



**Corporate Overview**

September 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.

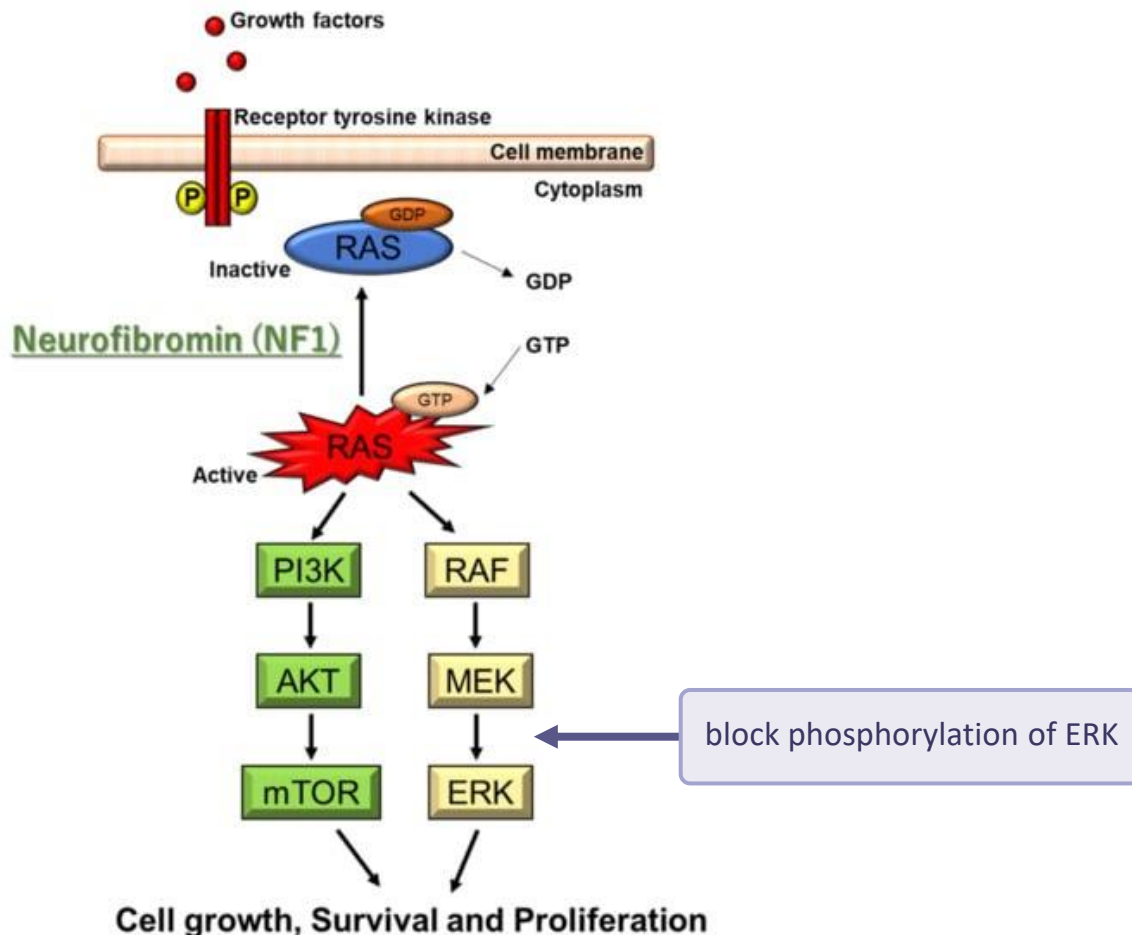
# MEKi Focused Pipeline

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)	$\alpha 5\beta 1$ 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 dysregulation 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 dysregulation.



# 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

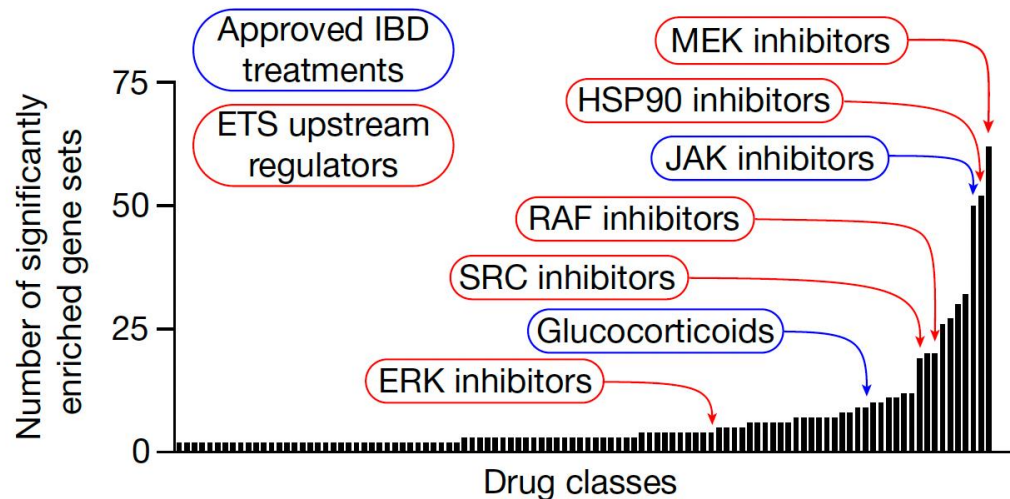
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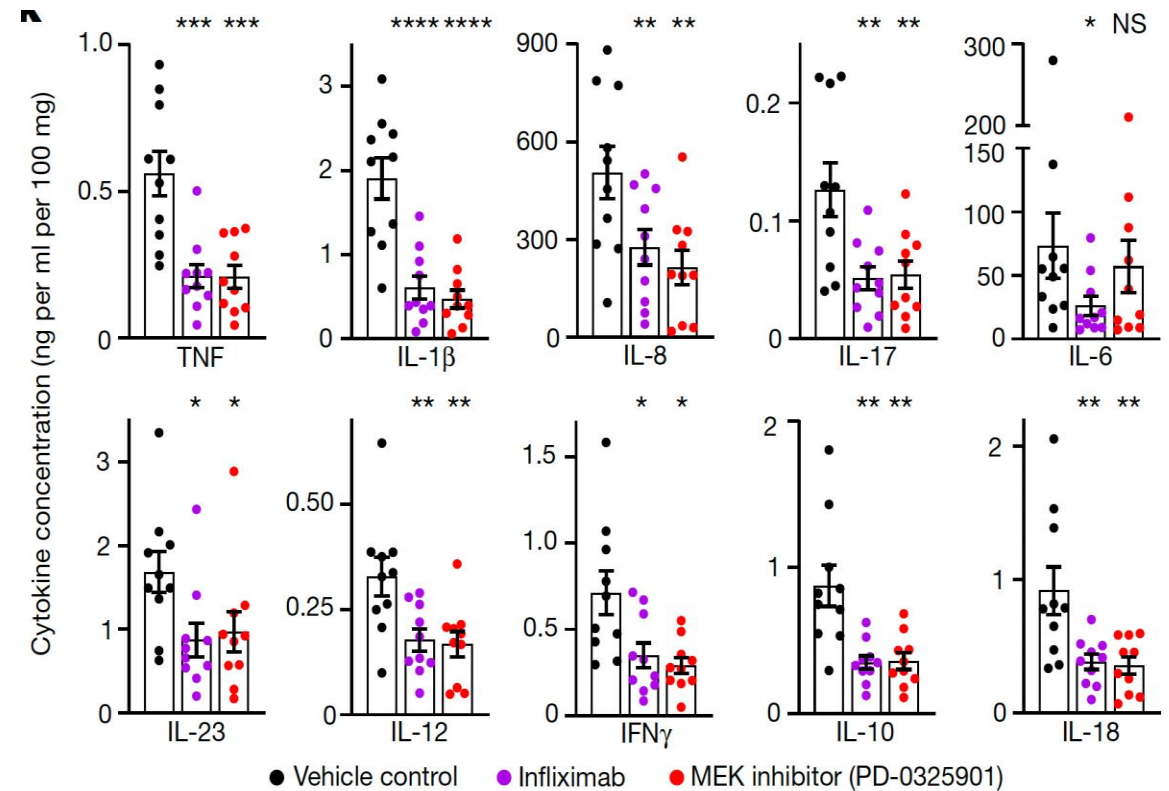
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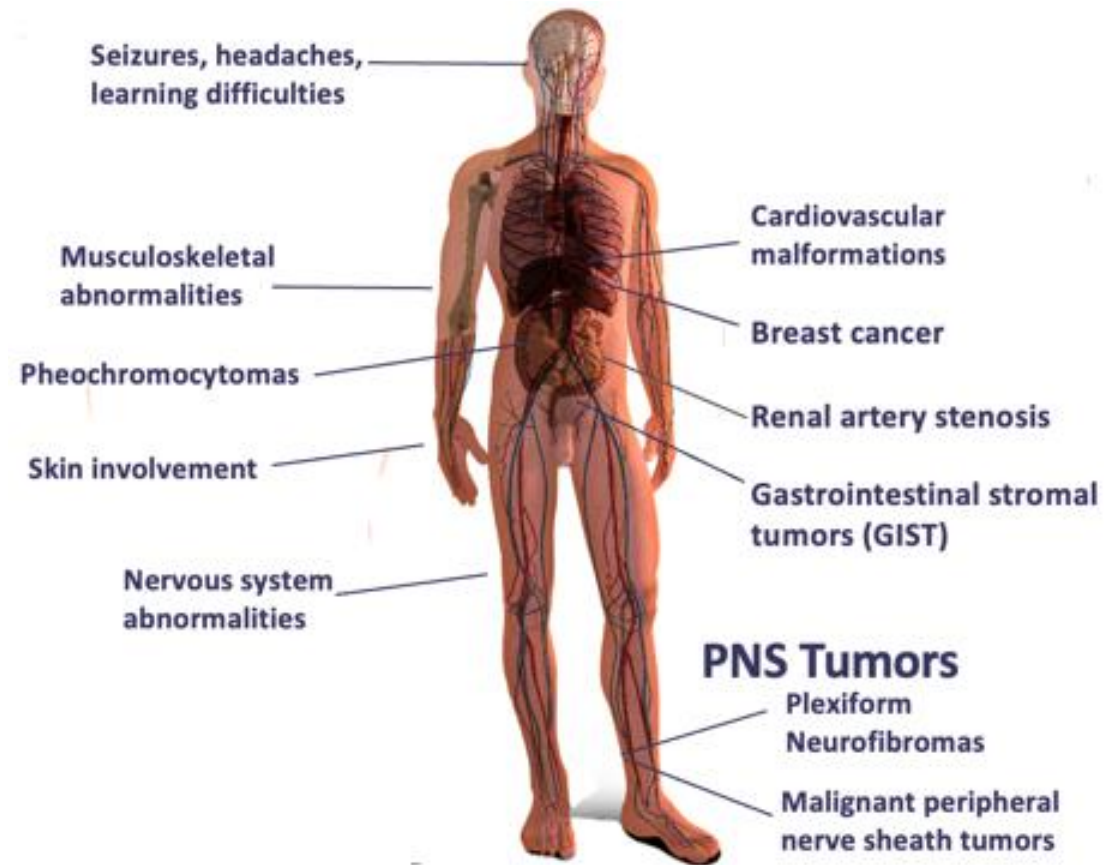
C. T. Stankey<sup>1,2,3,35</sup>, C. Bourges<sup>1,35</sup>, L. M. Haag<sup>4,35</sup>, T. Turner-Stokes<sup>1,2</sup>, A. P. Piedade<sup>1</sup>, C. Palmer-Jones<sup>5,6</sup>, I. Papa<sup>1</sup>, M. Silva dos Santos<sup>7</sup>, Q. Zhang<sup>8</sup>, A. J. Cameron<sup>9</sup>, A. Legrini<sup>9</sup>, T. Zhang<sup>9</sup>, C. S. Wood<sup>9</sup>, F. N. New<sup>10</sup>, L. O. Randzavola<sup>2</sup>, L. Speidel<sup>11,12</sup>, A. C. Brown<sup>13</sup>, A. Hall<sup>14,15</sup>, F. Saffioti<sup>14</sup>, E. C. Parkes<sup>16</sup>, W. Edwards<sup>16</sup>, H. Direskeneli<sup>17</sup>, P. C. Grayson<sup>18</sup>, L. Jiang<sup>19</sup>, P. A. Merkel<sup>20,21</sup>, G. Saruhan-Direskeneli<sup>22</sup>, A. H. Sawalha<sup>23,24,25,26</sup>, E. Tombetti<sup>27,28</sup>, A. Quaglia<sup>15,29</sup>, D. Thorburn<sup>3,14</sup>, J. C. Knight<sup>13,30,31</sup>, A. P. Rochford<sup>5,6</sup>, C. D. Murray<sup>5,6</sup>, P. Divakar<sup>10</sup>, M. Green<sup>32</sup>, E. Nye<sup>32</sup>, J. I. MacRae<sup>7</sup>, N. B. Jamieson<sup>9</sup>, P. Skoglund<sup>11</sup>, M. Z. Cader<sup>16,33</sup>, C. Wallace<sup>16,34</sup>, D. C. Thomas<sup>16,33</sup> & J. C. Lee<sup>15,6,35</sup>



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



# NF1: Large unmet medical need



NF1 is an autosomal dominant genetic disorder.

Affects approximately one in 3,000 newborns worldwide with ~100,000 patients living in U.S. with NF1<sup>1</sup>.

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).

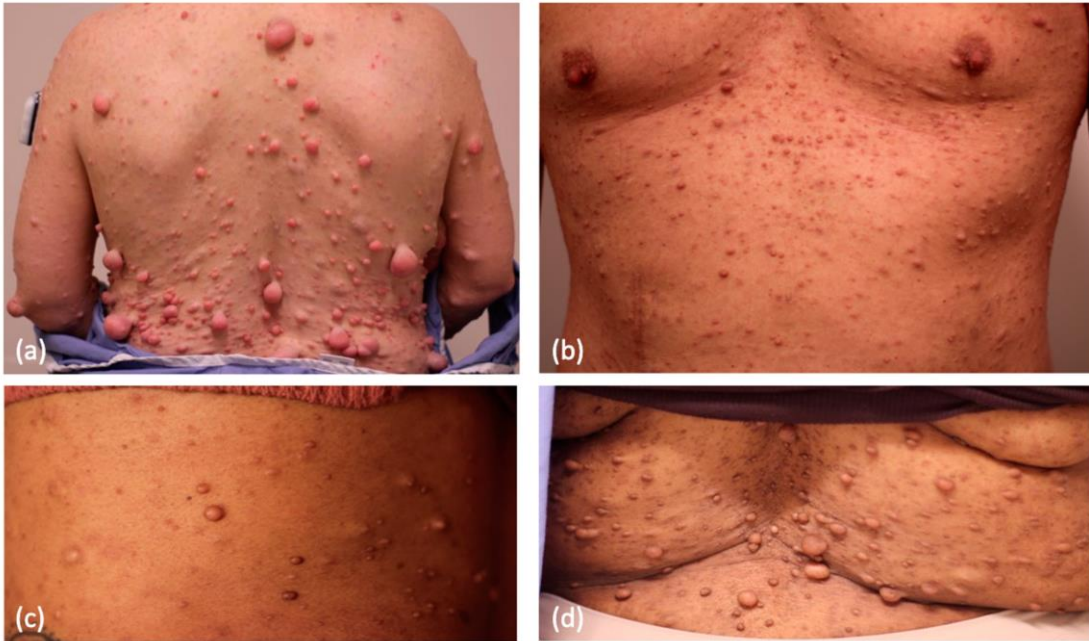
CN usually presents as skin bumps and can cause disfigurement and quality of life challenges. There are currently no approved treatments for CN.



# 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



# 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.<sup>1</sup>
- ORR of 44% - independent centralized review (ICR)REiNS criteria.<sup>2</sup>
- Average depth of response is only 27.9% (median best percentage change in PN volume from baseline).<sup>2</sup>
- Potentially linked to limited pERK inhibition and plateau effect seen in our preclinical cellular models.

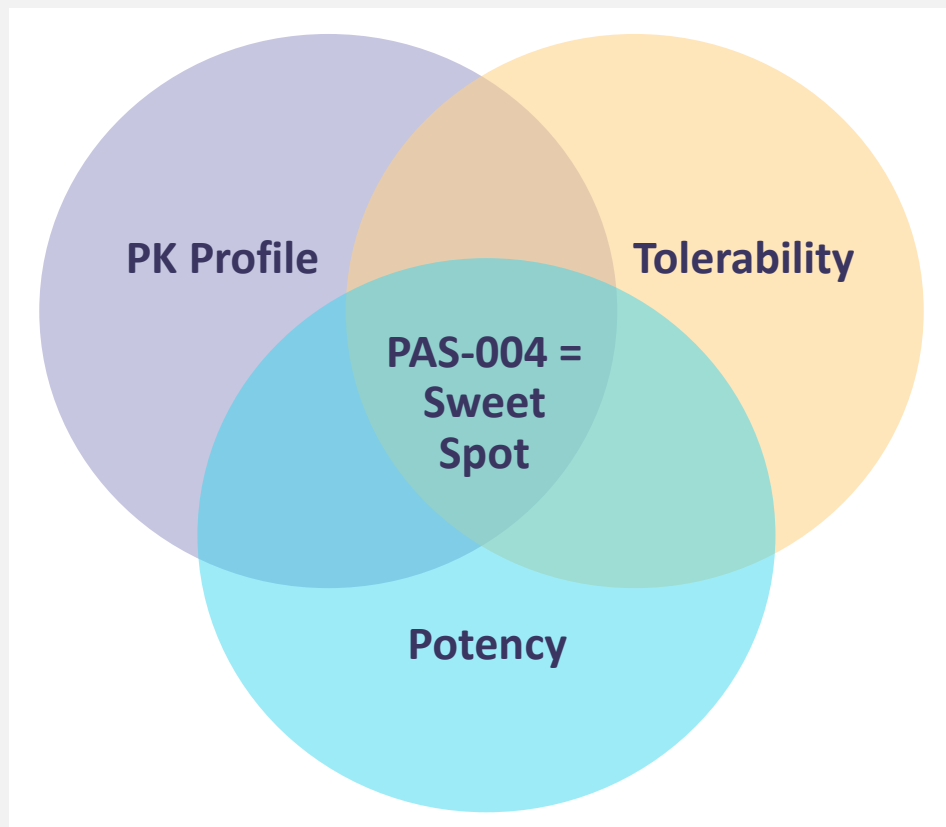
- **Long time to generate response**

- Time to response is long (median time to onset of response is 7.2 months).<sup>2</sup>

- **Poor tolerability and compliance**

- Requires BID (2x/day) dosing.<sup>3</sup>
- AE profile characterized by GI symptoms and skin tox.<sup>3</sup>

# 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).

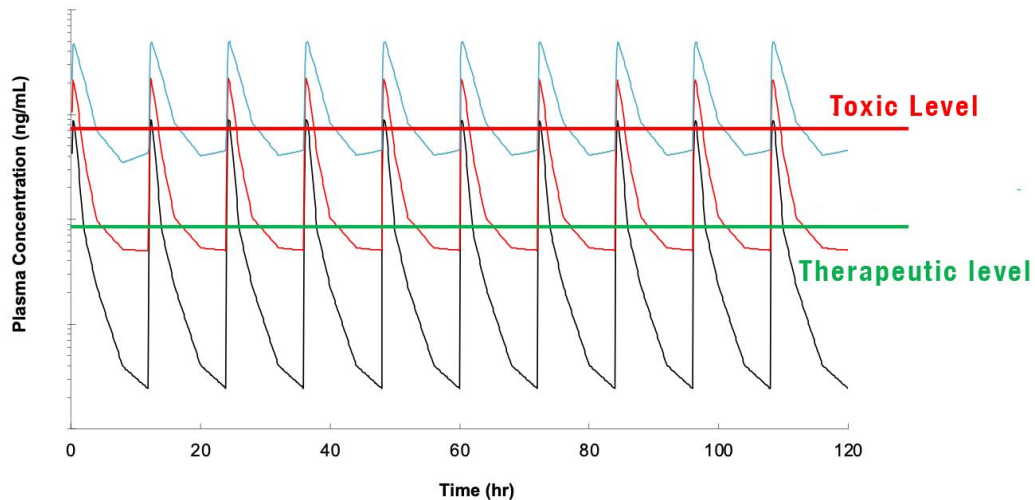
## Better combinability

- Superior properties may support better combination.

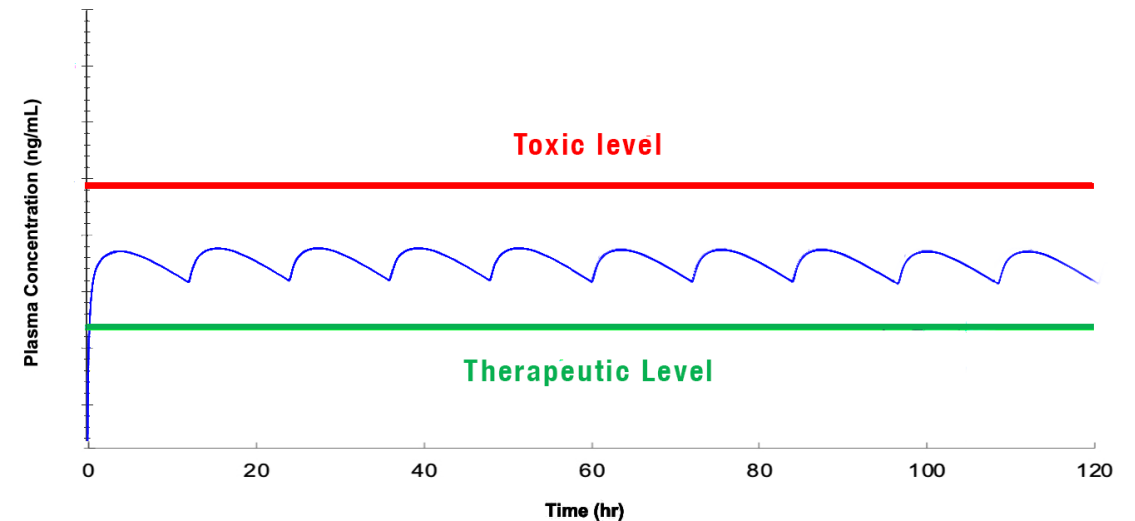
# Constant suppression of the MAPK pathway

- 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
<b>Selumetinib (Koselugo)</b>	AstraZeneca	Monotherapy (pediatric)	Neurofibroma (NF-1)	<ul style="list-style-type: none"> <li>• Short Half-Life</li> <li>• BID dosing</li> </ul>
<b>Trametinib (Mekinist)</b>	Novartis	+ B-Raf inhibitors	Melanoma, NSCLC, Thyroid cancer, BRAF V600E	<ul style="list-style-type: none"> <li>• Long Half-life</li> <li>• High Potency</li> </ul>
<b>Cobimetinib (Cotellic)</b>	Genentech	+ B-Raf inhibitors	Melanoma	<ul style="list-style-type: none"> <li>• Long Half-Life</li> </ul>
<b>Binimetinib (Mektovi)</b>	Pfizer	+ B-Raf inhibitors	Melanoma	<ul style="list-style-type: none"> <li>• Short Half-life</li> <li>• BID dosing</li> </ul>



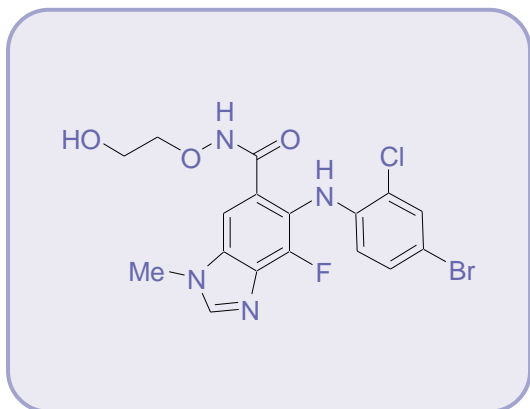
# MEK inhibitors in clinical development

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)	Immunering (IMRX)
<b>MEK Inhibitor</b>	PAS-004	Pimasertib	REC-4881	Mirdametnib	FCN-159	Avutometinib (MEKi + RAF clamp)	IMM-1-104 (Universal RAS)
<b>NF 1 Intention</b>	Yes	No	No	Yes	Yes	No	No
<b>Development Phase</b>	Phase 1	Phase 2	Phase 2	Phase 2b	Phase 2	Phase 2	Phase 1
<b>Clinical Trials Indications</b>	- 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
<b>~Market Cap (06/27/24)</b>	\$5 million	\$1.2 billion	\$1.7 billion	\$2.7 billion	N/A	\$72 million	\$42 million

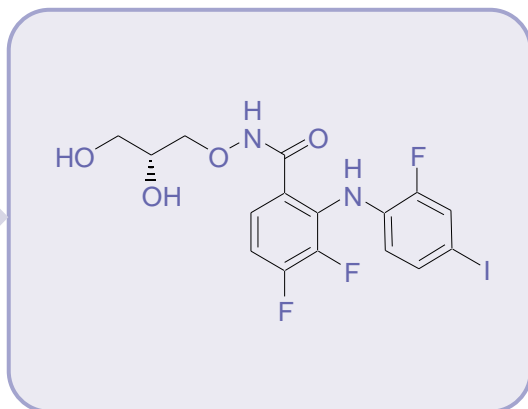
# PAS-004 was designed to address the liabilities of previous MEK inhibitors

Selumetinib



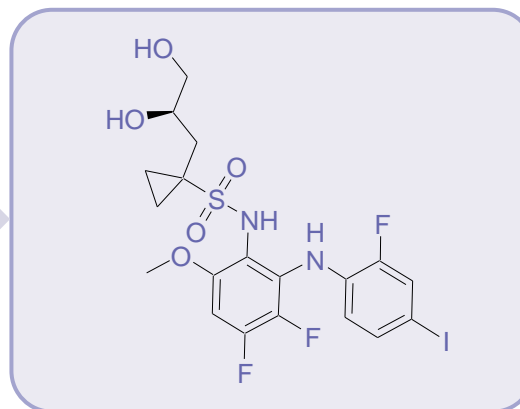
First Generation

Mirdametinib



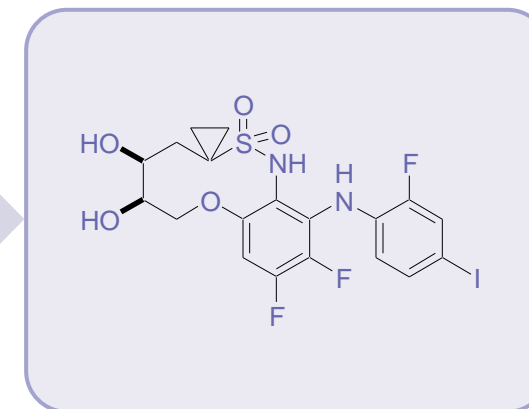
Introduction of diol in the side chain. Improved solubility, potency

Refametinib



Hydroxamide to sulfonamide. improved half-life and potency

PAS-004



Next Generation Macrocyclic

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) <sup>1</sup>	Cobimetinib <sup>2</sup>	PAS-004 (28-day GLP)
<b>Studies performed on Rats</b>			
pERK (EC <sub>50</sub> )	2 nM	2 nM	2 nM
(M) NOAEL Dose, 28-day GLP	(HNSTD) 0.125 mg/m <sup>2</sup> /day (0.02 mg/kg)	3 mg/kg (HNSTD)	5 mg/kg
28 <sup>th</sup> day, Cmax at NOAEL Dose	2.89 nM	54 nM	2404 nM
Cmax/ pERK IC <sub>50</sub>	<2	27	1202
<b>Studies performed on Dogs</b>			
NOAEL Dose	0.5 mg/m <sup>2</sup> /day HNSTD (0.025 mg/kg)	13-week study, <<1 mg/kg	0.5 mg/kg
28 <sup>th</sup> day, Cmax at NOAEL Dose	5.41 nM	67 nM (day 30), 0.3 mg/kg	820 nM
Cmax/ pERK IC <sub>50</sub>	<5	33.5	>>200
<b>Additional Information</b>			
hERG Inhibition (IC <sub>50</sub> )	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

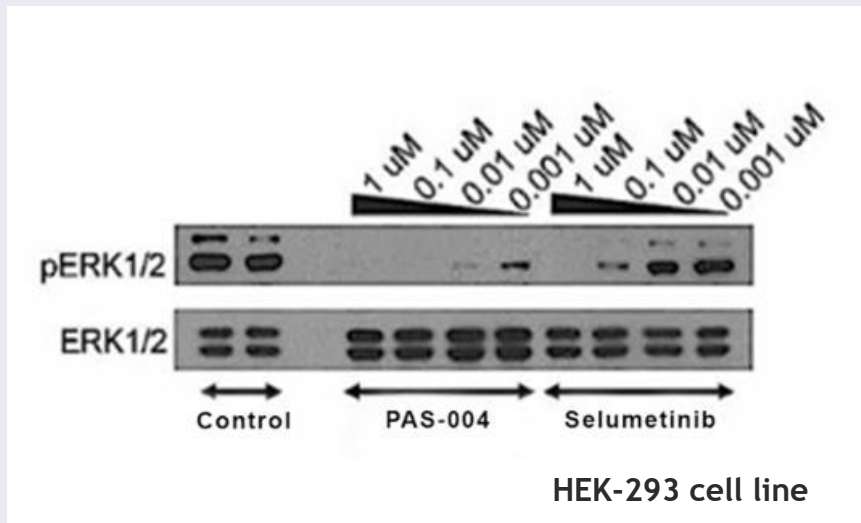
1. Center for drug evaluation and research, Pharmacology review, Application Number 204114Orig1s000

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

# Comparative Preclinical Efficacy of PAS-004

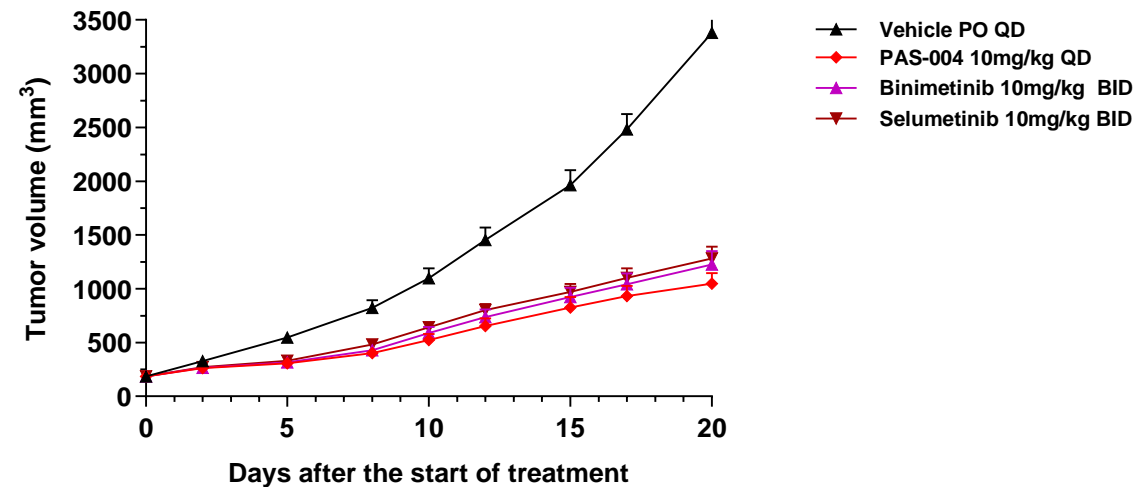
- Better potency (>10x) than Selumetinib in inhibiting p-ERK in vitro
- Superior efficacy when dosed 1x/day than approved MEKi dosed 2x/day

## PAS-004 vs. Selumetinib *In Vitro* Potency



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

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

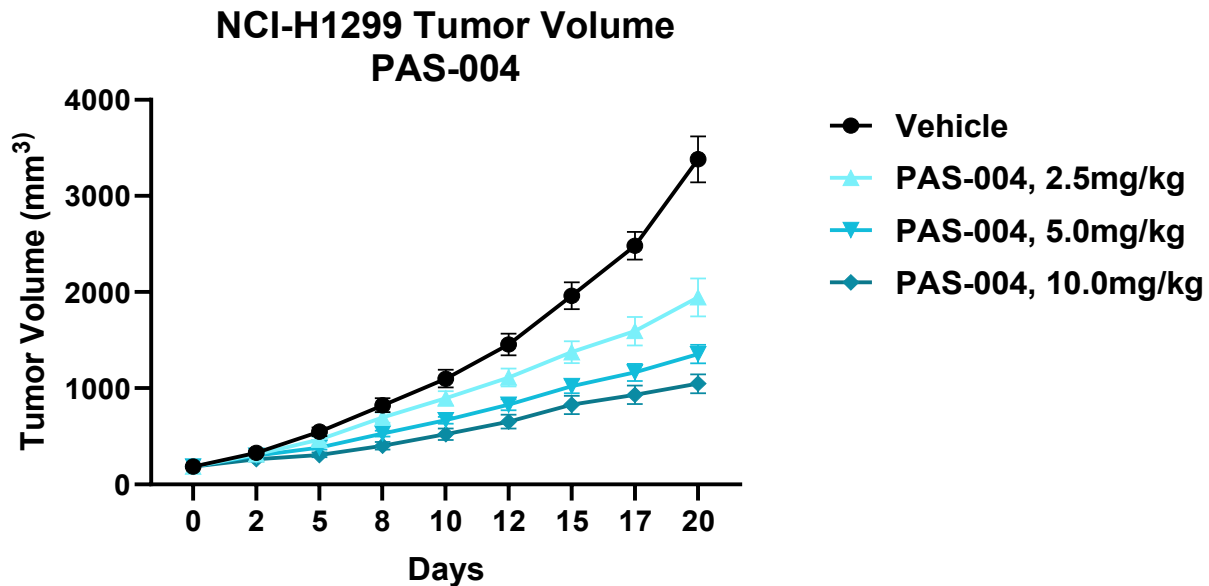


Study conducted at Wuxi AppTec

# Dose Dependent inhibition of pERK which correlate with clinical efficacy

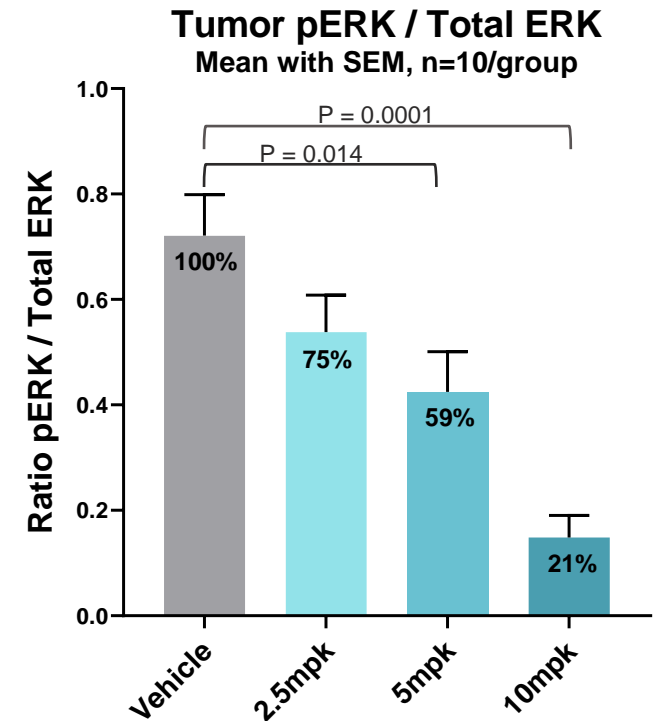
- Analysis of clinical data from approved MEKi indicates partial p-ERK is needed in NF1

## In Vivo Dose dependent efficacy (NCI-H1299 xenograft)



Study conducted at Wuxi AppTec

## In Vivo Dose dependent pERK reduction (NCI-H1299 xenograft)

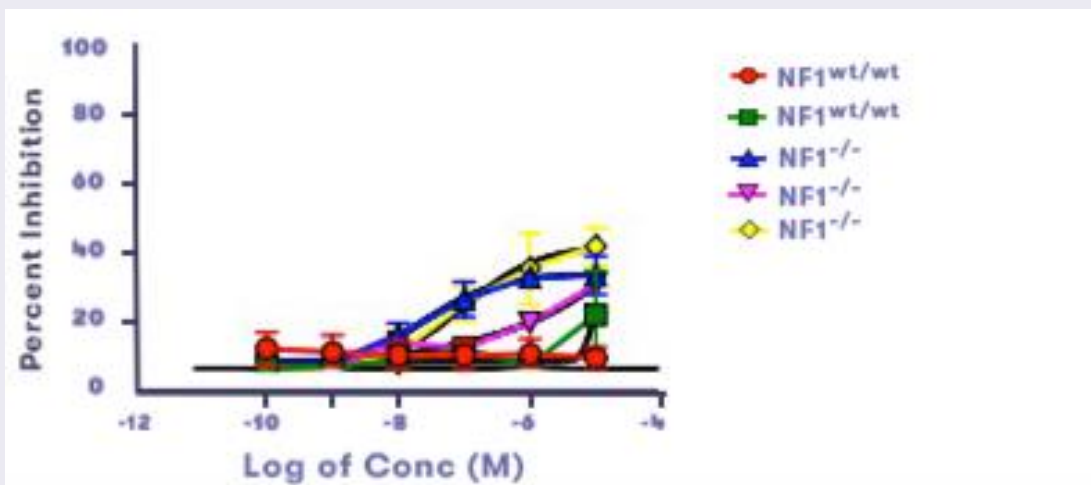




# PAS-004 is More Potent than Selumetinib in *In Vitro* NF1 Model

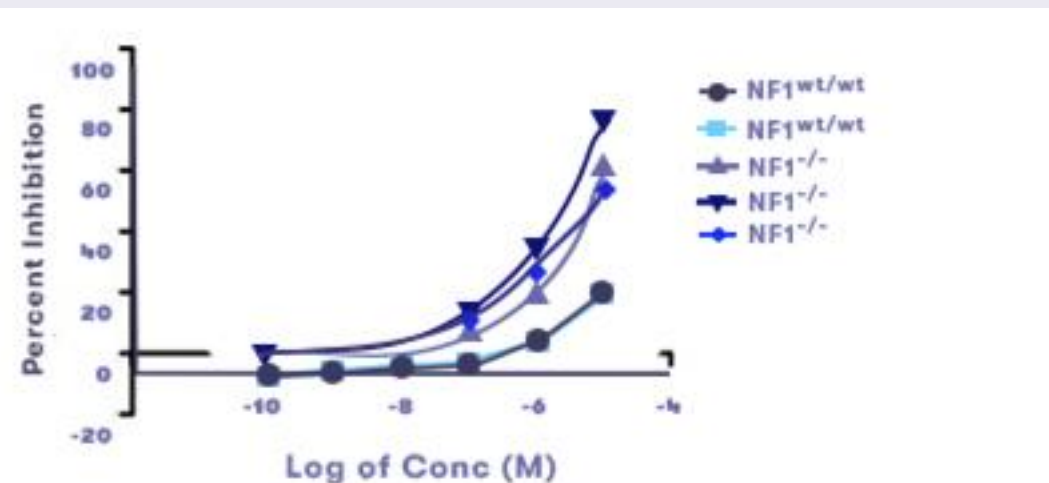
- PAS-004 is more potent in all 3 NF1 mutated cell lines than Selumetinib
- No Plateau Effect was observed for PAS-004 = potential for deeper activity in patient
- Limited activity against the control NF1 WT cells=support good safety profile

## Selumetinib



Study conducted at Ray Mattingly lab, Indiana University

## PAS-004

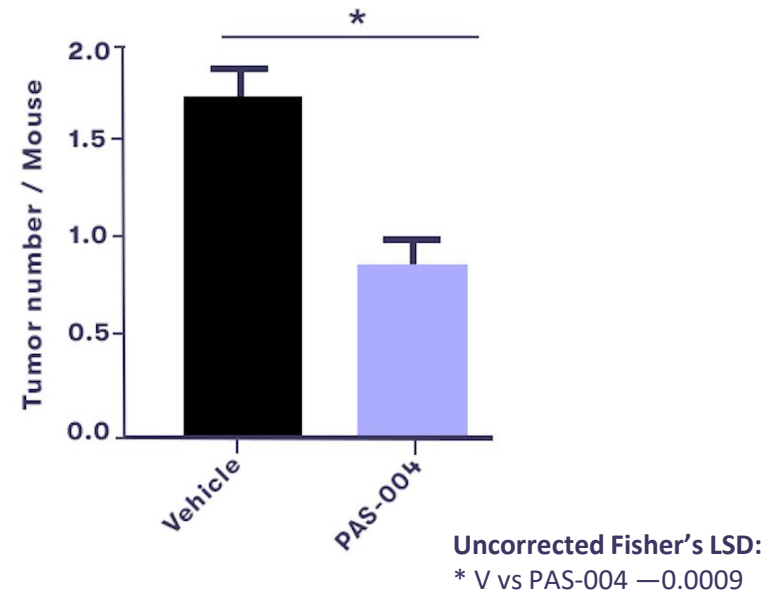
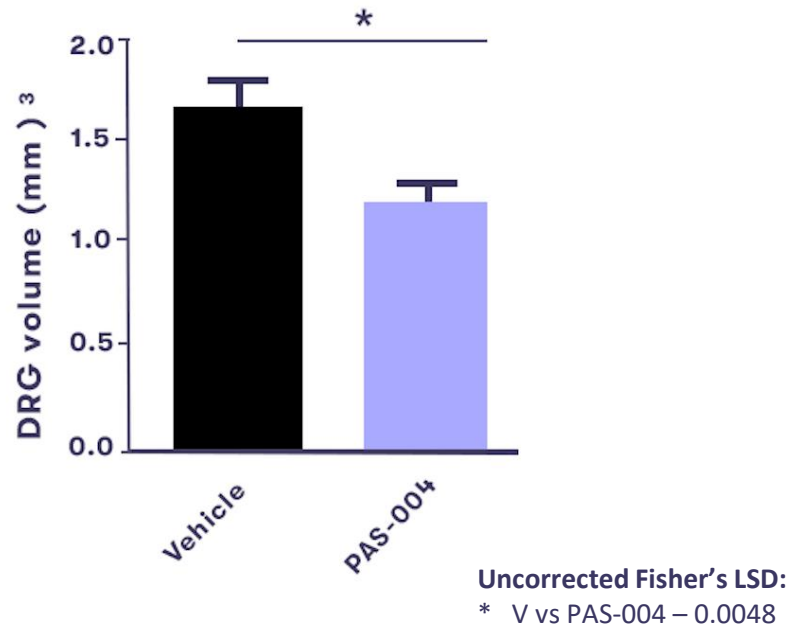


Study conducted at Ray Mattingly lab, Indiana University

# 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



# 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



## 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 **8 mg**  
(n=3+3)

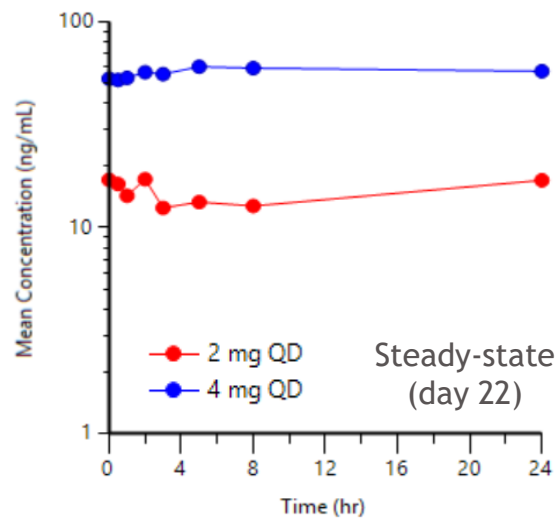
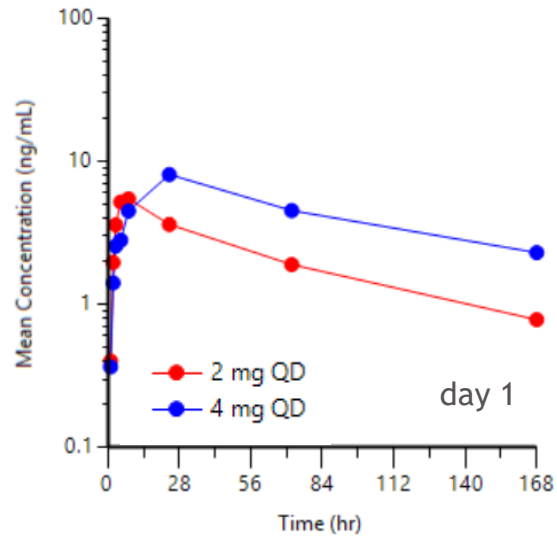
Cohort 4: PAS-004 **15 mg**  
(n=3+3)

Cohort 5: PAS-004 **22 mg**  
(n=3+3)

Cohort 6: PAS-004 **30 mg**  
(n=3+3)

Cohort 7: PAS-004 **37 mg**  
(n=3+3)

# Interim PK Results from PAS-004 2mg and 4mg cohorts



Dose Cohort	C <sub>max</sub> (ng/mL)	C <sub>min</sub> (ng/mL)	AUC <sub>0-24</sub> (ng*h/mL)
Day 1 Steady state (day 22)	Geometric Mean (Geo CV%)	Geometric Mean (Geo CV%)	Geometric Mean (Geo CV%)
2 mg Day 1	4.91 (101.3)	N/A	86.3 (89.2)
2 mg Day 22	16.2 (89.7)	10.2 (119.4)	354 (95.2)
4 mg Day 1	6.36 (135.6)	N/A	100 (97.1)
4 mg Day 22	61.3 (10.3)	51.5 (20.8)	1,390 (12.8)

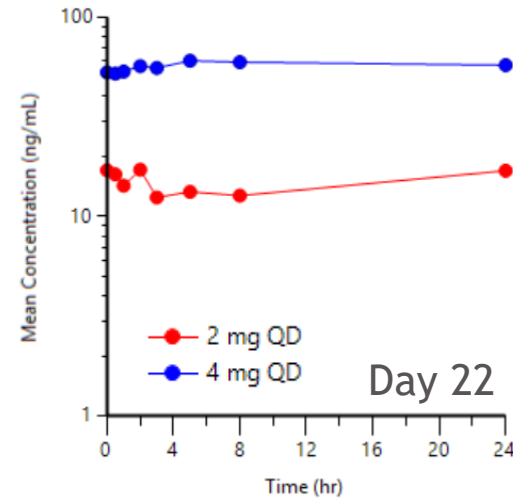
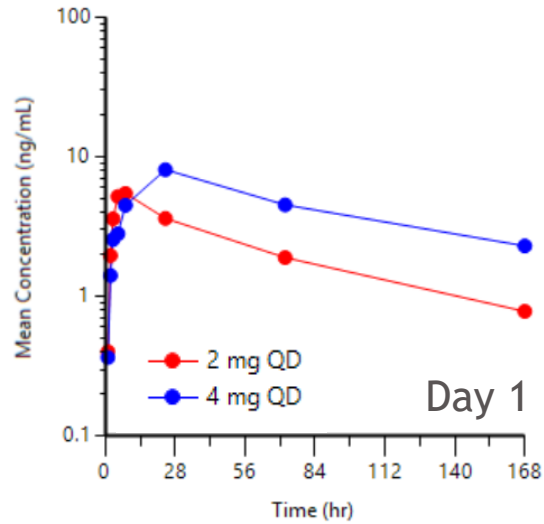
Following multiple QD dosing, accumulation is consistent with estimated  $t_{1/2}$  of 70h and suggests linear PK

Multiple QD dosing results in **little fluctuations in concentrations** (C<sub>max</sub>/C<sub>min</sub> ratio of 1.2)

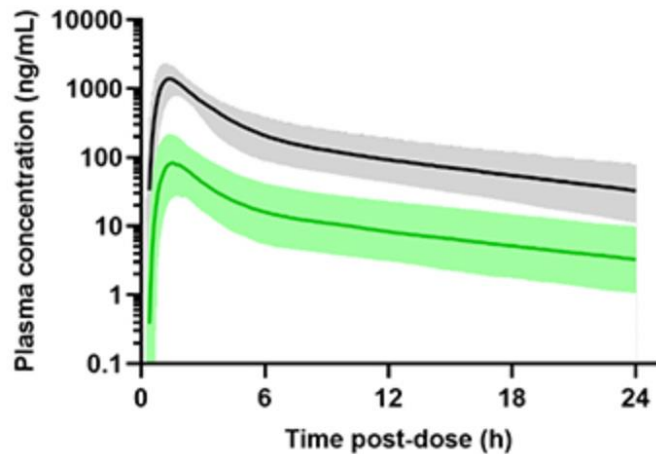
C<sub>max</sub> and C<sub>min</sub> are similar, indicating the **opportunity to achieve constant target inhibition**



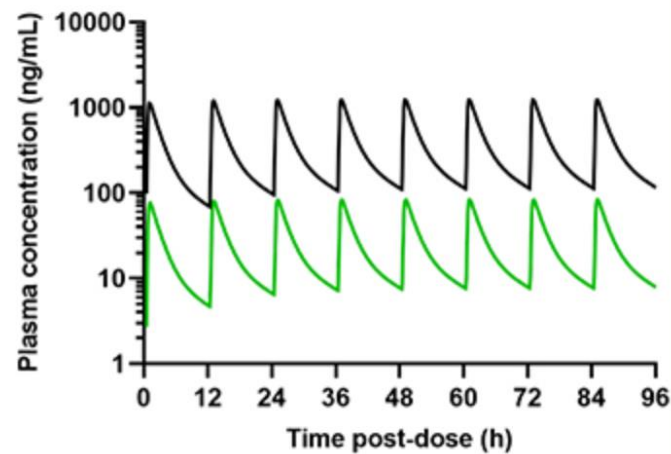
# Steady state PK profile differences (PAS-004 vs Selumetinib)



A) Population profiles - Adults - 75 mg SD



B) Mean steady state profiles - Adults - 75 mg bid

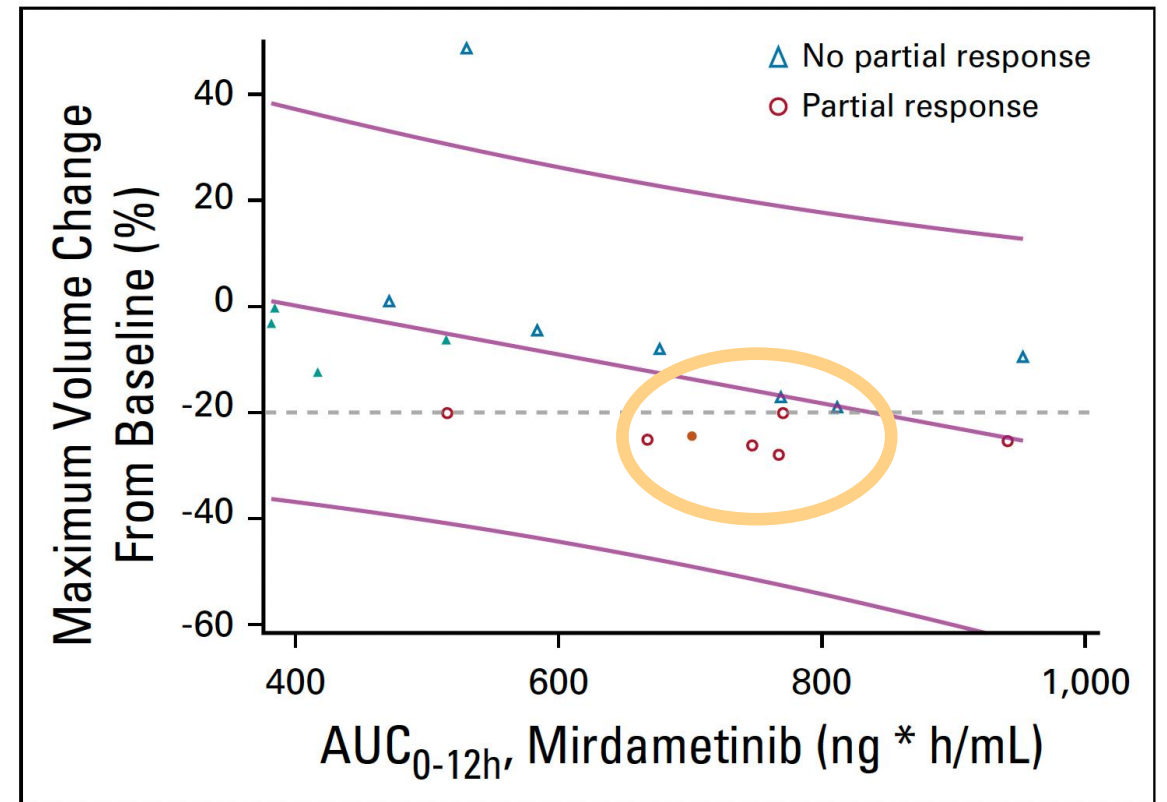


— Selumetinib  
— N-Desmethyl-Selumetinib (active metabolite)

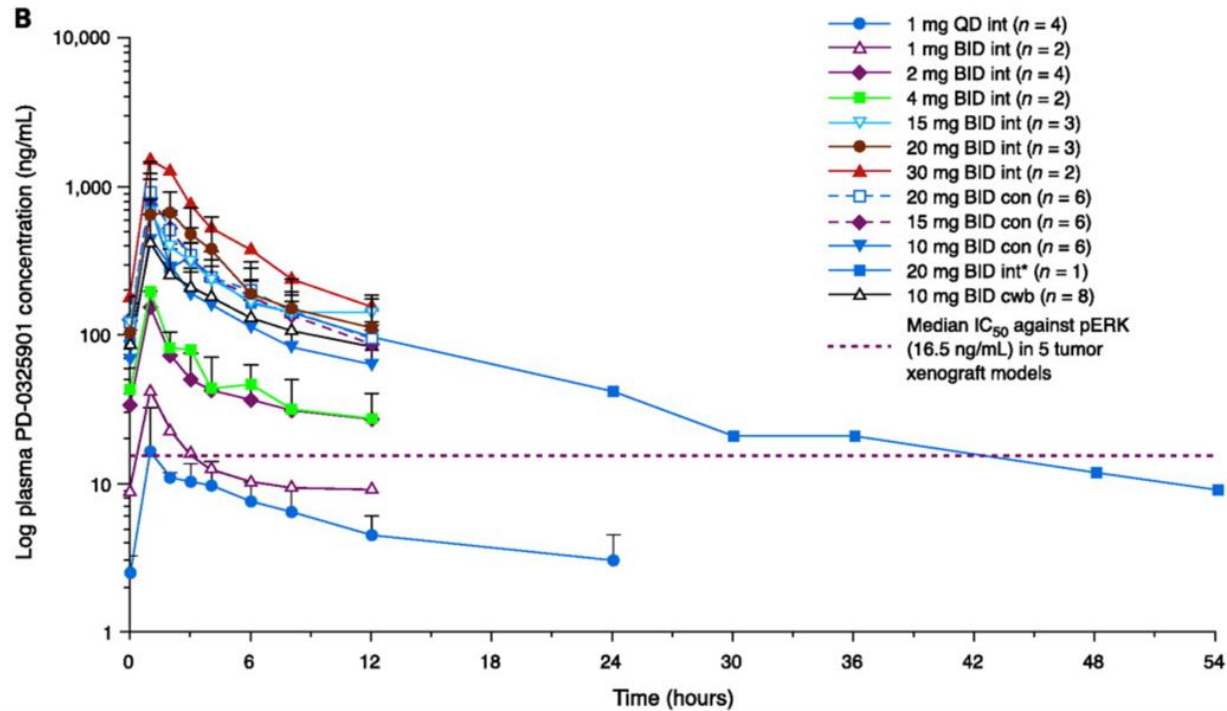
# AUC exposures and treatment response

Positive relationship between treatment response and mirdametininb exposure (AUC<sub>0-12h</sub>) (p = .052)  
Most responses were seen in patients whose AUC was ≥ 600  
Dose exposure of 4mg PAS004 at steady state (AUC<sub>0-24h</sub>) over 1300

Dose Cohort	C <sub>max</sub> (ng/mL)	C <sub>min</sub> (ng/mL)	AUC <sub>0-24</sub> (ng*h/mL)
Day 1			
Steady state (day 22)	Geometric Mean (Geo CV%)	Geometric Mean (Geo CV%)	Geometric Mean (Geo CV%)
2 mg Day 1	4.91 (101.3)	N/A	86.3 (89.2)
2 mg Day 22	16.2 (89.7)	10.2 (119.4)	354 (95.2)
4 mg Day 1	6.36 (135.6)	N/A	100 (97.1)
4 mg Day 22	61.3 (10.3)	51.5 (20.8)	1,390 (12.8)



# Mirdametininib PK and AE profile from Phase 1 trial in advanced cancer



**Table 3.**

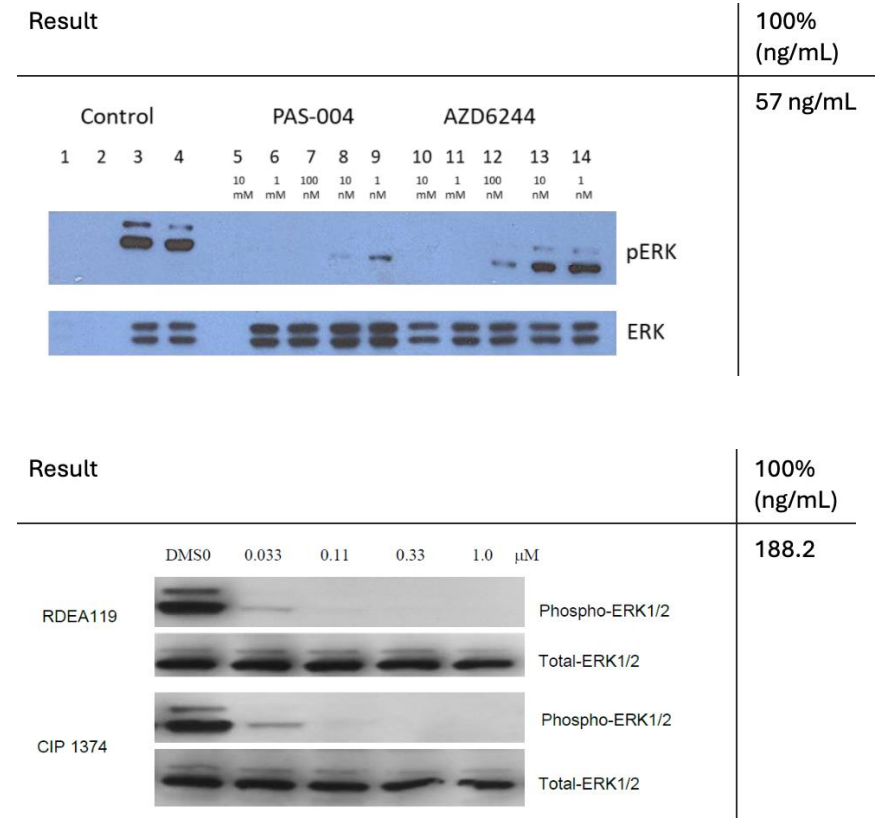
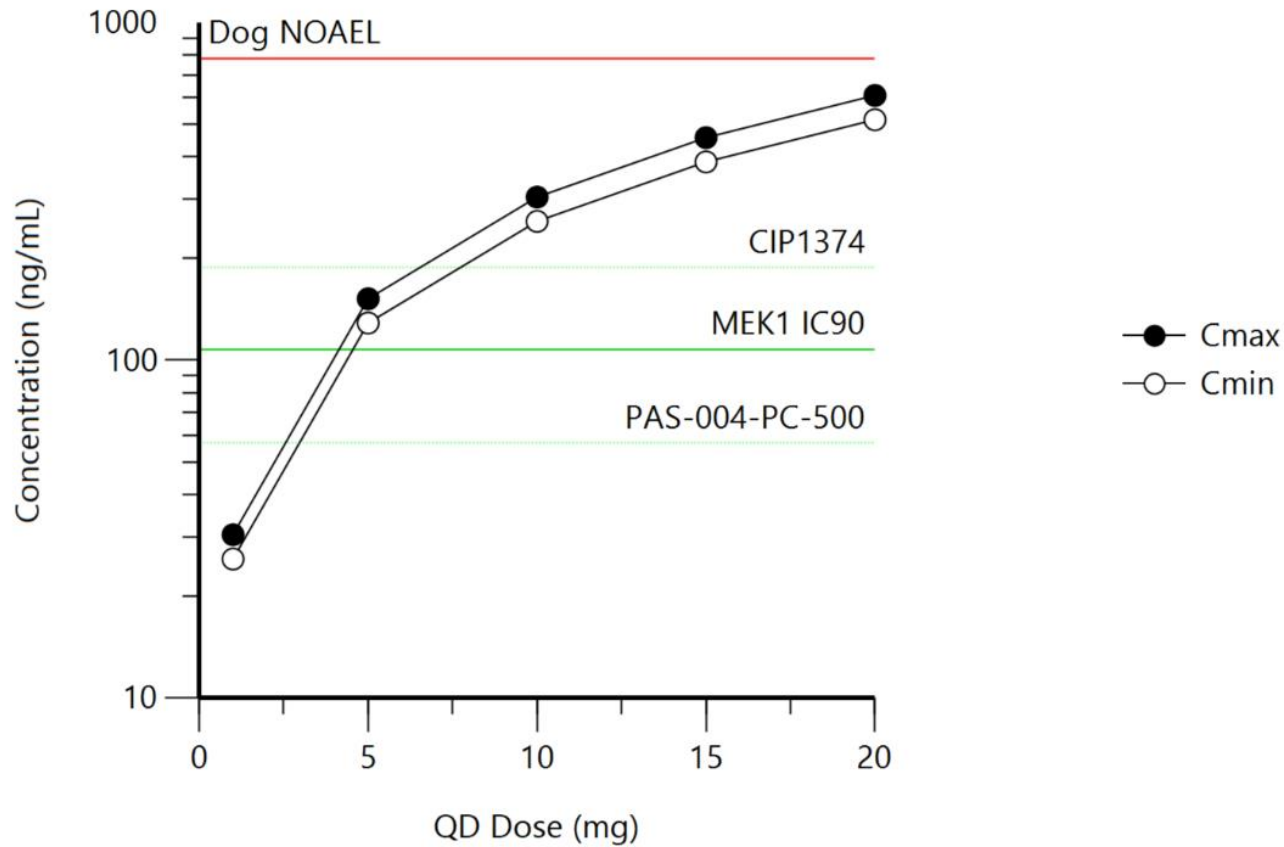
Most common treatment-related AEs (maximum grade, all cycles)

AE	Total no. patients with events	PD-0325901 schedules and dose levels (no. patients)					
		Intermittent					
		1 mg QD (n = 4)		1 mg BID (n = 4)		2 mg BID (n = 4)	
		All	G≥3	All	G≥3	All	G≥3
Rash	52	—	—	2	—	1	—
Diarrhea	36	—	—	—	—	2	—
Fatigue	40	2	—	1	—	3	—
Nausea	25	1	—	1	—	3	—
Peripheral edema	17	—	—	—	—	—	—
Balance and gait disorders*	15	—	—	—	—	—	—
Pruritus	15	—	—	1	—	3	—
Vomiting	14	—	—	—	—	1	—
Visual disturbance	9	—	—	—	—	1	—
Blurred vision	7	—	—	—	—	—	—
Periorbital edema	6	—	—	—	—	—	—

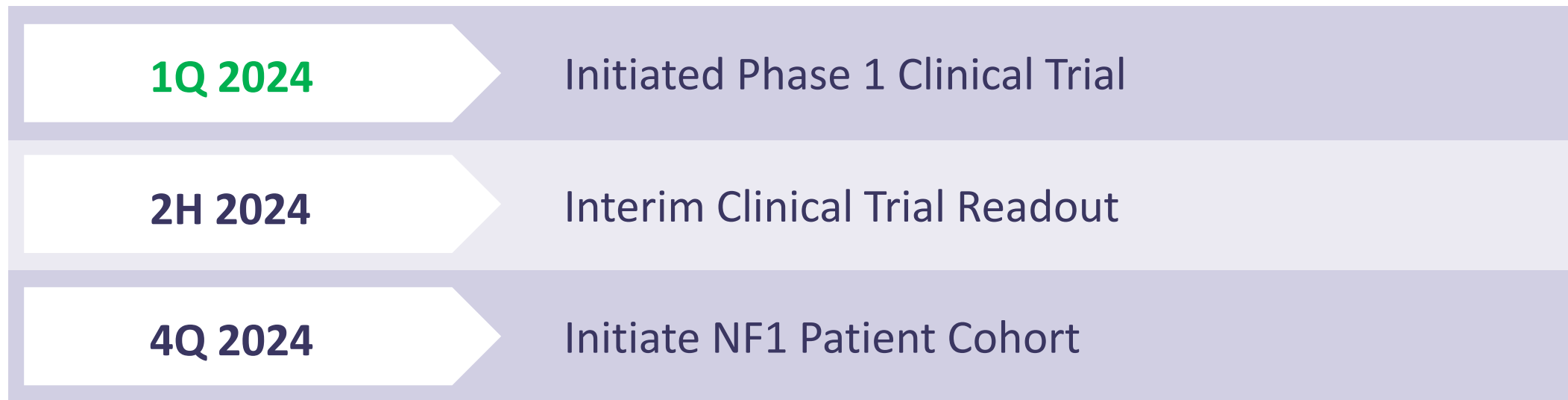
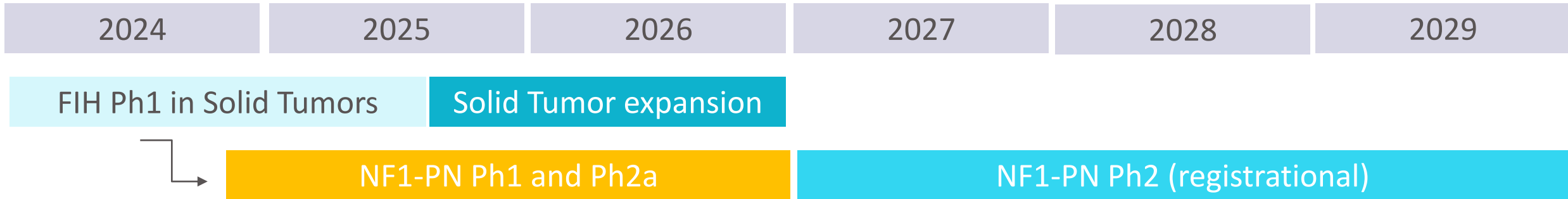
LoRusso PM et al. Phase I pharmacokinetic and pharmacodynamic study of the oral MAPK/ERK kinase inhibitor PD-0325901 in patients with advanced cancers. Clin Cancer Res. 2010 Mar 15;16(6):1924-37.

# Significant suppression of the MAPK pathway below NOAEL dose

PAS-004 NOAEL exposure levels obtained from 9 month chronic tox study in dogs



# Clinical Program Timelines to Registration and Near term Milestones





## PAS-003

Monoclonal Antibody Targeting  
 $\alpha 5\beta 1$  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

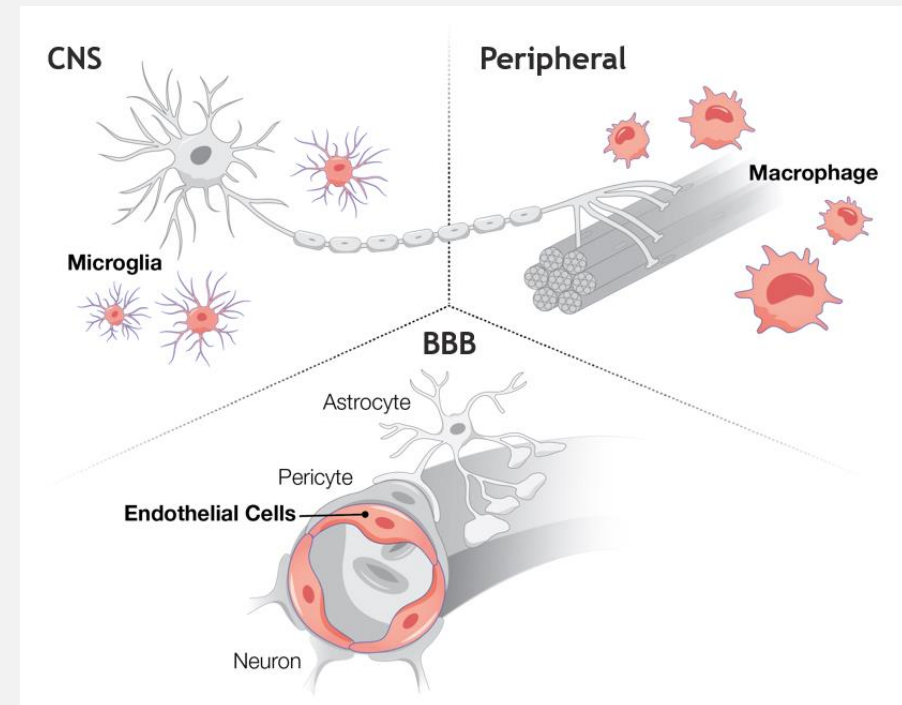
### Late Stage

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

# $\alpha 5\beta 1$ Integrin is a Druggable Target for ALS

- $\alpha 5\beta 1$  is overexpressed in human and mouse ALS
- $\alpha 5\beta 1$  integrin is a well characterized target
  - Anti- $\alpha 5\beta 1$  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  $\alpha 5\beta 1$ , fibronectin, is implicated in several inflammatory conditions of the CNS & PNS

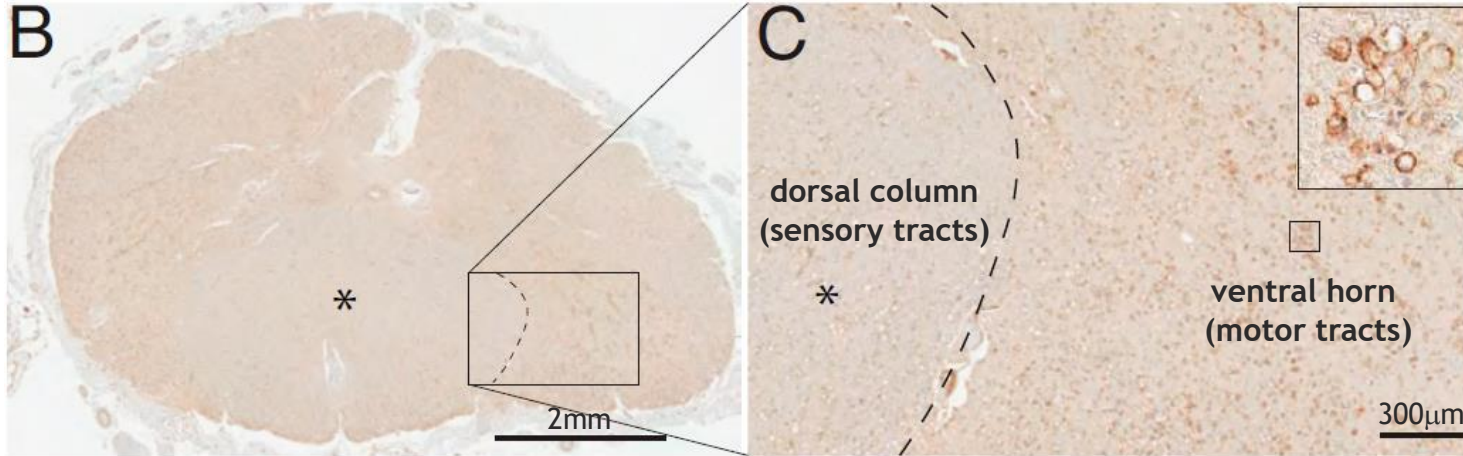
$\alpha 5\beta 1$  is expressed in 3 cell types central to neuroinflammation



# $\alpha 5\beta 1$ 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 (familial and sporadic form) and disease duration  
Elevation of  $\alpha 5\beta 1$  expression in all samples, irrespective of disease duration and subtype  
Striking spatial zonation of  $\alpha 5\beta 1$  integrin expression, confined to the primary motor cortex and spinal cord

$\alpha 5$  integrin expression is elevated in motor area of ALS postmortem spinal cord



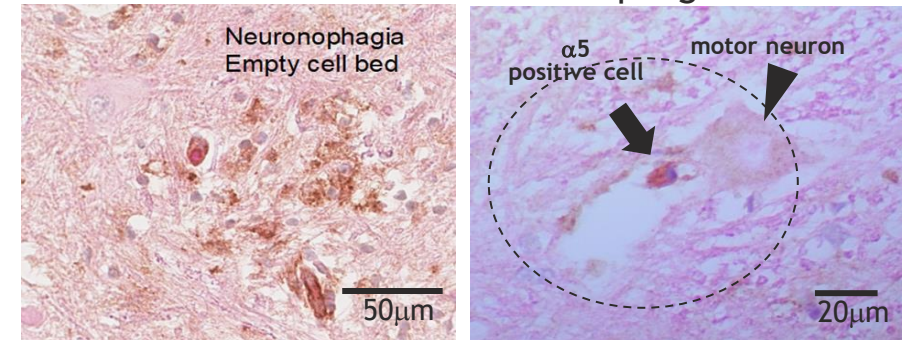
PNAS

RESEARCH ARTICLE | MEDICAL SCIENCES

## Elevated $\alpha 5$ integrin expression on myeloid cells in motor areas in amyotrophic lateral sclerosis is a therapeutic target

Aude Chiot<sup>ab,1</sup>, Shanu F. Roemer<sup>c,1</sup>, Lisa Ryner<sup>d</sup>, Alina Bogachuk<sup>ab</sup>, Katie Emberley<sup>ab,e</sup>, Dillon Brownell<sup>ab</sup>, Gisselle A. Jimenez<sup>ab</sup>, Michael Leviten<sup>d</sup>, Randall Woltjer<sup>f</sup>, Dennis W. Dickson<sup>g</sup>, Lawrence Steinman<sup>h,i</sup>, and Bahareh Ajami<sup>ab,2</sup>

### $\alpha 5$ at sites of neuronophagia



# $\alpha 5\beta 1$ Integrin is Elevated in Motor Areas of ALS Postmortem Tissue

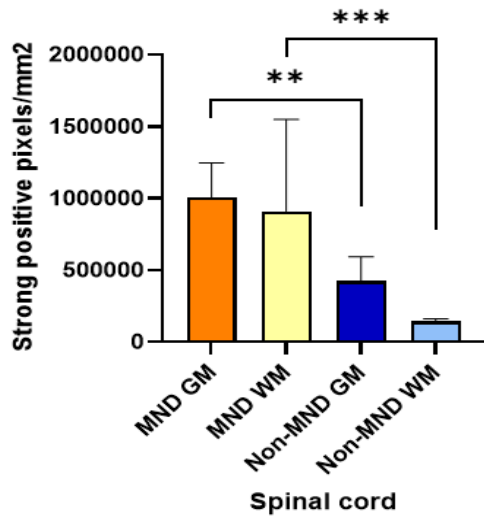
Elevation of  $\alpha 5\beta 1$  expression was not observed in human healthy controls

Specificity of  $\alpha 5\beta 1$  to ALS Pathology (no increase in other integrins expression)

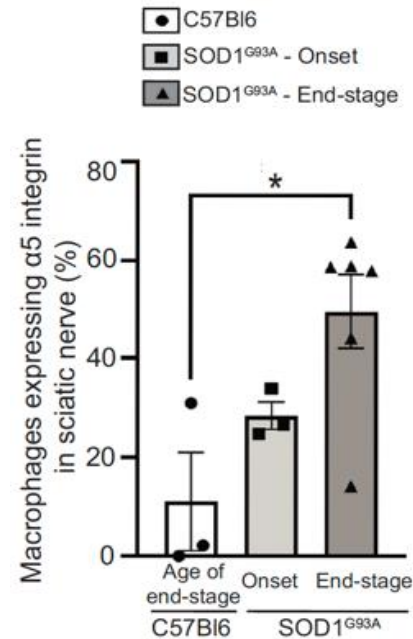
Expression of  $\alpha 5\beta 1$  increases with disease progression (preclinical SOD mouse model)

$\alpha 5\beta 1$  gene expression increases with disease progression (ALS human data)

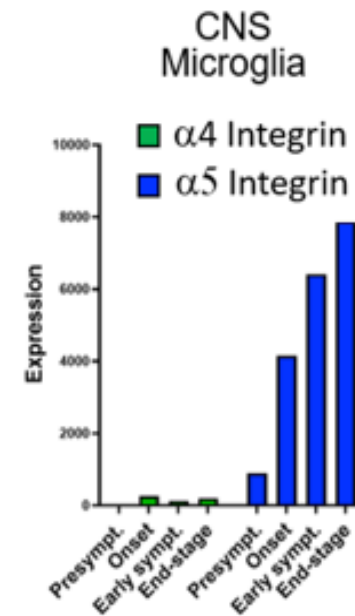
## $\alpha 5\beta 1$ in ALS vs HC



## $\alpha 5\beta 1$ disease progression



## $\alpha 5\beta 1$ vs other integrins



## ALS gene expression

### Spinal Cord Tissue

$\alpha 5$  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

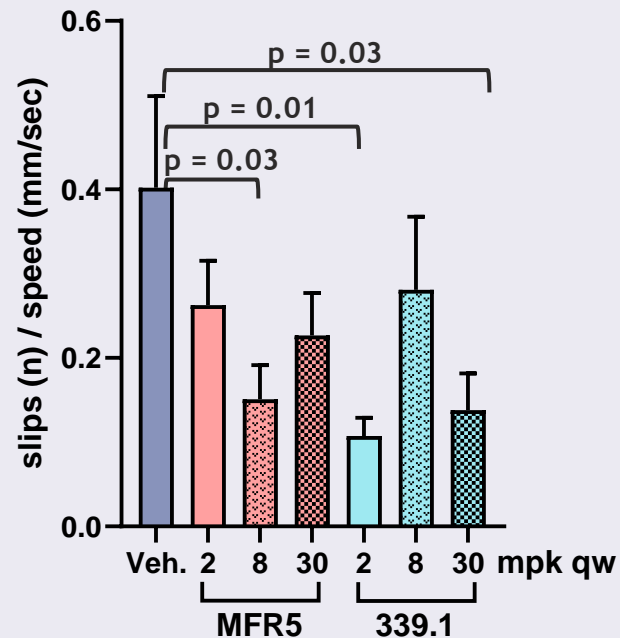
Ventral horn of ALS tissue (n=6)  
vs.  
Matched normal subjects (n=5)

# Mouse SOD1<sup>G93A</sup> Model: Anti- $\alpha$ 5 Treatment Improves Behavior, Survival & Reduces T Cell Infiltration into the CNS

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

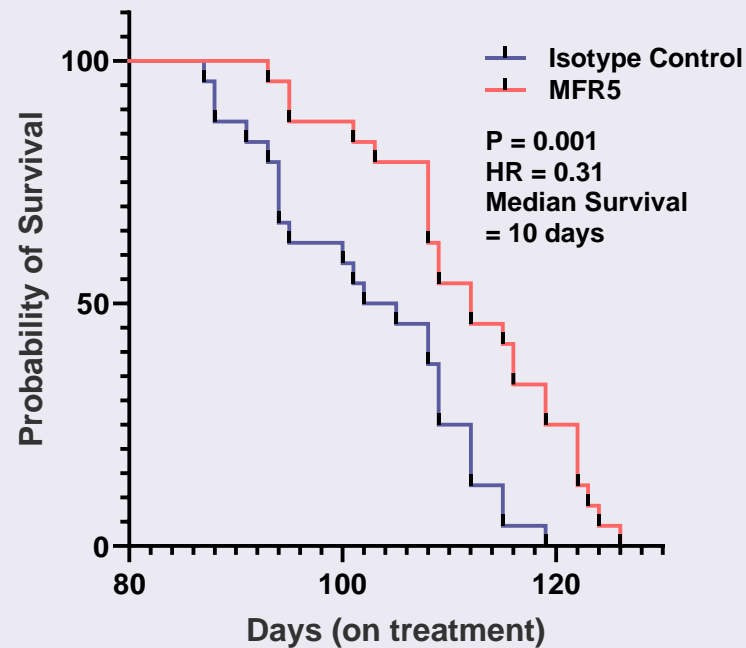
## Beam Walk

Beam Walk at 12 Weeks  
(n=24/group)



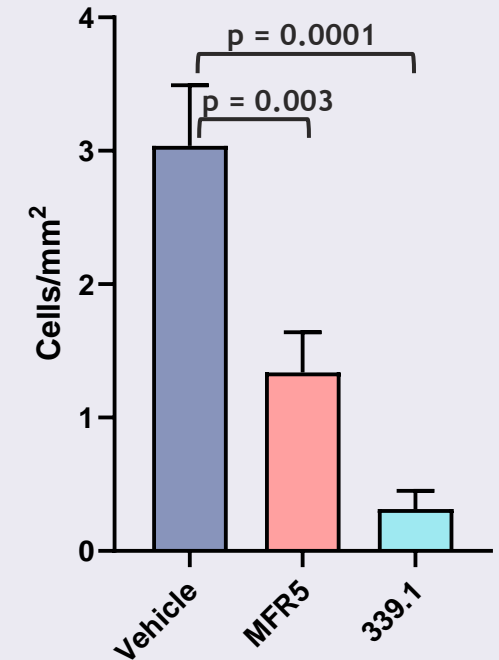
## Survival

MFR5 vs. Isotype Control  
(4mpk biw; n=24/group)



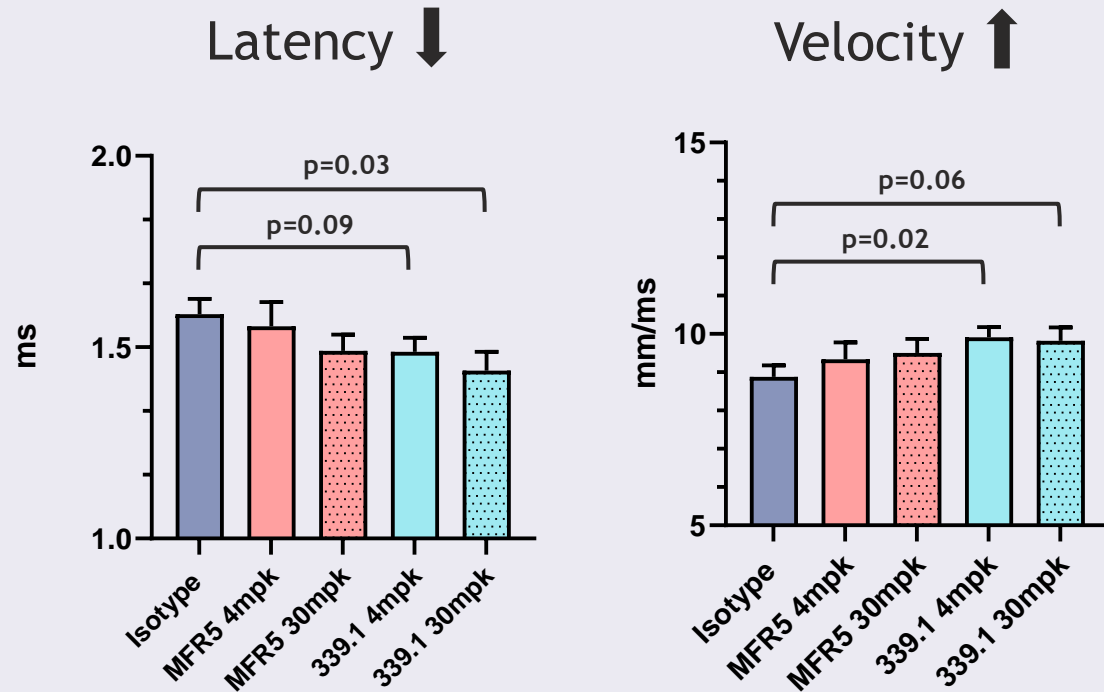
## CD4+ T Cells in Spinal Cord

Immunohistochemistry T Cells  
(6 mice/group; n=18 sections/mouse)

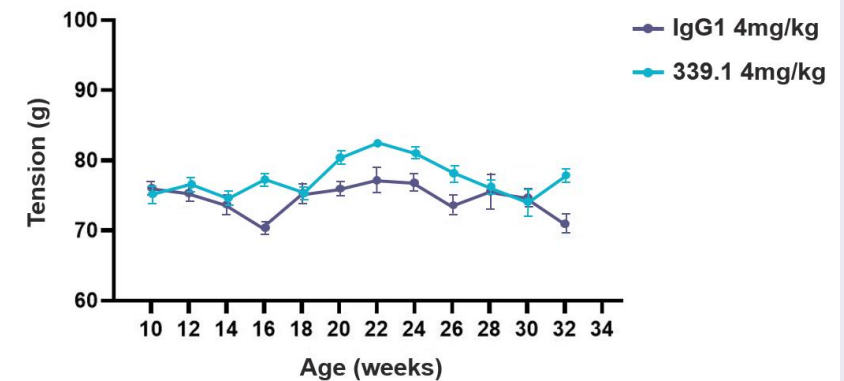
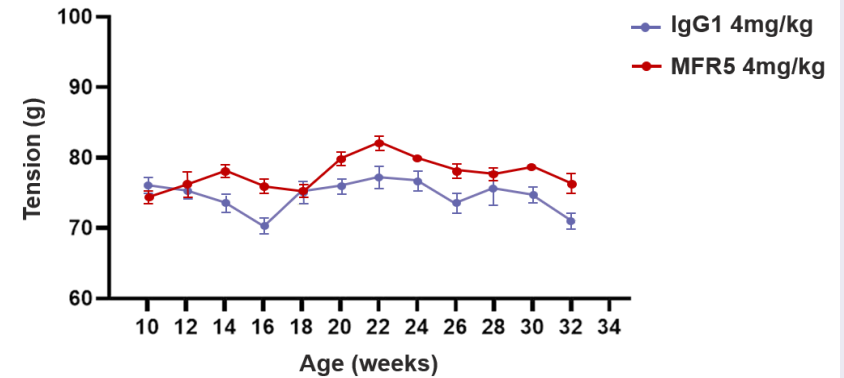


# TDP-43 ALS Mouse Models: Anti- $\alpha$ 5 Treatment Improves Muscle Function

## Muscle Electrophysiology CMAP in TDP-43<sup>rNLS8</sup> (Short Model)



## Grip Strength in Males TDP-43<sup>Q331K</sup> (Long Model)





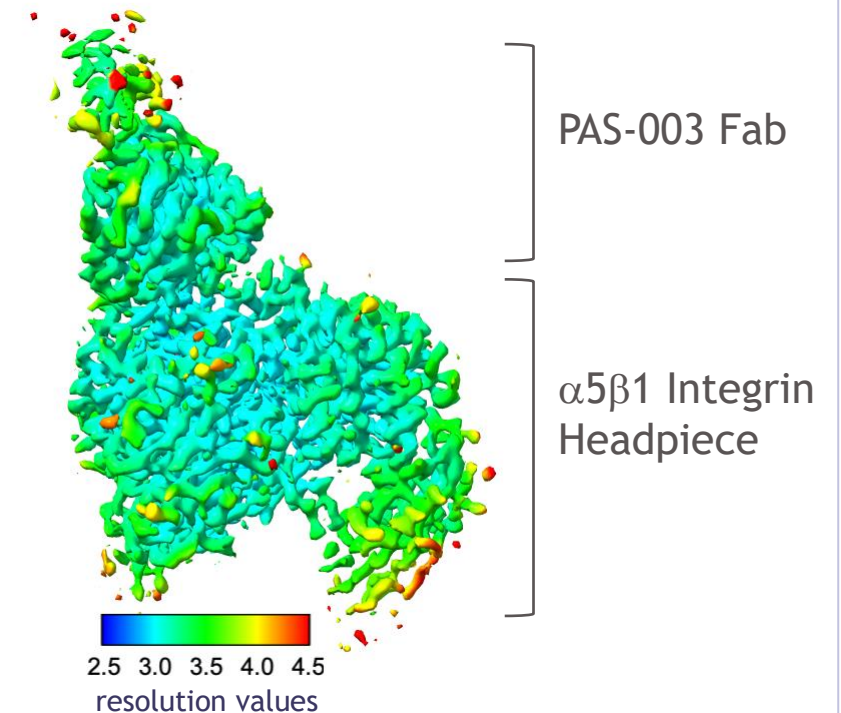
# PAS-003 Monoclonal Antibody Antagonist of $\alpha 5\beta 1$ for ALS

## Roadmap

- Humanized lead candidate selected
  - ✓ Blocks binding of primary ligand fibronectin
  - ✓ Inhibits adhesion & migration of  $\alpha 5$  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 $\alpha 5$ Integrin

Cryo-EM 3.2 Å Density Map



## PAS-001

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

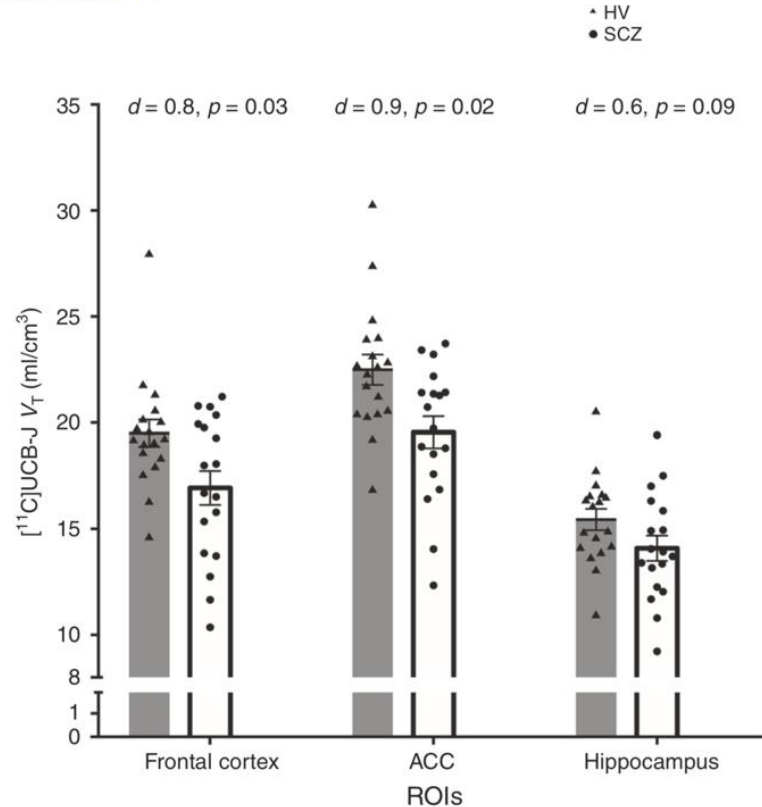
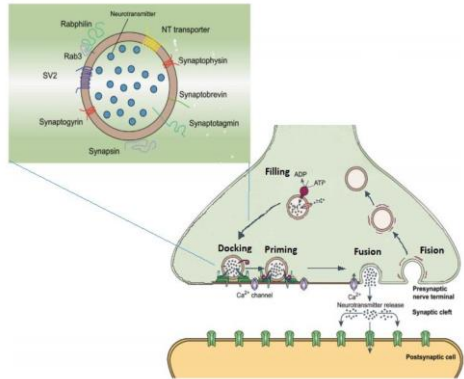
# Synaptic loss is present in schizophrenia both in-vivo and human post-mortem

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<sup>1,2,3,4</sup>, Els F. Half<sup>3</sup>, Thomas Whitehurst<sup>1,3,4</sup>, Ayla Mansur<sup>5</sup>, Marie-Caroline Cotel<sup>6</sup>, Lisa Wells<sup>7</sup>, Hannah Creaney<sup>6</sup>, David Bonsall<sup>7</sup>, Maria Rogdaki<sup>1,2,3,4</sup>, Ekaterina Shatalina<sup>1,2</sup>, Tiago Reis Marques<sup>1,3,4</sup>, Eugenii A. Rabiner<sup>7,8</sup>, Roger N. Gunn<sup>5,7</sup>, Sridhar Natesan<sup>1,3</sup>, Anthony C. Vernon<sup>6,9</sup> & Oliver D. Howes<sup>1,2,3,4\*</sup>



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

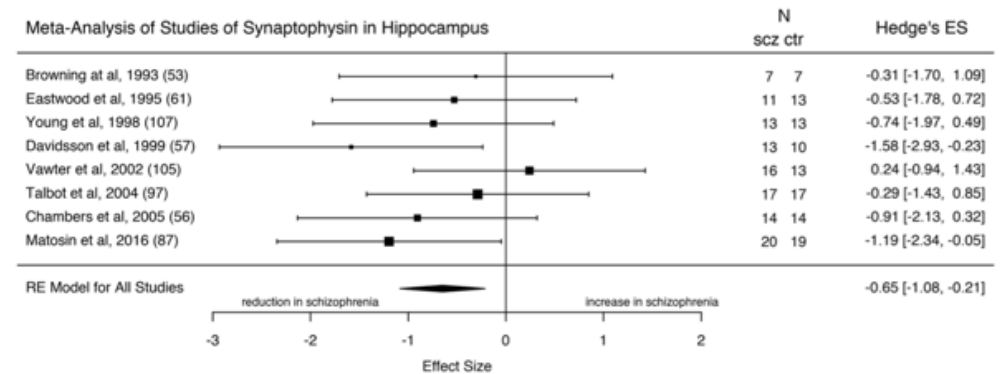
Emanuele Felice Osimo<sup>1,2,3,4</sup> · Katherine Beck<sup>1,2,5,6</sup> · Tiago Reis Marques<sup>1,2,5,6</sup> · Oliver D Howes<sup>1,2,5,6</sup>

Received: 1 November 2017 / Revised: 5 January 2018 / Accepted: 31 January 2018 / Published online: 6 March 2018  
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### Synaptic density in schizophrenia

551

#### Meta-Analysis of Studies of Synaptophysin in Hippocampus



**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



NATURE | ARTICLE

日本語要約

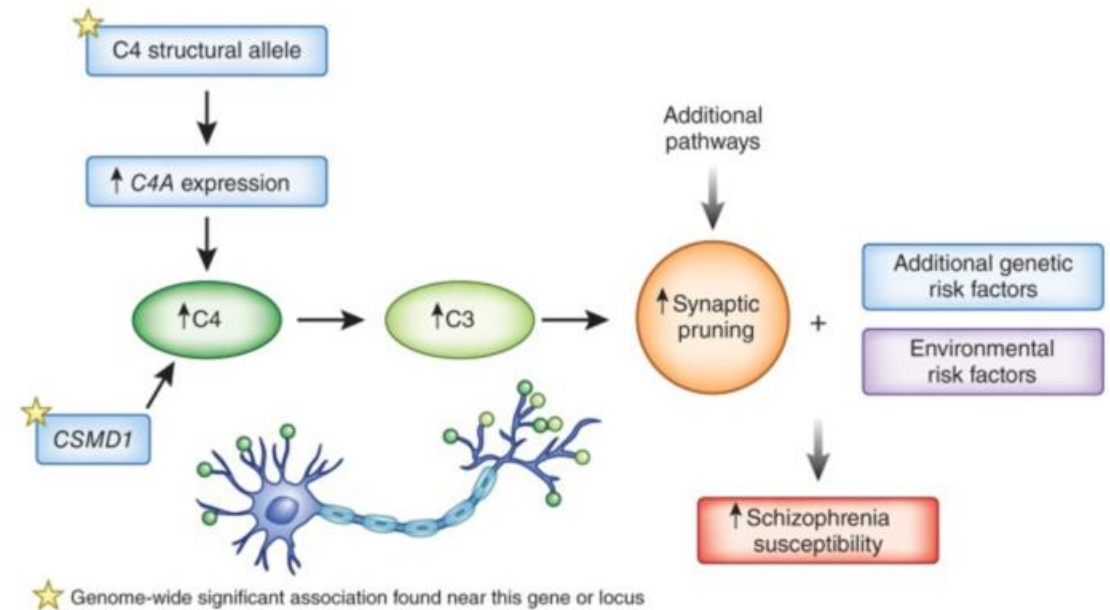
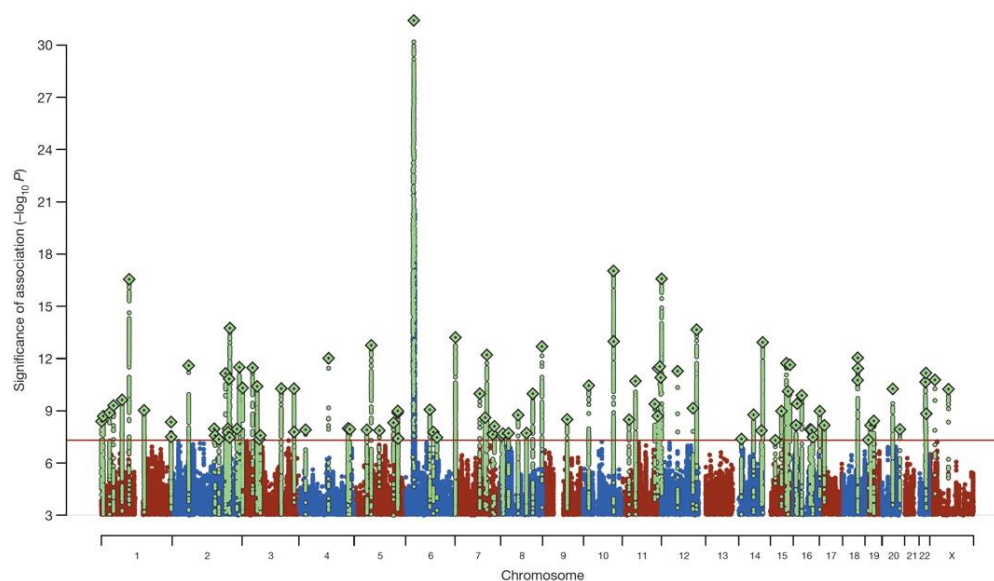
## Biological insights from 108 schizophrenia-associated genetic loci

Schizophrenia Working Group of the Psychiatric Genomics Consortium

Affiliations | Contributions | Corresponding author

Nature 511, 421–427 (24 July 2014) | doi:10.1038/nature13595

Received 06 March 2014 | Accepted 18 June 2014 | Published online 22 July 2014



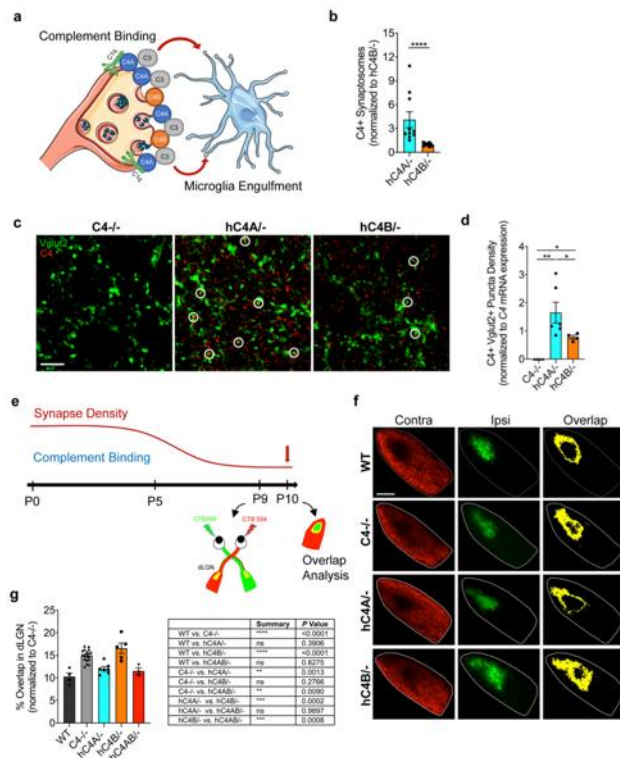
- the most strongly associated GWAS locus, located in the extended Major Histocompatibility Complex (MHC) region on chromosome 6.
- This locus contains multiple copies of two closely related genes that codes for variants of C4: C4A and C4B.

# 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<sup>1,5</sup>, Esra Yalcin<sup>1,5</sup>, Jessy Presumey<sup>1,5</sup>, Ernest Aw<sup>1</sup>, Minghe Ma<sup>1</sup>, Christopher W. Whelan<sup>2,3</sup>, Beth Stevens<sup>3,4</sup>, Steven A. McCarroll<sup>2,3</sup> and Michael C. Carroll<sup>1,2,3</sup>



**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*<sup>-/-</sup> mice were isolated and incubated with serum containing the same amount of C4 from *hC4A*<sup>-/-</sup> (*n* = 10) or *hC4B*<sup>-/-</sup> (*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>

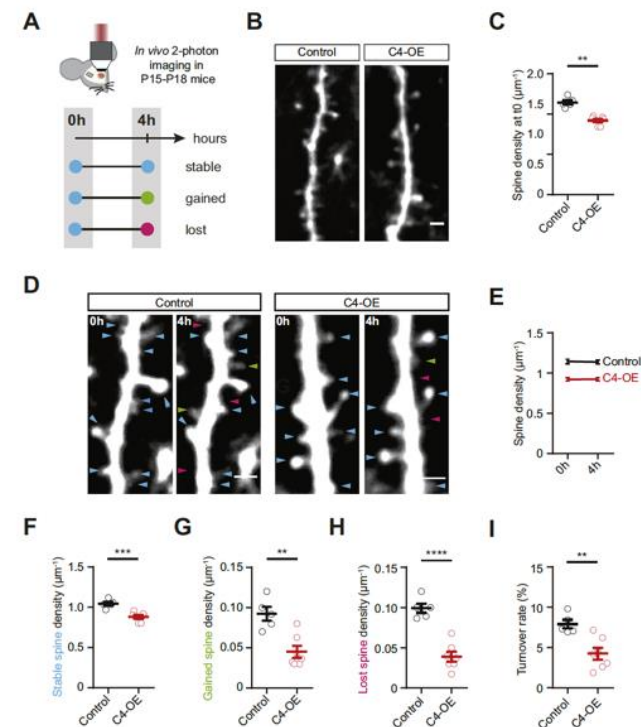
ARTICLE



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

Mélanie Druart<sup>1,2,3</sup>, Marika Nosten-Bertrand<sup>1,2,3</sup>, Stefanie Poll<sup>4</sup>, Sophie Crux<sup>4</sup>, Felix Nebeling<sup>4</sup>, Célia Delhay<sup>1,2,3</sup>, Yaëlle Dubois<sup>1,2,3</sup>, Manuel Mittag<sup>4</sup>, Marion Leboyer<sup>5,6</sup>, Ryad Tamouza<sup>5,6</sup>, Martin Fuhrmann<sup>4</sup>, Corentin Le Magueresse<sup>1,2,3</sup>

Received: 4 July 2020 / Revised: 5 March 2021 / Accepted: 26 March 2021 / Published online: 9 April 2021  
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# Discovery of Small Molecule Inhibitors of C4A Levels



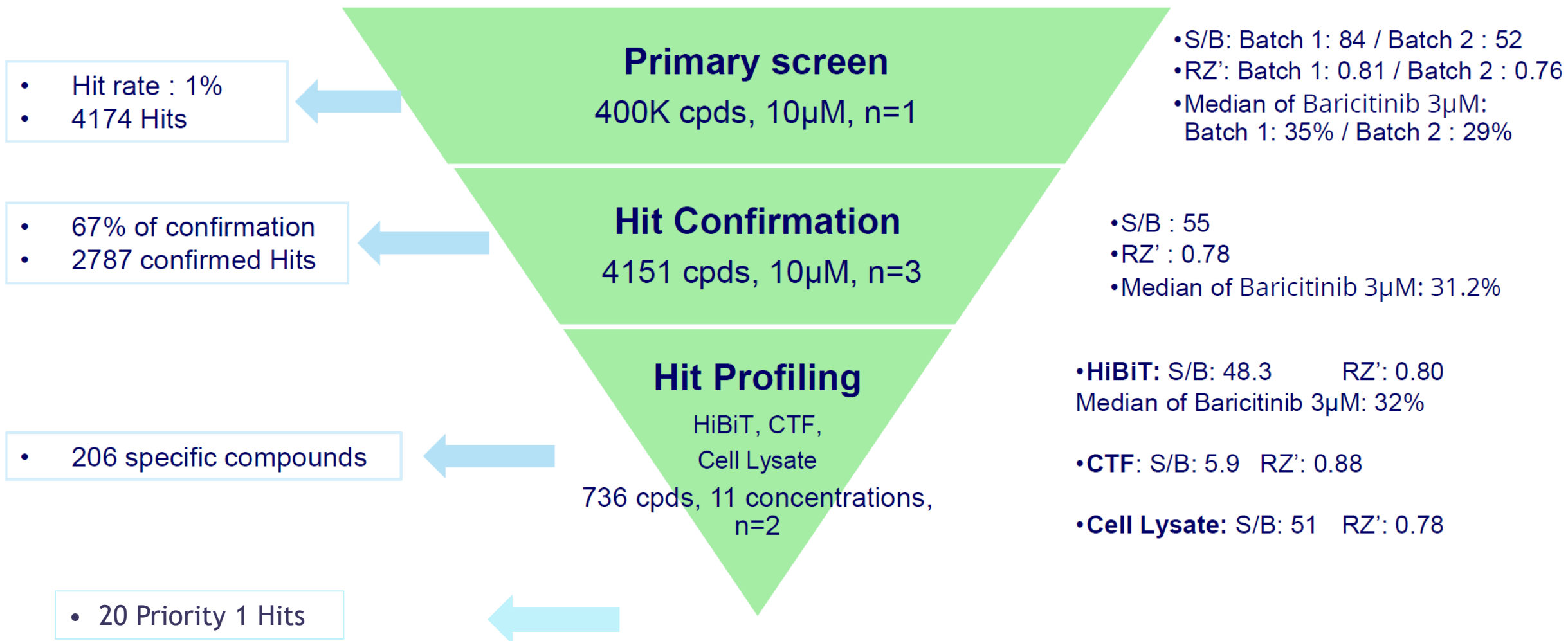
## Pasithea Therapeutics Corp. and Evotec SE Enter into Drug Development Agreement

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.

# Primary Screen for C4A Regulators



# 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**





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[www.pasithea.com](http://www.pasithea.com)

Contact:

Tiago Reis Marques

CEO

[tiago@pasithea.com](mailto:tiago@pasithea.com)