SBDD FROM A DIVERSIFIED NP-INSPIRED CHEMICAL SPACE

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EDELRIS

- Edelris is a private CRO company founded in 2005
- Located in Lyon (France)
- Currently 50+ employees (60% with Ph.D.)
- State of the art facility dedicated to chemistry
### Exploring the Chemical Space

<table>
<thead>
<tr>
<th>Registered molecules</th>
<th>GDB-17</th>
<th>Nuevolution DEL library</th>
<th>Possible drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>$10^8$</td>
<td>$10^{11}$</td>
<td>$10^{13}$</td>
<td>$&gt;10^{20}$</td>
</tr>
</tbody>
</table>

- **Volume:** $10^{-12}$ m$^3$
- **Copacabana beach Volume:** $10^8$ m$^3$

Consider a grain of sand as a molecule, the drug space would be the size of Copacabana beach.

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**How DNA-encoded libraries are revolutionizing drug discovery.** B. Halford *C&EN* 2017, 95, 28-33
DRUG DIVERSITY CAN HARDLY BE MATCH BY COMPOUND COLLECTIONS

The Pharmaceutical Industry in 2016. An Analysis of FDA Drug Approvals from a Perspective of the Molecule Type. BG Torre, F. Albericio, Molecules. 2017, 27, E368
PLAYING AGAINST THE ODDS

ENHANCING HIT RATE WITHOUT COMPROMISING THE EXPLORATION OF NEW MOLECULAR SPACES

- Structural Biology
- Innovative and validated chemical frameworks
- Keymical Space™

Hit generation
KEYMICAL SPACE™: NATURAL BY DESIGN

2-ABN Natural Products
(2-azabicyclo[3.3.1]nonane)

2-ABN inspired compound collection

Diversification of pharmacophores and exit vectors
REPRESENTATIVE FRAMEWORKS

- Strong diversity of frameworks
- High sp$^3$ fraction
EDEN (EDELRIS DISCOVERY ENGINE)

- **Out licensing access to Keymical Space™**
- **Partnering**

**Library enumeration**
- >350 scaffolds
- Target/Chemistry/
- New concepts driven

**3D-data-mining**
- >1.5 M fragment 3D-index
  for ligand rescaffolding
- >30M cpds dataset for VS

**Ligand & target based VS**
- Recore; SeeSAR; LeadIT
KEYMICAL SPACE™ PHYSCHEM PROPERTIES 1/2

N=710190_Diversity set

- Binned MolWeight
- Binned cLogP
KEYMICAL SPACE™ PHYSCHEM PROPERTIES 2/2

N=710190_Diversity set
RESCAFFOLDING STRATEGY: CASPASE-1 INHIBITORS

PLAYING AGAINST THE ODDS
SCAFFOLD HOPPING FROM COMPLEX 3D FRAGMENTS

Figure 2: Scaffold hopping process implemented to identify new Caspase-1 inhibitors

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>PGE-3935199</th>
<th>VRT-043198</th>
<th>IC_{50} (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11</td>
<td>5</td>
<td>17</td>
</tr>
</tbody>
</table>
RESCAFFOLDING STRATEGY: UNDISCLOSED TARGET

> 6 new ligand chemotypes proposed
> 21 compounds prepared
> 2 chemotypes pI50 > 8

<table>
<thead>
<tr>
<th>Chemotype</th>
<th>pI50</th>
<th>LogD(2.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.2</td>
<td>2.7</td>
</tr>
<tr>
<td>2</td>
<td>&lt;5.0</td>
<td>2.7</td>
</tr>
<tr>
<td>3</td>
<td>8.0</td>
<td>3.4</td>
</tr>
<tr>
<td>4</td>
<td>6.1</td>
<td>2.0</td>
</tr>
<tr>
<td>5</td>
<td>5.6</td>
<td>1.8</td>
</tr>
<tr>
<td>6</td>
<td>5.4</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Marko bioactive conformation hypothesis

3D-data mining

EDEN
- Keymical Space™
- Zinc Lead-like
- PDB ligands

Privileged scaffolds
- Conformational stability
- Scoring
- SB ligand optimization

Synthesis@Edelris
FBDD TOWARDS LOW MW SELECTIVE CYCLOPHILIN D INHIBITORS

- Cyclophilins are folding helper enzymes member of the Peptidyl Proline Isomerases (PPI) superfamily
- Cyclosporin A (CsA) is a potent inhibitor of CypD
- No SME disclosed as CyPD inhibitor when work was initiated
CYCLOPHILIN D LIGANDABILITY ASSESSMENT

- 7 Ligandable pockets identified (Fpocket)
- Known inhibitor CsA binds mainly to pocket 4
FRAGMENT X-RAYS

Edelris 1
$K_D = 7.1 \text{ mM (LE = 0.2)}$

Edelris 2
$K_D = 7.5 \text{ mM (LE = 0.16)}$

Pocket 3
Pocket 4

Tetrazole
$K_D = 3.9 \text{ mM}
LE = 0.21$

Isoxazole
$K_D = 22 \text{ mM}
LE = 0.15$

Oxalylamide
$K_D = 1.1 \text{ mM}
LE = 0.22$

Succinimide
$K_D = 45 \text{ mM}
LE = 0.11$

Optimal space occupation for fragment growing and linking
EDELRIS FRAGMENTS VERSUS CYCLOSPORIN A

Edelris 1

- MW = 209
- clogP = 0.6
- HAC = 15
- Fsp3 = 0.45

- $K_D = 7.1 \text{ mM}$
- LE = 0.2

Edelris 2

- MW = 248
- clogP = 1.4
- HAC = 18
- Fsp3 = 0.46

- $K_D = 7.5 \text{ mM}$
- LE = 0.16

- Fragment highly 3D (Fsp3 $\uparrow$)
- Moderate Ligand efficiency (LE)
- Optimal occupancy of pocket 3 unexplored by CsA
A MILLION FOLD IMPROVEMENT OF AFFINITY IN 3 MONTHS

10^6 potency improvement in two optimization cycles through an optimized space occupancy of pocket 3 and the creation of interactions with two additional residues (Arg124 and Ser123)
TOWARDS A FULLY NUMERICAL APPROACH?

Docking

1 µs MD

> main populated cluster (pink) highly superimposable with X-Ray data (yellow)

<table>
<thead>
<tr>
<th>Frag</th>
<th>Pop(%)</th>
<th>BE</th>
<th>pocket</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edelris 1</td>
<td>27</td>
<td>-5.44</td>
<td>5-7</td>
<td>0.363</td>
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<tr>
<td></td>
<td>36</td>
<td>-5.06</td>
<td>6</td>
<td>0.337</td>
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<tr>
<td></td>
<td>23</td>
<td>-4.62</td>
<td>3</td>
<td>0.308</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>-4.40</td>
<td>5-7</td>
<td>0.290</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>-4.36</td>
<td>4</td>
<td>0.291</td>
</tr>
</tbody>
</table>

Edelris 1
SPR : $K_D = 7$ mM
MD HIGHLY PREDICTIVE OF FRAGMENT BINDING

L20 (MSC2530594)

fragmentation

L3 (Edelris 1)
L12
L8
L17
PDB4J5B ligand

2/ Docking
3/ MD

L20
CONCLUSION

- Keymical space™ has proved to be very valuable for SBDD (strong IP from hit series, drug like properties)
- EDEN platform used successfully in biasing the unbiased
- Scoring remains a key issue (accuracy of affinity prediction highly target dependant)
- Molecular dynamics envisioned as a valuable approach to reduce false positives