Inhibitor of CD59 activity to activate the complement system for oncology and virology

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Technology description

Summary

MARKETS ADDRESSED:
ILYd4, used in combination with therapeutic antibodies, enhances their activity and may provide important therapeutic benefits to patients.
â€¢ Cancer: CD59 over-expression has been detected in cancer patients that no longer respond to antibody therapy. Dr. Qin showed the effect of ILYd4 on restoring Rituxan sensitivity in several cell types including several lymphoma and multiple myeloma cell lines, chronic lymphocytic leukemia cells and Ramos cells.
â€¢ Viral infection: CD59 is present in HIV and other enveloped virus particles, including CMV, herpes virus, Ebola virus and influenza virus.
Dr. Xuebin Qin has developed a platform to potentiate endogenous complement activity through the inhibition of CD59, including a lead molecule, ILYd4, and a suite of assays that can serve as drug development tools. ILYd4 is a high-affinity, specific inhibitor of human CD59. ILYd4 is a peptide fragment of domain 4 of intermedilysin (ILY), a bacterial toxin that lyses human cells expressing human CD59. Whereas Domains 1-3 of ILY form the lytic transmembrane pore responsible for cell lysis, Domain 4 binds CD59 to a region that contains CD59's active site. Thus, disruption of this binding interaction with ILYd4 inhibits the functionality of CD59 without lysing cells that express CD59.
Dr. Qin has generated pre-clinical proof-of-concept data in a series of in vitro and in vivo models for oncology and virology. His findings demonstrate that ILYd4 specifically blocks CD59's anti-MAC activity and restores antibody mediated cell/virion lysis:
â€¢ Anti-cancer PoC data: In vitro and in vivo data demonstrate the ability of ILYd4, in combination with a well-studied monoclonal antibody, to treat resistant tumor cells. Specifically, these assays reveal that ILYd4 restores Rituxan sensitivity and CDC to Rituxan-resistant cells.
â€¢ Anti-viral PoC data: In vitro assays of HIV infection demonstrate that ILYd4 enhances CDV. In addition, ex vivo assays using patient-derived HIV-1 antibodies and virions show that ILYd4 unleashes the capacity of HIV-1-induced antibodies to mediate CDV.
â€¢ Specificity of ILYd4: Unlike antibodies to CD59 which stimulate the complement system to elicit CDC/CDV and cause hemolysis, ILYd4 selectively disrupts the active site of CD59 without lysing cells

that express CD59. Therefore, ILYd4 specifically mediates cancer cell and virion lysis and does not produce off-target lysis of other cells such as human erythrocytes or peripheral blood mononuclear cells. In addition, the lab generated CD59 knockout mice that transgenically express human CD59. High doses of ILYd4 do not induce any hemolysis in these compound mice.

Application area

CD59 has been recognized as a potential therapeutic target based on its role in escaping complement-mediated attack, thus causing resistance to antibody treatments for cancer and viral infections.

Advantages

Certain cancer cells and human enveloped viruses over-express or incorporate CD59 in order to escape immune surveillance and complement dependent cytolysis and virolysis (CDC/CDV). CD59 is an endogenous GPI-anchored cell-surface protein inhibitor of the complement-mediated membrane attack complex (MAC). CD59 acts as a natural inhibitor to resist MAC complex formation through binding of complement proteins and sets the threshold for CDC/CDV.

Institution

Harvard University

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com