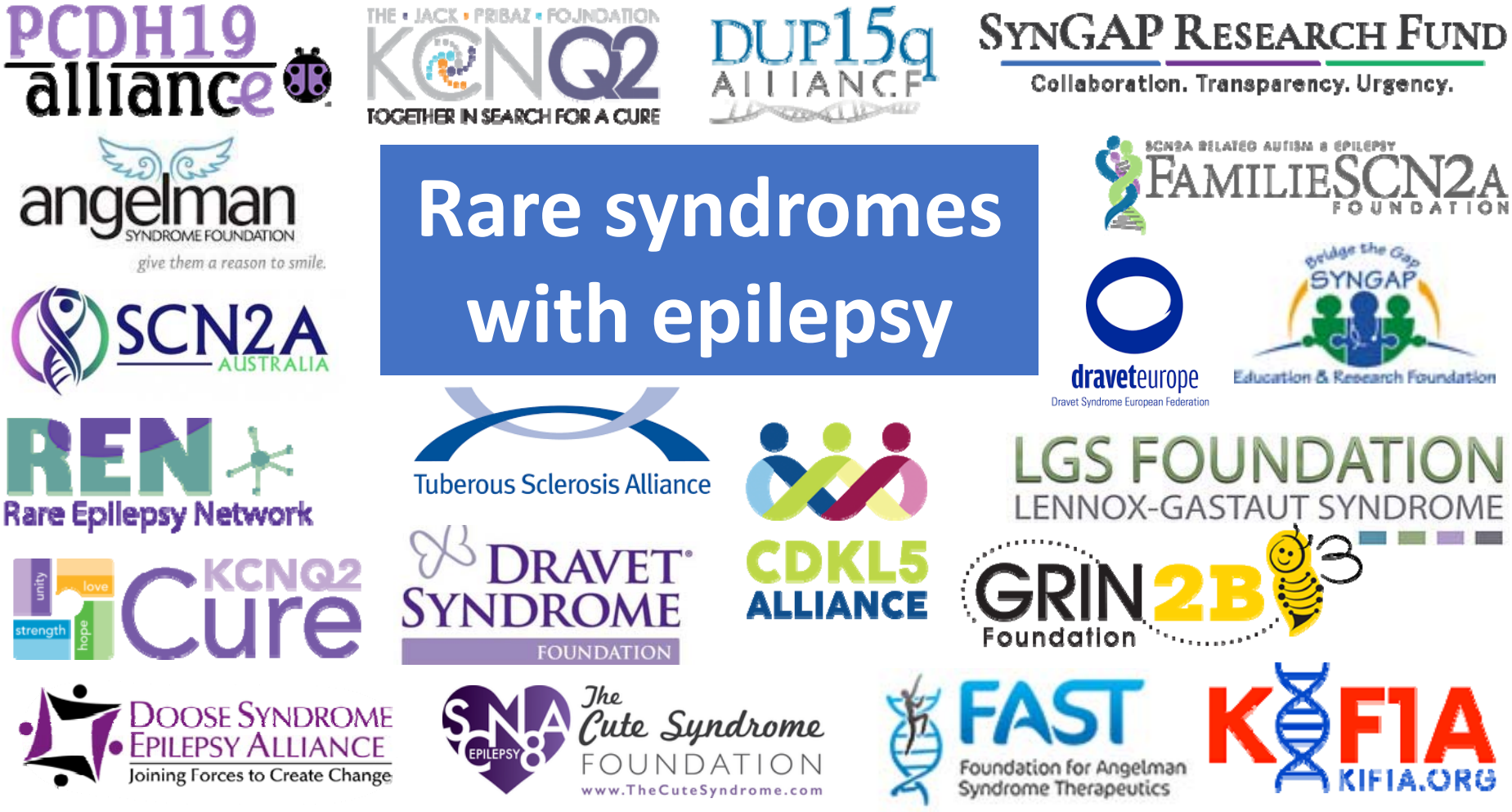
Epilepsy Therapeutics in Development

Ana Mingorance, PhD
Loulou Foundation (CDKL5 Deficiency Disorder)

amingorance@louloufoundation.org
@CNSDrugHunter

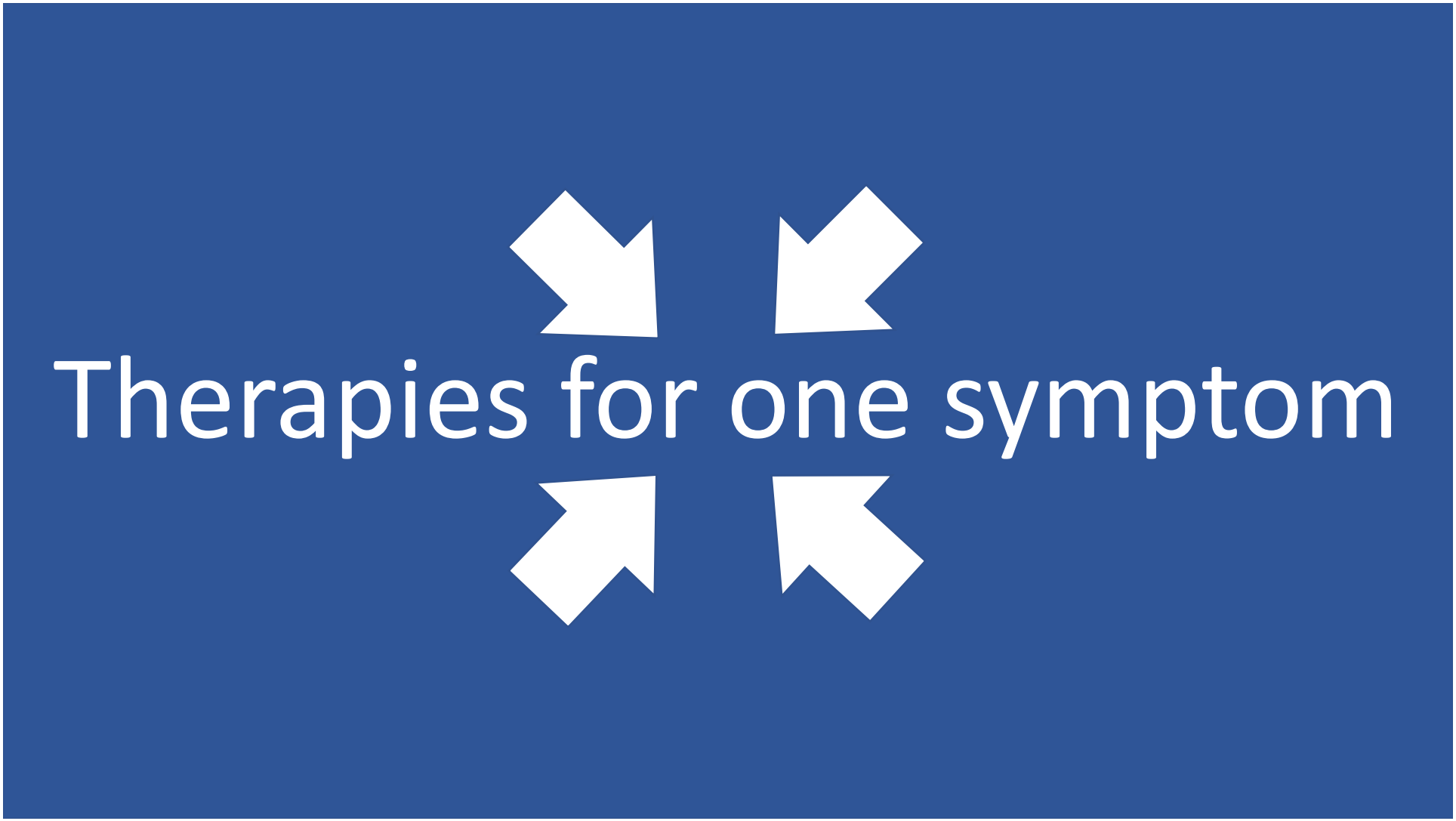
loulou FOUNDATION
Tackling CDKL5 Deficiency

Rare syndromes with epilepsy



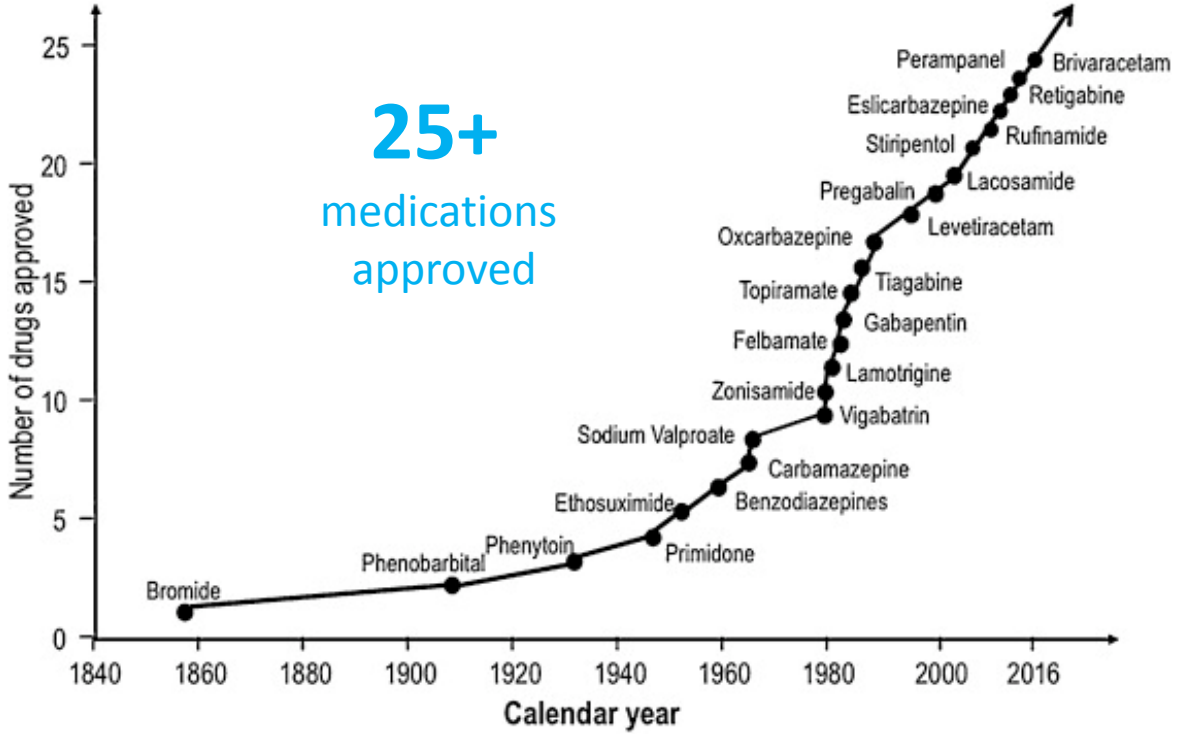
Neurodevelopmental disorder and epilepsy

For many years we didn't know these diseases existed


Therapies for one symptom

Epilepsy

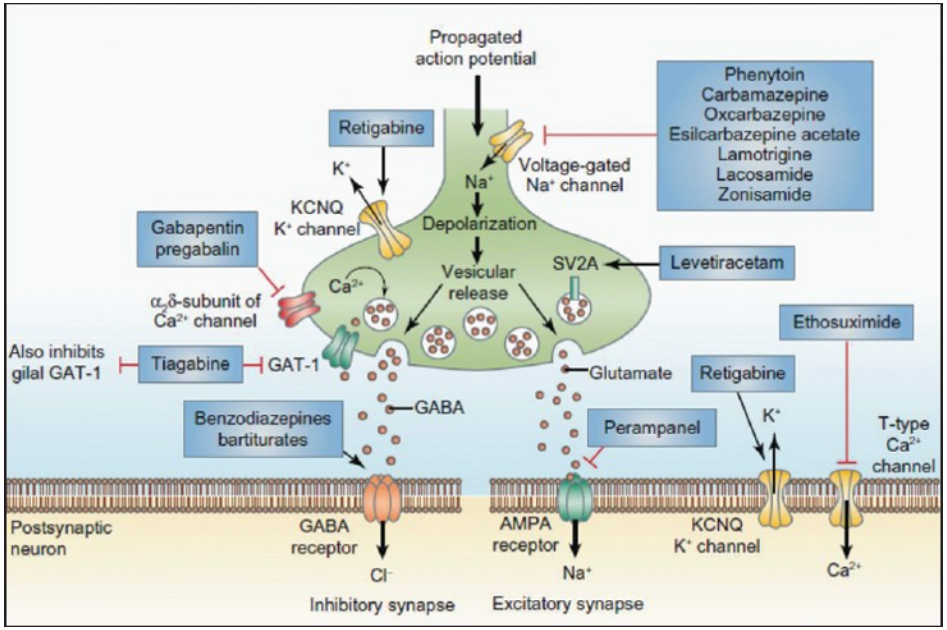
Epilepsy: a very successful field for drug development



- 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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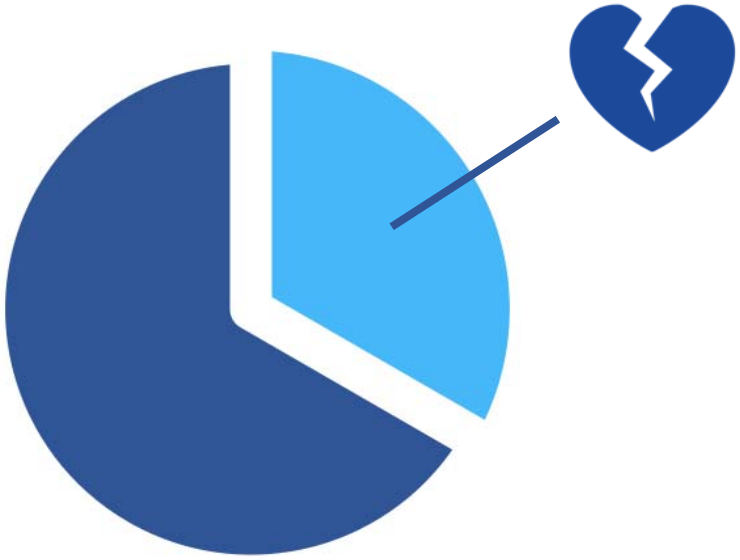
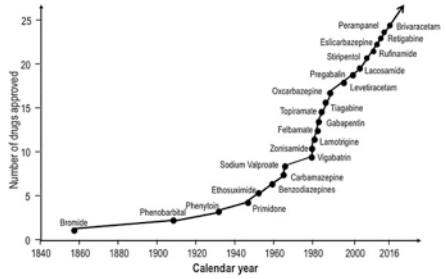


Ineffective in 1/3 of the patients

Diseases that combine **neurodevelopmental disorders with epilepsy** are notoriously drug-refractory.

Evolution of drug discovery in epilepsy



Overcrowded!

Big pharma scared

Boom → **Maturation** → **Now what?**

Fast progress

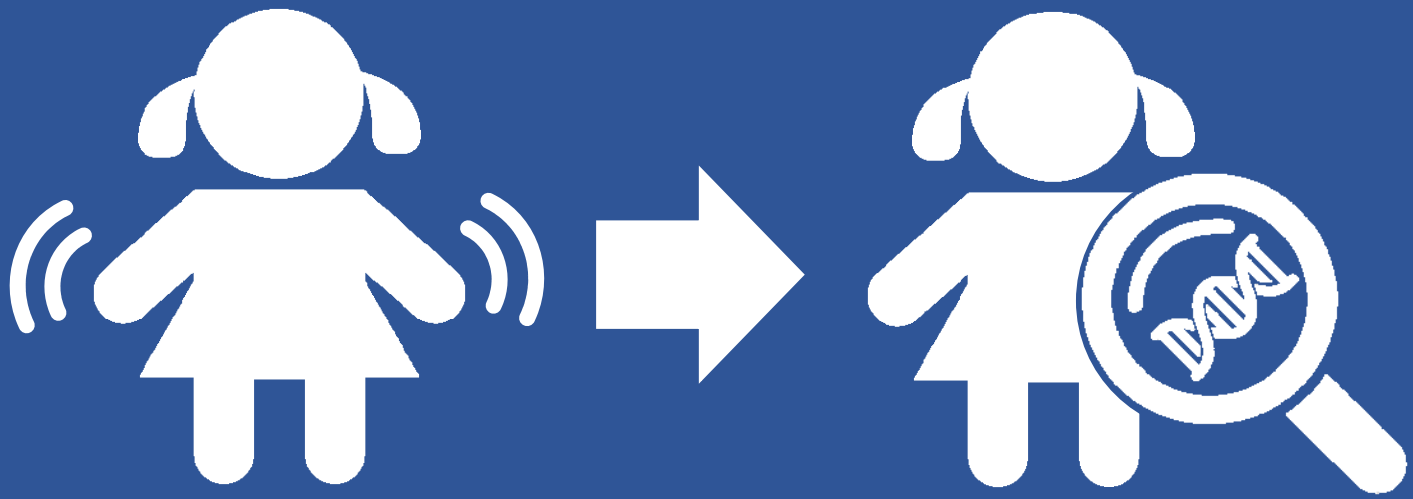
Many approvals

Broad label

Still a third refractory

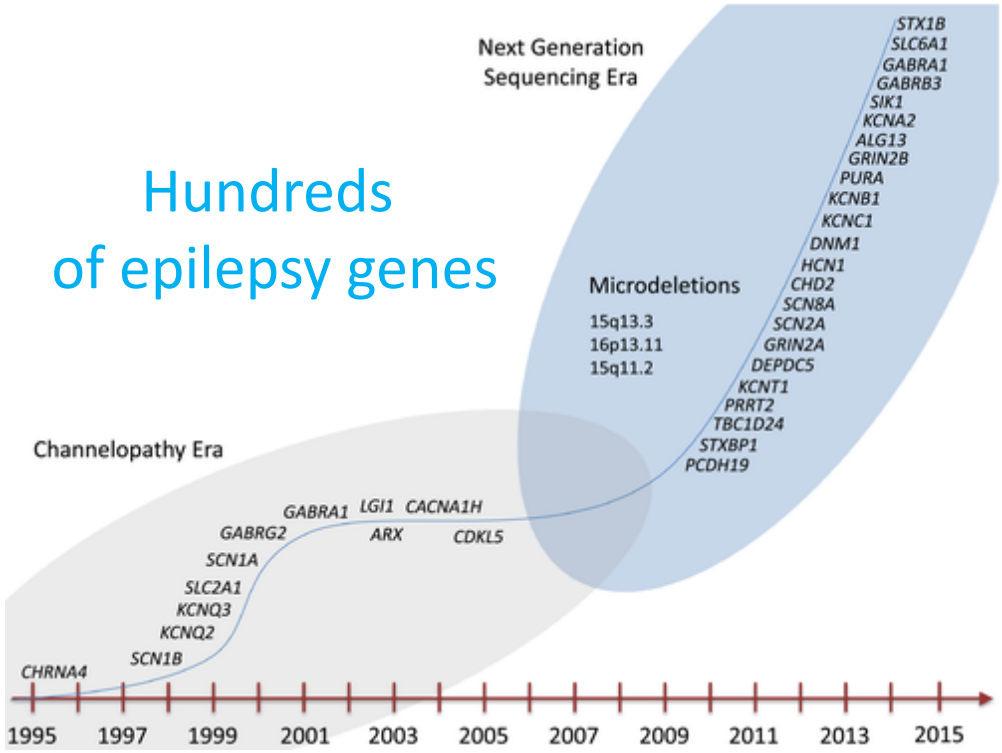
Harder to recruit

Smaller market slice



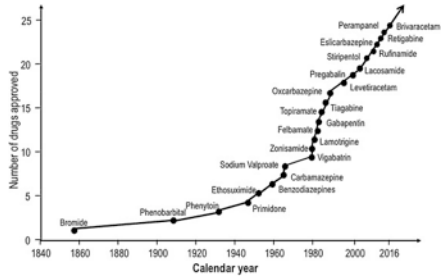
From symptoms to genes

Finding genetic causes of epilepsy



- First epilepsy genes were found for familiar epilepsy
- Later also found in de novo epilepsy (encephalopathies)
- Next Generation Sequencing (gene panels and exome) have led to 400+ epilepsy genes

Evolution of drug discovery in epilepsy



Boom

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Maturation

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Second boom in the epilepsy field

Orphan epilepsies

- Seen as “easier”
- Less patients, but also less competition and better price

From epilepsy to epilepsies

2010

Partial Onset / Focal Seizures

Generalized Seizures

2020

Lennox-Gastaut syndrome

Dravet syndrome

CDKL5 Deficiency Disorder

PCDH19 epilepsy

Tuberous Sclerosis Complex

……

At first, the interest in rare epilepsy syndromes was mainly driven by business reasons

LESS COMPETITION

ENOUGH MARKET

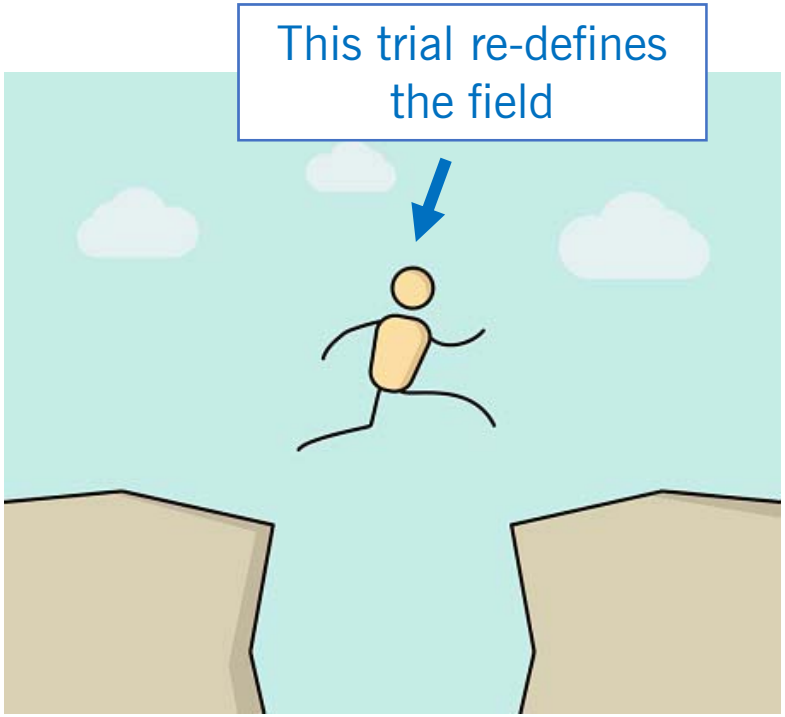
These were still “normal” anti-epileptic drugs

Often the first clinical trial. BIG value!

BEFORE

No clinical trial in that disease:

- Little known
- Seen as “no ready”



AFTER

The disease is now in the map:

- Companies hear about it
- Endpoint validation, trial site and patient identification
- Regulators education

More recently, the interest in rare epilepsy syndromes is driven by science reasons

We can not only diagnose it,
Now we can also treat it

Companies with these genetic approaches like the rare epilepsies because clinical trials are easier

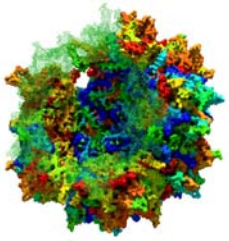
Anti-seizure drugs with new mechanisms

- Looking for refractory syndromes with few or no approved drugs
- BIG value for those syndromes

ASOs to boost or decrease expression

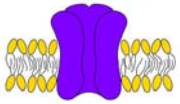
- Splicing ASOs to increase expression
- Antisense ASOs to reduce expression
- Potential for n-of-1?

Viral-based gene therapies



- For diseases with loss-of-function
- Ideal for smaller genes (to use AAV) but in haploinsufficiency can boost gene expression

Small molecule inhibitors, or activators

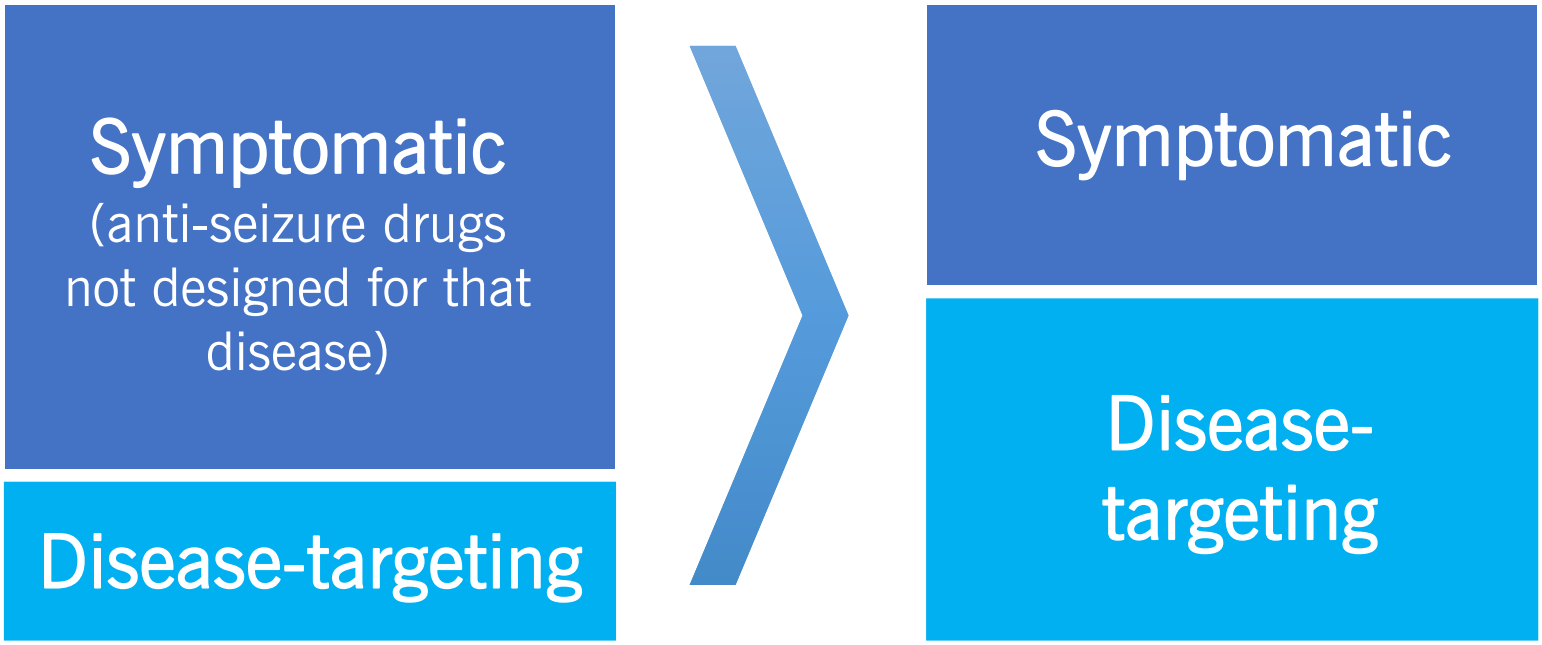


- Ion channel inhibitors for GoF mutations
- Ion channel openers for happloinsuf.

OTHER:

- Enzyme replacement therapy
- Small molecule read through
- X reactivation (?)
- Gene editing (?)

Right now we can see the two type of therapies in development for rare epilepsy syndromes



Not every syndrome at the same time

- Why are some syndromes chosen and no others?

Symptomatic
(anti-seizure drugs)

- **Number of patients**
- Unmet medical need (how the drug can help)
- Level of development of the field: “trial readiness”

Disease-targeting

- **Fit with their technology platform**
- Number of patients
- Level of development of the field: “trial readiness”

We have to **develop a field** before we can think of developing therapies

impatient patients

Take-home messages

1. Genetics have moved the epilepsy field **from symptoms to genes**
2. Rare epilepsy syndromes have revived the old field of **epilepsy** and attracted the new field of **genetic/protein therapies**
3. Epilepsy syndromes are rare diseases, where **patient communities** are major drivers of therapy development
4. Efforts are required to not only **develop treatments**, but to also **develop disease fields** so that they are all trial-ready