“The breast team leads the Cancer Center in therapeutic clinical trial accrual and accounts for 35 percent of all therapeutic trial accrual here,” said Anees B. Chagpar, MD, MSc, MA, MPH, Director of the Breast Center at Smilow Cancer Hospital at Yale-New Haven and Associate Professor of Surgery (Oncology). “That doesn’t include another five pending trials or our work in non-therapeutic studies. What I’m most proud of,” she added, “is that we engage our patients at every phase of their journey, in every discipline, to get the highest quality of care for them as well as the most data to help us improve treatments and quality of life for other patients down the line.”

Translational medicine depends upon a constant feedback loop between researchers and clinicians. In rare instances, one person embodies that loop. On the breast cancer team at Yale, it’s Lajos Pusztai, MD, D.Phil., Director of Breast Medical Oncology and Co-Director of the Cancer Genetics and Genomics Research Program. “He is a classic example of a physician/scientist with one foot in the lab and another in the clinic,” Dr. Chagpar said, who calls him one of the world’s top five genomics experts.

To understand his translational work, a bit of background about breast cancer is helpful. Fifteen or 20 years ago, breast cancer was classified as a single disease. Genomic analysis has demolished that monotype, replacing it with four broad classifications based on the receptors in breast cancer cells: HER2, ER (estrogen receptor), PR (progesterone receptor), and triple negative, whose cells lack any of the other three receptors. Triple negative breast cancer is proving to be the most genomically heterogeneous and also the most resistant to chemotherapy. At the moment, all four FDA-approved drugs that molecularly target breast cancer are aimed at HER2.

“There are about 25 or 26 other molecularly targeted drugs approved by the FDA,” Dr. Pusztai explained, “but they aren’t approved for breast cancer. They are for diseases like melanoma, kidney cancer, and lung cancer. We find the same abnormalities in breast cancer that our colleagues see in these other diseases, though less frequently. So the obvious question is, if a drug works in lung cancer or melanoma against a particular abnormality, will that drug work in a breast cancer with the same abnormality?”

That’s the idea behind several of Dr. Pusztai’s...
projects, including one with David F. Stern, PhD, Professor of Pathology. Dr. Pustzai asked Dr. Stern to use high throughput screening to test a wide array of combinatorial therapies on triple negative cell lines grown in the lab—not just the FDA-approved drugs but also another 150 experimental agents now in clinical trials. If anything looks worth pursuing, Dr. Pusztai will help Yale clinicians put together a Phase I trial for patients whose breast cancer hasn’t responded to the usual first-line treatments.

“It closes the loop, in a way,” says Christos Hatzis, PhD, Director of Bioinformatics, Breast Medical Oncology, who has worked with Dr. Pusztai for a decade. “We can start with clinical samples, do discovery, go back to the lab and test them, and if the results look promising enough, bring them back to clinicians to be further evaluated in small clinical studies.”

An example of this is a project Dr. Pusztai calls Map-It (Molecular Analysis Prior to Investigational Therapy), a study for patients with metastatic breast cancer. After radiologists collect biopsies, about 200 genes are subjected to molecular analysis through next-generation sequencing. “We are looking for molecular defects against which there are already FDA-approved drugs or investigational drugs,” Dr. Pusztai said. For example, a mutation in the EGFR (Epidermal Growth Factor Receptor) gene has been identified as a cause of lung cancer, and FDA-approved drugs that inhibit this receptor have proven effective. Dr. Pusztai wants to see if breast cancer patients with this mutation respond to the targeted drug.

On the immuno-therapy side, Dr. Pusztai is looking at the PD1 ligand inhibitor, which has shown great promise against melanoma and lung cancer by stimulating the immune system. Dr. Pusztai is leading a Phase I study to investigate the inhibitor’s effect on metastatic breast cancer. “Early-stage triple negative breast cancers are much more curable if lymphocytes are present,” he said, “and this drug revs them up into super lymphocytes.”

Another of Dr. Pusztai’s projects will help oncologists and breast cancer patients decide how long to continue endocrine hormone therapy, typically given for five years. Several large studies have shown that lengthening this to 10 years decreases recurrence and improves survival—but only by one or two percent, and the therapy itself carries health risks for some patients as well as additional costs.

Dr. Pusztai emphasizes that all of these projects depend on the collaborative support of many specialists within the breast team, from surgeons who take tissue samples to radiologists who do biopsies and pathologists who handle the samples, and on to molecular analysts and informaticists. To illustrate, he mentions another new project that requires the participation of the entire team: the creation of a bio-repository.

“Lajos’s idea is to develop a database for breast cancer,” Dr. Hatzis explained, who is deeply involved in the project. “A doctor will be able to type in the specific mutation and the specific gene, and the database will look for information about that mutation on that gene. If nothing has been reported, the database will aggregate up and look for any mutation on that specific gene. And if it’s a very rare mutation, it will aggregate to a higher level and look for any mutations in genes involved in that particular pathway.”

Next the database will link to the literature about specific treatments and rank them at different levels of evidence. The doctor can then look on clinicaltrials.gov to see if there are any trials at Yale or elsewhere involving a particular therapy. “It will be a clinically useful tool,” Dr. Hatzis added, in quite an understatement. He and Dr. Pusztai hope to have a prototype ready for use by Yale clinicians by the end of the summer, with a long-term goal of public access.

Dr. Chagpar notes that breast cancer research at Yale is getting more intricate and more tightly intertwined with the clinic. “We are able to translate from the bench to the bedside and back,” she said. “We will no longer treat breast cancer with a broad brush, but will very specifically understand what each person’s tumor looks like, how it behaves, and what drugs we can use to treat its mutations.”