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The BARNETT GAZETTE

The Barnett Institute of Chemical and Biological Analysis

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INSTITUTE RETREAT BOOSTS BIOTECHNOLOGY INITIATIVE



Marcelo Valle de Souza (left), Roger Giese and Roger Kautz enjoyed the company

This year's Barnett Institute Retreat was special: our eyes were opened to the wide world of biotechnology on campus. Research described by faculty affiliated with the Biotechnology Initiative from the Biology, Pharmaceutical Sciences and Psychology Departments nicely complemented discussion of recent advances in pushing the limits of bio-analytical techniques and instrumentation at the Institute.

After a brief introduction by Institute Director Barry Karger, Biotechnology Initiative Manager Graham Jones listed the Initiative's main goals: a five-year BS/MS degree program, development of ongoing biotechnology research and the building of new research facilities. Pharmacogenomics (defined as the effects of genetic polymorphisms on clinical outcomes), bioinformatics (genomics, proteomics, metabolomics) and improved capabilities in functional genomics are all high priority research areas.

Graham's own research is focused on the design of chemical proteases, the synthesis of molecules specific to DNA and RNA bulges, and the development of pro-drugs of anti-cancer agents. Through Graham's presentation, the scene was set for coverage of different aspects of neuroscience and drug discovery, which are major components of the Biotechnology Initiative.

Professor Jonathan Freedman (Pharmaceutical Sciences, *The Biochemical Basis of*

continued on page 2



Newly appointed Professor of Biology Kim Lewis (left) exchanges a thought with Barry Karger

Neuropharmacology) described our best view of a central dopaminergic neuron, indicating likely sites of drug action and the origins of addictive behavior. The focus is on amygdalohippocampal (AHA) cells in the part of the rat brain called the amygdala. He uses a patch clamp to measure conductivity in ion channels with sensitivity down to 1 molecule of protein. M-enkephalin causes the channels to open. He observes that the channels are closed for much longer in addicted rats, indicating inhibition of m-enkephalin binding by cocaine and other addictive drugs.

Professor Richard Melloni (Psychology, *Adolescent Drug Abuse and the Neurobiology of Aggression*) is well known for studies of how environmental and biological factors affect brain development. The biological factors include neuropeptides, anabolic steroids, hormones, pharmacological agents (psychiatric medication and drugs of abuse) that affect mood and levels of aggression. Regulation of vasopressin and serotonin levels in the brain are thought to be involved, but precise analytical data are needed to advance the neuropharmacology. Among the most promising tools in understanding the link between biological factors and aggression are gene microarrays used in conjunction with the design of brain region-specific neural vectors that are being developed in transgenic hamster models. Although the hamster genome remains to be sequenced, it already is known that protein polymorphisms are linked to aggressive hamster behavior.

Professor Kim Lewis (Biology, *From Drug Resistance to Drug Discovery*) described his four main research areas: adaptive resistance of bacteria, biofilms, sterile surface agents and dealing with "unculturable" microorganisms.

Bacteria resist destruction by triggering a pump that ejects antibiotics. How the substances are recognized is still a mystery. Antibiotics can be made more effective by blocking the pump, for example with berberin and its metabolites. It has long been known that bacteria in so called "biofilms" are resistant to antibiotics. Kim is looking for precursors to cell death in an effort to overcome this therapeutic barrier. He and his co-workers have demonstrated that surfaces can be sterilized by attachment of long chain polymers that have bactericidal end groups. Also of great practical value is the invention of "magic chambers" that allow microorganisms that previously were "unculturable" to grow robustly.

Professor Paul Vouros (Chemistry and Senior Faculty Fellow) next

summarized his group's current work. The focus is on 1) improved CE/MS interfacing; 2) Vitamin D metabolism; 3) the development of HPLC/MS in combinatorial chemistry; and 4) detection of DNA adducts at the molecular level. This last area was expanded upon by John Soglia, a senior graduate student in the Vouros group. John stressed the need to locate the adducted gene and measure DNA adducts *in vivo* at the attomole level. High sensitivity ^{32}P post-labeling has a number of drawbacks. This has prompted refinement of an integrated capillary LC/micro-electrospray injection/mass spectrometry system with excellent sensitivity to the point that isomeric adducts of 4-aminobiphenyl with human pancreatic DNA can now be distinguished.

Roger Giese (Pharmaceutical Science and Senior Faculty Fellow) and co-workers are heavily involved in trace analysis, primarily with highly sensitive electron capture-mass spectrometry (EC-MS) and capillary electrophoresis-laser induced fluorescence (EC-LIF). Roger's group is synthesizing fluorescent tags for DNA adducts and has a near-IR detector from Picometrics, Inc. Sensitivity in MALDI-MS is maximized with large laser spots (increased solute amount). Highly sensitive EC detection enables 1pg of glycolic acid to be detected. Sample contamination is an issue at these limits. Current goals are the measurement of DNA adducts in a drop of blood and estrogens at the 1 pg level.

After a brief history of separations, Director Barry Karger pointed out the enormous complexity of protein expression compared to genome analysis because of the dynamic range and the lack of amplification methods like PCR. He outlined the major thrust of proteomics research

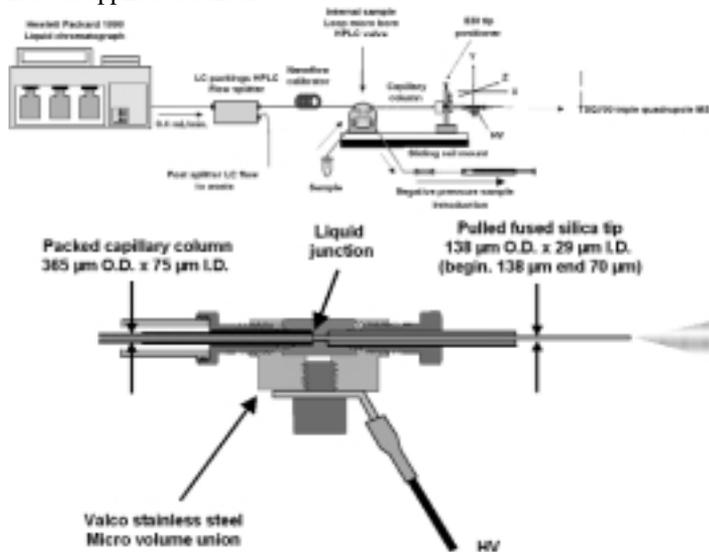


Institute members in the sunshine with Associate Director Bill Giessen in the background at the Institute. The goals of protein expression studies are diagnostics, target discovery, target validation and multiple pathways. Another focus is protein-protein interactions. Solutions to these complex analyses utilize 2-D gels, shot-gun LC/MS and protein chips, which Karger compared. Separations can be improved with shallow gradients but at the expense of long separation times. Under these conditions it is important to decouple the separation from the analysis. This can be accomplished in MALDI-TOF, where sample deposition can take place off-line.

This Retreat showed us how better analysis is enabling advances in fields embraced by the Biotechnology Initiative. We learned much about each other's work and are planning another Biotechnology Retreat in the Spring.

Cancer Links to Diet Probed

Cancer may be initiated by chemical modification of DNA. Work of Paul Vouros's group in collaboration with Dr. Robert Turesky of Nestec, Switzerland shows that modified DNA bases can be measured with as little as 300 ng DNA by combined LC and microelectrospray-MS/MS techniques. MS has more resolving and defining capability than the commonly used ^{32}P post-labeling analysis, with which the new method is becoming competitive. A key to sample resolution and reproducibility is low LC flow rates of 200 nL/min. As noted in a spotlight feature on the work of Paul and his colleagues (King, J., *Anal. Chem.*, 73, 353A (2001)), "The real test will be whether the method can detect DNA adducts from the lung tissue of, say, a chronic smoker." Such tests might one day answer the old question of 'Nature versus nurture', at least as applied to cancer.



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Multiplex CE Interfaced with MALDI MS

High sample throughput with MS analysis is a key objective in proteomics or clinical analysis. One approach to high throughput MS analysis in Barry Karger's group is based on simultaneous introduction of many samples and the high data acquisition rate of a Time-of-Flight (TOF) mass analyzer. They have introduced on-line coupling of liquid phase separation to MALDI/TOF MS using vacuum deposition on a moving surface and demonstrated principles of multiplex analysis with a capillary array, a high-repetition rate laser and a high-speed signal averager/compressor. Eight-peptide mixtures were separated by CE in an 8-capillary array, mixed with a matrix solution in a common liquid junction and deposited with another 8-capillary array on a Mylar tape in the source chamber of a TOF mass spectrometer. A 2 kHz, 355 nm frequency-tripled Nd:YAG laser with a fast scanning mirror was employed for desorption of the deposited streaks. Multiplex CE-MS of model peptide mixtures and protein digests has been demonstrated at an acquisition rate of 10 average mass spectra/second for each of 8 samples.

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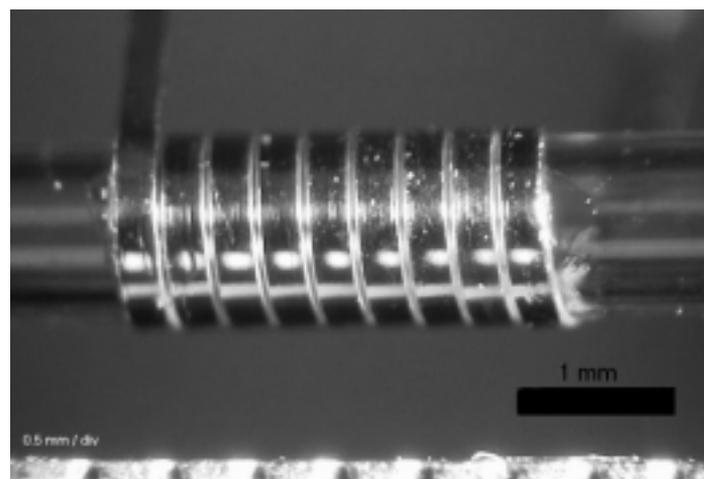
Pro-drug and Diagnostics Advances Reported

Research in the Graham Jones group has continued on the development of various enzyme and photo-activated pro-drugs and diagnostics. They recently succeeded in developing a photo-activated enediyne estrogen conjugate with nanomolar affinity for human estrogen receptor alpha, and are now investigating its biological activity against a panel of tumor cell lines. A similar strategy has been applied to estrogen-porphyrin conjugates that show selective cell killing of human breast cancer cells. Finally, Graham and his colleagues have succeeded in synthesizing a small molecule that can bind to and alkylate a highly specific DNA microenvironment. In collaboration with researchers at Harvard Medical School, they have now demonstrated that it is possible to inactivate unique bulges in DNA with extremely high selectivity. Bulged DNA microenvironments are implicated in a number of neurodegenerative diseases, but until now no compounds were available to address such targets. When nature provides us with opportunity it is our duty to respond. The Jones group is especially pleased with this new development, which will have far reaching implications.

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Microscale NMR Probe Debuts

Today's medicinal chemistry requires the design and synthesis of enough material for thorough analysis by LC, MS and NMR, in addition to cell or animal assays for activity. While micro-assays are being developed, NMR analysis may require 100 ug of sample or more. However, split and pool combinatorial libraries using solid-phase synthesis typically produce 1 ug or less. But combinatorial methods may soon be able to provide all the traditional med-chem analyses and assays. The Barnett Institute is collaborating with the Institute for Chemistry and Cell Biology (ICCB) at Harvard, which has developed a solid phase synthesis method that produces 10 ug of each compound. Roger Kautz at the Institute has been building NMR microprobes using solenoidal microcoils, a technique developed by Jonathan Sweedler and colleagues at the University of Illinois. These small coils have 30 times the sensitivity for mass-limited samples than conventional "small" 3 mm NMR coils. The challenge in using microcoils is placing sub microliter samples at high (10 mM) concentration into the coil



NMR Sample Concentration by ITP or IEF



from outside the NMR magnet. In collaboration with Sweedler's group, the Barnett Institute set a record for NMR sensitivity last January (J. Amer. Chem. Soc., 123, 3159 (2001)) by using capillary isotachopheresis to inject and focus 200 ng of analyte into a 30 nL micro-coil. Since then, Dr. Kautz has been exploring other methods of injecting and concentrating samples which would be applicable to uncharged compounds. He is currently building a probe with a large 1 μ L micro-coil flow cell connected via a low-volume (8 μ L) capillary to an injection system below the NMR magnet for flow injection of sample plugs. The prospects for very low level NMR analysis in a flowing system look bright.

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THIRTEEN YEARS OF SUCCESS: THE HPCE SYMPOSIA RECALLED

In 1989, Barry Karger was encouraged by scientific colleagues James Jorgenson, (University of North Carolina), Franz Everetts (Eindhoven University, The Netherlands), Stellan Hjerten (Uppsala University, Sweden) and Shigeru Terabe (Himeji Institute of Technology, Japan) to organize the first Symposium on High Performance Capillary Electrophoresis (CE) in Boston. Today, this Symposium is the major international conference devoted to CE and other microscale separation techniques.

Capillary electrophoresis began to emerge in the early 1980s, for example through Jorgenson's basic work and the studies of Karger, Everetts, Terabe and Hjerten. The end of the 80s saw growing recognition of the high performance of CE and the appearance of the first commercial CE instrument designed and sold by the late Bob Brownlee. With no major conferences to fill the void, CE was first integrated into the annual HPLC Conferences.

HPCE '89 was organized by Barry with major assistance from Northeastern faculty colleague Tom Gilbert and Mrs. Shirley Schlessinger, a well-known meeting planner from Chicago. This first meeting, held in Boston in April, 1989, was chaired by Dr. Karger and, to everyone's surprise, had close to 400 registrants. Well-known plenary lecturers included the late Calvin Giddings (University of Utah) and Georges Guiochon (University of Tennessee). The Karger-Gilbert-Schlessinger team was to orchestrate the HPCE meetings for the next decade.

The tremendous interest sparked by HPCE '89 led to HPCE '90, which was held in San Francisco just nine months later in January, 1990. The registration had grown to 500 and Beckman, Bio-Rad, Hewlett-Packard and Perkin-Elmer were well represented. These major manufacturers all had entered the CE instrument market. The end of January was selected for all the following HPCE meetings, the earliest of which were in California and Florida for better winter weather.

HPCE '93 in Amsterdam was the first occasion to hold the meeting outside the US. This and subsequent meetings attracted 750-800 participants. They triggered many active discussions and were the scene of debates that significantly advanced the field. In 1996, the meeting scope was expanded to become the International Symposium on Microscale

Separations and Analysis. The decision to expand and diversify was made on the basis of plenary and other lectures at earlier HPCE's. The last meeting chaired by Dr. Karger was HPCE '98, which was held in Orlando, FL.

At this point the HPCE reins were handed over to the California Separation Science Society (CASSS), of which Dr. William Hancock (a Barnett Institute Advisory Council member) is the President.

HPCE '01, co-chaired by Drs. Karger and Hancock in Boston in January, 2001, made a point of recognizing the start of the series thirteen years before. The Boston meeting featured well-attended, separate two-day mini-symposia on genomics and proteomics, as well as popular sessions arranged for discussion of new problems and perspectives.

The HPCE meetings continue to have a major impact on separation science and bioanalysis. CE was the technology used to sequence the human genome. Problems in new fields such as complex protein and polysaccharide measurement and the trace analysis of DNA adducts are being solved with the versatility and exquisite performance of CE. New formats such as microfluidic devices (microchips) extend the power of CE and the future is bright. The next meeting will be held in Stockholm, Sweden in April 2002.

We are delighted to welcome new research staff and graduate students to the Barnett Institute.

WELCOME

Dr. Karger's research group has the following recent new members: **Victor Andreev** as Principal Research Scientist. In St. Petersburg, Russia, Victor was head of a laboratory at the Institute for Analytical Instrumentation at the Russian Academy of Sciences; **Lijuan Li** is a new Postdoctoral Research Associate. Lijuan received her Ph.D. from the Department of Chemistry at Duke University in May, 2001 under Professor Linda McGown; **Aimin Tan** also is a new Postdoctoral Research Associate. Aimin completed a postdoctoral fellowship at the National University of Ireland, Cork, Ireland before joining the Barnett Institute; **Marcelo Valle de Sousa** is here as a Visiting Scientist. Marcelo is on sabbatical leave for 9 months from his position as Director of the Brazilian Center for Protein Research and Services at the University of Brasilia, Brazil; **Yu Yang** is a recently admitted graduate student. Yu received her M.S. in Bioanalytical Chemistry from Peking University, Beijing in July 1997.

Dr. Paul Vouros welcomes two new Ph.D. graduate students to his research group. **Terrence Black** received his B.S. in chemistry from the University of Richmond, Virginia, and **John Williams** obtained his B.S. in chemistry from Trinity College, Hartford, Connecticut. Prof. Graham Jones welcomes three new graduate students to his research group: **Erin Navin** received his B.S. degree from the University of Massachusetts, Boston, **Longfei Xie** graduated from Shenyang Pharmaceutical University in Shenyang, People's Republic of China and **David Keith** is a bachelors graduate of Indiana University of Pennsylvania, in Indiana, PA.

Danielle Lawton, a junior biochemistry major has joined the Humic Acid Group as an undergraduate research student.

TRANSITIONS

Aran Paulus recently assumed the position of Manager of the Advanced Research Team at Molecular Dynamics, Inc., Sunnyvale, CA. Prior to this he had been associated with the Genomics Institute of the Novartis Research Foundation, San Diego, CA. Aran was a Postdoctoral Research Fellow in Dr. Karger's lab in the late 1980's.

Congratulations to **Zoran Susic**, who received his Ph.D. in Chemistry in September after completing his research and thesis work with Dr. Karger. He has joined the research staff of Biogen, Inc., Cambridge, MA; **Hui He** recently completed his postdoctoral research with Dr. Karger and has joined the research staff of Schering-Plough Pharmaceutical Co. in New Jersey.

HOT OFF THE PRESS

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Wang, K.; Dickinson, L. C.; Ghabbour, E. A.; Davies G.; Xing, B. Investigation of Molecular Motion of Humic Acids by 1-D and 2-D NMR Spectroscopy, in *Humic Substances: Structures, Models and Functions*, Ghabbour, E. A., Davies, G., eds., Royal Society of Chemistry, Cambridge, 2001, pp. 69-78.

NEWEST PATENTS

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Karger, B. L.; Miller, A. W., "Expert System for Analysis of DNA Sequencing Electropherograms," *U.S. Patent* 6,236,944, May 22, 2001.

LISTEN TO THIS!

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Giese, R., "Trace Organic Analysis," ESA Inc., Chelmsford, MA, July, 2001.

Giese, R., "New Methodology for the Analysis of DNA Adducts," University of Massachusetts Medical School, Worcester, MA, September, 2001.

Ghabbour, E. A.; Davies, G. "The Thermodynamics of Metal Binding by Soil Humic Acids: Implications for Soil Processes," 6th International Conference on the Biogeochemistry of Trace Elements, Guelph, Ontario Canada, August, 2001.

Karger, B. L., "High Throughput Liquid Phase Microseparation - MALDI/MS for Proteomics," 49th ASMS Conference on Mass Spectrometry and Allied Topics, Chicago, IL, May 27-31, 2001.

Karger, B. L., Plenary Lecture, "Multiplex Separation/MS: A Powerful Tool for Proteomics", 25th International Symposium on High Performance Liquid Phase Separations and Related Techniques (HPLC 2001), Maastricht, The Netherlands, June, 2001.

Karger, B. L., Plenary Lecture, "High Resolution Separations in the Post Genome Era: LC, CE and MS for Genomics and Proteomics," HPLC Kyoto, Kyoto, Japan, September, 2001.

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UPCOMING EVENTS

- | | |
|-------------------------|--|
| October 30 | Hoehn Lectures
Professors Jeremy Nicholson
and John Lindon
Imperial College of Science and Medicine
London, UK
<i>Metabonomics</i> |
| October 31 | Advisory Council Meeting |
| February 5, 2002 | Saferstein Memorial Lecture |
| TBA | Barnett Lecture |
| July 21-26, 2002 | 20th Anniversary Conference
International Humic Substances Society |
| July 27, 2002 | Humic Substances Seminar VI |

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