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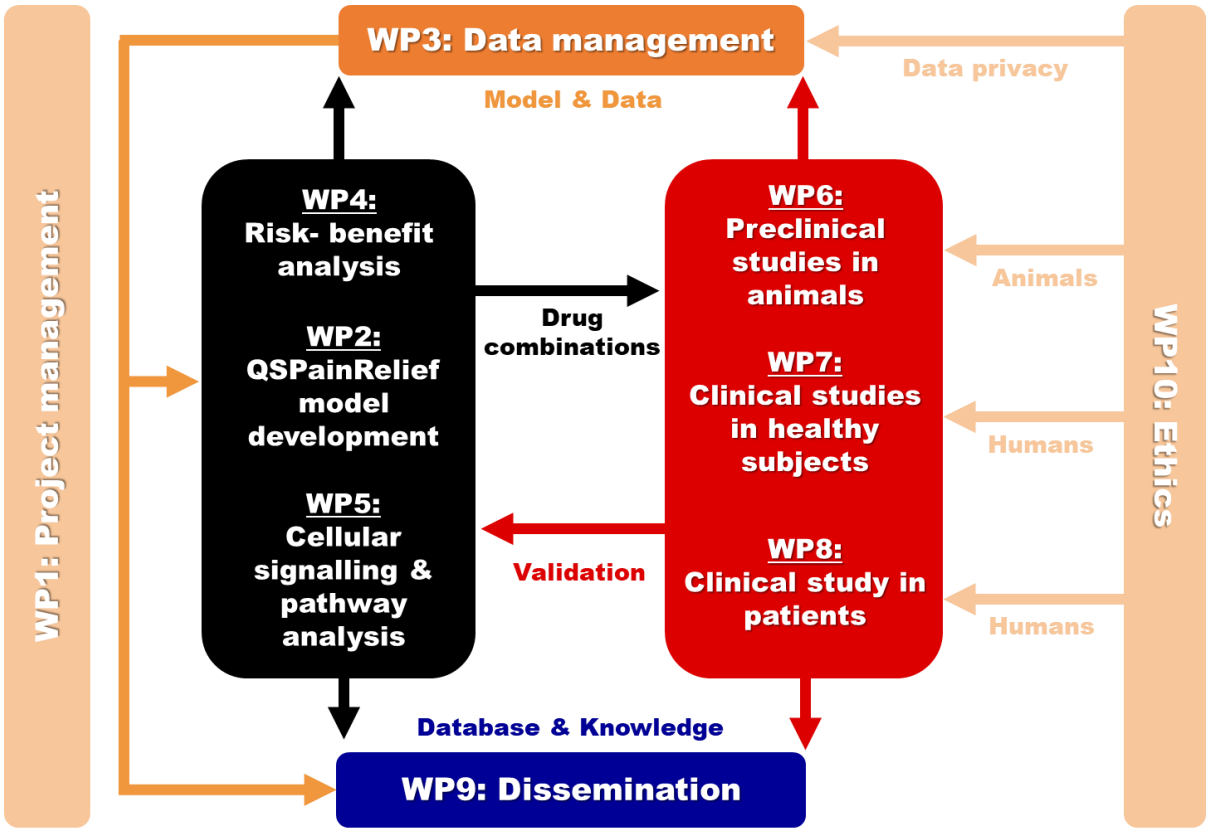
Newsletter 1 - December 2020

Welcome to our 1st newsletter! **QSPainRelief** is an international, collaborative **Horizon 2020** research project, funded by the European Commission,

that brings together **10 partner institutions** from 5 European countries and the USA. The 5-year-long project started in January 2020 and uses an innovative quantitative systems pharmacology (QSP) pain relief approach in developing effective combinational treatment of chronic pain in individual patients. In this half-yearly newsletter, we inform you of scientific advances in the project, new team members, events, and other relevant news. **Sign up here to receive our newsletter!**



QSPainRelief consists of 10 work packages (WPs) that feed into each other. From mathematical in silico *modeling, over animal research, and* ***clinical studies****, the project spans across a multitude of disciplines.*

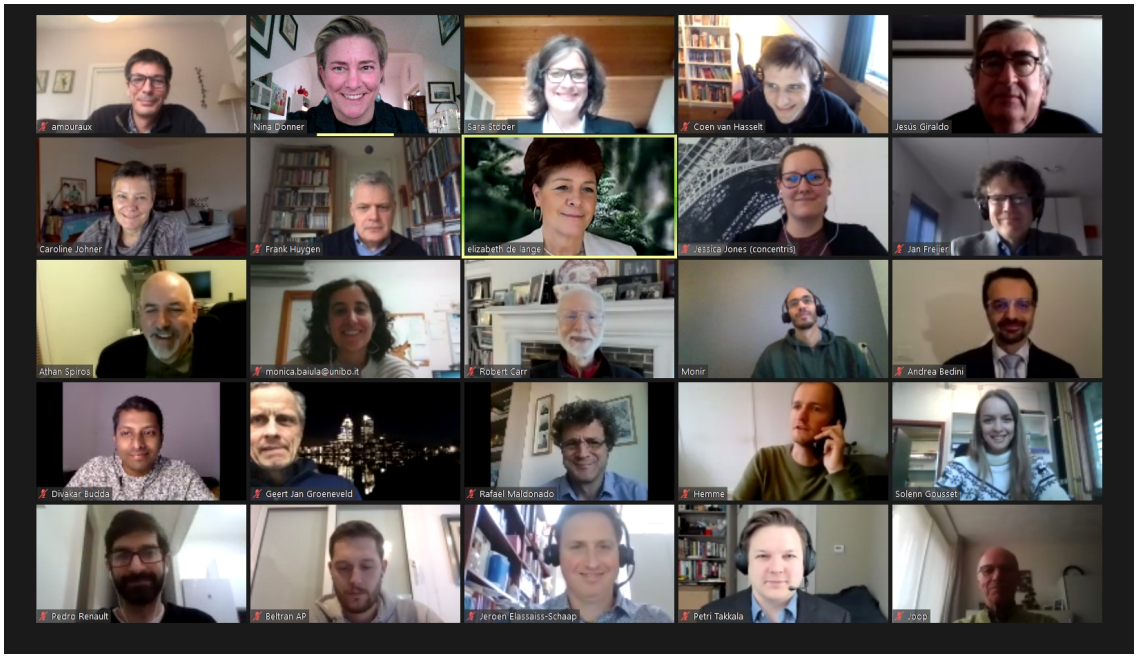
Who coordinates QSPainRelief?

Professor Dr. Elizabeth C.M. de Lange studied Biophysical Chemistry at the University of Groningen and holds a PhD in Pharmacology of Leiden University (**ULEI**). Liesbeth is professor in Predictive Pharmacology in the Division of Systems Biomedicine and Pharmacology of the Leiden Academic Centre of Drug Research (**LACDR**) at Leiden University (**ULEI**). Her

research is aiming at predicting human drug concentration-effect relationships for individual patients, in particular for diseases of the central nervous system (CNS), using preclinical studies and mathematical modeling. A recent success is a mathematical model that is able to predict CNS drug concentrations in multiple physiological CNS compartments (LEICNSPK3.0). She is the scientific coordinator of **QSPainRelief** and also leads work package 1 with support from **concentris** (**WP1**, project management), **WP3** on data collection and data management. Furthermore, with her team, she has an important role in **WP2** on the development of the *in silico* **QSPainRelief** model platform, in which the LEICNSPK3.0 model is an important part. In her free time, among many other things, she loves to be outside in nature.

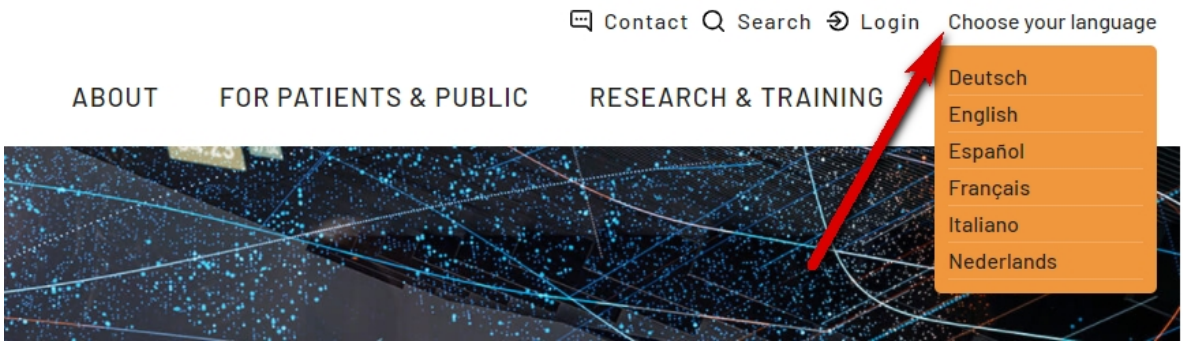
Successful 2nd GA Meeting

Originally planned in Cologne, the 2nd QSPainRelief General Assembly (GA) Meeting just took place as a virtual Zoom-meeting from 9-10 December 2020. The agenda included a special session for the project's early-career scientists (ECS) to present their thesis project or research contribution to QSPainRelief, and two Masterclasses, one on "Approaches on the treatment of chronic pain in the clinic" by **Prof. Dr. Albert Dahan** from Leiden University Medical Center (**LUMC**), and another one on "Operant self-administration mouse model of neuropathic pain" by **Prof. Dr. Rafael Maldonado** from University Pompeu Fabra (**UPF**). We are also very grateful for the attendance of, and constructive feedback from our external scientific and ethical advisory board (**SEAB**) members.



Major steps forward

- **WP2**: The first prediction by the central nervous system (CNS) drug distribution model (LEICNSPK3.0) on CNS exposure profiles for morphine has been made (in health, and after first identified CNS physiology changes associated with chronic pain). Also, the first version of the LEICNSPK3.0 model with target binding kinetics and resulting predictions of CNS target occupancy profiles for morphine has been developed.
- **WP3**: First versions of the database model are available, and the first steps towards a database have been taken. A huge amount of literature data on drug properties, values of CNS physiological parameters, and changes thereof, associated with chronic pain, have been collected and organized.
- **WP8**: The ethical approval to conduct the clinical QSPainRelief-patient study on CNS effects has been obtained. The research team at Université Catholique de Louvain (**UCL**) will conduct a clinical study in patients suffering from disabling post-operative to assess the different effects of combinatorial treatments on the CNS, using electroencephalography (EEG) and other non-invasive electrophysiological techniques, and relate these effects to real-life clinical efficacy and safety.
- **WP9**: The mentoring scheme for our early-career scientists (ECS) has started, and the training program is currently being tailored to the needs of our ECS, based on the individual training portfolios they submitted. Also, the "For Patients & Public" section of the QSPainRelief website is now available in 6 different languages (DE, EN, ES, FR, IT, and NL). Simply click on the "choose your language" feature in the upper right-hand corner.



Save the dates!

NeuPSIG International Congress on Neuropathic Pain (ICNP)

13 – 15 May 2021, Lisbon, Portugal

IASP World Congress on Pain

27 June - 1 July 2021, Amsterdam, The Netherlands

European Congress of Pharmacology (EPHAR)

5 - 8 December 2021, Prague, Czech Republic

Quantitative Systems Pharmacology Conference (QSPC)

19 - 22 April 2022, Leiden, The Netherlands

The QSPC 2021 meeting has been postponed to 2022 due to COVID-19.

19th World Congress of Basic and Clinical Pharmacology (WCP)

17 - 22 July 2022, Glasgow, United Kingdom

The QSPainRelief consortium just submitted a session-suggestion "Towards the improvement of treatment of chronic pain by mechanism-based modeling approaches" for WCP 2022. Fingers crossed that it'll be accepted into the program!

New team members

A cordial welcome to all our early-career scientists (ECS). We are very happy to have you within the QSPainRelief research team. We asked each of them to write a few sentences to introduce themselves.

Divakar Buddha: I am a PhD student at Leiden University (**ULEI**). I have a Master's degree in pharmacy (PharmD) and experience with clinical trial outcomes database (CTOD) curation for model-based meta-analysis. This shaped my interest in modeling and quantitative systems

pharmacology (QSP) for designing better medicines. Under the guidance of the **QSPainRelief** consortium and institutional scientists, I will (i) help curate the database, and (ii) study with mathematical models how medicines work at the receptor level in chronic pain. Thanks to the esteemed scientific panel of **QSPainRelief**, we are exploring the most complex and fascinating organ in the human body, the brain. Exciting and a lot to learn!

Berfin Gülave: I work as PhD student at Leiden University (**ULEI**). My interest as well as my background is neuroscience and pharmaceutical sciences. I always wanted to combine these two research fields, and within the **QSPainRelief**project, I have the opportunity of combining my interests with computational research. My role is to understand the first step within the drug dosing and ultimate effect pathways, i.e. the central nervous system (CNS) exposure.

Maarten Menschaart: Before joining the University Leiden (**ULEI**) as a bioinformatician, I received my Bachelor's degree in Bioinformatics in Nijmegen. My internships all focused on -omics, so working on setting up and maintaining a database for all **QSPainRelief** members, which I am currently working on, is a new and educational challenge for me. My interest in bioinformatics has always been programming/coding, which for me is a place to be creative and precise at the same time. In my spare time, I like to do sports of any kind, but I am mostly active in CrossFit.

Pedro Renault: I am a postdoc in the group of Dr. Jesús Giraldo at the Autonomous University of Barcelona (**UAB**). I obtained my PhD in Biophysics at the Federal University of Rio de Janeiro, Brazil. My work is focused on molecular biophysics, and in **QSPainRelief**, I'm responsible for conducting molecular simulations, which will

help us better understand the structure and dynamics of GPCR heterodimers.

Hemme Hijma: As a clinical scientist, PhD candidate, a clinical pharmacologist in training, and part of the Neurology and Pain research group of Prof. Geert Jan Groeneveld, I am involved in the set-up, execution, and reporting of human experimental pain studies at **CHDR** since 2017. Prior to joining CHDR, I obtained my MSc degree in Science and Business Management (a biomedical sciences-oriented study), and completed internships on remote clinical trials at Janssen Pharmaceuticals and on human genetics at the Regenerative Medicine Center Utrecht. Within the **QSPainRelief** consortium, my role is to lead the human experimental pain studies ascribed to work package 7 (**WP7**).

Monir Bertayli: I have a Master's degree in Biomedical Sciences, with specializations in Cell Biology and Immunology. I am a pharmacometrician within **PD-value**, working on the **QSPainRelief** project where I will be responsible for the design and implementation of the clinical utility index model. My main goal as a scientist is to help people by contributing in the search for cures or prevention of disease. I love to keep up to date with developments in the medical world, and in my free time like to keep in shape by running or going to the gym.

Carlo Rinaudo: Since October 2020, Carlo is working as a PhD student with Prof. André Mouraux at the Institute of Neuroscience (IoNS) at Université Catholique de Louvain (**UCL**). He holds a Master's degree in Medicine and will contribute to the clinical studies of work package

8 (**WP8**), namely the calibration and evaluation of the **QSPainRelief** platform using central nervous system (CNS) biomarkers in real-world patients.

Beltrán Alvarez: I am working with Prof. Rafael Maldonado on the **QSPainRelief** project as a postdoctoral researcher in the **NeuroPhar**research group at University Pompeu Fabra (**UPF**). My field of study is chronic pain, its comorbidities, and the pharmacological modulation of these painful and non-painful symptoms.

Petri Takkala: I recently completed my PhD in Medical Science and Neuroscience at the University of Toronto where I combined computational modeling of neuronal physiology with advanced electrophysiological and imaging experimental techniques to study the mechanisms of chronic pain. I joined In Silico Biosciences (**ISB**), Inc. as a Principal Scientist working on quantitative systems pharmacology (QSP) and building the *in silico* neural network models for the **QSPainRelief** project. As computational biology continues to grow in sophistication and complexity, I envision *in silico* modeling to play a more pivotal in drug discovery and therapeutic development, and to become instrumental in tackling complex challenges in translational research. In my personal time, I enjoy scuba diving and I look forward to pandemic-free summers to be able to continue to work towards my divemaster and instructor certifications.

Announcements & Achievements

Congrats to “the Ferrari of pharmacology”, our scientific coordinator, **Prof. Liesbeth de Lange**, who just won the “Lewis B. Sheiner Lifetime Achievement Award” from

the International Society of Pharmacometrics (**ISoP**)!

Liesbeth de Lange wins Lewis B. Sheiner Career Prize

13 November 2020

Pharmacologist Liesbeth de Lange has won the Lewis B. Sheiner Lecturer Award from the International Society of Pharmacometrics (ISoP). As Professor of Predictive Pharmacology she is working, among other things, on a mathematical model that can predict drug concentrations in the brain. On the occasion of the award, De Lange gave a lecture at the opening of the annual ISoP meeting on 9 November.

Cracking complex codes

De Lange had an important message for the public. 'I wanted to emphasise that complex issues cannot be answered with simple tests. I always compare it to a game of Mastermind: Nature is made up of codes and we researchers have to crack them in order to understand its complexity.'

A good example of this is De Lange's research into medicines in the brain. 'The brain has always fascinated me,' she says. 'I've been committed to the treatment of brain diseases such as Parkinson's or Alzheimer's for years. Our group is translating the processes in our brains into mathematical models.' De Lange is not held back by complexity and that has led to innovative and useful insights. Based on years of structured research, she and her colleagues created the so-called brain distribution model: a kind of navigation system that predicts whether and how a medicine reaches its destination in the brain, and what turns it could take.

In July, **Prof. Dr. André Mouraux** from the Institute of Neuroscience (IoNS) at Université Catholique de Louvain (**UCL**) and two colleagues in Italy and the United Kingdom were awarded the **2020 IASP Collaborative Research Grant**. Congrats! In addition, pain researchers and clinicians from Prof. Dr. André Mouraux's research group recently participated in a **TV documentary on chronic lower back pain**. Amongst other things, the French documentary "Matière Grise - Mal au dos: et si tout se passait dans la tête?" explains how central sensitization can be explored by using the techniques applied in the QSPainRelief-patient CNS study (**WP8**).

New publications

- Bruzzese A, Dalton JAR, and Giraldo J (2020) **Statistics for the analysis of molecular dynamics simulations: providing P values for agonist-dependent GPCR activation.** *Sci Rep.* 10: 19942. ***PDF***

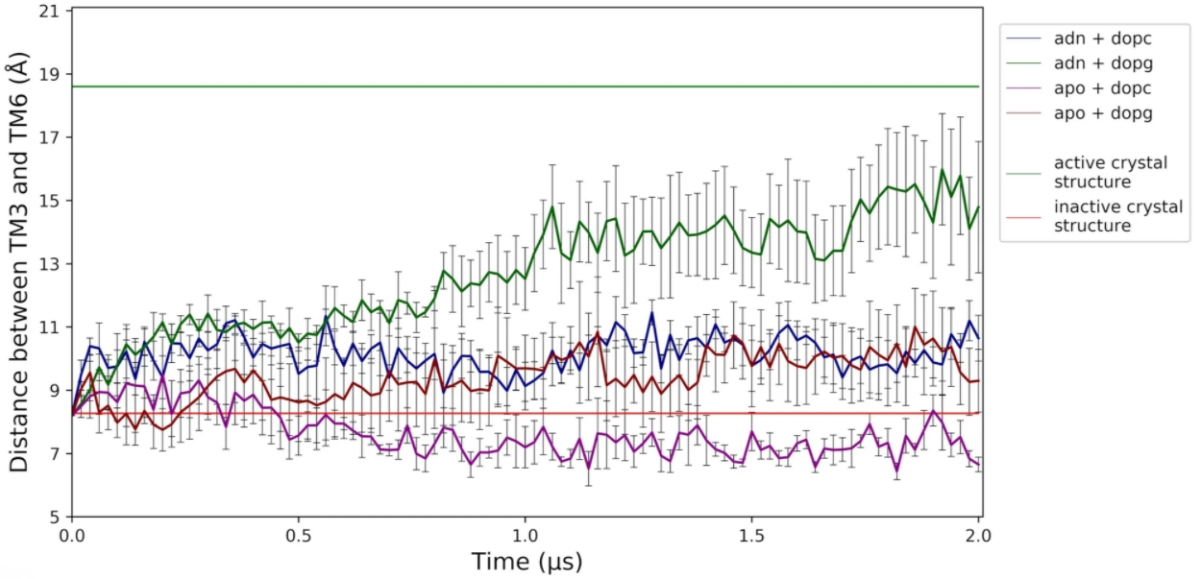


Figure 2A in Bruzzese, Dalton, and Giraldo 2020. *As an example for molecular dynamics, this graph depicts the distance in Angstrom (Å) between transmembrane helix 3 (TM3) and transmembrane helix 6 (TM6) of G-protein coupled receptors (GPCR) over time. Shown is the mean and standard error of the mean (SEM) for 4 sample replicas at various conditions. Lipid (DOPC, 1,2-dioleoyl-sn-glycerol-3-phosphocholine) / DOPG, 1,2-dioleoyl-sn-glycerol-3-phosphoglycerol) and ligand (adenosine, APO) experimental conditions were considered.*

Poster presentations

- Budda D, van Hasselt C, de Lange ECM (Nov. 2020) **Drug–target binding kinetic model to predict target engagement profiles of analgesics and their combinations with CNS active drugs for chronic pain treatment.***FIGON Dutch Medicines Days.*
- Gülave B, Saleh MAA, J.G. van Hasselt JGC, de Lange ECM (Nov. 2020) **Human CNS drug distribution of morphine in healthy and pain conditions.** *FIGON Dutch Medicines Days.*

QSPainRelief partners in Europe and in the USA.

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