IMMUNE THERAPY IN STS: WHERE ARE WE ?

And where are going?

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Pfizer
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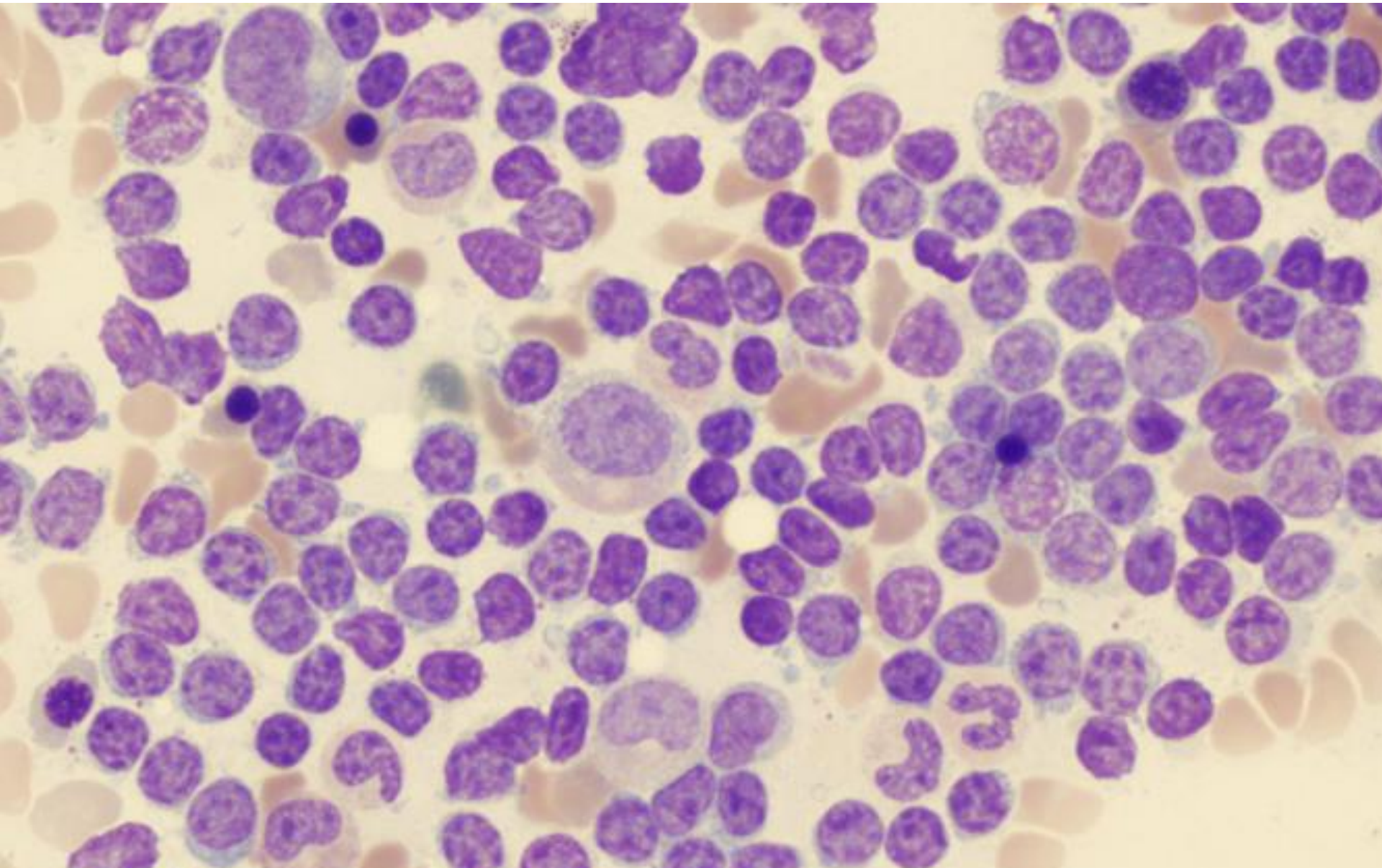
Bayer
Sarcoma Alliance for Research through Collaboration (SARC)
Arcus
Gem Pharmaceuticals
Presage Biosciences

Studying immunity (like studying cancer): Layer upon layer of complexity

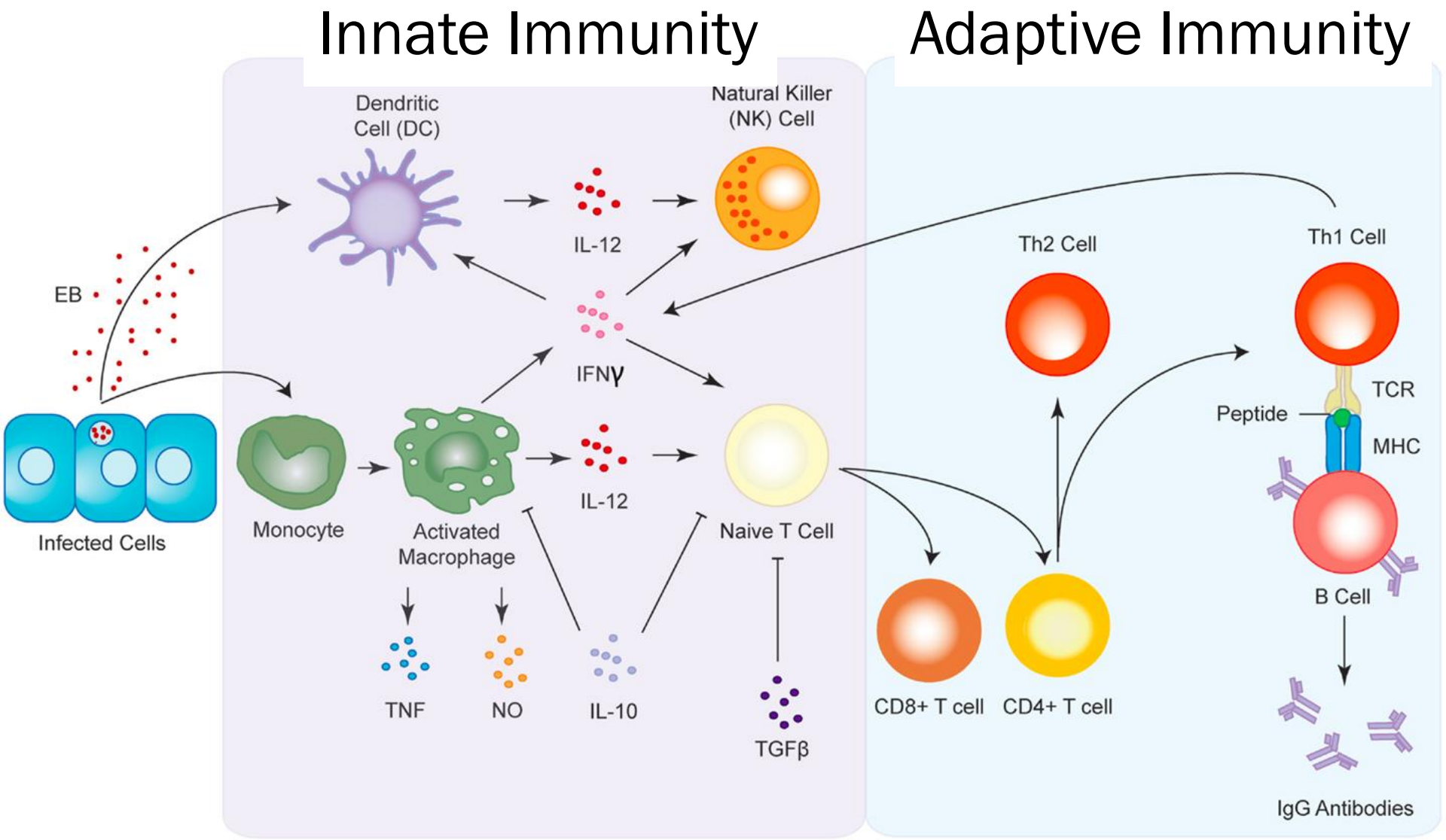
These layers are not just independent *or* dependent: they interact

Boring little lymphocytes ?



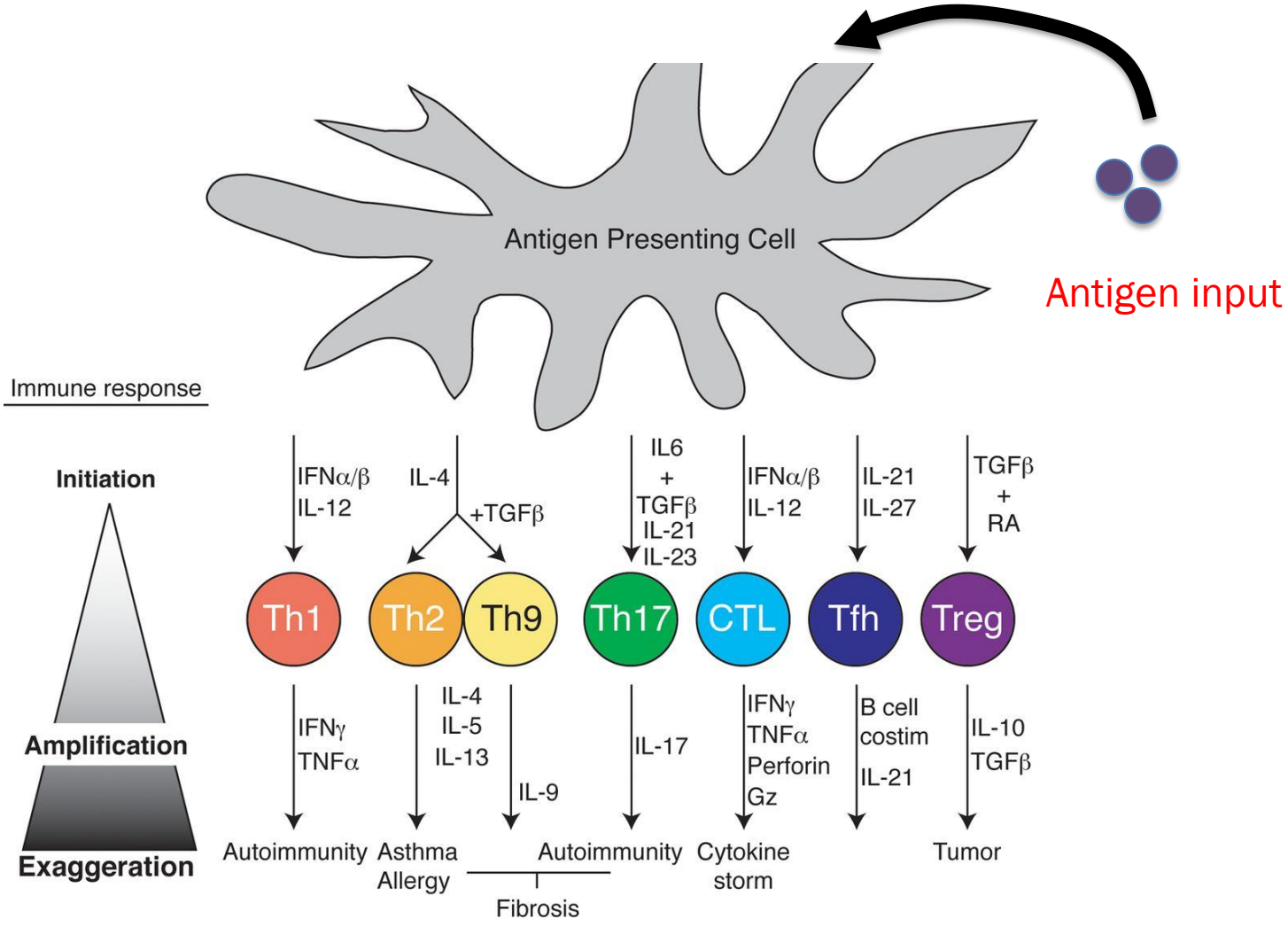
More variety than anyone initially appreciated

Two arms of the immune system



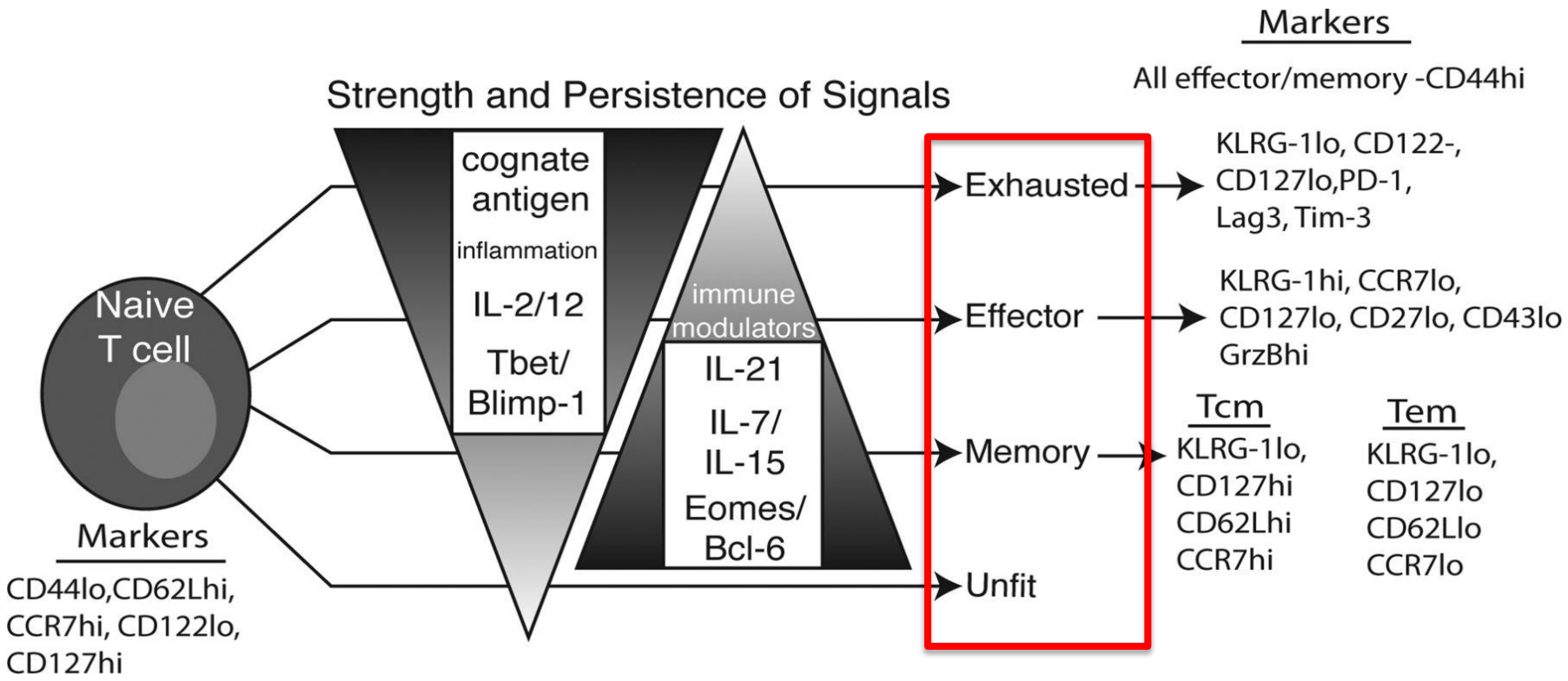
Redgrove KA Front Immunol. 2014; DOI 10.3389/fimmu.2014.00534

T cell subsets



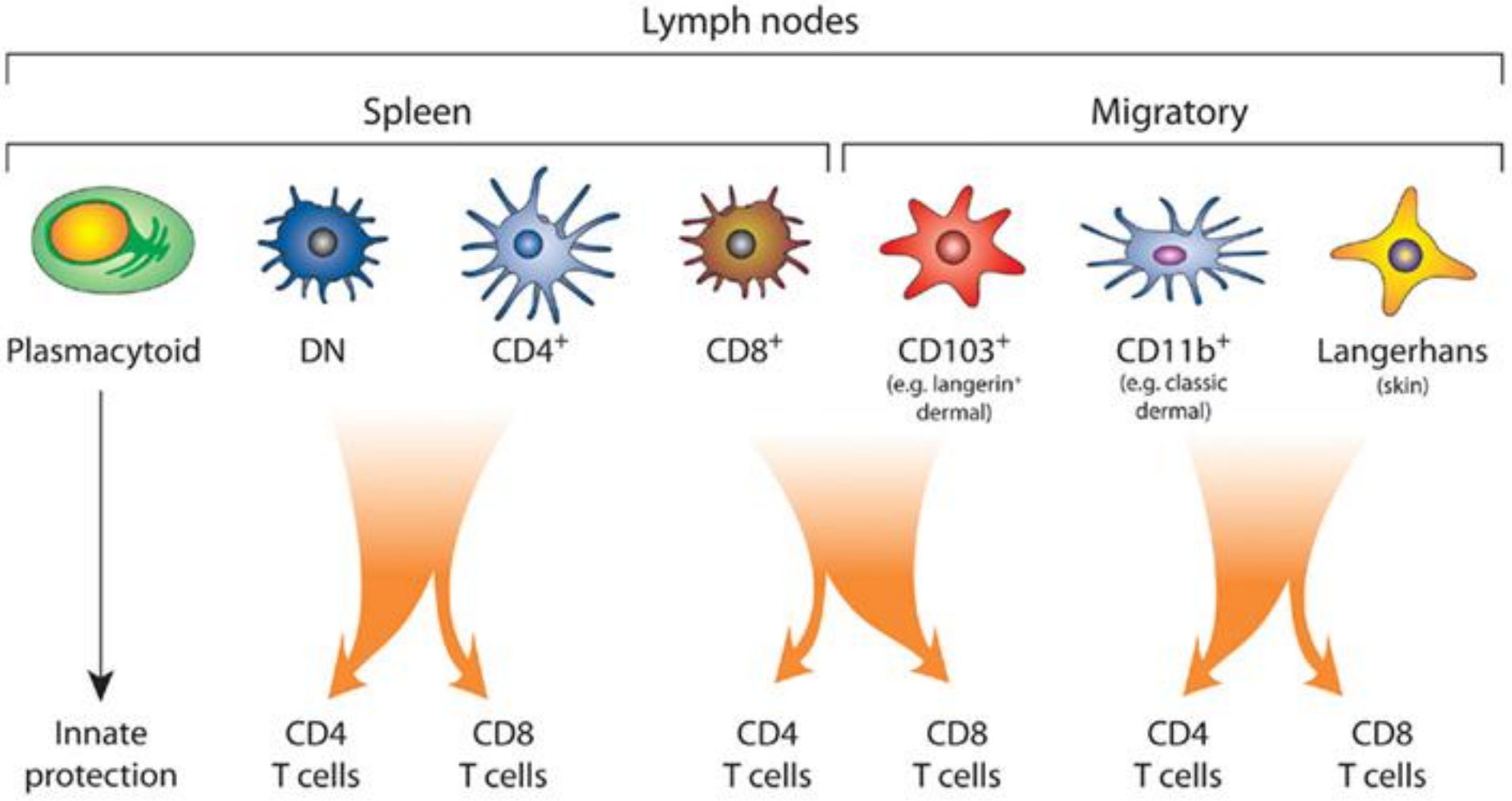
Bailey SR et al. Front Immunol 2014; doi: 10.3389/fimmu.2014.00276

Qualities of stimulated lymphocytes



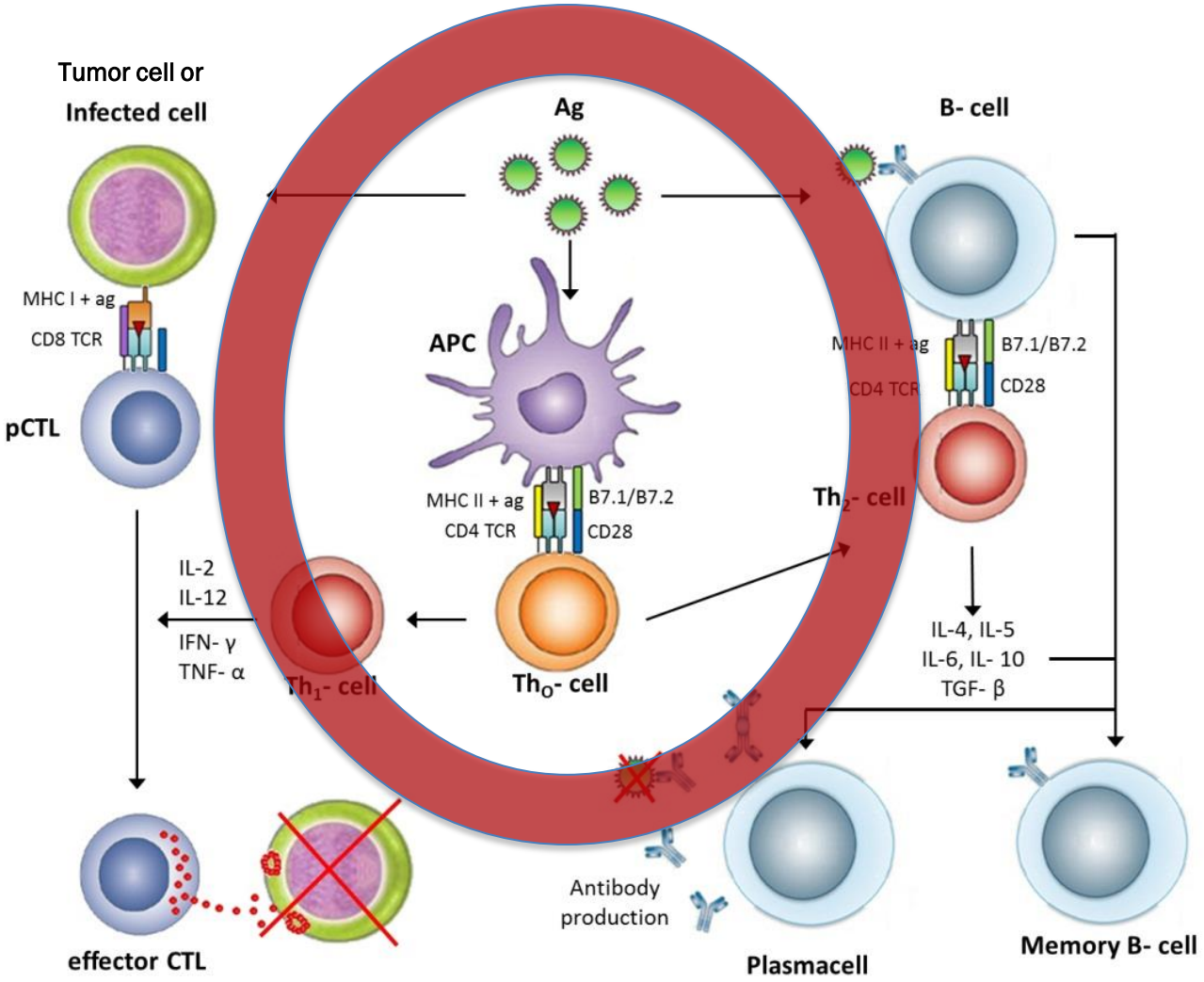
Pennock ND et al. Adv Physiol Educ. 2013; 37: 273

Dendritic cell classes



Caminischi I et al. Front Immunol 2012; DOI 10.3389/fimmu.212.00013

The basic immune response: Cancer as a specific example



De Haes W et al. DOI: 10.5772/51583

Components of an effective immune response against cancer

- Phagocytes / APCs
- T cells
- Tumor antigens
  - Viral
  - Differentiation antigens
  - Novel antigens
- B cells or antibodies – paradoxical effects

- …but tumors obviously grow despite all this

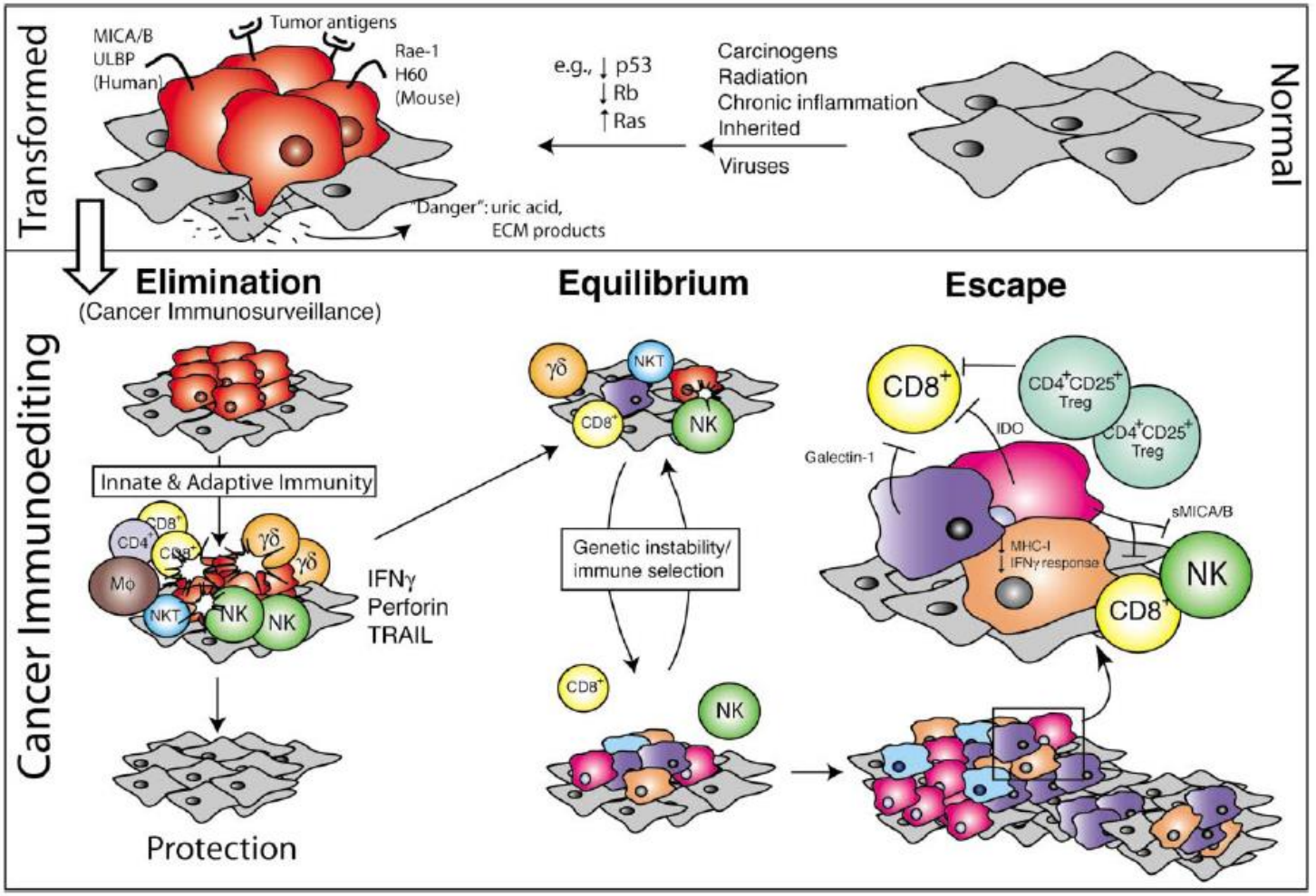
Cancer Immunology's Basic Concept: Immune surveillance of cancer

- If it is possible to *tolerize* the immune system against an antigen, cancer neoantigens must be present that elicit an effective anti-tumor immune response
- If animals and humans can reject tissue grafts, they must have mechanisms to reject cancers

Burnet, F.M. Prog. Exp. Tumor Res. 1970; 13: 1–27.
Thomas L. Cellular and Humoral Aspects of the Hypersensitive State. Ed: Lawrence H.S. New York, Hober-Harper, 529 ppg; 1959.

Amendment to immune surveillance:

Immunoediting (add some Darwin)

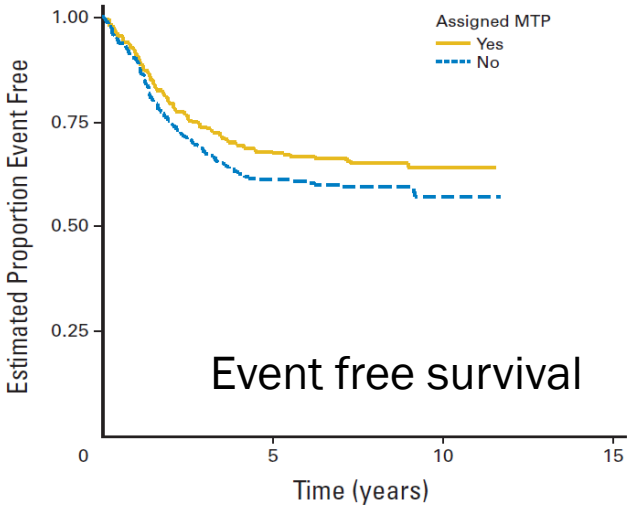


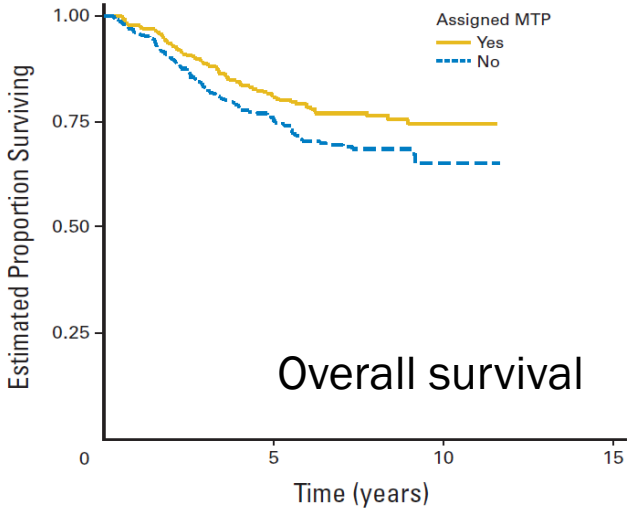
Dunn GP et al. Nature Immunol 2002; 3:991

Dunn GP, Old LJ, Schreiber RD. 2004; Immunity 21: 137

Immunotherapy: what is out there?

- Mifamurtide: Muramyl tripeptide - nonspecific immunotherapy for osteogenic sarcoma





- Limiting factor: cost
- Could MTP-PE work in other sarcomas?

Meyers PA et al. JCO 2008; 26: 633

Modifying the equilibrium between the immune system & cancer

1. Vaccines
   - Specific antigens
   - Whole cells
   - Adjuvants (TLR agonists, viral vectors)

I know the antigen

2. mAb against a specific antigen
   - Passive immunity – antibody directed cell mediated cytotoxicity (ADCC)
3. Activated T cells against a specific antigen
   - CAR-T cells

4. mAb against immune effectors
   - Immune checkpoint inhibitors
5. Stromal effects/effectors
   - IDO

I don't know the antigen, and I don't have to worry to find it

Examples

Vaccinology: NCI meta-analysis

- 440 patients
  - Melanoma (vast majority of patients)
  - Variety of antigens: MART1, gp100, NYESO1, TRP2, HER2, etc
  - RECIST Response rate: 2.6%

Rosenberg SA et al. Nat Med 2004; 10:909

Vaccines: adjuvant + ganglioside vs. adjuvant

- Gangliosides overexpressed in sarcomas even more than melanoma
- OPT821 adjuvant ± GM2/GD2/GD3 vaccine in patients with resected lung metastatic disease from sarcomas
- n = 136
- PFS 6.4 mo on both arms

Carvajal RD et al. J Clin Oncol 32:5s, 2014 (abstr 10520)

Set of vaccine targets examined for years: Cancer germ cell antigens (CGAs)

- Near universal expression of least some CGAs in synovial sarcoma
  - Examples: SSX, MAGE, BAGE, LAGE, NY-ESO-1
- Change in gene regulation of large number of X chromosome genes (most are on X)
- Antibodies against NY-ESO-1 are found in cancer patients with NY-ESO-1(+) tumors
- Vaccine strategies against NY-ESO-1 (+) tumors

NY-ESO-1 as model cancer-germ line antigen

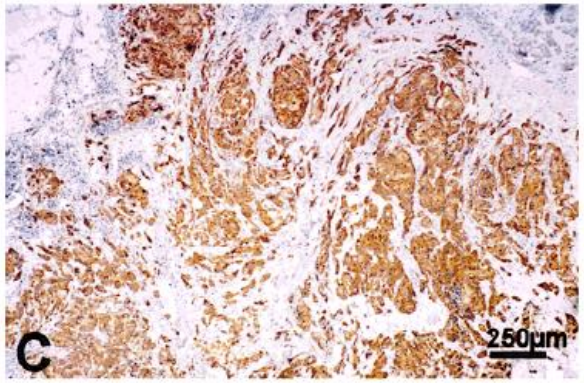
TABLE I – NY-ESO-1 EXPRESSION IN NORMAL TISSUES: IMMUNOHISTOCHEMICAL STAINING WITH MAB ES121 IN NORMAL TISSUES

Tissue	ES121 immunoreactivity
Salivary gland	–
Pancreas	–
Liver	–
Esophagus	–
Stomach	–
Adipose tissue	–
Small bowel	–
Large bowel	–
Thyroid	–
Adrenal	–
Lung	–
Spleen	–
Lymph node	–
Kidney	–
Urinary bladder	–
Prostate	–
Breast	–
Ovary (adult)	–
Vagina	–
Placenta	–
Cervix	–
Testis	++++ germ cells
Skin	–

TABLE III – NY-ESO-1 EXPRESSION IN HUMAN CANCERS WITH NY-ESO-1 MAB ES121

Histological type	Total tested	ES121 positive
Metastatic melanoma	11	4
Breast carcinoma	14	2
Urinary bladder carcinoma	9	2
Synovial sarcoma	3	2
Carcinomas of the head and neck	10	0
Colonic carcinoma	10	0
Leiomyosarcoma	4	0
Liposarcoma	5	0
Renal cell carcinoma	10	0

Diagnosis/histological type (total)	RT-PCR pos/total	IHC pos/total
ACC (33)	6/33	6/33
LCC (9)	2/9	4/9
SQCC (9)	4/9	2/9
Carcinosarcoma (1)	1/1	1/1
Total	13/52 (25%)	13/52 (25%)



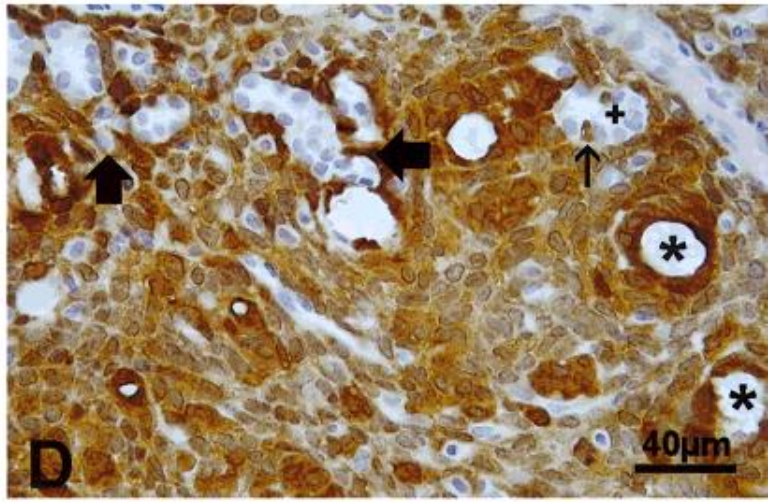
Melanoma

Jungbluth A et al. Int J Cancer 2001; 92: 856

Cancer-germ cell antigen expression: synovial sarcoma

Immunohistochemical analysis

	NY-ESO-1	MAGE-A1	CT7
Positive tumors	80% (20/25)	16% (4/25)	8% (2/25)
Homogeneous expression	56% (14/25)	0	0



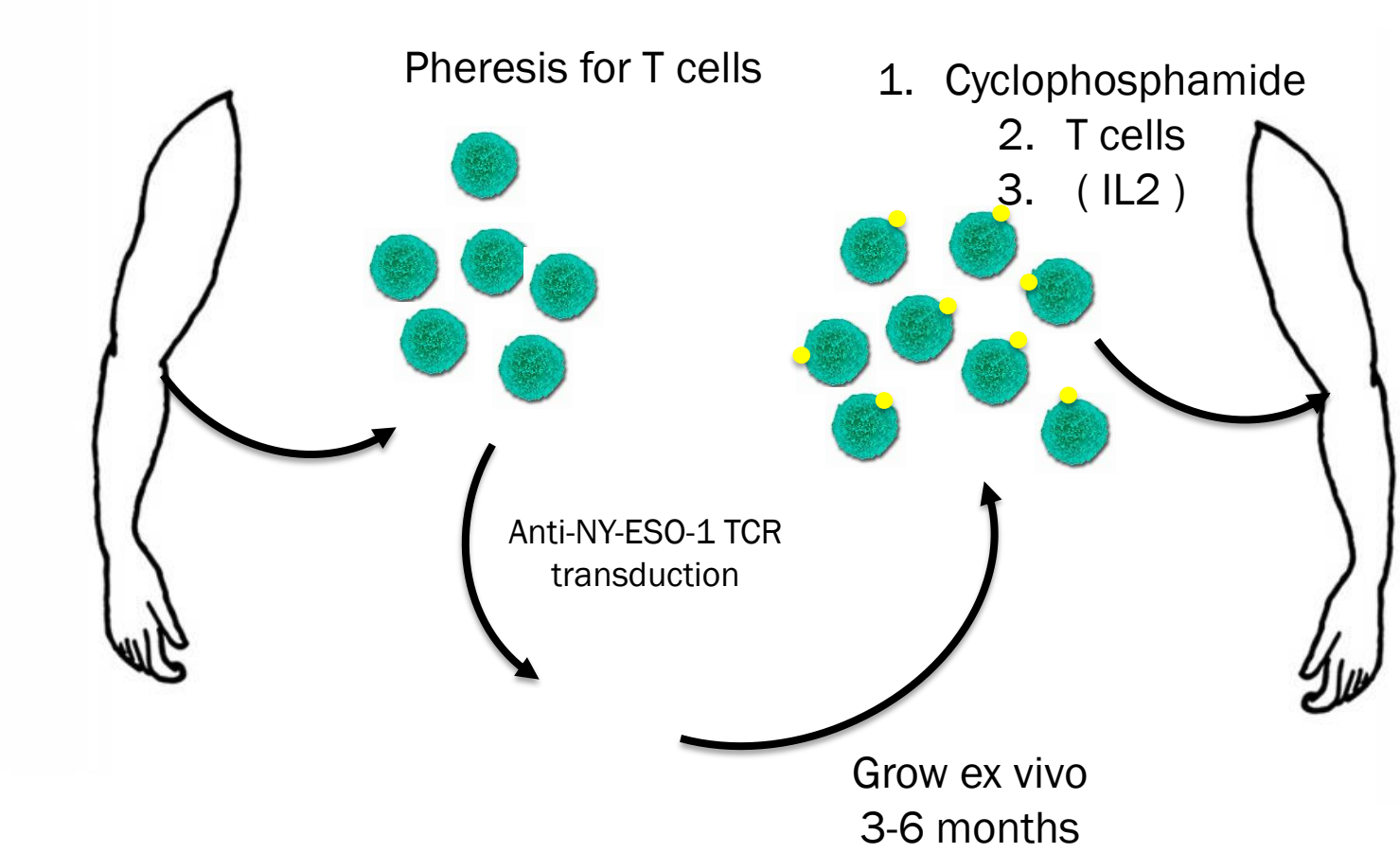
Jungbluth A et al. Int J Cancer 2001; 94: 252

Part II of a vaccine - adjuvant

- Many adjuvants impact Toll-like receptors (TLR)
  - Toll can serves a primitive immune system function in Drosophila, e.g.
- TLR agonists trigger stimulation of the innate immune system and link innate and adaptive immunity in a concerted fashion
- Natural adjuvants include viruses through induction of IFNg and other cytokines and chemokines
  - Viral agents as immunotherapeutics (HSV – melanoma)

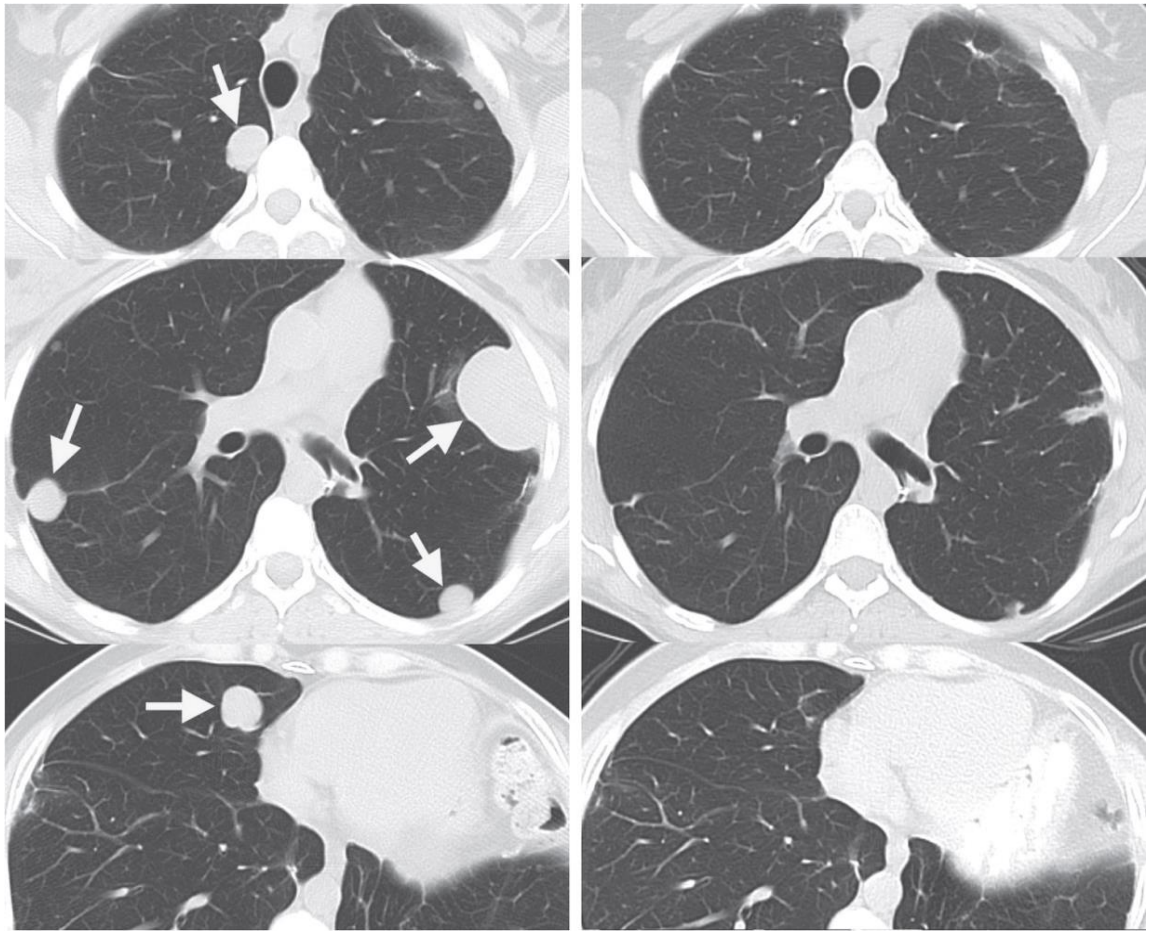
Cellular immunotherapeutics (much more to follow)

Anti-NY-ESO-1 T cell therapy



Robbins PF et al. J Clin Oncol. 2011; 29:917

Responding patient: single infusion



0 +14 months

Robbins PF et al. J Clin Oncol. 2011; 29:917

Synovial sarcoma CAR T cell protocol: NY-ESO-1 specific

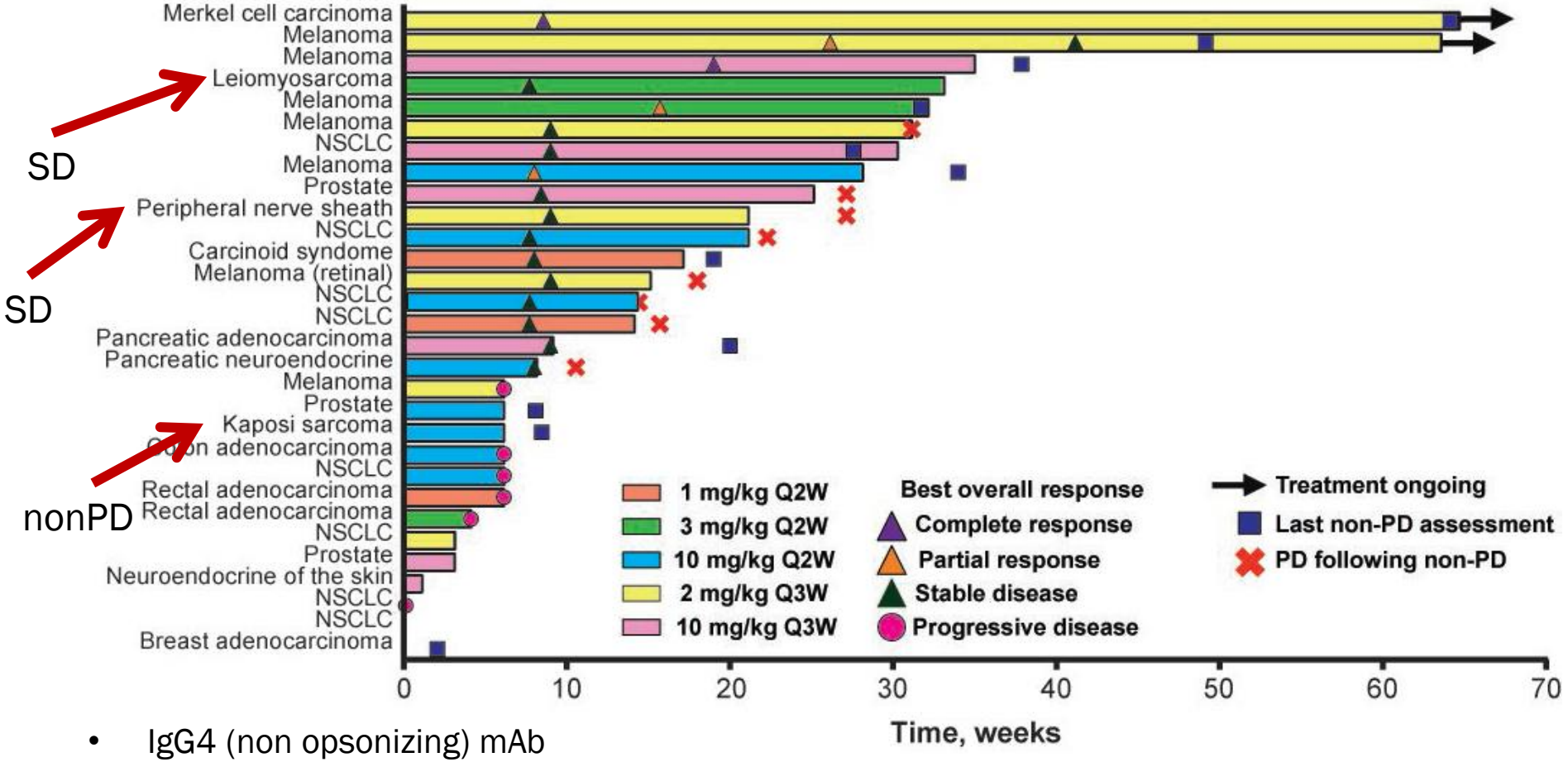
- Clinicaltrials.gov # NCT01343043
- NCI, MSKCC, CHOP
- Ages 4-55
- HLA-A*02:01 patients only; tumor must be NY-ESO-1 (+) by IHC
- No prior therapy for 3 weeks
- Evaluation for T cell #: days 0-14, 21, 28, 42, 60, months 3, 4, 5, 6, 9, 12; q6mo x 3 yrs

Immune checkpoint inhibitors

- Perhaps best evidence of immunoselection, immuno-editing
- Tumors escape recognition via negative co-stimulation of T cells
- Release ***pre-existing*** (but otherwise repressed) immune response for anticancer effect
  - Role of mutational burden? NSCLC, melanoma
    - Counter example: RCC
    - What about sarcomas?
- As we are learning in other diseases, can combine these agents with other agents

Pembrolizumab phase I: n=3 sarcoma pts

More at ASCO 2016…



- IgG4 (non opsonizing) mAb
- n=6 synovial sarcoma ipilimumab study without a responder (advanced disease)
- SARC28 pembrolizumab study; ALLIANCE nivolumab + ipilimumab accrued

Patnaik A et al. CCR 2015 Oct 7; PMID: 26446947

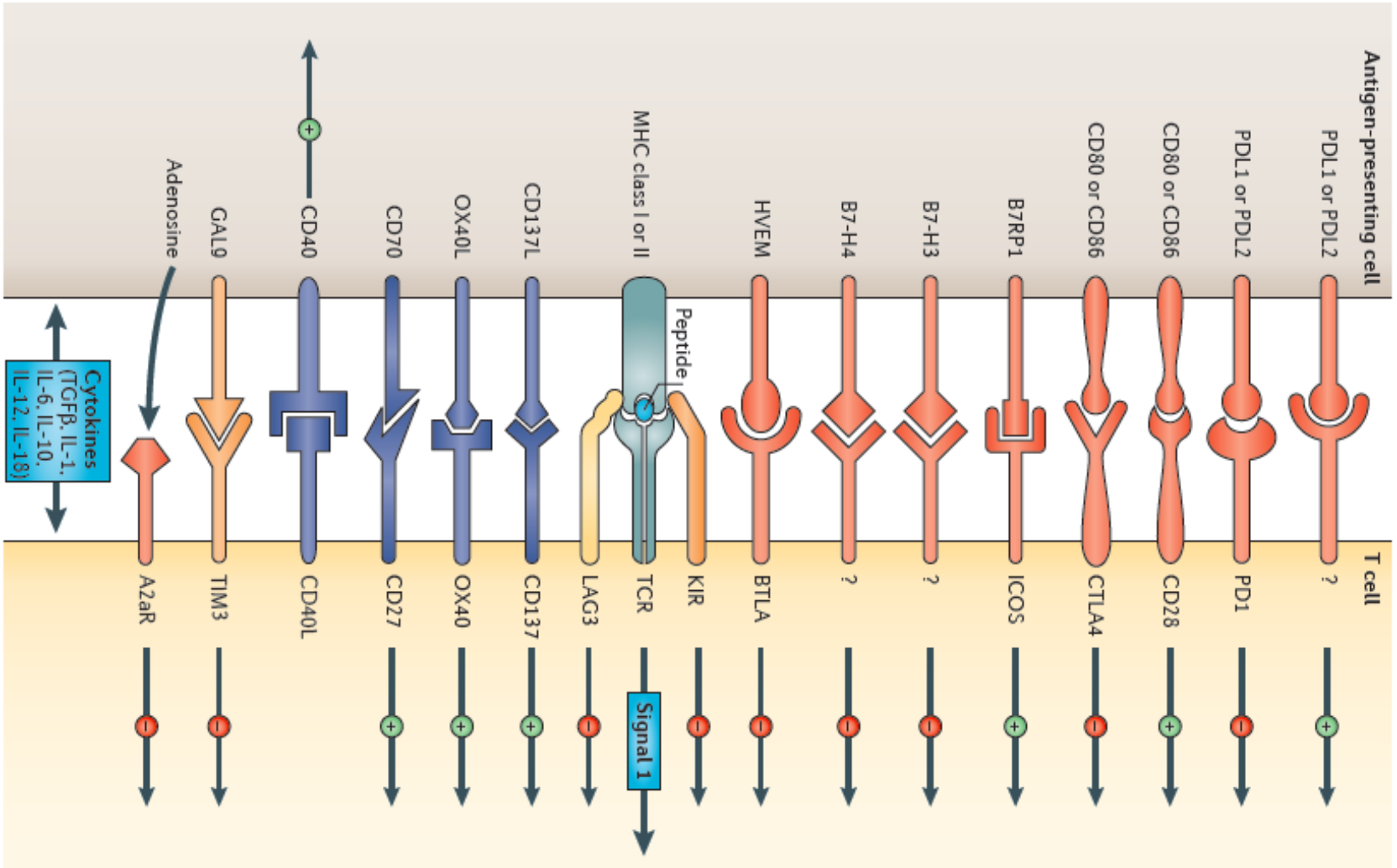
Maki RG et al. Sarcoma. 2013:168145. PMID: 23554566

How many co-stimulators?

APC

T cell

+ or -



Pardoll DM. Nature Rev Cancer 2012; 12: 252

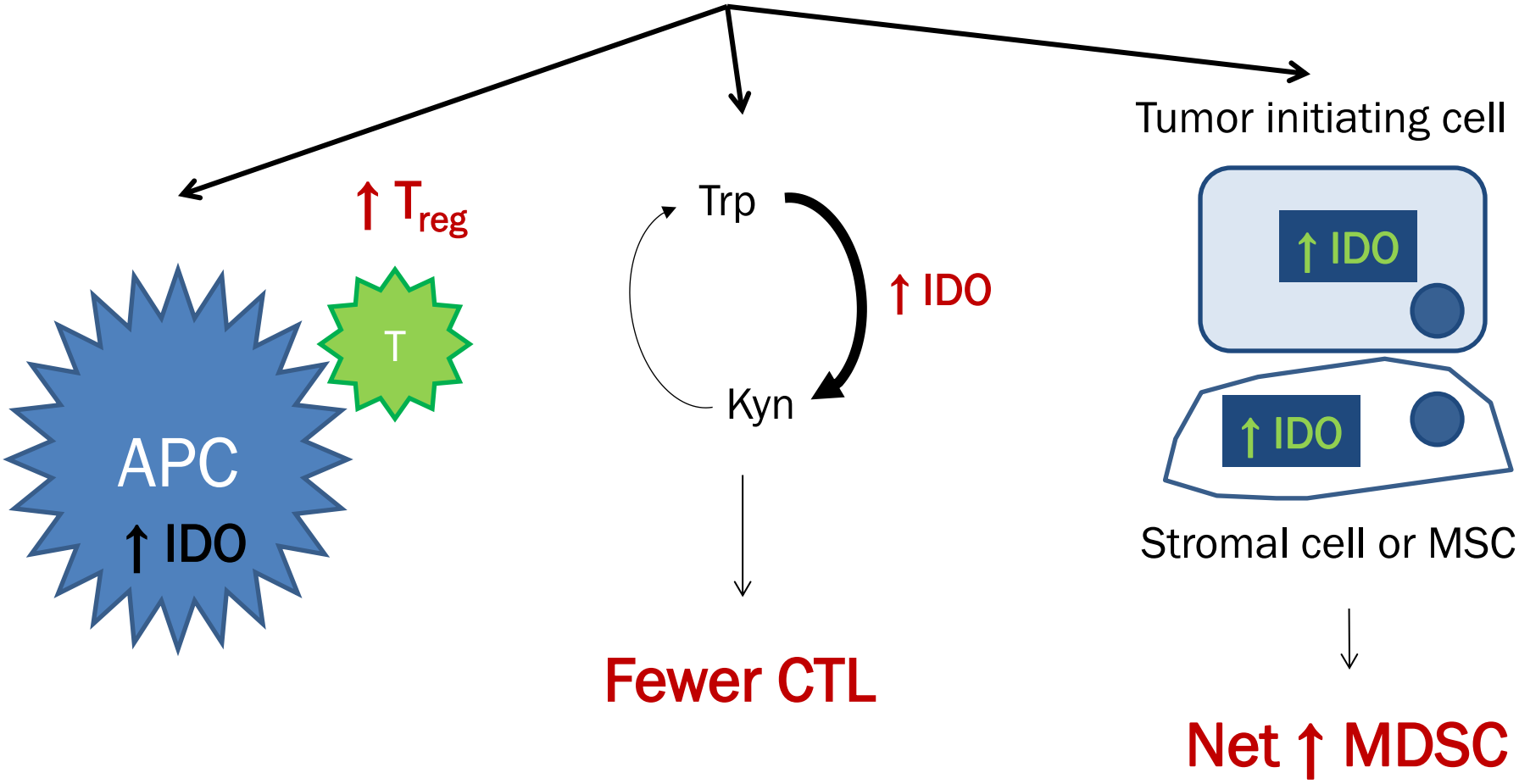
Microenvironment: IDO

Indoleamine 2,3-dioxygenase

- IDO is the 1st step in tryptophan catabolism (to kynurenine)
- Depleting tryptophan is permissive for cancer growth and is immunosuppressive
  - Akin to L-asparaginase in acute lymphoblastic leukemia
- IDO induction decreases tryptophan → decreased transcription factors GLK1 and GCN2 → **mTORC1** decreased
- ***Imatinib*** inhibits IDO; can it help T cells attack GIST?
- Single agent inhibitor studies underway
- IDO inhibitors can / will be combined with other therapeutics

Balachandran VP et al. Nat Med 2011; 17: 1094

↑ IDO turns off tumor immunity



Prendergast GC et al. C I I 2014; 63:721

CD47

- Different way to promote ADCC
- "Don't eat me" signal to APCs
  - Also found on RBCs
- Anti-CD47 – present antigen to immune system more effectively?
  - Hemolysis seen in some studies
- Also eminently combinable with other immunotherapeutic approaches

McCracken MN et al CCR 2015; 21: 3597
Liu J et al PLoS One 2015; 10: e0137345. PMID 26390038

Conclusions

- Plethora of options for immunotherapy studies
- Complication: Over 50 sarcoma subtypes / biologies
  - In which diagnoses is immunotherapy germane?
    - Translocation sarcomas: CAR-T vs specific antigen?
    - Aneuploid sarcomas: immune checkpoint agents?
    - ANY: TLR agonist, viral agents, IDO inhibitors, anti-CD47
  - Hard to test in any environment other than people
    - PBMC are not representative of what happens in the tumor
    - Feasible but very expensive to get repeat tissue biopsies
- Will we be talking about a mechanism this year, or looking at a few exceptional responders?


- FIN -