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Bench to bedside and back again: personalizing treatment for patients with GIST

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Gastrointestinal stromal tumor (GIST) is a great example of how science can affect outcomes in cancer patients. As a malignancy, GIST has fewer changes in its genome than do many other solid cancers. Thus, the discovery by Hirota and colleagues in 1998 that GIST contained mutations in *c-KIT* was a breakthrough for advancing the biology and treatment of GIST (1). Tyrosine kinase inhibitors such as imatinib mesylate (also known as Gleevec; Novartis), an oral 2-phenylaminopyrimidine derivative that acts as a selective inhibitor against several receptor tyrosine kinases, including KIT, platelet-derived growth factor receptor α (PDGFRA), and BCR-ABL, have significantly improved the outcomes for GIST patients, who previously faced a very poor prognosis. Clinicians at the bedside of their patients have seen the impact of these drugs and have also had to face the challenges of what to do when a novel, promising therapy fails. Unfortunately, about half of the patients with metastatic GIST who were treated with imatinib will have their tumor start to grow again by 2 years. Our study in 2003 was the first to identify genetic markers that could predict the response of patients with metastatic/recurrent GIST to imatinib with the use of multiple cell lines and clinical trial samples (2). We hypothesized that by evaluating gene expression profiles in treated GIST cells and then using these data to evaluate specimens from GIST patients taken before and after imatinib therapy (CSTI571-B2222 clinical trial), we would identify novel genetic biomarkers of this therapy and subsequently define additional downstream mediators of response. A total of 148 genes or expressed sequence tags were found to be differentially regulated, whereas 7 genes displayed a durable response after imatinib treatment. Among these 7 genes, *SPRY4A*, *FZD8*, *PDE2A*, *RTP801*, *FLJ20898*, and *ARHGEF2* were downregulated, and *MAFbx* was upregulated. Our studies also confirmed that both AKT and extracellular signal regulated kinase 1/2 signaling pathways are rapidly inhibited after exposure to imatinib but suggested that other signaling pathways may also be affected by imatinib treatment, which we further defined in subsequent studies (3, 4). Following on this work, we expanded the profiling studies conducted by Frolov and colleagues and directly assessed pretreatment biopsy samples from a prospective neoadjuvant phase II trial (Radiation Therapy Oncology Group 0132) and identified an

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expanded 38-gene signature that included 18 *KRAB-ZNF 91* subfamily members, 10 of which mapped to a single locus on chromosome 19p (5). siRNA synthetic lethal screens showed that members of this gene signature may not only have predictive value but may also have functional relevance to enhance imatinib activity. Most recently, these GIST studies led us to evaluate the role of insulin-like growth factor (IGF) 1 receptor, especially in GISTs that lack mutations in *KIT/PDGFRA/BRAF*, as well as in children, in whom treatment options are extremely limited. These so called “wild-type” tumors are clinically more resistant to imatinib-based therapies and have few genomic alterations (6, 7). We have shown an important role for IGF signaling in adult and pediatric wild-type GISTs (6–9), and clinical trials are currently being designed to exploit these types of discoveries. These are a few examples of how work at the bench can be translated into a better understanding of the disease and suggest ways to improve therapeutic modalities influencing how patients will be treated at their bedside. Based on these and other advancements defining the molecular landscape of the cancer, GIST may be one of the first solid tumors to be completely controlled in our lifetime.

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