DDT Vol. 7, No. 1 January 2002

# James Gimzewski discusses the potential of nanobiotechnology

Interviewed by Rebecca N. Lawrence

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**James Gimzewski has won many awards including the 1997 Feynman Prize in Nanotechnology for Experimental Work, the 1997 Discover Award for Emerging Fields, the 1998 Wired 25 Award from *Wired* magazine, and the Institute of Physics 2001 Duddell Medal and Prize, as well as holding two IBM Outstanding Innovation Awards. He also co-foundered the Institute of Nanotechnology, is a Fellow of the Institute of Physics and the Royal Academy of Engineering, and is on the Board of Editorial Reviewers for *Science* magazine.**

***Tell me a bit about your background and how you moved into nanotechnology.***
I joined IBM 19 years ago in the research division. There had just been a new invention in the laboratory called the scanning tunnelling microscope, a new type of microscope that could see atoms for the first time using sensors rather than optics, and which led to the Nobel Laureate for Physics for Heinrich Rohrer and Gerd Binnig in 1986. After this initial discovery came another technique using silicon cantilevers – these are very thin and have a length of typically 200 μm and a width of 1 μm. When they bend, the tips of the cantilevers can interact with a surface, generating a very small force (in nanoNewtons) that can be detected and recorded. From this, we became interested in trying to make biochemical sensors that would enable us to do chemical analysis. Christoph Gerber (at IBM) and myself started to explore many different ways to transduce chemical signals into mechanical motion, including through the use of the atomic force microscope (AFM).

***You recently moved from being Group Leader at the IBM Zurich Research Laboratory to the California NanoSystems Institute at UCLA – what prompted you to move out of industry and into academia?***
I have always done exactly what I want to do and I have never followed any company directives. IBM was quite happy with that and I got a lot of my financial support from outside the company, especially from the EU and many European universities so I was more or less moving into a similar environment to university anyway. Furthermore, you do not get any intellectual property rights when working for such a large corporation. I also wanted a change and wanted to work with young people.

***What are the key areas in nanobiotechnology that IBM is focusing on for the future?***
Most of the research they are doing relates to the company's core interests. However, they also have an interest in using silicon-based microfabrication for biosensors and they have a strong intellectual property portfolio in this area. I guess they will probably continue in the same areas that I was working on, e.g. mechanical sensors, massive array technologies, microfluidics and contact printing (which uses an elastomeric stamp to print at a resolution of <1 μm). In Zurich, their main focus is probably microfluidics and elastomeric stamping, and the techniques that this involves such as micromachining and micromechanics.

***What are you currently working on at the California NanoSystems Institute (CNI) and what you have found so far?***
One of the nice things of being at the CNI is that I have much more opportunity to discuss things with excellent biochemists, chemists and life scientists and this has opened my eyes and my imagination. There are three areas that I focus on, the first one being individual molecule manipulation. I am just getting a 4°K ultrahigh vacuum microscope that will enable me to examine, for example, single drug molecules atom-by-atom and to manipulate the atoms.

The second area I am working on is with Digital Instruments (Santa Barbara, CA, USA) to develop multiple cantilever sensors into a commercial machine. Independent of this, I am working on a method to use these cantilevers to immobilize cells for proteomics sensors (we showed in IBM that they could be used in this way with immunoglobulin and protein A) and to examine their potential for use with different proteins [e.g. the recent paper in *Nat. Biotechnol.* [1] where they detected elevated levels of prostate-specific antigen (PSA)]. I think there is great potential here but the problem is that the mechanical signals are very small and the bending is typically in the order of 10 or 100 nm, which is not big enough if you want to make sensors that can be used outside of the laboratory. I am therefore working on a way to amplify this signal using light.

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The third area I am focusing on is utilizing carbon nanotubes. Just before I left IBM, I discovered a method to produce single-walled carbon nanotubes. These had been discovered by Richard A. Smalley (Gene and Norman Hackerman Professor of Chemistry and Professor of Physics, Rice University, Houston, TX, USA, and winner of the 1996 Chemistry Nobel Prize) many years ago but, typically, they looked like 'wet spaghetti'. However, we have found a way to make crystals of them that look like 'dry spaghetti', i.e. they are all perfectly straight, perfectly aligned and identical. My current project, together with Smalley and a grant from the US Department of Energy, focuses on immobilizing single cells on a cantilever and then using these cells as sensors, which can be done using these carbon nanotubes. Because the nanotubes are identical, you can immobilize biomolecules on the end of the nanotube (this has been done by Charles M. Lieber of Harvard University, Cambridge, MA, USA) and then insert it into the cell nucleus and probe for cell molecular recognition

 1359-6446/02/$ – see front matter  PII: S1359-6446(02)02067-0

events. This will take quite a number of years to fully develop but it is certainly a very interesting area.

***What do you think have been the key developments so far in nanobiotechnology?***
I do not think there has been something that has been revolutionary but rather more an evolutionary process. For example, you are starting to see the application of silicon microtechnology to biotechnology and the development of different types of biochips, moving on from the Affymetrix chips. One of the things that everyone wants to get away from is fluorescent labelling because miniaturization reduces the size of the fluorescent signal causing detection problems. There have been some exciting developments in this area, for example, using nanomechanical detection, but I do not know if this will be the ultimate method of detection.

*There are two key problems: translation/understanding and integration.*

The other key development I see happening is concerning single cells and I really believe strongly that carbon nanotubes will provide the ideal probe for this. These nanotubes can go down in diameter to 1 nm, are stronger than any material in the universe and can be any length. The AFM is a beautiful example of an experiment where people have demonstrated the mechanical activity of cells.

We are now increasingly seeing nanoscale scientists and biologists working together to develop machines that both biochemists and biologists can use. This nanoscience field is becoming really exciting as we are moving away from it being just a world of physics. Initially, I think nanobiotechnology machines will be developed for large pharmaceutical companies, but after this, they will develop technologies appropriate for smaller companies.

***What are the current key problems and obstacles in this field that you think must be overcome before we can get to the next stage?***
There are two key problems: translation/understanding and integration. With regards to translation and understanding, people (e.g. biologists and nanotechnologists) are still talking different languages so we need to work on trying to get them to have a common understanding. Groups such as the CNI are based on the concept that these people are together physically in the same building.

Then there is systems integration. For example, biologists have a great understanding at the molecular and cellular level while other groups have great expertise in say lasers, optical wave guides, lithography, etc. We need to bring these groups of people together and integrate their technologies. That has been done in some places, e.g. at Oak Ridge National Laboratories (Oak Ridge, TN, USA), where they have just opened a national nanotechnology facility. This facility can be used by all US university researchers and is based on the premise to develop a facility where people can go from, say, silicon fabrication right through to biofunctionalization, i.e. it is not just used for information technology. These silicon fabrication-type technologies might still be crude compared with computer chip technology but as they will be directed towards the biotechnology area, there might be specific things from the point of view of biofunctionalization that silicon is not currently optimized for.

However, to get systems integration, we probably need to train a new generation of scientists. One of the reasons that I am at the University of California, Los Angeles (UCLA) is that I hope that we, and many other places in the world, will develop people who are optimized to think differently from the first generation through the establishment of nanocentres. The UK Government has provided key UK universities with £20 million to do this, and similar things are happening in other countries, for example, at the University of Basel (Switzerland).

My work is therefore, if you like, 'parasitic'. It very much reminds me of the early days of synchrotron radiation where a few people, including myself, were using a synchrotron that was designed for high-energy physics experiments for electron spectroscopy (which uses much lower-energy radiation). At the time, we were treated like dirt. However, today, we have all these synchrotron facilities around the world that are optimized for this very purpose and even for X-ray diffraction experiments in biological systems. I therefore think that once you actually start to set up such systems that are dedicated to biotechnology, we will really start to see the commercial possibilities.

***What impact do you think nanobiotechnology could/will have on the biotech and pharma industry?***
I see the ability to fabricate massive arrays in small spaces using microfluidics and the ability to improve time efficiency through further miniaturization. I also foresee being able to directly read the signals from microfluidics circuits in a manner similar to a microelectronics circuit where we do not require massive instrumentation. This would mean that we could do drug screening at a much higher level. For example, Vincent Gau (Chief Technical Officer, GeneFluidics, Beverly Hills, CA, USA) is currently doing some work on STD screening at doctors' surgeries. At the moment when you go to the surgery, you see the doctor, they take a urine sample, and then it takes several days to get the results. However, in the future, the patient could give the urine sample when they first arrive at the surgery and the results could then be ready by the time they go in to see the doctor. They could then be given the prescription immediately, reducing the length of time worrying for the patient and making the whole process cheaper.

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From 11 September 2001 onwards, it has become apparent how little we know about our environment, particularly biochemically, and so there is a tremendous need for biochemical sensors that are cheap, small and disposable. For example, say 20 years ago, people talked about the smoke detector as a new device, but today, it is a legal requirement in a restaurant for there to be a smoke detector. I can quite easily see that in the next couple of years, it could become a legal requirement to have a biodetector in a restaurant (e.g. to analyze say *Escherichia coli* in food) and in any public place, which can be used by uneducated people and that will detect the presence of viruses and different types of hazardous material. If this happens, it will become a very big business. I think we already have all the tools required lying around in laboratories but they need to be put together and this requires systems integration.

***What do you think we can learn from living organisms that will help us in our endeavours to develop new biological applications for nanotechnology?***
I find the cell, in particular, very fascinating: it is a little autonomous unit that exists in a liquid and, if you take a stem cell and put it in a liquid and add some goodies, you can turn it into anything you like. The ability to work with this individual cell using nanotechnology is very exciting and there are already many groups in the US working on this. The single cell is an ideal sensor for detecting various chemical and biochemical processes, and the genetic manipulation of cells could then be done through mechanical rather than biochemical means.

*I do think that smart drug delivery is an area where nanotechnology will play an extremely important role.*

In the living system on a larger scale, there has long been the concept that can you make smart drug delivery systems that can integrate with the human body and I think these types of things will come with time. However, when we first did our work with the cantilevers where we could detect a signal from SNPs, a newspaper called the *Bild* printed a front page story saying 'IBM creates nanobots that can cure cancer' with a picture of them swimming inside the human body and describing it as having a cancer-killing unit that used lasers to 'blast away' the cancer cells. Unfortunately, this led to many people phoning us up from around the world asking how to get some of these nanobots and so we now try not to talk about what we are doing very much. However, I do think that smart drug delivery is an area where nanotechnology will play an extremely important role – even time-release tablets (which have a relatively simple coating that dissolves in specific locations) involve the use of nanoparticles, so drug companies are already involved in nanotechnology in some way. I think there is tremendous potential for using nanotechnology to create intelligent drug release devices. For example, control of the interface between the drug/particle and the human body can be programmed so that when the drug reaches its target, it can then become active.

Unlike the silicon-based microfluidics devices I mentioned earlier, the use of nanotechnology for drug release devices requires autonomous device operation. For example, in contrast to converting a biochemical signal into a mechanical signal and being able to control and communicate with the device, autonomous device operation would require biochemical recognition to generate forces to stimulate various valves etc. in the drug delivery systems, and is therefore completely out of our control.

***As investors tend to view advancements in the field as still being a way off, how do you think we can best entice them to invest in this area?***
I think one way to entice them is to get small start-up companies to be funded at the Government level so there is a really strong incentive for people, particularly graduate students, to set up new companies. This already happens at UCLA and Stanford University and is really quite a big thing here. I do not think large pharmaceutical and silicon companies are particularly interested. They have efforts in nanobiotechnology but they are not really wanting to develop a prototype device for the market; they would rather have another small company develop it and then just buy it up if they want it.

There are many small start-up companies out there. You can expect 90% will fail but one of the 10% that get through could be, for example, the one that develops an anthrax detector that you can buy for US$10 and, at the moment, everyone would buy one. In the UK and Europe in particular, there is a real problem that investors do not want to invest in things where 90% go bust; however, they should be looking at the fact that 10% of them are really going to make some money. In time, the odds might improve as there will be an establishment of companies that are really making it big. However, especially in the UK, I am not sure how you train young people such that they really want to create start-up companies as there is a much more conservative feel to investment. It is also maybe the responsibility of the pharma companies to invest – they already do in a way, but it is in a very roundabout way through the back door.

***Why was the Institute of Nanotechnology set up and what does it hope to achieve?***
The Institute of Nanotechnology (http://www.nano.org.uk) was founded a few years ago by Ottilia Saxl who was involved at the time in technology transfer and part of its remit is to focus on the problem of how to get investors to put money into this area. We had discussed the idea of setting up an institute but many people were very sceptical about it because they did not want to even talk about nanotechnology in the UK at the time (it was almost treated as a 'dirty' word). This is because scientists are so conservative – there were people working in biotechnology, physics and chemistry and then came this new technology that was not in their area and so they said negative things about it. Then, when it becomes successful, suddenly they all transform themselves into nanotechnologists and start giving talks on nanotechnology.

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We started the institute with a lot of forward-thinking people like British Telecom, Seagate and others who were interested in nanotechnology, and it now includes an Institute of Nanotechnology Europe. The institute developed over a long time gathering a database of information, experts, expertise and developments. It is really a virtual institute and has created one of the best databases in nanotechnology. It tries to encourage nanotechnology propagation and companies that are interested in using or developing nanotechnology can join and get advice from experts. There are also increasingly large corporations such as ABB joining (they are one of the large heavy engineering companies making transformers and big motors – they are trying to find a new business area as there is much less money in their old core areas now). The European Board of the institute (of which I am paradoxically the Chairman) contains a variety of people including some from ABB and the European Commission.

Saxl has also started a nanotechnology institute in Australia. In the USA, there is

currently nothing yet so we are trying to make the right connections for funding this. One has to remember that the US is probably the most recent group to become involved in nanotechnology. It is a strange historical twist but it goes back to the Californian, K. Eric Drexler, who wrote a book called *Engines of Creation: The coming Era of Nanotechnology* (http://www.foresight.org/EOC/index.html), which is a fantasy-based book of things such as nanosubmarines and the idea that you can put dirt into a microwave-looking machine (an Assembler) and a hamburger would come out.

*Unfortunately, the Europeans are not always on the ball when it comes to money but they have some very good ideas.*

When he published the book, the US public and even Congress became very interested in this concept. The initial attitude to nanotechnology was negative, particularly in the USA, to the extent that if you put the word 'nanotechnology' in a proposal to the National Science Foundation (NSF), it would probably not get funded. At the same time, in Europe, the EU was busy funding nanotechnology and the Japanese were also heavily involved in trying to develop nanotechnology. It is only since Bill Clinton in the *State of the Union Address* announced that the NSF would provide US$500 million in funding for nanotechnology and talked about the importance of nanotechnology that the US went nanotechnology-crazy. Certainly, the US has now established themselves extremely strongly and if you are thinking of making money out of nanotechnology, California is the place, as people here have a great capability for making money out of anything. Unfortunately, the Europeans are not always on the ball when it comes to money but they have some very good ideas.

***Do you think we will just continue trying to create increasingly smaller systems?***

I think it is the other way around actually. I always thought of making things smaller and smaller and I think we can make things today that are really small. We can manipulate an atom and we can move an atom around but a few atoms jiggling about is not much good for society. Integration is therefore key, and so the task now is to work from the bottom up, i.e. from molecules to cells; from the atomic switch to the integrated circuit.

It is almost like Horizon Mission Methodology, where we think of what we want, and then we work out how to pull all the pieces together to achieve that. In fact, we are called the California NanoSystems Institute rather than the California NanoTechnology Institute because the nanotechnology is only the way you do specific things but the systems and the integration of the nanotechnology to make the systems is where the money and the future lies. We also need to get away from the concept of just miniaturizing because, the smaller things get, the more expensive they become. We are therefore moving away from the philosophies of microelectronics which is essentially where miniaturization came from, and which was driven by the need to produce more and more transistors at cheaper and cheaper prices. In biotechnology, we are going to see a paradigm shift towards making things faster, cheaper, more efficient and better.

*The systems and the integration of the nanotechnology to make the systems is where the money and the future lies.*

***What would you like to have achieved by the end of your career?***

I would like to see nanotechnology in our society in a role where we can see real societal benefit. My dream is that nanotechnology could reduce fear in the world through medical applications and personal security as this is the one thing that is a really negative element in the world.

## Reference

1 Wu, G. *et al.* (2001) Bioassay of prostate-specific antigen (PSA) using microcantilevers. *Nat. Biotechnol.* 19, 856–860

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