

# Biological Chemistry

This research primarily focuses on the interactions between transition metal complexes and DNA. This work aims at understanding the principles of DNA recognition, with the ultimate goal of being able to design compounds that can control gene expression - the next great target now that most of the human genome has been sequenced. We study the interactions of inert dinuclear ruthenium complexes with DNA and RNA. Dinuclear ruthenium complexes, rather than the more often studied mononuclear complexes, offer many advantages. Dinuclear complexes bind selectively at DNA and RNA non-duplex sites, e.g. bulges and hairpin-loops, where shape, size, functionality and charge govern selectivity and affinity.

In addition, we are also involved in the development of a new, and very promising, class of anti-cancer drug – multinuclear platinum complexes. We design and synthesise new complexes, determine their biological activity and examine their binding to DNA by NMR spectroscopy. In addition, we are exploring the possibility of reducing the toxicity and degradation by plasma proteins of multinuclear platinum complexes by encapsulating them in cucurbituril, an open-ended barrel shaped host molecule.



PhD student Yunjie Zhao operating a fluorimeter, PEMS, UNSW@ADFA. After completing her thesis in 2009 Yunjie has received a Research Publication Fellowship for a period of 3 months [Photo credit: K. Badek].

## Members

### Academic Staff:

**Assoc. Prof. Grant Collins** (g.collins@adfa.edu.au) BSc, PhD ANU, MRACI, CChem

### Research Assistant:

**Dr Damian Buck** (d.buck@adfa.edu.au) BSc, PhD ANU

### Research Students:

**Najia Adnan** - Research Topic - Analysis of DNA binding of pixantrone

**Fangfei Li** - Research Topic - Dinuclear ruthenium complexes as therapeutic agents

**Linta Peter Chalisery** - Research Topic - Supramolecular chemistry

**Michelle Pisani** - Research Topic – Dinuclear ruthenium (II) complexes as DNA-binding drugs

**Yunjie Zhao** - Research Topic - Cucurbit[n]uril- a delivery host for anti-cancer drugs.

### Research Collaborators:

**Prof. Richard Keene** (James Cook University, Townsville)

**Assoc. Prof. Janice Aldrich-Wright** (University of Western Sydney)

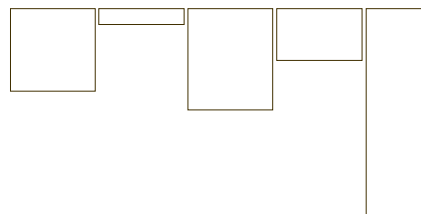
## Recent Research

### Assoc. Prof. Grant Collins

Over the last decade there has been considerable interest in **DNA secondary structures that deviate from the well-known double helix**. One example is a bulge structure in which there are regions of the duplex possessing one or more unpaired bases. These structural motifs are often associated with important biological functions: DNA bulge sites can be created during recombination between imperfectly homologous sequences, and are thought to play an important role in frame-shift mutagenesis. More recently, bulge sites have been shown to bind some DNA-repair proteins more tightly than duplex DNA and consequently are potential binding sites for therapeutic agents. Given their biological importance and potential as a target for novel drugs, there has been considerable research aimed at developing small molecules that can selectively target DNA bulge sites.

In collaboration with Prof. R. Keene (JCU) we have shown that non-intercalating, rigid, dinuclear ruthenium complexes associate weakly with the minor groove of duplex DNA; importantly however, these complexes demonstrate a much greater affinity for more open and/or flexible secondary structures such as bulge sites.

**Multinuclear platinum complexes**, developed by Farrell and coworkers, have shown considerable promise as anti-cancer agents. Unlike cisplatin, di- and trinuclear platinum complexes, where two or three platinum coordination centres are linked by diamine chains, form flexible long-range interstrand DNA adducts. It is from this novel DNA binding mode that multinuclear platinum complexes are thought to derive a different cytotoxic profile to cisplatin. Pre-clinical studies demonstrated that the multinuclear platinum complexes were considerably more active than cisplatin in a range of cell lines, and more importantly, maintained their activity in the corresponding cisplatin resistant cell lines. While multinuclear platinum complexes are highly cytotoxic, they have a



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relatively narrow therapeutic index. Phase I clinical trials indicated that the Maximum Tolerated Dose (MTD) for the trinuclear complex BBR3464 was much lower than platinum drugs already in the clinic. Furthermore, most of the platinum drug binds thiol containing plasma proteins in the bloodstream, and is subsequently degraded to nonactive metabolites. Consequently, methods that can reduce the toxicity and/or decrease the binding of thiol containing proteins could improve the clinical utility of multinuclear platinum drugs. We have demonstrated that encapsulation of the multinuclear platinum complexes within the cavity of a cucurbituril overcomes the problems associated with plasma protein binding, and hence, may represent a new drug delivery technique for this class of anti-cancer compound.

## Student Research

### Analysis of DNA binding of Pixantrone

**Najia Adnan** (n.adnan@adfa.edu.au) Masters

**Field of Study: Biological Chemistry**

The reversible DNA-binding of pixantrone and its activated reactive form should be identical, as the binding is due to the intercalation of the non-reactive planar polycyclic aromatic part of the drug. Consequently, we propose to examine the binding of pixantrone to a range of small segments of DNA (oligonucleotides) by nuclear magnetic resonance (NMR) spectroscopy. In order to compare the DNA-binding of pixantrone to other anthracyclines, initial NMR experiments will utilize a particular well-characterised oligonucleotide. Then, in conjunction with molecular modelling, a detailed picture of the reversible binding will be developed. In the second phase of the research, the reversible binding of pixantrone will be screened against a wide range of oligonucleotides that contain different base sequences and structures (such as base-bulges), using fluorescence intercalator displacement assays. Those sequences or structures that show the strongest pixantrone binding will then be used in subsequent NMR experiments.

### Dinuclear ruthenium complexes as therapeutic agents

**Fangfei Li** (fangfei.li@student.adfa.edu.au) PhD

**Field of Study: Biological Chemistry**

Fangfei Li has just started her PhD and is currently looking at the binding of a dinuclear ruthenium complex with a segment of DNA that contains two bulge regions by NMR spectroscopy and molecular modelling.

### Cucurbit[*n*]uril- a delivery host for anti-cancer drugs

**Yunjie Zhao** (y.zhao@student.adfa.edu.au) PhD

**Field of Study: Biological Chemistry**

Multinuclear platinum complexes and the organic drug albendazole offer real potential for the treatment of cancer. However, and as with many other anti-cancer agents, their clinical use is limited by pharmacological problems. The potential of a relatively new class of macrocyclic host molecules, called cucurbit[*n*]uril (Q[*n*]), to act as a delivery system for these drugs and overcome the clinical drawbacks has been investigated. In order to examine particular aspects of the cucurbit[*n*]uril binding of the drugs, new multinuclear platinum complexes and

benzimidazole carbamate derivatives have been synthesized, and their biological activity compared to the parent compounds.

### Dinuclear ruthenium (II) complexes as DNA-binding drugs

**Michele Pisani** (m.pisani@adfa.edu.au) Masters

**Field of Study: Biological Chemistry**

Dinuclear ruthenium (II) complexes preferentially bind non-duplex DNA and RNA sites. Consequently, these compounds have significant potential as therapeutic agents. In this study the binding of the dinuclear ruthenium complexes to DNA/RNA and various drug delivery agents (dendrimers and cucurbiturils) is being examined.

### Supramolecular chemistry

**Linta Chalissery** (l.chalissery@adfa.edu.au) Masters

**Field of Study: Biological Chemistry**

Developing analytical techniques for the purification of "cucurbiturils", a molecular host and a drug delivery vehicle. Available methods to purify cucurbiturils are inefficient and time-consuming. We are developing a method based on column chromatography that is much easier to implement in large scale.

## PhD Opportunities and Scholarships

There are PhD and Masters opportunities in all the research areas described above.

**For further information contact:**

**Assoc. Prof. Grant Collins** (g.collins@adfa.edu.au)

## Facilities

**Grant Collins, Anthony Day, Mok Rahman** and **Lynne Wallace** were successful in applying for a grant under the Major Equipment and Infrastructure Initiative (MREII). The Urgent upgrade of the console of the Varian Unityplus 400 MHz Nuclear Magnetic Resonance (NMR) spectrometer was awarded \$108,000 for 2008.

NMR spectroscopy is the central tool of experimental chemistry. It is used to determine the structure and shape of molecules, which, in turn, determine physical properties, and chemical and biological activity. NMR spectroscopy can also be used to follow reaction kinetics at the atomic level, establish the nature of interactions between two or more molecular species, and study diffusion of dissolved compounds.

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## Publications

### In Press

#### Book - Chapter

**Buck, D.P. & Collins, J.G.**, in press, NMR Studies of metallointercalator-DNA interactions, in *Metallointercalators-Synthesis, Techniques to Probe their Interactions with Biomolecules*, J.R. Aldrich-Wright (ed.), Springer.

#### Journal - Refereed

**Pisani, M., Zhao, Y., Wallace, L., Woodward, C.E.**, Keene, R., **Day, A.I. & Collins, G.**, 2009, Cucurbit[10]uril binding of dinuclear platinum(II) and ruthenium(II) complexes: Association/disassociation from seconds to hours; submitted in September, 2009.

#### Patent

**Day, A., Collins, J.G.**, Morris, D., Pourgholami, M. & **Zhao, Y.**, Cytotoxic benzimidazole carbamate derivatives and cucurbit[n]uril soluble formulations, patent pending, September, 2009.

### 2009 publications

#### Book - Chapter

Smith, J.A., **Collins, J.G.** & Keene, F.R., 2009, Groove binding ruthenium(II) complexes as probes of DNA recognition, in *Metal Complexes - DNA interactions*, N. Hadjilias & E. Sletten (eds), Wiley Publishing, Oxford, UK, pp. 319-346.

#### Journal - Refereed

Keene, F.R., Smith, J.A. & **Collins, J.G.**, 2009, Metal complexes as structure-selective binding agents for nucleic acids, *Coordination Chemistry Reviews*, 253(15-16), 2021-2035, doi:10.1016/j.ccr.2009.01.004.

**Pisani, M.**, Wheate, N.J., Keene, F.R., Aldrich-Wright, J.R. & **Collins, J.G.**, 2009, Anionic PAMAM dendrimers as drug delivery vehicles for transition metal-based anticancer drugs, *Journal of Inorganic Biochemistry*, 103(3), 373-380, doi:10.1016/j.jinorgbio.2008.11.014.

**Zhao, Y., Bali, M.S.**, Cullinane, C., **Day, A.I. & Collins, J.G.**, 2009, Synthesis, cytotoxicity and cucurbituril binding of triamine linked dinuclear platinum complexes, *Dalton Transactions*, 26, 5190-5198, doi: 10.1039/b905112k.

### 2008 publications

#### Journal - Refereed

**Buck, D.P.**, Spillane, C., **Collins, J.G.** & Keene, F.R., 2008, Binding of a dinuclear ruthenium(II) complex to the TAR region of the HIV-AIDS viral RNA, *Molecular Biosystems*, 4(8), 851-854.

**Buck, D.P.**, Abeyasinghe, P.M., Cullinane, C., **Collins, J.G.** & Harding, M.M., 2008, Inclusion complexes of the antitumour metallocenes Cp<sub>2</sub>MCl<sub>2</sub> (M = Mo, Ti) with cucurbit[n]urils, *Dalton Transactions*, 17, 2328-2334.

**Zhao, Y., Buck, D.P.**, Morris, D.L., Pourgholami, M.H., **Day, A.I. & Collins, J.G.**, 2008, Solubilisation and cytotoxicity of albendazole encapsulated in cucurbit[n]uril, *Organic & Biomolecular Chemistry*, 6, 4509-4515.

#### Conference- Abstract

**Zhao, Y., Day, A.I., Buck, D., Bali, M. & Collins, G.**, 2008, Cucurbit[n]uril for drug delivery, *1<sup>st</sup> International Conference on Drug Design and Discovery*, Dubai, UAE, February 2008.

**Zhao, Y., Bali, M., Day, A.I. & Collins, G.**, 2008, Cucurbit[n]uril for drug delivery, *Australasian Pharmaceutical Science Association Conference*, Canberra, December 2008.

#### Conference - Poster

**Zhao, Y., Day, A.I., Buck, D., Bali, M. & Collins, G.**, 2008, Cucurbit[n]uril for drug delivery, *1<sup>st</sup> International Conference on Drug Design and Discovery*, Dubai, UAE, February 2008.

**Zhao, Y., Bali, M., Day, A.I., & Collins, G.**, 2008, Cucurbit[n]uril for drug delivery; *Australasian Pharmaceutical Science Association Conference*, Canberra, December 2008.

## Grants

### External Grants

Prof. Richard Keene from James Cook University & **J.G. Collins**, Development of new materials based on multi-nuclear ruthenium complexes, ARC Discovery Grant, 2009-2011: \$320,000.

### UNSW Grants

**J.G. Collins**, The development of dinuclear ruthenium(II) complexes as therapeutic agents for the treatment of HIV-AIDS, Special Research Grant, 2008: \$7,600.

**J.G. Collins & A. Day**, Structural modification of the benzimidazole carbamate anti-cancer drugs - Toward improving potency, UNSW@ADFA RTS Scholarship, 2009.

## Seminars

**Assoc. Prof. Grant Collins**, Follow that Gene, Faculty Research Seminar, UNSW@ADFA, 9 September 2008.

## Service

### Assoc. Prof. Grant Collins

- Referee for submitted publications for numerous journals, e.g. *Chemical Communications*, *Dalton Transactions*, *Inorganic Chemistry*, *Journal of Inorganic Biochemistry*, *Journal of Biological Inorganic Chemistry*.
- Referee for ARC Applications and research applications submitted to several international granting agencies

## Visitors

**Cara Toscan**, a chemistry honours student from the University of Western Sydney visited PEMS during August 2008. She worked in Grant Collins' laboratory, studying the interaction of several potential anticancer platinum complexes with DNA by nuclear magnetic resonance spectroscopy.