

monkeys who were 26 to 32 years old, equivalent to 78 to 96 human years, Leventhal says. As expected, many cells in older animals responded to a range of orientations and directions. But when the researchers sprayed on GABA—the brain's major inhibitory neurotransmitter—or a GABA-like drug called muscimol, the proportion of cells selectively excited by a particular orientation nearly doubled and the proportion of direction-selective cells roughly tripled, approximating the proportions found in monkeys just 7 to 9 years old. GABA and muscimol had no effect on the selectivity of V1 neurons in the younger monkeys.

Leventhal suggests that GABA-dependent neural communication declines with age and that this decline is to blame for old animals' indiscriminate neurons. Indeed, when

the team blocked GABA in younger animals, their neurons lost their orientation and direction selectivity, in effect aging them 20 years in an instant.

No one knows why GABA communication might decline with age, but Ulf Eysel of Ruhr University Bochum in Germany says some evidence hints that the inhibitory cells that use GABA are particularly sensitive to disruptions of blood flow to the brain. Over time these effects may kill cells or reduce their ability to make and release GABA.

Leventhal has "really got something," says Donald Caspary, a neuropharmacologist at Southern Illinois University Medical School in Springfield. His group has found a similar decline in GABA-supported networks in the aging auditory system. As in visual areas, these networks are important

for helping the brain extract information from a noisy environment, Caspary says. Their deterioration could explain age-related trouble following a conversation at a loud party or navigating through traffic.

A drug that restores lost GABA function in the appropriate brain regions without serious side effects could be a blockbuster, and Leventhal and Caspary both say they've received quite a bit of interest from industry. Benzodiazepines—a class of tranquilizers that includes Valium—boost GABA function, but they've yet to be tested for reversing the effects of aging. The idea of a pill for restoring lost sensory function is no longer a pipe dream, says Caspary. "When we first said this in the lab 10 or 15 years ago, we all burst out laughing," he says. "But now it doesn't seem so ridiculous." —GREG MILLER

DEVELOPMENTAL BIOLOGY

Purified Signaling Protein Stimulates Stem Cell Proliferation

After decades of painstaking and often fruitless effort, a team of scientists has purified a versatile protein that stars in multiple cell dramas, from embryonic development to cancer. The protein, called Wnt, turns out to have yet another role, another team has found. It coaxes blood stem cells to divide briskly, lending hope that Wnt may make it easier to experiment on stem cells and perhaps apply them in therapy.

Both papers, which appear online this week in *Nature*, are the culmination of many years' work and a collaboration between neighboring labs at Stanford University in California. One lab was struggling with a persistent problem in biology: Stem cell pioneer Irving Weissman, Tannishtha Reya, and their colleagues wanted to boost the number of stem cells in a petri dish without letting them diverge into different kinds of tissue. Producing lots of undifferentiated stem cells is crucial for studying and guiding their development.

Nearby, developmental biologist Roel Nusse and his lab members were wrestling with their own albatross, the signaling protein Wnt, which had resisted all attempts to purify it. Humans produce at least 19 Wnt proteins, which guide the positioning of body segments during development and con-

trol genes that otherwise trigger cancer. "Many postdocs and students have broken their backs on this project," says Ken Cadigan of the University of Michigan, Ann Arbor, of Wnt purification efforts.

But Nusse refused to abandon hope of purifying Wnt, which clung to the cell wall and crumbled whenever scientists tried to extract it. The "eureka" moment came when

Nusse and postdoc Karl Willert determined that the protein was water-avoiding, or hydrophobic—a trait that its genetic sequence hadn't suggested. But if not embedded in Wnt's DNA, where was this hydrophobia coming from?

The answer emerged when the researchers weighed the protein and studied its metabolic activity. A lipid molecule latches on to Wnt before it's shuttled out of the cell, making it hydrophobic, they found. Removing the lipid blunted Wnt's abilities. That "explains a lot" about the trouble researchers have had purifying Wnt, says

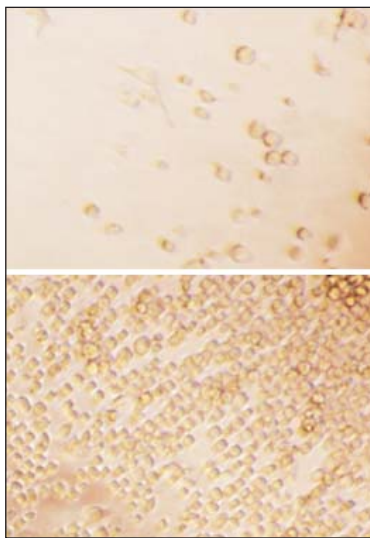
Hans Clevers, an immunologist at Utrecht University in the Netherlands. Nusse's team shifted its purification plan to one for proteins bound to lipids and successfully isolated a mouse Wnt protein.

Weissman's lab, meanwhile, was closely following Nusse's progress. A few years ear-

lier, the two groups had found that partially purified Wnt helps stem cells divide. More recently, the researchers had discovered that when levels of a protein normally triggered by Wnt, β -Catenin, are increased in stem cells, at least 30% of them remained immature and did not differentiate. But it still wasn't clear whether Wnt was acting alone, and Weissman's group anxiously awaited the pure protein. With unadulterated Wnt in hand, Reya, now at Duke University in Durham, North Carolina, and a graduate student added the protein to mouse stem cells from bone marrow, which generate a range of blood and immune cells. Over 1 week, Wnt-treated stem cells produced at least six times more daughter cells than did controls.

Stem cells boosted by Wnt or β -Catenin performed nearly as well as naturally occurring ones, Weissman's group found. The researchers infused the cells into mice whose bone marrow had been wiped out with radiation. As few as 45 of the Wnt-treated cells helped rebuild the animals' immune systems.

Although the infused cells did not mimic normal processes exactly, researchers are enthusiastic. "This is one of the first times that you see amplification of stem cell populations, which is what everyone's been looking for," says Leonard Zon, a geneticist at Children's Hospital Boston. Other proteins may work in a similar way: Guy Sauvageau of the University of Montreal in Canada has seen promise in a protein called HoxB4. "We're close to being able to tell clinical people that yes, they now have proteins that will allow the expansion" of stem cells, says Sauvageau. He and others say that having a readily replicating supply of stem cells may bring therapy one step closer. —JENNIFER COUZIN



Multiplying like bunnies. Adding Wnt to blood stem cells induces rapid expansion (*bottom*).