# Abstractions

**FIRST AUTHOR**

If the same person is found on the scene of multiple crimes, are they guilty by association? That's the question that Mark Pepys, a researcher at the Royal Free & University College Medical School in London, asked of C-reactive protein (CRP). This protein is produced in abundance in most cardiac diseases, including after heart attacks and strokes. Pepys has been on the CRP case since 1974.

There is no evidence that CRP causes cardiac problems, but Pepys says he has validated the protein as a therapeutic target by showing that high levels in the blood increase the damage caused by a heart attack. He is searching for a CRP inhibitor, but high-throughput testing of 500,000 known molecules yielded no leads. So he has drawn on his experience with a drug that targets a related protein and designed a new chemical entity. This has been synthesized and shown to bind tightly to CRP, blocking its inflammatory effect (see page 1217). Here, Pepys presents his case to *Nature*.

**Why are you interested in targeting C-reactive protein?**

Everyone has CRP. Whenever you're sick, CRP concentration increases. In everyone who has a heart attack, the CRP goes high. If it stays high, they don't get better. Clinical and experimental evidence suggests that the abundant CRP may be bad for you. So it's possible that you could reduce the damage from a heart attack if you could block the effects of the protein.

**What does your finding say about drug design versus high-throughput screening?**

It shows the potential for rational drug design — but the compound hasn't gone into patients yet, so we'll see.

**Any big breaks along the way?**

We had a big success with an inhibitor for another protein, which fed directly into the CRP project. This compound was two-handed with identical ends; it could therefore crosslink two target molecules and these were swiftly cleared from the patient's blood. Having previously solved the structure of CRP, we were able to design a two-handed compound that would crosslink this protein in a similar way.

**Are there limits to rational drug design?**

Yes. The structure of CRP suggested that shorter, twisted inhibitors would be better. But when we tried these they were much worse, whereas a longer, flexible molecule worked very well. The two CRP molecules crosslinked by the drug are slightly rotated on each other, and the length and flexibility of the inhibitor is evidently necessary to accommodate this. ■

# MAKING THE PAPER

## Kerstin Treydte

**Old juniper trees in the Himalayas yield a millennial log of rainfall.**

Earth has probably never warmed as fast as it has in the past 30 years. Now a study published on page 1179 of this issue tells us that it has probably never been as wet, at least not in the past millennium. Kerstin Treydte of the Swiss Federal Institute for Forest, Snow and Landscape Research in Birmensdorf, Switzerland, and her colleagues got their information from a knowledgeable source: trees that have been around long enough to witness the change.

"Our first question was: can we get precipitation information from tree rings?" says Treydte, who started working on the project in 1999, as a PhD student at the Research Center Jülich in Germany. Several studies had used tree rings to gain information about changes in temperature from year to year. But a relatively new technique of analysing oxygen isotopes in the rings promised information about the amount of snow or rainfall — a wetter year leads to wood that has less oxygen-18.

For three months in 2000, Treydte and colleagues camped out in the Karakorum and Himalayan mountains in northern Pakistan, an area known to contain old juniper trees. Using local shepherds as guides, they climbed different mountains and bored hundreds of pencil-like rods (called cores) through the trunks of trees. "We had worried a lot about where to look for trees and what instruments to use, but what turned out to be really critical to our work was to have local people helping us," says Treydte.

The work was physically demanding. "You really have to love the mountains," says Treydte. "I liked the place very much but in the end I was glad to go back." Back home, the hard work was not over. In the lab, she spent two years analysing all the samples. For each core, she counted the number of rings, cross-checking with other cores from the same tree. She cut individual tree rings from sufficiently old trees and extracted cellulose from them, which she then analysed to determine what ratios of oxygen isotopes they contained. "It was not technically difficult work, but you had to be very accurate," says Treydte. To her surprise, trees from one of the sites they sampled were more than 1,000 years old. "That was very exciting," she recalls.

The following year was spent trying to make sense of the data, but it was not until she left for her postdoc in Switzerland that she started to apply the necessary statistical analysis. By obtaining records from several local weather stations, she and her colleagues were able to correlate precipitation records spanning 30 to more than 100 years with the tree-ring isotope data. They then extrapolated weather information for the entire millennium.

This study is the first millennium-long log of precipitation. It finds that the latter part of the twentieth century was by far the wettest period, which suggests that humans may play a role in the climate of the world.

But according to Treydte, one of the biggest pay-offs of the study was getting to know people from a different culture. "One day the locals had a party for us and gave us permission to collect a sample from a very large juniper tree in the centre of the village, which has a very special, spiritual meaning for them," she says. When the team counted the tree rings, it turned out to be only 500 years old.

"We did not know how to tell them that, to us, this was a young guy," says Treydte. ■

# QUANTIFIED **ISRAEL**

**A numerical perspective on *Nature* authors.**

At Technion, the Israel Institute of Technology in Haifa, Moti Segev runs a nonlinear optics group that puts light to work in novel ways. Segev gives each member of his team a well-defined project to lead. He provides guidance and advice every day, but team members present the results of their own projects at conferences and take lead authorship on publications. Segev's guiding principle is to nurture original ideas, because ideas that are extensions of known ideas will be pursued by other, larger, groups. This week, the group presents the first ever nonlinear photonic quasi-crystal. This system is noteworthy because light passing through the ten-fold symmetrical structure changes the crystal's properties, and these changes then affect the light refracting from the crystal (see page 1166).

**185** citations have been made to the 2003 *Nature* paper written by Segev's group on solitons in photonic lattices.

**13** researchers working in Israel have reviewed papers submitted to *Nature* since January 2006 (<1% of all reviewers).

**157** submissions to *Nature* in the past year have been made from Israel (<12% of all submissions).

**12%** of submissions to *Nature* from Israel in the past year were made by researchers at the Technion.