

# New targets for innovative diagnostics and treatments: Introduction part 1



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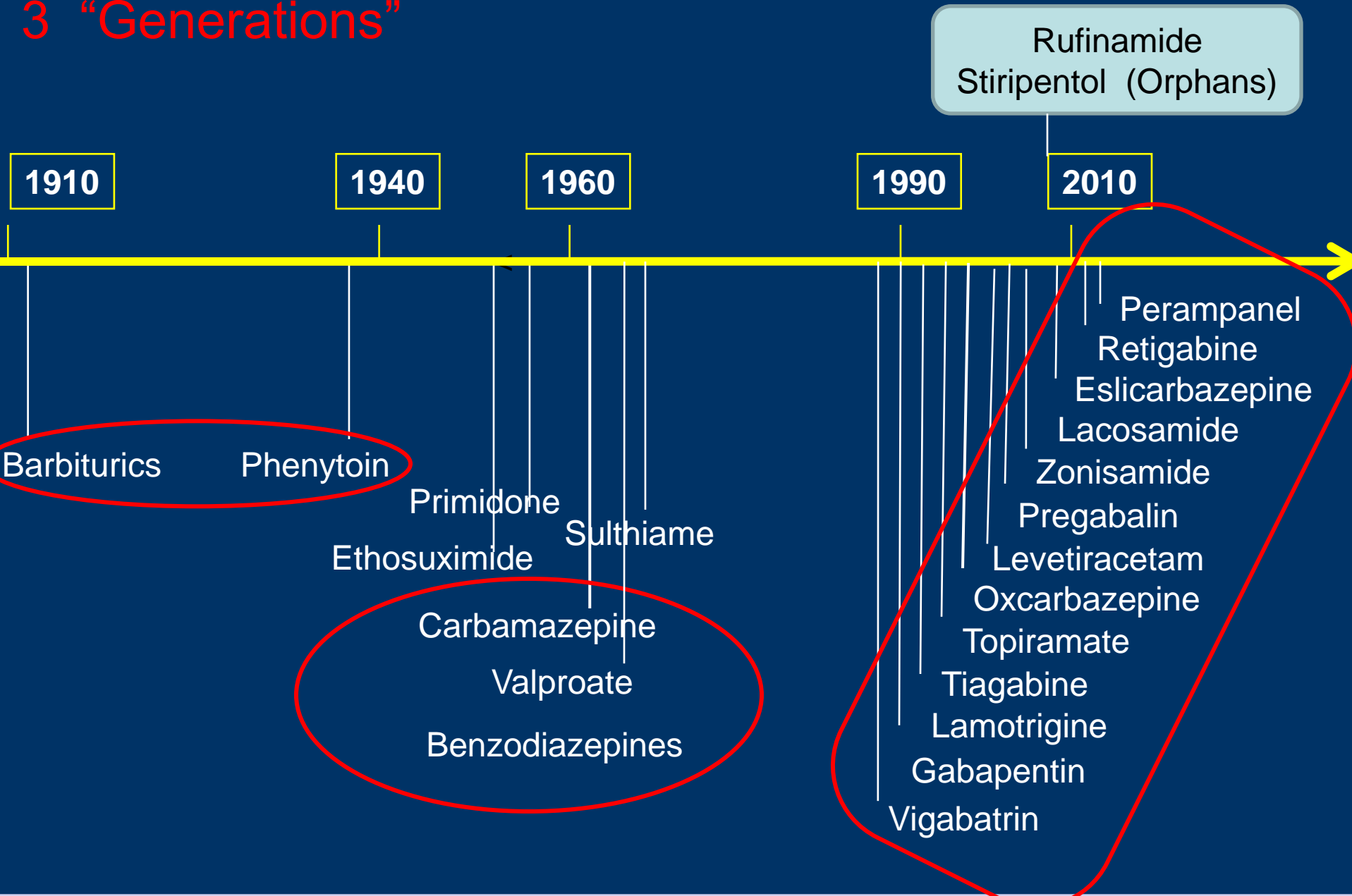
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Paris France



# Marketed AEDs (EU, March 2013)

## 3 "Generations"



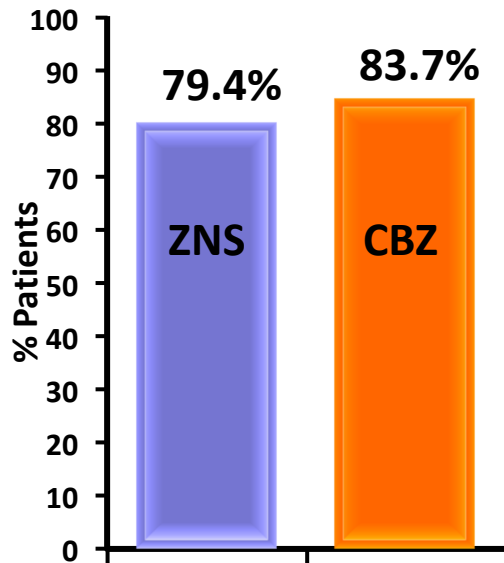
# Benefits to patients with 3rd generation AEDs

- Better tolerability, safety; less blood tests
- Less interactions (oral contraceptives)
- Lower teratogenicity (for some newer AEDs, like LTG, possibly LEV)
- Diversified our therapeutic options in terms of:
  - mechanism of action
  - spectrum of efficacy
  - possibilities for adapting to patient's co-morbidities and needs
- Orphan drugs targeting certain seizure types within specific syndromes  
(Dravet, Lennox-Gastaut)



More possibilities for individualizing drug therapy to a given patient

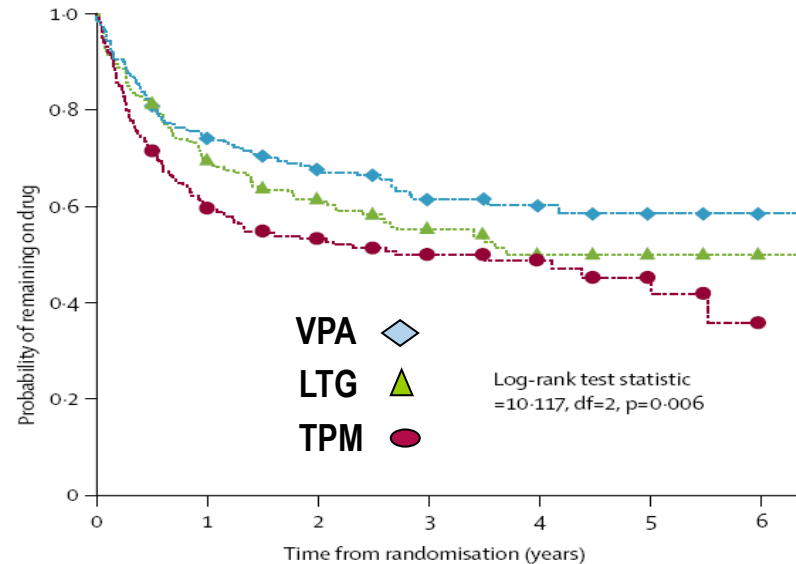
# The newer AEDs did not show superior efficacy over the prior generations



## New onset focal seizures

- ZNS equivalent to CBZ, but not of superior efficacy, like LEV
- Some other newer AEDs (VGB, TGB) were inferior to CBZ in similar head to head studies

*Baulac 2012, Glauser 2013*

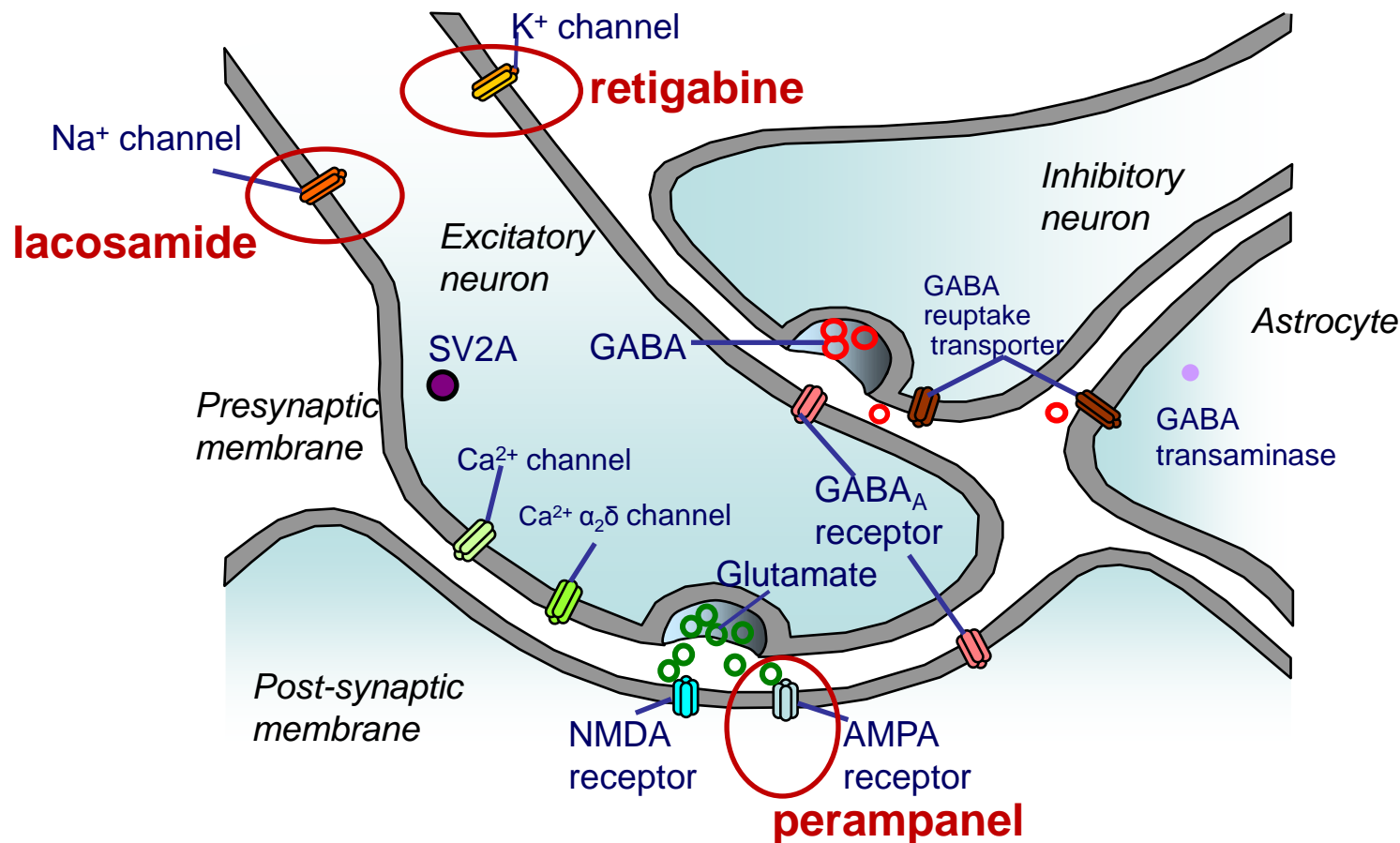


## New onset primary generalized seizures

- VPA of superior efficacy to LTG in primary GTC; TPM  $\leq$  Marson 2007
- VPA and ESM of superior efficacy and effectiveness to LTG in childhood absence seizures *Glauser 2010*

# Mechanisms of action ? All AEDs are targeting ion channels, or transmitter receptors

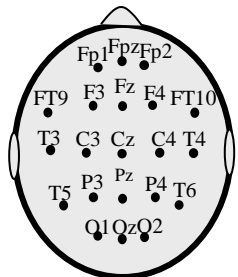
Including the most recently approved in EU



Adapted from LaRoche & Helmers 2004;  
Beyreuther et al, 2007

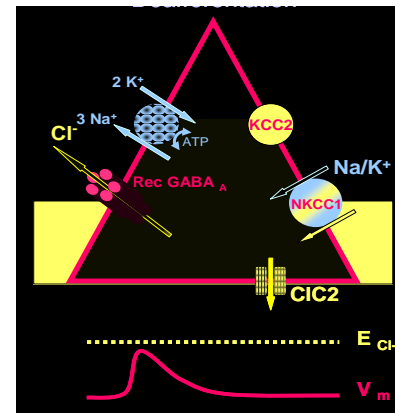
SV2A, synaptic vesicle protein 2A

# Multilevel approaches of the epileptogenic zone in human focal epilepsies

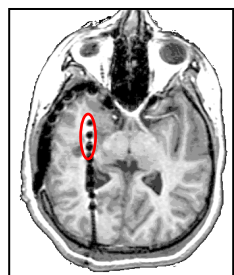


**EEG Scalp**

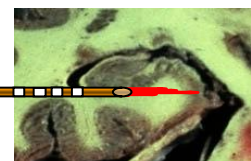
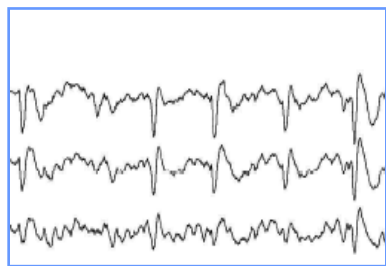
**Pre-surgical investigations in drug resistant focal epilepsies**



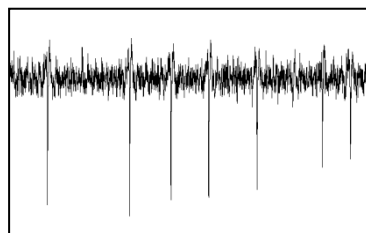
**New drug target: restoring Cl homeostasis Bumetanide**



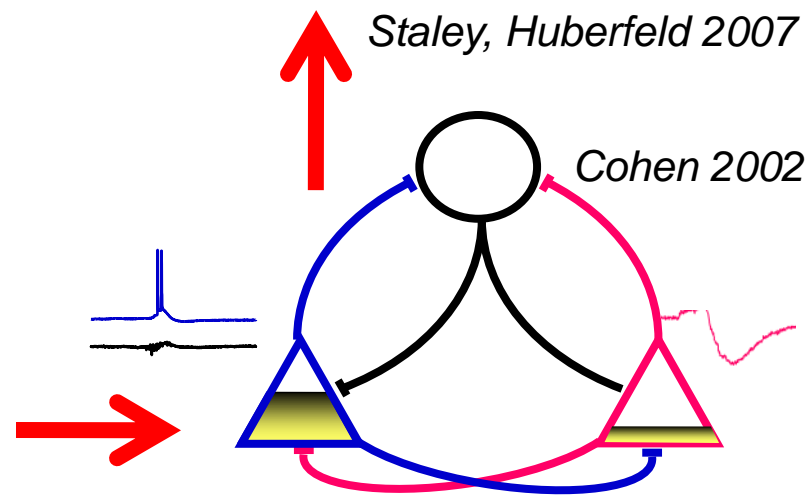
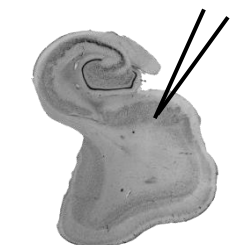
**EEG Intracranial**



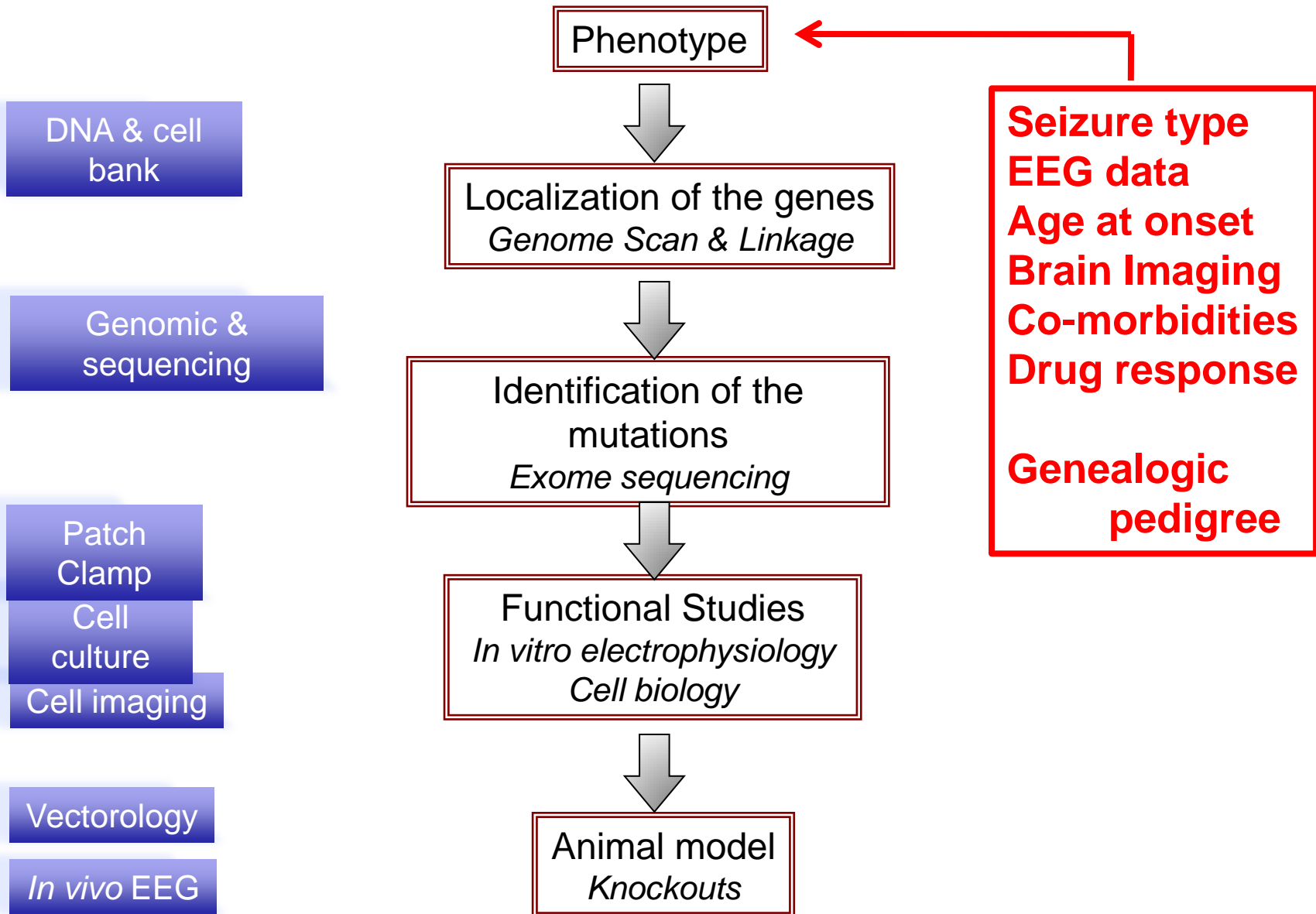
**Microelectrodes in vivo**



**EEG in vitro Post operatively**



# Molecular and physiological basis of genetic epilepsies as models for common epilepsies



# Genes in familial epilepsies: ion channels and beyond

## Ion channel related

## Not directly ion channel related

AchR

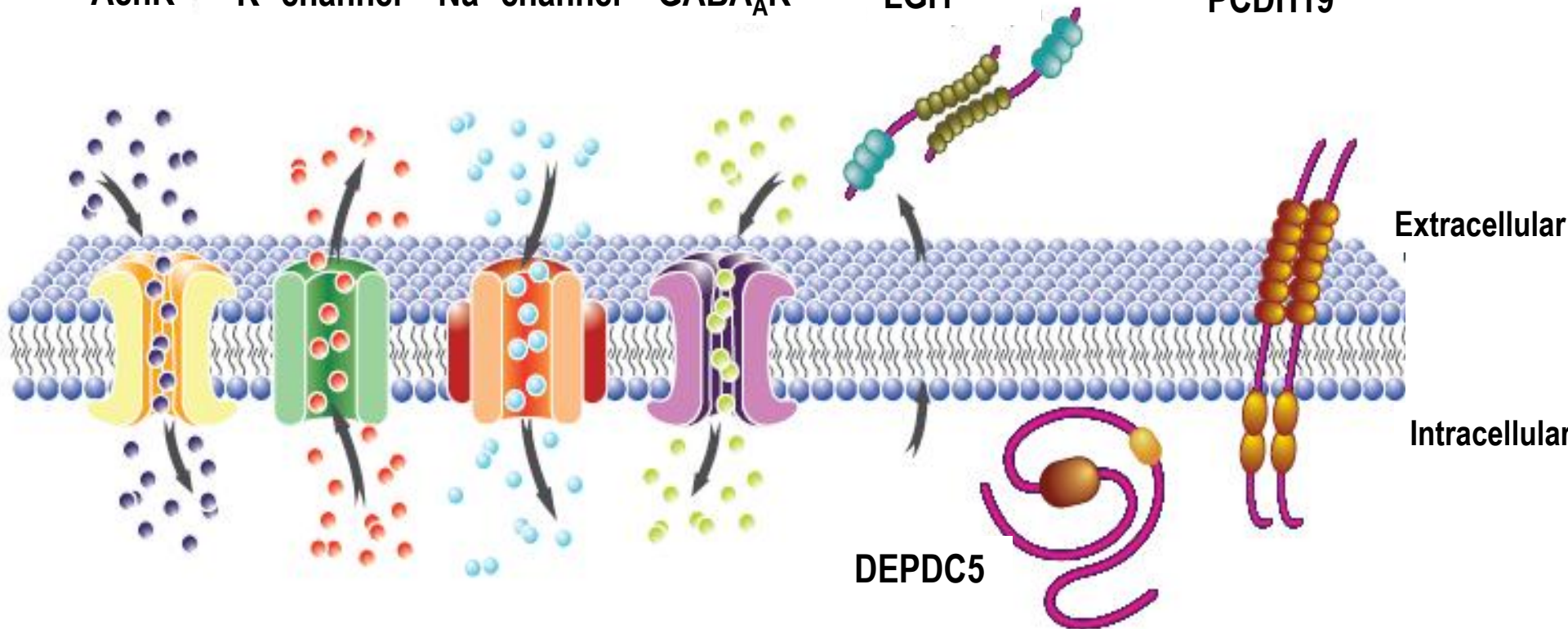
K<sup>+</sup> channel

Na<sup>+</sup> channel

GABA<sub>A</sub>R

LGI1

PCDH19



- AChR: Autosomal dominant frontal nocturnal epilepsy
- K<sup>+</sup>: Benign familial neonatal
- SCN1A: Dravet, GEFS<sup>+</sup>

- LGI1: Familial TLE auditory features
- PCDH19: Dravet syndrome
- DEPDC5: Diverse forms of focal epilepsies: FLE, FTLE, FFEVF



# New targets for innovative diagnostic and treatments : outline

- Dealing with a functional disorder, with intermittent expression
  - New biomarkers that can trace the epileptic neuronal network
  - Help localizing the epileptic zone – Improve surgical treatment
- Design innovative therapeutic strategies, devices
- New AED mechanisms of action for improved seizure control:
  - animal models, in vitro models, human post-operative tissues, genetic and molecular findings, etc...
  - Opportunities for identifying potential new drug targets
  - How to convert a target hypothesis into a pharmaceutical agent, having the desired effect ?



# Strategy and Outcomes with Antiepileptic Drugs

## Newly Diagnosed /treated

