Epilepsy in the developing brain
Antiepileptic drug trials

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Current status – Bad news

- AED (RCT) trials in paediatric Epilepsies
  - are performed **late** (after the trials in adults)
  - are **restricted** to epilepsies also shared by adults (FE, LGS)
  - are designed using **adult methodologies** of trials
- Most EE are still ***therapeutic orphans***
  - Among the 15 new AEDs approved since 1990,
    5 for LGS, 1 for IS/DS, none for others
  - 2/3 of **off-label prescriptions** in EE, 90% in neonates

Current status – Good news

- **Paediatric Regulation (EU 2006)**
  - Paediatric drug development mandatory (PIP)
    Paediatric evaluation structure (PDCO)
    Incentive measures (orphan drugs, PUMA, ..)
  - Since 2006, 2 new AEDs for EE
- **European Framework Program (FP7)**
  - Programs for Rare Diseases
  - Public/private partnerships (SME)
  - Networks (physicians, pharmacologists, scientists, industry, patients)
- **Priority List for off-patent paediatric drugs (EMA)**
  (uncomplete)
- **Guidelines of clinical investigation of AEDs** (EMA 2010)

Paediatric trials: ethical dilemma

- **Need for trials** (to avoid off-label use)
  - Demand for **paediatric** trials (EU)
  - Demand for **quality** trials (EU)
- **« Protect » children from research**
  - Avoid **unuseful** trials (use already available data)
  - Decrease **invasiveness** of trials (respect children specificities)
  - Expose the **minimum number** of children to trials

What needs to be done

1- Adapt the current process to EE

- **Promote access of EE to AED trials**
  - Minimise trials in Focal E (**extrapolate** from adult trials) *Chiron et al 2008, Rheims et al 2008*
  - Promote **early** EE trials (guidelines)
  - Identifying EE candidate(s) (**exploratory** step) *Chiron et al 2013*
- **Develop new endpoints specific for EE**
  - EEG endpoints (CSWS)
  - Cognitive endpoints (scales, composite scores)
  - Adapt duration to deterioration course

What needs to be done (cont')

2- Use innovative methodologies of trials

- **Small populations**
  - Homogeneous subpopulations of EE

    TS-IS/VGB n=10 *Chiron et al 1997,* DS/STP n=11 *Kassai et al 2008*
  - Enrichment withdrawal trials FE 1m-4y/LTG n=19 *Pina-Garza et al 2008*
- **Adaptative designs**
  - Sequential analysis (triangular test, bayesian)
- **Modeling and simulations**
  - Population PK 1m-4y: LVT *Chhun et al 2009*, TPM *Bouillon-Pichaut et al 2011*
  - Bridging dose studies 2y-10y PK/PD model: TPM *Girgis et al 2010*

What needs to be done (cont')

3- Develop new therapeutic targets

- **Based on genes identified in EE**
  - DS (*SCN1A*), IS (*CDKL5,ARX,..*), MPSI (*KCNT1*), ..
- **Based on mechanisms identified in EE**
  - TS (mTOR): everolimus
  - depolarising GABA (neonate, E.surgery, autism, ..): bumetanide
- **Based on inflammation processes associated to EE**
- **Considering induced-apoptosis**
  - Pregnancy, neonates and infants

What methods to improve

- **Promote transdisciplinary research**
  - Transgenic animal models ⟺ humans (ex: DS,TS)
  - Computational models ⟺ humans/animals (ex:FE)
  - Biomarkers (basic science, imaging, neuropsycho)
  - Adults ⟺ children
- **Promote translational platforms** (ex: neurATRIS France)
- **Promote translational training** (ex: ESDPPP-EUDIPHARM)
- **Promote translational networks** (ex:FP7 collaborative projects)
- **Promote exchanges with patients organisations**
- **Promote exchanges with Agencies** (EMA)

Expected impact

- **Improve the quality of care in children with EE**
  - Reduce the off-label use of AEDs
  - Give therapeutic options specific to EE
- **Improve the quality of life of children with EE**
  - Improve epilepsy control
  - Improve cognitive outcome
- **Provide a model for other rare paediatric diseases**