PEOPLE

Karen E. Knudsen, PhD, has been named director of the Sidney Kimmel Cancer Center at Thomas Jefferson University in Philadelphia, PA, as well as chair of its department of cancer biology. She has been serving in these roles on an interim basis since January.

An expert in the molecular basis of hormone-dependent prostate cancer, Knudsen aims to prevent and treat the disease. Her studies that identify tumor suppressor and hormone-receptor alterations have uncovered new targets for treating advanced disease and have led to innovative, biomarker-driven clinical trials. In addition, she is editor-in-chief of *Molecular Cancer Research*.

EMBL-EBI

Rolf Apweiler, PhD

EMBL-EBI

Ewan Birney, PhD

Rolf Apweiler, PhD, and **Ewan Birney, PhD,** have been appointed joint directors of the European Molecular Biology Laboratory—European Bioinformatics Institute (EMBL-EBI), effective July 1. The European hub for big data in biology, EMBL-EBI is based on the Wellcome Trust Genome Campus in Hinxton, UK. As part of EMBL, the institute collects, annotates, archives, and shares data from publicly funded life-science experiments with the global scientific community. Apweiler and Birney will continue to lead their respective research groups.

Apweiler is involved in many internal collaborations and initiatives, including the Human Proteome Organization Proteomics Standards Initiative. He has served on the editorial and advisory boards of several journals, and he has published more than 250 papers and book chapters.

Birney played a vital role in annotating the genome sequences of the human, mouse, and other organisms. He led the analysis group for the ENCODE project. His interests include functional genomics and statistical methods to analyze genomic information.

Precision Medicine Path for Prostate Cancer

A mainstay of metastatic prostate cancer treatment is the suppression of hormones that fuel tumor cells. However, almost all men with advanced prostate cancer develop resistance to these androgen-depleting therapies.

Recently, researchers showed that nearly 90% of patients with metastatic castration-resistant prostate cancer (mCRPC) have a genetic alteration that could be targeted by other clinical treatments. The findings suggest individualized approaches for these patients (Cell 2015;161:1215–28).

"This will have a major impact on how we move forward in [treating] this disease," says Johann de Bono, MD, a principal investigator in the study and head of the Division of Clinical Studies at the Institute of Cancer Research in London, UK. "Ninety-nine percent of our trials involve no patient preselection. With this information, we can now subdivide these patients, as we've done with breast and lung cancers."

In this first multicenter, international clinical trial, researchers conducted whole-exome and transcriptome sequencing of bone or soft-tissue biopsy samples from 150 patients living with mCRPC. Results showed that 62.7% of the patients who had a genetic alteration had androgen receptor mutations, a finding in line with current understanding of the disease.

More compelling, researchers found that of the nearly 90% of patients with genetic alterations, 65% had anomalies (other than androgen receptor mutations) that could be targeted by investigational or FDA-approved drugs currently used for other cancers. Among these alterations, almost 23% occurred in DNA repair pathways. For instance, some tumors had BRCA1 or BRCA2 mutations, which, in ovarian and breast cancers, have shown sensitivity to PARP inhibitors, drugs that interfere with DNA repair and prevent tumor cells from dividing.

In addition, researchers mapped more than a half dozen previously unknown genetic changes, such as mutations in the Wnt signaling pathway, which leads to regulation of cell development and migration, and a *PIK3CB* mutation with cancer-activating effects similar to *PIK3CA*. They also found that 8% of patients with mCRPC had germline mutations.

"This is a very important study on a number of fronts," says Karen Knudsen, PhD, director of the Sidney Kimmel Cancer Center at Thomas Jefferson University in Philadelphia, PA, who was not involved in the study. "It's the first large study looking at the incurable stage of the disease, where the unmet clinical need is. The large cohort gives us confidence and a much clearer picture of the drivers of disease, and they've uncovered new potential drivers that are targetable."

When the study is completed, researchers will have mapped and sequenced the tumors of 500 patients with mCRPC. Amassing such data, says de Bono, will lead to more targeted—and more affordable—sequencing.

"It will be critical to follow up with clinical trials that correlate clinical outcomes with molecular alterations," says Arul M. Chinnaiyan, MD, PhD, a senior author on the study and director of the Michigan Center for Translational Pathology at the University of Michigan in Ann Arbor. "The longer-term goal is to have this information ahead of time and be able to direct patients in a more precise way to the best therapy." ■

Cellular Backpackers Deliver Lymphoma Drugs

Researchers have developed a new technique that enlists T cells to ferry chemotherapy drugs into tumors and that improves the efficiency of drug delivery.

Cancer cells can elude chemotherapy by hiding out in lymph nodes and other protected locations. Even if a small amount of drug makes it to these refuges, it may not permeate the tissue to reach the tumor cells inside.

Researchers have tried to overcome these problems by having nanoparticles transport chemotherapy drugs, but not all tumors have the leaky blood vessels that enable the particles to leave the bloodstream and disperse into the tumor.

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 Chicago, 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 preclinical 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. ■