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Society for Immunotherapy of Cancer

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Cytokines in cancer: Biology and therapy

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11/8/2018

SITC, Washington D.C.

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Presenter disclosure information

Kim Margolin

The following relationships exist related to this presentation:

ImaginAb, consultant
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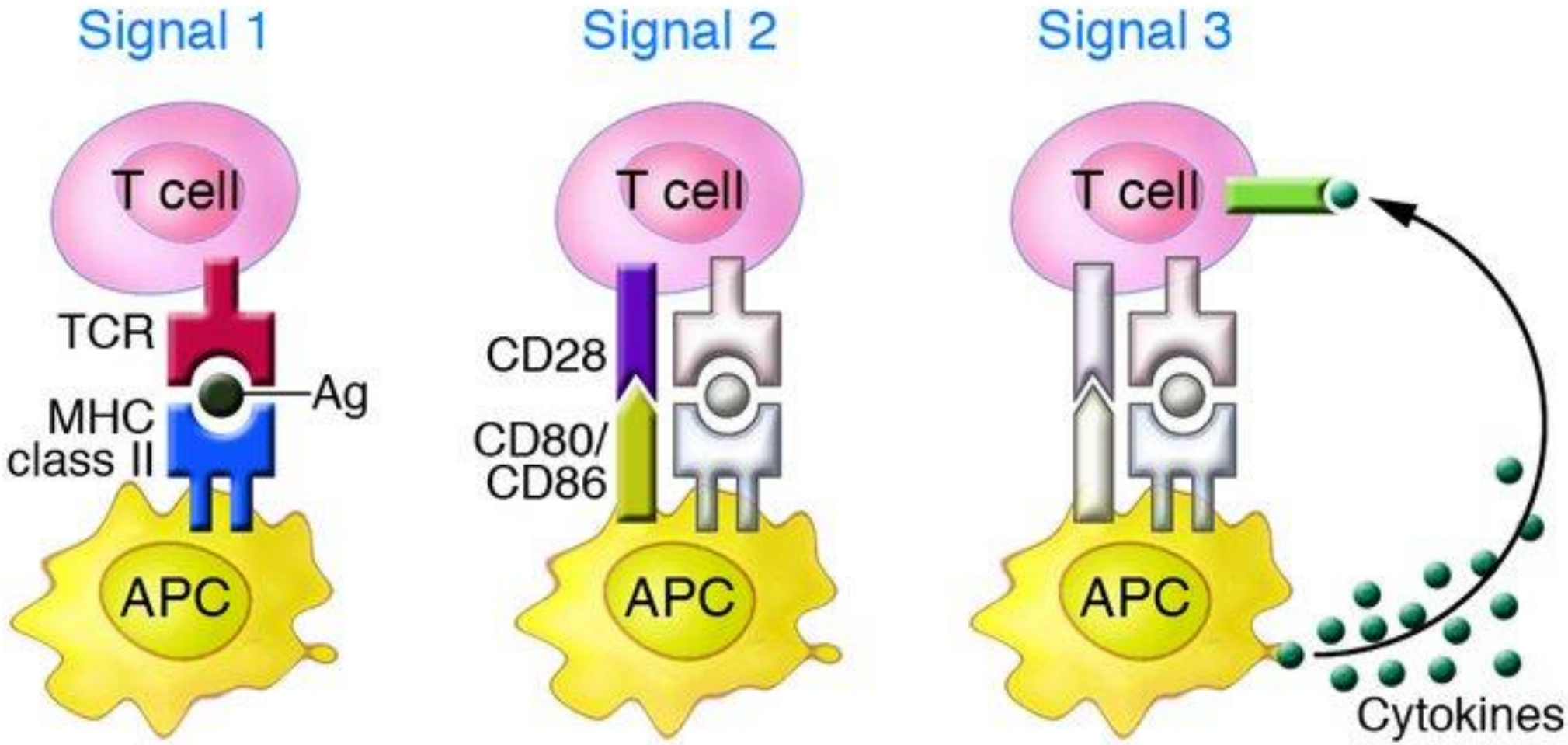
Organization of the talk

- Introduction to cytokine biology
  - Families of cytokines with structural and/or functional similarities
  - Cytokine-producing cells and stimulatory events
  - Target cells and mechanisms of action
  - Roles in normal physiology and inflammation
  - Functions in cancer biology and therapy
  - State of the art and future directions
- Specific cytokines used for Rx of malignancy
- Combination therapies involving cytokines

Overarching concept of cytokines

- Provide signal 3 to adaptive immune responses
  - Signal 1=TCR-MHC interaction around a peptide
  - Signal 2=costimulation through CD28:B7.1 engagement
  - Signal 3=cytokine enhancement
- Mediate important cell-cell communications in innate and adaptive immune response
- Modulate strength of inflammatory and immune responses
- Contribute to pro-tumor and anti-tumor effects in immunosurveillance

Signals 1,2,3 in the adaptive immune response



Type 1 and type 2 “polarized” responses—remarkable activity, but substantial plasticity

- Type 1—acute inflammation, innate→adaptive immunity
  - Antiviral
  - Anti-tumor cytotoxicity, especially CD8+ T cells
  - Associated with distinct gene expression signatures
  - Classical type 1 cytokines: IL-2, IFN-γ, TNF
- Type 2—chronic inflammation, suppressive effects, pro-tumoral
  - Physiologic limitation of type 1 responses for host protection
  - Mediators of some autoimmune, other inflammatory diseases

T-cell cytokines (interleukins) that signal through a common gamma chain (γc) receptor

Cytokine	Cytokine receptor structure
• IL-2	$\alpha\beta\gamma_c$ chain (high-affinity) or $\beta\gamma_c$ (low-affinity)
• IL-4	IL-4 receptor*, γ_c
• IL-7	IL-7 α receptor, γ_c
• IL-9	IL-9 receptor, γ_c
• IL-15	IL-15 α receptor (generally cell-bound), $\beta\gamma_c$
• IL-21	IL-21 α receptor, $\beta\gamma_c$

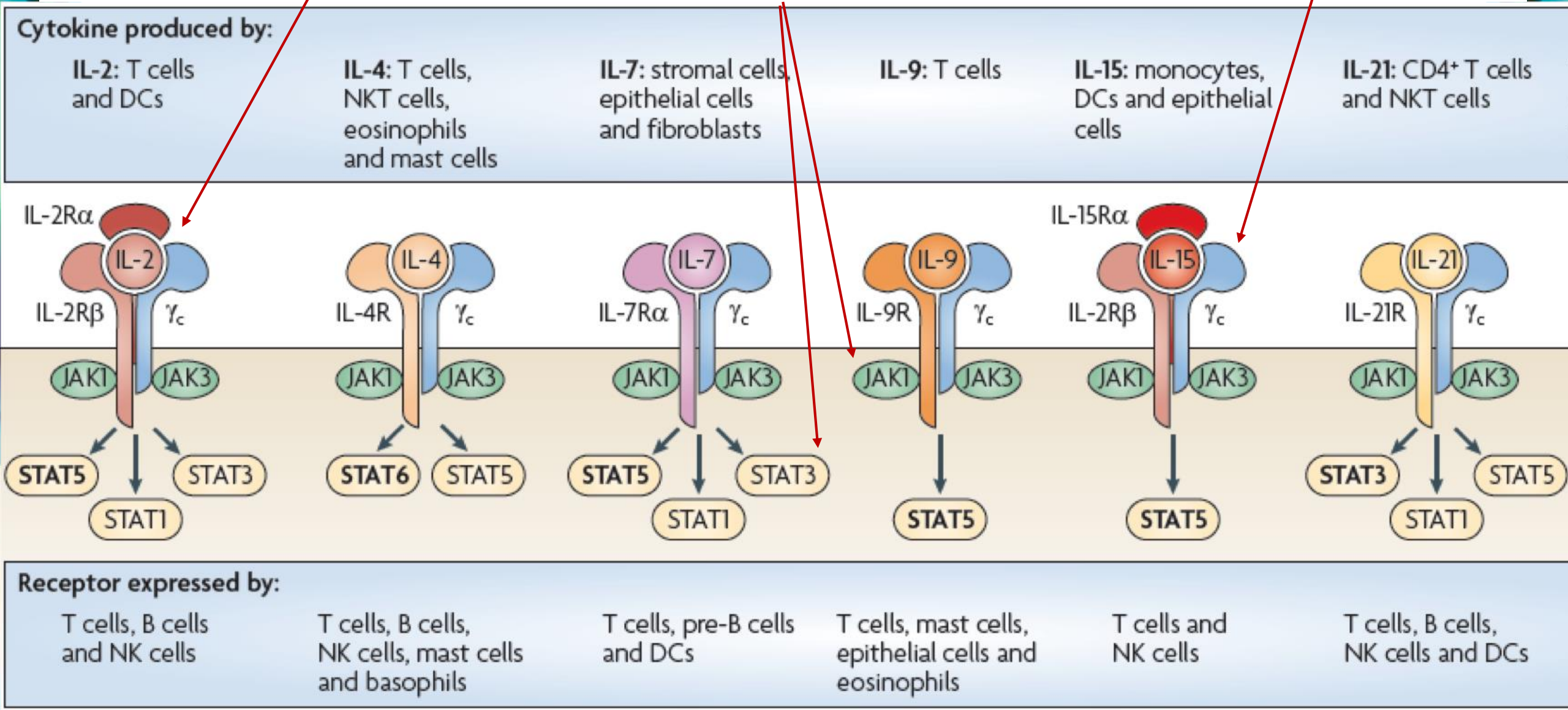
*Also used by IL-13

T-cell cytokines (interleukins) that signal through a common gamma chain (γc) receptor

Cytokine	Producer cell
• IL-2	$T_{h/c}$, DC, NK
• IL-4	T, NK, mast, eosinophil
• IL-7	Epithelial, stromal, fibroblast
• IL-9	T_h
• IL-15	Neutrophil, monocyte, DC, mast, B, fibroblast
• IL-21	T_{fh}, T_h17, NKT

*Also used by IL-13

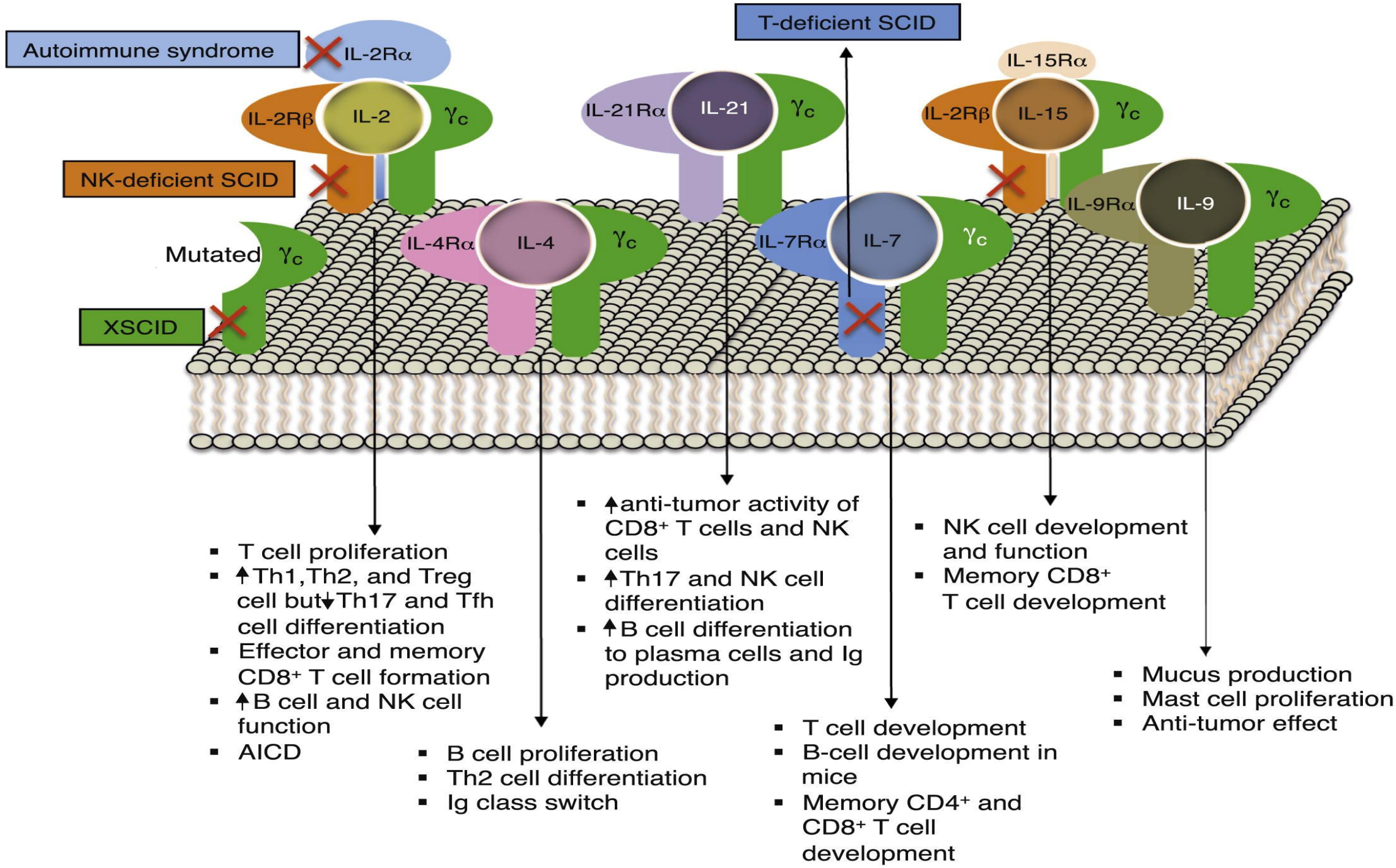
γc cytokines, signaling and receptors



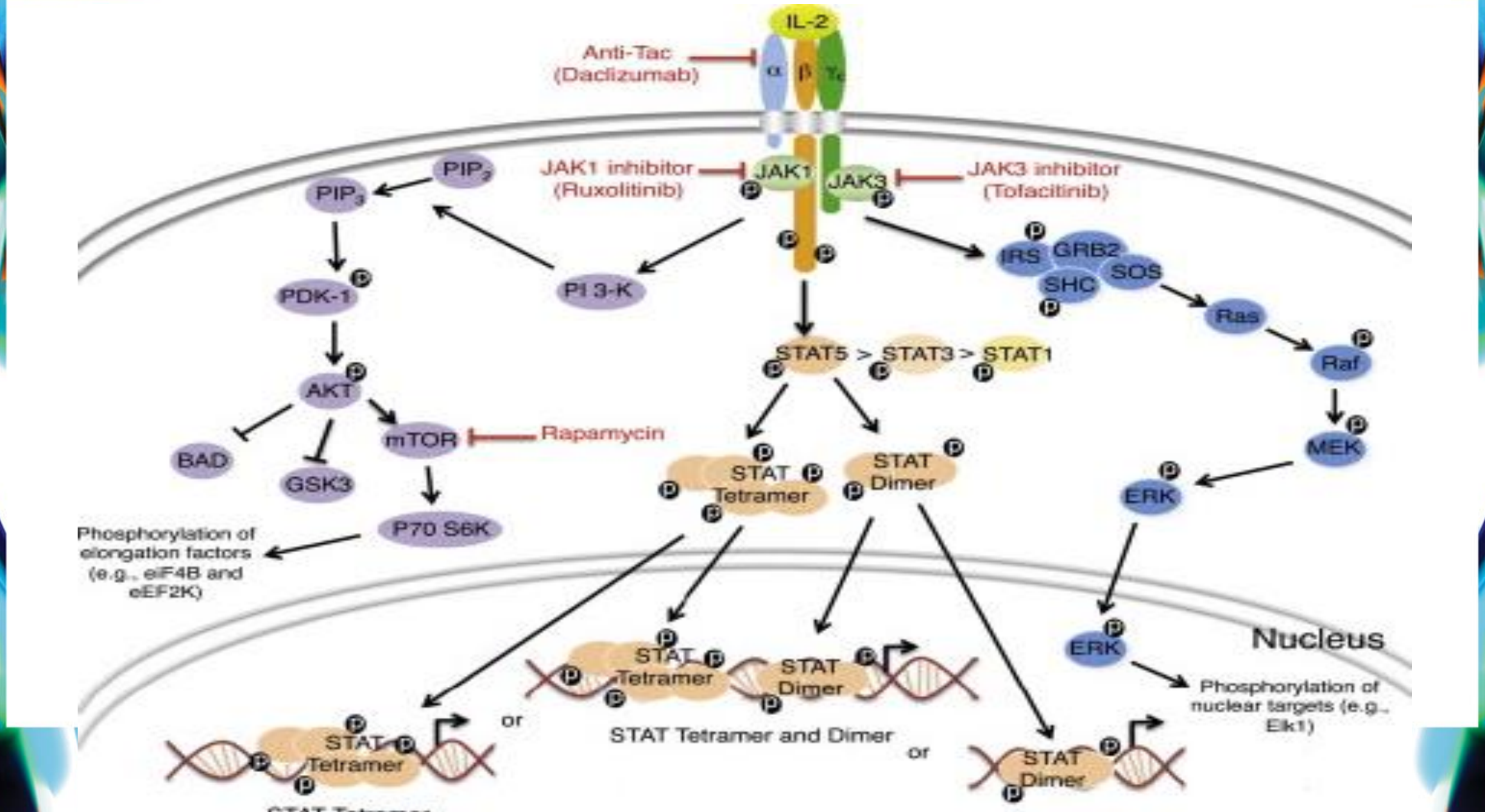
Nature Revie

Proliferative effects of γc cytokines

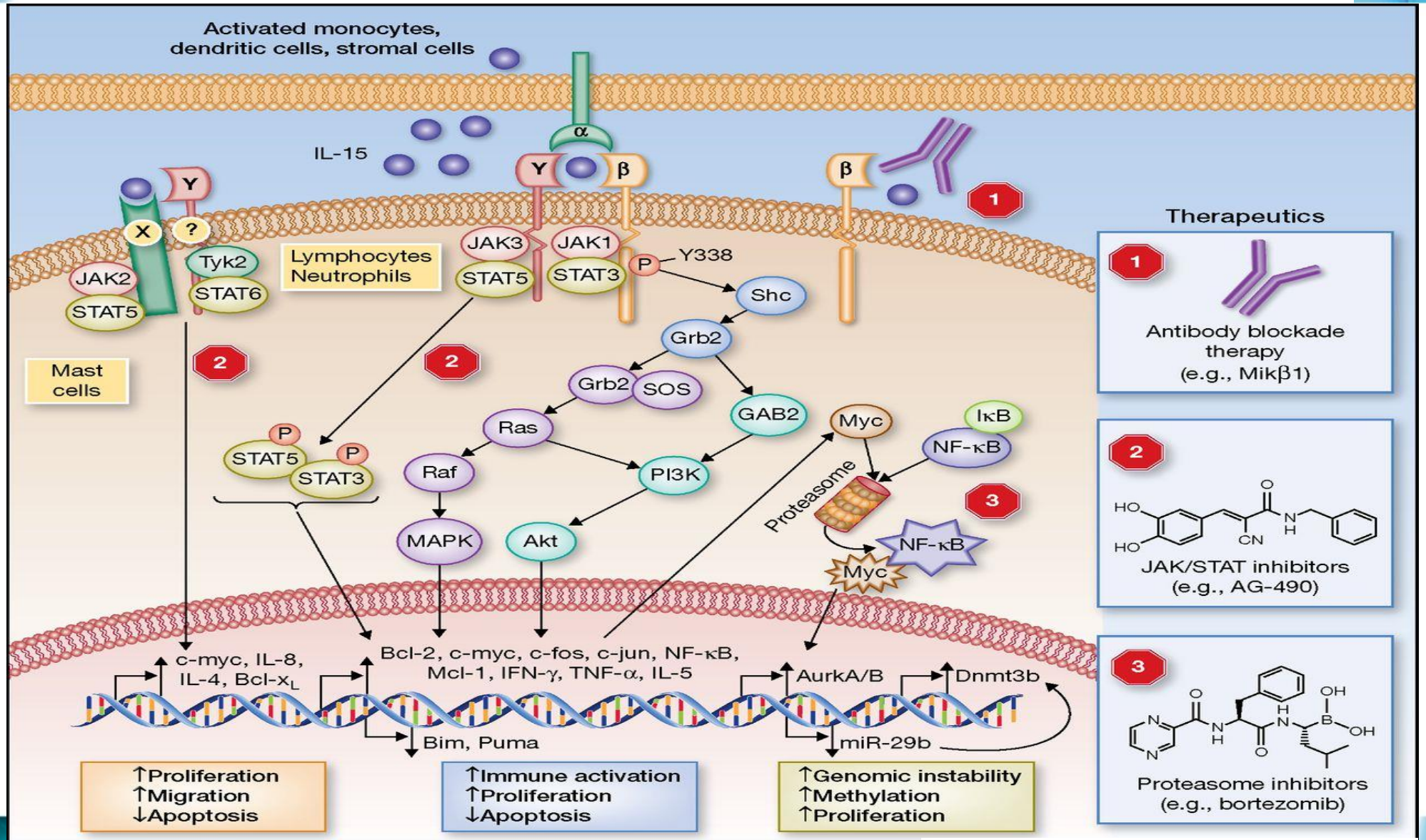
- IL-2—CD4, CD8, NK, and T_{reg}
- IL-7—naïve and memory T cells, thymocyte growth
- IL-15—NK, CD8, memory T cells, not T_{reg}
- IL-21—peripheral lymphocytes, including B cells


Autoimmune syndrome
IL-2Rα
IL-2Rβ
IL-2
γc
NK-deficient SCID
Mutated γc
XSCID
IL-4Rα
IL-4
γc
T-deficient SCID
IL-21Rα
IL-21
γc
IL-7Rα
IL-7
γc
IL-15Rα
IL-2Rβ
IL-15
γc
IL-9Rα
IL-9
γc
▪ T cell proliferation
▪ ↑Th1,Th2, and Treg cell but↓Th17 and Tfh cell differentiation
▪ Effector and memory CD8+ T cell formation
▪ ↑B cell and NK cell function
▪ AICD
▪ B cell proliferation
▪ Th2 cell differentiation
▪ Ig class switch
▪ ↑anti-tumor activity of CD8+ T cells and NK cells
▪ ↑Th17 and NK cell differentiation
▪ ↑B cell differentiation to plasma cells and Ig production
▪ T cell development
▪ B-cell development in mice
▪ Memory CD4+ and CD8+ T cell development
▪ NK cell development and function
▪ Memory CD8+ T cell development
▪ Mucus production
▪ Mast cell proliferation
▪ Anti-tumor effect

Detailed signaling by IL-2



Detailed intracellular signaling by IL-15



Anjali Mishra et al. Clin Cancer Res 2014

IL-9 and IL-17—helper cytokines with unique roles in inflammation and immunity

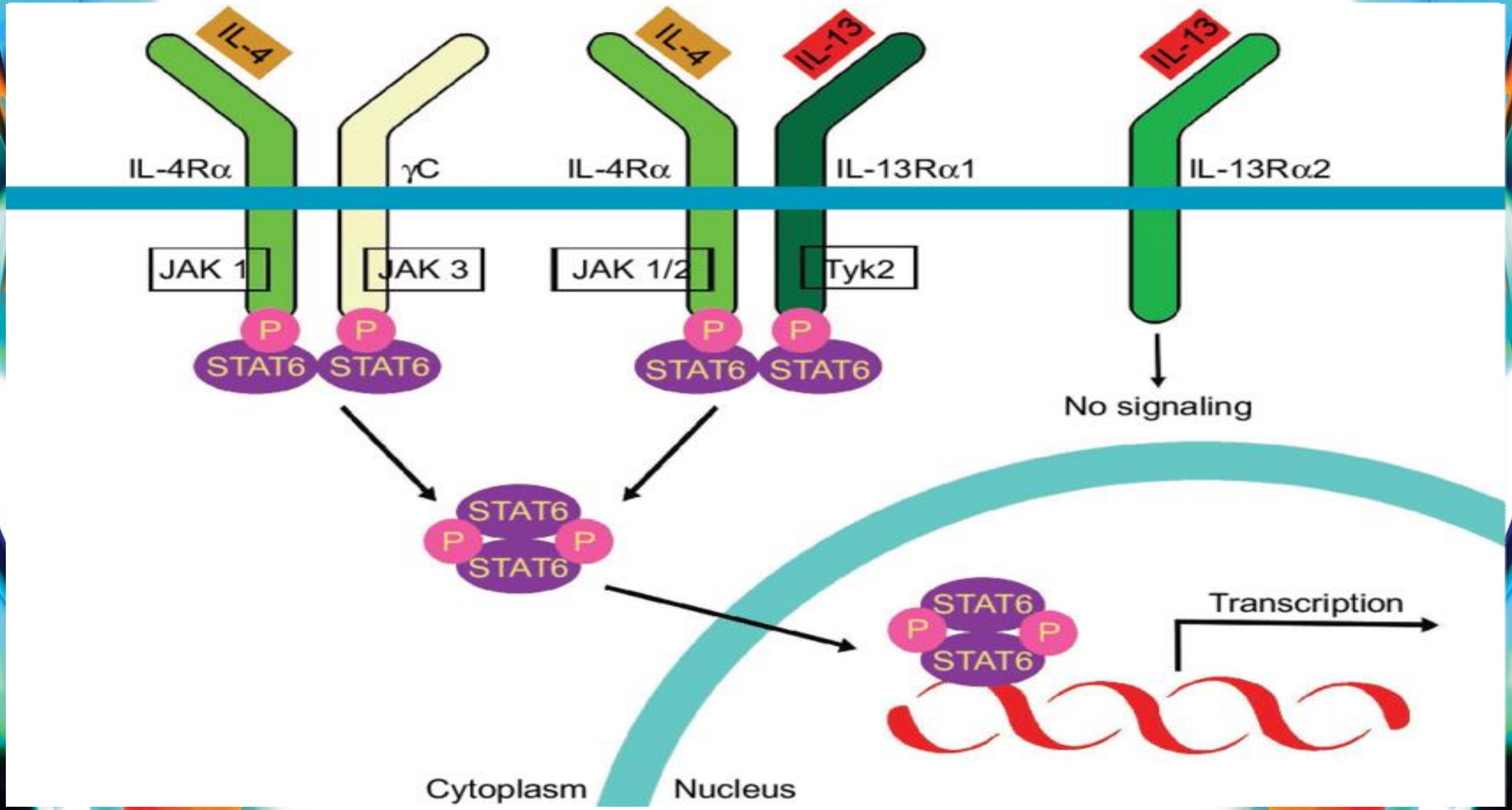
- IL-9, member of γ_c family from Th9 cells, acts on T cells but also epithelial cells, mast cells and eosinophils [allergy]
  - Some type 2 effects
  - Supports immunoglobulin production
  - **Th9 cells may mediate potent and long-lived (memory) antitumor effects**

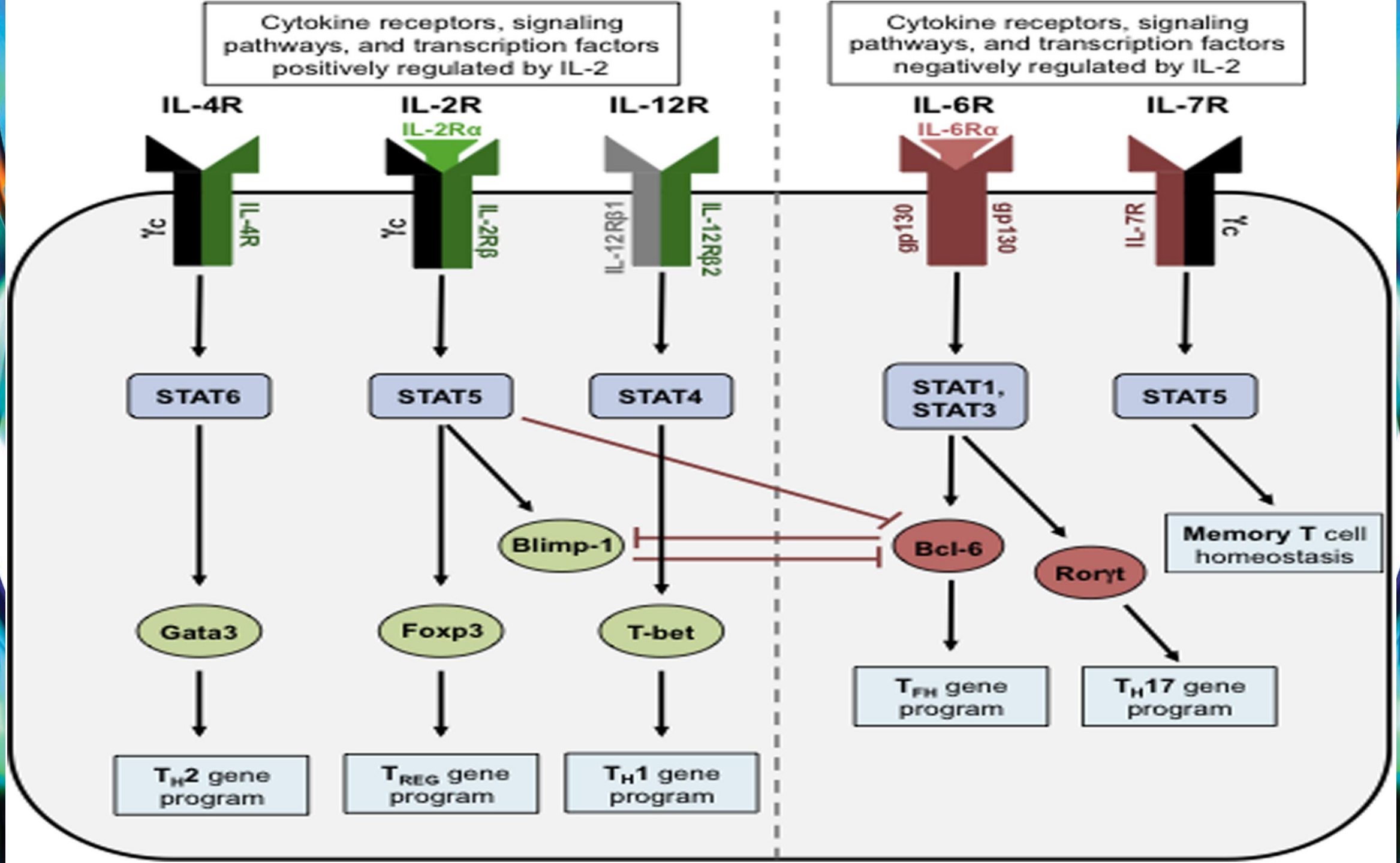
- IL-17, produced by Th17 cells, mediates some inflammatory states
  - May also support antitumor cytotoxicity
  - **Th17 may represent a long-lived memory subset like Th9 with implications for adoptive cell therapies of cancer**

Structure and functions of IL-4 and IL-13 and their receptors

- IL-4 is considered a Th2 cytokine
- IL-13 shares the α-receptor with IL-4 and functions in a heterodimer
  - Supports differentiation of CD4 T cells into Th2
  - Suppresses Th1 cells
  - Supports multiple functions of B cell development
  - Promotes functions of mast cells and basophils

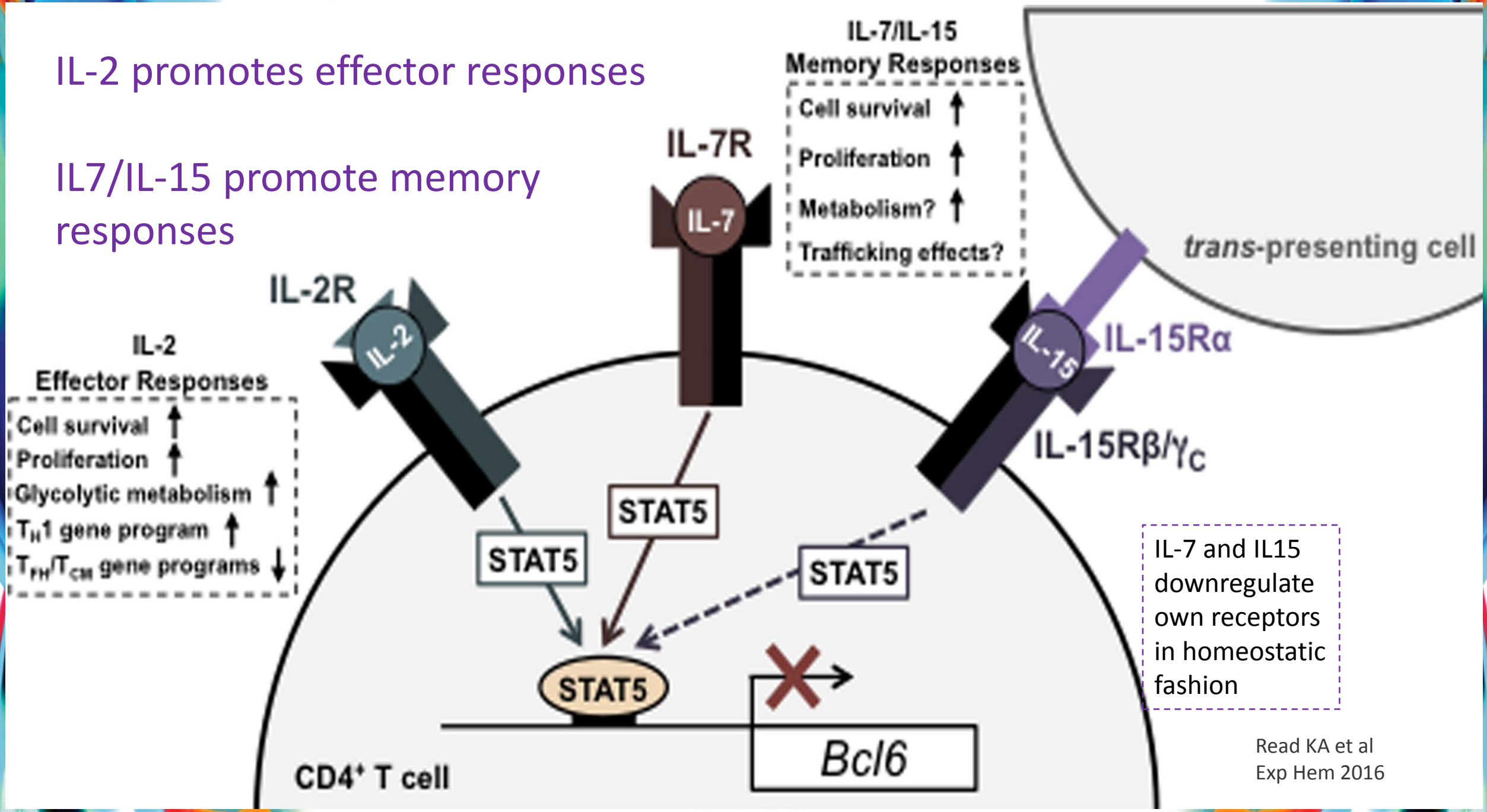
IL-4 and IL-13 and their receptors




Cytokine receptors, signaling pathways, and transcription factors positively regulated by IL-2
Cytokine receptors, signaling pathways, and transcription factors negatively regulated by IL-2
IL-4R
IL-2R
IL-12R
IL-6R
IL-7R
IL-2Rα
IL-6Rα
γc
IL-4R
γc
IL-2Rβ
IL-12Rβ1
IL-12Rβ2
gp130
gp130
IL-7R
γc
STAT6
STAT5
STAT4
STAT1, STAT3
STAT5
Blimp-1
Bcl-6
Rorγt
Memory T cell homeostasis
Gata3
Foxp3
T-bet
T_{FH} gene program
T_H17 gene program
T_H2 gene program
T_{REG} gene program
T_H1 gene program

IL-2 promotes effector responses

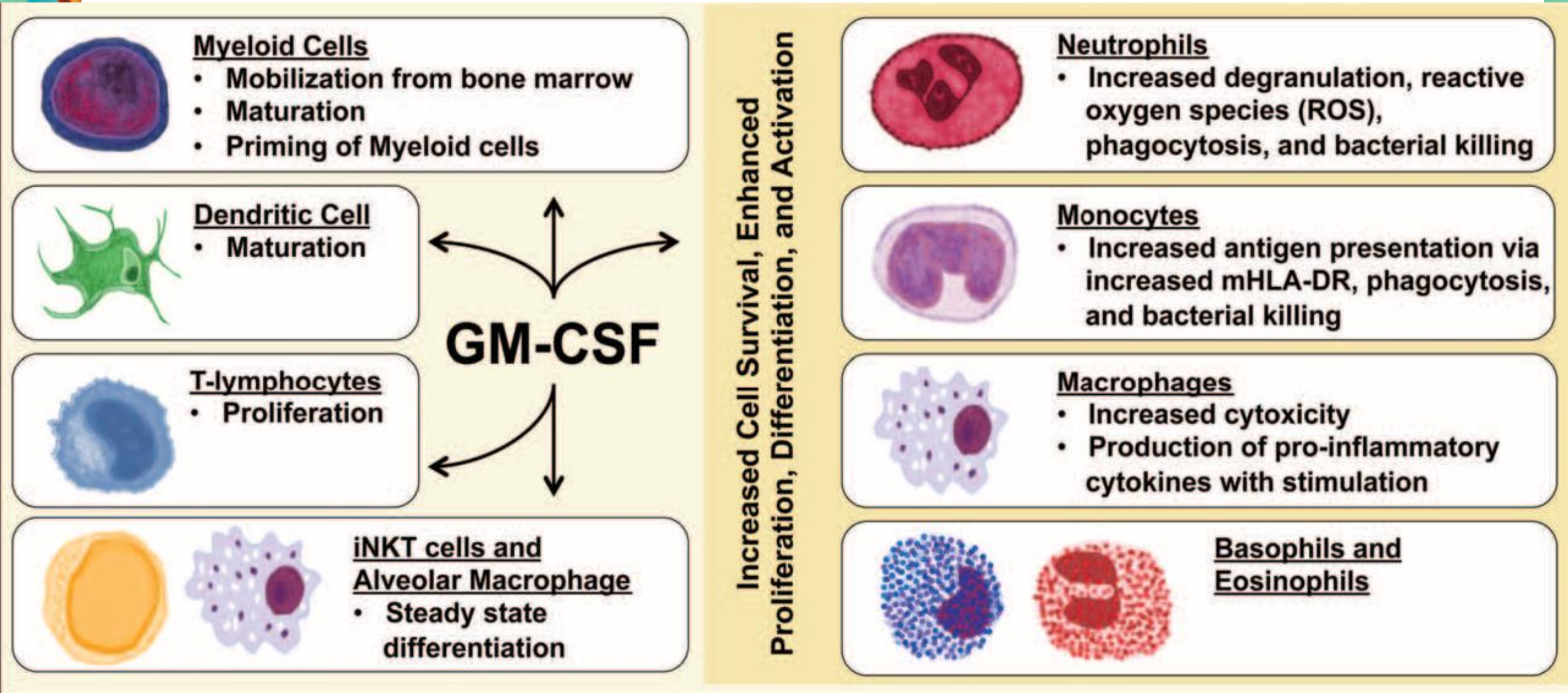
IL7/IL-15 promote memory responses



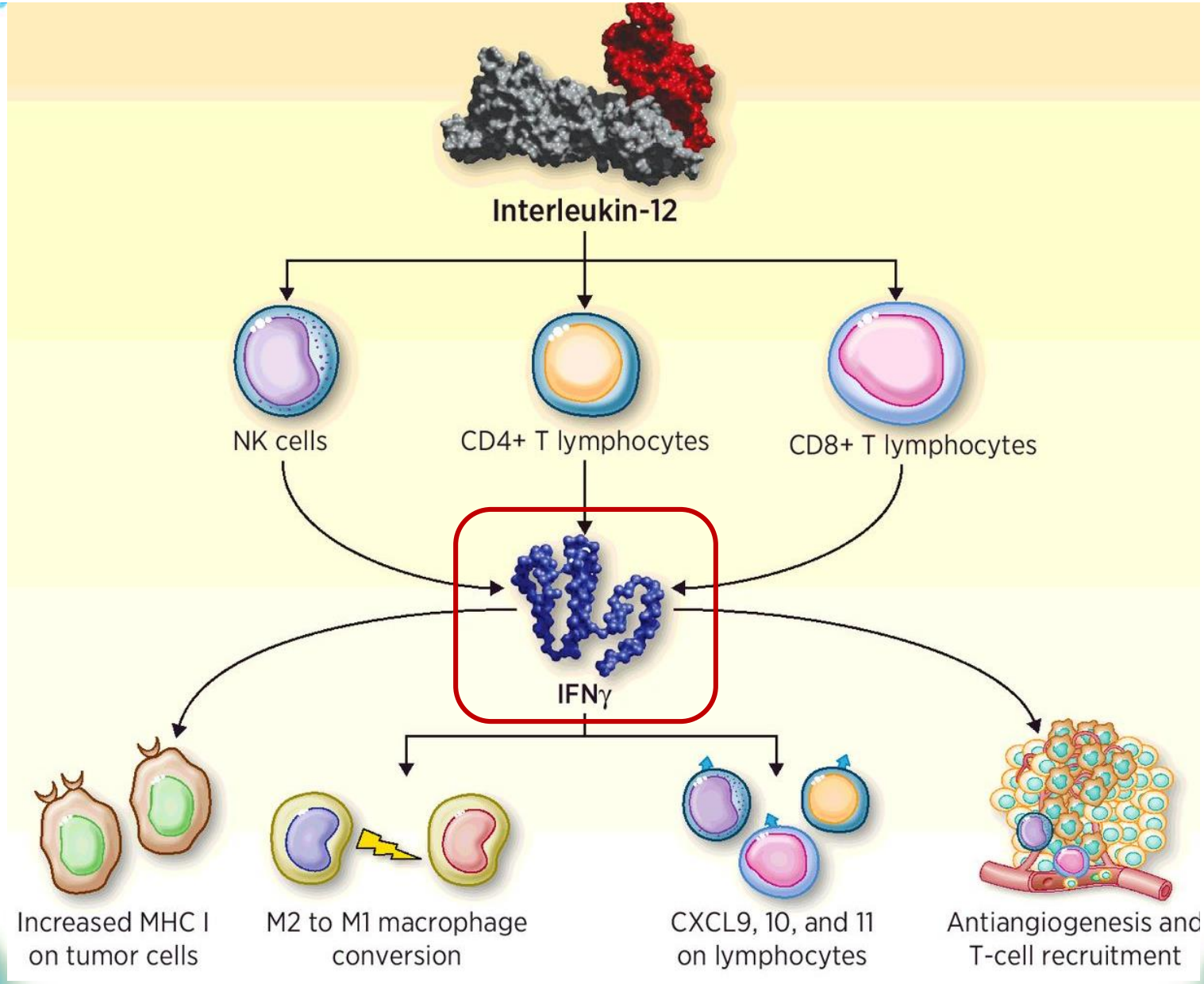
IL-7 and IL15 downregulate own receptors in homeostatic fashion

Read KA et al
Exp Hem 2016

GM-CSF—a pleotropic cytokine with immunotherapeutic potential



IL12—prototypical type 1 cytokine



Pedro Berraondo et al.
Clin Cancer Res 2018

IL-12: powerful and pleiotropic type I cytokine

- Strong inducer of IFN-γ from NK, CD8, CD4
- Unfavorable therapeutic index when given systemically
- May be amenable to loco-regional Rx, e.g. encoded in a plasmid, with electroporation
- Other TLR agonists work in large part by inducing IL-12 from DC
- IL-10 is major counter-balance but its biology is complex
  - Blockade
  - Agonism

} Both have been tested therapeutically

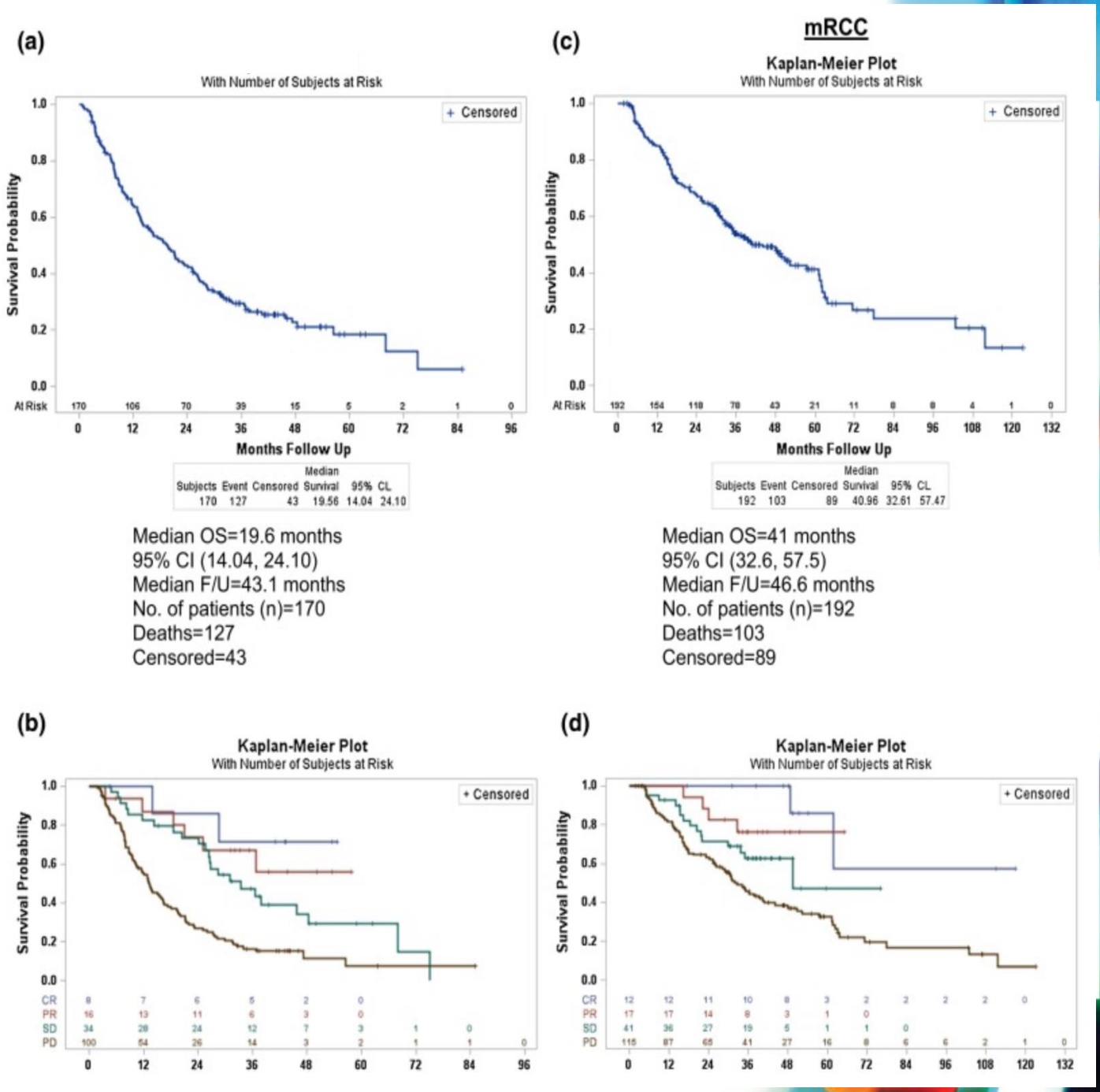
Current status of interferons in cancer therapy

Therapeutic outcomes of recombinant cytokines

- High-dose interleukin-2—FDA-approved for advanced melanoma, ccRCC
- Other forms of interleukin-2
- Interleukin-15
- Interleukin-7
- Interleukin-21
- GM-CSF—FDA-approved in TVEC

Interleukin-2

- High doses as single agent → durable remissions in ~10% of patients with metastatic melanoma or advanced clear-cell renal cancer
- Capillary leak syndrome w/multiple organ toxicities universal with HDIL-2
- Superceded by immunotherapies w/ better therapeutic index
- IL-2 remains important for selected indications



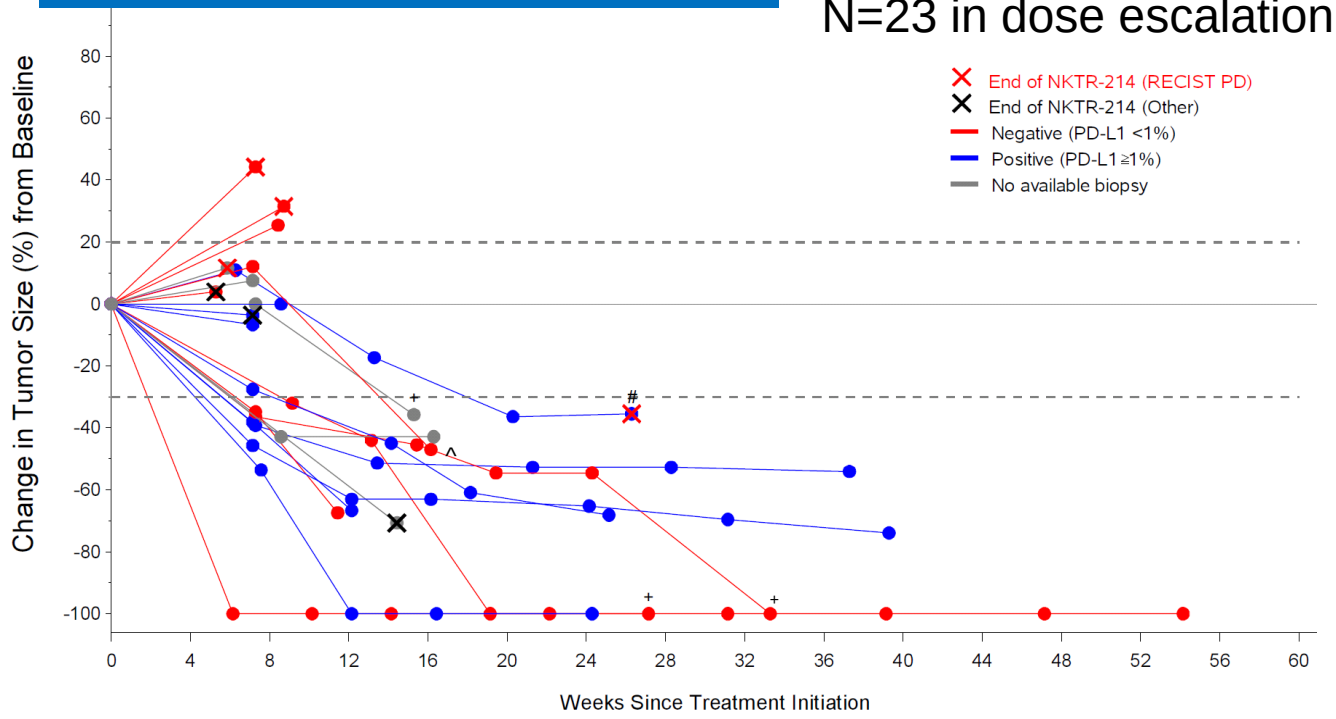
Alternative interleukin-2 regimens

- Combination with CTLA4 blockade disappointing and toxic
- Combinations at various doses with PD-1 blockade ongoing
- Engineered IL-2 molecules failed in ‘90s but have resurfaced
  - IL-2 agonist with selective βγ receptor binding avoids Treg stimulation
  - PEGylated IL-2 with measured hydrolysis from 5 to 1-2 PEG residues per IL-2 preferentially stimulates CD8, NK>>Treg and has promise with PD-1 blockade

NKTR214 plus nivolumab for untreated advanced melanoma

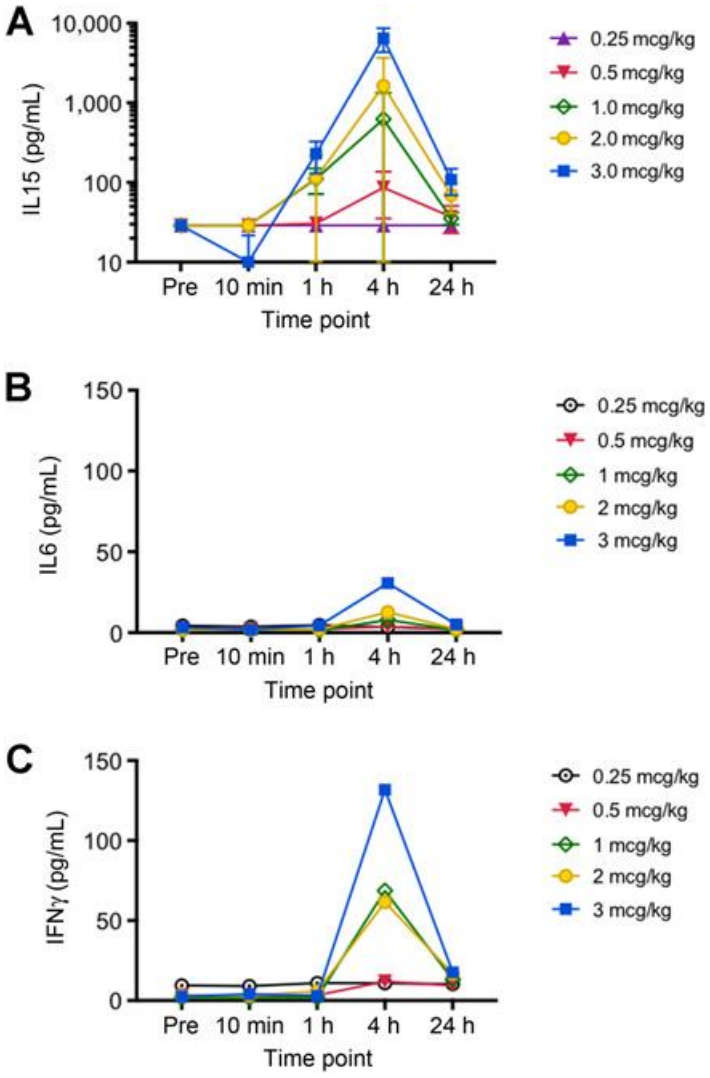
Best ORR by RECIST: ORR=12/23 (52%); DCR=18/23 (78%)
Best ORR by irRECIST: ORR=14/23 (61%); DCR=19/23 (83%)

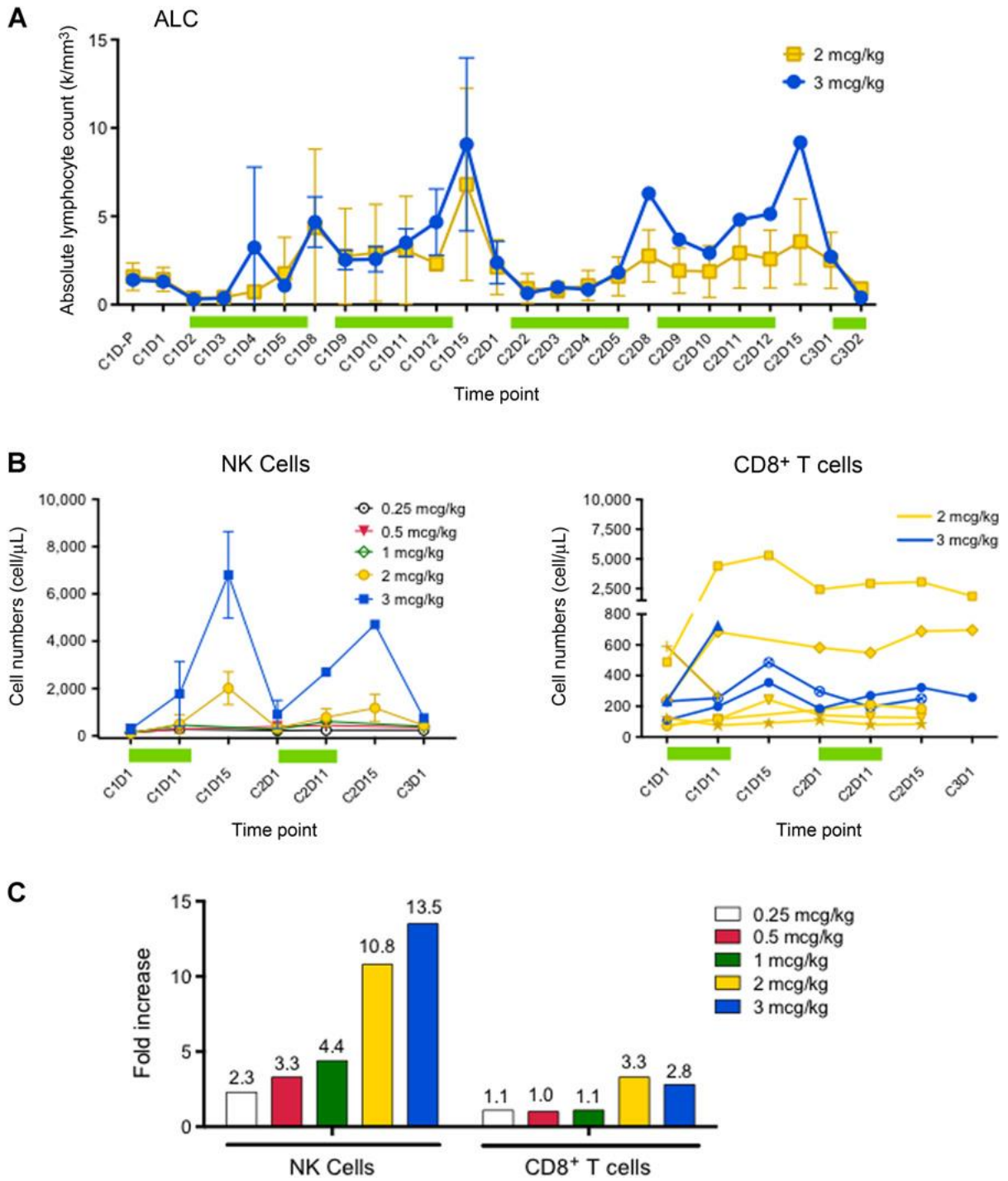
N=23 in dose escalation + expansion



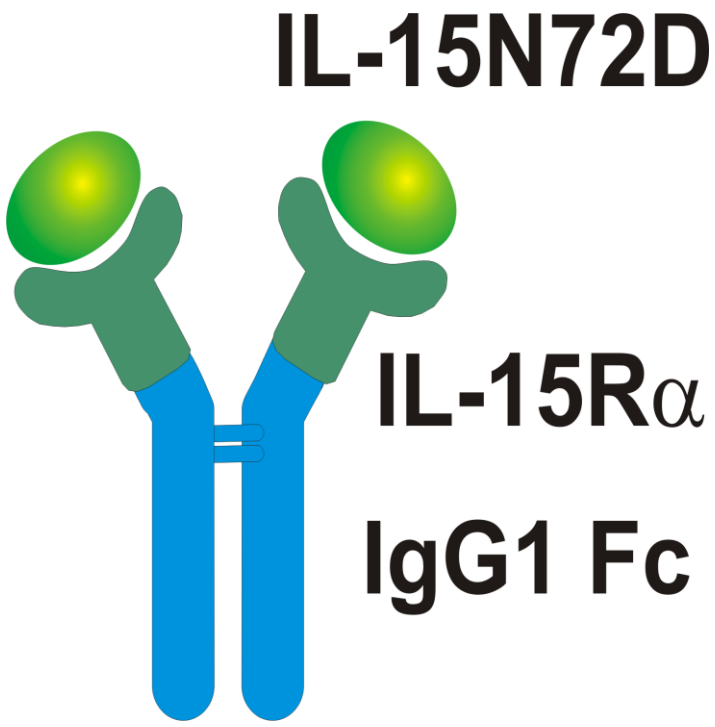
+ Best overall response is PR (non-target lesions still present)
# Best overall Response is SD per RECIST 1.1 and PR per irRECIST. Patient had PD per new lesion on confirmatory scan.
^ Best overall response is PD per RECIST 1.1 and unconfirmed PR per irRECIST. Patient achieved PR at 2nd scan after PD at 1st scan due to new lesion (enlarged lymph node).

Unmodified IL-15 (NCI) cytokine responses and effects on lymphocyte subsets





ALT-803: IL-15:IL5Ra-Fc fusion complex



- Increased binding to IL15Ra from N72D mutation
- Serum half-live = 25 hours

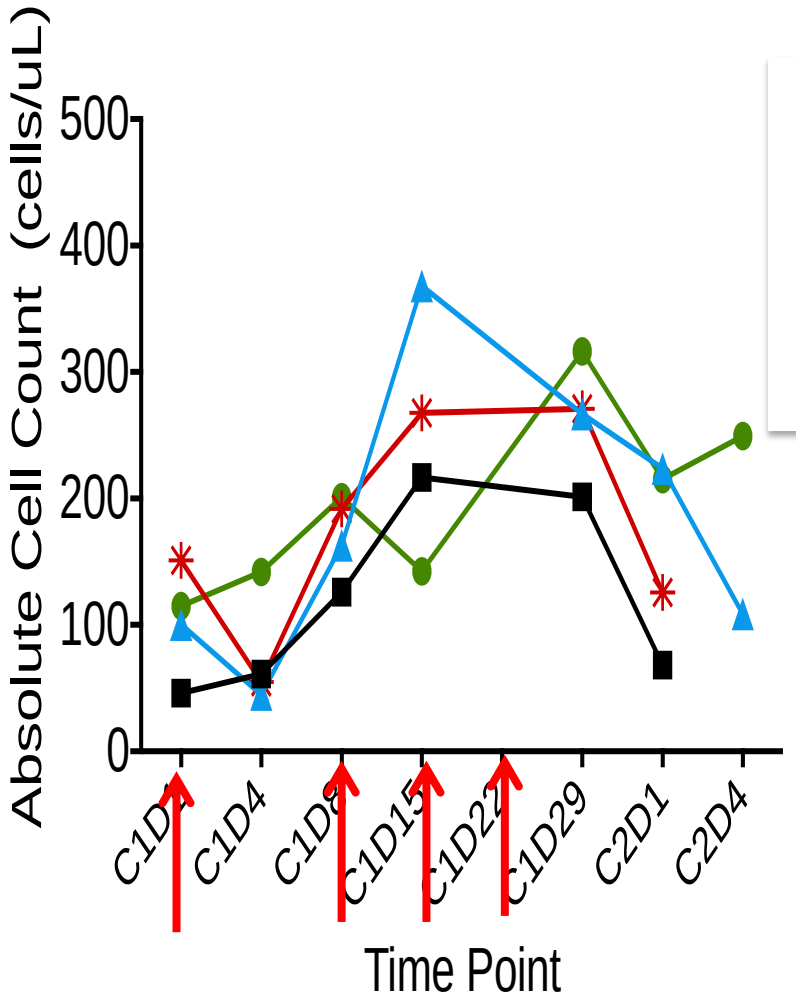
<u>CITN-06 trial</u>

- 4 solid tumors (mel, H and N, NSCLC, RCC)
- 4 dose levels given subcutaneously qwk x 4 of 6
- No objective responders but most heavily pretreated
- DLTs mainly local injection reaction

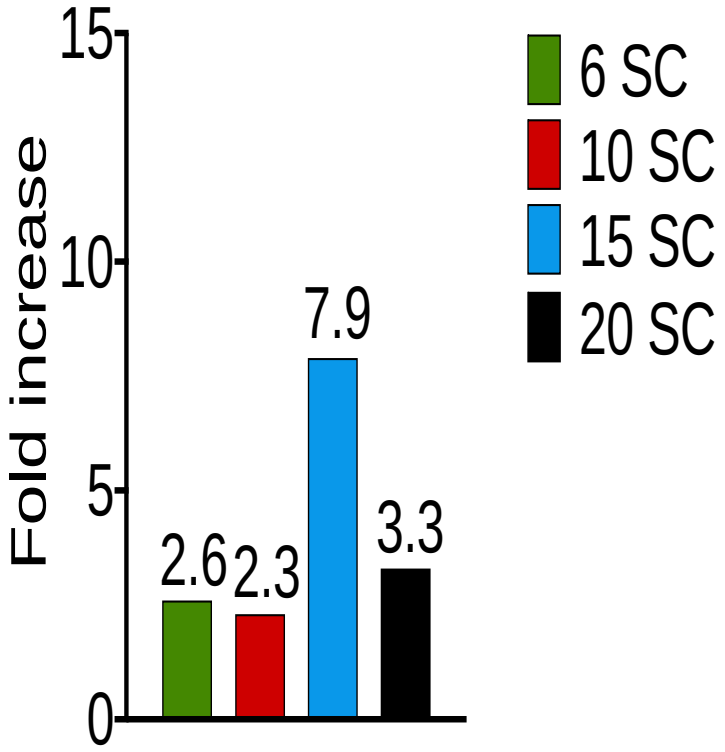
<u>U Mn trial</u>

- Heme malignancies in relapse after alloHCT
- 4 dose levels given subcutaneously q wk x 4 of 6
- DLTs mainly local injection reaction
- Activity in ~20% of pts
- Expansion of NK, CD8 cells without Treg expansion

Effect of subcutaneous ALT-803 on circulating total CD3-CD56+ NK cells: By dose cohort

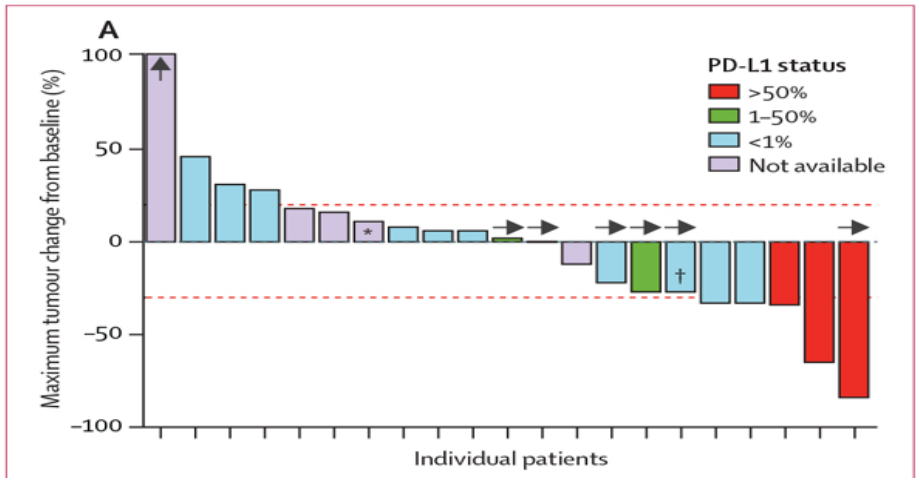


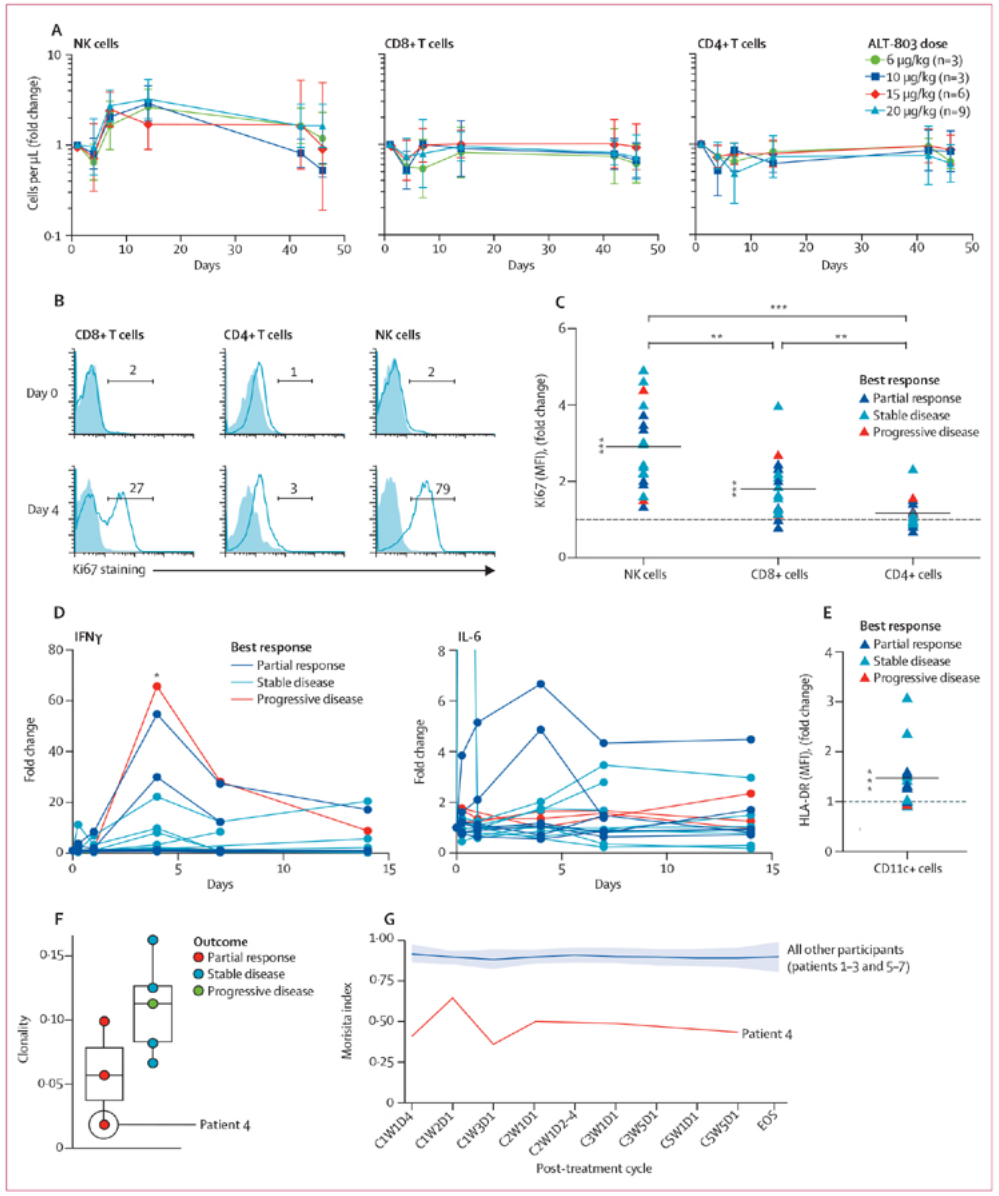
Weekly administration



ALT-803 plus immunomodulatory antibodies

- Rationales
  - Abs enhance ADCC by NK cells
  - ALT-803 stimulates especially CD56^{bright} NK → cytotoxicity vs tumor cells
- Trial data so far
  - + Nivolumab in NSCLC, some pretreated with immune checkpoint blockade
  - + Rituximab in indolent NHL





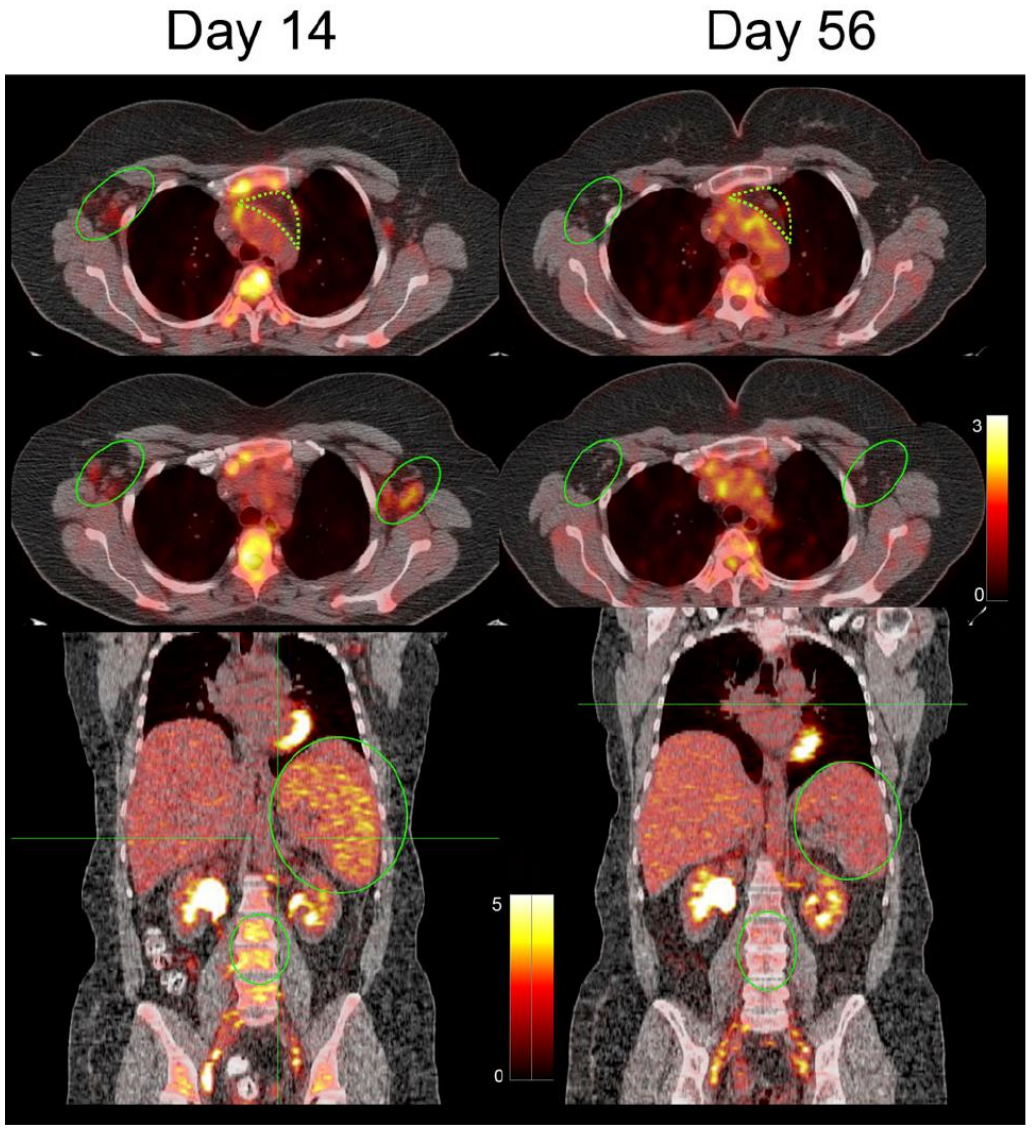
Interleukin-21

- Studied as single agent and w/ targeted and immune-checkpoint blockade
- Main role may be in *ex vivo* expansion of therapeutic T cells
- Pleiotropic w/ actions on lymphoid, myeloid, epithelial cells that include proliferation, survival, differentiation and function.
- Key role in B cell → plasma cells, development of $T_{follicular\ helper}$ cells, promoting functional germinal centers, Ig production.
- Induces a functional programme in $CD8^+$ cells that leads to enhanced survival, antiviral, antitumor activity.
- Key role in development of T_h17 cells → role in various inflammatory and autoimmune diseases [thus IL-21 *inhibitors* under investigation].

IL-7 increases T cells in lymph nodes, spleen & marrow as well as peripheral blood

PET-CT imaging of lymphoid organs & increased metabolic activity after rhIL-7

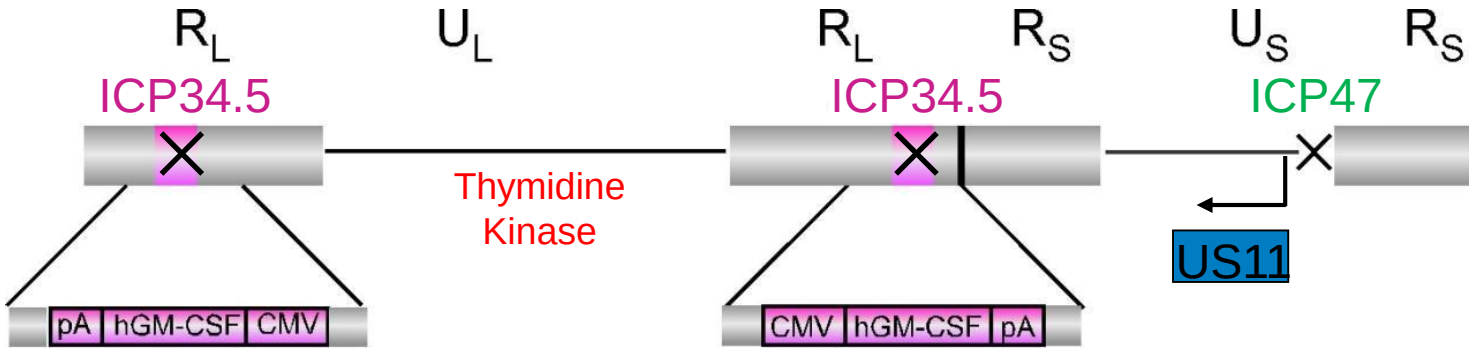
Increased metabolic Activity = pink
Maximal = yellow



[Sportès (Mackall) et al J. Exp. Med. 1681:2007]

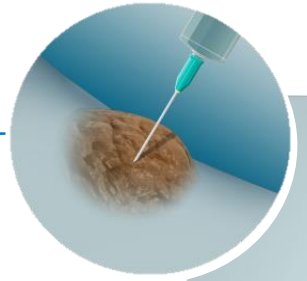
Generation of talimogene laherparepvec (TVEC)

Characteristic	Rationale
JS1 strain derived	• Improved tumor cell lysis over commonly used laboratory strains
Deletion of ICP34.5	• Provides tumor-selective replication • Decreases replication
Deletion of ICP47	• Prevents block to antigen presentation • Results in earlier/increased US11 expression
Earlier/increased US11	• Restores replication of ICP34.5-deleted HSV-1
Insertion of hGM-CSF (ICP34.5 locus)	• hGM-CSF driven off CMV promoter • Enhances anti-tumor immune response • Increased safety in the event of homologous recombination w/wild-type HSV-1

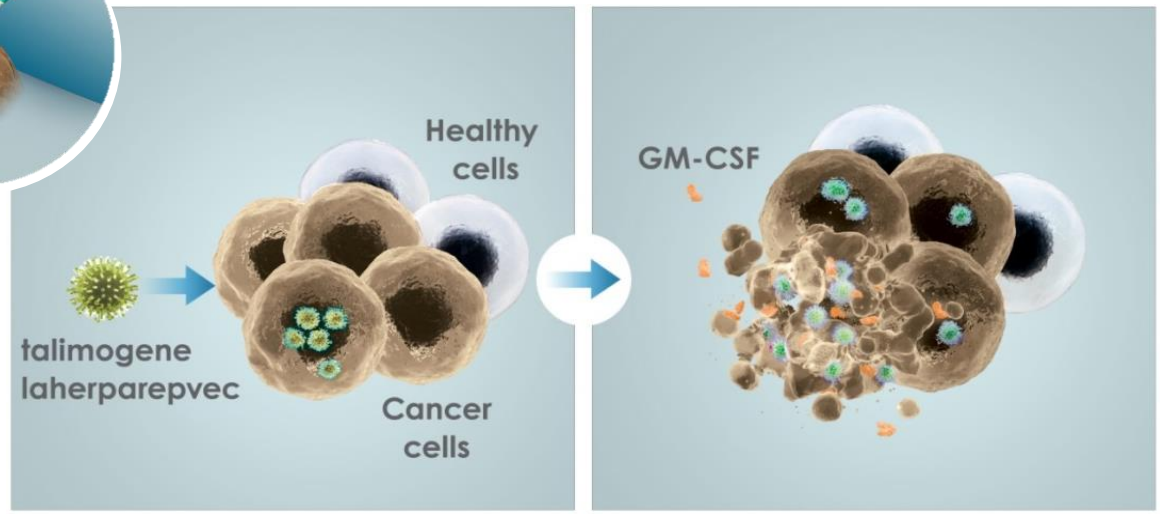


TVEC's mechanisms of action

Local: Virally-induced tumor cell lysis

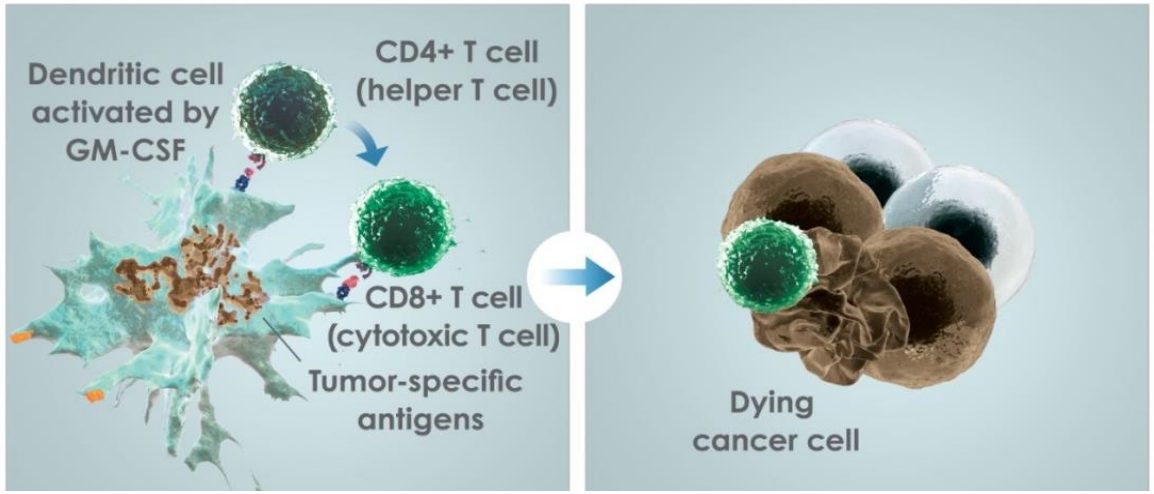


Selective viral replication in tumor tissue



Tumor cells rupture for an oncolytic effect

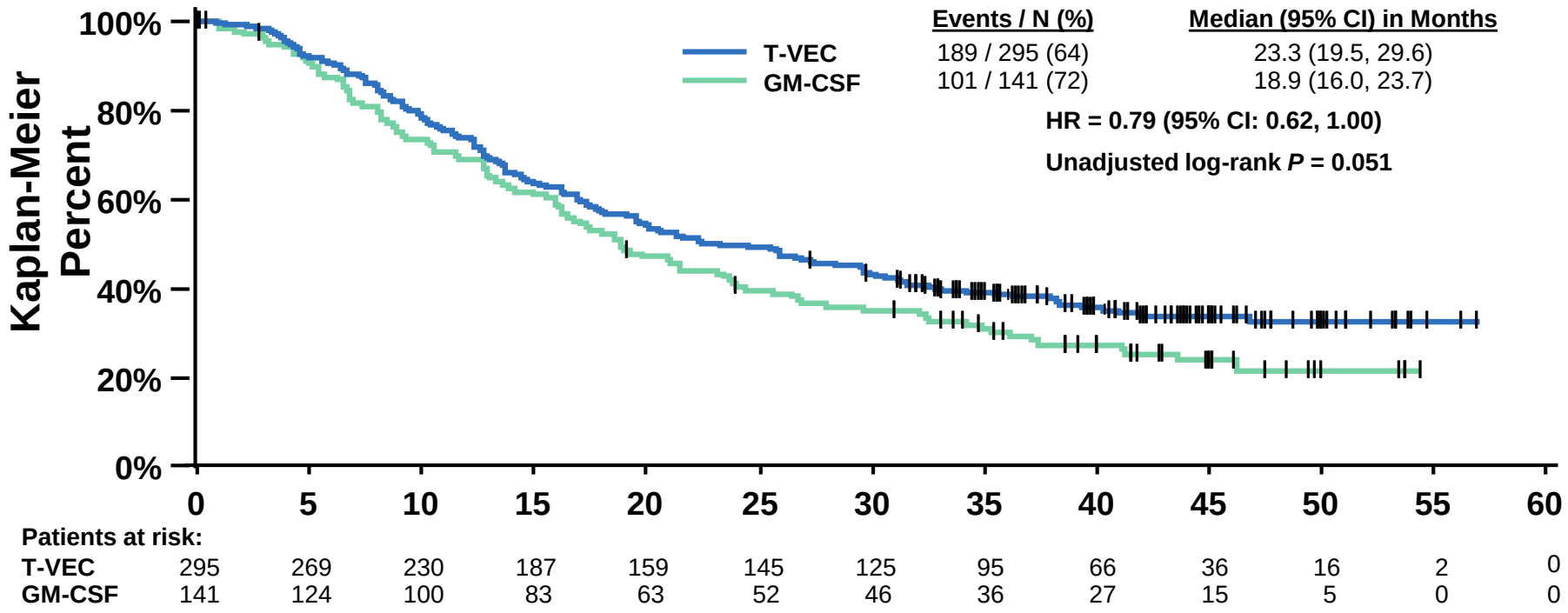
Systemic: tumor-specific immune response



Systemic tumor-specific immune response

Death of distant cancer cells

Overall survival—TVEC versus GM-CSF



CI, confidence interval; HR, hazard ratio;

Median OS is 4.4 months longer in the T-VEC arm

Andtbacka RH, et al. JCO May 2015

Future of cytokines in biology and therapy

- Ex vivo support of adoptive cellular therapy strategies
- Combinations for tumor vaccine development
- Novel combinations with other immuno-oncology agents
  - Immune checkpoint blockade
  - Inhibitors of suppressive small molecules and enzymes
  - Co-stimulatory agonistic antibodies
  - Your favorite combination here

Novel cytokine-based Rxs of malignancy and inflammatory states

- Denileukin-diftitox (Ontak)
  - IL-2 fused to diphtheria toxin
  - Targets cells expressing high-affinity IL-2Rα (CD25)
  - Was used in cutaneous T-cell lymphoma and some graft-vs-host disease
  - Off market
- ch14:18-IL-2
  - Looked very promising in pediatric neuroblastoma
  - Unfavorable therapeutic index, but the chimeric Ab ch14:18 (anti-GD2) approved
  - IL-2 is being added to enhance ADCC, expand effector cells

Thank you for your kind attention!

Do you have any questions?

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