# Challenge based learning (CBL)

# A bioprinted liver lobule to test novel anti-fibrotic therapies

**Note for teachers: A CBL user guide can be found at** www.jandeboerlab.com/TissueEngineering with instructions and tips to run an effective CBL teaching session.

**Background and vision**

Liver cirrhosis is the end-stage of chronic liver disease, which is fatal in many cases. The progression of chronic liver disease starts with inflammation, then fibrosis, cirrhosis, and finally liver failure. Pharmacological treatments exist and can be used to mitigate and slow down the progression of the disease but cannot cure it. If pharmacological treatments do not work, then liver transplant is the final option. It is well documented that liver transplantation is the best treatment for end-stage chronic liver disease. However, there is a shortage of donors and the number of patients added to the waiting list grows by the day. The long-term vision in the treatment of chronic liver disease is to develop effective and non-invasive bioengineered strategies that aim to reverse the progression of chronic liver disease at the fibrosis stage.

**Motivation and stakeholders**

Fibrosis is a pathological wound healing in which connective tissue replaces normal parenchymal tissue to the extent that it goes unchecked, leading to considerable tissue remodeling and the formation of permanent scar tissue. Fibrosis occurs in many parts of the body and pharmaceutical strategies are able to reduce tissue fibrosis by specifically targeting molecular and cellular targets of the process. Success treatment of liver fibrosis requires a liver specific strategy. Solutions to mitigate liver fibrosis should consider the needs, requirements and regulatory, financial and technical boundary conditions defined by stakeholders such as hepatic surgeons, internal medicine doctors, organ systems and biological engineers, and biomanufacturing specialists.

**Problem definition**

Current cellular systems to test anti-fibrotic drugs employ 2D cultured fibroblasts or use animal models. Conventional cell culture lacks the physiological complexity in which liver fibrosis occurs, and animal experimentation is ethically undesirable and animal physiology does not always recapitulate human metabolism. In order to understand and cure the pathophysiology of liver fibrosis, more physiological systems are needed that closely follow the architecture of the liver lobule. Advances on liver systems engineering could be twofold: fidelity in mimicking the architecture and function of the liver lobule and preventing the use of animal models, whose results are difficult to translate to humans. Therefore, there is a need to bioengineer the liver lobule by merging the current knowledge on organ systems to create new therapeutics for liver fibrosis.

**Challenge**

To generate a bioprinted liver lobule with its vasculature (central vein) to understand the progression and treatment of liver fibrosis with the use iPSCs as cell source. Focus on the spatiotemporal location and activation of liver cells like hepatocytes, fibroblasts, Kupffer, and endothelial cells

**Learning framework**

Reading the Organ Tissue engineering chapter and additional literature on liver physiology will help you to understand:

1. The anatomy, histology, and physiology of the liver.
2. The pathophysiology of chronic liver disease.
3. The architecture of the liver lobule.
4. The cellular and molecular aspects of fibrosis.

For a more focused examination of the challenge, read scientific literature and create a mind map to include information about:

1. State-of-the-art treatments in liver fibrosis treatment
2. Current available biofabrication methods for organ systems.
3. Cell and biomaterial sources used for bioprinting of liver lobules.

**End product**

# A three-minute video explaining the solution of your challenge. Please include your motivation and the steps to execute your solution.

# © Jan de Boer. CBL available for classroom use and CBL videos and can be found at www.jandeboerlab.com/TissueEngineering.