CONTROLLED RELEASE SOCIETY Volume 21-Number 1-2004



James Anderson CRS President elected to the National Academy

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Pharmacy for Farm Animals Joy Dempsey

Nottingham's Biophysical Analysis Group



Israeli Chapter Annual Meeting



Bozena Michniak *Editor*



Ijeoma Uchegbu *Editor*



Jaymie Griffin *Managing Editor*



Jerome Barra Consumer & Diversified Products Special Feature Editor



James Anderson President



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On the cover -



Join us for the 31st Annual Meeting & Exposition of the Controlled Release Society in Honolulu, Hawaii.

June 12-16, 2004

Dedicated to the science and technology of controlled release and delivery and promoting education by releasing science to deliver a better future.

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FROM THE Editors

B. Michniak, UMDNJ-New Jersey Medical School, USA and Ijeoma Uchegbu, University of Strathclyde, UK

The festive season is over; you got exactly what you wanted for Christmas - unwelcome relatives, presents that ended up in the bin on the same day and a hangover. Work beckons and you have to get that publication out before your rivals do, sequester more funds into your research accounts and simply work non stop until Christmas comes 'round once again! Please, please take a break. The first thing you have to do is find a quiet place where you will not be interrupted, sit down, put your feet up and read – your Newsletter that is. It is a cracking good read and may even make finding answers to those tricky "meaning of life" questions easier!

We are really pleased to have so many people who are prepared to write articles for nothing more than a warm thank you. Have you got a burning idea for an interesting article that will capture the imagination of the Pharmaceutical Sciences community? If so simply visit <u>www.controlled.release/publications</u> and get typing. It really is as easy as that. Not only do we need to swell the philanthropic ranks of the free lance whose reward is a contribution to the common good but we would also love to hear about your companies, awards, elevations or simply what makes you feel like having a good scream.

Speaking of awards, if you want to know what the winners of the 2003 GlaxoSmithKline Industrial Achievement award did to get the honour then you can find out by reading a summary of the research effort of this University of Nottingham group on page 6. I am sure that you would agree that not only is the science top rate but they photograph well to boot.

Ever wondered what it feels like to be inducted into the equivalent of science's hall of fame, well turn to page 3 and read how the President of the Society, Dr. Jim Anderson, felt when he found out that he had been elected to join the Institute of Medicine of the National Academy of Sciences. There is also a special message to our members from Jim on page 4.

We have some great chapter news from our colleagues who run the Israeli chapter of the Society. Details of their recently held and extremely well attended conference, by the look of things, appear on page 15. Have you just had a Chapter conference and want to bring your meeting to the world (well pharmaceutical science world) since the world could not make it to your meeting, then put pen to paper and tell us what you got up to.

Our Spotlight falls on Pharmaceutical Profiles Ltd. this time around. Join us in wishing this company all the best for the future. We always hope that success continues to follow our Spotlights like a shadow in the blistering heat. It was hard to choose from so many interesting companies but then we had to and I do hope that you agree that Pharmaceutical Profiles Ltd. is as interesting as they come. Keep those Spotlight submissions coming folks.

You know that I cannot end this piece without mentioning Hawaii. Well there it is I have mentioned it. An opportunity to meet up with old friends, find out what is hot and what is not, present your important findings in person, learn something new or simply enjoy this expression of paradise when your talk or poster is done. Hey who needs a reason, just be there!

Science is the one endeavour where you really do need to interact with others and the more that we communicate the easier it will be. My motto for 2004 is to network, network and network some more. From Bo, Jaymie and me, have a good one and make it count.

In Memoriam:

It is with great sadness that we report Dr. Zohar Merchant has passed away after a brief illness. Zohar was an active member of the Controlled Release Society since 1994 and was the chair of the Consumer & Diversified Products (C&DP) for 2003-2004. He was instrumental in establishing the C&DP group as part of CRS and was heavily involved in the organization of symposia for annual meetings.

Zohar was employed as a Technology Principal at Kraft Foods, where he had worked for 18 years. He authored over 40 publications and was awarded 8 patents. He received a number of awards at Kraft for leadership and innovation, including a 2003 Organizational Excellence award for exemplifying the essence of Kraft Research & Development. Zohar was known for his leadership, creativity, and community service in organizations including Chicago Asian American Coalition, Habitat for Humanity, United Way, and Chicago Food Depository. He is survived by his wife and a son. We will miss Zohar immensely and are grateful for his efforts and service to the CRS and C&DP group.

Editors Bozena Michniak & Ijeoma Uchegbu

Consumer & Diversified Products Special Feature Editor Jerome Barra

Managing Editor Jaymie Griffin

Thanks to members of the Publications Newsletter Subcommittee for helping with this issue: Martyn Davies, Agis Kydonieus, Harlan Hall, and Mike Rathbone.

The Controlled Release Society Newsletter is the official newsletter of the Controlled Release Society. The newsletter is published three times annually providing scientific and technical information pertinent to the controlled release community and news about society and chapter activities. Members receive the newsletter via mail. The newsletter may also be viewed online at www.controlledrelease.org.

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CRS President Elected to National Academy

CRS President James M. Anderson, M.D., Ph.D. is Elected to Membership in the Institute of Medicine of the National Academy

James M. Anderson, M.D., Ph.D., Professor of Pathology, Macromolecular Science and Biomedical Engineering, Institute of Pathology, Case Western Reserve University, has been elected to membership in the Institute of Medicine of the National Academy, effective October 1, 2003. Members are elected by the incumbent membership on the basis of professional achievement and of demonstrated interest, concern and involvement with problems and critical issues that affect the health of the public.

Dr. Anderson is an internationally recognized scientist in the area of tissue responses to biomaterials, medical devices, and prostheses. His expertise is broad-based, ranging from fundamental biomaterials research, to clinical device retrieval and evaluation, to policy development. He has made pioneering and significant advancements in our understanding of biological interactions and biology-based design criteria for biomaterials, prostheses, and medical devices. For medical devices, tissue engineering and biomaterial-based therapeutics, his broad-based contributions at the fundamental and clinical levels are insightful and innovative.

Dr. Anderson's innovative and imaginative research continues to provide important fundamental biological information, i.e., new biological design criteria, for the development of new materials and prostheses that modulate cellular interactions at implant interfaces. His recent studies on the surfacedependent mechanisms of foreign body giant cell formation and the apoptosis of adherent inflammatory cells as a mechanism for the persistence of cardiovascular infections provide insight and information into the development of materials and therapies for enhancing the performance of medical devices and prostheses. He has provided significant leadership and unique contributions to the science and engineering of biomaterials and medical devices through his interactions with the NIH, FDA, International Standards Organization (ISO), and the American Institute for Medical and Biological



Engineering (AIMBE). He is an outstanding mentor of graduate and medical students in Pathology, Polymer Science, and Biomedical Engineering. As evidence of the quality of his research, he is the recipient of the only NIH/NHLBI MERIT Award in Biomaterials.

Dr. Anderson is a 1963 Chemistry graduate of the University of Wisconsin-Eau Claire; he earned his Ph.D. in Chemistry from Oregon State University in 1967, and his Doctor of Medicine degree in 1976 from Case Western Reserve University School of Medicine. He has worked in the areas of biomaterials, medical devices, and prostheses for over 30 years and has authored or co-authored more than 300 publications in areas related to biomaterials. He is the Editor of the Journal of Biomedical Materials Research of the Society for Biomaterials; current President of the Controlled Release Society; and a consultant to industry, the National Institutes of Health, and the Food and Drug Administration.

CRS UPDATES

Vote in the 2004 election; renew your membership by February 28 to be eligible. Visit <u>http://www.controlledrelease.org/membership/</u>index.cgi to see what sets CRS apart from other societies.

REGISTER NOW! Early registration ends May 16, 2004. Visit <u>http://www.controlledrelease.org/meetings/hawaii/index.cgi</u> to join your friends and colleagues in gaining the best education in controlled release. Experience the essence of beauty and harmony on the Islands of Aloha. The 2004 Program Committee has prepared an extraordinary schedule!

WANTED - INDUSTRIAL EDITOR

The CRS Newsletter Publications Committee and Editors invite applications from industrial or academic based CRS members for the position of Industrial Editor. This position involves helping the Committee and Editors to solicit Newsletter articles from industry, and reporting current news and technology advances/updates in the drug delivery industry. Please email the Editors at <u>newsletter@controlledrelease.org</u> for more information or to express an interest in this opportunity.



From the President

by James Anderson President of the Controlled Release Society Case Western Reserve University, U.S.A.

Greetings to you in this New Year 2004. Just as some of you made New Year's resolutions for 2004, so the Controlled Release Society has a resolution for 2004 and beyond – education, education, and education! In the Society's mission statement, "The Controlled Release Society is a multi-disciplinary society dedicated to the science and technology of controlled release and delivery and promoting education by releasing science to deliver a better future," education is clearly the objective.

During a recent board meeting, your representatives voted to create the position of Education Secretary. This *ad hoc* (non voting) member will serve on the board for three years and will work under the direction of Scientific Secretary Martyn C. Davies. The board's unanimous choice for Education Secretary was Michael J. Rathbone of InterAg in New Zealand. Mike has been instrumental in gathering and compiling information from CRS members to further the call for education. Working closely with CRS members from five continents, Mike has planned a session in Hawaii titled Get Up and Get Educated. This session will target young scientists of CRS, while giving some of the older crowd an opportunity to share their wealth of knowledge. Of

course, you'll find me sitting with the young scientists listening to what the elders have to say!

> Another topic of discussion at the board meeting was raising members' dues. This was a difficult decision; however, the modest increase is necessary to

achieve educational goals and continue supporting students and chapters worldwide. Thank you for renewing your membership today.

The 31st Annual Meeting in Honolulu, Hawaii, will be scientifically and aesthetically outstanding. Reduced meeting registration fees are a CRS member benefit. Register for the meeting before May 16th to receive the lowest rate.

When you make your sleeping room reservations for Hawaii, remember to book your stay at the host hotel, the Hilton Hawaiian Village located right on Waikiki Beach. It is crucial to the financial health of CRS that you book your sleeping room at the host hotel.

When members stay at other facilities, CRS suffers serious monetary consequences. Annual meetings are planned years in advance and contracts are based on an expected number of attendees and number of sleeping room nights needed. These contracts bind us, legally and financially, for the total dollar amount the sleeping room nights represent. CRS works very hard to negotiate favorable contracts, and your assistance is necessary to fulfill the terms of the hotel contract.

Support CRS; book your sleeping rooms at the Hilton. Thank you for the positive impact you will have on the 31st Annual Meeting.

Remember – the meeting will be Hawaiian casual with no ties. I would much prefer a nice Hawaiian shirt. I look forward to seeing you all in Honolulu June 12-16, 2004.

Children's Program Available for Annual Meeting

The Hilton Hawaiian Village, host hotel for the 31st Annual Meeting & Exposition of the Controlled Release Society, offers a children's program.

The **Rainbow Express Keiki Club** is open to families registered and staying at the Hilton Hawaiian Village. The children's program operates seven (7) days a week, excluding major holidays, for children age 5-12.

Visit www.controlledrelease.org/meetings/hawali/children.cgi for more information.

New Initiative for Young Scientists

by Michael J Rathbone Education Secretary InterAg, New Zealand

Young Scientists and Education– a major focus in Hawaii If you are a Young Scientist interested in the area of controlled release drug delivery then the 2004 CRS Annual Symposium and Exposition in Hawaii is a meeting that you should not miss! Why? Well, several new initiatives are being organized for the meeting with a focus on education and Young Scientists.

The most noteworthy item is a two-day Education Program designed specifically to educate, update and extend Young Scientists knowledge. This must-attend event for knowledge gathering and networking is made up of four sessions and is scheduled to occur on the two days that immediately precede the main conference. It opens by highlighting the contribution that Young Scientists can make to the area of controlled release. Past recipients of the Controlled Release Society Young Scientists Award speak on their achievements and research activities to provide a personal perspective on the trials and tribulations of being a Young Scientist and forward advice on how to achieve as a Young Scientist. The session is followed by a 'Know Your Industry' session in which industry-based scientists will provide an insight into their roles within the pharmaceutical industry. The session will include talks from a discovery scientist, preformulation scientist, analytical scientist, formulation scientist, and scale-up/production scientist. The aim of the session is to provide the audience with an insight into the activities, opportunities and challenges such scientists face on a day-to-day basis. A lively mixer evening at the end of Day 1 has been organized to facilitate networking and social interaction. Day 2 of the Education Program opens with a Handsoff:Hands-on:Hands-up session on In Vitro Drug Release Testing. The 'Hands-off' session comprises informative lectures on what a drug release test is and its uses; how to develop and validate a drug release test; receptor phase considerations; and in vitro:in vivo correlations. The 'Hands-on' component involves practical demonstrations and hints on setting up a dissolution testing station, a review of the different apparatus and how to use them, and web sites that can be accessed on dissolution testing. The 'Hands-up' component of this session involves a panel of experts answering questions. The final session of the program 'Expand Your Knowledge' involves lectures on the current status and future prospects of the areas of human oral drug delivery, veterinary controlled release drug delivery and consumer and diversified products. Speakers in this session will not only provide a comprehensive overview of the area, but also highlight their current research activities.

If this is the first time you are attending the CRS Annual Symposium and Exposition, it can be daunting, it can be confusing, butdo not worry. The CRS Education Committee will be there to help! A special Orientation Session for young scientists will be available at the beginning of Day 1 which will be supported throughout the conference via an Education Booth which will be manned by members of the CRS Education Committee. The Booth will also display achievements to date of the Education Committee and feature a live web-based resource facility.

Hawaii will see a new education initiative introduced to the CRS Annual Symposium and Exposition (that you will just

want to get up early for): Get-up:Get-Educated Sessions. These early morning sessions will comprise '101' educational lectures, have a strong scientific base and are aimed at introducing the participants to an area with which they are not familiar. This year's sessions will be on pharmacokinetics and in vitro/in vivo correlations.



Finally, if you are a Young Scientist presenting at the Annual Symposium and

Exposition then your hard work and efforts may be rewarded at the Highlights of the Students Posters. The revamped session and award ceremony involves presentations, motivational talks and will be concluded by a social evening. Prominent members of the CRS will be in attendance to interact and provide feedback on the research activities of the younger members of the Society. This event promises to be a mix of social and scientific interaction that no Young Scientist can afford to miss.

So, I welcome all Young Scientists to attend the 2004 CRS Annual Symposium and Exposition in Hawaii, and look forward to interacting with each and everyone of you during the Conference. Please, do not hesitate to come up to me and introduce yourself.



SCIENTIFICALLY SPEAKING

The Application of Sub-micron Scale Surface Analysis to Drug Delivery

By Clive Roberts, Martyn Davies, Saul Tendler, Stephanie Allen and Phil Williams *The University of Nottingham, UK*

In the early 90's it became apparent to many that enormous potential existed within the Pharmaceutical and Healthcare sector in uniting new fundamental advances in surface and interfacial analysis and the then daunting task of the practical application of such approaches. To begin to exploit this potential has required the full embracement of the multidisciplinary ethos, linking researchers with skills in the pharmaceutical sciences, engineering, physics, chemistry, computational modelling and the biomolecular sciences. For our group at Nottingham we chose to develop and apply a range of complementary core technologies that includes atomic force microscopy (AFM), secondary ion mass spectrometry (SIMS), X-ray photoelectron spectroscopy (XPS) and surface plasmon resonance (SPR) supported by other techniques such as confocal/ fluorescence microscopy, FT-IR spectroscopy, optical tweezers, Raman, and scanning thermal microscopy (SThM). In broad terms these technologies provide the ability to visualize (AFM), chemically characterize (Tof-SIMS, XPS) and study kinetics (SPR) of surfaces at the nanoscale. In addition AFM provides the remarkable ability to manipulate nanoscale objects and to sense forces between them, a feature we have exploited to investigate interactions between individual biomolecules and also at a larger scale between individual drug/excipient particles. Focusing here on issues of direct relevance to pharmaceutical research a series of projects and resultant publications have demonstrated the potential of such nanoscale surface analysis for the (see http://www.nottingham.ac.uk/lbsa for details of publications):

- real-time *in situ* observation at a single molecule level of beta-amyloid fibrillization and the assembly and disassembly of a polymeric gene delivery vector.
- chemical and morphological deconstruction of a controlled release pellet through time of flight SIMS, FT-IR and environmental scanning electron microscopy.
- $\cdot\,$ identification of polymorphic drug forms from single crystals using AFM and SThM.
- measurement of individual drug particle interactions that for the first time take account of true morphology and contact area and allow accurate assessment of surface energy and hence have a direct impact on particle engineering strategies.
- measurement of intrinsic dissolution rate from identified individual faces of a drug crystal.
- identification of the mode of binding of model drugs to single molecules of DNA through their effect on the mechanical properties of individual molecules of DNA.

Two themes emerge from these applications, the opportunity to relate molecular structure to processes through the direct visualization of dynamic events in environments which at least approximate to *in vivo* conditions, and the desire to quantify the composition and relevant kinetics of drug delivery systems at the nanoscale in a manner which can be related to macroscale performance. This former theme includes, for example, recent studies focussed on the characterization of the molecular morphology of various gene delivery vectors created using cationic lipids and polymers. Both the formation and disassembly of these vectors has been observed dynamically under a range of lipid (or polymer) to DNA loadings and environmental stresses. This approach is illustrated by the data in figure 1which addresses the basic need to protect therapeutic DNA from *in vivo* degradation.



Figure 1. Real-time visualization of the effect of DNase I enzyme (arrowed) on a single polyamidoamine dendrimer-DNA (1:1 ratio) complex. The complex is still undergoing structural changes consistent with complexation before a clear enzymatic interaction takes place at 90 minutes (adapted from Nucleic Acid Research13 (2003) 4001-4005).

Here, we have applied AFM in liquid to visualize at the molecular scale and in real time, the effect of DNase I on generation 4 polyamidoamine dendrimer-DNA complexes. These complexes are revealed to be dynamic in nature, in some cases revealing the addition and loss of dendrimers to individual complexes. The formation of the complexes has been observed to provide a degree of protection to the DNA and that this protection can be related to the structural morphology of the formed complex, which is itself dependent on the dendrimer loading and the time allowed for complex formation. Current work aims through collaborations with groups modelling, developing and testing delivery vectors to link these data to transfection performance and to extend these studies to the visualization of interactions between delivery vectors and physical barriers such as the cell membrane.

An example of providing quantified data includes morphological, spectroscopic and kinetic studies of multilayered controlled release dosage forms (see examples in figure 2). TOF-SIMS effectively provides a spatially resolved mass spectrum analysis and in the example shown here allows molecular chemical information to be gained from all of the layers of a cross-sectioned controlled release bead simultaneously, *in situ*. The integrity of each of the layers can then be evaluated through imaging of specific ion species for



Figure 2. (a) TOF-SIMS characterization of a multilayer controlled release system facilitating spectroscopy identification of components and their relative spatial distribution with micron resolution. Characteristic mass ions are selected for each of the formulation components to allow the relative positions of each to be determined (adapted from Analytical Chemistry 72 (2000) 5625-5638). (b) Real-time confocal microscopy showing the mode of drug release from a reservoir based delivery system (image size 1mm x 1mm).

the drug(s), excipient, and coating materials. The spatial resolution of such data can be sub-micron. At this resolution the data shows excellent complementarity to other spectroscopic tools, AFM imaging and localized thermal analysis using SThM. Such synergy between analysis methods is exemplified by the confocal microscopy data shown in Figure 2b where the release of a drug from a similar reservoir based delivery system has been visualized. Since the fabrication of such multilayered controlled-release systems can be technically challenging compared with conventional dosage forms, evaluation and analysis that can relate structural integrity to drug release can provide direct feedback on formulation performance and opportunities. These and other works recently led to the presentation of the GlaxoSmithKline International Achievement Award to the

authors and to Nikin Patel, CEO of Molecular Profiles, a spin out of the LBSA group (figure 3).

As technologies in their youth, many of the approaches highlighted here continue to develop rapidly both in academic laboratories and as commercial products. This year for example has seen the advent of gold source **TOF-SIMS** ideal for pharmaceutical analysis and the appearance of new modes of AFM analysis for material property mapping. At Nottingham we are also developing in-house new functionalities, such as ultra-



Figure 3. Recipients of the GlaxoSmithKline International Achievement Award. From left to right, Martyn Davies, Clive Roberts, Stephanie Allen, Phil Williams, Nikin Patel and Saul Tendler.

resolution AFM probes tipped with carbon nanotubes and cryogenic AFM. Taken together these advances promise to keep providing new insights into the nanoscale world of drug delivery and in the future to aid the rational design of a range of therapeutic strategies.

Retrovirus-mediated gene transfer: opportunities for interdisciplinary research

By Natalia Landázuri[†], Joseph M. Le Doux^{†*} Georgia Tech and Emory University, U.S.A.

Gene therapy, the delivery of genetic material to cells to achieve a therapeutic effect, holds enormous potential for the treatment of genetic and infectious diseases, and in tissue engineering. Unfortunately, success in the clinic has proven elusive, largely due to limitations with the current generation of gene transfer vectors. Recognizing these limitations, an NIH-commissioned panel issued a report in 1995 that challenged the research community to conduct more basic science research to improve our understanding of gene transfer vectors and their interactions with cells. Significant progress has been made since the report was issued, but much of this work has proceeded in parallel, within two separate communities of researchers - those who work with viral vectors and those who do not - with little cross-talk between them. We believe that, ultimately, the most effective gene transfer vectors will be comprised of viral and non-viral elements. For these vectors to be developed, interactions between the two research communities must be initiated and fostered. In hopes of catalyzing these types of interactions, we have outlined below a number of opportunities for researchers from both communities to work together to improve gene transfer technologies.

Numerous opportunities exist for experts in non-viral and viral methods to work together to improve gene transfer technologies. In this paper we have chosen to focus on how non-viral gene transfer technologies can be brought to bear on some of the limitations of retroviral-mediated gene transfer. We have focused on retroviruses because for many gene therapy applications they are the vector of choice because they permanently integrate their genetic material into the genome of the target cell, resulting, in principle, in a long-term cure [1]. Retroviruses used for gene transfer are often derived from the Moloney murine leukemia virus (MLV), or from the human immunodeficiency virus type 1 (HIV-1), a subclass of retroviruses called lentiviruses. The most significant functional difference between these two viruses is that MLV retroviruses can only infect cells that are actively dividing, whereas lentiviruses derived from HIV can infect cells even if they are not dividing, an important advantage for many *in vivo* gene therapy protocols [2].

Retroviruses are composed of two identical copies of a single stranded RNA genome and viral enzymes that are contained within an icosohedral capsid of structural virus proteins. The

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PHARM NEWS

Summaries of Veterinary Controlled Release Papers / Reviews Selected by: David Brayden University College of Dublin, Ireland

1. Mucoadhesive vaginal tablets as veterinary delivery system for the controlled release of an antimicrobial drug, acriflavine. Gavini, E. *et al.* AAPS PharmSciTech. 2002;3:E20.

The aim of the study was the development of mucoadhesive vaginal tablets designed for the local controlled release of acriflavine, an antimicrobial drug used as a model. The tablets were prepared using drug-loaded chitosan microspheres and additional excipients (methylcellulose, sodium alginate, sodium carboxymethylcellulose, or Carbopol 974). The microspheres were prepared by a spray-drying method, using the drug to polymer weight ratios 1:1 and 1:2 and were characterized in terms of morphology, encapsulation efficiency, and in vitro release behavior, as MIC (Minimum Inhibitory Concentration), MBC (Minimum Bacterial Concentration), and killing time (KT). The tablets were prepared by direct compression, characterized by in vitro drug release and in vitro mucoadhesive tests. The microparticles have sizes of 4 to 12 microm; the mean encapsulation yields are about 90%. Acriflavine, encapsulated into the polymer, maintains its antibacterial activity; killing time of the encapsulated drug is similar to that of the free drug. In vitro release profiles of tablets show differences depending on the excipient used. In particular Carbopol 974, which is highly cross-linked, is able to determine a drug-controlled release from the matrix tablets for more than 8 hours. The in vitro adhesion tests, carried out on the same formulation, show a good adhesive behavior. The formulation containing microspheres with drug to polymer weight ratios of 1:1 and Carbopol 974 is characterized by the best release behavior and shows good mucoadhesive properties. These preliminary data indicate that this formulation can be proposed as a mucoadhesive vaginal delivery system for the controlled release of acriflavine.

2. Sustained-release injectables formed in situ and their potential use for veterinary products. Matschke C. *et al.* J Control Release. 2002; 85:1-15.

The controlled drug delivery of hydrophilic and lipophilic drug substances via the parenteral route has gained increasing importance in the development of pharmaceutical dosage forms. In particular, the animal health industry has generated strong interest in long-term drug delivery for both companion and farm animals during the past few years. At present sustained-release injectables formed in situ for s.c./i.m. administration have become an attractive alternative to common slow release technologies such as microspheres or standard implants. In this context, technologies based on PLA/PLGA; sucrose acetate isobutyrate (SAIB) and the amphipathic molecules Poloxamer; glycerol monooleate or PEG-PLA-PEG copolymers, are discussed. Release periods from hours to months can be obtained by choosing one of these drug delivery technologies. The release times are strongly dependent on the biodegradation of the polymers and the physico-chemical properties of the drug substance used. Furthermore, the use of different solvents for the matrix-forming agents and the individual loading capacity are critically assessed. Additionally acceptance of the excipients for parenteral use by the regulatory authorities is closely considered. Scientific articles as well as patent publications are reviewed to give a wide overview of the existing approaches and their future potential for animal health products.

3. Efficacy of ivermectin delivered via a controlled-release capsule against small lungworms (Protostrongylidae) in sheep. Rehbein S, Visser M. J Vet Med B Infect Dis Vet Public Health. 2002;49:313-6.

To evaluate the efficacy of an ivermectin controlled-release capsule (CRC), which delivers 1.6 mg ivermectin per day intraruminally for 100 days to sheep weighing 40-80 kg (IVOMEC Maximizer CR Capsule for adult sheep, Merial), against small lungworms two studies with 48 naturally infected adult female Merino Landrace

sheep were conducted. The sheep were allocated by restricted randomization based on bodyweight to untreated controls or received an ivermectin CRC. Eight sheep per group were necropsied 35, 70 or 105 days post-treatment. Lungworms were recovered by dissection or peptic digestion of the lungs. Baermann/Wetzel technique was used for faecal lungworm larval counts at weekly intervals. The efficacy of treatment was 100% against Dictyocaulus filaria and Protostrongylus rufescens (P < 0.05) at each necropsy day. The efficacy against Protostrongylus brevispiculum, Cystocaulus ocreatus and Neostrongylus linearis increased from 35 to 105 days after administration of the CRC and was found to be 100% (P < 0.01), 96.6% (P < 0.01) or 99% (P < 0.01), respectively, at 105 days post-treatment. The reductions of Muellerius capillaris counts varied and were 96.2% (P < 0.05) at 70 days posttreatment and 44.6% (P > 0.1) at 105 days post-treatment. Faecal lungworm larvae disappeared nearly completely from at least 3 weeks after the ivermectin CRC administration for all protostrongylid species including M. capillaris so that pasture infectivity will be subsequently significantly reduced.

4. In vivo release of oxytetracycline from a biodegradable controlled-release gel injected subcutaneously in Japanese quail (Coturnix coturnix japonica). Tell LA *et al.* J Vet Pharmacol Ther. 2003;26:239-45.

A long-acting, biodegradable, controlled-release formulation of oxytetracycline (CR-OTC) was evaluated in 18 adult Japanese quail (Coturnix coturnix japonica) following a single subcutaneous (s.c.) injection. Prior to characterizing the release of oxytetracycline (OTC) from the CR-OTC, the pharmacokinetic parameters of intravenously (i.v.) administered OTC were determined. Concentrations of free OTC were measured using a bioassay. The plasma concentration-time profile of OTC after a single i.v. injection at 20 mg/kg was best fit to an open two-compartmental model, with the following pharmacokinetic parameters: area under the curve (AUC) = 36.72 mg. h/L, terminal elimination half-life = 2.34 h, clearance (Cl) = 0.545 L/kg/h. Plasma [OTC] was >1.0 micro g/mL for at least 4 h following i.v. injection. The CR-OTC gel was well tolerated at a dosage of 1500 mg/kg s.c. Plasma [OTC] rose to >1.0 micro g/mL within 24 h; it remained >1.0 micro g/mL for at least 10 days in all birds sampled at that time point (n = 9)and for at least 18 days in two of nine birds. Using a deconvolution technique, it was determined that approximately 54.8% of the administered OTC was released from the CR-OTC over the 45-day observation period. This long-acting, biodegradable controlled-release OTC formulation may have potential for the treatment of chlamydophila infections and other OTC-sensitive bacteria in Japanese quail, however further studies are necessary to determine its safety and clinical application.

Four reviews for those interested in getting an overview of veterinary controlled release / drug delivery......

1. Modified release drug delivery in veterinary medicine. Rathbone MJ, Martinez MN. Drug Discov Today. 2002;7:823-9.

To successfully research and develop an animal pharmaceutical dosage form, a diverse array of issues covering basic medicine, pharmacology and technology must be addressed. Societal concerns regarding animal and public health, as well as the rapidly changing farming and economic environments, provide additional challenges that require integration into an already complex web of issues. Here, we examine the drive towards reducing the frequency of administration to animals and the closing of gaps between the human and veterinary drug product development.

2. Pharmaceutical challenges in veterinary product development. Ahmed I, Kasraian K. Adv Drug Deliv Rev. 2002;54:871-82.

There are many similarities between the human health and animal health industries. Both industries are research driven, have global presence, are highly regulated, and have to profit in a competitive business environment. However, there are also notable differences. This review highlights and discusses those differences as they relate to the pharmaceutical challenges in veterinary product development. This paper provides a brief review of the animal health pharmaceutical product landscape, segmentation, and market evolution; highlights challenges and special considerations in veterinary drug delivery; and identifies unmet needs in animal health along with recent advances.

3. Novel drug delivery strategies in veterinary medicine. Brayden, D. J. Ir. Vet. J. 2003; 56: 310-316.

Controlled release drug delivery technology has been more profitable in human rather than in veterinary medicine even though innovative and effective technologies have been developed for both. In veterinary medicine transdermal, subcutaneous implants and intra-mammary delivery systems have been more successful than either oral or nasal delivery technologies. In contrast to the products for food-producing animals, novel drug delivery products for companion animals are highly marketable and can command premium prices. Novel oral and nasal peptide and gene delivery technologies currently being developed for man may potentially be adapted for human medicine may prove adaptable for new and old diseases in small animals.

4. Bacterial ghosts as vaccine candidates for veterinary applications. Jalava K. *et al*. J Control Release. 2002;85(1-3):17-25.

The application of new strategies to develop effective vaccines is essential in modern veterinary medicine. The bacterial ghost system is a novel vaccine delivery system endowed with intrinsic adjuvant properties. Bacterial ghosts are nonliving Gramnegative bacterial cell envelopes devoid of cytoplasmic contents while maintaining their cellular morphology and native surface antigenic structures including bioadhesive properties. They are produced by PhiX174 protein E-mediated lysis of Gramnegative bacteria. The intrinsic adjuvant properties of bacterial ghost preparations enhance immune responses against envelope bound antigens, including T-cell activation and mucosal immunity. Since native and foreign antigens can be expressed in the envelope complex of ghosts before E-mediated lysis, multiple antigens of various origins can be presented to the immune system simultaneously. The advantages of bacterial ghosts include the simplicity of the production method, safety, independence from the cold chain, and versatility as a combination vaccine.



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SPOTLIGHT:

By Paul J Clewlow, PhD Pharmaceutical Profiles Ltd, UK

Human Microdosing: Selecting the Right Drug Candidates to take into the Clinic

An unprecedented number of new molecular entities (NMEs) are exiting discovery and entering full development. However, many have less than ideal biopharmaceutical and pharmacokinetic (PK) properties. With so many molecules to choose from, the problem has become one of selection, i.e. which compounds to take forward into full development. Currently, this selection process is made without the aid of *in vivo* human PK or absorption, distribution, metabolism and excretion (ADME) data. More importantly, perhaps, it follows one to two years of intensive and costly non-clinical work, which includes scale-up of the synthesis of the drug active, GMP manufacture and animal toxicology/ADME.

Accelerating Early Clinical Development: the Key to Future Success

Despite extensive non-clinical screening of potential clinical candidates with a wide variety of in silico, in vitro, ex-vivo and animal models, around 30% of NMEs still 'fail' in Phase I clinical testing¹. A high proportion of these product failures can be attributed to unsuitable PK or inappropriate ADME properties, which translate into efficacy or safety issues. In the future, successful pharmaceutical companies will need to determine, at a very early stage, which of their drug candidates is the most likely to pass the necessary human safety and efficacy hurdles to become approved medications. Hence, novel methodologies will have to be utilised to ensure that only the compounds with the best chance of success are taken forward into full development a task that is becoming increasingly difficult as the biopharmaceutical properties of molecules gain in complexity².

Human Microdosing Studies: an Innovative Approach to Drug Development

Researchers and regulators are continually searching for faster and more cost-effective ways of obtaining early human bioavailability data. A recent advance in analytical technology, known as Accelerator Mass Spectrometry (AMS), has made it possible to undertake clinical studies in humans using extremely low drug doses to obtain early PK and ADME data. These doses may be 100 times below the level calculated to yield a pharmacological effect.

AMS is an extremely sensitive analytical technique with the ability to detect drugs down to 10^{-18} (attogram) to 10^{-21} (zeptogram) Moles. A key biomedical application of the technology is in the area of human microdosing studies (also known as 'human phase 0 studies'). In these trials, one or more drug candidates are administered to humans in microgram quantities to obtain early PK and ADME data. The microdosing approach allows the early screening of many more drug candidates in man to ensure that only

optimal compounds are advanced into full Phase I clinical development. Because these studies are undertaken in the ultimate

CANDIDATE SELECTION USING MICRODOSING



target species – man – they offer greater predictability *versus* nonclinical animal and *ex vivo* models. Hence, human microdosing studies offer the promise of improved candidate selection and reduced attrition rates in early clinical development^{3.4}.

A typical human microdosing study involves the administration of microgram quantities of drug candidates, lightly-labelled with 14 Carbon (14 C), to healthy volunteers. Following collection of blood, urine and faeces from each subject, samples are analysed for 14 C content using AMS to determine C $_{\rm max}$, AUC and the terminal half-life of each compound. The data produced enables the selection of the drug candidate with the best PK profile to be taken forward into full Phase I development.

Advantageous European Regulatory Environment for Human Microdosing Studies

In July 2003, the European Medicines Evaluation Agency (EMEA) adopted a position paper on the non-clinical studies required to support clinical studies involving human microdosing⁵. This paper lays out a much-abbreviated non-clinical testing programme compared to a traditional 'first-in-man' Phase I study, namely a single dose, acute toxicology study in male and female rats, (*iv* and human route of administration, using 100 times the proposed human dose), 48 hour cardiovascular study in male and female dogs (*iv*-only, using 100 times the proposed human dose), Ames test (abridged protocol with 2 *Salmonella* strains) and an abridged human lymphocyte chromosome aberration, mouse lymphoma or *in vitro* micronucleus test. The time, cost and material savings that result from the human microdosing study approach allow drug candidates to be screened more quickly and conveniently in the target species – humans.

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NOVEL STARCH BASED MATRICES FOR THE ENCAPSULATION AND CONTROLLED RELEASE OF HEAT SENSITIVE COMPOUNDS PRE-PARED VIA MELT EXTRUSION TECHNOLOGY

Introduction. Especially during the past decades it was seen that the use of encapsulation technology has received a considerable attention for high volume applications in the fields of house hold products, personal care, agriculture, packaging and coatings¹ such as laundry products, cosmetics, CR vitamins, CR probiotics, CR agrochemicals or biological control agents, CR plant hormones or antifungal compounds. However, the environmental concerns, caused by excessive use of organic solvents, and especially the costs associated with conventional matrix forming technologies such as solvent evaporation, emulsion crosslinking, absorption or spray drying and the difficulties in controlling the release of the encapsulants, have prevented the use of these technologies for high volume applications. As a result, for these types of applications, most efforts are presently focused on a specific objective. This objective is application of continuous processing techniques and abundant matrix materials, by which encapsulation can be (cost) effectively and efficiently accomplished, with tailored release properties. Starch is one of the most used matrix materials, due to its favorable properties such as abundance, processability, biodegradability and ease in achieving chemical/physical or enzymatic modifications. It has been reported that with the use of extrusion technology for preparing starch matrices, the above mentioned objectives can be achieved leading to formulations that are optimally beneficial for a wide variety of compounds including heat sensitive and a certain application area².

Processing aspects. Extrusion process as an encapsulation method combines mixing, melting, compressing and forming under relatively low temperature if required, pressure and shear at relatively low moisture or solvent contents. It can be designed to fit a large group of heat sensitive active compounds ranging from volatiles to vitamins, drugs to living cells. A schematic representation of an extruder is shown in Figure 1.



Figure 1. Schematic representation of an extruder.

Most challenges lay in the adjustments of the temperature profiles, combined with the mixing efficiencies and thus designing the devices suitable for the requirements. It was shown² that control of the dispersion behavior during extrusion could be achieved even in case of incompatible active compounds (encapsulants) and matrix polymers (Figure 2).

By Gülden Yýlmaz, ATO B.V., The Netherlands





Figure 2. Hydrophobic active compound encapsulated (size of the dispersed droplets between 0.2-130mm) in a starch matrix prepared via extrusion

Modification of the starch matrix, either chemically, physically or enzymatically, can be incorporated in the encapsulation process and the permeability of the starch matrices can therefore be controlled by means of modifications and structural changes of starch as well as the device morphology. Using extrusion a range of products such as granulates (i.e. 300mm – 1cm), shaped articles, sheets, flakes or gels, can be obtained.

Controlled release from starch matrices prepared via extrusion. The release properties of the active compound that is encapsulated via extrusion in a starch matrix can be tailored by the processing conditions (temperature, shear helping to modify the matrix characteristics, crystallinity or modifications of the starch matrix) and formulation characteristics (other matrix components and load)^{3,4}. Resultantly highly specific barriers and controlled release behavior is achieved on the basis of processstructure-property relationship, using this technology for the production of controlled release devices. One example utilizing the potential of this technology is the encapsulation of amylase in pre-gelatinized potato starch matrices for moisture triggered release of another encapsulant where the release can be fine tuned via the applied enzyme concentration (Figure 3)³. Application of the moisture triggered release systems can be envisaged in the packaging industry

People On The Move

Dr. Joy Dempsey, Research Scientist, CSIRO Industries, Australia

Joy Dempsey is a self-confessed wool scientist; she just loves wool. So how did a wool scientist end up working in the area of controlled release technology? Joy began her career at the University of New South Wales in the School of Wool and Pastoral Science (Bachelor of Science [Wool and Pastoral Science] 1994), and then began researching the delivery of digestive fungi from African animals to Australian sheep so they could better withstand drought conditions at CSIRO Animal Production in Australia. She then returned to the University of New South Wales to complete a Ph.D. on the effect of protected proteins on wool growth in Australian sheep (2000). Afterwards she spent a few years in the Research and Development Department of the Australian Wool Testing Authority Ltd examining wool measurement techniques. In 2002, Joy was given the opportunity to return to CSIRO (Australia's premier scientific research organisation) as a postdoctoral scientist in Livestock Industries in the area of Pharmacology, Bioactive Delivery and Physiological Telemetry. Joy has since begun work in the area of reproductive control in cattle.

Joy has recently worked with some visiting scientists. Prof. Dr. Sevda Senel, Professor in the Department of Pharmaceutical Technology at Hacettepe University in Turkey, visited and shared her expertise on the use of chitosan for drug delivery. A project to transfer her knowledge of human drug delivery to farm animals was devised, as well as examining a suitable application method of a biological agent with anthelmintic properties to livestock to control internal parasites. Joy and Sevda were able to continue the discussions of transfer of animal and human drug delivery technology at the recent CRS meeting in Glasgow. The Shared Concepts in Human and Animal Health was the ideal platform for sharing this information more widely. Joy is also working with Leith Kieser and Rod Walker from Rhodes University in South Africa, members of CRS. They were able to devise a method for the measurement of anthelmintics in blood from sheep.

Joy submitted two papers to the recent CRS meeting, presenting one in the "Shared Concepts of Human and Animal Health" section entitled "Comparison of Novel Anthelmintic Dosing Strategies". This work concentrated on alternative delivery strategies of anthelmintics for control of internal



parasites in sheep. These strategies were designed to prolong the effective life of anthelmintics and delay the onset of resistance by the parasites. She also presented a poster on the "Explorations of Rumen Gases Using Diffusion Characteristics". The ability to measure greenhouse gas production, such as methane and carbon dioxide, in livestock would be a valuable tool for monitoring animal health via digestion and greenhouse gas output.

Joy is now part of the CSIRO Agrifood Top Five Flagship (www.csiro.au). This area has been identified as a National Research Priority for Australia and aims to increase the value of the Australian agribusiness sector. She is investigating the physiological basis for a device for predicting ovulation in cattle, and sees the potential of controlled drug delivery in this area for reproductive control. Timing of artificial insemination is currently by observation of cow behaviour, and she will determine what physiological measurements can be correlated with the timing of ovulation.

Journal of Controlled Release

by David. R. Friend MicroDose Technologies, Inc., U.S.A.

A number of articles covering a range of topics are to appear shortly in the Journal of Controlled Release. In one article, extra- and intracellular delivery of genetic material is examined by Urtti and coworkers. They study the role extracellular polyanionic materials, such as glycosaminoglycans (GAGs), have in limiting the interaction of DNA/cationic complexes with target cells. They conclude that some cell surface GAGs inhibit intracellular transfer of the DNA/cationic complexes.

Park and coworkers describe the effects of ethylene glycolbased polymers (star and dendritic architectures) on the solubilization and controlled release of paclitaxel. They found that these novel polymers were able to increase the water solubility of paclitaxel by 3 orders of magnitude. These solubilizing agents were also effective at controlling the dissolution rate of this poorly water-soluble drug. Novel permeation enhancing polymers are described by Schnürch et al. for the oral delivery of hydrophilic macromolecules. These permeation enhancing polymers contain thiol groups to inhibit protein tyrosine phosphatase, which is involved in controlling the closing of tight junctions in the gastrointestinal tract. Data are presented demonstrating the ability of these polymers to improve the oral bioavailability of heparin insulin in rats.

Another article due to appear soon covers the development and evaluation of a dissolution system that can detect the food effect on a polysaccharide-based matrix dosage form. It has proven difficult to simulate the conditions found *in vivo* following administration of a dosage form in the fed state using standard USP dissolution apparatus (Type 1 or 2). Thus, Tobin and coworkers have developed a method using USP apparatus Type 3 (Bio-Dis) in conjunction with materials (fats such as peanut oil).

CHAPTER NEWS 4th Annual Meeting of the Israeli Chapter of CRS (ICRS)

In September 2003 the 4th Annual Meeting of the ICRS was held in Haifa. This very successful two-day meeting took place at the Meridian Hotel where participants were treated to a splendid view of the Mediterranean Sea. This conference brought together a broad scientific community from both academia and industry with approximately 170 participants. The spirit of this important event was characterized by motivation, enthusiasm, engagement and an open and friendly atmosphere that fostered the establishment of contacts and the exchange of scientific and personal information. The attractive meeting program consisted of presentations on basic science, new industrial developments, guidelines for start-up companies and an introduction to the intellectual property world. Numerous lectures and posters, including invited speakers from abroad, presented a whole spectrum of subjects from the fields of oral, transdermal, pulmonary and intracellular delivery, pharmacokinetics, pharmacodynamics, new delivery systems and their mechanisms of action. The meeting was sponsored by the CRS and sections of the Israeli pharmaceutical industry.

The first day of the conference was divided into four sessions. The keynote speaker was Professor Gerrit Brochard from Leiden University and in his talk Professor Borchard discussed the development of colloidal carriers for pulmonary DNA vaccination. Further presentations in this session focused on the possibility of applying ultrasound to gene delivery and new approaches for prophylaxis against organophosphate poisoning using bioscavengers, the last presented by Prof. Rimona Margalit from Tel-Aviv University. The session was concluded with Prof. Daniel Cohn's lecture on in situ generated thermo-responsive biomedical systems.

Transdermal drug delivery was covered in the second session and initiated with a lecture given by Prof. Elka Touitou of the Hebrew University of Jerusalem, on new developments in the field with a special focus on ethosomes, fluid phospholipid vesicles for enhanced passive transdermal delivery, and their mechanism of action. Other issues discussed in this session included the delivery of drugs across the skin using the microinvasive technique of radio-frequency ablation and the

By Prof. Elka Touitou, President ICRS The Hebrew University of Jerusalem, Israel



Israeli CRS Chapter Annual Meeting attendees Dr. A. Pinhasi, Dr. H. Rackur, Prof. G. Brochard, Prof. R. Azhari, Dr. Y. Sela, Prof. E. Touitou, and Prof. A. Rubinstein

use of ultrasound as a means of active drug delivery as well as a diagnostic tool. This last paper was presented by Prof. Joseph Kost of Ben-Gurion University.

Following the lunch break, Dr. Helmut Rackur from Trave Pharma GmbH, Germany launched the third session of the conference with a talk on the enhanced solubility of nifedipine on complexation with cyclodextrin for controlled release formulations of this drug. Several aspects on the modeling of nutrient release from polymercoated fertilizers were further discussed. This session was concluded by Dr. Itschak Lamensdorf, from PharmaSense Inc., who addressed the topic of antisense delivery across the blood brain barrier.

The fourth session began with a presentation on the use of nanothechnology for the improved pharmacokinetic performance of macrolide antibiotics. Within this session, which also included three short oral presentations by graduate students, Dr. Zeev Elkoshi of Teva Pharmaceutical Industries presented a paper on bioequivalence studies for oral modified release products.

(Chapter continued on page 17)





The goal of a Phase I programme is to provide information regarding a drug's PK and pharmacodynamic (PD) properties to design a wellcontrolled and valid Phase II patient programme.

'First-in-man' studies, as the name implies, are the first time new drugs are tested in human subjects and sit on the interface between the pre-clinical and clinical development phases. Whilst 'first-in-man' studies provide valuable information on PK, PD, safety and efficacy, even more crucial data could be obtained from these studies using

AMS through the co-administration of lightly-labelled ¹⁴C drug with the test drug to obtain both PK data (using liquid chromatography-mass spectrometry/mass spectrometry) and ADME data (using AMS). Hence, the power of AMS could add considerable value to 'first-in-man' studies.

Conclusions

The recent adoption of a position paper by the EMEA, describing an abbreviated non-clinical safety package, has set the regulatory framework for the safe and ethical use of human microdosing studies to acquire very early PK/ADME data in man. These human Phase 0 studies offer the promise of providing pivotal early data for drug candidates in man, the ultimate target species, and can be used to greatly enhance the decision-making process at the pre-clinical/clinical interface. It is prudent to select the right molecule at this early stage before a great deal of time, money and resources are devoted to taking forward a potential drug into a Phase I study. By selecting the optimal molecules to advance into full development, there should be fewer failures at Phase I and a smaller number of healthy volunteers studied to select the right dosage for Phase II studies in patients. Ultimately, new drugs could be brought to market in a more efficient and cost-effective fashion than at present.

References

- 1. I. R. Wilding, Injecting innovation into the drug development process, SCRIP Magazine, October 2002
- I. R. Wilding, Evolution of the biopharmaceutics classification system (BCS) to oral modified release (MR) formulations; what do we need to consider? *Eur. J. Pharm. Sci.* 8: 157-159, 1999
- 3. G. Lappin and R. C. Garner, Big physics, small does: the use of AMS and PET in human microdosing of development drugs, *Nature Reviews Drug Discovery, Vol. 2, March 2003, 233 240*
- N. Serapa, Early human microdosing to reduce attrition in clinical drug development, *American Pharmaceutical Outsourcing, Sept/Oct 2003*
- 5. Position paper on non-clinical safety studies to support clinical trials with a single microdose, EMEA, London, 23 January 2003

(C&DP continued from page 13)

(e.g. sensors) and e.g. controlled release of antifungal agents in the presence of moisture. Another example is the biodegradable (based on Solanyl Ò) flower pots with controlled release fertilizer function. Other examples include encapsulated of volatile compounds such as essential oils, flavors, perfumes, herbicides, pesticides, pheromones, encapsulated vitamins, drugs and bacterial cells^{3,5}. In these studies, performed with model heat sensitive compounds it has been shown that the release profile (zero-order, Figure 4, to first-order) as well as the release rate can be tuned.



Figure 3. Triggered release of diacetyl from a starch matrix as a function of the enzyme concentration



Figure 4. Zero-order carvone release from starch based gels as a function of starch concentration

To conclude, these studies show the large potential of extrusion technology and starch for encapsulation and controlled release of even highly heat sensitive compounds, for consumer and diversified products as well as for the pharmaceutics industry.

References:

- 1. U.R. Pothakamury, G.V. Barbosa-Cánovas, *Trends in Food Science & Technology*, 1995, 6, 397-406.
- 2. G. Yýlmaz, R.O.J. Jongboom, H. Feil, W.E. Hennink,. *Carbohydrate Polymers*, 2001, 45, 403-410.
- G. Yýlmaz, G. Öngen, R.O.J. Jongboom, H. Feil, C. van Dijk, W.E. Hennink, *Biomacromolecules*, 2002, 3, 305-311.
- 4. G. Yýlmaz, R.O.J. Jongboom, H. Feil, W.E. Hennink, In *Proc. Int. Symp. Control. Rel. Bioact. Mater.*, 2001.
- 5. G. Yýlmaz, R. O. J. Jongboom, H. Feil, In *Proc. Int. Symp. Control. Rel. Bioact. Mater.*, 2002.

(Chapter continued from page 15)

The concluding event in the scientific program of the first conference day was a poster session. It was a well-organized session with many original papers and enjoyed participation by nearly all the conference attendees. The presentations focused on research in the basic sciences, delivery systems and new therapies. Discussions at the poster session were so lively and long that they ran well beyond the official closing time, and in the end participants had to be encouraged to leave. New start-up companies such as Transpharma, NTT and PharmaSense presented data on their drug delivery technologies. Four student presentations were selected to receive awards. One of the students, Maayan Duvshani-Eshet, was awarded a ticket to the next CRS 2004 Annual Meeting in Hawaii.

The second day was devoted to the Start-up opportunities in Israel. Israel is an important center for Start-ups, where interesting new ideas in the field of pharmaceutical, food, cosmetic, veterinary and medical research are launched. In this part of the meeting an industrial perspective on drug delivery system development was presented. During this session experts provided an introduction to intellectual property issues, and tips and guidelines for start-up companies. Mr. Reuven Ron from the Yissum Company, housed within The Hebrew University of Jerusalem discussed academia-industry relationships in biotechnology. Other speakers in this session gave interesting examples of industrially oriented developments in the field. The paper presented by Prof. Jean-Paul Marty from the University of Paris South focused on interesting treatments for nail-associated diseases. This paper was followed by The Hebrew University's Prof. Nissim Garti's talk on nanosized selfassembling structures for the solubilization and improved reactivity of nutraceuticals. The concluding remarks were made by Dr.



Anat Perex, Best Paper Prize Recipient; Prof. Roza Azhari, Treasurer; and Dr. Yoram Sela, Past President

Yoram Sela, the past president of the Israeli chapter of CRS.

Highly interactive discussions were a characteristic of the entire meeting with discussions being initiated sometimes during the course of a presentation when speakers asked for comments from the participants mid way between their presentations.

Various aspects of controlled drug release were not only discussed within a scientific setting but also in a social setting. For this purpose the Gala dinner was organized at the Meridian Hotel as a pleasant conclusion of the first day's sessions. During this event the winners of 1998 and 2001 Outstanding Poster Presentations received their awards. The past president and the organizing committee, especially Prof. Roza Azhari, the treasurer of the Israeli chapter of the CRS were recognized and thanked for their efforts and contributions to the success of the meeting.



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FEDERAL PROSECUTORS PREDICT CRACKDOWN ON PHARMACEUTICAL INDUSTRY The new Medicare drug benefit is certain to lead to heightened scrutiny of the pharmaceutical industry, warn government prosecutors. "The more the government pays, the more scrutiny there is," says Assistant U.S. Attorney Michael Loucks, in the latest issue of Rx Compliance

Report, published Nov. 24, 2003.

"Investigations into the pharmaceutical industry are keeping us busier than you can imagine," warns Loucks. Meanwhile the HHS Office of Inspector General tells Rx Compliance Report that its current open cases into pharmaceutical sales and marketing practices will take years to resolve.

DRUG PRICING BECOMES TOP GOVERNMENT PRIORITY:

Spiraling drug costs in state Medicaid programs have led nine states to file suit against drug companies for allegedly manipulating the AWP. The list of companies charged in similar suits, and the list of states joining those suits, will quickly grow in the months ahead, predicts John Guthrie, Director of Ohio's Medicaid Fraud Control Unit, in the latest issue of Rx Compliance Report.

According to Guthrie, the country's state Attorneys General are also heavily involved in a range of drug pricing investigations involving off-label promotion, Medicaid drug rebates, PBMs, Hatch-Waxman and DTC advertising. He says that scrutiny extends to manufacturers, wholesalers, pharmacy benefit managers (PBM), group purchasing organizations (GPO), insurance plans, HMOs, doctors, and retail pharmacies, among others.

INSMED PRESENTS POSITIVE DATA ON ANTICANCER DRUG CANDIDATE TO AACR-NCI-EORTC

Insmed Incorporated (Nasdaq-NMS :INSM) (Nasdaq: INSM) reported that data from recent studies of the Company's proprietary anti-cancer compound, recombinant human insulin-like growth factor binding protein-3 (rhIGFBP-3), will be presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, November 17-21, at the Hynes Center in Boston.

These studies conducted in the laboratory of Dr. Michael Pollak of McGill University were designed to further examine the radiosensitization properties of rhIGFBP-3 in vitro and to evaluate the inhibitory effects of rhIGFBP-3 administration on tumor growth in vivo.

The results of this study, published in the abstract titled, "IGFBP-3 Enhances Sensitivity to Radiation Therapy In Vitro and Inhibits Tumor Formation In Vivo in a Model of Human Breast Cancer," demonstrated the following:

- 1. As a single agent, rhIGFBP-3 significantly inhibited the growth of breast and colorectal carcinoma cells 55% and 49%, respectively (p<0.01).
- 2. rhIGFBP-3 significantly enhanced the effect of radiation by demonstrating a decrease in the survival fraction in both breast and colorectal carcinoma cells.
- 3. rhIGFBP-3 treatment prevented tumor development in 75% of the mice injected with human breast cancer cells, rhIGFBP-3 significantly inhibited tumor volume in the treated mice that did develop tumors by 67% compared to control (p<0.05).

RX COMPLIANCE REPORT SAYS SCRUTINY OF PHARMA IS EXPECTED TO GROW UNDER THE NEW MEDICARE DRUG BENEFIT

Congress passed a new drug benefit last week that marks the beginning of the end of the highly controversial average wholesale price (AWP) methodology that is currently used to pay for drugs covered by Medicare and Medicaid.

"These changes will have a major impact on the pricing and compliance activities of the entire pharmaceutical industry," says Paul Kalb, Chair of the Health Care Group at Sidley Austin Brown & Wood.

"It will literally take companies years to work through the marketing, pricing, and regulatory implications of this bill, which has almost as significant Medicaid implications for pharma companies as it does Medicare implications," says Bill Sarraille, a Partner with Sidley Austin, in the Nov. 24, 2003 issue of Rx Compliance Report, Nov. 24, 2003.

DRUG PRICING BECOMES TOP GOVERNMENT PRIORITY:

Spiraling drug costs in state Medicaid programs have led nine states to file suit against drug companies for allegedly manipulating the AWP. The list of companies charged in similar suits, and the list of states joining those suits, will quickly grow in the months ahead, predicts John Guthrie, Director of Ohio's Medicaid Fraud Control Unit, in the latest issue of Rx Compliance Report.

MEDTOX Receives ISO Certification and Is Granted New Patent for 'On-Site Drug Testing Method'

ST. PAUL, Dec. 4 /PRNewswire-FirstCall/ — MEDTOX Scientific, Inc. (<u>AMEX:TOX</u>), announced today that its subsidiary MEDTOX Diagnostics, Inc., has developed and implemented a Quality System to satisfy the needs of its customers and to improve quality management of the Company.

In October, MEDTOX Diagnostics, Inc., contracted TUV Rheinland to perform a certification audit to EN ISO 13485:2000 and a registration audit to CMDCAS ISO 13485 (Canadian Medical Devices

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capsid proteins are surrounded by a lipid bilayer derived from the plasma membrane of the host cell that produced the virus. Protruding from the lipid bilayer are virus envelope proteins, proteins that mediate important early interactions between the virus and its host cell. Retroviruses are produced using a two-part system composed of a packaging cell line and a retroviral vector. Packaging cell lines are genetically engineered to express all of the proteins necessary to form retrovirus particles. Retrovirus vectors encode the gene of interest, regulatory sequences to drive its expression, and a packaging sequence to ensure the genomes of the viruses are actively incorporated into retrovirus particles.

To produce retrovirus stocks, packaging cells are transfected with the retroviral vector, then two days later the cells incubated overnight with fresh cell culture medium. Within the transfected cells, viral proteins are produced and assembled around the genome of the virus to form retroviruses that bud from the surface of the cell into the surrounding cell culture medium (Figure 1). The virus-laden medium is then collected and used to transfer genes to target cells. The process of gene transfer (transduction) requires the completion of a complex series of steps that begins with the transport of the virus particle to the surface of the cell where the envelope proteins of the virus interact with their cognate cellular receptors. After the virus binds to its receptor, the lipid bilayers of the virus and cell fuse, releasing the RNA genome of the virus and associated virus proteins and enzymes into the cytosol of the cell. After the virus enters the cytosol, the RNA of the virus is reverse transcribed into DNA, which is transported to the nucleus and integrated into the chromosomal DNA of the host cell. Once integrated, the viral DNA is stable and inherited by daughter cells, and its expression leads to the synthesis of the therapeutic protein (Figure 2).



Figure 1: Production of recombinant retroviruses by packaging cell lines. Recombinant retroviruses are produced by transfecting packaging cells, genetically modified to express all of the proteins necessary to form a retrovirus particle, with plasmid DNA that encodes the therapeutic gene(s) of interest, the regulatory sequences that drives their expression, and a packaging sequence (y) that ensures the RNA genomes of the viruses are efficiently incorporated into the virus particles. The virus capsid proteins self-assemble around the RNA

genomes that contain the packaging sequence, then bud from the surface of the cell into the surrounding cell culture medium. In the process of budding, the virus particles incorporate a lipid bilayer, which contains the virus envelope proteins and other 'passenger' cellular proteins, from the plasma membrane of the cell.



Figure 2. Transduction of target cells by recombinant retroviruses. Cells are transduced by incubation with stocks of retroviruses. Retroviruses diffuse to the surface of the cells, and then bind to them via poorly defined non-specific interactions between the surface of the virus and the cell. The envelope proteins of the virus then interact with their cognate receptors on the surface of the cell, initiating fusion between the lipid bilayer of the virus and the plasma or endosomal membrane of the cell, releasing the internal components of the virus to the cytosol. In the cytoplasm, the RNA genomes of the viruses are reverse transcribed to DNA, then transported to the nucleus and integrated into the chromosomal DNA of the cell, after which the therapeutic gene(s) are expressed.

Current methods to produce and deliver retroviruses to cells suffer from a number of limitations that must be addressed before retroviruses are likely to be used routinely in the clinic. For convenience, we have grouped these limitations into three areas: (1) processing, (2) binding to cells, and (3) post-binding steps of transduction. Each of these stages can potentially benefit from advances that are currently being made in the field of non-viral gene delivery.

Retrovirus particles are difficult to concentrate to the levels necessary to achieve the desired therapeutic effect because they are fragile and easily inactivated by most standard processing methods. Gentle concentration methods that do not inactivate the viruses have been developed that concentrate them several-fold by filtering them through porous membranes [3-6]. Unfortunately, retrovirus stocks concentrated by these methods often do not transfer significantly more genes to cells than the original unconcentrated virus stocks. These surprising results are explained, in part, by the presence in virus stocks of high molecular weight inhibitors of retrovirus transduction [7-9]. For example, high molecular weight proteoglycans are present in virus stocks, inhibit transduction, and are not able to pass through the semi-permeable membranes of the devices used to concentrate the virus stocks. Instead, they are coconcentrated with the virus particles [9]. As a result, concentrated virus stocks contain high levels of retrovirus particles and inhibitors of transduction, with the net result being little, if any, improvement in the efficiency of gene transfer.

Novel methods are needed that can rapidly concentrate and purify retroviruses without inactivating them or coconcentrating them with inhibitors. For example, we have shown that charged polymers can be used to rapidly purify and concentrate retroviruses. When mixed together, retroviruses and the oppositely charged polymers polybrene and chondroitin sulfate C selectively form complexes with each other that can be concentrated and purified by a rapid, low-speed centrifugation step [10, 11]. Although gene transfer was enhanced several-fold, further increases in gene transfer have been hampered by the inability to separate the purified virus particles from the polymer complexes. To overcome this limitation, it would be beneficial to develop "intelligent" polymers that could interact specifically and reversibly with retrovirus particles. Intelligent polymers are classes of polymers that have recently been developed that are responsive to subtle changes in the environment, such as with temperature and pH [12]. Intelligent polymers could be designed to precipitate viruses by preferentially interacting with specific sites on the surface of the virus. Precipitated viruses could be concentrated, resuspended under conditions that induce the polymers to dissociate from the viruses, then the viruses purified from the dissociated polymers and stored for later use. Approaches such as these have been successfully used to purify enzymes and proteins, and may provide a powerful new approach for processing virus particles [12].

Improved methods to process retroviruses would increase the efficiency, but not the selectivity, of gene transfer. Selective gene transfer is also an important goal, particularly for *in vivo* applications, in order to maximize the likelihood of achieving the desired therapeutic effect, and to minimize the likelihood of undesired side effects caused by the inappropriate expression of the therapeutic gene in innocent bystander cells. Unfortunately, retroviruses are derived from wild-type viruses that are optimally designed, by millions of years of evolution, to efficiently infect multiple cell types. Several approaches have been taken to modify, restrict, or control the types of cells that retroviruses are able to infect (i.e., tropism). For example, wild-type retrovirus envelope proteins have been replaced with envelope proteins derived from viruses that bind to the desired cellular receptor, or they have been genetically or chemically modified to contain a domain or functional group that will specifically bind to a receptor that is uniquely expressed by the cell type of interest [13-18]. Unfortunately, these methods, which alter the tropism of the viruses by altering the structure of their envelope proteins, often reduce or eliminate the ability of the envelope proteins to cause the virus to fuse with the cell. As a result, viruses modified in this way often transduce cells too inefficiently to be of any practical use for human gene therapy.

In retrospect, these approaches may have been fundamentally flawed because they assumed that retrovirus binding is

dictated by interactions between the envelope protein of the virus and its cellular receptor. In fact, recent studies have demonstrated that retroviruses bind to cells via an envelope protein independent process, and that envelope receptor interactions are required only for post-binding steps of infection (i.e., fusion between the virus and cell) [19, 20]. Therefore, strategies to create targeted retroviruses must first eliminate their ability to bind non-specifically to cells. One approach might be to coat virus particles with a 'stealth' polymer such as polyethylene glycol (PEG), similar to approaches used to increase the *in vivo* half-life of proteins, bioactive molecules, and other pharmaceuticals [21, 22]. PEG has previously been used to protect non-viral vectors and virus particles from *in vivo* immunogenic reactions and complement inactivation, so it seems likely that viruses could also be PEGylated to prevent them from binding nonspecifically to non-targeted cell types [23, 24]. Once nonspecific binding is eliminated, the virus-binding 'stealth' polymers could be modified to display functional groups that would confer upon the viruses the ability to bind to receptors that are expressed only by the targeted cell type. Importantly, PEGylation would need to proceed in such as way as to preserve the fusogenic activity of the envelope proteins to ensure that post-binding steps of infection (i.e., fusion and entry) remained efficient.

In many cases inefficient post-binding steps of infection limit the efficiency of retrovirus transduction. For example, most

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retroviruses cannot transduce polarized lung epithelial cells via their apical surface, an important target for cystic fibrosis and other gene therapies of the lung. Retroviruses bind to these cells but are unable to fuse with them because the cells do not express receptors for the virus on their apical surfaces. Materials are needed that can help retroviruses complete postbinding steps of transduction. For example, materials are needed to replace, or augment, the function of the virus envelope proteins. Perhaps pH sensitive intelligent polymers could be designed that would coat the virus particle and that would, upon entering a low pH intracellular compartment, undergo a conformational change to reveal fusogenic functional groups that would induce the virus to fuse with the endosomal membrane of the cell [25]. Post-binding steps of transduction other than fusion also limit retrovirus transduction. For example, retroviruses require cells to be actively dividing, and lentiviruses require cells to be activated, in order to successfully transduce cells [26]. Polymers could be used to modify the surfaces of viruses with growth factors or other substances that would bind to and activate the host cell, increasing its susceptibility to post-binding steps of infection.

In summary, viral vectors are currently the only way to efficiently and permanently modify the chromosomal DNA of cells. Because our starting point for developing viral vectors begins with the sub-optimal 'design' of wild-type viruses, significant advances in virus processing and delivery are needed to improve the efficiency of gene transfer. Most efforts to overcome these limitations have been conducted by members of the 'viral-vector' community and have centered on the use of traditional molecular biology approaches to alter virus structure and function. These efforts have improved viral-mediated gene transfer, but incorporating some of the ideas and approaches being developed by the 'non-viral' community would likely accelerate our rate of progress. We invite members of both communities to work together towards this goal, and towards the broader goal of improving all gene transfer technologies.

REFERENCES

- 1. C. E. Thomas, A. Ehrhardt, M. A. Kay, Progress and problems with the use of viral vectors for gene therapy, Nat Rev Genet 4 (2003) 346-358.
- G. L. Buchschacher, Jr., F. Wong-Staal, Development of lentiviral vectors for gene therapy for human diseases, Blood 95 (2000) 2499-2504.
- 3. N. E. Bowles, R. C. Eisensmith, R. Mohuiddin, M. Pyron, S. L. Woo, A simple and efficient method for the concentration and purification of recombinant retrovirus for increased hepatocyte transduction in vivo, Hum Gene Ther 7 (1996) 1735-1742.
- M. Makino, G. Ishikawa, K. Yamaguchi, Y. Okada, K. Watanabe, Y. Sasaki-Iwaki, S. Manabe, M. Honda, K. Komuro, Concentration of live retrovirus with a regenerated cellulose hollow fiber, BMM, Arch Virol 139 (1994) 87-96.
- M. McGrath, O. Witte, T. Pincus, I. L. Weissman, Retrovirus purification: method that conserves envelope glycoprotein and maximizes infectivity, J Virol 25 (1978) 923-927.
- R. W. Paul, D. Morris, B. W. Hess, J. Dunn, R. W. Overell, Increased viral titer through concentration of viral harvests from retroviral packaging lines, Hum Gene Ther 4 (1993) 609-615.
- J. M. Le Doux, J. R. Morgan, M. L. Yarmush, Differential inhibition of retrovirus transduction by proteoglycans and free glycosaminoglycans, Biotechnol Prog 15 (1999) 397-406.

- J. M. Le Doux, J. R. Morgan, M. L. Yarmush, Removal of proteoglycans increases efficiency of retroviral gene transfer, Biotechnol Bioeng 58 (1998) 23-34.
- 9. J. M. Le Doux, J. R. Morgan, R. G. Snow, M. L. Yarmush, Proteoglycans secreted by packaging cell lines inhibit retrovirus infection, J Virol 70 (1996) 6468-6473.
- B. Zhang, H. Q. Xia, G. Cleghorn, G. Gobe, M. West, M. Q. Wei, A highly efficient and consistent method for harvesting large volumes of high-titre lentiviral vectors, Gene Ther 8 (2001) 1745-1751.
- 11. J. M. Le Doux, N. Landazuri, M. L. Yarmush, J. R. Morgan, Complexation of retrovirus with cationic and anionic polymers increases the efficiency of gene transfer, submitted to Human Gene Therapy (2001)
- 12. A. S. Hoffman, Bioconjugates of intelligent polymers and recognition proteins for use in diagnostics and affinity separations, Clin Chem 46 (2000) 1478-1486.
- S. T. Chen, A. Iida, L. Guo, T. Friedmann, J. K. Yee, Generation of packaging cell lines for pseudotyped retroviral vectors of the G protein of vesicular stomatitis virus by using a modified tetracycline inducible system, Proc Natl Acad Sci U S A 93 (1996) 10057-10062.
- 14. J. Reiser, Production and concentration of pseudotyped HIV-1based gene transfer vectors, Gene Ther 7 (2000) 910-913.
- 15. H. Neda, C. H. Wu, G. Y. Wu, Chemical modification of an ecotropic murine leukemia virus results in redirection of its target cell specificity, J Biol Chem 266 (1991) 14143-14146.
- T. J. Gollan, M. R. Green, Redirecting retroviral tropism by insertion of short, nondisruptive peptide ligands into envelope, J Virol 76 (2002) 3558-3563.
- J. A. Reddy, D. W. Clapp, P. S. Low, Retargeting of viral vectors to the folate receptor endocytic pathway, J Control Release 74 (2001) 77-82.
- N. Kasahara, A. M. Dozy,Y. W. Kan, Tissue-specific targeting of retroviral vectors through ligand-receptor interactions, Science 266 (1994) 1373-1376.
- 19. M. Pizzato, S. A. Marlow, E. D. Blair, Y. Takeuchi, Initial binding of murine leukemia virus particles to cells does not require specific Env-receptor interaction, J Virol 73 (1999) 8599-8611.
- S. Sharma, A. Miyanohara, T. Friedmann, Separable mechanisms of attachment and cell uptake during retrovirus infection, J Virol 74 (2000) 10790-10795.
- Y. Inada, M. Furukawa, H. Sasaki, Y. Kodera, M. Hiroto, H. Nishimura, A. Matsushima, Biomedical and biotechnological applications of PEG- and PM-modified proteins, Trends Biotechnol 13 (1995) 86-91.
- 22. R. Mehvar, Modulation of the pharmacokinetics and pharmacodynamics of proteins by polyethylene glycol conjugation, J Pharm Pharm Sci 3 (2000) 125-136.
- H. Kobayashi, S. Kawamoto, T. Saga, N. Sato, A. Hiraga, T. Ishimori, J. Konishi, K. Togashi, M. W. Brechbiel, Positive effects of polyethylene glycol conjugation to generation-4 polyamidoamine dendrimers as macromolecular MR contrast agents, Magn Reson Med 46 (2001) 781-788.
- 24. M. A. Croyle, N. Chirmule, Y. Zhang, J. M. Wilson, "Stealth" adenoviruses blunt cell-mediated and humoral immune responses against the virus and allow for significant gene expression upon readministration in the lung, J Virol 75 (2001) 4792-4801.
- 25. B. Jeong, A. Gutowska, Lessons from nature: stimuli-responsive polymers and their biomedical applications, Trends Biotechnol 20 (2002) 305-311.
- R. E. Sutton, M. J. Reitsma, N. Uchida, P. O. Brown, Transduction of human progenitor hematopoietic stem cells by human immunodeficiency virus type 1-based vectors is cell cycle dependent, J Virol 73 (1999) 3649-3660.

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Conformity Assessment System). The scope of the audit included the activities of Design, Development, Manufacture and Distribution of Point-Of-Collection diagnostic screening devices for drugs of abuse and other testing. Processes in various departments were audited to verify conformity to the quality standards and requirements.

The audit findings concluded that MEDTOX Diagnostics furnished proof that it maintains a quality management system fulfilling the requirements of EN ISO 13485 and CMDCAS ISO 13485. Quality Systems - Medical Devices and ISO 9001:2000 - Quality Management Systems - Requirements. The audit report states, "Management documented its commitment to implement and maintain the quality system by approval of the Quality Manual. The quality policy and the defined quality objectives were disseminated through all levels of the organization. The company implemented and maintained procedures and processes to achieve defined quality objectives. Personnel on all levels of the organization had the necessary awareness of the quality management system." "During the audit, no deviation was found."

MEDTOX Diagnostics has been issued the TUV Rheinland Product Safety GmbH quality system certificate to EN ISO 13485:2000 and the TUV Rheinland of North America Inc., quality system certificate to ISO 13485 under CMDCAS.

On November 25, 2003, the United States Patent and Trademark Office granted MEDTOX a business method patent for its "On-Site Drug Testing Method," U.S. Patent No. 6,653,139. This is a continuation of application Ser. No. 09/ 358.340, filed on Jul. 21, 1999, and now U.S. Pat. No. 6,376,251, issued on Apr. 23, 2003, which is based on provisional application No. 60/118,452 filed Feb. 3, 1999, and claims priority therefrom. MEDTOX believes this patent to be a significant addition to its growing intellectual property portfolio. There are approximately 25 million laboratory drug screens for drugs of abuse performed annually in the U.S. workplace market. In 2003, MEDTOX will perform between 1.5 and 2 million of those lab based DAU screens. In the last three years, there has been an increasing transition from laboratory screening for DAU to on-site or point-of-care (POC) screening with disposable devices. MEDTOX will

provide its workplace customers over 750,000 POC devices in 2003, of which an increasing number are purchasing the patented PROFILE-II Test System[®], that includes the patented PROFILE®-II A device with its on board adulterant test strip. The growing transition to POC screening will increase the value of these patents to MEDTOX and its strategic partners. Additionally, MEDTOX is unique in that it operates both a federally certified laboratory and a POC device manufacturing plant. This allows the Company to provide a seamless transition for clients moving from one model of screening to the other.

Delivery of the PROFILE-II Test System[®] is further enhanced by WebTox(TM), MEDTOX's proprietary web platform and interactive program management system. By placing the power of information directly in the hands of our customers, through the Internet, WebTox integrates point-of-collection screening and rapid laboratory confirmations with a feature-rich data reporting and tracking system. When fully implemented, WebTox will provide customers with testing results and tracking, chain-ofcustody verification, supplies ordering capability, statistical reporting, and sample collection and site location information.

The "On-Site Drug Testing Method" patent contains 29 claims applicable to a system for screening (testing) of other sample types in addition to urine, such as oral fluids, blood and serum. MEDTOX believes this patent may have applications beyond workplace drugs of abuse testing. MEDTOX is currently working with its intellectual property counsel to implement its strategic approach to maximizing opportunities for itself and its strategic partners surrounding this patent. In addition to patent protection for the onsite testing method, the United States Copyright Office has issued a registration for MEDTOX's copyright(s) in material relating to the method of its application and training. MEDTOX has sought the broadest protection possible for its proprietary on-site testing method.

Gean-Edwards Introduces New 'Definitely Diabetic®' Socks PRINCETON, Wis., Dec. 4 / PRNewswire/ — The Gean-Edwards Company has introduced a line of premium quality socks designed for people with diabetes. The "Definitely Diabetic®"socks were developed at the request of some of the company's customers with diabetes who subsequently tested them and proclaimed them to be ideal for their special needs.

"Our newest style features Outlast®, a high tech fiber that regulates temperature, and a seamless toe," says Elizabeth Skrypczak, Vice President and Product Manager. "The line also has our signature non-constricting, stay-in-place fit that many people with diabetes look for in socks."

Definitely Diabetic socks can be purchased online at www.geanedwards.com, 800-558-6565. The company is also seeking retail distribution outlets. The Definitely Diabetic socks retail for \$7.00 to \$16.00.

The Definitely Diabetic sock line offers six styles, two men's sizes, two women's sizes, four fiber blends, and up to six standard colors. Other important features of the Definitely Diabetic socks include a soft stretch cuff which provides a comfortable fit for those with circulatory problems. Contoured heels prevent the socks from riding down in the shoe. Further, cushioned soles help relieve pressure on the heels and balls of the feet, adding comfort and shock absorbency.

"Typically, our wholesale customers for our high-performance socks are pro shops and better sporting goods stores," says Skrypczak. "Since this is a different market, we are exploring new retail outlets for our Definitely Diabetic line. We know it's a viable market; the response from our online shoppers has been absolutely phenomenal."

The Gean-Edwards Company has been making top quality golf socks in the United States since 1939. After the golf industry decline in 2001, the company diversified and launched several new sock lines for other sports and casual wear.

Ranbaxy Is Granted Approval to Market Amoxicillin and Clavulanate Potassium Tablets USP (Chewable) PRINCETON, N.J., Dec. 4 / PRNewswire/ — Ranbaxy Pharmaceuticals Inc. (RPI), a wholly owned subsidiary of Ranbaxy Laboratories Limited (RLL), announced today that RLL has received tentative approval from the Office of Generic Drugs of the U.S. Food and Drug Administration to manufacture and market Amoxicillin and

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Clavulanate Potassium Tablets USP (Chewable), 200 mg/28.5 mg (base) and 400 mg/57 mg (base). The Division of **Bioequivalence has determined Ranbaxy's** Amoxicillin and Clavulanate Potassium Tablets USP (Chewable), 200 mg/28.5 mg (base) and 400 mg/57 mg (base), to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Augmentin[®] Chewable Tablets, 200 mg and Augmentin Chewable Tablets, 400 mg, respectively, of GlaxoSmithKline). Total market sales for Amoxicillin and Clavulanate Potassium Chewable Tablets were \$31.4 million (IMS - MAT: September 2003).

Augmentin[®] is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed as follows: Lower **Respiratory Tract Infections, Otitis** Media, Sinusitis, Skin and Skin Structure Infections, and Urinary Tract Infections. While Augmentin® is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to Augmentin[®] treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and (beta)-lactamase-producing organisms susceptible to Augmentin® should not require the addition of another antibiotic. Because amoxicillin has greater in vitro activity against Streptococcus pneumoniae than does ampicillin or penicillin, the majority of S. pneumoniae strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin and Augmentin[®].

According to Jim Meehan, Vice President of Sales and Marketing for RPI, "Amoxicillin and Clavulanate Potassium Chewable tablets will be made available nationwide through retail pharmacies, wholesalers and distributors as quickly as inventories can be reached to support the needs of the U.S. Healthcare system. We now offer a complete line of formulations for this anti-infective agent that will meet the needs of patients and prescribers at an affordable price."

BioAlliance Adds biothink® Network to Benefit Program; biothink Momentum and Subscription Base Growing ROCKVILLE, Md., Dec. 4 / PRNewswire/ — biosciences® Corporation and the Technology Council of Maryland (TCM) announced today an agreement that will provide marketing page 24 support of biosciences Corporation's lead product, biothink. biothink — a proprietary internet based solution to accelerate clinical research and medical product development projects — will become part of the BioAlliance member benefit program and be marketed broadly to the regional biotech community. biothink will be supported in its marketing effort in a five state Mid-Atlantic region by Maryland BioAlliance, the biotechnology network within TCM.

biothink[®] is the first independent network service allowing industry to "outsource the search" for expert knowledge in the biosciences. biothink[®] enables the knowledge and expertise of bioscience service providers (e.g. Clinical Investigators, Consultants and Clinical Research Organizations (CROs)) to be quickly and efficiently identified and matched with the needs of bioscience service customers (e.g. Biotech, Medical Device and Pharmaceutical companies) accelerating specific product development requirements.

"Access to knowledge resources in the biosciences is complicated, time consuming and expensive because of the highly diverse yet specialized market," states biosciences Corporation President, Edward R. Gubish, PhD. "Conventional knowledge recruitment hinders the pace of product development. We are committed to providing services that will accelerate clinical research."

Dyan Brasington, President of TCM stated, "Our members will have the opportunity to utilize the web-based biothink Network to connect with qualified and authenticated product development and clinical expertise."

Matt Gardner, Director of Maryland BioAlliance, explained, "biothink provides our members access to a broader range of knowledge and expertise of bioscience service providers to more quickly and efficiently identify and finalize agreements with needed vendors and clinicians. Our relationship with biothink is yet another example of our member benefits program."

Genzyme Announces Pricing of Convertible Senior Note Offering CAMBRIDGE, Mass., Dec. 4 / PRNewswire-FirstCall/ — Genzyme Corporation (<u>NASDAQ:GENZ</u>) today announced that it has priced and established terms for the private placement of \$600 million of convertible senior notes. The sale of the notes is expected to close on December 9, 2003. Genzyme has granted the initial purchasers of the notes a 30-day option to purchase up to an additional \$90 million of notes.

The notes will bear an interest rate of 1.25 percent and be initially convertible into Genzyme Corporation common stock at a conversion price of approximately \$71.24 per share (14.0366 shares per \$1000 principal amount of the notes).

Genzyme expects to use these proceeds to pay off amounts outstanding under its credit facility, to redeem outstanding three percent debentures and for general corporate purposes. Genzyme currently has approximately \$300 million outstanding under its credit facility. The company has \$575 million in outstanding three percent convertible debentures, which are first redeemable on May 20, 2004.

The notes, and the common stock issuable upon conversion of the notes, have not been registered under the Securities Act of 1933, as amended, or under the securities laws of any state or other jurisdiction, and may not be offered or sold in the United States, absent registration or an applicable exemption from registration requirements. This press release shall not constitute an offer to sell or the solicitation of an offer to buy these securities, nor shall there be any sale of these securities in any state or other jurisdiction in which such offer, solicitation or sale would be unlawful prior to the registration or qualification under the securities laws of any such state or jurisdiction.

GlaxoSmithKline to Be Cited for Commitment to Tropical Diseases; CEO to Speak at American Society of Tropical **Medicines Annual Meeting** PHILADELPHIA, Dec. 4/ PRNewswire-FirstCall/ -GlaxoSmithKline (<u>NYSE:GSK</u>) (GSK) CEO J. P. Garnier will be honored this evening by The American Society of **Tropical Medicine and Hygiene** (ASTMH) at the Society's annual meeting being held in Philadelphia. Dr. Garnier will accept the award in recognition of GSK's leadership in alleviating tropical infectious disease worldwide for the improvement of global health. The award will be presented by Dr. William Petri, Jr., President of ASTMH.

GSK will be cited for its vital contribution to healthcare in developing countries through action in three areas: investing in research and development that target infectious disease particularly affecting the developing world; preferential pricing of antiretrovirals, antimalarials and vaccines; and for community investment activities and partnerships that foster effective health care.

In addition to accepting the Society's award, Dr. Garnier will deliver the keynote address to the group, speaking on GSK's success in creating public- private partnerships as a model for combating tropical disease. In his remarks, Garnier is expected to say that while the world is responding to the immense challenges of developing world diseases such as HIV/ AIDS, TB and malaria, " ... lasting change can only be secured through partnership and collaboration."

Dr. Garnier will also discuss the work that GSK is doing along with the World Health Organization in the Global Programme to Eliminate Lymphatic Filariasis (LF). Also known as elephantiasis, LF is one of the world's leading causes of disability and disfigurement. GSK is committed to donating as much albendazole medicines as is required to eliminate the disease from the world by 2020. To date, the company has donated 240 million treatments to 38 countries. After just a few years of program activity, an estimated 90-100 million people have been reached, and several countries (including Egypt and several Pacific Islands) are seeing sharp declines in infection levels.

88% of Pharma Market Research Teams Conduct Competitive Intelligence DURHAM, N.C., Dec. 4 /PRNewswire/ — Pharmaceutical companies elevated both market research and competitive intelligence to strategic support functions in the new millennium. Though separately funded, many companies found that the two functions routinely overlap activities. Rather than duplicate efforts, companies began folding competitive intelligence groups into their formal market research departments.

Cutting Edge Information's study, available at <u>http://www.pharmamarketresearch.com/</u>, found that 88% of surveyed companies' market research teams were involved in collecting and analyzing competitive intelligence. Some companies, in fact, had completely dissolved their competitive intelligence departments, despite their overwhelming success. CI purists argue that combining market research and competitive intelligence eliminates CI's ability to collect, analyze and present unbiased data. According to Cutting Edge Information, the argument is valid, though unproven. Market researchers collect information to support specific product needs, which may translate to a data bias. However, market researchers are quick to point out that they follow a similar code of ethics as competitive intelligence professionals.

Cutting Edge Information's study also reveals that dedicated CI departments have an average lifespan of three years. The pharmaceutical industry in particular has been integrating competitive intelligence and market research efforts to engender greater strategic impact.

Communication between market research, competitive intelligence and other organizational functions is critical to optimizing the impact each has throughout the organization. Market researchers often fail to realize that whenever they collect competitor information, they are in fact collecting competitive intelligence. The same is true in reverse — competitive intelligence teams often collect information that can be very useful to market research project teams.

Both competitive intelligence and market research have undergone a strategic rebirth in corporate America. Companies have made concerted efforts to form strategic competitive intelligence teams. Some have met with success and others have not.

"Pre-Launch Pharmaceutical Market Research: Decision Support for New Product Development" showcases the following key metrics:

- Market research budgets for pipeline and mature products
- Staffing support for developing and mature products
- Phase-by-phase market research spending by company
- Primary vs. secondary research breakdowns
- Detailed activity timelines and breakdowns per development phase

To view the online summary of this report, visit <u>http://</u>

www.pharmamarketresearch.com/ . For more information on this report or to learn about other research being conducted by Cutting Edge Information, contact Diana Borja at <u>Diana Borja@cuttingedgeinfo.com</u> or 919-433-0218. **ACLARA and Cell Signaling** Technology, Inc. Enter into Antibody **Supply Agreement** MOUNTAIN VIEW, Calif. and BEVERLY, Mass., Dec. 4 /PRNewswire-FirstCall/ — ACLARA BioSciences, Inc. (NASDAQ:ACLA) and Cell Signaling Technology, Inc. (CST), today announced the signing of a supply and license agreement, for the use and resale by ACLARA of certain CST reagents in conjunction with ACLARA's eTag(TM) Assay System. These reagents include phospho-specific antibodies to key signaling molecules such as kinases and related materials. CST has expertise in the generation and commercialization of these types of reagents, and has built a strong reputation for quality products.

Signal transduction pathways, and the molecules that comprise them, chiefly kinases, have been an important focus for cell biology research for many years. The significant role they play in directing such critical processes as cell differentiation, proliferation and death is now moving them to the forefront of pharmaceutical discovery. For instance, the U.S. Food and Drug Administration has approved two kinase inhibitors for use in certain types of cancer: Gleevec(TM) from Novartis and Iressa® from AstraZeneca.

"We believe that, aided by highly specific antibodies such as those from CST, ACLARA's multiplexed, multi-label eTag Assay System will play an important role in the characterization of signal transduction pathways in cells and tissues, and the development of novel medicines targeting these pathways," stated Michael Dunn, ACLARA's chief business officer. The eTag system permits precise and reproducible quantification of the activation state of kinases and other phosphoproteins in complex biological samples, information that is very important to researchers probing cellular pathways."

"Cell Signaling Technology is very excited about ACLARA's eTag technology as an important discovery application for our antibodies," said Christopher Bunker, CST's director of business development. "CST's antibodies provide superior content that enable the unique types of cellular analysis only possible with the eTag platform, and we anticipate that this technology will be critical in advancing research toward targeted therapeutics."



Next issue deadline March 5, 2004 NON-PROFIT ORGANIZATION U.S. POSTAGE PAID PERMIT NO. 47 HOPKINS, MN

who...what...where...when

ADMET-1 Conference

February 11-13, 2004 San Diego, California, USA admet@scherago.com www.scherago.com/admet/ ph: +1 212-643-1758

WCOI6: World Congress of Oral Implantology 6 March 5-8, 2004

Honolulu, Hawaii, USA registration@wcoi6.com www.wcoi6.com ph: +1 763-765-2388

AAPS Workshop on Dissolution: New Technologies and Regulatory Initiatives March 29-31, 2004

Bethesda, Maryland, USA aaps@aaps.org www.aapspharmaceutica.com/ meetings/meeting.asp?id=28 ph: +1-703-243-2800

2nd Pharmaceutical Sciences World Congress

May 30-June 3, 2004 Kyoto, Japan pswc2004-info@bcasj.or.jp http://edpex104.bcasj.or.jp/ pswc2004/ ph: +81-3-3815-1681

31st Annual Meeting & Exposition

of the Controlled Release Society June 12-16, 2004 Honolulu, Hawaii, USA registration@controlledrelease.org www.controlledrelease.org ph: +1 763-512-0909

AMS International Materials & Processes

for Medical Devices Conference August 25-27, 2004 St. Paul, Minnesota, USA Cust-srv@asminternational.org www.asminternational.org/meddevices/ ph: +1 440-338-5151 ext. 5900

Conference of Research Workers in Animal Diseases

November 14-16, 2004 Chicago, Illinois, USA robert.ellis@colostate.edu www.cvmbs.colostate.edu/microbiology/ crwad/crwad.htm ph: +1 970-491-5740

For complete calendar information, and to add your own events, log on to www.controlledrelease.org/global

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