

Tackling AD at the roots: early intervention to address multiple hallmarks of AD

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VIVORYON THERAPEUTICS

Investment Highlights



COMPANY

- ◆ **STRONG BALANCE SHEET AND CORPORATE POSITION**
 - ◆ Led by seasoned biopharma experts
 - ◆ Strong IP position including composition of matter coverage beyond 2035
 - ◆ Recent investment from KKR



APPROACH

- ◆ **PURPOSE-BUILT PIPELINE** of small molecules addressing medical need in multiple disease areas including neuro-degeneration, oncology, inflammatory diseases and fibrosis
- ◆ **LEVERAGING IN-DEPTH UNDERSTANDING** of pathological pathways for the discovery and development of small molecules
- ◆ **FOCUSED ON TARGETED INTERVENTION** by enzyme inhibition to modulate the activity of proteins altered in disease settings



LATE-STAGE LEAD PROGRAM VAROGLUTAMSTAT

- ◆ **DIFFERENTIATED UPSTREAM APPROACH TO ALZHEIMER'S DISEASE** treatment targeting major hallmarks of disease with proven early signs of disease-modifying activity:
 - ◆ **Orally available** small molecule
 - ◆ Statistically significant **change from baseline in working memory** after 3-months treatment
 - ◆ **Upstream intervention** with dual MoA: Targeting Abeta and CCL2 modulation
 - ◆ **Addresses all three major hallmarks of AD:** Abeta aggregation, neuroinflammation and tau pathology, as well as synaptic function
 - ◆ **Favorable safety profile** and no signs of ARIA side effects in clinical setting



EXPERIENCED LEADERSHIP

Seasoned Biopharma Experts Covering All Relevant Aspects of Drug Development

EXECUTIVE DIRECTORS



Ulrich Dauer, PhD
Chief Executive Officer, Executive Director



Michael Schaeffer, PhD
Chief Business Officer, Executive Director



Florian Schmid
Chief Financial Officer, Executive Director



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Samir Shah, MD



DIVERSE PIPELINE ADDRESSING SEVERE DISEASES

	Program	Approach	Discovery	Preclinical	Phase 1	Phase 2a	Phase 2b	Phase 3
 AD	Varoglutamstat (PQ912)	SMI QPCT/L	VIVIAD - Ph2b in EU					
	Varoglutamstat (PQ912)	SMI QPCT/L	VIVA-MIND - Ph2a/b in US					
	Varoglutamstat (SIM0408, PQ912)	SMI QPCT/L	CTA approval in China					
	PBD-C06	mAb N3pE amyloid						
 Cancer		SMI QPCTL						
 NASH		SMI QPCTL						
 Fibrosis		SMI Meprin						



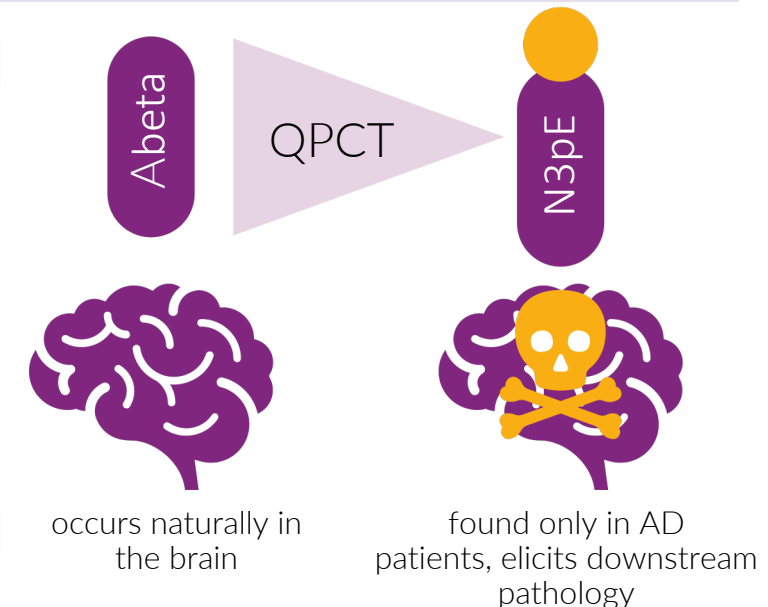
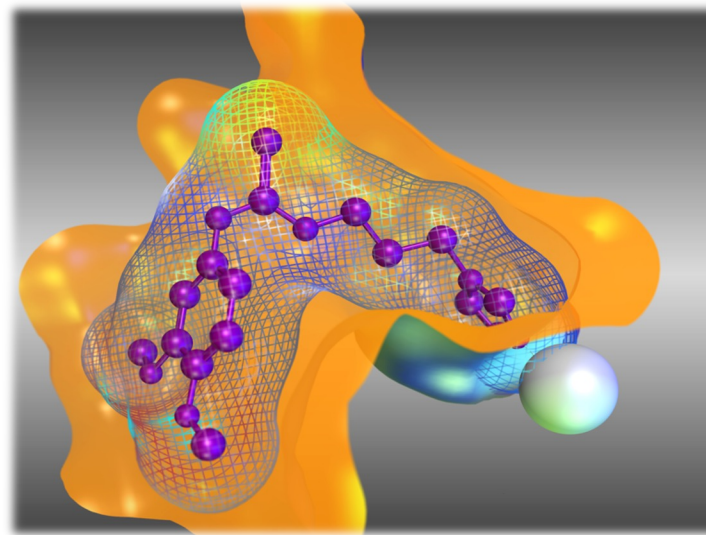
ALZHEIMER'S DISEASE

THE BURDEN

- ◆ ~30 million people suffering from AD worldwide, number expected to double by 2050, with ~12.7 million in the US alone
- ◆ Heavy burden on patients, families, caregivers and the public healthcare system
- ◆ No cure available, five established drugs on the market address symptoms only
- ◆ Aducanumab recently approved amid controversial discussion on reduced Abeta plaque load as surrogate marker for cognitive improvement

A PATH FORWARD

- ◆ VVY discovered QPCT-mediated formation of a neurotoxic Abeta variant, N3pE amyloid (pGlu-Abeta), as driver of AD pathology^{1,2}
- ◆ VVY is developing small molecule inhibitors to prevent N3pE amyloid formation - rather than aiming to clear existing plaques³

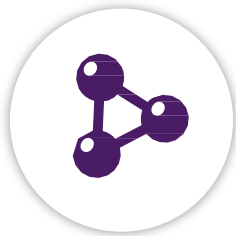


DRUG DEVELOPMENT IN ALZHEIMER'S DISEASE

THE CHALLENGE

- ◆ Low success rate and long development phase delay new treatments and discourage investment in AD drug development
- ◆ Studies across drug development programs have identified important strategies for decreasing the risk and increasing the likelihood of success in drug development programs
- ◆ These experiences provide guidance for our approach to AD drug development

THE “RIGHTS” OF AD DRUG DEVELOPMENT¹



Right Target

Targets appropriate biologic process for AD therapeutic intervention



Right Drug

Has appropriate PK/PD profile, brain distribution, preclinical efficacy and safety in Phase 1



Right Biomarkers

Guide participant selection, monitor target engagement, disease modification and side effects



Right Participants

Are in appropriate phase of AD (preclinical, prodromal, dementia)



Right Trial

Is prudently designed and run as well-powered study with appropriate endpoints and duration



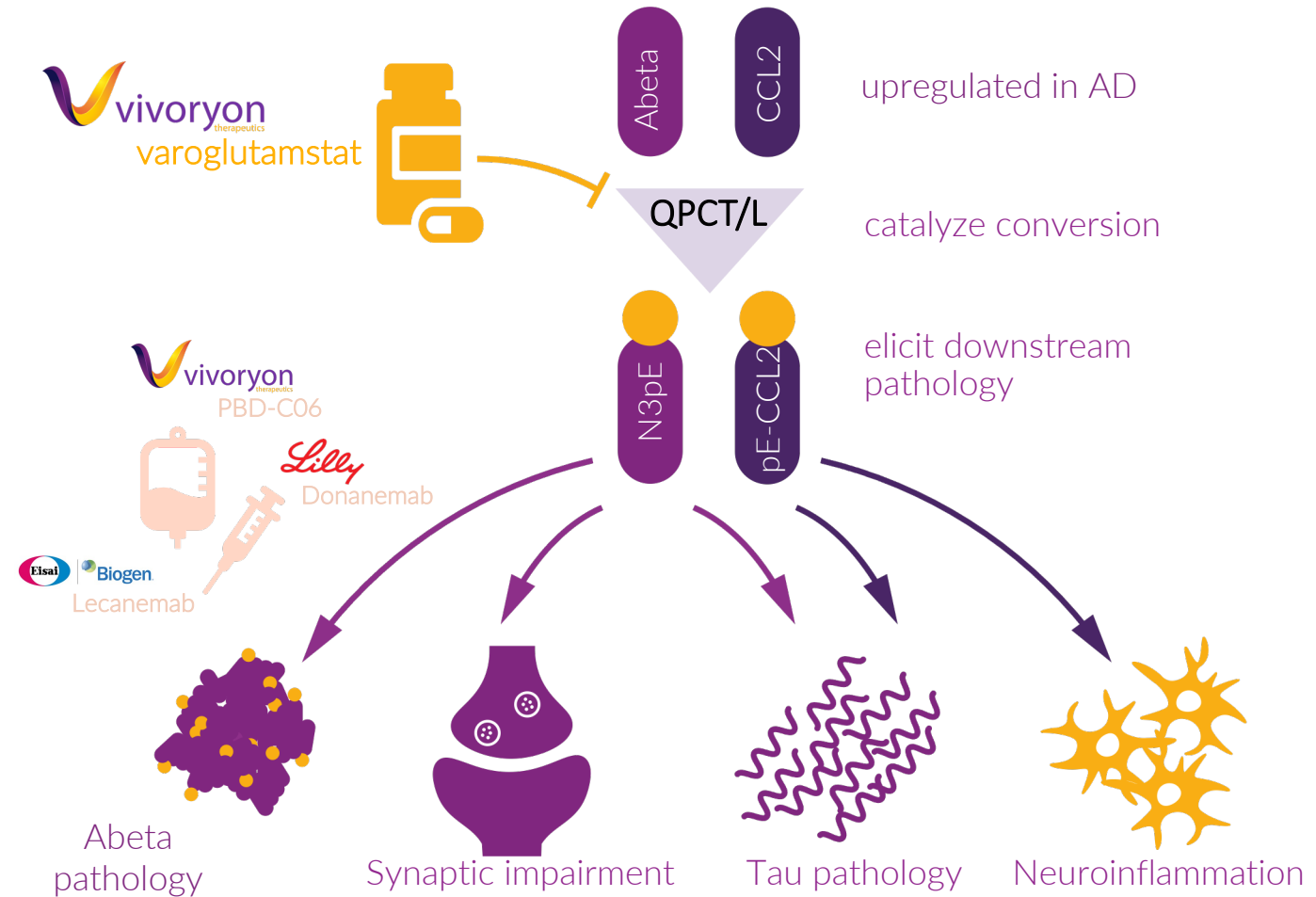
¹ adapted from Cummings, Feldman and Scheltens, 2019

LEAD PRODUCT CANDIDATE: VAROGLUTAMSTAT PREVENTS N3pE-FORMATION IN AD

ROLE OF QPCT/L IN AD PATHOLOGY

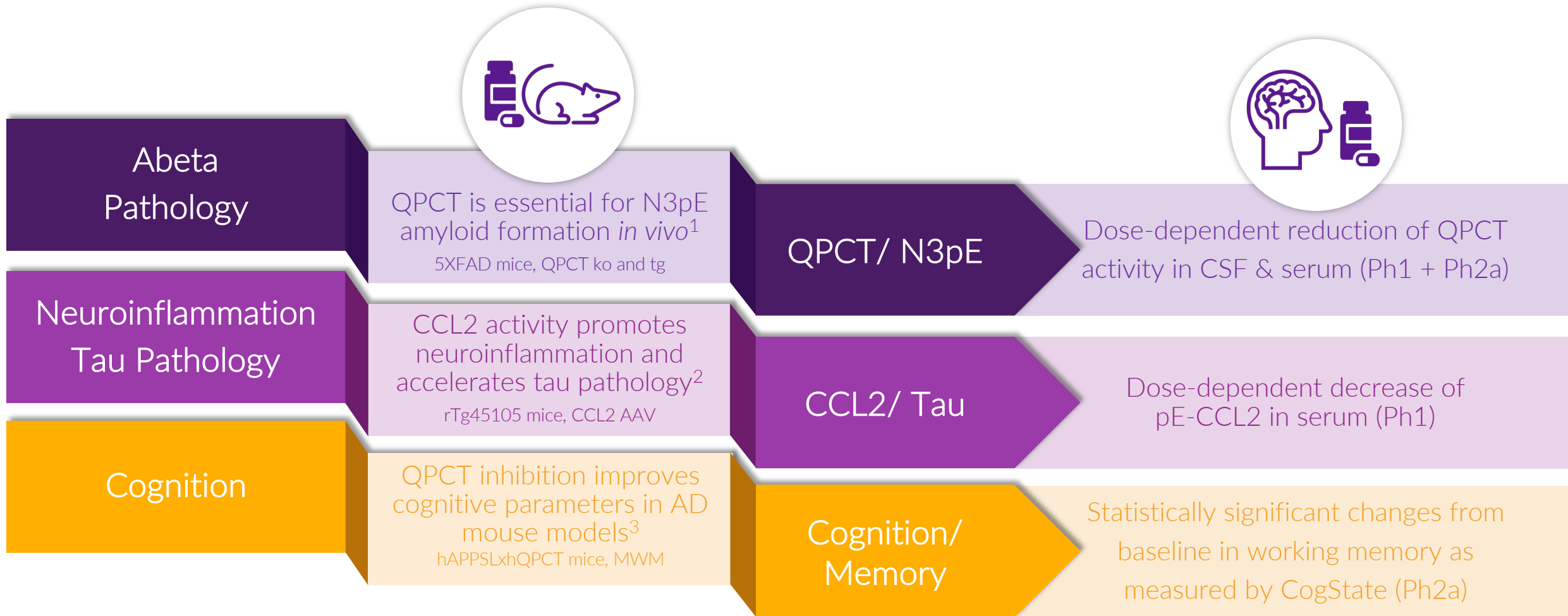
- ◆ Increased activity of glutaminy cyclase (QPCT) is associated with AD pathology in humans¹
- ◆ QPCT catalyzes formation of neurotoxic N3pE-Aβeta by cyclization of N-terminal glutamate on Aβeta²
- ◆ N3pE amyloid correlates with QPCT expression and MMSE status in AD patients and is not found in healthy individuals³
- ◆ Varoglutamstat and PBD-C06 target all aggregation states of Aβeta as N3pE is equally present in soluble and insoluble forms of Aβeta^{4,5}
- ◆ Targeting QPCTL (isoform of QPCT):
 - ◆ Inhibits neuroinflammation by modulating CCL2 activity
 - ◆ Increased levels of QPCTL and high pE-CCL2 levels correlate strongly with low MMSE scores⁶

VAROGLUTAMSTAT TARGETS UPSTREAM PATHOGENESIS



¹Gunn et al., J.Neurochem 2021; ²Schilling et al., Nat. Med. 2008; ³Morawski et. al., JAD 2014; Nussbaum et al., Nature 2012; ⁴Upadhaya et.al., Brain 2014, ⁵Hettmann et.al., Nature Sci.Reports 2020; ⁶Hartlage-Rübsamen et al., Acta Neuropathol, 2015

TRANSLATING *IN VIVO* EVIDENCE FOR RELEVANCE OF QPCT/L INHIBITION INTO HUMAN AD



VAROGLUTAMSTAT CLINICAL DEVELOPMENT STRATEGY

Clear Path To Potential Regulatory Approval Based on Well-Informed Trials Extensive Phase 1 and Phase 2 Trials



Phase 1

Assessment of safety and tolerability in 205 healthy volunteers



COMPLETED

- ◆ Varoglutamstat is well-tolerated – no DLT at 800 mg twice daily or up to 3.6g once daily

Phase 1

Assessment of safety and tolerability in 60 healthy Chinese volunteers



IN PREPARATION



Phase 2a SAPHIR

Assessment of safety and tolerability in 120 patients with early AD



COMPLETED

- ◆ Statistically significant changes from baseline in working memory after only 3 months of treatment (as measured by CogState)
- ◆ High target occupancy detected at doses of 150 mg BID and above



Phase 2b VIVIAD

Assessment of safety, tolerability and efficacy in 250 patients with MCI or mild AD



Fully recruited
Final readout Q1/2024

- ◆ Endpoints: safety, attention/working memory, NTB, biomarkers
- ◆ Parallel group, dose-finding part completed, study continues with DSMB recommended maximum dose of 600 mg BID or placebo
- ◆ Fully enrolled (259 pts); planned to allow for mean treatment duration of ~82 weeks

Phase 2a/b VIVA-MIND

Assessment of efficacy and safety in 180 patients with early AD



Expanded treatment duration in Phase 2a portion (72 weeks)
Study status update in Q1/2023

- ◆ Endpoints: safety, attention/working memory, CDR-SB, biomarkers

Pivotal study or accelerated approval

- ◆ FDA Fast Track designation granted in 2021
- ◆ Two possible scenarios for late-stage development
 - Application for accelerated approval (based on consistent / positive data of Phase 2b studies)
 - Phase 3 clinical development

Preclinical research

In vitro and in vivo studies

COMPLETED

- ◆ QPCT inhibition improves cognitive parameters in AD mouse models
- ◆ QPCT is essential for N3pE amyloid and pE-CCL2 formation in vivo

SAPHIR– GUIDING PHASE 2B TRIAL DESIGN

SUMMARY OF KEY PHASE 2A RESULTS

COGNITION

- ◆ Statistically significant changes from baseline in a working memory parameter within 3 months (One Back Test)
- ◆ Notable changes from baseline in attention (Detection Test, Identification Test)

CSF BIOMARKERS

- ◆ Strong QPCT-inhibition (target occupancy >80% at 600 mg BID, >70% at 300 mg BID)
- ◆ Reduction of neuroinflammatory and synaptic markers (pE-CCL2, YKL40, neurogranin)

SYNAPTIC FUNCTION (EEG)

- ◆ Statistically significant reduction in theta power (marker for synaptic dysfunction)
- ◆ Notable changes from baseline in functional connectivity as measured by AEC (*post-hoc* analysis)

INFORMED TRIAL DESIGN OF EU PHASE 2B

DOSING

- ◆ DLT reached at 800 mg BID; reported AEs mostly mild to moderate, fully reversible (skin and gastrointestinal)
- ◆ Varoglutamstat is well-tolerated at doses resulting in high target occupancy (600 mg BID)
- ◆ Dose adjustments for Phase 2b to prevent AEs while maintaining high target occupancy

PLANNING

- ◆ Composite Attention/Working Memory Simulation selected as Primary Endpoint
- ◆ Robust statistical planning with 3 CogState parameters (one back test, detection, identification)
- ◆ Based on available Phase 2a data matched with large historical control data set on longitudinal rate of progression for identical cognitive composite



MULTIPLE AVENUES TO VALUE GENERATION

Diverse Pipeline of Oral Small Molecule Inhibitors to Address Exceptionally High Medical Need

ALZHEIMER'S DISEASE

- ◆ Small molecule oral QPCT/L inhibitors with good blood-brain barrier penetration
- ◆ Inhibits production of N3pE amyloid (pGlu-Abeta): neurotoxic, glutaminylated, soluble Abeta peptides
- ◆ Statistically significant effects on CSF biomarkers, synaptic function & working memory after 12w treatment



INFLAMMATION/NASH

- ◆ Small molecule QPCTL inhibitors to modulate the CCL2-CCR2 axis
- ◆ *In vivo* proof of concept in NAFLD mice
- ◆ Investigated as single agent and in combination with meprin inhibitors



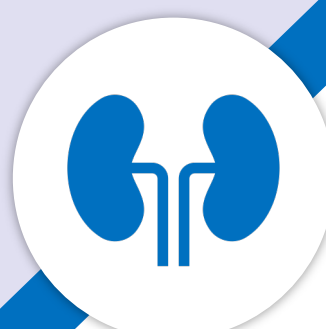
CANCER

- ◆ Small molecule QPCTL inhibitors to modulate cancer immune checkpoint activity
- ◆ Precision intervention to modulate the activity of pro-metastatic chemokines of the CCL family
- ◆ Opportunity for combination therapies



AKI/FIBROSIS

- ◆ Novel meprin alpha/beta single and dual selective small molecule inhibitors
- ◆ *In vivo* proof of concept in AKI animal model
- ◆ Unique recognition pattern allows design of selective and specific meprin protease inhibitors



QPCTL INHIBITION IN CANCER

Opportunity to Develop Oral Small Molecule Inhibitors in Immuno-Oncology

BACKGROUND

- ◆ Large unmet medical need remains to effectively and safely treat cancer patients
- ◆ Combination therapies as powerful tool
- ◆ Evidence for therapeutic potential of:
 - ◆ Leveraging the power of innate immunity: target the CD47-SIRP α axis
 - ◆ Interfering with metastasis: modulating potency/stability of CCL chemokines

OPPORTUNITY

- ◆ Novel orally administered small molecule approach with differentiated mode of action: no antigen sink effect, potential for improved tumor penetration
- ◆ Large patent portfolio: Composition of matter and indication coverage with expirations beyond 2035

OUR APPROACH



- ◆ Selective small molecule QPCTL inhibitor prevents:
 - ◆ Post-translational modification of CD47 to pE-CD47, thus abrogating CD47-SIRP α binding
 - ◆ Full maturation of CCL2, 7, 8, and 13 to pE-CCL2, 7, 8 and 13, leading to decreased potency and stability

PROOF OF CONCEPT

- ◆ *In vitro/in vivo* evidence of synergies with antibody-mediated immunotherapy, e.g. rituximab, daratumumab, trastuzumab, cetuximab, avelumab:
 - ◆ Combination increases phagocytosis and cytotoxicity over single agent activity
 - ◆ Significant increase of tumor doubling times in syngeneic mouse models



QPCTL INHIBITION IN INFLAMMATION/NASH

Opportunity to Develop Oral Small Molecule Inhibitors in Inflammatory Kidney and Liver Diseases

BACKGROUND

- ◆ Non-alcoholic fatty liver disease (NAFLD) is a chronic hepatic disorder characterized by steatosis in early stages, leading to non-alcoholic steatohepatitis (NASH) in more advanced stages
- ◆ NASH is expected to become the leading cause of liver transplantation in the US in the coming years
- ◆ Significant medical need to find effective therapies to manage NASH

OPPORTUNITY

- ◆ Novel orally available compounds with a differentiated mode of action targeting a subclass of therapeutically relevant chemokines
- ◆ *In vitro/in vivo* evidence of decreased inflammatory macrophages, and reduced liver fibrosis
- ◆ Large patent portfolio:
 - ◆ Composition of matter and indication coverage with expirations beyond 2035

OUR APPROACH

- ◆ Treatment of NAFLD by modulating the monocyte/macrophage-related immune response in affected livers using a QPCTL inhibitor
- ◆ CCL2 is upregulated in liver inflammation, our QPCTL inhibitor is used to destabilize CCL2

IN VIVO PROOF OF CONCEPT

- ◆ *In vivo* NASH model (STAM™) demonstrated reduction of inflammation score, inflammatory cytokines like CCL2 and TNFalpha



MEPRIN INHIBITION IN AKI/CKD

Opportunity to Develop Oral Small Molecule Inhibitors In Fibrosis and Kidney Diseases

BACKGROUND

- ◆ The estimated incidence rate of acute kidney injury (AKI) during hospitalization in the US is 2-5%, it arises in more than 50% of intensive care unit patients
- ◆ More than 1 in 7, that is 15% of US adults or 37 million people, are estimated to have chronic kidney disease (CKD)
- ◆ Significant medical need to find effective therapies to manage AKI/CKD

OPPORTUNITY

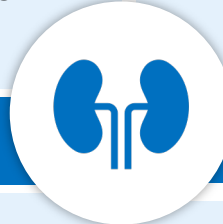
- ◆ Novel orally available picomolar small molecule inhibitors targeting metalloproteases meprin alpha and/or beta
- ◆ *In vivo* evidence of kidney protection in cisplatin induced AKI model
- ◆ Large patent portfolio:
 - ◆ Composition of matter and indication coverage with expirations beyond 2037

OUR APPROACH

- ◆ Block collagen remodeling in fibrosis by selectively inhibiting the meprin protease
- ◆ Provide kidney protection for patients treated with cytostatics by co-medication with meprin inhibitor

IN VIVO PROOF OF CONCEPT

- ◆ Evidence of kidney protection in cisplatin induced AKI model
- ◆ Effect on clinical parameters for kidney function demonstrated with with knockout animals and small molecule compound



POSITIONED FOR CONTINUED VALUE GENERATION

PRESENT FOCUS

Differentiated upstream approach targeting all three major hallmarks of AD
Allows intervention very early in disease pathogenesis

Lead candidate varoglutamstat in clinical Phase 2b in AD
FDA granted Fast Track designation in 2021
Phase 2a data showing statistically significant changes in working memory

FUTURE OPPORTUNITIES

Regional partnership with Simcere:
Development opportunities for varoglutamstat and PBD-C06 in AD in Greater China

Investigating potential to develop varoglutamstat in combination with mAbs in AD (own and external assets)
Advancing follow-up programs into the clinic beyond AD

UPCOMING CATALYSTS

VIVIAD European Phase 2b:
Final readout Q1/2024

VIVA-MIND US Phase 2a/b:
Study status update in Q1/2023



The background features a dark space with a glowing DNA double helix in shades of purple and pink. Two large, translucent spheres are positioned in the center. The sphere on the left is dark and textured, while the one on the right is bright blue and contains a network of white dots. A diagonal band of yellow and orange light sweeps across the right side of the image.

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