

Basic Principles of Tumor Immunotherapy

Samir N. Khleif, MD

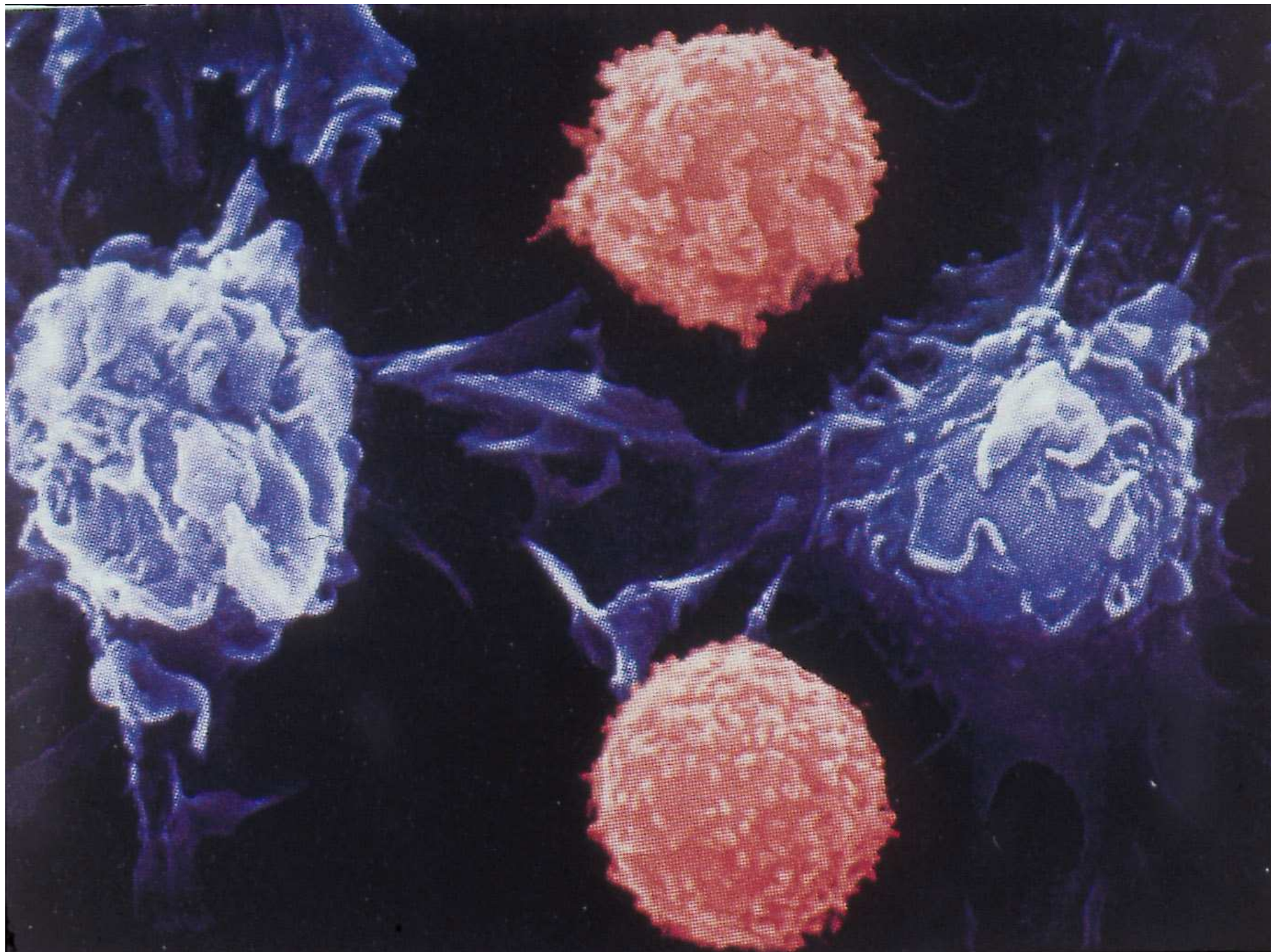
Director, GRU Cancer Center

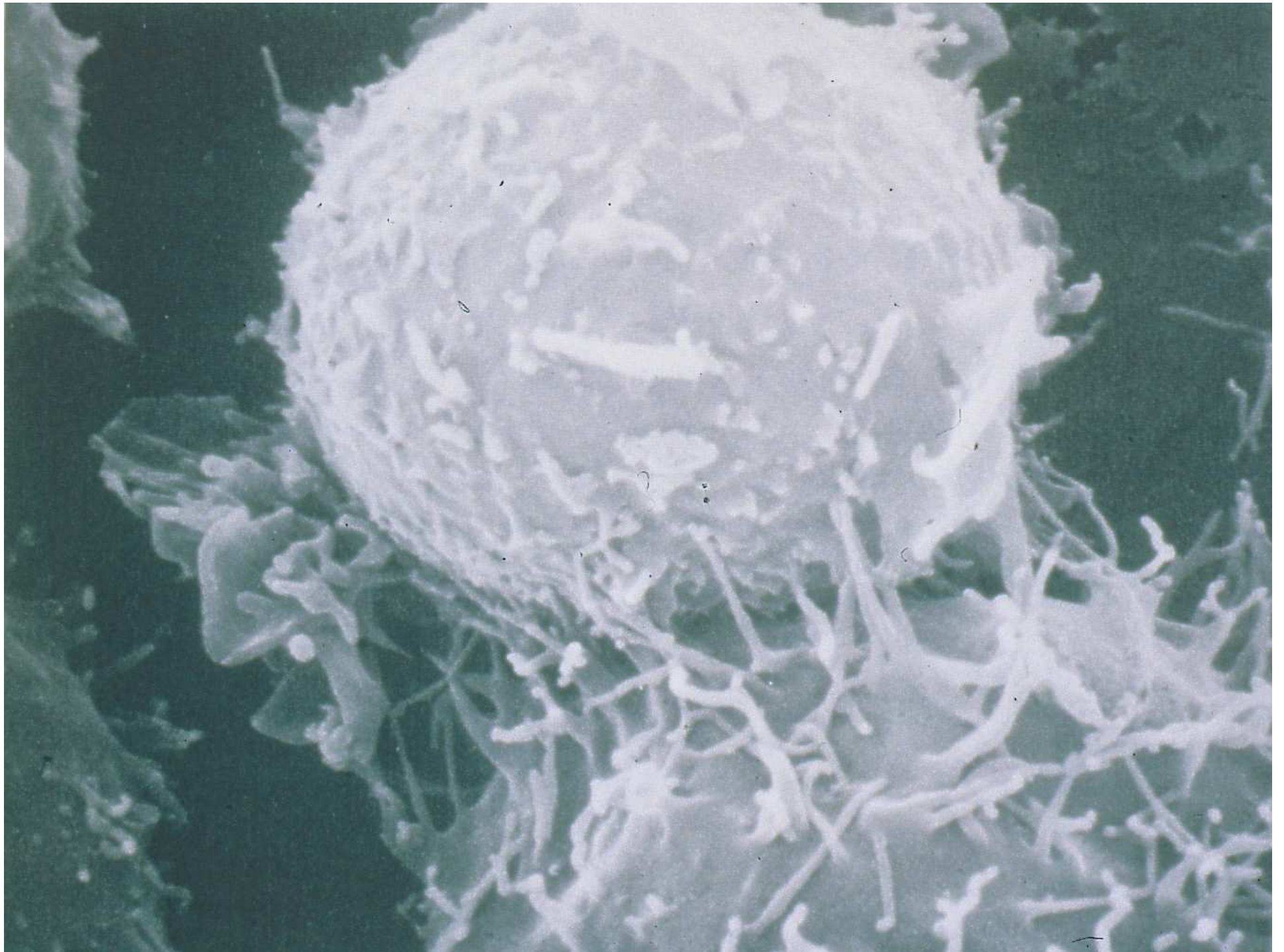
Director, Immuno-Oncology and Immune Therapeutics

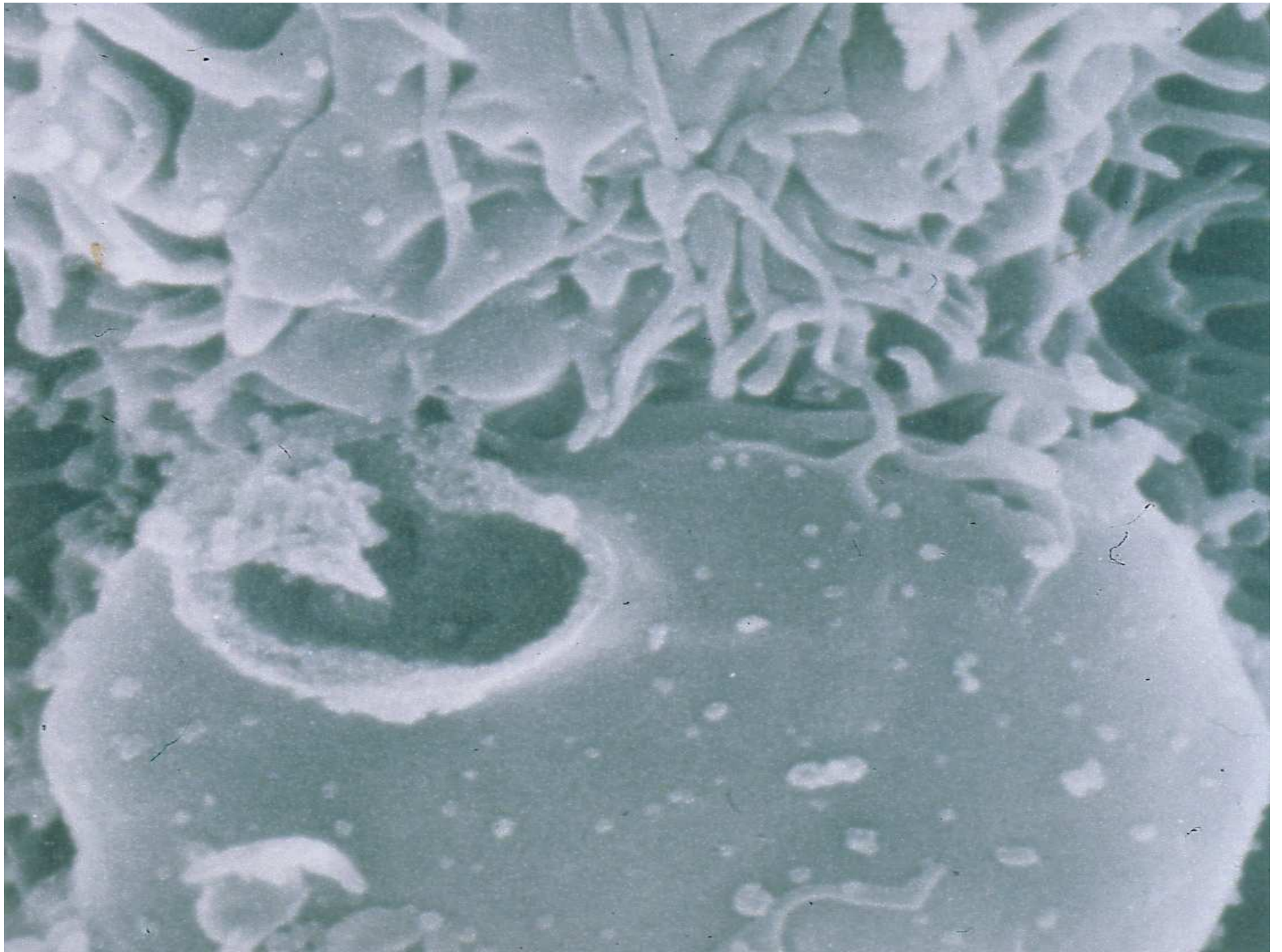
Professor of Medicine, Biochemistry and Molecular Biology

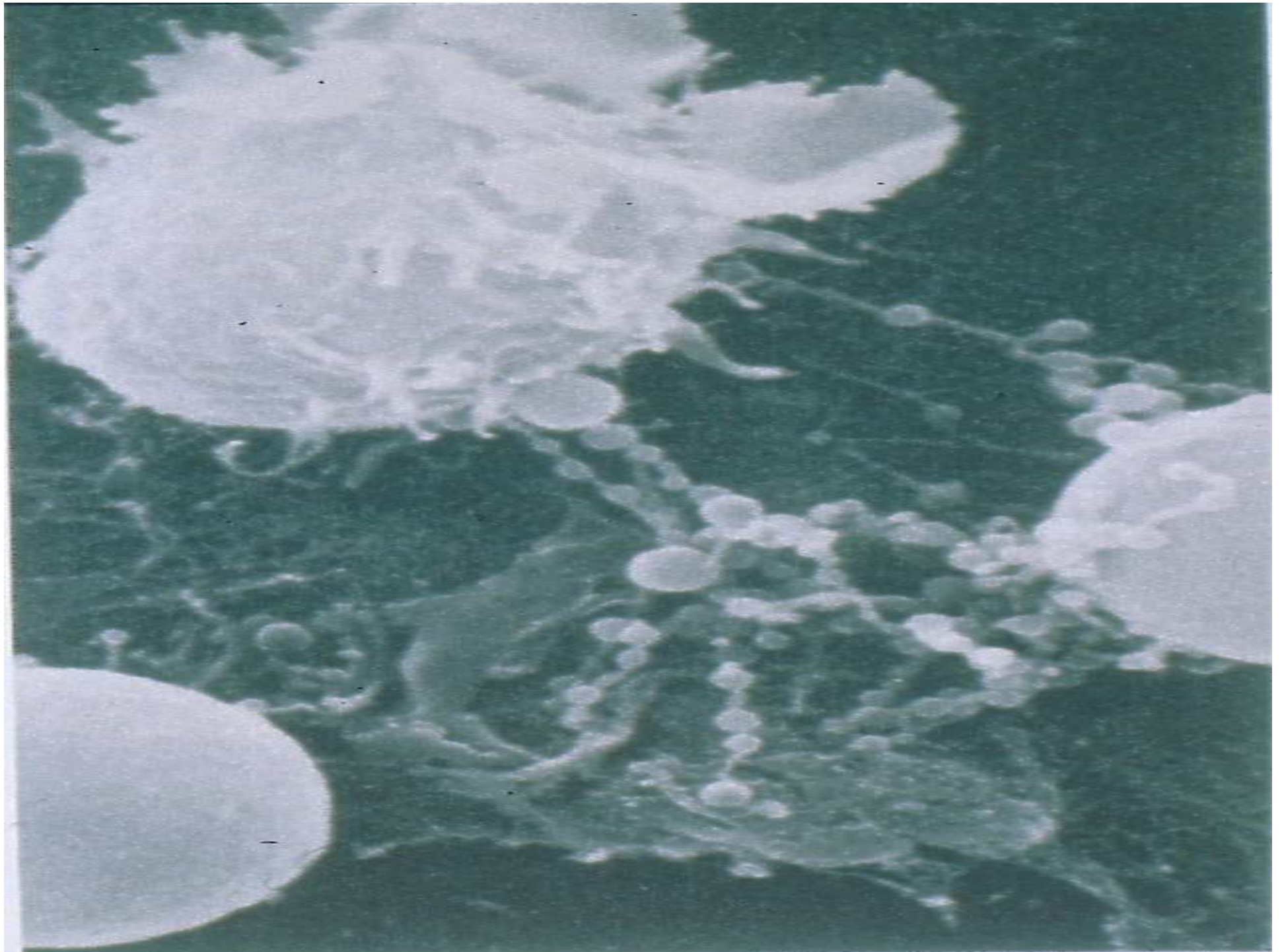
Disclosure

- Advisory Board: PDS Biotechnology, Admune Therapeutics, Merus
- Board Member: Advaxis Immunetherpies
- KOL/Consultant: J&J, AstraZenica, NewLink Genetics, Medimmune, Lycera
- Unrestricted preclinical Research funding: MedImmune, AstraZenica, NewLink Genetics, Advaxis Immunetherapies, PDS Biotechnologies, Amplimmune, CureTech



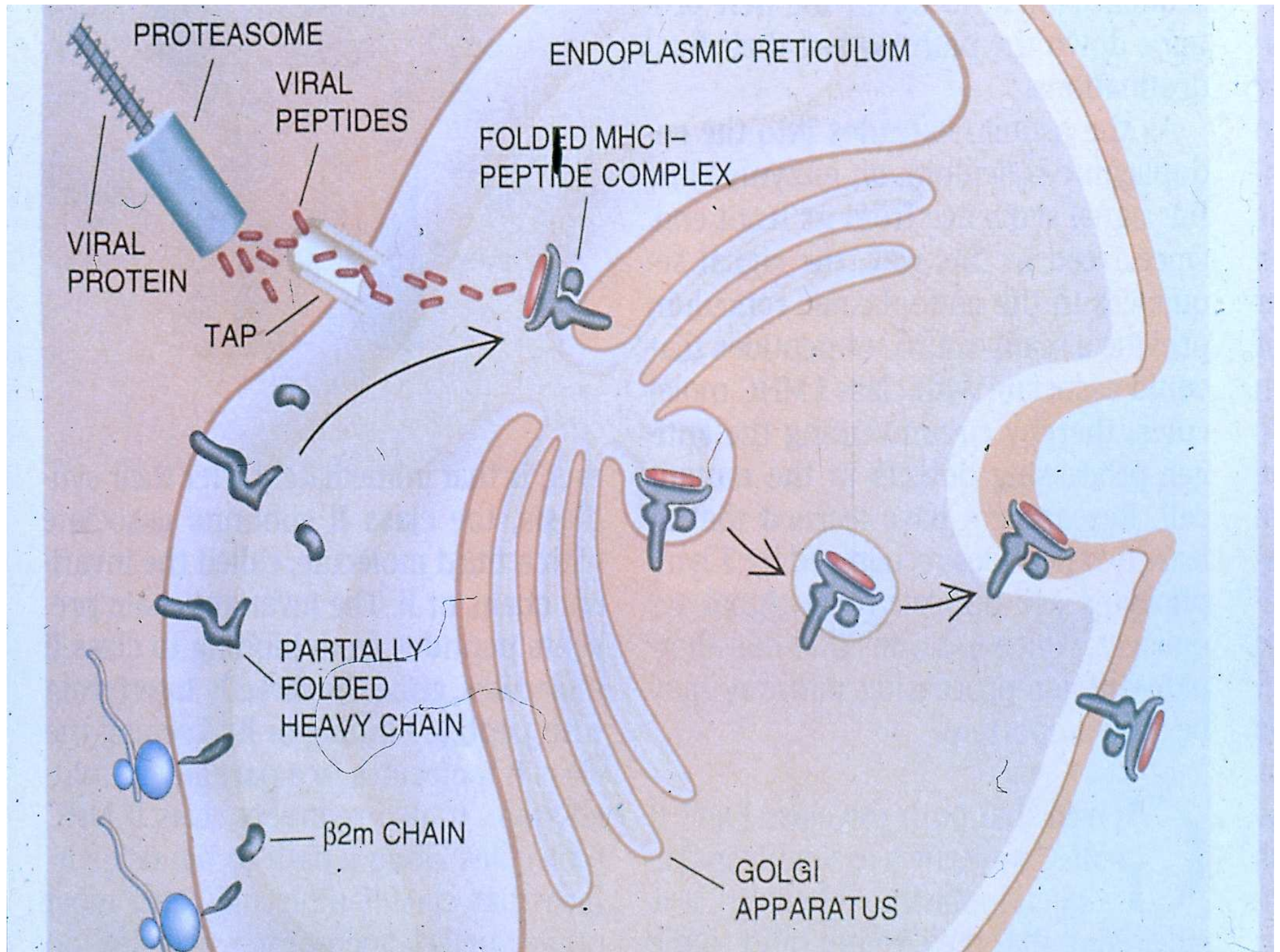


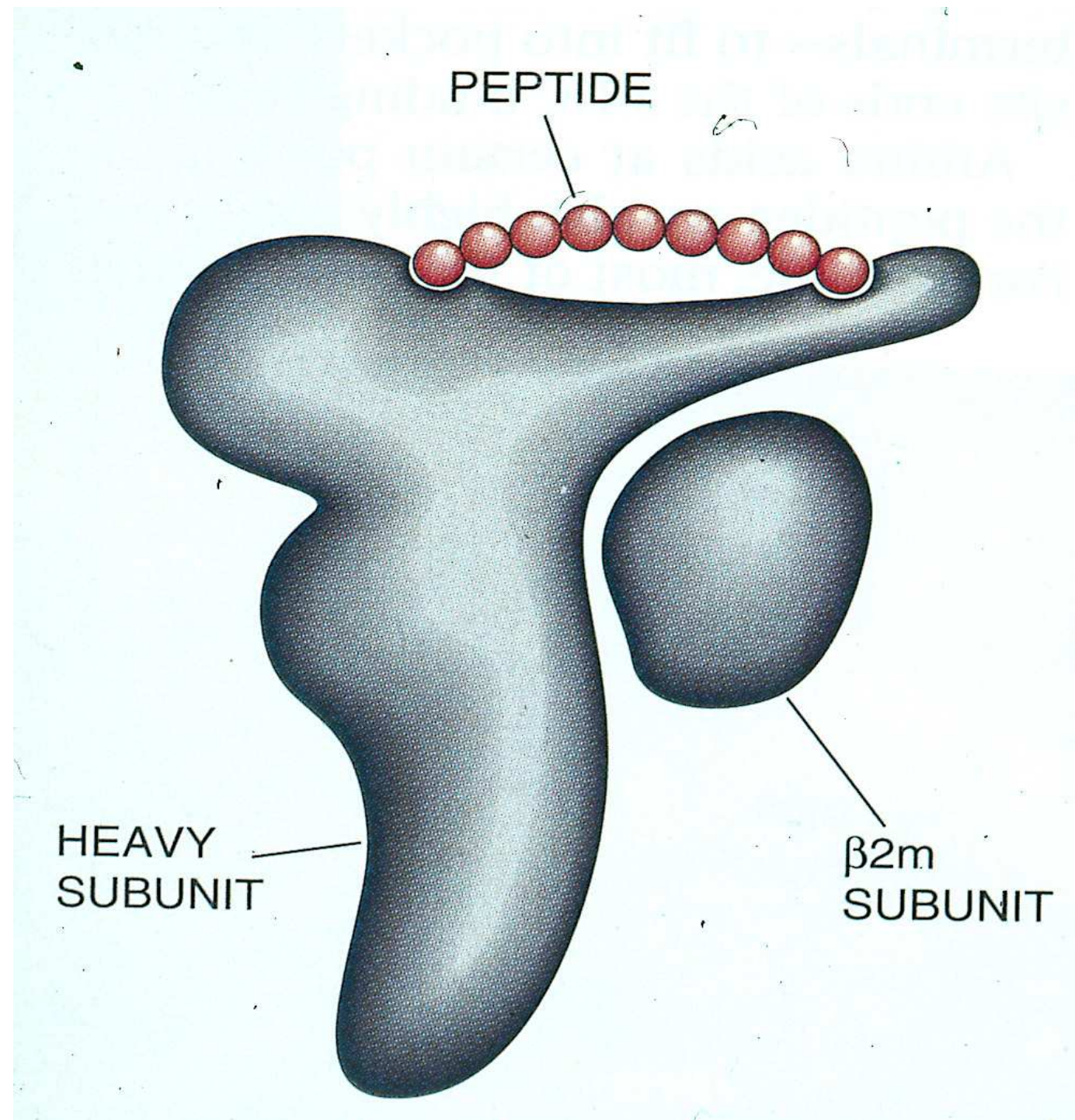




Cancer Vaccines

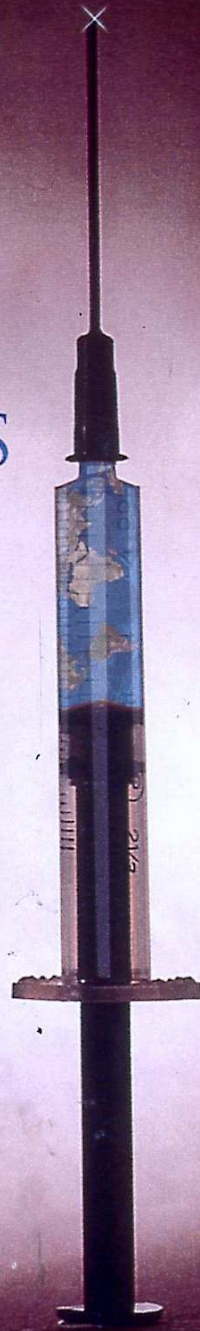
Samir N. Khleif, M.D.
Chief, Cancer Vaccine Section
National Cancer Institute, USA





VACCINES

FRONTIERS IN
MEDICINE





AN
INQUIRY
INTO
THE CAUSES AND EFFECTS
OF
THE VARIOLÆ VACCINÆ,
A 'DISEASE
DISCOVERED IN SOME OF THE WESTERN COUNTIES OF ENGLAND,
PARTICULARLY
GLOUCESTERSHIRE,
AND KNOWN BY THE NAME OF
THE COW POX.

BY EDWARD JENNER, M.D. F.R.S. &c.

— QUID NOBIS CERTIUS IPSIS
SENSIBUS ESSE POTEST, QUO VERA AC FALSA NOTEMUS.

LUCRETIVS.

London:

PRINTED, FOR THE AUTHOR,

BY SAMPSON LOW, N^o. 7, BERWICK STREET, SOHO:

AND SOLD BY LAW, AVE-MARIA LANE; AND MURRAY AND HIGHLEY, FLEET STREET.

1798.

CASE XVII.

THE more accurately to observe the progress of the infection, I selected a healthy boy, about eight years old, for the purpose of inoculation for the Cow Pox. The matter was taken from a sore on the hand of a dairymaid *, who was infected by her master's cows, and it was inserted, on the 14th of May, 1796, into the arm of the boy by means of two superficial incisions, barely penetrating the cutis, each about half an inch long.

In order to ascertain whether the boy, after feeling so slight an affection of the system from the Cow-pox virus, was secure from the contagion of the Small-pox, he was inoculated the 1st of July following with variolous matter, immediately taken from a pustule. Several slight punctures and incisions were made on both his arms, and the matter was carefully inserted, but no disease followed. The same appearances were observable on the arms as we commonly see when a patient has had variolous matter applied, after having either the Cow-pox or the Small-pox. Several months afterwards, he was again inoculated with variolous matter, but no sensible effect was produced on the constitution.

THE
ORIGIN
OF THE
VACCINE INOCULATION.

BY EDWARD JENNER, M.D. F.R.S. &c.

London:

PRINTED BY D. N. SHURY, BERWICK STREET, SOHO.

1801.

it now becomes too manifest to admit of contro-
verfy, that the annihilation of the Small Pox, the most dreadful
scourge of the human species, must be the final result of this
practice.

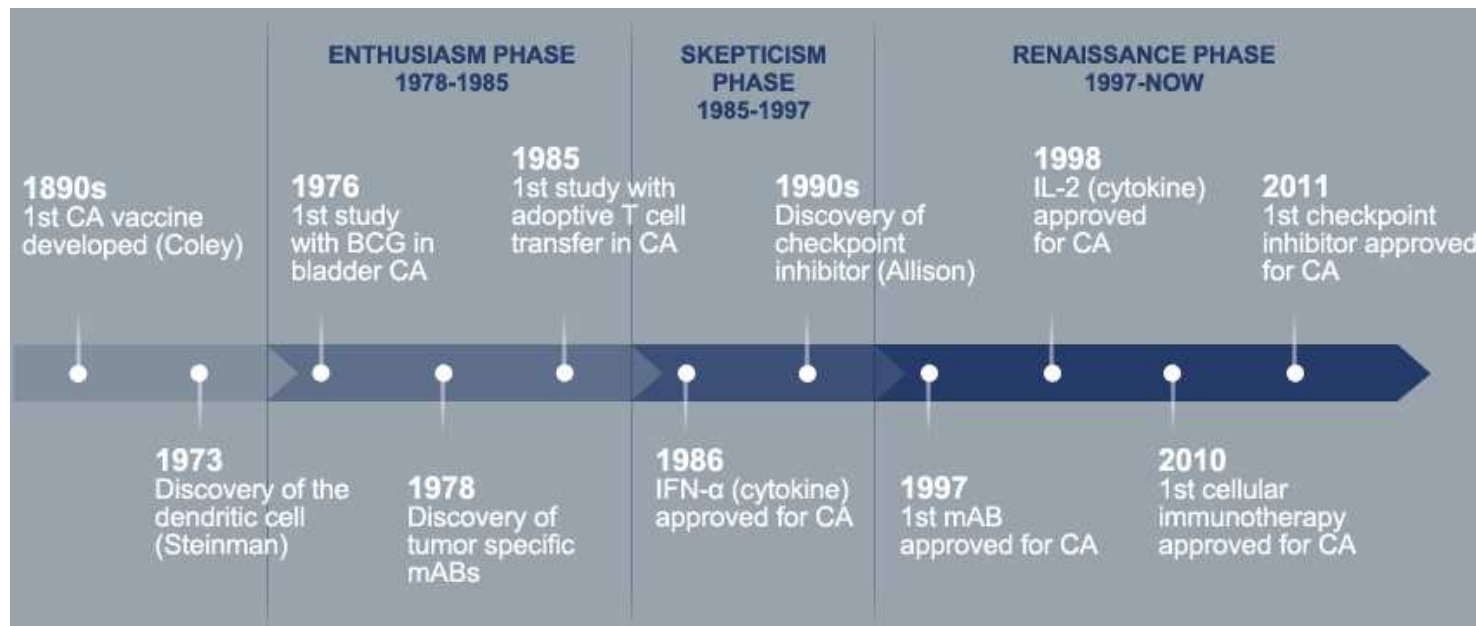


The History of Cancer Immunotherapy



- **1850s:**
 - **Germany:** patients' tumors shrink if infected → immune system could be harnessed to fight CA
 - **Europe:**
 - Ed Jenner's smallpox vaccine
 - Attempted to make a 'cancer vaccine' by injecting pts with crude extracts of tumors

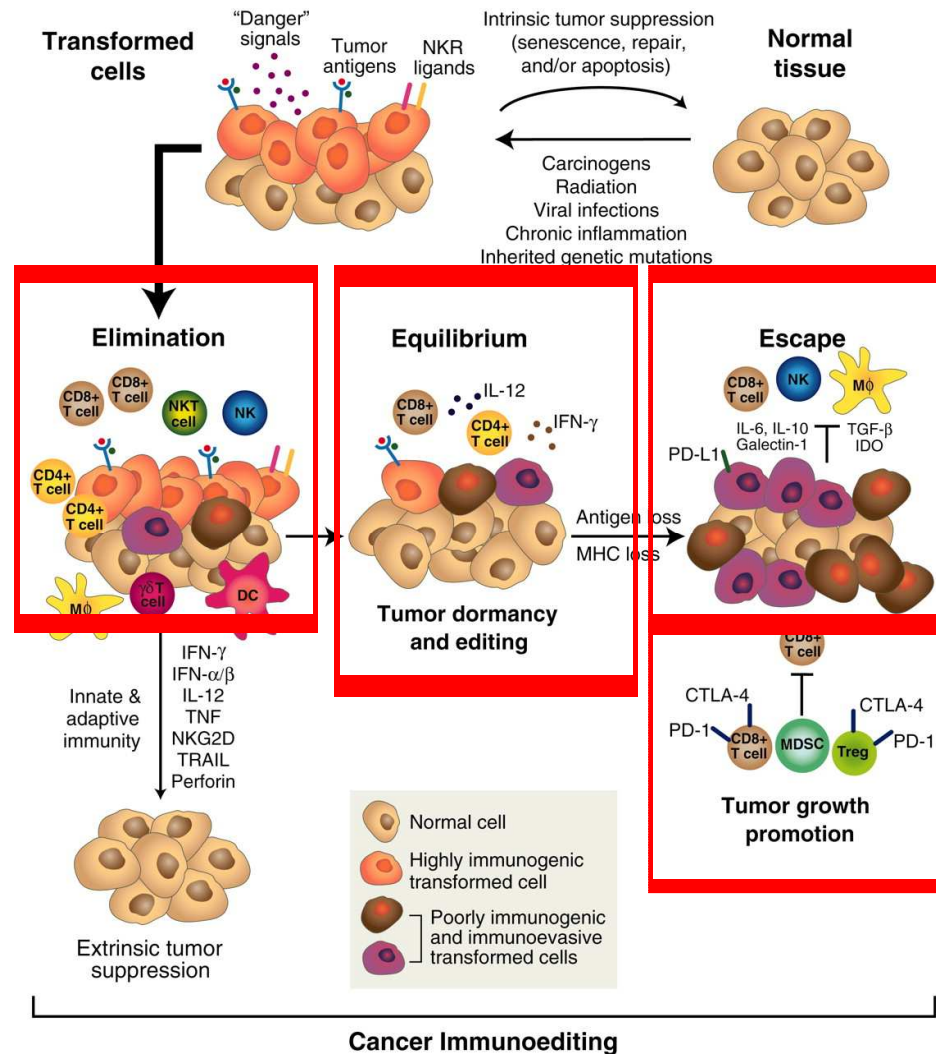
Cancer Immunotherapy Development



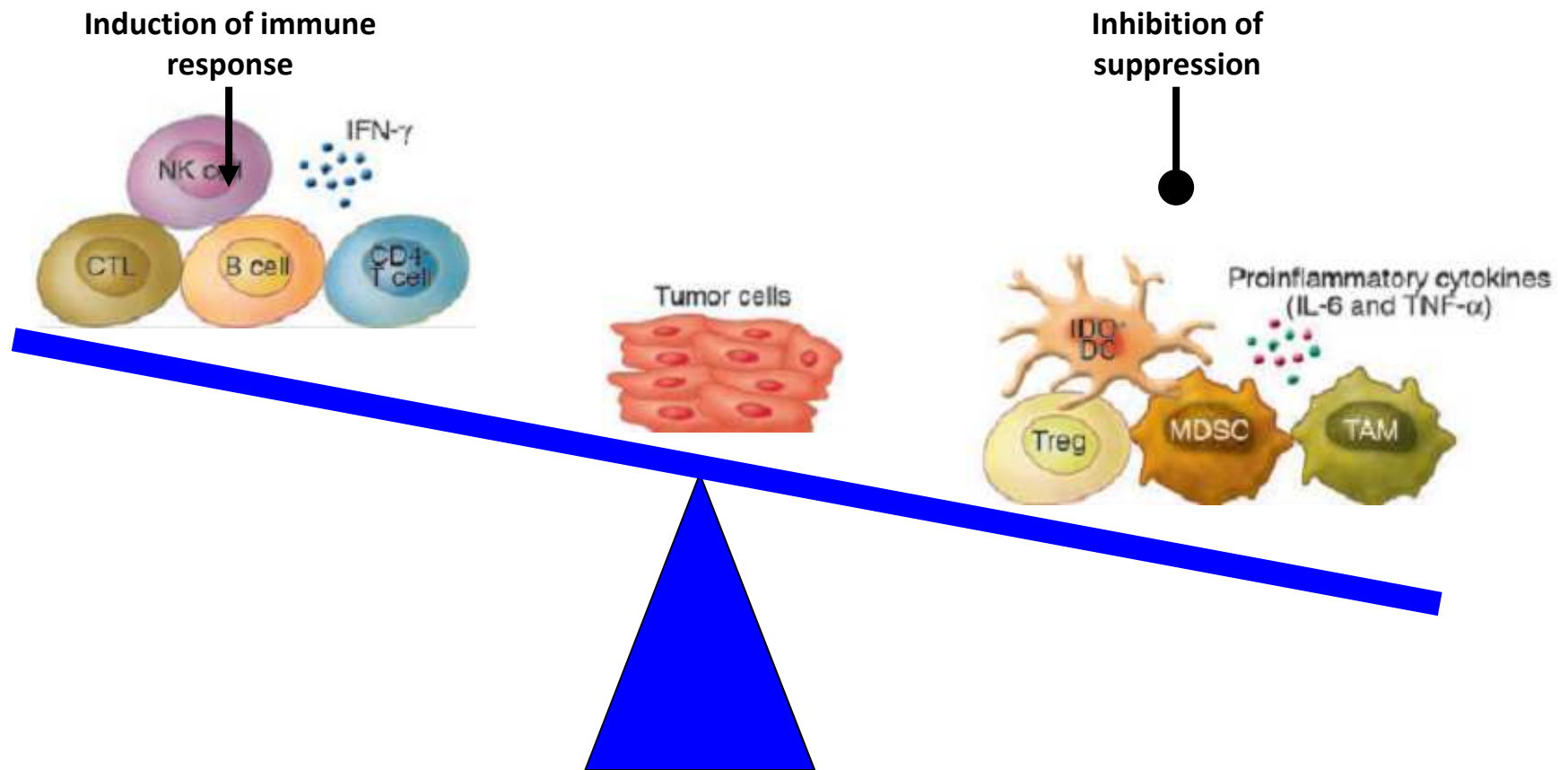
2014

**Approval of
2 anti-PD-1
antibodies
for
advanced
melanoma
and lung
cancer**

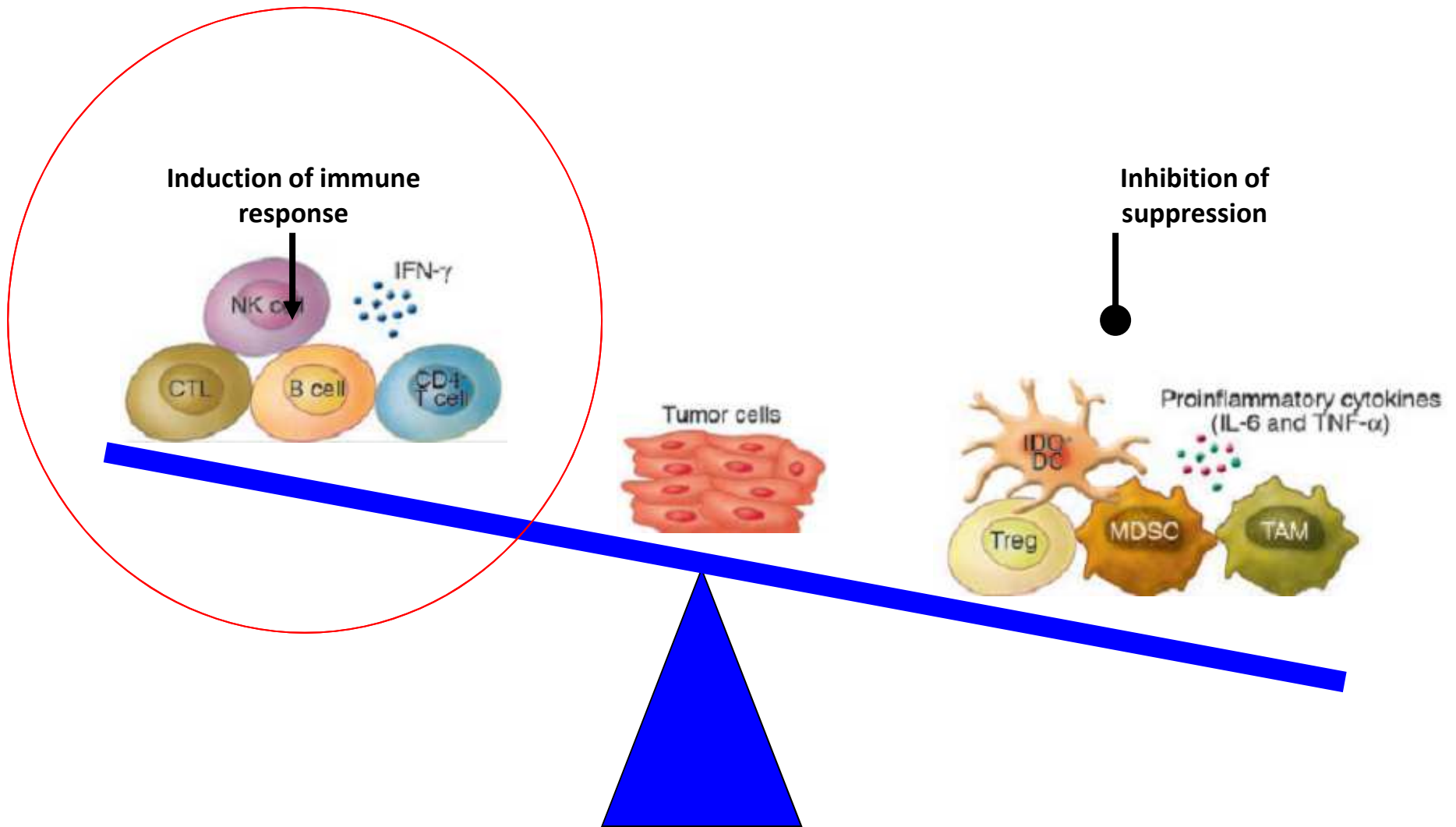
Cancer-Immunity Cycle



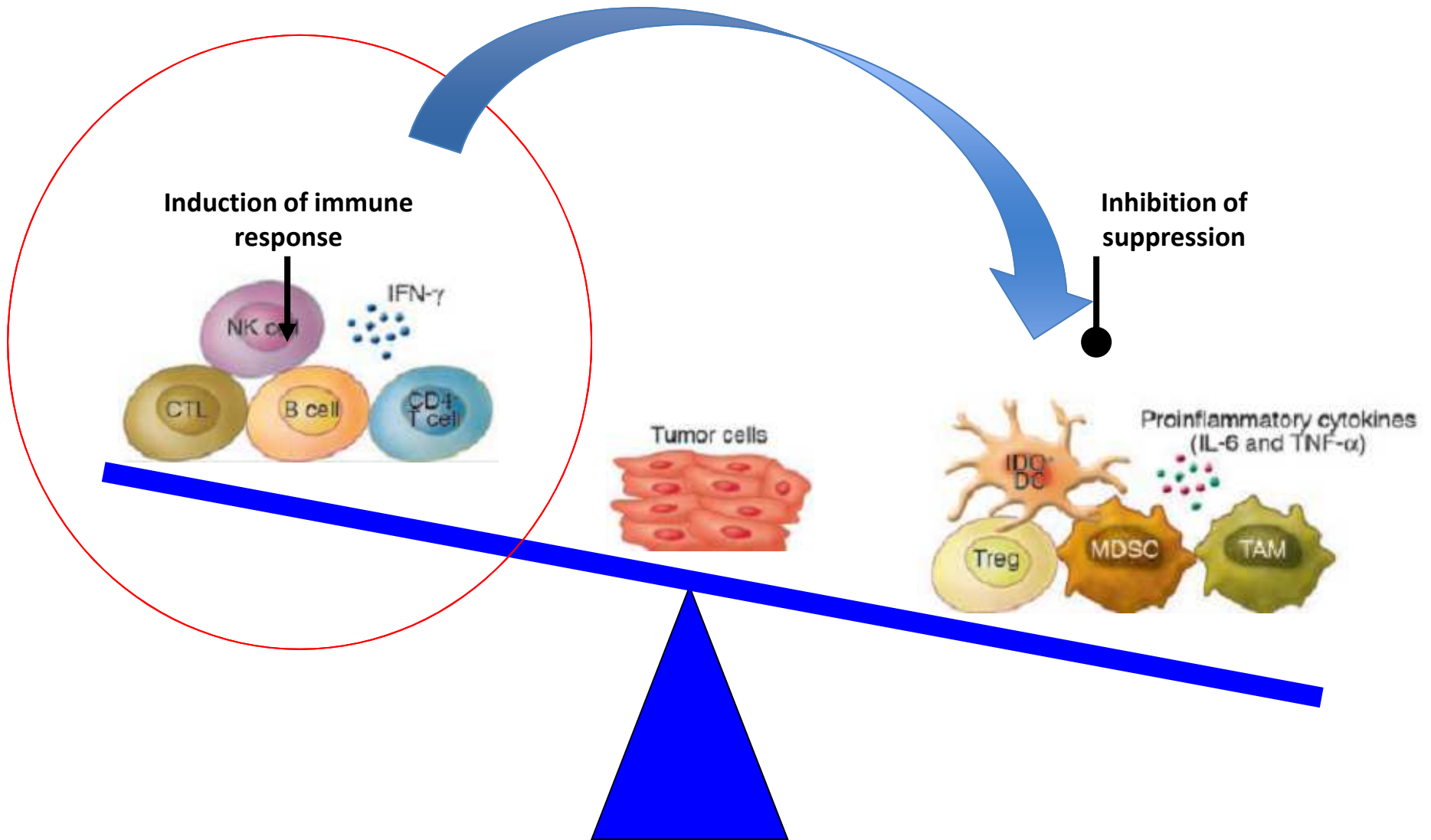
Effective Therapeutic immunebalance



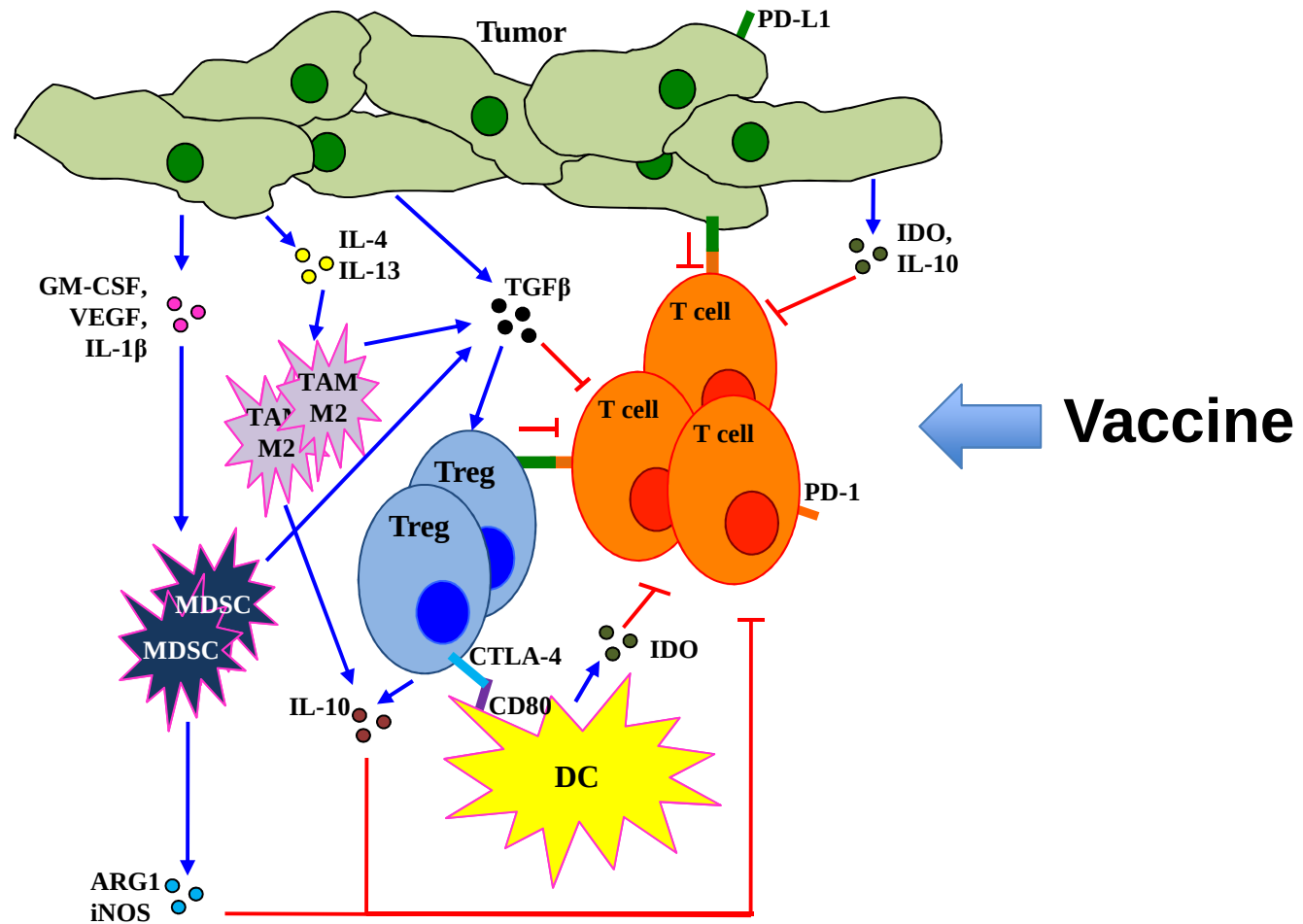
Effective Therapeutic immunebalance



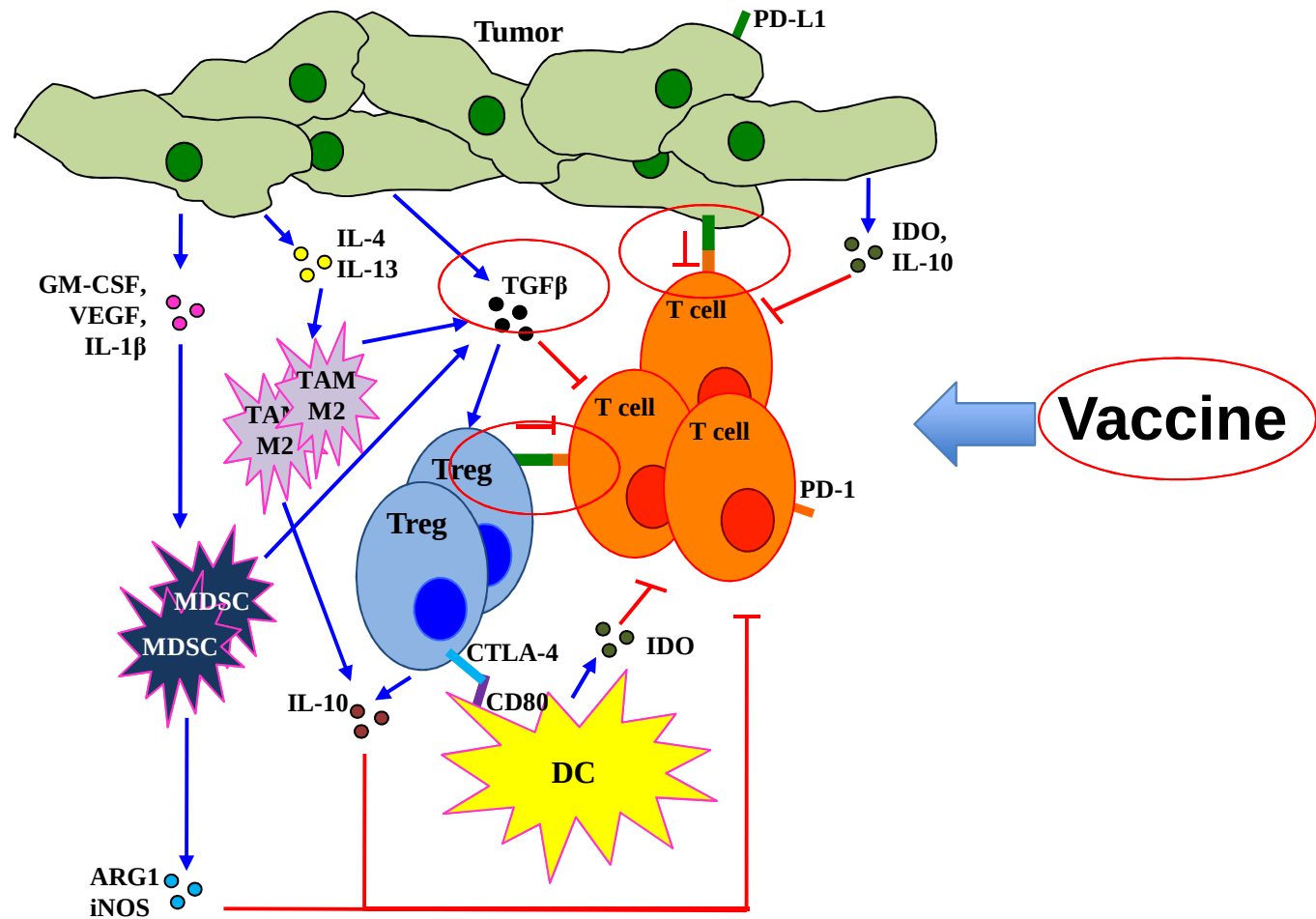
Effective Therapeutic immunebalance



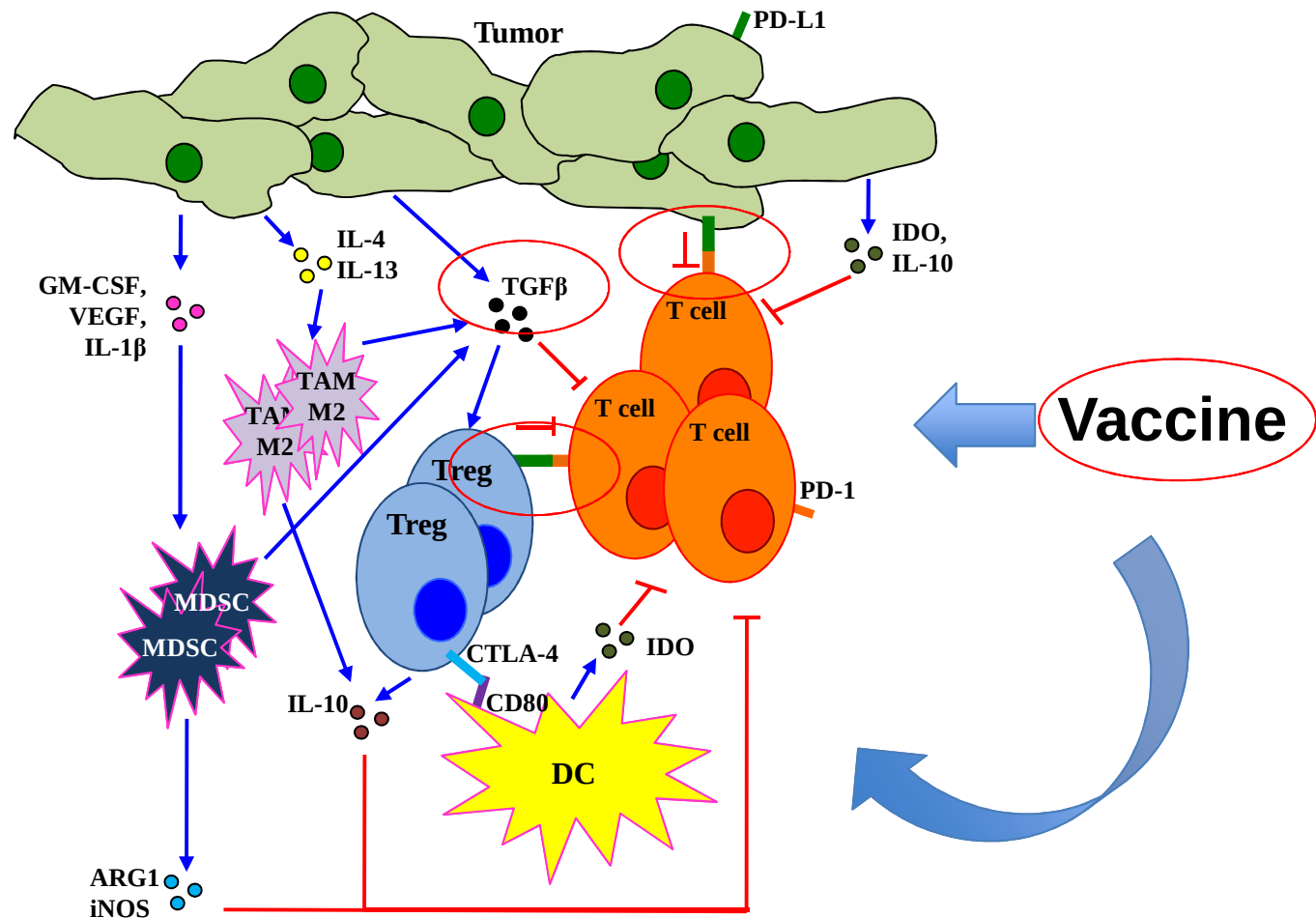
Tumor-Immune Modulatory Network

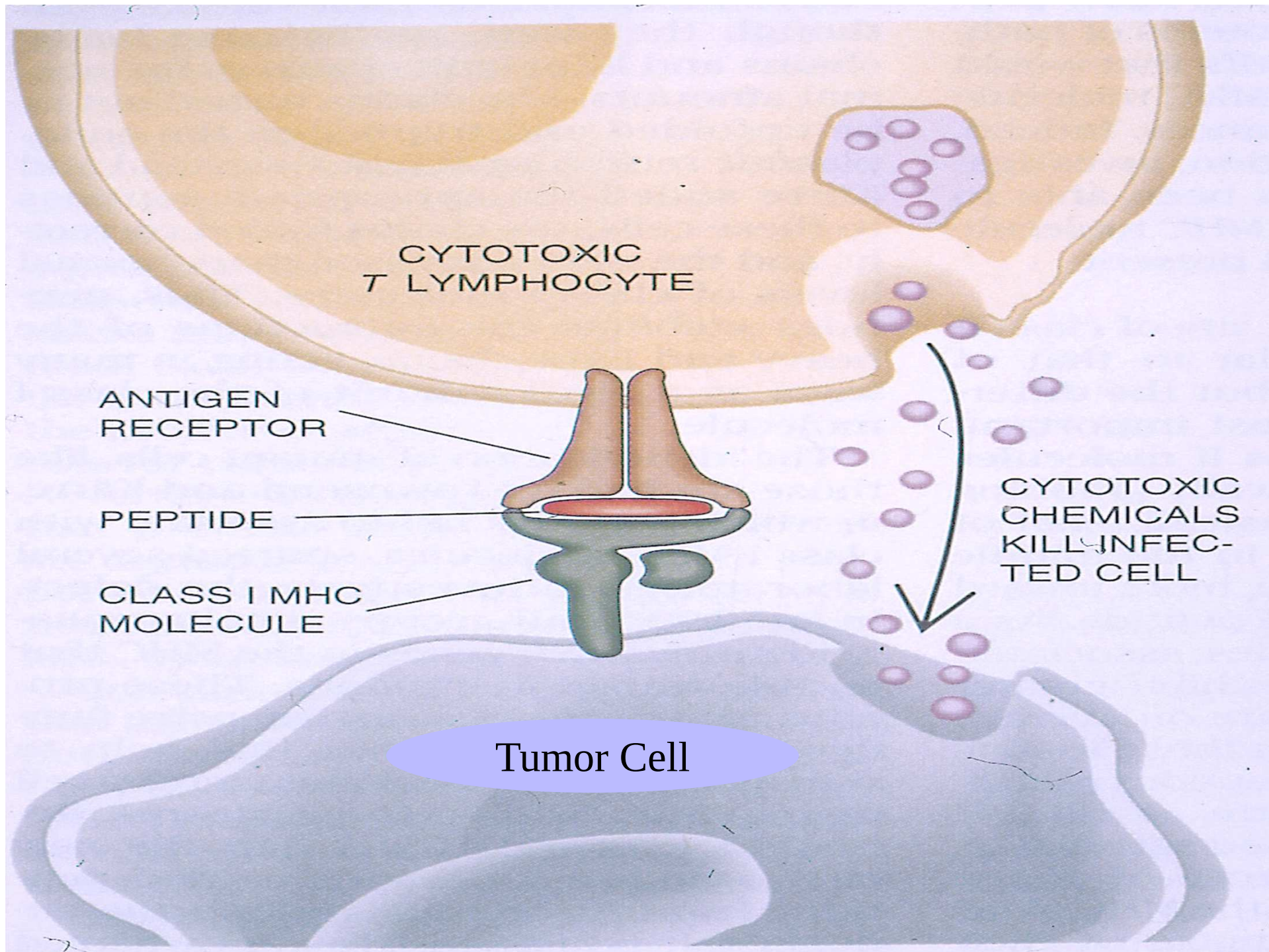


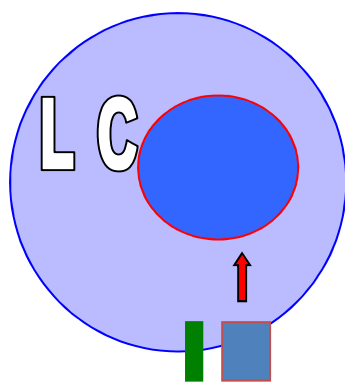
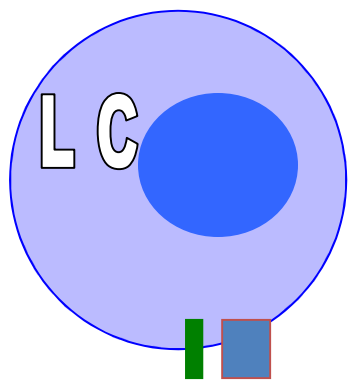
Tumor-Immune Modulatory Network



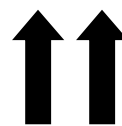
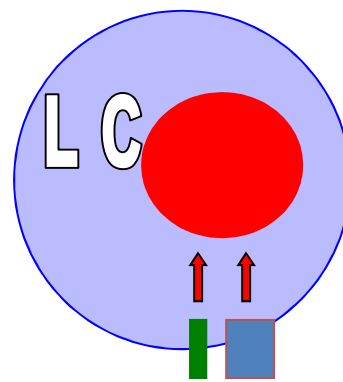
Tumor-Immune Modulatory Network





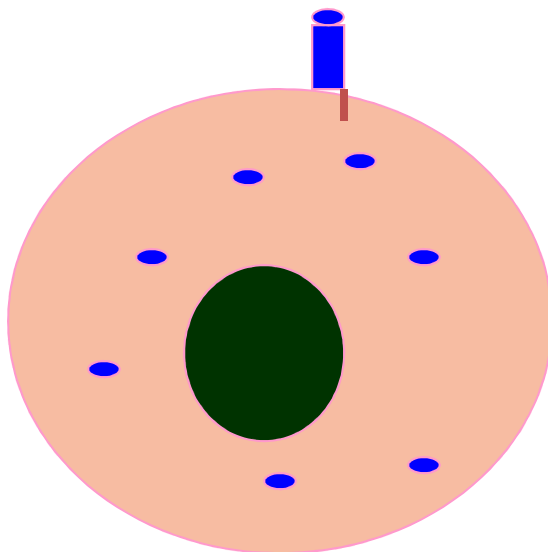


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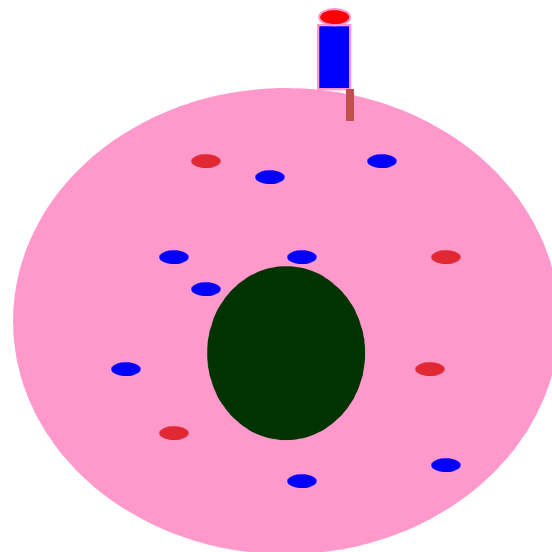


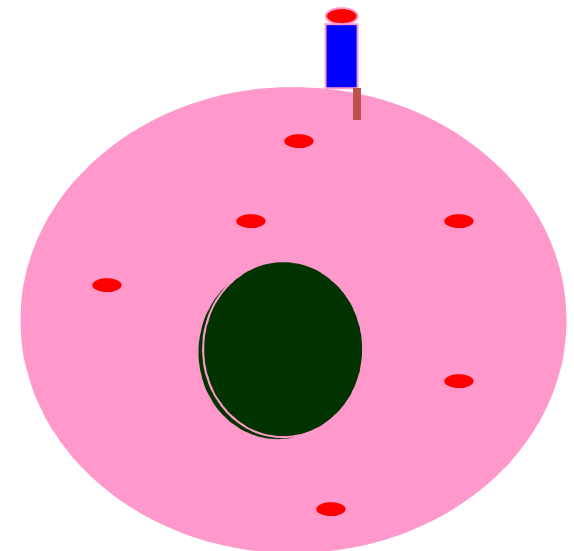
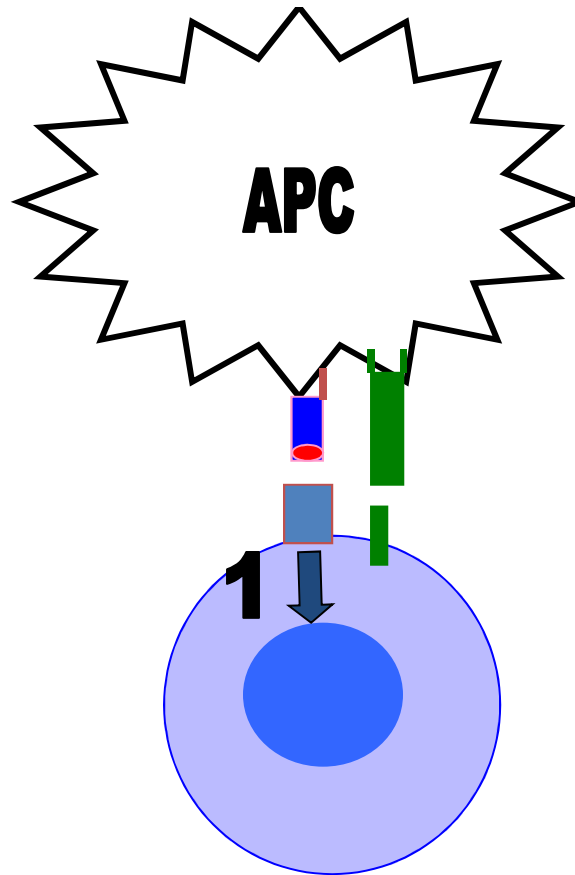
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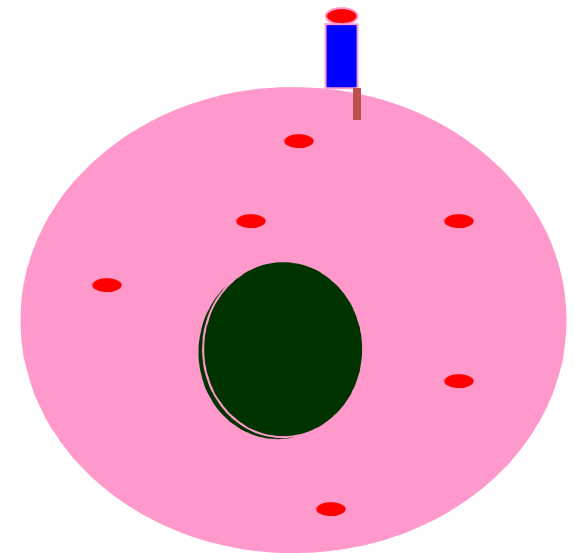
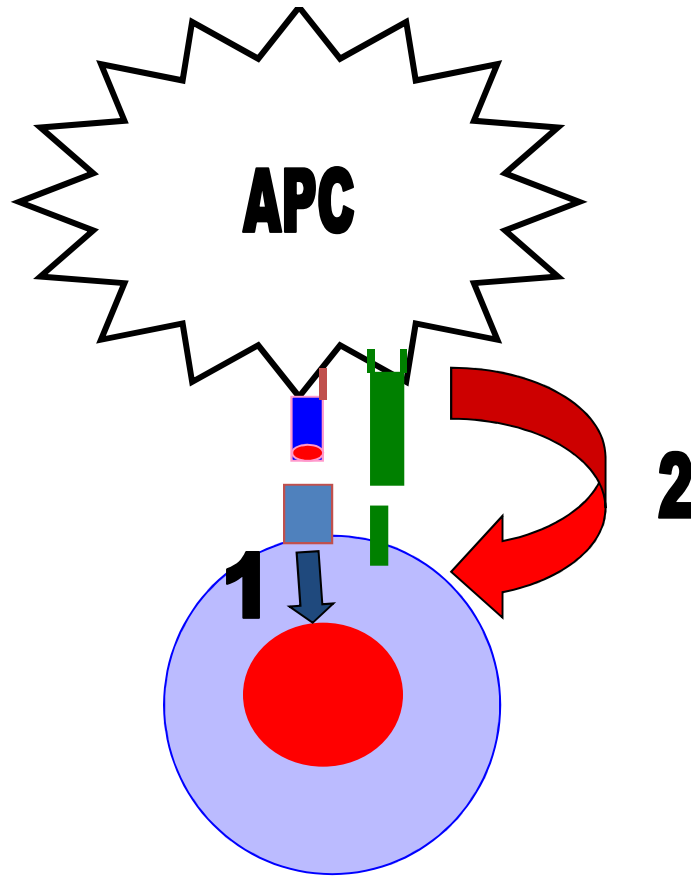
Normal Cell

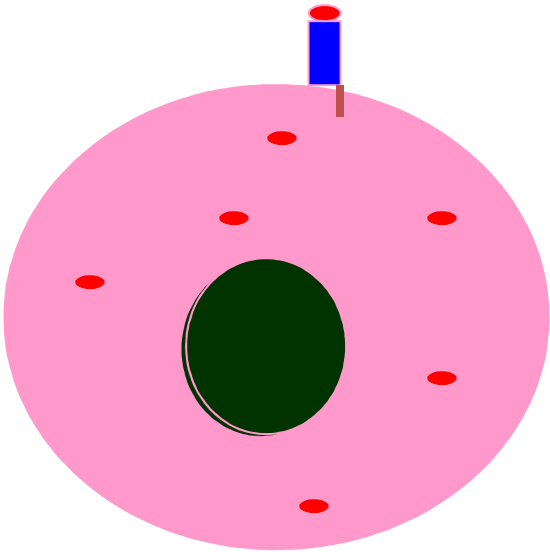
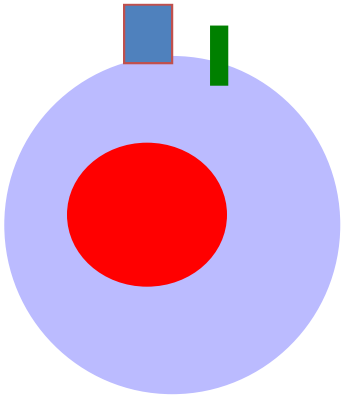
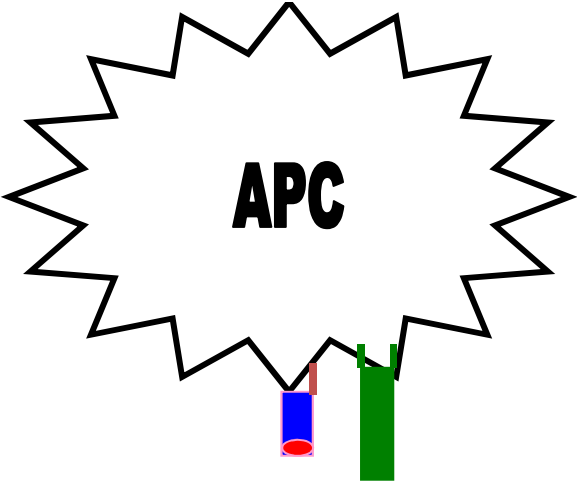


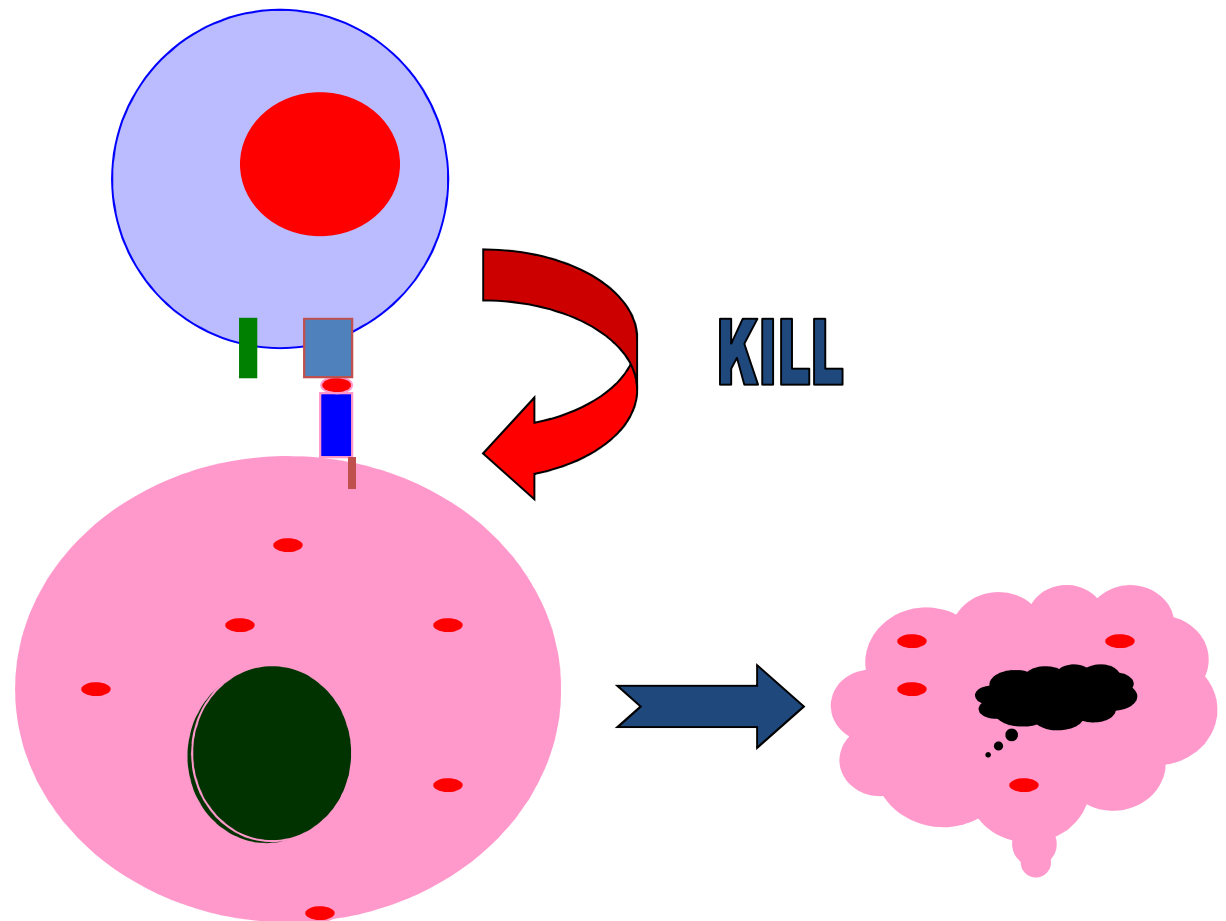
Tumor Cell

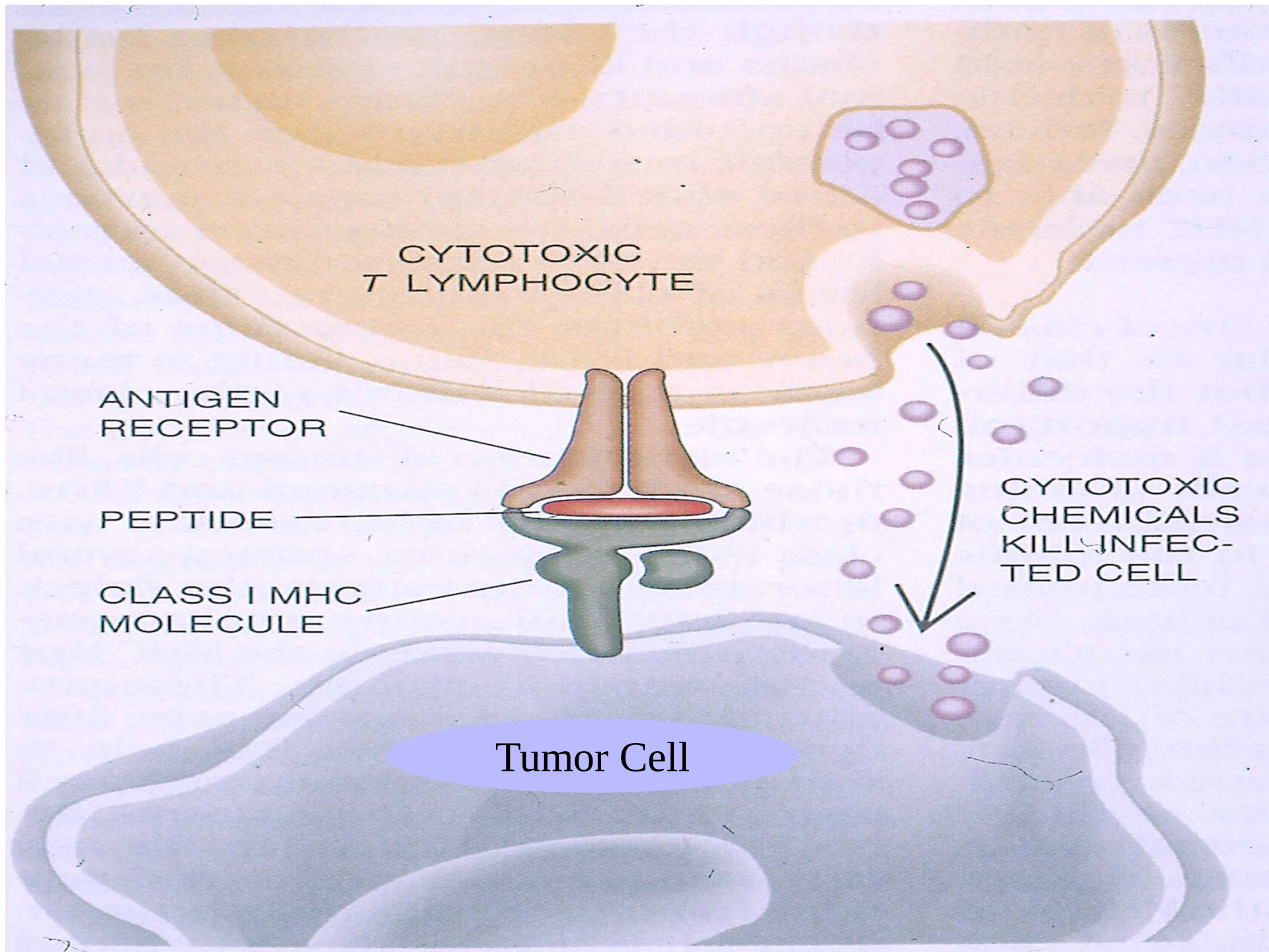


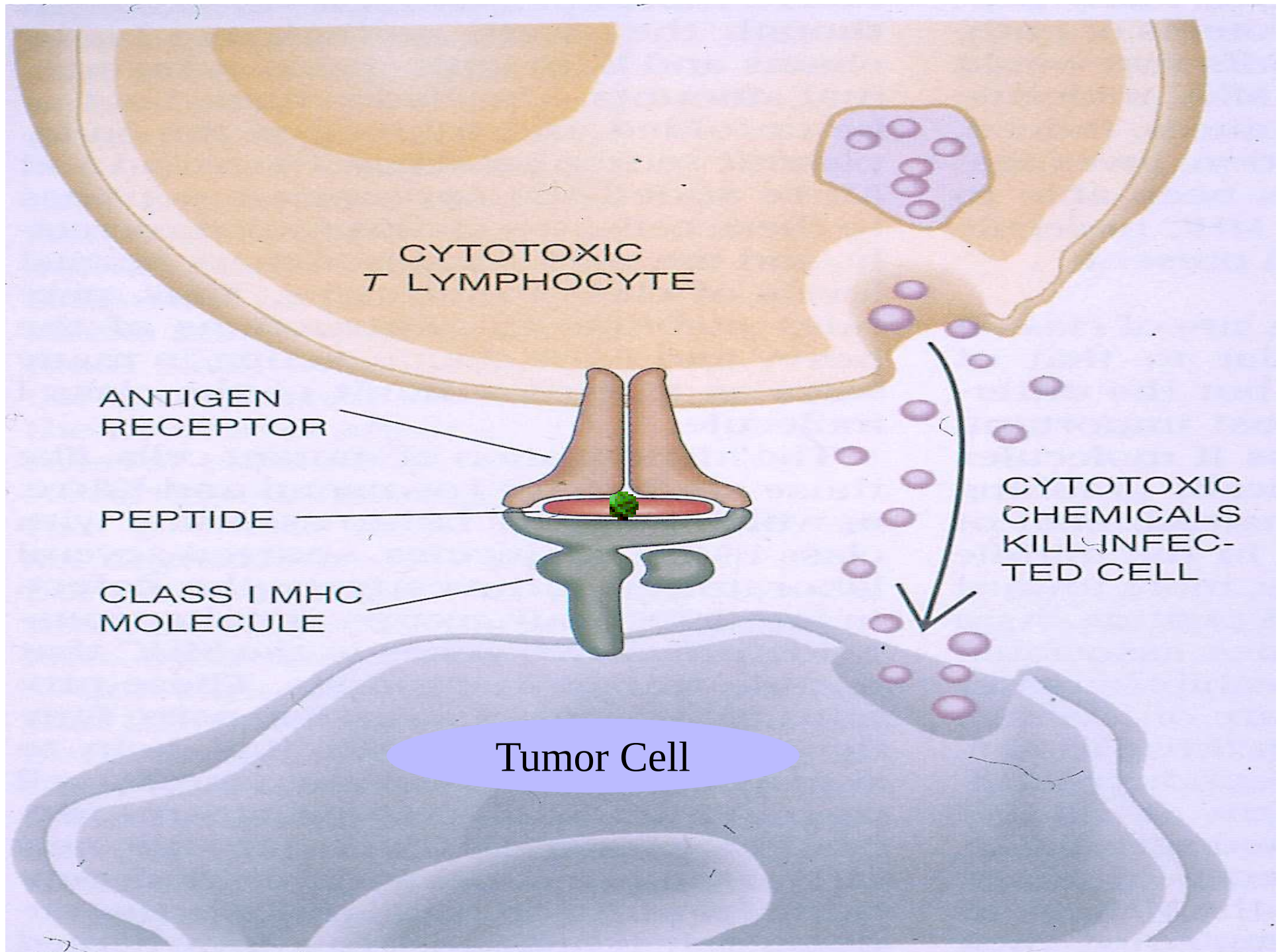




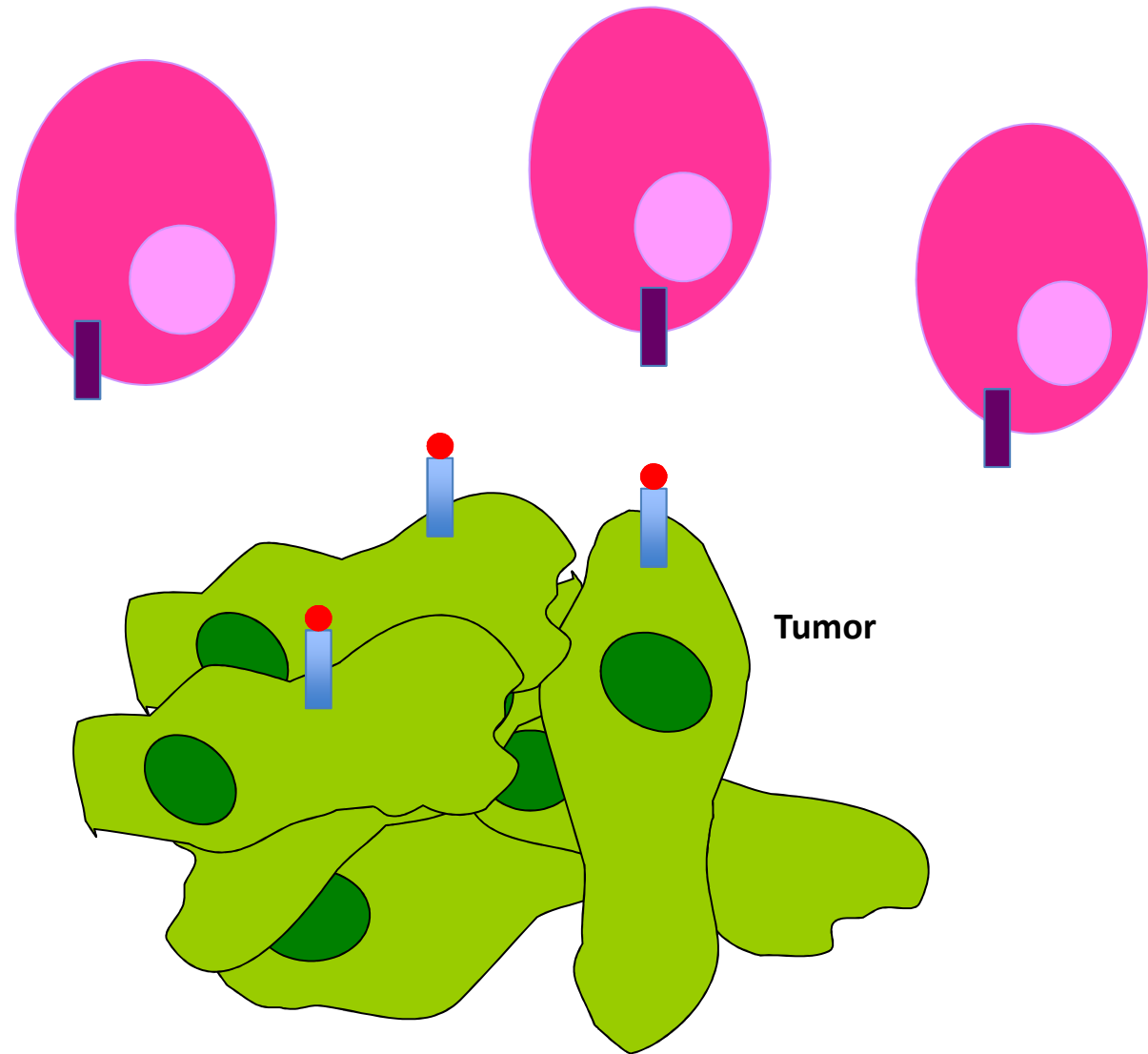




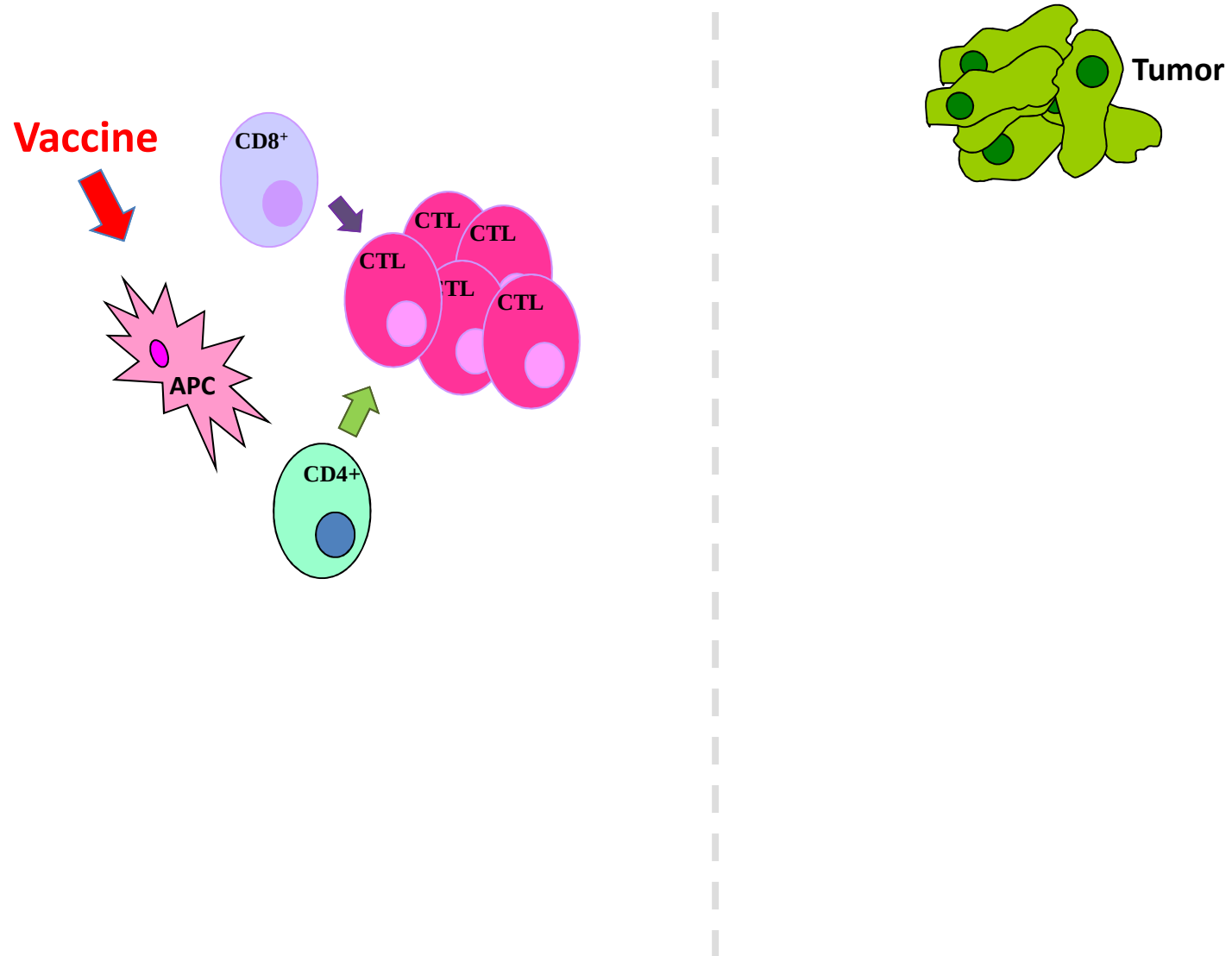


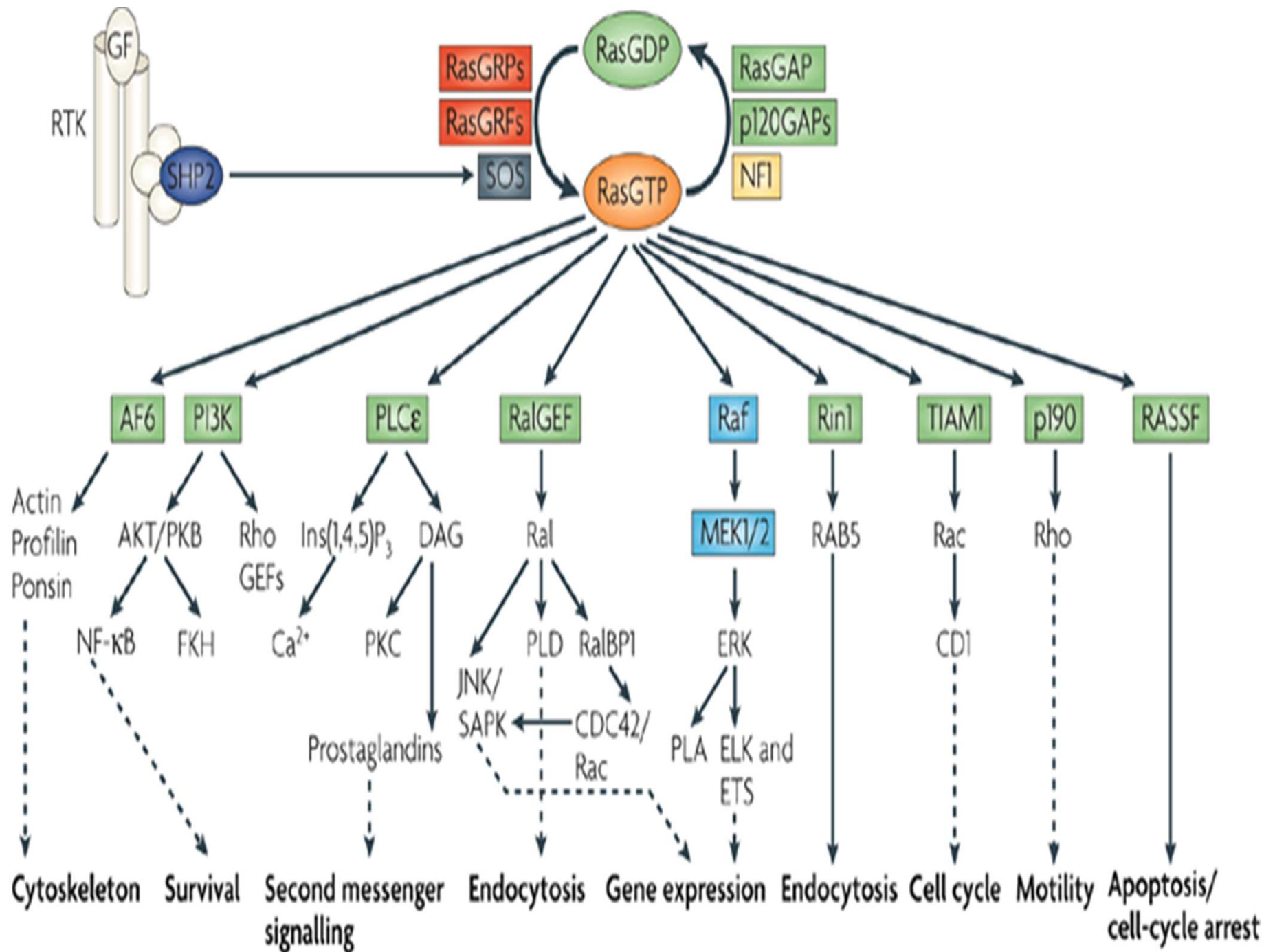


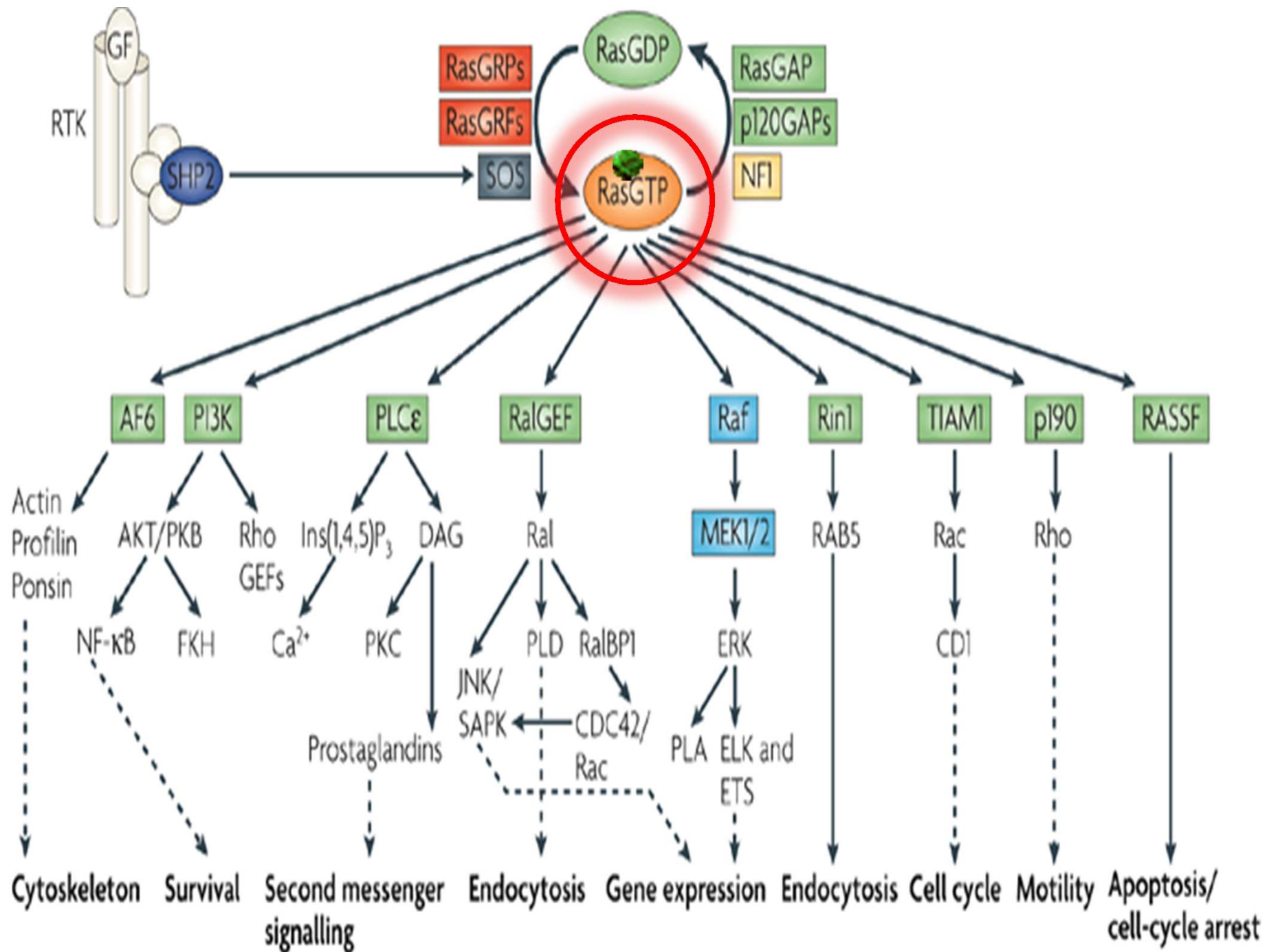
Cancer Vaccine Goal



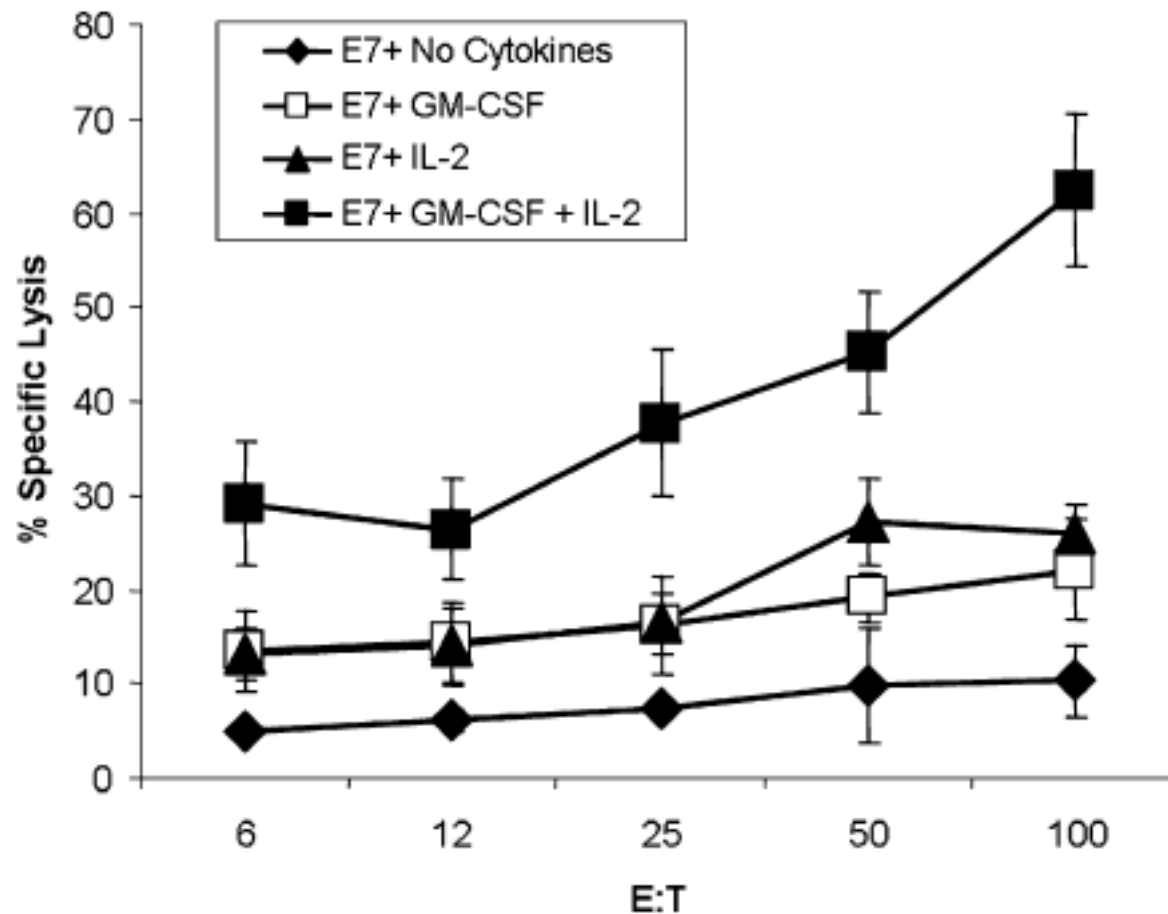
Cancer Vaccine





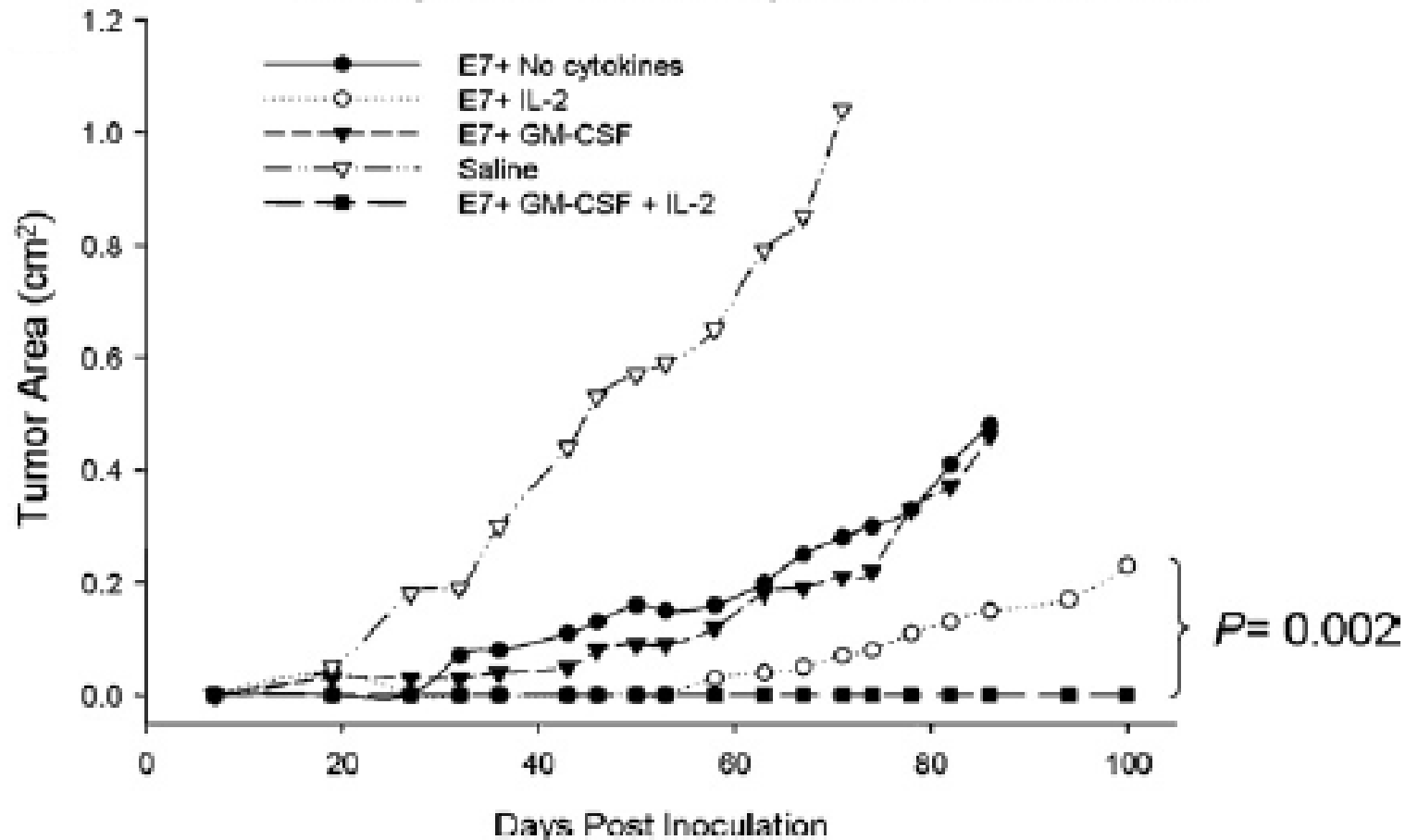


GM-CSF and IL-2 synergize for induction of CTL when combined with vaccine

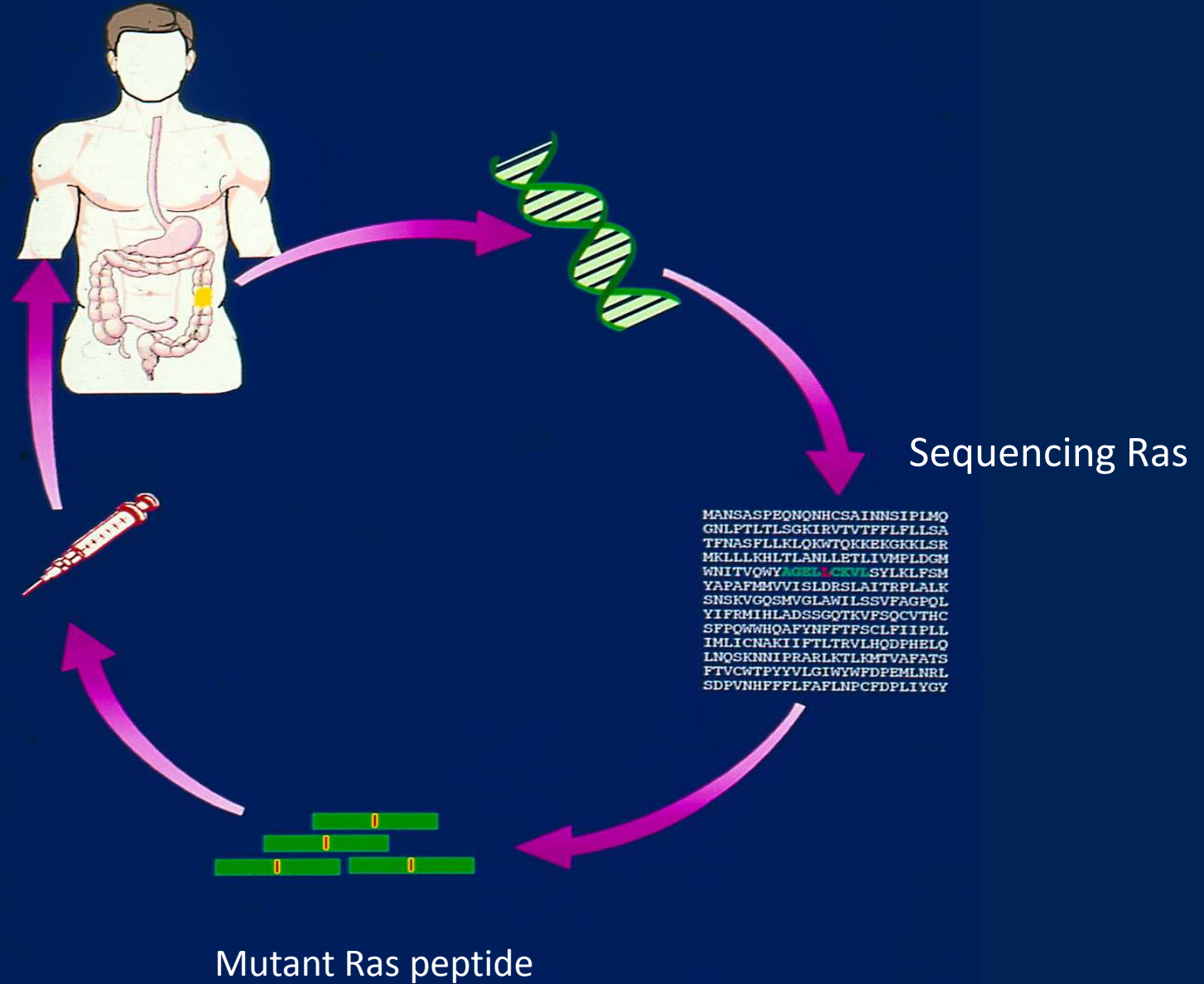


GM-CSF and IL-2 synergize for therapeutic efficacy when combined with vaccine

E7 + Cytokines are Therapeutic for TC-1 Tumors



Solid tumor with Ras mutation

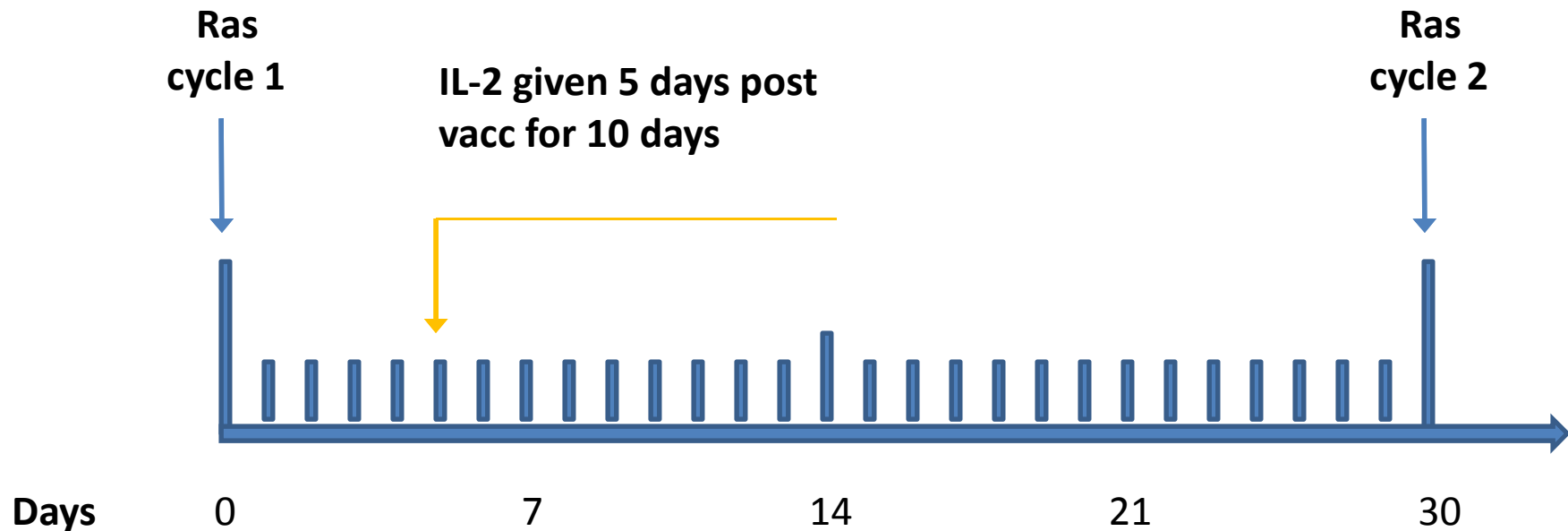


**Phase II Trial with Tumor Specific
Mutated ras Peptides and IL-2,
GM-CSF, or both for Adult
Patients with Solid Tumors**

Eligibility

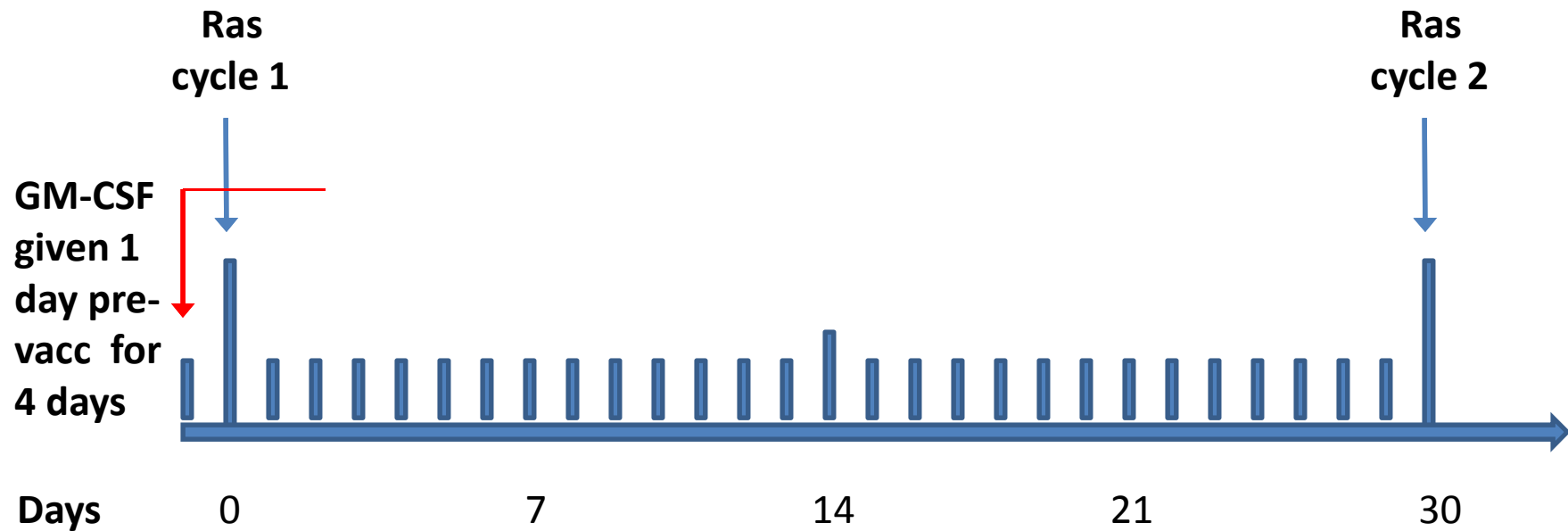
- **Ras Mutation: Gly to Cys, Asp, or Val**
- **Metastatic disease except CNS metastasis**
- **Failed prior treatment**

Vaccination Schedule Arm A



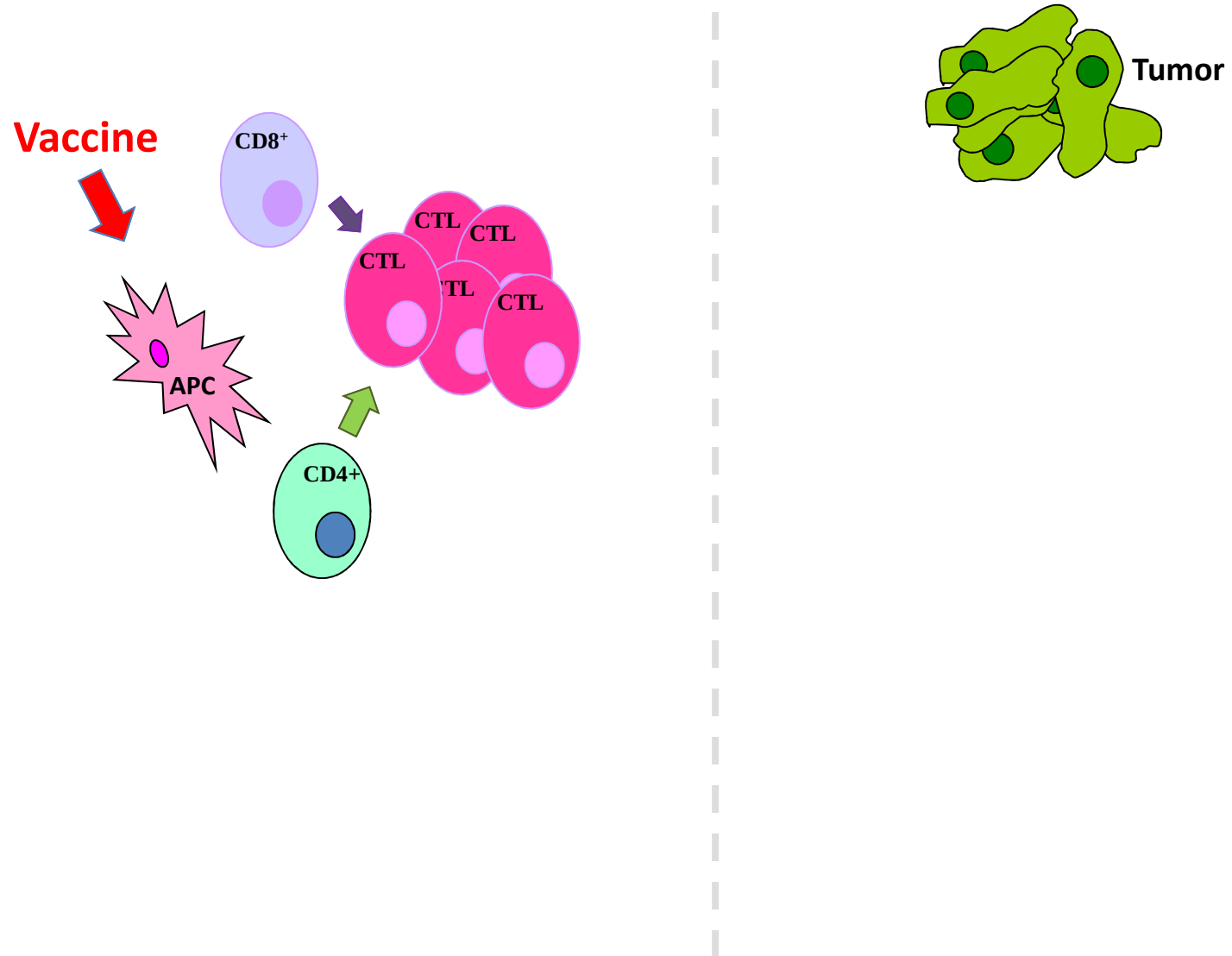
If SD, continue vaccination up to 15 cycles

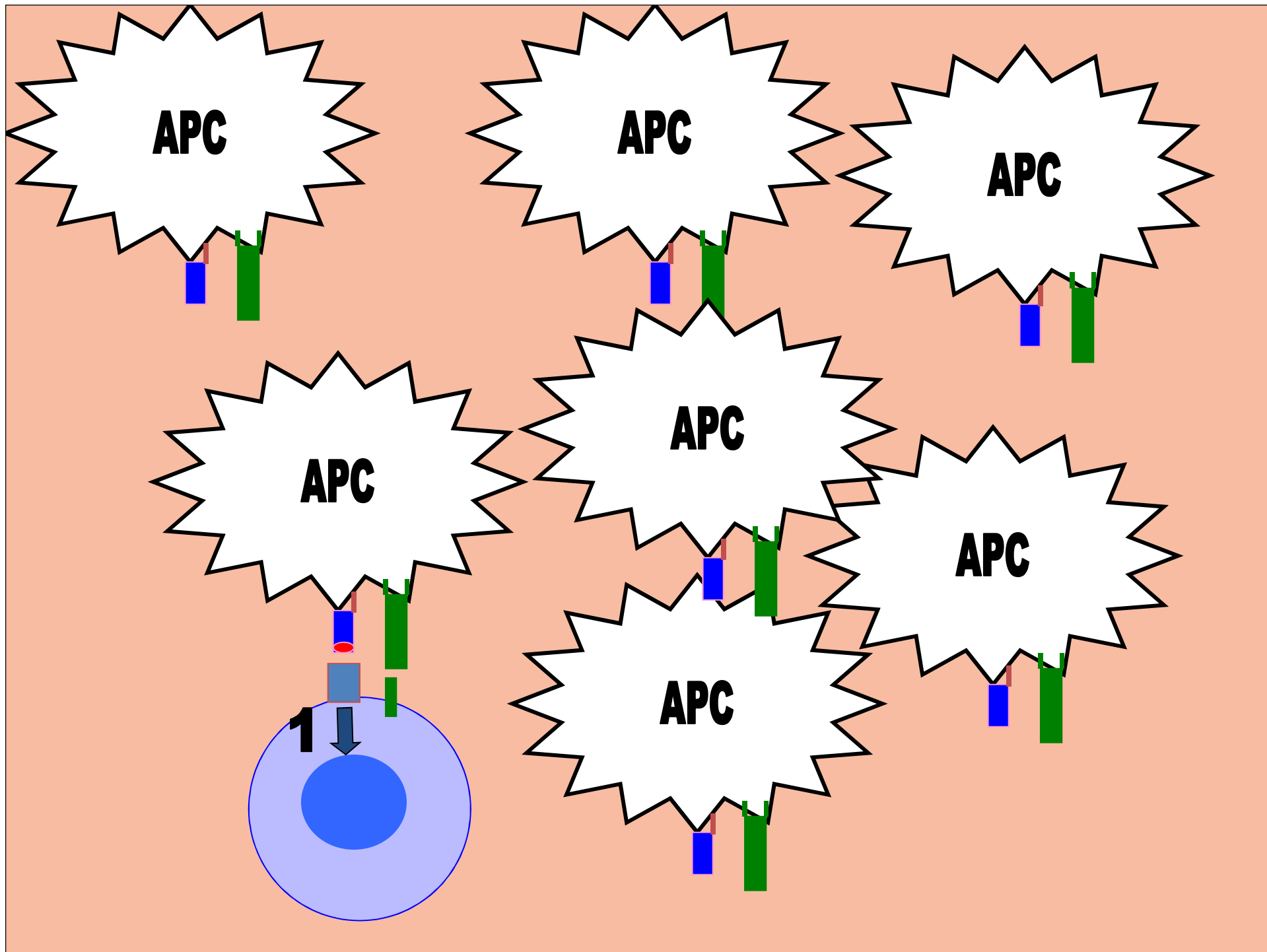
Vaccination Schedule Arm B



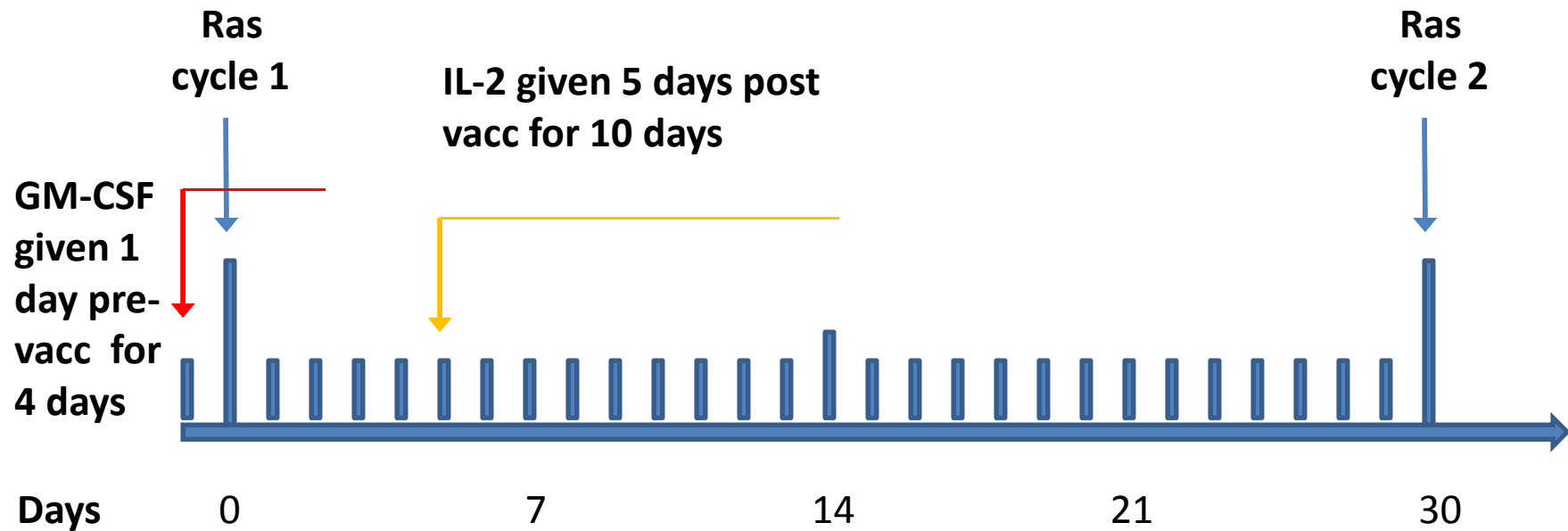
If SD, continue vaccination up to 15 cycles

Cancer Vaccine

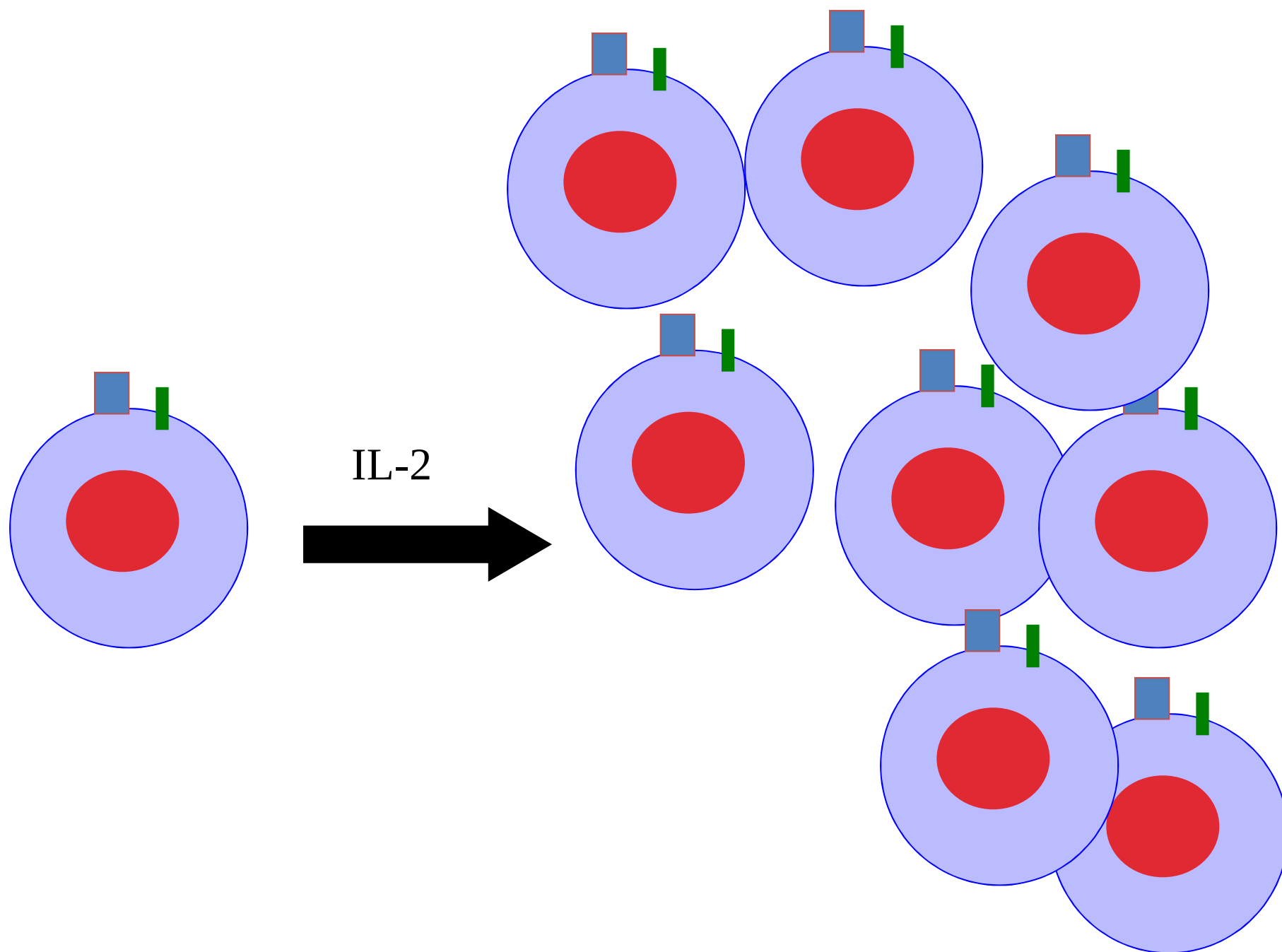




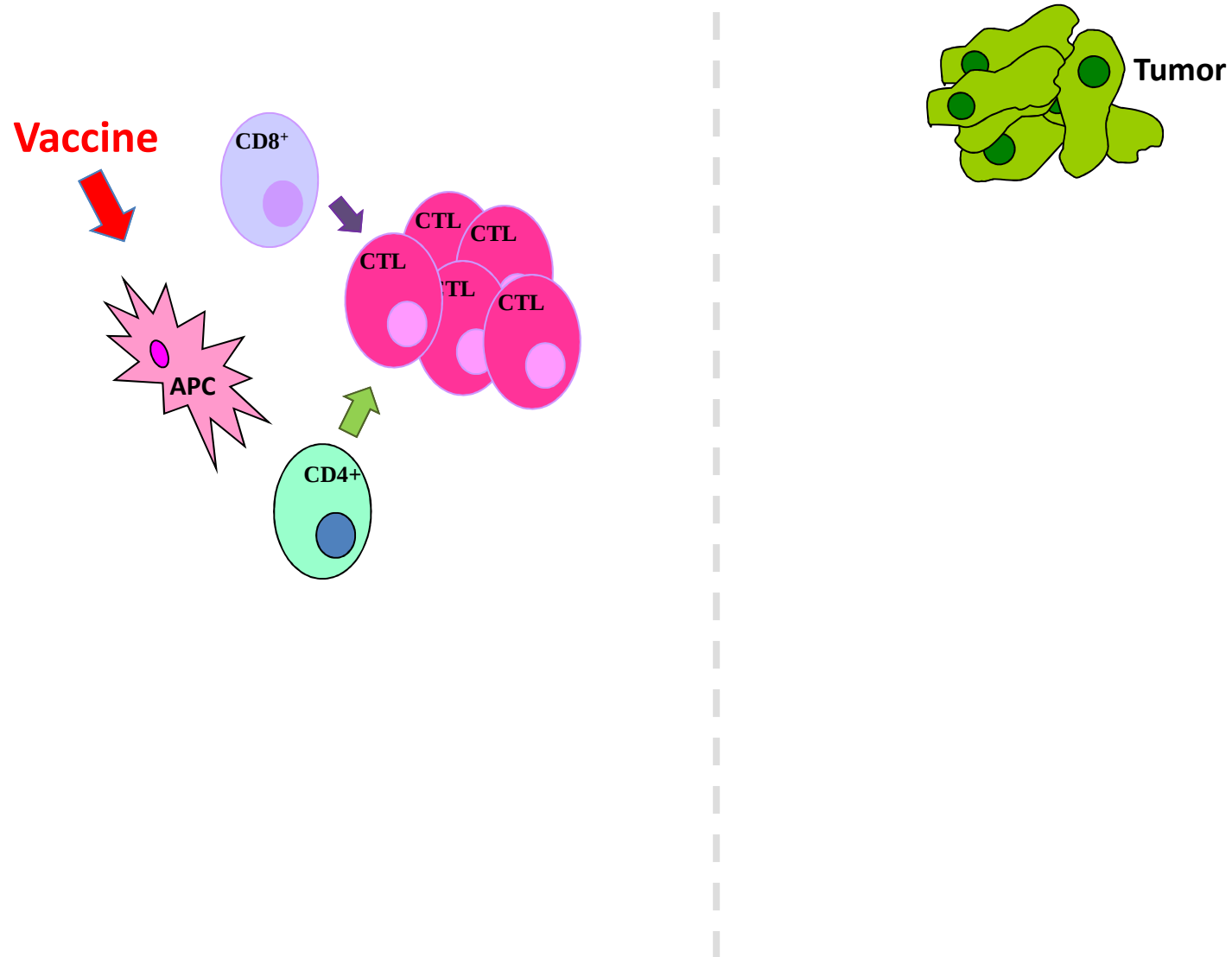
Vaccination Schedule Arm C

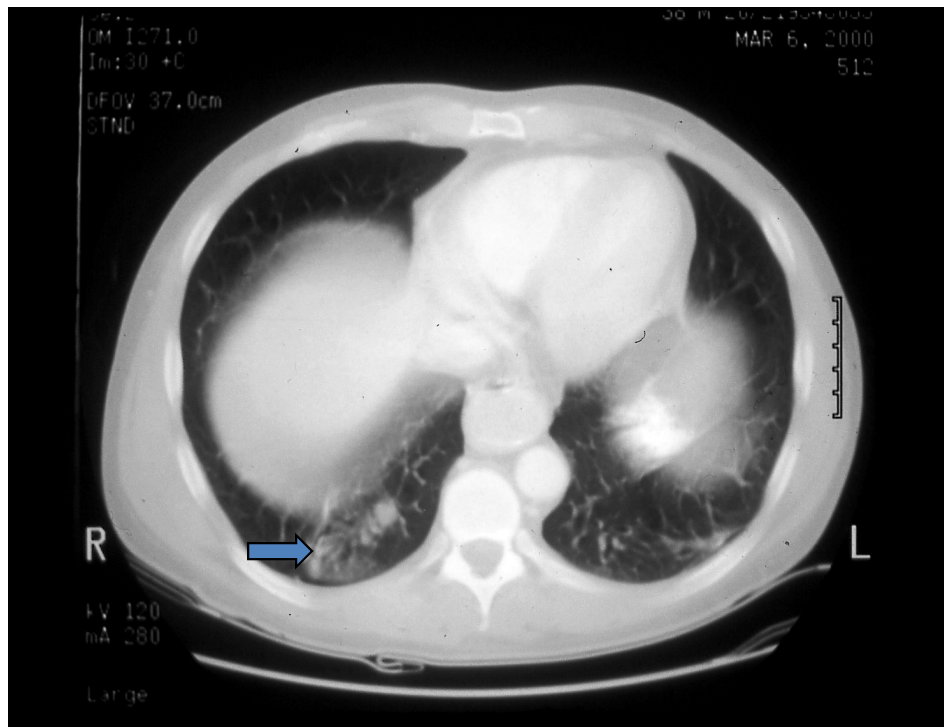


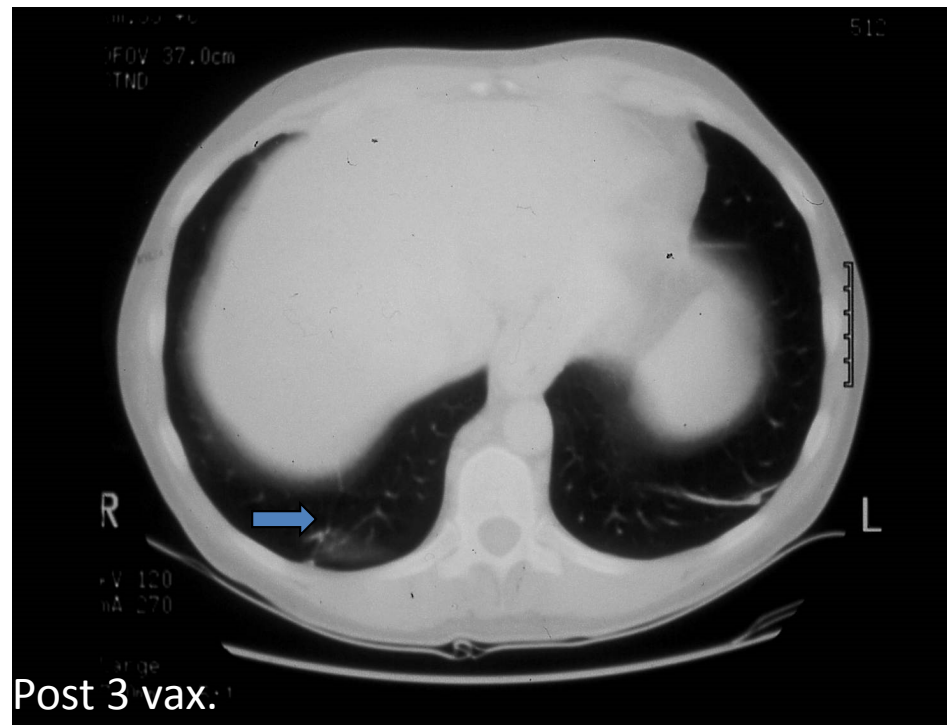
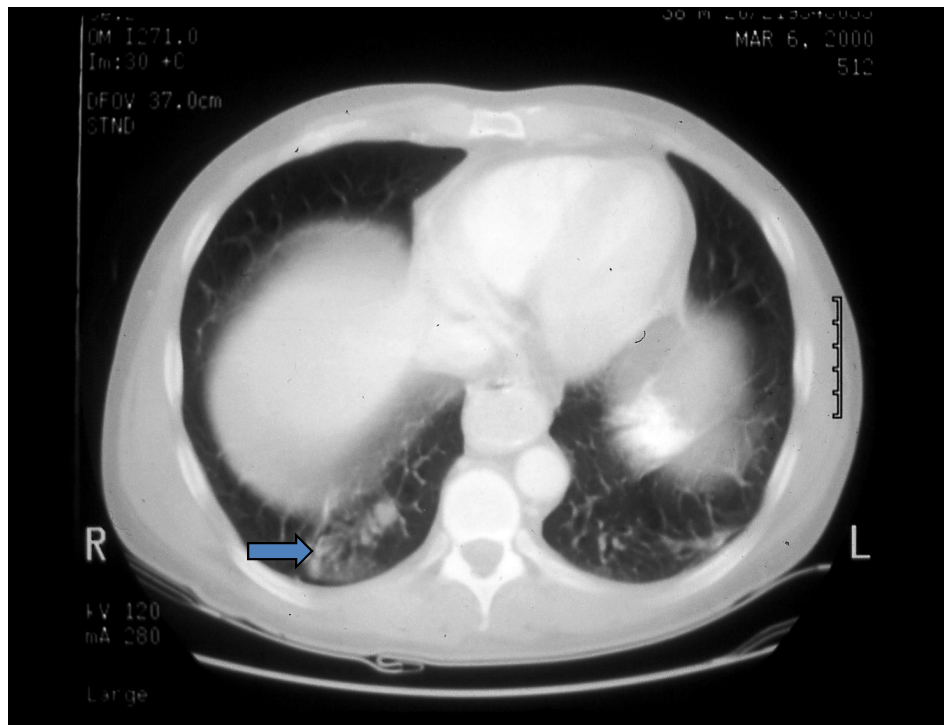
If SD continue vaccination up to 15 cycles

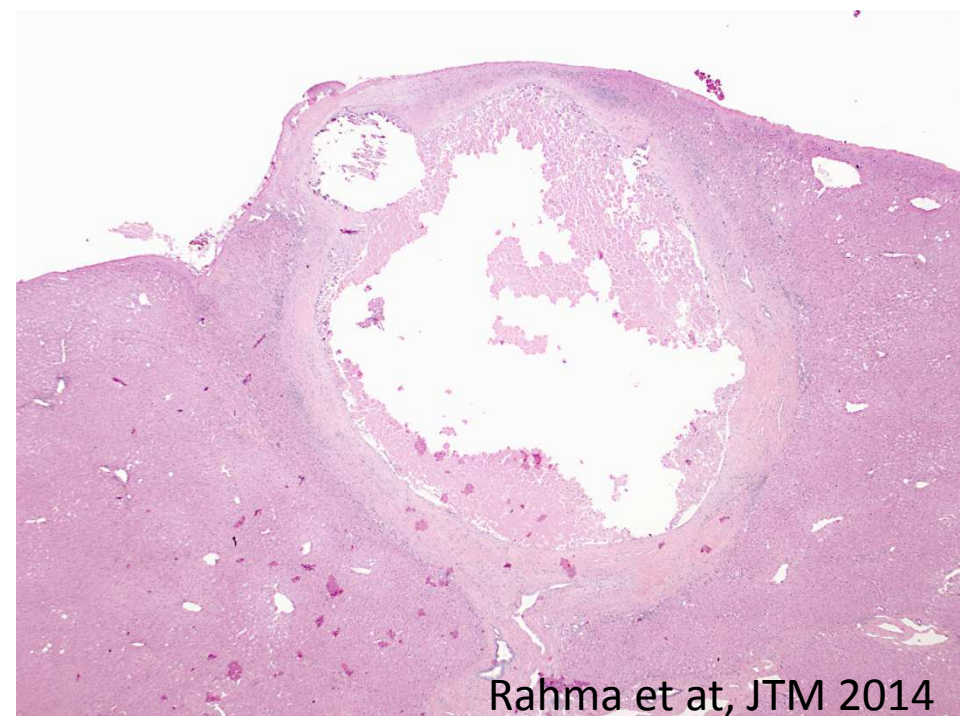
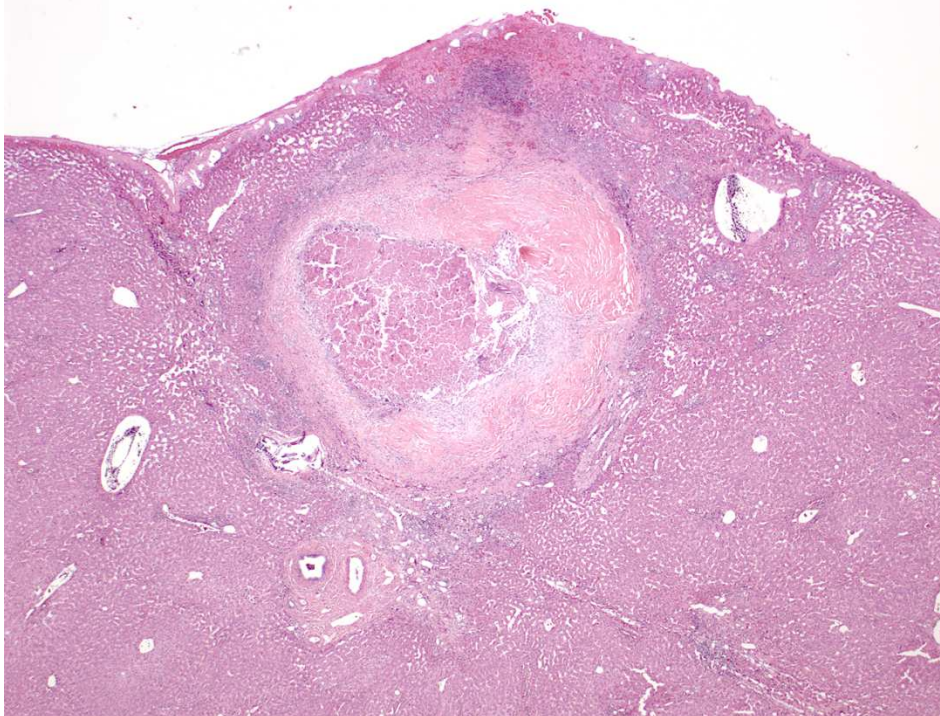
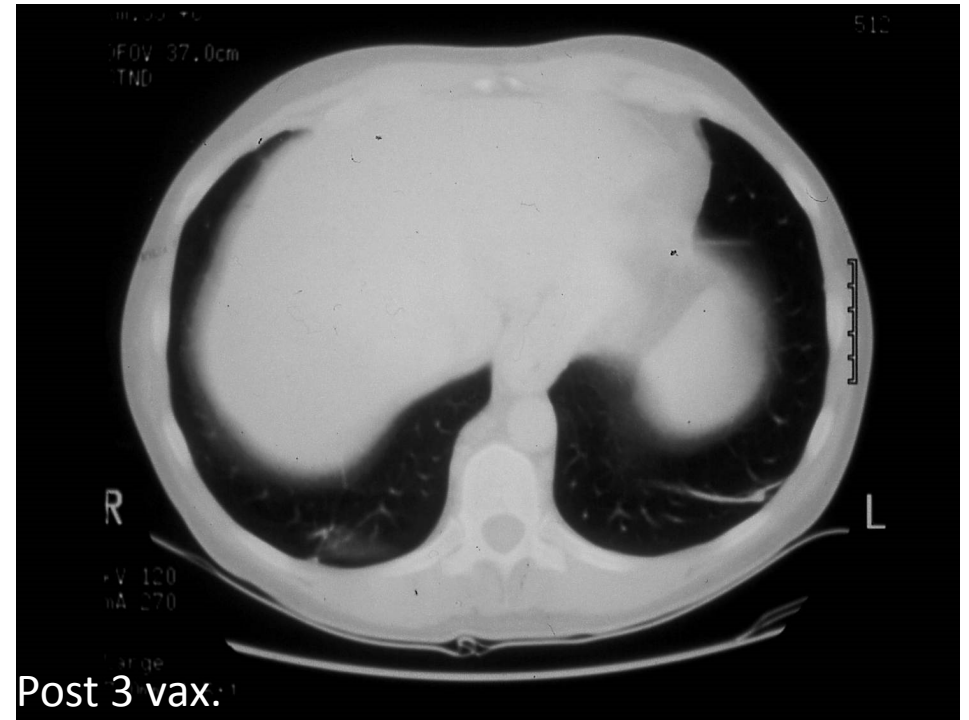
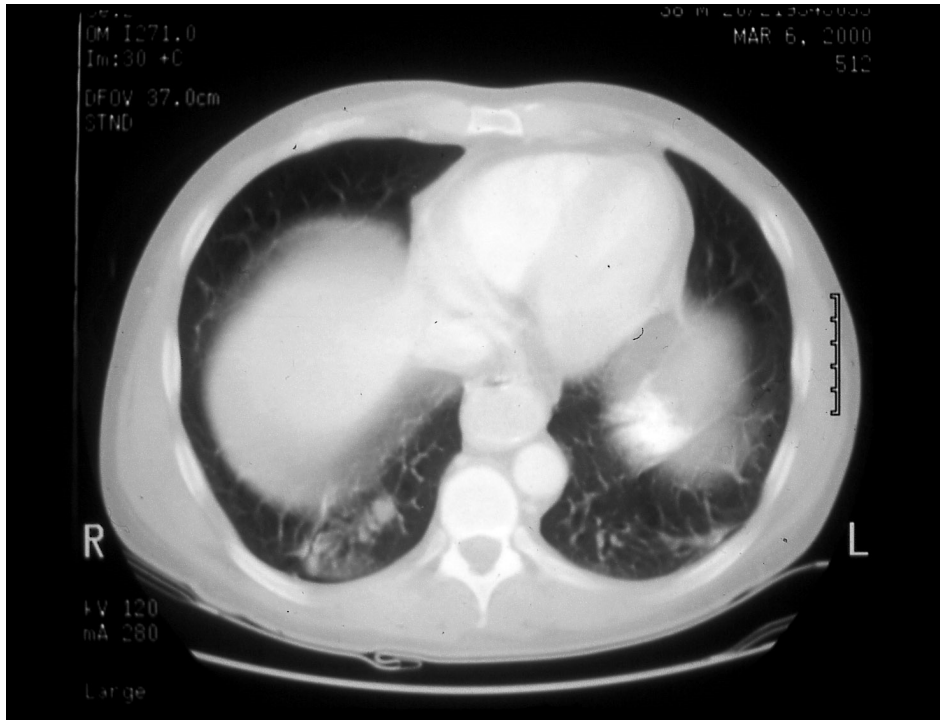


Cancer Vaccine









Patient Profile Arm A: IL-2

Age	Cancer	Mutation	Pre-vaccination Therapy	Stage on Enrollment	Disease extension on enrollment
56	Colon	ASP	Sx1, Cx3	IV	Liver, Lung, Para-aortic LN
57	Colon	ASP	Sx2, Cx2	IV	Lung
62	Colon	ASP	Sx1, Cx3, Rx1	IV	Lung
50	Pancreatic	ASP	Sx1, Cx2	IV	Pancreas, Liver, Adrenals, Omentum, Peritoneum, Infradiaphragmatic LN
60	Lung	VAL	Cx2, Rx1	IV	Chest Wall
59	Colon	VAL	Cx2	IV	Liver
52	Colon	CYS	Sx2, Cx2	NED	NED
68	Lung	CYS	Sx1, Cx5, Rx2	IV	Lung, Hilar Adenopathy
56	Colon	ASP	Sx2, Cx3, Rx2	NED	NED
63	Colon	ASP	Sx3, Cx3	IV	Liver, Lung
42	Pancreatic	ASP	Sx2, Cx1	NED	NED
39	Colon	ASP	Sx1, Cx1	NED	NED
67	Colon	CYS	Sx1, Cx2	IV	Liver
51	Colon	ASP	Sx2, Cx1	NED	NED
60	Pancreatic	VAL	Sx1, Cx4, Rx1	IV	Liver
61	Colon	ASP	Sx1, Cx3	IV	Liver, Lung

Patient Profile Arm B: GM-CSF

Age	Cancer	Mutation	Pre-vaccination Therapy	Stage on Enrollment	Disease extension on enrollment
55	Biliary	VAL	Sx2, Cx2, Rx1	NED	NED
33	Colon	CYS	Sx1, Cx2	IV	Liver
51	Colon	ASP	Sx1, C1	IV	Liver
48	Pancreatic	ASP	Cx1, Rx1	NED	NED
51	Colon	ASP	Sx1, Cx6	IV	Liver, Lung
38	Colon	ASP	Sx1, Cx2, Rx1	IV	Liver, Lung, Spleen, Abd Wall
60	Pancreatic	VAL	Sx1, Cx1, Rx1	IV	Gastric Wall
57	Colon	ASP	Sx4, Cx6	IV	Transverse Colon, Liver
52	Colon	ASP	Sx4, Cx1	IV	Lung
58	Pancreatic	ASP	Sx1, Cx3	IV	Pancreas, Liver, Lung
45	Pancreatic	VAL	Sx1, Cx2	IV	Liver
79	Colon	VAL	Sx4, Cx5	IV	Lung, Mediastinal LN
43	Colon	CYS	Sx3, Cx2	IV	Liver, Lung, Pelvis
78	Colon	ASP	Sx2, Cx1, Rx1	NED	NED
63	Colon	ASP	S1, Cx1	IV	Omentum, Liver, Lung
64	Colon	ASP	Sx1, Cx1	IV	Liver, Lung
71	Colon	VAL	Sx2, Cx4	IV	Liver, Lung
58	Pancreatic	VAL	Cx2	IV	Pancreas, Lung

Patient Profile Arm C: IL-2 + GM-CSF

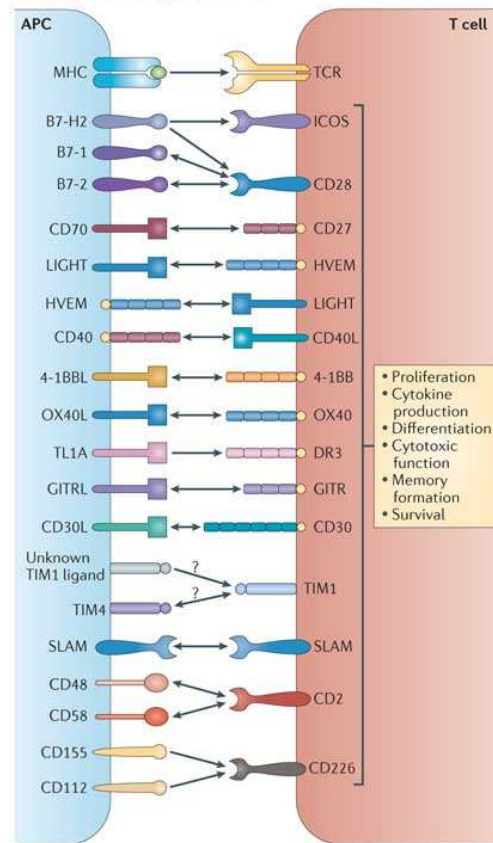
Age	Cancer	Mutation	Pre-vaccination Therapy	Stage on Enrollment	Disease extension on enrollment
40	Rectal	ASP	Sx2, Cx2, Rx1	IV	Lung
59	Colon	ASP	Sx1, Cx1	NED	NED
58	Lung	ASP	Cx3, Rx1	III	Lung
35	Colon	ASP	Sx2, Cx1	IV	RP, Pelvic LN
52	Rectal	ASP	Sx1, Cx3, Rx1	IV	Lung
36	Rectal	VAL	Sx5, Cx6, Rx1	IV	Lung
75	Colon	ASP	Sx2, Cx3, Rx2	IV	Liver
49	Colon	CYS	Sx1, Cx4, Rx1	IV	Lung
42	Colon	ASP	Sx2, Cx3	IV	Liver, Lung
48	Colon	ASP	Sx1, Cx4	IV	Liver, Lung
48	Rectal	ASP	Sx2, Cx1	NED	NED
54	Colon	VAL	Sx2, Cx3, Rx1	IV	Lung
57	Colon	ASP	Sx2, Cx1, Rx1	NED	NED
66	Pancreatic	ASP	Sx1, Cx3, Rx1	IV	Liver, Lung
56	Rectal	ASP	Sx1, Cx2	NED	NED
73	Pancreatic	ASP	Sx1	IV	Pancreas
51	Colon	ASP	Sx2, Cx3, Rx1	IV	Liver, Lung
57	Colon	ASP	Sx2, Cx3, Rx1	IV	Liver, Lung
66	Pancreatic	ASP	Cx2	IV	Liver

Patient Profile Arm C: IL-2 + GM-CSF

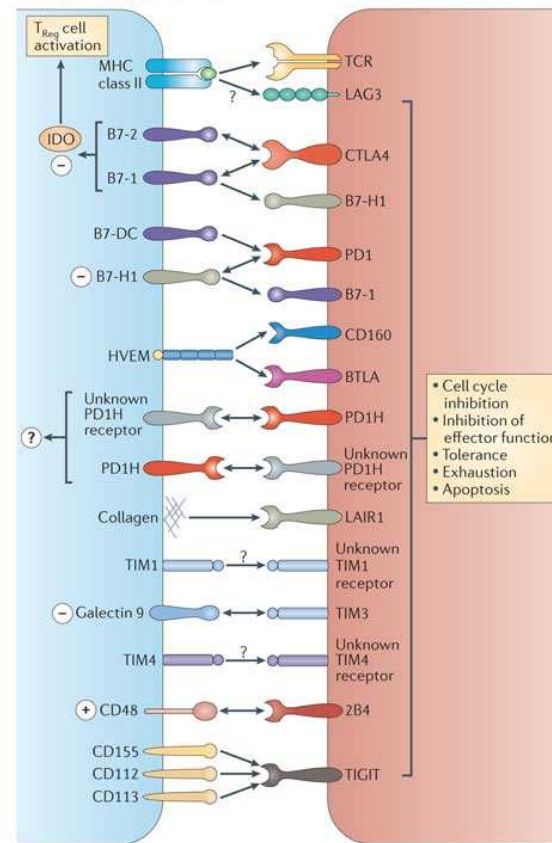
Age	Cancer	Mutation	Pre-vaccination Therapy	Stage on Enrollment	Disease extension on enrollment
40	Rectal	ASP	Sx2, Cx2, Rx1	IV	Lung
59	Colon	ASP	Sx1, Cx1	NED	NED
58	Lung	ASP	Cx3, Rx1	III	Lung
35	Colon	ASP	Sx2, Cx1	IV	RP, Pelvic LN
52	Rectal	ASP	Sx1, Cx3, Rx1	IV	Lung
36	Rectal	VAL	Sx5, Cx6, Rx1	IV	Lung
75	Colon	ASP	Sx2, Cx3, Rx2	IV	Liver
49	Colon	CYS	Sx1, Cx4, Rx1	IV	Lung
42	Colon	ASP	Sx2, Cx3	IV	Liver, Lung
48	Colon	ASP	Sx1, Cx4	IV	Liver, Lung
48	Rectal	ASP	Sx2, Cx1	NED	NED
54	Colon	VAL	Sx2, Cx3, Rx1	IV	Lung
57	Colon	ASP	Sx2, Cx1, Rx1	NED	NED
66	Pancreatic	ASP	Sx1, Cx3, Rx1	IV	Liver, Lung
56	Rectal	ASP	Sx1, Cx2	NED	NED
73	Pancreatic	ASP	Sx1	IV	Pancreas
51	Colon	ASP	Sx2, Cx3, Rx1	IV	Liver, Lung
57	Colon	ASP	Sx2, Cx3, Rx1	IV	Liver, Lung
66	Pancreatic	ASP	Cx2	IV	Liver

**What is the “go forward”
strategy?**

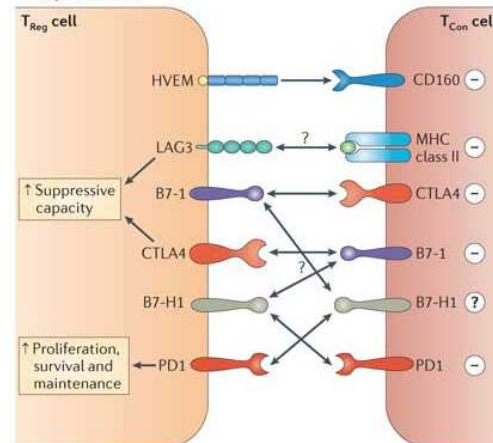
a Co-stimulation of T cells following interaction with counter-receptors on APCs



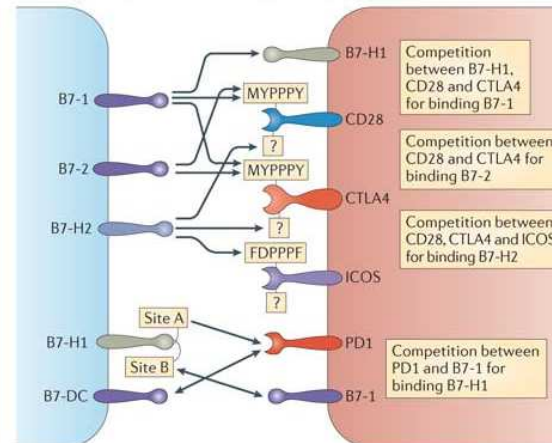
b Co-inhibition of T cells following interaction with counter-receptors on APCs



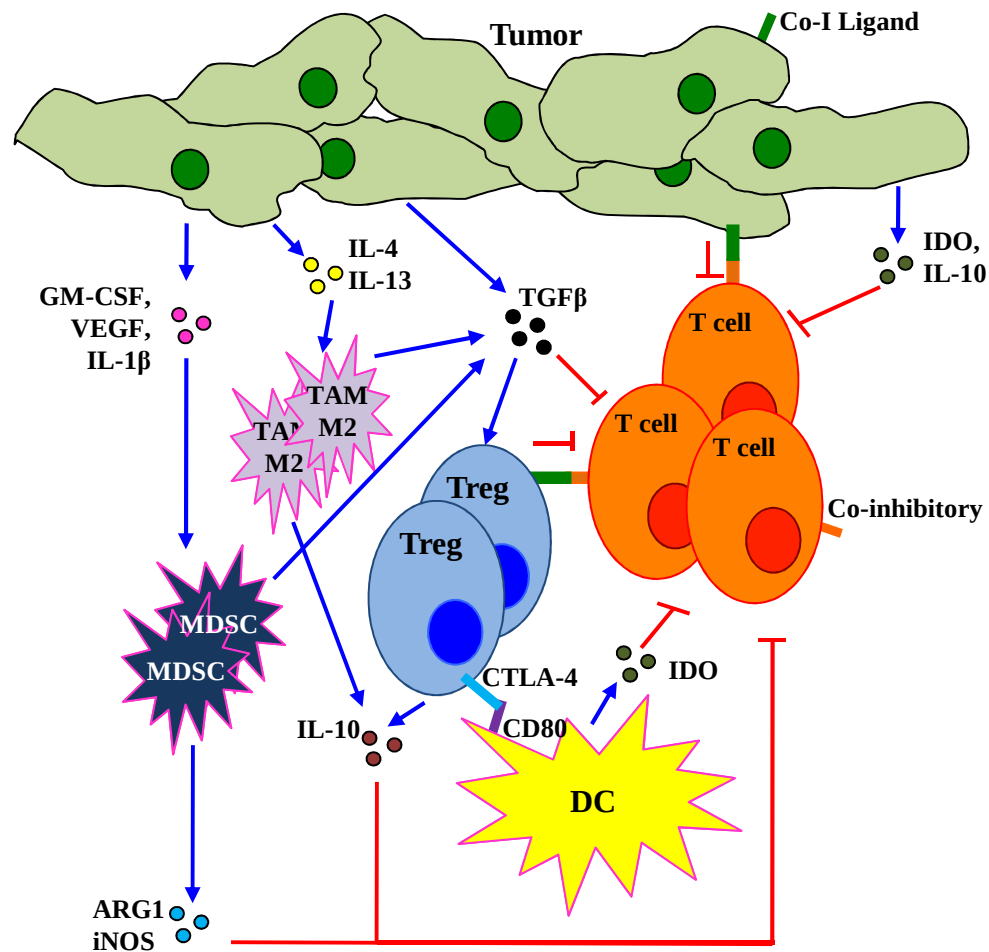
c T_{Reg}-T_{Con} co-signalling interactions



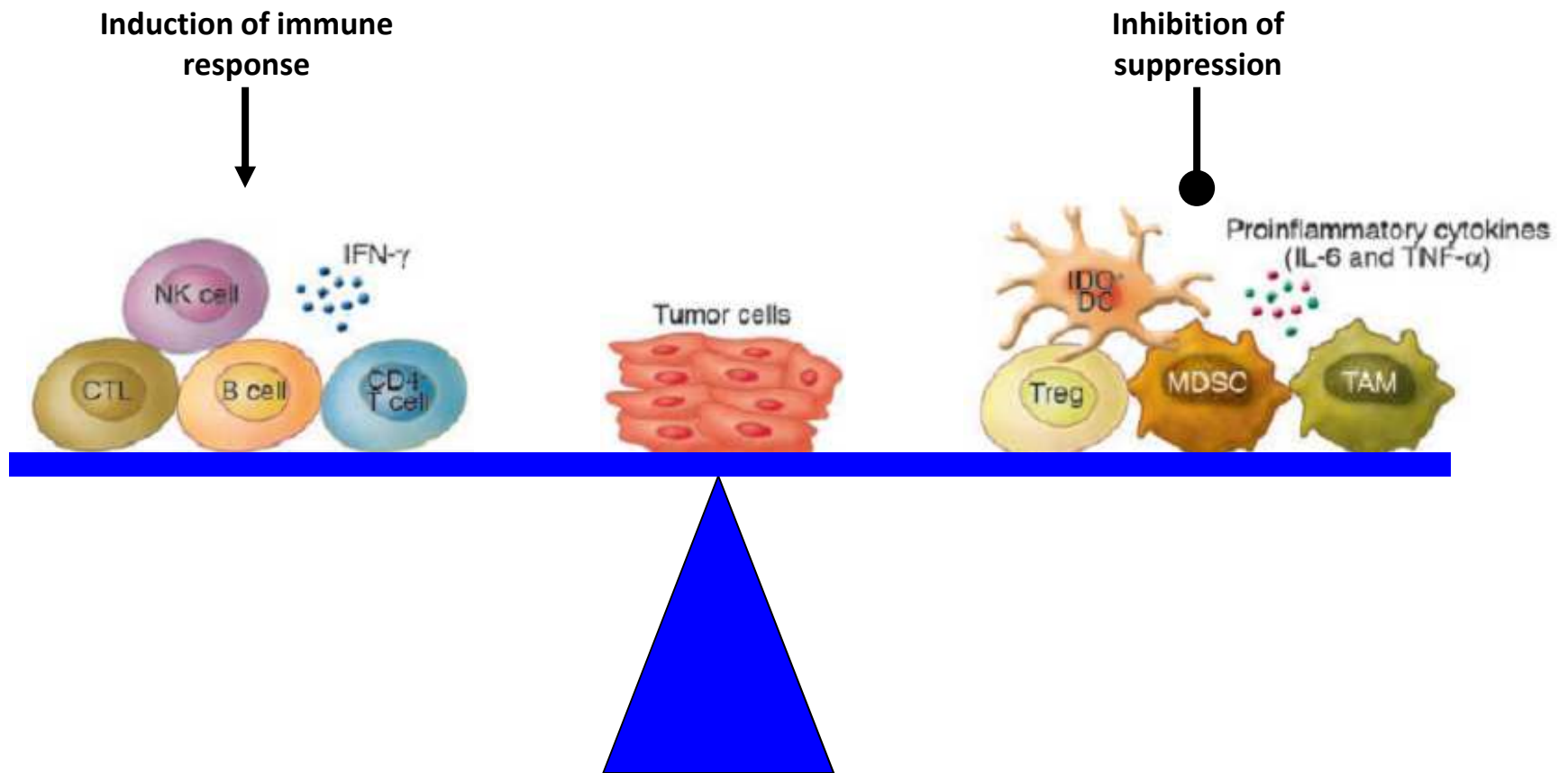
d Co-signalling interactions through multiple interfaces



Tumor-Immune Interaction



Effective Therapeutic immunebalance



Tumor-Immune Interaction

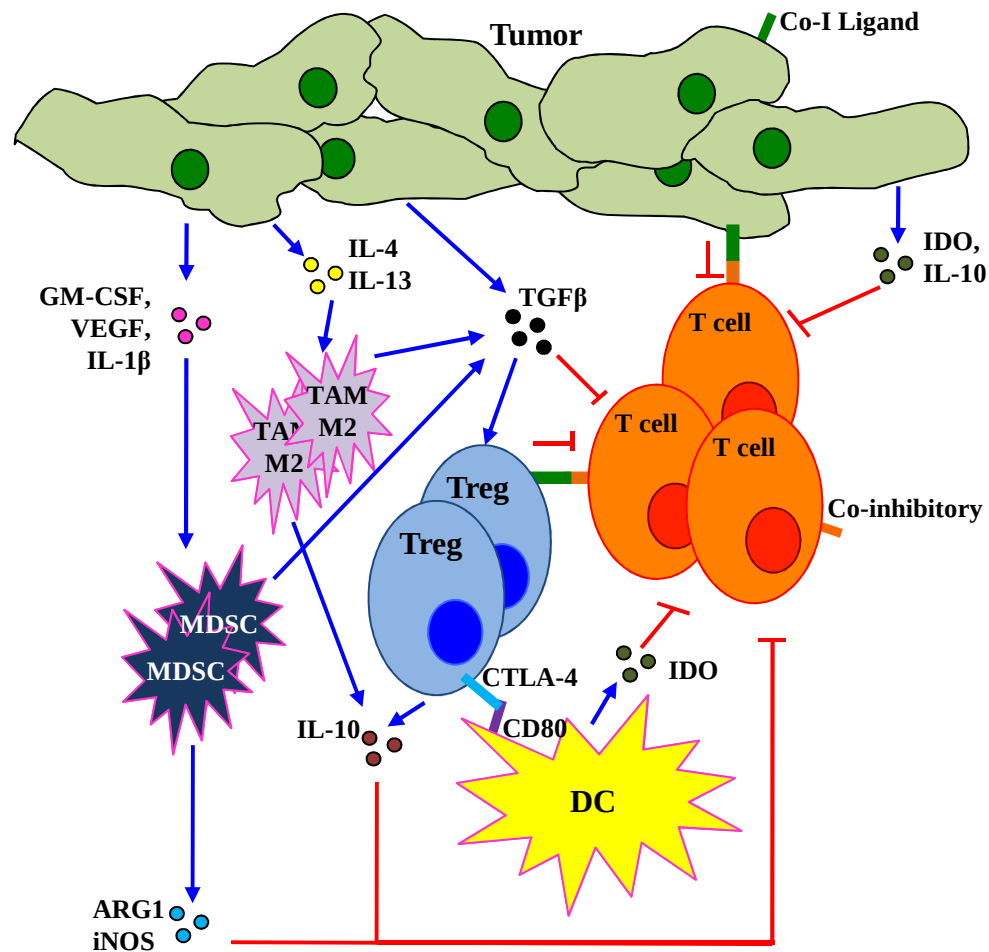
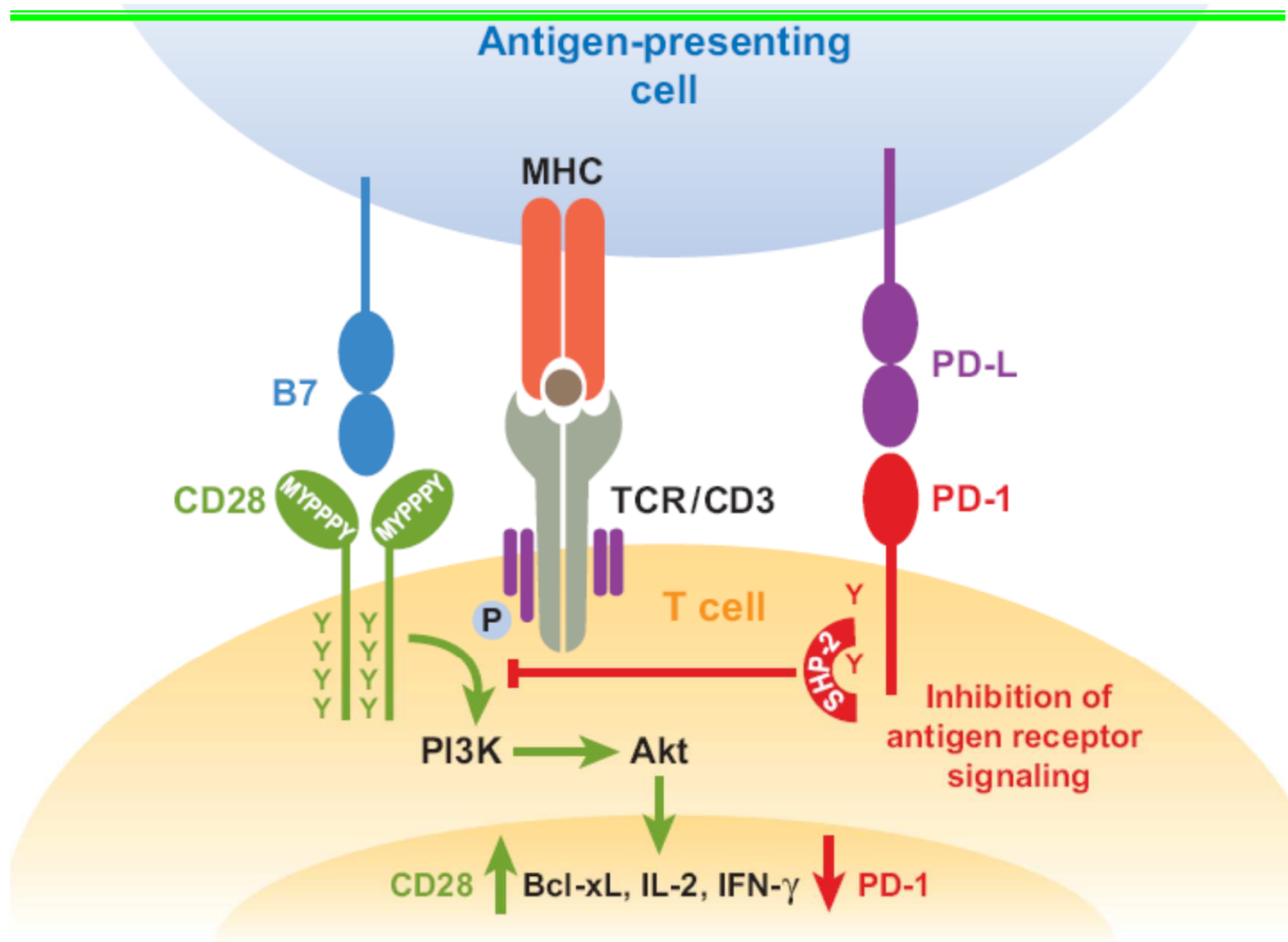


Table 1. Final Rankings of Agents with High Potential for Use in Treating Cancer

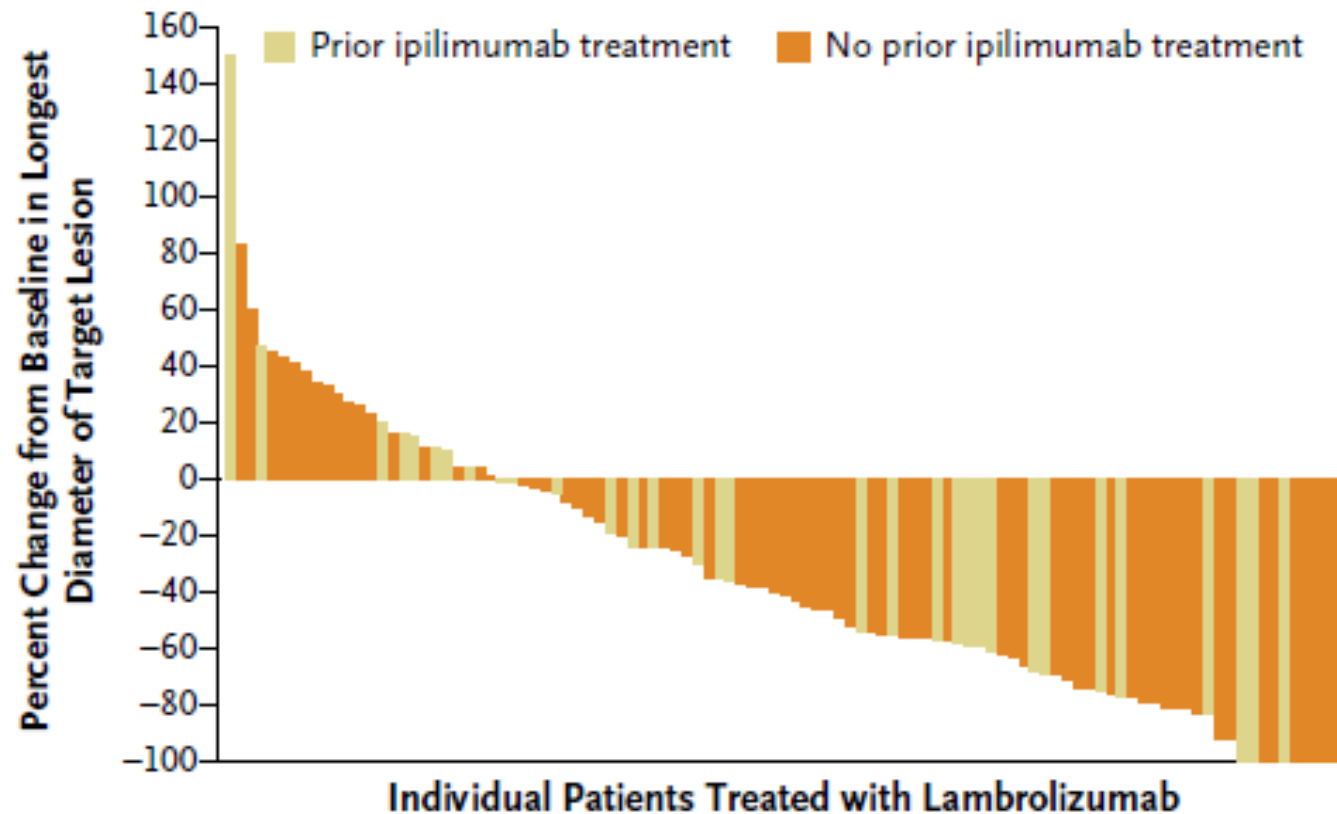
Rank*	Agent	Agent Category
1	IL-15	T-Cell Growth Factor
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5	IL-7	T-Cell Growth Factor
6	CpG	Vaccine Adjuvant
7	1-Methyl Tryptophan	Enzyme Inhibitor
8	Anti-CD137 (anti-4-1BB)	T-Cell Stimulator
9	Anti-TGF-beta	Signaling Inhibitor
10	Anti-IL-10 Receptor or Anti-IL-10	Suppression Inhibitor
11	Flt3L	Dendritic Cell Growth Factor/ Vaccine Adjuvant
12	Anti-Glucocorticoid-Induced TNF Receptor (GITR)	T-cell Stimulator
13	CCL21 Adenovirus	T-Cell Attracting Chemokine
14	Monophosphoryl Lipid A (MPL)	Vaccine Adjuvant
15	Poly I:C and/or Poly ICLC	Vaccine Adjuvant
16	Anti-OX40	T-Cell Stimulator
17	Anti-B7-H4	T-Cell Checkpoint Blockade Inhibitor
18	Resiquimod and/or 852A	Vaccine Adjuvant
19	LIGHT and/or LIGHT vector	T-Cell Stimulator
20	Anti-Lymphocyte Activation Gene-3 (LAG-3)	T-Cell Checkpoint Blockade Inhibitor

PD-1/PD-L1 Background

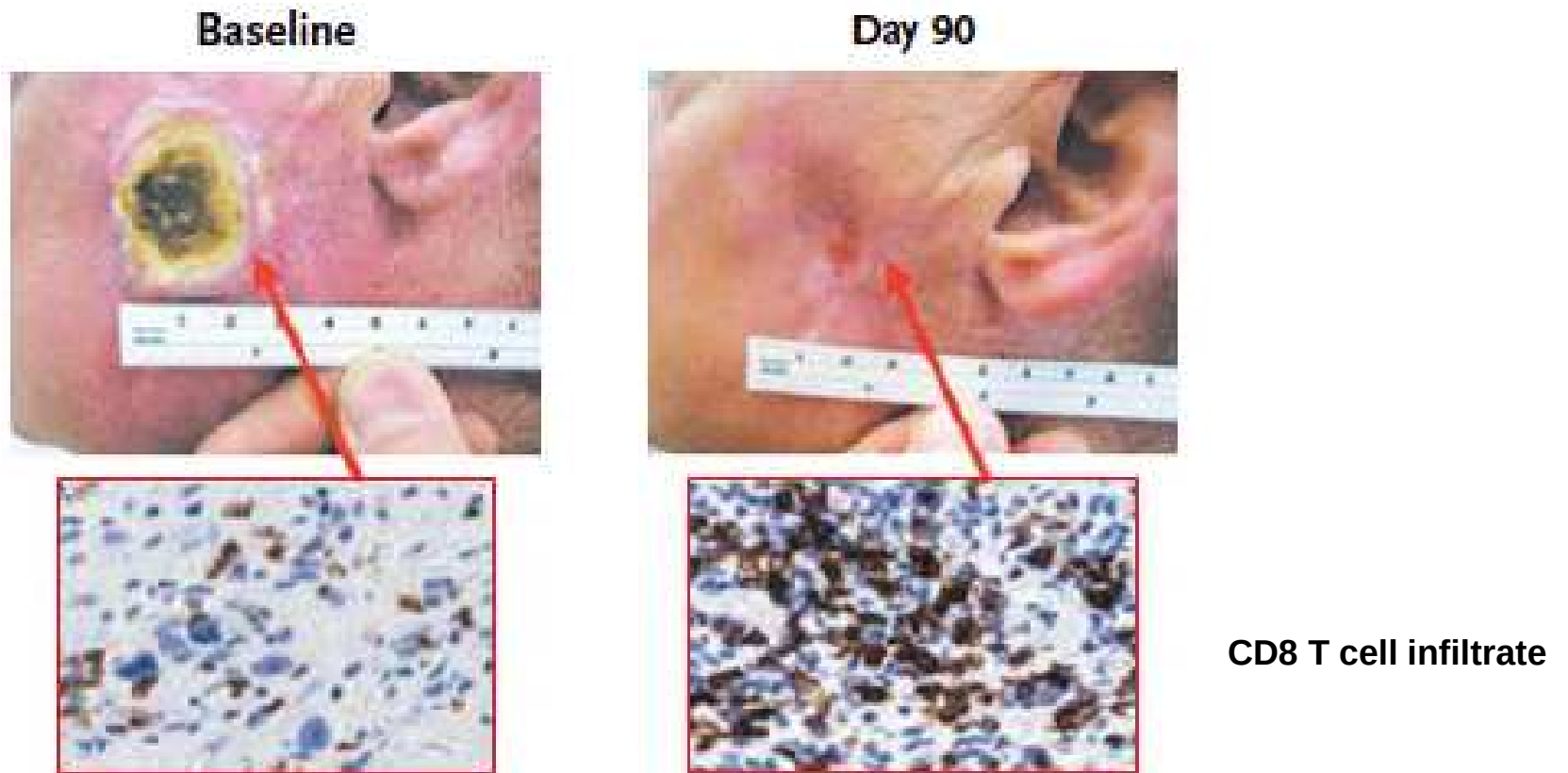


Safety and tumor responses with lambrolizumab (aPD1) in melanoma

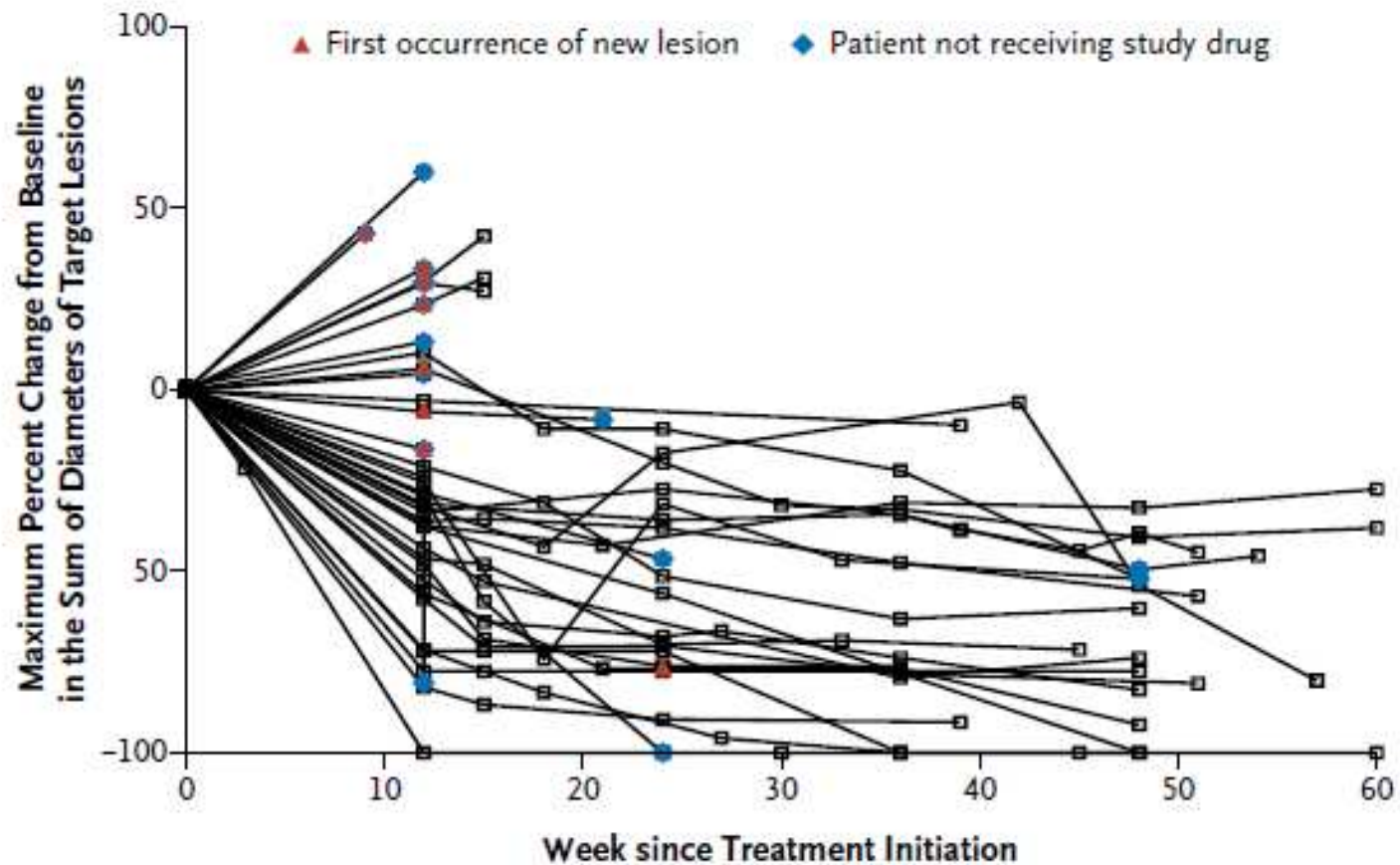
Best objective response



Safety and tumor responses with lambrolizumab (aPD1) in melanoma



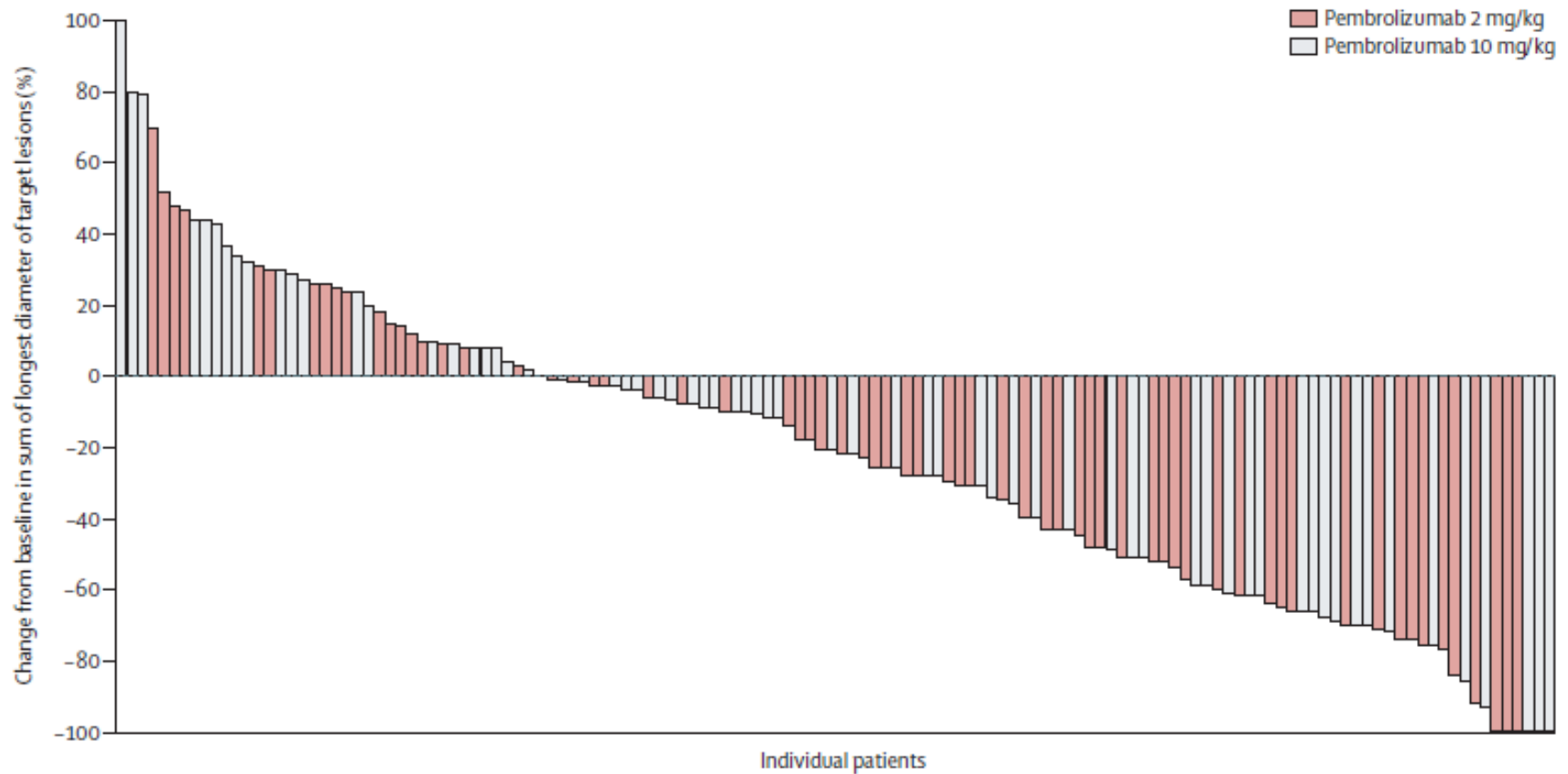
Safety and tumor responses with lambrolizumab (aPD1) in melanoma



Hamid O., et al. *The New England journal of medicine* 369(2), 134-144 (2013)

Treatment with pembrolizumab in ipilimumab-refractory advanced melanoma

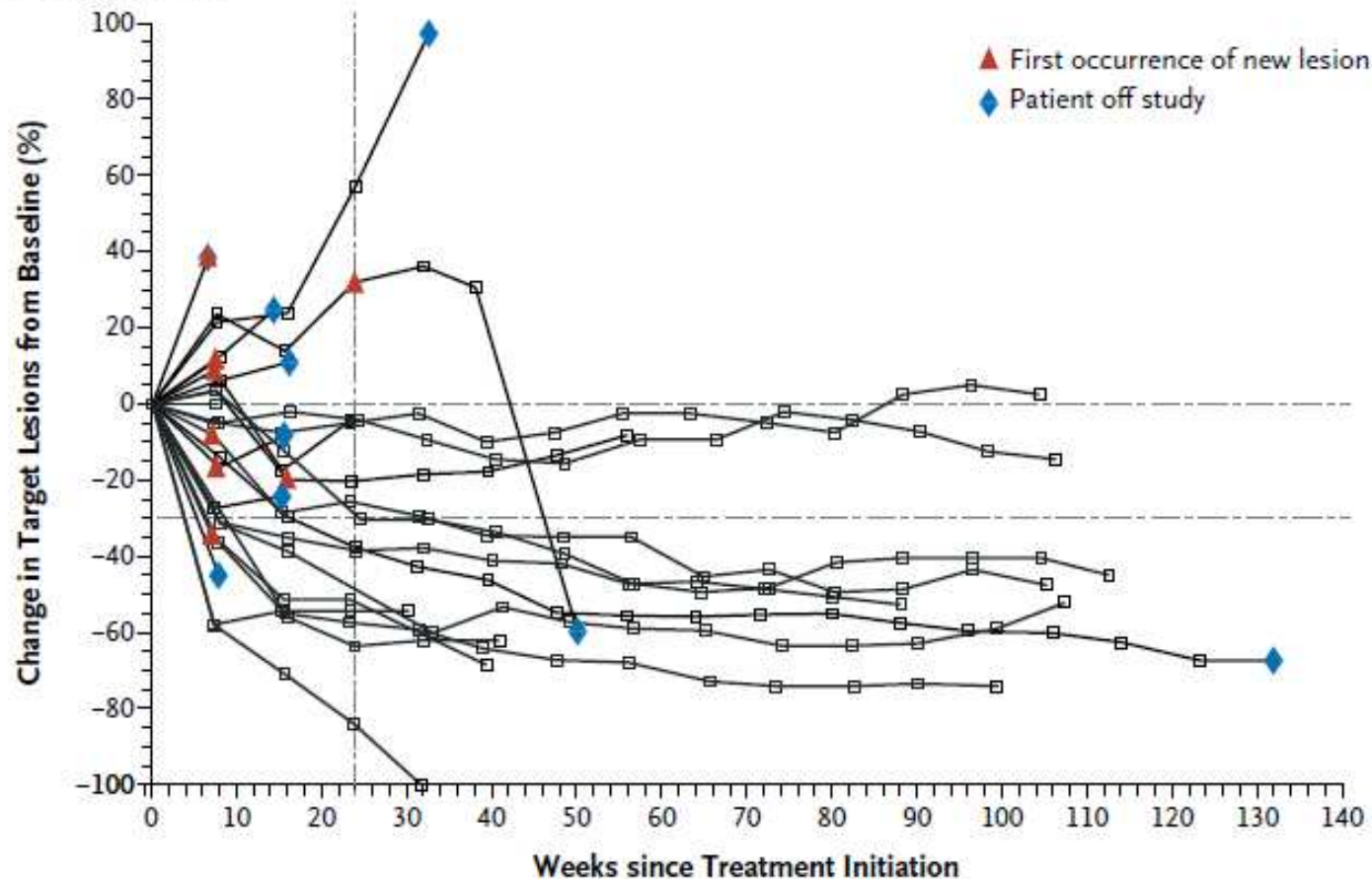
Best objective response



Treatment with Nivolumab (aPD1 BMS) in solid tumors

1.0 mg per kilogram of body weight every 2 weeks.

Patients with Melanoma

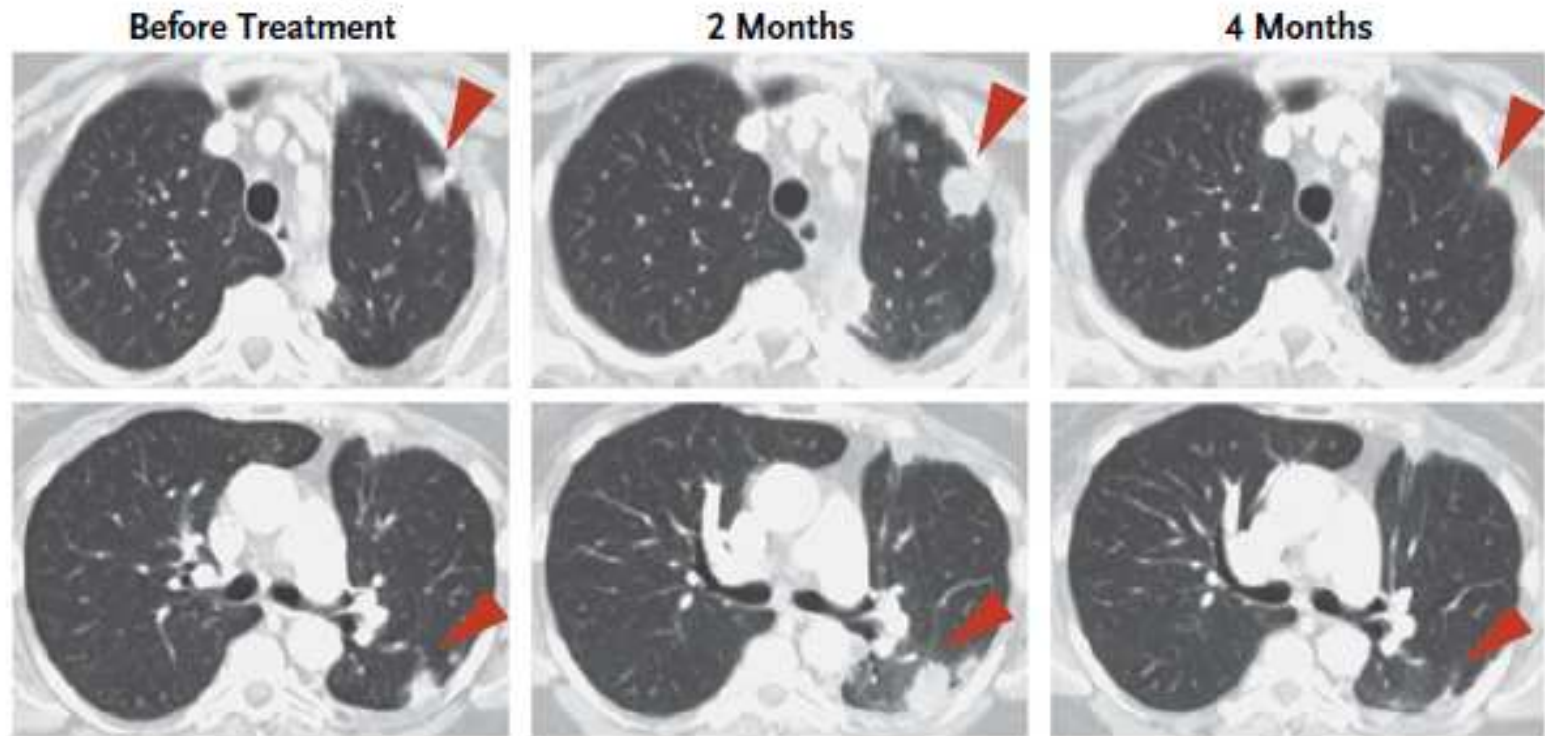


Topalian SL et al. *The New England journal of medicine* 366(26), 2443-2454 (2012).

Treatment with Nivolumab (aPD1 BMS) in solid tumors

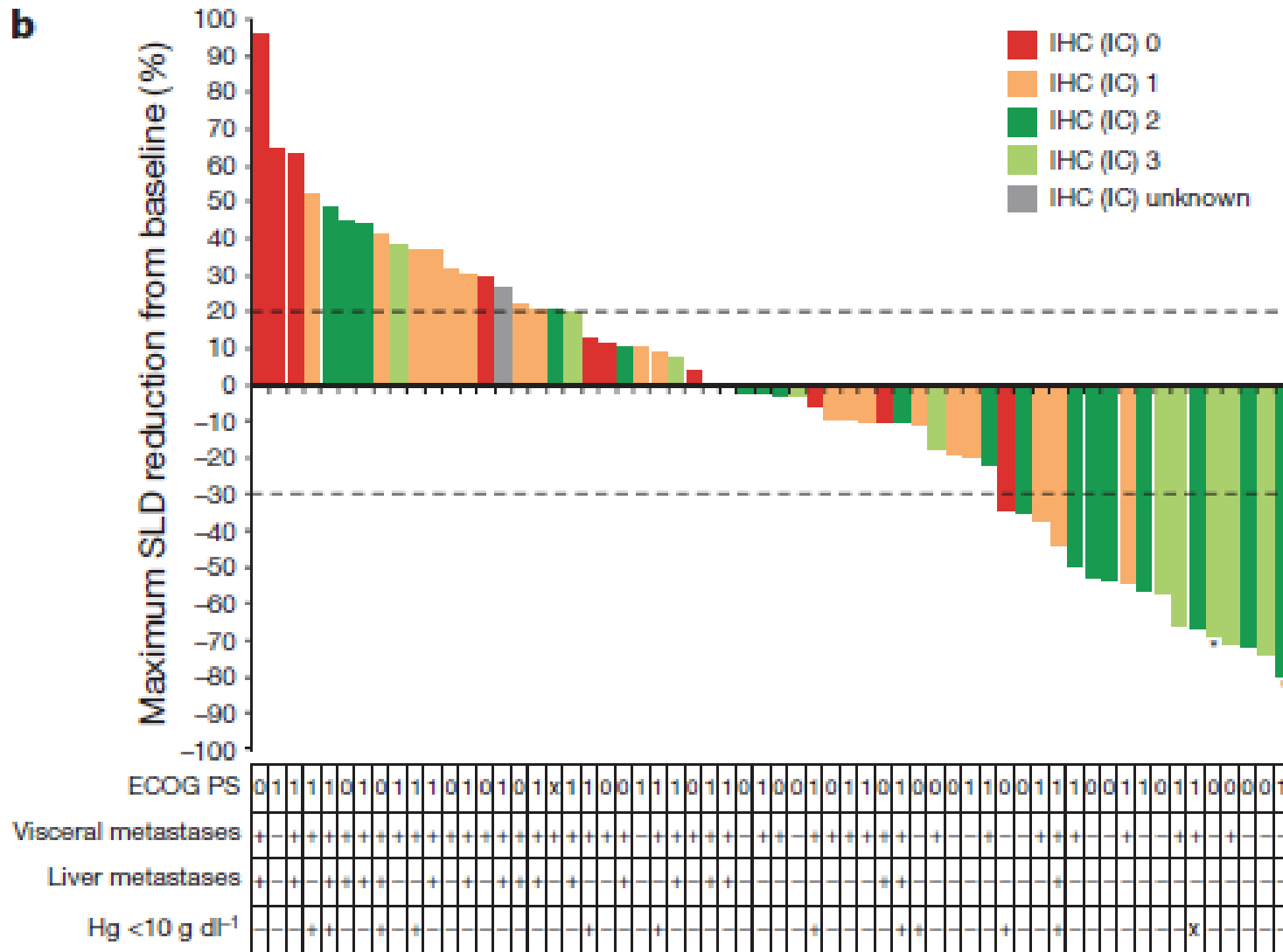
10.0 mg per kilogram of body weight

Patient with Non-Small-Cell Lung Cancer

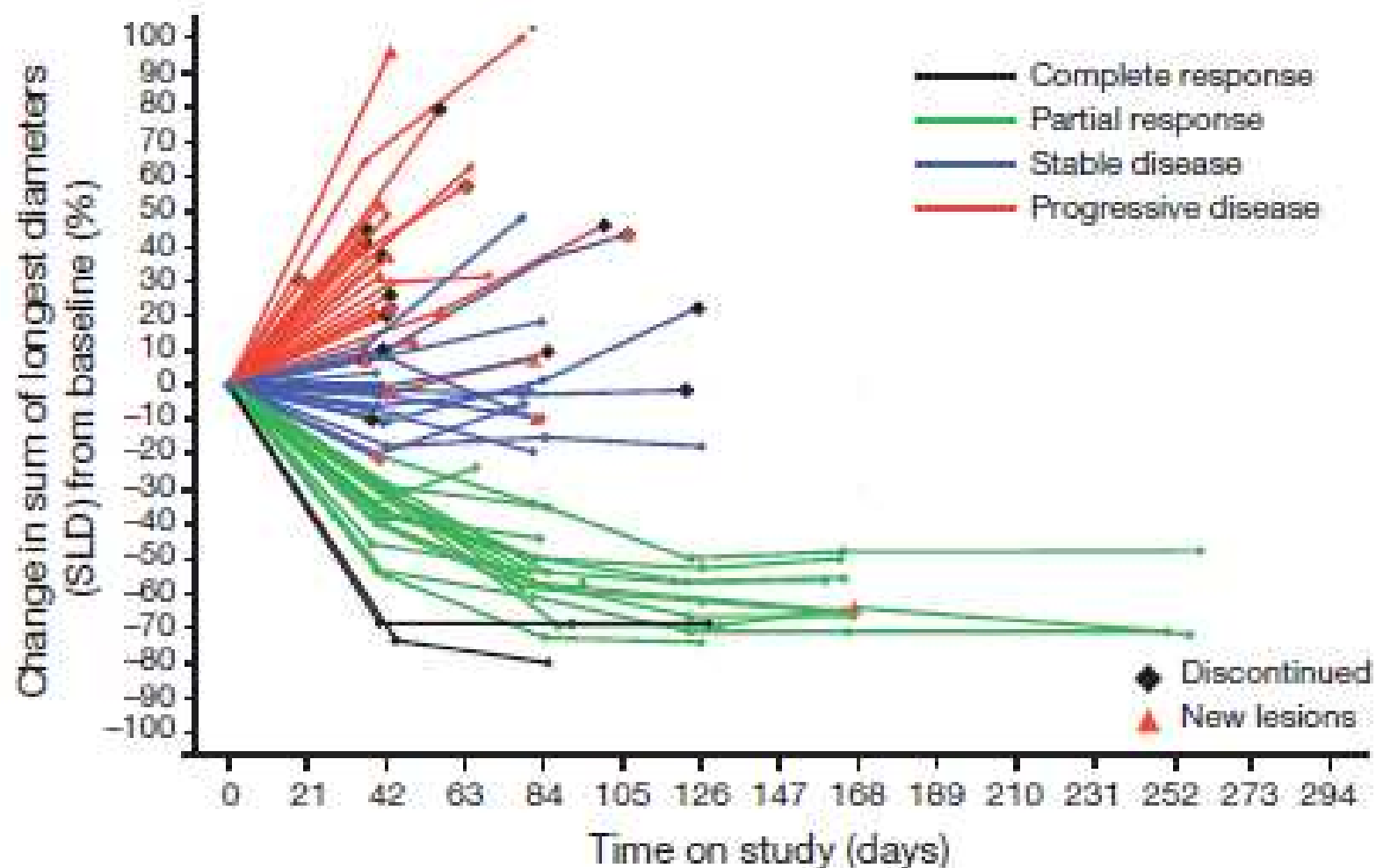


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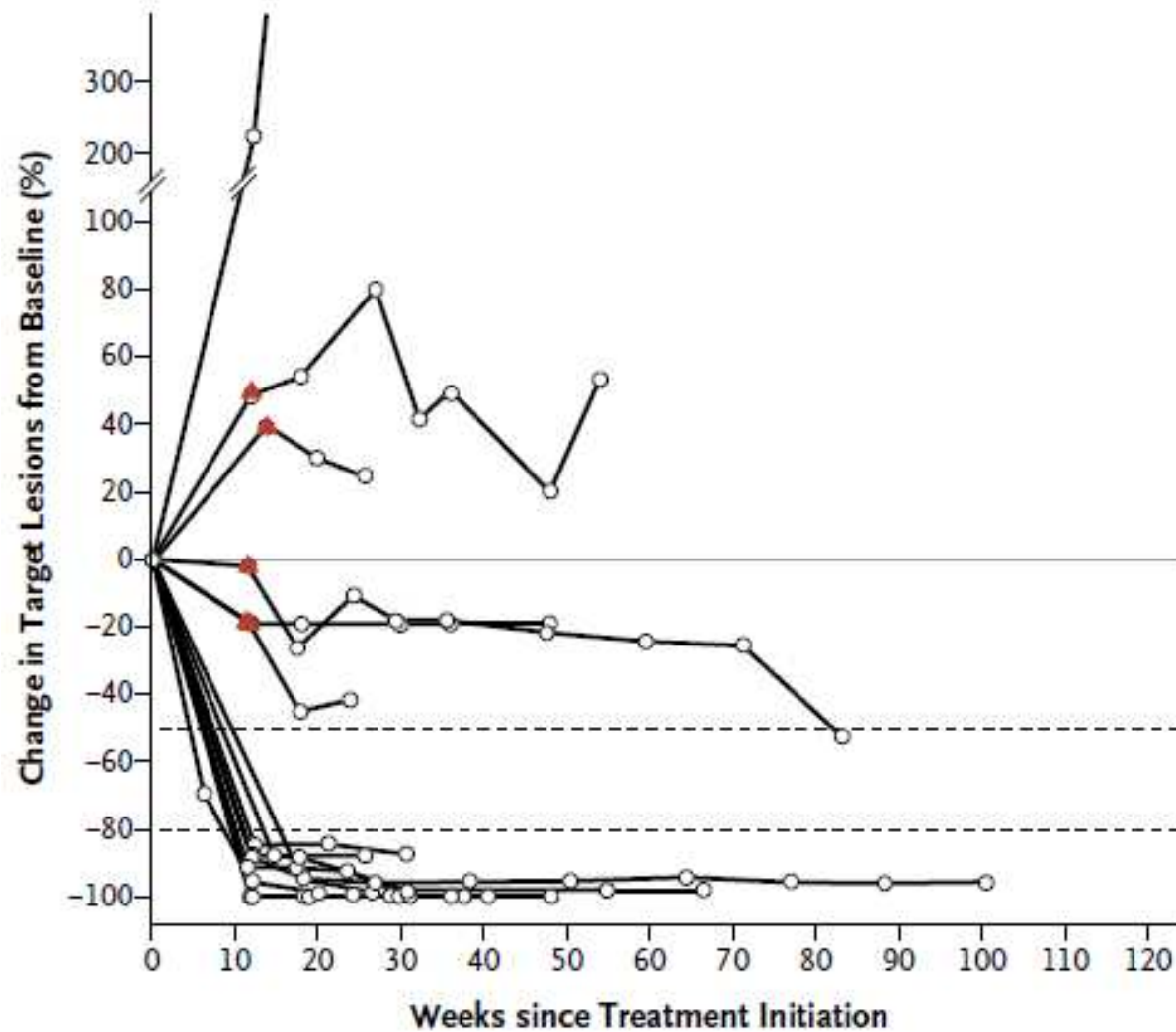
MPDL3280A (anti-PD-L1) in metastatic bladder cancer



MPDL3280A (anti-PD-L1) in metastatic bladder cancer

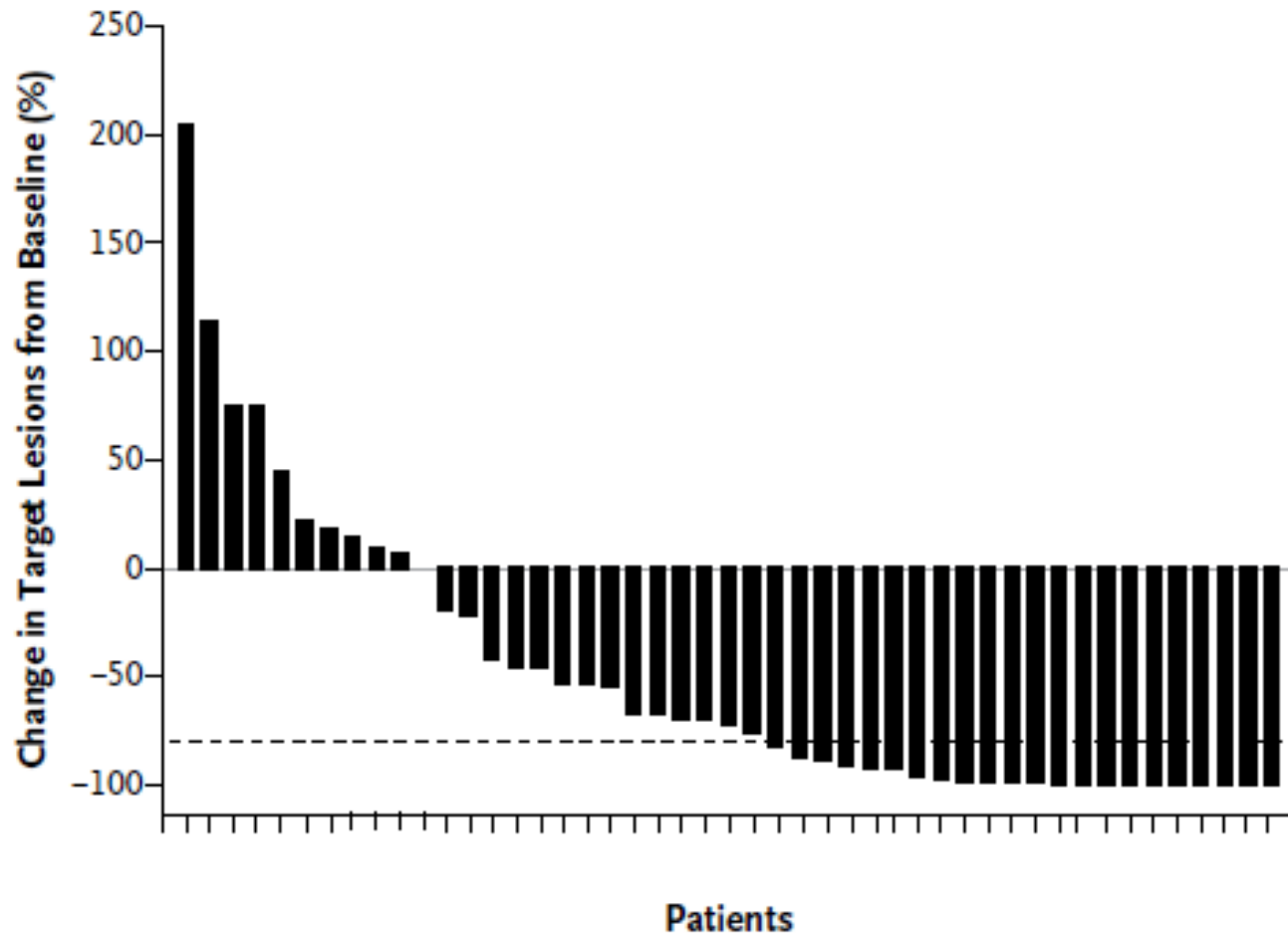


Nivolumab plus ipilimumab in advanced melanoma



Wolchok JD et al. *The New England journal of medicine* 369(2), 122-133 (2013).

Nivolumab plus ipilimumab in advanced melanoma



Wolchok JD et al. *The New England journal of medicine* 369(2), 122-133 (2013).

Tumor-Immune Interaction

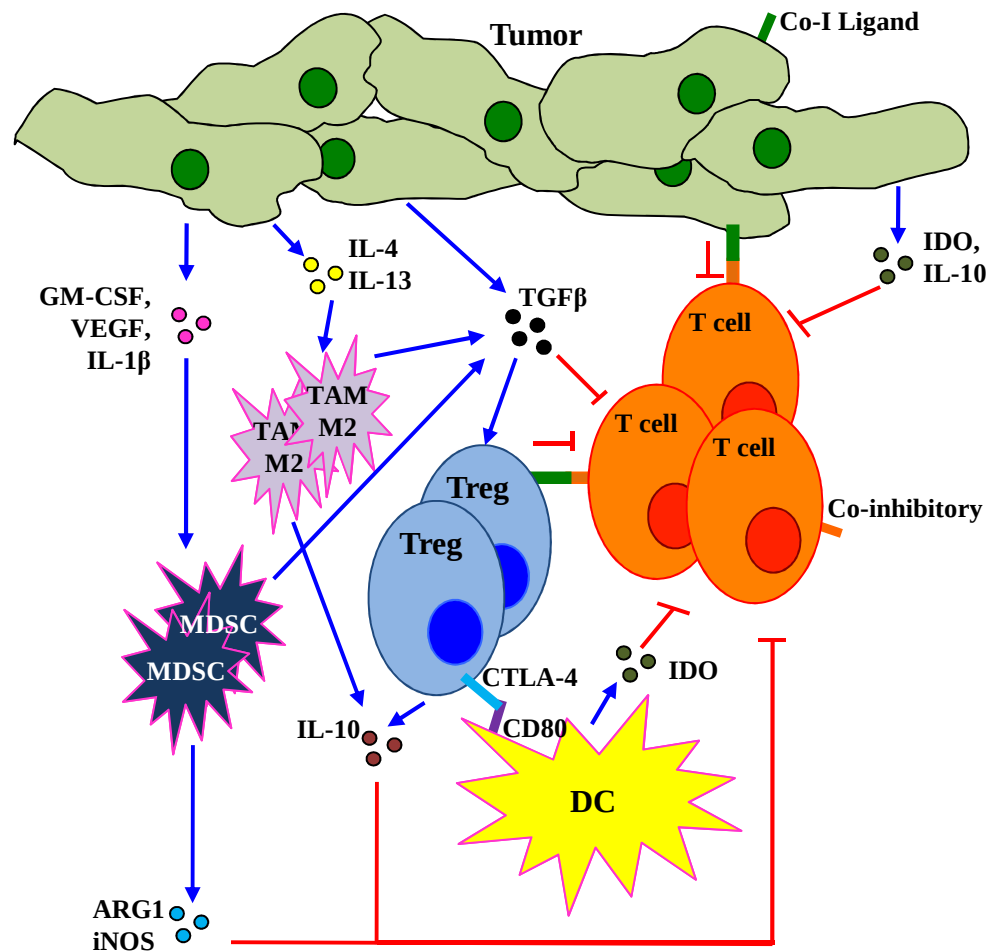


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Combinational Immunotherapy

- Vaccines
- Immune Modulators
 - Immune Agonists
 - Stimulatory cytokines (IL-2, IL-12, IL-15, TLR etc..)
 - Co-stimulatory molecules (OX-40, GITR, 4-1BB)
 - Immune inhibitors
 - Check point inhibitors (CTLA4, PD1/PDL1, LAG3, TIM3, iDO)
 - Inhibitory cytokines/factors (IL-10, TGFb)
- Standard Therapy
 - Chemotherapy
 - Radiation Therapy
- Small Molecules
- CARs

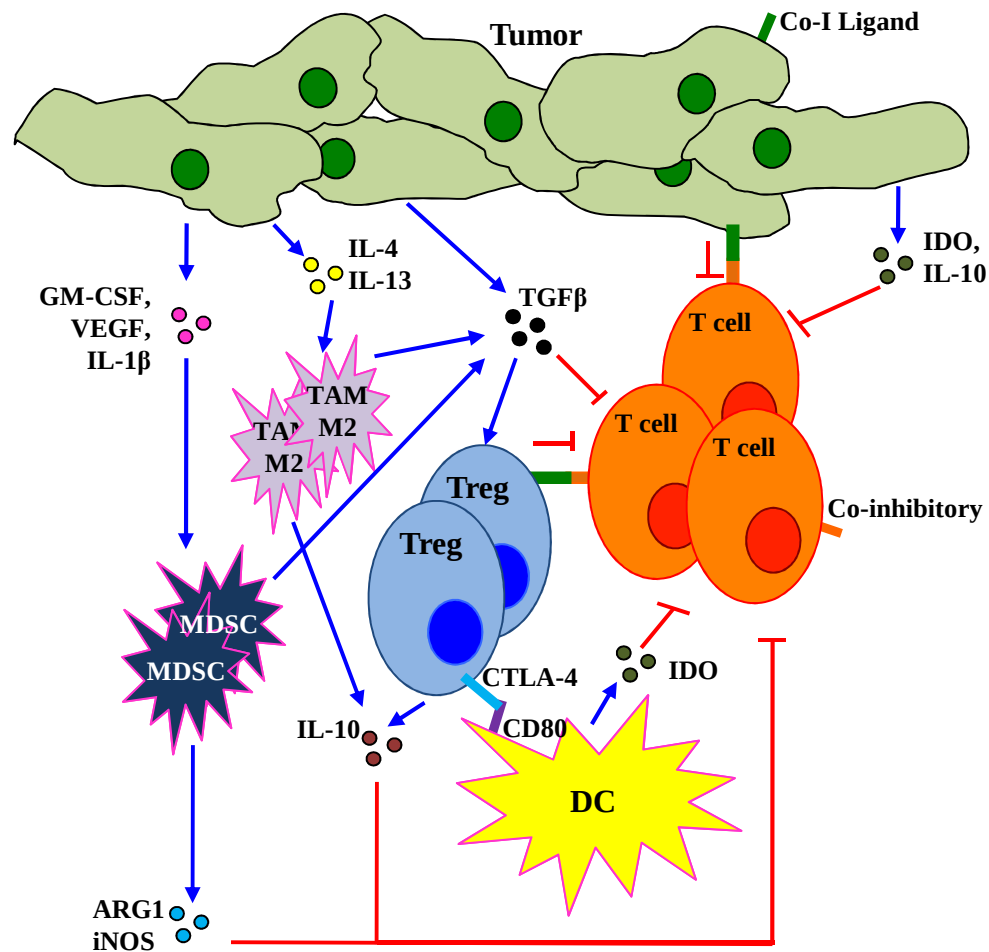
Combinational Immunotherapy

- Type of Combination
- Schedule of combination
- Prediction of response

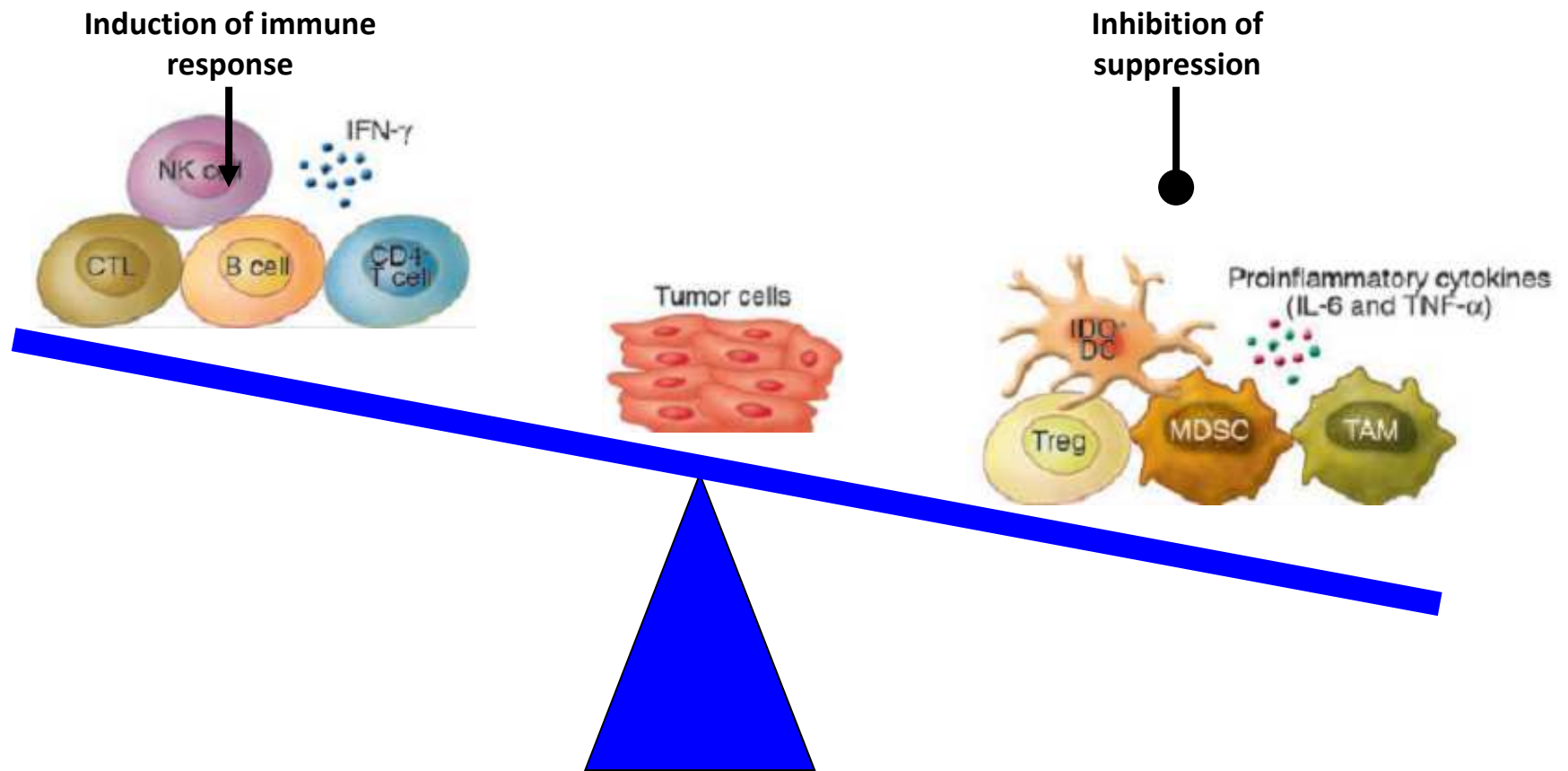
Regulatory Challenges

- What pre clinical data would be needed to move with the combination ?
- What clinical trial design ?
 - Efficiency
 - Cost
 - Time
- How to enable combinations from different developers

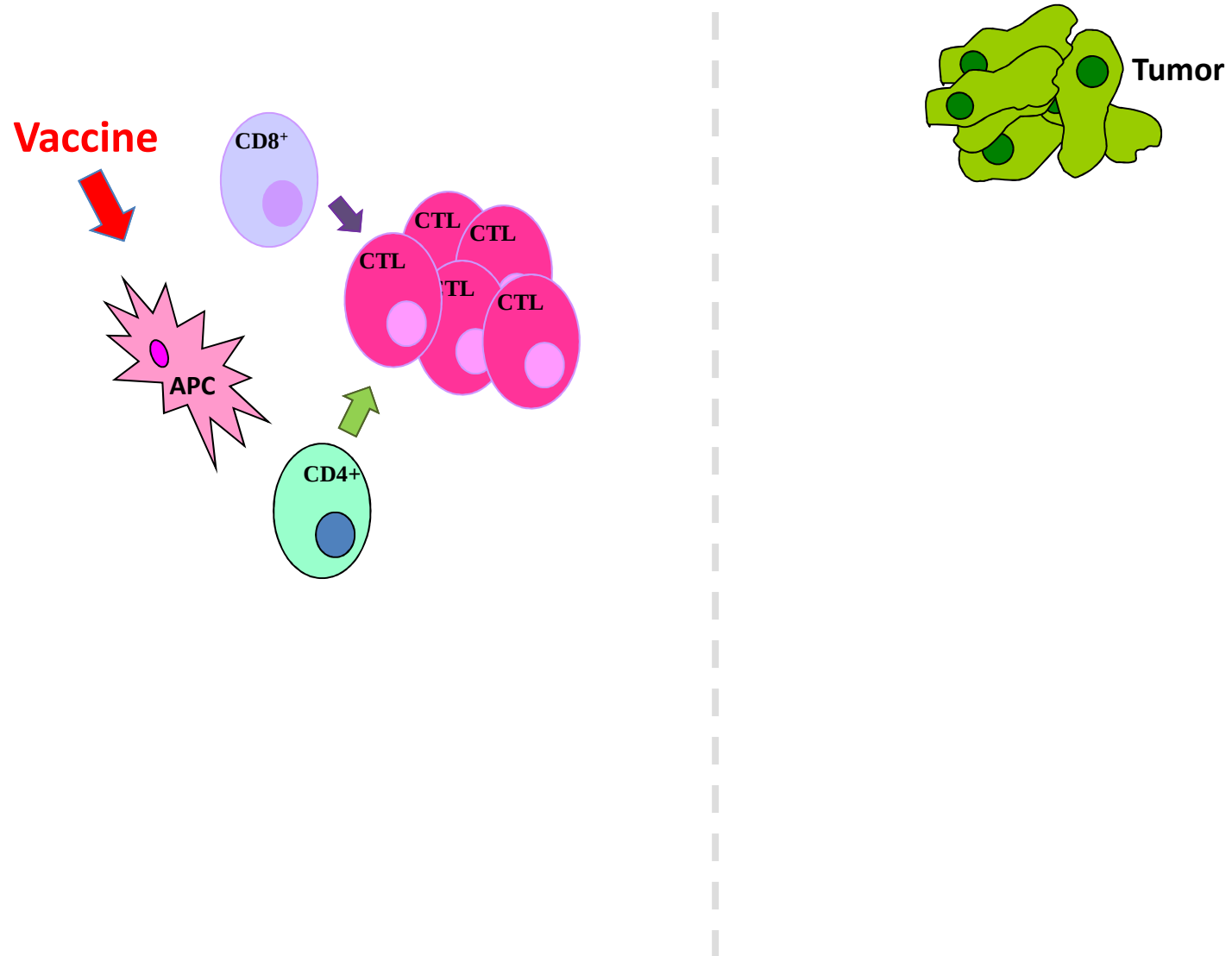
Tumor-Immune Interaction



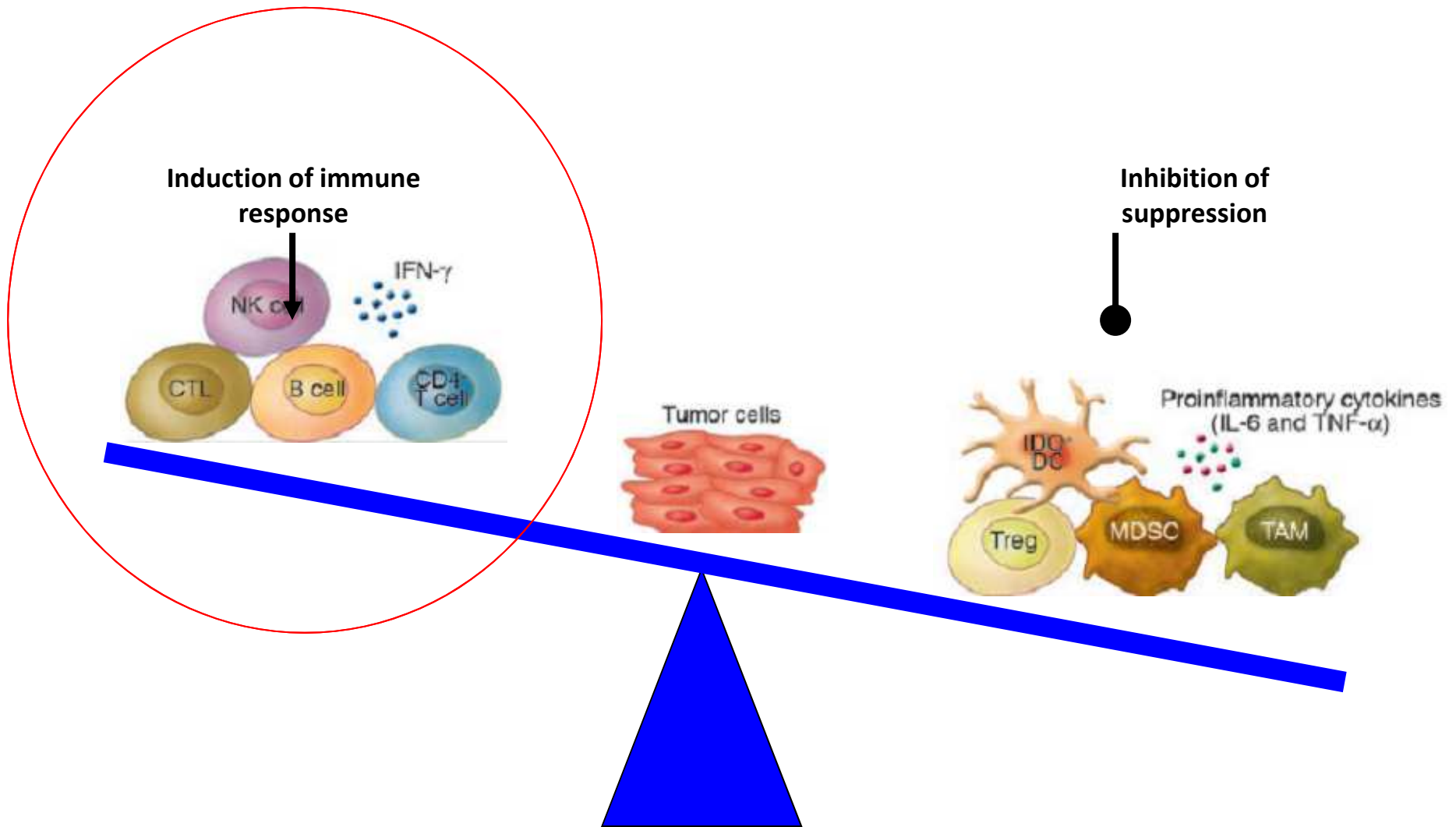
Effective Therapeutic immunebalance



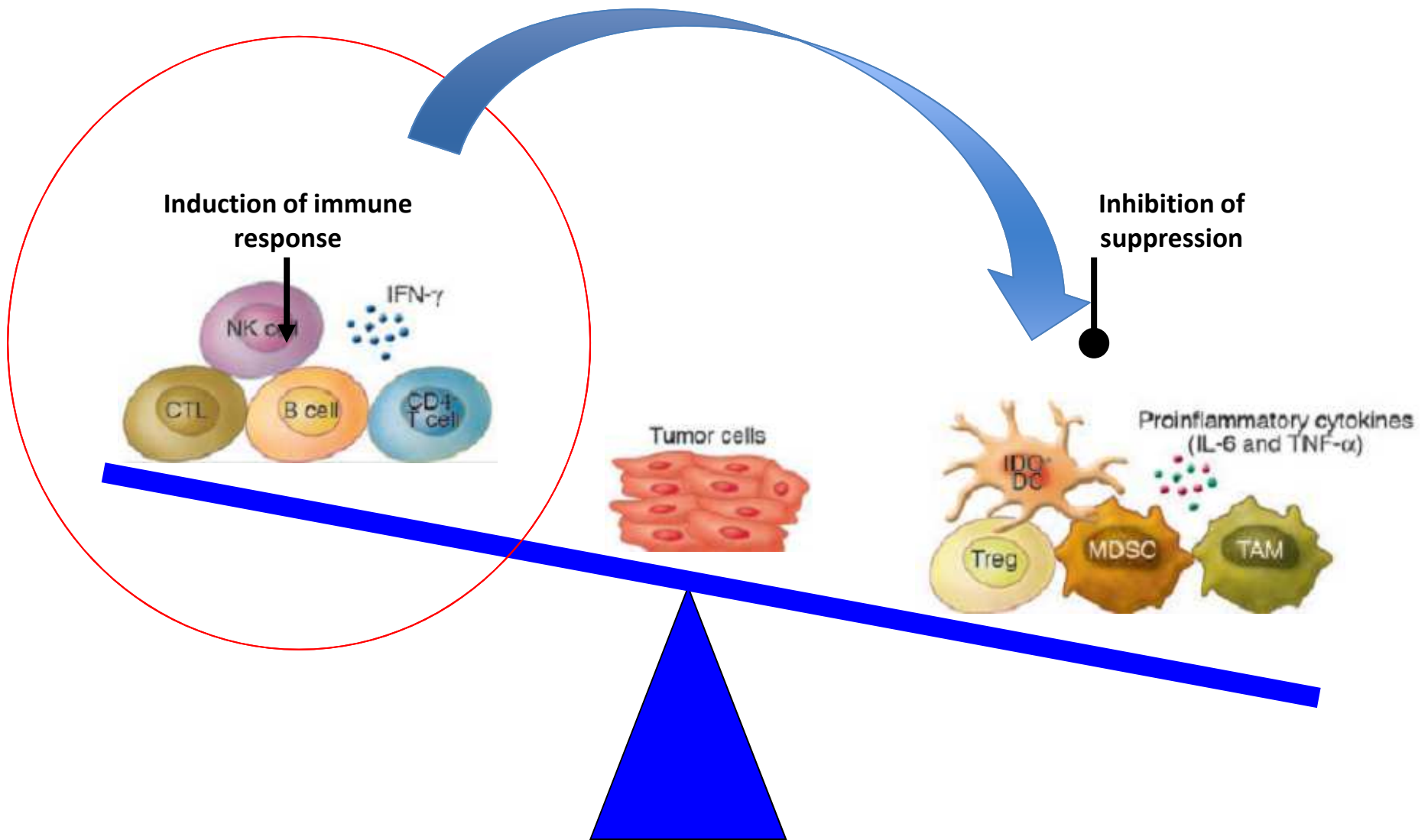
Cancer Vaccine



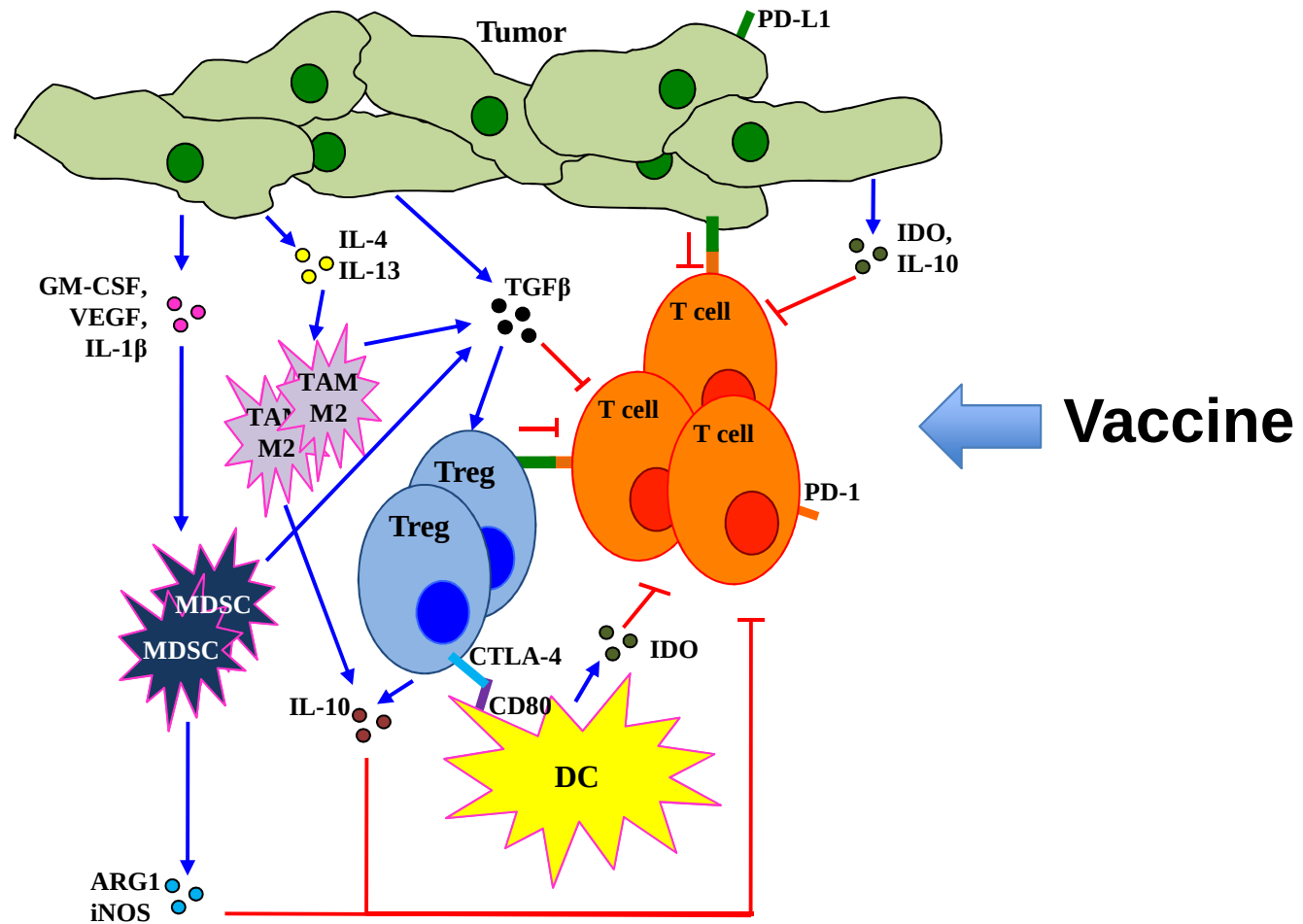
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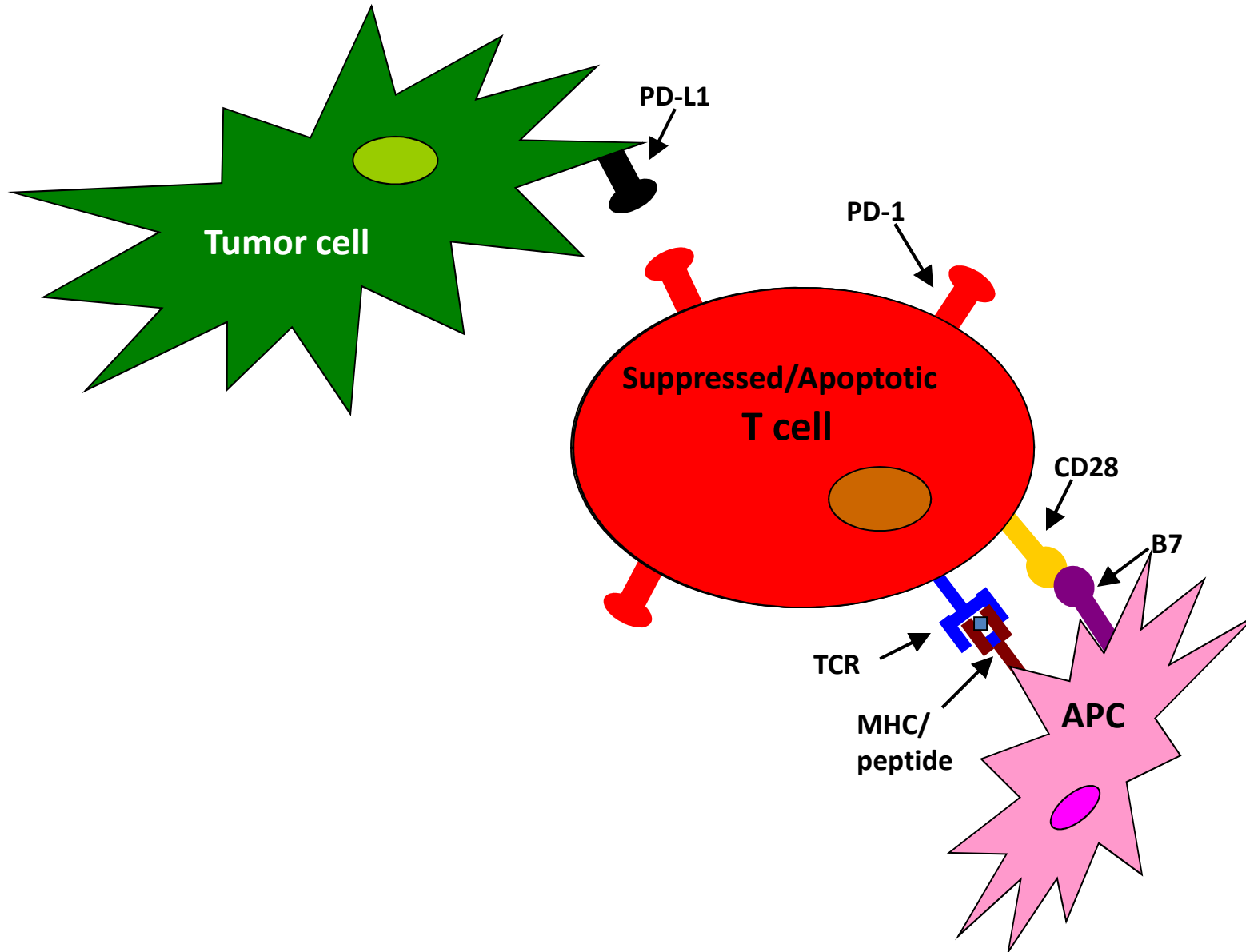
Effective Therapeutic immunebalance



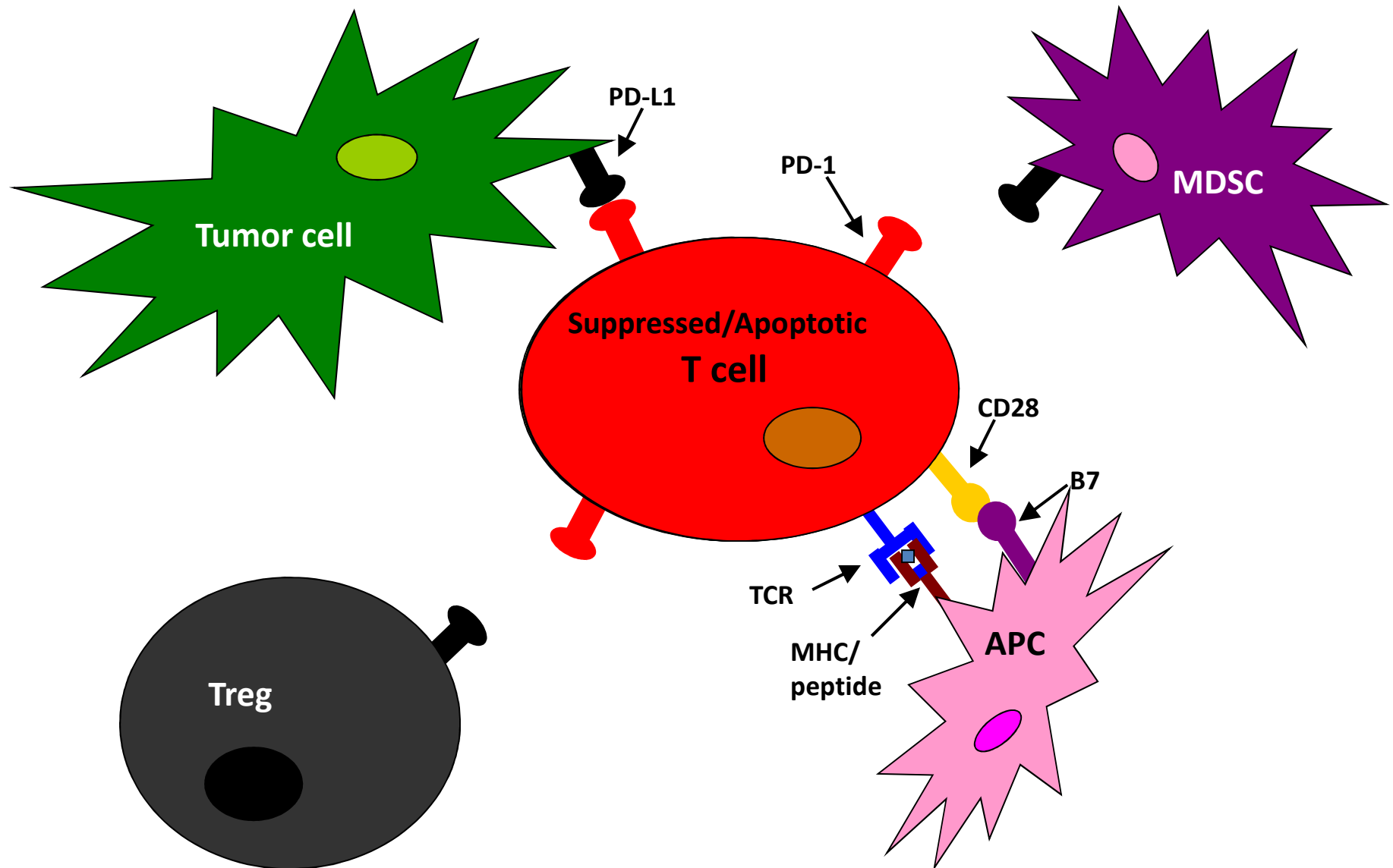
Tumor-Immune Modulatory Network



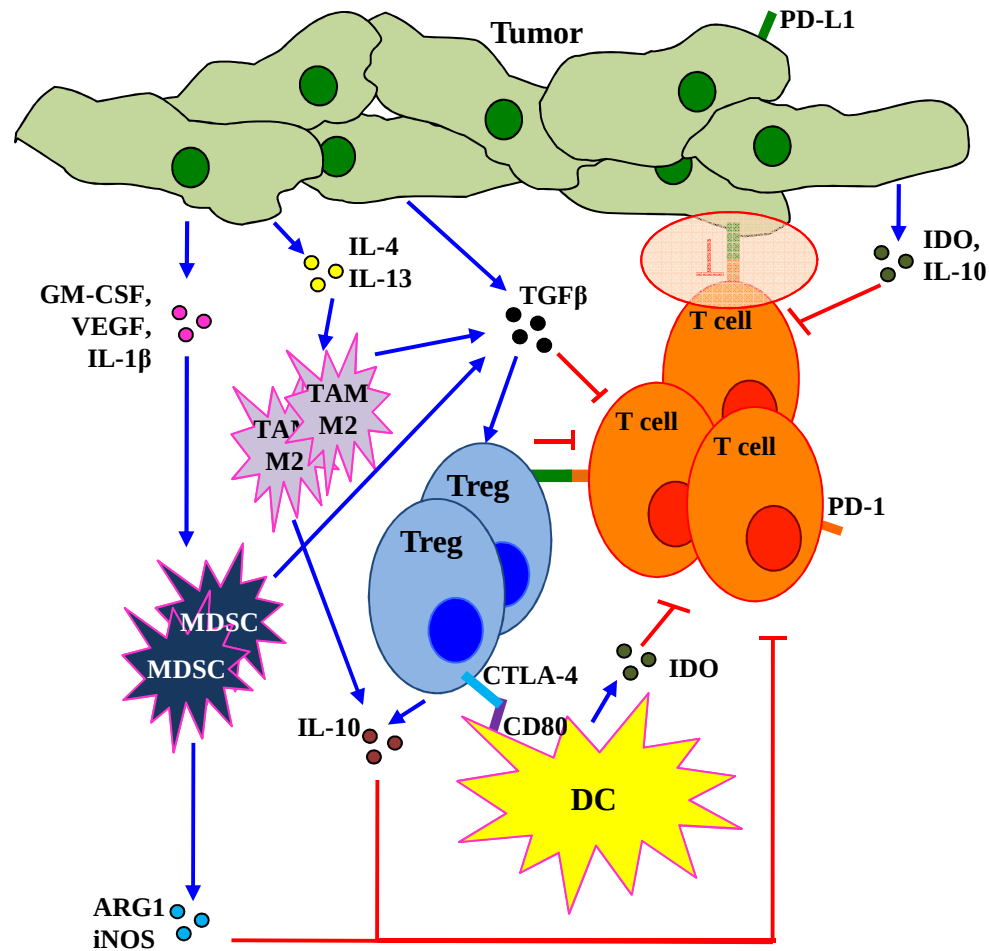
PD-1/PD-L1 Engagement Suppresses Effector T cells



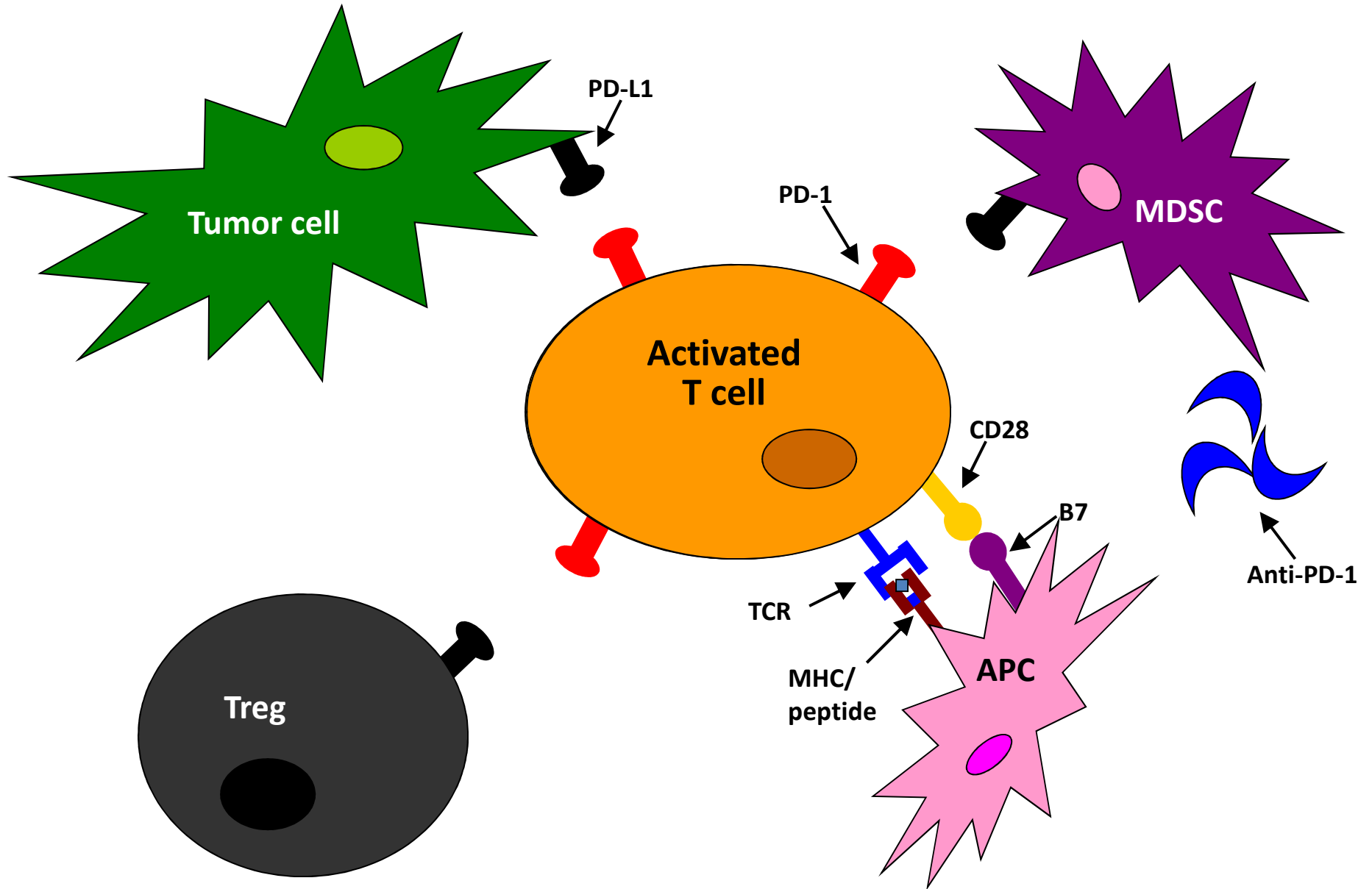
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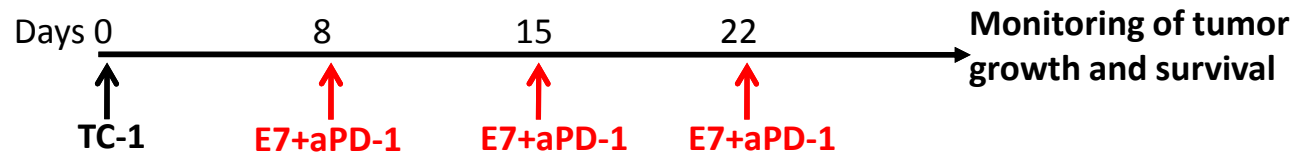
Tumor-Immune Modulating Network



PD-1/PD-L1 Engagement Suppresses Effector T cells



Evaluation of therapeutic efficacy of vaccine/anti-PD-1 combination in TC-1 mouse model



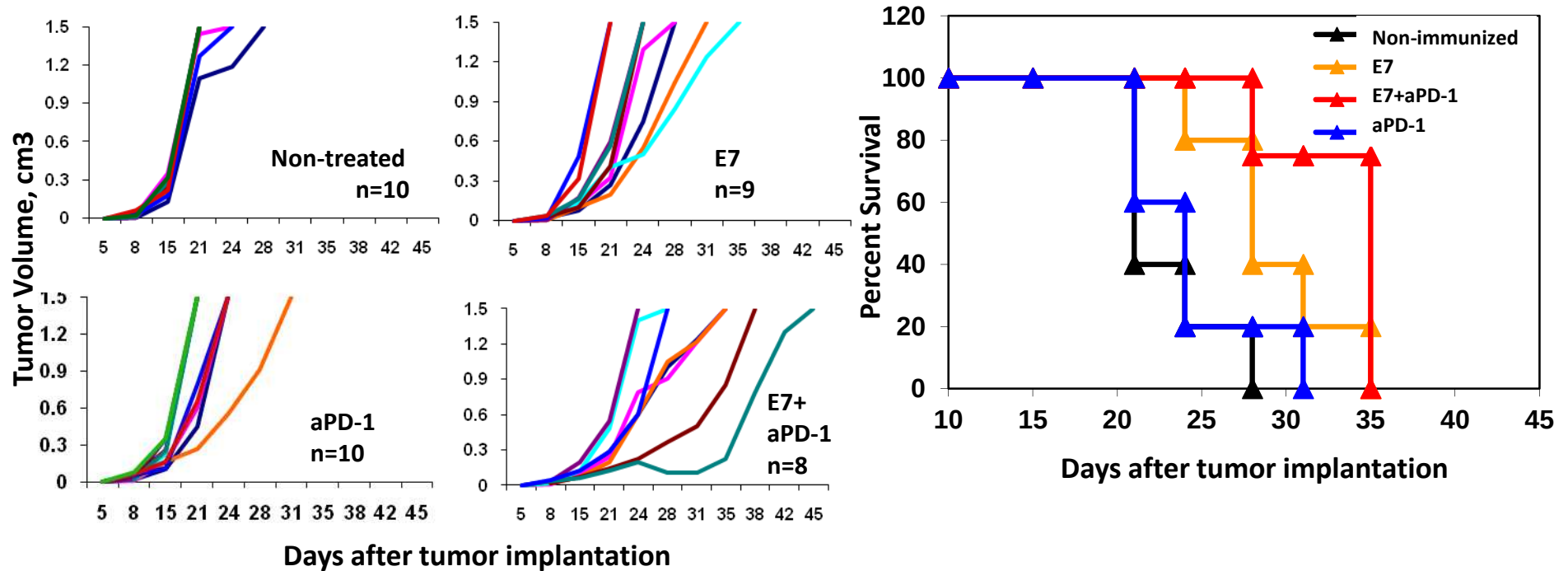
Groups:

1. Non-treated
2. aPD-1
3. E7
4. E7 + aPD-1

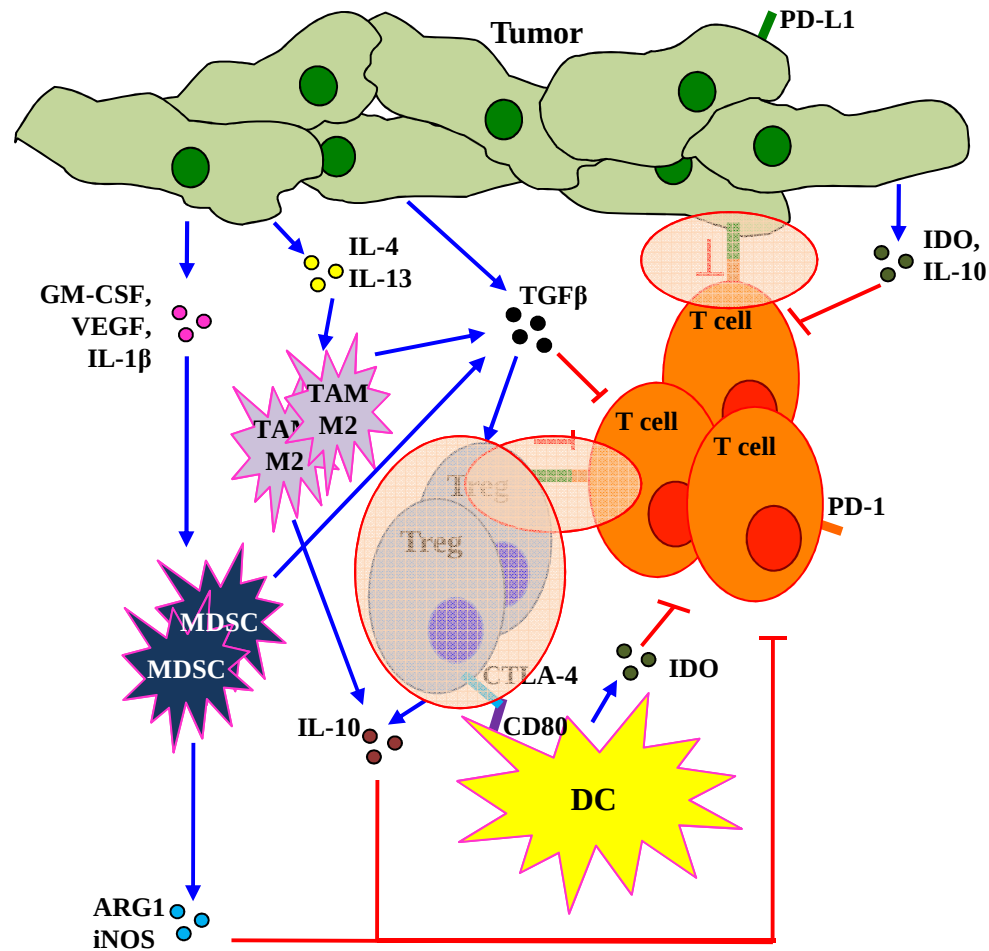


Day 7
after implantation of
50,000 TC-1 cell

Evaluation of therapeutic efficacy of vaccine/aPD-1 combination in TC-1 mouse model

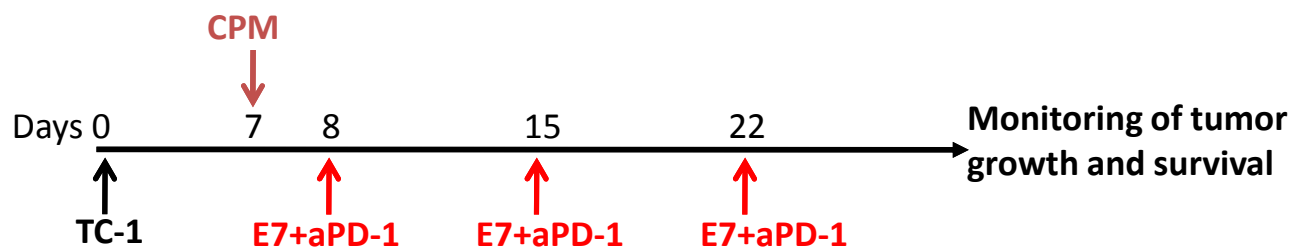


Tumor-Immune Modulating Network

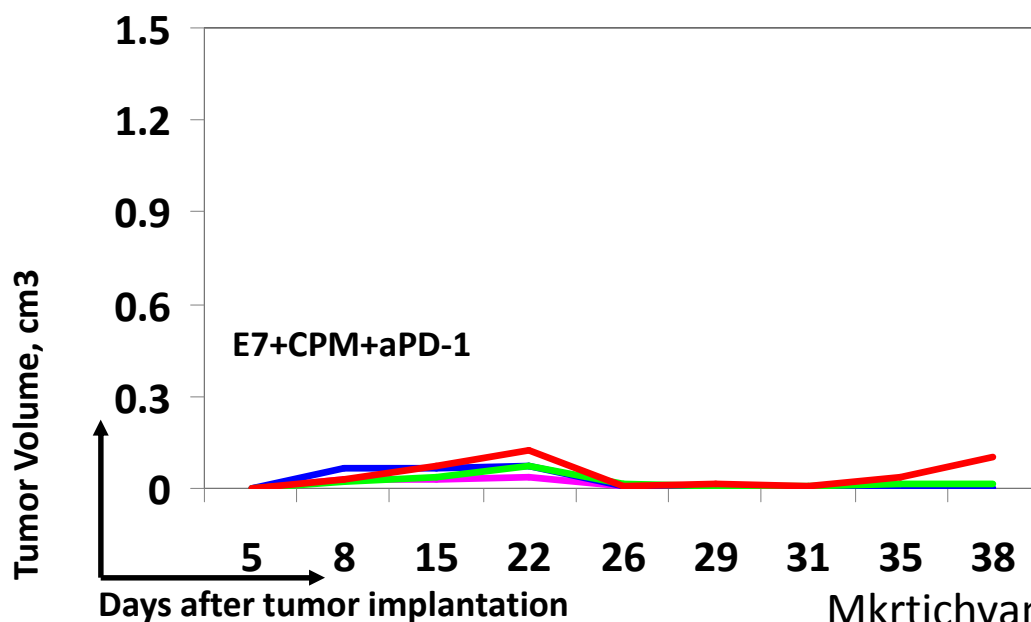
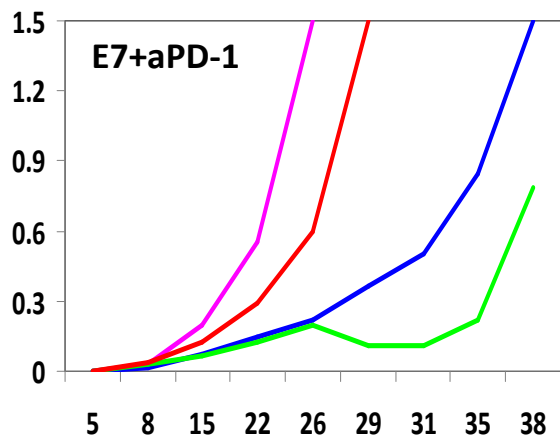
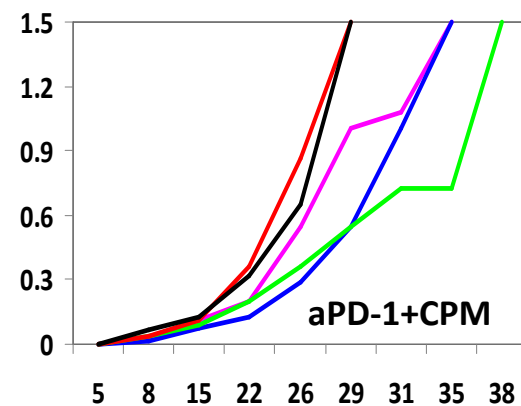
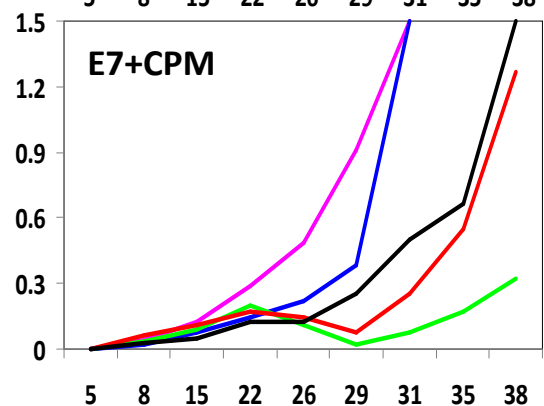
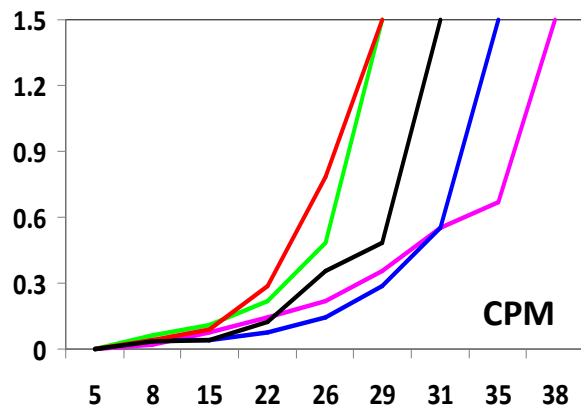
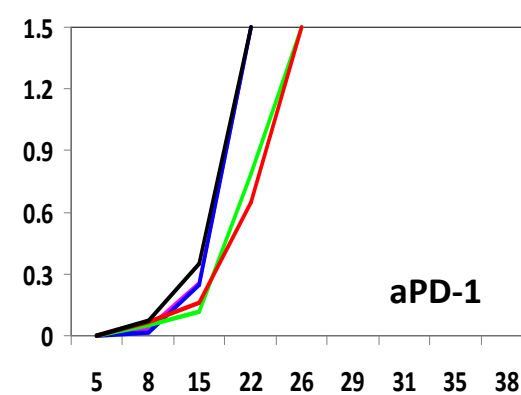
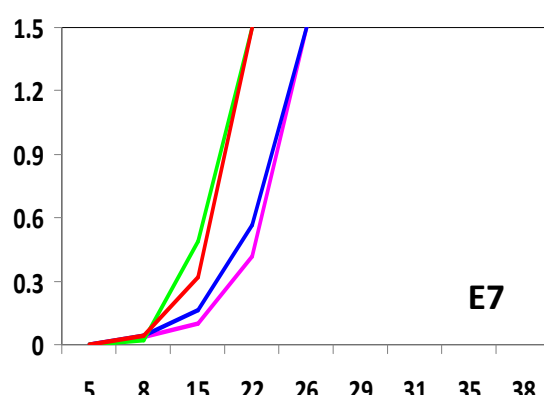
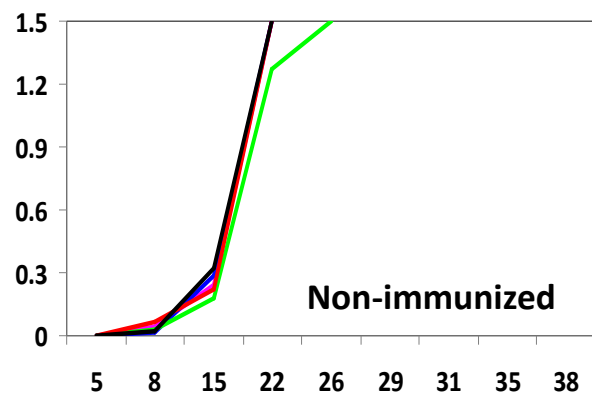


Treg cell inhibitor-cyclophosphamide (CPM)

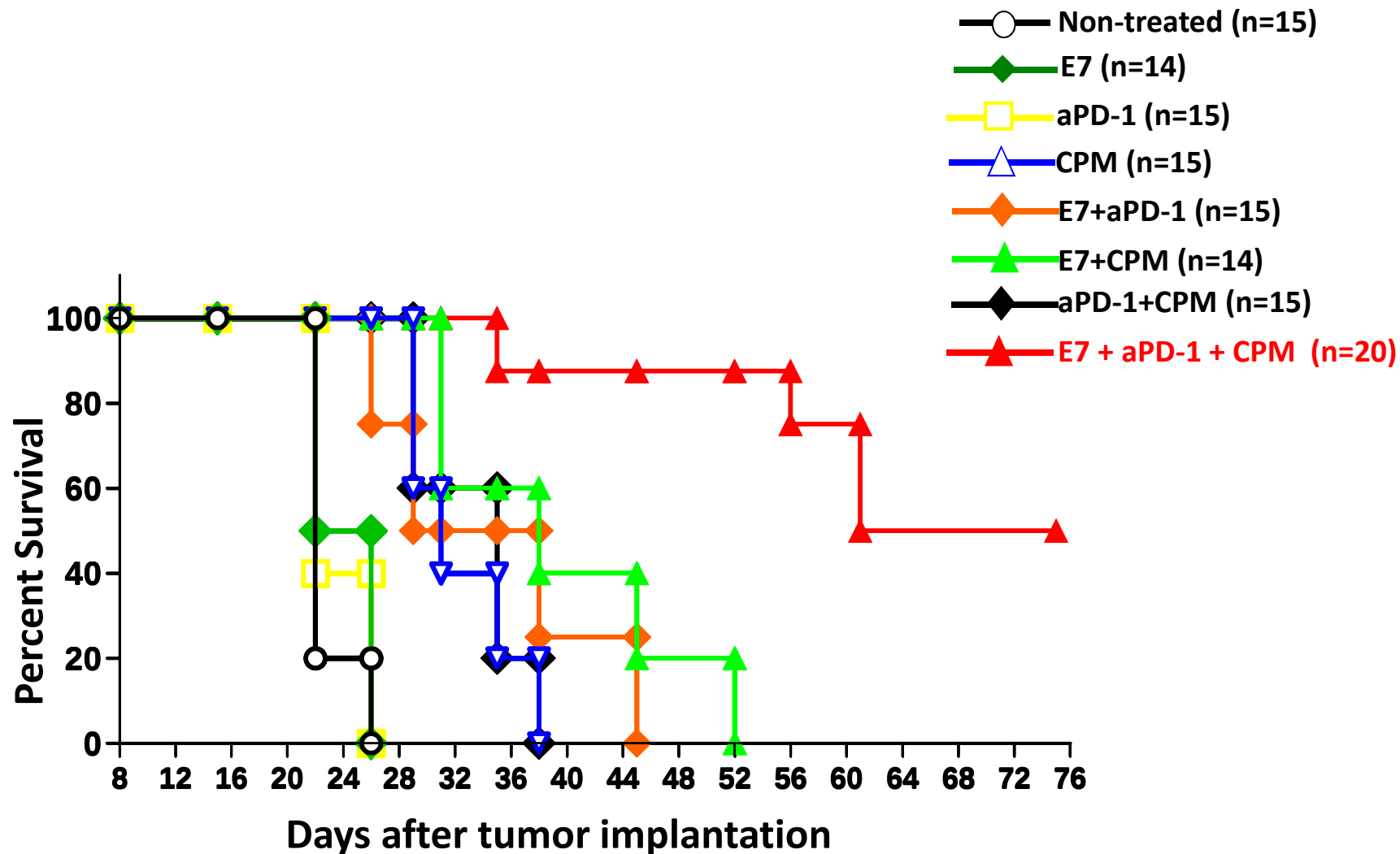
Low Dose CPM selectively targets Treg cells, leaving other T cell populations intact (*Lutsiak et al, Blood, 2005; Ikezawa et al, J Dermatol Sci, 2005*).



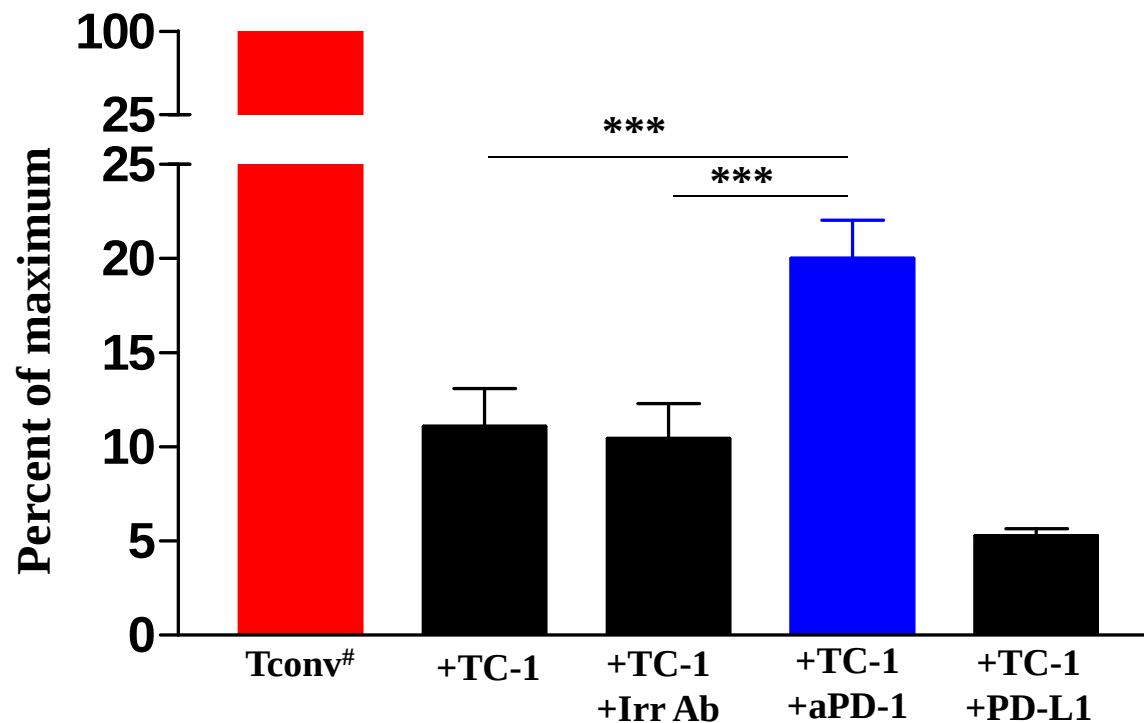
Tumor Growth



Vaccine/anti-PD-1/CPM combination promotes tumor rejection



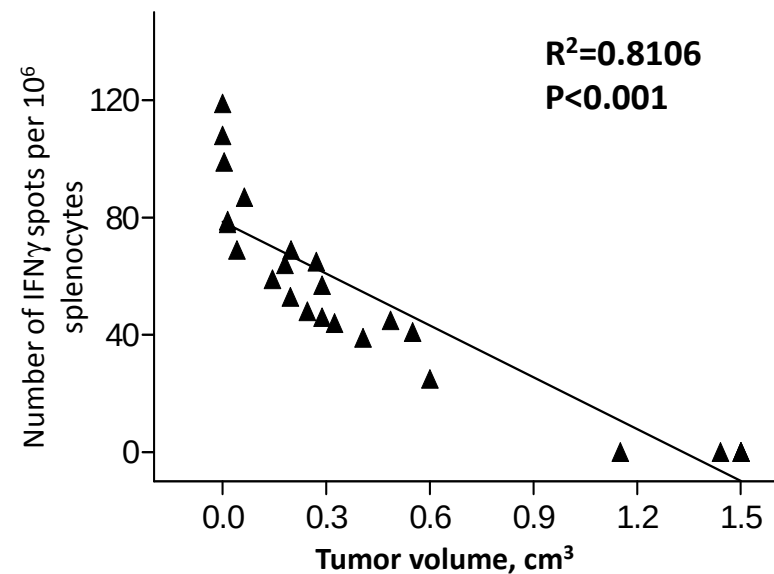
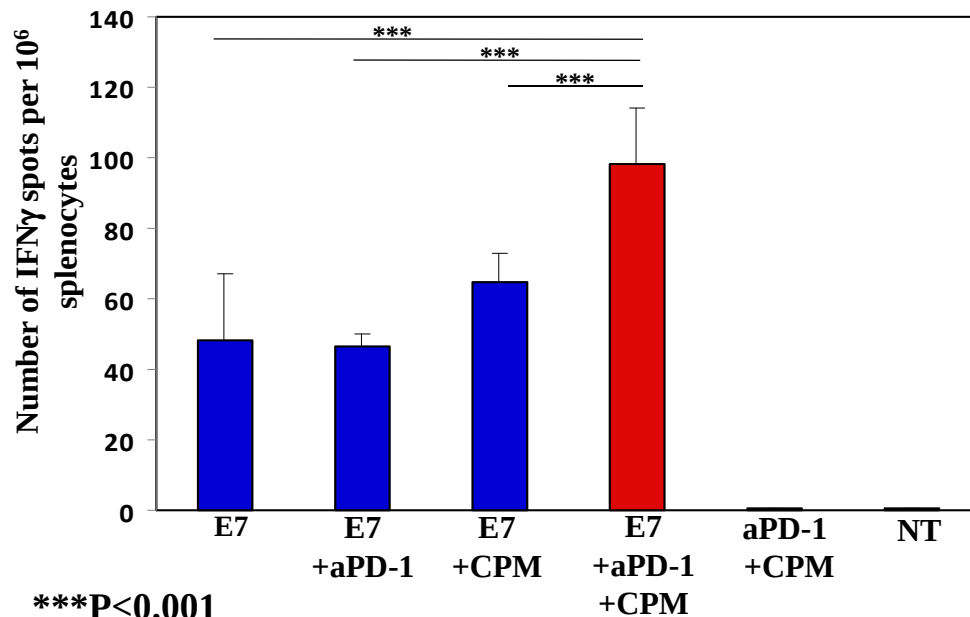
Anti-PD-1 Ab overcomes tumor-induced suppression of stimulated Tconv cell proliferation *in vitro*



***P<0.001

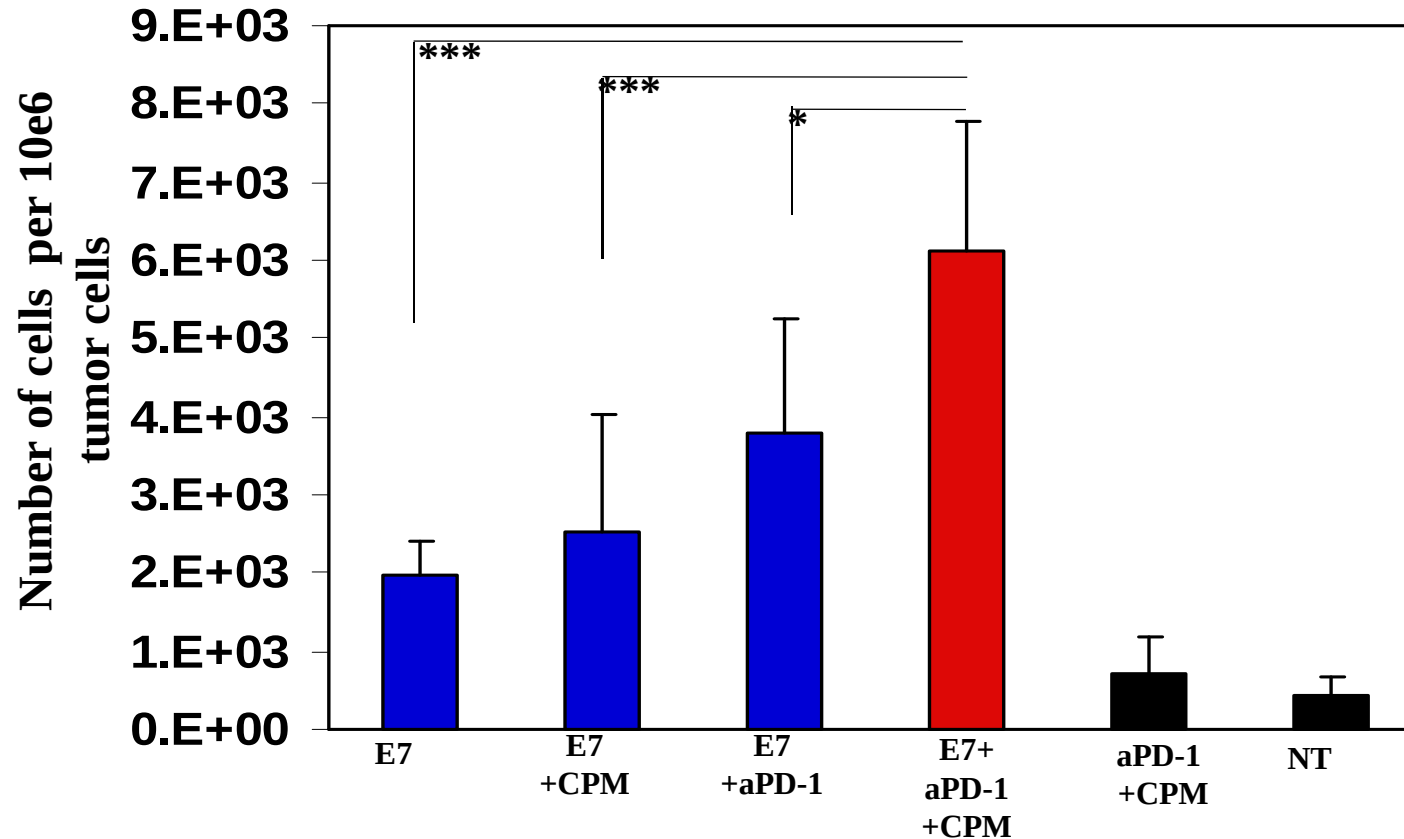
Mkrtichyan et al, 2012

Vaccine/anti-PD-1/CPM combination induces potent antigen-specific immune responses in tumor bearing mice



Vaccine/anti-PD-1/CPM combination increases the levels of tumor-infiltrated CD8⁺ T cells

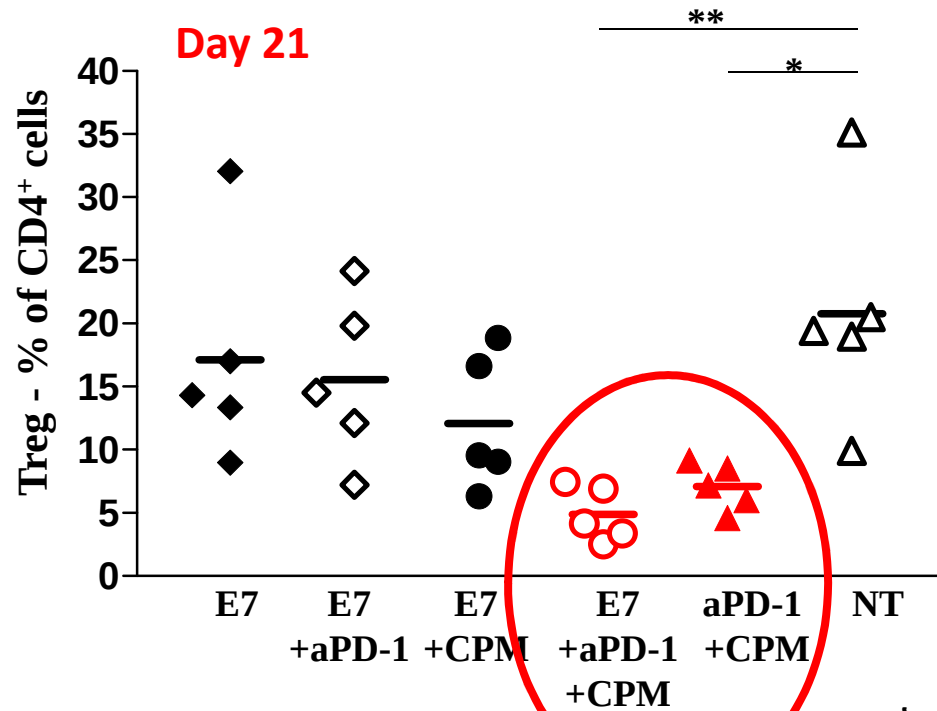
CD8⁺ cells



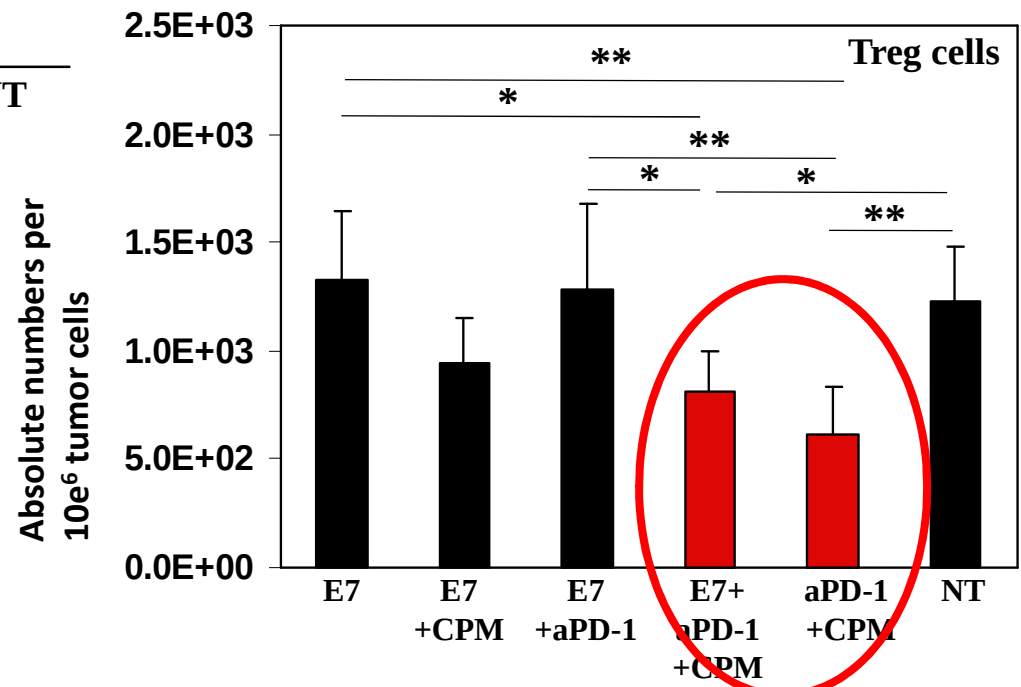
*P<0.05 and ***P<0.001

Mkrtichyan et al, 2012

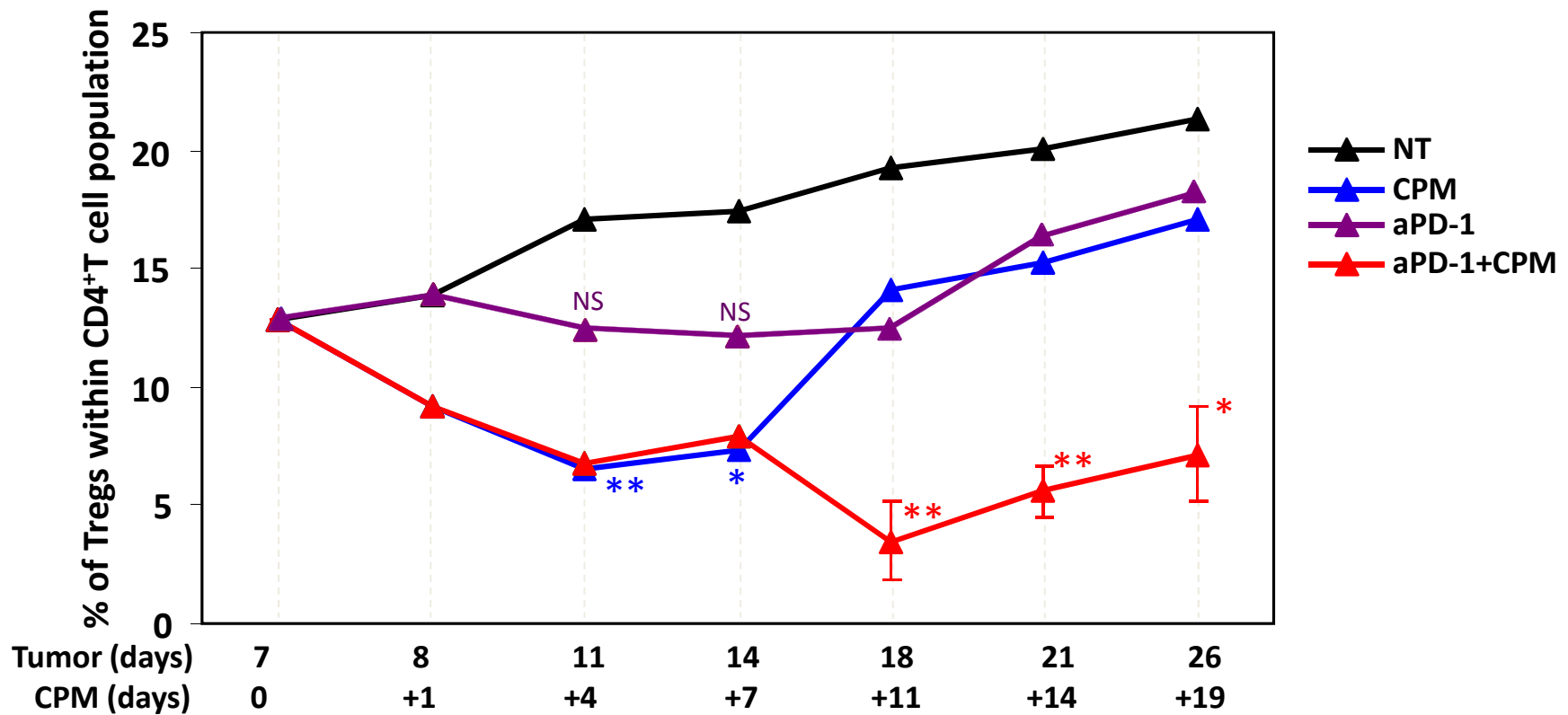
Anti-PD-1 Ab and CPM synergize to decrease the level splenic and tumor infiltrated Treg cells



*P<0.05 and **P<0.01

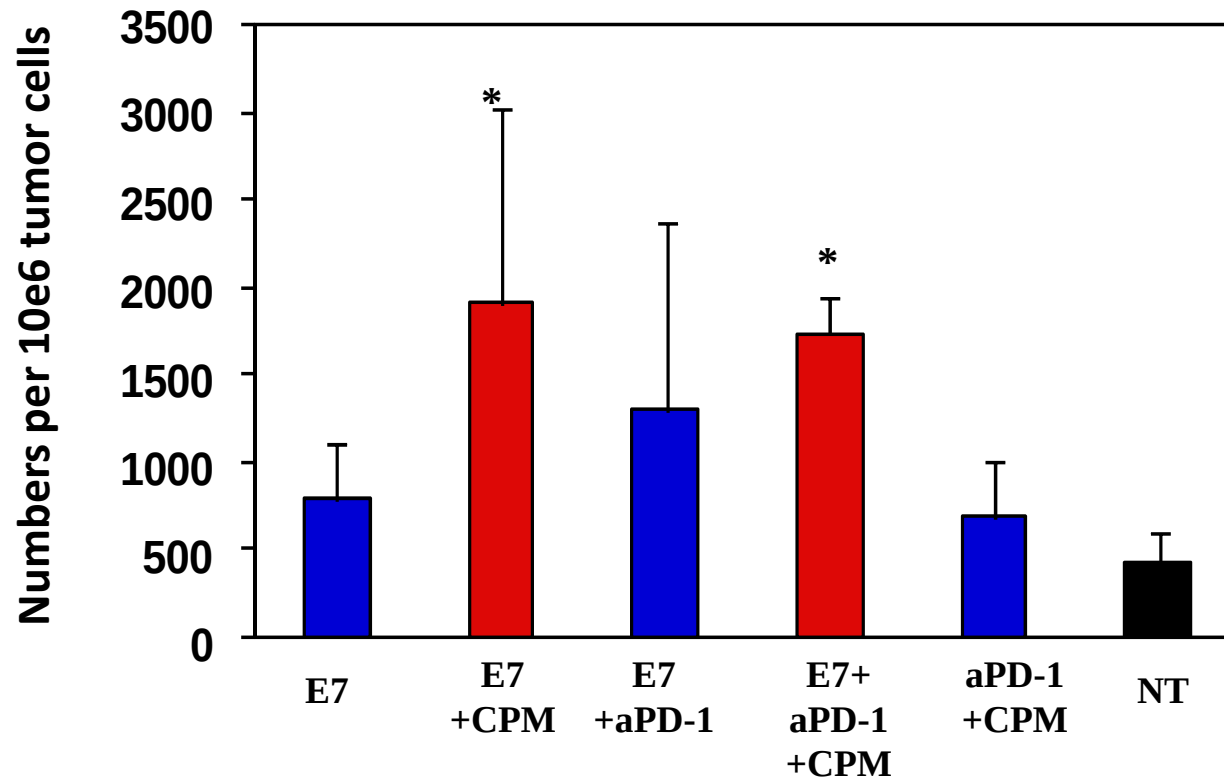


Anti-PD-1/CPM synergize to decrease and maintain low level of Tregs in periphery



Vaccine/CPM combination increases the levels of tumor-infiltrated CD4⁺ non-Treg cells

CD4 T cells

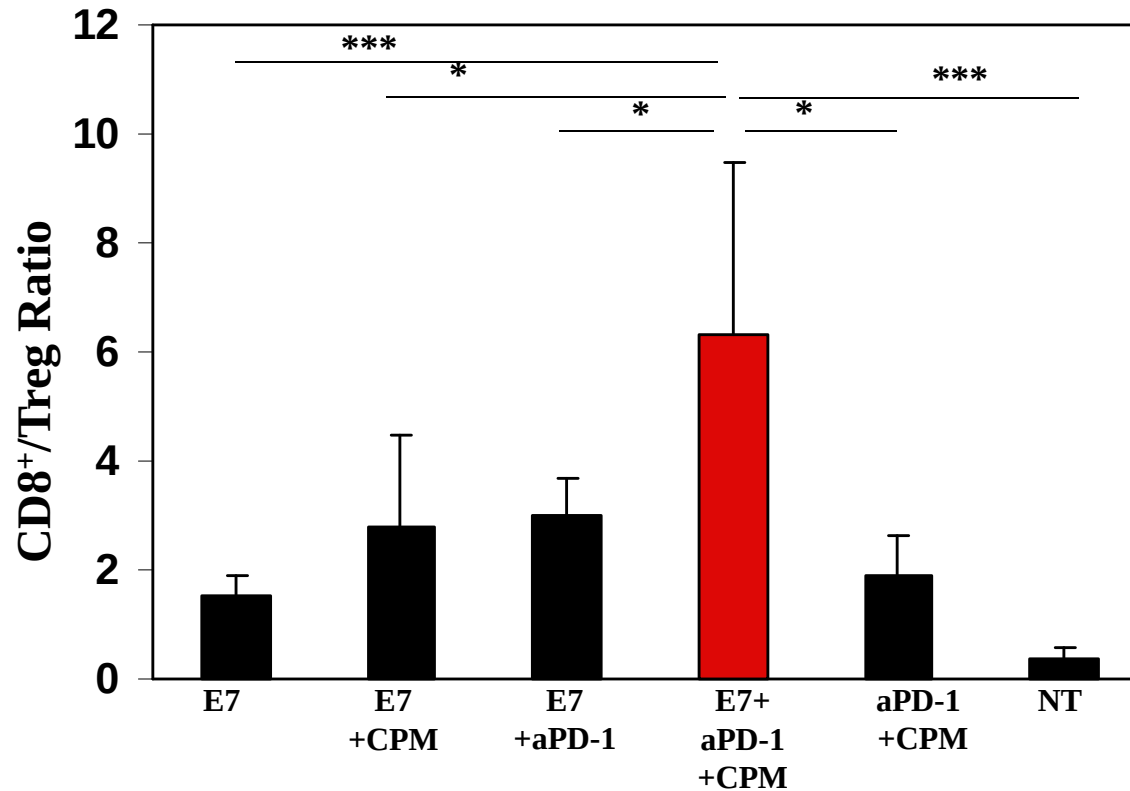


*P<0.05, ***P<0.001

Mkrtichyan et al, 2012

Vaccine/anti-PD-1/CPM combination increases the CD8/Treg ratio in tumor microenvironment

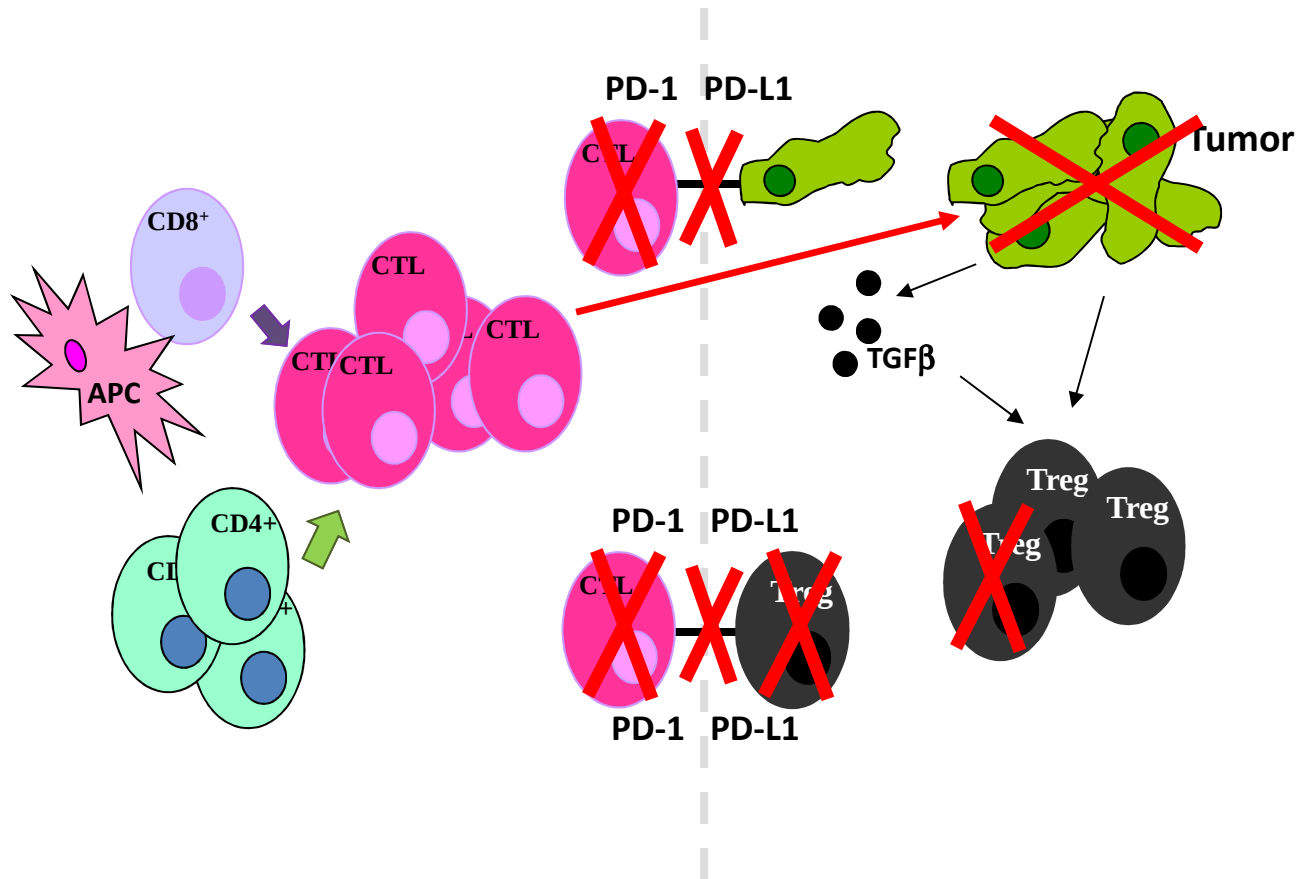
CD8/ Treg ratio



*P<0.05, ***P<0.001

Mkrtichyan et al, 2012

Vaccine/anti-PD-1/CPM: Corrective Immune Therapy



**How can we streamline clinical
development?**

Clinical Trial Translation

**A phase II clinical trial of CT-011 and CPM with
Provenge in prostate cancer patients**

Design

Part 1, Run In phase, up to 12 patients:

CPM 250 mg/m² (Day -1) +

Sipuleucel –T Day 0, 14 and 28 (3-6 patients)

CPM 125 mg/m²

CPM = Low Dose Cyclophosphamide

Apheresis 2-3 days prior to each dose of Sipuleucel-T for cell generation

Design

Part 2, Randomized, total 45 patients

A. Sipuleucel-T: Q 2 Wk X 3

B. Sipuleucel-T Day 0 +
CT-011 (3 mg/kg Day 2) Q 2 Wk X 3

C. CPM (Day -1 only) +
Sipuleucel-T Day 0 +
CT-011 (3 mg/kg Day 2) >>> Q 2 Wk X 3

CPM = Low Dose Cyclophosphamide

Apheresis 2-3 days prior to each dose of Sipuleucel-T for cell generation

Inclusion criteria

- CRPC with progression, testosterone < 50 ng/dL.
- PSA over nadir at least 2X, 3 weeks apart.
- Failed or refused chemotherapy.

Trial Endpoints

Primary endpoint

- Feasibility Provenge™+ CPM.
- Immune Response

Secondary endpoint

- Progression-free survival
- Overall survival (OS)
- Toxicity

Clinical Trials

- A Phase I clinical trial combining CT-011 with P53 vaccine**
- A phase II clinical trial of CT-011 and chemotherapy in pancreatic cancer patients as an adjuvant therapy.**

Do similar reagents act the same?

Clinical Trials

- Phase I/II NYESO Vaccine in combination with AKT inhibitors (AZ) in advanced ovarian cancer
- Combination of AKTi and anti PD1 (AZ) in advanced solid tumors

Clinical Trial Design for Vaccine and immune therapy...

**Do we need dose escalation
trials in vaccine ?**

- Reviewed all cancer vaccine trials on PubMed
- Phase 1, phase1/2, and pilot studies in therapeutic cancer vaccines
- Reported from 1990 through 2011

What is the rate of vaccine-related toxicity in relation to the number of vaccinated patients?

Inclusion criteria

- how does tumor get recognized by the immune system?
- What are the major impediment of the ability of the immune system to control tumors ?

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How does tumor get recognized by the immune system

1. Secretes factors that attract the T cells
2. Present foreign antigens on the HLA molecules
3. Secretes its own antibodies that recognize cancer

The following are co-inhibitory molecules expressed on the tumor

1. PD1
2. CTLA4
3. TIM3
4. OX-40

The following are inhibitory mechanism that help tumor escape the immune system

1. T-regulatory cells
2. Myeloid Suppressive Derived Cells
3. IDO
4. All of the above