Text: Louise Hagbard, Ph.D. **Photo:** Ola Jacobsen

STEM CELL INNOVATORS

DAVID C. HAY

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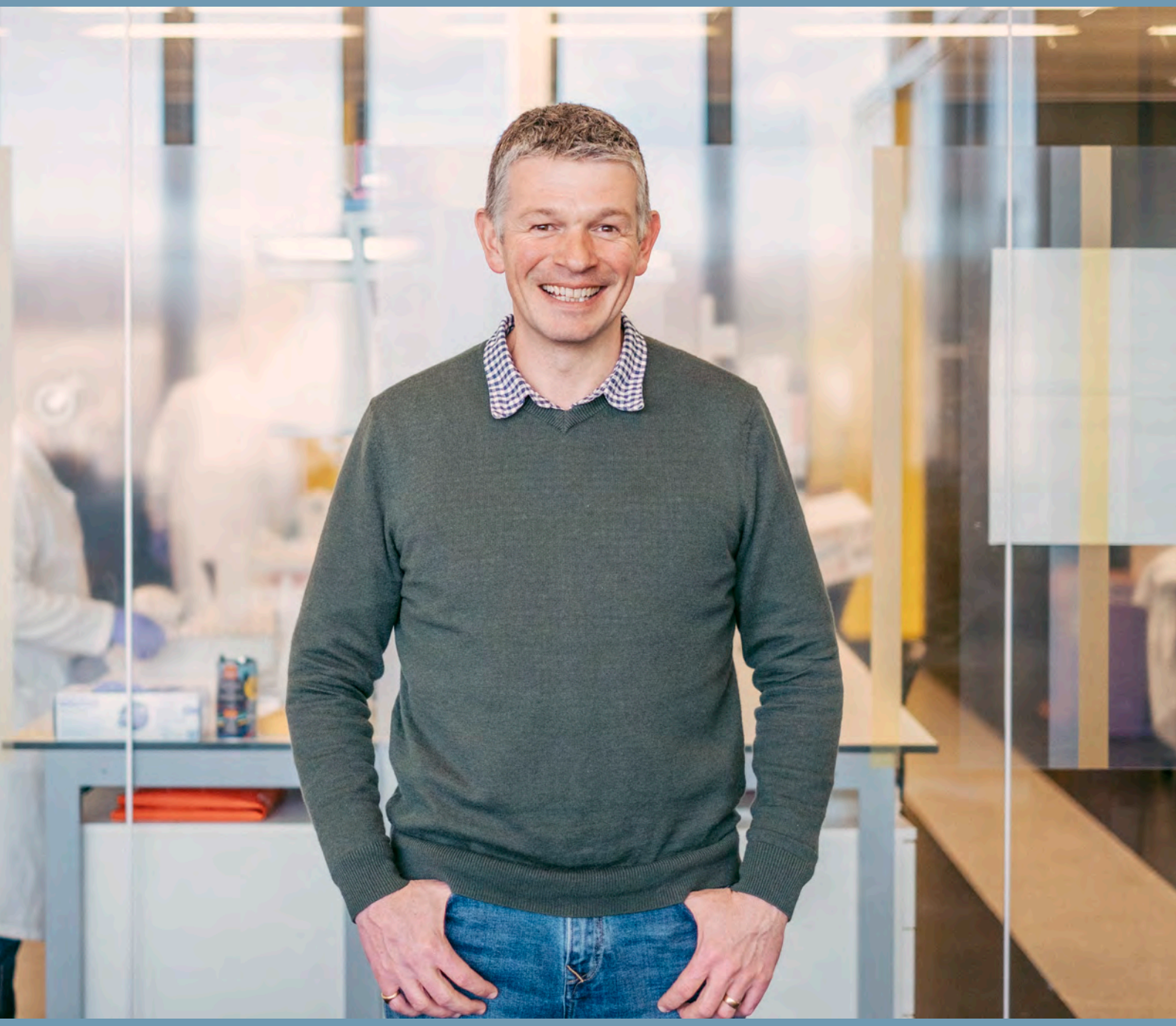

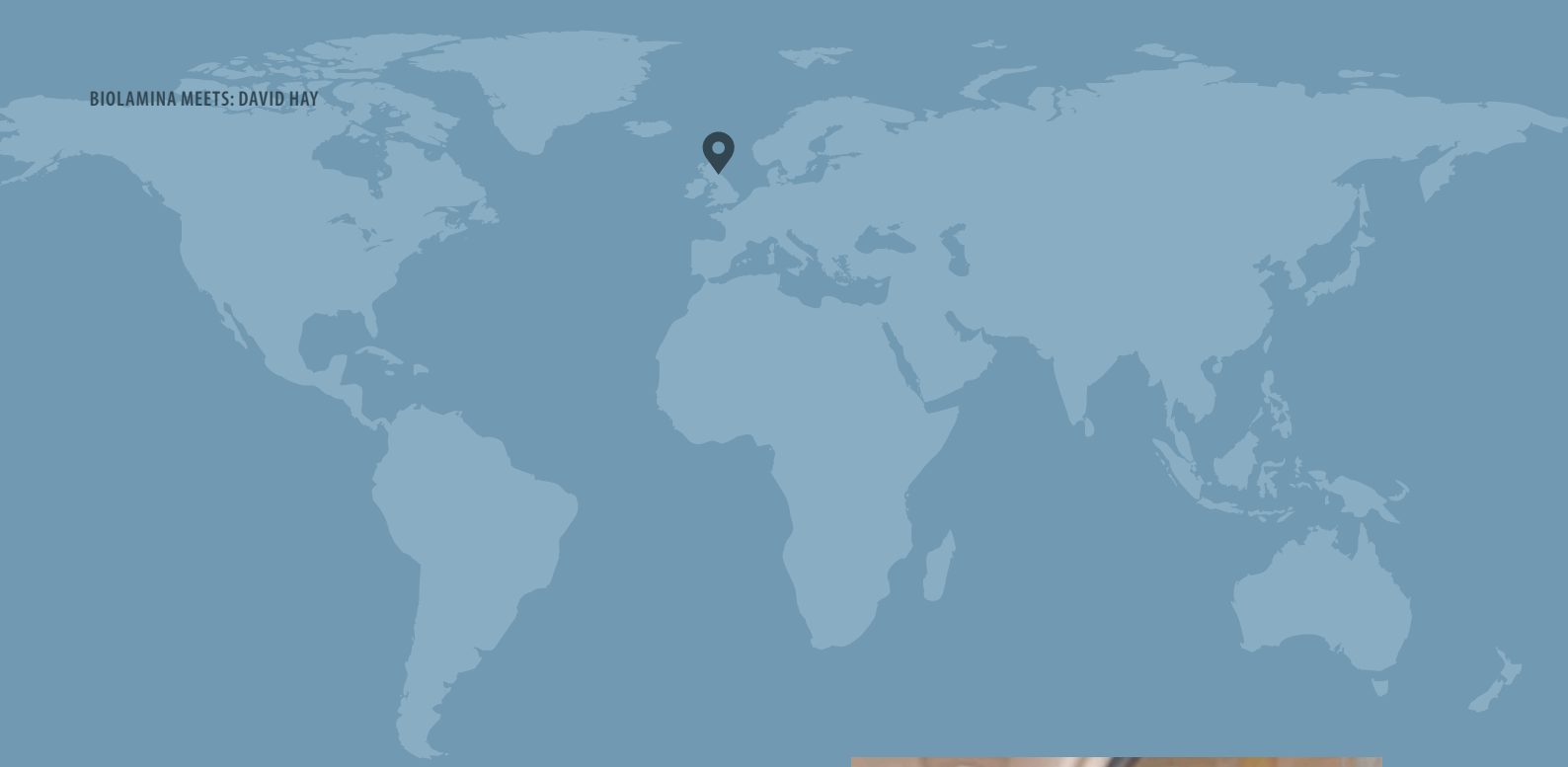

DAVID C. HAY, Ph.D.

GROUP LEADER AND PROFESSOR OF TISSUE ENGINEERING,
MRC CENTRE FOR REGENERATIVE MEDICINE,
UNIVERSITY OF EDINBURGH, UK.

ABOUT: **Dr. David Hay is group leader, Professor, and chair of Tissue Engineering at the MRC Centre for Regenerative Medicine at the University of Edinburgh. He has more than 15 years of experience in working with pluripotent stem cells, and his research focuses on hepatocyte derivation with the aim of translating stem cell-derived hepatocytes into scalable manufacturing processes, 3D culture systems, semi-automated screening platforms, and in the development of renewable sources of liver tissue. His research has led to a high number of well cited publications and a long-standing international reputation.**

Prof. David Hay is a director and co-founder of Stemnovate, which focuses on developing innovative cell-based platforms to model human organ function. He is also the scientific director and co-founder of Higher Steaks, a company that develops animal cell-derived meat products.

MRC CENTRE FOR REGENERATIVE MEDICINE

The MRC Centre for Regenerative Medicine (CRM) is a part of the University of Edinburgh, located at the Edinburgh BioQuarter site. The Centre is led by the Centre Director, Prof. Stuart Forbes and is a world leading, state-of-the-art facility, and a working place for almost 300 scientists and clinicians studying stem cells, disease and tissue repair. Research at the CRM is aimed at developing an understanding of the mechanisms underlying stem cell self-renewal and differentiation processes, and at developing new treatments for major diseases including cancer, heart disease, liver failure, diabetes, and Parkinson's.

↑ "What's nice with this building is we've got dedicated core facilities, including clean rooms, run by experts."

How did you get into stem cell research?

"I did biochemistry at St. Andrews and luckily did a lot of cell biology. The Dolly the Sheep story was inspirational and led me to Roslin Institute. At the Roslin Institute, they were growing human embryonic stem cells for the first time to make particular somatic cells that were of interest. I thought it was a great project because you wouldn't be working with cancer cells anymore and you wouldn't have the problems associated with getting primary materials from humans. Initially for us it was a case of being able to maintain and expand ES cells in an undifferentiated and healthy state. This was a big task, especially when you're using conditioned media that's different every time you'd make it. It was tough. However, I'm glad I stuck at it. I really enjoy it. I choose to focus on liver applications. The choice was liver or brain. After reading through the literature, I thought the liver was the most exciting organ to study. When the Roslin Institute went back to its agricultural roots, I got the offer from the University to move to the MRC Centre for Regenerative Medicine at University of Edinburgh. I began working with John Iredale, who was a great boss and mentor. We went from, I would say, quite an expensive and undefined process to a more reproducible process

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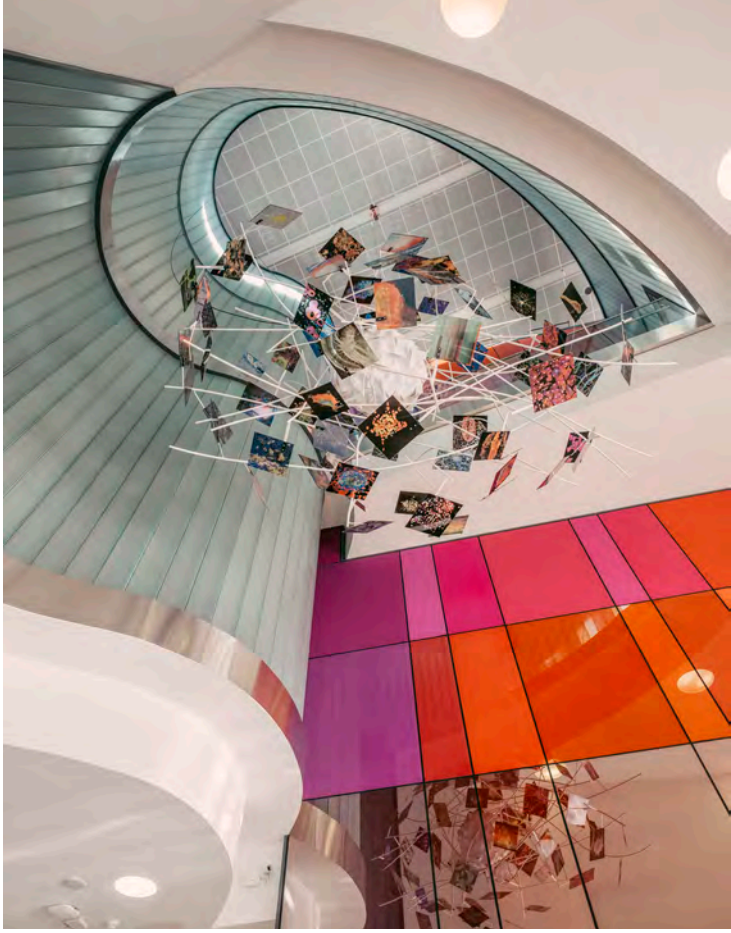


↑ Research at CRM is aimed at gaining fundamental understanding of stem cells and use this knowledge to develop new treatments for major diseases including cancer, heart disease, liver failure, diabetes, multiple sclerosis and Parkinson's.

> "Being able to model complex human disease in a dish has been one of my major driving forces."

that produced stem cell derived hepatocytes at a reasonable cost. I started my independent career in 2008 and I have secured funding from various grant awarding bodies and industry over the years to progress our work within the field."

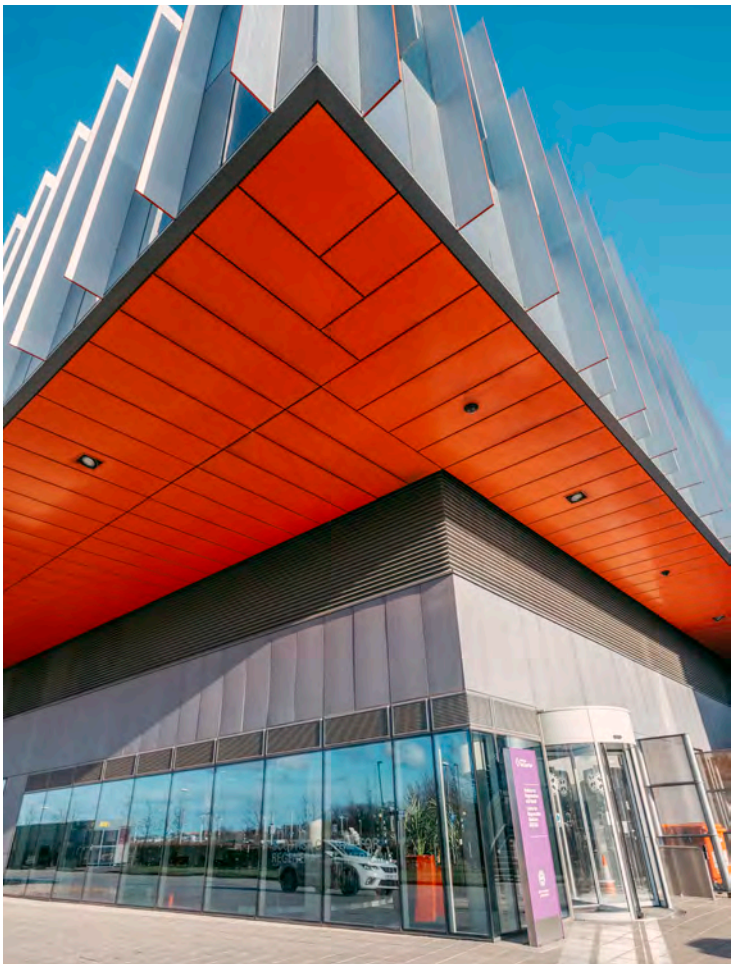
What is your aspiration for the field? What's the driver for you?

"Being able to model complex human disease in a dish has been one of my major driving forces. Our key focus is to use tissue engineering to produce better in vitro models of human liver. Another major driving force is to produce human liver tissue for the clinic. In the first instance, we are focussing on a liver tissue implant that we can deliver underneath the skin using local anaesthetic, that can provide the patient with liver support until a donor organ becomes available. The clinical challenge is going to be more complex, but I think we're really well placed in Edinburgh with expertise in cell biology, tissue engineering, medicine and surgery and the Scottish National Blood Transfusion Service for clinical grade manufacture. Our recent results provide proof of concept that we can support compromised liver function in immune competent and deficient recipients. We are now studying safety profile and dose optimisation. Exciting times ahead I hope!"

You're one of the key opinion leaders within liver research. When did you feel that happened for you?

"I think this was when we were able to transfer our procedure to other people, validating our process in their laboratories. This has proved valuable for both academic and industrial scientist's projects. Really, I think the thing that has served us well is simplicity. We've always tried to define the process components and keep methodology simple, so that other people can pick it up. That's where the interaction with Biolamina has been great. They have

↓ With new state-of-the-art facilities and a 270+ team of scientists and clinicians, CRM is positioned uniquely to translate scientific knowledge to industry and the clinic.



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In terms of regenerative medicine focus, how do you see stem cell derived hepatocytes being used?

"I think definitely they are being used at the moment to model human biology in a dish, whether it's drug metabolism or disease. And I think we're getting pretty good at maintaining cell phenotype in a dish now so we can look at repeated dosing. I'd like to think that in five years' time we could be generating liver tissue for phase one clinical trials. Our approach is relatively simple; implant liver cells underneath the skin of the recipient. Importantly, this procedure only requires a local anaesthetic. Although researchers have proposed the use of more complex approaches, including abdominal or liver delivery, we believe that this may expose the patient to greater risk of complications. To date, we have proof of concept *in vivo*. Of course the notion of putting stem cell derived tissues into patients make me nervous. However, that being said, the work from Pete Coffey's laboratory in London have shown that stem cell derived retinal pigment epithelial cells have provided hope for patients suffering from macular degeneration."

What do you think is the biggest hurdle to reach the clinic with a cell-based product?

"Making a safe product with dependable performance is going to key. In addition to this, the cost of manufacturing and deploying the stem cell graft will be an important consideration for healthcare providers."

↑ "I think we are really well placed in Edinburgh with expertise in cell biology, tissue engineering, medicine and surgery and the Scottish National Blood Transfusion Service for clinical grade manufacture."

HIGHLIGHTED PUBLICATION

Recombinant Laminins Drive the Differentiation and Self-Organization of hESC-Derived Hepatocytes
Cameron K. *et al.*
Stem Cell Reports, 2015 doi: 10.1016/j.stemcr.2015.10.016

The results presented in the paper represent a significant advance compared to any previous published data, especially regarding hepatic metabolic activity and functional organization. Human ES cells cultured on human recombinant laminin substrates show efficient hepatocyte specification, maturation, function, and stabilization of phenotype. The hepatocyte-like cells were arranged in lobule like structures, reminiscent of regenerating liver, with organized staining for MRP1 and MRP2 and were capable of biliary efflux.

So, what's in the pipe for the coming year?
"Definitely tissue engineering for the production of better in vitro models and tissue for the clinic. I think that is our key focus. We will combine those approaches with multiomic analyses and genome editing to better understand human tissue requirements and physiology.

Looking back at your career, is there anything that you are particularly proud of?
"I think our ability to produce useful liver models at scale and translate these technologies to academic and industrial settings has been a great team achievement."

Is there a special person in your career, someone who has inspired you?
"I probably talk about the person who got me into the science in the first place, my Ph.D. supervisor. Ron Hay is a very successful scientist, a good guy to work for and to go out with as well." •

DAVID HAY ON THE BIGGEST BREAKTHROUGH

(?) If you look back at these last 20 years from when the first hESC line was derived, what do you think is the biggest 'thing' since then?

(!) "Yamanaka's discovery's got to be up there. Fantastic! From the endodermal field point of view, I would say Kevin D'Amour's work studying activin made a huge difference. A real positive move for the field. Before, we were producing endoderm in relatively low amounts. With the use of activin you're going from 10–20% efficiency up to 80–90%, so we were very glad to jump on the back of that nice work by Kevin and the team."


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REVOLUTIONIZING CELL CULTURE