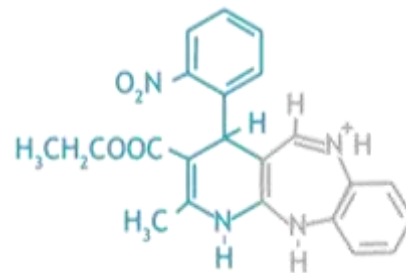
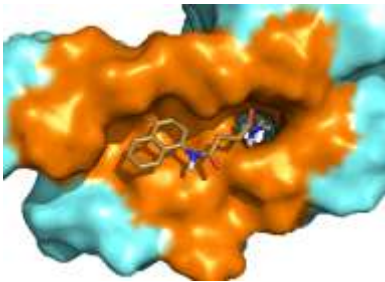


Innovative drugs for neurodegenerative diseases in Cuba

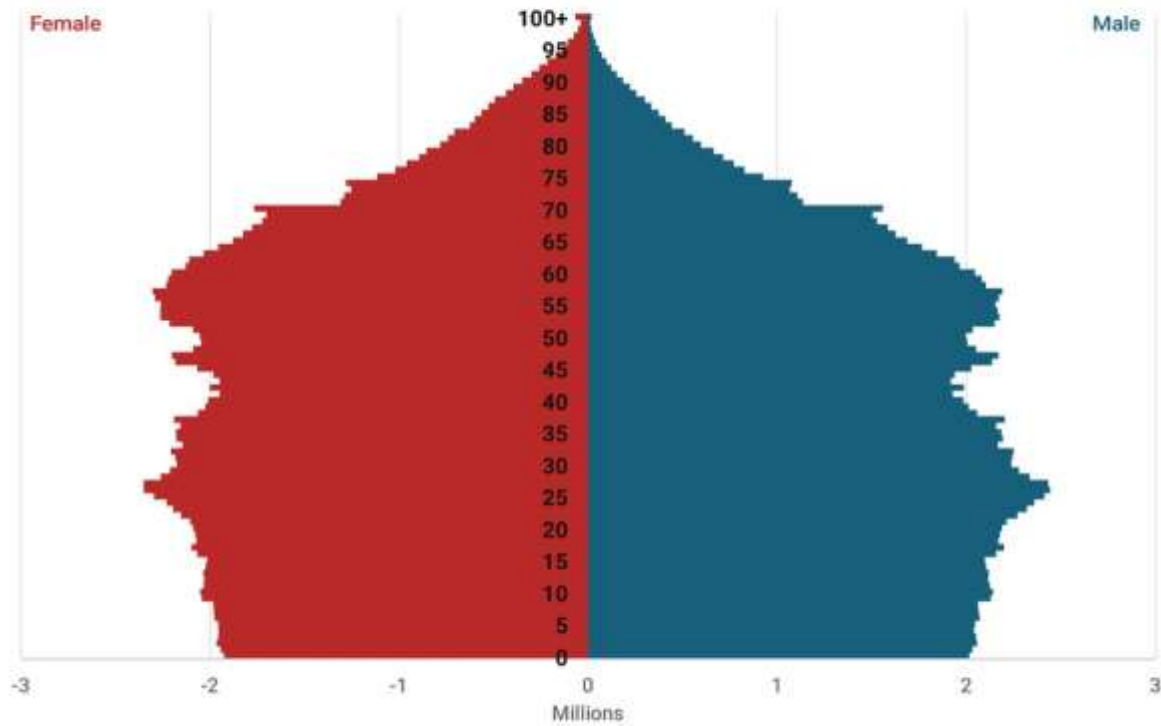
Mitchell Valdes-Sosa, MD, PhD

Director Cuban Neuroscience Centre

Member Emeritus of the Cuban Academy of Sciences



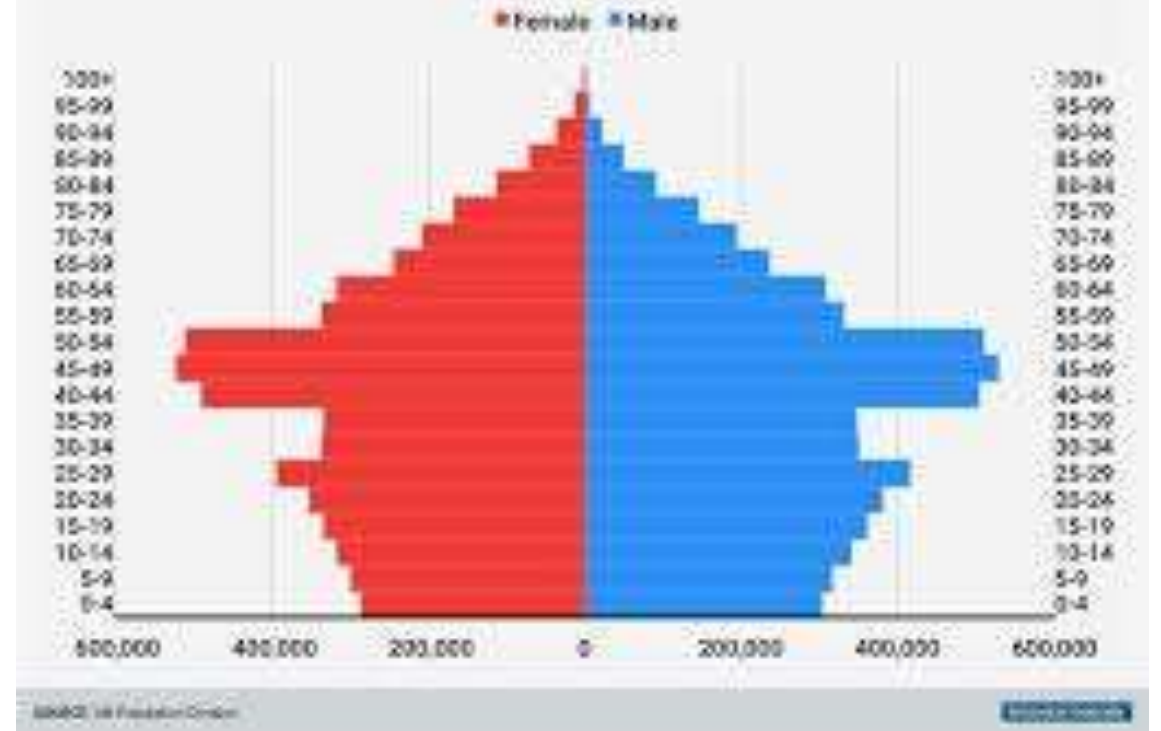
US population by age and sex, 2017



Source: US Census Bureau. Population estimates are for July 1, 2017.

BUSINESS INSIDER

CUBA POPULATION PYRAMID



SOURCE: US Population Census

Business Insider

Can US-CUBA collaborate on innovative drugs for neurodegenerative disease?

- Populations are ageing in both countries
- Unmet needs (no fully satisfactory treatment)
- Need to work on these topic easy to defend
- Precedent in first Cuban-American joint venture between the Center for Molecular Immunology and Roswell Cancer Center

Variants of collaboration

- Small scale
- Larger scale

Cuban portfolio of Neurotherapeutic molecules

Molecules	Indication	Preclinical	Phase I	Phase II	Phase III	Approval
NeuroEPO	Alzheimer's Disease	In progress	In progress	In progress	Concluded	conditioned
	Cerebellar Ataxia	In progress	In progress	In progress	Concluded	
	Parkinson's Disease	In progress	In progress	In progress		
	Dementia (no Alzheimer Disease)	In progress				
CNEURO-201	Alzheimer's disease (sympt. treatment)	Concluded				
	Alzheimer's disease (preventive treatment)	Concluded				
CNEURO-220	Alzheimer's disease	Concluded				
CIGB-845	Alzheimer's Disease	Concluded				
CIDEM 112/113	Alzheimer's Disease	Concluded				
	Parkinson's Disease	Concluded				



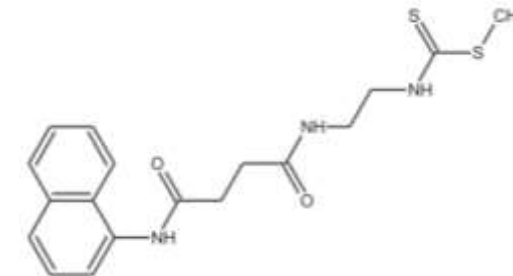
In progress



Concluded

CNEURO-201 (Amylovis)

CNEURO-201: Synthetic naphthalene-derived molecule with high affinity for β -amyloid plaques



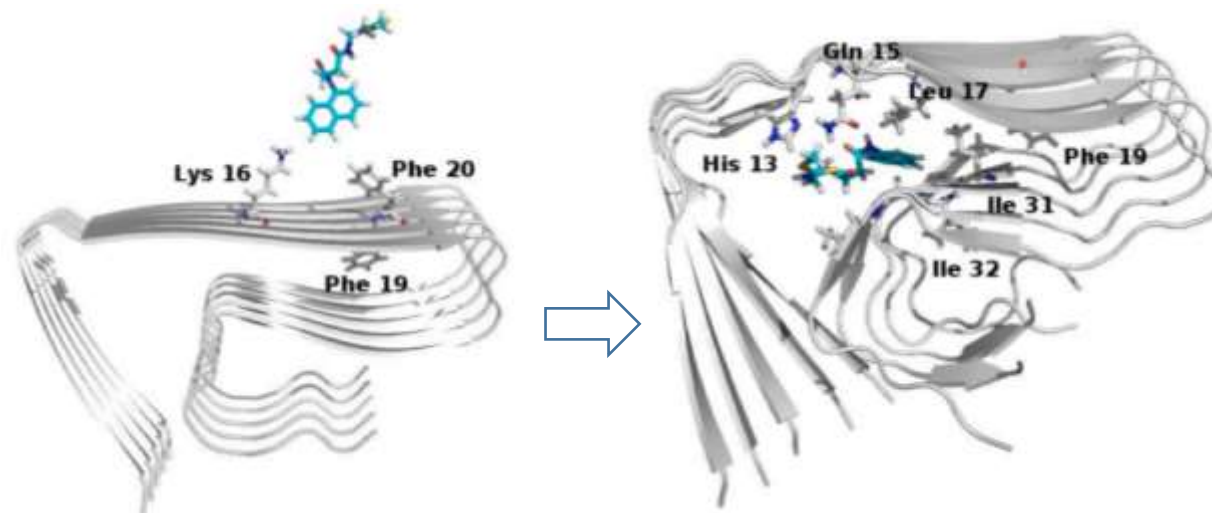
CNEURO-201 exhibits the most stable interaction with A β peptide and fibrils among a family of compounds

Complexes	ΔG (kcal/mol)	K_{eq}	Complexes	ΔG (kcal/mol)	K_{eq}
4-A β_{1-42} peptide	-4.9*	2.85×10^3	4-A β_{1-42} fibril	-3.3**	2.12×10^2
6-A β_{1-42} peptide	-6.3*	2.76×10^4	6-A β_{1-42} fibril	-6.3**	2.76×10^4
7-A β_{1-42} peptide	-5.5*	7.54×10^3	7-A β_{1-42} fibril	-4.6**	1.75×10^3
8-Aβ_{1-42} peptide	-7.4*	1.65×10^5	8-A β_{1-42} fibril	-7.7**	2.68×10^5

* 90 ns.

** 300 ns of MD simulation times.

Representative snapshots of the conformational evolution of CNEURO201-A β 1-42 fibril complex at 0 and 300 ns, using molecular dynamics simulations

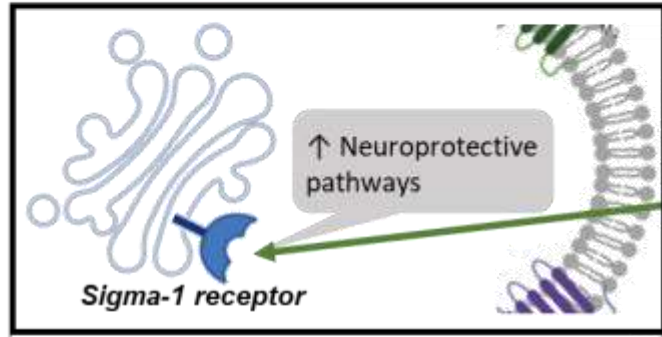


CNEURO-201/ β -amyloid interaction profile

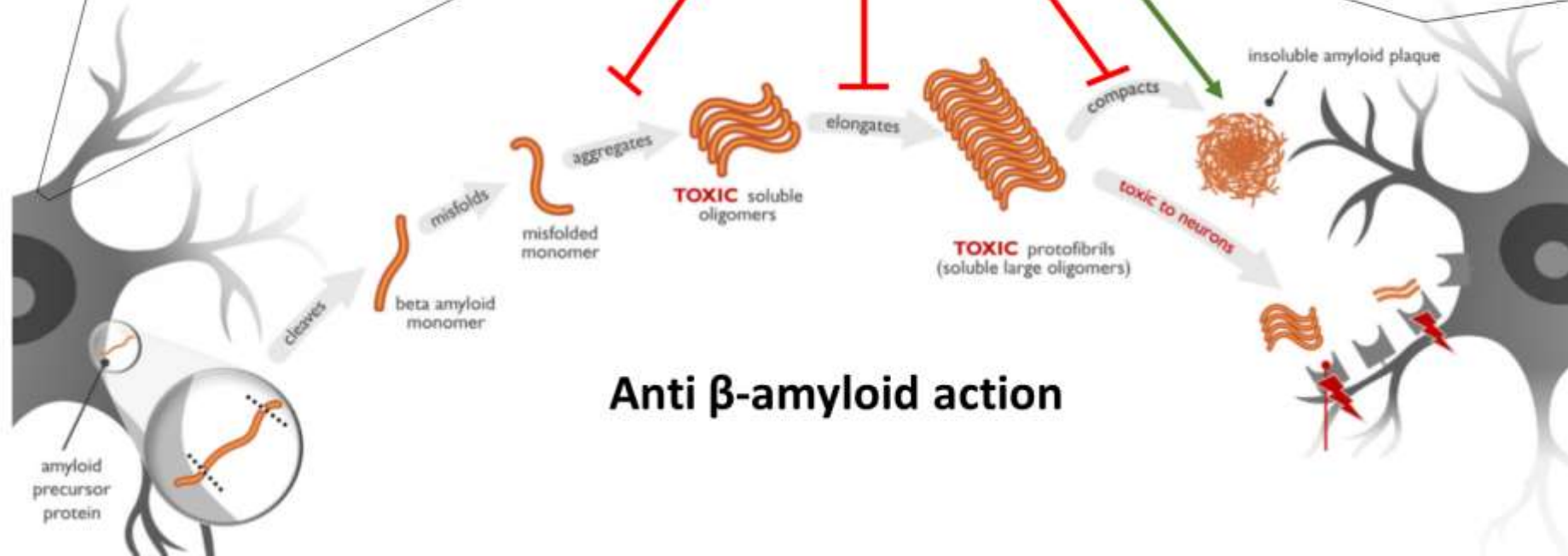
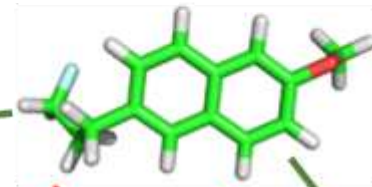
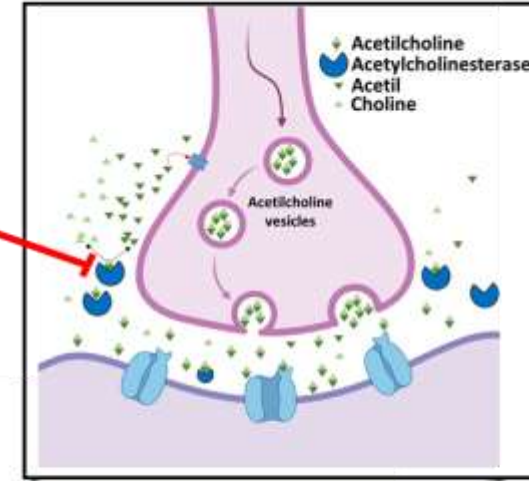
a) Hydrophobic interactions, b) van der Waals forces and c) hydrogen bond

CNEURO-201

Sigma-1 receptor agonist

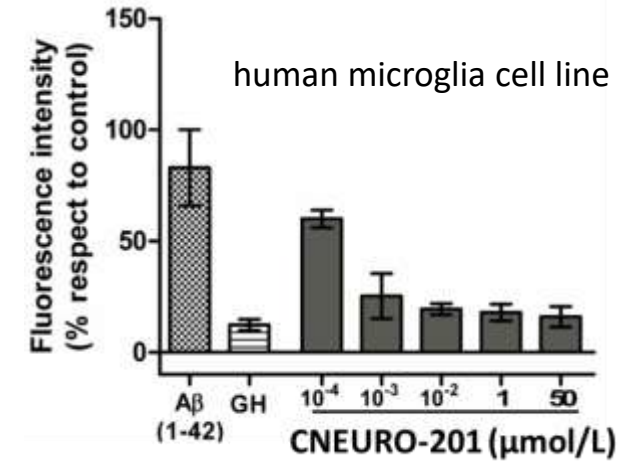
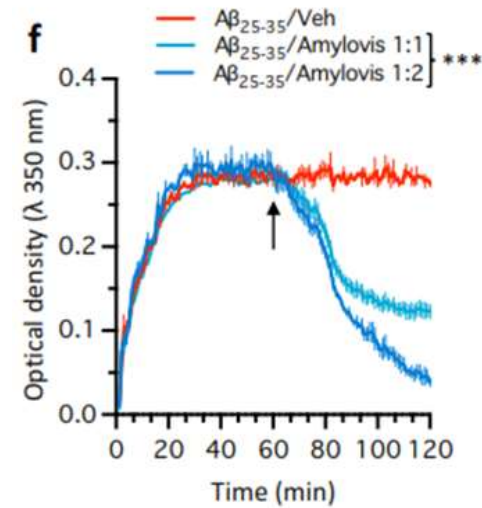
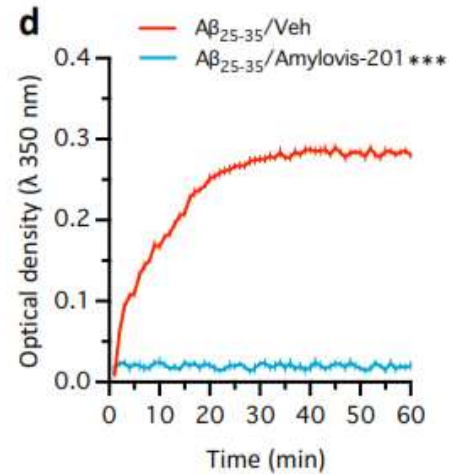


Anticholinesterase action

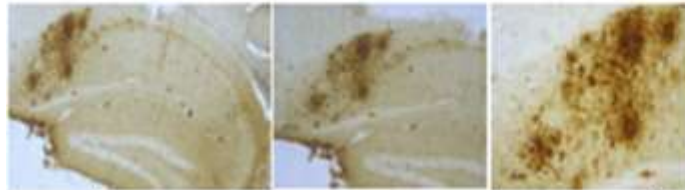


CNEURO-201 exhibits anti-aggregation properties

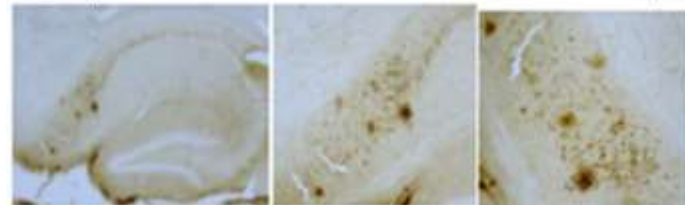
CNEURO-201 prevents *de novo* A β aggregation and disaggregates already formed fibrillar structures.



3xTg-AD Vehicle BAM-10

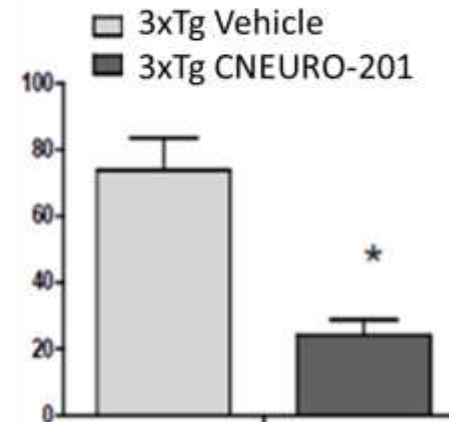


3xTg-AD CNEURO-201 BAM-10



Representative immunohistochemistry photo-micrographs of the subiculum and CA1 hippocampus, in sagittal sections.

% area with β -Amyloid
in subiculum



3xTg: transgenic for *Psen1*, *APP*, *MAPT*

JM-20 (CIDEM-112/113)

Benzodiazepine–dihydropyridine hybrid molecule

European Journal of Pharmacology 726 (2014) 57–65

Contents lists available at ScienceDirect



European Journal of Pharmacology

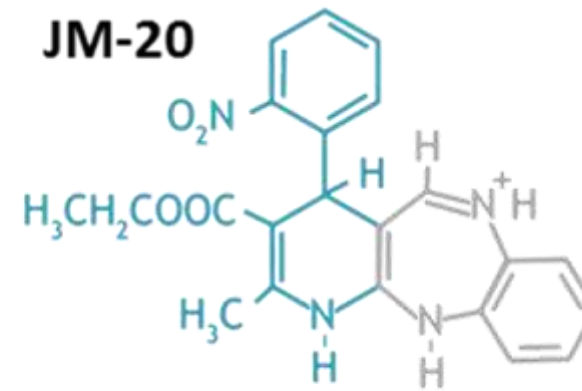
journal homepage: www.elsevier.com/locate/ejphar



Molecular and cellular pharmacology

JM-20, a novel benzodiazepine–dihydropyridine hybrid molecule, protects mitochondria and prevents ischemic insult-mediated neural cell death in vitro

Yanier Nuñez-Figueroa^a, Jeney Ramírez-Sánchez^a, René Delgado-Hernández^a, Marlene Porto-Verdecia^a, Estael Ochoa-Rodríguez^b, Yamila Verdecia-Reyes^b, Javier Marin-Prida^c, Michael González-Durruthy^c, Sergio A. Uyemura^d, Fernando P. Rodrigues^e, Carlos Curti^e, Diogo O. Souza^f, Gilberto L. Pardo-Andreu^{c,*}



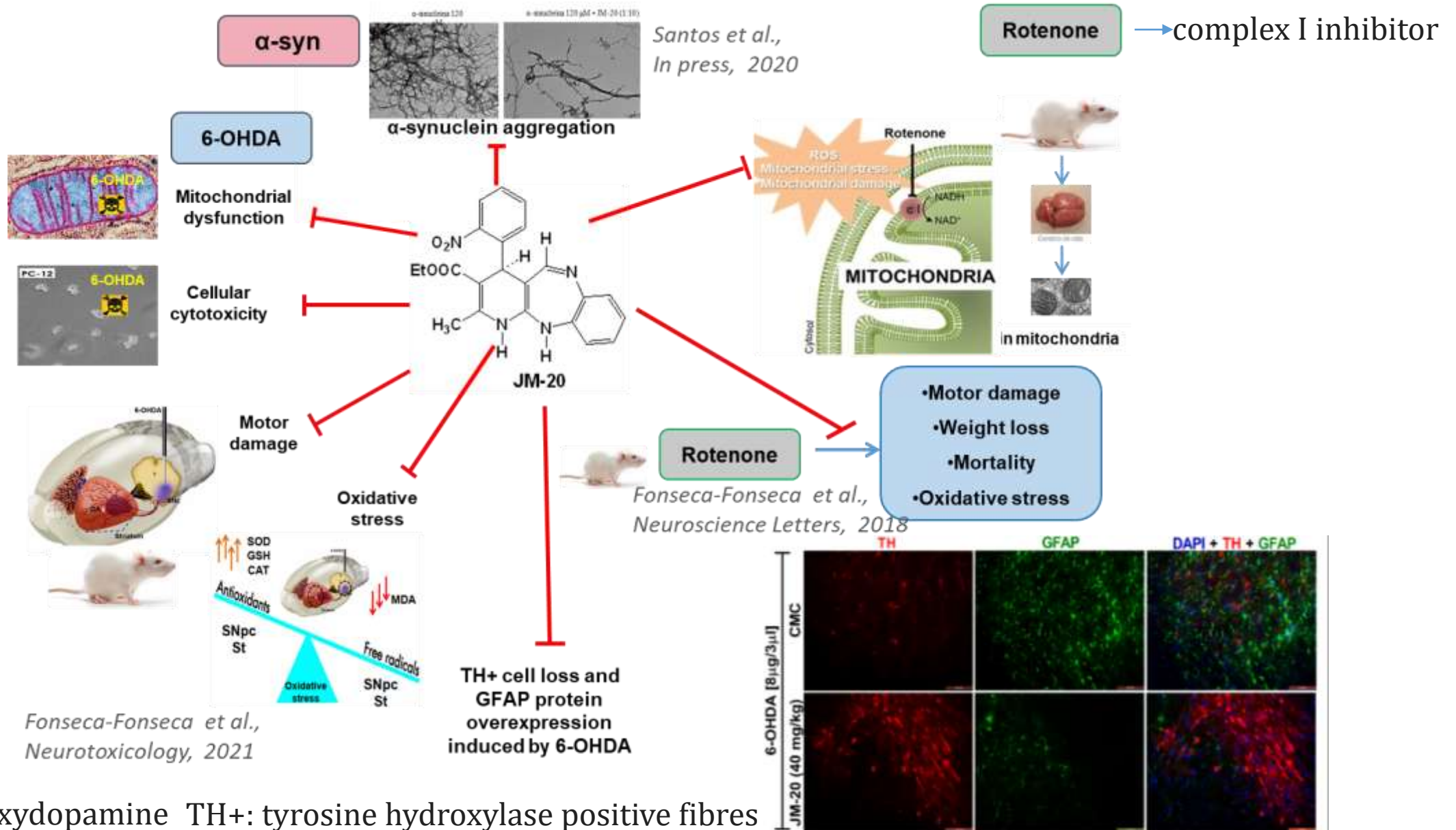
Dementia

Parkinson disease

CIDEM-112

CIDEM-113

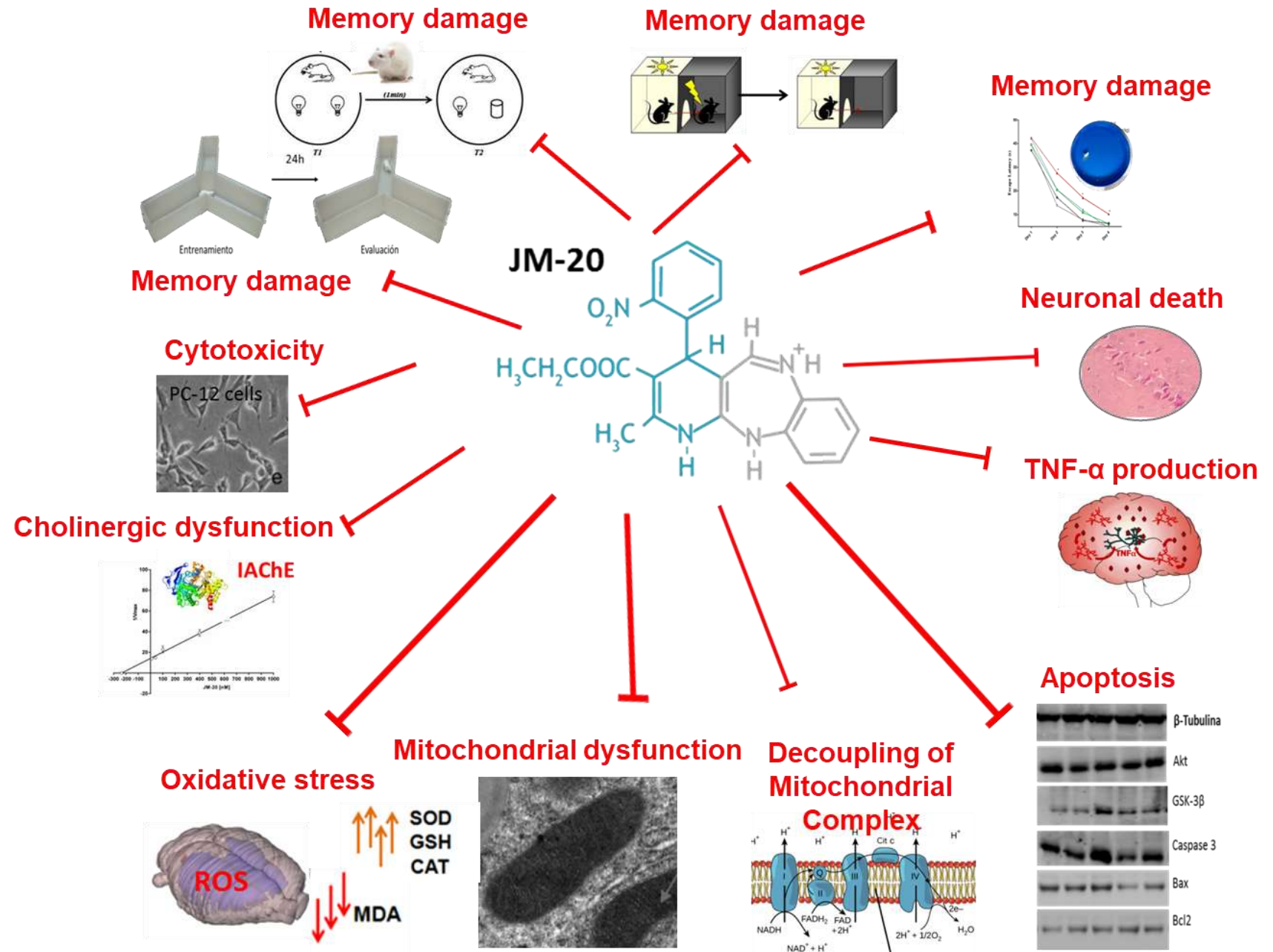
CIDEM-113 as a multi-target directed molecule: Parkinson



6-OHDA: 6-hydroxydopamine TH+: tyrosine hydroxylase positive fibres

CIDEM-112 as a multi-target directed molecule: Dementia

- Dementia models**
- Scopolamine (Cholinergic model)
 - AlCl₃ (neuroinflammation model)
 - Streptozotocin (neuroenergetic model)

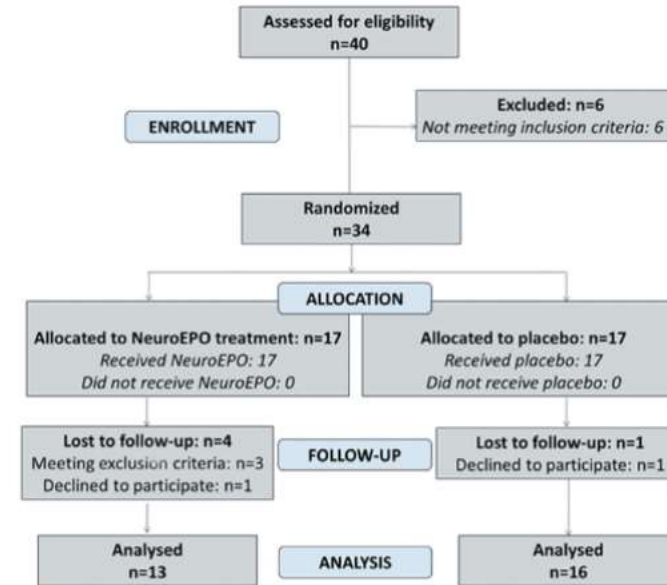


NeuroEPO in Spinocerebellar ataxia type 2

RESEARCH ARTICLE

Erythropoietin in Spinocerebellar Ataxia Type 2: Feasibility and Proof-of-Principle Issues from a Randomized Controlled Study

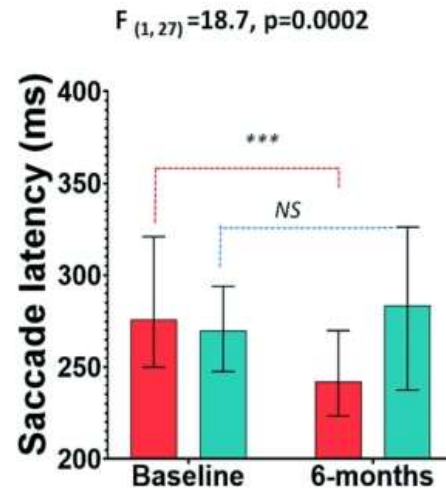
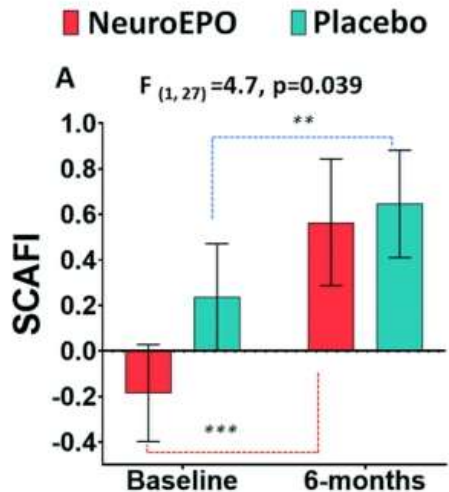
Roberto Rodríguez-Labrada, PhD,^{1,2} Ricardo Ortega-Sánchez, MD,¹ Patricia Hernández Casaña, PhD,³ Orestes Santos Morales, MD,³ María del Carmen Padrón-Estupiñán, MD,⁴ Maricela Batista-Nuñez, MD,⁵ Daise Jiménez Rodríguez, MSc,⁶ Nalia Canales-Ochoa, BSc,¹ Amoy Peña Acosta, BSc,¹ Jacqueline Medrano Montero, MD, PhD,¹ Pedro Enrique Labrada Aguilera, MD,⁵ Annelie Estupiñán Rodríguez, BSc,¹ Yaimée Vázquez-Mojena, MSc,^{1,2} Dennis Almaguer Gotay, MSc,¹ Judey Ayred-García, BSc,³ Idrián García-García, PhD,⁶ Reydenis Torres Vega, BSc,¹ Carmen Viada González, MSc,³ Carmen M. Valenzuela Silva, MSc,³ Yanelis Silva Ricardo, BSc,⁷ Jorge Columbié Ximelis, BSc,⁷ Kenia Tribin Rivero, MD,⁷ Roselin Valle Cabrera, MSc,⁸ Julio Cesar García-Rodríguez, PhD,⁹ Tania Crombet Ramos, PhD,³ Daniel Amaro-González, PhD,³ Teresita Rodríguez-Obaya, PhD,³ and Luis Velázquez-Pérez, MD, PhD, DrSc^{1,10*}



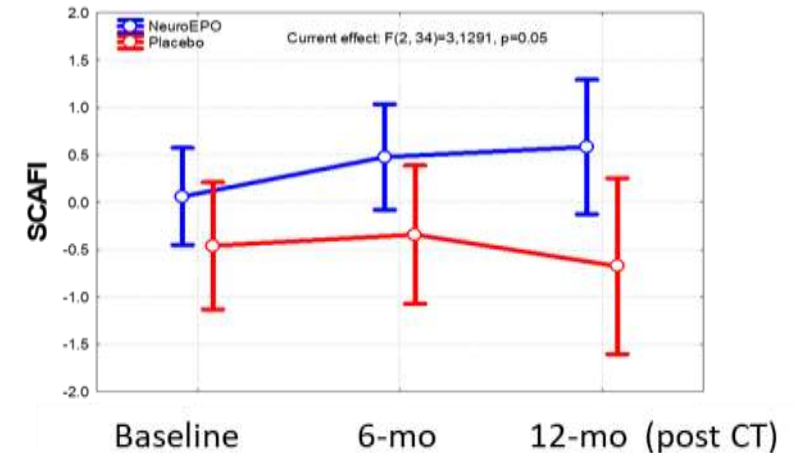
Improve

Ataxia features

Cognition



Follow-up assessment (six months after clinical study)



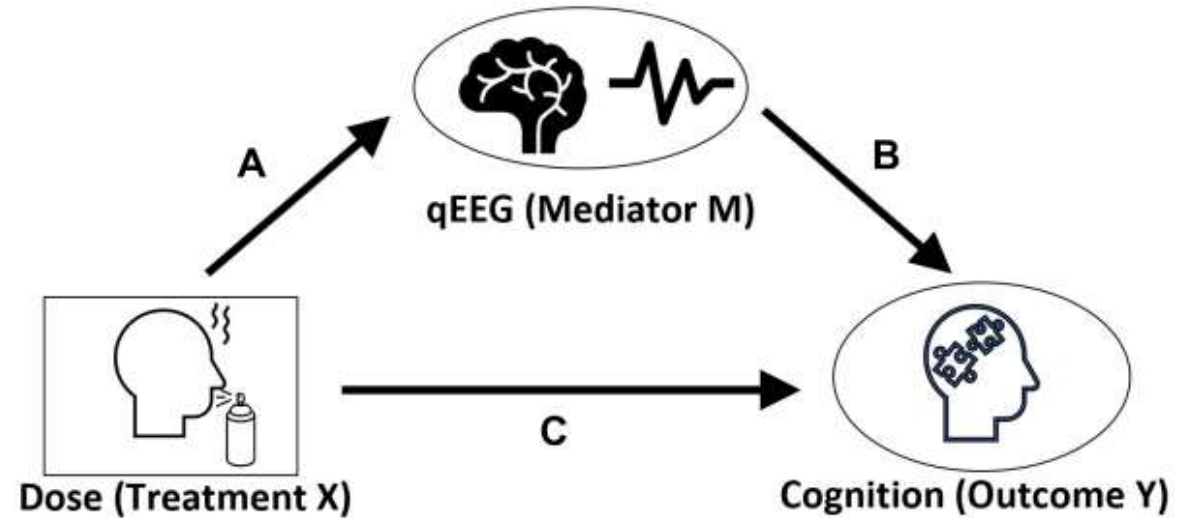
NeuroEPO in Parkinson's disease



The Effect of Neuroepo on Cognition in Parkinson's Disease Patients Is Mediated by Electroencephalogram Source Activity

María L. Bringas Vega^{1,2*}, Ivonne Pedrosa Ibáñez^{2*}, Fuleah A. Razzaq^{1*}, Min Zhang^{1*}, Lilia Morales Chacón², Peng Ren¹, Lidice Galan García², Peng Gan¹, Trinidad Virves Alba², Carlos Lopez Naranjo¹, Marjan Jahanshahi^{1,4}, Jorge Bosch-Bayard^{1,3*} and Pedro A. Valdes-Sosa^{1,5*}

OPEN ACCESS
Edited by:



- ❑ 66% of the total effect of the cognitive improvement was mediated by qEEG ($p = 0.0001$), with the remaining direct effect between dose and Cognition ($p = 0.002$), due to other causes.
- ❑ These results suggest that Neuroepo has a positive influence on Cognition in PD patients and that a large portion of this effect is mediated by brain mechanisms reflected in qEEG.

Concluding remarks

- ❑ Cuban scientists are in the race against neurodegenerative diseases as a primary goal of the National Program of Neurosciences and Neurotechnology
- ❑ The molecules act through different mechanisms exhibited and thus could potentially benefit different symptoms/patients
- ❑ The close collaboration between the Cuban Biotechnology and the Cuban Health System is as a key asset for this research
- ❑ People in both the US and Cuba could benefit from this work.



Finlay

Lazear



Reed

