| Project Details | |
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| Project Code | IIAR27Ba Watts |
| Title | Reprogramming Antibodies: Novel Chemical Re-bridging to Overcome Immune Resistance in the Tumour Microenvironment |
| Research Theme | Infection, Immunity & Antimicrobial Resistance |
| Project Type | Wet lab |
| Summary | Antibodies are powerful medicines that are used to guide the immune system to fight cancer. However, standard antibodies sometimes activate the wrong immune responses or fail to penetrate dense tumours. This project uses a novel chemical technique to "re-wire" the internal bridges of antibodies. This chemical modification makes the targeting arms more flexible to catch elusive cancer cells, while simultaneously turning off unwanted signals that contribute towards immune resistance. The student will bridge chemistry and biology, towards creating next-generation therapeutic antibodies and testing them in advanced tumour models to discover safer, more precise cancer treatments. |
| Description | Monoclonal antibodies (mAbs) are transformative in immuno-oncology, yet their efficacy is frequently limited by mechanisms of resistance within the tumor microenvironment (TME). Standard mAbs rely on a native disulfide bond network. Our host laboratory has pioneered an innovative bioconjugation technology utilizing "aryl bis-halo acetamides" for disulfide re-bridging. This highly efficient chemical linker natively re-bridges heavy-light chains while forcing a non-native, intra-chain re-bridging of heavy-heavy chain disulfides in the hinge region.<br>This unique architecture imparts two profound biophysical and immunological properties onto the mAb. First, it grants enhanced rotational mobility to the Fab domains, enabling bivalent binding to cell-surface antigens located further apart, thereby accommodating lower antigen density—a common tumour evasion strategy. Second, this conformational shift propagates to the upper Fc domain, reducing binding to activating Fc-gamma receptors (FcγRIIIa, FcγRIIa) by over 80% and decreasing FcγRI affinity by 5-fold. This synthetic "Fc-silencing" prevents unwanted (off-target) antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis (ADCP), which are known to lead to the fratricidal depletion of vital immune cells when targeting checkpoint receptors.<br>Key Research Question Can we utilize chemically attenuated Fc-effector function and enhanced Fab flexibility to gain a deeper understanding of immune resistance pathways within the tumour micro-environment, then use this information to develop next-generation antibody-based therapeutics that successfully overcome immune resistance without depleting critical anti-tumour T-cell populations?<br>The doctoral project is structured into interdependent Work Packages (WPs) which transition the student from fundamental synthetic chemistry through structural biophysics, and culminating in advanced in vitro and in vivo cellular immuno-oncology.<br>Specific Objectives and Workplan<br>Objective 1: Linker Synthesis & Bioconjugation. The student will synthesize a library of aryl bis-haloacetamide linkers and optimize mAb reduction and re-bridging. Following linker synthesis, the student will |

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| | optimize the reduction of monoclonal antibodies. Crucially, they will utilize water-soluble trialkylphosphines (such as TCEP) and employ novel in situ quenching methods using water-soluble PEG-azides developed by the host group to prevent unwanted reactions between the reducing agent and the electrophilic linkers.<br>The primary objective of WP1 is to generate a panel of structurally homogeneous, fully re-bridged antibody conjugates. The student will utilize high-resolution techniques including Liquid Chromatography-Mass Spectrometry (LC-MS), Size Exclusion Chromatography (SEC), and Circular Dichroism (CD) to confirm the preservation of the secondary and tertiary structure, and to definitively map the loci of the intra-chain heavy-heavy re-bridging.<br>• Objective 2: Biophysical Profiling. The student will utilize Bio-Layer Interferometry (BLI) to quantify the binding kinetics (kon, koff, and Kd) of the re-bridged antibodies against purified recombinant antigens. To directly assess the advantage of increased rotational freedom, the student will engineer cell lines expressing target antigens at varying, tightly controlled densities. The student will measure the functional avidity of the re-bridged antibodies, testing the hypothesis that they exhibit superior bivalent engagement at low antigen densities compared to unmodified, wild-type IgG1 controls.<br>• Objective 3: In Vitro TME Modelling. Under the co-supervision of Prof. Awen Gallimore at Cardiff University, the student will systematically evaluate the chemical Fc-silencing capabilities and T-cell modulating effects of the conjugates. Utilizing Prof. Gallimore's specialized in vitro systems, the student will utilize colorectal cancer organoid - T cell co-cultures to mimic the complex architecture of the tumour microenvironment (TME) (https://www.cancerimmunology.co.uk/organoid-biobank). The student will investigate how the re-bridged conjugates influence both the suppression mediated by regulatory T cells (Tregs) and the infiltration/activation of CD8+ effector T cells. The overarching objective is to demonstrate that the chemical Fc-silencing mechanism effectively blocks immune checkpoints (e.g., anti-CTLA-4, PD-1 or LAG3) to overcome TME resistance, without triggering macrophage or NK-cell-mediated ADCC/ADCP that would otherwise deplete critical T-cell populations.<br>• Objective 4: In Vivo Immuno-Oncology Evaluation. This WP will focus heavily on applied immuno-oncology, analyzing the drivers of immune resistance in solid tumors. The student will translate findings into existing mouse models of cancer (PMID: 41629131: 33093155: 32447412: 28947544), assessing pharmacokinetic stability, tissue distribution via fluorescence imaging, off-site toxicities and therapeutic efficacy (survival and intra-tumoral Teff:Treg ratios).<br>Student Ownership and Project Steering: While the core chemical framework is established, the student will have significant autonomy to steer the biological application. The student will take definitive ownership by selecting the primary clinical antibody substrates (e.g., Atezolizumab vs. Trastuzumab) and defining the specific immune checkpoint pathways to target in the TME. Furthermore, they will have the independence to prioritize specific T-cell infiltration assays within |

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| | organoid models based on their emerging data, allowing them to intimately tailor the project toward their specific interests in structural biophysics or translational cellular immunology. |
| Can be completed part time? | Yes |
| Supervisory Team | |
| Lead Supervisor | |
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