

# Translational tidbits

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## Tankyrase translation

With a few pharmas entering the search for tankyrase inhibitors for cancer, **Merck KGaA** is hedging its bets by joining forces with **The Institute of Cancer Research** and the **Wellcome Trust** to accelerate development of selective inhibitors of the enzymes.

The two tankyrases—tankyrase TRF1-interacting ankyrin-related ADP-ribose polymerase (TNKS) and TNKS2—are members of the poly(ADP-ribose) polymerase (PARP) family of enzymes that transfer ADP-ribose groups to a range of cellular proteins and are upregulated in a variety of cancers.

Last year, several groups identified selective compounds that inhibited tankyrases but not other PARPs, including teams at the **University of Oslo**, **Novartis AG's Novartis Institutes for BioMedical Research** and **Roche's Genentech Inc.** unit.<sup>1,2</sup> However, Genentech's program is no longer active, and the current development status of the University of Oslo and Novartis compounds was unavailable at press time.

Under the terms of the Merck KGaA deal, the pharma's Merck Serono unit and the team at the Institute of Cancer Research (ICR) will initially focus on translating existing leads from both groups into the clinic and identifying backup compounds. Merck Serono will make milestone payments to ICR and Wellcome—which originally funded the program at ICR—based on regulatory and sales goals, plus royalty payments on net sales of future products discovered or developed under the agreement.

The partners will combine their portfolios of tankyrase inhibitors, continue parallel screening efforts and work together on biomarker identification and animal studies.

The ICR team is led by Alan Ashworth, a professor of molecular biology at ICR, and Chris Lord, team leader and reader in cancer biology and therapeutics at ICR. The two have experience with small molecule inhibitors of PARP.

Andree Blaukat, head of translational innovation platform oncology at Merck Serono, told *SciBX* that both partners have confirmed the selectivity of their initial leads and that studies are under way to profile the therapeutic window of the compounds. “Our tankyrase inhibitors are also very selective, so they do not inhibit other PARPs at all,” he said.

Blaukat added that biomarker identification was also one of the key goals. “We will only move programs forward if we have biomarkers either preclinically validated or a very solid hypothesis for additional markers,” he said.

Although Merck declined to disclose funding details, Blaukat said that both Merck and ICR are contributing resources to the collaboration.

He added that each partner will contribute scientifically based on its particular strengths—for example, by performing animal models or biophysical analyses that are well established at the respective institutions.

## Case for Pluristem

**Pluristem Therapeutics Inc.** is wasting little time in advancing its second cell therapy product—PLX-RAD—toward the clinic. A week after the biotech said that it was ready to begin large-scale GMP manufacturing of PLX-RAD for a planned Phase I study in 2016, it announced a new research collaboration with **Case Western Reserve University** to test the cell therapy in preclinical models of human umbilical cord blood transplantation. Chairman and CEO Zami Aberman said that the company will begin GLP toxicology studies on PLX-RAD early next year.

The biotech's first cell therapy, PLX-PAD, is in Phase II or earlier testing to treat multiple cardiovascular, musculoskeletal and pulmonary disorders. Both PLX-RAD and PLX-PAD are composed of expanded populations of placenta-derived stromal cells, but the majority of cells in PLX-RAD are of fetal origin, whereas cells in PLX-PAD are mainly of maternal origin.

Under the collaboration, Pluristem will provide PLX-RAD to researchers at Case Western for preclinical studies to evaluate whether the cells can increase the speed of engraftment and the efficiency of new blood cell formation in mice receiving a human umbilical cord blood transplant. The partners will split research costs evenly.

Umbilical cord blood is an alternative to bone marrow for hematopoietic stem cell transplants and carries a lower risk for graft-versus-host disease (GvHD) than bone marrow. Cord blood transplants require less stringent matching but take longer to engraft. That lag leaves recipients highly vulnerable to infections for longer periods of time.

Earlier results from compassionate use cases suggested that PLX-PAD can restore the ability to produce hematopoietic cells and improve survival in patients who have failed a hematopoietic stem cell transplantation. However, Aberman said that the company decided to study PLX-RAD for this indication based on mouse data that showed it had a more pronounced benefit than Pluristem's first product.

A 2012 study from researchers at **Hadassah Medical Center** and Pluristem showed that in lethally irradiated mice, intramuscular injection of PLX-RAD resulted in a 98% survival rate versus 27% for vehicle or 67% for PLX cells of maternal origin that are similar to PLX-PAD.<sup>3</sup>

## Astellas takes AIM at Boston

After launching an external innovation strategy last year, **Astellas Pharma Inc.** is bringing the initiative stateside with two new Boston-based academic collaborations. The pharma is partnering with **Harvard Medical School** to find new treatments for ophthalmologic diseases and with **Dana-Farber Cancer Institute** to discover small molecule inhibitors of the *K-RAS* (*KRAS*) oncogene.

Under the terms of both deals, Astellas will fund the academic partners for up to three years and has the option for exclusive licenses from the respective institutions to develop any therapies obtained from the research collaborations. If Astellas exercises an option, it will develop and commercialize the compounds.

**Table 1. Selected public-private partnerships for October 2014.** Public-private partnership activity in October was buoyed by **Johnson & Johnson** (NYSE:JNJ) and **The ALS Association**, with each announcing a quartet of new collaborations or consortia. Notably, the GPCR Consortium was launched last month to bring together academic institutions in Asia and the U.S. with international biopharmas to define the structures of at least 200 GPCRs to aid drug development, and the Merck Serono unit of **Merck KGaA** (Xetra:MRK) partnered with **The Institute for Cancer Research** to advance anticancer inhibitors of tankyrase TRF1-interacting ankyrin-related ADP-ribose polymerase (TNKS) and TNKS2 that were independently discovered at the pharma unit and the institute.

Source: *BioCentury Archives; company websites*

Companies	Institutions	Business area	Disclosed value	Purpose
<b>General Electric Co.</b> (NYSE:GE)	The ALS Association; <b>ALS Finding a Cure Foundation</b>	Neurology	\$20 million	ALS Accelerated Therapeutics (ALS-ACT) partnership
<b>Xagenic Inc.</b>	<b>University of Toronto; Genome Canada</b>	Infectious disease	Up to \$12 million	Partnership for the development of low-cost chip and device for HCV testing
<b>Kineta Inc.</b>	<b>Oregon Health &amp; Science University; NIH; Vaccine &amp; Gene Therapy Institute of Florida; University of Washington</b>	Infectious disease	\$10 million	Partnership to develop new vaccine adjuvants that could boost the effectiveness of vaccines for infectious diseases
<b>Biogen Idec Inc.</b> (NASDAQ:BIIB); <b>Isis Pharmaceuticals Inc.</b> (NASDAQ:ISIS)	The ALS Association; <b>Cedars-Sinai; University of California, San Diego; Gladstone Institutes</b>	Neurology	\$5 million	Neuro Collaborative project to discover and develop potential new therapies for amyotrophic lateral sclerosis (ALS)
None	The ALS Association; <b>New York Genome Center; The Tow Foundation</b>	Neurology	\$5 million	New York Genome Center Consortium of Neurodegenerative Disease to employ big data approaches to identify causes of ALS
	<b>Children's Hospital of Philadelphia; Temple University; NIH</b>	Infectious disease	\$4.3 million	Partnership to investigate new methods to eradicate HIV that lurks in brain cells despite conventional antiviral treatments
	The ALS Association; <b>Emory University; The Netherlands ALS Center; University of Medical Center Utrecht; University of Massachusetts Medical School</b>	Neurology	\$1 million	Project MinE to understand the genetic basis of ALS
<b>Pluristem Therapeutics Inc.</b> (NASDAQ:PSTI; Tel Aviv:PSTI)	<b>Case Western Reserve University</b>	Hematology	Undisclosed	Partnership to do preclinical evaluation of Pluristem's PLX-RAD cells to improve hematopoietic stem cell transplant outcomes
<b>Amgen Inc.</b> (NASDAQ:AMGN); <b>Ono Pharmaceutical Co. Ltd.</b> (Tokyo:4528); <b>Sanofi</b> (Euronext:SAN; NYSE:SNY)	<b>ShanghaiTech University; Shanghai Institute of Materia Medica; University of Southern California</b>	Pharmaceuticals	Unavailable	GPCR Consortium to advance GPCR research for drug development
<b>Astellas Pharma Inc.</b> (Tokyo:4503)	<b>Harvard Medical School</b>	Ophthalmic disease	Unavailable	Partnership to discover pathologic mechanism for retinitis pigmentosa and identify new therapeutic targets
<b>AstraZeneca plc</b> (LSE:AZN; NYSE:AZN)	<b>University of Cambridge</b>	Neurology	Unavailable	Partnership to focus on advancing R&D in neurodegenerative diseases
<b>Bristol-Myers Squibb Co.</b> (NYSE:BMJ)	<b>The University of Texas MD Anderson Cancer Center</b>	Cancer	Unavailable	Partnership to evaluate Opdivo nivolumab, Yervoy ipilimumab and three undisclosed clinical stage immuno-oncology compounds separately and in combination
Johnson & Johnson	<b>China Pharmaceutical University</b>	Cancer	Unavailable	Partnership to investigate an antibody-drug conjugate to treat solid tumors
	<b>James Cook University</b>	Autoimmune disease	Unavailable	Partnership to study proteins produced by hookworms to treat inflammatory bowel disease (IBD)
	<b>Peking University</b>	Neurology	Unavailable	Partnership to identify agonists and antagonists for GPCRs to treat CNS diseases
	<b>Zhejiang University</b>	Endocrine/metabolic disease	Unavailable	Partnership to investigate the role of human lactate receptor, G protein-coupled receptor 81 (GPR81), in metabolic diseases such as dyslipidemia, obesity and diabetes
<b>Merck KGaA</b>	The Institute for Cancer Research; <b>Wellcome Trust</b>	Cancer	Unavailable	Partnership to identify inhibitors of TNKS and TNKS2 to treat various cancers

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**Table 1. Selected public-private partnerships for October 2014.** (continued)

Companies	Institutions	Business area	Disclosed value	Purpose
Proximagen Group plc (LSE:PRX)	MRC Technology	Autoimmune disease; inflammation	Unavailable	Partnership to progress small molecules targeting macrophage migration inhibitory factor (MIF) for the treatment of inflammatory and autoimmune disease
Regeneron Pharmaceuticals Inc. (NASDAQ:REGN)	Columbia University Medical Center; Clinic for Special Children; Baylor College of Medicine	Functional genomics	Unavailable	Partnership to study various inherited genetic diseases
Ubiquigent Ltd.	University of Dundee	Pharmaceuticals	Unavailable	Partnership to design, develop and market libraries of small molecules targeting ubiquitin system proteins

The collaboration with Harvard Medical School will be led by Constance Cepko, a professor of genetics and ophthalmology at Harvard, and will focus on identifying and validating gene therapies to prolong vision in individuals with retinitis pigmentosa—an inherited retinal degenerative disease characterized by loss of peripheral, night and color vision that leads to complete blindness. The partners hope that any resulting therapies might also be effective in other ocular diseases such as age-related macular degeneration (AMD) or glaucoma.

The collaboration with Dana-Farber will be led by Nathanael Gray, a professor of biological chemistry and molecular pharmacology at Harvard Medical School. Gray's group previously identified a K-RAS inhibitor that covalently binds the enzyme's catalytic site and confirmed the interaction with crystal structure studies.<sup>4</sup>

The partnership will support optimization of the compound and additional screening for druggable leads.

Kenji Yasukawa, SVP and chief strategy officer at Astellas, told *SciBX* that both of these partnerships are being managed by the Astellas Innovation Management (AIM) unit, which was established last year as part of a reshaping initiative. He said that the pharma is looking for new opportunities in drug discovery through external innovations.

"AIM is interested in platform technologies and new molecular entities in preclinical stages in the areas of oncology, emerging biology and therapeutic areas where unmet medical need exists," said Yasukawa. "AIM is looking to flexibly collaborate with various partners such as startup biotech companies, academia and venture capital groups around the world."

### Gain of function, loss of time

After recent revelations about biosafety incidents in U.S. government-run labs and criticism of the White House's handling of the Ebola response in the U.S., the Office of Science and Technology Policy announced in October a funding pause for new gain-of-function studies. The office also requested a voluntary freeze at labs with other funding sources.

Gain-of-function experiments confer new attributes to existing organisms and have been used to study how dangerous mutations affect the function of known pathogens. But safety concerns have led some researchers to question whether the risks inherent in this type of study outweigh the benefits.

Over the next year, the NIH's National Science Advisory Board for Biosecurity (NSABB) and the National Research Council of the National Academies (NRC) will work in tandem to generate a new policy

framework covering gain-of-function studies on influenza, Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) viruses.

The policy will fill a gap left in rules issued in September covering dual-use research of concern, which is research conducted for legitimate purposes that could be misapplied for harmful uses that pose a significant threat to public health and safety. The NSABB will review the risks and potential benefits of this type of research and draft a set of recommendations, and it is considering widening the funding pause to other pathogens.

NIH spokesperson Renate Myles told *SciBX* that the pause will affect 1 planned intramural project, 7 contracts and 10 grants on enhanced pathogenicity or respiratory transmissibility in mammals.

"The pause is a responsible step to take while the period of deliberation is under way," said Andrew Hebbeler, assistant director for biological and chemical threats at the Office of Science and Technology Policy. "The deliberative process will enable the life sciences community to assess the risks and benefits of gain-of-function studies and will result in the adoption of a U.S. government policy to guide future federal investments in this area of research."

Once the NSABB creates a set of draft recommendations governing approval and conduct of gain-of-function experiments, the NRC will hold a conference to review the recommendations with the scientific community. Final recommendations should be complete within 6 months, and the new policy is expected before the end of 2015.

### Public-private partnership round-up

The quartet of new research alliances seeded with funds from the amyotrophic lateral sclerosis (ALS) ice bucket challenge<sup>5</sup> and a stream of new R&D collaborations announced by multiple pharmas and large biotechs drove the bulk of public-private partnership activity in October (see Table 1, "Selected public-private partnerships for October 2014").

**Johnson & Johnson's** J&J Innovation unit coupled the official opening of its Asia Pacific Innovation Center in Shanghai with the announcement of four new collaborations between various subsidiaries of the pharma and research institutes in the region, the extension of an ongoing collaboration and a new partnering office at **Suzhou Industrial Park Biotech Development Co. Ltd.**, a life sciences incubator.<sup>6</sup>

Also in October, the GPCR Consortium was launched with the goal of defining the structures of at least 200 of the 826 known human GPCRs to aid drug development. The initial disease areas of focus are diabetes, cancer and mental disorders. Research outputs of the not-for-profit

consortium, such as 3D structures of GPCRs, will be compiled and released into the public domain.

Planned research under the consortium will be carried out at various academic centers including the iHuman Institute at **ShanghaiTech University, Shanghai Institute of Materia Medica** and the **University of Southern California**. The consortium was started by Raymond Stevens, a professor of molecular biology and chemistry at **The Scripps Research Institute** and founding director of the iHuman Institute.

The consortium's founding industry members are **Amgen Inc.**, **Ono Pharmaceutical Co. Ltd.** and **Sanofi**. It aims to recruit up to five additional industry members.

In addition, the Regeneron Genetics Center unit of **Regeneron Pharmaceuticals Inc.** announced research collaborations in October with **Columbia University Medical Center**, the **Clinic for Special Children** and the **Baylor College of Medicine** to study inherited genetic diseases.

The Columbia collaboration will focus on cardiometabolic diseases, familial cancer predisposition and rare genetic diseases; the Clinic for Special Children collaboration will study early onset and familial forms of pediatric disorders in Amish and Mennonite populations; and the Baylor collaboration will study the function of Mendelian disease genes discovered at the college.

Regeneron opened its Regeneron Genetics Center unit in January to enhance the biotech's in-house commitments to genomics-guided drug discovery.<sup>7</sup> The center is tasked with analyzing the genomes of at least 100,000 **Geisinger Health System** patients over the next 5 years.

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#### COMPANIES AND INSTITUTIONS MENTIONED

**Amgen Inc.** (NASDAQ:AMGN), Thousand Oaks, Calif.  
**Astellas Pharma Inc.** (Tokyo:4503), Tokyo, Japan  
**Baylor College of Medicine**, Houston, Texas  
**Case Western Reserve University**, Cleveland, Ohio  
**Clinic for Special Children**, Strasburg, Pa.  
**Columbia University Medical Center**, New York, N.Y.  
**Dana-Farber Cancer Institute**, Boston, Mass.  
**Geisinger Health System**, Danville, Pa.  
**Genentech Inc.**, South San Francisco, Calif.  
**Hadassah Medical Center**, Jerusalem, Israel  
**Harvard Medical School**, Boston, Mass.  
**The Institute of Cancer Research**, Sutton, U.K.  
**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.  
**Merck KGaA** (Xetra:MRK), Darmstadt, Germany  
**National Institutes of Health**, Bethesda, Md.  
**Novartis AG** (NYSE:NVS; SIX:NOVN), Basel, Switzerland  
**Novartis Institutes for BioMedical Research**, Cambridge, Mass.  
**Ono Pharmaceutical Co. Ltd.** (Tokyo:4528), Osaka, Japan  
**Pluristem Therapeutics Inc.** (NASDAQ:PSTI; Tel Aviv:PSTI), Haifa, Israel  
**Regeneron Pharmaceuticals Inc.** (NASDAQ:REGN), Tarrytown, N.Y.  
**Roche** (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland  
**Sanofi** (Euronext:SAN; NYSE:SNY), Paris, France  
**The Scripps Research Institute**, La Jolla, Calif.  
**Shanghai Institute of Materia Medica**, Shanghai, China  
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