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Feature Article

Partnerships Strengthen Finland Biotech

Country's Network of Collaborators Is Far-Reaching and Ultimately Critical to Success

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Finland, particularly the Oulu region, is focused on developing the connections between the life sciences, nanotechnology, and information technology. Oulu Bioforum, Oulu Innovation, and other centers in Finland, supported by partners in the German cities of Halle and Leverkeusen, recently hosted "Bio Meets Nano and IT" to promote interdisciplinary and business collaboration between those involved in these three areas.

High-throughput approaches are a special interest in the Oulu region. Hans Söderlund, Ph.D., VTT Technical Research Center described the development of a high-throughput multiplexed system for analysis of transcriptional signatures that is based on advanced microfluidic technology.

"To measure total gene expression by conventional means is cumbersome and expensive," he said. There are gene chips that can measure 40,000 genes and, at the other extreme, those that look at just a few. "We are interested in the space between 10 and 300 genes, looking at a large number of samples with high throughput."

Transcript analysis with affinity capture (TRAC), a VTT technology, has been spun off to PlexPress TRAC involves exposure of RNA through cell lysis and then the addition of a capture probe that binds to streptavidin-coated magnetic beads. This way, data on 2,880 transcriptional levels (96 samples in a 30-plex experiment) is available in about four hours, Dr. Söderlund reported. Applications include cancer cells exposed to drug candidates, RNAi knockdown assays, and cell-cycle monitoring.

In a collaboration with the University of California, Berkeley, the company has transferred TRAC onto nanovolume chips for online analysis and is also trying to transfer the technology onto a printed format, reflecting VTT's interest in getting wet chemistry onto chips to make low-cost biosensors. "We could, therefore, go up to high-throughput transcriptional profiling," added Dr. Söderlund.

Olli-Pekka Kallioniemi, Ph.D., of the Institute for Molecular Medicine discussed the Institute's medical systems biology approach, with the development of a high-throughput siRNA screen of cancer cells in 384-well plates. Scientists at the Institute are miniaturizing this to a functional cellular microarray where they will print siRNA from 20x384 well plates to see how the cells respond to the siRNAs.

"We can do the entire genome of siRNAs on a single microtiter-sized plate," he said. The cells adhere to the spot and are transfected by the siRNA. The work has been applied to a prostate cancer cell line in a druggable genome screen. "This is pushing the limit of anything available today. We are now beginning to approach reasonable accuracy and reproducibility."

In a collaboration with the University of Turku the team is looking at what genes are necessary for integrin signaling when cells invade. Live cell imaging of activated integrin siRNA hits in P13 cells can reveal what happens in cell morphology when this gene is knocked down.

“We use this to identify critical determinants of cell movements,” Dr. Kallioniemi said. “There are still lots of challenges, including the printing requirements for 40,000 siRNAs per experiment and managing up to 40,000 high-resolution images per experiment.” A further application is to improve the efficiency of hormonal therapies in prostate cancer by looking at the siRNAs that have an effect in androgen-deficient conditions.

Lab-on-a-Chip

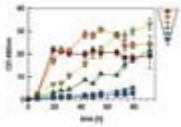
Oulu Innovation focuses on economic development in the high technology and high growth business sector in the Oulu region.

Lab-on-a-chip developments were discussed by Claude Vauchier of the Lab-on-a chip division at CEA-LETI. Smartdrop is based on electrowetting on dielectric technology, which allows actuation on individual droplets (60 mL to 2 µL), opening up the possibility of allow miniaturization and integration of various technologies like RT-PCR applications.

Meanwhile, Marko Pudas, Ph.D., CTO and cofounder of NanoGalax, described how his company has found a way to measure the adhesion of a single living cell to the extra cellular matrix (ECM) via integrin molecules. GalaxCell™ is based upon a piezo actuator and supporting microelectronics. It detaches the cell from ECM observed under phase contrast microscopy. This is potentially useful in cancer research to monitor the effect of drugs that can change the binding of cancer cells to the ECM. It could also be used in cell therapy as adhesion data is informative about the state of a cell’s differentiation. The work is now being extended to micromanipulation applications to gain further insights into cell properties.

Also in this space is SensApex, a spin-off from the University of Oulu that focuses on precise sensing, measuring, and handling/manipulation. The company’s first product is a remote-controlled and ultracompact micromanipulator. It offers stable manipulation in 3-D with sub-micrometer resolution and up to 18 mm movement range per axis. The system comes equipped with a stand-alone control unit with a location display and step-size adjustment.

Cell Cultivation



Biocatalyst-controlled cultivation of *E. coli* with EnBase in a 96-well plate

Developments in bioprocessing coming out of the University of Oulu led to the founding of BioSilta, which has developed a bacterial cell-cultivation technology based on a fed-batch method used in industrial processes. In EnBase™ any well of an MTP plate becomes a miniature bioreactor with a storage layer of starch-containing gel on the bottom and a liquid media layer containing an enzyme.

The enzyme acts as a pump that controls glucose release from the starch to the culture. This controlled nutrient-feeding technique provides much better conditions for bacterial cell culture, the company says, allowing up to 50 times the cell density and up to 10 times higher levels of recombinant protein compared to standard cultivation methods.

“EnBase allows you to scale down your research knowing that you can readily scale it up again,” explained CEO, Russell Golson. The product is available for a variety of formats: shake flasks, mini-shake flasks, starter tubes, and a range of deep well and standard MTP plates. A 24-well Opti-Set allows customers to try different glucose feeding concentrations alongside different media in a single-plate experiment.

“Cell culture conditions can be optimized in a short space of time,” added Golson. Applications of EnBase include increasing expression levels of recombinant proteins (with the University of Regensburg), achieving higher growth for B. subtilis (with the University of Greifswald), and increasing throughput on the Human Proteome Resource with collaborators at the Royal Institute of Technology in

Sweden.

In another cell culture development, Peggy Stock, Ph.D., researcher in the molecular hepatology group at the University of Halle, described CellTech-BioReactor, a new system for biochemical monitoring. The project, funded by the state of Saxony-Anhalt, is being developed by the NEMO network, a consortium of small German companies and research facilities. The CellTech-BioReactor consists of a small disposable bioreactor allowing rapid assessment of the impact of compounds on hepatocytes in 3-D culture on various scaffolds.

A sandwich hybridization assay detects changes in liver enzyme (CYP) gene expression that could be related to compound toxicity. The system, at the prototype stage, is highly specific for CYP type, according to Dr. Stock, who hopes it can help replace animal systems.

Biomolecular Interactions

SensApex' first product is a remote-controlled and ultracompact micromanipulator.

Analysis of biomolecular interactions were also discussed. Markku Kulomaa, Ph.D., of the University of Tampere presented new types of avidins, a chicken-derived protein used widely as a probe in the study of biological macromolecules. Both avidin and its bacterial analogue, streptavidin, have been modified by mutagenesis for improved properties.

For instance, the avidin-biotin technology would benefit from avidins with multiple binding sites, said Dr. Kulomaa.

Temperature and organic solvent stable avidins have been created using an approach that compares amino acid sequences of avidin and similar proteins. A number of novel and multipurpose avidins are now being produced by this approach, some of which (the antidins) utilize ligands other than the well-known biotin.

Novamass, an ADMET specialist company, is now a member of Systems Biology Worldwide, a joint Finland-India venture addressing many aspects of early drug development. Novamass continues to develop its core competence in drug metabolism analysis, with a focus on metabolite identification.

Relationship with India

Connections between Finland and India are growing stronger. One of the Indian companies at the meeting was Avesthagen, whose vision is to bring about the convergence of population genetics, functional foods, and pharma for personalized, predictive, and preventive healthcare. Its leading project is Avestagenome™, which involves biomarker discovery and predictive diagnostics. This involves the 70,000 strong Parsi population with its well-defined genealogy. The group is known for longevity, but also for increased incidence of neurological disease, stroke, heart disease, and certain cancers.

“This is the first population-based study with a global impact using a systems biology approach,” said Manan Bhatt, vp of external relations. The current focus of the genome project is upon Alzheimer’s, Parkinson’s, and breast and prostate cancers, with 20,000 samples to be collected by 2010. Currently, Avesthagen is carrying out genome, transcriptome, proteome, and metabolome analysis on samples collected for the Avestagenome project, and is in talks with Finnish and other collaborators on application of chip technology for designing molecular diagnostics.

Anna Erkkilä, head of the trade center and senior consultant of FinPro India in Mumbai, discussed the healthcare market in India and opportunities for life science companies. FinPro is a networking organization dedicated to internationalizing Finnish companies. She observed that demographic change was leading to a diamond-shaped healthcare market in India, with a big increase in middle-

income consumers. “Companies go to India because of the reduced cost, but now stay for the quality and competitiveness,” she said.
The diagnostics market is growing, particularly in the in vitro diagnostics area, the driver being an increase in health awareness among the population, although the challenges differ in rural areas. Imported products are often too expensive, so local production is the key. Needs include diagnostics for TB, HIV, malaria, heart disease, cancer, and diabetes.

In rural areas of India, the lack of a cold chain, long distances to transport materials, and high temperatures, as well as a lack of doctors, provide challenges.

Finland will grow its presence in India through funding available for Finnish-Indian early-stage companies in medical diagnostics from Tekes, the Academy of Finland, and the Department of Biotechnology, Ministry of Science and Technology, India.
