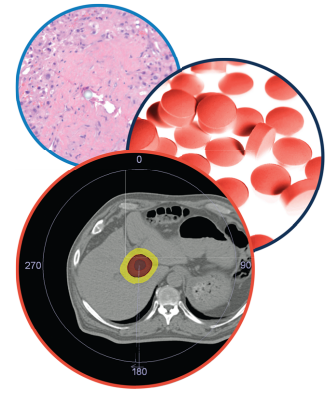
Interview



Hepatic Oncology

The future of liver transplantation: an interview with Pierre-Alain Clavien

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"We lose about a third of patients on waiting lists every year due to the lack of available grafts. With the help of such a machine, this number could be substantially reduced by providing healthy livers to critically ill patients."

In this interview, we catch up with *Hepatic Oncology* board member Pierre-Alain Clavien to discuss his involvement in the development of an integrated perfusion machine capable of preserving livers outside of the body for up to 1 week. The development could have huge implications for the future of liver transplantation as it is hoped it could allow more patients access to vital transplants.

Keywords: liver cancer • liver perfusion machine • liver preservation • liver transplantation

Please introduce yourself & give an overview of your career to date

My name is Pierre-Alain Clavien, I am Swiss born and trained in Switzerland, I then completed 3 years of research and my PhD at the University of Toronto (Ontario, Canada), following this, I did a 2-year fellowship in liver surgery and transplantation. I then spent 8 years at Duke University (NC, USA) where I led the liver surgery and the division of transplantation. In 2001, I became head of surgery and transplantation at University Zurich Hospital (Switzerland).

Can you please explain your involvement in the development of the perfusion machine capable of preserving injured livers for up to a week?

I did my PhD on liver preservation in Toronto, Canada, where I could identify and characterize the injury on the endothelial cells related to low temperature preservation. Under the financial support of the National Institutes of Health (MD, USA), I could continue this work in the USA, and then in Switzerland with the help of the Swiss National Foundation for Research (Berne, Switzerland). Thus I was able to continuously work on liver research over the past 26 years. However, only with the vision and substantial financial support of the Wyss Institute (MA, USA), could we build the machine now published in *Nature Biotechnology* [1]. Our perfusion machine was the result of a 5-year intensive development phase involving several engineers, surgeons and biologists with experiments performed initially in swine livers. This was a time-consuming process, but we eventually managed to maintain injured human livers functional for up to 10 days in the perfusion machine. These human livers, discarded in terms of predicted failure after transplantation, showed excellent function during preservation on the machine.

What are the implications of this development?

The first implication is that, after a few days of resuscitation in the machine, injured livers that would have been discarded could now be transplanted. The advantage of this technology – in the light of the current organ shortage – are obvious. We lose about a third of patients on waiting lists every year due to the lack of available grafts. With the help of such a machine, this number could be substantially reduced by providing healthy livers to critically ill patients.

The second aim was to create a platform for regenerating the liver outside of the body. This implication would enable us to take a small healthy part of a liver from patients with advanced liver tumors, and have this part of the liver grow on the machine. We know, that at least 7 days of regeneration are required to achieve an adequate size that would meet with the metabolic requirements of the human body. In this ideal scenario, after regeneration

Future Medicine

on the machine, we could remove the entire liver containing the cancer and replace it with the regrown healthy liver (so-called auto-transplantation). We are currently working on this application, but there is still a long way to succeed with a clinical application.

Why is research like this not readily funded?

Research is funded differently within the Wyss Institute, compared with competitive national funding. Switzerland has a leading position in basic research worldwide, but there is a long period between scientific discovery and its application in patients. Many research discoveries are not translated into practical applications because national funding/industry/investors typically are not investing at this transition stage. Due to lack of funding, early stage developments get stuck and do not become available for the benefit of patients. This is where Wyss Zurich (Switzerland), through the generous donation of Dr Hans Jörg Wyss, builds a bridge between basic research and application. Under such vision, our two leading universities ETH Zurich (Switzerland) and the University of Zurich (Switzerland) join their forces. Wyss funding platforms like this in Zurich (or other cities such as the Wyss Institute Harvard, in Boston) bring innovative projects to an accelerated clinical application.

What challenges needed to be overcome to make this breakthrough possible?

With this complex machine, we tried to mimic the human body, so that a liver should somewhat not realize that it is outside of the body. Many groups have tried to build a similar machine in recent years, but failed. The technology was designed to resemble the human body, which is central for any successful long-term preservation of the liver. We identified five key hurdles, each limiting successful long-term liver preservation, namely, control of sugar metabolism, prevention of red blood cells damage, blood quality disruption, control of oxygen supply and diaphragm movement simulation. All those hurdles were addressed with the imitation of an 'in body' situation.

What will be the next steps with the technology?

The next steps will be to carry out a transplant using a liver preserved in the machine, as this has been done only in pigs but not in humans yet. We are currently in the process of obtaining the authorization to carry out this procedure to demonstrate the safety and effectiveness of this machine. Yet, the ability to preserve a liver outside of the body has many other implications, including in the world of pharmacology (e.g., ability to test drugs outside of the body). This will not be our next step; however, there are several interested parties for this end.

How do you think the technology will evolve over the next 5 years?

We will now focus on the aforementioned regeneration application. This is a highly complex research field as there are many unknown growth factors contributing to liver regeneration. It would be a tremendous success for us, if we could achieve regeneration outside of the body in the next few years with our current strategies.

What steps will be needed to translate this technology into the clinic?

We need to carry out transplants in humans and secure long-term function of these livers. Then many livers that are currently not suitable for use, could be put on this machine. As well as this, also so-called 'high risk' livers could be preconditioned on the machine and benefit from the repair process.

Do you know roughly the time frame you're looking at for human transplants?

I hope they can be performed as soon as possible, potentially this year. However, there are still a number of administrative issues that must be resolved.

When you were starting your career did you have a particular hero that inspired you to follow that path?

After doing general surgery in Switzerland my goal was to deepen my knowledge in a special field. The available research opportunities led me to the field of working with livers. As the Toronto group was well-known for liver research, I enjoyed working in this field and continued. I did not really have a hero, but rather followed my beliefs, enthusiasms and opportunities offered by a few leaders that trusted me.

Do you have any advice for early career researchers who are starting out in a similar field?

Yes, be persistent and believe in what you are doing! Move away from negative minds. Nowadays, unfortunately, the ever-increasing administrative hurdles block the research progress, making innovation much more difficult than

it was 25 years ago. Thinking back to the 1960s when Thomas Starzl carried out the first liver transplant in human, I do not think that performing such a risky procedure would be possible today. Progress can only be made, when people are willing to take risks, and when society allows it.

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Reference

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