



An Interview with **Prof. Allan Hoffman**



Spotlight: Fertin Pharma



Glasgow's SECC was host to over 1,800 people



Transdermal Drug Delivery Technology



COMPLEX CHALLENGES, INNOVATIVE SOLUTIONS. For 35 years, ALZA has led the drug delivery industry in developing extraordinary products based on our transdermal, oral, implantable, and liposomal delivery platforms. More than 30 products in 80 countries are based on ALZA's novel drug delivery and targeting technologies. Today, ALZA's dedicated researchers and scientists are addressing the complex challenges of delivering small molecules and biopharmaceuticals, with the commitment to create better medicines that improve healthcare for patients worldwide. Visit www.alza.com to learn more.



© 2003 ALZA Corporation

LEADING THE NEXT GENERATION OF DRUG DELIVERY

CONTROLLED RELEASE SOCIETY
NEWSLETTER
Volume 20 • Number 3 • 2003
inthisissue
From the President
2003 Annual Meeting Highlights
Volunteer Leaders 7 We welcome new volunteer leaders and say thank you to those who have retired. 7
Thank you Program Committee and Sponsors 9 CRS thanks the Program Chairs and the many sponsors of the 30th Anniversary Annual Meeting of the Controlled Release Society. 9
Scientifically Speaking
Pharm News
Modified Release Products and Challenges in Oral Delivery
Spotlight: MEDICHEW
People on the Move
Transdermal Drug Delviery Technology 27 Read about a system that holds several advantages to conventional drug administration technology. 27
Matrix-Mediated Gene Delivery for Tissue Repair

Gene therapy; holding great promises for treating certain clinical conditions.

On the cover -



The chewing machine has been accepted in the European Pharmacopoeia as state of the art testing apparatus for release documentation of active substances in medical chewing gum.

From the Editors3
CRS Updates
Welcome New Members 13
Member Release
JCR Highlights 21
Patent Watch 22
In the News



Bozena Michniak *Editor*



Ijeoma Uchegbu *Editor*



Jaymie Griffin Managing Editor



Jerome Barra Consumer & Diversified Products Special Feature Editor



James Anderson President

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



Cheryl Stratos & Victoria Geis: East & Midwest: (703) 212-7735 Email: cstratos@drugdeliverytech.com; vgeis@drugdeliverytech.com Ralph Vitaro: International: (973) 299-1200 Email: rvitaro@drugdeliverytech.com Warren De Graff: West Coast: (415) 721-0644 Email: wjdegraff@drugdeliverytech.com For manuscript submission contact: Dan Marino, MSc: Email: dmarino@drugdeliverytech.com

FROM THE Editors

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

Phew! What an exciting few days we had back in July. Who would have thought that Glasgow, the scene of rather challenging weather conditions, would play host to the biggest and in my opinion the best Controlled Release Society Annual Meeting and Exposition ever? Incidentally, speaking of the weather, the CRS meeting did find itself wetly sandwiched between the brightest and warmest summer spells that Glasgow had experienced in a long time. For those of you who made the trip, I am sure that you will agree that the programme definitely had something for everyone, from the excellent plenaries, packed oral communication sessions, and fantastic posters, to the lively Pearls of Wisdom debates and the lay and young persons Intelligent Medicines session. If for some reason you could not make the trip, well on page 13 Clive Wilson, who planned the Bioactive Materials sessions, gives you a unique insight into how it feels to go live after the planning of such a global event. Definitely not a job for the fainthearted. Also on pages 6 and 7 our award winners are proudly on display.

Well if you enjoyed Glasgow you will positively love Hawaii in 2004. Right now behind the scenes things are moving at an absolutely frenetic pace and plans are under way to give you the most stimulating, exciting and resource packed series of scientific interactions that you have ever encountered. What a lovely venue that will be. Please do not forget to pack your swim wear!



Each Annual Meeting is accompanied by a few changes and one of the most important changes happens at the top of the tree and as such we give a warm welcome to our new President for the 2003 / 2004 session – Jim Anderson. As Jim Anderson takes the helm, we say a fond farewell to our hard working Immediate Past President – Sandy Florence. I am sure that you will all join me in giving Jim oodles of support as he steers the Controlled Release Society into new and exciting waters.

You told us in our last survey that you wanted science, science and yet more science and so we are proud to say first that we listened and second that we have five scientific articles for you on pages 10, 11, 15, 27, and 29. We have pioneered the "coffee break article" style, size and format and hope that you can read each piece during your 15 minute coffee break. Please let us know if you did manage to down one of these pieces in your coffee break. Do I hear you say "What coffee break?" Oh well. The proud company featured in our Spotlight section is Fertin Pharma. Bozena and I both agreed that that Fertin Pharma, featured on page 18, with their plans to exploit the humble chewing gum, beyond the current nicotine delivery boundaries, were worthy of your attention. What do you think? You can let us know by emailing Newsletter@controlledrelease.org.

From your Editors Bozena Michniak and I and our most capable Managing Editor Jaymie Griffin, I would like to say that we really hope that you enjoy this edition of the Newsletter. Please let us know if you did enjoy your read, or of course if you did not, by contacting us at <u>Newsletter@controlledrelease.org</u>. Enjoy the rest of the year!

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.

Newsletter articles reflect only the views of the authors. Publication of articles or advertisements within the Controlled Release Society Newsletter does not constitute endorsement by the Controlled Release Society or its agents of products, services, or views expressed herein. No representation is made as to the accuracy hereof and the publication is printed subject to errors and omissions.

Editorial contributions should be directed to Jaymie Griffin, Managing Editor, (newsletter@controlledrelease.org) and are subject to the terms and conditions of the Editorial and Publication Release. Publisher assumes no responsibility for the safety or return of artwork, photographs, or manuscripts.

Requests for advertisement placement may be directed to the Business Development Department; telephone +1 (763)512-0909, or email at visibility@controlledrelease.org. All advertisements are subject to "General Conditions of Sale."

Unauthorized reproduction in whole or in part is prohibited. Requests for permission should be directed to the Managing Editor.

©Copyright 2003 Controlled Release Society. All rights reserved.

Controlled Release Society 13355 Tenth Avenue North, Suite 108 Minneapolis, MN 55441-5554 +1(763)512-0909 telephone +1(763)765-2329 facsimile director@controlledrelease.org

Contact member@controlledrelease.org regarding new or existing membership service or publication purchase issues.

Contact register@controlledrelease.org regarding meeting registration.

Contact visibility@controlledrelease.org for information about exhibiting, advertising or other visibility opportunities.

Contact planner@controlledrelease.org for meeting program information.

AN ESSENTIAL PART OF THE MANUFACTURING PROCESS

For over 27 years, Pharmaceutical Technology has been the industry's complete source for essential information about the manufacture of conventional and biotech pharmaceuticals. In every issue, we deliver unparalleled intelligence on all areas of manufacturing to 33,741 BPA qualified subscribers. From Equipment to Contract Services to Drug Delivery to Information Technology and more, readers know they can count on us to cover their world. Which is why we are an essential part of the manufacturing process.

Source: BPA June 2003

Pharmaceutical Technology

www.pharmtech.com To advertise: 732.346.3027 To subscribe: 888.527.7008

FROM THE President

By Alexander Florence, University of London, UK

The Glasgow 30th anniversary meeting has come and gone. Those of you who made up the record attendance at a CRS meeting will know that the weather did not live up to its potential of the blue skies in the brochures, but the rain

outside was matched by the splendid programme inside the conference centre, which was the best place to be. I have heard only praise about the meeting; the only problem was that we had not anticipated the press of numbers at certain sessions, so some lectures had to be



Record attendence at the 30th Annual Meeting in Glasgow

repeated to placate those who could not get into the lecture rooms. A first for me, as I and others tried to get the adrenaline flowing again for our repeat performances for those who failed to get past the Glaswegian staff who were just obeying local rules on overcrowding. But what a good problem to have! Congratulations have been sent to all those involved in the planning and execution of the meeting. The sights are already set on the 2004 conference in Honolulu, where both the programme and the weather are guaranteed to oblige.

My year as President has also come and gone: 12 months is a short time in any organisation, even with the apprenticeship that one has as Vice President and President Elect. It is working together as a team that allows progress to be made, as I know Jim Anderson and President -Elect Jenny Dressmann will seamlessly move the Society forward while injecting their own dynamic to the process. My emphasis was on Society governance, education and ensuring that members received benefit from the Society, especially the many members of the CRS Local Chapters around the world, who can only, with difficulty, get to our annual meetings, Mike Rathbone has valiantly agreed to mastermind the educational initiative with several teams of volunteers, so we must all support this important sector of Society work.

In Glasgow as an educational experiment we had the first ever session for younger participants. Ijeoma Uchegbu, Clive Wilson and I found out how hard it was to address an audience made up of kids from 10- 70 years olds. This is the challenge that scientists and technologists all have: how to tell others and particularly the young what we do, how to excite them, how to show also, against stereotypes that we are not all mad professors, not all of us anyway. The *Pearls of Wisdom* sessions were exciting and well-attended. I think I won the



2003-2004 President Jim Anderson presents Immediate Past President Florence with a token of appreciation from the Controlled Release Society.

argument but lost the vote on how gene therapy has been derailed by delivery, an interesting outcome given the facts - but that's for another day.

*I*get to live another day as the Board position of Immediate Past-President has been resuscitated. So I look forward to working with Jim Anderson and the team for another year, and thank all who have given me so much support over the last twelve months. We will continue to innovate. If the experiments don't work out we will take heed and change direction.

CRS UPDATES

Upcoming Meetings

JOHNS HOPKINS SYMPOSIUM TO FOCUS ON QUALITY CARE & PATIENT SAFETY

Practical Approaches to Quality in Patient Care: A Tools & Solutions Symposium Oct. 29-31, 2003 — Wyndham Baltimore Inner Harbor Hotel, Baltimore MD http://mailiwant.com/ links.jsp?linkid=8128&subid= 1194606&campid=11884

CRS 7th US-JAPAN Symposium on

Drug Delivery Systems December 14-19, 2003 The Westin Maui Ka'anapali Beach, Maui Phone: 1-617-253-3123

AAPS Workshop on Dissolution: New Technologies and Regulatory Initiatives Co-Sponsored with CRS and USP

March 29 - 31, 2004 Hyatt Regency Bethesda Bethesda, MD

ADMET I Conference

February 11-13, 2004 Town & Country Hotel San Diego, CA www.scherago.com/admet

Pharmaceutical Sciences World Congress

2nd World Congress of the Board of Pharmaceutical Sciences of FIP Kyoto International Conference Hall, Japan May 29 – June 3, 2004 http://pswc2004.bcasj.or.jp/home.htm

<u>WANTED</u>

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

2003 Annual Meeting Highlic



Yoon Yeo accepts the 2002 CRS - 3M Drug Delivery Systems Award from President Alexander Florence.

Ronit Satchi-Fainaro accepts the 2003 CRS - Ethypharm Award from President Alexander Florence.

Dr. Ronald A. Siegel accepts the 2002 Jorge Heller Journal of Controlled Release

from Kim Briggs of

Elsevier Science.

Outstanding Paper Award







Prof. SS (Bob) Davis accepts the Eurand Career Achievement in Oral Drug Delivery award from Dr. Hing Kin Chan.



Sarah Lynn Tao accepts the Eurand Grand Prize award from Dr. Hing Kin Chan.



Mira F. Francis accepts the 2003 CRS – Capsugel, a division of Pfizer Graduate/Postdoc Award from President Alexander Florence.



Dr. Hiroshi Maeda accepts the 2003 CRS – Nagai Innovation Award from Professor Tsuneji Nagai.

Tejal Desai (was unable to be present) Eurand Grand Prize award





Drs. Glen S. Kwon and Duncan Craig accept their 2003 CRS – Young Investigators Award from President AlexanderFlorence.



Craig Bunt of InterAg accepts the 2002 Controlled Release Society Outstanding Veterinary Paper Award from President Alexander Florence on behalf of the award recipient Michael Rathbone.

Cecilia Prego accepts the 2003 CRS – Capsugel, a division of Pfizer Graduate/Postdoc Award from President Alexander Florence.





Ann Marie Kaukonen accepts the 2003 CRS – Capsugel, a division of Pfizer Graduate/Postdoc Award from President Alexander Florence.



Dr. Gordon L. Amidon accepts the 2003 CRS -Alza Founders' Award from Dr. Vincent Lee of ALZA Corporation.

Welcome 2003-2004 **Volunteer Leaders**

Board of Directors

President - James M. Anderson, Case Western Reserve University, Cleveland, OH, USA President-Elect - Jennifer Dressman, University of Frankfurt, Frankfurt/Main, Germany Vice President - Vladimir Torchillin, Northeastern University, Boston, MA, USA Scientific Secretary - Martyn C. Davies, University of Nottingham, Nottingham, UK Treasurer - Susan Cady, Intervet Inc., Flemington, NJ, USA Member-at-Large – Joseph Fix, Elan Drug Delivery Inc., King of Prussia, PA, USA Member-at-Large - Jeffrey Cleland, Novacea, Inc. South San Francisco, CA, USA **Immediate Past President** – Alexander Florence, University of London, London, UK **Board of Scientific Advisors** Gerrit Borchard, Leiden University LACDR, Leiden, The Netherlands Jack J. Burger, Quest International, Naarden, The Netherlands Duncan Q. M. Craig, Queens University Belfast, Belfast, UK Avi/Abraham Domb, Hebrew University, Jerusalem, Israel Philippe Dor, Alza Corporation, Mountain View, CA, USA David W. Grainger, Colorado State University, Fort Collins, ČO, USA Alexander V. Kabanov, University of Nebraska Medical Center, Omaha, NE, USA Denis Require, Ethypharm, Saint Cloud, France Patrizia Santi, University of Parma, Parma, Italy Steven P. Schwendeman, University of Michigan, Ann Arbor, MI, USA Kozo Takayama, Hoshi University, Tokyo, Japan Janet Tamada, Cygnus, Inc., Stanford, CA, USA Mark Tracy, Alkermes, Inc., Cambridge, MA, USA Ijeoma F. Uchegbu, University of Strathclyde,

Glasgow, Scotland, UK

Arto Urtti, University of Kuopio, Kuopio, Finland Nobuhiko Yui, Japan Advanced Institute of Science and Technology, Ishikawa, Japan

The Controlled Release Society sincerely thanks the following retiring volunteer leadership:

2002-2003 Retiring Board of Directors Mitsuru Hashida, Member-at-Large

2002-2003 Retiring Board of Scientific Advisors You Han Bae Achim Goepferich Derek O'Hagan Michael Powell Michael J. Rathbone

Some people claim to measure macromolecules.



Only Wyatt multi-angle light scattering detectors provide *absolute* measurements of molecular weights and sizes. Without calibration or reference standards. Without fuzzy math. So you can read the actual molecular concentration, weight-average molar mass and mean square radius of your sample.

In fact, Wyatt instruments are up to 25 times *more* precise than pseudo-light scattering techniques. And because we offer the *only* modular solution, you can choose the detectors you need from our diverse family of products.



Unlike everyone else, we design and manufacture *all* of our own instruments and software, ensuring the most accurate and reliable results. And we've been cited

in 80 times as many peer-reviewed papers. No wonder more corporate, academic and government labs rely on

Only Wyatt lets you see the results.

 M_{W} $dn dc N_A n_0$ $< r_g^2 > R_{(\theta)} M_w \pi dn$ $dc A_3 \lambda_0 r_h K^*$ $M_{\scriptscriptstyle W}$ $R_{(heta)}$ n_0 dn N_A λ_0 r_D $K^* M_w n_0 k^2 c \lambda_0 \pi N_A$

Wyatt instruments than all others combined.

Our commitment to your success includes unmatched service and support, along with our all-expenses-paid Light Scattering University[®] course in Santa Barbara, California

(U.S. customers only), that one participant described as "by far the best technology training course I have ever attended." We also provide ongoing access to our ten PhD scientists with broad expertise in liquid chromatography, polymer chemistry, protein science, bio-

chemistry and light scattering. So no matter

how great a challenge you face, our staff will help you find the solution.

For more information, please call 805-681-9009 or visit

us at wyatt.com. And see for yourself why Wyatt is the clear (choice.



All trademarks and registered trademarks are properties of their respective holders. ©2003 Wyatt Technology. All rights reserved

The Controlled Release Society

gratefully acknowledges the 2003 Annual Meeting and Exposition Sponsors!

Social Sponsors

American Chemical Society American Journal of Drug Delivery Degussa Roehm Pharma Polymers Ethypharm Eurand Guidant Corporation InterAG LTS Lohmann Therapy Systems Nektar Therapeutics Shire Laboratories, Inc.

Workshop Sponsors

Coating Place, Inc. Colorcon Limited The Dow Chemical Company Genencor International Kraft Particle & Coating Technologies, Inc. Vyteris

Award Sponsors

ALZA Capsugel Elsevier Science The Nagai Foundation Tokyo 3M Drug Delivery Systems

Student Travel Grant Sponsors

Colorcon Limited Genencor International Nektar Therapeutics



A sincere Thank You to the following individuals:



2002-2003 President Alexander Florence presents the 2003 Consumer & Diversified Products Co-Chairs Richard Wilkins, and Jack Burger with a token of appreciation from the Controlled Release Society.



2002-2003 President Alexander Florence presents the 2003 Bioactive Materials Program Chair Clive Wilson with a token of appreciation from the Controlled Release Society.



2002-2003 President Alexander Florence presents the 2003 Veterinary Program Co-Chairs Mike Rathbone and David Brayden with a token of appreciation from the Controlled Release Society.

page 9

SCIENTIFICALLY SPEAKING Chitosan Based Hydrogels, Vesicles and Solubilising Polymers

By Ijeoma F. Uchegbu, Department of Pharmaceutical Sciences, University of Strathclyde 27 Taylor St, Glasgow G4 ONR, United Kingdom.

Introduction

Palmitoyl glycol chitosan (Figure 1) is a uniquely versatile molecule which forms hydrogels, polymeric vesicles and a soluble polymer with solubilising potential. These 3 drug delivery systems are prepared by varying the level of hydrophobic substitution on the



Figure 1: Chemical structure of palmitoyl glycol chitosan.

aqueous soluble glycol chitosan molecule with a higher level of hydrophobicity giving rise to hydrogels¹⁻³, an intermediate level of hydrophobicity resulting in the formation of polymeric vesicles⁴ and a low level of hydrophobicity producing the solubilising derivative⁵. The carbohydrate chitosan is a deacetylated derivative of chitin. Chitin is the main component of shell fish



Inhale, Shearwater, and Bradford Particle Design: Now Nektar.

Nektar is the newest name in drug delivery, combining the strengths of three pioneering companies to help you create new product opportunities. With broadened capabilities and a focus on expanding your pipeline, Nektar offers multiple ways to improve the safety, efficacy, and bioavailability of drug products through advanced oral, injectable, and pulmonary delivery.

Nektar. Because a better molecule makes a better therapy.

Contact us at partnerships@nektar.com.

MOLECULE ENGINEERING, INCLUDING ADVANCED PEGYLATION PARTICLE ENGINEERING DRUG DELIVERY SOLUTIONS FOR ORAL, INJECTABLE, AND PULMONARY



Copyright © 2003 Nektar Therapeutics. Nektar is a trademark of Nektar Therapeutics. All rights reserved.

exoskeletons and is the second most abundant biopolymer after cellulose. In our laboratories the hydrophobisation of glycol chitosan is simply carried out by the reaction of glycol chitosan with an activated fatty acid derivative.

Hydrogels

A modification of approximately 20 sugar monomers in the glycol chitosan backbone with palmitoyl groups produces an aqueous insoluble polymer. Freeze drying an aqueous dispersion of the polymer in the presence of a drug results in a physically cross linked hydrogel (Figure 2) with drug entrapped within and in which cross-linking is mediated by the attraction of hydrophobic palmitoyl groups to one another, with a minor contribution from hydrogen bonding between polymer chains. Palmitoyl glycol chitosan hydrogels gain up to 20 times their weight on hydration^{1,2} without an appreciable gain in volume. There is no appreciable change in hydrogel volume due to the porous nature of the hydrogels and this porosity originates from the formation of ice crystals during the freeze drying step. Palmitoyl glycol chitosan hydrogels may be loaded with up to 33%w/w of drug³. A high level of drug loading is achieved as the drug is introduced during the freeze drying step. There also is no damage to the drug during cross-linking which could be a problem if chemical cross linking is carried out in the presence of the drug. Chemically cross linked hydrogels must be loaded after they have been cross linked and this typically results in low levels of drug loading. With the present physically cross linked chitosan based hydrogels, hydrogel fabrication and drug loading is carried out in the absence of organic solvents, which is an additional benefit.



Figure 2: Electron micrograph of a physically cross linked palmitoyl glycol chitosan hydrogel prepared by freeze drying a dispersion of the polymer. The hydrogel is porous as a result of the formation of ice crystals during the freeze drying process. Cross linking is achieved by the hydrophobic attractions between the pendant fatty acid groups in different polymer chains and also by hydrogen bonding between polymer chains.

Chitosan continued on page 14

PHARM NEWS Human Drug Registration Can Be Supported By Veterinary Data:

By Marilyn N. Martinez, Ph.D., Senior Research Scientist, Food and Drug Administration Center for Veterinary Medicine, HFV-130, 7500 Standish Place, Rockville, Maryland 20855

Summary Of A Pearls Of Wisdom Session

Until recently, new drugs and biologics intended for human use could not be approved for marketing without adequate and well controlled studies conducted in human subjects. However, a major shift in the role of animal model data occurred with the finalization of the rule titled "New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible¹ [for the purpose of this article, termed the "Animal Rule"]. Conditions under which the Animal Rule can be applied include:

- 1. When adequate and well-controlled efficacy studies in humans cannot be ethically conducted because the studies would involve administering a potentially lethal or permanently disabling toxic substance or organism to healthy human volunteers.
- 2. Field trials are not feasible prior to approval.

Thus, certain new drugs and biologics intended to reduce or prevent serious or life-threatening conditions can be approved for marketing based on evidence of effectiveness derived from appropriate animal studies. In light of this recent amendment, the CRS sponsored a Pearls of Wisdom debate titled "Human Drug Registration Can be Supported by Veterinary Data" at the 2003 annual meeting. The objective was to debate whether or not it is appropriate to consider extending the regulatory application of animal model data to include other situations. The following key questions were posed:

- 1. Should animal models be accepted as a component of substantial evidence of effectiveness in situations that may have otherwise been a candidate for accelerated approval?
- 2. Can animal models be used in lieu of human subjects to establish product bioequivalence for toxic compounds (e.g., generic anticancer drugs)?
- 3. Can we use animal models to develop a human-animal model *in vivo* bioavailability correlation for testing the impact of changing the formulation of parenteral control release products (e.g., long acting implants)?

During the recent Pearls of Wisdom session, Dr. Leslie Benet, Professor, Department of Biopharmaceutical Sciences University of California San Francisco debated the con position and Dr. Thomas Ingallinera, Senior Director of Pharmaceutical Operations & Site Manager (AAI Pharma), debated the pro position.

Dr. Ingallinera discussed the various situations animal data have provided an invaluable tool in the development of novel product formulations. In support of the use of animal models, he quoted the nineteenth century pioneer physiologist, Claude Bernard, who stated "there are too many dangerous experiments being conducted in man before being sufficiently studied in animals". Dr. Ingallinera examined the potential use of these data as a mechanism for reducing the number of human subjects, underscoring the great advantages such uses would have in encouraging approvals for low profit indications. He also discussed the numerous situations where animal models have provided excellent predictions of drug effects and pharmacokinetics in humans. While Dr. Benet agreed that animal data are valuable components of the drug development process, he has serious reservations about its use as a surrogate for human trials. In his experience, there are many examples where animal data fail to accurately predict human in vivo events. Using examples, he warned that unless animal models are fully validated and are demonstrated to accurately reflect the human clinical situation, they can lead to inappropriate decisions. Dr. Benet provided several pharmacokinetic and pharmacodynamic examples where data obtained in animal species failed to correlate to data obtained from human subjects. However, few companies develop validated animal models for human drugs, considering such a project too costly and problematic.

Examples illustrated the level of validation needed for animal models to be appropriately used as a surrogate for human clinical data. For instance, approval of the use of ciprofloxacin for the treatment of inhalation anthrax included an understanding of the disease process both in humans and the animal model, an awareness of the kinetic/dynamic relationship associated with the infectious micro organism (Bacillus anthracis) and extensive studies comparing ciprofloxacin pharmacokinetics in humans and Rhesus monkeys.² The question was raised whether or not there is any less uncertainty when human surrogate markers are applied rather than when animal data are used. While surrogate markers often represent risk factors for specific clinical outcomes that logically appear to reflect the desired therapeutic effect, there are examples where a beneficial effect on a surrogate marker has not resulted in the predicted clinical outcome. A well-known example of a failed surrogate endpoint is that of ventricular arrhythmias as a surrogate marker for mortality after myocardial infarction. The drugs tested were previously approved on the basis of their capacity to suppress ventricular arrhythmias. The unapproved use was the prevention of these arrhythmias after myocardial infarction, based on an assumption that the decreased arrhythmias would reduce patient mortality. However, when the effects of these drugs on mortality were formally studied in a randomized, controlled clinical trial, mortality actually increased with their use as compared to the placebo.^{3,4} The consensus was that despite its potential flaws, the risks associated with the use of surrogate markers do pose less potential for errors as compared to results obtained from animal models.

Pharm News continued on next page

Pharm News continued from previous page

Concerns regarding the need for model validation continued through discussions on the use of animals for granting approval of extralabel uses. Simply because products may be used for an unapproved indication, even if its use seems logical, we cannot assume that the product is actually effective. Therefore, it would be reckless to use animal model data without requiring the level of validation expected for products approved under the Animal Rule.

With regard to drug formulations and product bioequivalence, there was agreement on the utility of preclinical animal studies for selecting formulation candidates with the desired *in vivo* release characteristics. However, to use these data to support the determination of product bioequivalence is a much different issue. Given the numerous differences in species physiology that can influence formulation effects and known interspecies differences in product relative bioavailability,^{5,6,7} Aoyagi, Ogata, Kaniwa, Koibuchi, Shibazaki, Ejima, Tamaki,^{8,9,10} all agreed that humananimal model *in vivo* correlations would be necessary.

These conclusions directly impacted the question as to whether or not animal relative bioavailability data can be used to support the approval of very slow releasing products. While humananimal model *in vivo* correlations can be generated, Dr. Benet's presentation underscored some of the corresponding challenges. In particular, why would a drug sponsor devote the time and money needed to validate such correlations if the work needed in

Opening the Borders to Better Medicines

Therapeutic peptides and proteins, small-molecule drugs, genes and vaccines can now be delivered across the skin without the use of a needle injection. Altea Therapeutics introduces the PassPort[™] system, a new approach to controlled delivery across the skin. The system combines a wafer-thin array of filaments with a skin patch containing drug. One step activation rapidly and painlessly flashes a mild energy pulse into the surface layer of the skin, creating tiny aqueous channels. These micropores enable accurate and controlled delivery of therapeutic substances previously unable to move across the skin with conventional transdermal technologies.

Combines a wafer-thin array of filaments with a patch containing drug or vaccine.

ALTEA

Medicines Made Better

2056 Weems Road + Atlanta, GA 30084 + 678.495.3100 www.alteatherapeutics.com this regard is no less than that needed to develop a correlation between *in vitro* dissolution and human *in vivo* drug bioavailability?¹¹ Moreover, the development of such animal models would appear to be less desirable than *in vitro* correlations when considering the higher variability normally encountered with *in vivo* as compared to *in vitro* systems.

Finally, the audience was then asked to vote on whether or not they would want to know that the product they are taking is approved based on data derived solely from animal models. This question was raised because 21 CFR 314.610 states that such information must be included on the product label. The vast majority of individuals indicated that they would want to know that the product they were taking was not tested in humans. Of course, this also raises the possibility that patients receiving these medications can experience a "nocebo" –like effect, potentially counteracting the therapeutic benefits of the product being administered.^{12,13}

- ¹ Federal Register notice dated 5-31-02 (docket number 98N-0237).
- ² US FDA CDER Freedom of Information Summary, NDA 19-537/S-038, 19-847/S-024, 19-857/S-027, 19-858/S-021 and 20-780/S-008 (<u>http://www.fda.gov/cder/foi/nda/</u> 2000/19-537S038 Cipro medr.pdf). Accessed 8/29/03
- ³ The Cardiac Arrhythmia Suppression Trial Investigators (1989) *New England Journal of Medicine*, Vol 321:406-412.
- ⁴ The Cardiac Arrhythmia Suppression Trial II Investigators. (1992) New England Journal of Medicine Vol 327:227-233.
- ⁵ Martinez, Amidon, Clarke, Warren Jones, Mitra, and Riviere. (2002). *Advanced Drug Delivery Reviews*, Vol 54: 825-850.
- ⁶ Aoyagi, Ogata, Kaniwa, Ejima, Yasuda, and Tanioka. (1984). *Journal of Pharmacobiodynamics*, Vol 7:7-14. Kamimura, Katougi, and Omi. (1982). *Journal of Pharmaceutical Sciences*, Vol 71:1169-1172.
- ⁸ Aoyagi, Ogata, Kaniwa, Ejima, Nakata, Tsutsumi, Fujita, Amada. (1985). *International Journal of Clinical Therapeutics and Toxicology*, Vol 23: 578-584.
- ⁹ Ogata, Aoyagi, Kaniwa, Koibuchi, Shibazaki, Ejima, Shimamoto, Yashiki, Ogawa, Uda, and Nishida, (1982). International Journal of Clinical Therapeutics and Toxicology, Vol 20:576-81.
- ¹⁰ Martinez., Pedersoli, Ravis, Jackson, and Cullison, (2001). *Journal of Veterinary Pharmacology and Therapeutics, Vol* 24:125-135.
- ¹¹ US FDA CDER Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation and Application of *In Vitro/ In Vivo* Correlations. September 1997 (<u>http://www.fda.gov/cder/guidance/1306fnl.pdf</u>) Accessed 8/29/03.
- ¹² Flaten, Simonsen, and Olsen, (1999). *Psychosomatic Medicine* Vol 61:250-255.
- ¹³ Barsky, Saintfort, Rogers, and Borus, (2002), *Journal of the American Medical Association*, Vol 287:622-627.

MEMBER RELEASE

After the Party....

By Clive Wilson, University of Strathclyde, Glasgow, Scotland, UK

When the party is over, you usually come down to the debris of the night before, perhaps nursing a king-size hangover and an awful suspicion that you said something terrible last night, to someone important, and to someone who might remember. Well, I don't think CRS 2003 was like that. It will be remembered (I hope!) as one of the conferences to attend in drug delivery, veterinary, and consumer affairs. Being so caught up in the minutiae of the affair, I didn't expect to enjoy it but it was a blast (not a MSBlast, that came later...)

Organising a conference is a good idea (well, it seemed so back in 2000 when we got started) because as programme organisers, Ruth and I could pretty well select our own topics for discussion. For me, the problem generally is that the events which I want to attend usually clash and I am jumping in and out of the sessions. To combat this, I tried to construct the programme so that a person in a particular scientific discipline would have something of interest each day and yet each day would have a theme. In the end, it proved quite a difficult task. We ended by defining the problems, searching the solutions and looking to the future as a three day progression. The UKICRS and APS session on Wednesday encapsulated this and the approach of physician explaining the problem followed by scientist propounding a solution worked well as a formula. Another success was the Pearls of Wisdom; we had some good debates which were enjoyed by all. I thought that these might be mildly popular but I really underestimated the demand for some sessions and ended up being chastened by an angry scientists from Chicago trying to get in (originally I thought just the students would go, and then only for the beer). So, imagine my chagrin when at 5.30 I wandered into the refreshment area (free beer!) to find it almost completely empty. I really gauged the success by that!



Guests at the banquet gather outside the beautiful and historic Stirling Castle to await entrance.

The entertainment at Stirling Castle was up to its usual excellent standard. For me, it's always a favourite and even on dark days, its fun to walk around. I thought that the haggis experience would be too much for some but it was suitably gentrified - one of my colleagues dryly observed that it could have been served as a pudding with custard, but the food was good and the company even better.

What do I remember? Well mainly a lot of happy faces, eventually. Having your conference sabotaged by British Airways was unforseen. Usually they just lose my luggage (15 times in three years at Heathrow) but this time, they lost my delegates... The preparation was fun as well, Jack Burger, Martyn Davies and I made the trip to CRS Headquarters in the depths of winter followed by a celebratory night out at the local hostelry with BBQ ribs bigger than Texas and a night with Jack Burger, Mark Ricker and his wife Barb Ginner, Karen Kazmierczak, Mike Miller, and Ronda and Ford Thompson (did I miss anyone?) Oh, and Rosealee and David Lee threw a neat house party. Thanks also go to Martyn Davies and Ronda Thompson.

Well, gotta get ready for Hawaii. I wonder if I can get some of the organisers into Hawaiian dress?

Welcome New Members

Hosam Ahdelhady Aslihan Akkar Franklin Akomeah **Dean Allison Fotios Andreopoulos** Hyun Ju Bae Hannah Batchelor **Elena Batrakova** Kuljit Bhatia Gary Borgstadt Johan Borgstrom **Elisabet Borresen Reginald Bradley** Wendy Busby **Alexandr Bush** Youngro Byun Ada Cowan Joy Dempsey Ken Downie Matthew Dreher **Inayet Dumanli** James Dvorsky Maggie Dyer **Robert Dykstra** Sarah Eccleston **Stephen Edge** Nagib El Marzugi Yinka Falope **Stefan Fankhaenel** Sascha General Salvador Gomez-Lopera Patrick Gosselin **Torkel Gren** Vijay Gupte Yong So Ha Jochen Haas Elizabeth Hedberg **Kristin Hennemann** Stuart Hunt Patricia Hurter **Erika Johnston** Peter Kaastrup Amr Kandil Han Cha Kang Rodney Kasan John Kendrup **Cormac Kennedy** Sung Wo Kim **Pavlos Kouropis** Andrew Lam

Bruno Leclercq Simon Leppard Galit Levin Andrew Lewis Rosario Lizio **Douglas** Loe Hollace MacGregor **Graeme Macleod Michelin Markey Benjami** Martin Jason McConville **Clare Meaney** Afzal-Ur-Mohammed **Michael Moller** Surajit Mukherjee Showan Nazhat Abdessl Nazih Maria Nilsson Ubonthip Nimmannit **Ralph Niven** Sevgi Okten **Derek** Owen **Gaofeng Pan** Sang Jin Park Alison Paul Jack-Mic Renoir Varun Sethi Jeung-Y Shim **David Sliva** Jerome Sohier Mingna Song Hsing-W Sung Krittika Tanprasert Nilufer Tarimci Michael Unhoch Nontima Vardhanabhuti **Terry Vick** Serguei Vinogradov Ping Wang Kevin Ward Sandra Wiedersberg **Clarence Wobbe** Santosh Yadav Kang Yang **Chul Soo Yong** Betty Yu Hiroshi Yuasa Yucun Zhu

Chitosan continued from page 10

Drug release is controlled by the level of hydrophobic modification or cross linking density² and these hydrogels are able to achieve sustained drug release via the buccal route over a 5h period³. Due to the porous nature of these hydrogels, drug release is typically in the domain of hours and not days or weeks. This may be a disadvantage for implantable depot systems but is sufficient for delivery via the buccal, gastrointestinal, vaginal or rectal routes.

Polymeric Vesicles

In the 1990s the self assembly of hydrophobised chitosan into polymeric vesicles in both acid⁶ and neutral⁴ media was reported. Chitosan is insoluble at neutral and alkaline pH and hence to enable self assembly into polymeric vesicles at neutral pH, glycol chitosan was used as the soluble polymer backbone in these pendant amphiphiles⁴. This find widens the scope of the possible drugs which may be associated with these delivery systems. Polymeric chitosan vesicles (Figure 3) are similar to liposomes with the notable exception that the bilayer membrane is formed from a hydrophobised chitosan polymer - palmitoyl glycol chitosan^{4,7}.



Figure 3: Electron micrograph of polymeric glycol chitosan vesicles of about 200nm in size. Bar size = 250nm.

When palmitoyl glycol chitosan is used to make polymeric vesicles approximately 10 out of every 100 sugar monomers is palmitoylated. Polymeric vesicles are formed by the probe sonication of palmitoyl glycol chitosan in aqueous media and adding cholesterol to the bilayer of these polymeric vesicles improves their colloidal stability⁷. Polymeric vesicle size is directly related to the molecular weight⁷ of the polymer and hence molecular weight may be used to control vesicle size. Vesicle size control is especially important since vesicle size affects drug distribution on intravenous administration. Chitosan based vesicle sizes range from just under 1ìm to a lower size limit of



Figure 4: The uptake of a fluorescent dextran derivative by A431 cells. Tf-vesicles are vesicles bearing an iron transport ligand. Plain chitosan based vesicles (vesicles) increase the uptake of the dextran derivative.

200nm. Vesicles of less than 200nm have not been prepared with this polymer. These chitosan based vesicles are able to improve the intracellular delivery of drugs⁸ (Figure 4) and hence may be useful for this purpose. Palmitoyl glycol chitosan vesicles are also biocompatible⁴.

Solubilising Polymers

By attaching a minimum of 4 palmitoyl groups per 100 sugar monomers and by introducing additional hydrophilic groups a chitosan derivative is produced which is soluble in water – quaternary ammonium palmitoyl glycol chitosan - and also potentially solubilising⁵. We believe that this polymer acts by forming essentially intracellular molecular aggregates (Figure 5) and this material may prove useful for the solubilisation of drug compounds. Once again this soluble chitosan amphiphile is non-cytotoxic and more importantly non-haemolytic⁵.

Summary

Palmitoyl glycol chitosan, an amphiphilic chitosan derivative, may be fabricated into sustained delivery gels, polymeric vesicles



Figure 5: *Schematic representation of micelle formation by a soluble palmitoyl glycol chitosan* derivative. This micelle formation results in the solubilisation of compounds such as pyrene.

which are able to improve the intracellular accumulation of drugs and biocompatible solubilising polymers.

References

- 1. Noble L, Gray A I, Sadiq L, Uchegbu I F, Int. J. Pharm., 1999. 192: 173-182.
- Martin L M, Wilson C G, Koosha F, Tetley L, Gray A I, Senel S, Uchegbu I F, J. Control. Rel., 2002. 80: 87-100.
- 3. Martin L, Wilson C G, Koosha F, Uchegbu I F, Eur. J. Pharm. Biopharm., 2003.
- 4. Uchegbu I F, Schatzlein A G, Tetley L, Gray A I, Sludden J, Siddique S, Mosha E, *J. Pharm. Pharmacol.*, 1998. **50**: 453-8.
- Uchegbu I F, Sadiq L, Arastoo M, Gray A I, Wang W, Waigh R D, Schätzlein A G, *Int. J. Pharm.*, 2001. 224: 185-199.
- 6. Wakita M , Hashimoto M, Kobun. Ronbun., 1995. 52: 589-593.
- 7. Wang W, McConaghy A M, Tetley L, Uchegbu I F, Langmuir, 2001. 17: 631-636.
- Dufes C, Schatzlein A G, Tetley L, Gray A I, Watson D G, Olivier J C, Couet W, Uchegbu I F, *Pharm. Res.*, 2000. 17: 1250-1258.

Modified Release Products and Challenges in Oral Delivery

By Kurt Fegely and Ali Rajabi-Siahboomi, Colorcon, 415 Moyer Blvd., West Point, PA 19486, USA

The 2003 Controlled Release Society Meeting in Glasgow, Scotland included a multi-faceted workshop sponsored by Colorcon and the Dow Chemical Company, aimed at presenting current topics in the field of modified-release, oral drug delivery. Aspects of the workshop ranged from biopharmaceutical considerations of slow release systems to current and novel drug delivery techniques and regulatory themes related to the field of modified release. New characterization techniques were introduced to study and understand the *in-vitro* behaviour of the dosage forms and possibly relate them to the *in-vivo* situations.

The meeting started with Dr Randle Mrsny (Welsh School of Pharmacy, UK) reviewing our current understanding of the challenges and possible strategies associated with the transport of therapeutic moieties across the epithelial barrier. The physiological, biochemical and anatomical make-up of the epithelial barrier in relation to approaches (and fundamental concerns) that have been taken to modify the barrier in order to improve drug absorption were presented. The role of occludin in the function of tight junction regulation, along with transcellular and paracellular transport pathways, was highlighted.

Approaches to improve the bioavailability of poorly soluble / absorbable drugs across the gastro-intestinal tract were discussed

by Dr Abraham Rubenstein (The Hebrew University of Jerusalem, Israel). The method that has been evaluated by his group, the synchronous delivery of absorption enhancing compounds and/or protease inhibitors in combination with the therapeutic compound via slow release matrix formulations was presented. Through tailoring the formulation components to provide simultaneous release of the drug, absorption enhancer, and/or protease inhibitor, a marked increase in bioavailability was achieved.

Dr Jose Rocca (Kos Pharmaceuticals Inc., USA) presented the factors that limit the absorption of a drug throughout the gastrointestinal tract (GIT), including the significance of regional absorptions and transit time of the dosage form through these regions. One possible approach to overcome these issues is providing gastric retentive drug delivery systems. An overview of super porous hydrogels, as one such system was presented. These hydrogels swell to several times their original size in the stomach, which will not pass through the pyloric sphincter for several hours, acting as a reservoir for slow release of drug formulated within them. Ultimately, the hydrogel device disintegrates and passes though the GIT. A systematic rationale for the development of oral, modified-release dosage forms was presented by Dr Ali Rajabi-Siahboomi (Colorcon, USA). The key biopharmaceutical, pharmacodynamic, and pharmacokinetic factors must be considered prior to selecting a drug delivery system. Then, pros and cons of sustained release systems as well as new market trends for these drug delivery systems were presented. Current sustained release delivery strategies ranging from hydrophilic / hydrophobic matrices, osmotic systems and barrier membrane multiparticulate systems were reviewed.

Dr Roland Bodmeier (Free University of Berlin, Germany) presented a lecture on coating materials commonly utilized in extended drug release systems, along with traditional and novel methods to apply these systems to a substrate. The use of polymer additives to change the release profile of a given coating system via pore formation, pH dependent solubility, or differences in permeability were discussed. In addition, the process of polymer powder coating was highlighted as a means of potentially eliminating solvents from the coating process, with a curing step to ensure film coalescence.

Modified continued on page 17





journal of

controlled release

New Impact Factor 3.131

online submission

Journal of Controlled Release

http://authors.elsevier.com/journal/jconrel

Online submission is now available for Journal of Controlled Release. It is fast, efficient and provides step-by-step instructions on how to submit your article.

SUBMITTING ONLINE PROVIDES THE FOLLOWING BENEFITS:

Disks and hard copies are no longer required for initial submissions

 Online submission automatically converts submitted articles into PDFs, which are easily read and printed by referees.

Speeds up the editorial and production processes

 The electronic flow of manuscripts and related information speeds up the editorial review and production processes. This minimises publication time, meaning that your work can be published sooner.

Easily accessible anywhere in the world

 You can log in to submit your article or revisions wherever you have access to the Internet.

Your data is secure

 Data is held on our secure, central servers, which are regularly backed up, so there is no need to worry about loss of data.

QUESTIONS? Contact the global author helpdesk

 As with any new system, questions or problems may arise when you first start using online submission. That's why we have set up an author helpdesk at authorsupport@elsevier.com

To submit your article online or for further information visit: http://authors.elsevier.com/journal/jconrel



Modified continued from page 15

Dr Linda Felton (University of New Mexico, USA) rounded off the topic of modified release coating materials with an overview on delayed release coating technologies, materials, and novel methods of characterization. Criteria for selecting delayedrelease as a platform were reviewed, along with varying mechanisms commonly utilized to achieve a delay in drug release (time, pH, bacterial-enzymatic and combinations thereof).

The subject of granulation technologies applicable to hydrophilic matrices is still a highly desirable topic for the pharmaceutical industry. Paul Sheskey (The Dow Chemical Co., USA) reviewed various methods of wet and dry granulation. To facilitate wet granulation of hydrophilic polymer matrices, a novel process utilizing foam technology to deliver and distribute uniformly the water and/or the binder into the powder bed was outlined. This novel method will lead to shorter processing times, elimination of spray nozzles and safer handling of potent drugs.

Concluding the first day of the workshop, Neil Turnbull (Colorcon, UK) provided an in-depth review of current, novel, and forthcoming modified release technologies. The majority of novel technologies are still rooted in the current pharmaceutical excipients with broad regulatory acceptance, yet utilize processes (from outside the pharmaceutical arena) and novel geometries to achieve unique delivery mechanisms. To the formulation scientist, the ability to fabricate dosage forms which result in a myriad of release profiles is a powerful tool.

Imaging methods to characterize formulation interaction's noninvasively in order to examine phenomena that occur on the macroscopic and microscopic levels within and between a dosage form and its environment were reviewed by Dr. Colin Media (University of Nottingham, UK). The power of these techniques can be realized in the potential ability to watch and measure an event transpire within the interior of a dosage form, real time, without disruption of the mechanism while it unfolds.

In-vitro assessment of swelling, erodible matrices was reviewed by Dr Reza Fassihi (Temple University, USA) mainly focusing on dissolution testing methodology as a tool for quality control versus a developmental tool during the formulation and development of a hydrophilic matrix system. The importance of accurate, rugged dissolution methodology when attempting to establish meaningful in-vivo/in-vitro correlations were highlighted. Given the increasing role of dissolution testing with respect to bio-waivers and bio-equivalence testing, it is obvious that time spent accurately characterizing the release behavior of a dosage form is time well spent.

Dr Zeev Elkoshi (Teva Pharmaceuticals, Israel) presented an overview on single and multiple dose pharmacokinetic studies and their value related to bioequivalence studies in which the drug exhibits linear or non-linear kinetics. Through the use of case studies Dr Elkoshi was able to recommend that for drugs with linear pharmacokinetics, single dose studies were more useful for detecting differences in absorption rate, whereas multiple dose studies were more sensitive to differences in the extent of absorption. Drugs with non-linear kinetics did not prove to be as well defined, each situation should be reviewed on it's own merit. The case study of a drug that effects the pH environment of the stomach after administration clearly defined the need for single and multiple dose studies to account for the response of the dosage form to the original environment, and then the environment created by the clinical response.

The FDA and European regulatory aspects that govern the development of modified release dosage forms, and possible avenues for harmonization were briefly outlined by Dr Henning Blume (SocraTec, Germany). The discussion defined the types of pharmacokinetic studies required for submission depending on whether the dosage form was a new chemical entity, modified release form of an existing drug, or a generic equivalent. An exciting imaging technology was introduced that followed the transit of a magnetic dosage form through the gastro-intestinal tract at the same time monitoring the erosion of the matrix to yield an *in-vivo* dissolution profile. The technique emphasized the critical nature of food effect studies for certain dosage forms, and highlighted variable gastric emptying as the largest hurdle in establishing bioequivalence.

Overall the workshop was an excellent opportunity for formulation, development and academic scientists to gain an understanding of the fundamental, current and forthcoming modified release technologies in the market. The workshop was run over two days (19-20 July 2003) and attended by over 100 delegates.

A Revolution in Oral Drug Delivery

LYM-X-Sorb[™] is a unique delivery system providing controlled drug release.



SPOTLIGHT: MEDICHEW®

By Bo Tandrup, M.Sc., Business Development Manager Fertin Pharma A/S - Struergade 22 - DK-2630 Taastrup. Direct tel.: +45 72 15 13 87; Fax: +45 72 15 13 81; E-mail: btd@fertin.com

It is a well-known fact that the right drug delivery system is critical to the success of a pharmaceutical product. A novel drug delivery system creates additional patient benefits that will add new competitive advantages for a drug and, thus, conserve or increase revenue.

People of all cultures chew gum, and a variety of gums and gum-like substances have been enjoyed for thousands of years. The introduction and subsequent success of Nicotine chewing gum in the 1980's paved the way for a more general acceptance of chewing gum as a drug delivery system. Improved technology and extended know-how, together with the inclusion of medical chewing gum in the European Pharmacopoeia in 1998, have further contributed to the acceptance of this method of drug delivery. Today, medical chewing gum meets the same high quality standards as tablets. Furthermore, it can be formulated to obtain various release profiles of active substances, thus enabling distinct patient group targeting.

In addition to offering competitive marketing advantages, a chewing gum formulation offers a vast number of clinical benefits. As many active substances are buccally absorbed, efficacy can be greatly enhanced due to the associated fast onset of action and high bioavailability. Medical chewing gum also provides a topical effect in the oral cavity and in the throat.

From a patient convenience point of view, discreet and easy administration *without water* promotes higher compliance. Since it can be taken anywhere, a chewing gum formulation is an excellent choice for acute medication. The advantages for children and for patients who find swallowing tablets difficult are obvious.

Fertin Pharma is the world leader in the development of medical chewing gum. This position has been achieved through research not only at Fertin Pharma's own laboratories in Denmark, but also through many years of close cooperation with researchers and scientists from various hospitals and universities around the world.

Currently, Nicotinell[®] chewing gum developed and produced for Novartis and NiQuitin® chewing gum - produced for GlaxoSmithKline - are the major contributors to Fertin Pharma's success. The company has shown a remarkable 30% growth per year in the sales of medical chewing gum during the last five years and, due to an expected breakthrough outside the nicotine business, Fertin Pharma's position on the world market is expected to be markedly strengthened in the years to come. Consequently, the company has invested 50 million USD in new high-tech production facilities which are currently in the process of FDA approval.

The development team at Fertin Pharma possesses know-how and patents for profiling the release of both lipophilic and hydrophilic substances. The company makes use of several different release systems (solubilizers, matrixes, encapsulation techniques, etc.) and combinations of systems to create the optimal release profile for the relevant active substance. This release profile might be very fast or more prolonged (up to 20minutes) depending upon the product and target patient group. Additional finetuning of the profile can be done by placing the active substance in the coating as well as the core.

In order to obtain *in vitro* release rate results, Fertin Pharma has developed a chewing machine that has been accepted by the European Pharmacopoeia as the state of the art testing apparatus for release documentation of active substances in medical chewing gum.

To succeed in the market, a chewing gum formulation must have a pleasant taste and texture.

Most active substances have an unpleasant, bitter, or metallic taste. Since the active substance will be released in the oral cavity and remain there for a longer period of time than is the case with ordinary delivery forms (usual chewing time is 10 to 20 minutes), unique expertise in taste definition, taste masking, and taste modification are essential to the success of a medical chewing gum product. Moreover, there are no official standards



The chewing machine has been accepted in the European Pharmacopoeia as state of the art testing apparatus for release of active substances in medical chewing gum.

for unpleasant taste, so it is necessary to establish information on taste properties for all new active substances.

In most cases, it is desirable that the taste fades out when the active substance has been fully released. The release profile of the flavors and sweeteners, therefore, is usually designed to follow the release profile of the active substance.

One of the major challenges for the product developer is that any small adjustment in the amount of active ingredient, flavor, sweetener, or gum base component may lead to changes in several parameters. For example, the addition of extra solubilizer might change not only the release of the active substance, but also gum base texture, taste, and stability of the product. During the development process, therefore, it is necessary to test several parameters related to taste and texture continually. Every active ingredient requires a custom-made gum base.

Fertin Pharma has access to its own gum base production and has established a panel of professional "tasters" who are trained to evaluate organoleptic data related to chewing gum products. During the development process, a taste and sensory profile is compiled from evaluation results of the panel to ensure the best possible taste and texture.

People On The Move An Interview with Professor Allan Hoffman, Bioengineering Department, University of Washington



Allan Hoffman, Sc.D. is Professor in the Dept. of Bioengineering at the University of Washington, Seattle. He is a world-renowned scientist in the area of polymers and their applications in medicine and biotechnology. In particular, he synthesizes acid-sensitive polymers for incorporation into drug delivery formulations where acidic environments are encountered during delivery. The polymers are specifically designed to facilitate the escape of drugs such as DNA, oligonucleotides, peptides and proteins from the endosome to the cytosol before the drugs are trafficked to lysosomes, where they would be degraded by enzymes. Prof. Hoffman has other major contributions in the fields of surface modification and characterization of polymeric biomaterials, use of hydrogels for tissue engineering and coatings for implants, and design of site-specific conjugates of "smart" polymers and genetically engineered proteins. He has received numerous awards and recognitions. Among the many, in 1999, he was awarded the CRS "Excellence in Guiding Graduate Student Research" award and in 2000 received the Society for Biomaterials Founder's Award.

- **Q:** What do you think was the major scientific breakthrough in polymer science that had the most impact on the field in the last 50 years?
- A: The discovery of catalysts that permit the living free radical polymerization of polymers with controlled molecular weights and with linear, block or graft structures; and also the discovery of the polymer single crystal and the folded chain conformation in polymer crystallites.
- **Q:** Your research career was peppered with a number of very important and ground breaking papers, how would you like your contribution to science to be remembered?
- A: Many may think of me as having focused on surface modification of polymers, especially immobilization of biomolecules on synthetic polymer surfaces, along with medical and biotech applications of hydrogels and "smart" polymers. However, I would most like to be remembered for having "spread the word" of biomaterials and their applications (including drug delivery, of course) as a teacher in the classroom, and as a lecturer in many tutorial lectures and short courses here in America, and around the world. For example: I have taught courses in Biomaterials and Controlled Release here at the University of Washington for the past 30 years. I have also participated in a number of ACS short courses here in America. I gave the first course on biomaterials in France in 1976 (and I gave it in French!). I taught a three-day course on biomaterials and drug delivery in 1983 in Shanghai to 50 scientists from all over China. I've taught general courses on biomaterials and drug delivery three times in Sydney, Australia, at the University of New South Wales. I also gave similar courses in Ankara, Turkey and Kiev, USSR in different years. I've lectured on these general topics many times in Japan, starting with my first trip there in 1970. Thus, I've been privileged to influence many young researchers at a critical stage in their careers, and have lived to see many of them become leaders in our field. That is extremely gratifying.
- **Q:** Do you think it is getting easier or harder to make new discoveries?
- A: From one viewpoint it is definitely easier: we are armed with much more knowledge and many more exciting tools to probe the unknown, but there are more and more of us doing that,

so really being the "first" to discover something important is getting harder.

- Q: Controlled release as a science is a fairly new discipline and you were in this science when it all started, has it lived up to the hype?
- A: Yes, drug delivery R&D has delivered! There are many successful DDS developments and products, and some of the most significant were initially conceived and/or applied clinically by scientists at Alza Corp. (I should note here that I have been a consultant to Alza for the past 33 years, and continue consulting with them today). These include the reservoir device, the transdermal DDS (skin patch), the osmotic pump, and biodegradable microparticles. Of course many others have been involved in developing successful DDS, such as Davis and Geck and Ethicon who developed the degradable suture that led to our use of PLGA as a drug delivery matrix. On the other hand, there are some DDS that are more hype than success at this time, such as non-viral gene therapy and efficient delivery of peptides and proteins without the need to inject them.
- **Q:** Which biomaterial/drug delivery problems would you like to see solved in the future?
- A: Gene therapy and antisense therapy, since that will give us the ability to change cell phenotypes within a person's body, and not have to deal with foreign cells.
- **Q:** Who or what had the greatest influence in directing your science?
- A: First it was my father, who was an MIT chemical engineering graduate and kept telling me from an early age that I was going to go to MIT and study chemical engineering. Then it was two mentors at MIT, Alan Michaels and Ed Merrill, who both taught me how to visualize and utilize molecules. From there it was a string of great collaborators here at the University of Washington, starting with my postdocs Tom Horbett and Buddy Ratner, and continuing with Pat Stayton, my main colleague and collaborator these days. And, all along my academic career of over 45 years it was and continues to be my students who have taught and continue to teach me so much!

June 12-16, 2004 Hawaii Convention Center Honolulu, Hawaii, USA Abstract submission opans Novambar Isti Mark your calendar for the **31st Annual Meeting** and Exposition of the Controlled Release Society Join us for an incredible scientific program that includes the following esteemed Plenary Speakers: Stem Cells Plenary Speaker: Jane Lebkowski, Geron Corporation, USA Probiotic Therapy Plenary Speaker: George Madarlane, University of Dundee, UK World Epidemics and Novel Vaccines Plenary Speaker Rino Rappuoli, Chiran Corporation, Itlay The Brain and How to Reach It Plenary Speaker: William Pardridge, University of California-Los Angeles, USA **DNA Medicines** Plenary Speaker: Alain Rolland, Vical, Inc., USA Molecular Beacons Plenary Speaker: Wei Hong Tan, University of Florida, USA Visit www.controlledrelease.org or call +1 (763) 512-0909

for detailed meeting and registration information

Journal of Controlled Release Jighights

Efforts to increase skin permeability continue to be investigated. One method under investigation is electroporation; another method involves liposomes. Barry and coworkers, in an article published in the *Journal of Controlled Release*, have examined the combination of electroporation and liposomes (flexible or ultraflexible phospholipid vesicles). Interestingly, the combination of these two penetration-enhancing systems did not lead to enhanced skin permeability of estradiol. In fact, the liposomes appeared to have a repairing (and permeation retarding) effect on the stratum corneum.

In another recent article, LHRH peptides or BCL-2 homology 3 (BH3) peptide were conjugated to a specific anticancer agent via a polyethylene glycol (PEG) linker. These conjugates were

People continued from page 19

- Q: What advice would you give to today's young scientists?
- A: Focus on solving real and important problems. Go to professional meetings to present your work, and to discuss with and question others about their work. Enjoy making interesting molecules and applying them to solve real and important problems. That's exciting!
- **Q:** How would you encourage the public to vote for more science funding?
- A: Encourage newspapers, TV networks, and internet news media to hire scientifically knowledgeable journalists, and to include a section or segment on scientists and their useful discoveries EVERY DAY, not just once a week. In addition, perhaps we can ask retired scientists who have been successful managers to act as lobbyists to promote more funding for science.
- **Q**: When you find time to relax, what do you do to unwind or get away from it all?
- A: I swim every day at lunchtime; I like to think about molecules with my head in the water. I also enjoy a good cigar with my feet up on my deck.
- **Q:** From which of the scientific disciplines do you predict the next breakthrough?
- A: It will be BIO something, maybe even BIOengineering. We all need to learn as much as possible about how cells function.
- **Q:** Any regrets?
- A: Yes. I minored in quantum physics during my ScD course of studies. I never use it. I should have studied cell biology.
- **Q:** Tell us more about the Chandra Sharma Award of the Indian Society for Biomaterials and Artificial Organs.
- A: Chandra Sharma is a pioneering Indian scientist who initiated biomaterials research in India, and created a Biomaterials Research Institute in Trivandrum in the south

By David. R. Friend

designed to target cellular antiapoptotic defenses of ovarian cancer. Using a camptothecin-polyethylene glycol-peptide conjugate, Dharap et al. were able to increase the cytotoxicity of camptothecin, relative to unconjugated drug. PEG conjugation presumably leads to improved molecular targeting of the peptides.

The goal of an inhaled insulin product has not yet been reached but efforts continue. One such development effort, reported by Blair and coworkers, is a sustained release pulmonary formulation of sodium hyaluronate in dry powder form. Specific hyaluronate formulations were found to significantly increase the plasma mean residence time of insulin when administered to beagle dogs compared with powder insulin alone.

of India. The Indian Society of Biomaterials and Artificial Organs established an award in his honor, and I am the latest recipient. I will be the Plenary Speaker at their annual meeting in Mumbai in December of this year. Actually, I am very proud of the fact that I am invited to be Plenary Speaker at six meetings around the world this year. I am also proud of the Founders' Award of the Society for Biomaterials, which I received at the World Congress on Biomaterials in Hawaii in 2000. I am most proud of the two symposia held in my honor.

- **Q:** Tell us about the conferences in Maui in honor of your 60th and 70th birthdays:
- A: I have been extremely privileged to have my colleagues and collaborators organize two meetings in my honor. First, in 1992, it was Sung Wan Kim, Jim Anderson and Jan Feijen who organized a symposium in Maui to celebrate my 60th birthday in December of that year. Over 120 came from around the world, and the meeting was an outstanding scientific and fun time. Articles from this meeting were published in seven issues of the Journal of Biomaterials Science, with a great amount of work and support from Stuart Cooper, Editor. These articles were later incorporated into an 1100 page "Festschrift" book, published by VSP. Then, just last year in December, Buddy Ratner, along with Pat Stayton, Tom Horbett, and others, organized a symposium in honor of my 70th birthday. Over 140 came to this symposium, which was also a great event and a wonderful time, both in science and on the beach! Buddy, Tom, and Pat, along with Stuart, are working on another "Festschrift" at this time. I am really, really grateful for all those who have conceived, worked on, and participated in these two meetings!
- Q: Is there anything you'd like to say to anyone?
- A: I am immensely grateful for the wonderful friendships I have made over the years with my teachers, my colleagues and collaborators, and my students.

PATENT WATCH Consumer & Diversified Products

In the second half of 2002, 225 patents were found on the encapsulation of flavours and food additives via the Derwent World Patent Index. In Europe, 54 new patents were filed. From Asia-Pacific, 32 patents were published in Japan, 14 in China and 6 in Korea. In the US, 30 new patents appeared. The number of WO patents was 86. Last but not least, Canada, Brazil and South Africa all published one new patent. In the figure below, the numbers of filed patents per region are shown.



EMULSIONS, SPRAY DRYING & AGGLOMERATION

Emulsion based delivery systems were patented by a number of companies. For example, a process for making microcapsules from an oil dispersed in water, useful in slow release formulations or to provide a polymer barrier to reduce physical contact between a user and the encapsulated material, was claimed by Syngenta (WO 200268111). The process comprises heating of an oil-in-water dispersion containing a surfactant above its phase inversion temperature to form a bicontinuous phase composition, cooling below the phase inversion temperature and encapsulating the oil droplets formed. In another example, Shiseido (JP 2001354515) describes oil-water-oil type composite emulsions with excellent stability for use in cosmetics. The composite emulsion does not contain a surfactant as an emulsion stabilizer, hence the emulsion is highly safe for use in cosmetics. *Spray drying* as a tool to obtain a powdery product by removal of water was described in numerous patents. Examples are the isolation of soybean whey protein and oligosaccharides (CN 1364765 & 1364763 from Zhonglian Jiesei), isolation of protein hydrolysates from soy flour (WO 200269733, Council), to obtain cosmetics products (JP 2002212030, Kanebo Ltd), to dehydrate vegetable material (BR 200001989, Aragao Craveiro), the production of astaxanthin-containing powder for use in animal feed or carotenoid powder for food colouring purposes (WO 200277105 and JP 2002112712 from Fuji), oxygencontaining carotenoid powders to be used as dye in foods (BASF, DE 10064387), for the stabilization of fruit juice concentrate powders (WO 200243510, Mann), for the production of a batter modifier for fried foods such as croquette (JP 2002065193, Daiichi), to prepare a water-dispersible powder containing phytosterol useful in the treatment of coronary heart disease (WO 200217892, Novartis), fermented cabbage extract powder for use as health product (JP 2002097148, Toyo Shinyaku), instant dry powder curry paste and instant dry shrimp paste as foodstuffs (JP 2002119258 and JP 2002119254, Jaipakdiman) and to make preparations used to promote weight loss (US 6416793, Bioresponse LLC). Drying was also used by Nestle (EP 1198992) to prepare a soluble coffee beverage powder, which includes a soluble gas containing matrix. The powder

By Jack Burger, Quest International

provides a foamed upper surface upon restitution, where substantially all of the foam is made up of bubbles with a diameter of 0.05-0.5 mm, which closely assimilates the texture characteristics of an Italian espresso, but has a reduced bitterness. Cognis prepared 10-5,000 nm nanocapsules by forming an aqueous or organic matrix from an active agent and a wax followed by spray drying (EP 1243326). The nanocapsules are used in cosmetic and/or pharmaceutical preparations (e.g. shampoos, hair lotions, bubble baths, gels, lotions, wax/fat masses, sticks or ointments). In addition, the nanocapsules are sufficiently small to be stored between the fibrils of fibers (rather than adhered to the surface of the fibers), and are highly waterresistant (i.e. not subject to rapid dissolution and washing out). Salvona (WO 200245575) used spray drying to isolate in a dry powder form a multi-component moisture activated controlled release delivery system useful in oral hygiene products (toothpaste, chewing gum, confectionery) comprising solid nanoparticles encapsulated in moisture sensitive microparticles. Agglomeration or granulation was used by a number of companies. For example, Benedict Technology prepared instant tea material, useful for producing tea-like beverages, by extracting water-soluble components from specific plant species (Aspalathus and/or Cyclopia), concentrating, clarifying, spray drying and granulating to form an instantly soluble powder (ZA 299109559). Nestle (EP 1228694) used agglomeration to prepare an aromatizing agent for soups and instant noodles comprising granules formed of foaming agent particles and particles and/or droplets of an aroma compound agglomerated with an agglomerating agent. The aromatizing agent quickly releases aroma within a liquid and releases aroma on the surface of a liquid upon reconstitution. The aromatizing agent has reduced aroma dosage, and improves aroma perception of the product. The aromatizing agent has enhanced solubility, and the perception of aroma/flavor occurs even at cold solvent temperatures. A co-granulate of 50-1,000 micron for use as an emulsifier, stabilizer or thickener, comprising one or more proteins and one or more polysaccharides was claimed by Rhodia (WO 200244279). The co-granulate is dry but dust free and is easily rehydrated, giving good results at low concentrations.

COATING PROCESSES

Coating processes for chewing gum were applied by **Dandy** (WO 200276227) to prepare a coated chewing gum element with reduced pre-chewing deteriorating effects and by Wrigley (WO 200251260) to make coated chewing gum products involving applying antigas agent and a coating syrup comprising bulk sweetener to cores, and drying syrup to produce a coating containing antigas agent that provides relief in the gastrointestinal tract. Bilka (ÚS 20020086092) also used a coating process to apply a sugar syrup coating on confectionery pieces such as chewing gum. To avoid juice leaking from frozen fruits or fruit pieces after thawing, Dirafrost (EP 1228702) claims a preparation process in which a stabilizing powder is coated onto individually quick frozen fruits in a continuously agitating sealed preparation container. Moisture and oxygen stable compositions for flavoured tea fannings, comprising an inert core particle coated with active compound encapsulated in a matrix of high molecular weight carbohydrate, mono, di and trisaccharides and maltodextrin is claimed by Quest (EP1214892). The products are for use in, for example, tea bags and have an excellent stability against oxygen and long storage life. In Figure 1, a schematic cross-section of an inert core

Patent continued on next page

Patent continued from previous page

particle coated with active compound in the carbohydrate matrix is given.



Cross section

Fats and waxes are often used to coat active materials, either by dispersing the material in molten fat or wax followed by grinding after cooling or by fluid bed coating processes. **Bio-Obtention** (FR 2822381) made compositions comprising a vegetable extract rich in superoxide dismutase, which is a proteic extract of Cucumis melo, microencapsulated by coating with a liposoluble fatty material. Using the dispersion and grinding method, **CSM** (EP 1161878) made shortenings for dough consisting of predetermined amounts of an amphiphilic flavour encapsulated in preferably 98% of a vegetable fat. The use of the amphiphilic flavour is to mask the off-taste of the short and medium chain fatty acids present in the fat of the shortening when applied in dough.

PHASE SEPARATION PROCESSES

Micro-encapsulation following phase separation from *chitosan* was patented by Primacare (EP 1243319 and EP 1243322) and Cognis (EP 1243323 and EP 1184027). The two Primacare patents are nearly the same except for the cross-linker. Primare claims that upon use of an inorganic phosphate capsules with a harder shell and a smaller diameter are made while with an anionic surfactant the formed microcapsules have an increased amount of foam on release of the active agent. The two Cognis patents differ in the size of the formed capsules, viz. nano and microcapsules. The nanocapsules are claimed for use in cosmetic and/or pharmaceutical products (e.g. shampoos, ointments) and in flame retardants while the microcapsules are used in clear deodorants sticks. Kitosan Shokuhin filed an interesting patent on chitosan. In JP 2002087967, they claim the use of chitosan as an agent for treating and preventing impulsive disorders. The chitosan has a number average molecular weight of 35000 (5000 and an average molecular weight of 90000 (10000 and is incorporated in food and beverage products. In the patent, an example is given on the treatment of a 17 year old male having adolescent sexual impulse disorder with impulsive violence. After administration of 1300 mg of chitosan per day (1 tablet), the condition of explosive and violent action with respect to an unspecified person was stopped. The individual's impulse property was inhibited effectively.

Cross-linking of alginate with calcium chloride was used by Takeshita (JP 2002171914) to encapsulate easily oxidizable compounds and/or anaerobic micro-organisms for use in ice-creams.

CYCLODEXTRINS

Cerestar (WO 200249455) filed a patent on the stabilization of flavours, encapsulated in cyclodextrin, for use in prepared frozen food or microwaveable food products. The encapsulated flavours are added to food products during preparation. They provide more flavour stability during storage, give less off-flavour and can be used at lower levels compared with non-encapsulated flavour. The preparation of tea containing meringue for use as meringue confectionery was claimed by Ezaki (JP 2002176918). Cyclodextrin is used to stabilize the specific gravity of the meringue and to control the negative influence of the tea raw material on the texture of the meringue. Roquette (EP 1238987) filed a patent on the preparation of a compressible beta-cyclodextrin material with a high compressibility and stability, useful as a contained material for the production of capsules.

MISCELLANEOUS

Firmenich patented the preparation of a granular delivery system based on a matrix, by combining a carbohydrate and prehydrated agar, useful for providing controlled release of an encapsulated flavor and/or fragrance composition (WO 200265858). The granules are prepared by (a) combining and blending a flavor/fragrance with a matrix of an aqueous solution of carbohydrate, the agar, and optional emulsifier with

stirring at a temperature so that a uniform melt is obtained, (b) extruding the melt through a die, (c) chopping, cutting, grinding or pulverizing the material as it exits the die or after cooling the melt and (d) optionally drying. Extrusion was also used by **Gannon** (WO 200252951) to prepare a co-extruded dual component animal food product and by IFF (US 6368633) to make a particulate composition for use in flavoured chewing gum and in toothpaste.

Siemens (DE 10111458) filed a patent on a module for a system used in decentralized biochemical analysis, e.g. medical diagnosis, comprising a sensor chip mounted on a support with an encapsulation leaving its sensitive face accessible to fluids. Among other purposes, the module can be used in the food industry for analysis of electrolytes. In WO 200260275, Kraft Foods claims a process for the production of encapsulated particles for use in food products, in which a second liquid is forced through a feeding needle to surround a thin jet of a first liquid formed by an electrified needle. The two liquids are nonmiscible. The encapsulated particles comprise an inner core of the first liquid and an outer layer of the second liquid, having an average diameter of 100 micron to 15 nanometer. Warner Lambert (US 6361298) filed a patent on a concentrically aligned multiple nozzle apparatus for making seamless capsules used in e.g. beverages, which has a second duct for receiving a flow of heated carrier liquid with formed capsules from a first duc under laminar flow conditions. The new apparatus produces seamless capsules from a glassy carbohydrate in a cost efficient and effective manner. A multi-component structured liquid flow device, in which voltage applied to the liquid feed points is used to generate sheathed flow or liquid, was patented by the University of Malaga (WO 200260591) to produce nano or microcapsules with a size of 15 nm to 1000 micron. Haarmann & Reimer (DE 10212687) filed a patent on a composition for the thermal release of perfumes at above 120 ^oC by applying the composition to heated surfaces by means of piezoelectric actuators. The H&R compositions are useful for individual, personalized perfuming (e.g. cinema, museums).

Last but not least, *polyvinyl acetate* was used by Wrigley in chewing gum (WO 200247489) to encapsulate a mixture of fumaric and malic acid as acidulants, producing an extended period of tartness perception and increased salivation. A mixture of *agar* and dextrin was claimed by Chang (KR 2002006926) to produce microcapsules with encapsulated alpha-tocopherol, having improved storage stability and bioavailability, for use in food products. *Gelatin* capsules were used by **Baumgartner** (US 20020048553) to encapsulate flavours and dental health promoting ingredients for use in tooth paste.

Patent Watch continued on page 25



4 out of 5 patients say they would probably or definitely switch to a brand that offered an equivalent chewing gum formulation*

Fertin Pharma is a world leader in the development and manufacture of chewing gum drug delivery systems. If patient preference matters, call us today.

*Results are from a market survey conducted in spring 2002 among 6.195 patients in the USA and Germany who had used an OTC medication for common cold, pain, heartburn, or allergy within the past year.



www.fertin.com

Email: fertin@fertin.com Telephone: +45 72 15 13 00 Microencapsulation and controlled release of nutraceuticals is showing an unprecedented patent activity spearheaded by food and pharmaceutical companies. This activity is, presumably, a result of the recognition of nutraceuticals as adjuncts and/or preventive treatments for many diseases. Current economical data estimate that nutraceuticals and wellness foods market share claimed \$33 billion in the year 2000 and is expected to top \$47 billion by the end of this year. Following are examples of some innovative compositions and technologies cited in the last 6 months' patent literature:

Delivery system for pharmaceutical, nutritional and cosmetic ingredients (Natreon, Inc.) WO2003035094A1. A unique carrier/delivery system is described whereby a nutraceutical active can be incorporated into Shilajit, a naturally occurring sponge-like material traditionally used as a rejuvenating agent. Shilajit, a fulvic acid-rich matrix, is harvested from steep rocks in the Himalayas and other high mountains. In its pure form, Shilajit forms a stable water-soluble matrix punctured by voids of about 200-1000 Angstroms in diameter. Encapsulation of actives into the porous matrix is achieved by contacting the active with Shilajit suspension and further drying to form stable heteropolycondensate structure. This inventive composition is claimed to be beneficial for enhancing the bioavailability of hydrophobic actives and for their ease of application in compressed tabletting.

Sustained release vitamin composition (Allphamed Pharma &

GlaxoSmithKline) US20030148992 A1. This application describes an oral capsule formulation that can provide simultaneous immediate and sustained release of therapeutic materials. Embedding part of the active into the shell material provides the immediate release mechanism while the controlled release is manipulated via loading the active into an extrudedspheronized inner core. This design is claimed to be advantageous for delivering vitamins that cannot otherwise be stored in human system. In addition, it provides a release mechanism independent of the excipient. Use of cocoa procyanidins combined with acetylsalicyclic acid as antiplatelet therapy (Mars, Inc.) - US 6524630 B2. A therapeutic composition of a cocoa polyphenol extract and aspirin is disclosed. The formulation is claimed to be beneficial in alleviating symptoms of transient ischemic attacks traditionally treated with aspirin but without the risk of damaging platelets and/or gastrointestinal complications associated with NSAIDS. Various forms of delivery systems with controlled and/or sustained release are provided.

Zeaxanthin formulations for human ingestion (Zeaxanthin, Inc.) -USRE 38009E.

A process for stabilizing pure extracts of the R-R stereoisomer of zeaxanthin is described. This isomer is essential for the carotenoid's pronounced activity against phototoxicity and in treating macular degeneration. After harvesting from *Flavobacterium multivorum*, stereospecificty of the pure stereoisomer is claimed to be preserved via encapsulation into a micellar system. The product is, however, limited to low heat food processing applications.

Composition for intestinal delivery (Aqua Solutions, Inc.) US20030118547A1.

This application discloses an alternative approach to enteric coating for orally administered physiologically active agents. The composition comprises co-packing the active with neutralizing agents (to increase the pH in the digestive system), and enzyme inhibitors (to substantially prevent enzymatic digestion in the stomach). Examples of neutralizing agents include bicarbonates, citrates and other forms of antacids. Digestive enzyme inhibitors include anti-proteases, egg albumin, EDTA, etc.

Modified release dosage forms (McNeil-PPC, Inc.) WO2003026625 A1. A system for delayed release of actives from a dosage form is described. The patented system comprises (a) a core containing the active ingredient, and (b) a thick molded shell (4000 microns thickness and up to 50% weight of the dosage weight) surrounding the core. The uniqueness of this system lies in its

By Jamileh Lakkis, Ph.D., Pfizer, Inc.

claimed ability to provide an extended onset of dissolution (greater than one hour) regardless of the prevailing pH. Shell morphology is claimed to be very compact and is substantially free of pores.

Co-processed carbohydrate system as a quick-dissolve matrix for solid dosage forms (SPI Pharma, Inc.) WO2003051338 A1.

This invention discloses a quick dissolving formulation comprising directly compressible carbohydrate compositions. Sugars and/or sugar alcohols are first dissolved to form homogenous slurry followed by addition of the active. Subsequent seeding by carbohydrate crystals is claimed to be beneficial for controlled disintegration of the tablets. Morphology of the finished product showed the absence of filamentous structures, an important attribute for enhanced flowability and quick-dissolve properties.

Coating for orally administered compositions (Metagenics, Inc.) US20030082231 A1.

A chlorophyllin/methyl cellulose preparation for masking the taste of objectionable nutraceutical actives, in particular those containing sulfur compounds is claimed. Chlorophyllin is formed via delicate alkaline hydrolysis of natural chlorophyll in the presence of a monovalent metal ions and subsequent formation of chlorophyllin chelates. Cellulose-chlorophyllin solutions can be applied to objectionable tasting substrates via spray drying or fluid bed coating.

Method of making gluten colloidal dispersions and edible coatings there from (Opta Food Ingredients, Inc.) US5705207A.

This application refers to film forming compositions based on colloidal dispersions of gluten for providing good moisture barriers for hygroscopic substrates. Similarly, US20030021881 A1 (Homogeneous solid matrix containing vegetable proteins) claims that controlled release from gluten-based films can be achieved via incorporation of lecithin into the matrix. Varying lecithin concentration, can impact the film's susceptibility to

Patent Watch continued from previous page

hydration and its swelling capacity, thus controlling the release of the active in aqueous media.

Edible composition and dosage form comprising an edible shell (McNeil-PPC, Inc.) WO2003026616A1 A1.

A process for incorporating actives into a crystallizable carbohydrate matrix is described. The two-step process comprises injecting a flowable crystallizable material into a mold cavity containing the active followed by quick thermal shock to induce crystallization of the carbohydrate shell. The resulting dosage is claimed to be very homogeneous and free from striations and imperfections that can adversely impact the active's release mechanism.

Chewable product including active ingredients (Wm. Wrigley Jr., Co.) US20030021830 A1.

This patent discloses a process for embedding actives such as nutraceuticals or medicaments into a chewing gum base for their extended release. The active is mixed with the gum base followed by conventional mixing, forming, sheeting, scoring and pan coating. In a related application US20030049208 A1 (Overcoated chewing gum formulations), encapsulated actives are layered onto the chewing gum shell material via pan coating. This design is claimed to be effective in enhancing the release and bioavailability of the active by chewing and subsequent pressure generation in the buccal cavity.

Simethicone solid oral dosage form (McNeil-PPC, Inc.) US20030091624 A1. A composition for producing free-flowing compressible substrates is described. Simethicone (antigas agent) or similar oily material can be adsorbed onto silicified microcrystalline cellulose (Si-CMC) at relatively high ratios (1:2.2 oil:Si-CMC), thus leading to high payloads and smaller dosages.

Method of modulating release of saccharides and uses thereof (ISM Biolpolymer, Inc.) WO2003054208 A2. A process and a composition for adjusting the release of therapeutic oligosaccharides according to their target physiological function are claimed. Glucosamine, a derivative of chitin, is a well-known nutritional supplement for relieving various ailments such as joint

inflammation and



articular degeneration. When ingested, glucosamine is absorbed into the liver where it further degrades into smaller compounds that serve various biosynthetic processes. Currently, there is no application that allows equilibrated exchange between the body's rate of catalyzing its reservoir of the oligosaccharides and the modulation of its capability to use it in different pathways. This patent provides a method for controlled degradation of the polymers and for the synchronized release of mono and oligosaccharides with the animal's ability to assimilate them.

Tobacco products with stabilized additives having vitamin E activity (Rousseau Research, Institute) US6584980 B1.

A composition for making smoke or smokeless tobacco with less irritation and enhanced antioxidant properties is claimed. Powdered encapsulated vitamin E or its ester analog is mixed directly with tobacco during the curing or manufacturing process. Esterifying vitamin E blocks its antioxidant site with a combinable acid. Combustion, heat or enzymatic action that occurs during smoking (or chewing of smokeless tobacco) can dissociate the acid from the ester yielding free, fully active vitamin E at the point of use. When smoked, cigarettes containing vitamin E acid succinate were claimed to maintain good flavor without causing any throat or lung irritation compared to unfortified cigarettes.

Edible Film (Givaudan, S.A.) WO2003043659 A1.

An edible film containing actives and/or flavors that can rapidly disintegrate when placed in the mouth is described. The film comprises a hydrocolloid film- forming material and microparticles containing actives that can deliver breath freshening or specific medicaments. The described delivery system is claimed to provide great latitude when designing specific controlled release properties for a multitude of actives, in addition to masking the taste of objectionable actives. Payloads up to 20% of actives are also claimed.

Rotor-stator apparatus and process for the formation of particles (E.I.Dupont De Nemours & Co.) US2003033097A2. An apparatus for producing fine encapsulated particles via antisolvent, reactive, salting out or rapid cooling precipitation and crystallization is described. The apparatus is claimed to eliminate drawbacks of conventional postcrystallization techniques such as milling that can adversely impact bioavailability and shelf stability of encapsulated systems. The inventive assembly consists of two or more fluid jet streams, one containing slurry or a solution of the active material and another stream of the crystallizing/ salting out fluid. Novelty of this application lies in the use of an in-line rotor-stator mixer that is claimed to achieve intense micromixing of the incoming jets. The dried powdered products are claimed to possess uniform morphology and very narrow particle size distribution.

Transdermal Drug Delivery Technology

By Yiping Wang B.S.¹ and Bozena Michniak Ph.D.² ¹ Ernest Mario School of Pharmacy, Rutgers-The State University of New Jersey, Piscataway NJ ² Dept. of Pharmacology & Physiology, UMDNJ-New Jersey Medical School, Newark, NJ.

Transdermal drug delivery (TDD) systems hold several advantages to conventional drug administration technology, such as the potential of zero-order release, the ease of use, patient compliance and avoidance of the first-pass metabolism by the liver. A major drawback of TDD, however, is that it is difficult to deliver many drugs in therapeutically effective quantities transdermally due to the rigid structure of the uppermost layer of the skin, the stratum corneum (SC). A good drug candidate for passive transdermal delivery by conventional technology has to be effective at the daily dose of less than 10mg, with a molecular weight of less than 500 Daltons and required lipophicility (hydrophilic drugs are difficult to localize within the SC while very lipophilic drugs are more likely to stay in the SC rather than pass into the lower epidermal layer)^[1].

Because of all these restrictions, the development of TDD systems in major pharmaceutical companies cooled down in the 1990s. Over recent years the interest has re-emerged as the development of formulations, microelectronics and microfabrication technologies, combined with demands for painless delivery of biotherapeutics have occurred. The awareness of transdermal products by consumers from several OTC transdermal products also helped the development of such systems. The annual sale of transdermal products in US from 10/ 01 to 9/02 was \$2.4 billion. There was a 19% increase over the previous year and 27% higher than two years before^[2]. Development of transdermal delivery technologies can be viewed from several aspects including the development of new formulations, iontophoretic, sonophoretic, and microneedle transdermal delivery, as well as transubcutanous immunization.

New formulations – Skin penetration enhancers are used to facilitate co-administered drug permeation through and into the skin by several postulated mechanisms, while penetration retardants are used to prevent the permeation of agents such as sunscreens or insecticides through the skin. MacroChem Corp. synthesized the enhancers of the SEPA® series by condensation of ethylene glycol and decyl aldehyde. SEPA® enhance skin permeability by temporarily altering the fluidity of the lipid layers within the stratum corneum. MacroDermTM is a group of permeation retardants from the same company which are polymers are of low to moderate molecular weight and can be potentially used in sunscreen and insect repellant products to

Transdermal continued on next page



Transdermal continued from previous page

improve skin retention of the formulation and prevent the permeation of toxic components.

Some new gels and creams are available for making TDD systems. Atrix Laboratories, Inc. developed SMPTM gel, MCATM gel and BCPTM gel/liquid for topical, systemic delivery and wound healing. SMPTM gel allows the topical delivery of highly water-insoluble drugs and in this system, a dissolved drug is combined with a microparticle suspension of the drug to allow a controlled release of drug which then penetrates the skin. With a blend of cellulose polymers dissolved in alcohol, MCATM formulations dry quickly and form tenacious, moisture-resistant films that can deliver drugs continuously from hours to days and promote wound healing. BCPTM delivery system can be formulated either as film-forming gels for wound protection or liquids for topical applications to deliver drugs.

The Microsponge[®] and Polytrap[®] technologies developed by Cardinal Health Pharmaceutical Technology & Services involve using biologically inert, microscopic polymer particles that absorb, trap or bind to medicines and other compounds. The polymers are then blended into creams, gels, liquids or powders and applied to the skin where they steadily release medication.

Some pharmaceutical and cosmetic companies patented new formulations, agents and devices recently to reduce skin sensation and irritation (US6455076, US6426092, US6416760, US6352698, US 6346258, US6336049).

Iontophoretic delivery – The principle of iontophoresis utilized here is the flux of ionic or neutral compounds across skin can be enhanced by the application of a mild electric current on the skin. Drug permeation is proportional to the current density applied and the current below 0.5mA/cm² is normally thought to be safe and comfortable to patients. A significant advantage of ionotophoretic delivery is that the onset time can be dramatically reduced compared to conventional passive delivery. The lidocaine delivery system developed by Vyteris, Inc. is comprised of a patch and a dose controller (Fig.1). The system was designed to be effective in achieving dermal anesthesia within 10 minutes of application before needle injection and blood donation. Vyteris Inc. is also developing iontophoretic patches for patients with migraine and Parkinson's disease.



Fig.1. Iontophoretic transdermal delivery system developed by Vyteris, Inc.

ALZA Corp. developed a self-contained, disposable and electrically-driven fentanyl transdermal delivery system, E-Trans[®], which is currently in Phase II clinical trials.

Sonophoretic delivery – Low frequency ultrasound can increase the permeability of human skin by introducing cavitations. Sontra Medical Corp.'s SonoPrep[®]skin permeation device provides a

convenient way to enhance permeability through 15 seconds low frequency ultrasound treatment that allows sustained drug permeability of the skin for up to 24 hours.

Microneedle and microprojection delivery – Microfabrication technology used to make integrated circuits is now being utilized to produce microneedle patches. ALZA Corp. makes its microprojection patch, Macroflux® with a thin titanium screen with very precisely manufactured microprojections (Fig. 2). The needles or projections on the surface of the patch are sufficiently long to penetrate through the SC, but short enough not to stimulate nerves in deeper tissue and thus are painless. Effective transdermal deliveries of ovalbumin and antisense oligonucle-otides by Macroflux® have been demonstrated^[3,4].



Fig.2. Unloaded and drug loaded microprojections produced by ALZA Corp.

Transcutaneous immunization (TCI) – In the TCI system being developed by Iomai, Inc. cholera toxin, an immune stimulant, is delivered with vaccine antigen at the surface of the skin, targeting the Langerhans cells, a major component of the immune system. Activated Langerhans cells encapsulate the vaccine antigen and migrate to the regional draining lymph nodes hence inducing an immune response. Iomai's vaccine products for influenza, traveller's diarrhea, tetanus, and *H. pylori* are currently in clinical trials.

With all of these new technologies, the previous restrictions applicable to conventional passive TDD system will be overcome. We can expect the appearance of more efficient transdermal delivery of anesthetics and other drugs and some biotherapeutic agents including peptides, proteins and oligonucleotides in the near future.

References:

- 1. E.W. Smith and H.I. Maibach, Percutaneous penetration enhancers, CRC Press Inc, Boca Raton, 1995, p. 2.
- 2. G.W. Cleary, Transdermal & transdermal-like delivery system opportunities: today & the future, Drug Delivery Technology. 3(2003) 34.
- 3. J.A. Matriano, M. Cormier, J. Johnson, W.A. Young, M. Buttery, K. Nyam, and P.E. Daddona, Macroflux-microprojection array patch technology: a new and efficient approach for intracutaneous immunization, Pharm. Res. 19(2001) 63.
- W. Lin, M. Cormier, A. Samiee, A. Griffin, B. Johnson, C. Teng, G.E. Hardee, and P.E. Daddona, Transdermal delivery of antisense oligonucleotides with microprojection patch (Macroflux[®]) technology, Pharm. Res. 18(2001) 1789.

Matrix-Mediated Gene Delivery for Tissue Repair

By Ronda Schreiber, Ph.D.Selective Genetics, Inc. 11588 Sorrento Valley Road, San Diego, CA 92121, (858) 793-6641 (TEL), (858) 793-6833 (FAX), <u>rondas@selectivegenetics</u>

Gene therapy holds great promise for treating clinical conditions that require protein persistence at the treated site. As compared to protein therapy, which often requires multiple treatments due to the short half-life of many biologically active proteins, therapeutic genes can be engineered in vectors that are stable for weeks in vivo. Delivery by implanting or injecting the gene into the treatment site is attractive for treating localized diseases, such as injured tissues. Local gene delivery can be achieved by either implanting autologous or allogeneic cells that were transfected with the therapeutic gene ex vivo or by delivery of the gene in situ. Of these two approaches, in situ gene delivery is most attractive for repairing tissue, because the gene can be delivered to the repair cells within the injured site. We utilize biocompatible matrices to deliver genes encoding tissue growth factor proteins into injured tissues. The matrix provides a surface into which repair cells can migrate, internalize the gene, and produce the protein.

In order for a biomaterial to function as a gene delivery vehicle, it must possess several characteristics. The carrier matrix must be compatible with the specific tissue environment in which it is to be delivered. The material must support maintenance or differentiation of the cells that are most capable of synthesizing a functional tissue. In addition, the matrix must either be permeable to cells, or it must degrade at a rate that is compatible with the rate of tissue deposition into the treatment site. Importantly, the carrier matrix must support attachment of the gene vector and its subsequent internalization and expression by the local cells. Herein, we describe the role of matrices in delivering growth factor encoding genes for tissue regeneration.

The utility of biocompatible matrices as gene delivery vehicles is best illustrated by comparing the biologic effect of genes delivered locally to a tissue in aqueous solution, versus on a collagen matrix. In multiple tissues, we observed that the gene carrier matrix dictated the pattern of tissue deposition that formed in response to the gene. For example, we showed that gene expression by a plasmid gene vector encoding fibroblast growth factor 2 (pFGF2) delivered into skeletal muscle in a collagen-gelatin matrix was localized to cells contained within the treatment site ¹. In contrast, pFGF2 injected in saline to skeletal muscle stimulated transgene expression that extended beyond the treatment zone, into the adjacent, uninjured muscle.

We further showed that carrier matrices influence the subsequent biologic responses to the therapeutic gene protein product. In one reported study, adenovirus encoding platelet-derived growth factor b (AdPDGF-b) delivered on a collagen-gelatin matrix to dermal wounds stimulated the formation of a healthy repair tissue that was restricted to within the treatment margins ². Treatment of dermal wounds with an aqueous injection of AdPDGF-b, however, resulted in disorganized, hyperplastic tissue adjacent to, but not within the wound bed.

The types and quantity of matrix carriers used to deliver gene vectors affects the amount of gene expression at the treatment site. For example, we showed that adenovirus vector encoding the marker gene luciferase (AdLuc) stimulated greater luciferase protein expression when delivered to muscle wounds on a carrier matrix composed of 1% collagen and 1% gelatin, as compared to gelatin alone ¹.

Physical association between the carrier matrix and the gene vector is, intuitively, a major factor that dictates the amount and location of gene product. Therefore, we evaluated the effect of increasing collagen on gene retention within the matrix, in order to identify the matrix concentration at which gene vectors associated the strongest. We previously showed that, by 48 hours, greater than 90% of adenovirus formulated in 2.6% collagen was retained within the matrix, whereas only 80% of the vector associated with a 0.15% collagen formulation ³. A 2.6% collagen concentration, which is of an ideal consistency for syringe delivery to dermal wounds, is also the maximal amount of collagen needed to observe nearly complete adenovirus retention (Figure 1). A similar vector-matrix association was observed between collagen and plasmid. This non-viral vector associated maximally with collagen at a concentration of 1.5% (Figure 1).

To identify how carrier matrices affect gene expression, we compared transgene protein levels in cells cultured within a collagen matrix containing adenovirus encoding green fluorescent protein (AdGFP), versus in adherent cell monolayer incubated with AdGFP in culture medium. Cells cultured in collagen produced more GFP, as compared to cells cultured in the absence of collagen (Figure 2a). Furthermore, a greater percentage of cells cultured in collagen expressed GFP, as compared to cells cultured without collagen (Figure 2b). Hence, this study demonstrated the utility of carrier matrices in either inducing or maintaining cells in a state that is conducive to transgene expression.

Studies described in this report collectively underscore the role of biocompatible carrier matrices to deliver therapeutic genes for tissue repair. Our laboratory is evaluating the use of synthetic biomaterials whose permeability, degradation rates, and mechanical integrity can be developed for specific, optimal use in various tissue types. For example, we are evaluating the use of calcium phosphate ceramics to deliver bone growth factor encoding genes for spine fusion. This matrix serves dual purposes of having mechanical integrity required in a bony site, as well as being a potent transfection-enhancing agent for use with non-viral plasmid vectors. Such matrix composites hold promise to maximize the full potential of gene therapy for various tissue repair indications.



Figure 1. Release of gene vectors from collagen. Release of plasmid or viral particles from collagen as a measure of vector-matrix association, was determined by measuring vector release

Matrix continued on next page

Matrix continued from previous page

from the collagen matrix into a glycerol-Tris saline solution (pH 7.4) at ambient temperature, after 24 hours of incubation. Subsequently, buffer was analyzed by HPLC for the presence of plasmid or virus. Data are expressed as the percent of gene vector released of the total formulated into collagen matrix at the specified concentration. The "aqueous" formulation refers to vector added directly to the buffer, in the absence of matrix, therefore, serves as the measure of 100% vector release.



Virus Dose (MOI)



Virus Dose (MOI)

Figure 2. Fluorescence in cells transfected with AdGFP. 293 cells, an epithelial cell line, were transfected *in vitro* with a green-fluorescent protein-encoding adenovirus (AdGFP) at various doses of multiplicities of infection (MOI) for 48 hours. Cells were assayed by flow cytometry for fluorescence intensity, a measure of GFP expression per cell (Panel A), or for the percentage of fluorescent-positive cells, a measure of GFP expressing cells within the population (Panel B). Data are expressed as arbitrary fluorescent units (Panel A) or percent of fluorescent-positive cells (Panel B).

References

 Doukas, J., Blease, K., Craig, D., Ma, C., Chandler, L.A., Sosnowski, B.A., Pierce, G.F. *Mol. Ther.* 2002, *5*, 517-527.
Doukas, J.; Chandler, L. A.; Gonzalez, A. M.; Gu, D.; Hoganson, D. K.; Ma, C.; Nguyen, T.; Printz, M. A.; Nesbit, M.; Herlyn, M.; Crombleholme, T. M.; Aukerman, S. L.; Sosnowski, B. A.; Pierce, G. F. *Hum. Gene Ther.* 2001, *12*, 783-798.
Chandler, L. A., Gu, D.L., Ma, C., Gonzalez, A.M., Doukas, J., Nguyen, T., Pierce, GF., Phillips, M.L. *Wound Repair Regen.* 2000, *8*, 473-479.

Selective Genetics, Inc. 11588 Sorrento Valley Road San Diego, CA 92121 (858) 793-6641 (TEL) (858) 793-6833 (FAX) rondas@selectivegenetics To whom correspondence should be addressed: Barbara Sosnowski, Ph.D. (858) 793-6641 x 3014 (TEL) barbsosn@selectivegenetics.com

Medichew continued from page 18

To qualify as a clinically reliable and attractive drug delivery system, chewing gum must meet the same stringent demands as tablets. At Fertin Pharma, the production, quality assurance, and quality control are currently in accordance with cGMP standards and are certified in accordance with ISO9001:2000. In order to comply with the standards set by the US FDA, new FDA facilities are under construction.

Though chewing gum as a drug delivery system has currently gained wide acceptance only within smoking cessation and oral health care, vast interest in this mode of drug delivery for a wide variety of other indications exists and continues to grow. Clinical trials have confirmed the advantages to be gained by exploiting the effects of chewing gum per se, the convenience of the delivery system, and the possibilities of buccal absorption and local effect. Furthermore, one trial has indicated that chewing gum is possibly a safer drug delivery system for active substances that are susceptible to abuse.

If chewing gum as a drug delivery system is to be employed in additional therapeutic areas, it is important that the delivery form is acceptable to the end users. Clinical trials and market research have proven this to be the case. In the coming years it is very likely that new formulations will enter the market and that chewing gum will become a common drug delivery system.

MISSION:

Fertin Pharma will perform as a "best in class" partner for product development and the manufacturing of medical chewing gum. Our focus will be on financial performance and benefits for customers, patients, and employees.



InTheNews

Battle of the DNA Bulge May Help Thwart Cancer; UH Research Aims to Understand How Mistakes in DNA Replication Lead to Disease Studies at the University of Houston are shedding light on the mechanisms our bodies use to recognize and repair mistakes in our genetic code, mistakes that, left unchecked, could lead to cancer.

DNA is the body's blueprint found in every cell, and it carries all our genetic information. Every time a living cell divides to make new cells, it must first make a copy of its DNA, or transcribe it, similar to the way monks used to transcribe old scrolls. If a DNA transcription error is made, the body's "spellcheckers" may find it and fix it. But if they fail to detect and repair the mistake, the cell's instructions are altered.

"When a mistake gets through, you have a problem that could lead to a dangerous mutation," says B. Montgomery Pettitt, the Hugh Roy and Lille Cranz Cullen Distinguished Professor of Chemistry at UH. "If that mistake has turned a good instruction into a bad instruction that says 'please make nonsense,' then that could lead to cancer."

Pettitt and his research group are studying a particular type of DNA transcription error called a bulge, as well as the protein "spellcheckers" responsible for finding and repairing bulges.

"Some of the worst places to get these errors are in the genes that determine cell growth and death," Pettitt says. "One of the characteristics of cancer cells is that they are essentially immortal, and they're like Peter Pan — they never grow up. So this inhibiting of normal cell death is one of the real problems."

Ultimately, the UH studies may lead to more targeted cancer treatments, says Pettitt, who also is director of the Institute for Molecular Design at UH.

Pettitt presented his research on DNA bulges and recognition proteins Sept. 7, at the 226th annual American Chemical Society national meeting in New York, N.Y.

Pettitt's work describing DNA bulges comes fifty years after scientists first described what the normal structure of DNA looks like — a ladder twisted into a helix, or coil. The sides of that ladder are made of sugar and phosphate groups, and the "rungs" are chemical building blocks called bases. There are four different bases, abbreviated A, G, T and C. A pair of bases, joined together, makes up each rung.

As DNA is being copied, a protein untwists and unzips the double helix that joins the base pairs. Another protein then comes along and begins synthesizing the appropriate bases to latch on to each side of the now separated strands, resulting in two new DNA strands.

Pettitt and his group are particularly interested in the protein that proofs and checks the DNA strands for errors during this process.

"Understanding what these proteins look for as they 'proofread' the DNA, where they look, and how they recognize a DNA bulge will help us better understand what goes wrong when the protein can't recognize the errors," Pettitt says.

A DNA bulge occurs where an extra base winds up on one side of the DNA strand.

"A bulge is like having a ladder with one extra rung that only goes halfway across," Pettitt explains.

The bulge can be either a missing base, or an extra one that has been inserted during the DNA copying process. Most bulges happen during replication.

In the research presented at the ACS meeting, Pettitt's team looked at all the various ways a bulge can orient itself along the DNA strand. The researchers built sophisticated computer models of the bulges, based on experimental data. Their computer simulations help them determine how probable each of the various bulge orientation models is.

"No one has looked at these things in the way we have. What we found was that the bulge could sit there on the inside of the helix with nobody across from it, or it could flip outward and point into the solution," Pettitt says. These were the most likely orientations, but an errant base also could try to bully its way in to the strand and make weird distortions in the whole DNA ladder.

"There's a range of things that it can wind up doing," Pettitt says. "We want to focus on the orientations that happen a lot, those that are very probable."

As for how prevalent bulges are in general, Pettitt says, "this is something we're definitely working on." The UH research is funded by the National Cancer Institute, which is part of the National Institutes of Health.

LI-COR Biosciences Awards Instrument System to Muhlenberg College LI-COR Biosciences awarded its 2003 DNA Undergraduate Sequencer Award to Muhlenberg College in Allentown, PA. The college will use it as a centerpiece in its plans to integrate the study of chemistry and biology to promote a community of experimental learning. This is the second year LI-COR awarded a system including a DNA Analyzer, analysis software and training to an undergraduate institution as part of the company's commitment to encourage hands-on training in molecular biology for students. Colleges in the United States and Canada competed for the \$71,000 award by submitting essays on how a LI-COR system would enhance existing curriculums. Last year, Gustavus Adolphus College in Minnesota was the inaugural award recipient. Muhlenberg offers a year-round undergraduate curriculum including a summer program with students working on their own research projects. "Active participation in the process of science is one of the most effective methods of developing critical thinking and communication skills that last a lifetime," says Dr. Marten Edwards, assistant professor of biology. "We've taught the theory and the chemistry behind the process, now we can let students actually experience sequencing DNA," says Dr. Steven Weiner, assistant professor of chemistry. "The first week the LI-COR is in the lab, a student will be using it as part of an

a student will be using it as part of an ongoing study of mosquitoes and human disease," adds Edwards. "We already have plans to integrate the instrument into two classes this fall and several more next semester".

WellSpring Pharmaceutical Corp. Concludes Exclusive Option Agreement with Emory University for Rights to New Coronary Bypass Surgery Therapy WellSpring Pharmaceutical Corporation has concluded an option agreement for exclusive worldwide licensing arrangement with Emory University, Atlanta, GA for rights to new drug technology used in coronary artery bypass grafting (CABG). CABG is a surgical procedure that reroutes "bypasses" blood around clogged arteries to improve blood flow and oxygen to the heart. The American Heart

News continued from previous page

Association estimates that there were approximately 519,000 CABG surgeries performed in the United States in 2000. According to the American College of Cardiology, this procedure can be highly effective in relieving angina pectoris (acute chest pain) and, for certain kinds of patients, CABG can prolong life.

While the most common source of bypass grafts are venous grafts taken from the leg, newer techniques utilize arterial segments taken from the chest wall or the arm. The use of arterial grafts instead of venous grafts has increased in recent years. This is due to their superior patency (enhanced ability to carry more blood flow and oxygen) and a lowered incidence of restenosis (reclosure) requiring the use of stents to keep blocked segments open, or a second bypass operation. In contrast to venous grafts, which lack significant muscle in the wall of the vessel, arterial grafts have muscular walls. When harvested surgically, these grafts often go into spasm, which temporarily impairs their ability to carry blood. Recently, researchers at Emory have been conducting research into ways to relieve the arterial spasm of these grafts and improve the postoperative recovery of the

patient. The new Emory technology optioned to WellSpring employs the drug, phenoxybenzamine (Dibenzyline®; WellSpring Pharmaceutical Corporation). These researchers have found that bathing arterial grafts in a solution of phenoxybenzamine outside of the body prevents the muscular wall of the graft from going into spasm and significantly enhances the post operative recovery of the patient. Furthermore, the enhanced blood flow and reduced risk of a second surgery are the most important outcome benefits from this technique.

WellSpring currently manufactures and markets Dibenzyline[®] in capsule form for the treatment of a severe form of high blood pressure associated with certain cancers. The company intends to develop a new sterile liquid form of the drug specifically for use by cardiothoracic surgeons for CABG. Before Dibenzyline® can be marketed for such new use, FDA approval will be required. WellSpring expects to undertake the necessary studies needed for FDA approval commencing in 2004. Because the new technique is used outside of the body and, because Dibenzyline[®] is currently marketed as an approved drug in capsule form, it is

expected that the program required for approval of the new dosage form and use would be completed in a reasonable period of time.

WellSpring Pharmaceutical Corporation's Founder and CEO, Dr. Robert A. Vukovich, commented on the new agreement: "We believe that this new cooperative effort between Emory University and WellSpring Pharmaceutical will result in the addition of an important new medicine into the armamentarium of the cardiothoracic surgeon and facilitate the employment of newer surgical techniques for CABG which will improve the quality of life for bypass patients."

Epeius Biotechnologies Corporation Gains FDA Orphan Drug Approval for REXIN-G, the World's First Targeted Injectable Gene Therapy Vector, for Pancreatic Cancer Epeius Biotechnologies Corporation stated that the FDA has approved REXIN-G, the world's first tumortargeted injectable gene therapy vector, as an orphan drug for pancreatic cancer. The

News continued on next page



Send or email a letter describing current and proposed research activities, current *curriculum vitae*, including grant funding history, and the names of three references to:

William T. Beck, Ph.D. Professor and Head Department of Biopharmaceutical Sciences College of Pharmacy University of Illinois at Chicago 833 South Wood Street Chicago, Illinois 60612-7231

Applications will be received electronically at: <u>PKsearch@uic.edu</u>

For fullest consideration, applications should be received by October 1, 2003, but, if necessary, the search will continue until a suitable candidate is identified.

The University of Illinois at Chicago is an Affirmative Action/Equal Opportunity Employer

Faculty Position in Pharmacokinetics Department of Biopharmaceutical Sciences College of Pharmacy The University of Illinois at Chicago

The Department of Biopharmaceutical Sciences in the College of Pharmacy invites applications for a tenure-track faculty position at the Assistant, Associate, or Full Professor level in the field of Pharmacokinetics. Applicants must possess at least a PhD, PharmD, or MD degree. The Department of Biopharmaceutical Sciences has particular interests and strengths in pharmaceutics and pharmacology related to cancer therapy. The College of Pharmacy has complementary strengths in analytical and medicinal chemistry, proteomics, and clinical pharmacy, with emphasis on cancer chemoprevention, cardiovascular pharmacology, neuropharmacology, and infectious diseases. We are particularly interested in candidates with pharmacokinetic research interests that will complement these Departmental, College and University research efforts. The successful candidate should have a record of peer-reviewed grant support and publications in these areas and should be prepared to participate in the teaching programs in the College. Applications are especially encouraged from women and minorities.

The College of Pharmacy is ranked among the top five U.S. colleges of pharmacy in total funding from the National Institutes of Health. The Department of Biopharmaceutical Sciences consists of 17 tenured/tenure-track faculty positions. Departmental research funding totaled over \$4 million in FY02. The Department of Biopharmaceutical Sciences can offer newly-renovated first-class laboratory space and a competitive start-up package.

Located just west of downtown Chicago, the College of Pharmacy of the University of Illinois at Chicago is in the heart of the University of Illinois Medical Center, which includes the UIC College of Medicine, the UIC Hospital, and other allied health science Colleges. This Illinois Medical District has all the necessary clinical and core facilities to perform work in the desired areas of research.

News continued from previous page

FDA's decision to approve REXIN-G was based on objective demonstrations of medical plausibility of REXIN-G as an effective treatment for pancreatic cancer. The major benefit to the Company is market exclusivity for the REXIN-G product for all types of pancreatic cancer. This represents a highly significant milestone for Epeius Biotechnologies since its lead product, REXIN-G, is the first gene therapy product to gain FDA orphan drug designation for pancreatic cancer.

Epeius also stated that the Company has executed a screening agreement with the National Cancer Institute wherein NCI scientists will evaluate the activity of **REXIN-G** and other promising targeted gene therapy products at the NČI. In an interview with Dr. Frederick L. Hall, President and CEO of Epeius Biotechnologies, Dr. Hall emphasized that "Federal and State support is vital to an emerging biotech company like Epeius, to expedite the advancement of REXIN-G and other targeted genetic medicines to the clinic for the benefit of cancer patients. The screening agreement is an important first step."

Nabi Biopharmaceuticals Successfully Completes StaphVAX(R) Immunogenicity Study, Confirmatory Phase III Trial On Track Nabi Biopharmaceuticals has successfully completed an immunogenicity trial using material from the lot of StaphVAX(R) (Staphylococcus aureus Polysaccharide Conjugate Vaccine) intended for use in a confirmatory Phase III trial later this year. The immunogenicity trial was an openlabel, single-dose study in 40 healthy volunteers that evaluated the antibody response to StaphVAX.

"The results from this trial are an important proof that we can successfully transfer production of StaphVAX to a contract manufacturing facility. This study demonstrated that this lot of vaccine generates antibody levels that are at least as good as those generated from vaccine manufactured in our R&D pilot plant and used in our previous Phase III clinical trial," said Henrik S. Rasmussen, MD, PhD, senior vice president, clinical, medical and regulatory affairs. "In addition, the results from this immunogenicity trial continued to demonstrate an excellent safety and tolerability profile for StaphVÅX. While completing this study, we also made very good progress putting in place the necessary logistics for executing the 3,000 patient confirmatory Phase III trial and we remain on track to initiate the trial in the early part of the fourth quarter." The confirmatory StaphVAX Phase III trial will be conducted in the United

States in approximately 3,000 end-stage renal disease (ESRD) patients. ESRD patients represent the same patient population that was previously studied successfully and reported on in the February 14, 2002 issue of The New England Journal of Medicine. The primary endpoint of the confirmatory Phase III trial will be a statistically significant reduction of S. aureus bacteremia caused by types 5 and 8 S. aureus through eight months post-vaccination, the peak efficacy point in the first Phase III trial. The trial will include a booster vaccination at eight months, and the investigators will continue to follow the vaccine's ability to generate antibodies, efficacy and safety for up to six months following the booster dose.

GlaxoSmithKline's Supplemental New Drug Application for Requip® (ropinirole HCl) Filed for the Treatment of Restless Legs Syndrome

GlaxoŠmithKline has stated that its supplemental new drug application (sNDA) for Requip® (ropinirole HCl) for the treatment of Restless Legs Syndrome (RLS) has been filed by the U.S. Food and Drug Administration (FDA). If approved by the FDA, Requip® will become the first and only drug indicated for the treatment of RLS in the U.S. Currently, Requip® is approved by the FDA and marketed for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

RLS is a neurological disorder that is characterized by an uncontrollable urge to move the legs and painful or distressing sensations in the legs, often described as creepy-crawly or twitching, that occur during rest and are relieved through movement. Because symptoms most often appear during rest in the evening or at night, RLS can lead to appreciable sleep disturbances.

"Millions of Americans suffer from Restless Legs Syndrome, but to date, no medicine is approved to treat it," said Reijo Salonen, MD, GSK Vice President of Clinical Development and Medical Affairs for neurology. "For many of these patients, Requip[®], if approved, could provide relief from the distressing symptoms of Restless Legs Syndrome and have a positive impact on patients' sleep."

The sNDA for Requip[®] is supported by data including three 12-week doubleblind studies. In two of the studies, Requip[®] significantly improved symptoms of RLS and was generally well-tolerated. The third study showed that Requip[®] significantly reduced periodic leg movements of sleep (PLMS), a primary motor symptom associated with this disorder that contributes to the sleep disturbances seen in RLS. The most commonly reported adverse events with Requip in these studies were nausea (38% Requip, 8% placebo), headache (22% Requip, 21% placebo), and vomiting (12% Requip, 2% placebo).

In the treatment of Parkinson's disease, Requip[®] is generally well tolerated. In studies for Parkinson's disease, the most commonly reported side effects are nausea, somnolence, dizziness, headache and dyskinesia. Patients are advised to talk to their doctor about whether they have the potential to develop the sedating effects associated with Requip[®], which include somnolence, and the possibility of falling asleep while engaged in activities of daily living, including operation of a motor vehicle. Fainting or low blood pressure may occur during initial treatment or with an increase in dose. Hallucinations may occur at anytime during treatment. Requip[®] may potentiate the side effects of L-dopa and may cause and/or exacerbate pre- existing dyskinesias.

Results of ALS Model With Incara Compound to Be Presented at American **Chemical Society National Meeting Incara Pharmaceuticals Corporation** announced that its catalytic antioxidant compound, AEOL 10150, has demonstrated efficacy in an animal model of amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease). John P. Crow, Ph.D., Professor of Pharmacology and Toxicology at the University of Arkansas for Medical Sciences, who conducted the recent experiments, will present the results at the 226th American Chemical Society National Meeting in New York City. Dr. Crow was an invited speaker at a symposium on Redox- and Chelation-based Drugs, a component of the Medicinal Inorganic Chemistry Session held on Thursday, September 11, 2003.

Incara Pharmaceuticals Corporation is developing a new class of small molecule catalytic antioxidants that destroy oxygenderived free radicals, believed to be an important contributor to the pathogenesis of many diseases. Incara's catalytic antioxidants have been shown to reduce damage to tissue in animal studies of neurological disorders such as amyotrophic lateral sclerosis (Lou Gehrig's disease) and stroke, and in other non-neurological indications such as cancer radiation therapy, chronic bronchitis and asthma. Incara has completed pharmacology studies, selected a first indication for clinical development, conducted preliminary dose ranging toxicology studies and completed scale-up synthesis of its lead molecule.



NON-PROFIT ORGANIZATION U.S. POSTAGE PAID PERMIT NO. 47 HOPKINS. MI

Abstract submission deadline



- Biodegradable Polymers: From Chemistry to Clinic
- Cell Therapy and Stem Cells
- Colloidal and Nanophase Drug Carriers Controlled Release in
 - Agriculture and Aquaculture Controlled Release in Tissue
- Engineering Controlled Release of Flavors,
- Food Ingredients, and Nutritional Supplements
- for Drug Delivery
- Microencapsulation of Ingredients for Cosmetics and Personal Care
- Modification of Gastrointestinal Transit
- Nanoparticles and Nanotechnology in Consumer and Diversified Products
- Novel Approaches to Treatment of Erectile Dysfunction
- Oral Delivery

- Progress in Diabetes Therapies
- Proteomics and Genomics Aspects of Drug Discovery
- Receptor Mediated Drug Targeting
- Solubilization of Hydrophobic Drug Candidates
- Test Methods and Mechanisms for Controlled Release
- Therapeutic Approaches to Multi Drug Resistance
- Triggered Release