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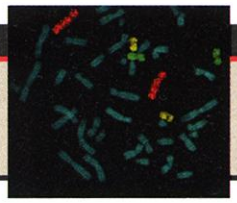
Dinosaur heart



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DOE's triple treat

SCIENCE AND BUSINESS

Patent Prompts Rochester to Sue for Slice of Drug Profits

The University of Rochester in New York has won what it calls the most lucrative patent ever awarded to an academic institution, triggering a major confrontation with the makers of several best-selling drugs.

Last week, after an 8-year review, the U.S. Patent and Trademark Office (PTO) gave the university a sweeping patent on the science underlying a new class of anti-inflammatory drugs known as COX-2 inhibitors. The market for such drugs is estimated at $10 billion by 2008. Within hours of the 11 April award, Rochester officials filed suit against the makers of a top-selling drug based on the discovery.

The suit claims that the university is entitled to significant royalties on Celebrex, an antiarthritis drug made by G. D. Searle & Co. of Skokie, Illinois, and the Pfizer Co. of New York City, which generated nearly $1.5 billion in sales last year. Rochester's claim could eventually expand to cover Vioxx, a Merck product that earned the Whitehouse Station, New Jersey, company nearly $500 million in 1999.

Searle attorneys argue that the patent is "overly broad.... Our preliminary look at their claim is that it will not be shown to be valid," says Robert Bogomolny, a senior attorney with Pharmacia Co. of Peapack, New Jersey, Searle's parent corporation. Without providing specifics, Pharmacia attorneys claimed that the work is not "novel," because other researchers published papers on similar COX-2 work prior to Rochester's 1992 patent application.

The new patent is based on research conducted in the 1980s and 1990s by Rochester physician and cancer researcher Donald Young and two colleagues, Michael O'Banion and Virginia Winn. Along with teams at several other universities, Young's group was investigating enzymes, now called cyclooxygenase-1 (COX-1) and COX-2, that appeared to play a role in inflammation (*Science*, 22 May 1998, p. 1191). Young's team found and cloned the gene that produces COX-2, then engineered cells to produce one or both enzymes. Experiments showed that COX-2 appears to be primarily responsible for inflammation, while COX-1 helps protect the stomach lining and kidneys. Compounds that inhibit COX-2 appear to be free from the negative side effects—such as ulcers and gastrointestinal bleeding—caused by aspirin and similar drugs that also block COX-1. The new generation of drugs leaves COX-1 alone, reducing the risk of ulcers.

Big headache. From left, Rochester's Donald Young, Virginia Winn, and Kerry O'Banion discovered and cloned the gene that produces the COX-2 enzyme, leading to a multibillion-dollar market for anti-inflammatory drugs like Celebrex.

Related studies were also done by teams led by Phil Needleman at Washington University in St. Louis, who is now Pharmacia's chief scientist, Harvey Herschman at the University of California, Los Angeles, and Danile Simmons at Brigham Young University in Provo, Utah. But in 1992, Rochester became the only school to move ahead with a patent application.

Last September, patent examiners informed the university that they were ready to approve the claim. While such notifications often prompt universities to begin negotiating with a company on a licensing deal, Rochester officials instead hired attorney Gerald Dodson of Morrison and Foerster in San Francisco. Last year, Dodson led the legal team that won a $200 million patent infringement judgment against the biotech company Genentech for the University of California, San Francisco (*Science*, 26 November 1999, p. 1655). "It's not like this was some stealth effort," says Rochester's attorney, Terrance O'Grady. "We just didn't want anything to jeopardize the patent."

Pharmacia executives say that news of the patent and lawsuit caught them off guard. "We are surprised, dismayed, and irritated about how this all began," says Bogomolny. "It is unusual, to say the least, for a patent dispute to begin with a lawsuit and press conference." He says the company is still deciding on its strategy, but will "defend its interests."

O'Grady believes that the PTO's 8-year review will help Rochester prevail. "The examiner examined every issue brought before [the PTO], so any challenger will have to raise a new concern," he says. But the university's extensive paper trail to justify its claims could also prove to be a weak link, says an outside attorney. Challengers "like to see big boxes full of paper," says Richard Aron Osman of Hillsborough, California. "The more there is, the more likely you are to find inconsistent statements" and other potentially damaging evidence.

Rochester officials say they want to resolve their claim at the bargaining table, not in the courtroom. "We're eager to negotiate," says O'Grady. But the school's opening bid of a royalty in the 10% range—which could generate more than $1 billion over the patent's 17-year life—is well above the 2% to 4% that industry sources say is typical.

However, even lower royalties could produce payments that dwarf a basic Cohen-Boyer gene engineering patent held by Stanford University and the University of California that has generated about $250 million since 1980. Some patent watchers are skeptical that the COX patent will prove so special. But they say the debate itself highlights the growing willingness of universities to seek a cut of the profits produced by taxpayer-funded research. "Universities are getting very active in protecting their intellectual property," says James Sieverson, head of the Cornell Research

CREDITS: (TOP TO BOTTOM) WAYNE SCARBERRY; SEARLE

Foundation in Ithaca, New York, and president of the Association of University Technology Managers, which monitors patenting activity on U.S. campuses. Still, he notes, "the kinds of patents that have this kind of potential financial impact are relatively rare, maybe one out of 1000."

–DAVID MALAKOFF

PALEOANTHROPOLOGY

Is Alexander the Great's Father Missing, Too?

The remains of Alexander the Great—the warrior who conquered much of the known civilized world in the fourth century B.C.—have been lost for more than 1500 years. But in 1977, Greek archaeologists unearthed a tomb in the town of Vergina, in northern Greece, that they claimed contained a worthy consolation prize: the remains of Alexander's powerful father, Philip II, who had started expanding the Macedonian empire and had enlisted Aristotle to tutor the precocious prince. A team of British scholars confirmed this identification in 1984. But on page 511, a paper by Greek paleoanthropologist Antonis Bartsiokas argues that close-up photographic analysis of the remains suggests that they are not those of battle-scarred Philip II, but belonged to a less important historical figure: Philip's son (and Alexander the Great's half-brother), Philip III Arrhidaeus.

The new report also offers the tantalizing possibility that some of the tomb's artifacts, including a helmet and a ceremonial shield, may have actually belonged to the great conqueror himself. "Are we lucky enough to have found the helmet of Alexander the Great?" wonders Eugene N. Borza, a leading expert on the ancient Macedonians and professor emeritus of ancient history at Pennsylvania State University, University Park. "It's too good to be true, but a tempting thought nonetheless."

There is general agreement that the Great Tumulus of Vergina, originally excavated by Greek archaeologist Manolis Andronicos, was a burial ground for some members of Alexander's royal family. Of the four tombs, one almost certainly contains the remains of Alexander's only son—murdered at a young age—but questions have always surrounded the identity of the male and female remains in the richest tomb, Royal Tomb II. A team including University of Bristol anatomist Jonathan H. Musgrave concluded in 1984 that markings on the skull and other bones appeared to correlate with reported injuries suffered by Philip II, including an arrow wound to his right eye during the siege of Methone in 354 B.C., 18 years before his assassination. That identification forms the centerpiece of a new museum at Vergina.

But Bartsiokas, the director of Greece's Anaximandrian Institute of Human Evolution and an assistant professor at Democritus University of Thrace, says his new close-ups of the bones, taken in 1998, do not reveal such damage. He scrutinized the bones to see whether the previously reported "notch" and "bone pimple" on the skull were consistent with healed wounds from an arrow injury. He rejects this hypothesis, reporting that the marks "bear no evidence of healing or callus formation" and are simply normal anatomical features. "Despite the severe injuries suffered by Philip II, there is no skeletal evidence whatsoever of any injuries to the male occupant of Royal Tomb II," he concludes.

Identity crisis. This skull, once thought to be that of the warrior king, Philip II of Macedonia, may instead belong to his son, Philip III Arrhidaeus.

CREDIT: ANTONIS BARTSIOKAS/ANAXIMANDRIAN INSTITUTE OF HUMAN EVOLUTION

He also notes that historical records show that Philip III Arrhidaeus—who had ruled for 6 years after Alexander's death and was murdered in 317 B.C.—had been buried for about 6 months before his exhumation and cremation by Cassander. And the condition of the skeletal remains were consistent with bones that had been "dry" of flesh before cremation. "Only the bones of Arrhidaeus would show these characteristics," Bartsiokas contends. As for the Vergina museum's description of Tomb II as that of Philip II, Bartsiokas says: "I hope they change that."

The later burial date leaves open the possibility that some of the artifacts in the tomb—including a helmet, a gilded silver diadem, an iron-and-gold cuirass, and the ceremonial shield—may have belonged to Alexander himself, who had died in 323 B.C. and whose remains were interred in Egypt before being lost. Borza says the Vergina tomb's items fit several historical descriptions of Alexander's paraphernalia.

Despite that exciting prospect, Musgrave—who made the original identification along with Manchester archaeologist John Prag and medical artist Richard Neave—stands by his group's findings. He insists that the facial bones he examined showed signs of healed wounds and suggests that the bones' condition may have degraded during the 15 years between his examination and that of Bartsiokas. He also contends that several details of Tomb II—including its apparent hasty construction—argue against it being the tomb of Philip III Arrhidaeus. Bartsiokas "has concentrated on evidence that is limited in the extreme to postulate a hypothesis that cannot be sustained," Musgrave says.

But Borza and Bartsiokas dismiss those objections. Borza argues that two artifacts in the tomb—a piece of ceramic pottery and a Macedonian silver wine strainer—are clearly dated later than Philip II's death. The new analysis of the bones, along with the late artifacts, says Borza, "drive the final nail in the coffin of the Philip II identification. Clearly, this is not the tomb of Philip II, but of the next generation."

–ROBERT KOENIG

GERMAN VOTE

Animal Rights Amendment Defeated

German scientists who experiment on laboratory animals can breathe a bit easier—for now. On 13 April Germany's lower house of parliament narrowly defeated an effort to amend the nation's constitution to guarantee animal welfare. Such an amendment could have led to court challenges of much of the country's lab-animal research.

The amendment, supported by the ruling