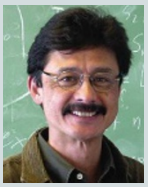
Abstractions



LAST AUTHOR

Harvested fish populations can fluctuate wildly compared with those left untouched by humans, although it is not clear to what extent harvesting causes these fluctuations. This makes fish-stock management a contentious commercial and ecological issue. On page 835, George Sugihara at the Scripps Institution of Oceanography in La Jolla, California, and his colleagues explain how fishing magnifies population fluctuations. Sugihara tells *Nature* that the very foundation of the prevailing fishing-management theory is wrong.

Why has it been so hard to prove that harvesting destabilizes species abundances?

Historically, we've only had species-abundance data for exploited species, which came from fishery records. We really needed data on the unexploited species to serve as a control to rule out environmental causes of population collapse. The state started keeping better records of all species after the crash of the California sardine fishery in the late 1940s, because it wasn't clear whether ocean climate conditions or fishing caused sardine declines.

Current fish-stock management practices rely on maintaining specific biomass targets. Why is that wrong?

Biomass doesn't provide any indication of individual fish sizes. Picture a pond with either a single 200-kilogram fish or 200 1-kg fish; they have the same biomass but respond differently to environmentally controlled fluctuations in food supply. Depending on food availability, the single fish may or may not grow. With food, the smaller fish not only grow but also reproduce, potentially outstripping available resources and causing a population crash — so boom-and-bust cycles occur. If a management policy does not forecast these fluctuations, when abundance is high it will respond by adjusting next year's harvest targets upwards, just when the population might be poised to crash on its own. This further destabilizes fish populations.

What should fish catches be based on?

Fish populations do not exist in equilibrium — they are unstable systems that depend on ever-changing environmental conditions. Models determining harvest limits should account for the average sizes of individuals as well as how environmental conditions affect fish abundance. We need to make it clear to fisheries managers that quantitative tools exist to significantly improve fisheries' forecasting. Greater accountability is also needed. As it stands, fisheries managers are not held accountable for making inaccurate predictions — and can be wrong for generations. ■

MAKING THE PAPER

Sakari Kauppinen

Therapies that target small RNA molecules show promise in animals.

It is only a few years since tiny RNA molecules called microRNAs were found to have roles in disease, but a therapeutic approach that targets one of them is already yielding promising results. Sakari Kauppinen and his colleagues at Santaris Pharma in Hørsholm, Denmark, in collaboration with the Connecticut-based company RxGen and Stanford University in California, have successfully blocked the activity of one type of microRNA in non-human primates. And the compound they developed has potential as a treatment for hepatitis C.

MicroRNAs regulate protein synthesis by binding to the messenger RNAs that provide the 'recipe' for protein construction, repressing the relevant protein's production. The mechanism is important in many biological processes, and has also been implicated in a number of disorders, including cancer and cardiovascular disease.

In 2005, Kauppinen —then at the University of Copenhagen — collaborated with Ronald Plasterk, who was then at the University of Utrecht in the Netherlands. They used synthetic RNA analogues called locked nucleic acids (LNAs) — which, when incorporated into a DNA molecule, enable it to bind more effectively to a complementary RNA sequence — to specifically detect microRNAs in zebrafish embryos. "LNA turned out to be an excellent tool for microRNA research. That same year, the first cancer-causing microRNAs were described," Kauppinen recalls.

Excited by these developments, Kauppinen contacted the management team at Santaris Pharma with the idea of developing an LNA-based approach to silence microRNAs. "We immediately connected on this idea," says Kauppinen, who was offered a position at the company to head the microRNA research team.

In 2006, Kauppinen and his colleagues at Santaris started testing LNA-based compounds aimed at targeting microRNA-122, a microRNA expressed in the liver that had been shown to assist the replication of hepatitis C virus in liver cells. MicroRNA-122 was an attractive target both because of its role in this important disease and because its activity can be easily monitored in animals. Three earlier studies had shown that when microRNA-122 was blocked in mice, the animals exhibited lower blood-cholesterol levels.

By screening several LNA-based compounds, the team found one that produced cholesterol-lowering effects in mice at very low doses. In addition, the compound effectively inhibited replication of hepatitis C virus in a liver-cell assay developed at Stanford.

Encouraged by the results, the team decided to move to a model closer to humans. "We wanted to know whether our compound was effective and our silencing approach safe," says Kauppinen. He approached colleagues at RxGen who were using African green monkeys to test potential therapies.

When the LNA compound was given to monkeys, the animals showed dose-dependent lowering of cholesterol (see page 896), and the effect was longer lasting than in mice. "It took about three months before cholesterol returned to baseline levels in the group that received the highest LNA dose," says Kauppinen. "And, encouragingly, the compound did not seem to have any toxic side effects in primates."

Santaris Pharma is now taking the first steps towards bringing the compound to the clinic as a potential hepatitis C therapy. "We have plans to do a safety study in healthy volunteers later in 2008," says Kauppinen. "The pace at which the field is moving is incredible." ■

FROM THE BLOGOSPHERE

Many scientific research papers tend to be jargon-ridden, written for a specialist audience, and generally a struggle to read. But how can busy scientists find, and hence learn from, well-written papers? Earmarking clearly written manuscripts as one comes across them takes time, as does looking more closely at papers unrelated to one's own discipline.

The Nature Network "good paper journal club" (http://tinyurl.com/49aaq5), run by a group of scientists and a *Nature* editor — Martin Fenner, Linda Cooper, Richard Grant and Maxine Clarke — is a collaborative online effort to help promote good scientific writing. Any scientist can join the group, select papers to be posted on the site and then discuss them online, and highlight the parts considered to be nicely written. The Network group has also set up a way to tag these exemplary papers in Connotea (http://www.connotea.org/tag/good%20paper%20journal%20club), a free online bookmarking service for scientific references. These easily accessible, shared resources should help provide guidance for scientists wishing to write their papers well. ■

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