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Roche Molecular Systems Research Team Uses 454 Sequencing System for High-Resolution HLA Genotyping

A study published this month in the journal *Tissue Antigens* reports that researchers at Roche Molecular Systems (SIX: RO, ROG; OTCQX: RHHBY) in Pleasanton, CA have used high-throughput sequencing technology from 454 Life Sciences, a Roche Company, to carry out high-resolution human leukocyte antigen (HLA) genotyping in research samples. In the study, the researchers performed ultra-deep amplicon sequencing of specific HLA class I and II gene loci with the Genome Sequencer FLX System and successfully assigned allele-level genotypes using software developed by Conexio Genomics. The results of the study have important implications for future research on a wide variety of human diseases and tissue transplantation.

HLA class I and class II genes play a critical role in the adaptive immune response. Importantly, they encode for the cell-surface proteins responsible for differentiating between self, non-self cells and other antigens. For example, accurate HLA genotyping is clinically important for hematopoietic stem cell (HSC) transplantation between unrelated donors and recipients to minimize the risk of graft rejection and graft versus host disease (GVHD). Accurate HLA genotyping is also critically important for research on many human diseases. "Specific alleles and haplotypes at the class I and class II loci are strongly associated with a variety of autoimmune disease as well as some cancers and infectious diseases," explained Henry Erlich study author and Director of the Department of Human Genetics at Roche Molecular Systems. "High resolution, high throughput HLA typing will be very valuable in these large research association studies."

Accurate HLA genotyping is complicated by the highly polymorphic nature of this genomic region. There are hundreds of different allele sequences at the various HLA class I and class II genes. Current methods, based on Sanger-sequencing technology, are limited in their ability to resolve "phase ambiguities" which occurs commonly when an individual is heterozygous at many positions that are very close to one another.

“The challenge is to determine which polymorphic sequences go together on which alleles,” explained Erlich. “In our research, we were able to successfully assign allele-level HLA genotypes at eight loci in 48 individual samples from the data produced in a single Genome Sequencer FLX System run. The abundance of long sequencing reads allowed us to unambiguously assign HLA alleles in a much faster and more cost efficient manner than with traditional technologies. We were also able to detect rare variants, such as the non-transmitted maternal allele in a SCIDS [Severe Combined Immunodeficiency Syndrome] sample, reflecting the presence of maternal cells in the subject’s circulation.”

This month, 454 Life Sciences will launch the latest GS FLX Titanium kits and software, offering increases in read length and throughput for amplicon sequencing. The new kits will improve targeting resequencing studies, such as HLA class I and II genotyping, by more completely covering loci with fewer amplicons and enhancing sensitivity for identifying rare variants and haplotypes. “Our early work with the GS FLX Titanium amplicon sequencing kits have demonstrated that we can now type more individuals per run and more exons per amplification reaction,” says Erlich.

“As proven by this study, 454 Sequencing Systems provides a cost-effective and reliable alternative to current research methods for HLA typing,” said Christopher McLeod, President and CEO of 454 Life Sciences. “This will only improve with the longer read lengths available in our latest series of GS FLX Titanium kits and software.”

For more information on 454 Sequencing Systems, visit www.454.com.

About Roche

Headquartered in Basel, Switzerland, Roche is one of the world’s leading research-focused healthcare groups in the fields of pharmaceuticals and diagnostics. As the world’s biggest biotech company and an innovator of products and services for the early detection, prevention, diagnosis and treatment of diseases, the Group contributes on a broad range of fronts to improving people’s health and quality of life. Roche is the world leader in in-vitro diagnostics and drugs for cancer and transplantation, and is a market leader in virology. It is also active in other major therapeutic areas such as autoimmune diseases, inflammatory and metabolic disorders and diseases of the central nervous system. In 2008 sales by the Pharmaceuticals Division totalled 36.0 billion Swiss francs, and the Diagnostics Division posted sales of 9.7 billion francs. Roche has R&D agreements and strategic alliances with numerous

partners, including majority ownership interests in Genentech and Chugai, and invested nearly 9 billion Swiss francs in R&D in 2008. Worldwide, the Group employs about 80,000 people. Additional information is available on the Internet at www.roche.com.

Bentley et al. High-resolution, high-throughput HLA genotyping by next-generation sequencing. (2009) Tissue Antigens.

The 454 GS FLX System is sold for life science research use only.

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For further information please contact:

Roche Diagnostics

Dr. Burkhard Ziebolz

Phone: +49 8856 604830

Email: burkhard.ziebolz@roche.com

454 Life Sciences Corporation, a Roche company

Dr. Ulrich Schwoerer

Phone: 203-871-2300

Email: ulrich.schwoerer@roche.com