

Improving the care of patients suffering from acute or chronic pain

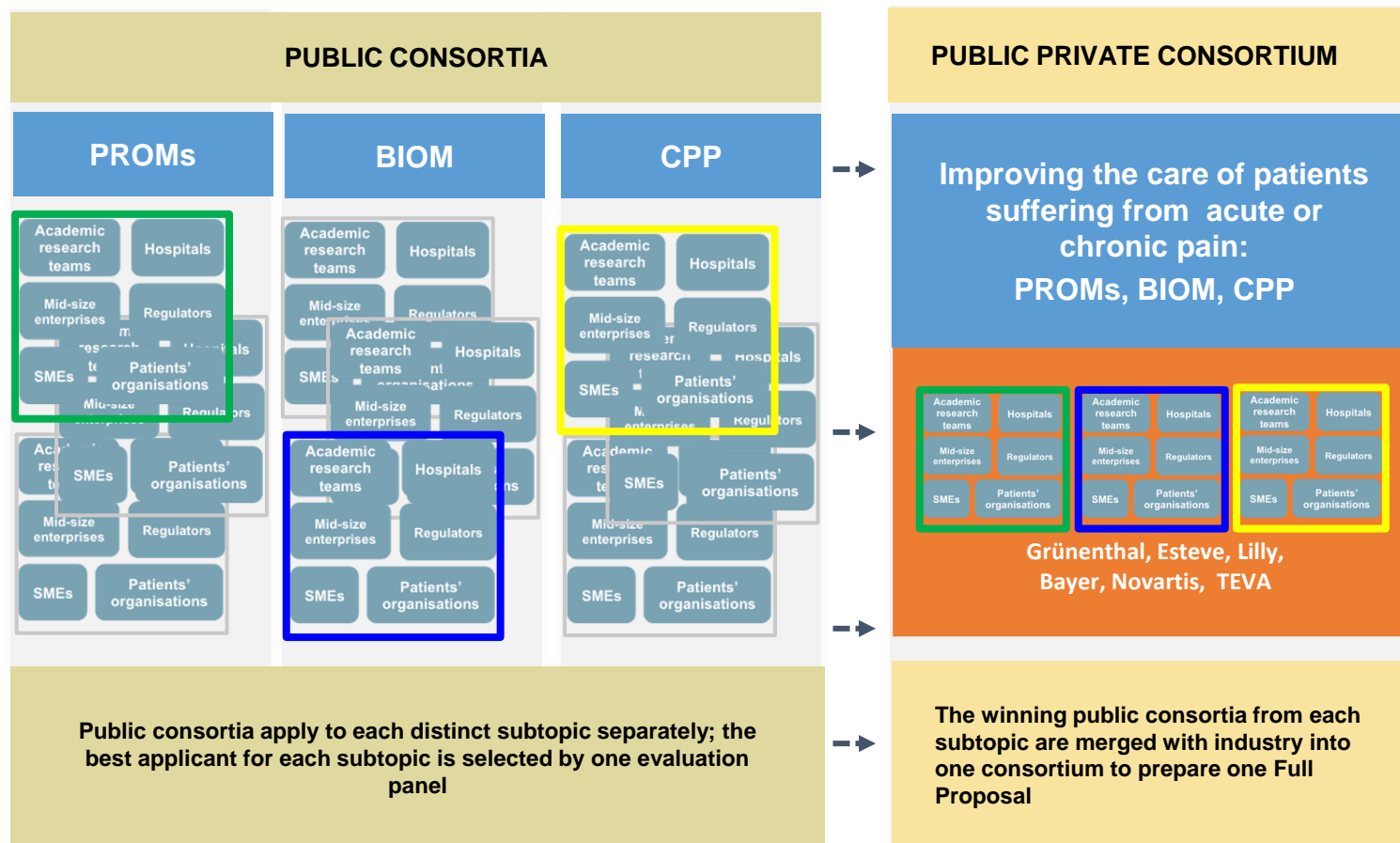
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Pain Topics

- The continued high need for improving health care in pain management is the scope of this Topic.
- The Topic consists of three Subtopics, each of which addresses a specific aspect and scientific challenge:
 - **Subtopic 3A:** using Patient Reported Outcome Measures to improve the management of acute and chronic pain (PROMs).
 - **Subtopic 3B:** improving the translatability of pharmacodynamic biomarkers in pain pathways of healthy subjects and preclinical species (BIOM).
 - **Subtopic 3C:** improving translation in chronic pelvic pain (CPP).

Call Process

Allow Sub-consortia for the three Subtopics at stage 1 and merge the winning Sub-consortia at Stage 2 into a single Consortium with the Industry Consortium:



Call Process

- Short Stage 1 proposals from Applicants should address only one Subtopic.
- If Applicants wish to submit for more than one Subtopic, then separate short proposals should be submitted.
- To allow cross-fertilisation and full data sharing within the Subtopic Consortia, and to ensure the highest impact whilst maintaining an economy of scale, a single Full Proposal will be submitted after merging the Applicant and EFPIA Consortia at Stage 2.
- The Full Proposal will include the individual activities of all three Subtopic Consortia, as well as common activities such as overall governance, communication, dissemination, and data and knowledge management.

Call Process

- At Stage 2, a single Full Proposal will be submitted by the Topic Consortium which will be created by merging the winning Applicant Consortia of Subtopics 3A, 3B and 3C with the Industry Consortium.
- All participants working under this Topic (i.e. Subtopics 3A, 3B and 3C) will be part of the same Grant Agreement.
- An overall Project Coordinator (a member of one of the winning Applicant Consortia) and an overall Project Lead (from the Industry Consortium) will be nominated by the Topic Consortium at the start of preparation of the Full Proposal.

Suggested Governance of the Topic

- Governance of the overall Project will be assured by a partnership between a Project Coordinator from the Applicants on one side and a Project Lead from the industry consortium on the other.
- The Subtopic-specific governance structures will be maintained and guaranteed for each Sub-topic by a partnership between one leading member of the respective Applicant Consortium together with one leading member designated by the Industry Consortium.

Overall governance

1 Topic Coordinator (Applicants) + 1 Topic Lead (Industry)

Sub-topic 3A PROMs

1 Sub-topic Coordinator
(Applicants)

+

1 Sub-topic Lead (Industry)

Sub-topic 3B BIOM

1 Sub-topic Coordinator
(Applicants)

+

1 Sub-topic Lead (Industry)

Sub-topic 3C CPP

1 Sub-topic Coordinator
(Applicants)

+

1 Sub-topic Lead (Industry)

Key deliverables

- Key deliverables for Subtopics: *refer to the relevant Subtopic slides.*

Deliverables of the overall Topic which have to be considered when preparing the submissions for each Subtopic:

- A joint approach to data and knowledge management is needed to ensure the same standards are used for the three Subtopics and that fully interoperable data integration and meta-analysis are possible.
- A common approach for communication and dissemination of data and results will be adopted, as well as for engagement with external stakeholders and collaborators, and ethical considerations.
- A comprehensive strategy for sustainability should be described.

Expected contributions of the applicants: Grant administration

- Work Package 1 “Project Management” of the Applicant Consortia should include elements to ensure proper functioning of each Subproject, bearing in mind that modifications will be necessary at stage 2 in the Full Proposal to adapt to an overall governance in which several activities can be shared within the full Consortium to ensure integration of the Subtopics and avoid redundancies.
- Governance of the overall Project and of the constituent Subtopics will be assured by a partnership between a Project Coordinator from the Applicant Consortia and a Project Lead from the Industry Consortium, with assistance from a Grant Manager.
- The Applicants must provide appropriate managerial resources for grant administration of the overall Project and of the Subtopics.

Need for public-private collaboration

**coordinated complementary cooperation
between**

**Industry
partners**

**Academic
Institutes**

Hospitals

**Small-Medium
Enterprises**

**Patients, patient
organization**

Experience

Expertise

REGISTRIES

**TRANSLATIONAL
APPROACHES**

**INNOVATIVE
METHODS**

**To improve the care of patients
suffering acute or chronic pain**

Pre-competitive nature

The Consortium, consisting of academia, hospitals, Small-Medium Enterprises (SMEs), patients and patient organizations and Industry partners, will cooperate in a pre-competitive landscape in which:

- Experience and expertise will be openly shared.
- Efforts will be combined to develop the tools needed to improve translation and patient centricity in selected aspects of pain therapy.
- Regular meetings and workshops will be held to openly discuss results and progress.
- Tools and results will be made available to the scientific community.
- Possible synergies arising from interactions with other existing Consortia will be sought.

Indicative budget and duration of the full project

- **Indicative budget:**
- The indicative EFPIA in-kind contribution will be EUR 11 230 000.
- The financial contribution of IMI2 for each Subtopic is:
 - **Subtopic 3A PROMs:** a maximum of EUR 4 250 000.
 - **Subtopic 3B BIOM:** a maximum of EUR 4 140 000.
 - **Subtopic 3C CPP:** a maximum of EUR 2 840 000.

If no Stage 1 proposal is considered adequate for a Subtopic, Stage 2 of the Call will still be initiated by merging the remaining Applicant and Industry Consortia, but the net IMI2 funding and the EFPIA in-kind contributions will be reduced appropriately.

- **Indicative duration of the project:** 39 months.

Subtopic 3A - PROMs

Specific challenges

- Identify PROMs which are validly indicative of treatment success
- PROMs need to be acceptable to HCPs in daily practice
- For validation purposes retrospective analyses will be necessary of PROMs used in clinical trials conducted during the course of drug development
- PROMs selected for use in trials which have not yet been completed will be evaluated in prospective analysis
- Identification and/or set-up of an appropriate registry in order to make the collected information available to HCPs
- Storage and analysis of the collected data by accepted statistical techniques
- The vision is that the success rate of pain treatments chosen by HCPs will be increased, thereby significantly reducing the suffering of patients and the burden on health services.

Objectives

- Standardize reporting of pain and treatment success by identifying and aligning on PROMs between clinicians/academic groups and companies
- Support usage of standardized PROMs for pain in real-world practice by Health Care Professionals (HCPs) to follow the experienced success of the treatment of individual patients
- Engage an existing network of hospital centers to set up an aligned approach and contribute to collection and analysis of the PROMs during pain treatment.
- Set up of a registry for storage and analysis of the data collected
- Aligned effort to identify chronification factors in pain

Expected impact on the management of pain and the R&D process

- More informed decisions on pain treatment for post-operative or other acute pain indications or chronic pain which lead to faster patient recovery and less resource consumption
- Improvement of pain relief
 - ➡ satisfied patients
 - ➡ faster recovery
 - ➡ less work loss
- PROMs for clinical trials in pain defined by patients and clinical experts in the first step of this project
 - ➡ easier to identify suitable PROMs for clinical trials
 - ➡ quantifies expected extent of improvement in treatments
 - ➡ co-operation between clinical experts and companies should create trust in each other for future projects

Suggested architecture of the project

■ Work Package 1

Project Management.

■ Work Package 2

Acute Pain.

- Identify PROMs from reviews and clinical trials in alignment with expert groups
- Implement PROMs in hospitals after surgery
- Employ a validated registry to collect, transmit, store, analyze, and visualize the data and measures prioritized by the expert consortium to identify the most appropriate post-operative pain treatment

■ Work Package 3

Chronification of acute pain

- Conduct a large multi-center, prospective observational trials to assess the incidence and characteristics of moderate to severe chronic post-surgical pain, and the factors which lead to chronification of pain

■ Work Package 4

Chronic pain

- Identify PROMs from reviews and clinical trials in alignment with expert groups
- Correlation of PROMs collected with different validated instruments for pain, QoL etc in chronic pain conditions to identify which most reliably predict treatment success

Expected contributions of the applicants

■ Work Package 2

- An existing network of hospital centers to set up an aligned approach in the use and documentation of PROMs in different surgeries
- A functional technology platform enabling research studies using PROMs, and meta-analysis of the results
- Sufficient IT expertise and infrastructure required to collect, transmit, store, analyze, and visualize data

■ Work Package 3

- An existing network of hospital centers with ability to set up large multi-center, prospective observational trial to collect data on chronic post-surgical pain by web-based or other electronic means for at least 6-12 months following surgery
- A functional technology platform enabling research studies using PROMs, and meta-analysis of the results
- Expertise in meta-analysis of data to identify factors leading to chronification of acute pain to nociceptive, neuropathic or mixed chronic pain conditions

Expected contributions of the applicants

■ Work Package 4

- Sufficient IT expertise and infrastructure to collect, transmit, store, analyze, report and visualize data
- Expertise in conduct of systematic reviews and meta-analysis
- Conduct of systematic research/meta-analysis on PROMs used to assess chronic neuropathic and chronic pelvic pain
- Conduct of correlation analysis and prioritization of PROMs used in chronic pain conditions (pelvic pain, dysmenorrhea, dyspareunia, neuropathic pain)

Expected (in kind) contributions of EFPIA members

- Literature review of reports on PROMs for post-operative pain patients that has to be updated by the applicant
- Prospective observational data collected after surgery and at the follow-up using validated questionnaires (EQ-5D, PGA, EOC) and sleep quality
- PROMs from controlled clinical trials with patients undergoing major surgeries of the upper limb results from validated PROMs (e.g. NRS, NPSI, QST) will be followed for up to 6 months after surgery. Pharmacogenetic samples will also become available
- PROMs from prospective multi-national multi-centre prospective randomized, double-blind, parallel-group, placebo-controlled clinical studies of chronic neuropathic pain conditions (e.g. PHN, PDN). Data at baseline for all patients and follow-up data of placebo patients up to 12 weeks.
- Prospective multi-national multi-centre prospective randomized, double-blind, parallel-group, placebo-controlled trial and observational clinical studies in another chronic pain condition (pelvic pain, dysmenorrhea, dyspareunia). Data at baseline for all patients and follow-up data of placebo patients up to 52 weeks

Who will gain what?

PUBLIC HEALTH

The project will identify optimal individualised pain treatments by using validated PROMs to significantly improve the quality of life of patients

GOVERNMENT AND PAYERS

Better pain relief will support early discharge from hospitals. The identification of pain chronification factors should significantly reduce burden on health care providers

ACADEMIA

The cooperative scientific process needed to identify validated tools to measure acute and chronic pain will improve pain treatments. Avoidance of pain chronification will form the basis for future investigations of additional therapies

INDUSTRY

The project will select PROMs appropriate for inclusion into future clinical trials and thus support further new developments in pain management

Key deliverables

- Selection of aligned PROMs for different acute and chronic pain conditions
- Network of Hospital centers that contributed to the project
- A functional technology platform enabling research studies using PROMs set-up based on suitable IT expertise
- Registry of the aligned and tested PROMs results to allow analyses of treatment success and open access
- Systematic Reviews and Meta-analysis of the results
- Publications to report on approach and findings of the project

Subtopic 3B - BIOM

Specific challenges

Key Output: Delivery of pharmacologically validated and standardised functional PD biomarkers in man, with accompanying back-translation to animals.

Key Question:

- 1. Which neurophysiological measures are most sensitive and robust to support dose finding and investigate PK/PD relationships in phase1/2 for targets within;**
 - **Peripheral nerves**
 - **Spinal cord**
 - **Descending control pathways**
 - **Central mechanisms**
- 2. Which of these measures can robustly be back translated to preclinical experiments**
- 3. Can these experiments be used for preclinical-clinical dose setting studies for new compounds?**

Impact:

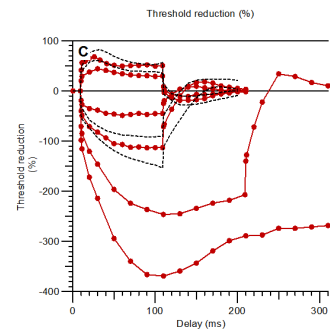
- This will aid dose setting in early clinical trials, positively impacting the outcome of POC studies and speeding the flow of new medicines to patients.
- Standardized methods could provide specific fingerprints of how analgesics work and give us a firm basis for moving into pain patients and animal pain models.

Identify pharmacodynamic biomarkers for targets within different compartments of pain pathway

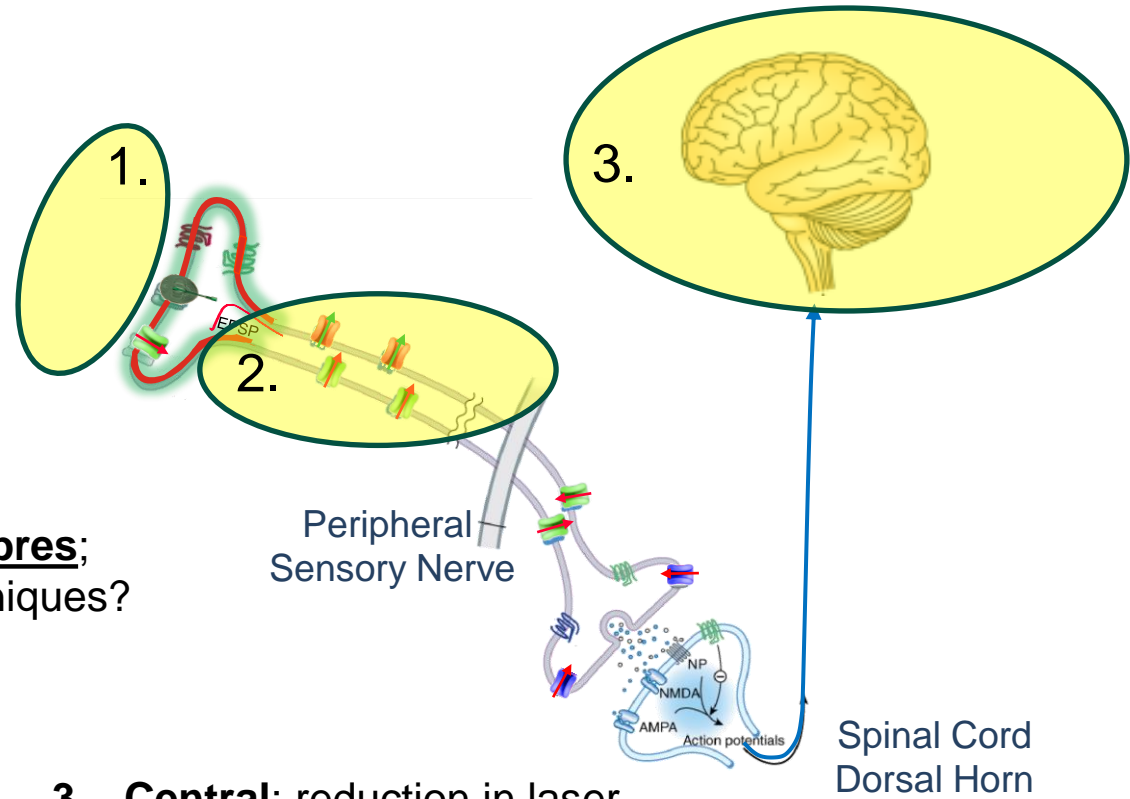
- 1. Nerve terminal**; inhibition of capsaicin-induced dermal blood flow?



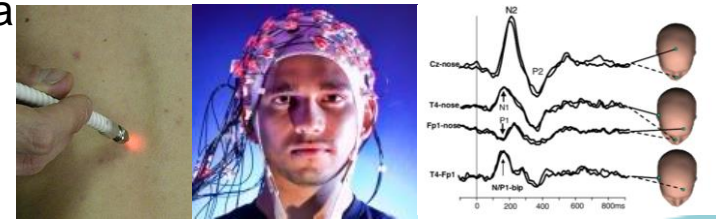
- 2. Ion channels within sensory fibres**; change in nerve excitability techniques? (threshold tracking)



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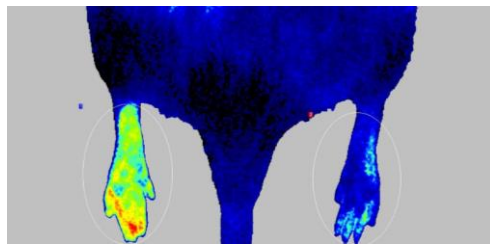


- 3. Central**: reduction in laser evoked event related potentials/gamma oscillations?

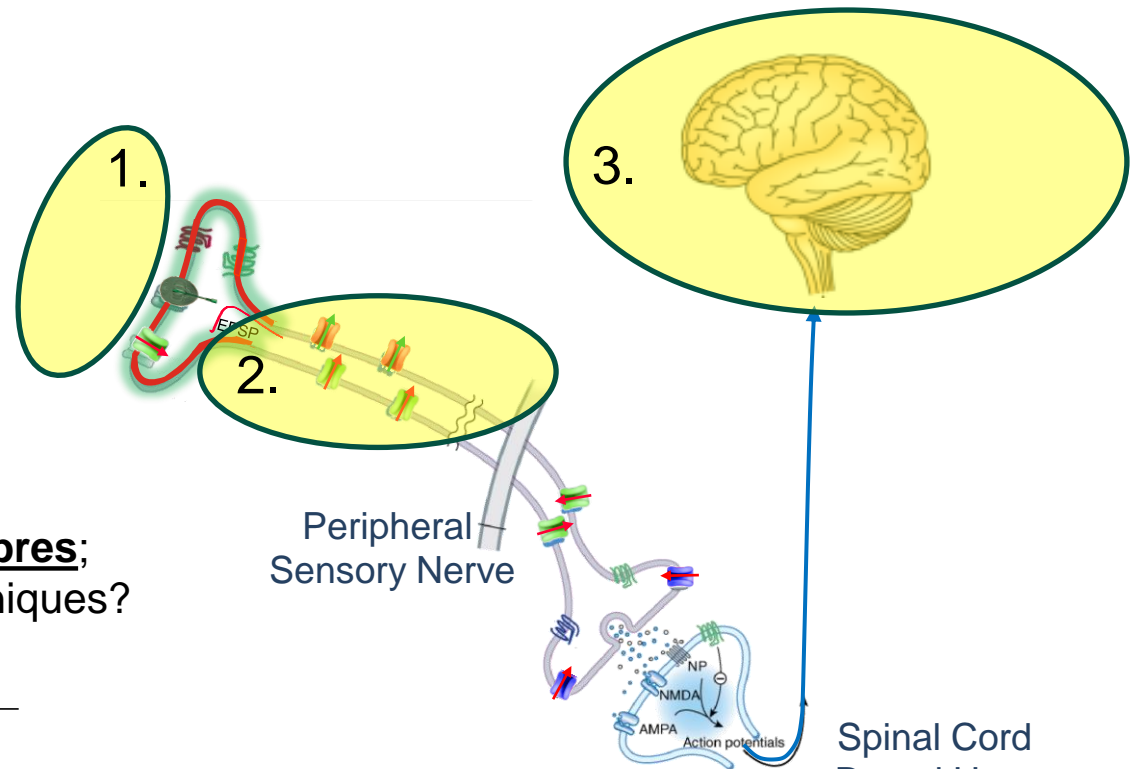
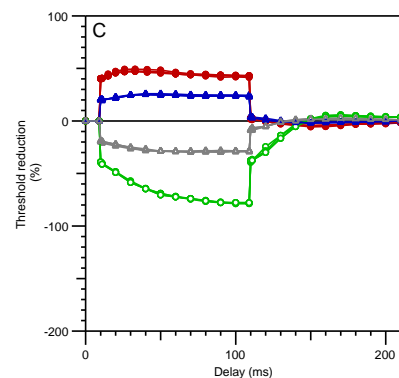
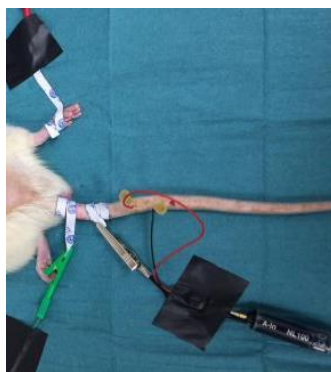


Identify translatable pharmacodynamic biomarkers for targets within different compartments of pain pathway

1. **Nerve terminal**; inhibition of capsaicin-induced dermal blood flow?



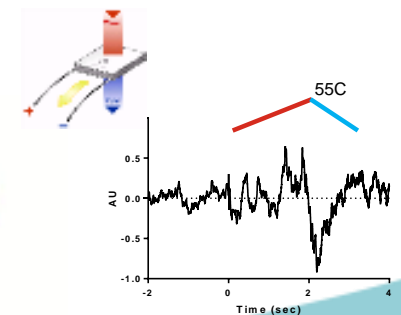
2. **Ion channels within sensory fibres**; change in nerve excitability techniques? (threshold tracking)



3. **Central**: reduction in laser evoked event related potentials/gamma oscillations?



Spinal Cord Dorsal Horn



Objectives

- 1. Establish standardized protocols to measure neuronal activity in pain pathways in healthy subjects during baseline and acute experimental pain, in the presence of 3 standard analgesics using techniques;**
 - threshold tracking (peripheral nerve excitability)
 - resting state EEG (central mechanism)
 - evoked EEG potentials, eg laser evoked pain ERPs (peripheral, spinal and central)
 - fMRI (central mechanism)
 - Others (open to call participants to come up with most relevant measures)
- 2. Methodological approaches translatable to animals;**
 - Threshold tracking in sensory and motor neurons in-vivo/in-vitro
 - EEG/ERPs during baseline (pharmaco-EEG) and acute experimental pain (laser ERPs) in awake behaving animals
 - Oxygen amperometry as a preclinical surrogate for fMRI baseline (pharmaco-fMRI) and acute sensory stimulation
 - **Additional** (open to call **applicants** to come up with most relevant measures)
- 3. PK in relevant compartments during multiple time points (>3) in both clinical and pre-clinical studies to develop PK/PD models and assess statistically the translatability of these models (ie could these PD measures be used to predict dose)**

Expected impact on the management of pain and the R&D process

- Well validated and robust PK/PD biomarkers used in early drug development allow phase-2 proof of concept experiments to be performed with confidence that the hypothesis in question can be tested.
- Improve the ability to identify potentially safe and effective doses and dosing regimens in proof of concept efficacy phase2 studies.
- Enable robust Go/No-go decisions to be made early in the development of new therapies, both reducing attrition and overall development costs.
- Increase the mechanistic understanding of currently available therapies potentially leading to the identification of new drug targets.

Suggested architecture of the project

- **Work Package 1** Project Management
- **Work Package 2** Consensus on clinical study designs
- **Work Package 3** Data engineering and statistics
- **Work Package 4** Clinical study implementation and operations
- **Work Package 5** Preclinical biomarker back-translation, with PK

Expected contributions of the Applicants

- Propose and review options for final clinical study design, including choice of biomarkers, primary endpoints, test drugs, doses and PK sampling times, statistical and analysis plans.
- Define statistical analysis pipelines for all clinical and pre-clinical outcome variables.
- Provide the infrastructures required to store, analyse and protect all collected clinical and preclinical data and ensure IT infrastructures would allow for long-term storage and open access to data
- **Complete responsibility for completing the set-up, execution and close-out of the clinical study.**
- Using the EFPIA preclinical data, generate PK/PD models for clinical and preclinical experiments.
- Identify and implement analysis routines to confirm which preclinical biomarkers are most predictive of clinical PD responses for drugs targeting different compartments in pain pathways.
- Development of novel methodologies and advanced analysis techniques to identify specific target engagement in different compartments of pain pathways

Expected (in-kind) contributions of EFPIA members

- Active participation in working groups to review and refine clinical protocols
- PK and/or PD data on selected drugs to help with choice of dose and PK sampling times
- Provision of an inventory of relevant clinical and preclinical methods, data and instruments that could be applied in the clinical/pre-clinical studies
- Analysis of all PK samples taken during clinical studies
- Contribute to the statistical and PK/PD modelling plans for clinical and preclinical outcome variables
- **Set-up, implement and validate all biomarkers and test drugs into rodent models**
- Participation in the development of PK/PD models for all biomarkers studied
- Examine whether drug exposures, proven to be effective with the validated PD biomarkers in the clinic, back-translate into more classical preclinical rodent models of efficacy

Who will gain what?

PUBLIC HEALTH

Faster development of new therapies
Prevent inconclusive phase2 studies being performed in patients

GOVERNMENT AND PAYERS

Reduced cost in developing new medicines

ACADEMIA

Increase the mechanistic understanding of currently available therapies potentially leading to the identification of new drug targets

INDUSTRY

Enable robust Go/No-go decisions to be made early in the development of new therapies, both reducing attrition and overall development costs.

Key deliverables

- Validation of at least five pharmacodynamic biomarkers, including laser-evoked ERPs, pharmaco-EEG, acute pain fMRI, pharmaco-fMRI and threshold tracking in peripheral nerves in both animals and healthy subjects
- Pharmacological validation of the biomarkers using at least three standard-of-care (SOC) drugs which target different compartments in pain pathways, i.e. with central, spinal or peripheral modes of action
- Develop PK/PD models for these biomarkers in animals and healthy subjects to generate a clear understanding of the translatability of these models in future clinical trials
- Definition of the preclinical biomarkers which can predict, and cannot predict, clinical target engagement
- Examine test-retest reliability using intra-class correlations for all biomarkers, and ideally of the pharmacological effect size and variability
- Compare effect sizes between techniques and SOC pharmacology for central, spinal, peripheral mechanisms of drug action
- Development of novel methodologies and advanced analysis techniques to identify specific target engagement in different compartments of pain pathways

Subtopic 3C - CPP

Specific challenges

- Chronic pelvic pain (CPP) related to endometriosis or bladder pain syndrome (BPS), or of idiopathic origin, seriously reduces a patient's quality of life, and causes many co-morbidities such as fibromyalgia, inflammatory bowel syndrome, depression, sleep-disturbances, or anxiety
- Despite the high prevalence of CPP, the cause and mechanisms of the underlying diseases are poorly understood
- No specific diagnostic or validated clinical biomarkers for CPP-associated diseases are available
- No criteria for useful stratification of patient populations have been identified yet
- Existing animal models are unspecific and their translational value is uncertain
- Research into drugs for treating CPP is hampered by poor understanding of the mode of action and a paucity of tools for investigations

Objectives

- Provide deeper understanding of the pathological conditions which lead to CPP
- Conduct thorough analysis of patient phenotypes to identify specific pain conditions, quality of life ratings, clinical, molecular markers etc. which could be used as biomarkers
- Use biomarkers for patient stratification and to select specific, effective therapies
- Identify disease-relevant biomarkers in preclinical models of CPP
- Compare clinical and preclinical biomarkers to assess the validity of preclinical models
- Use promising and clinically valid preclinical models to improve research on CPP in order to satisfy the medical needs of patients with new therapeutics

Expected impact on the management of pain and the R&D process

- Improvement of disease understanding will pave the way to new promising treatment options
- Diagnostic biomarkers which confirm or exclude CPP indications would permit stratification of patients, leading to great efficiency gains for health care systems
- Better disease understanding and the availability of better tools would foster basic research options significantly
- More predictive translational models will reduce attrition rates in projects addressing CPP thereby increasing the feasibility of drug development

Suggested architecture of the project

- **Work Package 1** Project Management
- **Work Package 2** Clinical Part: Analysis of bladder pain syndrome and endometriosis patient populations with respect to comorbidities, treatment responses and phenotypes
- **Work Package 3** Preclinical back-translation: Identification of animal models which best correspond to the findings of WP2
- **Work Package 4** Preclinical refinement: Using the findings of WP 2 and WP3, develop more refined and valid animal models

Expected contributions of the applicants

- Strong clinical expertise in target indications and capability/interest in developing corresponding pre-clinical models
- Strong preclinical expertise in models addressing the target indications strictly combined with strong expertise in assessment methodologies for allodynia and hyperalgesia, alternative behavioral endpoints, histology, and molecular biology
- Strong expertise in proteomics and/or metabolomics

Expected (in kind) contributions of EFPIA members

- Communication, dissemination of the results, and sustainability plan
- Providing commercially available samples from endometriosis patients and analysis thereof
- Rodent models employing various endpoints and NHP tissue for endometriosis
- Rodent models of BPS, evoked and non-evoked behavioural read-outs and translational value studies
- Provision of reference compounds

Who will gain what?

PUBLIC HEALTH

Identification of diagnostic biomarker for specific CPP conditions lead to faster diagnosis, stratification, and more precise help for patients

GOVERNMENT AND PAYERS

Better model understanding (project-feasibility) enlarges the likelihood that better diagnosis and effective treatment options reach the patients as effective drug product

ACADEMIA

Academia will get access to relevant models to perform basic research with the aim to understand mechanisms important for CPP and the underlying diseases. The optimized animal-models will provide relevant pre-clinical tissue to model the clinical situation

INDUSTRY

Provision of clinical biomarkers is one of the critical hurdles for designing straight forward clinical trials aiming for a PoC in CPP. Animal models with clear construct validity and reproducibility will provide the basis for preclinical target validation for projects addressing CPP

Key deliverables

- Identification of CPP specific biomarkers and their back-translation into animal models
 - Identification of human biomarkers of endometriosis and BPS. Focus of the project would be a diagnostic biomarker or stratification marker.
 - Back-translation of human biomarkers to NHP and rodents. Alignment of human biomarker strategy to existing/emerging animal models of endometriosis and BPS
 - Animal models of endometriosis and BPS shall be refined to improve translatability and should be confirmed in different labs
- Publications to report on approach and findings of the project

Questions?

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