Overview of current drug discovery approaches for childhood epilepsies

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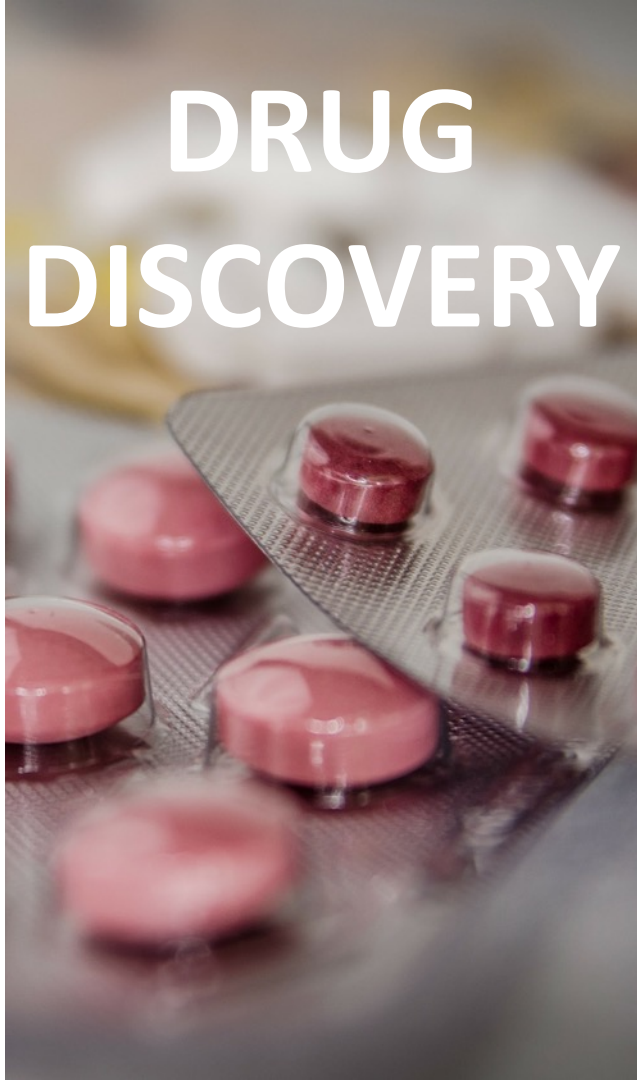
ACS Chemistry for Life®
American Chemical Society

ACS Fall 2019 National Meeting & Exposition

loulou FOUNDATION
Tackling CDKL5 Deficiency

SÍNDROME DE DRAVET
FUNDACIÓN
www.dravetfoundation.eu

HUMAN SIDE



DRUG DISCOVERY

HUMAN SIDE

The human side of catastrophic childhood epilepsies


Children

Every child is unique

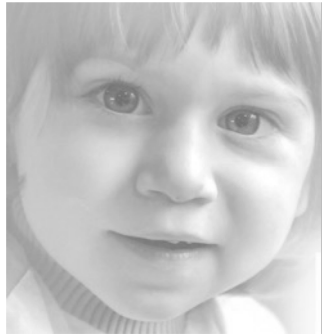
Some are also *rare*

Less than **1 in 2,000** births

Less than **200,000** people in the US

Rare epilepsy syndromes

Lucía



Eric

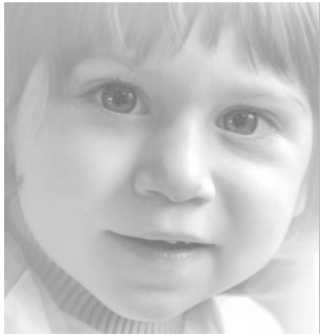
Lydia

Emergencies….


Seizures…


… and a diagnostic odyssey

Lucía



- **No mutation found**
- **Dravet syndrome**
- 10 big seizures a month
- 20% die early, often at night
- Major concerns: her risk of sudden death, her behavioral problems and moderate ID

Eric

- **Mutation in CDKL5**
- **CDKL5 Deficiency Disorder**
- Hundreds of seizures a month
- Severe disability
- Major concerns: his inability to hold his head up, communicate in any form, or use his hands

Lydia

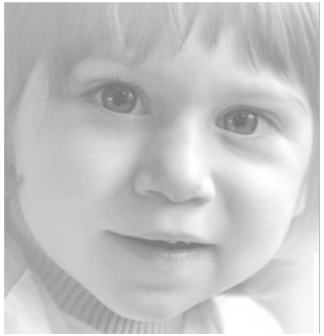
- **Mutation in KCNQ2**
- **KCNQ2 encephalopathy**
- Hundreds of seizures a month
- Severe disability
- Major concerns: if she will survive past age 3

catastrophe

noun [C] • **US** /kəˈtæs·trə·fi/

a sudden event that causes great suffering or destruction:

Lucía



Dravet syndrome

20,000+

Eric

CDKL5 Deficiency Disorder

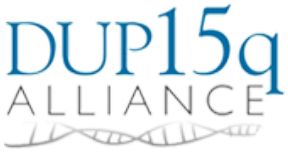
8,000+

Lydia

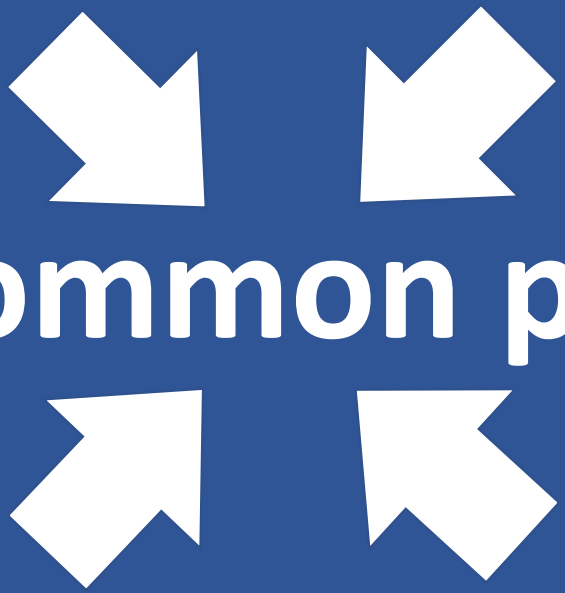
KCNQ2 encephalopathy

15,000+

Estimated number of cases just in the US



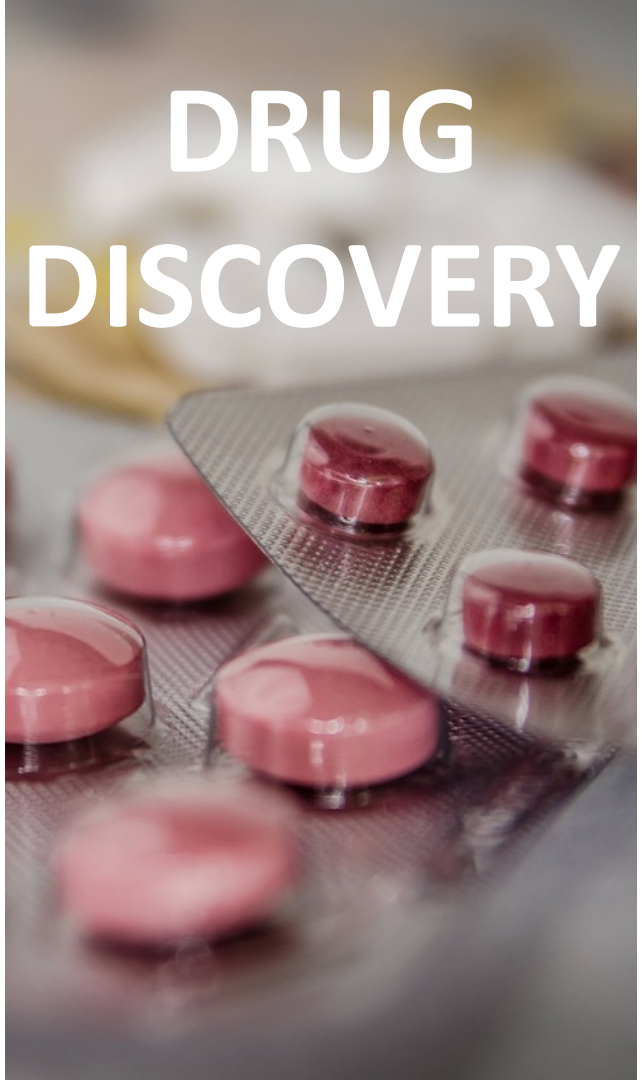
Rare syndromes with epilepsy



One common problem

Life-threatening refractory epilepsy

HUMAN SIDE

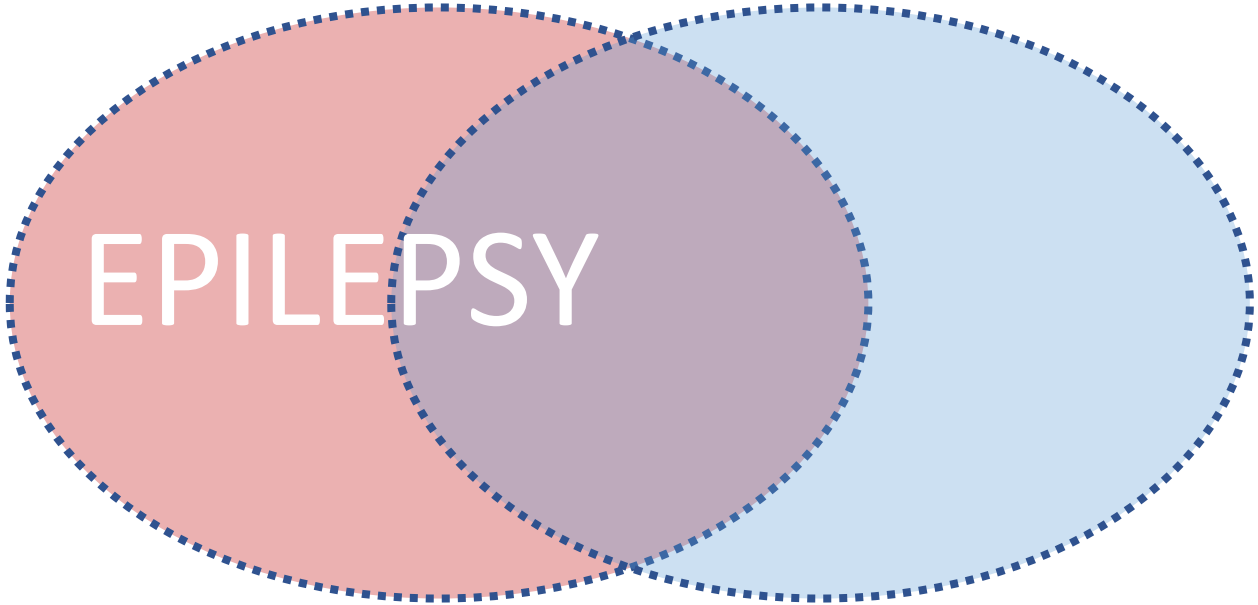


DRUG DISCOVERY

HUMAN SIDE

Drug discovery approaches for childhood epilepsies

The intersection of two fields



50 million people globally affected by epilepsy

Hyperexcitation

Hypersynchrony

Unknown / idiopathic

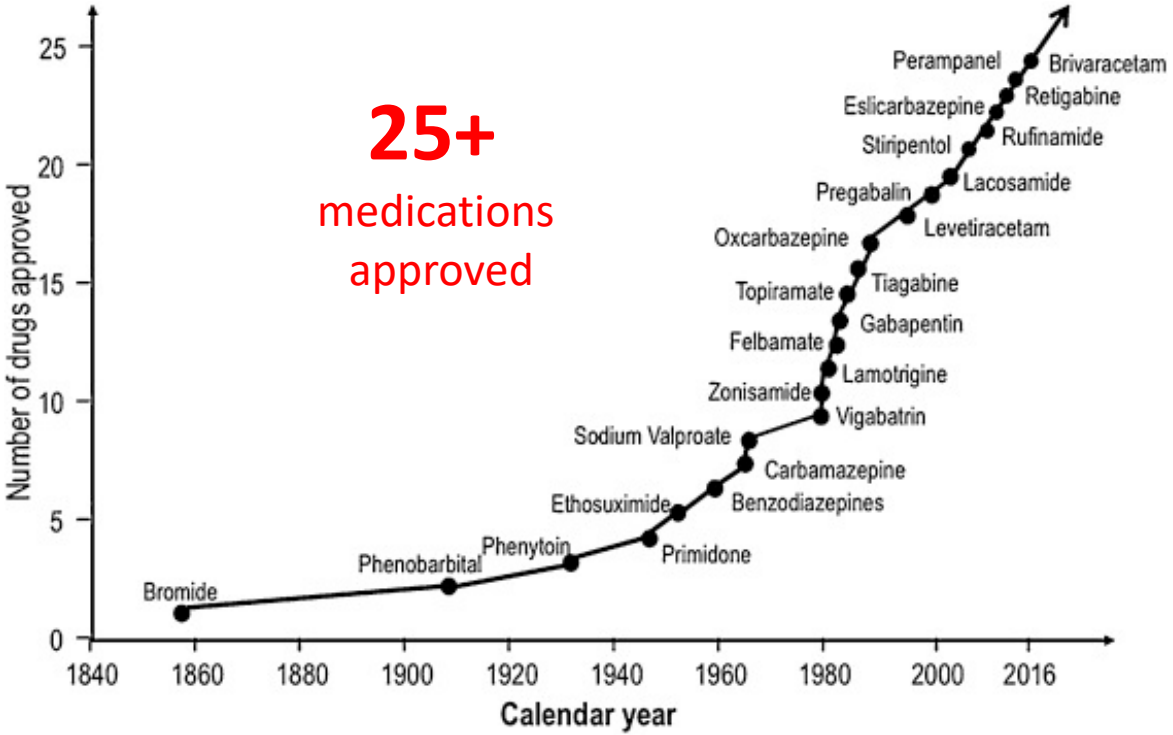
Brain trauma

Brain tumors

Brain malformation

Genetic mutations

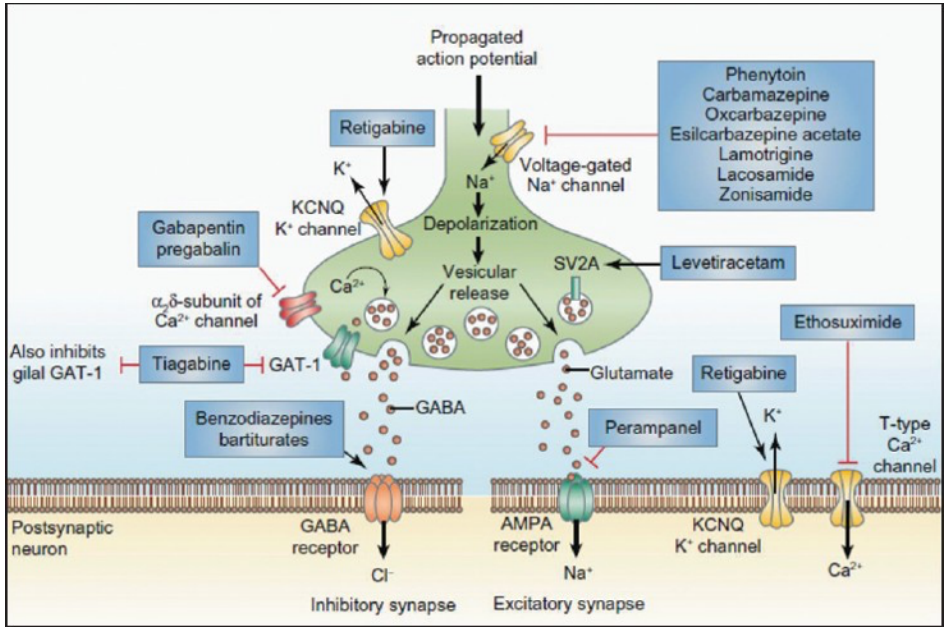
Epilepsy: a very successful field for drug development



- Easy clinical trials (seizure counting)
- Very large populations
- Chronic disease
- Good preclinical models
- Used to be very attractive for large companies

Most epilepsy drugs have the same mechanisms

GABA	Ca^{2+} channels
Na^{+} channels	Glu



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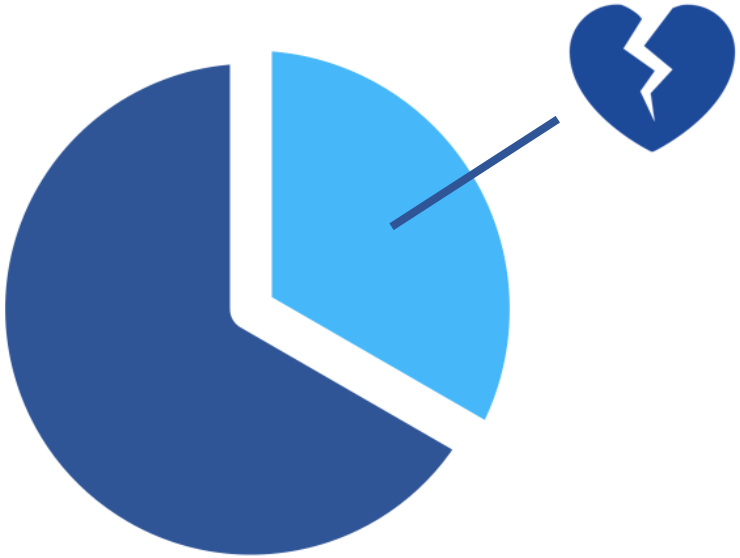


Ineffective in 1/3 of the patients

Catastrophic childhood epilepsies are notoriously drug-refractory.

Many refractory epilepsies are genetic

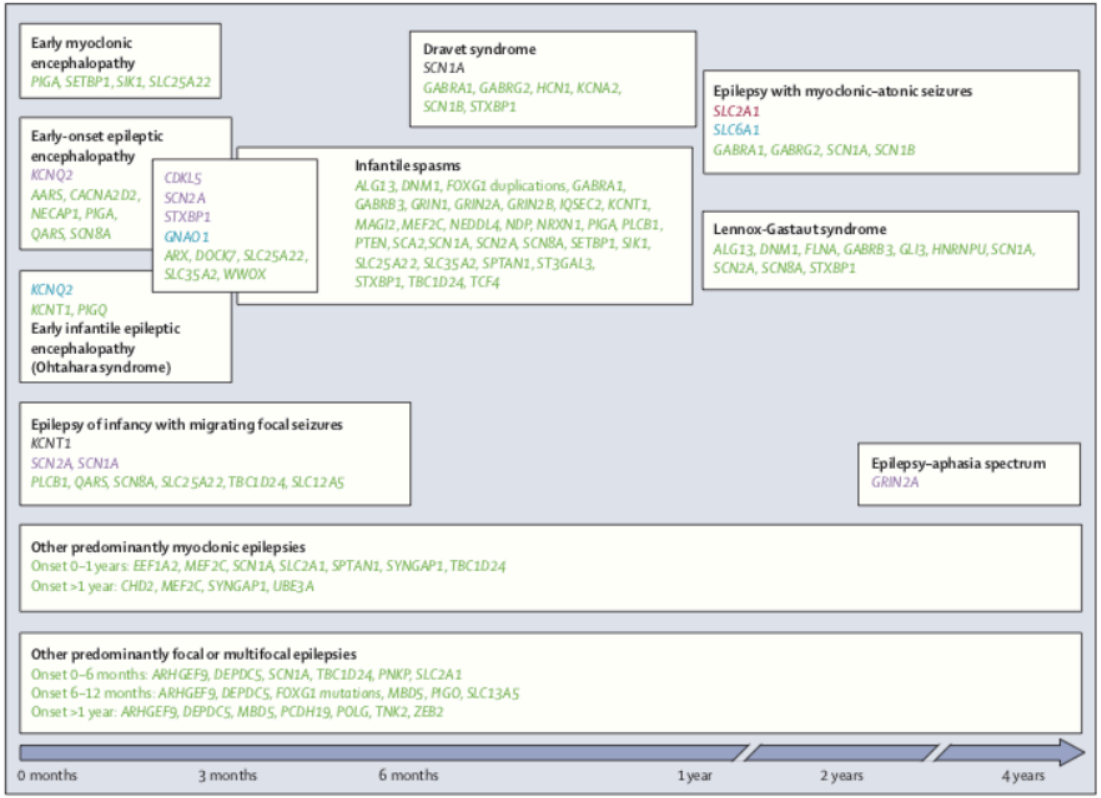
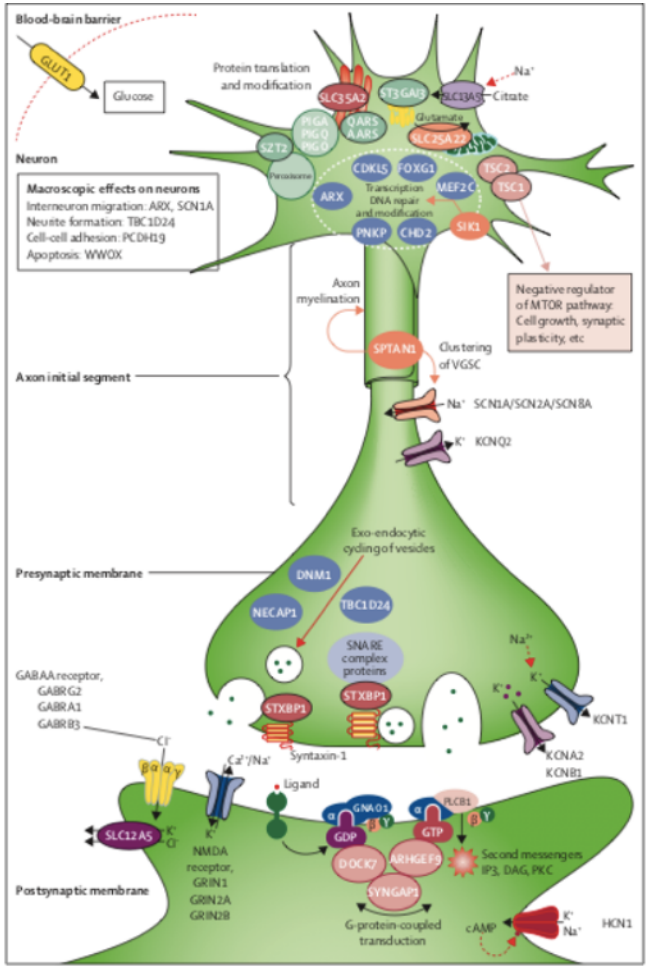


Figure 1: **Genetic causes of epilepsy syndromes**
Genetic causes, and proportion of cases caused by each gene, including only non-chromosomal, non-malformative, and non-metabolic disorders. Only genes with more than one case reported are included. Black font denotes genes that account for at least 50% of cases, purple font 10–50% of cases, and red font 5–10% of cases. Blue font denotes genes that account for less than 5% of cases, and green font denotes genes that account for an unknown percentage of cases.

McTague et al., Lancet 2016

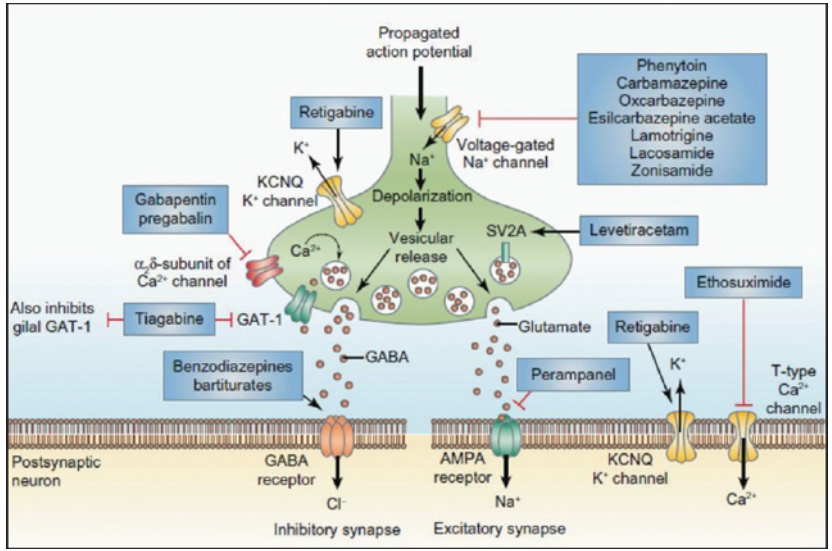
- Until 2001, the cause of epileptic encephalopathies was unknown
- In 2001, *SCN1A* was discovered as the cause of many cases of Dravet syndrome
- Today a genetic panel for epilepsy might contain more than 400 genes

RARE EPILEPSY GENES



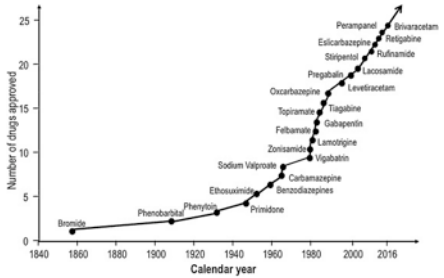
And they are caused by mutations in critical synapse genes

EPILEPSY DRUGS



McTague et al., Lancet 2016

Evolution of drug discovery in epilepsy



Overcrowded!

Big pharma freaks out.

Boom

Fast progress

Many approvals

Broad label

Maturation

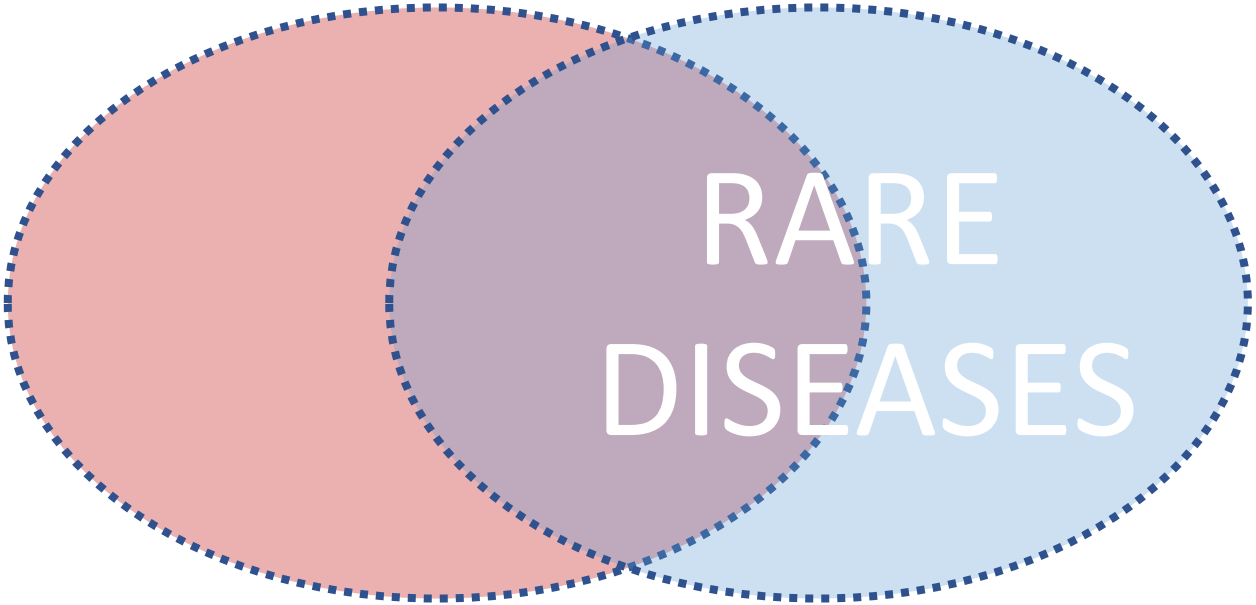
Still a third refractory

Harder to recruit

Smaller market slice

Now what?

Enter rare diseases….



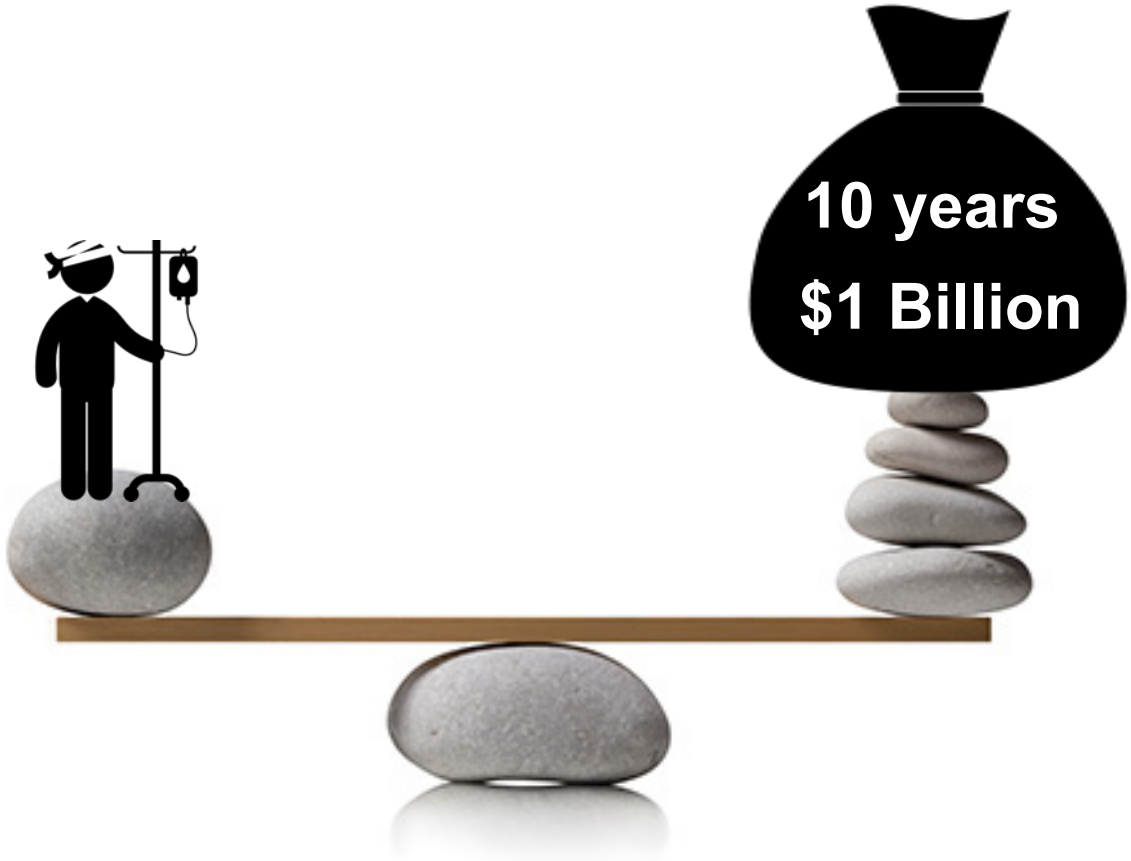
Less than **1 in 2,000** births

RARE DISEASES

7,000 rare diseases

350 million people in the world

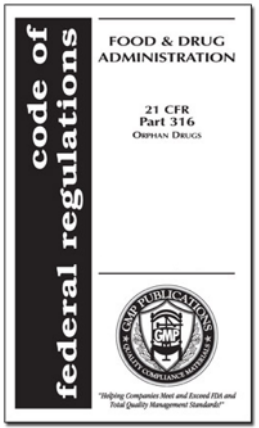
95% have no drug approved


10 years
$1 Billion

Orphan drugs

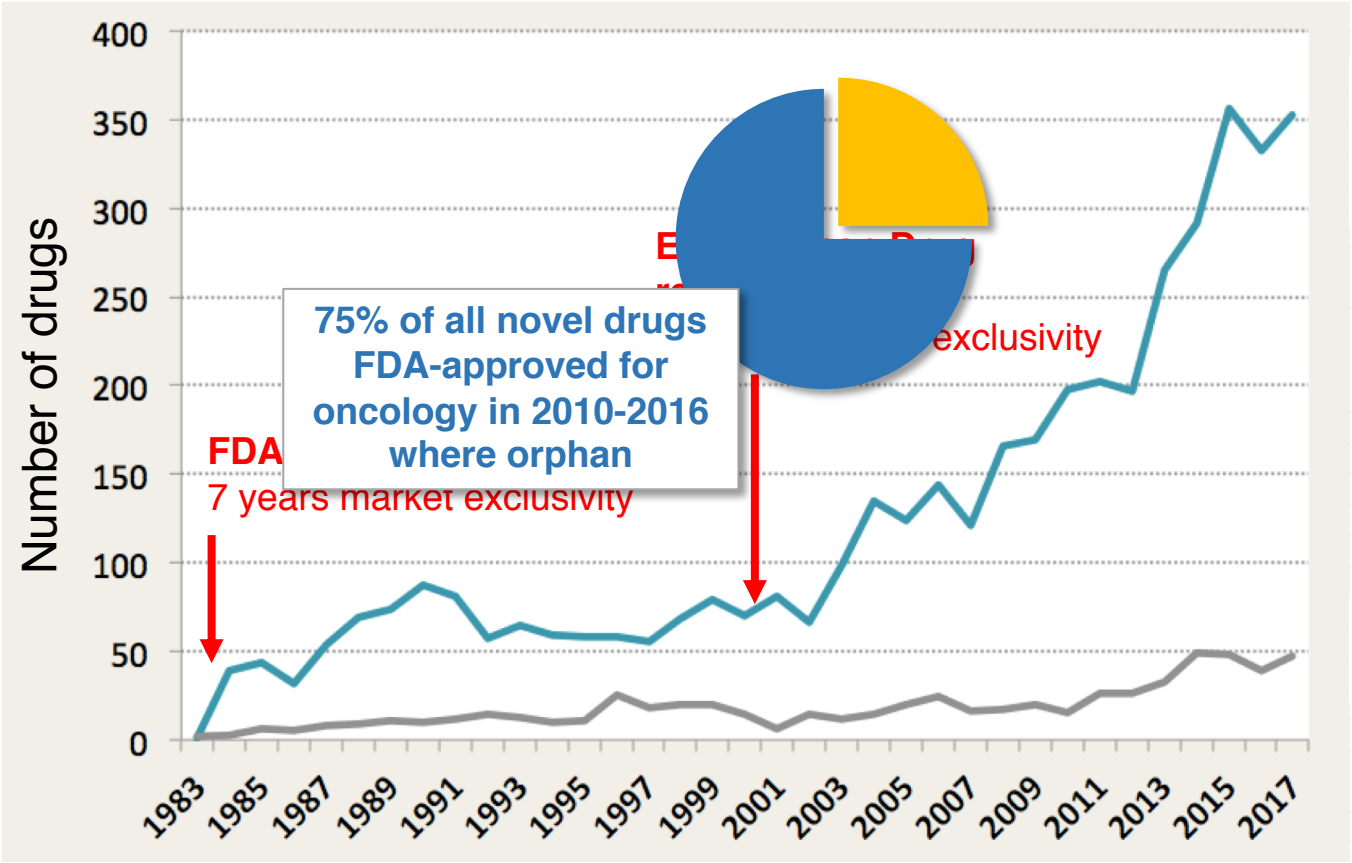
Drugs for **rare** diseases

An Orphan Drug Act was needed (1987)



- **7-year market exclusivity**
- **Tax credits**
- **Waiver of Prescription Drugs User Fees**
- **Rare pediatric priority review voucher**

- **Shorter development**: Often a pilot study followed by 1-2 pivotal
- Therefore **cheaper development** → opportunity for smaller companies
- Might command **higher price** (but smaller market!)



FDA orphan drug designations

(not yet approved)

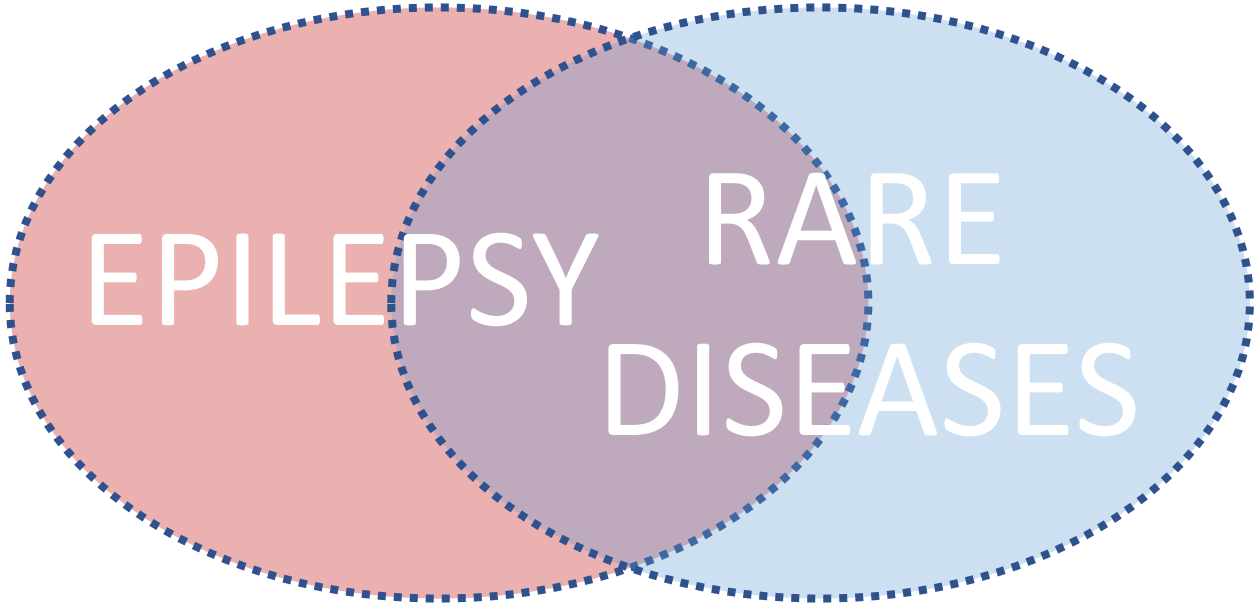
FDA orphan drug approvals

Source data compiled by James Love, Harvard Law blog

Orphanization

Personalized medicine

The intersection of two fields



Rare childhood epilepsies have given a **second life** to the field of epilepsy drug discovery

From epilepsy to epilepsies

2010

Partial Onset Seizures add on

Partial Onset Seizures monotherapy

Generalized Seizures add on

Generalized Seizures monotherapy

2018-2019

Lennox-Gastaut syndrome

Dravet syndrome

CDKL5 Deficiency Disorder

PCDH19 epilepsy

Tuberous Sclerosis Complex

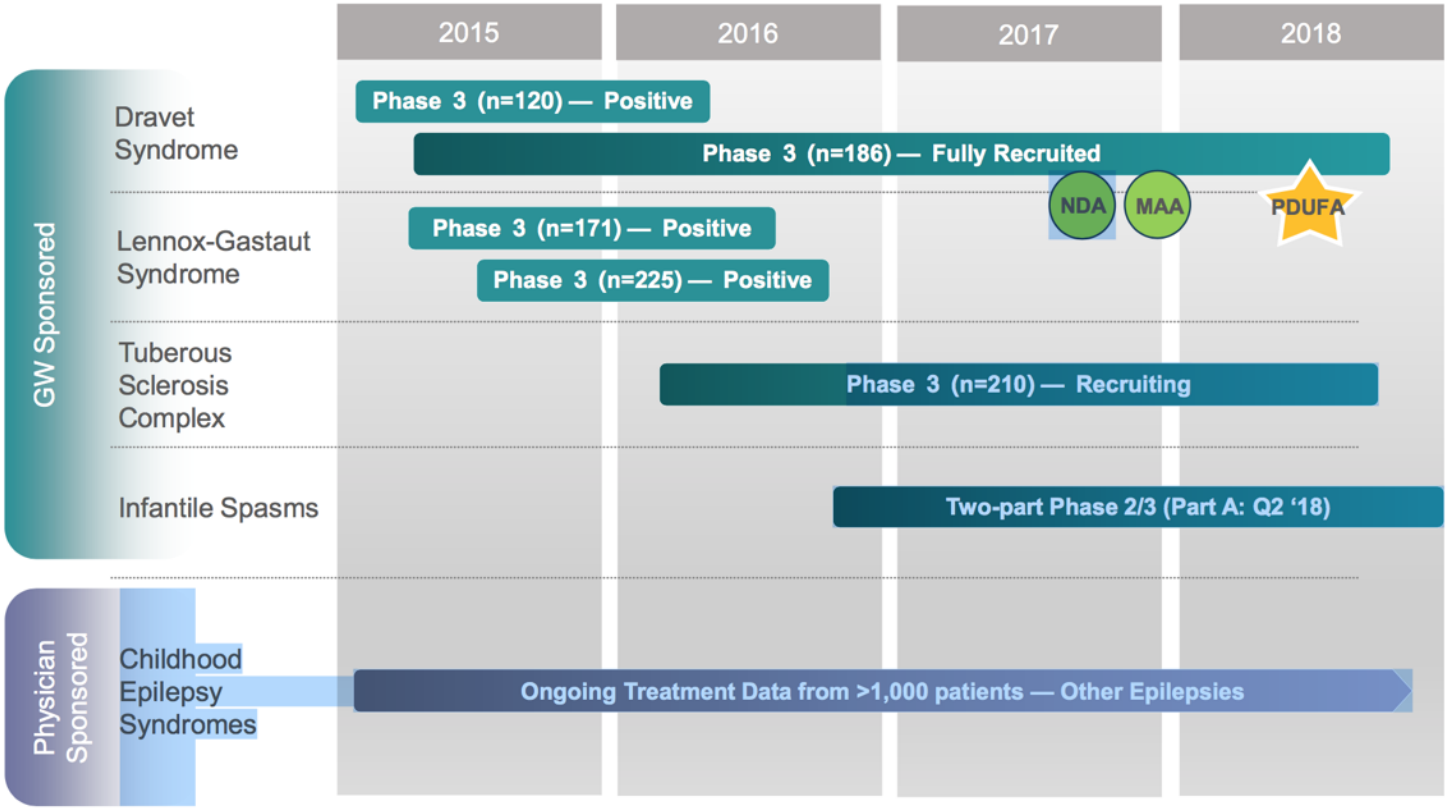
……

The pioneer


Epidiolex®
(cannabidiol)

Epidiolex® Phase 3 Program Overview

(old slide)



NDA submission accepted for Priority Review 27 June '18 PDUFA

MAA submission accepted Feb '18 with expected approval in Q1 2019

>97% of completers continued into Open Label Extension

GW pharmaceuticals

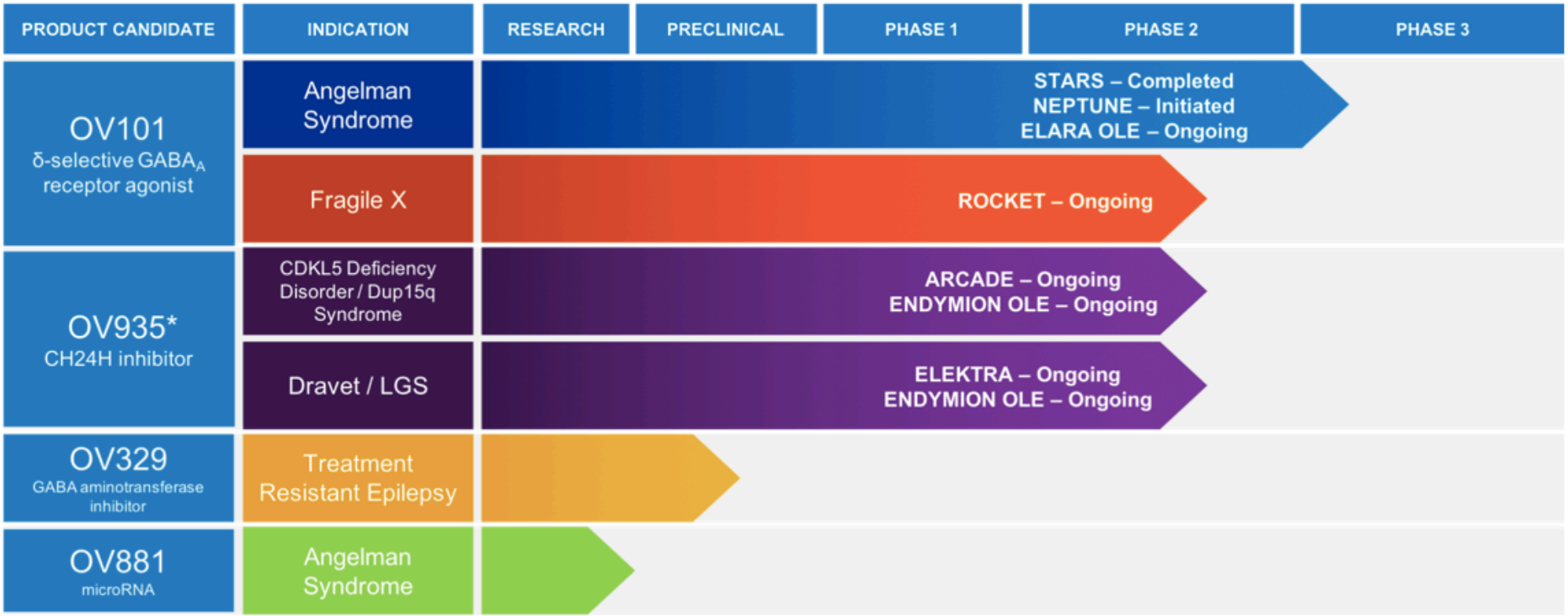
- 3,5 years IND to NDA
- De-risked protocols (epilepsy!)
- Big medical/patient interest
- Market exclusivity as orphan drug
- Opportunity for multiple indications

The new era of epilepsy drug development

Multiple syndromes for one drug

GANAXOLONE	PHASE 1	PHASE 2	PHASE 3
Orphan Refractory Seizure Programs			
	CDKL5 Deficiency Disorder (CDD)*		
	PCDH19-Related Epilepsy (PCDH19)*		
 	Refractory Status Epilepticus*		

A couple of syndromes for each drug



*Also known as TAK-935. Co-development program with Takeda Pharmaceutical Company Limited pursuant to a license and collaboration agreement.

Multiple drugs for epilepsy / syndromes

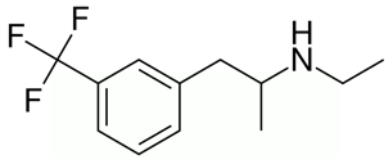
XENON

From epilepsy to epilepsies

Developing therapies for childhood epilepsies **makes (business) sense** in several scenarios

YOU CAN RECYCLE OLD DRUG

- 7 years of market exclusivity post-approval (10 years in other markets) encourages drug repurposing
- Very interesting opportunity for old drugs that have a weaker IP position

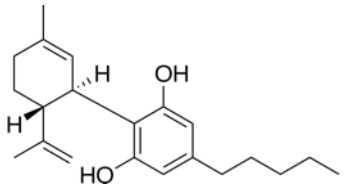


Zogenix

- 1973: Approved combined with phentermine (Fen-Phen) for appetite suppression.
- 1997: Removed from market.
- 2015 starts trials for Dravet syndrome.
- Expected US and EU decisions in 2020
- **Old drug: market exclusivity is key.**

CLUSTER OF RARE DISEASES

- Some mechanisms of action mean a drug can be developed in parallel for a group of related rare diseases
- This is one of the best approaches from the company perspective



Next presentation

GW pharmaceuticals

THE STEPPING STONE

- Some rare diseases serve as "gateway indications" to de-risk a compound before approaching the larger disease
- These are often genetic diseases

GLADSTONE INSTITUTES

Nav1.1 activators

Lundbeck

Dravet syndrome

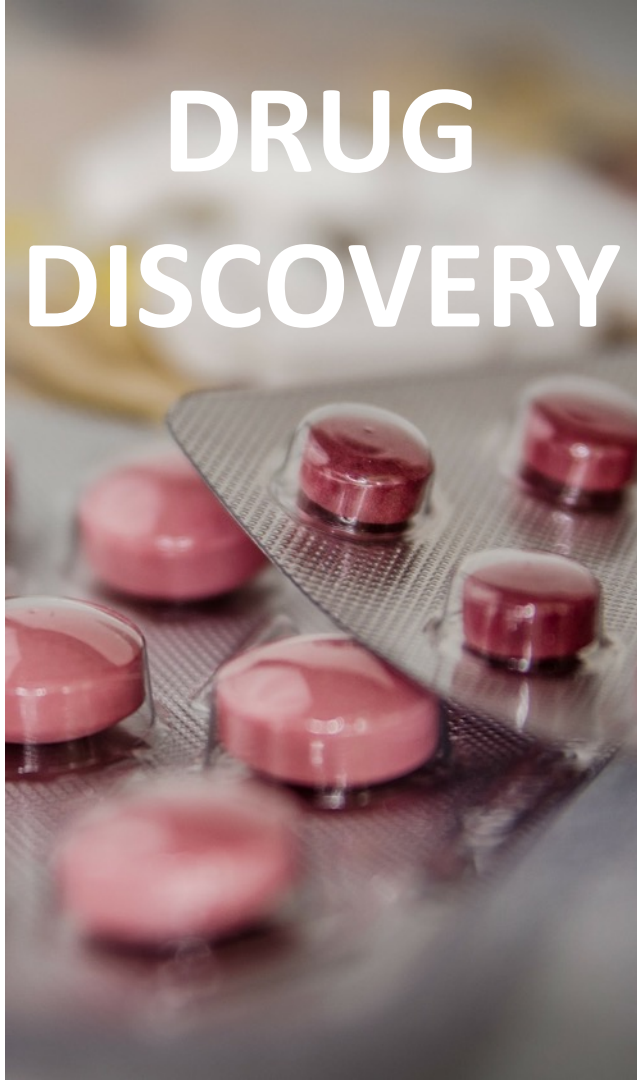
Alzheimer's disease
Schizophrenia

REPURPOSING

CLUSTER

STEPPING STONE

HUMAN SIDE



DRUG DISCOVERY

HUMAN SIDE

Epilepsy is often invisible.

Stigma.

Last month **20-year old Disney star Cameron Boyce** died of sudden death in epilepsy (SUDEP).

It drew media attention to epilepsy and its consequences

Epilepsy is the 4th more common neurological disease in the US.

Yet we hear little about it.

Efforts to make it **visible**

Miguel Cervantes

“Adelaide is 2 years old, but she functions much more like a newborn”, Cervantes said. "She doesn't sit or stand or talk or babble. We are always watching her to see if there is a seizure.”

Parents,

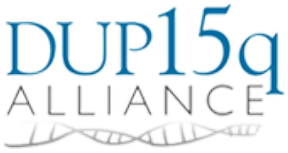
the **impatient** patients

Parents start…

Patient groups

Research Foundations

Companies



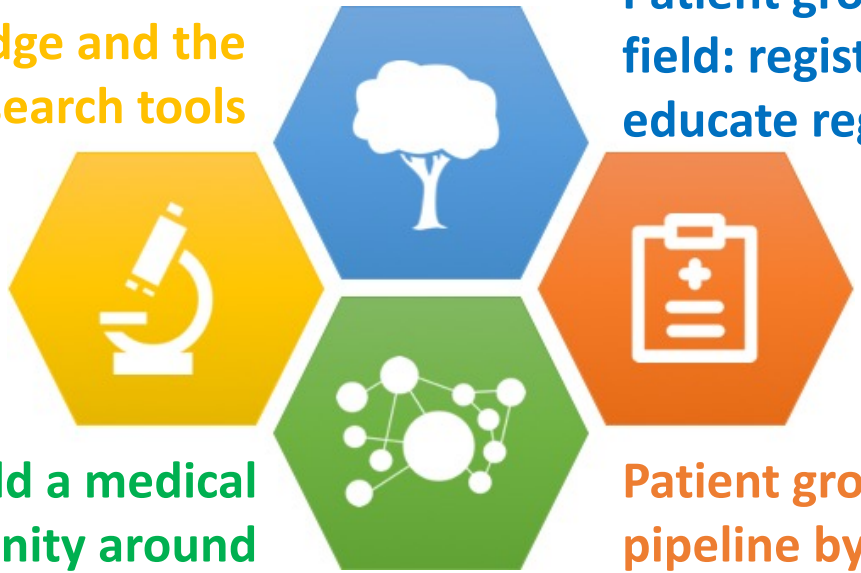
Rare syndromes with epilepsy

In rare diseases
patient groups are central to
drug development

For small companies: patient groups are **the ideal partner**

Patient groups build the basic knowledge and the research tools

Patient groups de-risk the field: registries, trial sites, educate regulators



Patient groups build a medical and research community around their disease (conferences)

Patient groups build a drug pipeline by attracting and supporting companies

For research groups: patient groups are **the best support**

Tools/reagents

Access to information

Funding

Connections

Access to samples

For companies and regulators:

patient groups are **the experts**

Drug discovery ~~for~~ *with* **patients**

Take-home messages

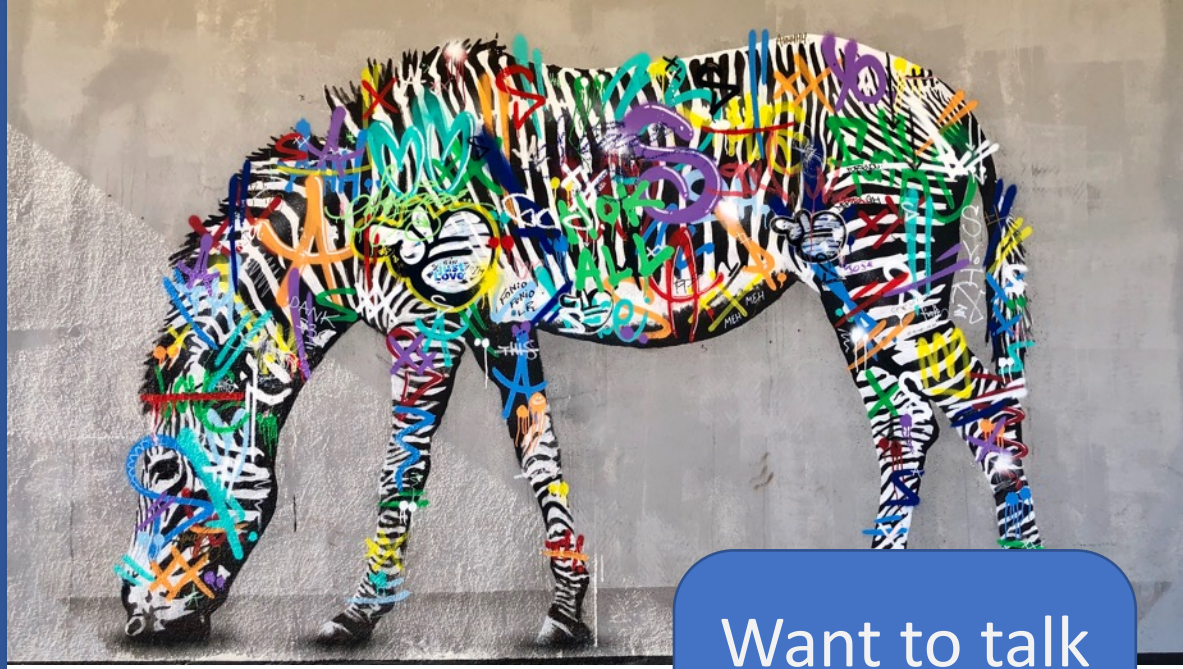
Rare epilepsy syndromes have much need for effective therapeutics.

The epilepsy field is going towards **orphan drugs.**

All rare diseases can be attractive if you find the right business reason for that company/drug.

If you have a **CNS active drug** and are not sure about potential indications, talk to me!

Thank you!



Ana Mingorance

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Want to talk about rare epilepsies?