EUROPAIN: First achievements of a consortium deciphering chronic pain
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Schematic Project Overview

**Studies in animals**

1. Neurobiological mechanisms of chronic pain.
   - Identification of novel pain targets

2. Improving animal models of pain

3. Translational pain models in humans

4. Quantitative assessment of pain in patients

5. Risk Factors for chronic pain

**Studies in man**

6. Bioinformatics / Data warehouse

7. Training centre

WP 8: project management

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Participants

**EFPIA**
- AstraZeneca
- Boehringer Ingelheim GmbH
- Pfizer Limited
- Eli Lilly and Company Ltd
- Esteve S.A.
- UCB Pharma
- Sanofi-Aventis R&D
- Grünenthal GmbH
- Astellas
- Abbott

**Academia**
- King’s College London
- University College London
- University of Oxford
- Imperial College London
- Christian-Albrechts-Universität zu Kiel
- Ruprecht-Karls Universität Heidelberg
- Technische Universität München
- BG Universitätsklinikum Bergmannsheil GmbH
- Klinikum der Johann Wolfgang Goethe-Universität
- Aarhus University Hospital
- Region Hovedstaden
- University of Southern Denmark

**Financing**
- IMI funding: 6 MEUR
- EFPIA contribution, mainly in kind: 12.5 MEUR
- Total project cost: 18.5 MEUR

**SME**
- Neurosciences Technologies S.L.
A CONSORT Diagram Of an IMI Consortium

Project preparation

Project year 1
10 EFPIA partners

Project year 2
8 EFPIA partners

Project mid year 3
9 EFPIA partners

End year 3 - ?
11 EFPIA partners

Project years 4-5

Project closure year 6

? EFPIA partners

12 universities, 1 SME

- One exit, One acquisition
- One joining, One reorg
- Two joining, One reorg -?

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The Neuropathic Pain Patient

• 18% of the European population suffer from treatment demanding chronic pain
• 5% of the population has neuropathic pain.
• Low quality of life and high burden of illness on patients and society
• High unmet need - 1/3 of chronic pain patients obtain adequate pain relief
• EUROPAIN aims at improved understanding of and facilitated development of new treatments for chronic pain.

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Risk Factors For and Prevention of Post Traumatic Neuropathic Pain

- Prospective studies in patients undergoing mastectomy, herniorrhapsy, thoracotomy and chemotherapy

Results provide new information on:
- Predictive factors for development of post traumatic neuropathic pain
- Phenotype data useful for patient stratification.
- Evaluation of the role of different surgical techniques
- This program has already produced 19 (!) publications (Kehlet and coworkers)
Placebo Effects In Clinical Pain Trials

- Placebo data from clinical trials conducted by AstraZeneca, Pfizer and Grünenthal are being pooled.
- Effects of patient characteristics as well as different design and operational questions are being analyzed together with Aarhus University (L Vase) to identify risk factors for large placebo responses in future trials.
Mechanistic Endpoints In Neuropathic Pain Trials

• "Oxcarbazepine in peripheral neuropathic pain: Predictors of response – a randomized, double-blind, placebo-controlled, cross-over study" (NCT01302275) is being conducted at two sites in Denmark.

• In-kind support into study design and initiation from AstraZeneca and Pfizer. FSI in end 2010.

• Patient recruitment is going very well.
Resting Brain Activity (RSN) based on MRI, can visualise functional changes in neural networks in chronic pain patients.

In chronic widespread pain, there is a functional disintegration in RSN.

Even in healthy subjects, ongoing activity between pain processing brain regions in the resting state will change with repeated exposure to pain.
Change in resting state pain network in healthy subjects exposed to repeated pain stimulation.

*Riedl et al, 2011*
Human pain modelling

Evoked pain

Ongoing/spontaneous pain

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Translational Pain Models In Humans

• Meta-analysis of human experimental pain studies
• Development and validation of new models – menthol model, freeze model, sleep deprivation, etc.
• Translational analysis across species – biomarkers in UVB, microneurography
• New measures – Arterial Spin Labelling (ASL) technique
A study in healthy subjects exposed to topical capsaicin shows increased fMRI activity in the brain stem in response to punctate stimuli in the area of secondary hyperalgesia.

Gabapentin, ibuprofen and a placebo were used to validate this model.
The Effect of Sleep Deprivation On Pain Thresholds  

Univ of Heidelberg and Lilly

Human volunteers are more sensitive to pain when sleep deprived…

…and so are rodents

*HS=Habitual Sleep, SD= Sleep Deprivation
Preclinical Modelling and Biomarkers

• Can we make models more predictive?
• What and how do and can we measure?
• Evoked pain
  
Ongoing/spontaneous pain

I'm in pain
The Challenge of Measuring Spontaneous Pain Behavior

- The Burrowing model validated Imperial College and Pfizer, then successfully implemented at Boehringer-Ingelheim, Grünenthal, Aarhus University and AstraZeneca across a variety of pain models.

The effect of Gabapentin on the burrowing of naive rats

Saline
30mg Gabapentin
100mg Gabapentin

The effect of Gabapentin (30 mg/kg) reverses TNT-induced burrowing deficit

Naive
Sham
TNT

Ibuprofen (30 mg/kg sc) reverses CFA-induced deficits in burrowing

Pre-CFA
Post-CFA
Microneurography Measuring Neuronal Excitability and Spontaneous Firing
(Neuroscience Technologies, Barcelona)

- Several models have been characterized.
- Automated analysis software developed.
- Publications on preclinical, clinical and translational aspects
- Cross species consistency exists in the response to nerve injury.
Translational Pain Biomarkers – Gene Expression In UVB Model

A collaboration between King’s College London, Pfizer, Boehringer-Ingelheim

Figure 2: Comparison of cytokine/chemokines expression in UVB irradiated

R² = 0.425
p = 0.053×10⁻⁶

CXCL5

Figure 3: Gene Over Expression in the rat paw skin after UVB irradiation

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Neurobiological Mechanism of Chronic Pain - Lipidomics  

Gerd Geisslinger - Frankfurt

Figure 5: Lipid profiling using LC-MS/MS measurements in the zymosan model

Figure 6: Lipid levels in paws at different times after zymosan injection

Gerd Geisslinger lab
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Operational excellence

- **In human studies**
  - Consensus on protocols and testing procedures.
  - Certification of investigators.
  - Common database for phenotypes.

- **In preclinical experiments**
  - Consensus for standardisation and best practise to ensure ethics and quality.
  - A library for methodology protocols.
  - Guidelines for designing and reporting animal studies.
Has This Effort Lived Up To Expectations?

• More than 70 publications – articles, abstracts, presentations, etc.
• Project deliverables and budget on track.
• Scientific results ready for implementation

What have we gained?

• Scientific interactions between pharma and major KOLs – mutual benefit
• Scientific interactions pharma – pharma
• Increased common understanding
What Are the Challenges and Learnings?

Overall challenges
• EFPIA partner reorganisations
• Bureaucracy

EFPIA partner challenges
• In-house FTE allocation
• Reorganisations

Academic partner and SME challenges
• Travel budgets
• Budgets underestimated at application
EUROPAIN - Bridging the Translational Gap

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