A global effort to find cancer genes

No matter what language you say it in, the word “cancer” causes fear around the world. And while the rates and severity of different cancers can vary greatly by region or ethnic group, that universal dread is a powerful motivating force for researchers seeking to better understand, diagnose, prevent, or treat cancer.

In recent years, that motivation has brought together cancer specialists from many nations, to form large international research coalitions. By pooling their knowledge and data, and using new genetic and computational tools, they’re making new inroads against many forms of cancer.

This year, two significant discoveries emerged from international collaborative efforts involving U-M cancer genetics researchers, and two of the most common cancers: colorectal and breast.

Molecular Medicine & Genetics faculty and students, as well as others from around the department, the Medical School and the School of Public Health, were central to both global research teams.

In each case, the discoveries of new, high-risk markers for these cancers may lead to better identification of the people who are most at risk of developing them.

And that, in turn, could allow those individuals to get more intensive screening to look for early signs of cancer, or perhaps special preventive care or treatments tailored to their genetic makeup.

Stephen Gruber, MD, PhD (right), played a key role in both projects. He attributes their success to the large number of patients and healthy volunteers from different populations who have allowed the researchers to explore their DNA, their family, and their personal histories.

The colon-cancer finding came from the ongoing Molecular Epidemiology of Colorectal Cancer project, a Michigan-Israel collaboration that, for the past 10 years, has studied thousands of Israeli Jews and Arabs. In addition to U-M researchers like Laura Rozek, PhD, of Molecular Medicine and Genetics, the team included scientists from Spain and Israel.

In the July issue of Cancer Biology and Therapy, this international team reported finding a significant link between genetic variation in a single region of human chromosome 8 and the risk of colorectal cancer.

The link was uncovered through detailed comparisons of genetic material from 1,900 colorectal cancer patients and 1,900 non-patients, and by evaluating the incidence of colon cancer among the immediate family members of colon cancer patients. Samples of tumor tissue from many cancer patients were also tested.

In all, people who carry the specific genetic variation, called a marker, were found to be 23 percent more likely to have colon cancer than individuals without the marker. The researchers estimate that this single genetic variation might account for 14 percent of colorectal cancer cases in Israel, where colon cancer is the leading cause of cancer deaths. The specific marker is called the T allele of rs10505477.

On the same day that Gruber and his colleagues published their findings, two other research teams reported also finding colon cancer markers in the same small area of chromosome 8, called 8q24. The fact that these studies were performed among other populations around the world suggests that this one genetic marker is highly influential across ethnic groups.
While there is not yet a screening test for the genetic variation that was pinpointed in the study, Gruber and his co-authors emphasize that genetic testing is available for other known genetic variations linked to colorectal cancer.

People with a strong family history of colon cancer, especially cases that began when relatives were younger than age 50, should get genetic counseling and have colonoscopies or other screening tests starting earlier in life than age 50. Every year in the United States, 150,000 new cases of colon cancer will be diagnosed, and more than 50,000 people will die from the disease.

Such counseling and testing is available through the Cancer Genetics Program in the U-M Comprehensive Cancer Center, which Gruber directs. In 2007, the clinic opened its first satellite location in Traverse City that offers care for all inherited cancer risks. This adds to the existing Ann Arbor location, and a Grand Rapids location that offers testing and counseling for breast cancer risks.

Of all the cancers, the genetic risks of colon and breast cancer are perhaps the best understood. But there is still a lot of room for discovery in this field—as evidenced by this past year’s second big discovery involving Gruber and other U-M researchers, including Kristen Stevens, MPH, a doctoral student in epidemiology at the U-M School of Public Health. And every discovery helps build new hope for the 180,000 Americans who are diagnosed with breast cancer every year.

As part of a multicenter international study, the team identified a new gene that, if mutated, may increase a woman’s risk of breast cancer by more than a third. They published their results in the journal Nature Genetics.

The researchers also found that the gene, HMMR, interacts with the well-known breast cancer gene BRCA1. Alternations in either gene cause genetic instability and interfere with cell division, which could allow breast cancer to develop.

In addition to using sophisticated computer analysis tools that combed through large amounts of existing data, the researchers also looked at the genes of 923 Jewish Israeli women with breast cancer and similar women without breast cancer. The Ashkenazi Jewish population in Israel carries a higher risk of breast cancer than other ethnicities.

This component of the study found that women with a variation in the HMMR gene had a higher risk of breast cancer, even after accounting for mutations in the BRCA1 or BRCA2 genes. In particular, the risk of breast cancer in women under age 40 who carry the HMMR variation was 2.7 times the risk in women without this variation. The researchers further verified the finding in Jewish women in New York.

Now, Gruber and his colleagues from around the world are working on further genetic research in several kinds of cancer, including new gene discoveries in colon cancer that will be published in 2008. And with every new finding, the global community comes a little closer to understanding and defeating a universal foe.
If DNA was a person, it would be a pampered Hollywood movie star. Surrounded by protective bodyguards, attended by lackeys who see to every need, and sheltered deep within the fortress of the nucleus, each cell’s DNA is almost entirely shielded from the outside world.

But once in a while, the vicious “paparazzi” get in and inflict terrible damage. Radiation, chemicals, free radicals, and other agents can harm DNA despite all its defenses. Sometimes, both strands can be cut completely through.

That’s when a squad of DNA repair specialists gets to work. Like Hollywood publicists and plastic surgeons, they swoop in to stitch the broken strands, mend the damaged area, and restore DNA to its working state.

But how does this process work, and what happens when it goes awry? Scientists are still working to figure this out. Among them is a new member of the MMG faculty, Xiaochun Yu, MD, PhD (below). His team’s work has direct implications to understanding why DNA damage can lead to cancer and other diseases.

Yu came to Michigan in late 2006 from the Mayo Clinic, where he had begun studying DNA damage repair with Junjie Chen. Now, with his laboratory fully up and running, he has joined a community of more than 10 U-M investigators and their laboratory teams who are working to understand how DNA reacts to insults.

This year, Yu and his colleagues published two important papers on the topic, each showing for the first time the involvement of different proteins in DNA damage repair. In both cases, the team demonstrated that the proteins acted as “first responders” to the site of DNA damage, reading the distress signals and calling in full-scale repair mechanisms.

Yu’s team found that both proteins, called RAP80 and CCDC98, are involved in attracting BRCA1 to the scene of DNA damage.

BRCA1 may be familiar to most people as the name of a gene that mutates in many women who have breast or ovarian cancer. But under normal circumstances, BRCA1 produces a protein that plays a key role in encouraging the repair of broken DNA inside every cell of our bodies.

In fact, this important role is what makes it so dangerous for a person to carry a mutated BRCA1 gene. The repair mechanism doesn’t work as planned and cancer can result.

Yu’s work with RAP80 and CCDC98 reveals a very detailed pathway that summons BRCA1 to the site of recent DNA damage. Working in animals, and using a focused beam of ionizing radiation to inflict damage on DNA, Yu and his team have pieced together the chain of events that appears to bring BRCA1 to the scene so that repairs can begin.

It seems that RAP80 can detect the presence of a small protein called ubiquitin on structures called histones—the “spools” around which strands of DNA are stored. When DNA damage occurs, histones are exposed, and ubiquitin attaches to them. In turn, RAP80 latches on to the ubiquitin, and then to CCDC98, which then brings BRCA1 to the right spot to attach and begin the repair process.

Now that they’ve identified the significance of these two proteins, Yu and his colleagues are working to understand their role further.

They’re creating two strains of “knockout” mice, one lacking each of the two proteins, to see what happens after DNA damage occurs in their cells. The team is also collaborating with Kathy Cho, MD, of Pathology to look for signs of RAP80 gene mutations in the cells of women who have been diagnosed with ovarian cancer, and with Elizabeth Petty, MD, of MMG to screen breast cancer cells for RAP80 mutations.

As the research continues, Yu hopes also to better understand how the chromatin—the complex of DNA, histones and other proteins—responds to damage.

And the more this can be understood, the better the odds that future research can find new ways of shielding the “Hollywood star” from the outside world.