Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

What's Next for Cancer Immunotherapy?

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE
CHAMPION OF THE EMERGENCY PHYSICIAN

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Disclosures

Personal Financial Disclosures

- None

Research Funding

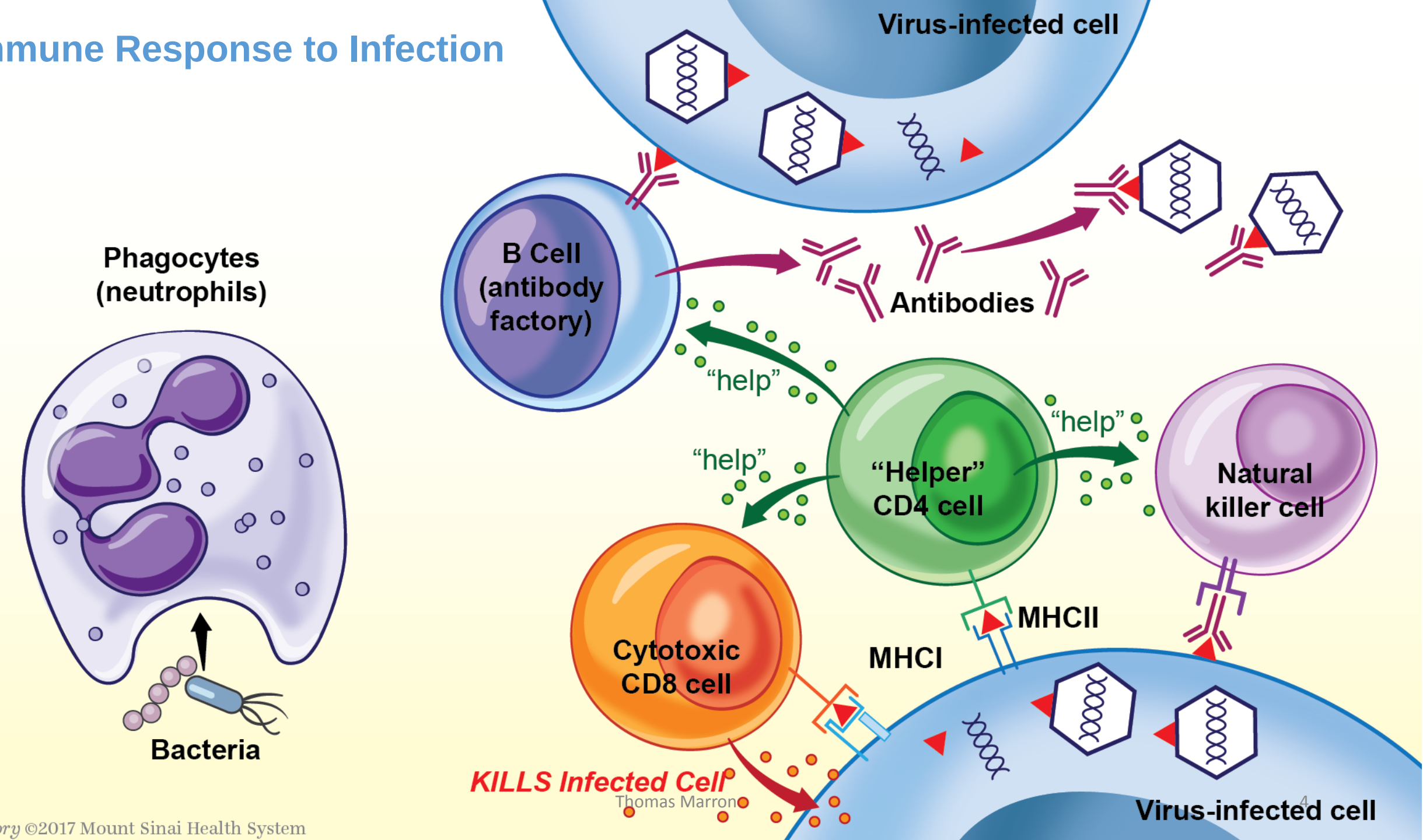
- Bristol-Myers Squibb
- Regeneron
- Merck
- CTI Biopharma

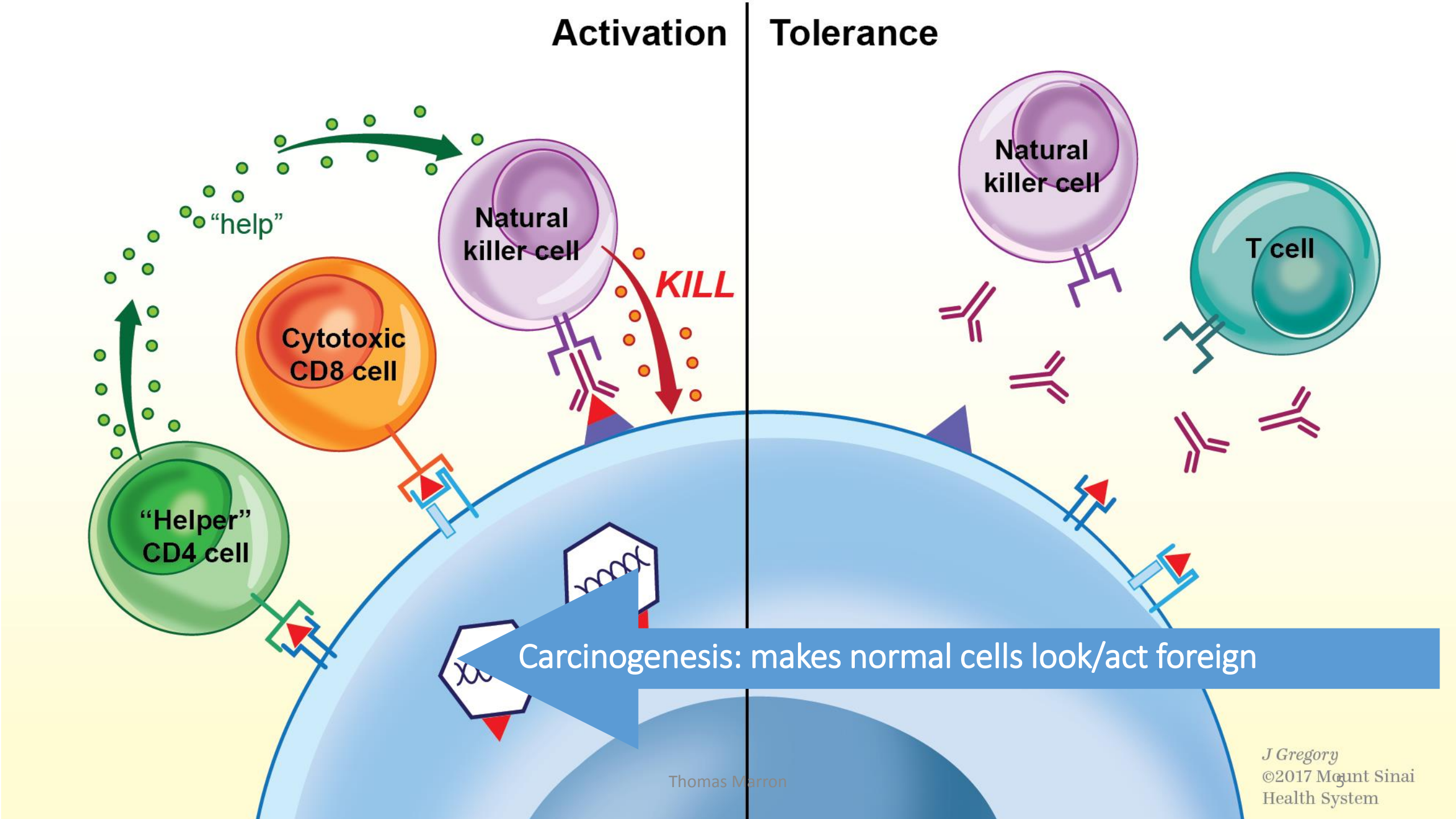
I will be discussing off-label use of novel therapies (no connection to my research)

Quick Review of Immunology 101

Your immune system recognizes self/foreign

Immune Response to Infection




Activation
Tolerance
"help"
Natural killer cell
KILL
Cytotoxic CD8 cell
"Helper" CD4 cell
Natural killer cell
T cell
Carcinogenesis: makes normal cells look/act foreign
J Gregory
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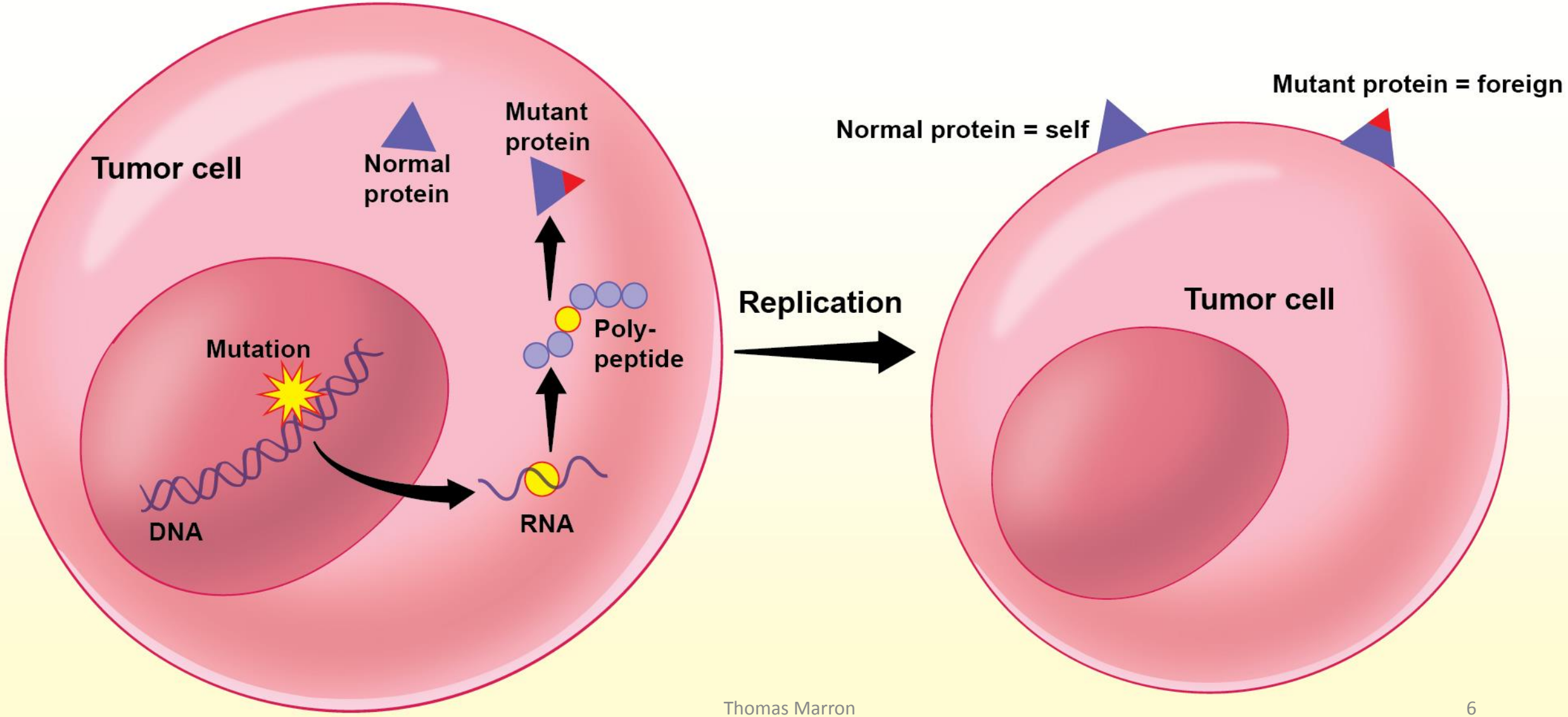
Neoantigens: Things that make tumor cells look different from normal cells

Similar to how virally-infected cells look different from normal cells



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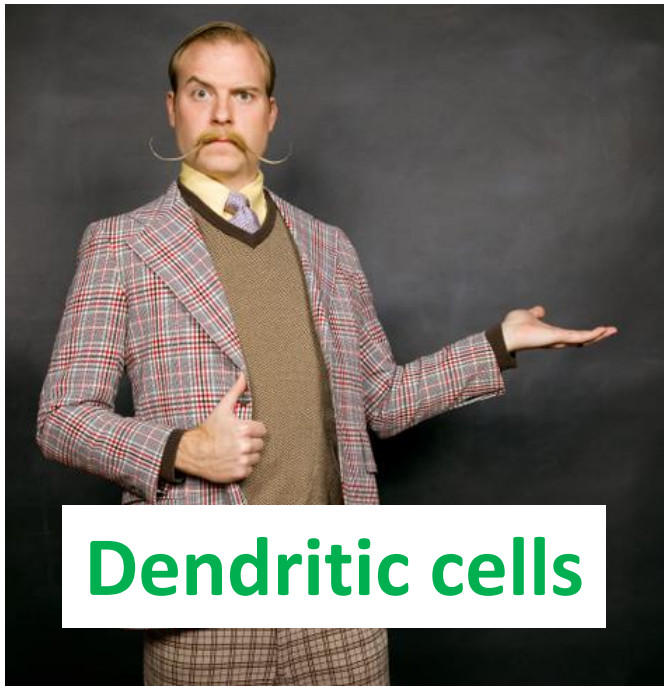
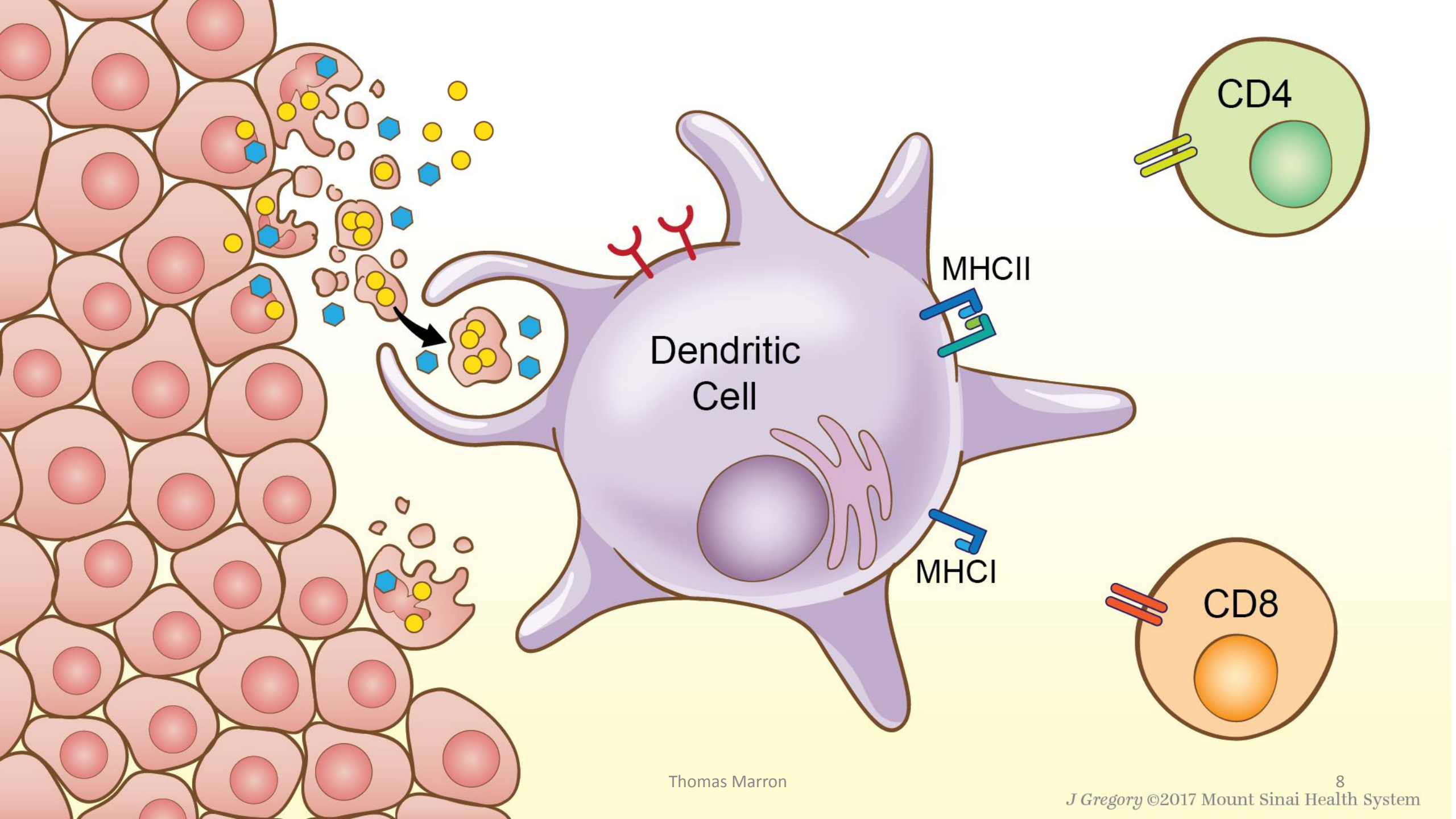
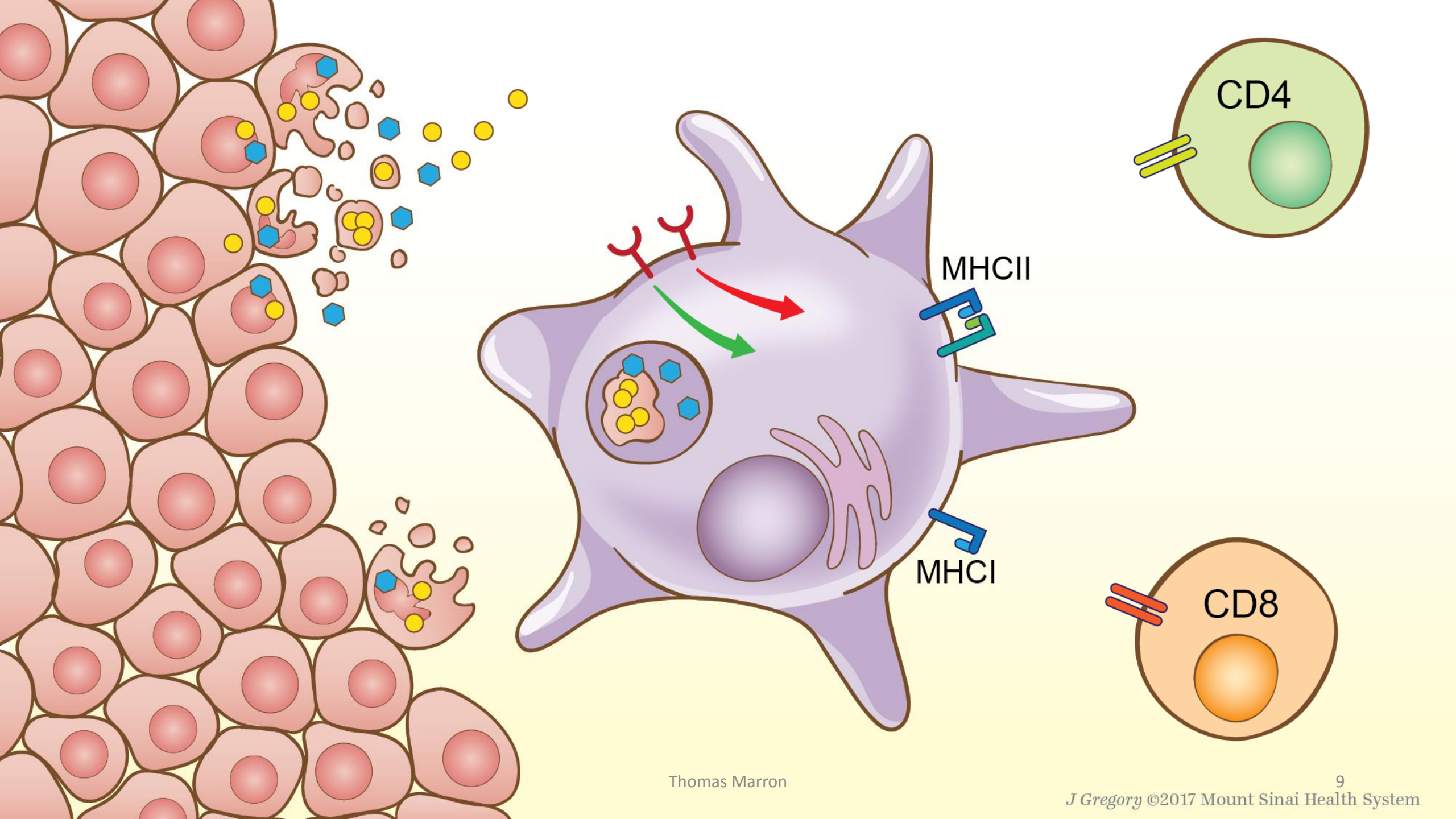
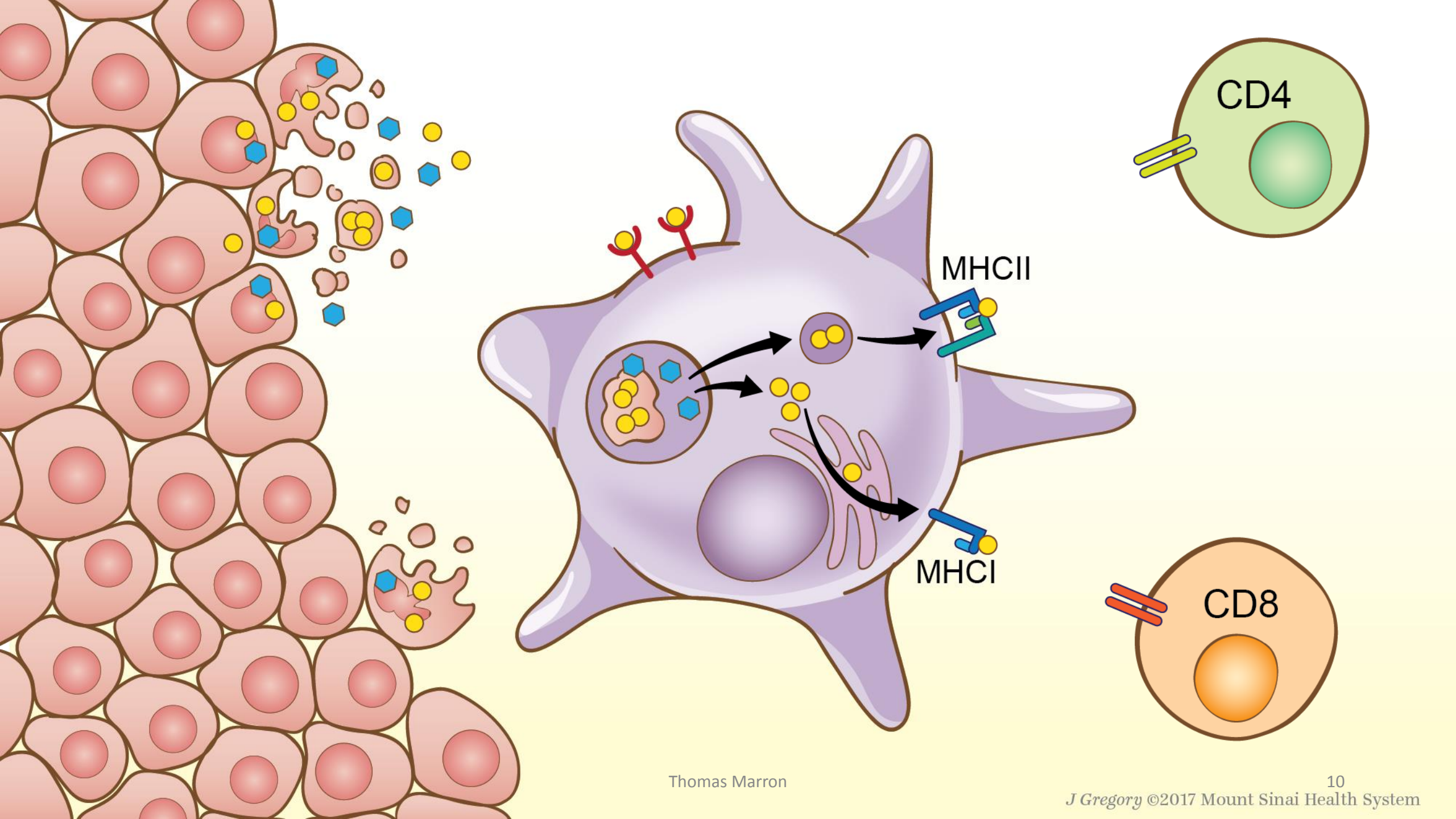
Quick Review of Immunology 102

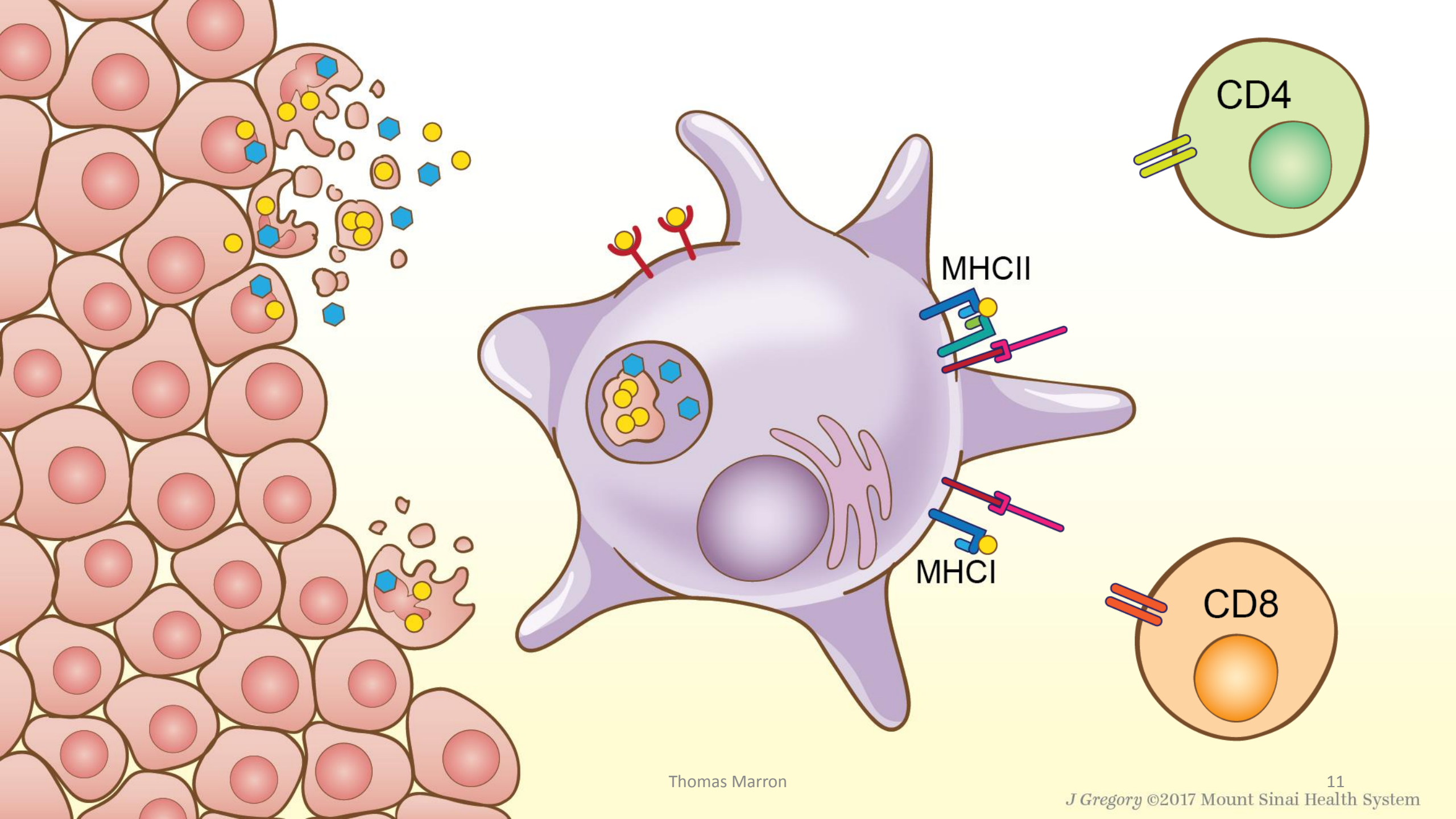
How to teach your cells to recognize "foreign" cancer





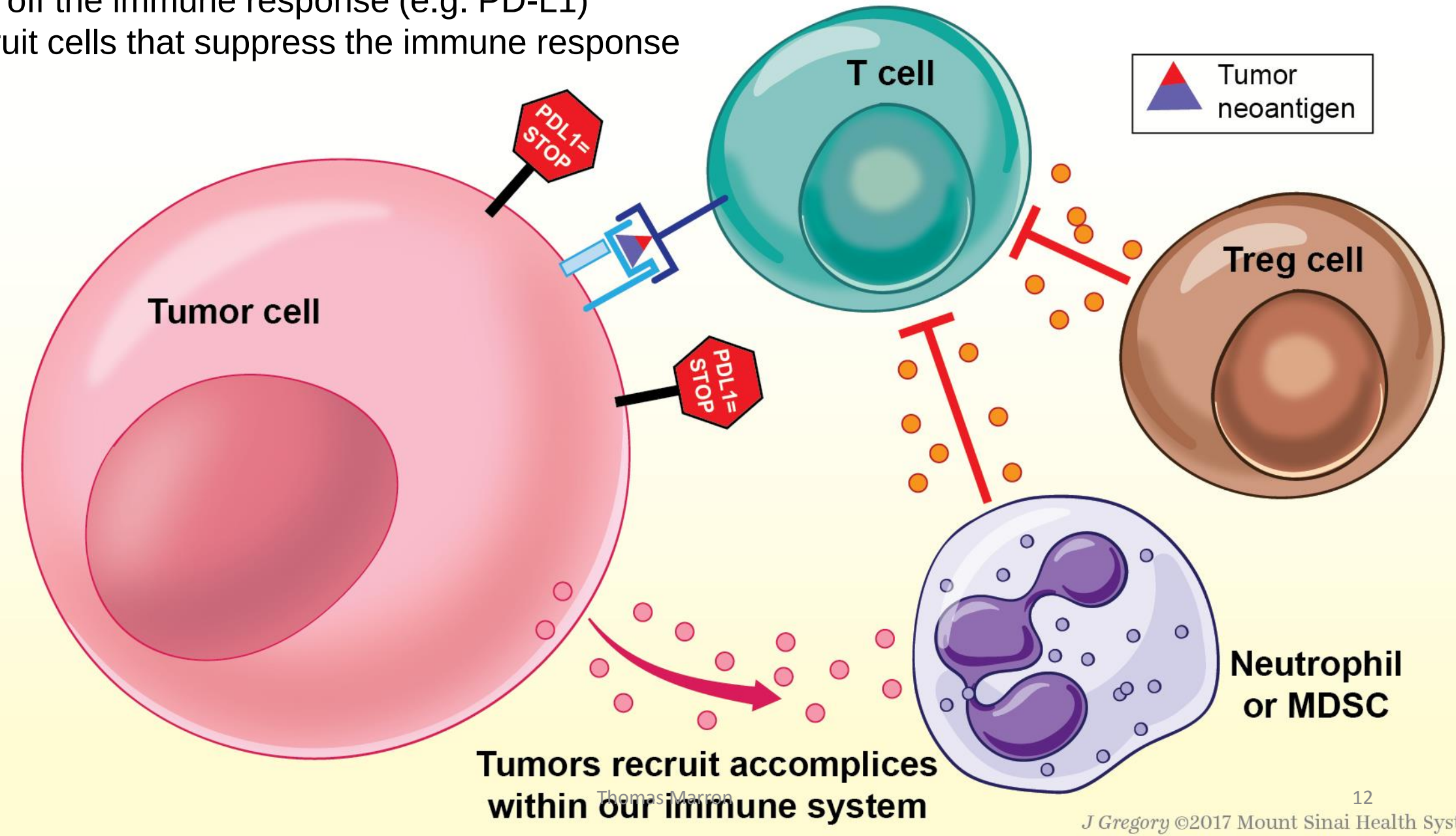






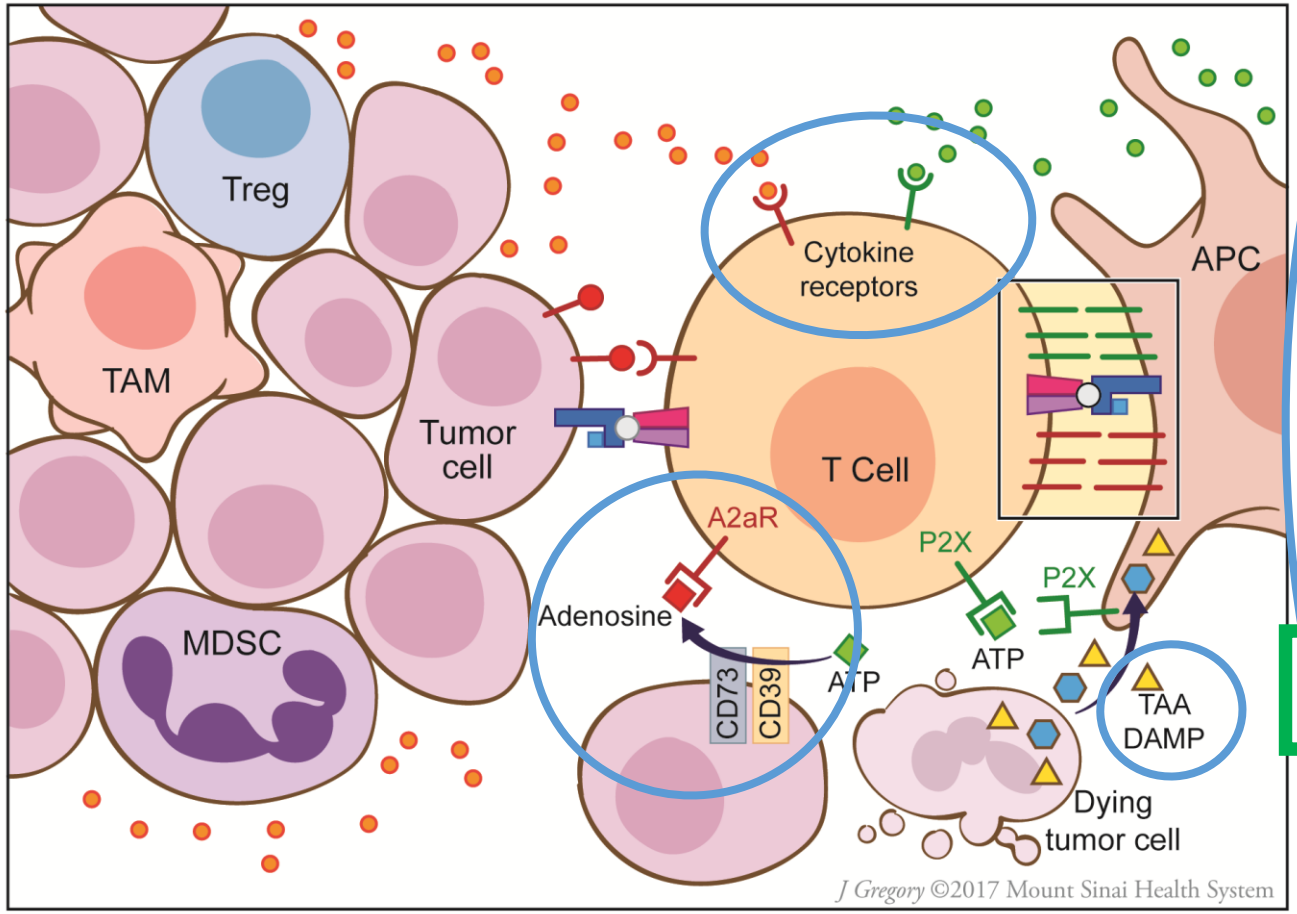
Tumors Hijack the Immune System

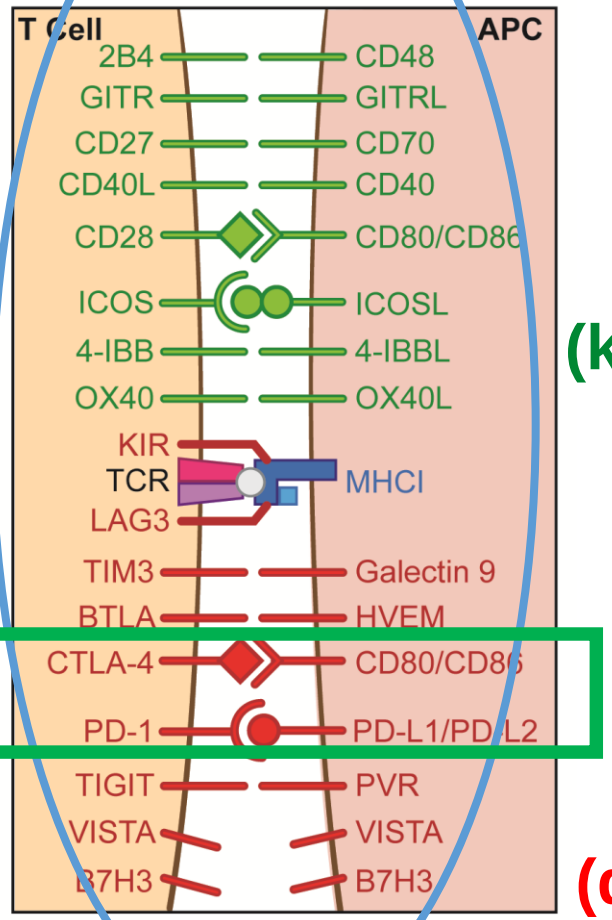
1. Turn off the immune response (e.g. PD-L1)
2. Recruit cells that suppress the immune response

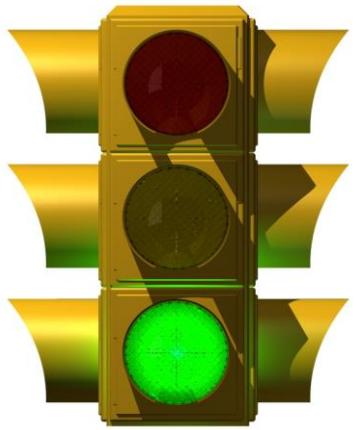


The tumor-immune micro environment is complex, many targets

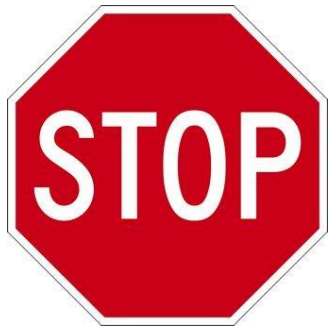
Many **ON**/**OFF** signals that we can manipulate with drugs to INCREASE inflammation







(kill the foreigner)



(don't hurt yourself)

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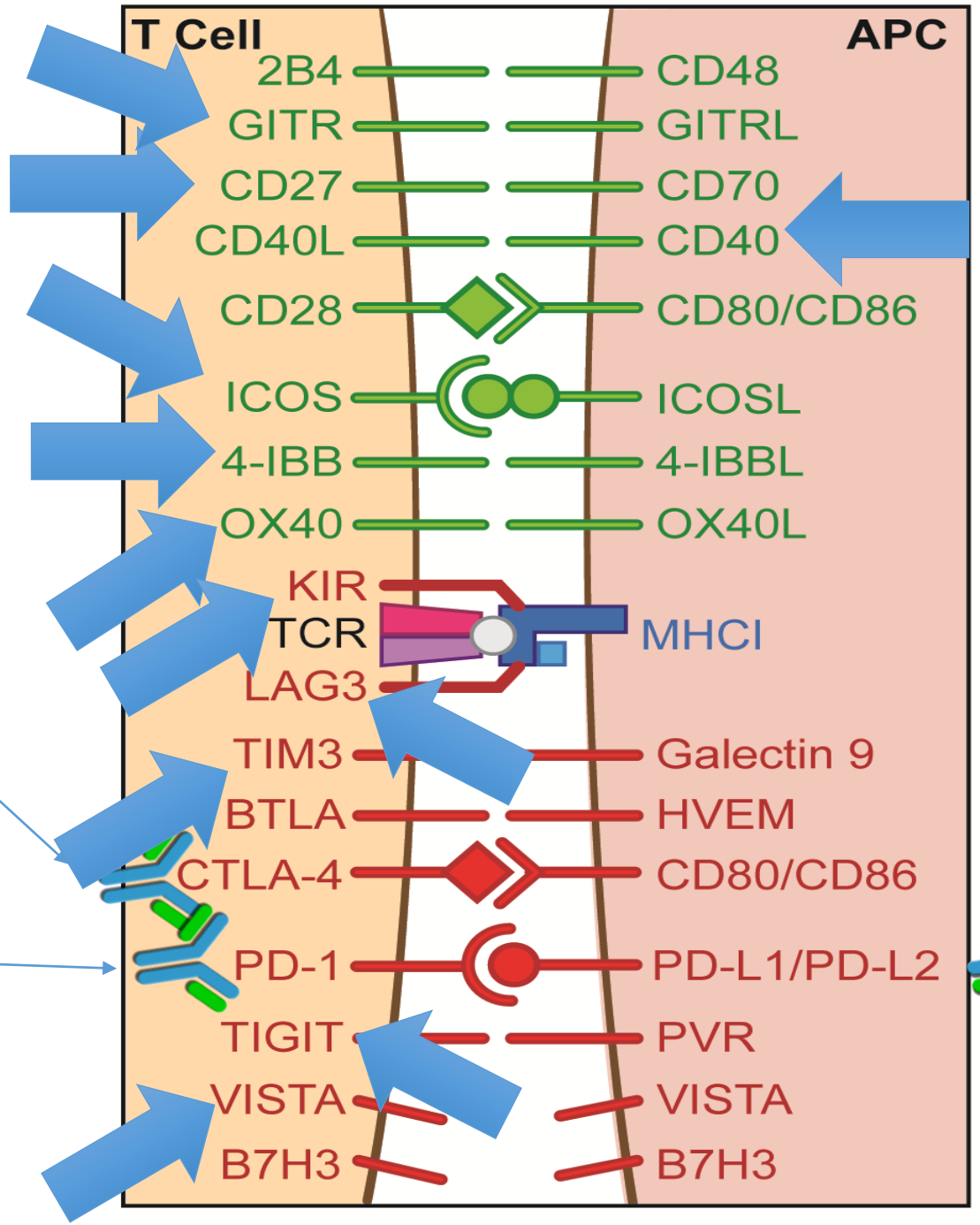

YERVOY® (ipilimumab) Injection for intravenous use 5 mg/mL

OPDIVO® (nivolumab)

KEYTRUDA® (pembrolizumab) Injection 100 mg

LIBTAYO® (cemiplimab-rwlc) Injection 350 mg

IMFINZI® durvalumab Injection for Intravenous Use 50 mg/mL

BAVENCIO® avelumab Injection 20 mg/mL

TECENTRIQ® atezolizumab INJECTION FOR INTRAVENOUS USE 1200 mg

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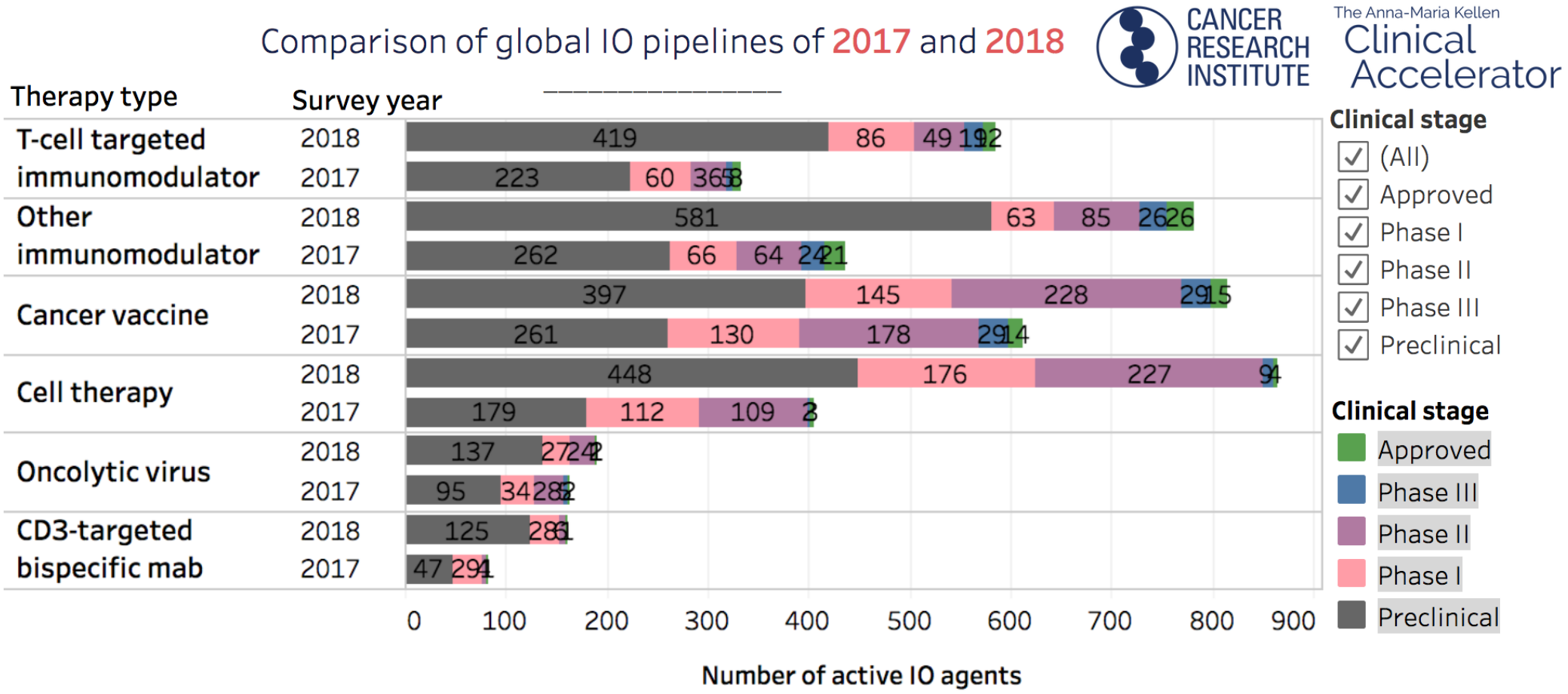
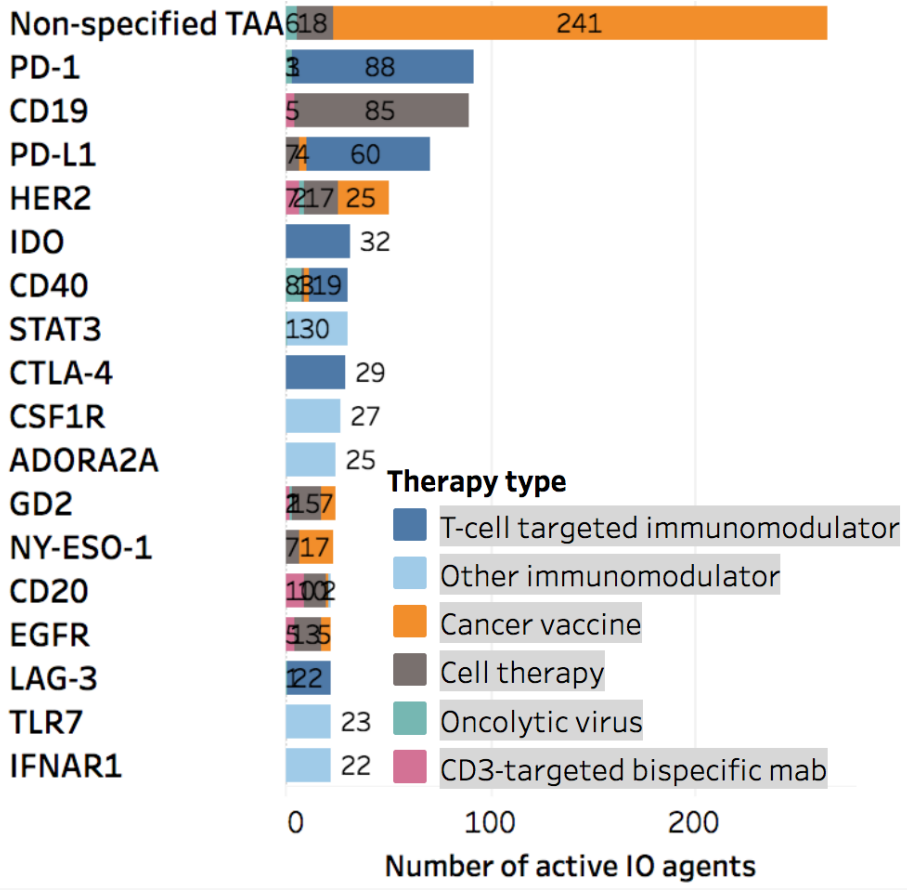
There are almost too many new cancer therapies in development

Tang et al, Nat Rev Drug Discov, Oct 2018; Created on Oct 10, 2018.

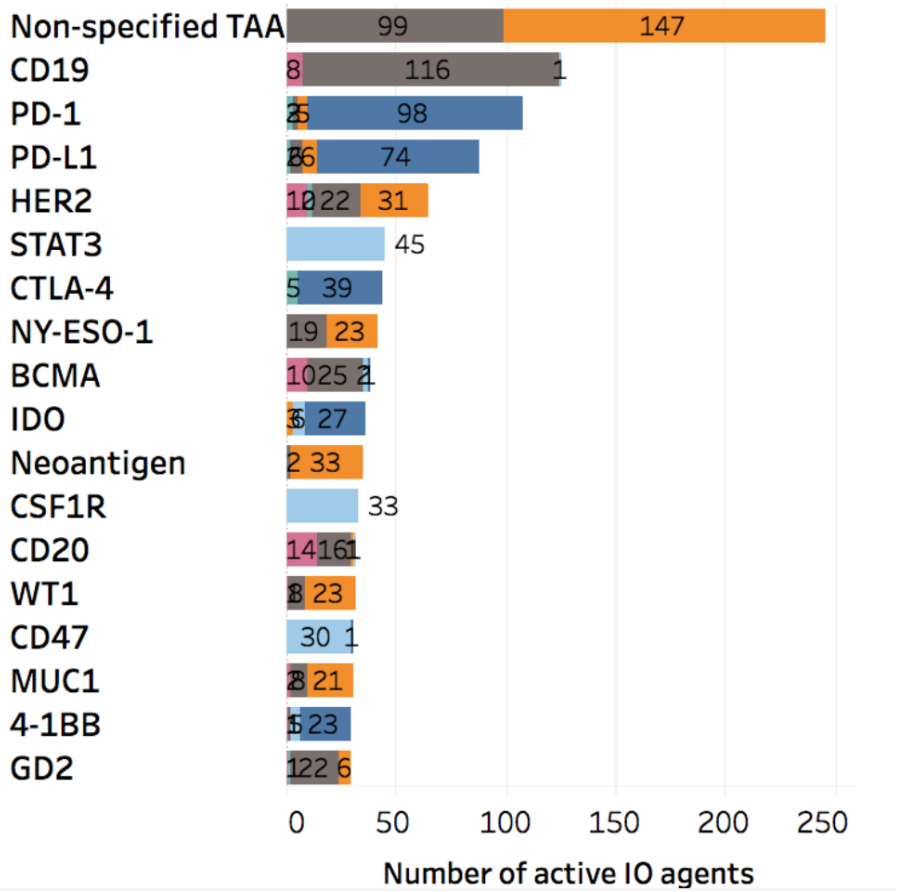


There is significant redundancy within the field (pros/cons)

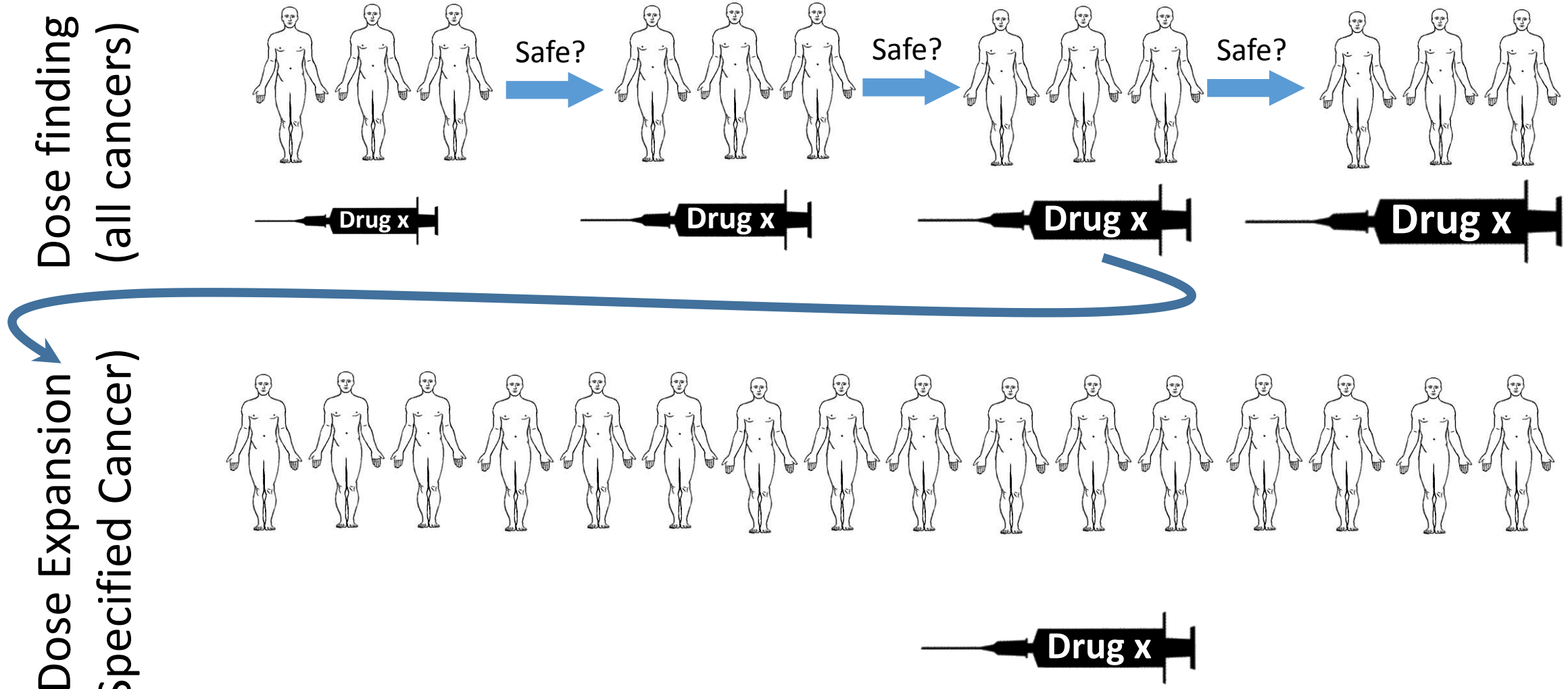
273 targets and 2,031 agents in 2017



417 targets and 3,394 agents in 2018



Overview of phase 1 clinical trials



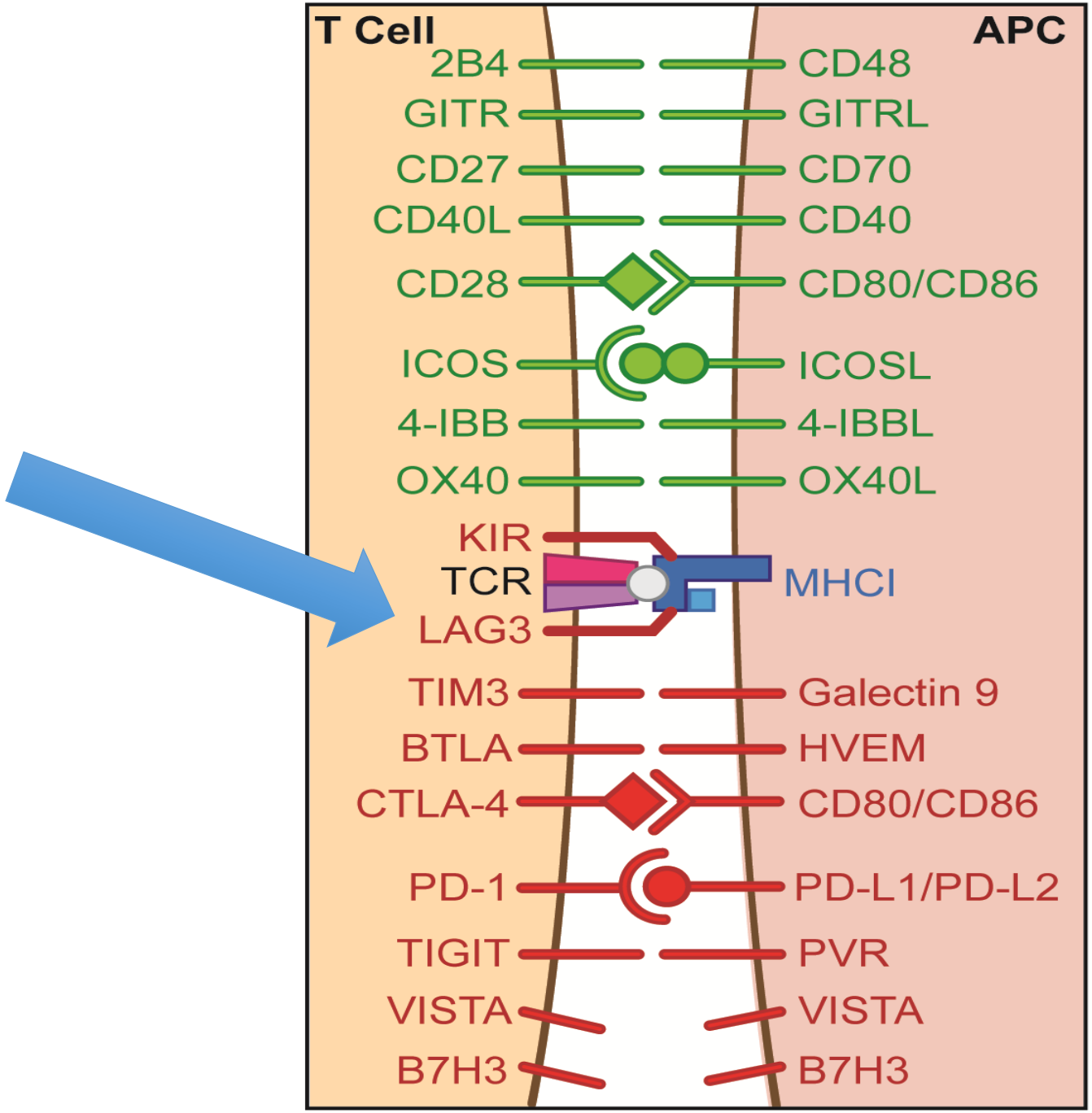
Interesting new combinations

1) New checkpoints (finding the next PD-1)
2) New combinations with PD-1
    1) New immune agents
    2) Chemotherapy
    3) Radiation
3) New approaches for people who don't respond to PD-1 (or progress post-response)
4) Recruiting other white blood cells to attack cancer

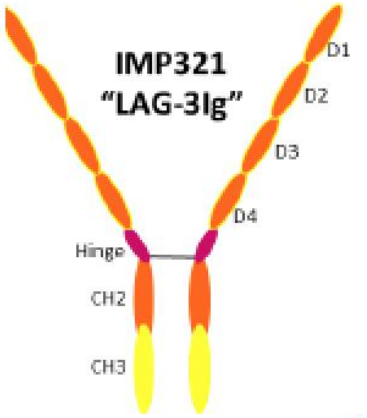
Results from a Phase I dose escalation trial (TACTI-mel) with the soluble LAG-3 protein (IMP321, eftilagimod alpha) together with pembrolizumab in unresectable or metastatic melanoma

Adnan Khattak[1], Victoria Atkinson[2], Andrew Haydon[3], Melissa Eastgate[4], Amitesh Roy[5], Christian Mueller[6], Chrystelle Brignone[7], Frederic Triebel[7]

[1] Fiona Stanley Hospital, Perth [2] Princess Alexandra Hospital, Brisbane
[3] Alfred Hospital, Melbournen [4] Royal Brisbane Womens Hosital, Brisbane
[5] Flinders Centre for Innovation in Cancer, Adelaide
[6] Clinical Development Immutep, GmbH, Berlin [7] R&D Immutep, Paris

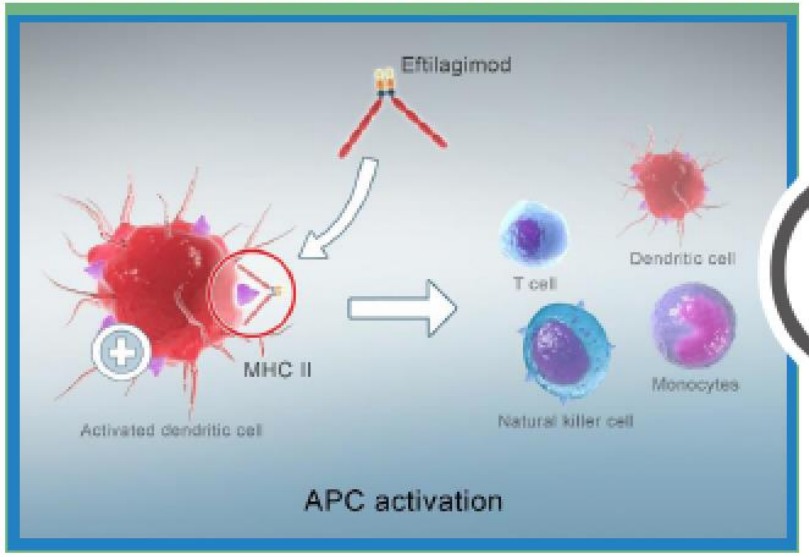


eftilagimod alpha (IMP321): APC activator (i.e. not an ICI)

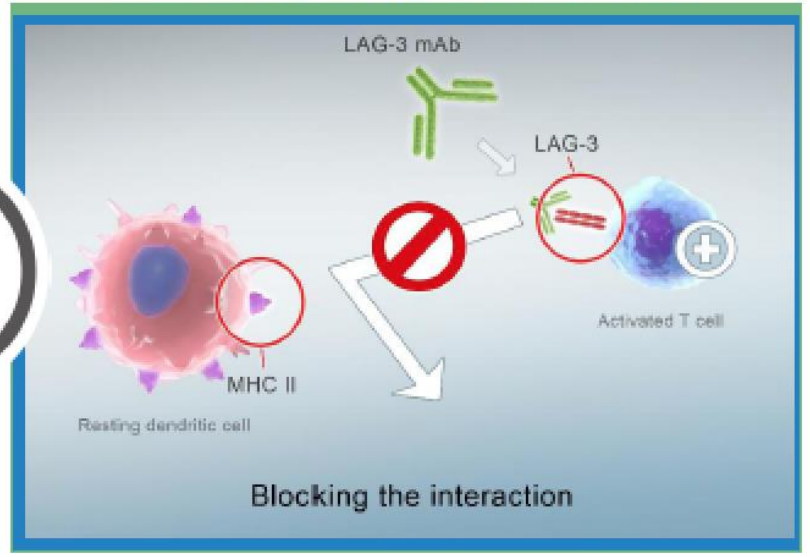


eftilagimod alpha:
- MHC II **agonist**
- **LAG-3 fusion protein**

"PUSHING THE ACCELERATOR ON IMMUNE RESPONSES"



"RELEASING THE BRAKE ON THE T CELL"



eftilagimod alpha (efti, IMP321):

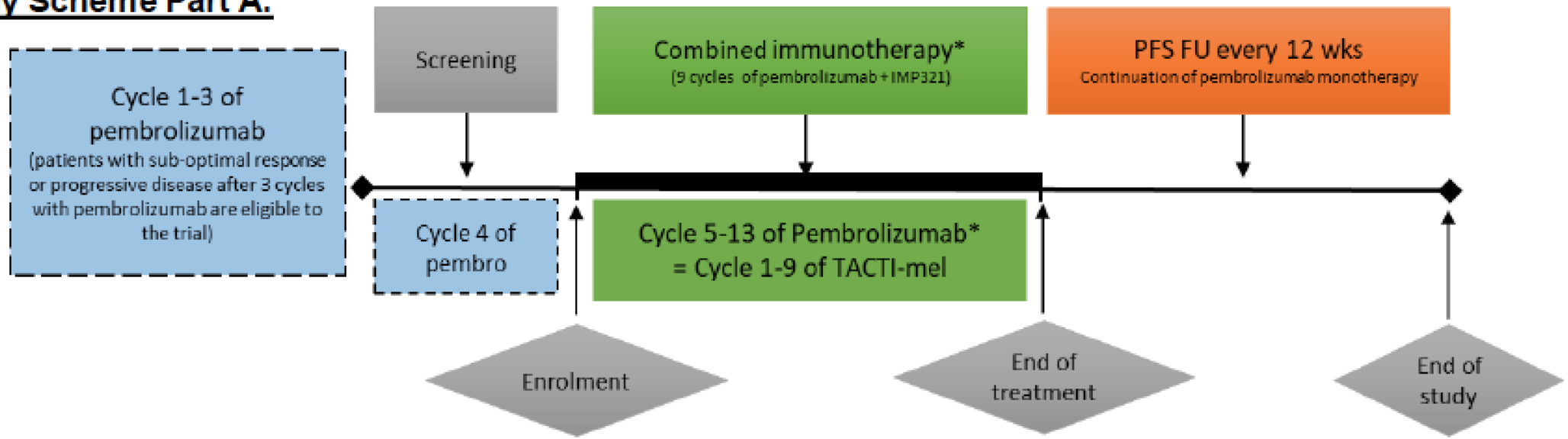
APC activator
- Boost and sustain the CD8+ T cell responses
- Activate multiple immune cell subsets

LAG-3 antagonist antibodies:

Immune checkpoint inhibitor (ICI)
- increase cytotoxicity of the pre-existing CD8 T cell response

TACTI-mel: Trial Design

Study Scheme Part A:



- 18 pts in total → 6 pts per efti dose group
- Patients received:
  - *2 mg/kg pembrolizumab i.v. every 3 weeks*
  - *1, 6, 30 mg efti s.c. every 2 weeks for up to 6 months*
- Imaging was done every 12 weeks

* - tumor assessments done acc. to irRC
irRC... Immune-Related Response Criteria, PFS-progression free survival, FU – follow-up

TACTI-mel: Safety Summary

Overview grade 3 / 4 TEAEs and rel. to study treatment

Preferred term	Grade 3 N (%)	Grade 4 N (%)	Rel to efti / pembro
Maculo-papular rash	1 (6 %)	-	No / Yes
Decreased renal function	1 (6 %)	-	Yes / No
Colitis	1 (6 %)	-	No / Yes
Altered liver functions	1 (6 %)	-	No / Yes

- No Dose limiting toxicities observed
- 6 pts (33 %) with ≥ 1 SAE; none related to any study drug
- 8 pts (44 %) with ≥ 1 AE with ≥ grade 3 (no grade 5)

Overview frequent TEAE (PT selected if ≥ 10 % of the pts)

Adverse Event*,	Any grade N (%)	Grade 3 or 4 N (%)	No of events
Arthralgia	3 (17)	-	3
Diarrhea	5 (28)	-	6
Fatigue	8 (44)	-	10
Hyperglycemia	3 (17)	3 (17)	3
Nausea	5 (28)	-	7
Rash##	7 (39)	1 (6)	7

*- Adverse events occurred in > 10 % of pts
- any kind of rash

- No new safety signals
- 1 pt died due to an AE (grade 4 Intercranial hemorrhage, not rel.)
- 1 pt discontinued due to an AE (not rel.)
- 3 pts experienced treatment delay due to an AE

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preliminary data, status Oct 15th 2018

TACTI-mel: Baseline Characteristics + Efficacy Summary

Baseline Characteristics	N = 18 (%)
Age (median)	67 yrs
Sex (f/m)	1 (6 %) / 17 (94 %)
Elevated LDH	**7 (39%)**
Metastasis stage M1c	**14 (78 %)**
Pre-treated with BRAF/MEK/ipilimumab	5 (28 %)
irPD/irSD to pembro after 3 cycles	11 (61 %)

Best Overall Response acc. to irRC	N = 18 (%)
irCR	1 (6 %)
irPR#	5 (28 %)#
irSD	6 (33 %)
irPD	6 (33 %)
Best overall response rate (ORR)	**6 (33 %)**
Patients with tumor shrinkage	**10 (56 %)**
Disease control rate	**12 (66 %)**

- incl. 1 pt with complete disappearance of all target lesions

- Very late stage of disease (M1c, elevated LDH) and majority not responding to pembrolizumab monotherapy

- If response is calculated from pre-pembro timepoint → ORR is 61 % acc. to irRC

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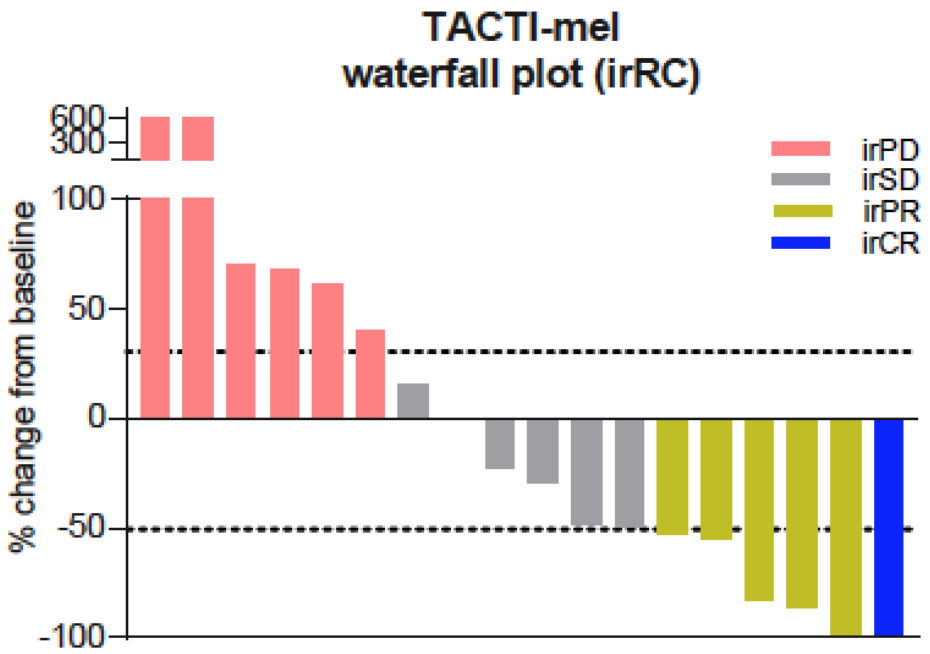
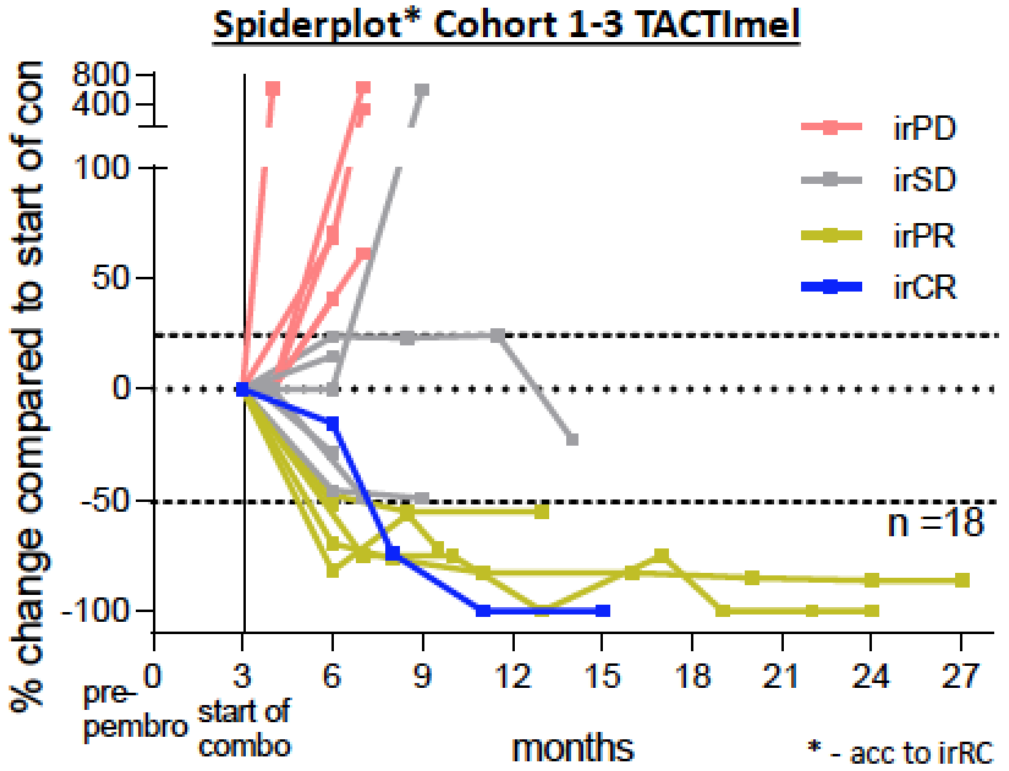
preliminary data, status Oct 15th 2018

TACTI-mel: Response patterns





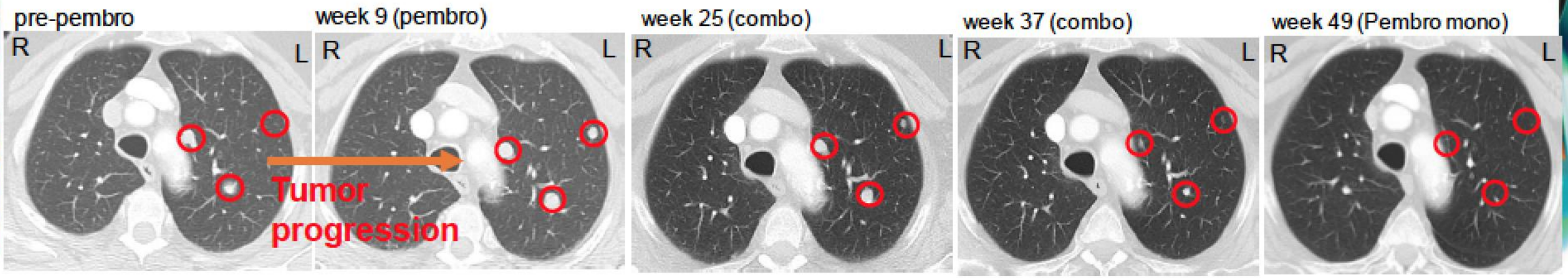
→ Tumor shrinkage in 10 (56 %) of these patients incl. 2 pts with complete disappearance of all target lesions

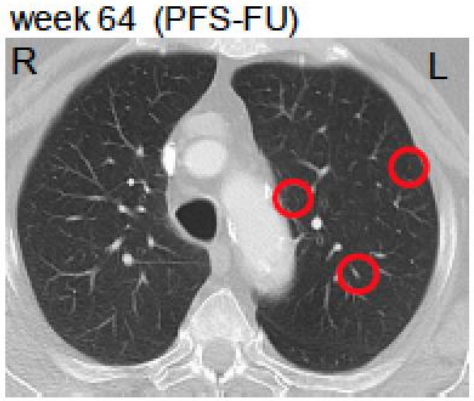
→ 1 pt with confirmed CR + 4 pts still on Tx after 12 months
→ 5 (28 %) pts with long term (>12 mths) treatment/benefit

preliminary data, status Oct 15th 2018

TACTI-mel: Single Case

- 84 year old male with multiple lung metastases from melanoma
- BRAF wild type





- **Patient progressing on pembrolizumab monotherapy**
- **At 1 yr all lesions disappeared → CR (confirmed)**
- **Patient without treatment and disease free → now lost to FU**

preliminary data, status Oct 15th 2018

SITC 2018 NOVEMBER 7–11 • WASHINGTON, D.C.

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Phase 2 Trial of Mocetinostat in Combination with Durvalumab in NSCLC Patients (Pts) with Progression on Prior Checkpoint Inhibitor Therapy

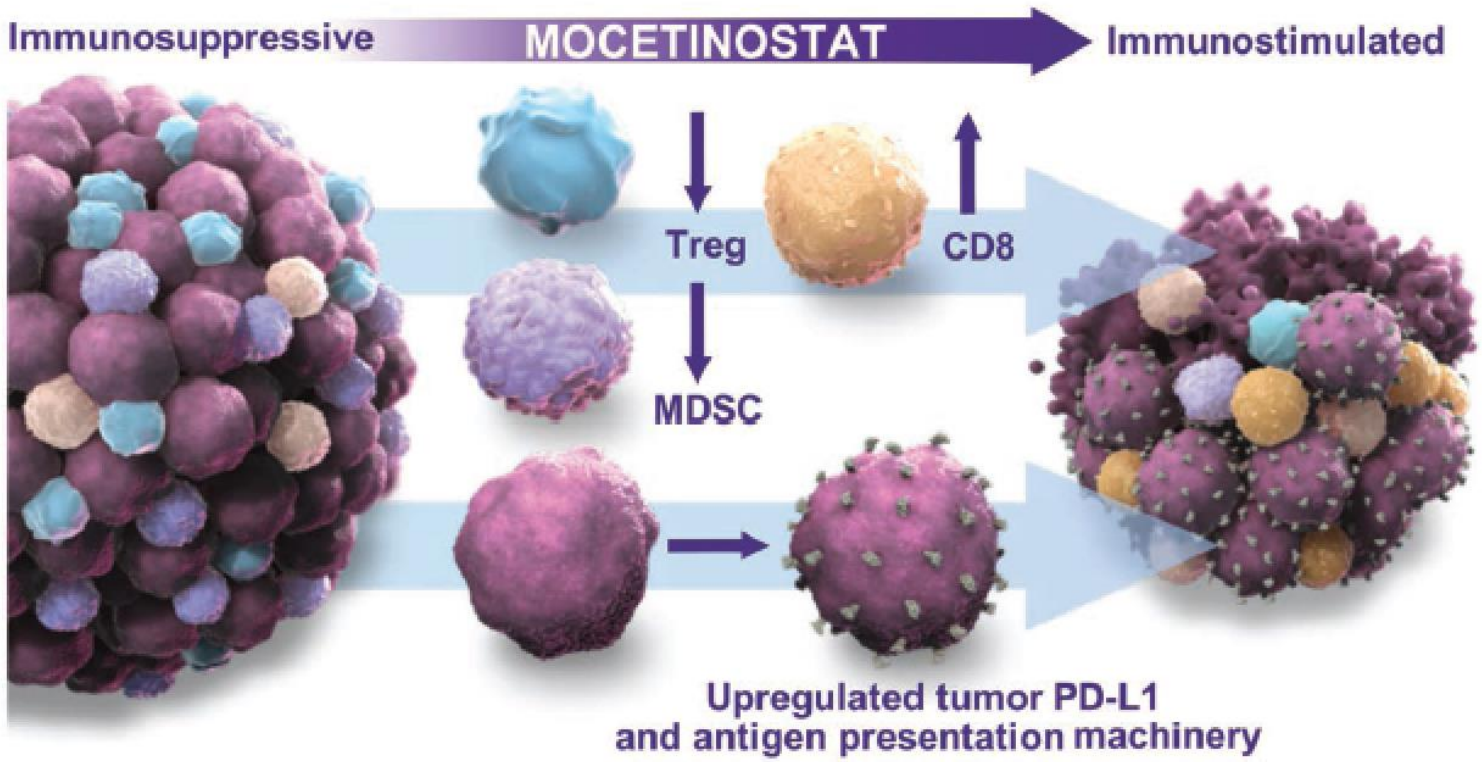
Melissa Johnson[1],Keith D. Eaton[2], Balazs Halmos[3], Edward Garon[4], Thomas Hensing[5], Nisha A. Mohindra[6], James Strauss[7], Timothy McCarthy[8], Rami Owera[9], Isan Chen[10], Peter Olson[10], Demiana Faltaos[10], James Christensen[10], Diane Potvin[10], Tavette Neskorik[10], Adam Pavlicek[11], Manish Patel[12]

[1]Sarah Cannon Research Institute, Nashville, TN, USA, [2]Seattle Cancer Care Alliance, Seattle, WA, USA, [3]Montefiore Medical Center, [4]University of California-Los Angeles, CA,USA, [5]Northshore University Health System, Evanston, IL, USA, [6]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA, [7]Mary Crowley Cancer Research Center, Dallas, TX, USA, [8]Virginia Cancer Specialists, Fairfax, VA, USA, [9]Woodlands Medical Specialists – Pensacola, FL, USA, [10]Mirati Therapeutics, San Diego, CA, USA, [11]Monoceros Biosystems, San Diego, CA, USA, [12]University of Minnesota Masonic Cancer Center, Minneapolis, MN, USA

0103-020 Background

Mocetinostat: Class I and IV HDAC Inhibitor

Immuno-supportive effects in the Tumor Microenvironment (TME)



Given the pleiotropic immune activating effects of moceotinostat, the combination **of mocetinostat and the PD-L1 blocking mAb durvalumab was tested in NSCLC patients with checkpoint inhibitor therapy (CIT) naïve disease or had progressive disease after prior CIT**

0103-020 Phase 2 Design

- Phase 1/2 study evaluating the tolerability and clinical activity of mocetinostat in combination with durvalumab
- ORR in accordance with RECIST 1.1 is the primary clinical benefit endpoint
- Predictive Probability Design for assessment of enrollment expansion in each stage and treatment arm
- Phase 1- Increased doses of mocetinostat administered (50, 70, 90 mg three times weekly [TIW]) in combination with durvalumab on day 1 of each 28-day cycle

			Stage 1	Expand if ≥ X Responses	Stage 2
Any Histology NSCLC Receipt of previous platinum doublet or immunotherapy for advanced disease	Checkpoint Naive (CIT-N)	**No/Low PD-L1 Expression**	n=9	≥ 1	n=8
		High PD-L1 Expression	n=17	≥ 6	n=27
	Checkpoint Experienced (CIT-E)	**Prior Clinical Benefit**	n= 9	≥ 1	n= 8
		No Prior Clinical Benefit	N= 9	≥ 1	N= 8

0103-020 Safety: Most Frequent (≥10%) Treatment-Related (Mocetinostat and/or Durvalumab)

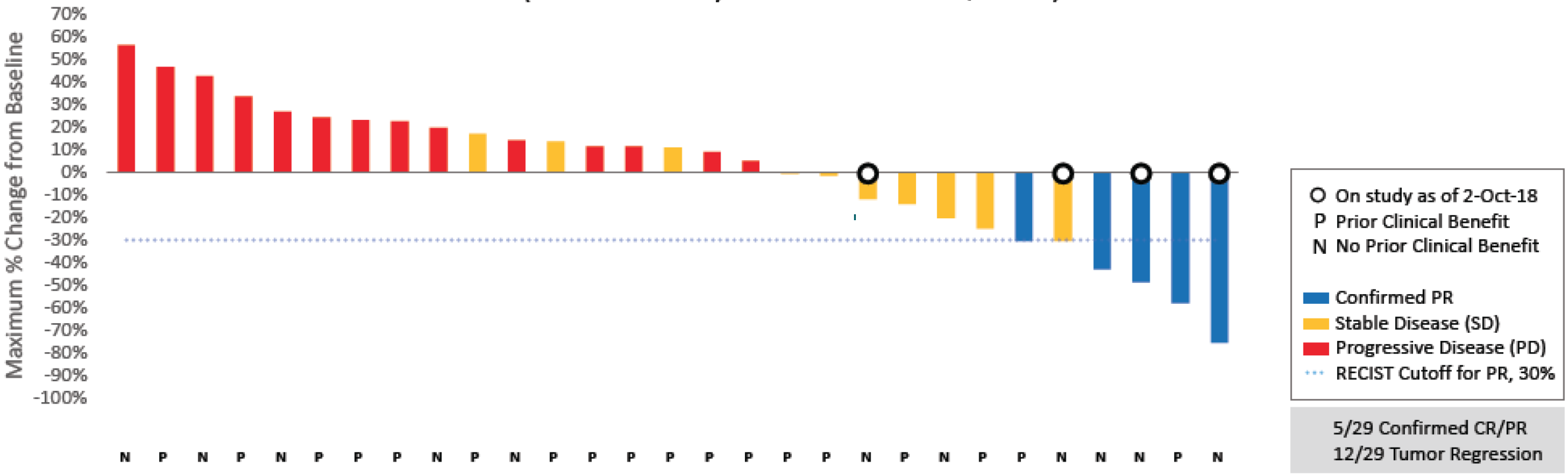
Adverse Event (Preferred Term)	Phase 2 Safety Population N=63	
	All Grades n (%)	Grade ≥3 n (%)
Fatigue	25 (40)	6 (10)
Nausea	22 (35)	1 (2)
Diarrhea	18 (29)	2 (3)
Decreased appetite	15 (24)	0
Vomiting	8 (13)	0
Fatigue	25 (40)	6 (10)
Cardiac disorders*	5 (8)	3 (5)

*Includes adverse events of atrial fibrillation, cardiac tamponade, pericardial effusion, and pericarditis
As of 02 October 2012 – all Phase 2 patients including CIT-Experienced and CIT-Naïve.

0103-020 Clinical Activity

PRELIMINARY MAXIMUM RESPONSE IN NSCLC PATIENTS WHO FAILED PRIOR CHECKPOINT THERAPY

(Clinical Activity Evaluable Patients, N=29)



5/29 Confirmed CR/PR
12/29 Tumor Regression

Monalizumab in combination with cetuximab in R/M SCCHN: Clinical results and preliminary biomarker analyses.

Roger B. Cohen[1],

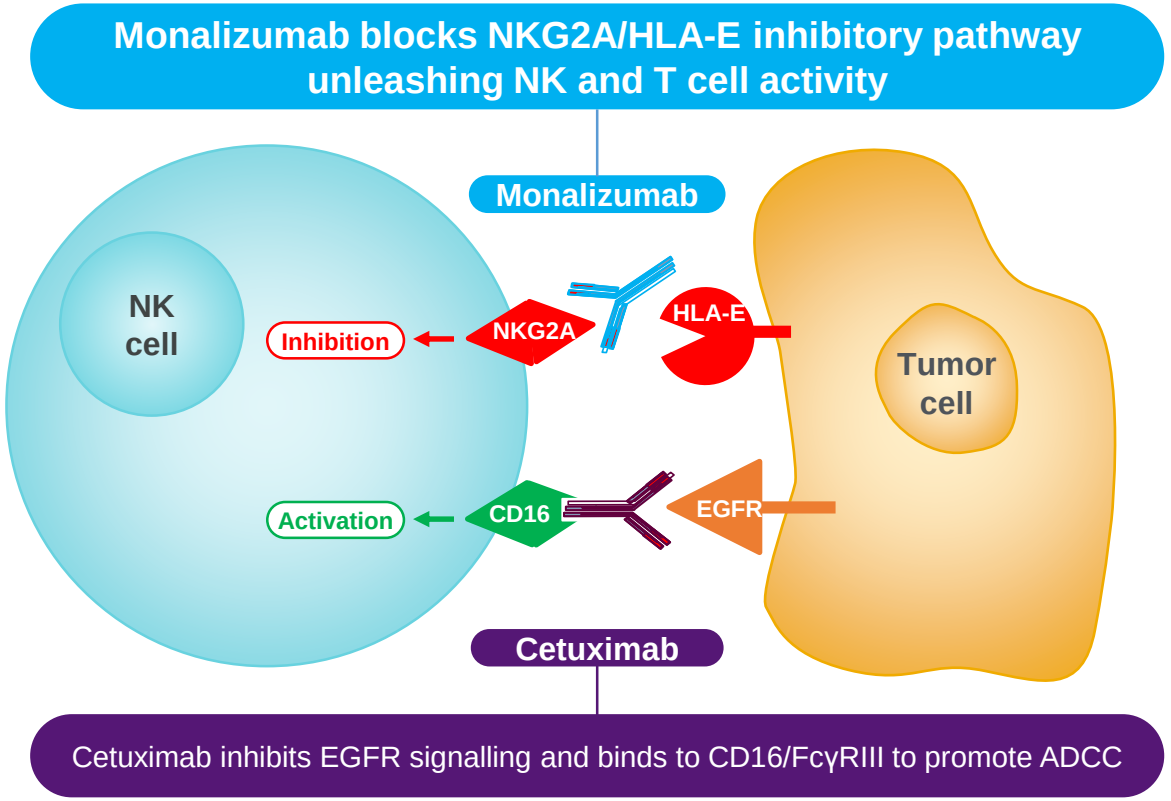
Jérôme Fayette[2], Marshall Posner[3], Gautier Lefebvre[4], Jessica Bauman[5], Sébastien Salas[6], Caroline Even[7], Dimitrios Colevas[8], Antonio Jimeno[9], Esma Saada[10], Barbara Burtness[11], Franceline Calmels[12], Robert Zerbib[12], Agnès Boyer-Chammard[12], Pascale André[12],Tanguy Seiwert[13]

1- Abramson Cancer Center, Philadelphia, PA; 2- Centre Léon Bérard, Lyon, France; 3- Mount Sinai Medical Center, New York, NY; 4- Oscar Lambret Institute, Lille, France; 5- Fox Case Cancer Center, Philadelphia, PA; 6- AP-HM, Marseille, France; 7- Gustave Roussy, Paris, Villejuif, France; 8- Stanford University Medical Center, Stanford, CA; 9- University of Colorado Cancer Center, Denver, CO; 10- Centre A. Lacassagne, Nice, France; 11- Yale University, New Haven, CT; 12- Innate Pharma, Marseille, France; 13- University of Chicago, Chicago, IL.

Dual antibody targeting in cancer immunology

Monalizumab:

- First-in-class humanized IgG_4 targeting NKG2A on NK and tumor infiltrating $CD8^+$ T cells.
- Blocks binding of CD94/NKG2A to HLA-E reducing inhibitory signaling and thereby unleashing NK and T cell responses.



Hypothesis: Dual targeting with the combination of monalizumab and cetuximab will provide greater antitumor activity than cetuximab alone.

André et al., Cell in press

IPH2201-203 study design

- Multicenter single arm study to evaluate the combination of monalizumab and cetuximab in patients with recurrent and/or metastatic SCCHN (R/M SCCHN)
- Cohort expansion in recurrent and/or metastatic SCCHN patients (NCT02643550).
- N= 40 patients enrolled. Data cut-off August 31, 2018.

Key eligibility criteria

- R/M SCCHN, HPV(+) or HPV(-)
- PD after platinum-based CT
- Maximum of 2 prior systemic regimens for R/M disease
- Prior IO allowed*

Treatment

monalizumab
(10mg/kg Q2W)
+
cetuximab
(approved dosage)

until progression or unacceptable toxicity

Primary objective

- ORR (RECIST 1.1)

Secondary objectives

- DoR, PFS, OS
- Safety

Exploratory objectives

- Translational analyses

* prior cetuximab allowed if for locally advanced disease with no PD for at least 4 months

Objective responses with monalizumab and cetuximab

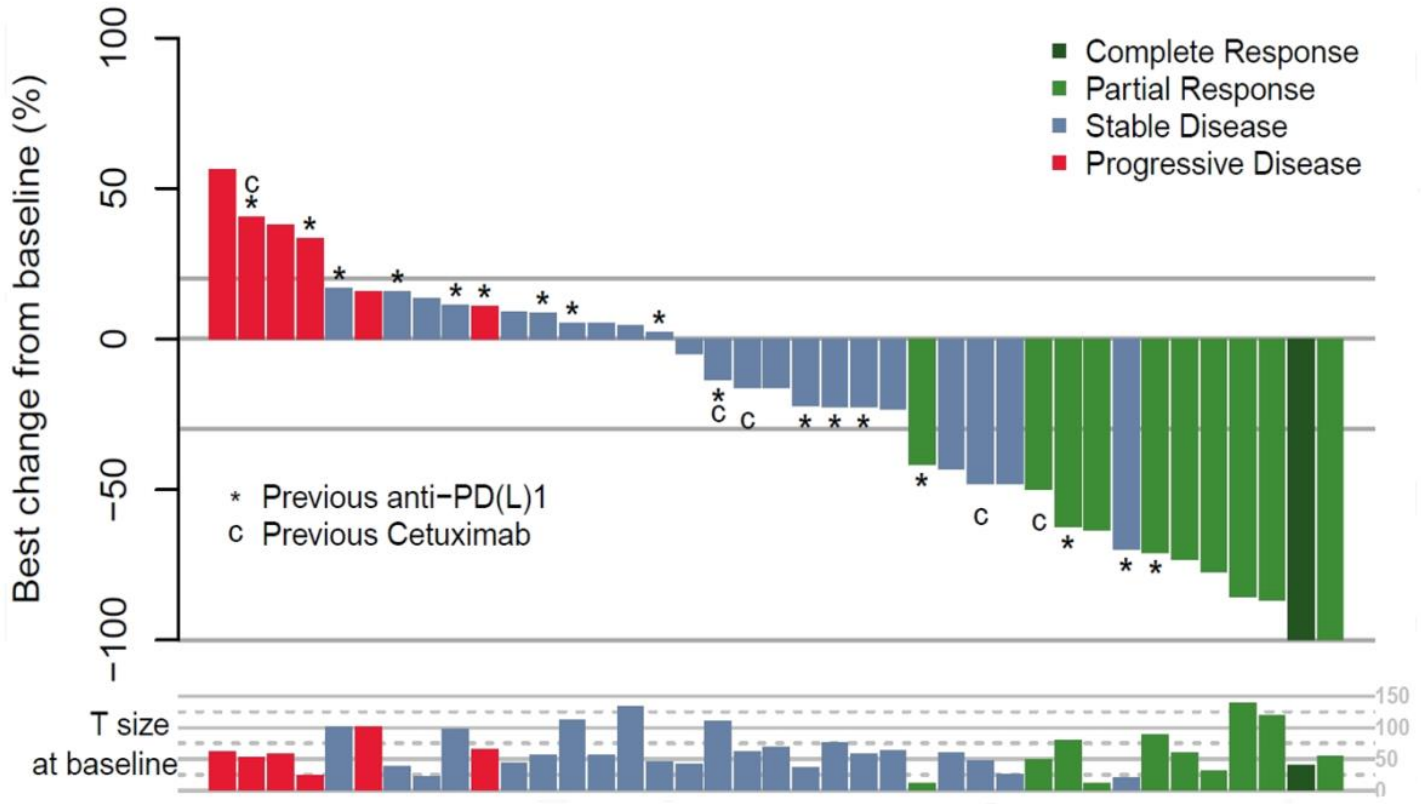
Overall Response Rate is 27.5%

[95% CI, 16.1-42.8]

1 confirmed CR & 10 confirmed PR

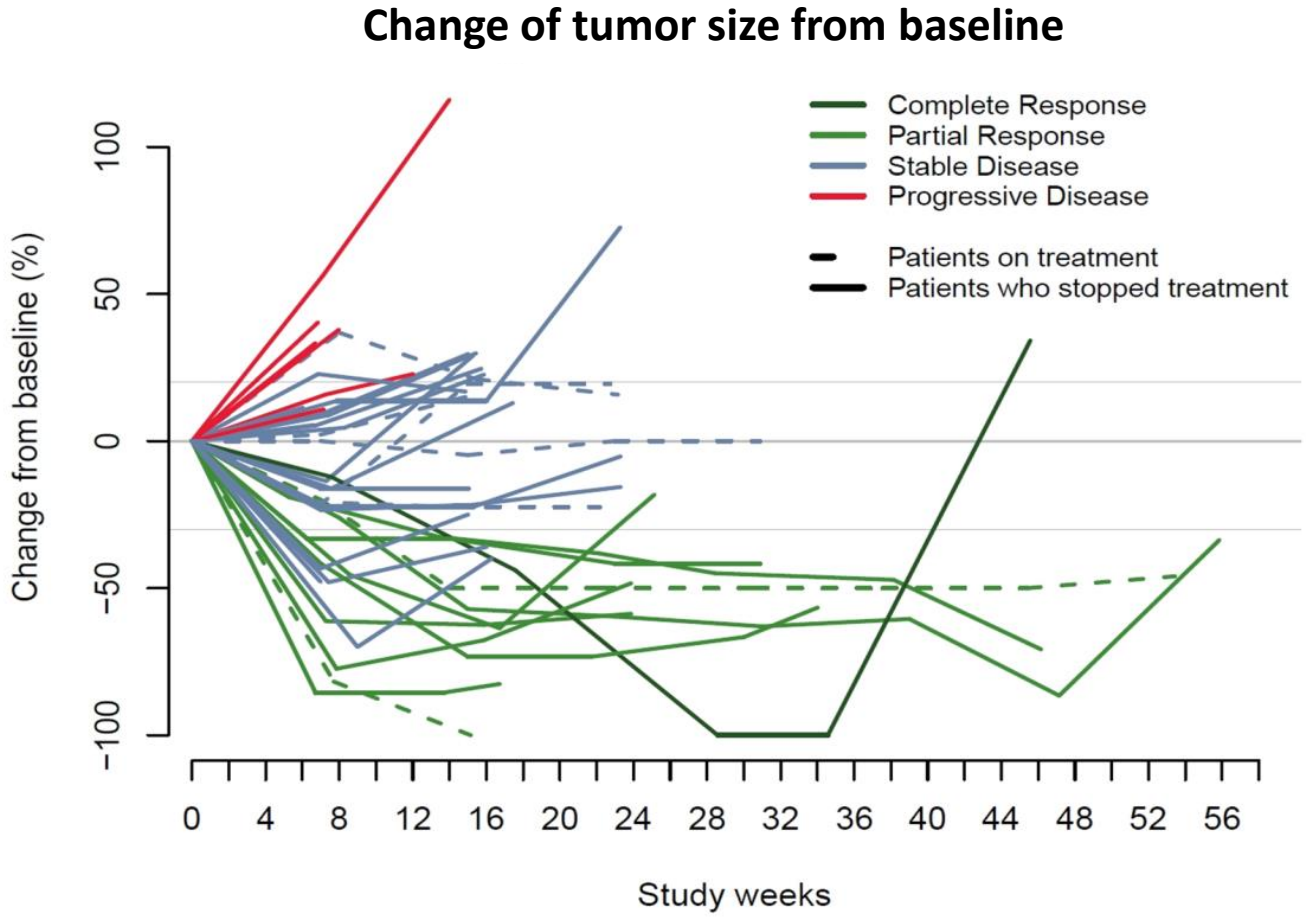
- ✓ Responses observed in IO naive (35% [19-55]) and IO pretreated patients (18% [6-41])
- ✓ Responses observed in platinum resistant patients and in HPV positive and negative disease

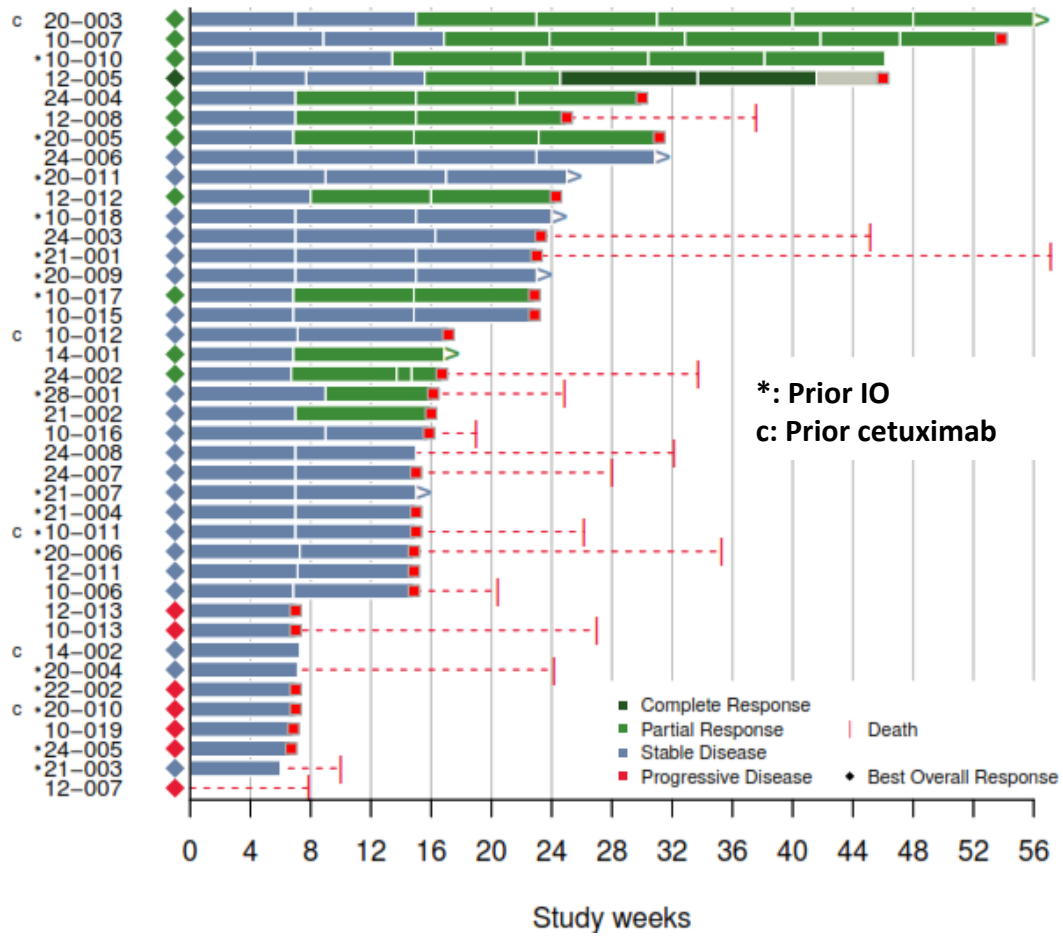
Best change of tumor size from baseline



One patient with death from clinical progression before the 1st post baseline radiological assessment is not represented in the graphs

Early and Durable responses with monalizumab and cetuximab





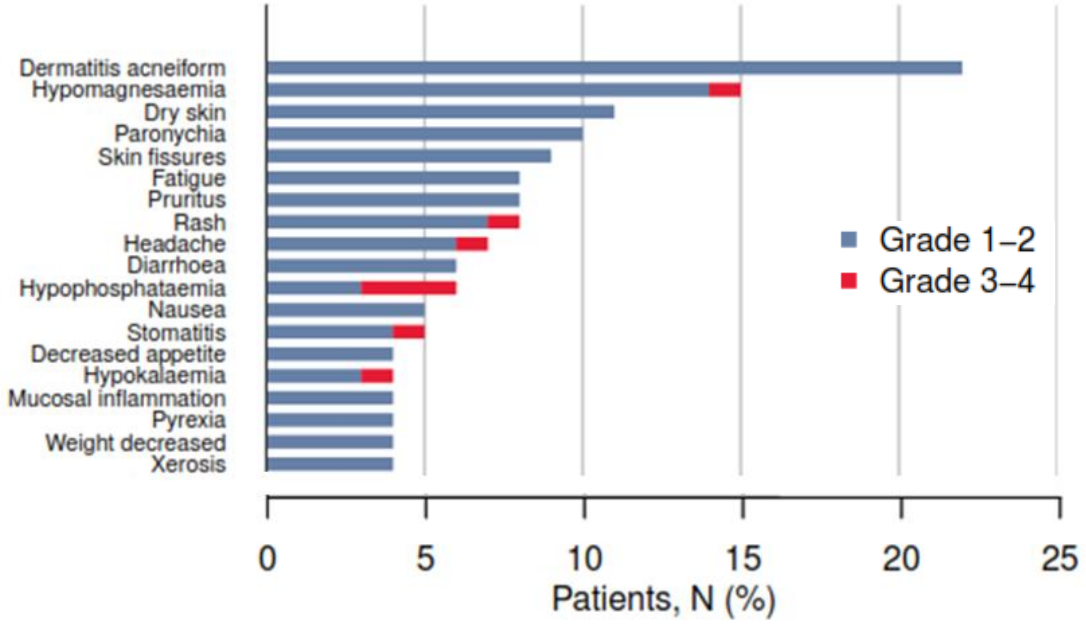
Median time to response is 1.6 months [1.5-3.9]

Median duration of response is 5.6 months [3.8-NR*]

*NR = Not Reached

Safety profile of the combination

AEs related to the monalizumab cetuximab combination



	All TEAEs N (%)		Monalizumab related TEAEs N (%)	
	All	**Grade 3-4**	All	**Grade 3-4**
AEs	40 (100%)	**20 (50%)**	30 (75%)	**7 (18%)**
SAEs	16 (40%)	**12 (30%)**	3 (8%)	**3 (8%)**

- No new safety signals for monalizumab
- Only one patient stopped treatment for an AE
- No potentiation of cetuximab side effects

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Questions?

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