Learnings from AstraZeneca's Open Innovation Program

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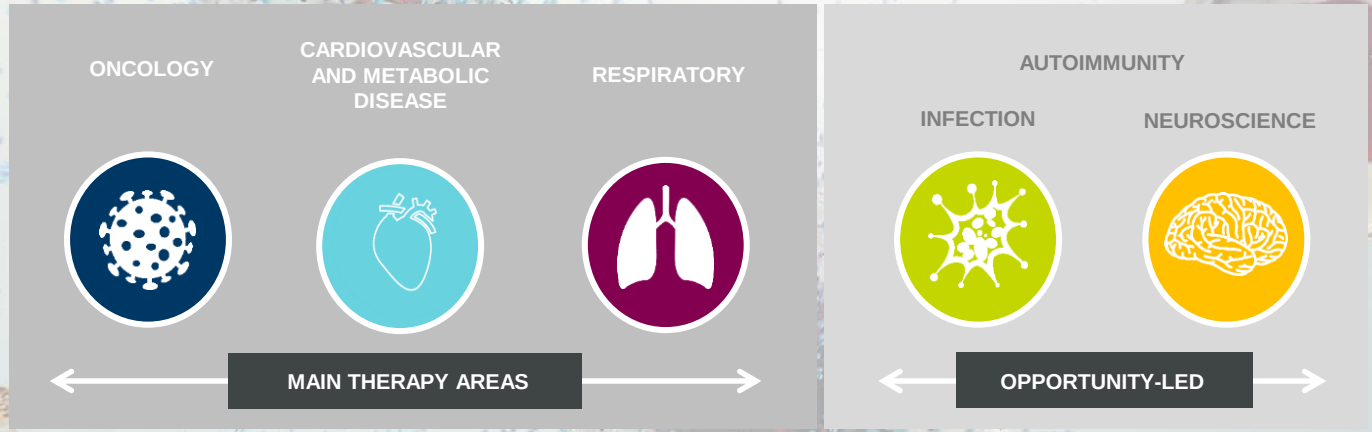
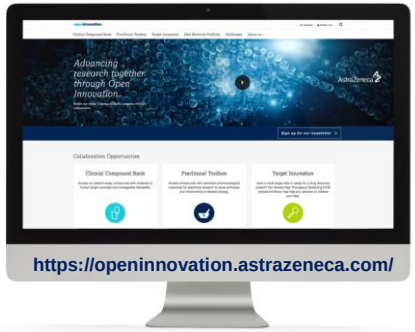
We focus on a deeper understanding of disease biology and mechanisms across three main therapy areas

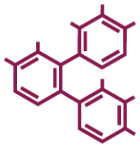


Rationale for Open Collaboration

Benefits to external collaborator and AstraZeneca



AstraZeneca



Compounds

Facilities

Drug Discovery Knowledge

External Scientists

Disease Knowledge

Patients / subpopulations

Technology

Questions that otherwise could not be asked

Open Innovation – Delivery

Clinical Compound Bank

Access **18** of our patient-ready compounds with evidence of human target coverage and manageable tolerability.

Delivered:
- **30** ISS clinical validation studies
- **26** externally funded; **5** completed

Disease indication agnostic

Preclinical Toolbox

Access **44** of our compounds with optimised pharmacological properties for preclinical research to study pathways and mechanisms of disease biology.

Delivered:
- **150+** projects approved

Primarily in AZ main therapy areas, but focusing on novel science

Target Innovation

Have a novel target idea or assay for a drug discovery project? Our diverse High Throughput Screening (HTS) compound library may help you advance or validate your idea.

Delivered:
- **62** projects on-going/complete

Provides access to 250k compounds
Now aligned to AZ R&D focus areas

Open Innovation – Delivery

New Molecule Profiling

Explore the properties and therapeutic potential of your novel compounds by leveraging our cheminformatic and screening technologies.

Delivered:
- **30,000** natural product compounds added to AZ's HTS library

Challenges

Offer and be rewarded for your innovative ideas and research expertise to help overcome difficult R&D barriers.

Delivered:
- 17 challenges run
- 2 collaborations delivered solutions

Data Library

Access preclinical data sets on our early development compounds for data mining and research purposes. to enhance understanding of translation to human efficacy and safety.

Launched June 2017
- Preclinical safety data
- Oncology combinations data


Clinical Compound Bank

MRC Collaboration For Translational Research

'Mechanisms of disease' 2011

AstraZeneca
MRC Medical Research Council
Investigators and academic institutions

- 22 AstraZeneca compounds initially available for clinical studies
- >100 clinical and pre-clinical proposals from 37 UK institutions
- Proposals submitted on all compounds & across a broad span of disease areas
- MRC funded >$10M
- >15 collaborative proposals funded across multiple disease areas

To investigate mechanisms of disease and the development of potential therapeutic interventions

Clinical Compound Bank

How does it work?

18 compounds currently available for clinical studies
44 compounds currently available for pre-clinical studies

Compound	Mechanism of action	Originating therapeutic area	Proposal type	CNS Penetrant
AZD4017	11-beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor	Metabolic Disease	Clinical & Preclinical	Low
AZD5069	Chemokine (C-X-C motif) receptor 2 (CXCR2) antagonist	Inflammation	Clinical & Preclinical	Unknown
AZD5213	Histamine receptor 3 (H3) antagonist (inverse agonist)	CNS	Clinical & Preclinical	Yes
AZD5904	Myeloperoxidase (MPO) inhibitor	Inflammation	Clinical & Preclinical	Low
AZD7325	Gamma-aminobutyric acid receptor A alpha 2 & 3 (GABAAα2,3) positive modulator	CNS	Clinical & Preclinical	Yes
AZD9150	Signal transducer and activator of transcription 3 (STAT3) antisense	Oncology	Clinical & Preclinical	Low
AZD9668	Neutrophil elastase (NE) inhibitor	Inflammation	Clinical & Preclinical	Low
AZD9977	Non-steroidal mineralocorticoid receptor (MR) modulator	Cardiovascular	Clinical & Pre-clinical	Unknown
Lesogaberan (AZD3355)	Gamma-aminobutyric acid receptor B (GABAB) agonist	GI	Clinical & Preclinical	Low
Saracatinib (AZD0530)	Src tyrosine kinase family inhibitor	Oncology	Clinical & Preclinical	Yes

Preclinical pharmacology

AZD5213 is potent (Ki 0.5nM; dissociation KB 0.2nM), competitive, rapidly reversible, functional antagonist (inverse agonist; IC_{50} of 3nM) at the human H3 receptor. It occupies H3 receptors with an *in vivo* pKi of 8.5, 8.3 and 8.4 (free concentration in brain) for rat, mouse and NHP, respectively. AZD5213 was tested against a broad panel of 335 other receptors and enzymes at 10μM without significant activity (>50% inhibition) for any. *In vivo*, it triggers the release of histamine as well as the neurotransmitters acetylcholine, dopamine and norepinephrine in rat prefrontal cortex following dosing or 0.33mg/kg, po and increased tele-methylhistamine in the CSF of cynomolgus monkeys at 0.1mg/kg, po. At similar dose levels, AZD5213 has been shown to reverse scopolamine-induced memory deficit, increase novel object recognition, and reverse neuropathic in various rodent models.

Safety and tolerability

AZD5213 has been administered orally to healthy volunteers in single doses up to 80mg and multiple doses up to 18mg QD for 10 days. The most frequent and dosing limiting adverse effects were sleep disorder, night sweats, and decreased quantity as well as quality of sleep. Other common AEs include mild to moderate nausea and headache.

Preclinical studies of up to 6 months duration have been performed.

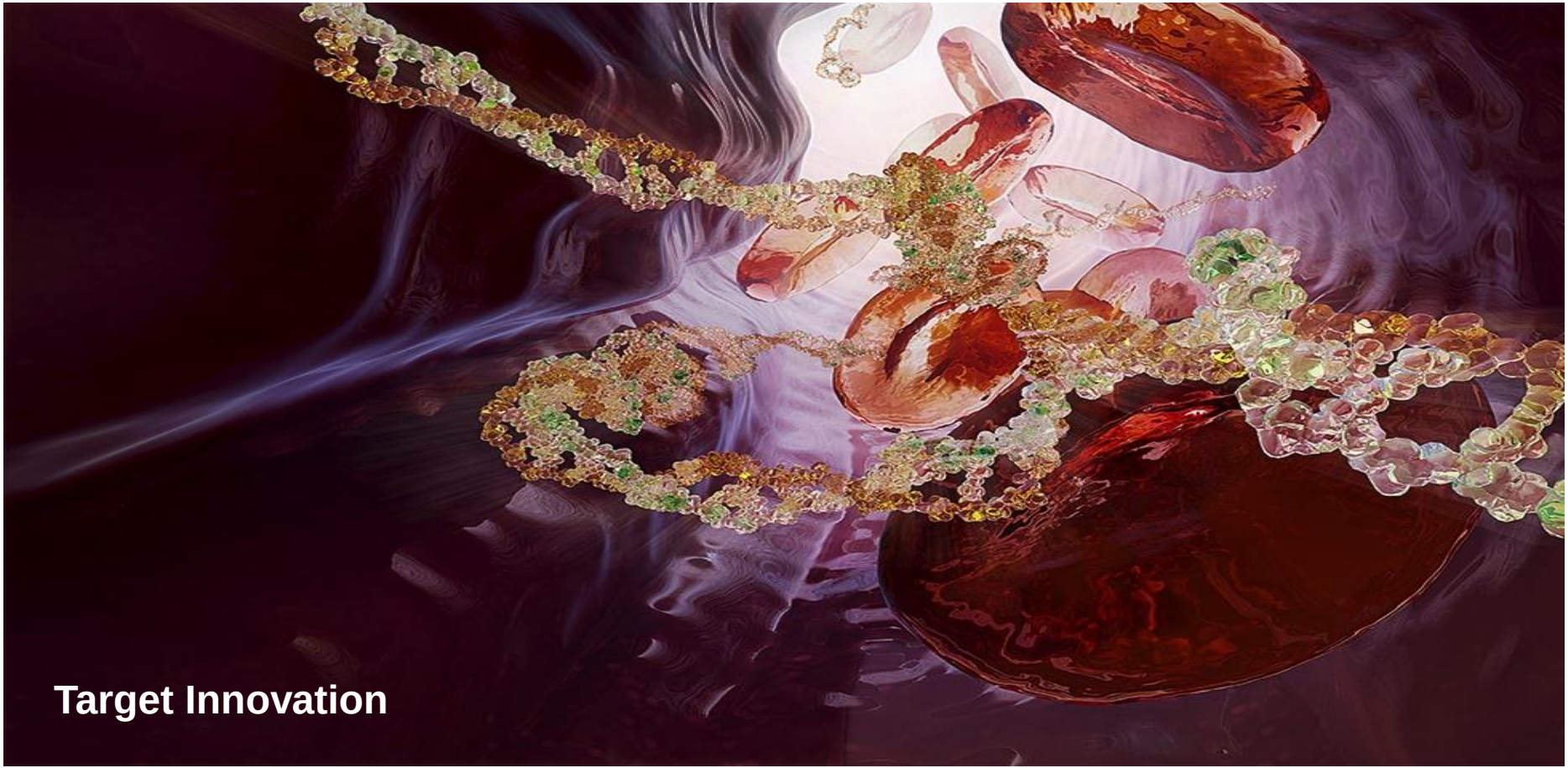
Clinical pharmacology

AZD5213 was rapidly absorbed (T_{max} of 0.7-2.0 hrs) after oral administration with an overall terminal t½ of 5-7 hours. *In vitro* studies show a low risk for DDIs. PET studies demonstrated saturable, concentration-dependent occupancy of H3 receptors with an estimated Ki,pI of 1.14nM. Receptor occupancy of ~50% was achieved at a dose of 0.1mg.

Suitable for and exclusions

Preclinical reprotoxicology data are available and have not identified any specific risks. Women of child-bearing potential using highly effective contraception can be included.

Indications and dosing regimen should consider the potential for and optimisation of efficacy while minimizing the mechanism-based adverse effect on sleep. Given the strong association between dose, plasma concentration and brain receptor occupancy as well as the rapid absorption and relatively short t½, data is available to potentially optimise benefit (day time efficacy) versus risk (night time sleep disturbance).


Target Innovation

Maximising the value of compound collections to create diversity

- Peer-to-peer compound exchange initiatives
- Reciprocal access to high quality compound libraries

Strategic Partnerships

Closer collaboration, more learning

- Based on principles of Target Innovation
- Partners bring extensive Drug Discovery expertise and experience
- Provides clear route forward for projects
- Develop long term relationship
  - Builds credibility on both sides
  - Opportunity to be more flexible
  - Can focus on specific areas of biology
- Multi-target deal simplifies contracting

Lead Discovery Center LDC

MRC T lifeArc

Kærtor Foundation

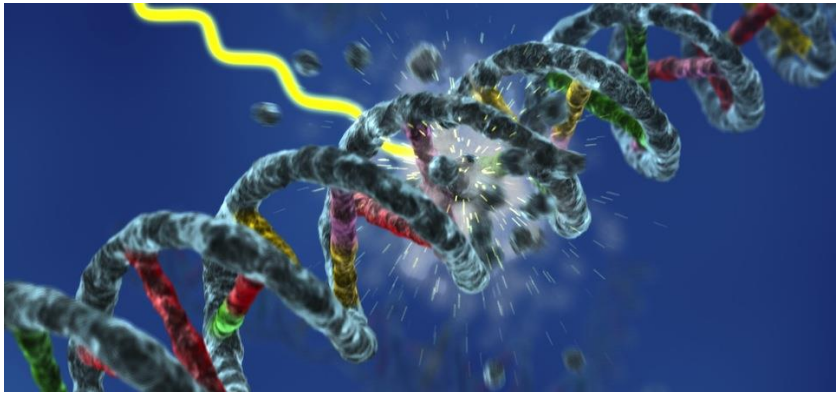
IRIC oR COMMERCIALIZATION OF RESEARCH Institute for Research in Immunology and Cancer

cdrd The Centre for Drug Research and Development

Collaborative Grants

Sussex University DDR Partnership

- 4-year multi-target collaboration
- Sussex University Drug Discovery Centre and AstraZeneca
- £6M funding from Welcome Trust
- Utilise Sussex deep expertise in DNA Damage Response coupled with AstraZeneca's hit identification and drug discovery capabilities



FINANCIAL TIMES

July 24, 2016 4:48 pm

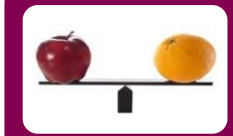
New drugs aim to kill cancer cells by destabilising their DNA

Clive Cookson, Science Editor

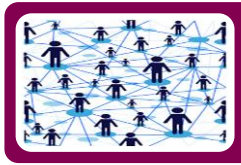
Barriers to Success

Contracting - can be slow even with a standard agreement

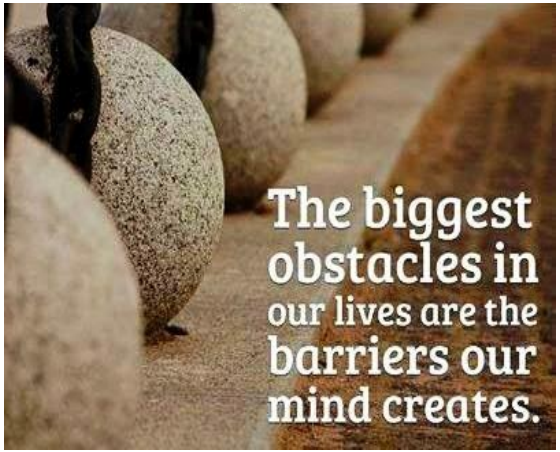
Resourcing and funding gaps for academic projects



Balancing innovation with organisational alignment and likelihood of success



Stakeholder engagement



Acknowledgements

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- **Birte Sebastian** – Communications

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openinnovation