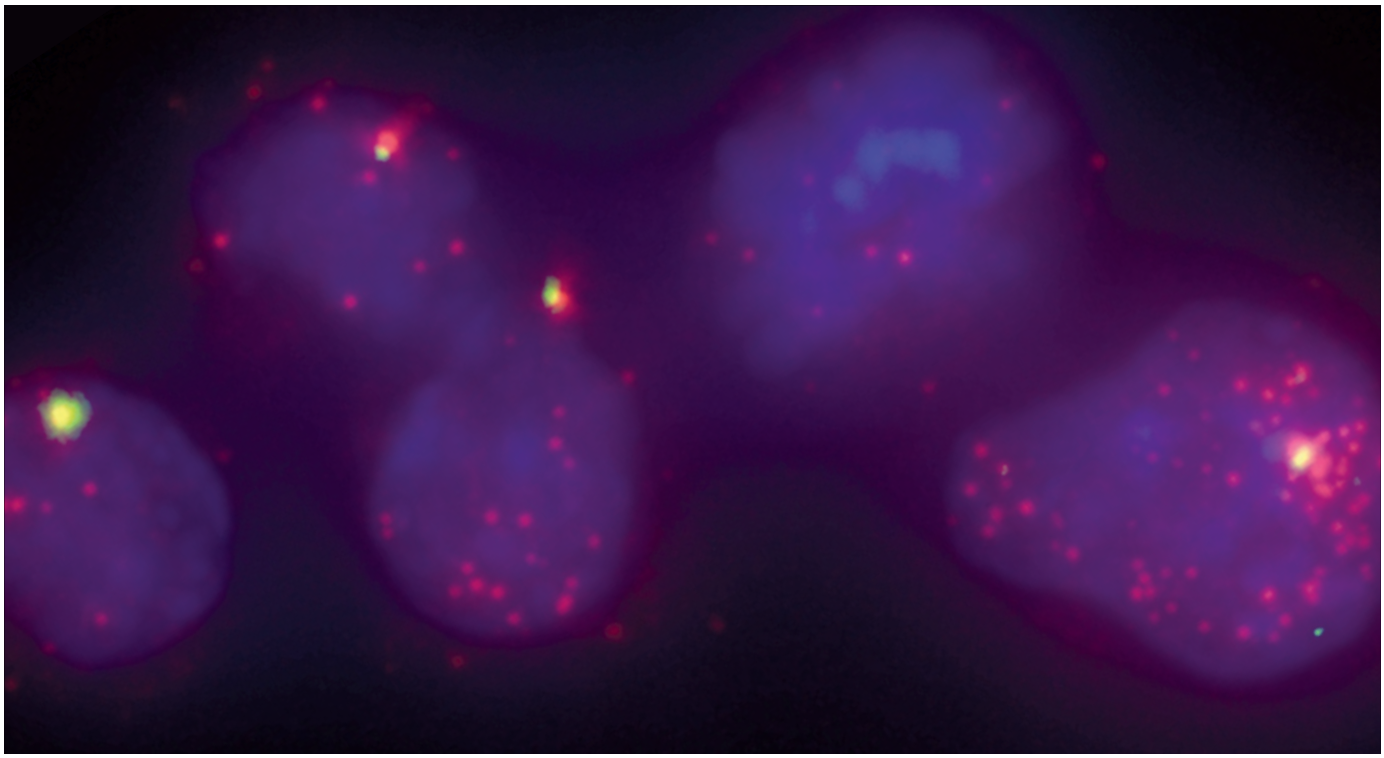
CAREERS

COLUMN A lab retreat offers a chance to reinvigorate a research programme **p.129**

CAREERS BLOG The latest discussions and news on research jobs **go.nature.com/z8g4a7**

NATUREJOBS For the latest career listings and advice **www.naturejobs.com**

JOHN RINN/ARJUN RAJ



Long non-coding RNA (red) regulates DNA and proteins in the nuclei of cells.

RNA

The genome's rising stars

As the once-fringe field of long non-coding RNA moves into the limelight, young researchers could reap the benefits.

BY AMY MAXMEN

When Saba Valadkhan lingered in the hallways at conferences, absorbed in discussions about the strands of 'junk' DNA that litter the human genome, she was not looking for work. She was consumed with curiosity about the possibility that long RNA sequences that do not encode proteins nevertheless have a function — enhancing or suppressing gene expression. Valadkhan's enthusiasm about the budding field of long non-coding RNA (lncRNA) did not go unnoticed: senior investigators were on the hunt for young researchers willing to pursue the topic. "Before I was even looking for job opportunities, I was told about people who were hiring," says Valadkhan. Soon after receiving her PhD for studies on small nuclear RNA — a type of non-coding RNA — at Columbia University in New York in 2003, she took a position as an assistant professor at Case Western Reserve University in Cleveland, Ohio.

John Rinn, now a molecular biologist at Harvard University and the Broad Institute of MIT and Harvard in Cambridge, Massachusetts, also had a rapid career launch; as a postdoc at Stanford University in California, he was noticed at meetings where he spoke about his research on how lncRNA silences genes involved in embryonic development. Rinn was offered several faculty positions, but was sold on the Cambridge post when Stuart Schreiber, a chemical biologist and a founding member of the Broad Institute, told him: "Every day I come to work dreaming of how I will bend the genome to my will." Rinn wanted to bend the genome with lncRNA to learn how to prevent and cure diseases.

At the time, modifying gene expression using lncRNA was not a common goal. In the early 2000s, most molecular biologists were interested in the 1–2% of the human genome that encodes proteins, which were presumed to be the brokers of biological functions. But with the rise of high-throughput sequencing, researchers learned that far from being without function, much of the rest of the genome was transcribed into non-coding RNA, including 20-nucleotide microRNAs, which suppress genes, and lncRNAs of 100 nucleotides or more. ▶

Last September, the multi-institution ENCODE project to catalogue human DNA elements (see *Nature* **489,** 46–48; 2012) revealed that three-quarters of the human genome is transcribed into non-coding RNA, and that there may be between 10,000 and 200,000 lncRNAs. Scientists have shown that these can activate gene expression and silence genes, and links with disease have begun to emerge.

Enthusiasm for lncRNA has replaced much of the science community's scepticism. Molecular biology and biochemistry departments have taken note of a flurry of high-impact manuscripts, and some are hiring scientists to work in the emerging field. Funding is becoming easier to find. And the first biotechnology companies focused on lncRNA have taken root.

"You start projects and you have no idea what to expect. It's that kind of challenge that I enjoy very much as a scientist."

Scientists hoping to work in the field will benefit from experience with model organisms and cell cultures, or from a background in bioinformatics. But they also need traits such as creativity, a willingness to collaborate and the confidence to weather disappointment — in emerging fields, no experiments are straightforward and foolproof. For some researchers, however, these risks are part of the allure. "We are part of a very fast-moving field," says Valadkhan. "You start projects and you have no idea what to expect. It's that kind of challenge that I enjoy very much as a scientist."

Despite the wave of enthusiasm, lncRNA studies may still be difficult to launch. "RNA has really been given the shaft," says Tom Cech, a chemist at the University of Colorado Boulder who shared the 1989 Nobel Prize in Chemistry for discovering that RNA can catalyse reactions. "People were reluctant to hear that RNA could do something other than lead to proteins back in the 1970s. But they are still surprised to hear it now."

There are no optimized experimental protocols and few clues to the habits of individual lncRNAs, so experiments often fail. And when they do work, investigators need to go the extra mile to convince reviewers that their results are real. "We had a difficult time publishing our studies for the first couple of years I was at Case Western," says Valadkhan. "It's so novel that, understandably, people are very sceptical."

"I have had so many conversations where people think I'm just full of crap," says Kevin Morris, a molecular biologist at the Scripps Research Institute in San Diego, California, who studies lncRNAs involved in HIV and cancer. "You need a thick skin to be in this field. You need to do it because you love it."

LOOKING UP

Nevertheless, more grants are being funded for lncRNA projects. At the US National Institutes of Health (NIH) in Bethesda, Maryland, 28 applications on the subject have been approved since the start of 2012. By contrast, just six were funded between 2008 and 2011.

Specific calls for lncRNA studies are also becoming more common. A 2012 funding announcement from the NIH's National Institute on Drug Abuse lists studies on interactions between lncRNAs and chromatin — the cluster of DNA and proteins in a cell's nucleus — as a high scientific priority. A programme announcement from the National Cancer Institute (NCI) calls for research on lncRNAs as biomarkers for cancer. Investigators can also submit projects that use lncRNA as a tool to approach other questions. For example, Kevin Howcroft, a programme director at the NCI, notes that people studying prostate cancer who might once have looked at proteins in a signalling pathway might now propose to analyse lncRNA.

There are other funding niches. Valadkhan's work on neuronal differentiation is funded by the ALS Therapy Alliance, a consortium based in Needham, Massachusetts, that raises money for research related to the neurodegenerative disease amyotrophic lateral sclerosis. Increasing the amount of a single lncRNA in a fibroblast, a common cell in connective tissue, can transform it into a neuron, so research on lncRNA could pave the way for treatments to reverse neuronal degeneration, says Valadkhan. The California Institute for Regenerative Medicine in San Francisco, which funds stem-cell research, has also awarded grants for research into how lncRNAs can change the fate of cells.

COMMERCIAL INVESTMENT

The private sector has also begun to notice lncRNA. In 2011, start-up company RaNA Therapeutics in Cambridge, Massachusetts, received $20.7 million from investors including the agriculture biotechnology firm Monsanto in St Louis, Missouri.

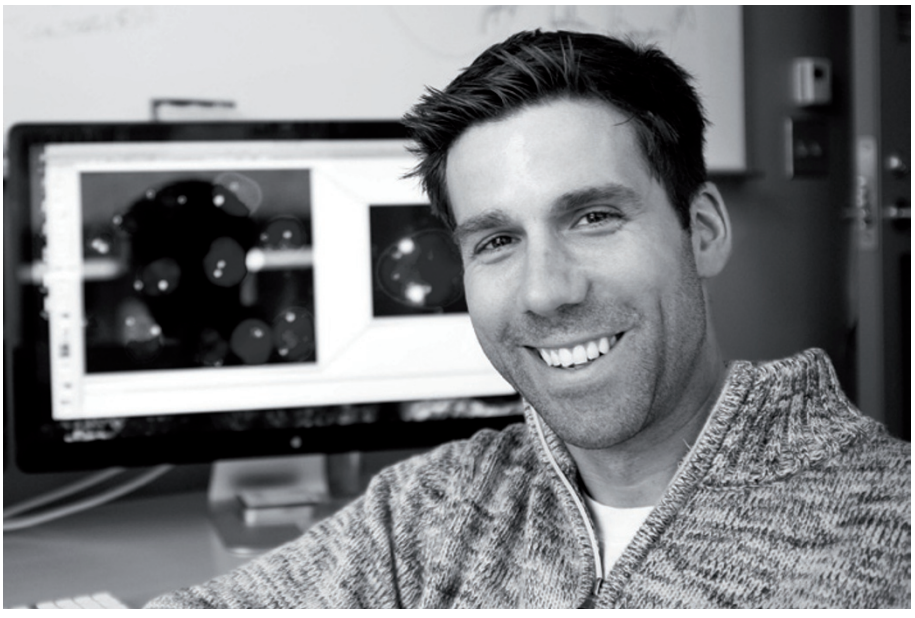
RaNA's goal is to manipulate lncRNA to control genes such as those that suppress tumours or cause cancer. Individual lncRNAs have specific targets, so treatments based on them might well have more predictable effects than those based on other RNAs. And they offer a rare chance to activate, rather than just block, gene expression.

In 2012, the company grew from 2 employees to 26. President and co-founder Art Krieg says that he plans to expand again in 2014 — and that he will put a premium on hiring people adept at teamwork. At the moment, RaNA's staff scientists are using high-throughput sequencing and a technique called chromatin immunoprecipitation to learn how lncRNA binds to proteins.

At least two other biotechnology companies focus on lncRNA. OPKO-CURNA, a subsidiary of OPKO Health in Miami, Florida, is investigating how to activate gene expression, for eventual use in treatments. And TransSINE Technologies in Yokohama, Japan, aims to produce lncRNA-based technologies to express antibodies and other proteins for laboratory assays.

Career success for scientists in the field requires knowledge of genomics and molecular biology. Some experiments also call for experience with model systems and cell culture, but Valadkhan, who has a background in biochemistry, learned many techniques on the fly.

Computational biology is important because it allows researchers to grapple with large data sets. Institutions including the Wellcome Trust Sanger Institute in Hinxton, UK, and the Broad Institute offer classes and workshops on bioinformatics; these typically range in length from days to weeks. Some workshops require familiarity with operating systems such as Unix and Linux and computing languages such as R, but students can learn to use such tools through books and online tutorials.



John Rinn wants to use non-coding RNA to learn how diseases can be prevented.

Universities with financially well-endowed genome centres provide easy access to sequencing and computer-savvy scientists and technicians. The leading US institutions for lncRNA research include Harvard, the University of Wisconsin–Madison, Stanford, the University of Colorado Boulder and Yale University in New Haven, Connecticut. In Europe, institutions including the University of Vienna and the nearby Research Center for Molecular Medicine of the Austrian Academy of Sciences have histories of RNA research, including lncRNA.

The Center for Life Science Technologies at the RIKEN Yokohama Institute, which opened this month, will focus in part on lncRNA. "We can develop technology for several years without the pressure of writing grants and publications because we have an institutional budget," says Piero Carninci, the first director of the centre's genomic-technology division, which will employ roughly 100 scientists, including 9 principal investigators.

Researchers investigating the role of lncRNAs in disease often collaborate with clinicians. Just such a partnership helped Claes Wahlestedt, now director of the Center for Therapeutic Innovation at the University of Miami Miller School of Medicine in Florida, to discover that a non-coding RNA drives the expression of an enzyme involved in the progression of Alzheimer's disease (M. A. Faghihi *et al. Nature Med.* **14,** 723–730; 2008).

When choosing a lab, researchers should remember that it can be an asset to have colleagues with a range of backgrounds, says Florian Karreth, a postdoc at Harvard Medical School in Boston, Massachusetts. "You don't want 20 people with a background in microRNA." In his group, he says, "there are people with experience in apoptosis, leukaemia and DNA repair, and it's great to learn from all of them". The 20 postdocs and a handful of graduate students and technicians often confer when starting experiments, and help each other to learn.

In the absence of a rich body of literature, ideas are often exchanged at conferences on RNA, epigenetics and genomics. As Valadkhan discovered, these are also good places to find jobs: senior scientists who attend may be looking for young investigators with creative ideas. Human lncRNAs are yet to be catalogued, and everyone wants to know more about their role in disease.

"I'm really looking for people who think originally and are very open," says Carninci. "It's a new field, and we know almost nothing. So it's important to find people who always question the dogma of the day." ■

Amy Maxmen *is a freelance writer in New York.*

COLUMN

Time to reflect

A lab retreat provides a chance to rethink and advance the research programme, says **Eleftherios Diamandis**.

DRAWN IDEAS/IKON IMAGES/GETTY

Labs sometimes struggle to stay competitive and energized, and periods of successful discovery may be followed by stretches filled with little more than attempts to address knowledge gaps or promote translation. These are essential processes, but innovation may suffer if such periods last too long.

As director of a 25-person research lab (ten graduate students, five technologists, six postdocs, a research coordinator and affiliates), I know that focusing too much on the day-to-day business of e-mails, manuscripts and grant applications can delay the introduction of new techniques and ideas. One way to inject enthusiasm and re-excite the team is through a lab retreat to discuss everyone's projects and work.

The lab director generally sets the agenda for a retreat, but he or she should consider involving other lab members. Getting everyone on board is important: lab staff should understand that this is not an exercise devoted to identifying the 'good' and 'bad' projects or people, but is rather an open conversation about long-term planning to determine who needs help and how the director and other lab members might give it to them. Retreats can help to identify new strategies and areas where lab members are duplicating efforts on the same questions.

The director should circulate instructions ahead of time, explaining what he or she expects to be covered in the presentations and discussion. Constructive criticism should dominate. Participants should understand that this is not merely an update on research progress, but is instead a soul-searching exercise. Lab members should be asked to consider self-assessment questions such as 'Am I innovating or imitating?', 'Will my results lead to significant publications if successful?', 'Are there other techniques I should be using?' and 'Am I being too risk averse?'. Each person should address the novelty of their project as opposed to simply 'what they're working on'.

The lab supervisor might open the retreat with some remarks on each of the lab's research focuses, addressing the self-assessment questions as they pertain to the entire lab. Each member can then give a short presentation (perhaps five to seven slides) on his or her project, with special emphasis on innovations and anticipated research impacts.

Questions and criticisms must go beyond those at a typical lab meeting, where most questions focus on specific experiments and technical details. At the retreat, questions should examine appropriate approaches and even whether a project is worth pursuing at all. This may reveal that hypotheses or strategies have weaknesses that need correction — or that suggest that a project should be abandoned.

To promote debate, the director should consider assigning one or two lab members the role of devil's advocate. At my lab's retreat last year, one postdoc presented his findings on the anticancer properties of cardiac glycosides — drugs used to treat heart failure and arrhythmia — in a model of pancreatic cancer. The opponents challenged him, noting that his effective drug concentrations were ten times higher than the safety limit in humans — it might be possible to treat the cancer, said one, but the patient would die of cardiac arrest. Discussion followed on ways of retaining the anticancer properties but avoiding the toxicity. Another critic suggested that it could be possible to find a drug that acts with the cardiac glycoside, enhancing its anticancer activity at safer doses. After the retreat, this idea led the postdoc to perform a high-throughput screen of a 10,000-molecule chemical library to find such an agent. He is now testing a drug combination in animal models.

Lab directors are responsible for proposing and contemplating the direction that a lab will take in future. But retreats help to foster an annual re-examination of projects. Members need to recognize that the success of a lab depends on their capacity to innovate. In the end, all will share the rewards. ■

Eleftherios Diamandis *is professor of laboratory medicine and pathobiology at the University of Toronto in Canada.*