Immune-Mediated Toxicities

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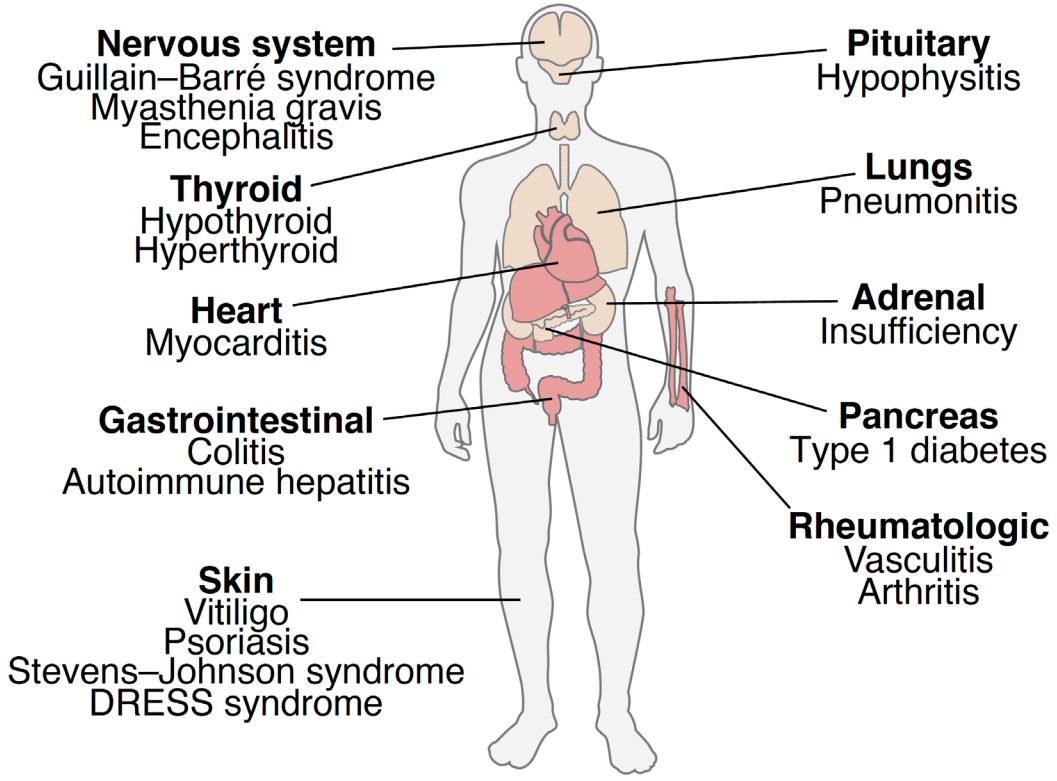

FOCIS Annual Meeting
Cancer Immunity & Immunotherapy Course
Boston, June 20th, 2023

CENTER FOR IMMUNOLOGY AND INFLAMMATORY DISEASES

Mass General Brigham
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Financial Disclosures

I have the following financial relationship to disclose:

- consultant for Bristol Myers Squibb

I will not discuss off label use or investigational use in my presentation.

Outline

1- Immune related adverse events (irAE) clinical presentation overview

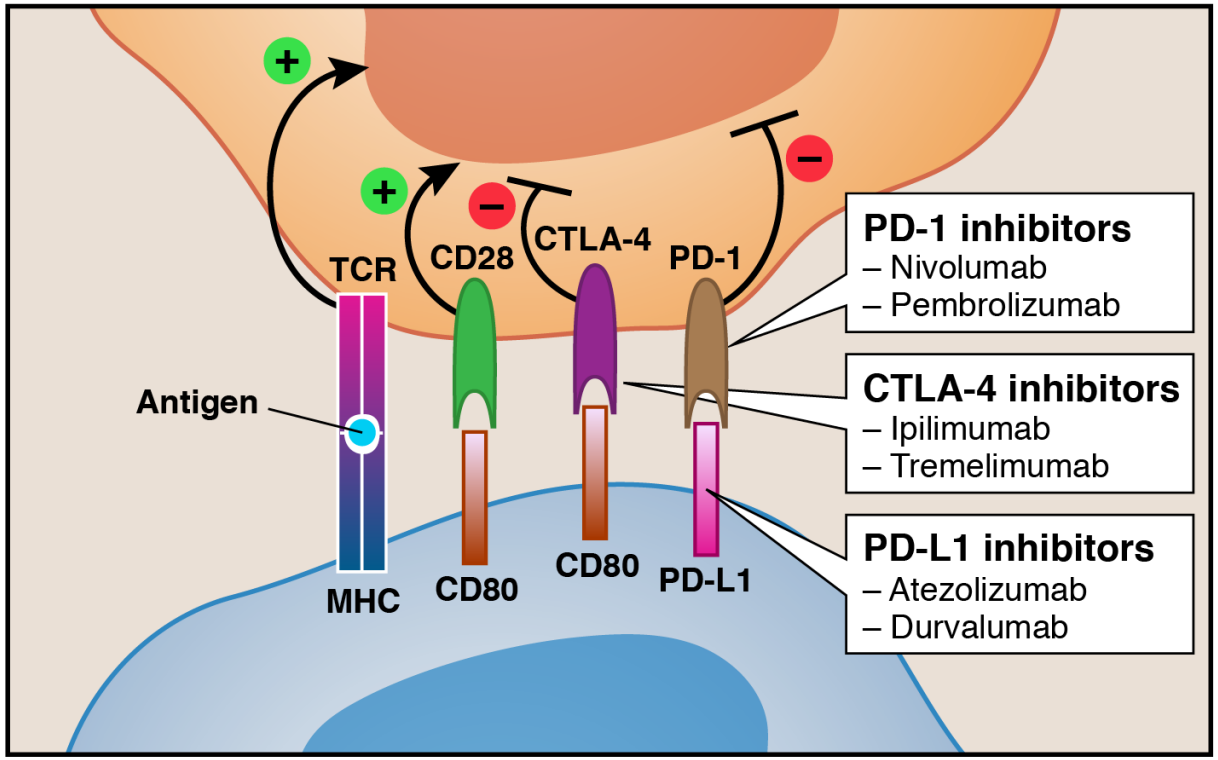
2- Challenges of mitigating irAEs

3- Proposed irAE mechanisms to-date

4- Defining key pillars for setting up irAE focused translational program

5- Pressing needs and gaps in the field

Immune Checkpoint Inhibitors (ICIs): over 80 FDA-approved indications in cancer

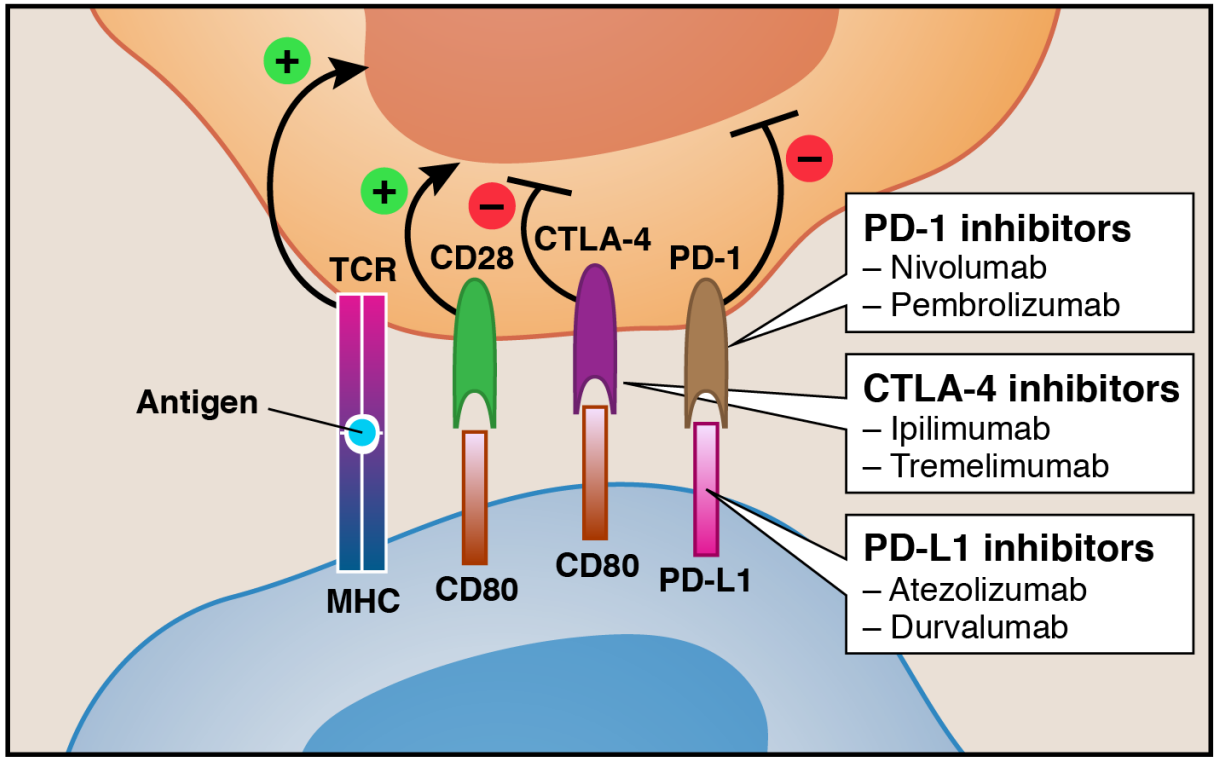


Response rate between 12%-65% depending on cancer type

Mechanism of action: “re-establish” T cells ability to attack tumor tissue”

Drake et al. (2014) *Nat Rev Clin Oncol*.

Immune Checkpoint Inhibitors (ICIs): How can we improve ICI therapeutic successes?



1- Trigger immune response in non-responders / cold tumors

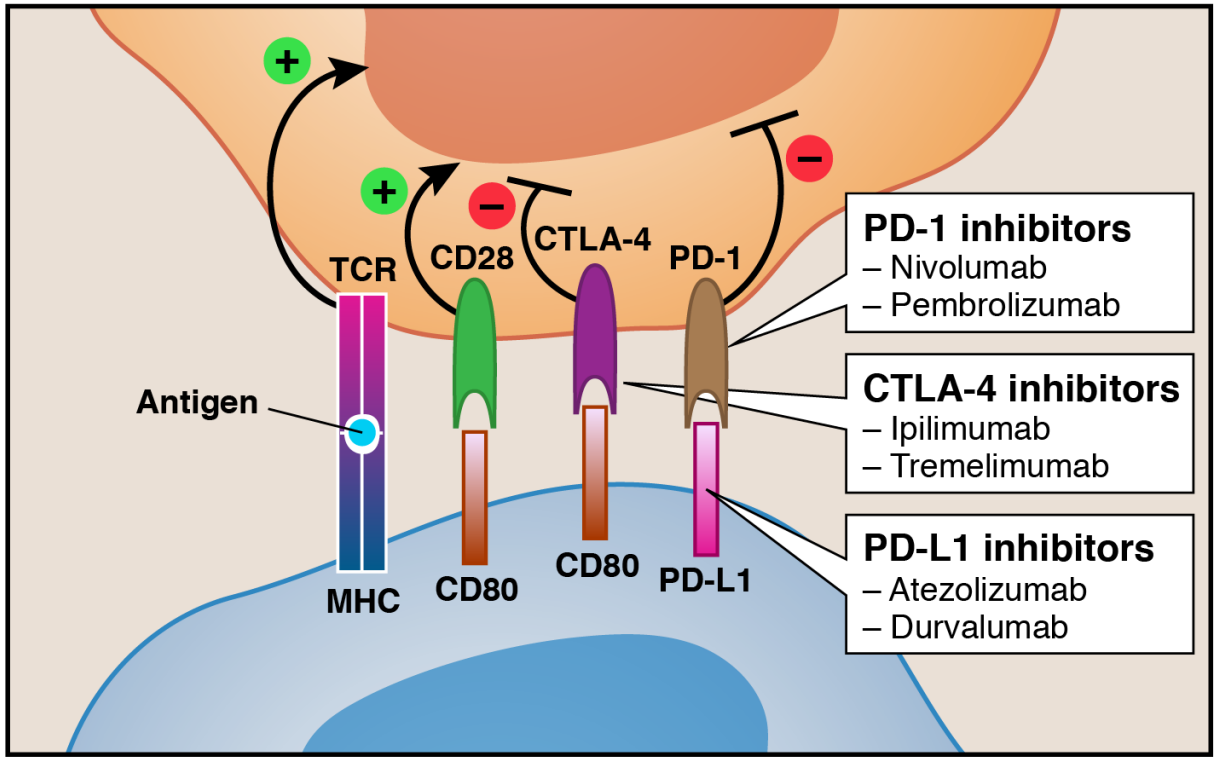
2- Overcome therapeutic resistance

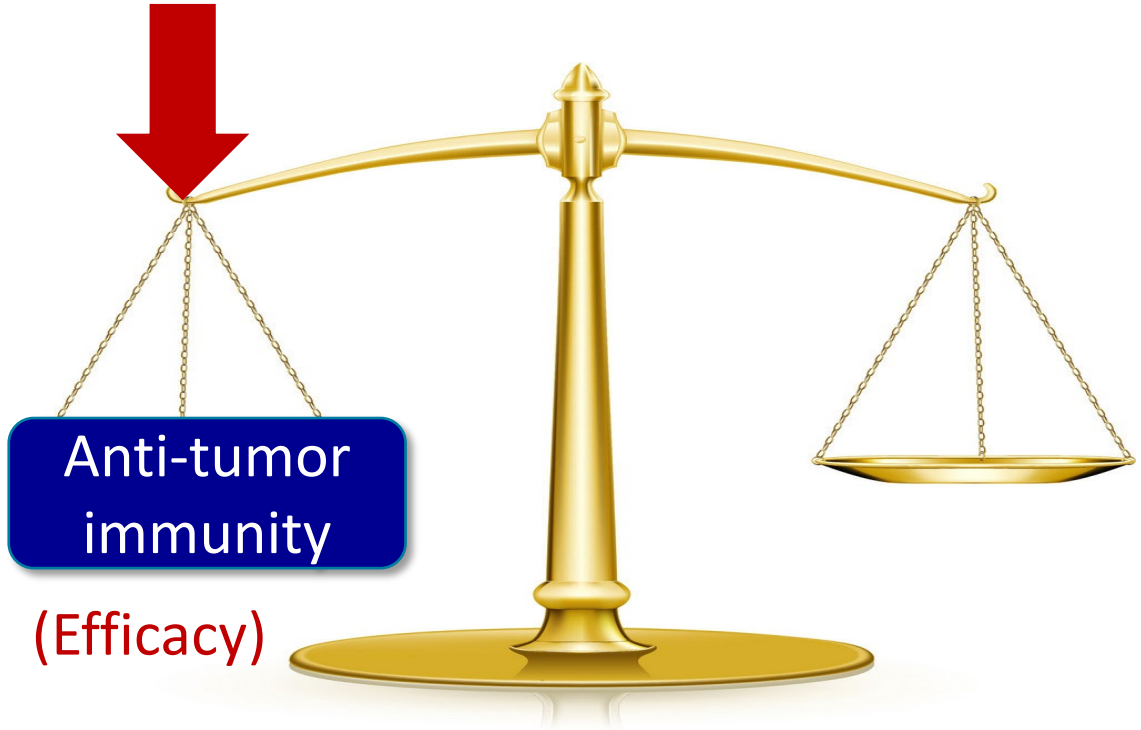
3- Predict and mitigate immune related adverse events (irAEs)

Mechanism of action: "re-establish" T cells ability to attack tumor tissue"

Drake et al. (2014) *Nat Rev Clin Oncol*.

Immune Checkpoint Inhibitors (ICIs): How can we improve ICI therapeutic successes?

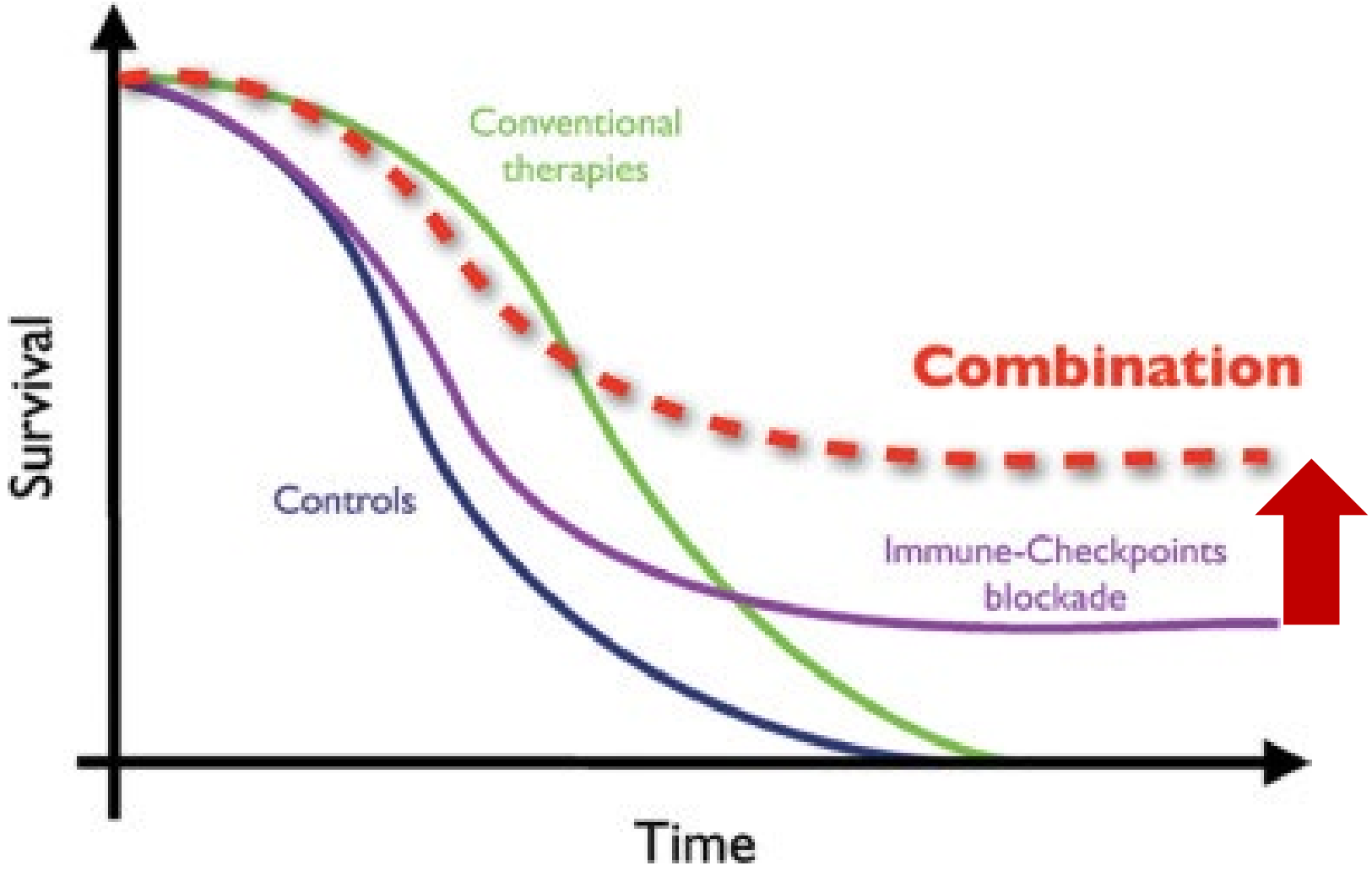




Mechanism of action: "re-establish" T cells ability to attack tumor tissue"

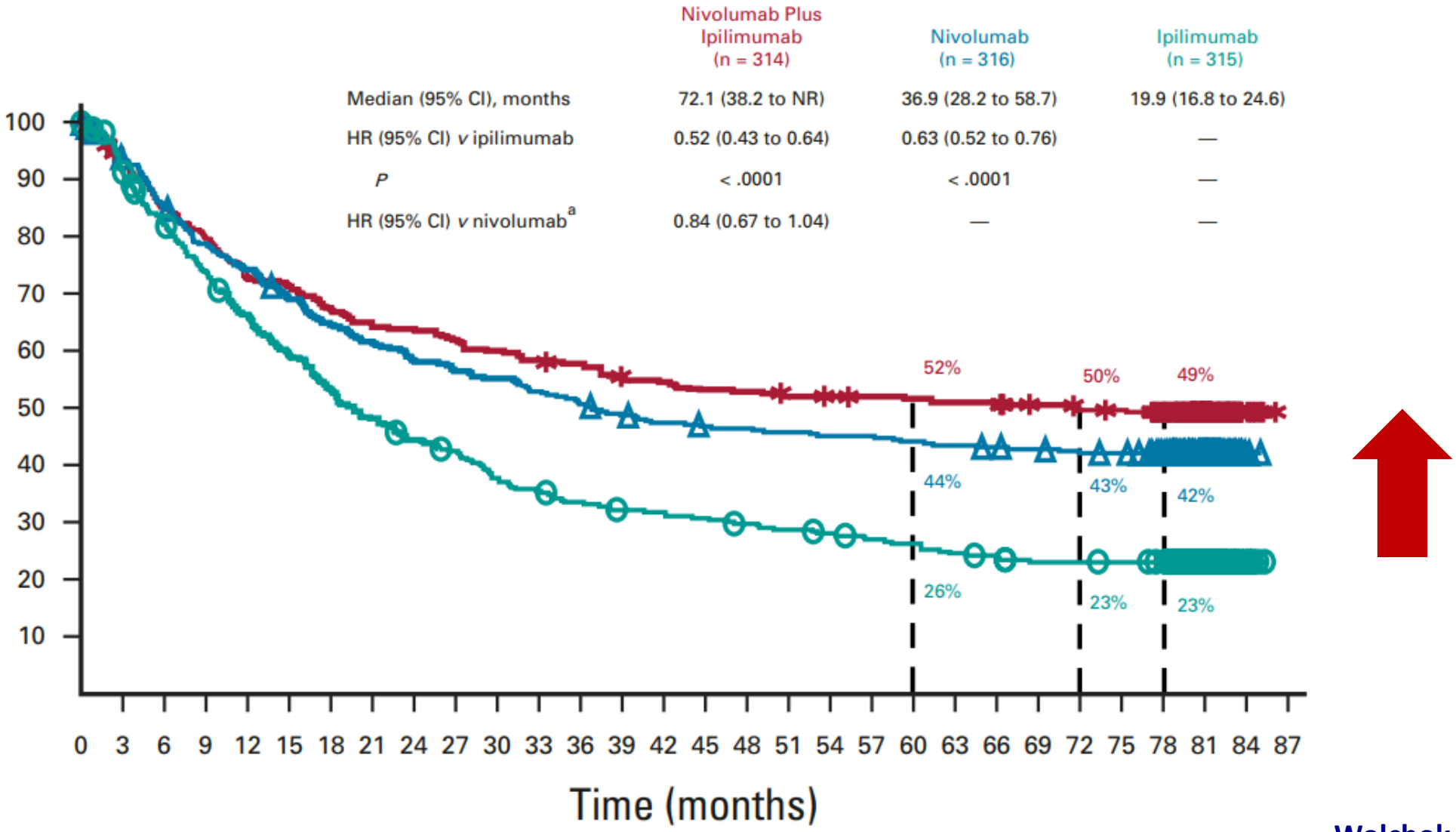
Drake et al. (2014) *Nat Rev Clin Oncol*.

Bending the Survival Curve



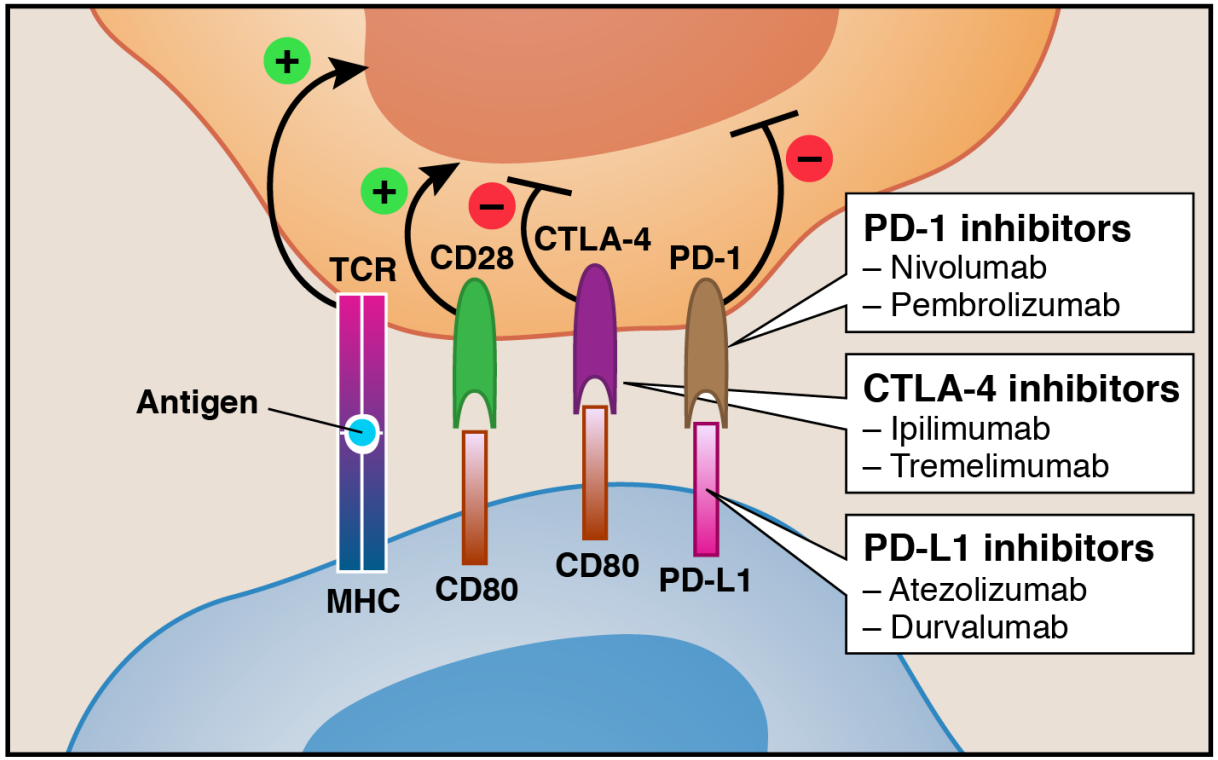
Champiat, Journal of Thoracic Oncology, 2014

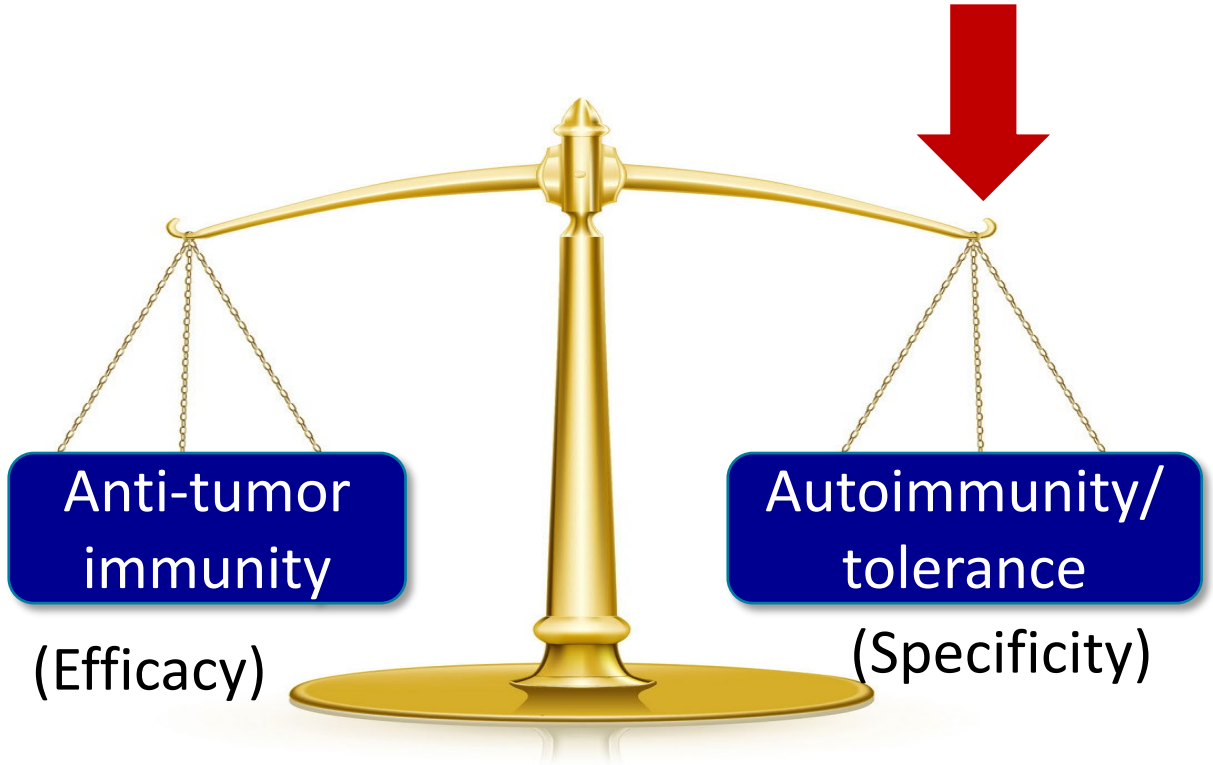
Bending the Survival Curve



Wolchok, JCO, 2022

Immune Checkpoint Inhibitors (ICIs): How can we improve ICI therapeutic successes?

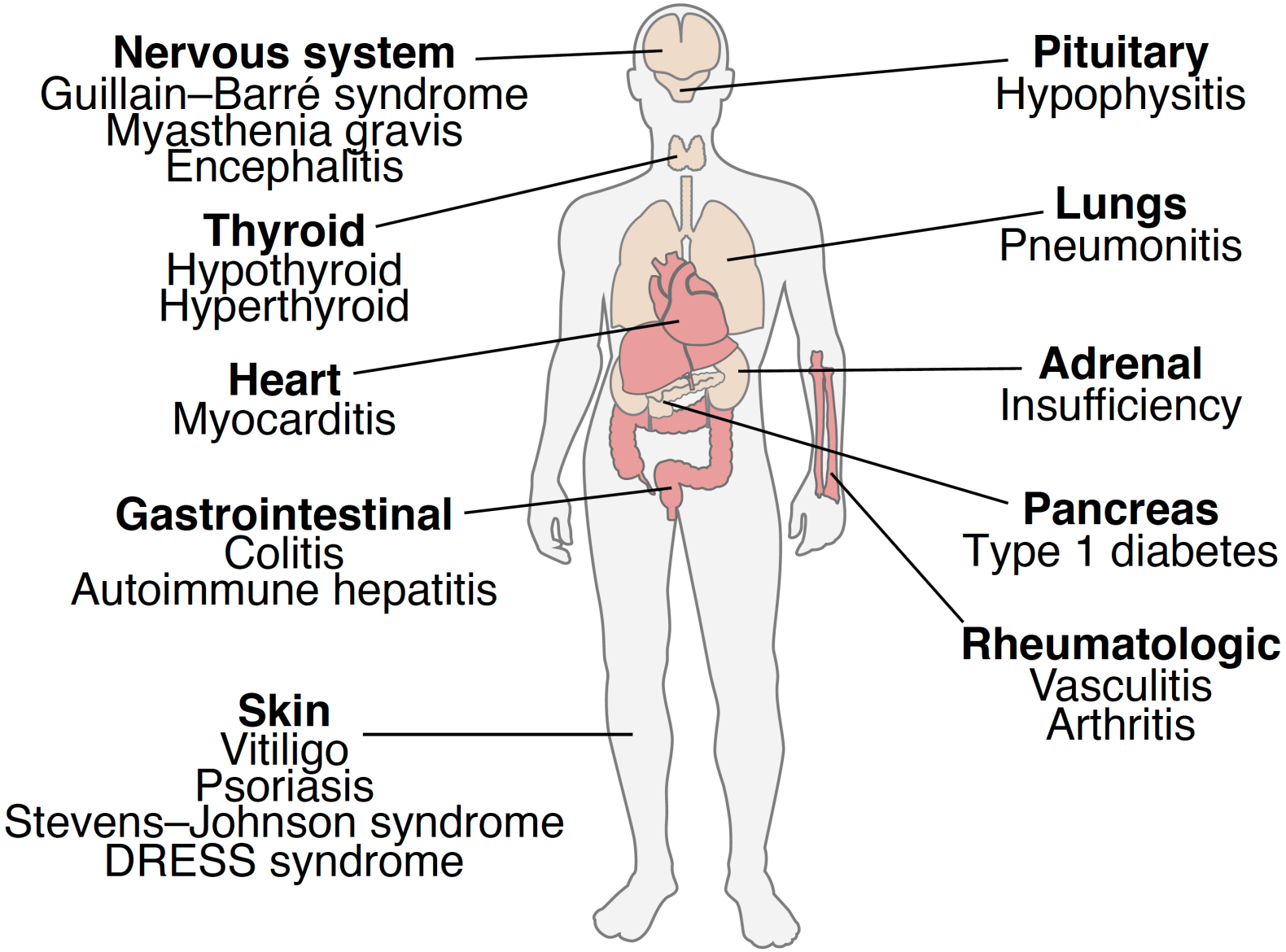


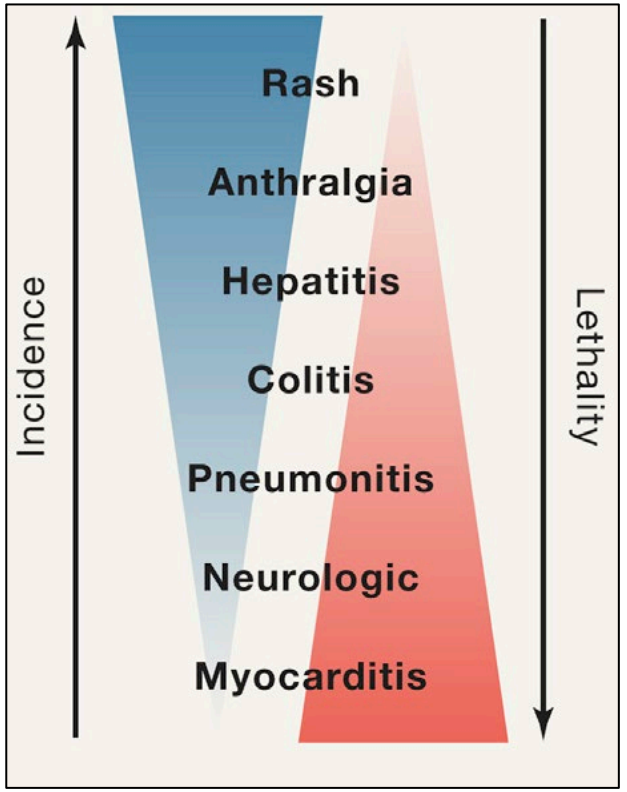


Mechanism of action: "re-establish" T cells ability to attack tumor tissue"

Drake et al. (2014) *Nat Rev Clin Oncol*.

Lifesaving potential ICI therapy is severely limited by immune related adverse events (irAEs)





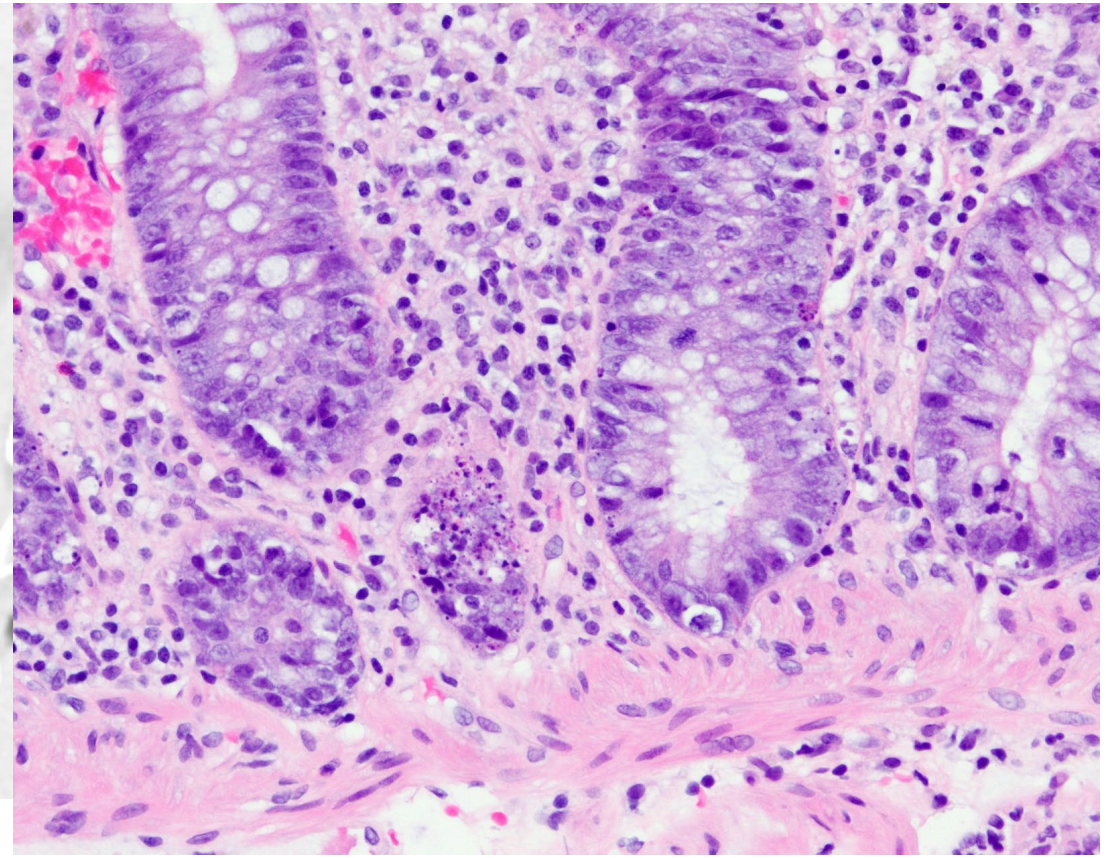
Dougan M et al. Cell. 2021

Case 9-2020: A 64-Year-Old Man with Shortness of Breath, Cough, and Hypoxemia

Reynolds KL, et al. N Engl J Med. 2020 ;382(12):1150-1159.

Case 9-2020 overview

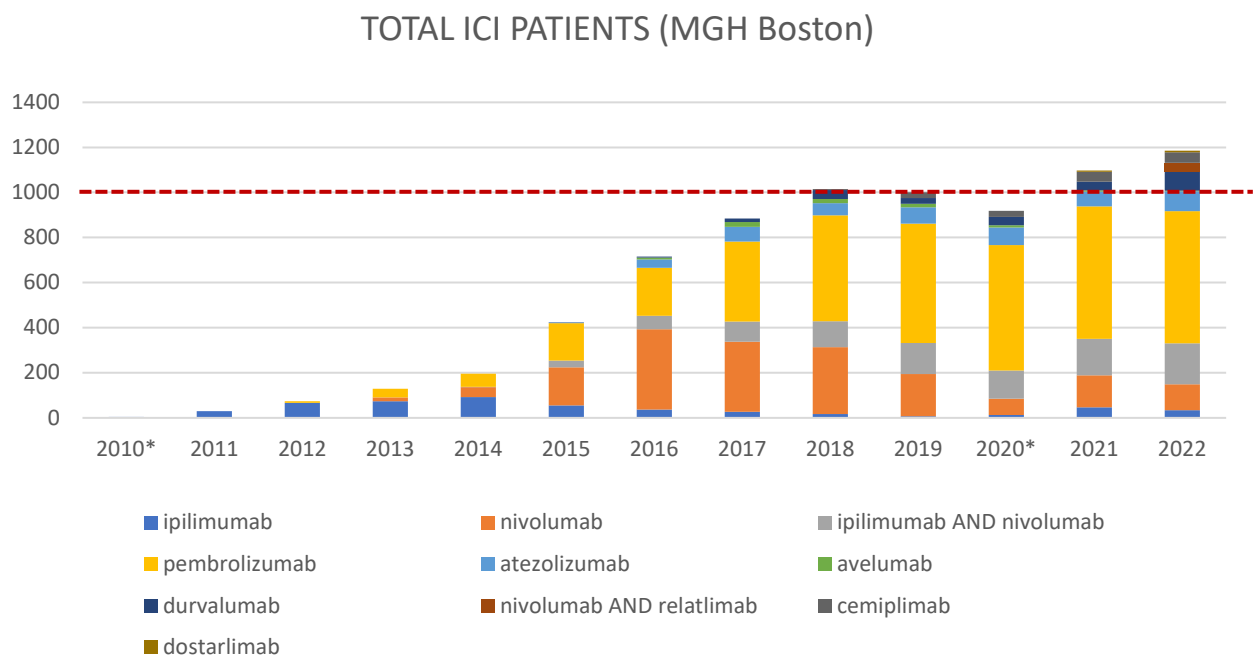
- 12/28/2015: Brain metastasis discovered (1.7 cm), Lung Lesion (2 cm)
- 1/11/2016: Brain metastasis resected, melanoma
- 3/9/2016: First Dose of Combination Immunotherapy
  - Ipilimumab 3 mg/kg (CTLA-4 inhibitor)
  - Nivolumab 2 mg/kg (PD-1 inhibitor)
- 3/30/2016: Second Dose of Combination Immunotherapy
- 4/4/2016: Admitted with Pneumonitis
- 5/12/2016: Admitted with Colitis
- 5/25/2016: Immune System Started to Attack Nerves
- 5/27/16: Intubated in intensive care
- 6/5/16: Expired
- Striking Findings at Autopsy:
  - Histological evaluation of lung nodule = necrosis
  - Neuropath Report = T cell (CD3) infiltrate causing sensory ganglionitis, loss of myelinated fibers, naked axons
  - Fungal Pneumonia/Fungal Colitis = Aspergillus Terreus



Reynolds KL, et al. N Engl J Med. 2020 ;382(12):1150-1159.

irAEs incidence will continue rising with ICI becoming standard of care

MGH treats over 1,000 patients/year with ICI



30% of US cancer patients eligible for ICIs

All Eligible Cancer patients in the US

36% Eligible for immune checkpoint inhibitor # 234, 730 + Trials

20% Serious Events #50,000 Pts/Year

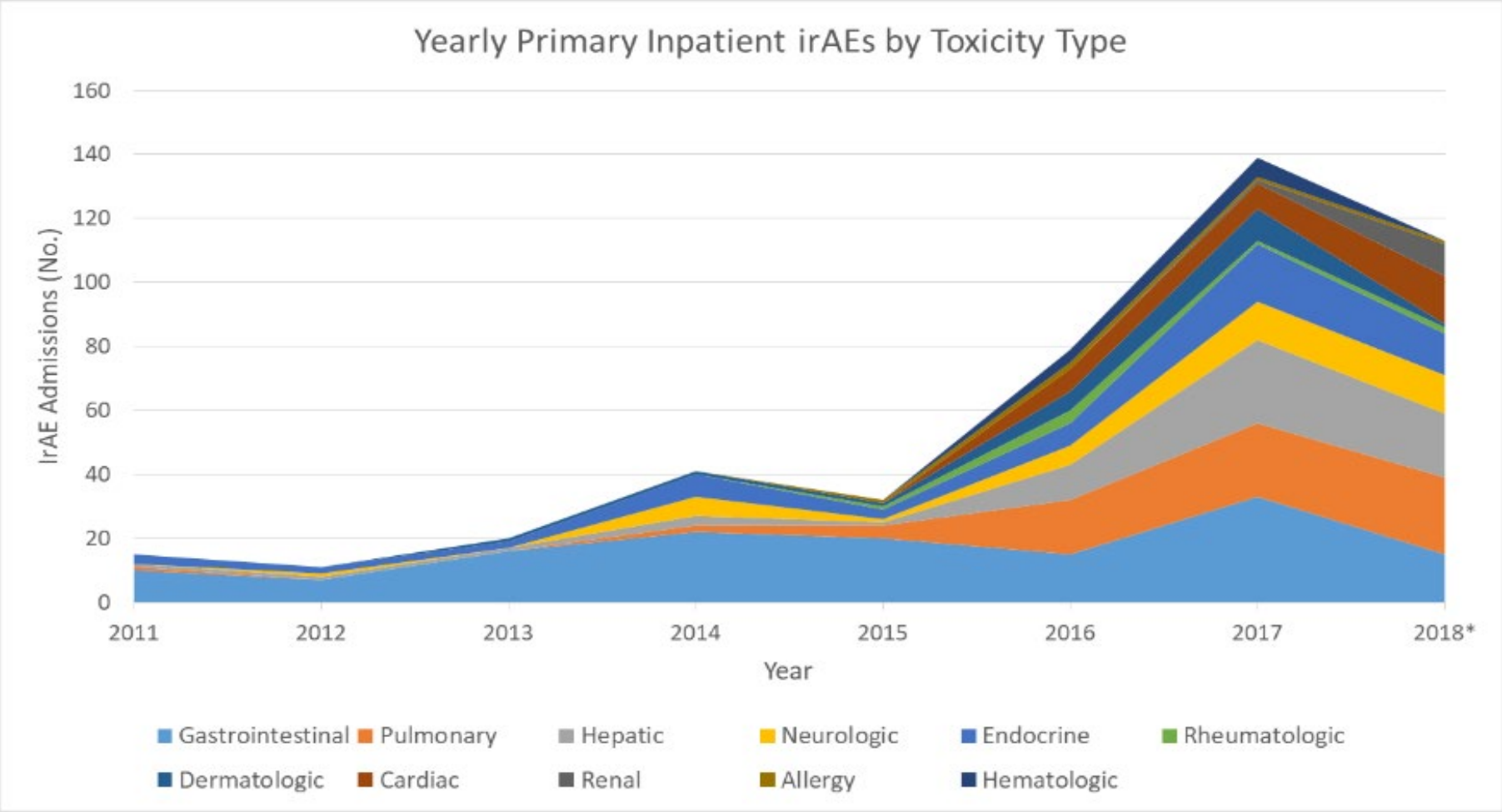
2% Fatal Events #4,700 Pts/Year

→ ***This is ONLY for monotherapy***

→ ***Not accounting for combination & adjuvant therapy***

Haslam, Jama Network Onc 2020

MGH inpatient irAE admissions



Molina GE, et al. Oncologist. 2021 Jun;26(6):514-522

Chronic irAE are more prevalent than previously recognized

- chronic irAEs: defined as those persisting **for >12 weeks** after discontinuation of an anti-PD-1/PD-L1
- chronic irAEs occur in **43.2% of patients** (ref. below)

- **Why the lack of irAE recognition?**

→ **acute** irAEs will at least **improve** with **steroids** and often resolve altogether

→ irAE reporting in **early** clinical **trials** focus on most **frequent irAE** (occur in ≥10% participants).

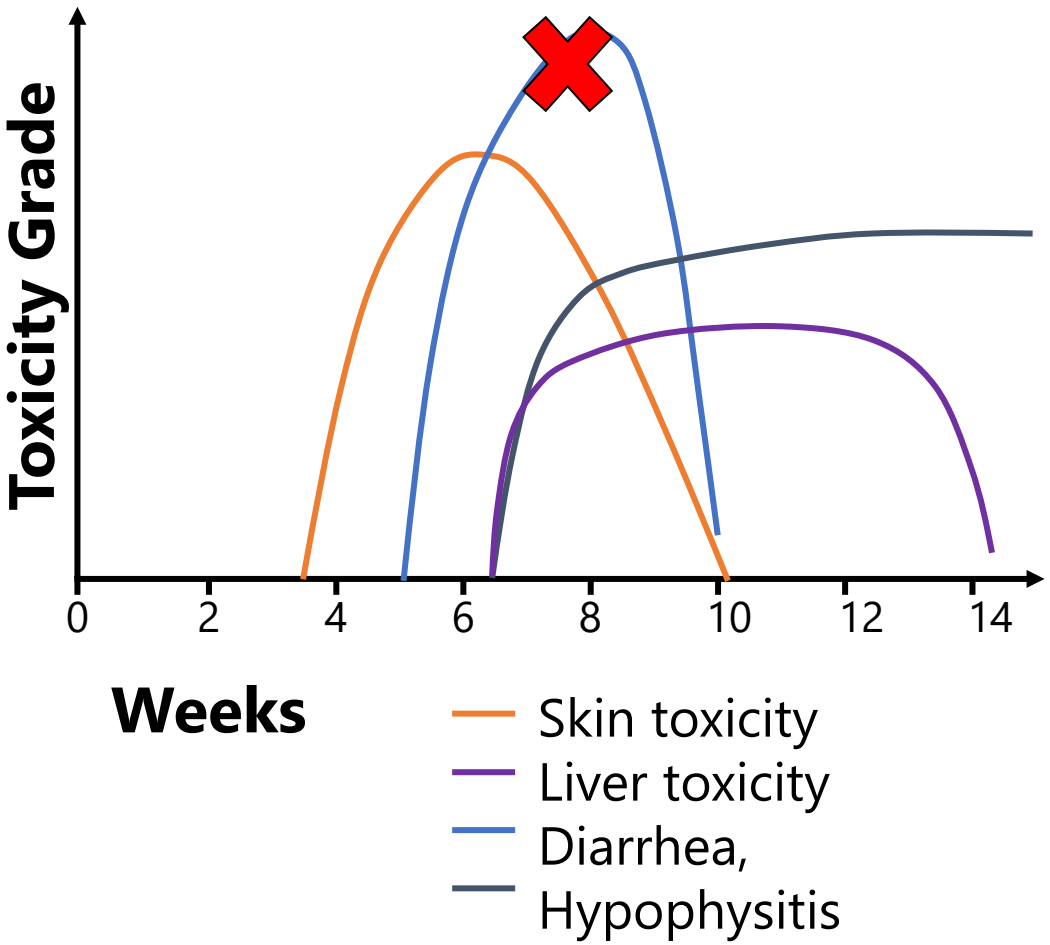
Low-frequency events are under-reported/recognized regardless of their aggregate prevalence

→initial clinical trials enrolled patients with **metastatic cancer**; characterizing chronic and long-term events is challenging because of **limited life expectancy** constraining long-term follow-up

→presence of **multiple co-morbidities** in cancer **patients** can impair the identification of chronic irAEs

Patrinely, J. R. Jr et al. JAMA Oncol. 7, 744–748 (2021).

Kinetics of immune-related adverse events



- Most irAEs occur by **week 24** (6 months)
- **Combination** therapy **more toxic** than monotherapy
- **Skin** most common
- Toxicity **incidences vary** across **ICI used**

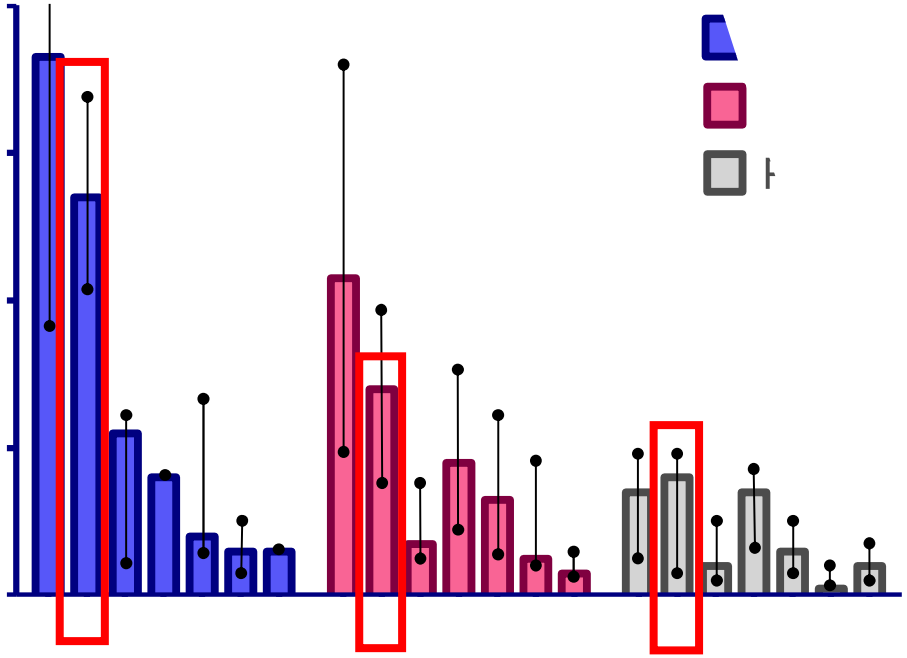
→ Colitis and hypophysitis more common with anti- CTLA-4

→ Thyroiditis more common with anti-PD1

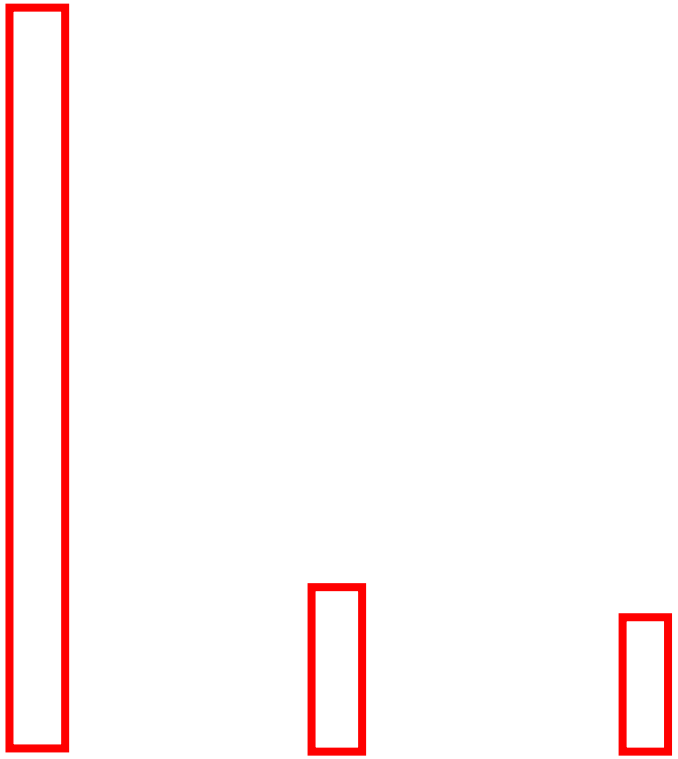
Weber, J Clin Oncol, 2015

The distribution, severity, and frequency of irAEs is related to the class of ICI used

Distribution of Grade 1-2 IRAEs



Distribution of Grade 3-5 IRAEs



GI Toxicities

Michot et al. European Journal of Cancer (2016)

Are anti-CLTA-4 and anti-PD1/PDL1 irAE different?

- **Histopathologically**, anti-CTLA4 irAEs are **not distinguishable** from anti-PD1/PDL1 irAE

- **Treatment of irAEs** appears is **dependent** on **the organ involved** and the **severity** of the inflammation, rather than on the class of checkpoint inhibitor that was used

Limited understand of irAE mechanisms = limited tailored treatment solutions

- **Distinct** immunopathogenic **mechanisms** result in **irAEs**, leading to **distinct** histopathological **phenotypes** in each affected **organs**

- **Example:** immune- related nephritis or musculoskeletal adverse events can be:

→lymphocyte driven

→complement mediated

→antibody mediated

→caused by sterile inflammation (eg., pauci- immune glomerulonephritis) without any immune infiltrates on histopathological analysis

- Should these different presentations be **treated differently**?

→ Current guidelines **do not** make such a **distinction**.

Esfahani et al. Nat Rev Clin Oncol. 2020 Aug;17(8):504-515

Grade of Toxicity & General Guidelines for Management

Problem: everything is reactive **NOT** proactive

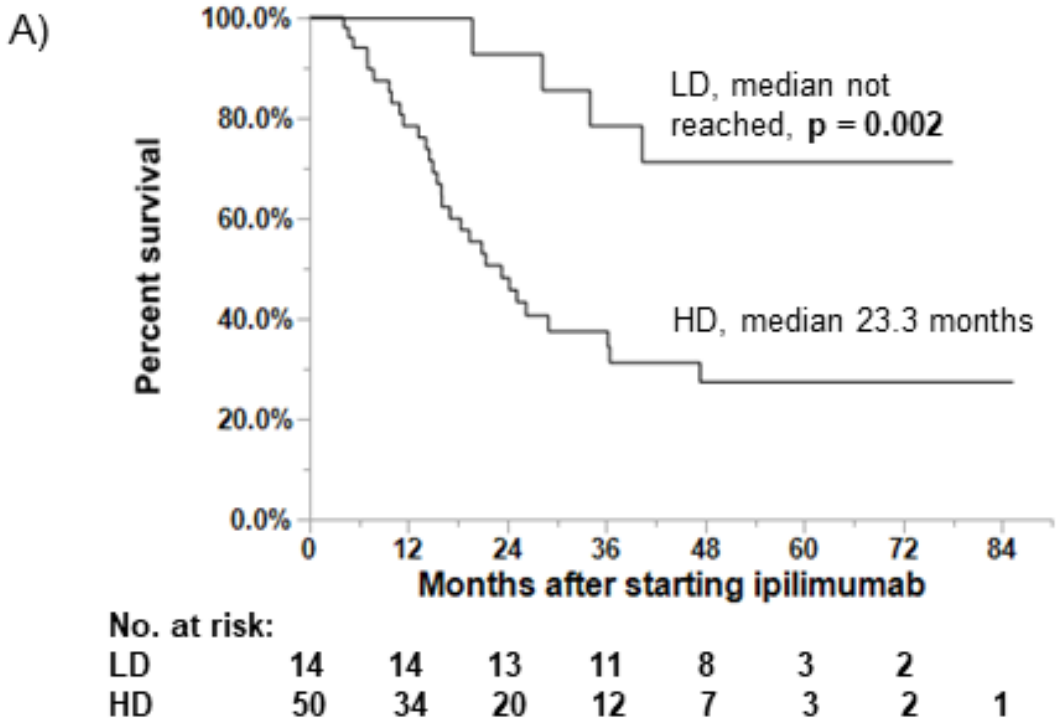
→poor understanding of irAE pathogenesis = we don't know what are we treating

Grade	Description	Setting	Treatment/intervention	Immunotherapy
1	Mild, asymptomatic	Outpatient	Observation	Continue
2	Moderate	Outpatient (close monitoring)	**Steroids** (0.5-1 mg/kg/day), oral	**Hold** pending resolution
3	Severe or medically significant	Inpatient	**Steroids** (1-2 mg/kg/day), IV	**Hold**
4	Life threatening consequences	ICU	**Steroids** (1-2 mg/kg/day), Consider additional agents (i.e. infliximab)	**Discontinue**

•**ESMO**: Haanen et al. Ann Oncol. 2017 Jul 1;28(suppl_4):iv119-iv142.
•**SITC**: Puzanov et al. J Immunother Cancer. 2017 Nov 21;5(1):95.
•**ASCO/NCCN**: Brahmer et al. J Clin Oncol. 2018 Jun 10;36(17):1714-1768.

Is it important to avoid steroids? Impact on survival

- *Faje et al. Cancer 2018: High-dose glucocorticoids for the treatment of ipilimumab-induced hypophysitis is associated with reduced survival in patients with melanoma. Cancer 2018;124:3706-3714.* **(referring to high dose steroids)**



Metastatic melanoma treated with ipilimumab monotherapy complicated by hypophysitis

Horvat et al. . *J Clin Oncol 2015;33:3193-8.*
Fajje AT, et al. Cancer 2018;124:3706-3714.
Arbour KC et al. J Clin Oncol 2018;36:2872-2878
Gourd E, et al. Lancer Oncol 2018; 19 (10).

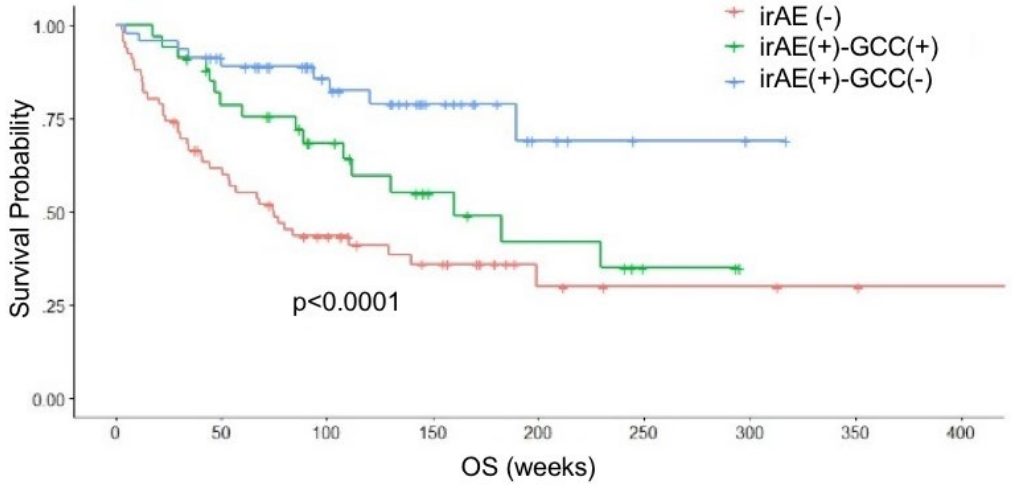
Is it important to avoid steroids? Immunosuppression & efficacy

- Arbour KC, et al. J Clin Oncol 2018. Impact of baseline steroids on efficacy of programmed cell death-1 and programmed death-ligand 1 blockade in patients with non-small-cell lung cancer. **(referring to baseline steroids)**

- Gourd E, et al. Lancer Oncol 2018: Baseline corticosteroids reduce activity of PD-L1 blockade **(referring to baseline steroids)**

- Bai X et al. Clin Cancer Res 2021: Early use of high-dose glucocorticoid for the management of irAE is associated with poorer survival in patients with advanced melanoma treated with anti-PD-1 monotherapy

→ The use of of high dose steroids during PD1/PDL1 treatment can have potential detrimental effect on anti-cancer response



→ 947 patients, 509 (54%) developed irAEs

Bai X et al. Clin Cancer Res. 2021 Nov 1;27(21):5993-6000

Better treatment solutions start with understanding irAE mechanisms

Why study toxicities directly in patients?

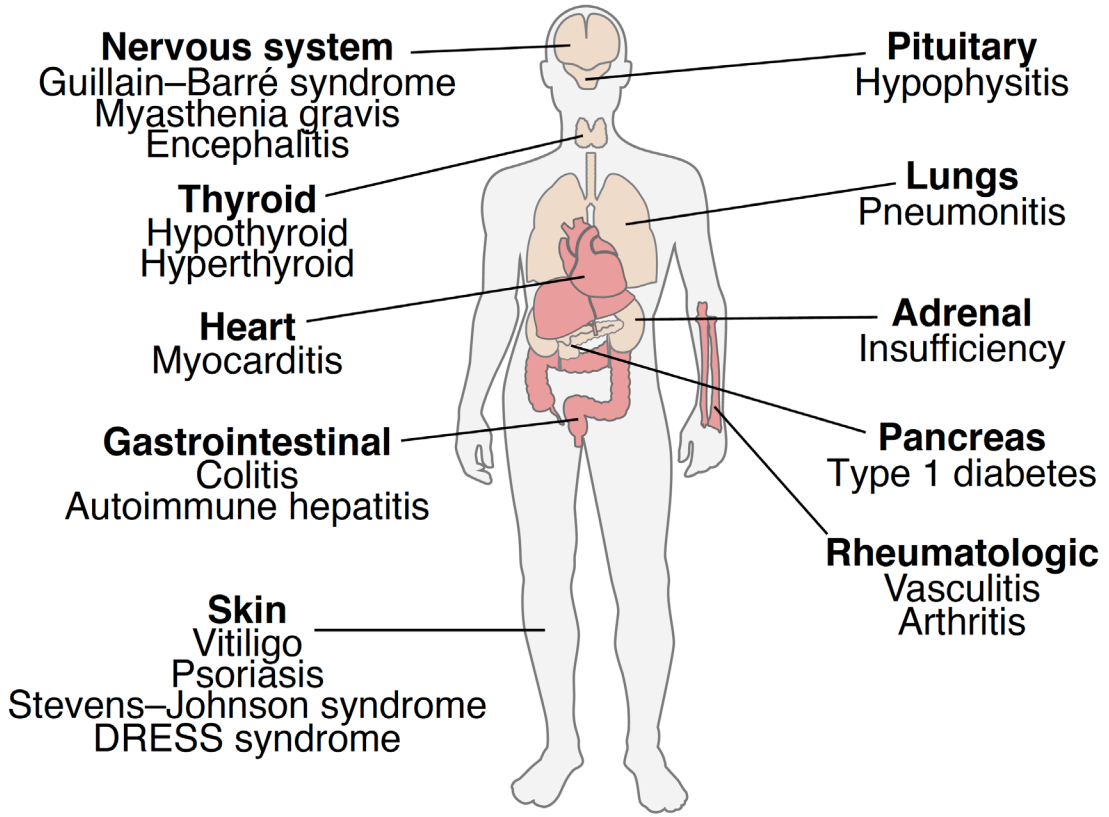
→ Many complications not-well (yet) phenocopied in pre-clinical models

irAE presentation can phenocopy autoimmune disease presentation

- **Autoimmune disease**: evidence exists for T cell-mediated or B cell- mediated immunity against self- antigens, which is **not the case for all irAEs**.

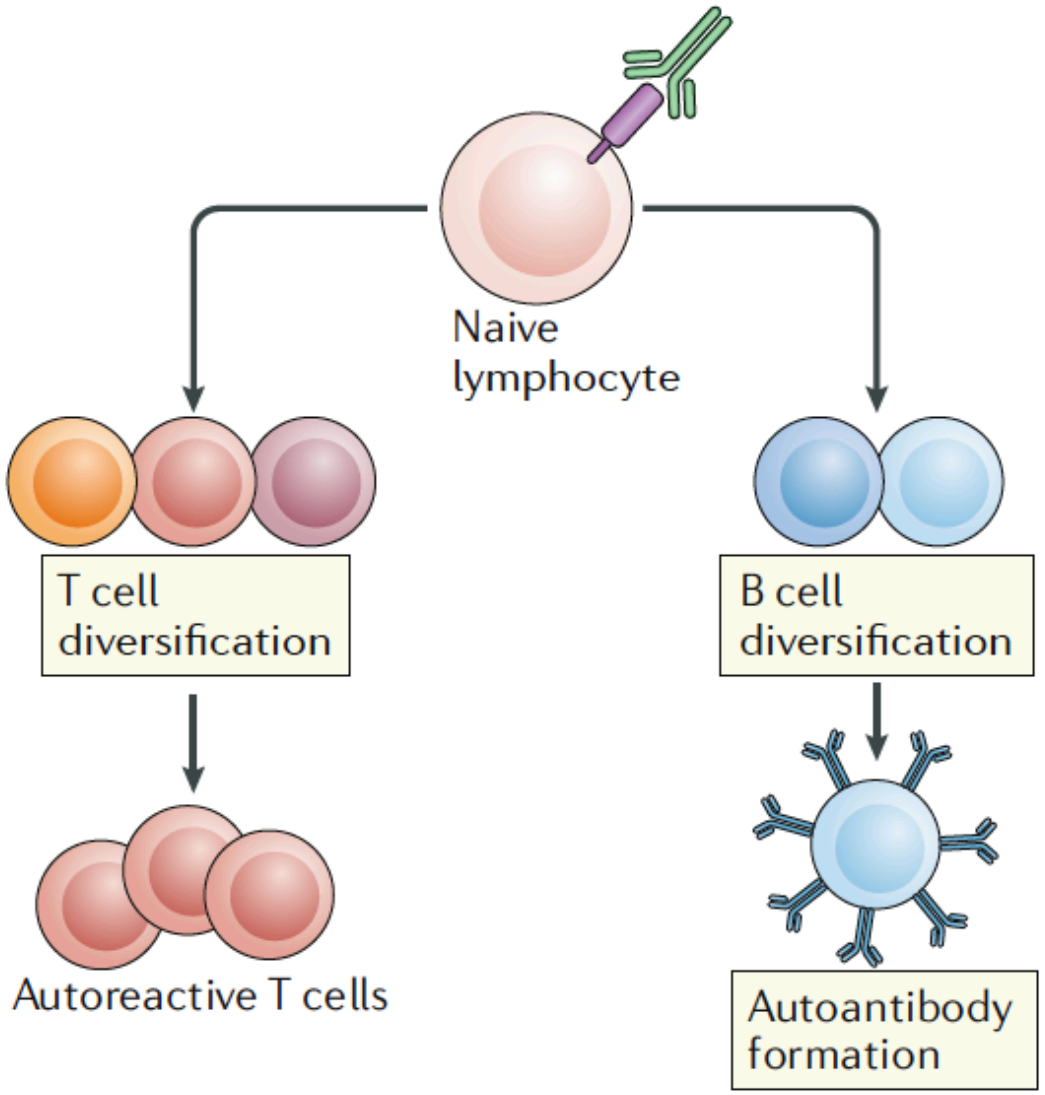
- **Auto-inflammatory component** → activation of innate immune cells = primary form of immune dysregulation; little/no evidence for specific, self-antigen- directed adaptive immune responses

- **Auto-inflammation theory** → host-directed tissue inflammation at anatomical sites; local factors contributing to target organ damage



→ Let's explore potential biological mechanism driving irAE

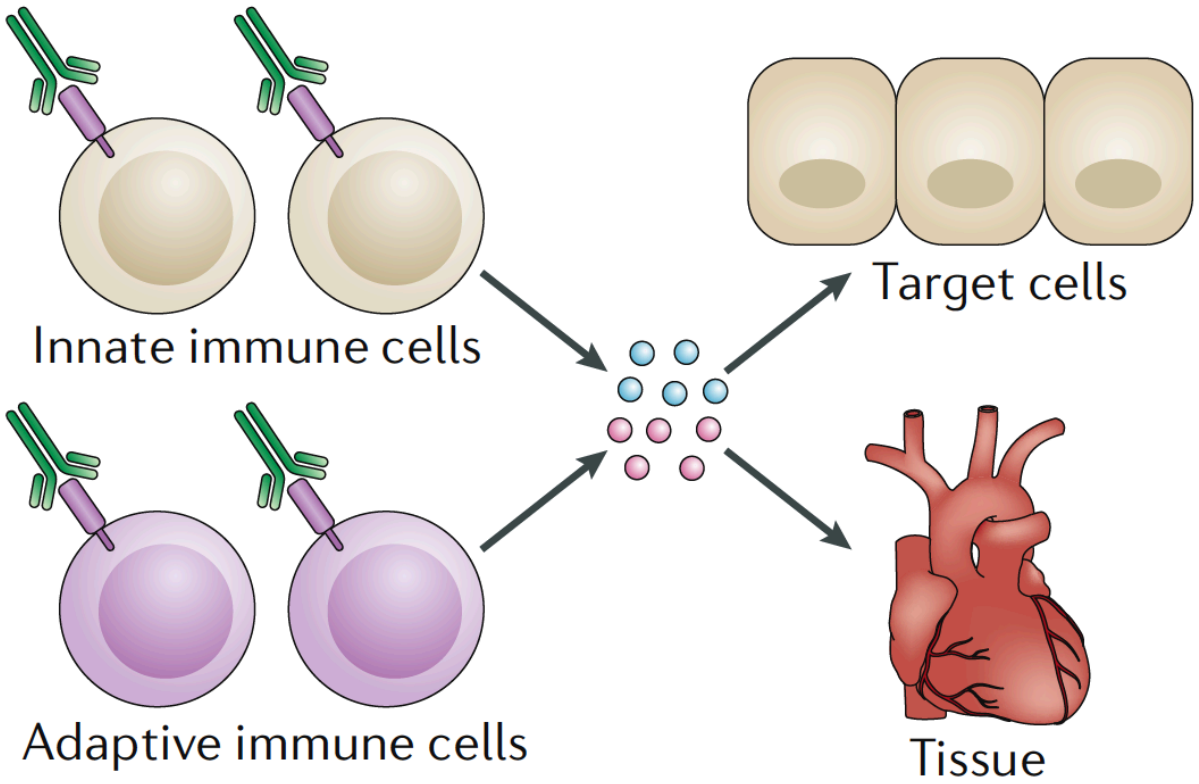
Breach of self-tolerance



- **T cells** play a **central** to the immunopathogenesis of most irAEs
- **T cells** are involved in numerous **self-directed** immune processes can result from **loss of T cell tolerance**
- **Presence nascent autoreactive T and B cells** having escaped central tolerance (inefficient purging) → pathogenic autoantibody formation
- **Autoreactive T / B cells** might be generated during **ICI therapy** as a result of **diversification** and sub-compartmental **expansion** of **lymphocytes**

Esfahani et al. Nat Rev Clin Oncol. 2020 Aug;17(8):504-515

Cytokine & chemokine production



- The **release of inflammatory mediators** from immune cells can lead to immune-mediated damage in tissues with an anatomic predisposition

  (e.g., interferon related signaling)

Esfahani et al. Nat Rev Clin Oncol. 2020 Aug;17(8):504-515

Cytokine & chemokine production

Translational Cancer Mechanisms and Therapy

Circulating Cytokines Predict Immune-Related Toxicity in Melanoma Patients Receiving Anti-PD-1–Based Immunotherapy

Su Y. Lim[1,2], Jenny H. Lee[1,2], Tuba N. Gide[2,3], Alexander M. Menzies[2,3,4], Alexander Guminski[2,3,4], Matteo S. Carlino[2,3,5], Edmond J. Breen[6], Jean Y.H. Yang[7,8], Shila Ghazanfar[7,8], Richard F. Kefford[1,2,5], Richard A. Scolyer[2,3,9], Georgina V. Long[2,3,4], and Helen Rizos[1,2]

Clin Cancer Res; 25(5) March 1, 2019

→ **Other studies** have highlighted the potential role of other cytokines, such as L17, IL6, TNF, IL-1β, IL-2, and GM-CSF, but not IL-6, IL-8, G-CSF, or MCP-1, IFN-γ, IL-8, CXCL9, CXCL10, CCL19, and CXCL11

→ **Limitation:** all studies remain small

→ Need **large validation** cohort

Exploratory Cohort: 98 melanoma patients on ICI

Exploratory Cohort: 49 melanoma patients on ICI

Experiment: 65 cytokines profiled before and during ICI therapy

Results:

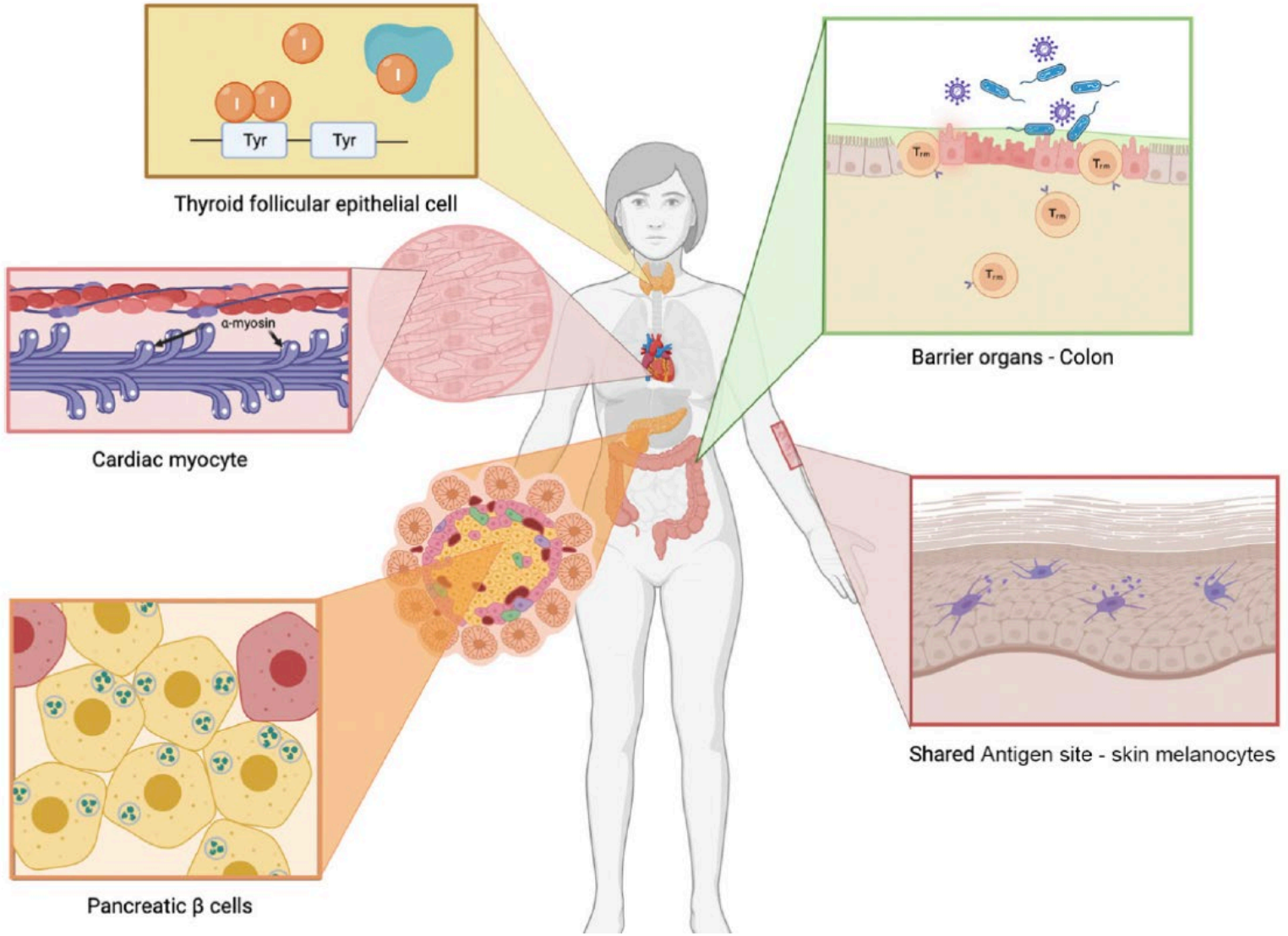
1- 11 cytokines associated with high grade irAE at baseline and during treatment

→ G-CSF, GM-CSF, Fractalkine, FGF-2, IFNA2, IL12p70, IL1a, IL1B, IL1Ra, IL2, IL13

2- Created a toxicity score – CYTOX – that they validated in independent cohort

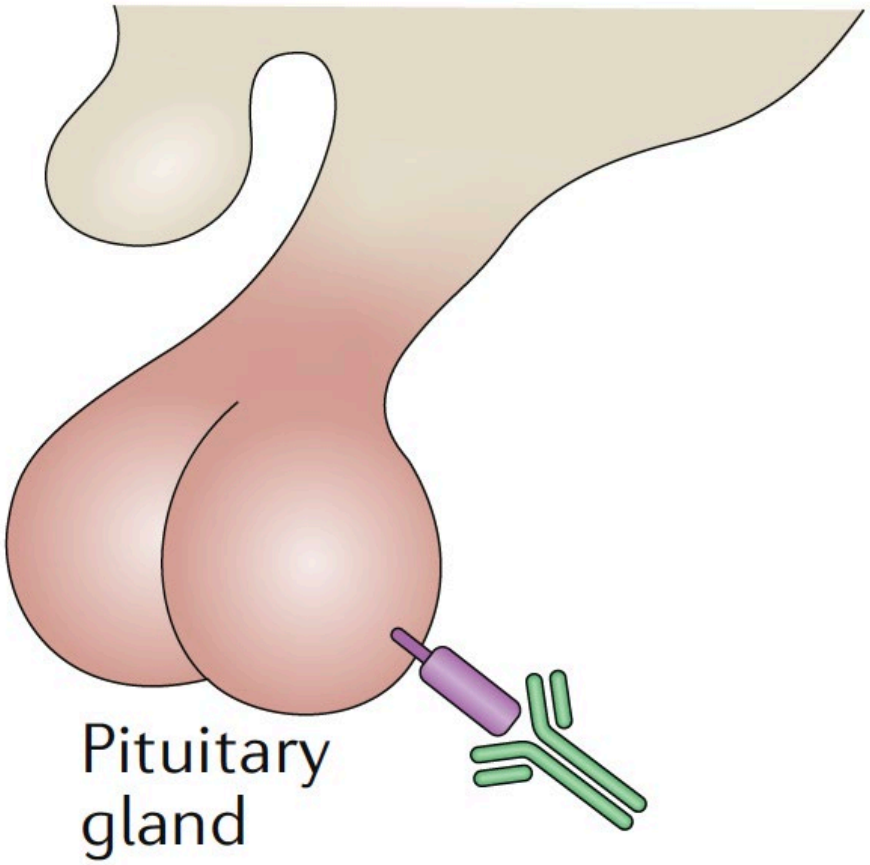
Review: Kang JH, et al. *Trends Immunol*. 2021;42(4):293-311.

Potential antigenic targets in immune-related adverse events: specialized proteins (endocrine organs), tissue restricted protein, microbiome



Wang et al. Trends Cancer. 2023 Apr 26:S2405-8033(23)00058-4

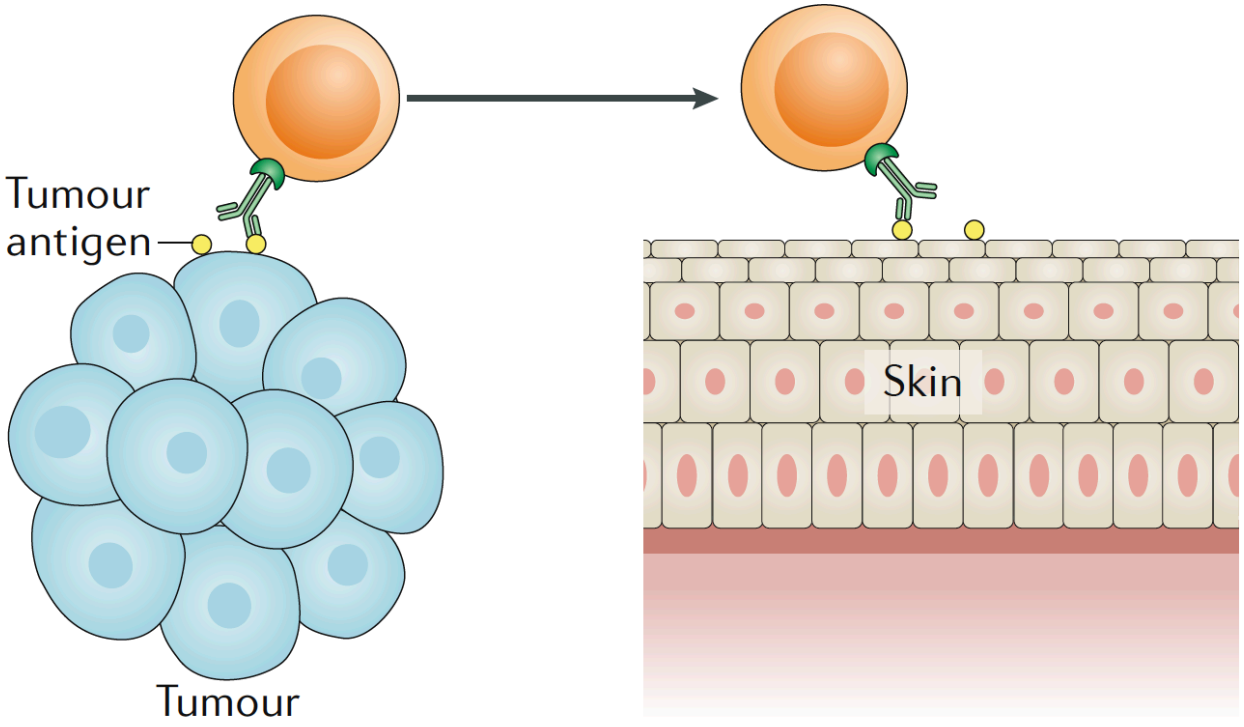
Off-target effects



- Off-target effects of ICIs on **non-haematopoietic cell expressing** the target immune checkpoint **ligand**
- **Hypophysitis** secondary **to anti-CTLA4** could be due to enhanced **complement-mediated inflammation** due to direct binding of an anti-CTLA4 antibody with CTLA-4 expressed on normal hypothalamic and pituitary tissue
- Does NOT explain hypophysitis in response to anti-PD-1 (rarer)

Esfahani et al. Nat Rev Clin Oncol. 2020 Aug;17(8):504-515

Cross-antigen reactivity



- Release of **host antigens** from **tumor cells** undergoing **cytotoxic attack** (e.g., vitiligo in melanoma patients on ICI)
- **Self-antigen** might be released when **non-transformed tissues** around tumor microenvironment are **damaged collaterally** by **immune** cells directed **against tumor**
- **Antigenic cross-presentation / bystander activation** can facilitate antigen presentation and autoimmunity

Esfahani et al. Nat Rev Clin Oncol. 2020 Aug;17(8):504-515

Cross-antigen reactivity

Article

T cells specific for α-myosin drive immunotherapy-related myocarditis

https://doi.org/10.1038/s41586-022-05432-3
Received: 31 January 2022
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Published online: 16 November 2022
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Margaret L. Axelrod[1], Wouter C. Meijers[1,2,3], Elles M. Screever[1,2,3], Juan Qin[1,4], Mary Grace Carroll[1], Xiaopeng Sun[1], Elie Tannous[1], Yueli Zhang[1], Ayaka Sugiura[1], Brandie C. Taylor[1], Ann Hanna[1], Shaoyi Zhang[4], Kaushik Amancherla[1], Warren Tai[1,5], Jordan J. Wright[1], Spencer C. Wei[6], Susan R. Opalenik[1], Abigail L. Toren[1], Jeffrey C. Rathmell[7,8,9], P. Brent Ferrell[1], Elizabeth J. Phillips[1,7,10,11,12], Simon Mallal[1,10,13], Douglas B. Johnson[1,8], James P. Allison[6,14], Javid J. Moslehi[1,4]✉ & Justin M. Balko[1,7,8]✉

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RESEARCH ARTICLE | TUMOR IMMUNOLOGY

Autoreactive napsin A–specific T cells are enriched in lung tumors and inflammatory lung lesions during immune checkpoint blockade

FIAMMA BERNER, DAVID BOMZE, CHRISTA LICHTENSTEIGER, VINCENT WALTER, REBEKKA NIEDERER, OMAR HASAN ALI, NINA WYSS, JENS BAUER, LENA KATHARINA FREUDENMANN, [...], AND LUKAS FLATZ +24 authors Authors Info & Affiliations

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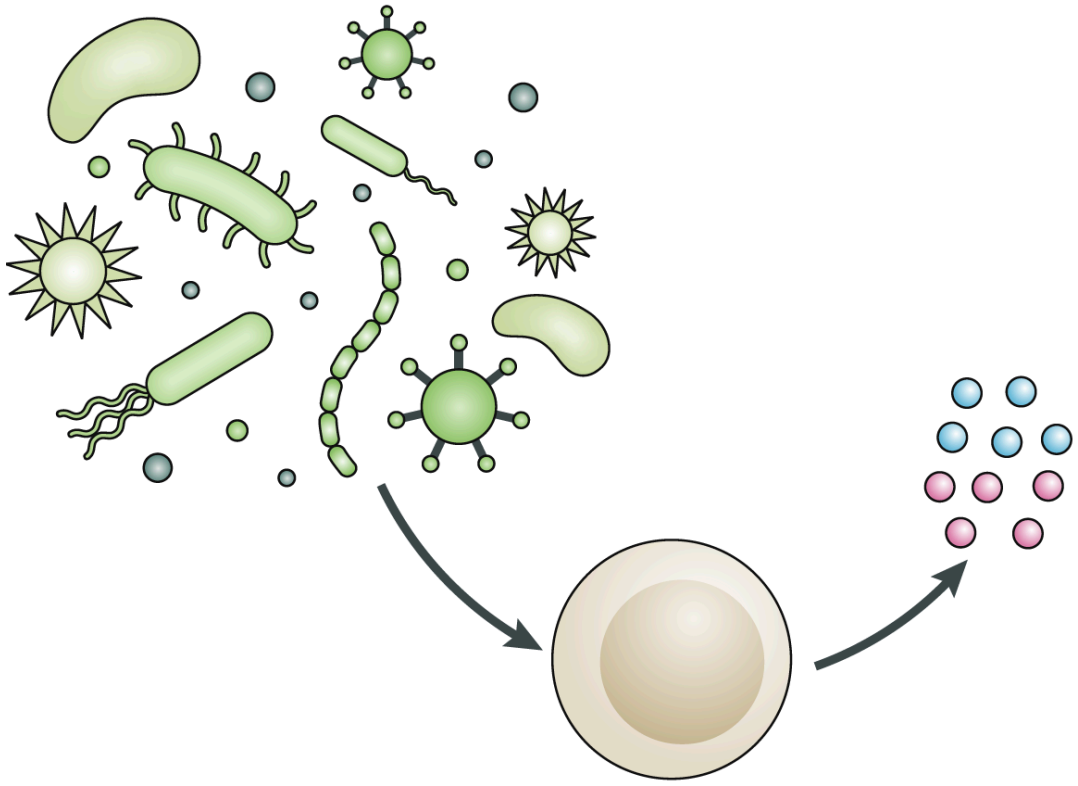
RESEARCH ARTICLE | CANCER

Epitope spreading toward wild-type melanocyte-lineage antigens rescues suboptimal immune checkpoint blockade responses

JENNIFER A. LO, MASAYOSHI KAWAKUBO, VIKRAM R. JUNEJA, MACK Y. SU, TAL H. ERLICH, MARTIN W. LAFLEUR, LAJOS V. KEMENY, MAMUNUR RASHID, MOHSEN MALEHMIR, [...], AND DAVID E. FISHER +27 authors Authors Info & Affiliations

SCIENCE TRANSLATIONAL MEDICINE • 17 Feb 2021 • Vol 13, Issue 581 • DOI: 10.1126/scitranslmed.abd8636

Microbiome shaping host immune response



The enrichment of the **microbiome** with certain bacterial species can:

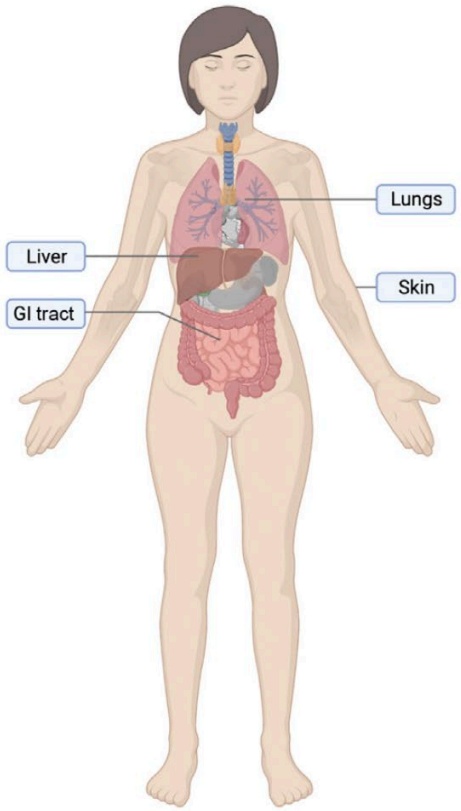
→ **protect** against or **induce** irAEs

→ **influences immune lineage** specifications towards pro-inflammatory or regulatory cell subtypes

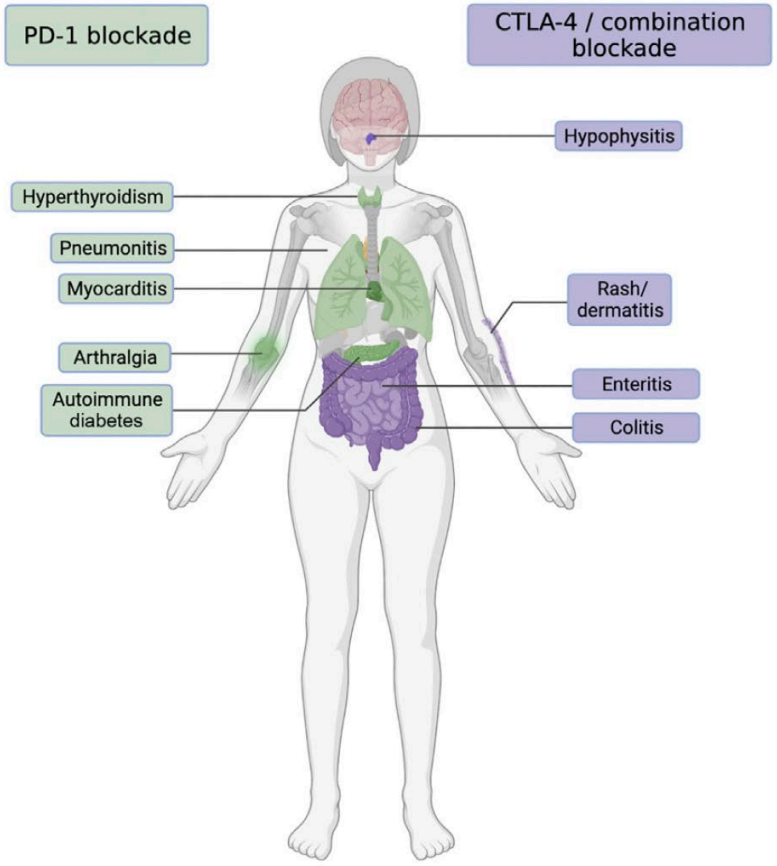
→ **Regulate the production** of pro-inflammatory or anti- inflammatory **cytokines**

Esfahani et al. Nat Rev Clin Oncol. 2020 Aug;17(8):504-515

Many toxicities occur at barrier organs including the skin, gastrointestinal tract and liver, and lungs



Major barrier organs



Most clinically important irAE

- irAE associated with barrier organs may suggests that the **antigenic targets** of the immune response may be the **commensal microbiome**

  → not proven

Wang et al. Trends Cancer. 2023 Apr 26:S2405-8033(23)00058-4

Microbiome shaping host immune response

ARTICLES
https://doi.org/10.1038/s41591-021-01406-6
nature medicine
Check for updates

Gut microbiota signatures are associated with toxicity to combined CTLA-4 and PD-1 blockade

Miles C. Andrews[1,2,3,26], Connie P. M. Duong[4,5,6,26], Vancheswaran Gopalakrishnan[1,26], Valerio Iebba[4,5,26], Wei-Shen Chen[7,8,26], Lisa Derosa[4,5,6,26], Md Abdul Wadud Khan[1], Alexandria P. Cogdill[4,5,6,7], Michael G. White[1], Matthew C. Wong[7], Gladys Ferrere[4,5,6], Aurélie Fluckiger[4,5,6], Maria P. Roberti[4,5,6], Paule Opolon[4], Maryam Tidjani Alou[4,5,6], Satoru Yonekura[4,5,6], Whijae Roh[7], Christine N. Spencer[9], Irina Fernandez Curbelo[10], Luis Vence[10], Alexandre Reuben[11], Sarah Johnson[1], Reetakshi Arora[1], Golnaz Morad[1], Matthew Lastrapes[12], Erez N. Baruch[7], Latasha Little[7], Curtis Gumbs[7], Zachary A. Cooper[13], Peter A. Prieto[14], Khalida Wani[15], Alexander J. Lazar[7,15], Michael T. Tetzlaff[15], Courtney W. Hudgens[15], Margaret K. Callahan[9,16], Matthew Adamow[16,17], Michael A. Postow[16,17], Charlotte E. Ariyan[18], Pierre-Olivier Gaudreau[1], Luigi Nezi[19], Didier Raoult[20], Catalin Mihalcioiu[21], Arielle Elkrief[22], Rossanna C. Pezo[23], Lauren E. Haydu[1], Julie M. Simon[1], Hussein A. Tawbi[24], Jennifer McQuade[24], Patrick Hwu[24], Wen-Jen Hwu[24], Rodabe N. Amaria[24], Elizabeth M. Burton[1], Scott E. Woodman[7,24], Stephanie Watowich[10], Adi Diab[24], Sapna P. Patel[24], Isabella C. Glitza[24], Michael K. Wong[24], Li Zhao[7], Jianhua Zhang[7], Nadim J. Ajami[7], Joseph Petrosino[25], Robert R. Jenq[7], Michael A. Davies[24], Jeffrey E. Gershenwald[1], P. Andrew Futreal[7], Padmanee Sharma[10], James P. Allison[10], Bertrand Routy[4,5,6], Laurence Zitvogel[4,5,6] ✉ and Jennifer A. Wargo[1,7] ✉

Cohort: 77 patients with advanced melanoma treated with ICI with a high rate of any ≥grade 3 irAE

Experiment: profiled the blood, tumor and gut microbiome

Results:

1- toxicities associated with more **diverse** peripheral T-cell **repertoire**;

2- significantly higher abundance of **Bacteroides intestinalis** in patients with toxicity;

3- upregulation of mucosal **IL-1β** in patient samples of colitis and in pre-clinical models

Tissue-resident memory (T_{RM}) cells

Checkpoint Blockade–Induced Dermatitis and Colitis Are Dominated by Tissue-Resident Memory T Cells and Th1/Tc1 Cytokines

Robin Reschke[1], Jason W. Shapiro[2], Jovian Yu[3], Sherin J. Rouhani[3], Daniel J. Olson[3], Yuanyuan Zha[4], Thomas F. Gajewski[1,3]

Cancer Immunol Res; 10(10) October 2022

Interferon-Gamma–Producing CD8$^+$ Tissue Resident Memory T Cells Are a Targetable Hallmark of Immune Checkpoint Inhibitor–Colitis

Sarah C. Sasson,[1,2] Stephanie M. Slevin,[1,2] Vincent T. F. Cheung,[1,2] Isar Nassiri,[3] Anna Olsson-Brown,[4,5] Eve Fryer,[6] Ricardo C. Ferreira,[7] Dominik Trzupek,[7] Tarun Gupta,[1,3] Lulia Al-Hillawi,[1,2] Mari-lenna Issaias,[8] Alistair Easton,[6] Leticia Campo,[9] Michael E. B. FitzPatrick,[1,2] Joss Adams,[10] Meenali Chitnis,[8] Andrew Protheroe,[8] Mark Tuthill,[8] Nicholas Coupe,[8] Alison Simmons,[1,3] Miranda Payne,[8] Mark R. Middleton,[2,8] Simon P. L. Travis,[1,2] The Oxford Inflammatory Bowel Disease Cohort Investigators, Benjamin P. Fairfax,[3,8] Paul Klenerman,[1,2] and Oliver Brain[1,2]

Gastroenterology 2021;161:1229–1244

Molecular Pathways of Colon Inflammation Induced by Cancer Immunotherapy

Adrienne M. Luoma,[1,2,13] Shengbao Suo,[3,13] Hannah L. Williams,[4] Tatyana Sharova,[5,6] Keri Sullivan,[7] Michael Manos,[4,8] Peter Bowling,[4,8] F. Stephen Hodi,[4,8] Osama Rahma,[4,9] Ryan J. Sullivan,[10] Genevieve M. Boland,[5,6] Jonathan A. Nowak,[11] Stephanie K. Dougan,[1,2] Michael Dougan,[7,14,*] Guo-Cheng Yuan,[3,14] and Kai W. Wucherpfennig[1,2,12,14,15,*]

Cell *182*, 655–671, August 6, 2020

Myosin specific T_{RM} cells mediate increased severity of immune checkpoint inhibitor myocarditis FREE

Hannah Maryam Kalinoski; Taejoon Won; Vitali Rusinkevich; Monica V Talor; David M Hughes; Megan K Wood; Jody E Hooper; Daniela Cihakova

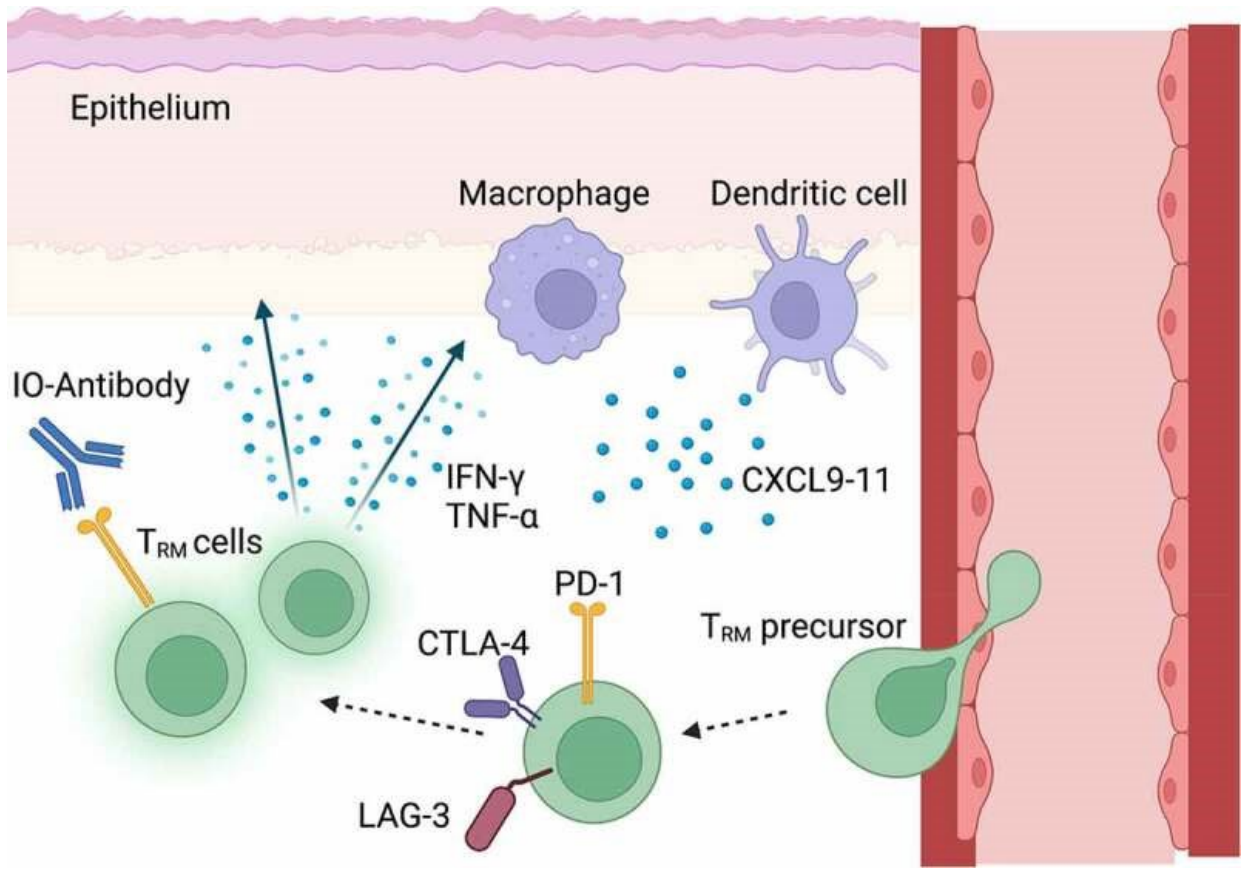
+ Author & Article Information

J Immunol (2021) 206 (1_Supplement): 98.52.

https://doi.org/10.4049/jimmunol.206.Supp.98.52

→ **Several studies have highlighted the potential role of tissue-resident memory T cells in mediating/ contributing to irAE pathogenesis across different tissues**

Tissue-resident memory (T_{RM}) cells



Reschke R, et al, *Oncoimmunology*. 2023;12(1):2197358.

- T_{RM} T cells are **long lived memory effectors** that make up a majority of T cells in most human organs
- Play an important role in **tissue surveillance** and **recall responses** to pathogens
- T_{RM} remain in tissue to expression of **retention molecules** (e.g., CD103, CD69, CD49a)
- T_{RM} **express PD-1** and other inhibitory receptors that control their re-activation
- Example of **potential cascade of events**:

Checkpoint blocking antibodies → bind & re-invigorate T_{RM}

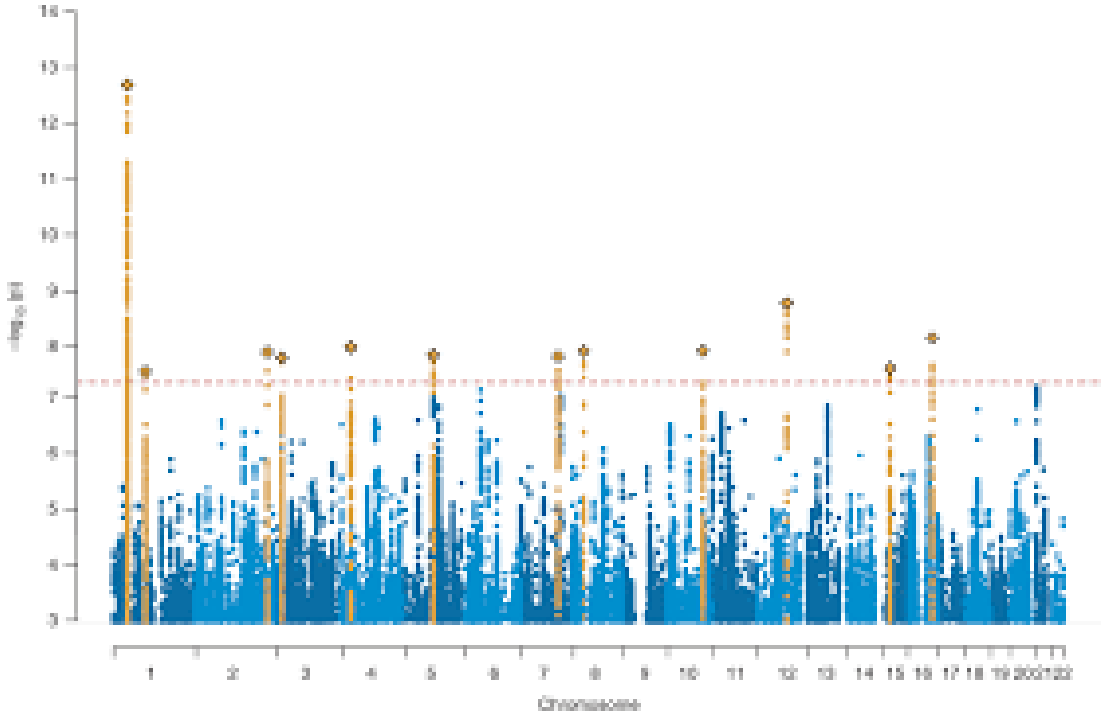
↓

T_{RM} expand and can produce Th1 cytokines (e.g. IFNg, TNFa) and activate myeloid cells

↓

Macrophages and DCs can produce CXCL9-11 that can recruit additional circulating T cells

Genetically predisposed individuals to irAEs



- Germline genetic factors are strong determinants of **immune homeostasis**
- Phenotypic **similarities** between **irAEs** and **autoimmunity** → shared genetic factors?
- Association between **toxicity and responses** in some cases → shared genetic factors
- **Limitation**: Majority of genetic association studies to-date have **small sample size** (<200 patients), and **lump** together all **irAE types**, limiting the chance of identifying true associations

Chin Iset al. *NPJ Genom Med*. 2022;7(1):73.

Genetically predisposed individuals to irAEs – IL7

Article nature medicine https://doi.org/10.1038/s41591-022-02094-6

Germline variants associated with toxicity to immune checkpoint blockade

Received: 5 April 2022
Accepted: 18 October 2022
Published online: 16 December 2022
Check for updates

Stefan Groha[1,2,3], Sarah Abou Alaiwi[4,6], Wenxin Xu[5], Vivek Naranbhai[5], Amin H. Nassar[4,6], Ziad Bakouny[5,6], Talal El Zarif[4,5], Renee Maria Saliby[5], Guihong Wan[3,7], Ahmad Rajeh[7], Elio Adib[4,6], Pier V. Nuzzo[4,8], Andrew L. Schmidt[5], Chris Labaki[5], Biagio Ricciuti[9], Joao Victor Alessi[8], David A. Braun[4,10], Sachet A. Shukla[2,5,11], Tanya E. Keenan[2,5,12], Eliezer Van Allen[2,5,13], Mark M. Awad[8], Michael Manos[5], Osama Rahma[5,6], Leyre Zubiri[14], Alexandra-Chloe Villani[2,3,15], Benjamin Fairfax[16], Christian Hammer[17], Zia Khan[17], Kerry Reynolds[3,18], Yevgeniy Semenov[3,7], Deborah Schrag[1], Kenneth L. Kehl[1], Matthew L. Freedman[2,5,20], Toni K. Choueiri[3,4,5,6,20] & Alexander Gusev[1,2,3,19,20]

- **Cohort**: 1,751 patients treated with ICI across 12 cancer types
  High grade irAE: 259 cases 1,375 controls
  All irAEs: 339 cases 1,412 controls

- **Results –** 3 genome-wide significant results

→**rs16906115 near IL7** was replicated in 3 independent studies

→IL7, a critical regulator of lymphocyte homeostasis

→Patients carrying the IL7 germline variant exhibited significantly **increased lymphocyte stability** after ICI initiation, which may be predictive of downstream irAEs and improved survival

Article nature medicine https://doi.org/10.1038/s41591-022-02095-5

IL7 genetic variation and toxicity to immune checkpoint blockade in patients with melanoma

Received: 6 April 2022
Accepted: 18 October 2022
Published online: 16 December 2022
Check for updates

Chelsea A. Taylor[1,2,19], Robert A. Watson[1,2,3,19], Orion Tong[1,2,19], Weiyu Ye[1,2], Isar Nassiri[1,2], James J. Gilchrist[1,4,5], Alba Verge de los Aires[1,2], Piyush Kumar Sharma[1,2], Surya Koturan[1,2], Rosalin A. Cooper[1,2], Victoria K. Woodcock[1,2,3], Elsita Jungkurth[1,2], Brian Shine[6], Nicholas Coupe[3], Miranda J. Payne[3], David N. Church[3,5], Vivek Naranbhai[7,8,9], Stefan Groha[10,11,12], Paul Emery[13,14], Kulveer Mankia[13,14], Matthew L. Freedman[7,11], Toni K. Choueiri[7,11,15,16], Mark R. Middleton[2,3,17], Alexander Gusev[10,11,12,18] & Benjamin P. Fairfax[1,2,3,17]

- Study design – to validate the IL7 association specifically

- **Cohort**: 214 melanoma patients on ICI
- **Results –** association with **rs16906115 near IL7** was replicated

→Patients carrying **the risk allele demonstrated**:
  - increased pre-treatment B cell *IL7* expression;
  - increased irAE risk;
  - divergent immunoglobulin expression;
  - more B cell receptor mutations;
  - distinct ICB-induced CD8+ T cell subset responses;
  - skewing of T cell clonality

Genetically predisposed individuals to irAEs – NLRC5 & HLA

Open access Short report

Journal for ImmunoTherapy of Cancer

Germline genetic variants are associated with development of insulin-dependent diabetes in cancer patients treated with immune checkpoint inhibitors

Jasmine I Caulfield,[1] Lilach Aizenbud,[1] Ana Luisa Perdigoto,[2] Eric Meffre,[3] Lucia Jilaveanu,[1] Dominika A Michalek,[4] Stephen S Rich,[4] Yariv Aizenbud,[5] Adebowale Adeniran,[6] Kevan C Herold,[2] Matthew R Austin,[1] Harriet Kluger [1]

→ **Cohort**: 13 patients with ICI-diabetes & 13 controls
→ **Experiment**: RNA and whole exome sequencing on tumors
→ **Results**: missense mutation in **NLRC5** in 9/13 ICI-diabetes

Cancer Immunology, Immunotherapy (2021) 70:1939–1949
https://doi.org/10.1007/s00262-020-02797-0

ORIGINAL ARTICLE

Genetic determinants of immune-related adverse events in patients with melanoma receiving immune checkpoint inhibitors

Noha Abdel-Wahab[1,2,3] · Adi Diab[3] · Robert K. Yu[4] · Andrew Futreal[5] · Lindsey A. Criswell[6] · Jean H. Tayar[1] · Ramona Dadu[7] · Vickie Shannon[8] · Sanjay S. Shete[4,9] · Maria E. Suarez-Almazor[1,10]

Several different **HLA alleles** associated with irAEs across multiple small studies → **larger studies are needed**

European Journal of Cancer 172 (2022) 98–106

Human leucocyte antigen genotype association with the development of immune-related adverse events in patients with non-small cell lung cancer treated with single agent immunotherapy

Afaf Abed [a,b,c,d,*], Ngie Law [e], Leslie Calapre [a,b], Johnny Lo [f,g], Vikas Bhat [d], Samantha Bowyer [c,d,e], Michael Millward [c,d], Elin S. Gray [a,b,**]

European Journal of Cancer 107 (2019) 8–14

Human leukocyte antigen variation is associated with adverse events of checkpoint inhibitors

Omar Hasan Ali [a,b], Fiamma Berner [b], David Bomze [b], Mirjam Fässler [b], Stefan Diem [c,d], Antonio Cozzio [e], Markus Jörger [c], Martin Früh [c], Christoph Driessen [c], Tobias L. Lenz [f,1], Lukas Flatz [a,b,c,e,*,1]

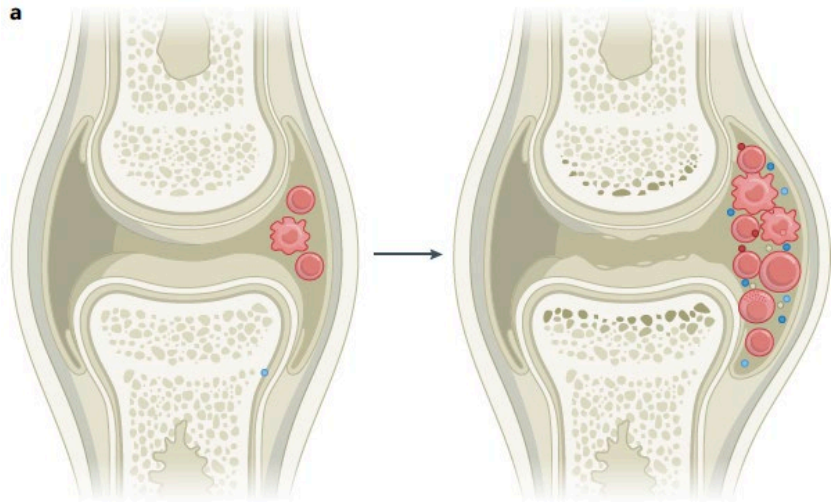
Frontiers in Immunology
DOI 10.3389/fimmu.2022.952099

Association between germ-line HLA and immune-related adverse events

Ning Jiang[1†], Yue Yu[1†], Min Zhang[2†], Yu Tang[1], Dawei Wu[1], Shuhang Wang[1], Yuan Fang[1], Yu Zhang[3], Lin Meng[2], Yingying Li[2], Huilei Miao[1], Peiwen Ma[1], Huiyao Huang[1] and Ning Li[1*]

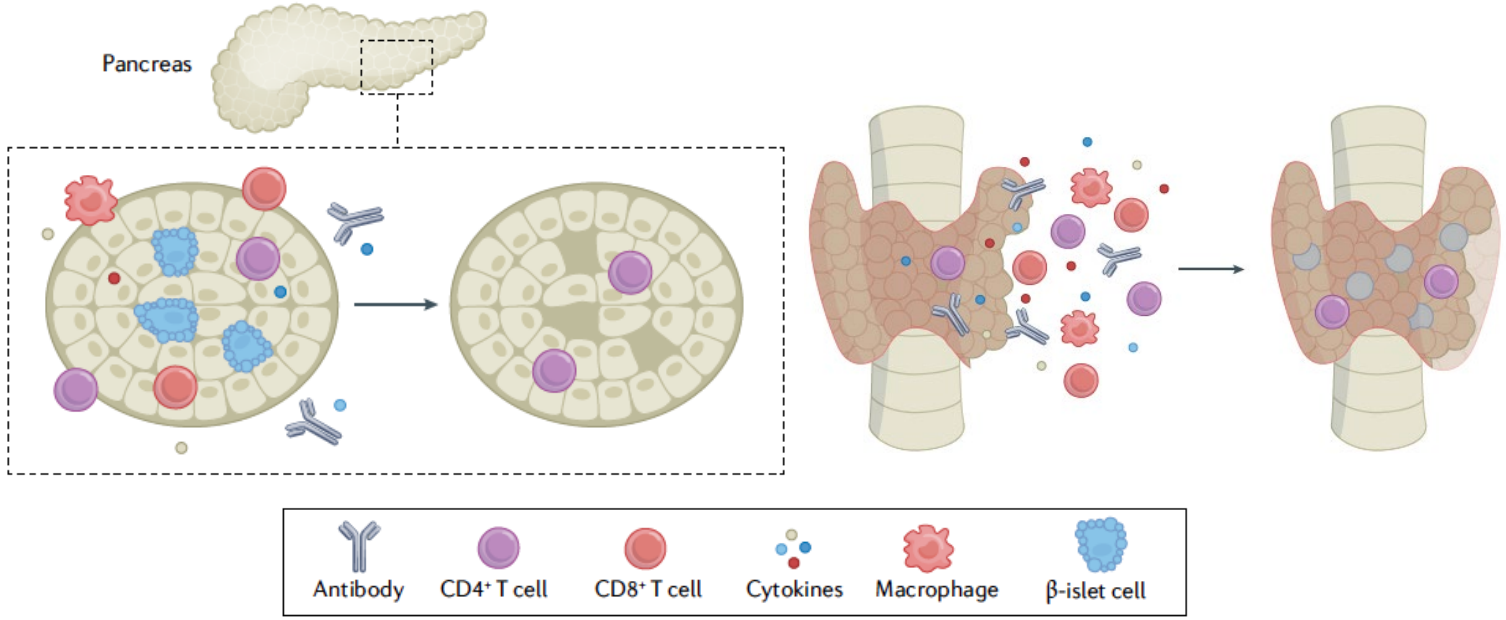
Why do some irAE fail to resolve: acute vs. chronic irAE

Smoldering inflammation scenario



- E.g., Rheumatoid arthritis-like inflammation of joints
- off-target T cell activation that may wax and wane over time

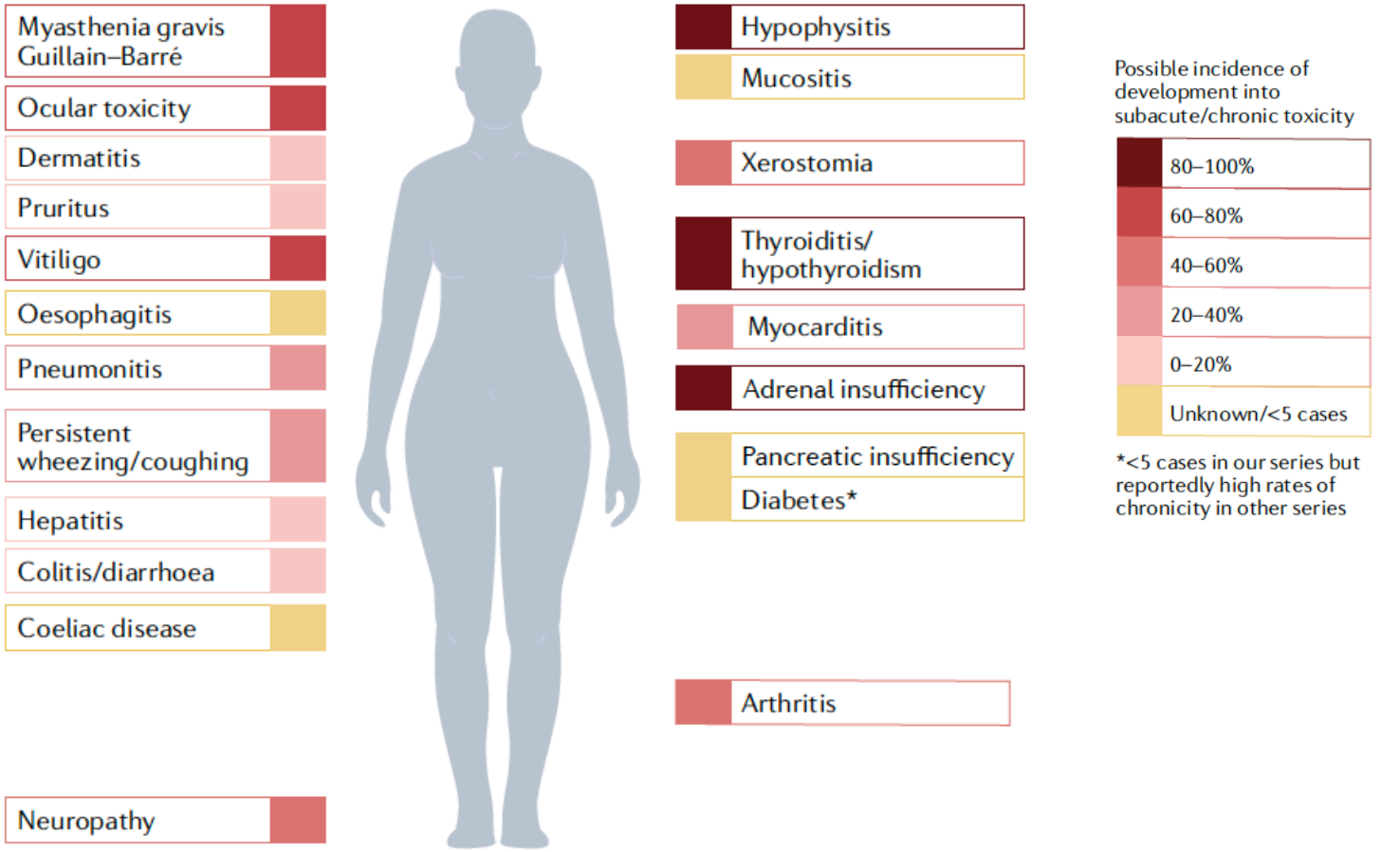
Burnout / irreversible scenario



- E.g., Endocrinopathies (pancreas, thyroid gland
- irreversible cellular damage precluding physiological recovery (e.g., destructions of hormone-secreting cells
- Require permanent hormone replacement therapy

Johnson D. Nat Rev Clin Oncol. 2022 Apr;19(4):254-267

Possible frequencies of chronic immune-checkpoint inhibitor-induced toxicities

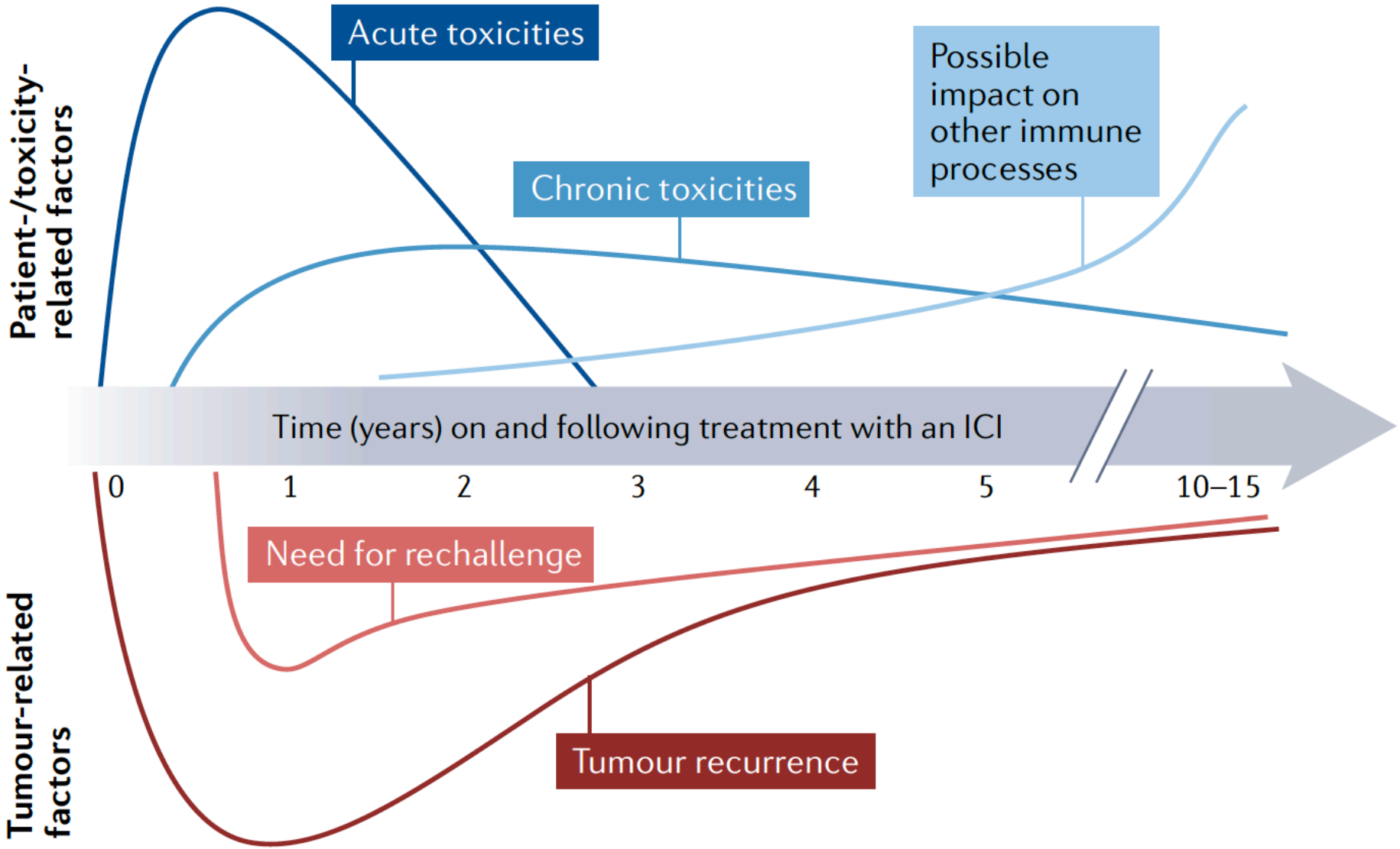


Percentages expressed are the percentages of acute toxicities that become chronic (defined as those that persist for at least 12 weeks following ICI discontinuation)

→ The exact risks of acute toxicities becoming chronic (defined as persisting for at least 12 weeks beyond treatment cessation) are currently unknown

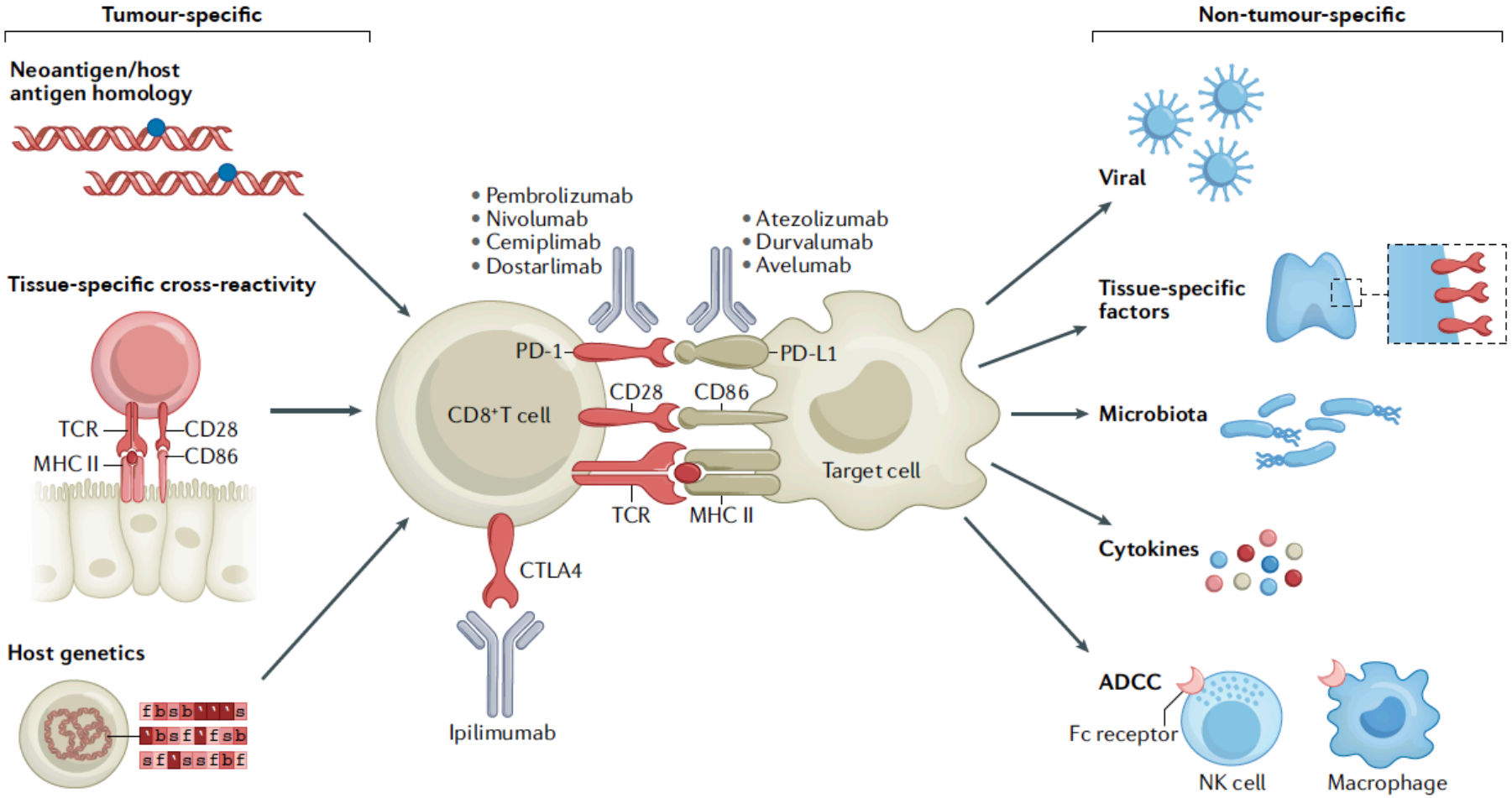
Johnson D. Nat Rev Clin Oncol. 2022 Apr;19(4):254-267

Time course and potential importance of key issues throughout the course of treatment with immune-checkpoint inhibitors



Johnson D. Nat Rev Clin Oncol. 2022 Apr;19(4):254-267

Key challenge: de-coupling tumor-specific versus non-tumor triggers associated with irAEs

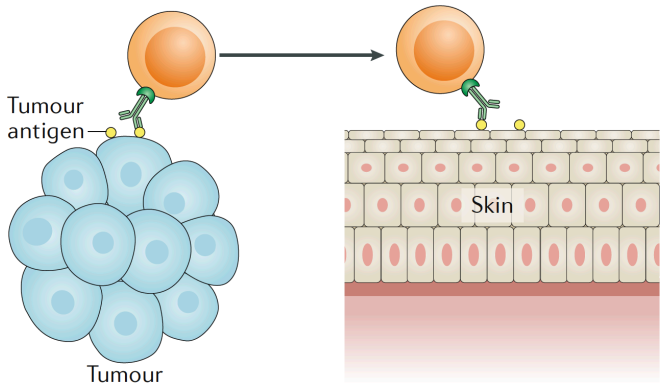


ADCC = antibody-dependent cellular cytotoxicity

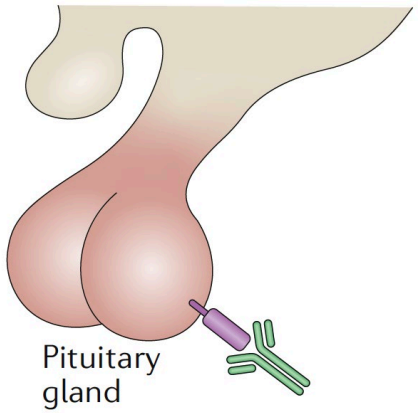
Johnson D. Nat Rev Clin Oncol. 2022 Apr;19(4):254-267

Multiple mechanisms have been proposed for irAEs – complex picture

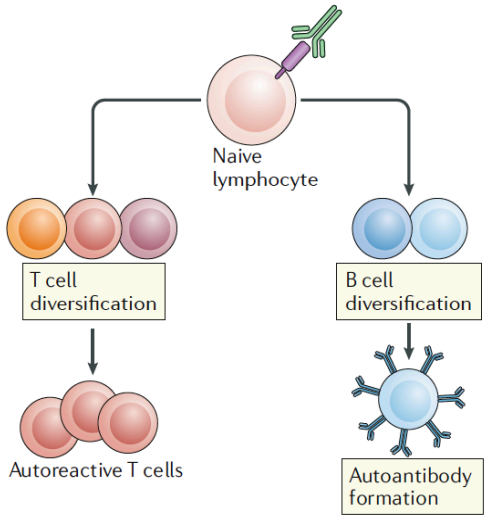
Cross-antigen reactivity



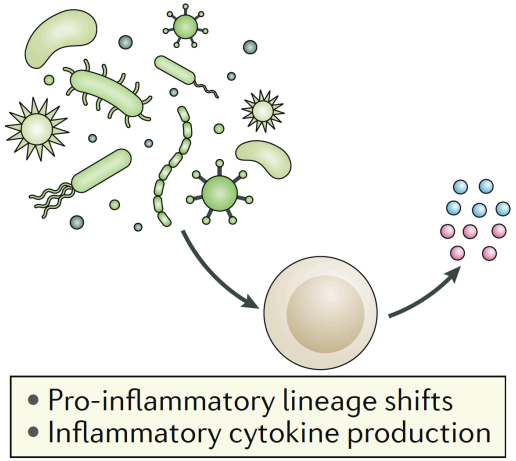
Off-target effects



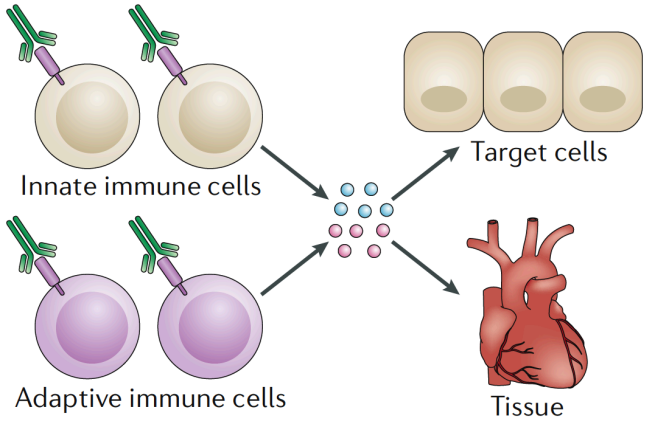
Breach of self-tolerance & increase level of pre-existing circulating autoantibodies



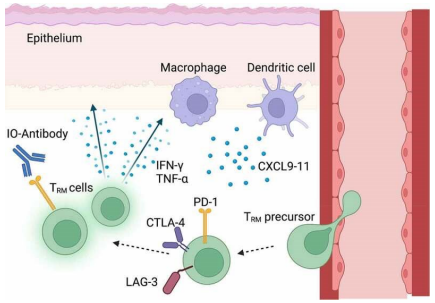
Microbiome shaping host immune response



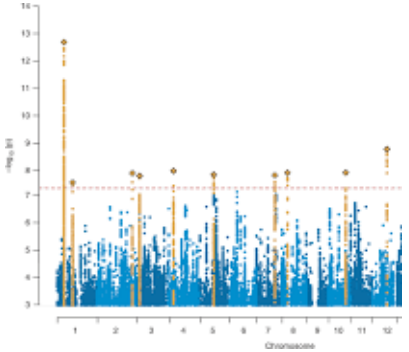
Cytokine & chemokine production



Tissue resident memory cells



Genetic predisposition



Likely other mechanisms involved given broad expression of PD-1 beyond T cells

Esfahani et al. Nat Rev Clin Oncol. 2020 Aug;17(8):504-515

Importance of pursuing translational effort to improve clinical care

- Understand spectrum of presentations would enable developing:

→ **Biomarkers**: identify patients at risk to (stop treatment b/f irAE become irreversible)

→**Rapid diagnostic tools**: irAE presentations are hard to diagnose

→ **Better targeted therapies** to treat irAE while maintaining anti-tumor immunity

Key elements to succeed in solving irAEs assembled

1- **Infrastructure** and **expert knowledge** for patient identification

2- Gathering **experts** across division of Medicine for **developing best practice** for clinical **care** and optimal **phenotyping**

3- **Platform** for oncologist, medicine experts and scientists **to connect**

4- **Champions** and **infrastructure** for sample **collection** (inpatient / outpatient)

5- **Collecting** the right tissue samples at clinically **relevant time points**

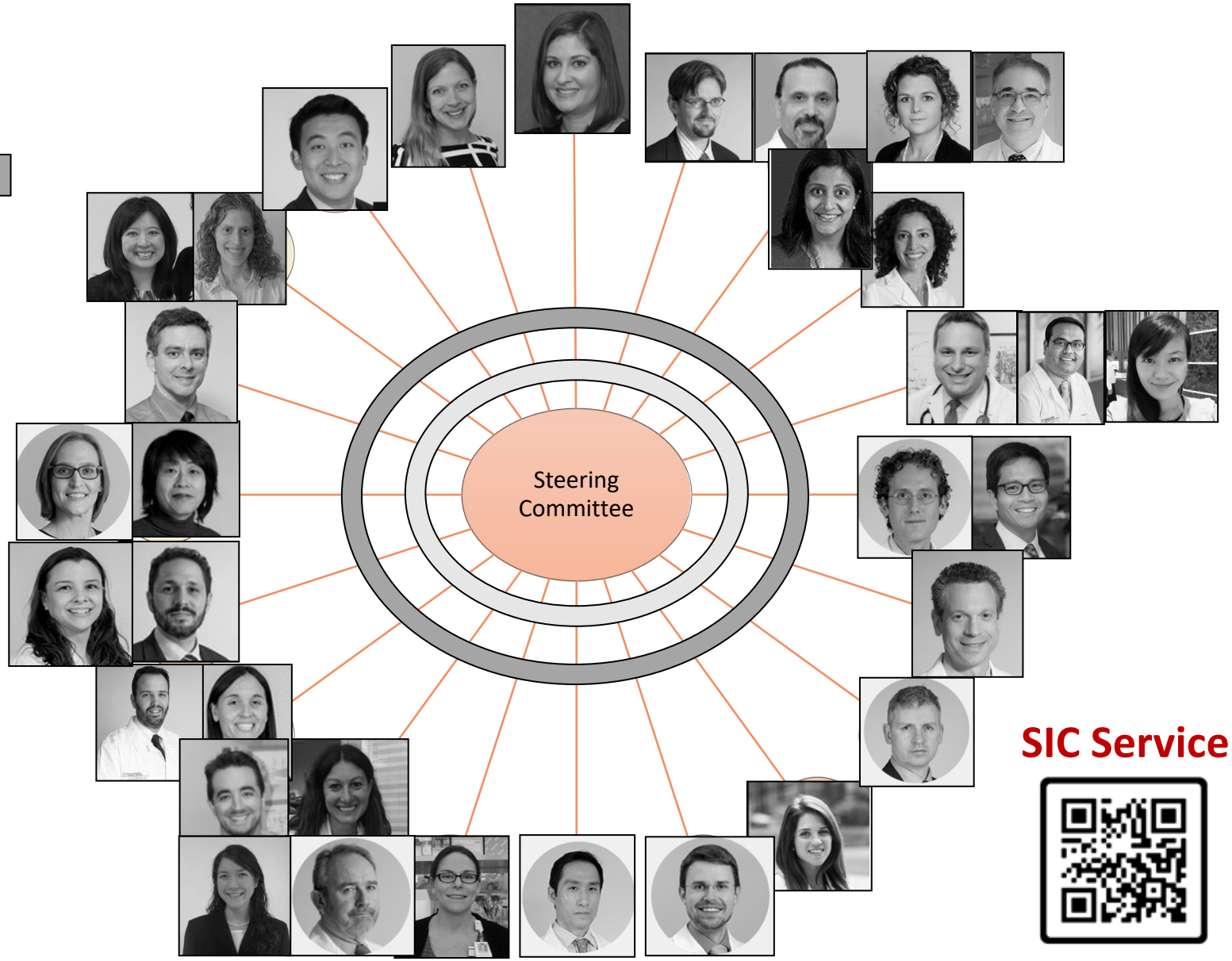
6- Access to **optimal technologies** to test biological hypotheses

Gathering experts & champions across division of medicine: Severe Immunotherapy Complication Service

Clinical Research

51 members across 6 department and 10 divisions of Medicine

20 members actively bridging between clinical and laboratory work

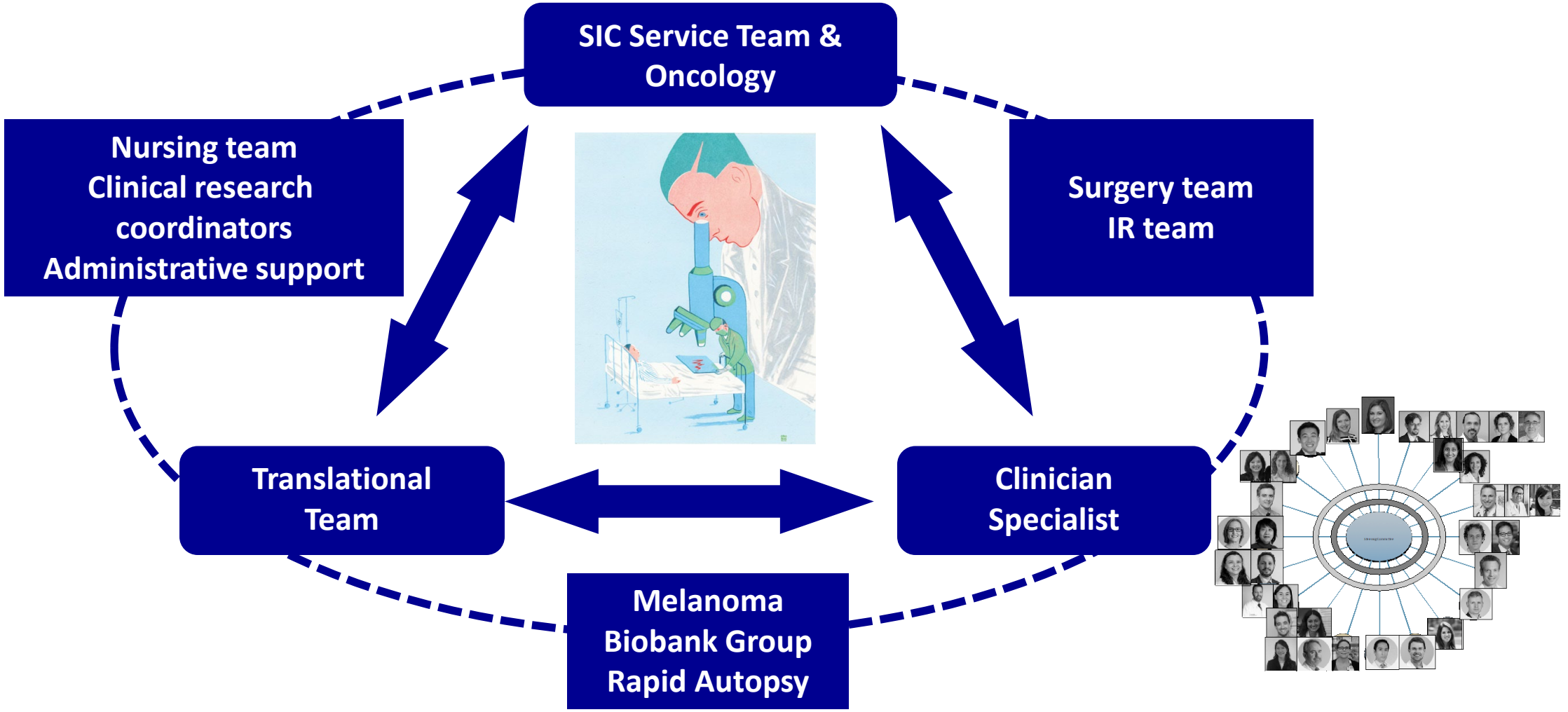


SIC Service

Translational Research

A patient centric approach:
Overview of the champions and infrastructure for sample collection

Leveraging MGH unique multi-disciplinary environment to empower our bedside-bench-bedside SIC translational research program



MGH patient cohort across irAE types (n=306):

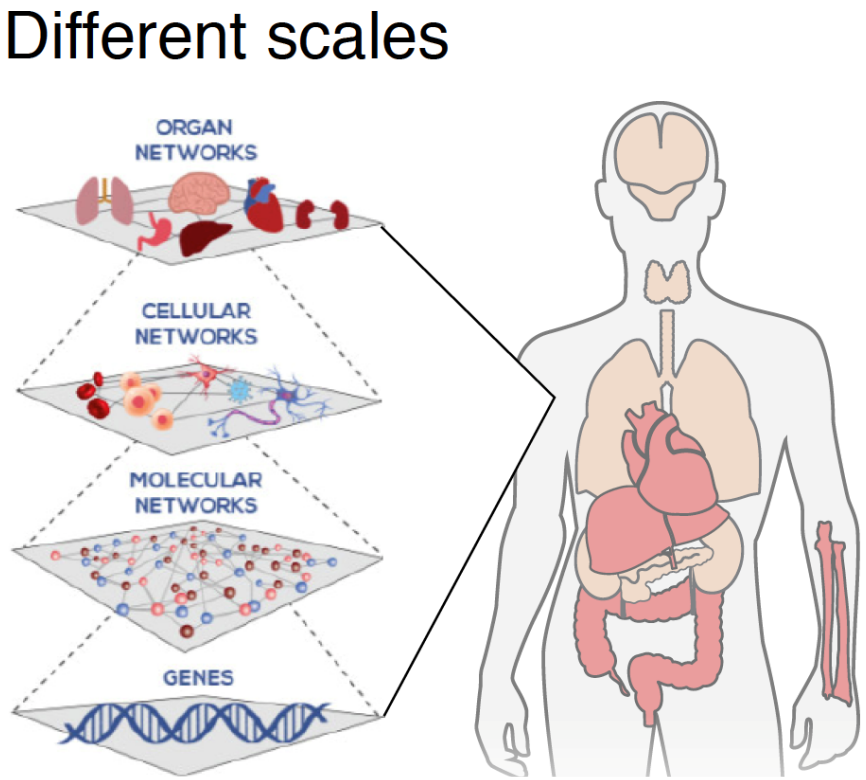
Colitis N=101		Arthritis N=56		Hepatitis N=43		Myocarditis N=35		Pneumonitis N=16		Nephritis N=36		Encephalitis N=9		Thyroiditis N=20
Cases N=55	Controls N=45	Cases N=45	Controls N=11	Cases N=29	Controls N=14	Cases N=19	Controls N=16	Cases N=7	Controls N=9	Cases N=15	Controls N=6	Cases N=2	Controls N=7	**T1DM** N=12

Cases	Controls
Patients on anti-PD-1 and/or anti-CTLA-4 with **histologically proven irAEs**	- Patients on anti-PD-1 and/or anti-CTLA-4 without irAEs

→1873 samples biobanked:

biopsies, blood, serum, plasma, body fluids, autopsy specimens

Solving irAEs requires collecting the right tissue samples at clinically relevant time points: exploration of scale, time, and modalities

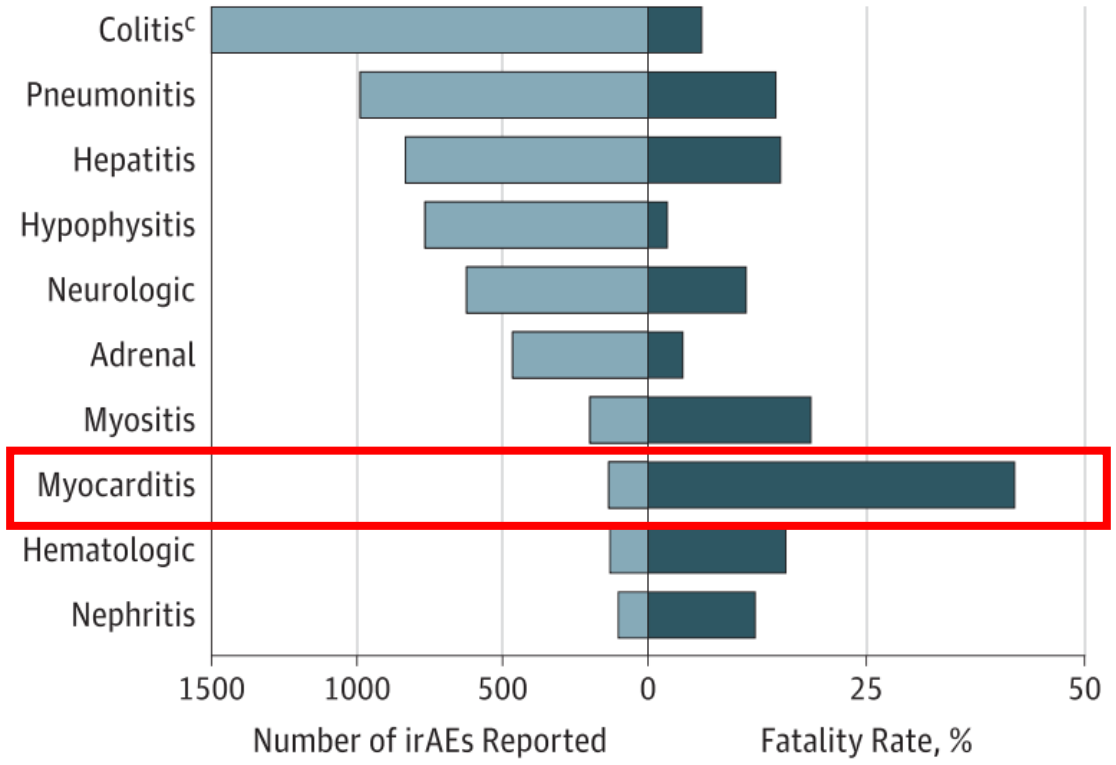


ICI-associated myocarditis is highly morbid

- ICI-Myocarditis occurs in **~1% of patients** but is often **fatal** in up to **40% of cases**

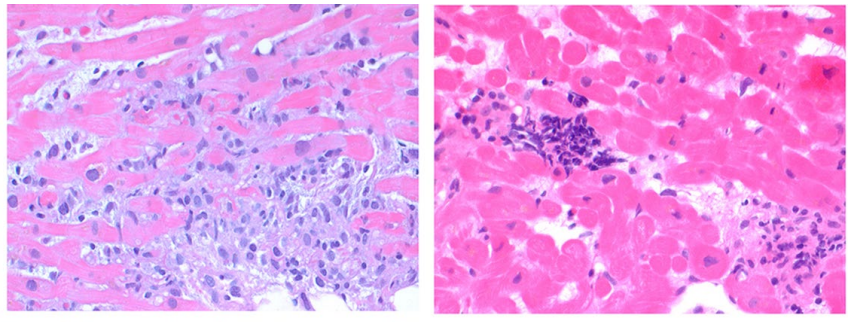
- **Major adverse cardiac events** (MACE)
  - including arrhythmias, sudden cardiac death, heart failure, or cardiogenic shock
  - occur in **~25-50%**

- **Diagnosed** by **MRI** or a **biopsy** showing T-cell infiltrates



High Grade **Low Grade**

H&E Staining



Wang DY, Johnson DB et al. JAMA Oncol, 2018

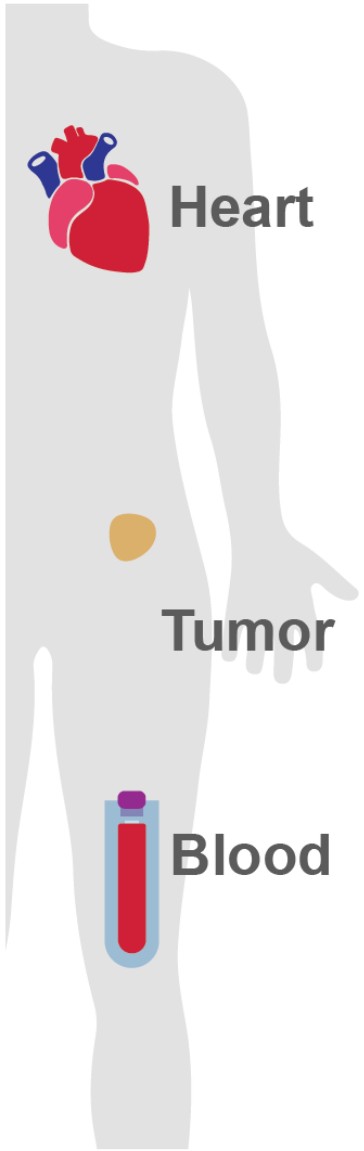
irMyocarditis Study Design

Heart tissue:
Control heart tissue (n=8)

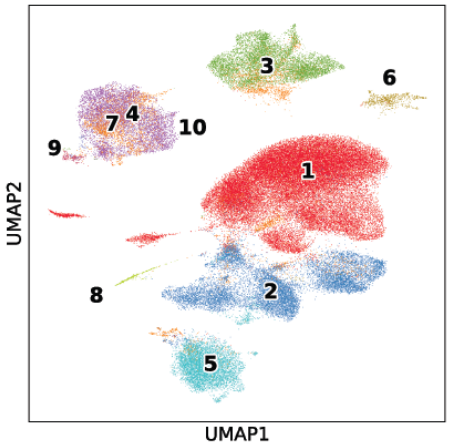
irMyocarditis (n=13)
7 PD-1/PD-L1 inhibitors
6 PD-1/CTLA-4 blockade
8 tumor histologies

Paired tumor tissue (n=4)

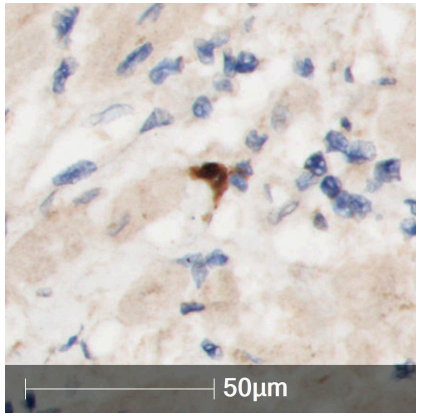
Blood specimens (n = 26)
Matched to heart
All pre-steroid samples



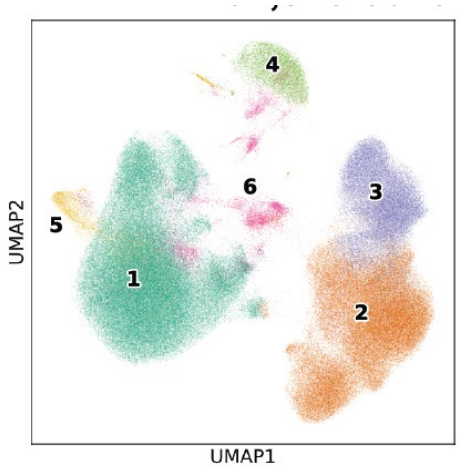
Heart single-cell RNA + TCRseq (n=84,576 cells)



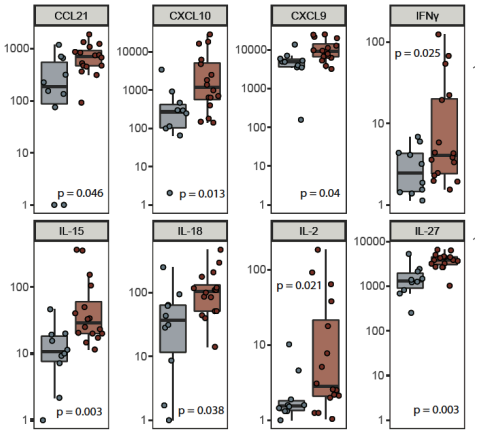
Immuno-histochemistry



Blood single-cell RNAseq+ TCRseq (n=232,929 cells)

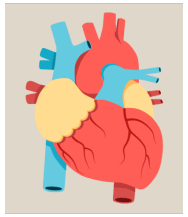


71 secreted factors (Luminex)

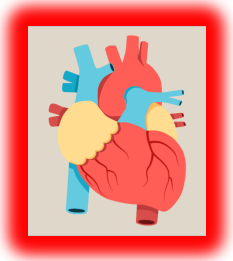


Approach Overview

Control heart and blood
- No ICI exposure
- On-ICI, no myocarditis



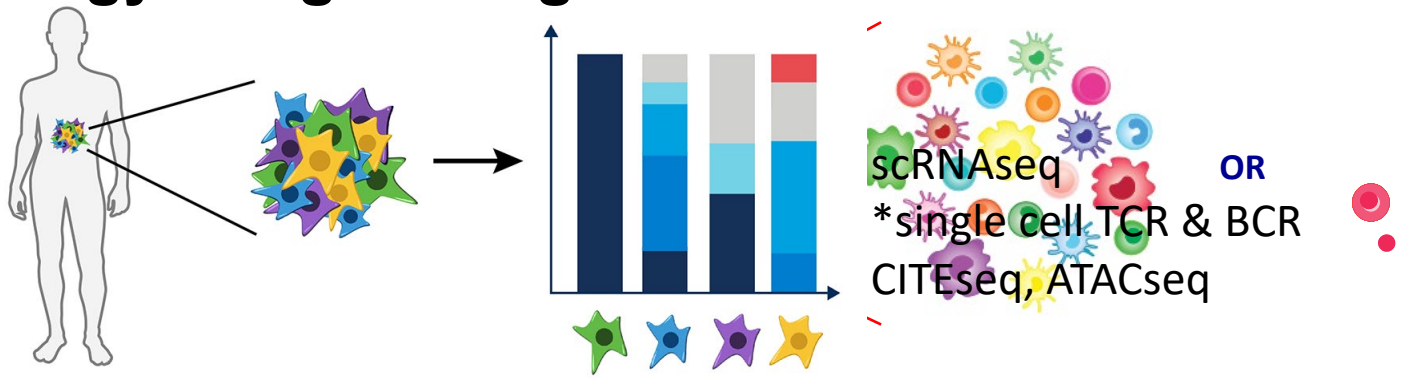
Myocarditis heart and blood
- Dx by MRI or histology



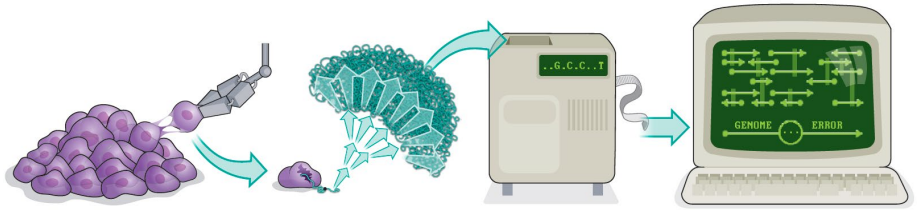
Compare cell populations
Compare gene expression
Compare TCR repertoire
Compare circulating factors

1. What cellular and molecular perturbations define irAEs? (tissue ecosystem)

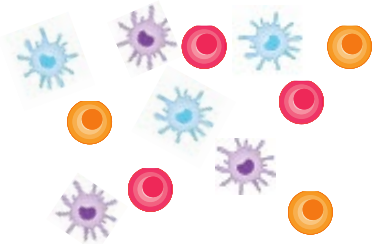
Strategy: Single-cell genomic dissection of tissue lesions



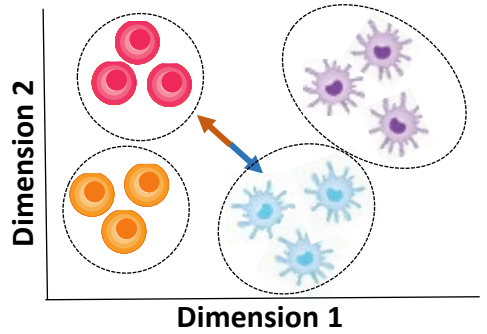
Single cell RNA sequencing



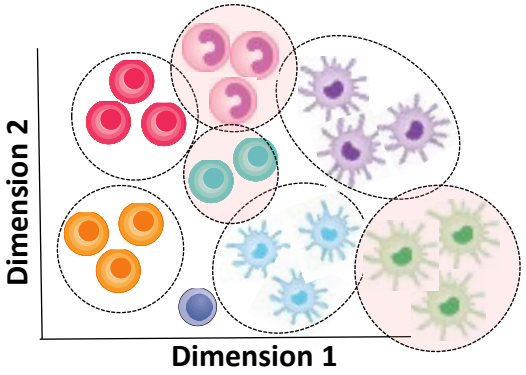
Cell subsets map



Cell populations in "control" patients

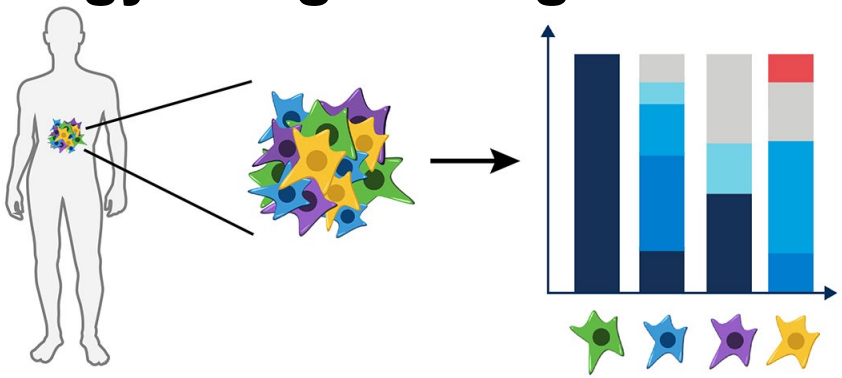


Cell populations in "disease" patients



1. What cellular and molecular perturbations define irAEs? (tissue ecosystem)

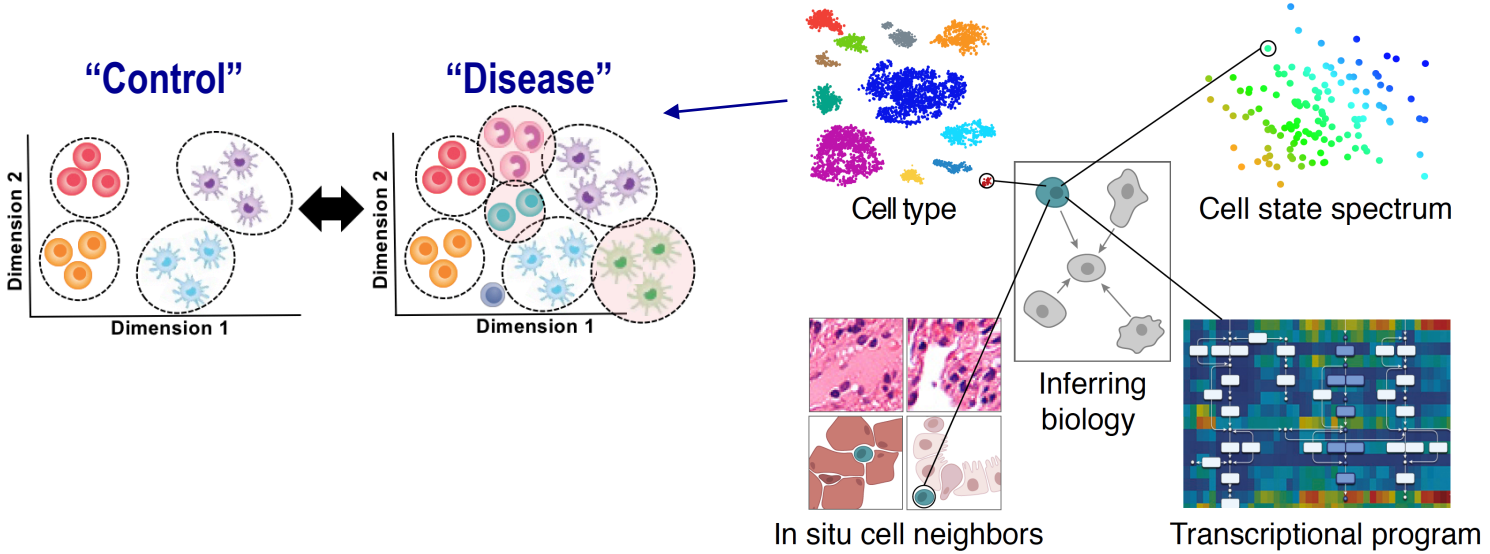
Strategy: Single-cell genomic dissection of tissue lesions



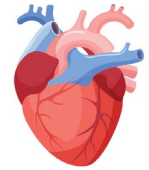
scRNAseq
*single cell TCR & BCR
CITEseq, ATACseq

1. Biopsy collection
2. Single-cell sequencing
3. Distinct profiles

Analyses: mapping cell types, states, regulatory programs and neighborhoods of cells



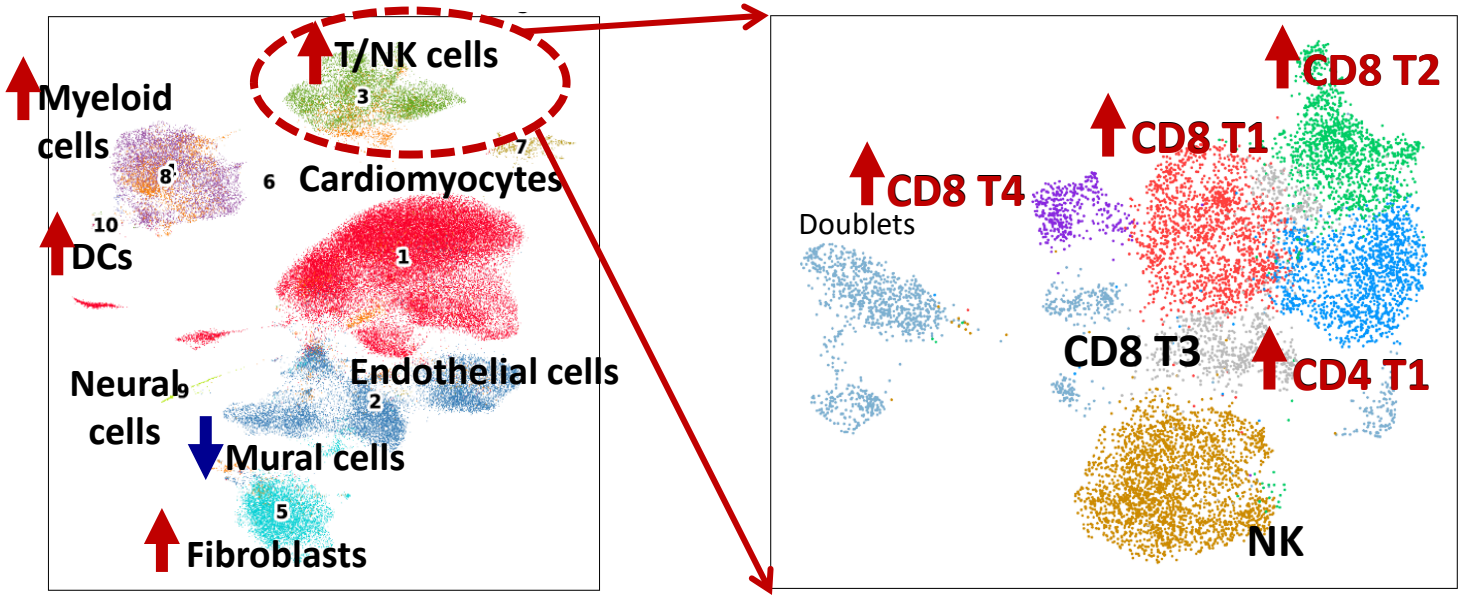
Question: Which cell populations are more abundant in irMyocarditis?



T cells, myeloid cells, dendritic cells, fibroblasts all shift in abundance

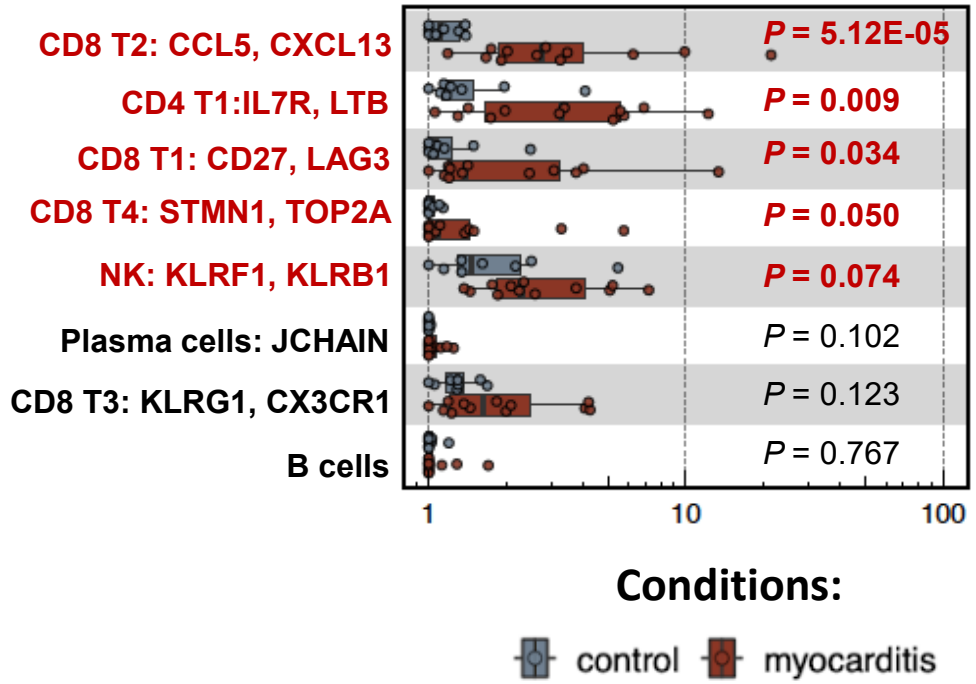
T cell subsets spanning effector and exhaustion programs enriched in cases

10 broad cellular populations identified by



6 T/NK CELL SUBSET IN HEART

T ABUNDANCE ANALYSIS



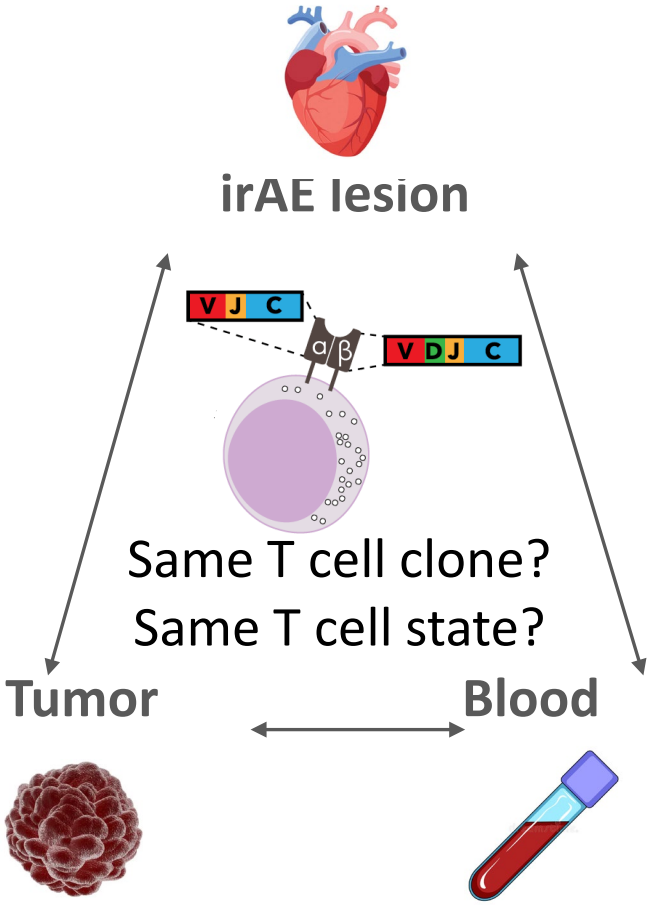
→ Should not be any T cells in the heart

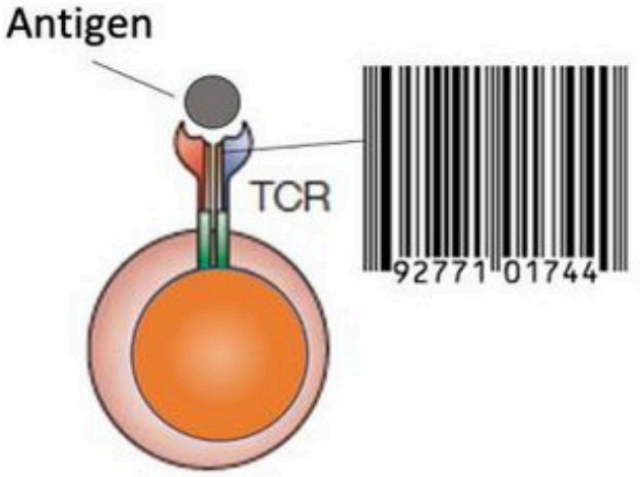
→ Are these the same T cells fighting the tumor?

2. Defining phenotypic spectrum of T-cell clones in irAE lesions, blood, and tumor

Strategy: TCR analyses in paired samples

Analyses: deriving principles across tissues and irAEs





Questions:

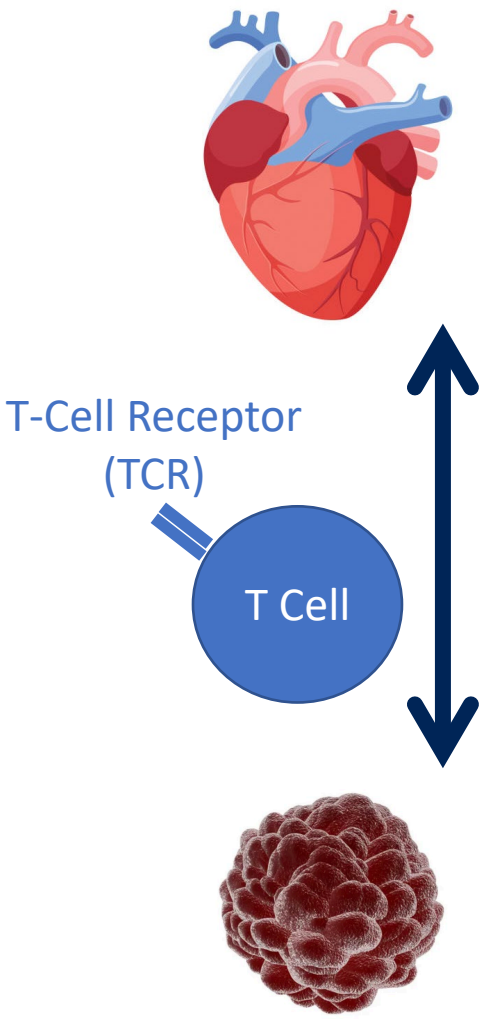
How does TCR repertoire diversity correlate with irAEs and with response to treatment?

Can we identify the same TCR clones in tumor, blood and irAE tissue lesions?

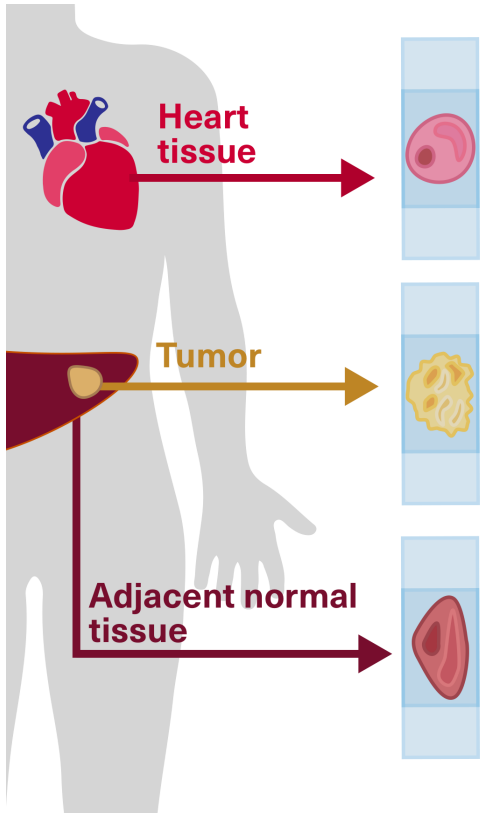
Are T cells recognizing the same antigens?

Can we identify shared T-cell receptor clones between heart and tumor?
Shared TCR clones could help identify (1) important biology or (2) non-invasive biomarkers

TCRs) serve as barcodes for T cells in heart or tissue

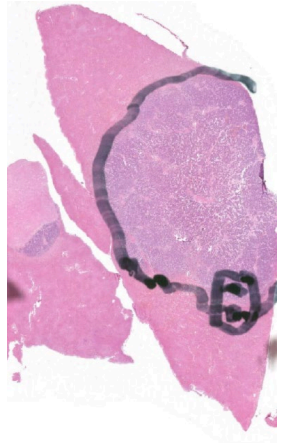


Autopsy cases (n = 4)

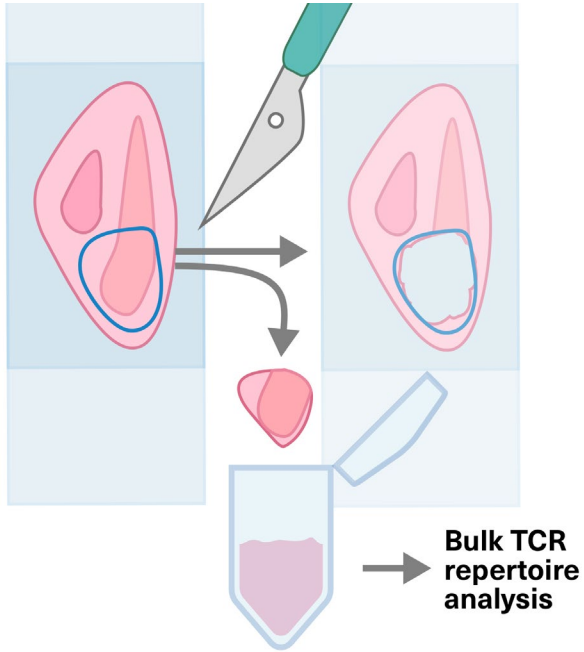


Inflammation in myocarditis tissue

Tumor invading normal parenchyma

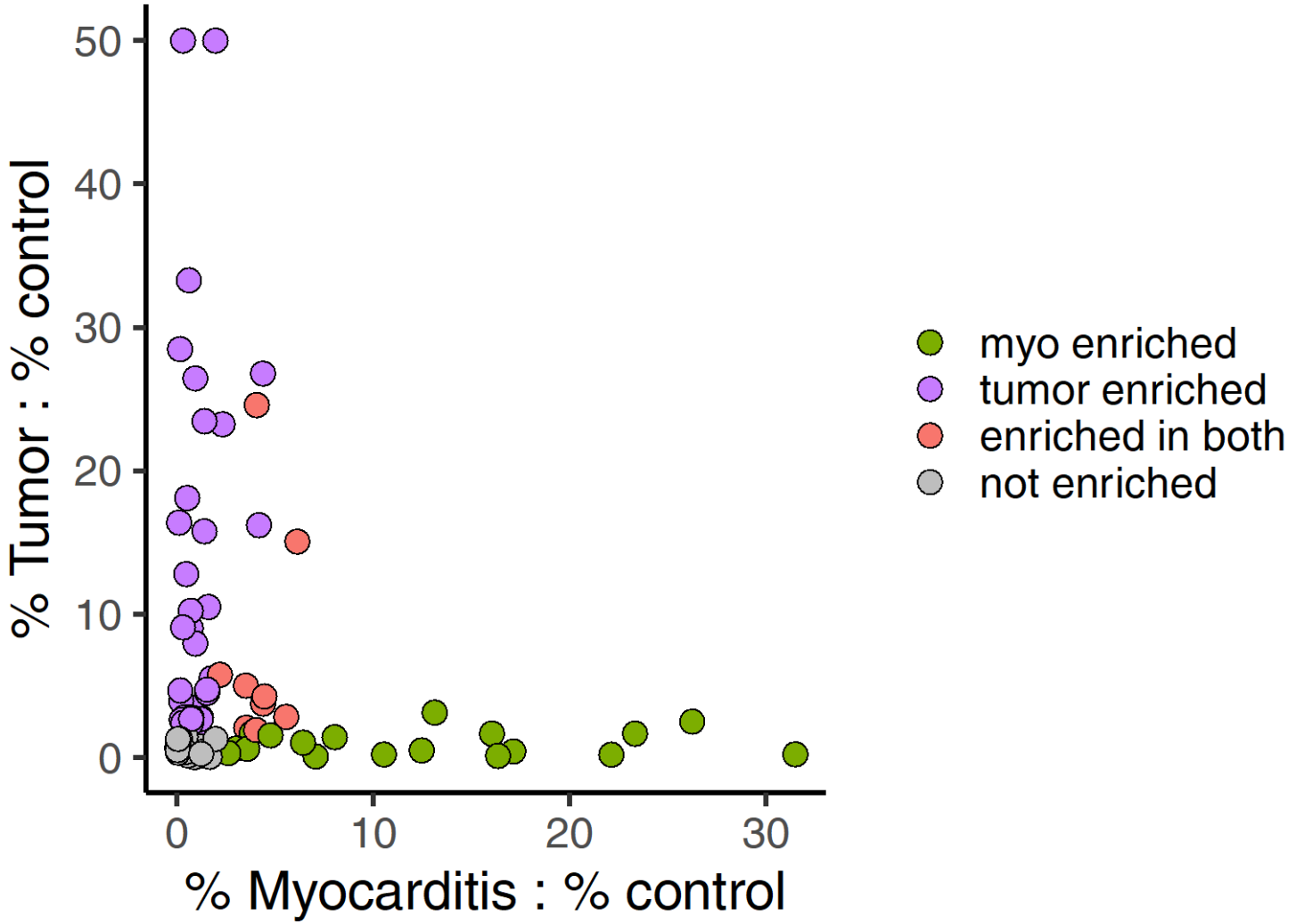


Microdissection strategy to analyze ONLY affected tissue



Question: Can we identify share TCR clones between paired heart and tumor?

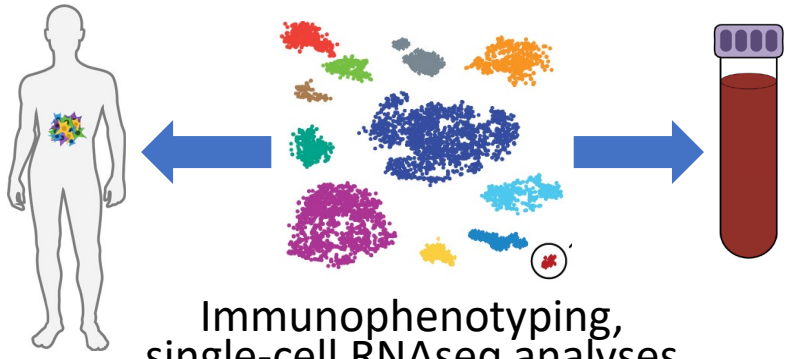
Most expanded TCR clones in tumors and heart are NOT shared, suggesting distinct biology between anti-tumor immune response and irMyocarditis



3. Does blood mirror tissue? Identifying biomarkers for patients at higher risk for irAEs

Strategy: secreted factor monitoring and blood analysis

Analyses #1: can blood mirror tissue?

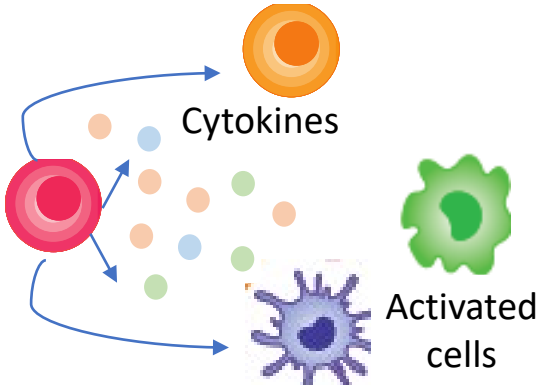


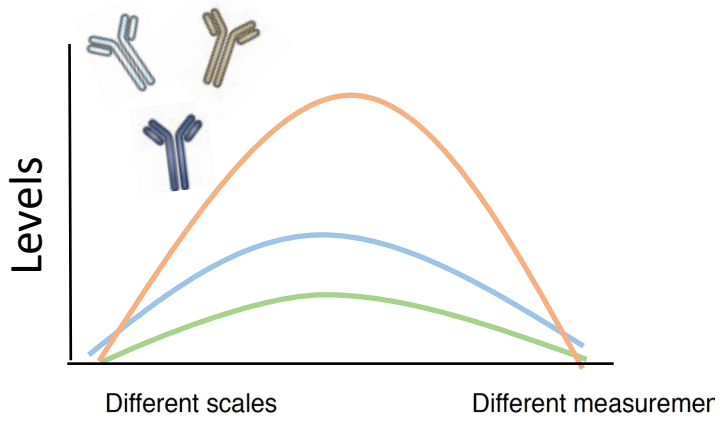
Immunophenotyping,
single-cell RNAseq analyses
(scRNAseq+TCR+BCR+204 proteins)

Biomarkers could be:

→ particular TCR /BCR clone
→ cell subset
→ gene signature
→ secreted factors
→ cell surface protein marker
→ germline susceptibility variant

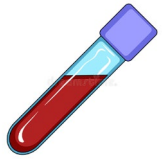
Analyses #2: cytokines and autoantibodies levels driving break of immune tolerance

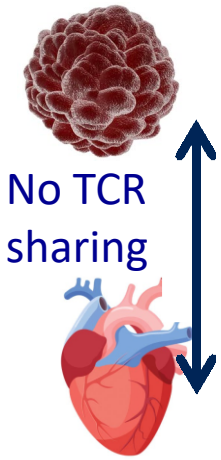




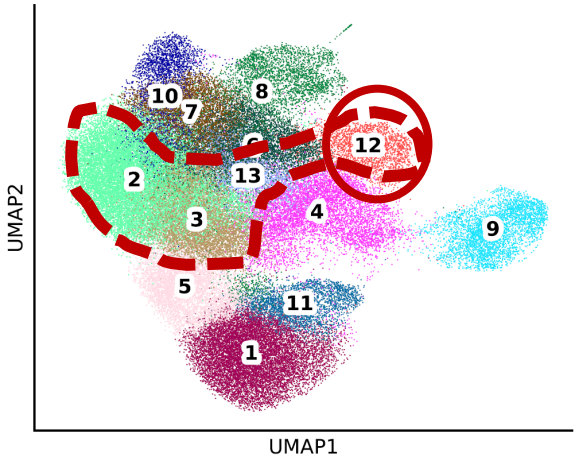
Question: Can we identify share TCR clones between paired heart and blood?

Yes! TCR sharing between heart and blood, with fatality association

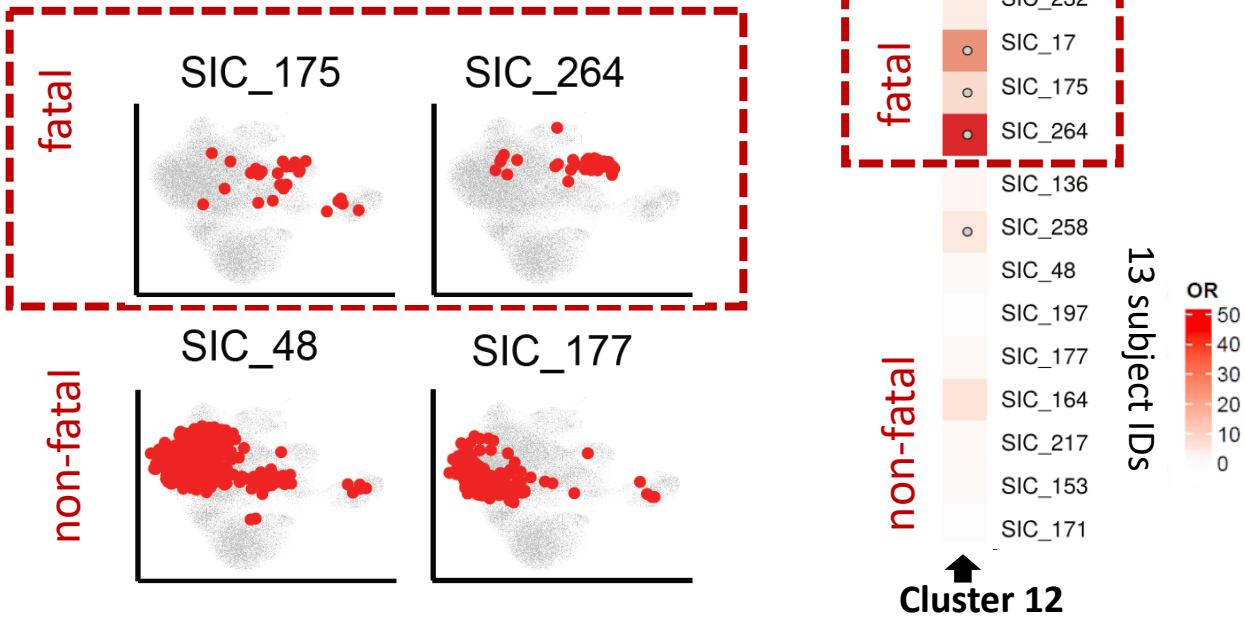




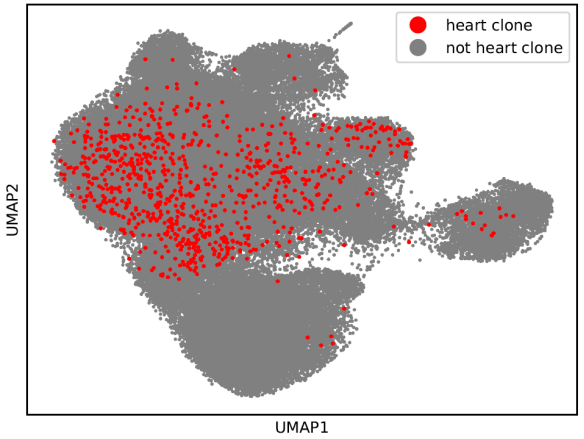
Blood CD8+T/NK Cell UMAP: 13 subsets, 75,480 Cells



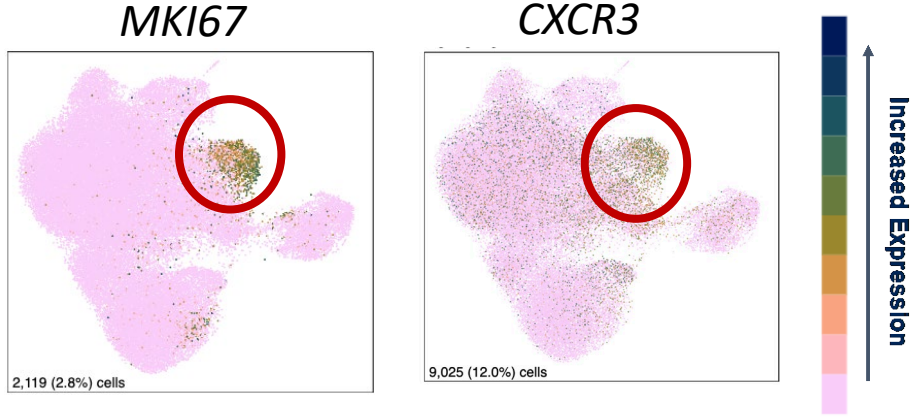
Fatal irMyocarditis TCR sharing is distinct



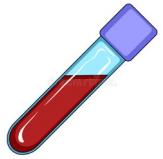
Red = TCR clones found in heart and blood



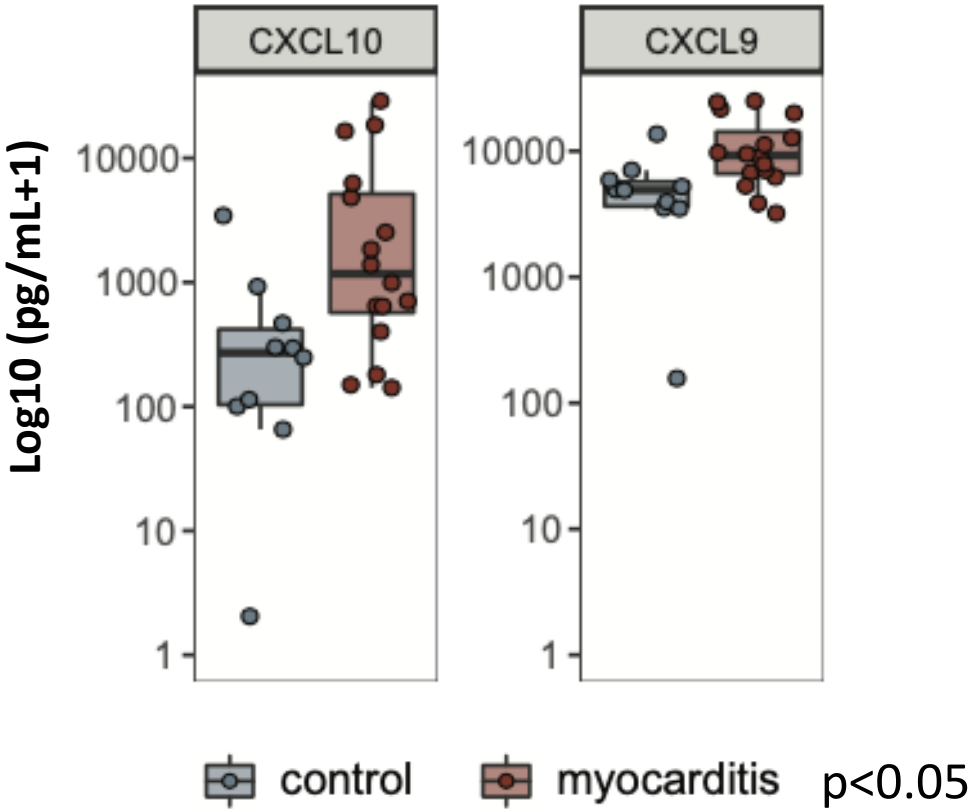
Cluster 12: Cycling, CXCR3^{Hi} CD8 T cells



Question: Are there secreted factors associated with ICI-myocarditis?



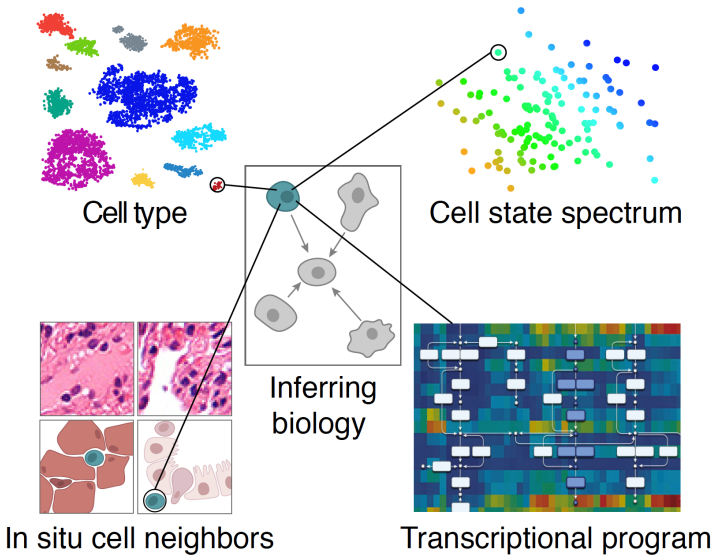
CXCR3 ligands and other factors involved in T cell recruitment elevated in patient blood



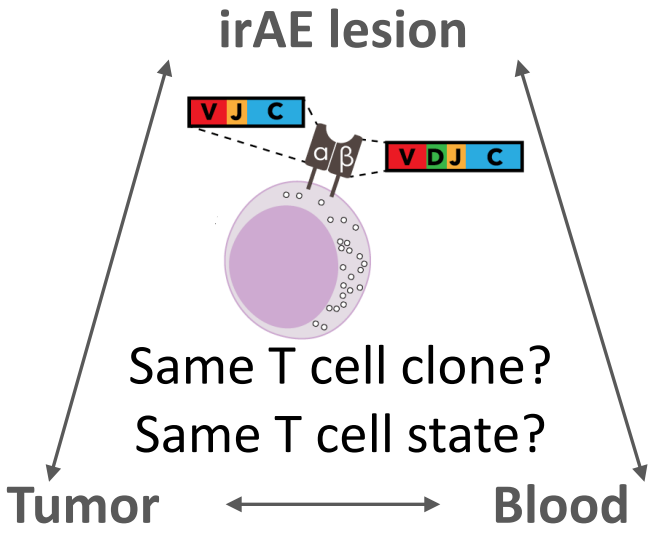
→ *Can these factors predict irMyocarditis? Are these factors also associated with anti-tumor response?*

Working towards unraveling the underpinnings of irAEs and identifying drug targets through 3 complementary strategies

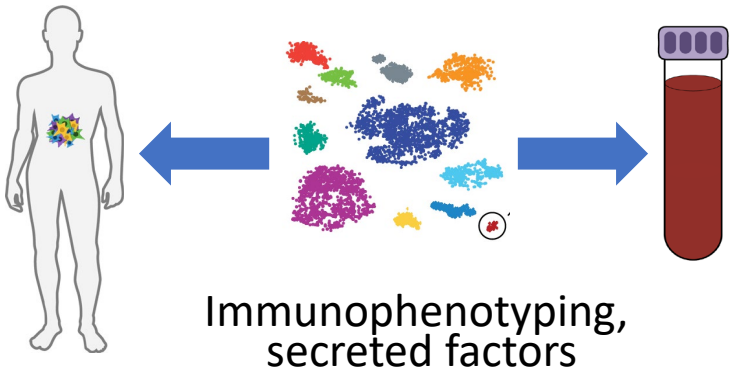
(1) What are the cell populations & transcriptional programs enriched in the hearts of myocarditis patients?



(2) Are T cell clones shared between tumor, heart and blood?



(3) Can we identify circulating biomarkers associated with myocarditis and outcome?

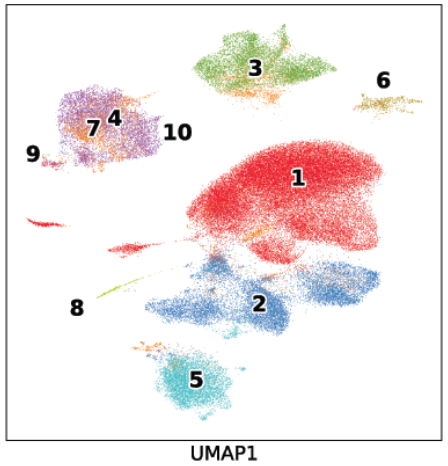


Immunophenotyping,
secreted factors
single-cell RNAseq analyses
(scRNAseq+TCR+BCR+204 proteins)

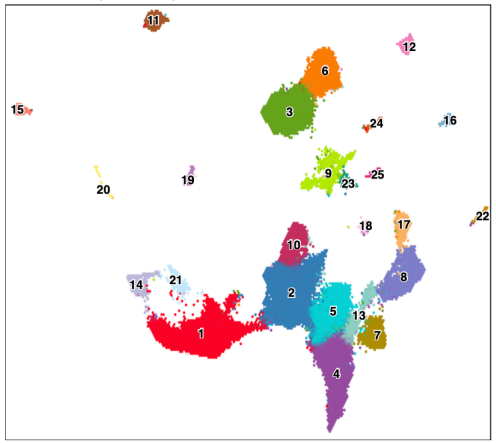
Overview of different ongoing single-cell multi-omics' efforts across organ systems

Colored by predicted populations

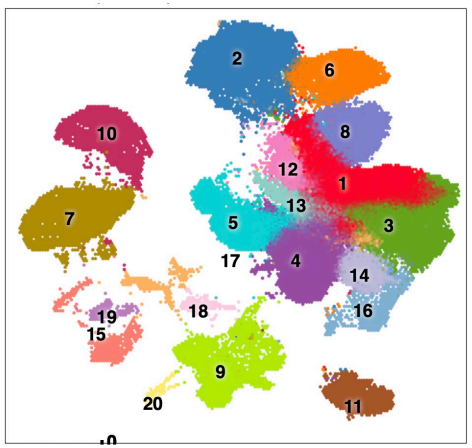
Myocarditis
(Daniel Zlotoff, Steven Blum, Neal Smith, Swetha Ramesh, Isabela



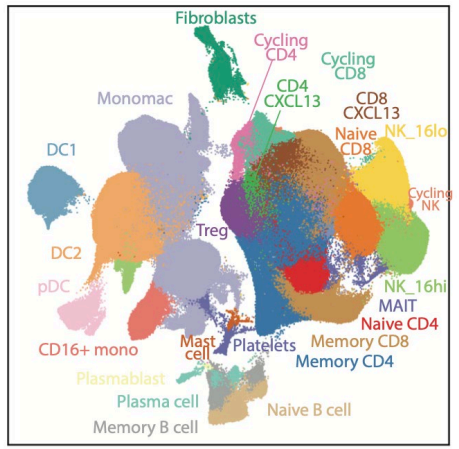
Colitis
(Molly Thomas & Kamil Slowikowski)



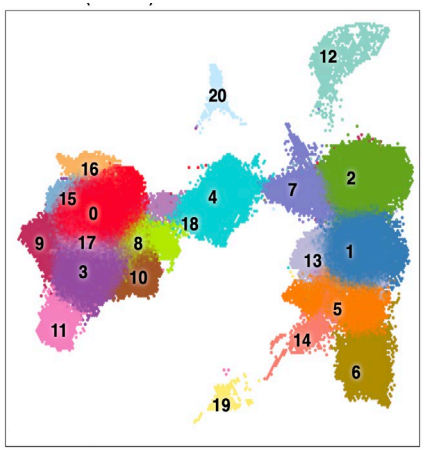
Hepatitis
(Molly Thomas, Tos Chan, Neal Smith)



Arthritis
(Mazen Nasrallah & Gary Reynolds)



Neurotoxicity
(Hoang Tran & Amanda Guidon)




Daniel Zlotoff


Steven Blum


Swetha Ramesh


Neal Smith


Isabela Kernin


Molly Fisher


Kamil Slowikowski


Mazen Nasrallah


Gary Reynolds


Michelle Rengarajan

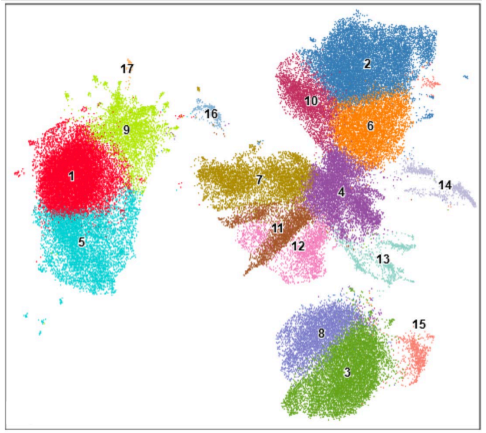

Tos Chan


Rachelly Normand

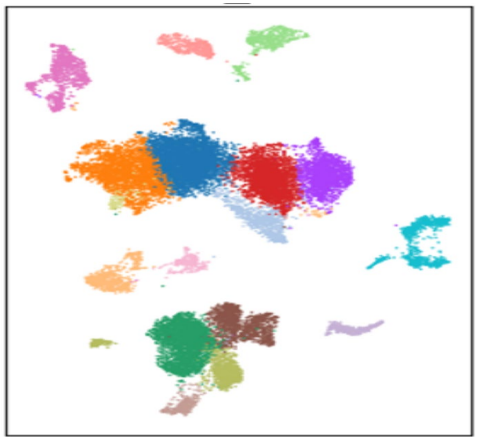

Yash Sonthelia


Hoang Tran

Nephritis
(Meghan Sise Isabela Kernin)

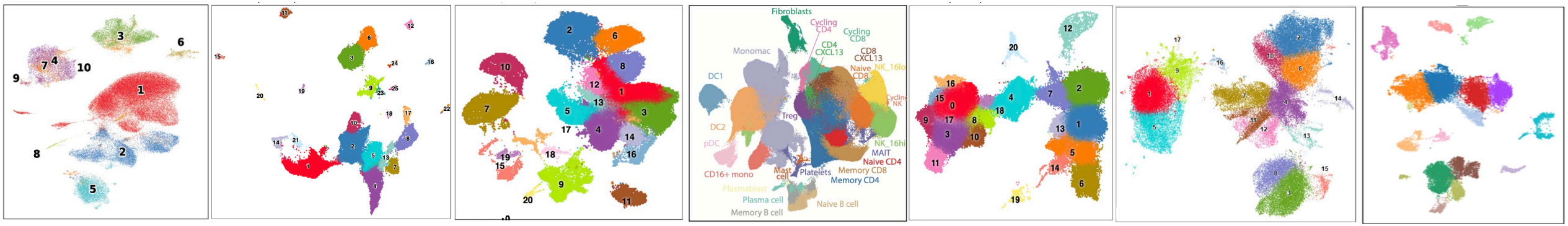


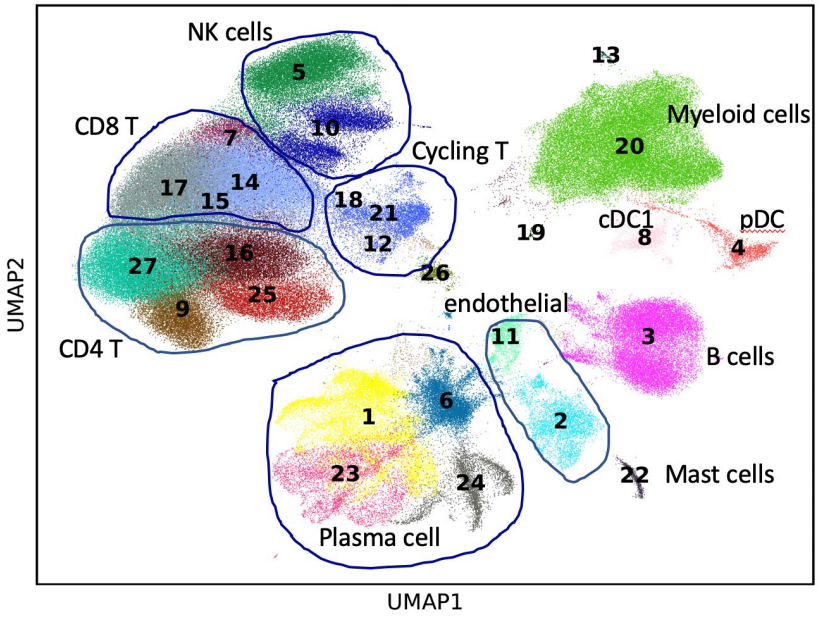
Endocrinopathies
(Michelle Rengarajan Rachelly Normand)



Where do we go from here?

Myocarditis **Colitis** **Hepatitis** **Arthritis** **Neurotoxicity** **Nephritis** **Endocrinopathies**

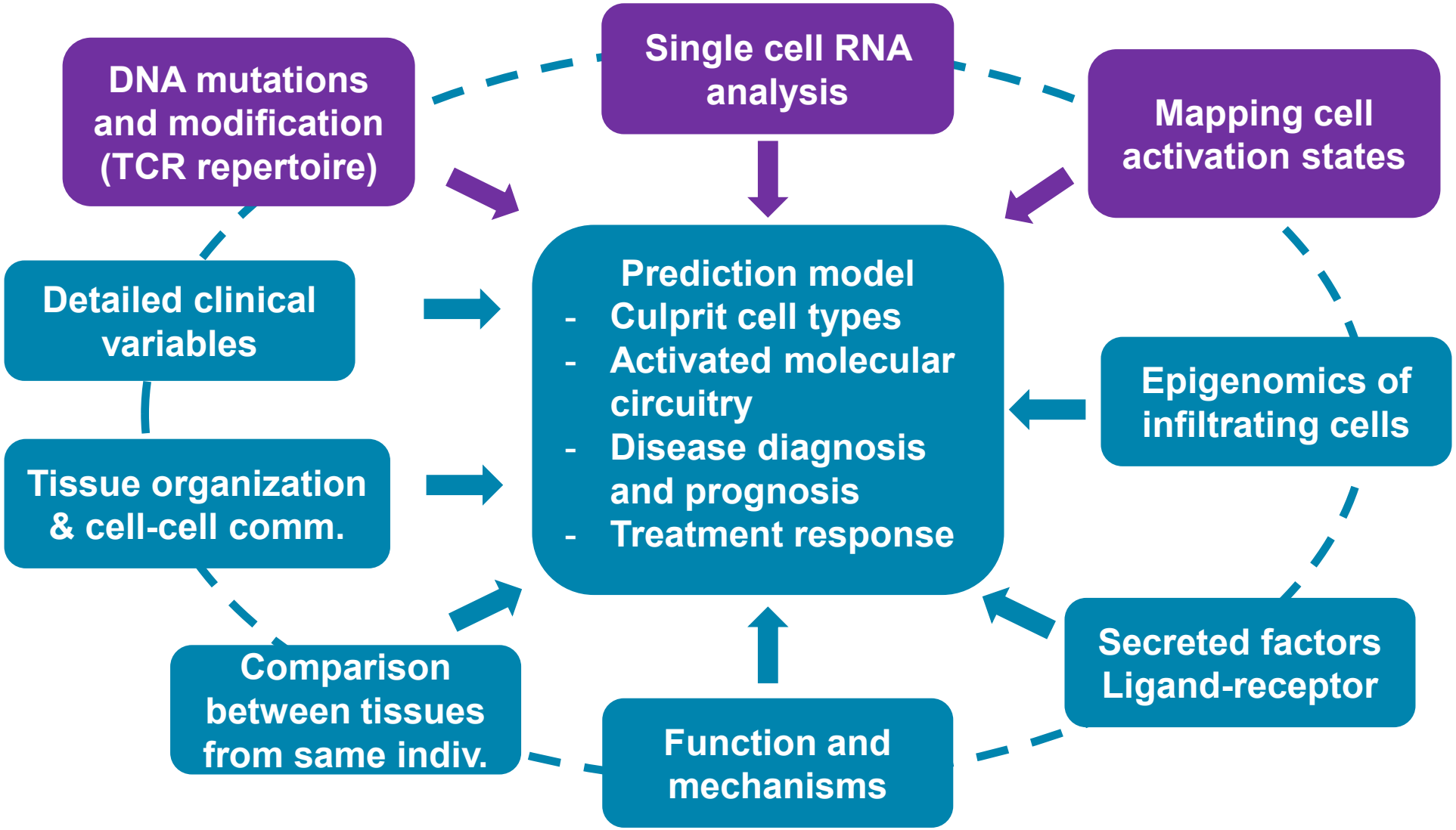




irAE meta-analysis to guide follow-up studies:

- Are all irAE presentations created equal biologically?
- What are the shared and distinct populations/pathways involved?
- Which biological programs are distinct from tumor response?
- Should irAE all be therapeutically modulated the same way?

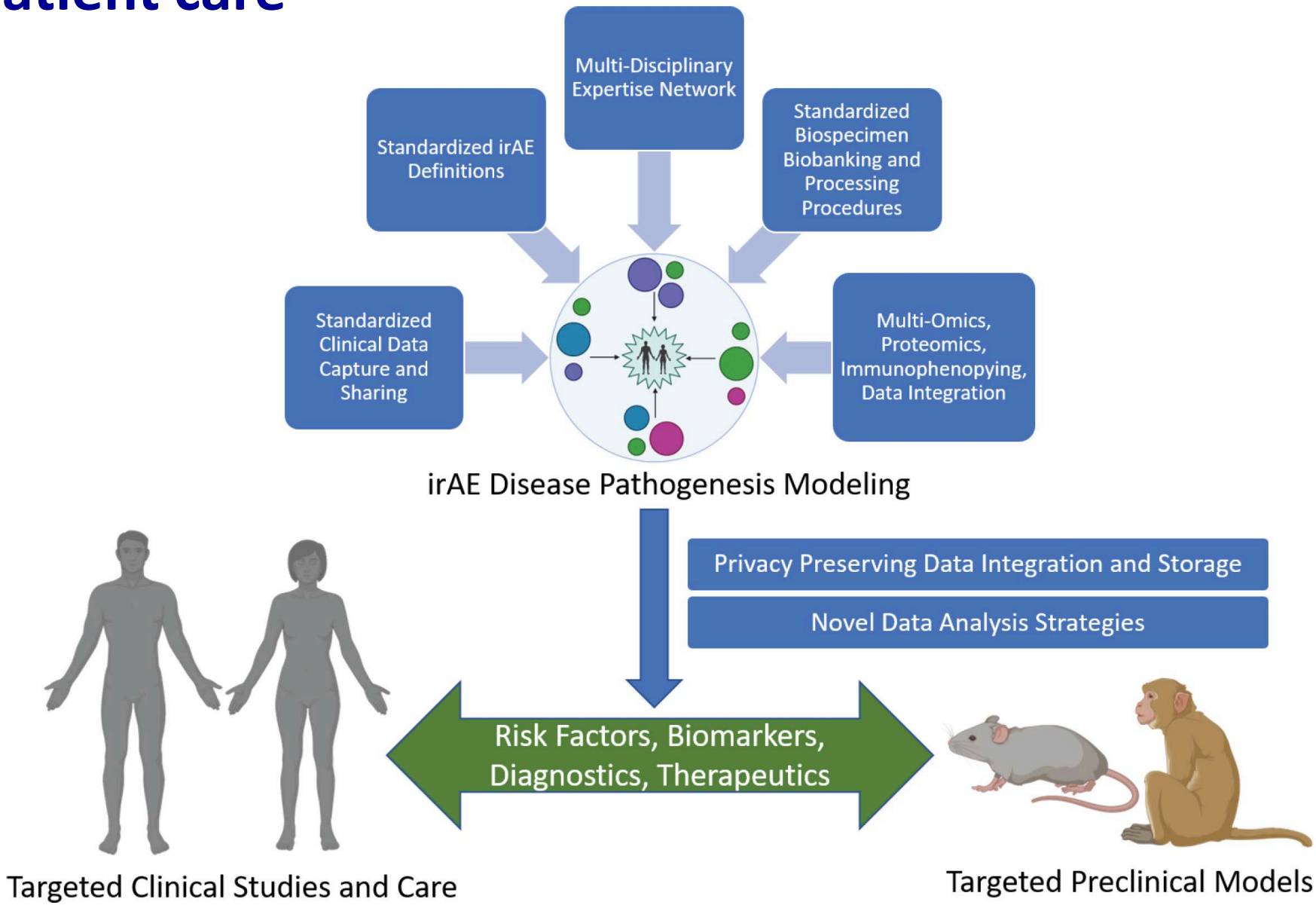
Working towards unraveling irAE underpinnings and identifying drug targets through multi-modal approaches



Pressing needs and gaps in the field of irAE biomarker & mechanisms discovery

- **Larger irAE cohorts needed** – cross institutional collaborations required for gathering enough samples to identify biomarkers **for rarer irAE presentations**
- **Serial time point collection** – tracking factors over time to define biomarkers (*e.g.,* pre-ICI, post-ICI/pre-irAE, at irAE diagnosis **pre-steroid**, post-steroid)
- **Distinguishing signature** of ICI-treatment response vs. irAE presentations
- **Developing consensus annotations –** irAE presentation & ICI-treatment response
- **ICI controls** – Analyzing the right types of controls to define irAE biomarkers (e.g., matching demographics, tumor, treatment, time points, no irAE)
- **Funding** – Currently few opportunities to study the underpinnings of irAE in patients

There is a critical need to work together to solve irAE & improve patient care



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Jaquelyn Nestor
Sergio Aguilar
Sherin Rouhani
Thomas Chen
Aonkon Dey
Hoang Anh Tran
Yash Sonthalia
Swetha Ramesh
Jonh McGuire
Nandini Samanta
Sidney Martin
Alice Tirard

Villani Lab Alumni
Pritha Sen
Mazen Nasrallah
Jessica Tantivit
Benjamain Arnold
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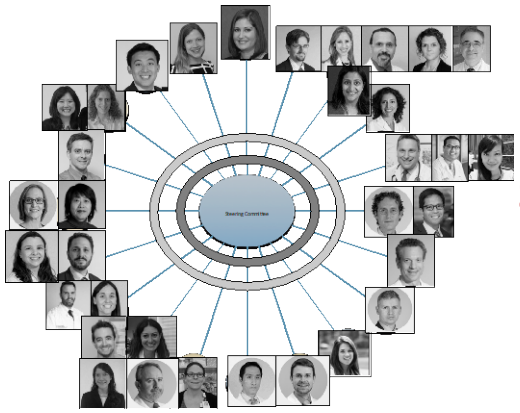

SIC Service

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The patients & families

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Always looking for talented trainees and postdocs!