SOM BIOTECH

The drug repositioning company

DRUG REPOSITIONING IN RARE DISEASES
HOW TO OPTIMIZE DRUG ACCESS FOR PATIENTS

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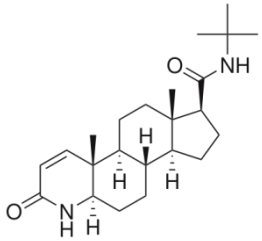
8TH NOV 2014. SESSION 4. TRACK 2: INTERDISCIPLINARY-TECHNOLOGIES

IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Success examples in repurposing



FINASTERIDE

Merck

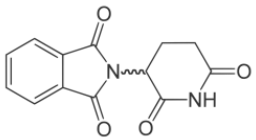
1992: Prostatic hypertrophy

17 €

REPROFILED

1998: Hair loss

52 €



THALIDOMIDE

Grünenthal

1957: Nausea

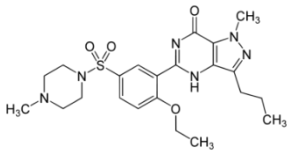
40 Pts

Celgene

2008: Leprosy / Multiple Myeloma

Thalomid®

6.000 €



SILDENAFIL

Pfizer

1992: Hypertension

REPROFILED

1998: Erectile Dysfunction

99 €

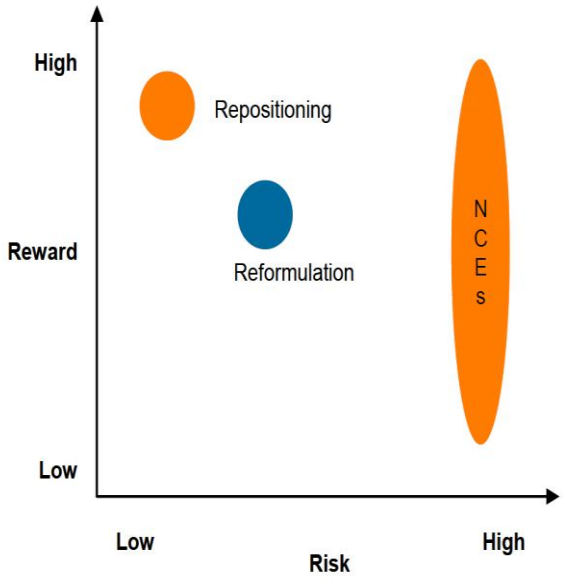
REPROFILED

2012: Pulmonary Hypertension

24 €

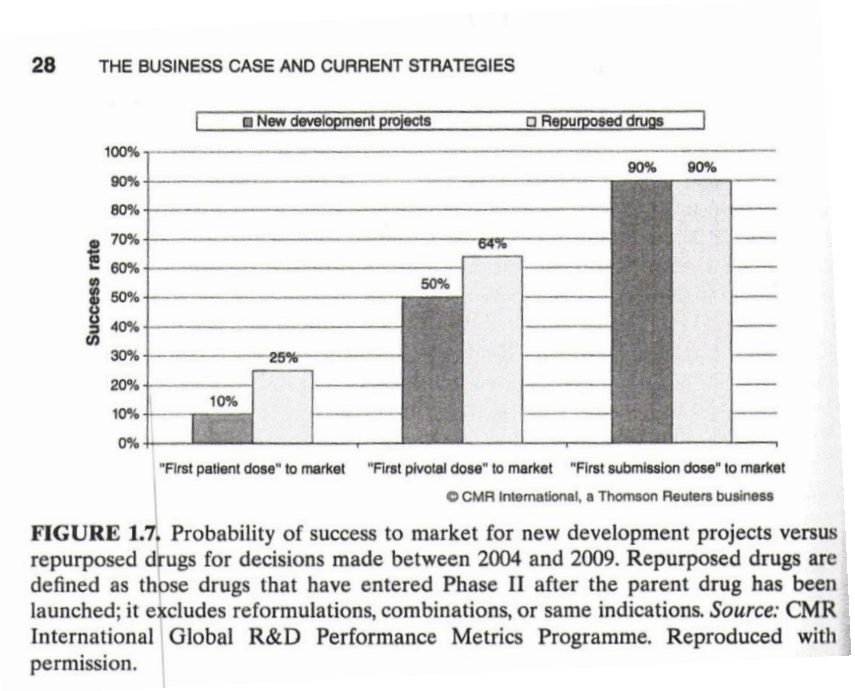
Why drug repurposing ?

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



Source: Norman Consulting

BUSINESS INSIGHTS



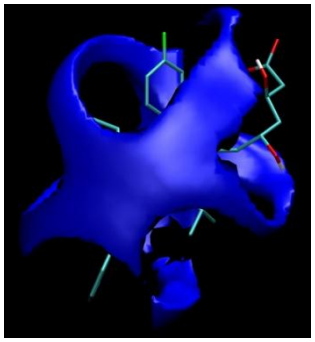
28 THE BUSINESS CASE AND CURRENT STRATEGIES

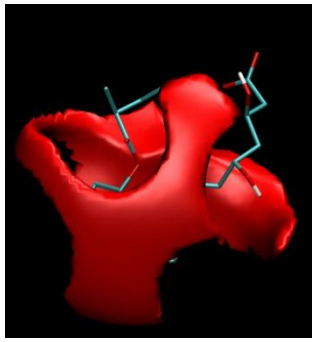
FIGURE 1.7. Probability of success to market for new development projects versus repurposed drugs for decisions made between 2004 and 2009. Repurposed drugs are defined as those drugs that have entered Phase II after the parent drug has been launched; it excludes reformulations, combinations, or same indications. *Source:* CMR International Global R&D Performance Metrics Programme. Reproduced with permission.

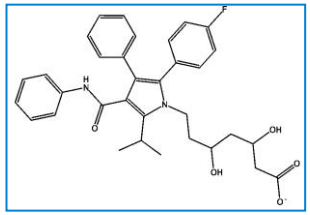
How we do drug discovery ?

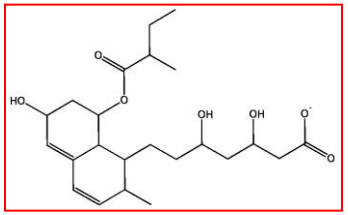
Ligand-based Virtual Screening technology - Identification of non-structural analogs

Molecular fields: 22 molecular interaction fields (Score)
3D space
Flexible alignment

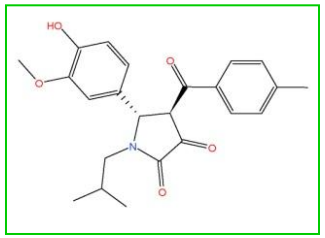








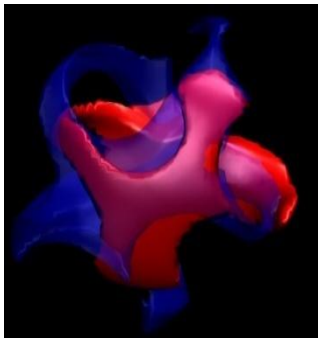
Reference Compound
HMG-CoA Inhibitor



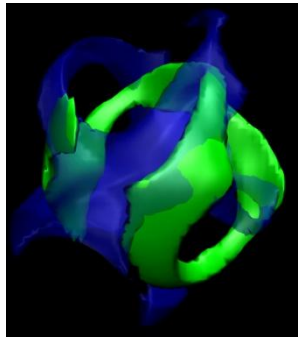
Active molecule
HMG-CoA Inhibitor

Inactive molecule

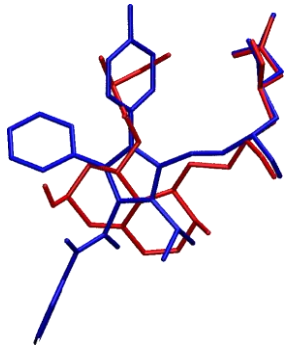
Flexible molecular fields alignment

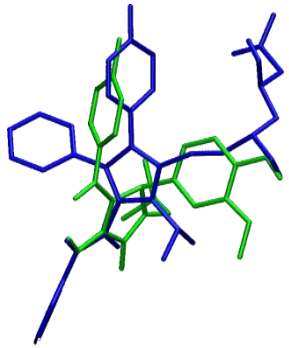


Score = 0.55

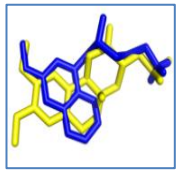


Score = 0.31





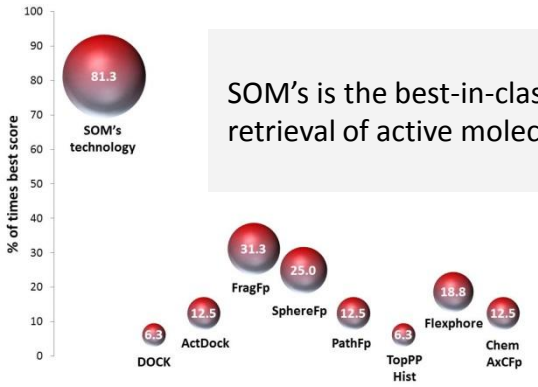
Our business Model




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

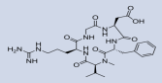
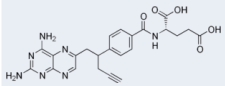
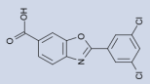
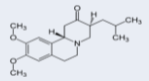
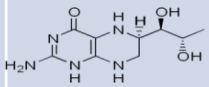
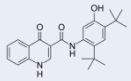
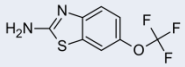
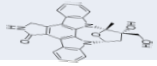
In Property

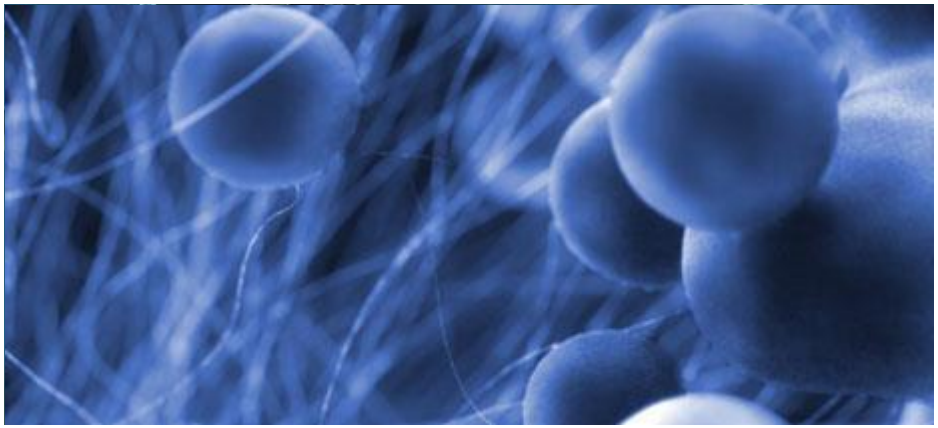
- Ligand-based Virtual Screening Technology
- Molecular field maps through 22 molecular potentials
- 3D maps; flexible alignment; intensive in CPUs use
- Identification of non-structural analogs



SOM's is the best-in-class in the retrieval of active molecules.

Orphan pipeline

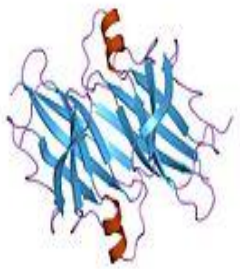
INDICATION	LIGANT	STRUCTURE	RESULTS	STATUS
Glioma (I)	Cilengitide		**SOM0777** Activity +++ Celular line +++	Non-exclusively licensed to Argon Pharma SL
T Cell Lymphoma	Pralatrexate		Three +++ hits identified	Abandoned. Already patented
TTR Amyloidosis	Tafamidis		**SOM0226** In vitro +++, Ex-vivo +++ Primary indication 1997	Open for out-license WW Patent ODS + Phase II POC ongoing
Huntington Disease (Chorea mov)	Tetrabenazine		**SOM3355** In vitro +++, BBB +++ Primary indication 1995	Open for license WW Patent Phase II POC under discussion
Phenylketonuria	Sapropterin		40 compounds under screening	No result yet
Cystic Fibrosis	Ivacaftor		Not yet	*In silico* process
Spinobulbar M Atrophy	*Undisclosure*	*Undisclosure*	Not yet	*In silico* process
Amyotrophic Lateral Sclerosis	Riluzole		Not yet	*In silico* process
Glioma (II)	*Undisclosure*	*Undisclosure*	Not yet	*In silico* process
Acute Myeloid Leukemia	Lestaurtinib		Not yet	*In vitro* process



SOM0226

A repositioned drug for

TRANSTHYRETIN AMYLOIDOSIS (ATTR)



Non Confidential Information

Transthyretin Amyloidosis (ATTR)

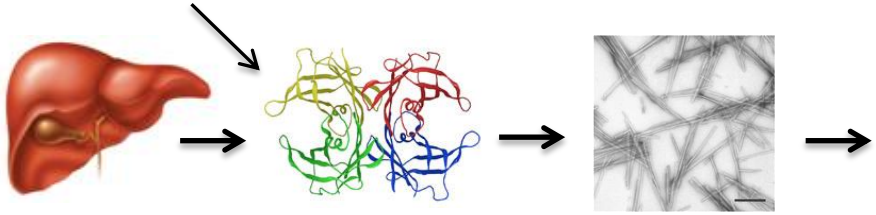
-**Orphan disease** caused by extracellular **deposition of amyloid fibrils** derived from normal or mutant transthyretin protein.

-Tetramer **dissociation, misfolding and aggregation** as amyloid fibrils.

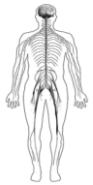
-It causes **nervous system and/or heart pathology** of adult onset.

-**Life expectancy of 5-15 years** after first symptoms.

Retina,
choroid plexus

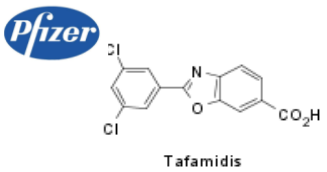


Transthyretin *(TTR):* ***trans****port of* ***thy****roxine (T4) and* ***retin****ol in blood and CSF.*

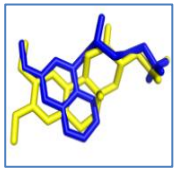
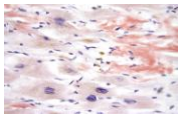


PHENOTYPE	TTR	PREVALENCE
FAP : Familial Amyloid Polyneuropathy	TTR V30M and other	WW <1/100,000
FAC : Familial Amyloid Cardiomyopathy	TTR V122I and other	WW <1/1,000,000 (3-4% Afro-American)
SSA : Senile Systemic Amyloidosis	Wild type TTR	2.75% >85y severe deposits
CNSA : CNS Selective Amyloidosis	Aggressive mutants TTR	Rare

SOM0226: the discovery process



Tafamidis

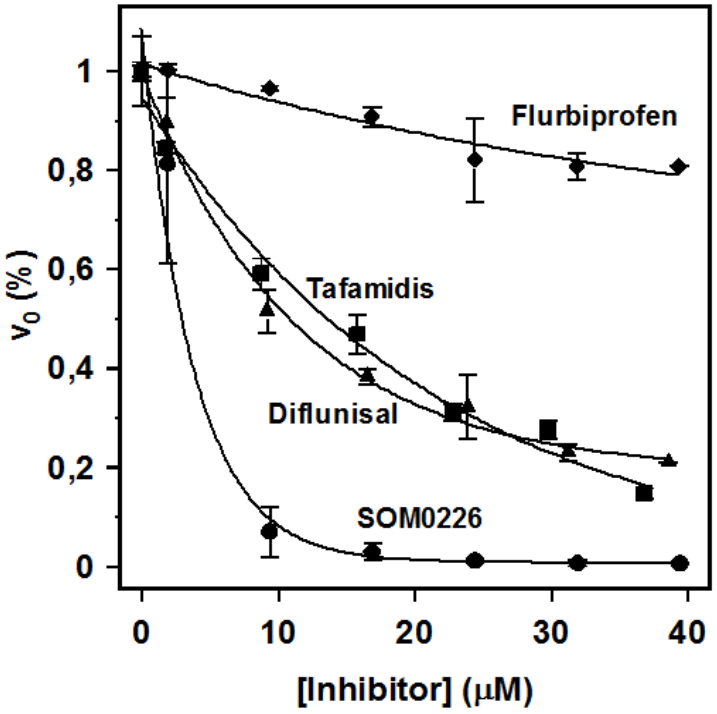
Reference compound: **Tafamidis**	• Specific stabilizer of transthyretin. • Authorized for TTR-FAP under "exceptional circumstances" by the EMA (orphan drug status). In pre-registration process by the FDA.
 Discovery	• Search for non structural analogs on compound libraries of approved drugs (9000 structures). • 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

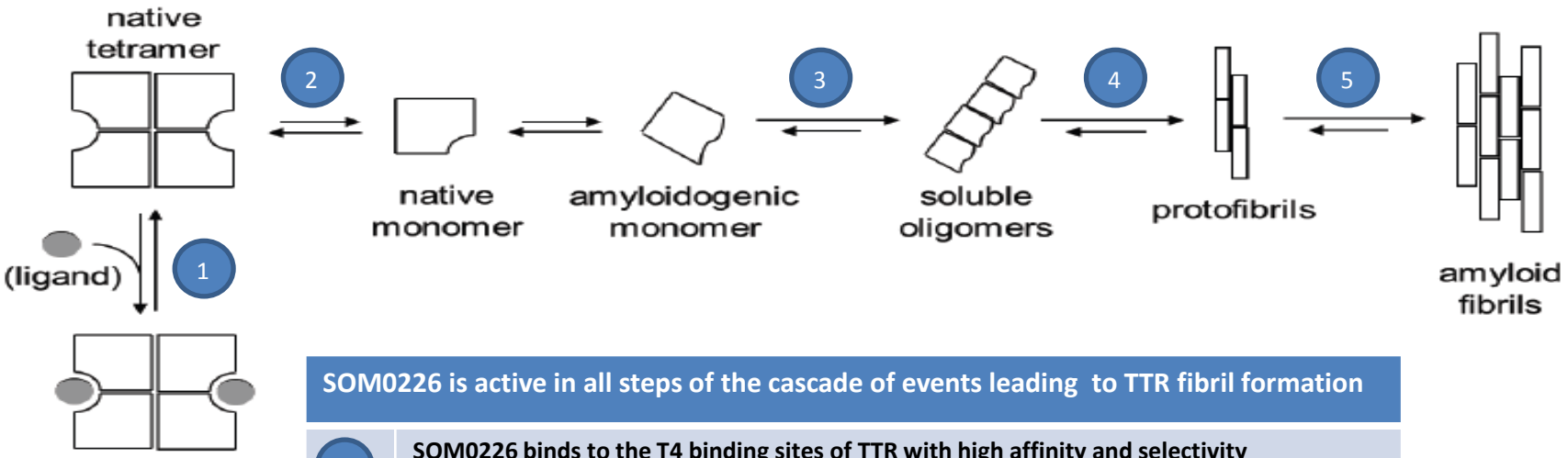
Kinetic Assay for High-Throughput Screening of Transthyretin Amyloid Fibrillogenesis inhibitors (*Dolado et al. 2005*)

***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

Steps	Cellular, *in vitro* and *ex vivo* assays		SOM0226	tafamidis
1	**Binding to T4 binding sites** 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*	IC50	41.3 nM	183.5 nM
2	**Stabilization of tetrameric TTR** 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*	↑Tetramer plasma ct: ↑Tetramer plasma FAP: Stabilization wtTTR:	33 % 57% 67%	11 % 27% 17%
3	**Inhibition of fibrillogenesis** 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*	IC50 (FAP): % inh. 1:1 (FAC):	4.8 µM 60%	16.9 µM 44%
4	**Inhibition of TTR-induced cytotoxicity** Cytotoxicity assays were performed in TTR-FAP and TTR-FAC relevant cellular assays. ✓ *SOM0226 prevents formation of toxic species, potentially reducing disease severity*	↓Caspase3 FAP: ↑cell viability FAC: ↑cell viability SSA:	29 % 37% 29%	12 % 27% 23%
5	**TTR fibril disruption assay** 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*	↓large aggregates: ↑ soluble particles:	47% 100%	19% 25%
Steps	***In vivo* studies**		**SOM0226**	**Tafamidis**
1 2	**Plasma TTR binding and stabilization** 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*	% inh. T4 binding % tetramer increase	100% Up to 300%	NA

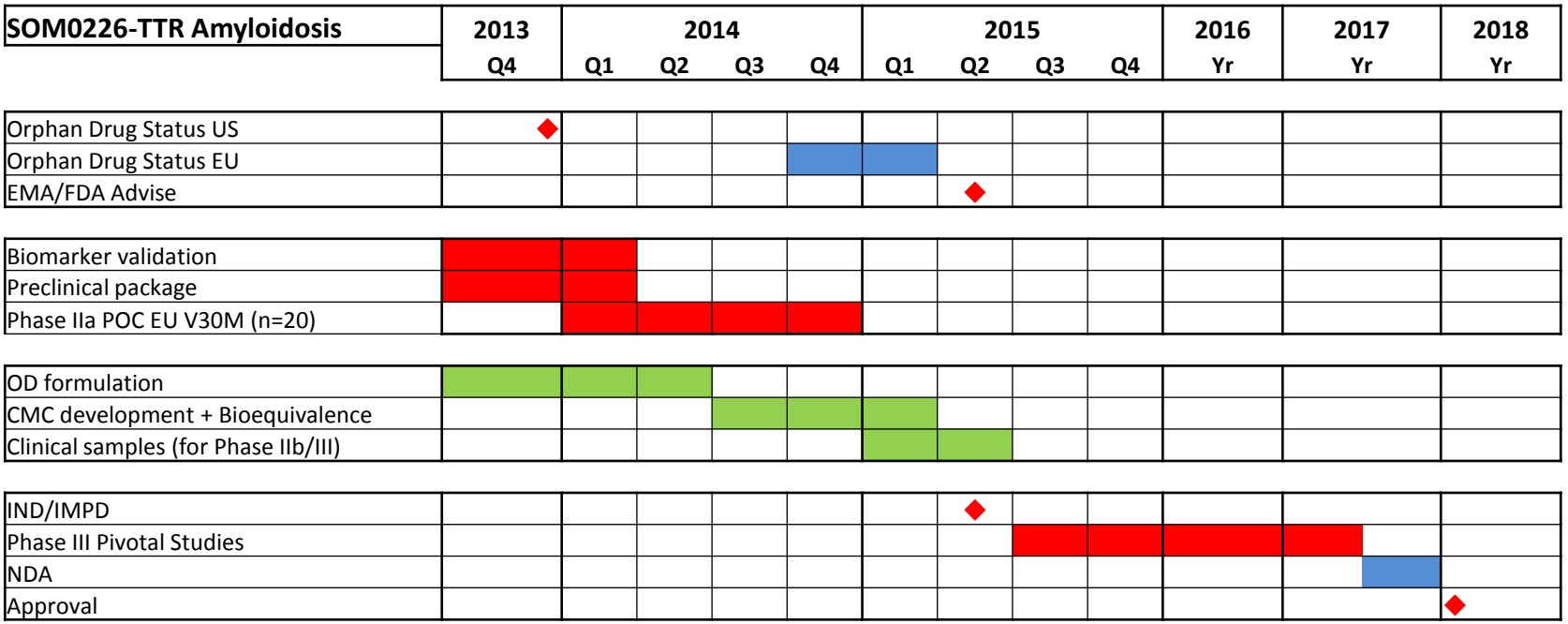
SOM0226: development plan

In-silico
Top 100 list
Report: MAR 2011

In vitro
Kinetic turbidity assay
Report: AUG 2011

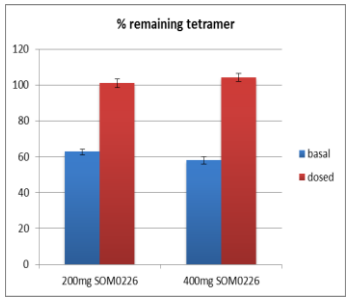
IP
PCT Patent
Filed: OCT 2011

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



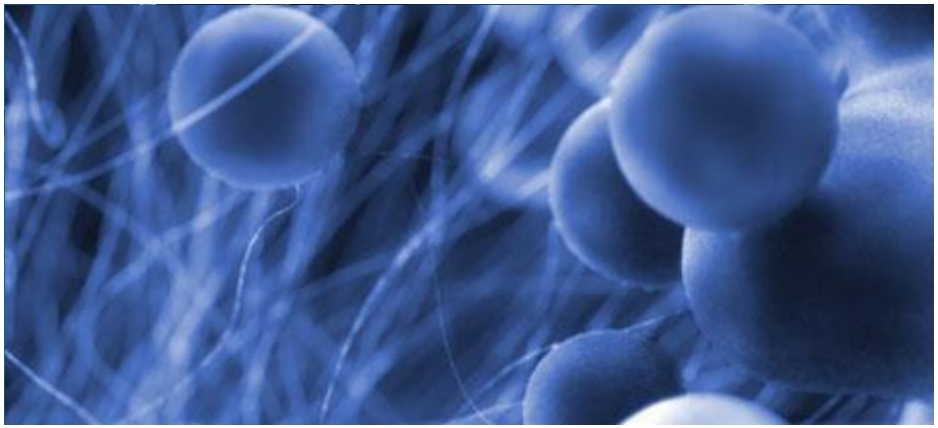
SOM0226: key success factors

- 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)

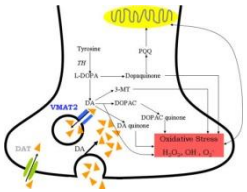
- Potential market over €1,500M/year/ww.
- FDA Orphan Drug Status granted and WW Patent in national phase.



SOM3355

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

Non Confidential Information



Huntington's disease

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

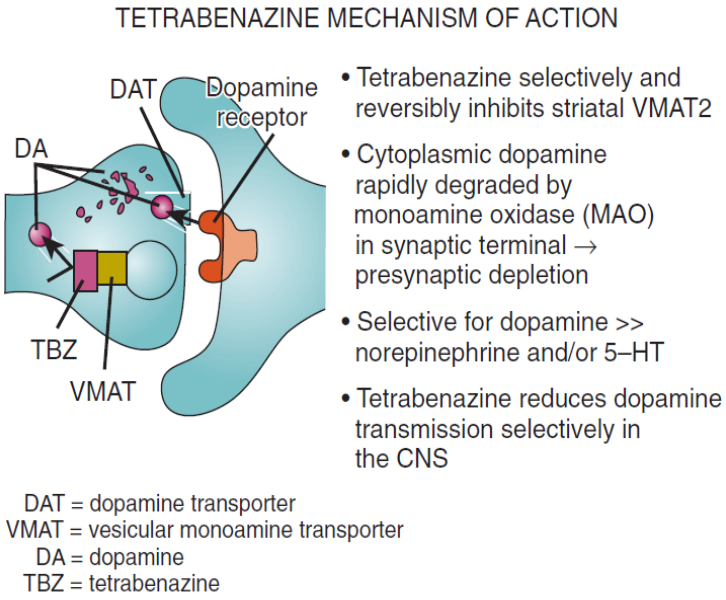
✓ Associated with increases in the length of a CAG triplet present in the **huntingtin ge**ne → expanded polyglutamine tract in Htt → formation of aggregates → cell dysfunction and cell death

✓Affected individuals encounter problems in:

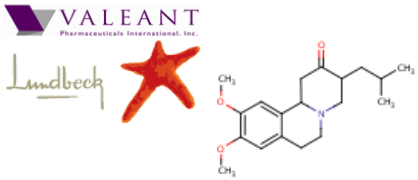
- Control of **body movements**, chronic progressive chorea
- **Intellectual functioning**
- **Emotional control**

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

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

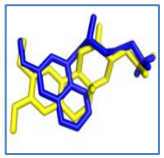


SOM3355: the discovery process



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

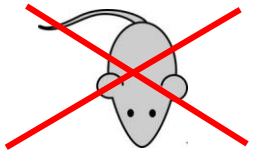


Discovery

- Search for non structural analogs on compound libraries of approved drugs (9000 structures).

***In vitro* validation**

- VMAT2 functional assay inhibition (50 drugs tested) → identification of best compound **SOM3355.**



***In vivo* validation**

- Test the efficacy of **SOM3355** in a mouse model of the disease (motor movement disorders).

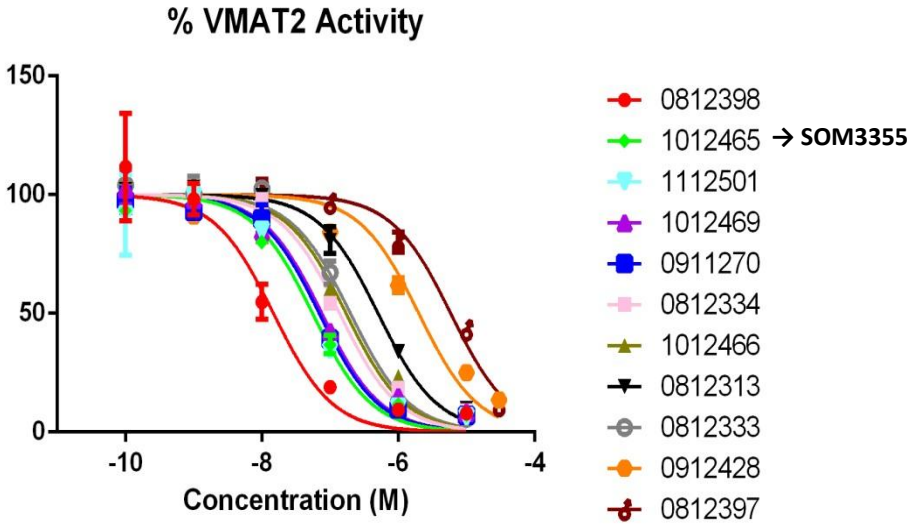
Clinical PoC

- Test the efficacy of **SOM3355** in patients affected by Huntington's disease.

SOM3355: *in vitro* screening (I)

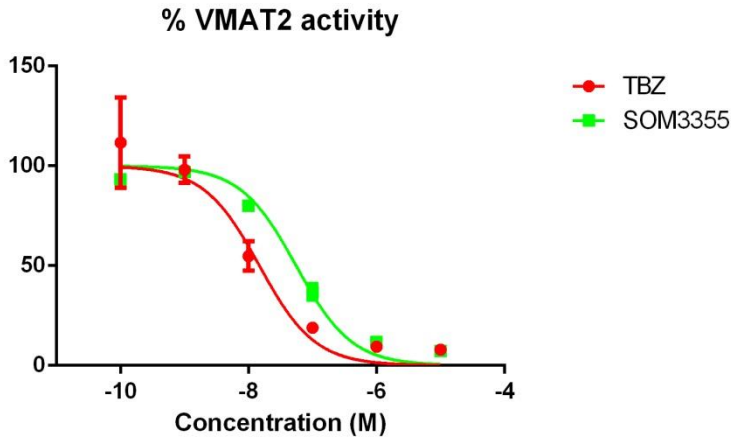
Vesicular Monoamine Transport -VMAT2- Functional Assay:

- **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

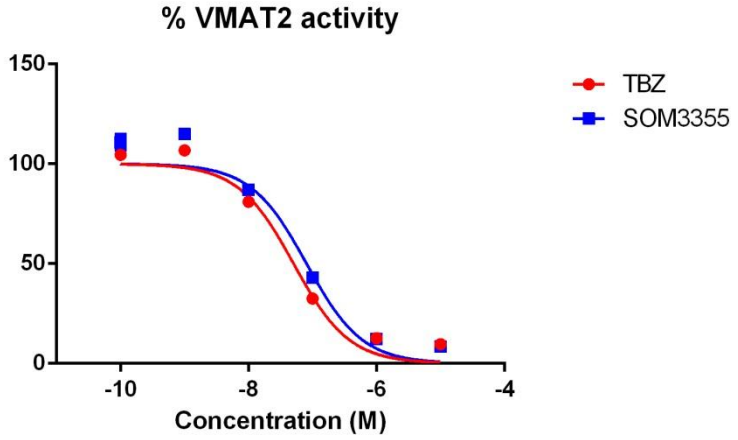


SOM3355: *in vitro* screening (II)

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



Product code	IC50
Tetrabenazine	10.5 nM
SOM3355	42.8 nM



Product code	IC50
Tetrabenazine	36.7 nM
SOM3355	60.3 nM

**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

SOM3355 Dose	Brain/plasma concentration ratio*
50 mg/kg	5.45
100 mg/kg	12.94

* 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

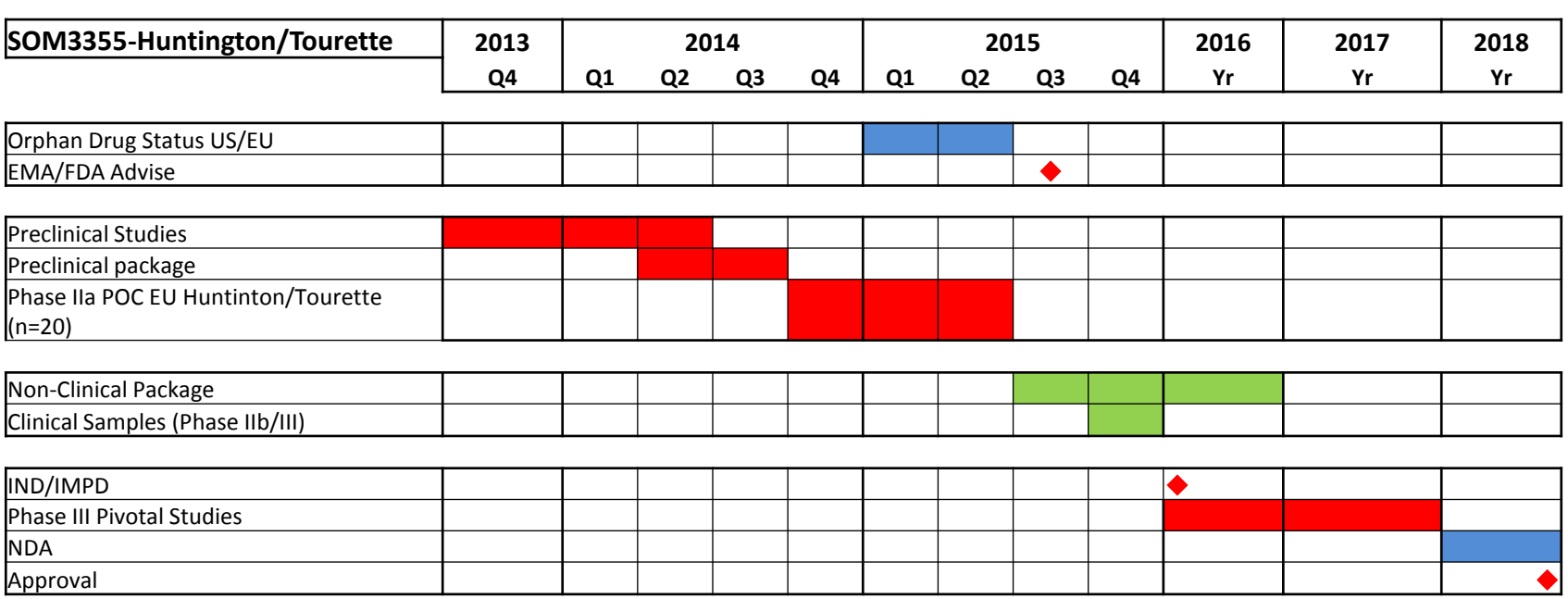
EP patent filed
'Therapeutic agents for use in the prophylaxis and/or treatment of hyperkinetic movement disorders'

JUN 2013

In vivo

- Quantification of SOM3355 brain levels after oral administration

2013-2014



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 Dose	Brain/plasma concentration ratio*
50 mg/kg	5.45
100 mg/kg	12.94

- 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.

Sant Pau

- European patent filed on 19th June 2013; EESR received on Dec 2013. June 2014 PCT filling
- Orphan drug status designation ongoing.

Thanks for your time !

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