EPSRC Centre for Doctoral Training (CDT) in Molecular Sciences for Medicine (MoSMed)

DNA Nanosensors for Metal Ion Cancer Biomarkers

Newcastle University School of Computing in collaboration with Durham University Department of Biosciences and Nanovery Ltd.

Supervisory Team

- **Dr Harold Fellermann**, School of Computing, Newcastle University
- **Assoc Prof Patricia Muller**, Dept of Biosciences, Durham University
- **Dr Alexander Jackson**, Nanovery Ltd.

Project overview/context

Cancer is a major cause of death with an estimated economic impact of £7.6bn per year in the UK alone. The earlier cancers are diagnosed the more successful therapies tend to be. We are developing diagnostic solutions for cancer based on programmable DNA nanodevices that are able to detect, amplify and report cancer markers in patient blood. This project will develop DNA nanodevices that detect raised concentrations of metal ions – a possible indicator for cancer onset and progression. This will be achieved through a combination of experimental and computational methods.

Research Project

Biomarker analysis becomes an increasingly important tool for clinical diagnostics of cancers. We have previously developed dynamic DNA nanodevices which detect miRNA cancer biomarkers at femtomolar concentrations, amplify the signal and report its presence through fluorescence. In this project, we propose to expand the diagnostic domain of our technology to detect bioactive metal ions, in particular copper.

Research Plan:

Objective 1 – Nanodevice design: We will develop a novel sensing component for our modular nanodevice that binds copper ions via an AS1411 aptamer [1]. This will synergise with the work in the Muller lab, in which the effect of copper on cancer progression, metastasis and response to chemotherapy is investigated [2]. We will modify this aptamer so that it can enable downstream reactions and integrate it with our current DNA nanodevice in a way that it triggers downstream amplification of the biomarker signal in its active (ligand bound) conformation, but not in its neutral conformation. This will therefore form an ideal biosensor to detect bioavailable copper as opposed to total copper levels ideally suitable to work in an in vivo environment.

Objective 2 – Assay design: The performance of different nanodevice designs will be analyzed via fluorescence assays for various metal ions at different concentration levels and in different media. We will identify critical design choices in the nanodevice design and operating procedures that allow us to maximize both sensitivity and specificity of the assay.

Objective 3 – DoE/lab automation: Assay design is made difficult by the vast number of parameters that enter the design and execution of our diagnostic assays. To account for this complexity, the project will develop automated rapid screening methodologies that utilize statistical design of experiments in conjunction with lab automation technologies such as liquid handling robots, to support rapid screening and optimization.

Objective 4 – Structural analysis and simulation: DNA nanodevices are particularly amenable to rational design, the project will make use of mechanistic models and simulation. In particular, we will perform atomistic and coarse-grained molecular dynamics structural simulations of the DNA aptamer/metal interactions as well as kinetic models of the nanodevice function. Where possible, simulations will be integrated in an automated assay pipeline to support rapid optimization.

Strategic Vision:

Due to their drastically reduced cost and rapid turnaround times, liquid biopsies are expected to revolutionize the current health care system by enabling regular, prophylactic, personalized diagnostics at GP level [3]. The resulting early detection of diseases can increase treatment success while simultaneously reducing treatment costs. Currently, liquid biopsy is restricted to a relatively small set of biomarkers, such as

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miRNAs. The overarching vision of the project is to extend the scope of liquid biopsies to wider application domains.

[1] A Bahreyni *et al.* High affinity of AS1411 toward copper; its application in a sensitive aptasensor for copper detection. *Anal. Biochem.* 575:1-9 (2019).

[2] L Dolma, PAJ Muller. GOF Mutant p53 in Cancers: A Therapeutic Challenge. *Cancers (Basel)* 2022, 14(20):5091

[3] SN Lone *et al.* Liquid biopsy: a step closer to transform diagnosis, prognosis and future of cancer treatments. *Mol Cancer* 21, 79 (2022).

Training & Skills

Academic training:

- Independent problem solving of complex research questions and scientific methods
- Experimental and computational design and analysis of DNA nanodevices
- Annual presentations at scientific seminars and international conferences
- Authoring of journal/conference publications
- Working in and communicating with a highly interdisciplinary team
- Dissertation writing

Industrial training:

- Design and analysis of DNA nanotechnology
- Laboratory health & safety training
- Training in standard laboratory protocols
- Transfer of academic solutions to industry level
- Evaluating novel solutions from an IP perspective and engaging in patent authoring
- Understanding biotechnology and nanotechnology business models & opportunities

Further Information

For enquiries please contact Harold Fellermann
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How to Apply

If applying to a **Newcastle project**, you must apply through the University's **Apply to Newcastle Portal**. Once registered select **'Create a Postgraduate Application'.**

Use 'Course Search' to identify your programme of study:

- search for the 'Course Title' using the programme code: **8207F**
- select **'PhD Molecular Sciences for Medicine (SNES)'** as the programme of study

You will then need to provide the following information in the 'Further Questions' section:

- a 'Personal Statement' (this is a mandatory field) - upload a document or write a statement directly into the application form. Please include the full title of the studentship, the studentship code, and how your interests and experience relate to the project.
- the relevant studentship code **(mos23_15)** in the 'Studentship/Partnership Reference' field. If you wish to apply for additional studentships, please make sure to add the relevant studentship reference each time, before submitting each separate application. For example, you may wish to apply for mos23_14 AND mos23_15. **You must include the relevant code for your application to be considered.**
- when prompted for how you are providing your research proposal - select 'Write Proposal'. You should then type in the title of the relevant research project. You do not need to upload a research proposal.
- An up to date CV.
- Please upload all documents in PDF format.

Equality, Diversity and Inclusion (EDI)

Within the MoSMed CDT we are committed to building a diverse community based on excellence and commitment. To that end in our recruitment of Doctoral Researchers we welcome applications from outstanding candidates of all backgrounds regardless of ethnicity, disability, gender identity, sexual orientation and will consider all applications equally based on merit.

Should you have any queries regarding the MoSMed application process to Newcastle University please contact Craig Hinds, the MoSMed CDT Manager: **mosmed.cdt@newcastle.ac.uk**

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