Body, heal thyself

An interview with Kenneth Chien, Professor of Cardiovascular Research at the Department of Cell & Molecular Biology, and the Department of Medicine at Karolinska Institutet in Sweden

EMBO reports (ER): Dr Chien, you pursue an interesting approach to regenerating heart muscle cells and blood vessels after myocardial infarct: injecting synthetic RNA molecules into damaged heart muscle should stimulate progenitor cells to form new tissue. What is the advantage of this method compared with other therapies that use stem cells?

Kenneth Chien (KC): There are a variety of approaches to regenerative therapeutics for cardiac diseases. Of course, the one that's been used most today is to take adult stem cells, which can be sufficiently obtained and/or expanded in large numbers. This is important, because the delivery systems are quite primitive and inefficient at this stage, and the human heart is so large and the number of cardiac muscle cells that you lose during an infarct is so great. The results have been mixed so far. The other approach is to reprogramme somatic cells and make them into stem cells; from those stem cells you can harvest heart cells and you inject those heart cells back into the heart muscle. Of course, the problem is that it requires transfer of genes and that it essentially represents gene therapy, which is an additional risk in addition to cell-based therapy. We are developing a therapeutic approach that directs the expression of paracrine hormones in the heart to expand the number of progenitor cells, but then would like the factor to disappear. You don't want long-term expression, as this could lead to unwanted side effects: perhaps an increase in the risk of tumorigenesis. mRNA fulfils all those criteria if it is modified to escape the immune system, which has been the big bugaboo. Now it looks as if it's largely been conquered.

ER: Therapies using mRNA have been around for decades, but it has always

had the problem of delivery, stability and triggering immune reaction.

KC: The new chemistry appears to solve that. What we have shown is that muscle cells take up this synthetic mRNA and will express almost any protein quickly. The technology will allow an intense, focused, one-time application to drive a therapeutic effect that might have a long-lasting effect by affecting, expanding and redirecting the fate of rare native tissue progenitors that are normally mobilized during injury and usually contribute to scar tissue.

ER: It is the localization and the timing that is important?

KC: Localization, timing, single injection. It doesn't disrupt the chromatin gene expression and the most important thing: it's gone afterwards.

ER: Do you think that injecting RNA to stimulate the production of endocrine factors instead of injecting stem cells could also lead to therapies for other diseases.

KC: These are very early days. Our work suggests that it is possible to manipulate the fate of endogenous progenitor cells in a solid organ *in vivo*, with a single injection of the right mRNA. But the signal has to be in the right place at the right time and hit the right cell. If it doesn't fulfil all these criteria and if it persists, other things could happen. The same signal—for example, a wnt signal—can be positive in one developmental window and negative in another.

ER: Stimulating the body's own stem cells could therefore be more interesting than stem cell therapy?

KC: You are using the body to do its own healing. In other words, you are harnessing a naturally occurring phenomenon, as opposed to asking a cell to change its mind to be something it never intended to be. These are the challenges of ES [embryonic stem] and iPS [induced pluripotent stem] cell therapy. With the mRNA paracrine pulse strategy, you are giving something and then it is going away. That is the beauty of it. The other question, of course, is can you use this for chronic diseases or for paediatric diseases? The technology is getting better and better. I predict that over time, it will be used for chronic injection and for things other than just a single injection approach.

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ER: Would this also resolve some of the regulatory problems that come with stem cell therapies?

KC: That's exactly one of the reasons why people are finding it attractive. Here you are taking advantage of the knowledge of regenerative biology and the knowledge of stem cell biology. But the therapy is not based on cells, it is based on the knowledge of signalling pathways.

ER: Do you think generally that regulatory frameworks hold up clinical stem cell research?

KC: I think that we have learned a lot from stem cell therapy trials. One problem is scalability; you need a lot of cells. A second

Kenneth Chien studied biology at Harvard College in Cambridge, Massachusetts, USA and received his MD and PhD at Temple University School of Medicine, USA, in 1980 and 1983, respectively. He was Assistant Professor of Medicine at the Cardiology Division, University of Texas in Dallas, and Associate Professor at the University of California, San Diego, USA, where he became Professor of Medicine in 2005. Chien also became Professor of Medicine & Cell Biology at Harvard Medical School and Professor of Stem Cell & Regenerative Biology at Harvard University in 2005. Chien is now Professor of Cell & Molecular Biology and Medicine at Karolinska Institutet and the Karolinska University Hospital in Stockholm, Sweden. He has published more than 270 scientific articles on heart muscle regeneration and how stem cells and progenitor cells in the heart develop into muscle cells and coronary blood vessels. His current research focuses on synthetic RNA molecules to activate progenitor cells in the heart to form new muscle and blood vessel tissue after myocardial infarct. Chien was also involved

in the establishment of the Institute of Molecular Medicine at Peking University, the premier site for cardiovascular science and medicine in China. Most of Kenneth Chien's work discussed in the interview is scheduled to be published this year in *Nature Biotechnology*, *Nature Cell Biology* and *Cell Research*.

problem is that you need a way to deliver them and you need a way to get them to survive; just injecting them doesn't mean they are going to survive. Third, you need to make sure that they get connected to the tissue and don't just form little islands where they talk to themselves and don't do what you want. You want to make sure that they don't have side effects; you want to make sure that they don't become a tumour. You need all this in a large enough scale to effect a change in a solid organ. That's a lot of stuff to ask of a cell that normally doesn't want to do that.

ER: Do you think that this is one of the problems why pharmaceutical companies are not interested in stem cell therapy?

KC: Speaking as someone who has also been involved in biotechnology, I think the business models have not kept up with the science. Cell-based therapy has to meet the same criteria that any conventional

therapy needs to meet, in terms of safety, but also in terms of cost and effectiveness. I can't envision the financial feasibility of someone making someone's own iPS cells, reprogramming them and injecting them back as a therapy. I don't think the business model is very clear. That's one of the reasons why I think these mesenchymal stem cell therapies have attracted interest from the investment community so far because this is off the shelf. It is kind of a business-driven model, as opposed to a science-driven model, as it is not clear what these cells are really doing. Most people now agree that these cells that are being injected in the heart have an effect on paracrine factors, so it may make sense to identify those factors and devise means to deliver the signals rather than the cells after injury.

ER: AstraZeneca is investing heavily in the mRNA technology that you are using, and it looks like it is a gamble for them because so far no RNA-based therapy has been approved.

KC: Genentech was a gamble too when it started and they did fairly well. I think there will be new therapeutics coming out of this, and other RNA therapeutics have been based on the loss of function, not the gain of function. There are a number of

situations, clinically, where expression of a single protein in a single point of the body at a single time could be helpful. It is not easy to achieve that. You give a drug, a protein, an antibiotic, it goes everywhere. Here you can give it right there at the time it is needed. It is almost surgical, a kind of a combination between surgical and molecular.

ER: Would these therapies also require a different regulatory framework than just treating them as drugs or transplantation? What are the main risks?

KC: The modified RNA has its own issues. One is immunity. That's got to be monitored absolutely carefully. That's why I think the first in-human studies will not be in the heart, but outside it. Then the next question is: how many injections can you give without triggering an immune reaction? I think that's the big issue.

ER: You are now closing down your lab at Harvard University in the USA to move to Karolinska University in Sweden and move your work towards a translational/human biology/clinical direction. What are the reasons for this change?

KC: I am a physician scientist and I always wanted to work in a human setting, but only recently has the technology been in place to do this at a mechanistic level. Right now, it is very troubling what is happening in the United States from the science funding perspective. Sweden is a unique venue: this is a country that has decided to put its faith in science and technology. They have the regulatory framework, high ethical standards and they fly in patients with rare diseases for which there is no cure. They pay for their care—where else is this going to happen? They are building a new three billion dollar hospital next to the Karolinska Institutet [KI]; last time I was there, it looked like Shanghai, there are so many cranes. Many of the senior professors at KI hold combined MD and PhD degrees. I believe that Stockholm will become a new hub for high-end translational science in the coming decade. At the same time, I am particularly concerned about what is happening politically right now in the US regarding funding for biomedical science. There is not the political will to support science and academic medical centres to the level that they really deserve. Harvard is a wonderful

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place and I will continue at Harvard in an educational role and fostering exchange programmes. It is at the federal level that I think is the concern.

ER: Do you think it is now easier to do translational clinical research in Europe than in the USA, given the funding and political situation?

KC: No, I think Sweden is in a unique position. I wouldn't say this for all of Europe, but I was quite taken by how they supported the work of Paolo Macchiarini [who performed the first adult stem-cell-grown trachea transplant at Karolinska] and I thought, what I want to do is less complicated than that. I knew the place, knew it was good, knew a lot of the people, but I didn't realize how well positioned they are for translational research. For my own work, I see it shifting more towards human biology, model systems and pilot human clinical research, and we are also going to start work in non-human primates in collaboration with China.

ER: Do you appreciate this shift from basic to clinical research?

KC: I am an MD and PhD and originally trained as a cardiologist, so it is like returning to my roots.

ER: So this is natural for you?

KC: Yes, it is natural. I'm kind of in the autumn of my career. So the question is how do I want to finish my career? It is a nice circle to come back and say "okay, this is what I should do". I could generate more mouse models and knockouts and knock-ins. But then the question is what about humans? Now, we can actually do mechanistic work in humans.

ER: Where do you see the role of China in regenerative medicine and stem cell research, given that you are also involved in the Institute of Molecular Medicine in Beijing?

KC: Right now, China has the largest concentration of young scientific talent in the world. If you look at the first author of many of the major breakthrough papers, many are Chinese. Another thing that they have is a huge patient population, with a more uniform genetic background. They also have most of the non-human primate

testing facilities and naturally occurring large primate colonies. One of the things that impressed me is that it has recently been shown that it is possible to generate a chimeric monkey. Coupled with the technology for knockouts in a primate ES cell system, it is going to become possible to make knockout monkey models. Once you have that, then you are in a position to develop a new technology platform for real translational medicine. With recent advances in monkey ES cells and the ability to engineer mutations easily in somatic cells of all types, I think it is going to be an exciting time. Obviously that is going to be very labour and resource intensive, and there are only a few places in the world that can do it. China is going to be one of the places and we want to work with them.

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ER: Given the public interest in stem cell therapies, the moral and ethical concerns with ES cell research, the expectations of patients and the promise of cures for a range of incurable diseases, do you think these things combine to put excessive pressure on research, or do you think that science is up to the challenge?

KC: I think there is a very delicate balance here and we need to be careful. When we think of gene therapy, we think of the disasters that have occurred clinically. Fortunately, that has not happened in stem cell therapy, at least in large sponsored trials. I would say that the issue is one of providing false hope to patients too soon, too early. There is such an incredible need for these regenerative therapeutics as the population ages, that naturally there is pressure to move forward quickly. We should move forward aggressively on the scientific end, but I don't think we should take a 'cowboy-style' approach. We should do it step by step: make sure we have a technology platform; make sure we have a delivery system; make sure we have a target cell; an assay system; that it can be verified; that we can fulfil all the scientific and safety criteria. Given the upcoming World Cup [in Rio], I would use a 'football' analogy: everyone

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wants to take a shot at the goal, but if you take your shot from the opposite end of the field, your chances of scoring are extremely low. So you move the ball down the field, position it properly and when you are in the right position, then you take your shot. Science moves the ball down the field. That's where I think we are: we are going to take our shots now.

ER: What do you think of the recent case in Italy, where the government granted permission for the use of an untested stem cell therapy in children, in response to massive pressure from the public, patients and parents?

KC: I think if there is absolutely no other clinical approach, then your threshold for trying new things is different. On the other hand, I think it is not a good idea to do that uniformly outside of an academic setting where you can't actually learn what is happening and then improve it. You don't know what is going to happen and a lot of unsuspected issues could arise. If nothing else, you are learning how to make it better, because it is an iterative process.

ER: Do you think regulatory agencies should better control and steer this process?

KC: You need balance. I think you come to a point where you do want to take that shot. Part of the job of these regulatory agencies is to ask: how far are they in the field? Is this ready? And what happens if they miss? A lot of these decisions will have to be science based, but they also have to be balanced in favour of patients. If you look at Paolo Macchiarini's work with the stem cell trachea, he basically operated on patients that had no alternative, who were going to die. Daring, high risk, high reward. There, the balance is toward the patients. So, I wouldn't say never to try a new thing, but there has to be scientific underpinning for it, at least from my own perspective. Every society, every country has to decide where that set point is, based on their cultural background and thresholds.

ER: Do you think that with our new knowledge of developmental biology, stem cell biology and chemistry coming together, we could see a new wave of therapeutics and therapies against a range of untreatable diseases? Where do you see the challenges?

KC: One of the issues with regenerative medicine is that there is going to be a window when it is possible. There are clearly

cases where the disease is so far gone that it will be impossible to reverse it. You have to find that pivotal point in the disease process, where you could still move it back. Cancer is the classic example: if you catch it early, you might get rid of it; if you let it go too far, you can't get rid of it. A lot of chronic diseases are like that. You have to find out where that window is and then you have to design your therapy to that window. It is not just a stem cell issue, it is

about understanding the disease at a much deeper level.

ER: Dr Chien, thank you for the interview.

*This interview was conducted by
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**Received 17 July 2013; accepted 18 July 2013;
advance online publication 13 August 2013**

EMBO reports (2013) 14, 755–758; published online
13 August 2013; doi:10.1038/embor.2013.115