

A 2003 report by the Federal Trade Commission identified continuations as among the worst problems in the patent system, allowing applicants to keep patents “pending for extended periods, monitor developments in the relevant market, and then modify their claims to ensnare competitors’ products.” “You get to take multiple shots ... and if one gets through, you’re fine,” says former Genentech lawyer Mark Lemley, now a law professor at Stanford University in Palo Alto, California, and an expert on continuations. The resulting uncertainty about competitors’

patents, he says, “deter[s] innovation” by discouraging research investment. Semiconductor giant Micron Technology calls the reform “long overdue.”

But opponents of PTO’s proposed change warn that it will dampen creativity and, as California biotech Amgen noted in its public comments, “curtail the rights of true innovators to seek legitimate patent protection.” Amgen officials say that biomedical research takes time and that continuations are needed to let inventors and PTO “fully understand” pending applications. Abuse is rare, they con-

tend. The National Institutes of Health (NIH) says that continuations are needed to alert PTO to data from experiments begun before the initial application but not available for many years. (Doll says NIH could deal with such data in an appeal.)

Doll says he doesn’t know when his office will issue final rules, although one of his aides told a northern Virginia audience last week that a decision is expected by January. And those rules may not be the last word. “An opportunity for a lawsuit” exists, admits Doll.

—ELI KINTISCH

IMMUNOLOGY

Mast Cells Defang Snake and Bee Venom

Venomous snakes are deadly predators; every year they kill perhaps 125,000 people, mostly in the developing world where antivenoms are less available. Researchers have long blamed immune warriors called mast cells for contributing to this toll by releasing additional toxic molecules into the victims’ bodies. But a study out today puts these cells in a surprising new light.

On page 526, a team led by Stephen Galli and Martin Metz of Stanford University School of Medicine in Palo Alto, California, reports that mast cells help protect mice against snake and bee venoms, at least in part by breaking down the poisons. The “paradigm-shifting” results provide “convincing evidence for a previously unrecognized role of mast cells,” says immunologist Juan Rivera of the National Institute of Arthritis and Musculoskeletal and Skin Diseases in Bethesda, Maryland.

Although mast cells help defend the body against certain parasites and bacteria, they can run amok, triggering allergic attacks including asthma and anaphylactic shock, which can be fatal. They do this by releasing molecules that induce inflammation and cause other effects that are protective in small doses but harmful if they get out of hand. These molecules include a variety of protein-splitting enzymes called proteases.

Among the proteins degraded by mast-cell proteases is endothelin-1, a potent constrictor of blood vessels that is involved in several pathological conditions including sepsis, asthma, and high blood pressure. About 2 years ago, the Galli group showed that under some circumstances this mast-cell activity protects mice against endothelin-1’s toxic effects, allowing the animals to survive an infection that would otherwise throw them into septic shock.

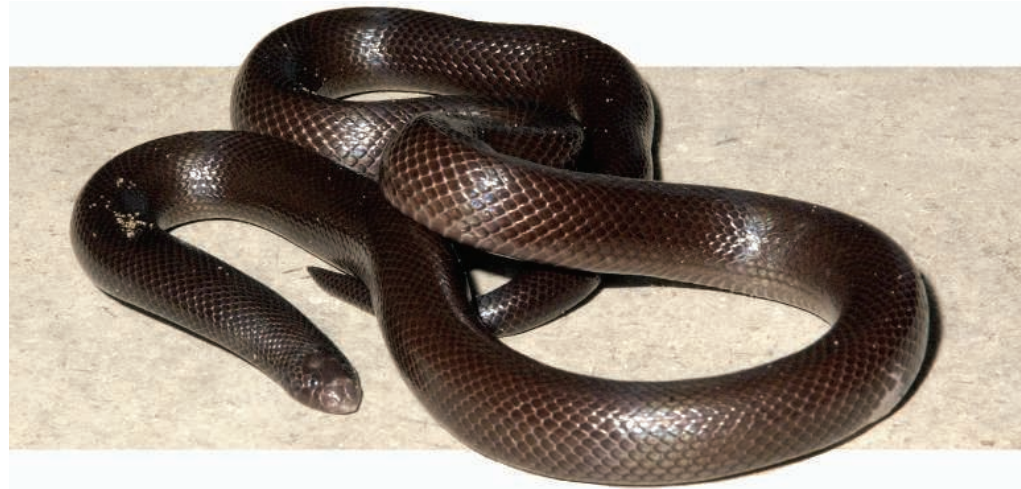
Nearly 20 years ago, Elazar Kochva of Tel Aviv University in Israel found that the amino acid sequence of sarafotoxin, a protein in the venom of the Israeli mole viper, closely resembles that of endothelin-1. Intrigued by that similarity, Galli wondered whether mast cells pro-

tect mice against the venom. He and his colleagues tested the effects of venom provided by Kochva on normal mice and on genetically altered ones that lack mast cells. The result was clear-cut: “It takes 10 times as much venom to kill normal mice as mast cell-deficient mice,” says Galli. And when mast cells derived from normal mice were engrafted into the mutant mice, the animals developed the same amount of venom resistance.

Because the Israeli mole viper lives in a limited area of the Middle East, it might be something of a biological oddity. So the

describes the experiments as “exceedingly elegant” demonstrations that mast cells are involved in reducing the toxic effects of venoms. Indeed, Rivera adds, “we need to rethink the role of the cells” and how they might participate in anaphylactic shock.

Both researchers caution that this mouse work doesn’t prove that human mast cells also serve as an antivenom system. They point out that mouse mast cells produce more proteases than do the human versions, although both make carboxypeptidase A. Galli notes that other mast-cell products may



Slithering into immunology. Venom milked from this Israeli mole viper provided the clue that led to the discovery that mast cells can protect against some snake and bee venoms.

Stanford team tested the venoms of the western diamondback rattlesnake and the southern copperhead, both of which are widespread in the United States. Mast cells protected mice from these venoms and also from honeybee venom. In the case of the snake venoms, Galli and his colleagues showed that a mast-cell protease called carboxypeptidase A contributes to the protection.

Hugh Miller, a mast-cell expert at the University of Edinburgh in the U.K.,

also play a role in venom protection. One such possibility, suggested 40 years ago but not yet tested, is the anticoagulant heparin, a negatively charged molecule that might bind to, and thus inactivate, venom’s positively charged components.

Given the diverse venoms that exist in nature, Galli says it’s unlikely that mast cells enhance resistance to all of them. But the new work shows that the cells definitely take the bite out of some.

—JEAN MARX