Ανοσολογικοί μηχανισμοί στην ανοσοθεραπεία καρκίνου

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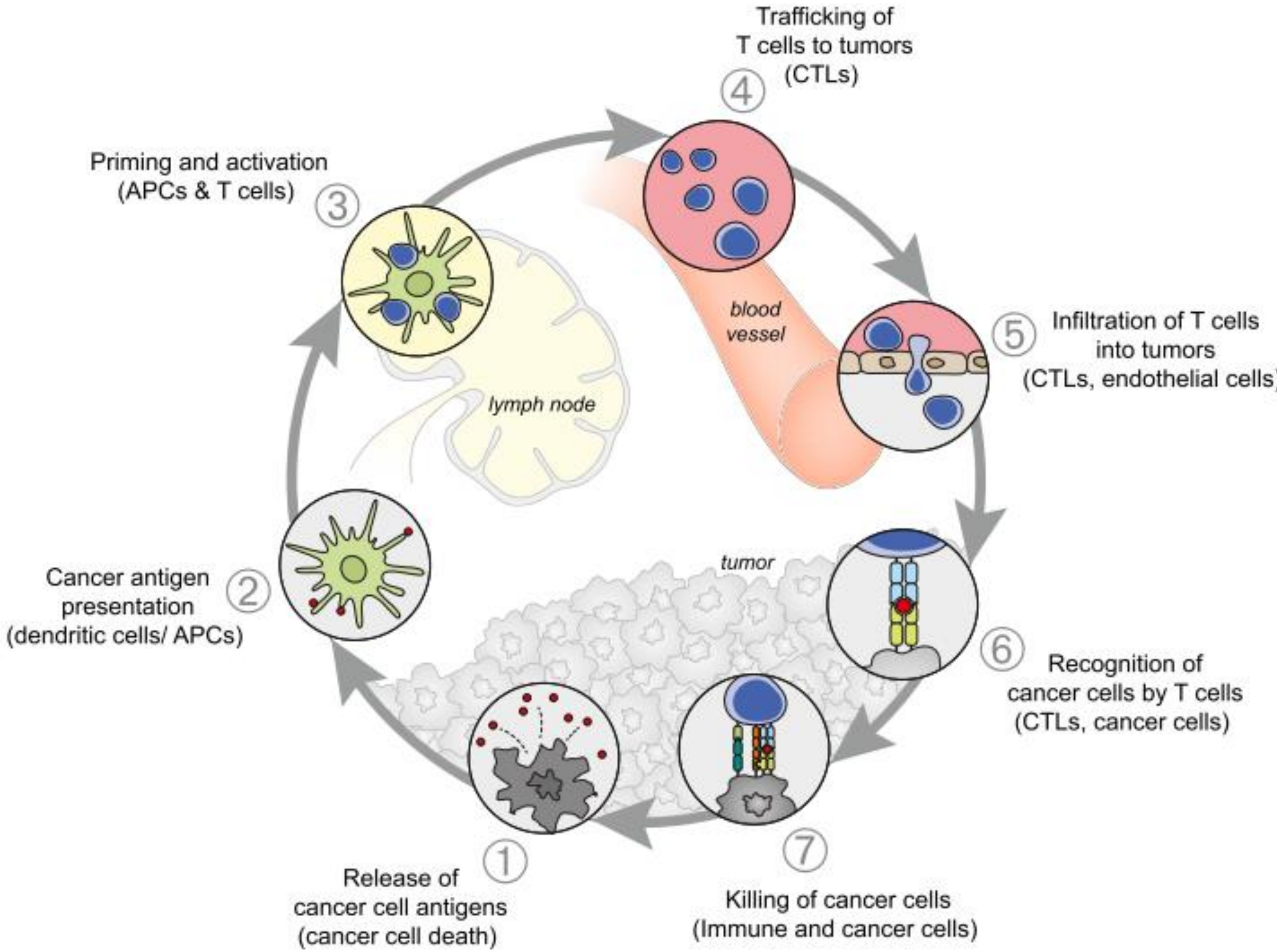
The Immune System Recognizes and Eliminates Cancer Via Multiple, Complex Me



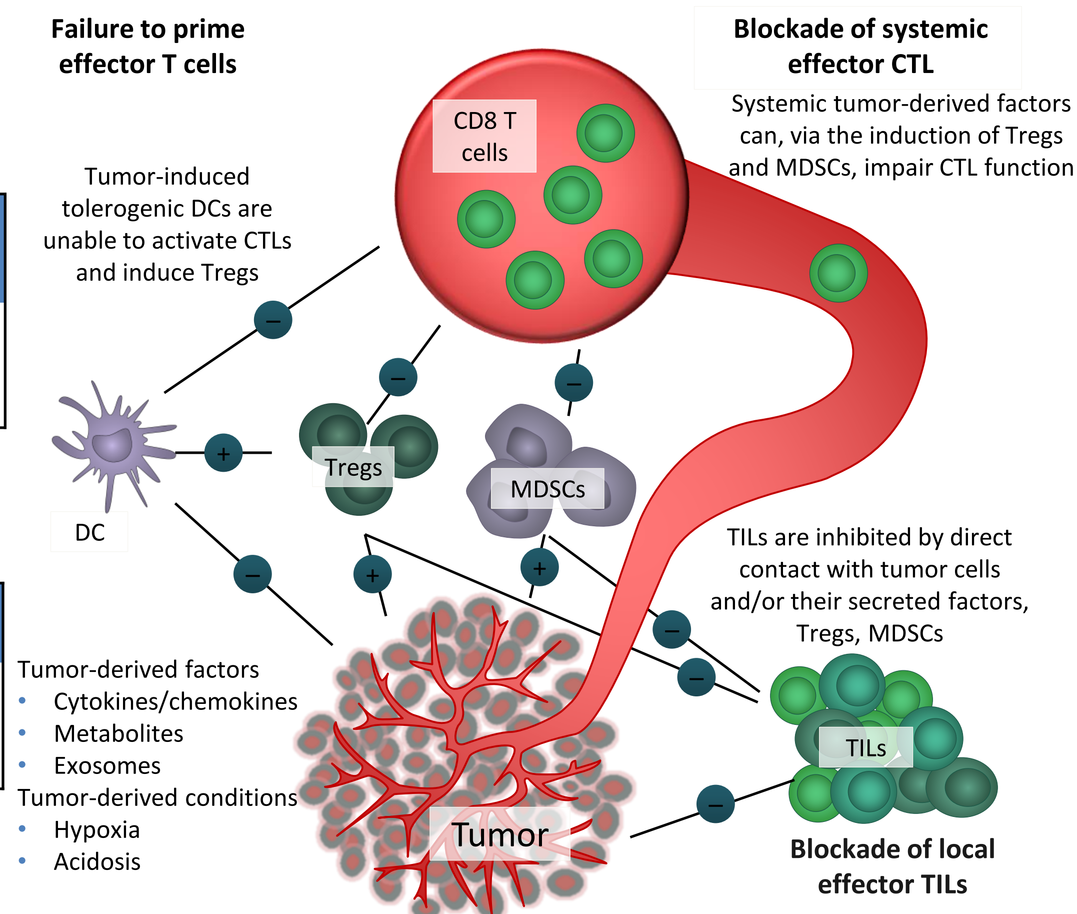
Tumor Immune Escape: Recruitment of Immunosuppressive Cells

- **Tumors can recruit a variety of immunosuppressive cells**

Key immune suppressor cell types:

Tregs (classically CD4$^+$CD25$^+$FoxP3$^+$)[1–3]
Can suppress immune responses via production of IL-10 and TGF-β, using up environmental T-cell survival factors, and dysregulating local T cells

MDSCs[1,4]
Produce TGF-β, arginase I and inducible iNOS, inhibiting CD8$^+$ T-cell function and inducing T-cell apoptosis

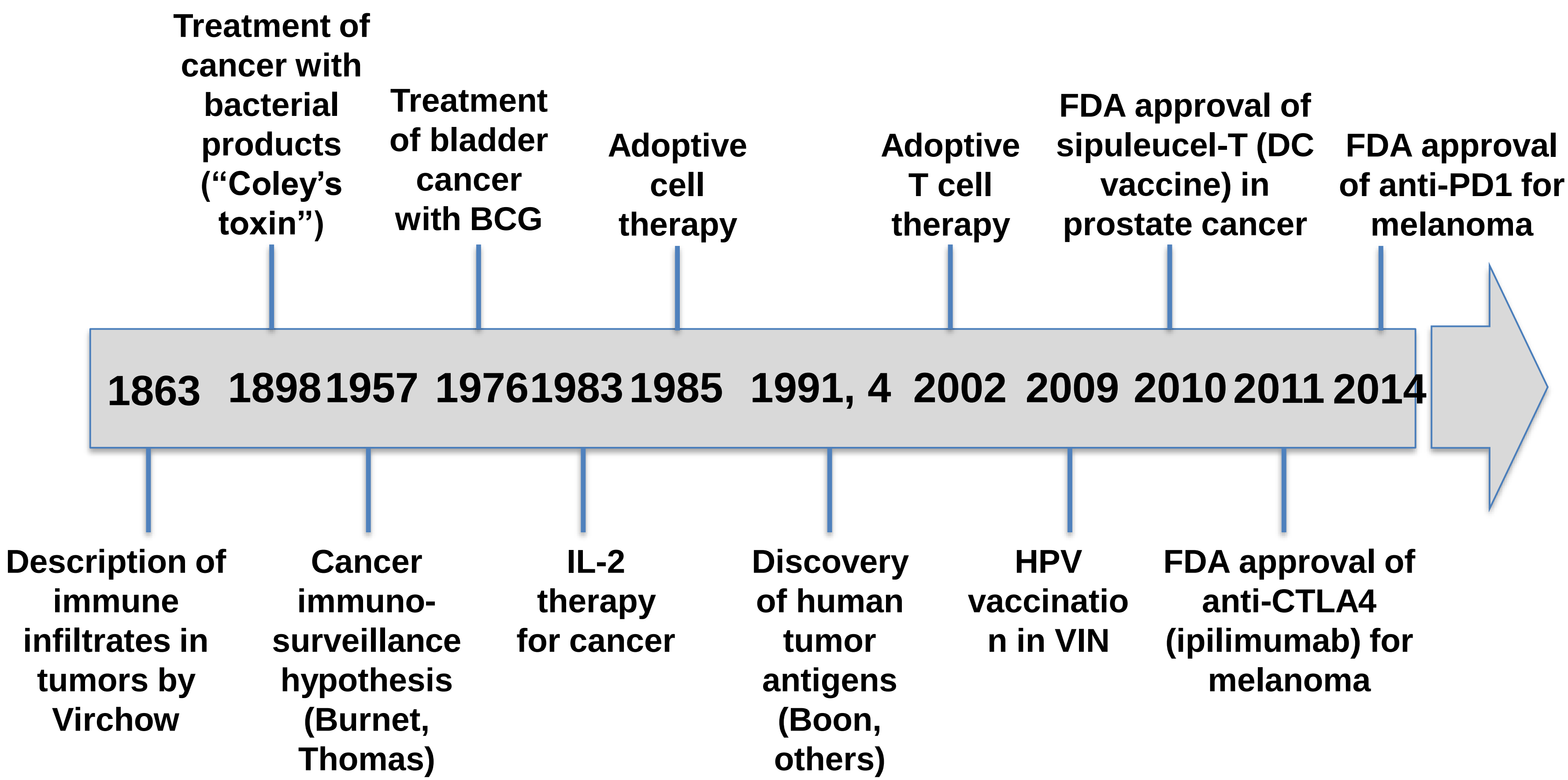


TGF-β = transforming growth factor beta.

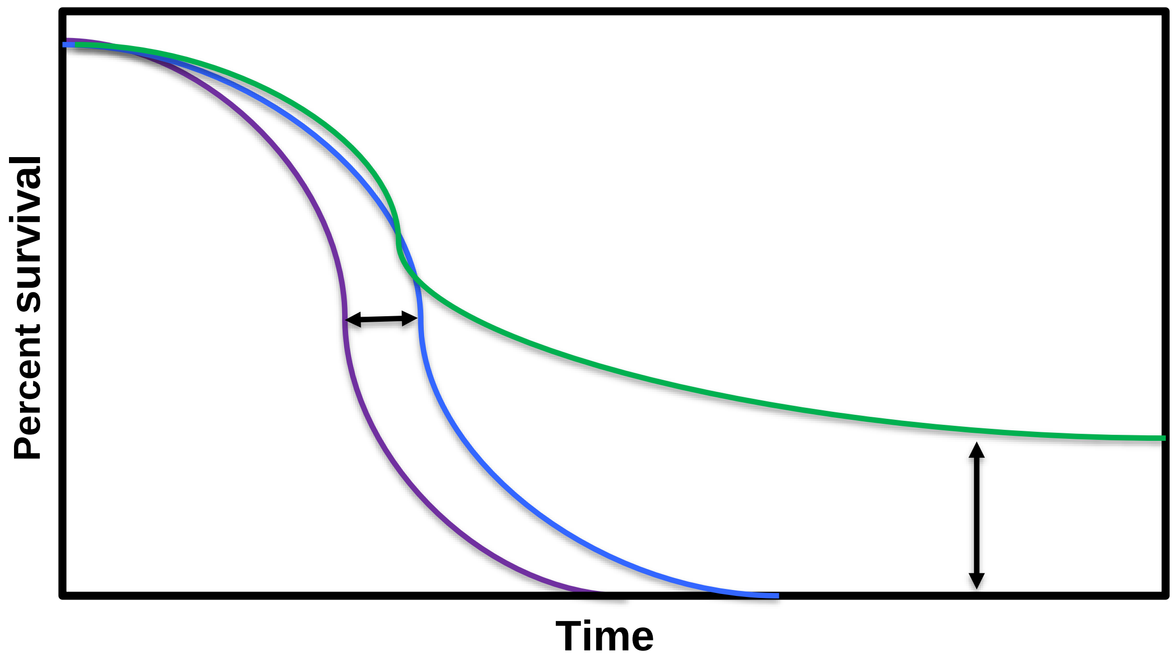
Adapted from Aerts JG et al.[5]

1. Kerkar SP, et al. *Cancer Res.* 2012;72:3125–3130. 2. Woo EY, et al. *J Immunol*. 2002;168:4272–4276. 3. Kryczek I, et al. *Cancer Res.* 2009;69:3995–4000; 4. Stagg J, et al. *Immunol Rev*. 2007;220:82–101. 5. Aerts JG, et al. *Cancer Res.* 2013;73:2381–2388.

The history of cancer immunotherapy: from empirical approaches to rational, science-based therapies

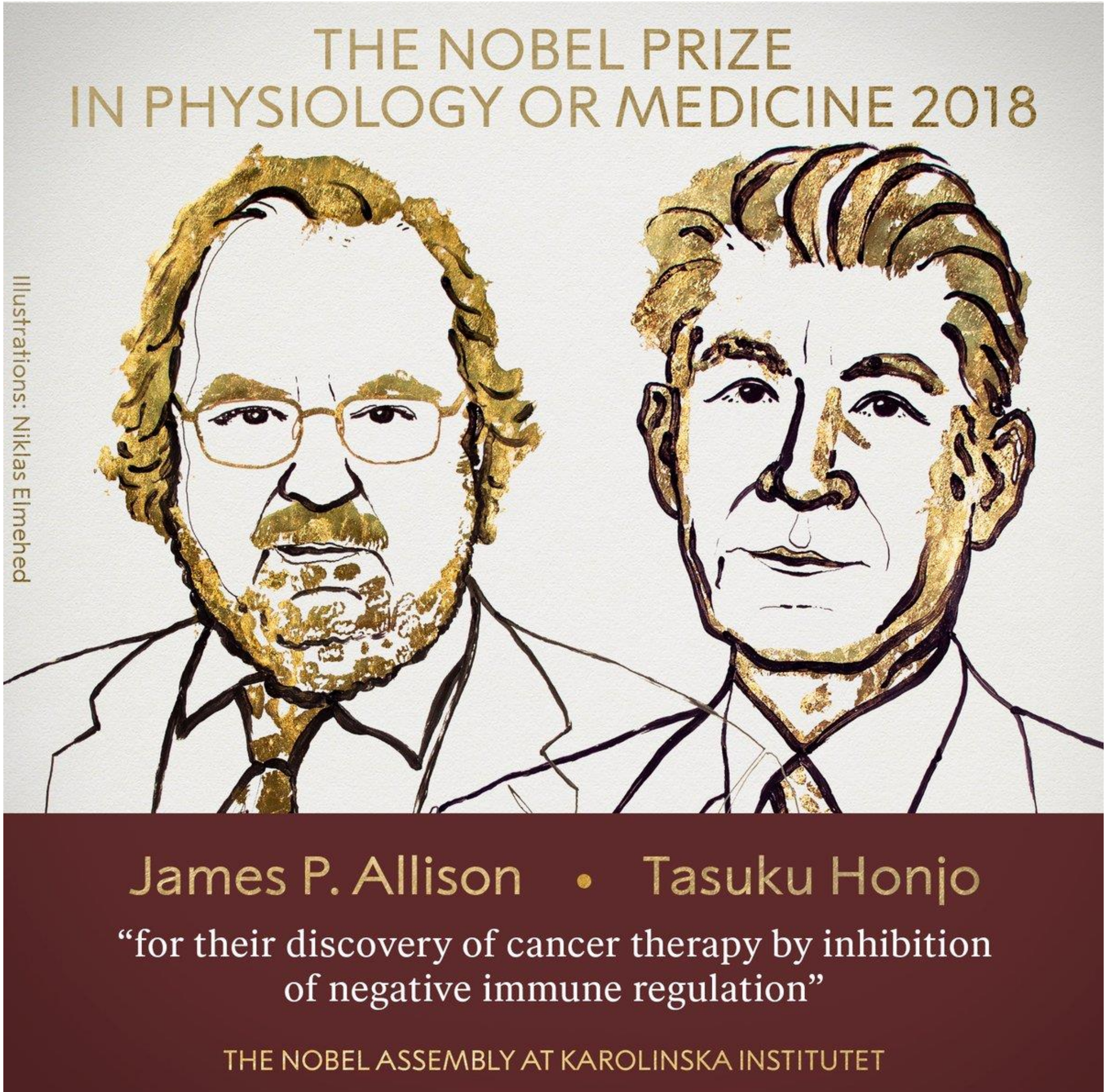


Increased overall survival upon Immunotherapy in advanced melanoma



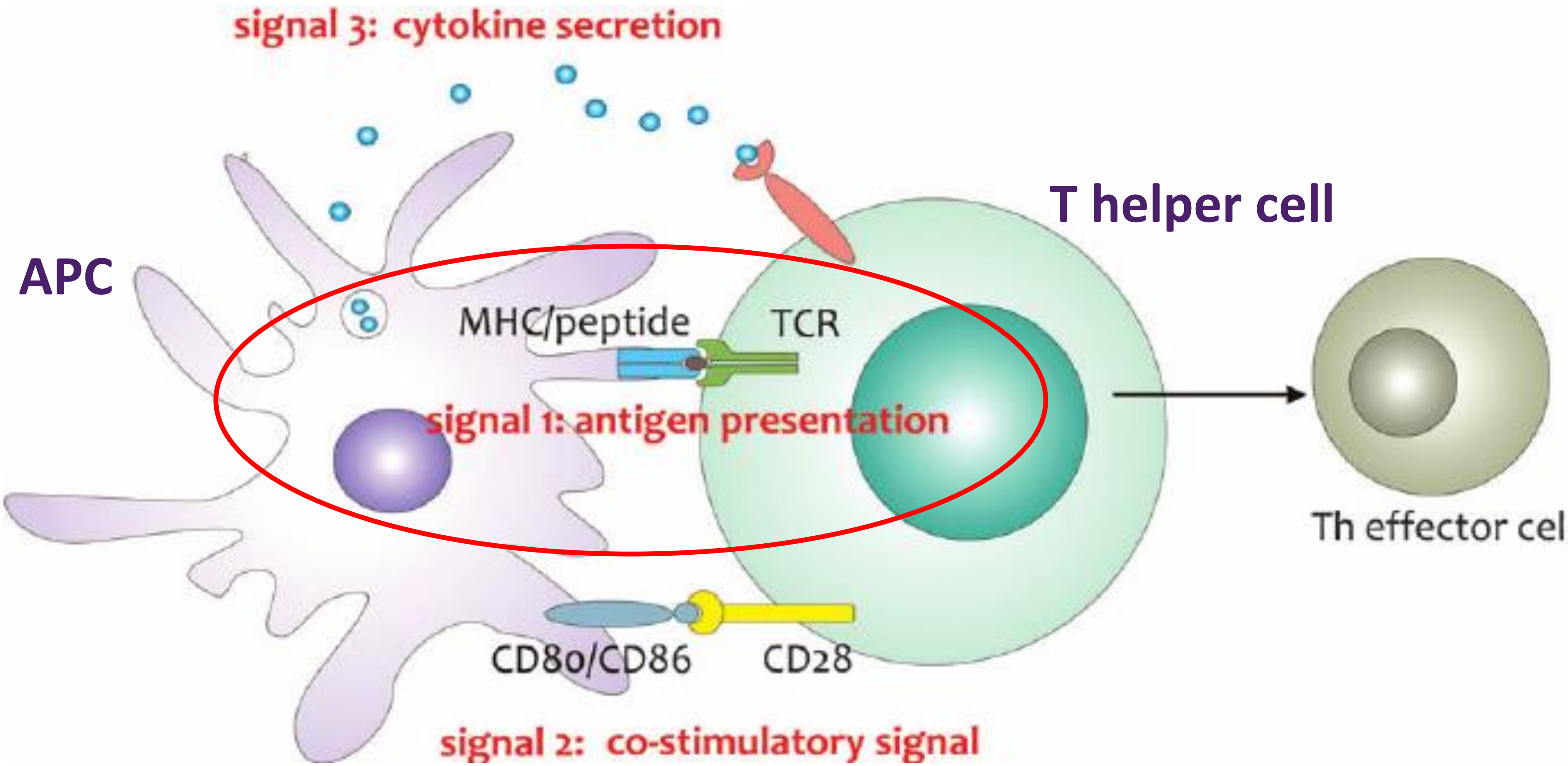
- Chemotherapy
- Targeted therapy ⇒ clinical responses in majority of patients
  ⇒ limited duration of responses
- Immune therapy ⇒ long lasting responses

adapted from Allison et al., 2015


THE NOBEL PRIZE
IN PHYSIOLOGY OR MEDICINE 2018
Illustrations: Niklas Elmehed
James P. Allison • Tasuku Honjo
"for their discovery of cancer therapy by inhibition of negative immune regulation"
THE NOBEL ASSEMBLY AT KAROLINSKA INSTITUTET

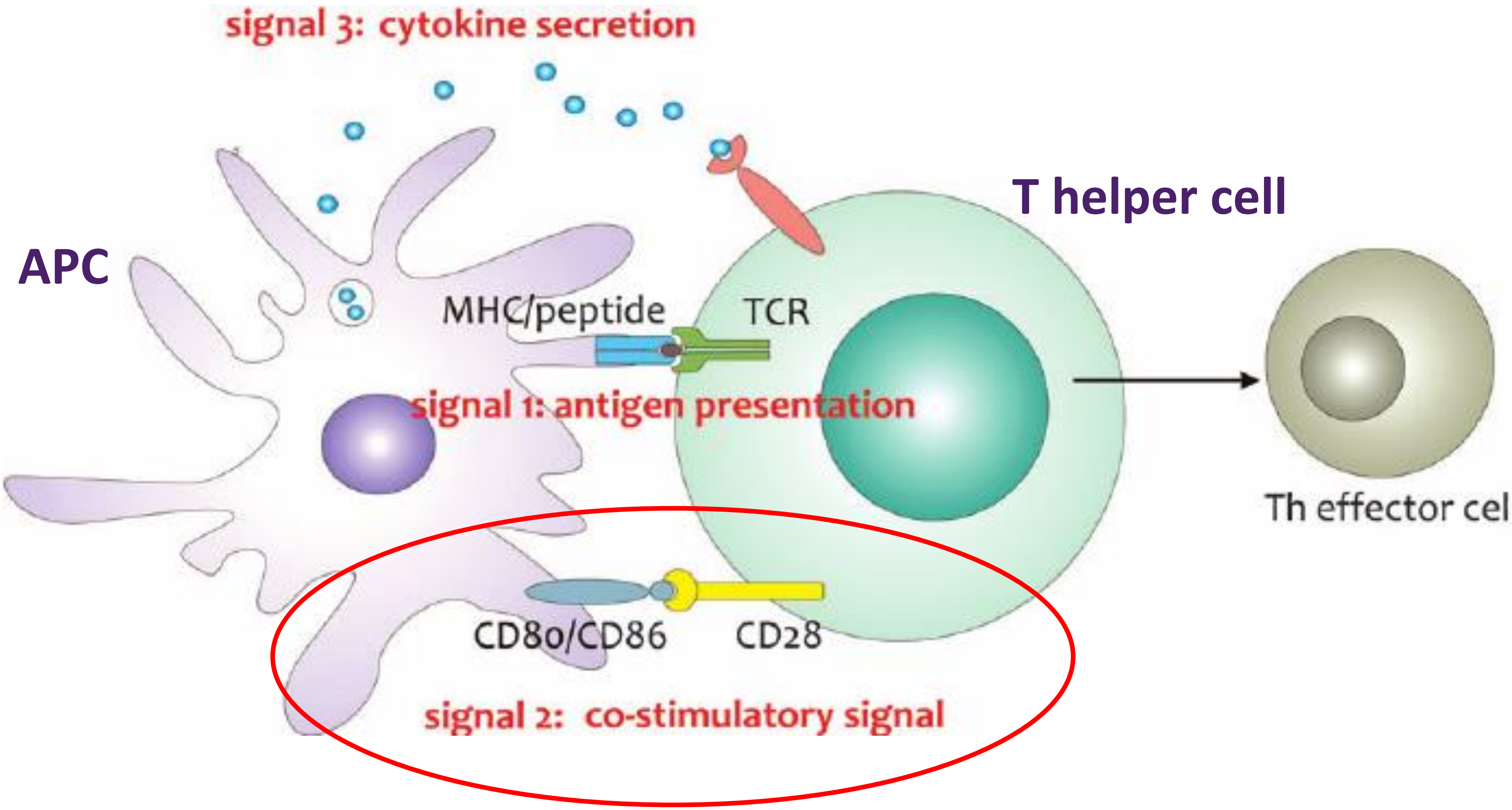
Immune Checkpoint Inhibitors

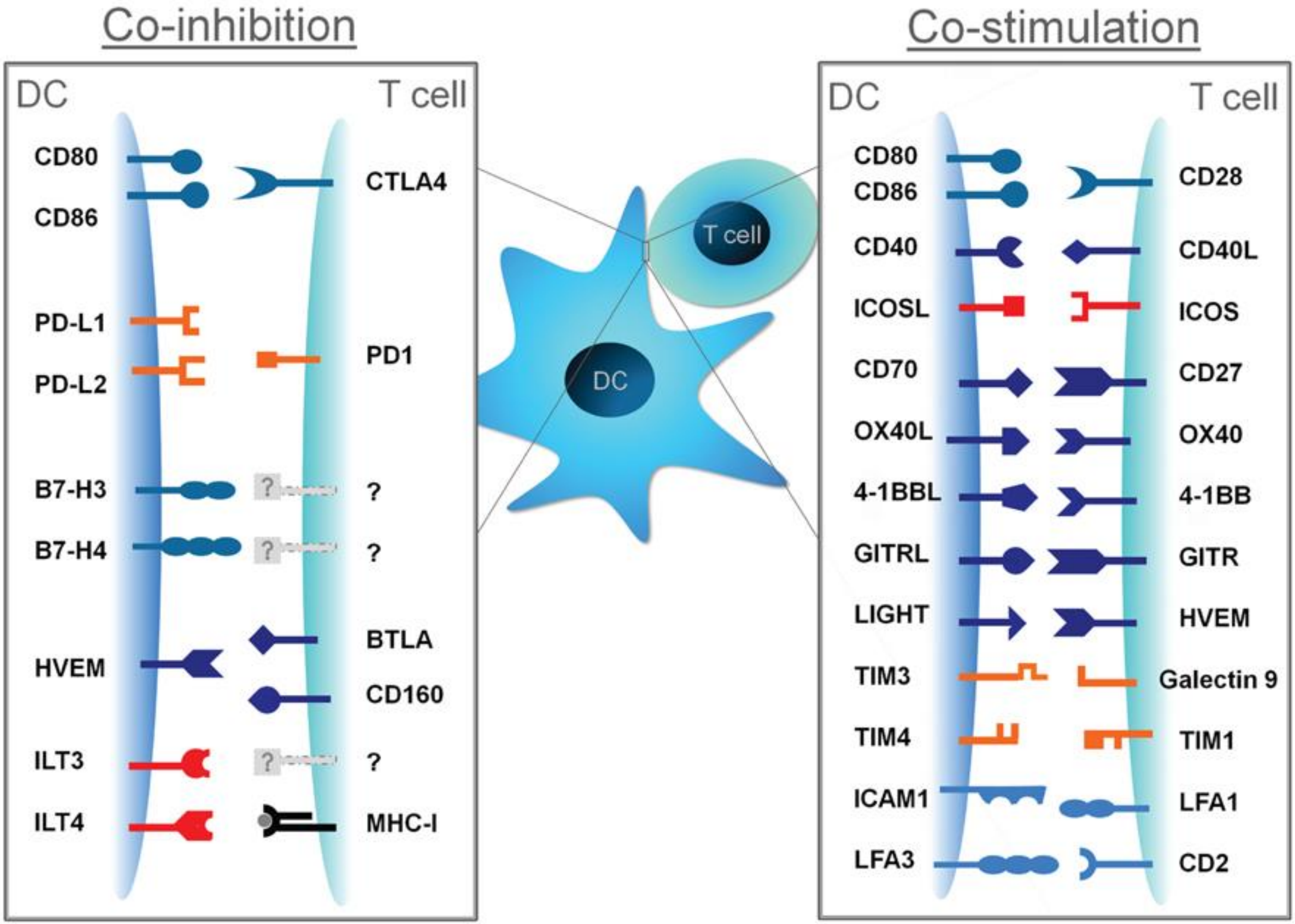
Η παρουσίαση αντιγόνου από αντιγονοπαρουσιαστικά κύτταρα είναι απαραίτητη για την διέγερση των Τ κυττάρων



Antigen Presenting Cell (APC)

Το 2ο σήμα ενεργοποίησης: συν-διέγερση/ co-stimulation





Co-inhibition
DC
T cell
CD80
CD86
CTLA4
PD-L1
PD-L2
PD1
B7-H3
?
B7-H4
?
HVEM
BTLA
CD160
ILT3
?
ILT4
MHC-I
T cell
DC
Co-stimulation
DC
T cell
CD80
CD86
CD28
CD40
CD40L
ICOSL
ICOS
CD70
CD27
OX40L
OX40
4-1BBL
4-1BB
GITRL
GITR
LIGHT
HVEM
TIM3
Galectin 9
TIM4
TIM1
ICAM1
LFA1
LFA3
CD2

FDA approved immune checkpoint inhibitors

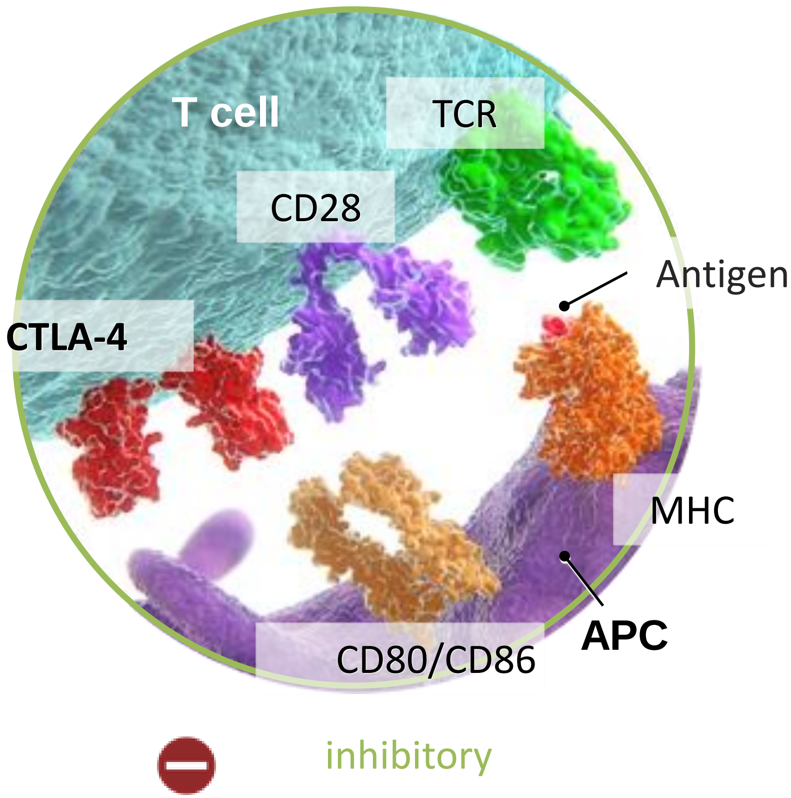
Table. FDA-approved immune checkpoint inhibitors

Drug	Target	Indication
Ipilimumab (Yervoy, Bristol-Myers Squibb)	CTLA-4	Melanoma
Nivolumab (Opdivo, Bristol-Myers Squibb)	PD-1	Melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgkin lymphoma, head and neck squamous cell carcinoma, urothelial carcinoma, colorectal cancer, hepatocellular carcinoma
Pembrolizumab (Keytruda, Merck)	PD-1	Melanoma, non-small cell lung cancer, non-squamous cell lung cancer, head and neck squamous cell carcinoma, Hodgkin lymphoma, colorectal, gastric and gastroesophageal junction adenocarcinoma, urothelial carcinoma
Durvalumab (Imfinzi, AstraZeneca)	PD-L1	Urothelial carcinoma
Atezolizumab (Tecentriq, Genentech)	PD-L1	Urothelial carcinoma, metastatic non-small cell lung cancer
Avelumab (Bavencio, EMD Serono)	PD-L1	Merkel cell carcinoma, urothelial carcinoma

Abbreviations: CTLA-4: cytotoxic T-lymphocyte antigen-4. PD-1: programmed cell death protein 1. PD-L1: programmed cell death ligand-1.

Source: Wendy Bottinor, MD

Anti-CTLA4

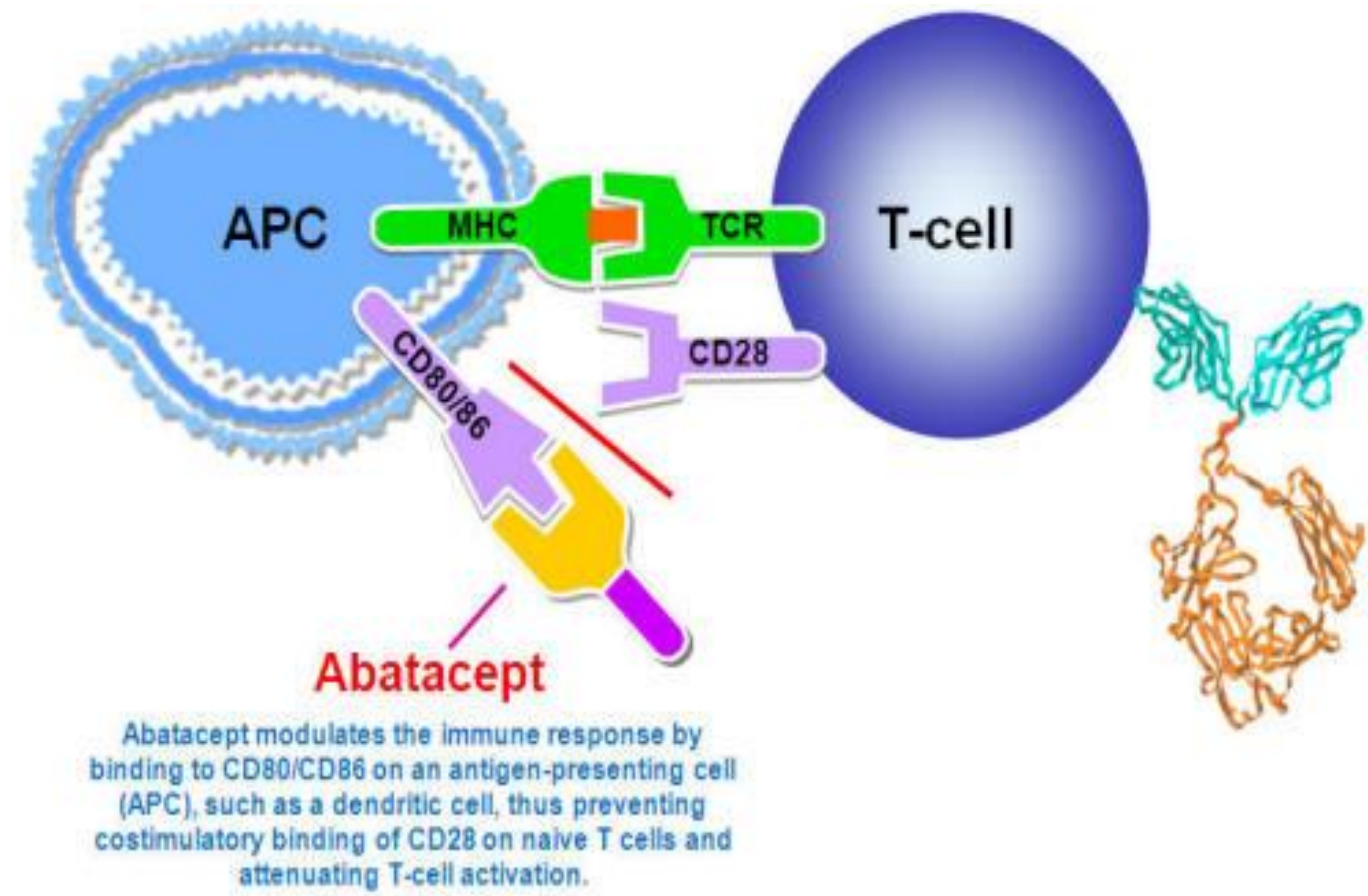


CTLA-4 is an immune checkpoint receptor on T cells that plays a key role in preventing T-cell overactivation. Tumor cells use the CTLA-4 pathway to suppress initiation of an immune response, resulting in decreased T-cell activation and ability to proliferate into memory T cells.

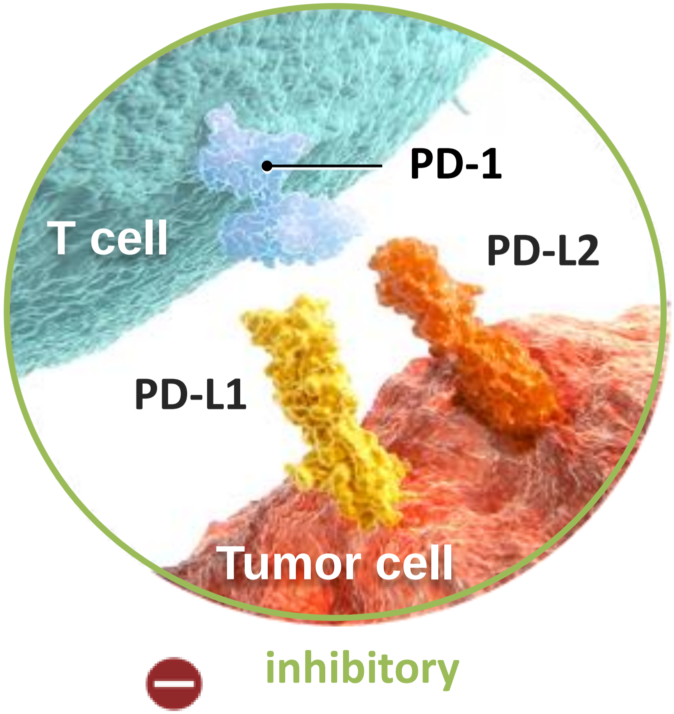
Preclinical data suggests that treatment with antibodies specific for CTLA-4 can restore an immune response through increased survival of memory T cells and **depletion of regulatory T cells.**

CTLA4 in Rheumatoid Arthritis

Ενεργοποίηση αρνητικής συνδιέγερσης επάγει καταστολή ενεργοποίησης Τ κυττάρων



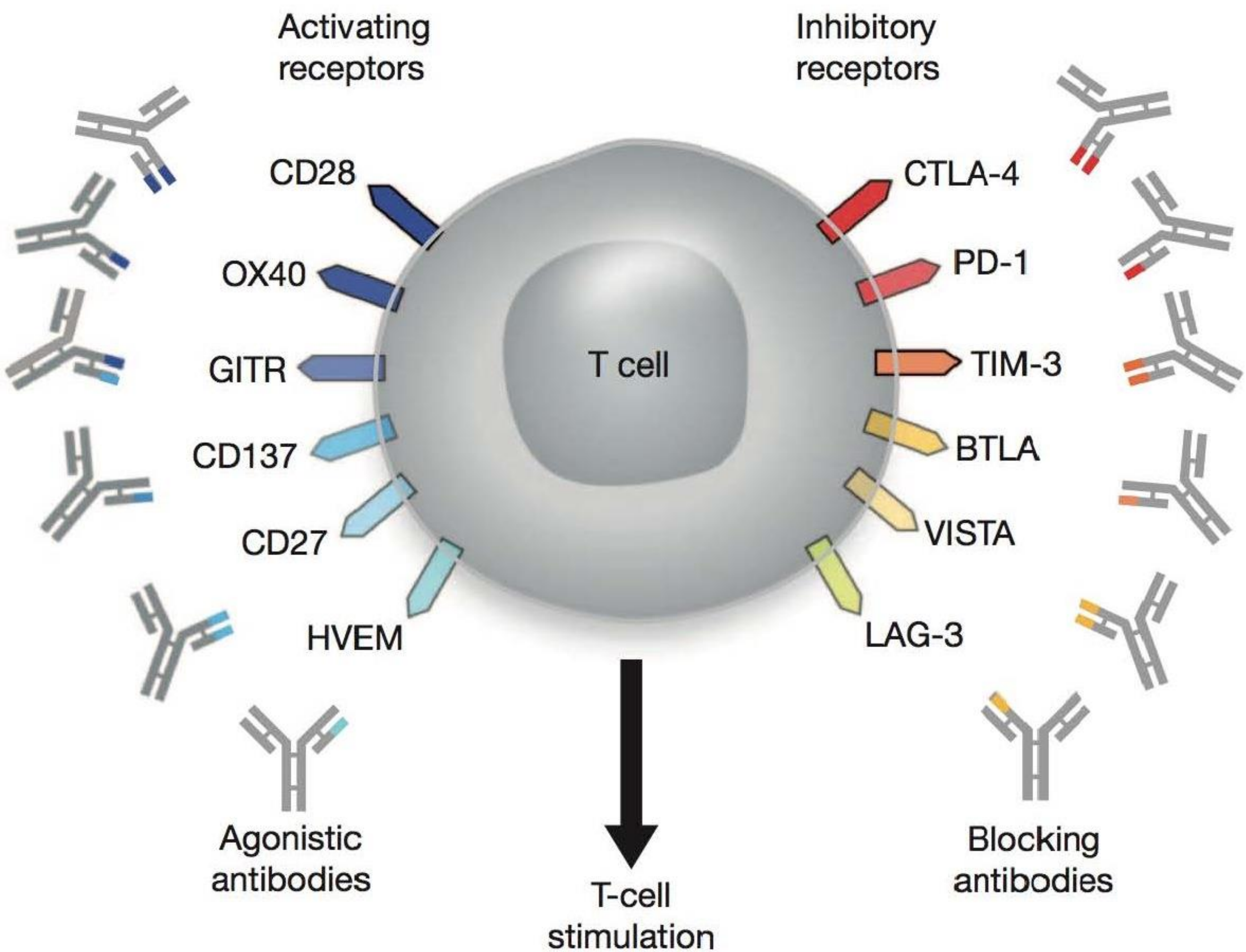
PD-1/PD-L1 interactions



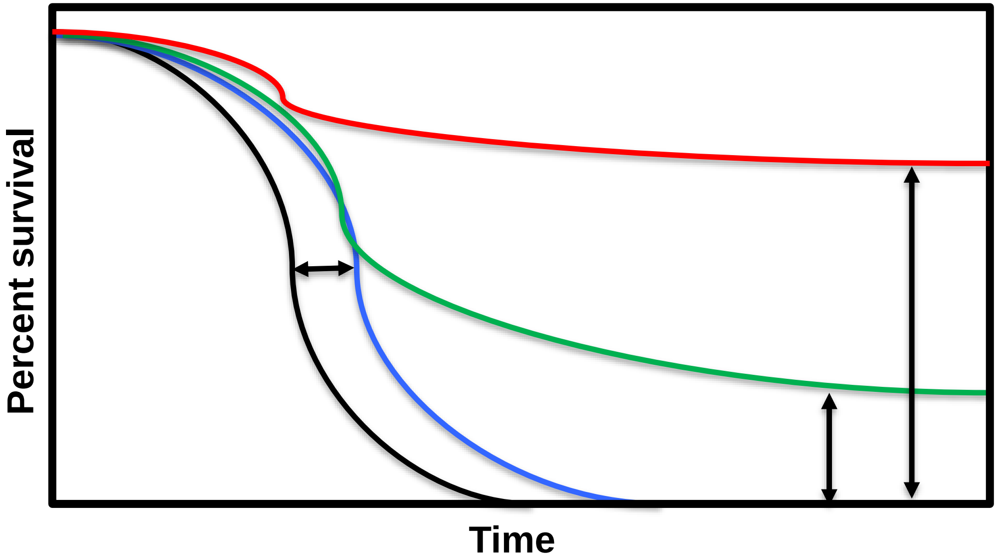
PD-1 is an immune checkpoint receptor on cytotoxic T cells that plays a key role in T-cell exhaustion and prevention of autoimmunity. Tumor-infiltrating T cells across solid tumors and hematologic malignancies display evidence of exhaustion, including upregulation of PD-1.

Preclinical data suggests that PD-1 blockade reinvigorates exhausted T cells and restores their cytotoxic immune function. Inhibiting both PD-1 ligands (PD-L1 and PD-L2) may be more effective at reversing T-cell exhaustion than inhibiting PD-L1 alone.

The landscape of T cell activating and inhibitory receptors



Future Directions in Immuno-Oncology



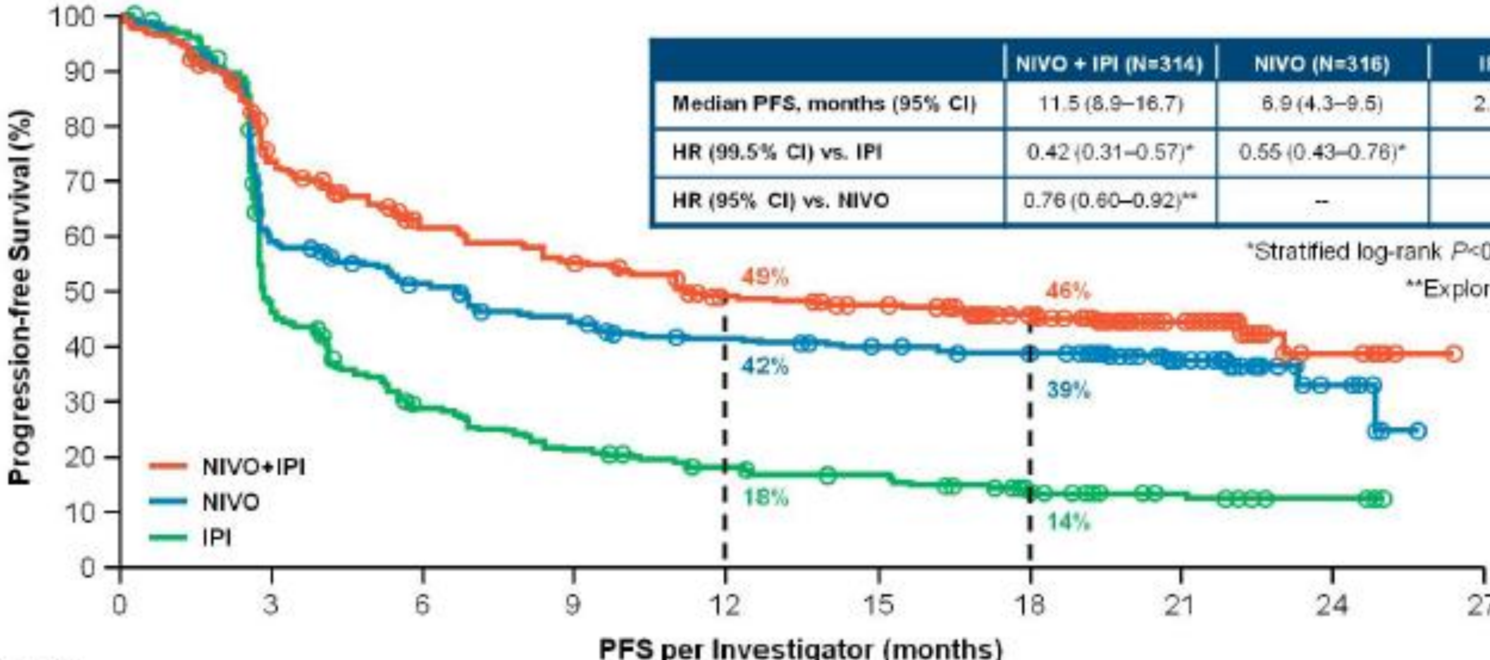
Chemotherapy

Targeted therapy

Immune checkpoint therapy ⇒ long lasting responses
⇒ applicable in various cancer types

Combination therapy ⇒ increase in response rate?
⇒ increase in efficiency?

Progression-Free Survival (Intent-to-Treat Population)



	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31–0.57)*	0.55 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.76 (0.60–0.92)**	--	--

*Stratified log-rank $P<0.00001$ vs. IPI

**Exploratory endpoint

Number of patients at risk:

	0	3	6	9	12	15	18	21	24	27
Nivolumab + Ipilimumab	314	219	174	156	133	126	103	48	8	0
Nivolumab	316	177	148	127	114	104	94	46	8	0
Ipilimumab	315	137	78	58	46	40	25	15	3	0

Database lock Nov 2015

Organs Systems Often Affected by Cancer Immunotherapy

I-O therapy-associated AEs target certain organ systems[1]
Skin[1–6]
Endocrine system[2,4,6,7–10]
Liver[2,6,11–12]
Gastrointestinal tract[2,6,9,13]
Nervous system[6,10,14,15]
Eyes[1,4,16–18]
Respiratory system[1,5,6,10,15,19]
Hematopoietic cells[6,9,12,20–22]

1. Amos SM, et al. *Blood.* 2011;118:499–509; 2. Phan GQ, et al. *PNAS.* 2003;100:8372–8377; 3. Rosenberg SA. *J Immunother Emphasis Tumor Immunol.* 1996;19:81–84; 4. Chianese-Bullock KA, et al. *J Immunother.* 2005;28:412–419; 5. Harris J, et al. *Med Pediatr Oncol.* 1994;22:103–106; 6. Chow LQ. *Am Soc Clin Oncol Educ Book*. 2013:280–285; 7. Bendle GM, et al. *Nat Med.* 2010;16:565–570; 8. Soni N, et al. *Cancer Immunol Immunother.* 1996;43:59–62; 9. Ronnblom LE, et al. *Ann Intern Med.* 1991;115:178–183; 10. Fraenkel PG, et al. *J Immunother.* 2002;25:373–378; 11. Lamers CH, et al. *J Clin Oncol.* 2006;24:e20–e22; 12. Roskrow MA, et al. *Leuk Res.* 1999;23:549–557; 13. Parkhurst MR, et al. *Mol Ther.* 2011;19:620–626; 14. Pellkofer H, et al. *Brain.* 2004;127:1822–1830; 15. Smalley RV, et al. *Blood.* 1991;78:3133–3141; 16. Dudley ME, et al. *J Clin Oncol.* 2008;26:5233–5239; 17. Yeh S, et al. *Ophthalmology*. 2009;116:981–989; 18. Robinson MR, et al. *J Immunother*. 2004;27:478–479; 19. Morgan RA, et al. *Mol Ther.* 2010;18:843–851; 20. Kochenderfer JN, et al. *Blood.* 2010;116:4099–4102; 21. Lin TS, et al. *J Clin Oncol.* 2010;28:4500–4506; 22. Herishanu Y, et al. *Leuk Lymphoma.* 2003;44:2103–2108.

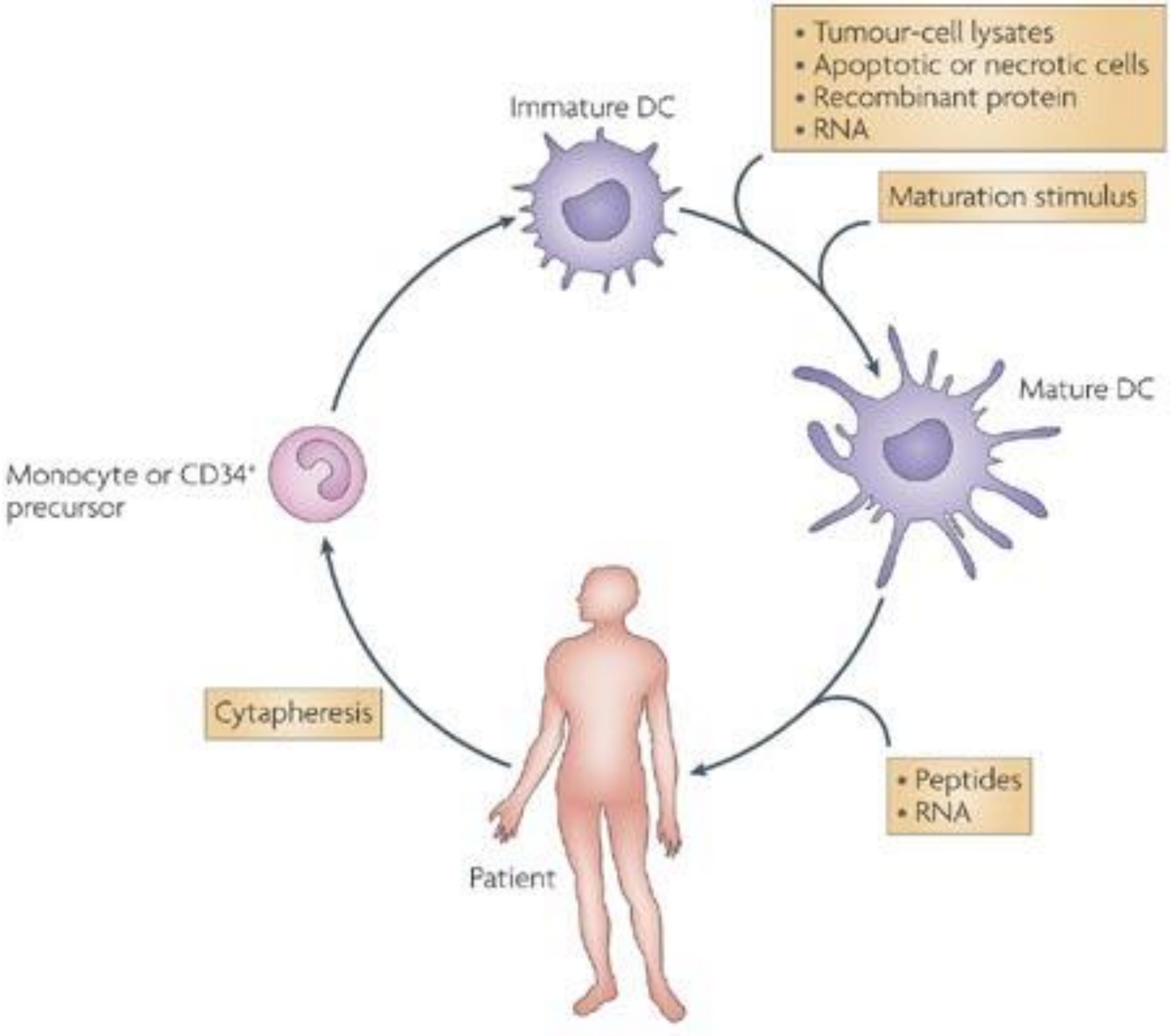
Immune Cell Therapies

Γιατί τα Δενδριτικά Κύτταρα (dendritic cells: DCs) είναι ξεχωριστά?

• τα πιο αποτελεσματικά από όλα τα APCs
• μεταφέρουν αντιγόνα από ιστούς στους λεμφαδένες
• Επάγουν όλες τις αντιγονοειδικές Τ αποκρίσεις
•Προκαλούν την επιθυμητή συνδιέγερση των Τ κυττάρων
• διατηρούν την «ανοχή» στα αντιγόνα εαυτού
• ενεργοποιούνται από μικροβιακά σήματα που προέρχονται από την φυσική ανοσία

Δενδριτικά Κύτταρα: τα ανοσοενισχυτικά της φύσης

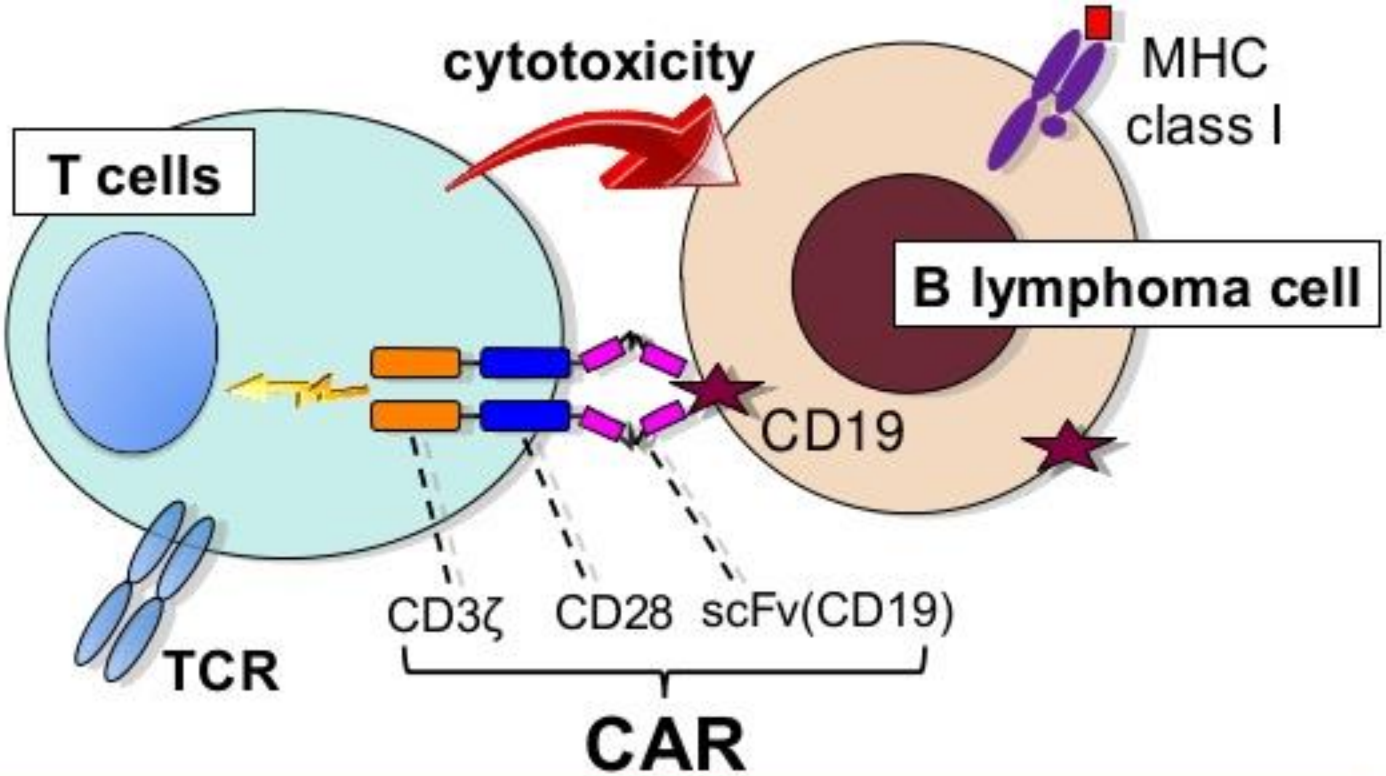
Dendritic cell vaccination



What is CAR T-Cell Therapy?

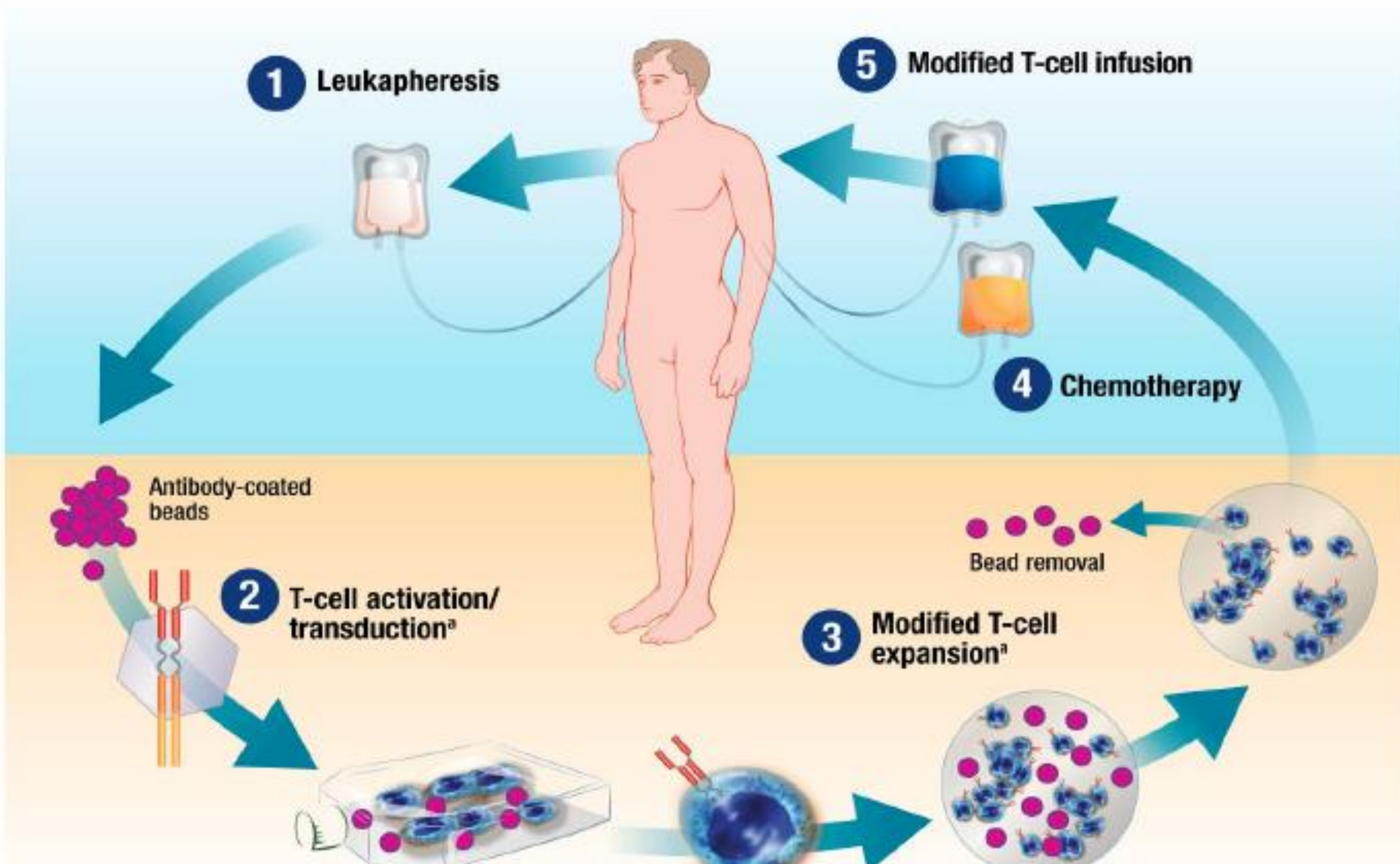
- It stands for (Chimeric Antigen Receptor) T-Cell Therapy
- T-Cells are isolated from the patient
- The T-Cells are then engineered to express CARS that recognize cancer cells
- Modified T-Cells are grown and expanded, and then infused into the patient
- This adoptive cellular therapy transfers cells into the patient with the goal of targeting malignant cells

Cytotoxicity of CD19-specific CAR-expressing T Lymphocytes against B Cell Lymphoma



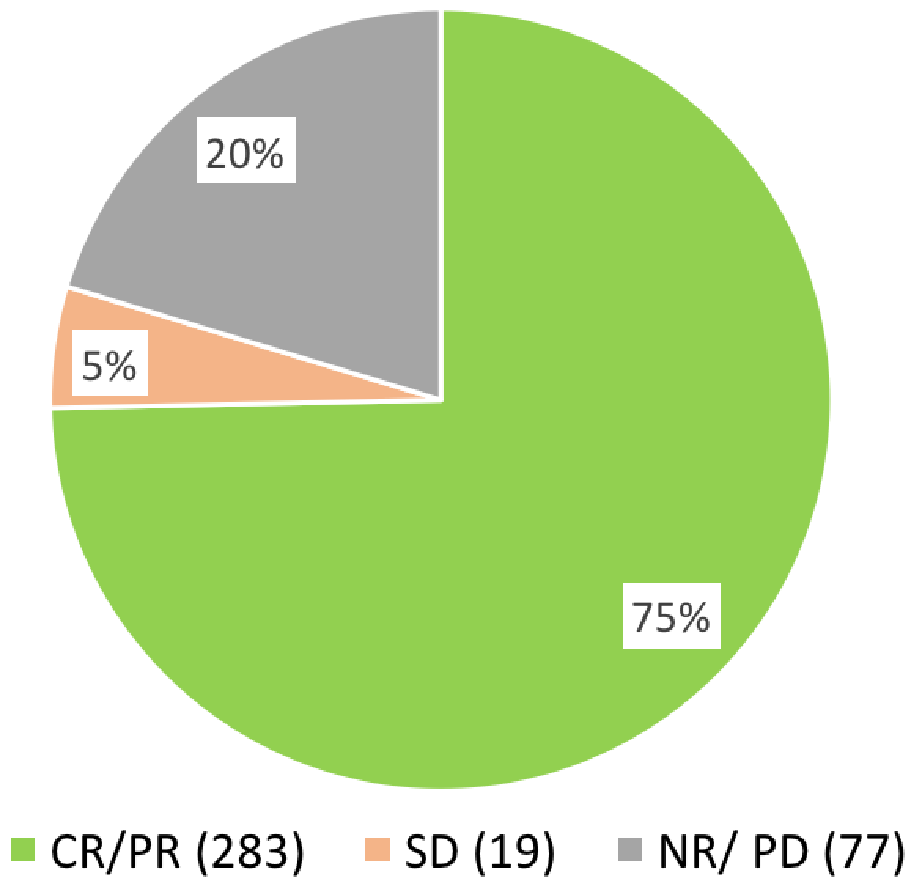
CD19-CAR T cells, which are engineered to express extracellular single-chain immunoglobulin variable fragments to CD19, linked to cytoplasmic T cell activation domains including CD3-ζ, showed remarkable therapeutic benefits toward $CD19^{+}$ B cell malignancies.

CTL019 is designed to hunt and destroy CD19-positive B-cell cancers in patients



a. Cellular reprogramming and ex vivo expansion are conducted at a cell processing facility.

Clinical outcome of CAR-T cell therapy trials in liquid malignancies, targeting CD19

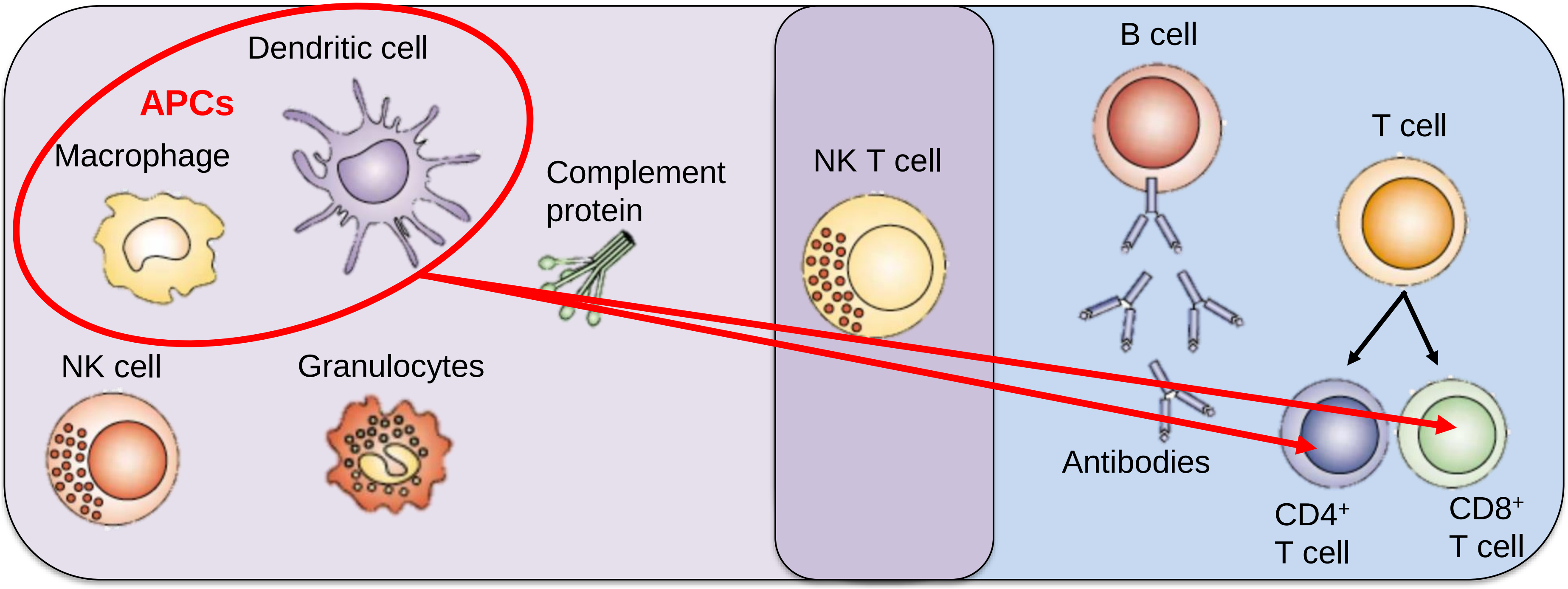


www.CellTrials.org

Thank you

Innate immunity

Adaptive immunity



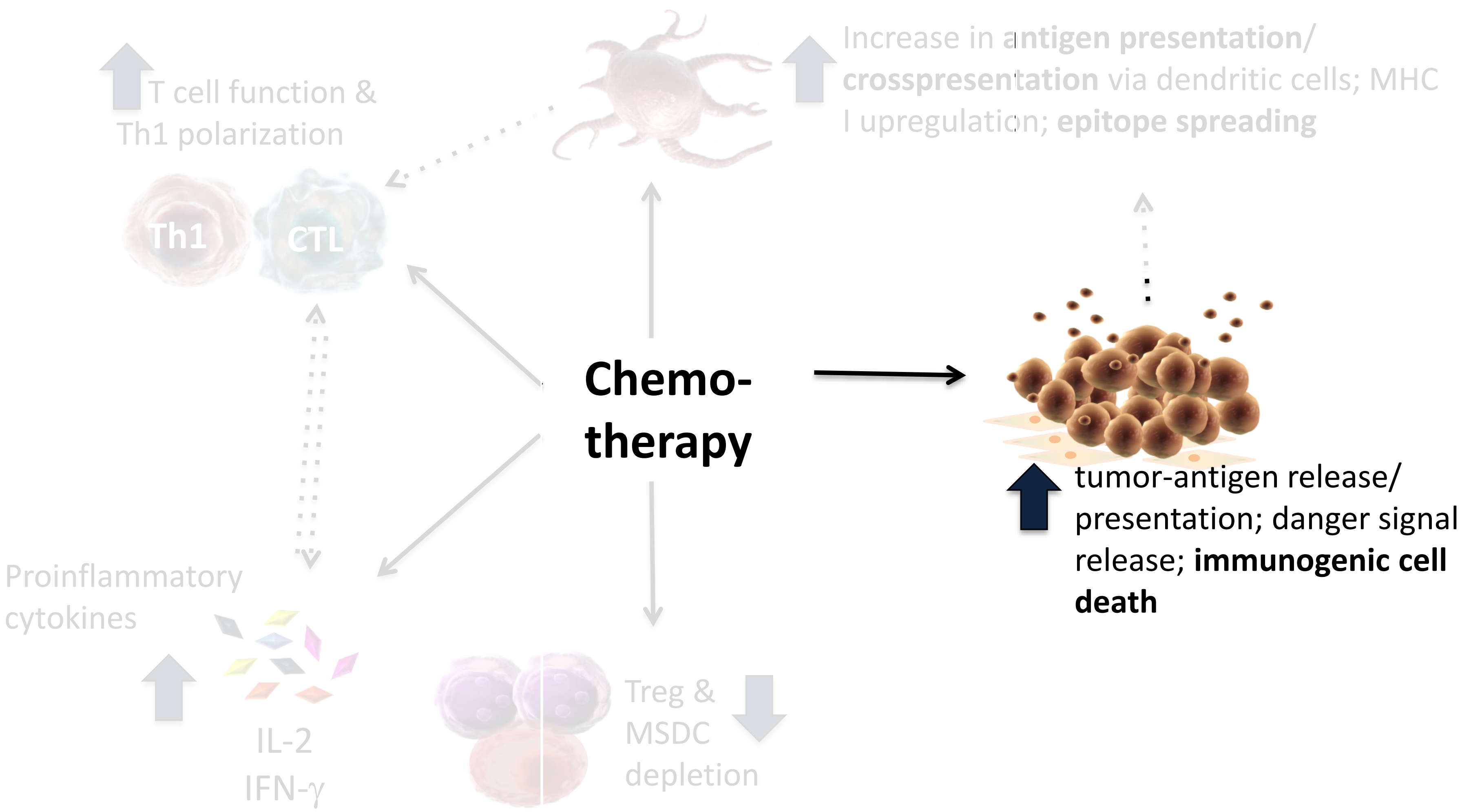
⇒ **fast response and low specificity**

- **Antibodies**
- **Cytokines**
- **Ag receptors (10^9 / individual)**

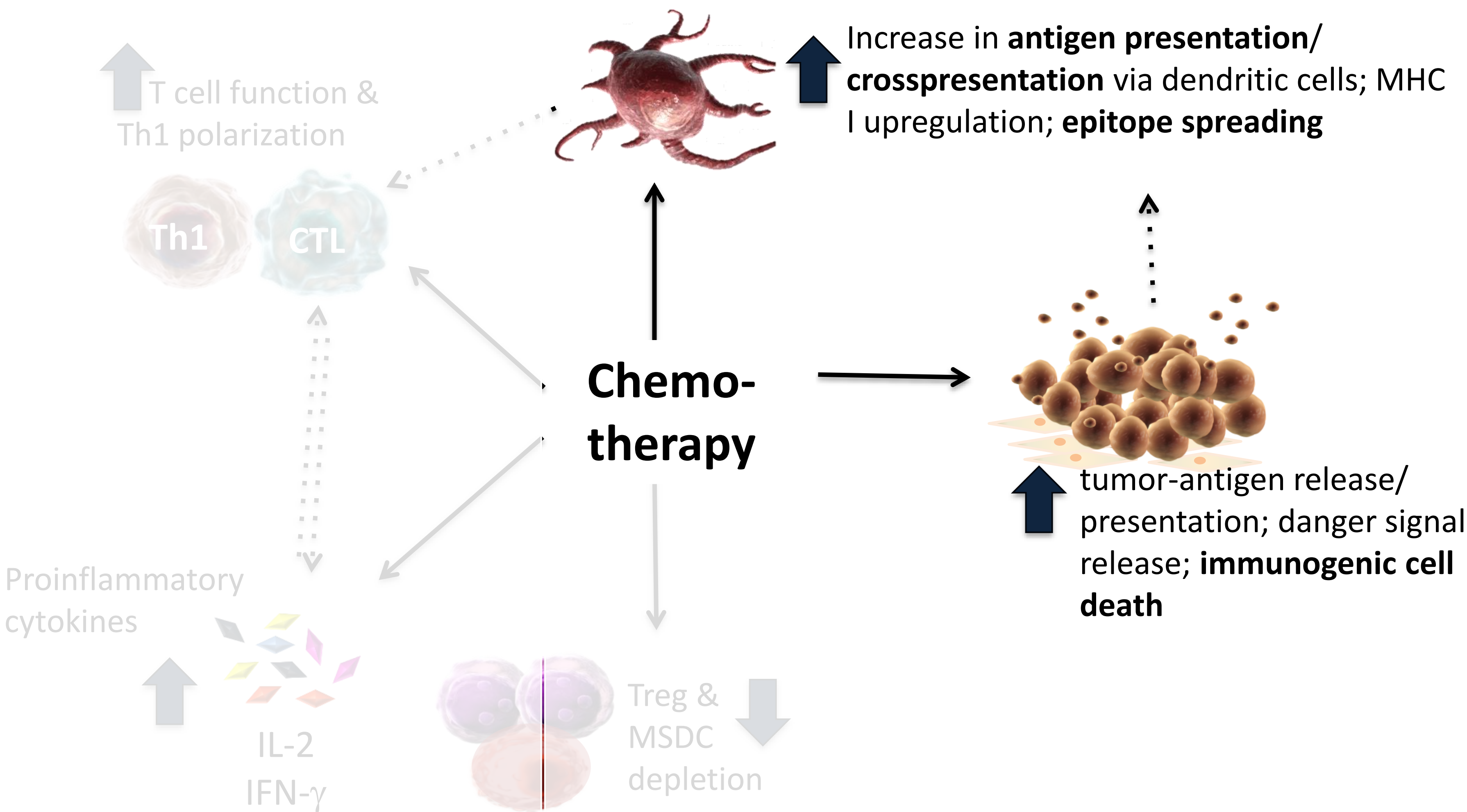
⇒ specificity, diversity, and memory

Dranoff, 2004

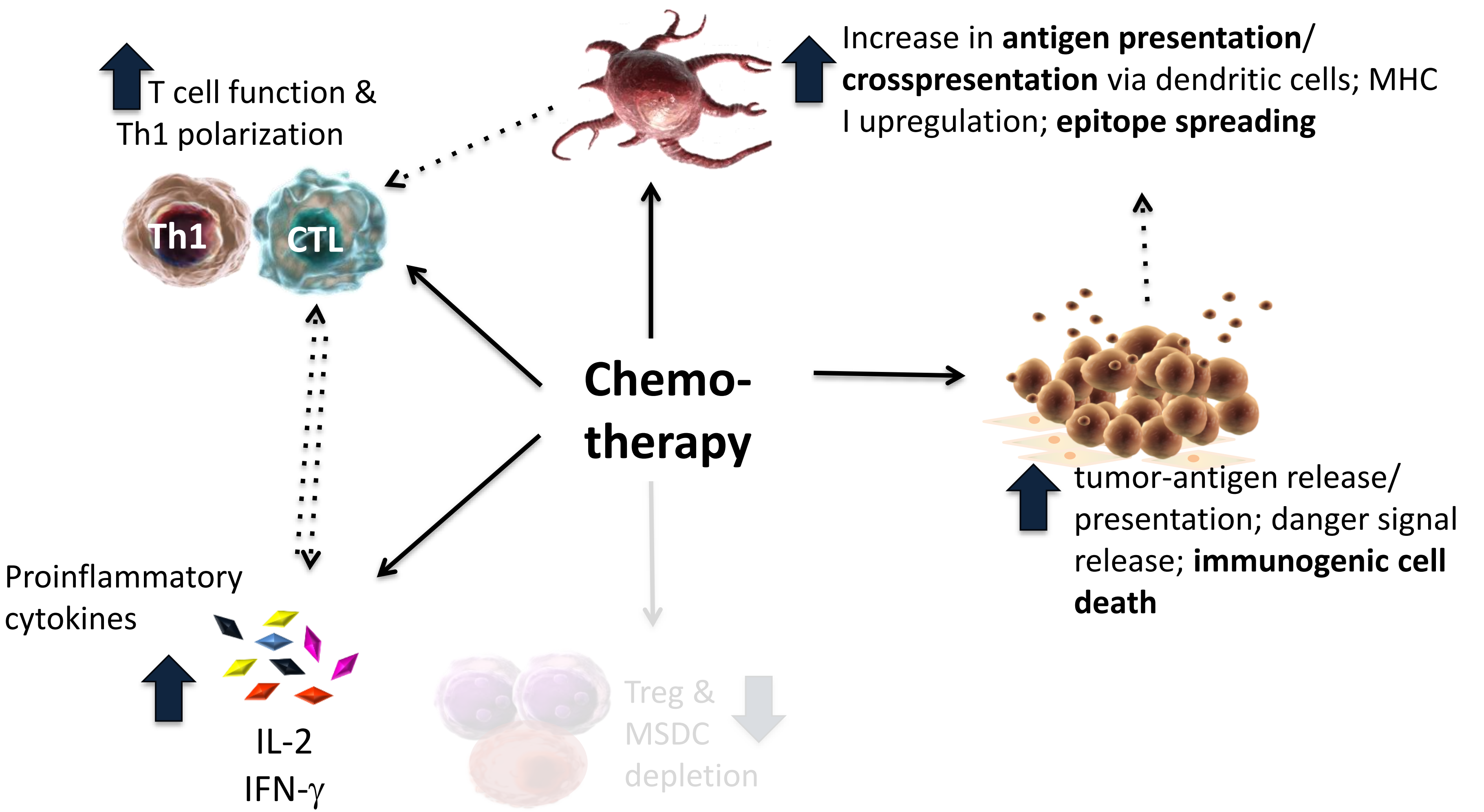
Chemotherapy: Pleiotropic stimulatory effects on the immune system



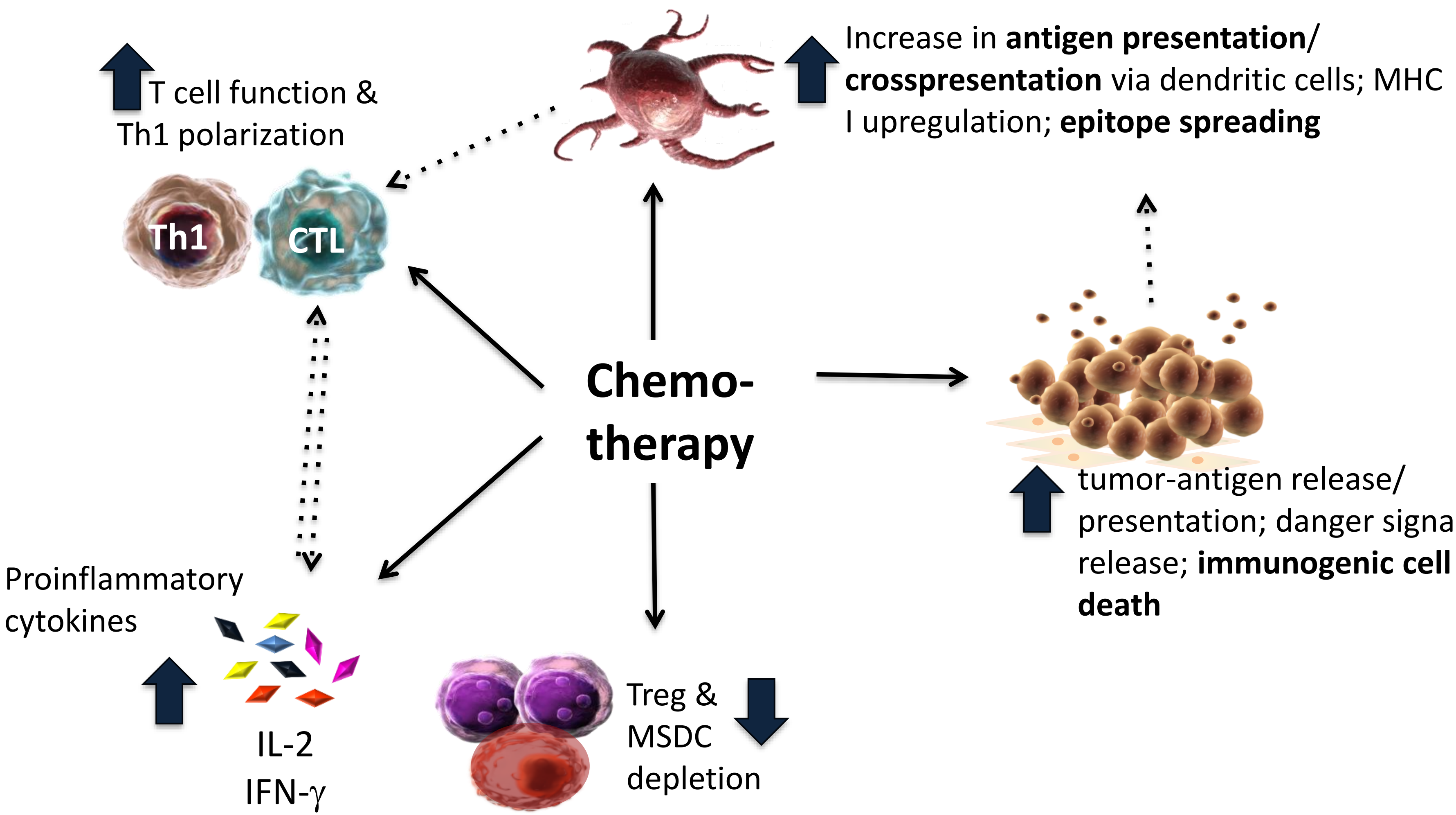
Chemotherapy: Pleiotropic stimulatory effects on the immune system



Chemotherapy: Pleiotropic stimulatory effects on the immune system



Chemotherapy: Pleiotropic stimulatory effects on the immune system

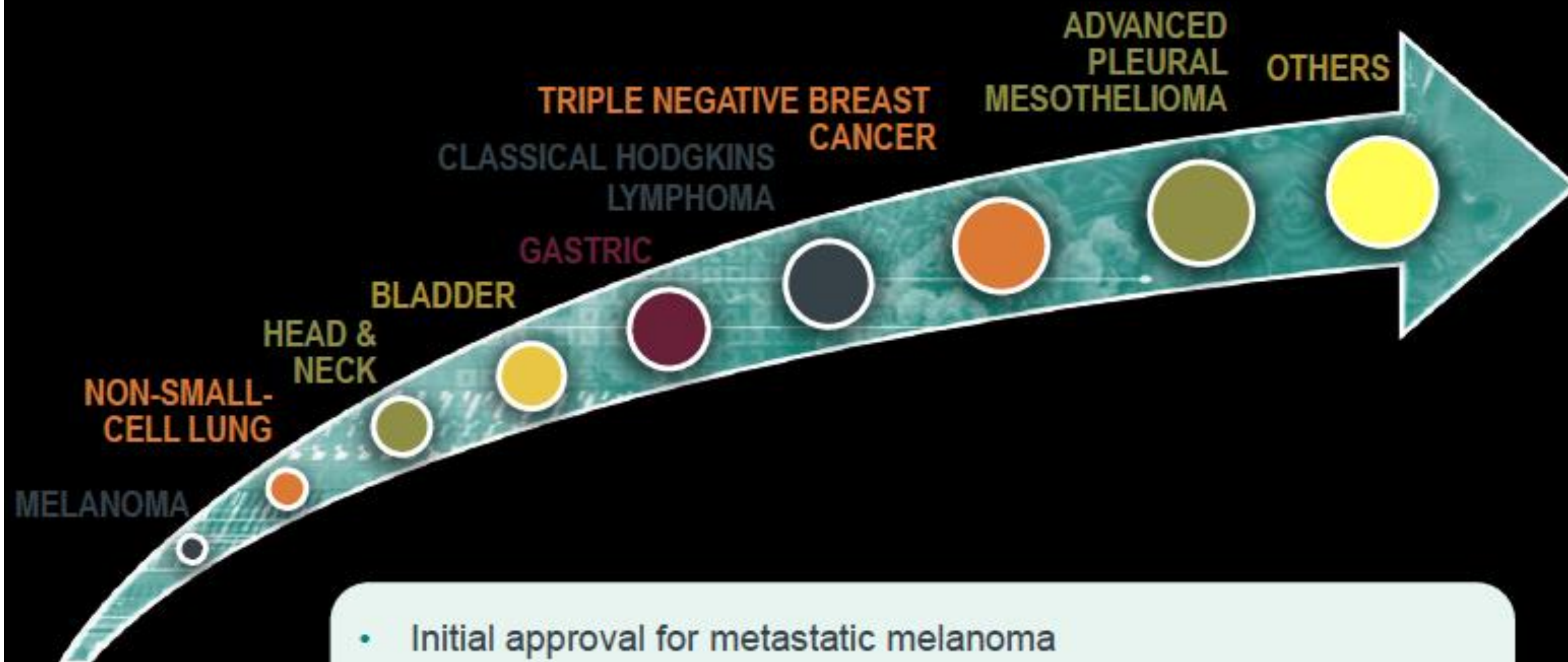


Immunedysregulation Polyendocrinopathy Enteropathy X-linked syndrome (IPEX)

Treg deficiency due to Foxp3 mutation

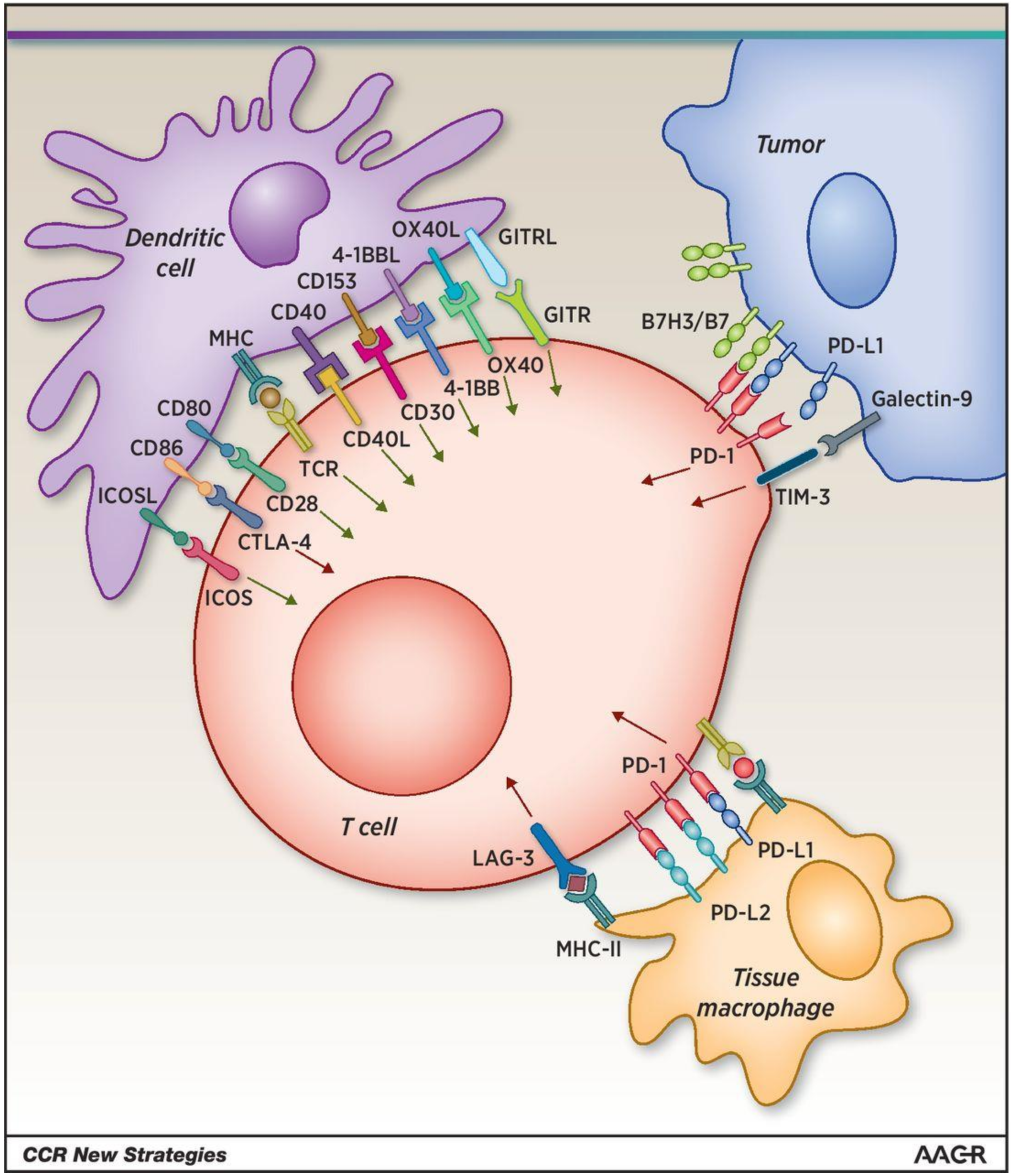
- **Neonatal onset diabetes mellitus**
- **Hypothyroidism**
- **Enteritis (diarrhea/villous atrophy)**
- **Hemolytic anemia & thrombocytopenia.**
- **Dermatitis**
- **Dermatitis (eczema)**
- **Death by 1-2 years of age**

>22,000 patients on pembrolizumab clinical trials since 2011



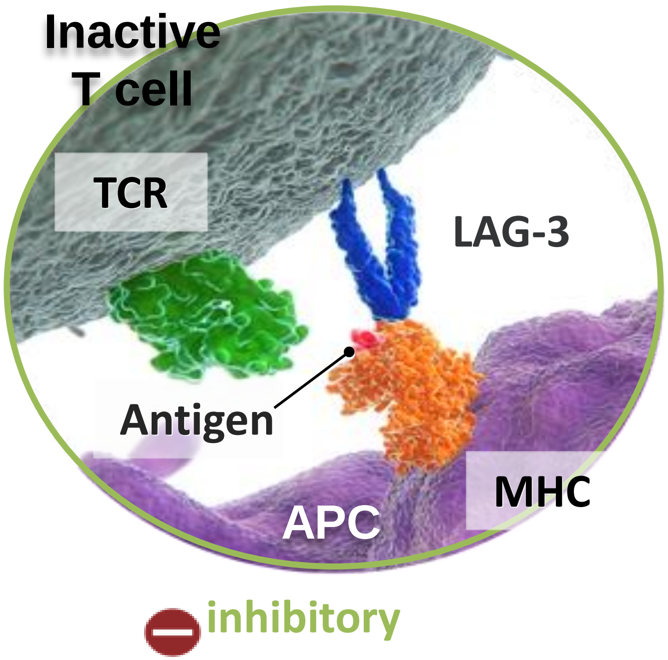
- Initial approval for metastatic melanoma
- Now approval for non-small-cell lung cancer, head and neck cancer
- Potential application in up to 30 different types of tumors

T lymphocytes are activated and negatively regulated by immune checkpoints.



Ryan J. Sullivan, and Keith T. Flaherty Clin Cancer Res 2015;21:2424-2435

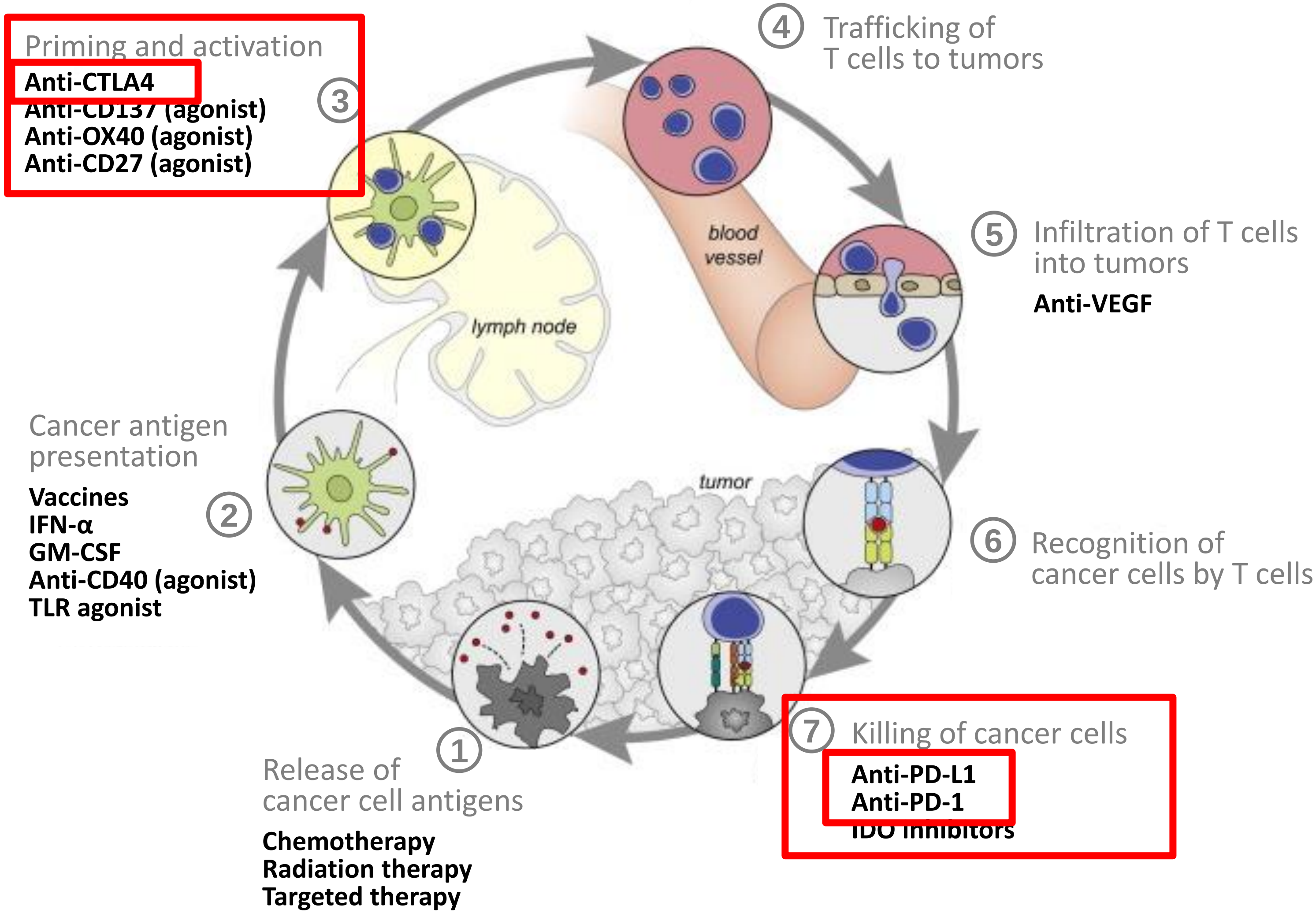
Clinical Cancer Research



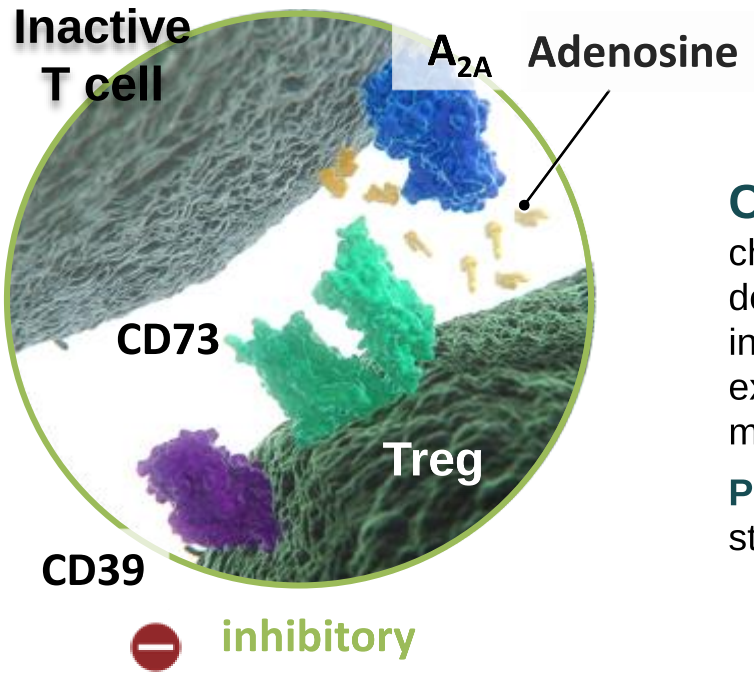
LAG-3 is an immune checkpoint receptor on the surface of both activated cytotoxic and regulatory T cells (Tregs).[44,45] When bound to the antigen-MHC complex, LAG-3 can negatively regulate T-cell proliferation and the development of lasting memory T cells.[46] Repeated exposure to tumor antigen causes an increase in the presence and activity of LAG-3, leading to T-cell exhaustion.[47,48]

Preclinical data suggests that inactivation of LAG-3 allows T cells to regain cytotoxic function.[49]

Immune Checkpoint Inhibitors



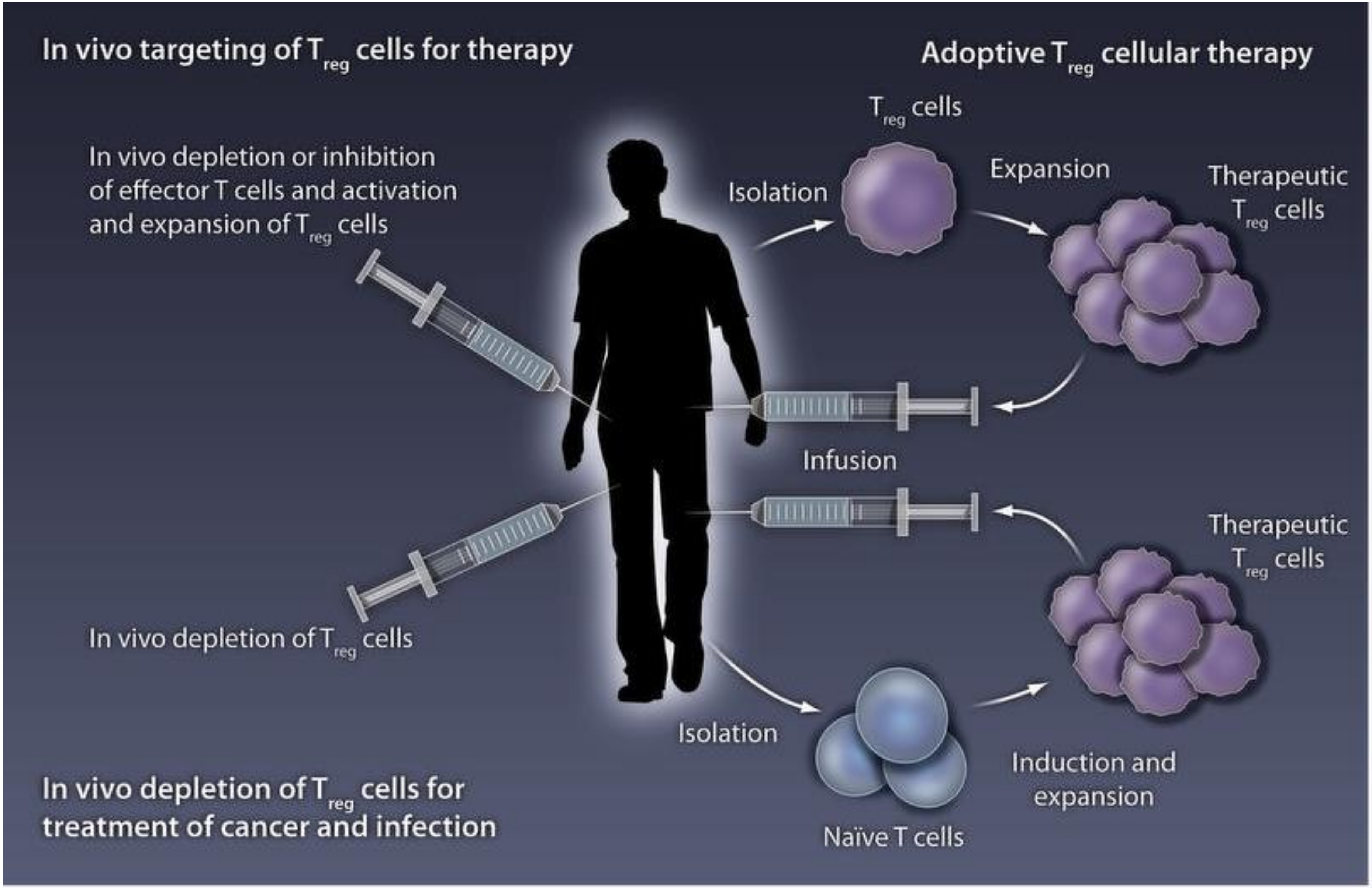
Chen and Mellman Immunity, 2013, 39:1-10



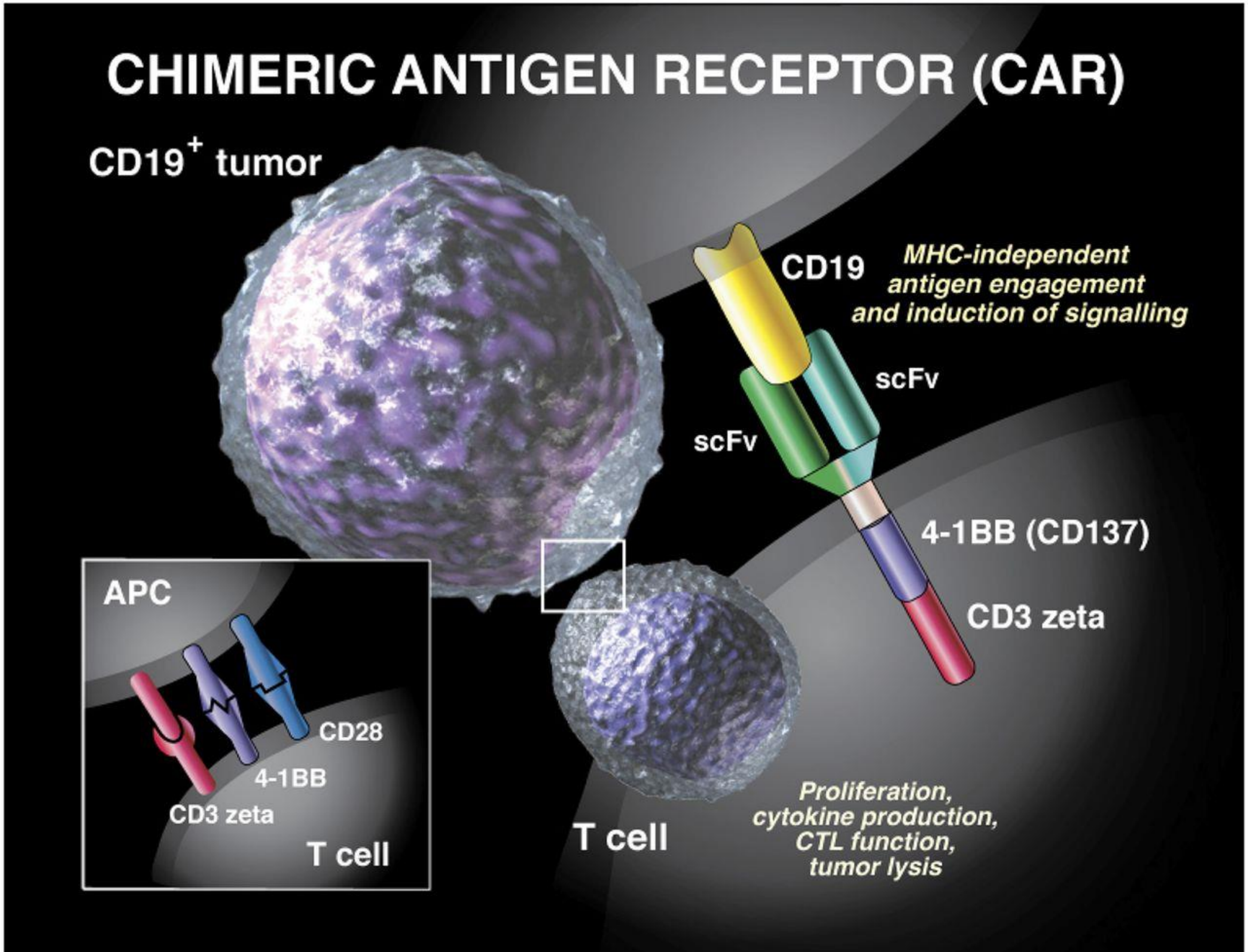
CD73 is a cell-surface enzyme on Tregs. CD73 is a critical checkpoint in the production of adenosine, which has been demonstrated to be a powerfully immunosuppressive molecule in cellular studies.[50] Tumor cells exploit this pathway by expressing CD73 and releasing adenosine into the tumor microenvironment.[51-53]

Preclinical data suggests that inhibition of CD73 activity can stimulate T-cell activity.[54]

Treg cell immunotherapy



CAR-T cell therapy



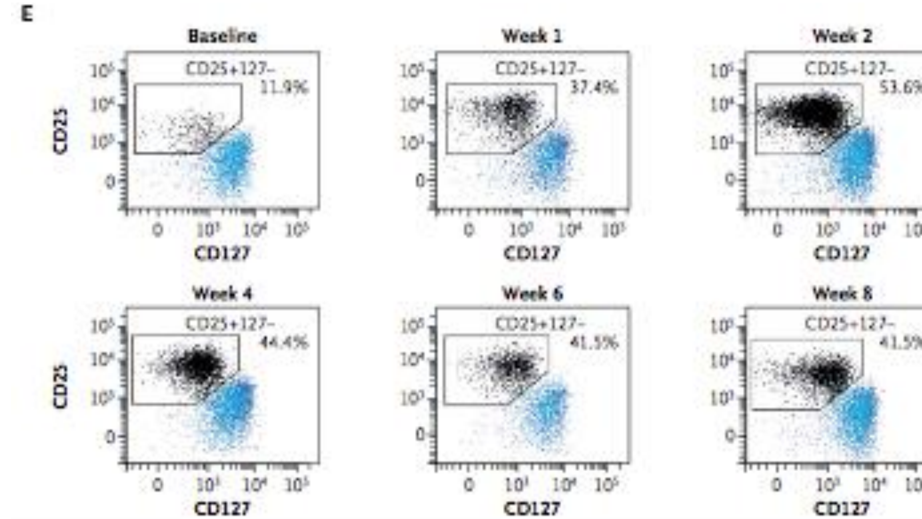
The NEW ENGLAND JOURNAL of MEDICINE

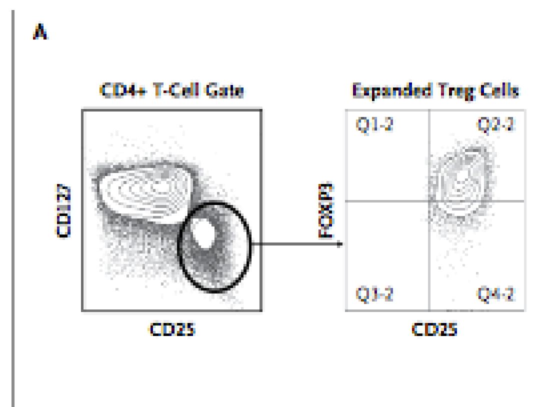
ESTABLISHED IN 1812 DECEMBER 1, 2011 VOL. 365 NO. 22

Interleukin-2 and Regulatory T Cells in Graft-versus-Host Disease

Daily low-dose interleukin-2 was safely administered in patients with active chronic GVHD that was refractory to glucocorticoid therapy. Administration was associated with preferential, sustained Treg cell expansion in vivo and amelioration of the manifestations of chronic GVHD in a substantial proportion of patients. (Funded by a Dana–Farber Dunkin' Donuts Rising Star award and others; ClinicalTrials.gov number, NCT00529035.)


A
B
C
D


E
Baseline
Week 1
Week 2
Week 4
Week 6
Week 8
CD25+127–
11.9%
37.4%
53.6%
44.4%
41.5%
41.5%
CD25
CD127


A
CD4+ T-Cell Gate
Expanded Treg Cells
CD127
CD25
FOXP3
Q1-2
Q2-2
Q3-2
Q4-2
CD25

Ralph Steinman used his findings to help design treatments that may have prolonged his life.

IMMUNOTHERAPY

A fight for life that united a field

Nobel-prizewinner Ralph Steinman tried to beat his cancer with vaccines based on the dendritic cells he discovered.

BY LAUREN GRAVITZ

After a young Ralph Steinman co-discovered a new type of immune cell in 1973, he spent years battling to prove its importance in defending the body against pathogens, and to show how it could be used to fight disease. Thirty-four years later, he would look to that same cell to try to save his life.

Dendritic cells — named for their tree-like branches — direct and regulate the body's immune system by programming other cells to recognize and destroy intruders. Steinman, a physician–scientist at The Rockefeller University in New York, set his sights on using the cells in vaccines to prevent chronic infections, such as HIV and tuberculosis, and in cancer therapies. So when he was diagnosed with advanced pancreatic cancer in March 2007, it was only natural that he would pin his hopes on the cells that had been his life's work. Together with collaborators around the world, he designed therapies that made use of his own dendritic cells.

"He was running an experiment on himself and was willing to help out with every kind of study. He wanted to help himself, but he also viewed it as an incredible opportunity to learn something," says Ira Mellman, who worked with Steinman to develop his treatments and is vice-president of oncology research at the biotechnology firm Genentech in South San Francisco, California.

On 3 October, Steinman shared the Nobel Prize in Physiology or Medicine for his work, but he never heard the news. At the age of 68, after a four-and-a-half year battle with cancer, he died three days before the award was announced (see *Nature* 478, 13–14; 2011).

I first met Steinman during my two-year tenure as a science writer in the Rockefeller communications department. I was new to the immunology beat, and he kindly and patiently talked me through the intricacies of dendritic cells and their vast potential. When word of his cancer diagnosis emerged, his students and postdocs talked about it in hushed tones, telling me that immunologists at Rockefeller and beyond were using Steinman's dendritic cells in a personalized immunotherapy. I vaguely pictured his colleagues injecting him with homegrown cells right there in his lab. I could not have been more wrong.

"Everybody around the world who had something to share came forward, and he analysed and chose what looked most promising," says Sarah Schlesinger, a physician–researcher at Rockefeller who worked closely with Steinman and oversaw many of his experimental treatments. "We worked with dozens of colleagues, who helped in designing his therapy, evaluating the tumour and evaluating his immune response, and many worked with us to create single-patient protocols to treat him with experimental immunotherapy that went through the FDA [US Food and Drug Administration]."

Researchers across the field were eager to help the man who had always been generous with his time and knowledge. "Ralph was a collaborator, a competitor, but before everything he was a friend," says Jacques Banchereau, who began working with Steinman in the early 1990s and is now head of inflammation and virology at Roche in Nutley, New Jersey. ▶