

# ANNOVIS

*- People Focused, Purpose Driven, Passion Powered -*

Attacks Neurodegeneration, Alzheimer's and  
Parkinson's Diseases by Improving the Information  
Highway of the Nerve Cell

Symbol: **ANVS** (NYSE)

**February 2024**



## FORWARD-LOOKING STATEMENTS

Forward Looking Statements and Other Important Cautions -- This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements relate to all information other than historical matters, such as expectations or forecasts of future events. Forward-looking statements may be identified by the use of words such as “forecast,” “intend,” “seek,” “target,” “anticipate,” “believe,” “expect,” “estimate,” “plan,” “outlook,” and “project” and other similar expressions that predict or indicate future events or trends or that are not statements of historical matters. Forward-looking statements with respect to the operations, strategies, prospects and other aspects of the business of Annovis Bio are based on current expectations that are subject to known and unknown risks and uncertainties, which could cause actual results or outcomes to differ materially from expectations expressed or implied by such forward-looking statements. These risks and uncertainties include but are not limited to: that clinical trials may be delayed; that the data reported herein is from a Phase 2a study and subsequent clinical trials are being conducted; and that any anticipated results from clinical trials may be delayed. These and other risks and uncertainties are described more fully in the section titled “Risk Factors” in Annovis Bio’s Annual Report on Form 10-K for the year ended December 31, 2022, and other periodic reports filed with the Securities and Exchange Commission. You are cautioned not to place undue reliance upon any forward-looking statements, which speak only as of the date made. Although it may voluntarily do so, from time to time, Annovis Bio undertakes no commitment to update or revise the forward-looking statements contained in this presentation, whether as a result of new information, future events or otherwise, except as required under applicable law.

# COMPANY HIGHLIGHTS

**Therapeutic focus/approach:** treatment of Alzheimer's disease (AD) and Parkinson's disease (PD) as neurodegenerative, axonal transport diseases

**Buntanetap (lead asset):** only drug to improve cognition in AD **AND** motor function in PD patients

**Unique MoA:** restores health of nerve cells and improves function by inhibiting production of multiple neurotoxic proteins associated with AD/PD

**Late-stage opportunities:** Phase 3 trial in early PD patients and Phase 2/3 trial in moderate AD will read out in first half of 2024

# INVESTMENT HIGHLIGHTS

## Targeting growing indications

- Parkinson's Disease – 1.2 million patients in US
- Alzheimer's Disease – 6 million patients in US

## Long Duration IP Estate IP extends well into 2040's

- Buntanetap – Multiple Chronic neurodegenerative diseases
- ANVS405 – Multiple acute brain and nerve injuries

## Multiple Catalysts

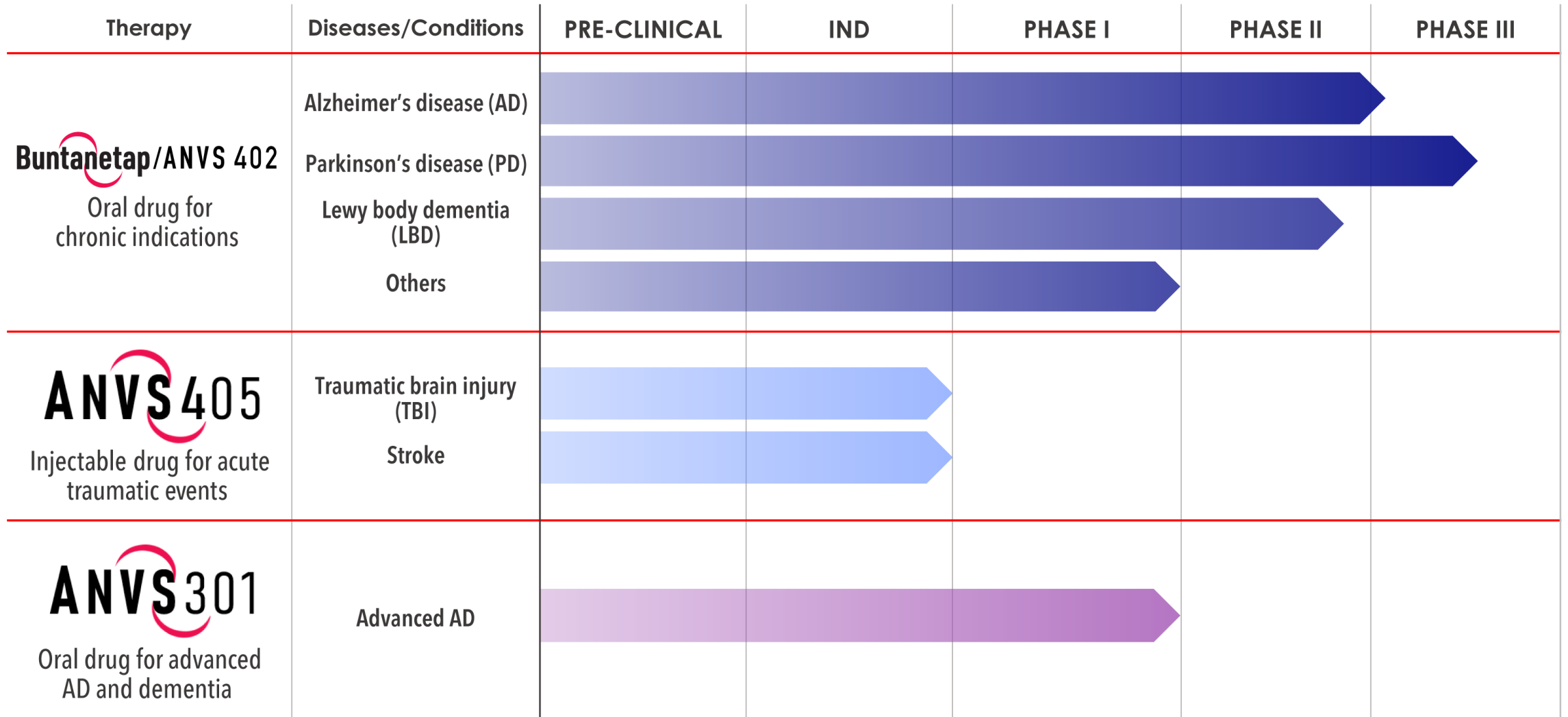
### Key clinical and regulatory milestones

- PD – phase 3, blinded, interim analysis received
- AD – first patient dosed in phase 2/3 trial Feb. 2023

## Capital-efficient approach

- On 9/30/23  
Cash balance \$ 6.4 mil.  
Debt \$ 0
- November 2023  
Raised \$10 mil.

# PIPELINE





A vertical photograph of a waterfall cascading over dark, wet rocks. The water is white and frothy as it falls. The background shows more rocks and some green foliage at the top.

NEUROTOXIC PROTEINS IMPAIR AXONAL  
TRANSPORT AND **CAUSE A TOXIC CASCADE**

**HIGH LEVELS OF NEUROTOXIC PROTEINS**

**IMPAIRED AXONAL TRANSPORT**

**SLOWER SYNAPTIC TRANSMISSION**

**INFLAMMATION**

**DEATH OF NERVE CELLS**

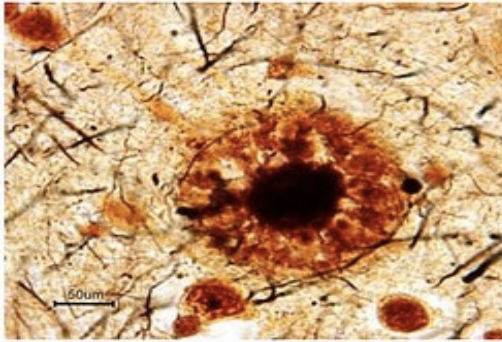
**LOSS OF COGNITIVE AND  
MOTOR FUNCTION**

# ANNOVIS' NEW APPROACH TO ATTACK AD AND PD

Chronic and acute brain insults lead to high iron levels, resulting in overexpression of neurotoxic proteins, impaired axonal transport, inflammation and neurodegeneration

## Amyloid $\beta$

Alzheimer's - Parkinson's



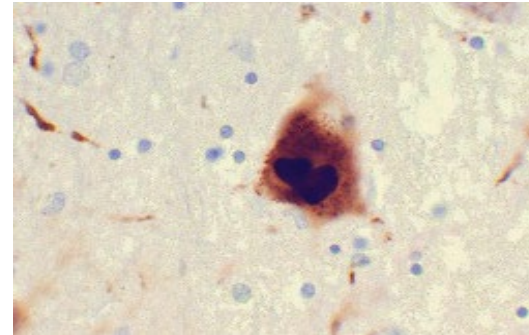
## Tau

Tauopathies - AD,  
PD, FTD, CTE



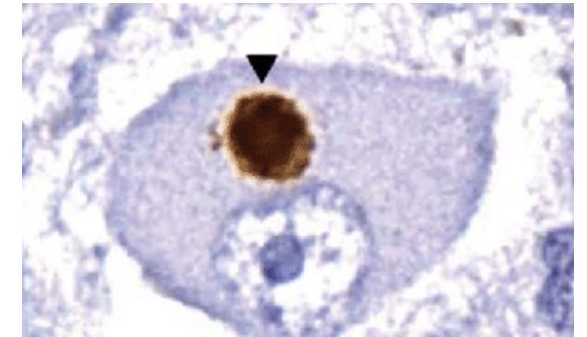
## $\alpha$ Synuclein

Parkinson's - Alzheimer's



## TDP43

ALS, AD, PD, FTD, CTE



Attacking one neurotoxic protein results in minimal effect

**Buntanetap inhibits the production of multiple neurotoxic proteins simultaneously**

# NEURODEGENERATION IS AN AXONAL TRANSPORT DISEASE

“Axonal transport disruption is linked to human neurological conditions.”

- Nature Review, September 2019

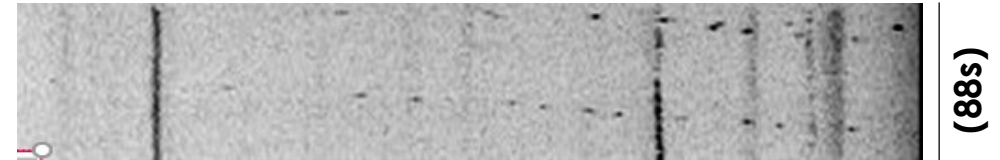
## Axonal transport is responsible for:

- Neurotransmitters GABA (anxiety), ACh (cognition), dopamine (movement), serotonin (mood)
- Neurotrophic factors NGF, BDNF
- All communication within and between nerve cells

← Retrograde (0.5 frame/sec) →

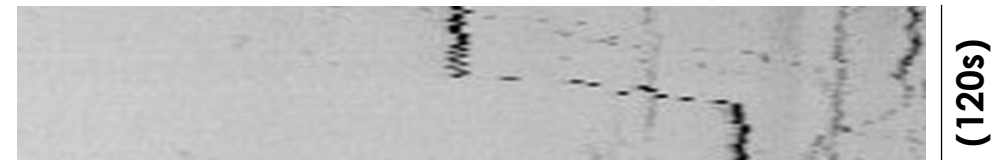
## Normal Transport

The *Normal Flow and Speed* of vesicles carrying BDNF across the axon.



## Abnormal Transport

Shows the *Blockage and Slowing* of BDNF across the axon. Black areas demonstrate where transport is slowed due to high levels of neurotoxic proteins.



## TREATED WITH BUNTANETAP

The *Flow and Speed* of axonal transport is improved.

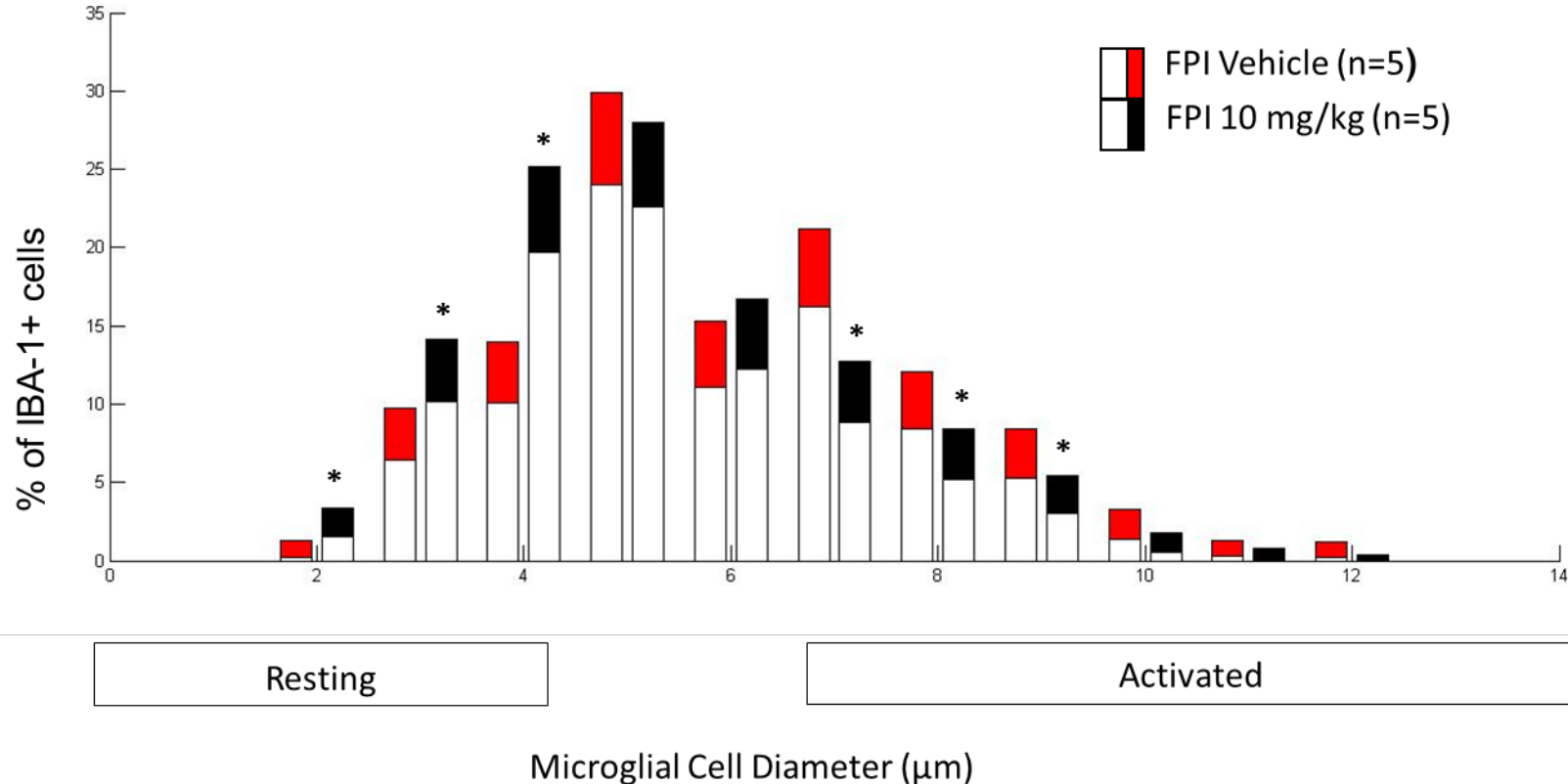


APP, Ab42, C99 – Mobley, UCSD; aSYN – Isacson, Harvard; Lee, U.Penn;  
Tau – U. Muenich & Zuerich; Htt – Mobley, UCSD; TDP43 – Taylor, Northwestern



# INHIBITS MICROGLIA ACTIVATION IN RAT BRAIN

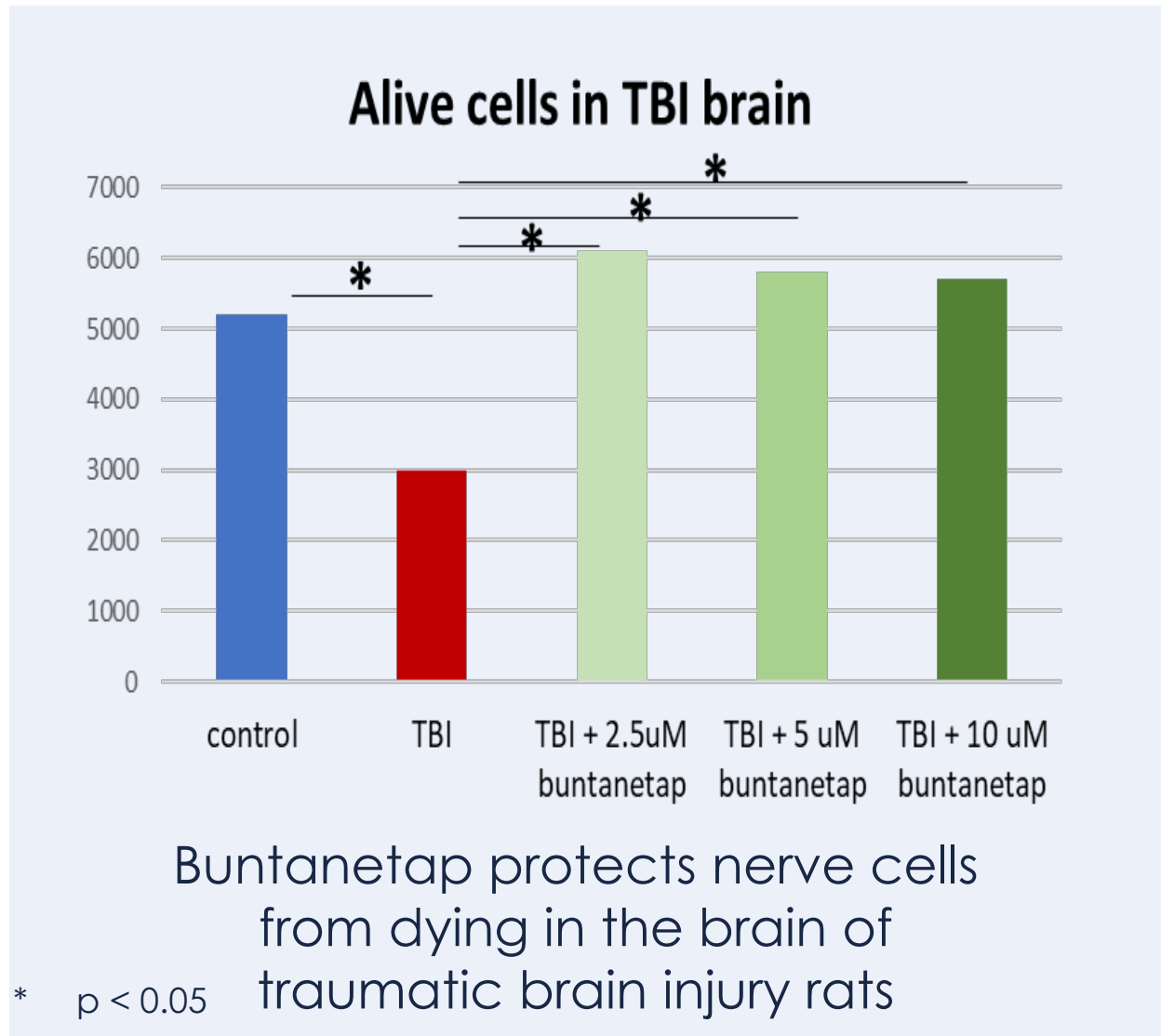
Data (Mean + 95% CI) analyzed with Bootstrapping method, \*p<0.05



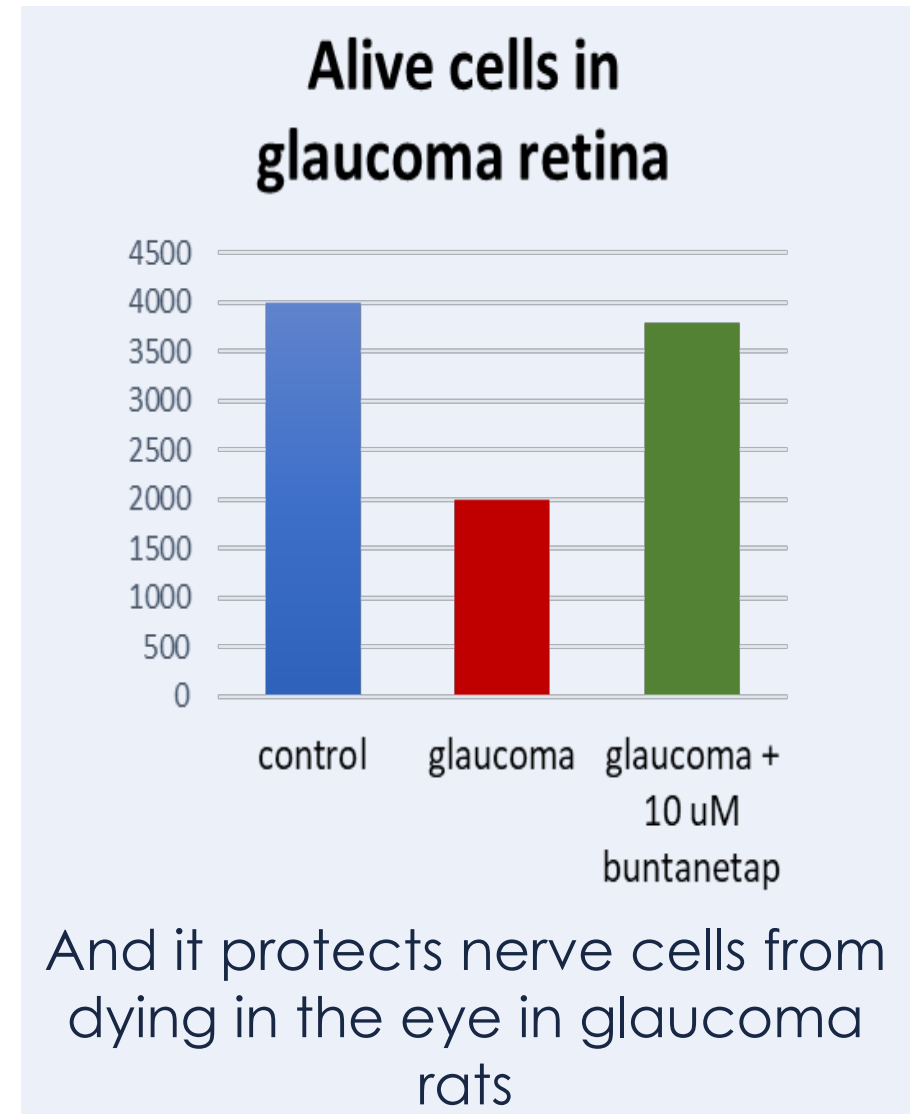
\* p < 0.05

ANVS401 increases the number of resting microglia and reduces the number of activated microglia – it reduces inflammation

# NEURODEGENERATION MEANS **DEAD NERVE CELLS**



Hatami A. et al: Buntanetap improves dopaminergic neuropathology and working memory in a rat model of traumatic brain injury; in preparation -UCLA



Sundstrom J. et al. Hershey Medical Center

# BUNTANETAP IMPROVES AXONAL TRANSPORT AND **IMPEDES THE TOXIC CASCADE**

## BY LOWERING LEVELS OF NEUROTOXIC PROTEINS

IMPROVED AXONAL TRANSPORT

INCREASED SYNAPTIC TRANSMISSION

LOWER INFLAMMATION

HEALTHY NERVE CELLS

IMPROVED COGNITIVE AND MOTOR FUNCTION



# STUDIES IN EIGHT ANIMAL AND HUMAN MODELS

FUNCTION	TEST	ANIMAL MODEL
Memory & learning - 4 models	Mazes	APP/PS1 Alzheimer mice Trisomic Down Syndrome mice Stroke mice Traumatic brain injury rats
Movement – 2 models	Colonic motility, grip strength	Alpha-synuclein Parkinson's mice Tau frontotemporal dementia mice
Vision	Sight	Glaucoma rats
Infections	Cell death	P. Gingivalis mice Covid mice



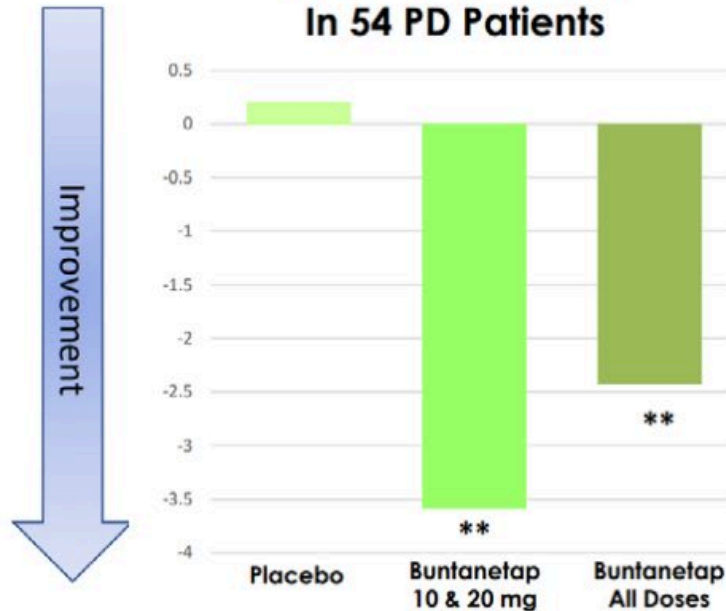
# BUNTANETAP PHASE 2 POSITIVE DATA IN PARKINSON'S DISEASE

## SIGNIFICANT IMPROVEMENTS IN BOTH MOTOR FUNCTION AND CODING SPEED

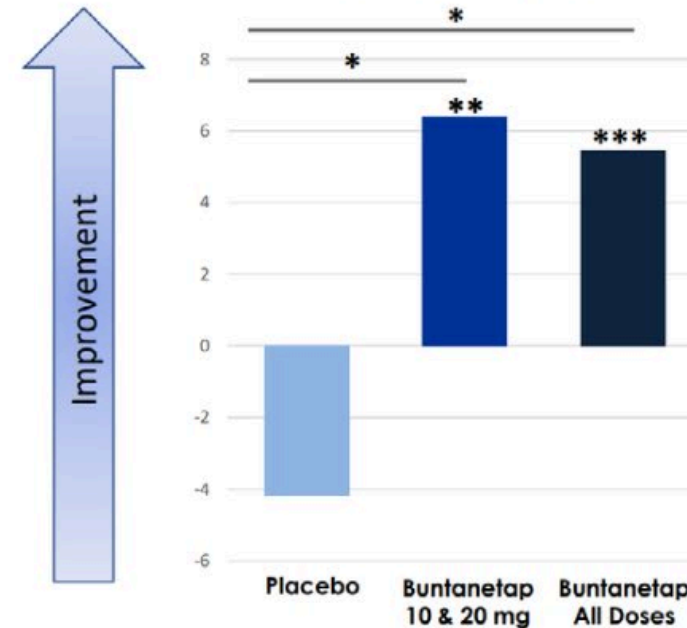
### Motor Function Improves...

### .... & Coding Speed

#### MDS-UPDRS Part III In 54 PD Patients



#### WAIS Coding in 54 PD Patients



\* p < 0.05  
\*\* p < 0.01  
\*\*\* p < 0.001

## FULLY ENROLLED PHASE 3 CLINICAL TRIAL IN **EARLY PD PATIENTS**

Therapeutic Area	Early PD
<b>Phase</b>	3
<b>Sites</b>	43 US + 24 EU = 67
<b>Patients</b>	3 X 174 = 523 = 471
<b>Dose</b>	placebo, 10 and 20 mg/day
<b>Start/End</b>	August 2022/December 2023
<b>Design</b>	Double-Blind, Placebo-Controlled Efficacy
<b>Endpoints</b>	MDS-UPDRS 2
<b>Other</b>	Total MDS-UPDRS 3 and total, PGIC, CGIS, WAIS, Biomarkers

# PD INTERIM EFFICACY AND SAFETY ANALYSIS 30% OF PATIENTS AT 2 MONTHS

Interim analysis for the two primary endpoints:

MDS-UPDRS 2 + 3  **Promising**

Interim analysis for safety by DSMB

no drug-related SAEs

each AE: < 2%

very low dropout rate: 6%

enrolled well ahead of timeline: 9 months for 523 patients

 **Well-tolerated**

**Continue as planned**

# DEVELOPMENT OF BUNTANETAP FOR **EARLY AND ADVANCED PD**

Interim Analysis



## Symptomatic Studies

Early PD  
Patients – 6 m

Naïve PD  
Patients – 6 m

Advanced PD  
Patients – 6 m

## Disease-modifying Study

Long chronic study in early PD - 18 m

Open Label Study for all  
treated PD Patients

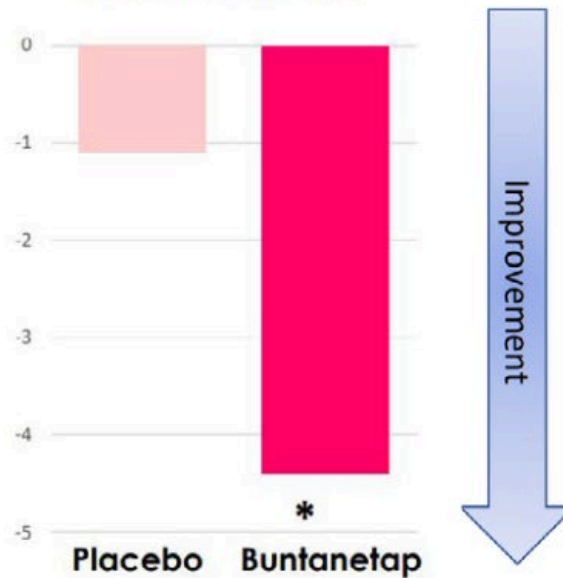


# BUNTANETAP PHASE 2 POSITIVE DATA IN ALZHEIMER'S DISEASE

## SIGNIFICANT IMPROVEMENTS IN BOTH COGNITIVE FUNCTION AND CODING SPEED

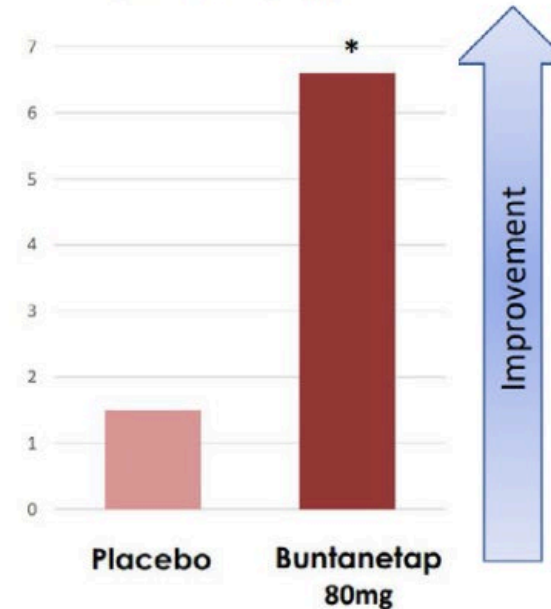
### Cognition Improves...

ADAS-Cog11 in  
14 AD Patients



### .... & Coding Speed

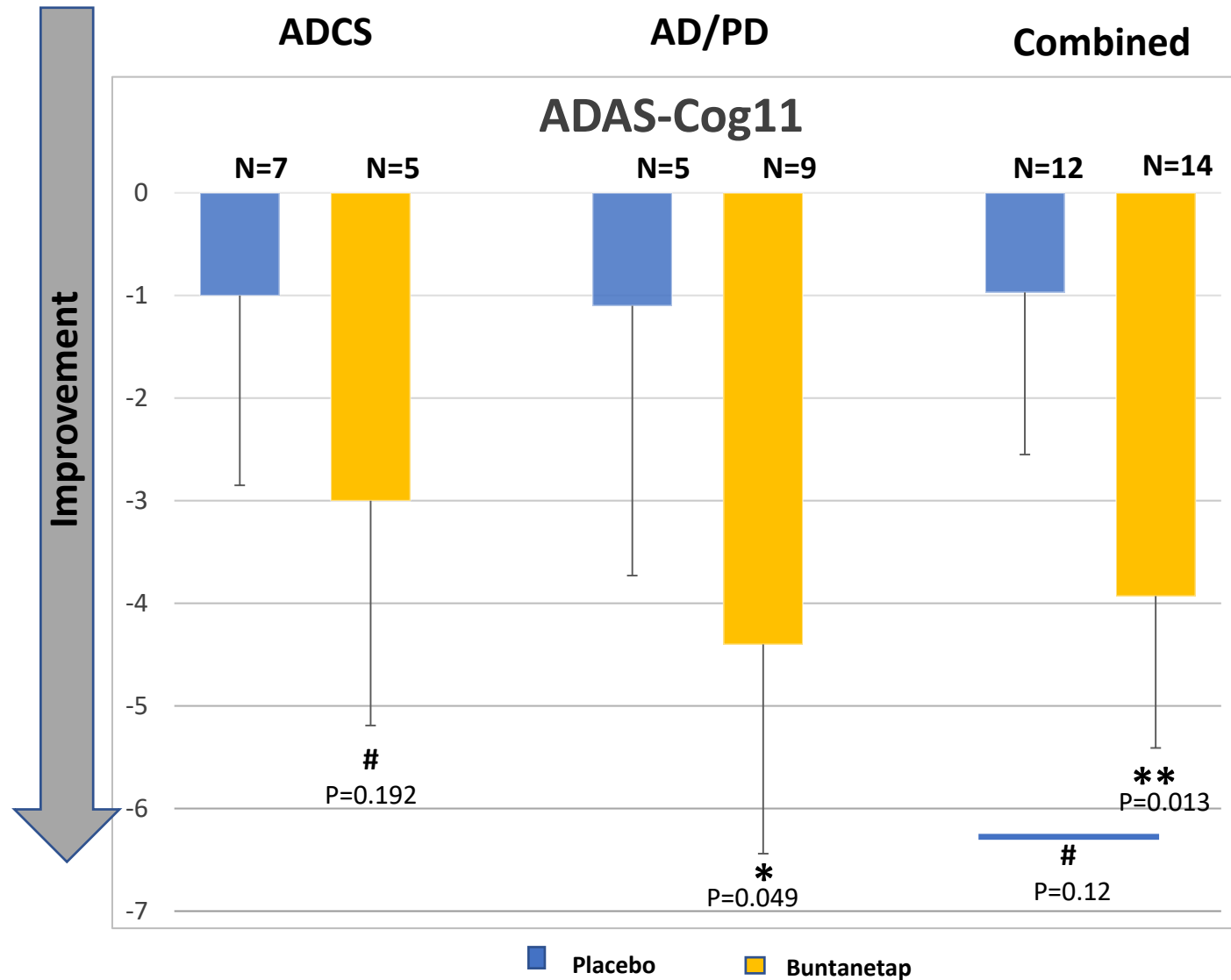
WAIS Coding in  
14 AD Patients



\*  $p < 0.05$

# ADCS EFFICACY AND COMBINATION

## ADAS-Cog IN TWO SMALL STUDIES – ADCS AND AD/PD



Buntanetap shows improvement of -3 and -4.4 points from baseline and of -2.9 points from placebo in two small exploratory studies in ADAScog 11 after one month of treatment. The data is either statistically significant or shows a strong trend

# strong trend

\* P = 0.05

\*\* p = 0.01

# ONGOING PHASE 2/3 CLINICAL TRIAL IN **AD PATIENTS**

<b>Therapeutic Area</b>	<b>Moderate AD</b>
<b>Phase</b>	2/3
<b>Sites</b>	64 US
<b>Patients</b>	4 X 88 = 353
<b>Dose</b>	placebo, 7.5, 15 and 30 mg/day
<b>Start/End</b>	February 2023/February 2024
<b>Design</b>	Double-Blind, Placebo-Controlled Efficacy
<b>Endpoints</b>	ADAScog 11, ADCS-CGIC
<b>Other</b>	WAIS, Biomarkers

# AD INTERIM EFFICACY AND SAFETY ANALYSIS 30% OF PATIENTS AT 6 WEEKS

Interim analysis for the two co-primary endpoints:

ADAScog 11, ADCS-CGIC



**Promising**

Interim analysis for safety by DSMB

no drug-related SAEs

each AE: < 5%

very low dropout rate: 4.7%

enrolled as planned: 9 months for 353 patients



**Well-tolerated**

**Continue as planned**



# DEVELOPMENT OF BUNTANETAP FOR EARLY AND ADVANCED AD

Interim Analysis



## Symptomatic Study



## Disease-modifying Study



Basket study for advanced disease  
1 month



ANNOVIS

# CORPORATE PATENT ESTATE



Patent/Application	Subject Matter	Status	Expiry
Provisional	Novel composition of matter for ANVS402	Pending	<b>2044</b>
Provisional	3 Combination Applications	Pending	<b>2044/5</b>
PCT	Neuropsychiatric Indications	Pending	<b>2044</b>
PCT	Other Diseases	Pending	<b>2043</b>
PCT	Brain infections	Pending	<b>2042</b>
PCT	Use of mechanism of action	One patent granted	<b>2038</b>
PCT	Acute neurodegenerative injuries	Multiple patents granted	<b>2036</b>
PCT	Chronic neurodegenerative diseases	Multiple patents granted	<b>2031</b>

# SENIOR MANAGEMENT TEAM



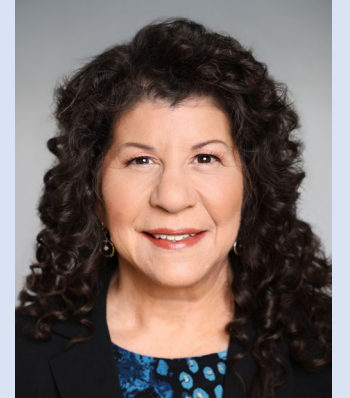
**Maria Maccacchini, PhD**  
Founder, President & CEO



**Andrew Walsh**  
VP, Finance



**Michael Christie**  
VP, Process Chemistry



**Eve Damiano, MS, RAC**  
SVP, Regulatory



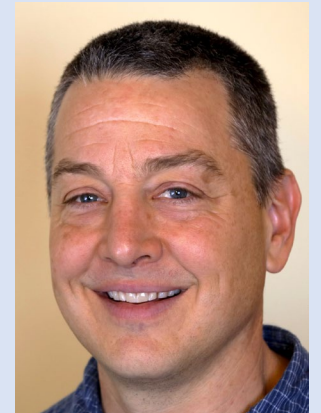
**Henry Hagopian, MBA**  
Chief Financial Officer



**Cheng Fang, PhD**  
SVP, R & D



**Melissa Gaines,**  
VP, Clinical Operations



**David Prohaska**  
VP, Tox & Pharmacol

# SCIENTIFIC ADVISORY BOARD



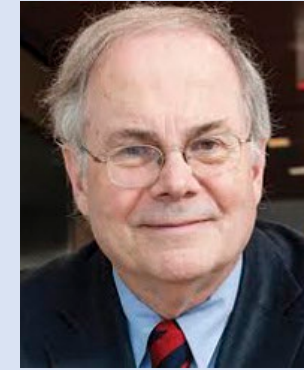
## **Sidney Strickland, PhD, Chairman**

Vice President and Dean for Educational Affairs and Research Professor, Patricia and John Rosenwald Laboratory of Neurobiology and Genetics at Rockefeller University. Dr. Strickland's laboratory investigates how dysfunction of the circulatory system contributes to Alzheimer's and other neurodegenerative disorders. He will serve as the Chairman of Annovis Bio's SAB.



## **Jeffrey Cummings, MD**

Dr. Cummings completed Neurology residency and a Fellowship in Behavioral Neurology at Boston University, Massachusetts. US training was followed by a Research Fellowship in Neuropathology and Neuropsychiatry at the National Hospital for Nervous Diseases, London, England. Dr. Cummings was formerly Professor of Neurology and Psychiatry, Director of Alzheimer's Disease Research and Director of the Center for Neurotherapeutics at UCLA. He was Director of the Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Cleveland and Florida.



## **Gregory Petsko, PhD**

Dr. Petsko is a member of the National Academy of Sciences, the National Academy of Medicine, the American Academy of Arts and Sciences and the American Philosophical Society. His research interests are directed towards understanding the biochemical bases of neurological diseases like Alzheimer's, Parkinson's, and ALS discovering treatments (especially by using structure-based drug design), that could therapeutically affect those biochemical targets, and seeing any resulting drug candidates tested in humans. He has also made key contributions to the field of protein crystallography.

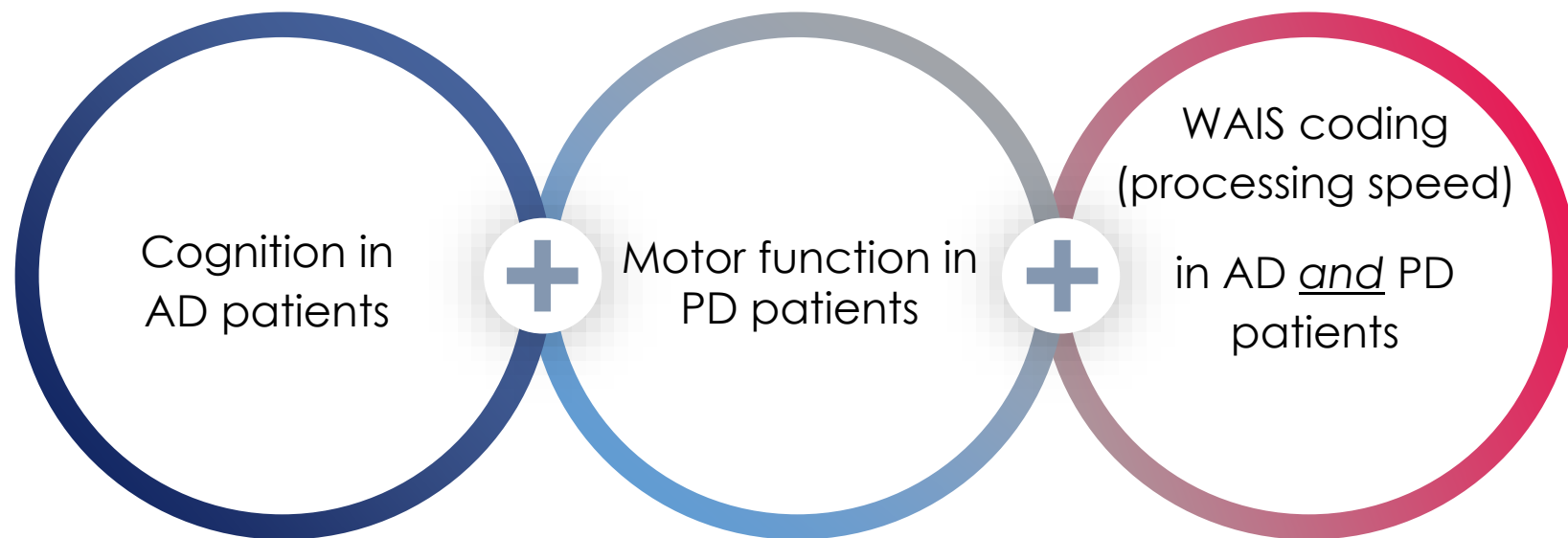


# KEY TAKEAWAYS

Annovis has a novel approach to address **AD and PD**

The first double-blind, placebo-controlled study that shows improvements in **AD** patients as measured by **ADAS-Cog** and in **PD** patients as measured by **UPDRS**

**Buntanetap** shows improvements in **Phase 2a** clinical trials:



**We started our phase 3 study for early PD, and our phase 2/3 in moderate AD**



## CONTACT US

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Improves **THE FLOW** of Axonal  
Transport in Alzheimer's Disease  
and Neurodegeneration

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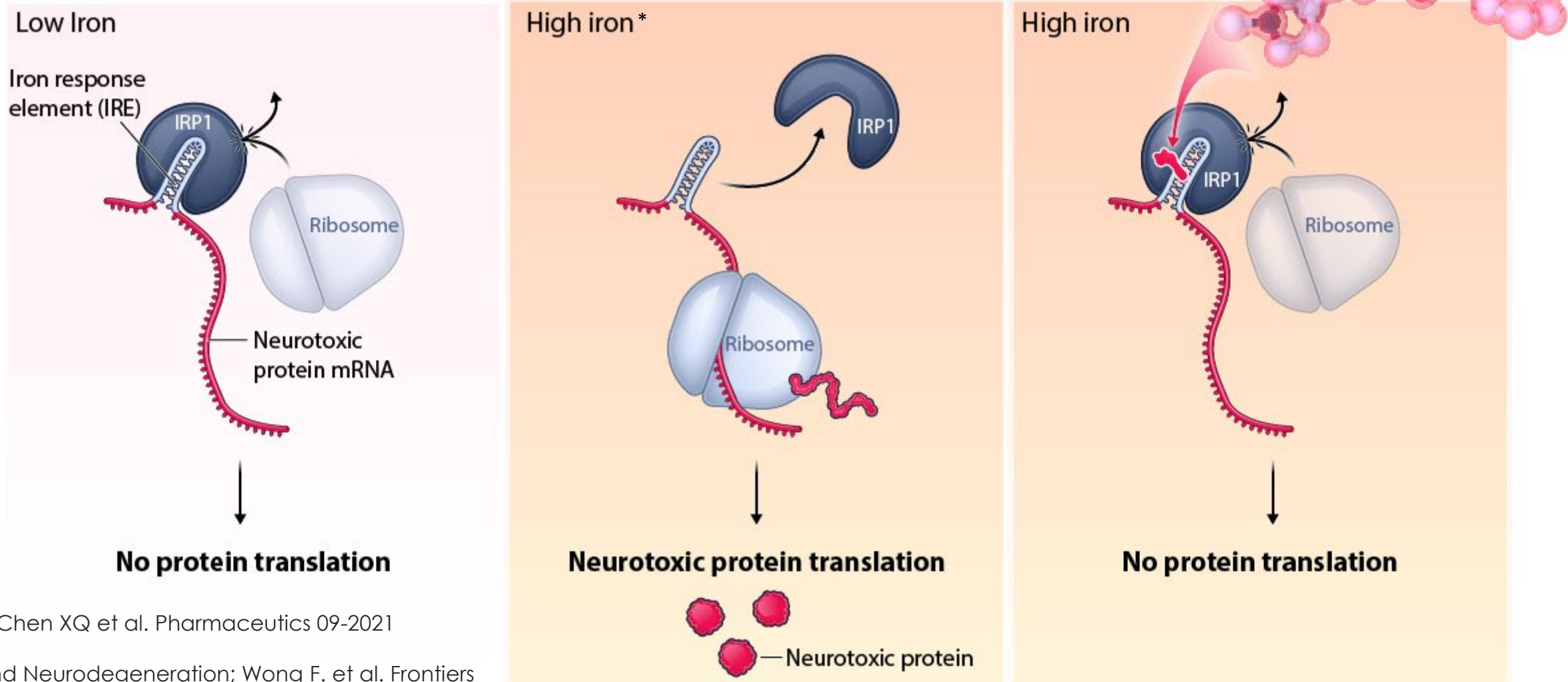


Appendix



# MECHANISM OF ACTION

**Buntanetap inhibits the translation of neurotoxic proteins**

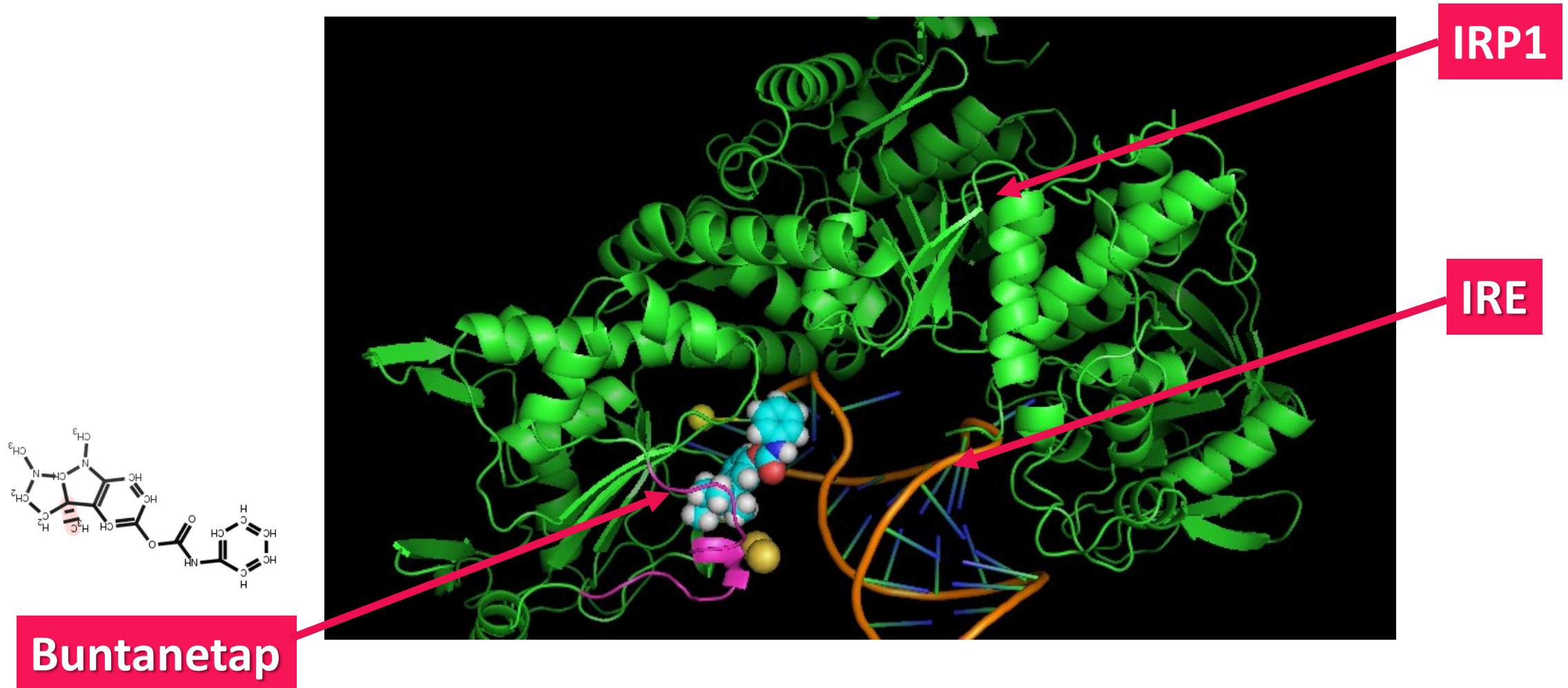


MOA; Chen XQ et al. *Pharmaceutics* 09-2021

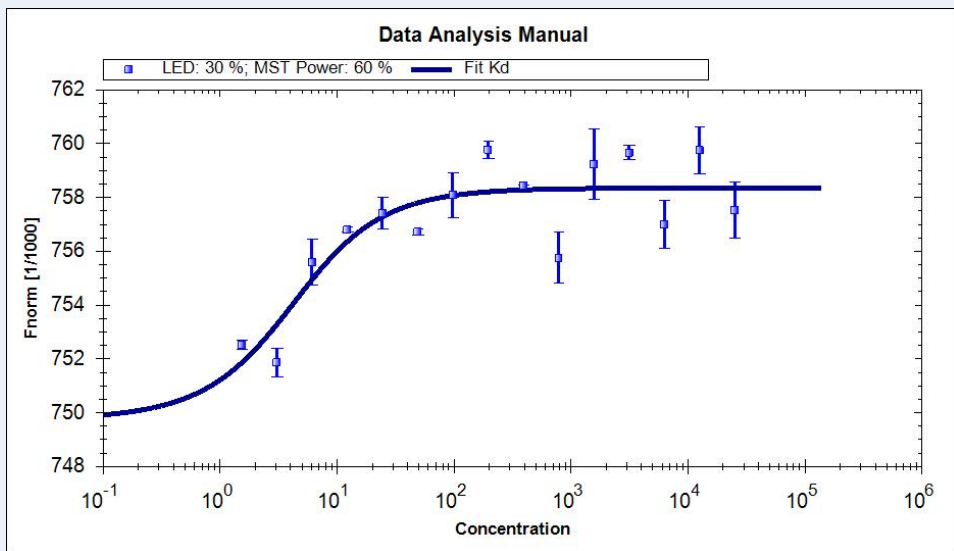
Iron and Neurodegeneration; Wong F. et al. *Frontiers Aging Neuroscience*; 03-2022

# MECHANISM OF ACTION

## Molecular Model of how Buntanetap locks IRP1 in the mRNA Binding Position

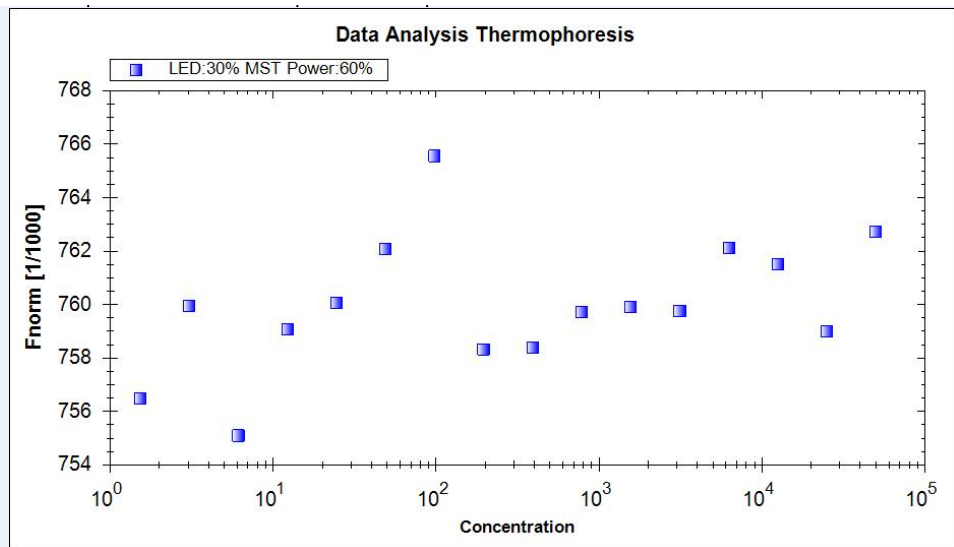


# IRE to IRP1 BINDING IS **SPECIFIC FOR** mRNAs CODING FOR **NEUROTOXIC PROTEINS**



**APP IRE/IRP1/Buntanetap**  
**Kd 3.2 nM**

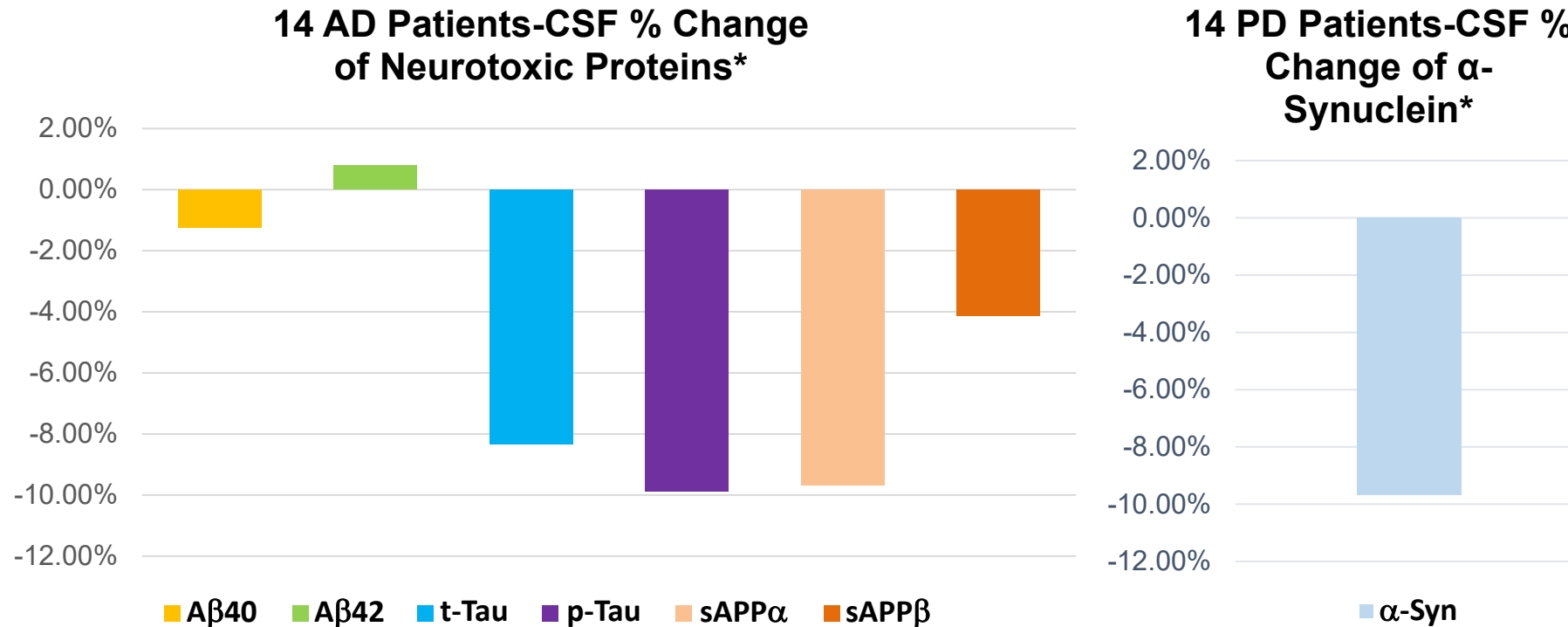
Fitting for Kd Formular	Fitted Value
Fitted Parameter	3.22+/-0.464
Dissociation Constant	2
Fluo.Conc	758.35
Bound	749.76
Unbound	8.59



**Ferritin IRE/IRP1/Buntanetap**  
**No Kd**

**Buntanetap binds specifically to the APP IRE, but not to the ferritin IRE**

# REDUCED NEUROTOXIC PROTEINS IN BOTH AD AND PD PATIENTS

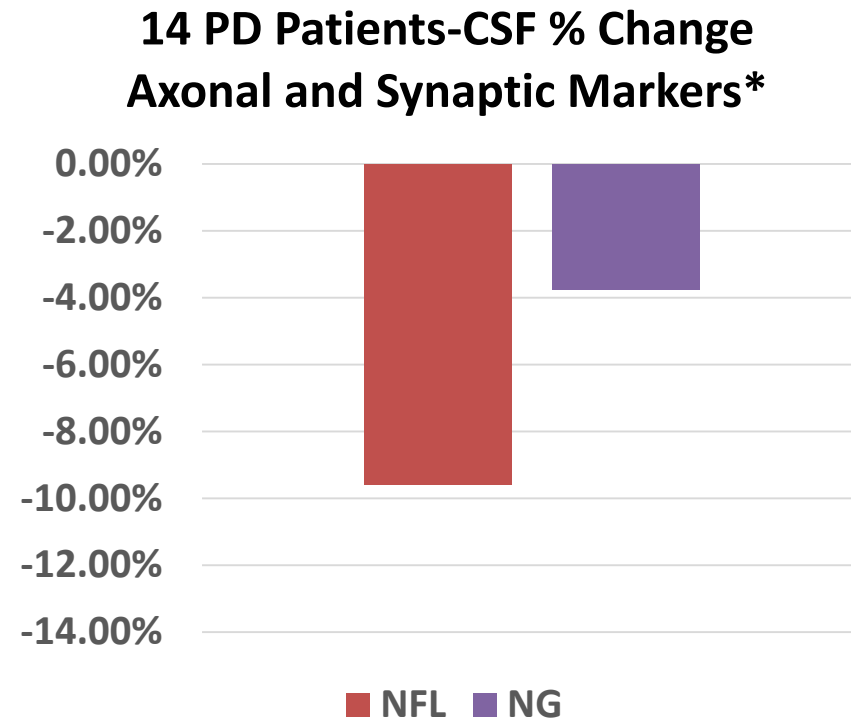
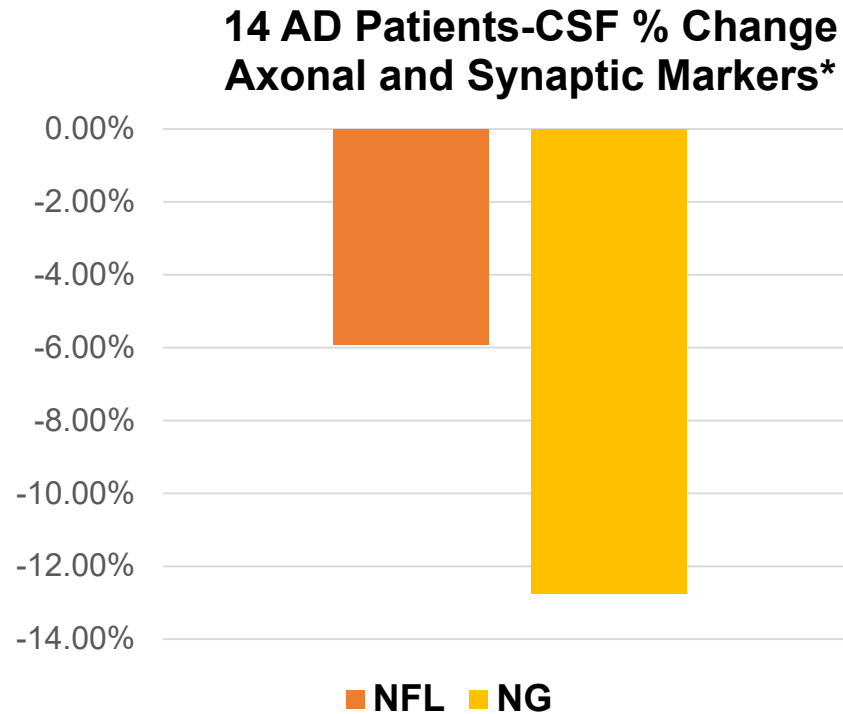


APP (and its downstream products), and p-Tau are the neurotoxic proteins involved in AD, while α-Synuclein is the neurotoxic culprit of PD. The reduction compares well to the reduction seen in animals at full efficacy.

\*All values are in comparison to placebo based on all data points



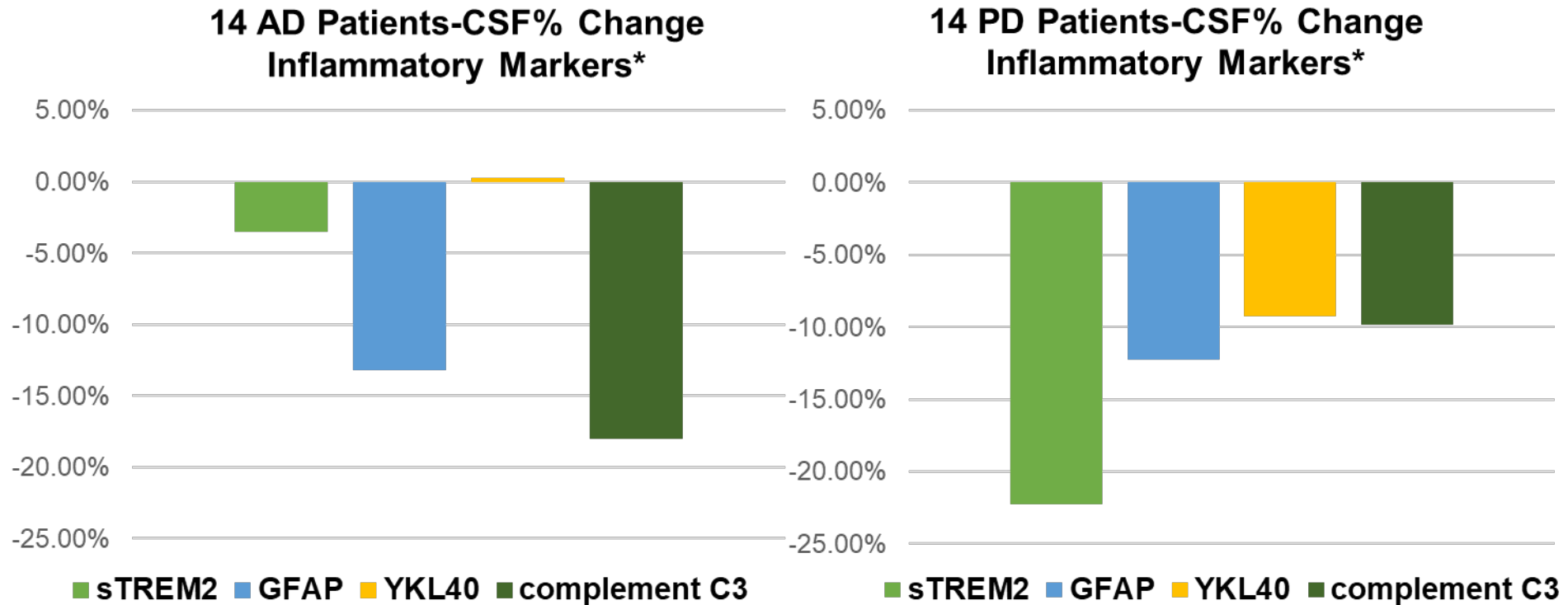
# REDUCED AXONAL AND SYNAPTIC DYSFUNCTIONS IN BOTH AD AND PD PATIENTS



Neuronal and synaptic markers are lowered in AD and in PD patients, showing that the nerve cells are potentially healthier.

\*All values are in comparison to placebo based on all data points.

# REDUCED INFLAMMATION IN BOTH AD AND PD PATIENTS



Inflammatory markers are lowered in AD and in PD patients, showing a normalization of inflammation in both neurodegenerative disorders.

\*All values are in comparison to placebo based on all data points