gene differs from the normal gene by only one nucleotide. In theory that means ribozymes could combat the effects of an oncogene, without affecting the gene's normal counterpart in other cells.

Several years ago, Scanlon's laboratory showed the promise of this approach when they made a ribozyme designed to cleave the mutated form of the *ras* oncogene in a human bladder carcinoma cell line. The *ras* gene sequence differed from its normal counterpart by just one nucleotide, and Scanlon designed a hammerhead ribozyme to recognize that changed sequence. When they put a gene for the engineered ribozyme into the bladder carcinoma cells, they found that not only was the mutant Ras protein not produced, but "the ribozyme was able to reverse the metastatic, invasive, and tumorigenic properties of the bladder carcinoma," says Scanlon. When the scientists put the ribozyme-containing carcinoma cells into mice, the cells didn't cause tumors.

But bladder carcinoma is treatable with conventional chemotherapy, and only 5% to 10% of bladder cancers have the *ras* mutation. Hence, to be useful, the ribozyme-based therapy must be effective in other forms of cancer. Scanlon is now studying eight other types of cancer, including such deadly forms as melanoma and pancreatic cancer, in which a high percentage of tumors carry the *ras* mutation, to see whether blocking *ras* can reduce tumorigenicity singlehandedly or in combination with other treatments.

Before such treatments ever make it to the clinic, there are concerns about safety to be answered. Ribozymes' specificity should keep them from affecting anything but their target, but NIH's Sarver points out that specificity has been studied for the most part in test-tube experiments. In a cell, things may be different. "Will it lose some of its specificity in the cell and cleave other cellular RNAs?" she worries. "It doesn't have to lose much specificity for this to be a problem." So far in experiments in cells, this doesn't seem to be happening, she adds, although safety needs to be borne out, and in most cases this will be done in animal trials.

Given these uncertainties, it may seem premature for a ribozyme therapy to be headed for human trials, and Hampel admits that his ribozyme's spectacular success in the test tube can be attributed to some lucky guesses. But while other groups work on removing the guesswork from ribozyme design, Wong-Staal says she and Hampel chose to move ahead with what they have. "We feel like somebody has to push the technology forward to a stage where we can evaluate it in the clinic." That is appropriate, says Sarver, because of the desperate nature of AIDS. "The first clinical uses [of ribozyme technology] will be with HIV," she says, "because people are willing to take more risks with HIV. It will be important for other applications to see how it fares." And given all the hope and unanswered questions about ribozymes as therapy, plenty of attention will be on those early HIV trials.

–Marcia Barinaga

Additional Readings

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CONSERVATION BIOLOGY

An Avian Arch-Villain Gets Off Easy

The populations of many migratory songbirds in North America are dwindling alarmingly, with one in three Eastern species showing significant declines in the 1980s, and some biologists think cowbirds are a major reason. After all, the brown-headed cowbird (*Molothrus ater*), a close cousin of the blackbird, has a reputation as an arch-villain of the avian world. Female cowbirds slip their eggs into the nests of other songbird species; by competing for food and attention from their foster parents, the cowbird nestlings often starve out the parents' own young. With cowbirds common in North America, such nest parasitism became a prime suspect in the songbird decline. But now it seems cowbirds may not deserve so much blame.

K. MASLOWSKI/VISUALS UNLIMITED

Unhealthy appetite? Hooded warblers with cowbird nestlings.

When cowbird biologists shared their data last month in Austin, Texas, at a research workshop on cowbird ecology and management, they found little direct evidence that the cowbird problem has grown worse in recent decades. Songbirds that seem to be suffering because of cowbirds are usually on the ropes for other reasons as well, such as loss of woodland nesting habitats and tropical wintering grounds. Contrary to earlier hopes, therefore, cowbird control may not offer a quick fix to the disappearance of songbirds. "The cowbird problem has perhaps been exaggerated in the press," says workshop organizer Terry Cook of the Nature Conservancy of Texas. "The real problem is the destruction of habitat."

Like many villains, cowbirds gained their bad name from a lot of circumstantial evidence and a little eyewitness testimony. Ten years ago, for example, half of all the nests of the least Bell's vireo (*Vireo bellii pusillus*) on Southern California's Camp Pendleton military base fell victim to cowbirds, and the vireo population was near extinction. When a cowbird-trapping program reduced parasitism to near zero, the vireo population shot up tenfold. "The correlation is very clear," says wildlife biologist John Griffith, a consultant on the Camp Pendleton program. "We didn't expect to discuss at the cowbird conference whether or not parasitism is a threat."

Few examples place cowbirds so clearly at the scene of the crime, however. Most of the evidence that cowbirds are decimating songbird populations is indirect. For example, cowbirds feed in open, grassy areas but dump many of their eggs in songbird nests in woodlands. As a result, the cowbirds thrive where open spaces dot the forest. New subdivisions and industrial parks create just that kind of environment, and conservationists reasoned that the cowbird threat should be increasing as a result.

A few small-scale studies and anecdotal accounts suggest that parasitism rates may indeed have increased, at least in some regions. No one, however, has done the extensive random sampling required to estimate parasitism rates across the entire continent, says longtime cowbird researcher Stephen Rothstein of the University of California, Santa Barbara. As a substitute, some researchers looked to the U.S. Fish and Wildlife Service's Breeding Bird Survey, a series of annual nationwide population censuses dating back to 1966. At last month's meeting, they reported their conclusion: little evidence of a cowbird population boom. "One reads a lot about [cowbird] populations exploding everywhere," says Rothstein, "but the data clearly show that there have been at best small increases in cowbird numbers since 1966....That was a real surprise."

Results like these have led most researchers to downgrade cowbirds from a continent-wide scourge to a regional concern. "Cowbirds are a spotty problem," says James Smith

of the University of British Columbia, summarizing the consensus of last month's conference, "but there is quite a bit of uncertainty about the size and location of all the spots." Areas of greatest concern, most agree, are California and the upper Midwest. In Florida, scientists are warily eyeing the closely related shiny cowbird (*Molothrus bonariensis*), which is now invading from the Caribbean with as-yet-unknown consequences.

Given such uncertainties, it's not surprising that cowbird experts disagree over whether and how to control cowbird numbers. Biologists are already trapping and killing them in the breeding grounds of a few endangered songbird species, such as the Kirtland's warbler (*Dendroica kirtlandii*) in northern Michigan and the black-capped vireo (*Vireo atricapillus*) in central Texas, as well as the least Bell's vireo at Camp Pendleton. Everyone agrees that such programs can make a crucial difference for rare, geographically restricted species. Still, the fact that a little cowbird trapping is good doesn't mean a lot will be better.

A small minority of cowbird biologists does favor more extensive cowbird control. Griffith, for example, advocates an aggressive program to poison cowbirds at their winter roosts in the southern United States, where as many as 10 million birds gather at a single site. "There's nothing but benefit that could come from it," he says.

Yet most cowbird specialists don't think full-scale war is warranted. Studies tracing the movement of banded birds show that cowbirds at a single winter roost come from widely separate breeding areas, and birds that breed together often winter at different roosts. Thus, winter roost control might end up destroying cowbirds from areas where they aren't a problem while providing little relief for hard-hit areas, says Rothstein. Many worry, too, that such programs could do more harm than good by alienating animal-rights groups and prompting a backlash against the small-scale, local efforts that do work.

Whatever the right course is for dealing with cowbirds, the recent data suggest that conservationists will have to focus on a much tougher problem: forest restoration, which would provide new nesting habitat for songbirds and reduce their contact with predators that hunt along forest edges—and, incidentally, with cowbirds. "If preservation of [songbirds] was made a national policy with resources in line with those that currently go into duck and deer management, I think you could see a real difference," says Stephen Laymon of the privately funded Kern River Research Center in Weldon, California. "Short of that, I don't see [much] hope."

–Bob Holmes

Bob Holmes is a free-lance science writer in Santa Cruz, California.

NUCLEAR PHYSICS

Isotope Makers Grab Hold of the Rock

Ever since the discovery that nuclei could be transformed into heavier ones by bombarding them with other nuclei, physicists have been cooking up new "artificial" isotopes and elements larger than any found in nature. But after scores of successes, including the artificial elements from neptunium (atomic number 93) to meitnerium (109), the quest seemed to be getting more and more arduous. A combination of physical realities seemed to have the researchers in a pincers grip: Creating still heavier nuclei requires more and more intense beams from ion accelerators to increase the odds of rare fusions, yet the resulting nuclei are so unstable that detecting them requires ever more sensitive detectors.

Now, however, the search has been revitalized by hints that just up the scale of atomic weight from the heaviest nuclei yet created is a "rock of stability," populated by heavier isotopes that may survive for years. Last April, a joint Russian-American team of physicists caught a glimpse of this rock when they created a new neutron-rich isotope of element 106 that survived for tens of seconds, and at the end of January they will try to get closer still with an effort to create neutron-rich isotopes of element 108.

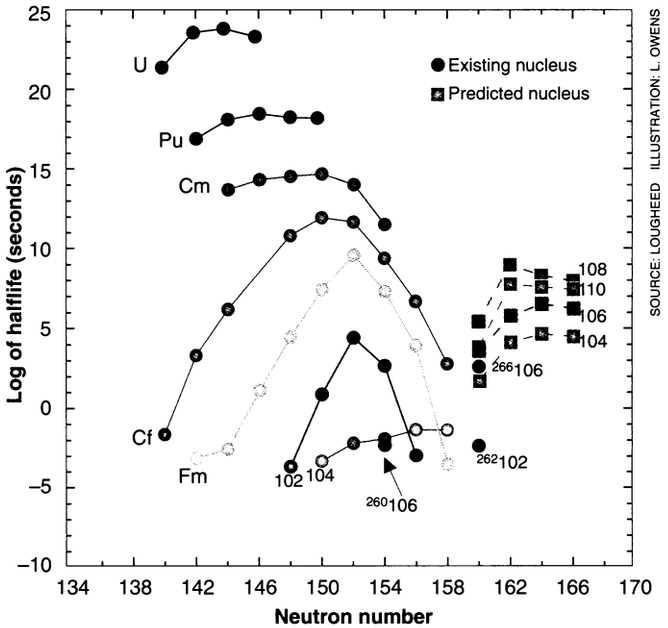
"The rock has now been discovered," says nuclear theorist Rayford Nix of Los Alamos National Laboratory. "It's a very, very significant piece of work," he adds, because "it has created a renaissance in this area of research." Little practical benefit is likely to come of the work: Only a few artificial elements have found uses, mostly as radioactive sources. But study of these nuclei at the edge of what is known promises insights into the workings of more ordinary nuclei.

In addition to their scientific value, these results are a vindication for Nix and his fellow theorists, who predicted the existence of these stable superheavy isotopes based on the way protons and neutrons in the nucleus arrange themselves in concentric spherical shells. Each shell has a maximum capacity defined by quantum mechanics. If the outermost shells are full, the nucleus is very stable; lead, for example, which has full outer shells, is among the stablest elements. In the heaviest nuclei created so far, the outer shells have many vacancies—hence their instability.

But theorists including Nix and his colleague Peter Möller predicted that some partially filled shells can deform into a slightly cigar-shaped configuration that adds stability. One such deformed shell is predicted for an as-yet-undiscovered isotope of element 108 that has 162 neutrons, more than any of its known isotopes. Adam Sobiczewski, a theorist from the Institute of Nuclear Studies in Warsaw, Poland, calculated that the deformed shell would endow this nucleus, called $^{270}108$, with a half-life of tens of years. That would put it at the center of the rock of stability.

The team of experimentalists, led by Yuri Lazarev of the Joint Institute for Nuclear Research at Dubna, near Moscow, and Ron Lougheed of Lawrence Livermore National Laboratory in California, set out to test the theory by bombarding a thin target of curium-248 with neon-22 ions. Their aim was to create a new neutron-rich isotope of element 106 with 160 neutrons ($^{266}106$) that should lie near the rock and therefore display some of its predicted stability: Sobiczewski's theoretical model suggested this nucleus would have a half-life of tens of seconds.

In 16 days of bombardment, the researchers fired 1.6×10^{19} neon ions at a target con-



A promised land. Artificial nuclei packed with neutrons may gain remarkable stability, according to theoretical calculations (dashed lines).