Abstractions

FIRST AUTHOR

The most prevalent form of uranium is its soluble uranyl dication: a radioactive contaminant that is notoriously difficult to extract from the environment because it is very unreactive. Polly Arnold and her co-author and husband, Jason Love, both based at the University of Edinburgh, UK, combined their different chemistry skills to produce a reactive uranium compound that defies long-held assumptions (see page 315). Arnold talks to *Nature* about how she and her co-workers proved the textbooks wrong.

Little is known about uranium's chemical properties. Why is that?

Textbooks are full of assumptions about uranium chemistry that have no direct proof. Compared with other metal atoms, uranium atoms are big and have many electrons, which makes it hard to describe their bonding using traditional chemical modelling programs. According to the textbooks, we shouldn't have been able to make this compound.

How were you able to make a reactive uranium compound?

The uranyl dication is made stable by its two uranium–oxygen double bonds. No one thought it was possible to make just one end of the compound chemically reactive. We used an organic molecule as a scaffold that was shaped in such a way that when the uranyl bound, it sat unsymmetrically. This made the dication less stable and allowed it to react with nearby organic groups in unexpected ways. We hope to put other molecules on the uranyl dication.

Were there safety issues with this work?

The uranyl dication is pretty safe. We only use depleted uranium, which is the residue left after uranium is processed to make fuel and gives off hardly any radioactivity.

Will this molecule be useful to clean up toxic waste?

Not directly, but we can use it to help us understand how uranium precipitates from groundwater, as well as how to make uranyl dications less mobile and contaminating. The compound will also be helpful for modelling the behaviour of plutonium ions in nuclear waste, because it is as reactive as plutonium but much less radioactive.

How did your husband come to be your co-author?

The funny thing is we've been trying to separate our careers since we met in the same lab 12 years ago, because we thought it would help us find dual jobs at one location. We've ended up with two very different skills that are quite complementary. It's turned out to be a very productive collaboration. ■

MAKING THE PAPER

Todd Golub

Interfering with genes reveals cause of bone-marrow disorder.

For cancer researcher Todd Golub, the paper on page 335 of this issue represents a return to an early enthusiasm. Working as a postdoc at Brigham and Women's Hospital in Boston in 1990, Golub got interested in an unusual bone-marrow disorder called 5q– syndrome. The condition, characterized by defective red-blood-cell development, severe anaemia and a tendency to progress to acute myeloid leukaemia, had been linked to a gene somewhere in a 1.5-megabase common deleted region (CDR) on chromosome 5, says Golub, "but we just didn't have the tools to identify the gene".

Things have changed a lot since then. "The tools available now are just spectacular," says Golub, who is now director of the cancer programme at the Broad Institute, a genomic-medicine centre in Cambridge, Massachusetts, run jointly by the Massachusetts Institute of Technology and Harvard University. One of those tools, RNA interference, or RNAi, and the help of a particularly persistent postdoc led to the discovery that the 5q– syndrome is caused by a defect in a gene called *RPS14*, which makes a ribosomal protein.

Gene deletions associated with cancer are usually expected to be biallelic, meaning that the deletion results in both copies of a relevant tumour-suppressor gene being inactivated. But no one had been able to find biallelic inactivation in 5q– syndrome. "There was growing evidence in cancer generally that just having one allele affected has an impact," Golub says. "We needed some way to test this hypothesis."

Enter RNAi, which allows researchers to use short stretches of nucleic acid to reduce the expression of a target gene, mimicking, in effect, the 'haploinsufficiency' that Golub and his collaborators suspected was the cause of 5q– syndrome. Postdoc Benjamin Ebert developed a set of 189 short hairpin RNAs that would target each of the CDR's 40 genes.

Ebert and Golub were surprised that the partial disruption of *RPS14* by several of these RNAs seemed to reproduce all the symptoms of 5q– in cultured cells. At first they thought the result was an error. "There were some amazing candidate genes" in the CDR, Golub says. "If we had ranked the genes from 1 to 40 on our level of excitement, I suspect that *RPS14* would have been last."

But a battery of additional tests confirmed that *RPS14* was indeed the culprit. "Many a postdoc has disappeared into the black hole of studying 5q– syndrome, never to emerge," Golub jokes. "A study like this requires an amazing and fearless champion, and Ben fearlessly took it on."

The identification of *RPS14* haploinsufficiency and the resulting reduced levels of protein as the cause of the 5q– syndrome links the condition to a variety of congenital bone-marrow disorders known to be related to disruptions in ribosomal proteins, leading the way to insights for their study and treatment.

The broader hope, according Golub, is that this study will pave the way for using RNAi screening as a general tool for gene discovery, especially for the many cancers and other diseases now thought to result from partial loss of gene function. ■

FROM THE BLOGOSPHERE

On her Nature Network blog, Lab Life, Anna Kushnir tells of how her blog got her invited to the SciFoo conference at the Googleplex last summer (http://tinyurl.com/323las). There, she met Moshe Pritsker and Nikita Bernstein of the online *Journal of Visualized Experiments* (*JoVE*). The meeting led to a part-time job starting a blog on *JoVE*'s website.

In her first *JoVE* blog post, Anna describes her difficulties in learning how to do transcardial perfusion on mice (http://tinyurl.com/yqwolr). "Oh how I could have used a video of the procedure... How I would have loved to rewind back to the part where he inserts the needle in just the right place in the heart to keep it beating while pushing the desired solution through the animal. Instead, I had two pages of manically scribbled, incomplete notes that I referred to as if they were sacred texts for the next two years." She writes that *JoVE*'s videos — professionally filmed and reviewed by editors for quality, integrity and authenticity — present even very difficult techniques in a "pausable, rewindable, and easily comprehensible format". ■

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