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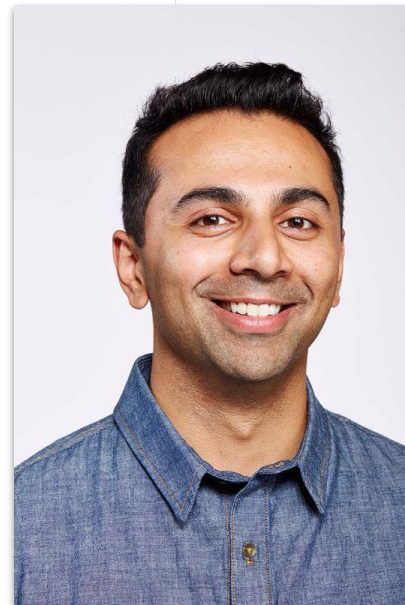
Precision Immune
Monitoring

Discovery of immune-related adverse event associations in metastatic melanoma

Ramji Srinivasan
Teiko CEO
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Problem

Who will get an immune-related adverse event?

Metastatic Melanoma

65 year old male

- Stage IV
- First Line
- Treated with nivolumab + ipilimumab

70 year old male

- Stage IV
- First Line
- Treated with nivolumab + ipilimumab

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Same cancer, same treatment, *different* irAE, but why?

Metastatic Melanoma

65 year old male

- Stage IV
- First Line
- Treated with nivolumab + ipilimumab
- No irAE

70 year old male

- Stage IV
- First Line
- Treated with nivolumab + ipilimumab
- **Severe irAE**

What's different?

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65 year old male

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70 year old male

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The immune systems?

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To measure the immune state

- Presence or absence of dozens of different individual cell types across hundreds of thousands of cells
- Presence or absence of unique markers on those cells
- Proportion of those cells in relation to one another

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To measure the immune state need to look at dozens of immune cell populations and functional markers

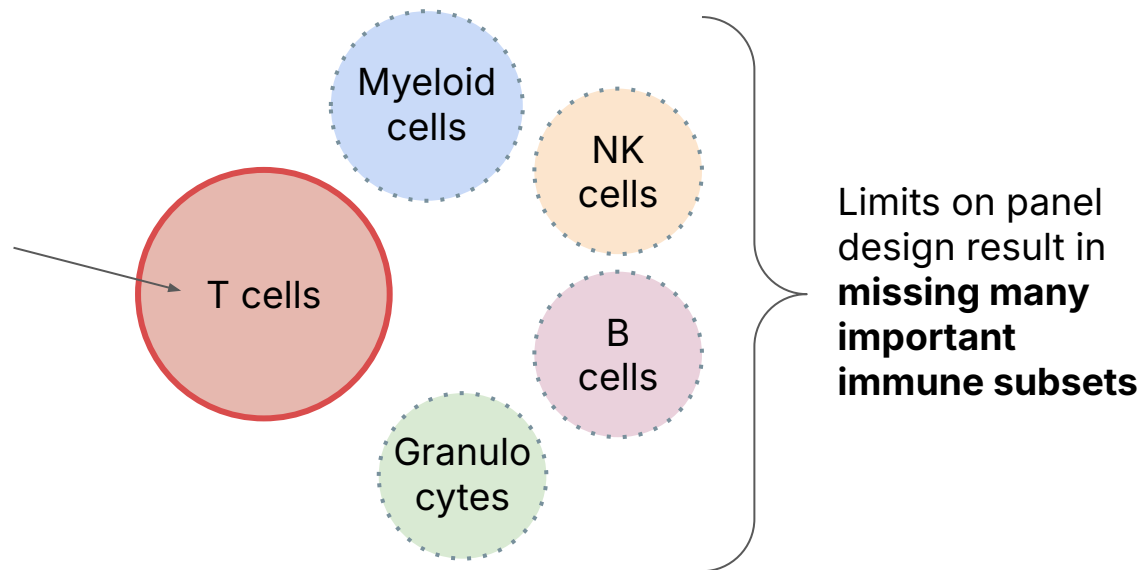~20 functional markers
(e.g. PD-1, LAG-3, Ki-67, CD86, etc.)

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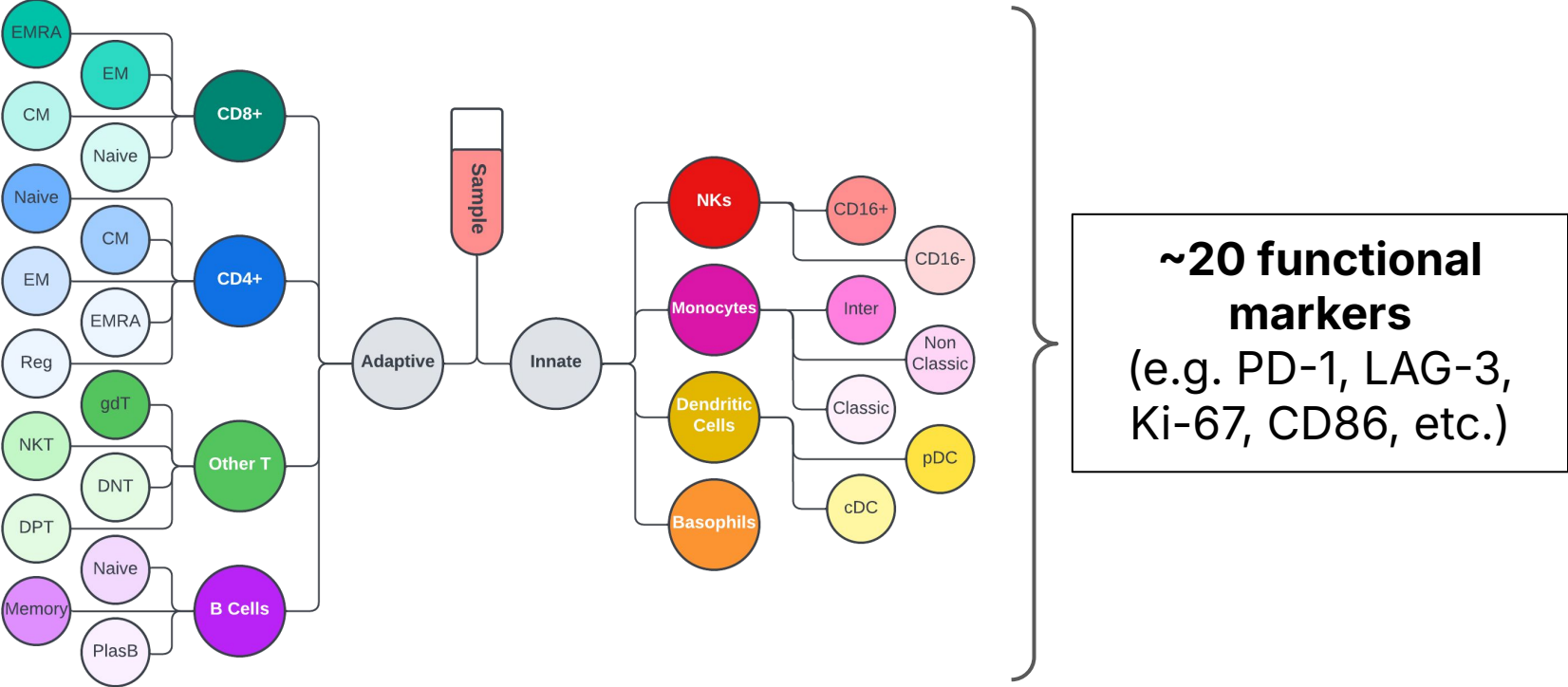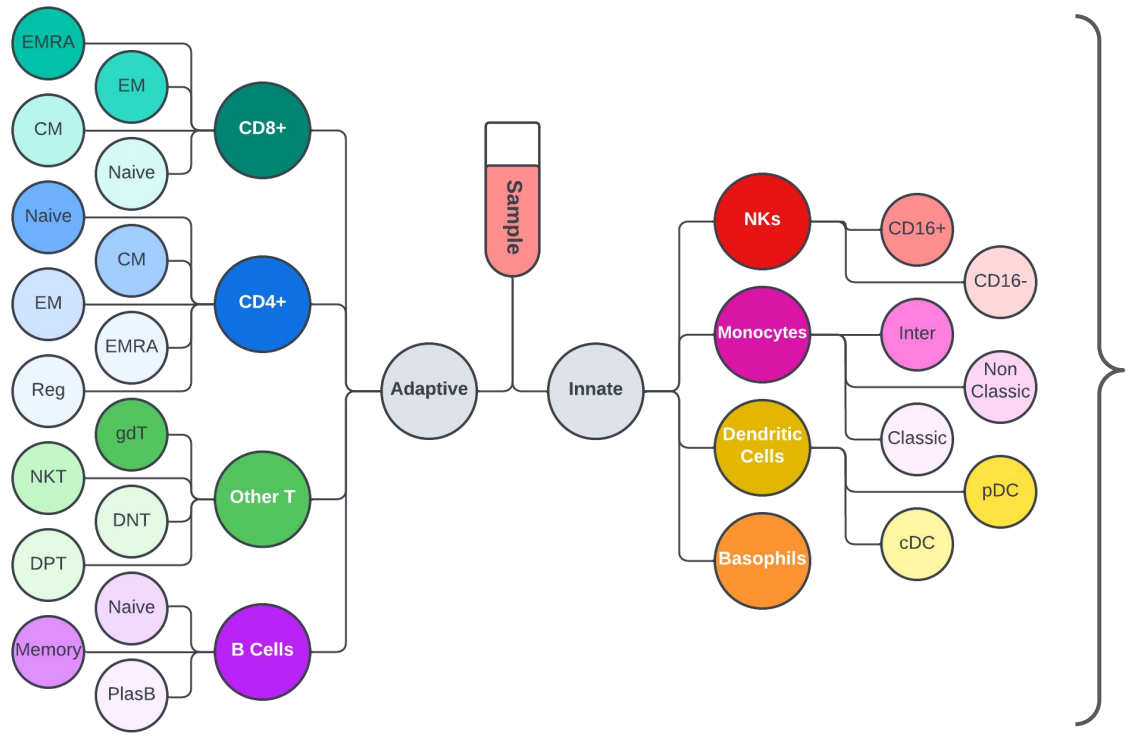
~20 functional markers
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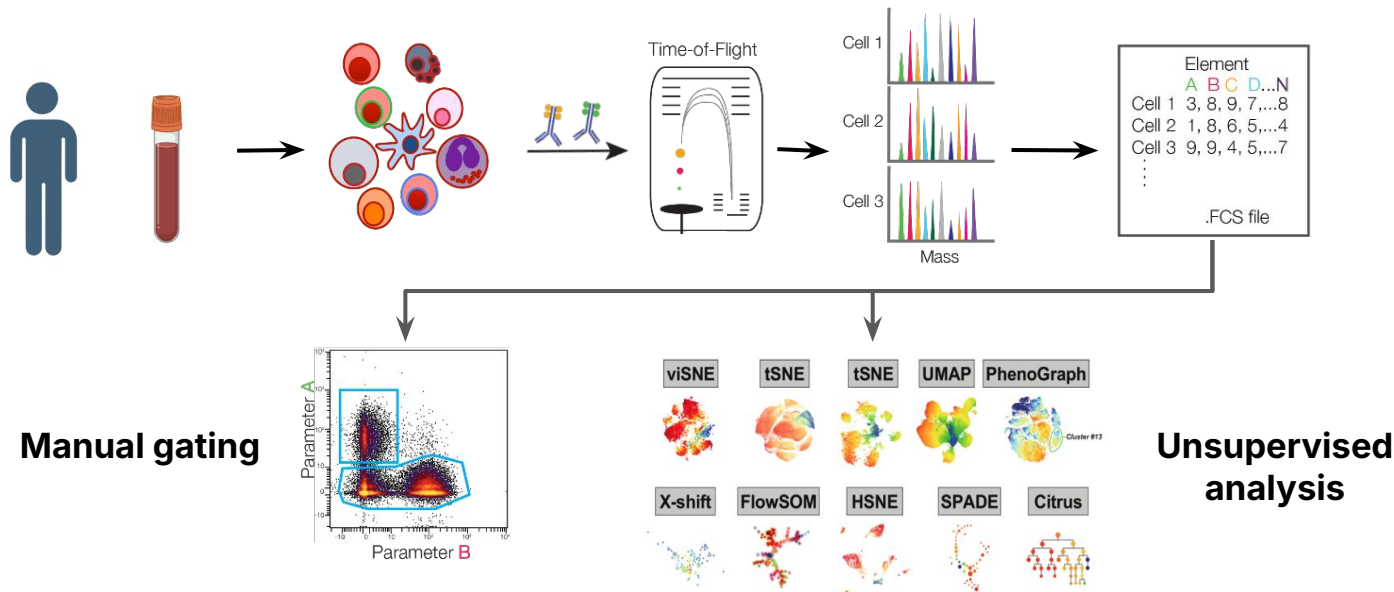Hundreds of thousands of cells

Current immune profiling technologies force tradeoffs about what cells to examine

Flow Cytometry

6-12 marker panels usually force you to **focus on one cell type**

Myeloid cells

NK cells

T cells

B cells

Granulo cytes

Limits on panel design result in **missing many important immune subsets**

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Mass Cytometry: Measuring many proteins in millions of single cells

Manual gating

Unsupervised analysis

Modified from Spitzer and Nolan, Cell (2016)

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~40 immune cell markers

	CD3	CD8	CD4	TH1	...	cDCs
Cell 1	737	3,517	3,318	2,201	...	4,288
Cell 2	253	1,011	1,153	2,326	...	656
...	...	...	...	...	...	3,242
Cell N	2,072	1,145	862	488	...	2,277

200-400K cells
[per sample]

Each entry is a signal intensity

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- **Severe irAE**

The immune systems?

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Overtreatment because no immune-related adverse events are expected

- Pain: Serious adverse events
- Cost: $150K / year for IO that needs to be stopped + restarted, steroids to manage irAE

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Undertreatment because immune-related adverse events are expected

- Time on wrong drug
- Patients don't get cured

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15-50% of patients will have a immune-related adverse event

Metastatic Melanoma

BEFORE THERAPY

Will the patient develop a **Grade 3+ adverse event (irAE)** in response to immunotherapy?

aPD-1 monotherapy

aPD-1 + aCTLA-4 combination therapy

Other (non-IO) therapy

CONSEQUENCES

Overtreatment because no irAE are expected
- Pain: Serious adverse events
- Cost: $150K / year for IO that needs to be stopped + restarted, steroids to manage irAE

Undertreatment because irAE are expected
- Time on wrong drug
- Patients don't get cured

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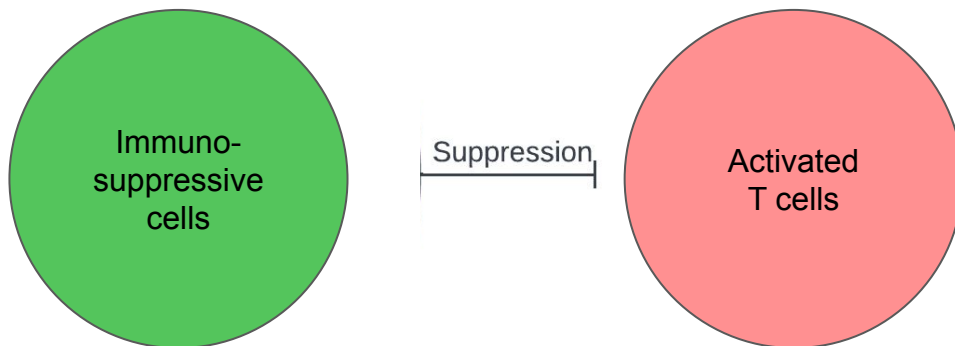- **Severe irAE**

The immune systems need to measured
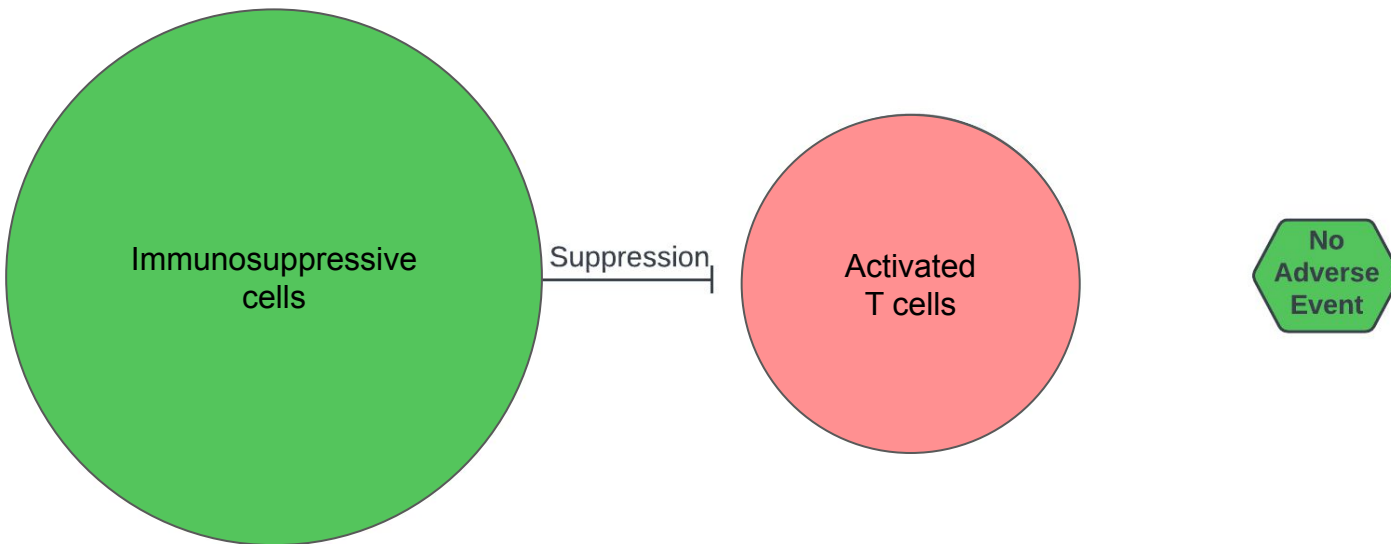
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Our research

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Successful immunotherapy is a balancing act

Goal: Attack the cancer, not the patient. But what's the right balance? And which immune cell types are most important for this balance?
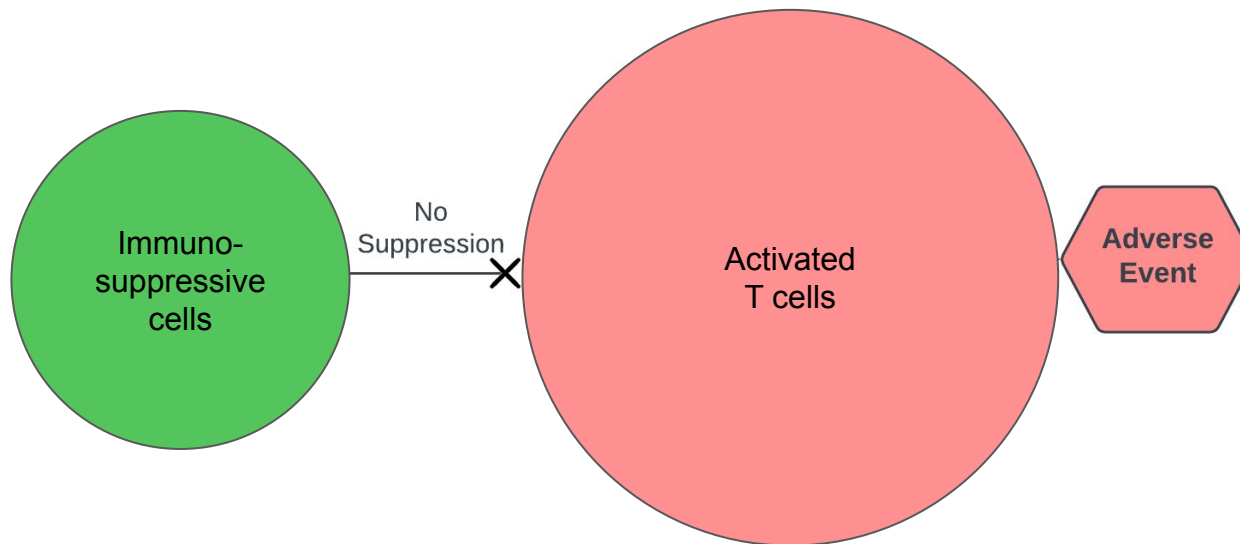

Immuno-suppressive cells

Suppression

Activated T cells

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Takeaway: our working hypothesis

Brakes working, no adverse event

Immunosuppressive cells

Suppression

Activated T cells

No Adverse Event

Data presented as a poster at SITC 2022. In collaboration with Dr. Siwen Hu-Lieskovan from the Huntsman Cancer Institute

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Takeaway: our working hypothesis

Brakes broken, adverse event

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Melanoma - Preliminary analysis for irAE immune signature with n=29 patients receiving immunotherapy
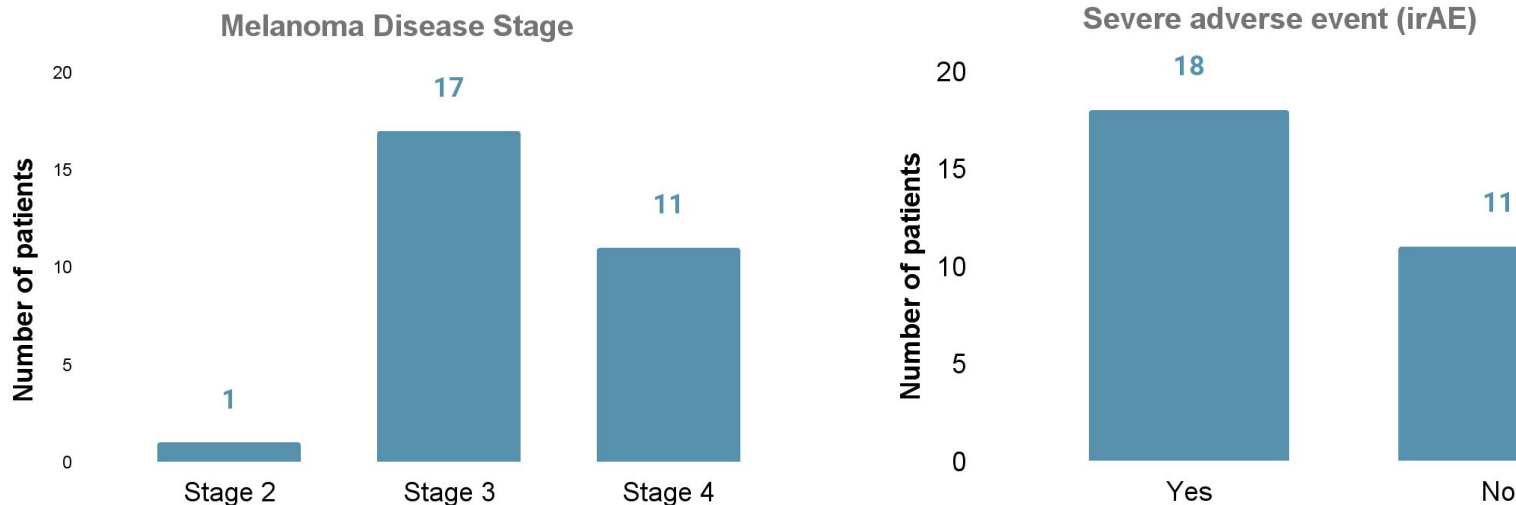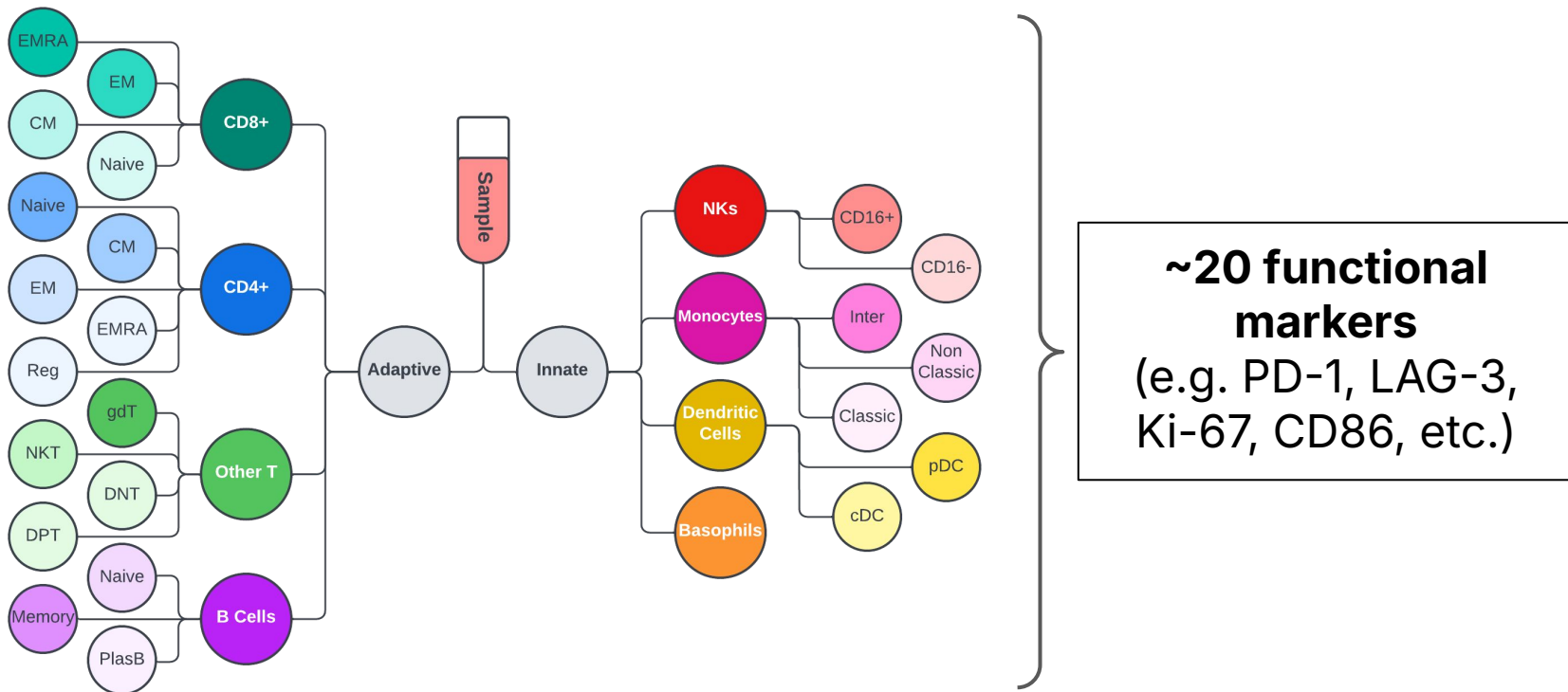
Melanoma Disease Stage

Severe adverse event (irAE)

Data presented as a poster at SITC 2022. In collaboration with Dr. Siwen Hu-Lieskovan from the Huntsman Cancer Institute.

Melanoma - PBMCs were isolated at baseline, before presentation of irAE, and at peak of irAE presentation

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Baseline

Pre-irAE

irAE Max

44 marker mass cytometry panel
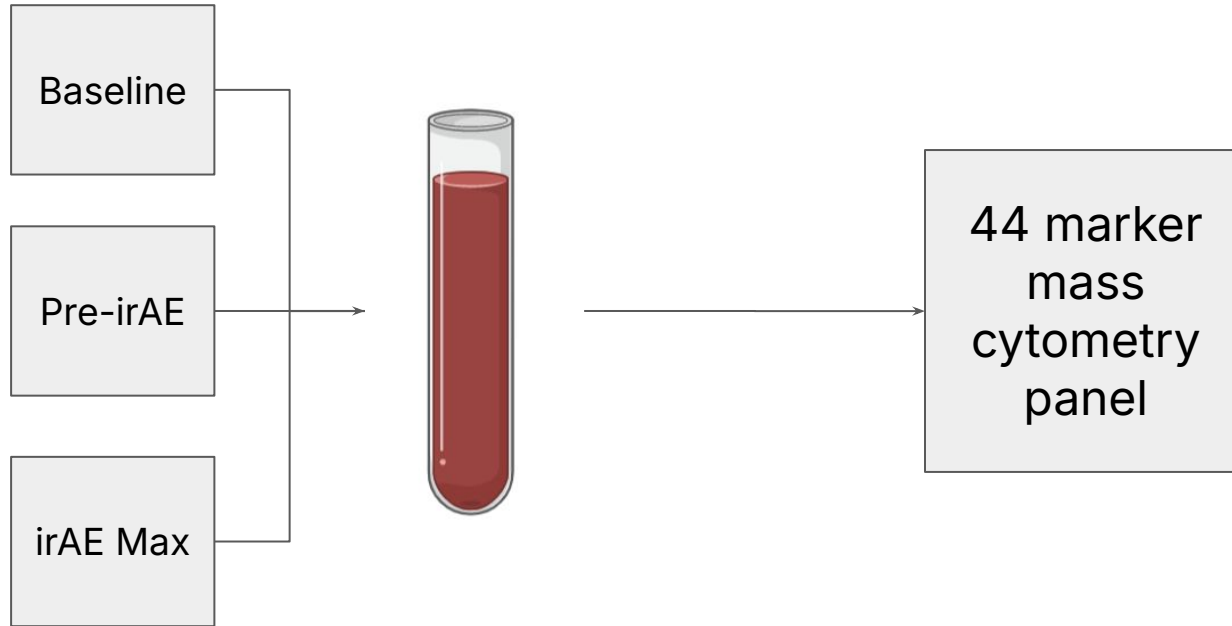
Melanoma - We looked at ~25 immune cell populations and ~20 functional markers for each sample

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~20 functional markers
(e.g. PD-1, LAG-3, Ki-67, CD86, etc.)

Melanoma - Severe irAEs are correlated with fewer pretreatment immunosuppressive TIGIT+ Tregs and CD161+ CD4 T cells

Data presented as a [poster] at SITC 2022. In collaboration with Dr. Siwen Hu-Lieskovan from the Huntsman Cancer Institute
Adjusted p-values for all comparisons p<0.01
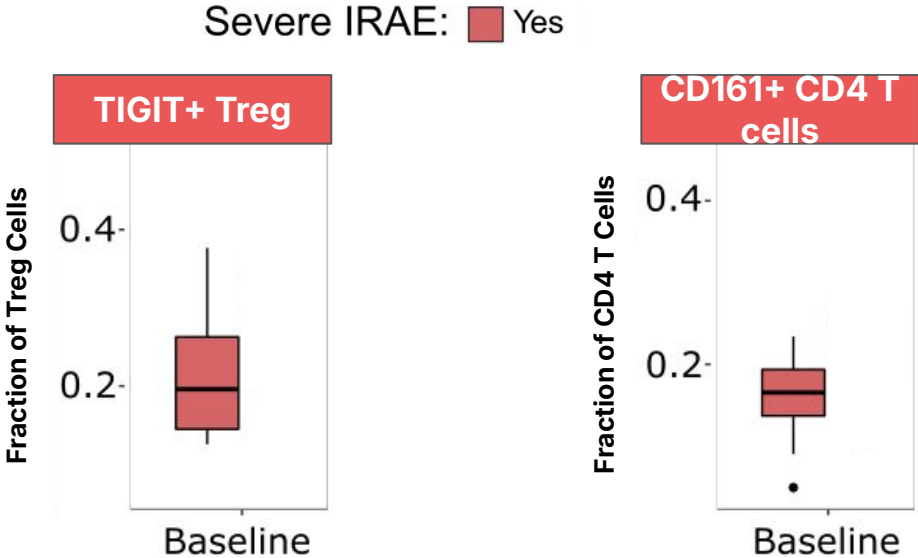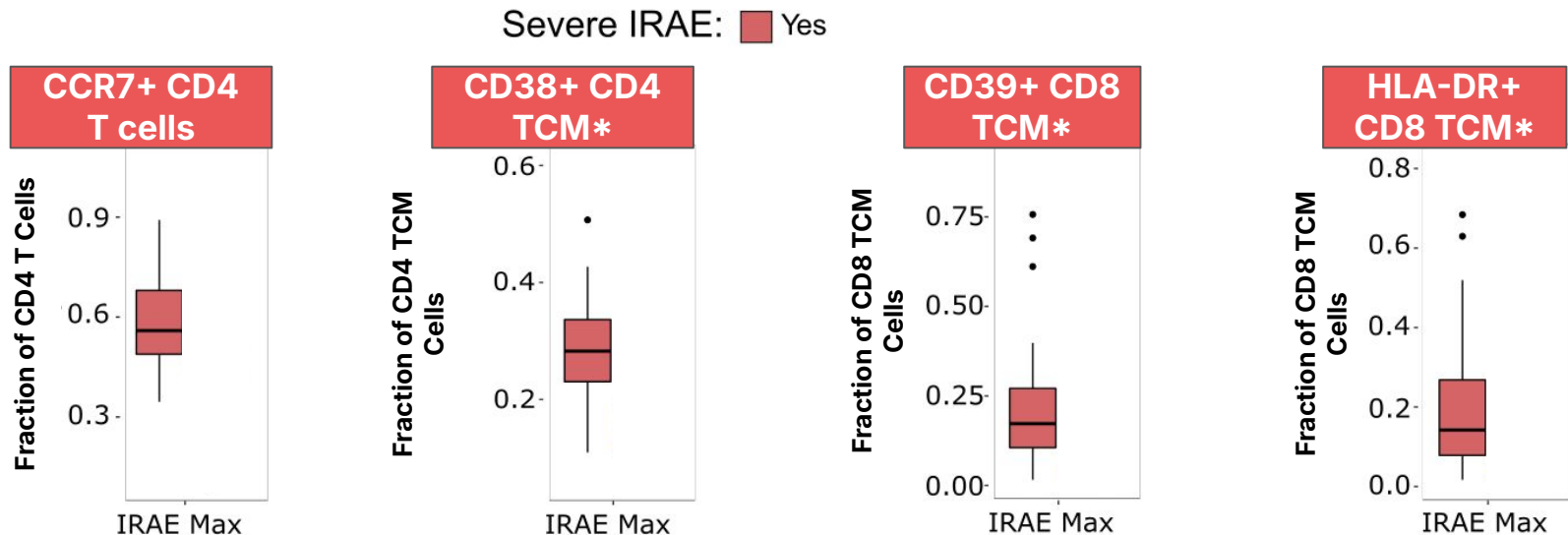
Melanoma - Severe irAE are marked by hyperactive T cells

TCM: Central Memory T cells, defined as CD27+ CD45RA- CD3+ T cells

Data presented as a poster at SITC 2022. In collaboration with Dr. Siwen Hu-Lieskovan from the Huntsman Cancer Institute
Adjusted p-values for all comparisons p<0.01

Melanoma - Severe irAE are marked by hyperactive T cells, of which signs are visible in advance of an irAE

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Severe IRAE: Yes No

CCR7+ CD4 T cells

CD38+ CD4 TCM*

CD39+ CD8 TCM*

HLA-DR+ CD8 TCM*

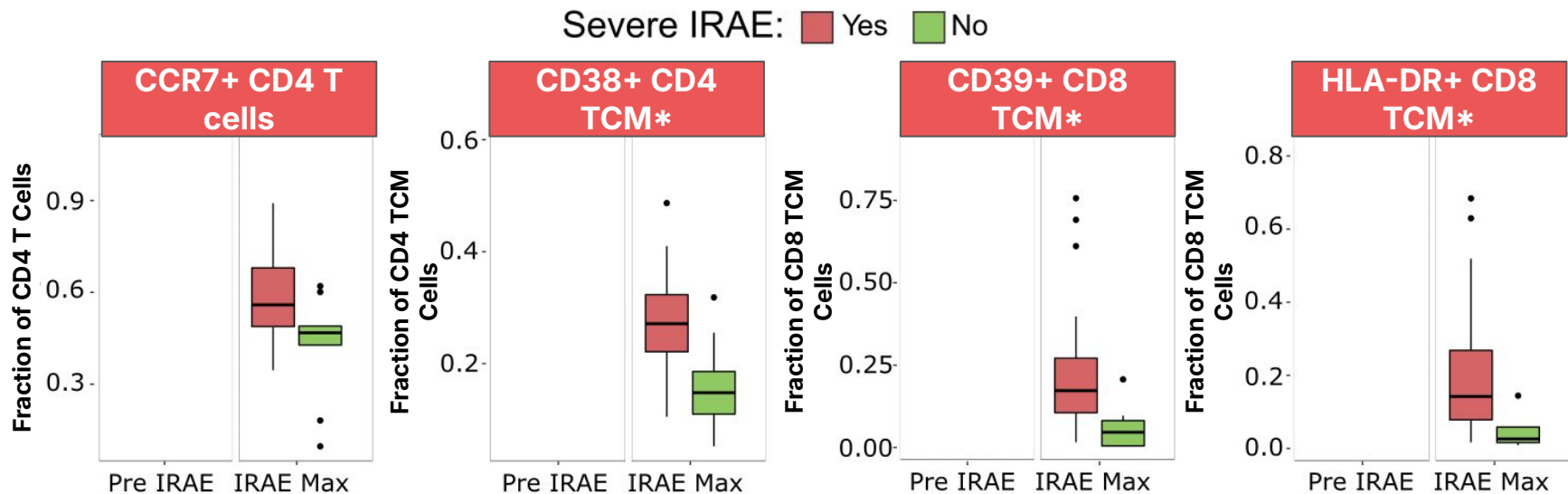TCM: Central Memory T cells, defined as CD27+ CD45RA- CD3+ T cells

Data presented as a poster at SITC 2022. In collaboration with Dr. Siwen Hu-Lieskovan from the Huntsman Cancer Institute
Adjusted p-values for all irAE max comparisons p<0.01, pre-irAE comparisons are not statistically significant

Melanoma - Unsupervised analysis can corroborate irAE features found manually

Data presented as a poster at SITC 2022. In collaboration with Dr. Siwen Hu-Lieskovan from the Huntsman Cancer Institute
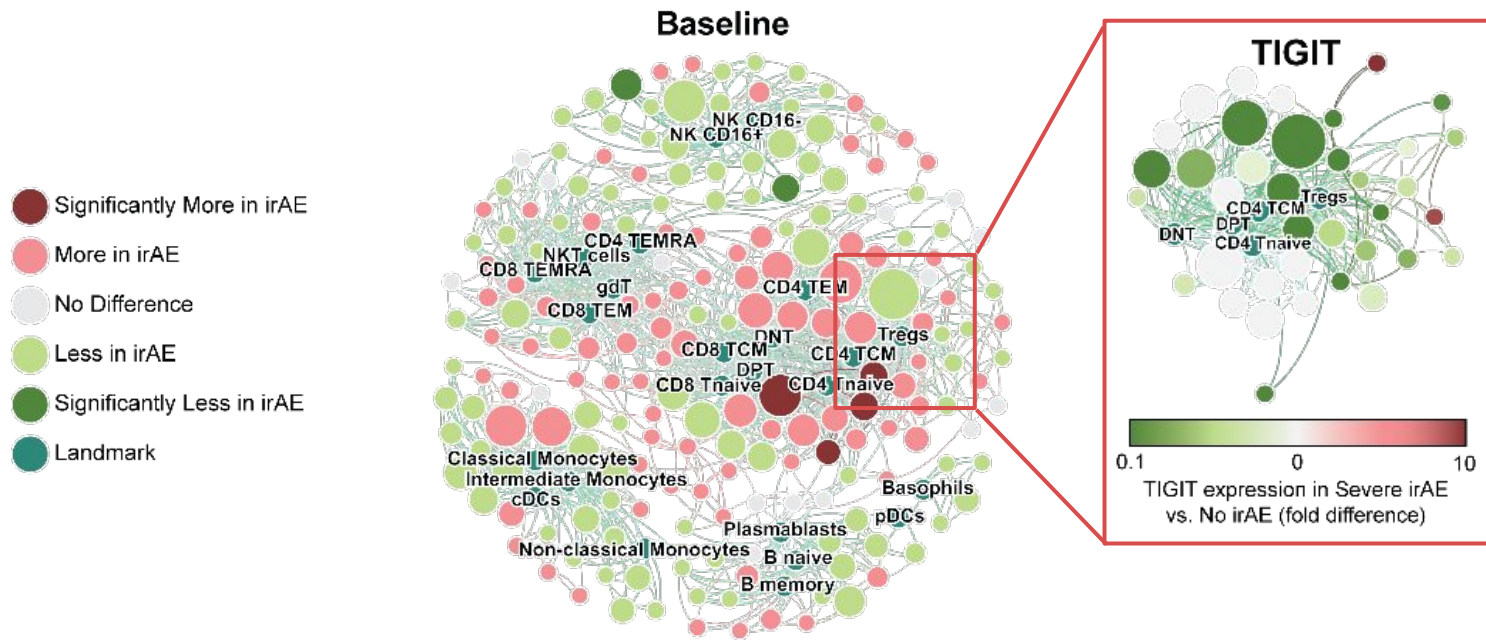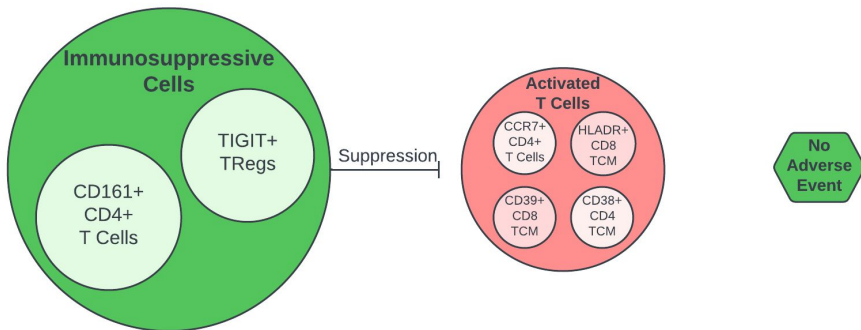
Melanoma - Unsupervised analysis can also identify and track novel cell populations associated with severe irAE
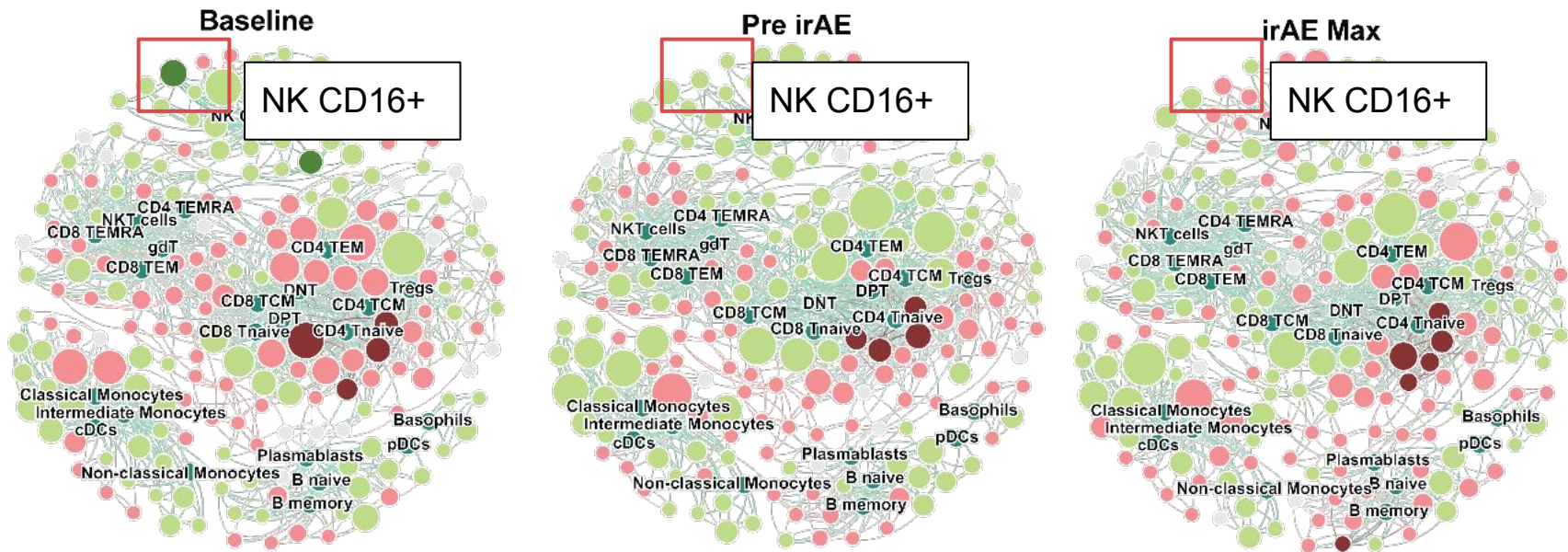
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Takeaway: our working hypothesis

Brakes working, no adverse event

Brakes broken, adverse event

Data presented as a poster at SITC 2022. In collaboration with Dr. Siwen Hu-Lieskovan from the Huntsman Cancer Institute

Future

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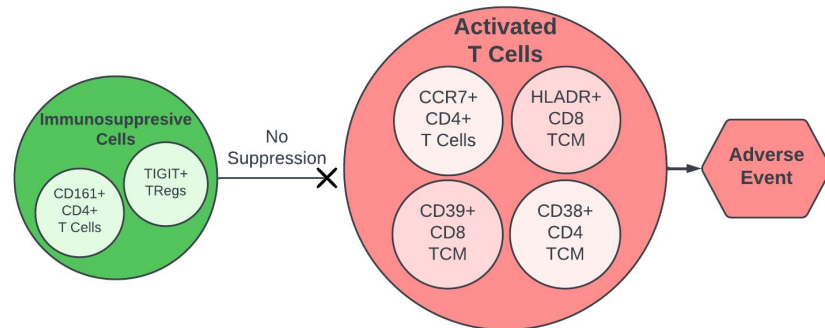
Immune signatures with immediate clinical utility

Metastatic Melanoma

No irAE: High frequencies of TIGIT+ Treg cells and CD161+ CD4 T cells
irAE: Low frequencies of TIGIT+ Treg cells and CD161+ CD4 T cells

IMMUNE PROFILING BEFORE THERAPY

- - → **Minimal risk of adverse event** to IO → aPD-1 + aCTLA-4 combination therapy

+ - → **Likely** adverse event to aPD-1 + aCTLA-4 **combination therapy** → aPD-1 alone

++ → **Likely** adverse event to **any aPD-1 IO** → BRAF/MEK therapy, clinical trial

IDEAL RESULTS

- Saved $150K/year cost of wasted IO and adverse event management
- Better therapeutic result
- Less pain and suffering

Your immune fingerprint can be used for:

Preclinical studies
- Tracking cell populations over time
- Target identification
- Mechanism of action
- Target validation

Clinical studies
- **Biomarkers of adverse events**
- Biomarkers of response
- Timing and dosing
- Patient selection

Cell therapy development
- Find donors who are suitable for autologous cell therapies
- Fine-tune characteristics of the cellular product
- Track and profile cell therapy product in vivo

Routine measurement of tumors → immune system

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Thank you!

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