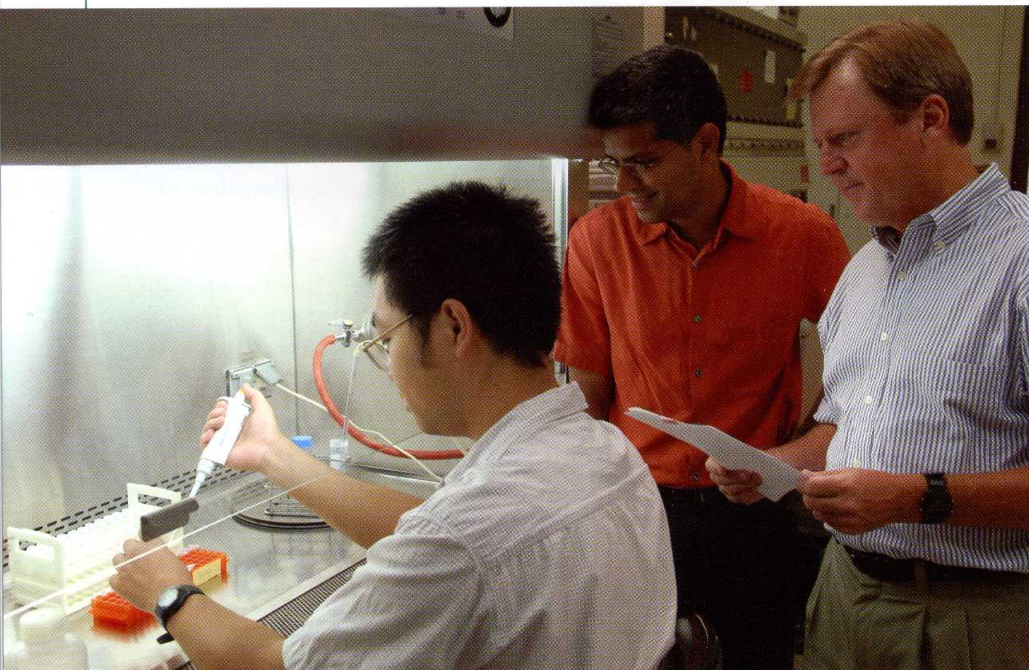


Science Features

NANOTECHNOLOGY

A PROMISING NEW FRONT IN THE WAR AGAINST CANCER



Researchers achieve promising breakthrough delivering cancer drug to targeted tumor cells

by David Reich
College of Engineering
Public Affairs Officer

Chemotherapy has been the primary tool in cancer treatment for some years. Usually, it involves massive amounts of cancer drugs delivered intravenously. Typically, although effective, a significant percentage of the drug fails to reach the intended tumor and is absorbed by other parts of the body with undesirable side effects.

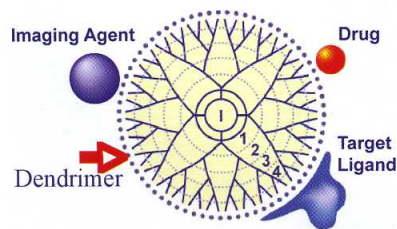
With the advent of nanotechnology, a promising new front has opened in the fight against cancer, and researchers are focusing on new “targeted” drug delivery systems capable of honing in and attacking tumor cells without affecting healthy tissue.

Chemical engineers, together with medical scientists, are working with tiny polymer constructs called dendrimers (~5-10 nanometers) that act as cancer-drug carrying ‘vehicles’ to target cancer cells, which can be highly resistant to drugs.

At Wayne State’s College of Engineering, a team led by Chemical Engineering Professor Rangaramanujam Kannan has shown how to effectively deliver a cancer drug to the doorstep of a tumor. More significantly, their unique dendrimer formulation can manipulate the resistance cancer cells to open themselves for drug delivery. Through collaborations with researchers at the Karmanos Cancer Institute, the investigation is set to move to the animal model stage. Kannan’s team has demonstrated their method to be as much as 20 times more effective against resistant cancer cells than current treatment methods. Their nanovehicles were the first reported polymer-based delivery vehicles that performed better than the drugs in cells. Considering the built-in advantages of these vehicles in vivo over free drugs the potential of their technology is significant.

A successful targeting method using nanotechnology not only introduces a powerful new tool in fighting cancer, but has other applications. One application is in cancer detection. Kannan’s team is working with other Karmanos researchers in developing imaging agents using dendrimers to create improved cancer detection and screening procedures.

“It costs hundreds of millions of dollars to develop a new drug that may be more effective; rather than discover a new drug, it’s much cheaper to deliver the same drug



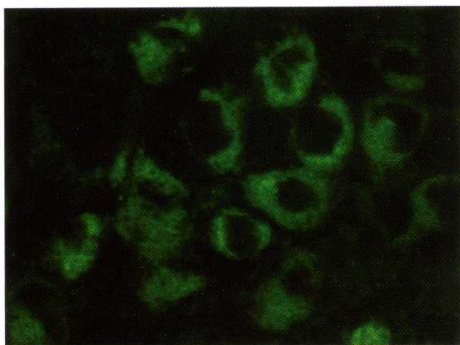
Schematic of the dendrimer-based targeted, nanovehicle that is imageable in vivo

more effectively,” says Kannan in explaining part of the motivation behind his compelling research.

Kannan (pronounced ‘con-nun’) has not only shown his talent as a premier researcher in the nine years he arrived at the college from California Institute of Technology in Pasadena where he earned his PhD, but also a talent for teaching and engaging his students.

Using the power of similes (he loves to compare, for instance, the role of a dendrimer to a school bus), Kannan outlines and explains to an interviewer the intricacies of his work and the background of the area of his expertise – polymeric nanomaterials and drug delivery – which involves more than a bit of knowledge in biology.

In April, Kannan’s group caught the attention of nanotech and cancer scientists when he reported in the journal *Bioconjugate Chemistry* success in attaching the common



Cellular localization of dendrimer-drug-imaging agent nanodevices FITC fluorescence seen inside the cell suggest rapid transport of drugs into cells by dendrimers.

cancer drug methotrexate to a dendrimer nanoparticle that overcame resistance to the drug in cancer cells (see nano.cancer.gov/news_center/nanotech_news_2006-04-03b.asp).

For the past few years, researchers have been able to use dendrimers -- nanoscopic, non-toxic, tree-like polymers -- to attach themselves to cancer cells in the body. The problem, however, has been in manipulating these nanovehicles to transport themselves through the tumors, into cells, and releasing the drug at the right time.

Kannan credits Karmanos collaborator Larry Matherly, professor, Cancer Biology/ Pharmacology, and his insights into how the drug works, as key to the team’s promising results. “He is a world expert in understanding methotrexate transport and folate receptors in leukemic cells.

“We believe a lot of the clues on how to make this whole technology go relies on understanding the mechanism by which these things act,” Kannan says. “To make these things go, first it has to be harmless, it has to get where you want it to go, it has to be taken by the cells, and finally, the dendrimer has to let go of the drug in the right place.”

Scientists have shown that if you attach folic acid to a dendrimer, then attach the cancer drug to it, the dendrimer will reach a tumor cell 100 times better than without the folic acid. Kannan calls the targeting agent folic acid “the roadmap” in his school bus analogy.

“On the cell surface there are receptors who can welcome the drug into the cell,” Kannan explains. “Some tumor cells over-express folate receptors. And you can attach some molecules like folic acid on your dendrimer that will find these receptors very effectively.”

Resistant cells are very sophisticated, but they can be tricked. “They are clever enough to figure that the drug is coming,”

says Kannan. “But they are not clever enough to figure out that the dendrimer is hiding it.”

Getting in the cell is certainly a big step, but not “a big deal” since it’s already been done, Kannan says. “Besides that, you

need the right environment around the dendrimer and the drug. And that is the big, big deal. That is where we are able to get significantly better performance than

what people have gotten in the literature before.”

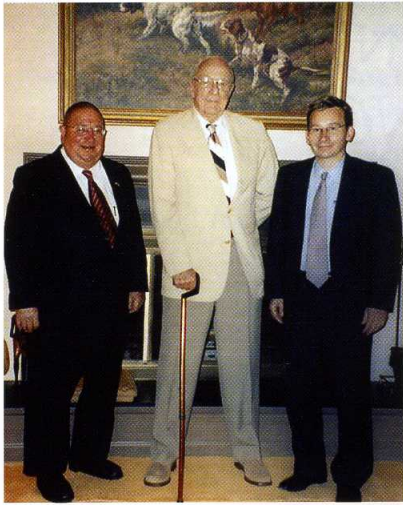
The dendrimer formulation with the “correct charge”-- so the drug will be released inside the cell in the right place -- is the key. “Inside the cell all kinds of things happen,” Kannan explains. “It first gets into something like early endosome, then late endosome, then goes into lysosome. Lysosomes are places where the drug can be released from the polymer. If the dendrimer does not spend enough time in the lysosome, then the drug will not be released. If you use anionic dendrimer, you have a better chance.

“If a dendrimer has a COOH end-group it means under the right environment, it will carry a negative charge. It can be anionic,” says Kannan. “Whether you have a highly negative, neutral, positive charge, plays a big role in how the dendrimer is taken into the cells and how the drug is released. This is a very big finding, a crucial step



Ranganamanujam Kannan

Dendrimers story continued on page 31



Robert Wingerter with Dean Ralph Kummler (L) and Jack Vanhecke, the college's development director

some new support for the university. I was motivated to recognize superior scholastic performance in the engineering college.”

“I established the awards in December 1967 to reward senior students for their outstanding scholarship, character and leadership. Back then, the awards were \$250, and I gave \$1,000 each year to fund the four annual awards.

Today, each awardee receives \$1,000, and my hope is that the endowment I created will support some future increases to parry the erosion of inflation.”

“Since 1968, 130 awards have been presented, and it is gratifying to receive photos and occasional notes of thanks from the students. Reading about past Wingerter award winners who are succeeding in business also is a great pleasure for me. Although it is difficult now to attend the award ceremonies as I occasionally used to, I still feel connected to the College of Engineering and am proud to stimulate students through this award recognition.”

Marion Ringe is a development officer in the WSU Office of Development and Alumni Affairs.

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to making these things work.”

Kannan and Matherly were able to achieve success only after lengthy trial and error applying their dendrimer formulations to tumor cultures consisting of both sensitive and resistant cell lines. “As time goes by, cancer cells become resistant to the drug,” Kannan says. “Larry can take a sensitive cell and knock out the receptor that takes in the drug and make the cell resistant. You treat them with the drug and you find the sensitive line gets killed. The resistive line puts up a big struggle even after being given a factor of 100 times more drug. If we take that same cell line, and treat it with the dendrimer conjugate we created, we need to give a factor of 8-25 times less drug.”

The researchers have been using mice in preliminary tests to learn more about the behavior of dendrimers. “Now that we know what kind of construct is working, we can go back and put targeting moieties (agents) on dendrimers and go and test them in animals.”

Kannan hopes to work with other

researchers at Karmanos, Children’s Hospital of Michigan and Kresge Eye Institute, that will lead to several clinical applications through translations of this nanomaterials research platform. “Our collaborators have animal models to test our dendrimer-based delivery systems,” says Kannan. The collaborations are with Anthony Shields, Fazlul Sarkar, Bonnie Sloane and Kami Moin and Neb Duric (all at Karmanos), Ray Iezzi (Kresge), Mary Lieh-Lai (Children’s), David Bassett (College of Pharmacy). Another close collaborator is Sujatha Kannan (Kannan’s wife) who was his mentor and is on the faculty at Children’s. She is working on using dendrimers for delivery to the brain.

“It’s a relative new technology with very broad applications, and Wayne State is a great collaborative environment to make it happen”, he says. □

R.M. Kannan is an associate professor in the Department of Chemical Engineering and Materials Science, and Biomedical Engineering. He is also a co-inventor, co-founder and chief technical officer of nanoScience Engineering Corporation, a nanotech start-up partly owned by Wayne State, that researches, develops and markets novel neofiller dispersion technologies.

