Project Details	
Project Code	MRC22IIARBr van der Kamp
Title	Anticipating antimicrobial resistance: predicting the resistance-spectrum of emerging β-lactamase variants using atomistic simulation and experiment
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Antibiotic resistance threatens human health. β-lactamases cause resistance to β-lactams, the most widely used antibiotics. Pathogenic bacteria frequently pick up newly evolved β-lactamases in their environment, leading to hard-to-combat bacterial infections. By using atomistic simulation and experiment, we can anticipate which new resistance patterns may arise and how. This will be an advantage in the 'biochemical warfare' between humans and bacteria.
Description	Rising antibiotic resistance is a major problem for human health. Resistance to β-lactams, the single most important antibiotic class, usually arises through their breakdown by β-lactamases (BLs). Many BL producing bacteria are multi-drug resistant and may cause untreatable infections. Worryingly, new BL variants conferring resistance are detected frequently. As bacteria usually harbour multiple BLs, it is often not clear which BLs cause resistance against which β-lactam antibiotics, and, importantly, how. Using multi-scale computer simulations, we have calculated the efficiency of β-lactam acyl-enzyme formation and breakdown for a number of known BLs, thereby predicting whether and how they confer resistance to specific β-lactams (e.g. Chem Comm, 50, 14736; ACS Catal, 10, 6188). By genomic analysis of clinical isolates (e.g. Antimicrob Agents Chemother, 65, e01193-20) as well as lab experiments (e.g. mSphere, 6, e00108-21), insights are obtained into the evolution of BLs with enhanced antibiotic breakdown activity. This multidisciplinary project aims to combine these strands to predict and understand the activity of newly arising BLs against key β-lactam antibiotics (cephalosporins, carbapenems). Computational assays based on multi-scale simulations will be used to assess formation and breakdown of the acyl-enzymes of 1) recently discovered, clinically relevant serine BLs (e.g. those recently identified by Toleman et al. from clinical isolates worldwide); and 2) BLs with increased resistance obtained in the lab (e.g. by our international collaborators in the Leiros group, Tromsø, Norway). This is challenging, as exact structures of these variants are typically not available and different reaction mechanisms will need to be explored. We will use recent advances in AI structure prediction (e.g. DeepMind's AlphaFold2), but also determine structures of selected acylenzymes experimentally (which cannot yet be predicted by AI; Spencer). Notably, we will predict new putative resistance-conferring BL variants from computational screening of mutations at key positions. Computational predictions of antibiotic breakdown by selected BLs and variants will be validated by experimental determination of beta-lactam hydrolysis using steady-state, and state-of-the-art stopped- and quenched-flow kinetic methods (Spencer). The project will provide training in cutting-edge techniques in multiple disciplines (computational chemistry, molecular biology/biochemistry, clinical microbiology/genomics) using state-of-the-art facilities in the context of a highly collaborative AMR research environment. The project

	will benefit from Bristol's excellent resources for high-performance computing (incl. one of the UK's largest university computer clusters) and related training. Insights obtained into the mechanisms behind the gain of β-lactam hydrolysis activity in novel BL variants will help anticipate new resistance challenges. This can inform both the use of existing antibiotics and the possible development of new beta-lactam antibiotics that might better evade future BL-conferred resistance. To accelerate knowledge transfer, findings will be discussed with our network of local, national and international collaborators prior to publication. We will also exploit the broad interest in antimicrobial resistance through public engagement activities.
Supervisory Team	
Lead Supervisor	
Name	Dr Marc van der Kamp
Affiliation	Bristol
College/Faculty	Life Sciences
Department/School	Biochemistry
Email Address	marc.vanderkamp@bristol.ac.uk
Co-Supervisor 1	
Name	Professor James Spencer
Affiliation	Bristol
College/Faculty	Life Sciences
Department/School	Cellular and Molecular Medicine
Co-Supervisor 2	
Name	Dr Mark Toleman
Affiliation	Cardiff
College/Faculty	
Department/School	School of Medicine
Co-Supervisor 3	
Name	Professor Adrian Mulholland
Affiliation	Bristol
College/Faculty	Science
Department/School	Chemistry
Co-Supervisor 4	
Name	
Affiliation	
College/Faculty	
Department/School	