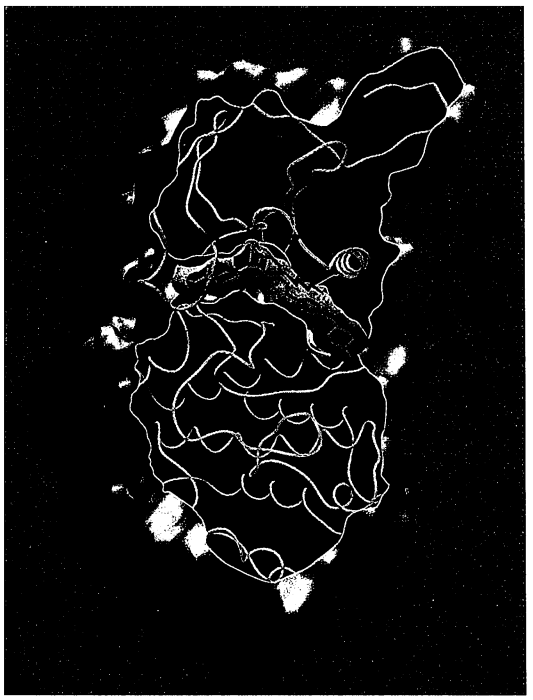


Distorted. Replacement of threonine with isoleucine (red) in the Bcr-Abl kinase active site binding of STI-571 (orange).

a surprise, says Brian Druker of Oregon Health Sciences University in Portland, who's also involved in the clinical trials but is not a co-author on the resistance paper. Because cells in blast crisis are supposed to be highly genetically unstable, Druker says he expected that a mutation in some other gene might cause the relapse, but "[Sawyers] has shown that it's reactivation of *BCR-ABL*." This is encouraging, Druker adds, because it means that targeting the Bcr-Abl kinase or the proteins it interacts with is still a promising strategy for combating the cancer.

Other work by the Sawyers team revealed the causes of the kinase reactivation. The researchers did not have enough DNA from two of the patients to analyze, but they found that in three of the remaining nine, the *BCR-ABL* gene was amplified: The extra copies of the gene overwhelmed the drug by producing more enzyme than it could handle. In the other six, the cause was a point mutation that changed a single amino acid in the enzyme's active site: A threonine was replaced by an isoleucine. "To me what's amazing is that it's exactly the same mutation in everybody," Sawyers says.

An x-ray crystallography analysis of an STI-571 variant bound to the Bcr-Abl active site, which was performed last year by John Kuriyan's group at Rockefeller University in New York City, shows that the threonine that was replaced in these patients is important for binding the drug (*Science*, 15 September 2000, pp. 1857 and 1938). Apparently, the mutation hinders STI-571 binding to Bcr-Abl, but it doesn't knock out the kinase activity. In fact, Sawyers suggests, that may be why they found only one point mutation; the enzyme may not be able to tolerate other changes without losing the kinase activity that drives tumor cell growth.

Now that the cause of STI-571 resistance is known in at least some patients, the next step is to try to get around it—a step that might also turn out to be necessary for patients with early CML. It's too early to tell whether the drug will eventually lose its effectiveness for them as well, but Druker worries that the fate of the advanced patients "could be a harbinger of relapse in our other patients."

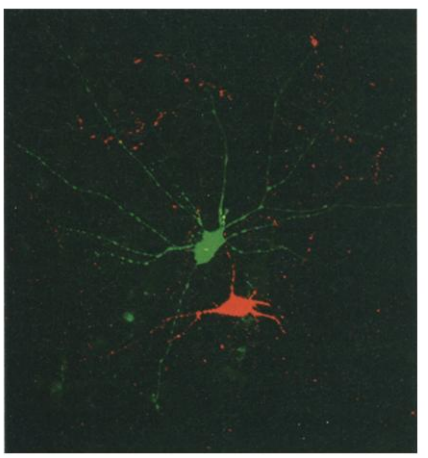
Possibilities for future treatments include designing additional kinase inhibitors that would be given along with STI-571, because the enzyme should be less able to become resistant to all the drugs at once. Another is to look for alternative targets for drugs that could also be given in combination with STI-571. Like most successful designs, STI-571 is likely to spark a host of refinements.

–JEAN MARX

NEUROSCIENCE

Synchronizing the Brain's Signals

Sometimes neurons get so excited that they fire in harmony. This synchronized firing has long excited neuroscientists, but they aren't sure what it means. Some have suggested that it allows the brain to perform sophisticated computations, such as tying together various aspects of an experience that are distributed in many different areas of the brain. But "there are still a lot of holes" in such theories, says Barry Connors of Brown University in Providence. For starters: How do neurons pick up on the synchrony and pass along the precisely timed message?



Feel the beat. Interconnected FS cells (in red and green) favor synchronized signals.

Now, Mario Galarreta and Shaul Hestrin of Stanford University may have provided a partial answer to these questions. On page 2295, they report results suggesting that networks of fast-spiking (FS) cells, a type of inhibitory neuron, could play a central role in detecting and fostering synchrony in the cortex, the large outer region of the brain that processes everything from complicated images to math problems. The study demonstrates that "if you are a neuron," says Daniel Barth of the University of Colorado, Boulder, "it is not just what you have to say that counts, it is exactly when you say it."

Galarreta and Hestrin set out to test just how precisely FS cells can register an incoming signal. They first teased pairs of cells, each consisting of one FS cell and one pyramidal cell, an excitatory neuron that commonly connects with FS cells, from slices of rat cortex. When they then stimulated the pyramidal cell and measured how long it took for the FS cell to respond, they found that it fired within 1 to 2 milliseconds—even faster than they expected.

Because the FS cells fire so quickly, the researchers suspected they might be capable of noticing—and responding to—precisely timed signals from several other neurons at once. Evidence that that might happen came when the researchers tested two interconnected FS cells and found that the cells fired best if stimulated by two signals, one to each cell, that were separated by less than 1 millisecond. But if the two inputs were 5 milliseconds apart, the cells were even less likely to fire than if only one signal had arrived.

In addition to their speedy response times, FS cells have other properties that might allow them to maintain and pass along a synchronized message. Not only do they exchange messages via the chemical neurotransmitter GABA, they're also more directly connected by what's called an electrical synapse, formed by the close juxtaposition of segments of the FS cell membranes. Thus, when one FS cell fires, a shadow of that burst quickly passes through the electrical synapse. This functionally immediate echo might allow a network of FS cells to pick up on a wide spatial distribution of synchronized signals.

The new study "offers a system that's exquisitely sensitive to timing," says Connors, and therefore it's "plausible" that networks of FS cells could detect and pass along synchronized signals. But, he cautions, many tantalizing questions remain. He'd like to know, for instance, whether the electrical synapses or the GABA-mediated connections make the network of two FS cells sensitive to the timing of incoming signals. And even more importantly, no one yet knows if the rest of the brain is paying attention to the precisely orchestrated performance.

–LAURA HELMUTH

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