

## PRIZE ESSAY



FINALIST

**Fotios Sampaziotis**

Fotios Sampaziotis graduated from the University of Athens in Greece with a

degree in medicine. He obtained a Ph.D. in stem cell biology from the University of Cambridge. During his doctoral research, he pioneered the use of bile duct organoids to model diseases of the biliary system, test multiple drugs, and identify new therapeutic agents. Currently, Fotios continues his research at the interface between basic science and clinical medicine as a clinical lecturer in hepatology at the University of Cambridge with clinical commitments in Addenbrooke's Hospital. His scientific work focuses on combining organoids, bioengineering, and animal studies to regenerate damaged bile ducts in the liver as an alternative therapy to liver transplantation.

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## REGENERATIVE MEDICINE

# Building better bile ducts

An organoid-based model promises to improve our understanding of bile duct disorders

By **Fotios Sampaziotis**

**T**he bile ducts form a network of tubes within the liver and transfer bile produced in the liver to the bowel. In biliary disorders, this transport system fails, leading to the accumulation of toxic bile in the liver, damage, and permanent scarring (cirrhosis), which can ultimately be treated only through liver transplantation. Indeed, bile duct diseases (cholangiopathies) are the leading disorder treated (70%) by pediatric liver transplantation and account for a third of adult transplanted livers.

Despite the impact of these conditions, our insight into bile duct disease pathogenesis is very limited due to the lack of effective laboratory models and difficulties in growing bile duct cells (cholangiocytes) *in vitro*. Furthermore, treatment options remain limited, with few effective drugs and a lack of healthy cells and tissue suitable for surgical reconstruction or replacement of diseased segments of bile ducts. My research has focused on addressing these challenges.

More specifically, my aim has been to develop a system that will allow the growth of human cholangiocytes outside of the body; to use these cells to model cholangiopathies *in vitro*; and to use the *in vitro* models to screen, test, and identify new drugs for bile duct disorders. I have also sought to use healthy cells to generate a bioengineered bile duct and demonstrate its potential for surgical reconstruction or replacement of the biliary tree in an animal model.

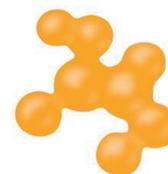
**CULTURING HUMAN CHOLANGIOCYTES**

Two major limitations have hindered culture of human cholangiocytes: access to bile duct tissue without surgery and loss of function during primary cholangiocyte culture. To circumvent access issues, I developed a protocol for generating cholangiocytes from human induced pluripotent stem cells (hiPSCs), which can be easily derived from patient skin samples.

To preserve the function and characteristics of human cholangiocytes *in vitro*, I grew the cells as “organoids” in three-dimensional

culture, demonstrating small cystic or tubular structures with a central lumen (1, 2). The structure of the evolving organoid around a lumen resembled native bile ducts and was associated with both improved cholangiocyte function and faster growth of hiPSC-derived cholangiocytes. This approach also enabled the growth of human primary cholangiocytes isolated from excised bile ducts or gallbladders in abundance for the first time (3).

To confirm that the organoid platform provided a growth advantage, while retaining normal cholangiocyte function, I compared the physiological and functional characteristics of cholangiocytes derived from hiPSC or primary culture with hu-



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man bile duct cells *in vivo*. These experiments allowed me to conclude that the organoid culture-generated cholangiocytes resembled their *in vivo* counterparts, providing the most accurate *in vitro* cholangiocyte platform to date.

**MODELING CHOLANGIOPATHIES IN VITRO**

I then hypothesized that cholangiocytes from patients with bile duct disorders will reproduce key features of these disorders when cultured *in vitro*. I tested this hypothesis using cholangiocytes from patients with Alagille syndrome (AGS), polycystic liver disease (PLD), and cystic fibrosis (CF). In all cases, the disease phenotype was reproduced in the lab (AGS, a lack of lumen formation; PLD, cyst formation; CF, defective chloride transfer in the organoid lumen), providing the first *in vitro* bile duct models for these disorders (1).

**DRUG SCREENING**

I subsequently used my disease models to screen known (octreotide) and new therapeutic compounds and demonstrated that an experimental therapeutic compound (VX809) initially developed for CF lung disease could be repurposed for the prevention of CF liver disease (1). This finding is particularly important because VX809 is

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already used in phase 2 clinical trials and could potentially be tested for the treatment of CF liver disease imminently. These results provide one of the first successful applications of in vitro drug screening for cholangiopathies.

### GENERATING AND TRANSPLANTING BIOENGINEERED BILE DUCTS

In some cases, such as biliary atresia—which constitutes the leading cause for pediatric liver transplantation—the common outflow of the biliary tree (common bile duct) is obliterated, and the only possible treatment is surgery. In this context, the use of a bioengineered bile duct could provide an alternative to liver transplantation.

To achieve this goal, I developed a method for generating bioengineered biliary tissue and bioengineered bile ducts using healthy cholangiocytes (3). The bioengineered organ retained the architecture, structural

properties, marker, and function (alkaline phosphatase and gamma glutamyl transferase activity) of a human bile duct.

The bioengineered ducts were transplanted into immunodeficient mice, successfully replacing the native bile duct. Furthermore, the mice receiving the artificial organ exhibited normal liver function and prolonged survival. To my knowledge, this is the first demonstration of organ engineering in the biliary system and the first report of the generation of a bioengineered organ using organoids.

### CONCLUSION

My research has generated a series of tools with unique translational applications for the field of cholangiopathies. I have demonstrated that my cholangiocyte organoid system can be used to generate the first in vitro models for bile duct disorders. These models can increase our insight in disease

pathogenesis and represent transferrable technology that can be used to benefit multiple groups working in the same field. Furthermore, this system can be used as the first drug screening platform for biliary disease, and I have demonstrated proof of principle for the potential of this system for drug discovery in a field where the only treatment option is liver transplantation.

Finally, through the generation of an engineered bile duct, I have provided proof of principle for regenerative medicine as a therapeutic approach for biliary disease and advanced the field of organ reconstruction by developing techniques that can be applied for the regeneration of a variety of different organs and tissues.

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