The University Of Sheffield.

Battaglia Research Group

SITraN Sheffield Institute for Translational Neuroscience

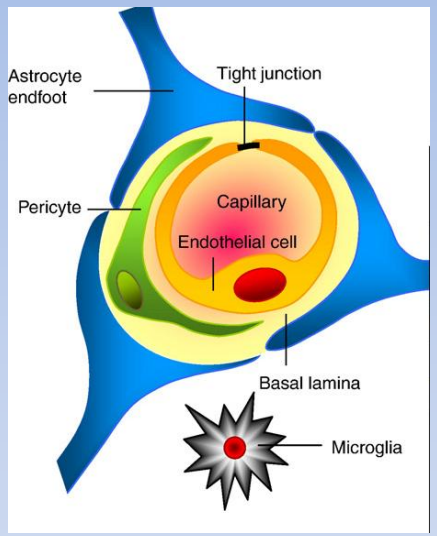
MRC Centre for Developmental and Biomedical Genetics

‘Developing Models of the Blood Brain Barrier’

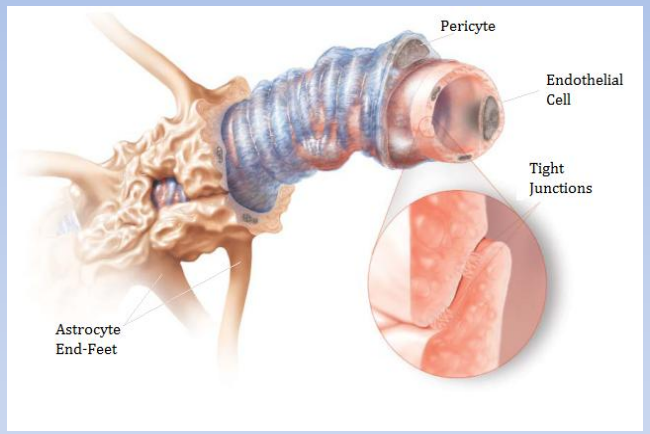
Gavin Fullstone

Supervisors: Prof. Giuseppe Battaglia (Biomedical Science), Dr Jonathan Wood (Sheffield Institute for Translational Neuroscience), Professor Mike Holcombe (Department of Computer Science)

Blood Brain Barrier



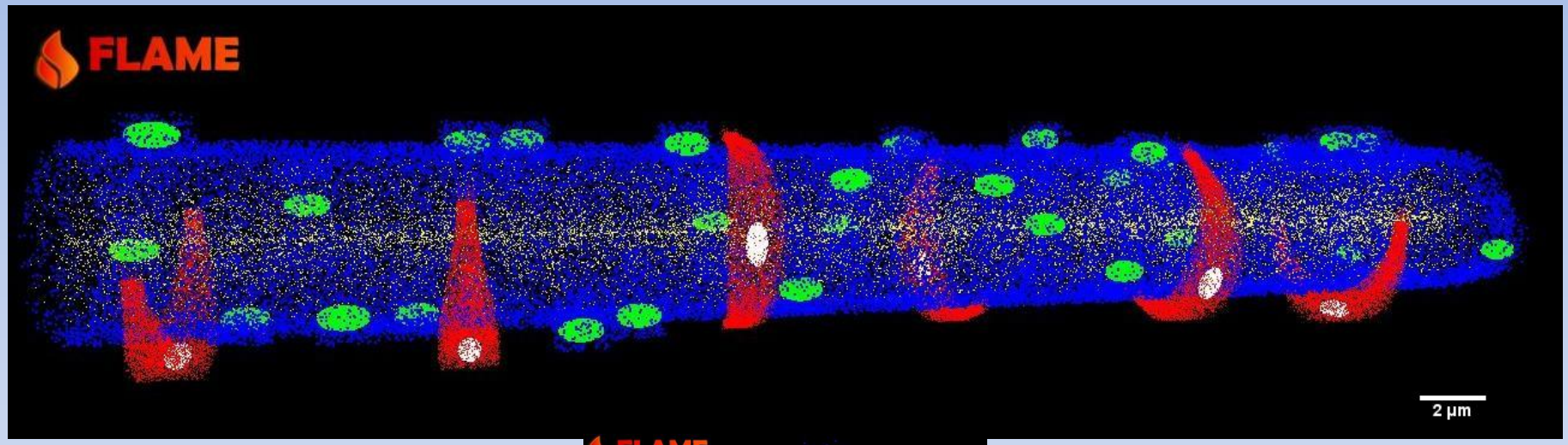
Neurobiology of Disease, 2010, 37, 13-25

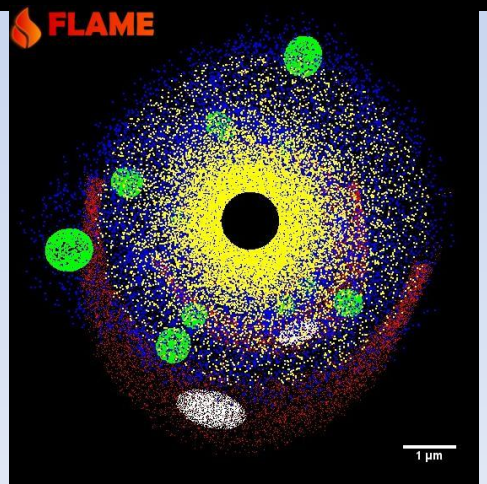


Science, 2002, 297, 1116-1118

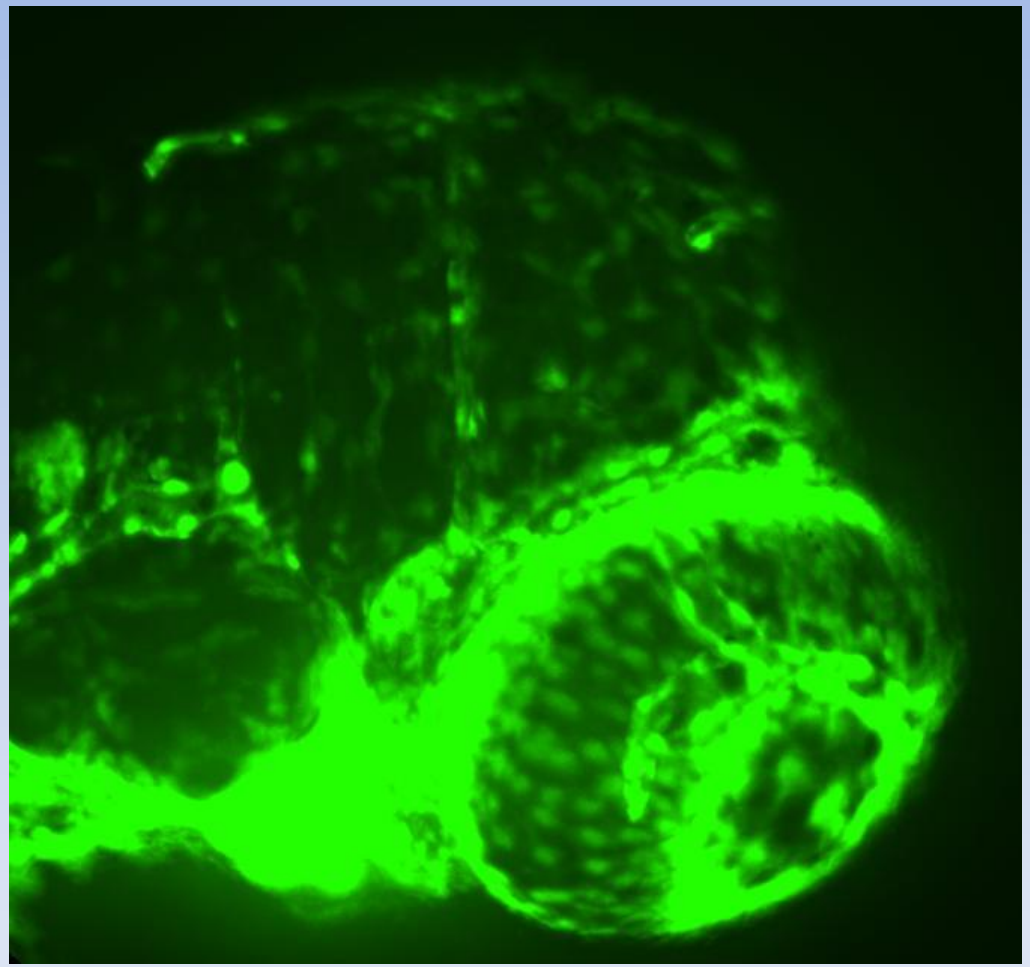
- Physically prevents the passage of almost all molecules
- Protects the brain from disease causing organisms and the immune system
- Only specific transport of certain molecules possible

Laminar Flow in a Blood Vessel





Validation: Zebrafish Embryos



Fli1 (endothelial marker):GFP zebrafish embryo at 3 days post-fertilisation

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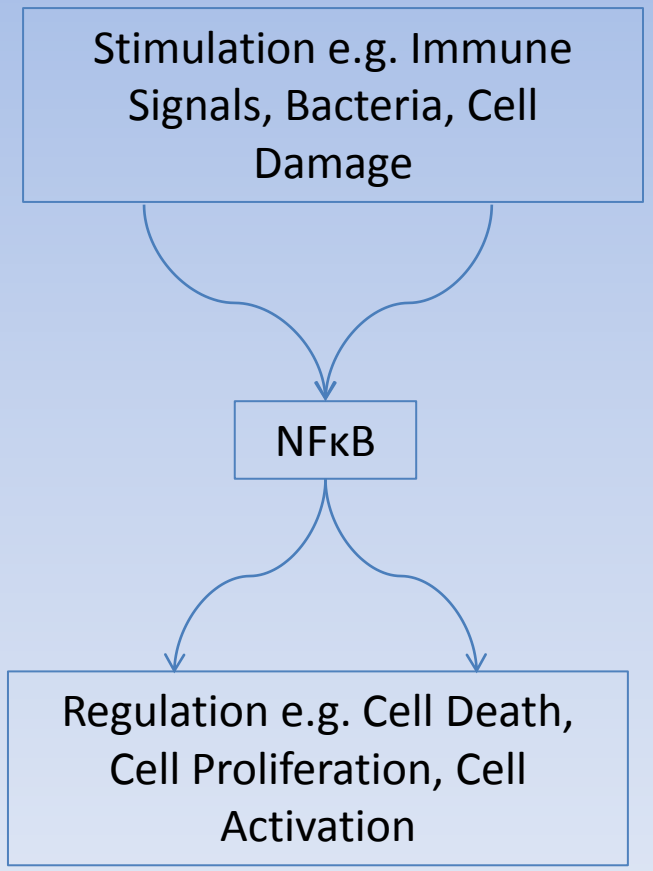
‘The Effect of Cell Size Changes on Dynamics of the NFκB pathway’

Gavin Fullstone

Supervisors: Prof. Eva Qwarnstrom (Cardiovascular Science), Prof. Mike Holcombe, Dr Sheila Francis (Cardiovascular Science)

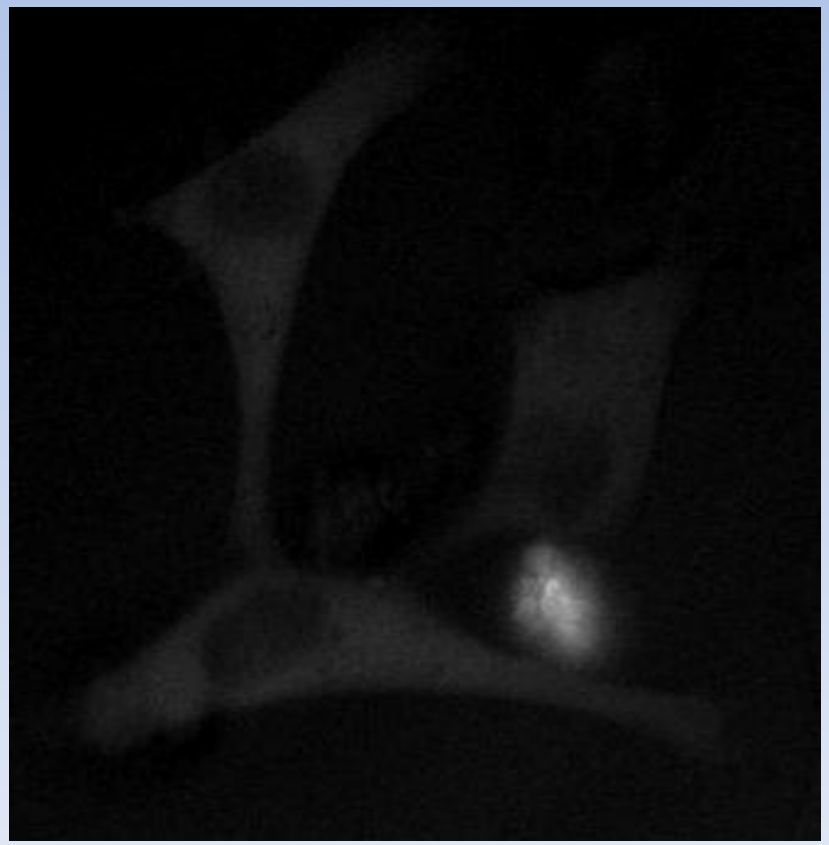
The NFκB Pathway

- Key immune pathway
- Implicated in cancer, autoimmune disease and atherosclerosis

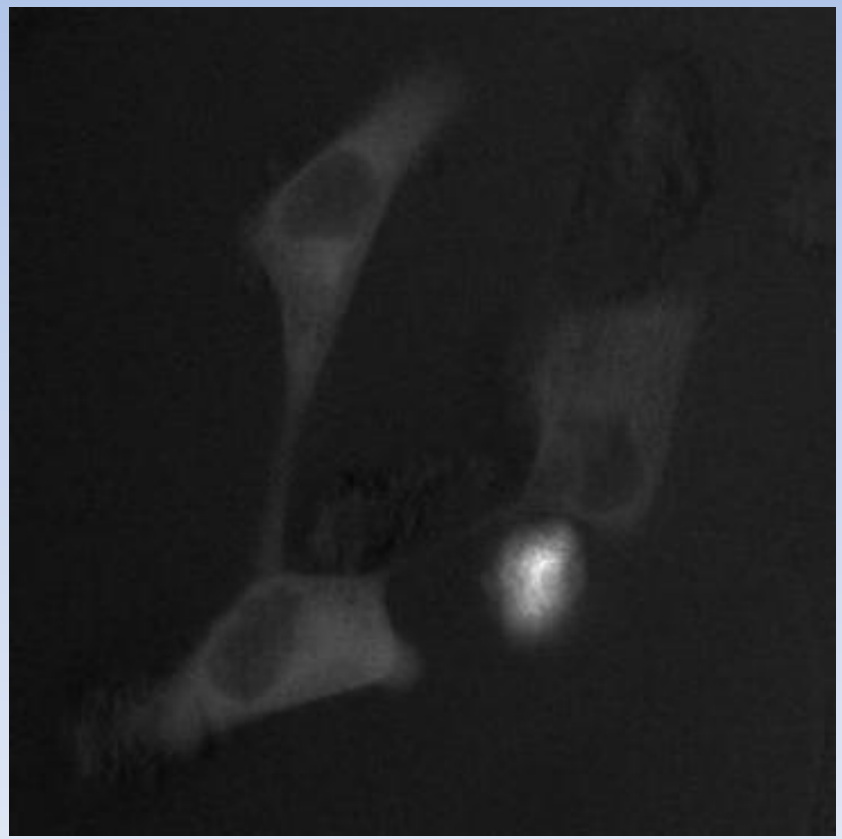


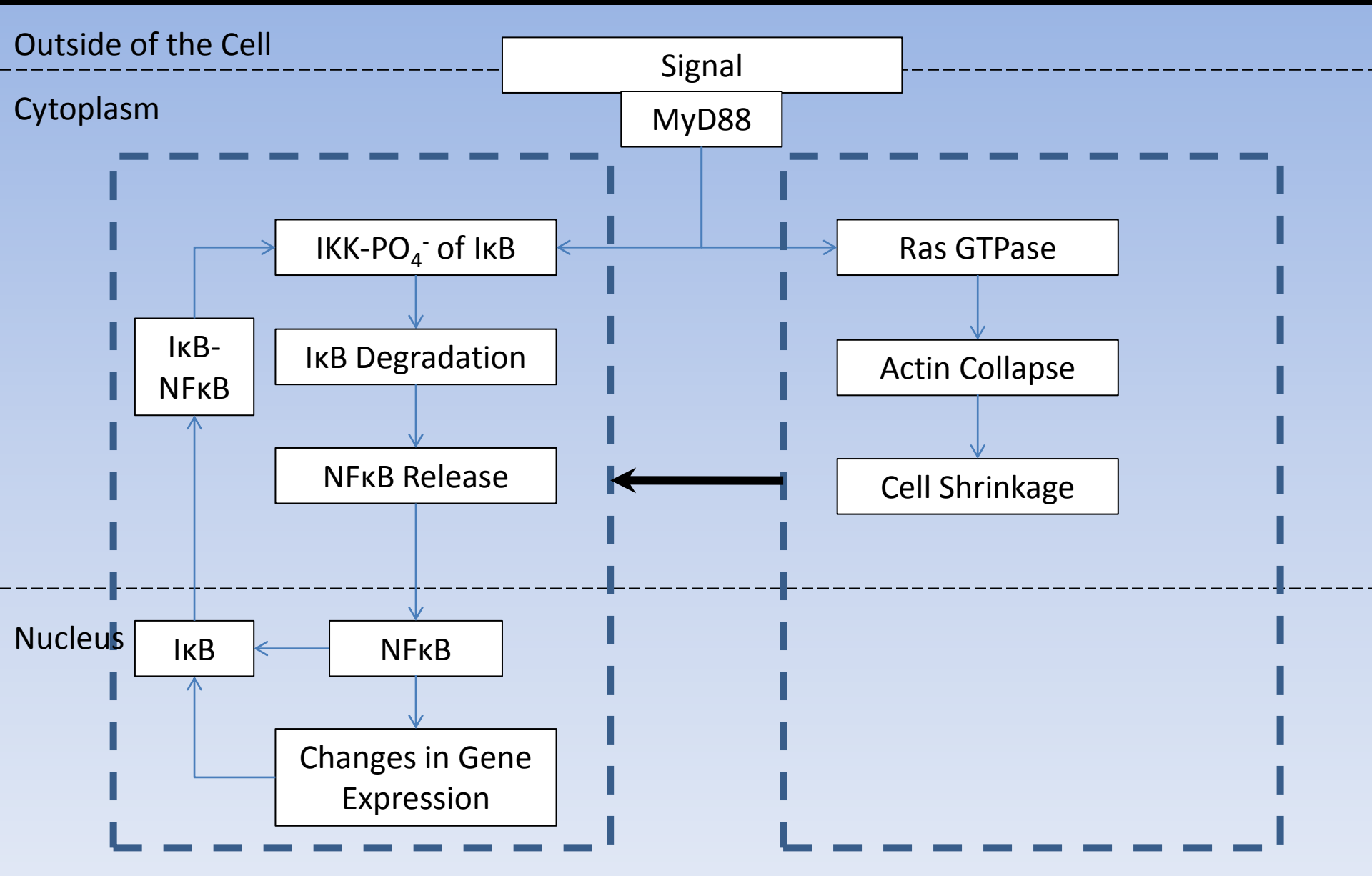
Observation: Cells Shrink after IL1 Stimulation

IκB-eGFP Hela Cells, before Stimulation



IκB-eGFP Hela Cells, 10mins Stimulation



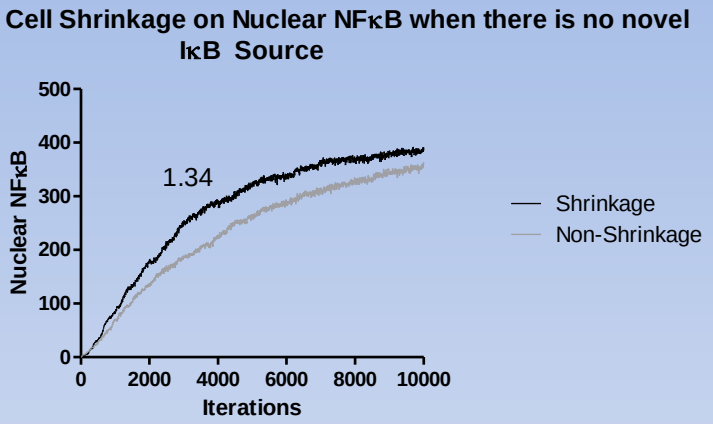

Outside of the Cell
Signal
Cytoplasm
MyD88
IKK-PO4- of IκB
Ras GTPase
IκB-NFκB
IκB Degradation
Actin Collapse
NFκB Release
Cell Shrinkage
Nucleus
IκB
NFκB
Changes in Gene Expression

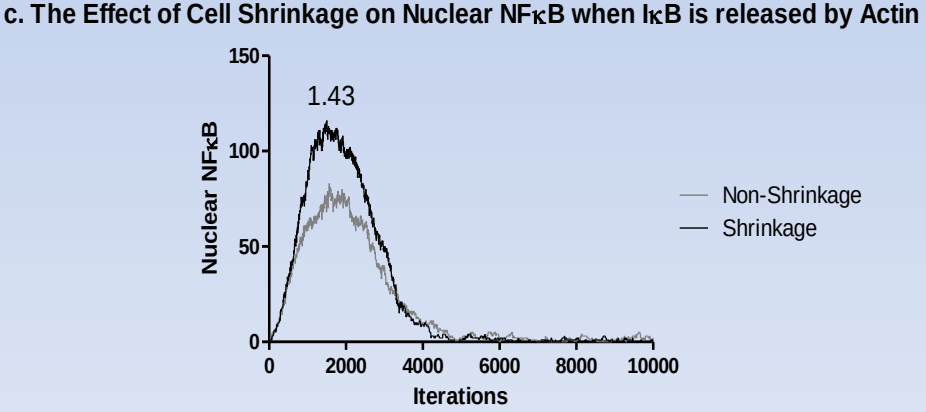
Question

How does the change in cell size and shape affect the dynamics of the NFκB pathway?

What we did?

- Cell could shrink by up to 20% volume (cytoplasm only)
- Ran models with and without shrinkage
- Demonstrated that at multiple levels of regulation the pathway operates faster
- Consequently, negative regulation of the pathway also occurs faster





Acknowledgements

- Mike Holcombe
- Giuseppe Battaglia
- Jonathan Wood
- Simon Coakley
- Eva Qwarnstrom

BBSRC bioscience for the future

FLAME Flexible Large-scale Agent Modelling Environment