A high affinity CXCR2 mAb that specifically and simultaneously inhibits MDSC traffic to the tumour microenvironment and tumour growth pathways in synergism with current cancer therapies.

- Recognised immuno-oncology target with characterised bimodal MoA
- Potential for ‘Best in Class’ drug suitable for highly metastatic solid tumour patients
- Synergistic efficacy when used in combination with approved treatments

THE CHALLENGE

Tumour immune evasion persists as a major challenge in patient resistant to chemotherapy, targeted therapies and checkpoint inhibitors (e.g. anti-CTLA-4, anti-PD1 and anti-PDL1 mAbs). While immuno-oncology treatments such as checkpoint inhibitors have revolutionised oncology, mortality rates remain considerable (PD-1 inhibitors are only 34% effective in melanoma and 35% in non-small cell lung cancer). New classes of immuno-oncology treatments are needed for enhanced efficacy of approved therapies and for patients who do not respond to checkpoint inhibitors.

Myeloid derived suppressor cells (MDSCs) traffic to the tumour microenvironment and promote immune evasion and tumour metastasis. Blocking CXC chemokine receptor 2 (CXCR2), in combination with approved therapies such as PD1 inhibitors, inhibits MDSC migration and tumour growth. CXCR2 inhibition further impairs tumour growth by targeting tumour angiogenesis pathways.

MDSCs are not involved in the checkpoint functions. Thus, combining inhibitors of PD1 signalling and CXCR2, which target separate immune evasion mechanisms, is highly attractive due to the real potential for synergistic immunomodulatory activity. Unlike many other targets, inhibition of CXCR2 is feasible using different classes of inhibitors including therapeutic antibodies (CXCR2 blockers are in late stage clinical development for autoimmune and inflammatory conditions).

The team has developed a unique knock-in mouse model using the human CXCR2 gene for studying the effect of antihuman CXCR2 in tumour models. The team will also use established in vitro cell-based assays, receptor studies, structural analyses and Fc engineering to develop the CXCR2 mAb for clinical trials.

THE TECHNOLOGY

Monash University researchers have developed superior murine mAb inhibitors that completely antagonise human CXCR2.

Targeting CXCR2 via a biological approach leads to higher affinity and specificity than current small molecules blockers. CXCR2 mAbs are expected to have greater efficacy, improved safety and faster development.

The team have identified three potent CXCR2 mAb leads that inhibit chemotaxis of human neutrophils to CXCR2-specific ligands such as GCP-2. These mAbs have overlapping epitopes over the entire N-ter region of human CXCR2. Humanisation of the lead CXCR2 mAbs is in progress.

THE OPPORTUNITY

Monash seeks a partner to accelerate humanisation of the identified CXCR2 mAb lead series as well as conduct in vivo testing in models of highly metastatic cancers (e.g. pancreatic, breast, colorectal, skin and lung cancer models).

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