Programa Cooperación Farma-Biotech

9º encuentro (4 de julio de 2013)

New family of Alzheimer's disease-modifying agents that hit multiple biological targets

Universitat de Barcelona

Fundació Bosch i Gimpera
Universitat de Barcelona

Barcelona, 4 de julio de 2013

GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

farmaindustria

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   b) Innovative mechanisms of action
   c) Differential features facing the market
   d) Current status of development
   e) IPR protection
   f) Pitfalls & Risks to be considered
3. Partnering Opportunities

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1. **The Research Group**
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1. The Research Group

Composition

Dr. Diego Muñoz-Torrero
(Associate professor)
2-4 PhD students
2-3 pregraduate students
1-2 international exchange students

Location

Laboratory of Medicinal Chemistry
Faculty of Pharmacy
University of Barcelona

Funding

Public funding (MINECO, AGAUR, Genoma España, etc.)

1. The Research Group

Main focus

Alzheimer's disease

Phases

Synthesis of short series of compounds (up to gram-scale)
Hit-to-lead optimization on the basis of SAR studies

In collaboration: molecular modeling to enable rational design
in vitro biological profiling
in vitro PAMPA-BBB
ex vivo BBB penetration assays
in vivo efficacy studies

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in vitro studies

Aβ aggregation
Vincenza Andrisano (Univ. Bologna)
Manuela Bartolini (Univ. Bologna)

BACE-1
Vincenza Andrisano (Univ. Bologna)
Angela De Simone (Univ. Bologna)

Antioxidant properties
Luciano Saso (Univ. Roma)

AChE and BChE
Albert Badia (UAB)
M. Victòria Clos (UAB)
Vincenza Andrisano (Univ. Bologna)
Manuela Bartolini (Univ. Bologna)

Patent filing and valorization
Àrea de Valorització i Llicències (FBG)

molecular modeling
(molecular dynamics, docking, thermodynamic integrations)
F. Javier Luque (UB)

lead optimization and selection of candidates

PK studies

PAMPA-BBB
Maribel Rodríguez-Franco (Inst. Quím. Médica, Madrid)
Belén Pérez (UAB)

***Ex vivo* studies (OF1 mice)**
M. Victòria Clos (UAB)
Belén Pérez (UAB)

in vivo studies

Caenorahbidis elegans
Mario Salmona (Inst. Mario Negri, Milán)
Luisa Diomede (Inst. Mario Negri, Milán)

Escherichia coli
Raimon Sabaté (UB)

Transgenic mice (APP/PS1 mice)
Antoni Camins (UB)
Mercè Pallàs (UB)
Isidre Ferrer (UB / IDIBELL)
Nibaldo Inestrosa (Pontificia Univ. Católica de Chile)

1. The Research Group

The pipeline

2 Projects on anti-Alzheimer agents with potential to efficiently treat the neurodegenerative process, under patent protection and valorization process

- **AVCRI175** (PCT/EP2013/059683, in collaboration with the group of Nibaldo Inestrosa)

Completed *in vivo* efficacy studies in APP/PS1 mice with positive results.

- **AVCRI211** (EP13173930.2, in collaboration with the group of Isidre Ferrer)

Promising results in preliminary *in vivo* studies in APP/PS1 mice with two compounds (reduction of brain amyloid burden, astrogliosis and microgliosis, preservation of synaptic proteins and cognitive functions).

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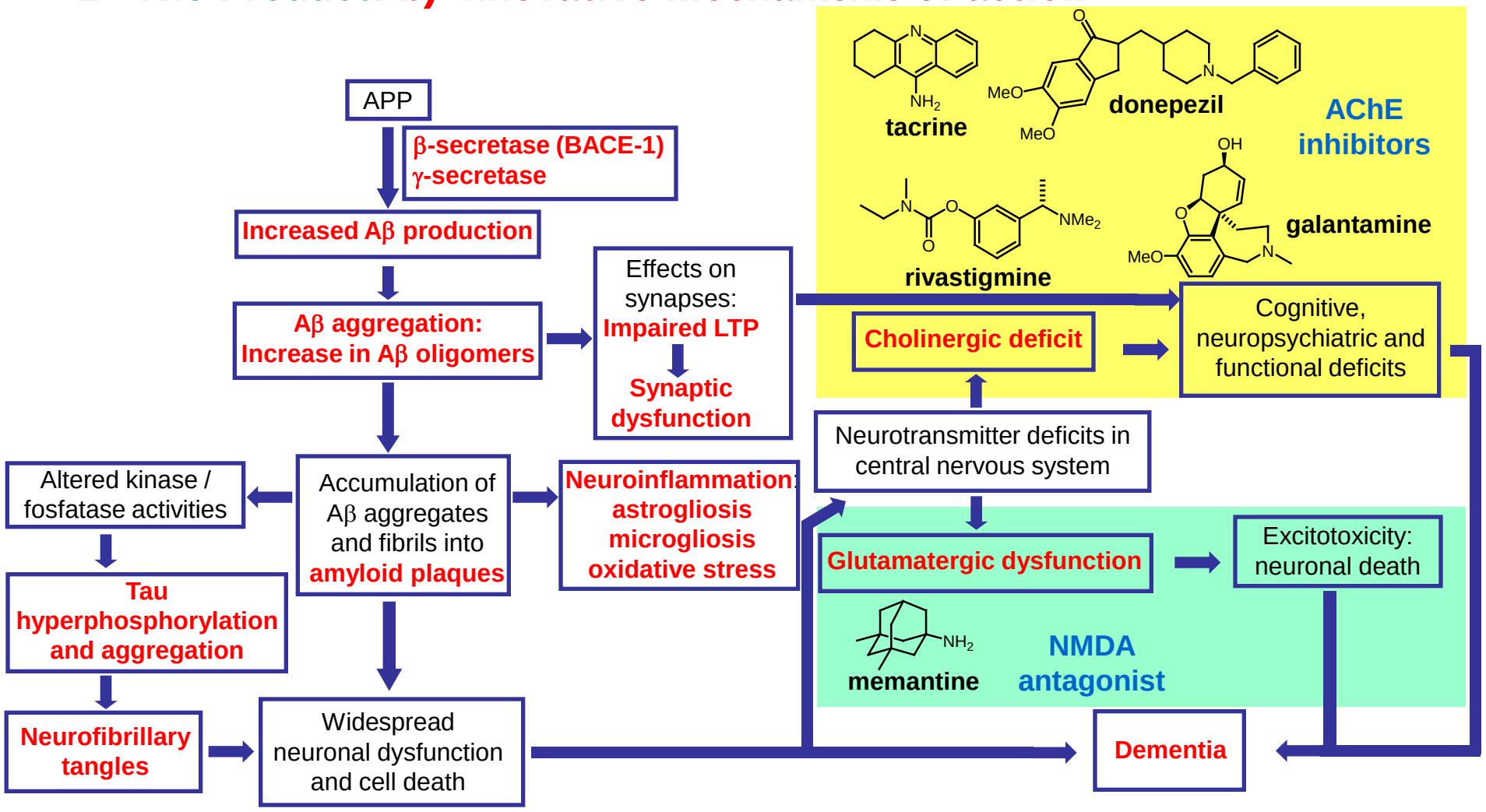
2. The Product: a) Target Indications

AVCRI175P1: **Alzheimer's disease**, with potential to be able to interfere with the underlying mechanisms of the disease, and, hence, to efficiently confront (to prevent, delay or slow down) the neurodegenerative process, if administered early, in a presymptomatic phase

2. The Product: b) Innovative mechanisms of action



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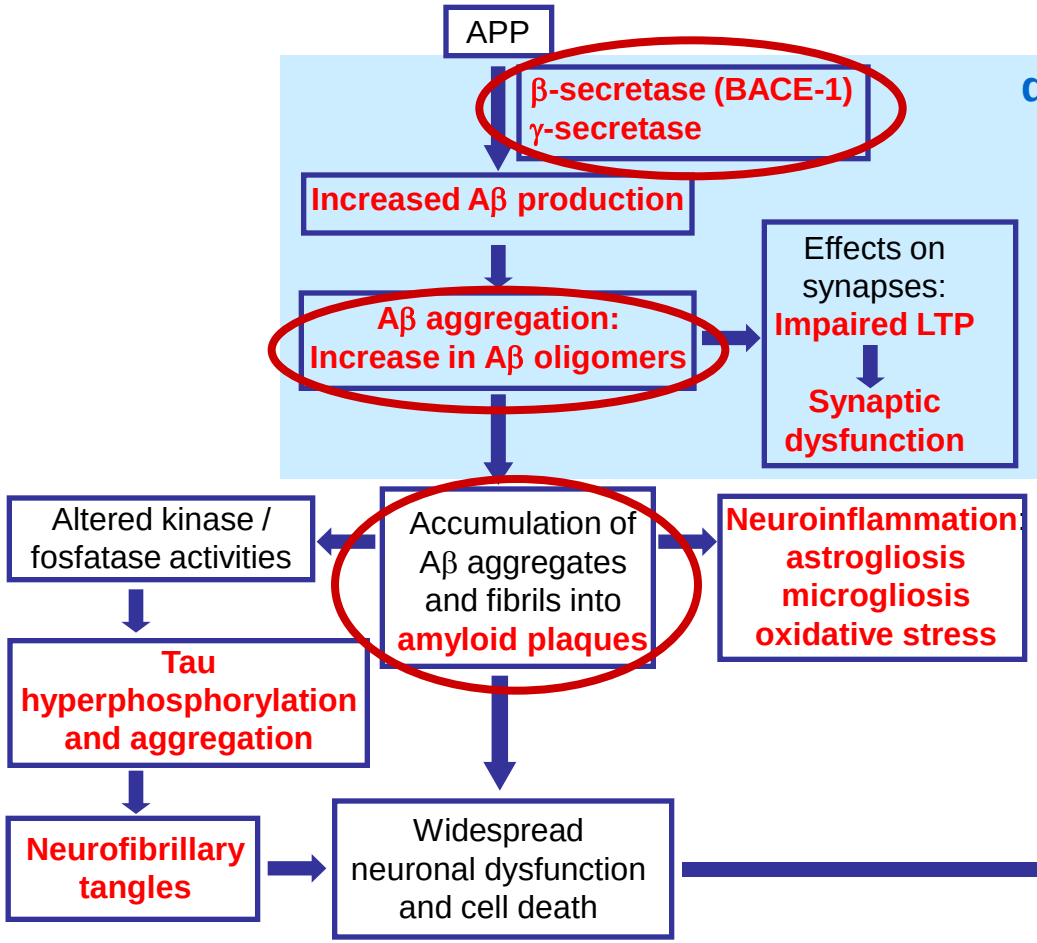


disease-modifying Anti-alzheimer drugs

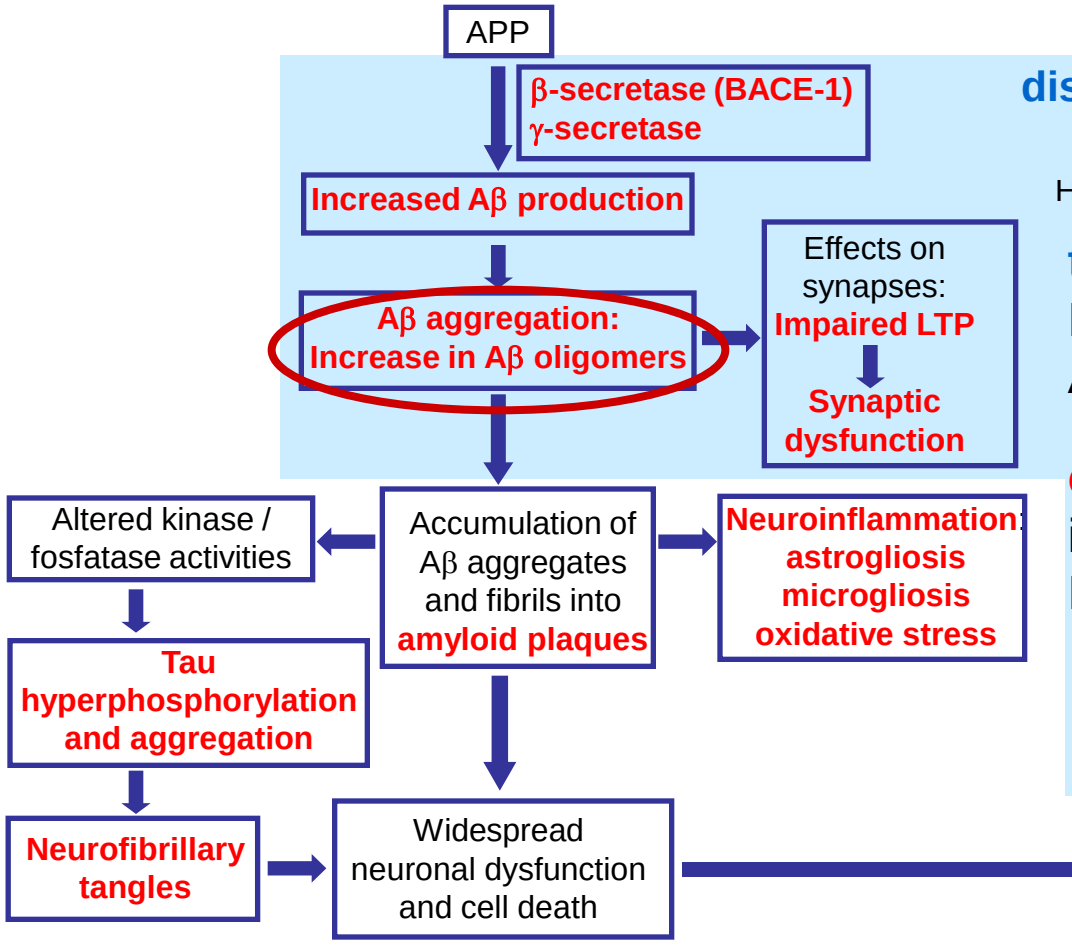
> 20% anti-Alzheimer drug candidates undergoing clinical trials target:

either Aβ aggregation / amyloid plaque formation

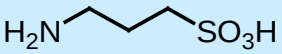
or Aβ production

or Aβ clearance

2. The Product: b) Innovative mechanisms of action



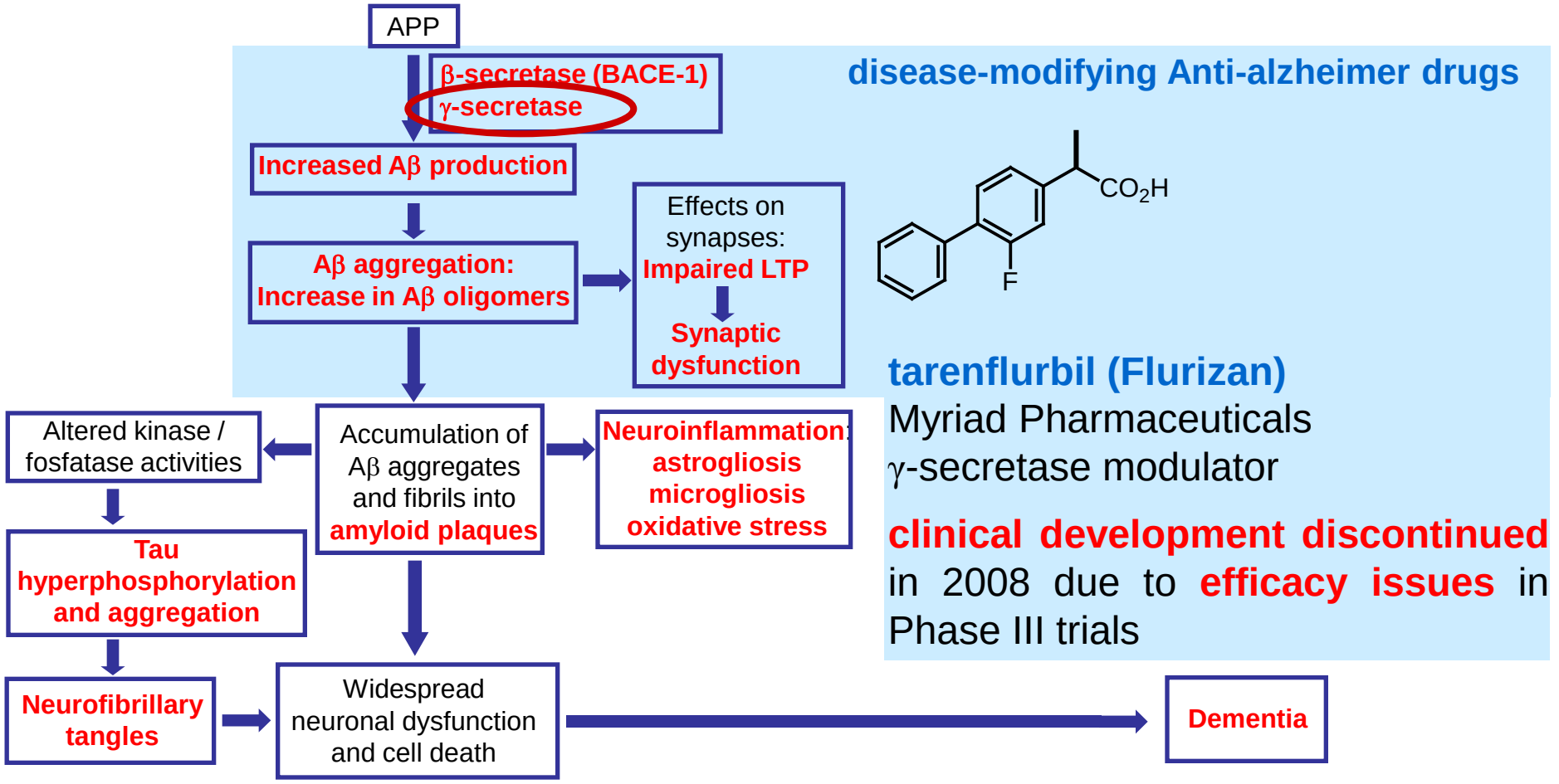
disease-modifying Anti-alzheimer drugs



tramiprosate (Alzhemed)
Neurochem
Aβ antiaggregating agent

clinical development discontinued in 2007 due to **efficacy issues** in Phase III trials

2. The Product: b) Innovative mechanisms of action



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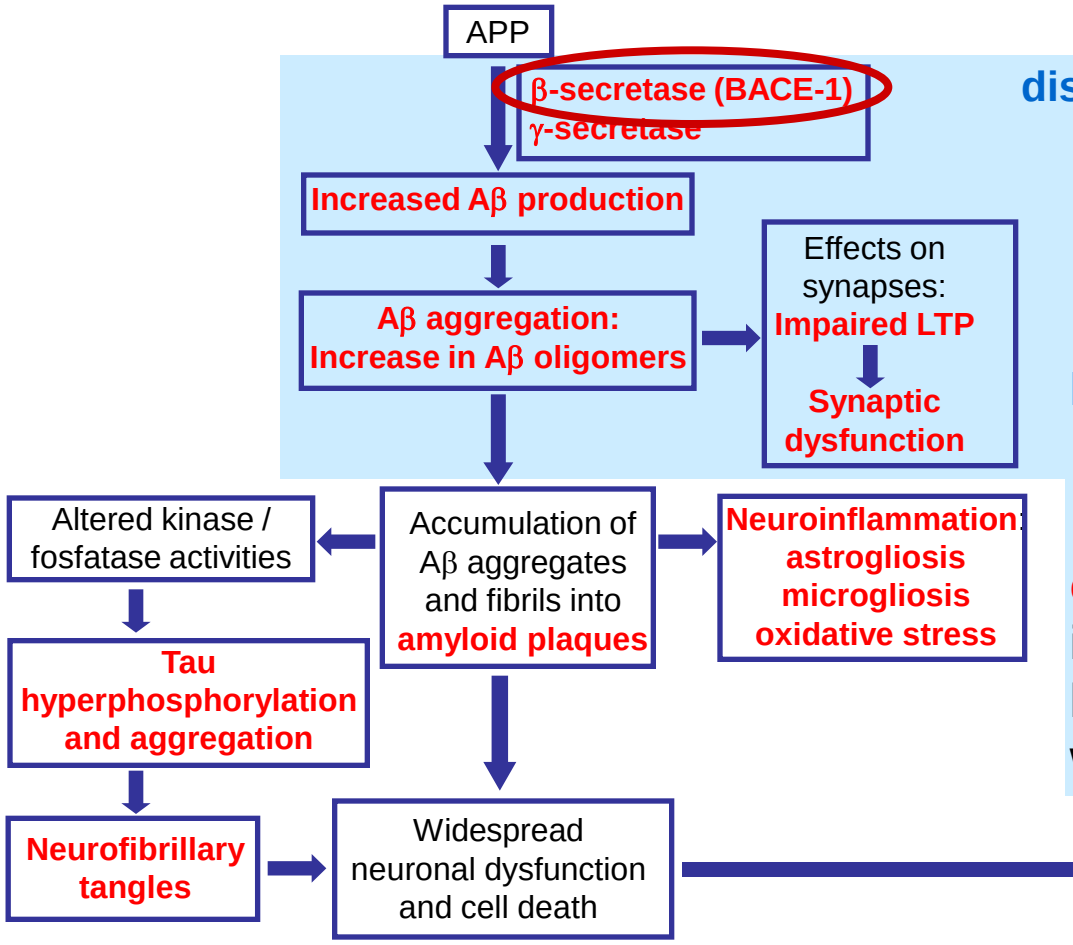
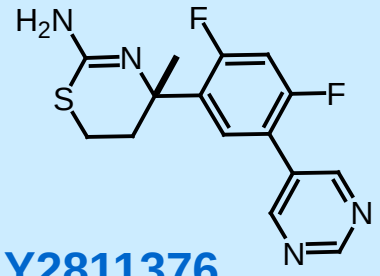


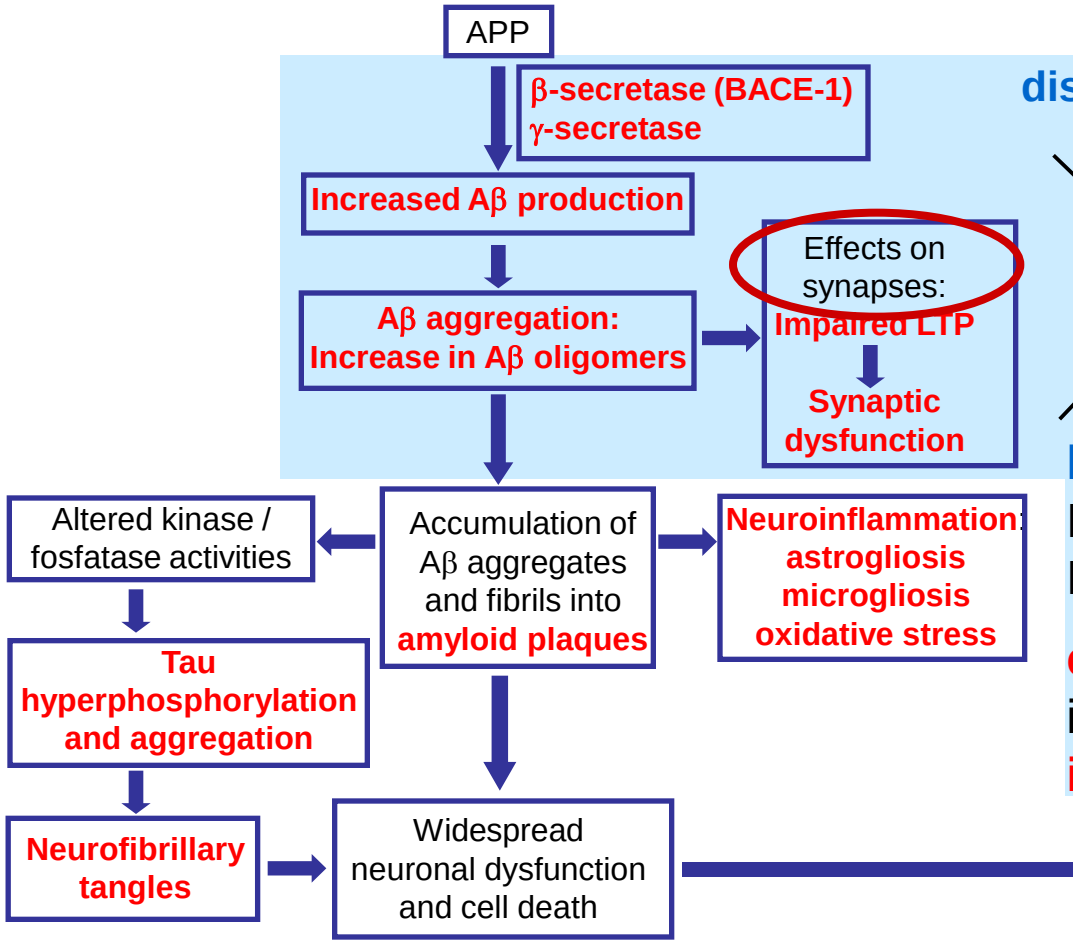
disease-modifying Anti-alzheimer drugs



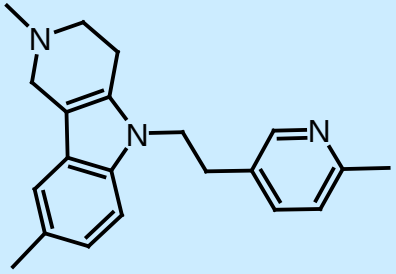
LY2811376
Eli Lilly
BACE-1 inhibitor

clinical development discontinued in 2011 due to **toxicity issues** in long-term preclinical studies when it was in Phase I trials

2. The Product: b) Innovative mechanisms of action



disease-modifying Anti-alzheimer drugs



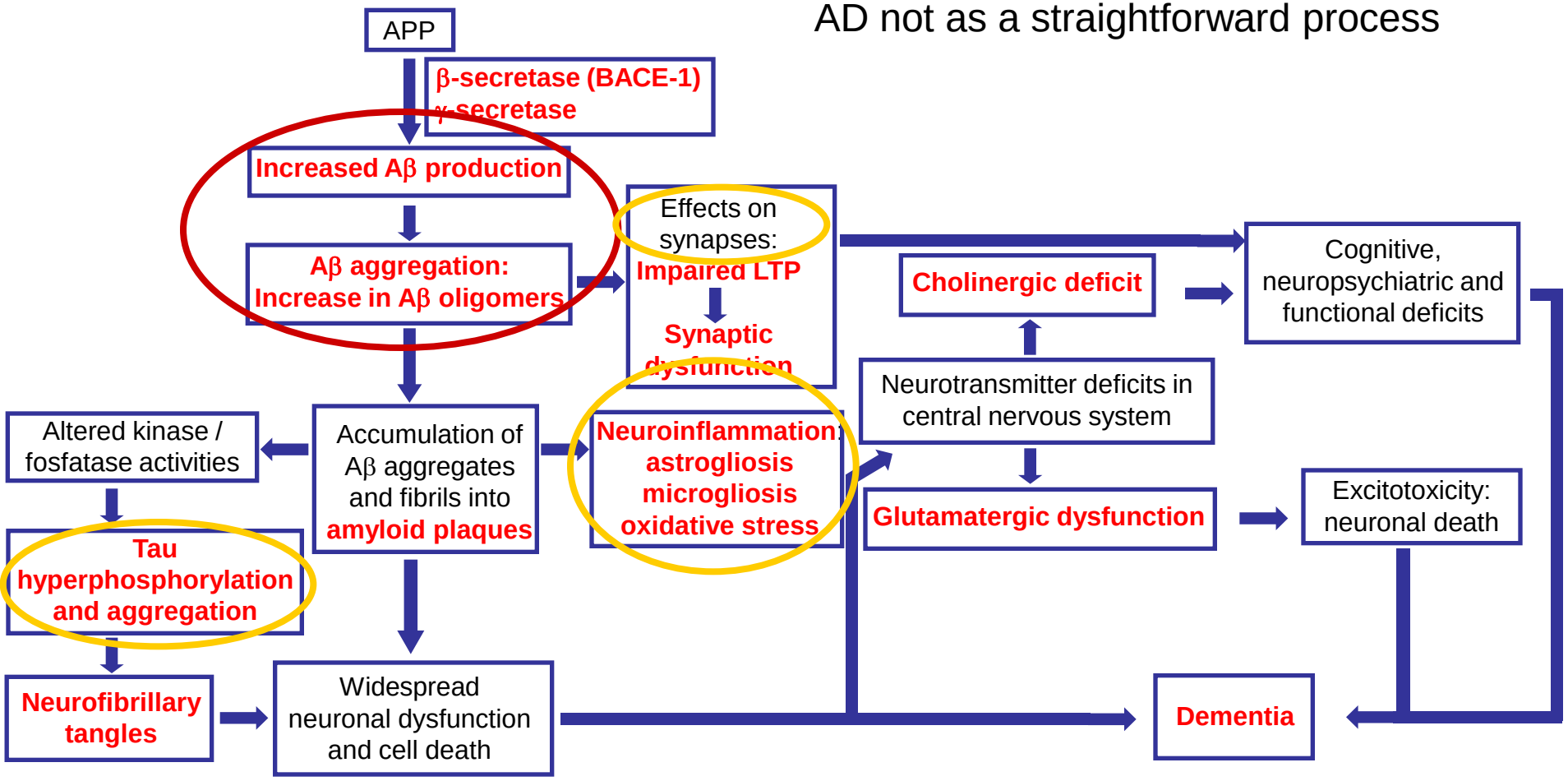
Iatrepirdine (Dimebon)
Medivation/Pfizer
Blocks neurotoxic action of Aβ

clinical development discontinued in January 2012 due to **efficacy issues** in Phase III trials

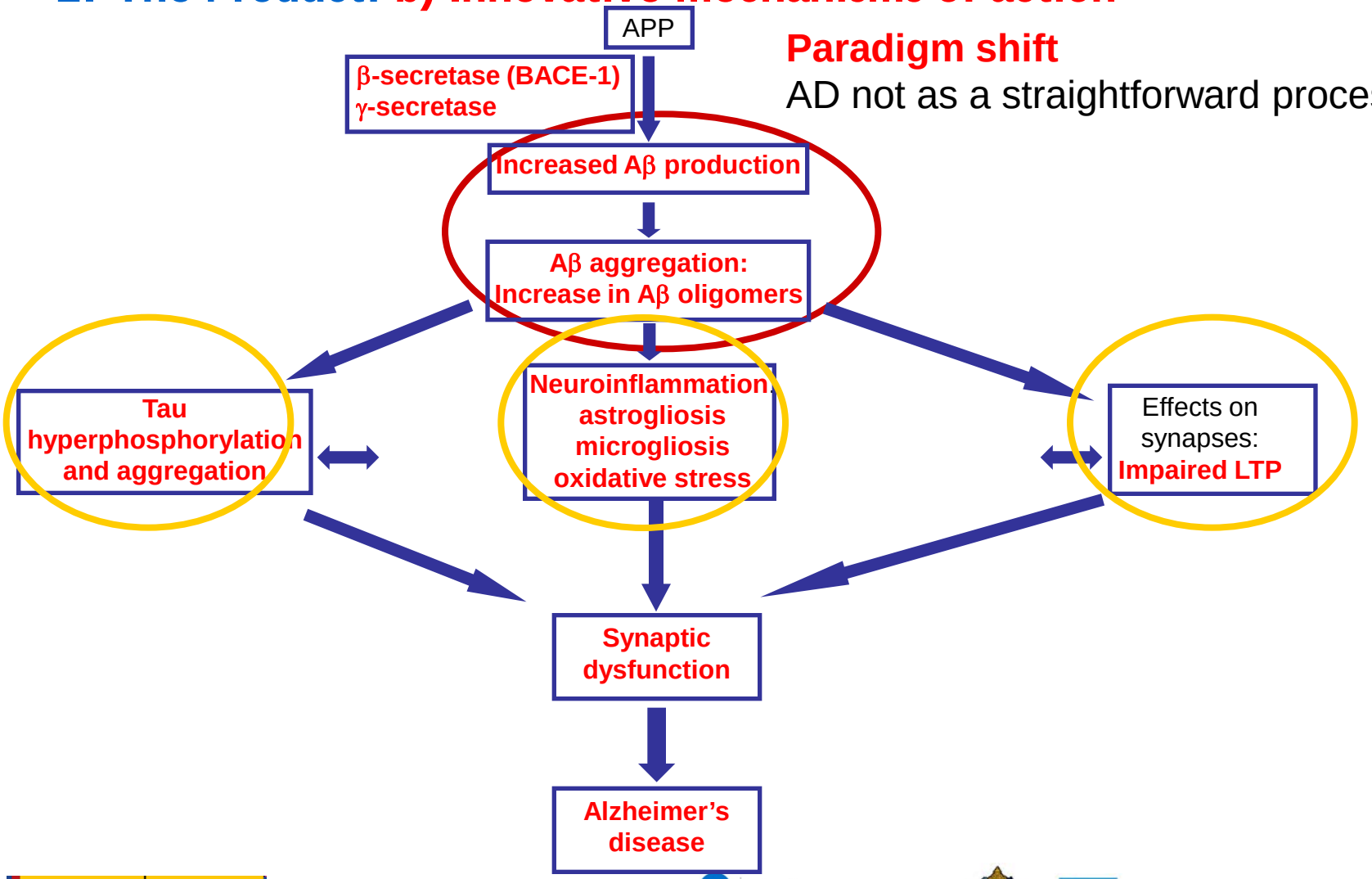
2. The Product: b) Innovative mechanisms of action

Paradigm shift

AD not as a straightforward process



2. The Product: b) Innovative mechanisms of action



Paradigm shift

AD not as a straightforward process

2. The Product: b) Innovative mechanisms of action

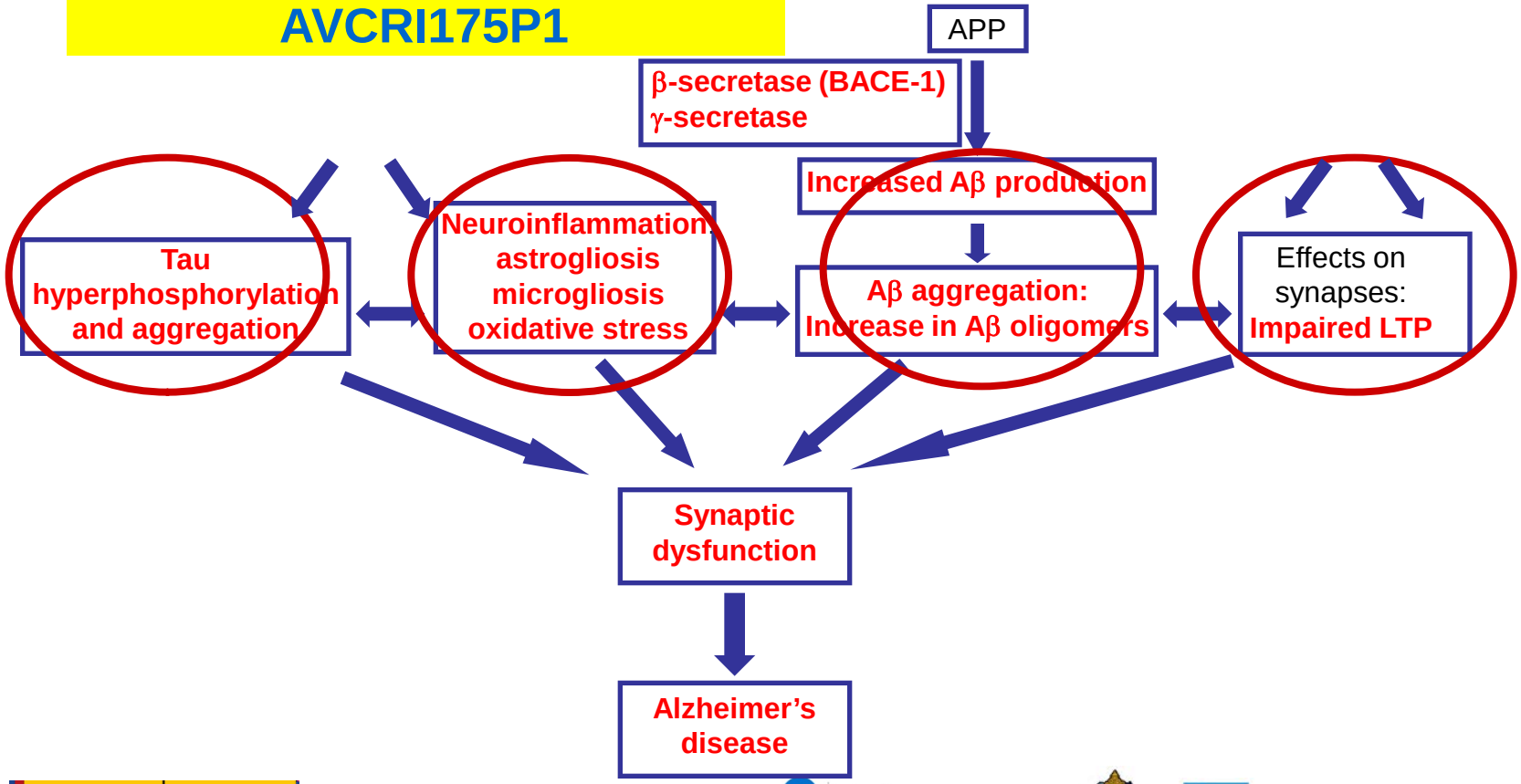
need of multi-target therapies

⬇

AVCRI175P1

Paradigm shift

AD not as a straightforward process
but as a **complex pathological network**



2. The Product: c) Differential features facing the market

- Marketed anti-Alzheimer drugs are **symptomatic**.

- Most putative disease-modifying anti-Alzheimer drug candidates in clinical trials are **single-target** compounds.

Drug name	Company / Organization	Target	Status
MK-8931	Merck & Co.	BACE-1	Phase II/III
AZD-3293	AstraZeneca	BACE-1	Phase I
CTS-21166	CoMentis	BACE-1	Phase I
E-2609	Eisai	BACE-1	Phase I
HPP-854	High Point Pharmaceuticals	BACE-1	Phase I
RG-7129	Roche	BACE-1	Phase I
Avagacestat	Bristol-Myers Squibb	γ-secretase	Phase II
D-(+)-Pinitol	Humanetics	γ-secretase	Phase II
EVP-0962	EnVivo Pharmaceuticals	γ-secretase	Phase II
GSI-1	Merck & Co.	γ-secretase	Phase I
(+)-Phenserine	QR Pharma	Aβ production	Phase II
APH-0703	Aphios	PKC activator	Phase I/II
MCD-386	MIthridion	α-secretase activator	Phase I
Scyllo-Inositol	Transition Therapeutics/Elan	Aβ aggregation	Phase II
[123I]MNI-168	Inst. for Neurodegenerative Disorders	Aβ aggregation	Phase I
Gantenerumab	Roche/MorphoSys	Aβ	Phase III
Solanezumab	Lilly	Aβ	Phase III
Bapineuzumab	Pfizer	Aβ	Phase II/III
AD-02	AFFiRiS	Aβ	Phase II
AZD-4694	Navidea Biopharmaceuticals	Aβ	Phase II
BAN-2401	Eisai	Aβ	Phase II
CAD-106	Novartis/Cytos Biotechnology	Aβ	Phase II
Crenezumab	Genentech	Aβ	Phase II
Heparin-derived oligossacaride-C3	Loyola University Medical Center	Aβ	Phase I/II
Alheimer's vaccine	AFFiRiS	Aβ	Phase I
BART	Biogen Idec	Aβ	Phase I
Indole-3-propionic acid	Intellect Neurosciences	Aβ	Phase I
SAN-61	DiaMedica	Aβ	Phase I

2. The Product: c) Differential features facing the market

- Marketed anti-Alzheimer drugs are **symptomatic**.
- Most putative disease-modifying anti-Alzheimer drug candidates in clinical trials are **single-target** compounds.

- **AVCRI175P1** is a **disease-modifying multi-target single-molecule** compound that hits:

In vitro

- BACE-1 (3-fold more potently than Eli Lilly's **LY2811376**)
- AChE and BChE
- Aβ42 aggregation

2. The Product: c) Differential features facing the market

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E. coli	• Aβ42 aggregation • Tau aggregation

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In vitro	• Is able to cross the BBB

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WT mice	• Protects against the synaptic failure induced by Aβ oligomers (induction of LTP + preservation of synaptic proteins)

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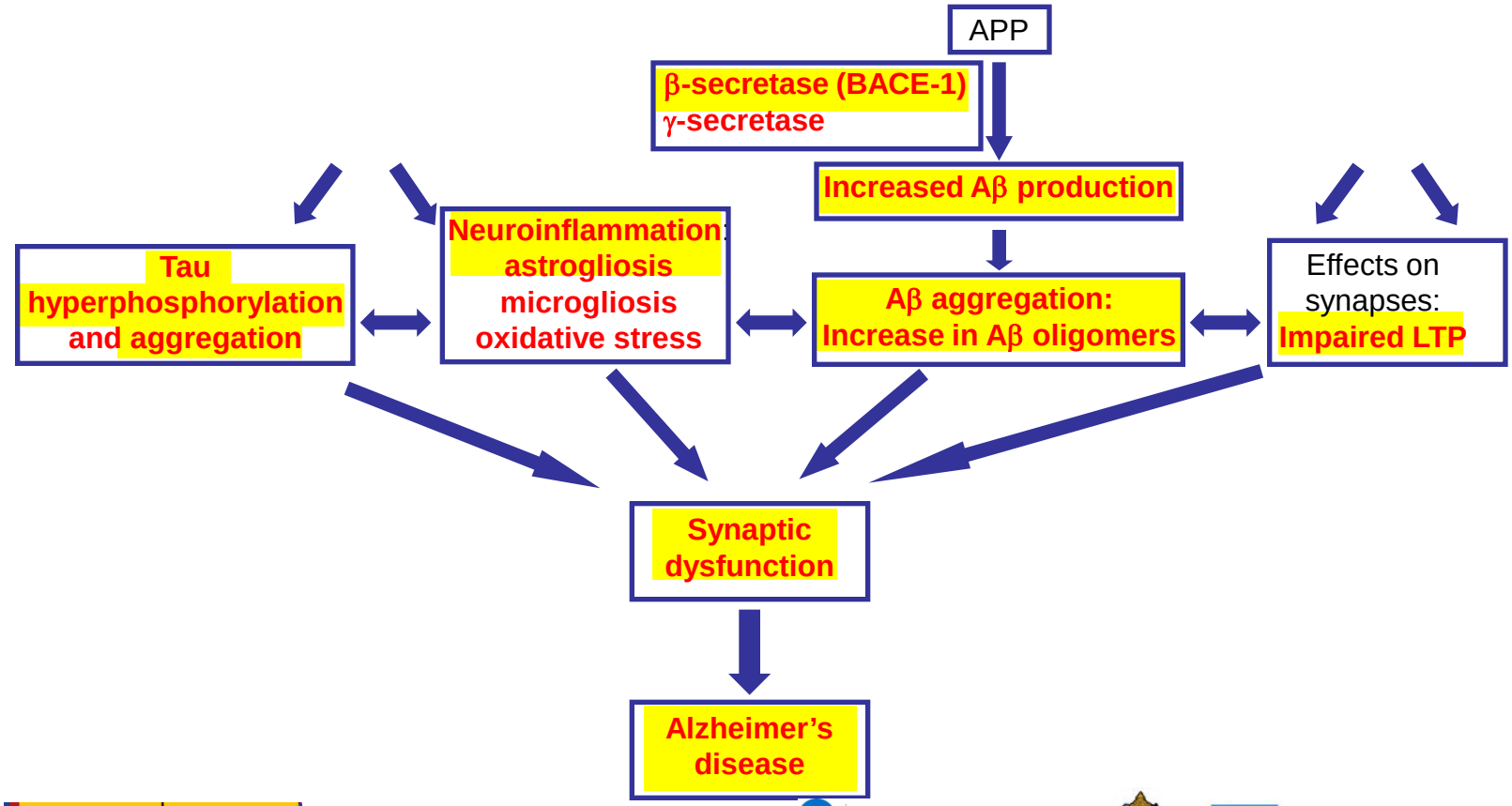
E. coli	• Aβ42 aggregation • Tau aggregation
In vitro	• Is able to cross the BBB
WT mice	• Protects against the synaptic failure induced by Aβ oligomers (induction of LTP + preservation of synaptic proteins)
APP/PS1 mice	• Protects against the synaptic failure of transgenic mice overexpressing Aβ (induction of LTP) and restores memory and learning • Reduces Aβ aggregates both in hippocampus and cortex • Diminishes neuroinflammation (astrogliosis) • Reduces tau phosphorylation in hippocampus and cortex

2. The Product: c) Differential features facing the market

- **AVCRI175P1** is a **disease-modifying multi-target single-molecule** compound that simultaneously hits the underlying mechanisms of AD, thereby leading to preservation of synaptic integrity and cognitive function



2. The Product: c) Differential features facing the market

- **Multi-target compounds in clinical trials**

Drug name	Company / Organization	Target	Status
Ladostigil tartate	Avraham	MAO-A/B BChE	Phase II
NP-0361	Noscira	AChE Aβ aggregation	Phase I
Leuco methylthioninium	TauRx Therapeutics	NO production Tau aggregation MAO	Phase III
Bexarotene	Cleveland Clinic Foundation	SAPK1 (JNK) ERK Retinoid RXR	Phase II
Etazolate	Diaxonhit	α-secretase GABA(A) R Phosphodiesterase PDE4	Phase II
PBT-2	Prana Biotechnology	Aβ Metal ion chelator	Phase II
AAD-2004	Global Neurotech Pharma (GNT Pharma)	Oxidative stress Aβ Prostaglandin E2 synthase-1	Phase I
AN2/AVex-73	Anavex Life Sciences	M1 R Sigma 1 R NMDA R Na channels	Phase I
Exebryl-1	ProteoTech	Aβ aggregation Tau aggregation	Phase I
[18F]MK-3328	Merck & Co.	MAO-B Aβ	Phase I
Memantine + donepezil	Adamas	NMDA R AChE	Phase II

Our compound is unique because it hits:

- ✓BACE-1
- ✓Aβ42 aggregation
- ✓Amyloid burden
- ✓Tau aggregation
- ✓Tau hyperphosphorylation
- ✓Neuroinflammation
- ✓Synaptic dysfunction
- ✓AChE and BChE

2. The Product: c) Differential features facing the market

- **AVCRI175P1** is a **disease-modifying multi-target single-molecule** compound that simultaneously hits the underlying mechanisms of AD, thereby leading to preservation of synaptic integrity and cognitive function

- **AVCRI175P1** is a **single molecule**, and, as such, has advantages over more classical multi-target multi-drug therapies (drug cocktails and fixed-dose combinations): no risk of drug-drug interactions, simpler dosing regimens and better patient compliance, simpler and more predictable pharmacokinetics, lower regulatory barriers and simpler clinical trials and drug registration procedures, etc.

- **Easy synthesis**, readily scalable

- Chiral compound, but **easy and readily scalable chromatographic resolution**

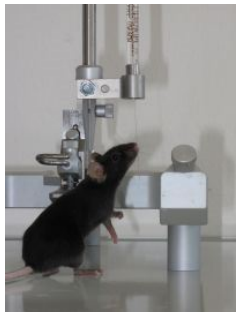
2. The Product: d) Current status of development

Synthesis initial series	*In vitro* tests	*In vivo* tests (*E. coli*)	SAR Hit-to-lead	Lead selection	*In vivo* tests C57bl6 mice	Proof-of-concept APP/PS1 mice (4-week treatment)	Candidate selection	Regulatory preclinical development

8 compds

2 additional compds

AVCRI175P1



Established transgenic mouse model of AD

2. The Product: e) IPR protection

- **PCT/EP2013/059683**

Protection of product, method of preparation, Alzheimer's disease indication

Priority date: 09 May 2013

Ownership: **75%** Universidad de Barcelona (UB), 25% Pontificia Universidad Católica de Chile

Management & License negotiation: Fundació Bosch i Gimpera (TTO of UB)

2. The Product: f) Pitfalls & Risks to be considered

Threats

- PK/PD & ADME development
- Molecular weight over 500 (MW=692), but demonstrated brain permeability
- Several multitarget compounds already in development (although hitting other targets) that may reach the market earlier

Weaknesses

- Compound in early development status
- Lack of comparative studies with current treatments for AD.

2. The Product: f) Strengths & Opportunities to be considered

Strengths

- Multitarget compound hitting several mechanisms underlying the pathogenesis of AD.
- Easy Synthesis and readily scalable.
- Non peptidic nature and predicted oral administration
- Is a single molecule: No drug cocktails or fixed-dose combinations: no risk of drug-drug interactions, simpler dosing regimens, etc.

Opportunities

- Market Needs: No disease-modifying drugs still available for Alzheimer. Drugs on the market only offer symptomatic benefit.
- Big market, predicted to growth exponentially in fore coming years (8,7 million of people expected for 2018)
- Starting patent expiry dates for current drugs on the market

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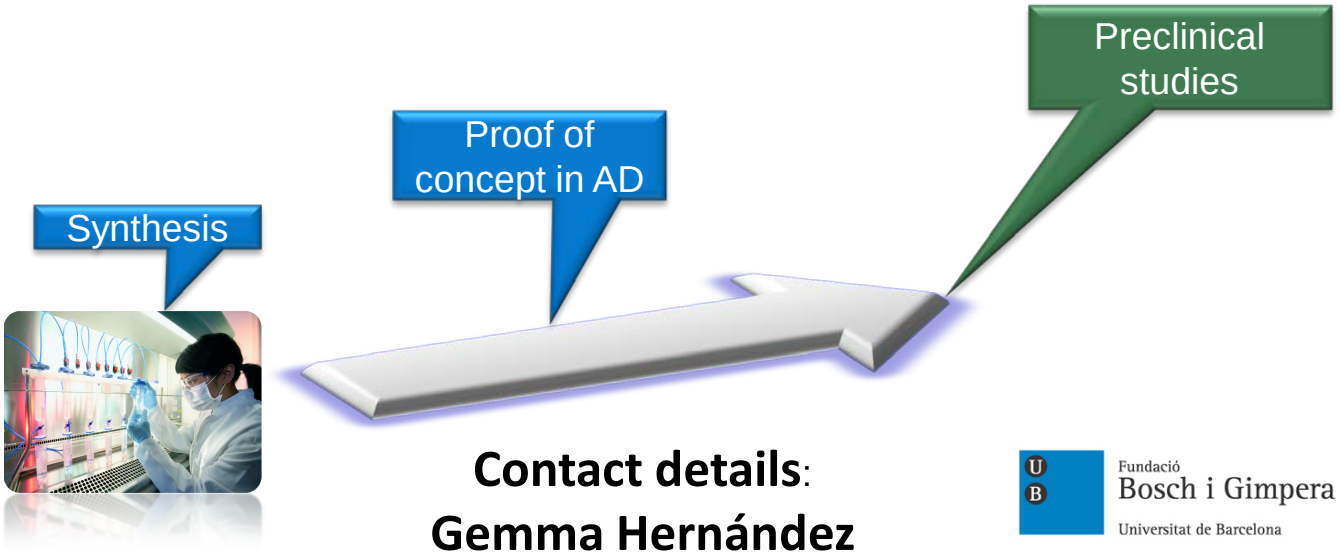
3. **Partnering Opportunities**

3. Partnering Opportunities

The project is available to licensing out through a collaboration and license agreement



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