■ CANCER

Next-generation CML therapy

A new clinical study shows encouraging results with a novel BCR–ABL inhibitor, including in leukemia patients with therapy-resistant mutations (*N. Engl. J. Med.* **367**, 2075–2088, 2012).

Imatinib, a BCR–ABL kinase inhibitor, has become the standard of treatment for patients with chronic myeloid leukemia (CML), and it epitomizes the successes and shortcomings of targeted therapy. Although the continuous use of this drug provides durable responses in many patients, secondary resistance can arise, driven by acquired mutations in the ABL kinase domain that preclude imatinib binding. Second-generation inhibitors have been efficacious in some resistant patients but are still powerless against emblematic gatekeeper mutations.

A third-generation kinase inhibitor, ponatinib, was recently developed and showed efficacy in cells expressing a resistant mutant version of the oncogenic BCR–ABL fusion. Now, Jorge E. Cortes *et al.* report their phase I trial results of this drug, which suggest that it has clinical promise for the treatment of relapsed disease. The multicenter dose-escalation trial included 81 patients with different stages of BCR–ABL-positive hematological cancer and who had not responded to first- or second-generation kinase inhibitors.

The study determined a maximum tolerated dose and the safety profile of the drug but, interestingly, also reports significant hematologic and cytogenetic responses in chronic-phase patients, as well as responses in a subset of patients with advanced disease.

Importantly, ponatinib is active against a range of resistant mutations, illustrating the potential of rational drug design to overcome the dynamic hurdles of cancer therapy resistance and bringing new hope to patients with CML. —*VA*

■ CANCER

A metabolic hub in cancer

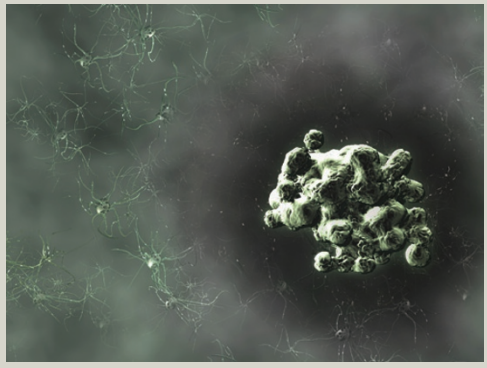
Different hallmarks of cancer exist, and the glycolytic switch, which allows tumor cells to increase aerobic glycolysis to cope with their metabolic needs, seems to be crucial for cancer cell survival and proliferation. A new study shows that a molecule involved in glucose homeostasis acts as a tumor suppressor by repressing this switch independently of any oncogene (*Cell* **151**, 1185–1199, 2012).

Carlos Sebastian *et al.* found that lack of sirtuin 6 (SIRT6), a protein involved in stress resistance, genomic instability and metabolic homeostasis, renders cells tumorigenic, even when the cells are not transformed. The tumor-suppressor effect of SIRT6 resulted from the inhibition of aerobic glycolysis, which was enhanced in tumors derived from *Sirt6*-deficient cells. The promotion of cancer initiation and progression in the absence of SIRT6 was independent of any oncogenic pathway and was suppressed upon inhibition of glycolysis, supporting the idea that this metabolic reprogramming drives tumor growth. A mouse model of colon carcinoma confirmed that deletion of *Sirt6* in the intestine increased malignancy, and, in human colon cancers, low amounts of SIRT6 correlated with shorter time to relapse.

As SIRT6 was also found to regulate ribosome biosynthesis through co-repression of MYC activity, SIRT6 may be a metabolic node that ultimately controls tumor cell replication and growth in the absence of any other oncogenic event.—*CP*

NEURODEGENERATION

α-Synuclein's sufficient



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α-Synuclein (α-syn) may promote Parkinson's disease–like pathology by cell-to-cell transmission in mice, according to a new report in *Science* (338, 949–953, 2012).

Previous studies have suggested that in Alzheimer's disease, pathology can spread between interconnected brain regions by cell-to-cell transmission of the pathogenic peptides amyloid-β and tau. In Parkinson's disease, Lewy body–like inclusions containing α-syn have previously been detected in embryonic nigral transplants from patients with Parkinson's disease, suggesting that Parkinson's pathology may be able to spread from host cells to the donor grafts.

Virginia M.-Y. Lee and her colleagues now report that in wild-type mice, a single injection of preformed fibrillar α-syn into the striatum is sufficient to induce intraneuronal α-syn accumulation and Lewy body pathology. Over time, pathology spread in a stereotypic fashion between connected brain regions, potentially seeding aggregation of endogenous α-syn. This eventually led to the loss of dopaminergic neurons, a reduction in dopamine within affected regions, and a concomitant impairment in motor function compared with untreated mice. These findings suggest that the aggregation of α-syn is sufficient to recapitulate the pathological hallmarks of Parkinson's disease and that it may promote disease by cell-to-cell transmission. —*KDS*

■ IMMUNITY

Two types of T cells

Chronic infections challenge T cell responses and can lead to T cell exhaustion. A recent study characterizes two distinct subsets of $CD8^+$ T cells in chronic viral infection, showing that they are both required to maintain a partially effective T cell response to viral infection (*Science* **338**, 1220–1225, 2012).

Michael Paley *et al.* studied a mouse model chronically infected with lymphocytic choriomeningitis virus and found that there were two different types of viral-specific $CD8^+$ cells, which were defined by their expression levels of the T-box transcription factors T-bet and eomesodermin (Eomes). T-bet and Eomes were reciprocally expressed in $CD8^+$ T cells, and Eomes expression increased during chronic infection.

$Eomes^{hi}$ cells produced less cytokines, had higher expression of the inhibitory receptor PD-1, produced higher amounts of granzyme B and had greater cytotoxic capacity than $T\text{-}bet^{hi}$ cells. $T\text{-}bet^{hi}$ cells showed low proliferation, whereas $Eomes^{hi}$ cells were highly proliferative. Using lineage-tracing experiments, the authors showed that $T\text{-}bet^{hi}$ cells can proliferate and give rise to $Eomes^{hi}$ cells in the presence of persistent antigen. Although deletion of Eomes reduced the expression of markers associated with exhaustion, such as PD-1 and Blimp-1, it did not improve control of chronic viral infection. In fact, deletion of either T-bet or Eomes led to an impaired maintenance of the $CD8^+$ T cell response and viral control, suggesting that both these types of T cells are important for viral control.

The authors then examined people chronically infected with hepatitis C virus. They found