Translational tidbits

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RNA sequencing standardized

The FDA has convened a consortium to review the status of RNA sequencing for drug development and outline hurdles for incorporating the technology into the standard pharmacogenomics toolbox.¹⁻⁴ The consortium concluded that although RNA sequencing still cannot give reliable absolute measurements of RNA, the data collected provide a baseline for assessing the value of new developments and can help drive the creation of regulatory standards and guidelines for use of RNA sequencing.

In 2005, the agency released its first guidance for pharmacogenomic data submissions, which provided a framework for evaluating protocols and data submitted with IND, NDA or BLA applications. In 2007, the FDA published a companion guidance detailing requirements for submission of differential gene expression data.

Since then, transcriptome profiling technologies have evolved substantially, and deep RNA sequencing (RNA-seq) has emerged as an alternative to the two established technologies for differential gene expression analysis—quantitative PCR (qPCR) and microarrays—owing to its increased detection sensitivity and its large dynamic range.

The Sequencing Quality Control (SEQC)/MicroArray Quality Control III (MAQC-III) consortium, organized under the auspices of the FDA, comprised academic and industry representatives and performed a multisite and cross-platform analysis of RNA-seq measurements under tightly controlled conditions. SEQC followed two similar community efforts previously undertaken by the same consortium—MAQC-I and MAQC-II—that were designed to standardize analysis protocols for microarray platforms.^{5,6}

Three leading high throughput sequencing platforms—Illumina Inc.'s HiSeq, Life Technologies Corp.'s SOLiD and Roche's 454—were used to analyze reference RNA samples with built-in controls for accuracy, reproducibility and information content in transcriptome profiling. Data were compared with standard qPCR and microarray platforms.

The main conclusion was that measurements of relative expression can be accurately and reproducibly performed across sites and platforms. However, RNA-seq exhibits varying degrees of gene-specific bias and does not provide reliable absolute measurements of RNA levels, which was also a limitation of microarrays and qPCR.

However, the SEQC data set contains more than 100 billion reads (10 terabases) and thus provides a unique resource as a baseline assessment for evaluating the strengths and shortcomings of RNA-seq analyses in clinical and regulatory settings.

According to Weida Tong, director of the Division of Bioinformatics and Biostatistics at the FDA's National Center for Toxicological Research and a coleader of the effort, it is the consortium's goal "to translate the lessons learned from SEQC to research, as well as to review activities at the FDA, which will include both drug review and diagnostic applications."

Tong told SciBX that at this point "the SEQC effort is more on the basic research side." But, he added, "there is a lot of similarity between SEQC and MAQC-I." He noted that "the major conclusions from MAQC-I were used for the FDA companion draft guidance to industry on pharmacogenomics data submission."

Serono partners in lupus

This month's partnership with Massachusetts General Hospital marks EMD Serono Inc.'s third lupus-focused collaboration in the past two years. The Merck KGaA subsidiary is tapping into its partners' patient samples for target discovery and biomarker analysis as it advances multiple lupus programs into the clinic.

Harsukh Parmar, SVP of immunology and neurology at the EMD Serono Research Institute, told SciBX, "Systemic lupus erythematosus [SLE] and lupus nephritis [LN] have key but complex challenges from a disease perspective, and biomarkers are needed that can define patient populations and measure response."

The goal of the MGH partnership is to use tissue samples from patients with lupus to identify candidate therapeutic targets, pathogenic immune cell types and biomarkers. Activities will include compound testing and gene expression analysis, as well as generating data to support Serono's clinical-stage LN programs.

Harsukh said that MGH's clinical expertise with lupus is key to the collaboration. "MGH has regular access to fresh tissue samples from patients with disease," he said. He also noted that the deal naturally complements Serono's recently announced partnership with the Broad Institute of MIT and Harvard.

In May, Serono and Pfizer Inc. partnered with the Broad Institute to perform genomic profiling of patients with SLE or LN. "This is an exploratory project and involves detailed phenotyping and genotyping using deep sequencing to biomarkers, including a longitudinal study of responses in patients with active disease and in remission," said Harsukh. "The study is the first of its kind."

The pharma will have real-time access to data and analysis as part of the collaboration.

In addition to its two partnerships this year, last January Serono entered into a collaboration with The Feinstein Institute for Medical Research to develop antibodies against an undisclosed lupus target. Harsukh said that in contrast to the MGH and Broad Institute partnerships, the Feinstein collaboration is target specific.

Financial terms and timelines for the collaborations were not disclosed.

The only targeted therapy marketed for SLE is GlaxoSmithKline plc's anti-BLyS (BAFF) mAb Benlysta belimumab. There are no targeted therapies marketed for LN.

Serono has one disclosed therapeutic in Phase II testing to treat SLE, atacicept, a soluble fusion protein containing the extracellular portion of transmembrane activator and CAML interactor (TACI). TACI binds

Table 1. Selected public-private partnerships for August 2014. Public-private partnership activity was sparse in August. Most notable was U.K. Prime Minister David Cameron's Aug. 1 announcement of over £300 million (\$509.4 million) in new investments with **Genomics England Ltd.** to support the national goal to sequence and analyze the genomes of 100,000 **NHS England** patients by 2017. Partner **Illumina Inc.** (NASDAQ:ILMN) made the largest investment in Genomics England, totaling about £162 million (\$275.1 million). Last month, **Pfizer Inc.** (NYSE:PFE) partnered with the **Crohn's & Colitis Foundation of America** under its Centers for Therapeutic Innovation initiative to discover new small molecules to treat Crohn's disease and ulcerative colitis. A joint committee will select four projects, and costs will be split evenly between the two parties.

Source: *BioCentury Archives*

Companies	Institutions	Business area	Disclosed value	Purpose
Illumina; Genomics England	Medical Research Council; NHS England; Wellcome Trust	Genomics	Over £300 million (\$509.4 million)	Analyze genomes of over 100,000 NHS England patients
Artes Biotechnology GmbH	Burnet Institute; PATH	Infectious disease	Undisclosed	Develop vaccines to prevent transmission of malaria infection from mosquitos to humans
Astellas Pharma Inc. (Tokyo:4503)	Cancer Research UK	Cancer	Undisclosed	Identify and validate targets to block the autophagy pathway in pancreatic cancer cells
CN Bio Innovations Ltd.	Imperial College London	Infectious disease	Unavailable	Develop <i>in vitro</i> models of HBV liver infection based on CN Bio's LiverChip platform
Huya Bioscience International LLC	Changzhou Centre for Biotech Development	Pharmaceuticals	Unavailable	Evaluate R&D projects supported by the Changzhou Centre for Biotech Development
Pfizer	Crohn's & Colitis Foundation of America	Autoimmune disease	Undisclosed	Discover small molecules to treat Crohn's disease and ulcerative colitis

tumor necrosis factor (TNF) family members including BlyS. Harsukh said that two additional lupus programs are in Phase I testing. More than 20 companies have targeted therapeutics for lupus in Phase I to Phase III trials.

Boosting U.K. genomics

Last month, U.K. Prime Minister David Cameron announced a series of new investments involving **Genomics England Ltd.** valued at over £300 million (\$509.4 million). The **U.K. Department of Health** established the company last year to lead the 100,000 Genomes Project that Cameron announced in late 2012.

The national project aims to sequence and analyze the genomes of 100,000 **NHS England** patients by 2017, with a focus on cancer and rare diseases. The project's four key aims are to bring benefit to patients, create an ethical and transparent program based on consent, enable new scientific discovery and medical insights, and kick-start the U.K. genomics industry.

The largest of the new round of investments comes from Illumina, which is investing about £162 million (\$275.1 million) over 4 years to help Genomics England develop the U.K.'s genomics industry. Genomics England also will pay for Illumina's sequencing services in a deal valued at about £78 million (\$132.4 million).

Illumina disclosed on July 9 that Genomics England selected its Illumina Cambridge Ltd. subsidiary as the preferred partner for the sequencing tasks of the 100,000 Genomes Project. The parties had previously partnered under the project in 2013 to sequence 10,000 genomes of children and adults with rare diseases.

The new investments also include the **Wellcome Trust's** plans to spend £27 million (\$45.8 million) for a sequencing hub that will house Genomics England's activities. The hub will be located at Wellcome Trust's genome campus near Cambridge.

Also included are the **Medical Research Council's** earmarking of £24 million (\$40.7 million) to provide computational resources to store, analyze and interpret sequencing data generated under the project and the NHS's plans to spend up to £20 million (\$34 million) to establish patient sequencing centers.

The new investments come on top of the £100 million (\$152.2 million) the U.K. government allocated to the 100,000 Genomes Project in December 2012.

Public-private partnership roundup

Outside the U.K., August was a quiet month for public-private partnerships (see **Table 1, "Selected public-private partnerships for August 2014"**).

Notably, Pfizer doubled down on the inflammatory bowel disease (IBD) space in August via its public-private partnership with the not-for-profit **Crohn's & Colitis Foundation of America (CCFA)**. The two partnered under the pharma's Centers for Therapeutic Innovation (CTI) initiative to discover small molecules for Crohn's disease and ulcerative colitis (UC).

A joint committee comprised of CTI and CCFA members will select up to 4 small molecule projects that the 2 parties will co-fund on a 50/50 basis for 2 years. The projects will be sourced from investigators at institutions that have signed a CTI small molecule participation agreement. Total funding amounts are undisclosed. The partnership is CCFA's first joint funding partnership with a pharma.

Pfizer launched its CTI initiative in 2010 to partner with academic medical centers. According to CTI's website, Pfizer typically takes joint ownership of IP rights in CTI-backed projects and provides milestone payments and royalties for successful programs.

Pfizer announced a partnership with **23andMe Inc.** earlier in the month to explore the genetic factors associated with the onset, progression, severity and response to IBD. The pharma plans to use the genetic information generated under the collaboration to help identify patients who are more likely to respond to treatments.

Pfizer has Xeljanz tasocitinib in Phase III testing for UC and in Phase II testing for Crohn's disease. The oral small molecule pan-Janus kinase (JAK) inhibitor is marketed to treat rheumatoid arthritis (RA).

The pharma also has the anti-human mucosal vascular addressin cell adhesion molecule 1 (MADCAM-1) mAb PF-00547659 in Phase II testing to treat UC and Crohn's disease, the human anti-IL-6 mAb PF-04236921 in Phase II trials to treat Crohn's disease and lupus, and

the multipotent adult progenitor cell therapy PF-05285401 in Phase II testing to treat UC.

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REFERENCES

1. SEQC/MAQC-III Consortium. *Nat. Biotechnol.* **32**, 903–914 (2014)
2. Li, S. *et al.* *Nat. Biotechnol.* **32**, 888–895 (2014)
3. Wang, C. *et al.* *Nat. Biotechnol.* **32**, 926–932 (2014)
4. Yu, Y. *et al.* *Nat. Commun.* **5**, 3230 (2014)
5. MAQC Consortium. *Nat. Biotechnol.* **24**, 1151–1161 (2006)
6. MAQC Consortium. *Nat. Biotechnol.* **28**, 827–838 (2010)

COMPANIES AND INSTITUTIONS MENTIONED

23andMe Inc., Mountain View, Calif.
Broad Institute of MIT and Harvard, Cambridge, Mass.

Crohn's & Colitis Foundation of America, New York, N.Y.
The Feinstein Institute for Medical Research, Silver Spring, Md.
Food and Drug Administration, Silver Spring, Md.
Genomics England Ltd., London, U.K.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Illumina Inc. (NASDAQ:ILMN), San Diego, Calif.
Life Technologies Corp., Carlsbad, Calif.
Massachusetts General Hospital, Boston, Mass.
Medical Research Council, London, U.K.
Merck KGaA (Xetra:MRK), Darmstadt, Germany
National Center for Toxicological Research, Jefferson, Ark.
NHS England, Redditch, U.K.
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
U.K. Department of Health, London, U.K.
Wellcome Trust, London, U.K.