Exploring ceramic vaccines, drug carriers

Make a bunch of virus-sized ceramic particles. Now coat them with a laboratory-designed, carbohydrate-like goo, and then let proteins derived from health-wrecking microbes or viruses stick to it. What have you got?

"We may have here a way of making vaccines that nobody has been able to make," says medical pathologist Nir Kossovsky of the University of California, Los Angeles. His tiny particles also might redeem hundreds of mothballed drug candidates — ones that showed early promise in test tubes but fizzled in animal or human trials.

The key to such applications — none of them even close to human trials — rests in the apparent ability of the coated microscopic crystals to preserve the precise, medically important shape of the delicate proteins adhering to them. That's encouraging, Kossovsky says, because in the body, proteins encounter many molecule-manipulating influences. And the most subtle changes in the shape or structure of a protein can spell dramatic shifts — sometimes with toxic consequences — in its biological behavior or therapeutic potential.

The UCLA researchers suspect that as drug and vaccine designers increasingly turn to protein-based agents for disarming viruses, diseased cells or health-threatening biochemicals, stabilizing the proteins' shapes will prove paramount.

In the winter JOURNAL OF APPLIED BIOMATERIALS, Kossovsky, Rointan F. Bunshah and seven collaborators describe experiments using ensembles of specially coated tin oxide ceramic crystals, each about 25 nanometers in diameter. The proprietary sticky coating — dubbed GF292 — prevents protein-deforming surface interactions between the particles and the attached molecules, Kossovsky explains.

Antibodies — the biochemical champs at finding and binding to specific molecular shapes — had no trouble latching onto transferrin molecules bound to the particles, the UCLA team found. This showed that transferrin, a protein carrier for iron in the blood, retained its precise antibody-attracting structure despite its attachment to the nano-particles, Kossovsky says.

The Epstein-Barr virus (EBV) causes mononucleosis and has been implicated in other ailments. With backing from a Toronto-based technology-development firm, which Kossovsky and Bunshah help manage, the UCLA researchers have begun attaching surface proteins from EBV to the nano-particles with the goal of making safer vaccines from "sterile" decoy viruses.

On rare occasions, vaccines made from real but "killed" viruses have initiated the disease they were designed to prevent. The UCLA researchers expect the immune system will respond to nano-particles robed in the surface proteins of a virus by making antibodies against the virus. Because the cores of the new vaccines are purely ceramic, these decoy viruses cannot cause infection.

Kossovsky also envisions coating the crystalline ceramics particles with oxygen-carrying hemoglobin molecules to make artificial blood.

Acknowledging that biological complexity makes most drug ideas bite the dust, Kossovsky nonetheless asserts, "We have something that is awfully promising." — *I. Amato*

New and primordial role for ribozymes?

According to some origin-of-life theories, the DNA-based genetic machinery found in almost all modern organisms arose from an ancient "RNA world" (SN: 10/7/89, p.229). Evidence for this scenario stems mainly from the recent discovery of ribozymes: RNA molecules capable of carrying out biochemical tasks that scientists once believed only protein enzymes could perform.

Unlike proteins, which can act as catalysts to direct the cell's complex workings, all ribozymes found so far chemically transformed only RNA (ribonucleic acid). But a new report hints ribozymes may be capable of altering non-RNA molecules as well. If confirmed, the work would enlarge the known range of reactions in which ribozymes participate and strengthen support for the concept of a primitive RNA world.

In the Nov. 27 BIOCHEMISTRY, Japanese scientists report that RNA from a yeast catalyzed the transfer of electrons from one non-RNA molecule to another. Such electron-shuffling processes, known as "redox" reactions, play a crucial role in the metabolism of organisms. Researchers at Mitsubishi Kasei Institute of Life Sciences in Tokyo and Tohoku University in Sendai identified the catalytic agent as 5-hydroxycytidine, a modified form of one of the four basic nucleoside building blocks making up every RNA chain.

The finding "indicates new possibilities for RNA as a living molecule," coauthor Hiroshi Yanagawa told SCIENCE NEWS. That an RNA can assist in redox reactions might mean that before proteins evolved, primordial RNAs served as catalysts driving life-sustaining metabolic processes, the Mitsubishi Kasei scientist suggests. His team proposes that 5-hydroxycytidine may be a vestige of such ancient RNAs.

But others say these claims lack supporting evidence. "Linking [5-hydroxycytidine] to an RNA world is a little premature" because such modified nucleosides are not necessarily "old" in an evolutionary sense, says biochemist Andrew D. Ellington at Massachusetts General Hospital in Boston. Moreover, he notes, scientists have long known that molecules containing modified nucleosides can help drive metabolic reactions.

Thomas R. Cech of the University of Colorado in Boulder also points out that the enzyme-like agent is *only* a modified nucleoside — not a "proper ribozyme," or folded chain of RNA nucleosides that binds a substance to foster a specific biochemical reaction. The Japanese team has yet to show that a yeast RNA containing the isolated agent meets this definition, suggests Cech, the 1989 Nobel laureate who coined the term "ribozyme."

However, Cech acknowledges, the new work does carry important implications. Until now, research has indicated that catalytic RNAs perform only a "limited range of reactions" — making and breaking bonds in RNA. But if a modified nucleoside within an RNA enabled that chain to alter substrates other than RNA, that would "extend the enzymatic repertoire [of ribozymes] beyond the currently known examples," he says. — *I. Chen*

Rat removal converts shrublands to grass

James H. Brown wasn't looking for greener pastures, but he found them anyway. When he and his colleagues fenced off sections of the Chihuahuan Desert in 1977, excluding certain rat species from small plots of shrubland in southeastern Arizona, they had but a single goal: assessing the rats' ability to compete with native ants for the area's supply of large plant seeds.

But 13 years after initiating the desert study and four years after his original associates published their last report on the project, Brown has doggedly stayed on the job to record a remarkable transformation among eight of 24 small plots of land — each surrounded by fine-mesh fences adjusted to exclude either all rodents or at least three species of kangaroo rats native to the sites. Each of these

Margaret Kurzius

Dipodomys merriami, *the most abundant of three species of kangaroo rats banished from desert study areas.*

2,500-square-meter study areas – formerly patchworks of scraggly shrubs and parched earth – has sprouted a dense blanket of knee-high grass. In contrast, none of the study areas that maintained their normal population of the hopping rodents underwent a similar transformation, notes Brown, an ecologist at the University of New Mexico in Albuquerque.

All three species of native kangaroo rats (genus *Dipodomys*) had to be excluded before the study sites – bordering a transitional region that includes both desert shrubland and grassland – began their startling botanical conversion, Brown says. This finding documents for the first time that the collective actions of several related types of animals – not just the behavior of a single species – can dramatically alter the fate of an ecosystem, he says.

Identifying a small group of animals, a "keystone guild," that can significantly change the ecology of a habitat may have profound implications for conservation efforts, Brown asserts. He and Edward J. Heske, also from the University of New Mexico, report their work in the Dec. 21 SCIENCE.

"People are only worried about the much more comprehensible and simple question of conservation – whether a species is there or not," comments marine ecologist James A. Estes of the University of California, Santa Cruz. "But if [an ecosystem] is tied together by a guild rather than a single species, our emphasis ought to be on conservation of the guild rather than the species."

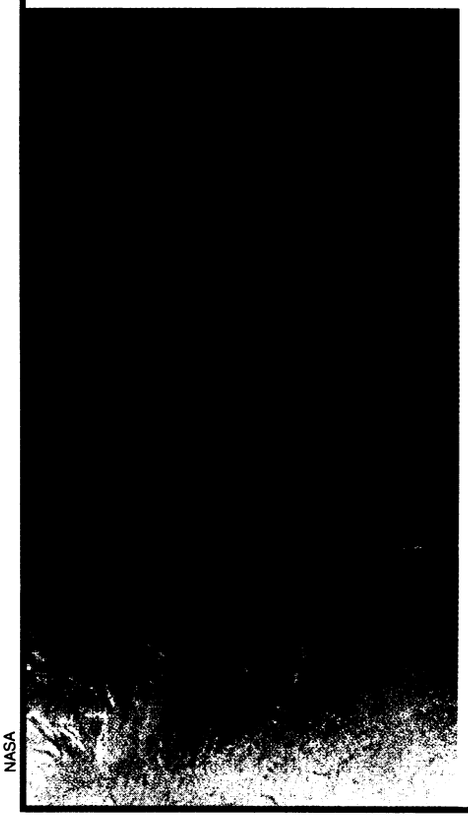
Brown suggests that if ecologists cannot prevent the extinction of species that appear to play a key role influencing their local environment, they should replace the lost animals with organisms able to serve a similar habitat-preserving function.

He adds that the ecological impact of eliminating a keystone guild, though initially subtle, can prove dramatic. For example, during the first five years of the desert experiment, only small changes occurred – the lack of kangaroo rats, which eat large seeds, spurred rainy-season growth of annual plants that bear these seeds. After nine years, however, grasses began to replace those plants, restoring lasting greenery to the once-sparse landscape. A perennial known as Lehmann's lovegrass increased 20-fold and the annual grass *Aristida adscensionis* tripled in abundance.

Brown says he hasn't determined why banishing kangaroo rats should promote grassland, but he suggests two possibilities: Frequent burrowing by the rats may prevent grass seeds from taking root, and the accumulation of dead organic material that the rats normally help decompose may hold vital moisture needed for the grasses to thrive.

– R. Cowen

Distant image of Earth's icy Antarctica



NASA

Rare ice-free areas appear amidst the vast whiteness of western Antarctica in this image captured by the Jupiter-bound Galileo spacecraft during its first swing past Earth. The dark Ross Sea (left) laps against the Ross Ice Shelf. Bare peaks of the Convoy Range and the barren Dry Valleys near the main U.S. research base at McMurdo add a dash of brown (lower center), as do the Darwin Mountains (far right).

Engineers at NASA's Jet Propulsion Laboratory in Pasadena, Calif., produced this photo by combining monochrome images made through red, green and violet filters to recreate the frozen terrain's subtle colors.

After rounding Venus last Feb. 10, Galileo zipped to within 962 kilometers of Earth. The craft captured this image on Dec. 8, from about 181,000 km.

NASA designed Galileo's course to use the gravity of Venus and Earth to accelerate the craft on its loop-the-loop journey. Galileo should begin close observations of an asteroid (Gaspra) next October, swing past Earth again in 1992, and finally orbit Jupiter in 1995. During its recent encounter, Galileo took about 3,500 images of Earth and its moon.

Some autism tied to rare fetal disorders

Any of a dozen rare diseases affecting the brain may, when experienced in the womb or during infancy, increase one's risk of autism, a new study concludes. Data gleaned from a study of nearly all Utah's residents show that one in 10 cases of autism occurred in individuals with a history of these disorders.

The findings support the theory that various types of brain damage early in fetal life set the stage for the devastating symptoms of autism, says psychiatrist Edward R. Ritvo of the University of California, Los Angeles. These symptoms include unresponsiveness to others, lack of language skills, and repetitive body movements. The disease afflicts one in 2,500 children worldwide.

From 1984 to 1988, Ritvo and his colleagues conducted a survey of autism among Utah's 1.6 million inhabitants. They located 233 autistic individuals possessing early medical records.

In the December AMERICAN JOURNAL OF PSYCHIATRY, the scientists report finding that 26 of the autistics had been diagnosed early in life with one of 12 rare diseases. These included such viral and bacterial infections as congenital forms of herpes, rubella and cytomegalovirus; chromosome and genetic abnormalities such as fragile X syndrome, Down's syndrome and tuberous sclerosis; and metabolic disorders such as congenital hypothyroidism and an enzyme deficiency known as Sanfilippo's syndrome.

Ritvo cites "astronomical" odds against these rare diseases randomly occurring among 11 percent of Utah's autistics. Indeed, Ritvo maintains, because some participants in the study were not screened for fragile X syndrome, nearly 17 percent of the autistics might have had one of these diseases.

The only clinical difference among the Utah autistics involved IQ – an average of 42 among the 26 with the rare diseases versus 60 among the rest. In the future, Ritvo says, his team will attempt to pin down critical parts of the brain altered by the rare diseases in autistics. He suspects these diseases may affect other areas of the brain in individuals who do not develop autism.

"The UCLA group has confirmed what's been suspected about autism for some time, but in a thorough epidemiological study," remarks psychiatrist Fred R. Volkmar of Yale University. For example, in the last 20 years, researchers have linked congenital rubella and Down's syndrome to autism, he says.

Ritvo says the Utah study provides "the best evidence to date" that in a significant minority of cases, autistic symptoms represent the final common pathway of several diseases that undermine brain function.

– B. Bower