DRUG REPOSITIONING IN RARE DISEASES
HOW TO OPTIMIZE DRUG ACCESS FOR PATIENTS
Dr. Raúl Insa

8th NOV 2014. SESSION 4. TRACK 2: INTERDISCIPLINARY-TECHNOLOGIES
Success examples in repurposing

FINASTERIDE

Merck
1992: Prostatic hypertrophy
17 €
1998: Hair loss
52 €

THALIDOMIDE

Grüenthal
1957: Nausea
40 Pts
2008: Leprosy / Multiple Myeloma
6.000 €

SILDENAFIL

Pfizer
1992: Hypertension
1998: Erectile Dysfunction
2012: Pulmonary Hypertension
99 €
24 €

Celgene
2008: Leprosy / Multiple Myeloma
6.000 €
Why drug repurposing?

Figure 5: Repositioning offers a low risk approach to potentially achieve substantial rewards.

![Diagram showing risk-reward ratio for repositioning and reformulation.](image)

Source: Norman Consulting
How we do drug discovery?

Ligand-based Virtual Screening technology - Identification of non-structural analogs

Molecular fields: 22 molecular interaction fields (Score)

3D space
Flexible alignment

Active molecule
HMG-CoA Inhibitor
Score = 0.55

Inactive molecule
Score = 0.31

Reference Compound
HMG-CoA Inhibitor
Our business Model

- Screening Known Drugs: Ligand-based *in silico* screening
- Experimental Validation: Relevant *in vitro, in vivo* or *ex vivo* models of the disease
- IP Protection: WW mode of use and/or composition of matter patent
- License Phase-II POC: ✓ Early licensing and add-hoc projects ✓ Late licensing

In Property

- Ligand-based Virtual Screening Technology
- Molecular field maps through 22 molecular potentials
- 3D maps; flexible alignment; intensive in CPUs use
- Identification of non-structural analogs

SOM’s is the best-in-class in the retrieval of active molecules.
# Orphan Pipeline

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>LIGANT</th>
<th>STRUCTURE</th>
<th>RESULTS</th>
<th>STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioma (I)</td>
<td>Cilengitide</td>
<td><img src="image" alt="Structure" /></td>
<td><strong>SOM0777</strong> Activity +++ Cellular line +++</td>
<td>Non-exclusively licensed to Argon Pharma SL</td>
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<tr>
<td>T Cell Lymphoma</td>
<td>Pralatrexate</td>
<td><img src="image" alt="Structure" /></td>
<td>Three +++ hits identified</td>
<td>Abandoned. Already patented</td>
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<tr>
<td>TTR Amyloidosis</td>
<td>Tafamidis</td>
<td><img src="image" alt="Structure" /></td>
<td><strong>SOM0226</strong> In vitro +++, Ex-vivo +++ Primary indication 1997</td>
<td>Open for out-license WW Patent ODS + Phase II POC ongoing</td>
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<tr>
<td>Huntington Disease (Chorea mov)</td>
<td>Tetrabenazine</td>
<td><img src="image" alt="Structure" /></td>
<td><strong>SOM3355</strong> In vitro +++, BBB +++ Primary indication 1995</td>
<td>Open for license WW Patent Phase II POC under discussion</td>
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<td>Phenylketonuria</td>
<td>Sapropterin</td>
<td><img src="image" alt="Structure" /></td>
<td>40 compounds under screening</td>
<td>No result yet</td>
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<tr>
<td>Cystic Fibrosis</td>
<td>Ivacaftor</td>
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<td>In silico process</td>
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<td>Spinobulbar M Atrophy</td>
<td>Undisclosure</td>
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<td>Not yet</td>
<td>In silico process</td>
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<td>Acute Myeloid Leukemia</td>
<td>Lestaurntinib</td>
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</table>
SOM0226

A repositioned drug for
TRANSTHYRETIN AMYLOIDOSIS (ATTR)

Non Confidential Information
Transthyretin Amyloidosis (ATTR)

- **Orphan disease** caused by extracellular deposition of amyloid fibrils derived from normal or mutant transthyretin protein.
- Tetramer dissociation, misfolding and aggregation as amyloid fibrils.
- It causes nervous system and/or heart pathology of adult onset.
- Life expectancy of 5-15 years after first symptoms.

**Transthyretin** (TTR): transport of thyroxine (T4) and retinol in blood and CSF.

<table>
<thead>
<tr>
<th>PHENOTYPE</th>
<th>TTR</th>
<th>PREVALENCE</th>
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<tbody>
<tr>
<td><strong>FAP</strong>: Familial Amyloid Polyneuropathy</td>
<td>TTR V30M and other</td>
<td>WW &lt;1/100,000</td>
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<tr>
<td><strong>FAC</strong>: Familial Amyloid Cardiomyopathy</td>
<td>TTR V122I and other</td>
<td>WW &lt;1/1,000,000 (3-4% Afro-American)</td>
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<tr>
<td><strong>SSA</strong>: Senile Systemic Amyloidosis</td>
<td>Wild type TTR</td>
<td>2.75% &gt;85y severe deposits</td>
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<td><strong>CNSA</strong>: CNS Selective Amyloidosis</td>
<td>Aggressive mutants TTR</td>
<td>Rare</td>
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SOM0226: the discovery process

Reference compound: Tafamidis

- Specific stabilizer of transthyretin.
- Authorized for TTR-FAP under “exceptional circumstances” by the EMA (orphan drug status). In pre-registration process by the FDA.

Discovery

- Search for non structural analogs on compound libraries of approved drugs (9000 structures).
- Refine with docking calculations on TTR binding site.

In vitro validation

- Kinetic turbidity assay inhibition (30 drugs tested) → identification of SOM0226.

Ex vivo validation

- T4 competition assays, tetrameric stability assays, TTR aggregation, disruption of TTR fibrils and cell toxicity assays.

In vivo and Clinical PoC

- Test the efficacy of SOM0226 in ATTR disease models and patients.
SOM0226: *in vitro* screening

Kinetic Assay for High-Throughput Screening of Transthyretin Amyloid Fibrillogenesis inhibitors (*Dolado et al. 2005*)

*In vitro* Kinetic Turbidity Assay:

- Rapid evaluation of potential TTR inhibitors (1.5 h assay).
- **Two main steps:**
  1) Incubation of mutant protein + inhibitor.
  2) Fibril formation induced by lowering the pH & monitoring absorbance.
- **Compounds tested:** 30 selected compounds.
- **Reference compounds:** Tafamidis & well-known TTR fibril inhibitors.
- **Parameters studied:** IC 50 and RA(%) - Reduction of fibril formation rate at high inhibition concentration.
- **Graphical representation:** Relative initial rates of fibril formation (V0%) are plotted against inhibitor concentration.
SOM0226: cellular & ex vivo assays

SOM0226 is active in all steps of the cascade of events leading to TTR fibril formation

1. SOM0226 binds to the T4 binding sites of TTR with high affinity and selectivity
   - T4 competition assays with human plasma and recombinant protein

2. SOM0226 stabilizes tetrameric TTR
   - Tetramer stabilization studies with human plasma and recombinant protein

3. SOM0226 blocks TTR fibrillogenesis
   - Fibrillogenesis inhibition experiments with different TTR variants

4. SOM0226 prevents the formation of cytotoxic aggregates
   - Cell viability and apoptosis assays.

5. SOM0226 induces disruption of TTR fibrils
   - Fibril disruption assays with pre-formed TTR fibrils
# SOM0226: comparative & summary results

<table>
<thead>
<tr>
<th>Steps</th>
<th>Cellular, <em>in vitro</em> and <em>ex vivo</em> assays</th>
<th>SOM0226</th>
<th>tafamidis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Binding to T4 binding sites</td>
<td>Binding was measured by T4 competition assays (PAGE and gel filtration) with recombinant and human plasma TTR from control and TTR-FAP patients. ✓ SOM0226 binds to TTR with high affinity to the thyroxin binding site</td>
<td>IC50 41.3 nM</td>
<td>183.5 nM</td>
</tr>
<tr>
<td>2 Stabilization of tetrameric TTR</td>
<td>Tetrameric stability was monitored by isoelectric focusing assays with plasma TTR protein from control and TTR-FAP patients, and by subunit exchange experiments with recombinant wild type TTR. ✓ SOM0226 stabilizes the TTR tetramer, potentially preventing amyloidogenesis</td>
<td>↑Tetramer plasma ct: 33 % 57% 67% ↑Tetramer plasma FAP: Stabilization wtTTR: 11 % 27% 17%</td>
<td></td>
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<tr>
<td>3 Inhibition of fibrillogensis</td>
<td>Protein aggregation and fibril formation was followed by kinetic and end-point turbidity assays, using different mutant forms of TTR (TTR-FAP and TTR-FAC). ✓ SOM0226 prevents TTR amyloidogenesis, potentially delaying disease progression</td>
<td>IC50 (FAP): 4.8 µM 60% ↑Caspase3 FAP: 29 % 37% 12 %</td>
<td></td>
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<tr>
<td>4 Inhibition of TTR-induced cytotoxicity</td>
<td>Cytotoxicity assays were performed in TTR-FAP and TTR-FAC relevant cellular assays. ✓ SOM0226 prevents formation of toxic species, potentially reducing disease severity</td>
<td>↑cell viability FAC: 37% 29% 23%</td>
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<tr>
<td>5 TTR fibril disruption assay</td>
<td>Fibril disruption was monitored by Transmission Electron Microscopy and Dynamic Light Scattering on recombinant TTR. ✓ SOM0226 disrupts fibrils potentially reverting the progression of the disease</td>
<td>↓large aggregates: 47% 19% ↑soluble particles: 100% 25%</td>
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## In vivo studies

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<tr>
<th>Steps</th>
<th>SOM0226</th>
<th>Tafamidis</th>
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<tbody>
<tr>
<td>1 Plasma TTR binding and stabilization</td>
<td>SOM0226 was orally administered to transgenic mice expressing human mutant TTR V30M. T4 competition and TTR stabilization assays were performed to plasma proteins from treated animals. ✓ SOM0226 selectively binds to plasma TTR in vivo and stabilizes it in a dose dependent manner</td>
<td>% inh. T4 binding ↑Tetramer FAP: % tetramer increase 100% Up to 300% NA</td>
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</tbody>
</table>
**SOM0226: development plan**

### In-silico
- Top 100 list
- Report: MAR 2011

### In vitro
- Kinetic turbidity assay
- Report: AUG 2011

### IP
- PCT Patent
- Filed: OCT 2011

### Ex-vivo
- Steps of ATTR process:
  - $T_4$ competition, TTR stabilization, aggregation & fibril disruption
  - Active in FAC and FAP Mutations
  - Dose finding study in transgenic mice
- Reports: 2012-2013

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<tr>
<th>SOM0226-TTR Amyloidosis</th>
<th>2013</th>
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<td>OD formulation</td>
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<td>CMC development + Bioequivalence</td>
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SOM0226: key success factors

- Indication for all types of ATTR (polyneuropathy, cardiomyopathy, senile).
- More potent and disruptive than Tafamidis.
- Good cost-effectiveness ratio. Low COGs.
- Phase II Proof-of-Concept recruiting in Vall d’Hebron (results expected by 1Q 2015)
- Strong anti off-labeling strategy.
  - Mode of use Patent
  - Orphan Drug Status
  - Innovative New Drug
  - New Formulation (ODSR)
- Potential market over €1,500M/year/ww.
SOM3355

A repositioned drug for HUNTINGTON’s DISEASE and other hyperkinetic movement disorders

Non Confidential Information
Huntington’s disease

✓ **Autosomal dominant** disease that leads to a **progressive, selective neural cell death**.

✓ Associated with increases in the length of a CAG triplet present in the **huntingtin gene** → expanded polyglutamine tract in Htt → formation of aggregates → cell dysfunction and cell death

✓ Affected individuals encounter problems in:

  ▪ Control of **body movements**, chronic progressive chorea
  ▪ **Intellectual functioning**
  ▪ **Emotional control**

✓ Symptoms appear **between 30 and 50 years** of age.

✓ Available approved symptomatic treatment: **Tetrabenazine** (Vesicular Monoamine Transporter-2 Inhibitor).
SOM3355: the discovery process

| Reference compound: Tetrabenazine | Selective and reversible striatal VMAT2 inhibitor  
|                                  | Approved for the treatment of chorea associated to Huntington’s disease by the FDA. Market exclusivity in the USA till Aug 2015 |
| Discovery                        | Search for non structural analogs on compound libraries of approved drugs (9000 structures). |
| In vitro validation              | VMAT2 functional assay inhibition (50 drugs tested) \(\rightarrow\) identification of best compound SOM3355. |
| In vivo validation               | Test the efficacy of SOM3355 in a mouse model of the disease (motor movement disorders). |
| Clinical PoC                    | Test the efficacy of SOM3355 in patients affected by Huntington’s disease. |
SOM3355: *in vitro* screening (I)

**Vesicular Monoamine Transport -VMAT2- Functional Assay:**

- **CRO:** PerkinElmer (USA)
- **Transporter source:** Rat cortical vesicles
- **Compounds tested:** 8 +2 selected compounds.
- **Reference compounds:** Tetrabenazine
- **Concentrations tested:** 6 (from 10 μM to 0.1nM)
- **Number of replicates:** n=2
- **Parameters studied:** Interactions of test compounds with vesicular dopamine uptake
- **Graph values:** VMAT2 IC50 values
**SOM3355: *in vitro* screening (II)**

Vesicular Monoamine Transport -VMAT2- Functional Assay with the best candidate (2 independent experiments):

<table>
<thead>
<tr>
<th>Product code</th>
<th>IC50</th>
</tr>
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<tbody>
<tr>
<td>Tetrabenazine</td>
<td>10.5 nM</td>
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<td>SOM3355</td>
<td>42.8 nM</td>
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</table>

![Graph showing % VMAT2 activity vs Concentration (M)](image1)

<table>
<thead>
<tr>
<th>Product code</th>
<th>IC50</th>
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<tbody>
<tr>
<td>Tetrabenazine</td>
<td>36.7 nM</td>
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<tr>
<td>SOM3355</td>
<td>60.3 nM</td>
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</table>

*Note: error bars are too small to be visible*
**SOM3355: in vivo BBB crossing**

In vivo experiment performed in order to quantify the ability of SOM3355 in crossing the BBB.

Brain/plasma concentration ratio quantification demonstrates that SOM3355 significantly penetrates the BBB.

- **Mice strain:** B6CBA
- **Doses:** 50 mg/kg and 100 mg/kg
- **Administration route:** intraperitoneal
- **Time to sacrifice:** 1 hour
- **Internal standard:** propanolol

<table>
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<tr>
<th>SOM3355 Dose</th>
<th>Brain/plasma concentration ratio*</th>
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<tbody>
<tr>
<td>50 mg/kg</td>
<td>5.45</td>
</tr>
<tr>
<td>100 mg/kg</td>
<td>12.94</td>
</tr>
</tbody>
</table>

* ng SOM3355/gram of brain in relation to ng SOM3355/gram of plasma
## SOM3355: development program

### In silico
- Top 100 list
- 2012

### In vitro
- VMAT2 inhibition assay
- 2013

### IP
- EP patent filed
- ‘Therapeutic agents for use in the prophylaxis and/or treatment of hyperkinetic movement disorders’
- JUN 2013

### In vivo
- Quantification of SOM3355 brain levels after oral administration
- 2013-2014

<table>
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<tr>
<th>SOM3355-Huntington/Tourette</th>
<th>2013</th>
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**Timeline:**
- Q4 2013: Preclinical Package
- Q1 2014: Phase IIa POC EU Huntington/Tourette (n=20)
- Q3 2015: IND/IMPD
- Q4 2015: Phase III Pivotal Studies
- Q1 2016: NDA
- Q4 2016: Approval

**Status:**
- Green: Completed
- Red: Ongoing
- Blue: Pending
- Orange: Approved

**Notes:**
- Orphan Drug Status US/EU and EMA/FDA Advise
- Preclinical Studies
- Clinical Samples (Phase IIb/III)
SOM3355: key success factors

- Prevention and treatment of hyperkinetic movement disorders associated to Huntington’s disease, Tourette syndrome, hemiballism and tardive dyskinesia.

- Similar potency to TBZ in vitro. It crosses the BBB.

- SOM3355 can be administered in a lower frequency compared to TBZ - which is administered TID.

- Good safety profile versus ‘black box’ for TBZ.

- Ready to clinical Proof-of-Concept.

- European patent filed on 19th June 2013; EESR received on Dec 2013. June 2014 PCT filling

- Orphan drug status designation ongoing.

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Thanks for your time!

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08028 Barcelona. Spain
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