David Glanz: Being diagnosed with cancer is no longer necessarily a death sentence. There have been fantastic progress in early detection and treatment for many kinds of cancer. But leukemia is a killer. In 2015, 1478 people across Australia died from the cancer in its various forms. But the good news is, scientists are hard at work to find ways to hold leukemia at bay. Today, we're talking to three of those scientists.

David Glanz: Hello, and welcome to this podcast, brought to you by the Australian Academy of Technology and Engineering. I'm David Glanz, and I'm joined by Professor David Huang, and two of his colleagues, Associate Professor Guillaume Lesse, and Associate Professor Peter Czabotar. David leads a research group at the Walter and Eliza Hall Institute of Medical Research in the Melbourne suburb of Parkville. And, along with his team, he's just been awarded the Academy's prestigious Clunies Ross Award for knowledge commercialization. So David, let's start at the beginning. What is leukemia?

David Huang: Leukemia is a special kind of cancer, and it's a cancer of white blood cells. So, the normal role of white blood cells in a body is to provide defense against infections. Unfortunately, in some people, these cells misbehave, so that they grow and proliferate in an uncontrolled way. And that can lead to significant problems in the patients because of the cancerous growth of the white blood cells.

David Glanz: I mentioned just now the number of people who die in a given year in Australia. How many people contract leukemia in its various forms?

David Huang: So, the numbers, it's, as you say, it's about 1500 in Australia a year. There are many different kinds of leukemia. And some of them are less aggressive than others. The kinds of leukemia that people get depend, in part, on the age of the patients and so on. So, the disease that we're particularly talking about here is a particular type of leukemia called chronic lymphocytic leukemia, also known as CLL. That's an interesting one, because it's probably the most common leukemia in Australia.

David Glanz: Okay, so, your team has made a big breakthrough. Can you explain what you've achieved?

David Huang: Essentially, what scientists here at the Walter and Eliza Hall Institute discovered in the late 1980s is that these leukemia cells not only grow faster, but in fact, it turns out these cells do not die when they should. And the reason these cells don't die when they should is because there's a protein in them called Bcl-2 that's overactive. So because of the overactivity of Bcl-2, these leukemic cells become very long-live and persist, giving rise to problems in the patient.

David Glanz: So, the trick is to find ways of affecting these Bcl proteins, and stop them doing what they're doing.

David Huang: Exactly. So, Bcl-2 works to keep the cells long-live. And essentially the trick and really, very much, the work of the team here with my colleagues, have been able to find a way to inhibit, to target these cells, to sort of no longer function. And essentially, this is what allowed the cancer cells to die. We essentially made a drug to specifically induce these leukemia cells to undergo cell suicide.

David Glanz: Okay. I understand that you've had some significant success in the various trails, the clinical trials.

David Huang: Yes, so one of our team members, Andrew Roberts, led the very first clinical trials of venetoclax in the world. Many of the first patients did a treatment here in Australia, with the trials that started in 2012. And what's amazing is that these patients the clinical trial were at very poor prognosis disease who essentially failed other forms of treatment. In about 80 percent of them, the doctors find significant response of the disease. And in fact, in many of the patients, this response been long-lived. We're now six years past the initial patients begin their trial. Many of them continue to respond to the trial. There've been subsequently many trials with this drug, and it continues to show a lot of promise. And what is even more encouraging, I talked about starting venetoclax in CLL, chronic lymphocytic leukemia. Now there are trials in this disease, and a whole range of other blood cancers, as well as systolic cancers, such as breast cancer.

David Huang: So, at our last count, I think we were able to count that there are about 80 clinical trials in the world going on with this drug. So we're very excited.

David Glanz: That's fantastic. You've mentioned venetoclax. Is that currently available to patients? Or, is that still going through a process of clinical trials?

David Huang: So, the clinical trials are being done for different indications of this drug. The drug has been approved by the TGA, but is not listed on the PBSS yet.

David Glanz: Okay, so patients can take it, but they would have to pay a substantial amount to access it?

David Huang: At the current time, that's correct.

David Glanz: Guillaume, the Clunies Ross Award is for knowledge commercialization. Tell me, what's your experience of working on this project with an industrial partner?

A. Prof Lessene: So, when you develop a drug, it's a very long and complicated endeavor. And what we can do here at WEHI is really the first steps towards that development. And while we were successful, that really enabled us to talk to commercial partner, Genentech and AbbVie, and really create that really big collaborative team that normally was using the biology, but developing these compounds all the way to the clinic. And that's the strength of that collaboration, to be able to

leverage their experience in really developing drug all the way to the clinic, which really requires an enormous effort.

David Glanz: As a researcher, does working with a commercial partner in any way inhibit the work that you do, or does it actually free you up to do work that you have always dreamt of?

A. Prof Lessene: Mostly, it really frees us for doing things we really need and we dream of when we develop a drug, because it is a very complex process, as I said. And really, all the complexity of that process can only be on lock when you have the backing of industries and commercials partners like these. So it was really an amazing experience to be able to do that with them.

A. Prof Lessene: At the same time, there's always some constraints in terms of intellectual properties that come with the project. But, we actually were able to deal with that relatively well. So it was, overall, an extraordinary experience.

David Glanz: And I've heard that Walter and Eliza Hall Institute has been able to sell part of the, I think, intellectual property around this for a substantial sum. What's the practical outcome of that kind of deal? Where does that money get reinvested?

David Huang: As part of this collaboration, we've obviously been very fortunate, not only, as Guillaume said, to be part of a very exciting collaboration. We also derive commercial income from it. I think for us as scientists, the real deal for this is really down the track. It's that we're able to do more science. And particularly, we're able to do more drug discovery. I think Guillaume here is really [inaudible 00:07:42] our Chemical Biology division and drives that initiative. And he'd be able to tell you what we hope to be able to achieve with putting more resources into a drug discovery.

A. Prof Lessene: So, yes, just to follow on what David was saying, I think the example of venetoclax and the Bcl-2, developing a compound targeting Bcl-2, exemplified how long it can take from the initial discovery in 1988, all the way to a drug to the market. What we want to do by reinvesting in drug discovery is to be able to shorten that time frame, at least in the part that we control, which is the early translation of the biology into small molecular. So that's where some investment will go within the institute.

David Glanz: It might sound like a silly question, but for researchers like you, how do you choose which cancer to focus on? Because clearly, some have a much bigger impact on the population than others. But all of them have their victims. So, what's next on the list and why?

David Huang: That's a very interesting question. I think, as researchers, what we often driven by, motivations are different. Some of us are driven by particular diseases. Some of us are driven because those diseases affects ones close to us. Some of us... like I'm just driven by a process that goes wrong in the leukemic cells that I

described to you at the very beginning. So we were very much interested in studying cell suicide mechanisms, and it turns out that that is a very important part of why the leukemia forms. So, there isn't a generic answer to your question, David, and I would say that here, as researchers, we are very much opportunistic and we take what best opportunity there is to discover drugs. And, I think what we're most excited by is the possibility of doing something in the lab that will help people suffering from those diseases, not more than five hundred meters away from where we sit.

Peter Czabotar: And just to follow on from that, I think this is a good example of why investment into basic research is very important. Because the original observations weren't necessarily expected in bcl-2, and consequences on cancer cells. It was because of those discoveries, which weren't necessarily aimed at finding, that treating a particular cancer, that we're now able to develop those discoveries into drugs that can actually treat cancer patients.

David Huang: This effort towards... journey towards venetoclax, as Guillaume says, has been a fantastic collaboration between us here at the Walter and Eliza Hall Institute. And colleagues at two pharmaceutical companies, Genentech and AbbVie... at various stages, we would have... the team would encompass hundreds of researchers covering different specialties. And I think even here locally, we've covered people like Peter, who are structural biologists, they're interested in the nitty-gritty details of how the molecule might work. All the way through to some like Andrew Roberts, who look after patients as part of his normal duties. I think that range of specialty, that collaborative spirit, has been amazing and wonderful part of this journey.

David Glanz: The thought crosses my mind that you mentioned that Bcl-2 functioned to keep cells alive longer. And in the context of a cancer, that's clearly a bad thing. But are we talking about sort of, if not the key to immortality, the key to much longer lives for human beings?

Peter Czabotar: It's actually quite the opposite. Cell suicide actually turns out to be very important for keeping us healthy. Billions of cells in our bodies die every day. And if they don't die in a controlled way, then they cause problems, like cancer. So actually, we want to be able to tell cells to die when they should, and keep cells alive when they don't.

Peter Czabotar: What it could be useful for, in understanding cell suicide or cell death, is in treating other diseases where too much cell death happens. We might be interested in trying to do the opposite to what we do with the Bcl-2 venetoclax drugs. For example, in skin conditions, you have too much cell death. And in those conditions, you might be able to turn the tap the other way, make those cells stay alive, rather than die. And if we can make drugs that do the opposite, we might be able to do that. But I don't see us ever finding the answer to immortality in this family of protein.

David Glanz: That's a shame. It could be the only way I ever get to finish what's on Netflix. But there you go. I don't quite understand, under what circumstances do you want to keep cells alive for longer?

Peter Czabotar: So, for example, if you had a situation, such as a heart attack, where you have tissue damage as a result of lack of oxygen, and the reperfusion of blood into those regions, you get a lot of cells dying. And that causes a lot of problems in those patients. You might want to keep those cells... but, you might be able to keep those cells alive by targeting this group of proteins. In this reverse mechanism, by making the protein more active, to keep the cell alive, or by targeting other members of the family, which are actually responsible for killing the cells, stopping those proteins from working. If you can make drugs that can do that, then you can keep those cells alive, and make the outcomes of those patients much better.

David Glanz: Now, the Clunies Ross Awards are the most prestigious awards presented by the Australian Academy for technology and engineering. You've won one of those three awards this year. What does it mean to you as a team?

David Huang: I think it's amazing to be recognized by your colleagues, friends, and community. I think I will say that I've been incredibly lucky to be part of this journey, part of this wonderful team. And I trained as a doctor. I didn't imagine in my research career that I would have been able to do something that actually makes a difference for patients. I think I... it means a lot to us because of the recognition it confers. And it also... we hope it means to the broader community that we get excited about science, we get excited about basic research and the value that it brings to us as a society.

David Glanz: What's the next project for the team? Or, do you still have many years to go, working on Bcl-2 and venetoclax?

A. Prof Lessene: There are lots of projects. We are still working definitely, we still have a lot of interests. As Peter was saying, we are also working to try to do the reverse, trying to maintain cells alive. But, we're also looking at other types of cell death that are also important in other types of diseases. So, there is a lot coming from the basic science here in the institute and all over Australia.

David Glanz: Okay. Thank you very much for your time.

David Huang: Mm-hmm (affirmative) Thank you.

Peter Czabotar: Great. All right. Thank you.