Chemoinformatic Tools for the Hit Discovery Process

European ScreeningPort GmbH

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ESP in a Nutshell

Established in 2007
Service provider for academics
  • High-throughput screening
  • High-content screening
  • Computational Chemistry
~20 people
Profitable since 3 years
Successful funding procurement
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• High-throughput screening
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~20 people
Profitable since 3 years
Successful funding procurement
HTS at ESP

Results handling

• Bioactivity
• Frequent hitter?
• Add. Information

<table>
<thead>
<tr>
<th>Compound</th>
<th>Inhibition (%)</th>
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</thead>
<tbody>
<tr>
<td>ESP-0815</td>
<td>83.2</td>
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<tr>
<td>ESP-666</td>
<td>79.3</td>
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<td>ESP-4711</td>
<td>71.4</td>
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<td>ESP-27</td>
<td>52.4</td>
</tr>
<tr>
<td>ESP-13</td>
<td>21.6</td>
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</table>
Instant JChem at ESP

Screening database handling

- ENZO, LOPAC, etc.
Instant JChem at ESP

Screening database handling
• ENZO, LOPAC, etc.

IMI project “New Drugs for Bad Bugs”
Innovative Medicines Initiative

Public-Private-Partnership

- EFPIA
- European Commission

Budget: 2 bn EUR

- 50 % EFPIA
- 50 % European Commission

Mission:

Improvement of drug development process by supporting a more eff. discovery and development of better and safer medicines for patients.
“New Drugs for Bad Bugs”

Fight against increasing antimicrobial resistance

• Annual treatment and societal costs: 1.5 bn EUR
• Only 2 new classes of antimicrobials in last 30 years
• Dev. of novel antibiotics financially not attractive
“New Drugs for Bad Bugs”

Several topics

• Topic 1: Clinical trials
  - COMBACTE
• Topic 2: Understanding mech. of bacterial resistance
  - TRANSLOCATION
• Topic 3: Drug discovery (gram-negative bacteria)
  - in evaluation

Overall budget

• 360.6 M EUR
“New Drugs for Bad Bugs”

ND4BB cross topic collaboration and dissemination
(Topic 1 WP1, Topic 2 WP8, Topic n WPn)

Topic 1: Clinical Development Steering Committee
Project level decision making body

Subtopic 1 A: Work Packages: 1 – 4

Subtopic 1 B: Work Packages: 5A-5D

*Current call

Future Open Call

Subtopic 1 C: Work Packages: 6 & 7

Topic 2: New Drugs into bad bugs Steering Committee
Project level decision making body

Work Packages: 1 – 8

Topic N: ND4BB Project n

Work Packages: 1 – n

ND4BB Data Hub (all data generated is submitted and is accessible to all consortium partners)

Topics in current call.

*Note: calls for additional beneficiaries required to implement WP5B & 5D will be managed by the Topic 1 consortium as outlined below

Subject to future open calls implemented by the IMI JU office
TRANSLOCATION

Consortium members
• 5 EFPIA, 1 non-EFPIA, 14 public, 5 SMEs

Tasks
• How potential drugs cross cell envelope?
  - New technologies for measuring the molecule transport
  - Understand the mechanism(s) of resistance
• Learning from success and failure
  - InfoCentre

www.imi.europa.eu/content/translocation
TRANSLOCATION

The ND4BB Information Centre

- Heterogenous data
  - Legacy data on successful and failed EFPIA programmes
  - HTS, H2L and L2C studies, in vitro, in vivo, modelling, etc.
  - Data from future topics
- Only derived data
  - IC$_{50}$, MICs, SAR tables, protein structures, study reports
- Electronic lab notebook
  - Going live in June
TRANSLOCATION

The ND4BB Information Centre

• Types of data

Bioassay related studies
- Compound Primary, Secondary and Selectivity screening
- Pathogen profiling results (MIC and Time-Kill analyses etc)
- Resistance profiling (e.g. from clinical isolates)
- Toxicity and liability results (Cyto-toxicity etc)
- In-vitro safety assays (P-450, HERG, Cardiac Ion channel panels)
- Chemi-informatic analyses (cLog P, TPSA, Ro5 parameters etc)
- In-vitro ADME studies
- Physico-chemical assessments (solubility, Log P, etc.)
- Transport assays - Influx (e.g. Mass Spec / Fluorescence)
- Transport assays Efflux (e.g. Mass Spec, Electrophysiology)
- Adjuvant related assay results
- Prodrug related assay results
- Aggregated compound Activity (e.g. Heat maps, SAR tables)
- Bioassay data (Other)

Computational, modelling and Simulation
- Molecular dynamics results
- Trajectories
- Molecular structure results
- Molecule topology results
- Parameter files
- Scripts and meta-data
- Chemi-informatic analyses (cLog P, TPSA, Ro5 parameters)
- Binding modes

Discovery (in-vitro) Structural and 'Omics related Data
- Genetic data
- Proteomic data
- Transcriptomic data
- Protein structural information
- Structural and 'Omics data (other)

Pre-clinical
- Study/Animal Model Protocols
- In-vivo efficacy results
- In-vivo biomarker results
- In-vivo 'Omics results
- In-vivo ADME studies
- In-vivo Pharmacokinetic (PK) studies
- In-vivo Pharmacodynamic (PD) studies
- Modelling of PK events (one compartment / two compartment)
- General in-vitro modelling (ADME, BBB penetration etc)
- Findings/Conclusions/Summary Documents
- Pre-clinical data (Other)
TRANSLOCATION

Data analysis team

• Deliver recommendations for future R&D
  - What factors are common to failed lead opt. efforts?
  - Which tools and procedures to use for identifying lead candidates to be progressed further?
  - Best practice for predicting resistance in the clinic
  - Which animal infection model best predicts clin. outcome?

• Hypotheses will be validated

• Ph.D. position available
  - www.screeningport.com/jobs
Thank You!