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smarter drug re-profiling

Corporate Overview
&
RP0217 Opportunity -- A Novel Anti-Inflammatory Agent

Dr Robert Scoffin
CEO

http;//www.re-pharm.com/ rob@re-pharm.com

Re-Pharm Rationale

> Re-Profiling only works with a strong Commercial Directive

Re-Pharm Approach

- Established Active
- New Indications
- New Doses
- New Formulations
- New Delivery Devices
- New Platforms
- New IP
- New HE Profile
- New Price
- New Sales

The Re-Pharm Expertise

- Computational Chemistry
- Cheminfomatics
- *In vitro* studies
- *In vivo* clinical trials
- Regulatory Approach
- Lifecycle Management
- Pricing/Modelling/Forecasting
- Launch Strategy
- Commercialisation

Experienced at Product Success

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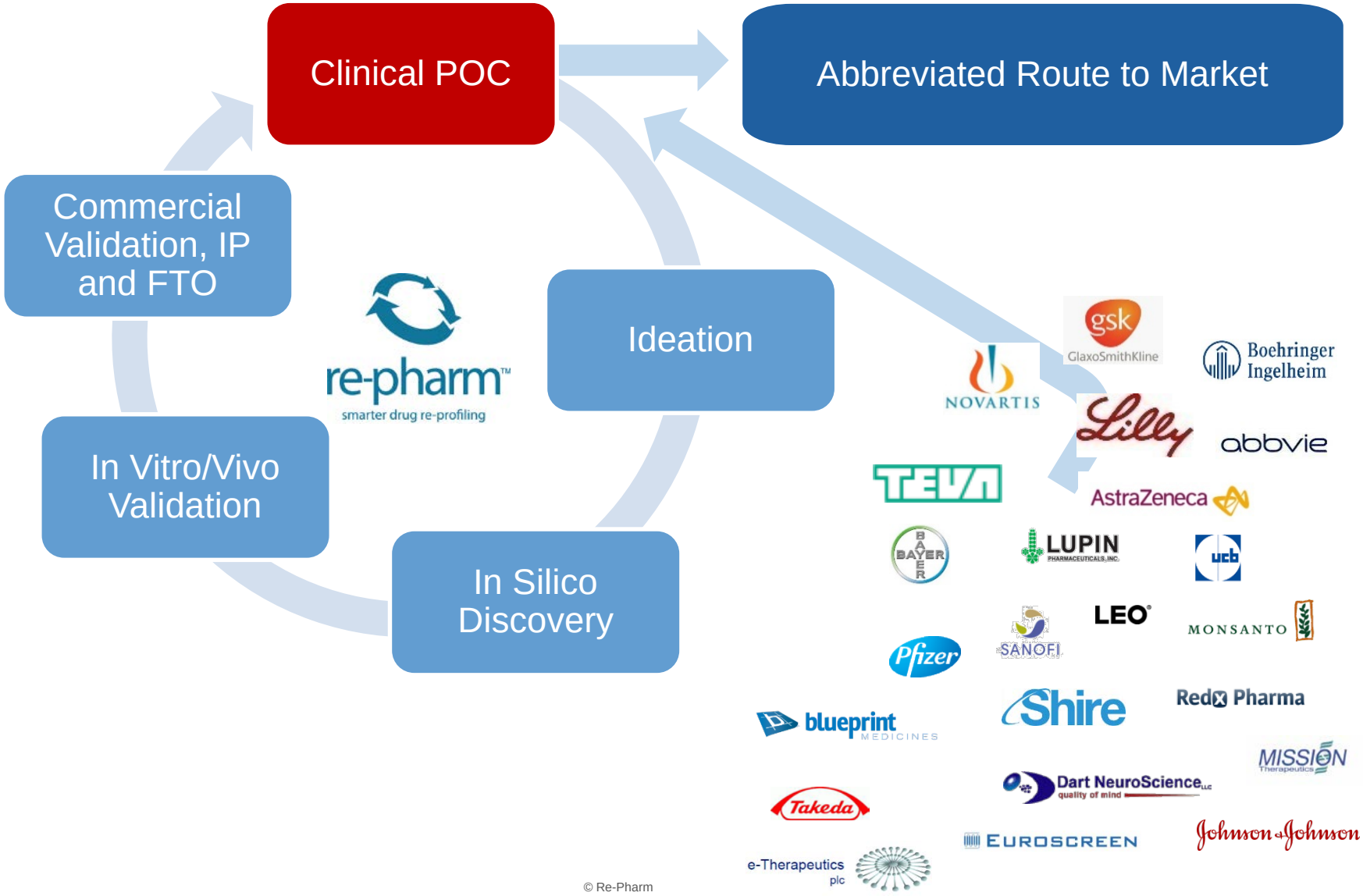
Re-Pharm Summary



RP0217 Intellectual Property & Unmet Need Analysis

- IP established
  - Multitude of Topical inflammatory conditions
  - RP0217 is degraded by light, so internal, topical conditions
  - Worldwide geographies

"An Ideal Anti-Inflammatory Would Be?"

Potent & Efficacious
without the Side Effects and safety issues associated with current treatment (i.e. Steroids)

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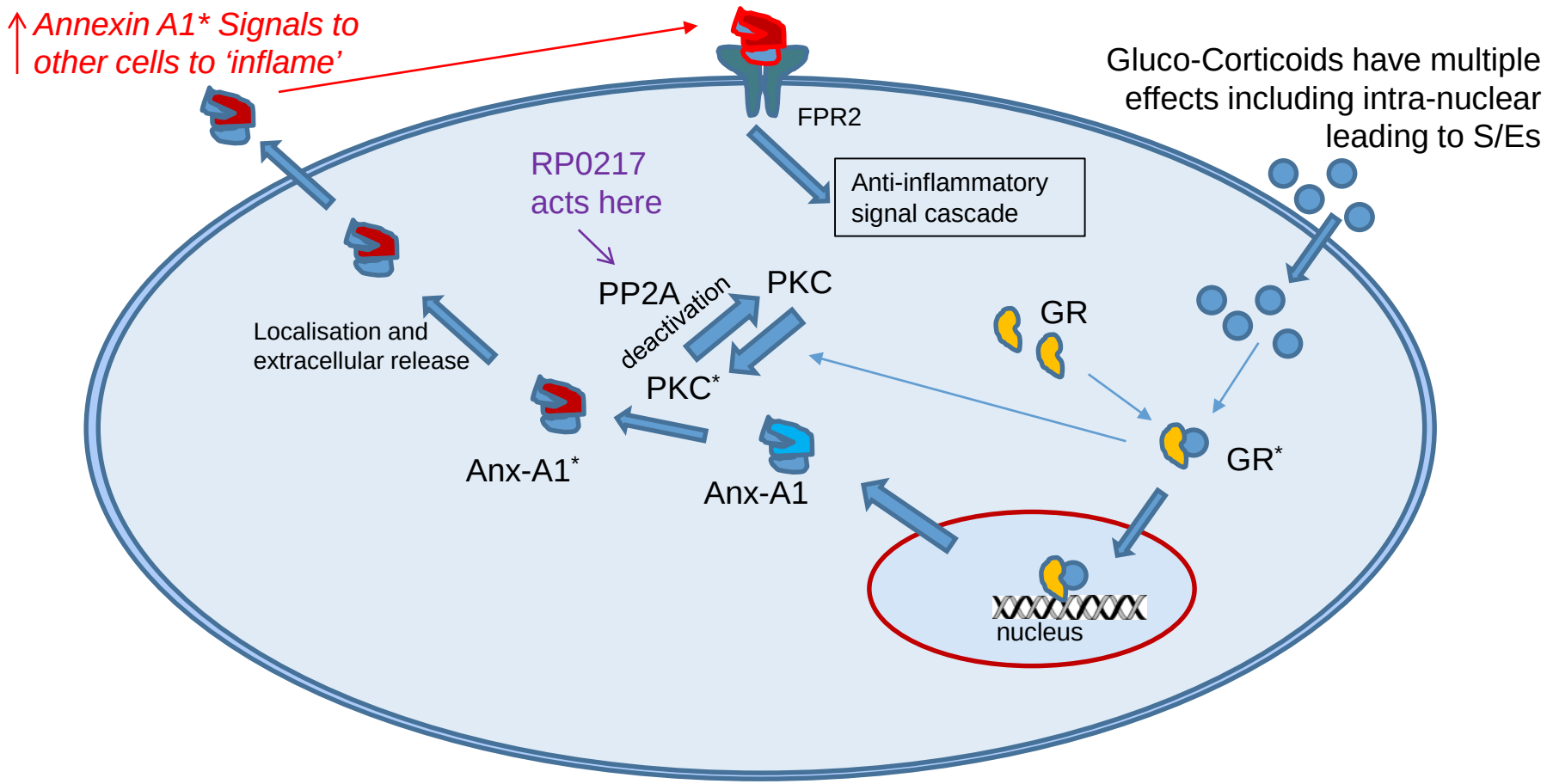
Annexin-A1 as a therapeutic target

Annexin-A1 is a fundamental and key component of the innate anti-inflammatory response. It is central to many existing steroid and NSAID responses.



This creates a powerful opportunity for therapeutic intervention in the inflammatory cascade

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Summary of PP2A/Annexin A1 Regulation

- *Annexin-A1* is a potent inflammatory agent and valid target for NTE Development*
- Glucocorticoids (GC) reduce the release of Annexin-A1* through multiple actions
  - Intra-cellular multitude of activity reduces Annexin phosphorylation
  - Intra-nuclear activity reduces Annexin levels too but causes side effects
- RP0217 is a Targeted PP2A Anti-inflammatory Agent
  - Intra-cellular PP2A activity reduces Annexin phosphorylation
  - NO intra-nuclear activity means NO Side-effects

"An Ideal Anti-Inflammatory Would Be?"

Potent & Efficacious
without the Side Effects and safety issues associated with current treatment (i.e. Steroids)

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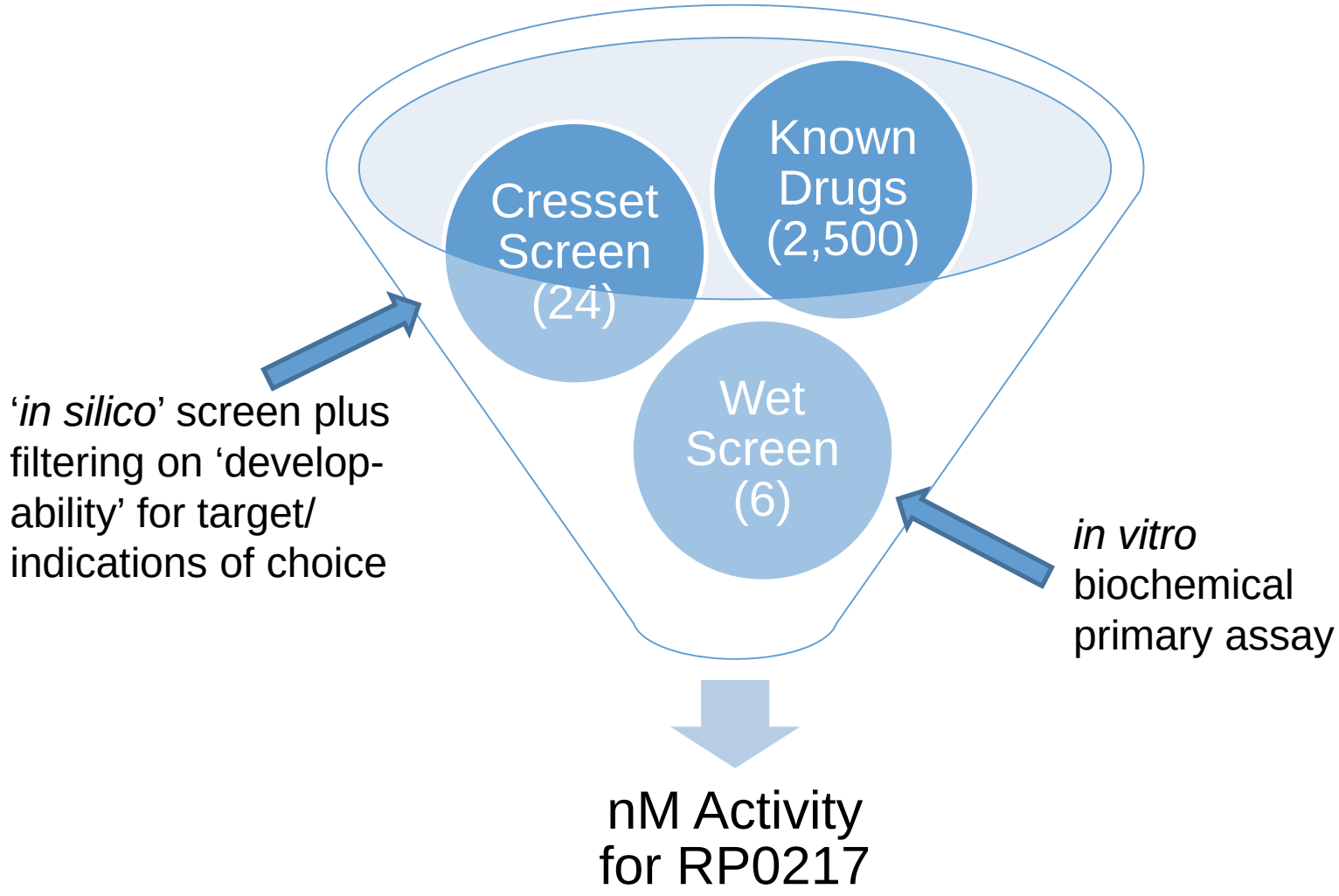
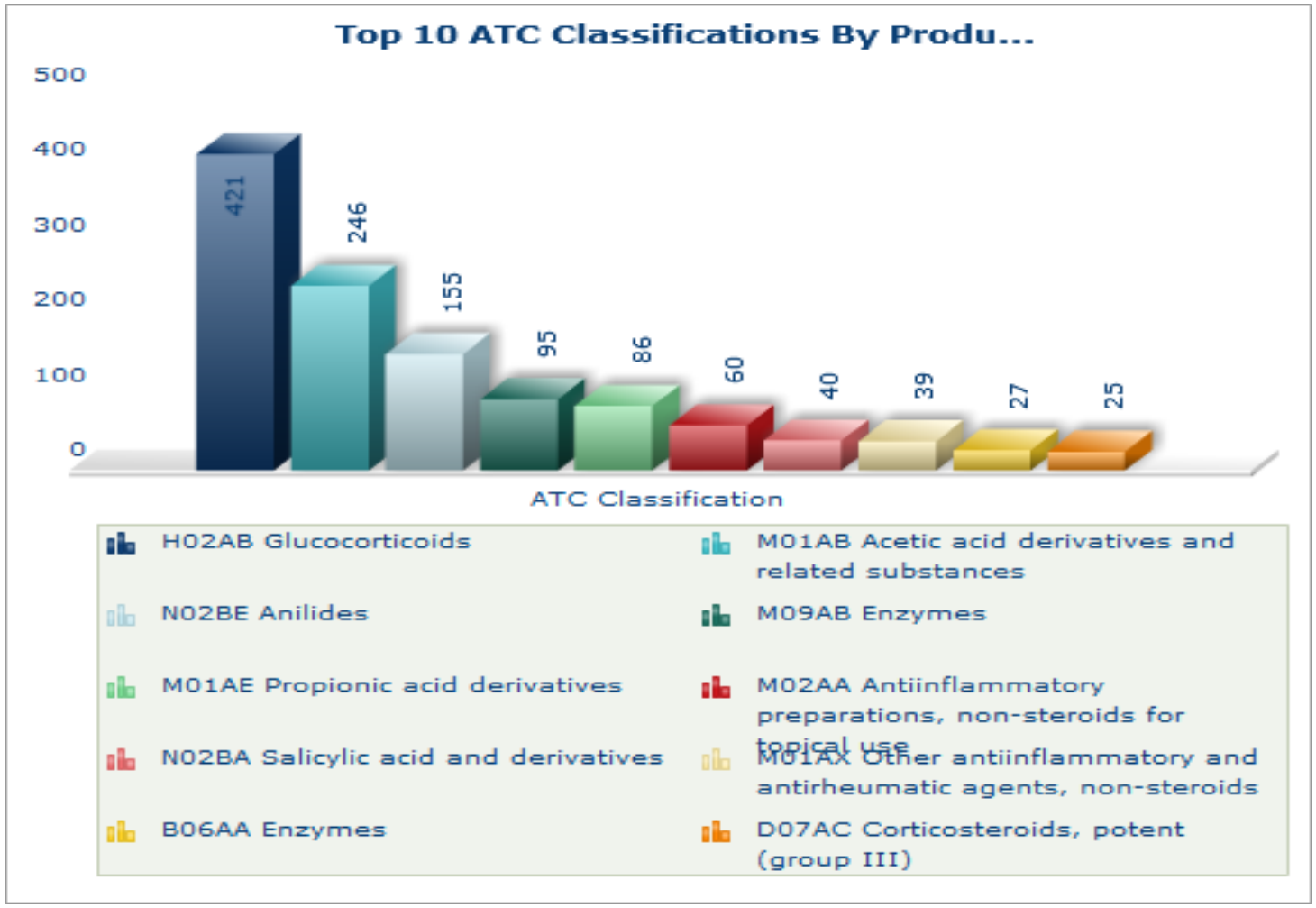
RP0217 Discovery of a new Anti-Inflammatory Agent

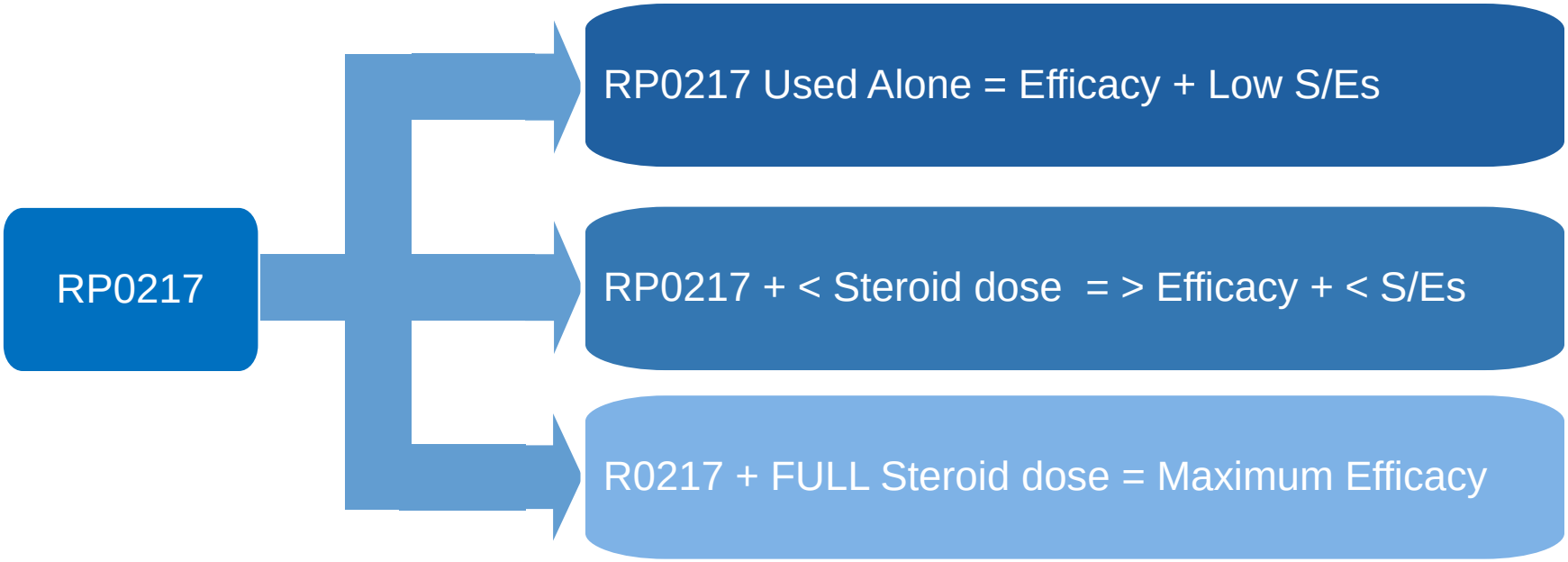


Current Sales of Anti-Inflammatories by ATC



RP0217 Advantages over Current Therapy Protocols

> Excellent Anti-Inflammatory Efficacy with Low Side Effects **Plus**…
  > Options for improved Efficacy/Safety profile in combination

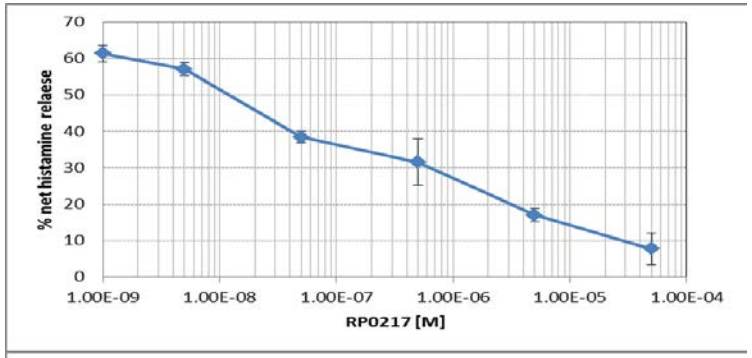


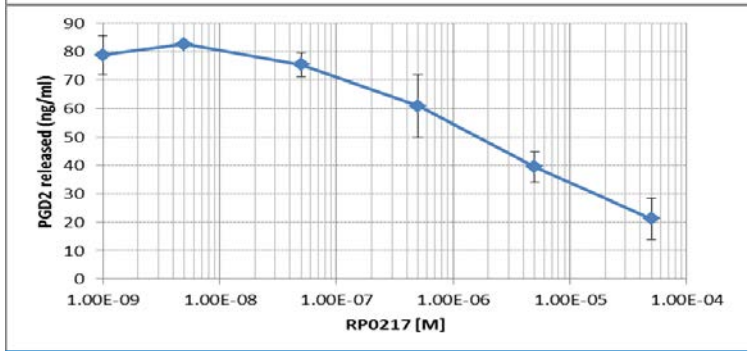
Excellent Efficacy with a Better Side Effect Profile

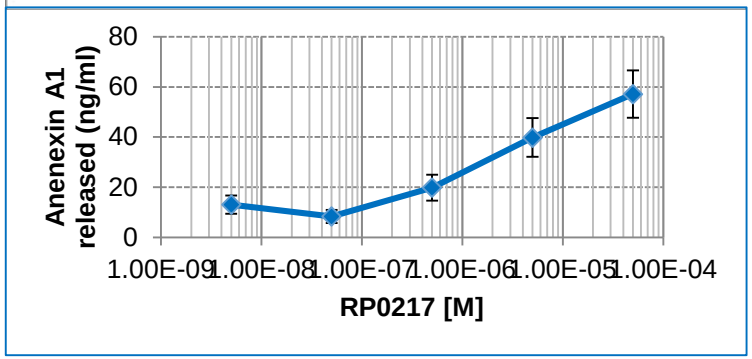
In Vitro Data to date…

Human Mast cells-stimulated with IgE

Potent anti-inflammatory activity and correlation with Anx-A1 stimulation







Attenuation of histamine & PGD_2 release

- RP0217 **potent** anti-inflammatory activity.

Effects correlate with increased Anx-A1 release

- Consistent with mechanism of action

Studies performed in 5 minute timescale

- Indicative of rapid onset effect

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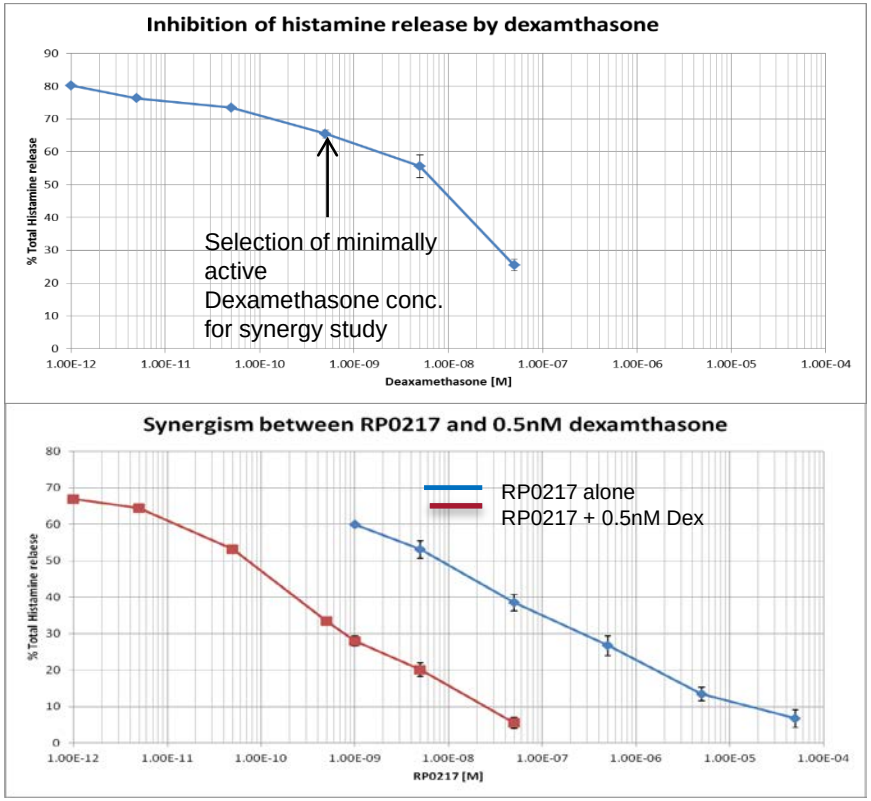
Demonstration that RP0217 synergises with Steroids



Human Cord Blood Mast Cells

- Selection of minimally active Dexamethasone concentration for synergy study
- Clear synergy with glucocorticoid ~100 fold left shift in D/R curve
- Clear anti-inflammatory activity at very low concentrations of RP0217 in combination with steroid (threshold ~$5x10^{-11}$ RP0217 + $5x10^{-10}$ Dexamethasone)
- Indication of “steroid sparing” activity-attractive profile for ocular allergy/inflammation

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Suggested Target Indications for RP0217

- Anti-Inflammatory indications targeted to date:
  - Allergic rhinitis/conjunctivitis
  - Uveitis
  - Asthma
  - Inflammatory Bowel Disease

Target Indications for RP0217

Allergic Rhinitis

Target Indications for RP0217

Allergic Rhinitis

- Steps to Commercialisation:
  - Proof of Concept
    - Anti-inflammatory activity demonstrated
  - Formulation Development
    - RP0217 is highly soluble in water
    - Spray solution is simple to formulate
    - Nasal spray is simple to deliver
  - Stability Testing
    - Existing IV high dose formulation is stable
  - Acute Local Tolerability in Animals
    - Rat or Dog studies for acute and long-term tox studies
    - Straightforward, well-established and quick
  - Pre-IND/Regulatory Agency Meeting

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Target Indications for RP0217

Allergic Rhinitis

- Steps to Commercialisation:
  - Acute Local Tolerability in Humans
    - Very short study length for safety and efficacy
    - Easy recruitment
  - Phase II Dose Ranging in Humans
    - Short studies as an acute therapy
  - Phase III Efficacy/Safety
    - Re-profiled molecule so high level of confidence in safety
    - Excellent efficacy data to date
  - NDA Submission & Processing
  - Approval & Commercialisation

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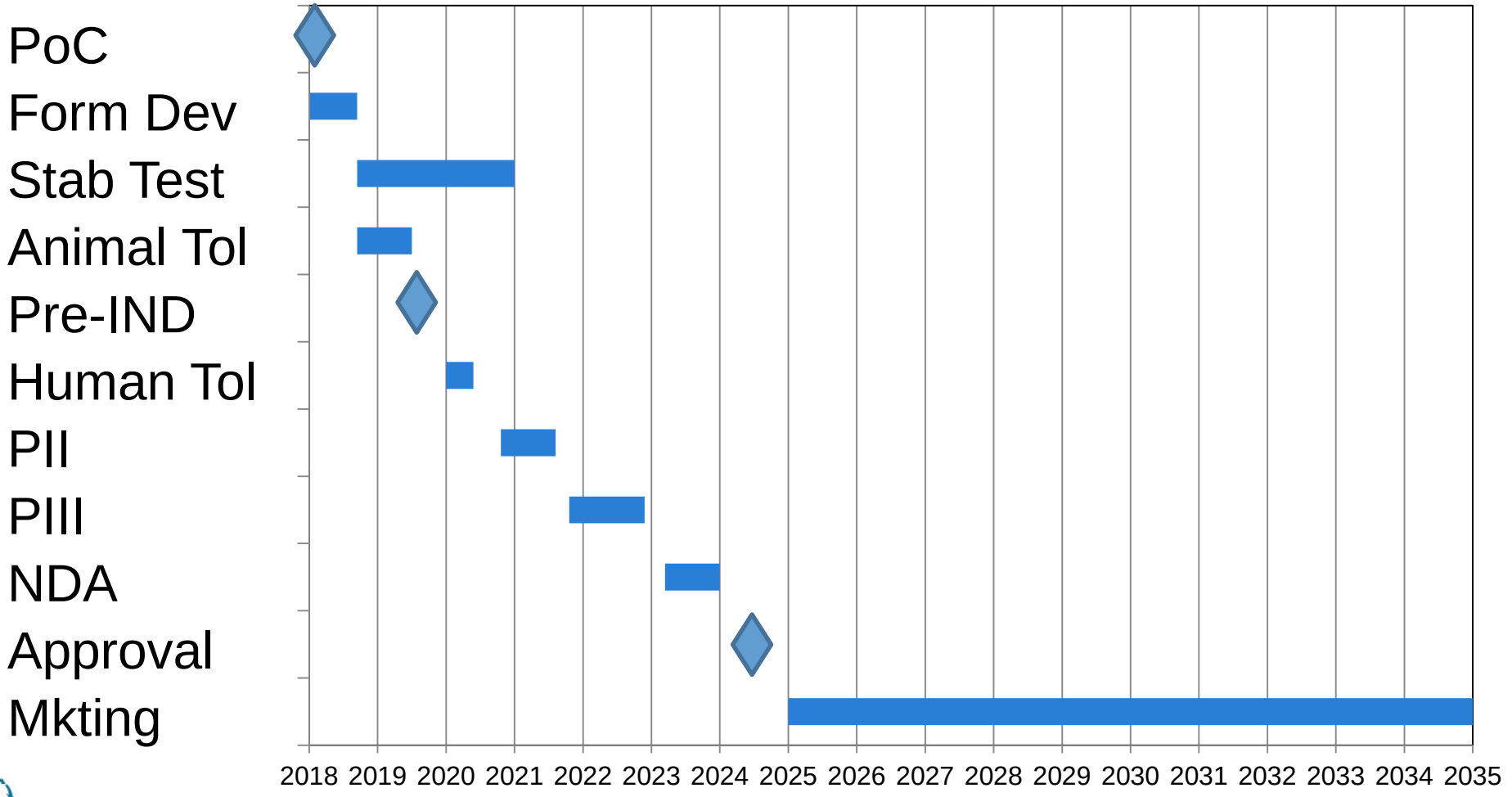
Allergic Rhinitis

- Summary
  - Easy Formulation
  - Fast Pre-clinical Development Plan
  - Fast Clinical Development Plan
  - Inexpensive
  - Low risk
  - Quick Commercialisation
  - Excellent Return on Investment Potential

Allergic Acute Rhinitis

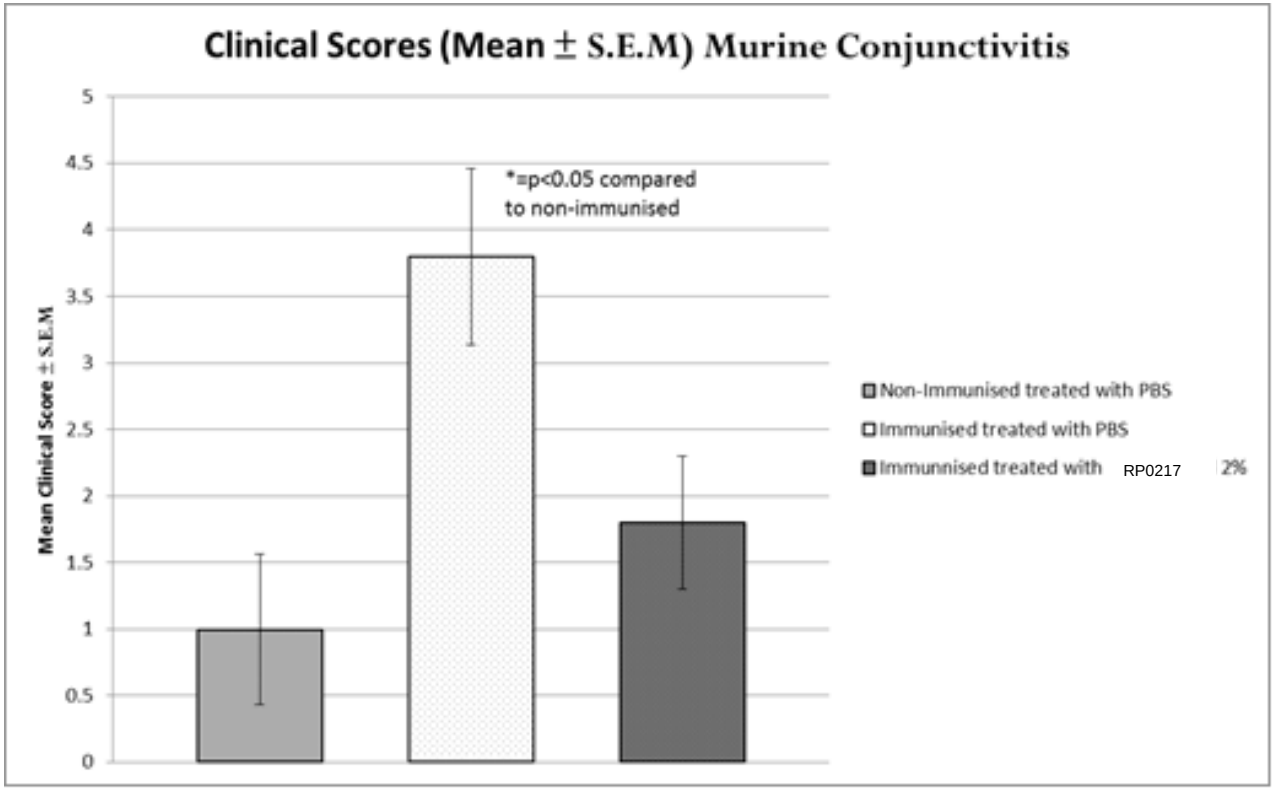
Timeline



Target Indications for RP0217

Ocular Indications
Allergic Conjunctivitis & Intra-vitreal for Uveitis

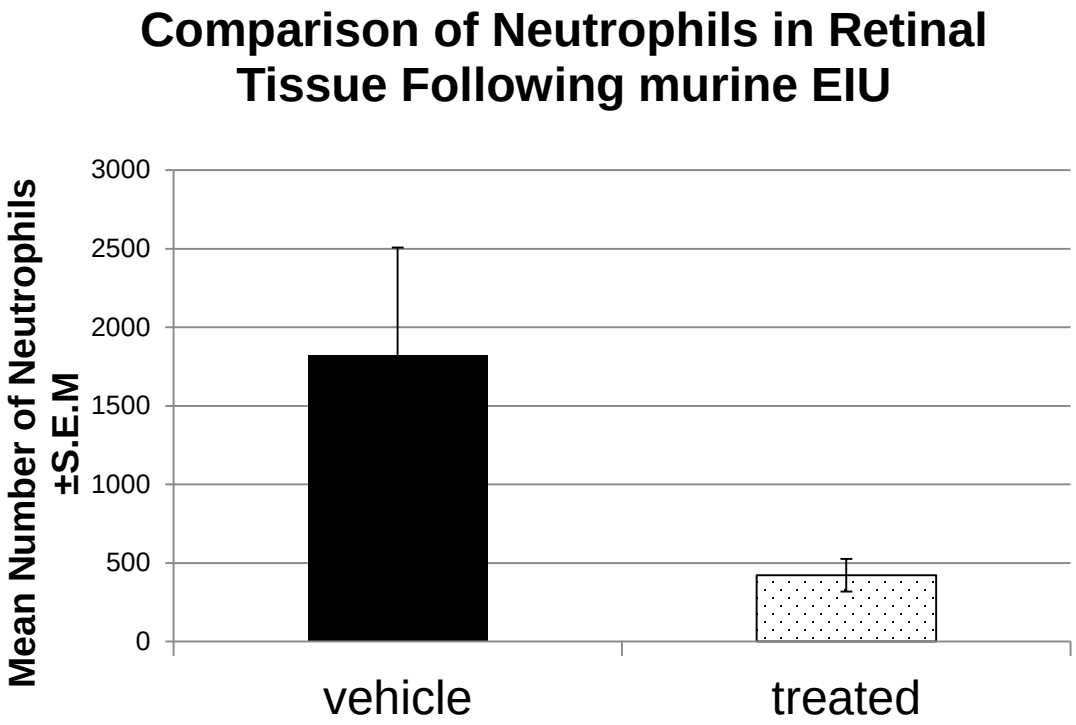
Clinical Scores Murine Conjunctivitis



RP0217 is a potent anti-inflammatory in an accepted model of allergic conjunctivitis

Uveitis-animal model data

- Standard model of Uveitis Endotoxin Induced Uveitis (EIU) in mice
- Intravitreal injection of LPS and either vehicle or RP0217 0.1µg
- 15 hours later (peak response) retinal tissue excised and neutrophil invasion (key measure) determined



RP0217 effectively reduces Neutrophil count

Uveitis Opportunity for RP0217

Existing Practice

Issues

- > Glaucoma/Cataract/Bone loss/Toxicity/Cataracts
- > Pricing/Reimbursement

Market Size/Type

- > ~USD2.3billion
- > Old steroids, Newer Immunosuppressants & Biologics
- > Injectable

Unmet Needs

- > New First Line Therapy
- > Effective & Good Safety Profile
- > Reasonable Cost
- > Injectable is Acceptable

RPO217 Product Offer:

Advantages

- > Potent with Good Safety Profile/experience
- > Promote as First Line Agent

Pricing Strategy

- > Opportunity to Price well as 'light sensitive' injectable (special vial injection packaging) or novel delivery mechanism/platform

Potential Sales

- > 10% value market share
- > USD 230M

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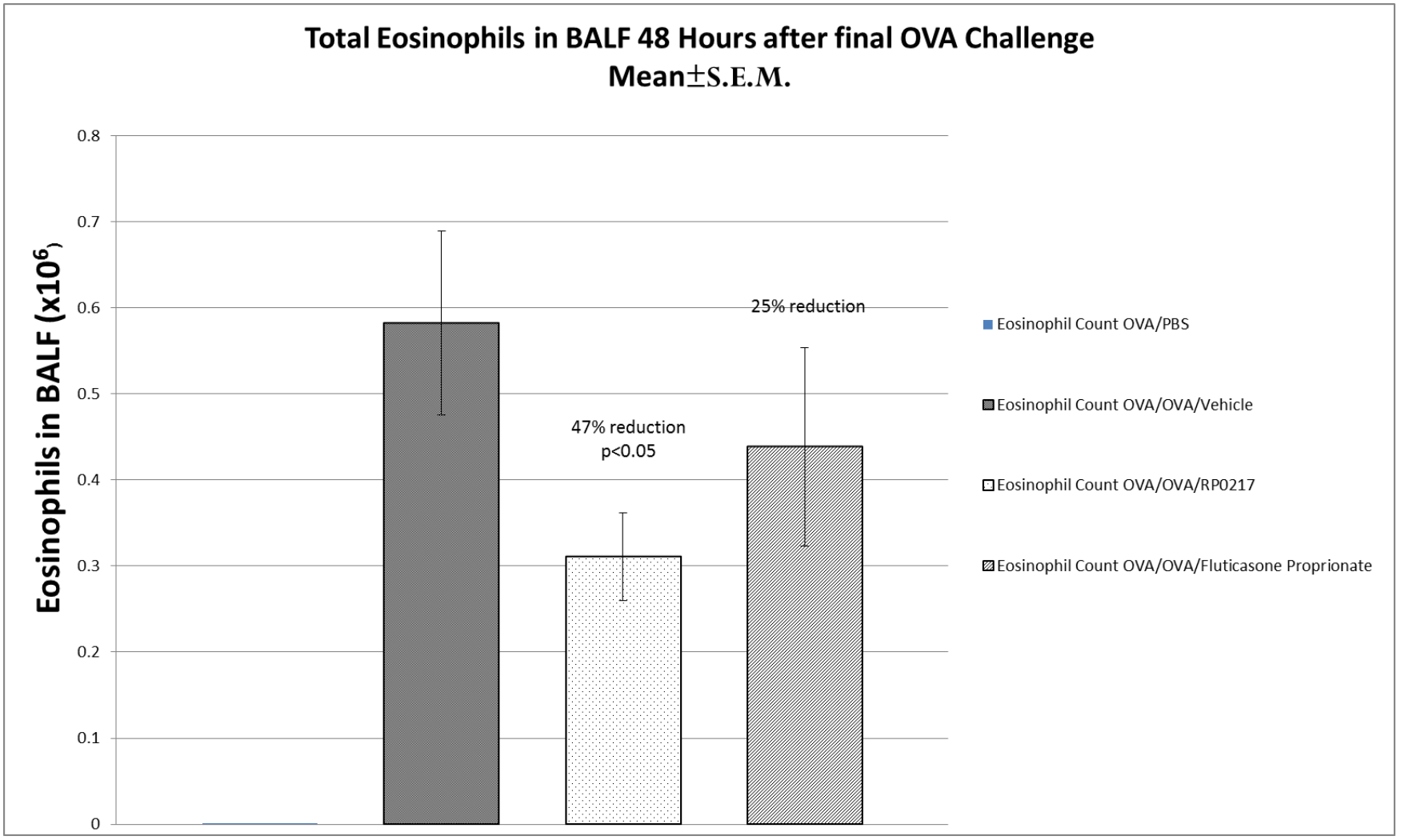
Target Indications for RP0217

Asthma

OVA model of Asthma



Asthma Opportunity for RP0217

Existing Practice

Issues

- > High Dose Steroid S/Es in Adults (5-10%)
- > Low Dose Steroid S/Es in Paeds

Market Size/Type

- > ~USD20billion
- > Old steroids, some newer Immuno-suppressants
- > Mainly Inhaled, some oral.

Unmet Needs

- > New Paediatric Therapy
- > Steroid Sparing Adult Therapy
- > Effective & Good Safety Profile
- > Reasonable Cost
- > Compliance with devices can be an issue (up to 85% may have poor compliance)

RPO217 Product Offer:

Advantages

- > Potent with Good Safety Profile/experience
- > First Line Agent for Paeds
- > Second Line Agent for Adults
- > Steroid Sparing therapy
- > Compliance benefit may ensue

Pricing Strategy

- > Opportunity to Price well with novel device

Potential Sales

- > 3% value market share
- > USD 600M

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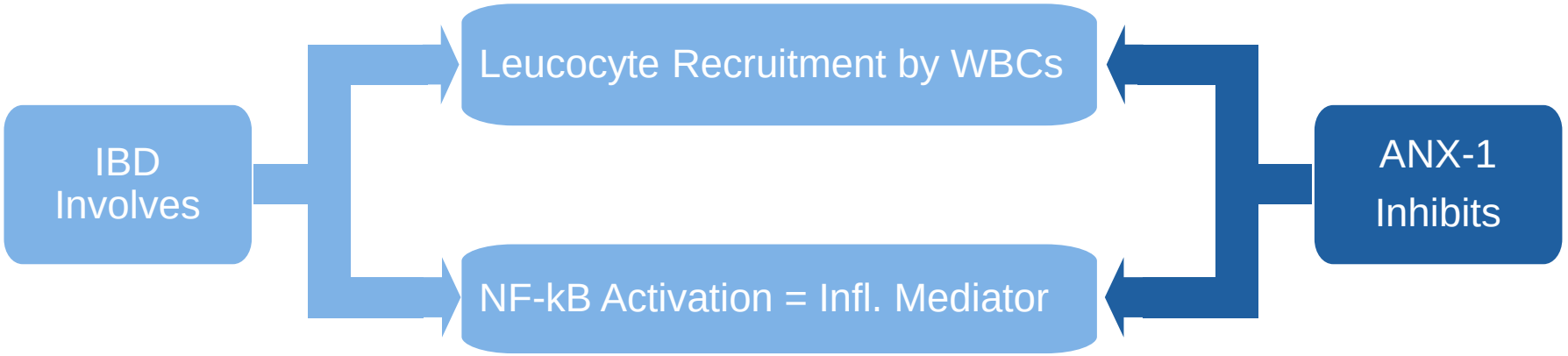
Target Indications for RP0217

Inflammatory Bowel Disease(s)

IBD Pathology

> Complex Inflammatory Condition BUT:



References:
1. ANX-A1 KO increased susceptibility and impaired recovery to DSS induced colitis (Bobbin et al. J. Immunol. 2008)
2. Peptide analogue of ANX-A1, MC-12 reduces inflammation in TNBS and DSS models of IBD & attenuates increase in NF-κB (Ouyang et al. PLoS ONE 2012)
3. Administration of ANX-A1 mimetic peptide in nano-particles accelerated recovery in mouse model colitis. Authors suggested localised delivery of ANX-A1 may represent a treatment for IBD (Leoni et al. J. Clin. Invest. 2015)

In the Clinic…

Humans with Crohns Disease

> **Reduced** ANX-A1 protein

> **Reduced** ANX-A1 mRNA in plasma

Many further studies show role of ANX-A1 also in mucosal repair (see appendix)

Treat with Infliximab

> **Increased** ANX-A1 in responders

> **NO** increase in ANX-A1 in non-responders

Conclusion:

> Reduced ANX-A1 is involved in Inflammatory Bowel Disease

> **Increasing** ANX-A1 with any therapy should alleviate clinical symptoms

> **Increasing** ANX-A1 with RP0217 should allow reduction in dosage of other drugs

Reference:
1. A role for ANX-A1 in the resolution of IBD (Sena et al Plos ONE 2013)

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IBD Opportunity for RP0217

Existing Practice

Issues

- > Existing first line products have poor efficacy
- > Oral Steroid Side Effects

Market Size/Type

- > ~USD2billion
- > Old steroids, some newer Immuno-suppressants
- > Mainly oral, some rectal.

Unmet Needs

- > New Paediatric Therapy
- > Steroid Sparing Adult Therapy
- > Effective & Good Safety Profile
- > Reasonable Cost
- > Compliance with devices can be an issue

RP0217 Product Offer:

Advantages

- > MoA suggests good Potency
- > Could be Steroid-sparing
- > Targeted delivery could strengthen IP

Pricing Strategy

- > Opportunity to Price well with novel delivery device

Potential Sales

- > 5% value market share
- > USD 100M

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RP0217 – The Opportunity

Conclusions

Potential Development path

- RP0217 is prescribed in many countries at high antibiotic doses with a good clinical safety record over >45 years
  - The anti-inflammatory activity is accessed at 100 to 1000 fold lower concentrations - mitigating concerns with respect to antibiotic resistance
- US 505(b)2 and equivalent European Biowaiver regulatory pathways can be utilized
  - No need for non-clinical safety studies to be repeated.
- Potential, following formulation development work, for study work to move straight to phase II for each indication.

Scientific rationale for RP0217 is strong, next stage PoC work to consider:

- *Animal/In Vitro Human Tissue studies*

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A New Therapeutic Entity - RP0217 – The Opportunity

- Strong IP – could be further enhanced in combination with delivery technology
- Strong MoA story – Original/Novel MoA
- Excellent Efficacy/Safety Profile
- Excellent potential for Combination therapy to be Additive
- Substantial Unmet Need in Uveitis/IBD
- Good potential pricing scenario – injectable/or in combination with delivery technology
- Extensive Safety Database – De-risked Development Pathway
- A highly abridged development path - no need for systemic toxicology

RoI is potentially high due to long IP, multiple indications, a good pricing scenario, a low cost, shortened development pathway, and substantial market need in several indications

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RP0217 Summary

Low Dose	Re-Profiled	Trusted	Extensive Database
Potent	Low S/Es	Synergistic	Proven *in vitro*
Strong IP	Target Indications	Unmet Needs	Good Pricing
Shortened Clinicals	Proven Team	Low Risk	**Good RoI Potential**

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RP0217 – The Opportunity

Appendix

Re-Pharm Summary

- Pre-Clinical stage company - building a drug development opportunity pipeline
- Focus on commercially valuable early stage assets:
  - **New Therapeutic Entities (NTEs)**
    - Re-positioned/Re-profiled
    - Biological understanding and Cresset modelling tools generate:
      - New Molecular ‘Presentation’ of product
      - New Indications
      - New Formulations/Delivery Platforms
      - New IP
      - New Price
- Combination of Cresset technology excellence & experienced team
  - Excellent Scientific re-profiling expertise
    - Computational Chemistry/Chemi-informatics
    - In Vitro/In Vivo Trials & Regulatory Strategy
    - Commercial Lifecycle Management
  - Proven track record in taking re-profiled compounds to market launch

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RP0217 in Inflammatory Bowel Disease (IBD)

Scientific Rationale

Cellular and mechanistic

> IBD involves activation of lymphocytes, macrophages and PMN's

> ANX-A1 inhibits leucocyte recruitment

> NF-κB activation appears to a key common inflammatory mediator in IBD

> ANX-A1 inhibits NF-κB

Evidence from animal models of IBD

> ANX-A1 KO increased susceptibility and impaired recovery to DSS induced colitis (Bobbin et al. J. Immunol. 2008)

> Peptide analogue of ANX-A1, MC-12 reduces inflammation in TNBS and DSS models of IBD & attenuates increase in NF-κB (Ouyang et al. PLoS ONE 2012)

> Administration of ANX-A1 mimetic peptide in nano-particles accelerated recovery in mouse model colitis. Authors suggested localised delivery of ANX-A1 may represent a treatment for IBD (Leoni et al. J. Clin. Invest. 2015)

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RP0217 in Inflammatory Bowel Disease (IBD)

Scientific Rationale

Clinical evidence - a role for ANX-A1 in the resolution of IBD

> Human mucosal cell based studies indicate a role for ANX-A1 in mucosal repair (Babbin et al. J. Biol . Chem. 2006)

> ANX-A1 secretion from colonic biopsy in patients with UC but not healthy controls (Vergnolle et al. Inflam Bowel Dis 2004). Given the known anti-inflammatory action of ANX-A1 authors suggest role to down-regulate the inflammatory response in IBD

> Comparison of ANX-A1 levels in mucosa of UC patients in remission with control (healthy and history of UC) shows up regulation, supporting the concept that ANX-A1 acts as a pro-resolution agent promoting mucosal repair (Vong et al. PLoS ONE 2012)

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RP0217 in Inflammatory Bowel Disease (IBD)
Strong Scientific Rationale (pre-clinical)

Mechanistic evidence

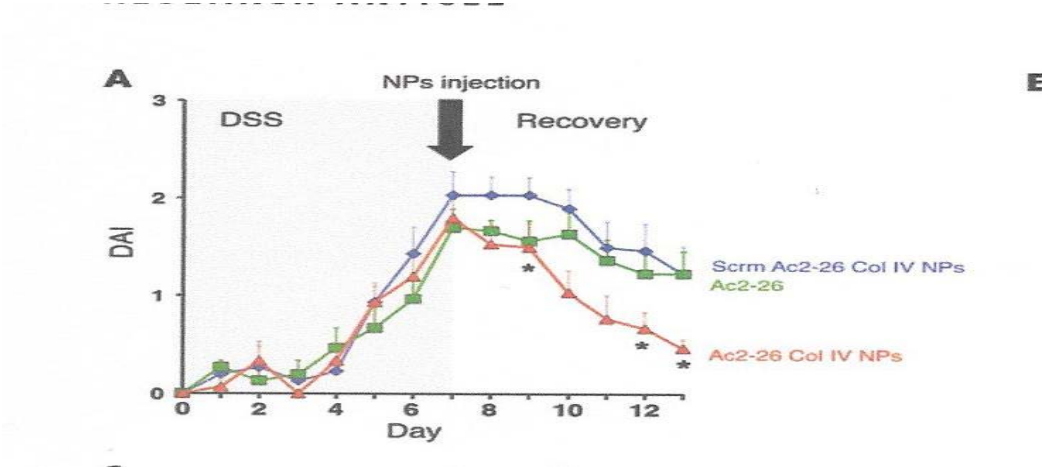
> Anax-A1 Inhibits key pathological drivers of IBD

  > Inflammatory cell recruitment & signalling pathways NFκB

Animal models of IBD

> Genetic deletion of ANX-A1 exacerbates colitis

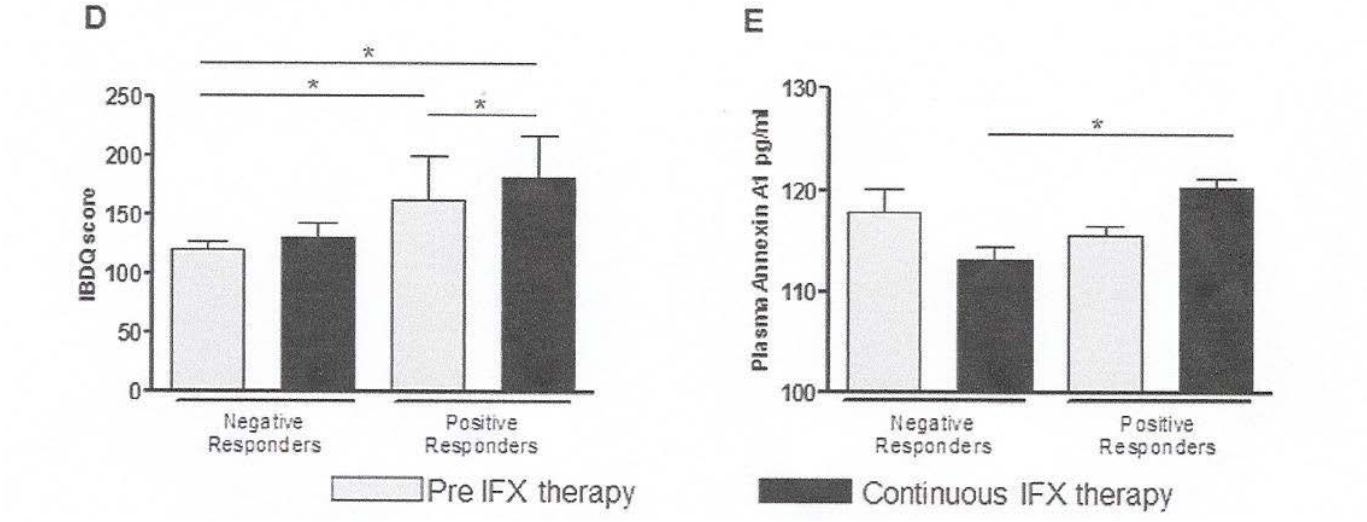
> Peptide analogues of ANX-A1 improve outcome. Particularly when delivered to the gut:-



Refs. Bobbin et al. 2008; Ouyang et al. 2012; Leoni et al. 2015

RP0217 in Inflammatory Bowel Disease (IBD)
Strong Scientific Rationale-Clinical evidence

- > Studies indicate Anx-A1 is involved in gut repair in IBD-Pro-resolution
- > Found in Gut of IBD patients and higher levels in patients in remission: supports pro-resolution role
- > Clinical study in patients treated with Infliximab finds increase in Anx-A1 in clinical responders but not in clinical non-responders:



Refs: Vergnolle et al 2004; Babbin et al. 2006; Vong et al. 2012 & Sena et al. 2013

RP0217 in Inflammatory Bowel Disease (IBD)
Strong Scientific Rationale

Summary

- Clinical and preclinical evidence supports concept that ANX-A1 is involved in resolving IBD
- Opportunity for novel treatment of IBD with RP0217
- Ideally by localised delivery e.g. oral formulation or enema
- Could be as monotherapy or:
  - Opportunity to boost activity of existing steroid therapy but with side effects of high dose steroids
  - Potential to enhance other existing therapies e.g. Infliximab

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