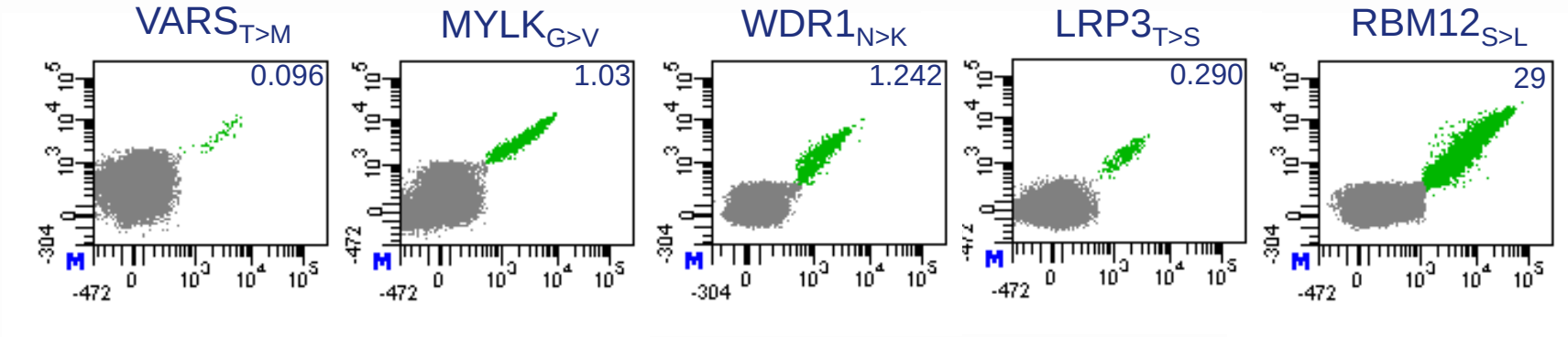






Pt 003: complete response upon TIL therapy

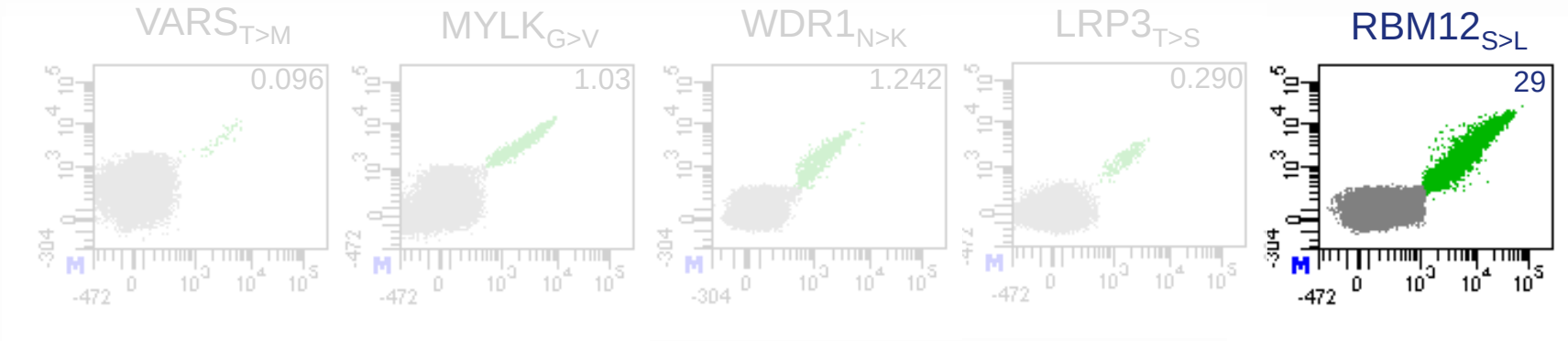
TIL infusion product



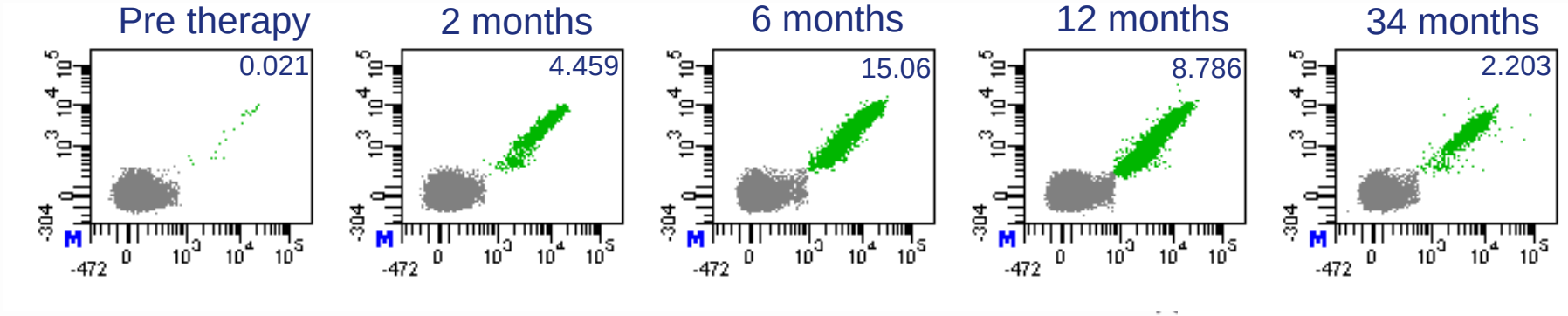
NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Pt 003: complete response upon TIL therapy

TIL infusion product

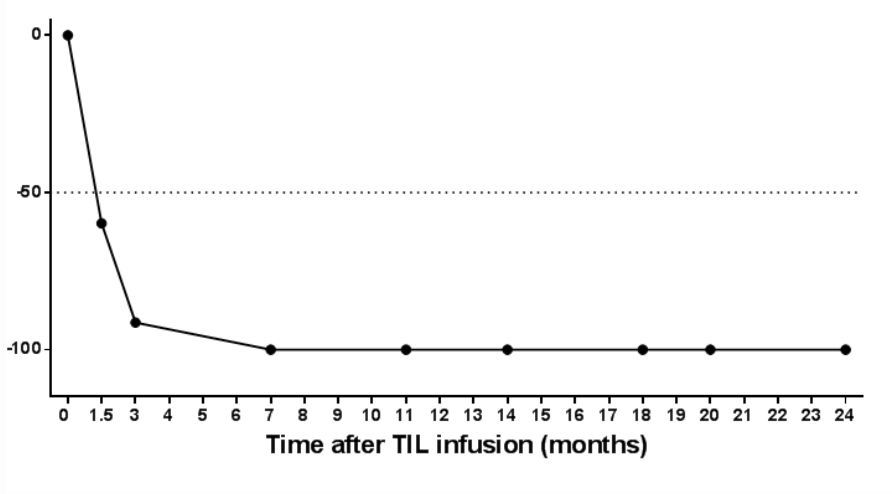


Peripheral blood

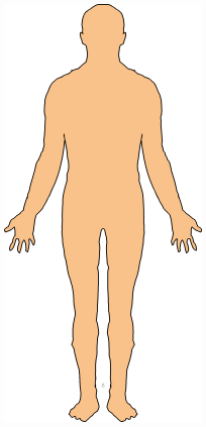


>450 fold increase in neo-antigen specific T cell reactivity upon TIL therapy

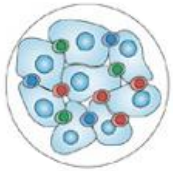
Pt 008: CR upon TIL therapy



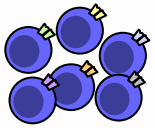
Resected tumor material



Isolate tumor cells



Isolate tumor-infiltrating T cells



Screen with MHC multimer technology

Identify tumor-specific mutations

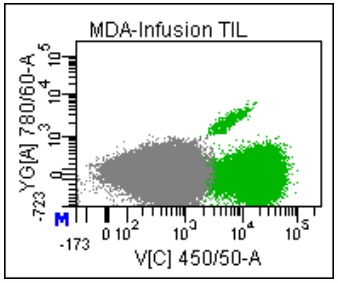
Predict potential epitopes

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Pt 008: CR upon TIL therapy

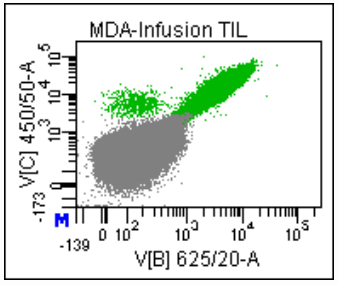
Infusion TIL product

0.172%



RASSF1$_{R>C}$

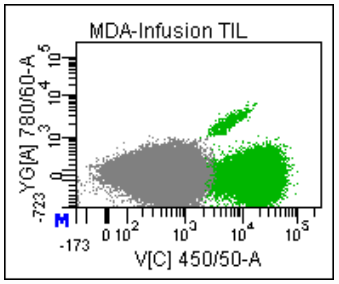
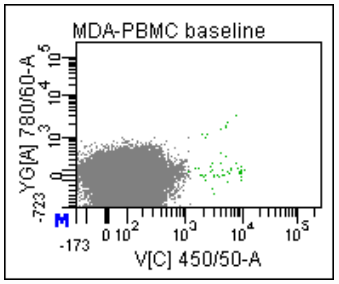
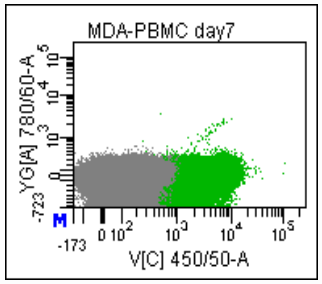
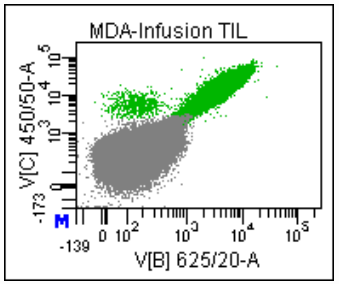
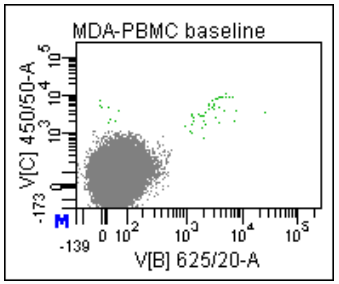
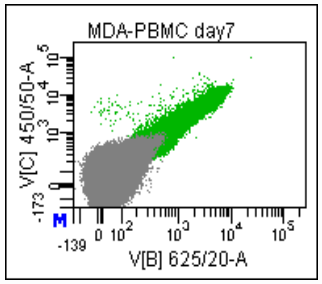
23%



DHX33$_{R>W}$

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Pt 008: CR upon TIL therapy

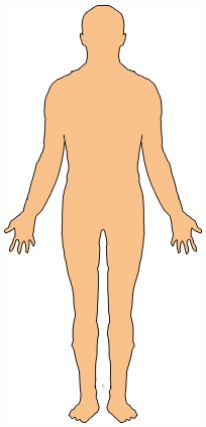
Infusion TIL product	Pre-therapy PBMNC	D7 post-therapy	
0.172%	0.002%	0.010%	**RASSF1$_{R>C}$**
			
23%	0.009%	54%	**DHX33$_{R>W}$**
			

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

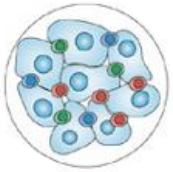
Major (>5000 fold) increase in neo-antigen specific T cell reactivity upon TIL therapy

Pt 004:

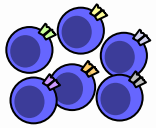
Resected tumor material



Isolate tumor cells



Isolate tumor-infiltrating T cells



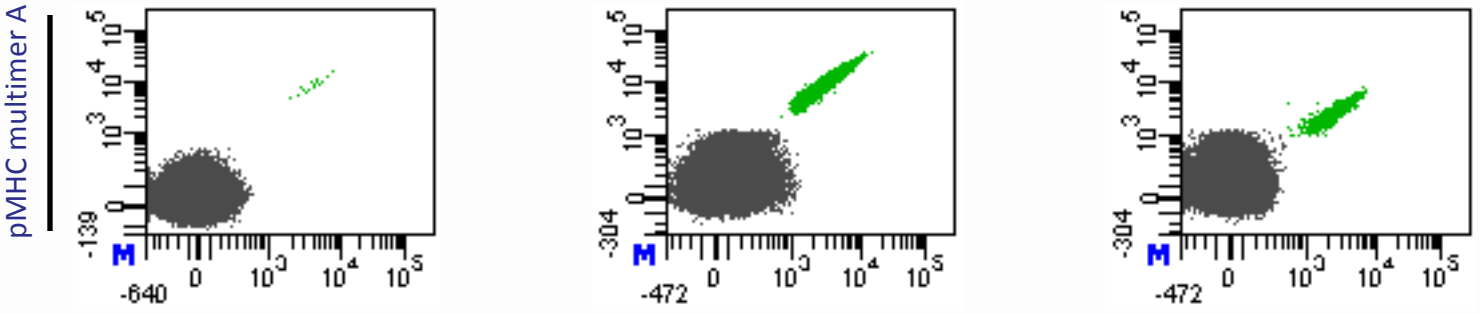
Screen with MHC multimer technology

Identify tumor-specific mutations

Predict potential epitopes

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Pt 004:



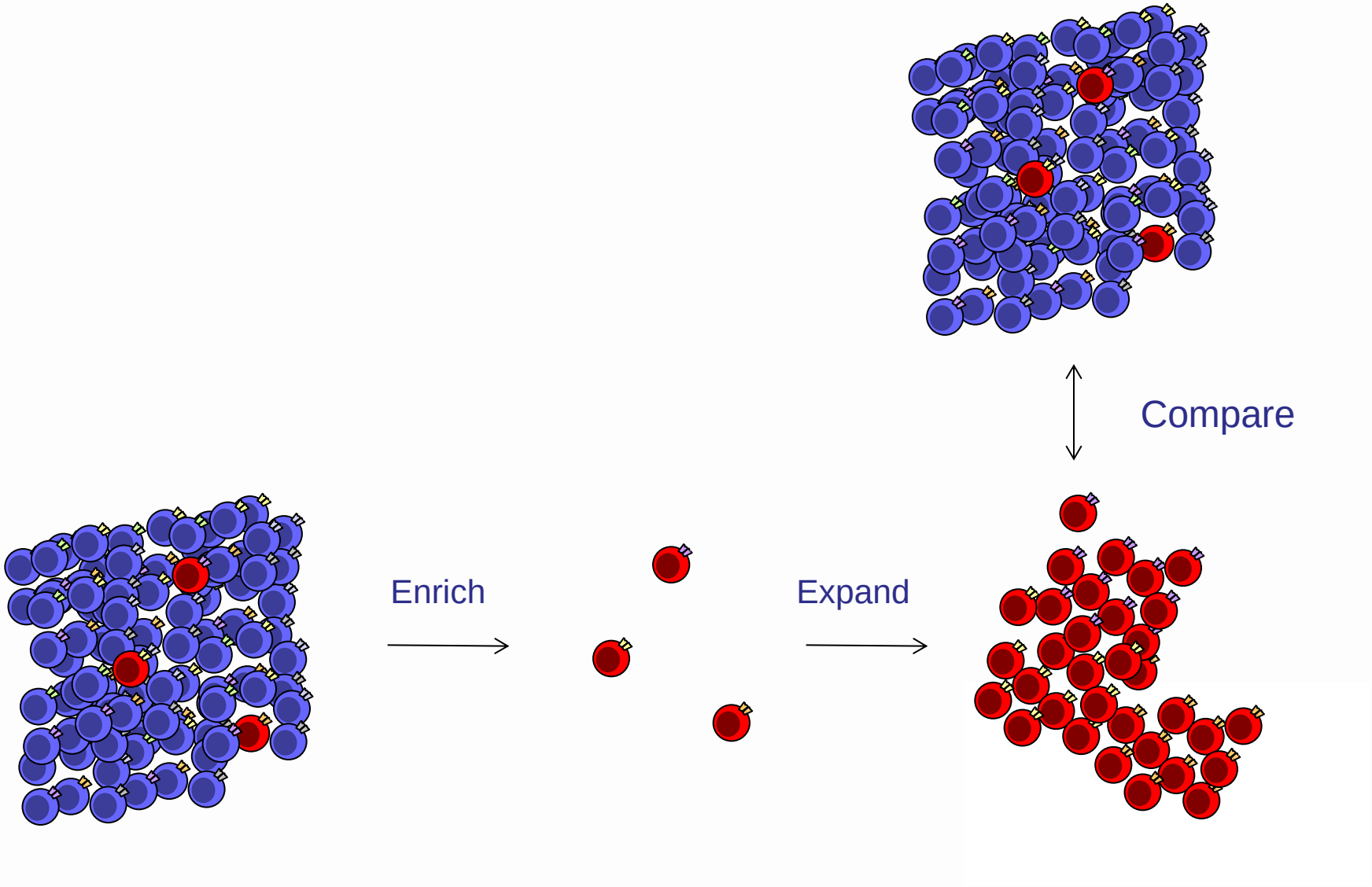
DNAH17$_{H>Y}$ (0.003%)
VLFEDAVA**H** > VLFEDAVA**Y**

CDK4$_{R>L}$ (1.604%)
A**R**DPHSGHFV > A**L**DPHSGHFV

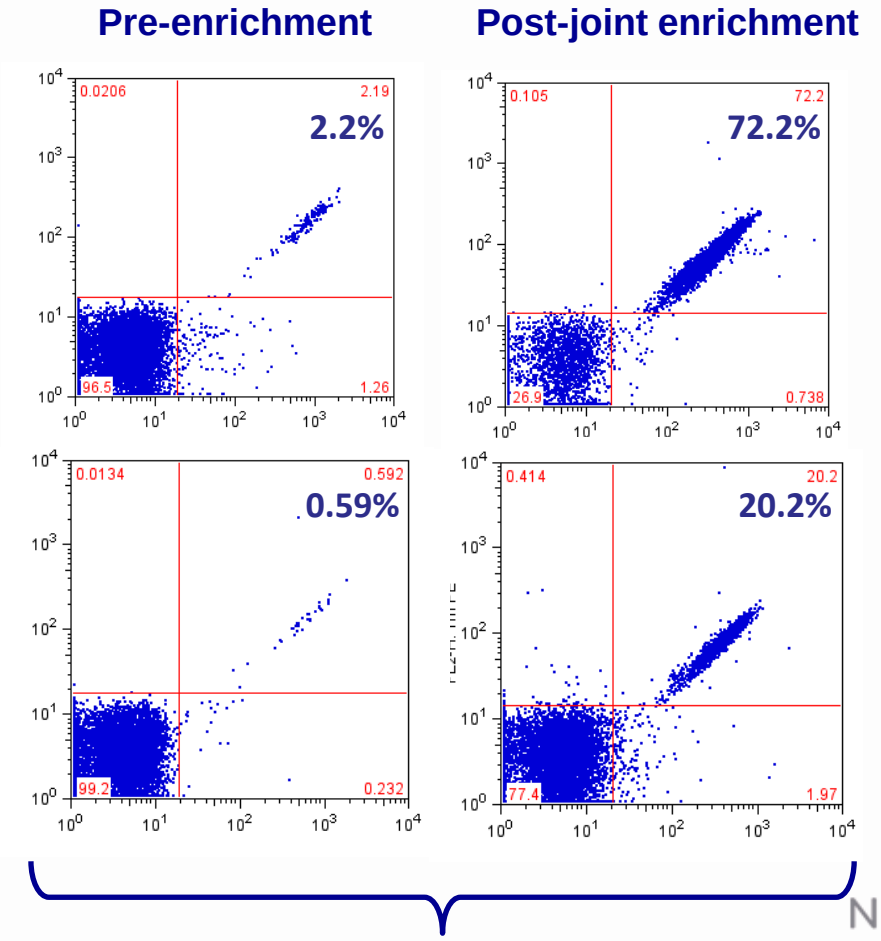
GCN1L1$_{L>P}$ (0.407%)
ALLET**L**SLLL > ALLET**P**SLLL

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Are neo-antigens superior cancer rejection antigens?

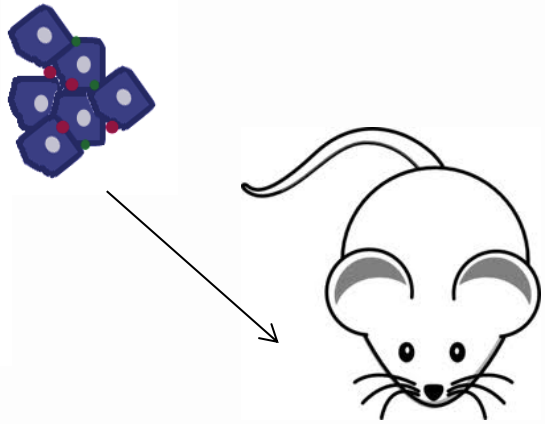


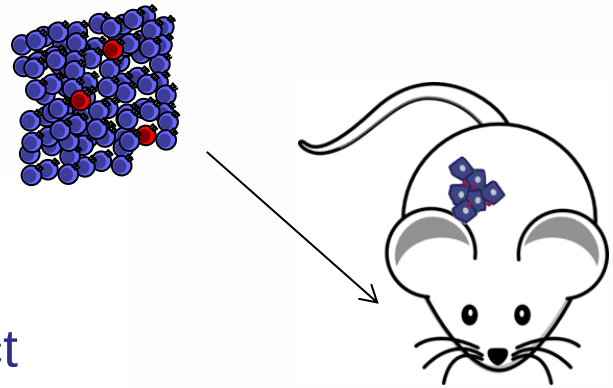
Are neo-antigens superior cancer rejection antigens?



NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

1)
Inject human
melanoma
(NSG-mice)

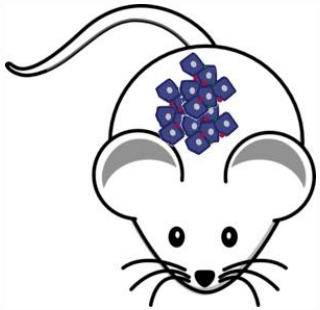




2a)
Inject autologous
bulk T-cell product

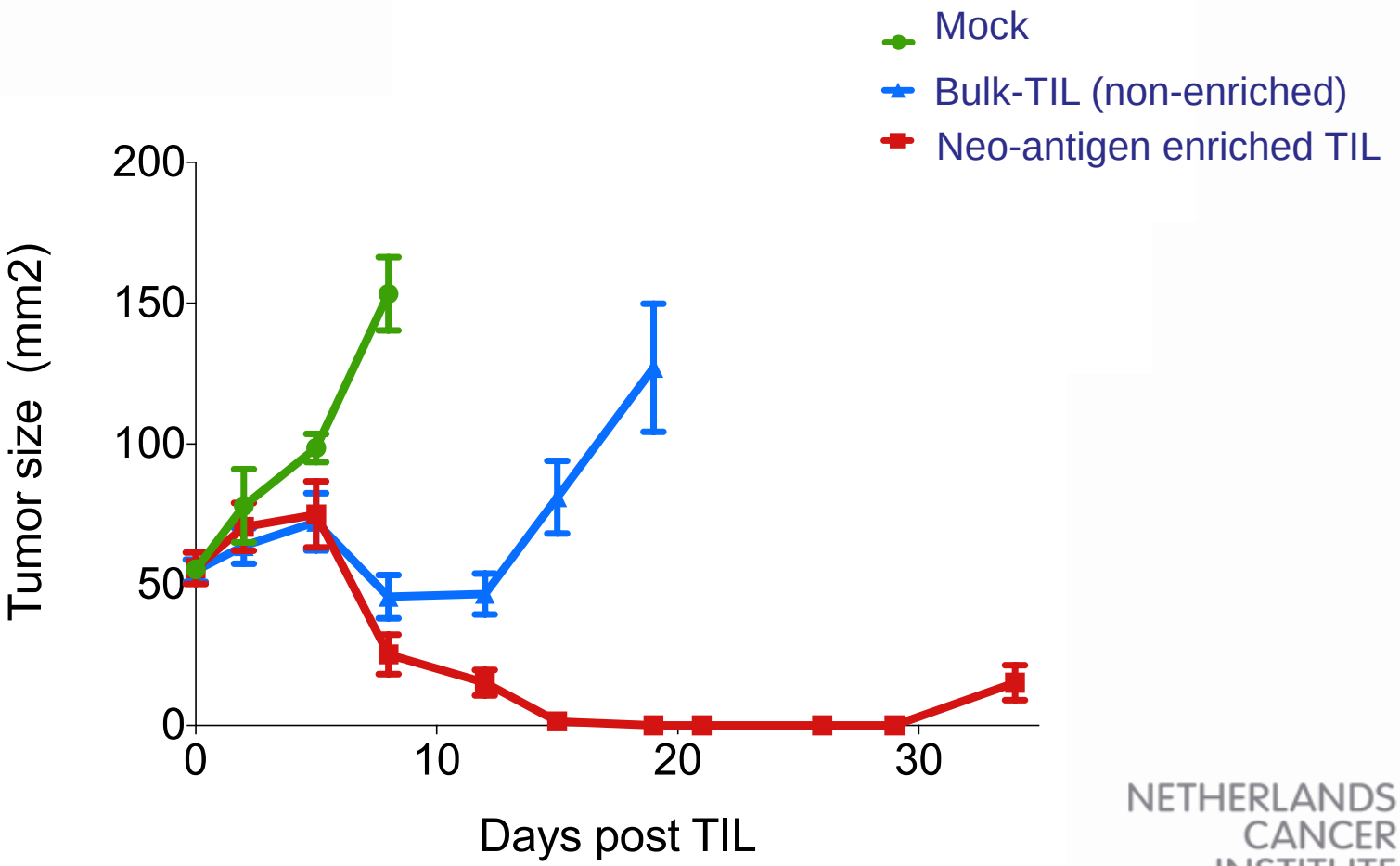
2b)
Inject autologous
neo-Ag enriched
T-cell product

3)
Monitor tumor growth



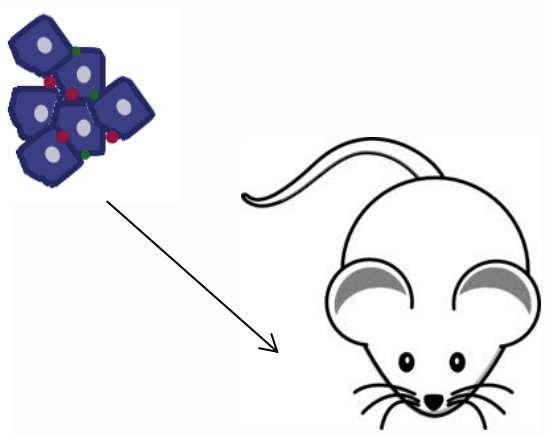
NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Neo-antigen enriched TIL can mediate superior tumor control



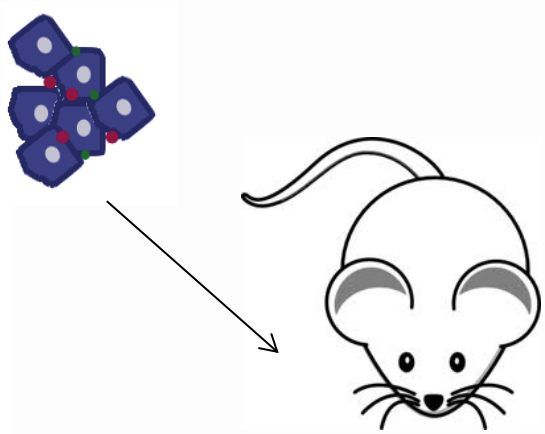
NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

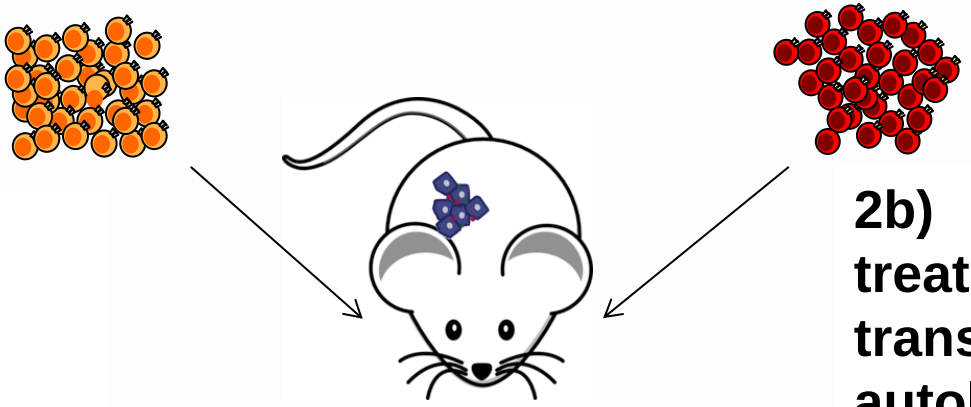
1)
Create human melanoma PDX model
(NSG-mice)



NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

1)
Create human melanoma PDX model
(NSG-mice)





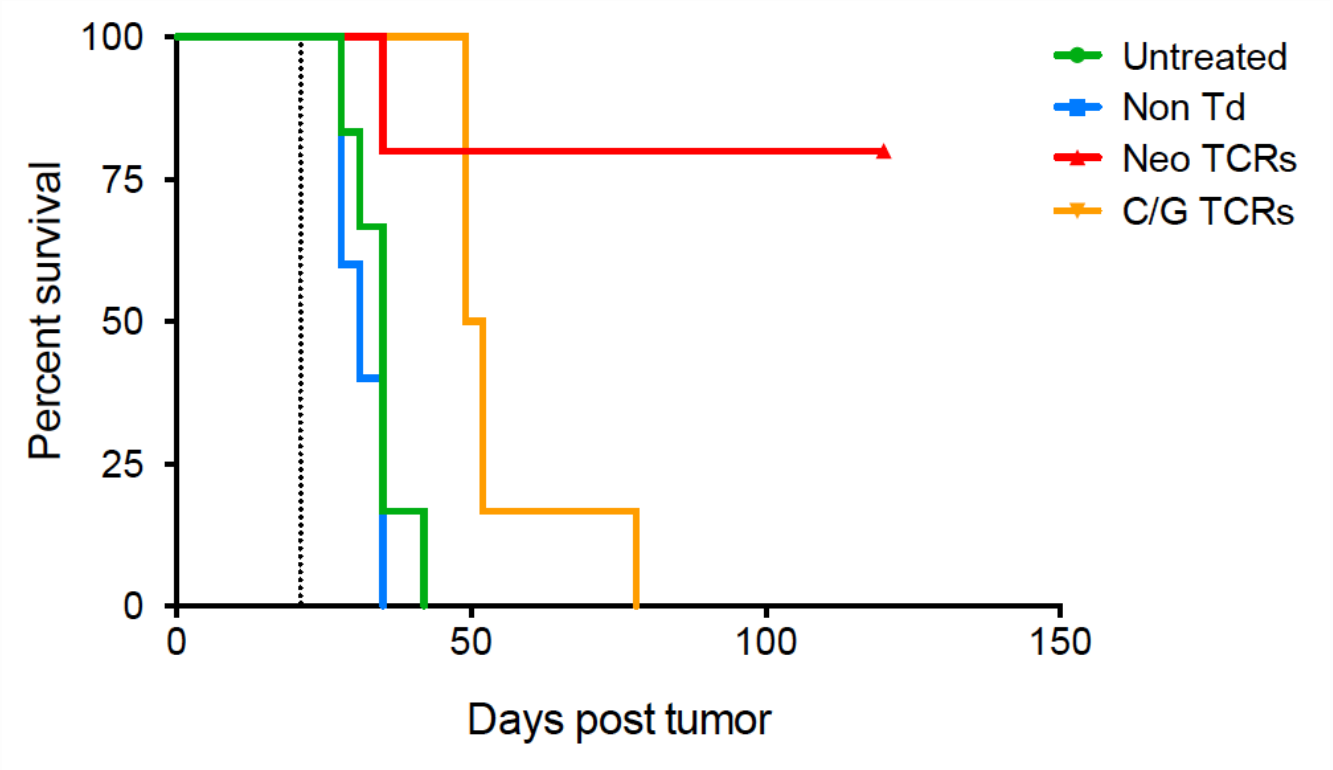
2a)
treat with T cells transduced with autologous C/T Ag specific TCRs

2b)
treat with T cells transduced with autologous Neo Ag specific TCRs

Assess whether neo-antigen specific TCRs outperform C/G specific TCRs

Do neo-antigen specific TCRs* outperform C/G antigen specific TCRs**?

caution: n=1 expt, repeat ongoing



NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

* 2 TCRs, against CDK4 and GCN1L1 neo-antigens

** 4 TCRs, against 3 MAGE-C2 epitopes, 1 MAGE-A10 epitope

What have we learned from TIL therapy?

- TIL contain oftentimes many melanoma-specific CD8 and CD4 T cell populations
  - Against shared antigens (MDA, C/T, overexpressed)
  - Against neo-antigens
- Upon infusion of TIL, the tumor-reactive CD8 and CD4 T cell compartment is broadened in melanoma patients

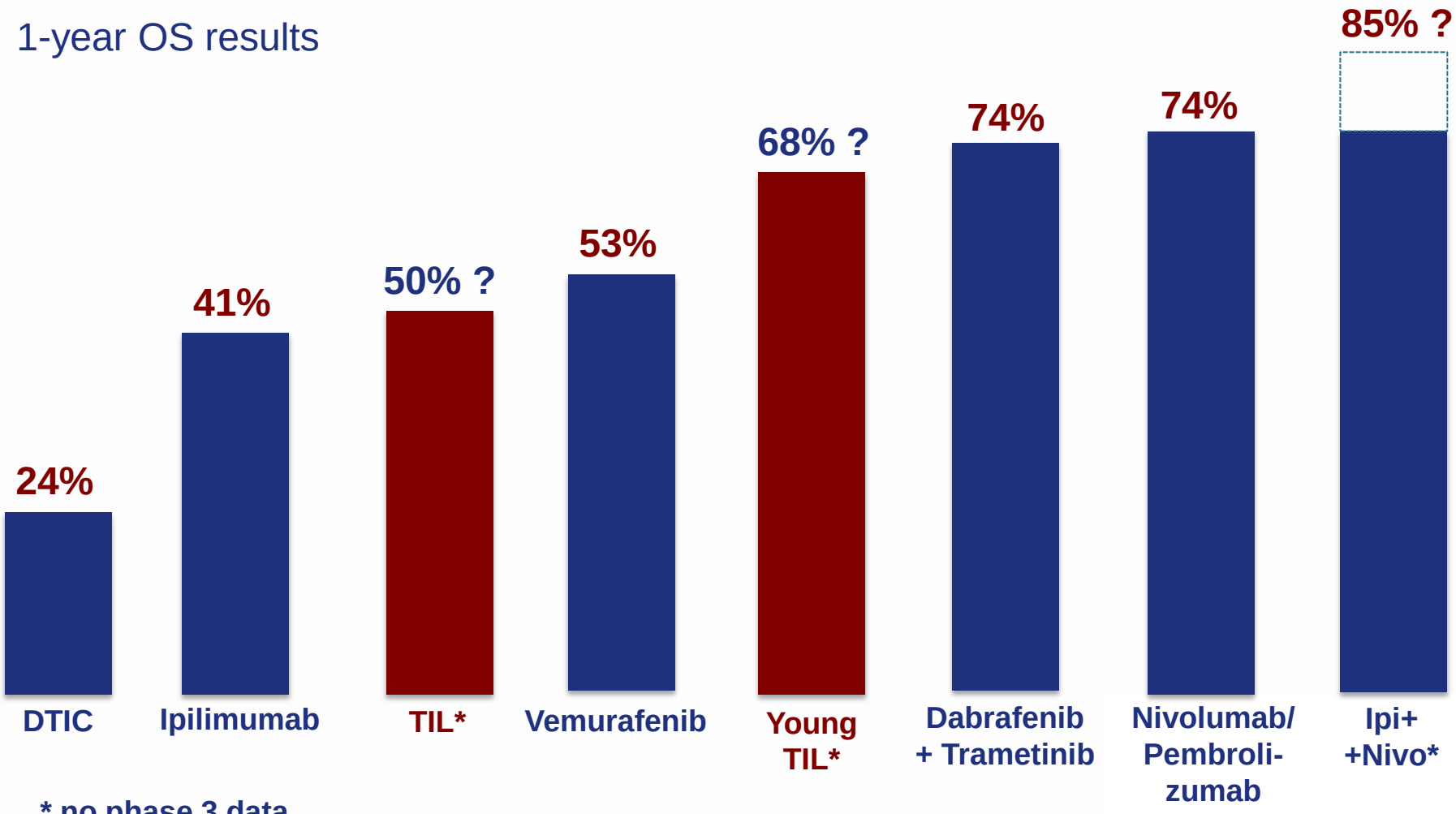
NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

What have we learned from TIL therapy?

- Objective clinical response rates vary between 38% and 72% of treated melanoma patients in phase II clinical trials (mostly heavily pretreated pts)
- Median OS in this group 16 months
- Patients with CR upon TIL have an excellent prognosis

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

How does TIL compare to other therapies?



McArthur et al. Lancet Oncol 2014; Hodi et al. NEJM 2010; based on Rosenberg and Dudley Curr Opin Immunol 2009; McArthur et al. Lancet Oncol 2014; based on Dudley et al. JCO 2013; Long et al. Lancet 2015; based on Robert et al. NEJM 2015; prediction based on Larkin et al. NEJM 2015 and Sznol et al. ASCO 2014

Comparison between TIL and checkpoint inhibitors

- TIL: one treatment
- Surgery is required
- Complex GMP and patient specific production process
- Drop-out rate up to 25% of pts
- In hospital (2-3 weeks)
- Predictable and manageable side-effects
- High treatment costs

- Ipilimumab: 4 infusions
- Anti-PD1: >>4 infusions
- Off-the-shelf product
- No ipilimumab in LDH > 2x ULN
- Outpatient clinic
- Unpredictable, but manageable side effects
- Even higher treatment costs

How to further develop TIL therapy

1. Approval of TIL therapy as treatment option for MM
   - RCT
   - A large phase II trial in checkpoint inh failing pts
2. Enrichment for tumor-reactive TIL

3. Generate a personalized TIL product

4. Expand TIL therapy beyond melanoma

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

How to further develop TIL therapy

1. Approval of TIL therapy as treatment option for MM
   - RCT
   - A large phase II trial in checkpoint inh failing pts
2. Enrichment for tumor-reactive TIL
3. Generate a personalized TIL product
4. Expand TIL therapy beyond melanoma

Taking the next step for TIL based ACT

Randomized phase III study comparing TIL based ACT to standard ipilimumab treatment in metastatic melanoma

To obtain EMA approval of 'classical' TIL therapy as an ATMP

- **NL:**
  - **John Haanen**: NKI-AVL, Amsterdam, The Netherlands
- **DK:**
  - **Inge Marie Svane**: Herlev Hospital, Copenhagen,
- **UK:**
  - **Robert Hawkins**: University of Manchester and the Christie NHS Foundation Trust, UK

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Phase II trial in refractory MM patients

- Lion Biotechnology

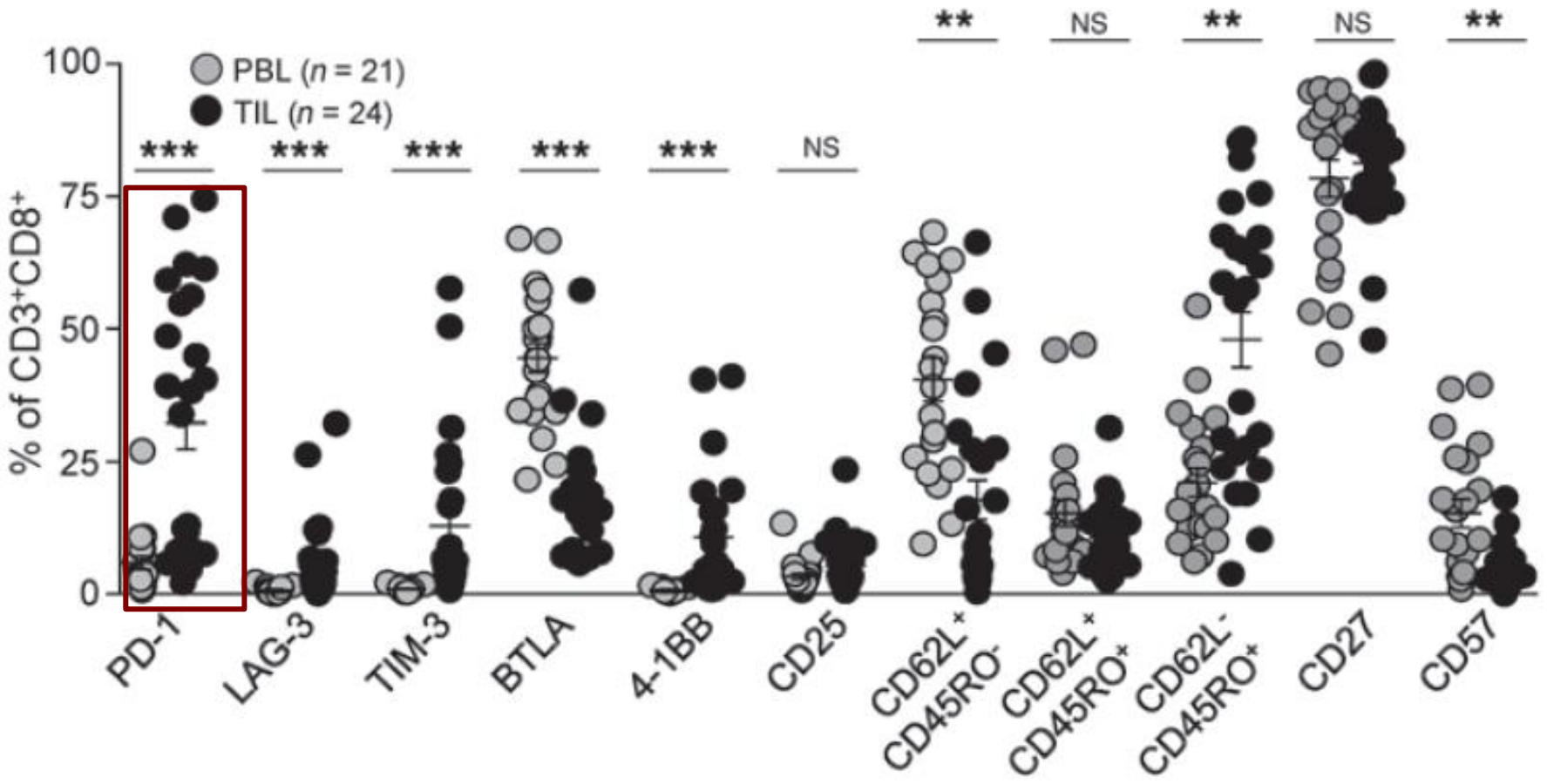
Pipeline

Sponsor	Indication	Phase 1	Phase 2	Phase 3
NCI/Lion Bio	2nd line metastatic melanoma	→ *Phase 2 Complete*		
NCI/Lion Bio	1st line metastatic melanoma in combination with vemurafenib	→ *Phase 1 in progress*		
Moffitt Cancer Center	1st line metastatic melanoma in combination with ipilimumab	→ *Pilot trials in progress*		
	1st line metastatic melanoma in combination with nivolumab	→ *Pilot trials in progress*		

How to further develop TIL therapy

1. Approval of TIL therapy as treatment option for MM
   - RCT
   - A large phase II trial in checkpoint inh failing pts
2. Enrichment for tumor-reactive TIL
3. Generate a personalized TIL product
4. Expand TIL therapy beyond melanoma

PD1 identifies patient-specific tumor-reactive TIL



Gros et al., J Clin Invest 2015

How to further develop TIL therapy

1. Approval of TIL therapy as treatment option for MM
   - RCT
   - A large phase II trial in checkpoint inh failing pts
2. Enrichment for tumor-reactive TIL

3. Generate a personalized TIL product

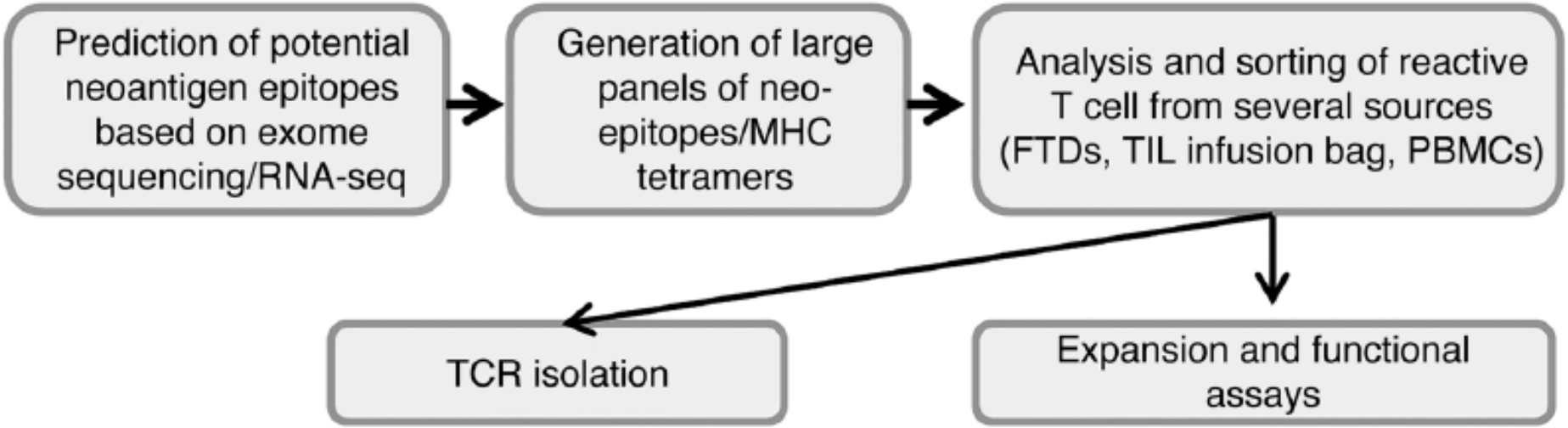
4. Expand TIL therapy beyond melanoma

The Journal of Clinical Investigation RESEARCH ARTICLE

Isolation of neoantigen-specific T cells from tumor and peripheral lymphocytes

Cyrille J. Cohen,[1,2] Jared J. Gartner,[2] Miryam Horovitz-Fried,[1] Katerina Shamalov,[1] Kasia Trebska-McGowan,[2] Valery V. Bliskovsky,[3] Maria R. Parkhurst,[2] Chen Ankri,[1] Todd. D. Prickett,[2] Jessica S. Crystal,[2] Yong F. Li,[2] Mona El-Gamil,[2] Steven A. Rosenberg,[2] and Paul F. Robbins[2]

[1]Laboratory of Tumor Immunology and Immunotherapy, Goodman Faculty of Life Sciences, Bar-Ilan University, Ramat Gan, Israel. [2]Surgery Branch and [3]Laboratory of Cancer Biology and Genetics, National Cancer Institute (NCI), NIH, Bethesda, Maryland, USA.



Cohen et al., J Clin Invest 2015

How to further develop TIL therapy

1. Approval of TIL therapy as treatment option for MM
   - RCT
   - A large phase II trial in checkpoint inh failing pts
2. Enrichment for tumor-reactive TIL
3. Generate a personalized TIL product
4. Expand TIL therapy beyond melanoma

Cancer Immunotherapy Based on Mutation-Specific CD4+ T Cells in a Patient with Epithelial Cancer

Eric Tran,[1] Simon Turcotte,[1]* Alena Gros,[1] Paul F. Robbins,[1] Yong-Chen Lu,[1] Mark E. Dudley,[1]† John R. Wunderlich,[1] Robert P. Somerville,[1] Katherine Hogan,[1] Christian S. Hinrichs,[1] Maria R. Parkhurst,[1] James C. Yang,[1] Steven A. Rosenberg[1]‡

VOLUME 33 · NUMBER 14 · MAY 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Complete Regression of Metastatic Cervical Cancer After Treatment With Human Papillomavirus–Targeted Tumor-Infiltrating T Cells

Sanja Stevanović, Lindsey M. Draper, Michelle M. Langhan, Tracy E. Campbell, Mei Li Kwong, John R. Wunderlich, Mark E. Dudley, James C. Yang, Richard M. Sherry, Udai S. Kammula, Nicholas P. Restifo, Steven A. Rosenberg, and Christian S. Hinrichs

Sciencexpress

Immunogenicity of somatic mutations in human gastrointestinal cancers

Eric Tran, Mojgan Ahmadzadeh, Yong-Chen Lu, Alena Gros, Simon Turcotte,* Paul F. Robbins, Jared J. Gartner, Zhili Zheng, Yong F. Li, Satyajit Ray, John R. Wunderlich, Robert P. Somerville, Steven A. Rosenberg†

Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.

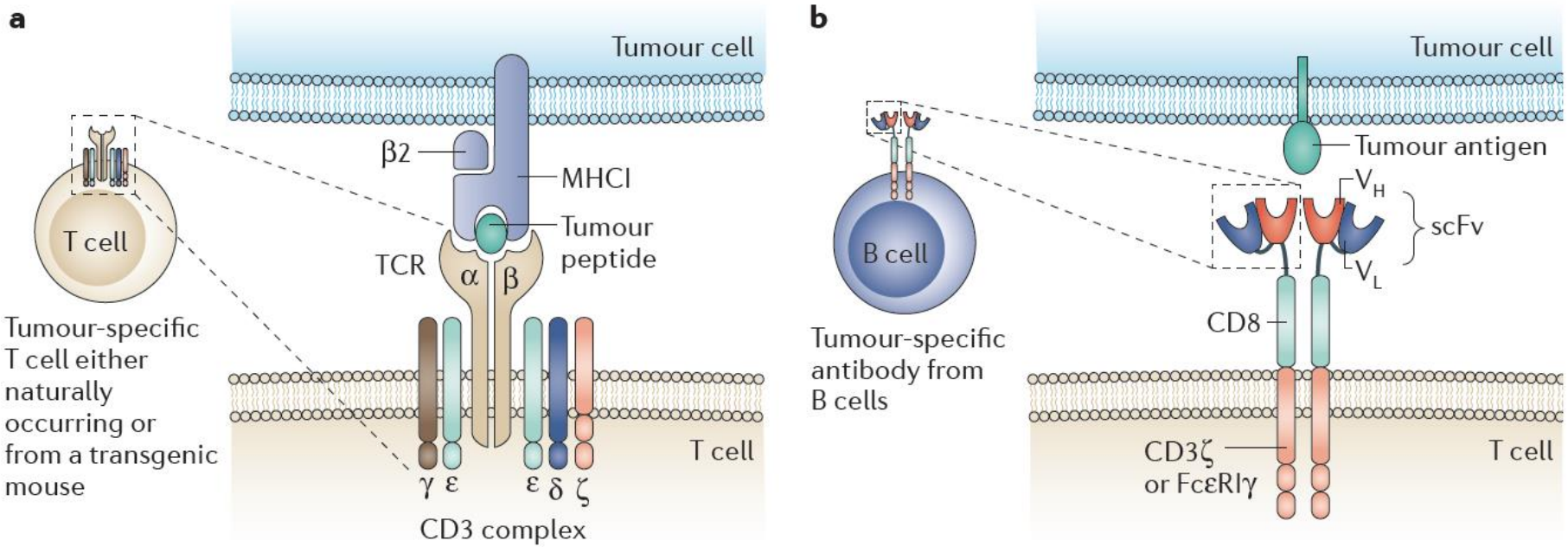
*Present address: Department of Surgery, Université de Montréal, and Institut du Cancer de Montréal, Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montréal, QC H2X 0A9, Canada.

Mutation-specific TIL in GI cancers harboring a low mutational load

Table 1. Mutation-reactive T cells in metastatic GI cancers. NE, not evaluated.

Patient ID	Age/sex	Tumor type	Number of mutations†	Number of mutations assessed‡	Number of TIL cultures assessed	Number TIL cultures with mutation reactivity§	Mutated protein recognized	Amino acid change	T cell type	Frequency of mutation-reactive TCR in tumor (%)
3737*	45/F	Bile duct	26	25	5	5	ERBB2IP	E805G	CD4	0.009
								E805G	CD4	0.375
3812	44/M	Bile duct	48	179	5	0	—	—	—	—
3942	46/F	Rectal	155	144	6	2	NUP98	A359D	CD8	0.67
						4	KARS	D356H	CD8	0.020
						3	GPD2	E426K	CD4	0.037
3948	48/M	Esophageal	84	211	5	2	PLEC	E1179K	CD4	NE
						2	XPO7	P274S	CD4	NE
						2	AKAP2	Q418K	CD4	NE
3971	49/M	Colon	118	118	23	11	CASP8	F67V	CD8	1.25
3978	46/F	Bile duct	39	38	9‖	1¶	ITGB4	S1002I	CD4	NE
3995	50/M	Colon	58	154	19‖	2	TUBGCP2	P293L	CD8	0.023
						15	RNF213	N1702S	CD8	0.60
						2	KRAS	G12D	CD8	0.055
4007	52/M	Colon	134	264	23	4	SKIV2L	R653H	CD8	0.090
								R653H	CD8	0.014
						5	H3F3B	A48T	CD8	1.19
4032	46/M	Colon	101	222	24	12	API5	R243Q	CD8	0.083
								R243Q	CD8	0.059
						1	RNF10	E572K	CD8	0.030
						7	PHLPP1	G566E	CD8	0.081
4069	57/M	Pancreatic	10	97	15	1	ZFYVE27	R6H	CD8	0.088

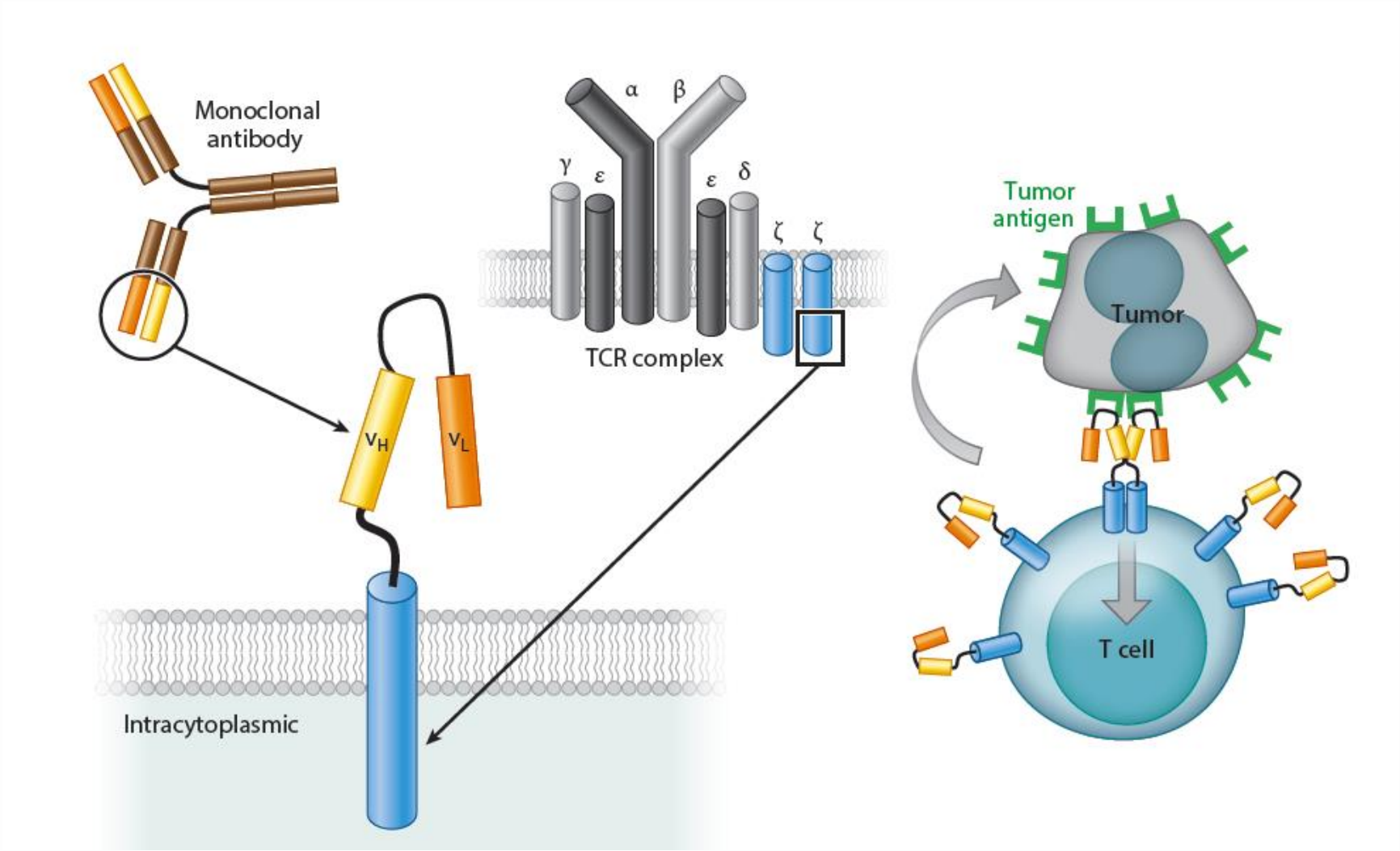
Infusion of gene-modified T cells



NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

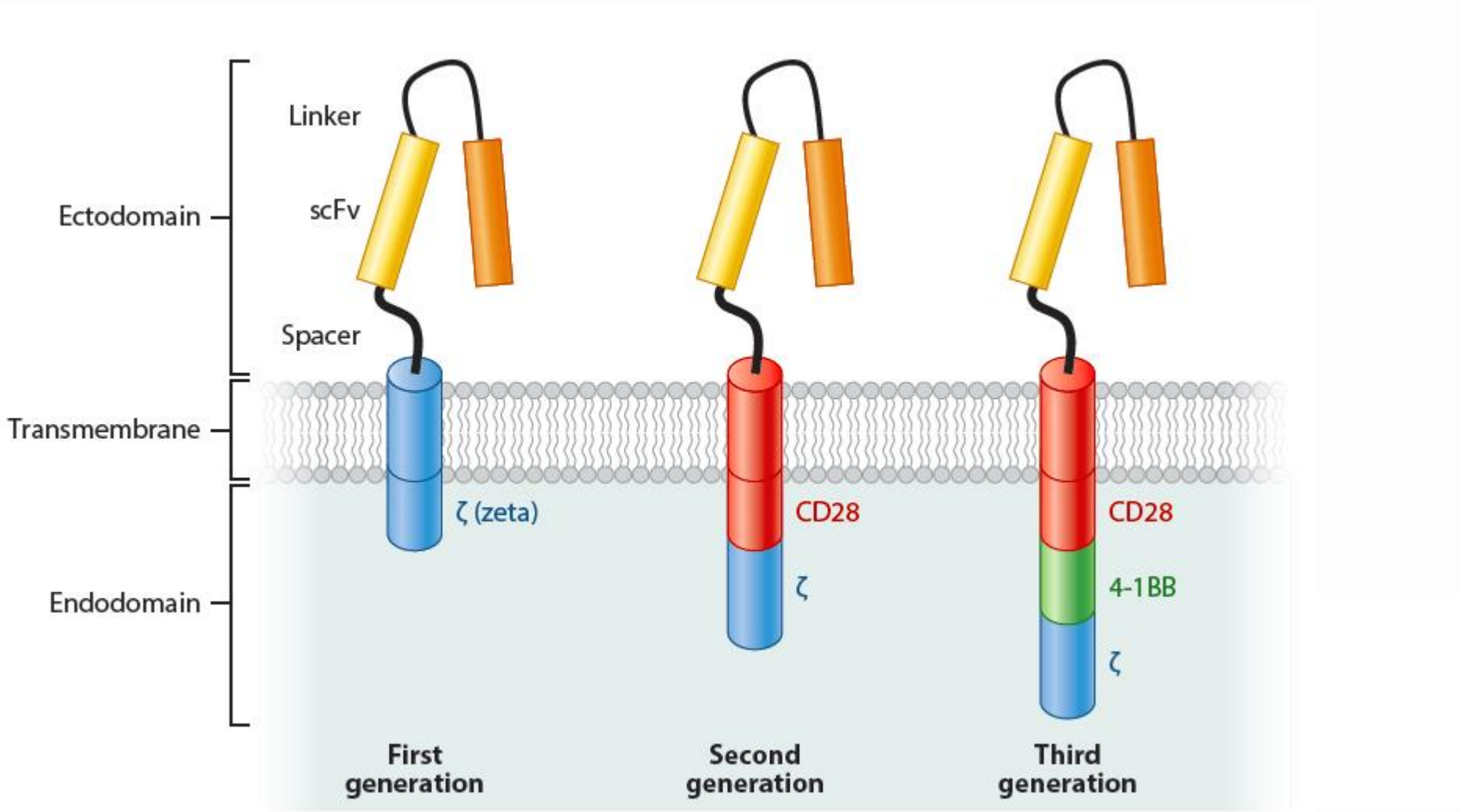
Kershaw et al. Nat Rev Cancer 2013

CAR T cell concept



Ramos et al. Ann Rev Immunol 2016

Further development of CARs



Ramos et al. Ann Rev Immunol 2016

Success of CD19 CAR T cell therapy

Study	CAR design	Trial design	Malignancy	Outcome[a]	Refs
Kochenderfer *et al.* 2010	Murine CD19scFv–CD28/CD3ζ	Case report	Follicular lymphoma	PR	[3]
Brentjens *et al.* 2011	Murine CD19 scFv–CD28/CD3ζ	Pilot (nine patients)	CLL (n =8), acute lymphoblastic leukemia (n = 1)	One PR	[4]
Kalos *et al.* 2011 Porter *et al.* 2011	Murine CD19 scFv–4-1BB/CD3ζ	Pilot (three patients)	CLL (n = 3)	Two CR, one PR	[5,6]
Savoldo *et al.* 2011	Murine CD19 scFv–CD3ζ and CD28/CD3ζ	Pilot (six patients)	Non-Hodgkin lymphoma (n = 6)	Two SD	[7]
Kochenderfer *et al.* 2012	Murine CD19scFv–CD28/CD3ζ	Pilot (eight patients)	Non-Hodgkin lymphoma (n = 4) CLL (n = 4)	One CR, five PR	[8]
Brentjens *et al.* 2013 Davila *et al.* 2014	Murine CD19 scFv–CD28/CD3ζ	Phase I (16 patients)	Acute lymphoblastic leukemia	CR 88%	[9,10]
Grupp *et al.* 2013	Murine CD19 scFv–4-1BB/CD3ζ	Pilot (two patients)	Acute lymphoblastic leukemia	Two CR	[11]
Maude *et al.* 2014	Murine CD19 scFv–4-1BB/CD3ζ	Phase I/II (30 patients)	Acute lymphoblastic leukemia	CR 90%	[12]
Lee *et al.* 2015	Murine CD19scFv–CD28/CD3ζ	Phase I (21 patients)	Acute lymphoblastic leukemia	CR 70%	[13]
Kochenderfer *et al.* 2015	Murine CD19scFv–CD28/CD3ζ	Phase I (15 patients)	Non-Hodgkin lymphoma (n = 11) CLL (n = 4)	CR 53% PR 26%	[14]

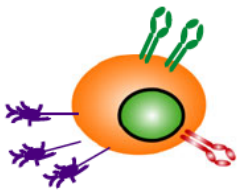
Srivastava & Riddell Trends in Immunol 2015

8. Toxicity management

Anti-cytokine therapy

Steroids

1. Target choice



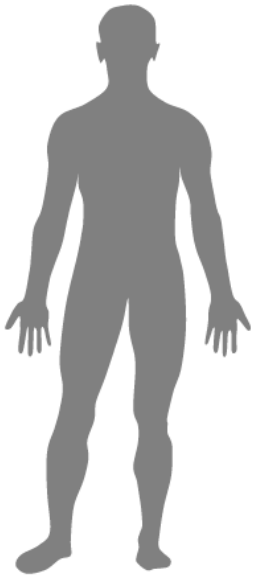
Tissue distribution
Surface density
Oncogene addiction

7. Safety systems

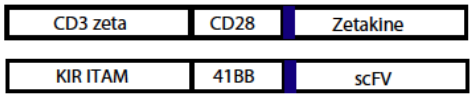
Suicide systems

Targets for clearance
by exogenous antibody

Transient expression
or persistence



2. CAR structure



3. Vector choice

Retrovirus
Transposons
RNA
Lentivirus

6. Host conditioning

Lymphodepleting chemotherapy

Lymphodepleting antibodies

Allogeneic transplant

5. Ex vivo preparation

Artifical APCs

Beads

Culture time

Cell dose and character

Cytokine support

4. Effector cells

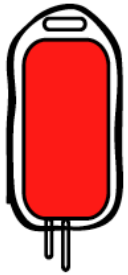
Third party

Cryopreserved

Gene edited

Viral specific

Patient derived



Flow sorting

Column spearation

Composition

NK cells
T cells
PBMCs

Maude & Barrett Br J Hematol 2015

TCR gene therapy

- 2006: MART-1 TCR gene therapy
  - RR 13% (n=15)

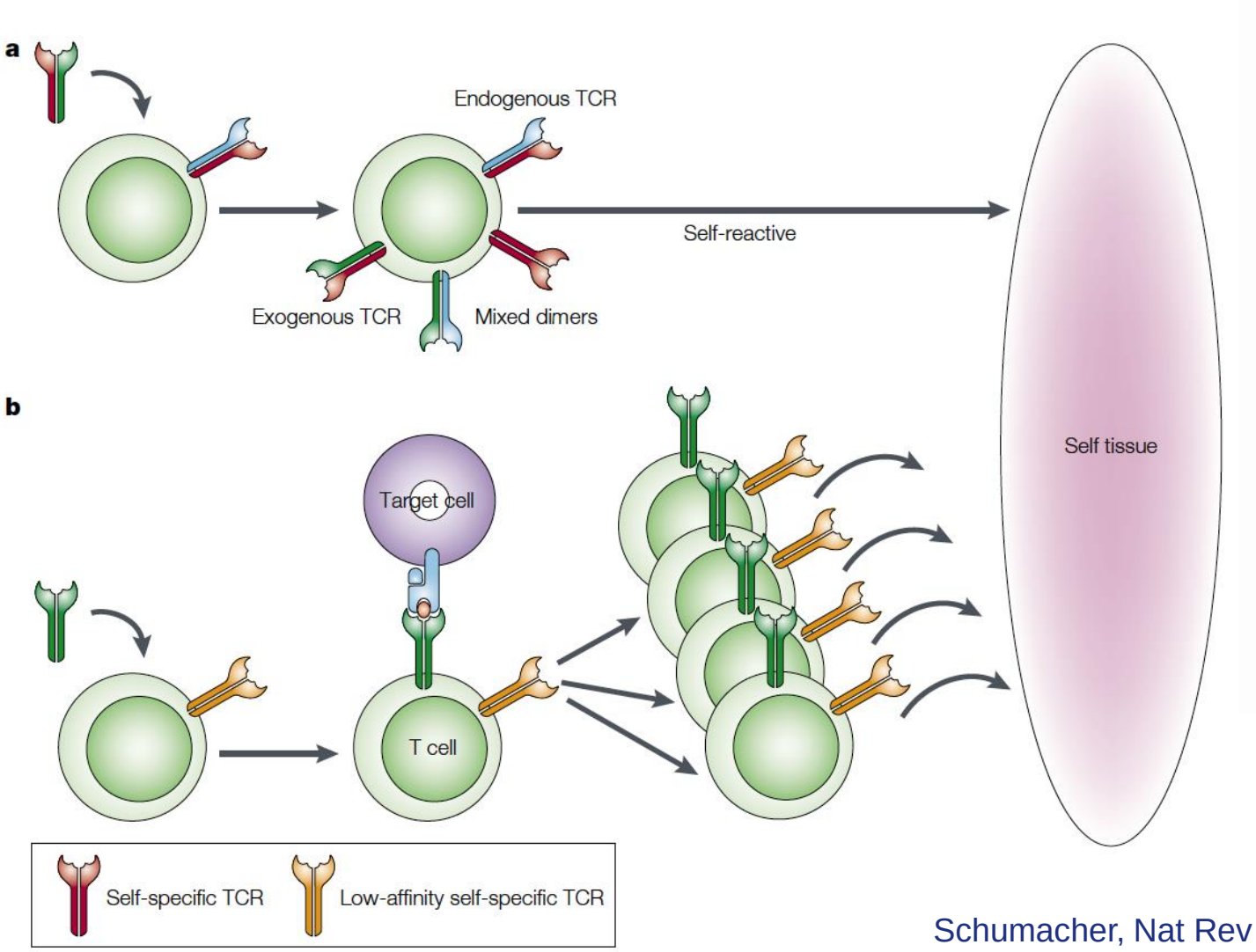
  (Morgan et al., Science 2006)
- 2008: MART-1 and gp100 TCR gene therapy
  - RR 30% (MART-1 TCR; n=20)
  - RR 19% (murine gp100 TCR; n=16)

  (Johnson et al., Blood 2009)
- 2011: NY-eso-1 TCR gene therapy
  - RR 45% (n=11)

  (Robbins et al., J Clin Oncol 2011)
- 2012 MAGE-A3 TCR gene therapy
  - Aborted due to unexpected toxicity

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Potential toxicities of TCR gene therapy (I)



Schumacher, Nat Rev Immunol 2002
Bendle et al., Nat Med 2010

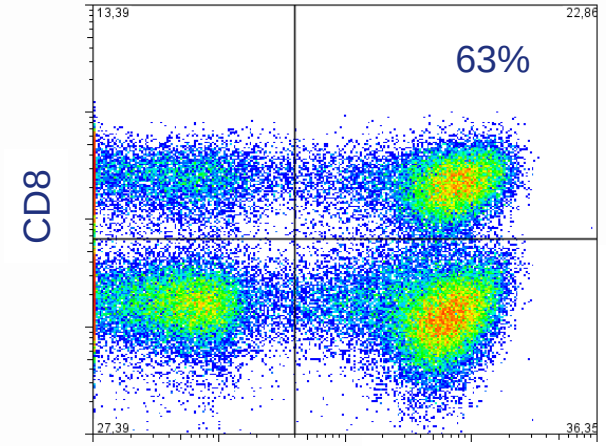
Selection of TCR and modification of vector

1D3$_{opt}$HMCys:

- 1D3 TCR recognizes MART-I epitope (from vaccinated patient)
- codon-optimized for optimal expression
- additional disulfide bond to prevent mispairing with endogenous TCR chains*
- murine instead of human constant region to further reduce mispairing
- 2A peptide between alpha and beta chain for equimolar production

Retrovirus:

- MP71 retroviral vector (good expression and used elsewhere in clinical trials)



* (Kuball Blood 2007, Cohen Cancer Res 2006&2007)

Potential toxicities of TCR gene therapy

- On and off-target toxicity
  - Melanocyte differentiation antigens
    - Vitiligo; uveitis; Vogt-Koyanagi-Harada syndr.
  - MAGE-A3
    - CNS toxicity (cross-reactivity with MAGE-A9 peptide)
    - Cardiac toxicity (cross-reactivity with myocardiac peptide)
  - CEA
    - colitis

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Take home message

- TIL research and therapy has contributed extensively to our understanding of cancer immunity
- TIL therapy and adoptive therapy of gene modified T cells will be developed further to become a (personalized) drug treatment
- These therapies may be combined with other (non)-immunotherapies in the future
- Use of gene modified T cells:
  - Extremely promising in hemato-oncology
  - Promising in solid tumors (especially TCR modified T cells)

Cancer exome-guided immunomonitoring

Nienke van Rooij

Marit van Buuren

Daisy Philips

Mireille Toebes

Laura van Dijk

Pia Kvistborg

Ton Schumacher

PDX models

Kristel Kemper

Daniel Peeper

Sanger Institute

Sam Behjati

Mike Stratton

Utrecht University

Can Kesmir

MHC-based technologies

Chemical Biology

Boris Rodenko

Huib Ovaa

CCIT, Copenhagen

Sine Hadrup

STAGE Therapeutics

Lothar Germeroth

SB, NIH

Marc Dudley

Steven Rosenberg

ELLA institute, Israel

Mchal Besser

Jakob Schachter

Cancer Immunotherapy Dream Team

Clinical translation

Sander Kelderman

Raquel Gomez

Joost van den Berg

Maaike van Zon

Noor Bakker

Renate de Boer

Bastiaan Nuijen

Christian Blank

Hans van Thienen

Marnix Geukes

Henk Mallo