PhD Opportunity

Imaging Approaches to Monitor and Optimise Solid Phase Oligonucleotide Synthesis

Overview: Your PhD project presents the opportunity to focus your postgraduate research towards addressing the lack of process analytical technology (PAT) available to monitor solid phase oligonucleotide synthesis (SPOS). As a PhD researcher in our team, you will investigate non-invasive imaging approaches to identifying colorimetric and shape-based signatures that track of each key step in the SPOS cycle. You will also investigate object detection methods to enable the dynamic swelling properties of the solid supports used in SPOS. In the service of industrial partners developing new therapeutics, you will be helping us understand the potential uses of our team's ground-breaking kinetic imaging software, *Kineticolor*, to:

(i) Monitor kinetics of detritylation, coupling, oxidation/sulfurization, and capping.
(ii) Develop complementary understanding of imaging-enabled kinetics for SPOS operations (inc. base deprotection and resin cleavage).
(iii) Characterise dynamic SPOS resin swelling properties as a function of oligomer growth.
(iv) Investigate the use of video analysis to track optimal aging of key reagents.

PhD term: 3 years
Eligibility: Honours or Masters-level degree in Chemistry or Chemical Engineering (2.1 or above). Due to funding, this post is open to UK national students only.
Keywords: chemistry, medicinal chemistry, digital chemistry, computer vision, reaction monitoring, image processing, industry, artificial intelligence

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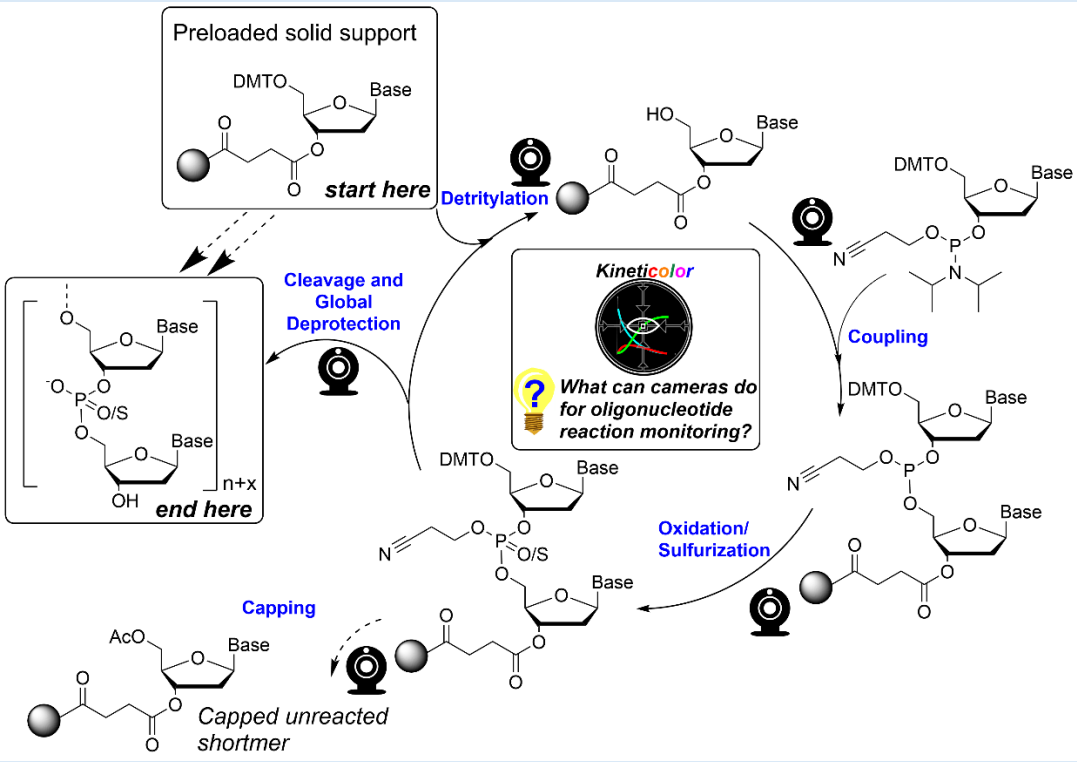
How to Apply: Send a 2-page CV and 1-page cover letter, detailing your reasons for applying, directly to Dr Marc Reid via the contact email address provided.
Informal enquiries and formal applications: marc.reid.100@strath.ac.uk (Subject: PhD 2025)
Deadline for Applications: 23:59 on Sunday, 16 February 2025



BACKGROUND

SPOS is widely used for the automated assembly of oligonucleotides, which are among the most sought-after therapeutic modalities.[1] The process involves sequential addition of nucleotide residues to a growing chain anchored to an insoluble support. Each cycle consists of a series of reactions – including detritylation, phosphoramidite coupling, P-sulfurization or P-oxidation, and unreacted 5'-OH capping – that must occur with high efficiency to produce the desired sequence (figure right). While SPOS is critical in enabling the rapid, scalable production of oligonucleotides, real-time monitoring of reaction progress remains a challenge. Innovations in PAT could thus enhance the precision and yield of SPOS, particularly for complex sequences or modified nucleotides.

RESEARCH PROBLEM

As rates of approval for oligonucleotide ("oligo") therapeutics rises, so too do the challenges to achieve sustainable manufacturing. A primary challenge in SPOS is the meticulous control of myriad variables (~30-50 depending on the oligo) required to prevent formation of complex and unwanted impurities. Reagents such as the phosphoramidite monomers are prone to fast degradation.[2] Conversely, sulfurizing reagents require variable "aging" times before use.[3,4] In-line control of these events has the potential to enhance the robustness of the synthesis, but current state-of-the-art PAT requires intervention that is not compatible with manufacturing operations. During SPOS, the reagents are pushed through a fix bed reactor generating a concentration gradient that, on larger scales, results in uneven distribution of reagents. Such variations can lead to batch inhomogeneity, compromising the commercial value of the oligo product. The current in-line techniques (UV and conductivity) used to monitor SPOS are not sensitive enough to reliably detect heterogeneity. While some of the more recent PAT development efforts for SPOS – including mid-IR,2 NMR,[2] and refractive index[5] – have demonstrated valuable progress, there remains a lack of available non-contact PAT, and PAT that can monitor reaction bulk in complement to molecular specifics. Without a sufficient suite of PAT to monitor SPOS, batch homogeneity can only be assessed after the synthesis is completed, leading to avoidable waste and high process mass intensity (PMI).[6]

YOUR ROLE

As a PhD Researcher in our team, you will lead both publishable and patentable research, working under the supervision of Dr Marc Reid (Senior Lecturer/Assoc. Prof. and UKRI Future Leaders Fellow). You will join an exciting team of both chemists, chemical engineers, and computer scientists working together. As part of this close-knit team, you will have the opportunity to develop innovative real-time reaction monitoring methods for aligned industrial partners across the Chemical sector. The early successes of our emerging research programme will give you exposure to knowledge exchange and commercial activity, as well as pioneering fundamental research that can be (and has been) published in a suite of high-impact and direct-to-end-user journals.

TRAINING

This project addresses a timely need for digital chemists, equipping you with skills in synthesis, kinetics, and advanced imaging technologies. Your lab-based training includes NMR, UV-vis kinetics, and EasySampler-enabled HPLC profiling, alongside the use of project management tools like Basecamp to foster leadership and planning skills.

The project involves lab-based video recording of SPOS reactions and statistical analysis to validate the imaging-based approach as a viable PAT method. Correlations between video data and traditional analytics (e.g., UV-vis and HPLC) will be explored to support this validation.

With support from a prestigious UKRI Future Leaders Fellowship, recently renewed with £567k in funding, your PhD position includes a project budget for consumables, travel to conferences, and possible project placements with aligned industrial project partners.

ELIGIBILITY

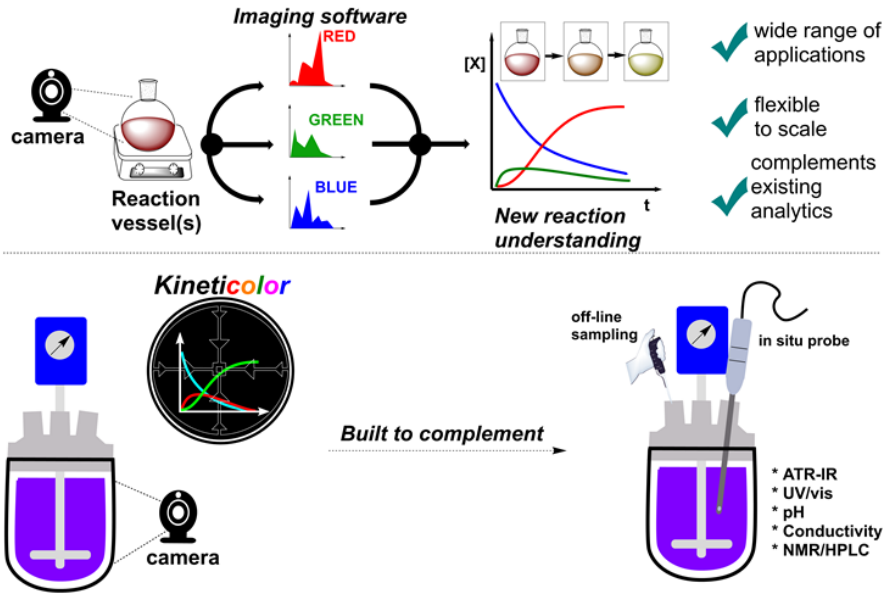
To be considered for the role, you will have a Masters-level degree in Chemistry, Chemical Engineering, or closely-related discipline. Whilst not essential for the role, applications are welcomed from candidates with relevant industrial work experience. Due to the funding source, this post is for UK nationals only.

***NOTE** – you do not need to see yourself as having 'ticked all the boxes' or being a direct fit for this role. We are keen to welcome and support candidates who are keen to learn and grow!*

References

[1] *Nat. Rev. Drug Discovery* **2020**, 19,673; [2] *OPRD* **2022**, 26, 764; [3] *Org. Biomol. Chem.*, **2016**,14, 8301; [4] *OPRD* 2004, 8, 852; [5] *OPRD* 2023, 27, 65; [6] *Curr. Opin. Green Sustain. Chem.* **2022**, 37, 100643; [7] *OPRD* **2022**, 26, 3073; [8] *Chem. Sci.* **2023**,14, 5323.

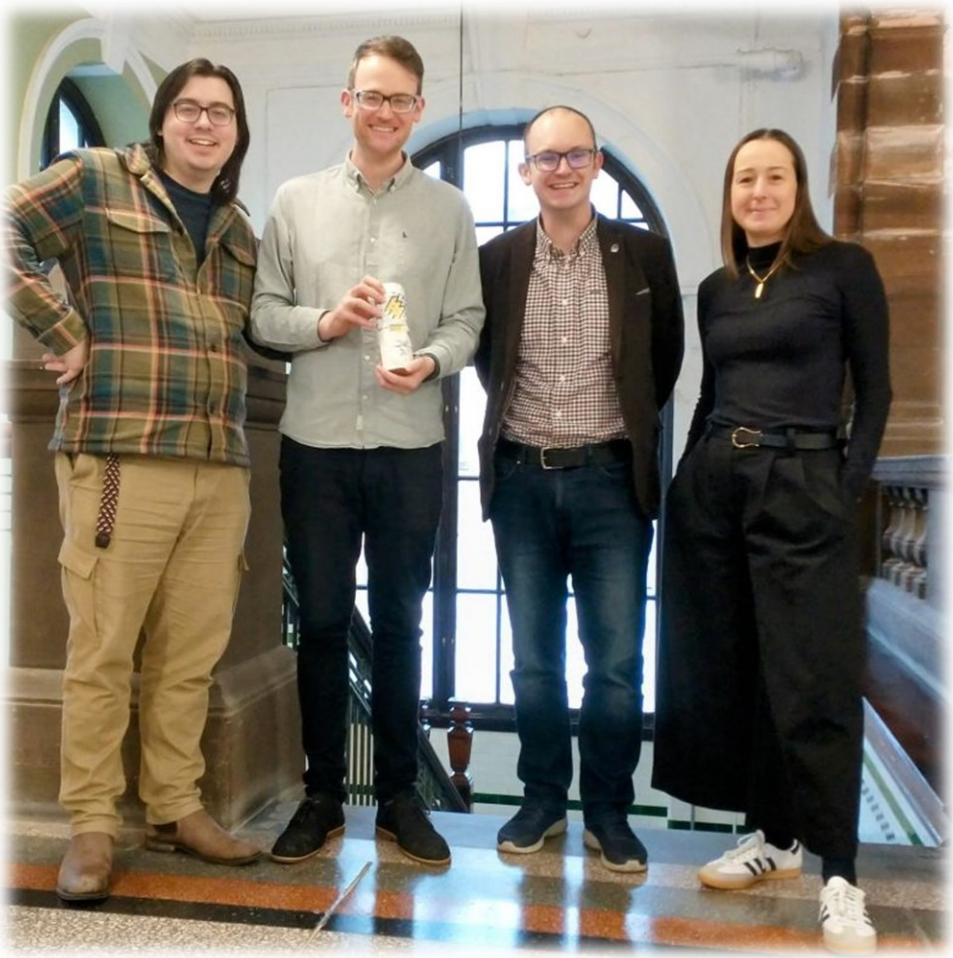
Key Publications from Our Kineticolor Team



[1] Parallel and High Throughput Reaction Monitoring with Computer Vision, *Angew. Chem. Int. Ed.* **2024**, DOI: 10.1002/anie.202413395.
[2] Computer Vision as a New Paradigm for Monitoring of Solution and Solid Phase Peptide Synthesis, *Chem. Sci.* **2023**, DOI: 1039/D3SC01383A.
[3] Computer Vision for Non-contact Monitoring of Catalyst Degradation and Product Formation Kinetics. *Chem. Sci.* **2023**, DOI: 10.1039/D2SC05702F.
[4] Teaching old presumptive tests new digital tricks with computer vision for forensic applications, *Digital Discovery* **2023**, DOI: 1039/D3DD00066D.
[5] Computer Vision for Kinetic Analysis of Lab- and Process-Scale Mixing Phenomena. *Org. Process Res. Dev.* **2022**, DOI: 10.1021/acs.oprd.2c00216.

Recent Group Photos

Left to right: Marc (the PI), Tim (postdoc), Kristin (2nd year PhD), and Barry (3rd year PhD, soon-to-be-postdoc!), enjoying one of our third escape room victory. Missing: Calum (2nd year PhD, who soon returns from his year-long placement in Singapore).



Left to right, founding members of our Kineticolor spinout company: Barry (3rd year PhD, incoming postdoc), Tim (postdoc), Marc (PI and inventor), and Helen (commercial champion).

Left to right, from the back: Barry (3rd year PhD, incoming postdoc), Tim (postdoc), Morven (final year MChem and two-time summer intern), Marc (PI), Kristin (2nd year PhD), Abbie (MSc postgrad), Hui Yun (MSc postgrad), Smruti (MSc postgrad), Nandita (MSc postgrad), Hannah (summer intern). Missing: Calum (2nd year PhD, still enjoying Singapore!).

***Left**: Kristin (2nd year PhD) picking up her 1st place poster prize on her first-year trip to Princeton.*
***Right**: Barry (3rd year PhD, centre) picking up his poster prize at an industry focused conference in Birmingham late last year.*

Learn More
Kineticolor LinkedIn Page: Kineticolor: Overview | LinkedIn
Group web page: Research — Marc' Site
More about Marc, the PI: Marc's CV and CV of Failures — Marc' Site

Informal enquiries and formal applications (before end of 16 Feb)

marc.reid.100@strath.ac.uk (Subject: PhD 2025)

Shortlisted candidates will be invited to an online interview shortly after the deadline. Depending on your circumstances, we may also be able to invite you to visit our lab and team in-person.

Thank-you for considering our team for your PhD adventure!

If you've read this far, you're probably wondering what 'missing Calum' looks like, so here he is, out in Singapore, sporting his *Kineticolor* merch. He rejoins us in Glasgow from mid-January!