Invention: Fibrosis is the term used to describe the formation or development of excess fibrous connective tissue in an organ or tissue as a reparative or reactive process, akin to the process involved in wound-healing. Unfortunately, fibrosis can lead to permanent scarring, organ failure, and eventually death. Researchers at Salk have discovered a link between pro-fibrotic pathways and bromodomain-containing proteins, in particular BRD4. They found that inhibition of BRD4 (and likely others) is able to protect and reverse the fibrotic response in primary human cells and mouse models by increasing the retention of vitamin A, vitamin D, and/or lipids in those target cells.

Applications: The prevention and treatment of fibrotic diseases and cancers such as, but not limited to, liver, kidney, lung, and pancreas.

Advantages: There is great potential in developing and using bromodomain inhibitors that are targeted and specific to treat fibrotic complications that include life-threatening conditions that currently have no clinically approved therapies, such as various cancers and organ failure.

Stage of Development: Inhibition of bromodomain and BET proteins by small compounds such as JQ1 has been shown to prevent fibrosis in primary hepatic stellate cells and mouse models.

Background:
When the liver is subjected to injury, the body triggers an inflammatory process that includes hepatic fibrosis. The accumulation of fibrous tissue in the organ (often composed of extracellular matrix proteins) results in cirrhosis, loss of liver function, portal hypertension and hepatocellular carcinoma. The most common causes of liver injury that lead to fibrosis include chronic hepatitis C virus (HCV) infection, alcohol abuse, chronic hepatitis B infection (HBV), and nonalcoholic steatohepatitis (NASH). NASH is a type of nonalcoholic fatty liver disease that represents the hepatic metabolic consequence of rising obesity and associated insulin resistance in the setting of an increasingly sedentary lifestyle. Fibrosis is not limited to the liver, as it can negatively affect other organs, including the kidney, lung, and pancreas, often leading to their respective organ failure and cancerous states.

Bromodomain and extra-terminal family member (BET) proteins are a group of proteins that recognize acetylated lysines, such as those on N-terminal histone tails, and are often described as epigenetic readers. One particular bromodomain protein, BRD4, was found to be a critical regulator for pro-fibrotic gene expression. The finding that inhibition of this protein’s activity, and possibly other BRD or BET proteins, can protect and reverse fibrosis indicates that these inhibitory molecules are a potential intervention therapy for fibrotic diseases and cancers associated with fibrotic events.

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