Summary report

This project focused on a new class of DNA-binding agents. Such agents are exciting and important because of the potential to regulate gene expression and the potential applications in anti-cancer and anti-viral therapy. The focus was on new synthetic agents that target a less common DNA structure: Y-shaped replication and transcription forks. These are particularly exciting targets as the ability to recognise and modulate replication or transcription processes could be a very powerful tool not only in the fundamental study of the processes such as replication but also in the modulation of cell cycle control.

The agents bind both to forks and duplex regions and the project of Dr Mucha aimed to explore in detail the DNA recognition and to understand what features of the nanoscale synthetic drugs, and which biomolecular binding mode, give rise to the observed biological effects and to probe that in more detail. Cylinders were prepared to try and probe different binding modes.

Dr Mucha's data, which are currently being prepared for publication, demonstrate (i) metallosupramolecular cylinders can recognise and stabilise 3-way junctions of both DNA and RNA (ii) molecular recognition of DNA and RNA junction indicates dependence between this unprecedented binding mode of cylinders and their biological activity in the cell (iii) the dual mode of 3-way junction recognition (DNA as well as RNA) indicates that beside DNA, a possible target is RNA (iv) the cylinder recognition approach might be extended to other DNA structures.

An aspect of Dr Mucha's work was the investigation of structural details of the cylinders in combination with DNA and RNA junction, further studies for crystal forms of metalocomplexes with nucleic acids were undertaken. This work has been done in collaboration with Prof. Roland K.O. Sigel from the University of Zurich (Switzerland), who is a world leading expert of crystal studies of DNA and RNA. Dr Mucha has been actively participating in preparation and discussion of these experiments.

Gel shift assays were also used to probe competitive binding from other biorelevant 'unusual' DNA structures. Further experiments are being carried forward by other group members and Dr Mucha will still be involved in discussions of this work after the end of his fellowship; several publications from this project are thus anticipated after the project end in 2012/2013.

An important aspect of the project outcomes is the training that Dr Ariel Mucha received and that will support him through his subsequent scientific career: new research skills and experiences include: supramolecular design and synthesis of DNA recognition agents, microwave synthesis, flash chromatography, TLC, HPLC/MS of oligonucleotides/metallosupramolecular helicates, circular dichroism and flow linear dichroism for probing drug-DNA interactions, radiolabelling/purification of DNA and RNA, gel electrophoresis techniques to study drug DNA interactions, cell tests. This broad suite of skills represented a very steep and challenging learning curve and it is to his credit that he made such progress towards the schedule of research tasks. He has also developed skills crucial to the successful implementation of research reinforcing his professional maturity. Within the group, he has taken part in all activities of that team, including seminars and the postgraduate training programme and he has contributed to guiding students within the group. This has significantly increased his experience in project management (e.g., defining working packages and deadlines, aligning with collaborators as well as own group members) and provided him with leadership experience. Dr Mucha became an experienced scientist and is able to prioritise himself (e.g., time

management for different workstreams in parallel; coaching for students and collaborators) and lead others (e.g., agreeing on priorities with collaborators and team members; influencing techniques). Dr Mucha has been trained in clearly presenting research results, set in the context of the research programme, through weekly reports, one-to-one meeting with Prof. Mike Hannon, oral presentations at internal group research seminars and through oral presentations and posters at scientific meetings. He received advanced training in Presentational Skills and managing younger researchers.

The impact of the fellowship has been (i) a better fundamental understanding of a new class of DNA recognition agents that have promise as future anti-cancer and anti-viral drugs and (ii) the advanced training of a very promising young researcher at the interface between chemistry and biomedicine.