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Tumor Infiltrating Lymphocytes (TILs)

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Society for Immunotherapy of Cancer

#SITC2020

Disclosure



Consultant to
Biological Industries (Sartorius group), BMS, MSD, Imanu Immunotherapy

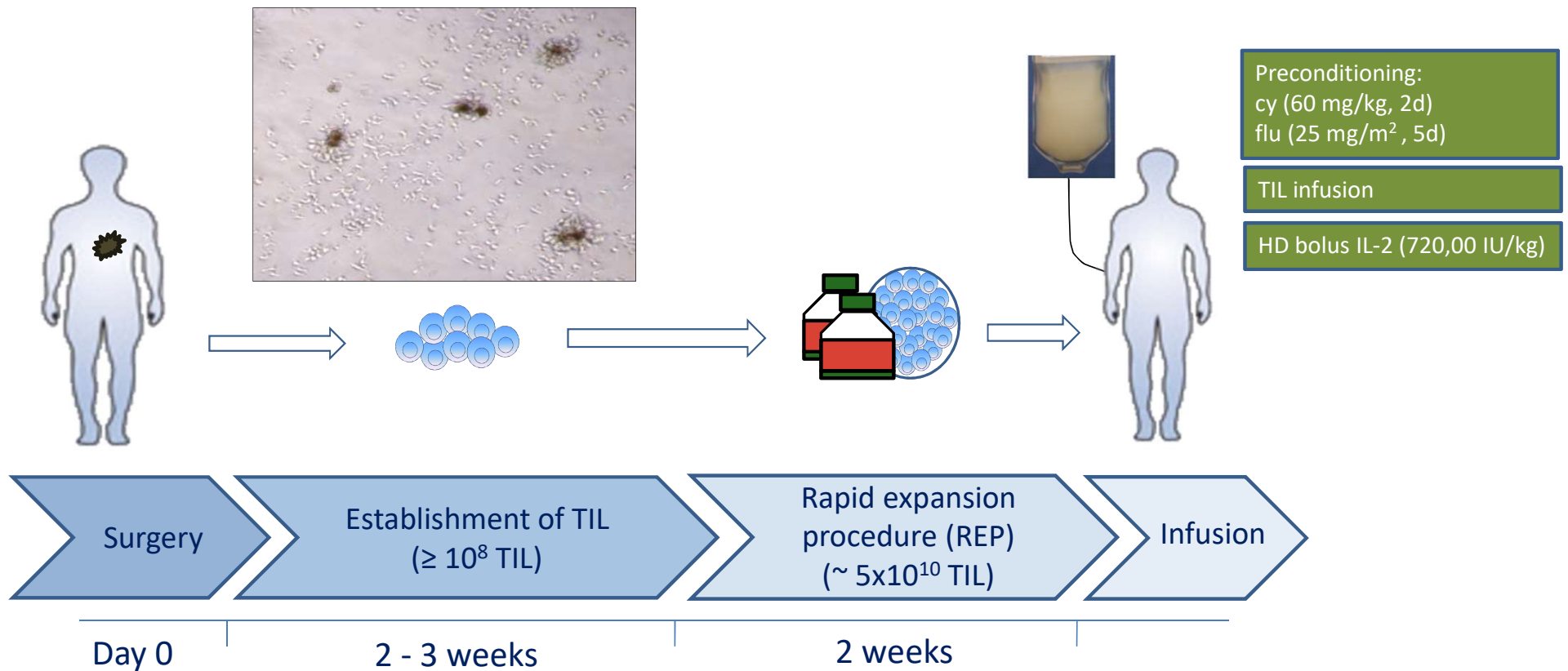
- Background TIL
- TIL in melanoma
- TIL in other solid tumors
- Tumor mutation-reactive TIL
- Impact of preconditioning chemotherapy
- TIL as research platform

TIL (versus CAR / TCR T)



- Inherent ability to infiltrate tumor tissue
- Highest frequency of tumor-reactive T cells
- Target multiple tumor antigens simultaneously
- Demonstrated clinical efficacy in solid tumors

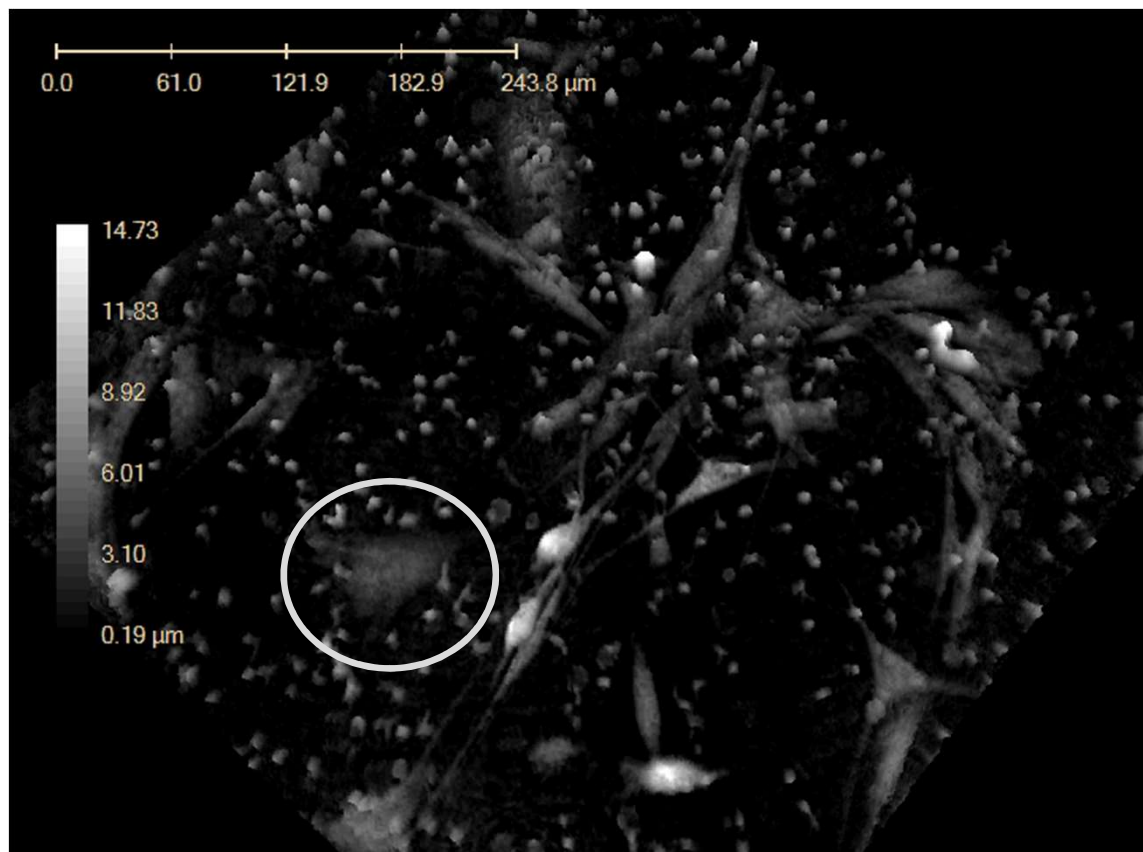
“Sheba” bulk TIL production



Besser MJ, CCR, 2010

Besser MJ. CCR, 2013

Itzhaki O. Mol Carcinog, 2020

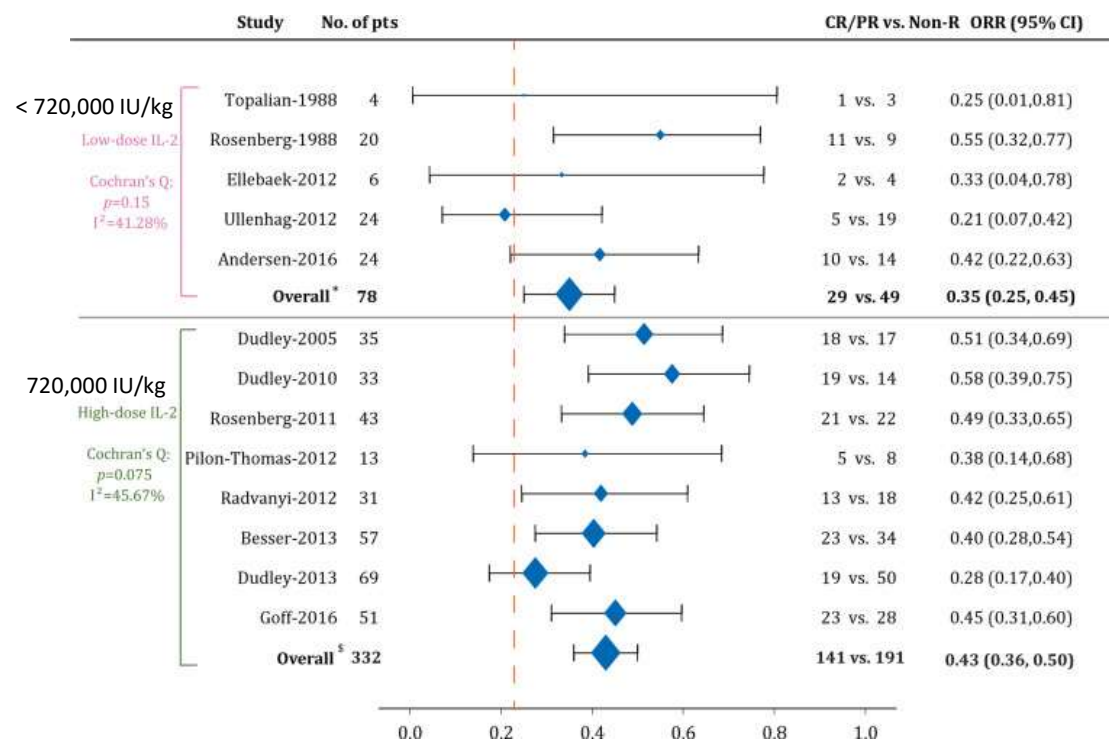


Co-culture
TIL from Patient 014PA and
autologous melanoma cells

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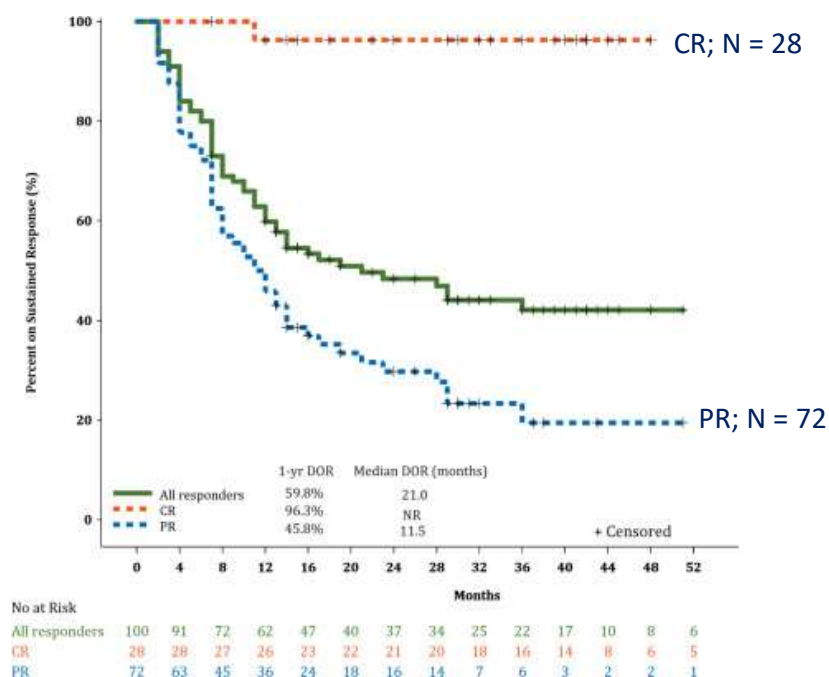
Bulk TIL in metastatic melanoma

Meta-analysis on 13 studies



Total 410 0.41 ORR; 0.14 CR and 0.27 PR

Survival of ORR (CR and PR)



Dafni U et.al. Annals of Oncol. 2019

Bulk TIL in metastatic melanoma (2020)



Itzhaki O. (2020) *Mol Carcinog.* Single-center (Sheba), Phase 2

Long term follow up

ORR 28% (n = 103); ir

6-year OS of ORR pat

Median OS CR:

PR: 34.9 months

NR: 6.7 months

Iovance Multi-center Phase 2, C-144-01

ASCO 2020:

Cohort 2 (cryo-preserved bulk TIL), n = 66

)

at 18.7 months

Impact of prior anti-PD1 therapy ???

TIL Summit 2020

Cohort 4 (cryo-preserved bulk TIL), n = 75

32% ORR (median follow-up 3.5 months)

All patients failed prior anti-PD1 therapy

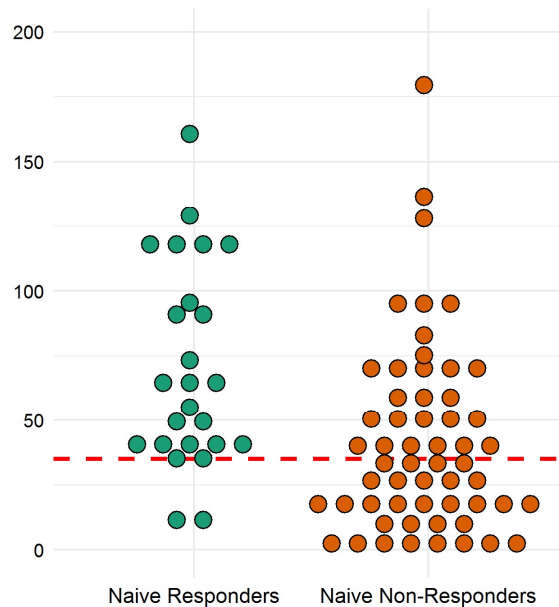
Prior anti-PD1 impact

- TIL ACT and PD-1 blockade share similar response and resistance mechanisms (Harel *Cell* 2019)
- We identified two major determinants of TIL ACT outcomes in PD-1 naïve patients



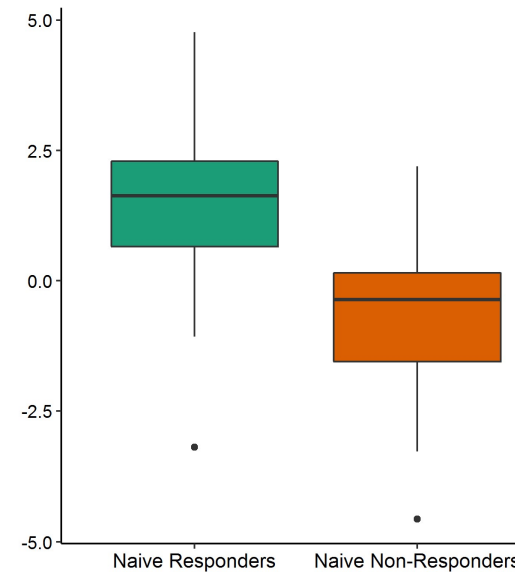
TIL product dependent

$$\text{TIL score} = \frac{\text{Fold expansion} * \%CD8}{\text{Age of culture}}$$



Tumor dependent

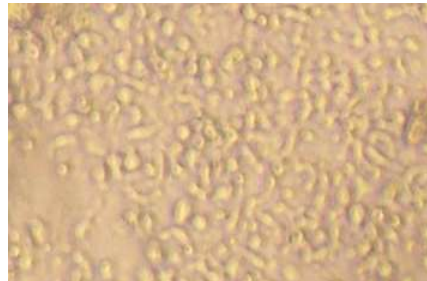
IFN γ score, a score based on interferon response and resistance gene expression signatures in responders and non-responders to immunotherapy



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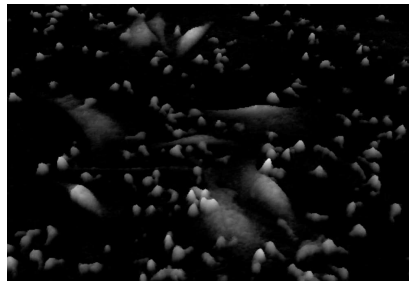
Bulk TIL in other solid tumors – pre clinical

RCC



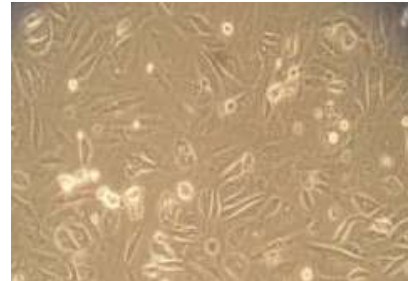
Markel G. (2009)
Anticancer Res.

NSCLC



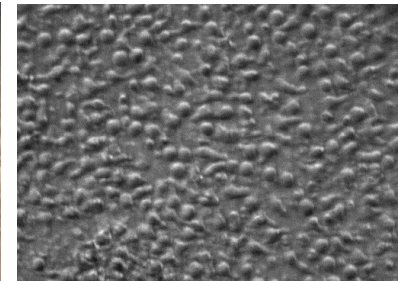
Ben-Avi R. (2018)
Cancer Immunol Immunother.

Prostate Ca

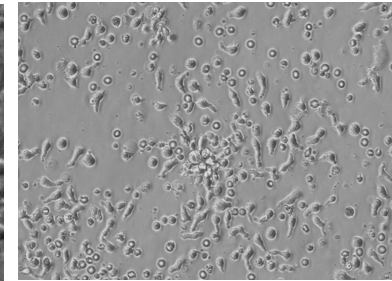


Yunger S. (2019)
Oncoimmunol.

Ovarian Ca



Bladder Ca



**TIL derived from
Prostate Ca
needle biopsies**

IFN γ secretion (pg/ml)

TIL	TIL only	TIL + target 1	TIL + target 2
PS-002	69	<u>479</u>	N/A
PS-003	267	<u>1677</u>	<u>4547</u>
PS-004	184	<u>585</u>	<u>743</u>
PS-005	<16	<16	N/A
PS-006	361	651	<u>772</u>
PS-007	<16	<16	N/A
PS-008	131	<u>615</u>	<u>281</u>



Yunger S. (2019) *Oncoimmunol.*

TIL in other solid tumors – clinical



NSLCL	bulk TIL + nivolumab in 18 evaluated patients; 2 CR and PRs (Moffitt Cancer Center / Iovance; ASCO 2020)
Ovarian Ca	bulk TIL in 6 patients; SD (Pedesen M, Harlev Hospital; <i>Oncoimmunol.</i> 2018)
Cervical Ca	bulk TIL in 27 patients; 41% ORR incl. 3 CR and 9 PR; short follow up (Iovance; ASCO 2019)
Gastric Ca	bulk TIL in 16 patients; 0% ORR (one SD) (Tran E, NCI, SITC 2015)



TIL selections in various tumor types required
Tumor-mutation specific TIL

Cholangiocarcinoma patient	(Tran E, NCI, <i>Science</i> 2014)
Colon cancer patient	(Tran E, NCI, <i>N Engl J Med.</i> 2016)
Breast cancer patient	(Zacharakis N, NCI, <i>Nat Med.</i> 2018)
GI cancers	n = 40; 12.5% PR (Parkhurst M, NCI, <i>Cancer Discov.</i> 2019)

Overview



- Background TIL
- TIL in melanoma
- TIL in other solid tumors
- **Tumor mutation-reactive TIL**
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Identification of neo-antigen specific T cell



WES: Generate map of nonsynonymous tumor-specific mutations



RNAseq: Determine which mutated genes are expressed



***In silico* prediction:** of epitopes for each mutation/ each HLA-allele



Screening: Co-incubation of TIL with candidate neo-peptide expressing APC



Selection of mutation reactive TIL based on expression of CD137 (4-1BB), CD134, CD154 or secretion of IFN γ

Pro:

- Technology works
- Neo-antigen TIL can be identified in most patients
- New technology are emerging
- Promising opportunity to improve TIL products by making them more personal

Contra:

- Costly
- Time-consuming (a few months)
- Miss out other tumor-antigens types (e.g. phospho-antigens, shared antigens, microbial antigens,...)

Identification of mutation-specific T cell

WES: Generate map of nonsynonymous
tumor-specific mutations



RNAseq: Determine which mutated
genes are expressed



In silico prediction: of epitopes for each
mutation/ each HLA-allele



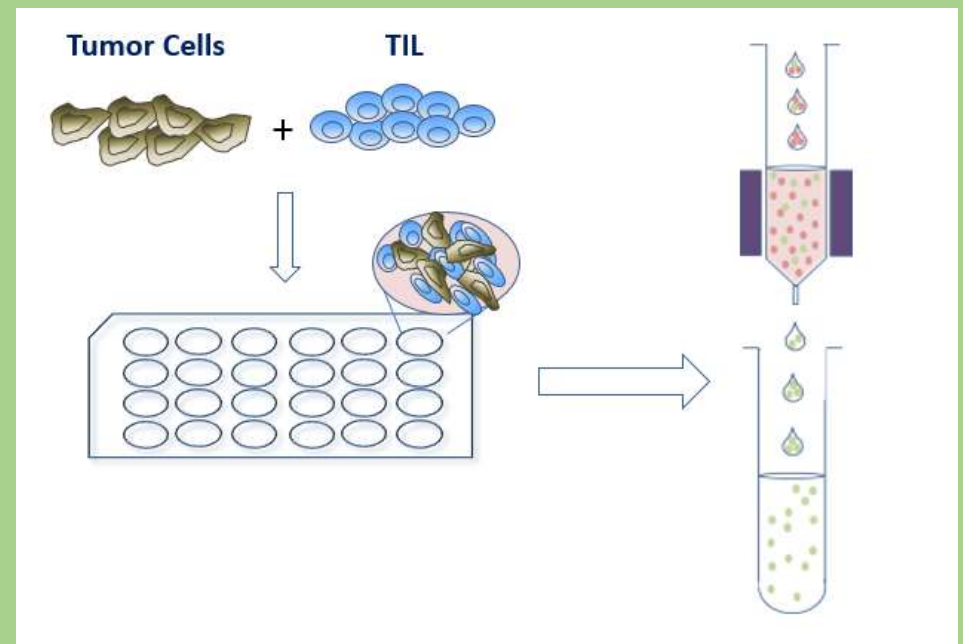
Screening: Co-incubation of TIL with candidate
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Selection of mutation reactive TIL based on
expression of **CD137 (4-1BB)**, CD134, CD154
or secretion of IFN γ

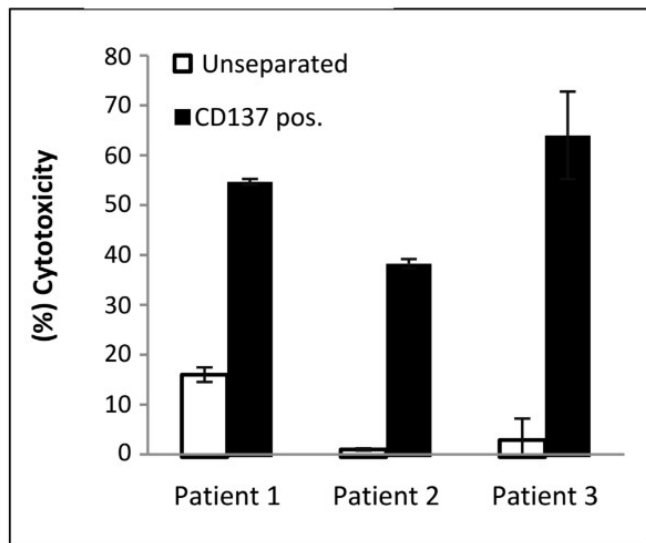
Co-culture

MACS with CD137 beads

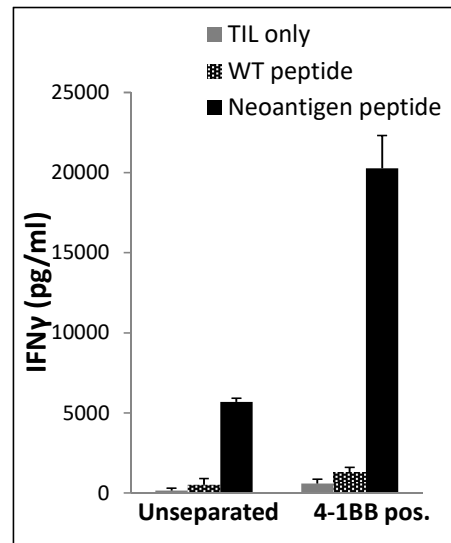


CD137-selected TIL

Significantly increased
anti-tumor reactivity



Enriched for
mutation-reactive TIL

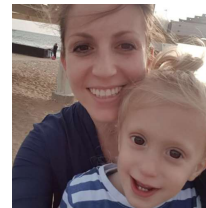


Pro:

- Simple
- Quick (2 days)
- Enrichment for all types of tumor reactive TIL

Contra:

- Autologous tumor cells required



Seliktar Ofir S (2017) Frontiers Immunol.

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ACT and non-myeloablative pre-conditioning

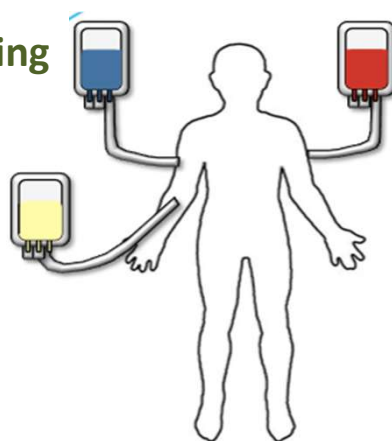


Cy / Flu Pre-conditioning

Acute toxicity

IL-2

Acute toxicity



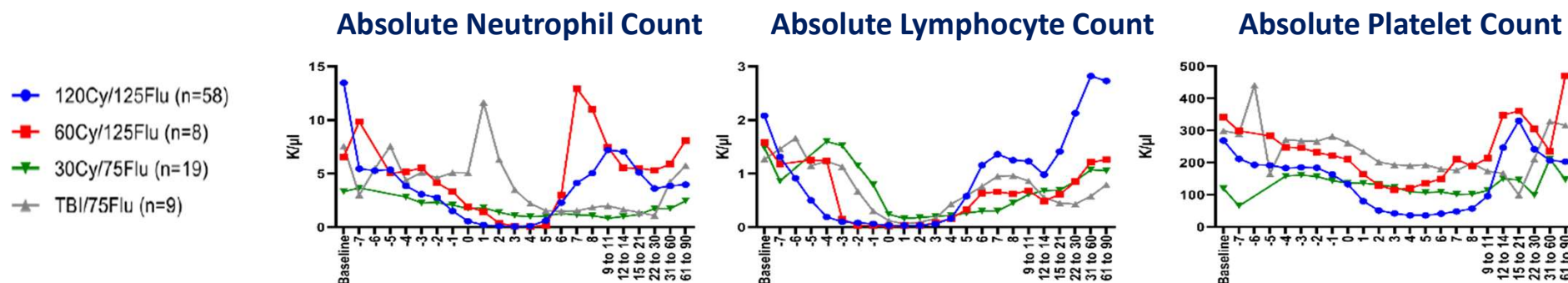
T cells

TIL: mild or no toxicity

CAR / TCR: severe toxicity

Cohort	Cyclophosphamide (mg/kg)	Fludarabine (mg/m ²)	Total Body Irr. (cGy)	Disease	T cells	n
120Cy/125Flu	2 x 60	5 x 25	-	Melanoma	TIL	58
60Cy/125Flu	2 x 30	5 x 25	-	Melanoma	TIL	8
30Cy/75Flu	1 x ~ 30 (900mg/m ²)	3 x 25	-	ALL	CD19 CART	19
200cGyTBI/75Flu	-	3 x 25	1 x 200	Melanoma	TIL	9

Comparison of NMA pre-conditionings



- Cell ablation
- Cell recovery
- Correlation to overall response
- Correlation to overall survival
- Impact of cytokine serum levels

120Cy/125Flu and 60Cy/125Flu:

Equal cell ablation and recovery

Less toxicity and time of hospitalization at 60Cy/125Flu

Nissani A (2020) JITC; Submitted

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TIL: The ideal platform to study immune-tumor interaction



- Checkpoint molecule discovery

Markel *J* 2006, Markel *C* 2010 Ortenberg *MCT* 2012, Baruch *Oncoimmunol.* 2020
Commercial: cCAM Bio (acquired by MSD), 4c Biomed

- Understanding resistance mechanism

Harel *Cell* 2019, Markovits *SMR* 2019

- Process development

Commercial: Xeno-free media (Biological Industries – Sartorius)

- Discovery of new classes of tumor-antigen

- Gain insights for CAR / TCR therapy in solid tumors

Itzhaki JITC 2020

TIL: The ideal platform to study immune-tumor interaction



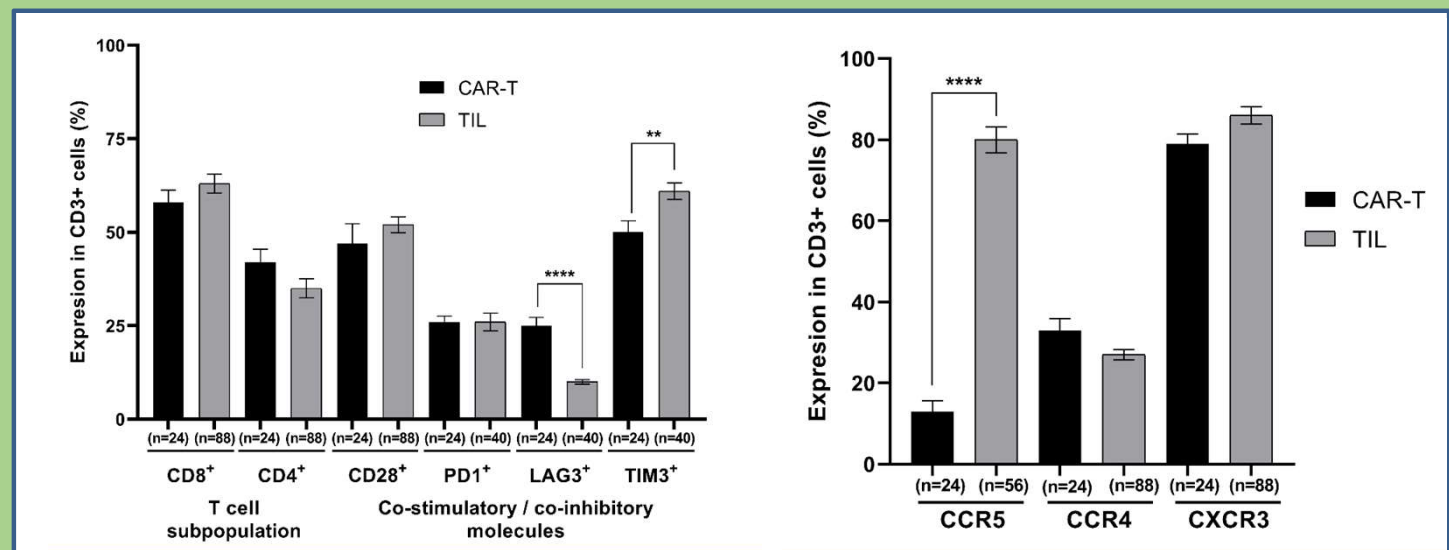
Since 2016: In-house produced “Sheba” CD19-CAR trial; over 150 treated patients

Indications (any CD19 expressing malignancy): B-ALL, B-NHL, CLL, AML

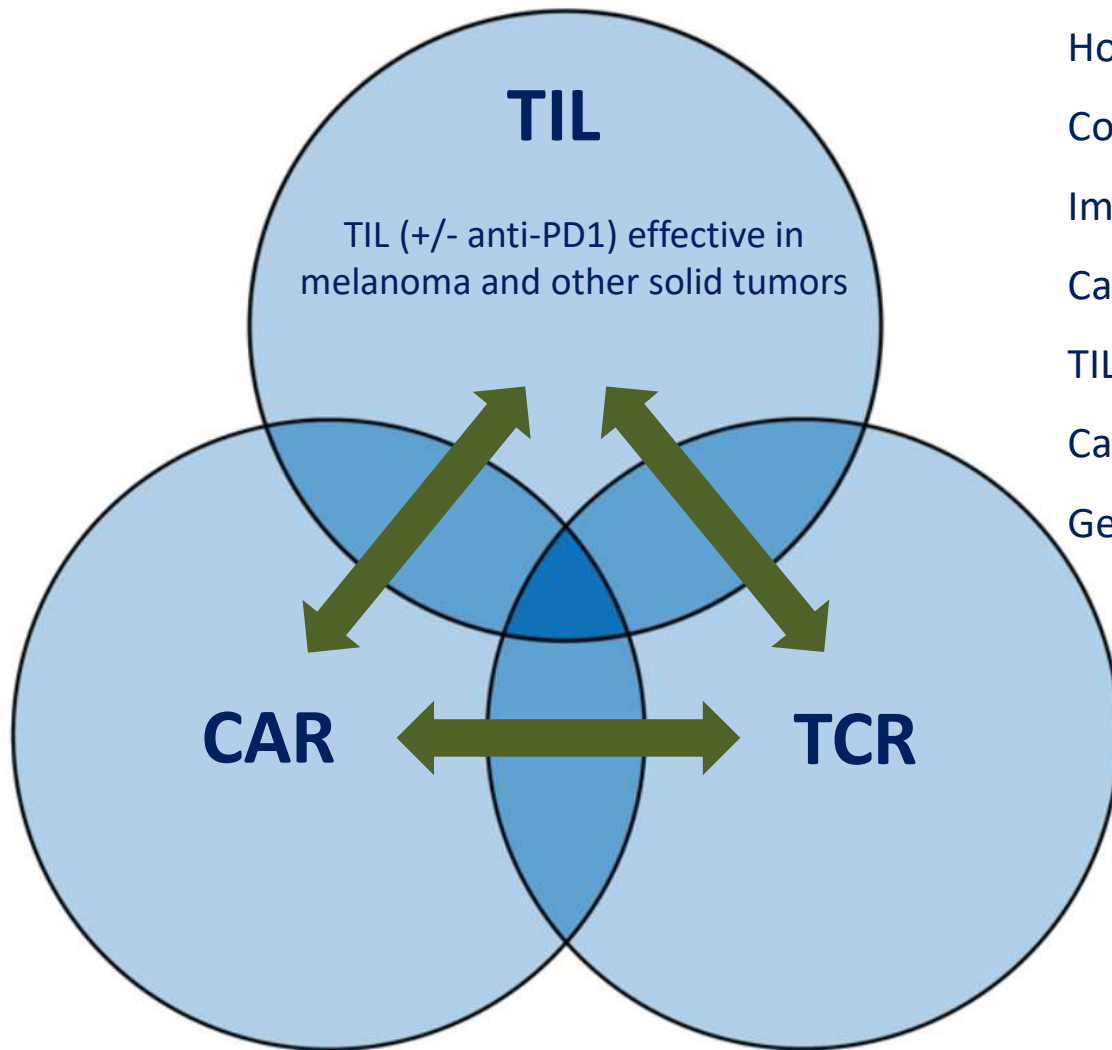
TIL are clinically effective in solid tumors; infiltrate solid tumors; overcome the harsh microenvironment



Comparison of TIL and CAR infusion products



Itzhaki O (2020) JITC



How does prior checkpoint therapy impact T ACT?

Combination of T ACT and anti-PD1 therapy

Impact of lympho-depleting preconditioning

Can we improve CAR T infiltration, by learning from TIL?

TIL platform for TCR discovery

Can we improve TIL by CAR / TCR transduction?

Gene editing of TIL

THANK YOU



Steve Rosenberg
James Yang
and all the team at the Surgery Branch
To all my fantastic colleagues!

Haya and Nehemia Lemelbaum

