Gli inibitori della PDE4 nelle Spondiloartriti

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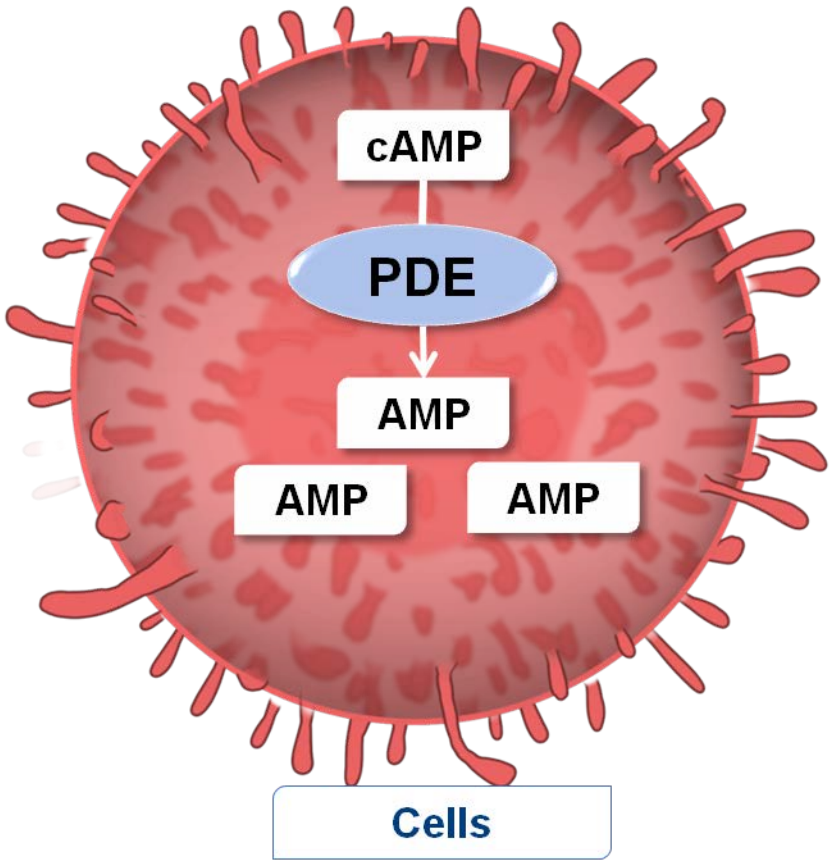
The Role of cAMP and PDE4 in Regulating Inflammation

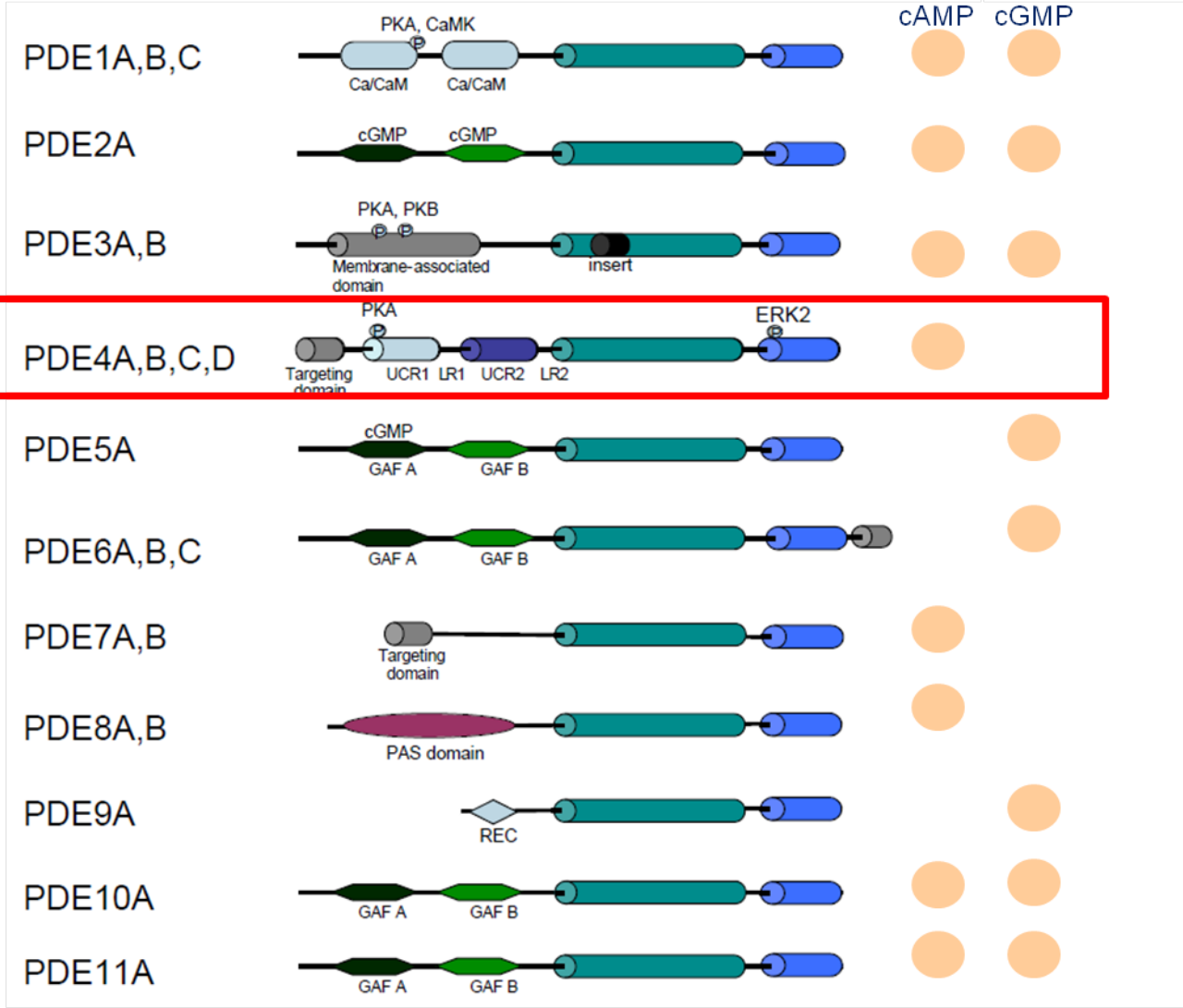
PDEs play a pivotal role in degrading cyclic nucleotides (cAMP and cGMP), key second messengers in cells[1-4]

cAMP is a second messenger for a variety of inflammatory mediators

PDE4 is a cAMP-specific PDE that has been shown to hydrolyze cAMP to AMP in inflammatory cells[1-2]

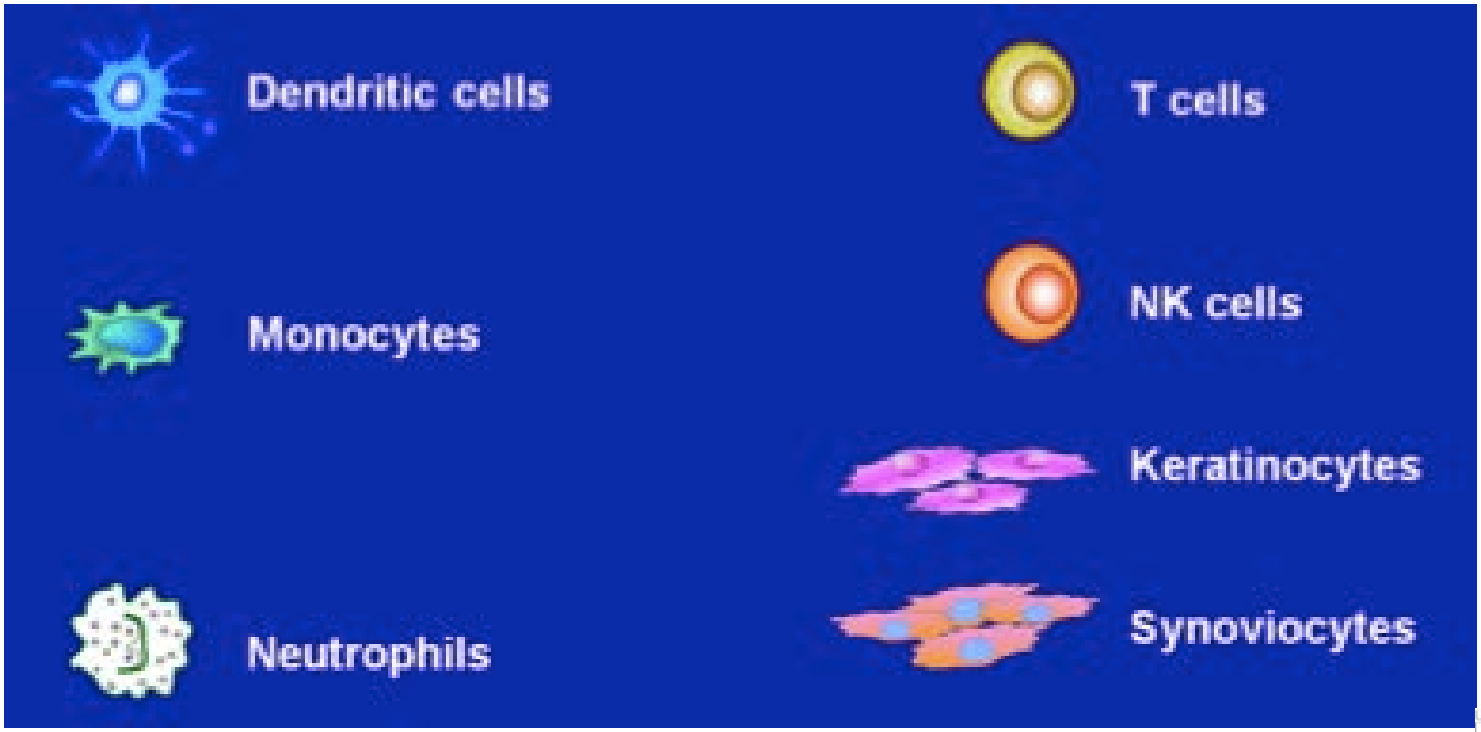


There Are 11 Distinct Families of PDEs



PDE4 Is Expressed in Multiple Cell Types

PDE4 is expressed in cell types identified to be relevant in psoriasis, psoriatic arthritis, and certain other chronic inflammatory diseases[1,2]

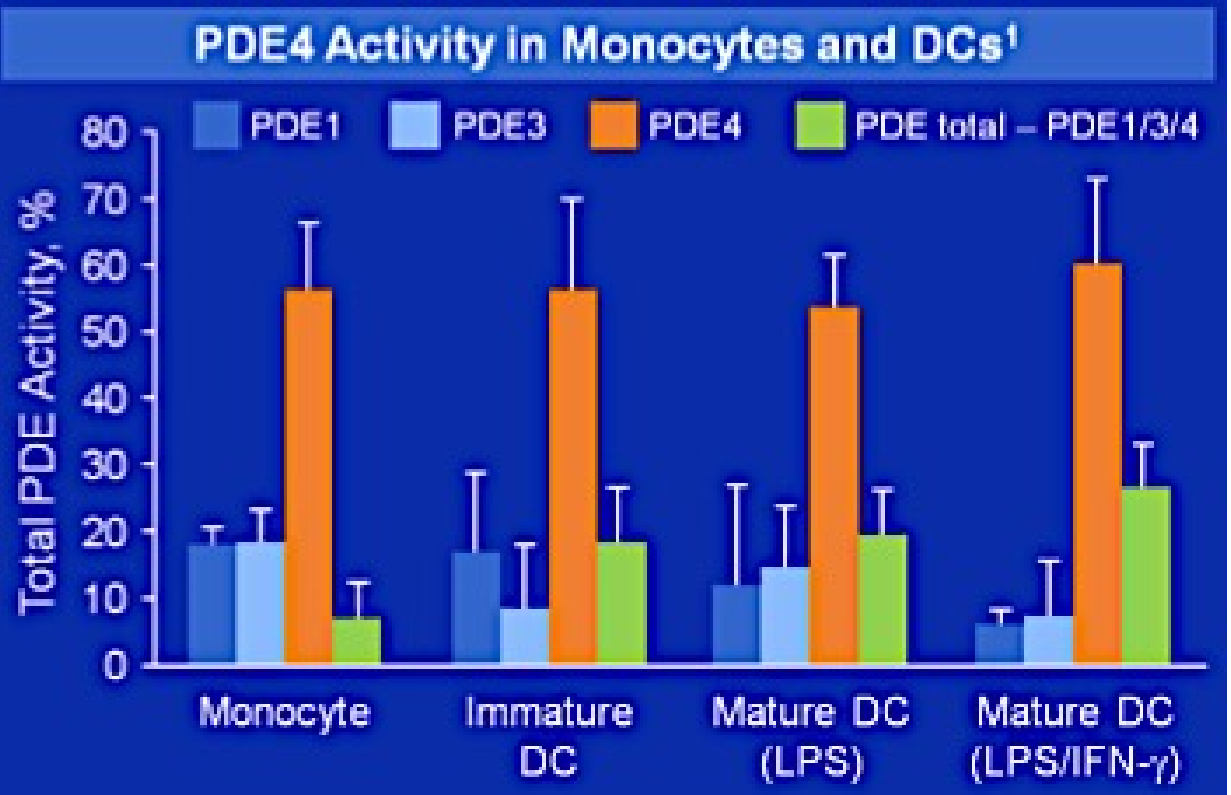


PDE4=phosphodiesterase 4.

1. Schett G, et al. *Ther Adv Musculoskel Dis*. 2010;2:271-278.
2. Schafer PH, et al. *Biochem Pharmacol*. 2012;83:1583-1590.

PDE4 Is the Predominant PDE in Immune Cells

PDE4 is the predominant PDE in inflammatory cells based on an in vitro analysis[1,2]



DC=dendritic cells; LPS=lipopolysaccharide; IFN=interferon; PDE=phosphodiesterase.

1. Heystek HC, et al. *Int Immunol*. 2003;15:827-835.
2. Gottlieb AB, et al. *J Drugs Dermatol*. 2013;12:888-897.

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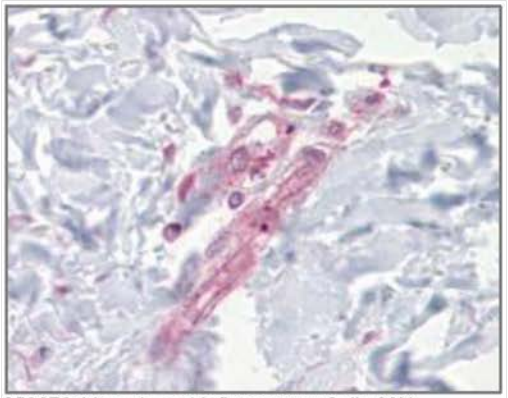
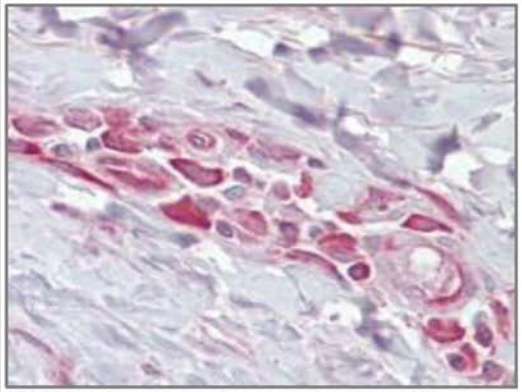
PDE4 Expression Is Elevated in Psoriatic Skin

PDE4A
Normal



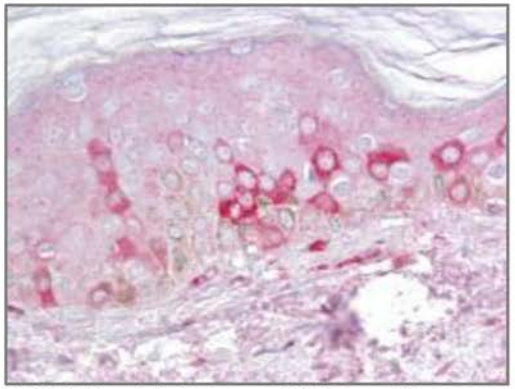
850076: Vessels and Inflammatory Cells 60X

PDE4B
Normal



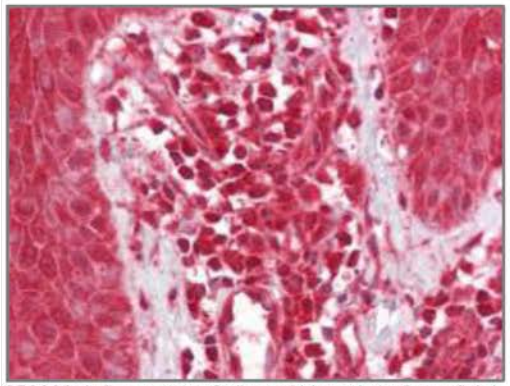
850000: Inflammatory Cells and Capillary 60X

PDE4D
Normal



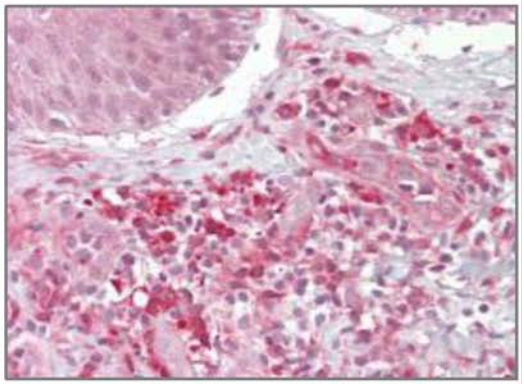
850158: 10 ug/ml, Squamous Epithelium 40X

Psoriasis



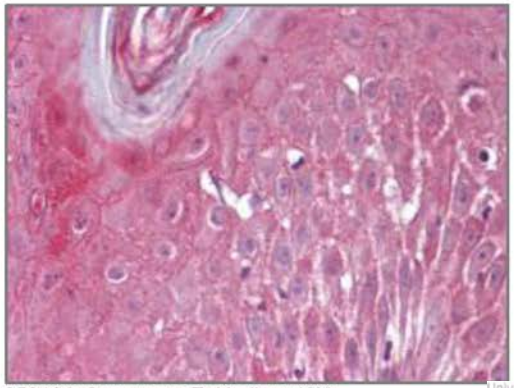
850082: Inflammatory Cells and Vessels in Superficial Dermis 40X

Psoriasis



850014: Inflammatory Cells and Vessels in Superficial Dermis 40X

Psoriasis



850164: Squamous Epithelium 40X

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Schafer P, et al. AAD 2013 [e-poster 6634].

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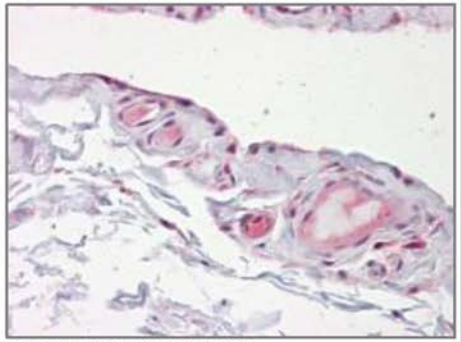
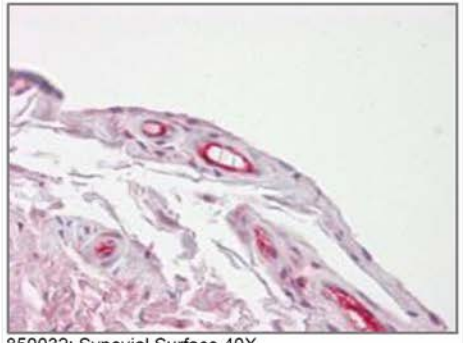
PDE4 Expression in RA Synovium and Anti-inflammatory Effects of Apremilast: Results

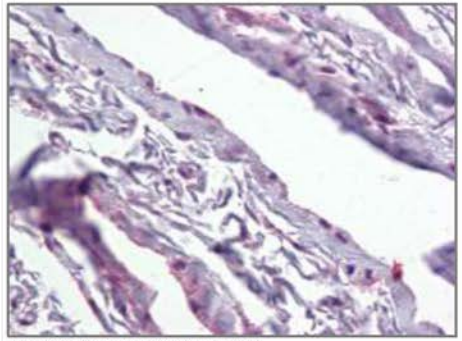
- PDE4 protein expression
  - IHC staining of synovial samples showed that, compared with normal samples, the superficial synoviocytes and subsynovial histiocytes in RA samples had more prevalent and more intense staining of PDE4A, PDE4B, and PDE4D

PDEA PDEB PDED

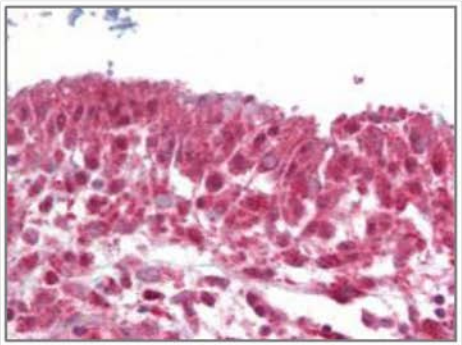
Normal Normal Normal

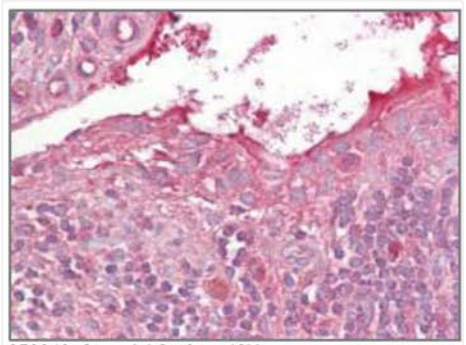

850104: Synovial Surface 40X

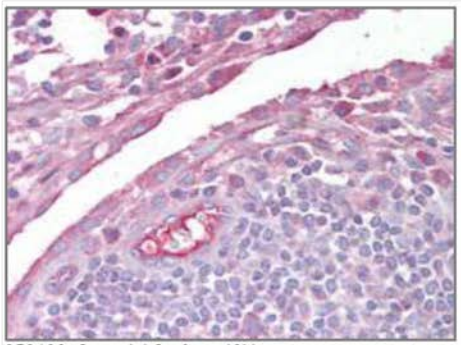

850032: Synovial Surface 40X


850188: Synovial Surface 40X

RA RA RA


850120: Synovial Surface 40X


850043: Synovial Surface 40X


850199: Synovial Surface 40X

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Apremilast: A novel oral agent for the treatment of patients with PsO & PsA

- Apremilast is an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4)
- Apremilast works intracellularly to modulate a network of pro-inflammatory & anti-inflammatory mediators

Psoriatic arthritis: Apremilast, alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs), is indicated for the treatment of **active psoriatic arthritis (PsA)** in adult patients who **have had an inadequate response or who have been intolerant to a prior DMARD therapy**

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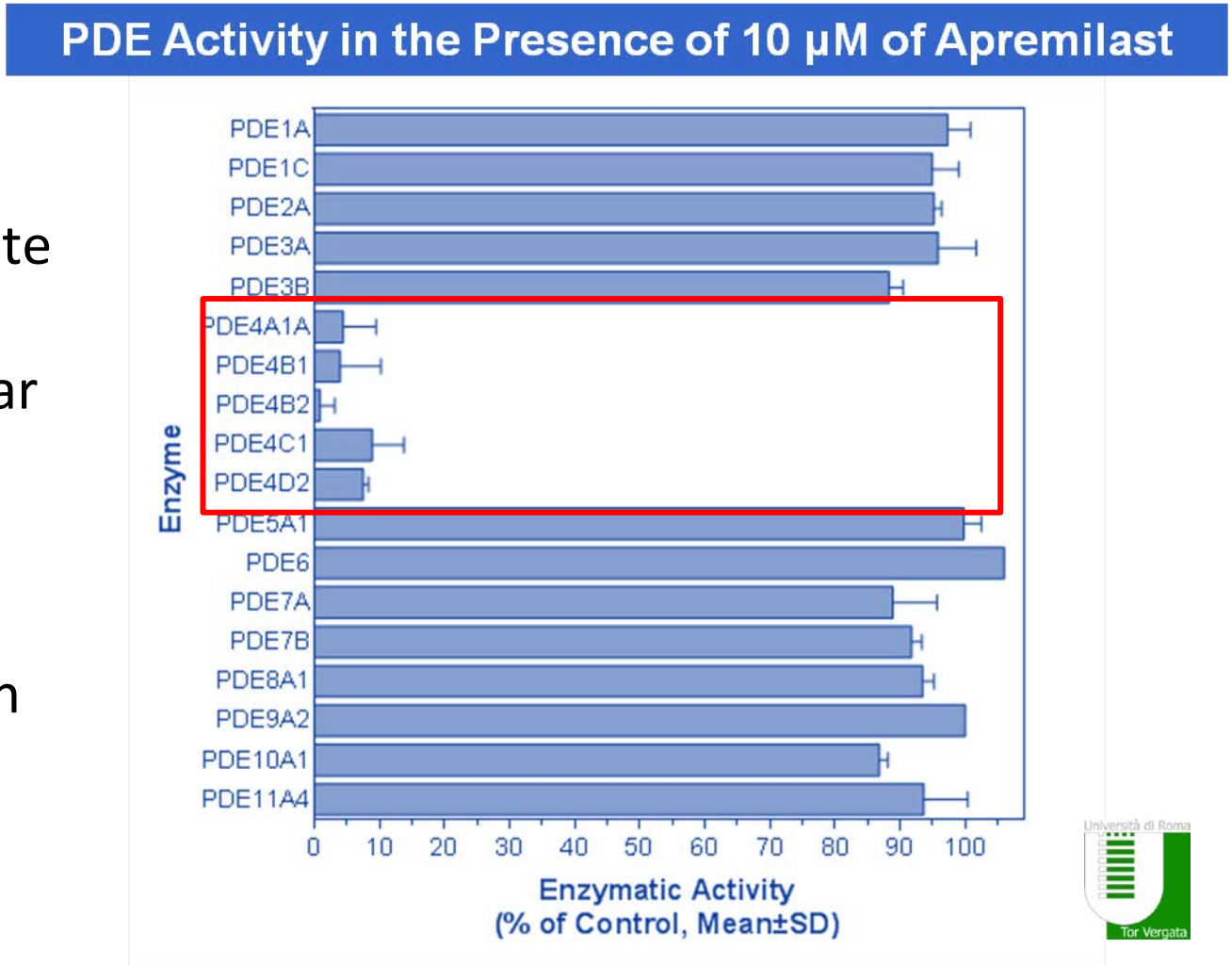
Enzyme Inhibition by Apremilast in Vitro Is Specific for PDE4

Apremilast potently binds the catalytic site of the PDE4 enzyme elevating intracellular cAMP levels

Apremilast selectively inhibits PDE4A, B, C, and D in vitro



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EXPERT OPINION

Apremilast for the treatment of psoriasis

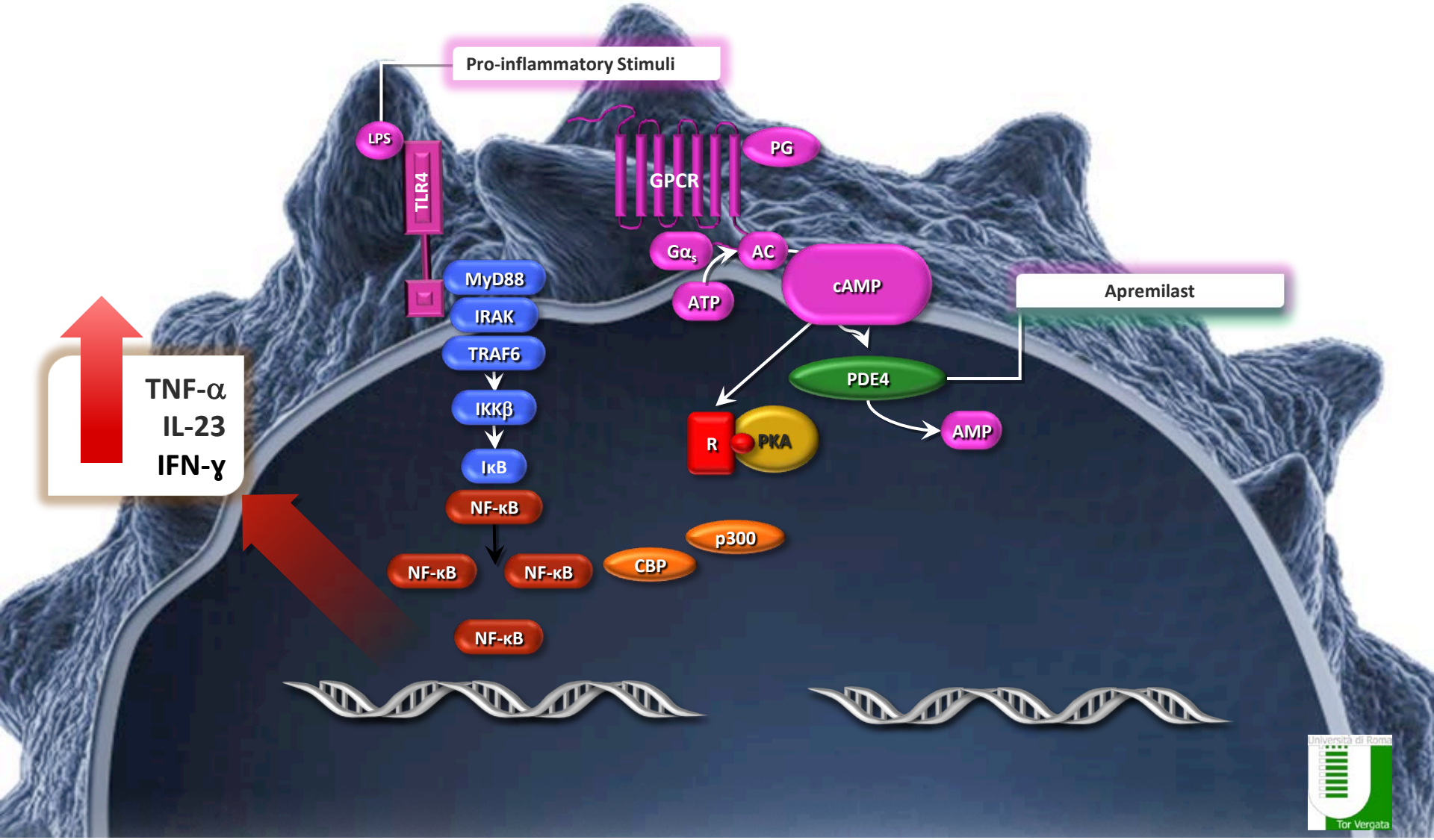
Maria Sole Chimenti, Talia Gramiccia, Rosita Saraceno, Luca Bianchi, Virginia Garofalo, Oreste Buonomo, Roberto Perricone, Sergio Chimenti† & Andrea Chiricozzi

Table 1. Principal physiologic effects of apremilast in psoriatic patients.

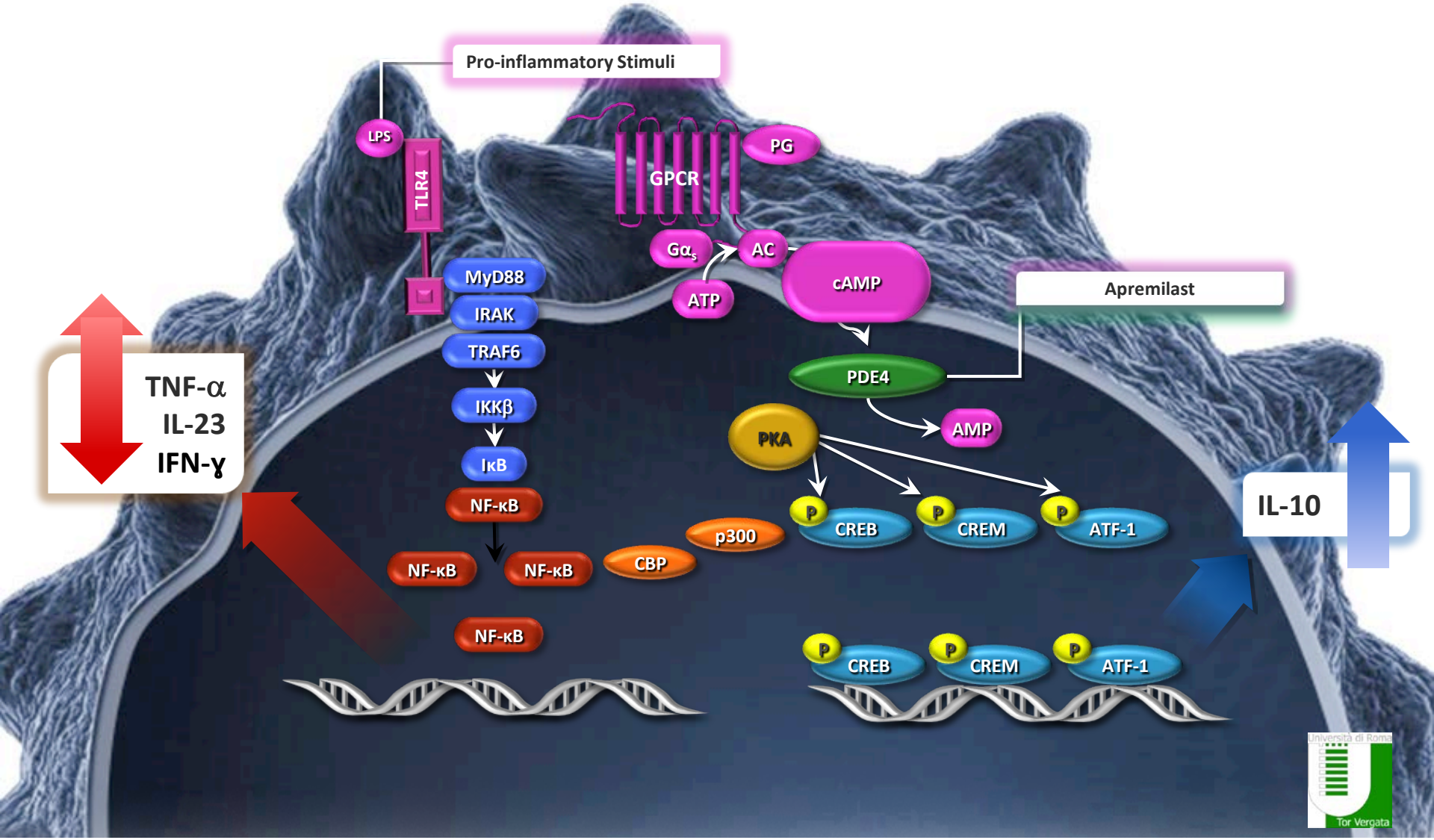
	Physiologic effects of apremilast
Intracellular effects [35,37]	Regulates the cAMP gradients Reduction of TNF-α and IL-23 Increasing anti-inflammatory cytokines such as IL-10
Skin effects [37,38]	Reduced infiltration of immune cells: mDCs in dermis and epidermis Reduction of inducible nitric oxide synthase mRNA expression Reduction of epidermal thickness (– 20%)
Synovial effects [38]	Reduced expression of TNF-α and IL-7, Reduction of MMP1, MMP3, MMP13 and MMP14 by synoviocytes
Bone effects [38]	Inhibited differentiation of osteoclasts Inhibited bone-resorbing activity Reduced production of RANKL by osteoblasts

cAMP: Cyclic adenosine monophosphate; mDCs: Myeloid dendritic cells; RANKL: Receptor activator of NF-κB ligand.

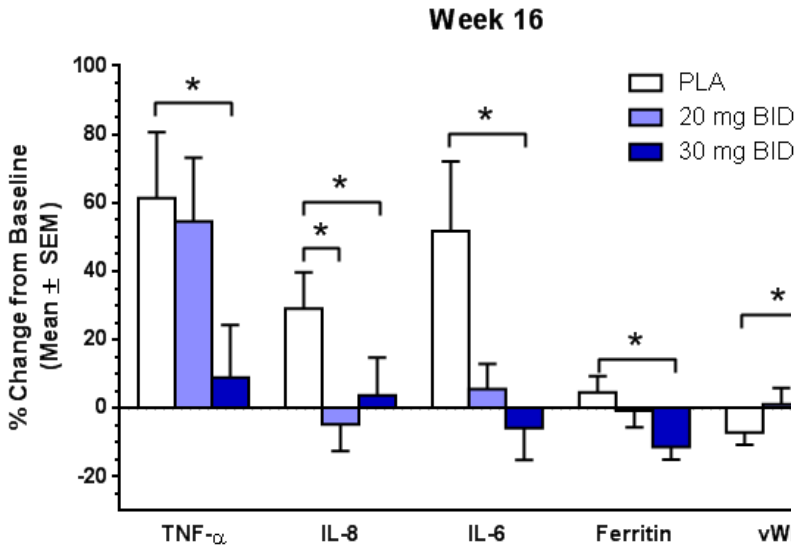
Apremilast Mechanism of Action

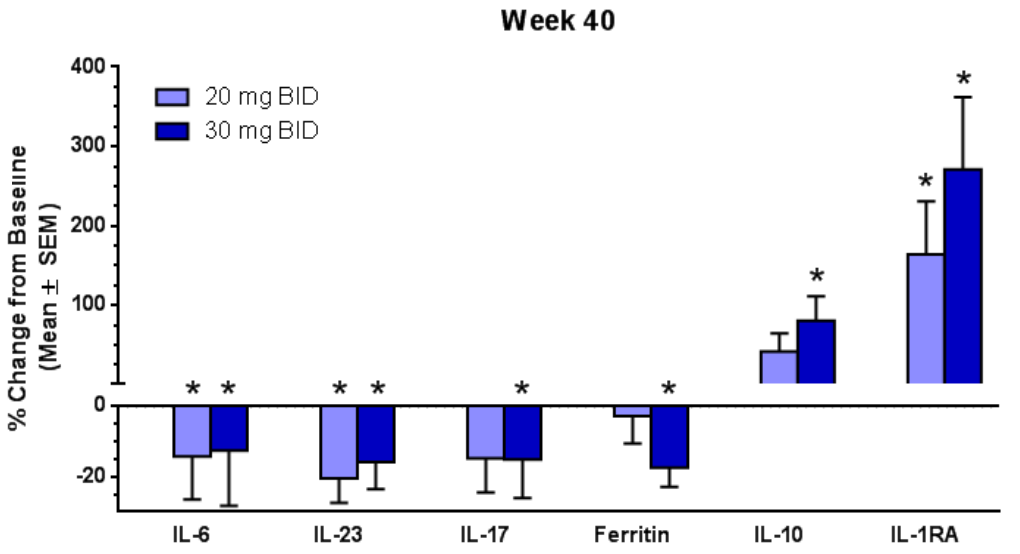


Apremilast Mechanism of Action



PALACE-1 PsA: changes in plasma biomarkers





*p<0.05 Apremilast vs. Placebo (rank ANCOVA 2 –sided p value);

*p<0.05 Wilcoxon signed rank test (2-sided p value for testing median of zero)

- Significant reduction of circulating **inflammatory cytokines**[1]
- Significant increases of circulating **anti-inflammatory cytokines IL-10 and IL-1RA**[1]

IL = interleukin; IL-1RA = interleukin 1 receptor antagonist.

1. Schafer PH, et al. J Immunol Res. 2015;2015:906349. doi: 10.1155/2015/906349

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APR: Oral pharmacokinetic profile

Attribute	Outcome
Absolute bioavailability[1]	~73%
Time to peak plasma concentration[1]	T_{max} = ~2.5 hours
Food effect [2]	Not clinically significant (AUC ↑24%; T_{max} delayed by 3 hours)
Plasma protein binding[1]	68%
Dose proportionality[3]	AUC dose proportional over 10 to 100 mg/day
Metabolism[1,4]	CYP oxidative metabolism (primarily CYP3A4), glucoronidation;Non-CYP hydrolysis
Plasma clearance[1]	10 L/hour
Elimination[1]	$t_{1/2}$ = ~9 hours
Special populations[1] Hepatic impairment Renal impairment* Age >65 years	No effect AUC ↑89%, C_{max} ↑42% (dose should be reduced in severe renal impairment) AUC ↑13%, C_{max} ↑6% (no requirement for a dose reduction)
Drug-drug interactions[1,5,6] Methotrexate Ketoconazole Rifampin†	AUC, C_{max} unchanged AUC ↑36% (not significant) AUC ↓72%; C_{max} ↓43% (concomitant use not recommended)

*The dose of apremilast should be reduced to 30 mg once daily in patients with severe renal impairment (CrCL <30 mL/min estimated by the Cockroft-Gault equation)
†Use with strong cytochrome P450 enzyme inducers (e.g. rifampicin, phenobarbital, carbemazepine, phenytoin) is not recommended because loss of efficacy may occur
T_{max} = time to maximum plasma concentration; AUC = area under the curve; CYP = cytochrome; $t_{1/2}$ = half-life; C_{max}= maximum plasma concentration.

1. OTEZLA Summary of Product Characteristics. January 2016. 2. Wan Y et al. AAPS 2011 [poster].
3. Wu A et al. SID 2011 [poster]. 4. Hoffman M et al. SID 2011 [abstract]; 5. Nissel J et al. EULAR 2011 [abstract]; 6. Liu Y et al. *Br J Clin Pharmacol* 2014;78:1050–7.

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Apremilast Mechanism of Action Summary

- Inhibits all PDE4 subtypes (A, B, C, and D)
- Does not inhibit other PDEs, kinases, or other known receptors or enzymes
- Does not bind to cereblon, the target of thalidomide
- Elevates intracellular cAMP
- Activates protein kinase A, resulting in phosphorylation and activation of CREB/ATF-1 transcription factors
- Inhibits NF-κB-driven transcription
- Regulates cytokine expression, inhibiting TNF, IL-23, and IL-17, and increasing expression of anti-inflammatory mediators such as IL-10

  Has Greater Effects on Innate vs. Adaptive Immunity
- Inhibits toll-like receptor activation in monocytes, dendritic cells, and neutrophils
- Does not affect B-cell or T-cell expansion or immunoglobulin production

PDE=phosphodiesterase; cAMP=cyclic adenosine monophosphate; CREB=cAMP responsive element binding protein; ATF-1=activating transcription factor; κB=nuclear factor kappa B; TNF=tumor necrosis factor; IL=interleukin.

Schafer PH, et al. *Cell Signal.* 2014;26:2016-2029. Schafer P. *Biochem Pharmacol.* 2012;83:1583-1590.

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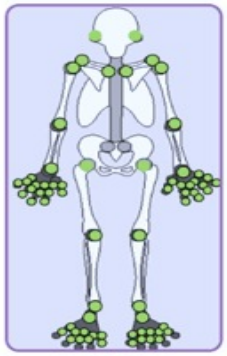
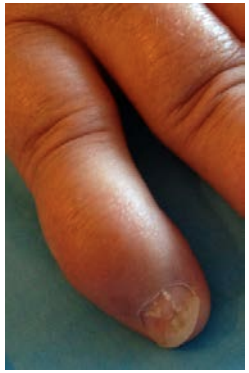
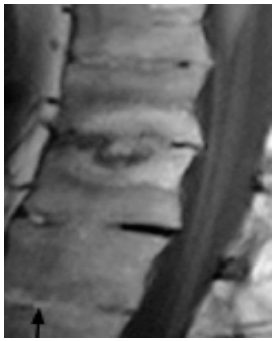




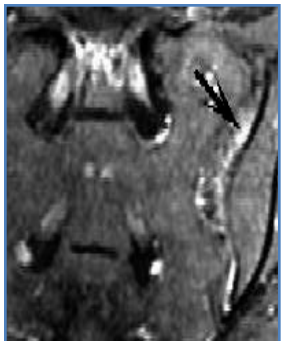
Peripheral Arthritis



Axial Involvement Spondylitis

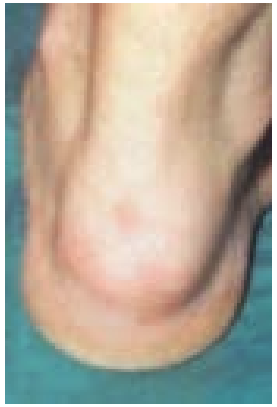
PsA

Dactylitis



Axial Involvement Sacroilitis

Enthesitis



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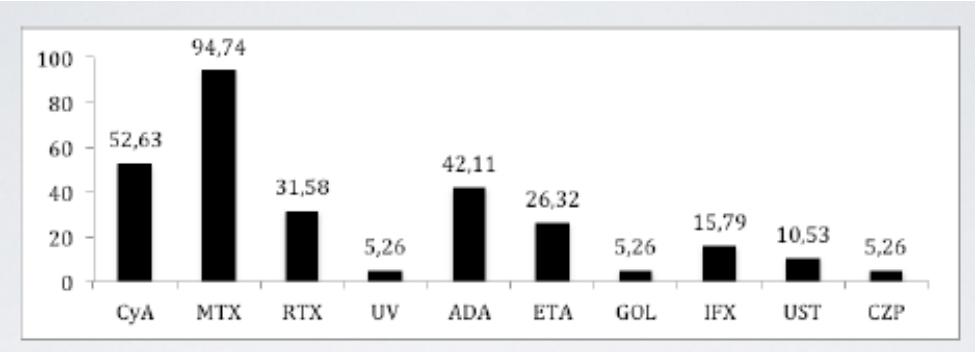
APREMILAST

Induction of **remission of psoriasis and psoriatic arthritis**: a real-life retrospective study on patients affected by malignancies, HBV or tuberculosis

Alessandro Giunta
Maria Esposito
Arianna Zangrilli
Maria Sole Chimenti
Nancy Dattola
Elena Campione
Valeria Manfreda
Ester Del Duca
Luca Bianchi

Patients, n	19
Males, n (%)	9 (47.37)
Females, n (%)	10 (52.63)
Age, y (range)	62.48 (43.29-82.35)
Body weight, kg	77 (48-110)
BMI, n (range)	27.80 (20.78-49.97)
PASI, n (range)	11.60 (0-60)
TJC, n (range)	15.52 (0-54)
SJC, n (range)	5,16 (0-20)
CRP, n (range)	7.25 (0.1-42.7)
ESR, n (range)	26.47 (9-70)
Pain VAS, n (range)	64.21 (0-100)
DAS28, n (range)	5.49 (2.28-8.19)
DLQI, n (range)	11.58 (1-24)



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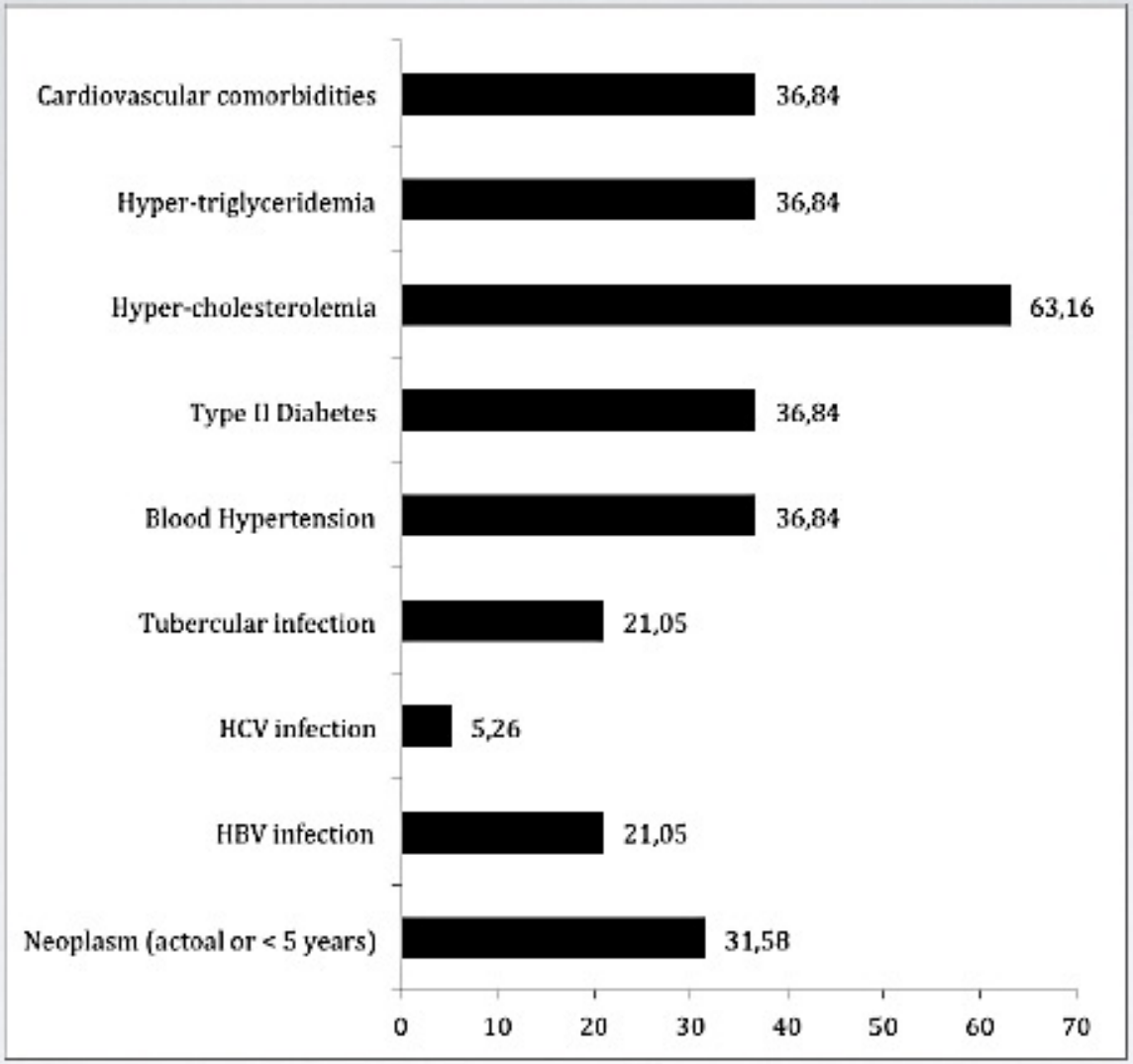
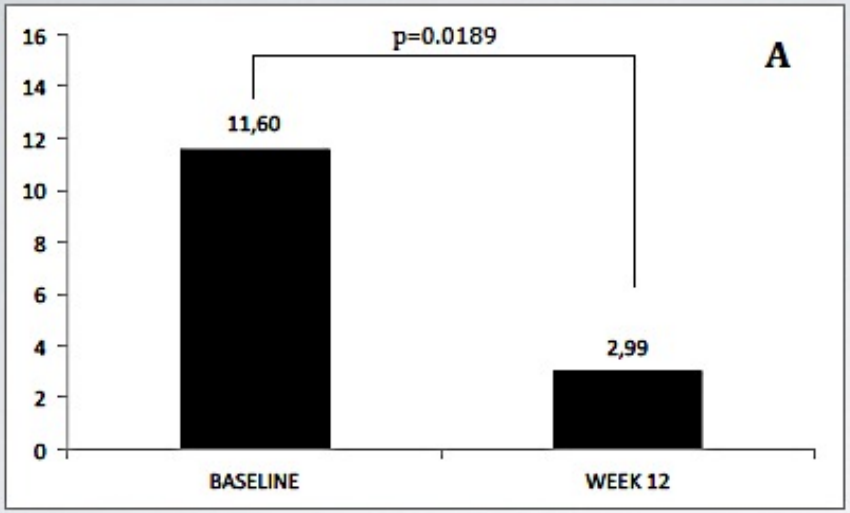
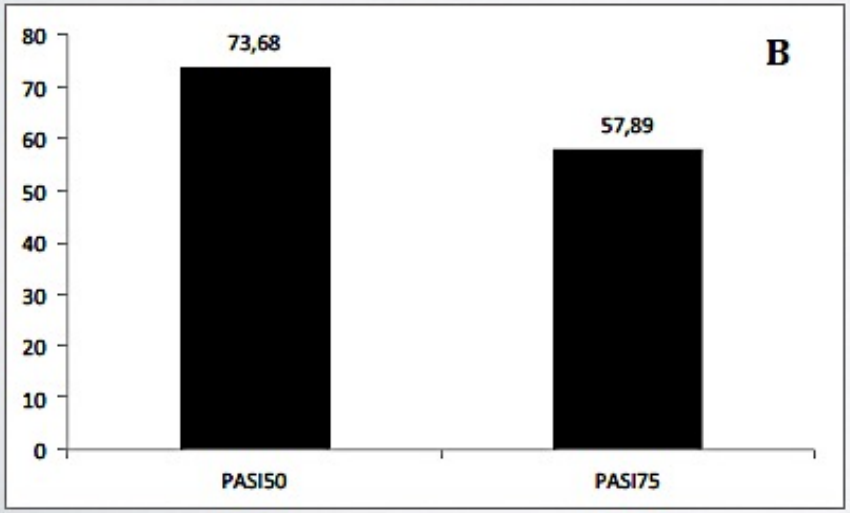


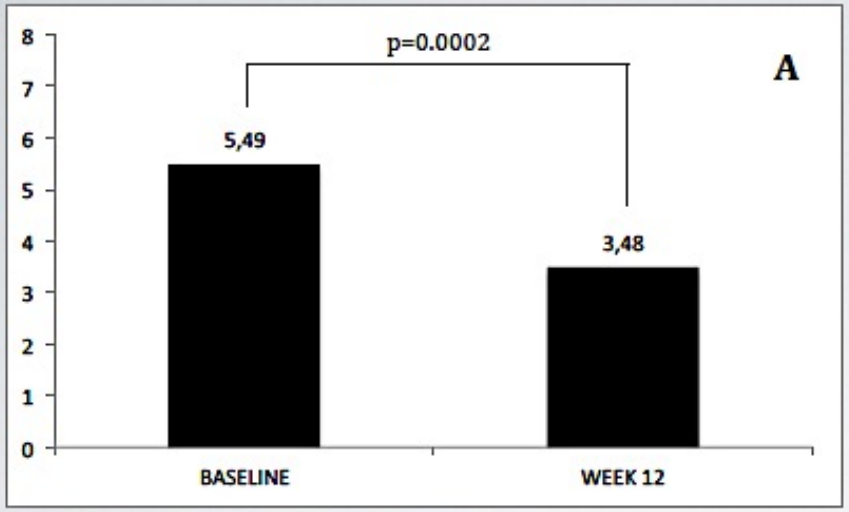
Figure 1. Patients comorbidities and concomitant diseases contraindicating other-than-apremilast biologics

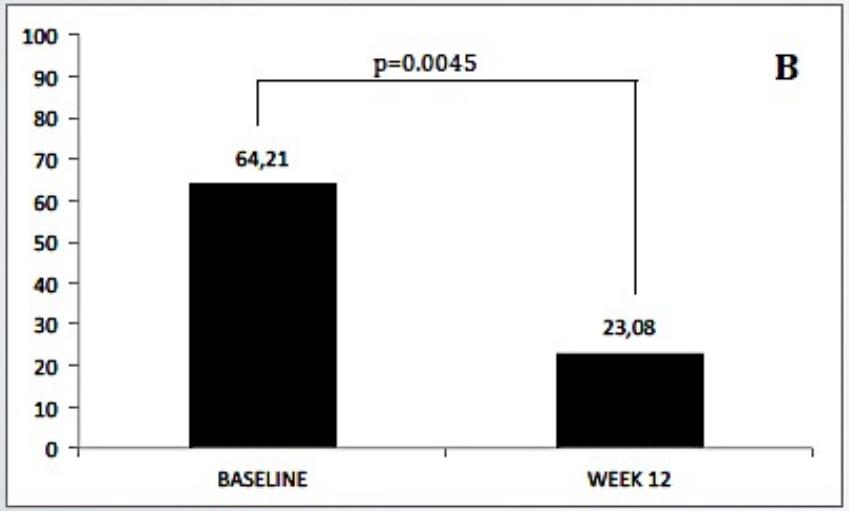
PASI





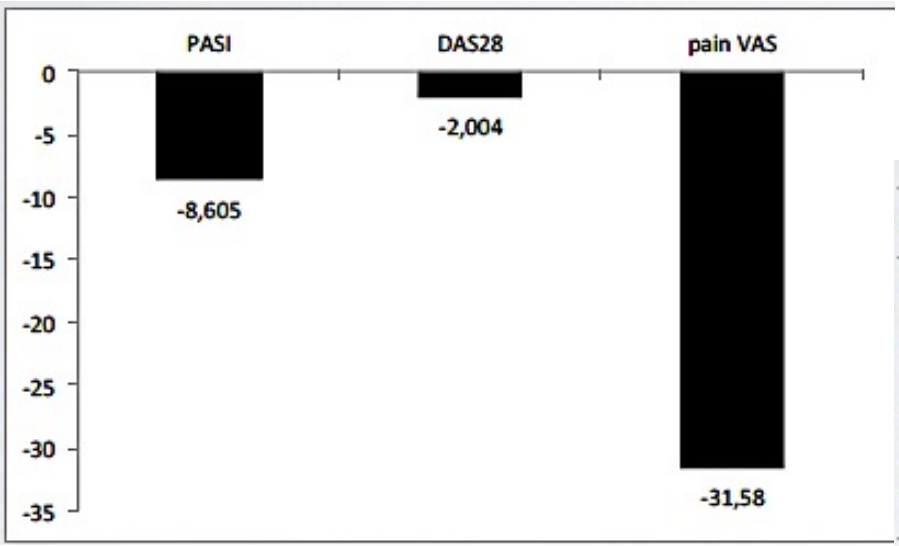
DAS28





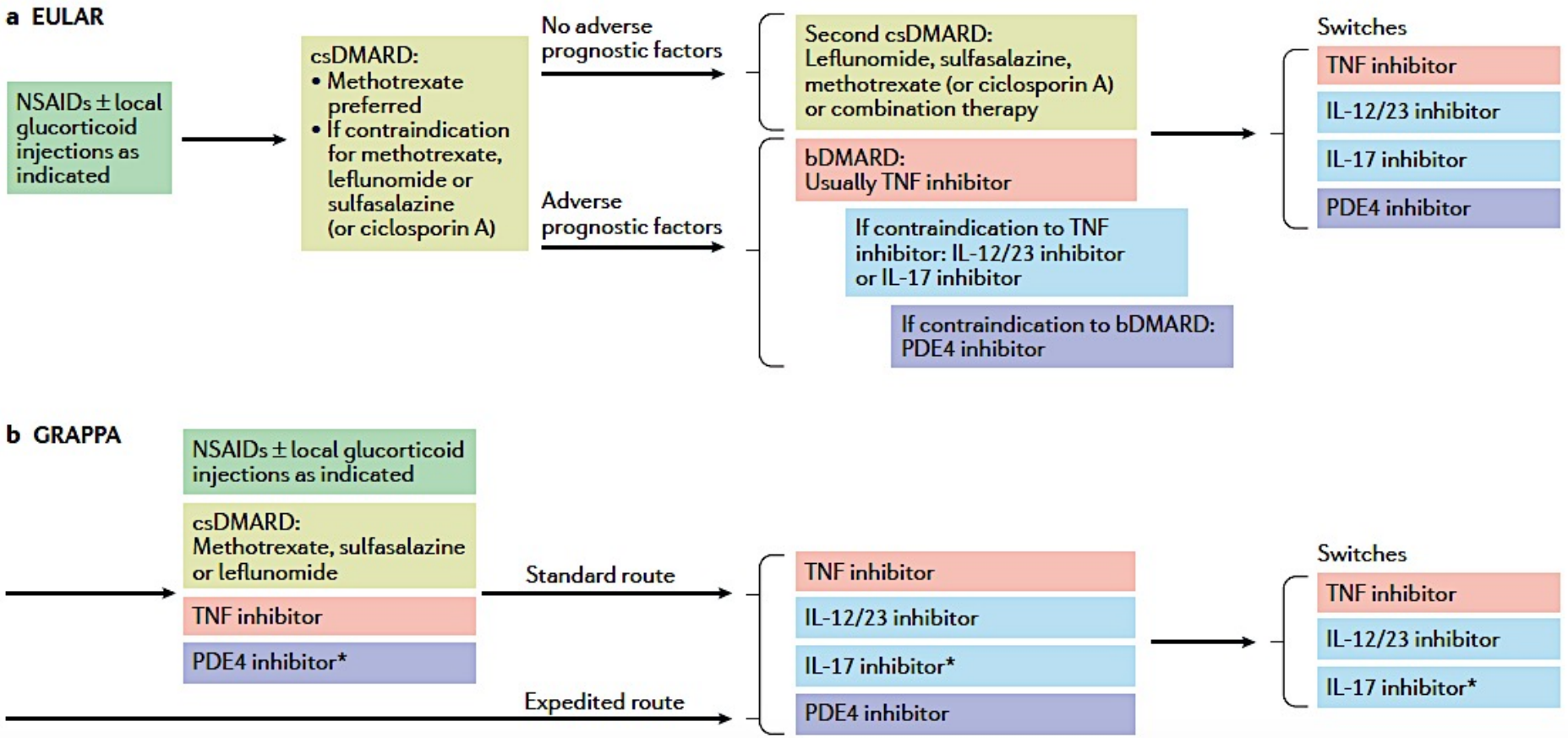
Pain-VAS

Query	2-tailed P value	Delta (means)	95% CI
PASI BL vs W12	0,0189	8,605	from 1,505 to 15,706
pain VAS BL vs W12	0,0045	31,58	from 10,43 to 52,73
DAS28 BL vs W12	0,0002	2,0037	from 1,0123 to 2,9950



Adverse events, n (%)	
Diharrea	2 (10.53)
Nausea	1 (5.26)
Insomnia	1 (5.26)
Gastrointestinal infection	1 (5.26)

2016 EULAR and GRAPPA sets of recommendations



*Conditional recommendation in the GRAPPA guidelines for drugs without current regulatory approval or where recommendations are based on abstract data only.

Gossec L, Nature Reviews Rheumatology 2016

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>80 trials clinici

- PsA
- PsO
- Behçet syndrome
- AR
- Atopic dermatitis
- Allergic contact dermatitis
- Parapsoriasi
- Psoriasi palmp-plantare
- Acne
- Prurito
- Dermatomiosite
- Lichen Planus
- RCU
- SPA

NIH U.S. National Library of Medicine
ClinicalTrials.gov

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- Consistent data confirm that apremilast represents an **effective and safe therapeutic** for PsA treatment.
- Optimal PsA treatment **as first-line therapy** and also in patients who are contraindicated or unresponsive to both other conventional and biological agents.
- Offer a better and **satisfactory management** of this disease that, although it is not a life-threatening disease, profoundly impairs patient quality of life.
- Apremilast should be considered in patients with **comorbidities** due to its favorable safety profile and to the unneeded monitoring of liver and kidney function.
- In the future, apremilast could be used for the treatment of **pediatric patients** instead of prescribing injectable agents

Gli inibitori della PDE4 nelle Spondiloartriti

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