ReST THERAPEUTICS

ReST THERAPEUTICS | RECOVERY FROM STRESS AND TRAUMA

FENM
a Cure for Post-Traumatic Stress Disorder (PTSD)

a *Disease Modifying therapy for Alzheimer's Disease (AD)*

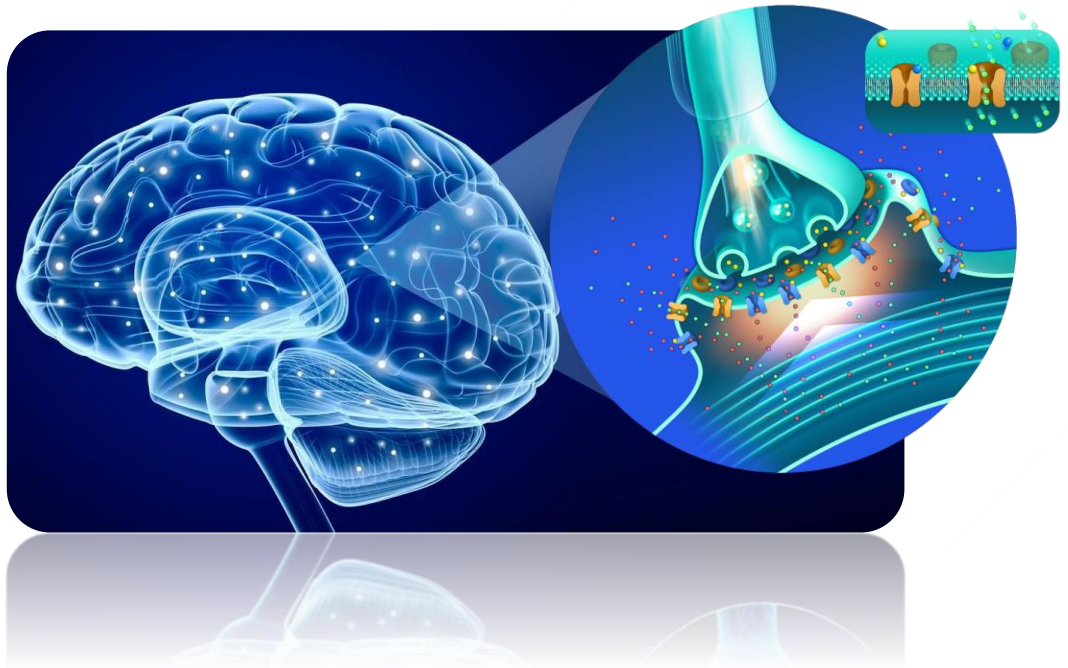
A platform addressing Neurological Diseases through targeted NMDA GluN2D Receptor inhibition

ReST, a unique therapeutic approach to AD & PTSD

Following FIH, we are now raising $20M to advance FENM until phase IIa

- **FENM**, a novel **targeted GluN2D** sub-type specific **NMDA antagonist**
- **Outstanding** *in vitro* and *in vivo* **published results** demonstrating **efficacy & specificity**
- Successful **seed round of $5.5M** covering the project up to FIH
- **Validation of FIH design by EMA Scientific Advice**
- **Experienced team, first class SAB and Renowned academic network**
- **Strong proprietary IP** giving **exclusive rights** until **2042 (PTSD**) and **2045 (AD)**
- **Discovery platform** including **[^{18}F]FENM** and several **proprietary derivatives** with multiple indications in NMDA related disorders

FENM responds to 2 major and related unmet needs: a quicker market access in line with US IRA



FENM specific MOA can unlocks untapped PTSD market: $15Bn+

2 major cerebral disorders with no relevant solutions : AD & PTSD

PTSD: *a civilian issue first!*

15.7 million people in US + EU

+ 1.1 million / y (US)
85/15 civilian vs veteran
6% prevalence in American Women

per patient: **$6,000/y direct cost + $20,000/y indirect cost***

total US: **$76Bn/y direct cost + $232Bn/y indirect cost***

****Otsuka Pharmacoeconomics 2021***

AD

35 million patients Worldwide

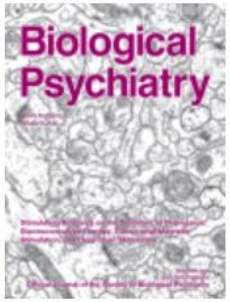
1/20 over 65 years
1/4 over 85 years
113 million anticipated in 2050

Established market
for low impact drugs

US MARKET - $9.9Bn
(forecast 2026*)*

NMDA Receptor family is at the cross-road of several serious cerebral disorders

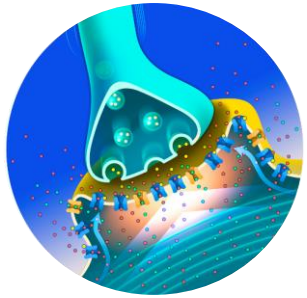
PTSD



2017: Consensus statement of the PTSD psychopharmacology working group (US Experts & KOL)

- NMDA-R is a key component of the synaptic plasticity underlying working & long-term memories
- Dysregulation of NMDA-R is critical in the physiopathology of PTSD
- **NMDA-R antagonist class ranks #1 as warranted drug developments**

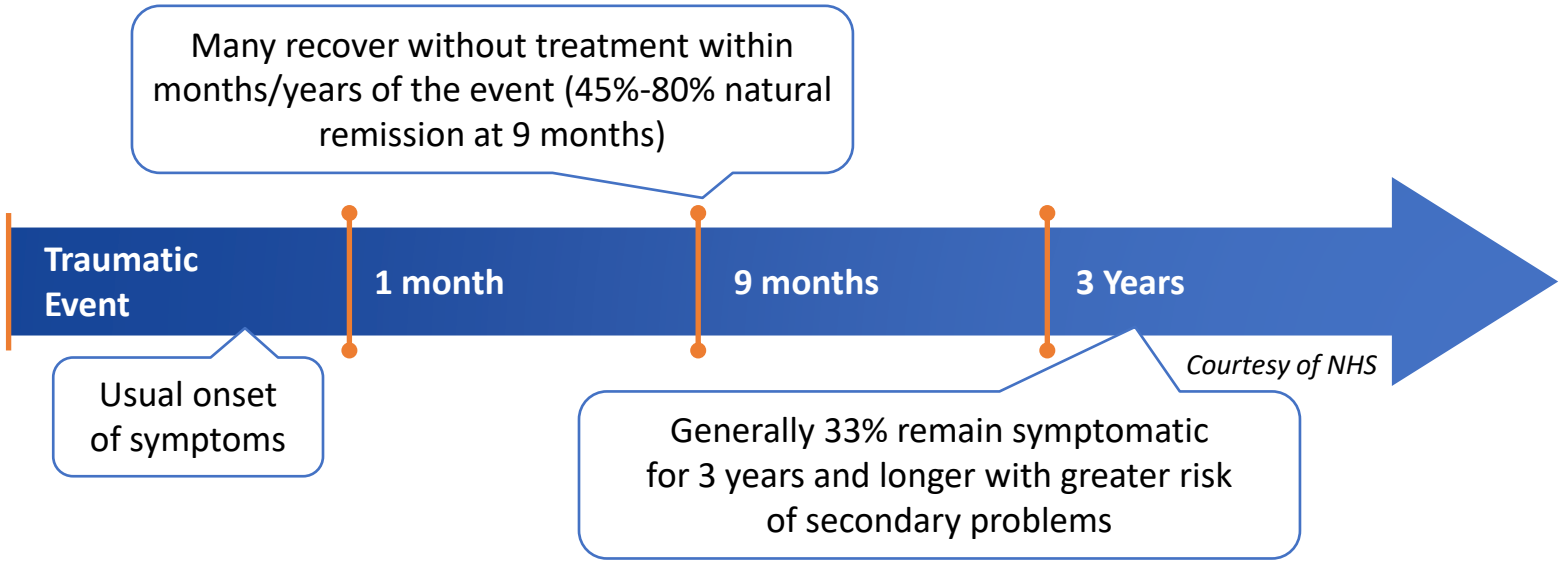
AD



First Market Authorization for Memantine in AD granted in 2002

- NMDA-R plays a central role in the synaptic excitotoxicity underlying AD's cognitive impairment
- NMDA-R hyperactivation is also linked to the tau neurofibrillary degeneration in AD
- **NMDA-R antagonists with larger therapeutic index than Memantine are needed**

PTSD is a highly debilitating syndrome, primarily a civilian issue … and with an unexpected link to AD



Courtesy of NHS

> Meta-analyses showed that the risk of being diagnosed with dementia for individuals with a diagnosis of PTSD is 1.61–1.99 times the risk for those without a PTSD diagnosis.

Günak et al.
British Journal of Psychiatry, 2020
PTSD as a risk factor for dementia : systematic review and meta-analysis

An experienced multidisciplinary team…

Gilles Rubinstenn

CEO & Co-founder

Life science entrepreneur, former co-founder and Pharma BU director of M2i, Inventor of FENM

Chemistry / BD

Aude Michaud

Development Director

+14y experience in the pharma industry, expert in scientific and clinical affairs

Project Development

Florent Perin-Dureau

CMO & Co-founder

+20y experience in clinical settings, expert in NMDA pharmacology, clinical trial design and RA

NMDA / Psychiatry

Aline Freyssin

Research Manager

Expert in neuroscience pharma development, PhD focused on AD and neurodegeneration

Translational AD

… supported by outstanding collaborations & advisors

John Krystal

MD

Worldwide reference and KOL in clinical research on PTSD

Christine Ann Denny

PhD

Reference in neurobiology of PTSD
Specialist of fear/stress induced depression and anxiety

Pierre Paoletti

PhD

Reference in molecular neurobiology
specialist of NMDA

Emmanuel Gras

PhD

Specialist in fluorine and radio-chemistry
Supports CMC development of FENM

Tangui Maurice

PhD

Reference in neuropharmacology of Alzheimer

Yale University

COLUMBIA UNIVERSITY

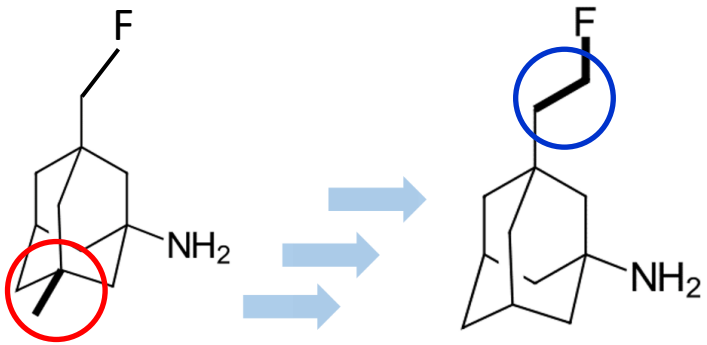
ENS PSL

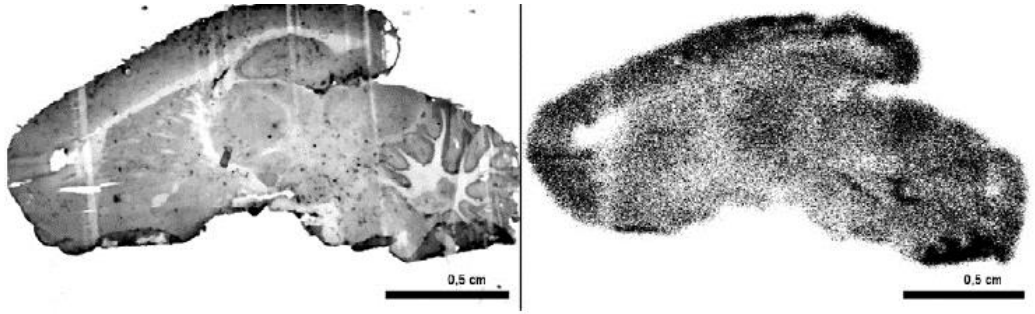
cnrs

UNIVERSITE MONTPELLIER

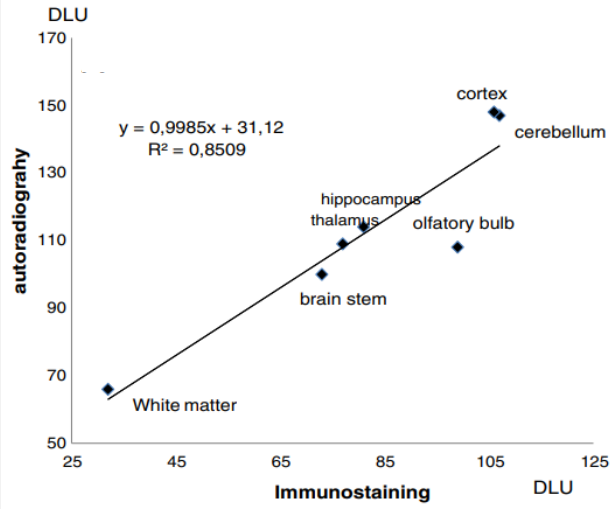
FluoroEthylNorMemantine (FENM) was primarily designed as an NMDA radiotracer, after the failure of FluoroMemantine

It turned out to be not only Specific but also Functional



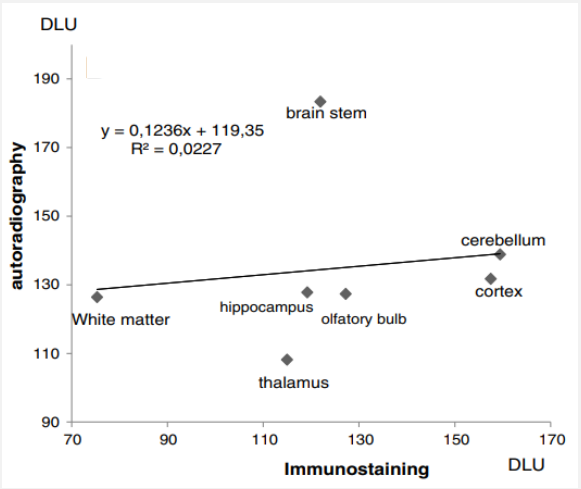


[18F]FENM accurately colocalizes with NMDA-R



[18F]FENM competes with Ketamine

a NMDA-R antagonist used as an anaesthetics



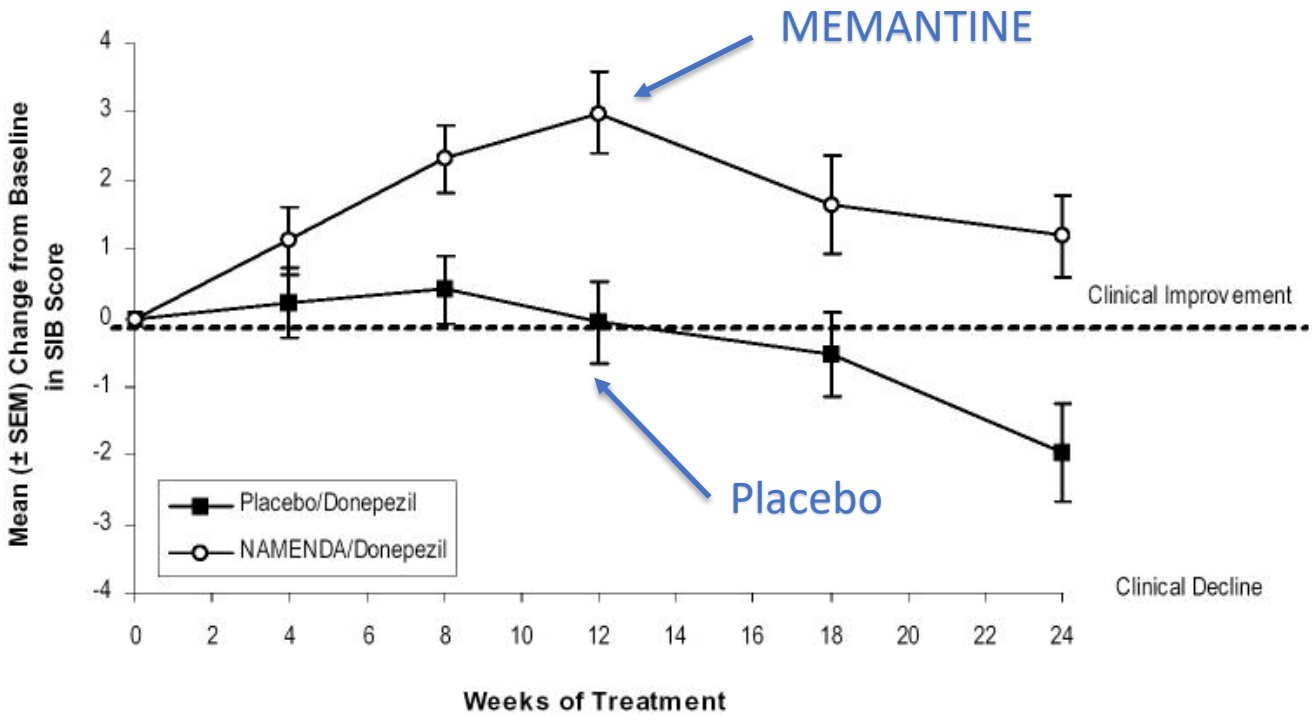
We know that in AD patients, Memantine's efficacy is lost over time

Results of the clinical trial in Namenda (FDA Summary of Product Characteristics)

Methodology

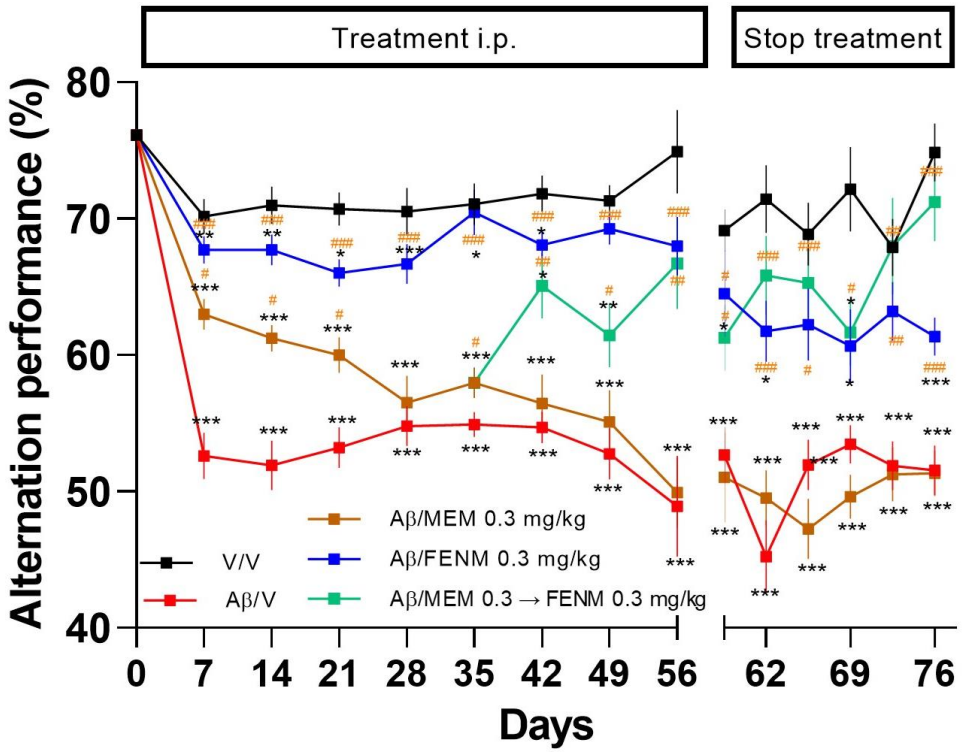
- 24 weeks duration, 404 patients with moderate to severe probable Alzheimer's disease who had been treated with donepezil […] were randomized to memantine hydrochloride or placebo while still receiving donepezil.
- For patients randomized to memantine hydrochloride, treatment was initiated at 5 mg once daily and increased weekly by 5 mg/day in divided doses to a dose of 20 mg/day (10 mg twice a day).

Results



Neuroprotection by FENM is persistent and takes over when Memantine effects vanish in AD translational model

Persistent Neuroprotection by FENM



Neuroscience 2022

2020

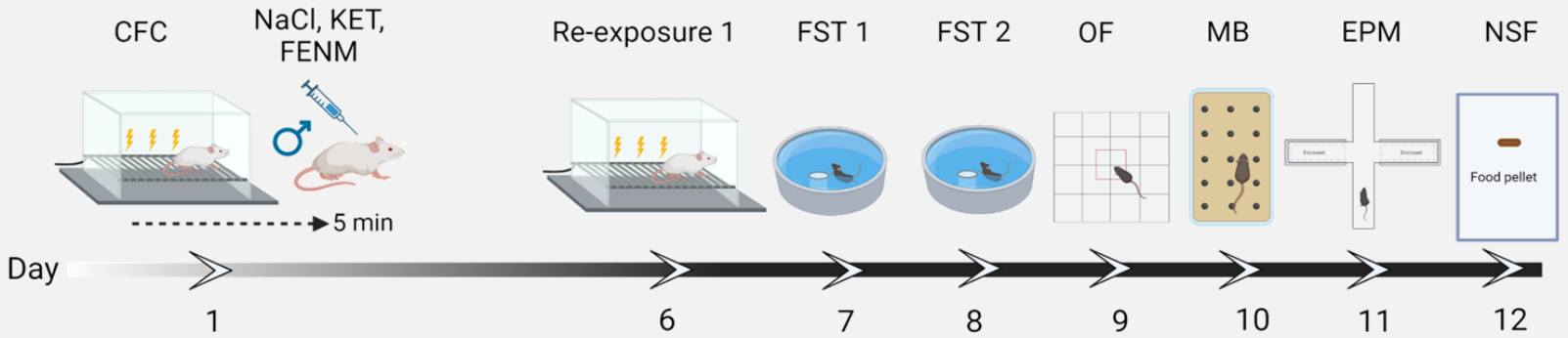
Consistent Neuroprotection by FENM

Parameter	FENM	Memantine
Biochemical analyses[b]		
Cyt C release	+	+
Lipid peroxidation	++	+
IL-6 ELISA	++	+
TNFα ELISA	+	+
Bax/Bcl2 ELISA	++	+
Morphological analyses[b]		
Pyramidal cell loss (CV)	++	++
GFAP IHC—Rad	++	+
GFAP IHC—Mol	++	–
GFAP IHC—PoDG	++	+
GFAP IHC—Ctx	++	–
Iba1 IHC—Rad	++	+
Iba1 IHC—Ctx	++	–

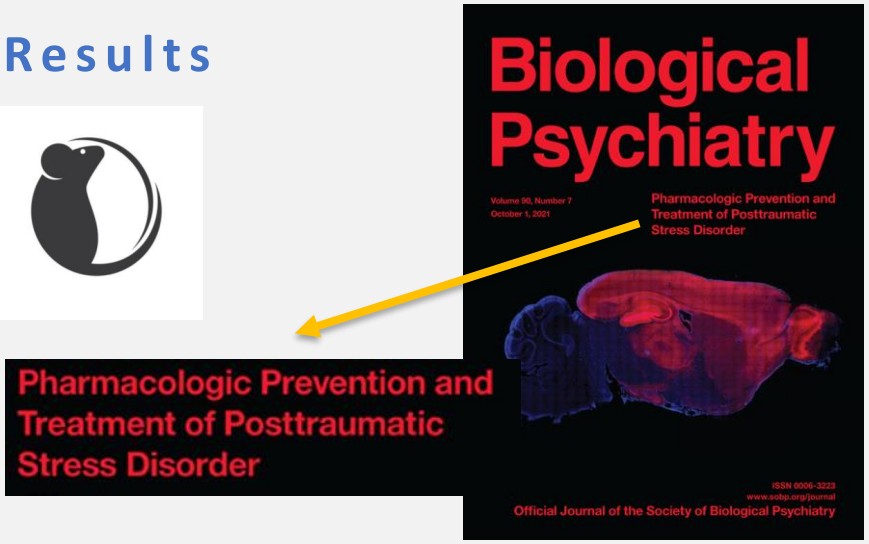
FENM: far more efficient than benchmark in PTSD animal models

Ketamine*, a drug used to treat MDD associated with PTSD, but failing to cure PTSD was used as a benchmark

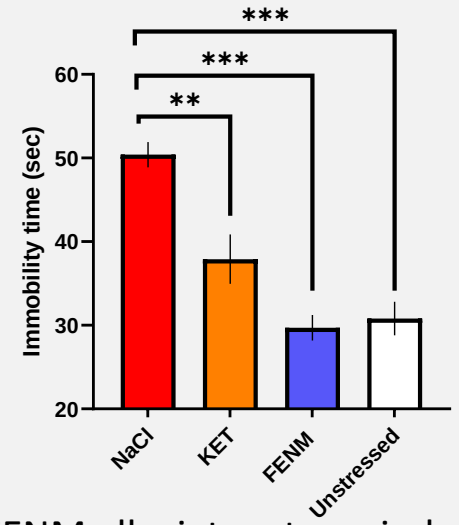
Methodology



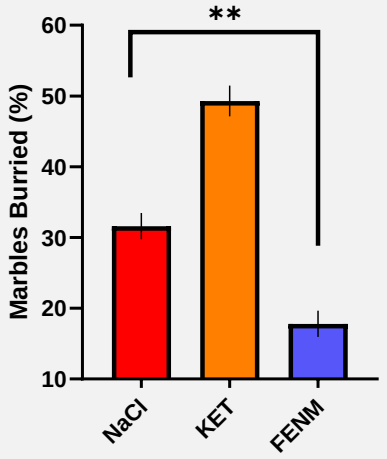
Results



2021



FENM alleviates stress-induced despair better than Ketamine

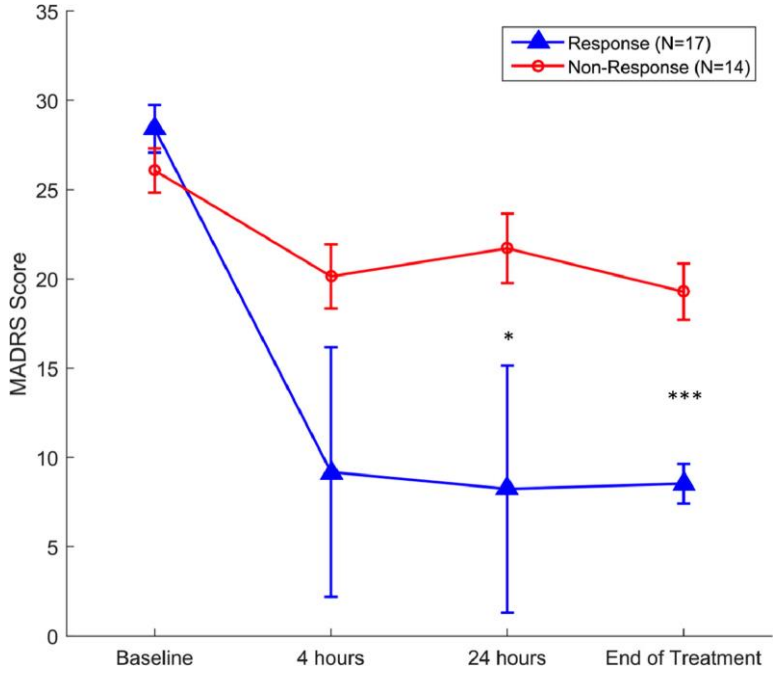


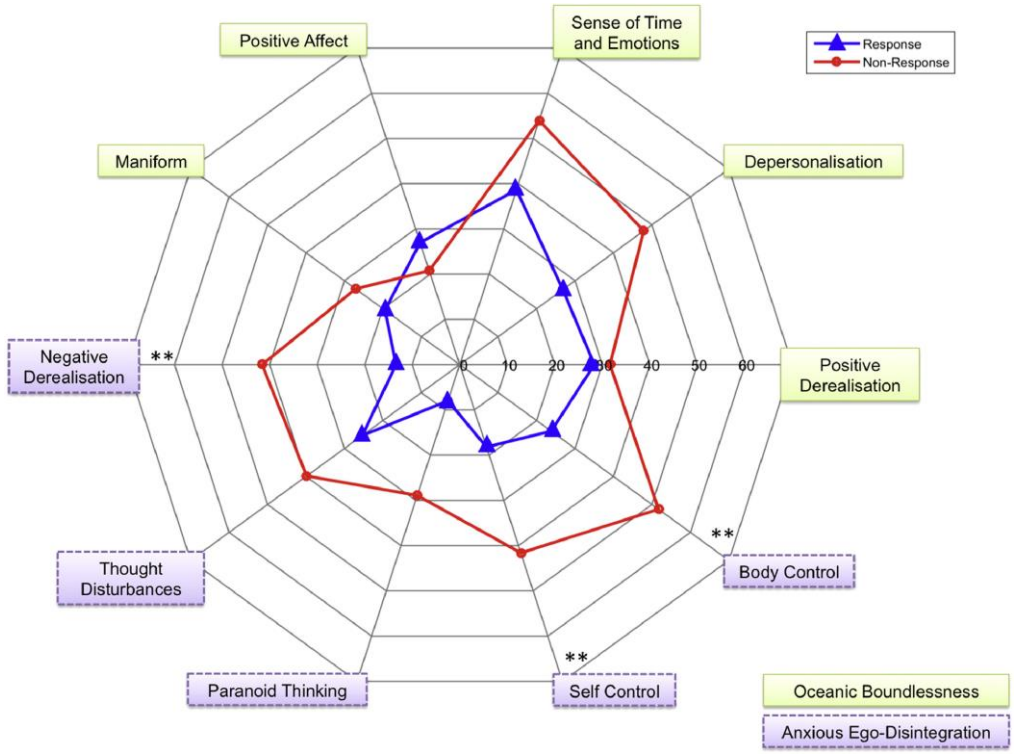
FENM decreases anxiety Ketamine doesn't

*Ketamine only works at the psychedelic dose level of 30mg/kg

As a fact, anxiety induced by Ketamine likely hampers its clinical potential in PTSD

Aust et al. Eur Neuropsychopharmacology (2019) 29, 529-538





Methodology

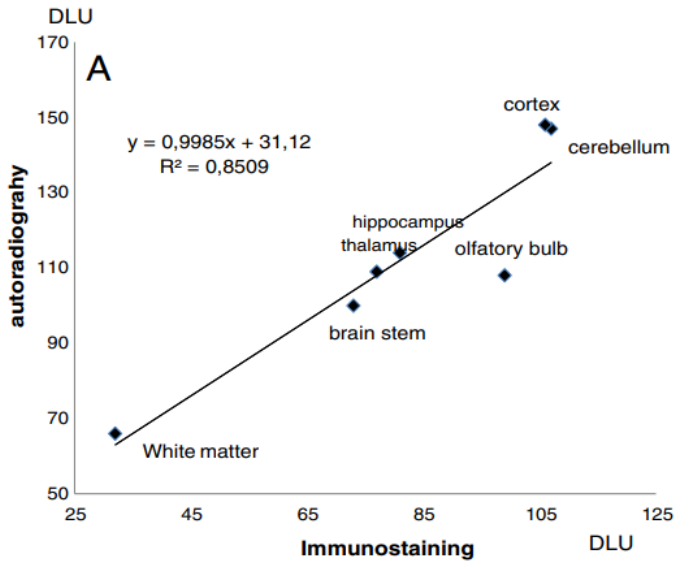
- 31 patients (16 women) with MDD primary diagnostic
- 3 ketamine infusions per weeks (0.5mg/kg) over 2 weeks.

Results

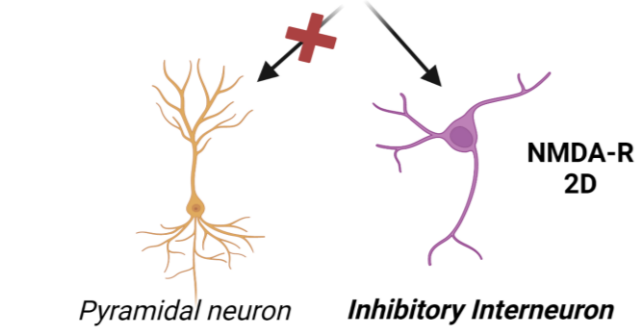
- Response to treatment measured by MADRS shows two different groups of responders and non-responders
- Which correlates with anxiety related experience during treatment session assessed by 5D-ASC

FENM targeted selective inhibition of NMDA-R GluN2D in inhibitory interneurons explains its efficacy

FENM accurately colocalizes with NMDA-R



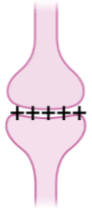
FENM



No adverse/counter effect due to to lack of PN direct inhibition

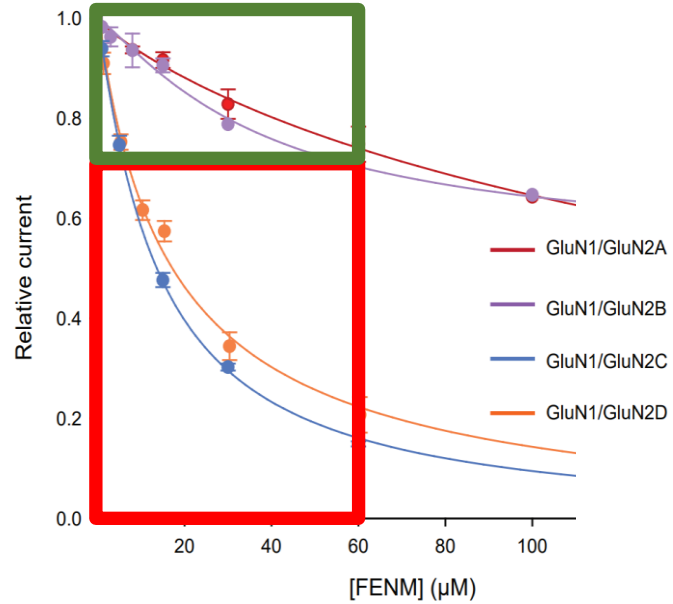
PN dishinibition

Synaptic enrichment



Efficient in PTSD

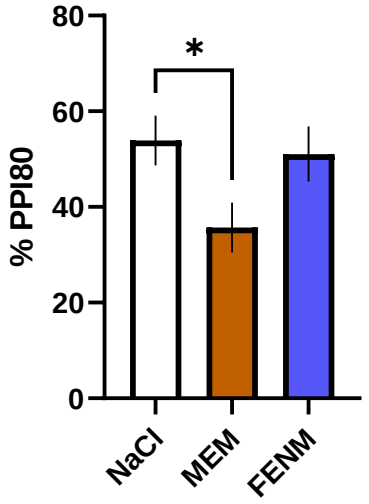
FENM selectively inhibits GluN2C & GluN2D



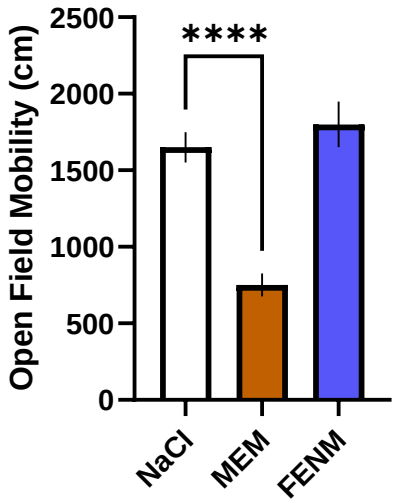
Mode of Action

FENM's MoA will trigger fewer side effects compared with less selective NMDA-R targeting drugs

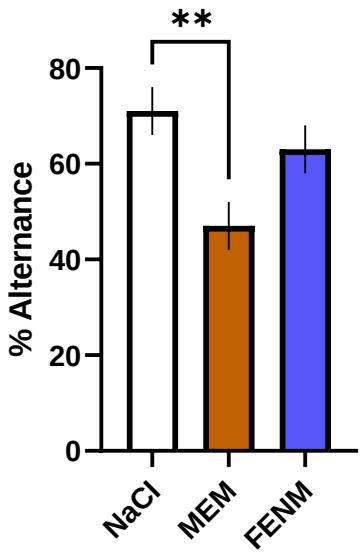
No sensory gating disruption



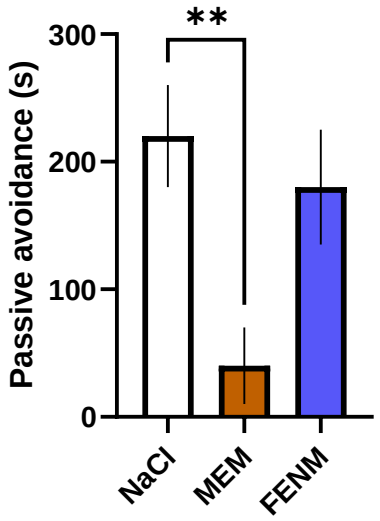
No sleepiness



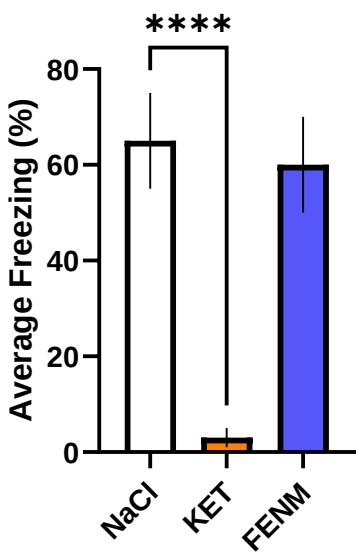
No working memory disruption



No long-term memory disruption



No memory encoding disruption



Which was checked in pre-clinical models and associates with the highly favorable regulatory (FDA/EMA) toxicology/safety profile

- High 28D NOAEL in rodent and canine (around 10x the anticipated MTD)
- High NOAEL in safety studies (FOB, Respiratory, Cardio)
- No genotoxicity

ReST has already achieved significant milestones

M2i, Lead the Change

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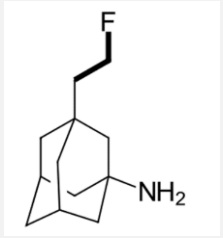
Design and first synthesis of FENM



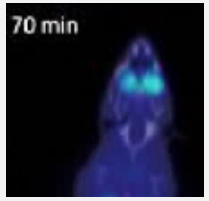
Preclinical POC and MOD for AD and PTSD

GMP clinical batches of both API and FD produced for FIH

2013 | 2015 | 2021 | 05-2022 | 10-2022 | 03-2023

CTA Appl. 05/2023

FENM is a functional radiotracer



FENM passes all regulatory tests to enter Clinical Phase

Positive EMA Scientific Advice on FIH

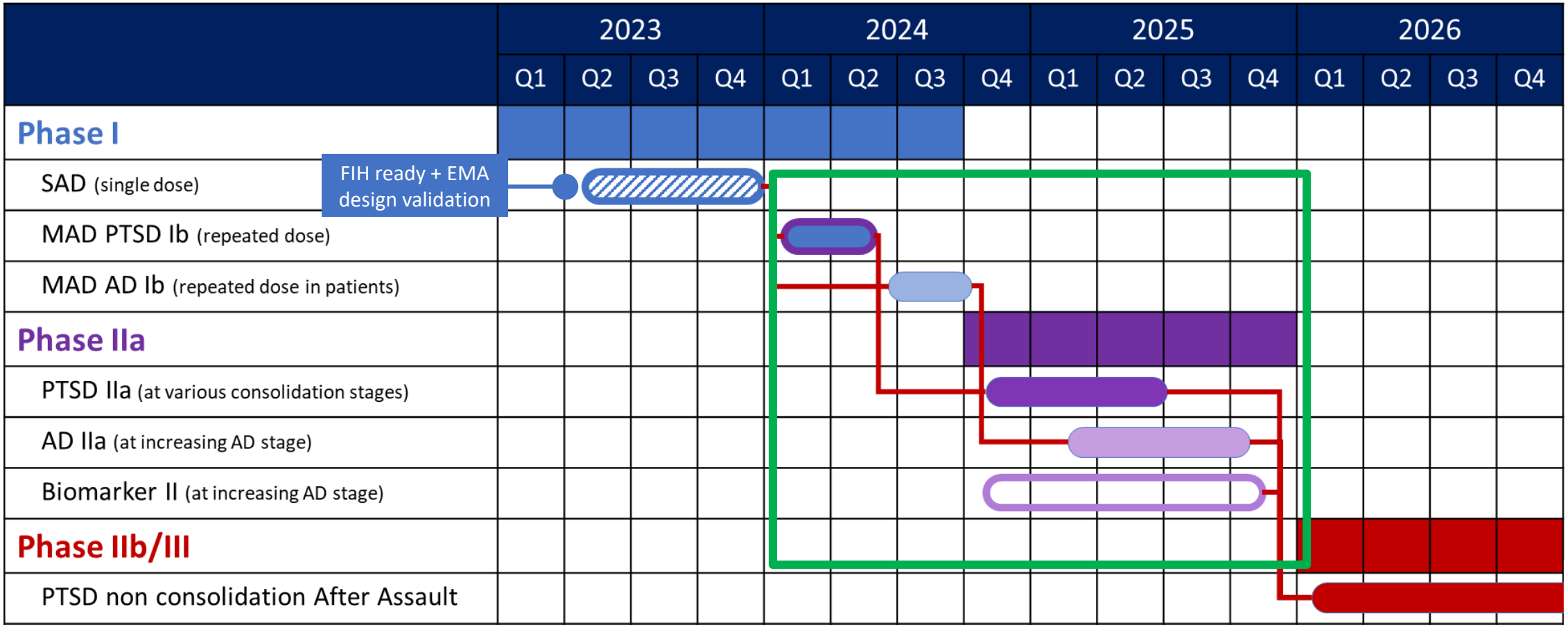
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ReST is now raising $20M to advance FENM, up to strong IIa milestone by YE 2025

	Key projects (including affected HR, SAB, …)	KPIs created
	**Clinical** - *up to and including:* Phase Ib+IIa PTSD…….$4.0M Phase Ib+IIa AD ……$3.8M Phase Ib/IIa/b [^{18}F]FENM ……$1.8M	**Tolerance at various PTSD stage + preliminary efficacy** **Tolerance at various AD stage** **Diagnostic/prognostic radiotracer**
	**Platform and IP scale-up**……$2.2M	**8 patents and 7 new leads for development and FENM IP protection**
	**Regulatory**……$3.7M	**Repro-toxicology + 6/9 months chronic for IIb/III studies**
	**CMC (API/FDF)**……$4.5M	**$0.3/day COGS GMP commercial level + DMF**

Depending on the clinical results, ReST can take the best decision on Phase IIb/III

ReST's clinical strategy



Phase I

~80 Healthy volunteers, primary to demonstrate:

- The safety of the drug and notably (Lack of off-target effects and psychotropic activity)
- Proper pharmacokinetic properties of the drug

Phase IIa

150-200 Patients, primary to demonstrate:

- PTSD Phase IIa: patients at various stages of PTSD consolidation (3 months, 6 months, 12 months, 24 months + 30 days administration)
- AD Phase IIa: patients at increasing AD 4 stages (30 days administration)
- Biomarker Phase II: [18F]FENM PET scan at the inclusion, after 30 days treatments, and at 6 months on the patients from AD Phase IIa

MA strategy for FENM in PTSD

SAM $4Bn to unlock by initial POC

- 375,000 Assaults per year in EU and US
- 60% develop long lasting PTSD (present at 12 months and lasting 24 months +)
- 0.2 QALY loss per year with PTSD
- QALY point value $50,000

Phase IIb/III PTSD

US multicentric 400 Patients :

- Women victims of sexual assault 3 months before or less
- High risk of developing an established PTSD at 12 months (“acute stress”, same symptoms and clinical items than PTSD)
- Randomized Controlled Trial : Placebo vs FENM
- Optimal dose regimens of FENM : based on the results of Phase Ia
- Duration of treatment : 6 to 9 months
- Primary endpoint : efficacy at 12 months after the trauma, clinical canonical scales for PTSD (CAPS-5 & PCL-5)
- Extended follow-up to 18 months : absence of apparition of a “delayed PTSD”

> FENM as a cure for PTSD with a value over $17,000

medico economics shows direct cost of $10-18,000 / patient

=$6,000 * 60% of patients * 3 to 5 years

medico economics shows indirect cost of $36-60,000 / patient

=$20,000 * 60% of patients * 3 to 5 years

Loss of Chance for untreated Assault Victims would grant FENM FastTrack to MA

FENM in PTSD's "paradoxically" *blue ocean*

No current treatment

Selective Serotonine Reuptake Inhibitors (SSRI)

- Only 2 FDA approved drugs for associated depression: Sertraline and Paroxetine
- Low-moderate efficacy
- 1st prescription remains the not recommended benzodiazepines

Drugs in development

NYX-783, NBTX-001, Brexpriprazole, Psilocybine, MDMA

- Most interesting proposal stimulates NMDA-2B
- Only treatment of consolidated PTSD, not prevention
- Complex & Costly to deliver and off-target effects (narcotic, abuse)

ReST proposal

FENM

- Targeted & Highly specific **NMDA GluN2D** inhibition
- Mechanism of action allows both treatment & prevention of PTSD
- No off-target effects, extremely safe profile

FENM is the only candidate to treat and prevent PTSD with high efficacy, long-term effect and no off-target adverse effects

FENM in AD's *red ocean*

Current treatments

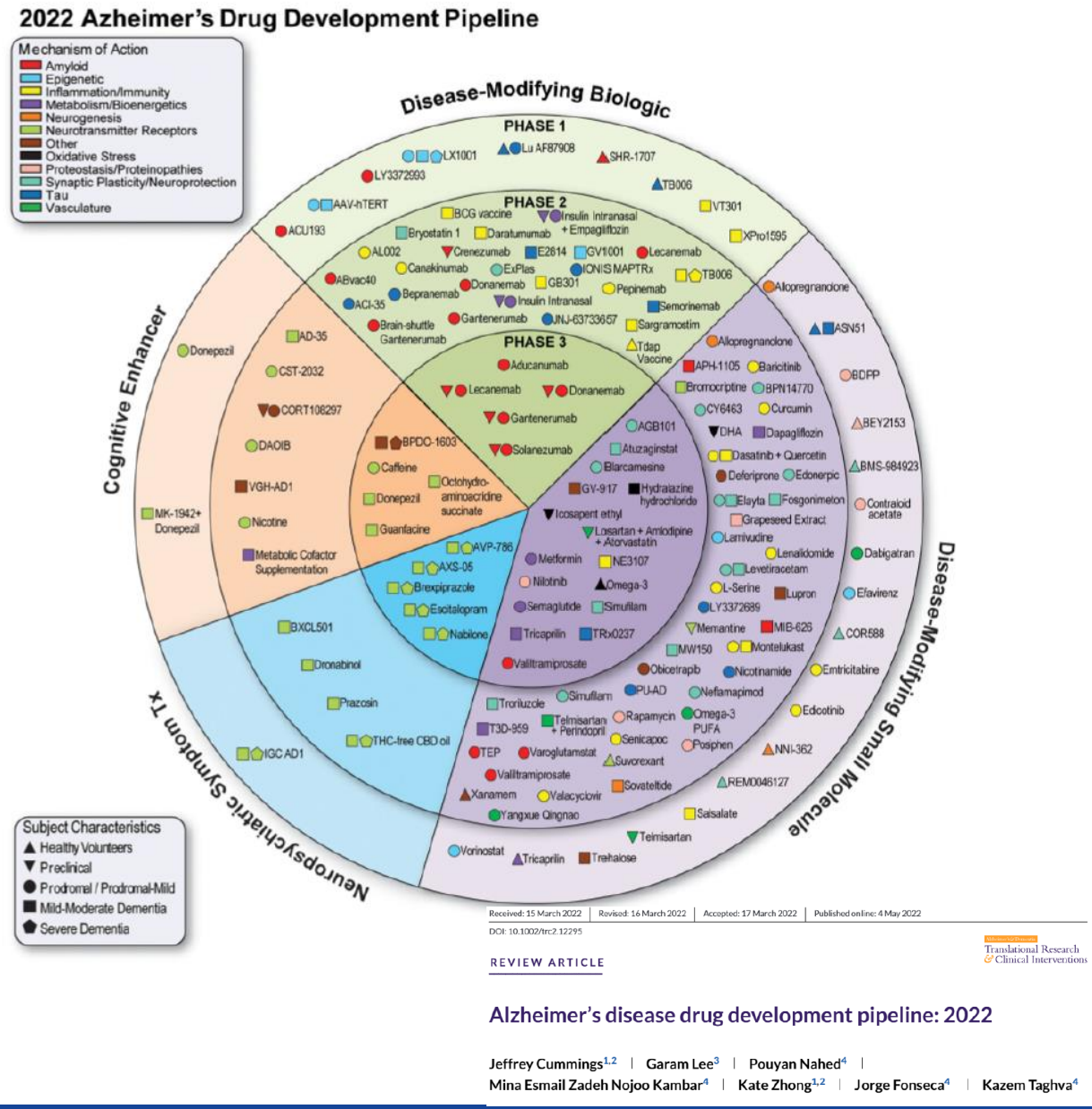
Memantine Donepezil (and 2 other AChEIs) Aducanumab

- FDA approved drugs with low and transitory efficacy
- Multiple albeit low off-target effects
- Biologics struggle and their prices are prohibitory

ReST proposal

FENM + [18F]FENM

- Efficient Neuroprotection
- Favorable PK/PD & Safety profile (better than Memantine)
- Synergy with AChEIs for easier Clinical Implementation
- [18F]FENM direct companion biomarker for development



FENM is the "*Memantine that should have been*" !

It will modify the course of AD at an early stage, and that will be affordable for millions

Investors can expect valuable exit opportunities

Cerebral disorders attract attention from large pharma

Company	Deal Size	Date	Capital raised	Stage	Main focus	Acquirer
AVANIR PHARMACEUTICALS	**$3.50Bn**	2015	$99.34M	Phase II	AD, Schizophrenia	**Otsuka**
naurex INC	**$1.72Bn**	2015	$165.22M	Phase III	Major depression disorders	**Allergan**
NeuroDerm	**$1.10Bn**	2017	$78.5M	Phase III	Parkinson	**Mitsubishi Tanabe Pharma**
CHASE PHARMACEUTICALS	**$1.00Bn**	2016	$38.2M	Phase II	AD	**Sunovion Pharmaceuticals**

EXITS POTENTIAL

gsk Pfizer Jazz Pharmaceuticals Otsuka Lundbeck janssen IPSEN Innovation for patient care Lilly

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THANK YOU

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