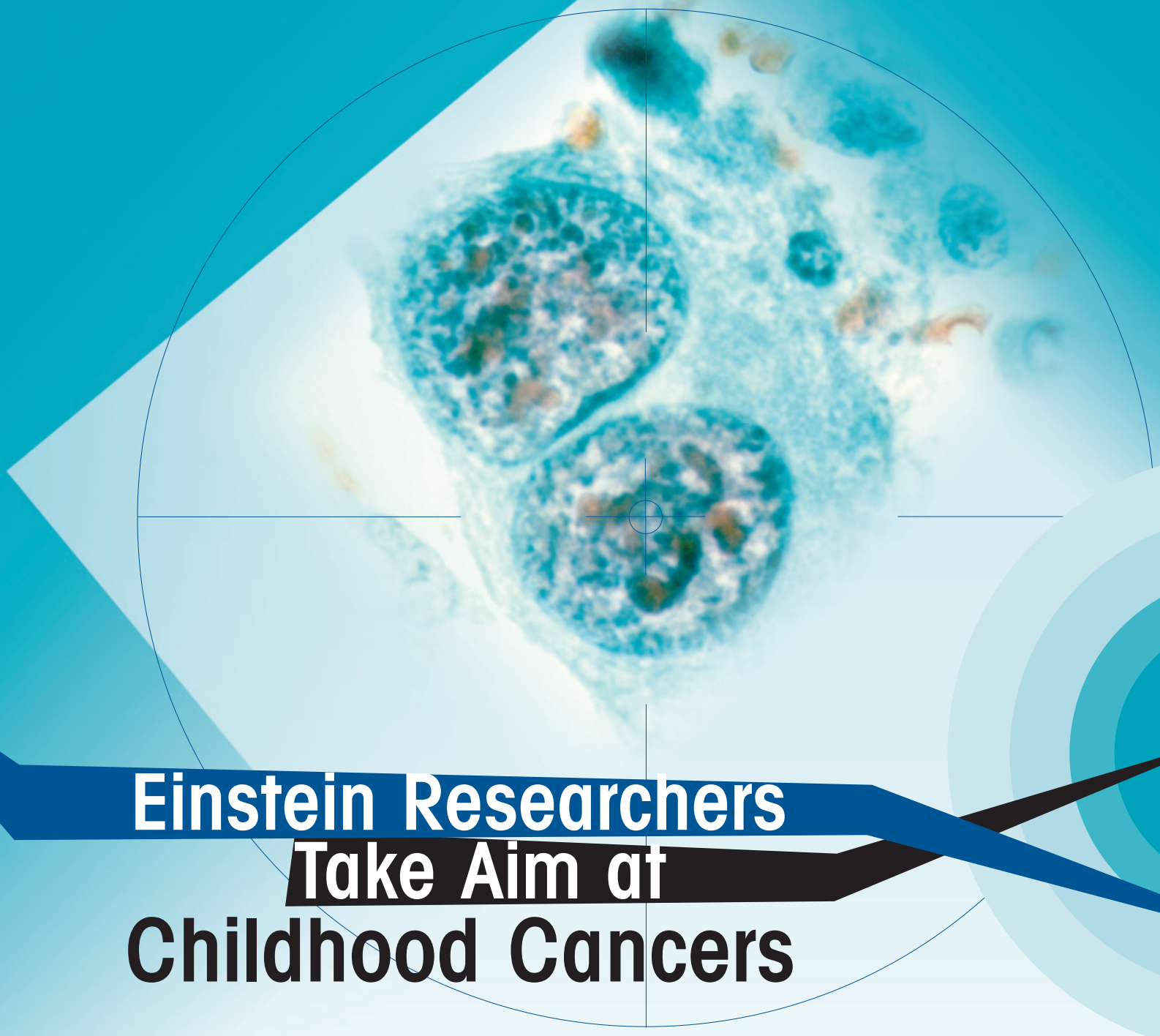


Einstein Researchers Take Aim at Childhood Cancers

Dr. Richard Gorlick

Dr. Richard Gorlick, Associate Professor of Pediatrics and of Molecular Pharmacology, came to Einstein from the Memorial Sloan-Kettering Cancer Center to head a new program in pediatric hematology-oncology at Einstein and a new Division in that specialty at Montefiore's Children's Hospital. He is a member of the Cancer Center's Experimental Therapeutics Program.

Has your move to the Bronx met your expectations, thus far?
Absolutely. I was brought in to expand and improve clinical services, and we've already made progress. The number of attending physicians has increased from three to nine, our patient volume has grown significantly, and we're now doing bone marrow transplantation—increasingly considered standard treatment for certain pediatric cancers. The nine kids who've so far received transplants have done extremely well, with no unexpected complications.

What attracted you to Einstein?
One of the real appeals was the high quality of the basic science. The laboratories within the cancer center are phenomenally strong, with outstanding researchers like Susan Horwitz and Vern Schramm, among many others. One of my missions here is to help move the most promising findings from the laboratory into the clinic as quickly as possible.

(continued on page 6)

Can you point to any accomplishments in that regard?
Drs. Sridar Mani and Ganjam Kalpana, my colleagues in the Einstein Cancer Center, have done interesting basic research on drugs that may be effective against pediatric brain tumors. Dr. Adam Levy, who was recruited from New York University to head up our neuro-oncology program, is working on translating these findings and initiating clinical trials at the Cancer Center. We would also like to test some promising agents that have come out of Dr. Schramm's laboratory. Dr. Anders Kolb, who was also recruited from Memorial Sloan-Kettering, heads our leukemia program, and is interested in pursuing clinical trials of Immucillins, the T-cell-inhibiting drugs developed by Dr. Schramm that have great potential for treating childhood T-cell leukemia. [Dr. Schramm is Chair and the Ruth Merns Professor in Biochemistry. Dr. Kalpana is the Mark Trauner Faculty Scholar in Neuro-oncology.]

Do you have a clinical specialty?
I take care of kids and young adults with sarcomas—malignant tumors that grow from connective tissue, either bone or soft tissues such as muscle. Within the sarcomas I specialize particularly in osteosarcoma, the most common malignant bone tumor in kids.

What's unique about treating children with cancer?
Most adult cancer patients are simply treated by a physician in an office with what's considered the standard of care, with only a small minority enrolling in clinical trials. But a real strength of pediatric oncology is its clear devotion to clinical trials. More than 90 percent of children diagnosed with cancer are treated in such trials as opposed to receiving standard care. That's in part because we're organized into national cooperative groups in which all the major cancer centers throughout the country agree to treat their patients using a common protocol. These are mainly Phase III trials—the final testing stage before approval—because that's where you need a lot of patients to answer questions regarding a drug or drug protocol's effectiveness.

"A real strength of pediatric oncology is its clear devotion to clinical trials."

Does this national collaboration extend beyond treatment to include research?
Yes, we're set up so that different medical centers serve as resource laboratories covering every type of pediatric cancer, and I'm active in those efforts. For the past nine years, my laboratory—initially at Sloan-Kettering and now here—has served as the national resource laboratory for osteosarcoma. Tumor specimens from throughout the country are sent to our laboratory for study.

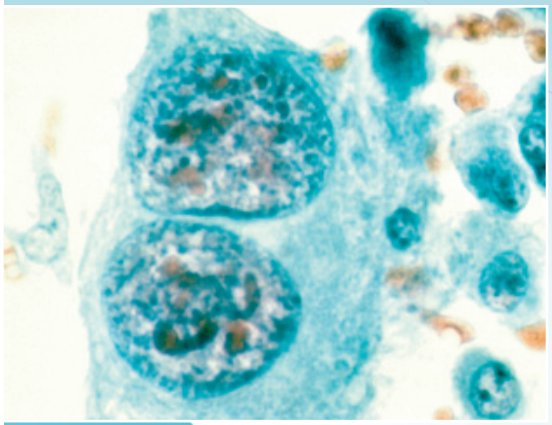
When do people develop osteosarcoma?
It's primarily a disease of young adults and teenagers, peaking in incidence at age 18. Younger kids get other types of sarcomas but not osteosarcomas typically.

Why?
Osteosarcoma may be related to bone growth—especially the time of peak growth, when cells are rapidly dividing. We know that girls—whose growth spurt occurs earlier than boys—tend to develop osteosarcoma at a younger age. Also, bone growth is more extensive in taller people, who get osteosarcoma more frequently than shorter individuals.

What's the prognosis for children diagnosed with osteosarcoma?
Before chemotherapy, only about five to 10 percent of patients survived, whereas now we cure about 70 percent.

So there's still room for improvement?
Definitely. With other pediatric malignancies such as leukemia—the most common childhood cancer—we've progressed to where 90 to 95 percent of patients survive. But that 70 percent survival for osteosarcoma patients hasn't budged for 15 years, so we seem to have reached the limit for helping patients with the drugs now available.

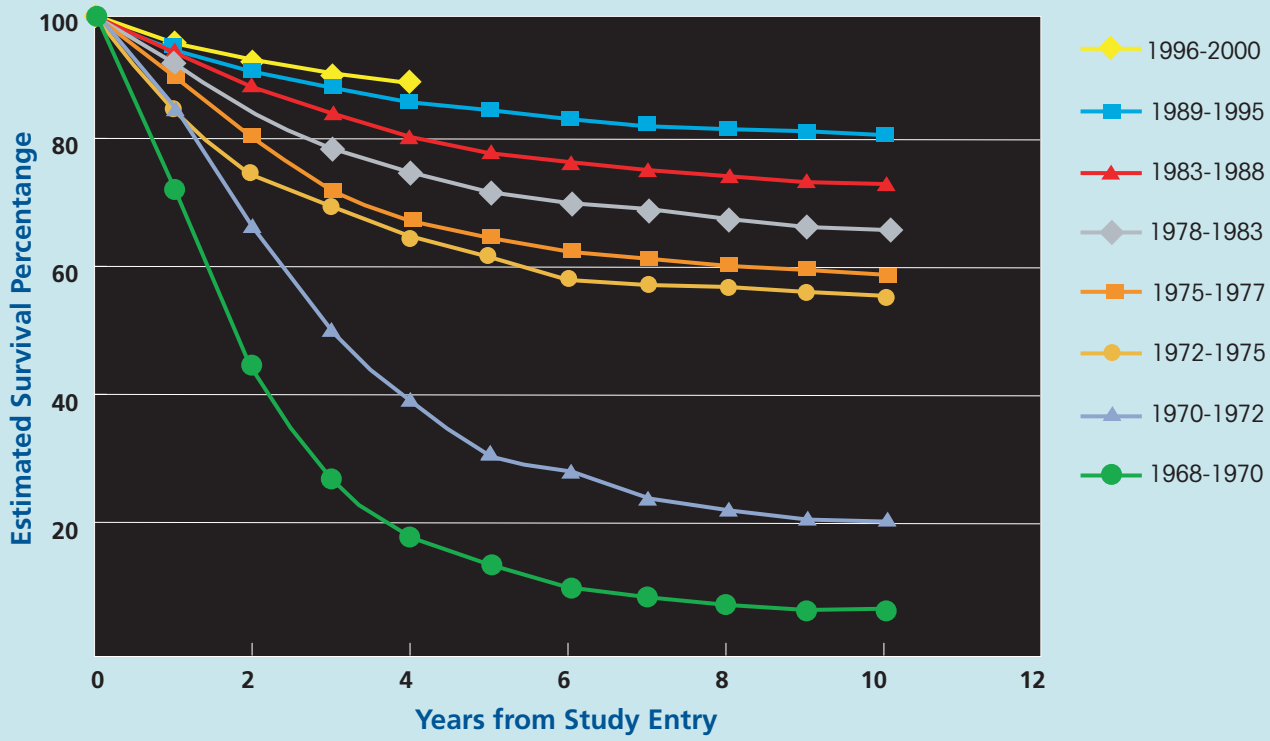
Do new drugs look promising?
Most deaths from osteosarcoma occur because the cancer has spread to the

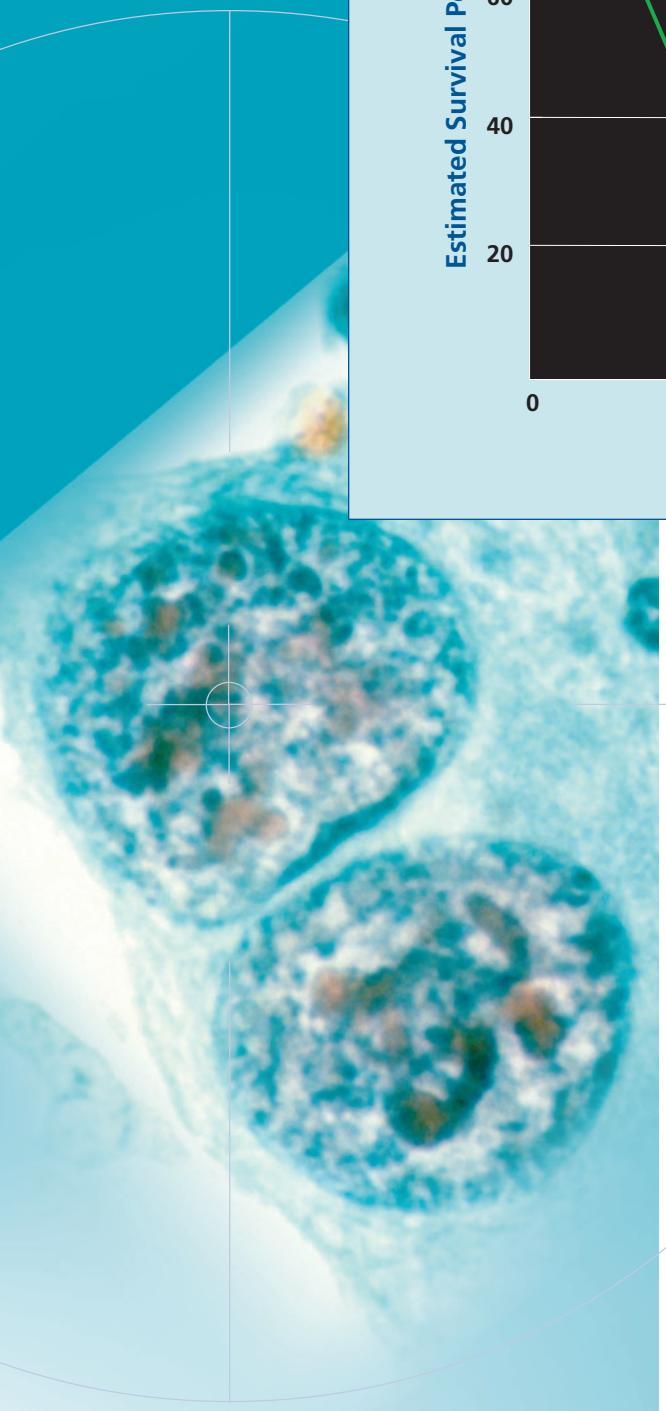


Human malignant osteosarcoma (bone cancer) cells taken from a leg mass, Pap-stained and magnified to 400x. Image courtesy of National Cancer Institute.

IMPROVED SURVIVAL IN CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA BY STUDY ERA

While survival rates for acute lymphocytic leukemia, the most common pediatric malignancy, and most other childhood cancers have improved dramatically, the survival rate for osteosarcoma patients has remained at 70 percent for the past 15 years.





"One of my missions here is to help move the most promising findings from the laboratory into the clinic as quickly as possible."

lungs. So we're studying an inhalation version of cisplatin, an anti-cancer drug normally given intravenously. The drug is encapsulated in liposomes—synthetic microscopic fat globules. Ideally, this aerosol form of cisplatin will defeat these metastases by producing higher drug concentrations in the lung while also causing fewer side effects elsewhere.

Any other promising candidates?
Osteosarcoma patients who develop colds sometimes experience dramatic tumor regression. Mild-mannered cold viruses called reoviruses home in on an activated signaling pathway in tumor cells, known as Ras, and they use this Ras pathway to replicate more efficiently within tumor cells. Reovirus multiplication causes the cells to lyse, or burst, while leaving healthy tissue unaffected. Dr Sanjay Goel, Assistant Professor of Medicine (oncology), just began a Phase I trial in which adult sarcoma patients and osteosarcoma patients 13 years of age and older are being treated with reovirus.

What is in the pipeline?
We're studying drug resistance to methotrexate, an important drug for treating osteosarcomas and other cancers. Methotrexate is an antifolate drug, meaning it prevents cells from using folates, the B vitamins that rapidly dividing cancer cells need in large amounts. Unfortunately, high-dose methotrexate often results in tumors becoming resistant to the drug. We've found several mutations in transport proteins, and these mutations impair methotrexate's entry into tumor cells, which may explain the resistance problem. By early next year, we hope to initiate a clinical trial of a methotrexate analog, called Pemetrexed, which shows promise for overcoming resistance by circumventing this transport problem. We've been doing this antifolate work in collaboration with Dr. Goldman, the director of the Cancer Center. It has been an exciting time, and we are looking forward to making good progress in the years ahead. ■