The Nobel Factory

or

what makes the LMB special

This is a lightly-edited transcript of a talk I gave in Malaysia in November 2011. The views expressed are my own, and do not necessarily reflect those of the LMB or the MRC. The slides I used were only for decoration, and aren't necessary in order to follow what I was saying.

The title, "Nobel Factory", is a nickname that the LMB has been given in a few newspaper articles. Although it's rather immodest, it is accurate: the LMB has produced more Nobel laureates per square foot than any other institute in the world, as far as I know.

There have been over a dozen Nobel prizes awarded to members of the LMB over the last sixty years. History is very much *not* my strong suit, so I'd urge you (or others who are reading this) to refer to the LMB Website (www.mrc-lmb.cam.ac.uk) for exact dates and so forth. Also, my apologies for anyone whose dates or achievements I've mis-stated or missed out!

A brief history of LMB

The LMB has its roots at the Cavendish laboratory (the physics department) in Cambridge just after WWII. We were very lucky to have a handful of key people (perhaps four or six) in Cambridge at the time. These pioneers were amongst the first to realize that biology could be approached from a molecular, mechanistic approach – to actually "see" the machines that did the work in the cell. Until then, the closest anyone had come to this was biochemistry and genetics, which deal with the processes (enzyme kinetics, patterns of heredity...), but with no knowledge of the physical entities that do these processes.

So, these few early people realized that *all* the biological questions could, perhaps, be examined in a different way. Suddenly, there was the realization that you could not claim to understand something until you could visualize the molecules involved, and see them at work. *Everything* in biology was suddenly new and unexplored. It was not like discovering a new continent (which, inevitably, is a bit like all the other continents); it was more like realizing that you could walk around behind the mirror and find an entirely new angle on the world.

Chief amongst these pioneers were the Austrian physicist Max Perutz, John Kendrew, and Francis Crick (again, a physicist; all were working on developing X-ray crystallography for complex biological molecules). These people were formally brought together on the Cavendish site under a new "MRC Unit for the Study of the Molecular Structure of Biological Systems" formed in 1947 at Max's request. They were joined in 1949 by Francis Crick, and in 1951 by Jim Watson.

In 1953, all these lines of research bore fruit. Perutz found the way to examine protein structure using X-rays, Huxley discovered that muscle contracts by having protein filaments that slide past each other, and Watson and Crick discovered the double helix. Of course, none of these people worked in isolation, and Watson and Crick in particular benefitted from the contributions of others including Rosalind Franklin and Maurice Wilkins, but it is fair to say that the key breakthroughs were made in the Unit.

Over the following years, more key people joined the unit (which was renamed as the "MRC Unit for Molecular Biology"), and more successes followed. Vernon Ingram discovered the molecular basis for sickle-cell anaemia; Sydney Brenner joined the unit and, along with Crick, Watson and others, helped to define the "central dogma" of molecular genetics – "DNA makes RNA makes protein" – and to unravel the details of the genetic code. Many of the basic elements of molecular biology (such as mRNA) were discovered there – this was a tremendously exciting time!

In 1962, the Unit moved to a new and larger building, and I was born (though I don't think these events are related!). The Unit was renamed "The MRC Laboratory of Molecular Biology". Fred Sanger (who had been in the biochemistry department of the University and had developed ways to read the amino-acid sequence of proteins) and Aaron Klug were among some of the notable people to join the lab at or around this time. In the same year, 1962, the Lab won not one but *two* Nobel prizes. Kendrew and Perutz won the Chemistry prize for their work on protein structure, and Crick and Watson won the Physiology or Medicine prize for their work on DNA. This gave the Lab a tremendous boost, and set it on a solid footing.

Over the following years, more of the growing numbers of molecular biologists joined the lab, making many of the most fundamental discoveries about proteins, nucleic acids and how they worked. Nobel prizewinners included Fred Sanger in 1980 (his second Nobel, this time for inventing RNA and DNA sequencing), Aaron Klug in 1982 for crystallographic EM, and Cesar Milstein and George Kohler in 1984 for the invention of monoclonal antibodies.

At around this time, I joined the lab as a research assistant during a 'gap year' between my first degree and my D.Phil. It will give you some idea of the character of the lab if I tell you a little about my "interview". I arrived, a fresh (well, fairly fresh) young student, in a new suit and tie and with my hair nicely combed. I was to be interviewed by the Great Man, Sydney Brenner (the Director at that time), and I expected to be ushered into a large wood-panelled office by his secretary.

Instead, someone in a lab-coat pointed me towards a tiny office the size of a phone-box, where I was greeted by Sydney. He was wearing Bermuda shorts and a rather garish Hawaiian-style shirt, making my suit somewhat out of place! Later that day, Sydney and I were talking when an old guy in a crumpled suit walked past. Sydney said "Hi Max", and this rather scruffy person said "Good efening" to us in a polite Viennese accent and walked on. I assumed (since it was in the evening now) that this guy was a security person, or perhaps some sort of maintenance man. I asked Sydney who it was. "Oh, that's Max. Max Perutz." This was another of the legendary figures I'd learned about as a "founding father" of molecular biology, and he was just in the lab doing his stuff like any other scientist.

Anyway, Sydney kindly took me on, and I wound up working with Greg Winter. The original plan was to rotate me through various labs so that I could pick up a variety of skills, but in the end I stuck with Greg. He was just then developing humanized antibodies - antibodies which are raised in animals, but for which the genes are then modified so that they are more "human like", and are easier to apply therapeutically. I spent most of my year building the first synthetic antibody gene. Nowadays, you can just email your gene sequence to a company and they'll make it for you in a week; but in those days the tools were less advanced and this was the largest synthetic gene anyone had made.

After my year at LMB, I went to do a D.Phil and then a post-doc in Oxford, and returned to the Lab in 1992. Greg was doing pretty well by then (!), and humanized antibodies were the first in a long line of antibody-like molecules which have gone on to be of tremendous therapeutic importance. Several of the world's top 10 pharmaceuticals (in terms of annual turnover) derive directly from Greg's work.

Shortly after my return, John Sulston and others invented genomics. That's a slight exaggeration, but not by much. They and others at the Lab had been studying the nematode, *C. elegans*, and now started a project to read its entire genetic code – a project unthinkable a few years before. As this work became larger in scale, it outgrew the Lab, and they moved to nearby Hinxton to establish the Sanger Centre. The Sanger Centre was later to contribute something like 40% of the sequence in the Human Genome Project, and many LMB scientists were central to this effort.

More Nobel prizes followed, including John Walker (1997) for work on the structure of ATP synthase (the cell's power-house), John Sulston, Sydney Brenner and Bob Horvitz for their work on *C. elegans* - actually there's an interesting story there, concerning the human genome project, and American called Craig Venter and some delicate politics, but I'd best not go into that - and, in 2009, Venki Ramakrishnan was recognized for his major role in understanding the eukaryotic ribosome – the cell's protein factory. I know that others at the Lab will be Nobel prizewinners over the next few years and beyond, and I'm also sure there are some laureates who I've forgotten to mention.

<u>So, what is it that made, and continues to make, the Lab so successful?</u>

Most of the LMB scientists would agree, more or less, on several factors as being key to the Lab's success. History is of course one of them – the Lab was fortunate to be born at the dawn of molecular biology, and was doubly fortunate to have those few, key people together in the right place at the right time. Unfortunately, it is difficult to re-create this history, in Malaysia or anywhere else! But other factors were responsible for the continuation of this early good fortune.

Shared resources have always been integral to the Lab, following on from the early days when the Lab consisted of a handful of like-minded people who had a common focus and naturally shared their resources, equipment, reagents and knowledge. Today this extends to all the facilities in the Lab.

Core funding is a tremendous help, not only because it makes people less possessive of their "own" equipment or reagents, but because frees researchers from the need to pursue grant-funded work which will give a quick return. Long-term support has underpinned many of LMB's successes. Researchers are also free to bring in grant money, but core funding supports much (maybe most) of the research and unites the Lab.

Central facilities are excellent, and freely and immediately accessible to all. They range from flow cytometry and mass-spec through to media prep and glasswashing. They also include mechanical and electronic workshops, which routinely make novel items for researchers, and which have produced the prototypes of many of the instruments that are now taken for granted in labs worldwide. The LMB is fortunate in this respect, since we have probably the most advanced workshops of any biology lab in the UK.

Small groups and hands-on group leaders. LMB groups are very small by today's standards – typically 3-6 people including the group head. Many group heads (though, sadly, fewer today than in the past) work at the bench alongside their postdocs and students; and all of them are very intimately involved in the research in an immediate, "gel-by-gel" way. Projects which become too large to be handled by small groups are sometimes given additional space and manpower for a time but then, like the nematode genome project or humanized antibodies, tend to move out to flourish elsewhere in academic or commercial settings.

Little paperwork. LMB scientists are notoriously averse to paperwork and bureaucracy, and the Lab frequently does battle with MRC Head Office to keep the lab as paper-free as possible. Necessary paperwork is handled, as far as possible, by administrative staff who are there, first and foremost, to let the scientists get on with their work – science. Most LMB scientists will feel that asking them to fill in more than one form per week is unreasonable!

On the same topic, our purchasing system is very good (although we still complain about it!). This may sound like a minor point, but I have to emphasize that this apparently simple thing is *absolutely essential* to good science. I (or anyone else at LMB) can order what I need almost as easily as making a purchase from Amazon. If authorization is needed (for more expensive items), that authorization is done electronically by one person, and usually within a few hours of the order being placed. Typically, I can order something on Monday it will arrive on Tuesday or Wednesday; if it's not there by Thursday I will feel that something is wrong.

I stress this point, because I know things are very different in Malaysia – scientists here frequently tell me that it takes endless paperwork and negotiation to place even a small order, and that this can take *weeks* rather than hours or days. If an order that should take 2 days to arrive takes, instead, 28 days, then 26 days of science have been lost.

But it is not *only* that a scientific career has been offset by constant 26 days. Science is cyclical – one experiment suggests the next, and needs new reagents. So, in practice, overall progress is slowed to a fraction of what it could be. Worthwhile science cannot always be planned in advance to allow for delays in purchasing, and I see this as one of the major (yet *simple*, *solvable*) problems for scientists in Malaysia.

(The problem is not unique to Malaysia – it occurs also in many UK and US universities. But these universities are often not amongst the Nobel awardees, and problems such as this are a major contributor.)

Absolutely no hierarchy. I've already mentioned my casual interview with Sydney Brenner, and this complete informality is typical of – and essential to – the Lab. I have *never* heard anyone addressed as "Dr. So-and-so" within the LMB – it's always "John" or "Barbara" or whatever. Respect and status within the Lab comes entirely from scientific excellence and a good brain, and must be maintained in the same way. A PhD student in LMB has no qualms about stopping a Nobel laureate or a Divisional Head in the corridor to ask them about something. Equally, if the laureate or Head suggests something which is dumb (and this can, of course, happen), the student will feel free to say why it is dumb! *All scientists within the lab are equal* in this way; some are smarter than others or have had greater successes, but there is no 'culture of status'. This extends not just from Heads to PhD students, but also embraces the technical support staff, many of whom are superb scientists in their own right; they are as involved as anyone else in discussions about the science.

Of course, this cuts both ways – the Nobel laureate may tell a PhD student that their idea is dumb! But at least the student knows that they're on a level playing field, and the laureate had better have a good reason for his opinion.

The only thing that matters is the science. All of the above points, really, can be summarized by this statement. Once you accept this philosophy, everything else follows as a necessity.

<u>Factors that can work against success.</u>
Although the previous slide covered some of the necessary factors for success, it's also necessary to avoid some things that can stifle good science.

On focussed research and commercialization. Research in many places (including many institutes in the UK and also in Malaysia) is shaped by very focussed funding calls and 'strategic plans'. Focus on important areas is good and necessary, but it is not often a way to generate new, Nobel-quality science. Focussed research, almost by definition, concentrates on fields where the need is already known and the outcomes are predictable. It's like setting up an oil-rig in an established oil field – you know the oil is there in quantifiable amounts, and it's a question of sharing it with the oil-rig next door and getting it out of the ground.

What is needed, besides the oil-drillers, are people out looking for new oil fields. For this reason, it is essential that good, long-term support is given to "prospectors" – scientists whom you trust to do good work and to shape their own research. You cannot tell in advance which of these prospectors will discover a new oil field, but you can at least trust them to be good prospectors, and you can be confident that some of them (not all!) will strike a new field. It is, at root, a question of identifying good people and then trusting their instincts; if you were able to identify the problem and know where to look for oil, you (and others) would already be drilling there.

And, to the extent that *some* funding should be targetted towards areas of immediate value, you have to ensure that your "oil-rig workers" are not pulled this way and that, by changes in direction every two or three years. Even targetted research needs a measure of stability if it is to bear fruit.

LMB does shape the research that its scientists do, but with a light touch. Emphasis may be placed on certain broad areas of research but scientists, once appointed, are free to wander widely within those areas. Also, commitments to research areas are made on a timescale of decades, not years.

Turning to commercialization (a related topic) I would *like* to be able to tell a nice and simple story, and to say that the LMB is a "pure research" lab – an ivory tower – and that commercial success happens as an accidental consequence of good science. This makes a convenient 'morality tale', but it is not entirely true.

People like to cite the fact that the MRC did not patent monoclonal antibodies, which now have worldwide sales in the billions of dollars. But, it was the *scientist* – Cesar Milstein – who argued that they could be commercially valuable and (to their shame) it was the MRC that disagreed. Since then, the lab has had tremendous commercial success – LMB patents bring in around £300 million (1.4 billion Malaysian Ringgit) per annum to the MRC. This is most of the MRC's commercial revenue (despite the fact that LMB is only one of many MRC Units) and is ten times greater than the running costs of the LMB. This has come about largely because LMB scientists have seen the importance, both scientific and commercial, of their discoveries. Foremost amongst these scientists is Greg Winter, whose antibody-related patents bring in the lion's share of the money.

However, having told the true story – a warning. It is very easy to see the commercial success of LMB, and to believe therefore that Malaysian science should aim for the big money. This is a terrible mistake – it is like trying to build only the tip of an iceberg.

The great commercial successes of LMB have all – without exception – stemmed from a long history of basic research. The science has been done because it was *good science* and *important science* – commercial success followed. Once again, it is a matter of trust. Trust the scientists, trust the science, and commercial successes will follow. But they may come from research that, at the outset, had no indications of this result.

On fashions and buzzwords. Hand in hand with "targetted research" go buzzwords and fashions. Like targetted research, these buzzwords often have value, but only if they are used wisely.

"Interdisciplinarity" and "collaborative" are examples of these fashions. Both of these are essential components of much (*but by no means all*) good science, and it is good to foster them. But, when scientists are put in the position of having to dream up a contrived "interdisciplinary" or "collaborative" research project simply to meet the funding criteria, things have gone terribly wrong. If collaboration and interdisciplinarity can help the science, then it is the scientists who will ensure that they happen, and who will identify the precise needs and opportunities. Funding bodies and policymakers must facilitate and enable, but collaboration and interdisciplinarity are a means, not an end. In the UK and in Malaysia, many scientists struggle to find "a physicist" or "a nanotechnologist" or "an overseas collaborator" not because they need them, but simply because the funding body says they must have one on the grant.

The same goes for all of these buzzwords and fashions. There is often value in what they represent, but the realization of that value must come from the bottom up, not from the top down. If a strategist could identify the fruitful collaborations, or the fruitful union of two disciplines, then they would be doing the research themselves.

What makes a good LMB Scientist?

If I've been at all successful in identifying the key factors that make the Lab successful, this is only half of the story. The scientists, of course, make the lab what it is.

It is far harder to define what makes a good scientist. Let me start by saying, though, that I have begun (in the last two or three years, out of the ten years over which I've been visiting Malaysia) to notice a subset of scientists here who are "good scientists". It's very hard to define, but one scientist can immediately tell if someone else "gets it" – if it "clicks". Such people are small percentage of the scientists in *any* country, but Malaysia has them and, if the necessary environment is provided, a few of them will go on to become great scientists.

But, turning back to the question of LMB scientists, my views on this are personal and perhaps other people would identify different qualities.

> **They pick important problems**. Not always problems of known and immediate utility (like finding a treatment for a specific disease), but *important* problems - problems that have very far-reaching consequences. Sometimes they are problems of medical relevance, or problems of enabling technologies, but at other times they are seemingly simple problems of basic science, such as how cells organize themselves in space to make an animal. That is an example of a very deep mystery; knowing the answer may not cure cancer tomorrow, but its impact on biology will be far reaching. Good science is not about finding answers – it's about asking the questions. Once a scientist latches on to such a question, their ingenuity and hard work will get them to the answer.
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> **Arrogance and selfishness,** which might more charitably be phrased as "self-assurance and single-mindedness", are also key to the personalities of many successful scientists at LMB and elsewhere. They trust in themselves – they know that the question they are asking is important, and that they have the ability to find the answer. This in turn makes them value their work to the extent of resisting anything that gets in the way (paperwork, meetings, teaching...). Of course, this is true of them as *scientists*, not as human beings. Of the great scientists I have been fortunate to know, most are considerate, modest and generous of spirit. But, in their research they have a tremendous self-confidence and will let nothing stand in their way. I should also mention that LMB scientists do not teach; they have been chosen for their talent in research, and are free to pursue this completely. Good research needs long, long periods of uninterrupted time to think and to work – even a modest teaching or administrative load interrupts the processes of thought and work.
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> Of course, confidence and single-mindedness do not guarantee that they are right. Yet, without them, there is no prospect of tackling difficult questions, or of persisting through years of work. If you have a fast car, it's often better to just drive somewhere than to sit in the car-park waiting for a map. Even if you don't get where you wanted to, you'll get somewhere new.
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> In the context of Malaysia, my perception (which, perhaps, is partly a stereotype but is also partly true) is that very few scientists have this complete confidence in themselves. Young lecturers here, some of them very smart indeed, often ask me if I think their research is good, or worth doing. I know much less about most areas of science than the people who ask for my opinion of their research.

I know also that Malaysia as a country looks to Western countries for affirmation that its science is going in the right direction. This is sad because, whilst there is much to be learned from how other people do science, some of your young scientists are entitled to be more self-confident – a certain amount of ego is necessary to get anywhere in science. "Malaysia boleh!" is a national motto, but somehow this confidence is not sustained in the scientists. Perhaps it will come with time, and it should be fostered. When a Formula 1 team sends its driver out, he is representing the work of a large number of people; but, in the race, he is the one who must have self-assurance and confidence – both from himself and from the team that has put him there.

Interdisciplinarity. I said earlier that "interdisciplinarity" is one of those buzzwords that can smother science, but also that it is an essential component of much (not all) good science. LMB scientists, on the whole, are very open to crossing the boundaries between disciplines.

Most importantly, though, they often learn the new discipline themselves, rather than relying entirely on experts from other fields. This is an important aspect of successful interdisciplinarity. When two people from different disciplines meet, there can be a very fruitful exchange of ideas. But the *greatest* ideas emerge when one person masters both disciplines, at least to a degree. The reason is that some ideas cannot be "created" between two people, unless each has an intimate knowledge of the other's field. The nanotechnologist doesn't know that his technology can solve a particular biological problem; and the biologist may not know that the nanotechnologist has a trick that can solve the problem. As a result, the two ships can sail past without appearing on each other's radar. Often, it's necessary to have all the ideas *in one head*, before the connections can be made – communication doesn't work well until people know what to communicate about.

So, LMB scientists typically dip into other fields and, if they find something interesting, they will master that new field enough to understand what it can do. The development of those ideas may then become truly interdisciplinary and involve experts from both fields, but the initial ideas come from one person being familiar, to some extent, with both disciplines.

I don't know how easy it is for scientists in Malaysia to "dip into" other fields. In LMB it's very easy – if I decide I need to know more about lasers, or microfluidics, or electronics, I am free to pursue that without someone saying "stick to biology, and leave those subjects to the experts".

The science is all that matters. I used this phrase in summing up the way the Lab is run, and it's also the essence of what makes the scientists. To them, the science is all that matters. It is *that* which gives them the ego they need to tackle difficult problems; it is *that* which makes them develop skills or collaborations in other disciplines. Everything follows from this simple idea.

LMB Now, and a warning.

LMB is about to move into a new and wonderful building, and the next few years will be very interesting. Personally, I am interested to know if the ethos of the lab can be transplanted – I hope it can.

I know that Malaysia looks to the UK and US as models for good science and, because you have been kind enough to ask me to give this talk, I know also that the LMB is taken as a specific example of good science.

But, a warning. Increasingly in the UK (and in the US, although I am less familiar with science there, personally), there is a disease in science. It is the disease of administration, of quantifiable deliverables, of evaluation, of focussed funding, of short-termism. It is the disease of "accountability" in place of "trust". We're very lucky in LMB to have resisted this tendency, but even here the first signs of the disease are perhaps beginning to show.

It would be a tragedy if Malaysia, where science is young and has so many possibilities, were to look to UK science and follow these very visible and negative tendencies. We, especially LMB, have succeeded not *because* of evaluations, constant policy-tracking and these other evils, but *in spite of them*.

LMB was lucky to have been there at the beginnings of molecular biology, and has preserved some of the best of the past; the same is somewhat true of UK science in general. But I do not believe that it is possible for Malaysia or any other country at the beginning of its scientific history to succeed unless it can follow what we do right, not what we do wrong.

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