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CiQUS Lecture

Recent Advances in Artificial Gene Editing and DNA Targeted Metallodrug Design

October 24, 2025
CiQUS Seminar Room | 11 AM

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Abstract

Artificial metallo-nucleases (AMNs) are promising DNA damaging drug candidates.¹ In this talk I will present new work demonstrating how the triazole linker produced by the copper(I)-catalysed azide-alkyne cycloaddition (CuAAC) 'click chemistry' reaction can be directed to build new AMN scaffolds with therapeutic potential.^{2,3} In one example, we selected biologically inert reaction partners to develop Tri-Click thiophene (TC-Thio), a bioactive C3-symmetric ligand in which three thiophene-triazole moieties are positioned around a central mesitylene core. This ligand was characterised by X-ray crystallography and forms multinuclear CuII and CuI complexes identified by mass spectrometry and rationalised by density functional theory (DFT). Single molecule imaging of DNA isolated from peripheral blood mononuclear cells showed the complex has comparable activity to the clinical drug temozolomide, causing DNA damage that is recognised by a combination of base excision repair (BER) enzymes. Ongoing efforts in our lab are focused on systematically studying the types of alkyne donors that influence DNA binding and damaging effects within the TC class and on the introduction of stable azide groups into ruthenium complexes,⁴ along with new mono-nuclear and polynuclear platinum compounds for DNA targeted applications.⁵⁻⁸

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Biosketch

Andrew Kellett is a Professor of Inorganic and Medicinal Chemistry in the School of Chemical Sciences at Dublin City University (DCU). He completed his BSc (Hons.) in Chemistry at Maynooth University (MU) and his PhD at Technological University Dublin (TUD). He began his independent career at DCU in 2011, and his research interests focus on the discovery of metallodrugs, artificial gene editing tools, and DNA damage and repair. He is the coordinator of two consecutive multi-million-euro EU-funded Marie Curie Training Networks, ClickGene and NATURE-ETN, and serves as a Principal Investigator within the newly funded MSCA Doctoral Network, MECHANISM: Mechanical Characterisation of Nucleic Acids using Single Molecule Methods. His lab is supported by Science Foundation Ireland (now Research Ireland), the Irish Research Council, the Research Ireland Centre for Pharmaceuticals (SSPC), and CÚRAM, the Research Ireland Centre for Designing the Next Generation of Medical Devices. In 2022, Prof. Kellett was awarded the SSPC 'Investigator of the Year' award, and in 2023, he received Dublin City University's President's Research Medal in "Natural Sciences, Health, Engineering and Related Areas," as well as a prestigious Irish Research Council Laureate Consolidator Award.

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