Antagonizing hepatitis

By Brian Moy, Staff Writer

A paper published in *Nature Medicine* suggests that serotonin antagonists could be useful for accelerating the clearance of potentially any type of hepatitis infection and minimizing liver cell damage. The finding could open up new therapeutic areas for biotech and pharma companies with serotonin antagonists on the market or in late-stage development for neurological conditions. The challenge will be finding antagonists with specificities that make it possible to treat hepatitis

without interfering with serotonin's other roles in the liver.

Researchers at the **University Hospital Zurich** showed that the release of endogenous platelet-derived vasoactive serotonin in the liver delayed the entry of activated virus-specific CD8⁺T cells into the livers of wild-type mice infected with lymphocytic choriomeningitis virus (LCMV), a model of human hepatitis. Virus-specific T cells play a major role in attacking chronic hepatitis.

Indeed, in the model, increased platelet recruitment to the liver correlated with lower sinusoidal microcirculation, delayed virus removal and greater liver cell damage. Low hepatic sinusoidal microcirculation—blood flow through the liver—is responsible for delaying infiltration of activated CD8⁺T cells, which can result in the persistence of infection.

Infected mice treated with exogenous serotonin also had delayed entry of CD8⁺T cells into the liver. The opposite was seen in serotonin-deficient mice. In those mice, the lack of platelet-derived serotonin after LCMV infection resulted in better viral clearance and less liver cell damage than was seen in wild-type mice.¹

Table 1. Targeting 5-HT₂. Previous studies have identified the serotonin 5-HT_{2A} and 5-HT_{2B} receptors, which are expressed by hepatic stellate cells, as regulators of sinusoidal blood flow.³ In hepatitis, decreased sinusoidal microcirculation caused by platelet-derived vasoactive serotonin delays removal of the virus and increases liver cell damage. Thus, existing antagonists targeting the 5-HT₂ family of serotonin receptors could have potential utility in accelerating clearance of hepatitis infection. However, the antagonist must be specific enough to prevent the reduction in sinusoidal blood flow without interfering with serotonin's other roles in the liver such as regulating hepatic stellate cell function, hepatocyte growth and bile duct epithelial cell proliferation. Below are selected antagonists or inverse agonists that target serotonin (5-HT₂) receptors in Phase III or on the market. Some of the compounds also target other proteins such as dopamine receptors.

Company	Product	Indication	Lead status
Eli Lilly and Co. (NYSE:LLY)	Zyprexa olanzapine	Bipolar disorder; schizophrenia	Marketed
Novartis AG (NYSE:NVS; SWX:NOVN)	Clozaril clozapine	Schizophrenia	Marketed
Pfizer Inc. (NYSE:PFE)	Geodon ziprasidone	Bipolar disorder; schizophrenia	Marketed
AstraZeneca plc (LSE:AZN; NYSE:AZN)	Seroquel/Seroquel XR quetiapine	Bipolar disorder; schizophrenia	Marketed
H. Lundbeck A/S (CSE:LUN)	Serdolact sertindole	Bipolar disorder; schizophrenia	Marketed
Johnson & Johnson (NYSE:JNJ)/Alkermes Inc. (NASDAQ:ALKS)	Risperdal/Risperdal Consta risperidone	Bipolar disorder; schizophrenia	Marketed
Vanda Pharmaceuticals Inc. (NASDAQ:VNDA)	Fanapta iloperidone	Schizophrenia	7/27 PDUFA date
Acadia Pharmaceuticals Inc. (NASDAQ:ACAD)	Pimavanserin (ACP-103)	Parkinson's disease psychosis	Phase III
Boehringer Ingelheim GmbH	Flibanserin	Hypoactive sexual desire disorder (HSDD)	Phase III
Dainippon Sumitomo Pharma Co. Ltd. (Tokyo:4506; Osaka:4506)/Merck & Co. Inc. (NYSE:MRK)	Lurasidone (SM-13496)	Schizophrenia	Phase III
Mitsubishi Tanabe Pharma Corp. (Tokyo:4508; Osaka:4508)	Anplag sarpogrelate	Prevent recurrence of cerebral infarction	Phase III
sanofi-aventis Group (Euronext:SAN; NYSE:SNY)	Eplivanserin	Insomnia	Phase III
sanofi-aventis	Volinanserin	Insomnia	Phase III
Schering-Plough Corp. (NYSE:SGP)	Org 50081	Insomnia	Phase III

“We were initially investigating the role of serotonin following virus-induced liver cell damage, and, to our surprise, absence of serotonin prevented liver cell damage during virus-induced hepatitis,” said Karl Lang, corresponding author on the paper. Lang, now a research assistant at the **University of Toronto**, is investigating the role of serotonin in later stages of hepatitis.

He said there are two possible approaches for developing serotonin antagonists for hepatitis: testing known serotonin antagonists in hepatitis patients or screening for new serotonin antagonists that do not cross the blood-brain barrier and analyzing these compounds for their ability to clear hepatitis in animal models (see **Table 1**, “**Targeting 5-HT₂**”).

According to Lang, potential side effects of serotonin antagonists that do cross the blood-brain barrier include nausea, drowsiness, dizziness, changes in appetite, weight loss or weight gain and sexual dysfunction.

Serotonin's receptors

With either approach it is likely that specificity will be the key consideration. The reason is that broadly antagonizing serotonin in the liver could also disrupt serotonin's role in regulating hepatic stellate cell function, hepatocyte growth and bile duct epithelial cell proliferation.

Previous studies have shown that platelet-derived serotonin regulates liver regeneration.²

According to Derek Mann, a professor of hepatology at **Newcastle University**, “pan-blockade of serotonin would be problematic, as serotonin is required for liver regeneration in response to injury.”

On the other hand, he said, “blocking specific receptors that drive inflammatory and fibrogenic responses could enable the negative effects of serotonin to be prevented while retaining the beneficial properties of serotonin.”

Michael Kauffman, CEO of **Epix Pharmaceuticals Inc.**, told *SciBX* that “because there are so many serotonin receptors, further research needs to determine which specific receptors are responsive to targeting in patients with hepatitis.” To achieve this, he said that “preclinical testing of known serotonin antagonists in animal models of hepatitis could identify which receptors play a role in disease.”

Kauffman added that “once the appropriate receptors are identified, it will be useful to take liver biopsies from patients with hepatitis and stain them for specific serotonin receptors.” At that point, he said, “we can move into clinical testing using the proper antagonists.”

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**—Michael Kauffman,
Epix Pharmaceuticals Inc.**

Around mid-year, Epix plans to start a Phase II trial of PRX-08066, a selective serotonin (5-HT_{2B}) receptor antagonist, to treat pulmonary hypertension associated with chronic obstructive pulmonary disease (COPD). Also this year, Epix plans to begin a Phase IIa trial of PRX-07034, a selective serotonin (5-HT₆) receptor antagonist, to treat cognitive impairment associated with schizophrenia.

Richard Ruddell, a research officer in the Hepatic Fibrosis Group of the **Queensland Institute of Medical Research** and an adjunct

lecturer at the **University of Queensland**, said that the *Nature Medicine* paper “does not hint at the receptor type mediating the effects of serotonin. Nonspecific antagonists may inhibit hepatic regeneration stimulated by serotonin as well as increase sinusoidal blood flow.”

Ruddell thinks the best results will come from hitting the 5-HT_{2A} and 5-HT_{2B} receptors. He and other researchers have identified those two receptors, and other serotonin receptor family members within the liver, as being particularly relevant to sinusoidal blood flow.

The 5-HT_{2A} and 5-HT_{2B} receptors, which are expressed by hepatic stellate cells, are thought to regulate sinusoidal blood flow by regulating the contractility of the cells.³

Additionally, Ruddell is investigating where serotonin receptors are located within the liver and how they are expressed during disease.

“At present, there are no ligands that will only bind to one receptor and not the other,” he noted. “If you can find an antagonist that is selective enough to prevent only the reduction in sinusoidal microcirculation invoked by serotonin within the liver, there may be a potential role for serotonin antagonists in treating hepatitis.”

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COMPANIES AND INSTITUTIONS MENTIONED

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