eRaDicate: Developing Innovative Ligands for Nuclear Receptors to Eradicate Cancer Relapse

NEWSLETTER ISSUE NO. 1

Introduction to the newsletter

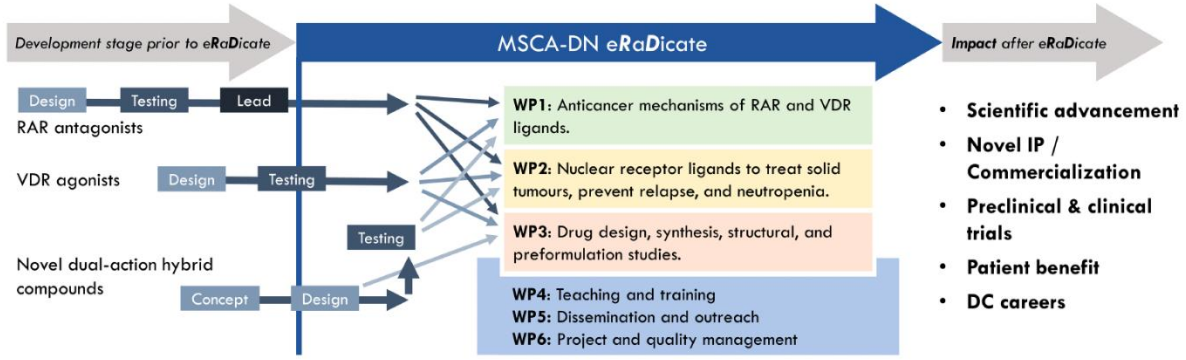
Welcome to the first issue of the eRaDicate project newsletter!

In this edition, we provide a general overview of the project, with special focus on Work Package 3 (WP3). You will meet the WP3 doctoral candidates (DCs), learn about their backgrounds, and discover the scope of their current research.

Upcoming issues will feature Work Packages 1 (WP1) and 2 (WP2).

eRaDicate project overview

The aim of the international, multidisciplinary, and intersectoral Marie Sklodowska Curie Doctoral Network **eRaDicate** is to develop new therapies against cancer stem cell-driven relapse and metastasis. Our 11 doctoral candidates (DCs) will be trained not only to perform original and independent research on an internationally competitive level, but will also be endowed with a creative, critical, and entrepreneurial mindset, coupled with persistence in following their objectives. The **eRaDicate** research programme is structured into three scientific work packages (WP1–WP3) to address its scientific objectives. It is built on the individual research projects of the DCs as an essential part of their doctoral training.



Work Package WP3 outline

An effective strategy for eliminating cancer stem cells (CSCs) involves the simultaneous induction of apoptosis and necroptosis. Since retinoid γ receptor (RARγ) antagonists promote necroptosis and vitamin D receptor (VDR) agonists induce both apoptosis and stem cell differentiation, combining these two classes of compounds may represent a novel and synergistic approach to eradicating cancer stem cells (CSCs). The **eRaDicate** project aims not only to evaluate the therapeutic potential of this combination but also to develop a new class of dual-action hybrid molecules. These hybrids are designed to independently target both nuclear receptors – RARγ and VDR - thereby uniting the effects of both compounds in a single chemical entity.

To date, structural studies have been limited to a truncated form of the VDR. For the final optimization of the hybrid compounds and to gain deeper insight into the binding mechanisms of vitamin D analogues, the project seeks to resolve the three-dimensional structure of the full-length human VDR. This structural information will enhance our understanding of conformational changes in VDR upon agonist binding and the recruitment of enzymatic coactivators, which are critical for chromatin decondensation at target gene promoters.

Another aspect of WP3 involves preformulation studies on selected active compounds and hybrid molecules to bring these compounds closer to clinical application and turn them into effective medicines. This will be achieved through extensive physicochemical

and biopharmaceutical evaluation as well as by determining the optimal formulation strategy, including the use of amorphous solid dispersions to improve the poor solubility of the molecules.

Doctoral Candidates' Profiles and their projects

Structure of the vitamin D receptor with vitamin D analogues

DC-UoW Aqsa Jabeen

Aqsa obtained her M.Phil. from the School of Biological Sciences at the University of the Punjab, Pakistan, where she developed a vaccine candidate against Fowl Adenovirus serotype 4 (FAdV-4). Her work focused on the recombinant expression, purification, characterization, and refolding of the knob domain of the fiber-2 protein of FAdV-4. She also contributed to the development of recombinant adenoviral vaccines against SARS-CoV-2, in the HEC-funded project "Development of Indigenous Recombinant Human Adenovirus 5-Based Vector Vaccines Against SARS-CoV-2 and Its Emerging Variants", based at the School of Biological Sciences, University of the Punjab. She further enhanced her expertise in protein crystallization and cryo-electron microscopy during an internship at the International Institute of Molecular and Cell Biology in Warsaw, Poland. As part of WP3, under the supervision of **Prof. Krzysztof Woźniak**, she is currently investigating the structure of the vitamin D receptor (VDR) and its interactions with innovative vitamin D ligands. Her research in **WP3** aims to resolve the full-length structure of VDR and explore its therapeutic potential. She recently presented her preliminary findings at the eRaDicate 1st School in Santiago de Compostela, in Spain, outlining X-ray crystallography and MicroED to investigate VDR–ligand complexes. This approach aims to provide high-resolution insights that will support the determination of the VDR's full-length structure and its therapeutic applications.

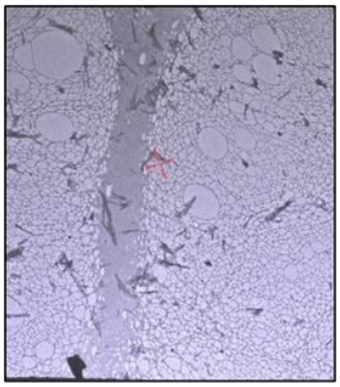


Figure 1: Crystals of VDR analogue (under ED microscope)

Video presentation:

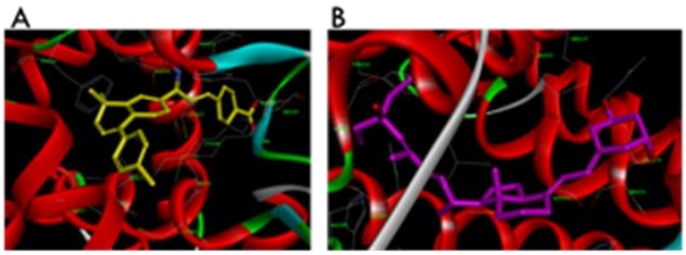
https://www.linkedin.com/posts/aqsa-jabeen-b16b36272_eradicate-mscaeradicate-eradicate-activity-7327771411513495554-oO4M?utm_source=social_share_video_v2&utm_medium=android_app&rcm=ACoAAEK7RcIBOgECL9oGyUC-LX-QtQd8-D-FXDY&utm_campaign=copy_link

Design and synthesis of a hybrid anticancer compound

MEDICAL UNIVERSITY OF WARSAW

DC-MUW **Mayur Arun Kadam**

Mayur grew up in a small village in Maharashtra, India, where he developed a passion for chemistry at a young age. He earned his BSc in chemistry and MSc in organic chemistry from the University of Pune. With four years of industry experience in a CRO, he has developed skills in designing synthetic routes and preparing innovative compounds with diverse biological activities. Currently, he is pursuing a PhD at the Medical University of Warsaw, under the supervision of **Prof. Andrew Kutner** and **Teresa Żołek, PhD, DSc**. Mayur's medicinal chemistry research in **WP3** focuses on designing and synthesizing hybrid compounds that target cancer stem cells by combining antagonists of the retinoic acid receptor gamma with agonists of the vitamin D receptor. Mayur recently presented his preliminary findings, including synthetic plan and retrosynthetic analysis of novel hybrid compounds, at the eRaDicate 1st School in Santiago de Compostela, Spain. His ultimate goal is to become an independent investigator in pharmaceutical sciences and drug discovery, continually expanding his knowledge and skills across international research environments.



In silico simulations of the docking of antagonist and agonist at the receptor active site. (A) RARg antagonist AGN205728 (in yellow) at RARg; (B) VDR agonist PRI-5202 (in magenta) at VDR.

Video presentation:

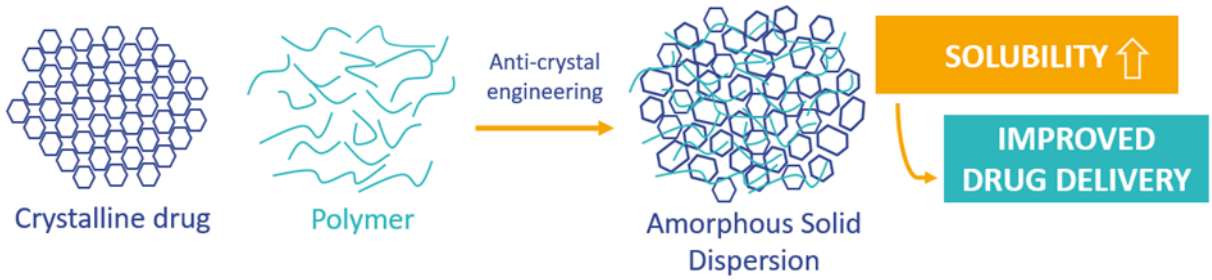
https://www.linkedin.com/feed/update/urn:li:activity:7326981097190293505/

Pre-formulation studies

DC-TCD **Agnes Graf**

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Agnes grew up in the heart of Europe, in a small town located at the intersection of Austria, Slovakia, and Hungary. She obtained her degree in Pharmacy from the University of Vienna, where she developed a strong interest in the interdisciplinary nature of the pharmaceutical sciences. She is particularly fascinated by how chemistry, physics, technology, and physiology converge in the process of drug design and development. Following her studies, Agnes gained practical experience in the clinical aspects of pharmacy. She worked in a community pharmacy and participated in a research project at the Medical University of Vienna, focusing on dose-finding in pediatric patients. Her growing passion for scientific



inquiry led her to pursue a PhD at Trinity College Dublin, under the supervision of **Prof. Lidia Tajber** and **Prof. Niamh O'Boyle**. Her research in **WP3** focuses on preformulation studies of anticancer agents, aiming to develop effective drug delivery systems and ultimately enhance clinical outcomes for patients. Specifically, Agnes is using anti-crystal engineering techniques to increase the solubility of VDR and RAR ligands. This will enhance drug delivery, thereby improving safety, efficacy, and ultimately clinical outcomes for patients. In March, Agnes participated in the mid-term meeting and the 1st eRaDicate School in Santiago de Compostela, where she presented her preliminary findings and engaged in discussions on the results presented by other DCs. Currently, she is completing her first secondment at the Medical University of Vienna, where she is learning models and techniques to assess the efficacy of anticancer compounds.

Video presentation: *https://youtu.be/YP3JF5_2Nwk*

Last events

eRaDicate Midterm Meeting in Santiago de Compostela, Spain

The Midterm Meeting of our MSCA-Doctoral Network, eRaDicate, was held at the University of Santiago de Compostela on March 24, 2025, and was a resounding success. The highlight of the day was the fantastic talks given by our doctoral candidates on their projects and preliminary results, which sparked engaging discussions and generated new ideas. The Project Officer from the European Research Executive Agency (REA) joined our meeting and shared valuable insights.

eRaDicate 1st School in Santiago de Compostela, Spain

The eRaDicate 1st School was held at the University of Santiago de Compostela in Spain, March 25-27, 2025. The first day started with a seminal keynote by eRaDicate scientific advisor Cesar Cobaleda, from the Centro de Biología Molecular Severo Ochoa (CBM) on Cancer Stem Cells. The afternoon was then focused on research culture and sustainability, followed by the fantastic tour through the old town of beautiful Santiago de Compostela. The second day was all about communication and discussing the next scientific steps of the DC's projects. On the final day, Riccardo Vencato shot professional individual presentation videos with each of DC's.

Upcoming event

The 2nd **eRaDicate** School, "Biology of Cancer & basic and advanced research techniques", organized by Prof. Ewa Marcinkowska (University of Wroclaw, Poland) and Dr. Rupert Ecker (TissueGnostics GmbH, Vienna, Austria), will be held online on 22-24 September 2025. The School will provide **eRaDicate** Doctoral Candidates the fundamentals of cancer research, basic didactic concepts, and an introduction to state-of-the-art methodology.

Publications of the eRaDicate Consortium

1. Powała A, **Żołek T, Brown G, Kutner A**. Structure and the Anticancer Activity of Vitamin D Receptor Agonists. *Int J Mol Sci* 2024, 25(12), 6624. https://doi.org/10.3390/ijms25126624.
2. Powała K, **Żołek T, Brown G, Kutner A.** Molecular Interactions of Selective Agonists and Antagonists with the Retinoic Acid Receptor γ. *Int J Mol Sci* 2024, 25(12), 6568. http://doi:10.3390/ijms25126568.
3. **Brown G**. The Emerging Oncogenic Role of RARγ: From Stem Cell Regulation to a Potential Cancer Therapy. *Int J Mol Sci* 2025, 26(9), 4357; https://doi.org/10.3390/ijms26094357.
4. **Brown G**. Cell Lineage Affiliation During Hematopoiesis. *Int J Mol Sci* 2025 Apr 3;26(7):3346. https://doi:10.3390/ijms26073346.
5. **Hantusch B**, **Kenner L**, Stanulović VS, **Hoogenkamp M**, **Brown G**. Targeting Androgen, Thyroid Hormone, and Vitamin A and D Receptors to Treat Prostate Cancer. *Int J Mol Sci*. 2024, 25(17), 9245. http://doi:10.3390/ijms25179245.

Edited by: Aqsa Jabeen, Mayur Kadam, Agnes Graf, Isabella Ellinger, Lidia Tajber, and Andrew Kutner **June 22, 2025**