



Queen Mary

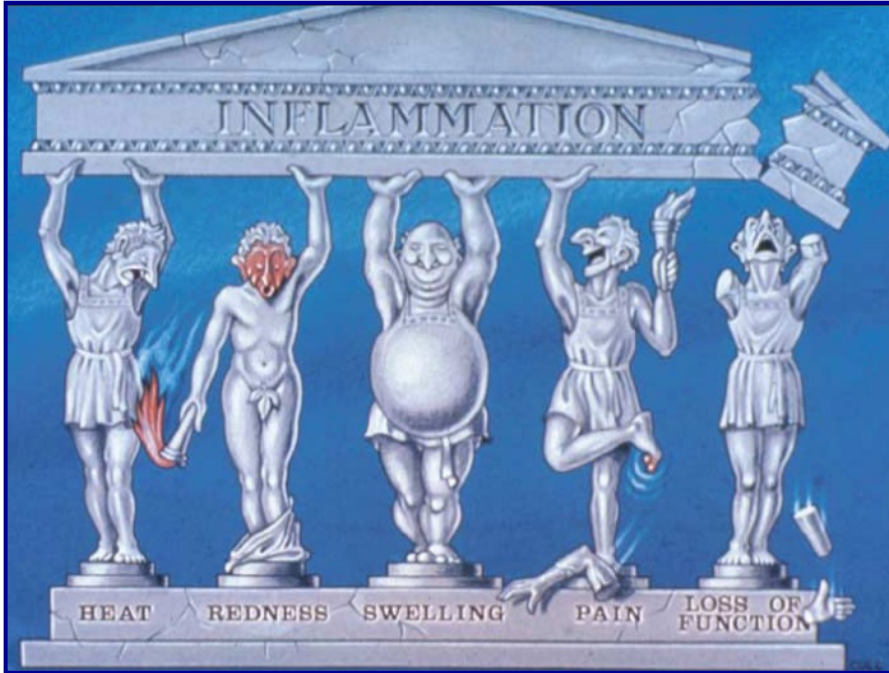
University of London

Medicine and Dentistry

# Resolution Pharmacology and AP1189

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# Inflammation



## Cardinal signs of inflammation:

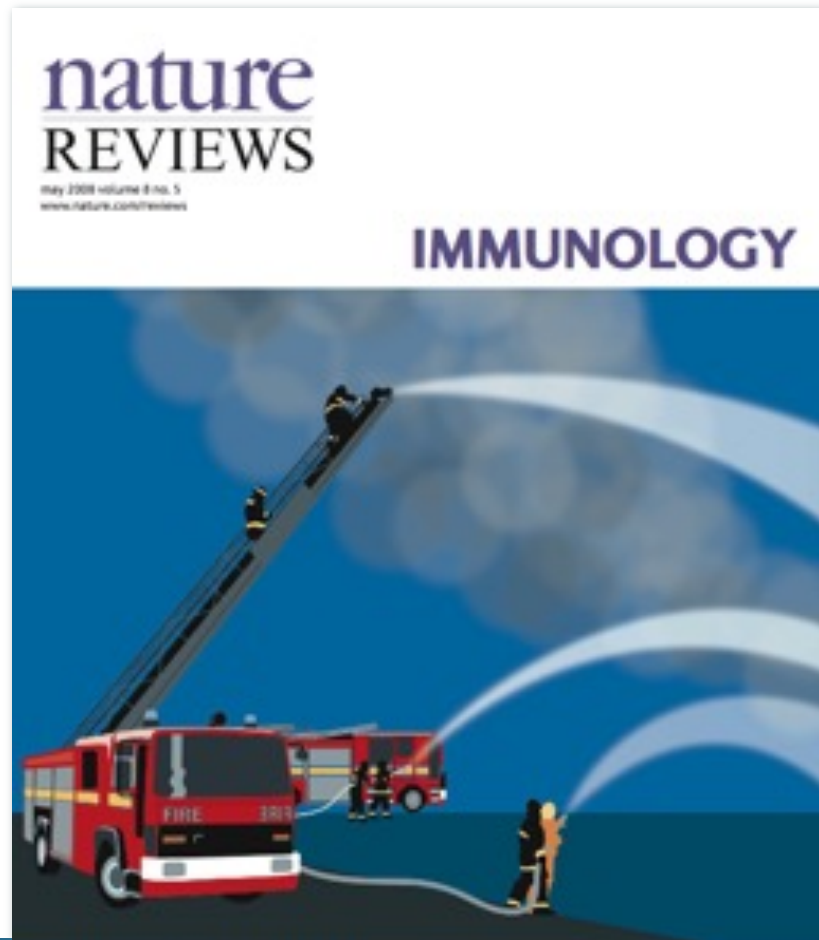
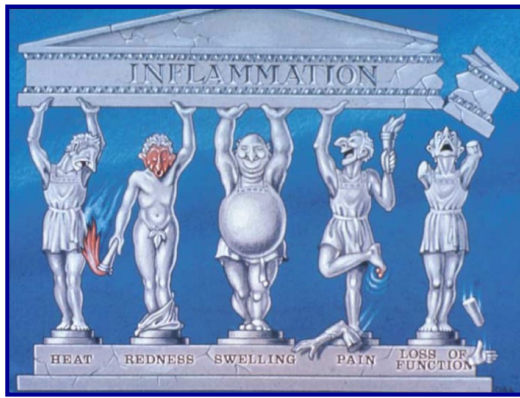
Calor (heat)

Rubor (redness)

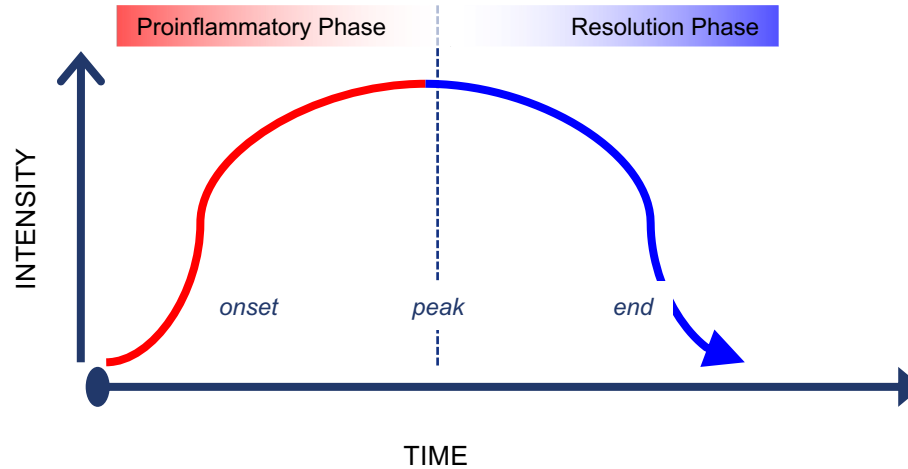
Tumor (swelling)

Dolor (pain)

*Aulus Cornelius Celsus, De medicina, c. A.D. 25*

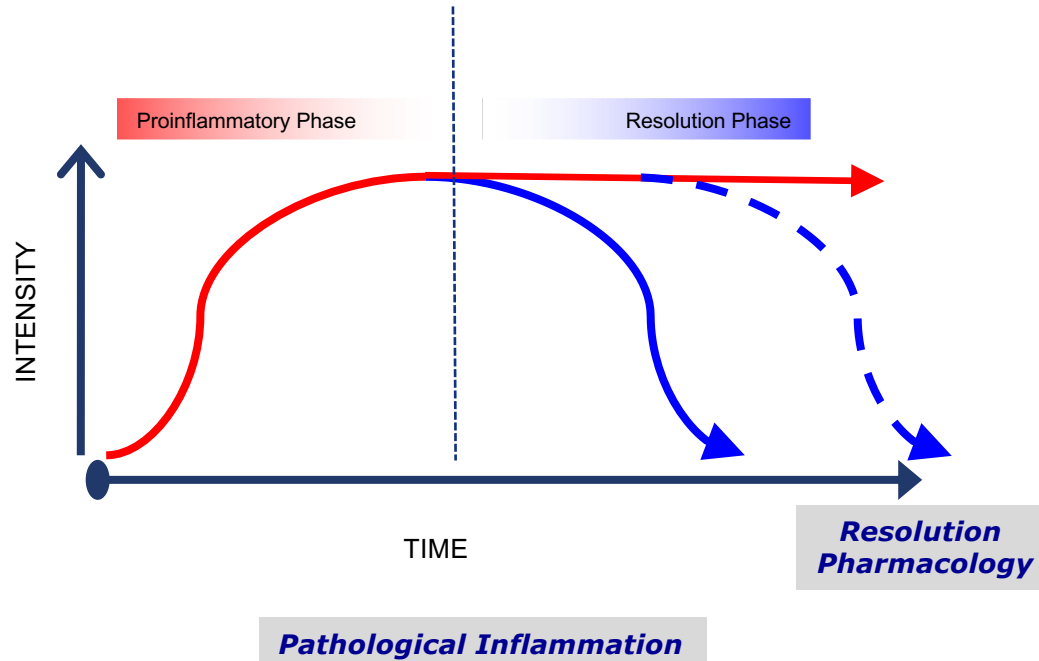


# The dynamics of inflammation



***Physiological Inflammation***

# The dynamics of inflammation





# **Pro-inflammatory mediators: Targets for anti-inflammatory therapy**

**Complement**

**Autacoids (Histamine; SP; CGRP)**

**Eicosanoids (PGs, LTs; ...)**

**Cytokines/Chemokines**

**Adhesion Molecules**



**Musculoskeletal Diseases**

**Allergy**

**Cardiovascular Pathologies**

**Cancer**

**Metabolic Diseases**

**Endocrine pathologies**

**Brain Diseases**

**Time, March 1<sup>st</sup> 2004**

# Focus – rheumatoid arthritis

## Problems with current anti-RA therapies

- Proportion of patients do not respond to therapy
- Secondary-effects (immunosuppression)
- Anti-drug antibodies (biologics)
- Ineffective on RA cardiovascular complications



Targeting Resolution Pathways provides a therapeutic opportunity for chronic ('complex') diseases

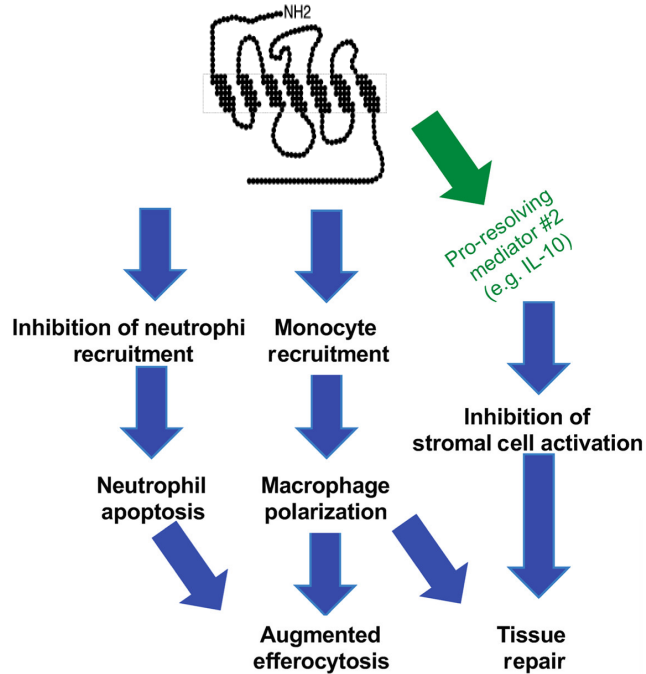
1. Immune diseases
2. Cardiovascular diseases
3. Metabolic diseases
4. CNS diseases

**INNOVATION:**

1. Integrated actions of resolution
2. Amplification through pro-resolving receptors

to promote tissue regain of HOMEOSTASIS or ALLOSTASIS

## Pro-Resolving Mediator #1

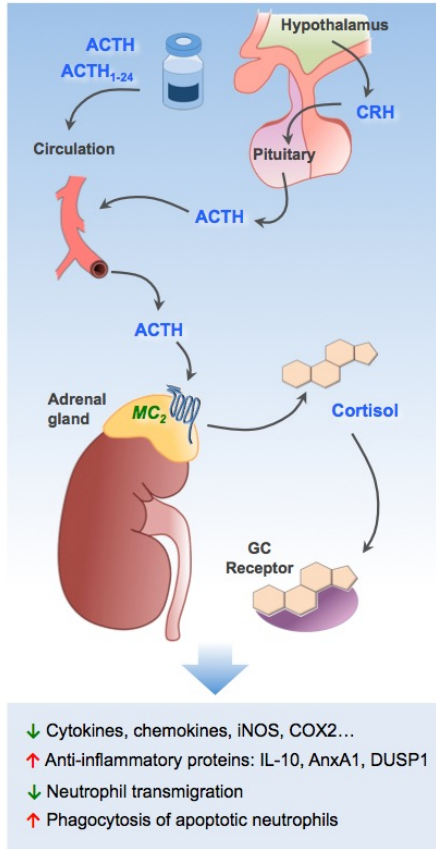


# AGONIST!

- Cell gene reprogramming
- Cell phenotype switch
- Long-lasting effects
- Resolution of tissue inflammation

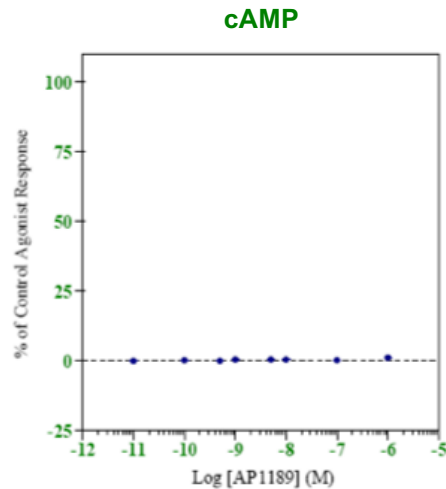
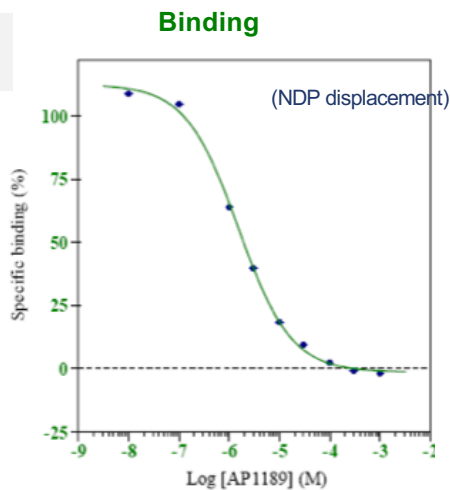
# The biased agonist AP1189

## GC-dependent mechanism



# AP1189 – MC small molecule

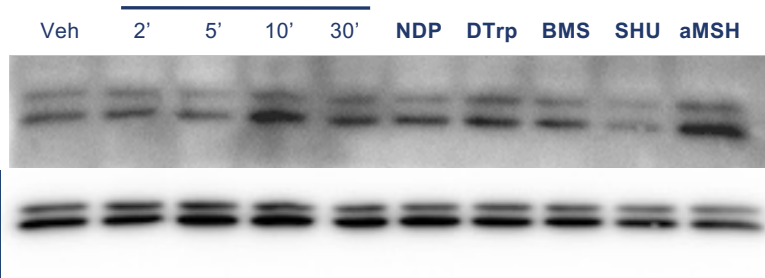
mMC<sub>1</sub>



AP1189 (1nM)

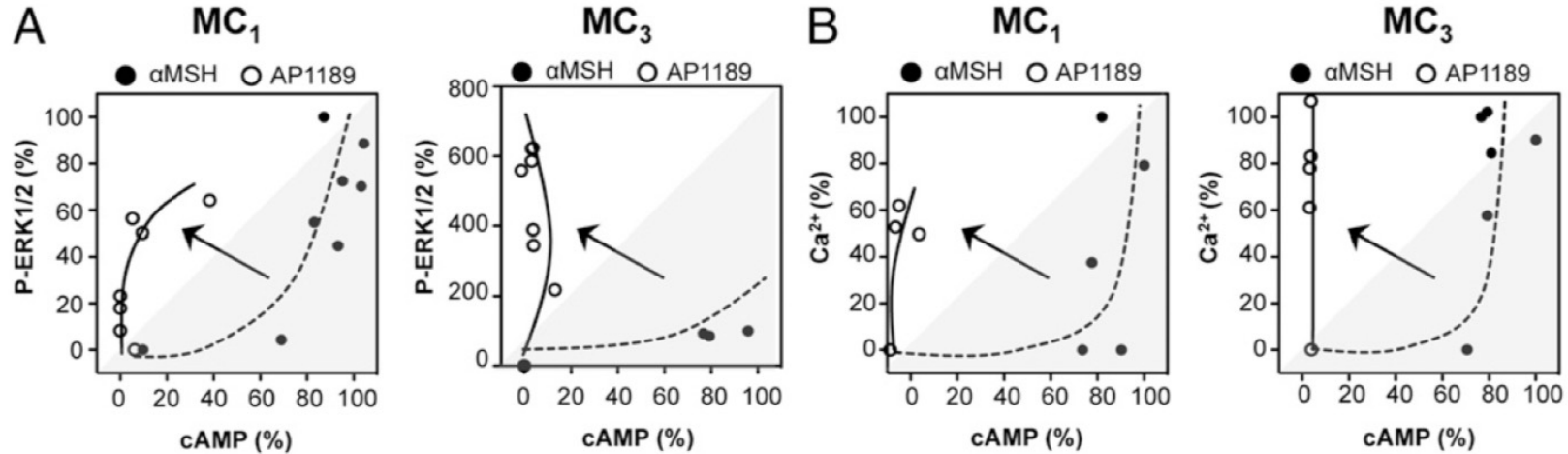
ERK1/2 phosphorylation

p-ERK1/2



MC1-HEK293  
cells

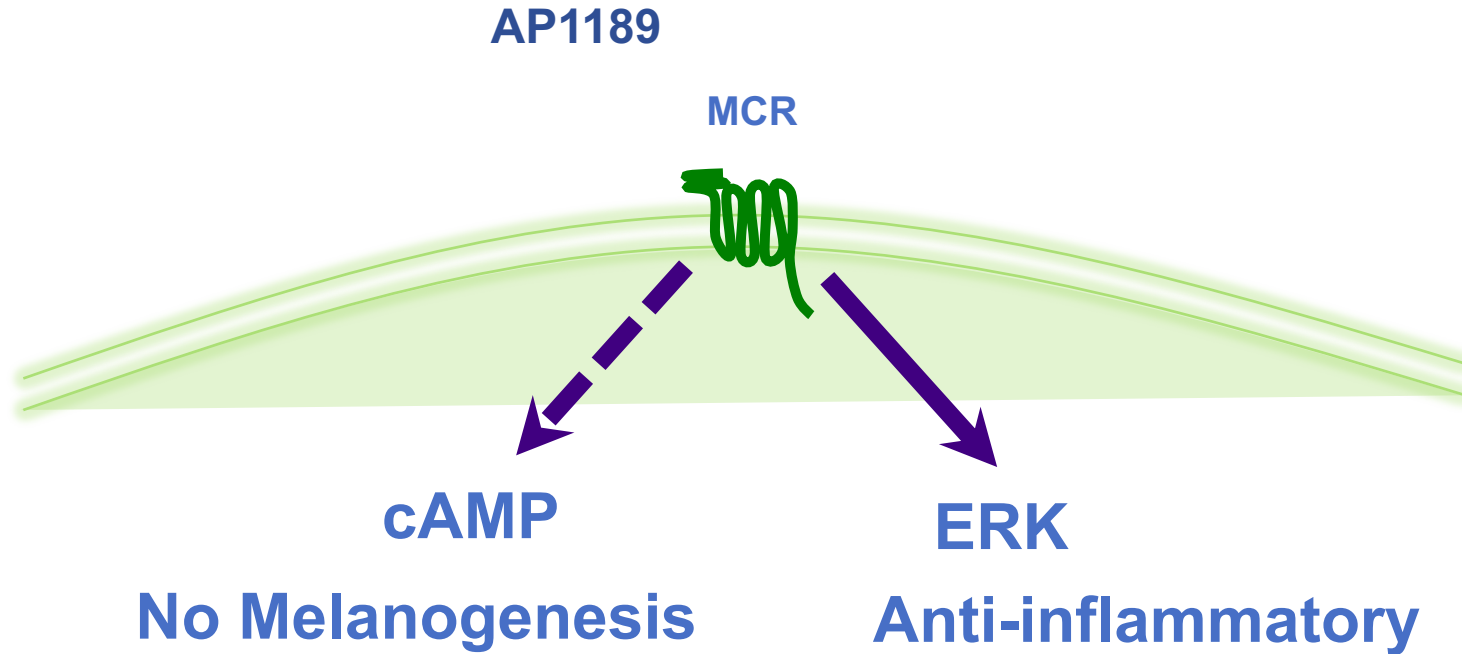
# AP1189 – Pan-Receptor Biased Agonist



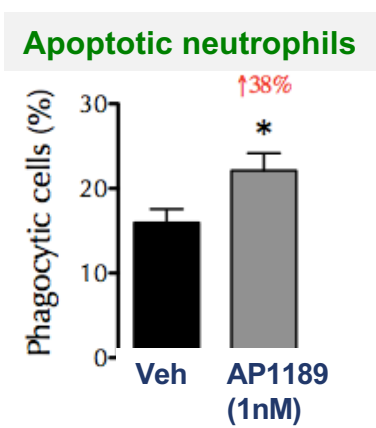
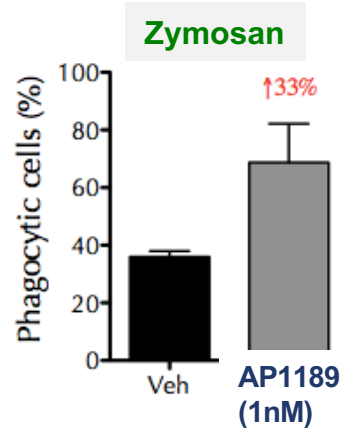
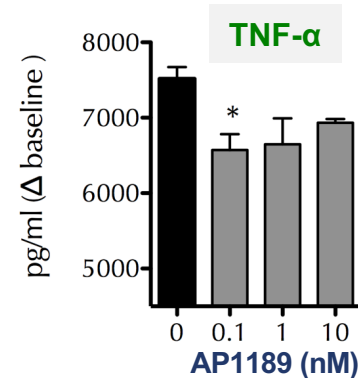
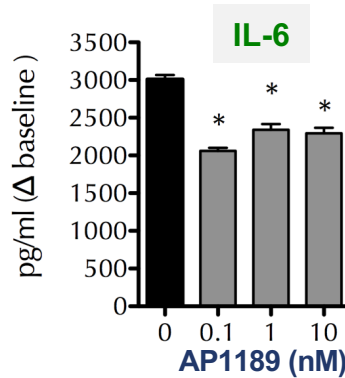
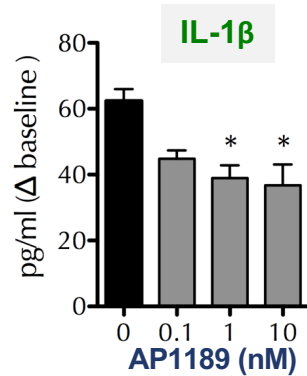
Erk/cAMP

Ca<sup>2+</sup>/cAMP

# Biased Agonist AP1189 = functional selectivity



# AP1189 – Pharmacological properties



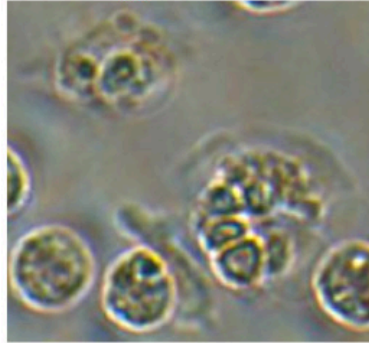
Primary macrophages  
Zymosan 25  $\mu$ g/ml,  
(6h, n=3)

Primary macrophages  
PMN 1:5 ratio,  
(1h, n=3)

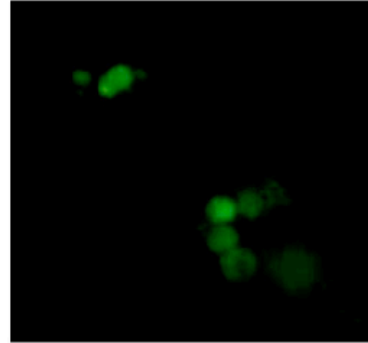


# AP1189 pro-resolving activities

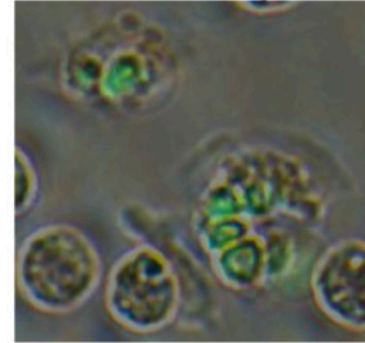
Bright field



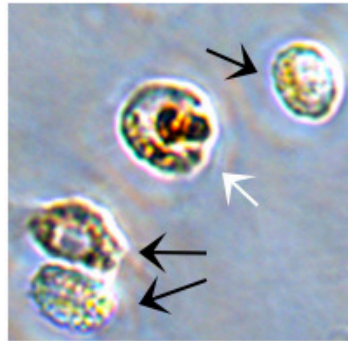
CFSE



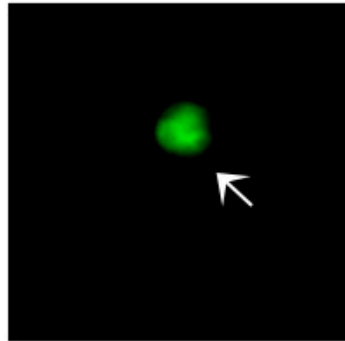
Overlay



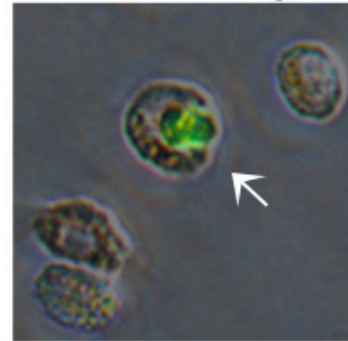
MPO



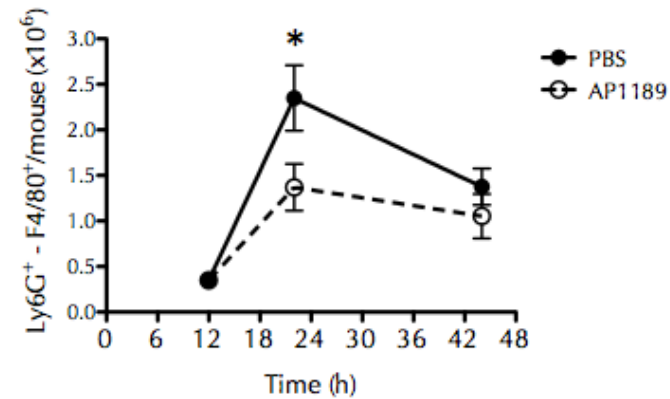
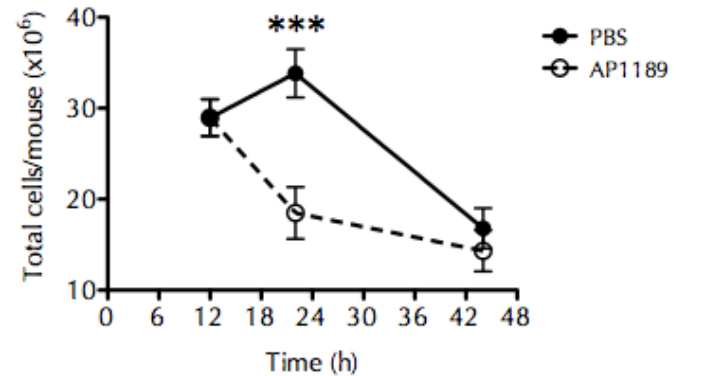
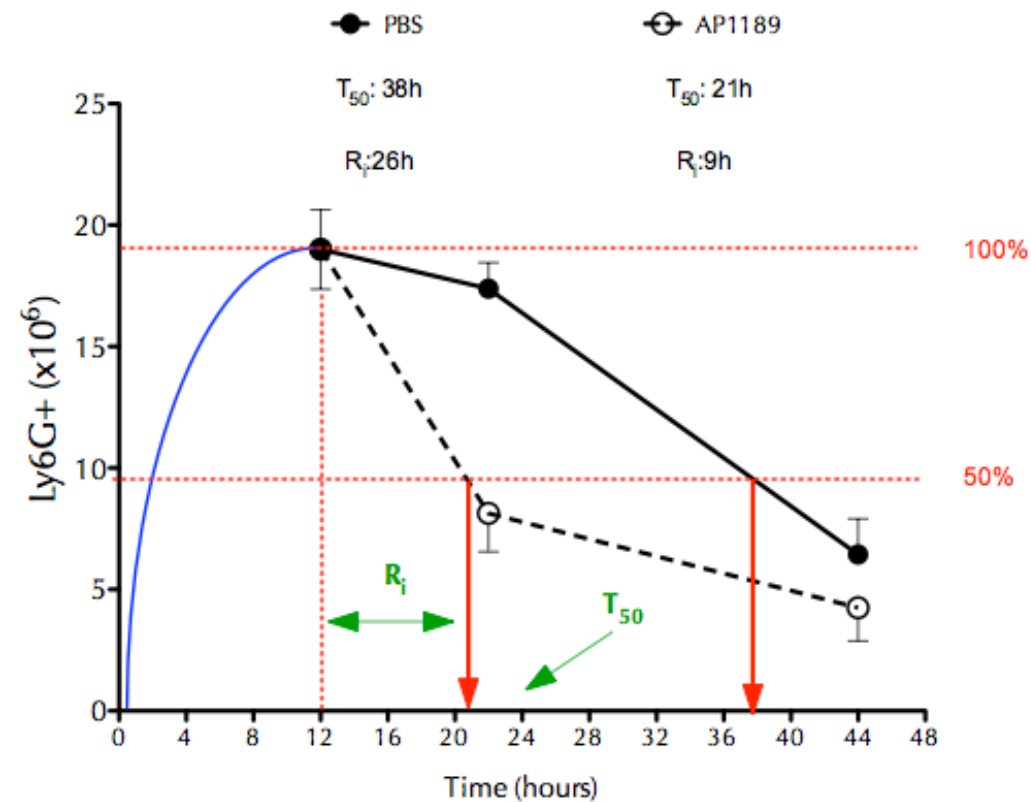
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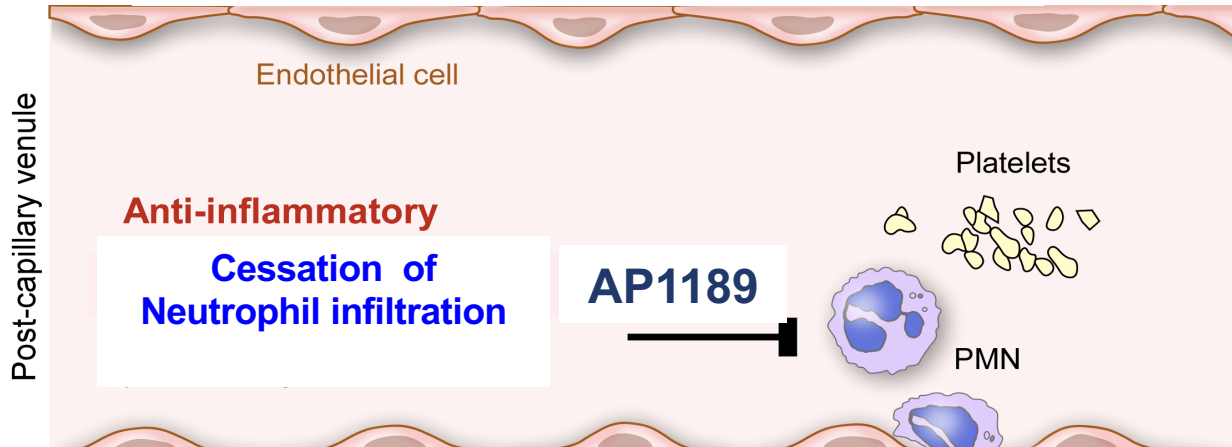
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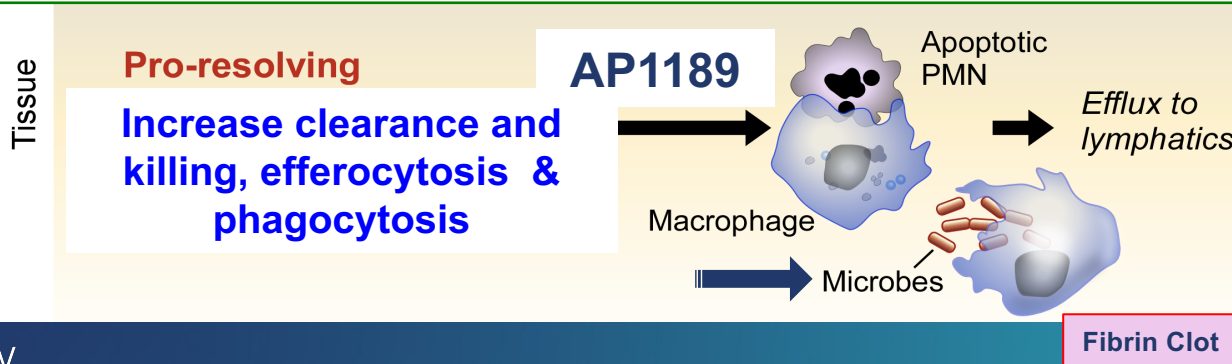
# AP1189 pro-resolving activities



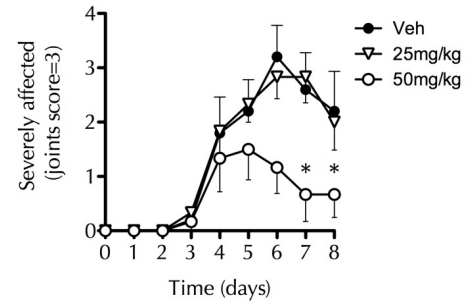
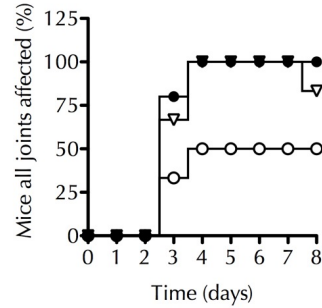
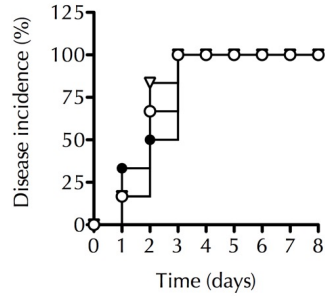
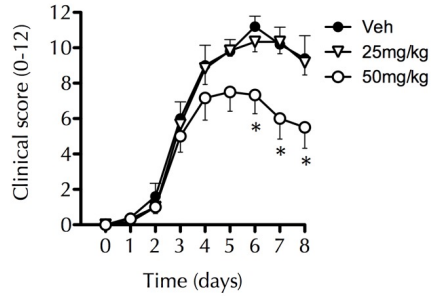
# AP1189 pro-resolving activities



**Pro-Resolution ≠ Anti-Inflammation**



# AP1189: anti-arthritic actions



**Pro-Resolution therapy**  
**≠**  
**Anti-Inflammatory therapy**

## ANTI- INFLAMMATION

## RESOLUTION Pharmacology

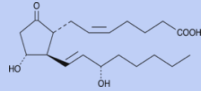
CLASSES

- ❖ Glucocorticoids
- ❖ NSAIDs
- ❖ Biologics
- ❖ Methotrexate
- ❖ Colchicine
- ❖ DMARDs
- ❖ Cyclosporin
- ❖ H1 antagonists
- ❖ Chromones
- ❖ Lukast drugs

- ❖ Annexin A1
- ❖ Melanocortins
- ❖ Galectins
- ❖ Chemerin 15
- ❖ Somatostatin
- ❖  $\omega$ -3 derived: Resolvins, Protectins, Maresins
- ❖ Lipoxin A<sub>4</sub>
- ❖ Adenosine
- ❖ Cannabinoids

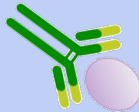
ACTIONS

Pg synthesis inhibition



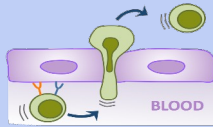
Diclofenac  
Ibuprofen  
(...)

Cytokine blockade



Infliximab  
Anakinra  
Tocilizumab

Inhibition leukocyte migration



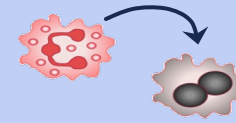
Natalizumab

Increase on  
Phagocytosis  
Efferocytosis



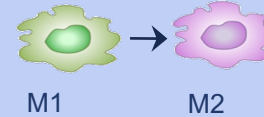
$\alpha$ MSH  
AnxA1  
RvD1

Induction of  
neutrophil  
apoptosis



LXA<sub>4</sub>  
CDK inhib.  
HDACIs

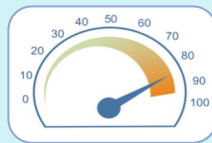
Macrophage  
phenotype switch



RvD1  
AnxA1

MoA

- ❖ Based on “inhibition”
- ❖ Directed actions
- ❖ Strong inhibition (80-90%)



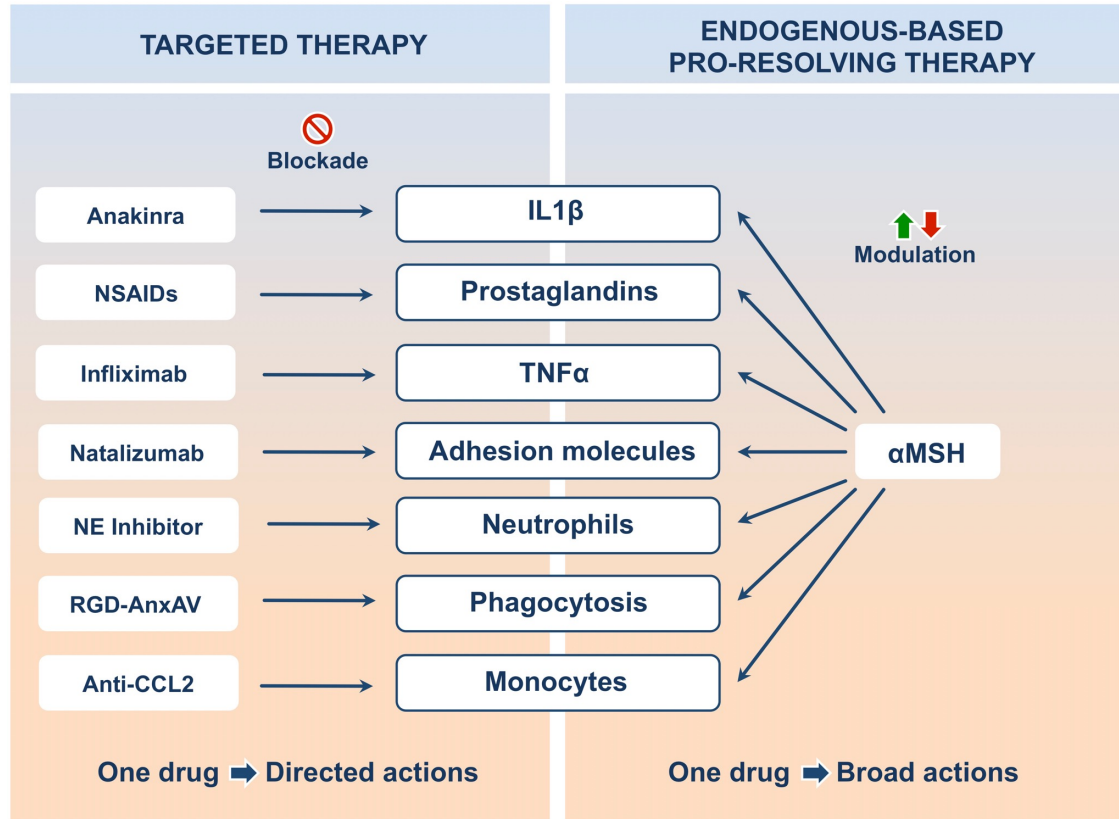
- ❖ Based on “activation”
- ❖ Broad actions
- ❖ Modulation (40-50%)



SIDE EFFECTS

- ❖ Immunosuppressive
- ❖ Resolution toxic
- ❖ Compensation/Tolerance

- ❖ Unknown



**180°**



***Resolution  
Pharmacology***



# Pro-resolving Molecules in Clinical Trial/Use

**AP214 Alpha-MSH analogue** (Action Pharma-> Abbvie, Phase III)

**TP-317 Resolvin E1** (Thetis Pharmaceuticals LLC; IBD)

**H<sub>2</sub>S-NSAIDs** (Antibethera; ATB-346, OA Phase III)

**CINOD, NO-PG** (Nicox; Ophthalmology, in clinical use)

**Activating Anti-ChemR23 mAb** (Ose Immunotherapeutics)

**ORACAL** (Tarsa; Bone Resorption Phase III)

**Dubloxins** (University College Dublin; Sepsis, Fibrosis)

**Resolvix** (Med'inn'Pharma; preclinical)

**Benzo-Lipoxin A<sub>4</sub>** (Forsyth; Periodontal disease; Phase I/II)

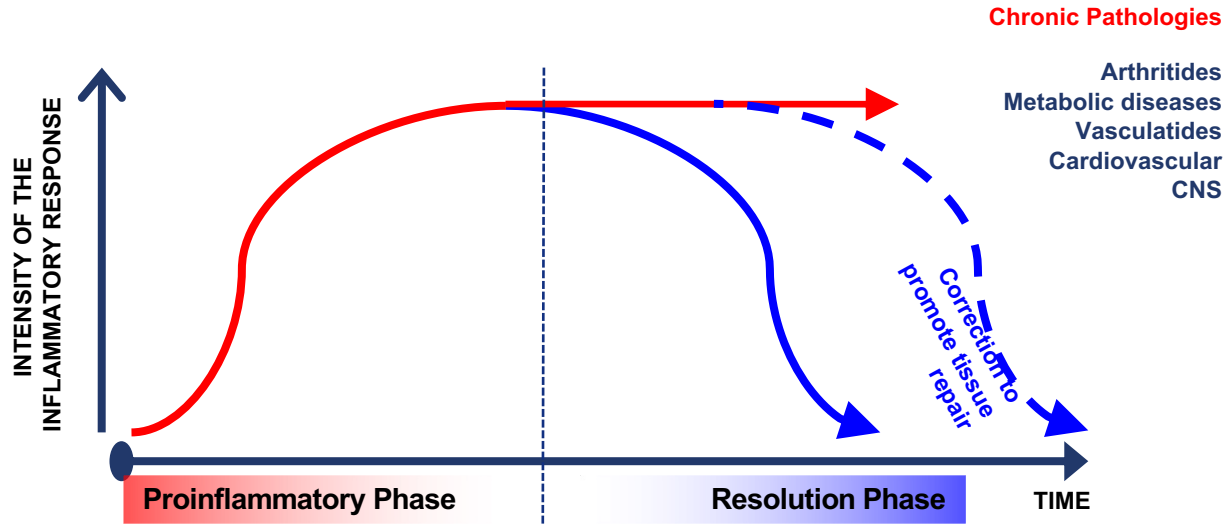
**FPR2 small molecule** (Bristol Myers Squibb; Phase I, Heart Failure/MI)

**AP1189 biased melanocortin agonist** (SynAct Pharma; Phase IIa/b)

**RTP-026 Annexin peptide** (ResoTher Pharma, Phase I, AMI)

**Adenosine Agonists** (several molecules)





**Current therapeutics often inadequate:**

- a) ~50% of patients do not respond
- b) Lack of tissue recovery/repair
- c) Major systemic toxicity
- d) Elicit an immune response

**Resolution-based therapeutics**

- a) Exploit patient's own tissue protective and reparative processes
- b) Modulatory action
- c) Lower burden of side effects

# Thank you.

