Alzheimer's Disease Research Portfolio

Dominic Walsh, Ph.D., Head of the Neurodegeneration Research Unit

R&D Day
September 21, 2021

Biogen

Forward-looking statements

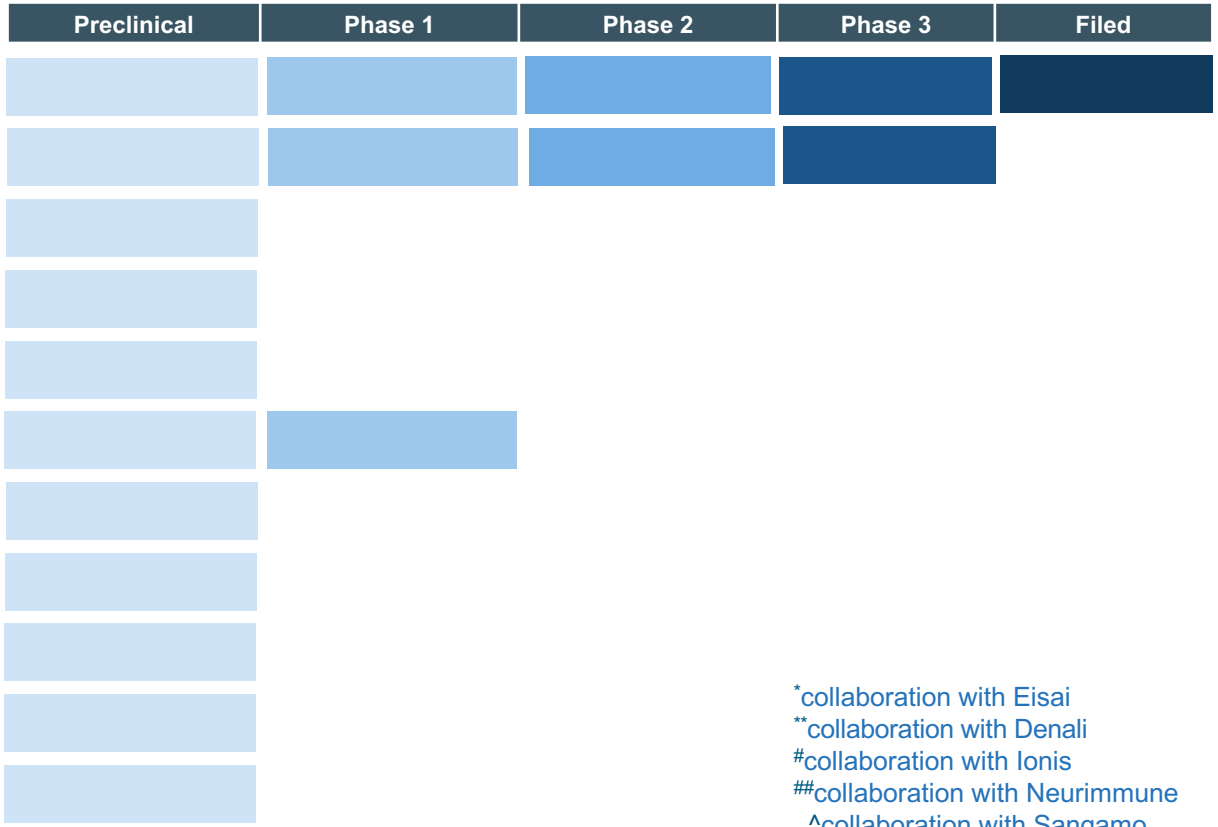
This presentation contains forward-looking statements, including statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, relating to: our strategy and plans; potential of, and expectations for, our commercial business and pipeline programs; capital allocation and investment strategy; clinical development programs, clinical trials, and data readouts and presentations; risks and uncertainties associated with drug development and commercialization; regulatory discussions, submissions, filings, and approvals and the timing thereof; the potential benefits, safety, and efficacy of our and our collaboration partners' products and investigational therapies; the anticipated benefits and potential of investments, collaborations, and business development activities; and our future financial and operating results; 2021 financial guidance. These forward-looking statements may be accompanied by such words as "aim," "anticipate," "believe," "could," "estimate," "expect," "forecast," "goal," "intend," "may," "plan," "potential," "possible," "prospect," "will," "would," and other words and terms of similar meaning. Drug development and commercialization involve a high degree of risk, and only a small number of research and development programs result in commercialization of a product. Results in early-stage clinical trials may not be indicative of full results or results from later stage or larger scale clinical trials and do not ensure regulatory approval. You should not place undue reliance on these statements or the scientific data presented.

These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including: our dependence on sales from our products; uncertainty of long-term success in developing, licensing, or acquiring other product candidates or additional indications for existing products; failure to compete effectively due to significant product competition in the markets for our products; failure to successfully execute or realize the anticipated benefits of our strategic and growth initiatives; difficulties in obtaining and maintaining adequate coverage, pricing, and reimbursement for our products; our dependence on collaborators, joint venture partners, and other third parties for the development, regulatory approval, and commercialization of products and other aspects of our business, which are outside of our full control; risks associated with current and potential future healthcare reforms; risks related to commercialization of biosimilars; failure to obtain, protect, and enforce our data, intellectual property, and other proprietary rights and the risks and uncertainties relating to intellectual property claims and challenges; the risk that positive results in a clinical trial may not be replicated in subsequent or confirmatory trials or success in early stage clinical trials may not be predictive of results in later stage or large scale clinical trials or trials in other potential indications; risks associated with clinical trials, including our ability to adequately manage clinical activities, unexpected concerns that may arise from additional data or analysis obtained during clinical trials, regulatory authorities may require additional information or further studies, or may fail to approve or may delay approval of our drug candidates; the occurrence of adverse safety events, restrictions on use with our products, or product liability claims; risks relating to the distribution and sale by third parties of counterfeit or unfit versions of our products; risks relating to the use of social media for our business; risks relating to technology failures or breaches; risks relating to management and key personnel changes, including attracting and retaining key personnel; failure to comply with legal and regulatory requirements; the risks of doing business internationally, including currency exchange rate fluctuations; risks relating to investment in our manufacturing capacity; problems with our manufacturing processes; fluctuations in our effective tax rate; the direct and indirect impacts of the ongoing COVID-19 pandemic on our business, results of operations, and financial condition; fluctuations in our operating results; risks related to investment in properties; the market, interest, and credit risks associated with our investment portfolio; risks relating to share repurchase programs; risks relating to access to capital and credit markets; risks related to indebtedness; change in control provisions in certain of our collaboration agreements; environmental risks; and any other risks and uncertainties that are described in other reports we have filed with the U.S. Securities and Exchange Commission (SEC).

These statements are based on our current beliefs and expectations and speak only as of the date of this presentation. We do not undertake any obligation to publicly update any forward-looking statements.

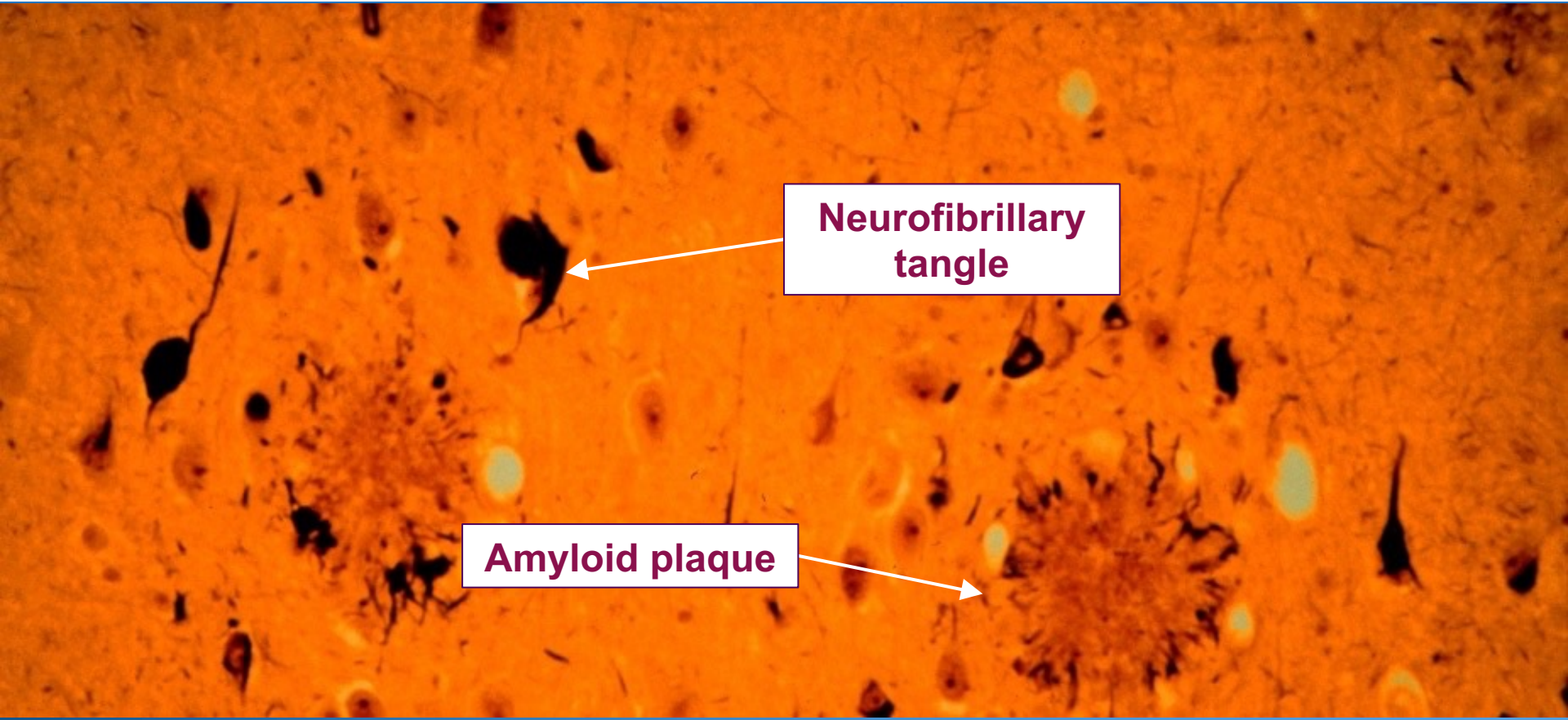
Biogen has an industry leading Alzheimer's disease portfolio

Target	Program	Modality
Amyloid-β	Aducanumab (ADUHELM™)*	mAb
	Lecanemab/BAN2401*	mAb
	Undisclosed asset	-
	Undisclosed assets	mAb
	ATV-Amyloid-β**	mAb
Tau	BIIB080#	ASO
	BIIB076##	mAb
	Undisclosed assets	Small molecule
	AAV-ZFP-MAPT^	GTx
Genetically defined populations and genetically linked targets	Undisclosed assets	mAb
	Undisclosed asset	Small molecule



*collaboration with Eisai
**collaboration with Denali
#collaboration with Ionis
##collaboration with Neurimmune
^collaboration with Sangamo

The defining pathology of Alzheimer's disease



The amyloid cascade hypothesis – a molecular roadmap for AD drug development

Mutations in *APP*

AD is common in trisomy 21

Duplication of *APP*

Mutations in *PSEN1* and *PSEN2*

***APP* is a GWAS risk loci for late-onset AD**

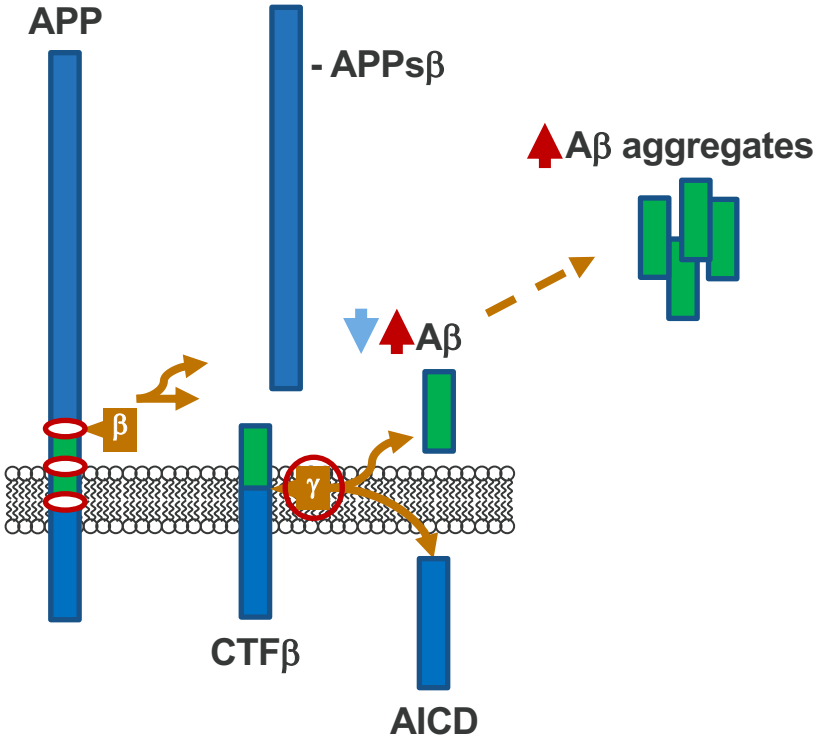
Many GWAS risk factors effect Aβ accumulation

Protective *APP* (A673T) SNP

PET natural history studies link amyloid to tau spread beyond the medial temporal lobe

Amyloid reducing agents reduce CSF tau/ptau

***in vivo* and *in vitro* experiments link Aβ to pathogenic changes in tau**



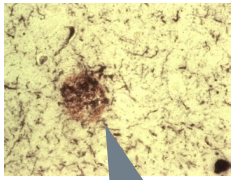
Aβ = amyloid beta; AD = Alzheimer's disease; AICD = APP intracellular domain; APP = amyloid precursor protein; APPsβ = beta-cleaved secreted APP; CTFβ = beta-cleaved C-terminal fragment; GWAS = genome wide association study; PET = positron emission tomography; PSEN = presenilin; SNP = single nucleotide polymorphism

The amyloid cascade hypothesis – a molecular roadmap for Alzheimer's disease drug development

Increased Aβ levels

Aβ oligomerization/aggregation

Aβ deposits leading to plaques formation



Plaques

Subtle effects of Aβ on synapses

Microglia activation cytokines & chemokines

Progressive synaptic and neuritic injury

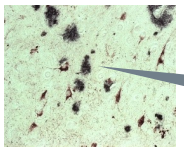
Altered neuronal homeostasis alter kinase/phosphates activities

tau hyper-phosphorylation/ aggregation

PHF

Loss of neurons

Alzheimer's disease



Tangles

Lipid Dyshomeostasis

Neuroinflammation

Vascular dysfunction

Metabolic stress

PHF = paired helical filaments

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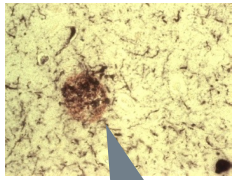

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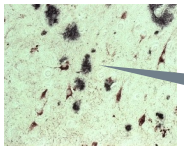

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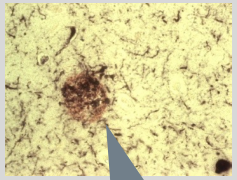

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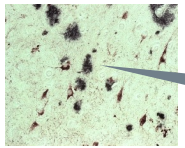


Tangles

Loss of neurons

Alzheimer's disease

Anti-Aβ

Alzheimer's Disease Research Priorities

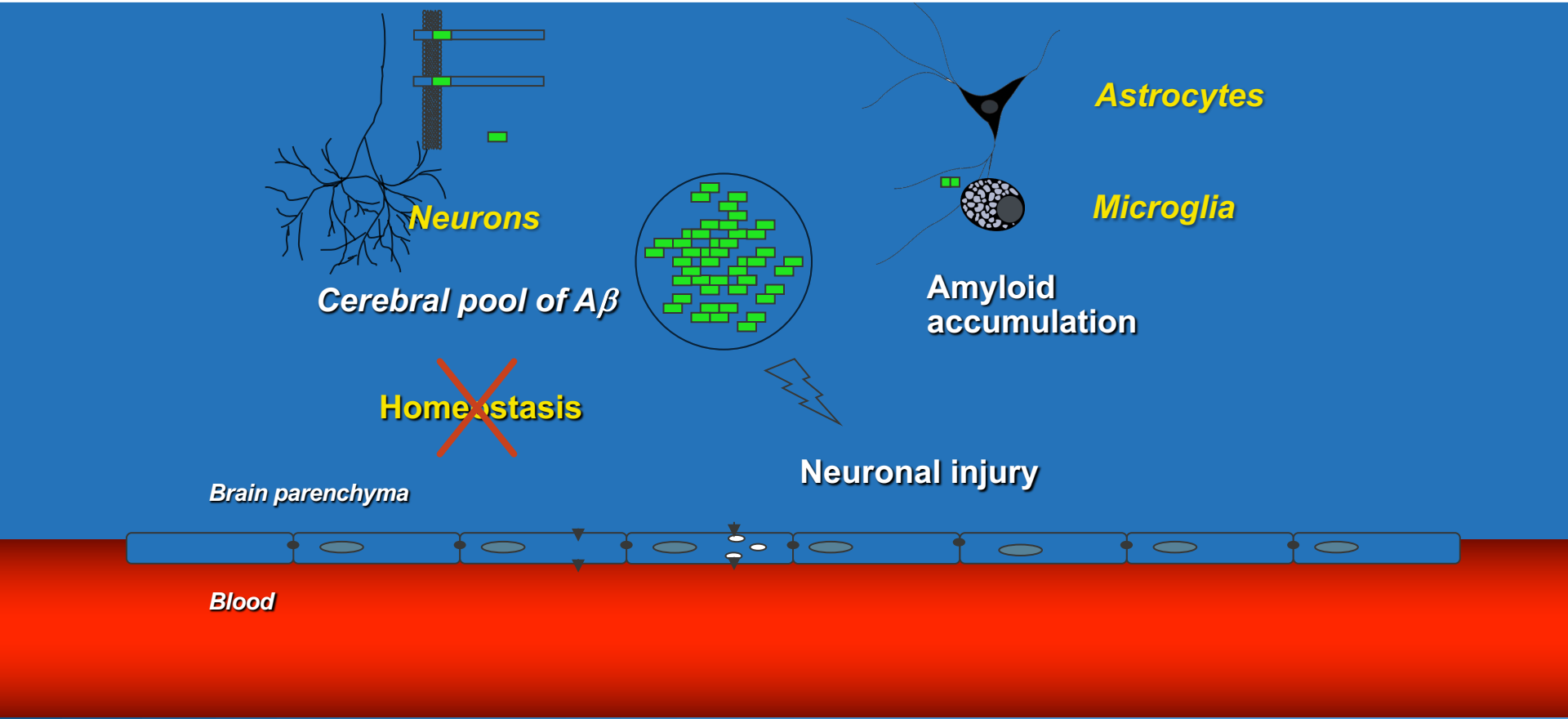
01 Advance next generation anti-Aβ therapies

02 Grow tau pipeline

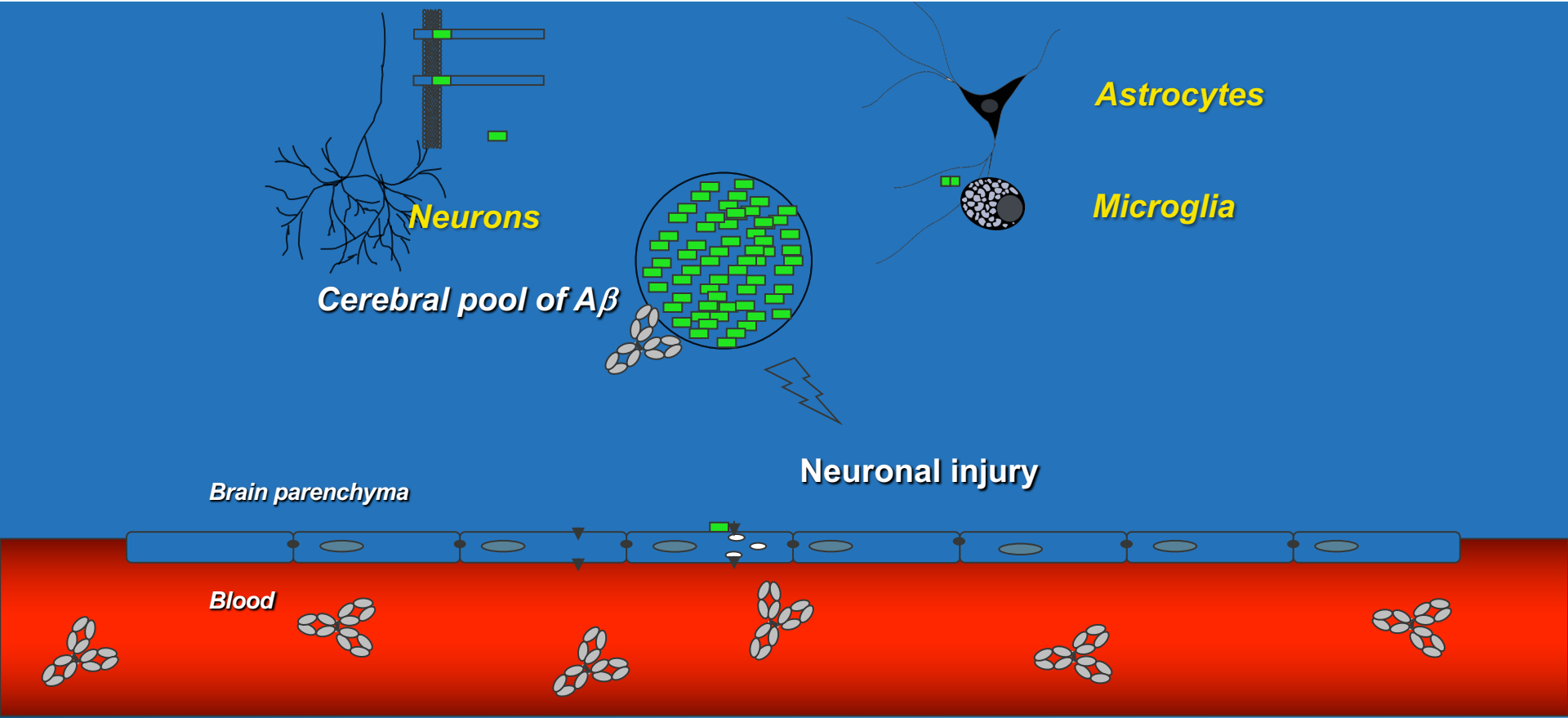
03 Progress drug discovery on genetic targets

04 Enable development of combination therapies

Aggregated Aβ mediates dysfunction



Aβ immunotherapy using aggregate-preferring mAbs



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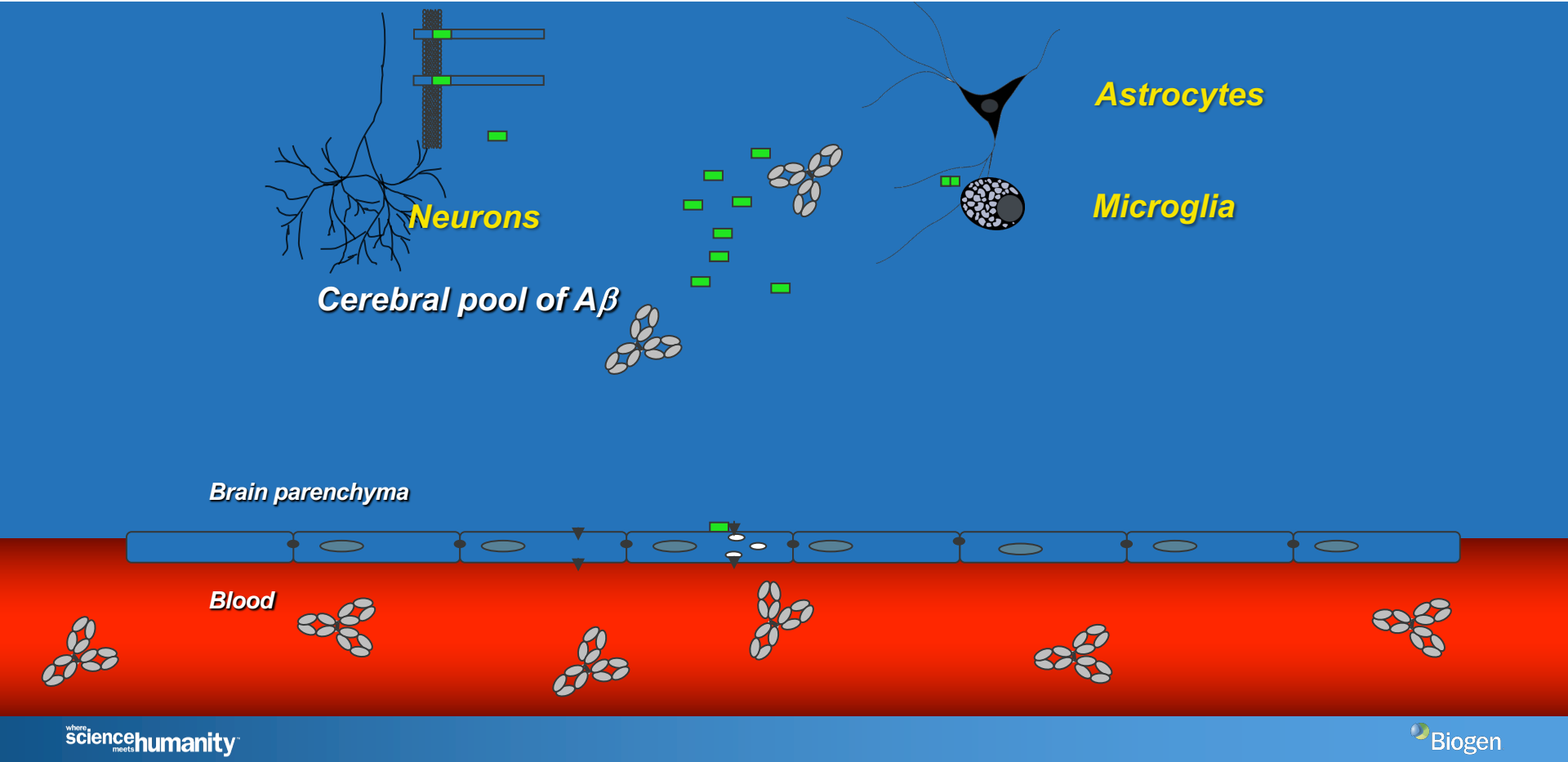
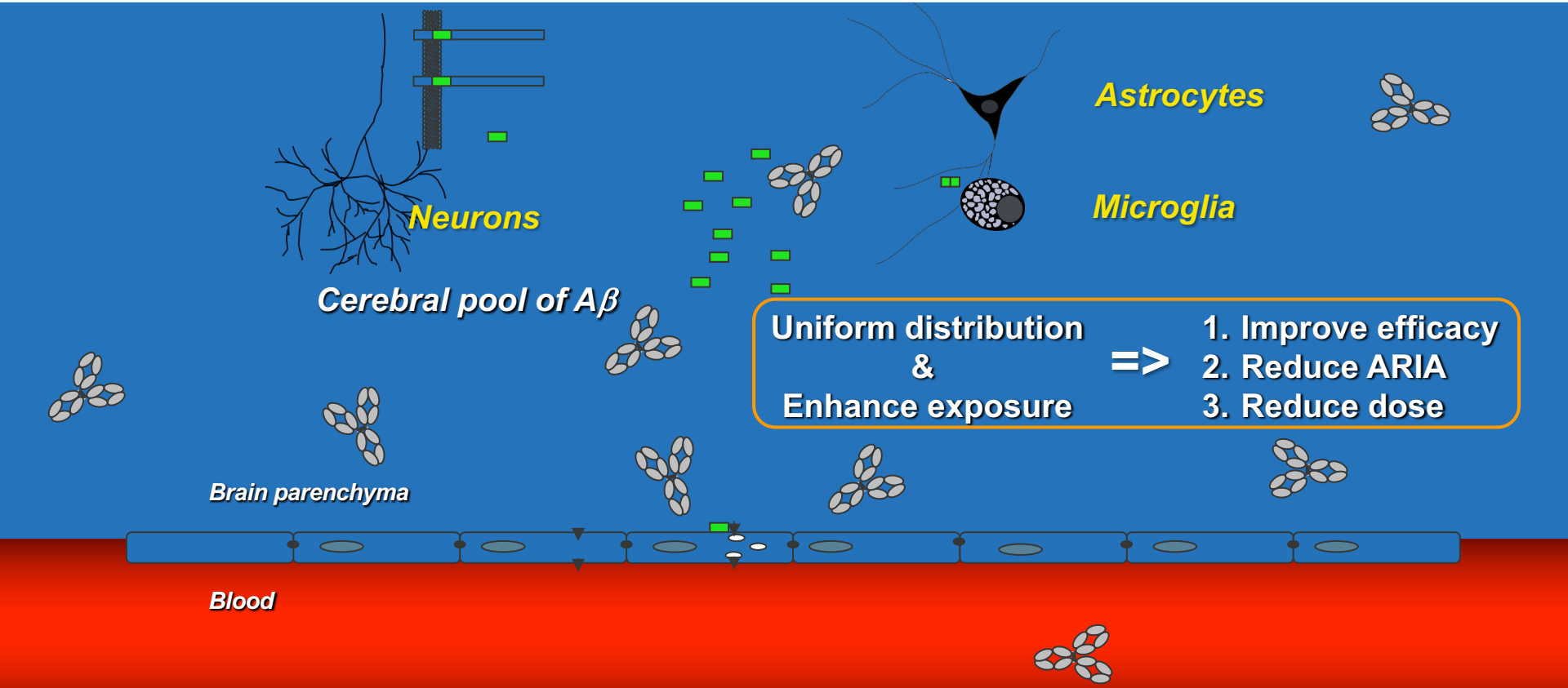
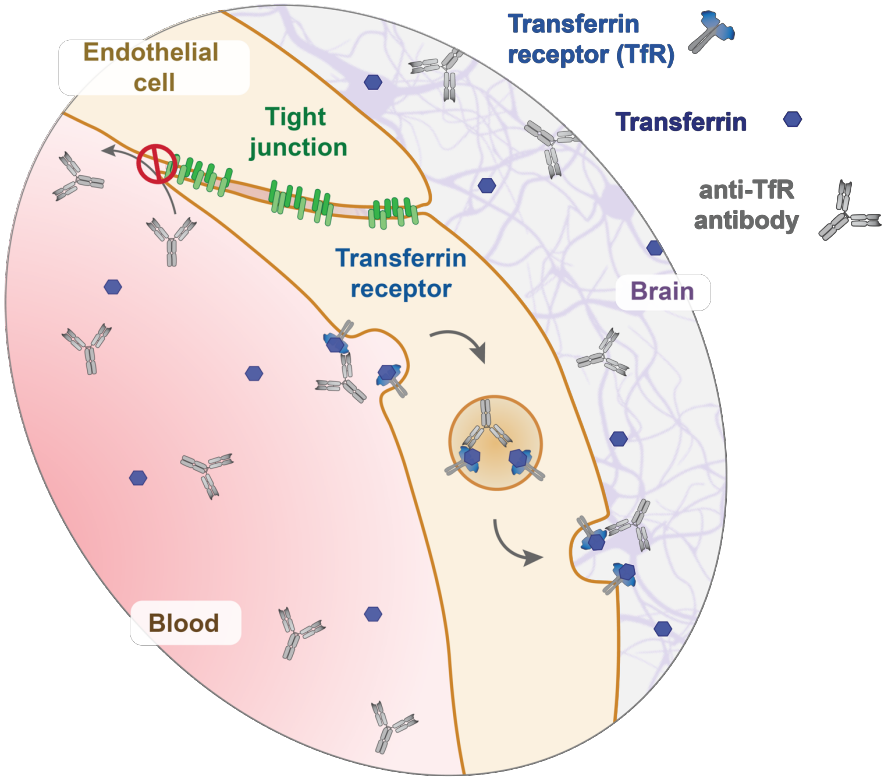


Next generation anti-Aβ immunotherapy



ARIA = amyloid-related imaging abnormalities

Increasing brain exposure by targeting transferrin receptor



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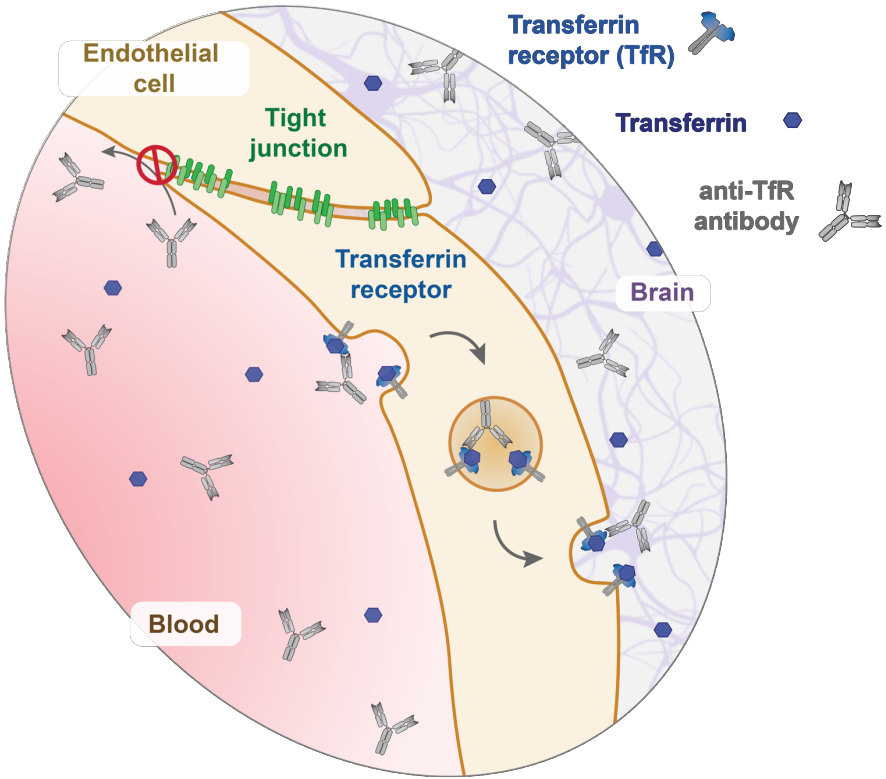


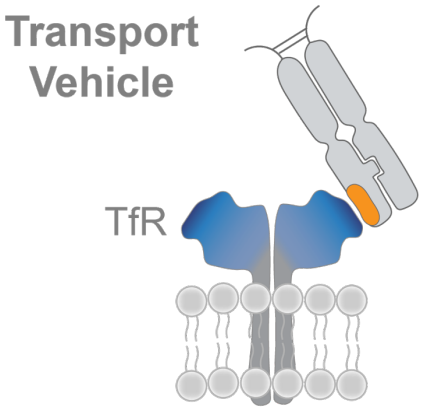
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

Published May 27, 2020

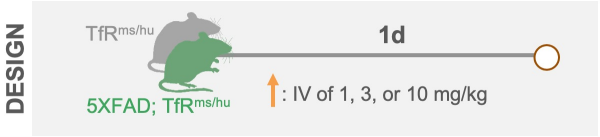
BLOOD-BRAIN BARRIER

Brain delivery of therapeutic proteins using an Fc fragment blood-brain barrier transport vehicle in mice and monkeys

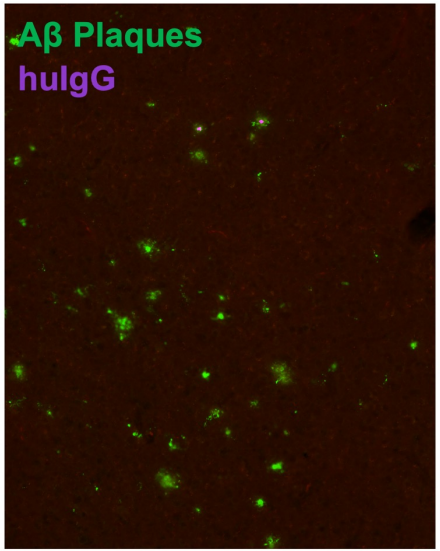
Mihalis S. Kariolis*†, Robert C. Wells†, Jennifer A. Getz, Wanda Kwan, Cathal S. Mahon, Raymond Tong, Do Jin Kim, Ankita Srivastava, Catherine Bedard, Kirk R. Henne, Tina Giese, Victoria A. Assimon, Xiaocheng Chen, Yin Zhang, Hilda Solanoy, Katherine Jenkins, Pascal E. Sanchez, Lesley Kane, Takashi Miyamoto, Kylie S. Chew, Michelle E. Pizzo, Nicholas Liang, Meredith E. K. Calvert, Sarah L. DeVos, Sulochanadevi Baskaran, Sejal Hall‡, Zachary K. Sweeney, Robert G. Thorne, Ryan J. Watts, Mark S. Dennis, Adam P. Silverman†, Y. Joy Yu Zuchero*†



ATV:Aβ shows increased binding to plaques



Anti-Aβ (10 mpk)



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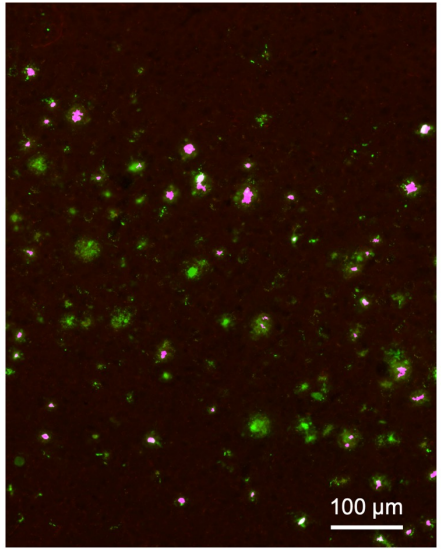
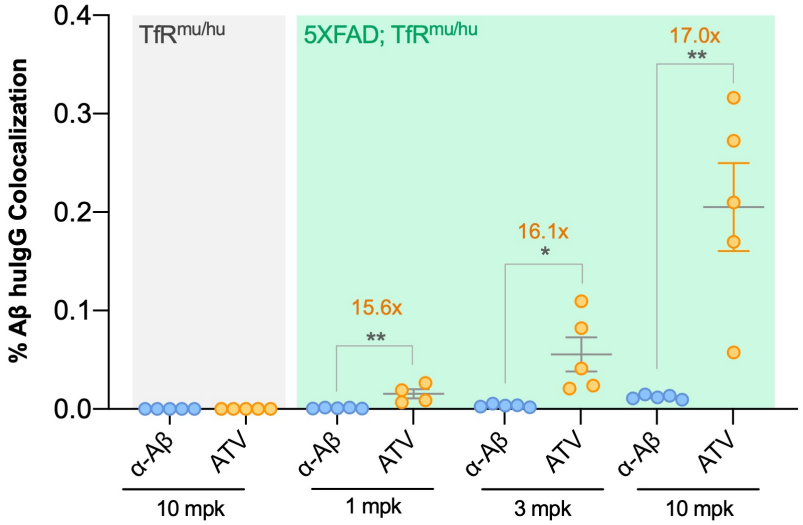


Aβ + huIgG Colocalization



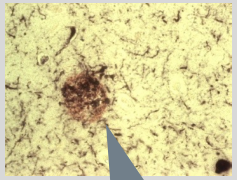
ATV = antibody transport vehicle; huIgG = human IgG

Beyond anti-Aβ

Increased Aβ levels

Aβ oligomerization/aggregation

Aβ deposits leading to plaques formation



Plaques

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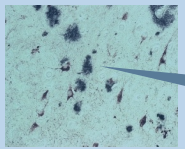
Alzheimer's disease

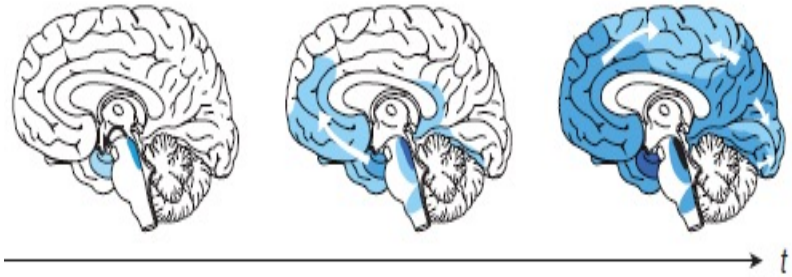


Tangles

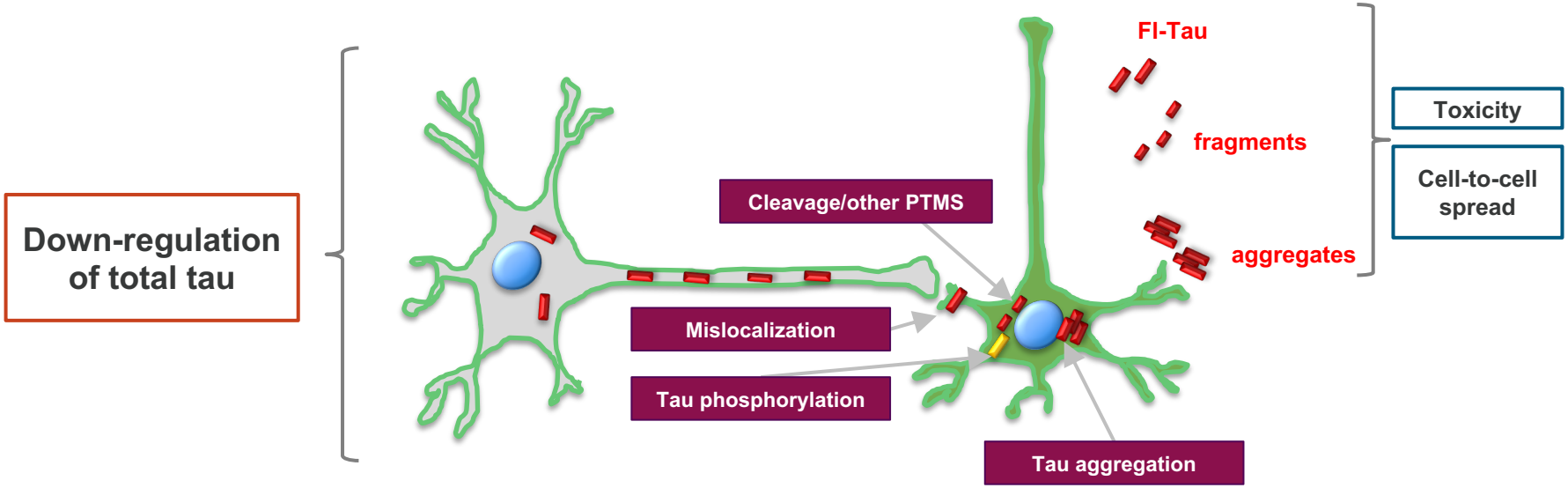
Anti-Aβ

Anti-tau

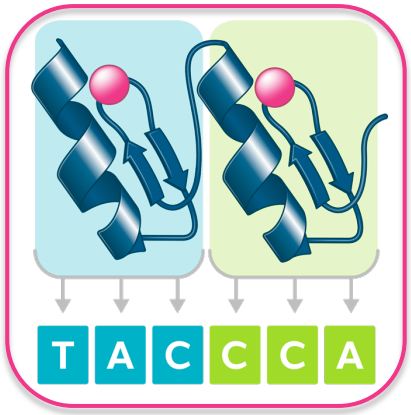
Human biology supports a central role for tau in Alzheimer's disease, but which forms of tau and mechanism by which they contribute to pathogenesis are unknown



Adapted from Braak & Braak 1997 *NBA*



Gene Targeting via Zinc Finger DNA-binding proteins



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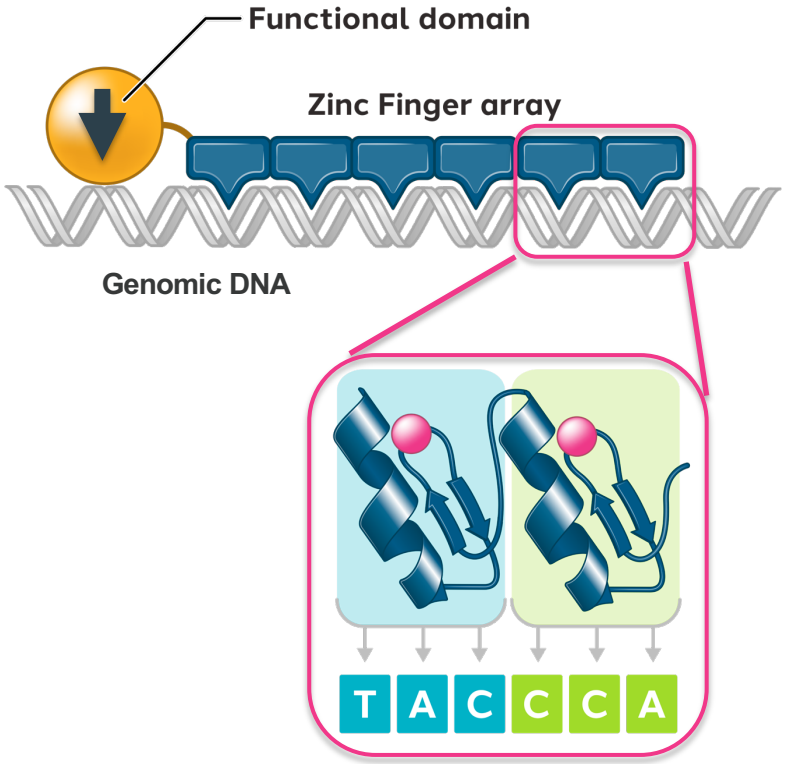

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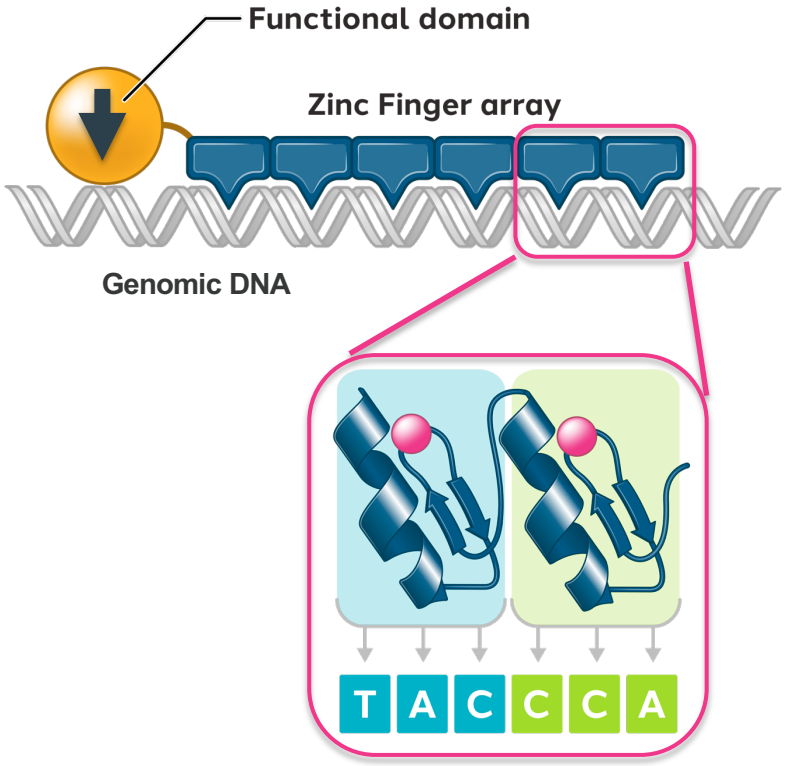
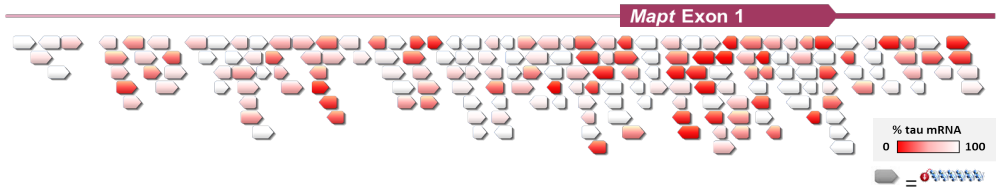


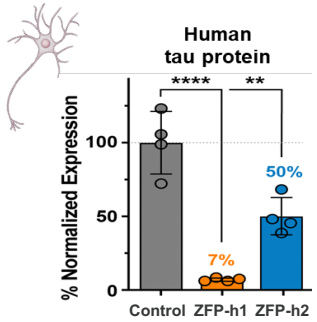
- **Human origin** – ZFP and KRAB derived from human genes
- **Versatile & customizable** – multiple functionalities
- **High-resolution targeting** – genome-wide coverage
- **Exquisite specificity** – tunable DNA:protein interface
- **Compact** – easily packaged into AAV and excellent accessibility to genomic DNA

ZFP-TFs demonstrated target engagement and pharmacodynamic effect in hTau mice and non-human primates

Identified optimal candidate by screening hundreds of ZFP-TFs

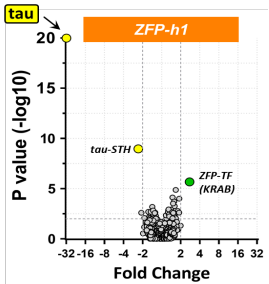


Potent and highly specific in human iPSC neurons

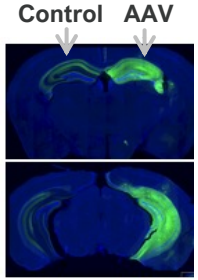


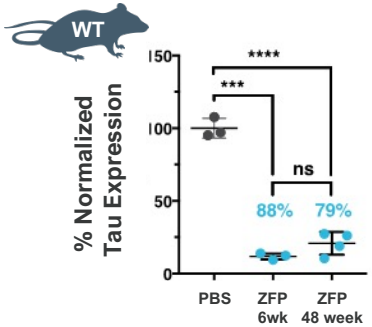
Global specificity

N=19,959 transcripts evaluated

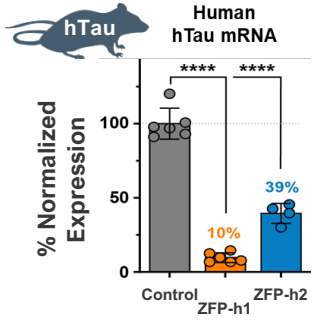


Durable repression





Tunable repression levels



Wegmann, Devos, Zeitler et al. *Science Advances*, 2021

AAV = adeno-associated virus; iPSC = induced pluripotent stem cells; WT = wild type; ZFP-TF = zinc finger protein transcription factor

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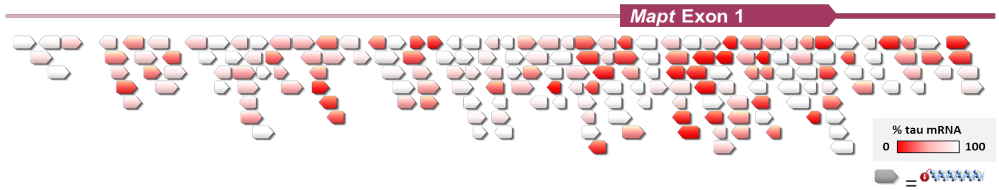

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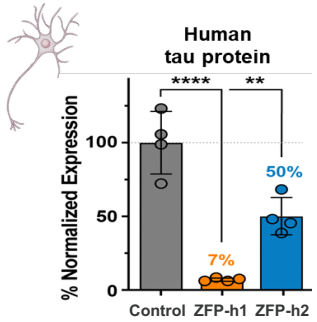

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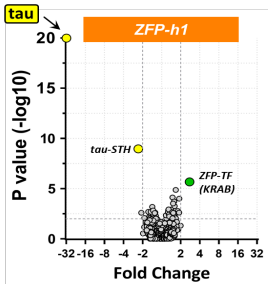

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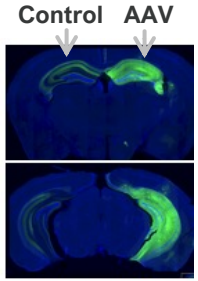

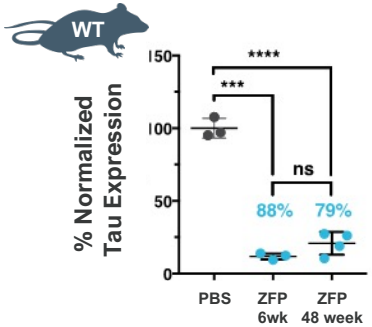

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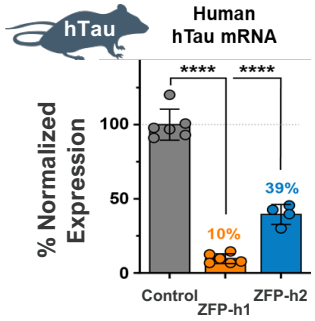

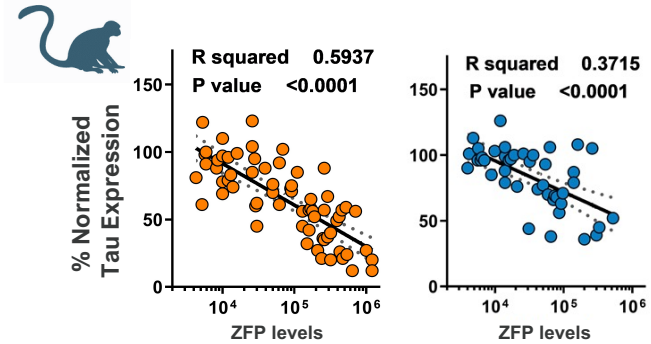

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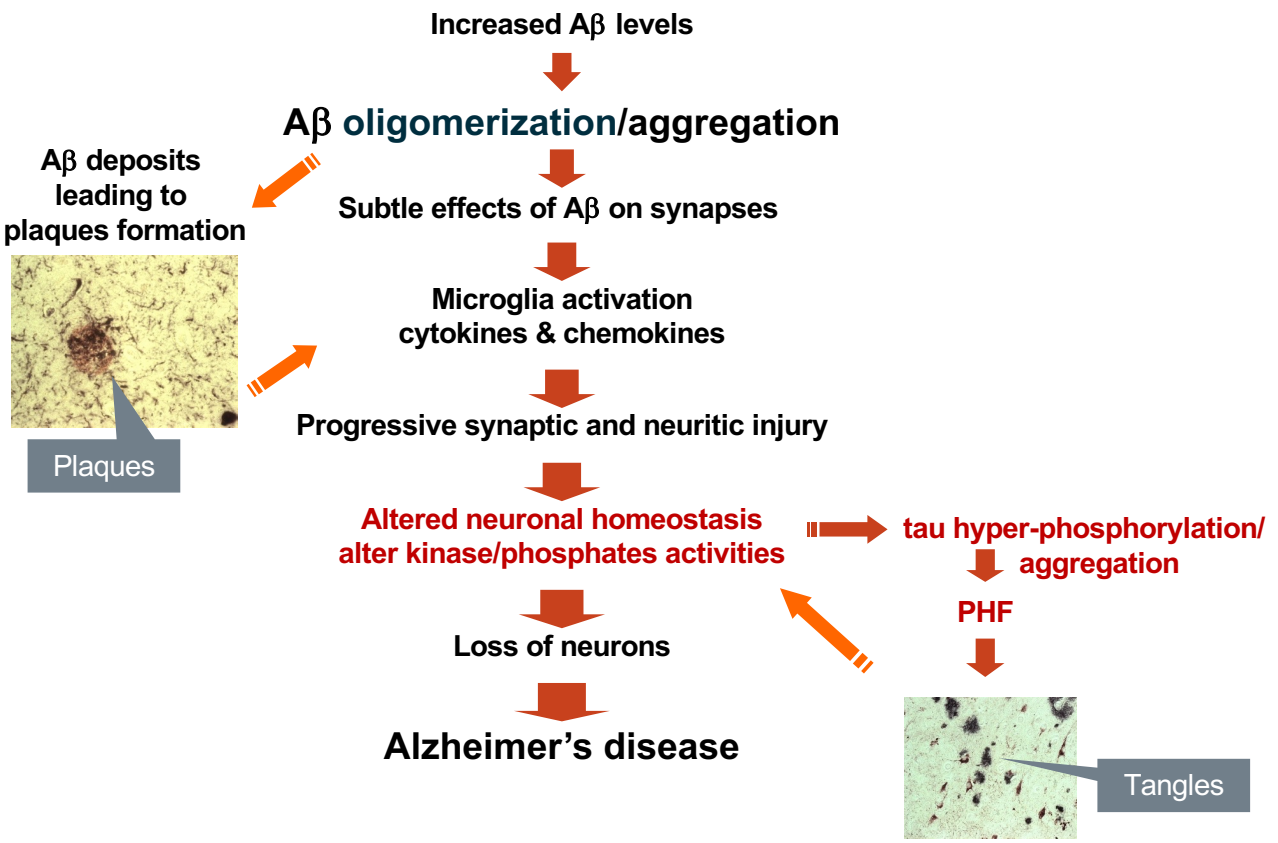
AAV = adeno-associated virus; iPSC = induced pluripotent stem cells; WT = wild type; ZFP-TF = zinc finger protein transcription factor

The amyloid cascade hypothesis – a molecular roadmap for Alzheimer's disease drug development



1. Advance next generation anti-Aβ therapies
2. Grow tau pipeline
3. Progress drug discovery on genetic targets
4. Enable development of combination therapies

Acknowledgments

Denali Team

Sangamo Team

R&D Day
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Biogen