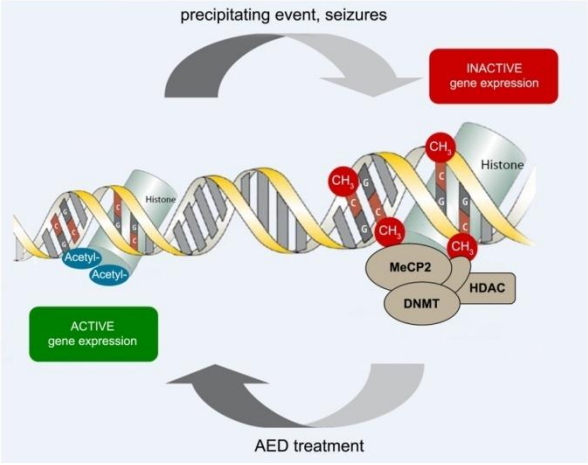
EUROPEAN SCIENCE FOUNDATION
SETTING SCIENCE AGENDAS FOR EUROPE

EUROCORES Programme
European Collaborative Research

EuroEPINOMICS
Functional Genomic Variation in the Epilepsies

EpiGENet

Epigenetic Pathomechanisms Promoting Epileptogenesis in Focal and Generalized Epilepsies



Epigenetics - Definitions

The interaction of genes with their **environment** which bring the phenotype into being

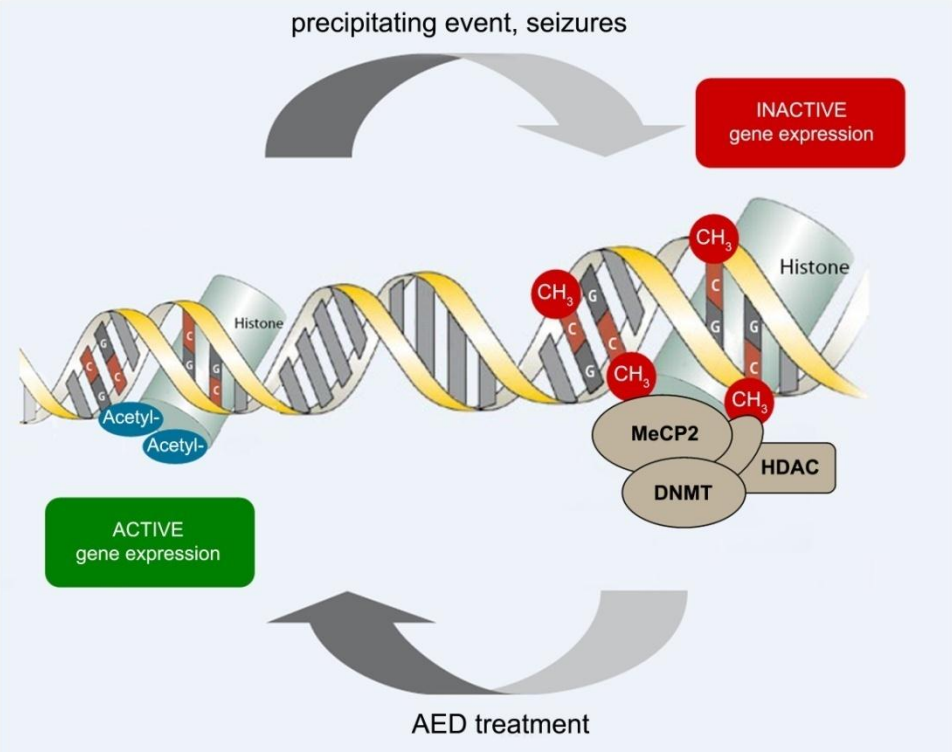
(Conrad Hal Waddington, 1940)

Mitotically and/or meiotically **heritable** variations in gene expression that are **not caused by changes in DNA sequence**

(Russo et al., 1996)

Structural adaptation of chromosomal region so as to register, signal, or perpetuate altered **activity states**

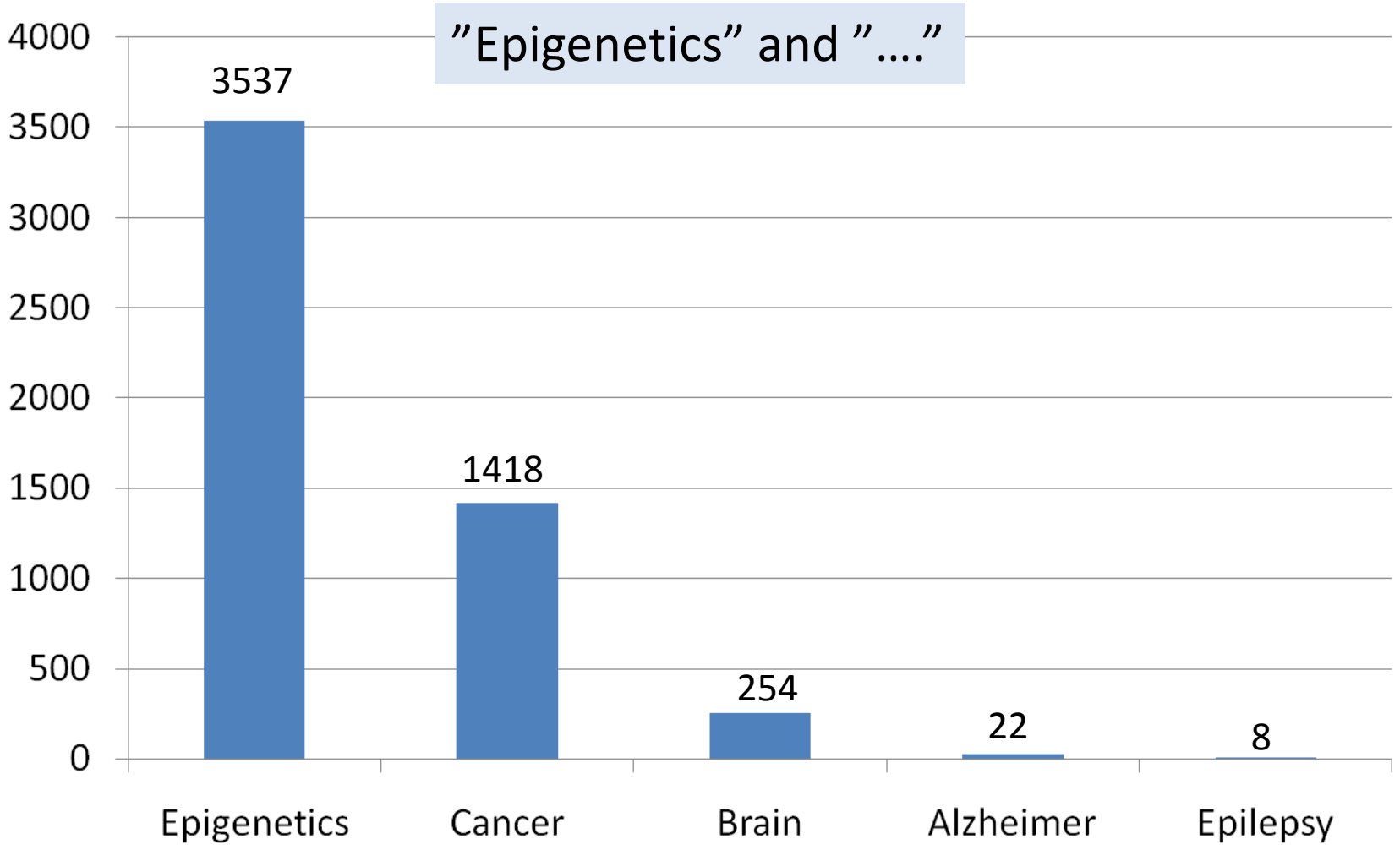
(Bird, 2007)



Kobow and Blümcke, Epilepsia 2011: in press

Epigenetics Statistics

PubMed Sept 15, 2011



EpiGENet - Hypothesis

Various types of epilepsies share common
epigenetic pathomechanisms

Objectives

To characterize common
epigenetic pathomechanisms of epileptogenesis

To identify
new targets for pharmacotherapy

Aims

- bioinformatic identification of **common** traits in CEG (candidate epileptogenesis gene) **expression** in **different epilepsy models**, and prediction of shared regulatory promoter elements - **transcriptomics**

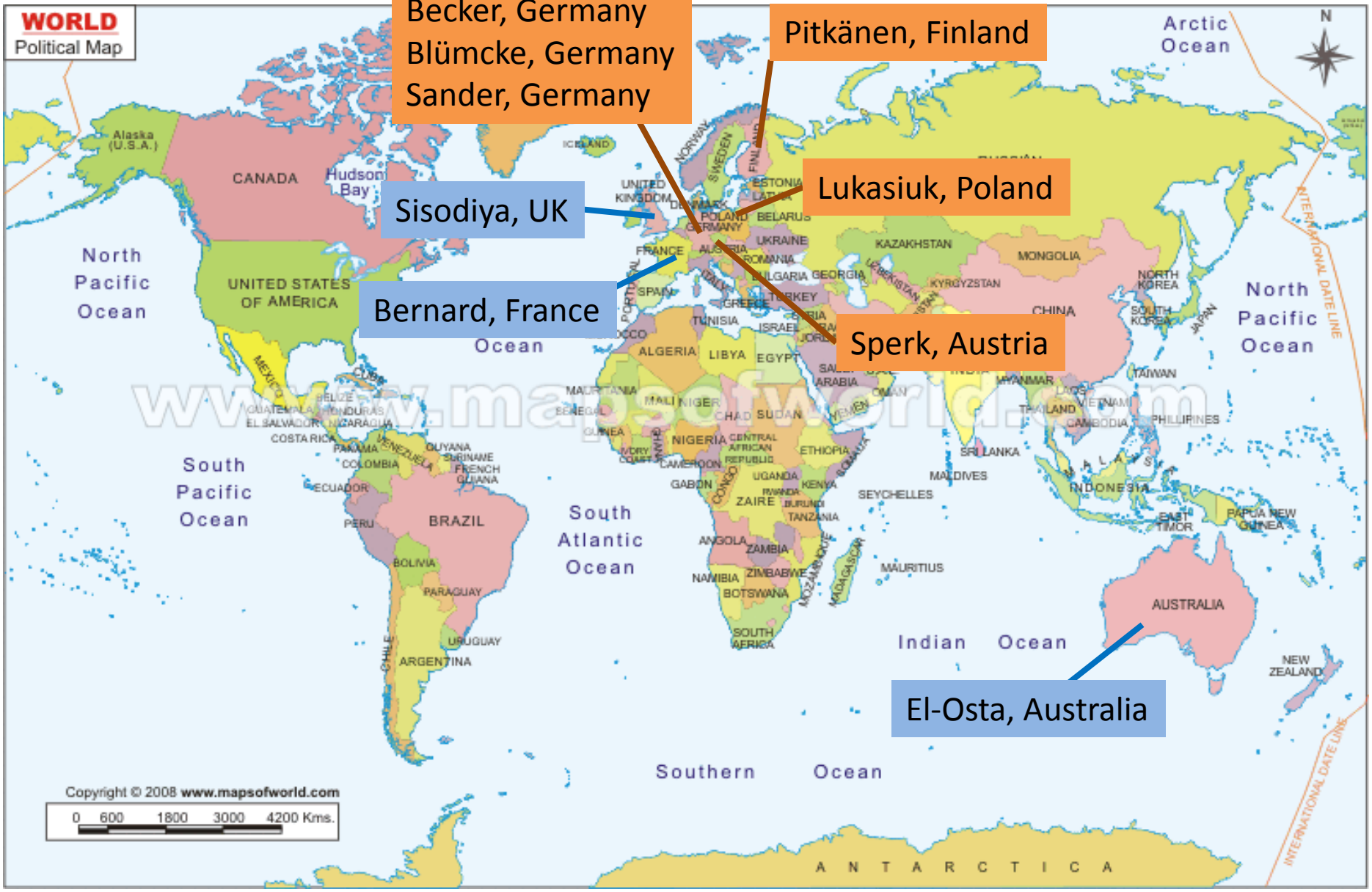
- molecular genetic dissection of **genetically regulated CpG methylation sites** conferring risk to generalized and focal epilepsies - **methylome**

- *in vitro* analysis of **joint epigenetic modulation patterns** including histone modifications, DNA methylation, and transcription factor modules - **candidate genes -**

- **validate identified CEGs and epigenetic mechanisms** in TBI and SE models as well as in human epileptic tissue or blood cells (from IGE patients) - **transcriptomics vs. methylome/candidate genes -**

- use of viral transfer of **shRNAs or epigenetic pharmacotherapy** to interfere with epigenetic mechanisms and attenuate or prevent the progression of chronic epilepsy in clinically relevant animal models

EpiGENet - Participating Centers



Individual Projects

IP1 - Pitkänen: Epigenetic modulation of epileptogenesis in pathologies associated with increased amyloidogenic APP cleavage - TBI and APP/PS1 mouse

IP2 - Lukasiuk: Integrated bioinformatic analysis of gene expression databases and methylation maps from experimental animal and human epilepsies

IP3 - Sperk: Promoter modification and gene silencing of neuropeptide genes in an experimental animal model and in human temporal lobe epilepsy

IP4 - Becker: Transcriptional mechanisms orchestrating epileptogenesis (ion channels)

IP5 - Blümcke: Genome-wide and CEG-specific methylation analysis in experimental and human epilepsy brain tissue

IP6 - Sander: Genom-wide search for genetically regulated CpG methylation sites predisposing to idiopathic generalized epilepsy

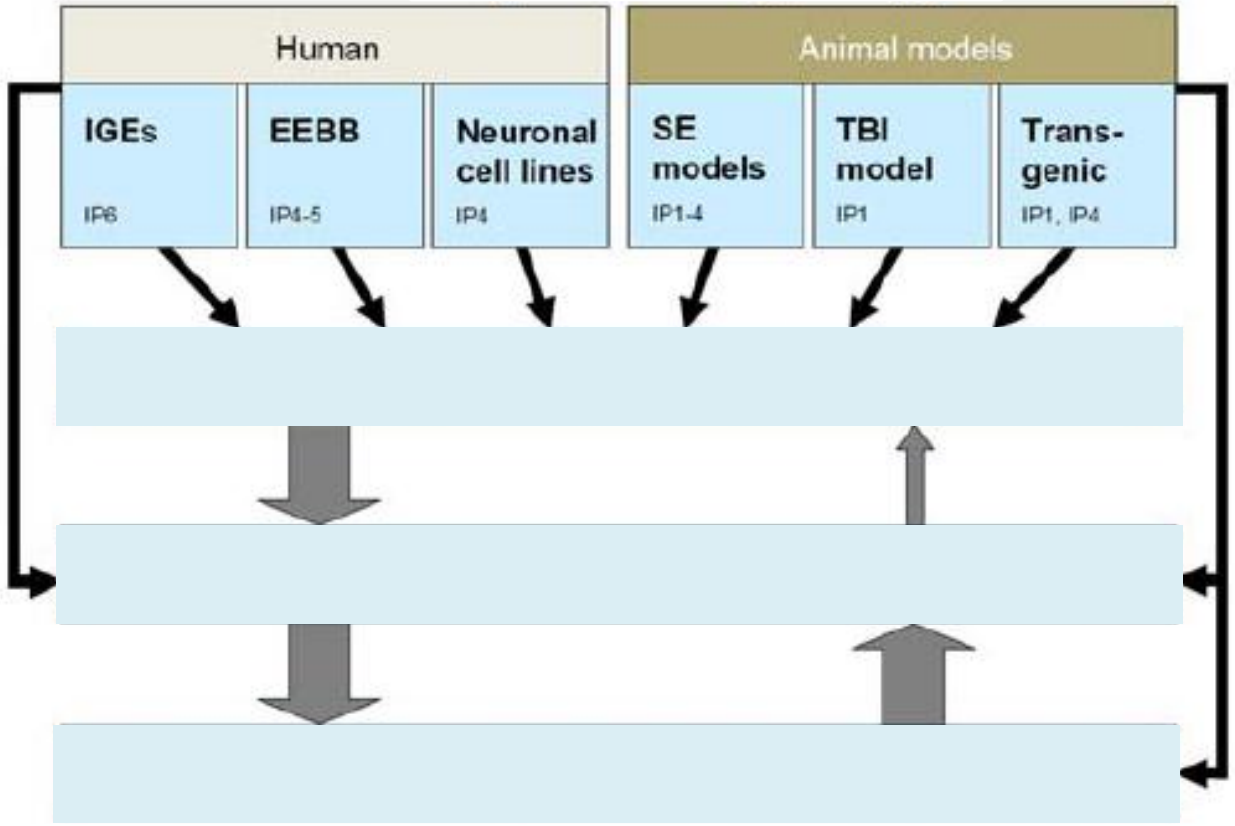
Individual Projects – Associate Partners

AP1 - El-Osta: Deep sequencing of the human methylome

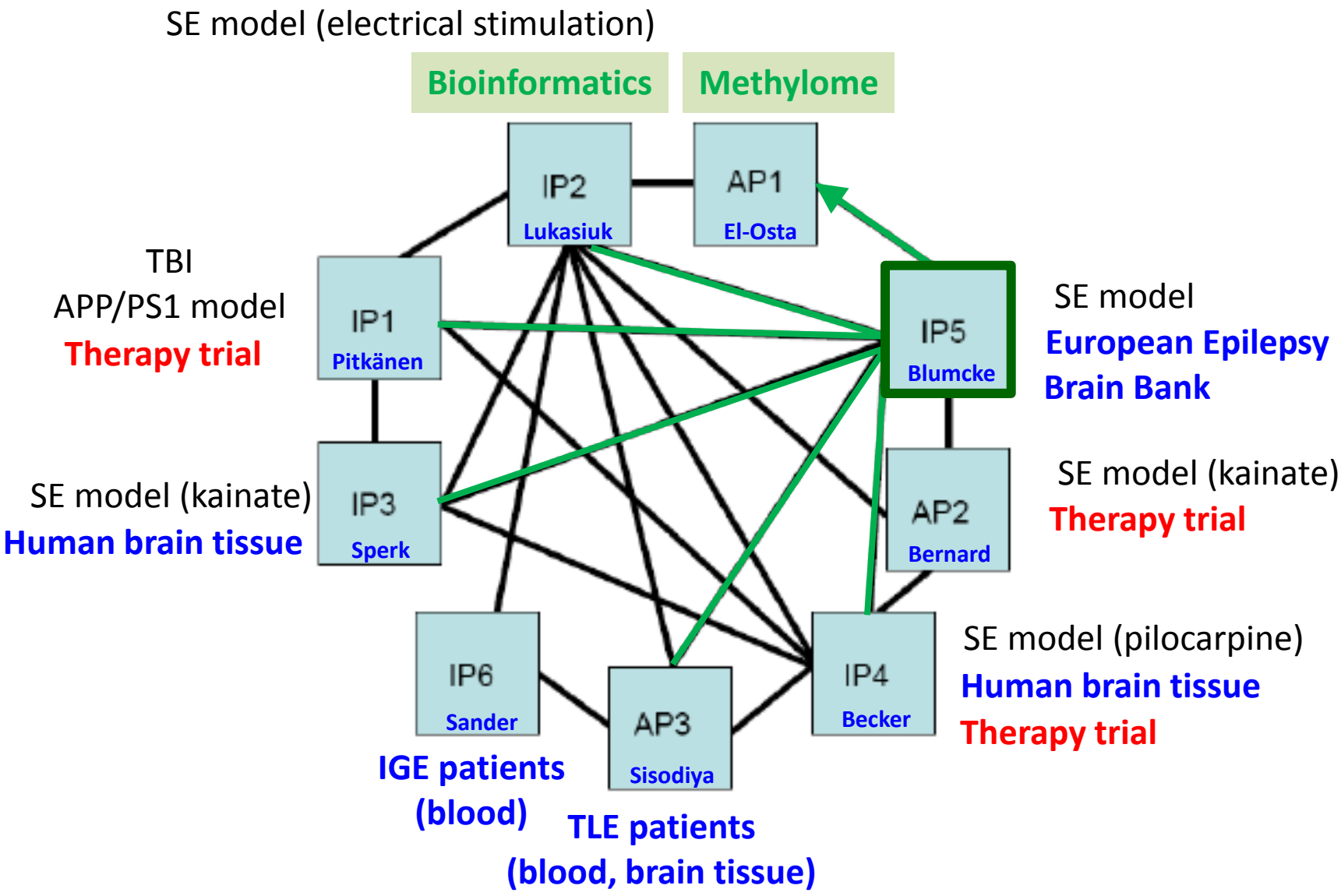
AP2 - Bernard: Epigenetic pharmacotherapy in a TLE animal model

AP3 - Sisodiya: Linkage analysis between epigenetics and pharmacogenetics in patients with temporal lobe epilepsy

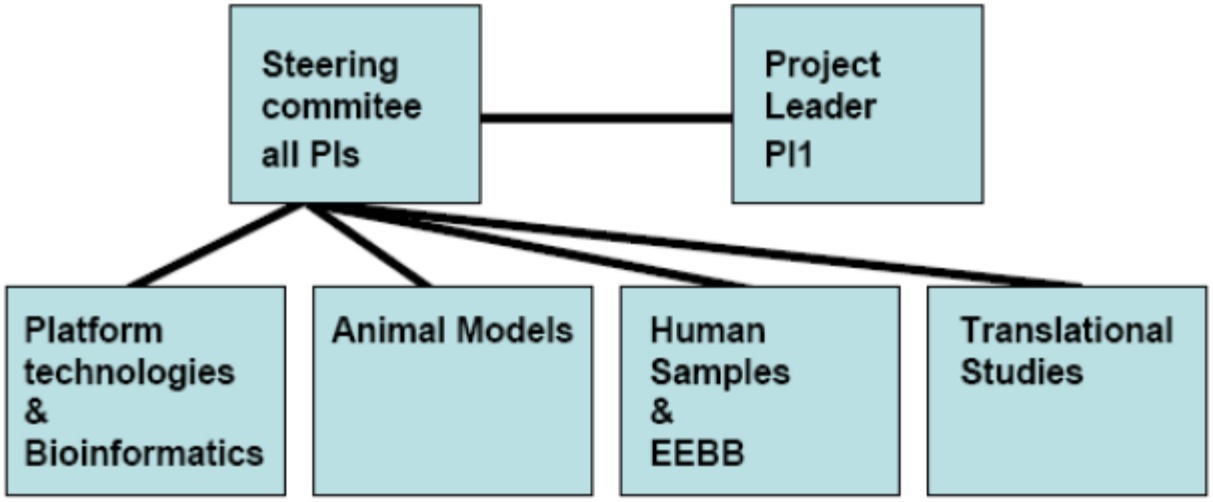
Integration of Projects



Integration of Projects



Management


Steering commitee all PIs
Project Leader PI1
Platform technologies & Bioinformatics
Animal Models
Human Samples & EEBB
Translational Studies

Discussion Points with Other CRPs

- sharing of materials
- sharing of methods
- joint meetings

Written Declaration on Epilepsy

http://www.europarl.europa.eu/wps-europarl-internet/frd/vod/player?language=en&menusearchfrom=bymep&pageby=unit&idmep=97016&discussionId=0&page=0&category=0&format=wmv&askedDiscussionNumber=0

EUROCORES: EuroEPINOMICS CRP: EpiGENet

Epigenetic Pathomechanisms Promoting Epileptogenesis in Focal and Generalized Epilepsies

Genome-wide search for genetically regulated methylation sites predisposing to idiopathic generalized epilepsies

EuroEPINOMICS Kick-Off Meeting
Strasbourg, 20th September 2011

DFG grant: SA434/5-1

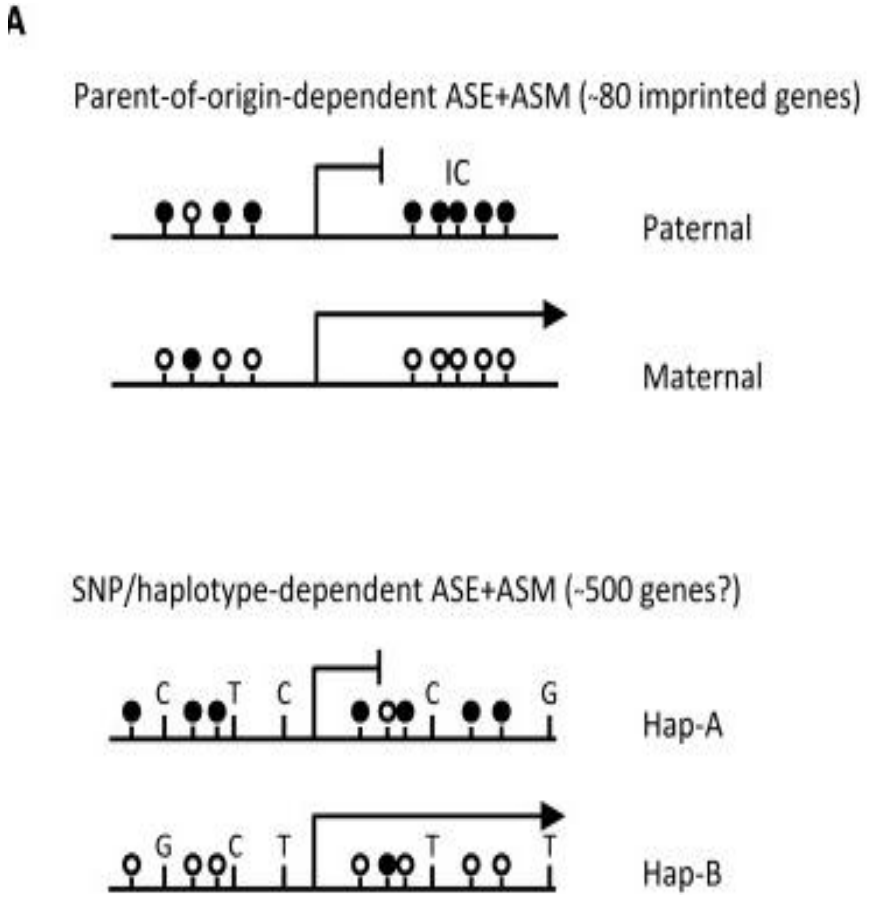
Cologne Center for Genomics

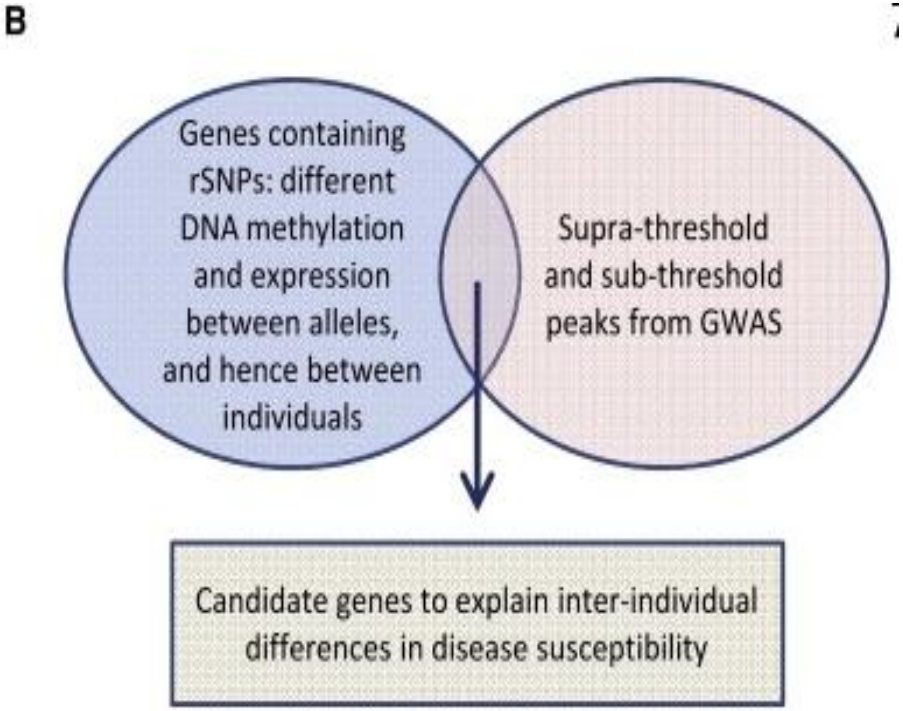
Universität zu Köln

Aims & Objectives

- **Hypothesis: Common susceptibility alleles have frequently a regulatory effect on methylation and/or gene expression**
- **Aims: Dissection of regulatory sequence variants conferring risk to idiopathic generalized epilepsies (IGEs)**
- **Search for genetically regulated methylation sites predisposing to IGE (Rational: 10% of all genes)**
- **Evaluation of genomic imprinting in chromosomal regions displaying parent-of-origin effects**

ASM for identifying regulatory SVs in GWAS





Combined genetic/epigenetic strategy for mapping disease susceptibility genes

Search for allele-specific methylation (ASM)

- **Correlation analysis** of **SNP alleles** and **quantitative CpG methylation states** in 400 IGE patients (blood cells), 150 mTLE patients (brain tissue)
- Genotyping of 569K SNPs (Affymetrix AXIOM CEU Array)
- Quantitative assessment of the methylation state of 450K CpG sites (Illumina Infinium HumanMethylation450 BeadChip)
- **Prioritizing ASM CpGs associated with IGE**
  Validation in 500 IGE parent-offspring trios
- **EPICURE IGE GWAS:** 2500 IGE patients vs 7000 controls
  600 IGE parent-offspring trios

Evaluation of genomic imprinting in chrom. regions displaying parent-of-origin effects

- **GWAS** in 600 IGE parent-offspring **trios**
- Dissection of **parent-of-origin associations**
- Regional search for **imprinted regions**
- Search for peudo-**recessive susceptibility alleles**
- **Validation in brain tissue** of mTLE patients
- **Replication** by pyrosequencing in extended samples