

TARGETING COMPLEMENT FACTOR H MEDIATED TUMOR IMMUNE AND COMPLEMENT EVASION AS A NEXT GENERATION APPROACH

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Background The complement system plays a crucial part in innate immunity, aiding the destruction of pathogens and removing anomalous cells. Complement Factor H (CFH) regulates the complement system through interactions with C3b (both soluble and membrane associated) to prevent unwarranted activation. This forms the basis of a self-versus non-self-recognition process, which in certain cancers, aberrant expression, or abnormal levels of CFH may protect and promote growth of tumors by impairing the activation of the complement system. An analysis of human antibody repertoire data retrieved convergent sequence clusters amongst both viral and cancer (pancreatic, prostate and melanoma) patient cohorts, and led to identification of human derived antibodies that are naturally tolerated with unique properties^{1,2,3}. A representative heavy chain from this cluster was paired with an appropriate light chain and engineered for desirable biophysical characteristics. Target identification revealed CFH, as a potential antigen.

Methods In this study, we tested the ability of human derived antibodies to CFH to activate direct cell killing via complement deposition, and to alter immune cell responses (potentially via alterations in complement receptor activation). This was performed using human in vitro co-culture, immunomodulatory assays, and in vivo syngeneic mouse systems. Additionally, pharmacokinetics and associated measurements were assessed to understand basic tolerability and exposure.

Results Anti-CFH resulted in increased CD11b+ cell tumor infiltration and subsequent C3d deposition in a B16/F10 syngeneic model. Macrophages adopted an inflammatory phenotype characterised by cytokine release profiles and lymphocyte activation.

Immune cell co-culture with tumor cells resulted in myeloid activation, altered cell populations, indirect activation of additional immune cell types, and reduction in viable cancer cells. Both single and dose range pharmacokinetic studies confirmed a lack of binding to circulating CFH, and unaffected levels of C3 that might be associated with systemic complement activation. In a preliminary assessment, no safety issues were identified in the study. Monotherapy in high CFH syngeneic models, suggests a unique epitope recognised by anti-CFH which is primarily associated with membrane associated C3b. Interfering with this binding uniquely enables localised inflammation associated with the alternative pathway of the complement system. Additional mechanistic studies are ongoing.

Conclusions A human derived antibody cluster against CFH is convergently present in various disease state patient groups and has novel immunostimulatory function through engagement of myeloid cells and the complement cascade.

REFERENCES

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<http://dx.doi.org/10.1136/jitc-2022-SITC2022.1353>