REVIEW PAPER

JMS Journal of Medical Science

INVITED EDITORIAL

ORBIS project – where have we arrived?

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DOI: https://doi.org/10.20883/medical.e936

Keywords: international and intersectoral project, drug synthesis, solid state pharmaceuticals, oral and skin delivery, biorelevant dissolution, biomedical analysis

Received: 2023-09-26
Accepted: 2023-09-29
Published: 2023-09-30

How to Cite: Skotnicki M, Jakubowska E, Smułek W, Davin S, Tajber L, Lulek J. ORBIS project – where have we arrived? Journal of Medical Science. 2023;93(3);e936. doi:10.20883/medical.e936

ABSTRACT

The Open Research Biopharmaceutical Internships Support project (ORBIS) was a response to the scientific, economic, and social challenge of increasing the effectiveness and productivity of the drug development process, both for innovative and (super)generic drugs. The overarching objective of the ORBIS project was to form a transnational and intersectoral cooperation network of academic and industrial organisations delivering a joint research programme. The research aimed at improving the preclinical pathway of drug development and manufacturing, focusing on technological and methodological improvements of the existing processes. The participating staff from all institutions have developed new skills, were exposed to new work and research environments, and have significantly broadened their career perspectives. More than 450 months of secondments were completed, and over 175 early-stage and experienced researchers participated in the exchange. This review aims to present some aspects of the scientific, training, and organisational activities of the consortium, bringing together representatives of both the academic sector as well as small and medium-sized pharmaceutical enterprises.

Introduction

When the Open Research Biopharmaceutical Internships Support project (ORBIS) received funding of 2,268,000 EUR in 2018 (Grant Agreement no. 778051), it was the second largest project under the Research and Innovation Staff Exchange (RISE) call of Marie Skłodowska-Curie

Actions (MSCA), Horizon 2020 programme (H2020-MSCA-RISE-2017). The main objective of this project was to promote international and inter-sectoral collaboration through research and innovation staff exchanges as well as two-way knowledge and/or idea exchange between the academic and industrial sectors. The concept of the project, detailed research objectives, and project plan were described in our previous articles [1, 2].

Initially, the implementation of the ORBIS project was planned for 48 months. Unfortunately,

Table 1. Institutions involved in the ORBIS project during the period 2018–2023.

Institution name and acronym	Role in the project	Participation time	City and country
Poznan University of Medical Sciences (PUMS)	Coordinator, Beneficiary	1st March 2018 – 31st August 2023	Poznań, Poland
APC Ltd. (APC)	Beneficiary	1st March 2018 – 31st August 2023	Dublin, Ireland
Celon Pharma S.A. (CLN)	Beneficiary	23th September 2021 – 31st August 2023	Łomianki/ Kielpin, Poland
JSC Farmak (FMK)	Beneficiary	1st March 2018 – 31st August 2023	Kyiv, Ukraine
Łukasiewicz Research Network – former Pharmaceutical Research Institute (PRI)	Beneficiary	1st March 2018 – 22nd October 2020	Warsaw, Poland
Physiolution GmbH (PHY)	Beneficiary	1st March 2018 – 31st August 2023	Greifswald, Germany
Poznan University of Technology (PUT)	Beneficiary	13th March 2019 – 31st August 2023	Poznań, Poland
University of Central Florida (UCF)	Third-Party (Partner Institution)	1st October 2021 – 31st August 2023	Orlando, FL, US
University of Chemistry and Technology Prague (UCTP)	Beneficiary	27th September 2021 – 31st August 2023	Prague, Czech Republic
University of Ljubljana (UL)	Beneficiary	28 September 2021 – 31st August 2023	Ljubljana, Slovenia
University of Helsinki (UH)	Beneficiary	1st March 2018 – 31st August 2023	Helsinki, Finland
Trinity College Dublin (TCD)	Beneficiary	1st March 2018 – 31st August 2023	Dublin, Ireland
Zentiva (ZNT)	Beneficiary	1st March 2018 – 31st August 2023	Prague, Czech Republic
Rutgers, the State University of New Jersey (RUTG)	Third-Party (Partner Institution)	1st March 2018 – 31st August 2023	Piscataway, NJ, US

unforeseen circumstances affected the execution of the project. However, a change in the status of one of the beneficiaries, a break of 18 months due to a global pandemic and some restrictions due to the ongoing war in Ukraine did not stop the ORBIS project. After a significant reduction in the number of planned secondments by two beneficiaries and quitting the consortium by a key partner, project tasks were continued with new beneficiaries from Europe and a new partner institution from the USA. At the end of the project, the consortium comprised thirteen beneficiaries and partners, including eight academic institutions and five pharmaceutical companies located in eight countries (**Table 1**).

The overarching objective of the ORBIS project was to form a transnational and intersectoral cooperation network of academic and industrial organisations delivering a joint research programme. The research aimed at improving the preclinical pathway of drug development and manufacturing, focusing on technological and methodological improvements of the existing processes. The participating staff from all institutions have developed new skills, were exposed to new work and research environments, and have significantly broadened their career perspectives. More than 450 months of secondments were completed, and over 175 early-stage and experienced researchers participated in the exchange. This review aims to present some aspects of the scientific, training and organisational activities of the consortium, bringing together representatives of both the academic sector as well as small and medium-sized pharmaceutical enterprises.

ORBIS research activities

TThe primary objective of work package WP1 (*Drug substances and pharmaceutical preformulation*) was to translate the discovery synthesis of a drug substance (active pharmaceutical ingredient, API) into technology development and to investigate the solid-state physicochemical properties of APIs. It aimed to improve unfavourable biopharmaceutical properties (e.g. solubility/dissolution) such actives and develop a strategy to enhance poor solubility and/or permeability of Biopharmaceutics Classification System (BCS) class II and IV APIs. A number of studies were carried out in WP1, including the synthesis of drug substances and their derivatives (Sidoryk *et al.* 2022), process scale-up and continuous processing development, investigations into intrinsic and derived solid state physicochemical properties of selected pharmaceuticals, preparation of crystalline/co-crystalline and/or amorphous/co-amorphous forms of selected API(s) [3, 4] and correlation of physicochemical properties of APIs/excipients with their formulability, manufacturability and biopharmaceutical performance. The advances were facilitated by a variety of analytical techniques, such as thermal analysis (thermogravimetric analysis, differential scanning calorimetry and temperature-modulated differential scanning calorimetry), X-ray diffraction (single crystal and/or powder), spectroscopic methods (Fourier-transform infrared and Raman spectroscopy, nuclear magnetic resonance etc.), dynamic vapour sorption, microscopy, solubility and dissolution testing or chromatography to mention a few. Furthermore, the team from the ORBIS project participated in public consultations regarding the *Pharmaceutical strategy for Europe* in the area of drug synthesis [5].

The purpose of WP2 (*Dosage forms and drug delivery systems*) was to design, develop and test new drug carriers and dosage forms for oral and topical delivery of APIs. Experimental work aimed to optimise manufacturability and/or maximise the efficacy of drug delivery by formulating advanced drug delivery systems, such as nanoparticles [6], minitablets, self-(micro)emulsifying drug delivery systems, mesoporous silica as an API carrier and mucoadhesive systems [7, 8]. Also, novel analytical techniques for characterisation of drug delivery systems were developed, such as powder flowability test for small volume, texture analysis, quantitative image analysis of drugs in the solid dosage preparations by Raman mapping etc. Quality-by-Design tools such as Process Analytical Technologies (PAT) were employed for the optimisation of manufacturing operations, e.g. high shear wet granulation [9].

As regards topical drug delivery, the research focused on the assessment and improvement of

selected drug penetration across individual layers of the skin, including transdermal transport. The studies were conducted in relation to different groups of drugs, for example, non-steroidal anti-inflammatory drugs, antifungal agents and also photosensitizing dyes. The investigated delivery systems and dosage forms included liposomes, transferosomes, nanoparticles and microemulsions [10], semi-solids (hydrogels, organogels, creams) [11–13] and adhesives (patches). *In vitro* and *ex vivo* drug permeation from the developed formulations was tested using animal and human skin samples. The skin was also the focus of investigations of cellular senescence [14].

In WP3 (*Biopharmaceutical evaluation of dosage forms and drug delivery systems*), novel bioanalytical methods were developed, validated [15] and applied to real samples, e.g., HPLC-FLD (high-performance liquid chromatography - fluorescence detection) determination of pregabalin in human serum [16] or methods for UPLC-MS/MS (ultrahigh-pressure liquid chromatography - tandem mass spectrometry) for determination of antibiotics and antitubercular drugs in human plasma or fat tissue [17]. The European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) bioanalytical method validation recommendations were compared, and a novel statistical model for incurred sample reanalysis was developed [18, 19].

Another area of WP3 research was the development of biorelevant/biopredictive *in vitro* methods for evaluating drug products. Food interaction with bisphosphonates was studied. The effect of different media buffers on API release from a formulation with a microenvironmental pH was also evaluated [20], and *in vitro* release testing methods aiming at predicting the *in vivo* behaviour of extended-release tablets were developed [21, 22].

WP3 team also contributed to methodological improvements through theoretical research linking bioanalytical and pharmacokinetic topics, e.g. on toxicology [23], improving the clinical performance of drugs [24] or design of clinical trials [25]. WP3 team participated in public consultation of the EMA document on pharmacokinetics and pharmacodynamics in the obese population.

ORBIS training activities

The primary goal of WP4 (*Training*) was to support the career development and employability of academic and industrial staff by enhancing their research and transferrable skills as well as increasing the competence of the pharmaceutical R&D sector. Each secondee had an opportunity to learn new processes, methods, and techniques specific to the work package in which they participated. The international and intersectoral mobility was an invaluable experience, especially for early-stage researchers, who learned to work in a multidisciplinary and multicultural environment. ORBIS exchange was an opportunity for researchers to develop a wide range of transferrable skills in terms of science, communication, career management, as well as sector-specific knowledge (**Figure 1**).

In addition to the training activities integrated into the secondments, the consortium organised four summer schools and three workshops (**Figure 2**), which attracted 255 participants.

The 1st School was organised by Trinity College Dublin, APC and Farmak and the primary scientific topic was related to WP1. It encompassed lectures on solid-state pharmaceutical materials, continuous processing, fundamentals and application of preformulation and PAT. The workshop presented practical approaches and real cases established at GMP manufacturing facilities, such as API process development and transfer of technologies from laboratory to pilot and industrial scales. The 2nd School (organised by the University of Helsinki and Zentiva) was related to WP2 and focused on challenges and perspectives in the development of oral dosage forms and advanced emerging technologies, with the workshop activities on spray drying for the development of microparticles, compression of minitablets and application of coherent anti-Stokes Raman spectroscopy in drug characterisation. The 3rd School, arranged by Poznan University of Medical Sciences with Rutgers University, presented state-of-the-art and recent progress in the development of topical and transdermal delivery systems (e.g. microemulsions, transdermal patches, microneedles) and their characterisation methods, followed by demonstrations of *in vitro* permeation testing using Franz cells and

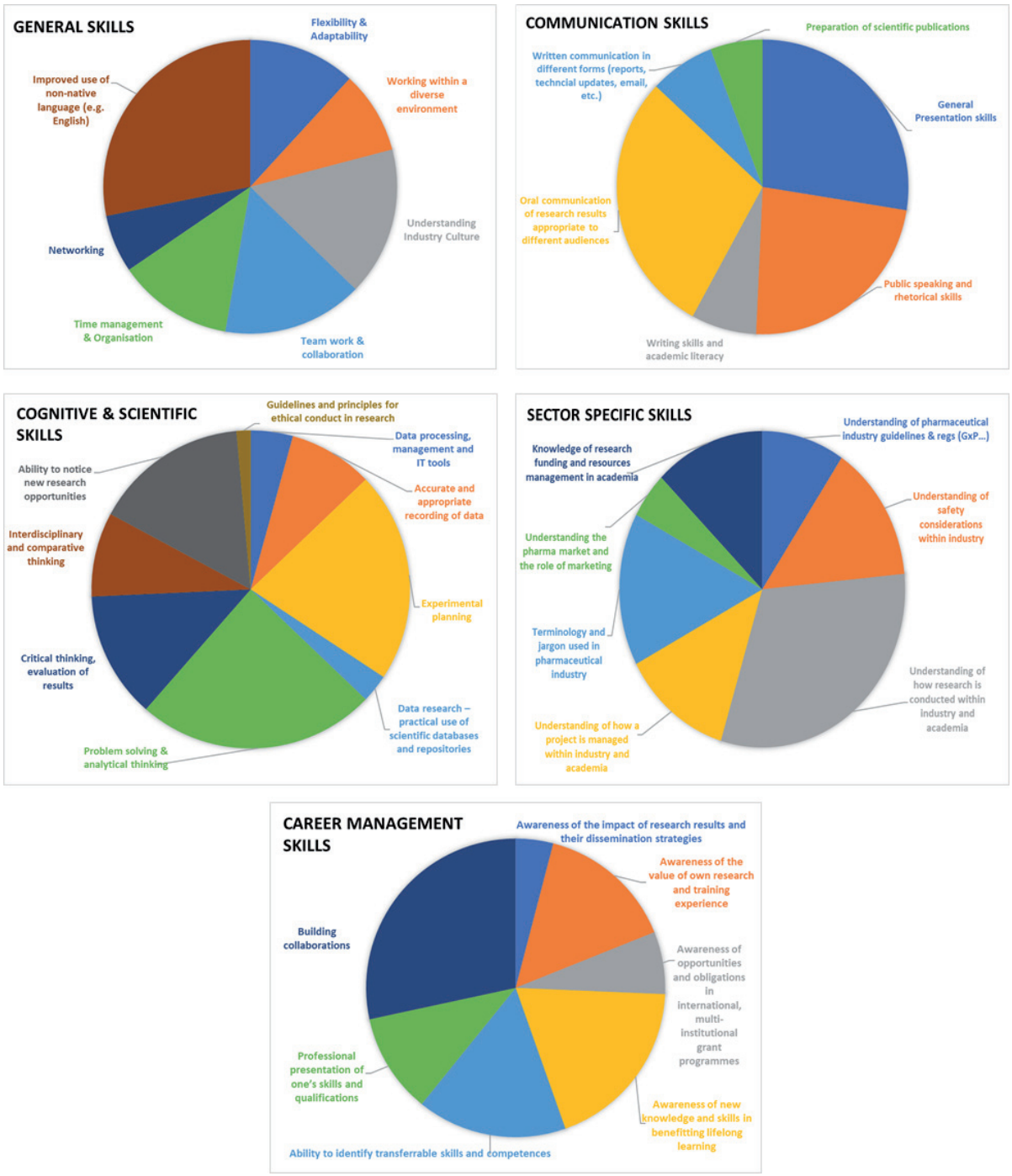

Figure 1. Summary of main transferrable skills identified and developed by the ORBIS secondees (self-reported; *n* = 48).

texture analysis of semisolid preparations. The 4th School (organised by Zentiva, Physiolution, University of Chemistry and Technology Prague) covered the WP3 topics of biopharmaceutics and novel techniques, drug delivery systems with increased bioavailability, in *vitro/in vivo* relationship, bioanalytical methods as well as non-traditional routes of drug absorption. The workshop concerned novel dissolution methods and *in situ* imaging techniques.

Additionally, consortium members had a unique opportunity to participate in a series of webinars created for ORBIS by a business coaching company DRevolve (Switzerland). The participants developed skills in networking, social media channels, and communica-

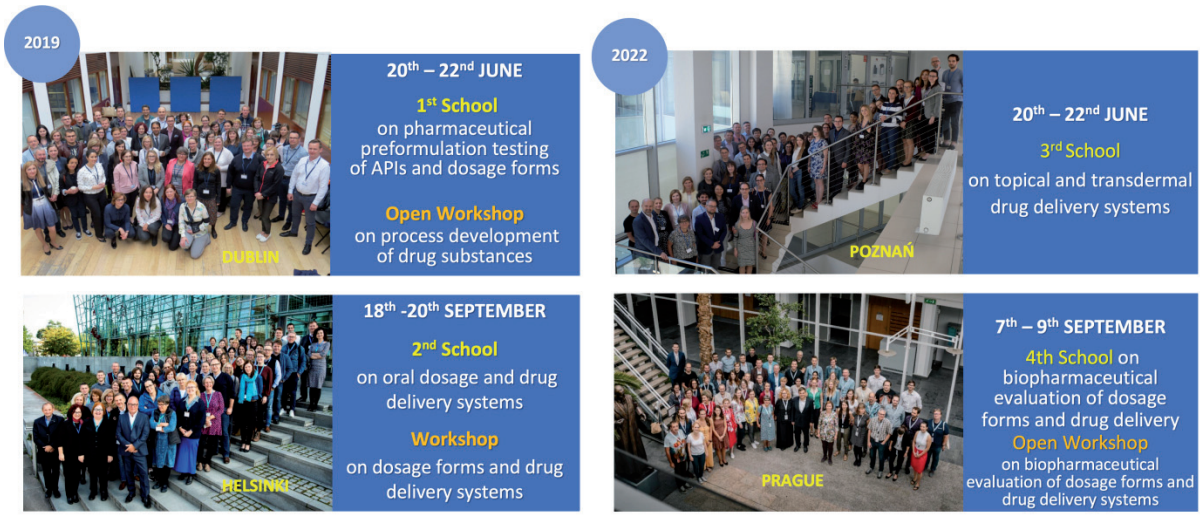

Figure 2 Overview of ORBIS Summer Schools and Workshops.

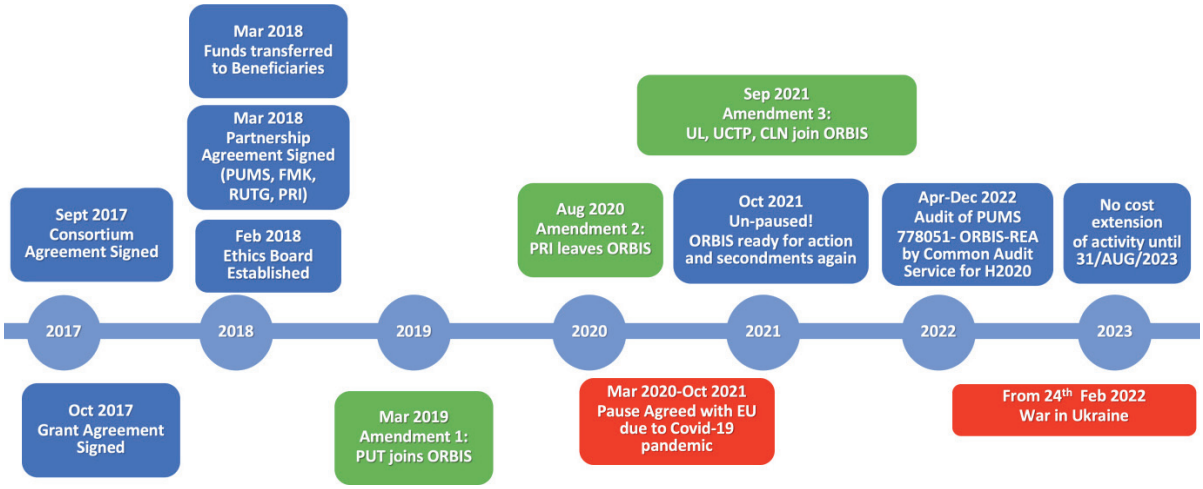

Figure 3. Project management timeline.

tion, as well as learned about cultural differences and the distinction between science and business approaches.

ORBIS management and dissemination activities

During the five years of the project, ORBIS faced many obstacles, including the unprecedented COVID-19 pandemic and the war in Ukraine. The project management team, headed by Janina Lulek (the project coordinator) and Bożena Raducha (the project manager), worked tirelessly to overcome the challenges, which required amending the grant agreement thrice (Figure 3). Day-to-day management by the General Assembly, Training Committee and Steering Committee supported by the Ethics Advisory Board, involved the control of secondments realisation, monitoring and submission of deliverables and milestones, communication with the EU Project Officer, evaluation and reporting of the project's research progress, as well as monitoring of ethical aspects.

Moreover, PUMS was responsible for organisation of the three meetings, i.e. Kick-off Meeting (12th–13th April, 2018, Poznan), Mid-Term Meeting (25th–26th September 2019, Poznan) and the Final Meeting (7th July, 2023, Poznan).

Project results were continuously disseminated in the form of peer-reviewed, open access

publications, presentations at seminars, conferences, and lectures. The ORBIS Final Conference, held on 5–6 July 2023 in Poznan, Poland, was a great success with nearly 200 participants. The project website www.orbisproject.eu, social media channels on Facebook, Twitter, YouTube and LinkedIn were active and updated throughout the project.

For example, communication and outreach activities were disseminated as lectures during the European Researchers Night in 2021 (https://www.youtube.com/watch?v=358a9Zvubas), scientific papers (26), notes and news pieces featured on various websites such as sectoral news channels e.g. https://maltabusinessweekly.com/zentiva-advances-pharmaceutical-research-through-orbis-project/16693/ or the local media channels (e.g.: https://radiopoznan.fm/informacje/pozostale/nie-byloby-innowacyjnych-terapii-gdyby-nie-wspolpraca-naukowcow-z-branza-farmaceutyczna), ensuring wide reception of the project's goals and achievements.

Conclusions

Despite the difficulties, the ORBIS project finished and became a massive success for all the consortium members, fulfilling all the required deliverables and milestones and realising all the planned research and training objectives. It is a testimony to the quality of the international and intersectoral collaboration established between the partners. Also, despite the substantial size of the consortium and the unexpected challenges (COVID-19 pandemic and war in Ukraine) the success rate of secondment completion was over 90%. The impact of the ORBIS project will last beyond those five years and ripple beyond the inner circle of participants. Over 175 researchers have been upskilled thanks to international and intersectoral mobility, improving their employability in academic and pharmaceutical sectors. The ORBIS project strengthened the European human capital in pharma research and innovation and has formed the cornerstone for future cooperation on innovative science for the advancement of medicines, strengthening Europe's intellectual potential in the R&D sector.

Acknowledgements

The authors would like to thank all members involved in the project, especially: Dr Dorota Danielak, Dr Katarzyna Kosicka-Noworzyń, Dr Bartłomiej Milanowski and Bożena Raducha (Poznan University of Medical Sciences, Poznan, Poland), Dr Aleksandra Dumicic (Zentiva k.s., Prague, Czech Republic), Dr Grzegorz Garbacz (Physiolution GmbH, Greifswald, Germany), Prof. Anne Juppo and Prof. Clare Strachan (University of Helsinki, Helsinki, Finland), Prof. Michal M. Masternak (University of Central Florida, Orlando, FL 32827 USA), Prof. Bozena Michniak-Kohn (The State University of New Jersey, Piscataway, New Jersey, USA), Dr Piotr J. Rudzki (Celon Pharma S.A., Lomianki/Kielpin, Poland), Prof. Stane Srčič (University of Ljubljana, Ljubljana, Slovenia), Prof. František Štěpánek (University of Chemistry and Technology, Prague, Czech Republic), Dr Oleg Syarkevych and Iryna Nagorichna (JSC Farmak, Kyiv, Ukraine), Prof. Adam Voelkel (Poznan University of Technology, Poznan, Poland).

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
This project has received funding from the European Union's Horizon 2020 Research and Innovation Programme under the Marie Skłodowska-Curie grant agreement No. 778051 and the Ministry of Science and Higher Education of Poland fund for supporting internationally co-financed projects in 2018–2022 (agreements No 3898/H2020/2018/2 and 3899/H2020/2018/2). This article reflects the authors' view only. Neither the Research Executive Agency nor the Polish Ministry of Science and Higher Education may be held responsible for any use of the information contained therein.

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