Synergy in science: an interview with Neal Copeland and Nancy Jenkins

Neal Copeland and Nancy Jenkins – partners in the lab and in life – are world leaders in cancer research, mouse genetics and developmental genetics. In this interview, they recall the adventure of their joint career and discuss their views on current challenges in cancer research.

Neal Copeland and Nancy Jenkins are perhaps the most synergistic couple in science: since meeting during their postdoctoral training in 1977, they have worked together to advance research at four different institutes, co-authored over 780 papers and given rise to dozens of successful new group leaders through their dedication to their trainees. Their earliest work together at Harvard Medical School focused on retroviruses, but they soon became experts in the then-cutting-edge discipline of molecular biology. They brought this expertise to their first career appointments at The Jackson Laboratory (JAX), where they helped to make great leaps forward in mouse genetics before moving to the National Cancer Institute (NCI), where they spent 22 years working on various projects in developmental genetics and cancer. In 2006, they moved to the Institute of Molecular and Cell Biology in Singapore, where their primary focus was to carry out a large-scale transposon mutagenesis screen to identify cancer-causing mutations in mice. In 2011, they returned to the United States to continue their work at the Methodist Hospital Research Institute. They have no plans to retire as yet.

What encouraged each of you to follow a career in science?

Neal: Both Nancy and I had fathers who were MDs, and we had both planned to follow the same path. At some point, though, each of us realised that medicine in the United States at that time was changing – it was becoming more bureaucratic. So, independently, we each made the decision to go into science – something we each had a real passion for – rather than into medicine.

"…if you can survive in science, it's the best job there is. You're running your own show – you're like an entrepreneur"

Nancy: The attractive thing about medicine to me was learning all about it, but not practising. I thought that doing research would be more exciting, because you could learn and do something different all the time. Little did I know how hard it would be though! And I think it's much harder now than it was when we started out. It's still doable, and I really hope that we don't lose a whole generation of great scientists due to the funding mechanisms being so constrained at the moment (at least in the United States). It's definitely a concern for the future.

Neal: But I think that if you can survive in science, it's the best job there is. You're running your own show – you're like an entrepreneur, really. You can set your own hours and work on whatever you want (provided someone will fund you). You're not tied to an office – you get to travel the world, and meet lots of wonderful people. Looking back, we wouldn't have done anything differently. It's been quite the adventure.

Early on in that adventure, your paths crossed. How did that come about?

Nancy: We ended up in the same lab at the Dana Farber Cancer Institute as postdocs, working on similar things – we had exactly the same interests. That can be terrific or terrible, depending on your point of view.

Neal: Eventually, we decided to get married, and we had to decide where to go, and whether to run two separate labs or run one lab together. This was in 1980, and women were still not at the top in science. Married couples didn't commonly get jobs in the same institute the way they do now. We decided that if we ran separate labs, we would start competing against one another and probably wouldn't stay married for very long! So, we decided to run a lab together and split everything 50-50. We decided to publish all papers together – not to worry about whom was last author, but just to go back and forth. I think if we had run separate labs, we probably would not have been so successful and would have been divorced by now. Anyway, we applied to several places and got an offer from JAX.

At that time, that was considered an unconventional path and a very risky decision. What made you decide to go there?

Neal: That's true. All of our colleagues at the time told us we'd destroy our careers if we went there – that we were crazy to consider it.

Neal Copeland and Nancy Jenkins are Senior Members of the Methodist Hospital Research Institute and Co-Directors of the Methodist Cancer Research Program. Neal Copeland is also Dean of Cancer Biology, and Nancy Jenkins is Dean of Genetics, at the Methodist Academy.
e-mails: ncopeland@tmhs.org; njenkins2@tmhs.org

Nancy: But there was one person that supported our decision: that was Gerry Rubin, a famous *Drosophila* geneticist, which I think is very telling.
Neal: At that time, Gerry was the youngest ever Assistant Professor in Harvard, and he was in the lab next door at Dana Farber.
Nancy: He was interested in using transposable elements to tag genes that could then be cloned – basically, he was doing forward-genetic screens in flies.
Neal: Gerry Rubin was trained in molecular biology, and he helped train Nancy and me, and we began studying retroviruses using some of these techniques.
Nancy: We decided that it would be interesting to use retroviruses as insertional mutagens in mice – similar to what Gerry Rubin was doing with P-elements (a type of transposable element) in *Drosophila*.
Neal: Most mouse geneticists at that time had *Drosophila* envy, because you could do so many great things in flies that you couldn't do in mice. We wanted to do fly-like experiments in mice – and to do that, we needed to learn mouse genetics.
Nancy: But mouse genetics was really a cottage industry at that time. The only places to work on mouse genetics were Harwell in the UK, and JAX or Oak Ridge National Laboratory in the US.
Neal: So, in the summer of 1980, despite what all of our friends said, we went to JAX. We were the first molecular biologists to go there and, over the next couple of years, we taught them molecular biology and they taught us about mouse genetics and about all of the mouse mutant strains. This really set up our whole careers.

How did you end up focussing your research on cancer?
Neal: Well that really began right at the beginning, during our postdocs. We and many others were trying to figure out, for example, how a murine leukaemia virus caused leukaemia and how Rous sarcoma virus caused a solid tumour. Around the time that we went to JAX, two papers were published showing that viruses caused cancer by insertional mutagenesis. Soon after we got there, we had a visit from Doug Lowy of the NIH, who had just cloned the first murine leukaemia virus. He had sequenced part of the virus and created a probe: he generously gave us this probe before his work was published, and we used it to search for new cancer genes. This was all serendipitous, just good timing really, and it allowed us to get started on our cancer project.

We also got involved in developmental genetics at JAX – again, serendipitously. We used Doug Lowy's probe to try and figure out the differences in the endogenous viral DNA between the many different strains of mice at JAX. One of the first things we found was that there was an endogenous virus present only in inbred strains with a coat-colour mutation called *dilute*. From there, it was easy to determine that this was a germline insertion (which probably happened in Asia many hundreds of years ago) that inactivated a gene to cause this coat-colour mutation. This was the first time it had been shown that a virus could insert into the mammalian genome and cause a mutation that induced an observable phenotype.
Nancy: This got us into development, and our lab then stratified into two parts: the cancer part studied mutagenesis using retroviruses, and the development part started with the *dilute* mutation and then spread out into all kinds of other mutations. We stayed at JAX for 3 years, then I started to get really tired of Maine winters.
Neal: Yes, it became clear that if we wanted to stay married, we were going to have to move!

So, then it was on to the NCI – where you worked for 22 years.
Neal: We'd been lucky during our time at JAX: we had learned a lot, knew a lot about mouse mutants and had published some nice data. But we still wanted to do fly-like studies in mice on a grand scale. To do this, we needed to find two positions in the same place and a lot of funding. We had a few job offers, but the one from the NCI was the most exciting – they offered us good positions and the freedom to set up a programme of the size we wanted without writing grants. Again, our friends told us we were crazy to turn down other opportunities at fancy universities – but again, I think we really made the right choice. At the NCI, we had the support that we needed to do what we wanted to do.
Nancy: When we got to the NCI, for various reasons, we got very interested in pre-genomic genomics – we were interested in linkage relationships between genes and in building a gene-based linkage map of the mouse genome. This was the prelude to the sequencing of the mouse genome.
Neal: To do this, we used a technique called interspecific mouse backcross mapping (now very old-fashioned). What you did is you took an inbred strain and crossed it to a wild mouse strain, then took their F1 progeny and crossed them back to the inbred strain parent, and then analysed DNA from several hundred progeny. Because there is genetic polymorphism between the wild and the inbred strain, you could easily do restriction fragment length polymorphism mapping, like they were doing in humans at the time. We generated a mapping panel of about 200 mice, isolated the DNA and started collecting probes. We first collected probes for genes for which we knew where they mapped on mouse chromosomes –
Nancy: – these were the anchors: several anchors for each chromosome.
Neal: We built a rudimentary genetic map based on genes, and covered all of the chromosomes with markers. Then, other people wanted to map their genes onto our map. We collaborated over a dozen years with hundreds of scientists from all over the world to map their genes.
Nancy: And this project had an important by-product. We knew a lot about mouse mutants and the genetic linkage map of the mutants, and we tried to fuse the mutant linkage map with the molecular map. So, what happened along the way was that it became possible to clone a lot of classical mouse mutations, either by a candidate-gene approach or by positional cloning. This was another big chapter in our career: we cloned a lot of important genes.
Neal: Because ours was a gene-based map, and because of the conserved linkage between human and mouse, we could also often guess where a gene would map in humans based on our mouse genome map. So, we also helped to identify many genes that were also associated with human disease.

"Every 4 years when we got reviewed I was worried that…they'd criticise our lack of continuity and so on…but it never happened. In fact, it was quite the opposite"

Nancy: Overall, we had the flexibility and freedom to do a lot of projects because we were at the NCI. There, as long as you were productive, you could carry on with your projects. Every 4 years when we got reviewed

I was worried that the shoe was about to drop – that they'd criticise our lack of continuity and so on, because we were always changing tack, but it never happened. In fact, it was quite the opposite – we always had great support.

What made you pick up and go to Asia?

Neal: We could have stayed forever and been well looked after – we had tenure with the US government. But we were getting older and we began to wonder whether we wanted another adventure. And every year the bureaucracy was getting worse, and we began to tire of it.

Nancy: I think we were ready for a change, really. We never really applied for anything though. We had lots of interesting offers, but we knew that we'd have to fund everything off grants, and we knew that we wouldn't be able to do what we wanted to do. This was at the time when grants were declining in the US, and we would have needed about ten grants to support our operation. That didn't seem appealing at our age.

At that time, a long-time Japanese collaborator and friend, Yoshi Ito, had recently left Kyoto and moved to Singapore. He asked us to come to help him troubleshoot some problems he was having with retroviral insertional mutagenesis, and have a visit – so we did.

Neal: We then went back again the following year to give a seminar, and learned that Singapore was investing billions of dollars into this new campus called Biopolis, which was going to be set up like the NIH intramural programme and be funded directly from the Singapore government. They invited us to set up a lab and offered to give us everything we needed. We've been travelling our whole lives and Asia is our favourite place to visit. We thought, if we're going to have an adventure, why not Singapore? We can live somewhere we love and help to build something, rather than stay in the US, where everything seemed stagnant. So we went there in 2006.

Nancy: And at that time we had to make a decision about what to bring, and we decided to only take the cancer work with us.

Neal: That's right. We'd been using retroviral insertion mutagenesis to uncover new cancer genes for about 20 years, but we were frustrated by this approach, partly because most retroviruses only induce haematopoietic cancers. We wanted to study other types of cancer, particularly solid tumours, which are what kill the most people. We'd been thinking about using transposable elements to induce cancer in mice. By the early 2000s, transposons had been adapted for mammalian cells (mainly to induce mutations in the germline), so we tried these out in somatic cells to see if they would cause mutations at high enough frequencies to induce solid tumours in mice.

Nancy: To be honest, we never thought this would work. The germline data published at the time showed that there were very few new insertions per generation (per gamete). If those frequencies were as low in somatic cells, they wouldn't induce cancer (because cancer is induced by multiple mutations in multiple genes). So, we were worried we wouldn't get the system hopping enough to induce tumours somatically.

Neal: But we made a lot of changes to the system and made a lot of lucky guesses. And it worked: in 2005, we published a paper showing that you could move transposons around the mouse genome at a high enough frequency to induce cancer. We then made a knock-in mouse expressing a floxed allele of the transposase enzyme (which mobilises transposons) in a ubiquitous locus (*Rosa26*); by crossing with various Cre deleter lines, we could induce transposase activity in a conditional (tissue-specific) way, and essentially model cancer in any tissue. This was the project we took to Singapore. Over a 5-year period, we modelled 16 different human cancers in mice using this transposon system. We generated a huge amount of data –

Nancy: – that we're steadily writing up –

Neal: – although the first paper we published was just this year.

Why did you leave Singapore?

Neal: R&D at Biopolis is funded in 5-year cycles – we got there at the beginning of a cycle. When we arrived, they said that they weren't going to assess whether our projects were making money for 25 years; they recognised that biological sciences take time to generate money. But after 4 years, they started thinking about their next cycle. They got impatient: they wanted to make money, and their plans changed overnight.

Nancy: They decided that basic researchers should work with pharma to move projects forward, and that was the beginning of the end of hypothesis-driven research at Biopolis. They took away a lot of the budget, and you needed to get it back by writing grants with pharma, that the government would match. And we're old – we've done hypothesis-driven research our whole lives! We weren't willing to do contract research for some pharma company, so we quit on the spot – without another job to go to. How brazen of us!

We started thinking about going back to the US, and it quickly became obvious that we should go to Texas if we wanted to do cancer research, because of the Cancer Prevention and Research Institute of Texas. This is a scheme modelled after the California Institute for Regenerative Medicine (CIRM), which they initiated to attract the best stem-cell scientists and build the best stem-cell research programmes.

Neal: As they did for the CIRM, they asked the voters of Texas to borrow $3 billion dollars ($300 million per year for 10 years) worth of bonds for cancer research and prevention, and that was approved. This funding kicked in about 3 years ago. Nancy and I discovered that they have multiple different types of grants – including one to recruit senior scientists to Texas who wouldn't necessarily come here otherwise. These types of grants, which involve just a 4-page proposal, are for 5 years of money, and you can ask for however much you want. We had to find an institute in Texas that would take us and would match whatever we requested – they had to be committed. We decided we wanted to come to the Methodist Hospital Research Institute for several reasons. We were instructed to write one proposal each, for a large amount – and 2 weeks after submitting we found that both proposals had been approved.

Nancy: To our amazement, only 5% of the amount we were awarded goes to overhead costs (the amount is capped at 5%, whereas this can be as much as 50% or more with US-government-funded grants). So, we have as much money to fund our lab now as we did in Singapore.

The institute you're at now has a translational emphasis: is this more a focus of your work now?

Neal: We've spent the last few years of our career trying to identify the mutations that cause different cancers. We now have this huge database of information, and we want to integrate that with new data that's coming out from human cancer genome sequencing. We're working with the Sanger Institute on these databases, both here and at the EBI [European Bioinformatics Institute] at

Sanger. Eventually, we want to use this information to identify new drug targets and develop drugs.

What would you say is the most important issue in the cancer field right now?
Neal: In contrast to what was thought initially, we're learning now that instead of only a handful of frequently mutated cancer genes, there are probably thousands of infrequently mutated cancer genes. Different combinations of genes are mutated in every patient, even within the same type of cancer, and even within the same tumour.
Nancy: So, the overriding issue right now is how to sort through all of this heterogeneity and complexity. And the main question is what to target for therapy. You need to target something that is common to most of the cancer cells – i.e. driver mutations, the ones that happen before the majority of branching occurs.
Neal: The other possibility is to target the signalling pathways or metabolic pathways that are commonly deregulated in all cells.

You've helped to train many great scientists. What are your thoughts on mentoring?
Nancy: We have taken training very seriously throughout our career. We've mostly had postdocs, because we haven't been at academic institutions, and we're very proud of having had some really terrific postdocs. When we were at the NCI, we generally gave our postdocs their whole project when they left – we gave them the mice, and we vowed never to work on the project again. And those postdocs generally had little competition and were highly successful in getting their first grants. So, being at the NCI not only allowed us to be successful, but it also helped a lot of other great young scientists leave our lab in a good position.

"We firmly believe in the Lunch Test – this is very useful. That is, if you can't have lunch with a person, they can't be in your lab"

What do you look for in the people that you hire?
Nancy: They need to be independent by nature. Our door is always open if we're here, but we're not always here. We can't be hand-holders, so we need to find people who are self-confident. And we firmly believe in the Lunch Test – this is very useful. That is, if you can't have lunch with a person, they can't be in your lab. They have to be able to mix with people. I will turn down the smartest person in the world if I think they're a jerk or a trouble-maker. It's not worth it to me. It's hard enough in science, particularly at that level, to be productive and interact with your colleagues without someone stirring the pot in a negative sense.
Neal: When we were young and still at JAX, we gave a talk at McArdle Laboratory for Cancer Research in Wisconsin. We met with Howard Temin, who was a Nobel Laureate and had mentored the person we did our postdocs with –
Nancy: – he considered himself our scientific grandfather.
Neal: He pulled us into his office afterwards to give us some advice about recruiting people to our lab. He told us that no matter how diligent we were in choosing people, no matter how many glowing reference letters they had, 50% would be successful and 50% would not. And that's exactly what we found. The other thing that we found is that you can't legislate hard work: some people are hard workers, and others are not. And we've seen that, invariably, the kind of job that a postdoc ends up with is exactly proportionate to how hard they work.

What advice do you have for people looking for a postdoc?
Neal: Find a lab that you think is going to be a great fit for you, and work in an area that you enjoy – because that's the area that you'll continue to work in. Work for somebody that has a history of treating people well (that's easy to find out), and work as hard as you can. But there is still an element of luck about all of this. We made some good choices that could have turned out to be bad choices – that was luck. And we worked on good projects that might not have led to anything.
Nancy: But I think luck happens to people in the lab who are working hard – it's a mix.
Neal: Yep – we've spent a lot of time in the lab. When we went to JAX for our first jobs in 1980, there was nothing to do. There was no cable TV, no internet, and it was a sleepy little town that shut down for 10 months of the year when there were no tourists around. There was nothing to do but work –
Nancy: – and that turned out to be a good thing!
Neal: The first 6 months we were there, I don't think we ever took a day off. We just worked all the time. We worked all day, we worked at night. And for our first 18 years at NCI – we travelled a lot, mostly on business – but when we were home we worked. We worked holidays, every Saturday, most Sundays.

What do you do when you're not working?
Nancy: We love travel, and food and wine are our hobbies.
Neal: I've built up quite a wine cellar and I'm a bit of a gourmet chef, and although I don't cook like I used to, I've done all the cooking since we were married –
Nancy: – good job!

Will you ever retire?
Neal: If Nancy has her way, no – I'm married to a slave driver! When we decided to leave Singapore, we could have retired. I'm 65 now, and Nancy is 62, and we're in a financial position that means we don't have to work. If we're going to work, it's because we want to and because we're having fun.
Nancy: I felt a tremendous obligation to our postdocs in Singapore: it was our decision to leave, but we had a responsibility to help them publish their papers. This was an overriding concern, and that drove me to encourage Neal not to quit.
Neal: Yeah, that was part of it. Also, when we got married, we decided not to have children. It would have been more difficult for Nancy to have a real career. There are women that do it –
Nancy: – but I wasn't going to be one of them –
Neal: – and we wanted to travel the world together. That's not easy when you have kids, because one parent usually has to stay home. We decided that wasn't the life we wanted – we wanted to be footloose and fancy-free. And that's been wonderful – our whole life has revolved around our work. And we're just not ready to quit yet.

So you're enjoying your new space in Texas?
Neal: Yes, we're really enjoying life here. We're in this shiny new beautiful building in the heart of this medical complex – our floor was only finished in November last year, and there's a brand new animal facility in our building. We're still in the process of re-deriving our mice and buying equipment, but we're on our way. The building is in the heart of the Texas Medical Center, which also houses the biggest cancer research complex in the world – the MD Anderson Cancer Center. There are more than 18,000 people

that work there, and they do hundreds of clinical trials. Across the street is Baylor College of Medicine, and then there's Rice University, next to Baylor. There are countless excellent scientists working at these institutes. If you want to do translational medicine, this complex is a really good place to be.

"There's nothing I'd rather be working on than what we're doing now. We've always had freedom to do what we wanted, so we've never felt restricted"

What's your secret: how have you worked together successfully for so many years?
Neal: I think the secret to many happy marriages, including ours, is that we are best friends. We've been best friends from the beginning, and we're so compatible. In fact, we're almost like twins: some people say we complete each other's sentences.
Nancy: I think compatibility really is the key. We've had several couples come through the lab or through the same institute and, to be honest, I've never seen the model repeated! I've never seen anyone else follow the path we chose: most people need a little bit of their own turf – our path is very unusual. It's down to personalities.

Do you ever disagree scientifically?
Neal: We do argue sometimes – everybody does – but surprisingly rarely, I would say.

If you could go back to the bench and start a whole new project, what would you do?
Nancy: There's nothing I'd rather be working on than what we're doing now. We've always had freedom to do what we wanted, so we've never felt restricted.
Neal: There are other interesting areas – neurobiology for example. But even with the tools we have now, it's not trivial. In fact, neurobiology is probably even more complex than cancer.
Nancy: That's probably true – and look how far we haven't gotten with cancer!

DMM greatly appreciates the willingness of Neal Copeland and Nancy Jenkins to share their unique thoughts and experiences. They were interviewed by Sarah Allan, Scientific Editor for DMM. This piece has been edited and condensed with approval from the interviewees.