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Crystallographic studies of ruthenium polypyridyl complexes bound to DNA G-quadruplexes: Towards design, specificity, and function

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Ruthenium polypyridyl complexes, along with offering a unique, modular approach to DNA binder construction; can be tailored to present desirable photochemical and electrochemical properties. As such, ruthenium based DNA intercalators possess the ability to serve many useful functions, for instance, as site specific fluorescent DNA markers, electrochemical probes and photoactivated base-specific oxidizers.[1,2] More recently, the ability to target higher order DNA secondary structures, such as G-quadruplexes, have been reported using modified metal polypyridyls.[3] Research directed at stabilising or damaging G-quadruplex DNA has increased substantially of late as a result of the assemblies proven existence in the living cell.[4] The formation or dissolution of such assemblies has been linked to several topical disorders and biological processes, such as the proliferation of cancers, telomere maintenance, and in the expression/suppression of genes.[5] As such, G-quadruplexes have been heavily researched as an exciting biological target for the binding of prospective small molecule drugs; whereby specifically binding and stabilising these assemblies can be seen as a pathway for the therapeutic modulation of pertinent biological processes. Development of such compounds is however made difficult by the fact that relatively few structural models detailing these binding modes are available (and are often difficult to acquire!).

Here we report how macromolecular X-ray crystallography can be utilised, in tandem with spectroscopic and biophysical techniques, in the elucidation of the DNA-binding properties of ruthenium polypyridyl species. Specifically, we report the first crystal structures of photoactive ruthenium complexes binding to G-quadruplexes.[6,7] Of particular note we will present our most recent structure of a ruthenium complex containing a chromophore with an extended π-surface bound to a unimolecular G-quadruplex.[8] The quadruplex in this case is a derivative of the telomeric repeat sequence, and interestingly this system folds into an antiparallel chair-form quadruplex; the first of its kind to be crystallised with a bound ligand.

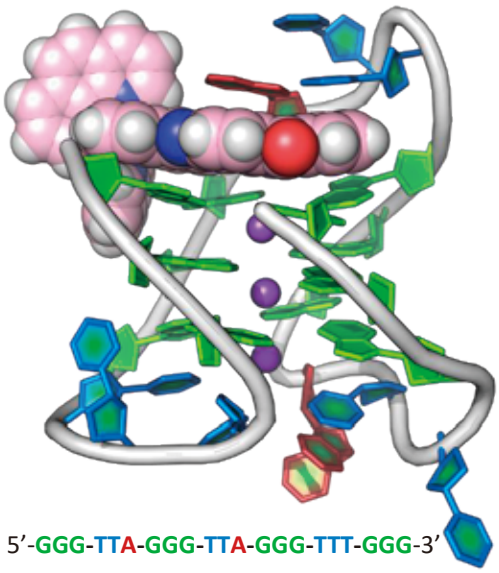

Figure – Crystal structure of a ruthenium polypyridyl complex bound to unimolecular G-quadruplex.

In addition to crystallographic data, we report how such stabilising interactions can affect the replication of quadruplex DNA by the action of polymerases, and how these interactions affect the *in cellulo* formation of quadruplex DNA; with particular focus on enantiospecificity, photophysical damage, and π-extended chromophores. Using these gained structural perspectives it is possible to suggest rationale for observed *in vitro* measurements, and allow for the superior design of ligands devised to target and selectively stabilize DNA secondary structure.

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BIOGRAPHY

Dr Kane McQuaid is a Postdoctoral Research Associate in the chemistry department at the University of Reading, UK. In 2020 Dr. McQuaid completed his PhD in the same department under the supervision of Professor Christine Cardin. His current area of interest is the study of ligand binding to G-quadruplexes, with particular focus on using X-ray crystallography to aid in the design of DNA-binding photoactive metal complexes.

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