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**Selgantolimod regulates Kupffer cell differentiation status and impairs HBV entry into hepatocytes**

*Roca Suarez A, Plissonnier M, Grand X, et al. TLR8 agonist selgantolimod regulates Kupffer cell differentiation status and impairs HBV entry into hepatocytes via an IL-6-dependent mechanism. Gut 2024; 73: 2012-2022. doi: 10.1136/gutjnl-2023-331396*

Selgantolimod (SLGN) is an agonist for the innate pattern recognition receptor Toll-like-receptor 8 (TLR8) which has been shown to be safe and well tolerated in chronic hepatitis B (HBV) patients. It has been shown to induce production of a wide range of inflammatory cytokines but the effect on immune responses within the liver was unknown. To explore this question, Roca Suarez *et al.,* leveraged publicly available single cell RNA sequencing data from the human liver cell atlas to identify the cell populations in the liver expressing TLR8 and therefore likely susceptible to SLGN. They found TLR8 primarily expressed on myeloid cells and focused on Kupffer cells (CD163 positive cells).

They treated CD163 positive cells isolated from liver tissue with SLGN and assessed the effect on gene expression through performed RNA sequencing. They found that SLGN changed the transcriptional profile of Kupffer cells promoting plasticity with downregulation of key genes that are usually expressed and increase of inflammatory cytokine production. They validated their findings in vivo through studying the livers of macaques treated with SLGN. They then cultured primary human hepatocytes with media from SLGN stimulated Kupffer cells and demonstrated they were less susceptible to HBV infection through reduction of sodium/bile acid cotransporter (NTCP), a key host factor implicated in HBV entry. Adding an interleukin-6 (IL-6) neutralising antibody was able to reverse the resistance to HBV and therefore the authors concluded that SLGN indirectly impairs HBV entry via an IL-6 dependent mechanism.

This mechanistic study therefore lends weight to use of Selgantolimod in the development of combination therapies against HBV.