Nuturing Mother Nature

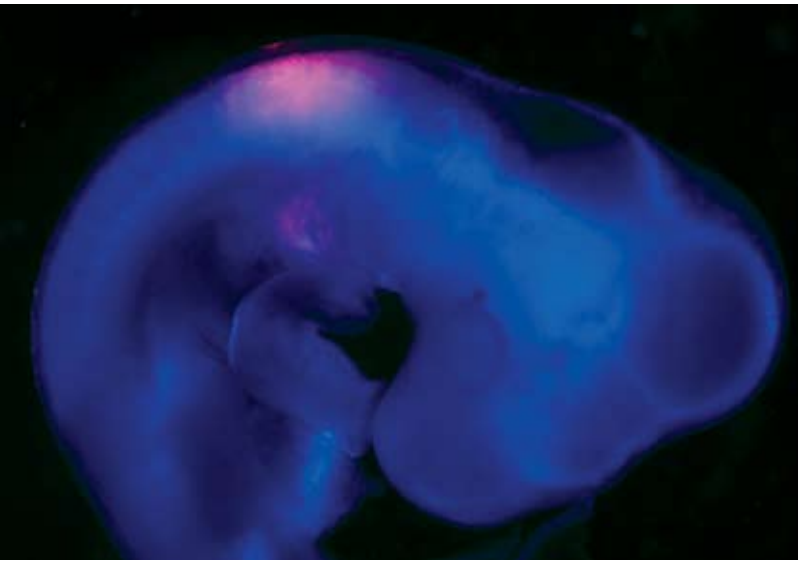
Unlocking mysteries of disease and birth defects has worldwide impact.

by Vicky Cerino

Nature versus nurture. It's an age-old debate about the relative importance of an individual's genetic and inborn biological factors versus personal experiences.

Millions of people are alive today because of the drive to improve the human condition. Scientists now have the power to study and alter the most fundamental area of life – the cell.

Two researchers at UNMC are trying to unlock the well-kept secrets of Mother Nature's biological processes in hopes of saving lives. The research of Thomas Rosenquist, Ph.D., and Alexander "Sasha" Kabanov, Ph.D., Dr.Sc., holds the promise of saving and improving human lives around the world.



This is a chicken embryo used to study the link between folate and birth defects. The photo shows an embryo that had a gene from a fluorescent jellyfish inserted into key cells that are vital for heart formation, allowing them to be tracked in the microscope during experiments (pink area).

On the road to China

Even before a child is conceived, how much can the mother do to ensure her unborn child's health?

Dr. Rosenquist and his colleagues have dedicated their lives to answering this question in order to reduce the death and devastation of congenital heart defects – the most common kind of birth defect-related deaths.

Among the questions they're trying to answer is how do genetic and environmental forces of nature interact to trump the sometimes heroic efforts made by women to have healthy children.

Dr. Rosenquist, UNMC vice chancellor for research, heads a $5.6 million program project grant consisting of three teams of scientists investigating how genes interact with certain drugs, environmental exposures and vitamin deficiencies, to cause abnormal heart development.

The five-year grant is the first National Institutes of Health-funded grant to test a unifying hypothesis for this type of gene/environment interaction. Research is being conducted at UNMC, Creighton University, the University of Neijmegen in Holland, Texas A&M University in Houston, and by a team with the California Birth Defects Monitoring Project.

Dr. Rosenquist's research caught the interest of Chinese pediatricians who wanted to know if Dr. Rosenquist's research could help them lower eastern China's high rate of congenital heart defects.

In December, UNMC researchers will travel to China to launch Project Healthy Heart. Dr. Rosenquist's team will collaborate with Xiaoming Shen, M.D., Ph.D., executive vice president of Shanghai Jaiotong University, and dean of the College of Medicine of Shanghai Medical College, Jaiotong University.

"China is interested in doing research in the area of public health and converting this research into useful prevention strategies," Dr. Rosenquist said. "We will help replicate in China what we've done here for the past four years. We'll analyze, provide training, and at the same time, establish research projects at Shanghai Medical College. The university

is ranked No. 1 in China for basic research."

Dr. Rosenquist and his team were the first to show an association between genes and the body's ability to absorb folic acid. They also were first to show a correlation between a low level of folic acid and a rise in homocystine levels, which is associated with impaired development of the spinal cord, brain and heart.

Although China doesn't require folic acid supplementation in food like the United States, which has proven to reduce birth defects, the genetic makeup of the people in Shanghai, and environmental exposures could be quite different from the United States, Dr. Rosenquist said. An alternative prevention strategy could be important.

"We could discover something entirely different, some other kind of change in the DNA in that part of China that makes them susceptible to birth defects," he said. "We'll try to figure out what some of the susceptibilities are in the mother's diet, folate and B-12 levels in the blood, the relationship between what the mother was exposed to during pregnancy and any gene mutations. We call it gene-environment interaction. This is where this type of research is going in the 21st century," Dr. Rosenquist said.

"The ultimate goal is to have tests that can predict the probability of having a baby with heart defects," Dr. Rosenquist said. "But it's going to take time."

Nanomedicine discovery reaches cancer clinical trial

Dr. Kabanov loved and admired his late father, a prominent Russian scientist whose work significantly impacted the lives of Russians with the development of a polymer – a type of plastic used to create the first synthetic vaccine delivery system for flu. To date, 50 million people have received the vaccine.

Dr. Kabanov also is making an impact on people with polymers. A scientific invention he and his colleagues discovered almost 20 years ago in Moscow could be a breakthrough for hard-to-treat cancers and other diseases.

A polymer is a large, long molecule that can fold and assume different structures. Dr. Kabanov's polymer uniquely combines carbon, oxygen and hydrogen.

"One of our approaches was to use polymers to deliver drugs to the cell. We've demonstrated that the combination of our polymer with a drug – called a block co-polymer -- kills the cancer cells 1,000 times better than the drug alone," said Dr. Kabanov, director of the UNMC Center for Drug Delivery and Nanomedicine and Parke-Davis Professor of Pharmaceutical Sciences, UNMC College of Pharmacy.

In fact, they found their drug delivery system could be used to treat multiple drug resistant cancer, a type that survives single or multiple chemotherapy treatments, leaving some patients vulnerable to the lethal spread of the disease. It also potentially can prevent development of drug resistance.

When Dr. Kabanov and longtime friend and colleague, Valery Alakhov, Ph.D., realized they'd made a breakthrough, they created Supratek Pharma, a clinical stage anticancer biotechnology company in Montreal. One of their polymer inventions, the Biotransport™ Nano-Carrier, has evolved from the laboratory to a clinical trial.

The nano-carrier has a unique ability to become soluble and transport molecules through natural barriers found in drug resistant tumors, the gastrointestinal tract and the blood brain barrier. The work is part of the growing field of nanomedicine that could potentially yield injectable devices 100,000 times smaller than the head of a pin.

Alexander Kabanov, Ph.D., Dr.Sc.

One of Dr. Kabanov's projects involves using polymers with the chemotherapy drug doxorubicin – creating a nanomedicine called SP1049C.

"We've discovered if a polymer is present, suddenly the drug resistant cancer cells were killed and healthy cells were not affected," Dr. Kabanov said. "These block co-polymers deliver a double-punch effect to resistant cancer cells by also triggering apoptosis – a programmed cell death mechanism."

Dr. Kabanov's work in polymers has garnered more than $15 million in research grants, and dozens of research papers published in prominent journals.

In June, during the American Society of Clinical Oncology meeting of the world's leading organization of clinical oncologists, Dr. Alakhov and his team presented results of their Phase II clinical trial. Patients with advanced metastatic esophageal cancer received SP1049C with compelling results.

Dr. Alakov, chief scientific officer of Supratek, said 47 percent of patients had more than 50 percent regression of tumors, with an average survival of about 10 months. This compares favorably with the six- to 10-month survival rates observed in patients treated with the most advanced drug combinations in the United States and Europe.

"The spectrum of the cancers where this could be used is very broad," Dr. Kabanov said. "The trial results send a strong message that SP1049C is active against highly resistant cancers, and could become an important treatment for many cancer patients over the next three to five years."

Researchers are preparing a pivotal international trial that will be conducted under U.S. Food and Drug Administration regulations in six to eight countries, including the United States, Canada, France, Australia, and Russia.

Dr. Kabanov hopes one day his work will save lives like the two grandmothers he lost to cancer when he was young. When a good friend in Omaha recently was diagnosed with breast cancer, he learned about the personal battle.

"I saw the suffering. Now I understand the gravity, implication and the importance of this struggle," Dr. Kabanov said. "The road is long in biomedical research. If we are successful in this application, that is the ultimate reward."