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Science and Engineering

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ORGAN-ON-A-CHIP: STREAMLINING ARTHRITIS RESEARCH AND THERAPEUTIC TRANSLATION

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Arthritis and the need for better modelling

- Arthritis is a group of diseases affecting 1 in 6 people in the UK, causing pain and disability.
- Arthritis is complex, involving and affecting all joint tissues e.g. cartilage, bone and synovium (figure 1).
- Most existing treatments for arthritis focus of addressing symptoms, rather than causes and there is a need for new, 'disease-modifying' therapeutics.

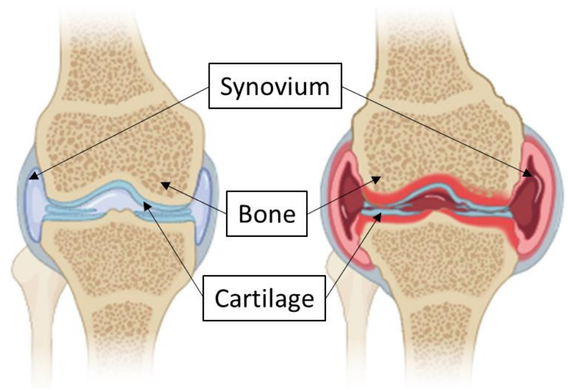


Figure 1: Normal (left) and arthritic (right) joint. Features of arthritis include synovial inflammation, cartilage degeneration and bone thickening.

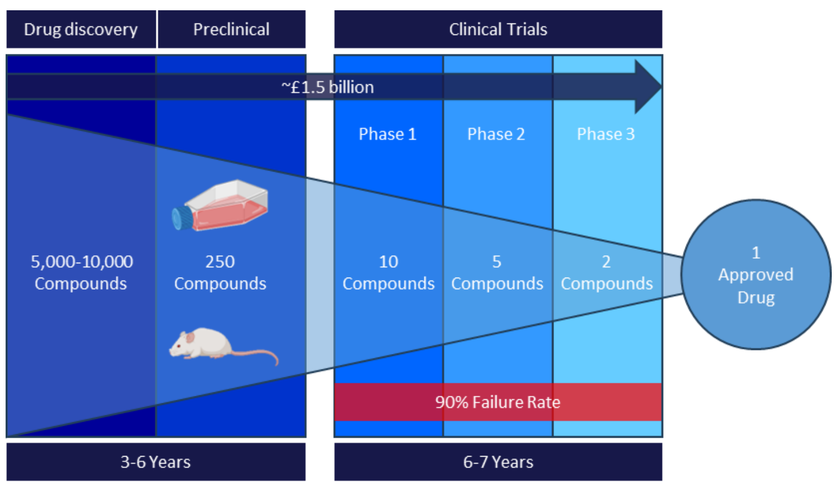


Figure 2: Attrition in the drug discovery pipeline.

- However, this search is hampered by a lack of appropriate models.
- There is a reliance on simple 2D cell-based models and animal models, both of which have poor reproducibility and limited relevance to human physiology.
- These systems are very inefficient, and consequently the current failure rate of new drugs at the pre-clinical stage is around 90% (figure 2).
- **There is an urgent need for improved models of human musculoskeletal tissues to support basic research and in which to test new therapies.**

Organ-on-a-Chip

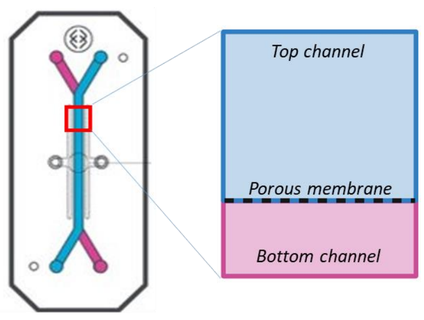


Figure 3: Schematic (left) and cross-section (right) of the Emulate Chip-S1. The Chip-S1 consists of two cell culture channels separated by a porous membrane.

- 'Organ-on-a-chip' is a technology which combines biology and engineering to create improved models that more accurately recreate the tissue or organ of interest, by including:
  - **Human cells:** *Cell lines, primary cells, stem cells*
  - **Extracellular matrix environment:** *Matrix molecules, topography, stiffness*
  - **Mechanobiology:** *Physiological mechanical stimuli as stretch & fluid shear.*
  - **Inflammatory signals:** *Pro-inflammatory cytokines, immune cells*

Organ-on-a-Chip Models of Human Musculoskeletal Tissues

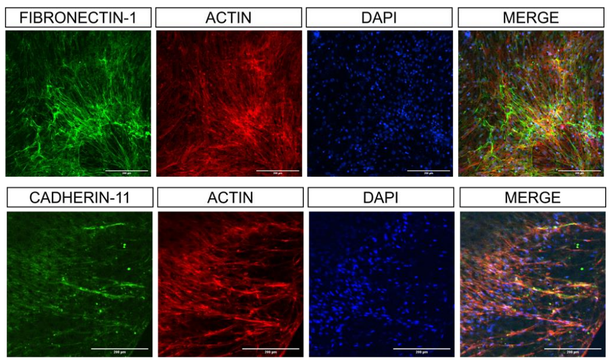


Figure 5: Synoviocytes demonstrated positive staining for characteristic synovial matrix proteins.

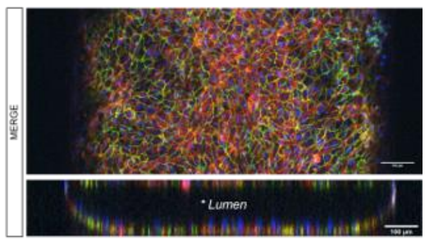


Figure 4: Endothelial cells formed a hollow lumen similar to a native blood vessel.

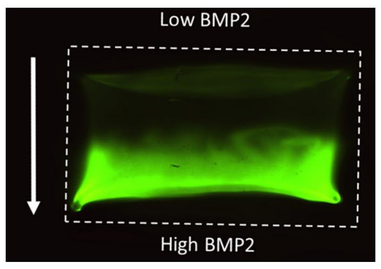
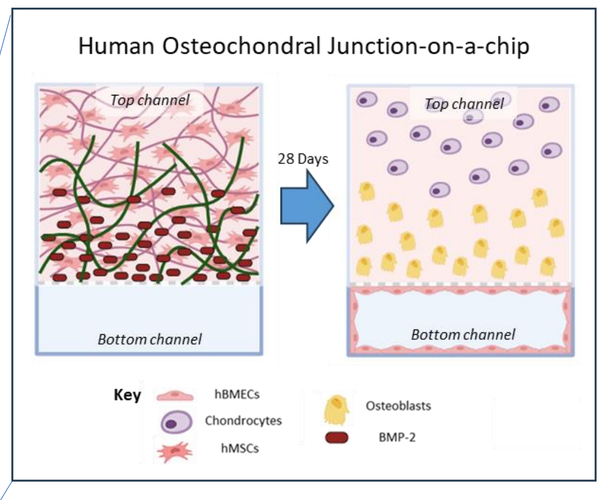


Figure 8: A growth factor (BMP2) gradient was formed within the chip.



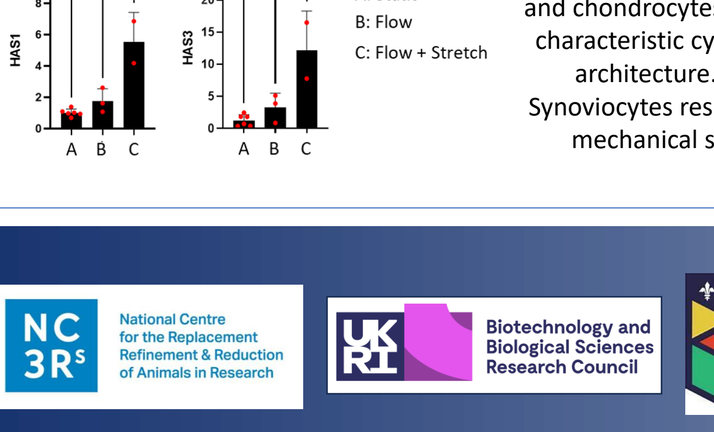
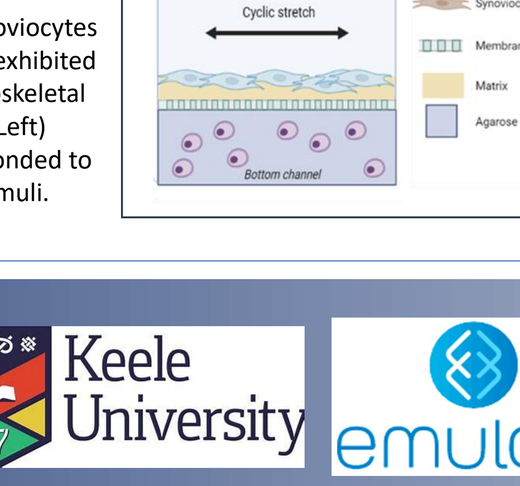


Figure 6: Synoviocytes responded to inflammatory stimuli by releasing pro-inflammatory mediators.



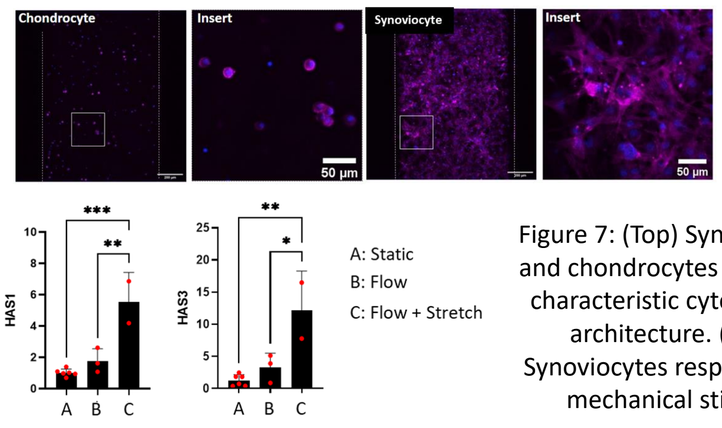
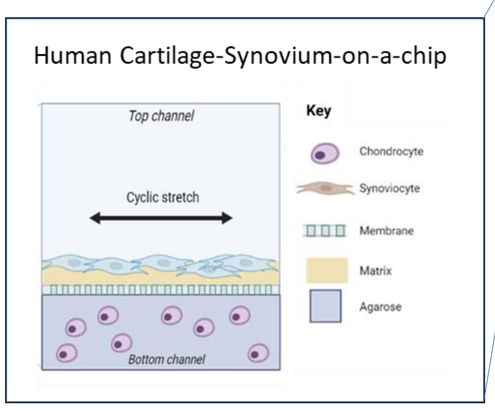


Figure 7: (Top) Synoviocytes and chondrocytes exhibited characteristic cytoskeletal architecture. (Left) Synoviocytes responded to mechanical stimuli.



Utilising our models

We have demonstrated that these systems behave in a similar way to the native tissues, including:

- Response to inflammation
- Response to mechanical stimulation
- Production of resident extracellular matrices.

These models offer versatile platforms to examine human musculoskeletal biology, identify novel drug targets and to test new therapeutics for arthritis.

NC3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research
UKRI Biotechnology and Biological Sciences Research Council
Keele University
emulate
NHS The Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Trust
Orthopaedic Institute Supporting Research & Education for Patient Benefit
VERSUS ARTHRITIS