dents simultaneously and that later in time, each of those two yielded two more—again at the same time. But almost three-quarters of the gene families he examined, including the *HOX* family, had different histories.

Hughes also took a close look at the order of genes on supposedly duplicated chromosomes, an analysis that he says also failed to support Ohno's hypothesis. If a whole chromosome was copied, then most or all of the genes should be more or less in the same order in both. But often they are not. "Everything we've looked at [fails to] support the hypothesis," Hughes concludes. He proposes instead that the genes occurring on multiple chromosomes moved to these different locations as a group and then stayed together because it was advantageous to the genome.

But Holland isn't giving up that easily, and his scenario could be a way of reconciling Hughes's findings with Ohno's proposal about the two duplications early in vertebrate evolution. He thinks the inconsistencies highlighted by Hughes might be resolved by assuming that the time between the two rounds of duplication was much shorter than Ohno imagined.

By Ohno's thinking, the first round produced two copies of each chromosome, or four total, because the chromosomes exist as pairs. At first those copies randomly paired off, but eventually they became different enough to have preferred partners, and each set of four became two sets of two, restoring diploidy, the typical chromosomal arrangement. Only after that had happened, which Ohno proposed would take many millions of years, would the second round of duplication have taken place.

At a meeting* in April in Aussois, France, Holland suggested instead that the second duplication occurred before the four chromosomes produced by the first duplication diverged, thus producing eight roughly equivalent chromosomes. If that had been the case, then the recombination and switching of parts of chromosomes that typically takes place between chromosome pairs would have involved all eight, with different genes moving around at different times. Thus, gene order would vary from chromosome to chromosome, and neighboring genes could appear to have duplicated at different times instead of all at once. This scenario would confound analyses such as that done by Hughes.

Other molecular events may change the genome in ways that obscure its true evolutionary history. Hiccups in DNA replication can spit out extra copies of genes or additional pieces of chromosomes. Mobile genetic elements can move genes and gene pieces around. And frequently, one copy of a gene loses its function and becomes unrecognizable as a gene. Sorting through all this to get a clear picture of how each organism's genome reached its present state will be hard, perhaps even impossible, says Meyer. Improvements in dating genes and identifying what instigates changes in a genome can help, however.

But if the work resolves how the evolution of genomes prompts the evolution of new organisms, it will make possible a much better understanding of our own recently sequenced genome. If researchers can figure out the histories of families of genes, they will be in a much better position to sort out which genes are equivalent between, say, human and mouse or human and zebrafish. Knowing that will help tremendously as researchers try to pin down the functions of human genes in mice or other organisms that are more amenable to genetic manipulations than humans. No matter what, says Hughes, "we have to really understand how the genome is arranged." And that is one thing that he and Ohno would agree on.

—ELIZABETH PENNISI

* The Jacques Monod Conference on Gene and Genome Duplications and the Evolution of Novel Gene Functions, Aussois, France, 26 to 30 April.

PATENT INFRINGEMENT

High Court Asked to Rule on What Makes an Idea New

Ten years after a U.S. company sued a Japanese firm for patent infringement, the Supreme Court will hear "the biggest patent case in decades"

When is imitation innovation—and when is it piracy? The U.S. Supreme Court will hear conflicting answers to those questions early next month in a patent infringement case that is being watched closely by academic and industrial groups.

The case, referred to as *Festo*,* centers on a 150-year-old legal concept known as the "doctrine of equivalents." The doctrine is designed to prevent businesses from making minor changes to a patented technology and then claiming it as a new invention. Companies that have patented proteins, for instance, have invoked the doctrine to prevent competitors from marketing molecules that have slightly different amino acid sequences but perform the same biological function.

Last year, however, a federal appeals court stunned many experts by ruling that the doctrine doesn't apply to any patent claim that was narrowed during the review process before the patent was issued. Because that happens to most patent claims, the ruling could have a broad impact—especially, some experts claim, in the biotechnology industry. The business, biotechnology, and patent law communities have filed dozens of friend-of-the-court briefs since the high court agreed in June to hear the case (see table); oral arguments are scheduled for 8 January.

CREDIT: (COURT) PAT BENIC/AP; SOURCE: U.S. SUPREME COURT

THE FIGHT OVER *FESTO**

Let the decision stand
Genentech; Applera (Celera); MedImmune; IBM; Kodak; Ford; DuPont; Intel; Cypress Semiconductor; United Technologies

Reverse it
20 major research universities and higher education groups; Celltech; Chiron; Bose; U.S. Chamber of Commerce; American Intellectual Property Law Association; Association of Patent Law Firms; Minnesota Mining and Manufacturing

Other positions
U.S. Solicitor General; Institute of Electrical and Electronics Engineers

* Selected parties

Supporters say that last year's ruling clarifies the law and should prevent nuisance lawsuits while it fosters better written patents and greater innovation. But many major research universities disagree, joining critics who predict that it will open the door to wholesale copying and undermine thousands of patents. With billions of dollars in licensing revenues potentially at stake, "this is the biggest patent case in decades," says Susan Braden, an attorney at Baker & McKenzie in Washington, D.C.,

* *Festo Corporation* v. *Shoketsu Kinzoku Kogyo Kabushki Co. Ltd.* (a.k.a. SMC Co.). U.S. Supreme Court Docket 00-1543.

who is representing the universities.

This isn't the first time that the Supreme Court has looked at *Festo*. The case entered the federal court system in 1992, when the Hauppauge, New York–based Festo Corp. charged that SMC Co. of Japan had infringed on its patent for a cylindrical part of a robotic arm by producing a similar mechanism. Festo won several early rounds, but in 1997 the Supreme Court asked the U.S. Court of Appeals for the Federal Circuit—a specialized court that handles patent cases—to review some tricky technical issues. In November 2000, the appellate court produced a 170-page decision that favored SMC, although seven of the 12 judges involved wrote separate opinions.

The court concluded that Festo had altered its cylinder patent during review by the U.S. Patent and Trademark Office (PTO), triggering what lawyers call "prosecution history estoppel." Estoppel is designed to prevent a patent applicant from narrowing a claim to satisfy PTO's requirement that inventions be original, then using the doctrine of equivalents to expand the reach of the patent and quash competitors. But the court declared "unworkable" current rules governing when estoppel could be claimed and ordered a new "complete bar" against invoking the doctrine to defend altered portions of patents. The court said it could still be used to defend unaltered claims.

The flaw in that ruling, critics say, is that virtually all key patent claims undergo revision during the tug-of-war between applicant and examiner. Patent seekers typically word their applications as broadly as possible, whereas PTO's examiners routinely narrow the language to leave more room for innovation.

Some biotech companies complain that *Festo* is especially inappropriate for DNA-based patents, because the engineered proteins that may become blockbuster drugs can be created by thousands—if not millions—of slightly different but related DNA sequences. "*Festo* provides a road map for a would-be copyist to avoid [literal] infringement," argues a brief filed by Chiron, an Emeryville, California–based biotech company that wants the court to overturn the ruling. To legally copy a patented protein, it says, a clever forger could simply review a patent's public case history then create a twin with functionally equivalent substitutes.

That's already happened, claims one British biotech company. In its brief urging *Festo*'s reversal, Celltech describes its suit against MedImmune, a U.S. company. MedImmune makes Synergin, a hot-selling drug that protects premature babies from lung infections. But Celltech says Synergin's hybrid mouse-human antibody differs from one of its creations by just a single amino acid out of more than 1300—a big enough difference to avoid literal infringement but not enough to alter the molecule's function.

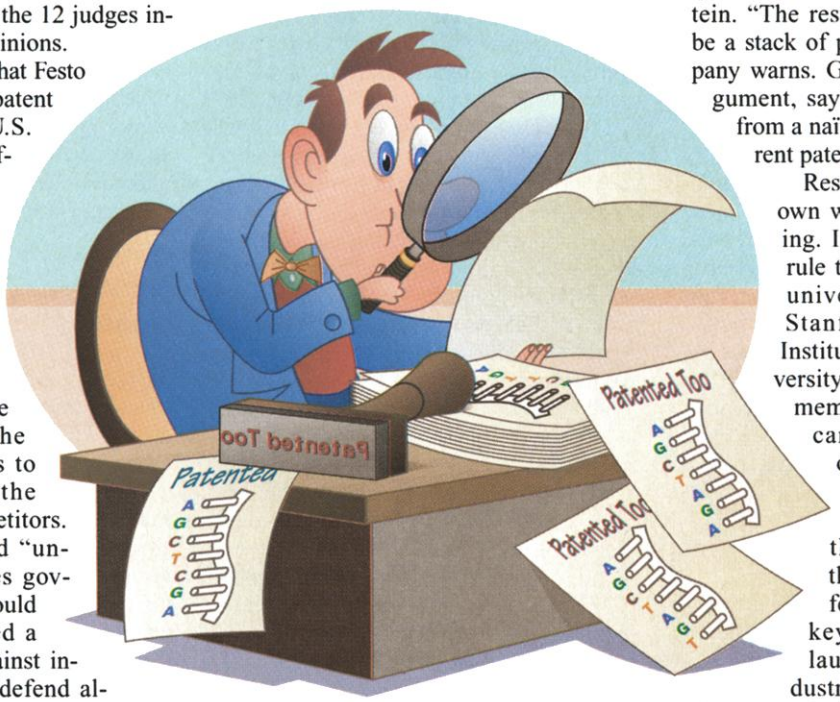

ILLUSTRATION: TERRY SMITH

Celltech has asked a U.K. court to find MedImmune guilty of infringing on its U.S. patent under the doctrine of equivalents, but the *Festo* decision has stalled the case. "Celltech's situation will be a common occurrence if [the *Festo* decision] stands as written," warn Celltech's attorneys. The case will likely be thrown out if the Supreme Court upholds the earlier ruling.

In its own brief supporting the lower court decision, MedImmune says Celltech's lawsuit is just the kind of "wasteful litigation" that the *Festo* ruling will help prevent. Celltech is using "creative [legal] arguments … in order to reclaim what [it previously] surrendered to the Patent Office" and win hefty licensing fees on Synergin, the company claims. Before the *Festo* case, it adds, uncertainty about how judges would apply the doctrine of equivalents often prompted companies "to take licenses and pay royalties as ransom, to avoid litigation."

Industry pioneer Genentech of South San Francisco, California, agrees that *Festo* will reduce that uncertainty. "Biotechnology will not only survive *Festo*, but will thrive under it," its brief predicts. One benefit, the company says, will be that firms will fine-tune their applications before filing them.

Chiron, however, sees a darker future. It warns that *Festo* will cause "an explosion in the verbiage a patent contains" as applicants try to cover every foreseeable minor variation on an invention. For protein patents, "mathematics alone make describing every possible variant impossible," it says, noting that 10^{36} nucleotide sequences could code for one type of protein. "The resulting patent claims would be a stack of paper miles high," the company warns. Genentech dismisses that argument, saying that such fears "derive from a naïve misapprehension" of current patent law and PTO policies.

Research universities have their own worries about the *Festo* ruling. In urging the court to overrule the decision, 20 schools and university groups—including Stanford, the Massachusetts Institute of Technology, the University of Wisconsin, and the 63-member Association of American Universities—note that over the last decade academic institutions have won more than 16,000 patents that have generated more than $4 billion in licensing fees. Among the patents are key discoveries that helped launch the biotechnology industry, create important cancer drugs, and produce popular products such as the Gatorade sports drink. If the doctrine of equivalents is weakened, they warn, academia will have less incentive to innovate—and the public will suffer.

Other players—from the Solicitor General of the United States (the government's lawyer) to the Institute of Electrical and Electronics Engineers—have their own prescriptions for curing *Festo* headaches. There is also the issue of whether the decision, if upheld, should apply retroactively to 1.2 million existing U.S. patents.

Next month's oral arguments are expected to draw a capacity crowd—a rarity for a patent case—with a star-studded legal cast that includes former Supreme Court candidate and Festo lawyer Robert Bork as well as SMC advocate Arthur Neustadt, a top patent attorney. But the curtain probably won't drop on this legal drama until late spring, when the court is expected to release its ruling.

–DAVID MALAKOFF