Development of a novel drug delivery platform to target NLRP3 inflammasome and its treatment in Post-traumatic Osteoarthritis

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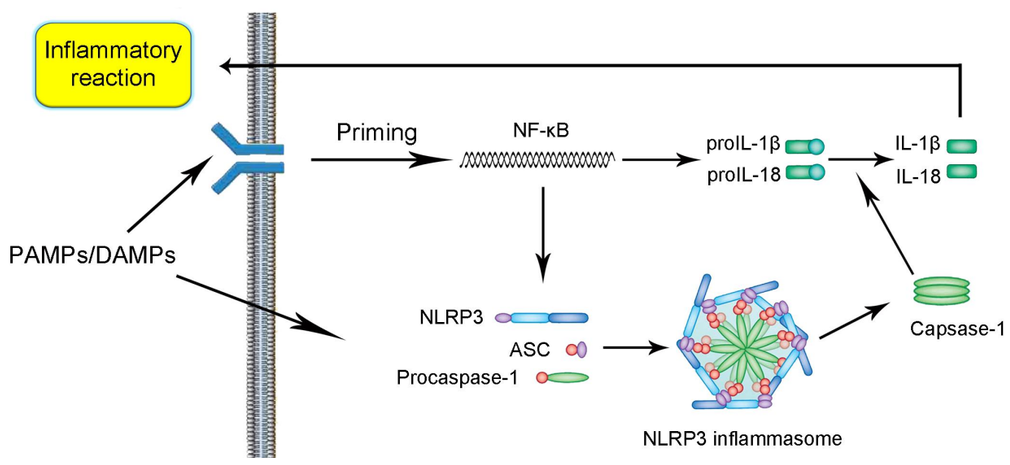
INTRODUCTION

- **Post-traumatic Osteoarthritis (PTOA)** comprises ~12% osteoarthritic cases[1].
- Chondrocytes respond to joint injuries by **releasing inflammatory mediators** which aggravate PTOA[2].
- Activation of **Nod-like receptor family protein 3 (NLRP3) inflammasome** through NF-κB signalling **induces Interleukin-1β (IL-1β) secretion and mediates inflammatory cell death**[3].

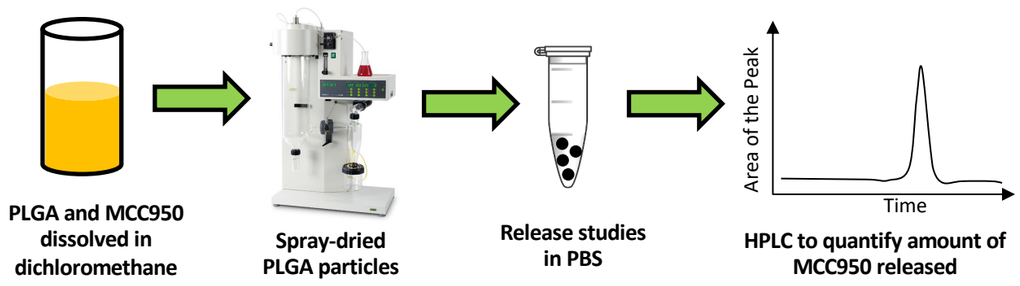


- **MCC950** is a selective NLRP3 inflammasome inhibitor and prevents IL-1β secretion[4].

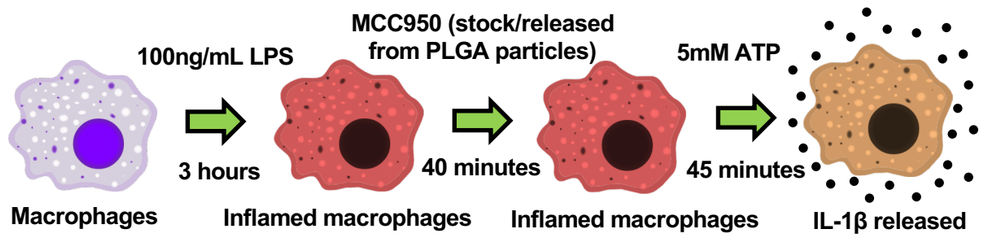
Overall Goal:
To develop a novel drug delivery platform releasing MCC950 to target NLRP3 inflammasome in order to reduce cartilage destruction and demonstrate therapeutic efficacy in PTOA.

AIMS AND METHODS

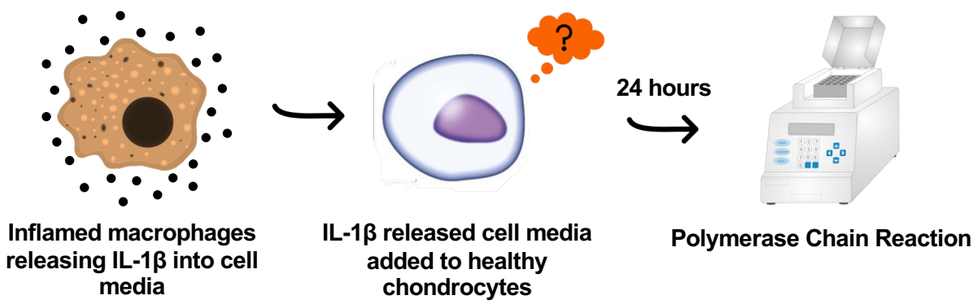
Aim 1: To obtain sustained release of MCC950 from PLGA microparticles



Aim 2: To investigate the potential of MCC950 released from PLGA microparticles to inhibit LPS-induced IL-1β secretion

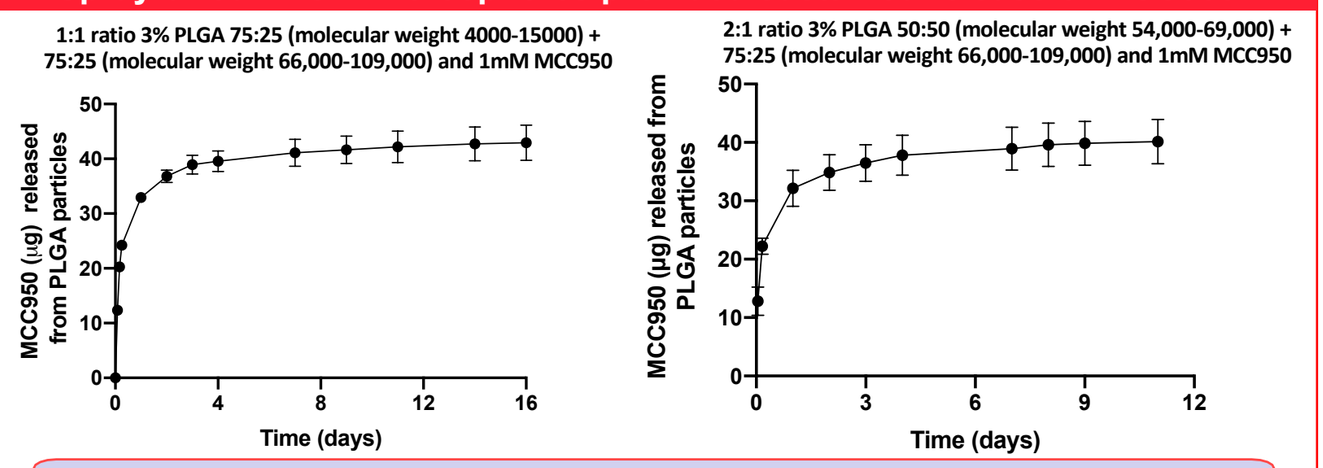


Aim 3: To explore the adverse effects of inflamed macrophages on chondrocytes



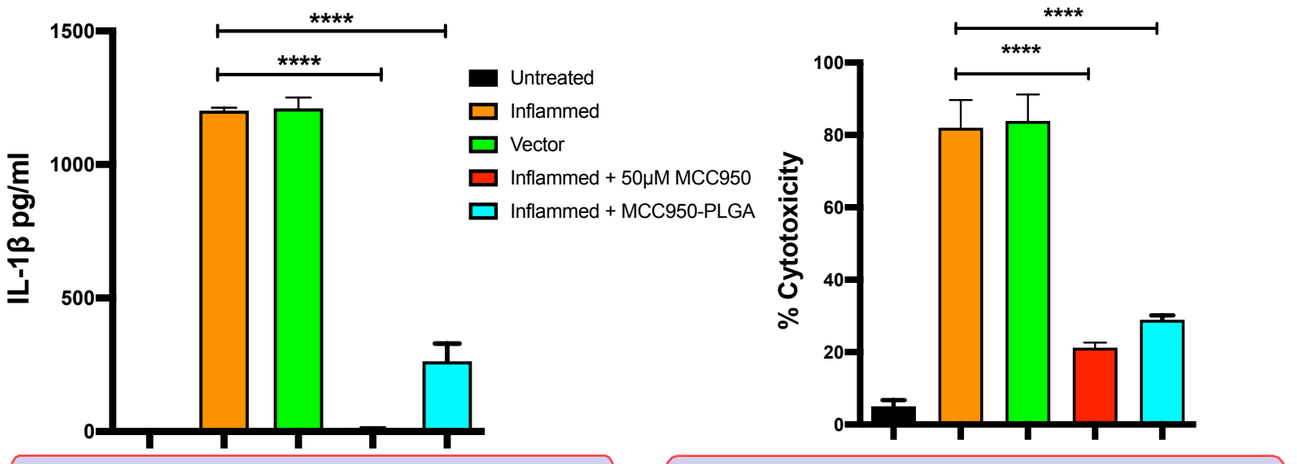
RESULTS

Spray-dried PLGA microspheres provided sustained release of MCC950



Sustained release of MCC950 from spray-dried PLGA particles over 2 weeks

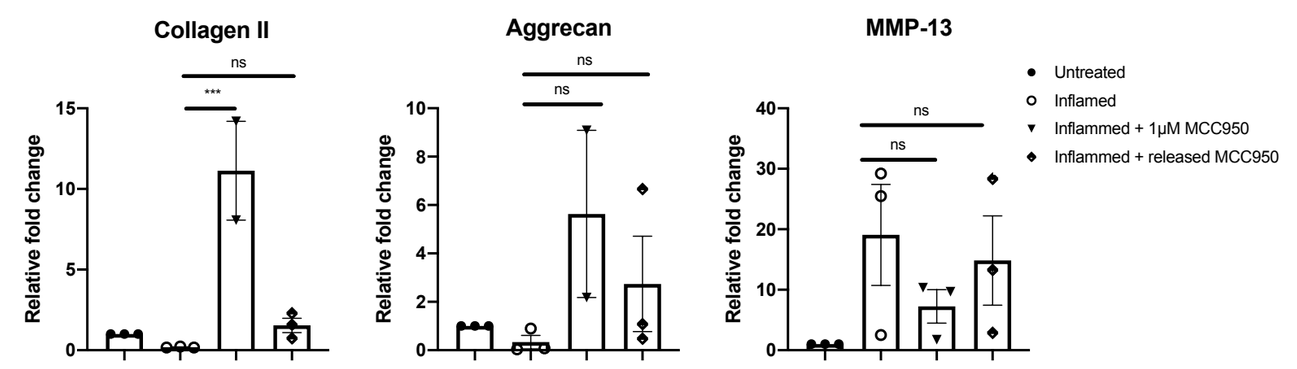
MCC950 inhibits LPS-induced IL-1β secretion in macrophages



Both 50μM MCC950 and MCC950 released from PLGA particles over 2 weeks inhibits pyroptosis significantly.

Addition of MCC950 reduced cytotoxic effects on inflamed macrophages

MCC950 reverses adverse effects of inflamed macrophages on healthy chondrocytes



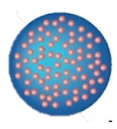
IL-1β release from inflamed macrophages inhibited chondrocyte collagen formation and increased inflammatory protein level MMP-13. Both 1μM MCC950 and MCC950 released from PLGA particles reversed these effects.

DISCUSSION AND CONCLUSIONS

1. Spray-dried MCC950-PLGA microparticles allow for sustained release of MCC950 over 2 weeks.
2. MCC950 released from particles remain strongly bioactive and inhibit IL-1β release from inflamed macrophages
3. MCC950 protected chondrocytes from the adverse effect of IL-1β released from inflamed macrophages.
4. MCC950 is potential drug delivery candidate for targeting IL-1β, which is believed to contribute to the pathogenesis of PTOA.

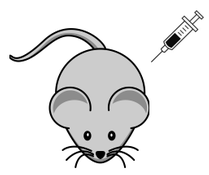
FUTURE WORK

- Optimisation of spray-dried PLGA particles for particle size and drug encapsulation



- Incorporate optimised PLGA particles into microparticles for joint delivery (Collaborator in Georgia Tech) to evaluate its safety and efficacy in the joint

- In-vivo study in PTOA rodent model



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