Persistence comes naturally to Nick Tonks, FRS, who has the distinction of having laid the foundations for the identification and functional characterization of a “superfamily” of 107 regulatory enzymes called protein tyrosine phosphatases, or PTPs. The experiment that led to his first breakthrough on PTPs was performed in the late 1980s, while he was working with Dr. Edmond Fischer, a revered mentor and future Nobel laureate, in the late 1950s. While working with “Eddy” Fischer, Tonks focused on PTPs, phosphatases that specialize in removing phosphates from tyrosine residues. Why tyrosine? Phosphorylation has different implications depending on the identity of the amino acid that is phosphorylated. Tyrosine phosphorylation has been implicated in growth and metabolic regulation and its disruption leads to major diseases such as cancer and diabetes. The cellular receptor for insulin, for example, was known to be a tyrosine kinase that became phosphorylated and activated when insulin bound to it. A PTP, then, would halt the insulin signal in a cell, by removing the critical phosphates that had activated the signal in the first place.

At the start of his career Tonks sought to purify a PTP, something that had not been done before. Then he could sequence it and try to understand its mechanism of action, how it was regulated, and its function. The key step was developing a “dead-end substrate” that would be recognized by the PTP and trapped by it, so that it could be used to extract the PTP from the complex mixture of proteins in a tissue sample. Tonks had discovered how to produce such substrates while doing undergraduate research at Oxford under Sir Philip Randle, and honed the technique as a doctoral student at the University of Dundee in Scotland under Sir Philip Cohen. It was this approach that Dr. Fischer thought would be very challenging, hence his admonition. But Tonks made it work, and, to the delight of all, it led to two papers that provided the foundation for the PTP field. By the time Tonks was recruited by Ed Harlow to join the faculty at Cold Spring Harbor Laboratory in 1990, there was already evidence that the PTP Tonks had purified, which he named PTP1B, was more than a “housekeeper” for tyrosine kinases, “cleaning up their mess,” as Tonks characterizes the then-prevailing wisdom about the entire class of phosphatases. In fact, he and Dr. Fischer had demonstrated the existence of transmembrane “receptor PTPs,” which, like receptor kinases, could themselves bind to ligands and directly control the response of cells to environmental stimuli.
Harnessing oxidation:
an alternative diabetes strategy

Tonks and colleagues have also been working to harness new knowledge they’ve obtained about how oxidation changes the structure of PTP1B. In excess, oxidation damages living tissues. But controlled production of limited quantities of oxidizing compounds such as hydrogen sulfide, in defined subcellular locations, “makes possible an exquisite level of regulation we didn’t know about before,” says Tonks.

Several concurrent projects in Tonks’ lab show great promise. With postdoc Navasona Krishnan, Tonks has “defined an entirely new mechanism for the inhibition of PTP1B in an insulin-resistant state,” which has the potential to lead to new therapies for diabetes.

Potentially, inhibitors of PTP1B have another important application, in HER2-positive cancers, such as breast cancer. The HER2 oncogene — the target for the drug Herceptin — is a tyrosine kinase. Published experiments have shown that mice engineered to express HER2 but to lack the PTP1B gene have “attenuated tumorigenesis and the tumors don’t metastasize.” This intriguing result suggests that PTP1B plays a role in transmitting the signal from HER2 and “that if you inhibit PTP1B you could have a new strategy for treating cancers that express HER2,” Tonks says. He and Associate Professor Senthil Muthuswamy are currently testing natural-product inhibitors in Muthuswamy’s mammary epithelial cell models of breast cancer. Discussions are under way to take this strategy into the clinic in 2012.

“I’ve been trying to do this kind of thing since the mid-1990s,” Tonks says. “And now, for the first time, we have the possibility of getting an inhibitor of that enzyme I purified 25 years ago to treat major human disease. The idea that one’s research can lead to treatments for real patients — well, there is no other way to put it. It’s just a huge motivating factor.” Peter Tarr