Diamonds for Drug Delivery

One of the challenges of chemotherapy is delivery of sufficient quantities of drug to tumor cells to kill them while sparing healthy cells and tissues. One strategy for achieving this balance is to use small particles, only nanometers in size, to deliver drugs to tumors. Each nanoparticle—which can be an organic molecule, such as a lipid or protein, or a metal like gold or iron oxide—can be loaded with hundreds of drug molecules, allowing more drug to get inside the tumor. So far, a handful of nanoparticle-drug combinations have been approved by the FDA or are in clinical trials for use in humans. Approved agents include Doxil (Centocor Ortho Biotech), which consists of the drug doxorubicin bound to liposomes; abraxane, paclitaxel bound to the protein albumin; and oncaspar (pegaspargase), the form of L-asparaginase that has been covalently attached to polyethylene glycol (PEG). In many patients, these agents are more effective and have fewer side effects than their conventional drug counterparts. Among agents currently in clinical trials, the drug preparation Aurimune (CytImmune Sciences), which consists of 27-nm gold particles coated with human TNF-α and PEG, has been shown to deliver 20-times-higher doses of TNF-α to patients' tumors than would have been possible with the drug alone.

Given these promising results, it is not surprising that new types of nanomaterials continue to come on the scene. One of the latest additions is nanodiamonds—carbon-based particles 2 to 8 nm in size with a truncated octahedral structure that gives each particle multiple facets, not unlike those of a diamond. The investigators from a recently published study (Chow et al. Sci Transl Med 2011;3:73ra21) reported that they had attached doxorubicin to nanodiamonds and used the resulting particles to treat mice with either breast or liver tumors. They found that nanodiamond-bound doxorubicin was retained in tumor cells in greater amounts, compared with doxorubicin alone, leading to increased tumor cell death and lower toxicity. This increased retention of the drug in tumor cells was due to the fact that the drug attached to the nanodiamonds remains in tumor cells longer than the drug on its own, according to the authors.

It remains to be seen how nanodiamonds will fare in clinical trials and whether they will have significant benefits over other nanoparticle-based delivery systems. For now, one promising trait of nanodiamonds appears to be their versatility. These particles can be outfitted with a variety of different surface functionalities that allow for binding to a wide range of drugs. ■

Bringing PI3K Delta Inhibitors to Cancer Treatment

Phosphatidylinositol-3-kinases (PI3K) are a family of lipid kinases involved in signaling cascades that play roles in various cell functions, including cell growth, division, and survival. Many human cancers have defects in the regulation of this pathway. While a number of cancer drugs function by inhibiting the activities of molecules involved in the P13K signaling pathway, such as the kinase AKT and mTOR, no inhibitors of PI3K are currently approved as cancer drugs. One such agent is now showing promising results in the clinic. PI3K comes in several isoforms that are expressed in different types of cells.

One isoform, P13K-delta, is produced primarily in immune cells. Calistoga Pharmaceuticals has produced an inhibitor for this particular kinase as a potential drug for treatment of hematologic cancers. The company presented preliminary but dramatic results of phase I trials of the drug, dubbed CAL-101, at the 52nd American Society of Hematology Annual Meeting in Orlando, Florida in December 2010. In a trial of patients with chronic lymphocytic leukemia (CLL) who had received prior therapies and had poor prognoses, CAL-101 treatment reduced tumor size in all 51 patients evaluated. The median progression-free survival exceeded 11 months. Similarly, in 30 patients with indolent non-Hodgkin lymphoma (iNHL) who had also received prior therapies, CAL-101 treatment resulted in a median progression-free survival exceeding 11 months. The drug is also effective in combination with standard therapies. For example, 6 of 6 patients with iNHL treated with CAL-101 plus bendamustine had an objective tumor response, with one patient achieving a complete response. In 7 patients with CLL, both patients receiving CAL-101 plus bendamustine and 3 of the 5 patients receiving CAL-101 plus rituximab had an objective response. The company has now advanced CAL-101 into phase II clinical studies. As a testament to these successes, Gilead Sciences purchased Calistoga Pharmaceuticals in February 2011 for $375 million. ■

Promising Developments for Pancreatic Neuroendocrine Tumors

Although their occurrence is rare, pancreatic neuroendocrine tumors (NET) are difficult to treat. By the time of diagnosis, most patients have advanced metastatic disease and their 5-year survival rate is below 43%. The only chemotherapeutic agent approved for treating NET—streptozocin, either alone or in combination with doxorubicin—has limited benefit for such advanced cases. Now, two new studies offer some optimism. Two phase III multicenter, double-blind, randomized, placebo-controlled trials have indicated that the drug sunitinib, an inhibitor of multiple tyrosine kinases, and everolimus, an inhibitor of mTOR, are effective against advanced pancreatic NET, even in patients in whom other treatments have failed.

In a trial of 171 patients, sunitinib increased disease-free survival from 5.5 months to 11.4 months compared with placebo. Similarly, in a trial of 410 patients, everolimus improved progression-free survival from 4.6 months to 11 months. The authors estimated that 34% of patients treated with everolimus were alive and progression free at 18 months, compared with 9% who had received placebo. Based on these results and those of earlier trials, the FDA has granted everolimus priority review designation for the application of advanced NET. In October 2010, the FDA granted accelerated approval to everolimus for treatment of subependymal giant-cell astrocytomas associated with the autosomal dominant disorder tuberous sclerosis, and data from trials in breast cancer are expected at the end of this year. Everolimus was originally approved in March 2009 for the treatment of adults with advanced renal cell carcinoma whose disease was resistant to sunitinib or sorafenib. ■