# 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)**

**April 2023**


## 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, 2021 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 started Aug 2022 and Phase 2/3 trial in AD started in January 2023

**Proven execution:** company senior leadership has consistently delivered on clinical timelines, enrollment progression, and data readouts

# INVESTMENT HIGHLIGHTS

**Targeting growing indications**

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

**Multiple Catalysts**

**Key clinical and regulatory milestones**

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

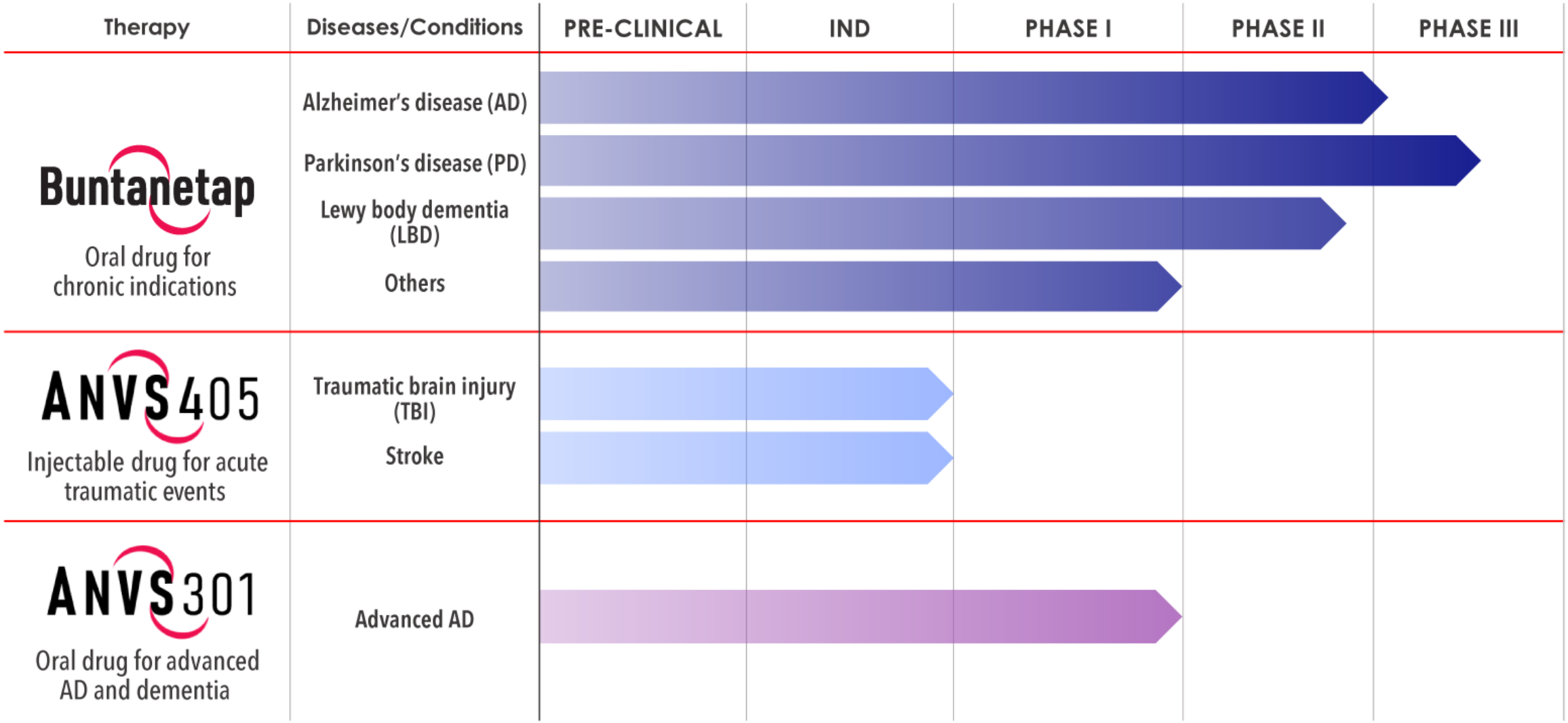
**Long Duration IP Estate**
**IP extends well into 2040's**

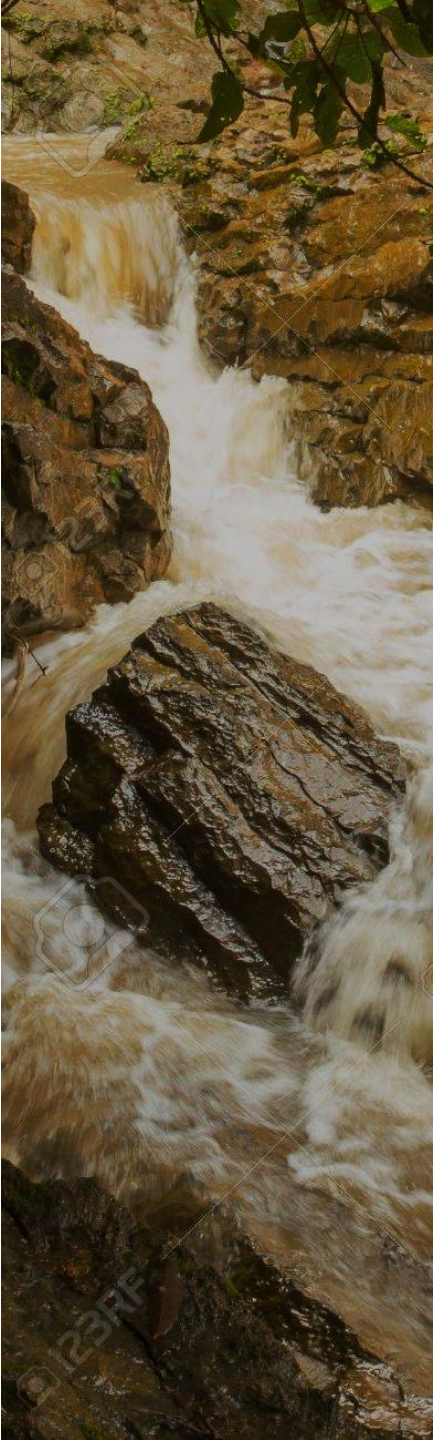
- Buntanetap – Multiple Methods of use for neurodegenerative diseases
- ANVS405 – Methods of use for acute brain and nerve injuries

**Capital-efficient approach**

- Completed $ 50 mil. equity raise in May 2021
- Cash balance $ 28 mil. Debt $ 0 as of 12/31/22

# PIPELINE


Therapy
Diseases/Conditions
PRE-CLINICAL
IND
PHASE I
PHASE II
PHASE III
Buntanetap
Oral drug for chronic indications
Alzheimer's disease (AD)
Parkinson's disease (PD)
Lewy body dementia (LBD)
Others
ANVS405
Injectable drug for acute traumatic events
Traumatic brain injury (TBI)
Stroke
ANVS301
Oral drug for advanced AD and dementia
Advanced AD



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

## HIGH LEVELS OF NEUROTOXIC PROTEINS

**IMPAIRED AXONAL TRANSPORT**

**SLOWER SYNAPTIC TRANSMISSION**

**INFLAMMATION**

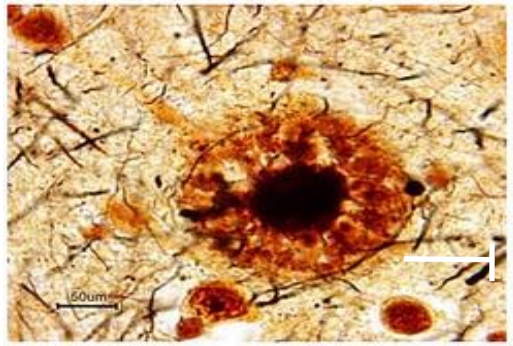
**DEATH OF NERVE CELLS**

**LOSS OF COGNITIVE AND MOTOR FUNCTION**

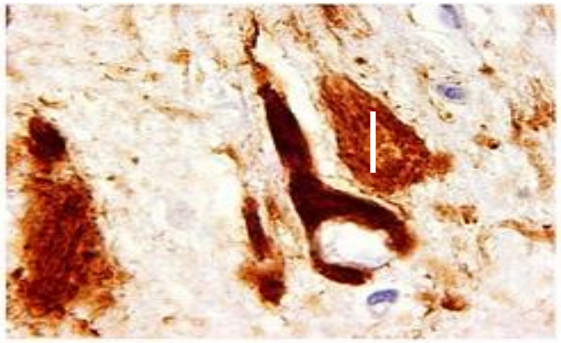
# ANNOVIS' NEW APPROACH TO ATTACK AD AND PD

**Chronic and acute brain insults lead to high levels of neurotoxic proteins, impaired axonal transport, inflammation and neurodegeneration**

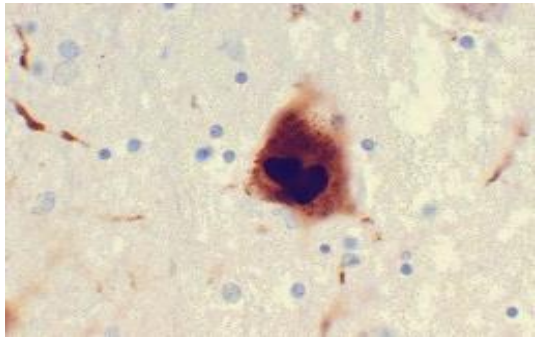
**Amyloid β**
Alzheimer's - Parkinson's



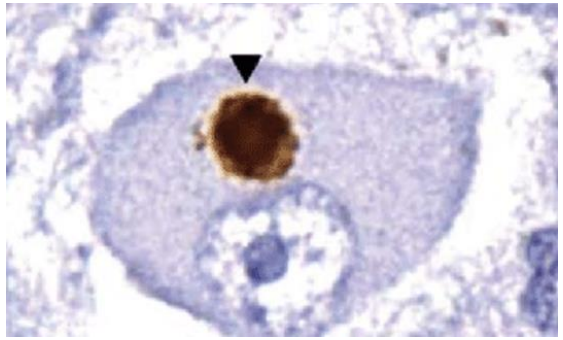
**Tau**
Tauopathies - AD, PD, FTD, CTE



**αSynuclein**
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:**

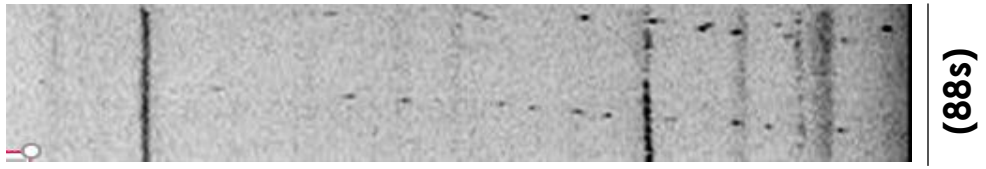
- Neurotransmitters GABA (anxiety), ACh (cognition), dopamine (movement), serotonin (mood)
- Neurotrophic factors NGF, BDNF
- All communication within and between nerve cells

Chen XQ et al. *Alzheimer's & Dementia; 08-2020*

Retrograde (0.5 frame/sec)

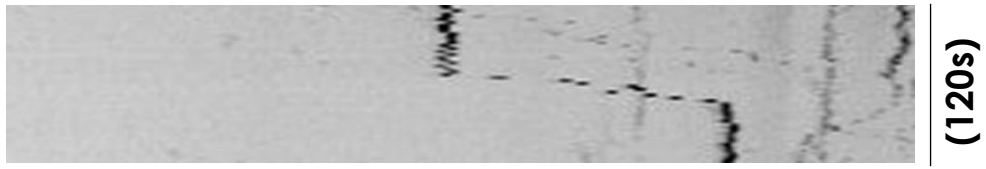
**Normal Transport**

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.

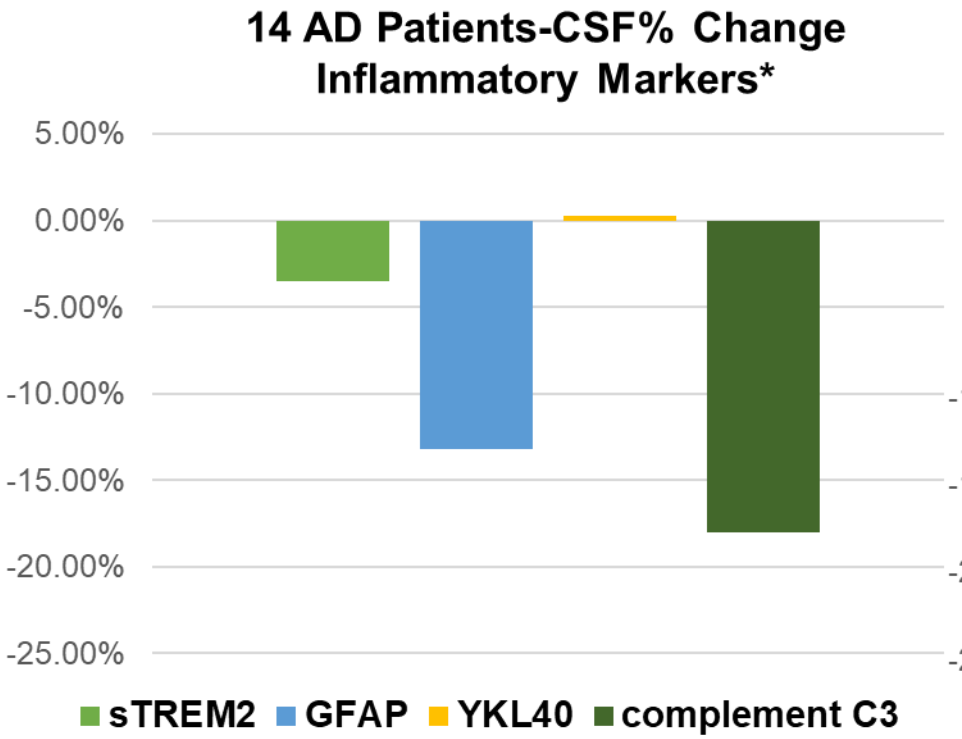


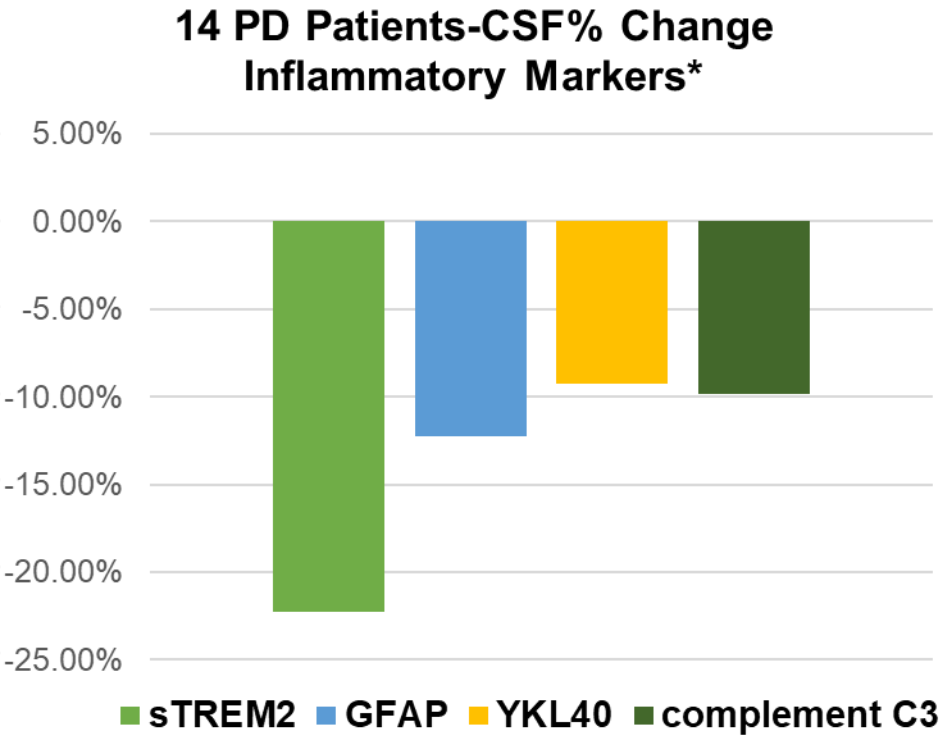

**TREATED WITH BUNTANETAP**

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

# REDUCED INFLAMMATION IN BOTH AD AND PD PATIENTS

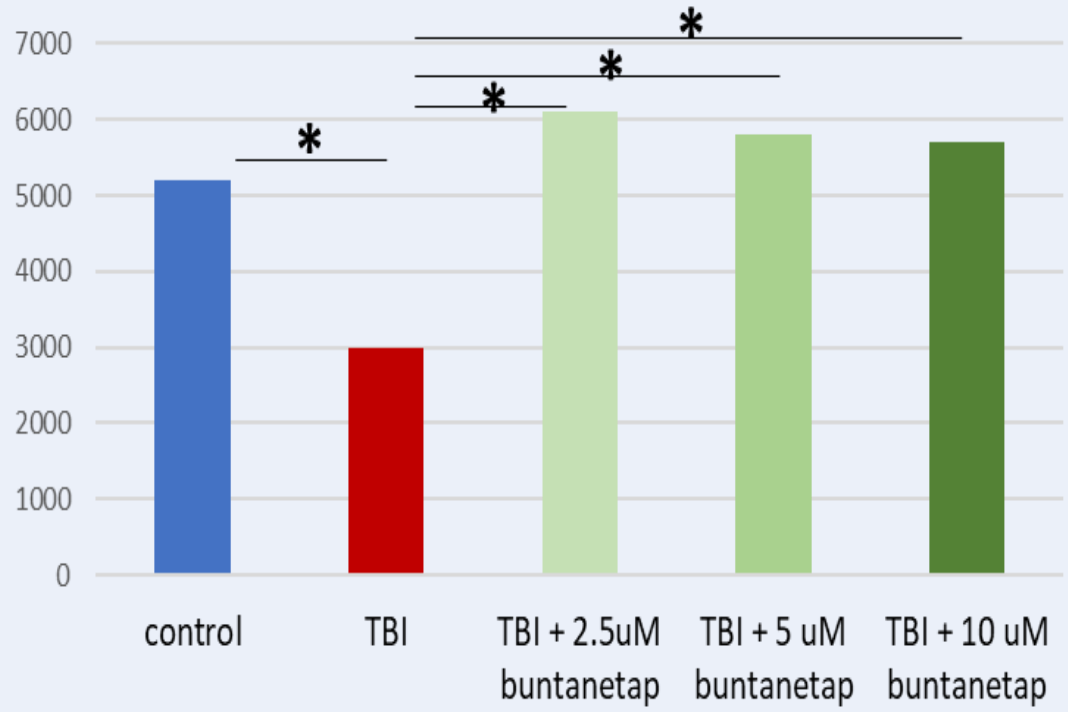


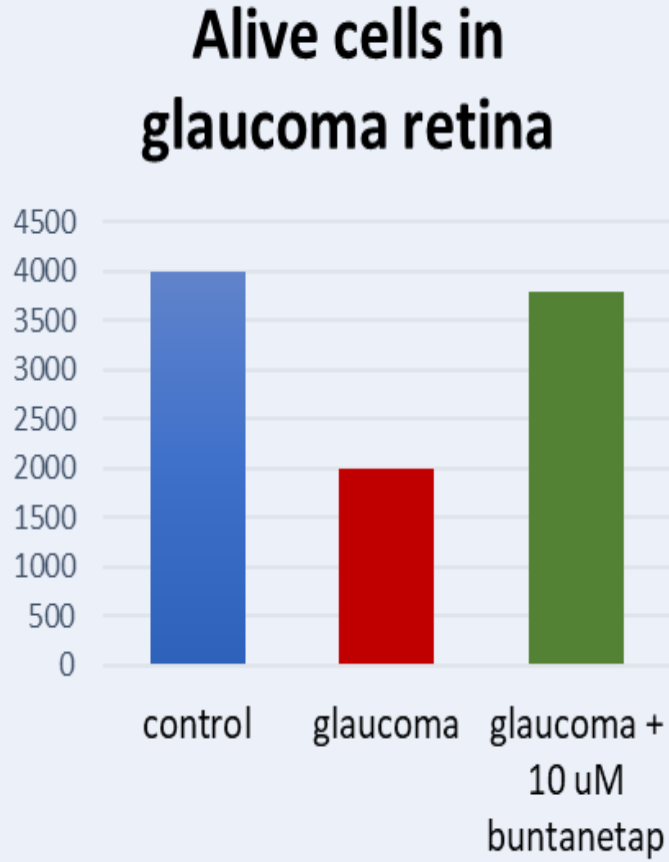

Inflammatory markers are lowered in AD and in PD patients, showing a normalization of inflammation in both neurodegenerative disorders.

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

# NEURODEGENERATION MEANS **DEAD NERVE CELLS**




Buntanetap protects nerve cells from dying in the brain or traumatic brain injury rats




And it protects nerve cells from dying in the eye in glaucoma rats

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

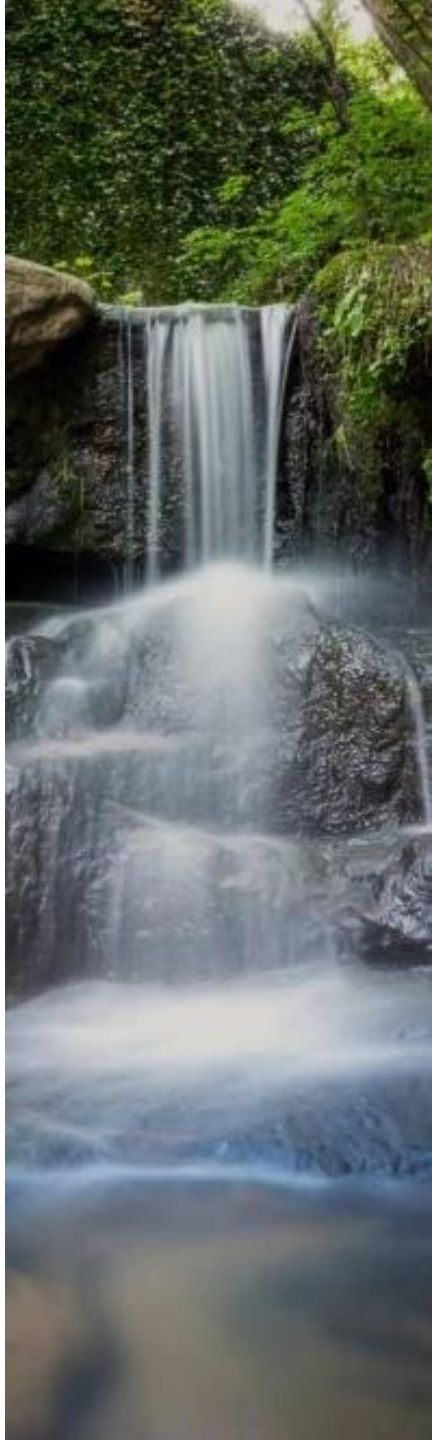
**IMPROVED AXONAL TRANSPORT**

**INCREASED SYNAPTIC TRANSMISSION**

**NO INFLAMMATION**

**HEALTHY NERVE CELLS**

**IMPROVED COGNITIVE AND MOTOR FUNCTION**

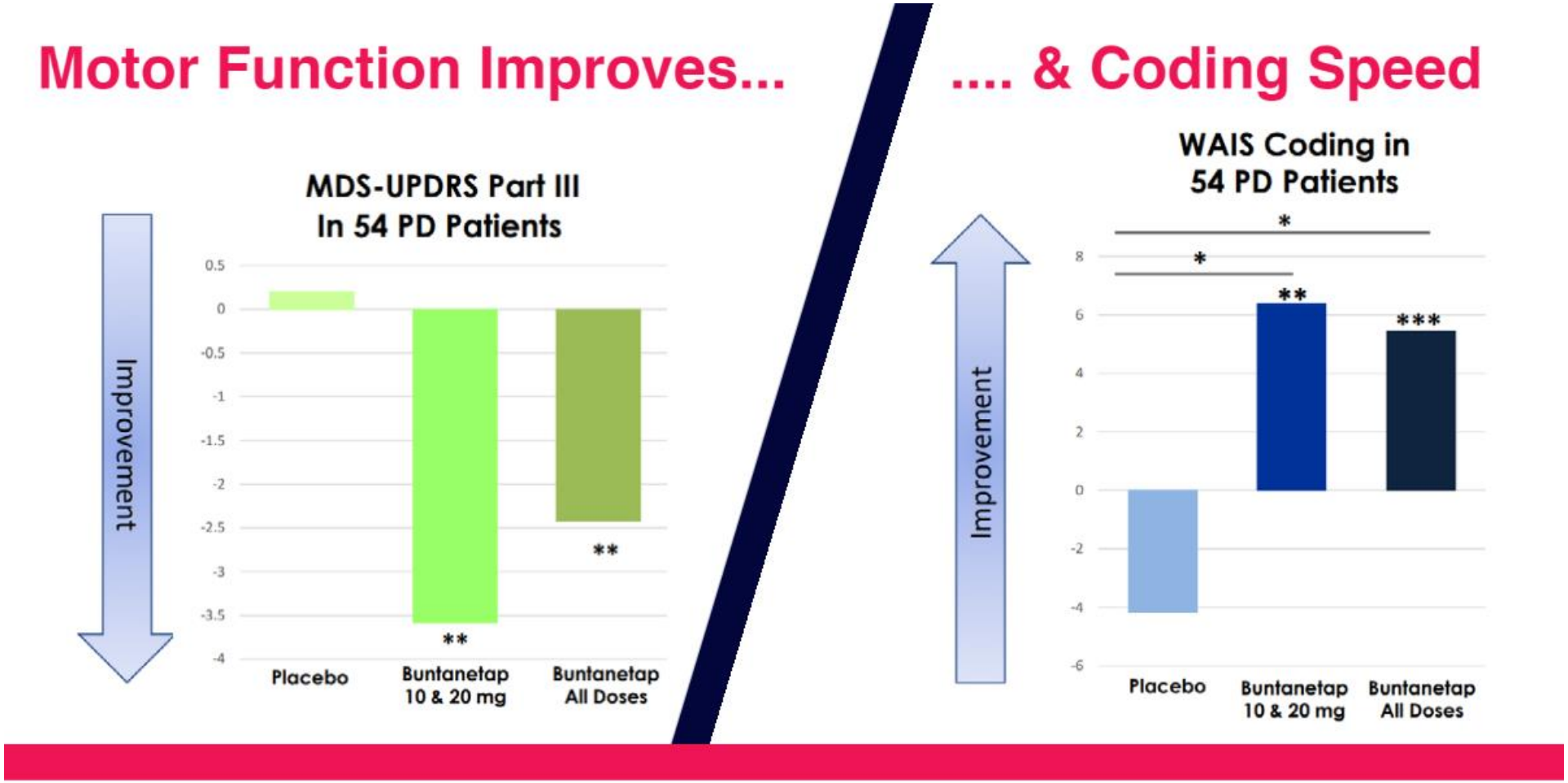


# STUDIES IN EIGHT ANIMAL AND HUMAN MODELS

| FUNCTION | TEST | SUBJECT |
|---|---|---|
| **ANIMALS** | | |
| Memory, learning | Mazes | AD mice, DS mice, stroke mice, TBI rats |
| Movement | Colonic motility, grip strength | PD mice, tau mice |
| Vision | Sight | Glaucoma rats |
| Infections | Cell death | P. Gingivalis mice, Covid mice |
| **HUMANS** | | |
| Cognition, memory, learning | ADAScog11 * | Early AD patients |
| Attention, thinking speed | WAIS coding ** | Early AD patients |
| Movement, coordination | MDS-UPDRS *** | Early PD patients |
| Movement speed | WAIS coding **** | Early PD patients |

# BUNTANETAP PHASE 2 POSITIVE DATA IN PARKINSON'S DISEASE

## SIGNIFICANT IMPROVEMENTS IN BOTH MOTOR FUNCTION AND CODING SPEED




* p > 0.05
** p > 0.01
*** p > 0.001

Fang et al: Buntanetap Proves Promising in Both Alzheimer's and Parkinson's Patients; J Prevention Alzheimer Disease 10-2022

# ONGOING PHASE 3 CLINICAL TRIAL IN **EARLY PD PATIENTS**

| Therapeutic Area | Early PD |
|---|---|
| **Phase** | 3 |
| **Sites** | 50 US + 50 EU = 100 |
| **Patients** | 3 X 150 = 450 |
| **Dose** | 0 , 10 and 20 mg/day |
| **Start** | August 2022 |
| **Design** | Double-Blind, Placebo-Controlled Efficacy |
| **Endpoints** | MDS-UPDRS 2 and 3 |
| **Other** | Total UPDRS, PGIC, CGIS, WAIS, Biomarkers |

NCT04524351 at ClinicalTrials.gov.

# INTERIM ANALYSIS 30% OF PATIENTS AT 2 MONTHS

## Possible outcomes

- MDS-UPDRS 2 + 3: increase, reduce or maintain the predicted number of patients
- MDS-UPDRS 2: is the predicted number adequate?
- MDS-UPDRS 3: is the predicted number adequate?

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

2 months
Interim Analysis
(expected in 2Q'23)

**Symptomatic Study**

**Early PD Patients**

6 months

**Disease-modifying Study**

**Long chronic study in early PD**

18 months

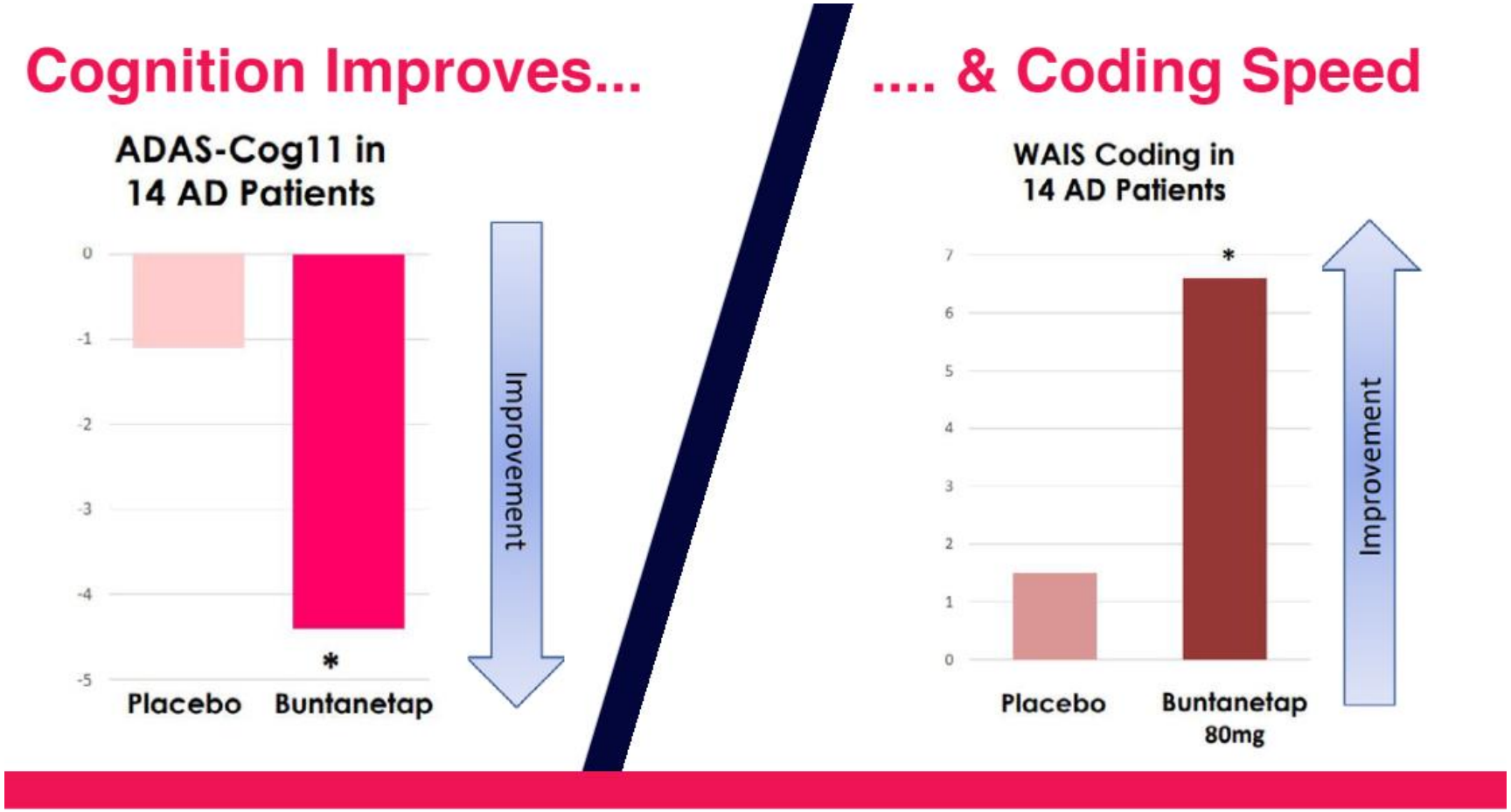
Basket study for advanced disease
1 month

**Advanced PD Patients**

6 months

# BUNTANETAP PHASE 2 POSITIVE DATA IN ALZHEIMER'S DISEASE

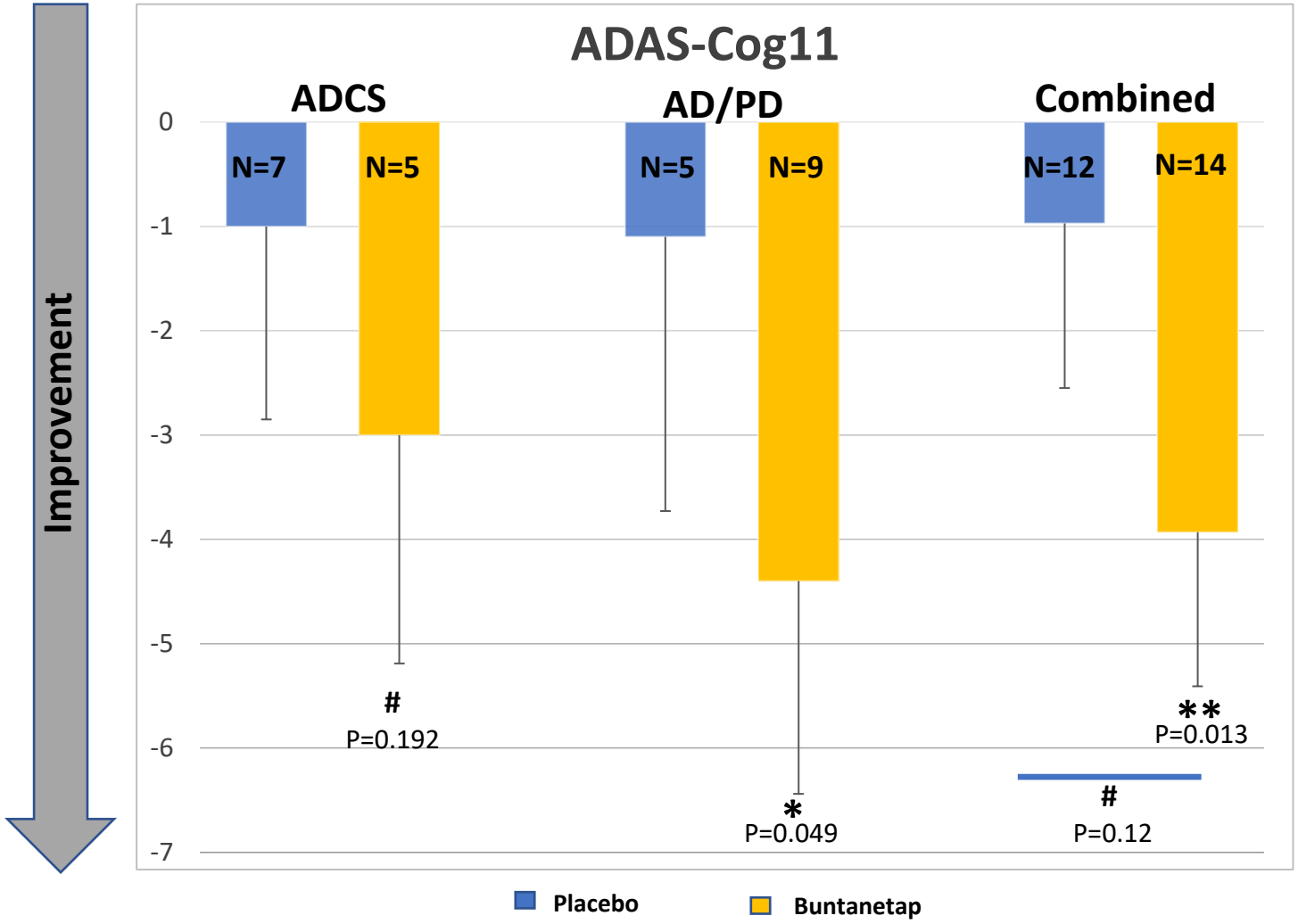
## SIGNIFICANT IMPROVEMENTS IN BOTH COGNITIVE FUNCTION AND CODING SPEED




* p > 0.05
** p > 0.01

Fang et al: Buntanetap Proves Promising in Both Alzheimer's and Parkinson's Patients; J Prevention Alzheimer Disease 10-2022

# EFFICACY IN TWO SMALL STUDIES – AD/PD AND ADCS




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

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

| Therapeutic Area | Moderate AD |
|---|---|
| **Phase** | 2/3 |
| **Sites** | 80 US |
| **Patients** | 4 X 80 = 320 |
| **Dose** | 0 , 7.5, 15 and 30 mg/day |
| **Start** | February 2023 |
| **Design** | Double-Blind, Placebo-Controlled Efficacy |
| **Endpoints** | ADAScog 11, ADCS-CGIC |
| **Other** | WAIS, Biomarkers |

# CLINICAL DEVELOPMENT PLANS FOR **ALZHEIMER'S DISEASE**

## Symptomatic Study

6 weeks
Interim Analysis
(expected in 3Q'23)

**Moderate AD**

3 months

End of phase 2 study meeting with FDA to discuss full development for disease-modifying studies

## Disease-modifying Study

**Long chronic study in early AD**

18 months

Basket study for advanced disease
1 month

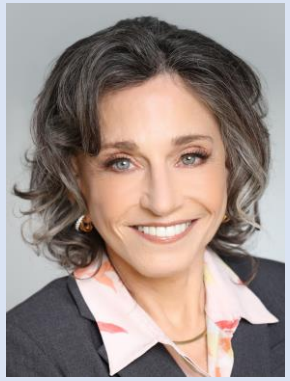
**Advanced AD**

6 months

# CORPORATE PATENT ESTATE


| Patent/Application | Subject Matter | Status | Expiry |
|---|---|---|---|
| Provisional | Combinations | Pending | **2044** |
| Provisional | Neuropsychiatric Indications | Pending | **2044** |
| Provisional | Other Diseases | Pending | **2043** |
| PCT | Brain infections | Pending | **2042** |
| PCT | Use of mechanism of action | One patent granted | **2038** |
| PCT | Acute neurodegenerative injuries | Multiple patents granted | **2036** |
| PCT | Chronic neurodegenerative diseases | Multiple patents granted | **2031** |

# SENIOR MANAGEMENT TEAM



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

**Michael Christie, PhD**
**VP, Process Chemistry**

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

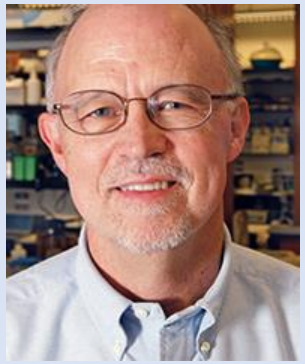
**Henry Hagopian, MBA**
**Chief Financial Officer**

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

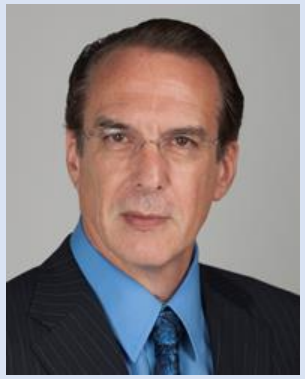
**Melissa Gaines,**
**VP, Clinical Operations**

**David Prohaska**
**VP, Tox & Pharmocol**

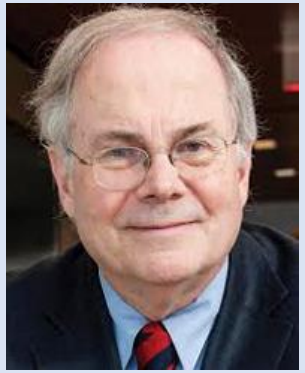
# SCIENTIFIC ADVISORY BOARD



**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.



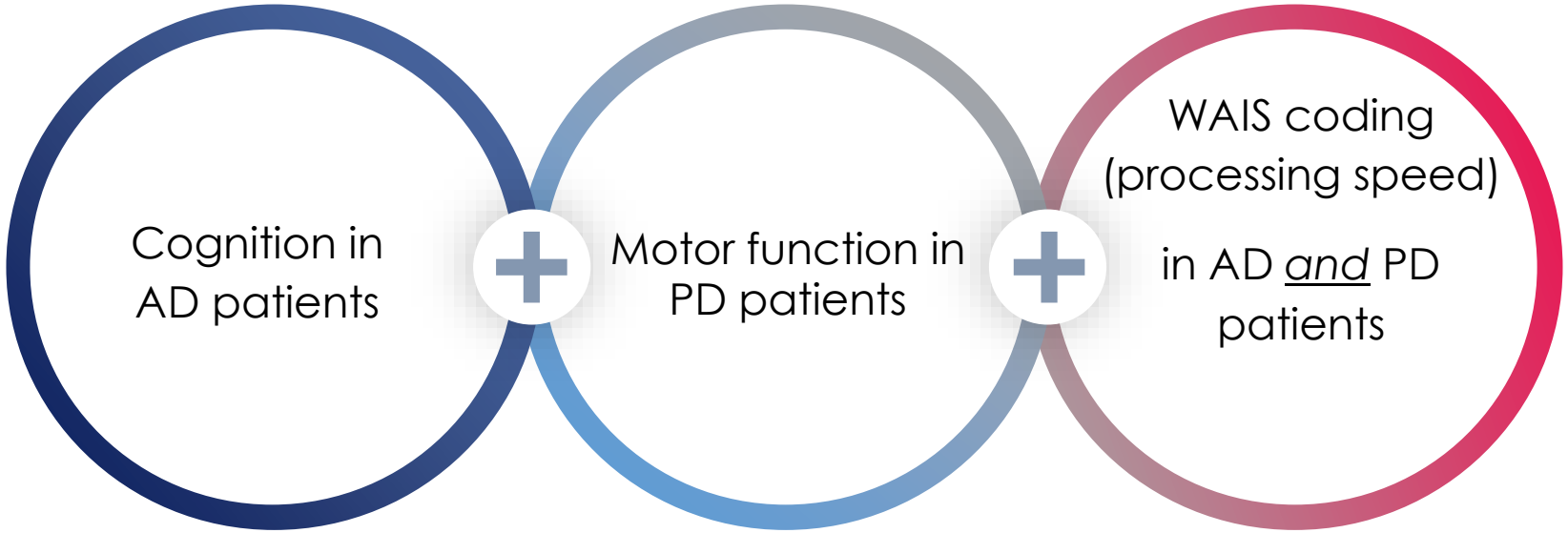
**Gregory Petsko, PhD**
Dr. Petsko is a member of the National Academy of Sciences, the National Academy of Medicine, the American Academy of Arts and Sciences and the American Philosophical Society. His research interests are directed towards understanding the biochemical bases of neurological diseases 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**

ANNOVIS

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

Symbol: **ANVS** (NYSE)

# CONTACT US

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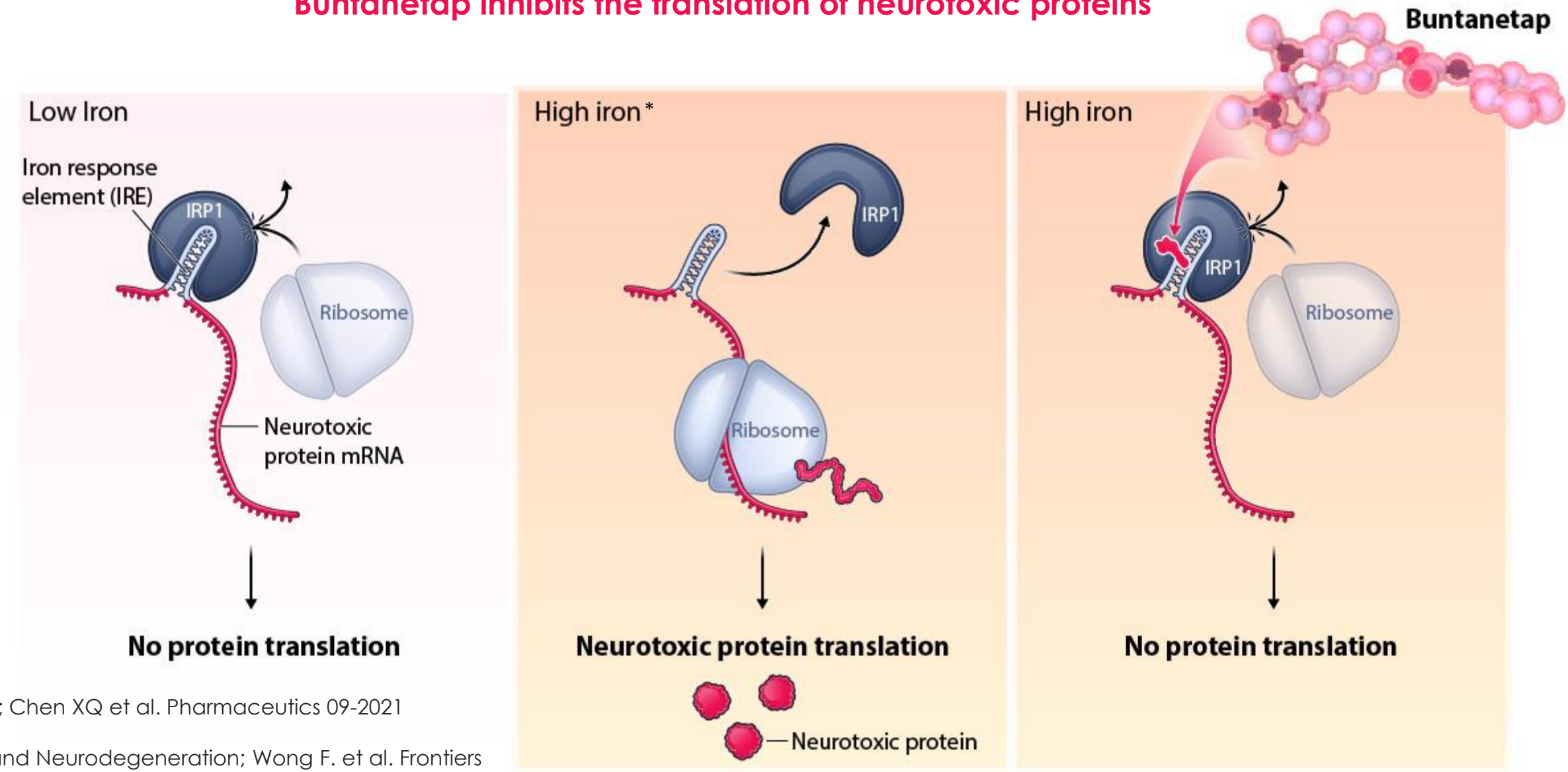
**www.annovisbio.com**

# Appendix

# MECHANISM OF ACTION

**Buntanetap inhibits the translation of neurotoxic proteins**

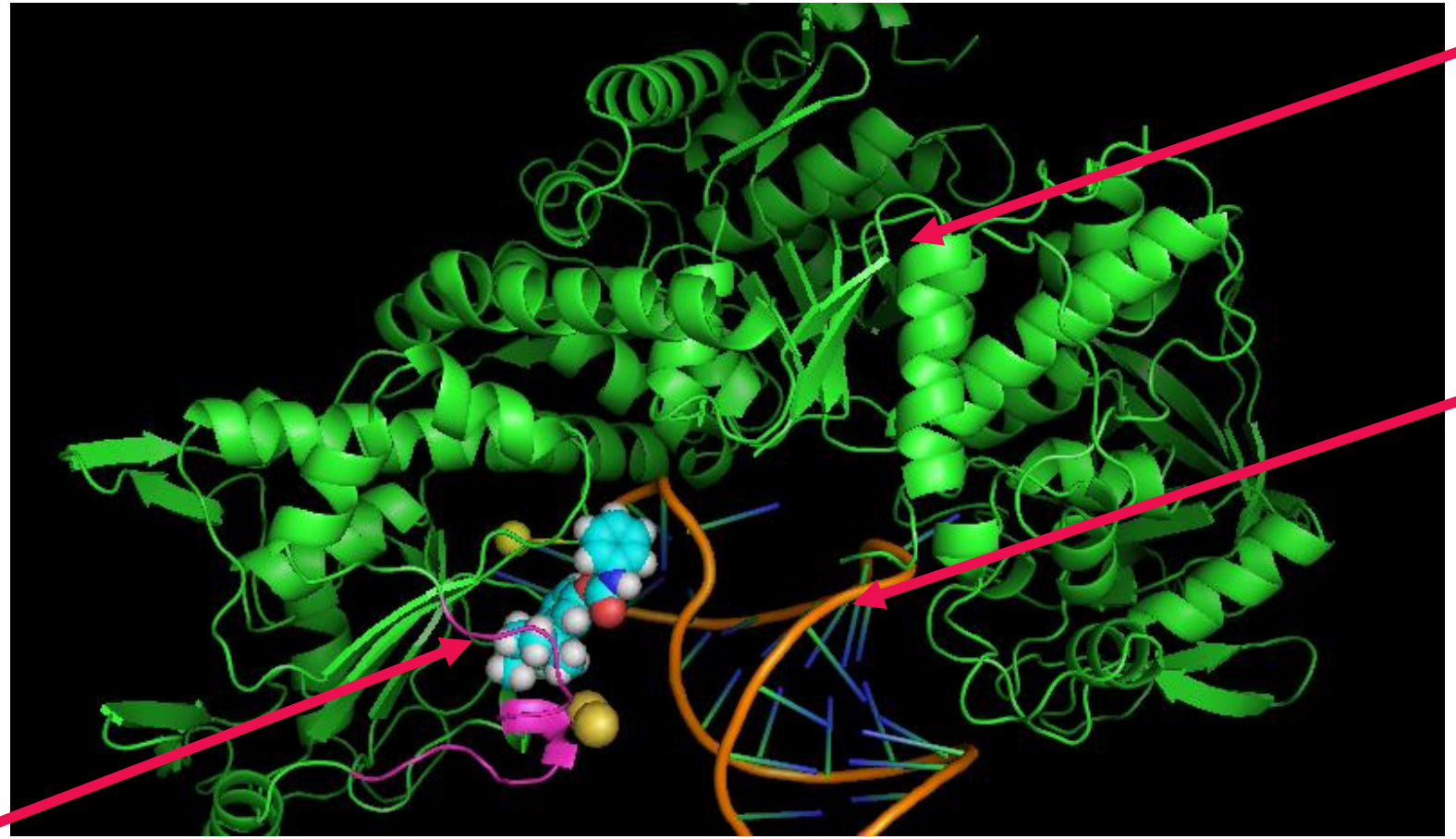


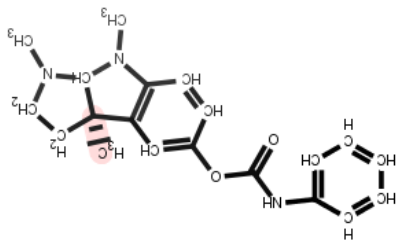

MOA; Chen XQ et al. Pharmaceutics 09-2021

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**

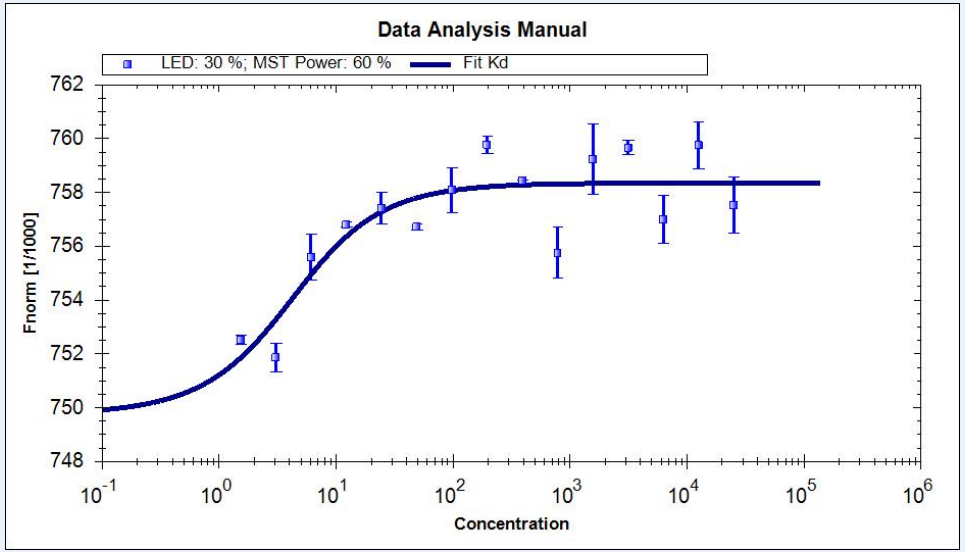


**Buntanetap**

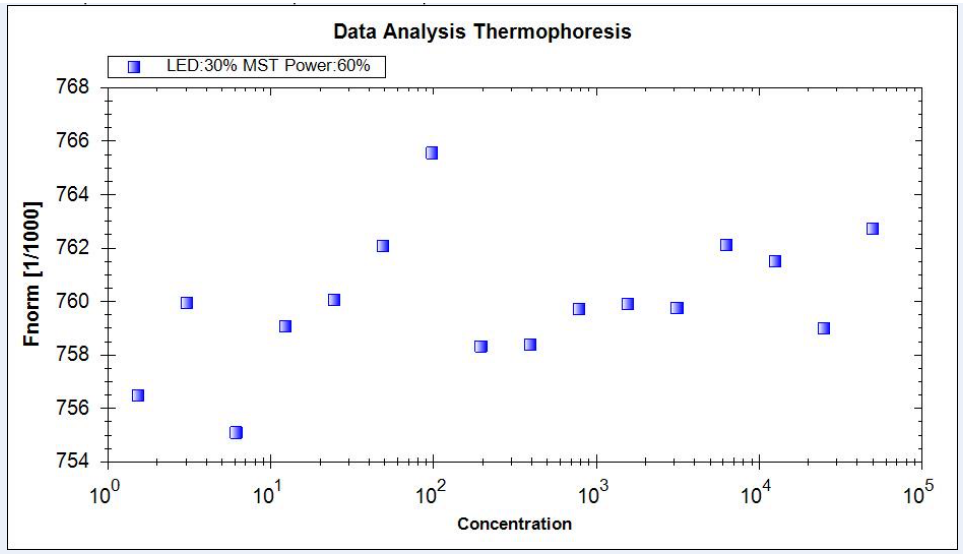
Eric Baldwin, NCI

# 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 | |
| Dissociation Constant | 3.22+/-0.464 |
| Fluo.Conc | 2 |
| Bound | 758.35 |
| Unbound | 749.76 |
| Amplitude | 8.59 |

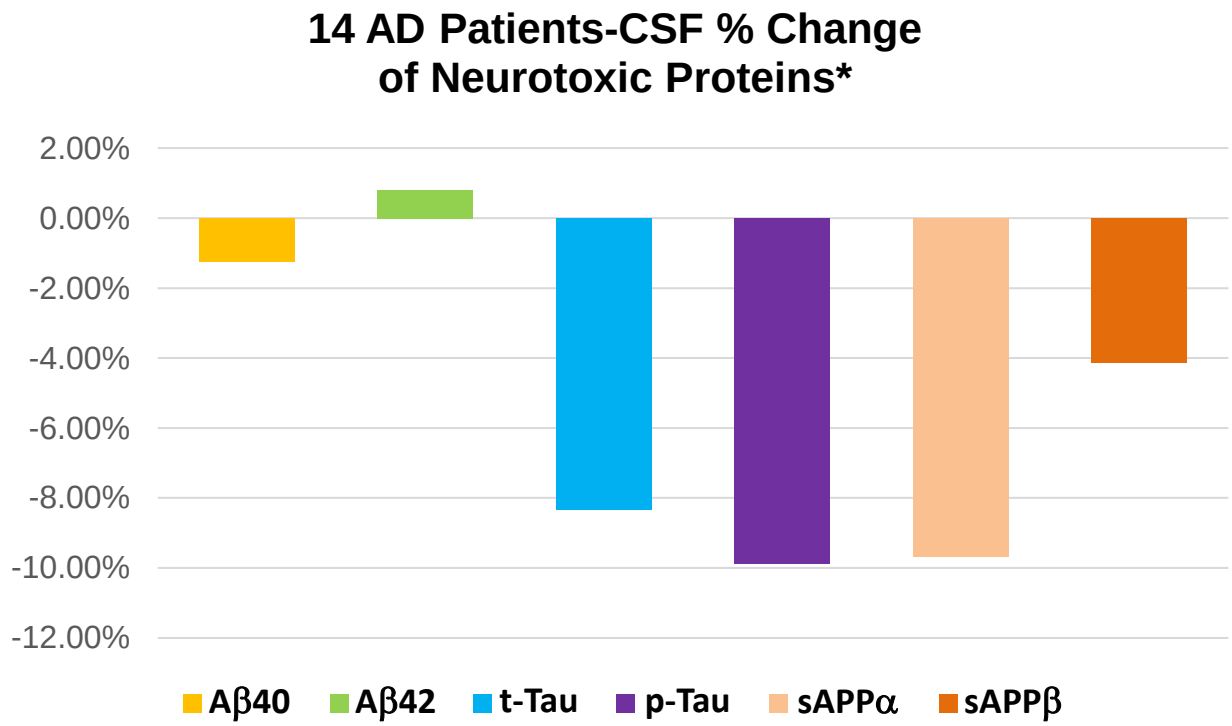


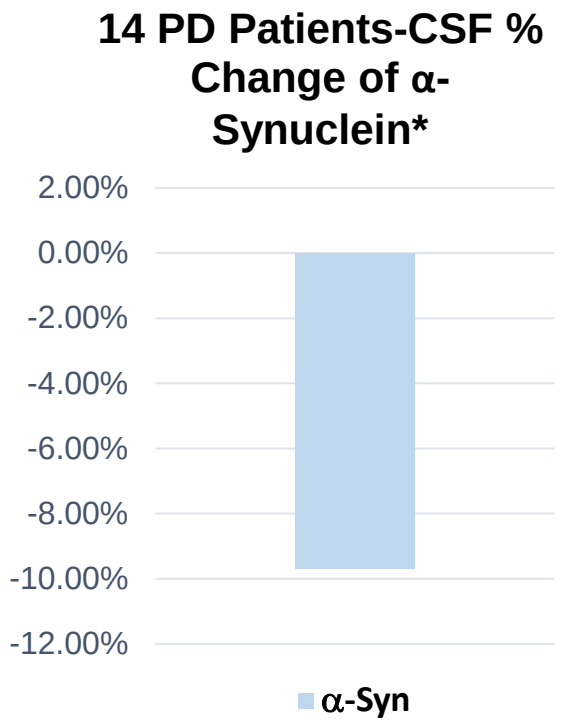

***Ferritin IRE/IRP1/Buntanetap***
***No Kd***

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

Chen XQ et al, *Pharmaceutics* **2021**, *13*(12), 2109

# REDUCED NEUROTOXIC PROTEINS IN BOTH AD AND PD PATIENTS



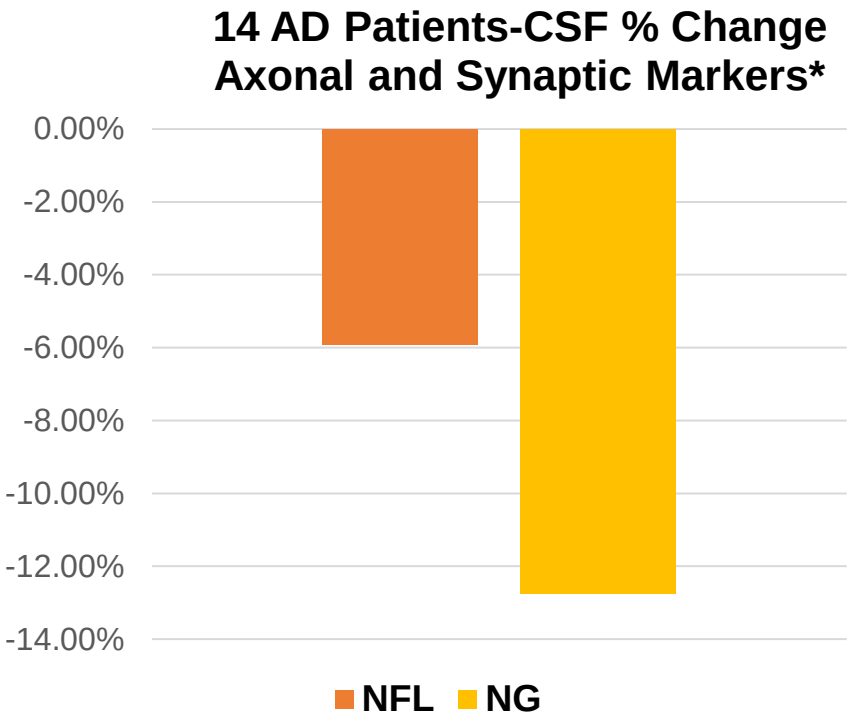

APP (and its downstream products), and p-Tau are the neurotoxic proteins involved in AD, while α-Synuclein is the neurotoxic culprit of PD. The reduction compares well to the reduction seen in animals at full efficacy.

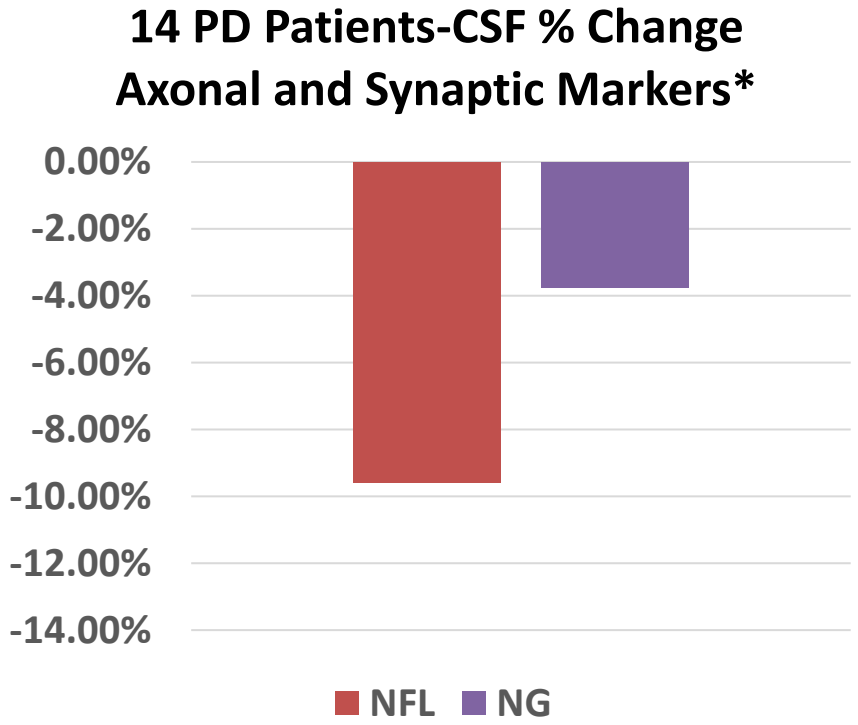
*All values are in comparison to placebo based on all data points



ANNOVIS

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

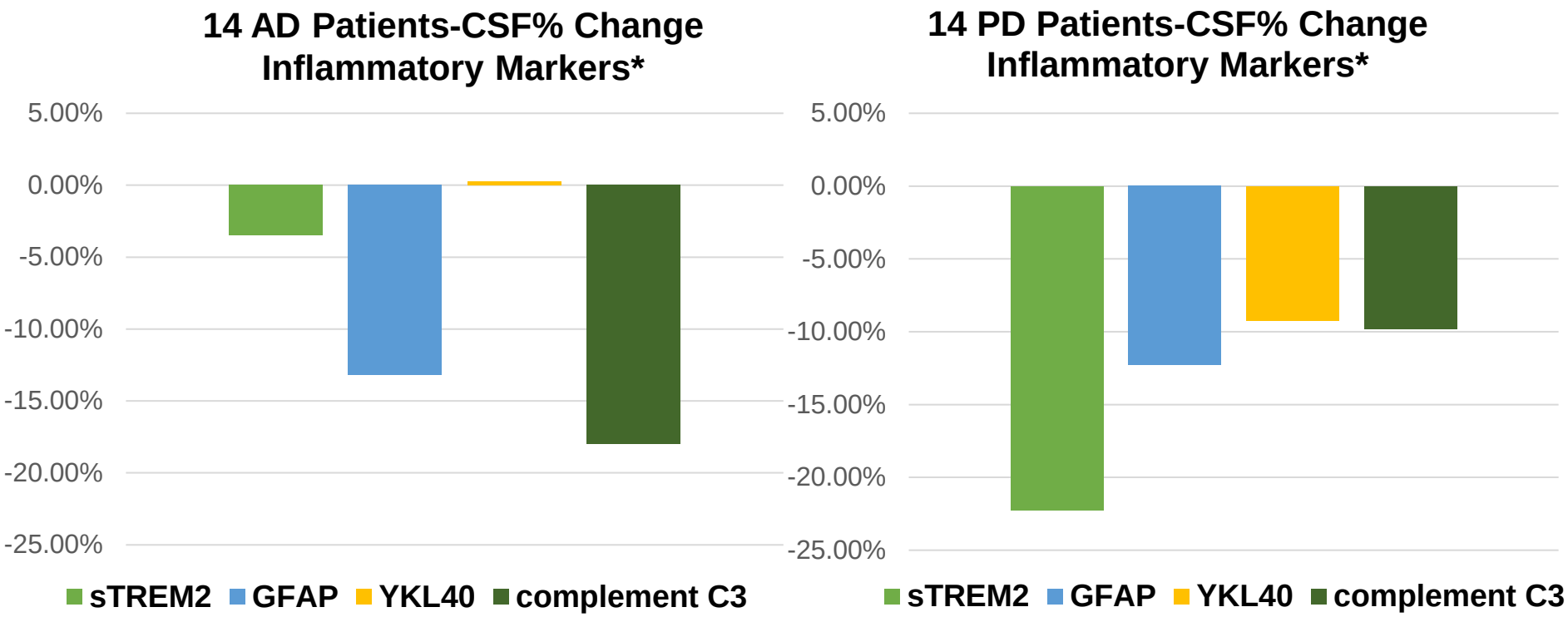



Neuronal and synaptic markers are lowered in AD and in PD patients, showing that the nerve cells are healthier.

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

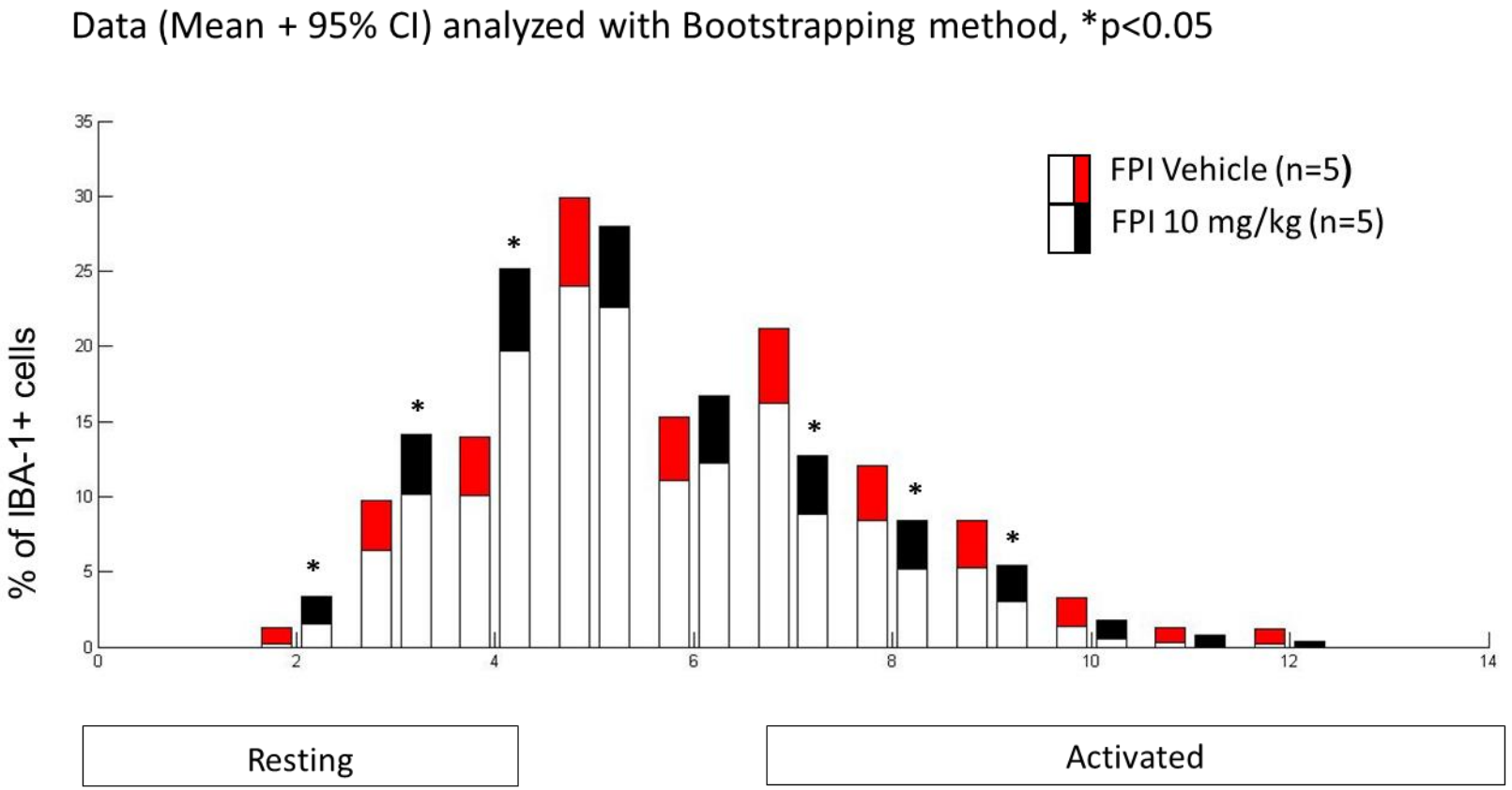
# REDUCED INFLAMMATION IN BOTH AD AND PD PATIENTS




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

# **INHIBITS MICROGLIA** ACTIVATION IN RAT BRAIN




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

*UCLA, Marie-Francoise Chesselet and David Hovda's lab*