publishing industry analysts as being worth millions of dollars at normal market rates.

The list of available journals does not—so far—include those produced by smaller publishers, including such prominent publications as *The New England Journal of Medicine*, *Science*, and *Nature*. "We decided to go for the largest publishers first [rather than] the most prestigious journals," Aronson says. Many big-name publications already have their own low- or no-cost distribution programs, but Aronson said that their participation in WHO's project would be welcome. Donald Kennedy, editor-in-chief of *Science*, says the journal would consider all invitations and is already weighing whether to join one effort to make scientific information more easily available in the developing world.

The six cooperating publishers are Reed-Elsevier, Wolters Kluwer, Blackwell, Harcourt General (which is merging with Reed-Elsevier), Springer-Verlag, and John Wiley & Sons. The Open Society Institute, a charitable group founded by finance billionaire George Soros that already runs its own journal distribution program, will help identify eligible institutions. The *British Medical Journal*, published by the British Medical Association, also played a role in developing the initiative.

–DAVID MALAKOFF

CELL BIOLOGY

Fresh Molecule Whets Appetite

As appetite researchers feast on a banquet of molecules that control eating behavior, yet another joins the spread. This one comes from a field that has produced samplings of other proteins that transmit signals—but none before that governs hunger.

"It's a different kind of molecule for influencing these pathways," says Jeffrey Flier, an endocrinologist at Beth Israel Deaconess Medical Center in Boston. The 20 to 25 players identified so far are either neuropeptides that transmit messages or cell surface receptors that register incoming information. By contrast, this new molecule, called syndecan-3, apparently helps one of these neuropeptides activate a receptor. Fiddling with the newfound regulator, researchers suggest, could open therapeutic avenues for controlling appetite.

Although syndecan-3 is an unexpected player in appetite control, it works with a molecule well known to regulate body weight, report Ofer Reizes, a postdoc in Merton Bernfield's lab at Harvard Medical School in Boston, and their colleagues in the 13 July issue of *Cell*. Syndecan-3 belongs to a family of proteins that grab signaling molecules and attach them to receptors. Long thought to act as molecular glue, these proteins—and in particular, their side chain appendages—have recently been shown to help send signals, some of which are crucial for embryonic development. And that's what the Bernfield team was exploring when it discovered syndecan-3's appetite-control powers.

The researchers were curious about the developmental role of a cousin of syndecan-3, called syndecan-1. To test its function, they engineered a mouse to overproduce the molecule. "We expected to see some sort of developmental anomaly—perhaps an extra digit," says Reizes. But the mice grew normally, at least for the first 6 weeks. Then they began to gain excess amounts of weight. By adulthood, they were obese.

The animals' behavioral and biochemical abnormalities resembled those found in obese mice with defects in an established appetite-control network called the melanocortin system. A key protein in the system, called the melanocortin-4 receptor (MC-4R), receives competing signals that tell an animal whether to eat. The receptor can bind a "satiety peptide" that activates the receptor and produces a feeling of fullness. Or it can bind an "antisatiety peptide" that obstructs the satiety peptide and induces hunger.

The researchers suspected that syndecan-1 was interfering with MC-4R, so they tested how cultured cells operate with and without the syndecan. They already knew that the antisatiety peptide by itself inhibits activation of the receptor. But when the researchers added syndecan-1, the receptor's activity took a deeper dive.

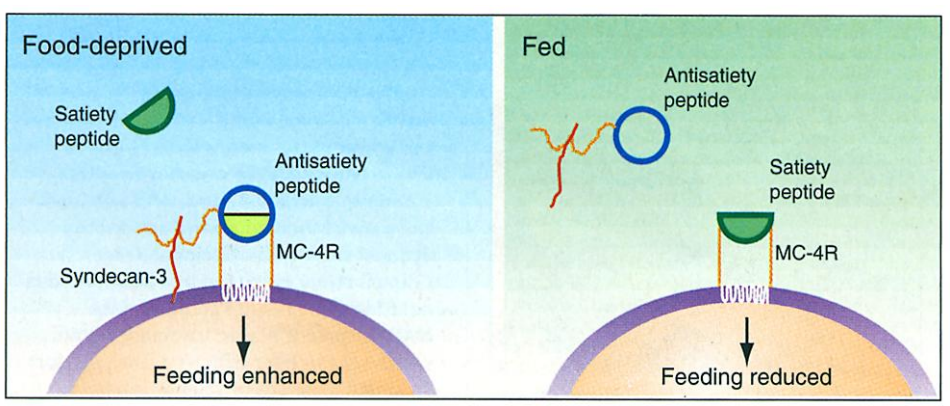
While intriguing, the results had a major limitation: Syndecan-1 normally resides in skin and related tissues, not in the brain. The transgenic mice were an exception, the team found—they produced syndecan-1 in the brain's hypothalamus, the part that regulates feeding behavior. "My initial response was, it's probably not interesting," says Flier, who advised the team. He suspected that the transgene was damaging the hypothalamus somehow rather than playing an active role in appetite control.

To get at the "real physiology," says Reizes, the group went after a relative of syndecan-1 that normally dwells in the brain: syndecan-3. They tested whether syndecan-3 concentrations rise when mice are hungry, as would be expected if the molecule works in concert with an antisatiety peptide. "Sure enough, that's exactly what we saw," says Reizes. And without syndecan-3, engineered mice don't eat even after fasting all night. "It's as if they don't perceive that they're hungry," says Reizes. This result "suggests that syndecan-3 may actually be a normal factor that modulates body weight," says Flier.

The researchers propose that when normal mice eat, they shed syndecan-3 from the surface of cells in the hypothalamus; the syndecan-3, in turn, takes the antisatiety peptide along for the ride, removing it from the MC-4R and liberating the receptor so it can bind the satiety peptide (see figure). To test this theory, they engineered two strains of mice. In one, syndecan-1—whose structure they understood well enough to tweak in the appropriate ways—was stuck to the cell membrane; in the other, it wasn't. Only membrane-bound syndecan-1 caused animals to gain weight. That result "strongly suggests that only the membrane-anchored form can potentiate the activity of the antisatiety peptide," says Carl Blobel, a cell biologist at the Memorial Sloan-Kettering Cancer Center in New York City. Perhaps, he suggests, a future therapy might clip syndecan-3 from the cell surface.

The new finding adds another molecule to the smorgasbord of biochemical factors that might predispose a person to obesity or leanness. "Studies of mechanisms that regulate feeding are at an exciting juncture," says Jeffrey Friedman, a molecular biologist at Rockefeller University in New York City. "A rudimentary wiring diagram can be drawn now that includes a number of molecules known to regulate feeding behavior. Syndecan-3 is a new and important element in this system."

–EVELYN STRAUSS



Shedding molecules, shedding pounds? Syndecan-3 collaborates with an antisatiety peptide.

ILLUSTRATION: MODIFIED FROM REIZES *ET AL.*