industry liaison meeting

Martin Hrabé de Angelis, Helmholtz Zentrum München

INFRAFRONTIER / IMPC / UAB Meeting, Barcelona, November 13th 2014
INFRAFRONTIER / IMPC and industry - context

• National and EU research policy and funding support collaboration
  - Knowledge transfer and innovation (Innovation Union)
  - Basic research and focus on ‘translation’

• Vendors / Suppliers / CROs / Biotech
  - Provide academia with platforms and tools to develop and work with mouse models
  - Support innovation
  - E.g. EU market for scientific instrumentation is worth 4b€/yr
Pharma / Biotech exploit mouse models for drug development
- Use of animal models in developing new therapeutic strategies for treating human diseases, and in drug discovery research, as well as in preclinical studies of drug safety and efficacy
- 34 / 100 of top drugs (by sales volume, USA) were enabled by the use of a mouse model

<table>
<thead>
<tr>
<th>Drug target</th>
<th>Drug name (utility)</th>
<th>2001 Sales*</th>
<th>Mouse phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin transporter</td>
<td>Paxil (depression)</td>
<td>$2,673.0</td>
<td>Altered open-field behaviour.</td>
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<tr>
<td></td>
<td>Zoloft</td>
<td>$2,366.0</td>
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<td></td>
<td>Prozac</td>
<td>$1,950.0</td>
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<td></td>
<td>Effexor</td>
<td>$1,542.0</td>
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<td></td>
<td>Celexa</td>
<td>$714.0</td>
<td></td>
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<tr>
<td>Dopamine, serotonin and histamine receptors</td>
<td>Zyprexa (psychosis)</td>
<td>$3,067.0</td>
<td>Multiple targets; however, related KOs display behavioural phenotypes (movement, activity and anxiety)</td>
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<tr>
<td></td>
<td>Risperdal</td>
<td>$1,845.0</td>
<td></td>
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<tr>
<td></td>
<td>Seroquel</td>
<td>$700.0</td>
<td></td>
</tr>
<tr>
<td>Dopamine and noradrenaline transporters</td>
<td>Wellbutrin (depression)</td>
<td>$931.0</td>
<td>Multiple targets; however, increased activity levels (dopamine transporter); increased struggle in tail suspension (noradrenaline transporter).</td>
</tr>
<tr>
<td>GABA receptor</td>
<td>Ambien (insomnia)</td>
<td>$704.0</td>
<td>Hyperactive, hyper-responsive.</td>
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<td></td>
<td>Stilnox</td>
<td>$902.0</td>
<td></td>
</tr>
<tr>
<td>µ-opioid receptor</td>
<td>Duragesic (pain)</td>
<td>$875.0</td>
<td>Increased sensitivity to pain.</td>
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<tr>
<td></td>
<td>Ultram</td>
<td>$601.0</td>
<td></td>
</tr>
</tbody>
</table>

*US$ in millions.

Knockouts model the 100 best-selling drugs—will they model the next 100?
Brian P. Zambrowicz & Arthur T. Sands
INFRAFRONTIER / IMPC and industry - challenge

- Raise awareness among industry stakeholders of INFRAFRONTIER / IMPC activities
- Ensure that the output of the INFRAFRONTIER / IMPC does benefit biopharmaceutical research and development programs (access to resources!)
- Alignment of INFRAFRONTIER services with industry demand
- Take into account the expert views and expectations of industry researchers working with mouse models
- Explore and exploit engagement modes with industry
Industry liaison meeting - meeting goals

• **Communication:** Raise awareness of INFRAFRONTIER services and emerging IMPC data and resources
  - Promote industry access to EUCOMM resources
  - What are best ways to communicate with industry?

• **Value add:** What can IMPC / INFRAFRONTIER provide to industry that they can’t or are not willing to do themselves

• **Partnering:** Presentation of successful industry engagement models and exploring new opportunities e.g. provided by H2020 instruments

• **Contribution:** What can industry offer the IMPC and INFRAFRONTIER?
Industry liaison meeting - participants

- Up to 80 participants
- INFRAFRONTIER / IMPC PIs, scientists, advisors
- IMPC Industry Sponsors
- BioPharma
- Research instrumentation developers
- CROs, suppliers and platform companies
- Funders
INFRAFRONTIER / IMPC / UAB industry liaison meeting / November 13th, 2014

Agenda

08:30 - 09:00 Registration of participants and coffee

INFRAFRONTIER / IMPC
09:00 - 09:05 Welcome address / Meeting objectives - Martin Hrabé de Angelis
09:05 - 09:25 Martin Hrabé de Angelis / INFRAFRONTIER
09:25 - 09:45 Steve Brown / International Mouse Phenotyping Consortium (IMPC)

Collaboration models of INFRAFRONTIER / IMPC partners and industry
Mouse production, phenotyping and preclinical services:
09:45 - 10:00 Alexandre Fraichard (genOway) / Access to EUCOMM-based KO mouse models
10:00 - 10:15 Tania Sorg (ICS / PhenoPro) / Mouse phenotyping services
10:15 - 10:30 Maria Denis (Biomedecode) / (Humanised) animal models of chronic inflammatory
diseases, preclinical drug evaluation services

10:30 - 11:00 Coffee break

Joint development of research instrumentation:
11:00 - 11:15 Lars Breuer - TSE systems GmbH
11:15 - 11:30 Giorgio Rosati - Tecniplast
11:30 - 11:45 Lucas Noldus - Noldus Information Technology
11:45 - 12:00 David Craig - ActualAnalytics
12:00 - 12:15 Valentina Villa - Ayoxxa Biosystems GmbH
12:15 - 12:30 Amit Vasanji - ImageIQ

12:30 - 13:30 Lunch break
Industry liaison meeting - agenda

12:30 - 13:30 Lunch break

Requirements and use of mouse models by BioPharma
13:30 - 13:45 John Mudgett (Merck)
13:45 - 14:00 Fatima Bosch (UAB) and Eduard Valenti (ESTEVE) / Gene therapy approaches for mucopolysaccharidosis: From preclinical studies in mice to the clinic
14:00 - 14:15 European Federation of Pharmaceutical Industries and Associations (EFPIA)
14:15 - 14:30 Discussion

Partnering session
14:30 - 16:00 INFRAFRONTIER / IMPC PIs and meeting attendees

Wrap up
16:00 - 16:15 Martin Hrabé de Angelis

www.infrafrontier.eu
The INFRAFRONTIER Research Infrastructure

Martin Hrabé de Angelis, Helmholtz Zentrum München

INFRAFRONTIER / IMPC / UAB Meeting, Barcelona, Nov 13th 2014
Selected from 150 proposals:

- BBMRI – biobanking
- EATRIS – translational research
- ECRIN – clinical trials
- ELIXIR – bioinformatics
- INFRAFRONTIER – animal disease models
- INSTRUCT – structural biology

(up-dated in 2008 and 2010 for additional projects)
Implementation and operation of cross-cutting services and solutions for the BMS cluster of ESFRI research infrastructure

Proposal: COordinated Research Infrastructures Building Enduring Life-science Services (CORBEL)
Building the INFRAFRONTIER Research Infrastructure

Preparatory Phase (2008-2012)

Infrafrontier Project

- **Capacity building** to meet the increasing demands
- Developing the **European Research Area**
- Developing a **business plan** based on a sustainable funding concept
- Providing a **strategic plan** for the implementation phase
- Reaching a **legal agreement** between all partners

Implementation and Operation (from 2013)

Infrafrontier Research Infrastructure

- Infrafrontier Legal Entity
- National Infrafrontier Partners

Infrafrontier-I3 Project

www.infrafrontier.eu
The INFRAFRONTIER Research Infrastructure

Systemic Phenotyping → INFRAFRONTIER Mouse Clinics → Archiving / Distribution

Access to scientific platforms, data and mouse models

www.infrafrontier.eu
Serving the biomedical research community

**ES Cell**
International ES Cell Resources

**EuMMCR**
Mouse Production

**Mouse Models**
European Mouse Mutant Archive

**Cohort Breeding**

**Systemic Phenotyping**
INFRAFRONTIER Mouse Clinics

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**Bottom-up access:**
Individual research projects

**Top-down access:**
large-scale research programmes

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Biomedical Research Community

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www.infrafrontier.eu
• 23 Partners
• 14 European countries + EMBL + Canada
• Mouse clinics
• EMMA archiving and distribution nodes
• Bioinformatics

www.infrafrontier.eu
Capacity building – Funding commitments

**Finland**
7 Mio € for upgrading and operation of EMMA node

**Germany**
42 Mio € for construction, upgrading and operation of mouse clinic and EMMA node

**Czech Republic**
33 Mio € for construction and operation of mouse clinic and EMMA node

**Austria**
2 Mio € for construction and operation of EMMA node

**Italy**
20 Mio € for construction and operation of mouse clinic and EMMA node

**France**
27 Mio € for construction and operation of mouse clinic and EMMA node

**Spain**
1 Mio € for developing a mouse clinic business case

**United Kingdom**
Funding in the IMPC context (National and NIH)

**Canada**
Funding in the IMPC context (National and NIH)
INFRAFRONTIER GmbH

established in 2013

Partners:

- DE – HMGU   11 Apr 13
- FR - CNRS    05 Dec 13
- CZ – IMG     05 Dec 13
- FI – U OULU  05 Dec 13
- GR - Fleming 05 Dec 13

•more to come ...

Next step: Setting up the INFRAFRONTIER ERIC

www.infrafrontier.eu
User access through www.infrafrontier.eu
4404 mouse mutant lines are displayed on the public EMMA strain list

Commercial access to IKMC resource via genOway as intermediary

Major collections

- 2198 mouse strains from IKMC resource
- 588 ENU strains
- 187 Cre expressing strains
- 86 mouse strains from Lexicon / Deltagen collection (Wellcome Trust KO mouse resource)
- 46 strains with Tet expression system
Demand lines

Cre resource
- 187 Cre driver lines account for 537 shipments

IKMC / IMPC resource
- 1429 shipments for IKMC mice
- 664 different IKMC strains were shipped

Turnaround times 2013 (order – shipment (including all paperwork, MTA etc.))

Mice on shelf: 6.1 weeks; frozen stock: 9.9 weeks; rederivation: 23.3 weeks
World-wide distribution of EMMA users

www.infrafrontier.eu
Phenotyping: The challenge

• The function of the majority of genes is still unknown

• We are remarkably poor at predicting the functions of genes – pleiotropy will be key to understanding diseases

• Functional data on genes are patchy – and are dependent on the experience and interests of the investigator

• Impact of environmental factors on health and disease is poorly understood
Phenotyping: The mouse clinic concept

- Open access phenotyping platform for the scientific community

- Offer a systemic primary phenotypic screen
  (more than 550 parameters)

- Provide interpretation of results

- „Hypothesis Generation Machine“

- Provide the possibility of follow-up studies in secondary and tertiary screens

www.infrafrontier.eu
German Mouse Clinic: The first systemic mouse phenotyping research infrastructure with open access

Selection:
Nat Med (2012)
Science (2010)
Hum Mol Genet (2012)
EMBO J (2014, 2010)
BBRC (2013)
Eur J Immunol (2014)
Development (2013)
Acta Neuropathol (2012)
Blood (2011)
Histol Histopath (2013)
J Cell Science (2011)
Genome Res (2014)
Faseb J (2012)
Eur J Endocrinol (2012)
J Comp Neurol (2012)
BMC Neurosci (2012)
German Mouse Clinic: Quality management system, ISO9001:2008 certification

- GMC
- ICS
- MRC MLC
Systemic phenotyping in the GMC

jnCL / Batten disease

- jNCL or Batten disease, lysosomal storage disease
- most common inherited neurodegenerative condition of childhood
- progressive loss of vision, seizures, and loss of cognitive and motor functions
- GMC approached by German NCL foundation to study mouse model of Cln3

Precise genetic mouse model of jNCL existant (recaputulates human disease progression)
Systemic phenotypic analysis in the German Mouse Clinic to reveal pleiotropic effects

Major results:
- New hypothesis: jNCL caused by impaired cellular transport
- New early biomarkers discovered such as impaired PPI and altered blood count prior to neurodegeneration
Dynamic advancement of the GMC

- **Systemic Mouse Phenotyping**
  - **GMC I**
  - 2001: first world-wide

- **Envirotyle “Challenge” Tests**
  - **GMC II**
  - 2005: proof-of-concept

- **Systemic Analysis of Compounds & Drugs**
  - **GMC III**
  - 2011: pilot project for diabetes
INFRAFRONTIER and the IMPC

- INFRAFRONTIER partners are major contributors to IMPC mouse production and phenotyping efforts
- EMMA is one of the main repositories for the IMPC resources
- Coordination and common strategies required
More information on https://www.infrafrontier.eu
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Systemic phenotyping in the GMC
Calcitonin receptor (Calcr -/-) Knock-out: Model for Osteogenesis

- Reduction of calcitonin action by inactivation of the murine calcitonin receptor causes **increased bone formation**
- Leads to **increase of sphingosine-1-phosphate (S1P)**
- S1P acts as an **osteoblastic molecule in vivo** -- starting point to develop new approaches for the treatment of osteoporosis

- Systemic phenotyping of calcitonin receptor Knock-out:
  - Only minor side effects
  - Increased ALP
  - Hypoactivity (OF, IC)

Keller, J. et al. (2014), *Nature Communications*