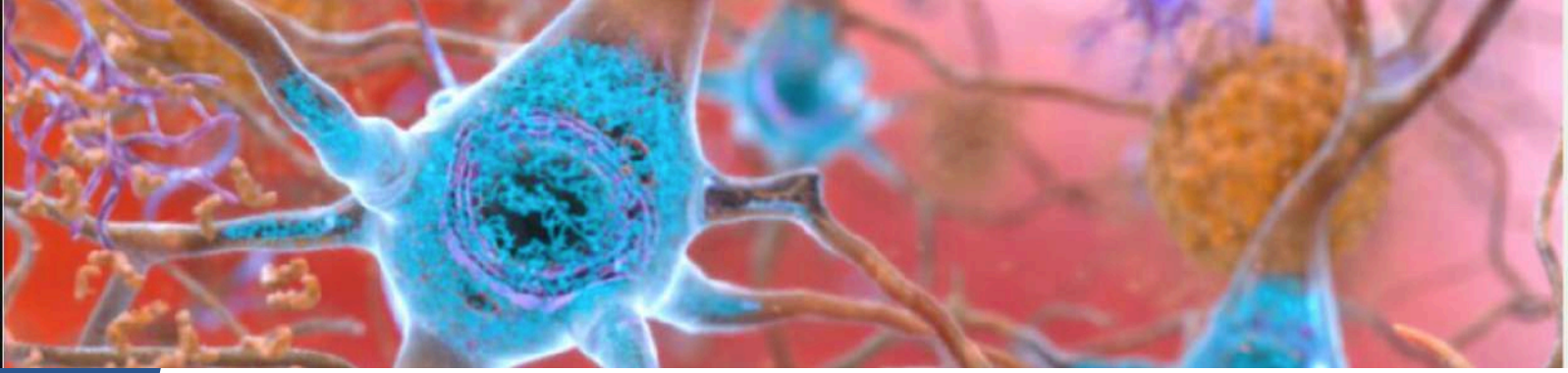


ASENT2021
Annual Meeting

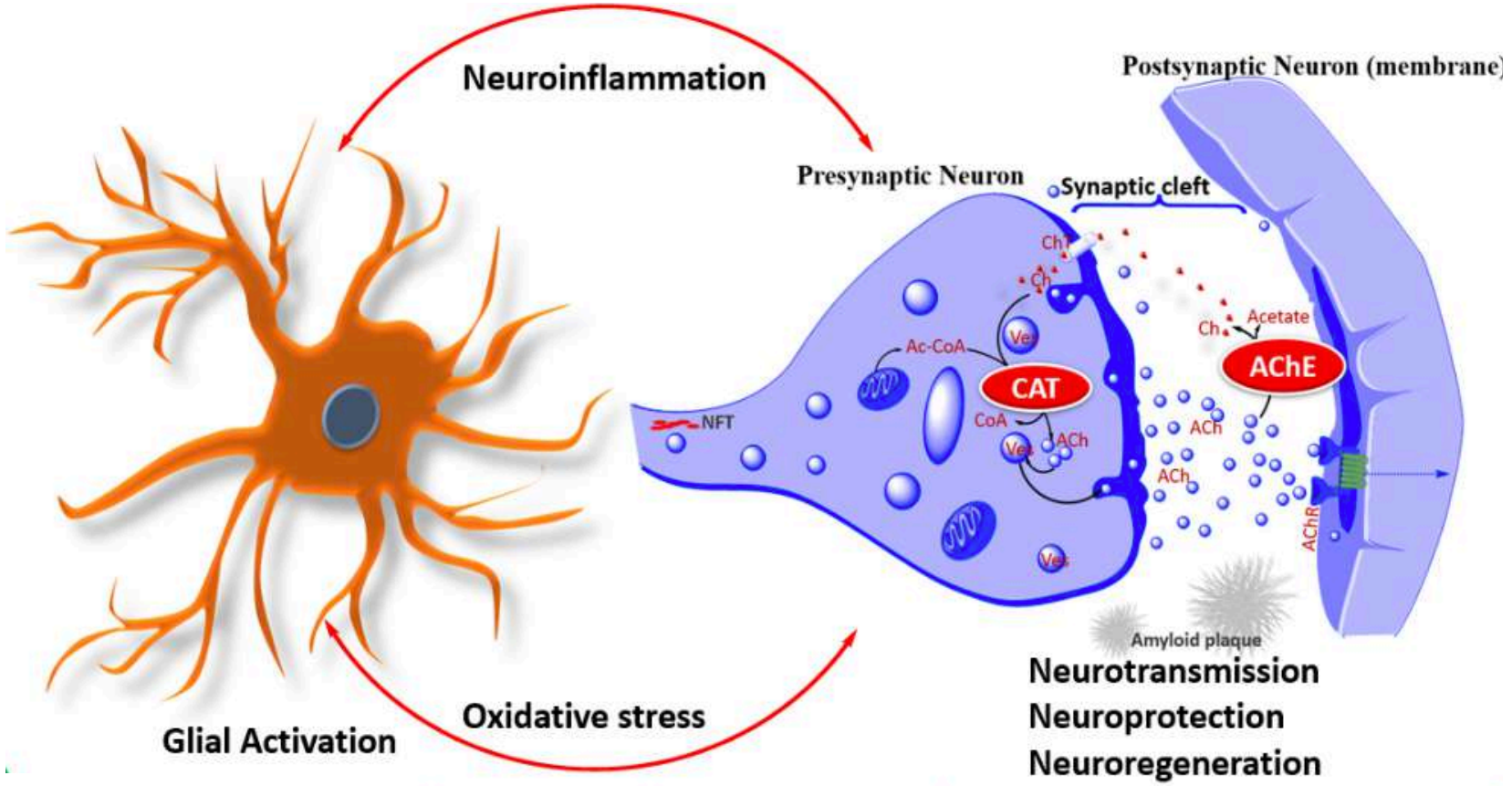
VIRTUAL NEUROTHERAPEUTICS CONFERENCE
FEB 22 - FEB 25, 2021

ASENT

"Optimizing Tilorone Analogs as Acetylcholinesterase Inhibitors Using Machine Learning and Recurrent Neural Networks"

Ana C. Puhl
Patricia A. Vignaux, Eni Minerali, Thomas R. Lane, Daniel H. Foil, Kimberley M. Zorn, Fabio Urbina, Peter B. Madrid and Sean Ekins

Alzheimer’s disease



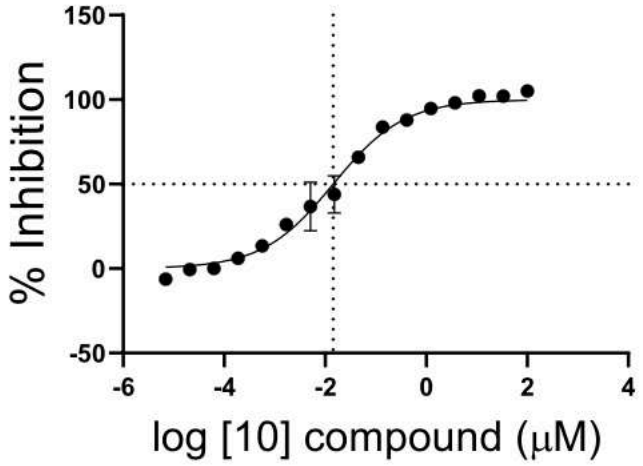
At least 50 million people are believed to be living with Alzheimer's disease worldwide
Decrease in brain acetylcholine (ACh) levels are implicated in the pathophysiology of cognitive dysfunction occurring in AD.

Molecules **2019**, *24*(8) 1519; **https://doi.org/10.3390/molecules24081519**

Discovery of of tilorone as a new inhibitor of AChE

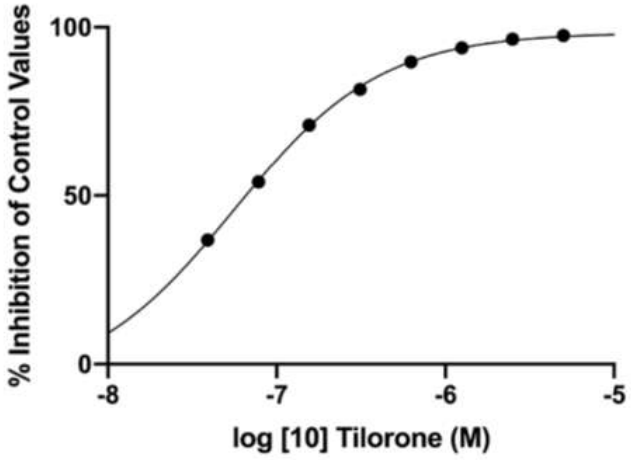
EelAChE

IC50 = 14.4 nM

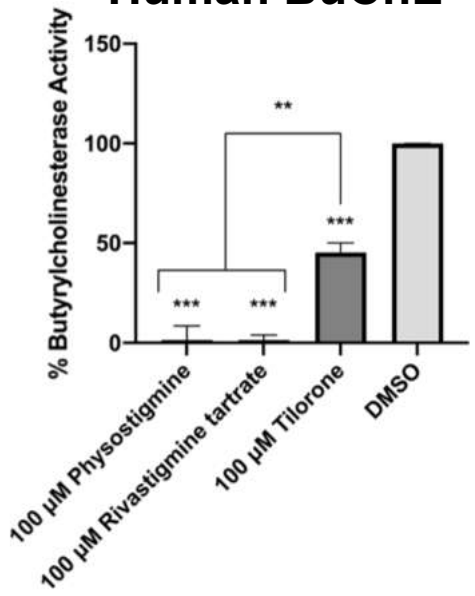


Human AChE

IC50 = 64 nM



Human BuChE



High-throughput screening eel enzyme **14.4 nM**

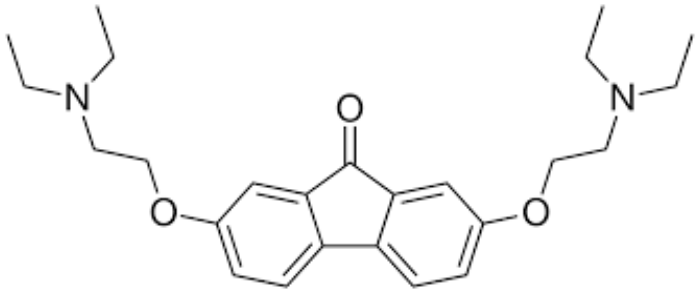
Validation human AChE **64.4 nM**

Selective for Butyrylcholinesterase **IC_{50} > 50 μM**

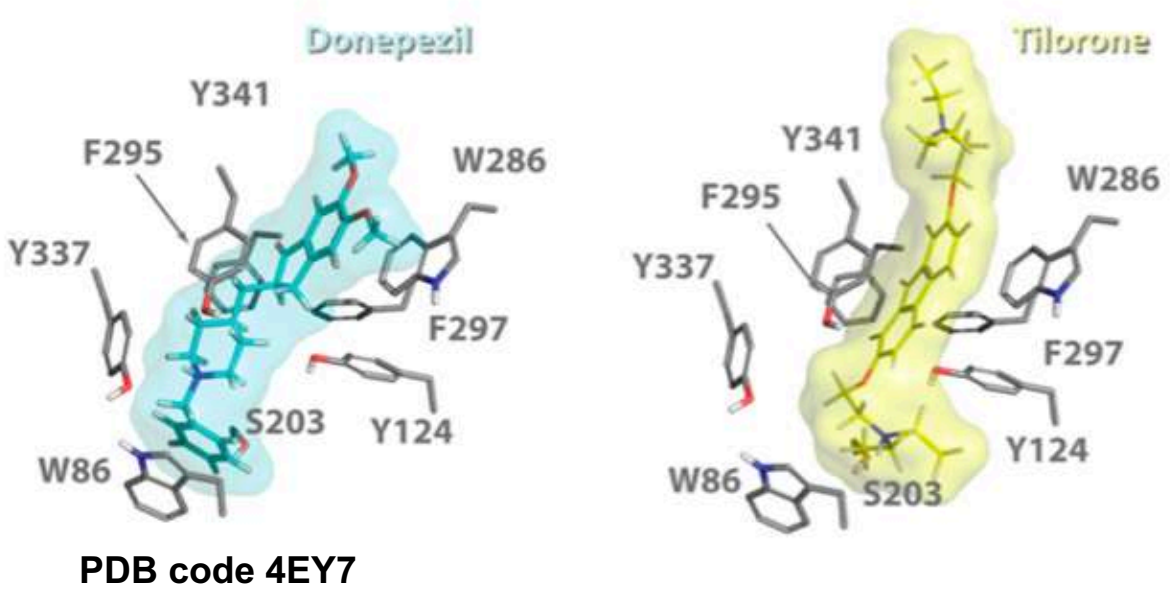
Chem Res Toxicol. 2021 Jan 5. doi: 10.1021/acs.chemrestox.0c00466

Docking and safety profile

Safety and selectivity profile



Docking



PDB code 4EY7

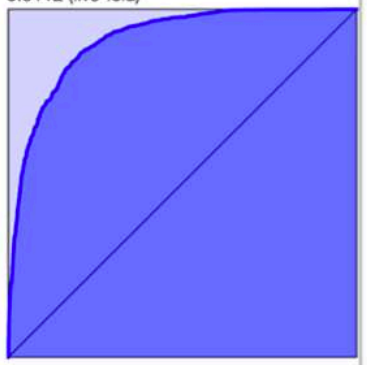
Tlorone had no appreciable inhibition of 485 kinases and only inhibited AChE out of 44 toxicology target proteins evaluated.

Tilorone likely interacts with the peripheral anionic site of AChE similar to the FDA approved AChE inhibitor donepezil.

Chem Res Toxicol. 2021 Jan 5. doi: 10.1021/acs.chemrestox.0c00466

Machine learning models to score tilorone analogs

AChE ChEMBL 27 (Homo sapiens IC50)

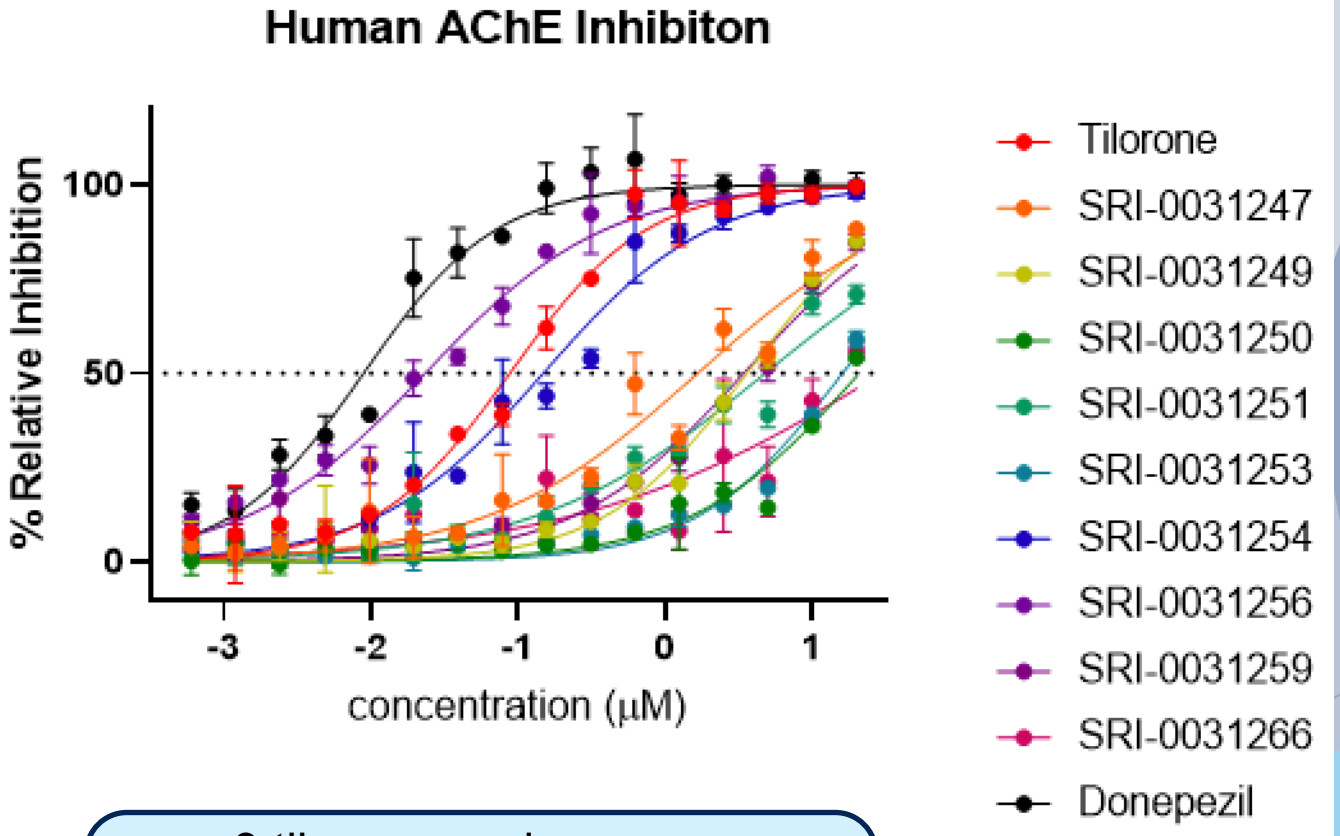
Origin:	Assay Central
Field:	alz/ache/homo_sapiens/v2_july2020
Comments:	Threshold: > 5.703312655247713
Training Actives:	2226 / 4601
ROC:	0.9112 (five-fold)
Curve:	

Truth Table:

		Predicted Yes	Predicted No
Actual	Yes	1942	284
Actual	No	487	1888

Precision:	0.7995
Recall:	0.8724
Specificity:	0.7949
F1 score:	0.8344
Kappa:	0.6655
MCC:	0.6681

Bayesian machine learning model consisting of 4601 molecules for hAChE



9 tilorone analogs were synthesized and tested
SRI-0031256 IC_{50} = 23 nM
donepezil IC_{50} = 8.9 nM

Conclusions

Tilorone is a potent inhibitor of AChE

Using machine learning models we identified and have synthetized more potent analogs

Recurrent neural network (RNN) for de novo molecule design

We applied for an NIH grant to study 30 targets for AD using machine learning

Funding:
R44GM122196-02A1 and 3R44GM122196-03S1 from NIGMS and 1R43ES031038-01 from NIEHS, HDTRA1-19-1-0020 and HR0011-19-C-0108

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