The ULTRA-DD project: delivering new tools and resources to speed up the development of truly innovative medicines

PSWC – May 2017

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Scientific Director of European Initiatives, SGC and ULTRA-DD

www.thesgc.org
www.ultra-dd.org
SGC & ULTRA-DD

**Translational Medical Research for Early Drug Discovery**

1. **High Throughput Structural Biology & Protein Science (2004 -)**
   Proteins of relevance to drug discovery. ~2000 structures deposited to date

2. **Chemical Probes (2008 -)**
   HighQ epigenetic and kinase chemical probes for disease studies

   Generation of recombinant antibodies using phage display technologies

4. **Target Enabling Packages (2015 -)**
   For disease associated & under-explored targets

5. **Tissue Platforms (2015 -)**
   Patient-Derived Cell Assays at Karolinska, Oxford, Montreal and Toronto

*Founded 2003, 300 Staff members, strict open-source, 25 MUSD/annum*
Global Research is Heavily Biased


This is where we focus
- Protein samples
- Assays
- Chemical Probes
- Chemogenomics set
- Antibodies
Open Source Partnership Concept

CREATIVE COMMONS

Public–Private Partnership
- Tools & Basic Knowledge
- NOVEL Proteins only!
  - Structure
  - Chemistry
  - Antibodies
  - Screening
  - Cell Assays

Public Domain
- Discovery and Exploration
  - No patent
  - No restriction on use
  - Open access to tools and data.
  - Target identification & validation

Drug Discovery and Development
Facilitated by access to increased amount of information in the public domain
- (re)Screening
- Lead Optimisation
- Pharmacology
- Metabolism
- Pharmacokinetics
- Toxicology
- Chemical development
- Clinical development

Proprietary

Commercial

The Inception of Open-Source Chemistry

COMMENTARY

Nature Chemical Biology 5:436 (2009)

- Small molecules to explore biology
- PPP = sharing expertise
- Open tools = exploration by all

Open access chemical and clinical probes to support drug discovery

Aled M Edwards, Chas Bountra, David J Kerr & Timothy M Willson

Drug discovery resources in academia and industry are not used efficiently, to the detriment of industry and society. Duplication could be reduced, and productivity could be increased, by performing basic biology and clinical proofs of concept within open access industry-academia partnerships. Chemical biologists could play a central role in this effort.
Chemical Probes Programme

- Produced in partnership with pharma
- Publicly available & no patents
- No restriction on use
- Well characterised, not yet drugs
- Interrogate biological function
- Target & Pathway validation

- Potent: in vitro IC$_{50}$/K$_D$ < 100nM
- Selective: 30 fold over near family members
- Cell Permeable: activity IC$_{50}$ <1 µM
- Clean in wide profiling panels (e.g. CEREP, DiscoveRx)
- Costs around 2MUSD/probe to develop

Other target families have their specific criteria
Selective inhibition of BET bromodomains

Panagis Filippakopoules, Jun Qi, Sarah Picaud, Yao Shen, William B. Smith, Oleg Fedorov, Elizabeth M. Morse, Tracey Keates, Tyler T. Hickman, Ildiko Felletar, Martin Philpot, Shonaigh Munro, Michael R. McKeown, Yuchuan Wang, Amanda L. Christie, Nathan West, Michael J. Cameron, Brian Schwartz, Tom D. Heightman, Nicholas La Thangue, Christopher A. French, Olaf Wiest, Andrew L. Kung, Stefan Knapp & James E. Bradner

Affiliations | Contributions | Corresponding authors

Nature 468, 1067–1073 (23 December 2010) | doi:10.1038/nature09504
Received 05 May 2010 | Accepted 17 September 2010 | Published online 24 September 2010
Disease Agnostic Exploration

- NUT midline carcinoma
- Septic Shock / Inflammation
- Myeloma
- Leukemia
- MYC regulation
- HIV infection
- Male Contraception
- Pathologic Cardiac hypertrophy
# Bromodomain Inhibitors in the Clinic - 2015

<table>
<thead>
<tr>
<th>Company</th>
<th>Compound</th>
<th>Named Indications</th>
<th>Stage</th>
<th>Initiated</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayer</td>
<td>BAY1238097</td>
<td>1. Neoplasms</td>
<td>Phase I</td>
<td>2015</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Gilead</td>
<td>GS-5829</td>
<td>1. Solid Tumors; 2. Lymphomas</td>
<td>Phase I</td>
<td>2015</td>
<td>Ongoing</td>
</tr>
<tr>
<td>GSK</td>
<td>GSK525762</td>
<td>1. Elapsed, Refractory Hematologic Malignancies; 2. NUT Midline Carcinoma (NMC) and Other Cancers</td>
<td>Phase I/II</td>
<td>2013</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Merck (Oncoethix)</td>
<td>OTX015</td>
<td>1. Acute Myeloid Leukemia; 2. NUT Midline Carcinoma; 3. Triple Negative Breast Cancer; 4. Non-small Cell Lung Cancer With Rearranged ALK Gene/Fusion Protein or KRAS Mutation; 5. Castrate-resistant Prostate Cancer (CRPC); 6. Pancreatic Ductal Adenocarcinoma</td>
<td>Phase I</td>
<td>2014</td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Acute Leukemia; 4. Other Hematological Malignancies; 5. Glioblastoma Multiforme</td>
<td>Phase I</td>
<td>2012</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Constellation</td>
<td>CPI-0610</td>
<td>1. Acute Leukemia, Myelodysplastic Syndrome, or Myelodysplastic/Myceloproliferative Neoplasms; 2. Previously Treated Multiple Myeloma; 3. Progressive Lymphoma</td>
<td>Phase I</td>
<td>2013</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Tensha</td>
<td>TEN-010</td>
<td>1. Acute Myeloid Leukemia and Myelodysplastic Syndrome; 2. Solid Tumors</td>
<td>Phase I</td>
<td>2014</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

- 7 compounds and 14 trials mid-2015
- 2016 update: 14 compounds in 30 trials mid-2016 (+BI, BMS, FORMA, Incyte, Plexxicon, Roche, Zenith)
HQ Test Systems

innovative medicines initiative

SGC

ULTRAADD
Changing the Treatment Approach

Early detection
More Specific
Treating the disease not symptoms.
Patient tailored intervention
Aiming for cure and prevention
Collaborative and iterative process

Needed
Early Disease
Genes, environment
Immune system activation
Immune attack
Inflammation
Tissue destruction
Organ failure

Current
Late disease detection and unspecified treatment options
No cures - symptomatic relief and bad long-term outcomes
Current therapies associated with many side-effects
Major healthcare concern and health economic burden
Affect ~5% of the population, most patients are women

No signs and symptoms
Unspecific symptoms
Disease diagnosis
Disability

At risk for inflammation
Pre-Disease Symptoms and biomarkers
Early Disease
Disease
Preclinical target validation using patient-derived cells

Aled M. Edwards¹, Cheryl H. Arrowsmith¹, Chas Bountra², Mark E. Bunnage³, Marc Feldmann⁴, Julian C. Knight⁵, Dhavalkumar D. Patel⁶, Panagiotis Prinos¹, Michael D. Taylor⁷, and Michael Sundström⁸ on behalf of the SGC Open Source Target-Discovery Partnership*

The Structural Genomics Consortium (SGC) and its clinical, industry and disease-foundation partners are launching open-source preclinical translational medicine studies.

Although the annual number of new drug approvals is trending upwards, the number of ‘first-in-class’ therapies has remained relatively constant — often fewer than 10 per year. For such new medicines for ‘pioneer targets’, attrition in Phase II proof-of-concept clinical studies remains the biggest hurdle¹, in large part because the target–disease associations derived from the currently dominant cell-line or animal preclinical models of disease were developed that enabled 90% of the total cells originating from the diseased joint to survive for 5–6 days was it possible to provide the first convincing evidence of the importance of TNF in joint inflammation, which was rapidly confirmed in animal models and then in proof-of-principle trials¹.

The discovery of anti-TNF therapy also provides two other lessons. First, success derived not only from the use...
Tissue Platforms - Organization

Scientific Committee
- Independent chair
- Academic KOLs

JMC
- SGC Chair
- Pharma Partners

Working Groups
- Driven by GLs
- Pharma scientists

LMT
- SGC Chair
- Local key PIs & GL

Ethics Committee
- SGC Chair

Pharma TP Meeting
- Boston 2015, Basel 2016

- Group Leader
- Senior Scientist
- 1-2 TAs
- 0.5 Research Nurse

- Assay Development
- Probe screen
- Verification studies
- Initial data analysis

- Interface to clinicians
- Patient consent
- Sample collection
- Ethical approvals

PhDs & PDFs for specific Projects
HQ Probes Meet HQ Assays

- Pos. Controls
- Neg. Controls
- Other Pharma
- Collab. Cmpds
- Lit. Cmpds

- Epi-Probes
- KinInh-Probes
- Other Probes
- PCG-Collection
- Bio-Probes

- Neurobiology/CNS
  - ALS
  - Parkinson's
  - Rett's Syndrome

- Inflammation
  - Ankylosing spondylitis
  - Psoriatic arthritis
  - Fibrosis, Dupuytren's
  - FOP

- Oncology
  - GBM
  - Colon
  - AML
  - Other

- SAIDs
  - Lupus
  - Myositis
  - Sjogren's syndrome
  - Systemic sclerosis

- PKIS

100-200
200-300
1000

T-DA 1
T-DA 2
Etc.
# Patient Cohorts

<table>
<thead>
<tr>
<th>Disease</th>
<th>Patients/Controls seen annually</th>
<th>Genetic characterization</th>
<th>Blood</th>
<th>Biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE</td>
<td>475/320</td>
<td>HLA, ImmunoChip</td>
<td>yes</td>
<td>Skin (20-30/year)</td>
</tr>
<tr>
<td>Myositis</td>
<td>300 (SweMyoNet) 2300 (EuMyoNet)</td>
<td>HLA, ImmunoChip</td>
<td>yes</td>
<td>Skin (10-20/year)</td>
</tr>
<tr>
<td>SS</td>
<td>40</td>
<td>-</td>
<td>yes</td>
<td>None</td>
</tr>
<tr>
<td>SSc</td>
<td>165/110</td>
<td>HLA, ImmunoChip</td>
<td>yes</td>
<td>Yes (20-30/year)</td>
</tr>
<tr>
<td>FOP</td>
<td>30</td>
<td>Genotypes</td>
<td>yes</td>
<td>None</td>
</tr>
<tr>
<td>AS</td>
<td>600</td>
<td>HLA, ImmunoChip</td>
<td>yes</td>
<td>Synovial fluid (30)</td>
</tr>
</tbody>
</table>

Fibrosis/DD accessed from external sites
Inflammatory Diseases

- Tissue Platform focused on Fibrosis, AS & FOP
- 5 staff members in place (GL, Senior Scientist, TA, PDFs)
- Laboratories established at the Botnar Research Centre
- Results to date from patients with AS and Fibrosis

Scientific Leadership

Prof. Jagdeep Nanchahal  Prof. Sir Marc Feldmann  Prof. Paul Bowness

Tak, Marisa, Lynn, Fiona, Liye
Auto-Immune Diseases

- Clinical research in *SLE, myositis, systemic sclerosis, SS (and RA)*
- Well characterized and managed patient cohorts
- Strong and supportive local clinical network
- Team of four staff, recruiting additional positions
- Results to date from patients with Myositis, Lupus and SSc

Scientific Leadership

Prof. Lars Klareskog
Prof. Per-Johan Jakobsson
Prof. Ingrid Lundberg
Dr. Louise Berg
Open Translational Medicine Resources

www.ultra-dd.org

ULTRA-DD Annual Conference and SGC Immunology Day
at Karolinska Institutet, Stockholm
1st of June 2017

The Project
ULTRA-DD
Unrestricted Leveraging of Targets for Research Advancement and Drug Discovery
Funded by the European Union and

Fig 2a IgG levels
Fig 2b %B cells
Fig 2c %memory B
Thanks to all contributors!

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