



Research into the causes of, and treatments for, arthritis

Dr Helen Wright



About me

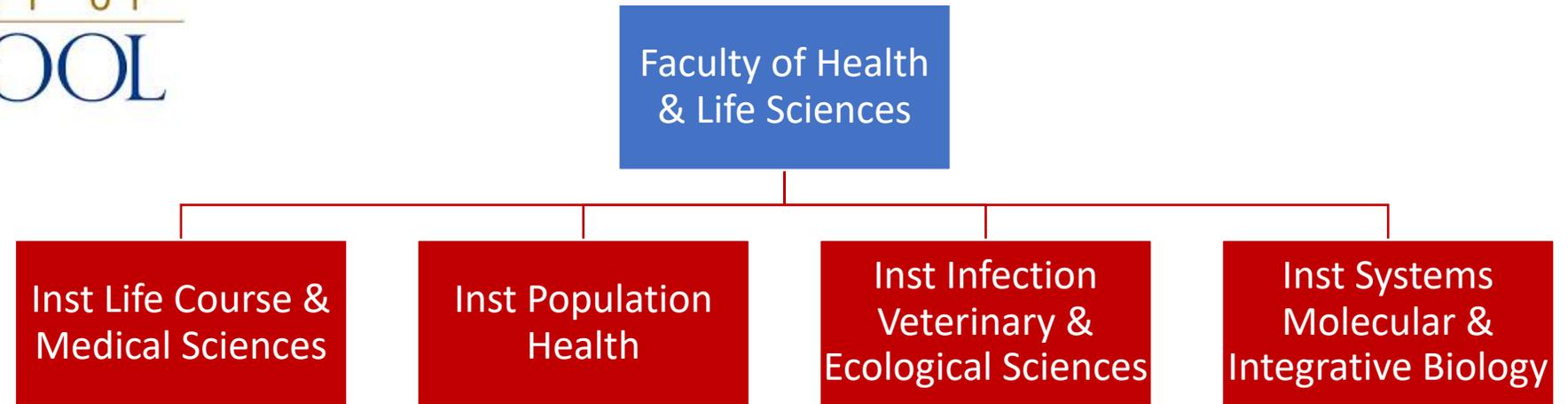
- Research fellow at the University of Liverpool
- My group are interested in immune cell function in health, ageing and disease



UNIVERSITY OF
LIVERPOOL

**VERSUS
ARTHRITIS**





Institute of Life Course and Medical Sciences

- Department of Musculoskeletal & Ageing Science:
“focus on new ways of understanding, treating, and preventing the age-related conditions of skeletal muscle, bone, joints, cartilage, tendons, and ligaments”
- Clinical, scientific and veterinary researchers
- Study arthritis in adults and children



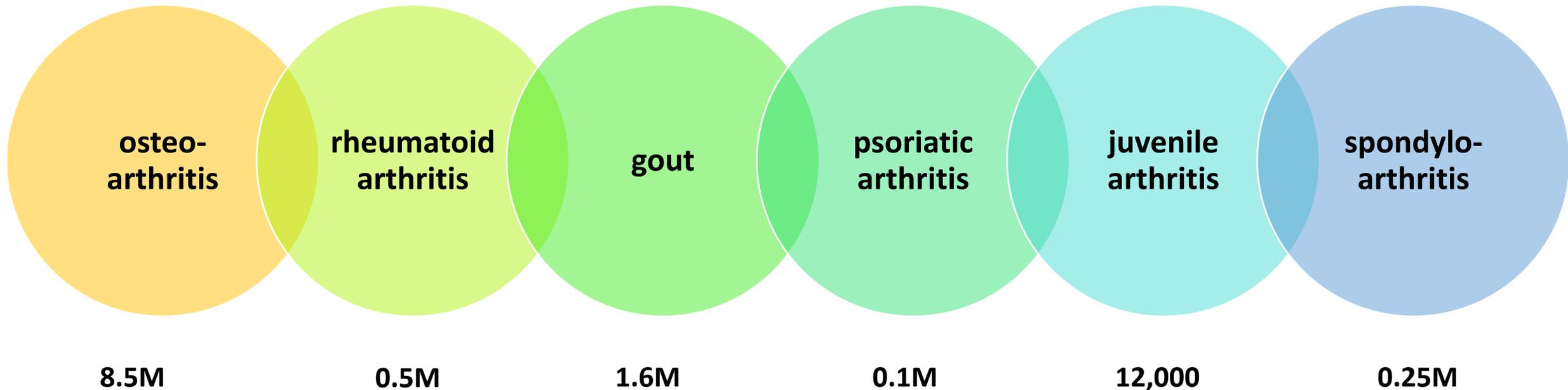
Outline

- Arthritis in the UK in 2022
- Osteoarthritis
 - Underlying biology of OA
 - Treatment options
 - Research into OA in Liverpool
- Rheumatoid arthritis
 - Underlying biology of RA
 - Treatment options
 - Research into RA in Liverpool
- How to get involved in arthritis research

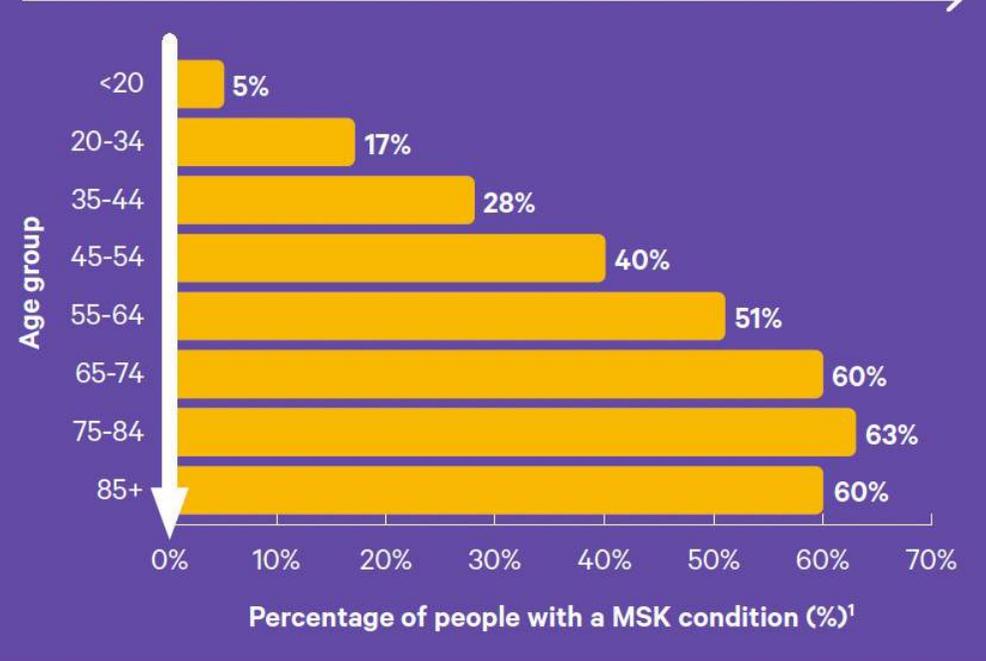
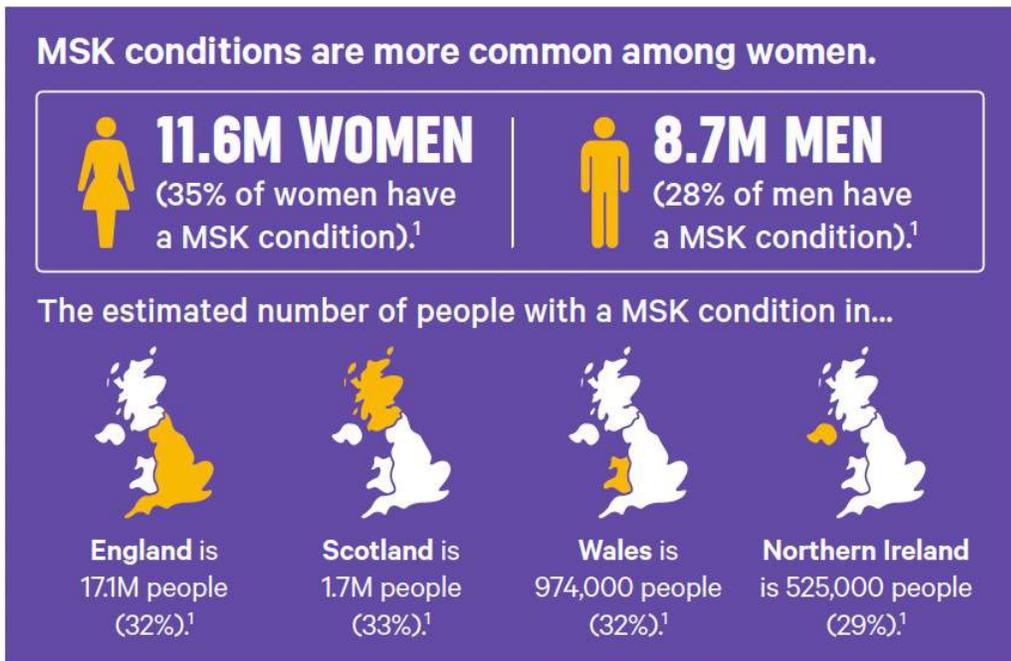
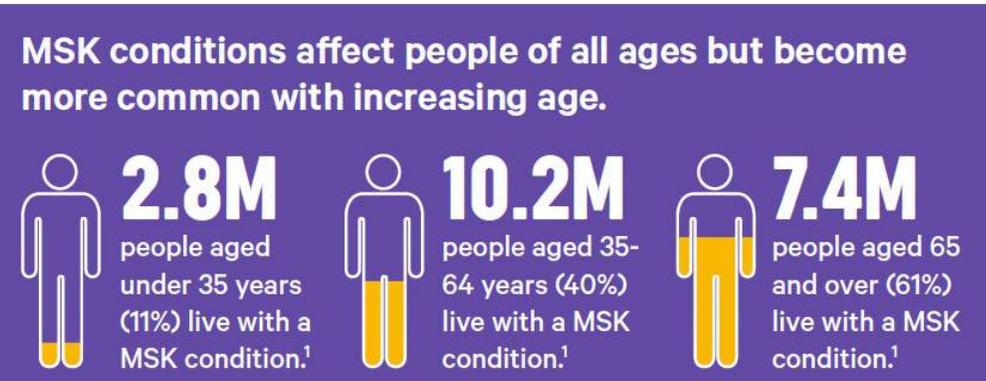


Arthritis in the UK

- Arthritis means pain, swelling and stiffness in a joint or joints
- Lots of different types of arthritis
- Affects over 10 million people in the UK, including children



Arthritis in the UK



07 KEY FACTORS AFFECTING MSK HEALTH

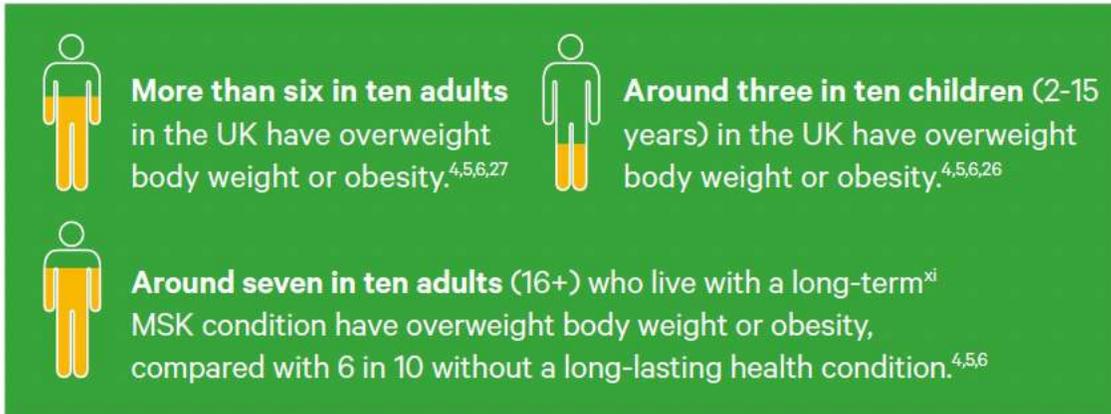
Physical inactivity

Inactive people are at increased risk of developing certain painful MSK conditions.



Obesity

Obesity increases an individual's risk of developing MSK conditions, such as osteoarthritis and back pain. While the development of MSK problems can make it difficult to maintain a healthy weight.



Multiple long-term conditions

The number of people living with two or more long-term conditions (multimorbidity) is growing increasingly common.



WHAT IS THE IMPACT?

MSK CONDITIONS

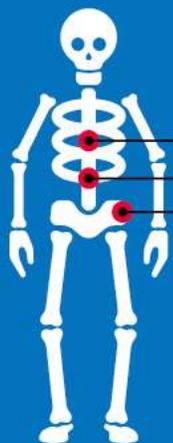


accounted for the third largest area of NHS programme spending at **£5 billion** in 2013-14.⁶⁵

Combined costs from worklessness and sickness absence in the UK amount to around **£100 billion** annually.⁶⁶



The cost of working days lost due to osteoarthritis and rheumatoid arthritis was estimated at **£2.58 billion** in 2017 rising to **£3.43 billion** by 2030.⁶⁸

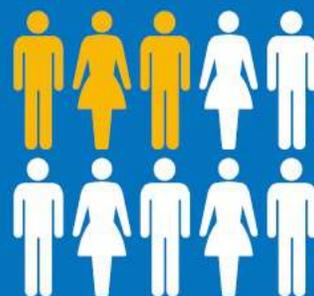


- Conditions such as back pain account for around 40% of all sickness absence in the NHS and costs around **£400 million per year**.⁶⁷
- Back pain cost the UK economy an estimated **£1.6 billion** direct and **£10 billion** indirect costs** in 2000.⁶⁹
- The hospital costs of hip fracture alone are estimated at **£1.1 billion** per year in the UK.⁷⁰

Treating the two most common forms of arthritis (osteoarthritis and rheumatoid arthritis) is estimated to have cost the economy

£10.2 BILLION

in direct costs* to the NHS and wider healthcare system in 2017. Cumulatively the healthcare cost will reach **£118.6 billion** over the next decade.⁶⁸



Nearly **three out of ten** (27%) people with arthritis are not aware of the welfare benefits they are entitled to.⁴⁹

The total work-related costs of axial spondyloarthritis due to early retirement, absenteeism and presenteeism is estimated to be at **£11,943 per person** with axial spondyloarthritis per year.⁷¹

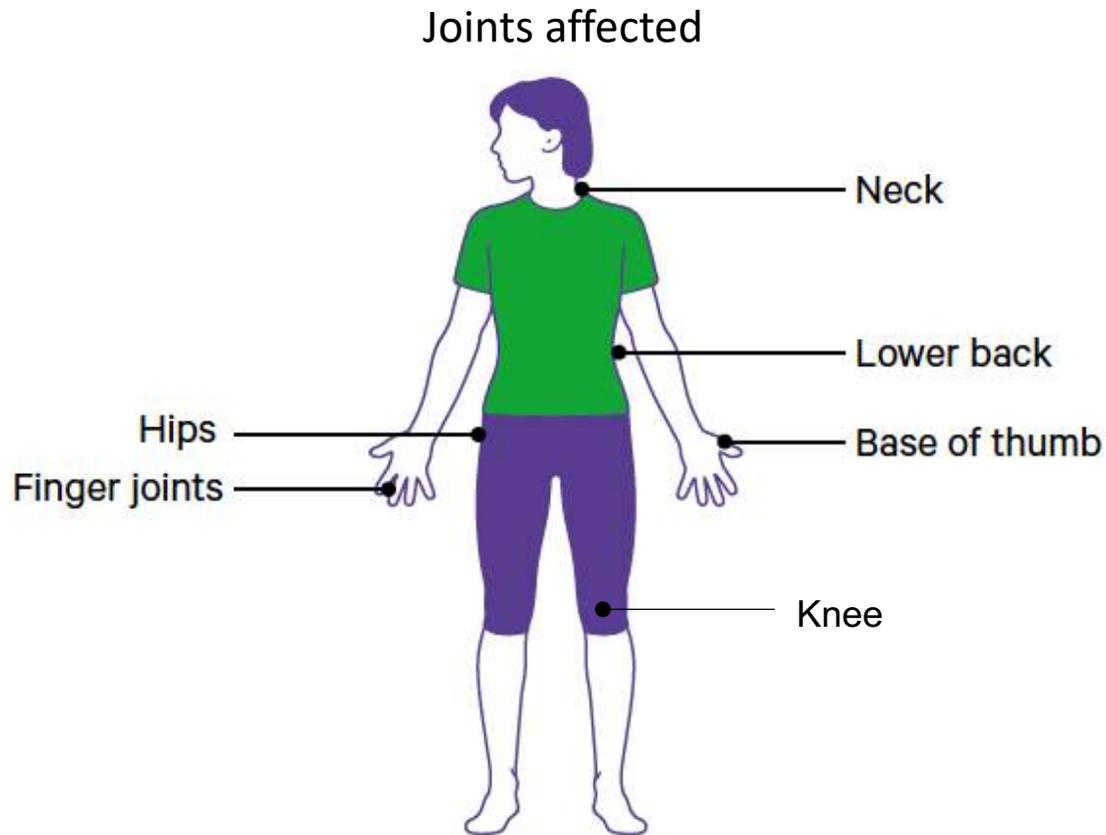
Half (51%) of gross local authority expenditure on adult social care is on people over 65 years, of which a substantial number will have a musculoskeletal condition.⁷²





Osteoarthritis and Rheumatoid Arthritis research at the University of Liverpool

What is Osteoarthritis?



- Pain – typically when moving and worse at the end of the day.
- Stiffness
- Symptoms can vary (i.e. good days, bad days)



How big is the problem?

OA has NO CURE

While treatment can reduce pain,

NO approved drugs prevent OA

NO approved drugs slow progression



- Osteoarthritis affects 8.5 million people over the age of 40 in the UK alone
- Almost 250,000 knee and hip replacements in the UK each year (£10-12K per procedure)
- Huge personal and economic cost
- Treatment limited: pain relief, exercise (to strengthen muscles and tendons supporting the joint) and surgery (joint replacement)

What does a normal joint look like?

Figure 1. A healthy joint

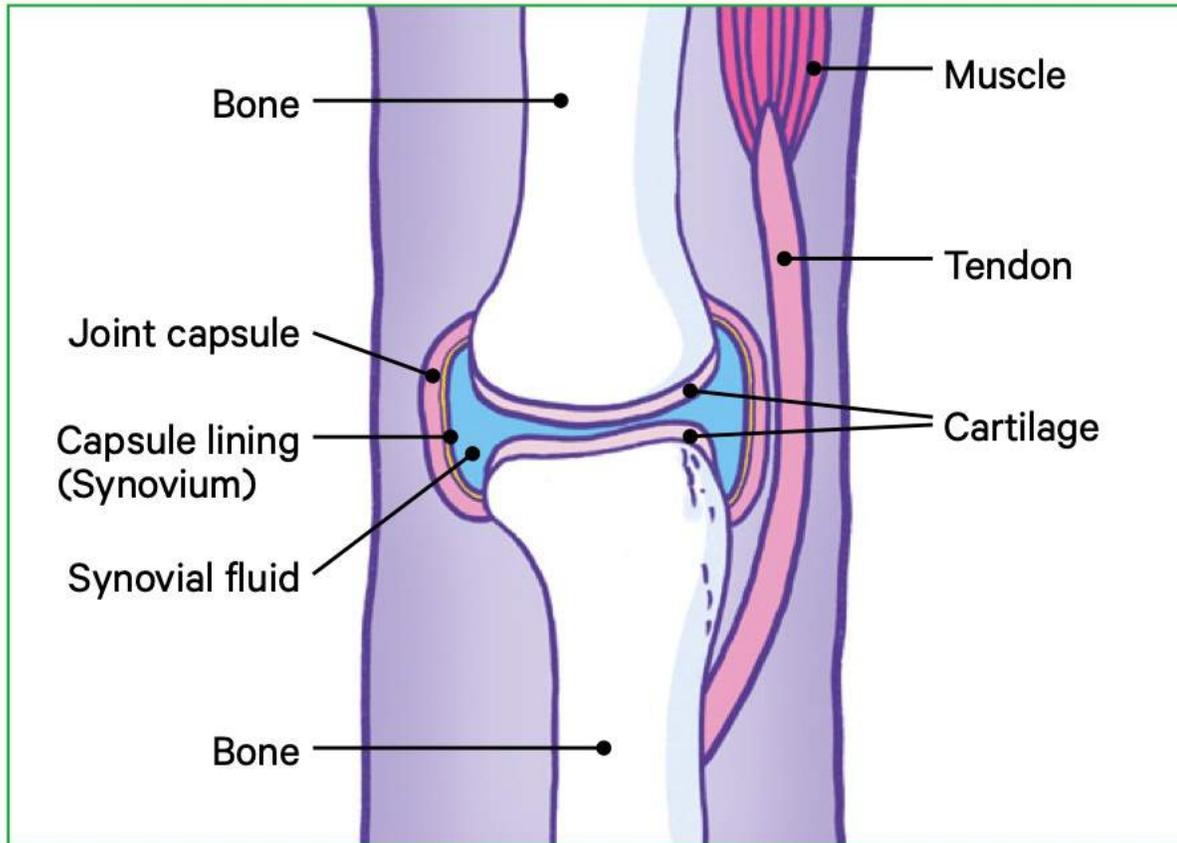
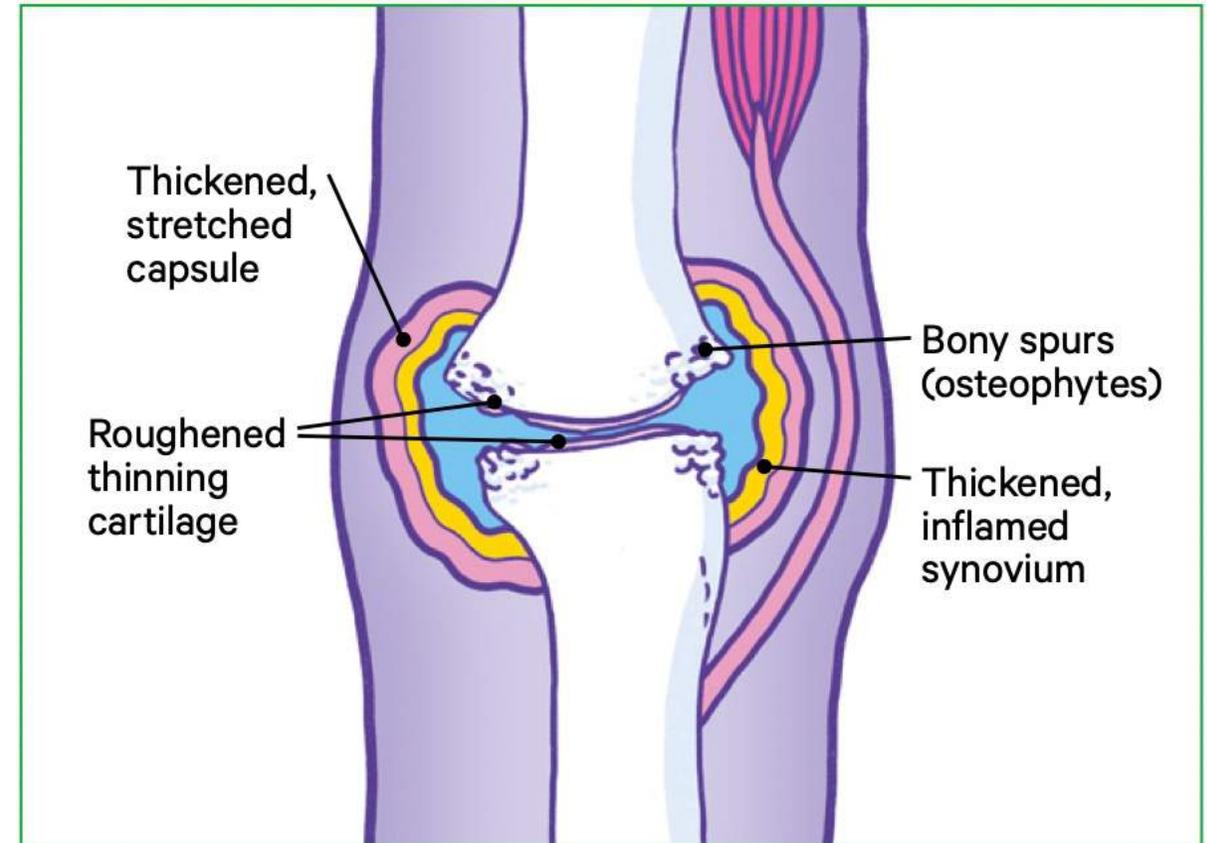


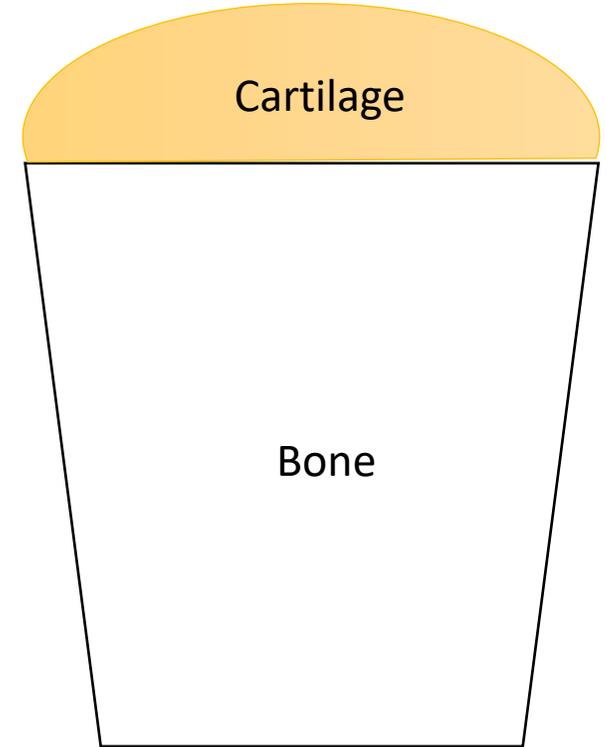
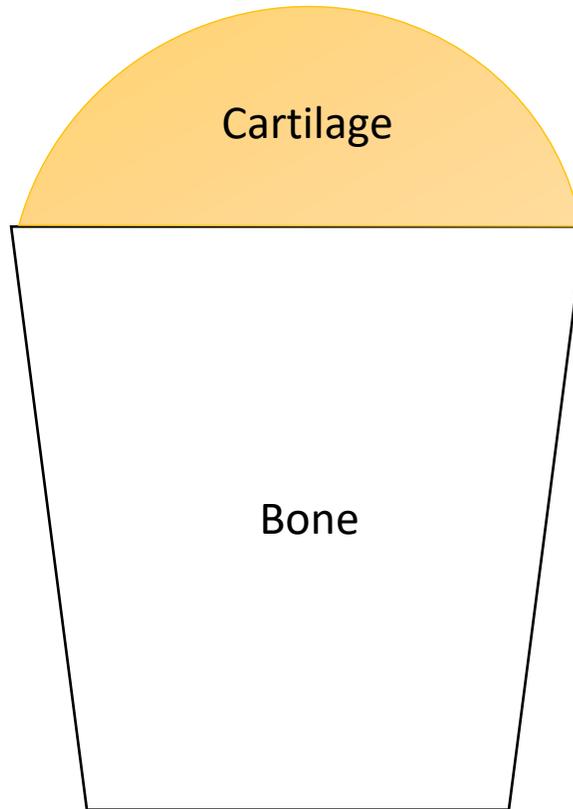
Figure 2. A joint affected by osteoarthritis



Cartilage provides a cushion to protect your joint



Compression on the joint

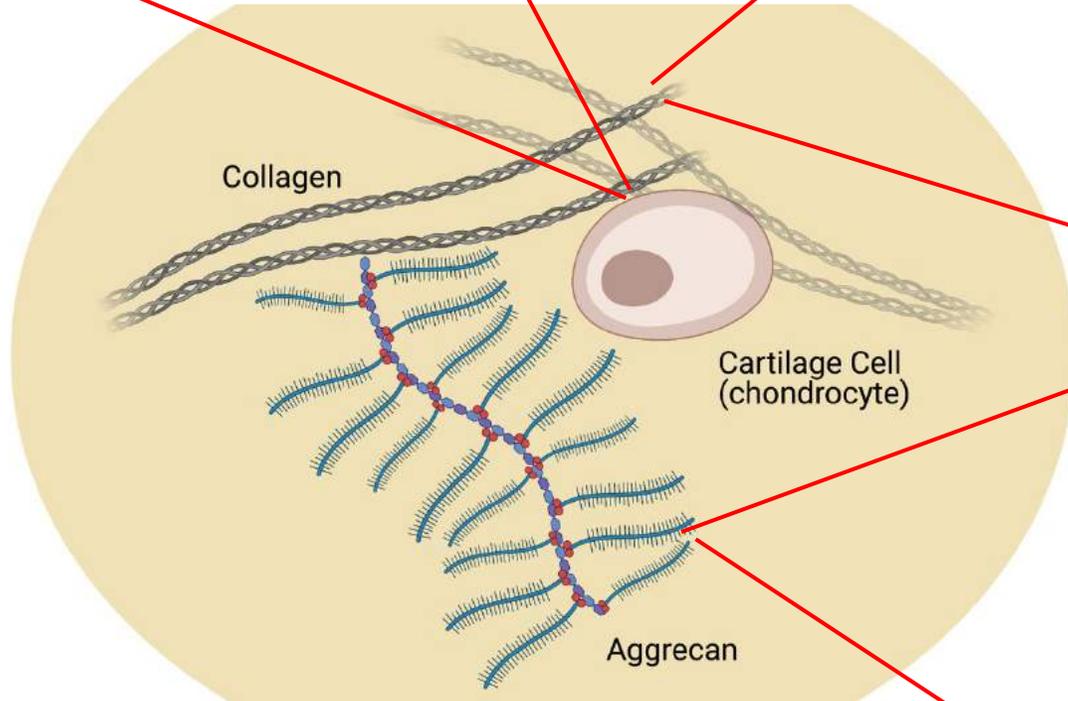




Cartilage cells – known as chondrocytes control what cartilage is made and what is broken down



Collagen – Provides the cartilage with its structure. Very strong and resistant to breakdown.



Aggrecan – Acts like a sponge, by attracting and holding water allowing the cartilage to resist compression

'Wear and Tear'

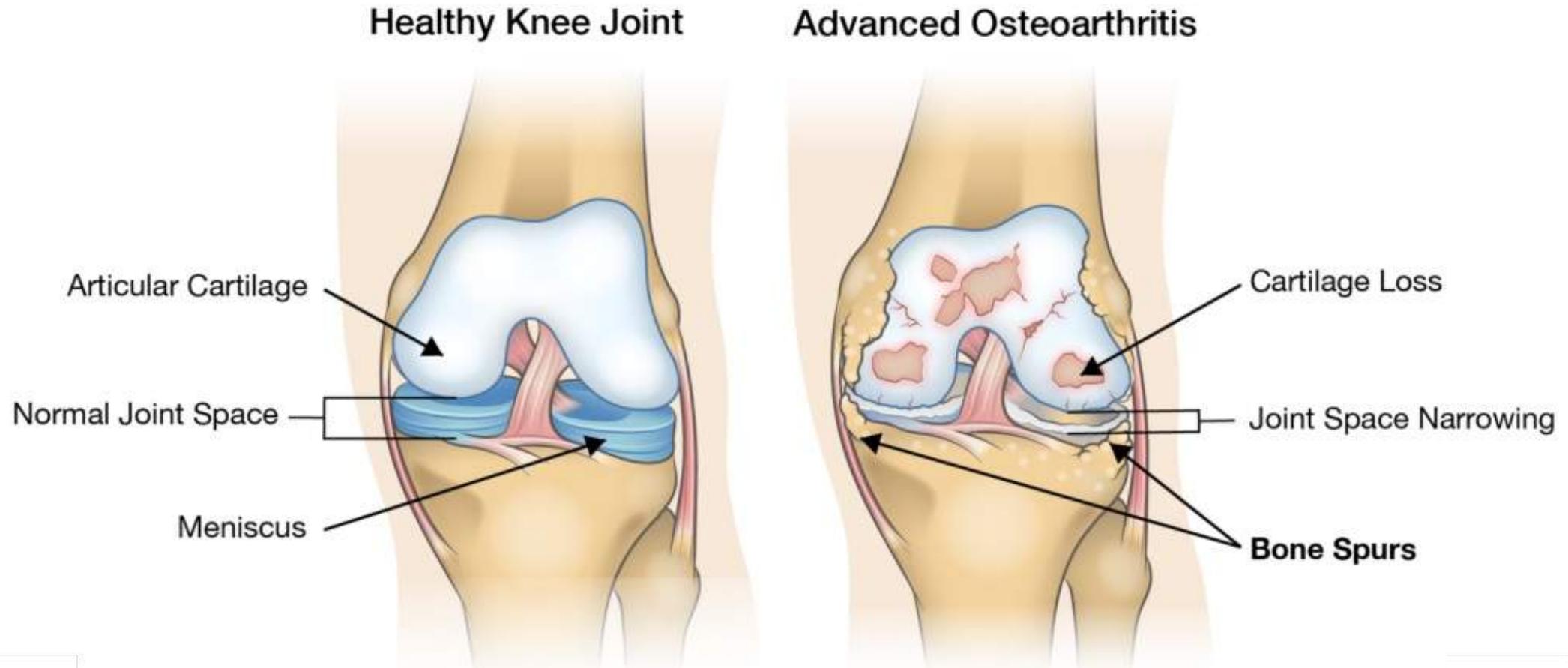
Definition:

- *'Wear and tear is the damage or change that is caused to something when it is being used normally...'*
- *'the damage that happens to an object in ordinary use during a period of time...'*

Osteoarthritis is not just wear and tear!



Cartilage breakdown is central to osteoarthritis

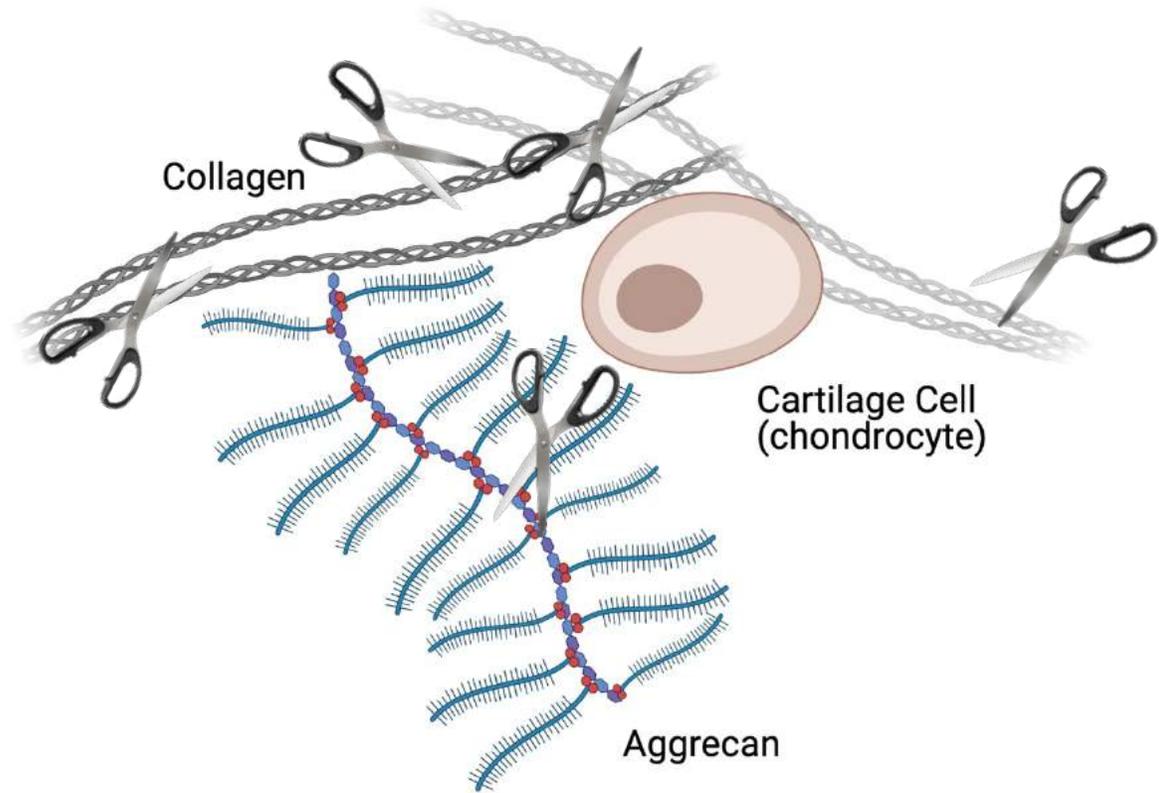


Osteoarthritis is not just wear and tear!

Enzymes called proteinases act like scissors to break the cartilage down in osteoarthritis

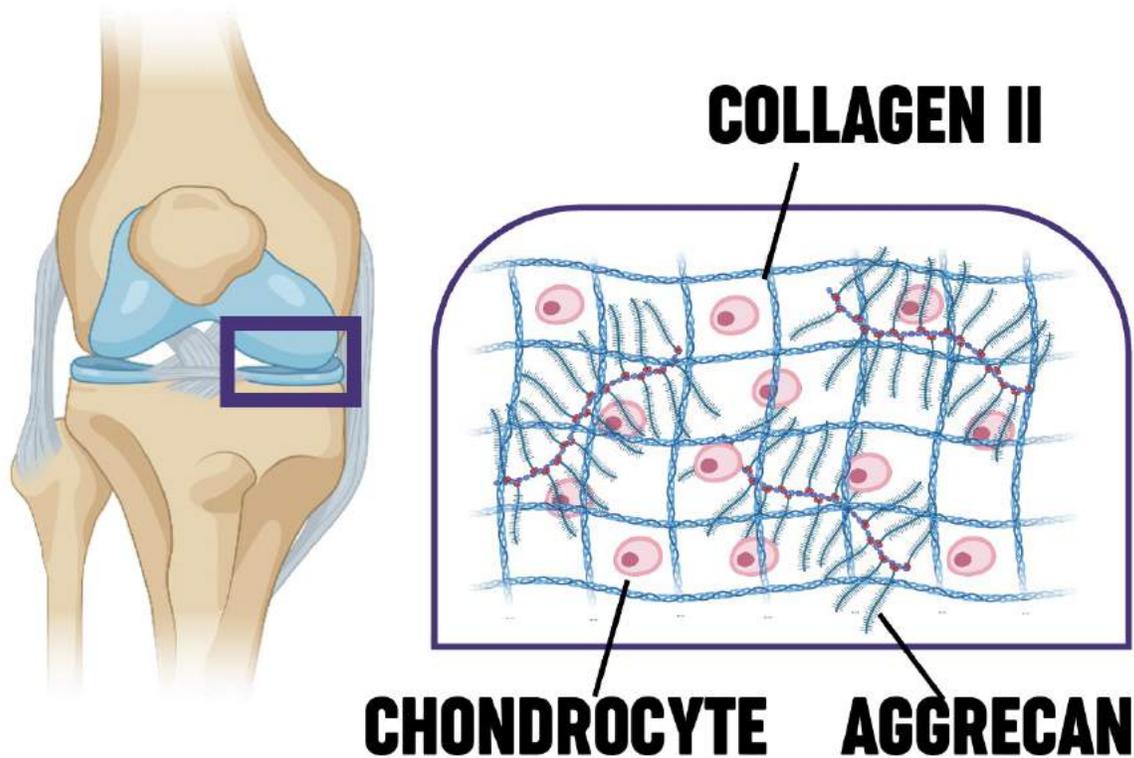


Proteinase = biological scissors

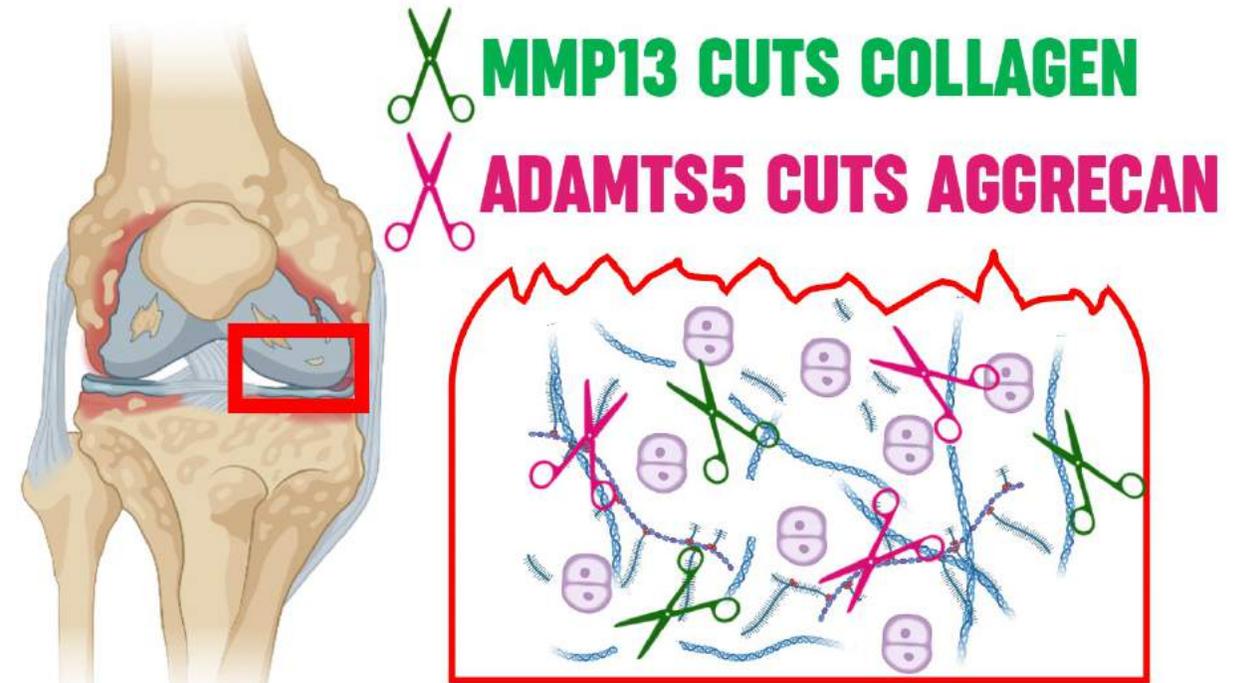


Enzymes called proteinases act like scissors to break the cartilage down in osteoarthritis

HEALTHY NORMAL

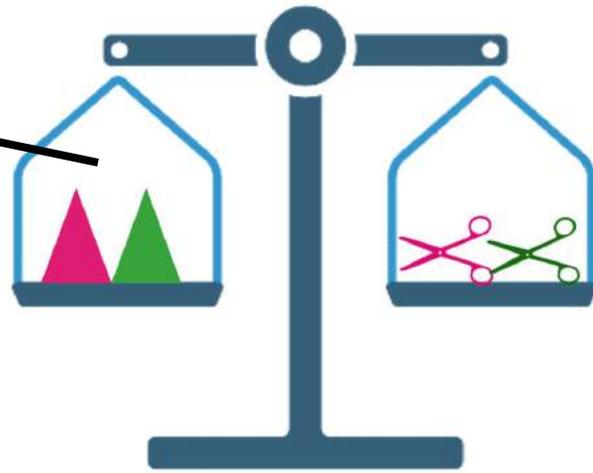


ADVANCED OA



Collagen breakdown is irreversible and should be a priority for therapy

HEALTHY NORMAL



ADVANCED OA



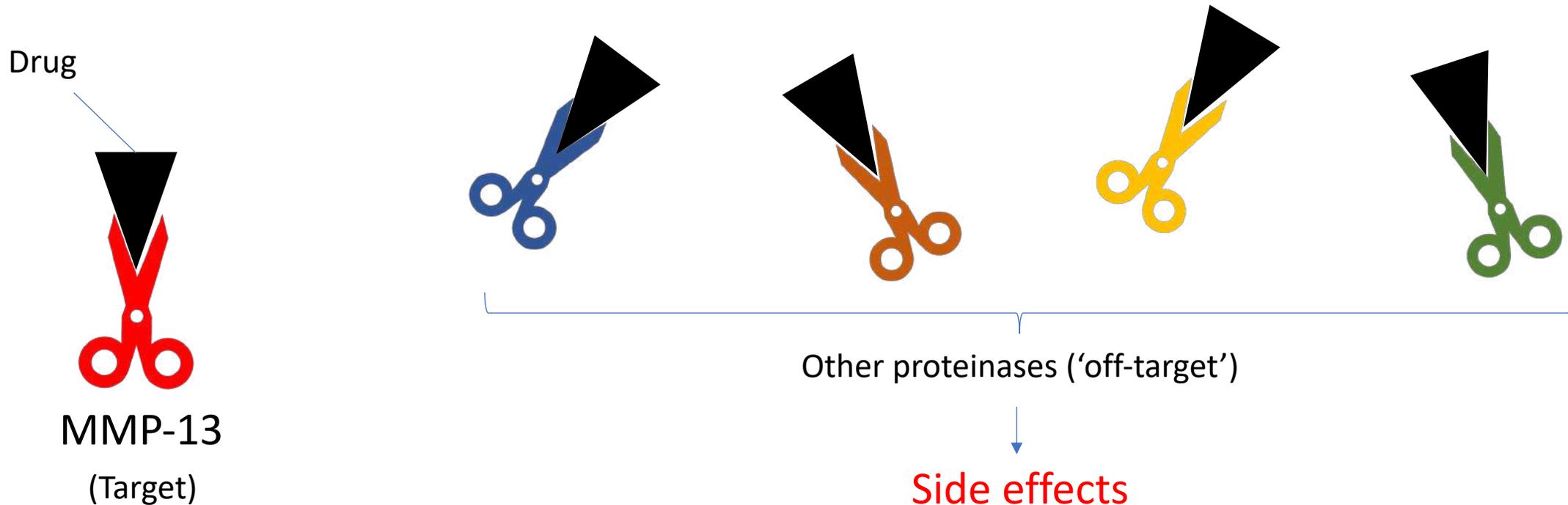
Inhibitors
of scissors

Collagen has a very strong structure and only a few enzymes can break it down – the collagenases

The major collagenase in osteoarthritis is called MMP-13

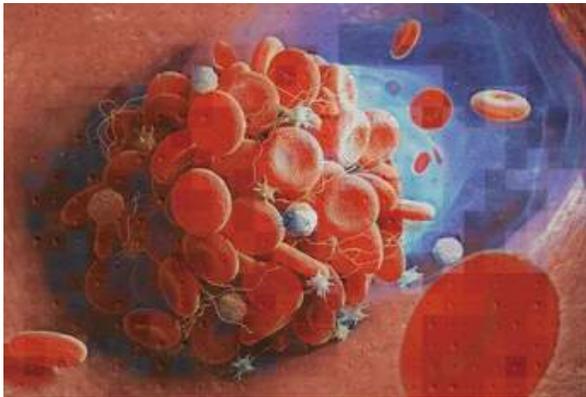
So, what's the problem?

- A great deal of excitement in 1990s that targeting collagenases would stop cartilage breakdown.
- BUT drugs were not selective enough and had side effects!

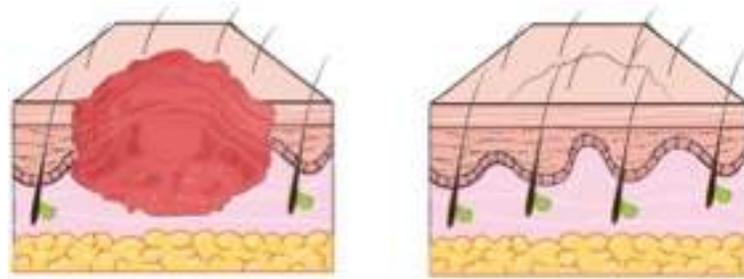


Proteinases have lots of normal jobs!

Blood clotting



Wound healing



Infection and Immunity



This means that we need to be very careful that we are only targeting the right proteinase in the right place!

Research: Proteinases don't work on their own!

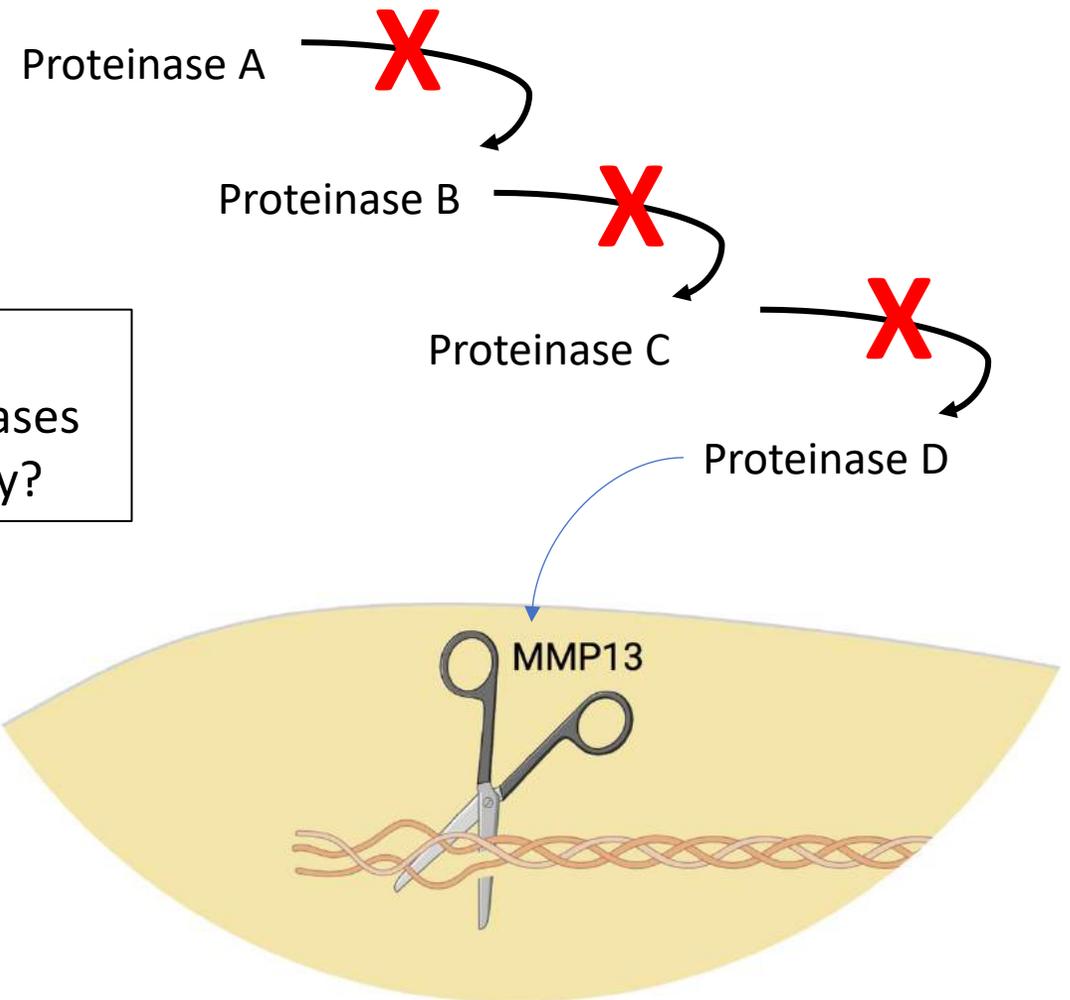
Dr David Wilkinson

Proteinases act like a relay race - they remain inactive until they are activated by another proteinase.

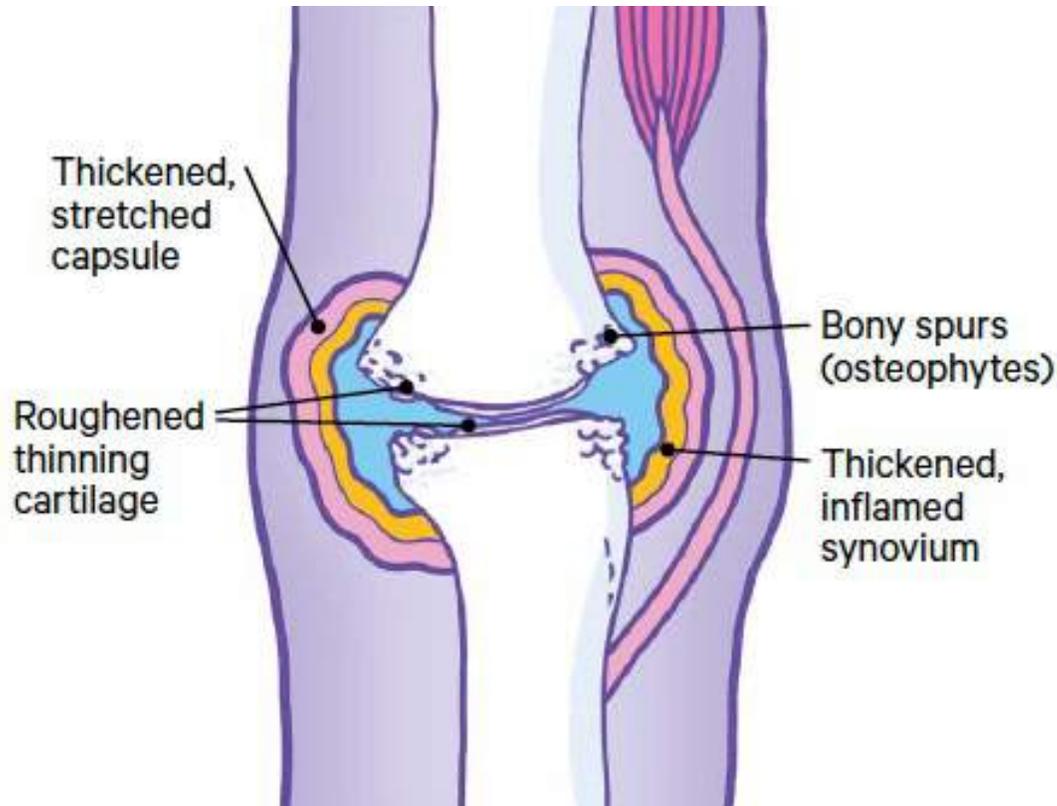


<https://www.liverpool.ac.uk/life-course-and-medical-sciences/staff/david-john-wilkinson/>

Can we target other proteinases in the pathway?



Other than cartilage breakdown, what else can happen in the OA joint?



Botched repair process: new cartilage and bone are made but it builds at the edge of the joint. Causes pain.



Inflammation in the synovium produces 'cytokines' which can make the cartilage cells make more damaging enzymes

Osteoarthritis research in our institute...

- What drives changes in chondrocytes in the development of osteoarthritis?
- What role do the other joint tissues have in osteoarthritis development?
- Can we use stem cells to make new cartilage?
- How does osteoarthritis compare between humans and other animals?
- How are the levels of proteinases controlled by the cartilage cells?

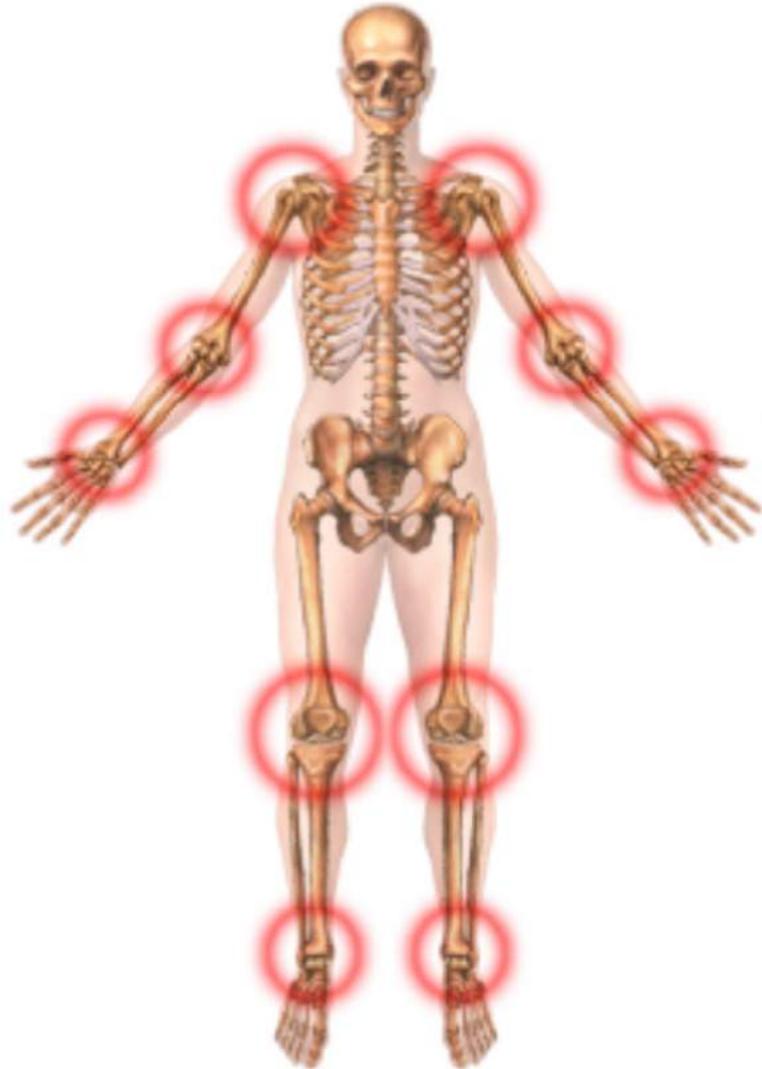


Dr David
Wilkinson



Dr Kazu
Yamamoto

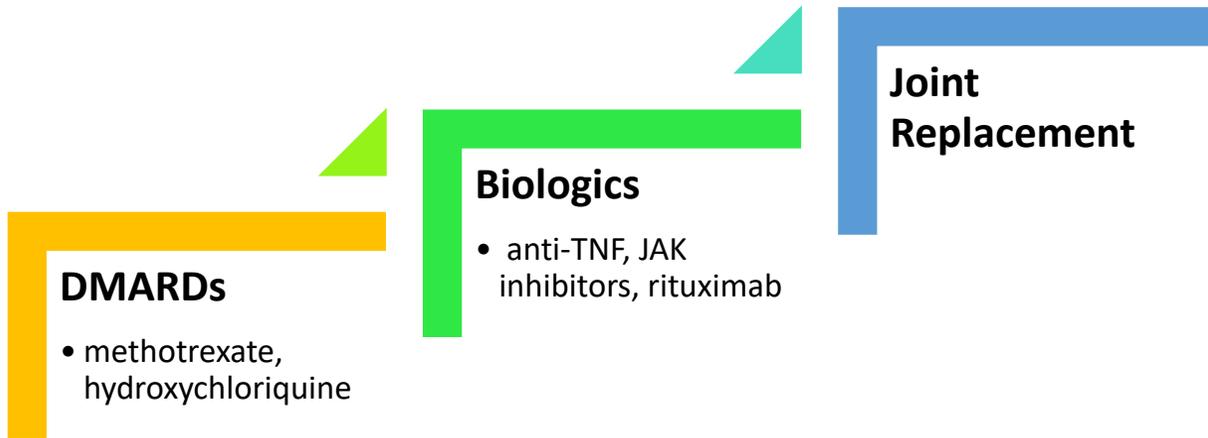
What is rheumatoid arthritis?



- Pain and swelling in joints (symmetrical)
- Stiffness in morning
- Fatigue
- Can lead to joint deformities (erosions)



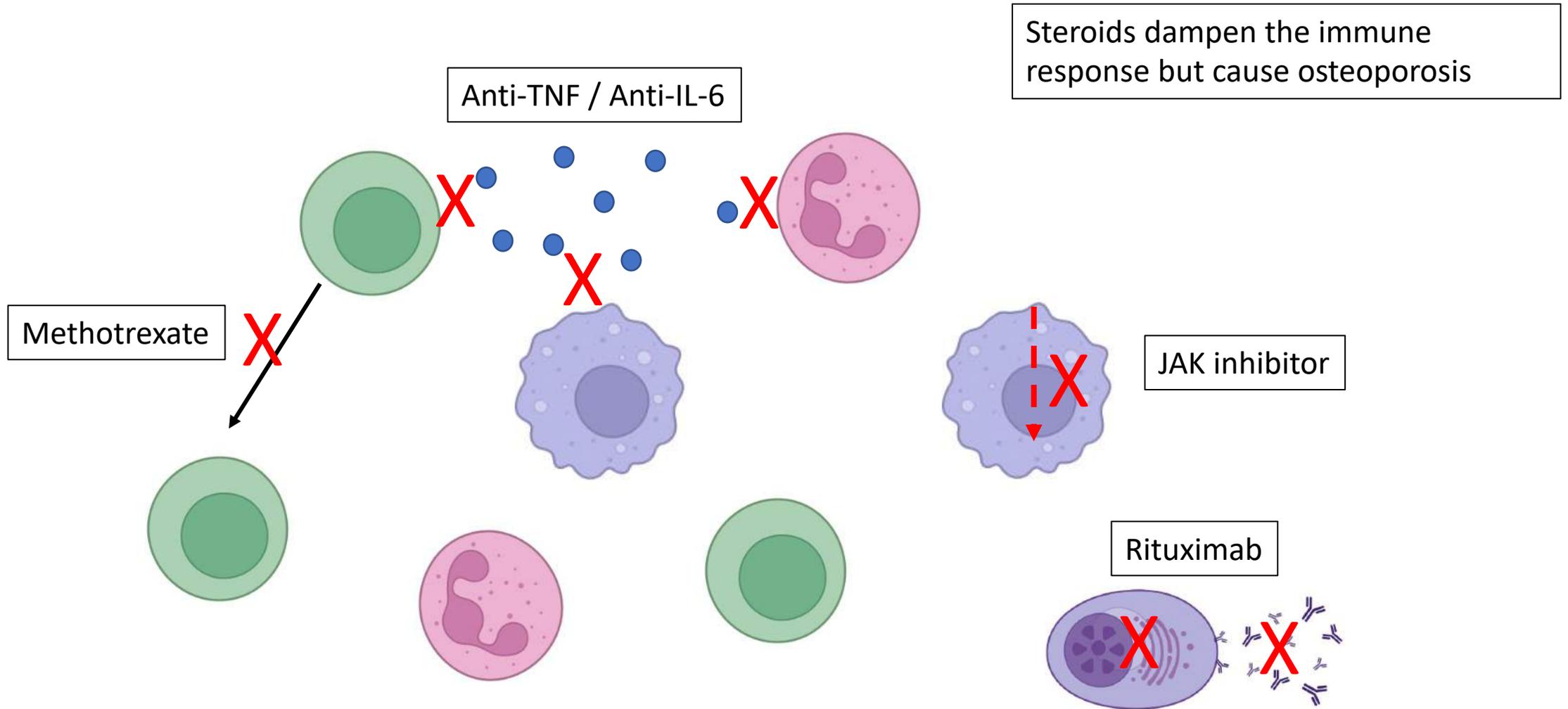
How big is the problem?



Side effects, immuno-suppressants, must “fail” one to step-up to next level

- Rheumatoid arthritis affects 0.5 million people over the age of 18 in the UK alone - affects 3 times more women than men
- Associated with other comorbidities: heart & lung disease, eye disease, osteoporosis
- Huge personal cost to individual and families, can lead to loss of work & permanent disability
- Treatments complex: pain relief, exercise, disease modifying drugs, biologic therapies, surgery (joint replacement)
- **How do we match treatment to patient?**

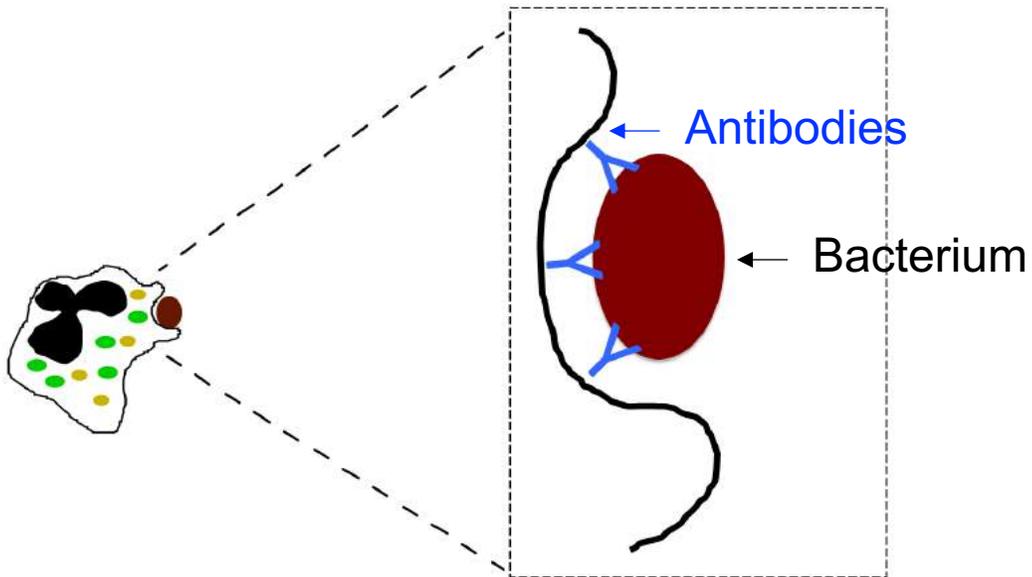
Current treatments for rheumatoid arthritis



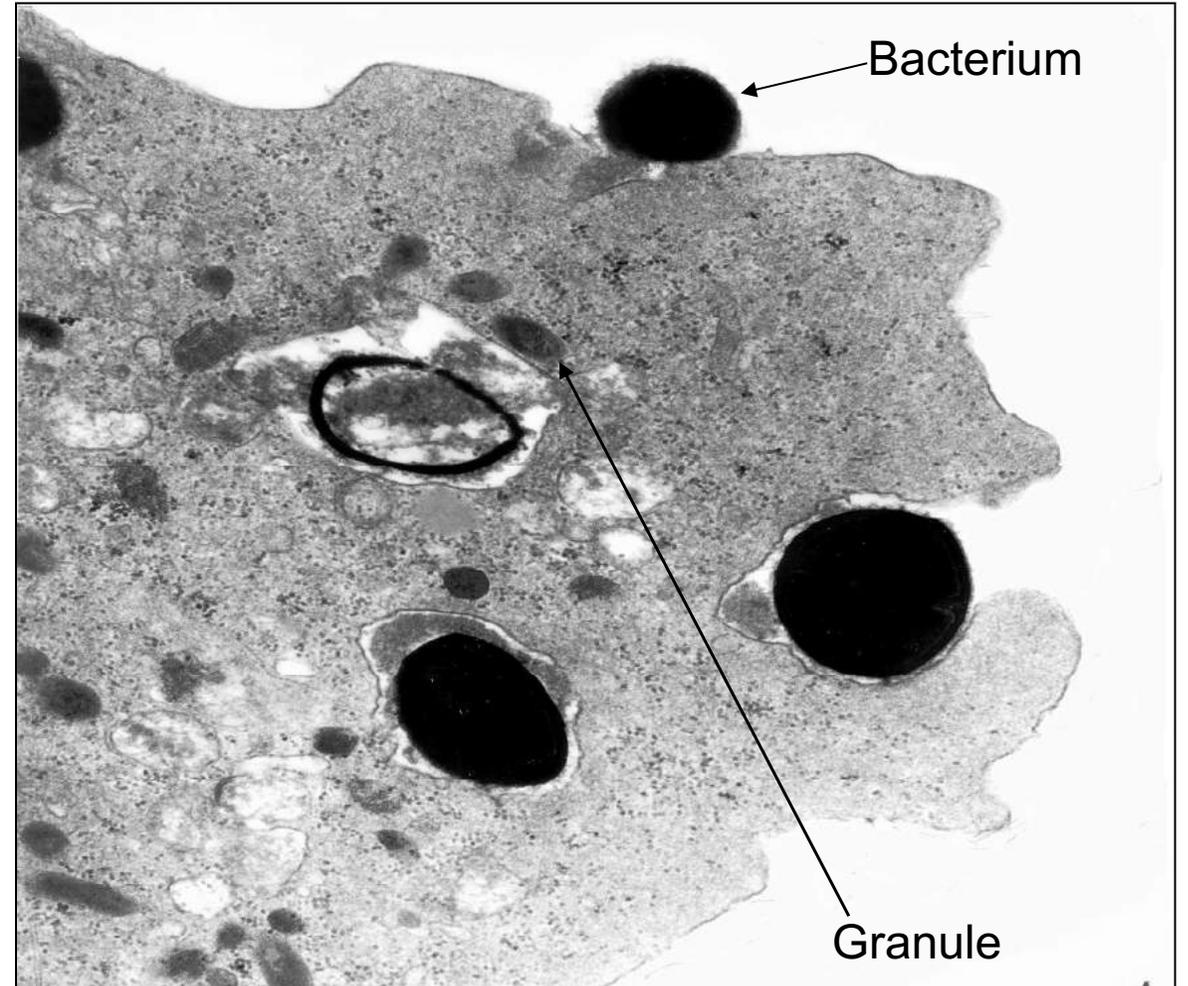
Auto-antibodies cause most forms of rheumatoid arthritis



Antibodies help immune cells recognise and eat micro-organisms



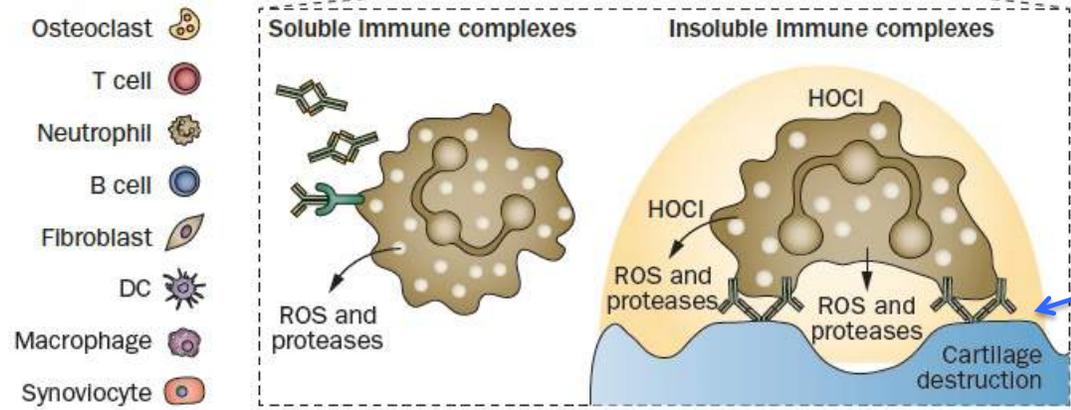
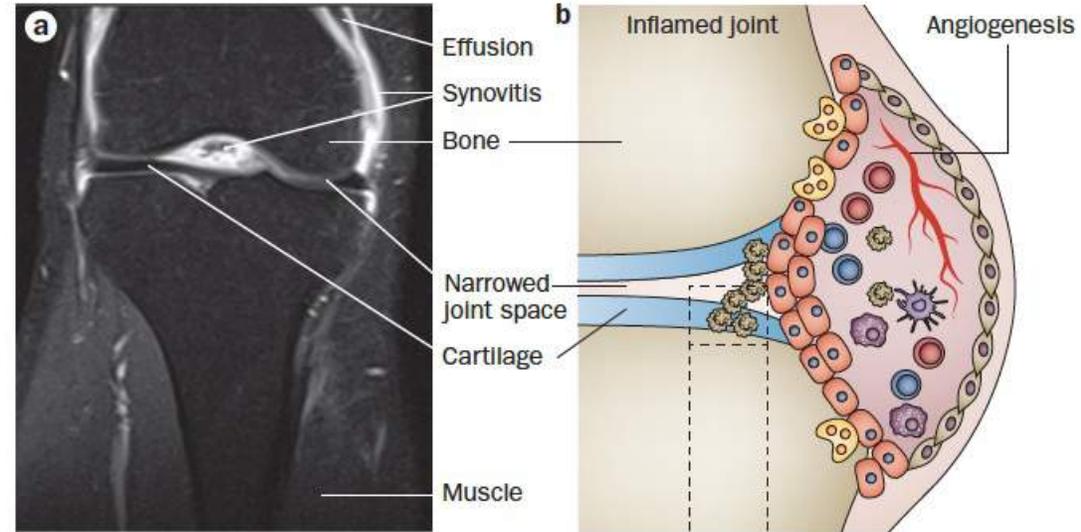
A Neutrophil "eating" bacteria



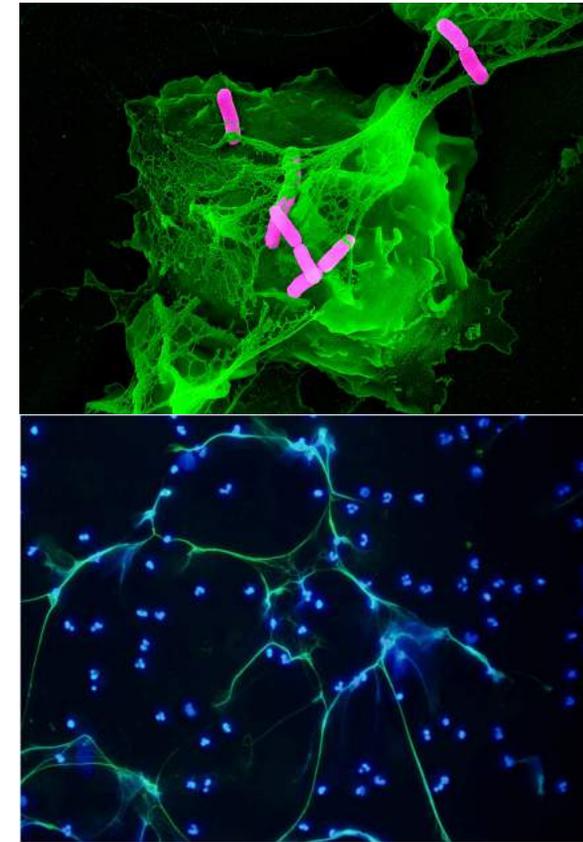
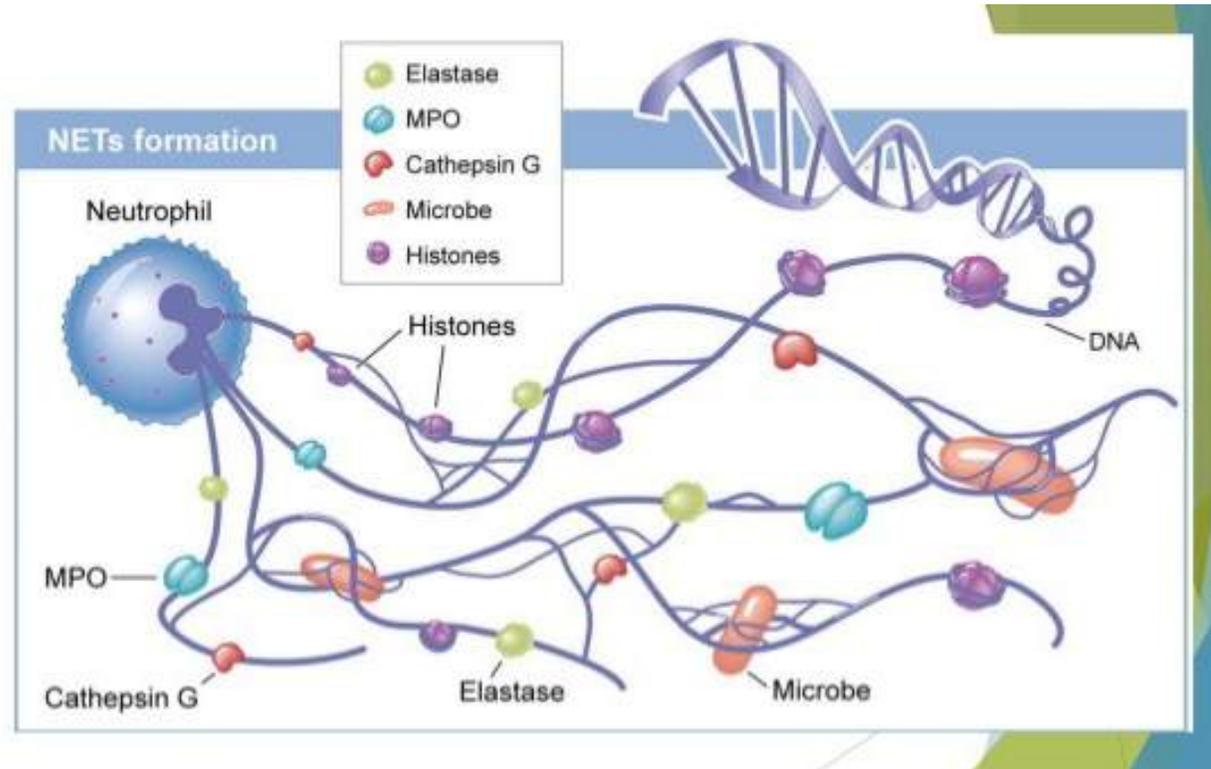
Auto-antibodies cause most forms of rheumatoid arthritis



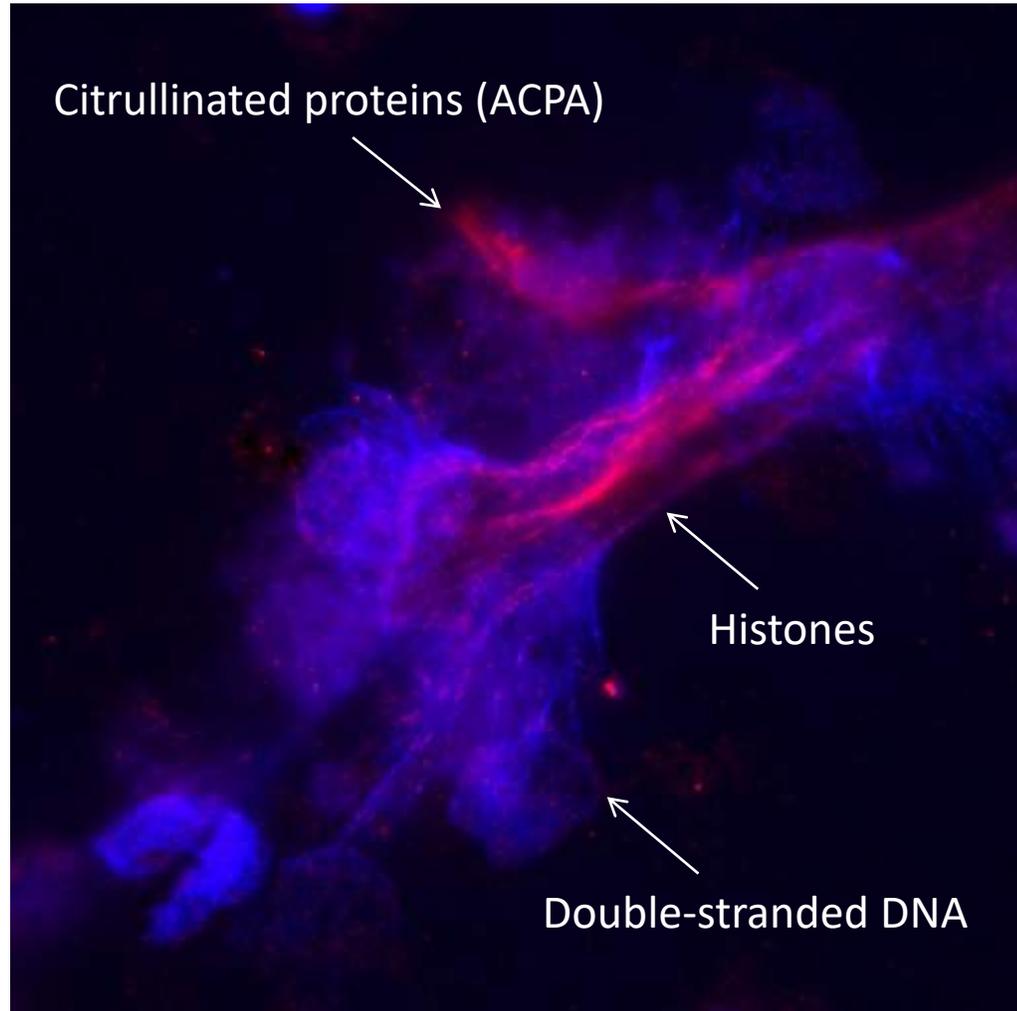
Auto-antibodies misdirect immune cells to attack the joint



What causes auto-antibodies to form? Neutrophil Extracellular Traps?



Evidence for NETs causing auto-antibodies



Patients with rheumatoid arthritis have auto-antibodies to citrullinated proteins (ACPA, anti-CCP)

Patients with another auto-immune disease called lupus have auto-antibodies to double-stranded DNA, histones and other proteins

These are all present in NETs

Auto-antibodies are the “molecular bridge” that cause the immune system to attack the body

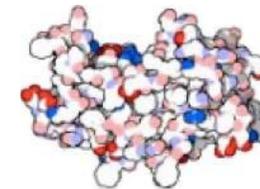
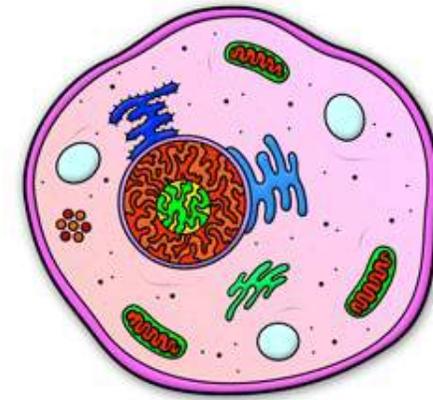
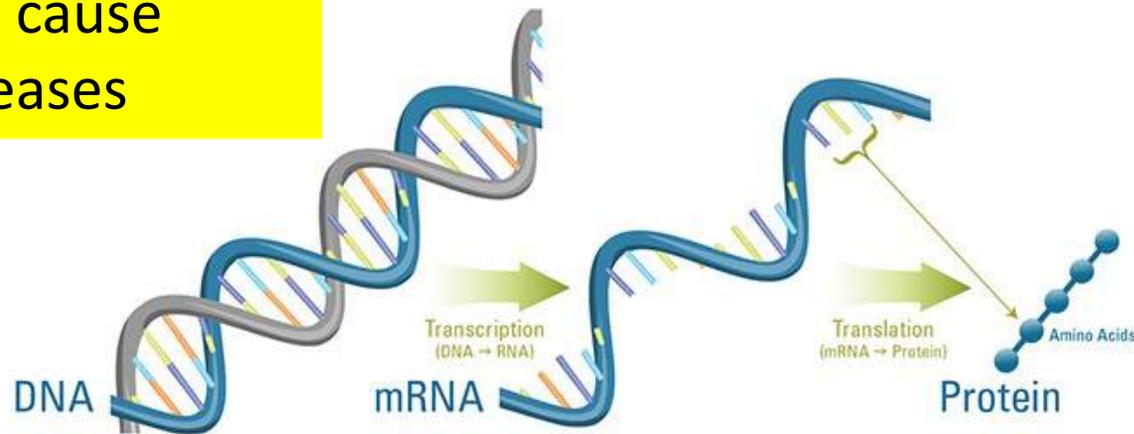
Can we stop NET production to treat RA?

Image of a NET taken under a microscope using special staining

Can we change how immune cells function in RA?

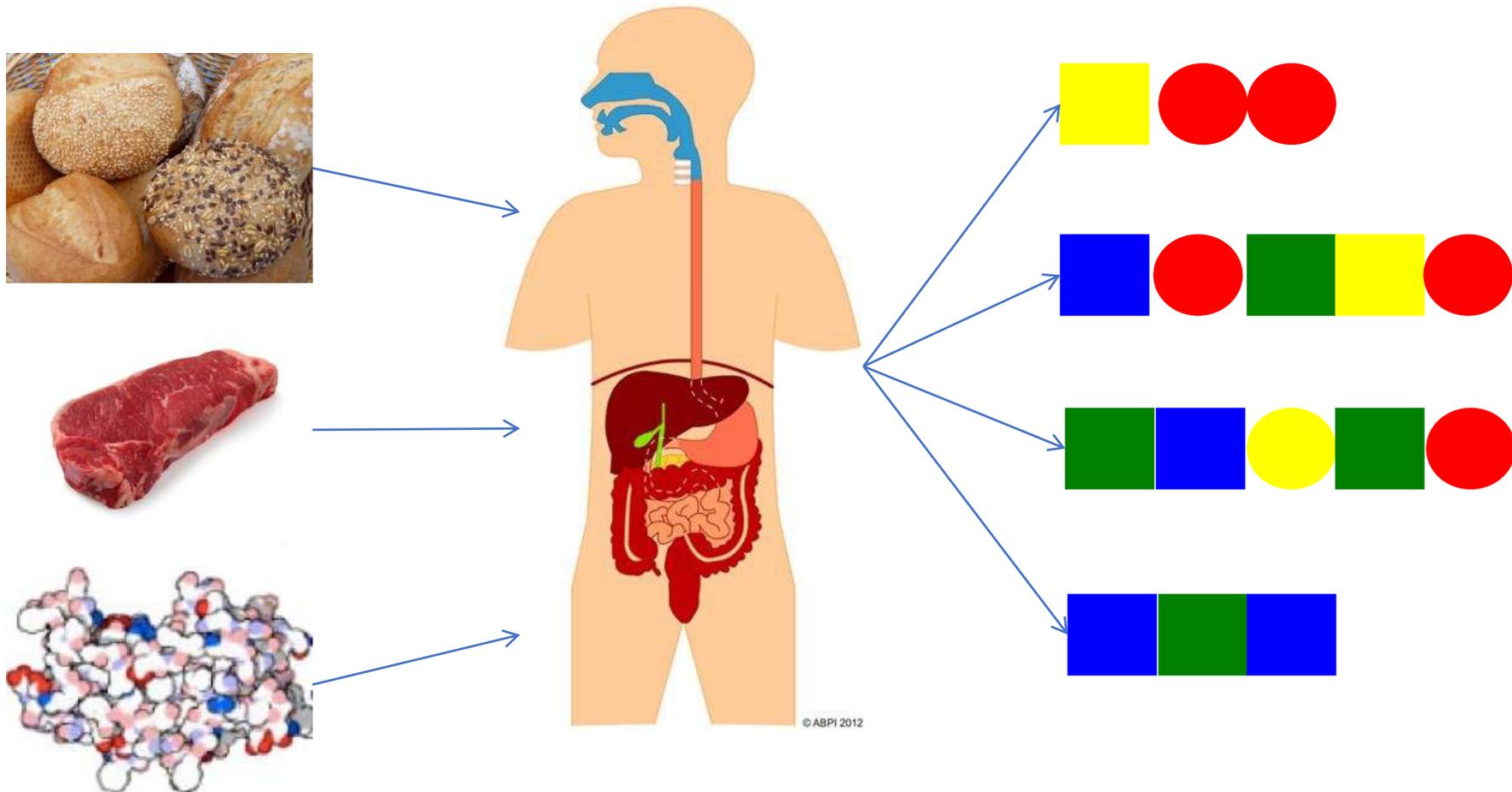
- Bodies are made up of cells
- All cells run on instructions written in DNA (genes)
- DNA needs to be copied (transcribed) and then turned into protein (translated) for something to happen

Certain genes can cause diseases

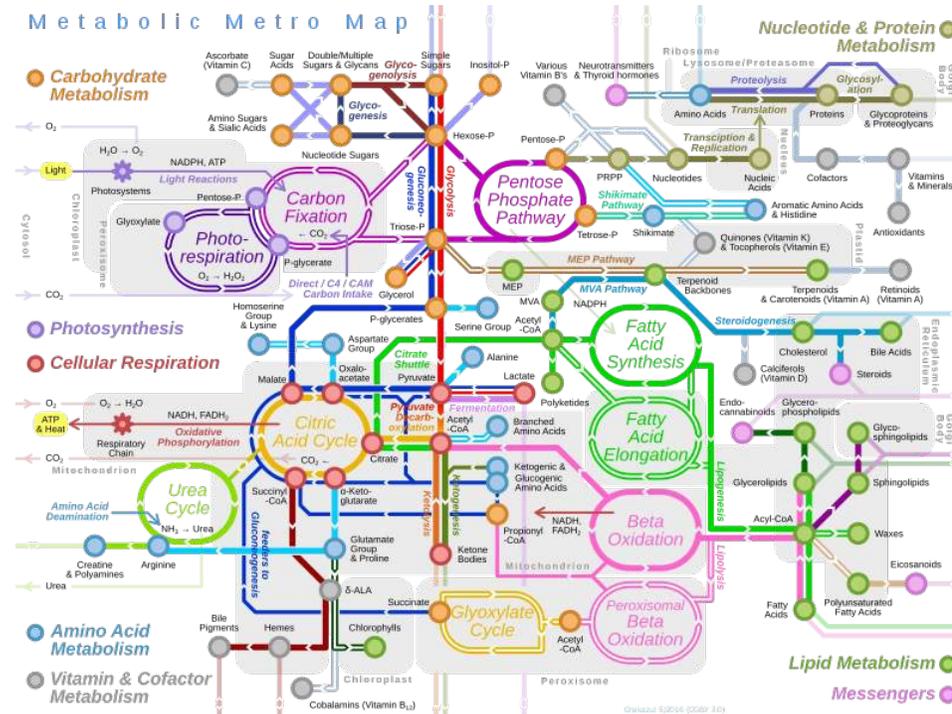
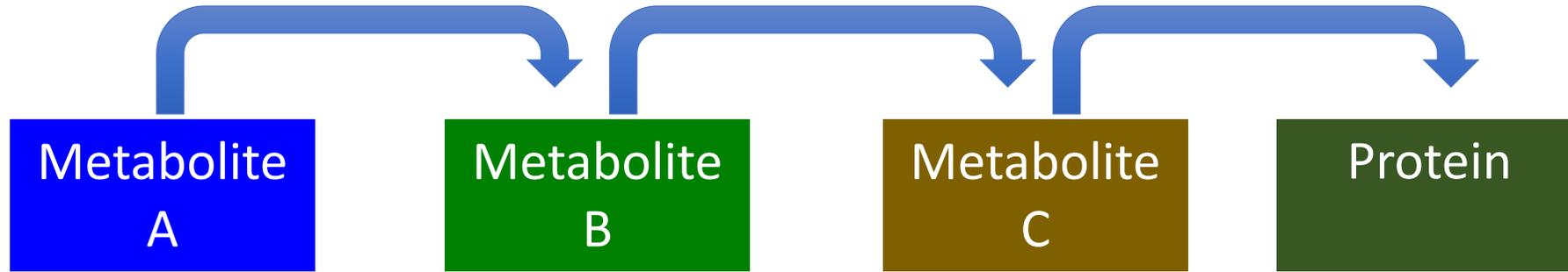


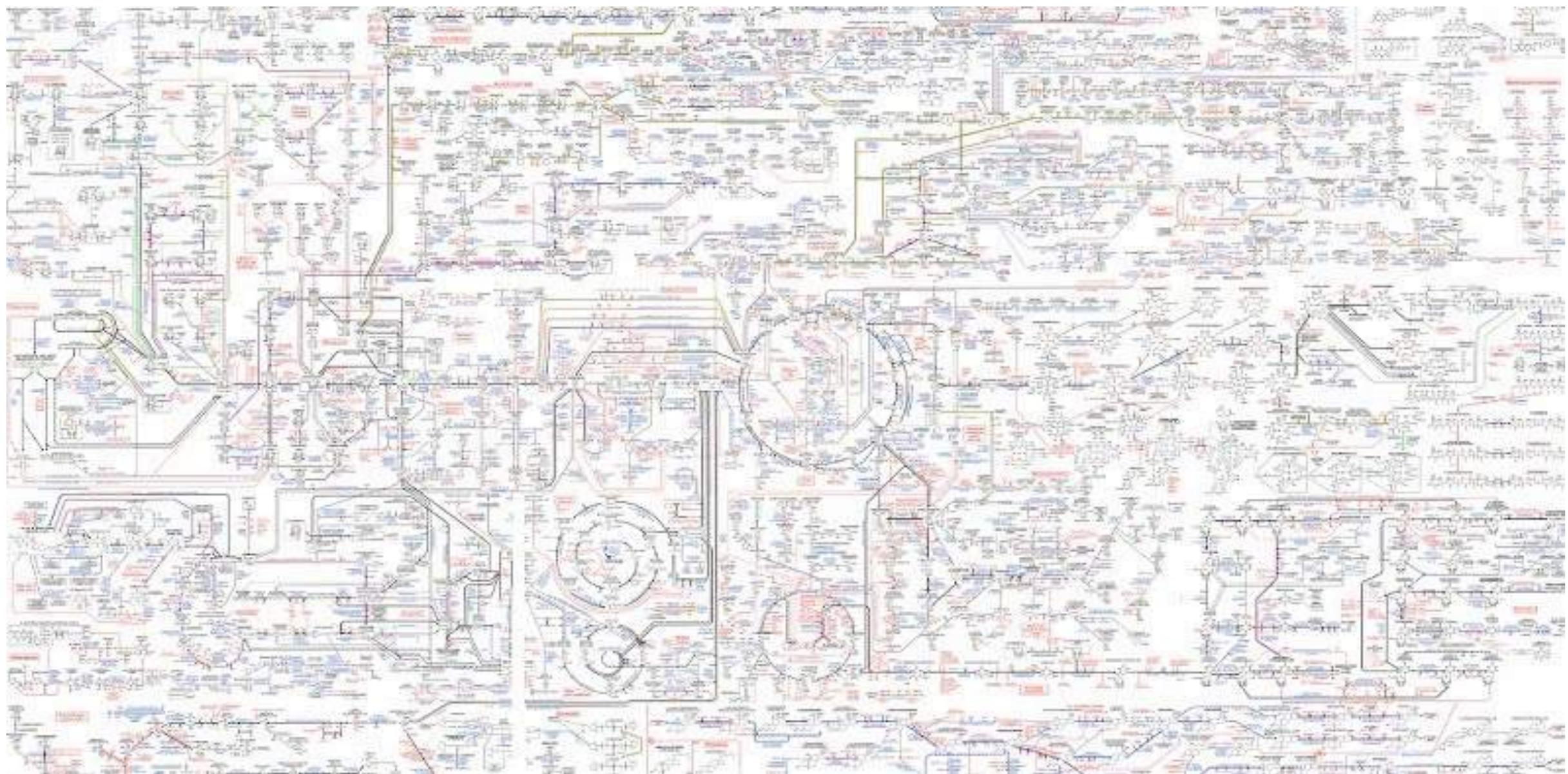
Proteins are a target of therapy e.g. anti-TNF

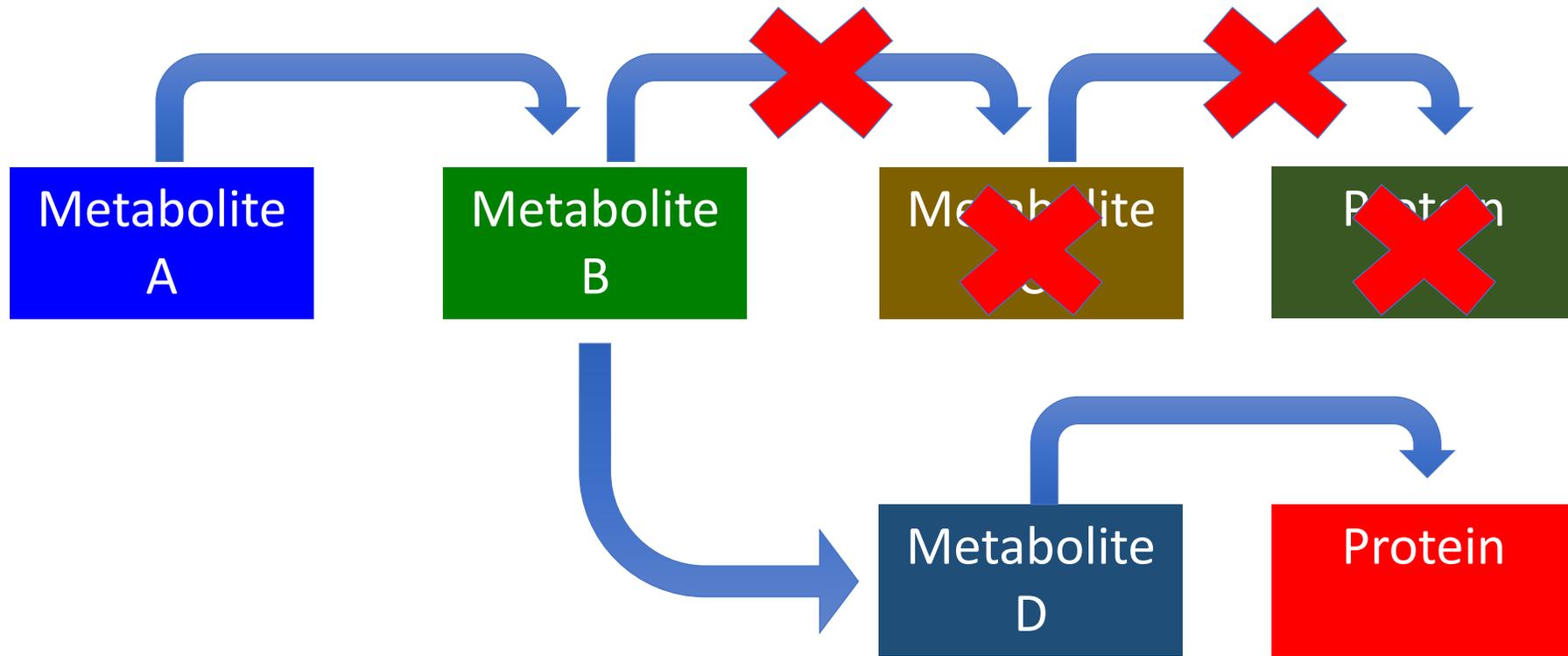
- In order to copy DNA and make protein the cell needs small building blocks (metabolites)
- We get metabolites from breaking down other molecules (e.g. food or larger metabolites)



- Cells can then use these small molecules to make DNA and protein
- We call this metabolism
- Metabolism happens along a set of known chemical reactions







- We know that metabolism is altered during inflammation
- Could this be a new target to treat inflammatory diseases such as rheumatoid arthritis?

Rheumatoid arthritis research in our institute...

- How does altered metabolism change the way immune cells function?
- Can we block NETs and could this be a new type of drug treatment for rheumatoid arthritis?
- Can we identify “biomarkers” to quickly get people with rheumatoid arthritis onto a drug that will work for them?
- How does our immune system change as we get older? In healthy ageing and in frailty?



How can you get involved?

- Learn more about arthritis research in Liverpool
- Help us identify the sorts of research questions we should be asking
- Help us learn what is important to people with arthritis
- Help us design our studies



Musculoskeletal biology patient involvement panel

- People with arthritis
- Meetings held 3 times per year
- Academics present project ideas
- Input from patient partners
- Student talks

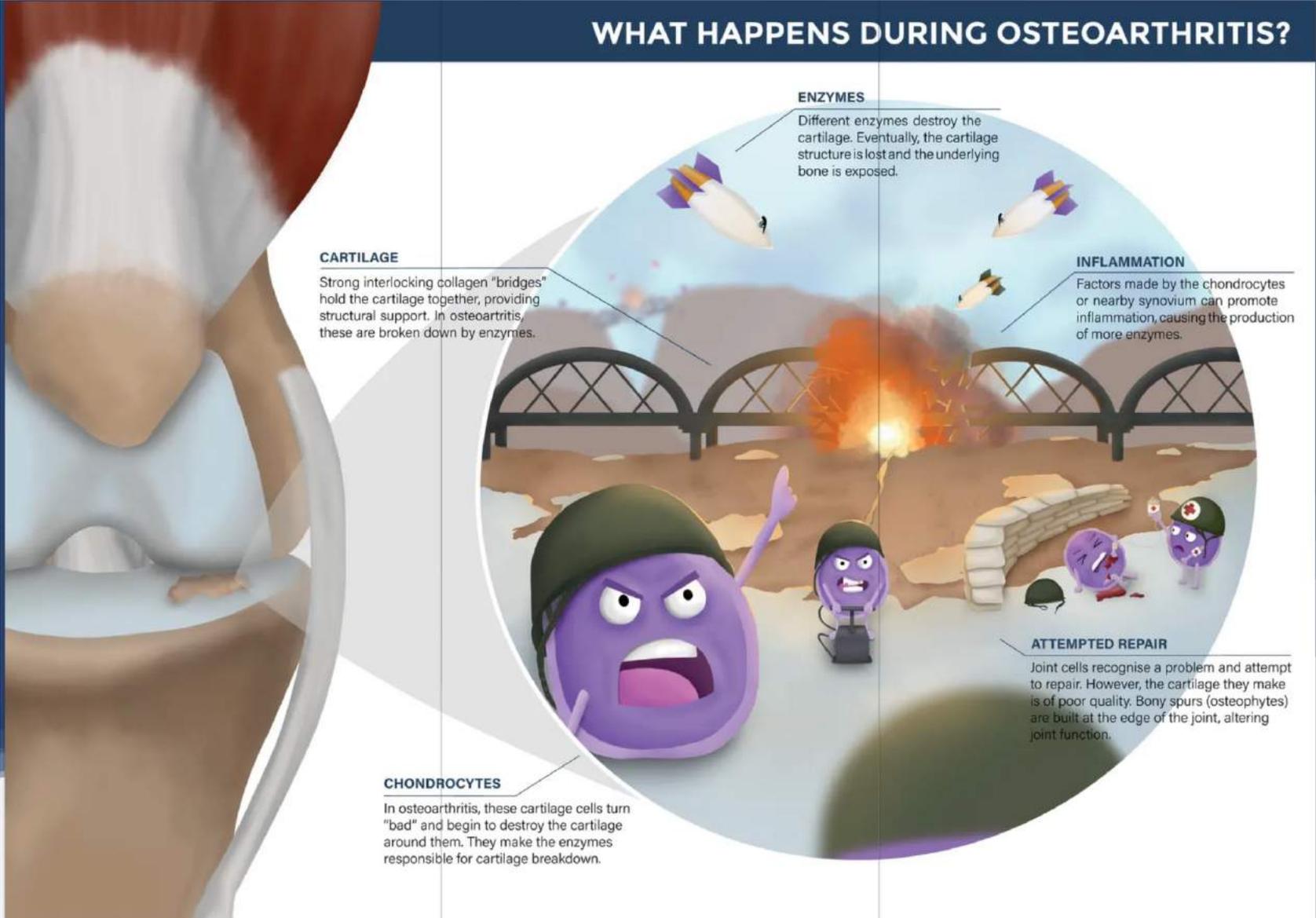
Behind osteoarthritis booklet:

<https://simplebooklet.com/behindosteoarthritis>



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<https://simplebooklet.com/behindosteoarthritis>





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Musculoskeletal Biology Patient Involvement Panel

Our patient involvement panel is a collaboration between our musculoskeletal biology researchers and members of the public, with personal or family experience of a range of musculoskeletal conditions.

<https://www.liverpool.ac.uk/life-course-and-medical-sciences/get-involved/public-patient-involvement/>

Email: [mskipip@liverpool.ac.uk](mailto:mskpip@liverpool.ac.uk)

Dr Helen Wright, University of Liverpool

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Dr Helen Wright PhD, BSc

Career Development Fellow Versus Arthritis / Tenure Track Fellow

Musculoskeletal & Ageing Science

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<https://sites.google.com/site/drhelenwright/>



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About

Personal Statement

Current Role:

Career Development Fellow Versus Arthritis / Tenure Track Fellow

Previous Roles:

Research Fellow, University of Liverpool

Arthritis Research UK Foundation Fellow, University of Liverpool

Post-doctoral Research Associate, University of Liverpool

You Tube videos:

<https://www.youtube.com/watch?v=n2nojadUN88>

<https://www.youtube.com/watch?v=ckBsd2BA5G4>