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## Start-ups Bring AI to Pathology

An early pioneer of computational pathology, Thomas Fuchs, PhD, of Memorial Sloan Kettering Cancer Center (MSKCC) and Weill Cornell Medicine, both in New York, NY, announced the launch of a new academic spin-off company in February. The start-up, known as Paige.AI, aims to replace pathology's glass slides and microscopes with digitized images and artificial intelligence (AI).

It's hardly alone in this endeavor. Software giants, medical device manufacturers, and dozens of small start-ups are developing pattern-recognition algorithms to help pathologists more accurately spot tumors on digitized images of tissue. However, thanks to $25 million from investors, intellectual property from MSKCC, and exclusive rights to the cancer center's library of 25 million pathology slides—one of the world's largest tumor pathology archives—Paige.AI has established itself as a front-runner in the development of a clinical-grade AI tool to guide cancer diagnosis and treatment.

"We have data at a scale no one else has," says Fuchs, the company's founder and chief scientific officer. Paige.AI is first deploying its machine-learning models, image classification software, and high-performance computers to diagnose prostate cancer. Algorithms for breast cancer, lung cancer, and other tumor types are also in development.

Fuchs sees biomarker analysis as one application of the technology: "The goal is to come up with new grading schemes and scores that can better stratify patients for different therapies." Additionally, he hopes AI can "help the pathologist be faster, more accurate, and more reproducible."

Another computational pathology start-up, PathAI, founded by Andy Beck, MD, PhD, recently won an international challenge that pitted algorithms from 23 teams against each other. Beck's algorithm—developed when he was on the faculty at Beth Israel Deaconess Medical Center in Boston, MA, with his lab and a colleague from the Massachusetts Institute of Technology in Cambridge—outperformed expert pathologists when it came to detecting metastases in lymph node slides from women with breast cancer (JAMA 2017;318:2199–210).

Now backed by $15 million in venture capital, Beck and his PathAI team aim to turn their expertise in pathology, biomedical informatics, and computational image analysis into commercially viable software that informs clinical decision-making, aids in drug development, and enables low-cost diagnostics in the developing world.

A number of obstacles stand in the way of the adoption of AI technology in clinical practice. First, to use the algorithms, slide digitization will need to become part of the primary diagnostic workflow, not an afterthought for archival purposes, says Jeroen van der Laak, PhD, of the Radboud University Medical Center in Nijmegen, the Netherlands.

In addition, with few applicable billing codes for AI services, "how do you deploy this in the clinical pathology workflow in a way that allows you to make money?" asks Anant Madabhushi, PhD, of Case Western Reserve University in Cleveland, OH. "That's not clear to me."

Beck acknowledges these challenges need to be overcome for computer-assisted diagnostic systems to be embraced. However, immediate opportunities for AI-powered pathology abound: For example, Bristol-Myers Squibb, one of PathAI's customers, is using the company's machine-learning algorithms to analyze tissue samples for a better understanding of drug responses in clinical trials.

"There's an explosion of data we can now generate from patient samples," Beck says. "We can bring huge value to drug development today." *–Elie Dolgin* ■

## Canine Research to Benefit Humans and Dogs Alike

The Jackson Laboratory (JAX) recently launched a program that aims to provide insights into cancer in humans by shining a light on tumors in their best friends: dogs. A $500,000 donation from an anonymous donor has funded a new canine biobank that will allow scientists to study cancer in an animal that offers several significant benefits.


Erin Blinn; The Jackson Laboratory

Patrick, a healthy Irish wolfhound, was the first dog to have a tissue sample added to a new canine biobank. He belongs to an anonymous family that donated $500,000 to fund the initiative.

Charles Lee, PhD, scientific director and professor at The Jackson Laboratory for Genomic Medicine in Farmington, CT, says that in the short time since the Tallwood Canine Cancer Research Initiative was announced, they have heard from several veterinary practices, as well as from researchers at the NIH and Tufts University in Medford, MA, who are interested in collaborating on projects involving both human and canine cancers.

To create the biobank, JAX will work with veterinary clinics across the country to collect healthy and tumor tissue from their canine patients through voluntary donations from pet owners. The first patient, Patrick, is a healthy Irish wolfhound who belongs to the family who funded this initiative. Researchers at JAX will use donor tumor samples to create patient-derived xenografts (PDX) in mice. These well-characterized models will then be shared with cancer researchers.

Through comparative genomic analyses, these PDXs can be used to learn more about the biology of human cancers, especially those that are rare among humans but common in some breeds of dog. For example, osteosarcomas are 27 times more common in large breeds such as rottweilers, Great Danes, and Irish wolfhounds than in humans, says Lee. "As we study the genomics of these tumors in dogs, we hope to see recurrent mutations

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in novel genes or associated regulatory elements that would give us new biological insights into the etiology of these same tumor types in humans."

Dogs possess several other features that make them ideal partners in cancer research. For example, dogs share their owners' environments and spontaneously develop tumors over time, as humans do. Like humans, they exhibit great phenotypic diversity. Furthermore, canine tumor progression often parallels cancer progression in people.

Even so, Daniel Gustafson, PhD, research director of the Flint Animal Cancer Center in Fort Collins, CO, warns that no one should expect canine cancer research to yield human-relevant results immediately.

"Dogs are not small furry people," he says. "It may not make intuitive sense, but understanding the differences between cancer in dogs and humans is the only way to see the similarities." He believes the initiative will be especially helpful in understanding the molecular basis of canine cancer, which will establish a foundation for comparative oncology.

The immediate beneficiaries of this research will most likely be dogs. "I have no doubt that the information garnered from these studies will also lead to incredible advances in personalized canine cancer therapy," says Lee. *–Kristin Harper* ■

## Apalutamide OK'd for Some Prostate Cancers

The FDA approved the antiandrogen apalutamide (Erleada; Janssen) on February 14 for the treatment of men with nonmetastatic, castration-resistant prostate cancer (CRPC), the first drug for these patients greenlighted by the agency. It is also the first drug approved on the basis of a new trial endpoint: metastasis-free survival (Cancer Discov 2017;7:1053–4).

The approval was based on results of the phase III SPARTAN trial, in which 1,207 patients with nonmetastatic CRPC at high risk for developing metastatic disease were randomly assigned to receive androgen-deprivation therapy with either apalutamide or placebo in a 2:1 ratio (N Engl J Med 2018 February 8 [Epub ahead of print]). High risk was defined as having a PSA doubling time of 10 months or less because "prior data have shown that these are the patients most at risk for developing metastases and death," said Eric Small, MD, of the Helen Diller Family Comprehensive Cancer Center at the University of California, San Francisco, senior author of the study. Small also presented the study's findings at the 2018 Genitourinary Cancers Symposium, held in San Francisco, February 8–10.

Apalutamide decreased the risk of metastasis or death by 72%, Small reported. Median metastasis-free survival among men receiving the antiandrogen was 40.5 months compared with 16.2 months among those receiving placebo, an improvement of more than 2 years—evidence that the transition from nonmetastatic to metastatic CRPC can be slowed. Overall survival (OS) data is not yet mature, but an interim analysis showed a trend in favor of apalutamide, Small said.

Apalutamide was well tolerated, with 10.6% of men discontinuing its use due to side effects, compared with 7% of men receiving placebo. Rash, hypothyroidism, and fractures were more common in the apalutamide group.

A next-generation competitive inhibitor of the androgen receptor, apalutamide also prevents translocation of the androgen receptor to the nucleus and impedes androgen receptor–mediated DNA transcription, Small explained.

"There's been no obvious standard of care for these patients," commented Sumanta K. Pal, MD, of City of Hope Comprehensive Cancer Center in Duarte, CA, making the findings "very clinically meaningful."

Also at the symposium, Maha Hussain, MD, of Northwestern University in Chicago, IL, reported results of a phase III trial of a second antiandrogen, enzalutamide (Xtandi; Pfizer, Astellas), in patients with high-risk nonmetastatic CRPC. In that trial, dubbed PROSPER, researchers enrolled 1,401 men and randomly assigned them to receive enzalutamide or placebo in a 2:1 ratio. Like apalutamide, enzalutamide significantly prolonged metastasis-free survival compared with placebo—36.6 months versus 14.7 months, a difference of nearly 2 years. As with apalutamide, an early OS analysis favored enzalutamide.



In the phase III PROSPER trial, enzalutamide prolonged metastasis-free survival nearly 2 years longer than a placebo in men with castration-resistant prostate cancer, Maha Hussain, MD, reported.

"Enzalutamide is a drug familiar to the prostate cancer community, given existing approvals in the setting of more advanced disease," said Pal. "The familiarity that oncologists already have with enzalutamide may help with clinical adoption." Enzalutamide was approved in 2012 to treat metastatic CRPC.

The SPARTAN researchers and Pal noted that participants in the trials were deemed to have nonmetastatic disease based on conventional imaging techniques, such as CT and technetium bone scans. "While it's true that this is the current standard, imaging techniques such as… PET and PSMA PET may potentially improve our ability to detect disease earlier and thereby change our management strategy," said Pal. *–Suzanne Rose* ■

## Arvinas, Pfizer Team Up on PROTACs

Taking an entirely different approach to fighting cancer, biotechnology start-up Arvinas (New Haven, CT) has spent the past 5 years developing proteolysis-targeting chimeras (PROTAC). The technology is based on a simple concept: Proteasomes break down proteins that have been tagged with ubiquitin by E3 ubiquitin ligases, so tagging oncogenic proteins for degradation will potentially stop their oncogenic signal.

Recently, Arvinas teamed up with Pfizer in a discovery-based deal worth up to $830 million, while continuing to develop other promising PROTACs in its internal pipeline.

Craig Crews, PhD, founder and chief scientific advisor of Arvinas, started working on PROTAC technology at New Haven's Yale University during

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AACR American Association for Cancer Research

CANCER DISCOVERY

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