June 2024

NEWSLETTER N° 02

TransPharm Press

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https://transforming-pharma.eu/

TRANSPHARM KEY FEATURES

- 12 partners
- 9 countries
- 8 M€ grant
- 48 months

TRANSPHARM MAJOR OBJECTIVES

- Optimize the use of existing and new data for greening drug synthesis and development
- Identify greener and more sustainable-by-design APIs as proof of concept.
- Reduce the inputs and outputs of API synthesis through introducing shortcuts in API synthesis schemes.
- Provide new methodologies to assess the sustainability of pharmaceuticals over their entire life cycle.

STUDIES ON CIP-HEMI DERIVATIVES AND METHOD DEVELOPMENT FOR ACCELERATED ENVIRONMENTAL BIODEGRADATION TESTING

In TransPharm, our researchers are actively exploring the potential to enhance the environmental biodegradability of the fluoroquinolone antibiotic CIP-Hemi, while minimizing its ecotoxicity and ensuring the retention of critical pharmacological parameters such as antimicrobial effectiveness, metabolic stability, and human safety. TransPharm also aims to contribute to the development of biodegradation tests suitable to screen many pharmaceutically relevant compounds within a short period of time, by using an in-silico prediction model for environmental biodegradation or miniaturized in-vitro biodegradation assay. In the last month, we gained a better understanding of selected pharmacological properties, (bio)degradability, ecotoxicity (against cyanobacteria) and bioavailability of CIP-Hemi derivatives and set the foundation for the development of accelerated environmental biodegradation tests.

TransPharm members are designing potential CIP-Hemi derivates using *in silico* tools to improve the properties of CIP-Hemi further. After synthesis, *in vitro* tests for metabolic stability and hepatotoxicity in human, antimicrobial activity, and the environmental properties, including biodegradation, bioaccumulation, ecotoxicity and bioavailability were performed. In parallel, a model to predict environmental biodegradation of pharmaceuticals, and the miniaturization of a biodegradation *in vitro* test are being developed.

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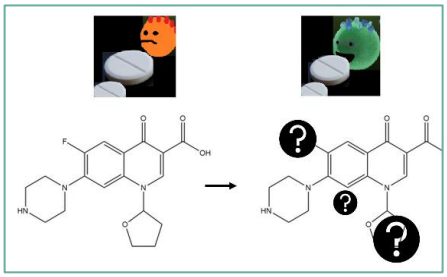

Leuphana University Lüneburg selected 13 new CIP-Hemi derivates, from which several were successfully synthesized and tested, showing metabolic stability and no hepatotoxicity in human *in vitro*. A preliminary antimicrobial activity screening showed activity against relevant pathogenic microorganisms, whereas CIP-Hemi and its derivatives are 10 to 1000 times less ecotoxic than ciprofloxacin against the cyanobacterium *Microcystis aeruginosa* (OECD-201; tests conducted by UGent), demonstrating selective antimicrobial activity. Concerning bioavailability, an examination of three derivatives suggests similar behaviour to their parent compounds (i.e., other fluoroquinolones). The bioavailability and ecotoxicity of CIP-Hemi derivatives are closely associated with environmental pH and dissolved organic carbon, the impact of which can be predicted with an existing ciprofloxacin bioavailability model construct. Ghent University (UGent) will further investigate a compound of interest with a comprehensive ecotoxicological study, incorporating aquatic organisms from diverse trophic levels in the ecosystem, to learn more about their environmental behaviour. Even though the biodegradability of the tested derivatives could not be improved compared to CIP-Hemi, biodegradation tests of several fluorinated compounds, led to a better understanding of the structure-biodegradability relationship of this compound, benefiting the upcoming design of alternative derivatives. Another focus will be the design of the quinolone scaffold, proven to be fully biodegradable and shared by many other groups of pharmaceuticals. In parallel with to improving biodegradability, photolysis and hydrolysis tests were performed to study compound properties, showing that CIP-Hemi is rapidly photolyzed by sunlight (the study was performed during a very sunny day quite rare in Lüneburg!)

Regarding the *in silico* model development to predict environmental biodegradation of pharmaceuticals, University Helsinki explored exploring different modelling approaches and refining the best model (SVC), obtaining an accuracy of 83%. The next step will be to investigate if a three classes model (not readily, partially, and readily biodegradable) leads to more accurate predictions than the two initial classes due to the distribution of biodegradability values in the set (not biodegradables are predominant).

Rigorous optimization of the different unit operations necessary for miniaturization and automation of the closed bottle biodegradation test (OECD-301D) have also taken place at University Helsinki, aiming for an increased assay throughput. These optimizations have eventually led to a three-stage development plan, to automate oxygen measurement (step 1), incorporate automated sampling (step 2), and miniaturize the test volumes with the help of a flow-through assay design (step 3), this last step being highly challenging. Currently, the details of the software and hardware design are being implemented, aiming at first prototype tests taking place in summer 2024. A lot of resources, time, and costs could be saved already using smaller vials (e.g. 1 mL) instead of 250 mL closed bottles and the oxygen sensing runs automatically. For this reason, Leuphana University Lüneburg is currently investigating the impact of different test volumes and different bacteria concentrations.

TransPharm WP2 members are looking forward to the upcoming steps to design better performing CIP-Hemi derivatives and new biodegradation testing tools.

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Klaus Kümmerer, Professor at Leuphana and WP2 leader

Professor Dr. Klaus Kümmerer, the Director of the Institute of Sustainable Chemistry and of ISC3 Research & Education Hub located at Leuphana Universität Lüneberg, was recently decorated with the Federal Cross of Merit on Ribbon of the Order of Merit of the Federal Republic of Germany for his many years of pioneering commitment to sustainable chemistry.

Professor Dr. Klaus Kümmerer is particularly renowned for his pioneering work on the concept of "benign by design". This approach focuses on reducing environmental impacts by designing molecules with minimal harm to the environment. He has successfully implemented this concept in practical applications, such as the development of less harmful ionic liquids and biodegradable antibiotics, such as in TransPharm where the partners are working on additional compounds, improvements of *in silico* and testing tools, and greening compound synthesis.

In September 2023, he was awarded the prestigious Wöhler Award for Sustainable Chemistry by Gesellshaft Deutscher Chemiker (GDCh). This award recognises his groundbreaking research achievements in various areas of Sustainable Chemistry. Some of his other notable contributions include advancements in developing the understanding and role of chemistry within sustainable and circular economy.

Furthermore, Professor Dr. Klaus Kümmerer has shown a strong commitment to incorporating sustainable issues into chemistry education. He has designed and established relevant courses of study, ensuring that future chemists are well-equipped to address sustainability challenges in their field.

Professor Dr. Klaus Kümmerer receives the Federal Cross of Merit from the hands of Science Minister Falko Mohrs.

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EXTERNAL ADVISORY BOARD UPDATE ON GREEN PHARMA

A positive collaboration for greener healthcare: bridging the private and public sectors

Dr Fiona Adshead,
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« The Sustainable Healthcare Coalition is a collaboration between the NHS and private sector companies that engages stakeholders and leaders in the UK and internationally to accelerate and amplify action on net zero healthcare. Providing pre-competitive access and exchange across private and public healthcare sectors, it aims to aid understanding and to foster action to address the sustainability issues facing healthcare, through collaborative action. Our focus is on measuring impact and, by providing practical tools for change, with projects targeting enhanced measurement capability and demonstrating improvement in healthcare sustainability, producing the world-first standards for footprinting of pharmaceutical and medical device products.

This was followed up by development of a care pathways assessment methodology to help understanding of the environmental impacts of whole care pathways and how products and services fit into that wider picture. One example of how this can reap sustainability and resource benefits is shown by a deep-dive sustainability assessment of a renal unit in north-east England, pointing reduction efforts to its footprint hotspots and developing an internationally applicable carbon calculator by a spin-off, for use by in-centre haemodialysis units.

Being part of the Sustainable Markets Initiative Health Systems Taskforce has led to contributing to wider collaborative efforts. The commitments from the SMI member companies include adoption of the SHC care pathways guidance for application to decarbonising health systems and supporting development and adoption of methodology for clinical trials sustainability assessment.

With the increasing focus on sustainable healthcare, the Coalition will continue to expand its thinking and activity, seeking further innovative approaches to reduce the environmental impact of healthcare at scale, and use its collaborative approach for stepped-up action to gain a better understanding of what is good for people, health systems, business, the environment, and our common future. »

« At our Takeda Lessines facility, we take bold actions to reduce our carbon footprint in every aspect of our operations. We are for example the first biopharmaceutical manufacturing site in the world to recycle 50% of our wastewater back into our production process. Our ambition? To become a net-zero GHG emissions manufacturing site in our operations by 2030! How? By a very well-structured program based on avoiding & reducing energy consumptions; installing renewable energy capacity and, last but not least, innovate & dare to switch! »

Simon Gilleman
Sustainability Manager

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WORKSHOP N°2 TRANSPHARM

The second iteration of the yearly TransPharm workshops will be held in collaboration with Ajinomoto and CAPTURE and is titled **"Advancing Green Chemistry: Not just how we make it but what we make".**

Join our workshop to:

- Explore sustainable solutions: learn about biobased and biodegradable fine chemicals
- Engage and exchange: participate in discussions and share successful green chemistry applications
- Discover global developments: focus on sustainability, circularity and reducing carbon footprints
- Collaborate for progress: find new partnership opportunities to advance green chemistry.

Let's shape for a greener future!

More detailed information will follow soon – the preliminary date is 04/12/2024.

SECOND ROUND INNOVATIVE HEALTH INITIATIVE (IHI) CALL

Some of the TransPharm partners are involved in the IHI call 4 – topic 6 (second round).

The innovative health initiative (IHI) is a partnership between the EU and European life science industries. It brings together stakeholders from healthcare sectors to foster EU-wide research and innovation, aiming to translate scientific knowledge into tangible innovations.

The primary goal of the project call is to revolutionize pharmaceutical and biopharmaceutical manufacturing towards sustainability by implementing high-TRL innovative, sustainable technologies and integrating greener processes in industry practice. Further, the project call aims to establish standardization and harmonization of the sustainability assessment frameworks and methodologies throughout the entire healthcare industry. The deadline for submission was April 23rd, 2024. We are hopeful for a positive outcome.

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PHARMA POLLUTION HUB

A new independent initiative to drive societal-wide change

The Pharma Pollution Hub is a new think tank based in the UK that is dedicated to finding solutions to reduce the environmental impacts of pharmaceutical pollution through a systems-based, social innovation approach. As an independent body, it brings together stakeholders from across industry, government, academia, and the civil sector, to collectively understand the broader social, economic, cultural, and political drivers of pharmaceutical usage, and co-develop strategies for meaningful and pragmatic societal-wide change.

What has the Pharma Pollution Hub been doing so far?

As well as coordinating the development of strategies for action, the Hub also hopes to accelerate change through harnessing the resources and expertise of the academic community, and facilitate transdisciplinary discussions on particularly challenging topics. It's first event was a workshop on Integrating Pharmaceutical Pollution into healthcare decision making (particularly life cycle analyses), held in September 2023, with representation from TransPharm members Ad Ragas, Caroline Moermond and Rodrigo Vidaurre. It also recently ran an open discussion on Integrating Pharmaceutical Pollution into Sustainable Finance Initiatives (report to be available on the website soon).

To get the latest updates about the Pharma Pollution Hub, you can check their website and social media: ***Email:*** *info@pharmapollution.org* **– *X:*** *@pharmapollution* **– *LinkedIn:*** *@Pharma Pollution Hub*

COLLABORATION WITH THE SISTER PROJECTS

In the call HORIZON HLTH 2021 IND 07 01 about Green Pharmaceuticals 5 projects were approved. It is now the aim to cooperate on 3 common topics:

*Working Group 1 -**Life Cycle Assessment**, with the aim of sharing knowledge and information on the life cycle assessments of pharmaceuticals*
*Working Group 2 - **API synthesis**, to explore possible synergies on the different API synthestis approaches developed by the different projects*
*Working Group 3- **Communication and Dissemination***

GREEN PHARMACEUTICALS
Funded projects under the call HORIZON-HLTH-2021-IND-07-01

- TRANSPHARM
- SUSPHARMA
- ETERNAL
- IMPACTIVE
- ENVIROMED

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WE WERE THERE

- LCM 2023 International conference on life cycle management – September 2023
- 11th Conference on Industrial Ecology ISIE 2023 – July 2023, Leiden
- Sustainable Healthcare Coalition Partner Engagement Meeting – September 2023
- CESPE conference 2023 – September 2023, Ghent, Belgium
- ISPOR Europe 2023 – November 2023, Copenhagen, Denmark
- EU conference - Research Perspectives on the Health Impacts of Climate Change - February 2024, Brussel, Belgium
- Flow Chemistry Europe 2024 – March 2024, Malaga, Spain
- SETAC Europe 34th Annual Meeting – May 2024, Seville, Spain
- 8th Green and Sustainable Chemistry Conference – May 2024, Dresden, Germany

Publisher: UGent

Person in charge: Nathalie De Coensel

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https://transforming-pharma.eu/

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Upcoming events

- 9th EuChemS Chemistry Congress – July 2024, Dublin, Ireland
- SSbD24 Conference – November 2024, Monte Verità, Switzerland
- TransPharm Workshop N°2 in 2024

More details will be disclosed shortly.

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