Targeting the adenosine immunosuppressive pathway for cancer immunotherapy with small molecule agents

**A₂R, CD73 specific and A₂R/CD73 Bispecific small molecules for Immuno-Oncology**

### Overview
- **Project concept:** Discover specific and bispecific small molecules inhibiting the adenosinergic pathway for immuno-oncology therapies
- **Strategy:** Create patentable high quality assets
- **Project status:** Selection of CD73/A₂R specific and A₂R/CD73 specific small molecules
- **Primary indication:** Combination with immune checkpoint therapies for non responder patients
- **Administration:** Oral administration
- **Biomarker:** Patient stratification: CD73 positive tumour
- **Activity of adenosine pathways and CD73 expression**

### A₂R & CD73 combination prioritized

Modulating adenosine levels in the tumour microenvironment will limit tumour growth and improve anti-tumour immune activity.

Results expected from the A₂R/CD73 bispecific molecule:
- Overcoming immune suppression
- Enhanced T lymphocyte & NK cell activity
- Decreased tumour cell proliferation
- Inhibiting tumour angiogenesis
- Inducing blood vessel normalization
- Improving blood vessel extravasation

### Rapid A₂R/CD73 specific small molecule discovery

10-criteria selection process

| Criteria | Terms | A₂R affinity | CD73 affinity | CD73 activity | Anti-CD73 mAb | Anti-CD73 mAb
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Oral administration</td>
<td>2. Solubility</td>
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### GPCRs: World Leading SPR-Driven Fragment Screen

- Both GPCR and Globular Protein Coverage
- Uses wild type GPCR Protein
- Not thermosubilized
- Identifies orthosteric and allosteric ligands

### In vivo performance validation

**A₂R activity**

- Recovery of IL-2 production by T cells

**IL2 production induced by 0021546 compound**

### Conclusion & next steps

- Adenosinergic franchise
- A₂R specific antagonist in Candidate identification phase
- A₂R/CD73 bispecific in Lead identification phase
- Programmed well placed to deliver development candidates in 2017
- Potential to deliver CD73 selective inhibitor and to extend bispecific approach to include targets such as CD39
- Platform or specific program open to partnering

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**Excella, Evotec, Boston, Eton, Evotec Elancet Ltd, Luton, Evotec Biosciences, Sheffield, UK, United Kingdom**

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**Abstract #2634**

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