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Harnessing the power of the immune system to fight disease

Vaxxinity R&D Day – New York, NY
November 10, 2022

Forward Looking Statements

This presentation contains forward-looking statements within the meaning of the federal securities laws. Forward-looking statements generally are accompanied by words such as “will,” "expect," “continue,” “plan,” "target," “potential,” "milestone," "opportunities," and similar expressions that predict or indicate future events or trends or that are not statements of historical matters. These forward-looking statements include statements regarding our discovery, research and development activities, in particular our development plans for our product candidates and potential future candidates, including anticipated clinical development timelines, and the potential for such product candidates to be used to treat human disease. These statements are based on various assumptions, whether or not identified in this presentation, and on the current expectations of management. These forward-looking statements are provided for illustrative purposes only and are not intended to serve as, and must not be relied on as, a guarantee, an assurance, a prediction, or a definitive statement of fact or probability. Actual events and circumstances are difficult or impossible to predict and will differ from assumptions. These forward-looking statements are subject to a number of risks and uncertainties discussed in our Annual Report on Form 10-K for the year ended December 31, 2021 and Form 10-Q for the quarter ended September 30, 2022, which have been filed with the Securities and Exchange Commission (SEC) and are available on the SEC's website at www.sec.gov. Actual results could differ materially from the results implied by these forward-looking statements. There may be additional risks that we presently do not know, or that we currently believe are immaterial, that could also cause actual results to differ from those contained in the forward-looking statements. In addition, forward-looking statements reflect our views and expectations, plans, or forecasts as of the date of this presentation. While we may elect to update these forward-looking statements at some point in the future, we specifically disclaim any obligation to do so, except as required by law. These forward-looking statements should not be relied upon as representing our assessments of any date subsequent to the date of this presentation.

Welcome & Opening Remarks

Mei Mei Hu, CEO

Agenda – From Treatment to Prevention of Chronic Diseases

VAXX Platform	8:30a	**Opening Remarks**	Mei Mei Hu, CEO
		Platform Introduction	J.C Dodart, SVP Research
Neurodegenerative Diseases	9:05a	**UB-312 Anti-αSyn Vaccine in Parkinson's**	Brian Fiske, PhD JC Dodart, SVP Research
		UB-311 Anti-Aβ Vaccine in Alzheimer's	Dr. Jeffrey Cummings, MD, ScD Ulo Palm, CMO
	10:45a	***Break***	
Migraine & Hypercholesterolemia	10:55a	**UB-313 Anti-CGRP Vaccine in Migraine**	Stephen Silberstein, MD Justin Boyd, Director Translational
		VXX-401 Anti-PCSK9 Vaccine in Hypercholesterolemia	Robert Scott, MD JC Dodart, SVP Research
Closing and Next Steps		**Closing Remarks**	Mei Mei Hu, CEO

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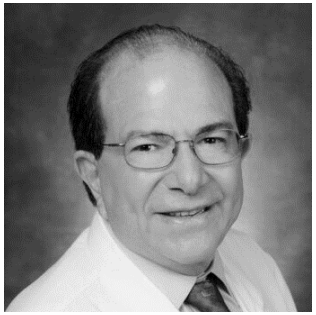
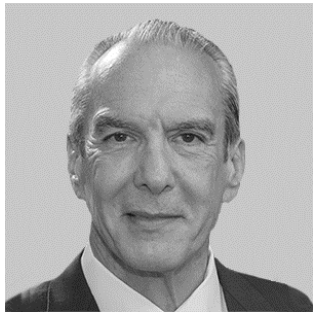
Vaxxinity welcomes our esteemed guest speakers

Brian Fiske, PhD
Co-CSO
The Michael J. Fox Foundation



Stephen Silberstein, MD
Professor, Director
Jefferson Headache Center



Dr. Jeffrey Cummings, MD, ScD
Vice Chair of Research
UNLV Dept. of Brain Health

Robert Scott, MD
Former VP Global Development Head Amgen (evolocumab), and former CMO Abbvie

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An expansively disruptive approach to chronic disease:

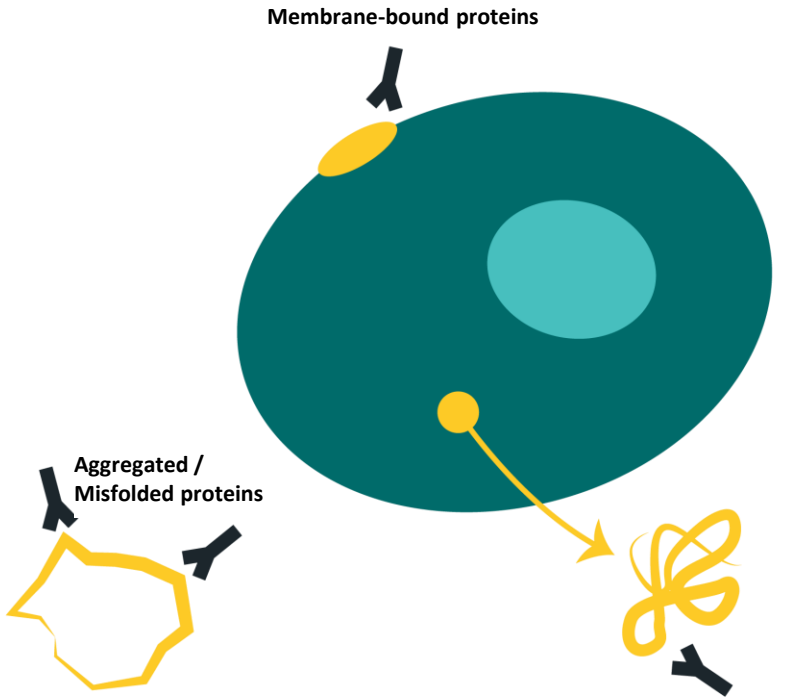
Efficiency of vaccines + Validation of mAbs in chronic disease = New class of therapeutics

Alzheimer's | Parkinson's | Migraine | Hypercholesterolemia | Others

VAXXINES are a potential new class of medicine for chronic diseases…

Opportunity: Any target accessible by a mAb is a potential opportunity for a VAXXINE to leapfrog to first line

1. Expansive market potential
2. High probability of technical success
3. Accelerated R&D timelines
4. Greater capital efficiency over time vs. mAb or other cell and gene therapies



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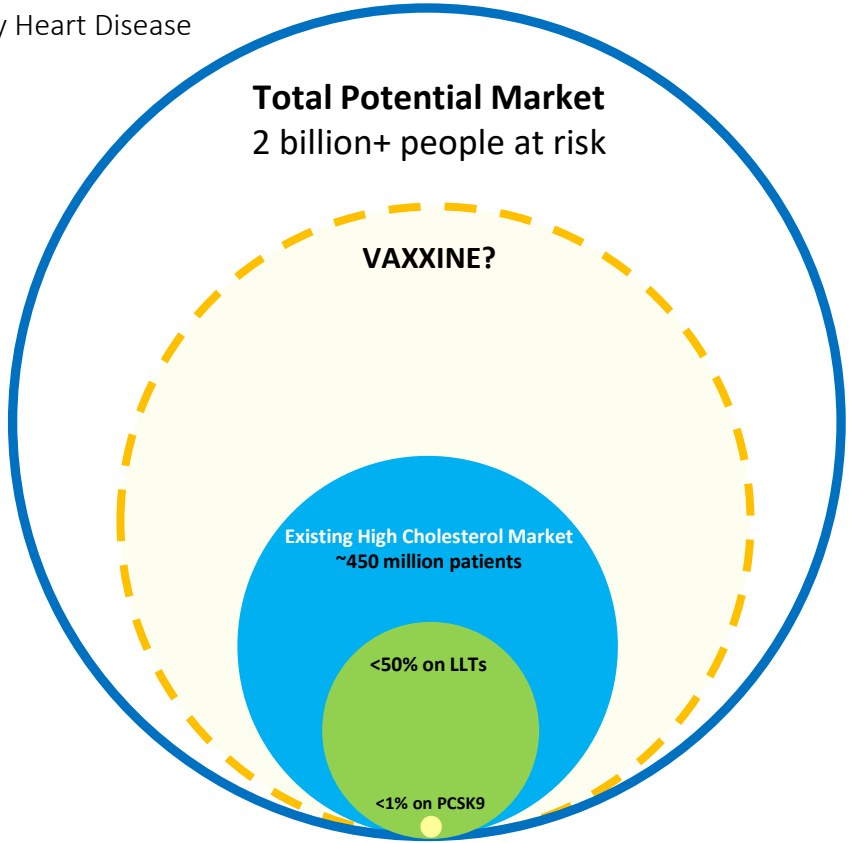
…with profound social and economic implications

Example: Atherosclerotic Coronary Heart Disease



Sources: *Parihar 2018, Johns Hopkins Medicine, Cortellis, WHO*

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Our approach is to systematically de-risk, de-risk and de-risk

DE-RISK technology

- Leverage a validated platform with over 3B doses commercialized
- Successfully achieved GMP manufacturing scale-up
- Successfully achieved multiple POPs/POCs in clinic and animals

DE-RISK biology

- Pursue validated targets and proven MOAs
- Diversify across portfolio

DE-RISK regulatory and development path

- Use surrogate endpoints and provocative challenge models
- Fast-follow predecessor approvals

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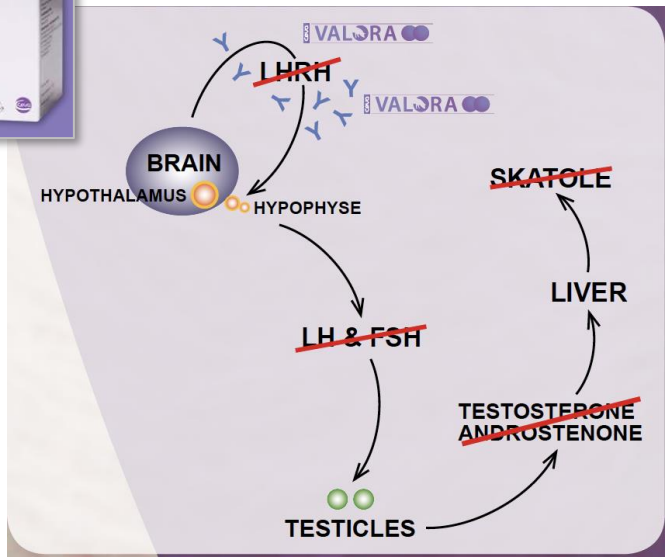
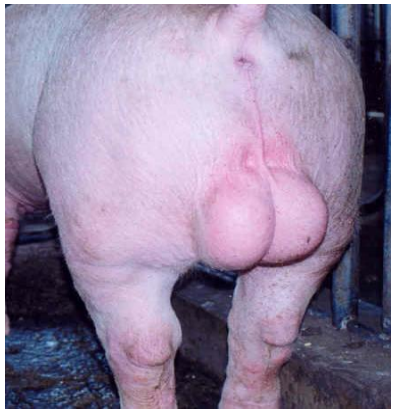
VAXXINE platform achieved first commercial validation in animal health with millions of doses commercialized

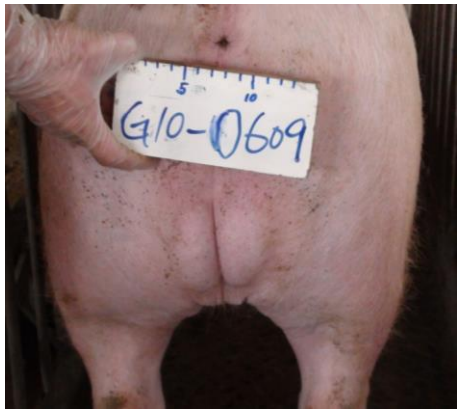
Anti-LHRH vaccine for immunocastration



Control



Treated



Sources: *Ceva Valora Brochure, United Biomedical, Inc. field trials*

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Clinical data collected from Vaxxinity's platform to date

>4,250
participants dosed

10
repeat doses administered in patients over up to 3 years

>10
targets where animal proof of concepts successfully achieved

4
investigative VAXXINE medicines in clinical trials

8
clinical trials conducted (ongoing and completed)

Across these programs, we have shown that our VAXXINES in the clinic:

- Have a good safety profile and are generally well-tolerated
- Consistently overcome immune tolerance and generate high affinity antibodies against desired target
- Induce antibodies that cross the BBB
- Are reversible and can be rapidly boosted
- Are durable for months after priming injection regimen

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VAXXINES have significant advantages for the development of medicines for chronic diseases

Major challenges with common chronic diseases

- Large population affected
- Lifetime treatment required
- No or limited disease modifying treatment available

MAbs have validated targets, but face challenges

- Expensive
- Burdensome administration
- Side effects like ARIA-E
- Not globally accessible or scalable
- Not ideal for prevention or long-term treatment

Advantages of VAXXINES

- ***Safe*** *and* ***effective***
- *Can* ***combine multiple targets***
- ***Convenient*** *and* ***affordable****, allowing for* ***prevention and long-term treatment***
- ***Accessible*** *to* ***hundreds of millions*** *of patients*

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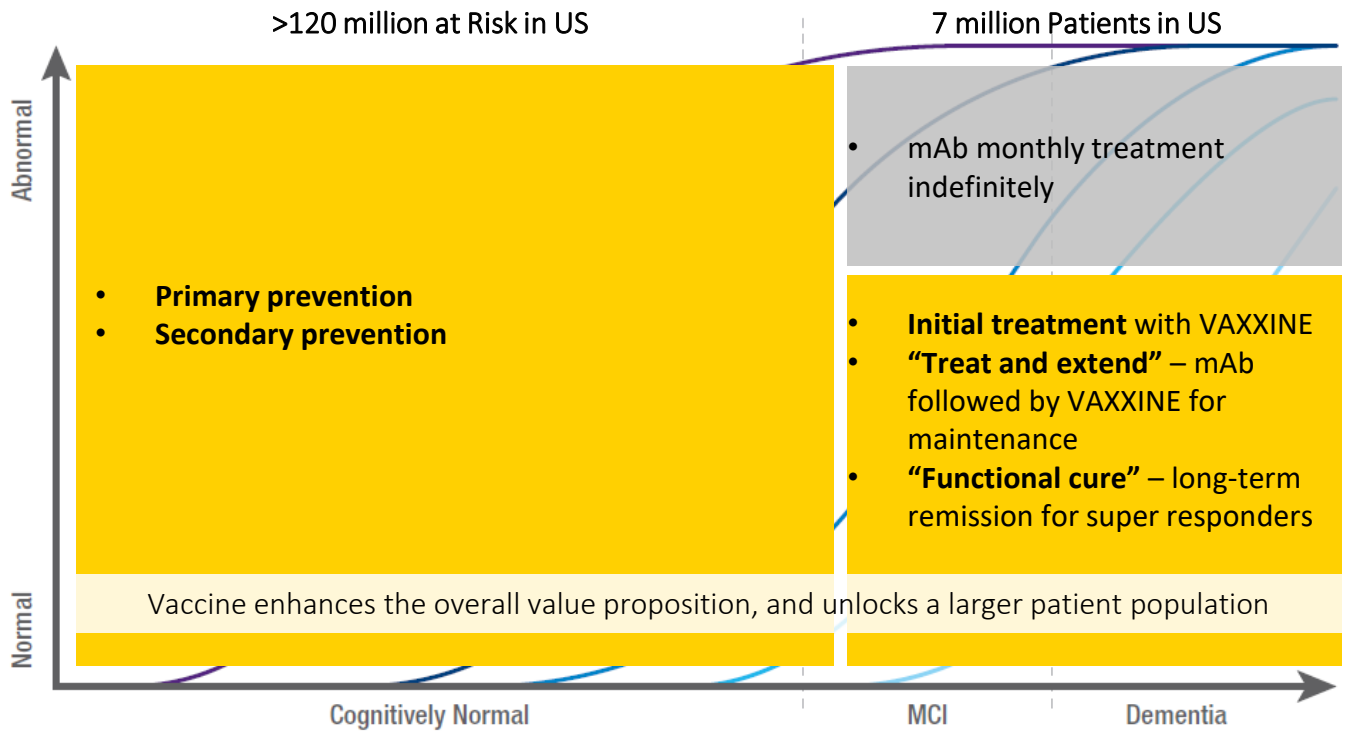
Enabling a disruptive expansion of addressable markets

Example: Alzheimer's Disease



Similar paradigms can be applied to other indications

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Vaxxinity's development pipeline: progress since IPO

	Vaxxine Program (Target)	Indications	Milestone
Neurodegeneration	UB-311 (Aβ)	*Alzheimer's disease*	FDA Fast Track Designation
	UB-312 (αSyn)	*Parkinson's disease, Lewy body dementia*	Phase 1 Part B Positive Read-out
	Anti-tau	*Alzheimer's disease*	Leads identified
Common Chronic	UB-313 (CGRP)	*Migraine*	Phase 1 trial started
	VXX-401 (PCSK9)	*Hypercholesterol-emia*	Lead identified
Infectious Disease	UB-612 (SARS-CoV-2)	*Covid-19 prevention*	Fully enrolled Phase 3; Read-out 4Q22

New pre-clinical targets: ANGPTL3, Myostatin + Activin A and undisclosed

Bold = pipeline at IPO; light = progress since IPO

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Important Milestones Announced This Year

Parkinson's VAXXINE (UB-312) Phase 1 Part B initiated and EOT analyzed

- Positive Ph1 Part B EOT: successfully immunized Parkinson's patients and generated antibodies
- Well-tolerated
- High responder rate
- Penetration of antibodies into CSF

Hypercholesteremia VAXXINE (VXX-401) lead identified

- Robust Proof of Concept achieved in NHP
- Safe and well-tolerated in GLP tox (NHP)
- Positive advice from health authority

Migraine VAXXINE (UB-313) CTA approved and Ph1 initiated

Alzheimer's VAXXINE (UB-311) received Fast Track Designation from FDA

DEMOCRATIZE HEALTH.

Our vision is to provide cheaper, safer, more convenient, and effective medicines for chronic disease to all.

Platform Introduction

JC Dodart, PhD, SVP Research

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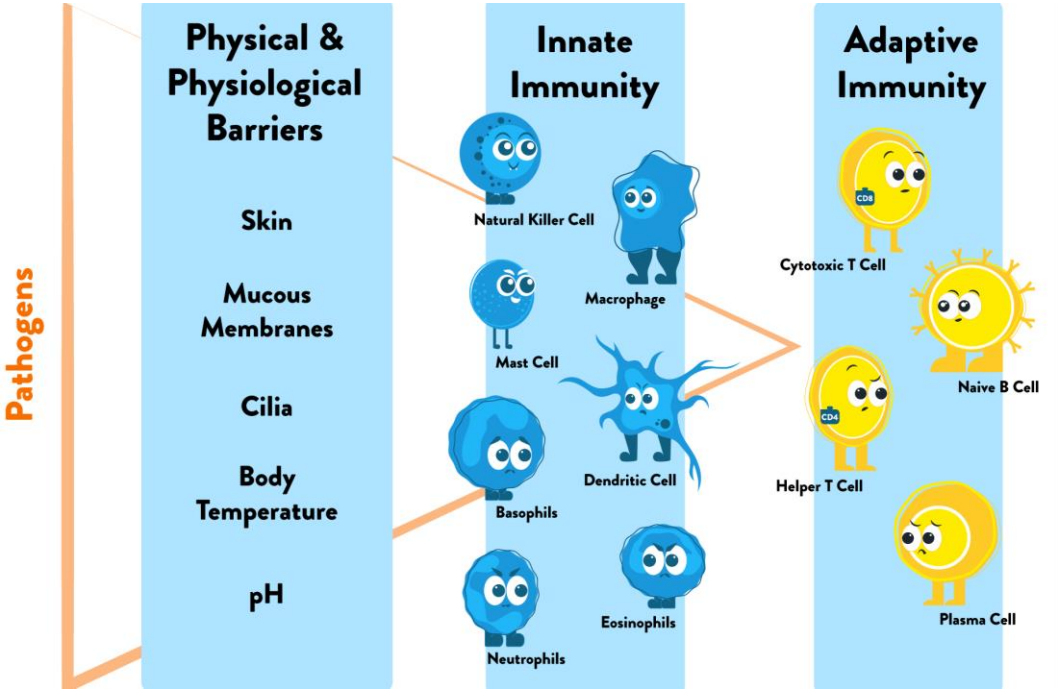
How regular vaccines work



- ✓ Vaccines for infections diseases simulate the presence of a pathogen and train both the innate and adaptive immune to fight against the real pathogen.
- ✓ For chronic diseases involving an endogenous target, only a small subset of antibody-producing cells need to be recruited

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Vaccines for chronic diseases: the challenges

Safety

Challenge: overcome immune tolerance while avoiding T cell mediated cytotoxicity and autoimmune responses

Response Rate

Challenge: overcome immune tolerance across patient populations and ethnicities

Immunogenicity

Challenge: produce highly efficient antibodies and achieve therapeutic levels of antibody

Off-Target

Challenge: induce only antibodies highly specific to the peptide or protein target

To avoid these challenges, the industry moved towards mAbs

MAbs are highly efficacious, but VAXXINES could improve accessibility to treatment and have clear advantages for prevention

		Monoclonal Antibodies (mAbs)	VAXXINES are Designed to be…
Efficacy Mechanism		✓ Specific and targeted ✗ Limited duration	✓ Specific and targeted ✓ Long duration of action
Safety Mechanism		✓ Target specific	✓ Target specific
Administration	Dose frequency	✗ Bi-weekly or monthly	✓ Quarterly to annually
	Route	✗ IV infusion or SC	✓ IM injection
Cost	Manufacturability	✗ Complex biologic process	✓ Simple, chemical process
	Accessibility	✗ Expensive	✓ Cost-effective
	Scalability	✗ Capital- and time-intensive	✓ Low CapEx, rapid

To date no head-to-head comparison of any competing products to any of our product candidates in any clinical trial have been completed

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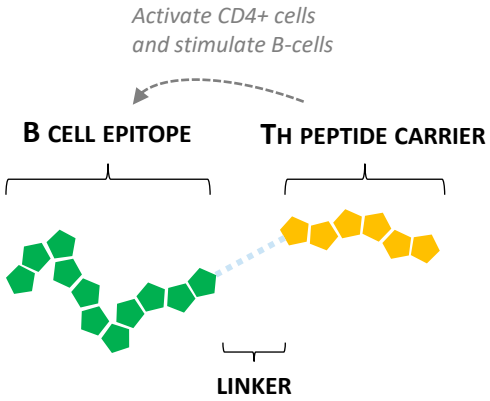
Our synthetic peptide VAXXINE platform combines the power of mAbs *with the convenience and accessibility of vaccines*

Components
B cell epitopes
Th peptide carriers
Proprietary linker and formulation

The VAXXINE Platform



Advantages
Overcomes immune tolerance with high response rate and titers
Target-specific antibodies
Durable response
Synthetic, low-cost, scalable
Plug & Play, modular

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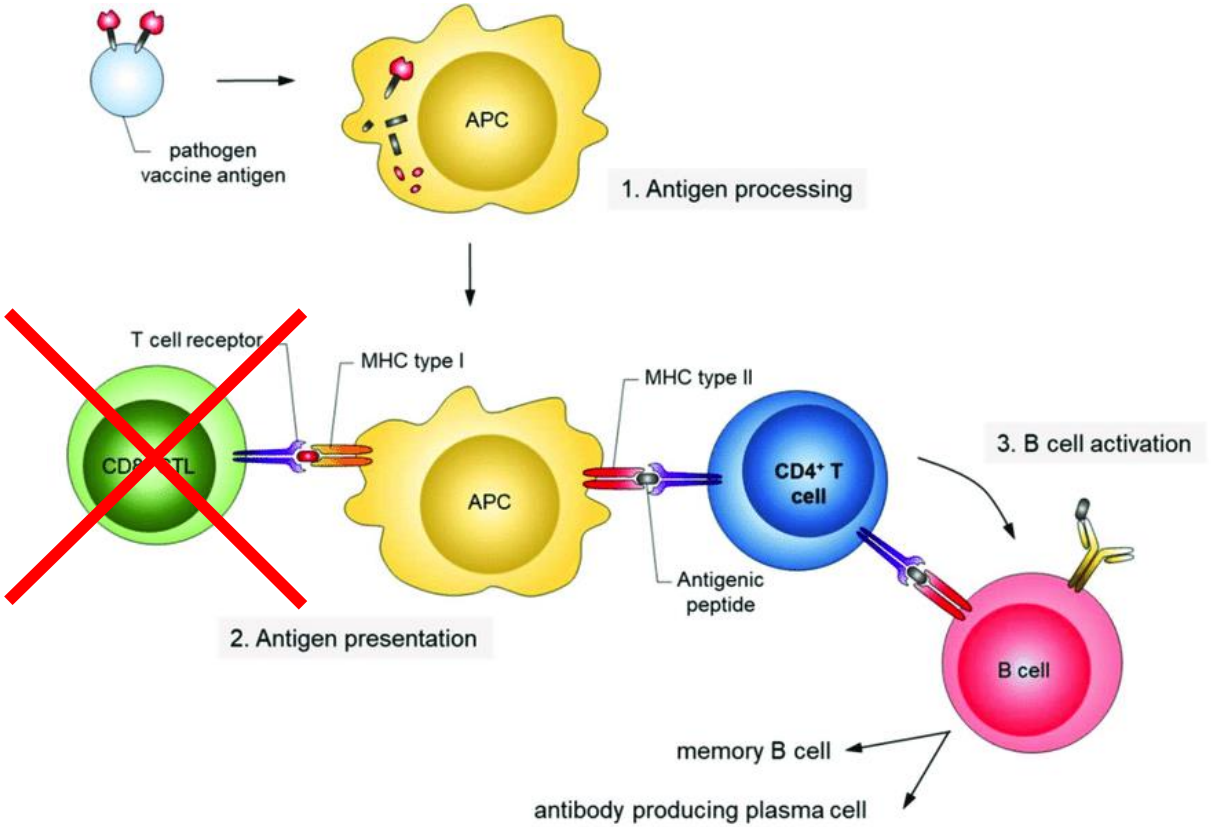
VAXXINES ≠ vaccines



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Vaxxinity has a different approach to vaccines

	Vaxxinity	ACI	Affiris	Axon	Araclon	Novartis
Technology	Proprietary T Helper peptides	B Cell epitope focused	B Cell epitope focused	B Cell epitope focused	B Cell epitope focused	B Cell epitope focused
MoA	T Helper peptide drives selective Th2 response	LP formulation drives immune response	KLH + Adjuv drive immune response	KLH + Adjuv drive immune response	KLH + Adjuv drive immune response	VLP + Adjuv drive immune response
Indications (target)	Aβ, αSyn, tau, CGRP, PCSK9, SARS-CoV-2	Neuro (Aβ, tau)	(αSyn, PCSK9)	Neuro (tau)	Neuro (Aβ)	Neuro (Aβ)
Proven technology	GMP commercial scale & commercialization	NA	NA	NA	NA	NA

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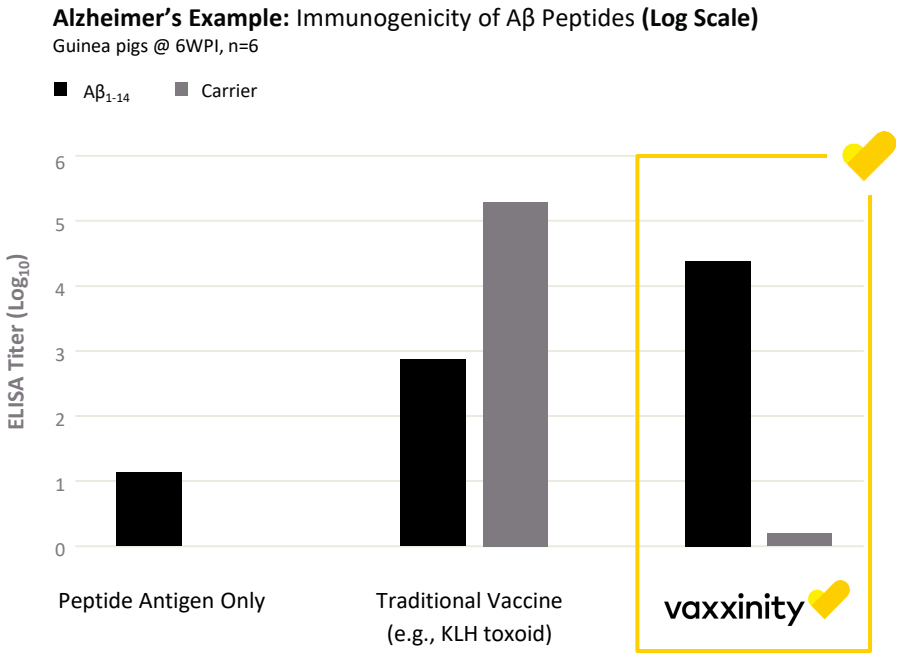
Unlike traditional vaccines, VAXXINES can break immune tolerance to elicit a robust B-cell response with minimum off-target activity



Similar data were published under Wang et al., Vaccine (2007)

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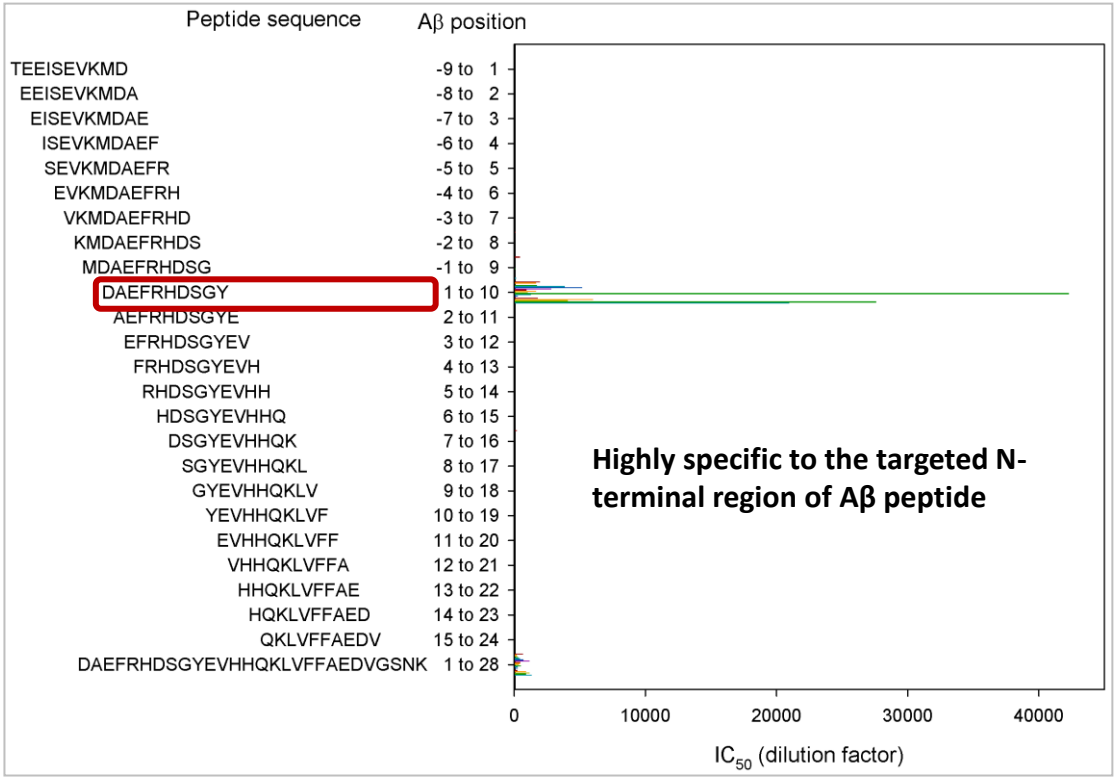
VAXXINES elicit antibodies highly specific to desired epitope

Selective Recognition N-terminal Ab Peptides and not other AAP sequences

UB-311 Ph1 Patient Serum



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VAXXINES outperform vaccines

	Vaxxinity	ACI	Affiris	Axon	Araclon	Novartis
Technology	Proprietary T Helper peptides	B Cell epitope focused	B Cell epitope focused	B Cell epitope focused	B Cell epitope focused	B Cell epitope focused
MoA	T Helper peptide drives selective Th2 response	LP formulation drives immune response	KLH + Adjuv drive immune response	KLH + Adjuv drive immune response	KLH + Adjuv drive immune response	VLP + Adjuv drive immune response
Indications (target)	Aβ, αSyn, tau, CGRP, PCSK9, SARS-Cov-2	Neuro (Aβ, tau)	(αSyn, PCSK9)	Neuro (tau)	Neuro (Aβ)	Neuro (Aβ)
Stage	Ph3	Ph2	Ph 1	Ph2	Ph2	Ph 2
Subjects dosed (trials)	>4,250 (8)	132 (5)	72 (3)	180 (4)	151 (2)	>170 (4)
Seroconversion rate	>95%	49%	86%	97%	92%	68%
Proven technology	GMP commercial scale & commercialization	NA	NA	NA	NA	NA

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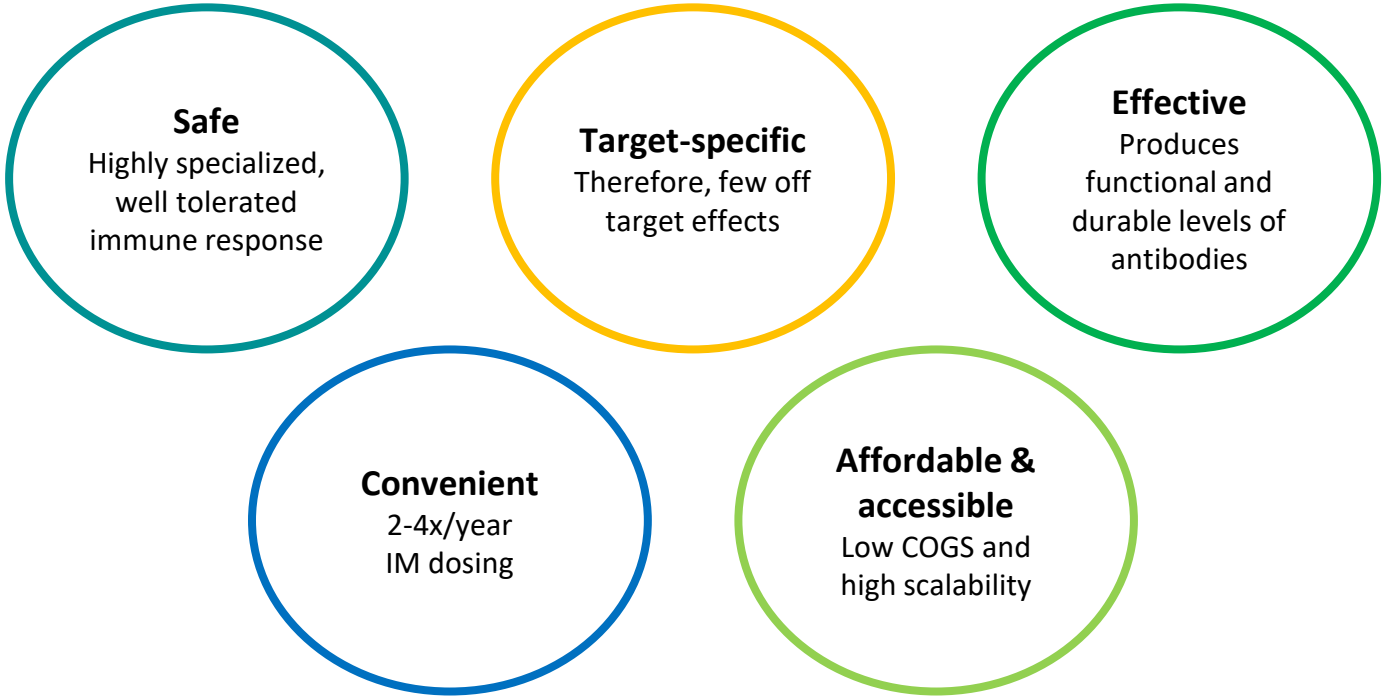
Vaxxine Platform Summary



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Neurodegenerative Disease Pipeline

- UB-312 Anti-αSyn Vaccine in Parkinson's
  Brian Fiske, PhD, CSO, The Michael J. Fox Foundation
  JC Dodart, SVP Research, Vaxxinity

- UB-311 Anti-Aβ Vaccine in Alzheimer's
  Jeffrey L. Cummings, MD, ScD, Vice Chair of Research, UNLV Department of Health
  Ulo Palm, CMO, Vaxxinity

Progress and promise in therapies targeting alpha-synuclein for Parkinson's disease

Vaxxinity Research & Development Day

November 10, 2022

Brian Fiske, PhD

Co-Chief Scientific Officer

The Michael J. Fox Foundation for Parkinson's Research

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

Here. Until Parkinson's Isn't.

- Launched in **2000** by actor Michael J. Fox
- Global strategic funder and facilitator: more than **$1 billion** deployed to Parkinson's disease research and drug development
- Vision seeks **a world without Parkinson's disease**
- Mission execution through a **strategic research vision** centered on *enabling* advances in disease *definition*, *measurement* and *treatment* across the Parkinson's disease progressive journey
- Accelerating cures by **connecting community**: people with Parkinson's, care providers, researchers, industry, regulators, payers, policy-makers, strategic partners and other visionary philanthropists

MJFF <> Vaxxinity Partnership

Funding and strategic collaborations seek to help company advance a promising therapeutic for PD

- **Engagement**

  Initial introduction in 2017 led to further follow-up meetings and discussions critical for refining MJFF best supporting roles

- **Funding**

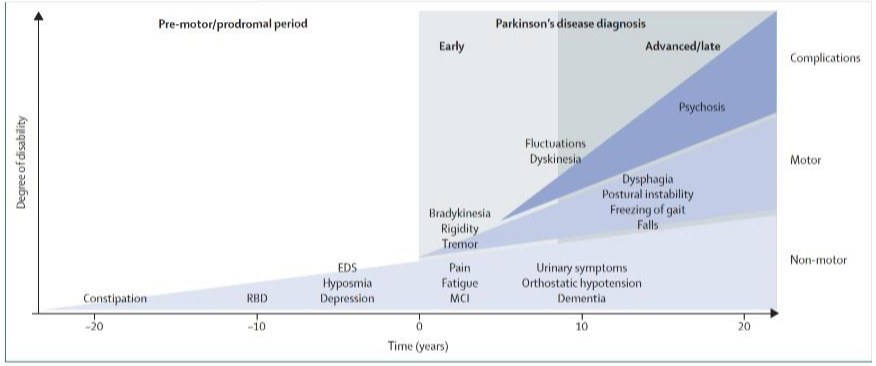
  MJFF funded Vaxxinity biomarker study in support of UB-312 clinical development

- **Collaboration**

  Vaxxinity participation and attendance at MJFF PD Research Exchange and PD Therapeutics Conference

The Challenge of Parkinson's Disease

Progressive and heterogeneous disease course requires targeting variety of patient needs and underlying biology



Key Symptoms

- Motor and non-motor features
- Disease 'subtypes' (e.g., gait vs tremor dominant)

Pathology

- Loss of dopamine cells in substantia nigra (among other regions)
- Presence of intraneuronal 'Lewy body' pathology (alpha-synuclein) in many but not all cases (other pathology, too)

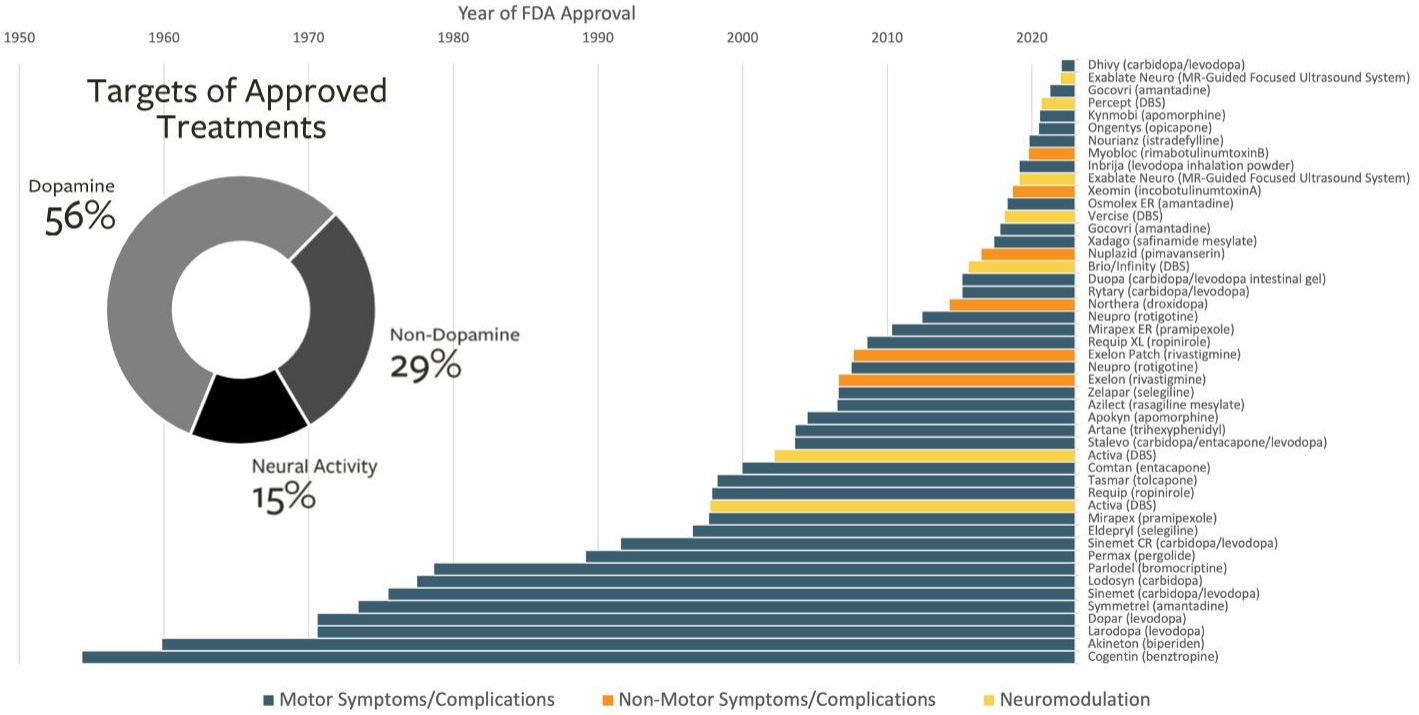
Approved Treatments

- Dopamine replacement and neuromodulation (surgical stimulation or ablation) address some motor features
- Some non-motor treatments (often not PD-specific)
- Treatment complications arise over time (dyskinesias, psychosis)
- ***No disease-slowing therapies available***

image: Kalia and Lang, *The Lancet*, 2015

Approved therapies for Parkinson's disease

Disease-specific treatments primarily target motor features with some emering focus on non-motor symptoms



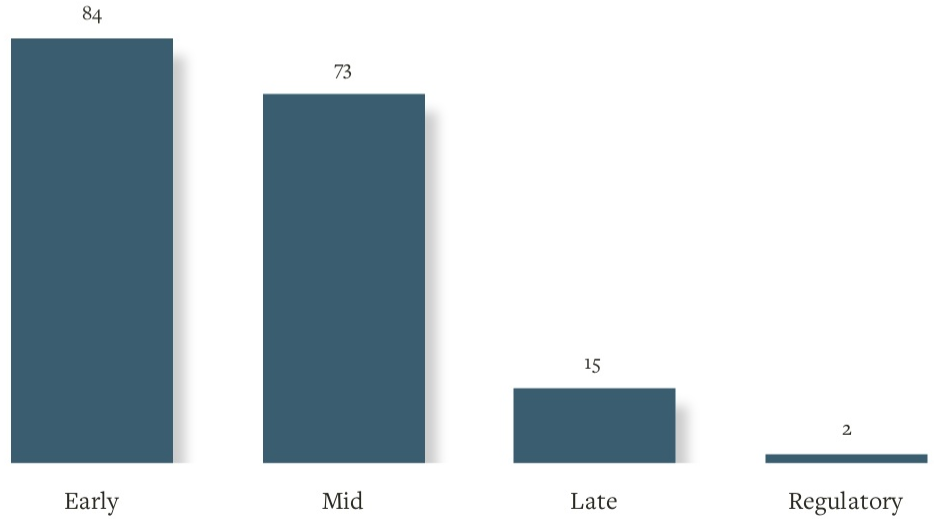
The PD Clinical Pipeline is robust

A diverse mix of approaches offers an important barometer on progress toward improving patient lives

Treatments focus on variety of patient needs

- Disease progression (alpha-synuclein, LRRK2, GBA, other pathogenic targets)
- Motor improvement (particular emphasis on advanced needs like fluctuations, OFF and gait impairment)
- Non-motor features (cognition and dementia among others)
- Complications (dyskinesias, psychosis)

MJFF-Monitored (n=174) PD Programs by Phase



Alpha-Synuclein: a leading PD translational target

Key supporting evidence builds strong validation argument for therapeutically targeting alpha-synuclein pathology

Genetics

- SNCA point mutations/multiplications linked to rare autosomal dominant forms of familial PD
- Variation at SNCA locus associated with risk of sporadic PD

Pathology

Alpha-synuclein main protein component of Lewy bodies/neurites in brains of people with PD

Cell-to-Cell Transmission

- "Spread" of alpha-synuclein pathology between neurons observed in early human tissue transplants
- Pre-formed fibril injection models provide preclinical proof of mechanism

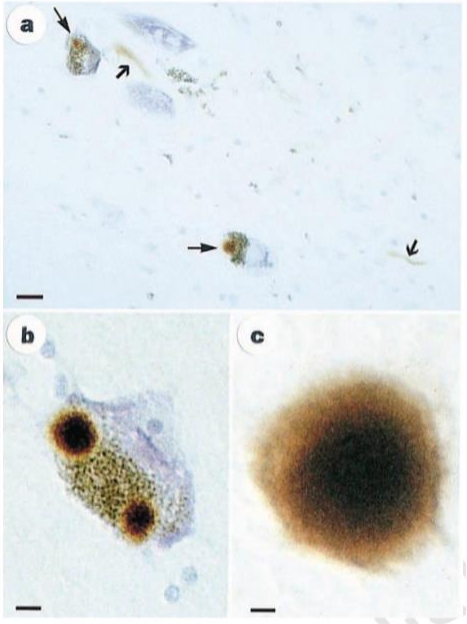


image: Lewy patholgy immunostained for alpha-synuclein from PD postmortem brain (Spillantini et al., *Science* 1997)

Alpha-Synuclein Therapeutic Development

Strong target rationale fuels diverse pipeline of treatments in clinical development targeting alpha-synuclein

	Drug	Sponsor(s)	Approach	Status
	UB 312	Vaxxinity	active immunotherapy (vaccine)	Phase 1
	ACI-7104/PD 01	AC Immune/Affiris	active immunotherapy (vaccine)	Phase 1
	MEDI 1341/TAK 341	AstraZeneca/Takeda	passive immunotherapy (monoclonal antibody)	Phase 1
	ABBV 0805	Bioarctic Neuroscience (AbbVie)	passive immunotherapy (monoclonal antibody)	Phase 1
	UCB 7853	UCB	passive immunotherapy (monoclonal antibody)	Phase 1
	Lu-AF82422	Lundbeck	passive immunotherapy (monoclonal antibody)	Phase 2
	prasinezumab	Prothena/Roche	passive immunotherapy (monoclonal antibody)	Phase 2
	cinpanemab	Biogen/Neuroimmune	passive immunotherapy (monoclonal antibody)	Discontinued
	Anle-138b	MODAG/Teva	small molecule aggregation inhibitor	Phase 1
	UCB 0599	UCB/Novartis	small molecule aggregation inhibitor	Phase 2
	ATH-434	Alterity Therapeutics	small molecule aggregation inhibitor	Phase 2
	kenterin	Enterin	small molecule aggregation inhibitor	Phase 2
	buntanetap	Annovis Bio	small molecule translation inhibitor	Phase 3
	ION 465/BIIB 101	Ionis Pharmaceuticals	antisense translation inhibitor	Phase 2

Programs targeting alpha-synuclein may focus on Parkinson's disease and/or multiple system atrophy.
Additional programs not listed target clearance mechanisms that may also reduce alpha-synuclein burden.

A Biomarker-Informed Path for Alpha-Synuclein

Critical measures for linking biology to clinical outcome

Key Biomarker Needs

- **Target engagement**
  Do you get to the desired site and engage the desired target?
- **Pharmacodynamic Response**
  Do you get a biological response to engaging the target?
- **Disease Monitoring**
  - *Proof-of-Principle* - do you see a pathology change?
  - *Proof-of-Concept* - do you see a clinical change?
- **Safety**
  Can you detect any on- and/or off-target toxicity?
- **Patient Selection**
  Can you enrich for people with the desired target-associated pathology?

Seeding Amplification Assays

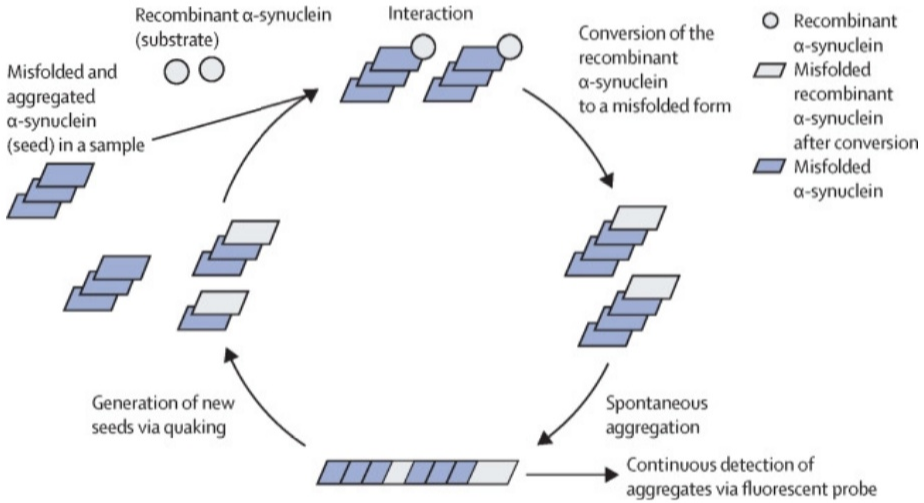
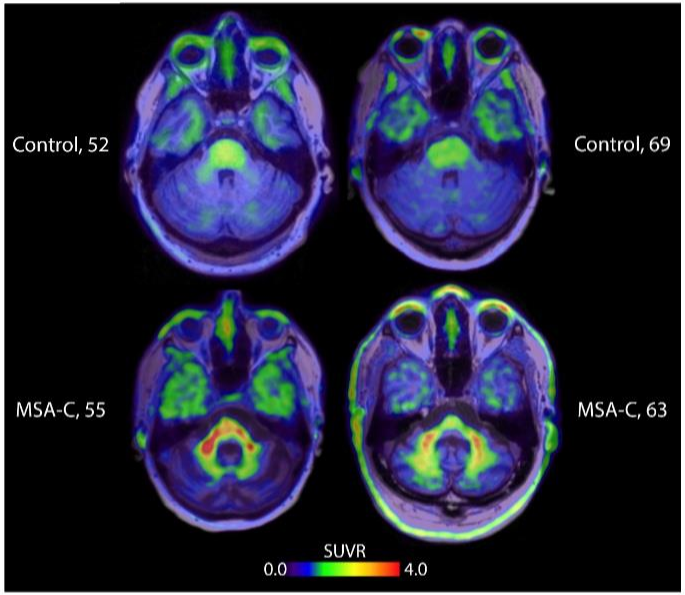


image from Zerr, *Lancet Neurology* 2021

Alpha-Synuclein Neuroimaging

Measurement of alpha-synuclein pathology in brain remains critical field barrier but progress has been seen

AC Immune ACI-12589



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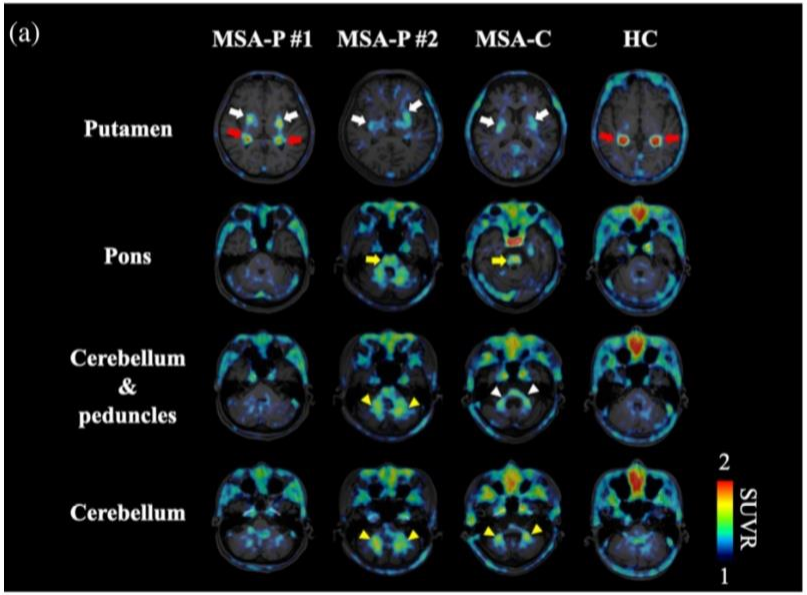

(Left) - image from Mar 16, 2022 press release https://ir.acimmune.com/news-releases/news-release-details/ac-immune-reports-first-live-images-alpha-synuclein-human-brain
(Right) - image from Matsuoka et al., *Mov Disorders* 2022

Clinical Endpoints for PD

Targeting progressive nature of PD is challenged by scales insensitive to change in function

- Existing standards (MDS-UPDRS) offer rater and patient-reported assessments of motor and non-motor features of PD but struggle with detection of meaningful, regulator-preferred patient-reported functional change especially in early disease stages
- Establishing patient-focused outcome measures requires linking disease understanding with meaningful concepts of clinical benefit and risk to build true 'fit-for-purpose' assessment tools
- MJFF is partnering with field leaders, regulators and other like-minded organizations to establish a pre-competitive consensus toward improved clinical endpoints

Final Thoughts and Looking Ahead

Key trends and indicators of future promise for developing PD therapies targeting alpha-synuclein

- **Precision medicine is coming**

  Explosion in disease understanding (genetics, biology, clinical progression) points to possibility of more defined PD 'subtypes' (including ability to screen for 'asyn'-opathy forms)

- **An eye towards 'prevention'**

  Greater ability to identify those at risk for PD matched with robust treatment pipeline drives rationale to consider design of prevention studies

- **Proteinopathy field is evolving**

  Data from AD field (e.g., aducanumab, lecanemab) offer compelling hope to PD immunotherapy field (including vaccine approaches) as we wait for more asyn trial data


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Neurodegenerative Disease Pipeline

- UB-312 Anti-αSyn Vaccine in Parkinson's
  Brian Fiske, PhD, CSO, The Michael J. Fox Foundation
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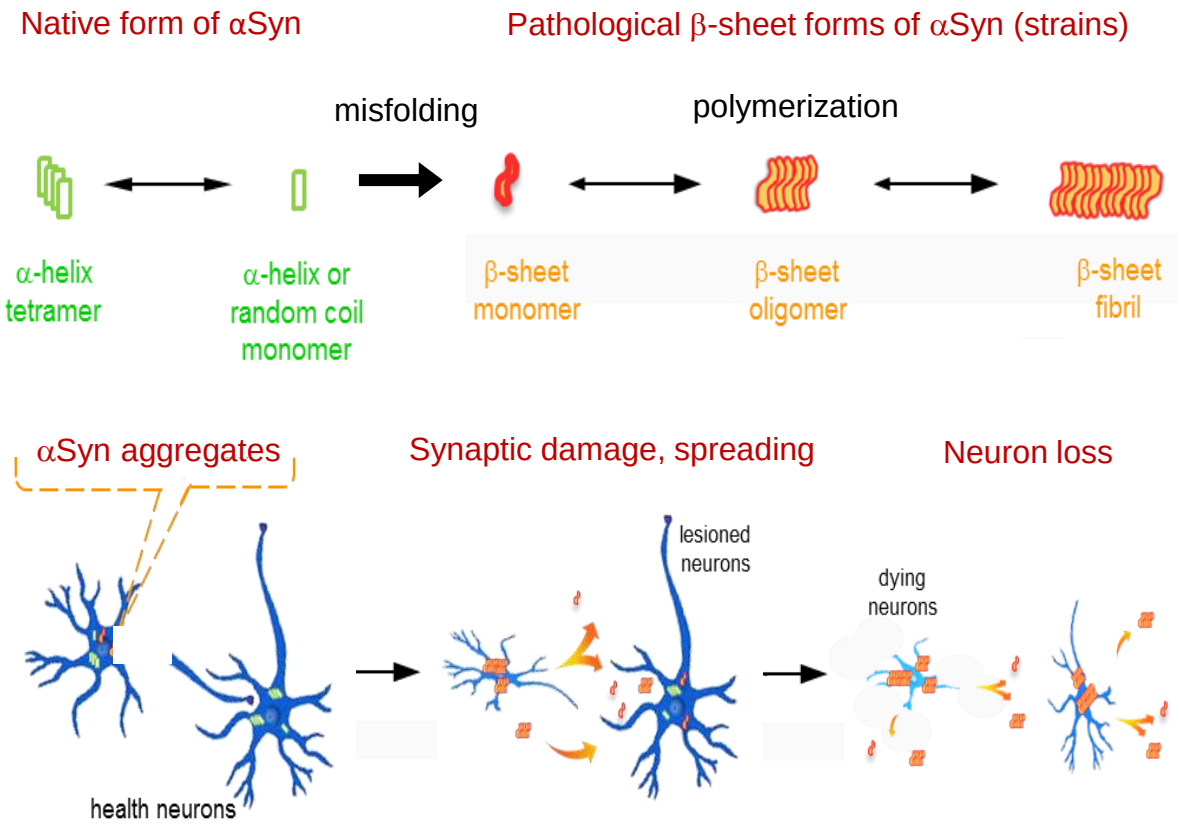
- UB-311 Anti-Aβ Vaccine in Alzheimer's
  Jeffrey L. Cummings, MD, ScD, Vice Chair of Research, UNLV Department of Health
  Ulo Palm, CMO, Vaxxinity

Aggregated αSyn underlies Parkinson's disease and other synucleinopathies



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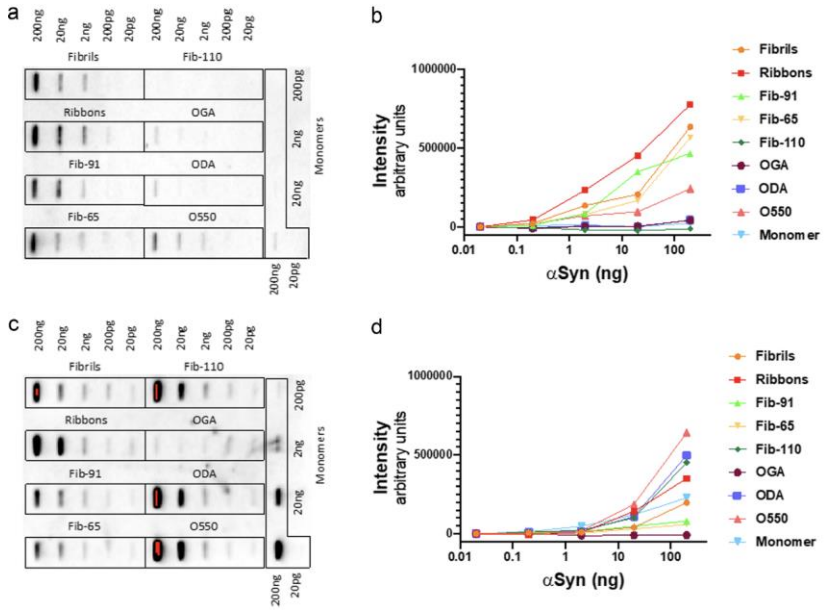
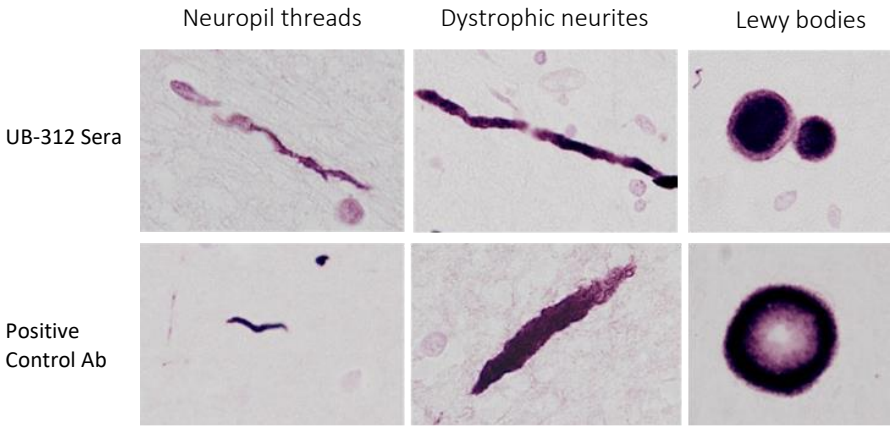
UB-312 induces antibodies highly specific to pathological forms of αSyn





Immunostaining of Parkinson's disease brain sections with sera collected after immunization with UB-312.

Nimmo JT, Verma A, Dodart JC, Melki R, et al., 2020. Alzheimer's Research & Therapy.

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Ongoing Phase 1 trial is evaluating the safety and immunogenicity of UB-312

Objective	Determine the safety, tolerability, and immunogenicity of UB-312
Sample	Part A: n = 50 healthy volunteers 40-85yo Part B: n = 20 PD patients (H&Y ≤ 3)
Dosing	3 doses of UB-312 (various dose levels) or placebo at weeks 0, 4, and 12
Primary endpoints	Frequency of AEs Immunogenicity (anti-αSyn Abs in blood and CSF)
Exploratory measures	Antibodies against different molecular forms of αSyn Total and free αSyn concentrations Part B only MDS-UPDRS, MoCA PMCA in collaboration w/ MJFF

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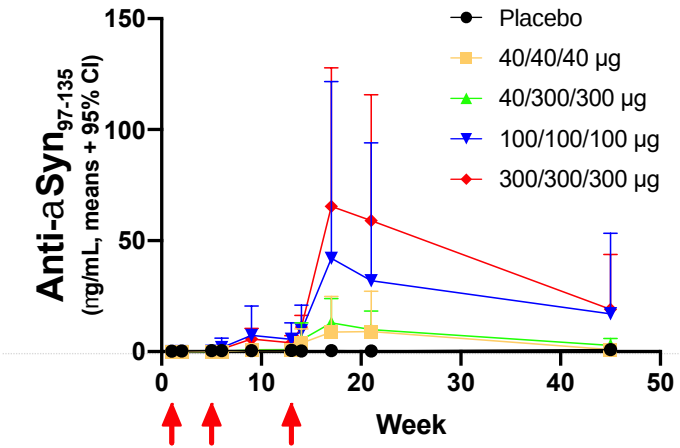
In Ph1 Part A, UB-312 overcomes immune tolerance at target dose, and generates antibodies at levels detectable in CSF

100% response rate in subjects at target dose

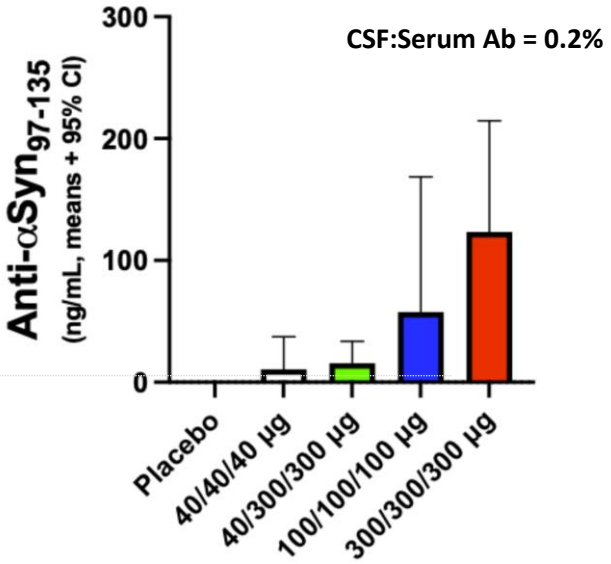
Anti- αSyn Antibodies in Serum
UB-312 Ph1 Part A (n=28*)



UB-312 or placebo administration

Antibodies penetrate BBB, detectable in CSF at rates at or higher than most passive mAbs

Anti-αSyn Antibodies in CSF (Week 21)
UB-312 Ph1 Part A (n=28*)



*28 subjects received all 3 doses, 22 subjects did not

Yu et al., Movement Disorders 2022

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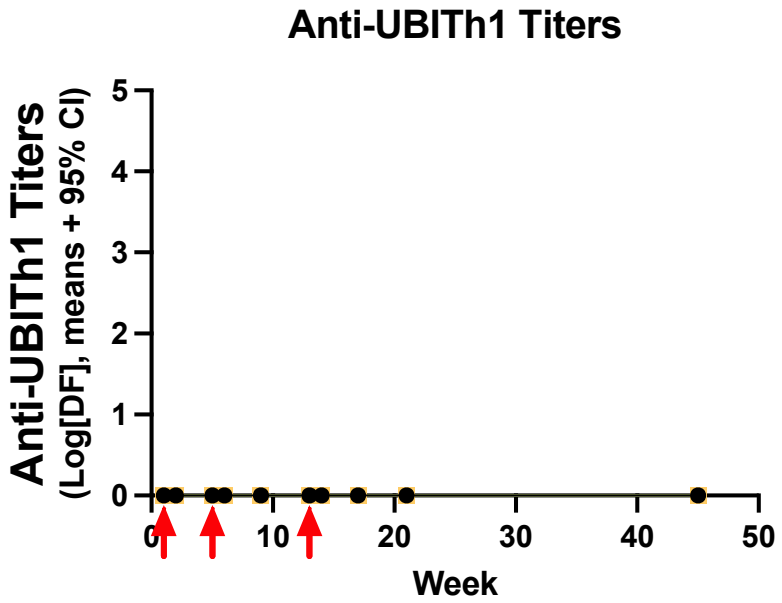
No antibodies against the Th carrier peptide



VAXXINES elicit antibodies against the target antigen, not the carrier

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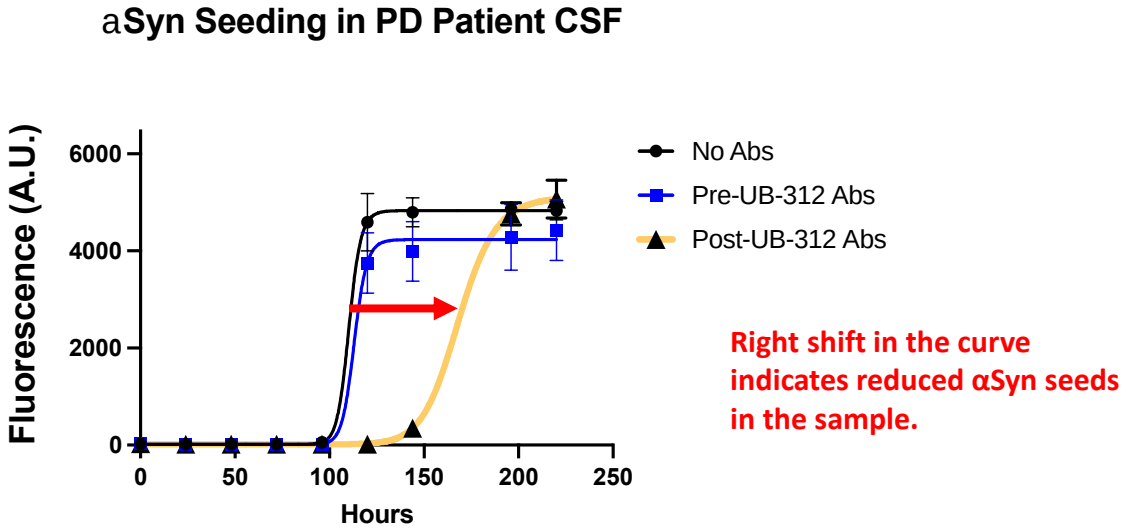
UB-312-induced antibodies slowed αSyn aggregation

Antibodies taken from Ph1 Part A subject sera



Right shift in the curve indicates reduced αSyn seeds in the sample.

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UB-312 Ph1 Part A Adverse Event Summary

Part A

- Most common TEAEs*:
  - Headache
  - Nasopharyngitis
  - Vaccination-site pain
  - Lumbar puncture-site pain
  - Fatigue
- No deaths or SAEs reported
- Similar safety profile between UB-312 groups and placebo group

Yu et al., Movement Disorders 2022
Classifications are based on Medical Dictionary for Regulatory Activities (MedDRA) version 21.1.
*TEAE, treatment-emergent adverse event, any post-baseline AE irrespective of study group or study drug relatedness

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UB-312 Ph1 Part B Summary

- **Positive Ph1 Part B EOT:** successfully immunized Parkinson's patients and generated antibodies
- Well tolerated
- High responder rate
- Penetration of antibodies into CSF
- Trial still blinded and ongoing, full dataset mid-2023

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UB-312 is a blockbuster commercial opportunity

- Large unmet medical need with no approved disease-modifying treatment
- Indication expansion opportunity
- Total addressable market as high as > 2.2 B patients per year
- Pricing range to aim for first-line coverage / prevention
- Sales are sustainable, scale with aging population

Primary Prevention of Synucleinopathies
132 M in US
2.2 B worldwide

REM-Sleep Disorder
Co-indicated with DLB and PD

Dementia with Lewy Body
~1.4 M in US
5.5 – 8.5 M worldwide

Early Parkinson's
1 M in US
10 M worldwide

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Neurodegenerative Disease Pipeline

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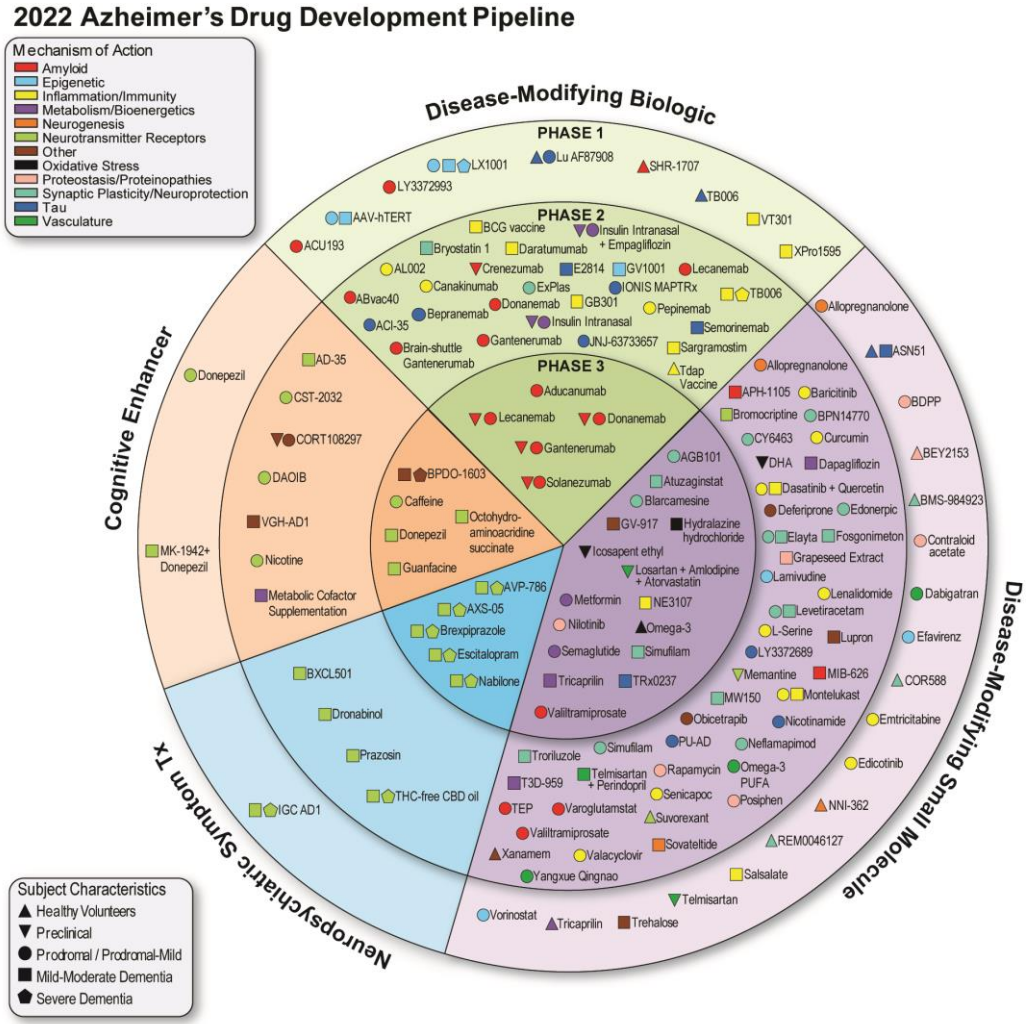
UB-311 and Anti-Amyloid Vaccines for the Treatment of Alzheimer's Disease: Therapeutic Context and Rationale

Jeffrey Cummings, MD, ScD

Chambers-Grundy Center for Transformative Neuroscience

Department of Brain Health

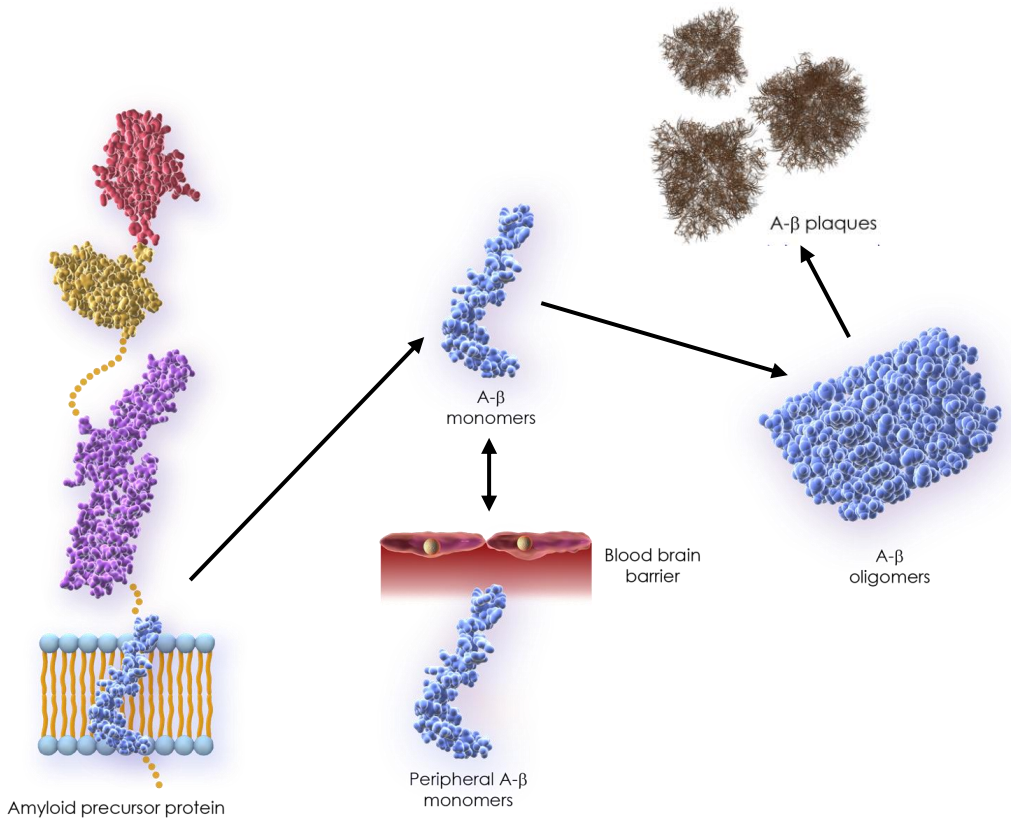
University of Nevada Las Vegas (UNLV)



Universe of Alzheimer's Drug in Current Clinical Trials

- 143 agents in 172 trials
- Phase 3 – 31 agents
  - DMTs – 21 (5 biologics)
- Phase 2 – 82 agents
  - DMTs – 71 (26 biologics)
- Phase 1 – 30 agents
- DMTs – 83.2% of the agents
- Cog Enhancers – 9.8%
- NPS tx – 6.9%

Cummings J, et al. Alz&Dem:TRCI 2022 May 4;8(1):e12295. doi: 10.1002/trc2.12295



The Amyloid Hypothesis is Alive and Well

- Amyloid plaques are required for the pathological diagnosis of AD
- First detectable change in AD (amyloid PET)
- A$\mathcal{B}$ triggers "downstream" events in AD models (e.g., neurofibrillary tangles, inflammation)
- Mutations causing AD increase the A$\mathcal{B}$ production
- Trisomy 21 (triplication of the amyloid precursor protein gene) causes AD in Down's syndrome
- A$\mathcal{B}$ oligomers (soluble) are neurotoxic in cell/tissue studies
- A$\mathcal{B}$ oligomers (soluble) impair synaptic function and memory-related physiology in animal models
- Transgenic mice with AD-causing mutations have increased amyloid and memory impairment
- A$\mathcal{B}$ clearance is slowed in AD compared to normal older individuals
- A$\mathcal{B}$ plaque lowering is associated with slowing of cognitive decline (monoclonal antibodies)

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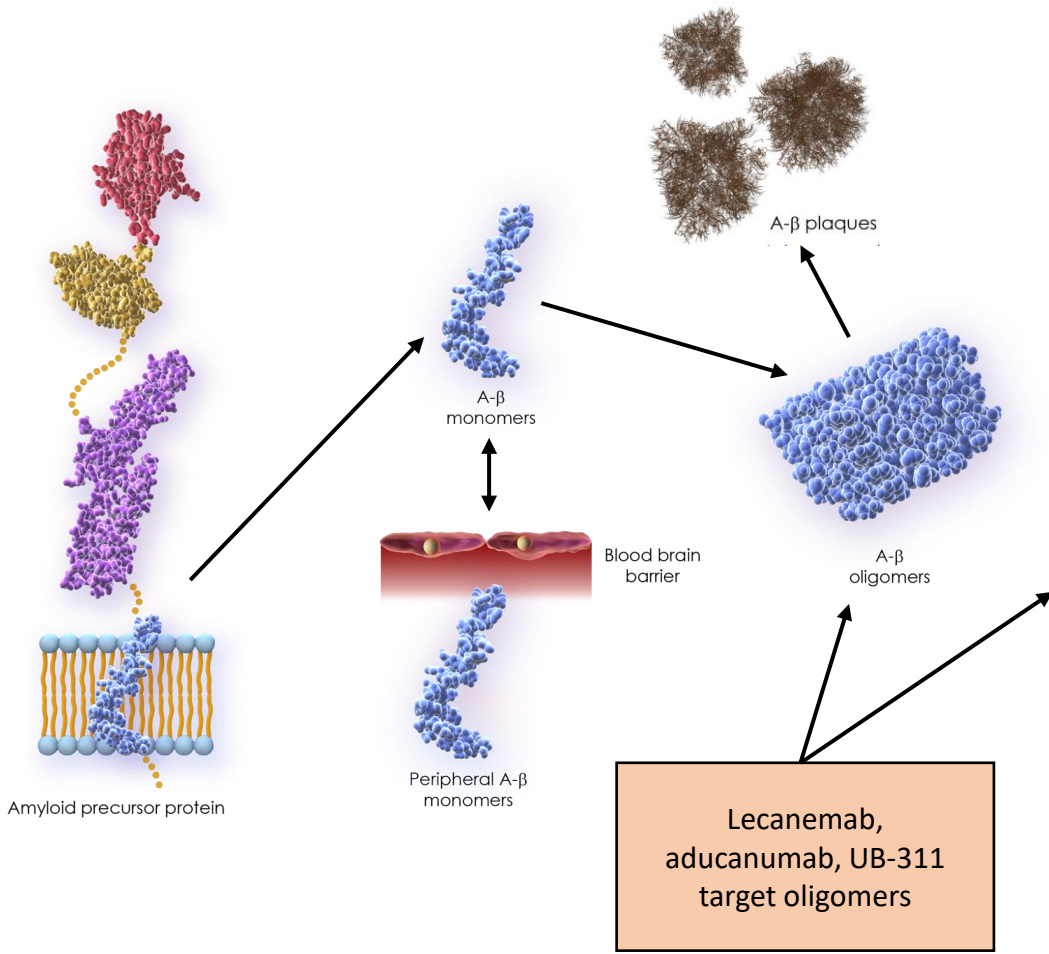

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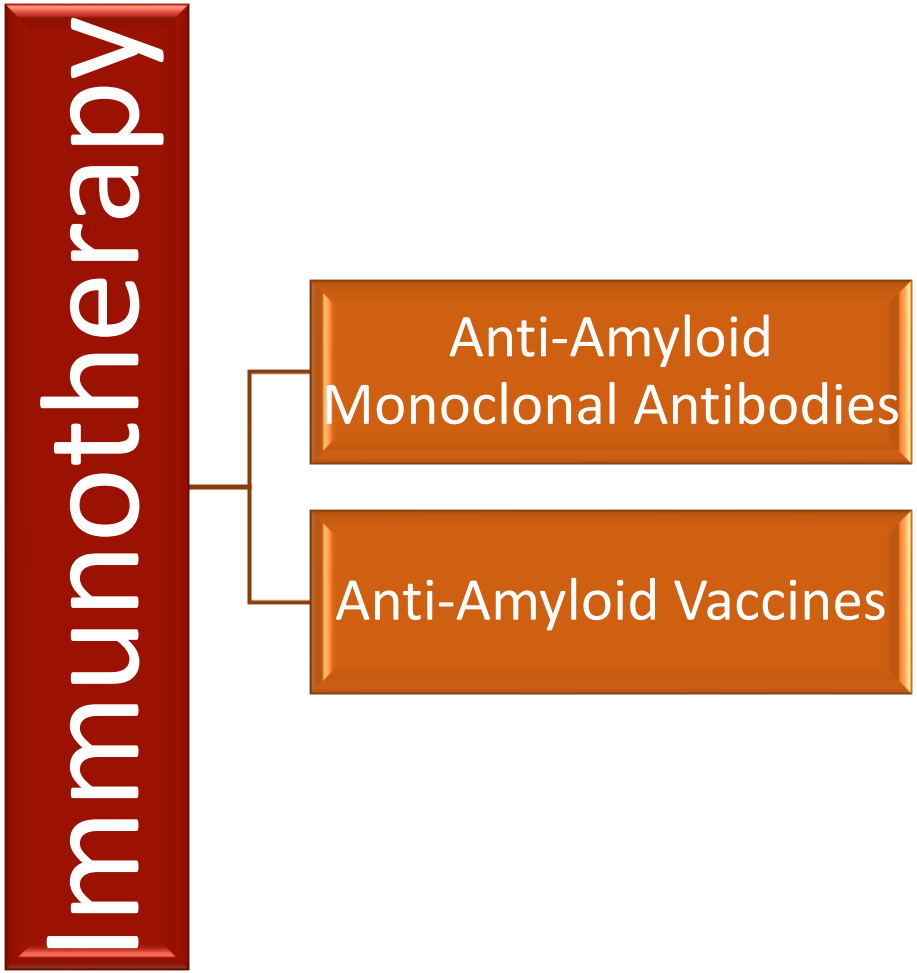
Lecanemab, aducanumab, UB-311 target oligomers



Anti-Amyloid Monoclonal Antibodies

- Aducanumab
- Donanemab
- Lecanemab
- Gantenerumab

Passive infusion of antibodies generated externally

Anti-Amyloid Vaccines

- UB-311 (P2B)
- ABvac-40 (P2)
- ACI-24 (P2)
- ALZ-101 (P1)
- ALZN002 (P1/2a)

Active production of antibodies by the adaptive immune system

Monoclonal Antibodies

- Proof of concept of amyloid lowering and slowing of disease progression/ ameliorating cognitive decline
- Demanding on patients, families, and health care systems
  - Lecanemab – IV infusion every other week
  - Gantenerumab – subcutaneous administration
  - Donanemab and aducanumab – IV infusion once monthly
  - ARIA

UB-311 (Potential Roles in the AD Therapeutic Landscape)

- Given every 3 or 6 months or less frequently
- Potential roles:
  - Treatment - symptomatic patients
  - Secondary prevention – amyloid in the brain; prior to cognitive decline
  - Primary prevention – no amyloid in the brain; prevention of amyloid accumulation
  - ARIA may be less severe with slower amyloid removal

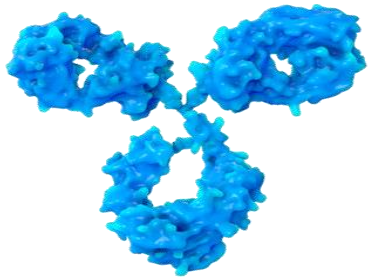
Potential Role of Anti-Amyloid Vaccine in Future Alzheimer Care

AD Drug Development Progress

- Amyloid as target confirmed
- Immunotherapy supported
- New tools available
  - Identify patients (amyloid PET, tau PET)
  - Pharmacodynamic response (amyloid PET)
  - Monitoring (p-tau 217; p-tau 181)
- New outcomes and analyses
  - Preclinical Alzheimer's Cognitive Composite (PACC)
  - Bayesian analyses
  - Global statistical test
  - AD Composite Score (ADCOMS)
  - Amsterdam Activities of Daily Living

Vaccine

- Feasible, accessible
- Equity
- Prevention
- Safety



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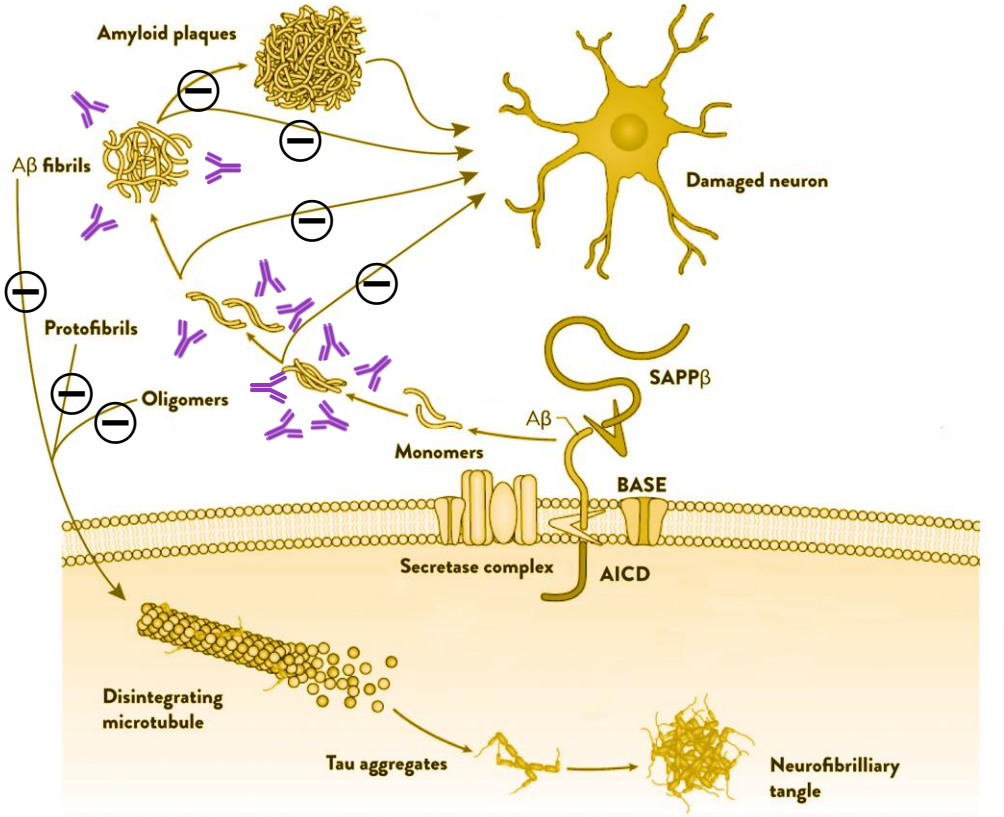
UB-311 targets soluble toxic Aβ species species to reduce neurotoxicity



Immunization reverses memory deficits without reducing brain Aβ burden in Alzheimer's disease model

Jean-Cosme Dodart[1], Kelly R. Bales[1], Kimberley S. Gannon[1], Stephen J. Greene[1], Ronald B. DeMattos[2], Chantal Mathis[3], Cynthia A. DeLong[1], Su Wu[1], Xin Wu[1], David M. Holtzman[2] and Steven M. Paul[1]

[1] *Neuroscience Discovery Research, Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285, USA*

[2] *Center for the Study of Nervous System Injury, Alzheimer's Disease Research Center, Department of Neurology, Molecular Biology and Pharmacology, Washington University School of Medicine, 660 S. Euclid Avenue, Box 8111, St. Louis, Missouri 63110, USA*

[3] *CNRS UMR 7521, Université Louis Pasteur, 12 rue Goethe, 67000 Strasbourg, France*

Correspondence should be addressed to S.M.P. (paul_steven_m@lilly.com)

Published online: 8 April 2002, DOI: 10.1038/nn842

We have previously shown that chronic treatment with the monoclonal antibody m266, which is specific for amyloid β-peptide (Aβ), increases plasma concentrations of Aβ and reduces Aβ burden in the PDAPP transgenic mouse model of Alzheimer's disease (AD). We now report that administration of m266 to PDAPP mice can rapidly reverse memory deficits in both an object recognition task and a holeboard learning and memory task, but without altering brain Aβ burden. We also found that an Aβ/antibody complex was present in both the plasma and the cerebrospinal fluid of m266-treated mice. Our data indicate that passive immunization with this anti-Aβ monoclonal antibody can very rapidly reverse memory impairment in certain learning and memory tasks in the PDAPP mouse model of AD, owing perhaps to enhanced peripheral clearance and (or) sequestration of a soluble brain Aβ species.

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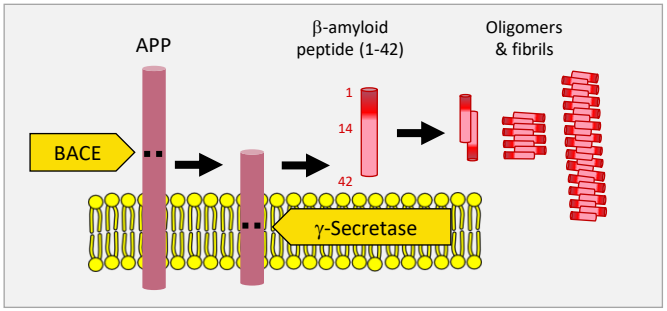
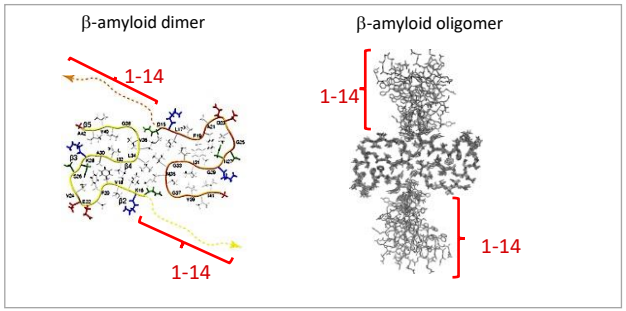
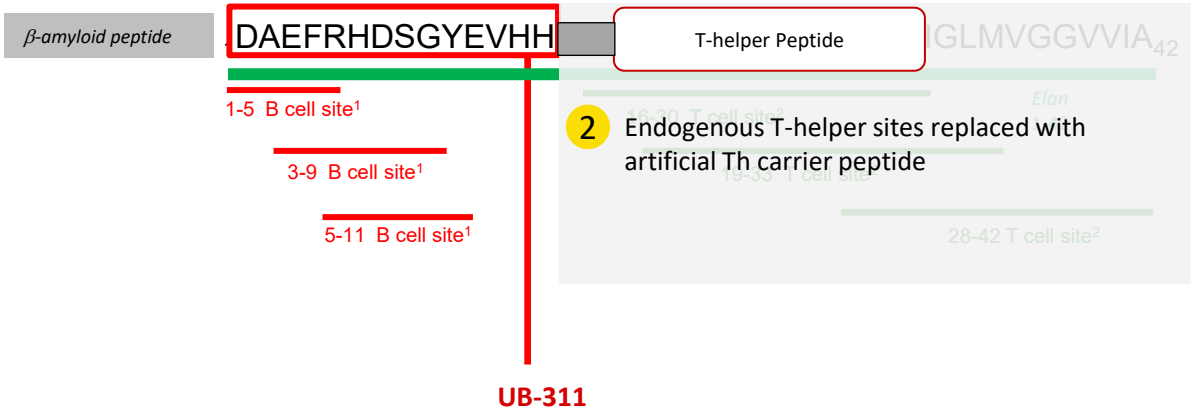
UB-311 was designed to target aggregated Aβ safely, without T cell inflammation







1 Targets N-terminal of amyloid with optimized 1-14 epitope exposed on aggregated Aβ

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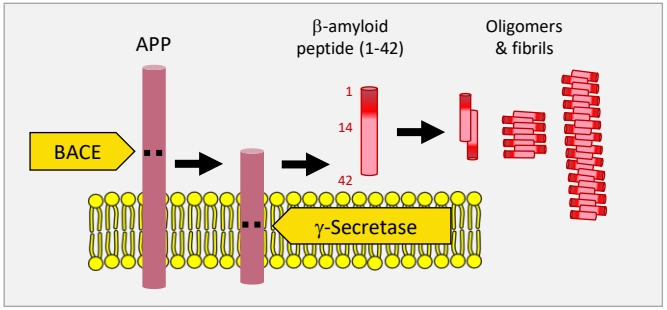
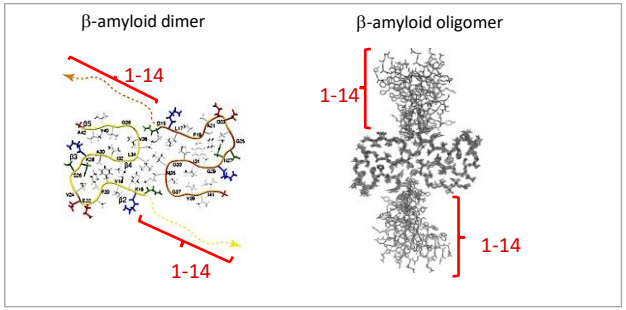
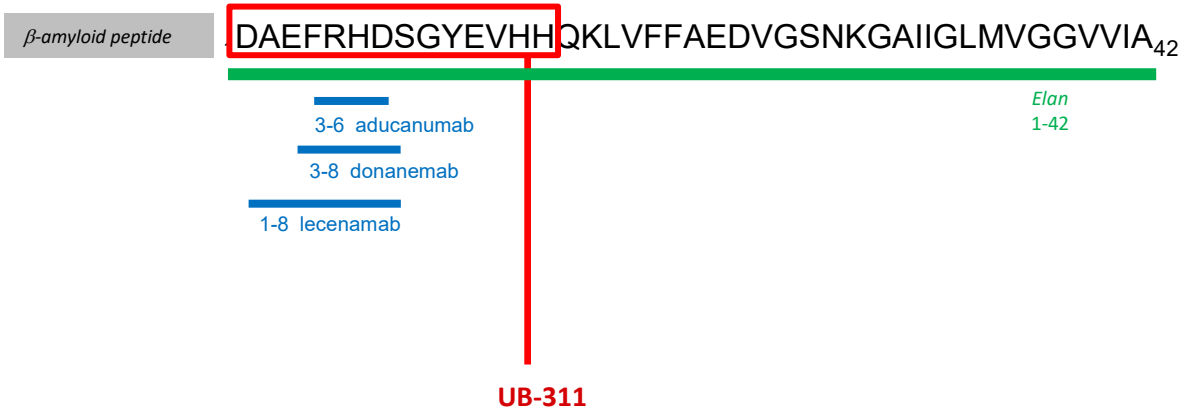
UB-311 was designed to target aggregated Aβ safely, without T cell inflammation







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Completed Phase 2a trial evaluated the safety, immunogenicity, and clinical effects of UB-311 in patients with mild Alzheimer's disease

Objective	Determine the safety, tolerability and immunogenicity, and evaluate the effects of UB-311 on cognitive and functional performance
Sample	N=43 early AD (MMSE 20-26, CDR 0.5-1.0)
Dosing	3 doses of UB-311 (300µg) or placebo EITHER Q3M or Q6M booster doses of 300µg or placebo
Primary endpoints	Frequency of AEs, ARIA Immunogenicity (anti-Aβ antibody levels)
Secondary endpoints	CDR-SB, MMSE, ADAS-Cog13, ADCS-ADL, NPI Amyloid burden determined by PET fMRI

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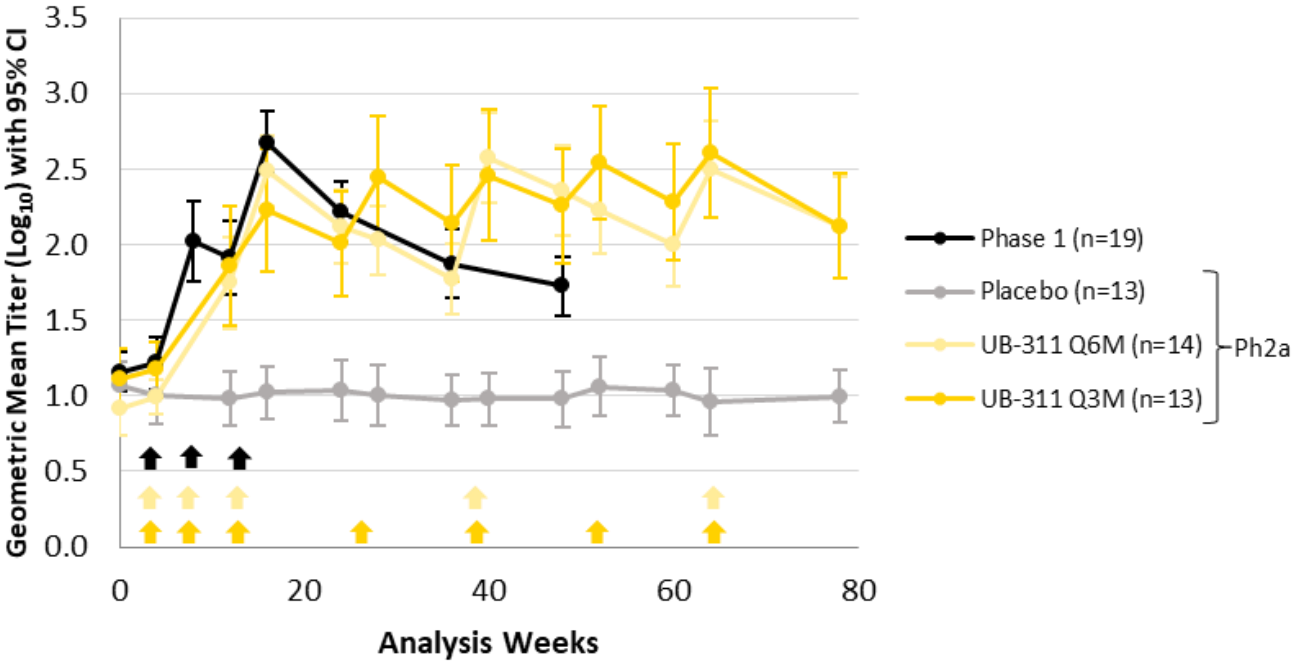
UB-311 yields high response rate and high titers in Ph1 and Ph2a

Anti-Aβ Antibody levels from Ph1 and Ph2a Alzheimer's trials



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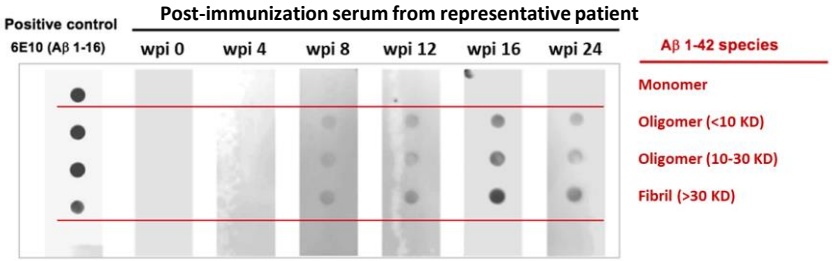
UB-311 induced antibodies bind selectively and hold on to the desired target

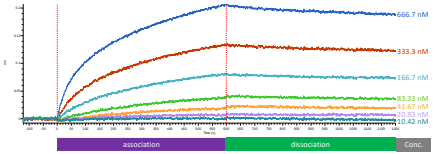
Selective Recognition of Aggregated Aβ, Dot Blot

Ph1 Patient Serum

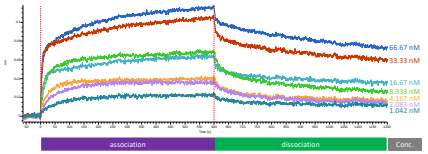


Slow Dissociation Rate from Aβ Dodecamers Indicates Robust Neutralizing Effect

Purified Abs from Ph1 Patient Sera



UB-311



Aducanumab

	K_D (nM)	k_{on} ($M^{-1}s^{-1}$)	k_{off} (s^{-1})
UB-311 generated total IgGs	11.6	9.95×10^3	1.15×10^{-4} s^{-1}
Aducanumab	0.287	5.56×10^6	1.59×10^{-3} s^{-1}
Ratio	40X	560X	0.072X

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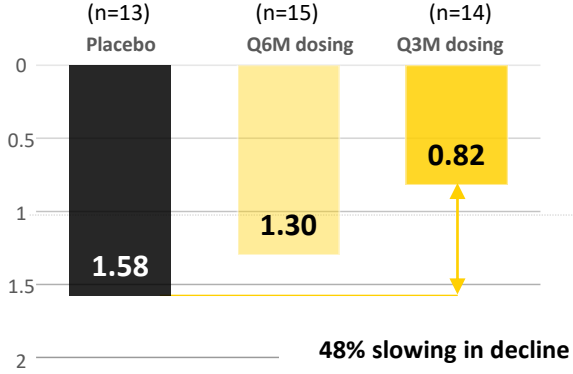
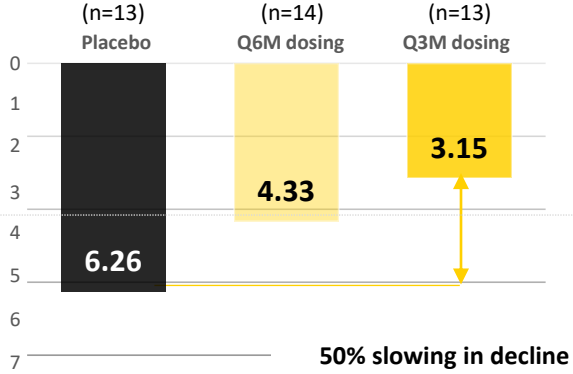
~50% slowing of cognitive and functional decline across key measures

Cognitive Measures

CDR-SB Change from Baseline at Wk 78

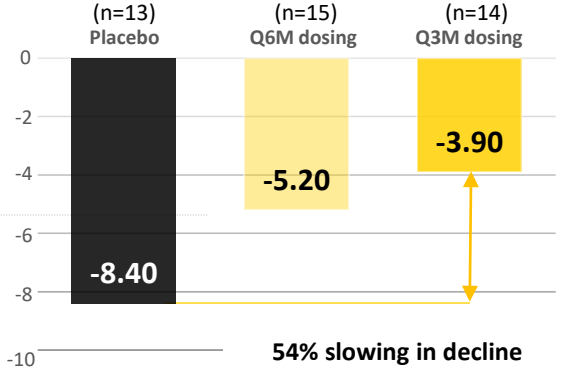


ADAS-Cog Change from Baseline at Wk 78



Functional Measure

ADCS-ADL Change from Baseline at Wk 78



- Phase 2a double-blind, placebo-controlled study
- *Not powered for statistical significance*

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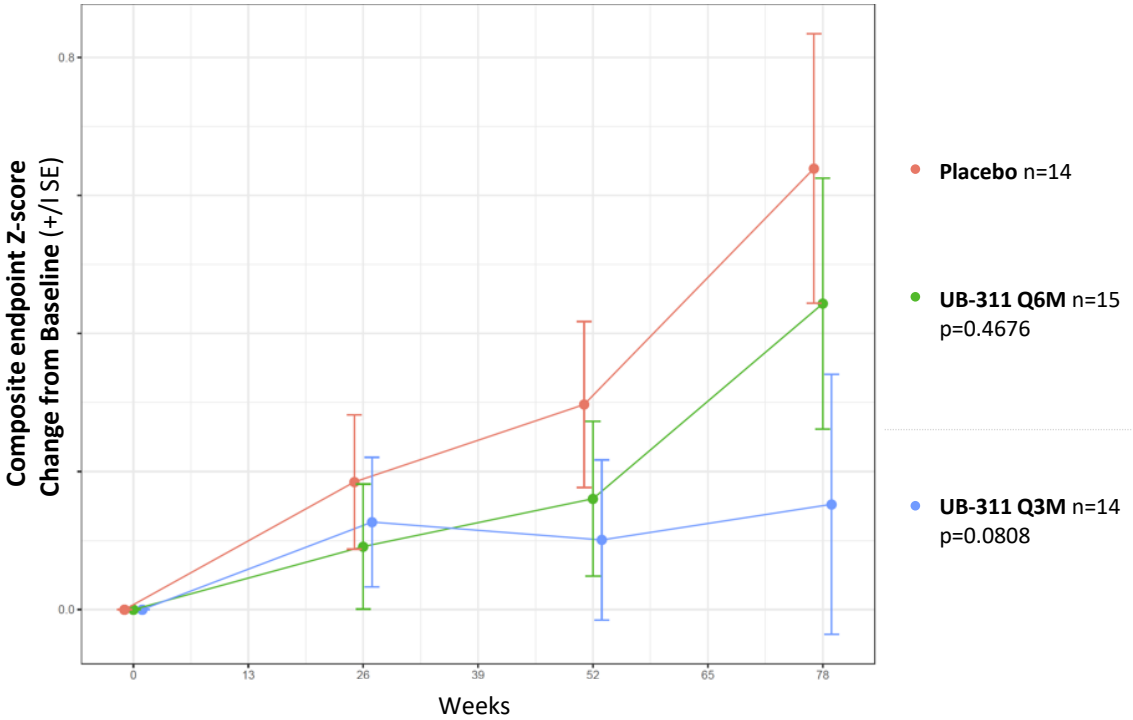
Clinical and biomarker composite exploratory endpoint suggests dose dependent disease-modifying effect in Ph2a

***Post hoc* composite exploratory endpoint*:** Clinical (ADAS-Cog, CDR-SB, ADCS-ADL) + Brain Connectivity (fMRI) + Pathology (PET SUVR)



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UB-311 was well tolerated, no ARIA-E observed in Phase 2a

n (%)	UB-311 Ph1	UB-311 Ph2a Main Trial		
	UB-311 n=19	Placebo n=14	UB-311 Q6M n=15	UB-311 Q3M n=14
Patients with an AE	16 (84.2)	13 (92.9)	13 (86.7)	10 (71.4)
Patients with an SAE	1 (5.3)	2 (14.3)	3 (20.0)	1 (7.1)
Patients permanently discontinuing treatment due to AE	0	1 (7.1)	0	0
Patients permanently discontinuing treatment due to ARIA	0	0	0	0
Number of all-cause deaths	0	0	0	0
ARIA-E	NR	0	0	0
ARIA-H* microhemorrhage	NR	2 (14.3)	2 (13.3)	1 (7.1)
ARIA-H* superficial siderosis	NR	0	0	1 (7.1)

- **Most common TEAE is site injection reactivity** occurring equally in placebo and treatment groups
- **No TEAE causing discontinuation or withdrawal** in Phase 1 or Phase 2a main study

Presented at CTAD 2020 conference (UB-311) and CTAD 2019 (aducanumab)
One case of ARIA-E was observed in the UB-311 Ph2a Long Term Extension trial

*New ARIA cases only

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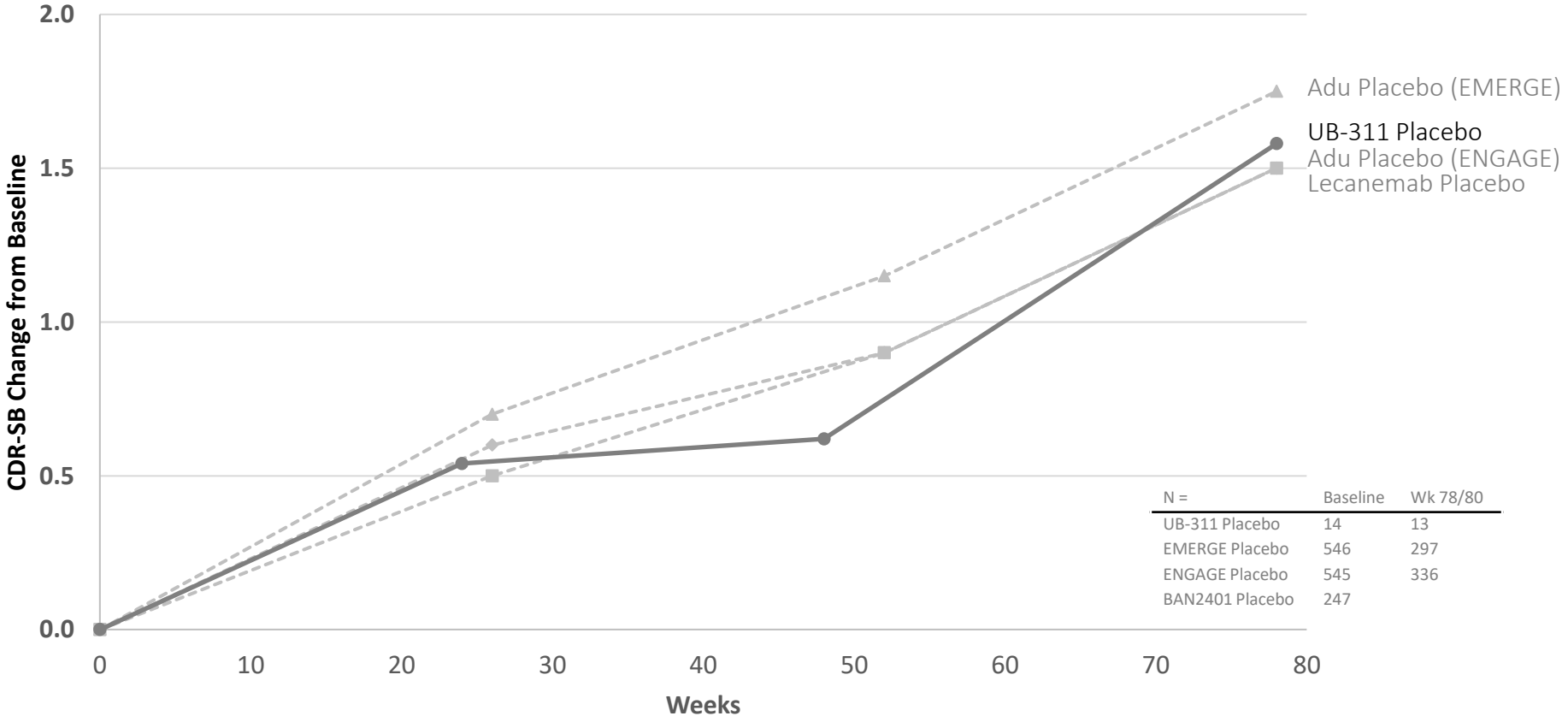
UB-311 Ph2a Baseline Demographics Similar to mAb Programs

	UB-311 Ph2a			Aducanumab			Lecanemab		Donanemab
Mean (SD)	Placebo	Q6M Dosing	Q3M Dosing	PRIME	ENGAGE	EMERGE	Ph2b	CLARITY	TRAILBLAZER
N	14	15	14	165	1,647	1,638	854	1,795	257
Age Inclusion	60 – 90 yo			50 – 90 yo	50 – 85 yo		50 – 90 yo	50 – 90 yo	60 – 85 yo
Age	72.0 (7.6)	72.5 (6.8)	73.4 (6.8)	72.5	70.1	70.7	71.3	72	75.2 (5.5)
MMSE Inclusion	20 – 26			pAD: 24 – 30 mAD: 20 – 26	24 – 30		22 – 30	22 – 30	20 – 28
MMSE	21.9 (1.8)	22.4 (2.4)	23.3 (2.1)	24.1	26.4	26.3	25.6 (2.4)	25.6 (2.2)	23.5 (3.1)
CDR Inclusion	0.5 – 1.0			pAD: 0.5 mAD: 0.5 – 1.0	0.5		MCI: 0.5 mAD: 0.5 – 1.0	MCI: 0.5 mAD: 0.5 – 1.0	NA
Share of CDR=0.5	71%	67%	86%	77%	NR	NR	85%	NR	NR
CDR-SB	3.39 (1.9)	3.50 (2.2)	3.11 (1.3)	3.18	2.41	2.48	3.0 (1.4)	3.2 (1.3)	3.5 (1.9)
ADAS-Cog13	23.6 (6.1)	20.1 (6.2)	23.7 (7.8)	NR	22.5	22.2	22.2 (7.4)*	25.3 (7.3)*	27.6 (7.6)
ApoE4 Carriers	93%	80%	71%	65.1%	69.5%	66.8%	72%	69%	73%
PET SUVR	1.36	1.39	1.40	1.443	1.39	1.38	1.41	NR	100% PET+

*ADAS-Cog14, NR = Not Reported

UB-311 Ph2a and lecanemab Ph2b placebo groups perform similarly



N =	Baseline	Wk 78/80
UB-311 Placebo	14	13
EMERGE Placebo	546	297
ENGAGE Placebo	545	336
BAN2401 Placebo	247	

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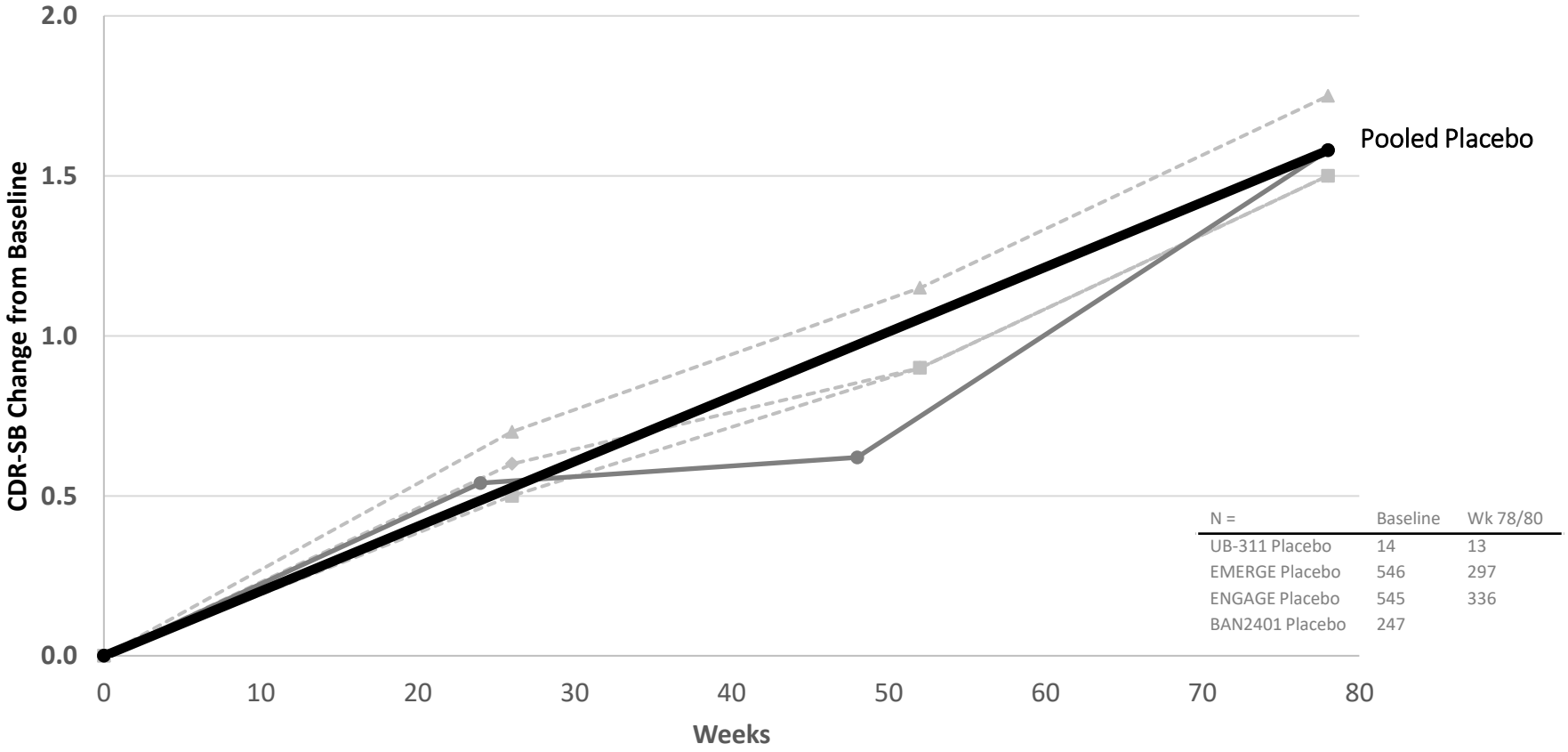
UB-311 Ph2a and lecanemab Ph2b placebo groups perform similarly



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UB-311 Placebo	14	13
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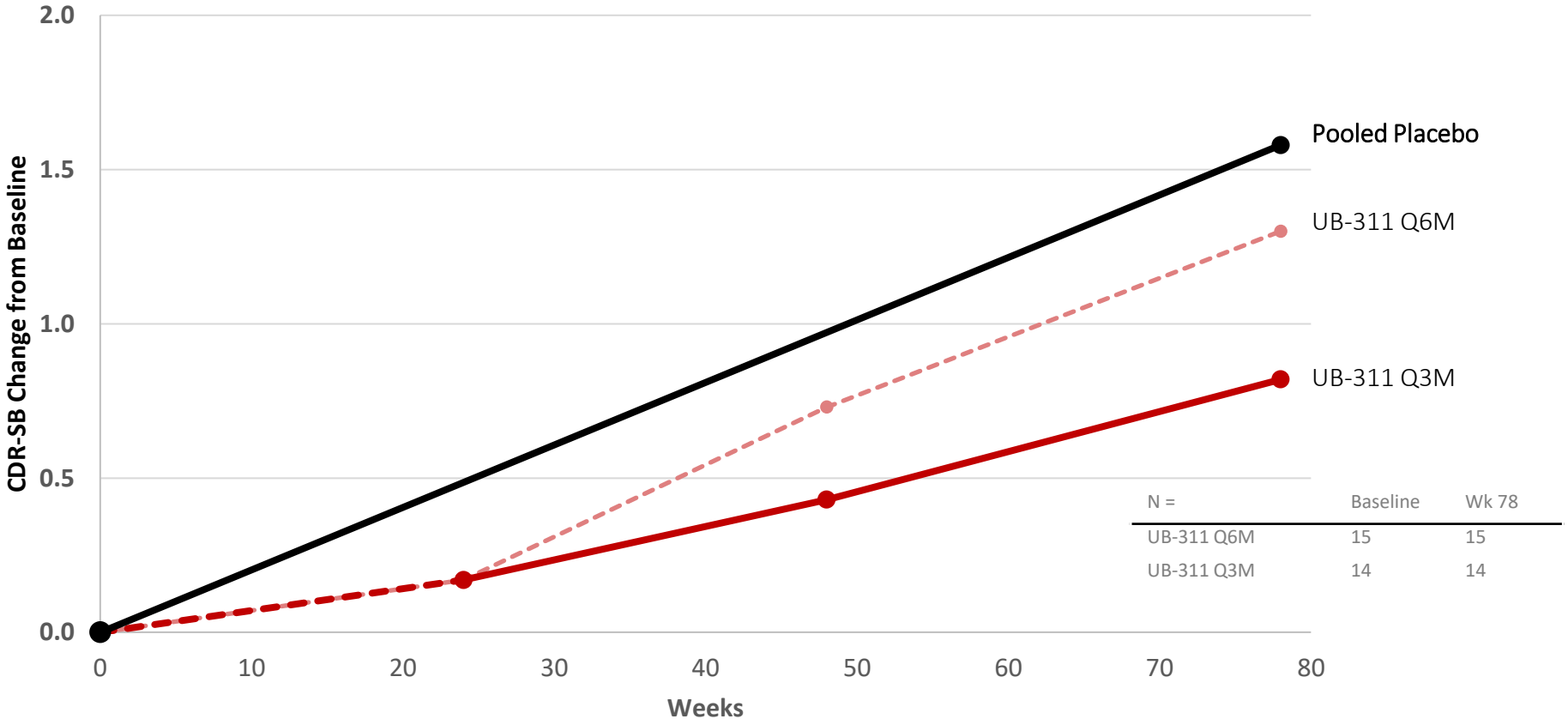
CDR-SB: Reduction in rate of decline with UB-311



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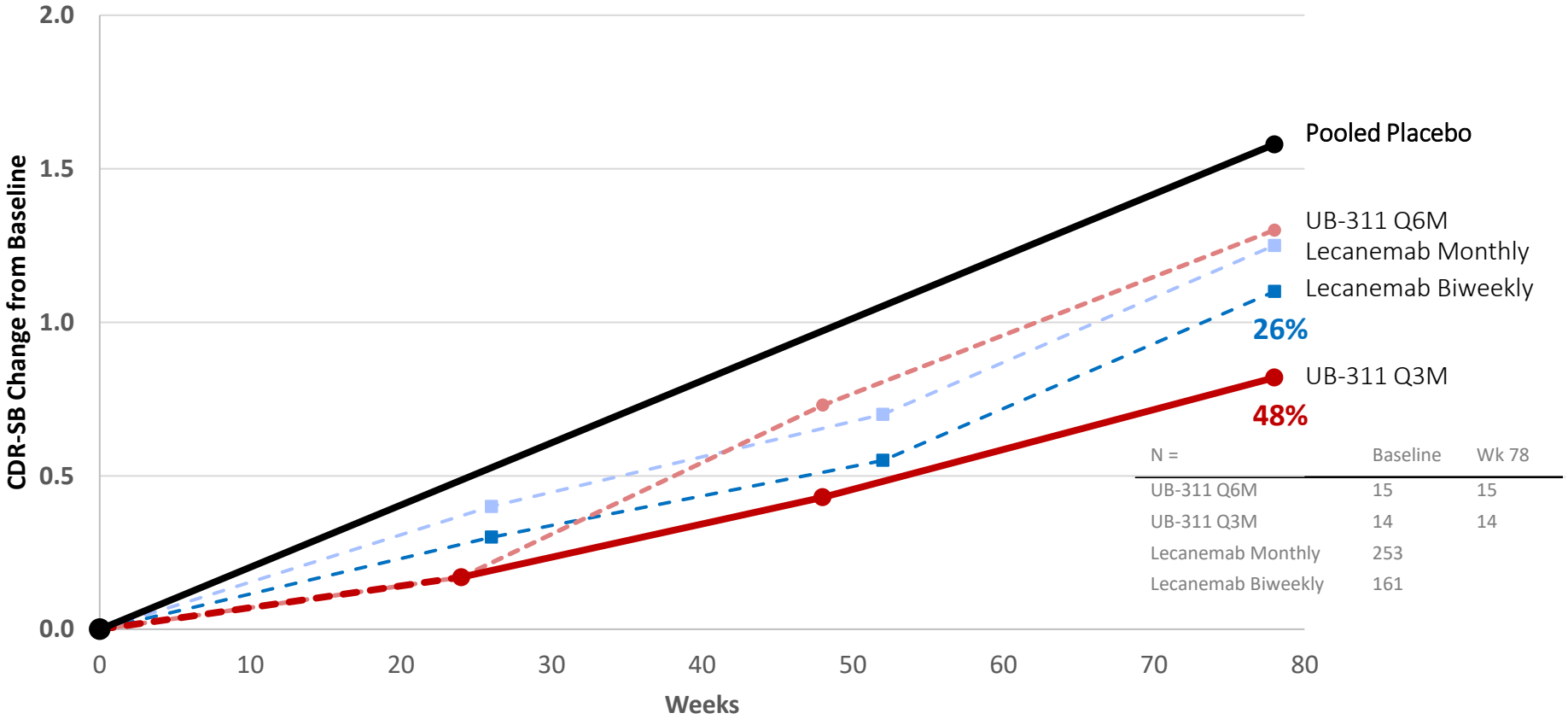
CDR-SB: Reduction in rate of decline with UB-311 & lecanemab



Not a head-to-head comparison

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FDA grants Fast Track Designation to UB-311 following Phase 2b/3 trial feedback

FDA feedback (EOP2)

- Aligned that CDR-SB should be primary endpoint of pivotal trial
- Could allow acceptance of P2b trial for initial licensure, with commitment to conduct additional trial post-licensure

Fast Track Designation granted for treatment of AD in Apr 2022

- Recognition that UB-311 nonclinical & clinical data demonstrate potential to address unmet need for serious condition
- Potentially enables use of rolling review, priority review, and/or accelerated approval (data based)

The amyloid hypothesis has been validated

"Additionally, the lecanemab Clarity AD study results prove the amyloid hypothesis, in which the abnormal accumulation of Aβ in the brain is one of the main causes of Alzheimer's disease, when targeted with a protofibril-binding therapy"

- Haruo Naito, Chief Executive Officer at Eisai

"Following donanemab's TRAILBLAZER-ALZ study, this lecanemab study may further support the benefit of removing amyloid plaques for people with early, symptomatic Alzheimer's data"

Dan Skovronsky, Chief Scientific Officer at Lilly

"Importantly, the study shows that removal of aggregated amyloid beta in the brain is associated with a slowing of disease in patients at the early stage of the disease"

Michel Vounatsos, Chief Executive Officer at Biogen

After all these mAbs, how will a vaccine address unmet need in Alzheimer's disease?

MAbs have validated Aβ, but significant unmet need remains:

1. **Increase access** through convenience and affordability
2. **Increase efficacy**
3. **Eradicate the disease** through prevention

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UB-311 could be the first vaccine to prevent Alzheimer's disease worldwide

Highly prevalent neurodegenerative disease affecting >40 MM patients

	De-risked	
Biology / MOA	✓	• Validated target • High responder rate (98%) • High antibody affinity and specificity to aggregated Aβ • Penetration of BBB
Clinical	✓	• Safe and well-tolerated (no/limited ARIA-E and ARIA-H) • Efficacy and biomarker endpoints consistently favor UB-311 • Ease of administration (Q3M IM)
Regulatory	✓	• Alignment with FDA on Ph2b • Fast Track Designation granted
Manufacturing	✓	• Platform proven scale-up to commercial GMP • Successfully commercialized in animal health over 3B doses

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Q&A

Common Chronic Disease Pipeline

- UB-313 Anti-CGRP Vaccine in Migraine
  Stephen Silberstein, MD, Professor of Neurology, Director, Jefferson Headache Center
  Justin Boyd, Director of Translational Science, Vaxxinity

- VXX-401 Anti-PCSK9 Vaccine in Prevention of Atherosclerotic Heart Disease
  Robert Scott, MD, Fmr VP Global Therapeutic Area Development Head, Amgen
  JC Dodart, SVP Research, Vaxxinity

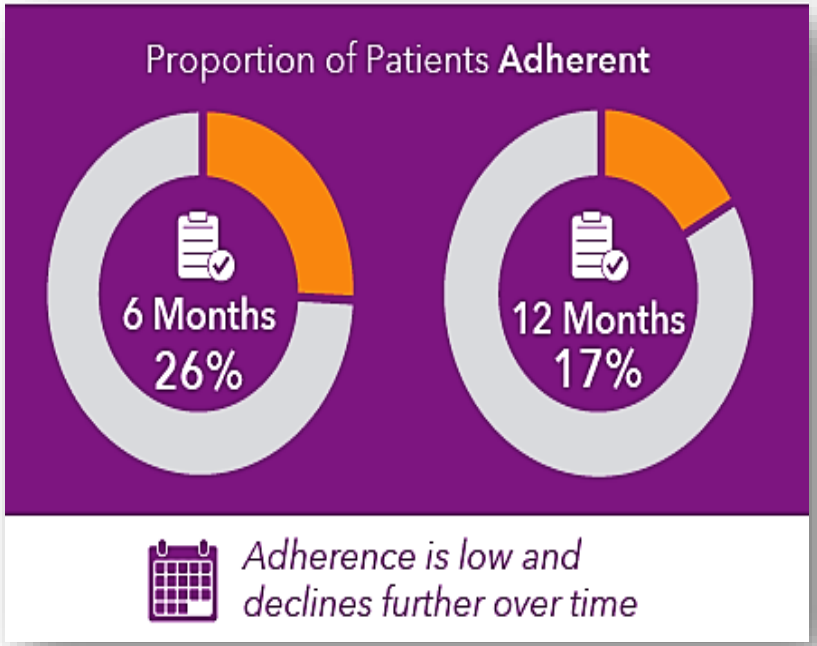

OCTOBER 7, 2002
TIME
Preventing
HEADACHES
The latest research offers new hope for all of us
www.time.com AOL Keyword: TIME

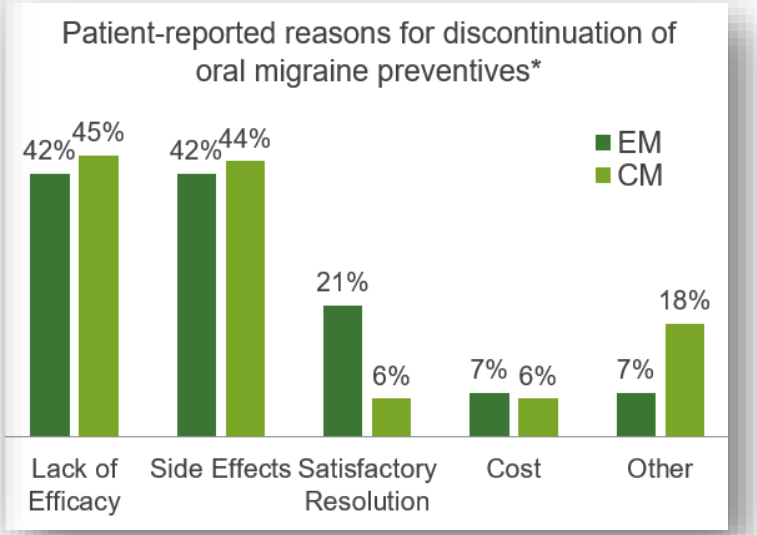
Consider Prevention When

1. **Migraine significantly interferes with patients' daily routine, despite acute treatment**
2. **Frequency attacks (>1/week) with risk of CDH or MOH**
3. **Acute medications ineffective, contraindicated, troublesome AEs, or overused**
4. **Patient preference**
5. **Special circumstances such as**

Hemiplegic Migraine	Basilar Migraine
Migraine with Prolonged Aura	Migrainous Infarction

Migraine Treatment Adherence





1. Tepper SJ, et al. *Headache*. 2004;44(9):856-864. 2. Estemalik E, Tepper S. *Neuropsychiatr Dis Treat*. 2013;9:709-720 3. Hepp Z et al. J Manag Care Pharm 2014;20:22–33. 4. Hepp Z et al. Cephalalgia 2015;35:478–488. 5. Hepp Z et al. Cephalalgia 2017;37:470–485. 6. Blumenfield et al Headache 2013;53(4):644-655; 7. Luykx et al Clin Pharma Therp 2009;85:3:283- 288

CLASSIFICATION

SYSTEMIC

Enteral

Oral

Sublingual

Rectal

Parenteral

Inhalational

Injections

Transdermal

- Intravenous
- Intramuscular
- Subcutaneous
- Intra-arterial
- Intra-articular
- Intrathecal
- Intradermal

LOCAL

- Skin topical
- Intranasal
- Ocular drops
- Mucosal-throat, vagina, mouth, ear
- Inhalational
- Transdermal

Intramuscular Route

ADVANTAGES

- Absorption uniform
- Rapid onset of action
- First pass avoided
- Gastric factors avoided

DISADVANTAGES

- Only can give 10ml
- Local pain and abscess
- Expensive
- Local hematoma in anticoagulated pt

Likes and Dislikes

- **Oral Route**
  1. Slow absorption
  2. Irritable and unpalatable drugs- nausea and vomiting
  3. Food–Drug interactions and Drug-Drug interaction
- **Intramuscular Route**
  1. Absorption uniform
  2. Rapid onset of action
  3. First pass avoided
  4. Gastric factors avoided

Oral Route

- **DISADVANTAGES**

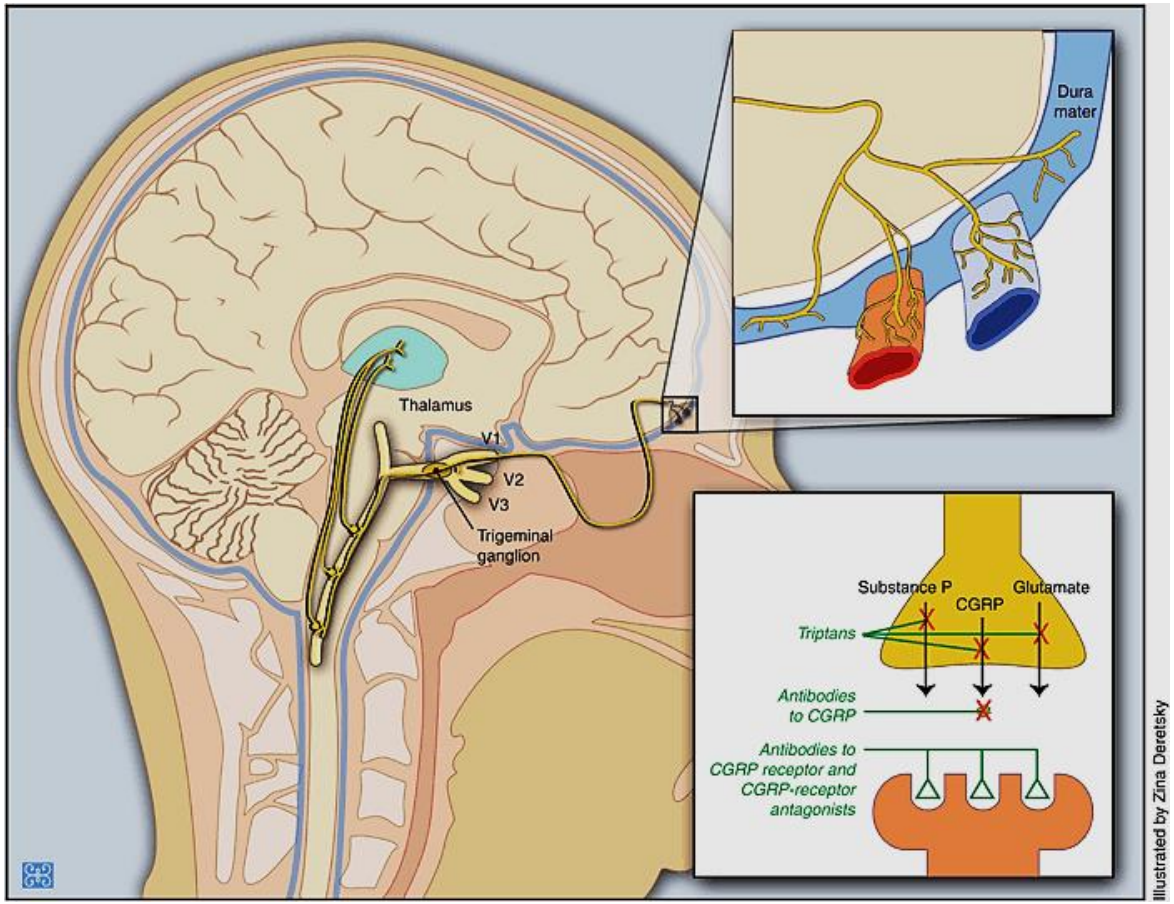
1. Slow absorption
2. Irritable and unpalatable drugs- nausea and vomiting
3. Food–Drug interactions and Drug-Drug interactions

Preventive Medications

- **Anticonvulsants**
  - **Divalproex***
  - **Topiramate***
- **Antidepressants**
  - **TCAs, SNRIs**
- **B-Blockers**
  - **Propranolol*/ Timolol*/ Metoprolol/Atenolol /Nadolol**
- **5-HT antagonists**
  - **Methergine**
  - **Pizotifen**
- **Neurotoxins**
  - **OnabotulinumtoxinA (CM)* ***
- **Angiotensin system**
  - **ACE inhibitors**
  - **Antagonists**
- **mAbs**
  - **Erenumab */ Fremanezumab ***
  - **Galcanezumab */Eptinezumab***
- **Neutroceuticals**
  - **Riboflavin, Coenzyme Q10**
  - **Feverfew, Petasites**
- **Gepants**

***FDA Approved ** CM only**

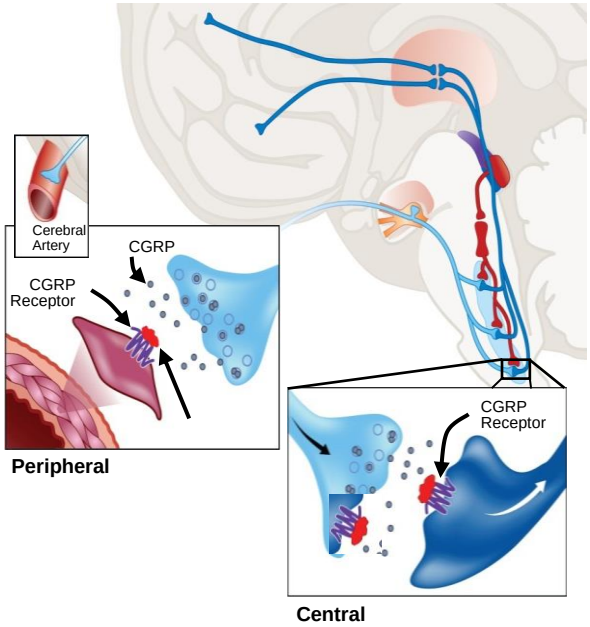
Targeting CGRP In Migraine



Silberstein Clin. Pharm. Ther. 93:78-85, 2013

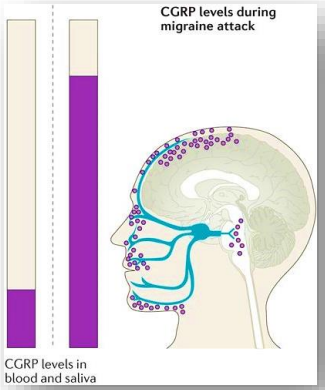
Calcitonin Gene-Related Peptide (CGRP)

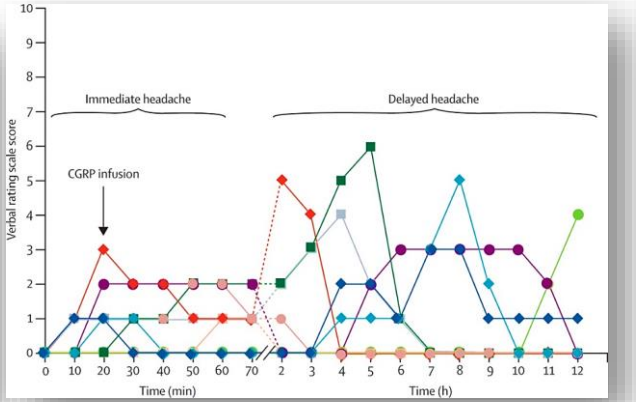
- 37 amino acid neuropeptide
  - Most abundant peptide in Dura and TG
- In C nociceptive neurons
  - Receptor on dural mast cells:
- Released (with glutamate) by activated TGN
- Actions: vasodilation, mast cell degranulation, sensory transmission

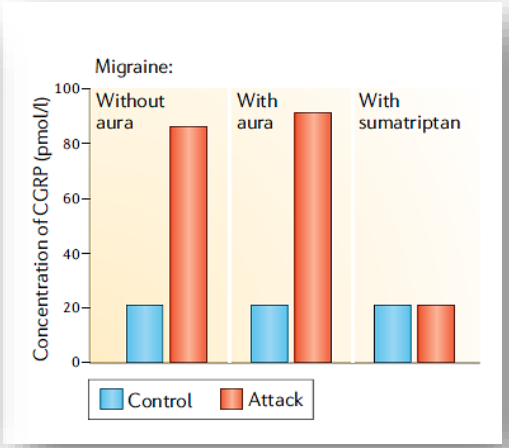


TGN=trigeminal ganglion neurons

Role of CGRP in Migraine







CGRP elevated in spontaneous migraine

IV CGRP induces headache

Successful acute migraine therapy lowers CGRP[3]

CGRP = calcitonin gene related peptide; IV = Intravenous

1. Goadsby PJ, et. al. *Ann Neurol.* 1990;28(2):183-187; 2. Lassen LH, et al. *Cephalalgia.* 2002;22(1):54-61; 3. Juhasz G et al *Cephalalgia*. 2005;25(3):179-183; Figure 1. Schuster NM, Rapoport AM. *Nat Rev*. 2016;12:635-650; Figure 2. Olesen J et al. *Lancet*. 2009;8(7):679-690; Figure 3. Edvinsson L, et al. *Nat Rev*. 2018;14(6):338-350.

Indications for Initiating Treatment: CGRP or Its Receptor Diagnosis of ICHD-3 migraine

A. **4–7 monthly headache days and both** of the following:

   a) Inability to tolerate (due to side effects) or inadequate response to a 6-week trial of at least 2 on the LIST

   b) At least moderate disability (MIDAS>11, HIT-6>50)

B. **8–14 monthly headache days and** inability to tolerate (due to side effects) or inadequate response to a 6-week trial of at least 2 on the LIST

C. **Diagnosis of ICHD-3 chronic migraine and EITHER a or b:**

   a) Inability to tolerate or inadequate response to a 6-week trial of at least 2 on the list

   b) In ability to tolerate or inadequate response to a minimum of 2 quarterly injection (6 months) of onabotulinumtoxinA

- **LIST (**Topiramate; Divalproex sodium/valproate sodium; Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol; Tricyclic antidepressant: amitriptyline, nortriptyline; Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine ; Other Level A or B treatments (established efficacy or probably effective) according to AAN-AHS guideline

AHS Position Statement On Integrating New Migraine Treatments Into Clinical Practice Headache 2019; 59:1-18

Common Chronic Disease Pipeline

- UB-313 Anti-CGRP Vaccine in Migraine
  Stephen Silberstein, MD, Professor of Neurology, Director, Jefferson Headache Center
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  JC Dodart, SVP Research, Vaxxinity

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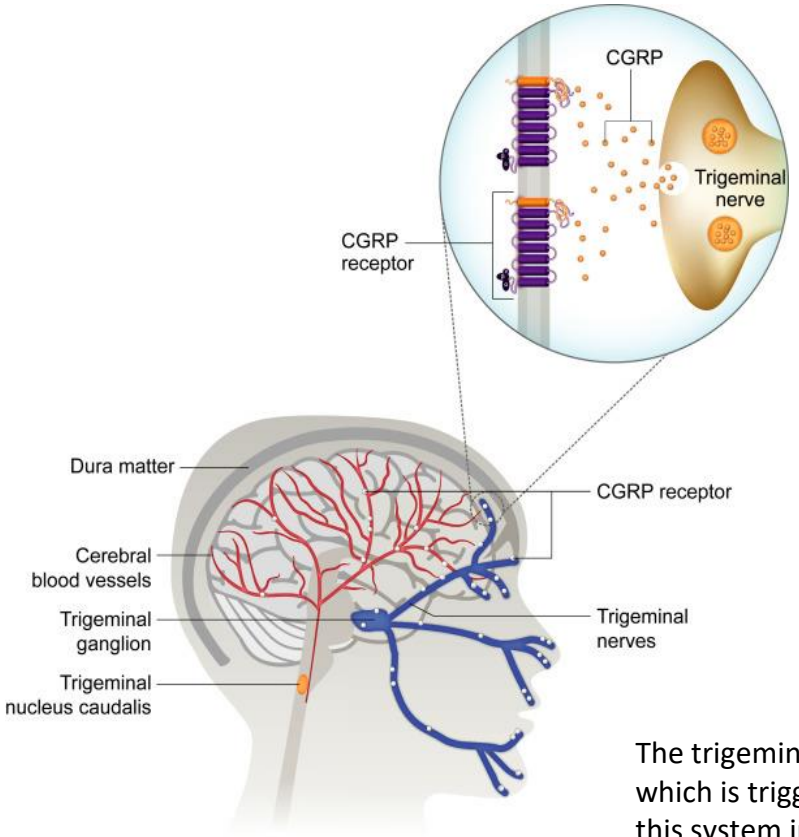
CGRP is a validated target to reduce migraine frequency and severity



- Migraine is a complex, debilitating neurological disorder affecting millions of people worldwide. Multiple studies have confirmed that release of **calcitonin gene-related peptide** (CGRP) is increased during acute migraine attacks.
- The underlying mechanisms are not yet fully known.
- CGRP receptor antagonists, anti-CGRP antibodies and anti-CGRP receptor antibodies have proved effective for migraine pain relief, strongly supporting the hypothesis that CGRP has a major role in migraine pathophysiology.

The trigeminal ganglion is central to the trigeminovascular reflex, which is triggered to protect against vasoconstriction; triggering of this system in patients with migraine leads to the perception of pain.

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UB-313 Vision: First choice for migraine sufferers to reclaim their lives

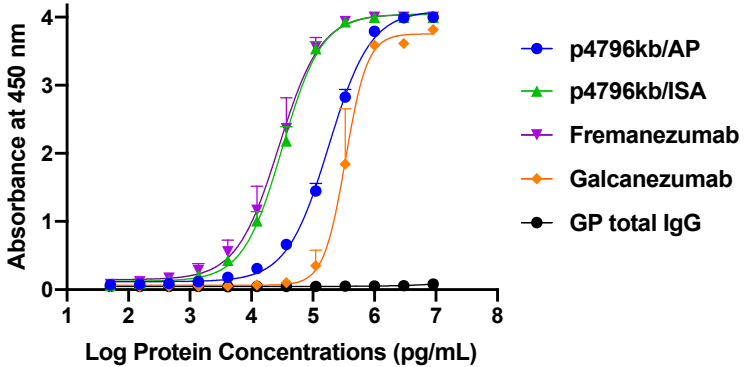
Data through Preclinical POC

- **High titers** across species
- Selectively targets **CGRP C-terminus**
- **Binding potency** comparable to mAbs
- **Inhibits CGRP-induced cAMP** in human cells dose-dependently
- **Activity in translatable animal model** comparable to mAbs

Status: Ph1 FIH trial initiated, topline data 1H23

Antibodies induced by UB-313 show potent binding and neutralizing of CGRP

Binding potency of anti-αCGRP are comparable to therapeutic monoclonal anti-CGRP antibodies.



CGRP vaccine derived antibodies exhibit efficacy comparable to mAbs in cells and animals.

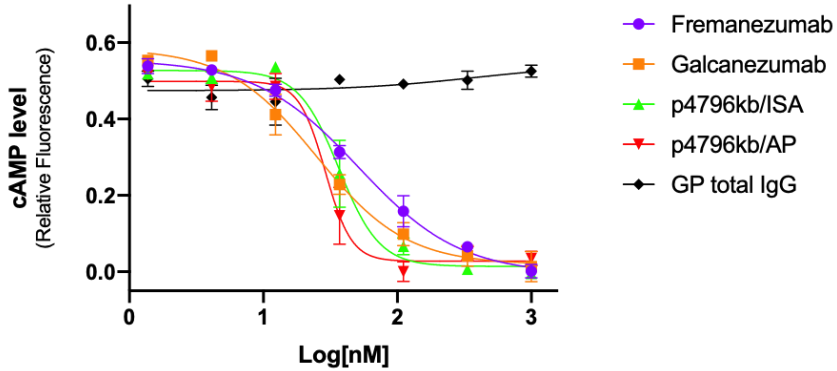


Table 1: Binding kinetics of anti-αCGRP antibodies from guinea pigs immunized with p4796kb peptide immunogen

Ligand vs Analyte	Ka (1/Ms)	Kd (1/s)	KD	Chi² (RU²)
Fremanezumab vs CGRP	3.59×10^{5}	1.73×10^{-6}	4.83 pM	2.36×10^{-2}
Galcanezumab vs CGRP	1.01×10^{6}	1.08×10^{-5}	10.7 pM	1.88×10^{-1}
p4796kb vs CGRP	3.50×10^{6}	4.57×10^{-5}	13.1 pM	6.97×10^{-2}

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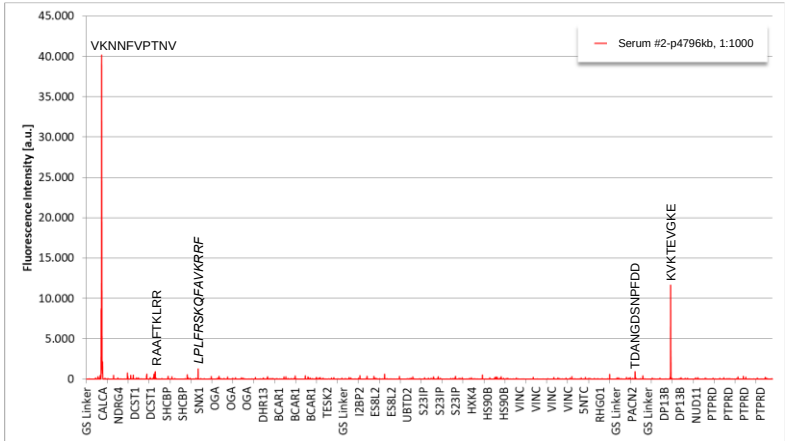
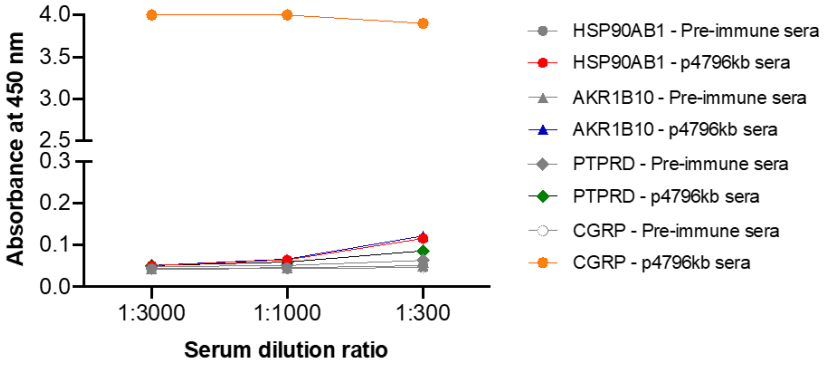
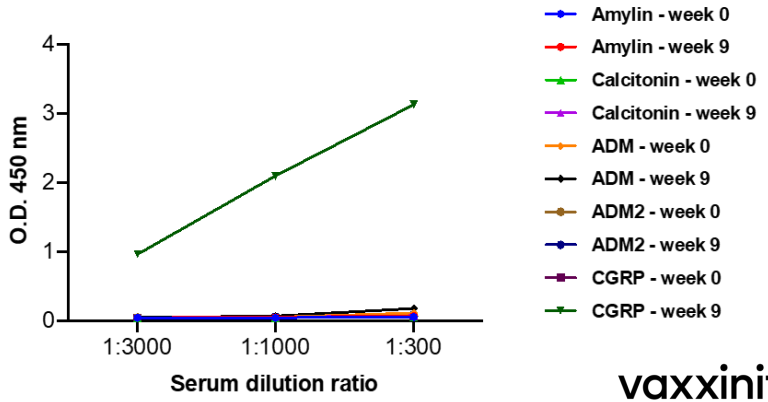
Antibodies induced by UB-313 are highly specific, they only bind CGRP

PEPperMAP® Hit Validation following a HuProt™ Human Proteome Microarray Screen (>20,000 human proteins screened)



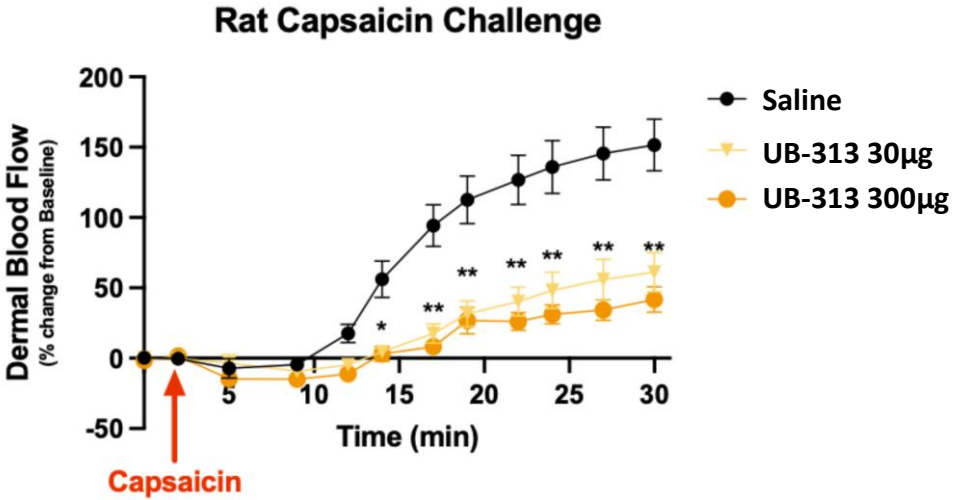
VAXXINES overcome immune tolerance against desired targets only





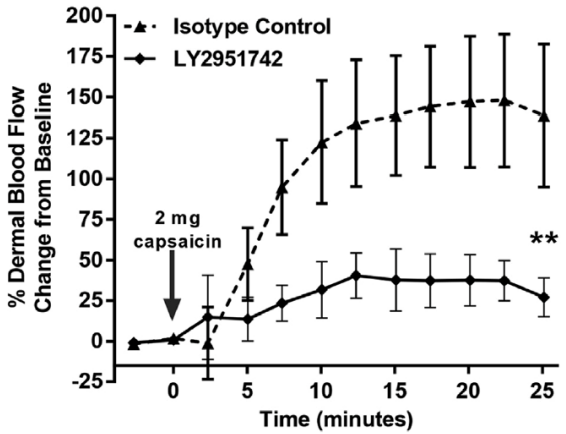
Immunization with UB-313 blocks the effects of capsaicin-induced DBF in rats

VAXXINE



Rats (n = 6-8 / group) were immunized with the "rat version" of UB-313 and challenged with Capsaicin. Local DBF was measured by Laser Doppler Imaging.
*p < 0.05; **p < 0.01

Galcanezumab



Benschop et al. 2014. Development of a novel antibody to calcitonin gene-related peptide for the treatment of osteoarthritis-related pain. *Osteoarthritis and Cartilage 22, 578-585.*

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UB-313 in ongoing Phase 1 trial to evaluate safety, immunogenicity, and target engagement

Objective	Determine the safety, tolerability, and immunogenicity of UB-313
Sample	N=40 Healthy Volunteers (18-55 yo)
Dosing	3 doses of UB-313 (various dose levels) or placebo at weeks 0, 4 and 12
Primary endpoints	Frequency of AEs Immunogenicity (anti-CGRP antibody levels)
Secondary endpoint	Effect on capsaicin-induced dermal blood flow (DBF) as a surrogate marker of target engagement

UB-313 is another blockbuster commercial opportunity

- Increased convenience and lower cost opens potential to leapfrog mAbs & Botox for first line prevention of chronic + episodic migraine (can be used with acute/rescue medication)
- Geographic expansion opportunity
- Pricing range to aim for first-line coverage / prevention
- Sales are sustainable

Chronic + Episodic Migraine: Worldwide
> 400 M patients

Chronic + Episodic Migraine: US
~15 M patients

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Q&A

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Rob Scott MD – Relevant Experience

Pfizer

Led Cardiovascular & Metabolic Group, responsible for post NDA development of Lipitor

Amgen

Led CardioRenal Group, responsible for development of Repatha

Abbvie

Chief Medical Officer
Head of Development

Cerenis Therapeutics

Chief Medical Officer
Head of Development
Development of Synthetic HDL

Kanan Therapeutics

Founder, Chairman
Responsible for R&D activities for PCSK9 small molecule and vaccine

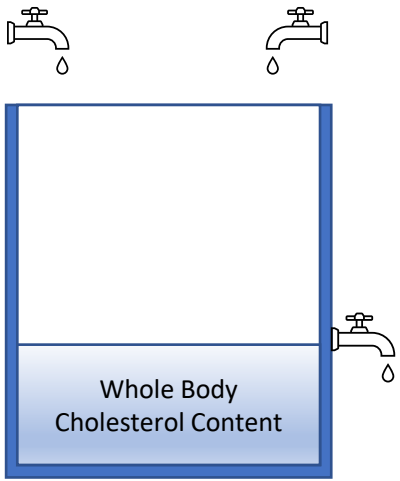
FDA

CardioRenal Advisory Committee
Endocrine & Metabolic Advisory Committee

Hunter Gatherer Cholesterol Balance

Exogenous Absorption

Cholesterol in diet



Endogenous Production

All cells capable of Cholesterol Production
Mainly liver

Excretion

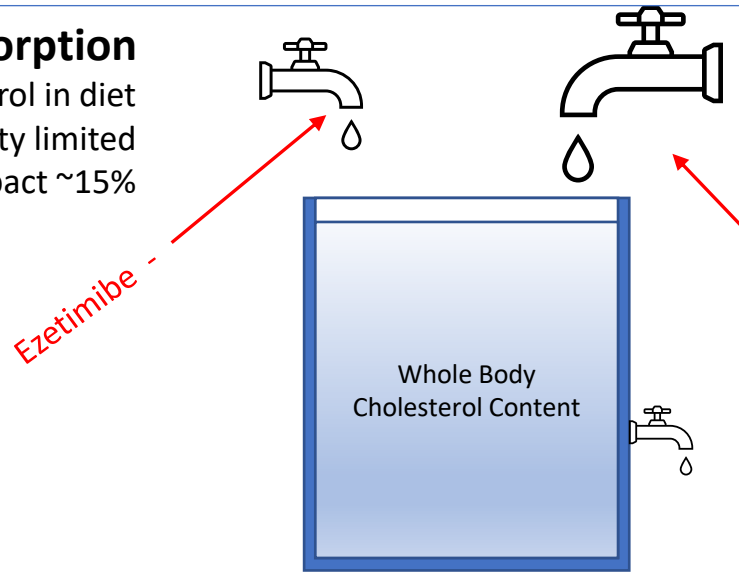
Bile Salts
Conversion to Steroid Hormones

Rob Scott, Unpublished personal opinion.

Westernized Modern Human Cholesterol Balance

Exogenous Absorption

Cholesterol in diet
Absorption capacity limited
Relatively minor impact ~15%



Endogenous Production

All cells capable of Cholesterol Production
Impacted by diet through body weight
Mainly liver

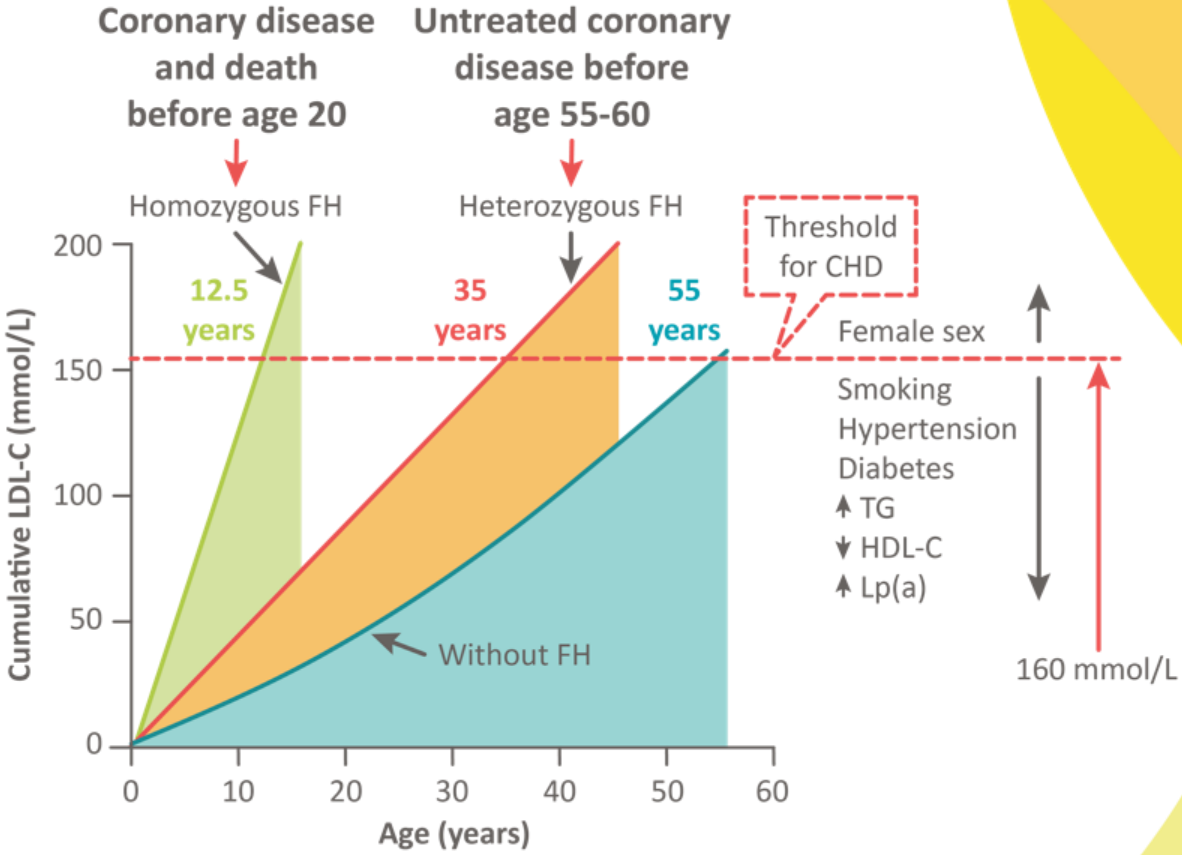
Excretion

+ Cholestyramine

Bile Salts
Conversion to Steroid Hormones

Rob Scott, Unpublished personal opinion.

Cumulative LDL-C burden determines CV risk in FH



ASCVD = atherosclerotic cardiovascular disease;
HDL-C = high-density lipoprotein cholesterol;
Lp(a) = lipoprotein(a); TG = triglycerides

Nordestgaard BG *et al*. *Eur Heart J* 2013;**34**:3478-90.

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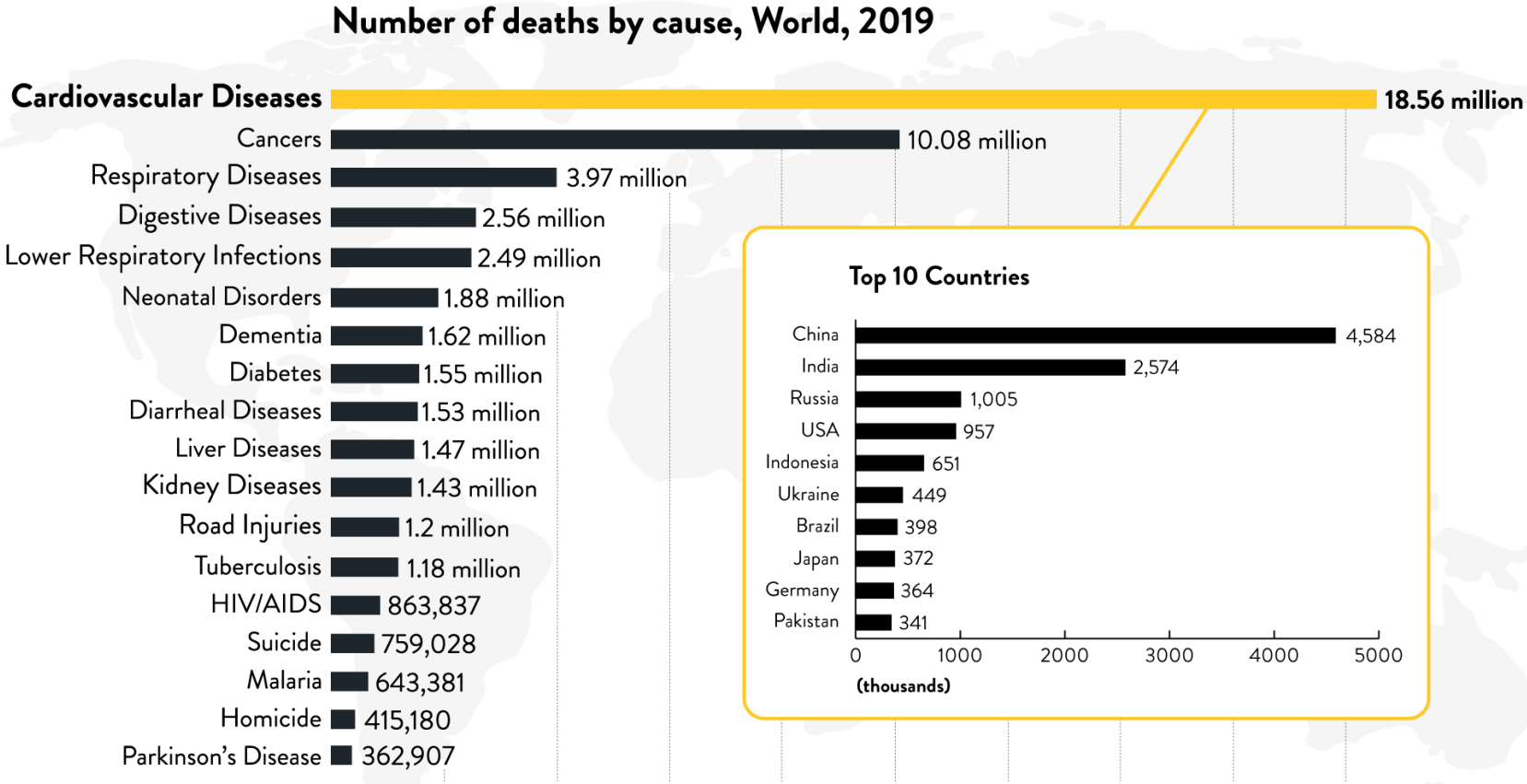
  JC Dodart, SVP Research, Vaxxinity

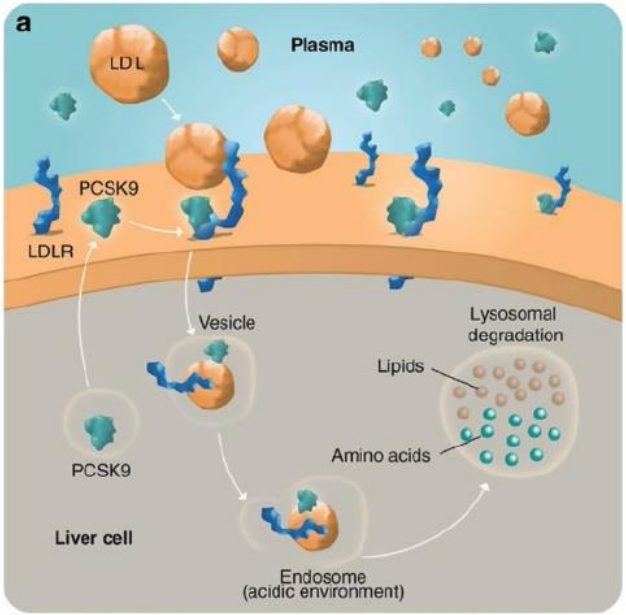
Cardiovascular disease is the leading killer in the world



 Source: Our World in Data, 2019

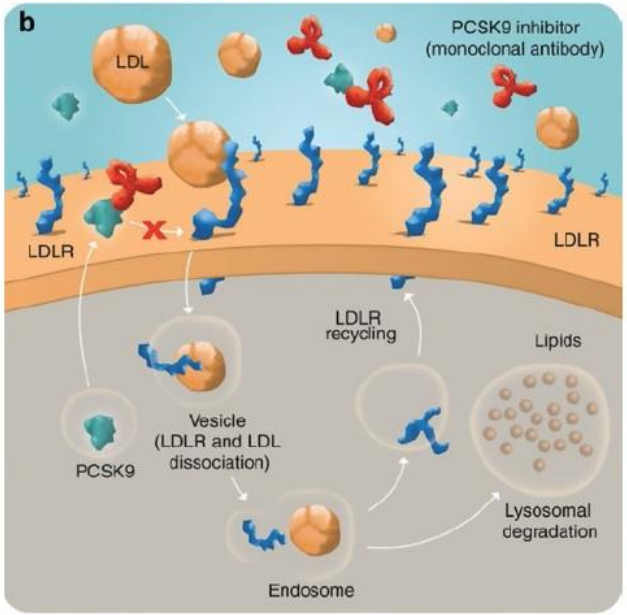
PCSK9 is a well validated target to reduce LDL-c

How does PCSK9 work?



a) Secreted PCSK9 binds to LDLR on the liver cell surface and mediates the lysosomal degradation of the complex formed by PCSK9 - LDLR - LDL.

How does Inhibitors work?



b) In the presence of a monoclonal antibody that binds to PCSK9, the PCSK9-mediated degradation of LDLR is inhibited, resulting in an increased uptake of LDL-cholesterol by LDLR as more LDLR are recycled at the cell surface.

Source: Kühenbühl S, et al. Unmet Needs in LDL-C Lowering: When Statins Won't Do! Drugs. 2016 Aug;76(12):1175-90

- **3 inhibitors on market**

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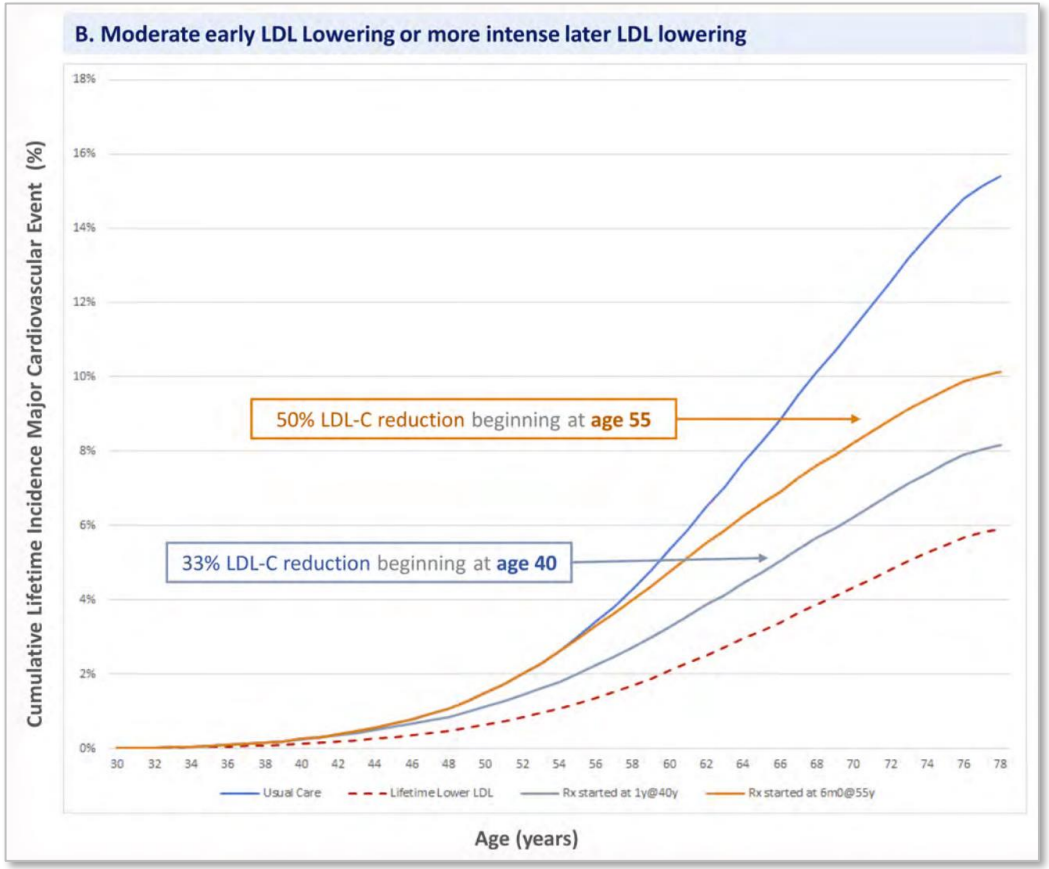
Moving from “lower is better” to “**earlier is better**”



Earlier intervention >>
More reduction

Excerpt from World Heart Federation Cholesterol Roadmap 2022

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Large unmet need remains in preventing atherosclerotic heart disease

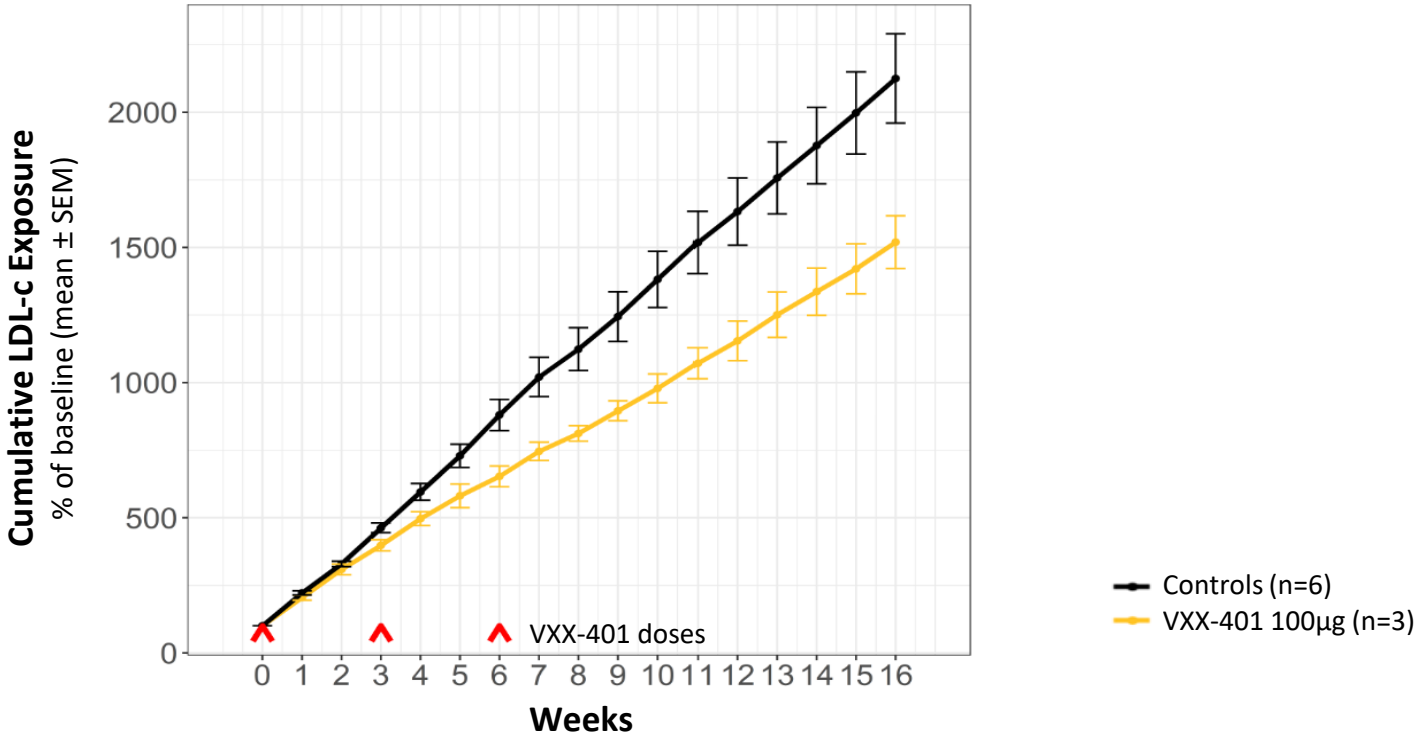
- **Low adherence:** <50% of those prescribed statins remain on after one year
- **Low accessibility:** PCSK9 inhibitors, and even statins in many countries, remain unaffordable
- Less than 50% of patients in need are on LLTs (<1% on PCSK9)

Need for convenient and accessible lipid lowering therapy that can reduce cumulative LDL-C exposure earlier to lower lifetime risk

Our anti-PCSK9 vaccine VXX-401 reduces the cumulative exposure to LDL-c

Cumulative LDL-c % of Baseline Over 16 Weeks

Study in non-human primates



Two outliers were removed from VXX-401 treatment group

42% is the difference between the VXX-401 and control slopes by linear regression

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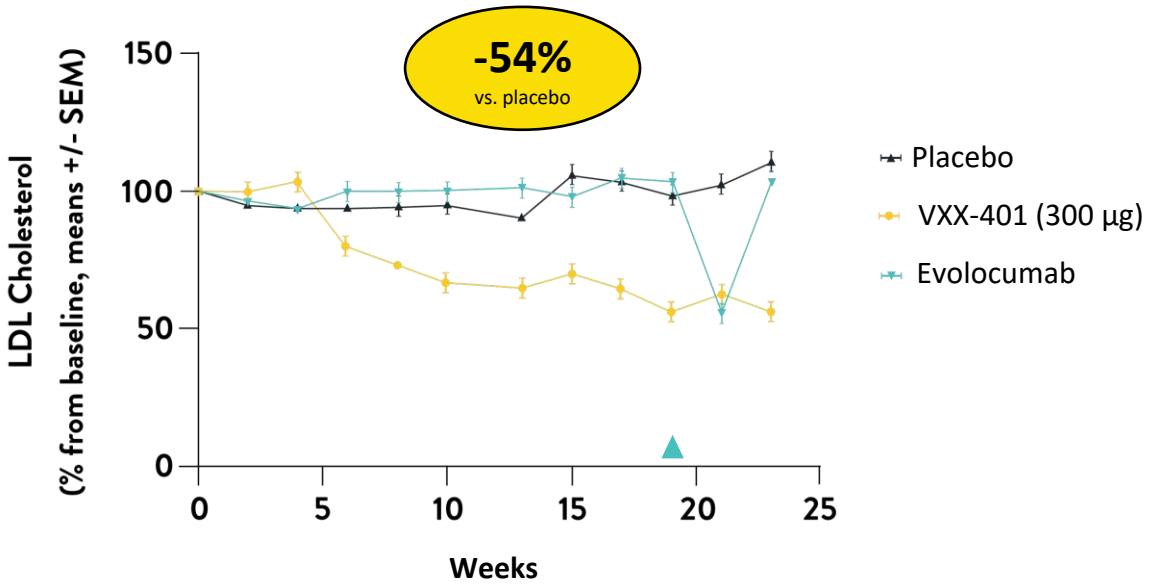
VXX-401 may offer similar LDL-c reduction to mAb

VXX-401 Reduces LDL-c Comparable to Single Dose of Approved MAb



Placebo and VXX-401 groups received IM injections at weeks 0, 3, 6, 13, 16, 19.
Evolocumab group received one 3 mg/kg SC injection at week 19.
N = 3 NHPs in VXX-401 group, 6 NHPs across 2 control groups
This was a non-optimized vaccine formulation using the same peptide immunogen as VXX-401.

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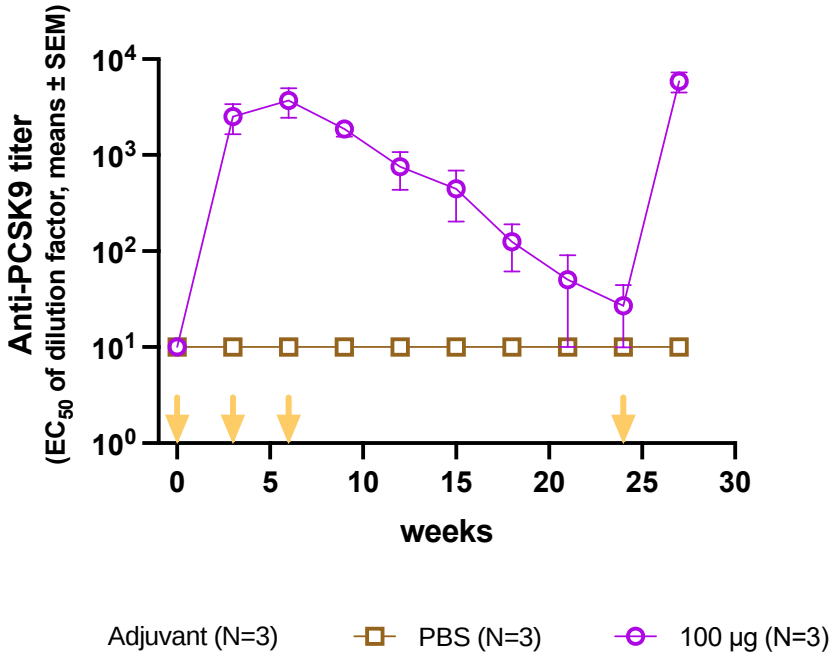
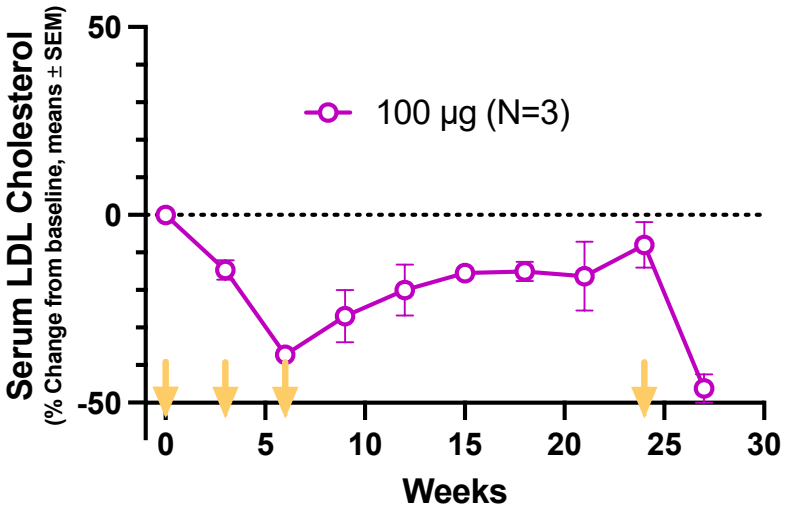
VXX-401 in NHPs: LDLc lowering follows antibody production

High and modulable antibody titers



Serum LDL-C can be reduced on-demand

(data are represented as differences from controls)



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A Phase 1/2 trial will evaluate the safety, immunogenicity, and pharmacodynamics of VXX-401 alone and in combination with statins

Objective	Determine the safety and tolerability of VXX-401, and an optimal priming/boost regimen for LDL-C reduction and PCSK9 concentrations
Sample	N=160 subjects with LDL-c 100-189mg/dL (80 on statin 80 naïve)
Dosing	3 or 4 doses of VXX-401 (various dose levels) or placebo at weeks 0, 4, (8), and 12 1 booster dose of VXX-401 (various dose levels) or placebo
Primary endpoints	Frequency of AEs LDL-C in blood PCSK9 in blood
Secondary endpoint	Lipid profiles Immunogenicity (Anti-PSCK9 antibody levels in blood)

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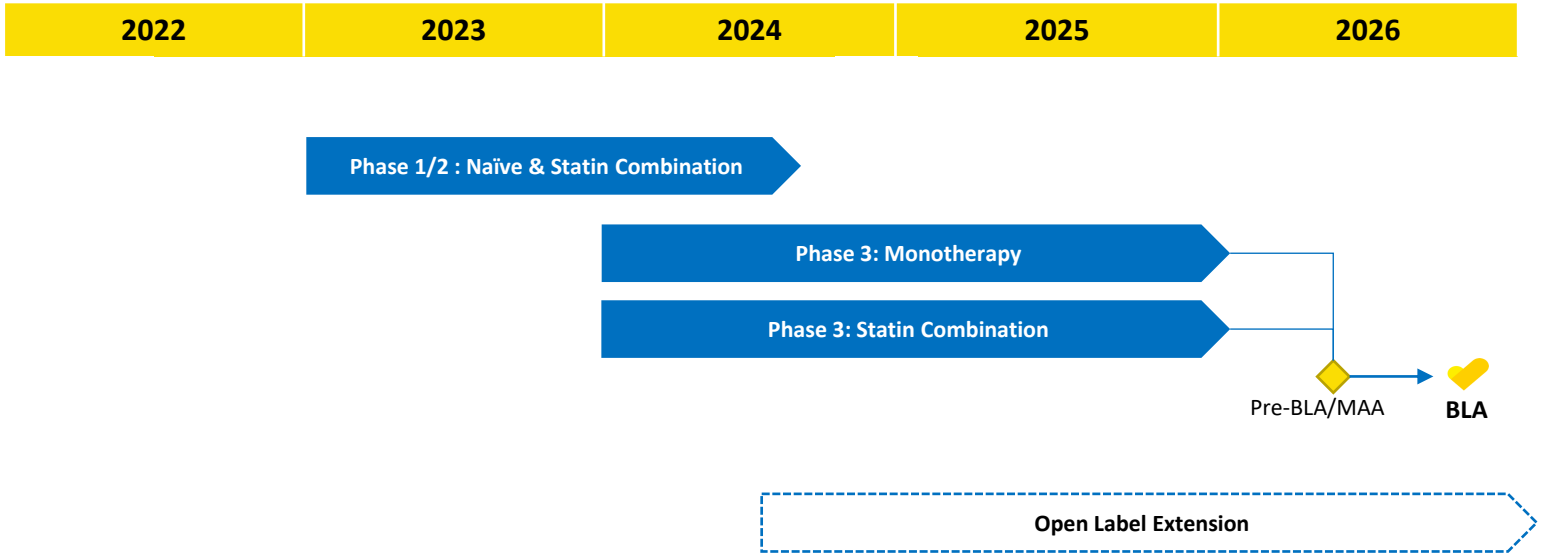
VXX-401 Clinical Development Plan: Hypercholesterolemia

Less than 4 years to potential BLA with accelerated path



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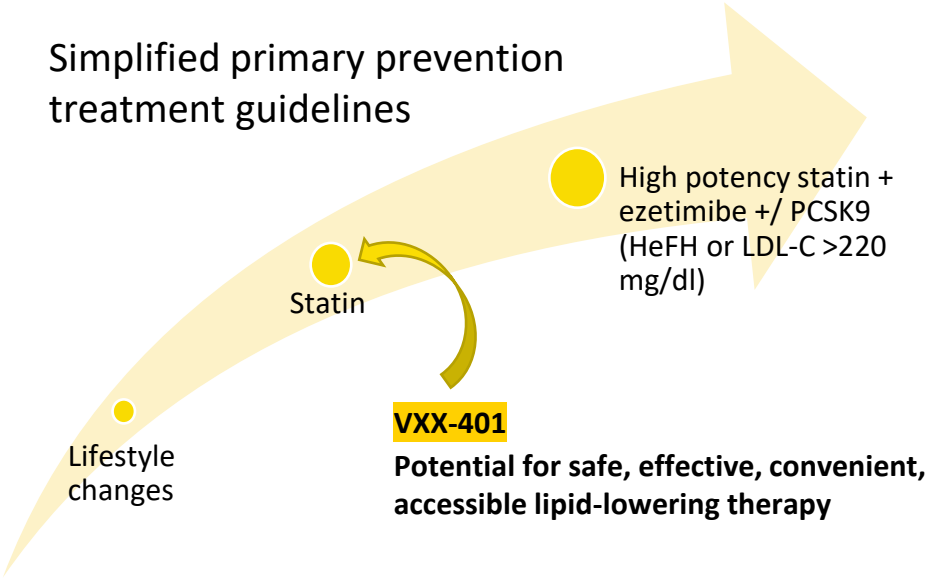
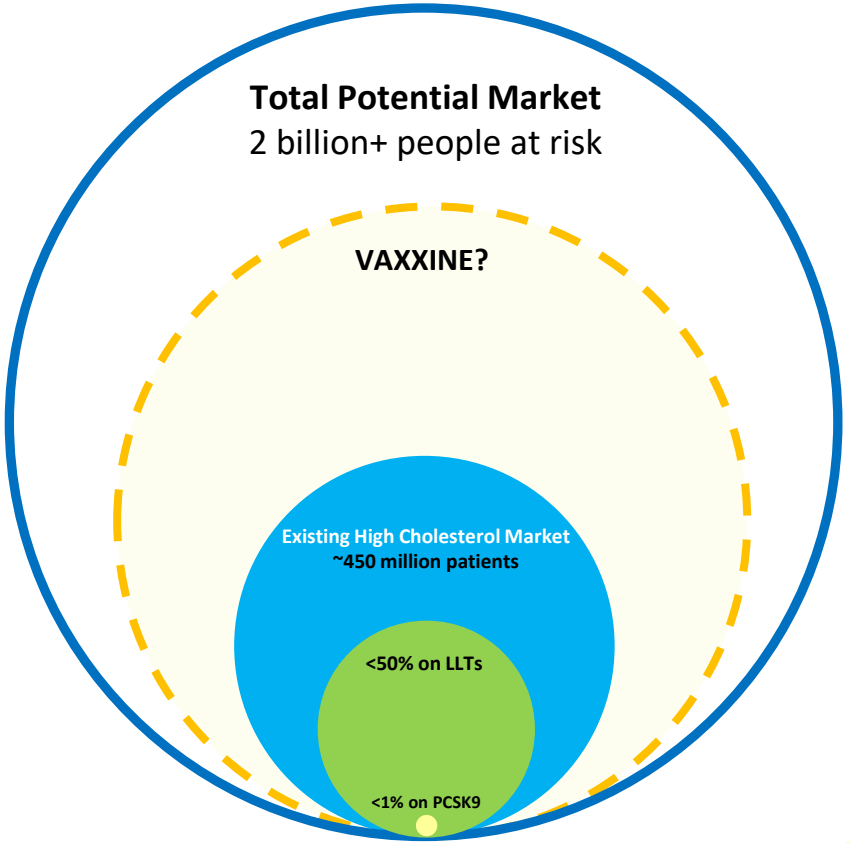
VXX-401 has large commercial opportunity in meeting major global public health need

Simplified primary prevention treatment guidelines





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Q&A

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Closing Remarks

Mei Mei Hu, CEO

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Milestones this year continue to validate quality and applicability of our science

- **Parkinson's VAXXINE (UB-312) Phase 1 Part B initiated and EOT analyzed**
  - Positive Ph1 Part B EOT: successfully immunized Parkinson's patients and generated antibodies
  - Well-tolerated
  - High responder rate
  - Penetration of antibodies into CSF
- **Hypercholesteremia VAXXINE (VXX-401) lead identified**
  - Robust Proof of Concept achieved in NHP
  - Safe and well-tolerated in GLP tox (NHP)
  - Positive advice from health authority
- **Migraine VAXXINE (UB-313) CTA approved and Ph1 initiated**
- **Alzheimer's VAXXINE (UB-311) received Fast Track Designation from FDA**

Upcoming Near-Term Catalysts

Program	2022 2H	2023 1H	2023 2H
UB-311 (Aβ)		Begin large scale efficacy trial with partner	
UB-312 (αSyn)	EOT Analysis	Ph1 Part B Read-out	
Anti-tau		Lead ID	
UB-313 (CGRP)	Ph1 Start	Ph1 Topline	
VXX-401 (PCSK9)	Lead ID	Ph1 Start	Ph1 Topline
UB-612 (SARS-CoV-2)	Ph3 Topline	*MAA* submission complete* Authorization	

September 30, 2022
Unaudited balance sheet

Cash and cash equivalents**	$102.2M

Anticipated cash runway sufficient for at least the next 12 months

Completed milestone

Upcoming milestone

*Conditional MAA in one or more countries
**Includes restricted cash of $3.1 million

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DEMOCRATIZE HEALTH.

Our vision is to provide cheaper, safer, more convenient, and effective medicines for chronic disease to all.