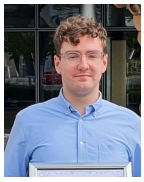
SSPC Hybrid Molecules & Bioconjugation at a Glance - Part 2

Bioconjugation and molecular hybrids are at the forefront of pharmaceutical innovation, offering transformative solutions for targeted drug delivery and enhanced therapeutic efficacy. These technologies enable the precise attachment of drugs to biological molecules and other molecular cargo, improving stability, solubility, and specificity. SSPC has a critical mass of renowned researchers in this area and the Centre plays a pivotal role in this field, leveraging its advanced research capabilities and talented researcher pool to develop cutting-edge advancements. SSPC's expertise provides bespoke solutions that address complex industry challenges, driving innovation in drug substance research and manufacturing processes for the pharmaceutical and biopharmaceutical sectors.

Investigating the Structure-Activity Relationships of Zn(II) Ionophores

Assoc. Prof. Rob Elmes
Dr Luke Marchetti
Maynooth University

Johnson&Johnson

Thioquinolines have potential impact in health and wellbeing due to their prospective use as anti-microbial agents, providing a novel method to combat to treat bacterial infections in the rise of anti-biotic resistant bacteria. This research collaboration with industry investigates the structure-activity relationships of thioquinoline-based Zn(II) transporters. The anticipated application of these Zn(II) ionophores will be as anti-microbial agents and treatment of various diseases such as neurodegenerative disease and pancreatic cancer. The research will establish a synthetic method to achieve 8-thioquinoline targets, followed by the evaluation of their Zn(II) binding affinity and transport efficacy in in vitro models. It conducts biological evaluation in mammalian, bacterial, and fungal cell models and identifies lead compounds based on initial biological evaluations and perform further structural modification to improve biological activity. These Hydroxyquinolines have had limited success as treatments for neurodegenerative diseases in clinic trials. The proposed thioquinolines have the potential to improve patient well-being and outcomes in patients suffering with such diseases.

Solid-Phase Synthesis of Peptides and Conjugates: New (including green) Methods & Applications

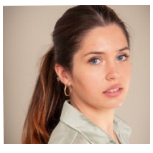

Prof. Marc Devocelle
Dr Siobhan O'Flaherty
RCSI

Manufacturing processes in the Pharmaceutical sector relies on the use of organic solvents, some of them being on the REACh list of undesirable substances, or already under regulation restricting their use (e.g., DMF since December 2023). Such processes include Solid Phase Peptide Synthesis (SPPS). This research aims to improve the sustainability of SPPS and complement techniques of peptide conjugation/modification to circumvent some of their limitations, for the preparation of peptide APIs and conjugates, including lipidated sequences and polymer conjugates. The greenest option for SPPS is sequence assembly in aqueous media, necessitating the development of protection and coupling strategies compatible with this solvent. An approach not only meeting this objective, but also circumventing the use of coupling reagents, which do not currently satisfy green chemistry requisites, is developed with this project.

Despite the number of established and new methods to produce peptide conjugates, there is scope to develop new conjugation chemistries endowed with original properties. This work investigates a click-chemistry approach for the conjugation of complex (drug-like) molecules, meeting the reactivity, stability and selectivity requirements of the peptidic and non-peptidic components. The applicability of the method is assessed with the aim to increase the peptide's activity, extend its half-life and potentially reduce its immunogenicity, among other benefits.

Naphthalimide Derivatives for Imaging and Targeting

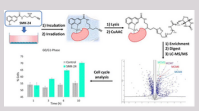




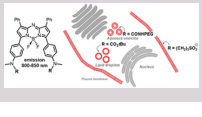
Prof. Thorri Gunnlaugsson
Dr Eoin Scanlon
Laura Ramírez Lázaro, PhD
Trinity College Dublin

Lack of selectivity from cancer treatments is a huge problem for cancer patients as a lot of cancer drugs kill both cancer and healthy cells. Development of selective anticancer drugs by functionalising molecules with known anticancer properties with targeting ones enables them to attack cancer cells over healthy cells. This group of researchers are overcoming this issue by attaching them to peptides or sugars that are known to undergo efficient undertake by cells. The work involves developing a drug compromised of a RGD cyclic peptide moity as the targeting agent, a naphthalimide core such as the amonafide as the drug and a sugar to prevent the drug from being toxic before is released without impacting healthy cells. Imaging on this project carried out by **Prof. Donal O'Shea,** Molecular and Cellular Imaging Core Facility at RCSI**,** featured in Hybrid Molecules & Bioconjugation at a Glance, Part 1.

Publication highlights



Probing the metalloproteome: an 8-mercaptoquinoline motif enriches minichromosome maintenance complex components as significant metalloprotein targets in live cells, McKenna, S. M., Florea, B., Zisterer, D.M., Van Kasterern, S. I., McGouran, J. F., 2024, RSCC, *Chem. Biol.*, 776-786



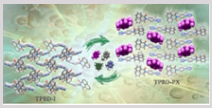
Substituent directed cellular imaging in the 800-850 nm range with BF2-azadipyrromethene fluorophores. Caulfield, C., **Wu, D.**, Garre, M., **O'Shea, D.F.**, *RSC Adv.* 2023, 13, 14963-149732

Crystal Engineering of Azole-Based Supramolecular Assemblies


Prof. Michael Zaworotko
Dr Maryam Rahmani
University of Limerick

Developing crystal engineering studies to address challenges such as enhancing medicinal properties or facilitating separation/purification processes can be achieved through the rational design of supramolecular assemblies. Here we reveal that crystal engineering can be used to (i) design novel azole-based materials such as ionic cocrystals (ICCs) to improve the physicochemical properties of drug molecules, and (ii) develop nonporous 0D molecular materials for separating isomers with similar physical properties. The research results in improved efficacy of azole-based drug products and enhanced insight into azole-based 0D nonporous materials for key separation processes within the chemical industry.

Publication



Highly Selective p-Xylene Separation from Mixtures of C8 Aromatics by a Nonporous Molecular Apohost. Rahmani, M., Matos, C., R., M., O., Wang, S., Bezrukov, A. A., Eaby, A. C. Sensharma, D., Hjiej-Andaloussi, Y., **Vandichel, M., Zaworotko, M.J.**, *Am. Chem. Soc*, 2023

Lipid Discovery for Biomolecule Delivery

Assoc. Prof. Rob Elmes
Maynooth University
Dr Örn Almarsson
Axelyf CEO

The project is being led by Associate Professor Rob Elmes of Maynooth University and championed by Dr Örn Almarsson (CEO & co-founder, Axelyf). The team aims to exploit the fundamental principles of supramolecular chemistry to develop a series of innovative technologies to enhance the current state-of-the-art and drive forward the field of bio-therapeutics based on nucleic acids.

This collaboration aims to impact patients' lives through the development of next-generation delivery technologies for emerging therapeutics, such as the mRNA class of compounds.

SSPC Expertise

Prof. Thorri Gunnlaugsson
Prof. Donal O'Shea
Dr Rob Elmes
Prof. Marc Devocelle
Prof. Alan Dobson
Dr Darren Griffith
Prof. Sarah Hudson
Dr Ioscani Jimenez del Val
Dr Constantina Papatriantafyllopoulou
Prof. Andrew Kellett
Dr Joanna McGouran
Prof. Susan Quinn
Dr Eoin Scanlan
Dr Jerry Reen
Prof. Wolfgang Schmitt
Prof. Michael Zaworotko
Prof. Kevin Kavanagh
Assoc. Prof. Finbarr O'Sullivan
Prof. Damien Thompson

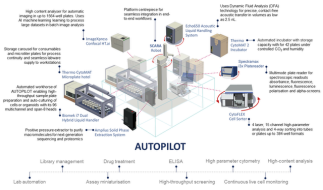
Rational Design of a Phosphate-Binding Zinc(II) Complex for Targeted Gene Therapy


Prof. Andrew Kellett
Dr Georgia Menounou
Dublin City University

The hybrids are unique and operate in a different way to existing state-of-art gene editing technologies (e.g. ZFNs, TALENs, and CRISPR). This research focuses on the development of a chemistry-based gene editing technology using a unique class of advanced site-selective bio-compatible hybrid molecules. These hybrids will consist of a metallodrug 'clicked' to a triplex forming oligonucleotide (TFO). The metallodrug will furnish the probe with potential DNA hydrolytic activity. The cleaving and targeting moieties in this technology will work synergistically to provide both sequence-selectivity to the metallodrug which, in turn, provides high stabilisation to the triplex. The objective is to develop hybrid biomaterials using click chemistry, for gene knockout in human cells. The outcomes of the project have potential applications in bio-diagnostics and therapeutics. This technology is expected to have a societal impact in battling cancer offering an overall improvement of well-being for cancer patients and their families.

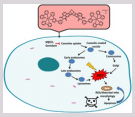
Infrastructure

AUTOPILOT, Automated High-Throughput Analysis of Cellular Phenotyping

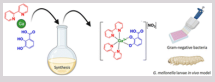


Led by **Prof. Andrew Kellett,** Dublin City University, the **AUTOPILOT** system from SFI's Infrastructure call. This system is a unique, custom build, robotically controlled platform enabling high-throughput cell characterisation including phenotyping by flow cytometry, high content analysis, proteomics, and cell culture analysis. It enables numerous automated workflows to be performed simultaneously, essentially facilitating analysis of any perturbation to cellular function by a large pool of compounds or in a number of model systems.

Publication highlights



Tracking the cellular uptake and phototoxicity of Ru(ii)-polypyridyl-1,8-naphthalimide Tröger's base conjugates. Bright, S.A., Erby, M., Poynton, F.E., Monteyne, D., Pérez-Morga, D., **Gunnlaugsson, T.**, Williams, D.C., **Elmes, R.B.P.**, *RSC Chem Biol.*, 2024, 5, 4, 344-359



Synthesis, characterisation and antibacterial activity of novel Ga(III) polypyridyl catecholate complexes. **More O'Ferrall, L., Piatek,** M. Twamley, B., **Kavanagh, K.**, O'Connor, C., **Griffith, D.M.**, *Dalton Trans.*, 2023, 52, 11958-11964

For more information on SSPC and the SSPC Hybrid Molecule & Bioconjugation Community, please contact SSPC Industry Engagement Manager aisling.arthur@ul.ie