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Institute of Medical Research
DISCOVERIES FOR HUMANITY

Targeting plasmacytoid dendritic cells as treatment for systemic lupus erythematosus

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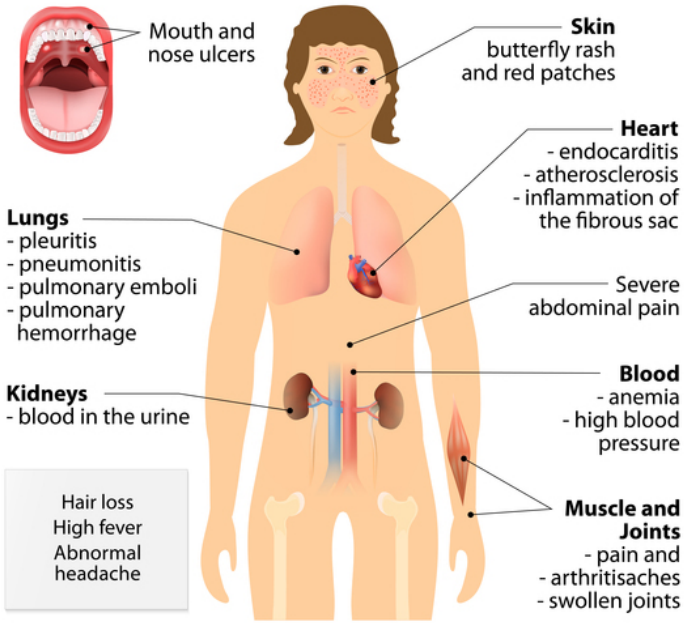
Melbourne, Australia

Systemic lupus erythematosus (SLE)



- **Chronic autoimmune disease** of the connective tissue.
  - Lupus nephritis, inflammation of the kidney, is a major contributor to morbidity and mortality among SLE patients
- SLE affects **20-40 people out of every 100,000**
  - Most prevalent in non-Caucasians and in women, incidence is highest between 15–44 years.
  - **Currently no cure** with treatments predominantly aimed at easing symptoms.
  - Mainstay therapeutic options delivered by off-label therapies with undesirable safety profiles

Bhattacharya, 2011; Borchers et al., 2012; O'Neill and Cervera, 2010; Danchenko et al., 2006
https://ghr.nlm.nih.gov/condition/systemic-lupus-erythematosus (accessed 24/09/2018)

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Plasmacytoid dendritic cells – a potential SLE treatment

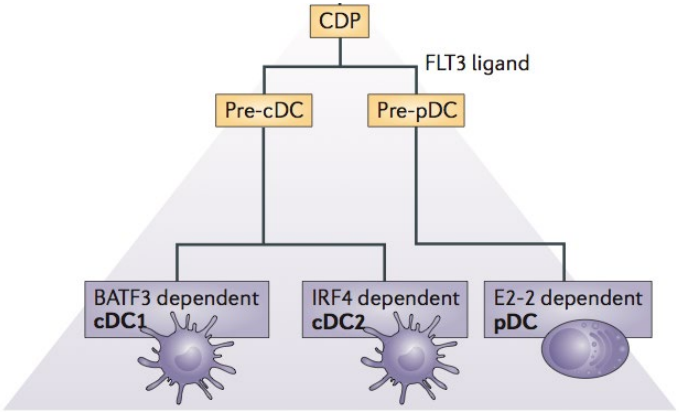
- **Plasmacytoid DCs** (pDCs) are over-activated in SLE patients and play an important role in disease pathogenesis
  - Drive disease through over-production of interferons (IFN)

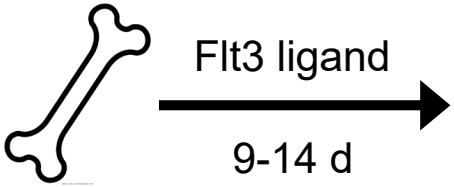
- Mature pDCs and IFN-α are already targets for immunotherapy
  - e.g. CSL362 anti-IL-3Rα mAb and Anifrolumab, Astra Zeneca's anti-IFN-α mAb

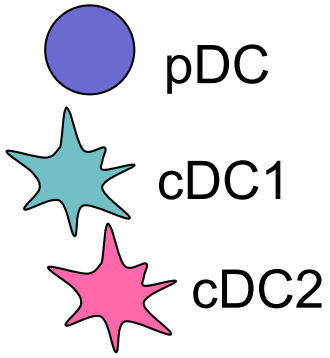
- **Can pDCs be targeted at the developmental stage?**

Plasmacytoid dendritic cells – a potential SLE treatment

- Researchers at WEHI have developed an *in vitro* system to generate mouse DCs
  - Produces large numbers of DCs (60-100 million from one mouse) expressing appropriate cell surface markers







Naik, Proietto, *et al*. 2005
Naik *et al*. 2010

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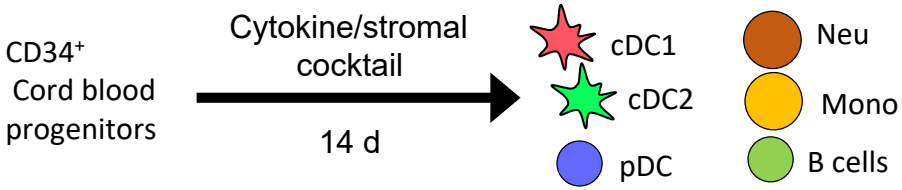
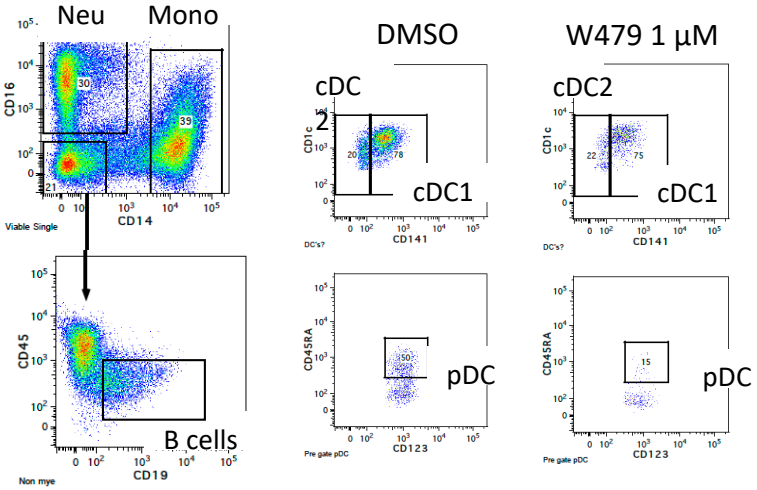
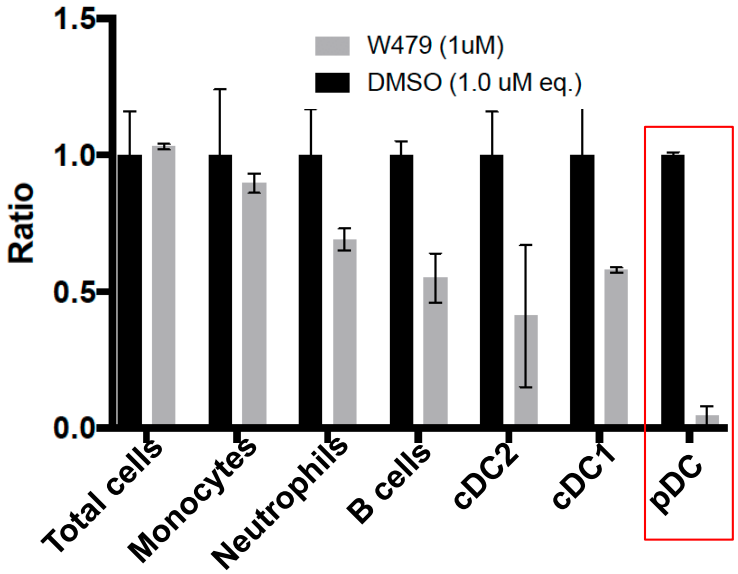
pDC inhibitor program at WEHI

WEHI researchers have identified a novel inhibitor that **effectively depletes human pDCs**







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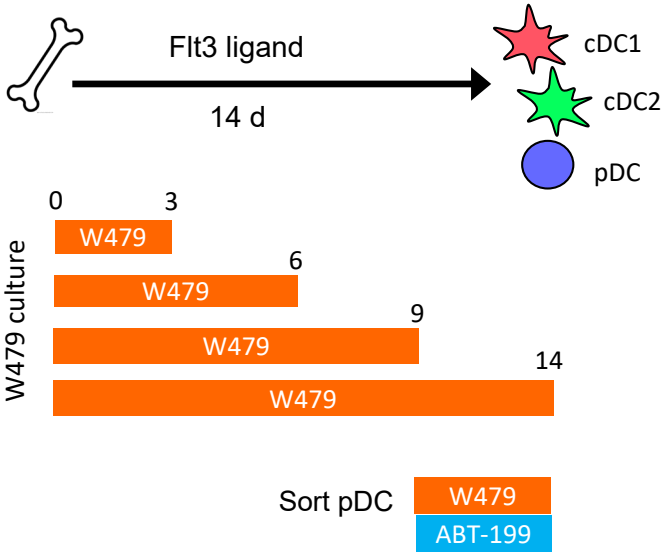
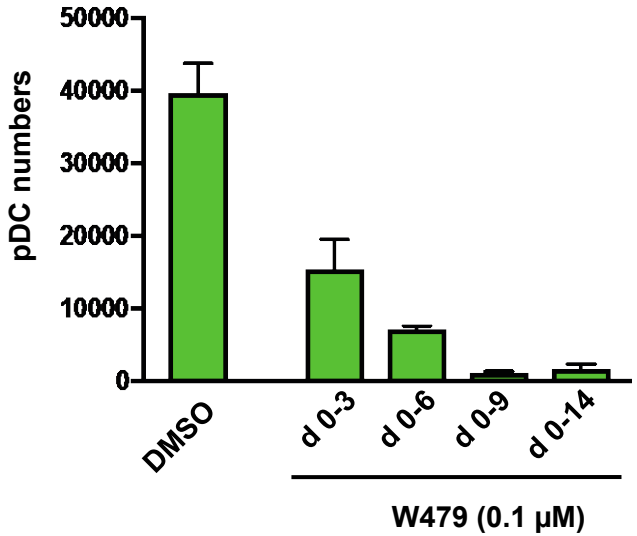
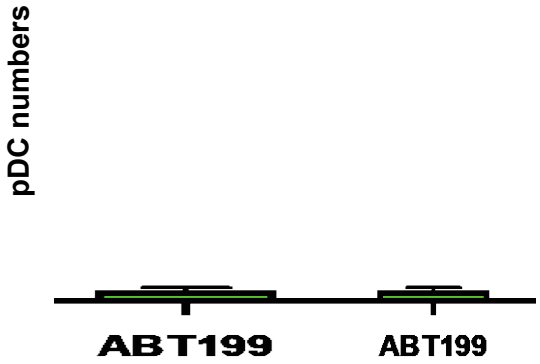
pDC inhibitor program at WEHI

Research in mice showed that the inhibitor, and backup compounds, **block pDC development** (but not survival) and **ameliorate IFN production**







Lee, *et al.* 2017.

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pDC inhibitor program at WEHI

Currently:

1. Undertaking medicinal chemistry studies to identify SAR and mode of action
2. Refining the compound (stability) to allow for ***in vivo* validation** in genetic and human xenograft models of SLE

Dr Shalin Naik, PhD

- Immunologist
- Research group studies how immune cells develop from hematopoietic stem cells

Associate Professor Guillaume Lessene, PhD

- Medicinal chemist
- Research group focuses on cellular pathways controlling cell death

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What we want/partnering opportunities

We are seeking **a co-development partner** to:

1. Identify the target of the inhibitor
    - Cross-linking immunoprecipitation (CLIP): variant with UV cleavable linker available, assay requires further optimisation
    - Cellular Thermal Shift Assay (CETSA)
2. Develop a lead candidate which would allow testing of *in vivo* efficacy and safety
    - Preclinical validation pathways using genetic and human xenograft models of SLE established at WEHI
    - Real time 4D 2-photon confocal microscopy available for *in vivo* efficacy studies

Goal**: Positioning the technology for pre-clinical toxicity program and IND filing**.

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