AI-Driven Drug Discovery Group

BIOMEDICAL RESEARCH

Our group aims to leverage AI to design innovative, safer and more effective small-molecule therapeutics for cancer treatment. We are a diverse, multidisciplinary team with expertise in data science, organic chemistry, and cancer biology working together to translate discoveries into medicines. We collaborate closely with industrial partners and international Open Science initiatives to advance machine and deep learning (ML/DL) across drug discovery and development.

Relocating in October 2025, VHIO's new AI-Driven Drug Discovery Group, led by Dr. Albert A. Antolin, will contribute to translate the Institute's leading oncology research into new medicines for cancer patients. Although primarily computational, we operate a small on-site wet lab to enable rapid experimental validation of our predictions using *in vitro* cancer models – bridging computational with experimental research. This multidisciplinary approach is critical for facilitating collaboration and accelerating progress into early clinical trials (Antolin AA, *et al. Cell Chem Biol*. 2024). We are also particularly committed to training the next generation of cross-disciplinary scientists to become future leaders in the field.

Overall, we envision a future where multimodal Big Data will be rapidly collected from the preclinical and clinical settings and leveraged using AI to accelerate the cycle of cancer drug discovery and development – enabling the rapid discovery of safer and more effective therapeutics for patient benefit (Workman, Antolin, *et al. Expert Opin Drug Discov*. 2019).

Research Lines

Our research is centred on three pillars. First, we develop **new ML/DL approaches to enable small-molecule drug design**, with a strong emphasis on practical hit-to-lead

optimisation. On this front, we co-organize international computational challenges (e.g. DREAM Target 2035 Drug Discovery Challenge), Dr. Antolin chairs the MAINFRAME AI Network (https://aircheck.ai/mainframe), and we contribute to LIGAND-AI – a global initiative launching in 2026 to generate protein–ligand data at unprecedented scale in partnership with pharmaceutical companies to improve ML approaches (Edwards AM, *et al., Nat Rev Chem*, 2025).

Secondly, we are also interested in **applying systems chemical biology approaches to better understand the effects of approved drugs and harness them in personalized and precision oncology**. For example, we have recently discovered the unexpected biological activity of the metabolite of a cancer drug that could open new avenues for its precise use in prostate cancer (Hu H, *et al. Cell Chemical Biology*, 2024) – and we are continuing this line of research with the synthesis and characterization of the first drug metabolite compound library. We have also used ML to better understand how certain drugs produce a side-effect termed phospholipidosis (Hu H, *et al. Cell Chemical Biology*, 2023). We are interested in the development and use of computational methods to predict the mechanism of action of compounds – their binding to specific protein targets (polypharmacology) – and we are collaborating with industry to harness high-content microscopy (cell painting) and ML/DL to predict polypharmacology. We also collaborate with international initiatives to collect and standardize data in chemical biology (e.g. Antolin AA, *et al. Nucleic Acids Research*, 2023).

Finally, central to our final objective, we **collaborate closely with oncologists, translational scientists and industry to apply our computational approaches in new cancer drug discovery projects**. For example, we are currently developing new small-molecule immune-oncology therapeutics to potentiate cell therapies – demonstrating how different therapeutic modalities can work together to achieve better outcomes. We are also designing multi-target inhibitors to prevent or delay the emergence of drug resistance in colorectal cancer – one of the main challenges faced by targeted therapies.

Team

Group Leader
Albert A. Antolin

PostDoctoral Fellow
Leticia Manen-Freixa

PhD student
Luca Ruvo

MSc Student
Albert Turon

Visiting PhD Student
Muhammad Waqas

Publications

Highlighted publications (for a full list see (https://pubmed.ncbi.nlm.nih.gov/?term=antolin+aa)

1) Edwards AM, Owen DR; Structural Genomics Consortium Target 2035 Working Group. Protein-ligand data at scale to support machine learning. *Nat Rev Chem*. 2025*, in press*. doi: 10.1038/s41570-025-00737-z.

2) Manen-Freixa L, Antolin AA. Polypharmacology prediction: the long road toward comprehensively anticipating small-molecule selectivity to de-risk drug discovery. *Expert Opin Drug Discov*. 2024 19, 1043-1069. doi: 10.1080/17460441.2024.2376643.

3) Hu H, Serra C, Zhang W, Scrivo A, Fernández-Carasa I, Consiglio A, Aytes A, Pujana MA, Llebaria A, Antolin AA. Identification of differential biological activity and synergy between the PARP inhibitor rucaparib and its major metabolite. *Cell Chem Biol*. 2024. 31, 973-988. doi: 10.1016/j.chembiol.2024.01.007.

4) Hu H, Tjaden A, Knapp S, Antolin AA, Müller S. A machine learning and live-cell imaging tool kit uncovers small molecules induced phospholipidosis. *Cell Chem Biol*. 2023. 30, 1634-1651. doi: 10.1016/j.chembiol.2023.09.003.

5) Antolin AA, Sanfelice D, Crisp A, Villasclaras Fernandez E, Mica IL, Chen Y, Collins I, Edwards A, Müller S, Al-Lazikani B, Workman P. The Chemical Probes Portal: an expert review-based public resource to empower chemical probe assessment, selection and use. *Nucleic Acids Res*. 2023 51, D1492-D1502. doi: 10.1093/nar/gkac909.

6) Antolin AA, Clarke PA, Collins I, Workman P, Al-Lazikani B. Evolution of kinase polypharmacology across HSP90 drug discovery. *Cell Chem Biol*. 2021 28, 1433-1445. doi: 10.1016/j.chembiol.2021.05.004.

Projects

Title: Systems-based characterization of drug metabolites to exploit them in precision medicine (META-PRIME). Funding entity: Agencia Estatal de Investigación – Ministerio de Ciencia e Innovación. Ref: PID2022-136344OA-I00. Duration: 09/2023 – 08/2026. Role: PI.

Title: design KRAS inhibitors that overcome resistance. Funding entity: VIVAN Therapeutics (industry). Duration: 05/2023 - present. Role: PI/coordinator (with Prof. Workman (ICR) and Dr. Villegas (VIVAN)).

Title: Developing a pharmacophoric model for scaffold hopping. Funding entity: AtG Therapeutics (industry). Duration: 11/2024 - present. Role: PI.

Title: "Miguel Servet" Fellowship. Funding entity: Instituto de Salud Carlos III. Ref: CP22/00122. Duration: 07/2023 – 06/2028. Role: PI.

Project Funding