UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): April 27, 2022

PRAXIS PRECISION MEDICINES, INC.
(Exact name of registrant as specified in its charter)

Delaware	001-39620	47-5195942
(State or other jurisdiction of incorporation)	(Commission File Number)	(I.R.S. Employer Identification No.)

Praxis Precision Medicines, Inc.
99 High Street, 30th Floor
Boston, Massachusetts 02110
(Address of principal executive offices, including zip code)

(617) 300-8460
(Registrant's telephone number, including area code)

Not Applicable
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trade Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 par value per share	**PRAX**	**The Nasdaq Global Select Market**

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01. Regulation FD Disclosure.

On April 27, 2022, Praxis Precision Medicines, Inc. (the "Company") held its previously announced 2022 Epilepsy Day. A copy of the slide presentation for Epilepsy Day, which has been made available through the Events & Presentations page of the Investors + Media section of the Company's website, is attached as Exhibit 99.1 to this Current Report on Form 8-K (the "Form 8-K").

The information in this Item 7.01 of this Form 8-K and Exhibit 99.1 attached hereto shall not be deemed filed for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall any of it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Copy of Praxis Precision Medicines, Inc. presentation slides dated April 27, 2022 (furnished herewith)
104	Cover page from this Current Report on Form 8-K, formatted in Inline XBRL

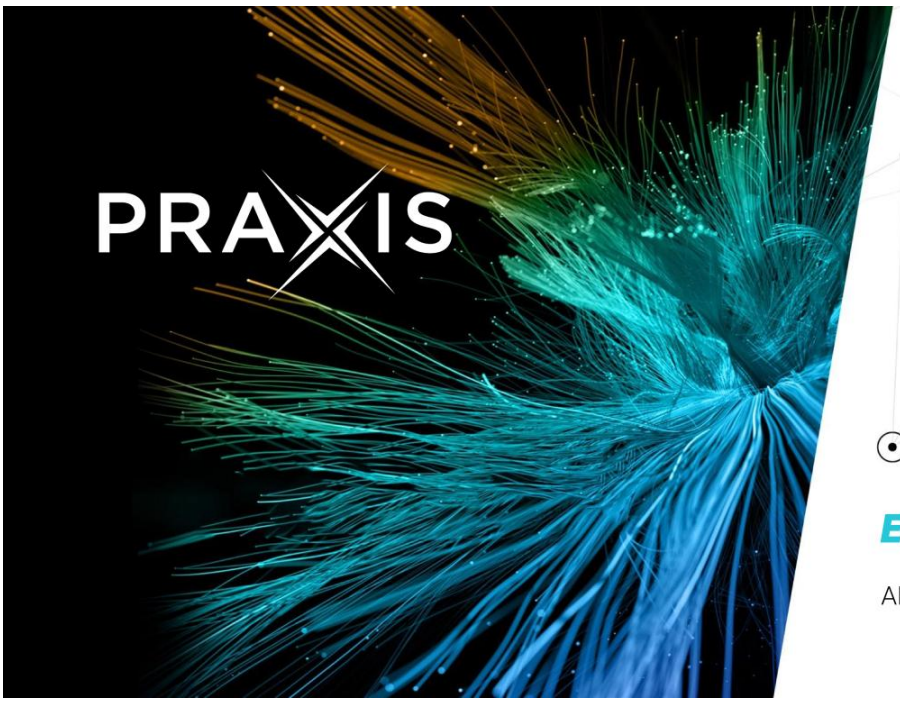
SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

PRAXIS PRECISION MEDICINES, INC.

Date: April 27, 2022

By: /s/ Marcio Souza
Marcio Souza
Chief Executive Officer



EPILEPSY DAY

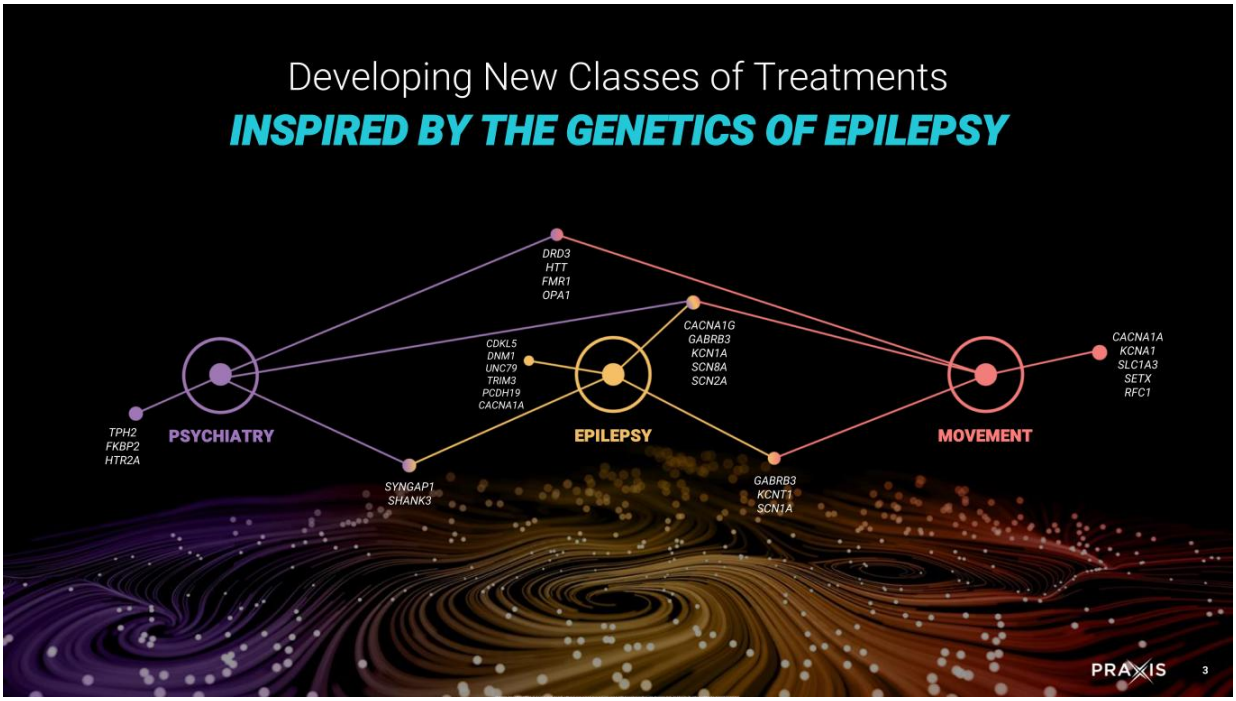
APRIL 27, 2022

Forward-looking statements

This presentation may contain "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995 relating to our business, operations, and financial conditions, including but not limited to express or implied statements regarding the current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our development plans, our preclinical and clinical results and other future conditions. Words such as, but not limited to, "believe," "expect," "anticipate," "estimate," "intend," "plan," "would," "should" and "could," and similar expressions or words, identify forward-looking statements. Any forward-looking statements in this presentation are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this presentation, including, without limitation, risks relating to: (i) the success and timing of our ongoing clinical trials, (ii) the success and timing of our product development activities and initiating clinical trials, (iii) the success and timing of our collaboration partners' ongoing and planned clinical trials, (iv) our ability to obtain and maintain regulatory approval of any of our product candidates, (v) our plans to research, discover and develop additional product candidates, (vi) our ability to enter into collaborations for the development of new product candidates, (vii) our ability to establish manufacturing capabilities, and our and our collaboration partners' abilities to manufacture our product candidates and scale production, (viii) our ability to meet any specific milestones set forth herein, and (ix) uncertainties and assumptions regarding the impact of the COVID-19 pandemic on our business, operations, clinical trials, supply chain, strategy, goals and anticipated timelines. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will prove to be correct. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements.

For further information regarding the risks, uncertainties and other factors that may cause differences between Praxis' expectations and actual results, you should review the "Risk Factors" section of our Annual Report on Form 10-K filed for the period ended December 31, 2021 and other filings with the Securities and Exchange Commission.

Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and our own internal estimates and research. While we believe these third-party sources to be reliable as of the date of this presentation, we have not independently verified, and make no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, all of the market data included in this presentation involves a number of assumptions and limitations, and there can be no guarantee as to the accuracy or reliability of such assumptions. Finally, while we believe our own internal research is reliable, such research has not been verified by any independent source.


Developing New Classes of Treatments
INSPIRED BY THE GENETICS OF EPILEPSY
DRD3
HTT
FMR1
OPA1
CACNA1G
GABRB3
KCN1A
SCN8A
SCN2A
CDKL5
DNM1
UNC79
TRIM3
PCDH19
CACNA1A
CACNA1A
KCNA1
SLC1A3
SETX
RFC1
TPH2
FKBP2
HTR2A
PSYCHIATRY
EPILEPSY
MOVEMENT
SYNGAP1
SHANK3
GABRB3
KCNT1
SCN1A
PRAXIS
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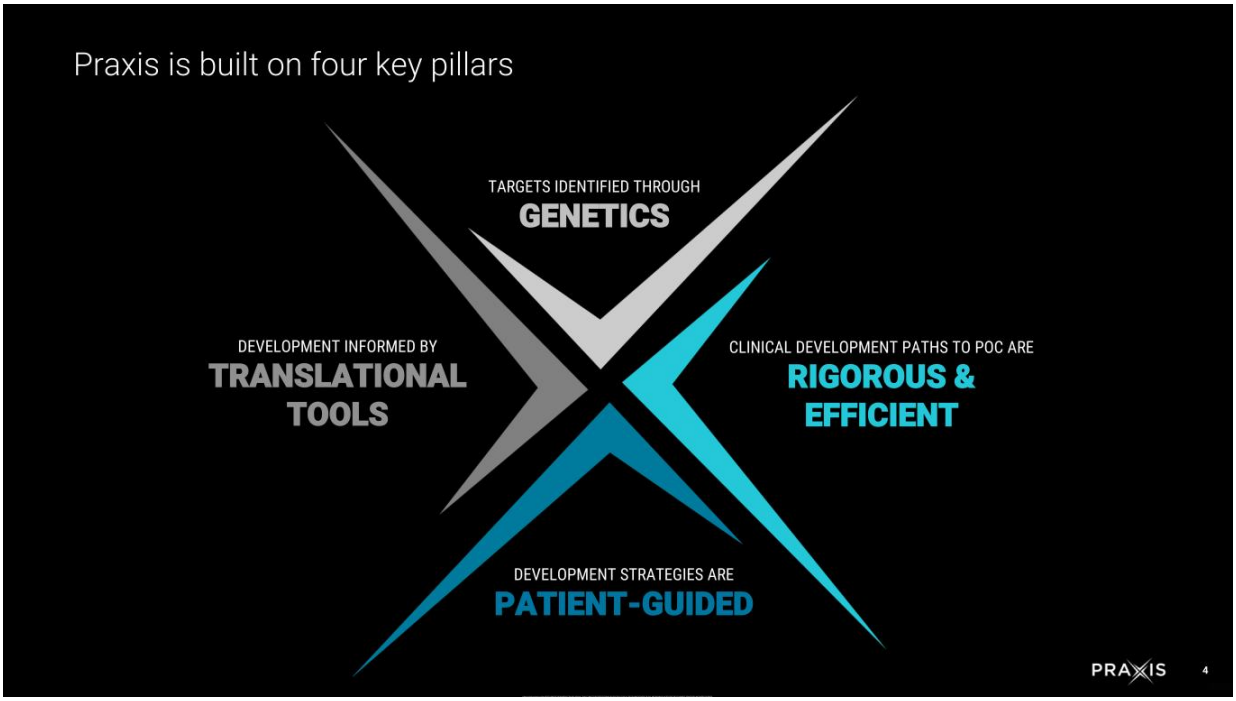
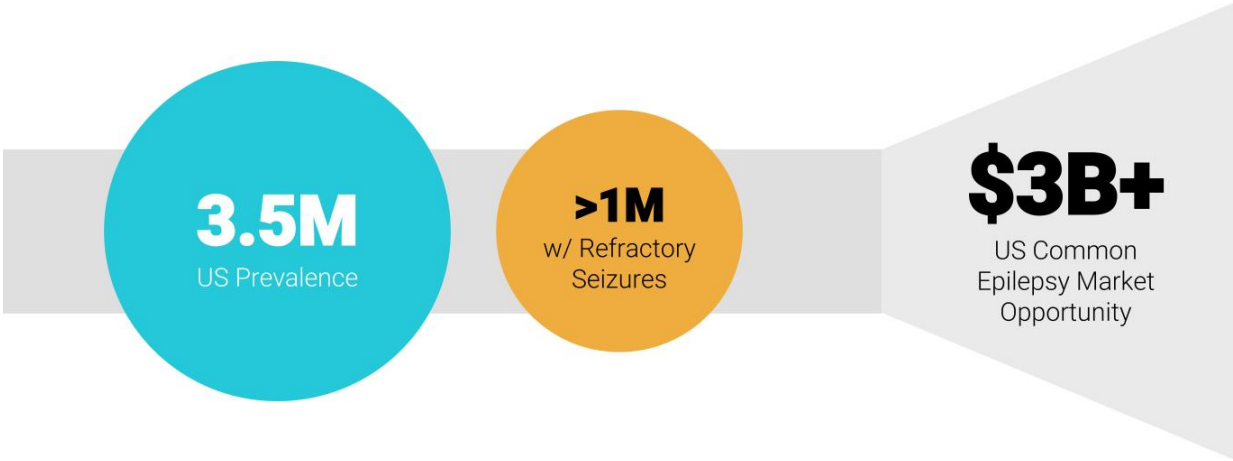
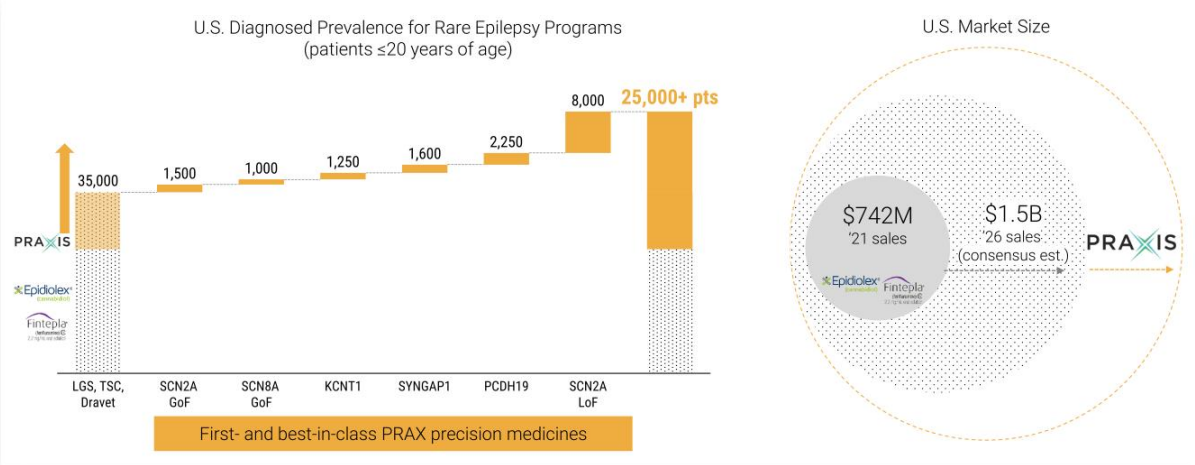

Praxis is built on four key pillars
TARGETS IDENTIFIED THROUGH
GENETICS
DEVELOPMENT INFORMED BY
TRANSLATIONAL TOOLS
CLINICAL DEVELOPMENT PATHS TO POC ARE
RIGOROUS & EFFICIENT
DEVELOPMENT STRATEGIES ARE
PATIENT-GUIDED
PRAXIS
4

We aim to address unmet need in the $3B+ US common epilepsy market

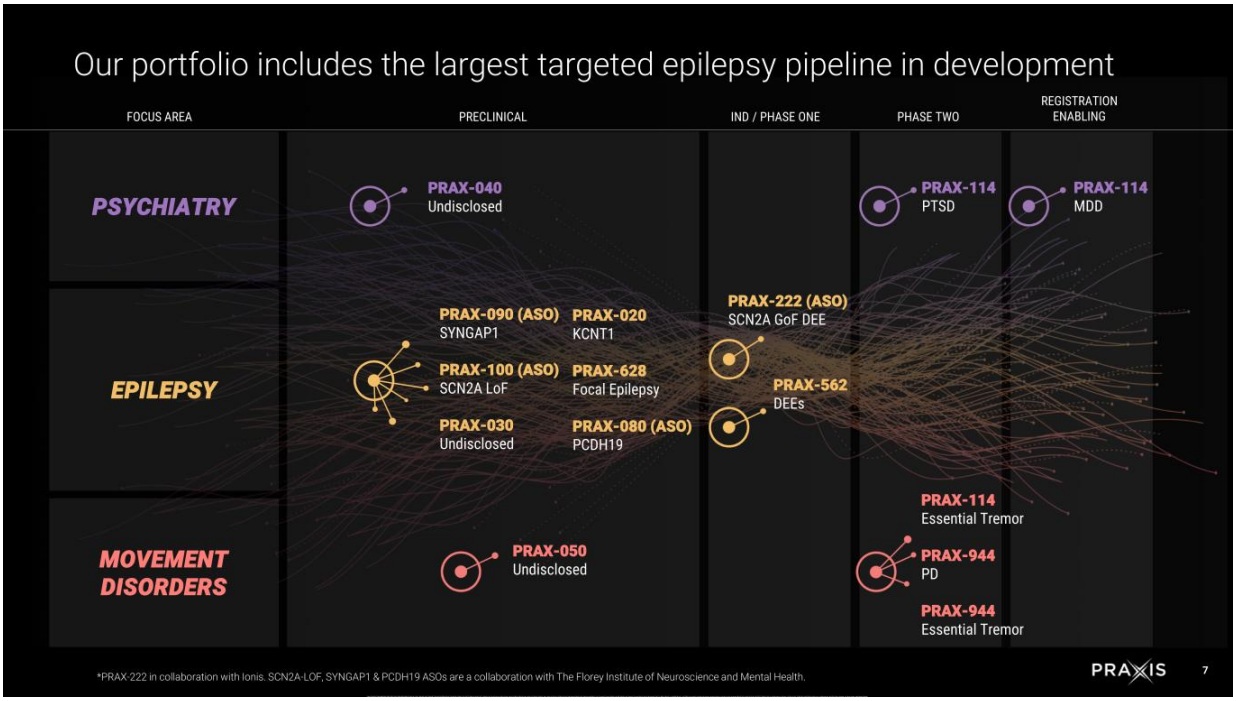


Source: CDC, EvaluatePharma; Tang F. et al. Front. Neurol. (2017)

Delivering first and best-in-class precision medicines for 25,000+ rare epilepsy patients



LGS: Lennox-Gastaut Syndrome; TSC: Tuberous Sclerosis Complex
Source: Ambit Genetic Testing and Claims Data Analysis; EvaluatePharma; Sanders S. J. *et al. Trends Neurosci.* (2018); Wolff M. *et al* Brain (2017);


Our portfolio includes the largest targeted epilepsy pipeline in development
FOCUS AREA
PRECLINICAL
IND / PHASE ONE
PHASE TWO
REGISTRATION ENABLING
PSYCHIATRY
EPILEPSY
MOVEMENT DISORDERS
PRAX-040
Undisclosed
PRAX-090 (ASO)
SYNGAP1
PRAX-020
KCNT1
PRAX-100 (ASO)
SCN2A LoF
PRAX-628
Focal Epilepsy
PRAX-030
Undisclosed
PRAX-080 (ASO)
PCDH19
PRAX-050
Undisclosed
PRAX-222 (ASO)
SCN2A GoF DEE
PRAX-562
DEEs
PRAX-114
PTSD
PRAX-114
MDD
PRAX-114
Essential Tremor
PRAX-944
PD
PRAX-944
Essential Tremor
*PRAX-222 in collaboration with Ionis. SCN2A-LOF, SYNGAP1 & PCDH19 ASOs are a collaboration with The Florey Institute of Neuroscience and Mental Health.
PRAXIS
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Introductions

JACQUELINE FRENCH, M.D.

Professor of Neurology at NYU Grossman School of Medicine and President, Director and Founder of the Epilepsy Study Consortium

- Trained in Neurology at Mount Sinai Hospital in New York; fellowship training in EEG and epilepsy at Mount Sinai hospital and Yale University.
- Serves as the Chief Medical/Innovation Officer of the Epilepsy Foundation.
- Past president of the American Epilepsy Society; past Secretary of the American Society of Experimental Neurotherapeutics.
- Recipient of the American Epilepsy Society Lennox Award (2017) and Service Award (2005), the Epilepsy Foundation Hero award (2013), and is an ILAE Ambassador for Epilepsy.

DANIEL FRIEDMAN, M.D., MSc.

Professor of Neurology at NYU Grossman School of Medicine and Co-director of the Video-EEG laboratory at NYU Langone Medical Center

- MD from Case Western Reserve University School of Medicine; neurology residency training at the Hospital of the University of Pennsylvania and his epilepsy/clinical neurophysiology fellowship at the Neurological Institute/Columbia University Medical Center.
- Serves on the executive committees of the North American SUDEP Registry and the Epilepsy Study Consortium as well as the professional advisory board of the Epilepsy Foundation of America.

Today's Agenda

JACQUELINE FRENCH, M.D.

- **Unmet Needs in Epilepsy Management:** Challenges with clinical management of epilepsy today and possibility for precision-based therapies tomorrow

STEVE PETROU, Ph.D.

- **Praxis Epilepsy Innovation Strategy:** Using genetics to elucidate new epilepsy targets with high probability of success
- **Our Science in Action:** A deep-dive into our disease modifying epilepsy programs

DANIEL FRIEDMAN, M.D., MSc.

- **Perspectives from Clinical Practice:** Shortcomings of existing treatment landscape provide opportunities for differentiation

BERNARD RAVINA, M.D., MSc.

- **Accelerating towards Registration:** Our clinical development strategy for most advanced epilepsy programs

Q&A SESSION

- **Q&A Panel with Speakers**

Unmet Needs in Epilepsy Management

Jacqueline French, M.D.
NYU School of Medicine

Disclosures

- I receive salary support from the Epilepsy Foundation and for consulting work and/or attending Scientific Advisory Boards on behalf of the Epilepsy Study Consortium for Adamas, Aeonian/Aeovian, Alterity Therapeutics Limited, Anavex, Arkin Holdings, Arvelle Therapeutics, Inc., Athenen Therapeutics/Carnot Pharma, Autifony Therapeutics Limited, Baergic Bio, Biogen, BioMarin Pharmaceutical Inc., BioXcel Therapeutics, Bloom Science Inc., BridgeBio Pharma Inc., Cavion, Cerebral Therapeutics, Cerevel, Clinical Education Alliance, Coda Biotherapeutics, Corlieve Therapeutics, Crossject, CuroNZ, Eisai, Eliem Therapeutics, Encoded Therapeutics, Engage Therapeutics, Engrail, Epalex, Epihunter, Epiminder, Epitel Inc, Equilibre BioPharmaceuticals, Fortress Biotech, Greenwich Biosciences, Grin Therapeutics, GW Pharma, Janssen Pharmaceutica, Jazz Pharmaceuticals, Knopp Biosciences, LivaNova, Longboard Pharmaceuticals, Lundbeck, Marinus, Mend Neuroscience, Merck, NeuCyte Inc., Neumirna Therapeutics, Neurocrine, Neuroelectrics USA Corporation, Neuropace, NxGen Medicine Inc., Ono Pharmaceutical Co., Otsuka Pharmaceutical Development, Ovid Therapeutics Inc., Passage Bio, Pfizer, Praxis, PureTech LTY Inc., Rafa Laboratories Ltd, Redpin, Sage, SK Life Sciences, Sofinnova, Stoke, Supernus, Synergia Medical, Takeda, UCB Inc., Ventus Therapeutics, West Therapeutic Development, Xenon, Xeris, Zogenix, Zynerba.
- I have also received research support from the Epilepsy Study Consortium (Funded by Andrews Foundation, Eisai, Engage, Lundbeck, Pfizer, SK Life Science, Sunovion, UCB, Vogelstein Foundation) Epilepsy Study Consortium/Epilepsy Foundation (Funded by UCB), GW/FACES and NINDS.
- I am on the editorial board of Lancet Neurology and Neurology Today. I am Chief Medical/Innovation Officer for the Epilepsy Foundation.
- I have received travel reimbursement related to research, advisory meetings, or presentation of results at scientific meetings from the Epilepsy Study Consortium, the Epilepsy Foundation, Arvelle Therapeutics, Inc., Biogen, Cerevel, Clinical Education Alliance, Engage, Lundbeck, NeuCyte, Inc., Neurocrine, Otsuka, Sage, UCB, Xenon, Zogenix.

Incidence of epilepsy

- By a conservative estimate, 50 million people worldwide have epilepsy[1]
- The annual incidence ranges from 20-70 cases per 100,000
- Overall, 5% of persons report a seizure at some time in their lives (excluding febrile seizures)
- Incidence rates are highest in childhood, plateau from 15-65 years of age, and rise again among the elderly
- About 30% of patients with seizures have an identifiable neurologic or systemic disorder, and the remainder have either idiopathic or cryptogenic epilepsy
- The diagnosis is based on the description of the seizures and the clinical context in which they occur, often supplemented by the results of electroencephalography

1. Brodie MJ and Dichter MA. *N Engl J Med*. 1996;334(3):168-175.

Antiseizure medicine: 2022

1st Generation
- Phenytoin
- Carbamazepine
- Sodium Valproate
- Phenobarbital
- Primidone

2nd Generation
- Felbamate
- Gabapentin
- Lamotrigine
- Topiramate/
- Tiagabine
- Oxcarbazepine
- Levetiracetam

3rd Generation
- Zonisamide
- Pregabalin
- Lacosamide
- Rufinamide
- Vigabatrin
- Clobazam
- Perampanel
- Eslicarbazepine
- Cannabidiol (Epidiolex)
- Brivaracetam
- Cenobamate
- Fenfluramine
- Ganaxolone

Outcome with initial drug therapy-all comers as of 2000

	Seizure Free
First drug monotherapy	47%
Second drug monotherapy	13%
Third drug monotherapy	1%
Duotherapy	3%
Total seizure free	**64%**

Kwan P and Brodie MJ. *N Engl J Med.* 2000;342(5):314-319.

How far have we advanced?

- Studies in the 1980's established the critical ratio of treatment response in both adults and children:
  - 60-70% respond to ASM
  - 30-40% are "treatment resistant"
- With 20 new ASMs in the last few decades, we would anticipate a change in the ratio
- Unfortunately, there has not been a substantial change in this ratio in recent times

Outcome with initial drug therapy

	Seizure Free 2000[1]	Seizure free 2012[2]
First drug monotherapy	47%	49.5
Second drug monotherapy	13%	
Third drug monotherapy	1%	
Duotherapy	3%	6%
Total seizure free	**64%**	**68%**

1. Kwan P and Brodie MJ. *N Engl J Med.* 2000;342(5):314-319.
2. Brodie et al, Neurology. 2012 ;78(20):1548-54

AED Therapy: Current status and unmet needs

We Have

Treatment for two thirds of patients

We Need

- Treatment for the one third of adult patients who are refractory
- Treatment for difficult pediatric syndromes
  - Many now identified as monogenetic
- Ability to predict efficacy/tolerability
- Improved options for newly-diagnosed patients
  - Finding treatments that do not impact quality of life
- Attention to comorbidities: depression, cognitive slowing, memory impairment
- Antiepileptogenic/disease modifying therapy

Adherence burden

- About 2/3 of patients can have seizures controlled with a new ASM
- But these people are burdened by a daily requirement to take ASM, with dire consequences if even a single day is missed
- This can be a lifetime obligation!

We have no problem finding new drugs with novel mechanisms*

- Brivaracetam - binds SV2A & blocks voltage-gated Na+ channels
- 2-deoxy-glucose inhibits glycolysis
- Ganaxolone - GABAA-PAM tonic inhibition
- Huperzine A - NMDA antagonist
- Cenobamate - inhibits voltage gated sodium channels and positive GABAA modulator
- CVL-865 - α2/3/5 preferring GABA-PAM
- JNJ-40411813 - mGluR2 PAM
- XEN901 - Selective Nav1.6 sodium channel blocker
- XEN1101 - K^+ Channel opener

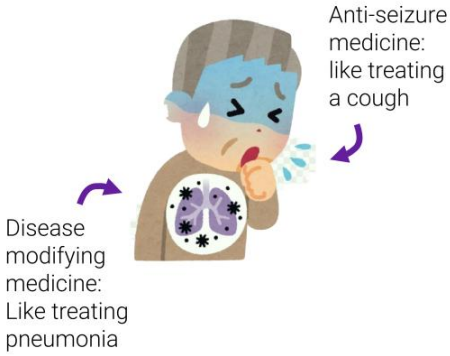
*Presented at Eleventh Eilat Conference (April 6-10, 2012)

Novel mechanisms

- To date, *novel* mechanisms have not translated into better efficacy or tolerability

Antiepileptic drug?

- ILAE is considering an “official” name change for the venerable Antiepileptic Drug, dividing drugs into:
  - Anti-seizure medication (ASM)
  - Disease modifying Epilepsy Medication (DMEM)
- This is to highlight that most medications do not alter the course of epilepsy and are essentially “symptomatic therapy”.
  - What does this mean?



Can we predict a better drug?

- A drug could differentiate in a number of important ways:
  - Disease modifying
  - Targeted at a specific population
  - Clear and indisputable advance in treating resistant epilepsy
  - Seizure freedom
  - Better tolerability
  - Less issues for women of childbearing potential
  - Specific efficacy in difficult syndromes (eg Dravet, Lennox-Gastaut)
  - Longer acting

Seizure freedom is important

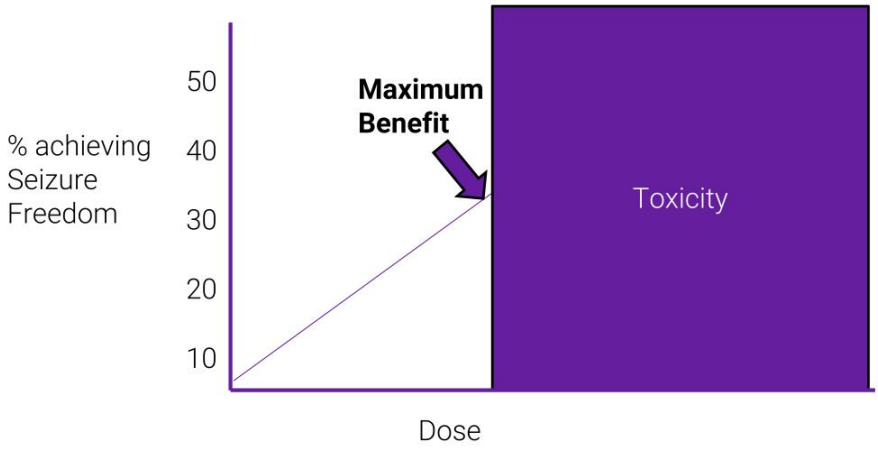
- In add-on studies, less than 5% of subjects are able to obtain seizure freedom, even for the 3 months of randomization
- There is a great opportunity to develop a new therapy that increases rate of seizure freedom, or even 75-90% seizure reduction

But it all comes down to risk vs benefit

- Don’t forget that the balance of adverse effects/risk of harm to benefit is important, even to individuals with treatment resistant epilepsy

Source: h.fraimow

Can better side effect profile lead to better efficacy?

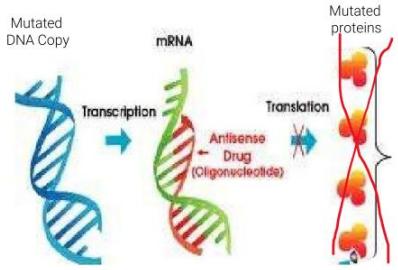


Precision therapy?

- Recent studies of emerging anti-seizure drugs in orphan diseases
  - Dravet syndrome
    - Fenfluramine
    - Cannabidiol
  - Lennox-Gastaut syndrome
    - Clobazam (US)
    - Rufinamide
    - Cannabidiol
    - Fenfluramine
- Is this "precision medicine"?
  - To date, these studies have only determined the drug under study is more effective than placebo in a specific syndrome.
  - The studies have not proven **either** that the drug is more effective than other potential therapies, **or** that the drug will be more effective for this syndrome than for any other syndrome tested.

Precision therapy with Disease Modifying Epilepsy Medications (DMEM)

- Targeted drugs (The hope for the future)
  - Correct pathology caused by a specific mutation or mutations
  - Everolimus and Tuberous sclerosis complex (TSC)
    - A mutation in *TSC1* or *TSC2* causes hyperactivity of the mammalian target of rapamycin (mTOR) pathway.
    - Everolimus "normalizes" mTOR pathway, and is truly a "targeted" treatment for TSC
  - Targeted genetic therapies
    - Gene replacement therapies
    - Anti-sense oligonucleotides (ASO's)-In genetic diseases with "haploinsufficiency" (one bad gene copy) can eliminate nonsense protein from "bad" MRNA, allow good copy to take over production



Do epilepsy patients represent a satisfied market?

- In one word, No!
- Many issues with existing ASMs
- 1/3 continue to have seizures
- 1/3 (by estimation) have dose-related side effects
- No disease modifying treatments

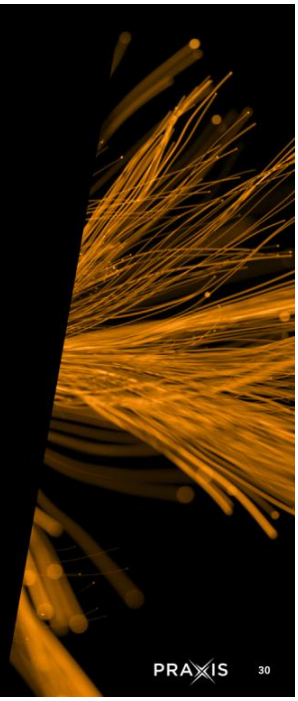
Do neurologists treating epilepsy patients represent a satisfied market?

- In a word, No!
- All but 3 of the new ASMs either:
  - require long titration with complex instructions

  or
  - Have complicated pharmacokinetic interactions
- Many patients continue to have seizures
- Many ASMs have potential for life-threatening interaction
- Co-morbidities such as depression, cognitive dysfunction not addressed

Praxis Epilepsy Innovation Strategy

Steve Petrou, Co-founder and CSO

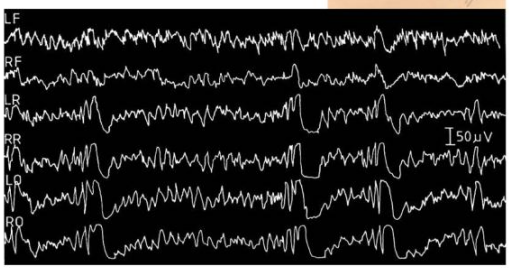


WHY EPILEPSY?
WHY NOW?

Our understanding of the genetics of epilepsy has come a long way in the eighty years since Lennox

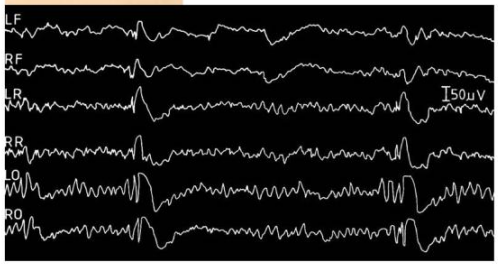
Carolyn

- 16 yrs – early morning tonic clonic seizures, myoclonus
- 23 yrs-psychosis



Eleanor

- 17 yrs – early morning tonic clonic seizures, myoclonus
- 22 yrs-psychosis



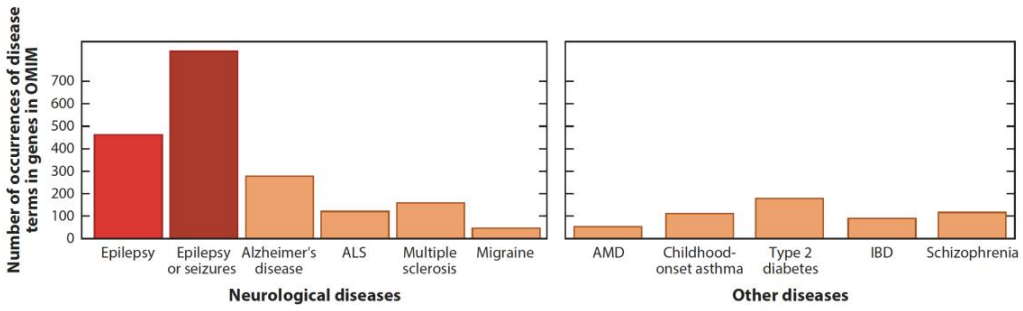
Lennox series (studied 1941)

Essentially all neurological disorders have complex genetic inheritance

Very common	Migraine, Depression
Common	**Epilepsy**, Autism, Schizophrenia, Alzheimer's Disease
Not common	Multiple Sclerosis, Motor Neuron Disease etc.

What distinguishes epilepsy, if anything?

Today, the field has an outsized understanding of epilepsy genetics relative to other CNS (and non-CNS) diseases



OMIM: *Online Mendelian Inheritance in Man ; a catalog of human genes and genetic disorders*

Perucca et al. Annu Rev Genomics Hum Genet 2020

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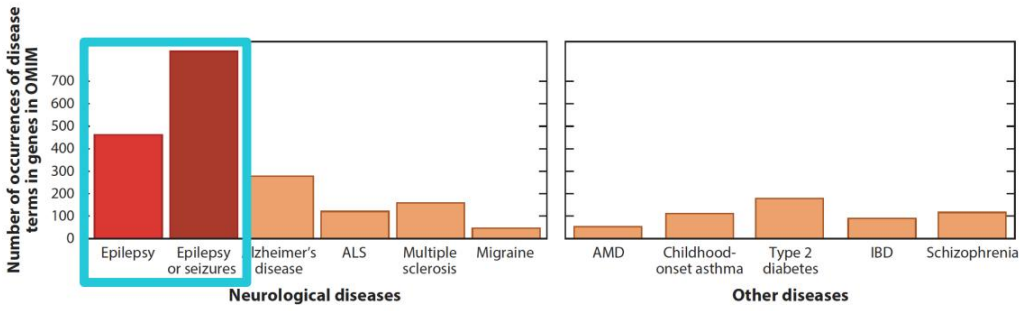
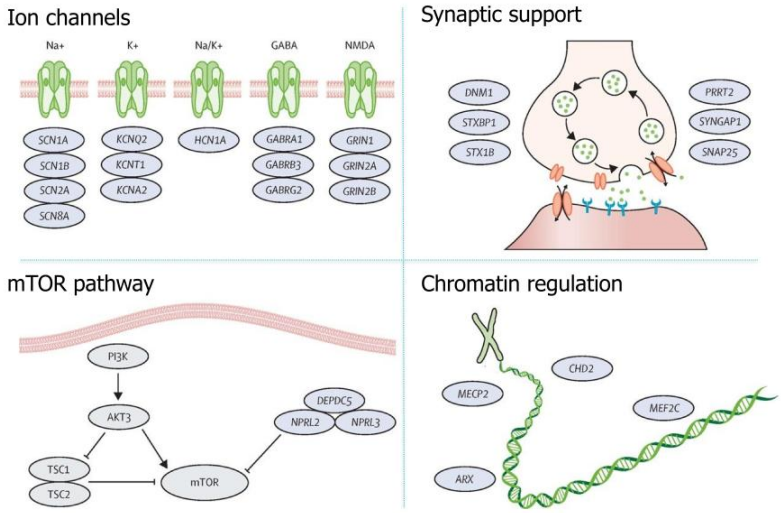


OMIM: *Online Mendelian Inheritance in Man ; a catalog of human genes and genetic disorders*

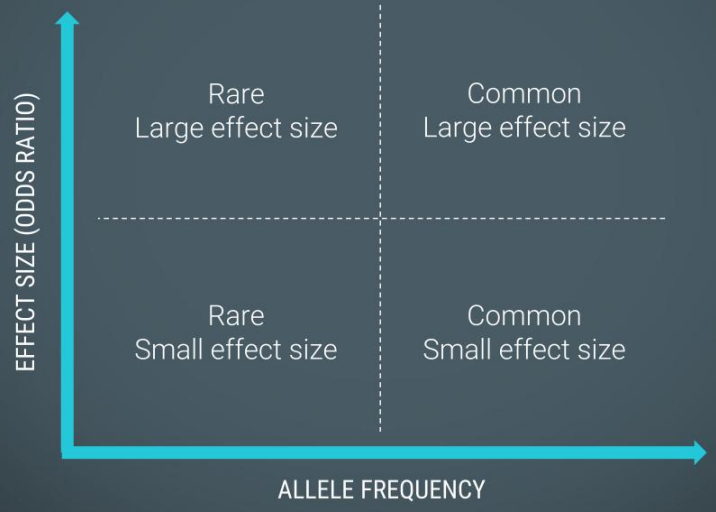
Perucca et al. Annu Rev Genomics Hum Genet 2020

Classes of genes identified in genetic epilepsy are critical to other neurological disorders

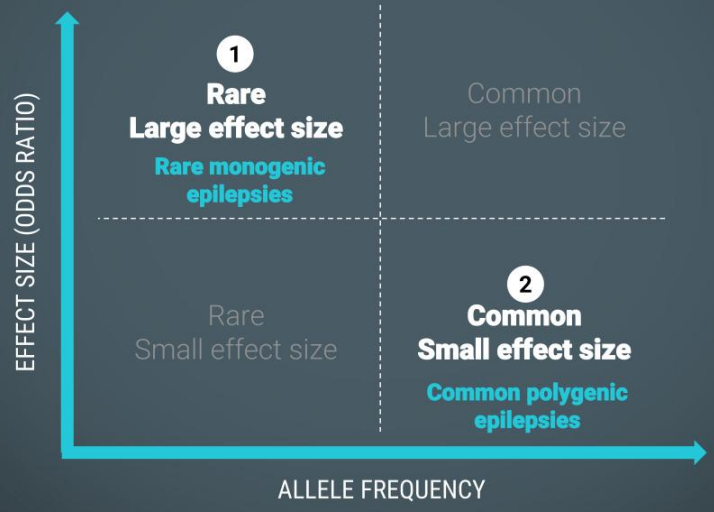


Adapted from Ellis CA, Petrovski S, Berkovic SF. Epilepsy genetics: clinical impacts and biological insights, The Lancet Neurology, Volume 19, Issue 1, 2020, Pages 93-100

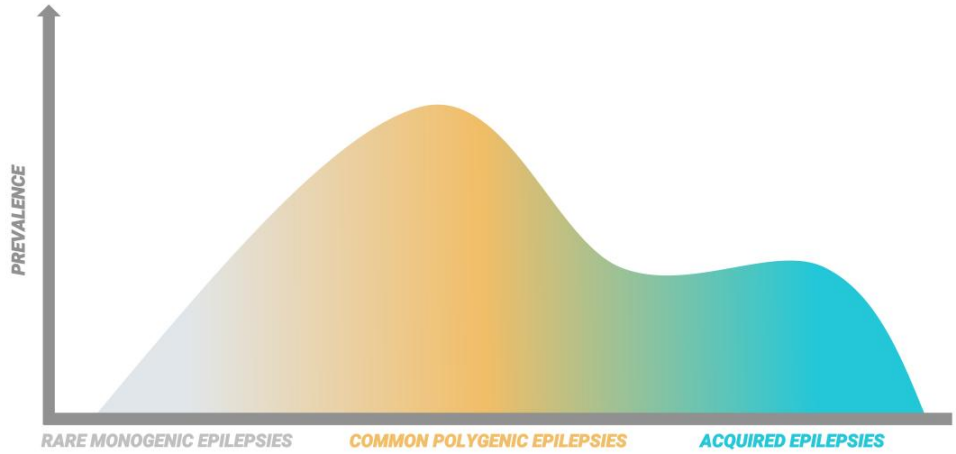
Framework for evaluating each epilepsy gene and new opportunities for therapy development



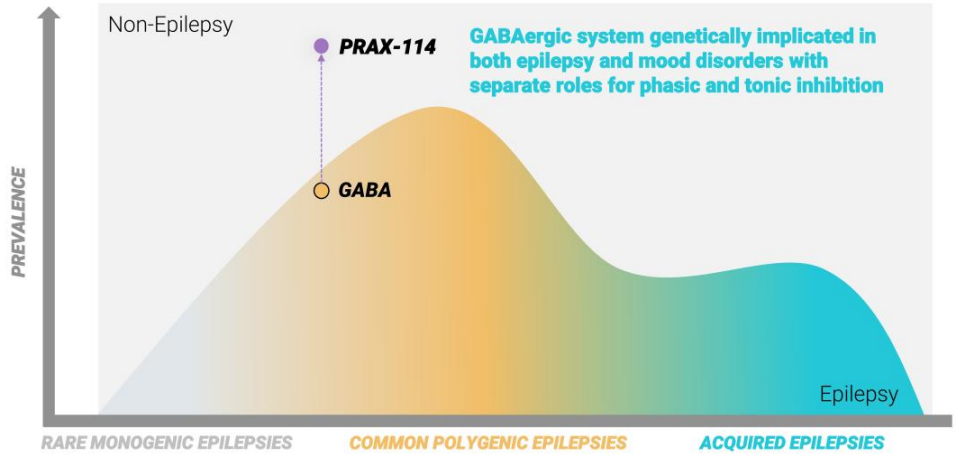
The majority of epilepsy-causing variants fall within these two quadrants



Current understanding of the landscape of genetic and acquired epilepsies

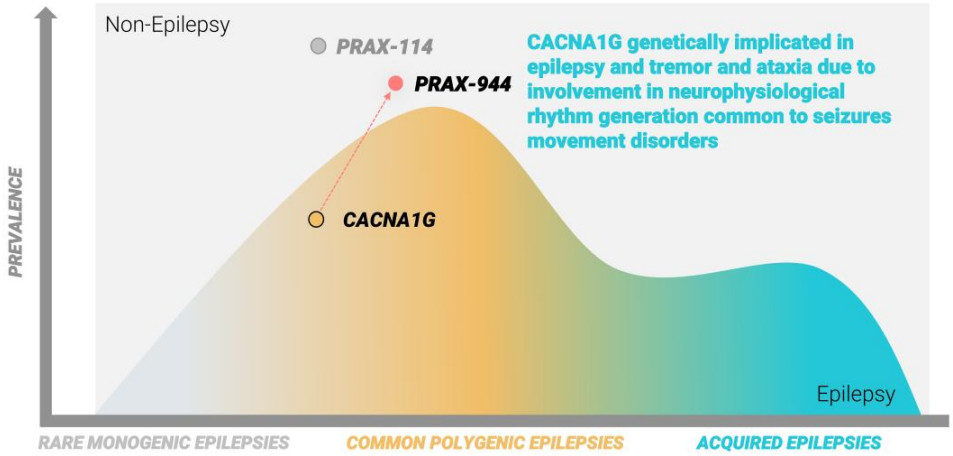


Epilepsy genetics guiding the Praxis portfolio build



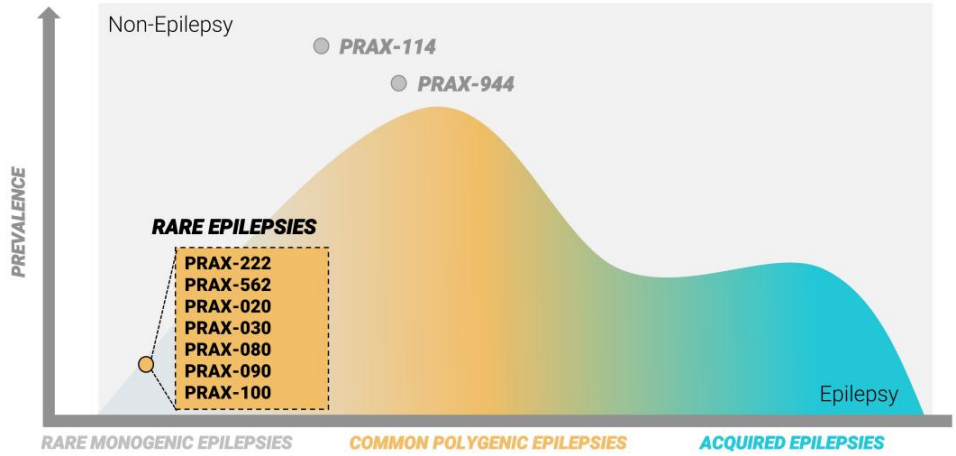
Prevalence relative; not plotted to scale

Epilepsy genetics guiding the Praxis portfolio build



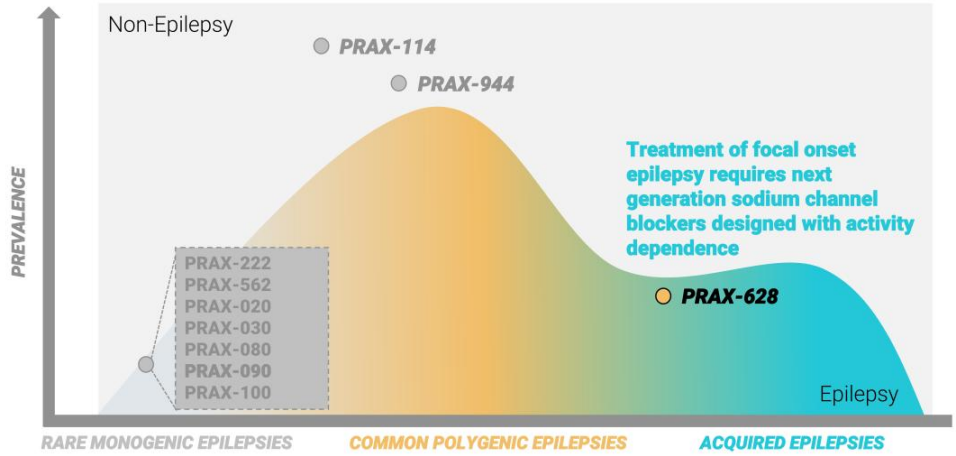
Prevalence relative; not plotted to scale

Epilepsy genetics guiding the Praxis portfolio build



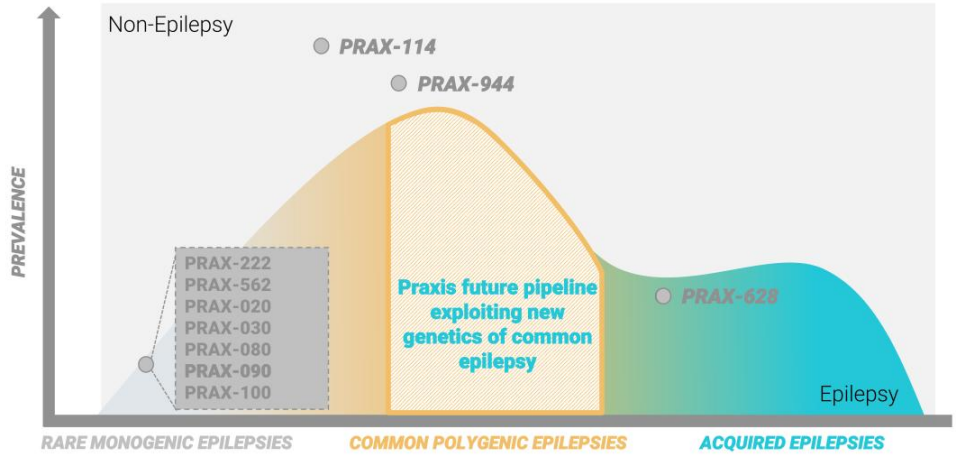
Prevalence relative; not plotted to scale

Epilepsy genetics guiding the Praxis portfolio build



Prevalence relative; not plotted to scale

Praxis targeting the largest and untapped segment



Prevalence relative; not plotted to scale

These three imperatives guide our epilepsy portfolio build

Focus directly on underlying genetic defects in rare epilepsy

- **PRAX-222*** *ASO*
- **PRAX-020** *SMALL MOLECULE*
- **PRAX-080*** *ASO*
- **PRAX-090*** *ASO*
- **PRAX-100 *** *ASO*
- **PRAX-030** *SMALL MOLECULE*

Focus on implicated genes in common diseases

- **PRAX-114** *SMALL MOLECULE*
- **PRAX-944** *SMALL MOLECULE*
- **TARGET ID BY POLYGENIC RISK VARIANTS** *SMALL MOLECULE*

Focus on nodes of pathophysiological convergence informed by genetics

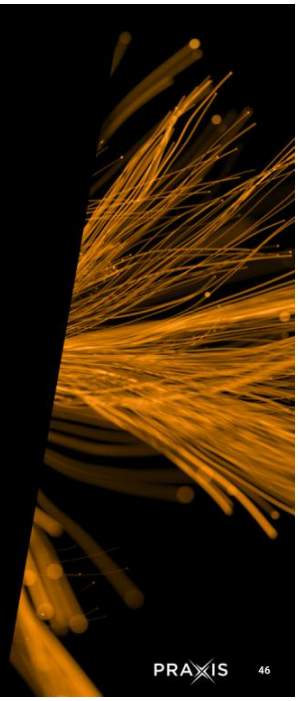
- **PRAX-562** *SMALL MOLECULE*
- **PRAX-628** *SMALL MOLECULE*

TARGETS IDENTIFIED THROUGH **GENETICS**

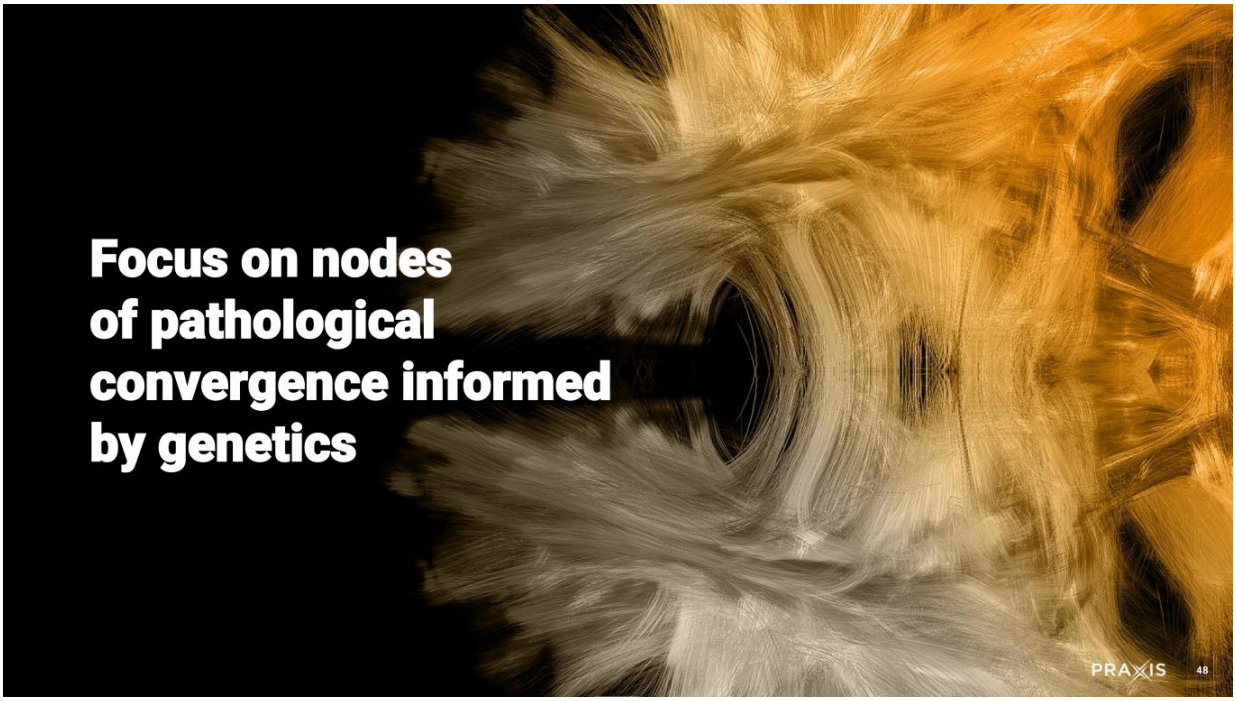
*PRAX-222 in collaboration with Ionis. PCDH19 (PRAX-080), SYNGAP1(PRAX-090), SCN2A-LOF(PRAX-100) ASOs are a collaboration with The Florey Institute of Neuroscience and Mental Health.

Our Science in Action

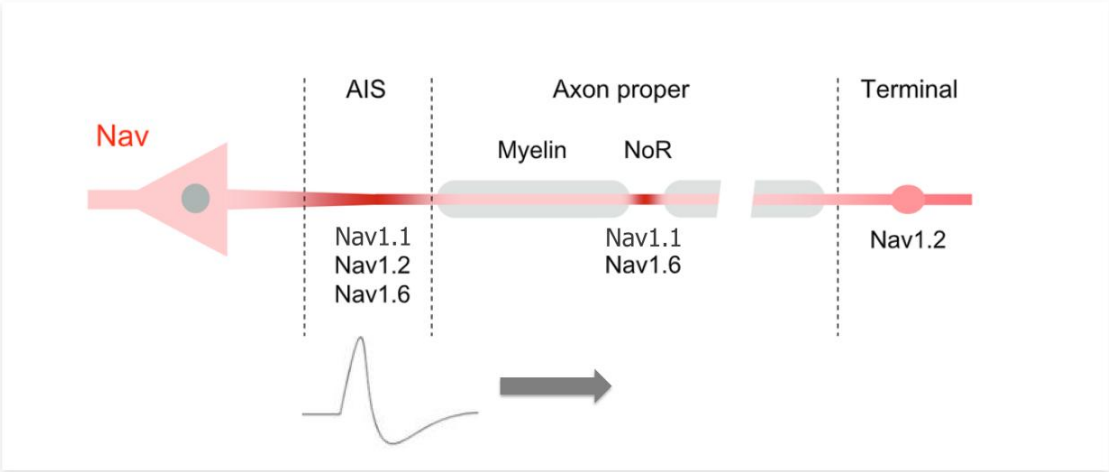
Steve Petrou, Co-founder and CSO



Leveraging our understanding of genetics to discover and develop therapies enabled by a translational toolkit and strategic collaborations

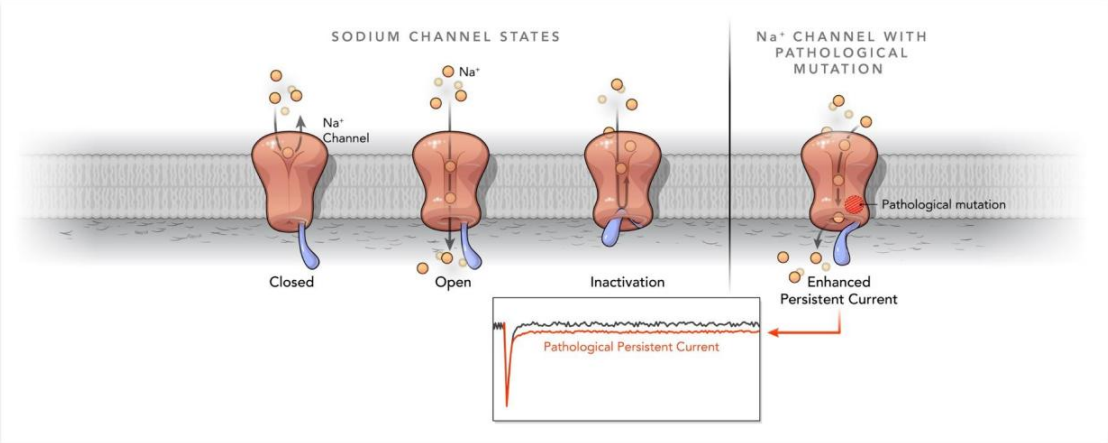

Focus on nodes
of pathological
convergence informed
by genetics
PRAXIS
48

Voltage-gated sodium channels (NaV) are the key arbiters of neuronal excitability in the CNS



Debanne, D., Campanac, E., Bialowas, A., Carlier, E. and Alcaraz, G., 2011. Axon physiology. Physiological reviews, 91(2), pp.555-602.

Persistent sodium current (I_{Na}) is a critical driver of pathological hyperexcitability in the CNS disorders

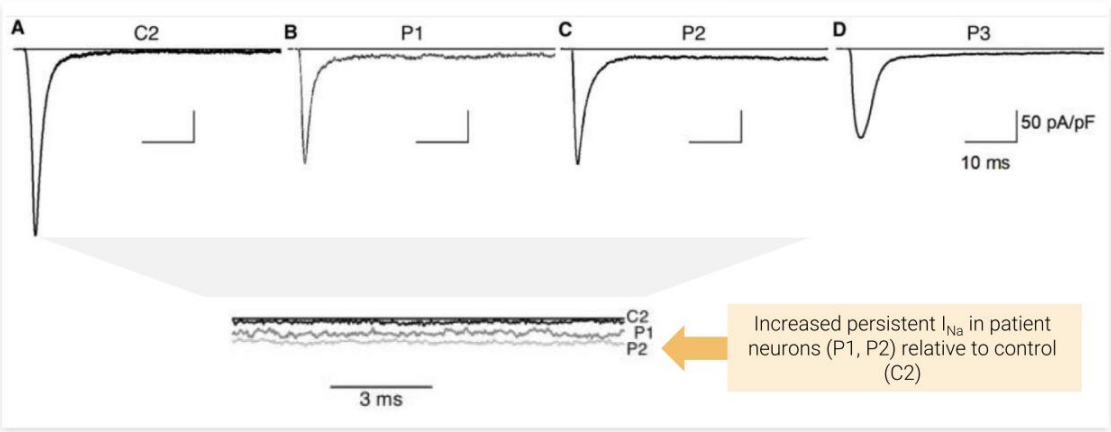


SCN8A GoF DEE patients have elevated persistent I_{Na}


BRAIN
A JOURNAL OF NEUROLOGY

Variant-specific changes in persistent or resurgent sodium current in SCN8A-related epilepsy patient-derived neurons

Andrew M. Tidball,[1] Luis F. Lopez-Santiago,[2] Yukun Yuan,[2] Trevor W. Glenn,[1] Joshua L. Margolis,[1] J. Clayton Walker,[1] Emma G. Kilbane,[1] Christopher A. Miller,[1] E. Martina Bebin,[4,5] M. Scott Perry,[4] Lori L. Isom[1,2,3] and Jack M. Parent[1,6]



Increased persistent I_{Na} in patient neurons (P1, P2) relative to control (C2)

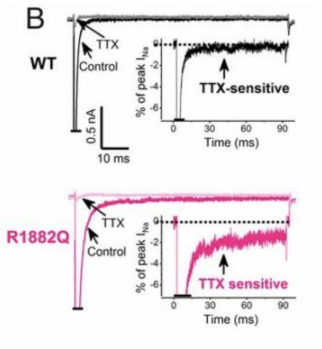
SCN2A GoF DEE patients have elevated persistent I_{Na}

PNAS

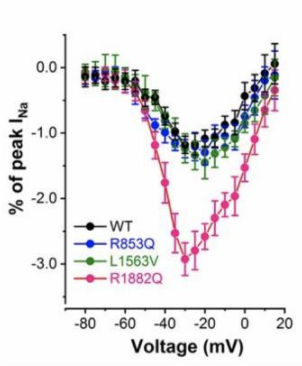
Dynamic action potential clamp predicts functional separation in mild familial and severe de novo forms of *SCN2A* epilepsy

Géza Berecki[a,1], Katherine B. Howell[b,c,d], Yadeesha H. Deerasooriya[a], Maria Roberta Cilio[f,g], Megan K. Oliva[a], David Kaplan[a], Ingrid E. Scheffer[a,b,e,h], Samuel F. Berkovic[b], and Steven Petrou[a,i,j,k,1]

[a]Ion Channels and Disease Group, The Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, VIC 3052, Australia; [b]Department of Neurology, Royal Children's Hospital, Parkville, VIC 3052, Australia; [c]Department of Pediatrics, University of Melbourne, Parkville, VIC Australia; [d]Murdoch Children's Research Institute, Parkville, VIC 3052, Australia; [e]Department of Mechanical Engineering, University of Melbourne

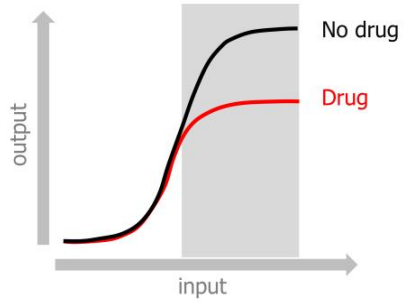


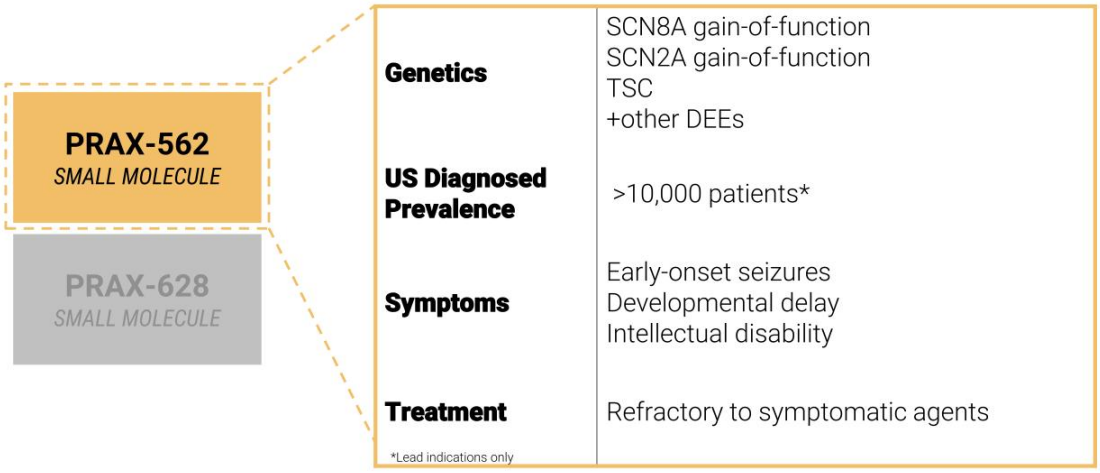
Increased persistent I_{Na} in disease neurons relative to WT



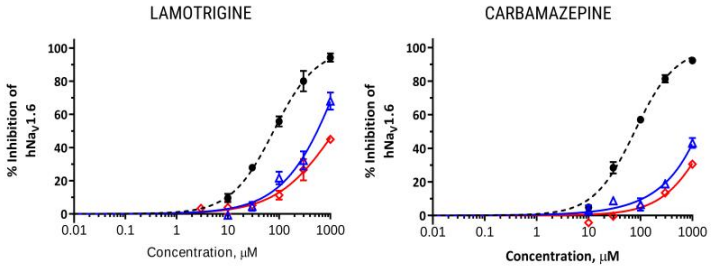
“Next generation” sodium channel blocker program at Praxis

- Praxis sodium channel “functional” selectivity drug discovery program
- Design molecules with *in vitro* profile including
  - preference for persistent current
  - rapid binding and unbinding kinetics
- Goal is to selectively dampen hyperexcitable neuronal activity sparing physiological activity to enhance tolerability and allow higher dosing for better efficacy




PRAX-562
SMALL MOLECULE
PRAX-628
SMALL MOLECULE
Genetics
SCN8A gain-of-function
SCN2A gain-of-function
TSC
+other DEEs
US Diagnosed Prevalence
>10,000 patients*
Symptoms
Early-onset seizures
Developmental delay
Intellectual disability
Treatment
Refractory to symptomatic agents
*Lead indications only

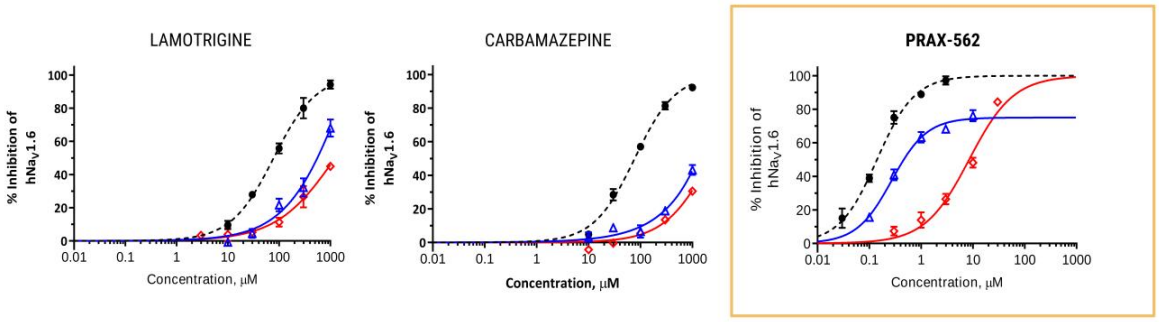
Standard Na_V blockers do not preferentially target disease-state hyperexcitability, driving limiting side effect profile



"Na_V Fingerprint"
Persistent I_{Na} Inhibition
Peak I_{Na}, UDV-10Hz (Disease-State Dependence) Inhibition
Peak I_{Na}, Tonic Block Inhibition

Source: Praxis data on file

We discovered PRAX-562 as a more potent and selective persistent I_{Na} blocker, more disease-state selective, with a wider therapeutic window

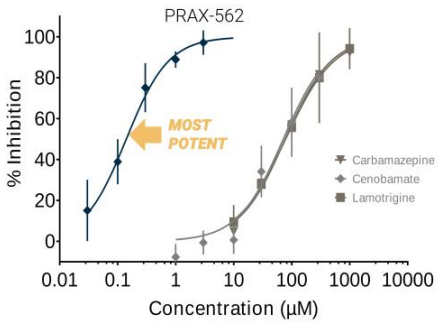


"Na_V Fingerprint"
Persistent I_{Na} Inhibition
Peak I_{Na}, UDV-10Hz (Disease-State Dependence) Inhibition
Peak I_{Na}, Tonic Block Inhibition

Source: Praxis data on file

Broader in vitro panel indicates PRAX-562 has best-in-class preferences

% INHIBITION OF $hNa_V1.6$ PERSISTENT I_{Na} (SAME DATA AS ON PRIOR SLIDE)

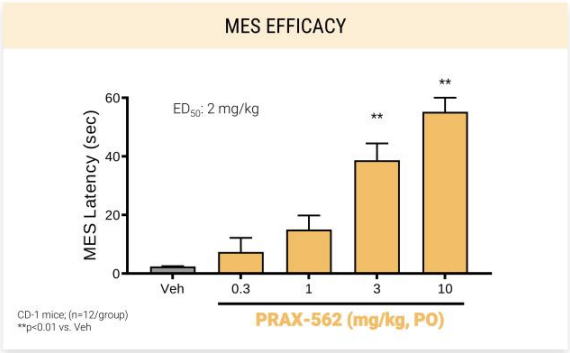


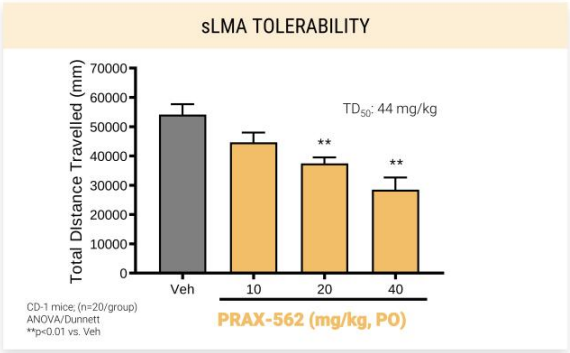
COMPARISON OF POTENCY AND SELECTIVITY

	Persistent I_{Na} IC50 (nM)	Ratio of persistent to peak inhibition
PRAX-562	***141***	***60*** ← ***MOST SELECTIVE***
Carbamazepine	77,520	30
Cenobamate	73,263	23
Lidocaine	68,230	19
Lamotrigine	78,530	16
Vixotrigene (BIIB074)	3,676	14
Lacosamide	833,100	n/a*
Valproic Acid	<10% @ 1 mM	No inhibition

*solubility concerns

Our mechanistic hypothesis translates to a wide therapeutic index in vivo



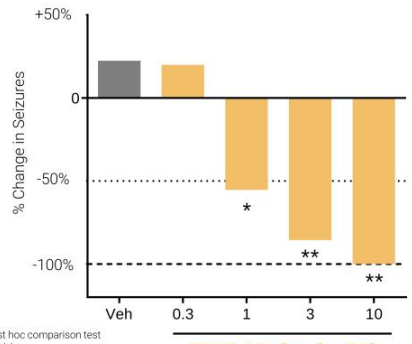


Molecule	Plasma Therapeutic Index
PRAX-562	17.2x

Therapeutic Index (TI) = TC50 / EC50

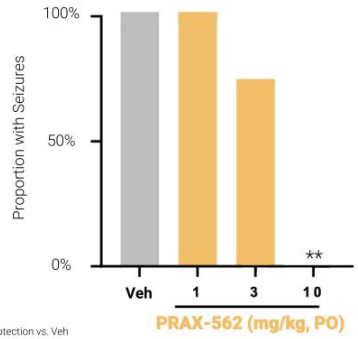
PRAX-562 completely blocks seizures in SCN2A and SCN8A GoF mutation mouse models

IN VIVO POC IN SCN2A SPONTAEOUS SEIZURES[1]



Sidack's post hoc comparison test
*p<0.05 vs. Veh
**p<0.001 vs. Veh

IN VIVO POC IN SCN8A AUDIOGENIC EVOKED SEIZURES[2]

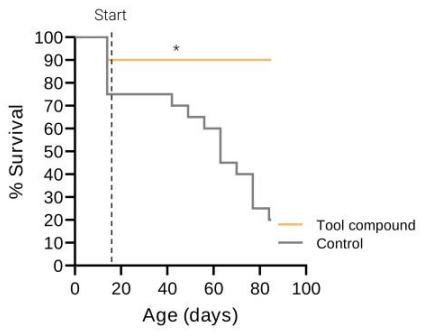


**Significant protection vs. Veh
χ^2_2 = 16.0, Fisher's p = 0.0002

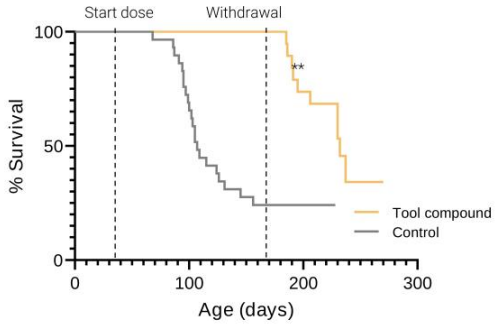
[1] PRAX-562 inhibition of spontaneous seizures in Q54 GoF mice.
[2] PRAX-562 inhibition of audiogenic seizures in N1768D D/+ mice

Modulating persistent current increases survival in the same genetic models

IMPROVES SCN2A GoF SURVIVAL[1]



IMPROVES SCN8A GoF SURVIVAL[2]

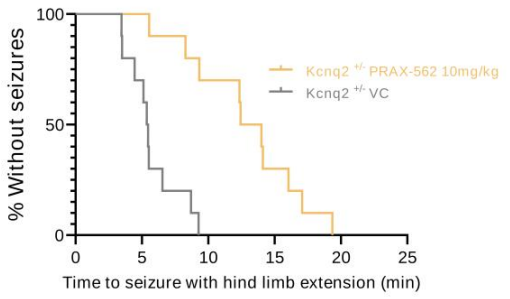


Data indicates PRAX-562 mechanism is disease modifying

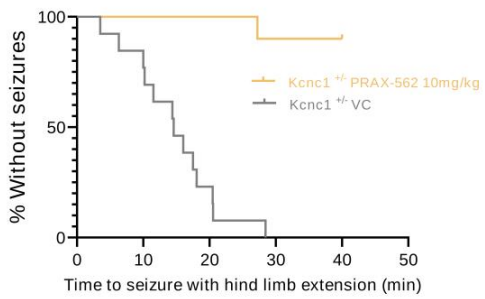
*p<0.005; n=18-20 per group; Cox proportional hazards model
**p<0.001; n=29-32; Mantel-Cox log-rank test
1)Q54 GoF mice.
2)N1768D D/+ mice.

PRAX-562 is highly efficacious in KCNQ2 and KCNC1 DEE models

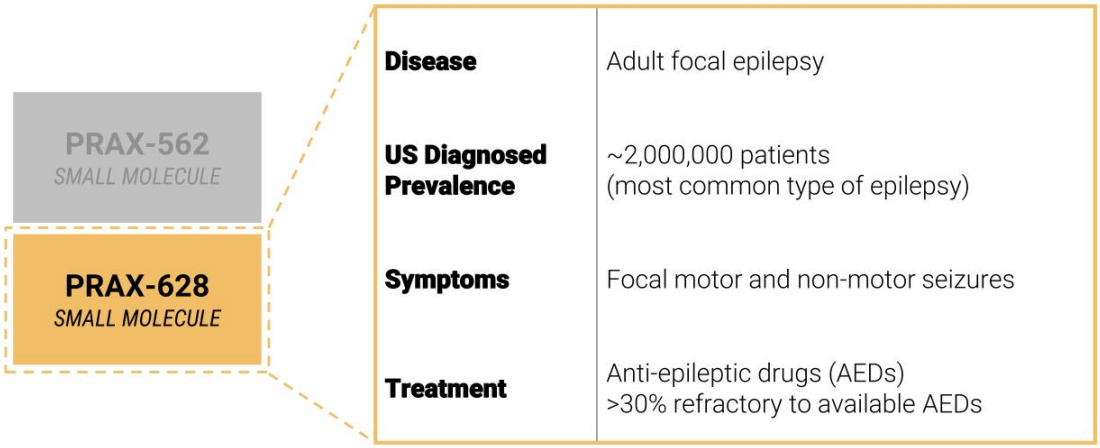
KCNQ2 K556E PTZ SEIZURE MODEL[1]



KCNC1 R320H PTZ SEIZURE MODEL[2]



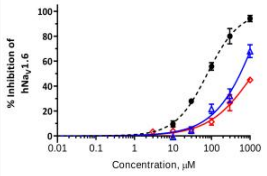
[1]WT and KCNQ2 +/K556E mice were treated with PRAX-562 at 10 mg/kg or vehicle 1-hr prior to PTZ injection (100 mg/kg s.c.); N=10 per group
[2]N=10-14 per group
Source: Praxis data on file.


PRAX-562
SMALL MOLECULE
PRAX-628
SMALL MOLECULE
Disease
Adult focal epilepsy
US Diagnosed Prevalence
~2,000,000 patients
(most common type of epilepsy)
Symptoms
Focal motor and non-motor seizures
Treatment
Anti-epileptic drugs (AEDs)
>30% refractory to available AEDs

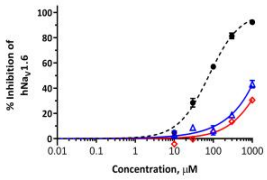
Our internal discovery effort focused on developing a Na_V blocker with high disease state dependence and wide therapeutic index

LOW DISEASE-STATE DEPENDENCE
THIN THERAPEUTIC INDEX

LAMOTRIGINE



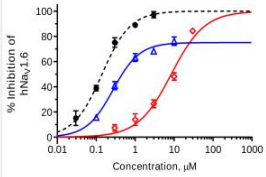
CARBAMAZEPINE



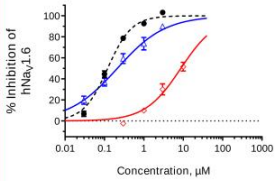
"Na_V Fingerprint"
Persistent I_{NaL} Inhibition
Peak I_{NaV} UDV-10Hz (Disease-State Dependence) Inhibition
Peak I_{NaV} Tonic Block Inhibition

HIGH DISEASE-STATE DEPENDENCE
WIDE THERAPEUTIC INDEX

PRAX-562

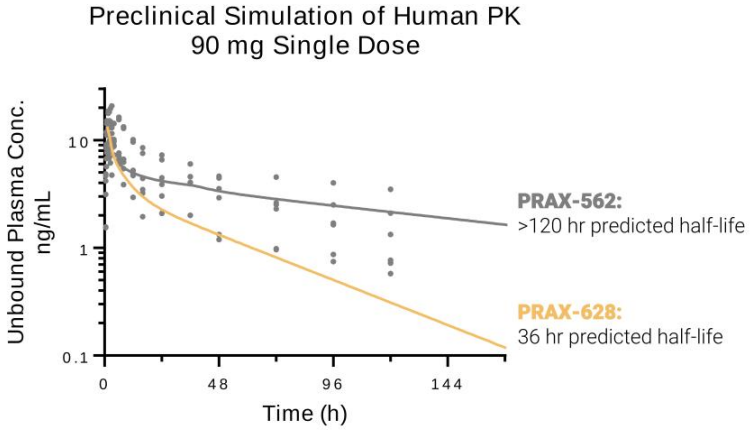


PRAX-628



Source: Praxis data on file

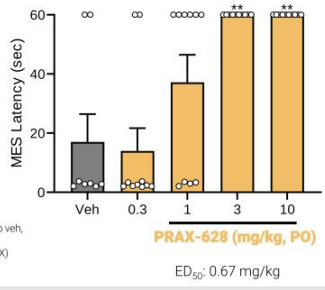
PRAX-628 has unique pharmacological properties that enable acute dosing in a broader patient population



Modeling 90mg, single dose of PRAX-628 or PRAX-562. Preclinical simulation recapitulates PRAX-562 clinical data.

PRAX-628 protects mice from seizures with a wide therapeutic window

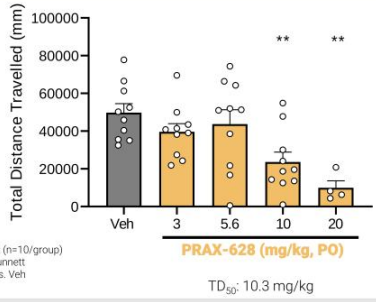
MES EFFICACY



CD-1 mice; (n=8/group veh, n=10 PRAX)
ANOVA/Dunnett (PRAX)
**p<0.01 vs. Veh

ED_{50}: 0.67 mg/kg

sLMA TOLERABILITY



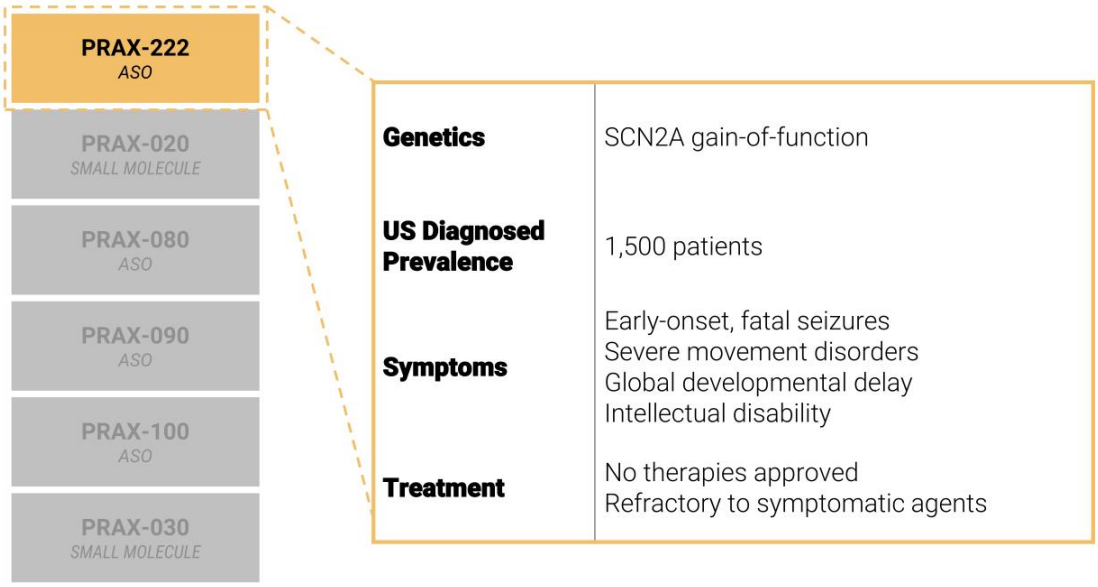
CD-1 mice; (n=10/group)
ANOVA/Dunnett
**p<0.01 vs. Veh

TD_{50}: 10.3 mg/kg

Molecule	Plasma Therapeutic Index
PRAX-628	16.7x

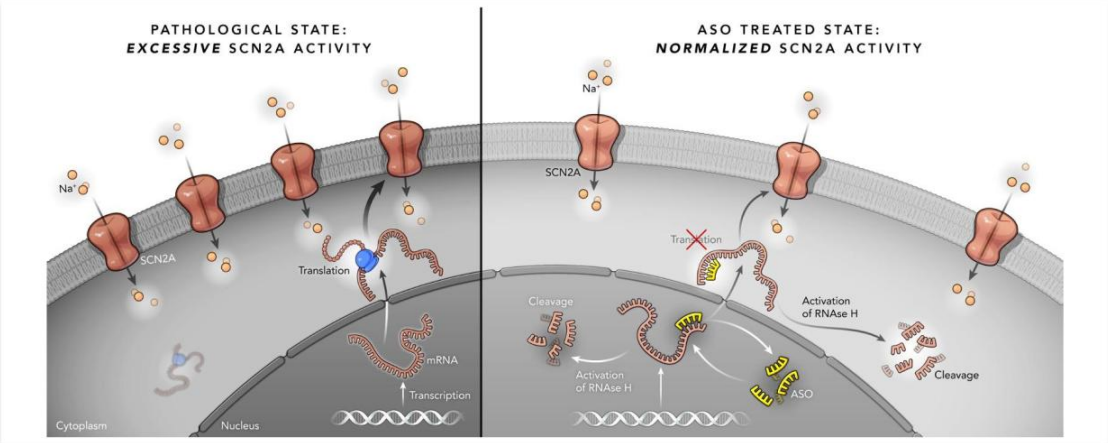
Therapeutic Index (TI) = TC_{50} / EC_{50}


Focus directly on underlying genetic defects in rare epilepsy
PRAXIS
66



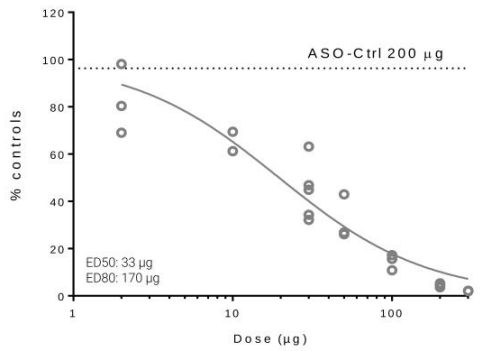
Note: PRAX-222 in collaboration with Ionis. PCDH19 (PRAX-080), SYNGAP1(PRAX-090), SCN2A-LOF(PRAX-100) ASOs are a collaboration with The Florey Institute of Neuroscience and Mental Health.

PRAX-222 is an ASO designed to down-regulate SCN2A expression in patients with gain-of-function mutation

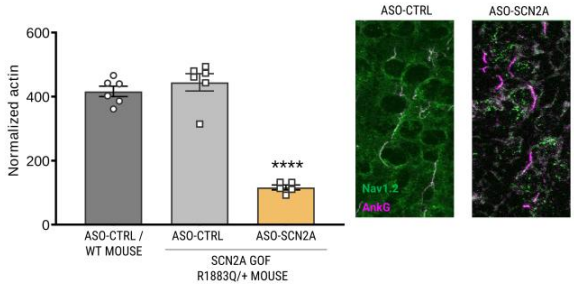


In vitro, PRAX-222 down-regulates both mRNA and protein

SCN2A mRNA KNOCKDOWN

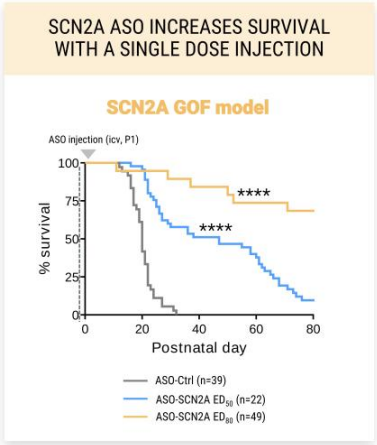


SCN2A PROTEIN KNOCKDOWN



ASOs were administered at P30 and brains were collected 14 days post-ICV for qPCR analysis

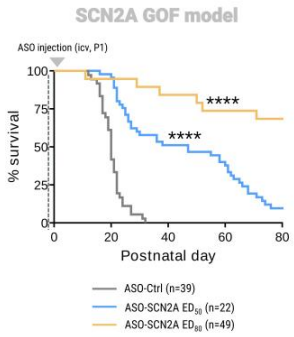
A single dose of PRAX-222 increases survival well beyond standard of care in SCN2A GoF mice



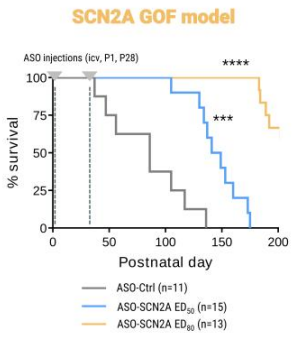
***p<0.001
****p<0.0001
All experiments conducted with SCN2A R1882Q mouse model

A second dose of PRAX-222 significantly extends survival of SCN2A GoF mice

SCN2A ASO INCREASES SURVIVAL WITH A SINGLE DOSE INJECTION



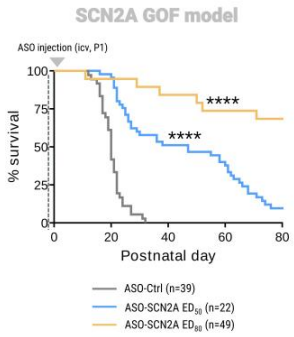
RE-DOSING SIGNIFICANTLY EXTENDS SURVIVAL



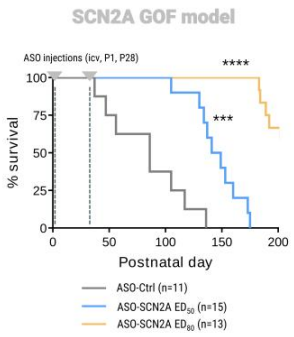
***p<0.001
****p<0.0001
All experiments conducted with SCN2A R1882Q mouse model

PRAX-222 also extends survival of SCN2A GoF mice if first administered later in life, well after disease onset

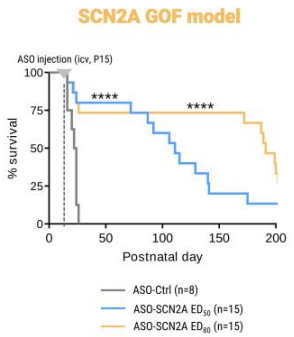
SCN2A ASO INCREASES SURVIVAL WITH A SINGLE DOSE INJECTION



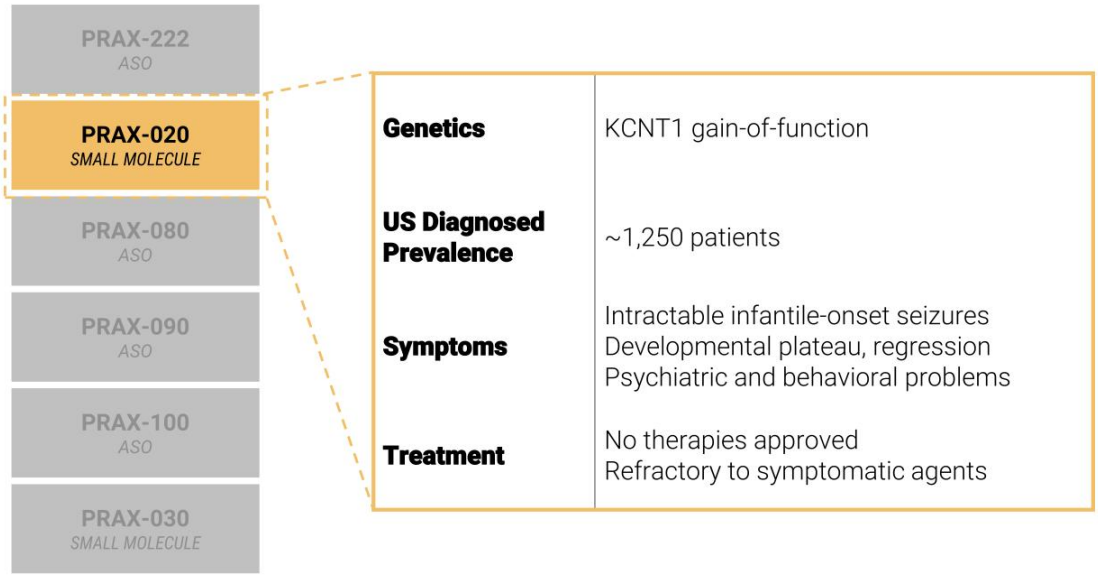
RE-DOSING SIGNIFICANTLY EXTENDS SURVIVAL



ADMINISTRATION POST-DISEASE ONSET ALSO EXTENDS SURVIVAL

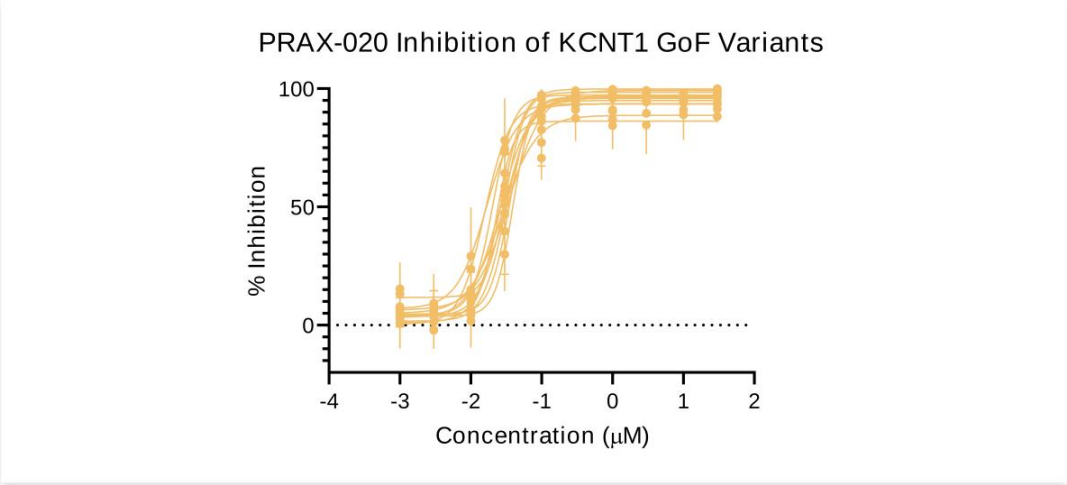


***p<0.001
****p<0.0001
All experiments conducted with SCN2A R1882Q mouse model



Note: PRAX-222 in collaboration with Ionis. PCDH19 (PRAX-080), SYNGAP1(PRAX-090), SCN2A-LOF(PRAX-100) ASOs are a collaboration with The Florey Institute of Neuroscience and Mental Health.

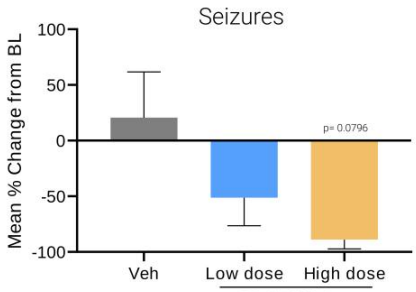
PRAX-020 is a small molecule designed to selectively inhibit KCNT1 GoF variants



Source: Praxis data on file.

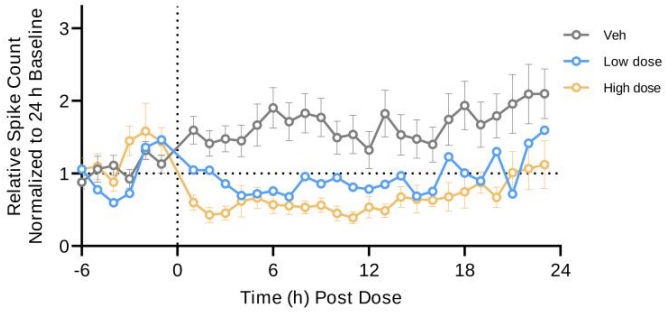
PRAX-020 eliminates seizures in KCNT1 transgenic mice and suppresses interictal spikes

PRAX-020 REDUCES SEIZURES*



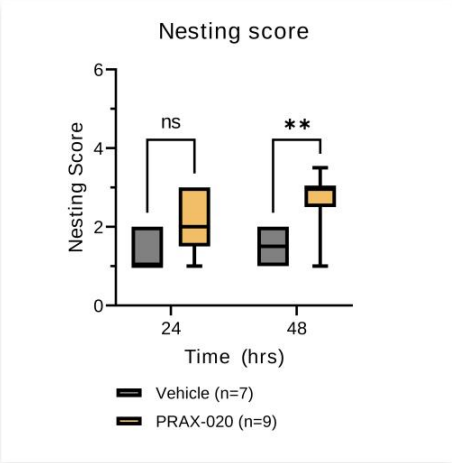
CD-1 mice; (n=12 veh, n=5-7/group PRAX)
ANOVA/Dunnett (vs. veh)

...AND DECREASES INTERICTAL SPIKE FREQUENCY



*In 24 hours
Source: Praxis data on file.

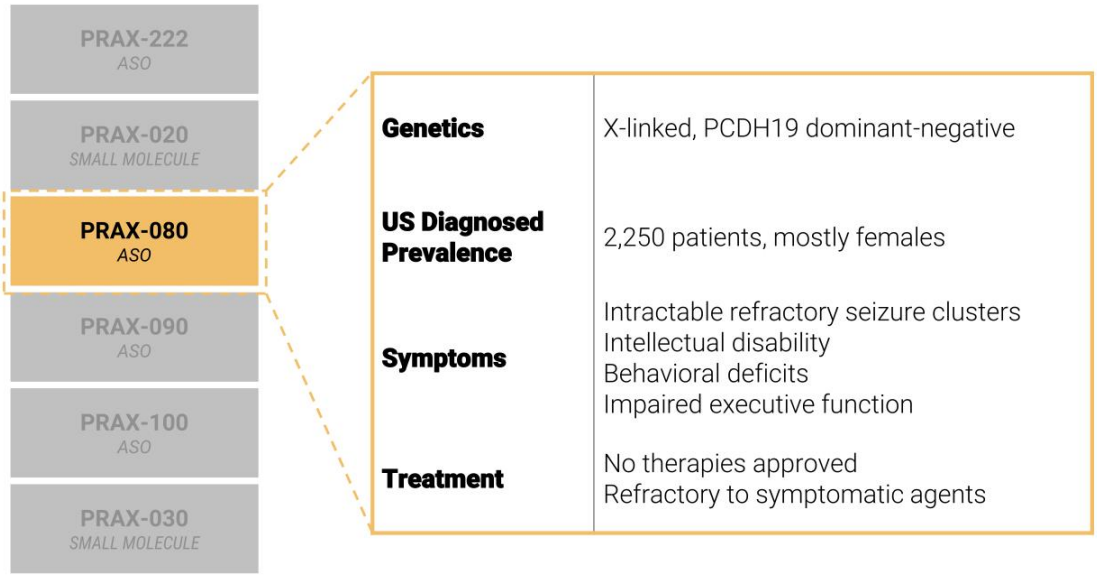
PRAX-020 KCNT1 inhibition may translate to rescue of behavioral and cognitive phenotype



No nesting

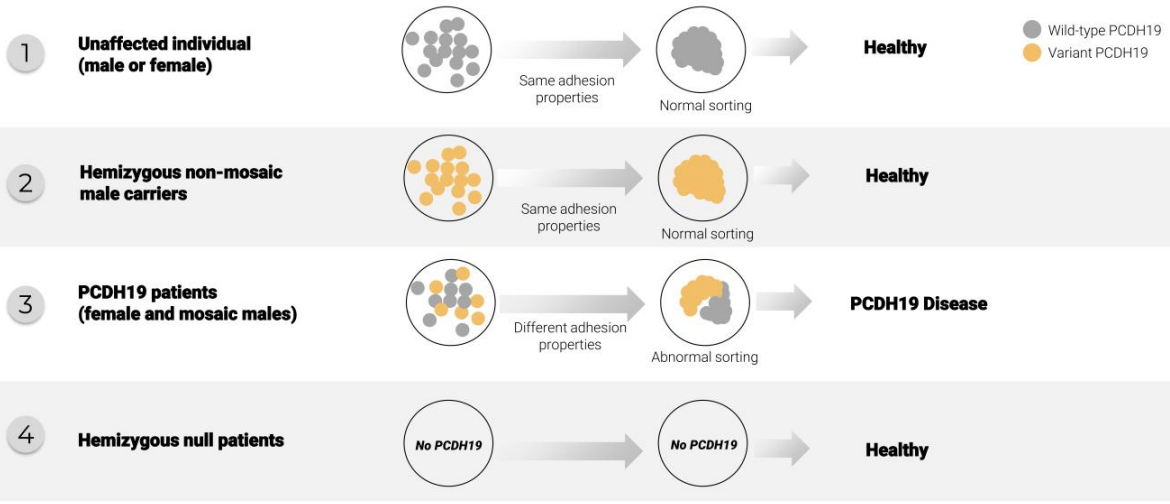
Nesting

Source: Praxis data on file.



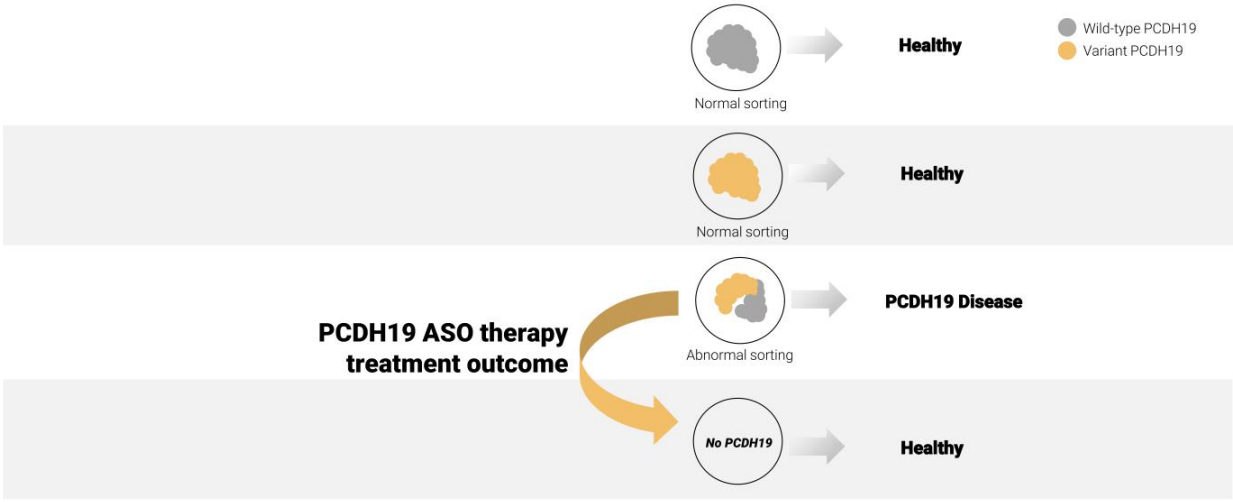
Note: PRAX-222 in collaboration with Ionis. PCDH19 (PRAX-080), SYNGAP1(PRAX-090), SCN2A-LOF(PRAX-100) ASOs are a collaboration with The Florey Institute of Neuroscience and Mental Health.

In PCDH19, hemizygous null patients and hemizygous non-mosaic male carriers are asymptomatic and preserve ability to form normal neuron networks



Source: Beyond the Ion Channel; Depienne C. et al *PLOS Genetics* (2009)

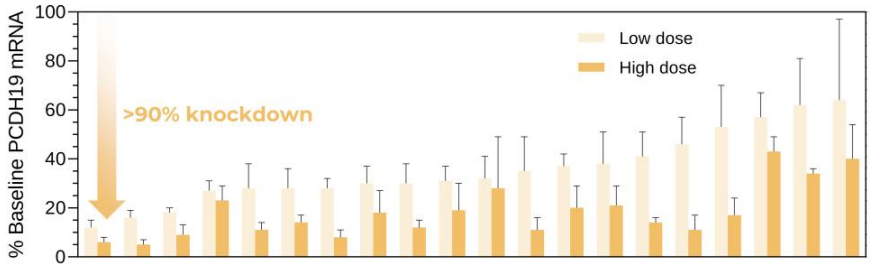
We aim to knock down PCDH19 to restore cell-cell adhesion and rescue phenotype



Source: Beyond the Ion Channel; Depienne C. et al *PLOS Genetics* (2009)

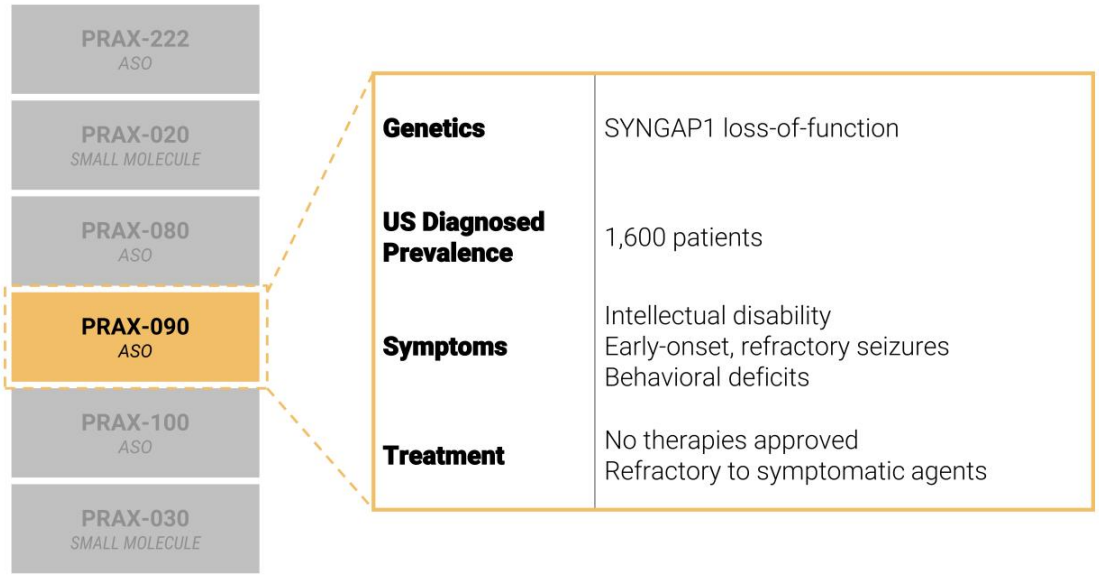
Hits identified achieve >90% in vitro knockdown PCDH19 mRNA

PCDH19 ASO MRNA KNOCKDOWN



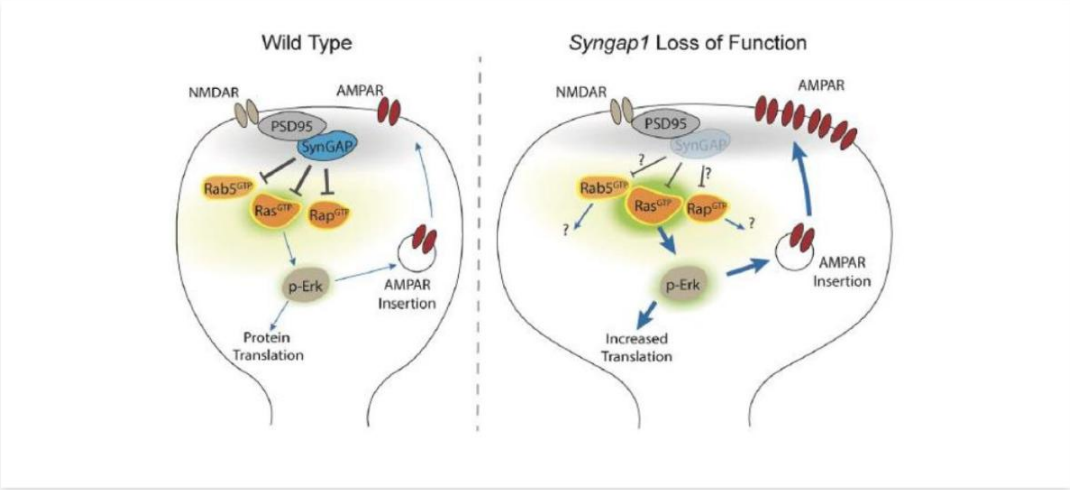
On track to deliver lead candidate in 2023

Source: Data on file.



Note: PRAX-222 in collaboration with Ionis. PCDH19 (PRAX-080), SYNGAP1(PRAX-090), SCN2A-LOF(PRAX-100) ASOs are a collaboration with The Florey Institute of Neuroscience and Mental Health.

SYNGAP1 is a synaptic RAS GTPase activating protein



Source: Weldon, M. et al . Journal of Neurodevelopmental Disorders. (2018)

Re-expression of SYNGAP1 in adult mice improves measures of seizure and memory

eLIFE
elifesciences.org

Re-expression of SynGAP protein in adulthood improves translatable measures of brain function and behavior

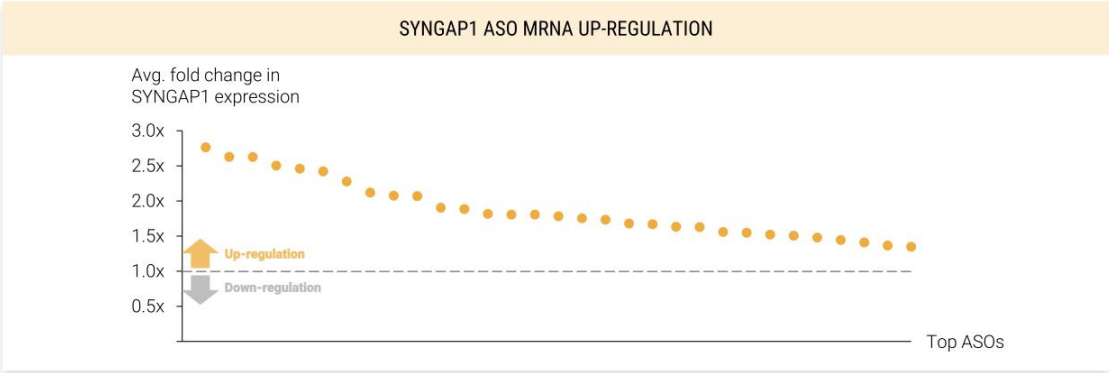
Thomas K Creson[1,2†], Camilo Rojas[1,2†], Ernie Hwaun[3], Thomas Vaissiere[1,2], Murat Kilinc[1,2], Andres Jimenez-Gomez[4,5], Jimmy Lloyd Holder Jr[4,5], Jianrong Tang[4,5], Laura L Colgin[3], Courtney A Miller[1,2], Gavin Rumbaugh[1,2*]

Improvements in:	SYNGAP1 restoration
EEG	✓
Seizures	✓
Memory	✓

SYNGAP1 haploinsufficiency is the cause of disease, so ASO-mediated up-regulation could rescue disease phenotype

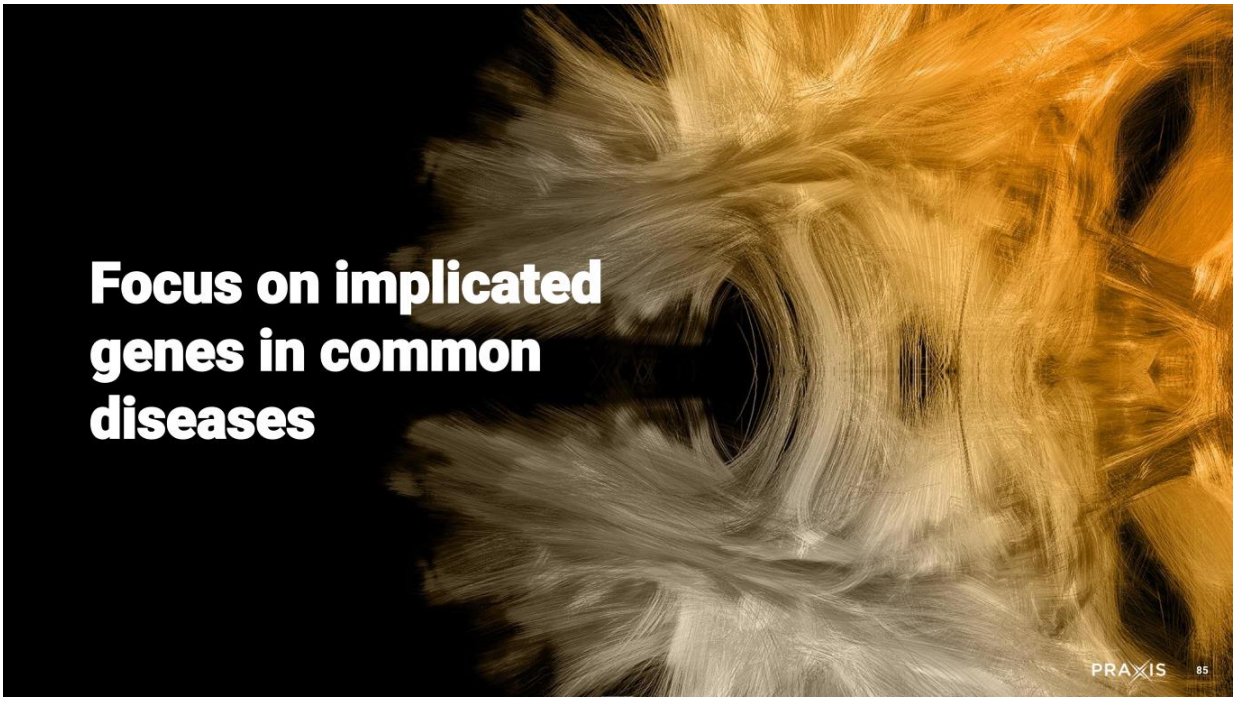
Source: Creson et al., *eLife* (2019)

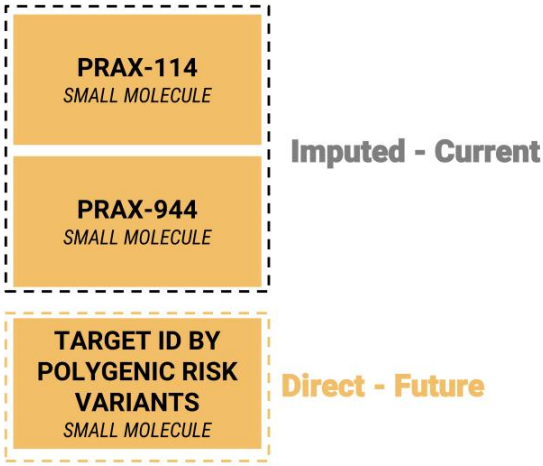
Hits identified achieve approx. 3-fold improvement in SYNGAP1 expression

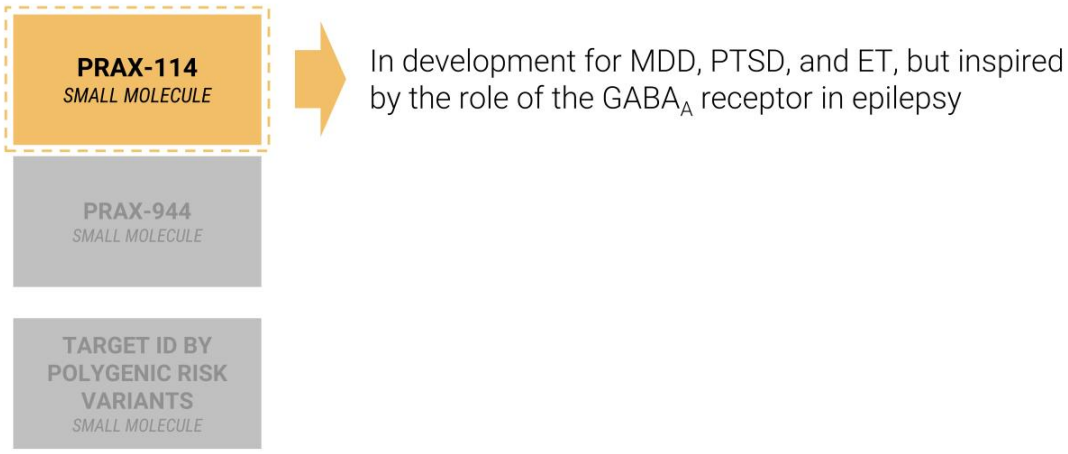


On track to deliver lead candidate in 2023

Source: Data on file.


Focus on implicated genes in common diseases
PRAXIS
85


PRAX-114
SMALL MOLECULE
PRAX-944
SMALL MOLECULE
Imputed - Current
TARGET ID BY POLYGENIC RISK VARIANTS
SMALL MOLECULE
Direct - Future


PRAX-114
SMALL MOLECULE
PRAX-944
SMALL MOLECULE
TARGET ID BY POLYGENIC RISK VARIANTS
SMALL MOLECULE
In development for MDD, PTSD, and ET, but inspired by the role of the $GABA_A$ receptor in epilepsy

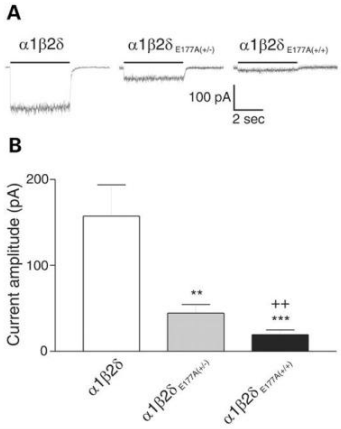
$GABA_A$ receptors with delta (δ) subunit dysfunction give rise to epilepsy

OXFORD JOURNALS
Human Molecular Genetics

Human Molecular Genetics, 2004, Vol. 13, No. 13 **1315–1319**
DOI: 10.1093/hmg/ddh146
Advance Access published on April 28, 2004

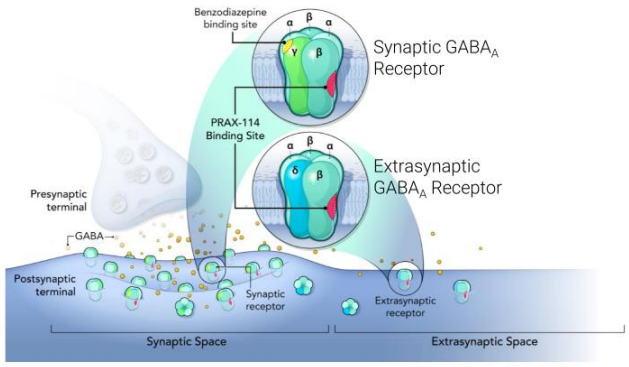
GABRD encoding a protein for extra- or peri-synaptic $GABA_A$ receptors is a susceptibility locus for generalized epilepsies

Leanne M. Dibbens[1,2,*,†], Hua-Jun Feng[4,†], Michaella C. Richards[1], Louise A. Harkin[1,2], Bree L. Hodgson[1], Darren Scott[1], Misty Jenkins[6], Steven Petrou[6], Grant R. Sutherland[1,2], Ingrid E. Scheffer[5], Samuel F. Berkovic[5], Robert L. Macdonald[4] and John C. Mulley[1,3]



Source: Dibbens, L.M. *et al. Human Mol Genet.* (2004)

PRAX-114 preferentially potentiates the delta (δ) subunit of the $GABA_A$ receptor, which sits in the extrasynaptic space



GABA: Gamma-aminobutyric acid; $GABA_A$ PAMs: $GABA_A$ receptor positive allosteric modulators

PRAX-114 shows 10.5-fold greater potentiation of extrasynaptic than synaptic $GABA_A$ receptors

		Potentiation		Fold Potentiation
	Dosing	$\alpha_4\beta_3\delta$ %*	$\alpha_1\beta_2\gamma_2$ %	$\alpha_4\beta_3\delta$/ $\alpha_1\beta_2\gamma_2$
PRAX-114	Oral	300%	29%	10.5
Zuranolone	Oral	300%	117%	2.6
Ganaxolone	IV, Oral	300%	794%	0.4
Zulresso	IV	300%	306%	1.0

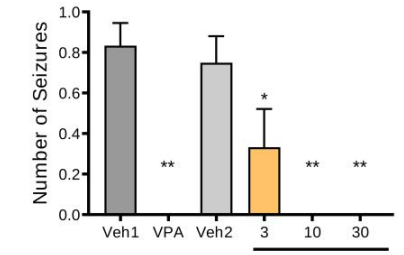
$\alpha_4\beta_3\delta$: extrasynaptic $GABA_A$ receptor $\alpha1\beta_2\gamma_2$: synaptic $GABA_A$ receptor

* Equivalent of full activation by GABA

Source: Dibbens, L.M. *et al. Human Mol Genet.* (2004); Praxis data on file

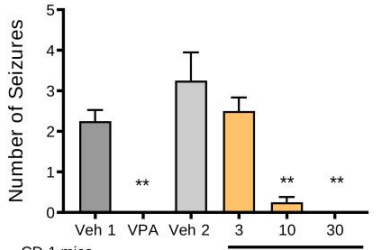
PRAX-114 has demonstrated anti-seizure effect in preclinical epilepsy models

PTZ-INDUCED TONIC SEIZURES



CD-1 mice
(n=12/group)
t-test (VPA)
ANOVA/Dunn (PRAX)
*p<0.05 vs. Veh
**p<0.01 vs. Veh

PTZ-INDUCED CLONIC SEIZURES



CD-1 mice
(n=12/group)
t-test (VPA)
ANOVA/Dunn (PRAX)
**p<0.01 vs. Veh

PRAX-114 protects 100% of animals from PTZ-induced tonic and clonic seizures

Source: Praxis data on file.

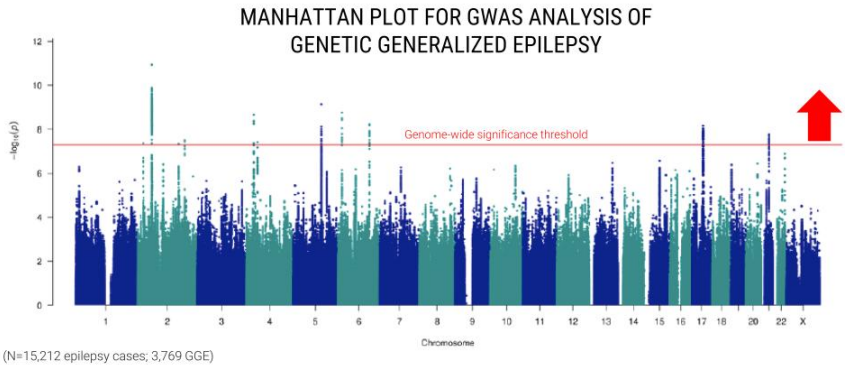
PRAX-114
SMALL MOLECULE

PRAX-944
SMALL MOLECULE

TARGET ID BY POLYGENIC RISK VARIANTS
SMALL MOLECULE

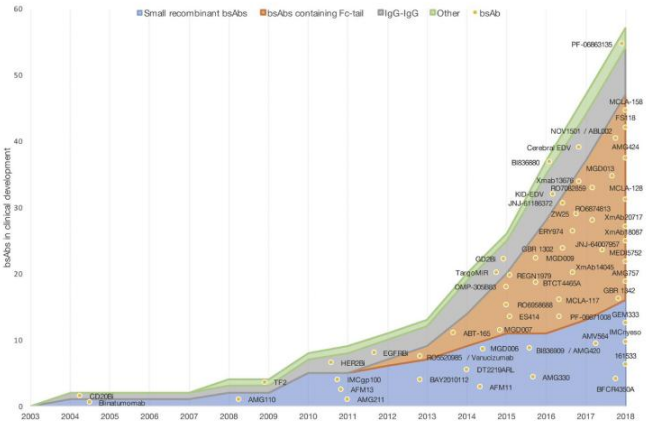
Direct - Future

GWAS studies have elucidated common polygenic risk variants among genetic generalized epilepsy patients



(N=15,212 epilepsy cases; 3,769 GGE)

Disruption potential comparable to bi- and tri-specific antibodies in immuno-oncology space



Dozens of bispecific antibodies in clinical development

Emerging clinical data show polyspecific antibodies produce greater efficacy by targeting multiple tumor antigens at once

Source: Suurs, F. V. *et al. Pharmacology & Therapeutics.* (2019); Ma, J., *et al. Front Immunol.* (2021)

These three imperatives guide our epilepsy portfolio build

Focus directly on underlying genetic defects in rare epilepsy

- **PRAX-222*** *ASO*
- **PRAX-020** *SMALL MOLECULE*
- **PRAX-080*** *ASO*
- **PRAX-090*** *ASO*
- **PRAX-100 *** *ASO*
- **PRAX-030** *SMALL MOLECULE*

Focus on implicated genes in common diseases

- **PRAX-114** *SMALL MOLECULE*
- **PRAX-944** *SMALL MOLECULE*
- **TARGET ID BY POLYGENIC RISK VARIANTS** *SMALL MOLECULE*

Focus on nodes of pathophysiological convergence informed by genetics

- **PRAX-562** *SMALL MOLECULE*
- **PRAX-628** *SMALL MOLECULE*

TARGETS IDENTIFIED THROUGH **GENETICS**

*PRAX-222 in collaboration with Ionis. PCDH19 (PRAX-080), SYNGAP1(PRAX-090), SCN2A-LOF(PRAX-100) ASOs are a collaboration with The Florey Institute of Neuroscience and Mental Health.

Perspectives from Clinical Practice: Shortcomings of existing treatment landscape provide opportunities for differentiation

Daniel Friedman, M.D., MSc.

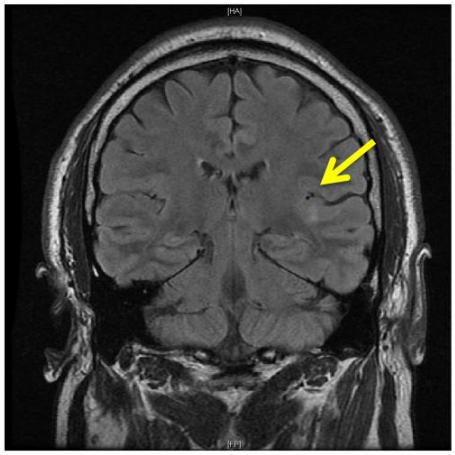
Disclosures

- Receive salary support from the Epilepsy Study Consortium (which has received funding from multiple pharmaceutical companies including Biogen, Cerivell, Crossject, Eisai, Engage, SK Lifesciences, Xenon, Zynerba)
- Consultant for Eisai, Neurelis
- Research support from Empatica, Epitel, Epilepsy Foundation, NIH, CDC, NSF
- Honorarium/Travel from Medtronics, Eisai, Epilepsy Foundation
- Scientific advisor board: Receptor Life Sciences
- Ownership interest: Neuroview Technology, Receptor Life Sciences

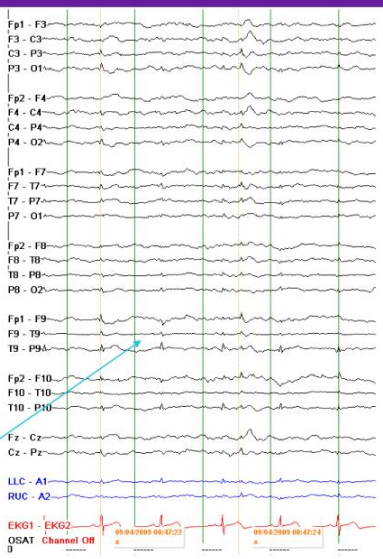
Case presentation

- 28 year old woman with a history of depression presents to the office after an ER visit for a witnessed convulsive seizure.
- Evaluation in the emergency room was unremarkable.
- Upon careful history taking, for several years she has had rare episodes where she hears a “buzzing” in her ears and then feels confused for a few seconds that she attributed to panic attacks.
- An MRI and EEG are ordered….

Case presentation



Focal cortical dysplasia

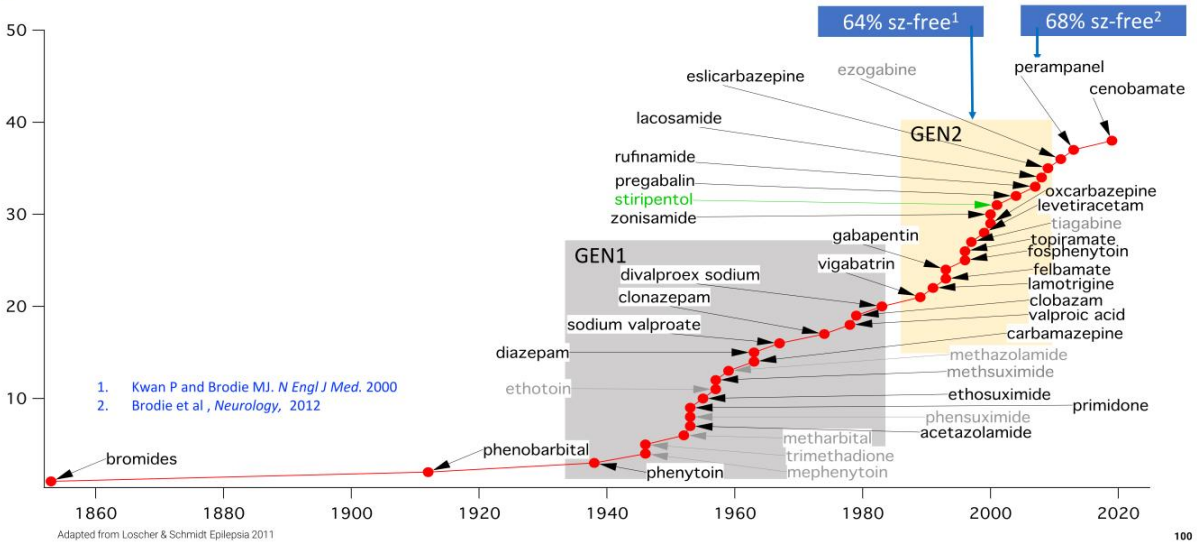


Left temporal spikes

Navigating therapeutic choices

- Patient is diagnosed with epilepsy
- Next step is symptomatic treatment – prevention of recurrent seizures
  - To reduce risks of mortality from seizures- accidents, drownings, SUDEP
  - To reduce risks of morbidity from seizures- fractures, burns, long term cognitive and psychiatric changes
  - To improve quality of life, allow for safe driving
- How do we pick an anti-seizure medication?

ASMs for common epilepsies – Where are we now?



1. Kwan P and Brodie MJ. *N Engl J Med.* 2000
2. Brodie et al , *Neurology,* 2012

Adapted from Loscher & Schmidt Epilepsia 2011

Despite the high number of marketed ASMs, more choices are needed

Phenobarbital	Leviteracetam
Phenytoin	Zonisamide
Carbamazepine	Pregabalin
Valproate	Lacosamide
Gabapentin	Clobazam
Felbamate	Ezogabine/Retigabine
Lamotrigine	Eslicarbazepine
Vigabatrin	Perampanel
Topiramate	Brivaracetam
Oxcarbazepine	Cenobamate

28 yr old woman with depression and new onset focal epilepsy

Despite the high number of marketed ASMs, more choices are needed

Phenobarbital
Phenytoin
Carbamazepine
Valproate
Gabapentin
Felbamate
Lamotrigine
Vigabatrin
Topiramate
Oxcarbazepine
Leviteracetam
Zonisamide
Pregabalin
Lacosamide
Clobazam
Ezogabine/Retigabine
Eslicarbazepine
Perampanel
Brivaracetam
Cenobamate

28 yr old woman with depression and new onset focal epilepsy

Who is on oral contraceptives and is concerned about weight gain

Despite the high number of marketed ASMs, more choices are needed

Phenobarbital
Phenytoin
Carbamazepine
Valproate
Gabapentin
Felbamate
Lamotrigine
Vigabatrin
Topiramate
Oxcarbazepine

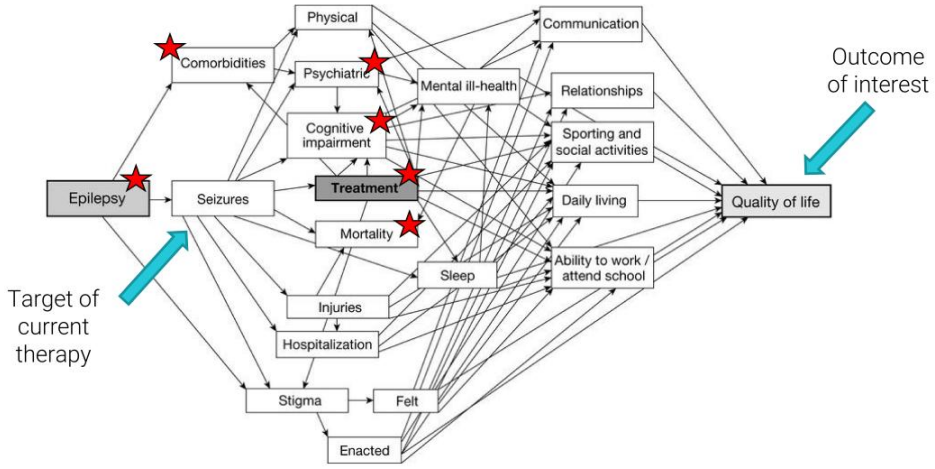
Leviteracetam
Zonisamide
Pregabalin
Lacosamide
Clobazam
Ezogabine/Retigabine
Eslicarbazepine
Perampanel
Brivaracetam
Cenobamate

28 yr old woman with depression and new onset focal epilepsy

Who is on oral contraceptives and is concerned about weight gain

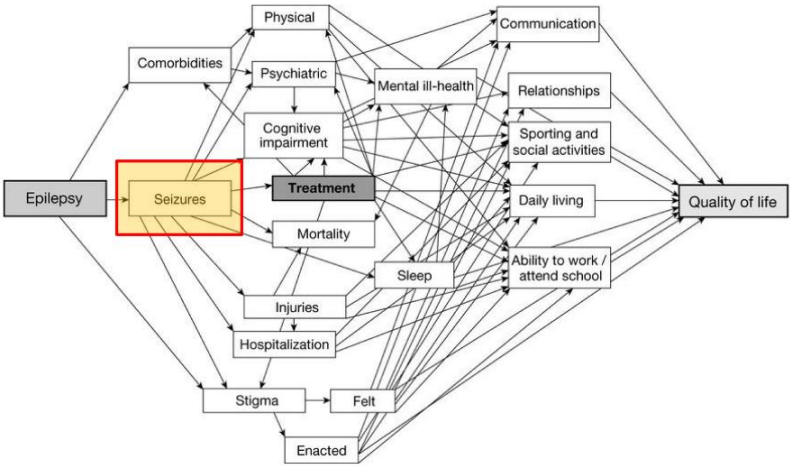
Who wants to have children in the near future

Where is there room for improvement?



Kerr *Acta Neurologica* 2012

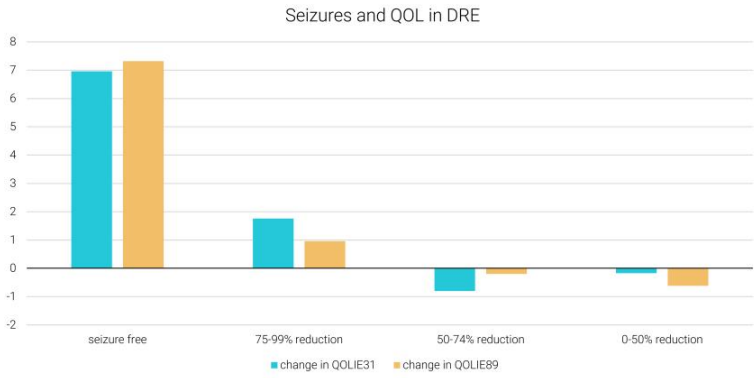
Where is there room for improvement?



Kerr *Acta Neurologica* 2012

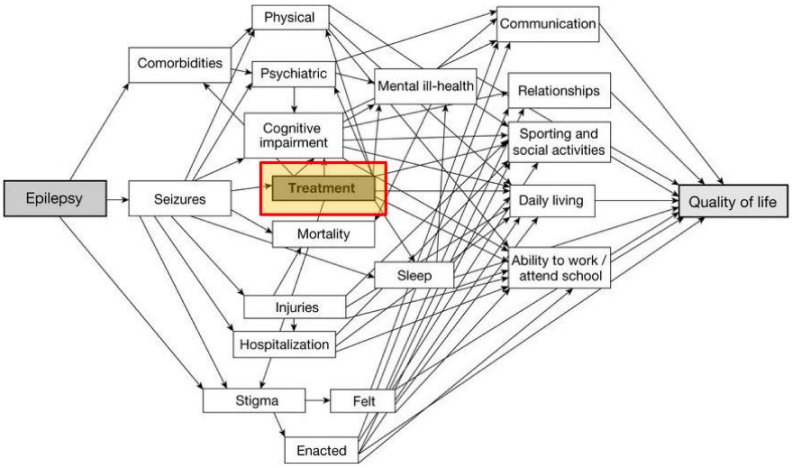
Efficacy

Seizure freedom is perhaps the largest single driver of QOL in patients with DRE focal epilepsy



From Birbeck et al, Epilepsia 2002

Where is there room for improvement?



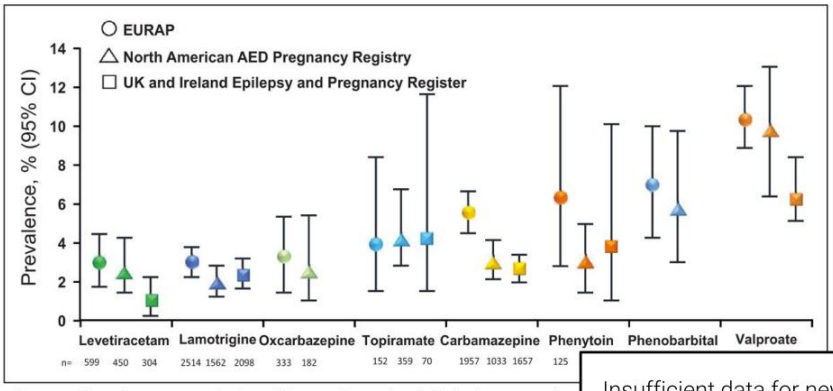
Kerr *Acta Neurologica* 2012

Tolerability

- Medication side effects are significant burden for people with epilepsy
- Adverse events are a large contributor to negative QOL
- Multiple types of intolerability:

Type	Examples
Acute, *predictable* (related to mechanisms of action), serum concentration dependent, common	Fatigue, vertigo, ataxia, CNS depression, cognitive changes, diplopia, tremor, mood changes
Acute, unpredictable (related to individual vulnerability), rare	Rash, immunological reactions, liver toxicity, bone marrow toxicity, aseptic meningitis
Chronic, related to cumulative exposure, common, predictable	Bone density loss, weight changes, neuropathy, visual field changes, gingival hyperplasia, connective tissue disorder
Pharmacodynamic and kinetic drug interactions, predictable	Added CNS toxicity, decreased OCP effectiveness, hepatotoxcity

Teratogenicity & neurodevelopmental outcomes

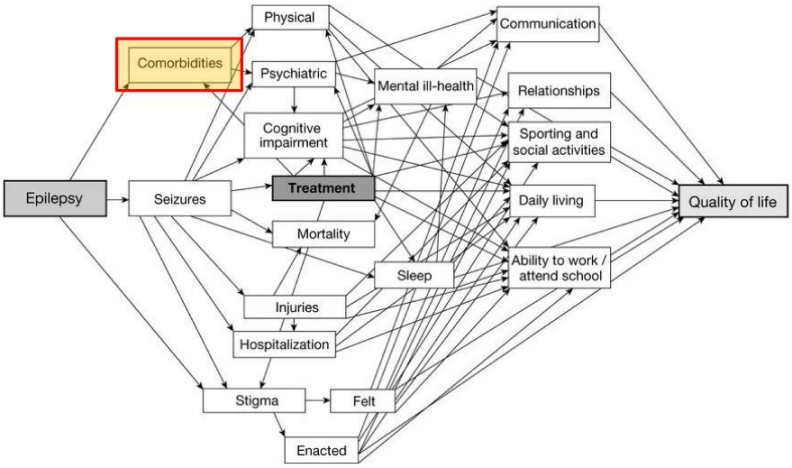


Rates of major congenital malformations for ASMs in monother

Insufficient data for newer ASMs like lacosamide, perampanel, brivaracetam

Tomson et al, Curr Opinion Neurol 2019

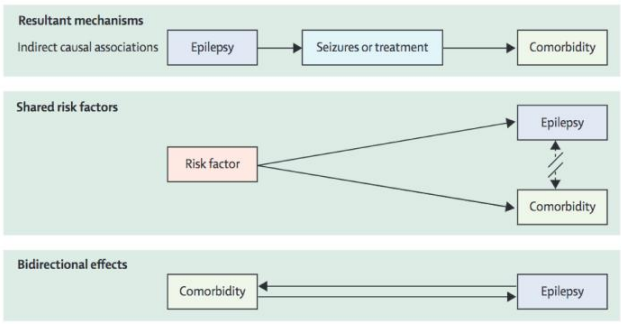
Where is there room for improvement?



Kerr *Acta Neurologica* 2012

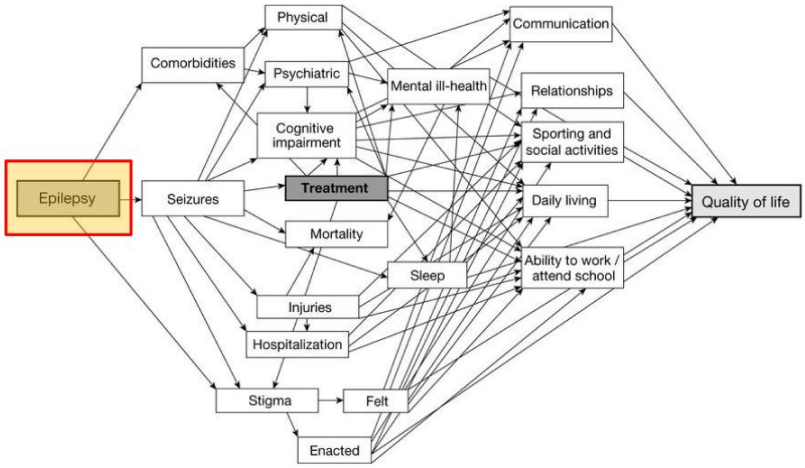
Comorbidities

- Depression, anxiety, memory disturbance are common focal/IGE epilepsy comorbidities
- More common among drug-resistant patients
- Causes include:
  - Seizures
  - Medication effects
  - *Underlying biological abnormalities leading to epilepsy*



Keezer et al Lancet Neurol 2016

Where is there room for improvement?



Kerr *Acta Neurologica* 2012

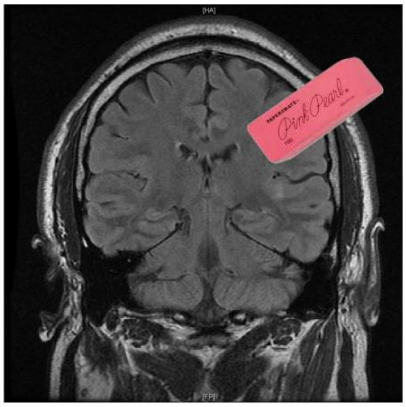
Disease modification

Current therapies are symptomatic – treat seizures & not underlying disorder

- Do not address the underlying mechanisms that lead to altered seizure thresholds, comorbid symptoms
- Need to be taken chronically

No treatments:

- Alter the underlying mechanism leading to increased seizure susceptibility
- Prevent epilepsy after a high-risk injury
- Turn drug-resistant epilepsy into drug-sensitive epilepsy



Promise of identifying novel targets for therapy

- Improved efficacy
- Disease modification - remittance of epilepsy, change DRE -> treatment responsive
- Modify comorbidities
- Improve tolerability
- Limit off target effects and neurodevelopmental outcomes

Conclusions

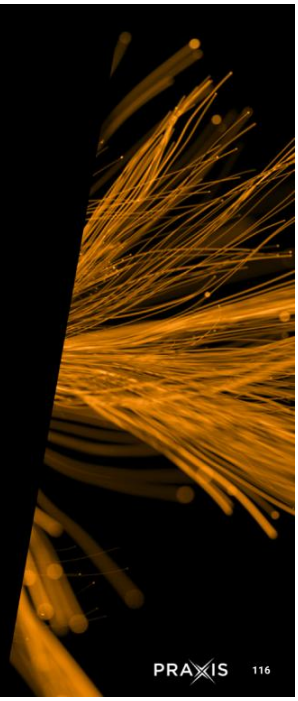
Despite 18+ marketed ASMs for focal and generalized seizures, options fall short for many patients with common epilepsies, too

- Lack of efficacy
- Intolerable side effects
- Limited choices for women who may become pregnant
- Burden of daily of medication taking

Shortcomings of available ASM present opportunities for differentiation of new therapies

Accelerating Path towards Registration

Bernard Ravina, CMO



Advancing best-in-class therapies for epilepsies

PRAX-222
(SCN2A)

PRAX-562
(SCN2A, SCN8A, TSC, +other DEEs)

PRAX-628
(FOCAL EPILEPSY)

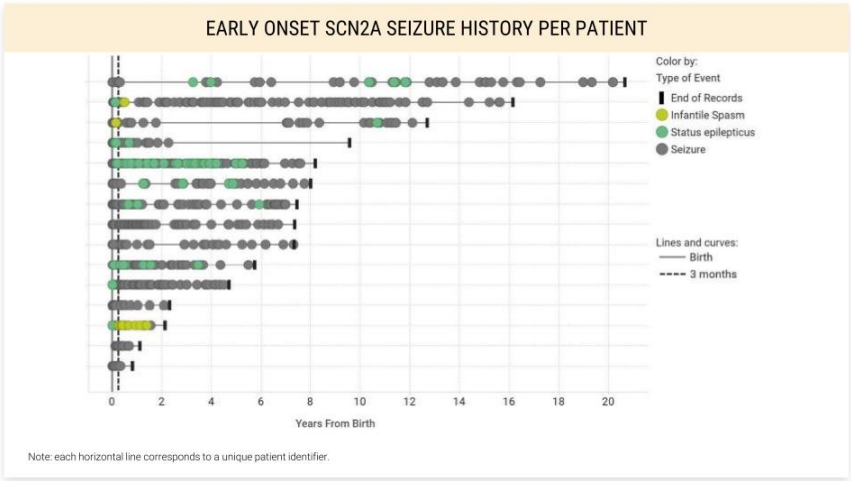
Preclinical data suggest PRAX-222 has potential to be disease-modifying for early onset SCN2A gain-of-function DEE

PRAX-222

INTRATHECALLY-ADMINISTERED ASO for SCN2A GOF DEE

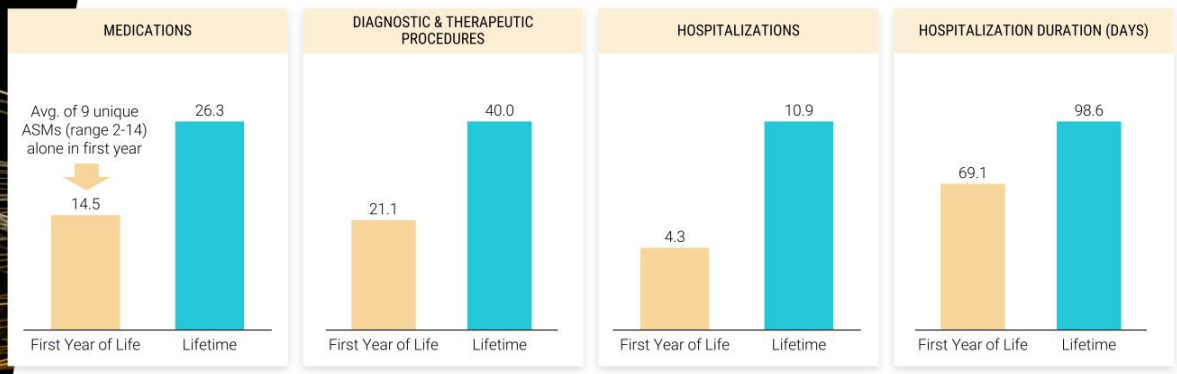
- Dose-dependent reduction in interictal spikes, seizures and increased survival
- Improvement in behavioral and locomotor activity in animal models
- Survival benefit extended with repeat dosing

Patients experience significant seizure burden from birth



Patient record demographics (N=15): 7 males, 8 females. Average age of seizure onset at 5.1 days (range: 1-44 days).
Source: Praxis data on file.

Significant burden of disease through lifetime of early onset SCN2A patients

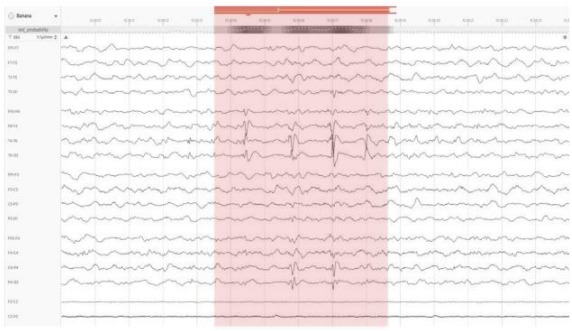


Median 17 days in hospital per year

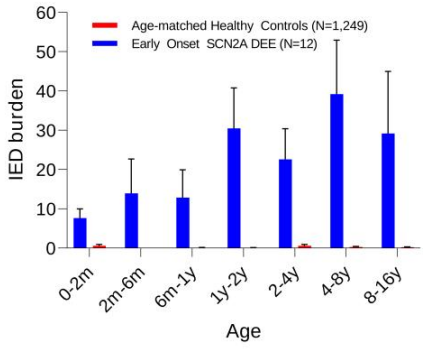
ASM: Antiseizure Medications
Note: Hospital Duration is the mean total days in hospital for all patients over the duration of the medical records.
Source: Praxis data on file.

Patient-guided insights drive development, such as EEG measure of interictal epileptiform discharges (IEDs)

IEDS DETECTED IN 11-YEAR-OLD WITH EARLY ONSET SCN2A



MEDIAN IED BURDEN PER EEG

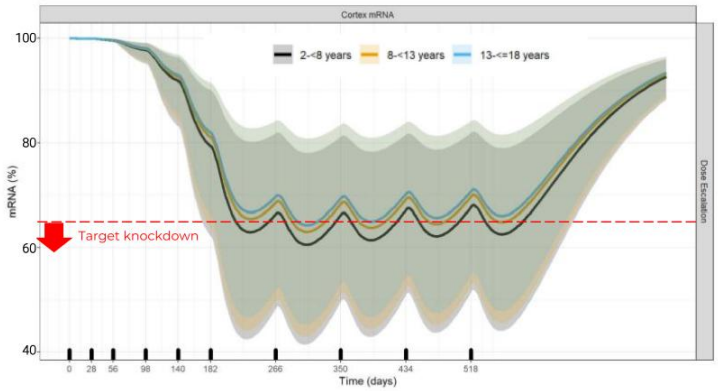


Source: Praxis data on file.

Design principles for the PRAX-222 seamless trial submitted to FDA

Seamless	Multiple parts to identify and confirm a safe, efficacious dose and optimize dosing schedule
Placebo-controlled	Placebo controlled, with confirmatory phase design parameters informed by earlier phase
Patient Population	Pediatric patients with confirmed SCN2A variant and baseline threshold of countable seizures
Statistical considerations	Each patient contributes data to more than one stage of the study
Endpoints	Collect data on seizure frequency and neurodevelopment, cognition assessments
Dose	Dose, escalation, and dosing interval informed by clinical safety data and a priori rules

PK/PD modeling informs starting dose and proposed escalation based on level of knockdown anticipated to achieve clinical benefit and tolerability



Median and 95% prediction interval illustrated

Simulated mRNA knockdown in human cortex in pediatric patients

Safely achieves distribution in key areas of brain based on NHP data

Source: Praxis data on file.

Next steps for PRAX-222 Clinical Program

Enroll observational study
Ongoing

- Further characterize the population
- Quantify EEG seizure burden, IED, variability in seizure frequency as potential biomarker

Initiate PRAX-222 Seamless Study
Mid-2022

- Assess safety, tolerability, PK and efficacy of ascending doses in pediatric patients (aged 2-18 yrs) with early onset SNC2A DEE

Observational study: https://www.scn2a.com

Preclinical and emerging clinical data demonstrate PRAX-562 will be a first- and best-in-class NaV blocker for DEEs

PRAX-562

SCN2A, SCN8A, TSC, +other DEEs
PAN-NA_V BLOCKER
SMALL MOLECULE

- Superior selectivity for disease-state Na_V channel hyperexcitability
- Unprecedented therapeutic window translating to superior safety and efficacy
- Convenient auto-titration regimen with stable PK

PRAX-562 path to rapid clinical proof of concept in DEEs

PHASE 1 HEALTHY VOLUNTEERS

SAD/MAD, ASSR Biomarker w/ 14-day Treatment Duration

TOPLINE REPORTED 4Q21

- *Well tolerated with no MTD at exposures above therapeutic range (EC_{50})*
- *Approximately 4-5 day half life*
- *Dose dependent reduction in ASSR*

PHASE 1 HEALTHY VOLUNTEERS

PK, ASSR Biomarker w/ 28-day Treatment Duration

READOUT IN 2Q22

- *No MTD at exposures multiple fold above therapeutic range (EC_{50})*
- *PK approaches steady state after 28 days*

PHASE 2 DEEs (SCN2A, SCN8A, and TSC)

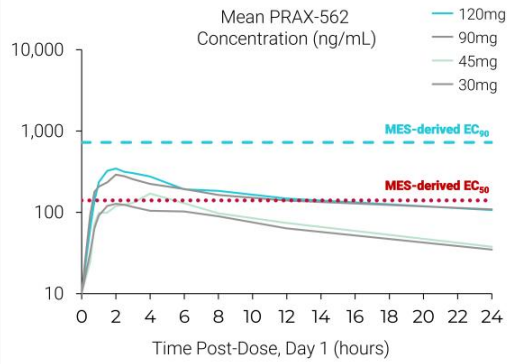
Seizure Reduction, Safety

TO BE INITIATED 2H22

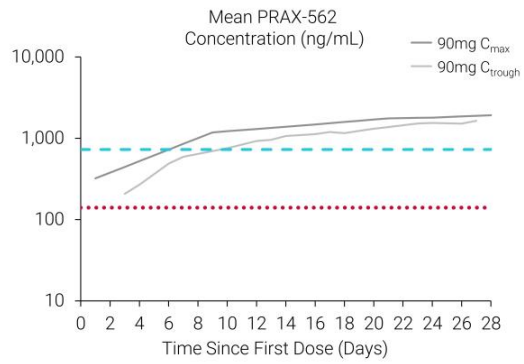
Targeting efficient path to registration

PRAX-562 in healthy volunteers safely exceeds projected therapeutic exposure

PRAX-562 EXPOSURES ON DAY 1



EXPOSURES AT 28 DAYS, WELL ABOVE PREDICTED THERAPEUTIC EXPOSURE*

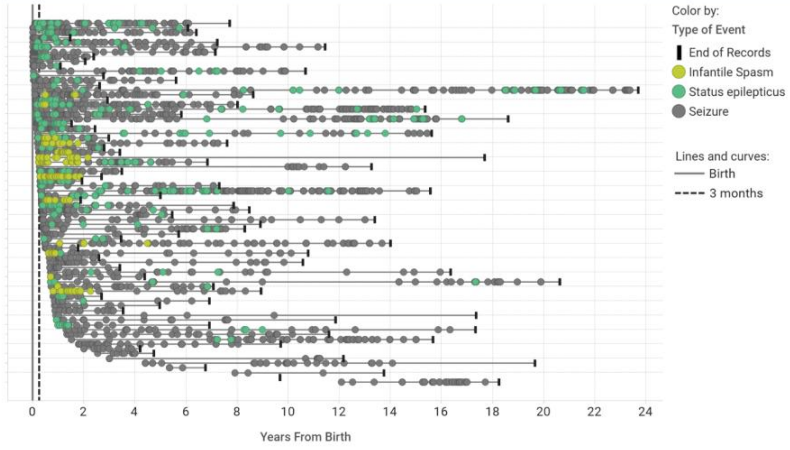


*Preliminary data from 562-102 study from first 12 participants enrolled in the study; C_{Max} is representative of concentration at 2.5 hours post-dose.
Source: Praxis data on file.

PRAXIS

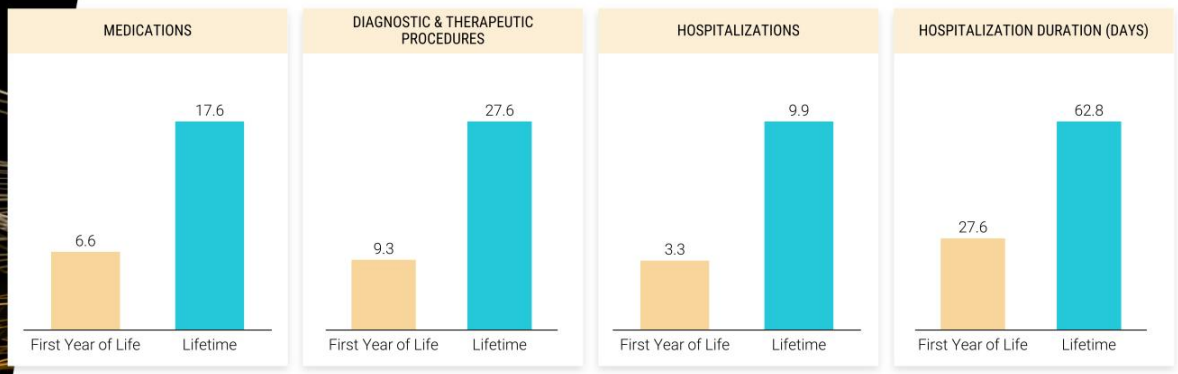
SCN8A DEE patients experience significant disease burden

SCN8A SEIZURE HISTORY PER PATIENT



Source: Praxis data on file.

SCN8A DEE patients experience significant disease burden



Median 6 days in hospital per year

Source: Praxis data on file.

PRAX-562 in DEEs: Path to clinical proof of concept

Rapid proof of concept	Open-label to identify a safe, efficacious dose and optimize dosing schedule in patients
Endpoints	Collect data on seizure frequency and neurodevelopment, cognition assessments
Initial patient population	Pediatric patients with confirmed SCN2A, SCN8A, or TSC and baseline threshold of countable seizures

Preclinical data demonstrates PRAX-628 will be a best-in-class NaV blocker for focal epilepsy

PRAX-628

FOCAL EPILEPSY

PAN-NA_V
ACTIVITY DEPENDENT
BLOCKER

SMALL MOLECULE

- Superior selectivity for disease-state Na_V channel hyperexcitability
- Unprecedented therapeutic window translating to superior safety and efficacy
- PK differentiated for broad epilepsy population

PRAX-628 clinical development program for focal epilepsy

Three epilepsy drugs in clinic by end of 2022

PRAX-222
(SCN2A)

Initiate Seamless Study: Mid-2022

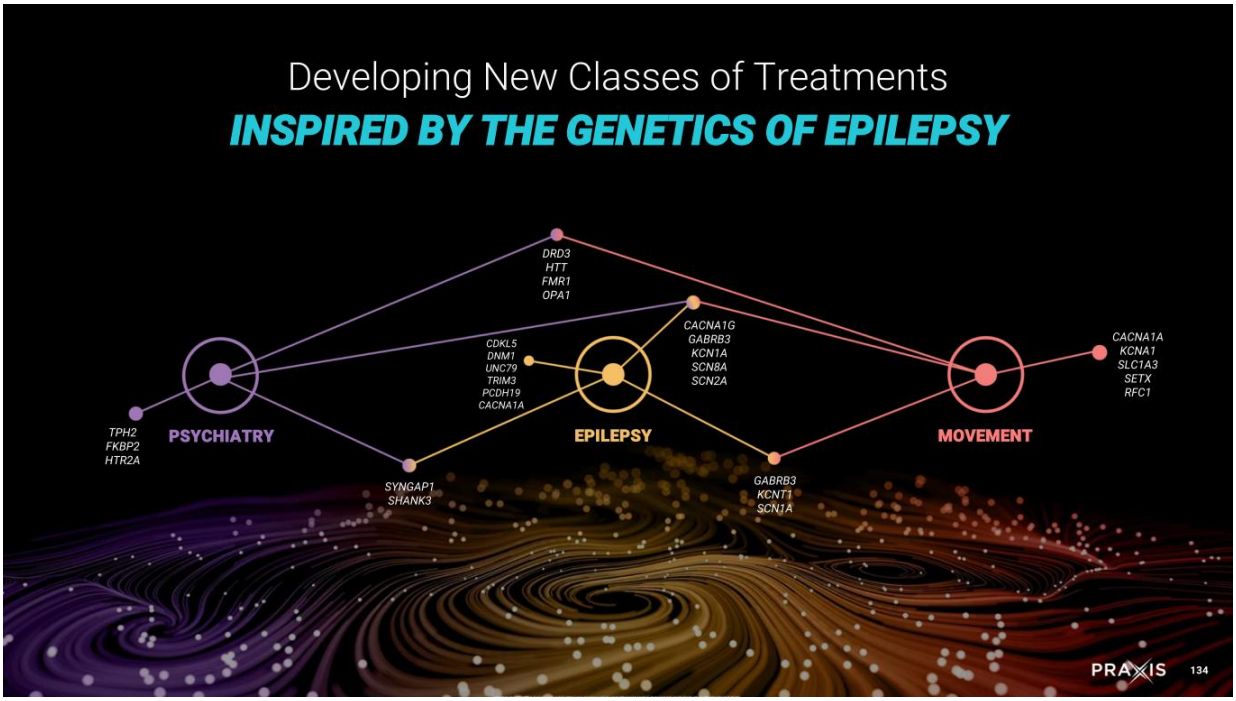
PRAX-562
(SCN2A, SCN8A, TSC)

Initiate Phase 2 Study: 2H22

PRAX-628
(FOCAL EPILEPSY)

Initiate Phase 1 Study: 4Q22

PRAX-222 and PRAX-562 received Orphan Drug Designations for severe pediatric epilepsy indications from the FDA and EMA, and Rare Pediatric Disease designation from the FDA


Developing New Classes of Treatments
INSPIRED BY THE GENETICS OF EPILEPSY
DRD3
HTT
FMR1
OPA1
CACNA1G
GABRB3
KCN1A
SCN8A
SCN2A
CDKL5
DNM1
UNC79
TRIM3
PCDH19
CACNA1A
CACNA1A
KCNA1
SLC1A3
SETX
RFC1
TPH2
FKBP2
HTR2A
PSYCHIATRY
EPILEPSY
MOVEMENT
SYNGAP1
SHANK3
GABRB3
KCNT1
SCN1A
PRAXIS
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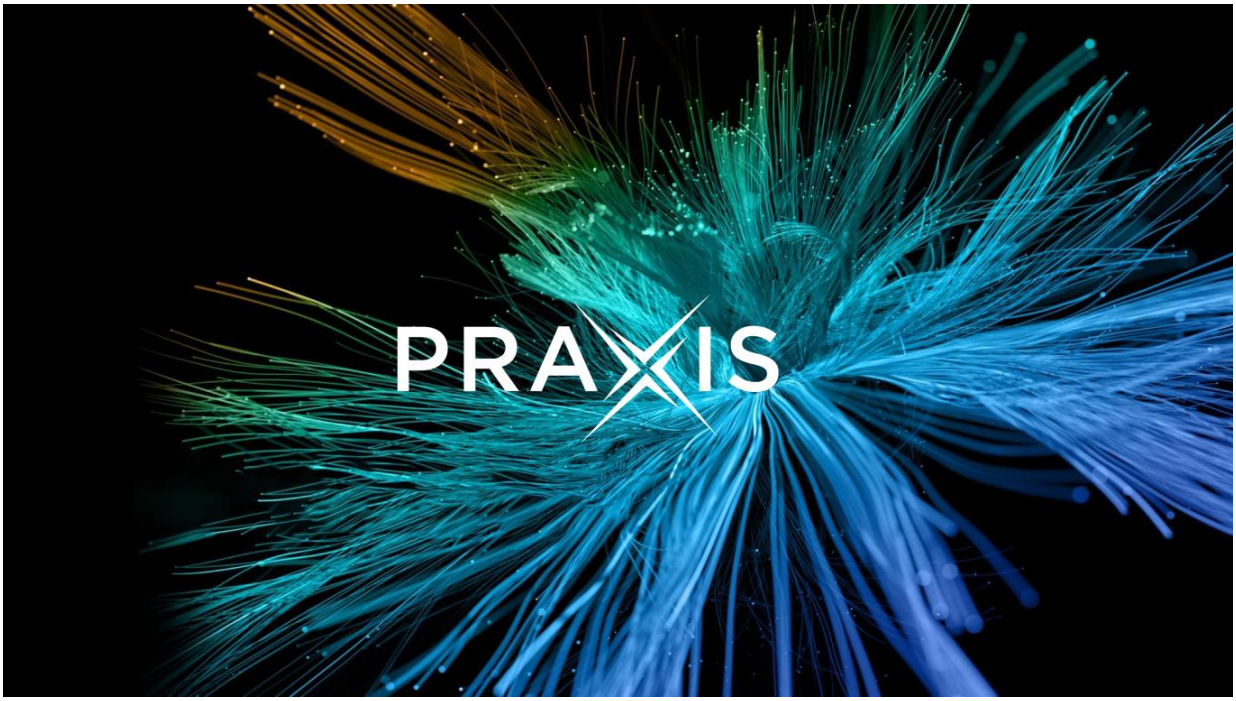
PRAXIS