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Institute of Medical Research
DISCOVERIES FOR HUMANITY

Intercepting inflammation with RIPK2 inhibitors

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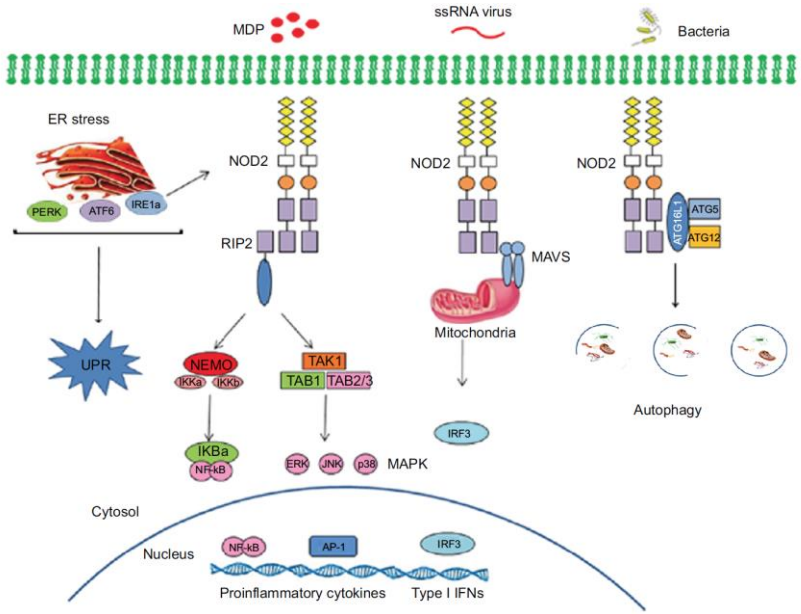
RIPK2 serine threonine kinase is a key driver of inflammation



- NOD2 receptors are intracellular sensors of a range of stimuli
  - peptidoglycan from bacteria
  - ssRNA viruses
  - intracellular bacteria
- RIPK2 is an essential mediator of the response to bacterial peptidoglycan
- RIPK2 signaling drives expression of proinflammatory cytokines and type I interferon

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RIPK2 and inflammatory bowel disease

- Crohn's disease and ulcerative colitis are highly prevalent gastrointestinal autoimmune disorders
  - Over 3 million cases worldwide
  - Chronic disease often with relapsing remitting course
  - Life threatening in patients with fulminant disease

- Hyperactivation of NOD2:RIPK2 receptors is a key driver of IBD
  - RIPK2 inhibitors have shown efficacy in preclinical models of inflammatory bowel disease
  - we have identified WEHI-345 as a novel RIPK2 inhibitor (46nM IC_{50})
  - treat active inflammatory episodes and maintain remission

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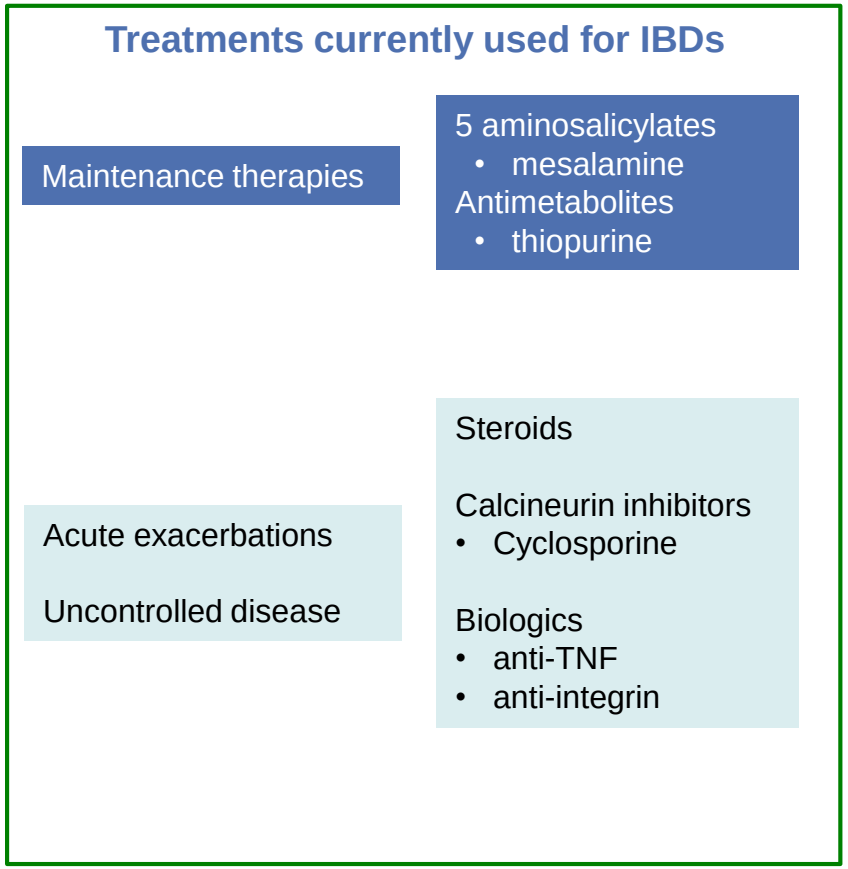
RIPK2 inhibition: a novel anti inflammatory approach

- Directly inhibits the key signaling cascade in IBDs
  - Interrupting this signal at the source is likely to be more efficacious than downstream processes
- Large Pharma are developing RIPK2 inhibitors
  - Published molecules are potent and specific but have liabilities
- We have established
  - Structure enable drug discovery program
  - Enzymatic assays for RIPK2 and related kinases
  - Novel *in vitro* cell based and *in vivo* assay systems for target validation studies



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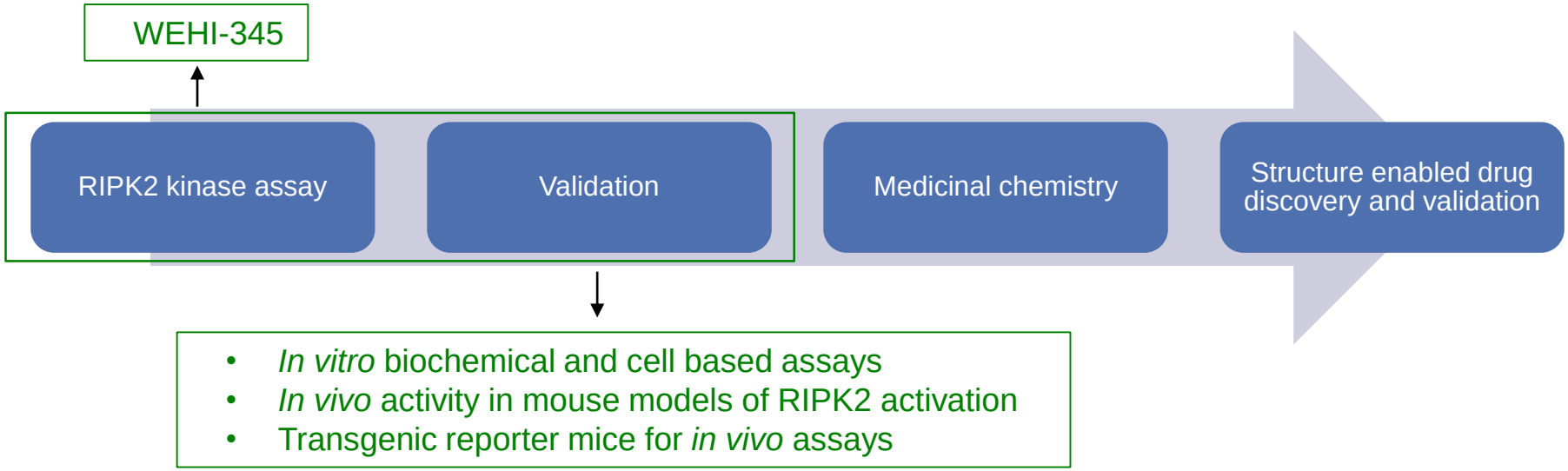
RIPK2 inhibitor program at WEHI

- WEHI-345 is a potent and specific RIPK2 inhibitor
  - Acceptable *in vivo* pharmacokinetics and supportive efficacy data in mouse models of sepsis and diabetes
- Represents an excellent molecule for lead optimization studies
  - structure enabled medicinal chemistry
  - *In vivo* validation studies



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What are we after?

- We are seeking a co-development partner to support lead optimization of our series of RIPK2 inhibitors
  1. Medicinal chemistry
  2. Structural biology
  3. *In vitro* biochemical and cellular assays of RIPK2 activity
  4. *In vivo* validation of RIPK2 inhibition in SAMP1/YitFc mouse model of ileitis
  5. Position the technology for pre-clinical toxicity program and IND filing

- Ultimate goal is to develop clinical candidate as well as back-up compounds with appropriate potency, safety and pharmacokinetic profiles for the treatment of inflammatory bowel diseases

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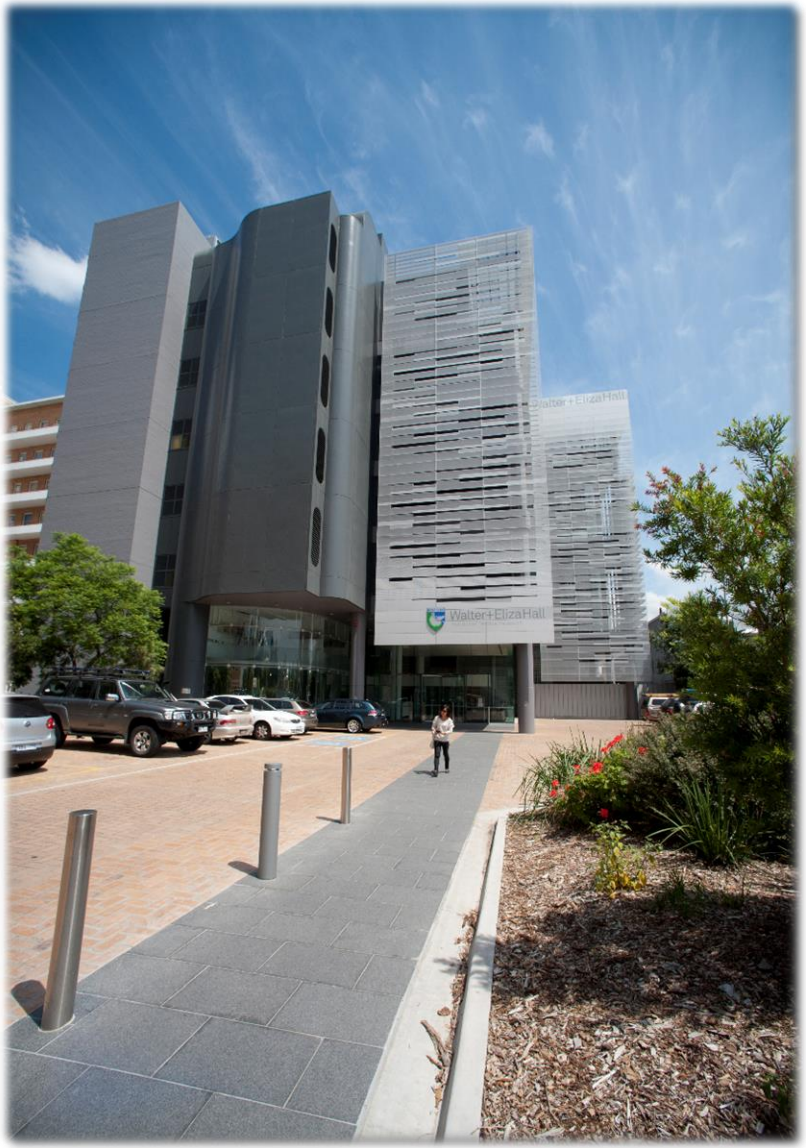

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