Innovative Medicines & Early Development
Delivering the next wave of scientific innovation
Mene Pangalos, Executive Vice President, Innovative Medicines
AstraZeneca is a place where science thrives

5Rs Framework enables pushing the boundaries of science

Right target
Right tissue
Right safety
Right patients
Right commercial potential
AstraZeneca continues to attract the best scientists
A few examples of recent hires into the IMED Biotech Unit

Jérémie Boucher, Principal Scientist, Diabetes
Previously Harvard
38 publications including Cell, Nature and Nature Medicine

Donald Stanski
Early Clinical Development
Previously Stanford / Novartis / FDA
110 publications including Journal of Clinical Pharmacology and Therapeutics and Anesthesiology

Tim Eisen
Early Clinical Development & Professor at University of Cambridge
163 publications including NEJM, Lancet, Nature

Robert Unwin
Chief Scientist, Chronic Kidney Disease
Previously UCL
153 publications including Lancet, Science, Nature Medicine, Nature Genetics

Ralph Knoll
Chief Scientist, Cardiac Regeneration
Previously Imperial College
54 publications including Cell, J Mol Med

Outi Vaarala
Translational Science
Previously Helsinki University
206 publications including NEJM, Lancet, Diabetes

Tony Johnson
Early Clinical Development
Previously Cambridge University / BMS
79 publications including Diabetes Care, Circulation

James Matcham
Biometrics
Previously Amgen
**Strengthening scientific reputation through a focus on high quality publications**

<table>
<thead>
<tr>
<th>Publication Quality</th>
<th>1Q 2014</th>
<th>2Q 2014</th>
<th>3Q 2014</th>
<th>4Q 2014</th>
<th>Total 2013</th>
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<tr>
<td>All other</td>
<td>143</td>
<td>6</td>
<td>172</td>
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<tr>
<td>High quality = 5-15</td>
<td>73</td>
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<td>High impact = &gt;15</td>
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<td>Total 2013</td>
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<td>247</td>
<td>327</td>
<td>498</td>
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</table>

**Bar Diagram**

- High impact = >15
- High quality = 5-15
- All other

**Table Notes**

- Feedback suppression of PI3Kα signaling in PTEN negative tumors is relieved by selective inhibition of PI3Kβ.
- Ubiquitylation and Cdt1 drive disassembly of the CMG helicase at the end of DNA replication.
- Lessons learned from the fate of AstraZeneca’s drug pipeline: a five-dimensional framework.
- Skeletal Muscle PGC-1α Modulates Kynurenine Metabolism and Mediates Resilience to Stress-Induced Depression.
- Direct Targeted Quantitative Molecular Imaging of Neurotransmitters in Brain Tissue Sections.
- Strengthening scientific reputation through a focus on high quality publications.
- Innovative Medicines & Early Development.
Connecting Cambridge & Gothenburg to create a scientific powerhouse in Europe

Examples of scientific collaborations

AstraZeneca R&D Centre

[Map showing locations in Europe with markers for Cambridge and Gothenburg, and various scientific institutions]
Application of inhaled technology in modifying respiratory disease
Future therapies for respiratory disease supported by advanced inhaled technology platforms

- Broad range of inhalation technologies
- Improved symptom control
- Cutting edge science to modify disease
- Next-generation treatments for asthma and COPD
Targeted therapies to drive efficacy in asthma

**AZD0449: iJAK inhibitor for asthma**
- Well-validated pathway
- STAT signalling critical player
- FTIM 2015
- Collaboration with Rigel

**AZD1419: iTLR9 agonist for early-onset asthma**
- Sustained correction of Th2 imbalance
- Phase II H1 2015
- Collaboration with Dynavax

5 weeks AZD1419 blocks lung inflammation in mice
AZD7624: Inhaled P38 inhibitor for patients with COPD

- Well-validated pathway
- Aimed at steroid insensitive patients
- Direct targeting of immune cells in lung
- Phase II Q4 2014

Phospho p38+ alveolar macrophages in COPD lung

Inflammatory cytokines in human alveolar macrophages

Significant attenuation of LPS-induced TNF-α

(In-house IHC data)
Leading in DNA damage response (DDR)
Leading “first in class” DDR portfolio

- Olaparib (PARP inhibitor)
  - Single-Strand Break Repair
  - Multiple Phase III and Phase II studies

- AZD6738 (ATR inhibitor)
  - Stalled Replication Fork Signalling
  - Phase I

- ATM (protein kinase)
  - Double-Strand Break Repair
  - Lead Optimization

- AZD1775 (Wee1 kinase inhibitor)
  - Cell Cycle Checkpoint Regulator
  - Multiple Phase II and Phase I studies

Two additional early pre-clinical projects

Potential for novel-novel combinations
AZD6738: First-in-class ATR inhibitor for ATM-low NSCLC

- Leads to tumour cell death
- Potent and selective inhibitor
- FTIM Q4 2013
- Combination with carboplatin 2015
AZD6738:
First-in-class ATR inhibitor for ATM-low NSCLC

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Breadth of portfolio allows combinations with strong scientific rationale

Breast cancer - Lynparza & AZD1775 in TNBC

Gastric cancer - Lynparza & AZD6738 in ATM-deficient GC

Lung cancer - Lynparza & AZD1775 in NSCLC and SCLC

Ovarian cancer - Lynparza & AZD1775 in platinum-resistant ovarian cancer

**AZD1775 combination with Lynparza in a TNBC PDX model**

- Vehicle control
- Olaparib
- AZD1775
- Olaparib + AZD1775

Tumour volume (mm) vs. Days (treatment stopped after Day 28)
Pioneering research in oligonucleotide therapeutics
Collaborating with the best partners to harness cutting-edge science in oligonucleotide platforms
Exclusive agreement with Moderna to harness pioneering messenger RNA technology

**Intracellular translation**

**Regenerating blood vessels and cardiomyocytes***

- MI + Luc modRNA (100 µg)
- MI + VEGF-A modRNA (100 µg)

**Expresses in a variety of CV cell types**


![Graph showing VEGF protein levels](image)

- Epicardial Progenitor Cells
- Aortic Smooth Muscle Cells
- Endothelial Cells
- Cardiac Fibroblasts

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Collaboration with Isis Pharmaceuticals to harness pioneering antisense therapeutics

• Antisense approach
• Potential to inhibit validated but ‘undrugable’ targets
• Gen 2.5 chemistry shows improved potency
• Progress:
  – STAT3RX (AZD9150) – Phase I in DLBCL and HCC
  – AR (AZD5312) – Phase I ongoing
  – 3 discovery projects underway

STAT3: Durable partial responses seen in 2 DLBCL patients in Phase I

STAT3 inhibition seen in tumour microenvironment & leukocytes
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Increased responses for combination of STAT3 ASO with PD-L1 mAb

Increased effector T-cells in tumour post STAT3 inhibition
Building a world-class Personalised Healthcare capability
Establishing a leading position in personalised patient care – across all therapy areas

- **90M**: Dollars invested in diagnostic partnerships
- **1st**: Circulating tumour DNA-based diagnostic approved for *Iressa*
- **>70%**: Percentage of clinical pipeline with a PHC approach
- **50%**: Percentage of launches by 2020 with companion diagnostic
- **2nd**: Rank in companion diagnostic partnerships and biomarker publications
- **~30**: Launches planned with companion diagnostic over next 5 years
Following the science will ensure maintaining a healthy and sustainable pipeline

**Phase I**
- MED18111 rhFII bleeding
- AZD1979 MCH obesity
- MED1814 Abeta AD
- AZD3293 BACE AD
- AZD6423 NMDA suic. ideation
- AZD9291 + MED14736 EGFRm NSCLC
- AZD9291 + selumet. EGFRm NSCLC
- AZD9291 + MET EGFRm NSCLC
- AZD8186 PI3Kβ prostate
- AZD6738 ATR solid tumours
- AZD9150 STAT3 DLBCL
- AZD5312 ISIS AR prostate
- AZD7624 IP38 COPD
- AZD1419 TLR9 asthma
- AZD8999 MABA asthma
- AZD7594 iSGRM asthma
- ATM AVI BL/BLI SBI
- AZD0914 Gyrase serious infections

**Phase IIa**
- AZD4901 NK3 PCOS
- AZD2115 MABA COPD
- AZD3241 MPO MSA
- AZD0548 LABA asthma (Almirall LAS10097)
- AZD5847 oxazolidinone TB
- CXL BLI/cephalosporin MRSA
- AZD1722 NHE3 ESRD-Pi
- AZD5213 H3 Tourette
- AZD5213 H3 PDN
- AZD3241 MABA COPD
- AZD8999 MABA asthma
- AZD0914 Gyrase serious infections

**Phase IIb**
- AZD1775 Wee-1 ovarian
- RDEA 3170 gout
- Pearl BD (MDI) PT008 COPD
- Pearl BD (MDI) PT009 asthma
- Pearl triple PT010 COPD
- Lymparza PARP prostate
- AZD5213 H3 PDN
- AZD5363 AKT breast
- AZD2014 mTOR breast
- MET Met pRCC
- AZD4547 FGFR solid tumours

*AZD6244, ARRY-142886

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IMED approach supports delivery of sustainable pipeline

- Reduced IMED spend by 39% (and headcount by 42%) since 2010
- Back-up programmes reduced from 48% to less than 2% since 2010
- Cost per candidate drug $50-60m (industry benchmark $80-110m)
- Probability of success increased from ~6% to ~16% since 2010
- 5 Phase III programmes delivered since 2012
Being open for collaboration in an environment where the best scientists thrive will deliver a sustainable flow of scientific innovation.