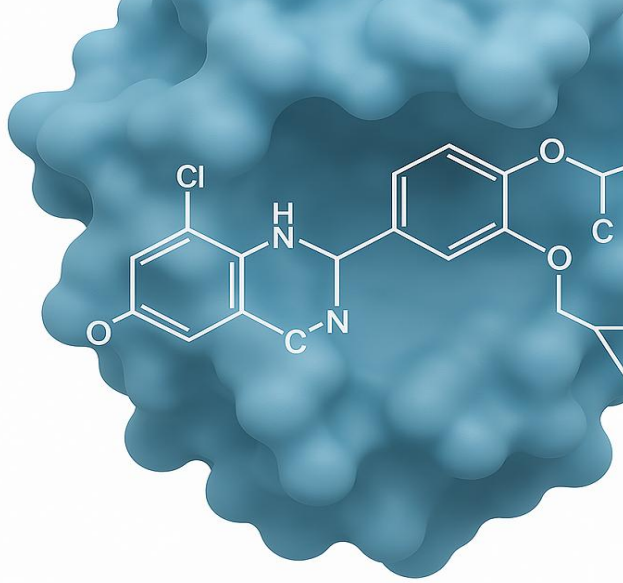
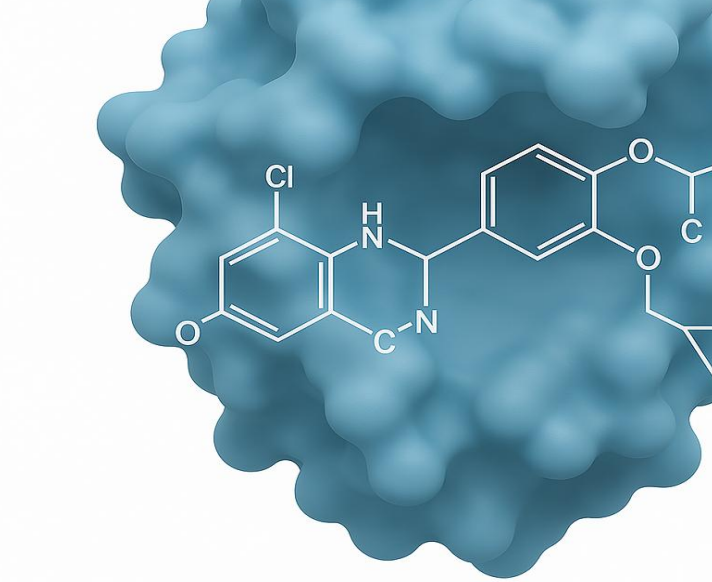


PDE4 inhibitors

Conflicts of interest statement

Conflicts of interest

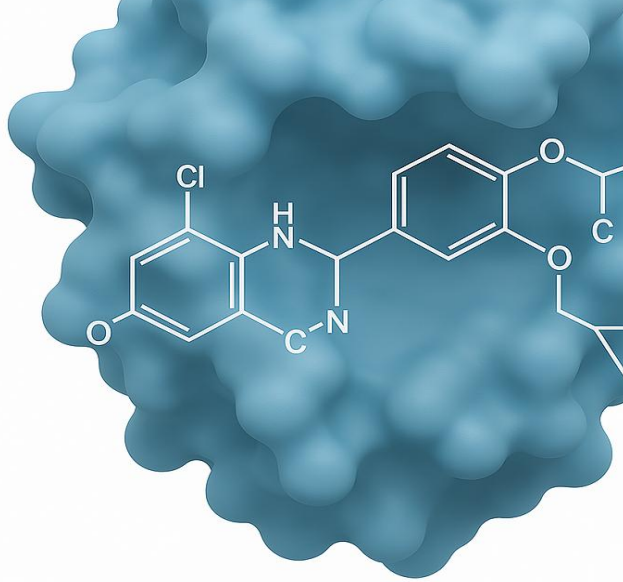


Morten Lind Jensen

- Prior Novo Nordisk employee
- Prior UNION Therapeutics employee
- Prior Cantargia employee
- Current ResoTher Pharma employee
- Current SynAct Pharma employee
- 4 years roflumilast user

Charles Kromann

- No relevant conflicts of interest
- 4 months roflumilast user

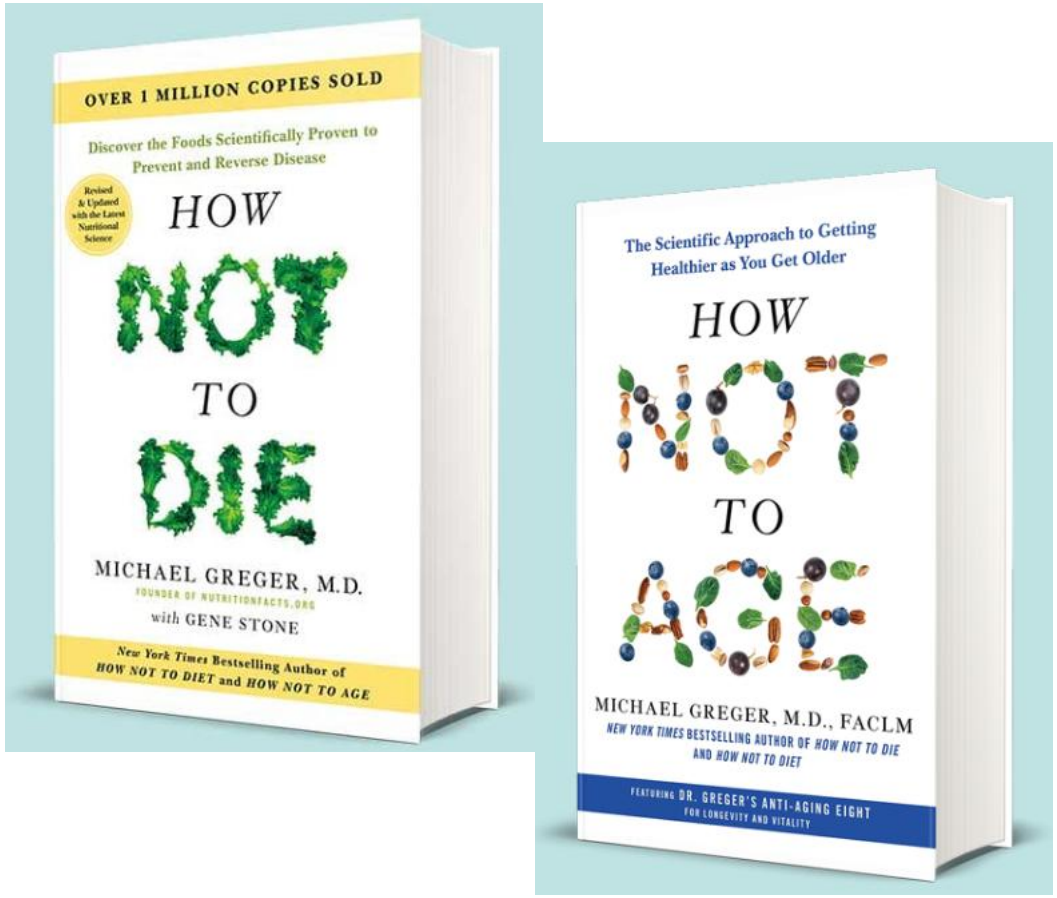


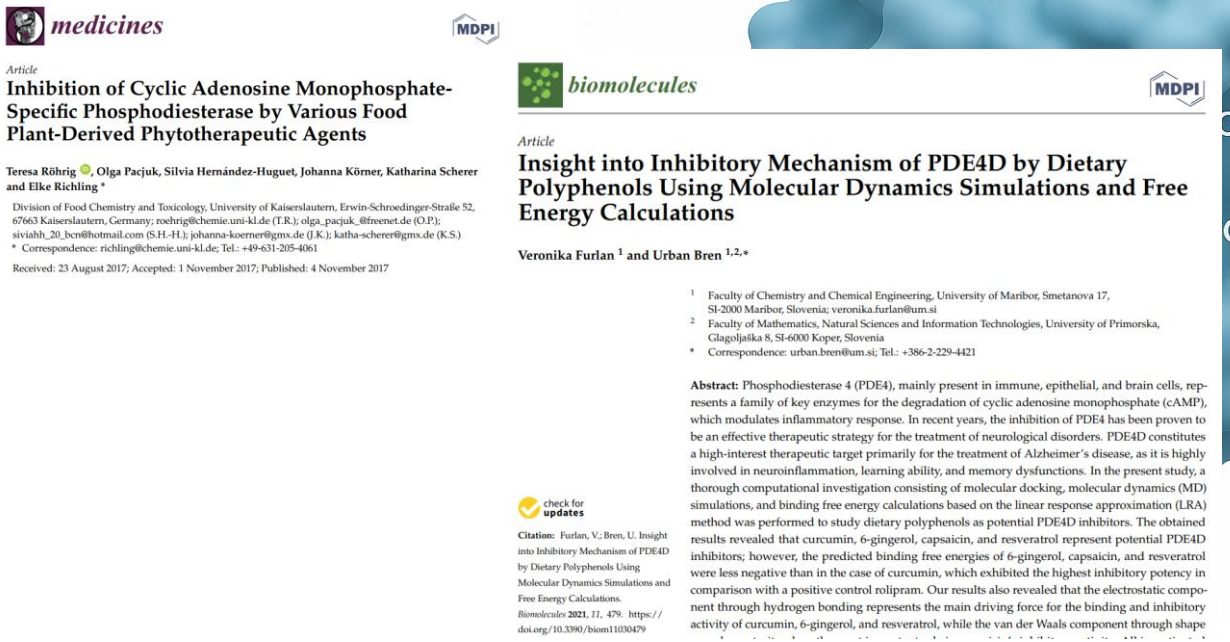
PDE4 inhibitors

Introduction

PDE4-I in food

Where you look for healthy stuff…





medicines — MDPI

Article

Inhibition of Cyclic Adenosine Monophosphate-Specific Phosphodiesterase by Various Food Plant-Derived Phytotherapeutic Agents

Teresa Röhrig, Olga Pacjuk, Silvia Hernández-Huguet, Johanna Körner, Katharina Scherer and Elke Richling *

Division of Food Chemistry and Toxicology, University of Kaiserslautern, Erwin-Schroedinger-Straße 52, 67663 Kaiserslautern, Germany; roehrig@chemie.uni-kl.de (T.R.); olga_pacjuk_@freenet.de (O.P.); siviahh_20_bcn@hotmail.com (S.H.-H.); johanna-koerner@gmx.de (J.K.); katha-scherer@gmx.de (K.S.)
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biomolecules — MDPI

Article

Insight into Inhibitory Mechanism of PDE4D by Dietary Polyphenols Using Molecular Dynamics Simulations and Free Energy Calculations

Veronika Furlan [1] and Urban Bren [1,2,*]

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[2] Faculty of Mathematics, Natural Sciences and Information Technologies, University of Primorska, Glagoljaška 8, SI-6000 Koper, Slovenia
* Correspondence: urban.bren@um.si; Tel.: +386-2-229-4421

Abstract: Phosphodiesterase 4 (PDE4), mainly present in immune, epithelial, and brain cells, represents a family of key enzymes for the degradation of cyclic adenosine monophosphate (cAMP), which modulates inflammatory response. In recent years, the inhibition of PDE4 has been proven to be an effective therapeutic strategy for the treatment of neurological disorders. PDE4D constitutes a high-interest therapeutic target primarily for the treatment of Alzheimer's disease, as it is highly involved in neuroinflammation, learning ability, and memory dysfunctions. In the present study, a thorough computational investigation consisting of molecular docking, molecular dynamics (MD) simulations, and binding free energy calculations based on the linear response approximation (LRA) method was performed to study dietary polyphenols as potential PDE4D inhibitors. The obtained results revealed that curcumin, 6-gingerol, capsaicin, and resveratrol represent potential PDE4D inhibitors; however, the predicted binding free energies of 6-gingerol, capsaicin, and resveratrol were less negative than in the case of curcumin, which exhibited the highest inhibitory potency in comparison with a positive control rolipram. Our results also revealed that the electrostatic component through hydrogen bonding represents the main driving force for the binding and inhibitory activity of curcumin, 6-gingerol, and resveratrol, while the van der Waals component through shape

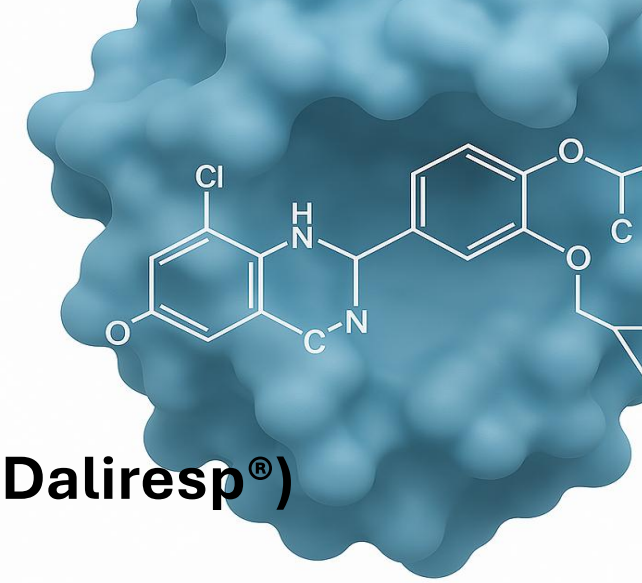
check for updates

Citation: Furlan, V.; Bren, U. Insight into Inhibitory Mechanism of PDE4D by Dietary Polyphenols Using Molecular Dynamics Simulations and Free Energy Calculations. *Biomolecules* **2021**, *11*, 479. https://doi.org/10.3390/biom11030479

…you often find PDE4-inhibition

Dietary element	Content	Inhibition of…
Turmeric	Curcumin	PDE2 & PDE4
Oranges, lemons, grapefruit	Hesperidin	PDE4
Celery, parsley, thyme, peppers	Luteolin	PDE1–5 (incl. PDE4)
Onions, capers, apples, tea	Quercetin	PDE4
Ginger	Gingerol	PDE (cAMP spec)
Coffee	Fraction 8 melanoidins	PDE

Marketed oral PDE4 inhibitors



Apremilast (Otezla®)

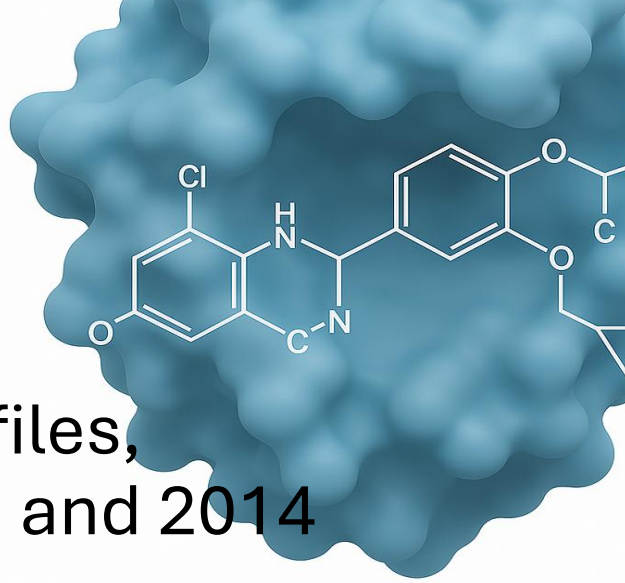
- Psoriasis
- U.S. represents ~42.8 % of the global apremilast market in 2024 (~USD 2.67 billion global
- Prescribed to over one million adults worldwide
- Classic PDE4i side effects
- DK: Specialist (derm/rheum) prescription at around 210 DKKr/day

Roflumilast (Daxas®/Daliresp®)

- COPD
- Generic
- Classic PDE4i side effects
- DK: General prescription at around 15 DKKr/day

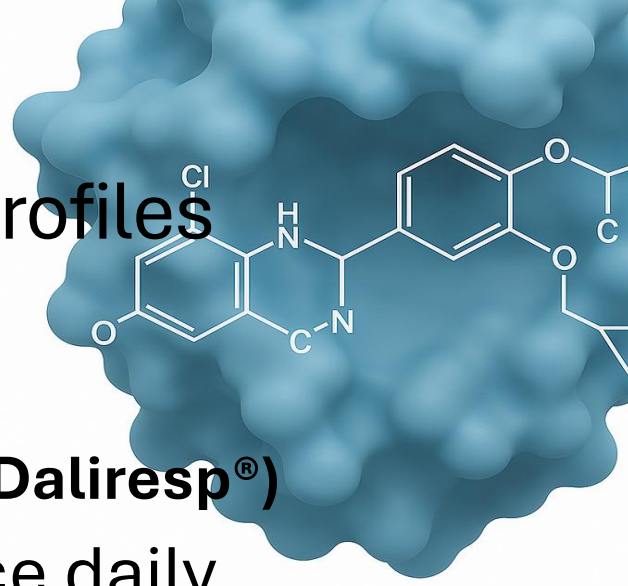
Topical (Zoryve®) available in the US since 2022

PDE4-inhibitors have well established safety



- Roflumilast and apremilast have excellent safety profiles, demonstrated through market experience since 2011 and 2014
- Side effects are
  - gastrointestinal (appetite loss, nausea, loose stools),
  - headache and dizziness (related to excessive water loss),
  - and potentially depression (drug class risk inherited, but CNS side effects look more like temporary sleep disturbance during initiation)

Marketed oral PDE4 inhibitors differ in isoenzyme profiles



Apremilast (Otezla®)

- Dose 30 mg / twice daily

PDE4 isoform	Apr IC50 nM	Rofl IC50 nM
A1	78	0,7
A4	42	0,9
B1	61	0,7
B2	97	0,2
C2	244	4,3
D2	54	0,3
D3	54	0,4
D4	41	0,2
D5	61	0,4

C2 normalised

Roflumilast (Daxas®/Daliresp®)

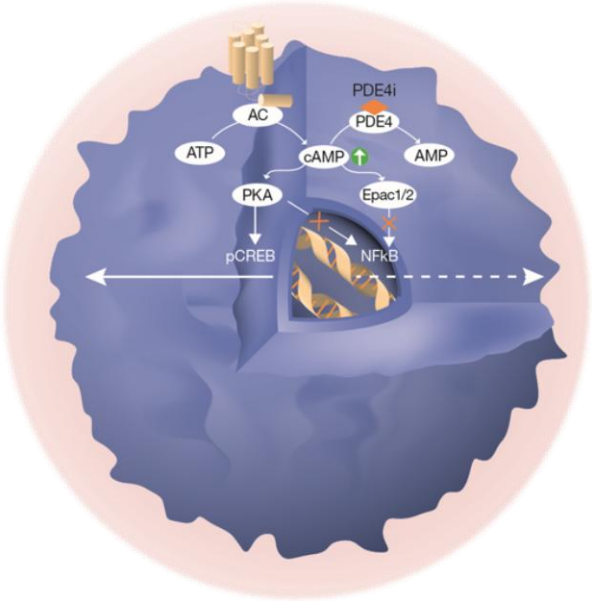
- Dose 0.5 mg / once daily

PDE4 isoform	Apr IC50	Rofl IC50
A1	0,3	0,2
A4	0,2	0,2
B1	0,3	0,2
B2	0,4	0,05
C2	1	1
D2	0,2	0,1
D3	0,2	0,1
D4	0,2	0,1
D5	0,3	0,1

PDE4 B/D subtypes are central mediators of inflammation, constituting a promising target for broad cytokine inhibition and therapeutic application within immunology

PDE4 inhibition increases intracellular cAMP

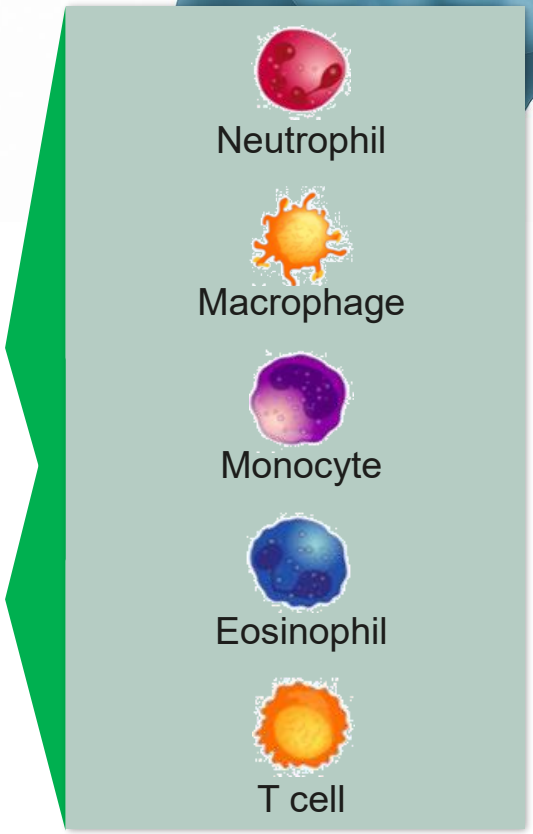
- Increased production of anti-inflammatory mediators by activation of the pCREB pathway
- Reduced production of pro-inflammatory cytokines through inhibition of NFkB pathways



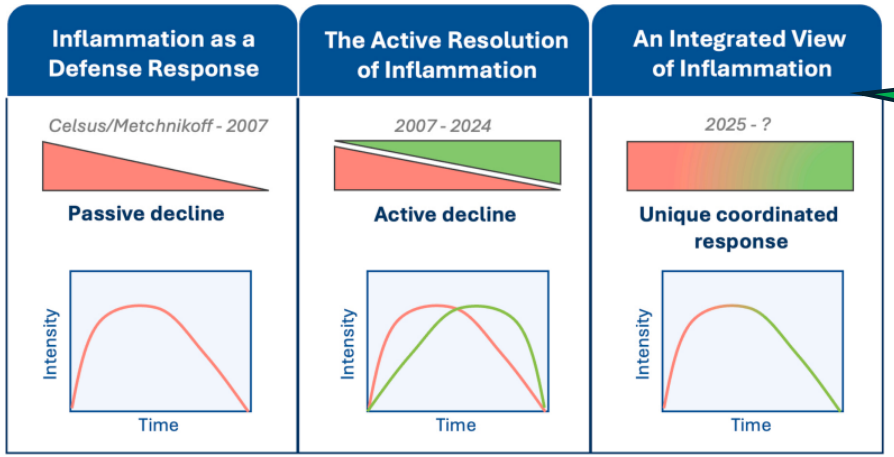
Four PDE4 subtypes are identified

PDE4
- PDE4A
- PDE4B
- PDE4C
- PDE4D

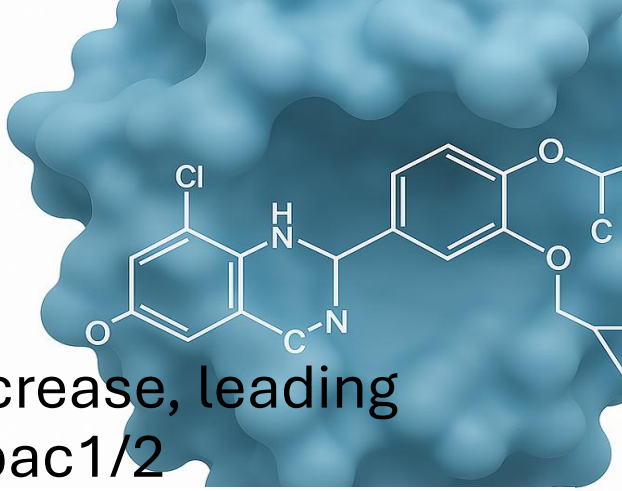
PDE4 B/D subtypes are driving inflammation



Notes: cAMP = Cyclic adenosine monophosphate. pCREB = phosphorylated cAMP response element-binding protein. NFkB = Nuclear factor kappa-light-chain-enhancer of activated B cells.
Sources: Silverberg et al. (2023); Blauvelt et al. (2023)

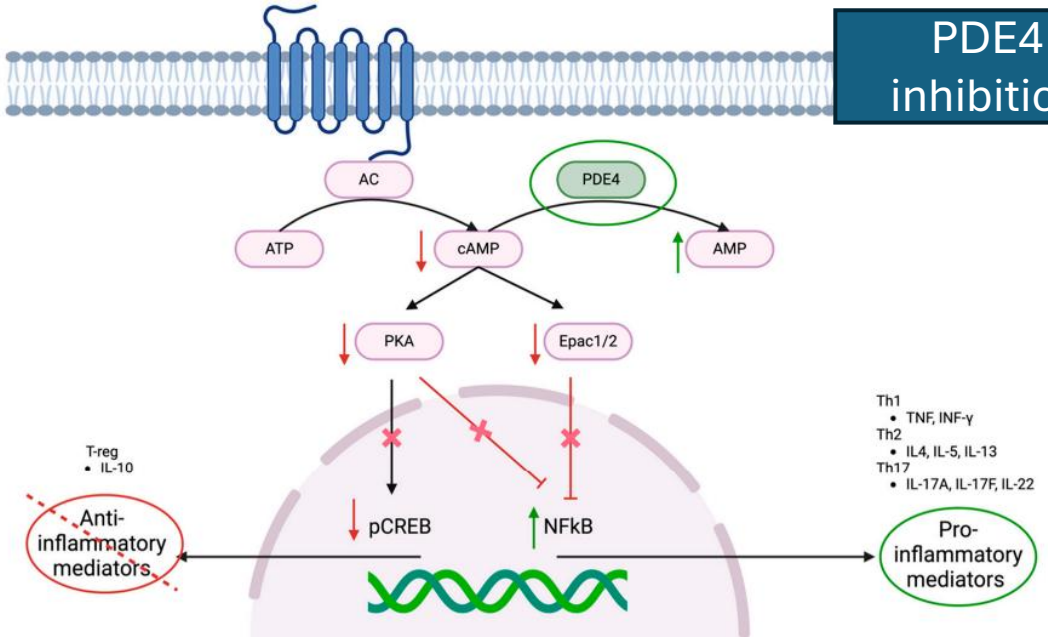


cAMP is thought to be important for active pro-resolution signalling[1]

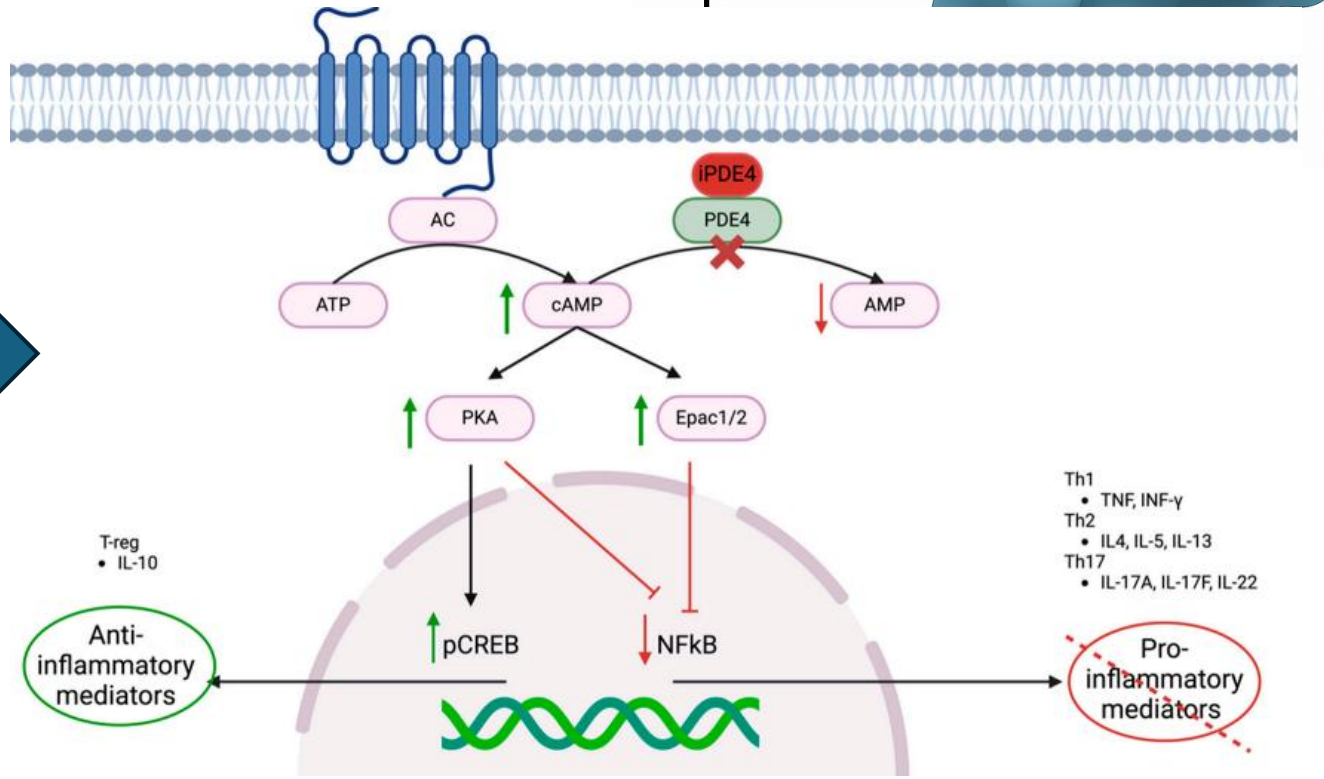


PDE4 inhibition gives cAMP increase, leading to the activation of PKA and Epac1/2

Pro-inflammatory state: Lower levels of cAMP prevent the activation of PKA and Epac1/2



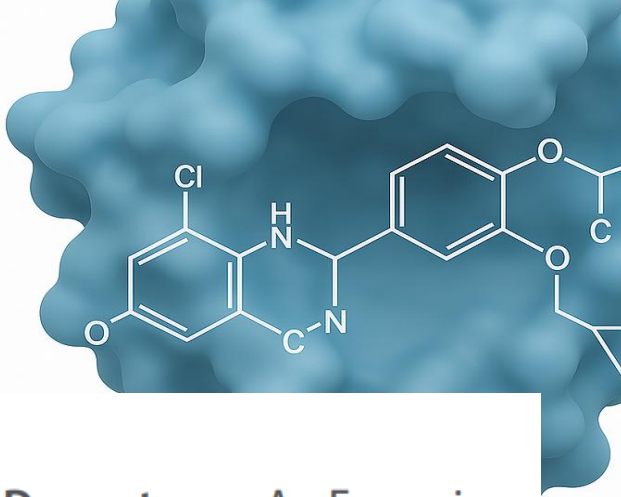
PDE4 inhibition



1 Resolution Pharmacology: State-of-the-art and therapeutic landscape, Peretti et al, 2025

Illustrations from Carmona-Rocha et al 2025

PDE4-inhibitors have broad application



Efficacy and safety of oral roflumilast for moderate-to-severe psoriasis—a randomized controlled trial (PSORRO)

Mette Gyldenløve,[a,g] Howraman Meteran,[b,c] Jennifer A. Sørensen,[d] Simon Fage,[e] Yiqiu Yao,[d] Jesper Lindhardsen,[f] Christoffer V. Nissen,[d] Tanja Todberg,[a] Simon F. Thomsen,[d] Lone Skov,[a,g] Claus Zachariae,[a,g] Lars Iversen,[e] Mia-Louise Nielsen,[d] and Alexander Egeberg[d,g,*]

[a]Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Denmark
[b]Department of Internal Medicine, Respiratory Medicine Section, Herlev and Gentofte Hospital, University of Copenhagen, Denmark
[c]Department of Respiratory Medicine, Amager and Hvidovre Hospital, University of Copenhagen, Denmark
[d]Department of Dermatology, Bispebjerg and Frederiksberg Hospital, University of Copenhagen, Denmark
[e]Department of Dermatology, Aarhus University Hospital, Denmark
[f]Center for Rheumatology and Spine Diseases, Rigshospitalet, University of Copenhagen, Denmark
[g]Department of Clinical Medicine, University of Copenhagen, Denmark

Summary

Background Roflumilast is a targeted inhibitor of phosphodiesterase (PDE)-4 and has been approved for treatment of severe chronic obstructive pulmonary disease for more than a decade. Generic versions are available in the United States. PDE-4 is involved in the psoriasis pathogenesis, but the efficacy and safety of oral roflumilast in patients with psoriasis have not previously been studied.

The Lancet Regional Health - Europe
2023;30: 100639
Published Online 21 April 2023
https://doi.org/10.

Pioneers in the room!

...It seems that PDE4 inhibitors can safely and effectively assume a role analogous to that of TCS in treating a wide variety of inflammatory conditions encountered in dermatology daily."

REVIEW

PDE4 Inhibitor-Responsive Dermatoses: An Emerging Concept in Dermatology

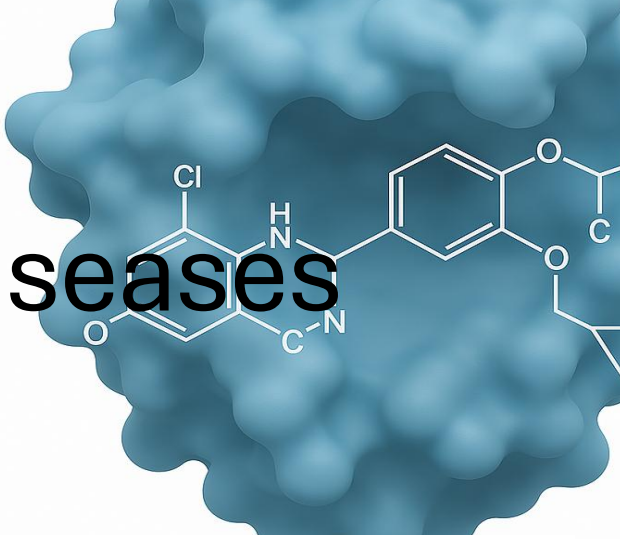
by COURTNEY A. CHAU, BS; HILARY E. BALDWIN, MD; JAMES Q. DEL ROSSO, DO; JULIE C. HARPER, MD; EDWARD LAIN, MD, MBA; TODD SCHLESINGER, MD; ALI SHAHBAZ, MD; HEATHER WOOLERY-LLOYD, MD; JENNIFER C. JAWORSKI, MS; MELISSA S. SEAL, PhD; DIANE HANNA, DNP, DCNP; and PETER LIO, MD

Ms. Chau is with the Icahn School of Medicine at Mount Sinai in New York, New York. Dr. Baldwin is with the Department of Dermatology at Rutgers University Robert Wood Johnson Medical Center in New Brunswick, New Jersey. Dr. Del Rosso is with JDR Dermatology Research Center, LLC in Las Vegas, Nevada and Advanced Dermatology and Cosmetic Surgery in Maitland, Florida. Dr. Harper is with the Dermatology and Skin Care Center of Birmingham in Birmingham, Alabama. Dr. Lain is with Sanova Dermatology in Austin, Texas. Dr. Schlesinger is with Clinical Research Center of the Carolinas in Charleston, South Carolina. Dr. Shahbaz is with Texas A&M School of Medicine in Bryan, Texas and Westlake Dermatology and Cosmetic Surgery in Austin, Texas. Dr. Woolery-Lloyd is with the Dr. Philip Frost Department of Dermatology and Cutaneous Surgery at the University of Miami Miller School of Medicine in Miami, Florida. Ms. Jaworski, Dr. Seal, and Dr. Hanna are with Arcutis Biotherapeutics, Inc. in Westlake Village, California. Dr. Lio is with the Departments of Dermatology & Pediatrics at Northwestern University Feinberg School of Medicine in Chicago, Illinois

J Clin A[illegible]ermatol. 2025;18(12):50–65.

Many inflammatory skin conditions share mechanistic pathways involving multiple receptors and cytokines. Perhaps there is no better endorsement of this idea than the foundational concept of "steroid-responsive dermatoses." Similarly, targeting the phosphodiesterase 4 (PDE4) enzyme, which exists at the crux of several pathways that contribute to inflammatory skin diseases, offers an avenue by which the pathogenesis of multiple conditions may be interrupted. This suggests that PDE4 inhibitors may assume a similar complementary framework for treating "PDE4 inhibitor-responsive dermatoses." Certain formulations of PDE4 inhibitors (including apremilast, crisaborole, and roflumilast) have undergone rigorous investigation in clinical trials and demonstrated robust efficacy and safety in many dermatologic conditions, achieving United States Food and Drug Administration approval for atopic dermatitis, psoriasis, and seborrheic dermatitis. Herein, we summarize the clinical evidence supporting the emerging concept of "PDE4 inhibitor-responsive dermatoses" and propose that PDE4 inhibition offers an additional pathway to achieving desired clinical outcomes. **KEYWORDS:** Steroid-responsive dermatoses, PDE4 inhibitor-responsive dermatoses, crisaborole, apremilast, roflumilast, phosphodiesterase 4 inhibition

Several new PDE4-Inhibitors are in development for inflammatory skin diseases



- Off-label use of apremilast and roflumilast
- New indications
- New molecules - both oral and topical

pharmaceutics

MDPI

Review

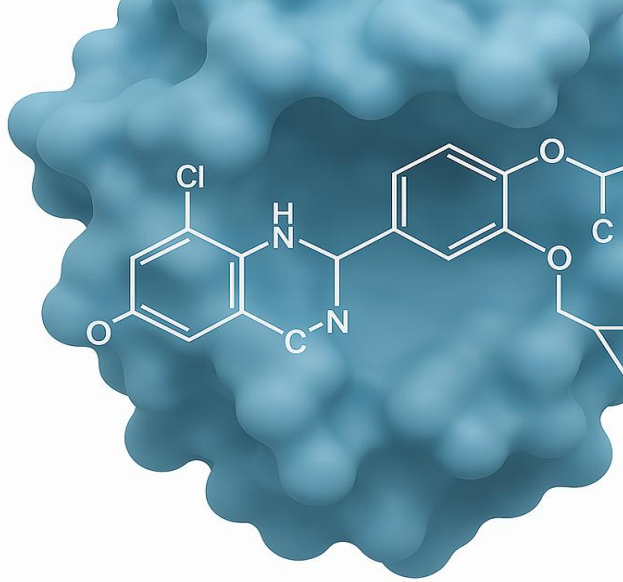
Exploring the Therapeutic Landscape: A Narrative Review on Topical and Oral Phosphodiesterase-4 Inhibitors in Dermatology

Elena Carmona-Rocha [1,2,3], Lluís Rusiñol [1,2,3] and Lluís Puig [1,2,3,*]

1 Department of Dermatology, Hospital de la Santa Creu i Sant Pau, 08041 Barcelona, Spain; ecarmona@santpau.cat (E.C.-R.); lrusinol@santpau.cat (L.R.)
2 Institut de Recerca Sant Pau (IR SANT PAU), 08041 Barcelona, Spain
3 Unitat Docent Hospital Universitari Sant Pau, Facultat de Medicina, Universitat Autònoma de Barcelona, 08041 Barcelona, Spain
* Correspondence: lpuig@santpau.cat; Tel.: +34-935537007; Fax: +34-935537008

Abstract: Phosphodiesterase-4 (PDE4) is involved in the synthesis of inflammatory cytokines that mediate several chronic inflammatory disorders, including psoriasis and atopic dermatitis. In recent years, the therapeutic armamentarium in dermatology has expanded with the introduction of PDE4 inhibitors, both in oral and topical formulations. PDE4 inhibitors have gained increasing interest due to their remarkable safety record and ease of prescription, as evidenced by the recent influx of literature detailing its off-label uses.

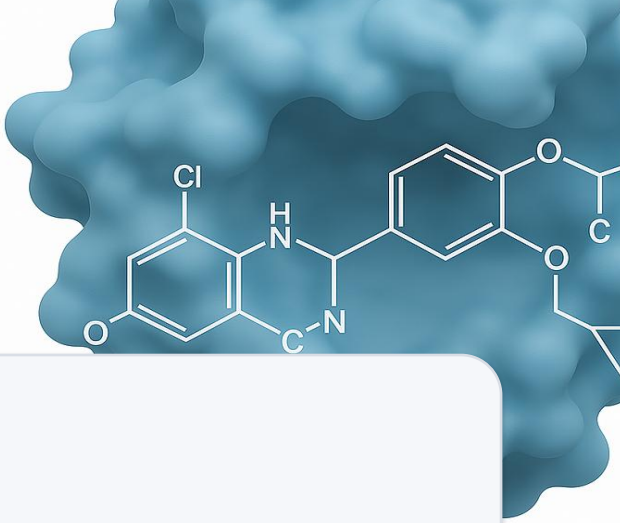
Link to review paper



PDE4 inhibitors

Opgjorte kliniske data fra over et års erfaring med Roflumilast

Daxas i praksis



Introduktion til roflumilast september 2024

Første patient i oktober 2024 (AD i tralokinumab + Xolair): markant effekt på kløe

Herefter forsøgt på: HS, AD, psoriasis/PPP, keratosis pilaris, lichen planus, seboroisk dermatitis, perianal kløe, blefarit, medikamentelt eksantem

Patienter i alt

41

Klinikliste

DAXAS (aktiv/remission)

27

Aktiv: 24 | Remission: 2

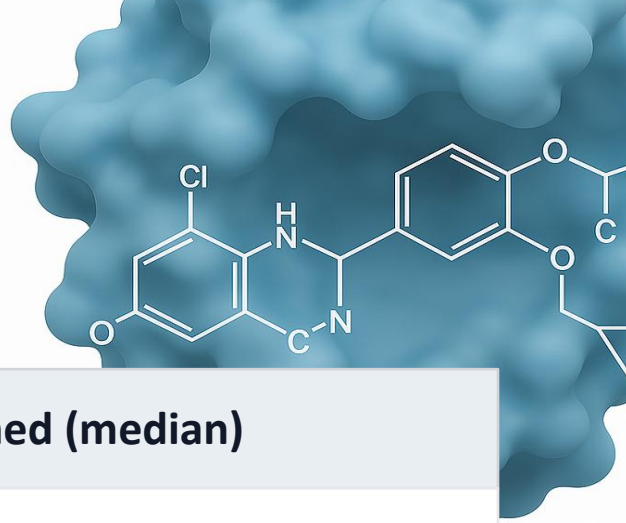
DASTO (stoppet)

14

Mangl. effekt / bivirkninger

Dataindsamling: spørgeskemaer for patienter i fortsat behandling (n=17 analyseret)

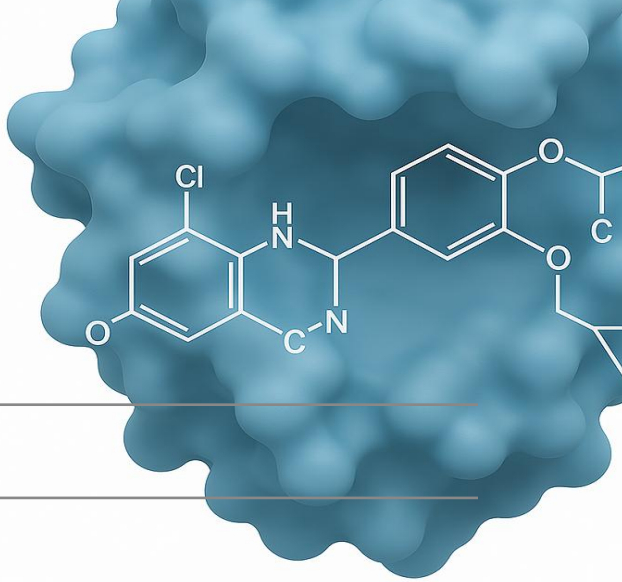
Kohorte

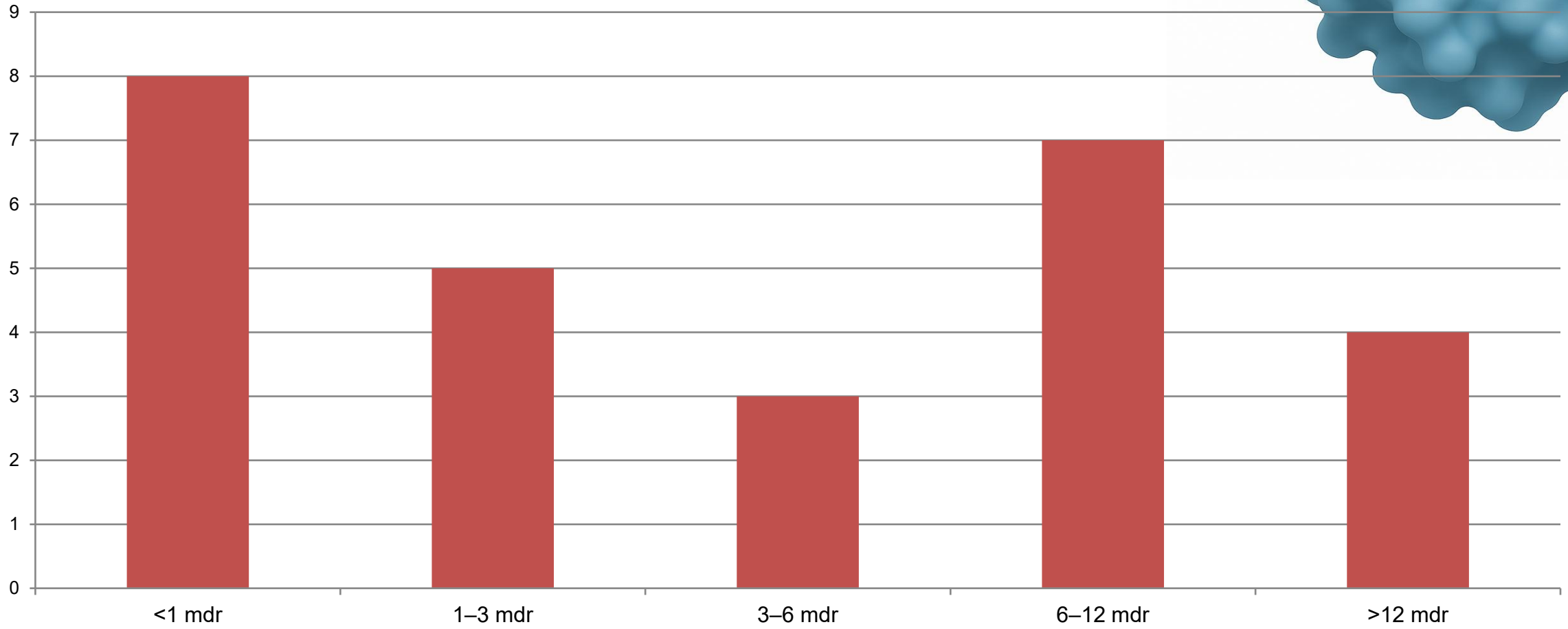


Gruppe	n	Køn (K/M)	Alder / varighed (median)
Aktiv behandling	25	19/6	Alder 38 år | Varighed 5,6 mdr
Stop pga remission/god effekt	2	1/1	Alder 41 år | Varighed 11,3 mdr
Stoppet	14	8/6	Alder 50 år | Varighed 0,5 mdr*

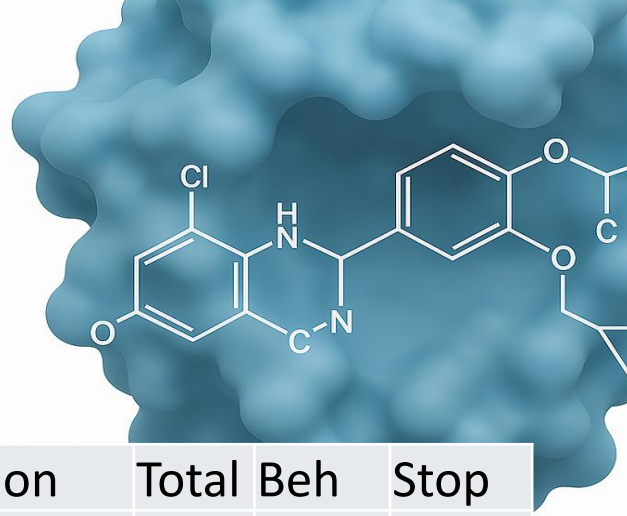
- DAXAS-kohorten er yngre end DASTO-kohorten.
- Ophør i DASTO sker typisk tidligt i forløbet.
- To patienter er stoppet pga remission/god effekt (DAXAS).

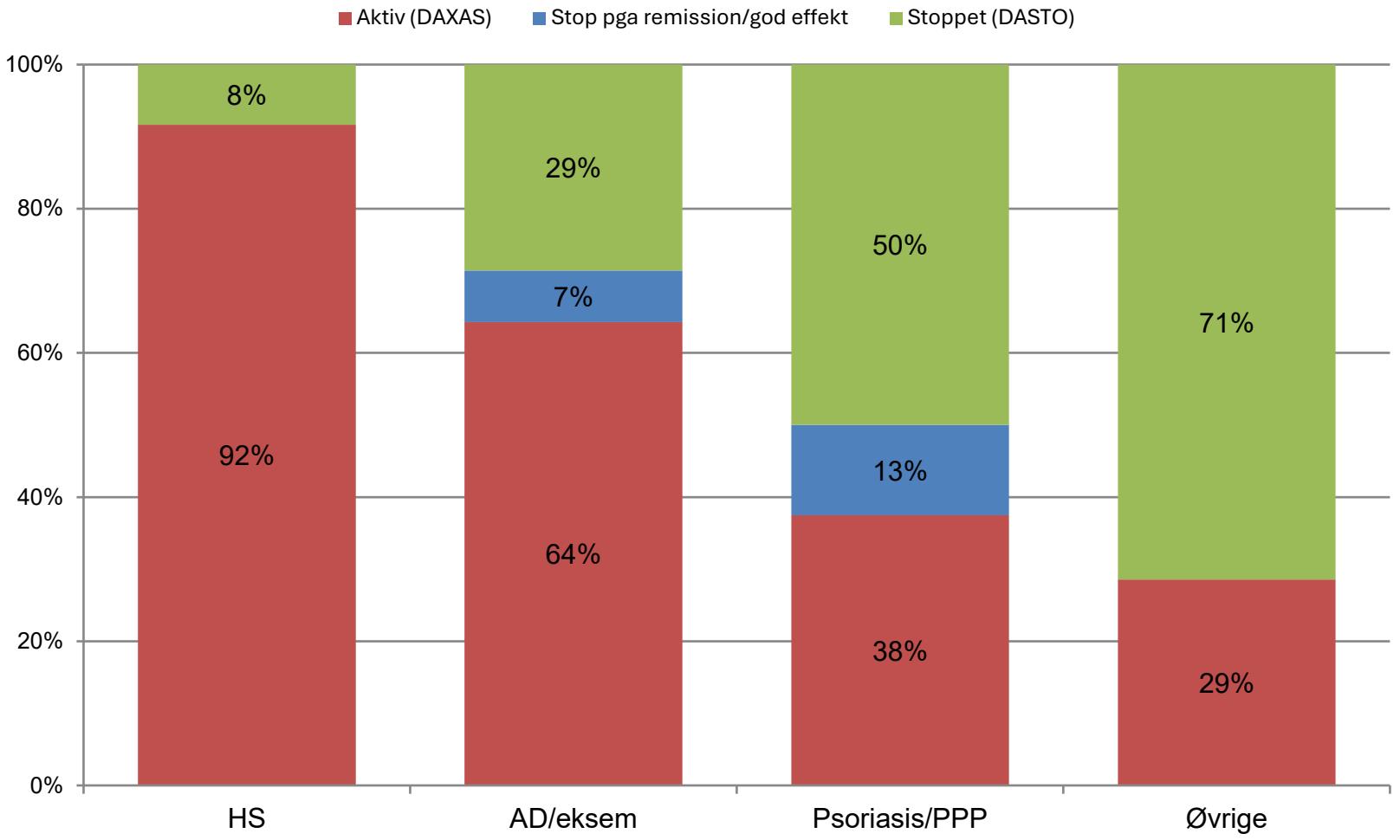
Behandlingsvarighed





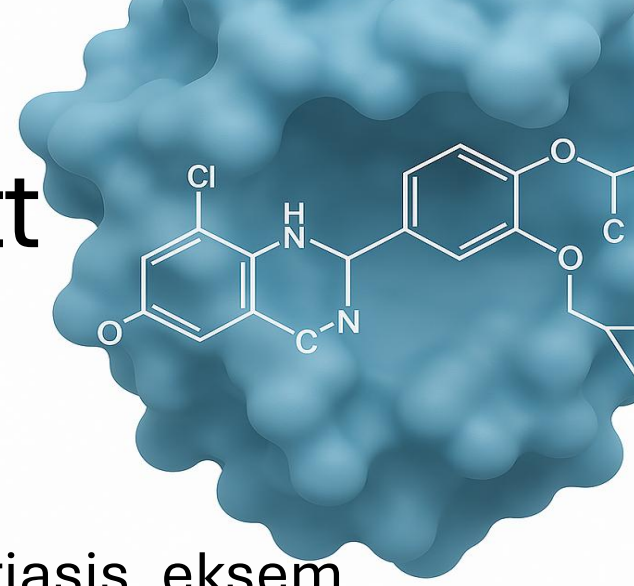
Behandlingsophør vs Indikation





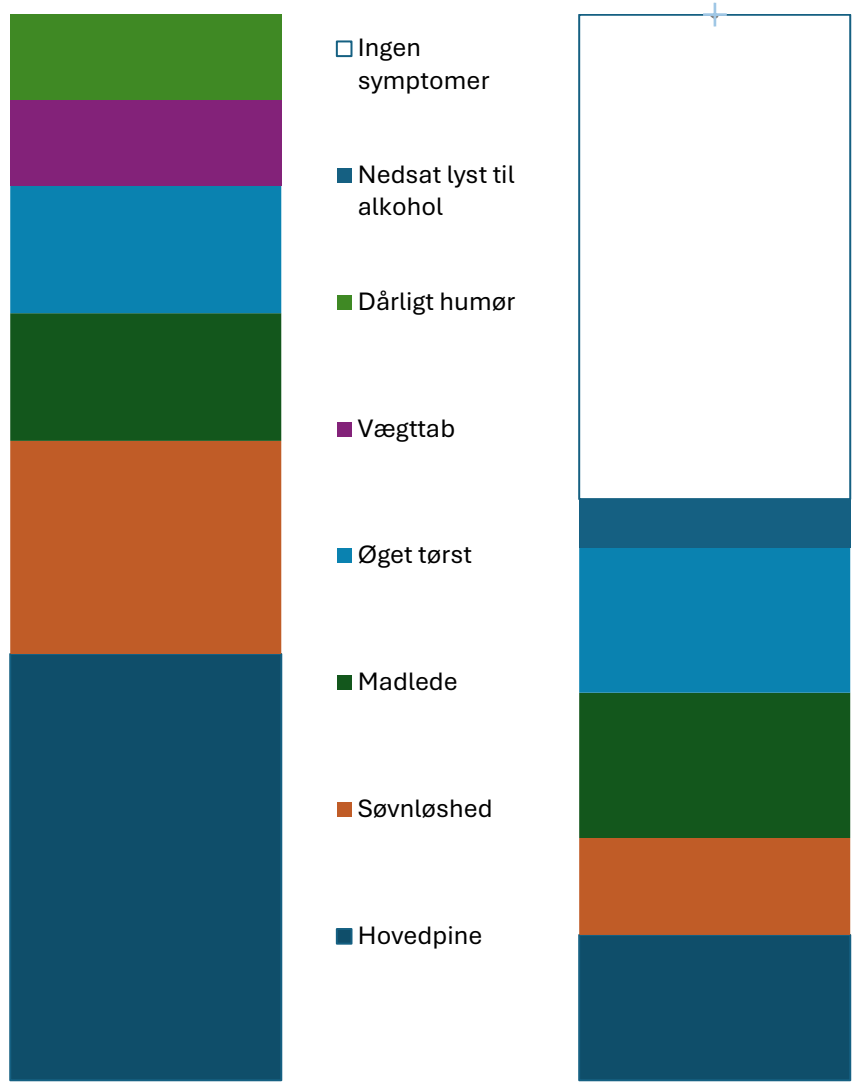
Indikation	Total	Beh	Stop
AD	15	10	5
HS	12	11	1
PSO	7	4	3
Andre	7	2	5
	41	26	14

Spørgeskema til aktivt behandlede ptt



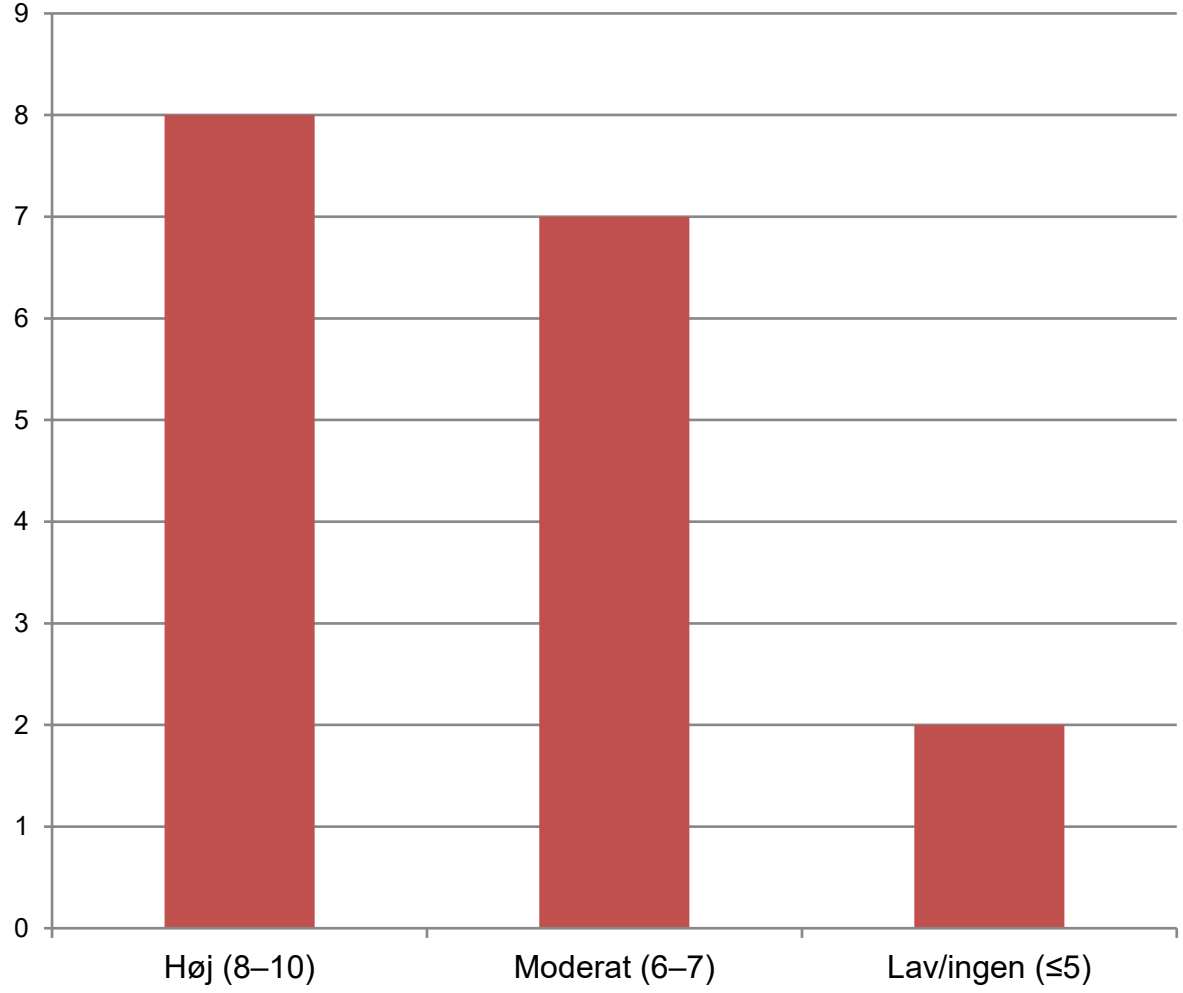
- **Besvaret af 17 ptt behandlet >1mnd**
- **Baggrund:** Alder og køn
- **Indikation:** Hudsygdom behandlet med Roflumilast (HS, psoriasis, eksem, andet)
- **Behandlingsvarighed:** Tidsintervaller fra <1 måned til >12 måneder
- **Bivirkninger:**
  - Symptomer oplevet tidligt i behandlingsforløbet
  - Aktuelle symptomer på besvarelsestidspunktet
- **Behandlingseffekt:**
  - Patientrapporteret effekt på hudsygdom (1–10 skala)
- **Samtykke:** Anvendelse af anonymiserede data til undervisning og evt. forskning

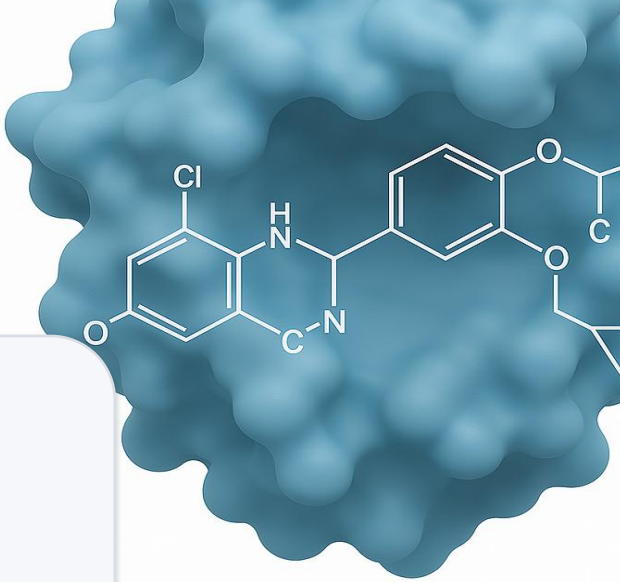
Bivirkninger start vs fortsat behandling



Bivirkning	Tidligt	Aktuelt
Hovedpine	59%	18%
Søvnløshed	29%	12%
Nedsat sult	18%	18%
Øget tørst	18%	18%
Vægttab	12%	0%
Dårligt humør	12%	0%
Nedsat lyst til alkohol	0%	6%
Ingen symptomer	0%	59%

Oplevet effekt på hudsygdom



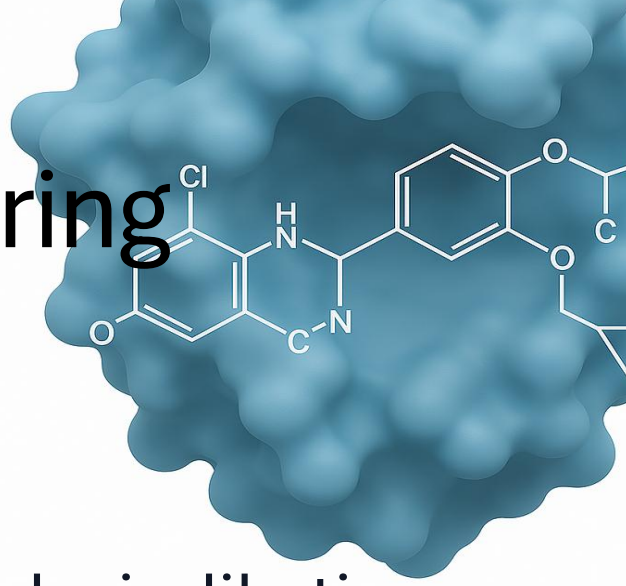


Gns: 7.7
Median: 7

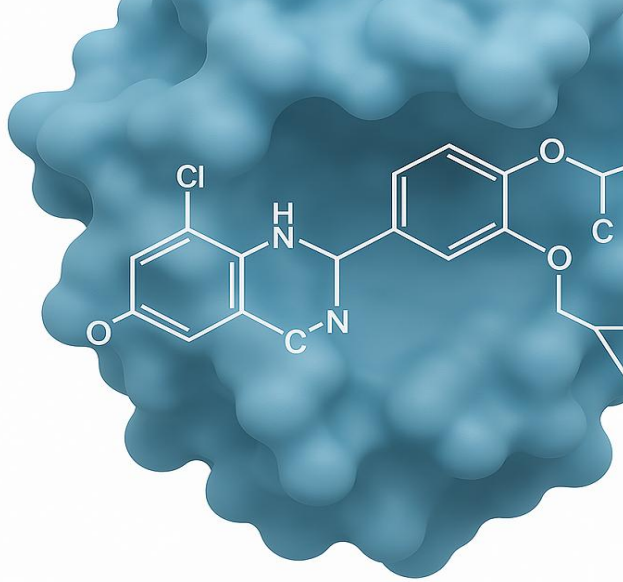
Fortolkning

- 8/17 angiver høj effekt
- 2/17 angiver lav/ingen effekt

Foreløbige take homes fra klinisk erfaring



- Off-label roflumilast anvendes på flere dermatologiske indikationer; størst volume og effekt i HS og AD/eksem.
- Optrappes langsomt for at undgå adverse effects
- Aktiv kohorte er yngre end kohorten, der stopper
- Behandling fortsættes ofte i måneder til >1 år.
- I spørgeskema-subset ses overvejende moderat til høj patientrapporteret effekt og markant færre aktuelle bivirkninger end tidligt i forløbet.



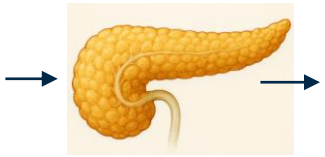
PDE4 inhibitors

Broader perspectives on PDE4 inhibition

PDE4 targeting implies that there is a broader impact than on immune cells only

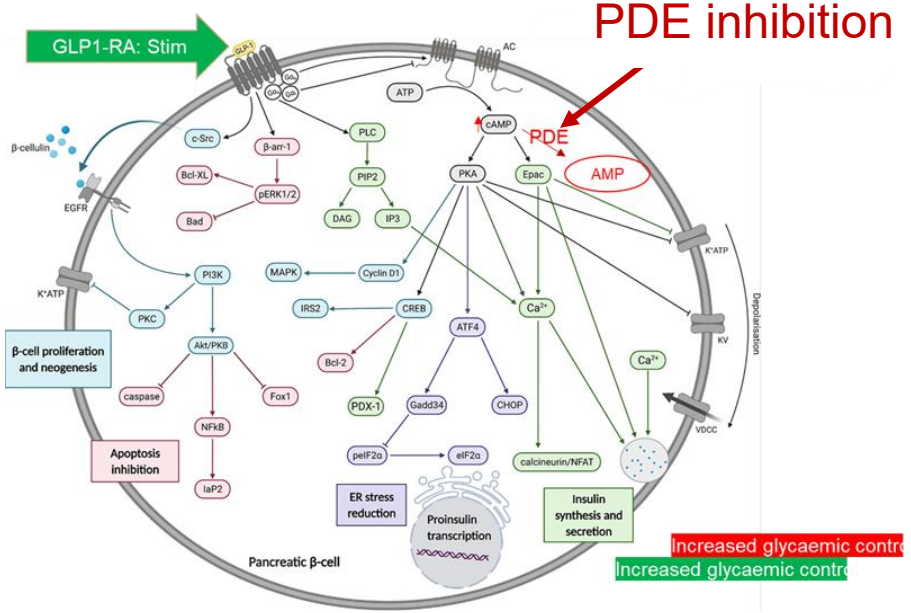
Organism

- Phosphodiesterases (PDE) are enzymes in all cells, which breaks down cAMP and cGMP, ubiquitous second messengers
- PDEs are expressed differently in different organs and cells. **PDE subtypes and isoforms define how and where they work**
- For example, the PDE4 subtype only breaks down cAMP, and thus do not impact cGMP signaling.



Tissue

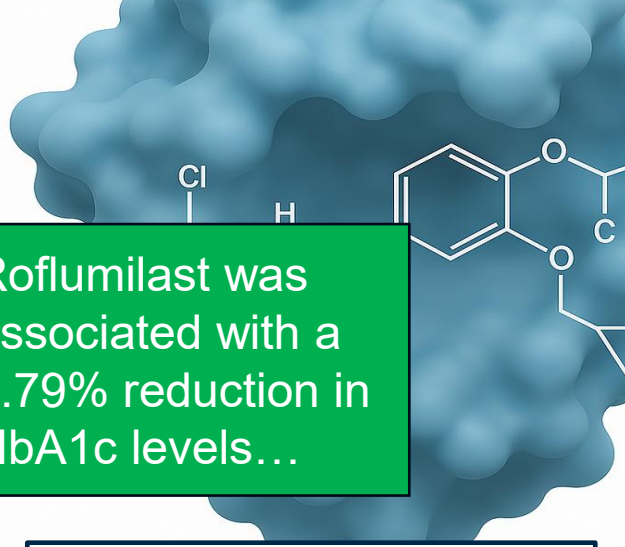
- The specific **PDE4D5 isoform is highly expressed in metabolic cells** such as pancreas and adipocytes
- PDE4-inhibitors are small molecules with intracellular effects, and exert the effects on specific PDE4-isoforms



Cell

- Intracellular signaling by cAMP is controlled by intracellular **distribution of cAMP and adenylyl cyclases (AC)**, compartmentalization, **and rapid breakdown** of cAMP by specific PDE subtypes and isoforms.
- Intracellular signaling by G-protein coupled receptors leading to activation of the membrane bound adenylyl cyclase is **amplified** if the relevant PDE4-isoform is inhibited.
- Metabolic AMPK-mediated intracellular signaling by changes in bicarbonate concentrations activating the cytosolic ACs is **amplified** if the relevant PDE4-isoform is inhibited.
- Thus, **cellular effects are amplification** of GPCR mediated signaling if the relevant PDE4 isoform is inhibited, and **amplification of the effects of physical activity** if the relevant cytosolic PDE4 isoform is inhibited.

Recent broader research findings with marketed PDE4-inhibitors support broader impact than labelled anti-inflammatory effects



Effect of the Phosphodiesterase 4 Inhibitor Roflumilast on Glucose Metabolism in Patients with Treatment-Naive, Newly Diagnosed Type 2 Diabetes Mellitus

E. F. M. Wouters, D. Bredenbröker, P. Teichmann, M. Brose, K. F. Rabe, L. M. Fabbri, and B. Göke

Maastricht University Medical Center (E.F.M.W.), 6229 HX Maastricht, The Netherlands; Nycomed, a Takeda Company (D.B., P.T., M.B.), D-78467 Konstanz, Germany; University Kiel (K.F.R.), D-24118 Kiel, Germany; Krankenhaus Grosshansdorf (K.F.R.), Center for Pulmonology and Thoracic Surgery, D-22927 Grosshansdorf, Germany; Department of Pulmonology (K.F.R.), Leiden University Medical Center, 2333 ZA Leiden, The Netherlands; University of Modena and Reggio Emilia (L.M.F.), I-41121 Modena, Italy; and University of Munich (B.G.), D-80539 Munich, Germany

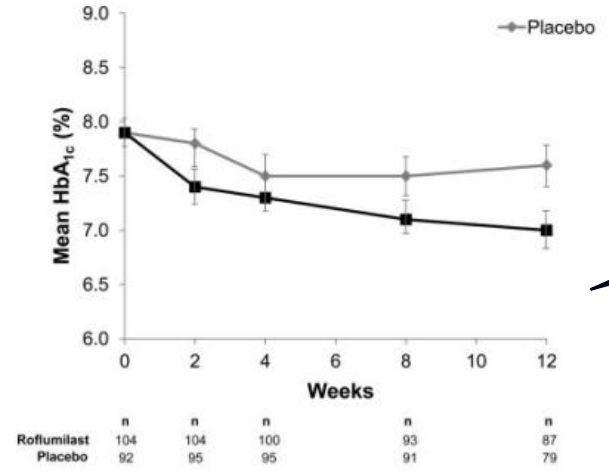
Context: The phosphodiesterase 4 inhibitor roflumilast is a first-in-class antiinflammatory treatment for severe chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis and a history of frequent exacerbations. In previous clinical studies, a transient and reversible weight decrease was reported with roflumilast, suggesting the systemic actions of this drug may impact metabolism.

Objective: Our objective was to investigate the effects of roflumilast on glucose homeostasis and body weight.

Design and Setting: We conducted a 12-wk, randomized, double-blind, placebo-controlled multicenter study with outpatients.

Patients: Patients (n = 205) with newly diagnosed type 2 diabetes mellitus (DM2) but without COPD were included in the study.

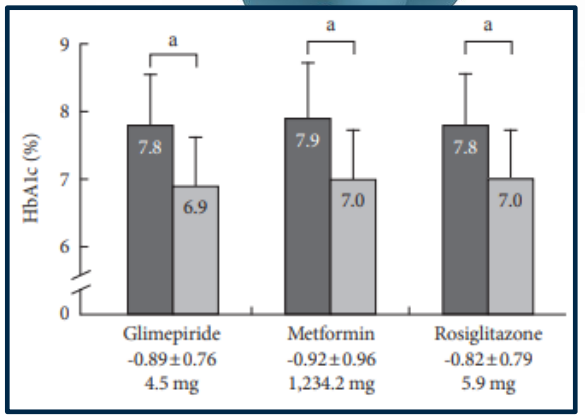
Interventions: Roflumilast 500 μg or placebo was administered once daily.



HbA_{1c} = haemoglobin alpha-1 type c; n = number of patients with data available.

FIG. 1. Changes in mean HbA_{1c} levels over 12 wk in patients with newly diagnosed, treatment-naive DM2 (Study M2-401). Time intervals between visits differed slightly between individual patients. *Bars* represent confidence intervals.

Roflumilast was associated with a 0.79% reduction in HbA1c levels…



… which is similar to classic T2D drugs with same starting HbA1c level

Original Article

Diabetes Metab J 2011;35:26-33
doi: 10.4093/dmj.2011.35.1.26
pISSN 2233-6079 · eISSN 2233-6087

dmj
DIABETES & METABOLISM JOURNAL

Comparison of the Efficacy of Glimepiride, Metformin, and Rosiglitazone Monotherapy in Korean Drug-Naïve Type 2 Diabetic Patients: The Practical Evidence of Antidiabetic Monotherapy Study

Kun Ho Yoon[1], Jeong Ah Shin[1], Hyuk Sang Kwon[1], Seung Hwan Lee[1], Kyung Wan Min[2], Yu Bae Ahn[1], Soon Jib Yoo[1], Kyu Jeung Ahn[3], Sung Woo Park[4], Kwan Woo Lee[5], Yeon Ah Sung[6], Tae Sun Park[7], Min Seon Kim[8], Yong Ki Kim[9], Moon Suk Nam[10], Hye Soon Kim[11], Ie Byung Park[12], Jong Suk Park[13], Jeong Taek Woo[14], Ho Young Son[1]

Recent broader research findings with marketed PDE4-inhibitors support broader impact than labelled anti-inflammatory effects

… which is aligned with non-clinical studies demonstrating weight loss with maintenance of lean body mass, stimulation of muscle and bone cells

Effects of oral roflumilast therapy on body weight and cardiometabolic parameters in patients with psoriasis – results from a randomized controlled trial (PSORRO)

Mette Gyldenløve, MD, PhD,[a,b] Jennifer Astrup Sørensen, MD,[c] Simon Fage, MD,[d] Howraman Meteran, PhD,[e,f] Lone Skov, DMSc,[a,b] Claus Zachariae, DMSc,[a,b] Filip Krag Knop, PhD,[b,g,h] Mia-Louise Nielsen, PhD,[c] and Alexander Egeberg, DMSc[b,c]

Background: Weight loss is reported with oral roflumilast, which is approved for chronic obstructive pulmonary disease (COPD). Recently, the drug has shown efficacy in psoriasis, a disease strongly linked to overweight/obesity.

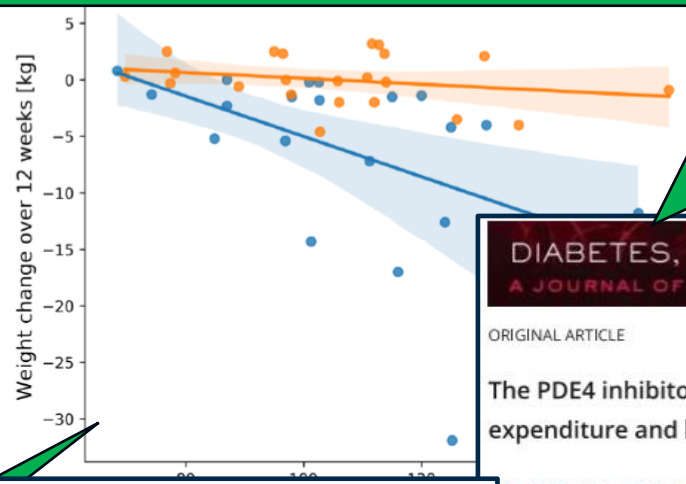
Objective: To describe the effects of oral roflumilast on body weight and cardio-metabolic parameters in patients with psoriasis.

Methods: Posthoc analyses from the PSORRO study, where patients with moderate-to-severe plaque psoriasis were randomized 1:1 to oral roflumilast 500 μg once-daily or placebo for 12 weeks, followed by active, open-label treatment through week 24 in both groups. Changes in body weight, blood pressure, gastrointestinal symptoms, and laboratory tests were registered. No lifestyle or dietary interventions were applied.

Results: Forty-six patients were randomized. Baseline characteristics across groups were comparable mean weight was 103.6 kg. In patients receiving roflumilast, median weight change was −2.6% and −6 week 12 and 24, respectively. Corresponding numbers were 0.0% and 1.3% in patients initially all placebo. Reduced appetite was more frequent with active therapy. No changes in blo laboratory tests were observed.

Limitations: Posthoc analyses and low numbers.

Conclusion: Oral roflumilast induced weight loss and reduc upport the growing evidence of roflumilast as an attractive treatment alter psoriasis. (J Am Ac Dermatol 2024;91:64-71.)



DIABETES, OBESITY AND METABOLISM
A JOURNAL OF PHARMACOLOGY AND THERAPEUTICS

ORIGINAL ARTICLE

The PDE4 inhibitor roflumilast reduces weight gain by increasing energy expenditure and leads to improved glucose metabolism

lia Möllmann, Florian Kahles MD, Corinna Lebherz MD, Ben Kappel MD, Christer Baeck MD, PhD, rank Tacke MD, PhD, Christian Werner MD, Massimo Federici MD … See all authors

ORIGINAL RESEARCH
published: 07 June 2021
doi: 10.3389/fendo.2021.662451

Roflumilast Suppresses Adipogenic Differentiation *via* AMPK Mediated Pathway

www.aging-us.com AGING 2018, Vol. 10, No. 9

Research Paper

Phosphodiesterase 4 inhibitor activates AMPK-SIRT6 pathway to prevent aging-related adipose deposition induced by metabolic

*, Lu Zhang[1], Nannan Zhang[1], Qingfei Liu[1], Zhao Wang[1]

J Appl Physiol 125: 287–303, 2018.
First published April 12, 2018; doi:10.1152/japplphysiol.00798.2017.

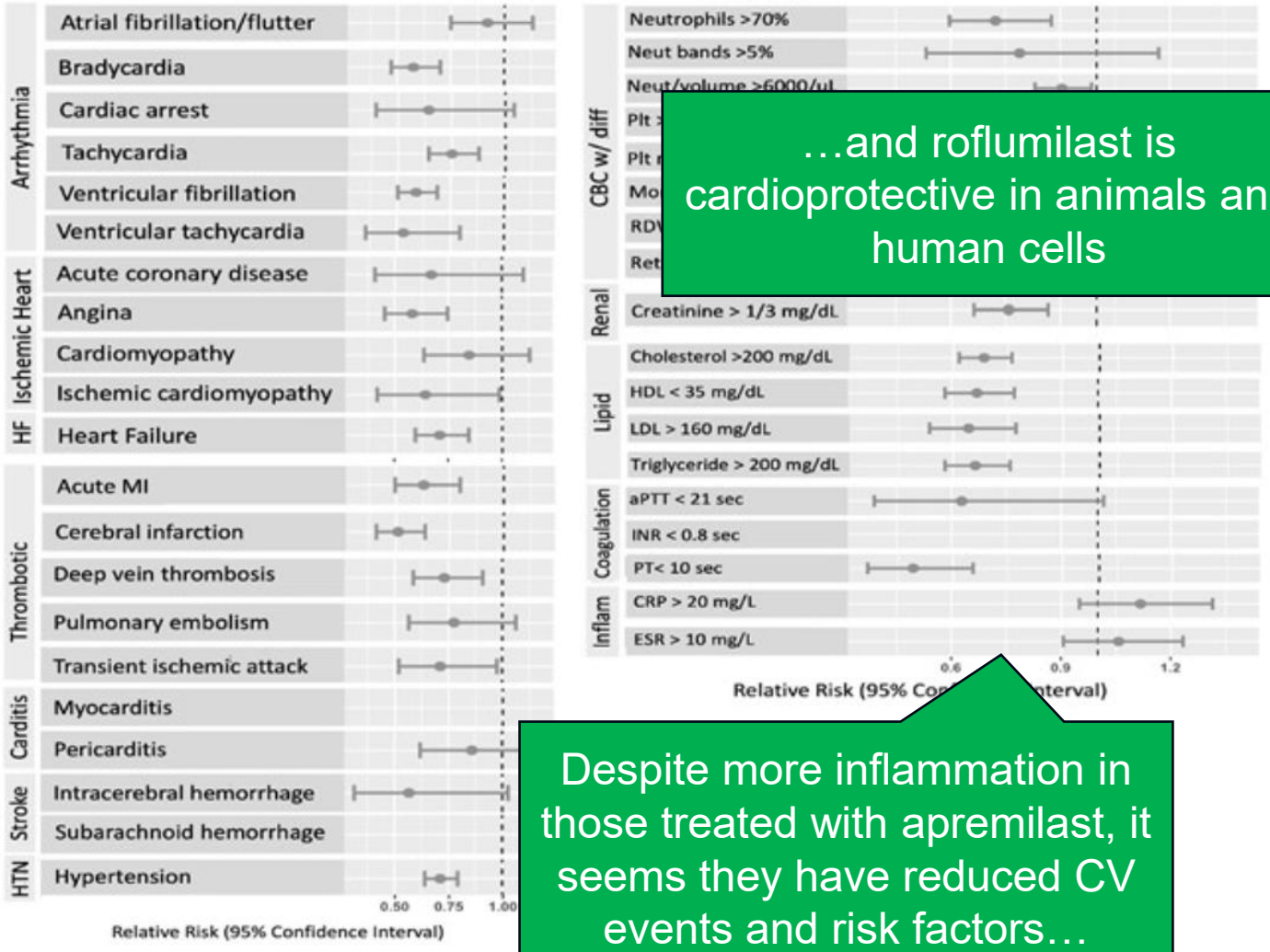
RESEARCH ARTICLE

The phosphodiesterase-4 inhibitor roflumilast reverts proteolysis in skeletal muscle cells of patients with COPD cachexia

Esther Barreiro,[1,2] Ester Puig-Vilanova,[1] Anna Salazar-Degracia,[1] Sergi Pascual-Guardia,[1] Carme Casadevall,[1,2] and Joaquim Gea[1,2]

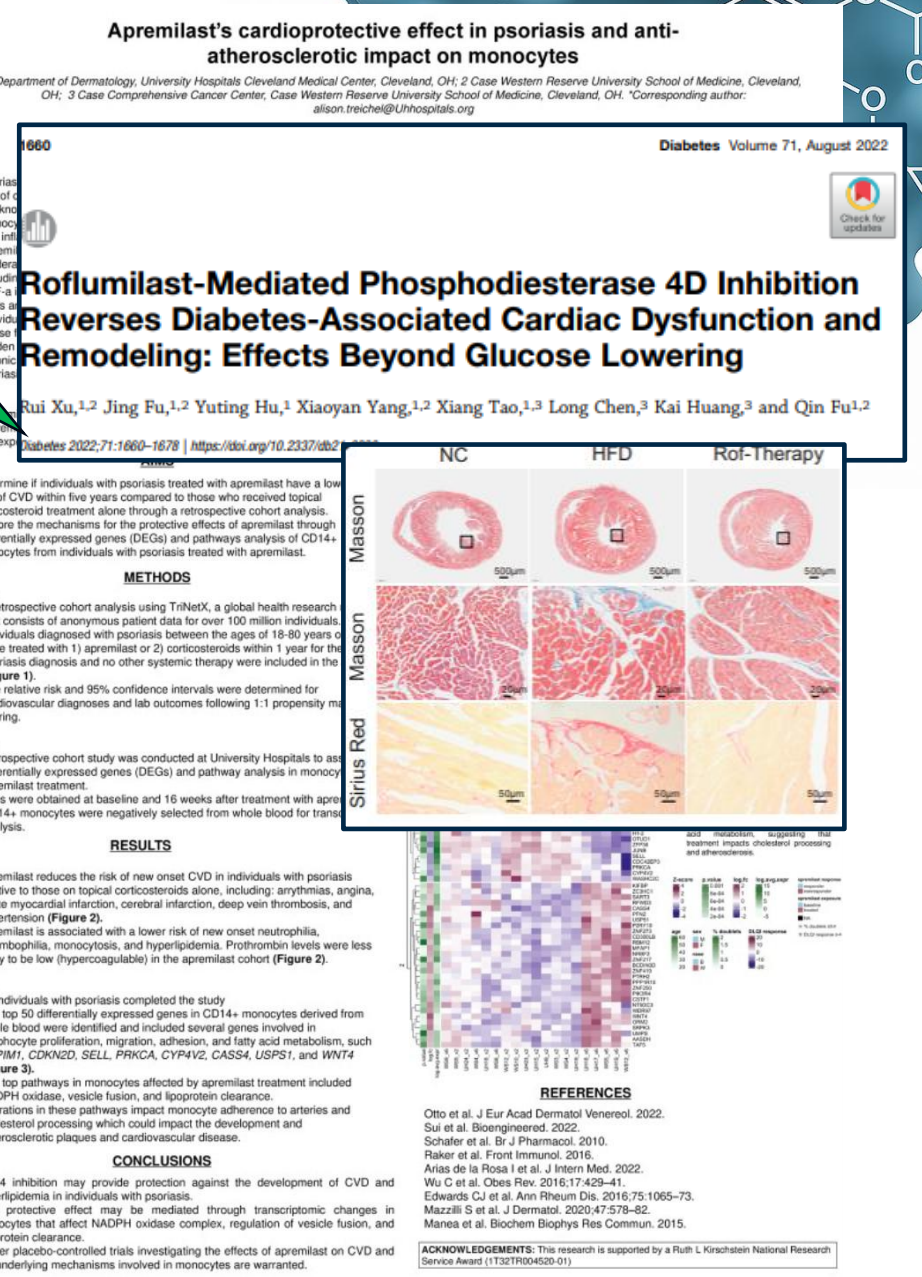
Weight loss related to the degree of over-weight…

Recent broader research findings with marketed PDE4-inhibitors support broader impact than labelled anti-inflammatory effects



…and roflumilast is cardioprotective in animals and human cells

Despite more inflammation in those treated with apremilast, it seems they have reduced CV events and risk factors…



Apremilast's cardioprotective effect in psoriasis and anti-atherosclerotic impact on monocytes

1 Department of Dermatology, University Hospitals Cleveland Medical Center, Cleveland, OH; 2 Case Western Reserve University School of Medicine, Cleveland, OH; 3 Case Comprehensive Cancer Center, Case Western Reserve University School of Medicine, Cleveland, OH. *Corresponding author: alison.treichel@Uhhospitals.org

1660 Diabetes Volume 71, August 2022

Roflumilast-Mediated Phosphodiesterase 4D Inhibition Reverses Diabetes-Associated Cardiac Dysfunction and Remodeling: Effects Beyond Glucose Lowering

Rui Xu,[1,2] Jing Fu,[1,2] Yuting Hu,[1] Xiaoyan Yang,[1,2] Xiang Tao,[1,3] Long Chen,[3] Kai Huang,[3] and Qin Fu[1,2]

Diabetes 2022;71:1660–1678 | https://doi.org/10.2337/db2

NC HFD Rof-Therapy
Masson
Masson
Sirius Red

1. Determine if individuals with psoriasis treated with apremilast have a low risk of CVD within five years compared to those who received topical corticosteroid treatment alone through a retrospective cohort analysis.
2. Explore the mechanisms for the protective effects of apremilast through differentially expressed genes (DEGs) and pathways analysis of CD14+ monocytes from individuals with psoriasis treated with apremilast.

METHODS

AIM 1:
- A retrospective cohort analysis using TriNetX, a global health research that consists of anonymous patient data for over 100 million individuals.
- Individuals diagnosed with psoriasis between the ages of 18-80 years were treated with 1) apremilast or 2) corticosteroids within 1 year for the psoriasis diagnosis and no other systemic therapy were included in the **(Figure 1)**.
- The relative risk and 95% confidence intervals were determined for cardiovascular diagnoses and lab outcomes following 1:1 propensity scoring.

AIM 2:
- A prospective cohort study was conducted at University Hospitals to differentially expressed genes (DEGs) and pathway analysis in monocy apremilast treatment.
- Labs were obtained at baseline and 16 weeks after treatment with apre
- CD14+ monocytes were negatively selected from whole blood for trans analysis.

RESULTS

Aim1:
- Apremilast reduces the risk of new onset CVD in individuals with psoriasis relative to those on topical corticosteroids alone, including: arrythmias, angina, acute myocardial infarction, cerebral infarction, deep vein thrombosis, and hypertension **(Figure 2)**.
- Apremilast is associated with a lower risk of new onset neutrophilia, thrombophilia, monocytosis, and hyperlipidemia. Prothrombin levels were less likely to be low (hypercoagulable) in the apremilast cohort **(Figure 2)**.

Aim 2:
- 14 individuals with psoriasis completed the study
- The top 50 differentially expressed genes in CD14+ monocytes derived from whole blood were identified and included several genes involved in lymphocyte proliferation, migration, adhesion, and fatty acid metabolism, such as *PIM1, CDKN2D, SELL, PRKCA, CYP4V2, CASS4, USPS1,* and *WNT4* **(Figure 3)**.
- The top pathways in monocytes affected by apremilast treatment included NADPH oxidase, vesicle fusion, and lipoprotein clearance.
- Alterations in these pathways impact monocyte adherence to arteries and cholesterol processing which could impact the development and atherosclerotic plaques and cardiovascular disease.

CONCLUSIONS
- PDE4 inhibition may provide protection against the development of CVD and hyperlipidemia in individuals with psoriasis.
- This protective effect may be mediated through transcriptomic changes in monocytes that affect NADPH oxidase complex, regulation of vesicle fusion, and lipoprotein clearance.
- Larger placebo-controlled trials investigating the effects of apremilast on CVD and the underlying mechanisms involved in monocytes are warranted.

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ACKNOWLEDGEMENTS: This research is supported by a Ruth L Kirschstein National Research Service Award (1T32TR004520-01)

Apremilast's cardioprotective effect in psoriasis and anti-atherosclerotic impact on monocytes, Treichel A et al., EADV Amsterdam 2024, P3195

Recent broader research findings with marketed PDE4-inhibit
broader impact than labelled anti-inflammatory effects

Academic effort to generate clinical evidence for cognitive improvement in neurodegenerative diseases, but no large RCT to document efficacy…

…but a vast amount of non-clinical and academic evidence support the potential

molecules

Review

An Overview of PDE4 Inhibitors in Clinic
Early 2022

Letizia Crocetti [1], Giuseppe Floresta [2], Agostino Cilibrizzi [3] and Maria

Compound

Ibudilast (MN-166)

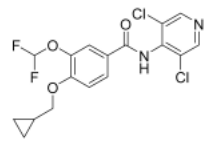
Phase I (Migraine Headache) NCT01389193 (20

Phase III (Fragile X Syndrome) NCT05367960 (20 NCT05358886 (20 NCT05163808 (20

Dohme LLC disease) NCT00362024 (2016)

Molecules 2022, 27, 4964 17 of 25

Table 4. Cont.

Compound	Chemical Structure	Company	Phase	NCT Number [a]
Roflumilast			Phase II	NCT04658654 (2022)

Biochemical Society Transactions (2019) 47 1557–1565
https://doi.org/10.1042/BST20190763

PORTLAND PRESS

Review Article

Understanding PDE4's function in Alzheimer's
disease; a target for novel therapeutic approa

Amy J. Tibbo, Gonzalo S. Tejeda and George S. Baillie

Institute of Cardiovascular and Medical Science, College of Veterinary, Medical and Life Science, University of Glasgow, Glasgow, U.K.

Correspondence: George S. Baillie (George.Baillie@glasgow.ac.uk)

Inflammopharmacology
https://doi.org/10.1007/s10787-023-01305-x

ORIGINAL ARTICLE

PI3K/AKT signaling activation by roflumilast ameliorates
rotenone-induced Parkinson disease in rats

Heba A. Farid[1] · Rabab H. Sayed[2]

Received: 28 May 2023 / Acce
© The Author(s) 2023

Alzheimer's Drug Discovery Foundation

Cognitive Vitality.org

Last updated on January 31, 201

…ientists at the Alzheimer's Drug
…ude analysis of drugs, drugs-in-
…food/drink, non-pharmacologic
…he potential benefit (or harm) for brain
…n affect brain health (e.g.,
…drome). In addition, these reports
…ilable, and from preclinical models.

OXFORD

International Journal of Neuropsychopharmacology (2020) 23(10): 700–711

doi:10.1093/ijnp/pyaa048
Advance Access Publication: July 9, 2020
Regular Research Article

REGULAR RESEARCH ARTICLE

The Phosphodiesterase-4 Inhibitor Roflumilast, a Potential Treatment for the Comorbidity of Memory Loss and Depression in Alzheimer's Disease: A Preclinical Study in APP/PS1 Transgenic Mice

Hao Wang, Fang-fang Zhang, Yong Xu, Hua-rong Fu, Xiao-dan Wang, Lei Wang, Wei Chen, Xiao-yan Xu, Yong-feng Gao, Ji-guo Zhang, Han-Ting Zhang

Evidence Summary

Possible cognitive enhancement ability at low doses that don't trigger gastrointestinal side effects. Has anti-inflammatory activity, and may promote metabolic regulation.

Neuroprotective Benefit: May boost cognitive function for verbal memory. Neuroprotection may be mediated by induction of neurotrophic factors and reduction of neuroinflammation.

Aging and related health concerns: May reduce vascular inflammation and promote glucose tolerance. Could be beneficial as an adjunct therapy in cancer by improving sensitivity to chemotherapeutics.

Safety: Gastrointestinal-related events are the most common side effects at the standard dose. Metabolized in the liver and interacts with other drugs that use cytochrome P450 liver enzymes.

ELSEVIER

journal homepage: www.elsevier.com/locate/biopha

biomedicine & PHARMACOTHERAPY

Review

Roflumilast and cognition enhancement: A translational perspective

Jos Prickaerts [a], Jill Kerckhoffs [b,c], Nina Possemis [d], Wendy van Overveld [e], Frank Verbeek [e], Teun Grooters [e], Anke Sambeth [b], Arjan Blokland [b,*]

Recent broader research findings with marketed PDE4-inh broader impact than labelled anti-inflammatory effects

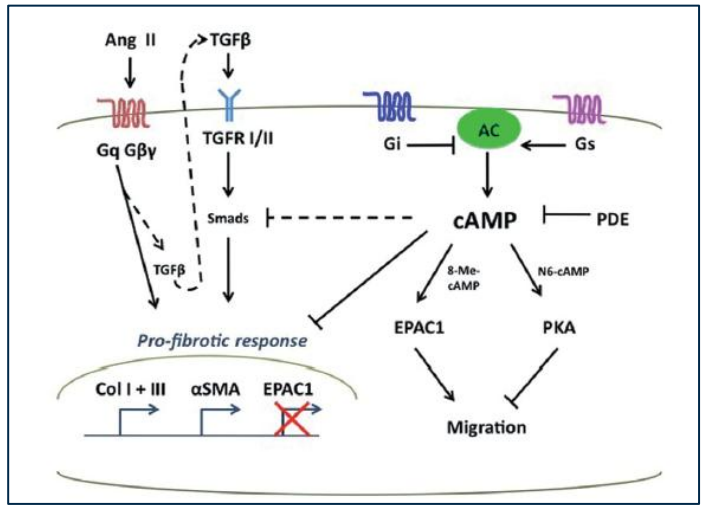
PDE4 inhibition is thought to reduce organ fibrosis…

…and BI has completed a large scale Ph3 study in IPF, a classic model disease for fibrosis

Published in final edited form as:
Hepatology. 2019 December ; 70(6): 1958–1971. doi:10.1002/hep.30761.

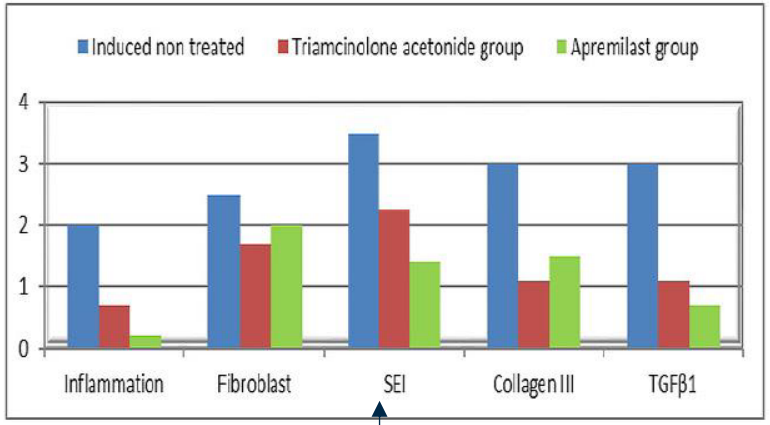
PDE4 Inhibition as a therapeutic target for alcoholic liver disease: from bedside to bench

Walter E. Rodriguez[1,2,3,*], Banrida Wahlang[1,2,3,*], Yali Wang[1,2,3,*], Jingwen Zhang[1,2,3], Manicka V. Vadhanam[1,2,3], Swati Joshi-Barve[1,2,3,4], Philip Bauer[5,6], Robert Cannon[7], Ali Reza Ahmadi[8], Zhaoli Sun[8], Andrew Cameron[8], Shirish Barve[1,2,3,4], Claudio Maldonado[5,6], Craig McClain[1,2,3,4,9], Leila Gobejishvili[1,2,3,4]



1) British Journal of Pharmacology (2012) 166 447–456
2) Archives of Razi Institute, Vol. 76, No. 6 (2021) 1803-1813
3) N Engl J Med. (2022), 9;386(23):2178-2187

Topical PDE4 inhibition treat **hypertrophic scars** better than a class III steroid in vivo[2]



SEI = Scar Elevation Index

ORIGINAL ARTICLE

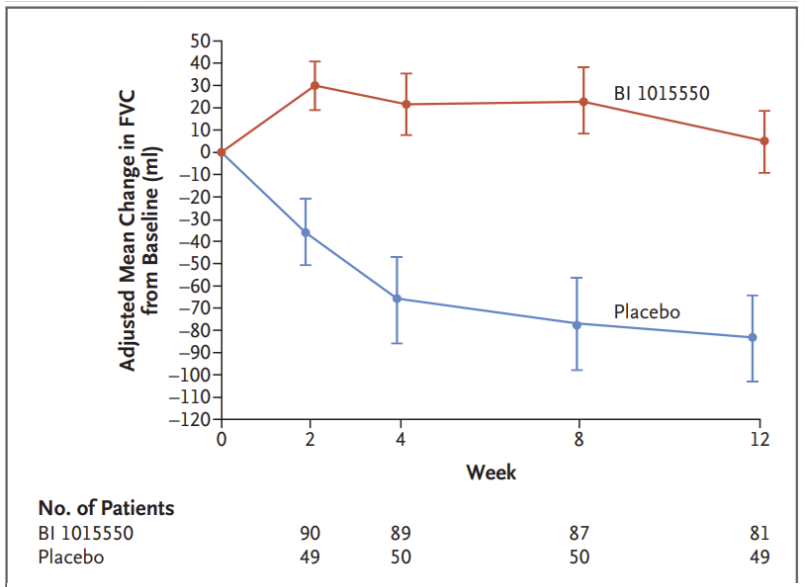
Nerandomilast in Patients with Idiopathic Pulmonary Fibrosis

Authors: Luca Richeldi, M.D., Arata Azuma, M.D., Vincent Cottin, M.D. , Michael Kreuter, M.D., Toby M. Maher, M.D., Fernando J. Martinez, M.D., Justin M. Oldham, M.D., +9 , for the FIBRONEER-IPF Trial Investigators* Author Info & Affiliations

Published May 18, 2025 | N Engl J Med 2025;392:2193-2202 | DOI: 10.1056/NEJMoa2414108 | VOL. 392 NO. 22

CONCLUSIONS

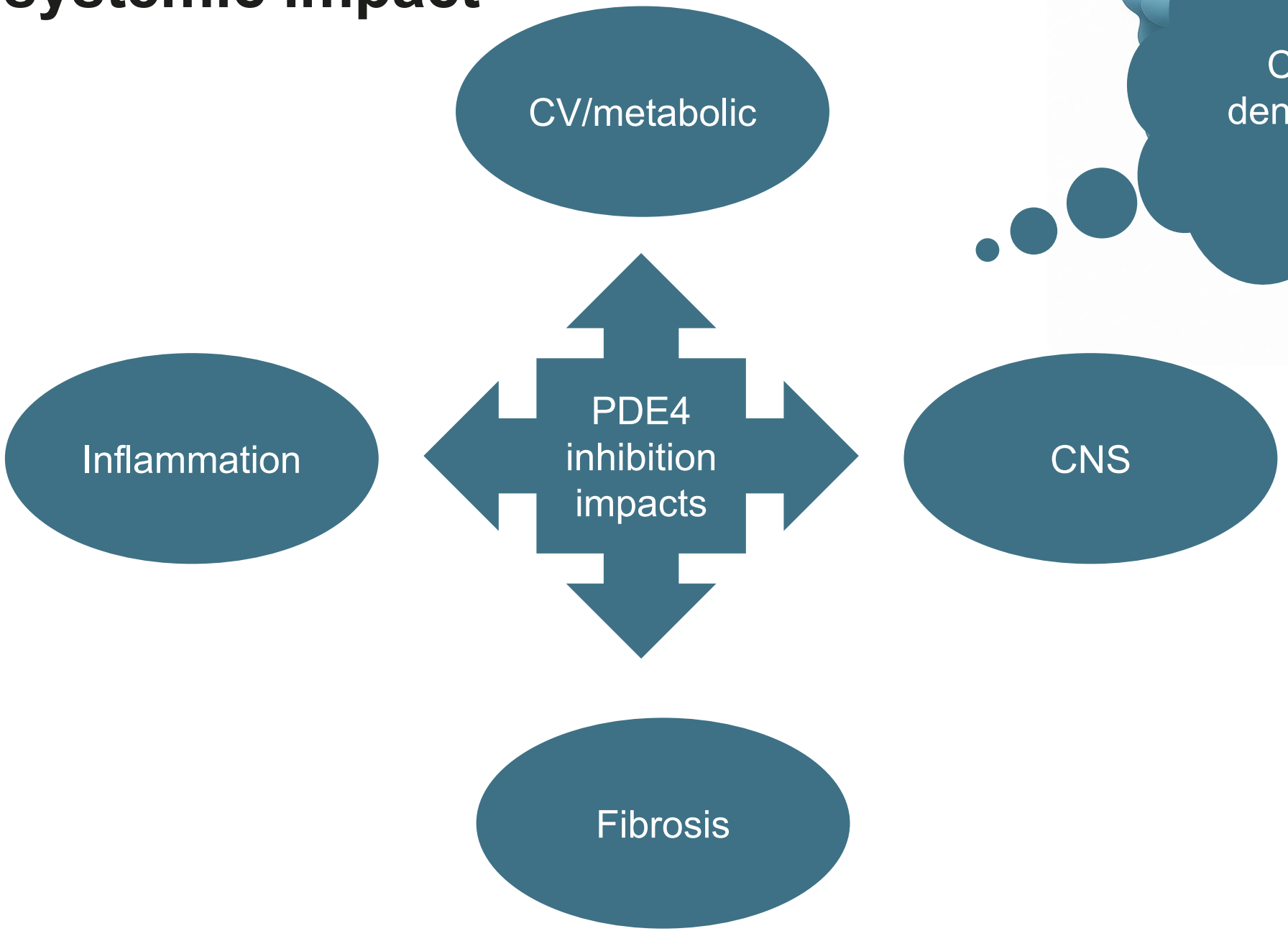
In patients with idiopathic pulmonary fibrosis, treatment with nerandomilast resulted in a smaller decline in the FVC than placebo over a period of 52 weeks. (Funded by Boehringer Ingelheim; FIBRONEER-IPF ClinicalTrials.gov number, NCT05321069.)



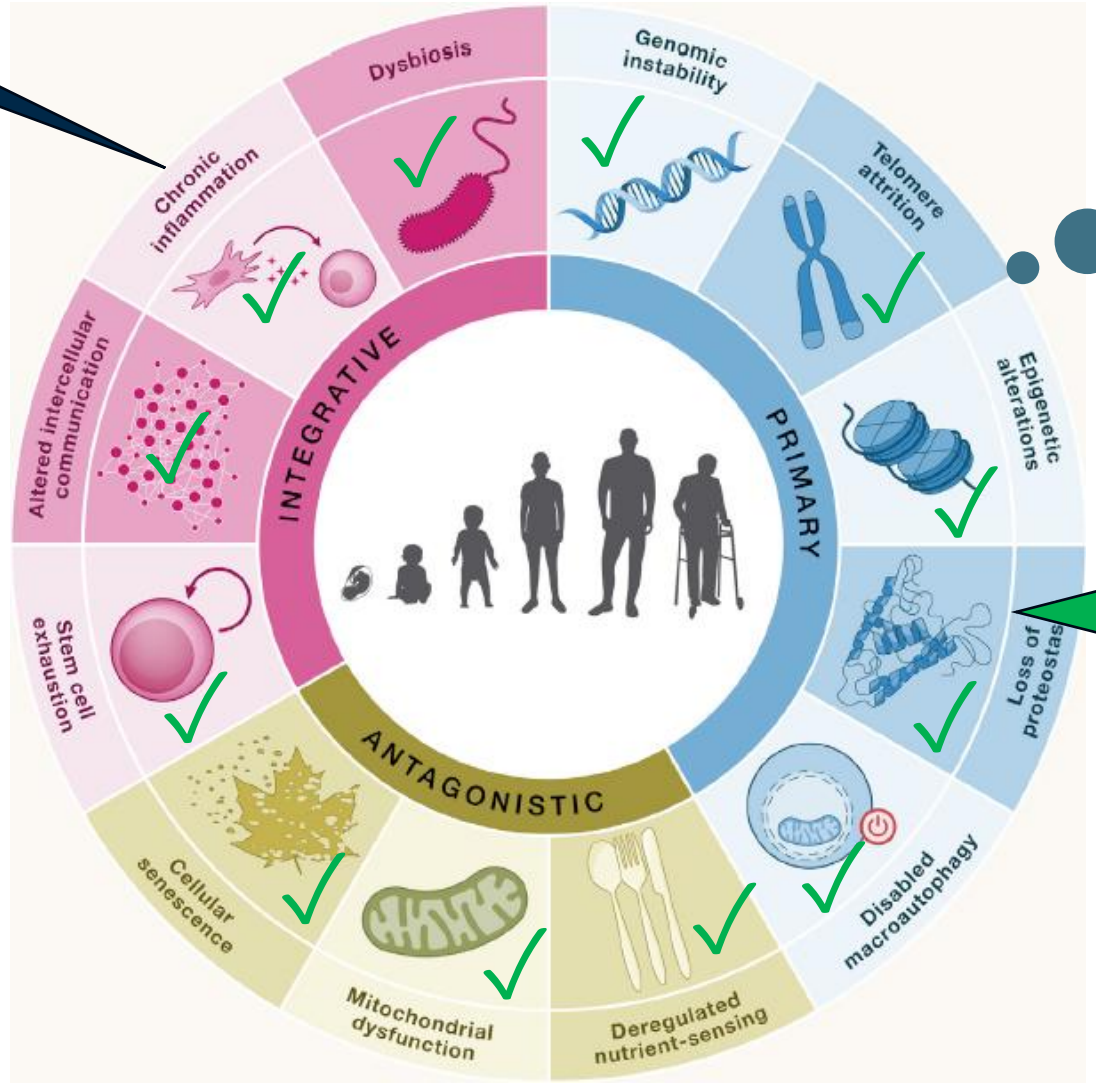
Oral PDE4 inhibition prevents decrease in lung function in **idiopathic pulmonary fibrosis**[3]

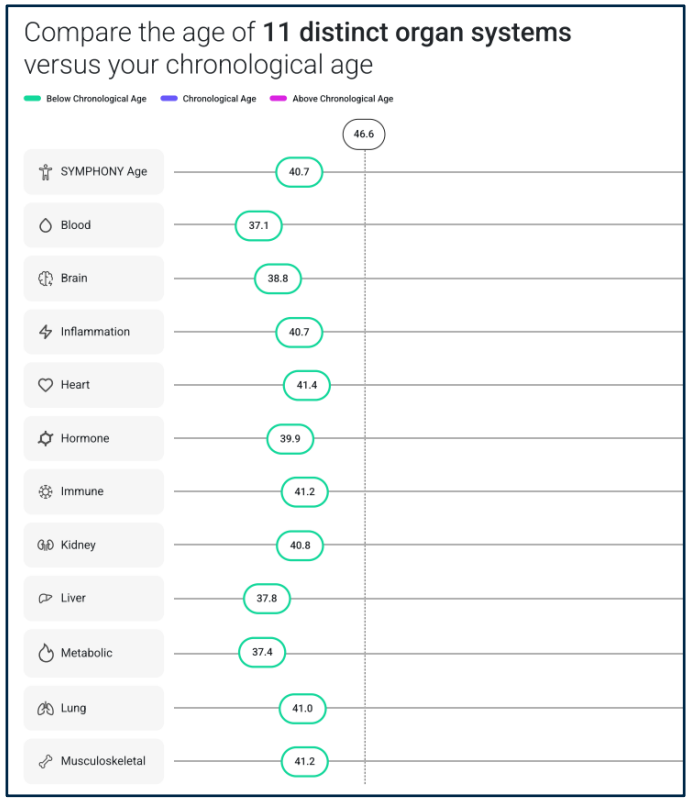
- Ph2, double-blind, placebo-controlled trial
- With BI-1015550, an oral PDE4B inhibitor [27]
- In patients with idiopathic pulmonary fibrosis

Broad systemic impact



Anti-inflammatory properties



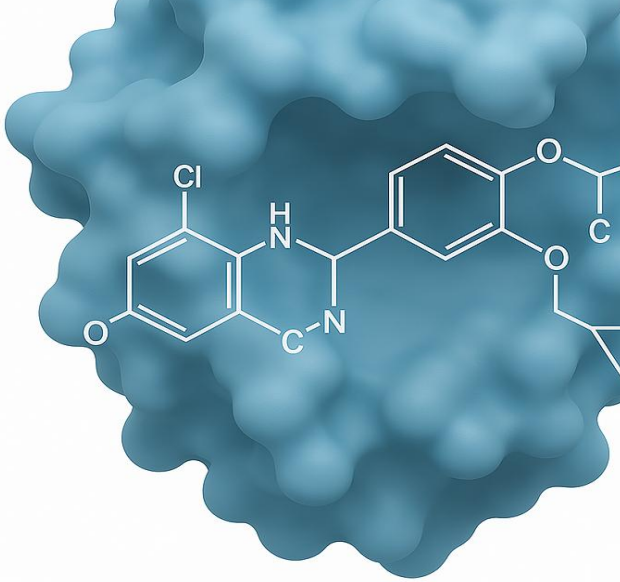


Aging?

Public research from many teams indicate broad beneficial effects and most Hallmarks, studying MOA, signalling cascades, cells, animals or humans

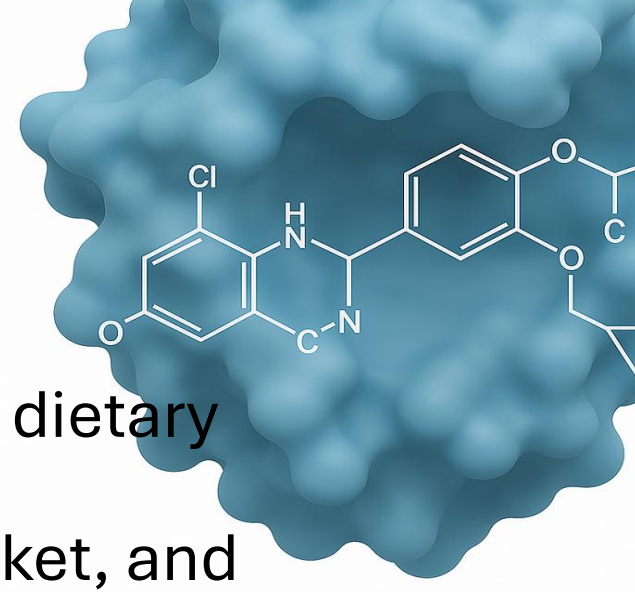
Hallmarks of aging: An expanding universe: https://doi.org/10.1016/j.cell.2022.11.001

Why might roflumilast be considered a longevity drug?



- **Generic and Safe**
- **Multi-pathway Inflammaging Suppression**: Direct inhibition of multiple inflammatory pathways implicated in aging and age-related diseases
- **Selective Immunomodulation:** Restores immune balance rather than causing broad, indiscriminate immunosuppression
- **Tissue Preserving:** Reduces fibrotic changes often seen in chronic disease and age acceleration
- **Oral, Accessible, and Well-Tolerated:** Its oral formulation and favorable side effect profile (relative to immunosuppressive drugs and biologics) enhance suitability for long-term preventative use
- **Additional Benefits:** Roflumilast may address metabolic syndrome, obesity, and possibly reduce the risk of chronic respiratory diseases, which are prevalent in aging and contribute to morbidity and mortality

Summary



- PDE inhibiting molecules are found in many of beneficial dietary ingredients
- Oral and topical PDE4 inhibitors are available on the market, and others are in development
- MOA is gaining attention in the scientific and clinical literature
- Off-label clinical experience with roflumilast in a private derm practice indicate that
  - Transparent information about side effects is necessary, most will have classic side effects at treatment initiation, many will be without significant side effects at continued treatment
  - Patients with HS and AD seems to be most happy with the treatment
- PDE4 inhibition positively impact many of the systemic functions which deteriorate with aging