Biochemistry

The seeds of better chemotherapy?

In recent years, oncologists have explored the prospects of injecting liposomes – microscopic drug carriers constructed from fat-like chemicals – to treat cancers. A pair of new studies strongly suggests that these drug-delivery vehicles may boost the safety or potency of anticancer drugs.

Doxorubicin "is the single most useful drug in breast cancer," says oncologist Joseph Treat at the Medical College of Pennsylvania in Philadelphia. However, the compound is also highly toxic to noncancerous tissue – especially the heart.

Two years ago, Pieter Cullis at the University of British Columbia in Vancouver described animal data showing that liposome packaging dramatically reduced doxorubicin's normal cardiac toxicity (SN: 6/4/88, p.360). Treat, collaborating with cancer researchers from Georgetown University in Washington, D.C., and heart pathologists at the National Heart, Lung, and Blood Institute in Bethesda, Md., now reports similar doxorubicin protection in an uncontrolled trial involving 20 patients with advanced breast cancer – each receiving an average of five high-dose intravenous infusions of drug-laced liposomes. These patients, Cullis says, provide "the first indication in humans that [liposome encapsulation] reduces cardiotoxicity."

Formerly, Treat observes, nearly every patient receiving cumulative doxorubicin doses of at least 180 milligrams per meter squared of body surface exhibited significant heart damage. At higher doses, some even developed congestive heart failure. But in the Nov. 7, 1990 JOURNAL OF THE NATIONAL CANCER INSTITUTE, his team reports that biopsies of patients receiving doses as high as 600 to 880 mg/m^2 showed little or no heart damage. This "almost complete lack of toxicity is remarkable" and "very, very significant," Treat told SCIENCE NEWS.

Moreover, the improved safety does not appear to come at the expense of doxorubicin's efficacy. The researchers report that nine of the treated individuals improved; five experienced a complete remission of their major metastatic tumor. Treat says he wants to follow up on these findings by participating in multi-institutional trials that compare the outcomes of patients randomly assigned to treatment with either regular doxorubicin or the liposome-encased drug.

Dutch researchers are now attempting to advance the liposome concept one step farther: They're incorporating anticancer drugs into low-density lipoproteins (LDLs).

With their spherical shape and high lipid content, these natural cholesterol-shuttling agents in the blood resemble liposomes. But LDLs offer two potentially dramatic advantages over conventional liposomes, according to P. Chris de Smidt and Theo J.C. van Berkel of the University of Leiden in The Netherlands. First, because cancerous tissues exhibit an unusually high "demand" for cholesterol, their cells develop high numbers of LDL receptors. As a result, injections of drug-laden LDLs should home in on malignancies more than on healthy tissues, the researchers say. Second, because the body tends to recognize LDLs as natural, de Smidt and van Berkel say drug-containing LDLs might be thought of as "stealth liposomes" – lab-engineered cancer munitions that can evade the body's own defense against foreign substances.

Indeed, the Leiden pair reports in the Dec. 1, 1990 CANCER RESEARCH that two LDL-bound injected drugs – methotrexate and floxuridine – successfully dodged the body's natural clearance mechanisms to circulate at least six times longer in the blood of rats than did unbound drugs. Because the LDLs survived longer than the drugs they had been carrying, de Smidt and van Berkel say the drugs may not have been chemically bound to the LDLs firmly enough. But the findings are promising enough, they say, to warrant human investigation of these potential drug carriers.

Cosmology

Return of the cosmological constant

When Albert Einstein wrote down the equations for his theory of general relativity more than 70 years ago, he felt compelled to add a mathematical term representing an unknown, repulsive force to counter the gravitational attraction of mass. The introduction of this "cosmological constant" gave Einstein a way to reconcile his theory with the then-current belief that the universe is neither expanding nor contracting. However, the subsequent discovery that the universe actually is expanding led cosmologists to abandon the cosmological constant. Einstein himself eventually repudiated the notion, describing its introduction as the biggest blunder of his life.

A group of astrophysicists at the University of Oxford in England has now resurrected the idea to solve a different problem. They introduce a cosmological constant to show how matter in an expanding universe dominated by cold dark matter could lead to the formation of great walls, great attractors and other huge aggregations of galaxies.

In its simplest form, the cold-dark-matter theory holds that gravity amplified tiny fluctuations in the distribution of matter in the early universe to produce the collections of galaxies that astronomers observe today. Moreover, more than 99 percent of the mass in the universe is dark, consisting of as-yet-unidentified particles that interact only weakly with ordinary matter. The model also assumes a universe having a "critical" density of matter – the density separating a universe that expands forever from one that would eventually contract.

Although such a model can account for structures on the scale of individual galaxies and large clusters of galaxies, theorists have considerable difficulty using it to explain the formation of structures on even larger scales. At the same time, measurements by the Cosmic Background Explorer spacecraft indicate that the distribution of matter in the early universe was incredibly smooth.

"The [cold-dark-matter] model is attractive because it links the formation of cosmic structure to plausible physics of the early universe, so it would seem reasonable to retain the basic picture as far as possible," George Efstathiou and his colleagues argue in the Dec. 20, 1990 NATURE. "A positive cosmological constant could solve many of the problems of the standard [cold-dark-matter] model and should be taken seriously."

To save the cold-dark-matter model, Efstathiou and his colleagues introduce such a cosmological constant, which, in effect, endows the vacuum of space itself with a small energy density. Because the cosmological constant affects the overall geometry and expansion of the universe, its introduction allows the researchers to assume a lower value for the density of the universe – only 20 percent of that usually assumed.

Calculations based on these new assumptions show that this model can produce sufficiently large galactic structures and still account for the smoothness of the microwave background. In such a universe, cold dark matter would dominate the expansion for about half of its history. Then the force represented by the cosmological constant would take over.

Efstathiou and his co-workers "present what may be the strongest case to date for a nonzero cosmological constant," Edmund Bertschinger of the Massachusetts Institute of Technology comments in the same issue of NATURE. However, he says, "a nonzero cosmological constant would have profound and . . . disturbing implications for fundamental physics."

The new cold-dark-matter model will remain speculative until researchers furnish direct, empirical evidence supporting the notion of a positive cosmological constant, Bertschinger adds. That may require studying the distribution and motion of distant galaxies formed when the universe was young, or determining more precisely the age of the universe and the rate at which it is presently expanding.