pasithea THERAPEUTICS

Corporate Overview

Sept 2024

Company Disclaimer

Certain statements set forth in this presentation by Pasithea Therapeutics Corp's (the "Company") contain forward-looking statements, within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, that reflect the Company's plans, beliefs, expectations and current views with respect to, among other things, future events and financial performance (collectively referred to herein as "forward-looking statements") including plans to develop, manufacture and commercialize its product candidates, the treatment potential of PAS-004, the translation of preclinical data into human clinical data, the design, enrollment criteria and conduct of the ongoing Phase 1 clinical trial of PAS-004 in advanced cancer patients, the ability of initial clinical data to de-risk PAS-004 and be confirmed as the study progresses, including the safety, tolerability, pharmacokinetics, pharmacodynamics and potential efficacy of PAS-004, the potential advantages and effectiveness of the Company's clinical and preclinical candidates, the timing of additional trial updates, recommended phase 2 dose and additional safety data, the indications to be pursued by the Company in future clinical studies including NF1-PN, the filing with, and approval by, regulatory authorities of our product candidates, the sufficiency of funds to operate the business of the Company, statements regarding the Company's ability to advance its pipeline and further diversify its portfolio, the Company's cash needs and availability, including our projected cash runway and current operating plans, and the plans and objectives of management for future operations. Forward-looking statements involve known and unknown risks, uncertainties, assumptions and other important factors that could cause our actual results, performance or achievements or industry results to differ materially from historical results or any future results, performance or achievements expressed, suggested or implied by such forward-looking statements.

These include, but are not limited to, statements about the Company's ability to develop, obtain regulatory approval for and commercialize its product candidates; our ability to submit Investigational New Drug applications ("IND"), or IND amendments or comparable documents in foreign jurisdictions in order to commence clinical trials on the timelines we expect; initiation of preclinical studies and clinical trials, and results of preclinical studies and clinical trials for our product candidates; the Company's success in early preclinical studies, which may not be indicative of results obtained in later studies or clinical trials; the potential benefits of our product candidates, including efficacy and safety profiles of our product candidates; the Company's ability to obtain regulatory approval to commercialize our existing or any future product candidates; the Company's ability to identify patients with the diseases treated by our product candidates, and to enroll patients in clinical trials; the Company's expectations regarding collaborations and other agreements with third parties and their potential benefits; the Company's ability to obtain, maintain and protect our intellectual property; the Company's ability to identify, recruit and retain key personnel; the Company's expected use of cash and cash equivalents to fund its operations; the Company's financial performance; developments or projections relating to the Company's competitors or industry; the impact of laws and regulations; the Company's expectations regarding the time during which it will be an emerging growth company under the JOBS Act; and other factors and assumptions described in the Company's public filings with the Securities and Exchange Commission ("SEC") and other documents we file from time to time with the SEC.

These statements are based on the Company's historical performance and on its current plans, estimates and projections in light of information currently available to the Company, and therefore, you should not place undue reliance on them. The inclusion of forward-looking information should not be regarded as a representation by the Company or any other person that the future plans, estimates or expectations contemplated by us will be achieved. Forward-looking statements made in this presentation speak only as of the date of this presentation, and the Company undertakes no obligation to update them in light of new information or future events, except as required by law.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

Leadership Team with Broad Range of Experience and Success

Dr. Lawrence Steinman - *Executive Chairman & Co-Founder*

- Endowed Chair in the Neurology Dept. at Stanford University. Member of the National Academy of Sciences.
- Founded and served on board of successful biotech companies, including Neurocrine Biosciences Inc. (Founder and Board Member) and Centocor (Board Member and head of SAB) until sold to J&J.
- Drug development pioneer in MS, with research that led to the development of the drug Tysabri.

Dr. Tiago Reis Marques - *Chief Executive Officer & Co-Founder*

- Fellow at Imperial College and lecturer at King´s College London.
- Renowned psychiatric researcher and lecturer with decades of experience in the biological mechanisms of mental health and brain disorders.

Dr. Graeme Currie - *Chief Development Officer*

- 30 years of drug development experience in both pharmaceutical and biotech companies.
- Senior leadership roles at Dynavax Technologies, Regeneron Pharmaceuticals, Inc., PDL BioPharma, Inc. and Gilead Sciences, Inc.
- Dr. Currie has successfully led drug development programs and has held key roles in the development of 7 approved drugs.

Daniel Schneiderman - *Chief Financial Officer*

- 20+ years of experience in the capital markets and operations.
- Senior financial roles at translational biotech companies, including, MetaStat, Inc., Biophytis SA and First Wave BioPharma, Inc.

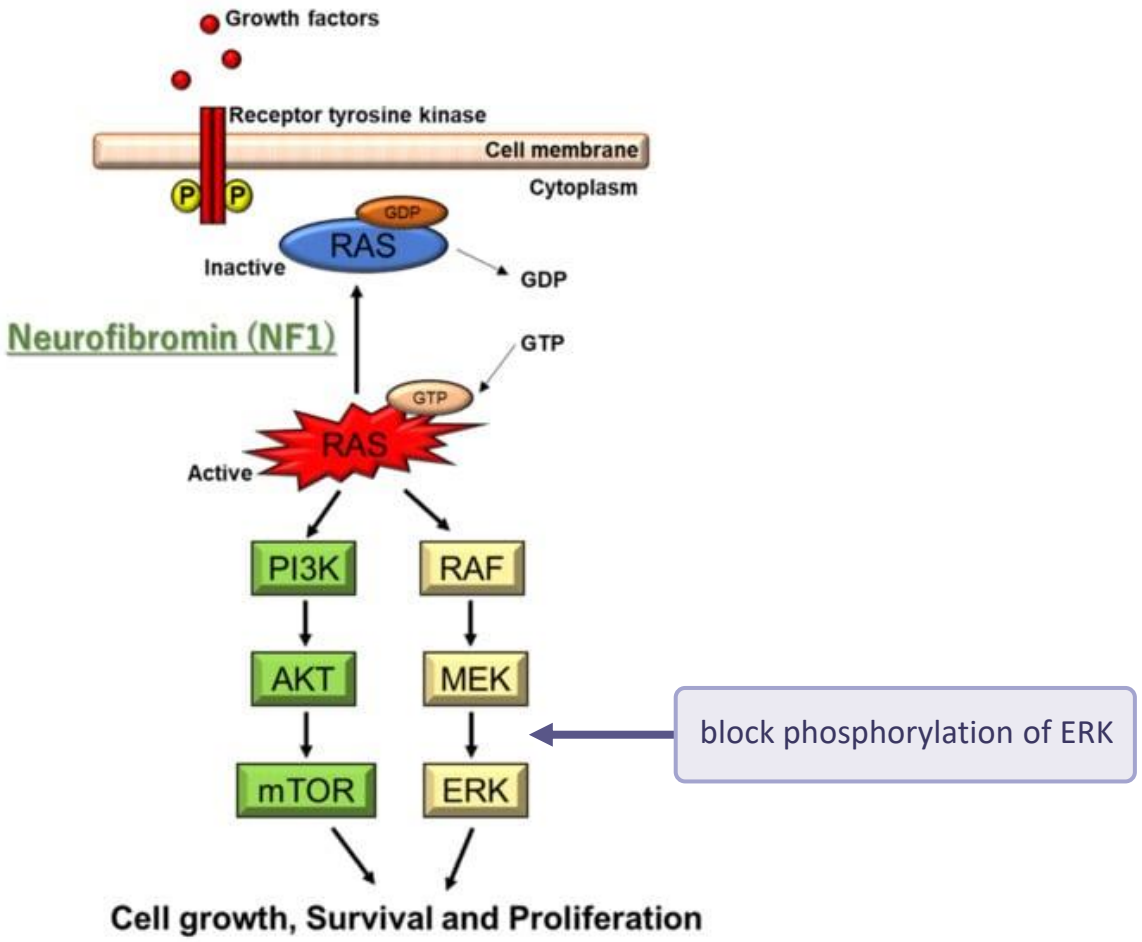
MEKi Focused Pipeline

Program	Drug modality	Indication	Target	Target ID / Validation	Lead Selection	IND Enabling	Phase I	Milestones
PAS-004	Macrocyclic Small molecule	Neurofibromatosis Type 1 (NF1) and solid tumors	MEK 1/2	FIH Phase 1 trial initiated Q1 2024				**Interim data 2H 2024**
PAS-003	Monoclonal antibody	Amyotrophic Lateral Sclerosis (ALS)	$\alpha5\beta1$ Integrin					**Partnership opportunity**
PAS-001	Small molecule	Schizophrenia	C4A					**Partnership opportunity**

PAS-004

Next Generation MEK Inhibitor for
The Treatment of Neurofibromatosis
Type 1 (NF1) and Solid Tumors

MAPK Pathway disregulation is implicated in Cancer and NF1/Rasopathies



The mitogen-activated protein kinase **(MAPK) pathway** is a chain of proteins that are essential for cell function by regulating cellular transcription, proliferation, survival and other functions.

When abnormally activated, the MAPK pathway is critical for the formation and progression of tumors, fibrosis and other diseases.

Alterations in RAS or RAF have been described in many cancers, including melanoma and colorectal where MEK inhibitors are approved.

NF1 arises from mutations in the NF1 gene, which encodes for neurofibromin, a key negative regulator of MAPK Pathway by inactivating RAS.

Other diseases (Rasopathies) are known to be caused by MAPK disregulation.

MEK inhibitors have broad opportunity - modulate the ETS2 pathway

- ETS2 gene is a central regulator of human inflammatory macrophages
- MEKi as a class are the strongest known ETS2 inhibitors
- MEKi modulation provides potent anti-inflammatory activity, phenocopying ETS2 knock-out, modulating multiple cytokines

Article

A disease-associated gene desert directs macrophage inflammation through ETS2

https://doi.org/10.1038/s41586-024-07501-1
Received: 17 April 2023
Accepted: 1 May 2024
Published online: 05 June 2024
Open access
Check for updates

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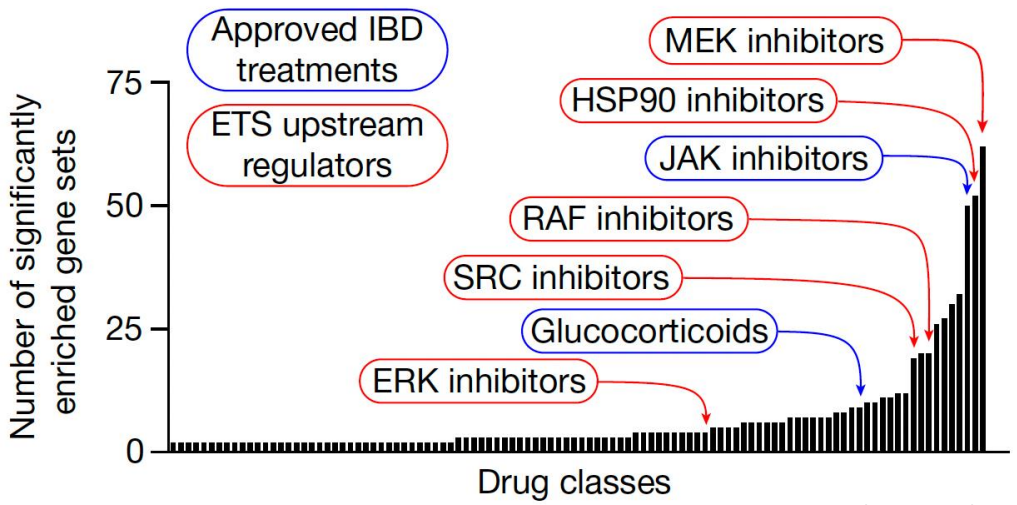
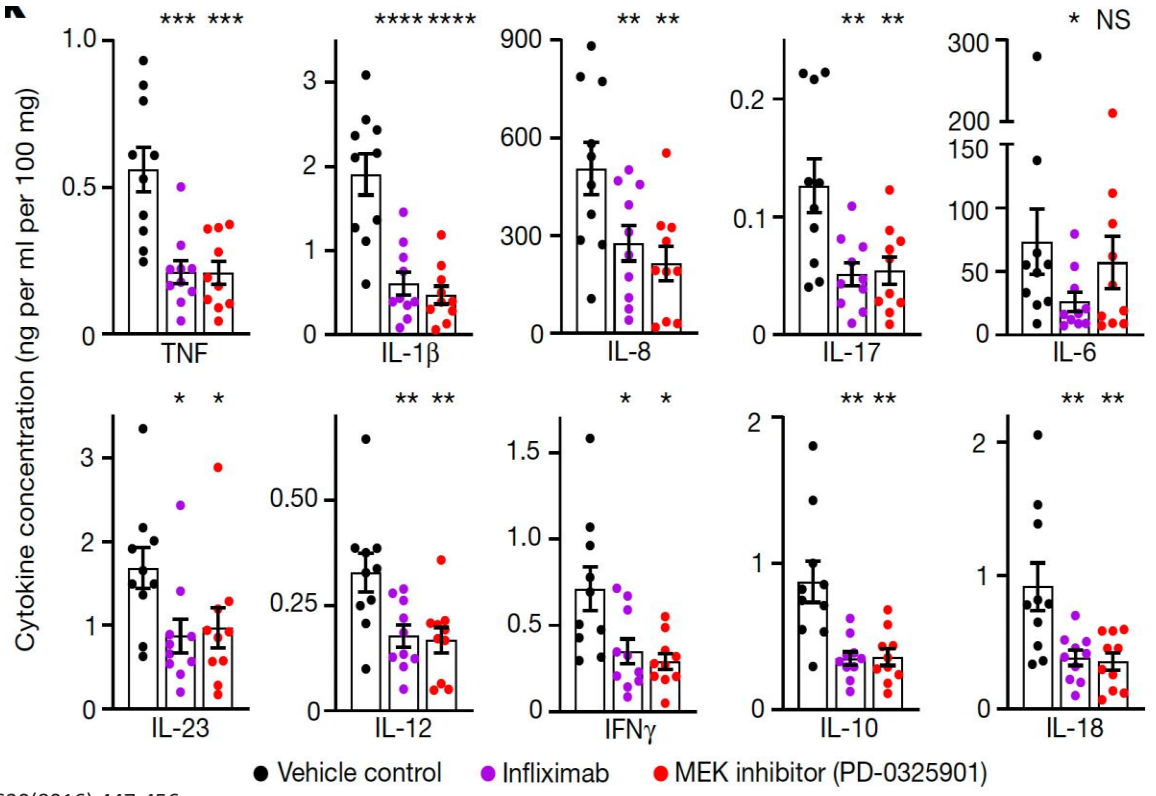
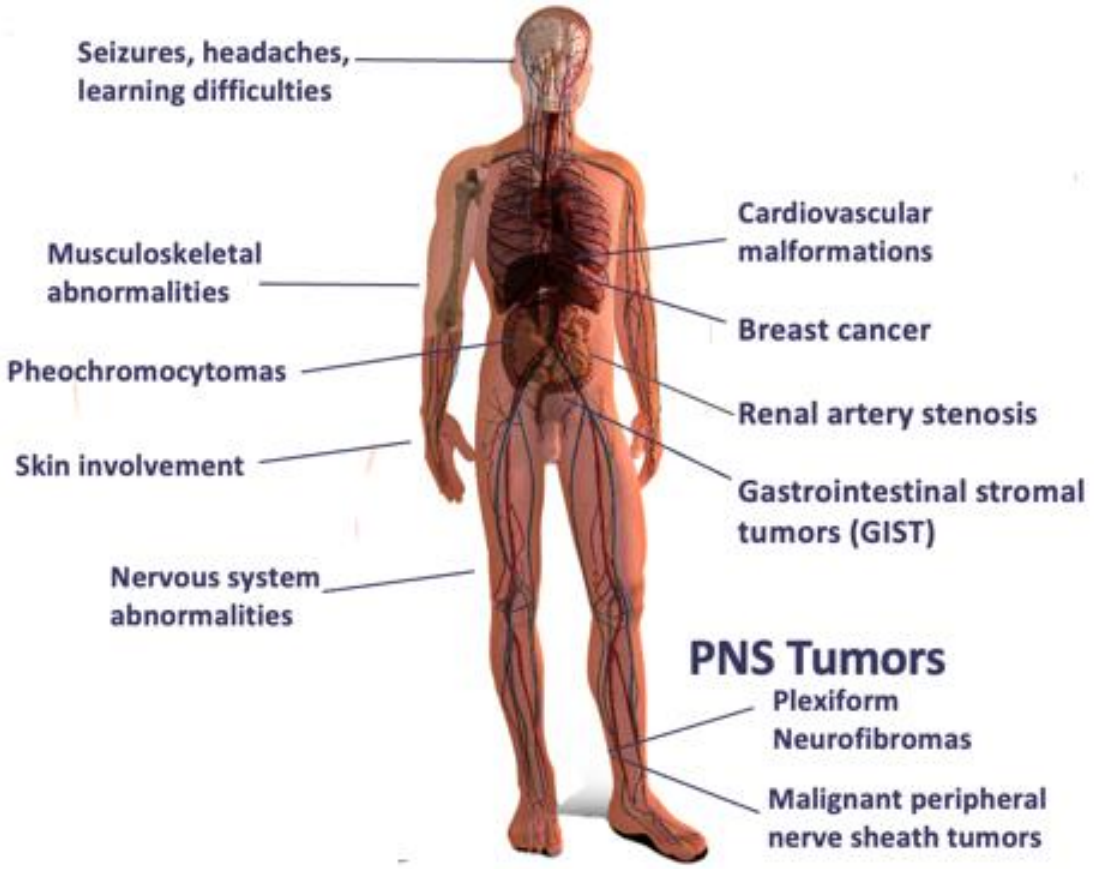




Stankey CT et al. Nature. 2024 Jun;630(8016):447-456. .

NF1: Large unmet medical need



NF1 is a autosomal dominant genetic disorder.

Affects approximately one in 3,000 newborns worldwide with ~100,000 patients living in U.S. with NF1[1].

30-50% of NF1 patients develop plexiform neurofibromas (NF1-PN).
>95% develop cutaneous neurofibromas (NF1- CN).

PN are benign peripheral nerve sheath tumors that can cause severe complications, including disfigurement, pain, motor dysfunction, and neurological impairment and have malignant transformation potential.

Surgical resection of PN is challenging. The MEK inhibitor Selumetinib is the only FDA approved agent for NF1-PN treatment and only in the pediatric population (ages 2-18).

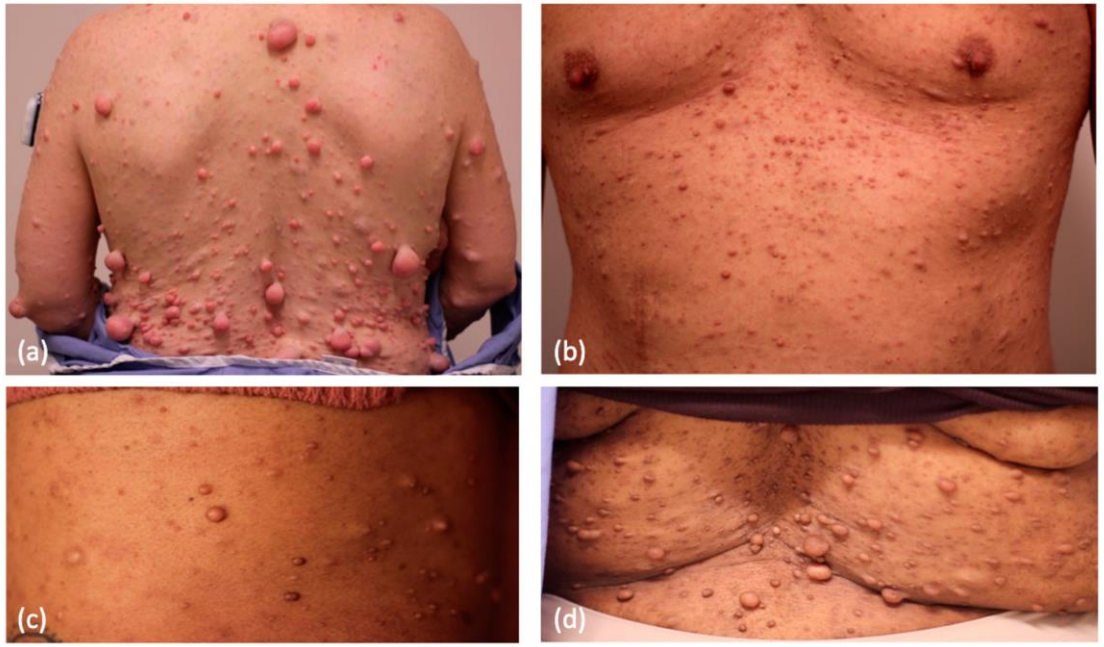
CN usually presents as skin bumps and can cause disfigurement and quality of life challenges. There are currently no approved treatments for CN.

1. Division of Cancer Epidemiology & Genetics at the National Cancer Institute

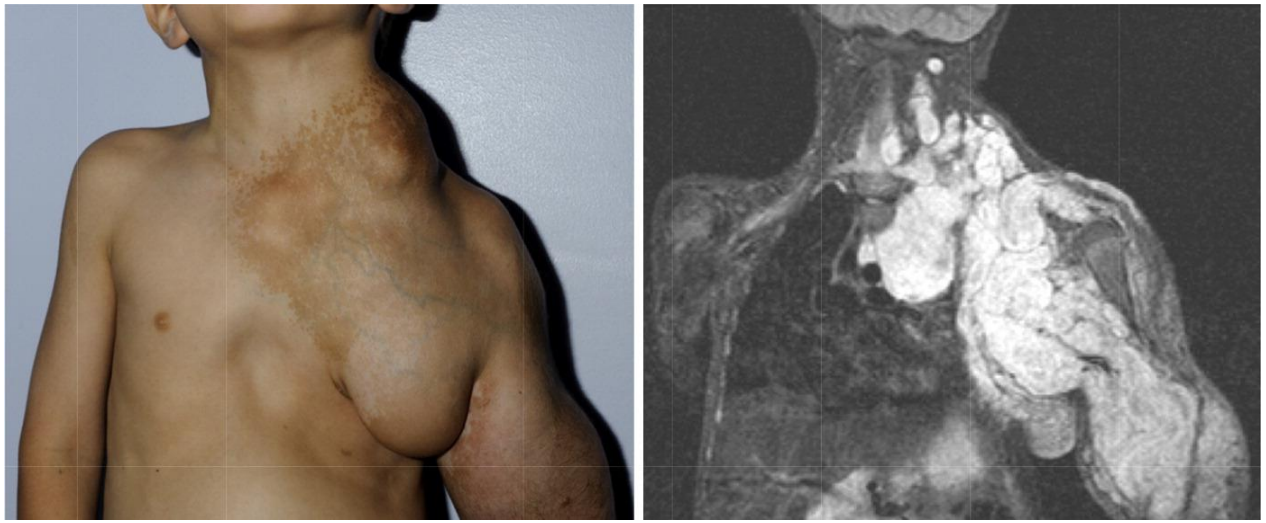
NF1 Tumor Conditions

- Neurofibromas are noncancerous (benign) tumors that are derived from Schwann cell lineage
- Plexiform Neurofibromas can undergo malignant transformation

Cutaneous Neurofibromas



Plexiform Neurofibromas



Dagalakis U et al., J Pediatr. 2014 Mar;164(3):620-4.
Poplausky, D et al. Cancers 2023, 15, 2770.

Where and how to improve on existing treatment option

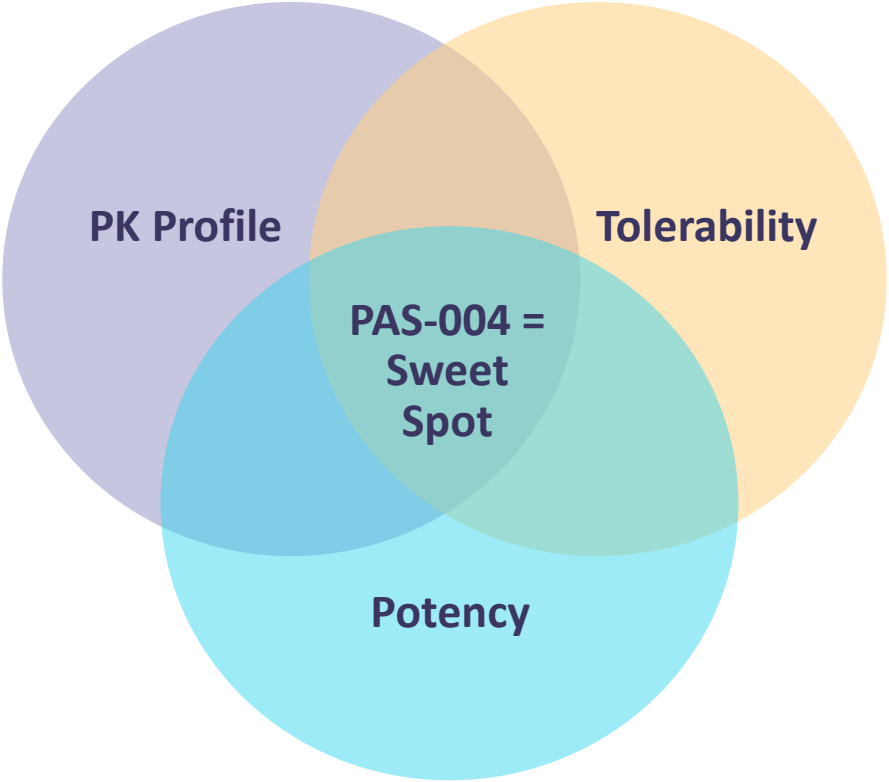
- **Current approved MEKi has suboptimal profile**
  - Discontinuation rate of 38.2% at 18 months and 47.8% at 24 months.[1]
  - ORR of 44% - independent centralized review (ICR)REiNS criteria.[2]
  - Average depth of response is only 27.9% (median best percentage change in PN volume from baseline).[2]
  - Potentially linked to limited pERK inhibition and plateau effect seen in our preclinical cellular models.

- **Long time to generate response**
  - Time to response is long (median time to onset of response is 7.2 months). [2]

- **Poor tolerability and compliance**
  - Requires BID (2x/day) dosing. [3]
  - AE profile characterized by GI symptoms and skin tox. [3]

1. Lyons et al; Medication adherence and persistence on selumetinib treatment in pediatric database analysis; Poster presented at Global NF Conference, June 2024
2. Results from results from SPRINT Phase 2 Stratum 1; DCO June 2018
3. KOSELUGO Prescribing Information (https://alexion.com/Documents/koselugo_uspi.pdf)

Macrocycle Structure positions PAS-004 into the “Sweet Spot” for NF1



Sustained suppression of phospho-ERK (Potency)

- Long half life allows continued suppression of target, potentially leading to better efficacy.

Improved risk-benefit profile (Tolerability)

- Macrocyclic molecules are more rigid with possible less “off target” side-effects vs other MEK inhibitors with additional interactions.
- Expected 90% pERK reduction at NOAEL dose.
- Improved patient compliance due to 1x a day or less dosing.

Improved PK/PD (PK profile)

- 96% oral bioavailability seen in preclinical models.
- Long half life (approved drugs in NF1 have short half life requiring BID dosing).

Better combinability

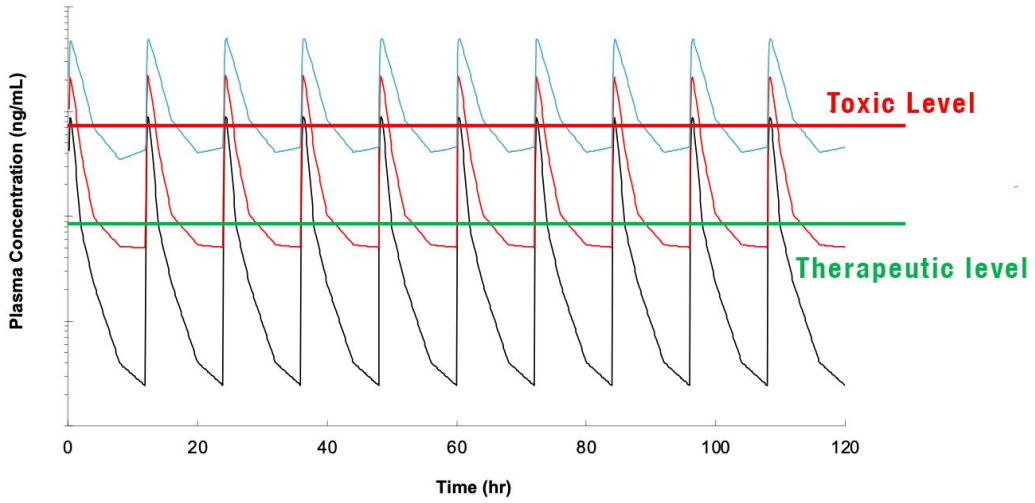
- Superior properties may support better combination.

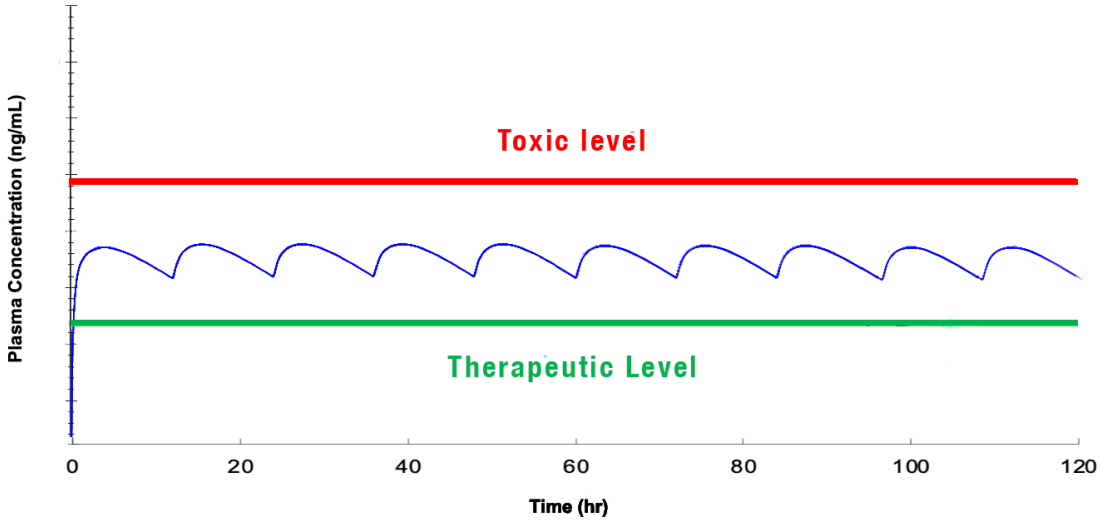
Constant suppression of the MAPK pathway

- PK profile suited to enhance efficacy and avoid toxicity

Short half life = No accumulation
Target is not continuously inhibited

Long half life = Accumulation to reach steady state
Target is continuously inhibited





For illustrative purposes only

Approved MEK Inhibitors

Typical liabilities associated with approved MEK Inhibitors:

- High toxicity and dose limiting side effects
- Toxicity and PK profile limits use in combination therapies (such as chemo and/or IO agents)

Drug	Company	Development Approach	Tumor Type	Key Properties
Selumetinib (Koselugo)	AstraZeneca	Monotherapy (pediatric)	Neurofibroma (NF-1)	• Short Half-Life • BID dosing
Trametinib (Mekinist)	Novartis	+ B-Raf inhibitors	Melanoma, NSCLC, Thyroid cancer, BRAF V600E	• Long Half-life • High Potency
Cobimetinib (Cotellic)	Genentech	+ B-Raf inhibitors	Melanoma	• Long Half-Life
Binimetinib (Mektovi)	Pfizer	+ B-Raf inhibitors	Melanoma	• Short Half-life • BID dosing

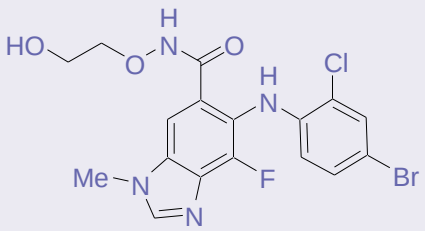
MEK inhibitors in clinical development

Majority of MEK inhibitors in clinical development for Oncology indications

	Pasithea (KTTA)	Day One (DAWN)	Recursion (RXRX)	Spring Works (SWTX)	Fosun Pharma (656 HK)	Verastem (VSTM)	Immuneering (IMRX)
MEK Inhibitor	PAS-004	Pimasertib	REC-4881	Mirdametnib	FCN-159	Avutometinib (MEKi + RAF clamp)	IMM-1-104 (Universal RAS)
NF 1 Intention	Yes	No	No	Yes	Yes	No	No
Development Phase	Phase 1	Phase 2	Phase 2	Phase 2b	Phase 2	Phase 2	Phase 1
Clinical Trials Indications	- Advanced Solid tumors - Bridge to NF1 pediatrics and adults	- Recurrent or progressive solid tumors	- Familial Adenomatous Polyposis (FAP)	- NF1 pediatrics and adults - Advanced solid tumors	- Phase 2 data in NF1 patients	- Low Grade Serous Ovarian Cancer	- Advanced Solid tumors
~Market Cap (08/30/24)	$4.6 million	$1.36 billion	$2.0 billion	$3.1 billion	N/A	$100 million	$33 million

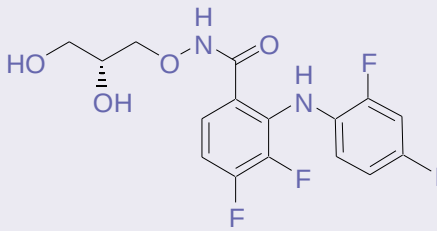
PAS-004 was designed to address the liabilities of previous MEK inhibitors

Selumetinib



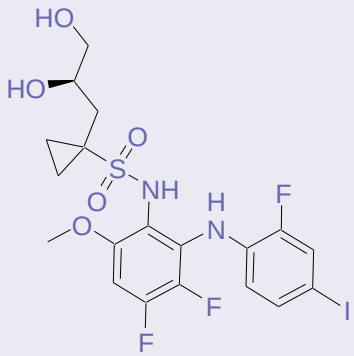
First Generation

Mirdametinib



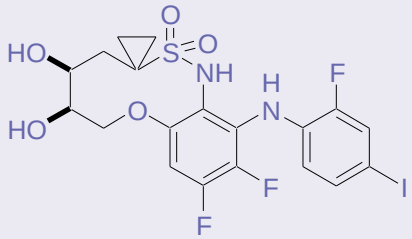
Introduction of diol in the side chain. Improved solubility, potency

Refametinib



Hydroxamide to sulfonamide. improved half-life and potency

PAS-004



Next Generation Macrocycle

- **Modification in chemical structures can have big impact on drug properties**
  - **Primary alcohol reduced potential for active metabolites**
- **PAS-004 is the first MEK inhibitor with a Macrocyclic structure**
- **Improved oral bioavailability, PK properties and Potency**

Biochemical (MEK1/2 enzyme)	
Assay	IC_{50} = 40 nM
Mechanism-based Cellular	
Assay (p-ERK)	IC_{50} = 2 nM
Rat PK	$T_{1/2}$ = 11.5 h; %F = 39%
Dog PK	$T_{1/2}$ = 52 h; %F = 96%
Chemistry	9-step synthesis

PAS-004 profile is superior to Approved MEK inhibitors

- Higher Cmax, Less Potent at hERG Inhibition (ie. less cardiotoxicity) and Long Half Life

	Trametinib (21 day-GLP)[1]	Cobimetinib[2]	PAS-004 (28-day GLP)
Studies performed on Rats			
pERK (EC_{50})	2 nM	2 nM	2 nM
(M) NOAEL Dose, 28-day GLP	(HNSTD) 0.125 mg/m^2/day (0.02 mg/kg)	3 mg/kg (HNSTD)	5 mg/kg
28th day, Cmax at NOAEL Dose	2.89 nM	54 nM	2404 nM
Cmax/ pERK IC_{50}	<2	27	1202
Studies performed on Dogs			
NOAEL Dose	0.5 mg/m^2/day HNSTD (0.025 mg/kg)	13-week study, <<1 mg/kg	0.5 mg/kg
28th day, Cmax at NOAEL Dose	5.41 nM	67 nM (day 30), 0.3 mg/kg	820 nM
Cmax/ pERK IC_{50}	<5	33.5	>>200
Additional Information			
hERG Inhibition (IC_{50})	1 µM	0.5 µM	13 µM
Pharmacokinetic, Rat Half-life	5.5h	5.56h	11.5h
Pharmacokinetic, Dog Half-life	13h	6.21h	52h

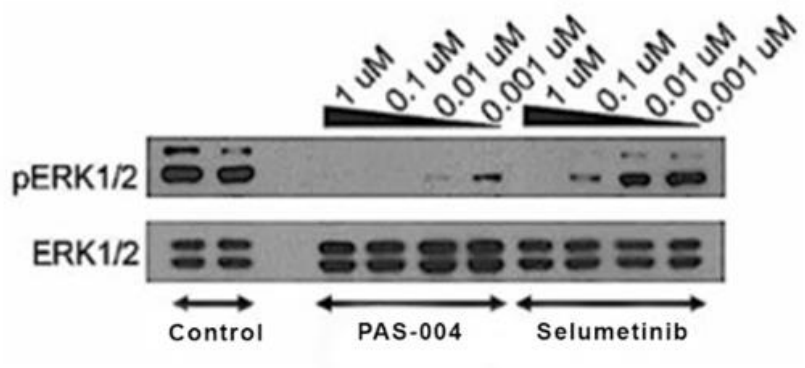
HNSTD = Highest non-severely toxic dose

1. Center for drug evaluation and research, Pharmacology review, Application Number 204114Orig1s000
2. Center for drug evaluation and research, Pharmacology review, Application Number 206192Orig1s000

Comparative Preclinical Efficacy of PAS-004

- Better potency (>10x) than Selumetinib in inhibiting p-ERK in vitro
- Superior efficacy when dosed 1xday than approved MEKi dosed 2xday

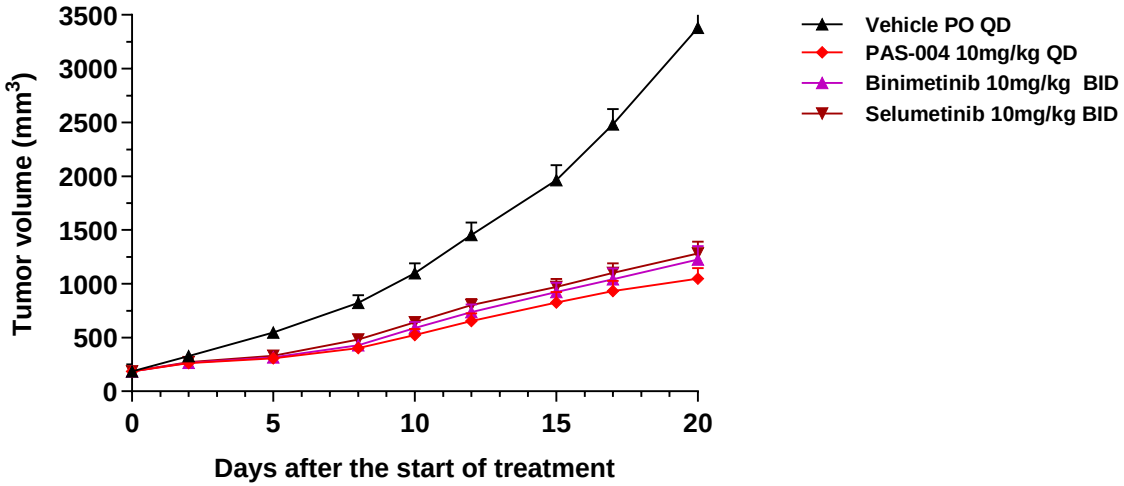
PAS-004 vs. Selumetinib *In Vitro* Potency



HEK-293 cell line

Study conducted at Dr. Worman's. Lab, Columbia University

PAS-004 vs. Approved MEKi *In Vivo* Efficacy

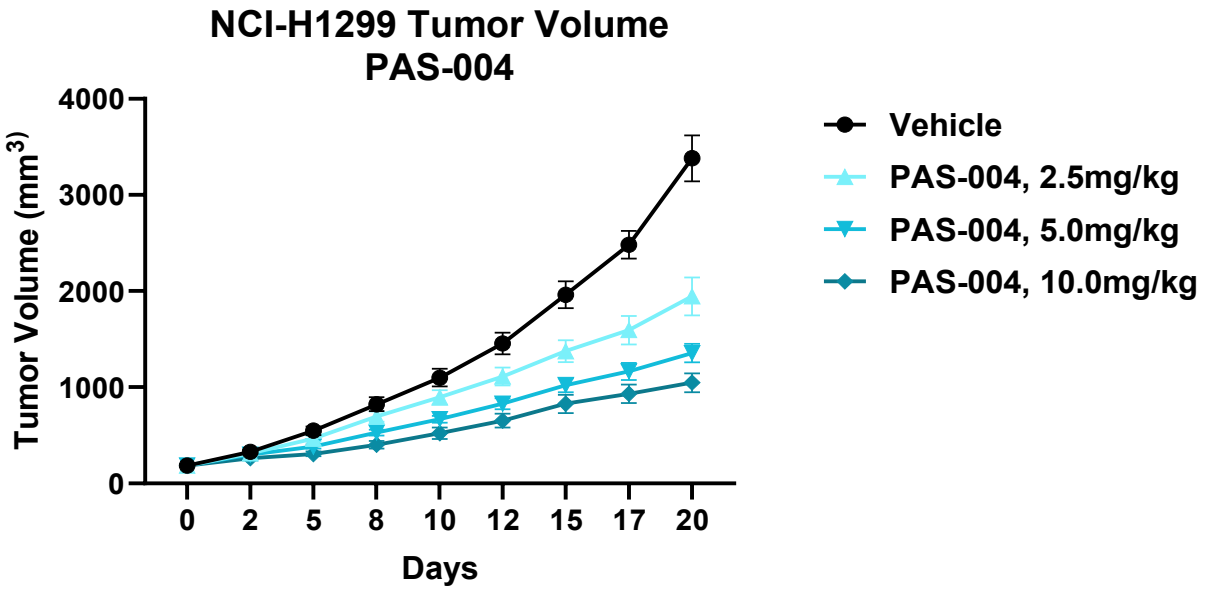


Study conducted at Wuxi AppTec

Dose Dependent inhibition of pERK which correlate with clinical efficacy

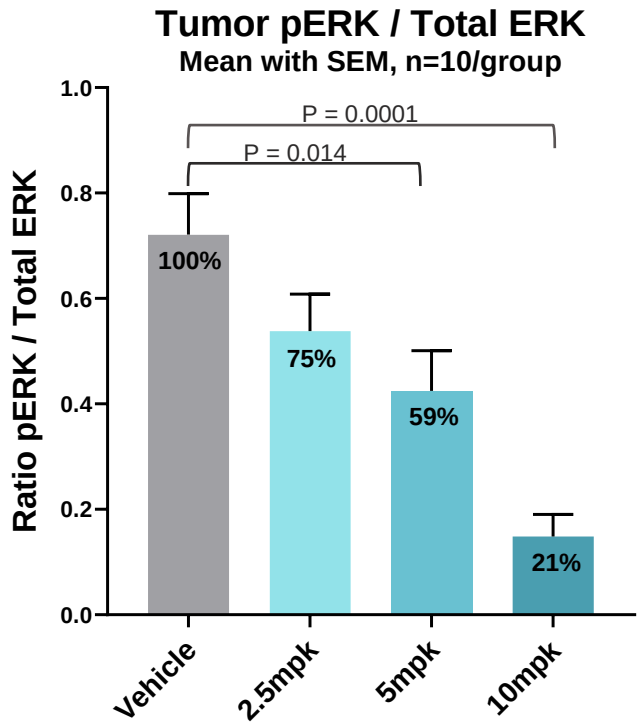
- Analysis of clinical data from approved MEKi indicates partial p-ERK is needed in NF1

In Vivo Dose dependent efficacy (NCI-HI299 xenograft)



Study conducted at Wuxi AppTec

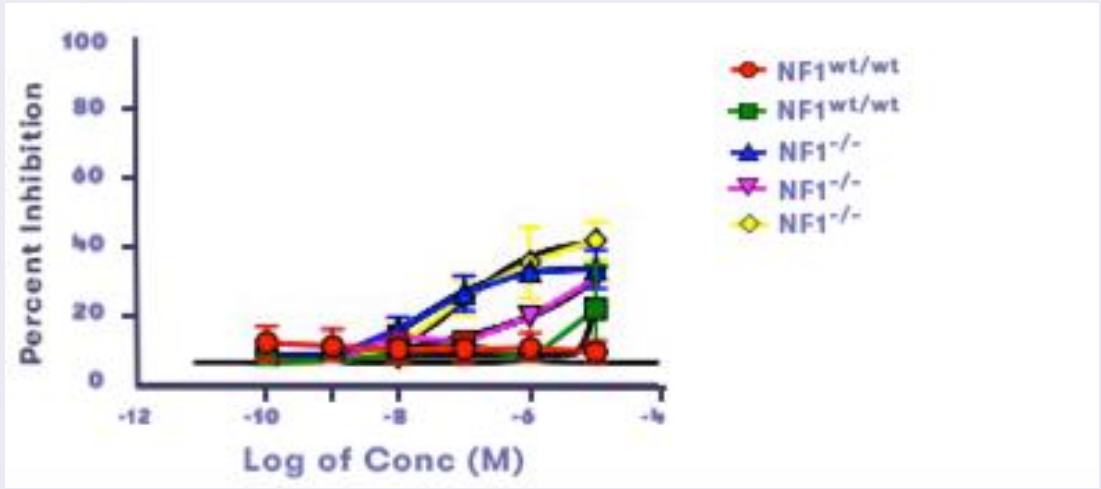
In Vivo Dose dependent pERK reduction (NCI-HI299 xenograft)



PAS-004 is More Potent than Selumetinib in *In Vitro* NF1 Model

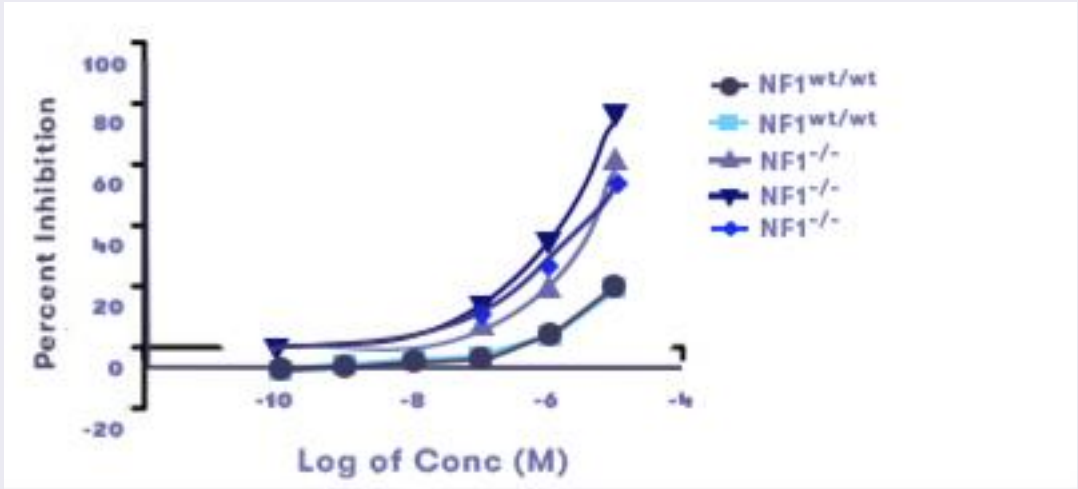
- PAS-004 is more potent in all 3 NF1 mutated cell lines than Selumetinib
- No Plateau Effect was observed for PAS004 = potential for deeper activity in patient
- Limited activity against the control NF1 WT cells=support good safety profile

Selumetinib



Study conducted at Ray Mattingly lab, Indiana University

PAS-004



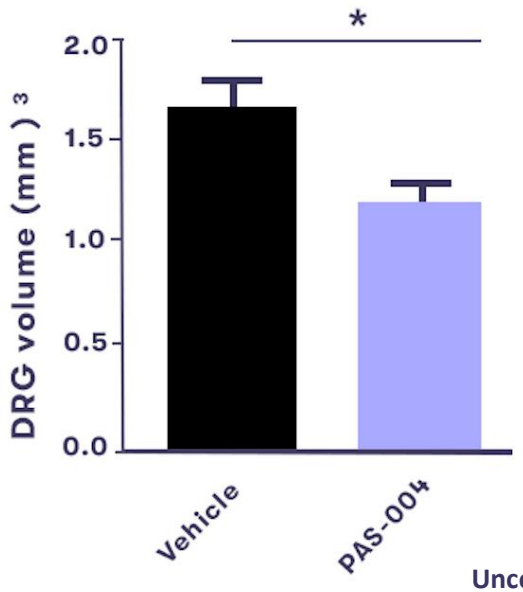
Study conducted at Ray Mattingly lab, Indiana University

Reference for the 3D culture assay: Ray Mattingly et al, Wayne State Exp. Neurology 2018, 289

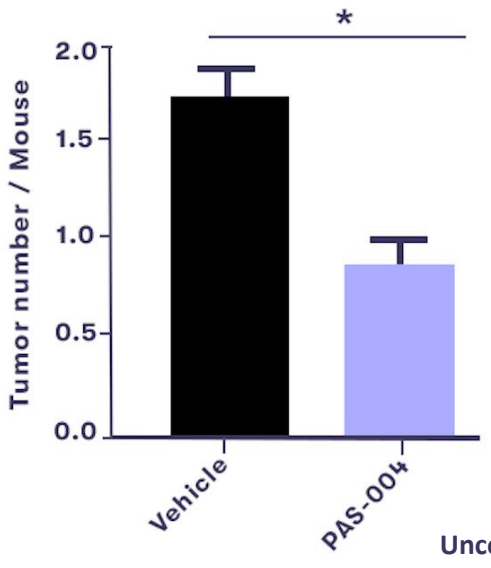
PAS-004: Genetic Engineered Mouse Model (GEMM) of NF1

- PAS-004 exhibits significant reduction in tumor volume
- PAS-004 exhibits significant reduction in tumor number
- PAS-004 is dosed 1x day, where other agents require 2x day

PAS-004 efficacy in GEMM model



Uncorrected Fisher's LSD:
* V vs PAS-004 – 0.0048



Uncorrected Fisher's LSD:
* V vs PAS-004 —0.0009

Intellectual Property

- **Composition of Matter Patent Issued**
  - US patent 9034861, Exclusivity protection until Sept 2032 with extension estimated to be March 2037
  - Additional 6-month exclusivity for pediatric application
  - Patent issued in multiple geographies

- **New patents filed in Jan 2024**
  - Based on identification of a stable crystalline form – composition of matter
  - Anticipated patent protection at least until 2045

- **Orphan Exclusivity**
  - Received orphan-drug designation from the FDA for the treatment of NF1
  - For rare diseases: 7 years in U.S. and 10 years in European Union

- **Potential new patent filings**
  - Process Patent, follow-up compounds

PAS-004 Phase I Clinical Trial

Patient Population (n=~36)

Patients with MAPK pathway driven solid tumors with a documented RAS, NF1, or RAF mutations or patients who have failed BRAF/MEK inhibition

Up to 7 sites in US and Eastern Europe

NOVOTECH The Asia Pacific CRO

next ONCOLOGY

ARENSIA EXPLORATORY MEDICINE

TRIAL OBJECTIVES

Primary	To evaluate the safety and tolerability of PAS-004 in patients with MAPK pathway driven advanced solid tumors.
Secondary	Pharmacokinetic (PK) profile
	Pharmacodynamic (PD) effects (ERK phosphorylation)
	Define the recommended Phase 2 dose
	To evaluate the preliminary anticancer activity

SAD & MAD Dose Escalation

Cohort 1: PAS-004 **2 mg** (n=3+3)

↓

Cohort 2: PAS-004 **4 mg** (n=3+3)

↓

Cohort 3: PAS-004 **6 mg** (n=3+3)

↓

Cohort 4: PAS-004 **9 mg** (n=3+3)

↓

Cohort 5: PAS-004 **12 mg** (n=3+3)

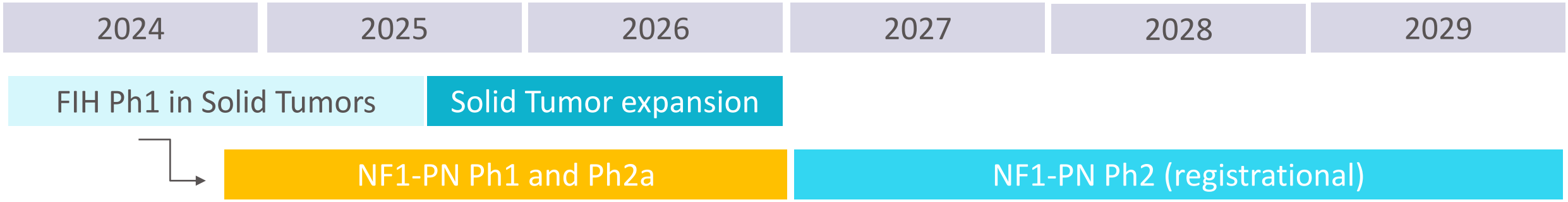
↓

Cohort 6: PAS-004 **15 mg** (n=3+3)

↓

Cohort 7: PAS-004 **18 mg** (n=3+3)

Clinical Program Timelines to Registration and Near term Milestones



1Q 2024	Initiated Phase 1 Clinical Trial
2H 2024	Interim Clinical Trial Readout
4Q 2024	Initiate NF1 Patient Cohort

PAS-003

Monoclonal Antibody Targeting $\alpha5\beta1$ Integrin for Amyotrophic Lateral Sclerosis (ALS)

ALS is a Devastating Disease with Few Treatment Options and Limited Impact

- Amyotrophic lateral sclerosis (ALS) is a degenerative neurological disorder that causes muscle atrophy and paralysis
- Current treatment options have limited effects on symptoms and slowing of disease progression
  - Rilutek (riluzole, now generic)
  - Radicava™ (edaravone)
  - Relyvrio (AMX0035; sodium phenylbutyrate and taurursodiol)
  - Qalsody (tofersen; for mutant SOD1 gene carriers)
- Tremendous need for better treatments

Average age of onset is mid-50s

Sporadic: 90%-95% of all cases

SOD1: 3%
C9orf72: 8-10%
TDP43: ≈90%

Familial: 5%-10% of all cases

Male-Female ratio: 3:2
Incidence: 1.0-2.5/100,000
Prevalence: 5/100,000

Clinical Manifestations:

Early stage

Dysphagia, Dysarthria,
Emotional lability,
Spasticity, Fasciculations,
Cramps, Muscle weakness, Atrophy

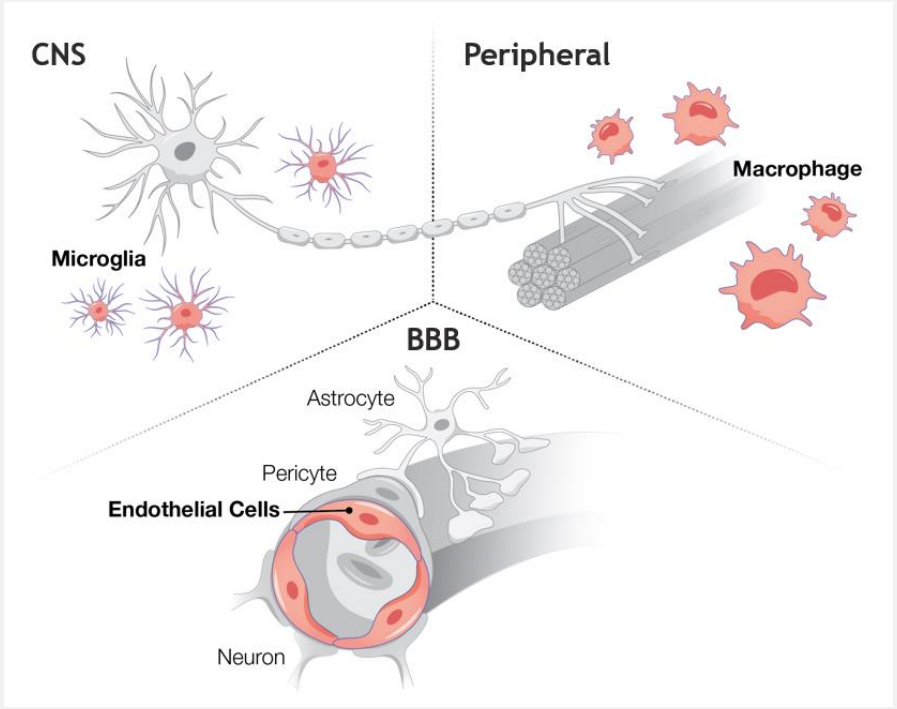
Late Stage

Dementia
Respiratory failure
Aspiration pneumonia
Oculomotor nerve affected
May resemble locked-in syndrome

α5β1 Integrin is a Druggable Target for ALS

- α5β1 is overexpressed in human and mouse ALS
- α5β1 integrin is a well characterized target
  - Anti-α5β1 mAbs developed for cancer by PDL/Biogen, Pfizer & Genentech
  - Volociximab advanced to Phase II with acceptable safety profile
- Blocking integrins relieves inflammation
  - Three FDA-approved mAbs targeting integrins – Tysabri, Entyvio & ReoPro
- The primary ligand of a5b1, fibronectin, is implicated in several inflammatory conditions of the CNS & PNS

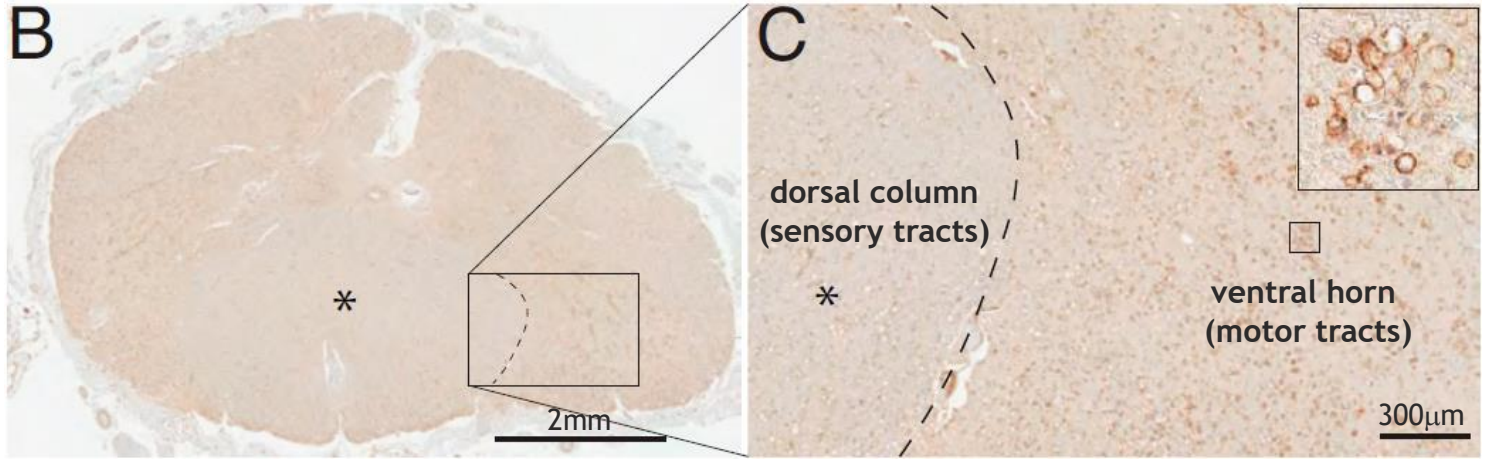
α5β1 is expressed in 3 cell types central to neuroinflammation



α5β1 Integrin is Elevated in Motor Areas of ALS Postmortem Tissue

Data collection and analysis conducted at Mayo Clinic (in collaboration with Pasithea scientists)
132 autopsy samples with various clinical ALS phenotypes (familiar and sporadic form) and disease duration
Elevation of α5β1 expression in all samples, irrespective of disease duration and subtype
Striking spatial zonation of α5β1 integrin expression, confined to the primary motor cortex and spinal cord

α5 integrin expression is elevated in motor area of ALS postmortem spinal cord

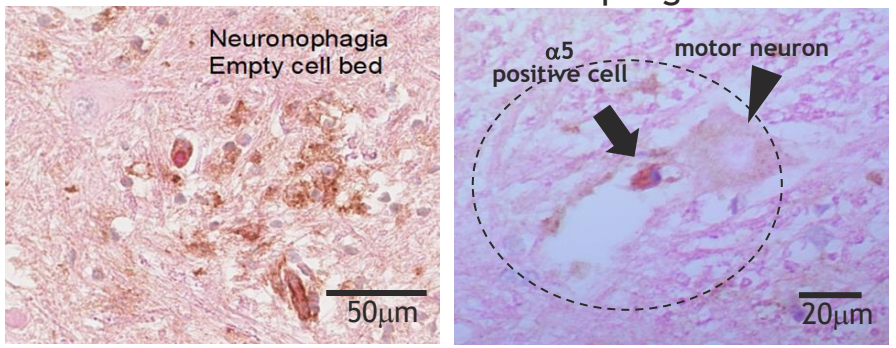


PNAS RESEARCH ARTICLE | MEDICAL SCIENCES

Elevated α5 integrin expression on myeloid cells in motor areas in amyotrophic lateral sclerosis is a therapeutic target

Aude Chiot[a,b,1], Shanu F. Roemer[c,1], Lisa Ryner[d], Alina Bogachuk[a,b], Katie Emberley[a,b,e], Dillon Brownell[a,b], Gisselle A. Jimenez[a,b], Michael Leviten[d], Randall Woltjer[f], Dennis W. Dickson[c], Lawrence Steinman[g,2], and Bahareh Ajami[a,b,2]

α5 at sites of neuronophagia

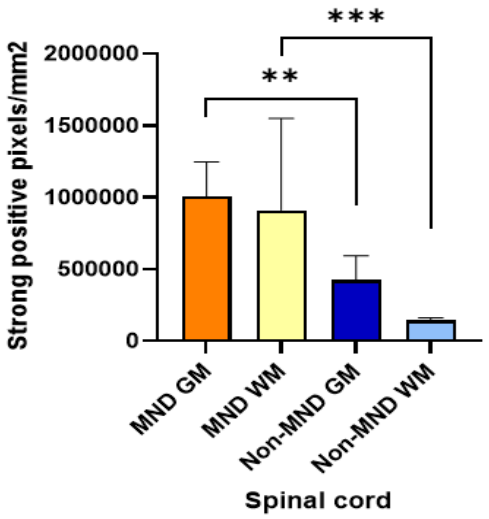


pasithea THERAPEUTICS

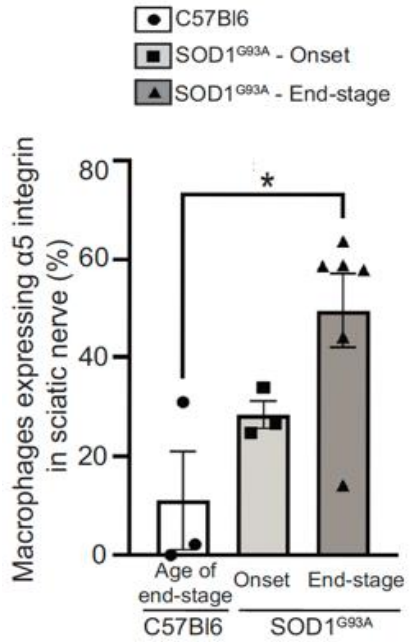
α5β1 Integrin is Elevated in Motor Areas of ALS Postmortem Tissue

Elevation of α5β1 expression was not observed in human healthy controls
Specificity of α5β1 to ALS Pathology (no increase in other integrins expression)
Expression of α5β1 increases with disease progression (preclinical SOD mouse model)
α5β1 gene expression increases with disease progression (ALS human data)

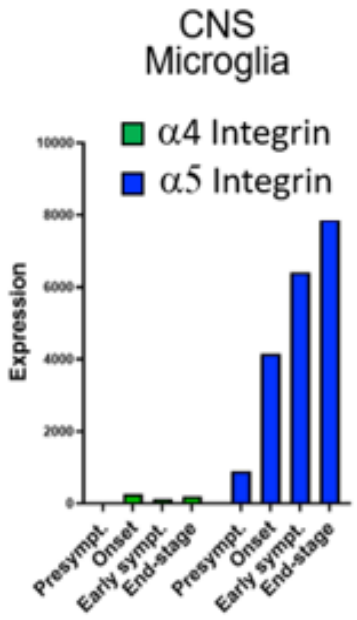
α5β1 in ALS vs HC



α5β1 disease progression



α5β1 vs other integrins



ALS gene expression

Spinal Cord Tissue

α5 is the top differentially expressed alpha integrin in ALS motor-region of spinal cord tissue

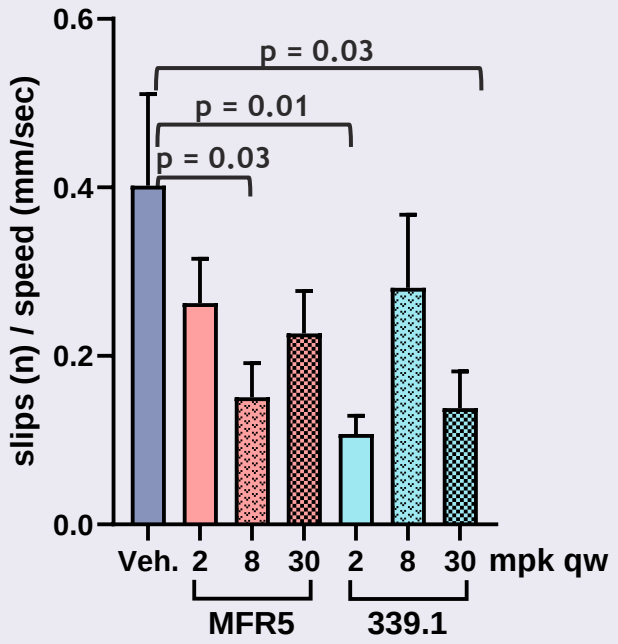
Gene	Fold Change	P-value
ITGA5	2.9	2.00E-04
ITGA11	2.5	5.00E-05

Ventral horn of ALS tissue (n=6)
vs.
Matched normal subjects (n=5)

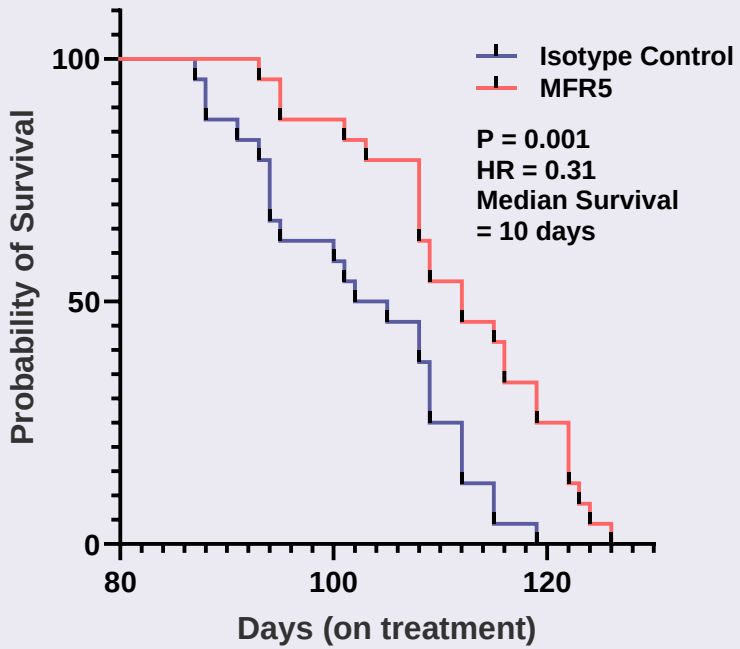
Mouse SOD1^{G93A} Model: Anti-α5 Treatment Improves Behavior, Survival & Reduces T Cell Infiltration into the CNS

- Preclinical Gold-Standard model
- Data replicated in 3 different studies

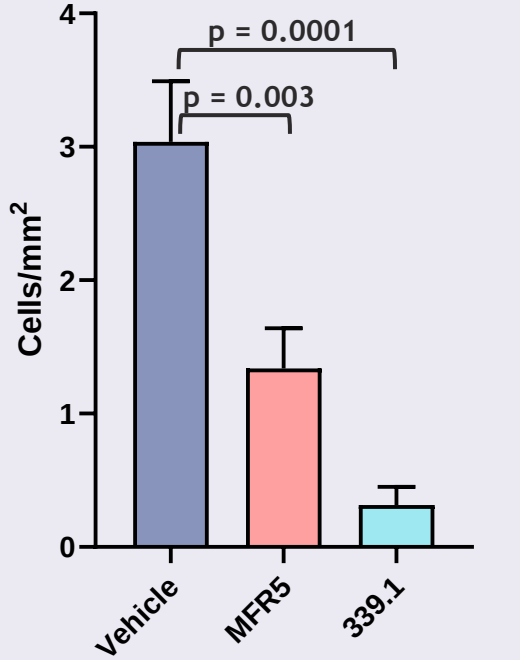
Beam Walk



Survival

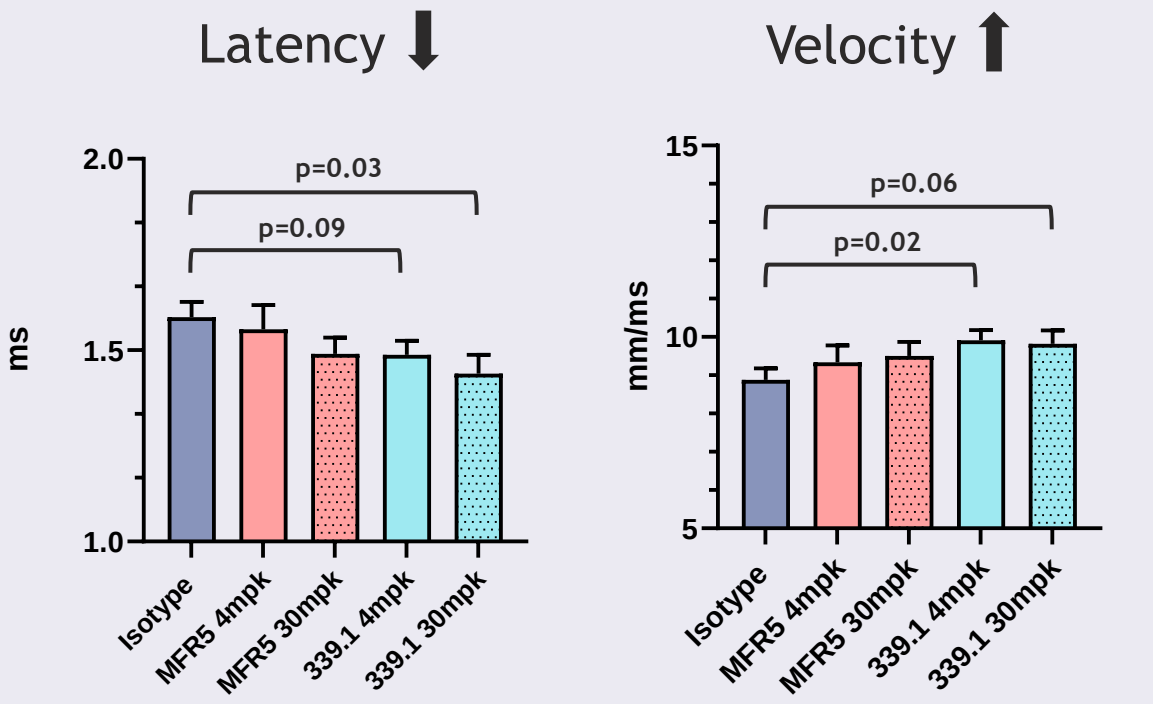


CD4+ T Cells in Spinal Cord

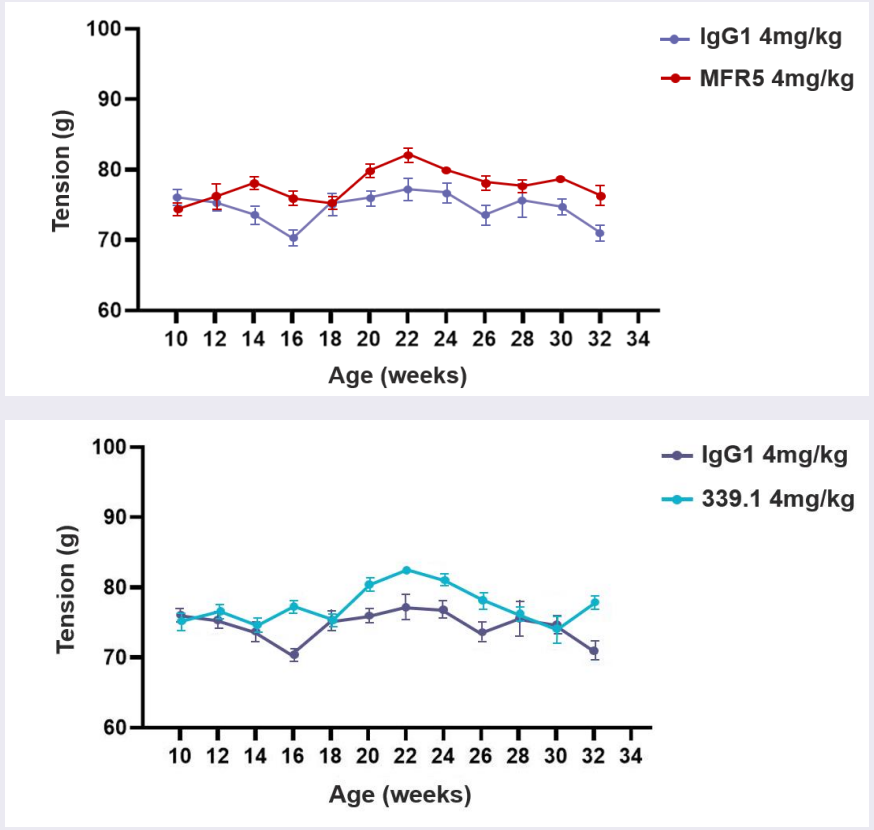


TDP-43 ALS Mouse Models: Anti-α5 Treatment Improves Muscle Function

Muscle Electrophysiology CMAP in TDP-43^{rNLS8} (Short Model)



Grip Strength in Males TDP-43^{Q331K} (Long Model)



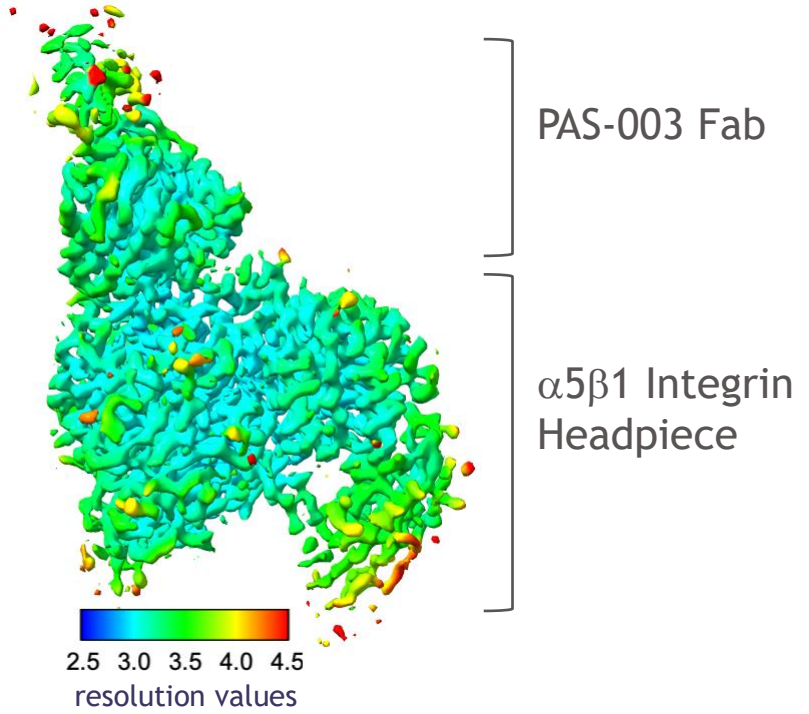
PAS-003 Monoclonal Antibody Antagonist of α5β1 for ALS

Roadmap

- Humanized lead candidate selected
  - ✓ Blocks binding of primary ligand fibronectin
  - ✓ Inhibits adhesion & migration of α5 expressing cells
  - ✓ Exhibits favorable developability profile
  - ✓ Composition of matter and use patents filed
- Identify partner to support IND-enabling studies
- Discuss orphan drug designation with FDA

PAS-003 Interaction with α5 Integrin

Cryo-EM 3.2 Å Density Map



PAS-001

Small molecule targeting the Complement Component 4A (C4A) for the treatment of Schizophrenia

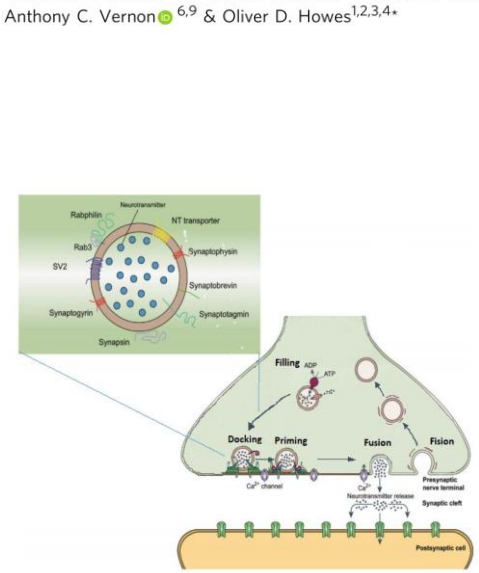
Synaptic loss is present in schizophrenia both in-vivo and human post-mortem

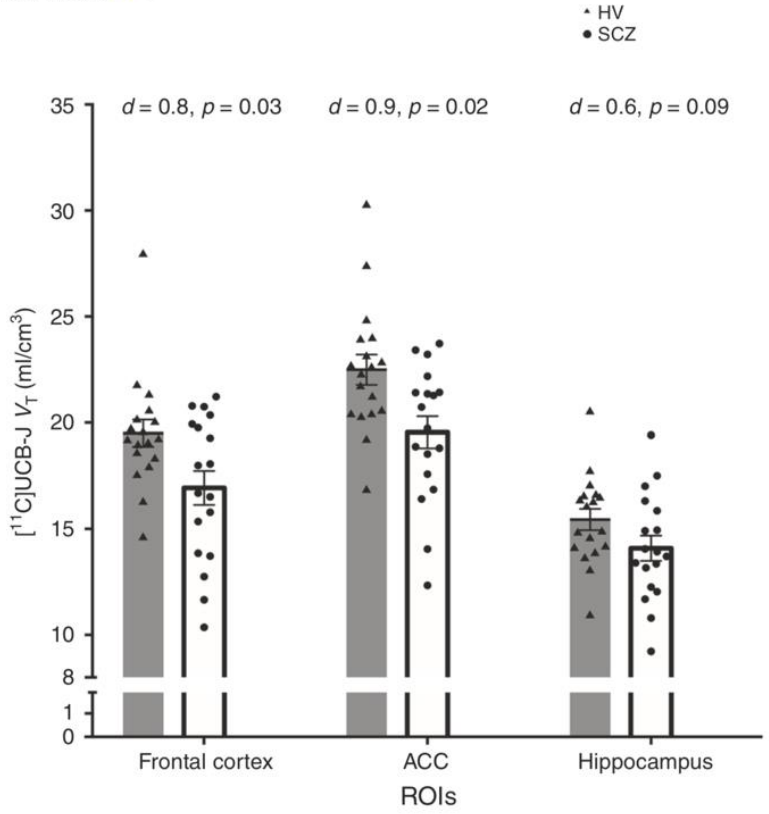
ARTICLE

https://doi.org/10.1038/s41467-019-14122-0 OPEN

Synaptic density marker SV2A is reduced in schizophrenia patients and unaffected by antipsychotics in rats

Ellis Chika Onwordi[1,2,3,4], Els F. Halff[3], Thomas Whitehurst[1,3,4], Ayla Mansur[5], Marie-Caroline Cotel[6], Lisa Wells[7], Hannah Creeney[6], David Bonsall[7], Maria Rogdaki[1,2,3,4], Ekaterina Shatalina[1,2], Tiago Reis Marques[1,3,4], Eugenii A. Rabiner[7,8], Roger N. Gunn[5,7], Sridhar Natesan[1,3], Anthony C. Vernon[6,9] & Oliver D. Howes[1,2,3,4]*





Molecular Psychiatry (2019) 24:549–561
https://doi.org/10.1038/s41380-018-0041-5

REVIEW ARTICLE

Synaptic loss in schizophrenia: a meta-analysis and systematic review of synaptic protein and mRNA measures

Emanuele Felice Osimo[1,2,3,4] · Katherine Beck[1,2,5,6] · Tiago Reis Marques[1,2,5,6] · Oliver D Howes[1,2,5,6]

Received: 1 November 2017 / Revised: 5 January 2018 / Accepted: 31 January 2018 / Published online: 6 March 2018

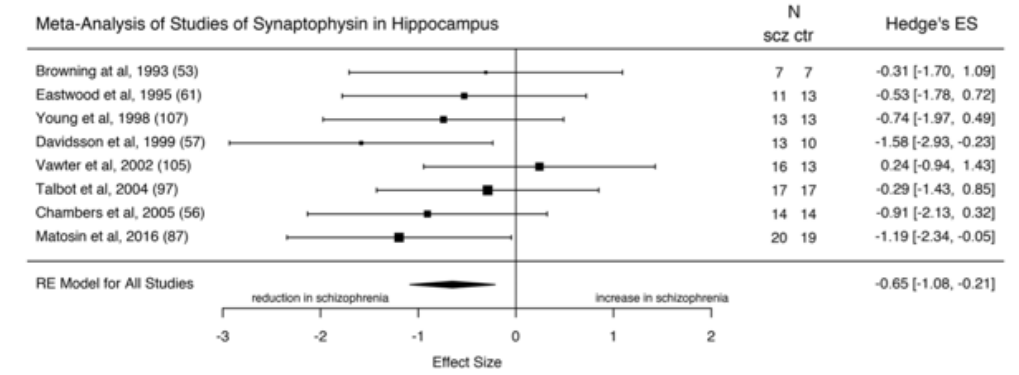
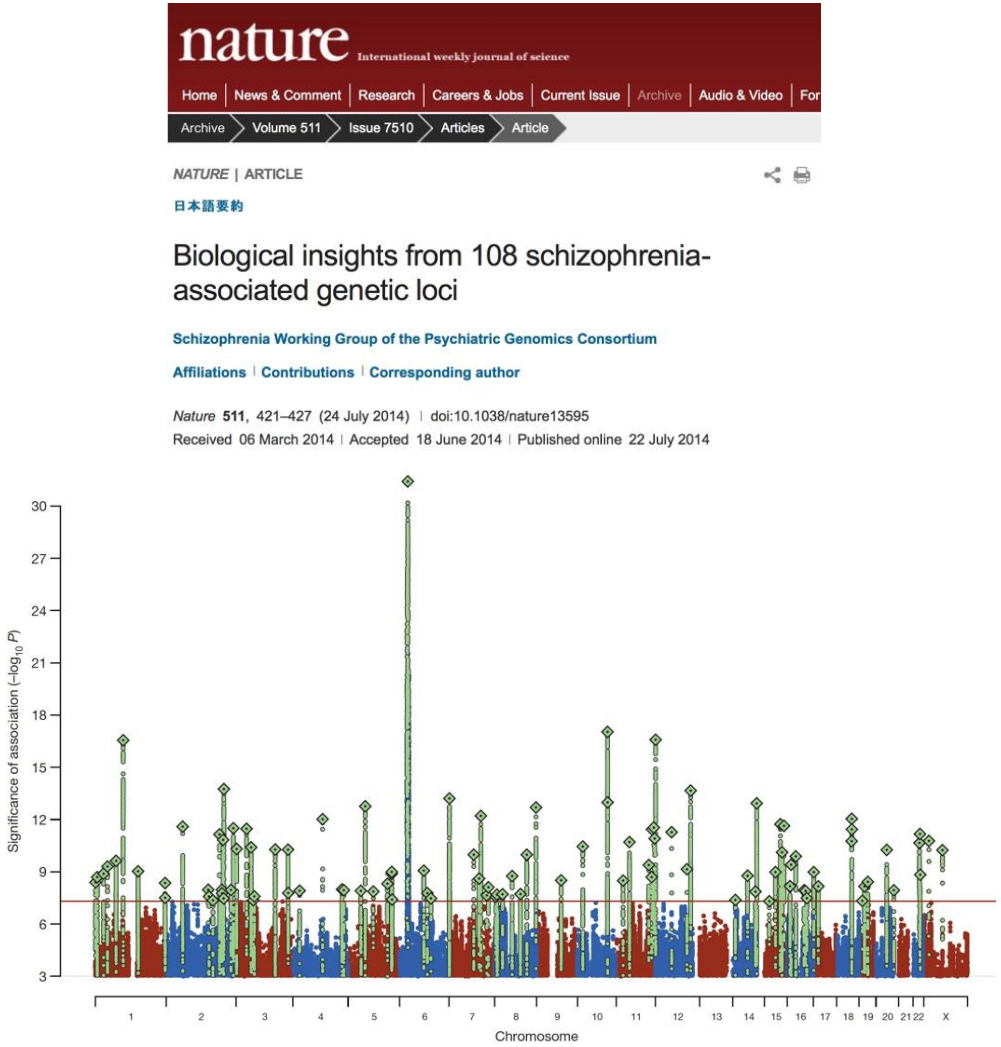
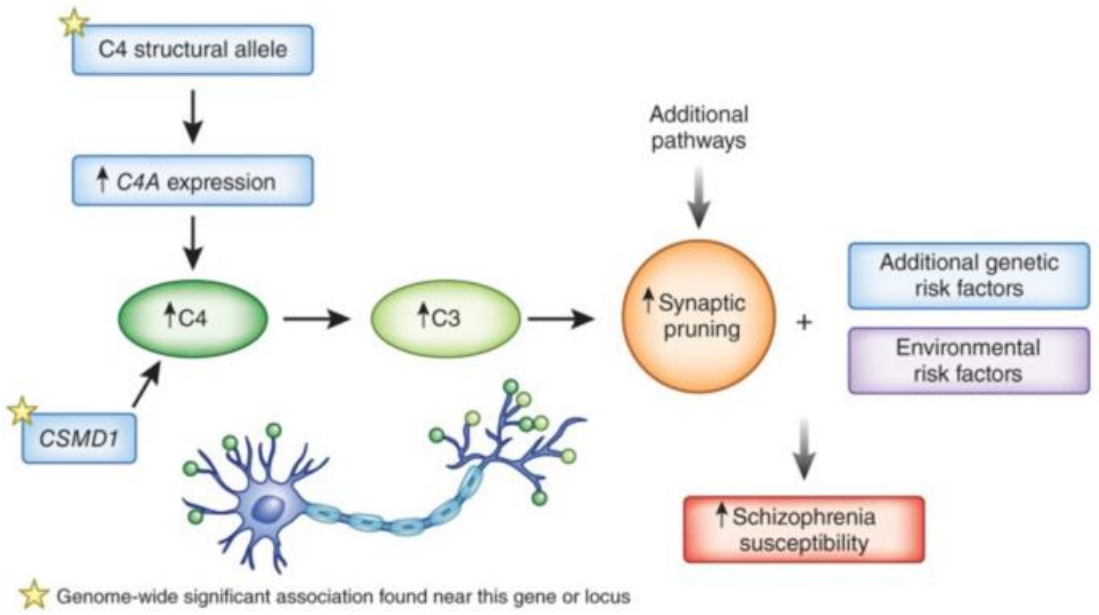


Fig. 2 Forest plot showing the effect sizes for studies of synaptophysin in hippocampus in schizophrenia patients as compared to controls. There was a significant reduction in schizophrenia (effect size = −0.65, $p = 0.0036$)

C4 the first and only gene linked to a specific mechanism underlying the disease





- the most strongly associated GWAS locus, located in the extended Major Histocompatibility Complex (MHC) region on chromosome 6.
- This locus contains multiple copies of two closely related genes that codes for variants of C4: C4A and C4B.

Increase in C4A leads to synaptic loss and behavioral changes in preclinical models

ARTICLES
https://doi.org/10.1038/s41593-020-00763-8
nature neuroscience

Check for updates

Overexpression of schizophrenia susceptibility factor human complement *C4A* promotes excessive synaptic loss and behavioral changes in mice

Melis Yilmaz[1,5], Esra Yalcin[1,5], Jessy Presumey[1,5], Ernest Aw[1], Minghe Ma[1], Christopher W. Whelan[2,3], Beth Stevens[3,4], Steven A. McCarroll[2,3] and Michael C. Carroll[1]✉

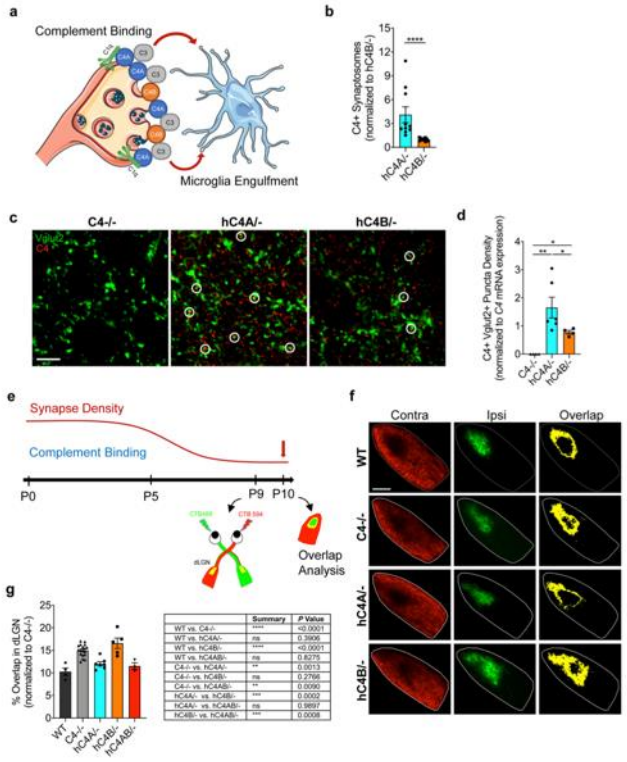


Fig. 2 | Human C4A is more efficient than C4B in synaptic pruning. **a**, At the synapse, complement-dependent pruning is carried out by the classical complement cascade. After C1q tagging, C4 binds the synapse and C3 is then activated for microglia recognition by the receptor CR3. Microglia engulf the complement-bound synapses for refinement. **b**, Synaptosomes from $C4^{-/-}$ mice were isolated and incubated with serum containing the same amount of C4 from h$C4A^{/-}$ ($n = 10$) or h$C4B^{/-}$ ($n = 9$) mice. C4 deposition on synaptosomes was detected and quantified by flow cytometry (serum from three independent experiments; Mann–Whitney test, two-tailed, $^{****}P < 0.0001$). **c**,**d**, C4

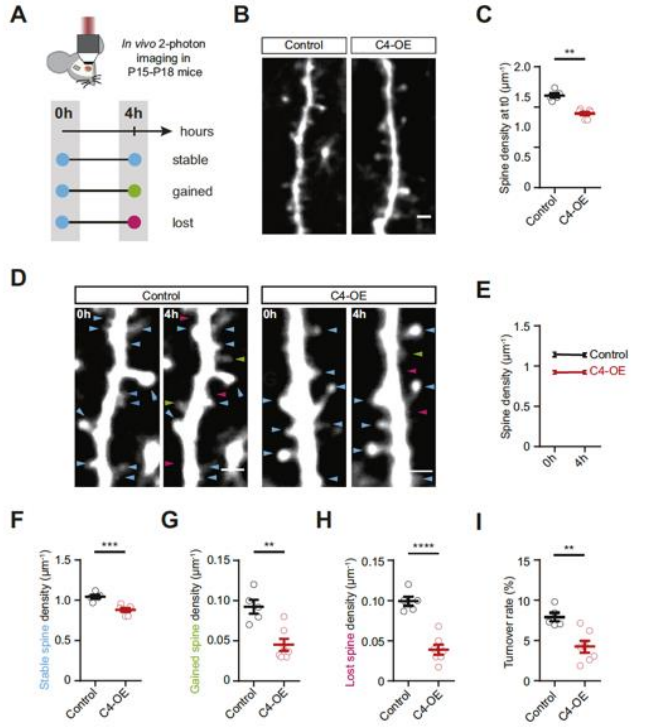
Molecular Psychiatry (2021) 26:3489–3501
https://doi.org/10.1038/s41380-021-01081-6
ARTICLE

Check for updates

Elevated expression of complement C4 in the mouse prefrontal cortex causes schizophrenia-associated phenotypes

Mélanie Druart[1,2,3] · Marika Nosten-Bertrand[1,2,3] · Stefanie Poll[4] · Sophie Crux[4] · Felix Nebeling[4] · Célia Delhaye[1,2,3] · Yaëlle Dubois[1,2,3] · Manuel Mittag[4] · Marion Leboyer[5,6] · Ryad Tamouza[5,6] · Martin Fuhrmann[4] · Corentin Le Magueresse[1,2,3]

Received: 4 July 2020 / Revised: 5 March 2021 / Accepted: 26 March 2021 / Published online: 9 April 2021



Discovery of Small Molecule Inhibitors of C4A Levels

pasithea THERAPEUTICS

Pasithea Therapeutics Corp. and Evotec SE Enter into Drug Development Agreement

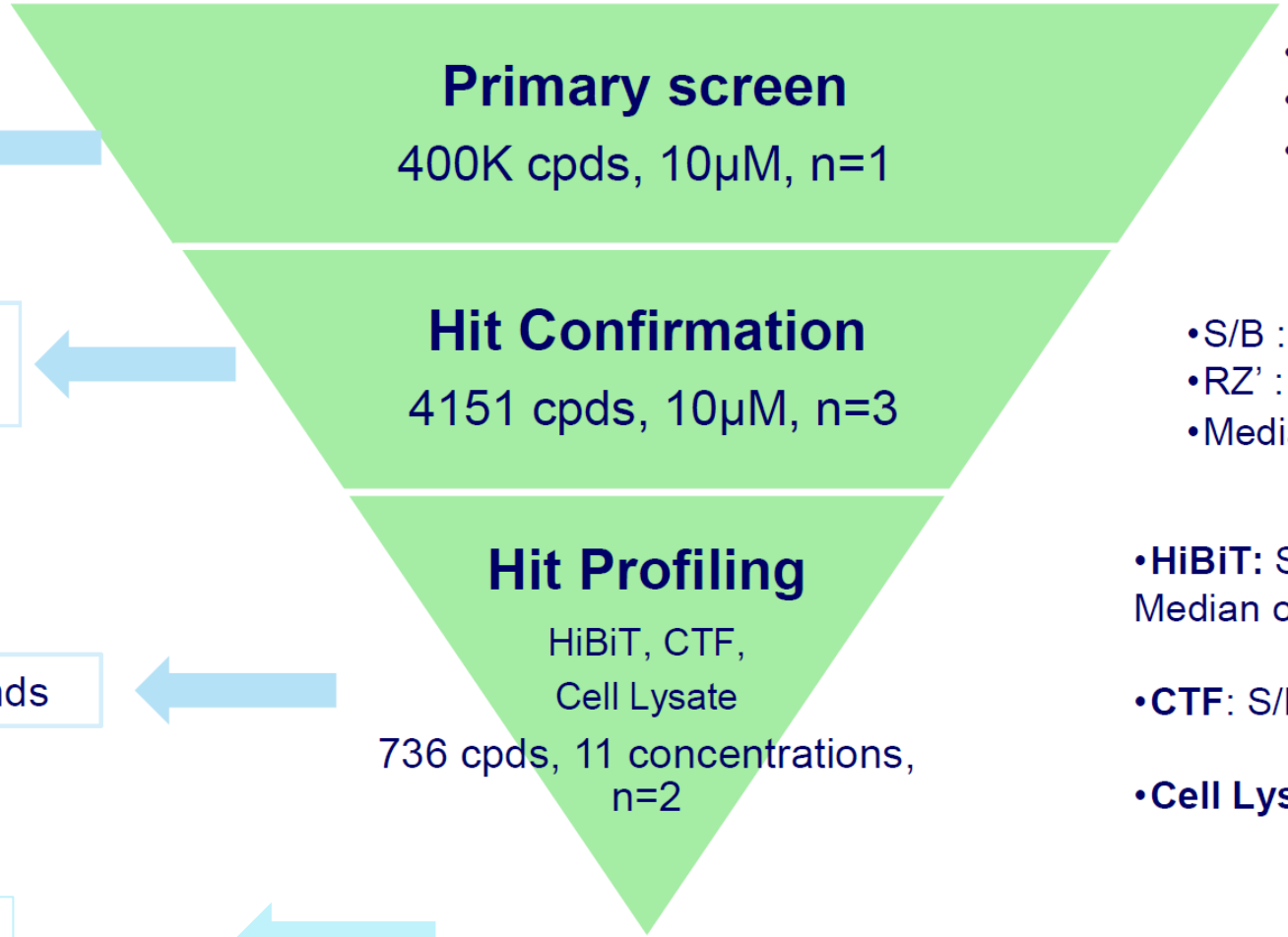
October 11, 2021 6:50am EDT

-- Company contracts leading global drug development company to advance initial drug candidate --

MIAMI BEACH, Fla., Oct. 11, 2021 (GLOBE NEWSWIRE) -- Pasithea Therapeutics Corp. (Nasdaq: KTTA) ("Pasithea" or the "Company"), a biotechnology company focused on the research and discovery of new and effective treatments for psychiatric and neurological disorders, today announced the initiation of a new chemical entity ("NCE") development program and named Evotec as its NCE research partner.

Ref for bp #3

Primary Screen for C4A Regulators



- Hit rate : 1%
- 4174 Hits

- 67% of confirmation
- 2787 confirmed Hits

- 206 specific compounds

- 20 Priority 1 Hits

- S/B: Batch 1: 84 / Batch 2 : 52
- RZ': Batch 1: 0.81 / Batch 2 : 0.76
- Median of Baricitinib 3µM: Batch 1: 35% / Batch 2 : 29%

- S/B : 55
- RZ' : 0.78
- Median of Baricitinib 3µM: 31.2%

- **HiBiT:** S/B: 48.3 RZ': 0.80
  Median of Baricitinib 3µM: 32%
- **CTF**: S/B: 5.9 RZ': 0.88
- **Cell Lysate:** S/B: 51 RZ': 0.78

Summary

- **Novel target agnostic small molecule program targeting C4A regulation**
  - Transcription, translation, post-translation
- **Extensive Genetic and Preclinical and human data supporting the target**
  - C4A increases lead to excessive synaptic elimination
- **Patient research conducted by the CEO of Pasithea, Dr. Tiago Reis Marques**
  - Co-author in several landmark studies for the synaptic hypothesis of schizophrenia
- **20 priority 1 hits with high drug-likeness and brain penetrance scores**
- **Research plan in place to advance to a lead candidate**

www.pasithea.com

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CEO
tiago@pasithea.com