

Another approach uses immune cells as carriers, relying on T cells' tendency to home in on lymph nodes and the ability of T cells and macrophages to infiltrate tumors. For instance, researchers have inserted liposomes containing doxorubicin into macrophages, which then transported the liposomes into tumors in mice; the macrophage-delivered drug slowed the tumors' growth. A limitation of this approach, however, is that the drug has to exit the transporting cell to do any good.

To increase the amount of drug reaching tumor cells, Darrell Irvine, PhD, of the Massachusetts Institute of Technology in Cambridge, and colleagues devised a technique they call cell backpacking (*Sci Transl Med* 2015;7:291ra4). The backpacks are lipid nanocapsules loaded with SN-38, a version of irinotecan (Camptosar; Pfizer). On its own, SN-38 is a poor cancer drug because it's insoluble and doesn't readily enter tumors. The researchers reasoned that they could improve the drug's performance by using T cells to carry it to tumors.

Irvine and colleagues attached the backpacks to T cells and infused them into mice that had a rodent version of Burkitt lymphoma. The researchers found that the T cells traveled to three of the main locations where B-cell tumors form in this cancer: the lymph nodes, spleen, and bone marrow. Once they are in the animals' bodies, the SN-38-loaded capsules slowly break down and the drug diffuses out. Irvine and colleagues determined that the T cells delivered 63 times more SN-38 to tumor-bearing lymph nodes than injections of nanocapsules that contained the drug but weren't attached to T cells.

That increase made a difference for the mice. The overall tumor burden was 60 times lower in the animals that received the T cells loaded with SN-38 than in animals that received the drug alone. In addition, animals that received the altered T cells survived for 35 days, compared with control animals that lived just 24 days. "You get a tremendous increase in potency" with the cell backpacking method, says Irvine.

"I think what they've presented is promising," says Susan Clare, MD, PhD, of the Northwestern University Feinberg School of Medicine in Chi-

cago, IL. The higher pressure inside tumors can keep drugs out, but T cells are able to enter, she says. Clare adds that the technique might work for other cancers, including breast cancer.

The researchers didn't use antigen-specific T cells, but those cells might be able to home in on tumors in particular organs, Irvine says. He and his colleagues are looking into forming a company that would further develop the backpacking approach and potentially launch clinical trials. ■

Biomarkers Define Distinct Types of Diffuse Glioma

Two reports in *The New England Journal of Medicine* lay the foundation for molecular classification of diffuse gliomas, a heterogeneous group of brain tumors currently diagnosed by their appearance under the microscope. In the studies, genetic markers performed far better than histologic criteria to define three major disease subgroups, each associated with a different clinical profile.

The findings are timely, coming just as clinicians are meeting to revise the World Health Organization (WHO) diagnostic classification of brain tumors to include—for the first time—molecular criteria.

The two studies took different approaches. One, from The Cancer Genome Atlas (TCGA) Research Network, used unsupervised clustering of molecular data on protein expression, DNA methylation, mRNA and miRNA expression, and DNA copy number and mutations in 293 lower-grade (WHO grades II and III) gliomas (*N Engl J Med* 2015;372:2481–98). The other, from researchers at the Mayo Clinic in Rochester, MN, and the University of California, San Francisco, assessed three previously identified biomarkers in 1,087 gliomas encompassing grades II through IV (*N Engl J Med* 2015;372:2499–508).

In both studies, the molecular data settled into three robust, cohesive tumor groups that could be defined based on isocitrate dehydrogenase (*IDH*) mutational status and the presence or absence of a 1p/19q chromosome codeletion. The Mayo study

distinguished two additional tumor groups, one with mutations in the telomerase reverse transcriptase gene (*TERT*) promoter and the second with both *TERT* and *IDH* mutations.

The major groups—tumors with neither *IDH* mutations nor 1p/19q codeletion, with *IDH* mutations only, or with *IDH* mutations and 1p/19q codeletion—accounted for more than 95% of the grade II and III tumors in the two studies, showed little overlap, and correlated only modestly with histologic class or grade. Both studies found that the distinct types had significantly different age of onset and median survival, and developed characteristic secondary genetic alterations.

Notably, the majority of low-grade tumors that were wild-type for *IDH* actually possessed the genetic profile and aggressive course seen in patients with grade IV glioblastomas. Many in this group had *TERT* promoter mutations, which are common in glioblastomas. In the TCGA study, these tumors had a median survival time of 1.7 years, compared with 6 to 8 years for tumors with *IDH* mutations.

"We think we are capturing early glioblastomas," says neuropathologist Daniel J. Brat, MD, PhD, of Emory University School of Medicine in Atlanta, GA, the lead author of the TCGA study. "There is no way to identify that behavior under the microscope without additional testing," he adds.

IDH mutations and 1p/19q codeletion are already routinely assessed in gliomas to provide ancillary information to the histologic diagnosis that affects treatment decisions. The new work supports the idea that the two, along with *TERT* promoter mutations, could improve diagnosis.

The findings will also affect pre-clinical research and drug development efforts, says neuro-oncologist Ingo K. Mellinghoff, MD, of Memorial Sloan Kettering Cancer Center in New York, NY, who was not involved with the study. Having the detailed genetic profiles of each glioma subtype will enable researchers to develop more appropriate animal models. For clinical trials, the results will allow testing of drugs geared toward particular tumor types and molecular targets. "It will really change the way people think about the disease," Mellinghoff says. ■