Targeting Tau in Neurodegenerative Disease

NASDAQ: ACIU | SVB Leerink CNS Event | June 23, 2020

AC Immune

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About AC Immune

- Pioneering new ways to treat neurodegenerative diseases associated with misfolded proteins
- Listed on Nasdaq since September 2016 (ticker: ACIU)
- 71.9 million shares outstanding[1] (free float approximately 37%)
- Cash position of CHF 277.9 million as of Q1 2020; sufficiently funded through at least Q1 2024
- Based at the EPFL campus in Lausanne, Switzerland
- 132 full-time employees

(1) As of December 31, 2019

Broad and robust pipeline in neurodegenerative diseases

Driven by validated proprietary technology platforms for sustained growth

Clinical-stage pipeline (★ data readout expected in 2020)

TARGET	PRODUCT CANDIDATE	INDICATION	DISCOVERY	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	PARTNER
Tau	**semorinemab** *(anti-Tau antibody)*	AD[1] treatment *(prodromal / mild)*					★	Genentech A Member of the Roche Group
		AD treatment *(moderate)*						
	ACI-35.030 *(anti-pTau vaccine)*	AD treatment					★	Janssen
	ACI-3024 *(Tau inhibitor)*	AD treatment				★		Lilly
	Tau-PET[2] tracer	AD and PSP[3]						Life Molecular Imaging
Abeta	**crenezumab** *(anti-Abeta antibody)*	AD prevention[4]						Genentech A Member of the Roche Group
	ACI-24 *(anti-Abeta vaccine)*	AD treatment (*Down syndrome[5]*)				★		
		AD treatment					★	

Biologic
Small Molecule
Diagnostic

(1) Alzheimer's disease; (2) Positron emission tomography; (3) Progressive supranuclear palsy; (4) Prevention trial API-ADAD in Colombia; (5) AD-like cognitive impairment associated with Down syndrome

Broad and robust pipeline in neurodegenerative diseases

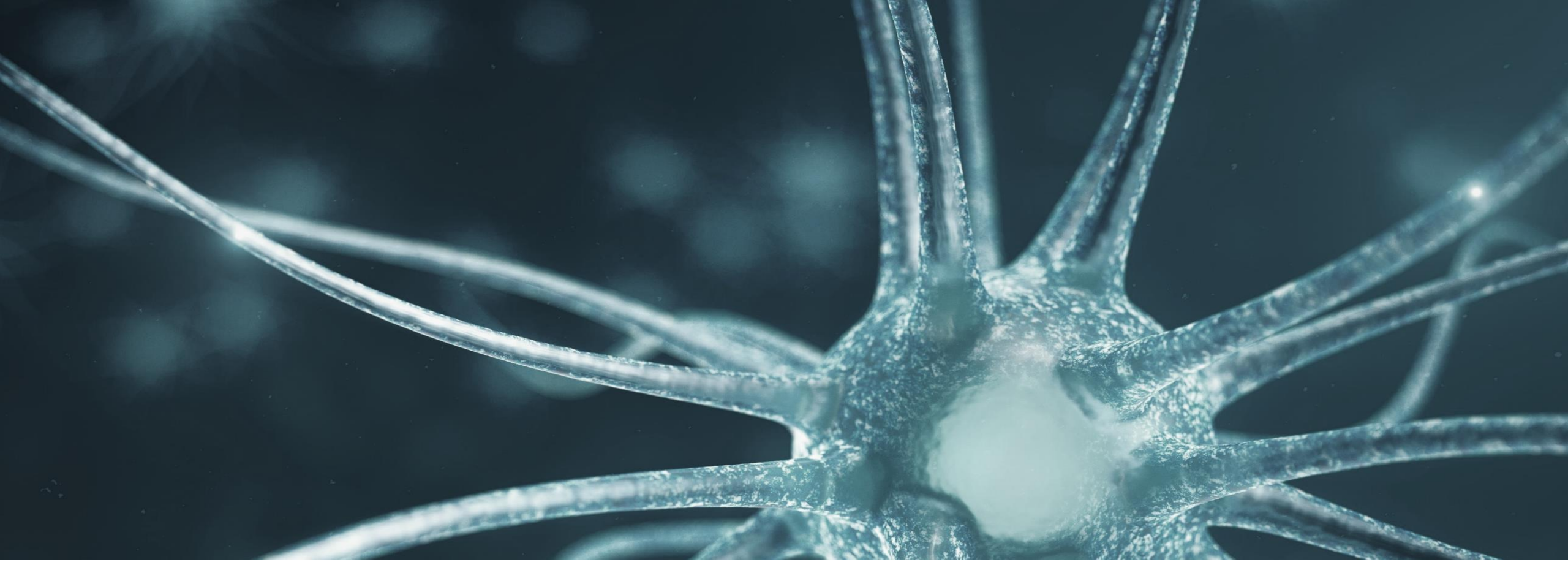
Driven by validated proprietary technology platforms for sustained growth

Early-stage pipeline (★ key milestone in 2020)

TARGET	PRODUCT CANDIDATE	INDICATION	DISCOVERY	PRECLINICAL	PHASE 1
a-synuclein (a-syn)	**a-syn-PET[1] tracer**	PD[2], a-synucleinopathies			★
	anti-a-syn antibody	PD, NeuroOrphan		★	
	Morphomer a-syn *(a-syn inhibitor)*	PD, a-synucleinopathies		★	
TDP-43[3]	**anti-TDP-43 antibody**	NeuroOrphan		★	
	TDP-43-PET tracer	TDP-43-opathies			
Inflammasome	**anti-NLRP3[4]-ASC[5] antibody**	NeuroOrphan		★	
	Morphomer-NLRP3-ASC	Non-CNS[6]		★	
	Morphomer-NLRP3-ASC	NeuroOrphan			

Biologic
Small Molecule
Diagnostic

(1) Positron emission tomography; (2) Parkinson's disease (3) TAR DNA-binding protein 43; (4) (NOD)-like receptor protein 3; (5) Apoptosis-associated speck protein containing a CARD; (6) Central nervous system



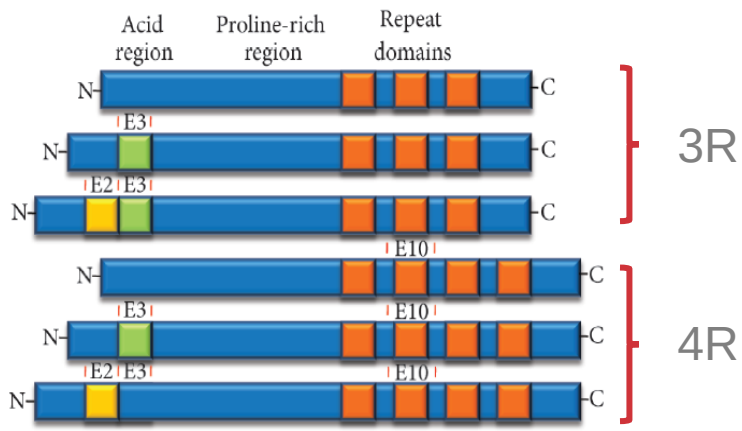
Tau in Alzheimer’s disease and neurodegenerative disease

What is Tau and how is it related to neurodegenerative disease?

- Group of highly soluble protein isoforms that function in maintaining microtubule stability in axons
  - 3R/4R isoforms in AD[1]; 4R isoform in PSP[2], CBD[3]
- Pathology begins with hyperphosphorylation, misfolding and aggregation into insoluble neurofibrillary tangles (NFTs)
  - Recognized hallmark of AD, along with Abeta[4] plaques
- Accumulation of intracellular NFTs leads to neuronal injury and death, inflammation, and neurodegeneration
- Extracellular pathological Tau species seed misfolding of Tau in adjacent healthy neurons, resulting in spreading of Tau neuropathology

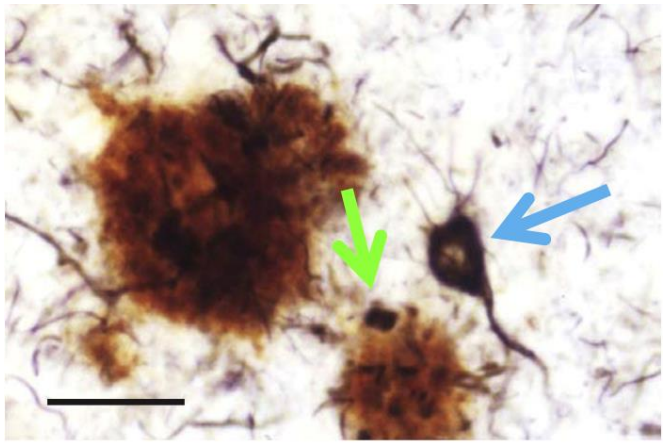
- Tau is a promising therapeutic target for antibodies and small molecules in Alzheimer's and other neurodegenerative diseases

Domain structure of Tau isoforms



Adapted from Wolfe, Scientifica 2012

Immunohistochemistry (AD neocortex)



Abeta plaques (brown); Tau NFTs (black)

Nelson et al, Neuropathol Exp Neurol 2012

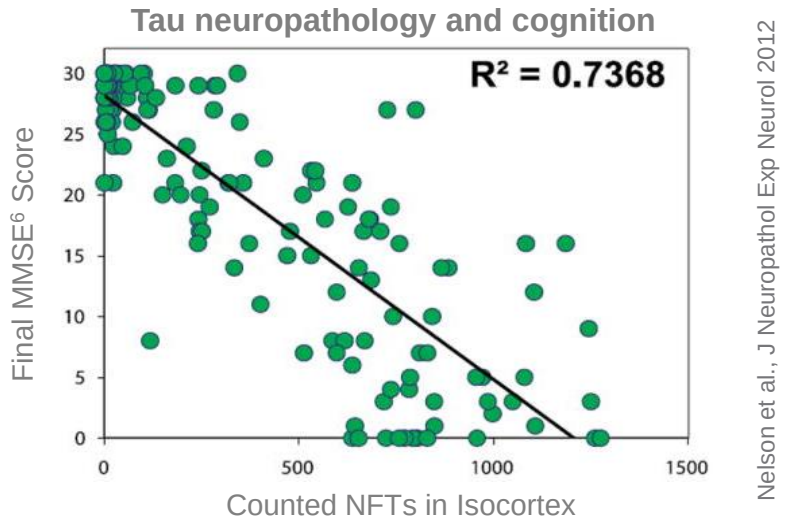
(1) Alzheimer's disease; (2) Progressive supranuclear palsy; (3) Corticobasal degeneration; (4) Amyloid-beta

Tau Pathology: Correlation with the rate of cognitive decline

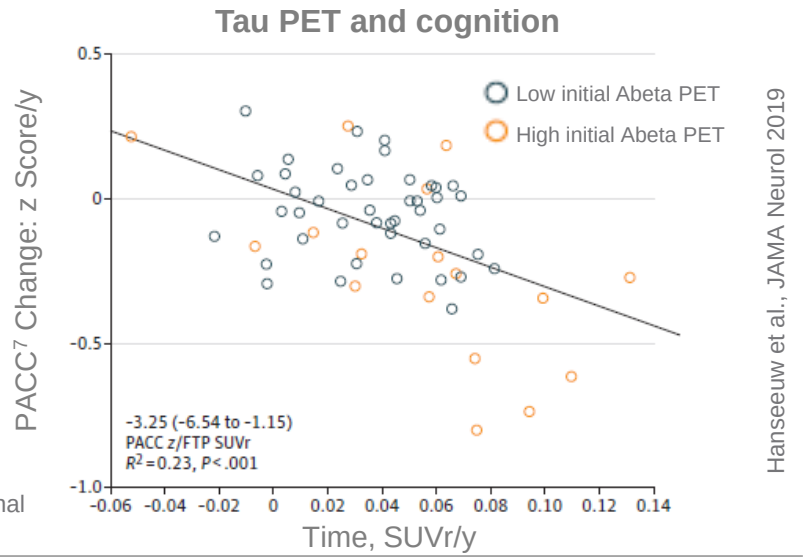
A key driver of Alzheimer's disease pathology with wide therapeutic window

- The density of NFTs in selected cerebral cortical fields significantly correlates with final cognitive status[1] (top right)
- Tau changes (measured by PET[2] imaging) are more closely associated with the rate of cognitive decline[3] (bottom right)
- There is a rapid, catastrophic rise in Tau once Abeta reaches a critical threshold; Abeta increase predicts subsequent Tau increase[3]
- Abeta pathology is associated with early changes in soluble CSF[4] Tau[5]; opportunity for early anti-Tau treatment (before significant aggregation)

- Tau-targeted approaches may have a much broader therapeutic window to potentially disrupt, slow or prevent disease progression at both early and advanced stages



Nelson et al., J Neuropathol Exp Neurol 2012



Hanseeuw et al., JAMA Neurol 2019

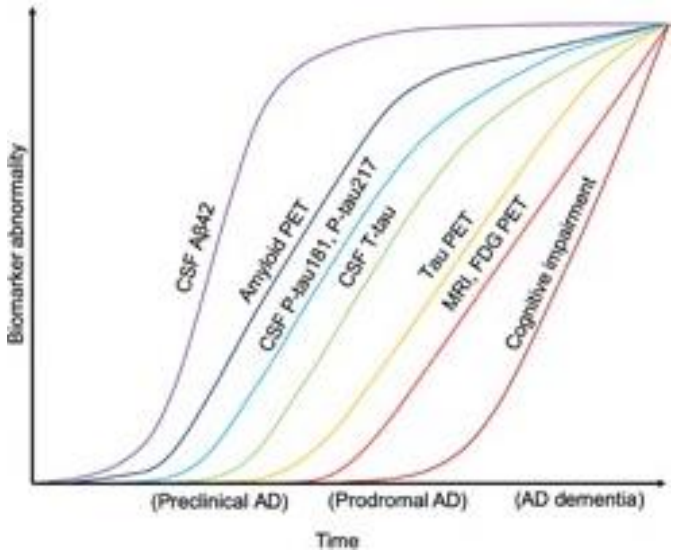
(1) Nelson et al., J Neuropathol Exp Neurol 2012; (2) Positron emission tomography; (3) *Hanseeuw et al., JAMA Neurol 2019,* (4) cerebrospinal fluid; (5) Mattsson-Carlgren et al., Sci Adv 2020; (6) Mini-mental state examination; (7) Preclinical Alzheimer cognitive composite

Recent studies highlight the value of pathological Tau as a biomarker

Opportunities for accurate diagnostics and optimized drug development

- CSF[1] pTau[2] (pTau181 and pTau217) start to increase after Abeta PET[3] positivity[4], followed by total CSF Tau (right)
- CSF pTau217 in particular correlates with Tau PET and with Abeta CSF/PET measures[4]
- CSF pTau levels increase in preclinical AD[5] several years before Tau PET positivity; CSF Tau mediates the association between Abeta PET and Tau PET (80%)[6]
- High CSF pTau predicted increased Tau PET rates[4], which is associated with more rapid cognitive decline[4,7]
- Plasma pTau may also be available for AD screening/diagnosis[8,9]

Relationship between CSF and PET biomarkers



Mattsson-Carlgren et al Sci Adv 2020

- Recent findings extend the Abeta cascade hypothesis and identify soluble Tau as a potential biomarker for preclinical disease intervention
- Tau is a potentially powerful diagnostic and prognostic biomarker in AD and NDD[10]

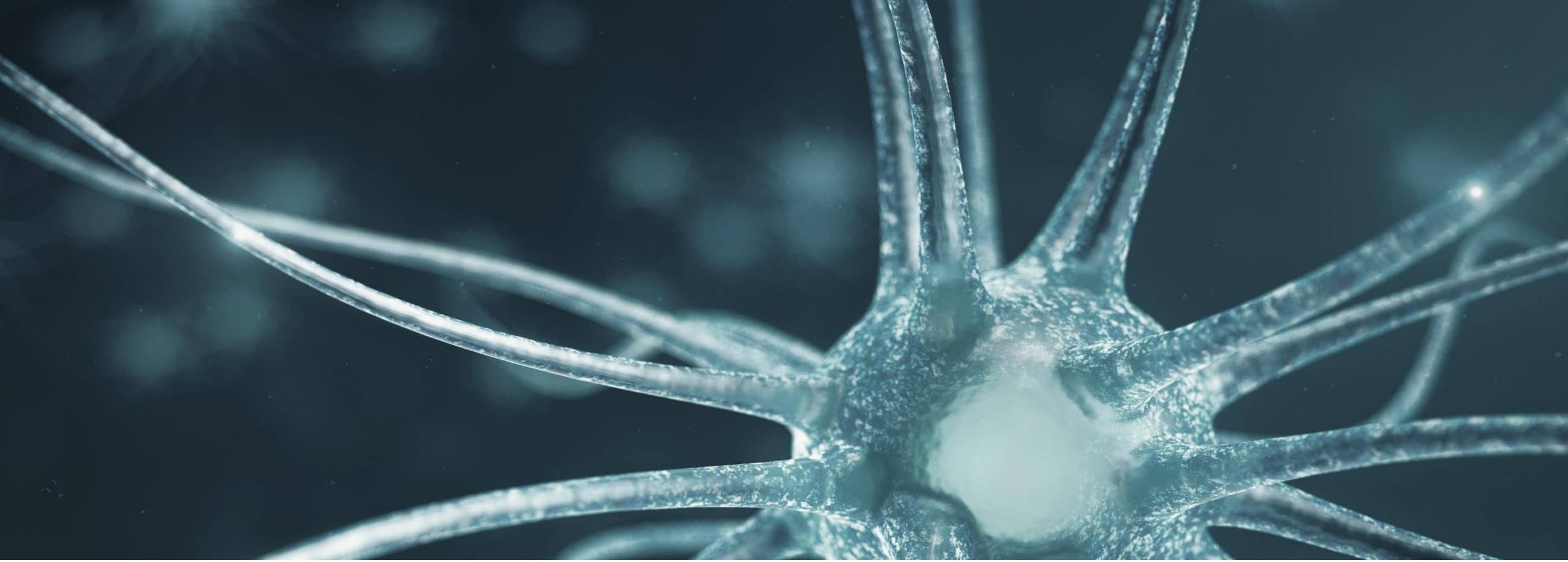
(1) Cerebrospinal fluid; (2) Phosphorylated Tau; (3) Positron emission tomography; (4) Mattsson-Carlgren et al., Sci Adv 2020; (5) Alzheimer's disease; (6) Janelidze et al., Nature Communications 2020; (7) Hanseeuw et al., JAMA Neurol 2019; (8) Karikari et al., Lancet Neurobiology 2020; (9) Bateman et al., Nature Medicine 2020; (10) Neurodegenerative diseases

Tau implications for therapies and diagnostics in AD[1]

- Extended Abeta cascade hypothesis:
  - Abeta pathology may induce changes in soluble Tau release and phosphorylation, followed by Tau aggregation several years later[2], which may be a key driver of cognitive decline at early and late stages
  - Recent studies implicate the NLRP3[3] inflammasome as an important driver of Abeta-induced Tau pathology, highlighting additional opportunities for therapeutic intervention

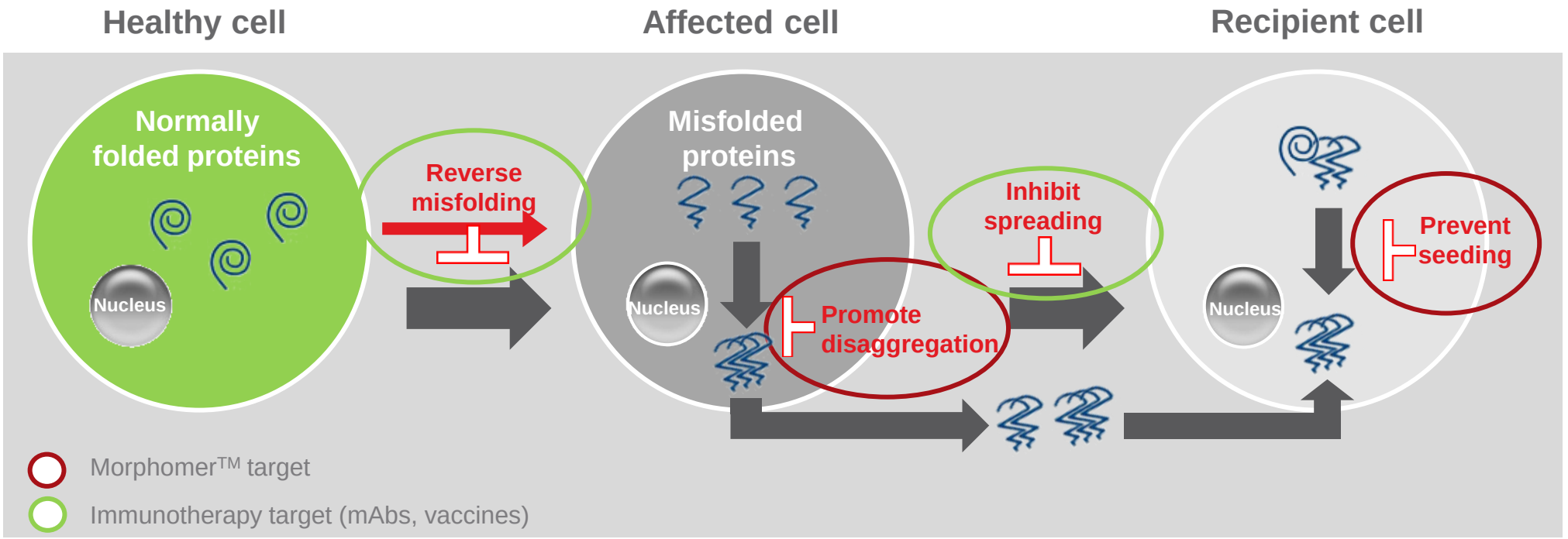
- Recent progress in Tau diagnostics may enable broad therapeutic Tau applications:
  - Non-invasive Tau PET[4] signal increases throughout course of disease; correlates with cognitive decline
    - Enables screening and stratification of patients
    - May permit rapid assessment of pharmacodynamic effects of disease-modifying drug candidates
    - Second-generation tracers: greater specificity for AD-type Tau and other Tauopathies (i.e. PSP[5])
  - CSF[6,4] and plasma[7] pTau in development as a biomarker for preclinical disease

(1) Alzheimer's disease, (2) Mattsson-Carlgren et al., Sci Adv 2020; (3) (NOD)-like receptor protein 3; (4) Positron emission tomography; (5) Progressive supranuclear palsy; (6) Cerebrospinal fluid; (7) Karikari et al., Lancet Neurobiology 2020



Targeting Tau at AC Immune

Targeting pathological Tau at key points in the disease pathway



- Targeting both intracellular seeds and extracellular spreading by combination therapy of Morphomers and immunotherapy enables full control of Tau pathology progression
- Highly selective Tau imaging diagnostic enables more precise patient characterization and potentially more precise prediction of AD[1] progression

(1) Alzheimer's disease

AC Immune: broadest anti-Tau pipeline with key clinical readouts

Product candidates	Therapies and Diagnostics:			
	antibody	vaccine	small molecule	diagnostic
Status	Phase 2[1,2]	Phase 1b/2a[3]	Phase 1	Phase 2
Partner	Genentech, A Member of the Roche Group	janssen, Pharmaceutical Companies of Johnson & Johnson	Lilly	Life Molecular Imaging
Next Readout	**Q2 2020**[1] followed by **Q2 2021**[2]	**Q2 2020** interim analysis[4]	**H2 2020**[5]	**Q4 2020** PET[6] tracer[7]

(1) Prodromal/mild trial primary completion (estimated; last patient, last visit); (2) Moderate trial primary completion estimated; (3) In Alzheimer's disease; (4) Trial of anti-pTau vaccine; Cohort 1; safety and tolerability; (5) Phase 1 completion expected in Q2 in healthy volunteers followed by data disclosure by partner in H2 (expected); (6) Positron emission tomography; (7) Trial in progressive supranuclear palsy patients (test-retest)

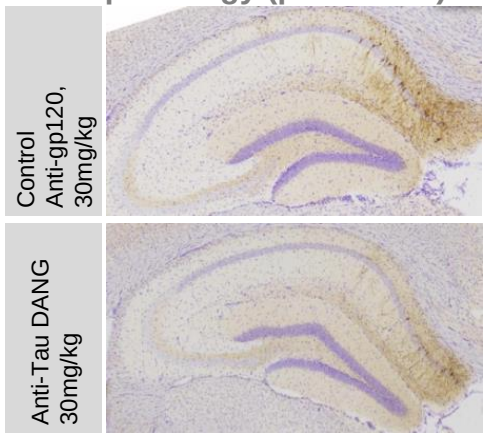
Semorinemab – Phase 2 in AD[1]

Anti-Tau antibody

Genentech
A Member of the Roche Group

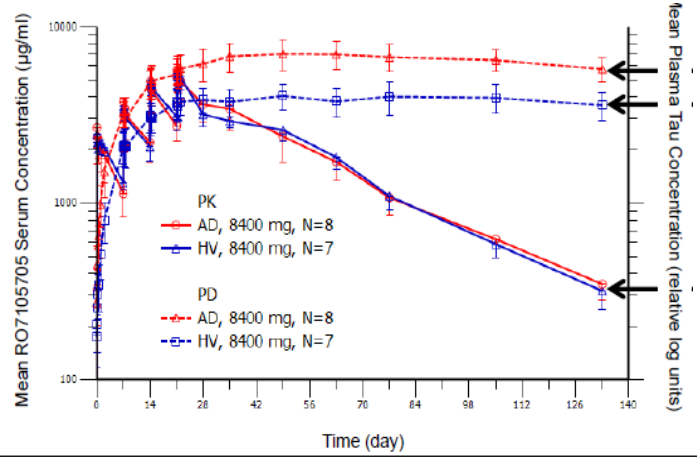
Target	Designed to intercept the cell-to-cell spread of pathological Tau in extracellular space of brain
Key results	▪ Tau pathological spread is dose dependently reduced independent of effector function ▪ Proven target engagement through dose-dependent rise of plasma Tau (mice, cynos, humans)

Dose dependent reduction of Tau pathology (preclinical)



AD/PD conference, Vienna, April 2017

Phase 1 results: Pharmacodynamic response: Plasma Tau concentration 2x higher in AD than in HV[2]



- Compared to HV, AD patients exhibited two-fold greater levels of plasma Tau following semorinemab administration, despite identical semorinemab exposures in the two populations
- Median half-life of 32.3 days
- No dose-limiting toxicities at high doses

Kerchner *et al*, CTAD 2017

Development status	**Phase 2 design (prodromal to mild AD; Tauriel): Primary completion (estimated; last patient, last visit) in Q2 2020** ▪ 460 prodromal-to-mild AD patients (MMSE[3] 20-30, CDR-GS[4] = 0.5 or 1) ▪ 3 active doses or placebo for 72 weeks, followed by 96-week open label study ▪ Primary endpoints: safety measures and CDR-SB[5]; secondary endpoints: RBANS[6], ADCS-ADL[7], AIADL[8], ADAS-cog13[9] and Tau burden (PET[10]) **Phase 2 design (moderate AD; Lauriet): Primary completion estimated in Q2 2021** ▪ 260 patients (MMSE 16-21; CDR-GS = 1 or 2) ▪ 1 dose or placebo for 49 weeks, followed by open-label study ▪ Primary endpoints: ADAS-cog11[9] and ADCS-ADL[8]; secondary endpoints: CDR-SB, MMSE, safety

(1) Alzheimer's disease; (2) Healthy volunteers; (3) Mini-mental state exam; (4) Clinical Dementia Rating-Global Score; (5) Clinical Dementia Rating-Sum of the Boxes; (6) Repeatable Battery for Assessment of Neuropsychological Status; (7) Alzheimer's Disease Cooperative Study - Activities of Daily Living (8) Amsterdam Instrumental Activities of Daily Living; (9) Alzheimer's Disease Assessment Scale-cognitive subscale; (10) Positron emission tomography

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Multiple upcoming clinical catalysts to drive value in 2020

Three Tau programs reporting clinical data

Clinical

			DISCOVERY	PRECLINICAL	PHASE 1	PHASE 2
Q2	**semorinemab** *(anti-Tau antibody)*	Phase 2 primary completion (estimated; last patient, last visit)	AD[1] Treatment (Prodromal / mild)			
Q2	**ACI-35.030** *(anti-pTau vaccine)*	Phase 1b/2a in AD interim analysis[2]	AD Treatment			
H2	**ACI-24** *(anti-Abeta vaccine)*	Phase 1b full study reporting in Down syndrome[3]	AD Treatment in Down syndrome[4]			
H2	**ACI-24** *(anti-Abeta vaccine)*	Phase 2 12-month interim analysis in AD	AD Treatment			
H2	**ACI-3024** *(Tau inhibitor)*	Phase 1 results (healthy volunteers) disclosed by partner (expected)[5]	AD Treatment			

Preclinical

			DISCOVERY	PRECLINICAL	PHASE 1
Q1	**anti-a-syn anibody**	Start IND[6]-enabling studies for lead candidate **(achieved ☑)**	PD[7], NeuroOrphan		
Q2	**Morphomer a-syn** *(a-syn inhibitor)*	Identify first biologically active small molecule	PD, synucleinopathies		
Q2	**anti-TDP-43[8] antibody**	Declare clinical lead; start IND-enabling studies	NeuroOrphan		
Q4	**a-syn PET tracer**	Advance 3rd-gen candidate to clinical stage	PD, a-synucleinopathies		
Q4	**Morphomer-NLRP3[9]-ASC[10]**	Declare lead (non-CNS[11])	NeuroOrphan		
Q4	**anti-NLRP3-ASC antibody**	Declare pre-lead	NeuroOrphan		

Biologic
Small Molecule
Diagnostic

(1) Alzheimer's disease; (2) Cohort 1; safety/tolerability; immunogenicity; (3) Phase 1b completion expected in Q2; (4) AD-like cognitive impairment associated with Down syndrome; (5) Phase 1 completion expected in Q2; (6) Investigational new drug; (7) Parkinson's disease; (8) TAR DNA-binding protein 43; (9) (NOD)-like receptor protein 3; (10) Apoptosis-associated speck protein containing a CARD; (11) Central nervous system

AC Immune

Drivers of value creation in 2020 and beyond

Ongoing strong financial position

CHF 277.9 million in cash[1], ensuring the Company is fully financed through Q1 2024

Pipeline progression

Industry-leading molecules against multiple key targets;
i.e. anti-a-syn and anti-TDP-43 antibodies advancing to preclinical development

5 clinical data readouts in 2020

Multiple near-term value inflection points,
including the 1st Phase 2 readout of an anti-Tau antibody in Alzheimer's disease

Pioneering precision medicine

Addressing large market opportunity with differentiated, patient-focused approach

(1) As of March 31, 2020