SSPC Hybrid Molecules & Bioconjugation at a Glance - Part 1

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.

Aggregation-Induced Emission for Bioimaging


Prof. Thorri Gunnlaugsson
Dr Adam Henwood
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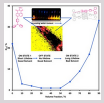
Two aggregation-induced emission (AIE) 1,8-naphthalimides agents exhibiting "turn-on/turn-on" emission behaviour are reported. They are emissive in good solvents of low/intermediate polarity (THF/hexane) but undergo drastic quenching in polar solvents (DMSO/MeOH) due to solvatochromic and energy gap law effects. Water also quenches the emission up to a critical volume (<50% water in THF), after which hydrophobicity drives them to aggregate into nanoparticles, restoring their emission. The mechanisms are revealed through spectroscopy and theory with distinct excited-state decay kinetics observed between the two turn-on/turn-on states. Self-assembly of the agents with the biocompatible poloxamer P188 generates luminescent particles that are taken up into MDA-MB 231 human breast cancer cells, at which point they disassemble, releasing naphthalimide agents, which then localizes in the lipid droplets. Time-resolved fluorescence lifetime imaging (FLIM) distinguishes extracellular 2-P188 particles emitting from the "aggregated on-state" and intracellular, free molecules of naphthalimide agents emitting from the "disaggregated on-state" within the lipid droplets. A patent application has been filed with the European patent office for this work.

Publication



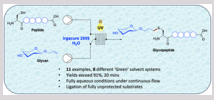
Time-resolved fluorescence imaging with colour-changing, "turn-on/turn-on" AIE nanoparticles. **Henwood, A.F.**, Curtin, N., Estalayo-Adrian, S., Savyasachi, A. J., Gudmundsson, T. A., Lovitt, J. I., Sigurvinsson, L. C., Dalton, H. L., Hawes, C. S., Jacquemin, **D., O' Shea, D. F., Gunnlaugsson, T.**, *Chem*, 2024,10,578-599

Bioconjugations in Flow for Drug Conjugates and Theranostic Imaging Agents

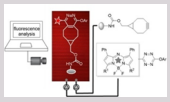

Prof. Donal O' Shea
Dr Sheila Fitzgerald
RCSI

This research programme was aimed at generating in flow bioconjugation protocols through the development of novel drug hybrids for the dual purpose of diagnostic imaging and therapeutic effect. Potential bioconjugation pathways through biorthogonal chemistry in flow were investigated and identified optimal conditions applicable to a wide range of biomolecules. It also looked at conjugating existing therapeutic drugs to NIR imaging agents to yield potential drug hybrids. Flow conjugation pathways were identified that can be applied to a wide range of molecules to rapidly generate targeted imaging agents without any purification requirements. The use of Flow chemistry allows for a reduction in solvent consumption and volumes of reagents which results in safer, greener and more economic synthesis.

Publications



A thiol-ene mediated continuous-flow approach for ultrafast bioconjugation using 'green' solvents. González, I. R., Joshua T. McLean, J. T., **Fitzgerald, S.**, Mezzetta, A., Guazzelli, L., **O'Shea, D. F. & Scanlan, E. M.**, *Org. Biomol. Chem.*, 2024,22, 2203-2210



Continuous Flow Bioconjugations of NIR-AZA Fluorophores via Strained Alkyne Cycloadditions with Intra-Chip Fluorogenic Monitoring. Fitzgerald, S., O' Shea, D., *Chemistry A European Journal*, 2022,28,11

Accelerated Microfluidic Chemical Ligation for Synthesis of Peptide and Protein Therapeutics


Dr Eoin Scanlon
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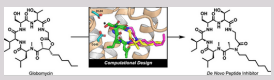
Novel methodologies improve synthetic routes to therapeutics, allowing easier synthesis and purification along with a reduction in costs both financial and environmental. Newly emerging green solvents allow reduction in the use of environmentally harmful or toxic solvents such as dimethylformamide. The aim of this research is to develop thiol-ene based methodologies for synthesis of peptide pharmaceuticals, develop these methodologies for in-flow application with potential for large scale manufacture and investigate alternative solvents for improving the environmental impact of peptide therapeutic manufacturing. In-flow peptide synthesis will allow easier scale-up of peptide therapeutic manufacture.

Publications

Radical-mediated thiol-ene 'click' reactions in deep eutectic solvents for bioconjugation. Nolan, M.D., Mezzetta, A., Guazzelli, L. & **Scanlan, E.M.** *Green Chem.*, 2022, 24, 4, 1456-1462



Computational Design of Cyclic Peptide Inhibitors of a Bacterial Membrane Lipoprotein Peptidase, Craven, T. W., **Nolan, M.D.**, Bailey, J., Olatunji, S., Bann, S. J., Bowen, k., Ostrovitsa, N., Da Costa, N. M., Ballanitine, R. D., Weichert, D., Levine, P.M., Stewart, L.J., Bhardwaj, G., Geoghegan, J.A., Cochrane, S. A., **Scanlan, E. M.**, Caffrey, M. Baker, D. *ACS Chem. Biol.*, 2024, 19, 1125-1130.

Potent Antimicrobial Effect Induced by Disruption of Chloride Homeostasis


Assoc. Prof. Rob Elmes
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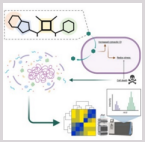
Maynooth University

Artificial transmembrane ion transporters have proposed applicability to medicinal chemistry, where perturbation of normal cellular homeostasis has already been shown to induce apoptosis in mammalian cells. In this study, Robert Elmes (Maynooth University) and co-workers reported the synthesis and structural characterisation of a new class of fluorescent anion transporter that effectively kill Gram-positive bacteria by disrupting normal sodium and chloride ion concentrations. The so-called "squindoles" take advantage of hydrogen-bonding interactions to bind chloride with high affinity and act as efficient anion transporters. The most active transporter shows potent inhibitory activity against Staphylococcus aureus (SA) and methicillin-resistant Staphylococcus aureus (MRSA). The mode of action is directly related to the anion-transport ability, whereby an influx of chloride into bacterial cells significantly affects their proteome and induces several known stress responses. Most importantly, treated bacteria did not show significant development of resistance mechanisms upon prolonged treatment with these compounds, rendering them a promising tool in the fight against antimicrobial resistance.

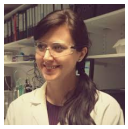
Publication



Potent antimicrobial effect induced by disruption of chloride homeostasis. Brennan, L.E., Kumawat, L.K., **Piatek, M.E.**, Kinross, A.J., McNaughton, D.A., **Marchetti, L.**, **Geraghty, C.**, **Wynne, C.**, Tong, H., Kavanagh, O.N., **O' Sullivan, F.**, Hawes, C.S., Gale, P.A., **Kavanagh, K.**, **Elmes, R.B.P.**, *Chem*, 2023,9,3138-3158

Design of Metal Organic Framework to Remove DMSO from an Aqueous Stream





Prof. Thorri Gunnlaugsson
Prof. Wolfgang Schmitt
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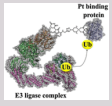
Trinity College Dublin

MSD

A common challenge in the pharmaceutical industry is the removal of residual solvent from manufacturing processes and resulting products. In partnership with Industry, this research project designs, syntheses and structurally characterizes coordination polymers (including MOFs) for the use in solution to extract/absorb residual organic solvent "contamination" from bulk solutions. The synthesis of coordination polymers includes the reaction between organic ligands and metal ions to produce amorphous and crystalline material. The structural stability of this material towards degradation in the solution is then confirmed allowing for its further use within pharmaceutical industry setups.

Publication highlights

A novel thiol-saccharide mucolytic for the treatment of muco-obstructive lung diseases. Addante, A., Raymond, W., Gitlin, I., Charbit, A., Orain, X., Scheffler, A.W., Kuppe, A., Duerr, J., Daniltchenko, M., Drescher, M., Graeber, S.Y., **Healy, A.M.**, Oscarson, S., Fahy, J.V., Mall, M.A., *Eur Respir J.*, 2023,61(5),2202022



First-in-class metallo-PROTAC as an effective degrader of select Pt-binding proteins. **O'Dowd, P.D.**, Sullivan, G.P., Rodrigues, D.A., Chonghaile, T.N., **Griffith, D.M.**, *Chem. Commun*, 2023, 2023,59, 12641-12644

A Click Chemistry-Based Artificial Metallo-Nuclease. **Gibney, A.**, de Paiva, R.E.F., Singh, V., Fox, R., **Thompson, D.**, Hennessy, J., Slator, C., McKenzie, C.J., Johansson, P., McKee, V., Westerlund, F., **Kellett, A.**, Angew. Chem. *Int. Ed. Engl.*, 2023,62(38)e202305759

The First Sulfate-Pillared Hybrid Ultramicroporous Material, SOFOUR-1-Zn, and Its Acetylene Capture Properties. Sensharma, D., O'Hearn, D.J., Koochaki, A., Bezrukov, A.A., Kumar, N., Wilson, B.H., **Vandichel, M., Zaworotko, M.J.**, *Angewandte Chemie, Int. Ed.*, 2022,61(8)e202116145

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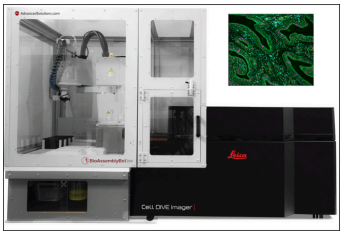

The Molecular and Cellular Imaging Core Facility at RCSI, funded by the HEA, SFI, HRB, Cancer Research Ireland, and the EU, primarily focuses on live cell imaging applications and supports users from different fields in biomedical research. Services include confocal GFP imaging, fluorescence resonance energy transfer (FRET), fluorescence recovery after photo bleaching (FRAP), FLIP and photo-activation/photo-conversion techniques also in combination with patch clamp. The centre supports research projects and provides training in basic epi-fluorescence and confocal microscopy applications, image processing, and advanced live cell imaging.

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