MEDICAL UNIVERSITY OF WARSAW

Modern methods of pharmacotherapy in dermatology

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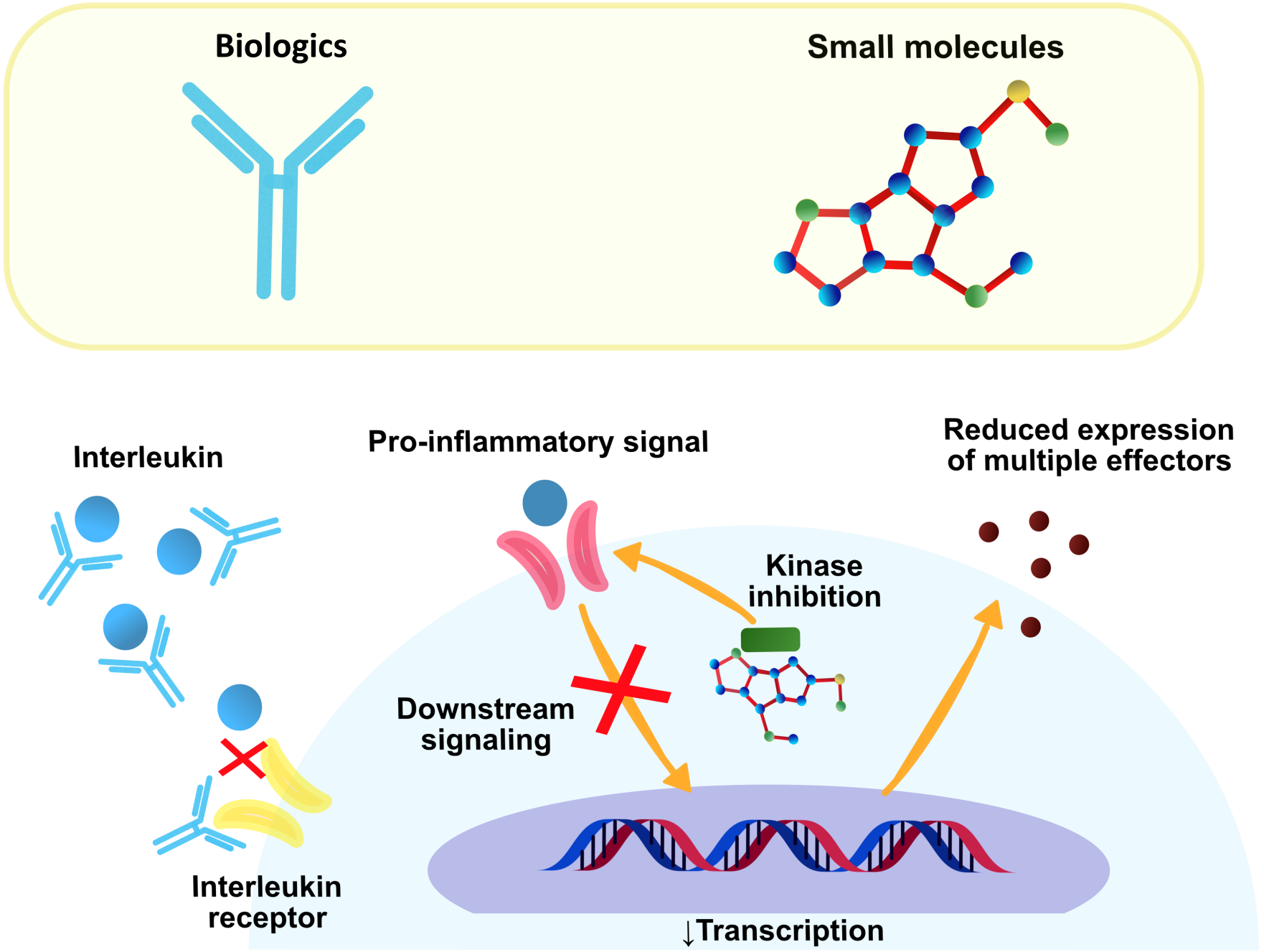
Modern methods of pharmacotherapy in dermatology

- Two groups of pharmaceuticals:
  - Biologics
  - Small molecule inhibitors (intracellular pathway inhibition)


Biologics
Small molecules
Interleukin
Pro-inflammatory signal
Reduced expression of multiple effectors
Kinase inhibition
Downstream signaling
Interleukin receptor
↓Transcription

Modern methods of pharmacotherapy in dermatology

- Medications used in:
  - Psoriasis
  - Allergic skin diseases
  - Autoimmune disorders
  - Skin cancers

Biologics

- Also known as biological products
- Composed of sugars, proteins, nucleic acids or complex combinations of these substances
- Isolated from human, animal, or microorganism sources
- Produced by biotechnology methods and other cutting-edge technologies

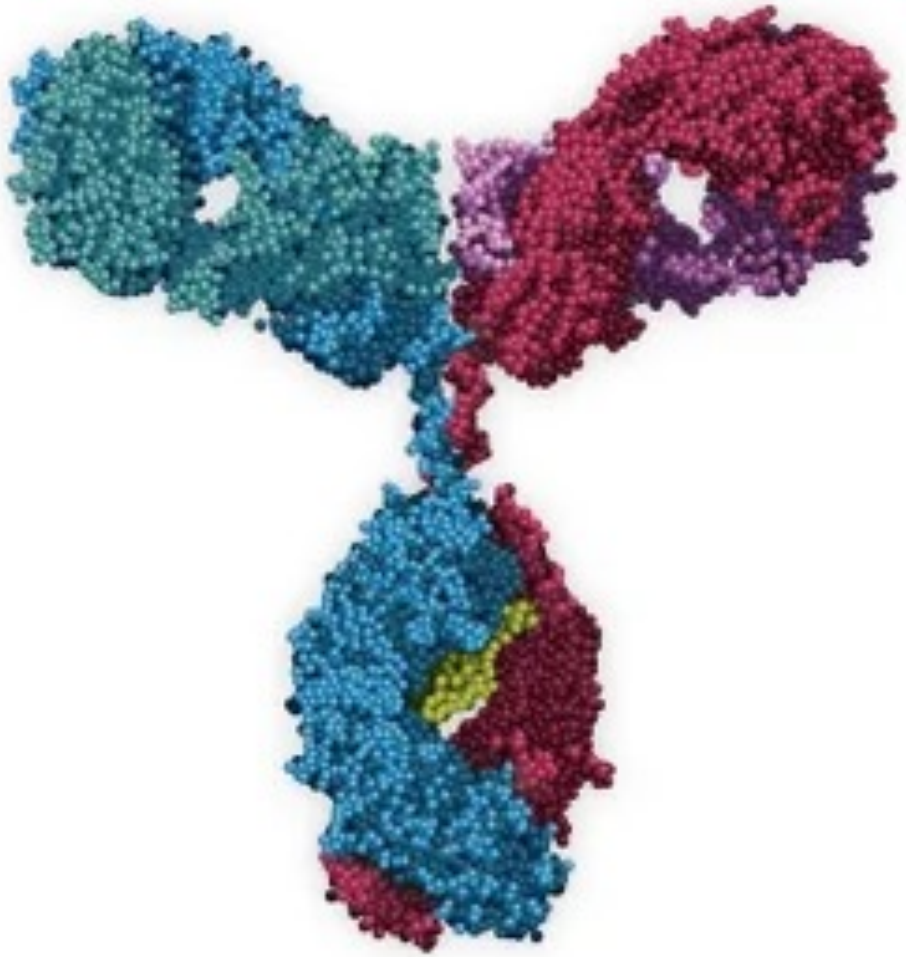
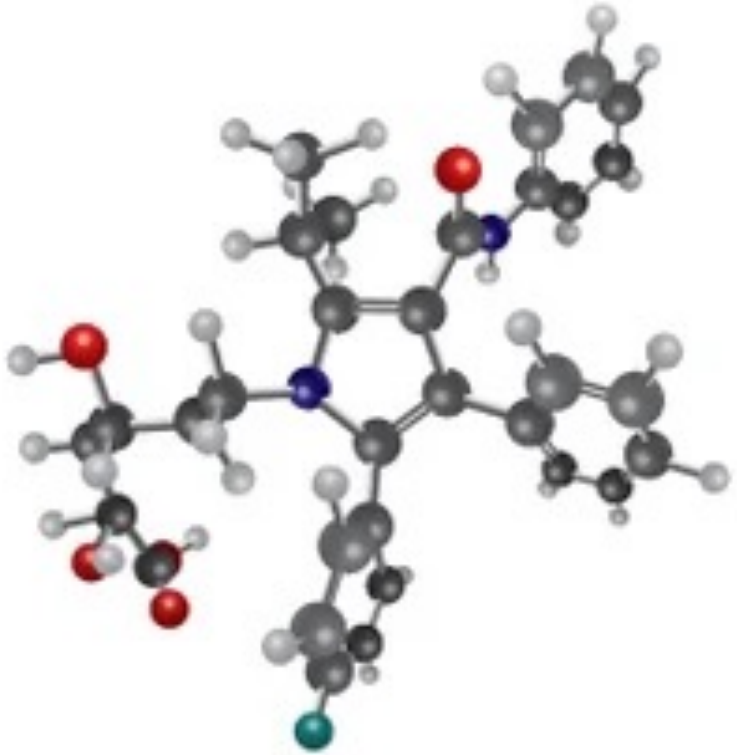
Biological therapy – treatment with biologics

Biologics - properties

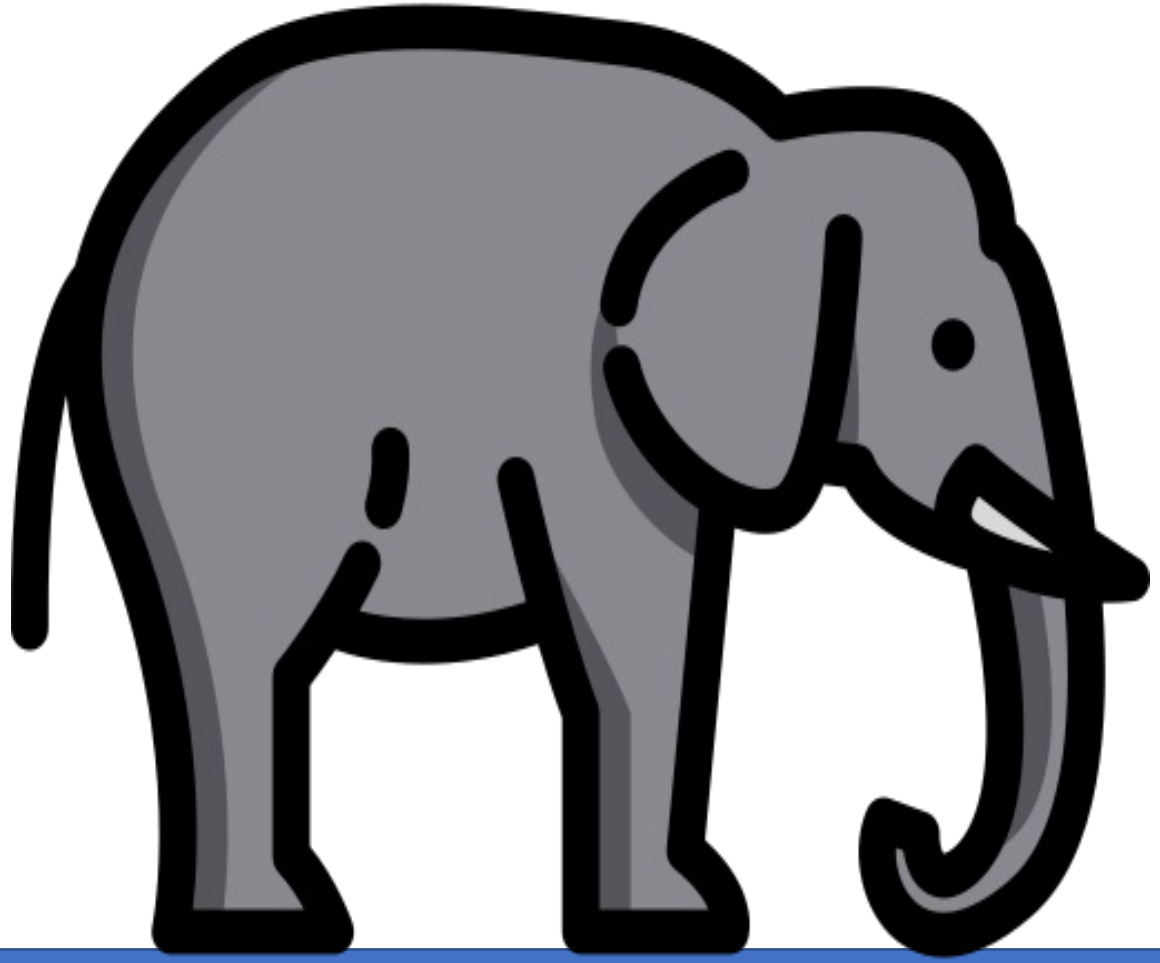
- Immunogenic
- Administered parentarally (decomposed in the GI tract)
- Biological effect depends on the structure (primary, secondary, tertiary and quaternary)
- Sensitive to environmental conditions (require special care during production and storage)

Biologics vs traditional drugs

Biologics	Traditional drugs
Large molecule (up to several hundred thousand Da)	Small molecule (up to several hundred Da)
Complex structure impossible to describe with a chemical formula	Simple structure possible to describe with a chemical formula
Biotechnological synthesis (derived from living organisms)	Chemical synthesis (standardized and repeatable)
Original drugs → biosimilars	Original drugs → generic drugs

Biologic	Traditional Drug
	
Herceptin (breast cancer) molecular weight = 185,000 daltons	**Lipitor (hypercholesterolemia)** molecular weight = 559 daltons

Biologics



Traditional drugs

Biosimilars (follow-on biologics)

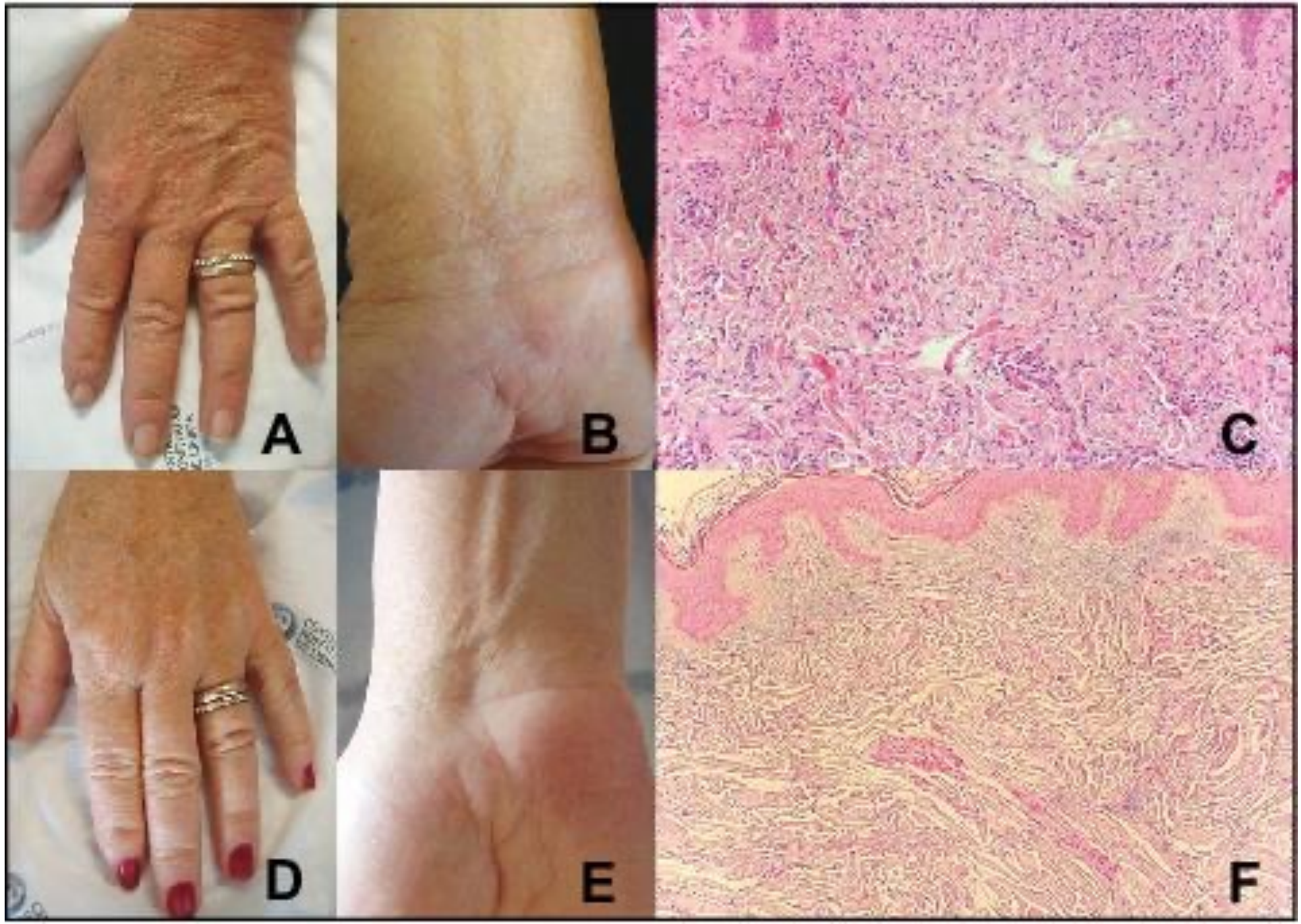
- There are no generic biologic drugs (the process of production is complex and is never reproduced thoroughly by other manufacturers)
- Biosimilars = similarities in terms of biologic activity, safety, efficacy

Biologics used in dermatology

- Polyclonal antibodies
- Monoclonal antibodies
- Fusion proteins

Polyclonal antibodies

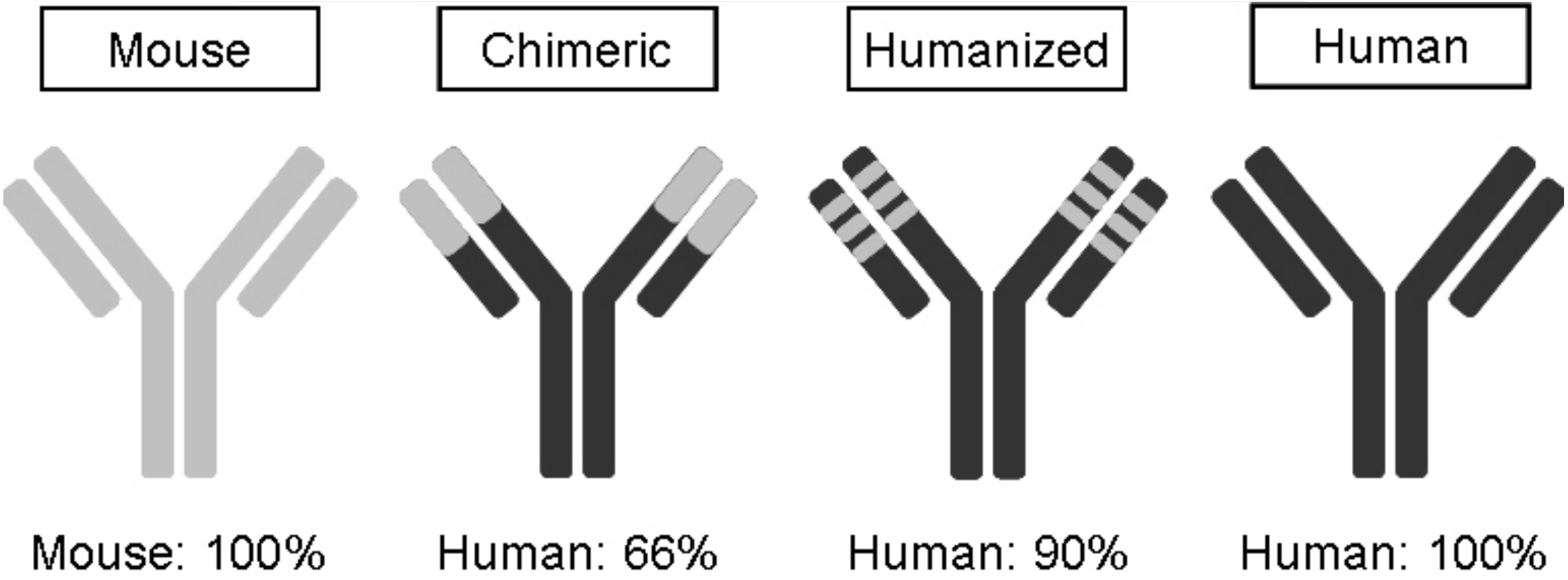
- An array of antibodies specific against different antigens
- Example: intravenous immunoglobulin (IVIG) used in several dermatoses (toxic epidermal necrolysis, pemphigus, scleromyxedema etc.)
- Obtained from multiple clones of B cells (IVIG - derived from large pools of normal donor serum)


A
B
C
D
E
F

Monoclonal antibodies

- An array of antibodies with the same specificity and similar affinity to a given antigen
- Obtained from a single clone of B cells

Monoclonal antibodies



Monoclonal antibodies (nomenclature)

1. Prefix – variable (manufacturer)
2. Application:
   a) Immunology –L(I)–
   b) Interleukins –K(I)–
   c) Cancer –T(U)–
3. Source:
   a) Mouse –O–
   b) Chimeric –XI –
   c) Humanized –ZU–
   d) Human –U–
4. MAB – monoclonal antibody

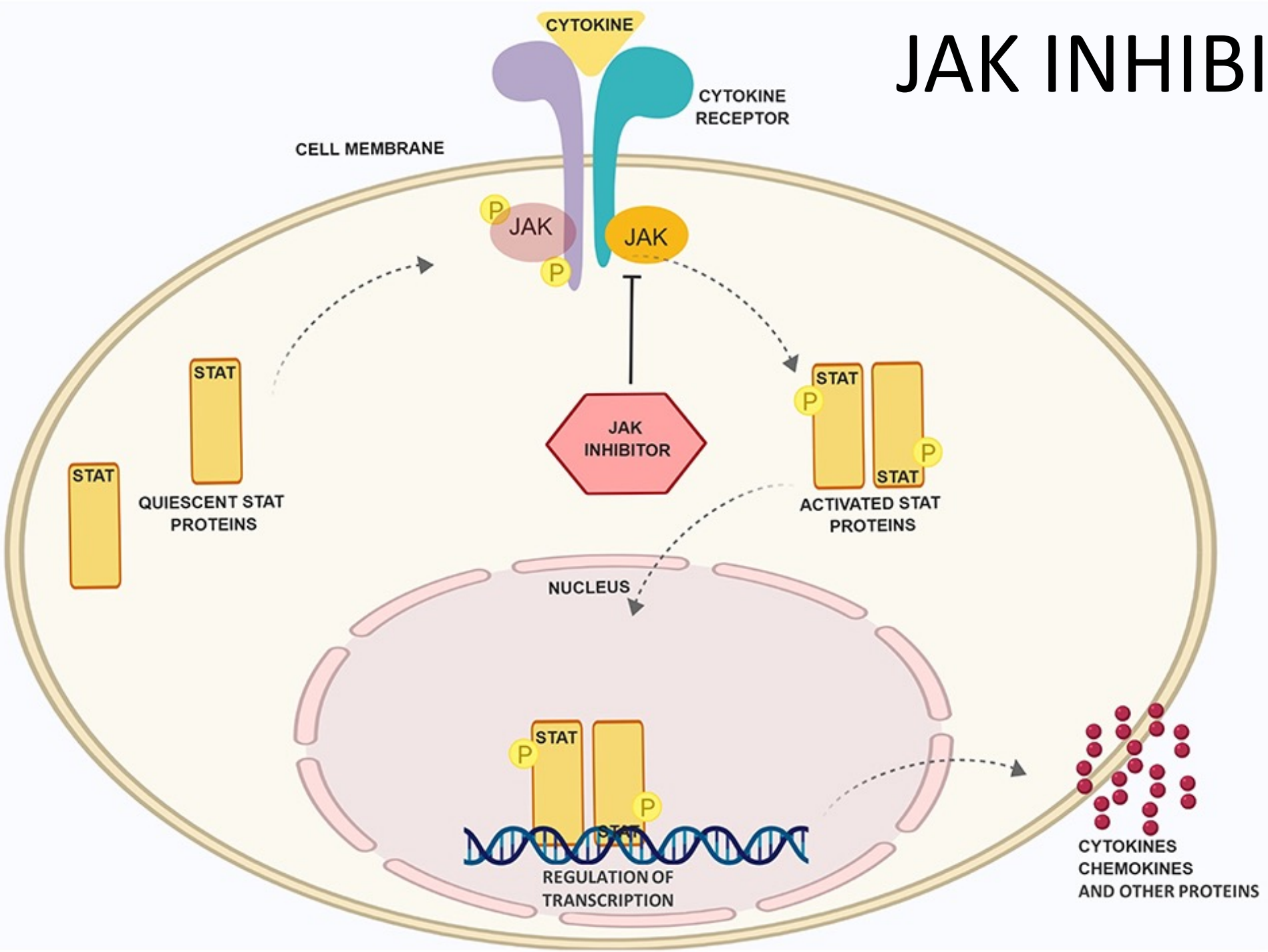
Fusion proteins

- Polypeptides obtained from the fusion of several independent proteins
- New function and/or properties (e.g. prolonged half-life, enhanced binding to an antigen)
- The suffix of fusion proteins is -cept

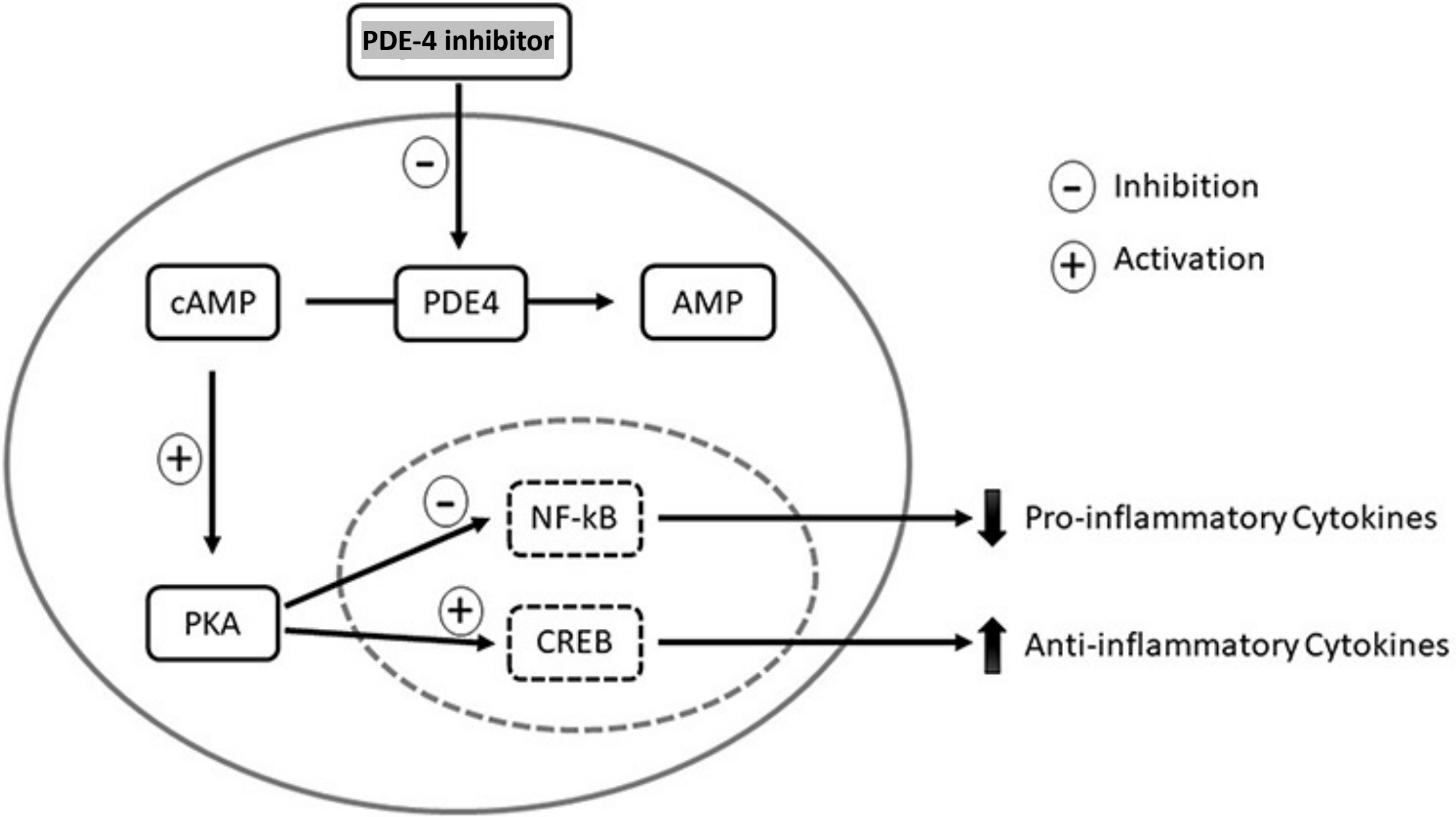
Small molecule inhibitors

- Inhibit intracellular pathways of downstream receptor signaling
- Examples of groups used in dermatology:
  - Janus kinase (JAK) inhibitors
  - Phosphodiesterase-4 (PDE-4) inhibitors
  - BRAF inhibitors
  - Hedgehog signaling pathway inhibitors

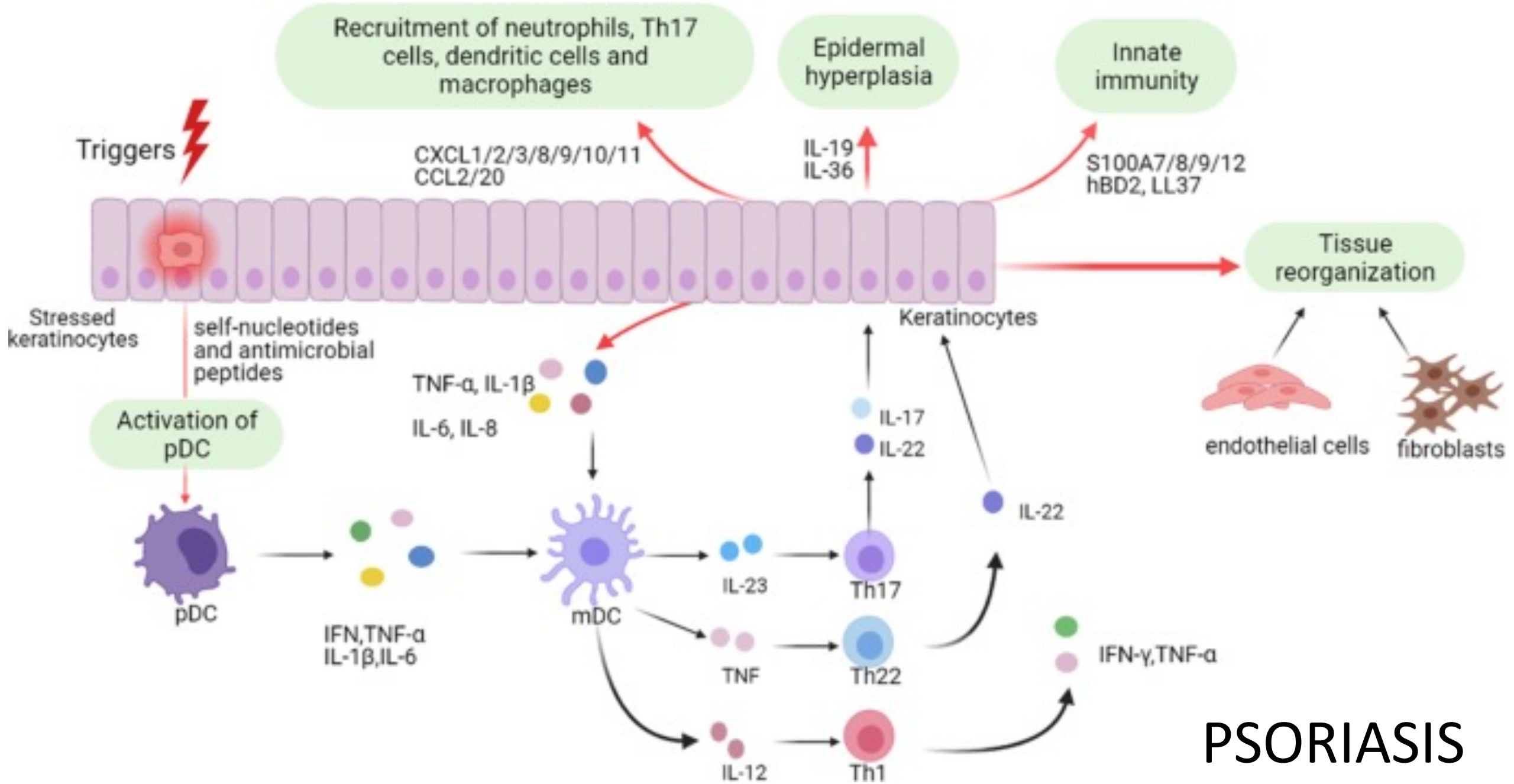
JAK INHIBITORS



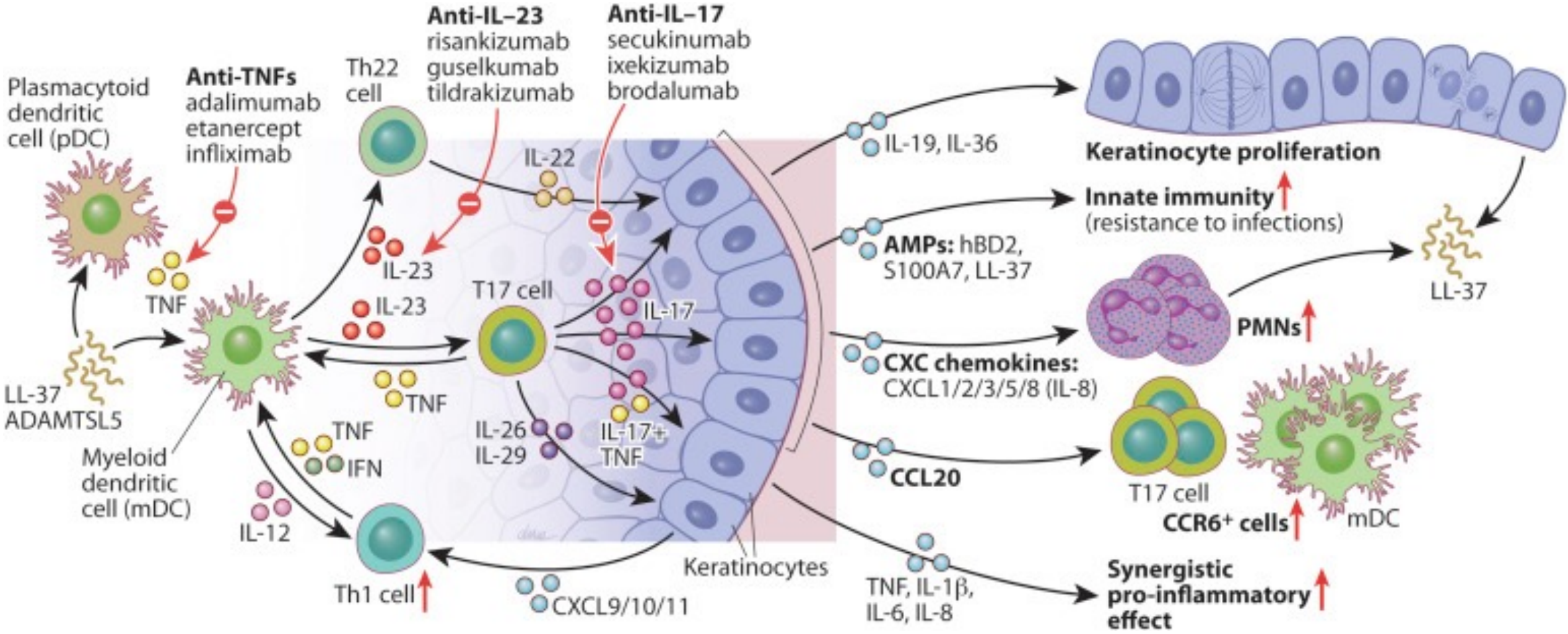
PDE-4 INHIBITORS



PSORIASIS


Recruitment of neutrophils, Th17 cells, dendritic cells and macrophages
Epidermal hyperplasia
Innate immunity
Triggers
CXCL1/2/3/8/9/10/11
CCL2/20
IL-19
IL-36
S100A7/8/9/12
hBD2, LL37
Tissue reorganization
Stressed keratinocytes
self-nucleotides and antimicrobial peptides
Keratinocytes
TNF-α, IL-1β
IL-6, IL-8
IL-17
IL-22
endothelial cells
fibroblasts
Activation of pDC
IL-22
pDC
IFN,TNF-α
IL-1β,IL-6
mDC
IL-23
Th17
TNF
Th22
IFN-γ,TNF-α
IL-12
Th1
PSORIASIS

PSORIASIS

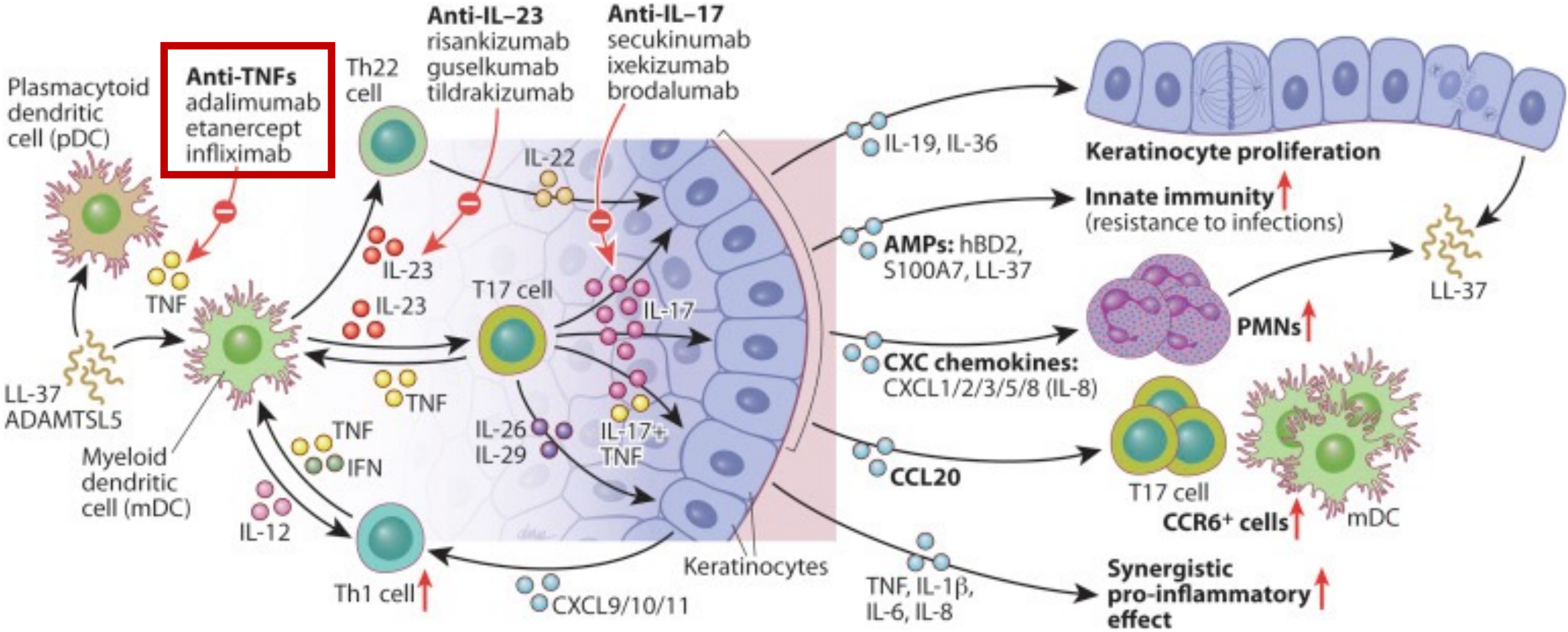

Plasmacytoid dendritic cell (pDC)
Anti-TNFs
adalimumab
etanercept
infliximab
Th22 cell
Anti-IL–23
risankizumab
guselkumab
tildrakizumab
Anti-IL–17
secukinumab
ixekizumab
brodalumab
IL-22
IL-19, IL-36
Keratinocyte proliferation
Innate immunity
(resistance to infections)
AMPs: hBD2,
S100A7, LL-37
LL-37
TNF
IL-23
T17 cell
IL-17
PMNs
CXC chemokines:
CXCL1/2/3/5/8 (IL-8)
LL-37
ADAMTSL5
Myeloid dendritic cell (mDC)
TNF
IFN
IL-26
IL-29
IL-17+
TNF
CCL20
T17 cell
CCR6+ cells
mDC
IL-12
Th1 cell
CXCL9/10/11
Keratinocytes
TNF, IL-1β,
IL-6, IL-8
Synergistic
pro-inflammatory
effect

Biologics in psoriasis (targets)

- TNF-α
- IL-12 and/or IL-23
- IL-17

TNF-α inhibitors

- Monoclonal antibodies:
  - Chimeric – infliximab (intravenous)
  - Humanized – certolizumab (subcutaneous)
  - Human – adalimumab (subcutaneous)
- Fusion protein – etanercept (subcutaneous)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Th1 cell
CXCL9/10/11
Keratinocytes
TNF, IL-1β,
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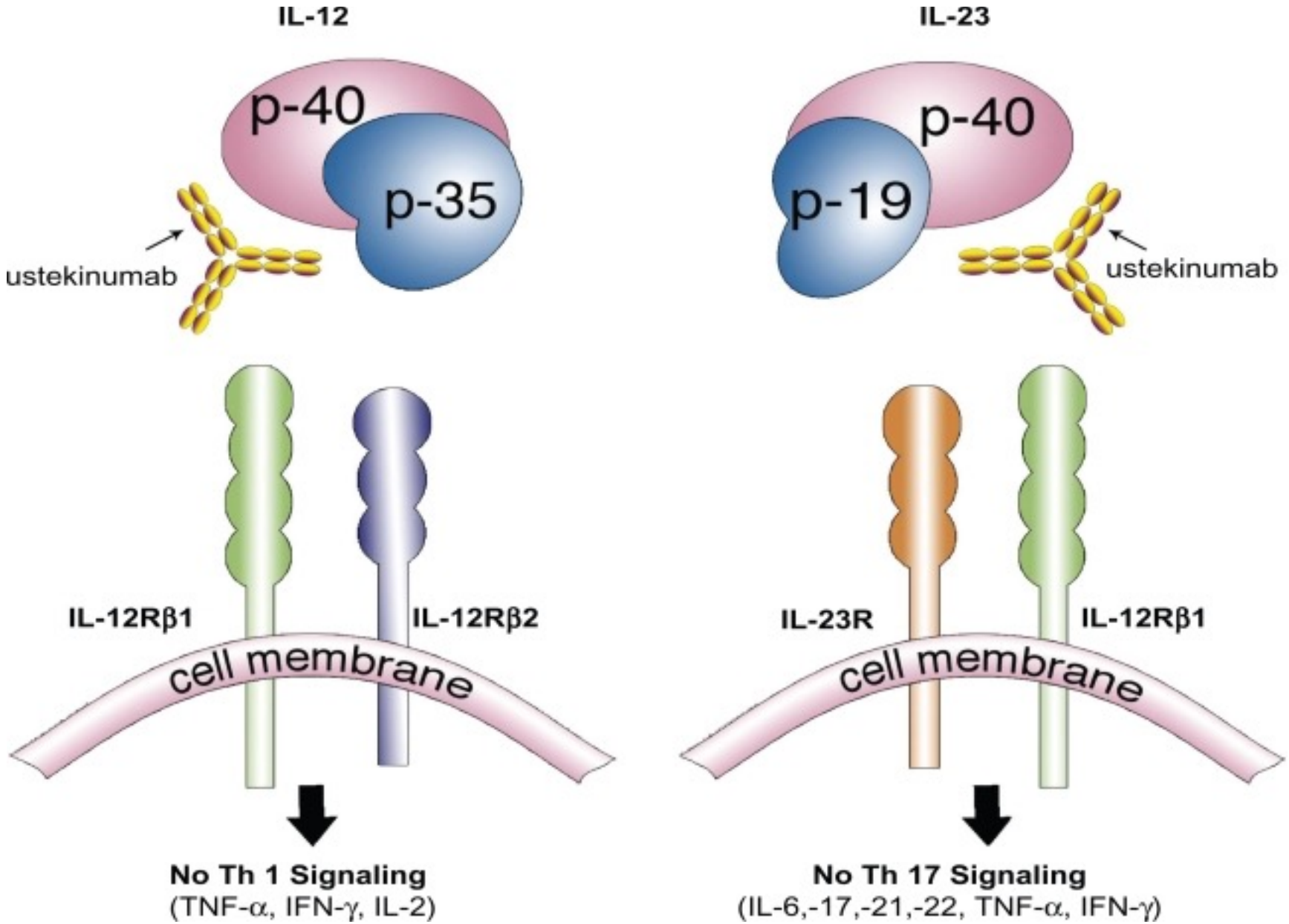
Synergistic
pro-inflammatory
effect

IL-12/23 inhibitors

- Ustekinumab – human monoclonal antibody targeting the p40 subunit (present in both IL-12 and IL-23)
- Administered subcutaneously

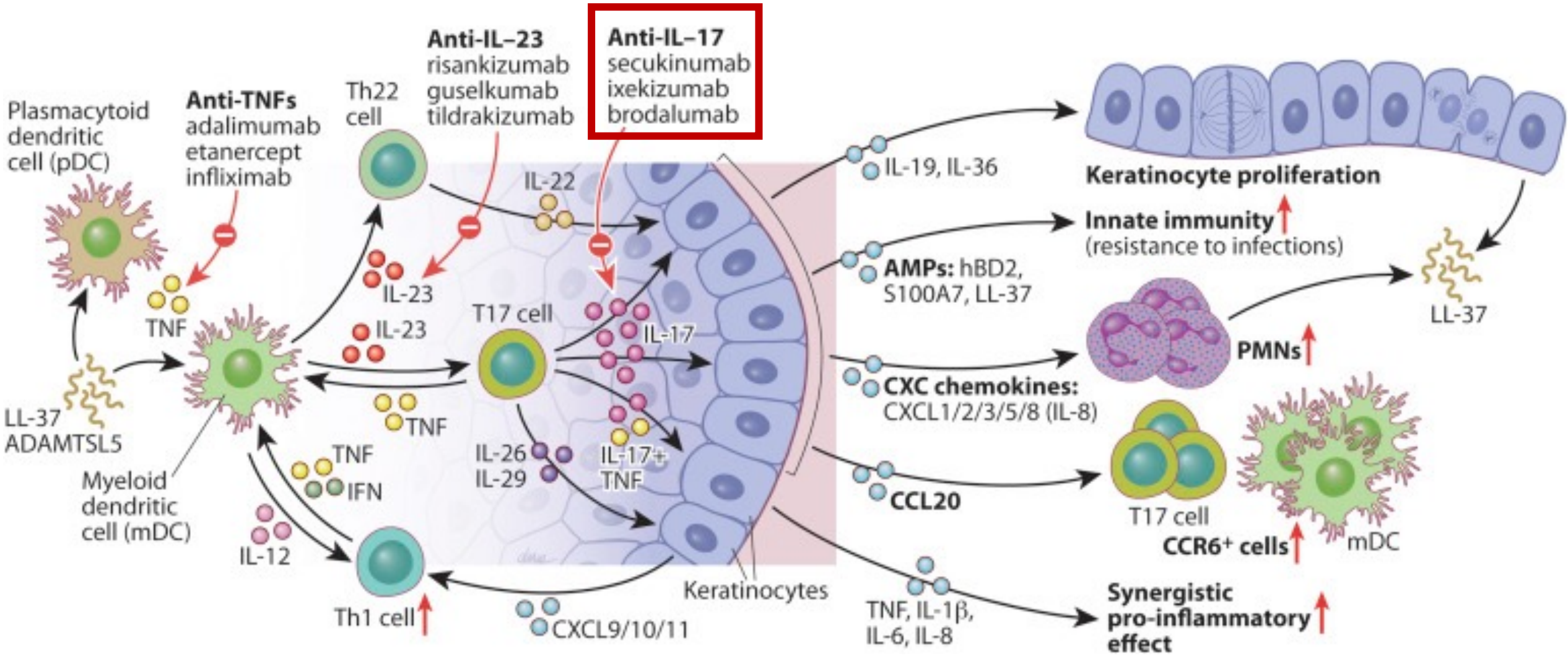

IL-12
p-40
p-35
ustekinumab
IL-12Rβ1
IL-12Rβ2
cell membrane
No Th 1 Signaling
(TNF-α, IFN-γ, IL-2)
IL-23
p-40
p-19
ustekinumab
IL-23R
IL-12Rβ1
cell membrane
No Th 17 Signaling
(IL-6,-17,-21,-22, TNF-α, IFN-γ)

IL-17 inhibitors

- Ixekizumab – humanized, subcutaneous

- Brodalumab
- Secukinumab

} human, subcutaneous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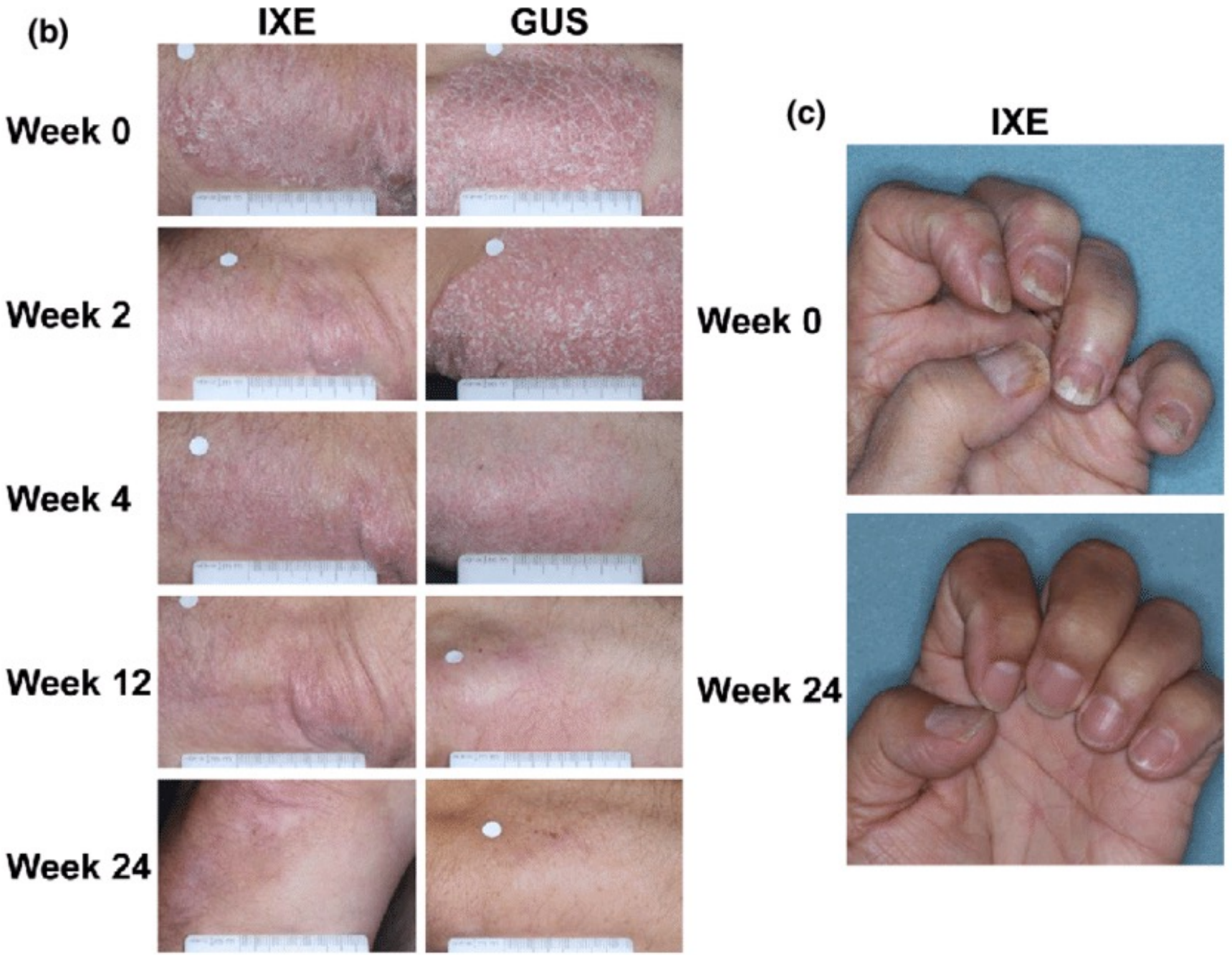
TNF, IL-1β,
IL-6, IL-8
Synergistic
pro-inflammatory
effect


IXE
GUS

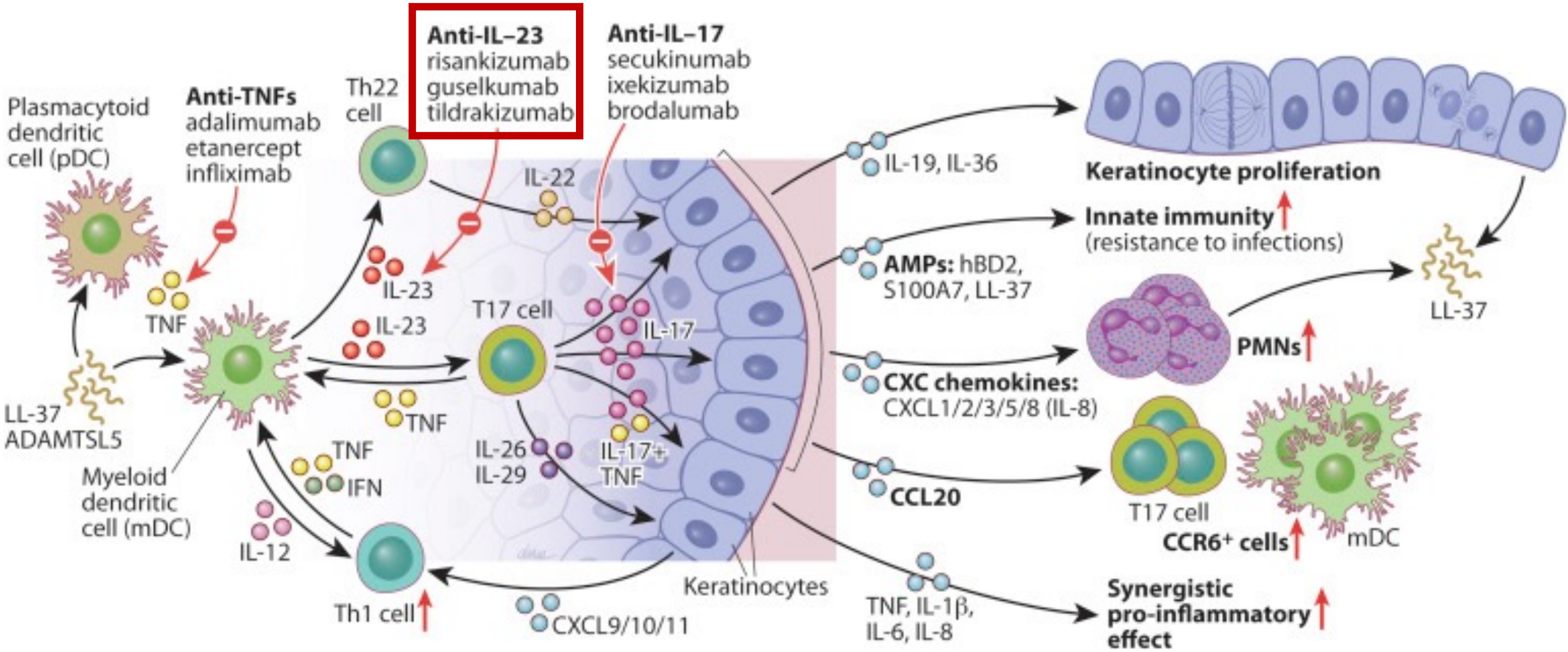

(b)
IXE
GUS
Week 0
Week 2
Week 4
Week 12
Week 24
(c)
IXE
Week 0
Week 24


IL-23 inhibitors

- Tildrakizumab
- Risankizumab

} humanized, subcutaneous

- Guselkumab – human, subcutaneous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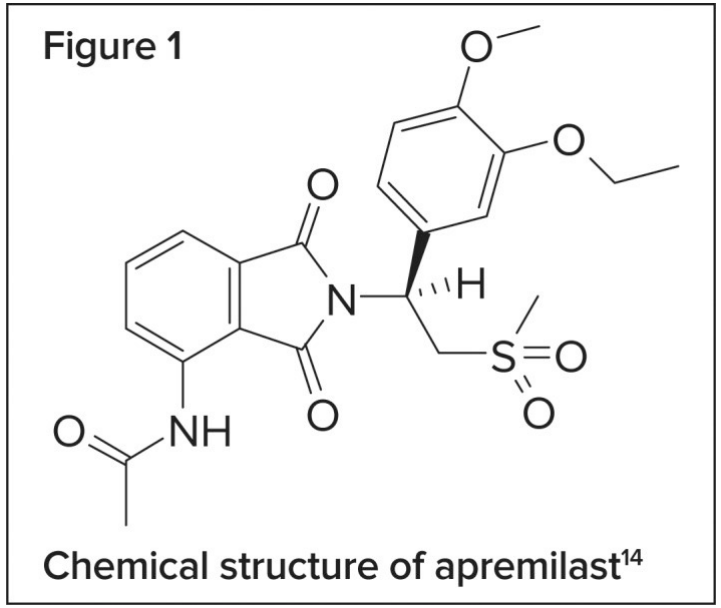
CCL20
T17 cell
CCR6+ cells
mDC
Th1 cell
CXCL9/10/11
Keratinocytes
TNF, IL-1β,
IL-6, IL-8
Synergistic pro-inflammatory effect

Apremilast

- Oral PDE-4 inhibitor
- Dual effect:
  - Downregulation of TNF-α, IL-23, and interferon (IFN)-γ
  - Increase in anti-inflammatory mediators (e.g., IL-10)

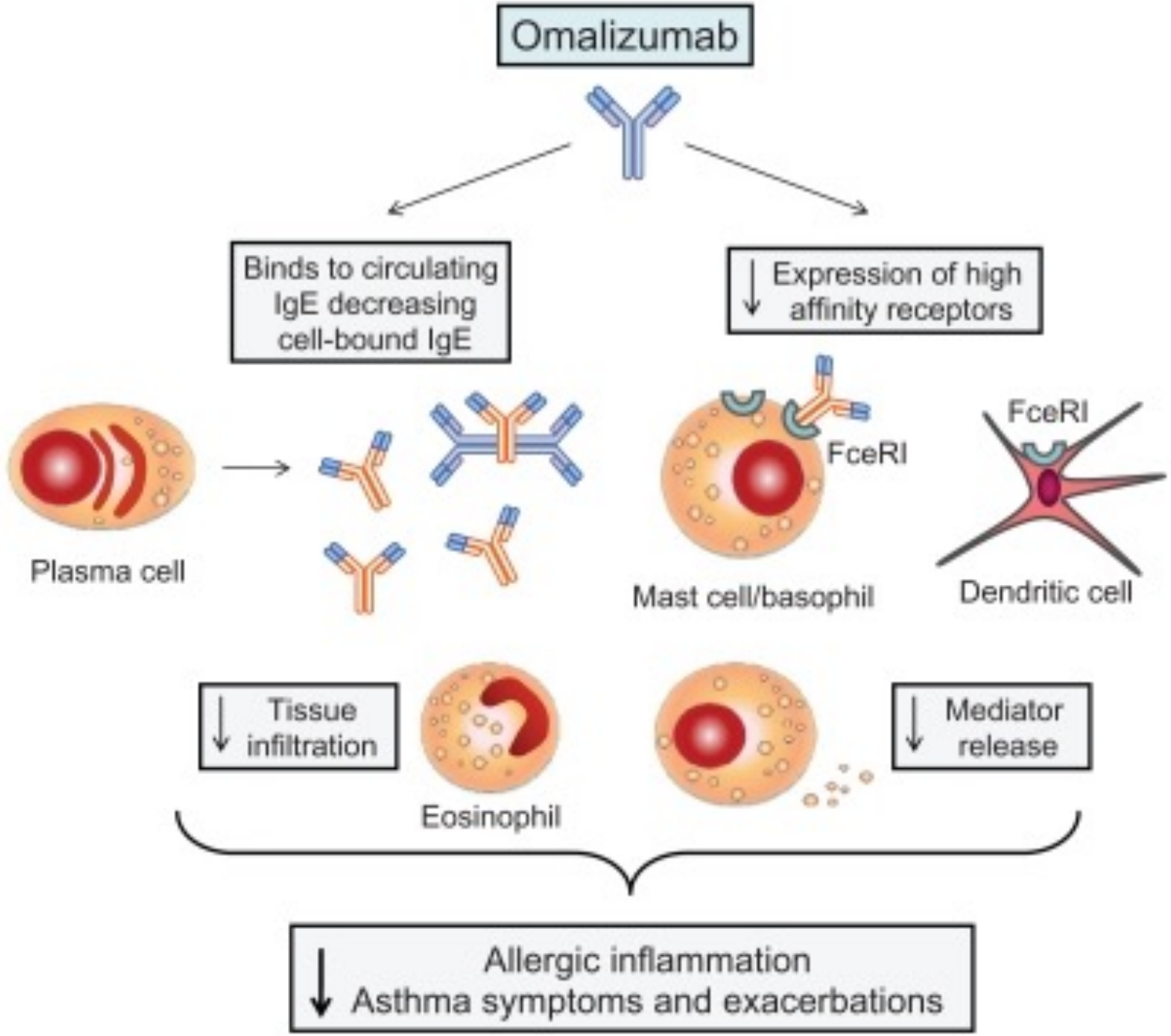


URTICARIA

Omalizumab

- Humanized monoclonal antibody (95% of human IgG1 sequences)
- Downregulation of circulating IgE
- Inhibition of IgE binding to FcεRI on effector cells (mastocytes, basophils)

Inhibition of immune cell activation and chemotaxis	Downregulation of inflammatory mediator release	Decreased antigen presentation


Omalizumab
Binds to circulating IgE decreasing cell-bound IgE
↓ Expression of high affinity receptors
Plasma cell
FceRI
FceRI
Mast cell/basophil
Dendritic cell
↓ Tissue infiltration
Eosinophil
↓ Mediator release
↓ Allergic inflammation
Asthma symptoms and exacerbations

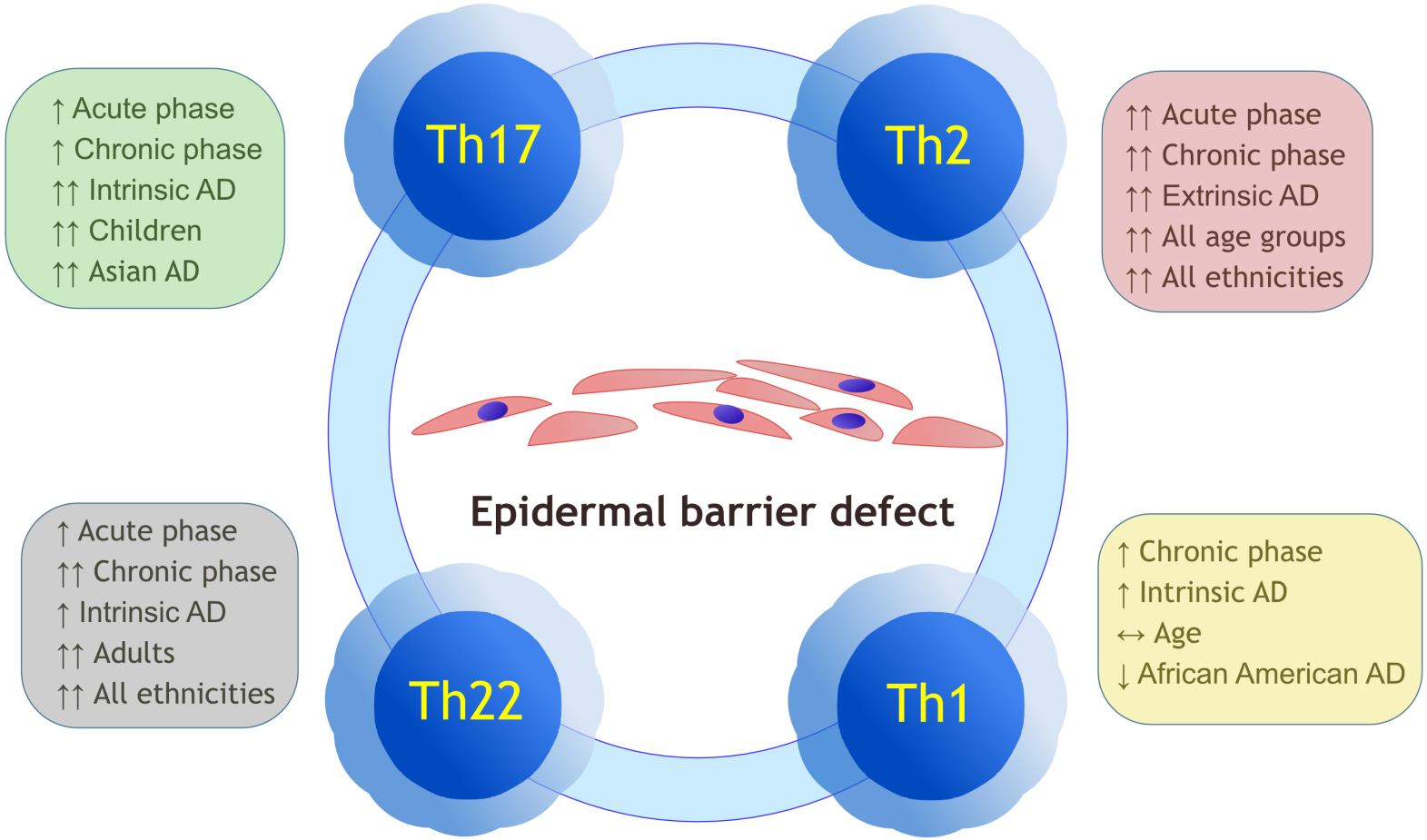
Omalizumab - indications

Chronic spontaneous urticaria

Off-label use in cold urticaria, delayed pressure urticaria, cholinergic urticaria, symptomatic dermographism, bullous pemphigoid

ATOPIC DERMATITIS

Heterogenous immune pathways in different populations



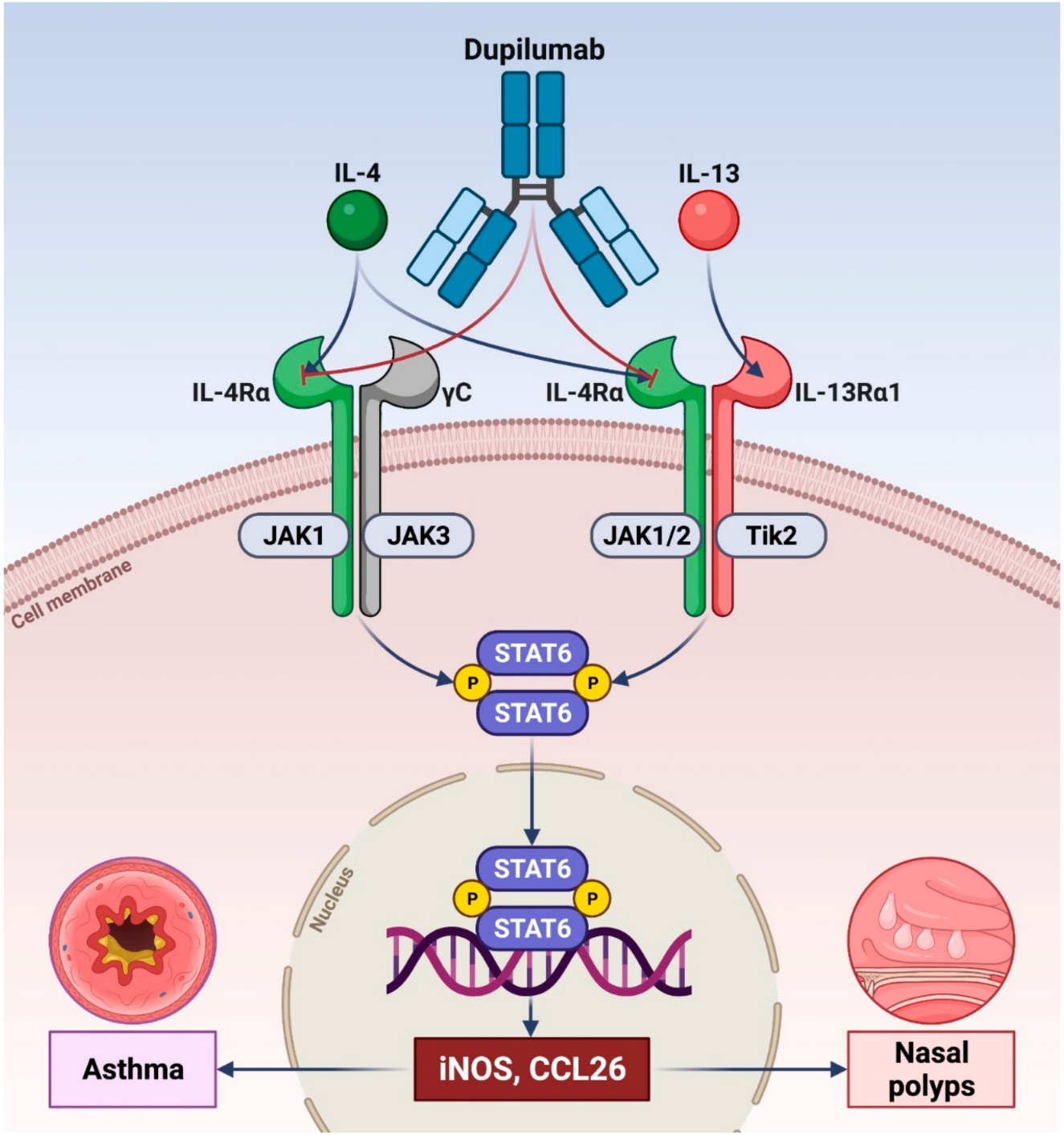
Novel medications for AD

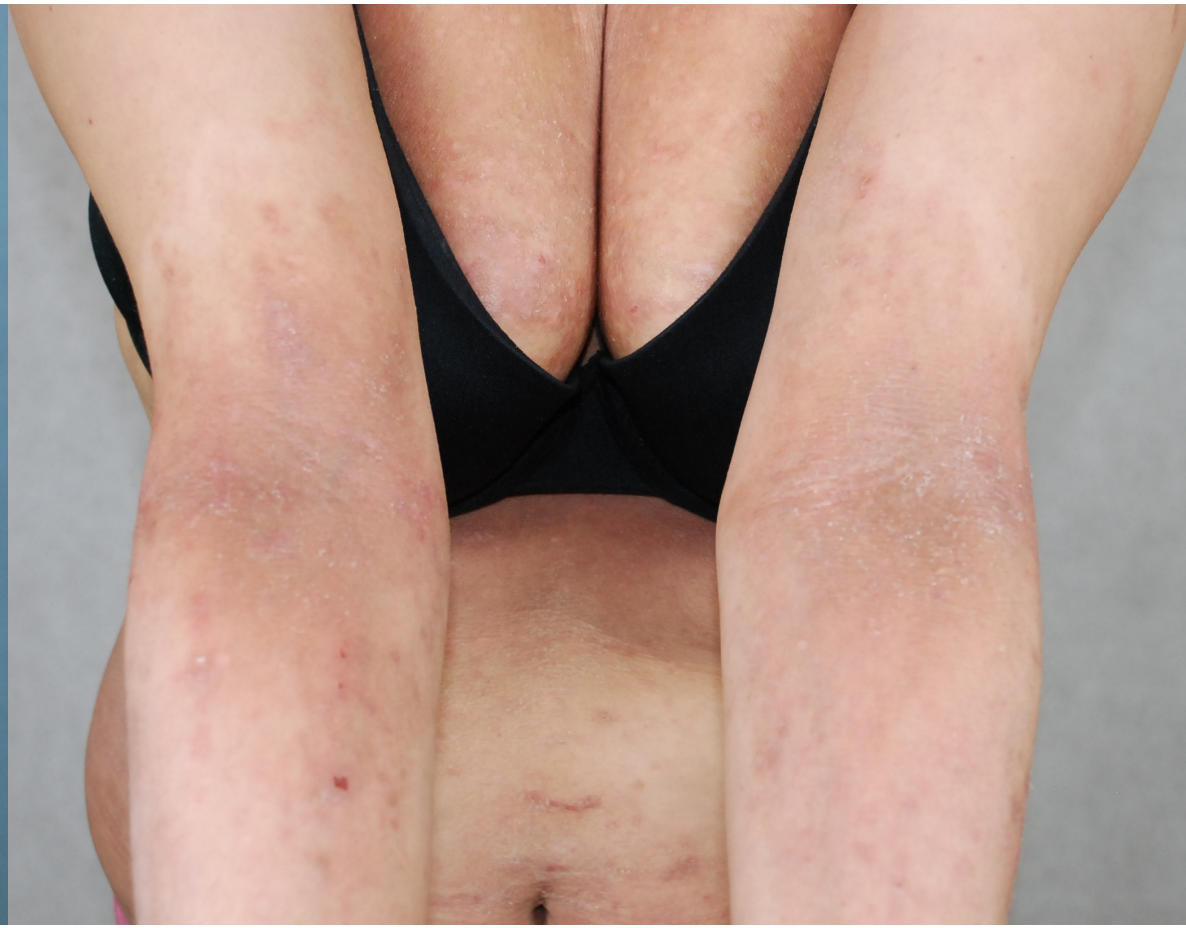
- Monoclonal antibodies:
  - Dupilumab
  - Tralokinumab

- JAK inhibitors:
  - Baricitinib
  - Upadacitinib
  - Abrocitinib

Dupilumab

- Human monoclonal antibody targeting IL-4Rα subunit present in IL-4 and IL-13 receptors
- Inhibits Th2 inflammation
- Administered subcutaneously
- Favorable outcomes and safety profile
- Additional benefits in patients with concomitant allergic diseases (asthma, allergic rhinitis)


Dupilumab
IL-4
IL-13
IL-4Rα
γC
IL-4Rα
IL-13Rα1
JAK1
JAK3
JAK1/2
Tik2
Cell membrane
STAT6
P
P
STAT6
Nucleus
STAT6
P
P
STAT6
Asthma
iNOS, CCL26
Nasal polyps



Tralokinumab

- Human monoclonal antibody targeting IL-13
- Inhibits Th2 inflammation
- Administered subcutaneously

JAK inhibitors selectivity

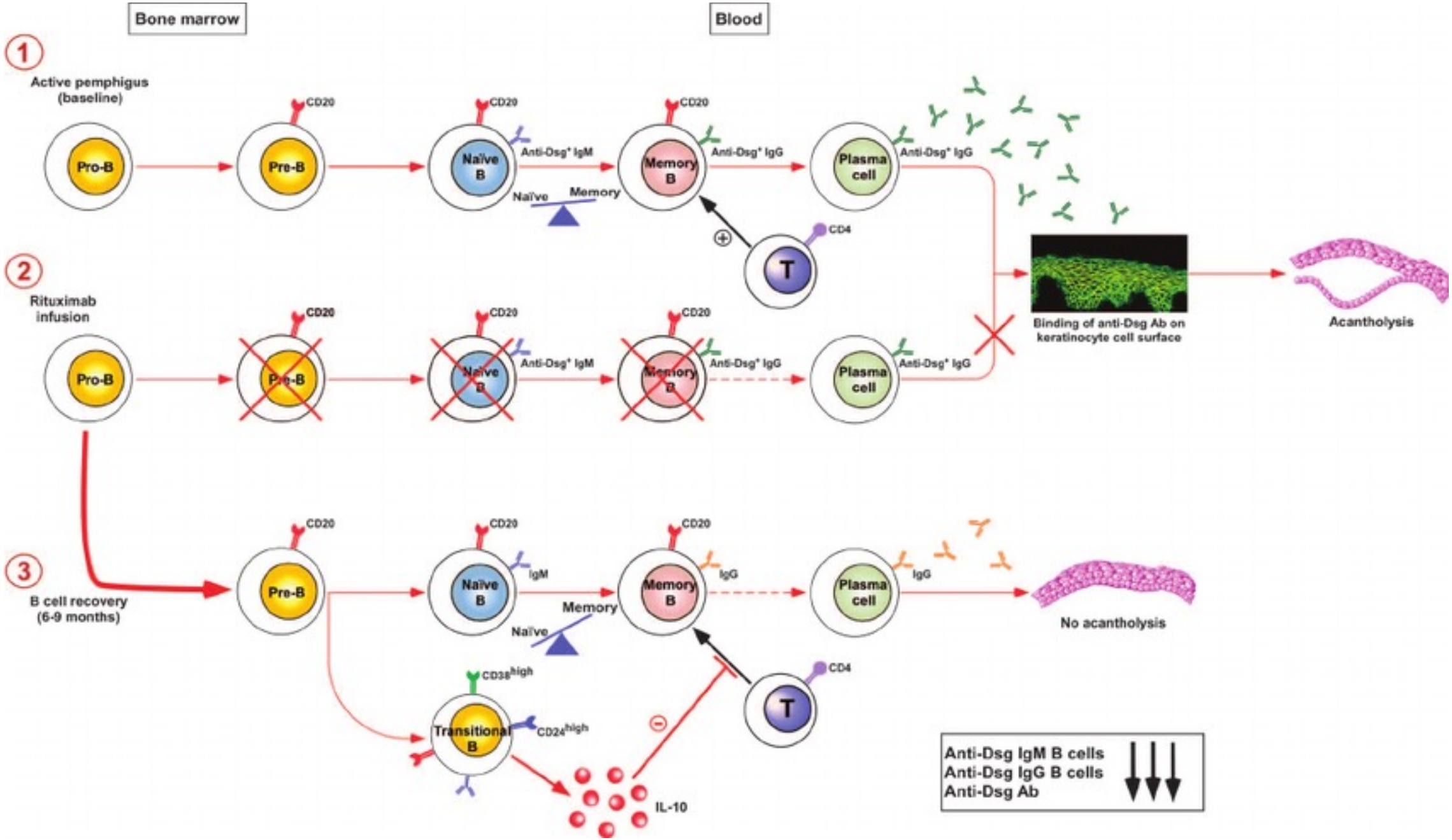
- Baricitinib – JAK1 and JAK2
- Upadacitinib – JAK1
- Abrocitinib – JAK1

- Downregulation of a wide array of pro-inflammatory factors
- Administered orally

Pemphigus

Rituximab

- Monoclonal chimeric antibody targeting CD20
- Result: depletion of peripheral B cells and decrease in autoantibody production
- Administered subcutaneously


Bone marrow
Blood
1
Active pemphigus (baseline)
Pro-B
Pre-B
Naïve B
Memory B
Plasma cell
CD20
Anti-Dsg+ IgM
Anti-Dsg+ IgG
Naïve
Memory
CD4
T
2
Rituximab infusion
3
B cell recovery (6-9 months)
IgM
IgG
CD38high
CD24high
Transitional B
IL-10
Binding of anti-Dsg Ab on keratinocyte cell surface
Acantholysis
No acantholysis
Anti-Dsg IgM B cells
Anti-Dsg IgG B cells
Anti-Dsg Ab

MELANOMA

Novel medications for melanoma

- Monoclonal antibodies:
  - Ipilimumab
  - Pembrolizumab
  - Nivolumab

Inoperable or metastatic melanoma

- Small molecules:
  - Vemurafenib
  - Dabrafenib
  - Trametinib
  - Cobimetinib

Inoperable or metastatic melanoma with V600 BRAF mutation

Monoclonal antibodies (immunotherapy)

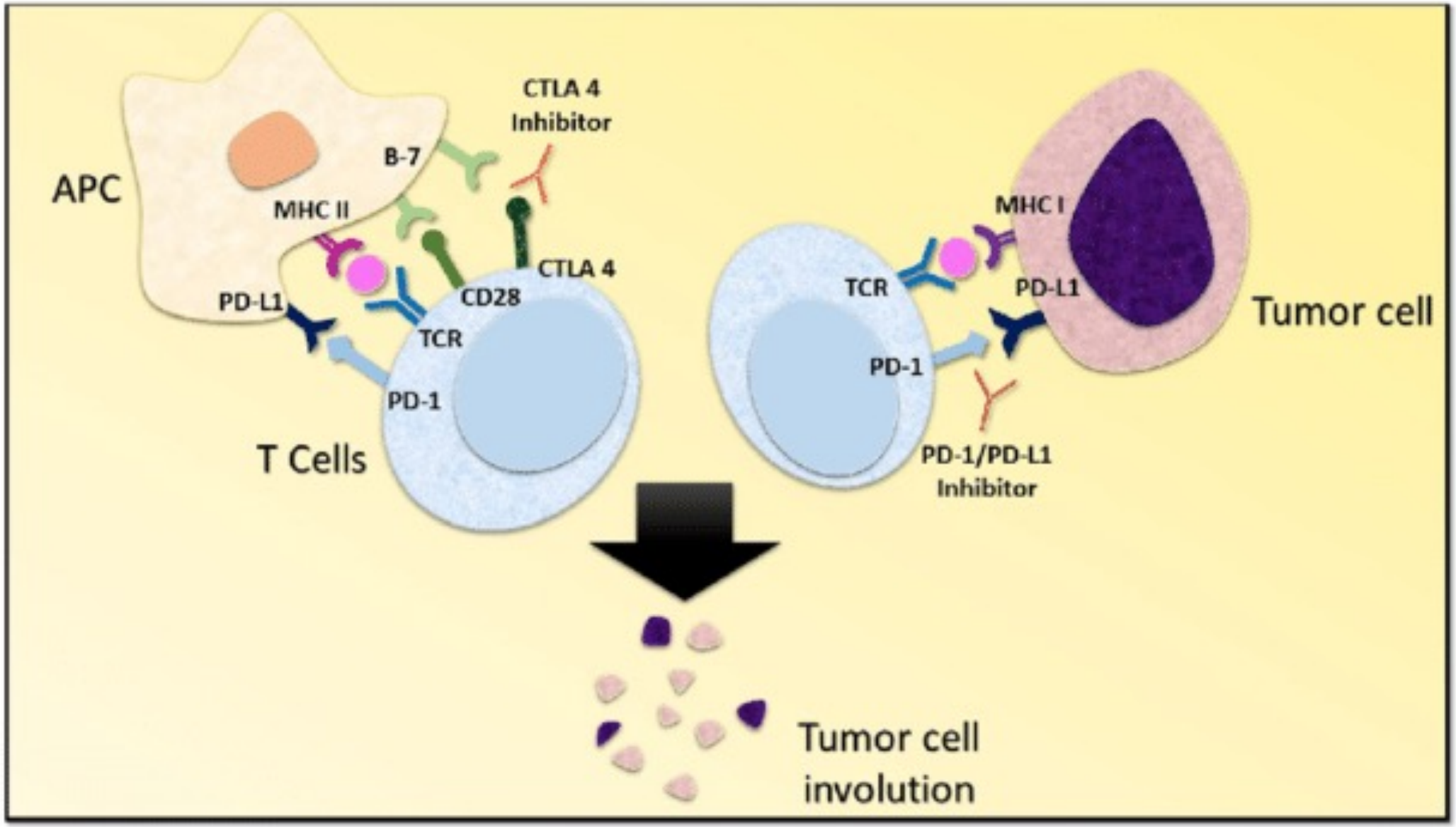
- Ipilimumab – anti-CTLA-4 human antibody

Activation of T cells infiltrating melanoma

- Pembrolizumab
- Nivolumab

} anti-PD-1 human antibodies

Inhibition of negative T-cell regulation signals, potentiation of T-cell mediated responses


APC
CTLA 4
Inhibitor
B-7
MHC II
CTLA 4
CD28
PD-L1
TCR
PD-1
T Cells
MHC I
TCR
PD-L1
PD-1
Tumor cell
PD-1/PD-L1
Inhibitor
Tumor cell
involution

Small molecules

- Vemurafenib
- Dabrafenib

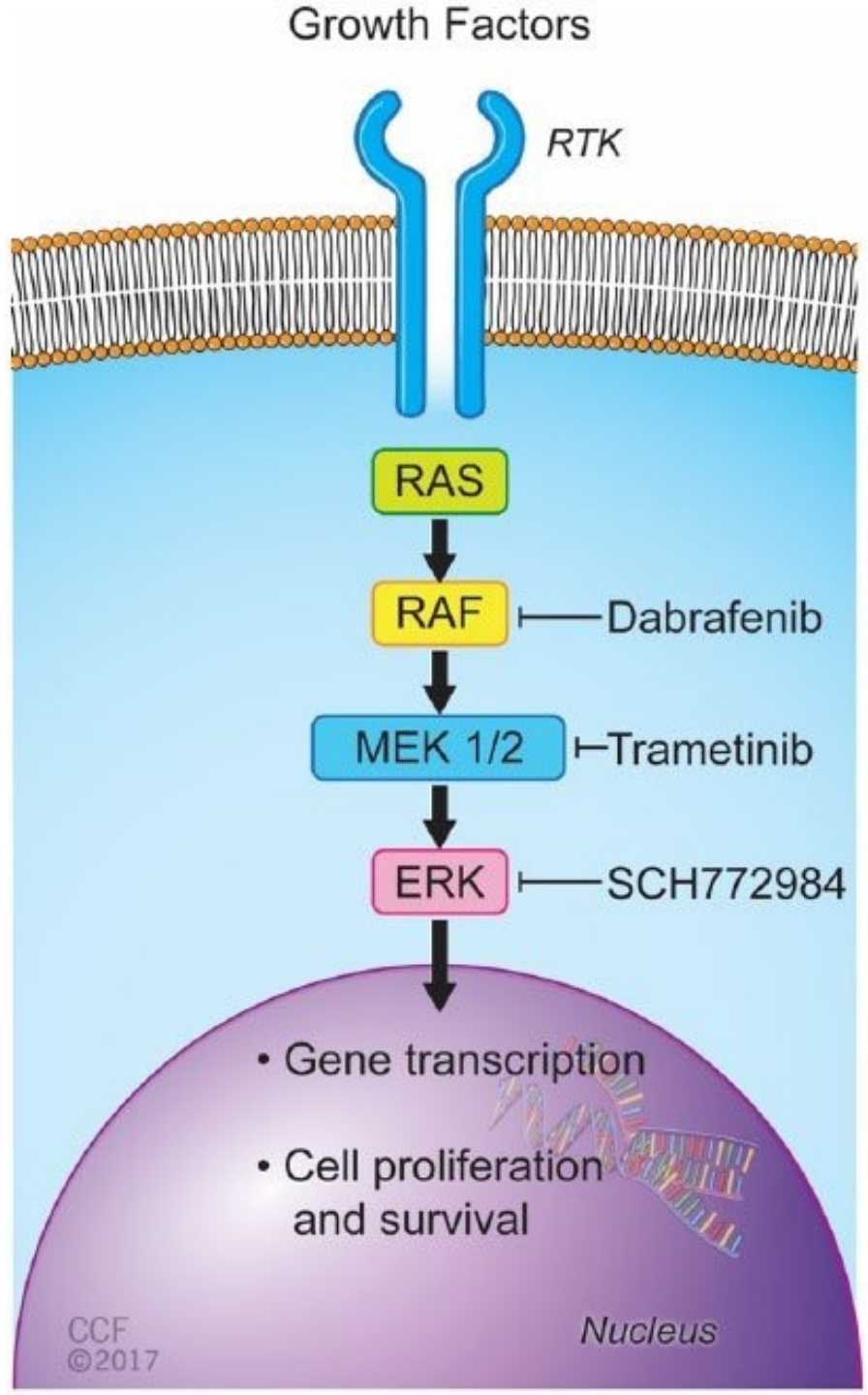
} BRAF inhibitors

- Trametinib
- Cobimetinib

} MEK inhibitors

Small molecules

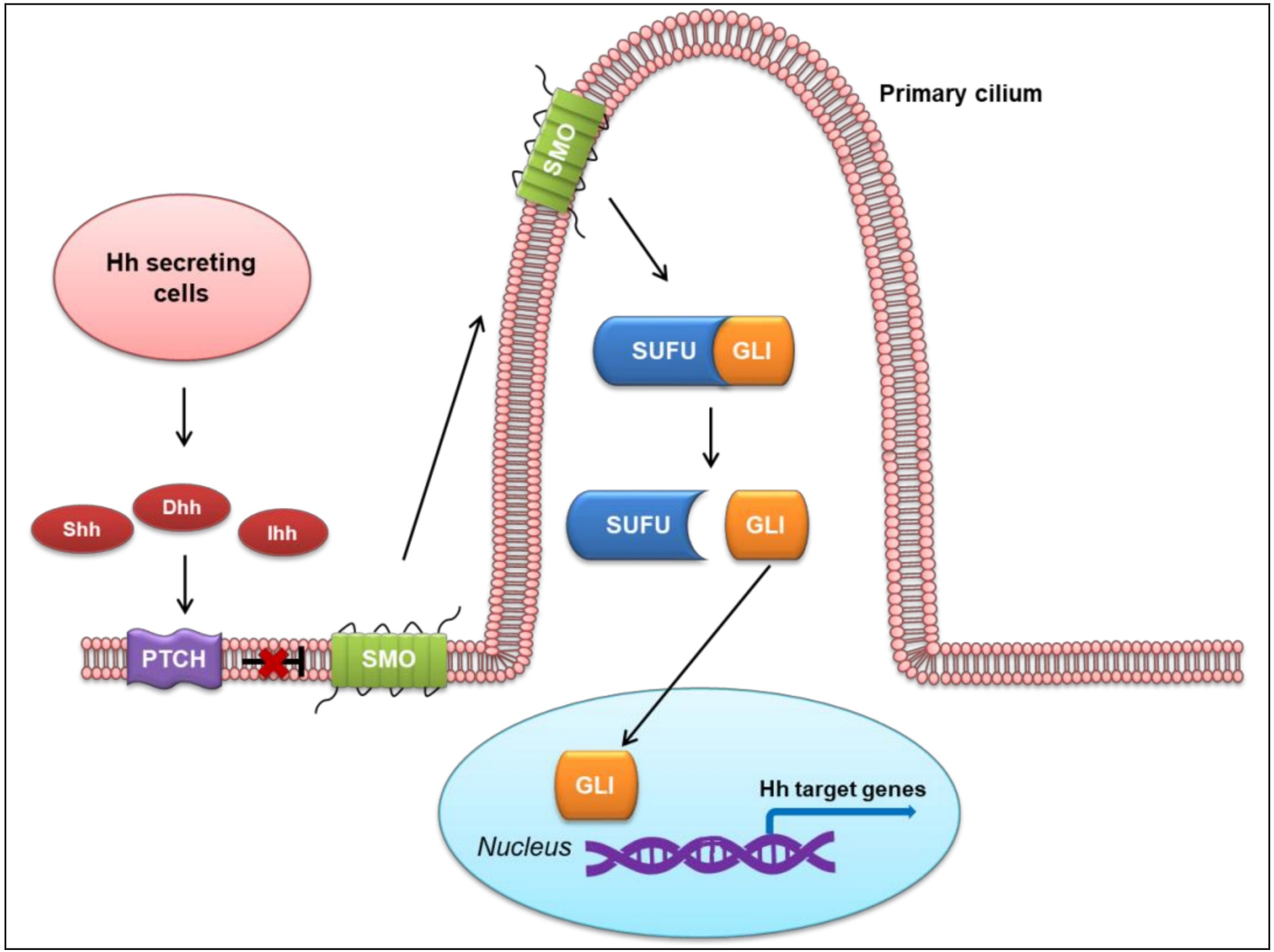
- BRAF mutations → a constitutive activation of the MAP/ERK pathway and subsequent cell proliferation without external growth signal
- MEK - a part of the MAP/ERK pathway
- BRAF and MEK inhibitors are used in combination to potentiate the effect on melanoma cells and reduce the risk of resistance


Growth Factors
RTK
RAS
RAF
Dabrafenib
MEK 1/2
Trametinib
ERK
SCH772984
• Gene transcription
• Cell proliferation and survival
Nucleus
CCF ©2017

BASAL CELL CARCINOMA

Hedgehog pathway inhibitors

- Medications: vismodegib, sonidegib
- Mechanism of action: SMO inhibition → hindrance of spontaneous cell proliferation mediated by the mutated Hedgehog pathway
- Indications:
  - metastatic basal cell carcinoma
  - locally advanced basal cell carcinoma that has recurred following surgery
  - BCC cases not qualifying for surgery and radiation


Primary cilium
SMO
Hh secreting cells
SUFU
GLI
Dhh
Shh
Ihh
SUFU
GLI
PTCH
SMO
GLI
Hh target genes
Nucleus