on Molecular Targets and Cancer Therapeutics in Boston, MA. Sawyers, who conceived the effort and chairs its steering committee, explained that the explosion of sequencing projects "has created a treasure trove of data," but that the data often remain at the institution that conducted the sequencing, limiting their potential value and statistical significance.

"These data are typically insufficient in number or lack the necessary clinical outcomes data to be clinically meaningful," said Sawyers. "Thus, to effectively benefit patients, the genomic and clinical outcomes data from as many institutions as is practical should be combined through a data-sharing initiative."

Launched and funded for 2 years with $2 million from the AACR, the Project GENIE registry already contains more than 17,000 genomic records, many related to late-stage and rare cancers. Size is just one of the strengths of Project GENIE, and one trait that similar efforts lack. It will also include both retrospective and prospective data contributed by its seven founding members:

- The Center for Personalized Cancer Treatment, Utrecht, the Netherlands
- Dana-Farber Cancer Institute (DFCI), Boston, MA
- Institut Gustave Roussy, Villejuif, France
- Johns Hopkins University's Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD
- Memorial Sloan Kettering Cancer Center, New York, NY
- Princess Margaret Cancer Centre, Toronto, Canada
- Vanderbilt-Ingram Cancer Center, Nashville, TN.

As these institutions treat new patients, additional data—stripped of all identifying information to maintain patients' privacy—will be added to the registry, which includes only clinical-grade sequencing data that have been used in clinical decision making. All of the sequencing data are Clinical Laboratory Improvement Amendments–and International Organization for Standardization–certified.

To overcome some of the challenges of merging data from different institutions,

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Charles L. Sawyers, MD, explains the genesis of the GENIE Project at the press conference where the data-sharing project was announced.

project partner Sage Bionetworks of Seattle, WA, will ensure the data's provenance, perform quality assurance, and make other needed changes to harmonize the data; none of the participants will need to change their platforms or protocols for data collection, which would have been a deterrent to participation. "Cleaned" data will then be transferred to a cloud-based platform where it can be viewed and analyzed through cBioPortal, based at MSKCC, explained Justin Guinney, PhD, director of computational oncology at Sage.

Sawyers and Barrett Rollins, MD, PhD, a member of the AACR Project GENIE steering committee and chief scientific officer at DFCI, said that the searchable database may aid researchers and patients in multiple ways—for example, by developing new hypotheses for translational and clinical studies; validating biomarkers of treatment response and prognosis; identifying new patient populations that might benefit from existing treatments; and discovering novel drug targets.

Before the first data are made public next November, researchers from the seven member institutions will pose a significant clinical question to validate and demonstrate the benefits of AACR Project GENIE. After that, other scientists can propose additional queries. More data will be available over time.

"We believe it's an extremely valuable project," said Rollins. "We want to share it with cancer researchers around the world…It's a database like no other." –*Suzanne Rose* ■

Novartis Compiles Mouse Avatar "Encyclopedia"

Seeking to reduce the number of preclinical drugs that fail along the road to regulatory approval, scientists at the Novartis Institutes for Biomedical Research (NIBR), headquartered in Cambridge, MA, have generated an extensive collection of patient-derived tumor xenograft (PDX) models. Called the PDX Encyclopedia (PDXE), it augments NIBR's Cancer Cell Line Encyclopedia, established in 2012 (Nat Med 2015;21:1318–25).

"Our goal is to develop cancer therapeutics with a much higher probability of success in patients," says William Sellers, MD, vice president and global head of oncology at NIBR, "and we recognized the limitations of doing so with *in vitro* systems." The PDXE currently contains over 1,000 models, representing a spectrum of solid cancers, and genomic landscape analyses indicate "close alignment between our models and human data as described by The Cancer Genome Atlas," Sellers says.

The researchers are harnessing their collection to carry out PDX clinical trials (PCT) that mirror human studies in design: In a given PCT, each mouse receiving the therapy of interest bears a unique tumor xenograft from an individual patient. By treating a group of such mice, the therapy's efficacy against the cancer type in question can be determined, and "we can capture the heterogeneity of responses between patients," explains Hui Gao, PhD, a senior investigator at NIBR.

So far, PCTs have yielded data "highly consistent with what's seen in humans," Sellers says. For instance, *BRAF*-mutant PDXs responded well to BRAF inhibition—and even better with the addition of a MEK inhibitor. Ideally, he adds, PCTs will prove predictive of new therapeutic indications; to that end, "we're using this system to profile all of our clinical candidates and additional compounds."

Sellers and his team also validated cell line–derived results suggesting that high levels of two proteins, DR5 and caspase-8, predict sensitivity to TAS266, a novel antibody that activates

DR5 signaling, thereby triggering apoptosis. In an initial PCT assessing melanoma response to TAS266, just 18% of mice appeared susceptible. A retrospective biomarker analysis then revealed that the response rate to TAS266 was actually 80% in the subset of mice with elevated DR5 and caspase-8.

Importantly, the researchers found that therapeutic activity *in vitro* wasn't necessarily seen *in vivo*, and vice versa. "The disconnect was surprising," Gao says. Novartis's investigational IGF1R inhibitor LFW527 appeared to increase the efficacy of the MEK1/2 inhibitor binimetinib (MEK162; Array BioPharma) in colorectal cancer, non–small cell lung carcinoma, and prostate adenocarcinoma cell lines. When this combination was tested in relevant PCTs, no such synergy was observed—the modest response rate achieved with binimetinib in colorectal cancer "actually worsened" when LFW527 was added, Gao notes.

"It turns out that prior to our analysis, this combination was tried in the clinic, with negative results," Sellers says. "IGF1R inhibitors have long been touted and always look terrific *in vitro*, but they have yet to work out *in vivo*." On the other hand, a clinical investigation of Novartis's CDK4/6 inhibitor, LEE011, combined with BRAF inhibition is under way, based on encouraging PCT results that weren't seen in cell line studies.

The researchers will continue expanding the PDXE, and hope to eventually add difficult-to-establish models, such as glioblastoma and prostate cancer, to the collection. They're also exploring ways to address the limitations of PDXs, chiefly that the mice, being immunodeficient, can't be used to assess candidate immunotherapies.

"Every model system is imperfect in its own way," Sellers says. "We'll use the PDXE in ways best suited to its strengths. Take drug combinations, for instance—the number of permutations is well beyond what could be tested in humans. We think our system will prove very useful here; it should also help significantly with biomarker validation." *–Alissa Poh* ■

First Oncolytic Viral Therapy for Melanoma

The FDA has approved talimogene laherparepvec (Imlygic; Amgen) to treat surgically unresectable skin and lymph node lesions in patients with advanced melanoma. Also called T-VEC, this is the first oncolytic virus to gain regulatory endorsement.

T-VEC, a genetically modified herpes simplex virus type 1, is thought to have two distinct means of antitumor activity: Its selective replication in cancer cells causes them to rupture and die; meanwhile, it also releases the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF), which spurs the patient's own immune system into tumor-fighting mode. However, Amgen has stated that T-VEC's "exact mechanism of action is unknown and being further investigated."

T-VEC's approval was based on data from the multicenter phase III OPTiM study, in which 436 patients with surgically unresectable metastatic melanoma were randomized to receive injections of T-VEC directly into their lesions, or GM-CSF given subcutaneously (J Clin Oncol 2015;33:2780–8). Among patients in the T-VEC arm, 16.3% achieved durable responses—tumor shrinkage lasting at least 6 months—compared with 2.1% in the control group. The median overall survival with T-VEC was 23.3 months, versus 18.9 months with GM-CSF, which was not statistically significant, prompting the FDA and Amgen to emphasize that T-VEC "has not been shown to improve overall survival." The therapy also had no effect on melanoma that had spread to other internal organs.

T-VEC was well tolerated by patients, with the most common side effects being fatigue, chills, and fever. Given the live nature of this therapy, cold sores and other herpetic infections were also observed.

According to preliminary data from a small phase I study, T-VEC plus the immune checkpoint inhibitor ipilimumab (Yervoy; Bristol-Myers Squibb) may also show promise in melanoma: Half of the study's 19 patients responded, 22% completely. In addition, T-VEC is being evaluated alongside another checkpoint inhibitor, pembrolizumab (Keytruda; Merck), which blocks interactions between the ligand PD-L1 and its receptor, PD-1. A recent review noted that "as oncolytic viruses often induce interferon release in the local tumor microenvironment, and interferon is known to upregulate PD-L1 expression on tumor cells, this combination is especially interesting" (Nat Rev Drug Discov 2015;14:642–62).

Marc Ernstoff, MD, director of the melanoma program at Cleveland Clinic's Taussig Cancer Institute in Ohio, notes that T-VEC has only "modest single-agent activity," and "its place in the growing immunotherapy armamentarium is still unclear." He adds, though, that "its unique mechanism of immune stimulation and high therapeutic index provide significant opportunities for multiagent regimens that can further leverage the immune path to durable tumor destruction."

"It's worth noting that we had only three approved agents for melanoma in the 30 years before 2011," says John Kirkwood, MD, director of the melanoma skin and cancer program at the University of Pittsburgh, PA. T-VEC is the 10th new therapy approved for melanoma in the last 5 years, which the Melanoma Research Alliance has hailed as "a truly unprecedented rate of progress." *–Alissa Poh* ■

Innate Immune Cells May Prevent Metastasis

A specialized type of white blood cell that helps defend the body from infection also appears to control the spread of cancer. Researchers have found that these innate immune cells, called patrolling monocytes (PMo), slow tumor metastasis to the lung in multiple mouse models (Science 2015;350:985–90).

Most of the body's monocytes are the classic variety, which gobble up bacteria, viruses, and dying cells when recruited to sites of infection. Approximately 10% to 25% are PMo—active surveyors that can travel against blood flow to clear pathogens and other unwanted cells. In the context of cancer, the team discovered that PMo can "sense tumor cells, move toward them, help orchestrate their killing,