I am often asked the question, “When are we going to get a Glivec for CLL?” I answer that it is not so simple; CML is caused by a single chromosomal translocation which produces and abnormal enzyme (the bcr-abl tyrosine kinase) that Glivec can block. CLL is not caused by a single translocation; in fact there are many types of chromosomal abnormality and none of them are amenable to a simple tyrosine kinase blockade.

I may have been wrong. Dasatinib is a second generation bcr-abl inhibitor, developed for patients with Glivec resistance. Most resistance is caused by mutations of the *abl* gene and dasatinib can inhibit most of the mutated molecules in a way that Glivec cannot. However, some Glivec resistance is not caused by this sort of mutation and Dasatinib will still be effective, even when the other second generation tyrosine kinase inhibitor, nilotinib is not. It appears that this sort of resistance is mediated through the activation of some of the src-family kinases, particularly lyn and hck. Dasatinib is more promiscuous than Glivec and inhibits other kinases than bcr-abl, including the src-family kinases.

It has been shown previously that lyn is constitutively activated in CLL, sending an anti-apoptotic signal [Contri et al. Chronic lymphocytic leukemia B cells contain anomalous Lyn tyrosine kinase, a putative contribution to defective apoptosis. *J. Clin. Invest.* **115**: 369-378 (2005)] and a recent paper from the Cologne group published on-line in Blood shows that incubation of CLL cells with dasatinib markedly reduces lyn tyrosine phosphorylation and also the downstream signalling pathways involving MAP kinase, Erk1/2, Akt and p38. Incubation with dasatinib increased apoptosis, an effect that was not inhibited by p53 deficiency or functional loss, but the effect of dasatinib was greater in CLLs with unmutated rather than mutated *IGHV* genes. The combination of fludarabine and dasatinib was additive. One caveat to this exciting news. When CLL cells were co-cultivated with the bone marrow stromal cell line, HS5, a degree of protection was provided against dasatinib induced apaotosis, suggesting that the CLL cells might be safe from such an attack when residing in lymph nodes or bone marrow. [Veldurthy et al. The kinase inhibitor dasatinib induces apoptosis in chronic lymphocytic leukemia cells in vitro with preference for a subgroup of patients with unmutated IgVH genes. *Blood* 2008 (Jun 12. Epub ahead of print)]