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### **New High-Throughput Genotyping Center**

#### **Pharmacogenomics and Complex Disease Research**

#### **New Center for Pharmacogenomics and Complex Disease Research Incorporates Applied Biosystems Integrated Solutions for High-Throughput SNP Genotyping**

When genetic disease investigator Dr. Scott Diehl had the opportunity to set up a large-scale genotyping center to meet the challenge of understanding complex disease genetics in the 21st century, he turned to an old ally, Applied Biosystems.

Dr. Scott Diehl, Director of the new Center for Pharmacogenomics and Complex Disease Research (CPCDR) at the New Jersey Dental School, within the University of Medicine & Dentistry of New Jersey (UMDNJ).

Dr. Scott Diehl's high-throughput genotyping laboratory is an example of iScience in action. Through its Integrated Laboratory Services ([ILS](#)) and informatics services, [Applied Biosystems](#) helped to design the laboratory and workflows using a variety of state-of-the-art genotyping systems that are integrated with a customized LIMS system. Dr. Diehl used Applied Biosystems ILS, which provides contract

Based on his positive experiences using evolving Applied Biosystems technology for more than a decade, and being particularly impressed by recent SNP-genotyping work the company's professional services had done for him in its Foster City service lab, Dr. Diehl believed that Applied Biosystems could provide the best solution for smoothly integrating the multiple platforms, software, chemistries, and databases required to carry out high-throughput SNP-based genotyping for elucidating the genetics of complex diseases.

Now, after over a year of intense planning and extensive interactions amongst numerous experts from different disciplines at Applied Biosystems, working together with key staff of his own laboratory group, Dr. Diehl believes that he has made the correct decision and that his new Center is being superbly outfitted to embark on an effort that will yield important insights into an area of study that has previously proven very difficult to crack; i.e., complex diseases.

#### **The Center for Pharmacogenomics and Complex Disease Research**

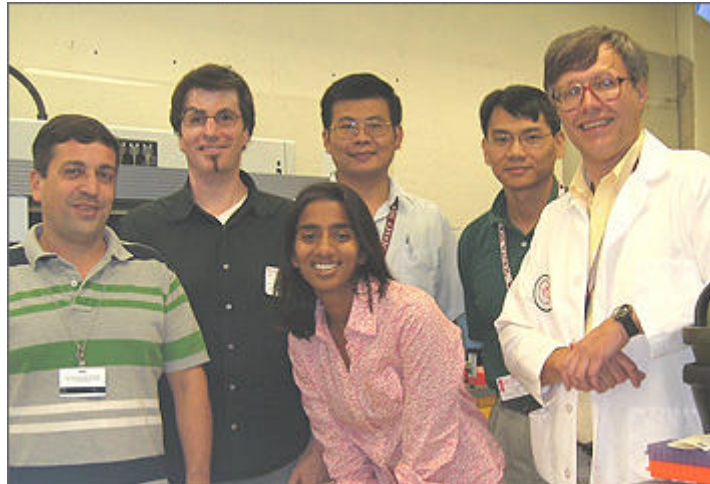
[Dr. Diehl](#) is the Director of the new Center for Pharmacogenomics and Complex Disease Research ([CPCDR](#)) at the New Jersey Dental School, within the University of Medicine & Dentistry of New Jersey (UMDNJ). He moved to this position about two years ago after previously serving as Chief of the Molecular Epidemiology and Disease Indicators Branch of the

research services, to keep his projects NIH's National Institute of Dental and Craniofacial Research.

moving forward until the laboratory was

up and running.

Dr. Diehl's research has, for many years, focused on trying to understand the genetic basis of oral cancer, nasopharyngeal carcinoma, and periodontitis (both juvenile and adult); diseases that are believed to have complex etiologies involving both environmental and genetic factors. He will be continuing his work on these diseases at the new Center as it comes online.



In Dr. Diehl's laboratory from left to right are: Bill Iannuccilli, Lewis Wogan (of Applied Biosystems), Baq Haidri (of Applied Biosystems), Austin Huang, David Kuo, and Scott.

The Center will also serve a much broader purpose of advancing this scientific approach among collaborators throughout the University and at other academic and private sector institutions, including perhaps some of the many large pharmaceutical companies headquartered in the New Jersey area. According to Dr. Diehl, the CPCDR's mission is to provide opportunities to all of these groups for developing genetic research projects focused on inherited human genetic variation.

*"Our strategy is to spark collaborative interest in SNP-based approaches to complex diseases and to pharmacogenomics. We think of complex disease studies as being aimed at understanding etiologies related to inherited variation in susceptibility; multigenic susceptibility; and gene-environment interactions as the causes of these disorders. Pharmacogenomics studies, on the other hand, are targeted at inherited genetic variation and how this affects responses to therapies, drug therapies primarily, but potentially other kinds of therapies as well."*

#### **Applied Biosystems SNPlex? Genotyping System Key to Center's Lab Setup**

Dr. Diehl chose to outfit his new laboratory facility (three labs occupying approximately 1,500 square feet) with the key elements of Applied Biosystems' new [SNPlex? Genotyping System](#), organized and integrated through a meticulously-designed, Applied Biosystems customized laboratory information management system (LIMS) to work smoothly in his particular workflows and with his existing TecanR robotic liquid handling systems, and to also

accommodate archival genetic data from different platforms.

The Center's laboratories include eight [GeneAmpR PCR System 9700](#) thermal cyclers (for DNA sample preparation), an [ABI PRISMR 3730 DNA Analyzer](#) (for SNP and microsatellite genotyping and sequencing), [GeneMapperR Software](#) (for allele calling), [SNPbrowser? Software](#) (for viewing multiple SNP sources in one centralized location and selecting SNPs for association studies; assays for these SNPs can be ordered online from Applied Biosystems), and [BioTrekker? Software](#) (a program that allows the user to search for and retrieve millions of genotypes and to quickly produce files suitable for statistical analysis).

The Center also has access to an [Applied Biosystems ABI PRISMR 7900HT Sequence Detection System](#) for quantitative nucleic acid determination and for SNP genotyping using [TaqManR SNP Genotyping Assays](#) or [Custom TaqManR SNP Genotyping Assays](#). High-throughput liquid handling will be done by Tecan robots integrated with the lab's LIMS.

### **Validated SNPs and Validated SNP Assays an Enormous Asset**

SNPs of interest can be identified through the [SNPbrowser? Software](#), and then assays for those SNPs can be ordered from Applied Biosystems via a convenient online ordering mechanism. The researcher can order ready-to-use [TaqManR SNP Genotyping Assays](#) for the entire Applied Biosystems library of almost two million SNPs or design custom multiplex assays for the [SNPlex? Genotyping System](#).

Dr. Diehl emphasized the tremendous enabling effect that the availability of validated SNPs and validated SNP-genotyping assays has on genotyping studies.

*"I think it's obvious to many, but maybe not to all, that just having those thousands of gene-based [TaqManR SNP Genotyping Assays](#) that are already tested and ready to go is a tremendous savings of effort versus trying to just go into the databases to pick a gene of interest and then stare at the dozens, sometimes hundreds, of SNPs that are in the dbSNP-type databases and not know which of these are good SNPs, whether the SNP assays one designs are really going to work, or what the SNPs' allele frequencies are.*

*"So that's definitely a major asset to have that information available up front; to be assured that, when you choose a SNP, you know it's going to work and you know it's going to be polymorphic, in most populations."*

*"In my experience, now approaching one million genotypes, I've nearly always found that the [TaqManR SNP Genotyping Assays](#) have worked great!"*

### **Flexible Software for Creating Centralized Genotype Table**

Dr. Diehl noted the great importance of being able to have a centralized genotype table that is genotyping-platform-independent. *"You don't want to have 15 different tables where you're storing genotyping information on people from the same human project; so we need a*

*genotype-central database."*

He is looking forward to using the new [BioTrekker? Software](#) from Applied Biosystems to do this and has been working with Applied Biosystems software developers to provide them with information on the needs he and other researchers would like to have fulfilled by flexible software that works just as well regardless of where the genotypes come from and can store them all *"happily together,"* as Dr. Diehl put it.

### **Top-Flight LIMS System Is Crucial**

Finally, and perhaps most importantly, the Center has worked with the Applied Biosystems Informatics Software and Services (ISS) to deliver an integrated Informatics solution built on the Applied Biosystems Life Sciences [LIMS software](#) to meet the specific needs of the CPCDR. This tailored LIMS solution will allow all the elements of the Center's genotyping workflows to talk to each other and will support the collection of data from different sources.

Dr. Diehl emphasized the critical importance of this LIMS system. *"It is essential,"* he said. *"We just can't turn on these powerful genotyping machines without a really strong and robust information management system, otherwise we'll be drowning in data and really not be able to make any sense of it."*

### **New Center Will Generate Over 100,000 Genotypes Per Day**

Dr. Diehl anticipates that, using the newly implemented integrated technology from Applied Biosystems, his Center will soon be generating over 100,000 SNP genotypes per day<sub>i</sub> and this will allow the types of powerful association studies necessary to unravel the complex etiologies of complex diseases. The CPCDR hardware and software systems have been designed for easy expansion to provide over twice this throughput when the Center's growth requires this in the future.

### **Confronting the Challenge of Complex Diseases**

Dr. Diehl described the challenge of trying to solve the puzzle of complex diseases and indicated how the Applied Biosystems integrated technology will help his Center meet that challenge.

*"We have large numbers of candidate genes for these complex diseases. In periodontal disease, for instance, there is clearly an immune-response component and there is also an inflammation component, and when one looks at the human genome and looks at the candidate genes that one might come up with for that kind of a broad biological problem, the list is hundreds of genes long."*

*"And we need to look beyond even just these primary disease processes. In a disease like periodontitis, we know that there are rare syndromes that have mutations in collagen genes, for example (structural genes that control the integrity of the tissue), where there are single major gene mutations that cause a number of clinical problems including periodontal disease."*

*So, when we put together all aspects of the known processes of disease pathogenesis, we end up with a huge number of candidate genes, not quite the whole genome, but over 1,000 genes we're very interested in.*

*"We have to face this complexity-we can't just put on blinders that simplify the problem, and say, 'Some data implicate interleukin-1 (IL-1) so let's only look there.' Einstein said it best: 'Make everything as simple as possible, but not simpler.'"*

*"I think our ability to rule out candidate genes is very limited. If we're honest and modest about our understanding of the biological processes, we just have to be able to test a large number of these genes."*

### **SNPlex Genotyping System Provides Necessary Power and Efficiency**

*"It's my view that in order to really get to the bottom of this, we're going to have to test a large number of genes in large populations; because in order to have the power to be able to test multiple genes, we need far more than the typical sample sizes that one still sees in the literature often today; 20 cases, 20 controls is just not nearly enough power; so we have to have large numbers of samples; at least hundreds, if not thousands, of cases and controls and we also have to test large numbers of candidate genes, as well as multiple SNPs within each gene.*

*"So it's a big challenge and that's where we need the high-throughput and relatively low-cost assays because that's the other limiting factor. If you have a system that can do 100,000 genotypes a day, but it's a dollar a genotype, well, we're going to be out of money in a couple of days and that's the end of our work for the year. So we have to keep pushing the cost-per-assay down while we push the number of genotypes per day up."*

*"The Applied Biosystems [SNPlex? Genotyping System](#) looks especially promising in that regard," Dr. Diehl noted.*

### **Prior Experience with Applied Biosystems Played Key Role in Decision**

Dr. Diehl's long experience with Applied Biosystems technology over the course of over a decade of genetic disease research dates back to his work with Applied Biosystems staff in developing methods for fluorescent detection and analysis of microsatellite marker loci in the early 1990s (1). This was enhanced by his very positive recent experience working with the Applied Biosystems Integrated Laboratory Services (ILS) group to carry out SNP-based genotyping for some of his ongoing head and neck cancer studies. These experiences were key factors in Dr. Diehl's deciding to implement the Applied Biosystems integrated genotyping system at his new Center.

While still at the NIH, Dr. Diehl had contracted with Applied Biosystems to have the ILS group carry out SNP genotyping using the latest, state-of-the-art, developing technology available in

house at Applied Biosystems headquarters in Foster City, California

Under this agreement, the ILS group carried out assay development and validation for Dr. Diehl, for his oral cancer and nasopharyngeal carcinoma genotyping studies. The group then performed hundreds of thousands of [TaqManR SNP Genotyping Assays](#) for Dr. Diehl for these investigations.

*"My positive experience of having had hundreds of thousands of [TaqManR SNP Genotyping Assays](#) successfully performed in Foster City has led to my enthusiasm for bringing these techniques into my own lab,"* Dr. Diehl said. He was especially pleased with how well these assays worked even for DNA samples that had been partially degraded or were of very low concentration.

### **Applied Biosystems Experts Involved in Lab Planning from the Outset**

So when Dr. Diehl was ready to move ahead with planning for his new laboratory, Applied Biosystems was right there with him, providing experts from multiple areas/disciplines to make sure that the entire operation was organized optimally in every way possible, from the outset, so as to ensure smooth, productive, and efficient work flows when the Center goes into operation.

Representatives from the ILS group traveled to the CPCDR to look at the instruments Dr. Diehl already had and to make recommendations on the technology he would need. The ILS experts also analyzed the workflows and how to best organize the various instruments needed for the lab so as to achieve optimal efficiencies.

The Informatics Professional Services members also participated at the same time to make sure that it would be able to provide an integrated LIMS solution that will be capable of dealing with the full range of genotyping and DNA sequencing methods and platforms that his Center requires.

### **Work with Informatics Professional Services Inspires Confidence in Overall System**

Dr. Diehl described the extensive interactive effort that has underlain the development of the customized LIMS systems for his new Center and he highlighted how his experiences and close interactions with the Informatics Professional Services team have given him great confidence in the ultimate success of the effort.

*"I've been working with the Informatics Professional Services team from Applied Biosystems, initially writing up high-level summaries for each step in our workflows that we call Use Cases. These break down each workflow into all the different major steps.*

*"My staff and I have devoted several months working with the Informatics Professional Services team, both on site, and of course, with many phone call and email follow-ups. And we now have our finalized set of Use Cases. We will use these as our blueprints for building and*

*implementing the protocols and software needed for running the high-throughput lab. We are now moving to the next level and actually developing what are called design documents that describe every step of each process in full detail.*

*"These are complex laboratory processes and it has been impressive to me to see first-hand how the current implementation of the LIMS software will be able to handle these."*

### **Recent LIMS Training Session Adds to Confidence**

Just recently, Dr. Diehl and his staff went through a week of LIMS training (sort of a LIMS boot camp), and this left him with a little bit of information overload, but with an even stronger confidence in the ability of the system to meet his needs.

*"It's an impressive system, it really is," he said. "I was already confident that this could be done, but to see it first-hand is giving me confidence that it will be done in our Center soon."*

*"At times it's terrifying, I think, to look at the challenges we face to keep track of all this information, but I'm confident that the experience of the Informatics Professional Services team has put us in a position to meet these challenges successfully."*

### **Now Prepared to Meet the Challenges**

Thanks to the productive interaction of experts from multiple disciplines from Applied Biosystems working together with experts for multiple disciplines in Dr. Diehl's new Center, a state-of-the-art integrated system for high-throughput genotyping is being created. With this integrated system, Dr. Diehl is confident that his new Center is well prepared to tackle the daunting challenge of unraveling the mysteries of complex diseases.

### **References**

1. Ziegler, J., Su, Y., Corcoran, K.P., Nie, L., Mayrand, P.E., Hoff, L.B., McBride, L.J., Kronick, M.N., and Diehl, S. "Application of Automated DNA Sizing Technology for Genotyping Microsatellite Loci," *Genomics* **14(4)**: 1026-1031 (December 1992).

*By Mike O'Neill*