發展anti- CD33 (Siglec-3)抗體以治療慢性B型肝炎及阿滋海默症

主要領域 感染性疾病

- 產品/技術簡介
  - CD33 (Siglec-3)為具有免疫酪胺酸抑制模體(ITIM)的骨髓細胞受體(myeloid membrane receptor)，與免疫檢查點受體PD-1相似。我們近期的研究發現CD33為B型肝炎病毒之模式識別受體，且B型肝炎病毒經由CD33傳遞抑制訊息以壓制宿主免疫。我們亦發現CD33- rs12459419C等位基因(CD33高度表現)與B型肝炎病患中發生肝癌的高風險群有密切關聯。我們更進一步生產拮抗性單株抗體對抗CD33，發現其能提升宿主免疫反映，與TLR7 agonist GS-9620 (Gilead)具有強列的協同效應。我們將利用Dr. James Paulson (The Scripps Research Institute) 提供之mCD33 剔除/hCD33轉殖小鼠測試抗體對於重新活化宿主免疫以清除B型肝炎病毒之效應。由於阿茲海默症病患中微膠細胞(microglia)之吞噬作用下降，且CD33- rs12459419C等位基因與阿茲海默症高風險緊密相關。我們已發現CD33單株抗體能夠增強吞噬作用，因此我們將利用Dr. Matthew. Macauley (Alberta University)提供之阿茲海默症小鼠模型，測試其在體內清除β澱粉樣蛋白之能力。
- 應用
  - 激活慢性B肝炎病人免疫力以產生抗HBsAg抗體，清除B 型肝炎病毒。
  - 活化微膠細胞，增強清除β澱粉樣蛋白的能力。
- 優勢
  - 目前沒有任何抗CD33單株抗體，能阻斷HBV的免疫抑制
  - 目前沒有任何抗CD33單株抗體，能增強巨噬細胞/微膠細胞的吞噬能力。
- 專利現況
  - 已針對抗CD33抗體組成以及治療B型肝炎和阿茲海默症之應用申請國際專利。

Development of Anti- CD33 (S iglec-3) mAb for the Treatment of Chronic Hepatitis B Infection and Alzheimer Diseases

Research Area Infectious Disease

- Technical statement
  - CD33 (Siglec-3) is a myeloid membrane receptor which contains an immunoreceptor tyrosine-based inhibitory motif (ITIM) similar to the immune checkpoint receptor PD-1. Our recent study identifies CD33 as a pattern recognition receptor to hepatitis B virus (HBV), and demonstrates that HBV suppresses host immunity via CD33. We further generate antagonistic mAb against CD33, which can reverse HBV-mediated immunosuppression and upregulate host immune responses to TLR ligands. Moreover, the anti-CD33 mAbs have synergistic effect with TLR7-7 agonist GS-9620 (Gilead). Thus, we would like to test whether anti-CD33 mAb alone, or in conjunction with GS-9620, can reactivate host immunity to clear HBV infection in hCD33D mCD33 mice (human CD33 transgenic mice with deletion of endogenous mouse CD33) provided by Dr. James Paulson (Scripps). We also find that CD33-rs12459419C allele (higher expression of CD33) is strongly linked with higher risk of developing hepatocellular carcinoma (HCC) in chronic HBV(CHB) patients. Previously, CD33-rs12459419C is reported to associate with high risk of Alzheimer's disease (AD), and the phagocytic activity of microglia is downregulated in AD microglia due to activation of CD33. We have demonstrated that anti-CD33 mAb is able to enhance beta-amyloid uptake in vitro, thus we will test its effect to enhance microglia activity to clear beta-amyloid in the AD mouse model.
- Applications
  - Once we get positive results from animal studies, the human anti-CD33 mAb will go to CMC (chemistry, manufacturing, and control) and investigational new drug (IND) application.
- Advantages
  - There is no any anti-CD33 mAb capable of block-HBV-mediated immunosuppression, and enhance the phagocytic activity of macrophage/microglia.
- Patent status
  - We have filed patents for the composition of anti-CD33 mAbs, as well as its application to treat CHB and AD.

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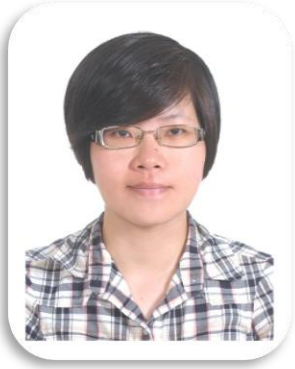

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