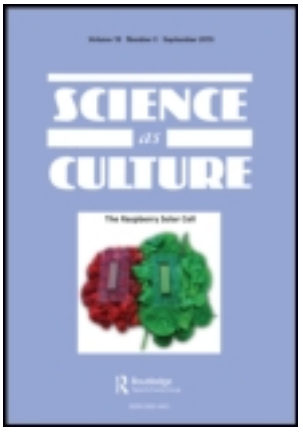

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Industry in the Middle: Interview with Intercytex Founder and CSO, Dr Paul Kemp

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While the discovery of new cellular capacities in the late 1990s has been prominently and controversially linked to human embryonic stem cell derivation, a consequence is that the far more substantial social, political and economic implications of living human cell-based therapies already in use, or very near to market, have been less visible. While hES cells continue to occupy centre-stage, it is the much larger market in other living human cell products that is paving the way forward in terms of regulatory systems, ethical protocols, business models, and technological infrastructure, such as automated manufacturing, delivery systems, and packaging. The field of Regenerative Medicine, which encompasses Tissue Engineering as well as stem cell technologies—including those using embryonic stem cells—may soon come to be of greater ordinary significance for larger numbers of people than was ever expected from human embryonic stem cell-derived products. As the launch of a new generation of human biological repair products enters the final stages of clinical trials here in the UK, CSO and bioentrepreneur Paul Kemp, widely regarded as one of the most influential global industrialists in the field of Regenerative Medicine, provided an interview for this special issue of *SaC* to Sarah Franklin and Lamprini Kaftantzi in November 2007 at his company headquarters in Manchester.

In preparing our questions for this interview, we focussed on the issue of translation in order to address a very practical set of issues shaping the emerging market in living human cell-based products. Specifically, we wanted to know about the regulatory obstacles to licensing and accrediting this type of product, which raise safety issues that are in many respects the complete opposite of those involved in pharmaceutical manufacture. Unlike batches of standardized tablets that can be quality controlled *en masse* in large factories, and which involve inert substances, the emerging market in bespoke biological products, made from living human cells, raises huge logistical questions.

As our interview with Paul Kemp demonstrates, all of the regulatory and quality control issues are at present in the midst of being formulated and road-tested, and this is a process

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in which industrialists play a key role, as they are the ones with direct experience of all aspects of product manufacture and delivery. This is why we include an article on cell-based products in a special issue devoted to stem cells: as far as many human cell-based products are concerned, the future is now. Following Hannah Landecker, whose insightful historical account of 'how cells became technologies' provides an important backdrop to today's debates about stem cells, the motivation for this interview was to return to one of the important emerging themes of the stem cell translation—that stem cells are first of all cells!

Paul Kemp is well placed to address the topic of the challenges involved in the effort to bring human cell-based products to market. He has been involved in commercial Regenerative Medicine for over 20 years both in the US and the UK and has firsthand knowledge of both its scientific and corporate infrastructure. Like his products, he is a hybrid entity himself, combining the expertise and experience of a scientist and entrepreneur with an industrialist's practical knowledge of law, policy, ethics and marketing—especially in the labyrinthine bureaucracy that is the EU. Most notably, Paul brings to his current effort to launch four new human cell-based products a history of involvement with one of the breakthrough applications that launched an earlier wave of investment in living human cell-based products. After post-doctoral research on the biochemistry of collagen cross-links in skin at Manchester University, he joined Organogenesis Inc, the world's first tissue engineering company launched in Cambridge, Massachusetts in 1986 and now located in Canton, MA. As a Senior Scientist at Organogenesis, Paul was instrumental in the development of Apligraf®, a skin replacement product which became the world's first FDA-approved living human cell-based therapy and was seen by many to pave the way to a new era of health products based on reuse of the body's own tissue for repair.

Apligraf's development, however, yielded a very important lesson. While the product itself was successful clinically, challenges to its licensing partnership with Novartis dogged both the product's profitability and the tissue engineering sector generally. In 2002 Organogenesis separated from its partner Novartis and filed for Chapter 11 bankruptcy. Today it has revived, by becoming fully integrated and developing its own sales force and Apligraf® has now been used to treat over 200,000 patients. Interestingly, the company's own volatile history has become an increasingly valuable resource in what is today something of a reprise of the early 1990s, with high expectations for both products and profits as they enter their 'hockey stick' moment on the threshold of potentially enormous markets. Equally impressive are the uncertainties that continue to beset the fortunes of Regenerative Medicine, and its social and economic implications if, as anticipated, it transforms the basic philosophy of healthcare away from Big Pharma models towards a more bespoke, cells-by-Fed-Ex future over the next 10–20 years.

Few people are in a position to assess this emergent situation more knowledgeably than Paul Kemp at what is likely to be seen in retrospect as a crucial turning point in market development as new generations of biological products on both sides of the Atlantic approach commercial lift-off. In 1997 Paul returned to the UK where he founded a new company, Intercytex Ltd, in 1999 (www.intercytex.com). Intercytex focuses on the cellular induction of human tissues and organs and has near-to-market products in hair and skin regeneration. These products offer a combination of cosmetic (hair regrowth, skin rejuvenation) and clinical applications (chronic ulcer and burn treatments). All of Intercytex's products are living human cell-based applications involving novel systems of manufacture, quality control, validation, storage, packaging and distribution. To enable in-house

manufacture for all of its commercial products in the US and Europe, for example, a bespoke GMP facility has been built in Manchester for which an MHRA license was granted in May 2004. The facility is home to some of the most innovative robotic automation systems for cell processing in Europe.

In launching Intercytex, Paul Kemp not only needed new products, but new models of translation. In his interview for *Science as Culture*, Kemp's description of translational strategies confirms the familiar science studies axiom that society does not exist so much in parallel with science as inside of it. The four products currently under development by

Figure 1. Intercytex (ICX.L) has its own GMP compliant clinical production facility plus research and development laboratories in Manchester, UK. It employs 80 people and also has headquarters in Cambridge (UK) and Boston. *Credit*: Sarah Franklin.

Figure 2. Working in close collaboration with The Automation Partnership (based in Nottingham), and with £1.85 M funding from the DTI, Intercytex has developed and process-validated a dedicated robotic system to enable commercial-scale production of living human cells. *Credit*: Sarah Franklin.

Intercytex turn out to be inextricable from the innovation, manufacture and delivery systems that are needed to bring them to market—which are literally built into the products—as are the means of ensuring compliance with regulatory and ethical guidelines, which, in turn, these products have helped to shape. Revealingly, the model for this translation process from living human cell-based products to the market and the clinic is a very familiar social one—of conversation. In this firsthand account of 'biocapital in action' it turns out to be the loud hum of a refrigerator that can sink a product placement scheme, and the non-transparency of aluminium that can literally foil a surgical application, while it is the existence of Fed Ex and DHL that may ensure a viable future for the new biologicals.

SaC: So the topic of the interview is translational challenges for the stem cell field and we wanted to start with one of the most familiar challenges. How do you see the regulatory challenge?

PK: I think first we need to emphasize that stem cells are just a subset of Regenerative Medicine, and embryonic stem cells are just a subset of stem cells. And all the controversy—or at least all the controversy that is front and centre in the media—is about embryonic stem cells. And that has had ripple effects on stem cells, all stem cells, because everything was painted with the same brush. There are issues about Regenerative Medicine that are not embryonic stem cell related and those include issues that the

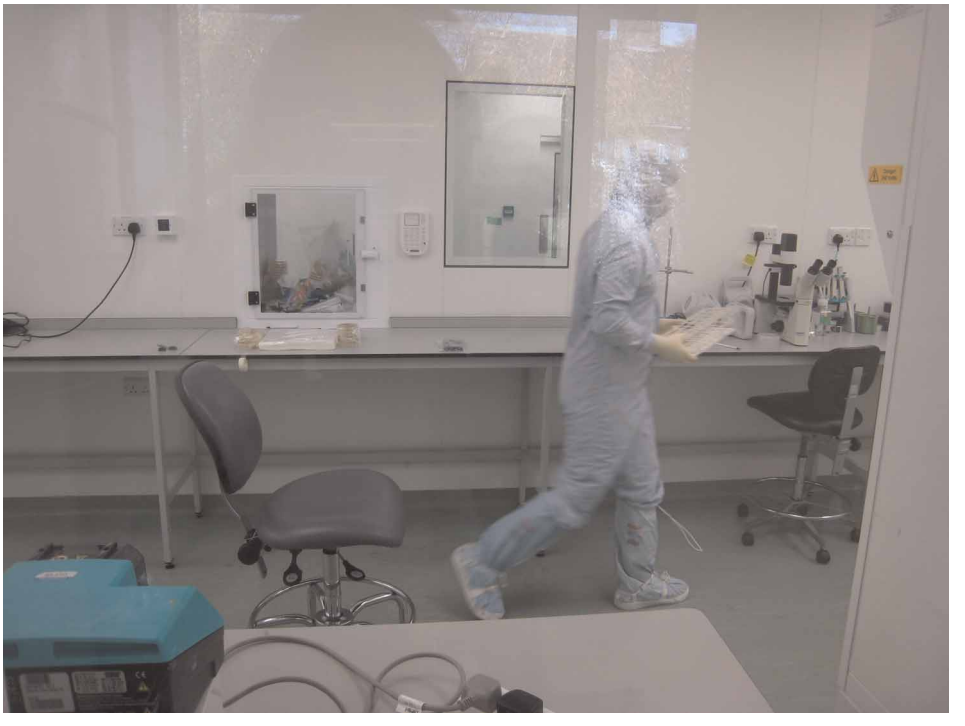

Figure 3. Quality control is one of the major challenges faced by Intercytex and similar companies developing integrated cell technology platforms for the large scale manufacture of living, human cell-based products. *Credit*: Sarah Franklin.

FDA have. I mean if you're talking about the ethical and societal issues about embryonic stem cells, that's just one small subset of the whole field of Regenerative Medicine. One big problem is that some people get confused when they hear Regenerative Medicine and think embryonic stem cells are one and the same. They're not. And probably if you look forward in time, I would hazard to guess that there will be few, if any, therapeutic products coming from embryonic stem cells because the world would have circumvented them. They're already doing it now with the work on iPS (induced Pluripotent Stem) cells that began in Japan and has rapidly spread around the world. So we have learned a lot from embryonic stem cells but I would hazard to guess that we'll never be implanting them commercially. If there was absolutely no other way of doing it than using embryonic stem cells, then yes, but I doubt that being the case. So I think that embryonic stem cells are going to be a flash in the pan, a temporary issue. The issues of Regenerative Medicine are larger: there's all the positive things we will be able to do in the future—diabetes, Parkinson's, strokes, will all be things of the past. We'll all be replacing parts of us. And that is going to change society in ways I don't think society's even thought of at the moment. You know, if you took a group of people, I would guess most of them are homogenous from a cell point of view. Relatively few people have had whole organ transplants, such as kidneys or hearts, but there are now around about quarter of a million people who have had another person's cells applied in the form of Apligraf® alone,

which is more than all other solid organ transplants put together. Now whether those cells have persisted, we don't know yet, but it's an indication of how quickly they will take off when these indications are successful. And then most of us will be wandering around as a mix of cells.

SaC: So if we talk about autologous transplants, would you say that the regulatory picture is comparatively straightforward? That would probably be an exaggeration.

PK: Intercytex are developing both autologous AND allogeneic products and the regulatory issues are somewhat different. The main issue with autologous is the fact that you are growing cells from more than one patient at the same time in the same facility so there is the theoretical risk that you could be infecting patient A with some virus that patient B has got. So process controls are critical to ensure that this cannot take place. The concerns are more addressable with allogeneic because it is standard to produce huge cell banks and test them extensively to ensure they are virus free. With autologous, it's everyday is a new day. You don't know what's coming in. So not only have we got to protect ourselves, we've got to protect all the other patients from contaminating patients. So we assume everyone is contaminating. We don't wait to find out if they are. We just assume they are.

SaC: Ok. So if we move to the question of regulatory standardization, which was obviously a major issue in the 1990s, in that you had products being approved in the United States but having a great deal of difficulty getting them approved in Europe, is that a challenge that will be readily surmounted in the near future for products that are in the pipeline?

PK: It will be. The ATMP (Advanced Therapy Medicinal Products) regulations are coming in to force this December.[1] You know, that's going to make an enormous change because that's going to be one regulatory application for 500 million people. FDA is one for 300 million. So with two, you've got almost a billion people. That's going to utterly change things. There's little nuances in the regulations that are going to be awkward but they're all surmountable. There's nothing that's a killer. The regulations in Europe are there. At the moment, they're asking more questions than the FDA. They're asking more 'what if?' questions. And for example, at the moment, to test our hair product, with QC [Quality Control] testing of the hair product costs around about £1,500 just to do the testing per patient you know, that's not the cost of manufacturing. So the regulators ask loads of questions. You know, it went from drugs and devices, then biologics, and then what? The move from drugs to biologics was a big move when they did it because you're talking about proteins and synthesized products. But the move from biologics to cells is even bigger. Biologics are a single molecular entity, they're one thing and they're not changing. Once it's made, it's made. It just sits there slowly degrading, but sits there. Cells are dynamic things, changing by the moment.

SaC: Some people think it would be useful if the EMEA (European Medicines Agency) were sending their people to Washington to talk to the people at the FDA, to begin to harmonize things now, and other people think that would be anathema because you'd just be dragging over a bunch of other regulations that really should be kept separate at this point.

PK: It never works.

SaC: You've been there, so you would know.

PK: It's a dual-edged sword at the moment. The confusion in the regulatory systems is understandable, it's not that they're doing anything wrong. You can play it to your advantage in a way because in industries like ours you can actually, direct it. So you can influence it. If we were a start-up drug manufacturer now, we would just have to follow the

rules. We wouldn't have any chance of changing the rules. Whereas, [in this new area] we have chances you know, and they come and seek advice all the time. And I'll show you, you talk automation, I'll show you in a minute because we're actively in consultation with the MHRA (Medical Health and Regulatory Authority) at the moment about this automation. Because it's a robot that was designed for one purpose and we're using it to try and see if we can do another purpose. And we're, we're doing this in consultation with the MHRA now.

SaC: Okay. Well, let's move along then because I know our time is limited and we could probably spend forever talking about the FDA. But can I just move ahead to the investment model that you mentioned in your Regenerative Medicine Network talk in London,[2] which was the idea of using essentially a cosmetic product like the hair regeneration product as, I think the expression you used is a bread and butter product to fund the riskier R&D avenues. Do you still consider that an innovation model that you're sticking to or is that changing?

PK: No, no. It is a model at the moment. And there isn't one model, it's a whole mixed bag from one end of the spectrum, making something and selling it yourself to the other end of the spectrum, doing a bit of research and then selling the data and there's everything in between. And probably what's going to end up is a mixture. You will do some of it all yourself with some products in some regions, and you will license out some technologies in other regions, and everything in between. The same product could be treated differently in different regions. You could sell it yourself in your home territory or in Europe say. You could have a distribution agreement in which it's purely distributed in somewhere like America and you could have a different licensing agreement in Asia where your licensing partner's got to get it through their regulatory system. And that is completely unknown territory. You know, we're talking about America and Europe and everyone just kind of pushes Asia to the side. Doesn't even consider it. The only decision that's normally made at the moment about Asia is that Japan is so anti-cell therapy from a regulatory point of view that no one's even considering trying to go there. It's so far away, which is a shame because it's a huge market and a very sophisticated market as well. And they do a lot of research in that area too which is a shame.

SaC: A lot of tissue engineering.

PK: Yes, but it just gets in the way because the regulators in some countries just sit on it so there's this narrow gate. I think a lot of people in the field use the regulations as an excuse—you know, why has it taken so long, because of the regulations. I don't think that way at all. The regulators in some countries such as the USA and UK are bending over backwards to try and get these things [sorted]. The reason it takes so long is that these things don't work as well as hoped to start with. And they will but it takes a whole lot of time.

SaC: In terms of the ongoing challenge of getting enough investment given all the obstacles, the two main questions are first what strategies you're using to attract investment, and second is Big Pharma a bigger part of the picture now than it used to be, or is the picture really still the same, that they're probably going to hold back?

PK: It's changing. Big Pharma is definitely changing and particularly mid-Pharma in that you can see a change in the wind in a way in that people are beginning to say, oh, regenerative medicine, I keep hearing a lot about that area. We're getting contacts from people and companies we've never heard of, mid-size companies, who are looking at this area. Big Pharma is involved in stem cells at the moment but from a high through-put screening point of view. I would bet you all of them are involved in some

ways in stem cells at the moment but not yet from a therapeutic point of view (since this interview Pfizer has started a division of Regenerative Medicine: see www.pfizer-regenerativemedicine.com). There's definitely a change. I think people can understand that the Gartner Curve [showing 'hype cycles'][3] is up and down and up again. On that everybody's agreeing. I don't think anyone now is in disagreement that it's on an upturn. They're all saying the same thing in different ways.

SaC: Different diagram, same message.

PK: And the big people are beginning to look at what is happening. In terms of financial input it's strange because I was just at a stem cell meeting in America, the Stem Cell Summit in Boston,[4] and what they were saying is that there are basically four pots of money. There's Big Pharma money, there's the you and I money in the stock market, trade investors sort of thing. There are financial institutions, pension funds and so on, and there's charitable money from high net worth individuals. And these high net worth individuals are playing a big part in this field—more so probably than in other medical areas—and they're kind of pump primers because the you and Is are interested, but usually if it's a disease that affects our family or ourselves. The big pension funds are pure money. Their first concern is, can it make money in the short term? Yes/No. And Big Pharma wants the products, and the fund investors won't invest unless Big Pharma invests, so there's no clear sponsor of regenerative medicine at the moment. So it's these high net worth individuals [who] seem to be picking up a lot of the slack, particularly in America at the moment, and they are investing huge amounts, hundreds of millions of dollars.

SaC: That's very interesting that philanthropic individuals are playing such a large role and taking leadership roles as with Proposition 71 in California. And at Harvard even the scientists in a way are doing scientific philanthropy. Does that make a difference for a company like yours?

PK: Not personally, no. It's a feature of the industry. For example there's Peter Andrews' company, Axordia.[5] They have a multi-million pound investment from an anonymous investor. They don't even know who it is—all they know is he's in America. Well there's the Christopher Reeve foundation, the Michael J. Fox foundation and there's a married couple and they have invested $300 million of their own money in the field of stem cells and regenerative medicine. So that's an unusual feature of this sector. Charities and philanthropy will fund the research that's going to make some of these things an actuality and then Big Pharma's going to get interested because it actually does work and finally the investment funds are going to get interested because it's actually now a business.

SaC: So in terms of how you're orientating your own efforts to attract funds, which pots are you aiming at or do you have another strategy?

PK: At the moment, because we're a public company, it's institutional money, most of our largest investors are institutions. This philanthropic money is less of a feature in Europe and less of a feature in the UK part of Europe. It's definitely more an American phenomenon, and in Europe, it's more of a mainland Europe phenomenon. As for the you and I money, Germans have a lot of retail investors as they're called.[6] You know, us putting a few hundred pounds of our own money in. That's more common in Germany than it is here.

SaC: Yes, that's another really fascinating topic we could talk about a lot I think. But before we get onto scale-up and automation, one of the things that you've pointed out is that distribution is really in some ways the biggest challenge for this field.

PK: It's an overlooked one. QC testing as I mentioned before is really expensive. It's expensive and it's slow. And that has not been thought of when academics have been developing products. Now most of the products aren't being developed by academics, so it's not so much of an issue now. But when I first started, these things were coming straight out of universities. No one had ever thought much about what is it going to cost to test it and how much to ship it. A good example is Apligraf® and Dermagraft. I was involved in developing Apligraf® and our big competitors at the time were involved in Dermagraft.[7] Dermagraft was cryo-preserved, Apligraf® wasn't and originally it was felt that this was a disadvantage because, at the time, Apligraf® had a 10-day shelf life and Dermagraft could be stored cryo-preserved for much longer periods of time. But Apligraf® had taken the whole supply chain into account. The problem with cryo-preserving was it was more difficult to ship because it had to be shipped at minus 80 degrees Centigrade, and then kept at minus 80 degrees once it got to the clinic. So that was a massive cost which wasn't really taken into account. Then once you get it to the hospital, now what? You've got to store it in a minus 80 freezer which is a big piece of kit and very expensive. So they gave them away, another cost. But now you're not going to want it, you know, if this is your surgery, you're not going to have one of these big huge freezers humming away in the corner. So you would put them in the plant room which in hospitals is quite often in the back where all the central heating is. So now you've got to get it from there to the surgery at minus 80. So there's stories of nurses running through corridors you know, with this box of steaming [liquid nitrogen] you know, okay, so you do that. Now you've got to thaw it to use it and when you thaw it, you can kill it by thawing it wrong. And you would never know because you don't quality control it anymore. So you've got that worry and then the other one that finally killed it was that these things are going to cost about $1,000, $2,000 a unit, and if you were the financial controller in a hospital you're not going to want 100 units, a quarter of a million dollars worth of products sitting in a freezer somewhere around the back of the hospital that might be used four months from now. You're not going to want to have that amount of capital just sat there. So they were buying them as they needed them. So they had these massive freezers with one or two units in them which were being run around. The field's mainly moved away from cryo-preserving. Forget the technical hurdles of doing it. So we're learning a lot as we go on. What we aren't learning, and I think we need to, is that distribution has changed dramatically over the last 10–20 years. You know, the earth is flat as it were. While I was in America, I ordered a computer from Dell from America, it was actually manufactured in Ireland, and it was waiting for me in the UK when I got home, and that's normal. No one even thinks about it—it's so transparent now you don't even notice it. You don't notice when you go to Tesco's and you're buying flowers that were grown in Africa. That system's all in place. We don't use it. We don't access all the infrastructure that is available.

SaC: But as you say, it's massive now.

PK: So that's going to amazingly effect society as it ages. In three years' time the first baby boomers hit Medicaid. At the moment, 6,000 people a day are hitting 65 in America and it's going to be 11,000 a day in three years' time and just continue at that rate. And most people over 65 have three chronic illnesses that need constant treatment and cell therapy has the potential of curing them rather than treating them, but at a large unit cost. So instead of a small amount per day to treat chronic conditions over years, it's one spike, a few thousand and you're done kind of thing. So the infrastructure's going

to be different but you could organize it so you could be making things almost to order and getting around these logistics [of storage and delivery] by using things that are already out there, already designed and already proven for other industries for moving living things around the world.

SaC: That's a fascinating picture. And when you talk about the QC, the process validation for absolutely every step along the way, you're taking it from the provenance of the material through the manufacturing, then out into the distribution, then into the treatment and then however long into the treatment you need to go.

PK: Yes, Yes.

SaC: That's an absolutely massive process. So what percentage of your staff has to be dedicated to that QC process?

PK: We have more people QC-ing product than making it at the moment. That ratio will change as we scale-up as QC is a fixed cost—even if you're making one, you've still got to quality control it. If you're making a million, you're still only quality controlling a percentage of it. But yes, it is a huge amount of effort and we're going to have to rethink it in terms of what we're doing compared to standard medicines in which you make a huge batch and it lasts for years. So you can quality control it like mad cause you're only going to do it every once in a while. We're making it every day, a batch every day, and in relatively small batches, and we need to get them onto the patient quite quickly, so we can't spend months testing it you know.

SaC: And as you said earlier, you can partly help shape what QC will be defined as, but that takes a lot of up-front investment.

PK: Yes. For example, there's a test called mycoplasma test, I don't know if you're aware of mycoplasma, tiny little living things.[8] The test itself costs about £400 or £500 to do and takes about 40 days to get an answer. So it's a huge test. It's a very rare thing to have it. It's kind of a chronic disease. If you've got it, it'll stay with you for a long, long time, but it's rare. So you could retest for mycoplasma, you know, all over the place, at all different points. We're going to have to change how we do it because you just can't do that.

SaC: Just eats up a massive amount of time.

PK: Time and money and we don't get the result until way after this product's been used anyway, so what's the point? If you test all your raw materials going in and if you test all your people who come into contact with that and everyone's clean, then where's it going to come from? You know, you could work on the principle that if it can't get in there, why bother testing it? You can test it every once in a while just to check, but it's impossible for us to [check it all the time]. I think using that kind of logic, not just for mycoplasma but for other tests, I mean you validate the process. You can't have got contaminated, so why bother to check 20 times a day to see if you have?

SaC: That makes sense. We wanted to ask you about the innovation model that's been circulating a lot in sociology which is the idea that instead of a linear model of innovation where there's a discovery or some new kind of breakthrough in basic science that leads eventually to patient applications, it might work better the other way around—the idea that it's more from the user context that effective avenues of translation become apparent. Does that make any sense to you as a model?

PK: Oh yes, absolutely. Um, you know, I keep going back to the first example of cell therapies which is organ transplantation. It works, it's been around for 50 years now and it's saved many many lives. For example even this morning on the radio it was

announced that one of the hospitals in Cambridge has stopped doing heart transplants because the death rate's gone up from one in ten to seven in 20.[9] Hearts are still the same. The success rate of heart transplants is not improving because people have been getting better hearts. It's because people have been getting better at using them. It's the same in all cell therapies and it's going to get better and better through that same reiterative loop. What we're trying to do [at Intercytex] is to leverage what we've learned with products such as Apligraf®, what was good about them, and what was not so good about them, so we can create second generation products. I was involved in Apligraf®, but I know when we started Apligraf® we couldn't have that conversation because you couldn't get surgeons to say I don't like this bit, I don't like that bit because they had no frame of reference. Now they say, well what I don't like about Apligraf® is that it is difficult to get out of the dish, it has two sides, so you've got to be careful about which way you put it up. All those aspects now you can now build in for the next generation. You know, everything I said about cryo-preserving, I didn't know that to start with. So now you can go round and round in the classic product development cycle. You ask the customer what they want and they can tell you. You couldn't do that at the start because they didn't know what they wanted and they didn't know what was possible, so you could only have this theoretical conversation but now you can have a real one. You can talk in specific practicalities now. So that's a classic product development strategy, asking the customer what they need. Of course a bit of an issue in what we do is who on earth is the customer? Is it the patient, is it the doctor, is it the insurance company and so on. So that's a little more complex, because these things are physical objects, but people have opinions and they can change. If it's a tablet, you know, there's much less discussion about I wish it could do this, be like this, be a bit bigger. It is what it is.

SaC: It makes a lot of sense from a social science point of view that something like a conversation would be an extremely effective innovation model and yet it seems sometimes to be a lesson that industry hasn't necessarily learned as much as it might have done, even though in a way, it's obvious. But if we talk about those conversations that you have with surgeons about the fact that it needs to be turned over, the freezer can't be in the basement, would that mean that for your company here in Manchester that it's quite important to have good working relationships with people in the NHS so there's a really active ongoing interface between those two communities?

PK: Yes. And it's not just here, we do it with Americans and UK people and non-UK Europeans because medical practice is very different in those three areas. So we do a lot of feedback in from doctors. We have panels of them. We don't have standard medical panels because we don't want to, we want to keep going out in different areas for different products at different times, to get more and more input about what's needed.

SaC: Okay. Last question. In terms of public perceptions of the field, which is the favourite question of the UK government right now, you know, all MRC grants now have to have a public perception element built in. There's been concern that the amount of expectation generated in the public may backfire and create a bubble that will burst, and contribute to a negative perception of this sector. Is that something that you think about very much or is that just part of the normal picture for any new product?

PK: No, I think about it a lot and we constantly strive to make sure that what we say to the outside world is measured and not open to misinterpretation. There's a massive amount of interest in what we do, particularly with regards to our hair programme, and we are very careful not to over-hype it, probably to our detriment in a way because we're seen as very

low key and for these institutional investors, you need a bit of hype. So there's a very careful game here.

SaC: That must be one of the hardest balances to maintain given how much investment you'd get like that if you said you could cure baldness.

PK: Yes. And you might get a little bit of financial interest because of all this hype and then it'd just die off. It was like everything else so it's not like we are just being quiet and getting on with our job. We're actively not hyping, actively stopping it wherever we can find it. I try, whenever I talk, I try to stop the academics in Regenerative Medicine going off because they're usually the guys who can say they have a five to ten year clinical horizon and it never moves and it's always, it's five to ten years you know.

SaC: The whole organ thing.

PK: Yes. And the heart one's a good model because a few years ago there was something called LIFE and they said they were going to collect $10 billion from this and develop a worldwide consortium. And everyone jumped on the bandwagon and agreed. It was some American, I've forgotten his name now, but it was going to be like the moon race and we're going to create the heart in a dish and we're going to grow them and they had a timeline. You know, year three, we're going to be doing this, year five, and it was typically five years to the clinic, 10 years to a product. Never raised any money. It just completely evaporated. It was an embarrassment that they would ever consider they could do this. And when you asked them, they said, oh, we were talking one evening at a meeting and someone said, what's the most ambitious project we could think of and someone said a heart. So we said, let's go for it.

SaC: Next the brain!

PK: Yes, but they missed their brain out. What's going to happen with the heart is that there will be bits of it. You know, they're working on heart valves, they're working on blood vessels, they're working on recovering muscle. You will be replacing bits of the heart, you will never have a whole heart in a dish. The cost of that would just be astronomical and to grow this thing. I mean you will be fixing bits of it.

SaC: Yes. The complexity of a whole heart defies any possible kind of engineering from the bottom up.

PK: Even if the complexity were less of an issue, even if we could do it, just the cost of it would still be impossibly high, you just couldn't do it for the cost. It would take months to grow. Plus there are already hearts available. There's millions of them going all the time, it's called heart transplant. And they're perfect, they're great. They're just thrown away. I think complex organs are going to be used more efficiently, and that's where they're going to stay, as organ transplants. Regenerative Medicine's going to be doing things that other transplantations can't.

SaC: As you say, the pieces. Just one more thing, you mentioned academia, the role of academia. What about the role of the research councils, you know, the MRC, thinks it has to justify itself to the Treasury by saying, well, we're going to regain the public's investment but not through commercial activity, we're going to fill in some of the gaps that industry won't go towards and in the longer term, new health products will come out of that, and they will ultimately pay for themselves, but probably not for 50 years, kind of thing. I mean do you think academia should just stick to being academia and doing the things that the commercial sector can't do and probably won't do?

PK: No. I think they should do two things and there should be two kinds of academia. If you take the pancreas for an example. People have been trying to make a regenerative

medicine pancreas for 20 years, since day one. It's an obvious application. And they've tried to do it through a development point of view, no research, straight to development you know. So they've tried everything. It's almost been like, have an idea, start a company, try it. They've spent, I can't remember the number now, but it's hundreds of millions of dollars have been spent on this and there's no animal data, no successful long-term animal data. They tried the Edmonton technique and it works in a few kids in Mexico but now all of those are back on insulin. There's failure after failure after failure. I think how it's going to eventually be cracked is by some developmental biologist working in some university, completely irrespective of trying to cure diabetes, looking at how the pancreas develops in the first instance. So that's, you know, basic developmental biology which in the first round of Regenerative Medicine was completely ignored. We were trying to make spare parts for a machine but we didn't understand how the machine was built in the first place. We're beginning to understand that now. So probably the breakthrough in pancreas is going to come from some weird serendipitous finding which is totally unrelated, and that's what academia needs to do, to have money to try the weird stuff, you know, not the applied stuff. Because it's going to come from some lab that you don't even know of like that Japanese group that reprogrammed the fibroblast. You would never have thought of that, no one would have guessed, they came from completely another way.

SaC: Left field, which is the classic way things get discovered by the MRC.

PK: Yes. And only universities can do that, only government money in universities will ever do that. And then there's the other aspect which is the nitty-gritty development, you know, like a shipping box, a box that can serve the whole of the industry. At the moment, the best maintained box can maintain its temperature for about 72 hours at most which is not long enough. So you've got to interfere with that box to recharge it which adds a huge cost. If someone could come up with a box that doubled that, maintained two or three degrees Centigrade temperature, doesn't matter what the temperature is outside—the box will maintain that temperature inside. If it could stay at minus two and three for five or six days that would be an enormous advantage. A quicker mycoplasma test. Things like that. Little, little bits. You know, not building a new car but coming up with a windscreen wiper. Those tiny aspects of it in practicalities, which is not the same as serendipitous basic research. So what's not needed is someone just having a thought about how we're now going to make a heart valve. Oh, maybe I'll make it out of ... and they come up with these crazy ideas, hardly any thought put into them, you know, do a little bit of research and try and come up with something that is massively complicated.

SaC: It's interesting because there's such a push for academia to be more goal orientated and yet in a way, what you're saying is that academia works best when it's lightly goal orientated and allowed to do things along the way that weren't expected.

PK: Yes, it works best in two regions. One when it's just left on its own, but there's relatively few scientists who can play in that arena. But also when it is, yes, goal orientated but the goals have to be really small goals, not big ones. And academics quite often think, well, if it's not a big goal, I'm not interested. You know, a little, a little thing and little aspect of the field. I think it's the same in other fields. In computers for example, I'll bet there are some people looking at how to develop a quantum computer that can have power way beyond anything we can imagine at the moment, and then there's people working on little ways of getting resistors to be cheaper. But no one in the middle trying to make

another Apple. That's done. And I think that's where our field's split into two sides, and the middle field is industry.

SaC: Right well that's, that's a model of innovation, exactly what we're looking for. Thank you very much for that. And thank you once again for giving us your time today.

Notes

[1]For further information on the current UK position concerning regulation of new biological products, see: http://www.hta.gov.uk/_db/_documents/Joint_Policy_Statement_on_Advanced_Therapy_Medicina_Products_v0_7.pdf.

[2]For a transcript of Dr Paul Kemp's lecture on the history of tissue engineering and its relevance for regenerative medicine today, see: http://www.regenmednetwork.com/archive/january_2006_meeting/january_2006_meeting.html.

[3]The Gartner Curve was developed as a means of theorizing 'cycles of hype'. See: http://www.gartner.com/pages/story.php.id.8795.s.8.jsp. The first cycle is generated by a 'technology trigger', followed by a sharp 'peak of inflated expectations'. This is followed by a 'trough of disillusionment' and a longer 'slope of enlightenment' culminating in a 'plateau of productivity' when a technology becomes increasingly stable.

[4]For further information about the Harvard Stem Cell Summit, see: http://www.hsci.harvard.edu/files/Summit%20agenda%20for%20web.pdf.

[5]See http://www.axordia.com/andrews/index.php.

[6]For example see: http://www.celent.com/PressReleases/200710252/Zertifikate.htm.

[7]See http://www.dermagraft.com/.

[8]There are over 100 recognized species of the genus *Mycoplasm*, a procaryote with a high resistance to antibiotics. They are characterized by a lack of a cell wall and are implicated in many diseases. They are a frequent source of contamination in research laboratories and in cell lines but they are difficult to detect. Mycoplasma tests include agar plating, PCR, and DNA staining but these are costly and time consuming. The market for mycoplasma assays is growing rapidly due to the frequent requirement to test for this form of contamination as well as bacterial or fungal contaminants. See for example: http://www.bioreliance.com/mycoplasma_testing.html.

[9]See further: http://www.bmj.com/cgi/content/extract/335/7627/955-a.