Moffitt researchers will go to great lengths in pursuit of the next breakthrough in understanding, treating or preventing cancer. Some are studying data from patients literally a half a world away – Israelis with colon cancer, Swedes with melanoma, even Australians with ovarian cancer.

Their work is done in offices or labs on our Tampa campus. It’s shared via email, internet, occasional international meetings and regular conference calls at all hours to accommodate multiple time zones.

They are on the forefront of a concept called global team science: contributing to and analyzing patient data from numerous cancer studies worldwide in collaboration with their scientific colleagues around the globe.

To understand why such collaboration is vital, it helps to understand the type of research involved. Unlike experimental studies that use a new intervention or treatment in animal models or clinical trials and compare the results to those of existing standards of care, global team science efforts often involve observational, case-control studies. These studies compare two groups of people: one group with a certain type of cancer (cases) and another group without that cancer (controls). They are called observational because researchers don’t assign participants to a treatment or intervention. The study volunteers may only be known as data on a spreadsheet or specimens to be processed. The premise is to look for differences (genetics, environmental exposures, other factors) between the two groups in hopes of explaining why and how the cancer occurred – information that is a first step toward new treatment or prevention strategies.

Valid research results require large numbers of observations, not easily accomplished when the cancer under study is rare.

Peter Kanetsky, PhD, MPH, chair of Moffitt’s Cancer Epidemiology Department, leads several such efforts. “I had dark hair when I started,” he says half-jokingly, recalling his early days at the University of Pennsylvania where he recruited families at high risk for melanoma to a study called GenoMEL. Established in 1997 as a non-profit consortium of melanoma research groups worldwide, GenoMEL was founded to study variation in a gene called CDKN2A that predisposed these families to melanoma. GenoMEL now counts Dr. Kanetsky as one of three principal investigators. He also is instrumental in two more international research consortia: GEM (Genes, Environment and Melanoma) studying melanoma patients from the U.S., Canada, Italy and Australia; and TECAC (the International TEsticular CAncer Consortium) with testicular cancer patients from throughout the U.S. and European countries including Germany, the Netherlands, Norway, Denmark, Italy and the U.K.

Dr. Kanetsky co-authored a paper with his international TECAC...
colleagues that appeared in Nature Genetics this June. Their results uncovered eight new genetic markers associated with an increased risk of developing testicular germ cell tumors (TGCT), the most common cancer in men aged 20 to 39 years in the U.S. and Europe. Testicular cancer is relatively rare with only 8,850 cases expected this year in the United States, and 95 percent of all cases begin in the testicular germ cells responsible for producing sperm.

The modest number of TGCT patients illustrates one need for global collaboration. “When you’re studying common cancers such as breast cancer or prostate cancer one might be able to get away with a local study,” explains Dr. Kanetsky. “In a rarer cancer where numbers are scarce, you have to reach further. Very often that means reaching to other continents, to other collaborators who might be doing similar research in the rarer cancer that you are studying.” For their June 2017 paper, TECAC researchers analyzed combined data from more than 3,500 TGCT cases in five previous international studies.

Dr. Kanetsky says there are two sides to power in numbers. While they are necessary to observe genetic differences for rarer cancers, he points out, “you can also observe more modest effects as you increase those numbers. The more numbers we get into our studies, the better our ability to make inferences about small effects.”

And when it comes to genetic predisposition to cancer, small effects can add up to big problems.

Clear genetic culprits, like high-risk BRCA genes in breast cancer or CDKN2A in melanoma, have been identified by studying
families who’ve had multiple members diagnosed with these cancers. While these high-risk genes dramatically increase a person’s risk for the cancer, they account for only a small portion of cancer cases overall.

That leaves investigators searching for lower-risk genetic variations, like needles scattered throughout the haystack of a person’s genome. This haystack’s magnet is an innocent looking piece of plastic no bigger than a thumb drive. Called a microarray, it’s a chip containing hundreds of thousands of microscopic spots. Each one corresponds to strategically selected markers of genetic variation called “snips,” or single nucleotide polymorphisms (SNPs). Everybody has countless SNPs in their genome. They may have little or no impact at all. The SNPs measured in these arrays have been picked from points throughout the genome because they’re associated with certain heritable traits or a variety of diseases.

DNA swabbed from a person’s cheek, isolated from saliva or extracted from a tube of blood is loaded onto the chip and scanned by automated lab machines to see how strongly it matches the array’s SNPs. Matches that turn up more frequently in people with a particular cancer than in healthy controls are said to be associated with the cancer. And they can be more common than you might think.

“Typically, these genetic factors are common variants – meaning, anywhere from five to 50 percent frequency in the overall general population – and on average, have very small effects on disease risk,” explains Stephanie Schmit, PhD, MPH, an assistant member in Moffitt’s Cancer Epidemiology Department. While BRCA or CDKN2A can magnify a person’s cancer risk 400 to 700 percent, these variants might only increase the odds of developing cancer by a few percent. “Because the effect sizes are so small,” she says, “it takes a lot of people to be able to detect them.”

Dr. Schmit has been in the lab studying colorectal cancer with one such array since she was a PhD student. Much of her work has been in conjunction with two global efforts: the Molecular Epidemiology of Colorectal Cancer Study (MECC), a population-based case–control study of over 10,000 individuals in northern Israel, and the ColoRectal Transdisciplinary Study (CORECT), an international consortium studying nearly 100,000 participants. She is the lead author of a paper pending publication that identifies 11 previously unknown risk variants for colorectal cancer.

“I didn’t recruit a single one of these 100,000 research participants myself,” says Dr. Schmit, “but I’m taking advantage of this wonderful research infrastructure and resource that hundreds of investigators and their teams have built over more than 30 years. Progress is incremental - it’s going to take time, but we’re really making some good strides.”

Variants like those identified by Dr. Schmit’s global group provide new points on the genome to investigate. But unlike high-risk genes, these low risk-conferring variants don’t lead almost unequivocally to cancer. It may take many of them - along with environmental and lifestyle factors - to tip a person into a high-risk category for a given cancer.

Once new variants are found, the question becomes – what do they do? And how might we intervene to lower the risks? Moffitt’s contribution to those answers comes in part from a researcher with his own global connections.

PROBING HOW THEY WORK

Alvaro Monteiro, PhD, trained as a scientist in his native Brazil, France, Belgium and Japan. In the late 1990s he worked in the labs of New York City’s Rockefeller University which counts dozens of Nobel Prize laureates and Lasker Award recipients among its scientists. It wasn’t until his daughter was born and New York’s Twin Towers came down that he seriously entertained an offer to come to Tampa from his colleague, Moffitt Center Director Tom Sellers, PhD, MPH.

Early in his career, Dr. Monteiro focused on figuring out how high-risk genes predispose families to certain cancers. Dr. Sellers wanted him to set up a Moffitt lab to analyze a number of low-risk variants found through an international project they both participated in, called COGS (Collaborative Oncological Gene-environment Study). COGS was a huge undertaking, uniting four global consortia focused on genetic susceptibility to breast, ovarian and prostate cancers. It designed its own custom array with over 200,000 SNPs, producing a vast amount of data. Dr. Monteiro set up his lab in Moffitt’s Cancer Epidemiology Department, and joined the effort to explain how the newly discovered variants worked to increase cancer risk.

In earlier studies of familial cancers, each anomaly mapped neatly to a gene responsible for building a protein. Scientists inferred that the mutated genes make defective proteins, leading to cancer. But with the new COGS variants, says Dr. Monteiro, “the first thing we saw right off the bat was that 90 percent of them are located in regions of the genome that do not code for proteins.”

It turns out many of these low-risk variants are regulatory elements. “We think they have smaller effects on cancer risk because, instead of producing a bad protein, they just change the levels of proteins that are produced,” says Dr. Monteiro. But regulatory region anomalies don’t map so neatly to their targeted protein-coding genes. The two may not even be physically close,
“I didn’t recruit a single one of these 100,000 research participants myself, but I’m taking advantage of this wonderful research infrastructure and resource that hundreds of investigators and their teams have built over more than 30 years.”
instead relying on the folds that fit a six-foot strand of DNA into a tiny cell to bring them together.

Finding the connections would require an entirely new approach. “None of the methods were there,” says Dr. Monteiro. “We've spent the past five to seven years adapting the experimental methodology and the standard operating procedures of how we go about figuring this out.”

Through its work with a National Cancer Institute consortium called GAME-ON (Genetic Associations and Mechanisms in Oncology), Dr. Monteiro's lab helped to develop a framework with bioinformatics and custom arrays to sift through the massive amounts of data produced worldwide by all of these genome-wide association studies, looking for the mechanisms of how variants increase cancer risks.

Understanding the mechanism is the key to expanding or designing new treatments or prevention therapies, says Dr. Monteiro. “And once you identify what’s gone wrong with the biology, you can make generalizations. You might have a person who doesn’t have exactly the same variant, but their cancer has the same mechanism and therefore might respond to any therapies we develop in those cases.”

He says it also changes the way scientists think about developing those new drugs and therapies. It’s no longer simply a matter of finding a way to interfere with the gene that’s producing a defective protein. Since over 90 percent of the new, low-risk variants being discovered are regulatory elements, researchers now broaden their focus to interfering with faulty regulation of the genes.

Each new variant identified provides another clue to how myriad forces interact to cause cancer. Dr. Monteiro was one of several Moffitt Cancer Center researchers who took part in a major international study published in Nature Genetics this March. It identified 12 new genetic variants associated with an increased risk of developing epithelial ovarian cancer, the most common and dangerous type of the disease. All 18 previously identified ovarian cancer risk variants were also confirmed. The study, led at Moffitt by Dr. Monteiro's Cancer Epidemiology colleague, the late Catherine Phelan, MD, PhD, MMS, was a collaborative effort of more than 400 scientists from the U.S., U.K. and Australia. It utilized a next-generation tool called OncoArray to survey and compare over a half a million SNPs among nearly 100,000 women worldwide.

“The importance is that we are clawing into that fraction of the genetic contribution to cancer that is not explained right now,” says Dr. Monteiro. “We're making dents on it,” he adds, hopeful that eventually all of those dents will yield the answers we seek.

With help from Moffitt, this global team of scientists is set on providing answers for cancer patients worldwide.