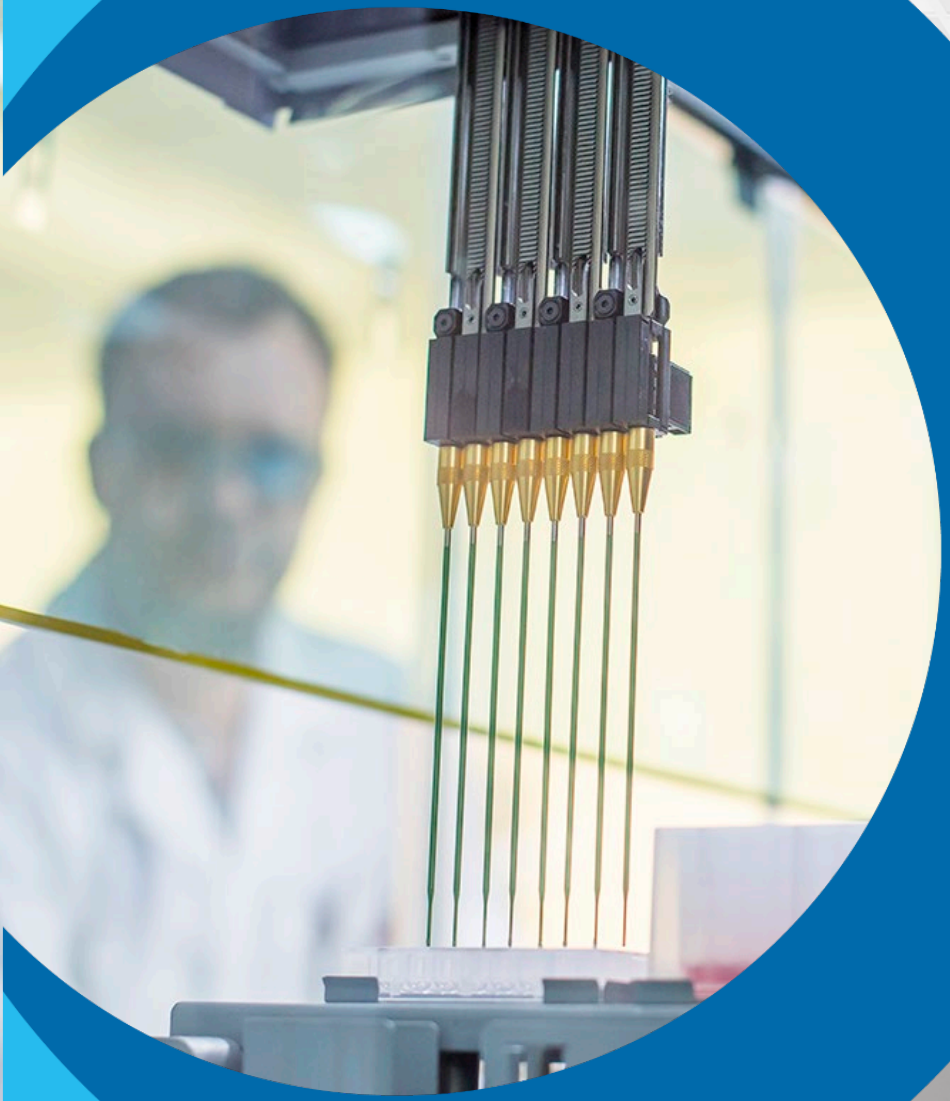


SYGNATURE DISCOVERY

A Journey through Anti-Inflammatory Drug Discovery

Dr John Unitt

ELRIG Networking Events - Nottingham

June 13th 2019

Enabling Success

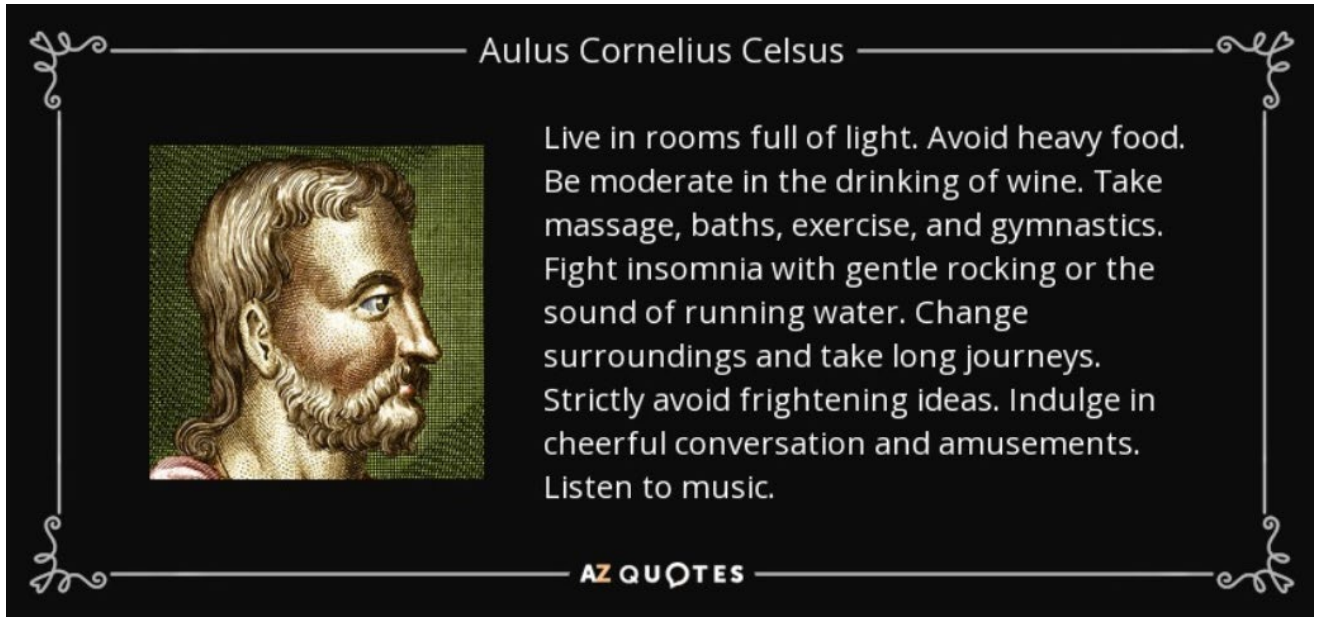
www.sygnaturediscovery.com

Outline

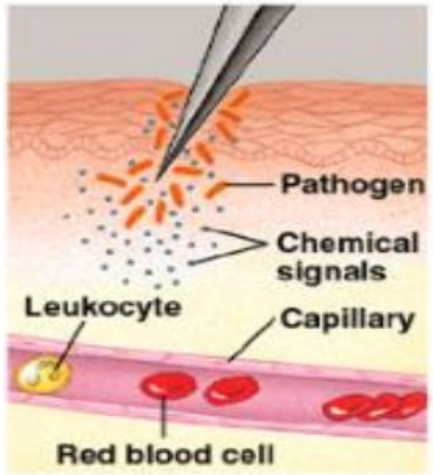
- What's inflammation?
- Drug Discovery Trends and Landmarks
- Current Challenges and the Future

What is inflammation?

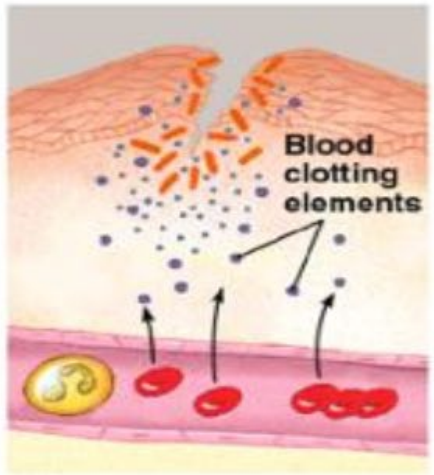
- Part of body's response to insult and initiation of healing process
- Causes
  - Wound
  - Infection
  - Auto-immune
- Original characterised by Celsus 50 AD
  - Pain, swelling, heat, redness, immobility
- Phases
  1. Acute
  2. Chronic
  3. *Resolution*
- Overlap with immunology
  - **Immuno-inflammation**



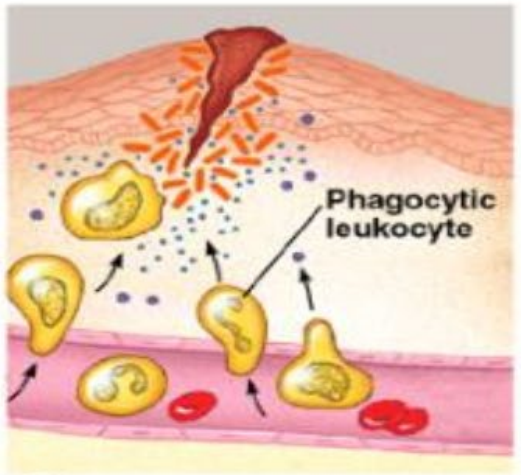
Acute Inflammation



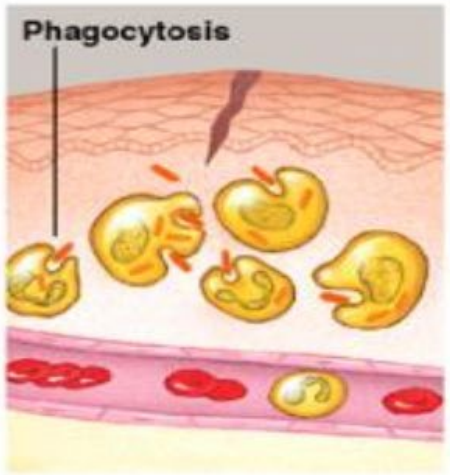
❶ Histamine & prostaglandins released



❷ Capillaries dilate
Clotting begins

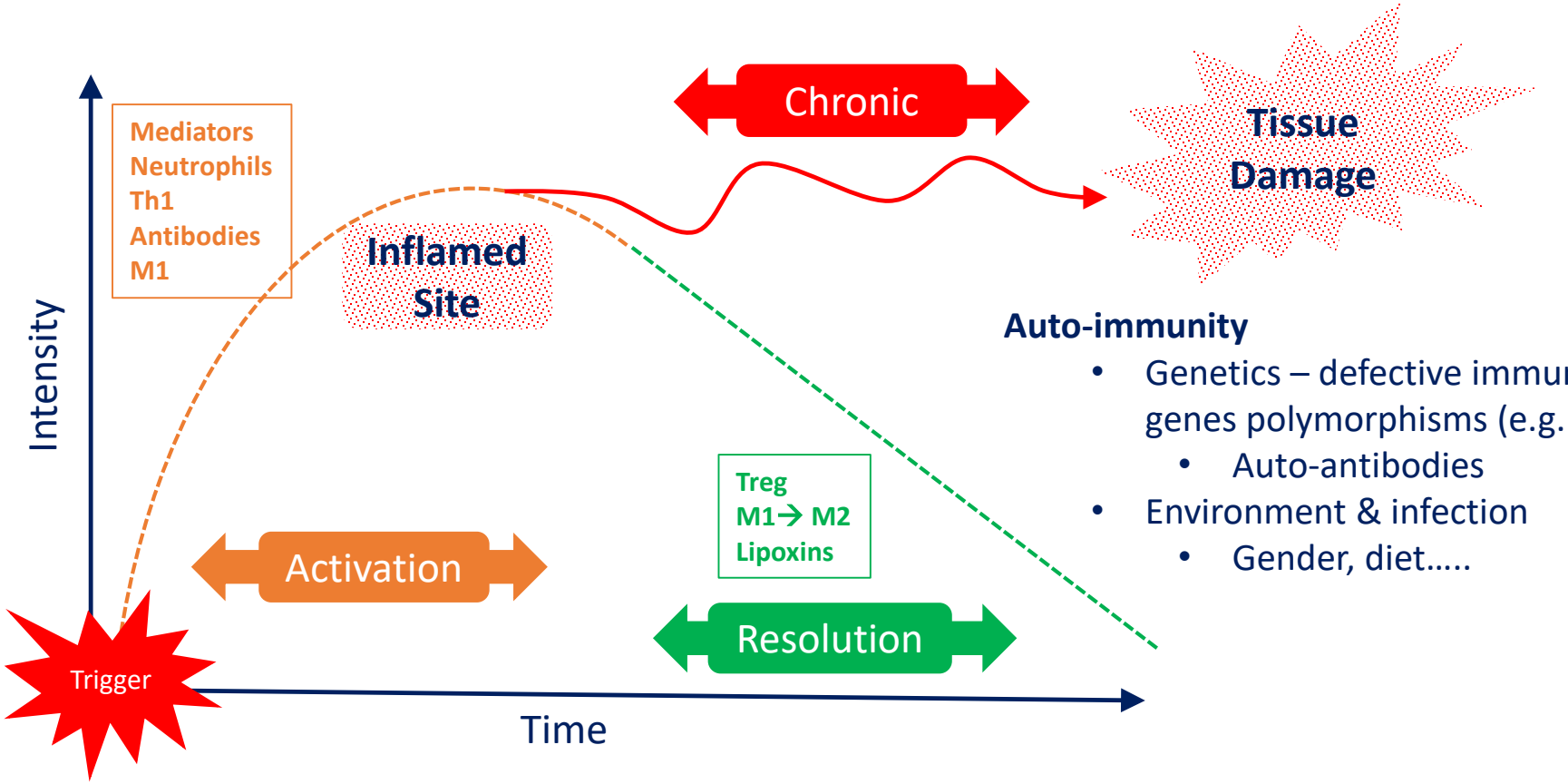


❸ Chemotactic factors attract phagocytic cells



❹ Phagocytes consume pathogens & cell debris

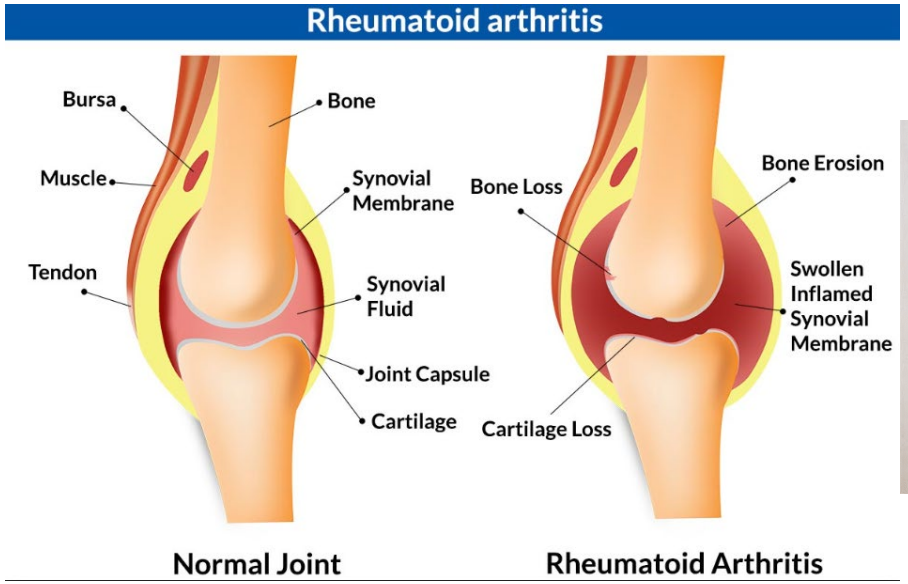
Chronic Inflammation

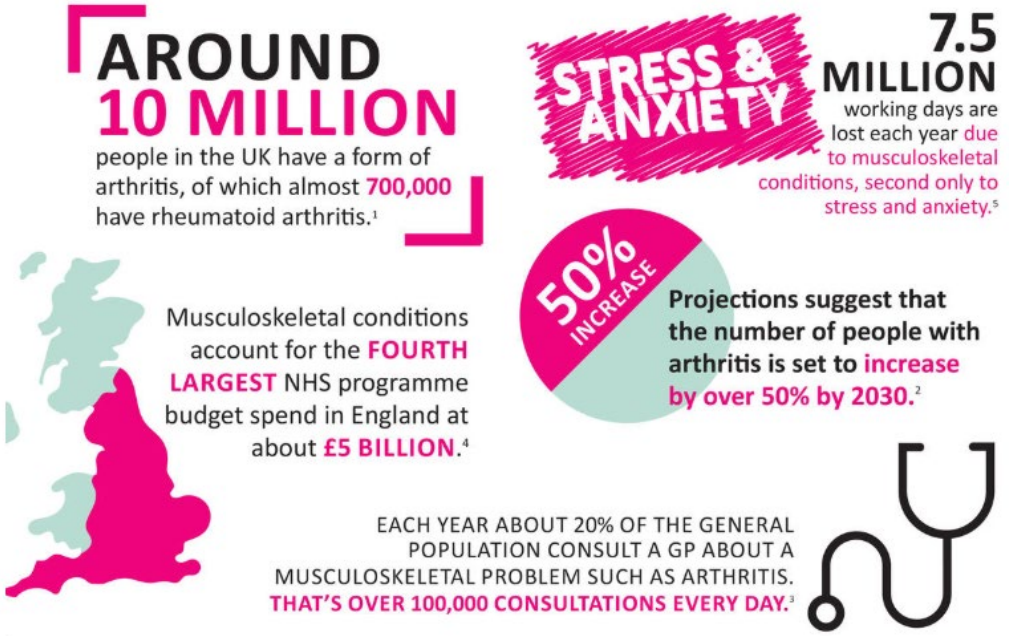


Auto-immunity

- Genetics – defective immune regulation genes polymorphisms (e.g. HLA)
  - Auto-antibodies
- Environment & infection
  - Gender, diet…..

Auto-immune diseases
Rheumatoid Arthritis

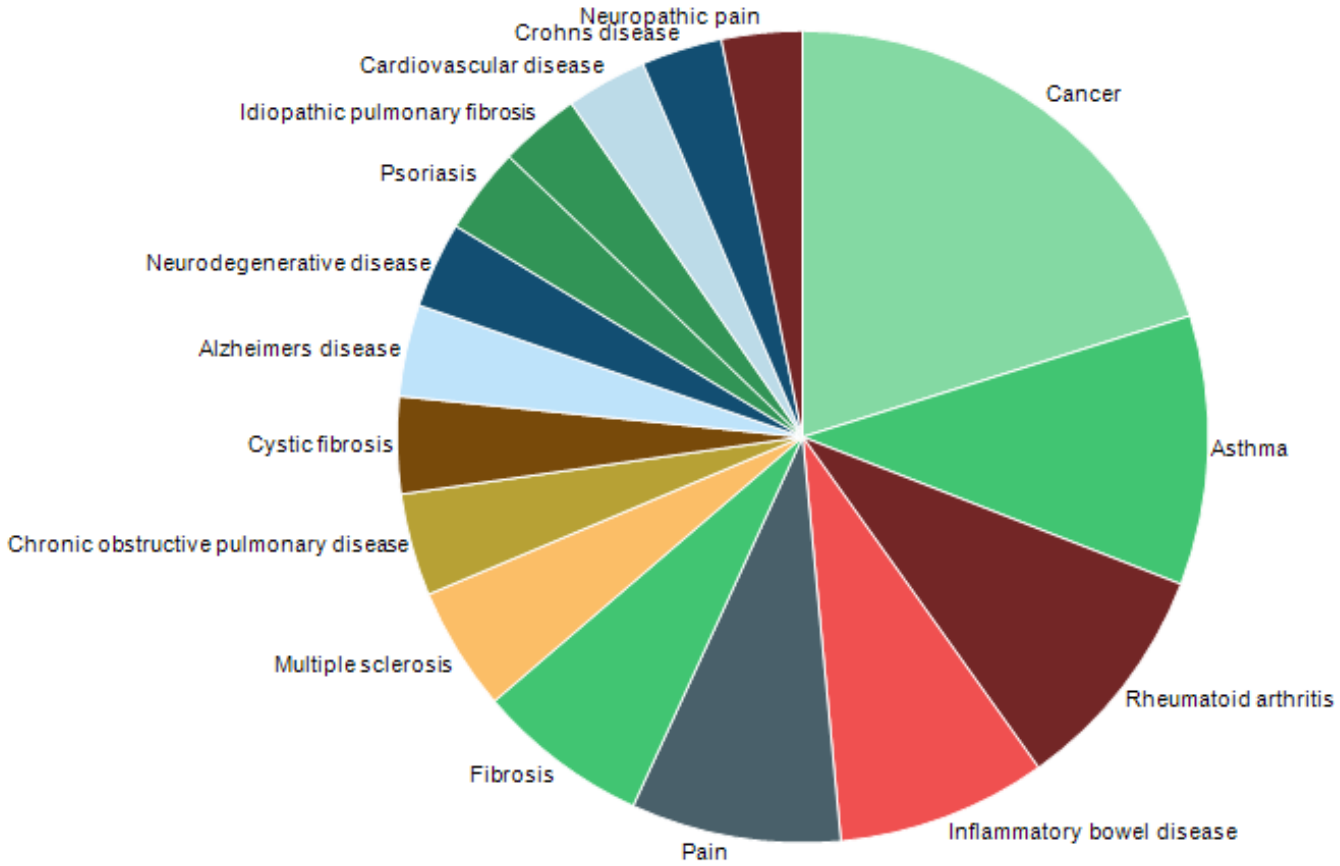




From RAAID

Inflammation under pins nearly all diseases

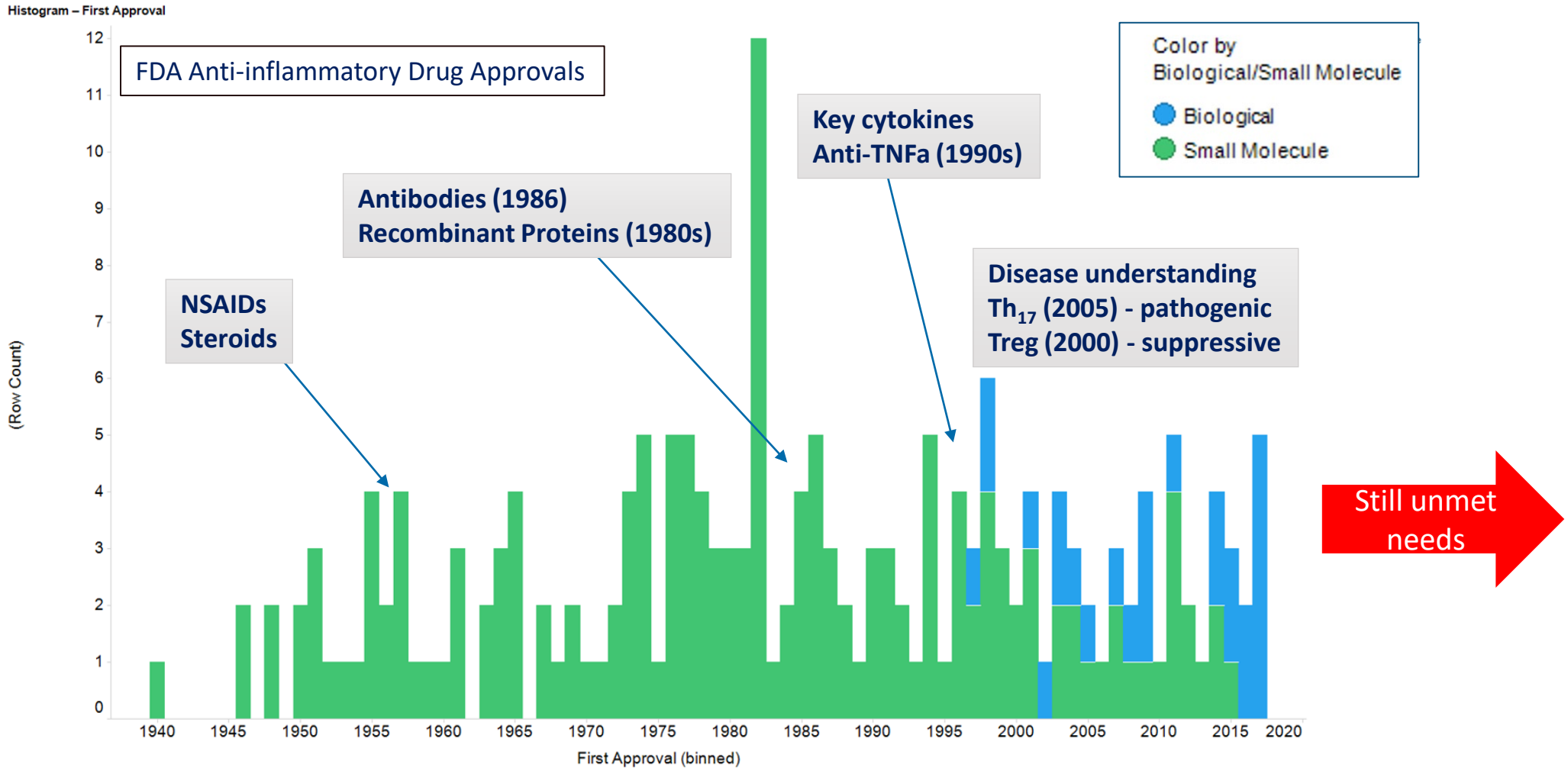
No. of projects in Discovery Phase Linked to Inflammation?



Outline

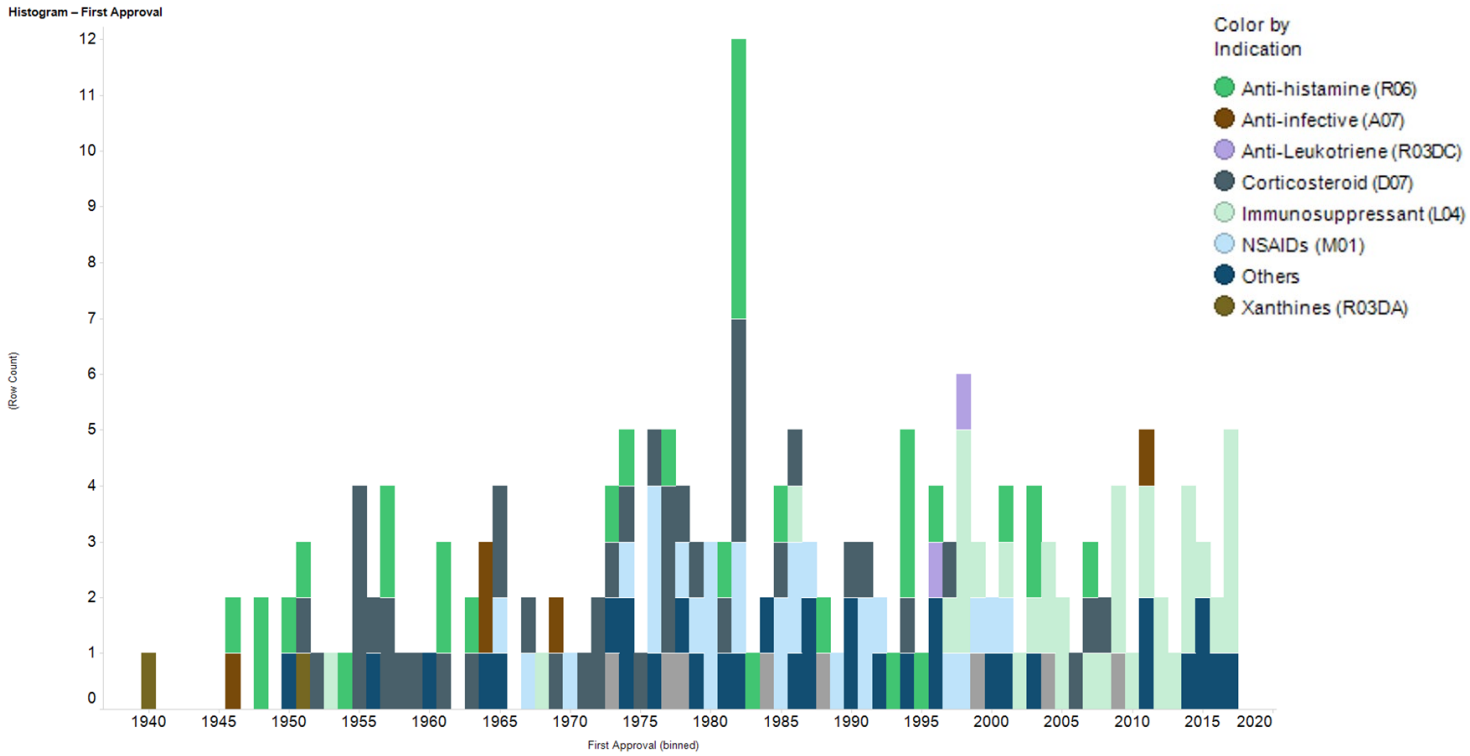
- What's inflammation?
- Drug Discovery Trends and Landmarks
- Current Challenges and the Future

Small Molecules to Biologics



Signs and Symptoms to Disease Modifying

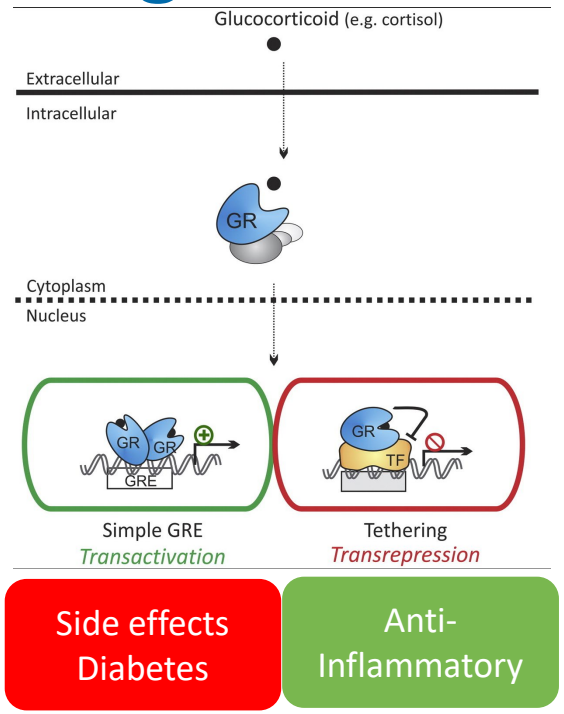
- Signs and symptoms
  - NSAIDs
  - Steroids
- Disease modifying
  - Immune cell anti-proliferatives
    - Methotrexate, leflunomide…
  - Anti-cytokines
    - Humira (anti-TNFα)
    - Benlysta (anti-BAFF)
    - IL-1, IL-6, IL-12/23, IL-17
    - CD20 (B cells)
    - CD3 (T cells)
    - JAK inhibitors
  - Increase in efficacy & permanence



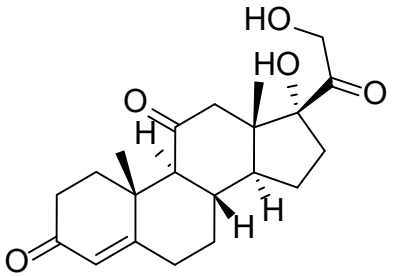
Steroids

Glucocorticoid Receptor Agonists

- Nuclear hormone receptor
- Cortisone (1950)
  - Highly efficacious
  - Systemic side effects
- Topical delivery
  - Inhaled
    - Budesonide (1981)
  - Skin
    - Dexamethasone (1958)
- Dissociated (SEGRAs)
  - Separate good (anti-inflammatory) from side effects (diabetogenic etc.)
  - Shown *in vitro*, but not *in vivo*
  - Still some discovery effort on going……



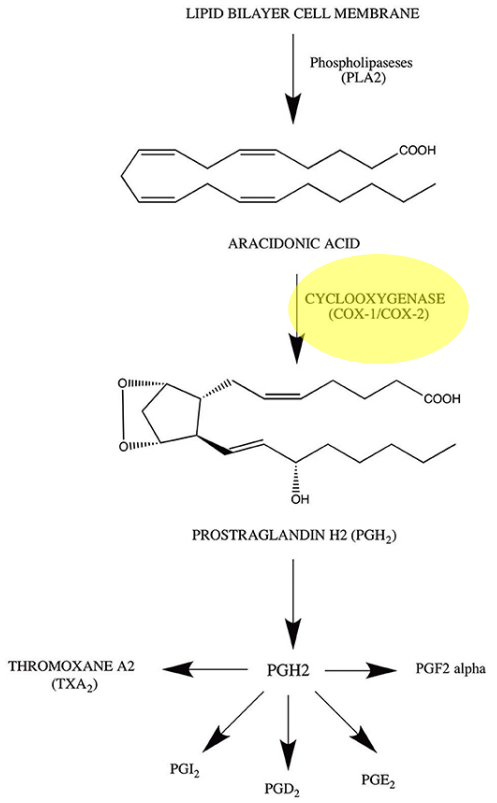
Sundahl *et al.* (2015) Pharm. Ther. 152:28

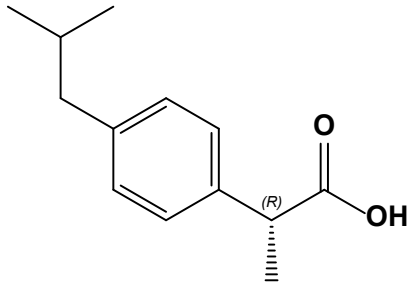


Cortisone

Non-steroidal ant-inflammatory drugs NSAIDs

- Aspirin/Ibuprofen/Indomethacin (Pre-1970s)
  - Anti-inflammatory, but limited by GI side effects
- Mechanism identified by John Vane (1970s)
- COX1 and COX2 (1988)
  - COX1: housekeeper/constitutive
  - COX2: inducible, pro-inflammatory
  - Go for COX-2 selective!
- Vioxx – first COX-2 selective
  - Increase cardiac AEs
  - Withdrawn from market
- Roles of COX-1 and 2
  - Further research
- Protection of gastric damage
  - NO-NSAIDs
  - Local NO delivery

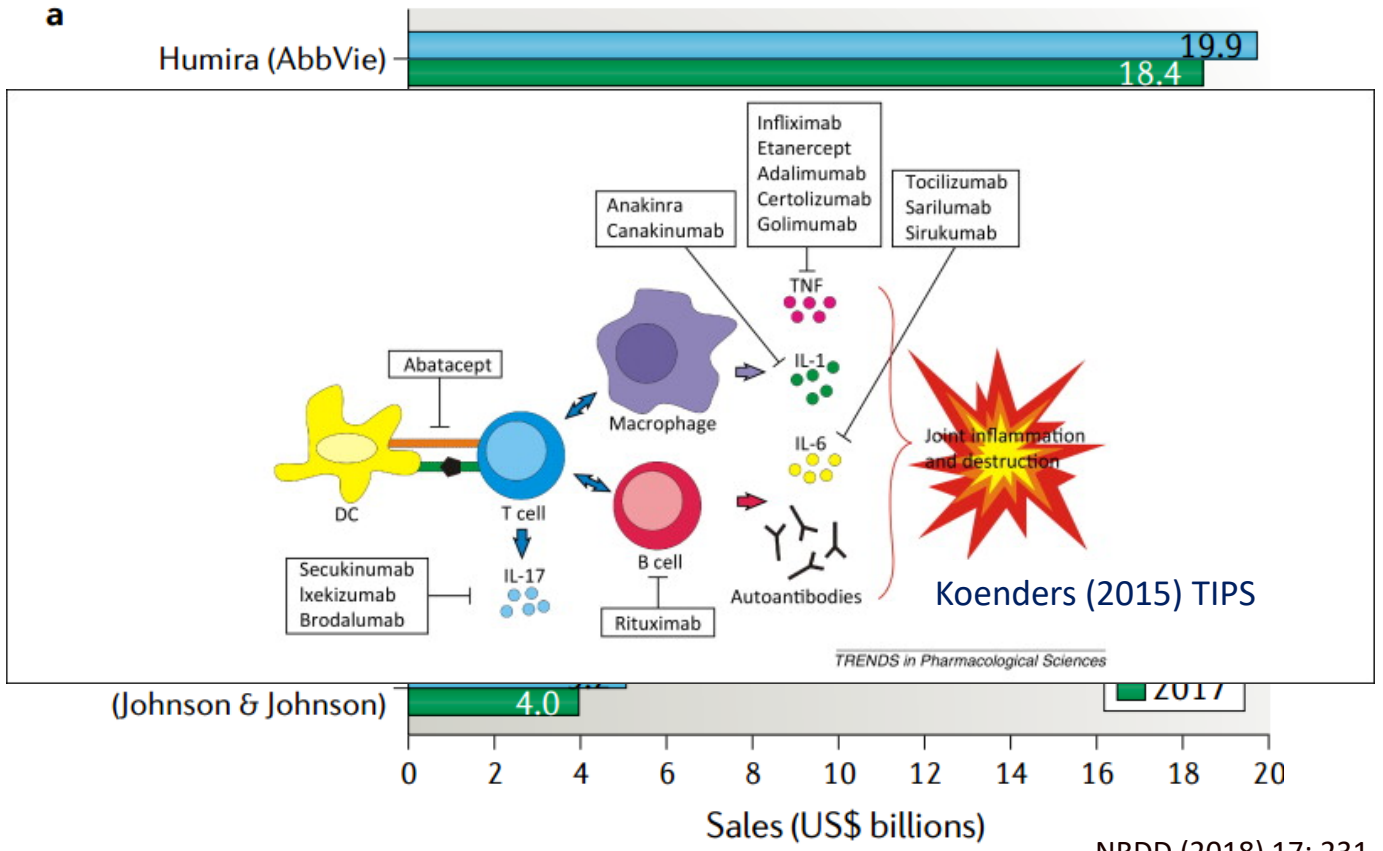




Ibuprofen

Anti-Cytokine Biologicals

- Auto-immune disease therapies
  - Driven by increase in disease understanding
  - Biological drug capability
- Key cytokine inhibition
  - Highly efficacious
  - Multiple targets
  - Now top selling drugs
- Still room for improvement
  - Confounded by complex disease polygenetics and environment factors
  - Patient response rates roughly…..
    - 1/3 respond
    - 1/3 don't respond
    - 1/3 respond then lose efficacy
  - Infection and malignancy due to chronic use

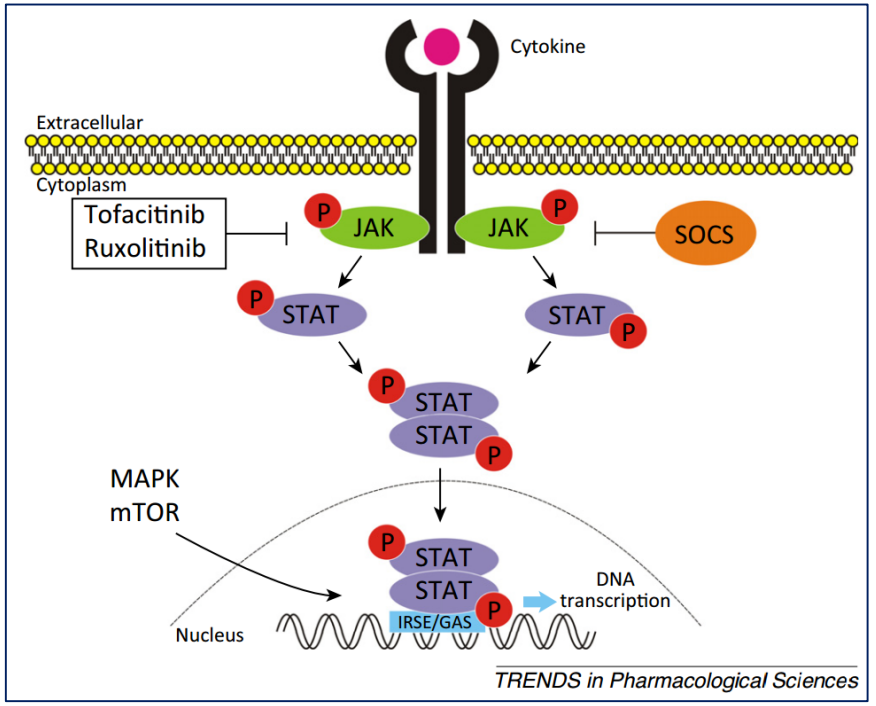


Koenders (2015) TIPS

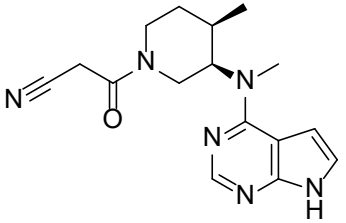
NRDD (2018) 17: 231

JAK Kinase Inhibitors

- 4 JAK kinases
  - JAK1, 2, 3 and Tyk2
- Key players in major cytokine signalling pathways
  - Pathogenic Th17 → IL-17/IL-23
- Tofacitinib – Pan JAK inhibitor
  - Efficacious, but CV AEs via JAK 2 (EPO)
- Push for more selectivity
  - Phase II – Filgotinib – JAK 1 selective
  - Decernotinib - JAK 3 selective
- Similar efficacy and adverse effects to anti-TNFα
- JAK selectivity profile v. efficacy relationship still remains to be defined



Khan (2016) Immunopharmacology. 93



Tofacitnib(2017)

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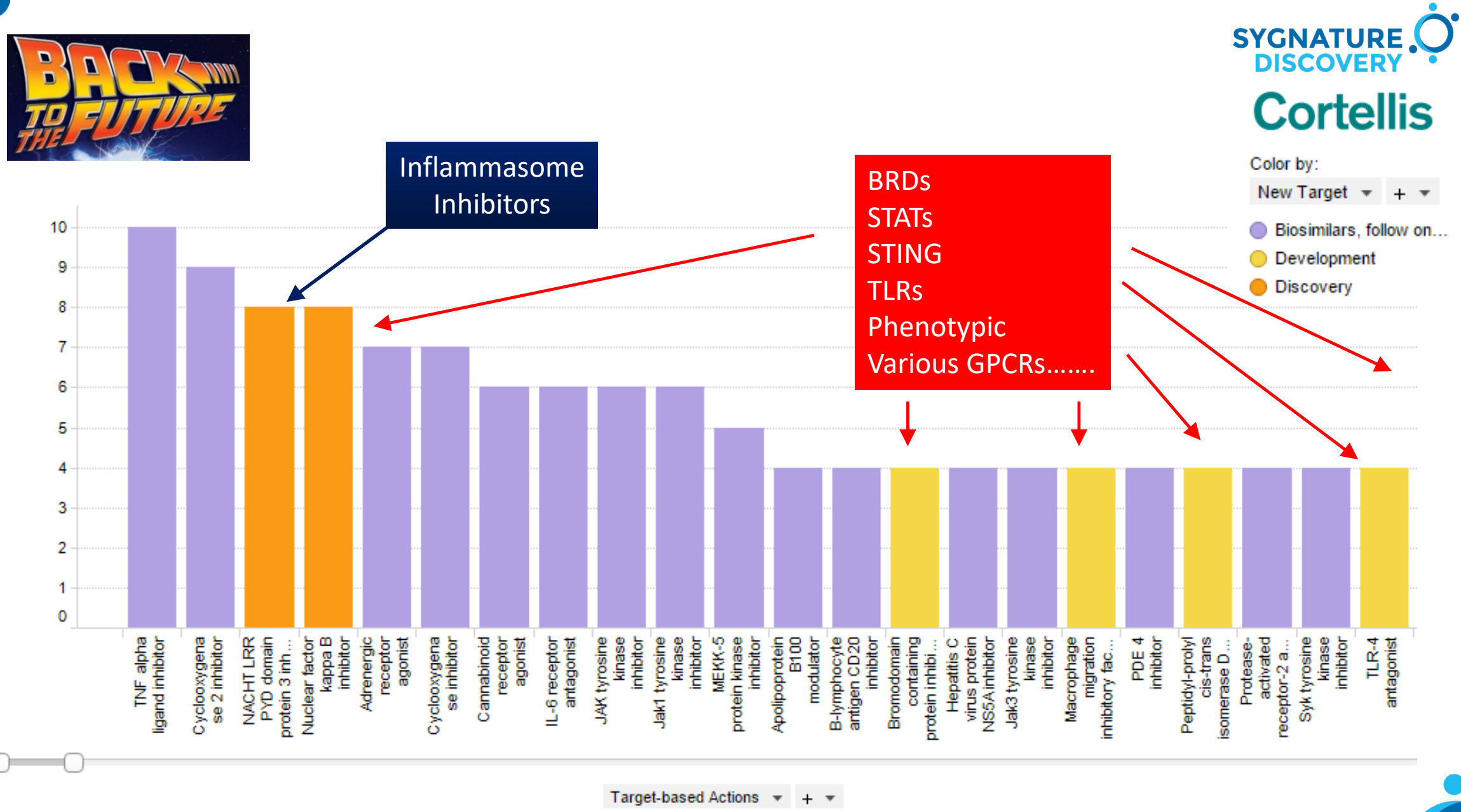
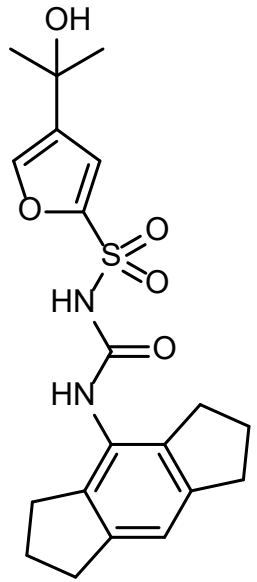

BACK TO THE FUTURE
SYGNATURE DISCOVERY
Cortellis
Inflammasome Inhibitors
BRDs
STATs
STING
TLRs
Phenotypic
Various GPCRs…….
Color by:
New Target
Biosimilars, follow on…
Development
Discovery
UniqueCount(Drug Name)
10
9
8
7
6
5
4
3
2
1
0
TNF alpha ligand inhibitor
Cyclooxygenase 2 inhibitor
NACHT LRR PYD domain protein 3 inh…
Nuclear factor kappa B inhibitor
Adrenergic receptor agonist
Cyclooxygenase inhibitor
Cannabinoid receptor agonist
IL-6 receptor antagonist
JAK tyrosine kinase inhibitor
Jak1 tyrosine kinase inhibitor
MEKK-5 protein kinase inhibitor
Apolipoprotein B100 modulator
B-lymphocyte antigen CD20 inhibitor
Bromodomain containing protein inhibi…
Hepatitis C virus protein NS5A inhibitor
Jak3 tyrosine kinase inhibitor
Macrophage migration inhibitory fac…
PDE 4 inhibitor
Peptidyl-prolyl cis-trans isomerase D…
Protease-activated receptor-2 a…
Syk tyrosine kinase inhibitor
TLR-4 antagonist
Target-based Actions

Inflammasome Inhibitors

- Family of intracellular multiprotein complexes
  - Makes pro-inflammatory IL-1/IL-18
  - Activated by non-infectious agents
    - Less risk of infection (c.f. other anti-cytokines)
  - Supported by human monogenetic diseases
- Pfizer 1990s
  - CP-456773 (from phenotypic hit)
  - Inflammasome (2015)
- Canakinumab → IL-1 inhibition
  - Clinical cancer and CV benefit
  - Multiple indications
- New target with broad application



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Glutathione *S*-Transferase Omega 1-1 Is a Target of Cytokine Release Inhibitory Drugs and May Be Responsible for Their Effect on Interleukin-1β Posttranslational Processing*

Received for publication, November 13, 2002, and in revised form, February 24, 2003
Published, JBC Papers in Press, March 6, 2003, DOI 10.1074/jbc.M211596200

Ronald E. Laliberte, David G. Perregaux, Lise R. Hoth, Philip J. Rosner, Crystal K. Jordan, Kevin M. Peese, James. F. Eggler, Mark A. Dombroski, Kieran F. Geoghegan, and Christopher A. Gabel‡

From the Departments of Antibacterials, Immunology and Inflammation, and Exploratory Medicinal Sciences, Pfizer Global Research and Development, Pfizer, Inc., Groton, Connecticut 06340

nature medicine

A small-molecule inhibitor of the NLRP3 inflammasome for the treatment of inflammatory diseases

Rebecca C Coll[1,2], Avril A B Robertson[2], Jae Jin Chae[3], Sarah C Higgins[1], Raúl Muñoz-Planillo[4], Marco C Inserra[2,5], Irina Vetter[2,5], Lara S Dungan[1], Brian G Monks[6], Andrea Stutz[6], Daniel E Croker[2], Mark S Butler[2], Moritz Haneklaus[1], Caroline E Sutton[1], Gabriel Núñez[4], Eicke Latz[6–8], Daniel L Kastner[3], Kingston H G Mills[1], Seth L Masters[9], Kate Schroder[2], Matthew A Cooper[2] & Luke A J O'Neill[1]

Nature Reviews Drug Discovery | Published online 29 Sep 2017; doi:10.1038/nrd.2017.186

Anti-inflammatory drug cuts risk of heart disease — and cancer

Results from Novartis's huge trial of the interleukin-1β blocker canakinumab could revitalize efforts to target inflammation in atherosclerosis, and have demonstrated unanticipated activity in lung cancer.

Inflammasome Inhibitors

Jecure THERAPEUTICS 2016

Genentech A Member of the Roche Group

Jecure THERAPEUTICS 2018

IFM THERAPEUTICS 2016

NOVARTIS

IFM THERAPEUTICS 2019

INFLAZOME 2016

idera

gsk

Clinical safety and efficacy?

Other inflammasomes & disease indications?

IFM Quatro

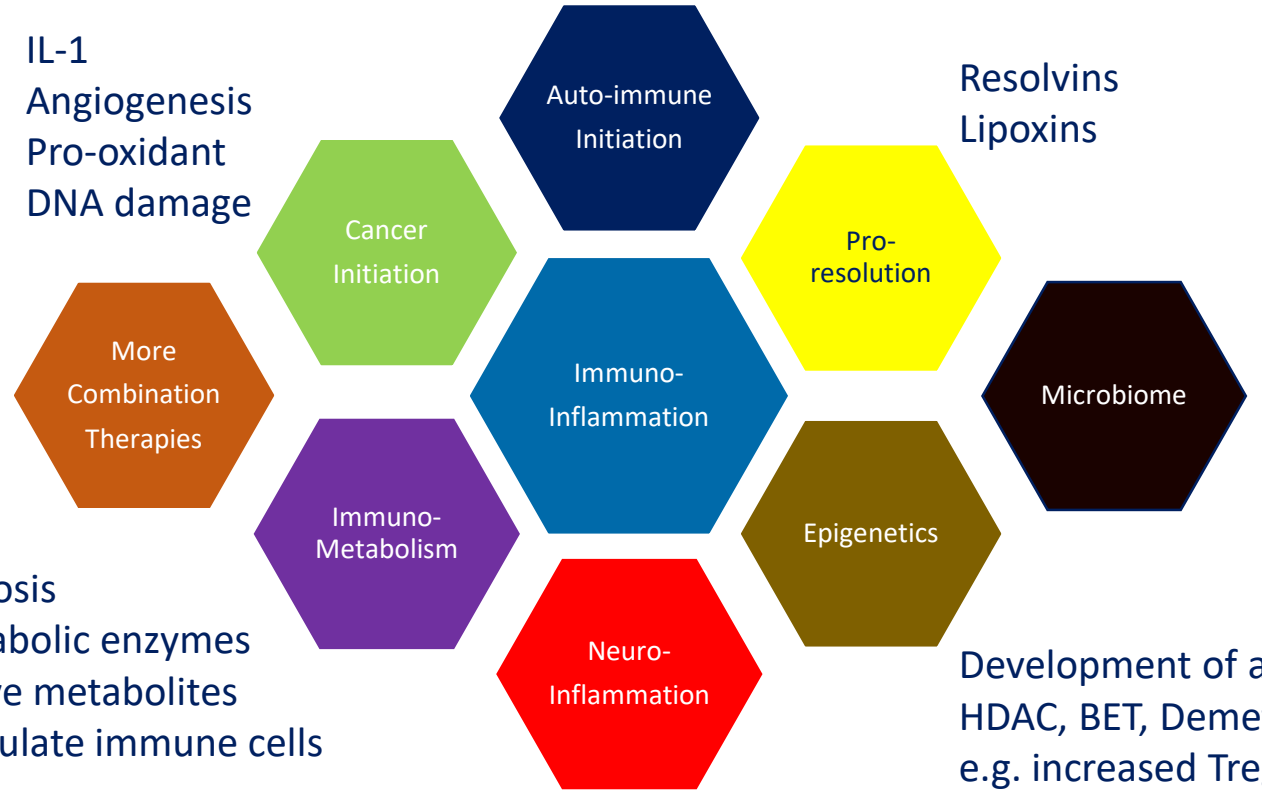
Challenges

- Current therapies are highly effective
  - BUT need continuous use and have increased risk of malignancy/infection
- Can we cure and/or prevent autoimmune diseases?
  - What initiates autoimmune disease?
    - Most current drugs target later stage disease and not initiation
  - Predictive biomarkers of onset?
    - Early signals prior to disease symptoms -> early intervention and prevention
- Need to induce remission in all patients
  - Only achieved in a minority at the moment
  - Why do some patients not respond?
    - Need greater understanding of disease heterogeneity
    - Personalised medicines – patient specific

Future

TregTherapeutics

Reset the Treg/Th17 balance
Ex vivo Treg efficacious in AI disease



IL-1
Angiogenesis
Pro-oxidant
DNA damage

Resolvins
Lipoxins

Anti-TNFα
+Synoviocyte
+Angiogenesis

Gut microbiome modulators for IBD
- Pre- and Pro-biotics
- Healthy microbiome

Acidosis
Metabolic enzymes
Active metabolites
Modulate immune cells

Development of autoimmunity
HDAC, BET, Demethylase
e.g. increased Treg generation & function

Microglia
CNS access
Abs → small molecules

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