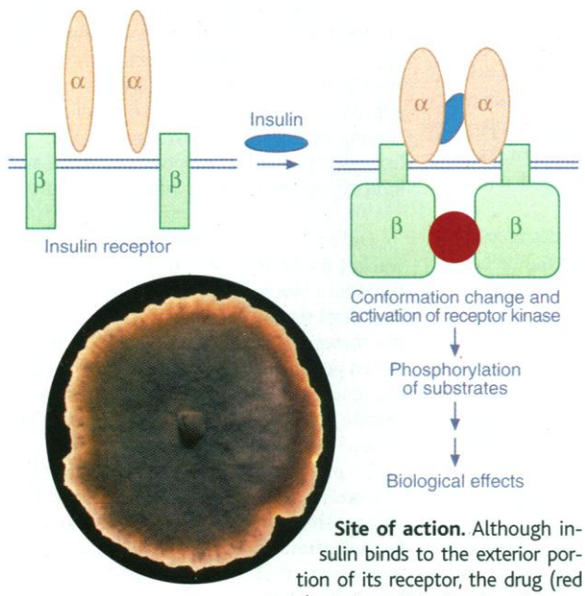
any misdeeds. "I couldn't believe that he could come up with such a story," Goeddel testified. And he denied that he used patented UC material as the basis of Genentech's discovery. Genentech's attorneys also spent a day attacking Seeburg's credibility, pointing out many inconsistencies in his testimony over the years. They reminded the jury that Seeburg—as co-inventor on the UC patent—stands to make a lot of money if UC wins this case.

Only about half the testimony has been presented so far in this trial, and there could be more surprises before the end. Barring an early settlement, this complicated dispute may go to the jury for a decision by the end of the month. **–ELIOT MARSHALL**

DIABETES RESEARCH

New Lead Found to a Possible 'Insulin Pill'

A lowly fungus that grows deep in the African forests near Kinshasa could soon be a pharmacological celebrity. Collected years ago and then analyzed by researchers from Merck Research Laboratories in Madrid, Spain, who hoped to find new drugs in rainforest flora, the fungus, called *Pseudomassaria*, attracted little notice at first. But now another Merck team, led by Bei Zhang and David Moller of the company's Rahway, New Jersey, laboratory, has found that *Pseudomassaria* produces a unique agent that could lead to a new type of antidiabetes pill. Such a treatment would be welcomed by the millions of diabetics who now must inject themselves with insulin or choose from a few orally administered drugs with serious side effects.



Site of action. Although insulin binds to the exterior portion of its receptor, the drug (red circle) produced by the *Pseudomassaria* fungus *(inset)* binds to the inner part.

CREDIT: ZHANG *ET AL.*

In work reported on page 974, the team gave the compound, a small, five-ringed molecule of the quinone family, to mutant mice with symptoms similar to those of patients suffering from adult onset or type 2 diabetes. These include high blood sugar, defects in insulin production, and also a decreased ability of the tissues to respond to insulin. The agent reduced these symptoms in the animals, the researchers found, apparently by tweaking the same cellular receptor that insulin acts on. But, unlike insulin, the fungal compound is not a protein and, thus, could likely withstand the body's potent digestive juices. "This is an insulin mimetic molecule which could become a drug that may be able to be given by mouth," says endocrinologist Arthur Rubenstein, a diabetes expert at Mount Sinai Hospital in New York. "The potential is enormous."

To find the new compound, Zhang and Moller took advantage of the known activity of the insulin receptor, which is embedded in the cell membrane. The portion protruding to the exterior spots and attracts insulin molecules, while an inner portion is a kinase enzyme, which responds to insulin's nudging by tacking phosphate groups onto various proteins in the cell. This leads to changes in the activities of those proteins, which in turn allow cells to take up and use the sugar glucose, thereby lowering its blood levels. The insulin-triggered upswing in the receptor's phosphate-adding activity is also useful to researchers hunting for antidiabetes drugs, because they can use it to pinpoint chemicals that mimic insulin's effects.

For their drug-fishing expedition, the Merck team used hamster ovary cells engineered to produce the human insulin receptor. Then, following a strategy frequently used to search for new drugs, the researchers set up a screening assay in which they divided the cells among thousands of miniature petri dishes. After trying some 50,000 mixes of synthetic chemicals and natural extracts on these cells, the investigators scored a major hit with an extract prepared from *Pseudomassaria* culture broth. Zhang and Moller then sent the extract to Merck chemist Gino Salituro, who set about purifying the active agent, a daunting task, as the fungal extract contained hundreds of compounds.

When Salituro finally pulled out the active ingredient, chemical analysis showed that it is a quinone. That was a surprise, Moller says, because none of the other antidiabetes drugs currently in use or under investigation belongs to that class of compounds. "From looking at its chemical structure, it does not have any obvious biological activity," he says. Yet in tests on cultured cells, the *Pseudomassaria* product, known as L-783,281, stimulated the phosphorylating activity of the insulin receptor by up to 100 times more than other natural compounds tested.

And its effects appear to be specific. L-783,281 does not spur the activity of receptors with similar protein-phosphorylating ability, including the receptors for epidermal growth factor, platelet-derived growth factor, and insulin-like growth factor. L-783,281 apparently diffuses through the cell membrane and binds directly to the kinase portion of the insulin receptor, activating it.

Achieving such specificity has always been "an elusive goal," says Zhang. Other antidiabetes drugs work in various ways, such as increasing insulin production by the pancreas or binding to the outer portion of the insulin receptor, but they may have other effects as well. This can lead to serious side effects such as excessively low blood sugar or blood pH, gastrointestinal problems, or in the case of the recently controversial antidiabetic agent Rezulin, liver failure.

Preliminary animal tests with L-783,281 also look promising. The Merck team tested the compound in two mutant mouse strains that have classic diabetes symptoms. In both strains it suppressed the skyrocketing blood sugar levels by up to 50%—comparable to the reduction seen with current oral antidiabetic therapies, Moller says. The compound also reduced the elevated insulin levels seen in one strain, presumably because blood sugar levels dropped, causing the pancreas to lower its insulin production.

If further animal trials confirm that L-783,281 or chemical variants resembling it are both effective in lowering blood sugar concentrations and safe, Merck says clinical trials might be feasible. People have been talking about making an insulin-replacement pill for a long time, Zhang says, and "now we have shown it's possible." **–TRISHA GURA**

Trisha Gura is a science writer in Cleveland, Ohio.

SWEDEN

Academics Applaud Renewed Support

STOCKHOLM—Think of Thomas Östros as the calm after the storm. Following years of turmoil and distrust between scientists and policy-makers, Sweden's youthful minister of education and science has spent his 7 months in office reassuring academic scientists that the government values their contribution and has no intention of letting outsiders call the shots. And that empathy, combined with the promise