cells to chemotherapy. Encouragingly, normal cells seem able to withstand inhibition of STAT3, making it an appealing target."

Unfortunately, "STAT3 is extremely difficult to target," adds Gunning. "That's why there aren't any STAT3-targeting drugs in the clinic yet."

Gunning and his colleagues are taking an innovative tack: They developed a dumbbell-shaped protein-membrane anchor that prevents STAT3 from moving into the nucleus. A cholesterol molecule at one end of the compound hooks into the cell membrane, while a molecule at the other end binds to the cancer-promoting protein, blocking its rendezvous with DNA.

A series of *in vitro* fluorescence-based experiments, including work in human breast-cancer cells, indicated that the technique is effective in pinning STAT3 to cell membranes. The work is the first example of a protein-membrane anchor that can capture and immobilize a cancer-promoting protein, says Gunning. The Toronto team plans to sequester other proteins and study their compound's effectiveness against leukemia and breast cancer in animal models. ■

Cancers Show Chaos in DNA Methylation

Tumor cells show abnormal patterns of DNA methylation—a key epigenetic mechanism by which methyl groups attached to DNA reduce gene expression. A broad and deep look at DNA methylation across the genome in multiple tumor types has produced two startling results.

"People expected that cancers would have some unique DNA methylation signatures that distinguish them from normal cells," says Andrew Feinberg of Johns Hopkins University. "What we found instead, starting with colon cancers, is that at certain places in the genome, the pattern is chaotically different from normal. At places that we call cancer-specific differentially DNA-methylated regions (cDMR), there's a very clear pattern with a random loss of the methylation signature.

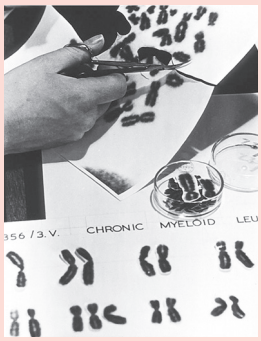
"At the very same places where you get the loss of the normal pattern in colon cancer, you also see it in breast, lung, thyroid, and Wilms' tumors," adds Feinberg, senior author on a paper published in June (Nat Genet 2011;43:768–75). "It looks like a single disruption in methylation that may be a kind of commonality in multiple cancers." The genomic regions where this occurs are important in controlling normal cell differentiation.

In the paper, the researchers followed up this work on 290 tumor samples, done with a custom high-throughput array-based relative methylation analysis, with whole-genome bisulfite testing of normal, precancerous, and cancer colon tissue samples.

This created the second surprise: Very large blocks of the genome—in fact, making up more than one third of it—are substantially hypomethylated in these tumors. These regions are associated with the regulation of genes involved both in normal development and in cancer.

Overall, the results sound a cautionary note about some current methylation-based diagnostic and therapeutic approaches, which may assume a specific methylation profile in cases where the data instead show "anti-profiles," Feinberg suggests. ■

BATTLES IN THE WAR ON CANCER: GLEEVEC HITS ITS TARGETS



Courtesy of World Health Organization

In early research on CML, researchers cut up photographs of chromosomes and sorted and arranged the pairs for comparison.

When President Nixon signed the National Cancer Act 40 years ago, the prognosis for people with chronic myeloid leukemia (CML) was grim. The only treatment was busulfan, says Brian Druker of the Oregon Health and Science University Knight Cancer Institute. "This chemotherapy drug did virtually nothing to improve survival, which at that time was no more than 3 to 5 years."

But a 1996 paper by Druker and colleagues gave patients a reason to hope (Nat Med 1996;2:561–66). Knowing that patients with CML harbor a chromosome translocation that creates the mutant gene *BCR-ABL*, researchers tested a kinase inhibitor dubbed STI571, which targets *BCR-ABL* activity. When they added the compound to CML cells in a Petri dish, the cells died overnight. Later, when mice implanted with CML cells were given the agent, their tumors regressed. STI571 even killed leukemia cells in samples of patients' bone marrow.

Druker's team launched a phase I clinical trial of STI571, or imatinib (Gleevec; Novartis). The results, reported in 2001, were dramatic: Of the 54 patients who received daily doses of at least 300 mg, 53 had normal blood counts within a month. Food and Drug Administration approval for imatinib quickly followed.

That triumph spurred the development of additional targeted therapies, including a few to combat CML in patients who relapse while taking imatinib. Japanese investigators showed that KIT mutations are present in most patients with gastrointestinal stromal tumor (GIST) and that imatinib inhibits KIT. Fine-tuning of drug regimens for these diseases continues. In June, for example, researchers reported that GIST patients could significantly delay the disease's recurrence and prolong their survival by taking imatinib for 3 years after surgery instead of 1 year, the current standard.

"Only after we knew imatinib worked, did we realize how the approach might be generalized to other cancers with driver mutations," says Memorial Sloan-Kettering's Charles Sawyers, who worked with Druker. "GIST was serendipitous."

This article is the first in a 5-part series commemorating the passage of the National Cancer Act in 1971.