CONTROLLED RELEASE SOCIETY

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NEWSLETTER

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30th Anniversary

Prof. Sandy Florence
From the President

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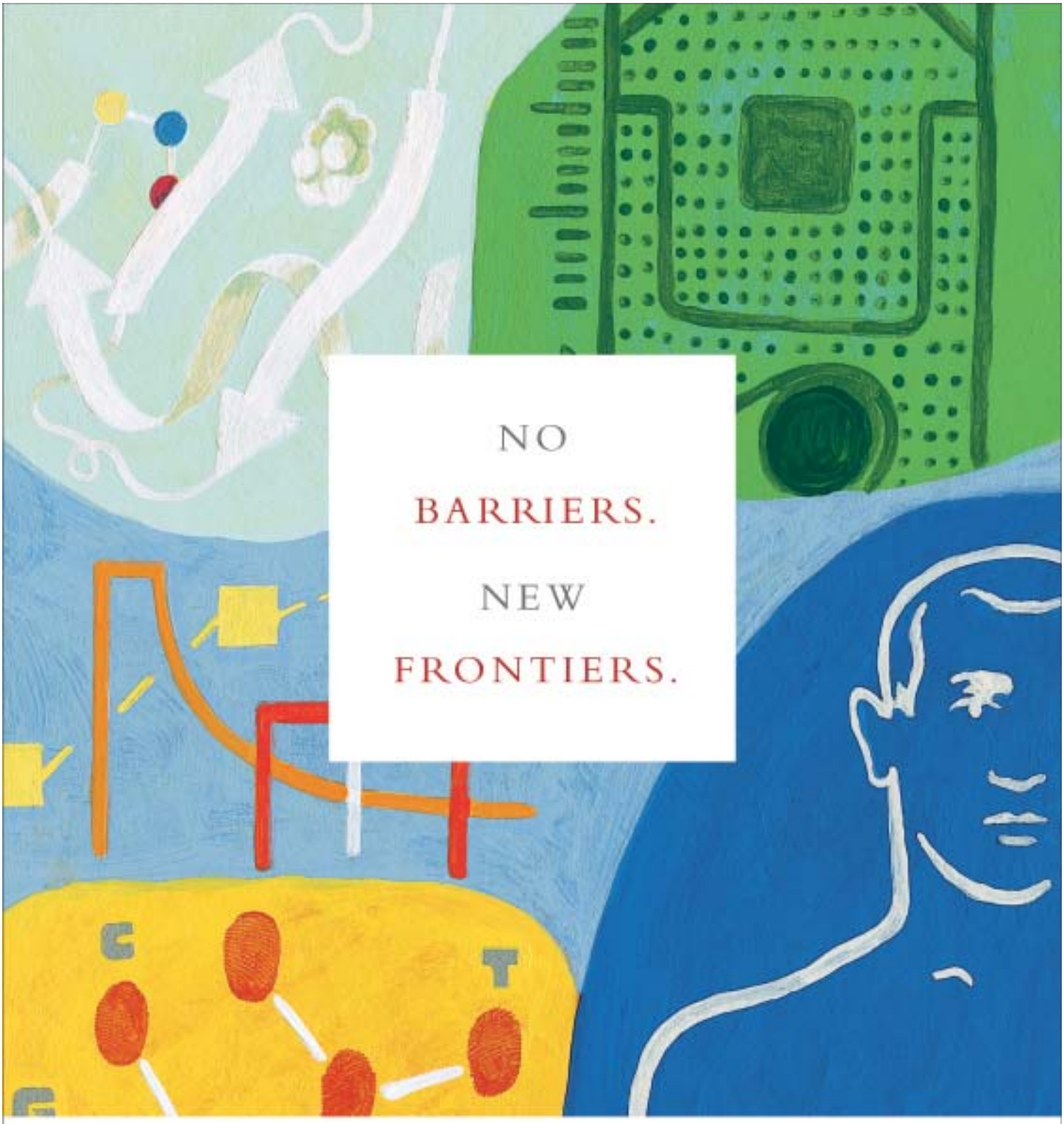
Walter A Shaw, Ph.D
Spotlight: Lym-Drug Products, LLC.

Kelvingrove Art Gallery & Museum
Register for the 30th Annual Meeting & Exposition
Glasgow, Scotland, United Kingdom
July 19 – 23, 2003

Victor Yang, Ph.D.
Receives Paul Dawson
Biotechnology Award



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CONTROLLED RELEASE SOCIETY
NEWSLETTER
Volume 20 • Number 2 • 2003

inthisissue

On the cover –

Join us for the 30th Annual Meeting in Glasgow, Scotland!

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


Bozena Michniak
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Bozena Michniak & Ijeoma Uchegbu

Consumer & Diversified Products Special Feature Editor
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Thanks to members of the Publications Newsletter Subcommittee for helping with this issue: Martyn Davies, Agis Kydonieus, Harlan Hall, and Mike Rathbone.

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

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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.

FROM THE *Editors*

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

This is the time for planning your trip to Glasgow, Scotland, for the 30th Annual Meeting of the Controlled Release Society. The motto for the meeting "Come for the Science, Stay for the Scenery" eloquently describes the venue. The CRS has a reputation for its high quality of posters and podium presentations at its annual meetings and imagine adding the beauty of Scotland in the summer and a banquet at Stirling Castle to the repertoire. The program covers three tracks: bioactive materials, consumer and diversified products, and veterinary products. The plenary keynote speakers are John Urquhart from the University of California, Sir George Radda from the UK Medical Research Council, Linda Griffin of MIT, Stephen Mann of University of Bristol and Phillip Low of Purdue University all distinguished leaders in their fields. For the first time, the CRS annual meeting will have a series of debate sessions called "Pearls of Wisdom" to mark the 30th anniversary meeting. The speakers will have 15 minutes to present their case with the proponent preceding the opponent and then the session will be open for discussion. The moderators will keep the debate lively and end with a summary of key points. Some of the discussion topics include "Academia and Industry-who are the Real Inventors?" and "Gene Therapy-Derailed by Delivery Problems" as well as "The Management and Valuation of Intellectual Property in Industrial/University Research Relationships"-all very significant and with potential controversial issues which will make this a very interesting and potentially successful session. I invite all of our members to come and partake of the science and the landscape, history and golf courses. There is something here for everyone. Ijeoma and I, together with the excellent help from Jaymie Griffin, the Managing Editor of the Newsletter, have been putting some of your ideas in place while still keeping some of our regular articles such as "Member Release" and "Scientifically Speaking" in place. We have added several new sections including career follow-ups with scientists who had received CRS awards in the past and in the future there will be interviews with senior scientists. In addition, we would like all our members to give thought to submitting quality articles to the Newsletter. We would all like to see the Newsletter issues grow and contain interesting articles on science and our drug delivery world both academic and industrial. We would encourage small companies to contact the Editors and submit material that describes their novel and significant technology and the large ones, news on important appointments, drug approvals and new products. Let's not forget academia, and we would appreciate hearing about "hot topics" in science, faculty and student awards, and other worthy pieces of news.

CRS UPDATES

Correction

In the last issue of the CRS Newsletter, the article entitled; *Performing Scale-up and Scale-down of Controlled Release Processes in an Environment of Time and Cost Constraints* was written by Dr. Irwin C. Jacobs, Director of Chemical Technology, Particle and Coating Technologies, Inc., St. Louis, MO. USA. Telephone: 314-535-1516. Fax: 314-535-1514. Email: ijacobs@pctincusa.com.

Winter In Utah

A special thank you to the University of Utah, Doctors Sung Wan Kim, Henry Kopecek and their staff for the scientifically successful Winter Symposium and 11th International Symposium on Recent Advances in Drug Delivery Systems. The 300 plus attendees enjoyed the 30 Invited Speakers, 23 Podium Presenters and 73 Poster Presenters and exhibitors.

CRS Bylaw Election Outcome

The ballots for the Bylaw Election have been returned, and the results are as follows:

1. The first sentence of Article V, Elections, Section 2 shall read as follows:
   *Election of officer(s) and members of the Board of Scientific Advisors will be held prior to the annual meeting of the Society by secret ballot and **may be conducted by any lawful means, including electronic mail**.*

   98% Approved 2% Did not approve

2. Article VII, Amendments, shall read as follows:
   *These Bylaws may be amended by three-fourths vote of the members present at any Annual Business Meeting or by **three-fourths vote of the actual voting members** conducted by mail, proxy **or other lawful means including electronic mail**, provided the notice of the proposed amendment has been given in writing to the Secretary and transmitted by him/her to the members 30 days before the vote.*

The vote was tallied separately on this amendment.

A. Approve the proposed amendment concerning three-fourths vote of actual voting members requirement for voting on bylaw amendments conducted by mail, proxy.

   93% Approved 7% Did not approve

B. Approve the proposed amendment concerning voting on bylaw amendments conducted by mail, proxy or other lawful means including electronic mail.

   90% Approved 10% Did not approve

These amendments have been incorporated into the Society's bylaws.

Want thousands of leaders in the controlled release industry around the world talking about you?

By *Janelle Bauer, Marketing and Public Relations Coordinator, the ARDEL group*

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**Figures based on 29th Annual Meeting attendees.*

Welcome New Members

Adeyinka Abinusawa
Shavej Ahmad
Mahmoud Ameri
Masso Antoni
Partha Banerjee
Catherine Boegen
Julie Bukar
Beth Burnside
Allison Campbell
Mary Chan-Park
Jianjun Cheng
Charles Claude
Charles Conover
Robert Cook
Robin Currie
Anne Dahlin
Nick Davies
Richard Delaney
David DeWitt
Guangbing Ding
Dennis Discher
Heather Evans
Neil Farrow
John Fields
Andrea Gazzaniga
Diego Gianolio
Thierry Glauser
Vivian Gray
Francesca Greco
Andrew Guise
Jared Hahn
InKwon Han
Bridgit Hawkins
Gene Jamieson
Yulai Jin
James Johnson
Brian Jones
Steffi Joschek
Thomas Kean
Zeena Khayat
Moon Kyoung Kim
Bruce Klitzman
Michael Kopcha
Kavitma Koushik
Daniel Latham
Michael Leane
Jin-Hee Lee
Shaoling Li
Douglas Mace
Babu Medi
Jurgen Mensch
Kenneth Miller
Hilda Mulvihill
Suresh Naik
Basavaraj Nanjwade
Ajit Narang
Rachit Ohri
Patrick Okoye
Yoshinori Onuki
David Oupicky
Aristarchos Papagiannaros
Pyeong-uk Park
Patricia Parker
Anders Pedersen
Rosa Pereira
Stephen Pham
Karen Phelps
Swayam Prabha
Stefan Proniuk
Maxime Ranger
Sanjeeb Sahoo
Pradeep Sanghvi
Rachel Schek
Philipp Seib
David Senogles
Ashutosh Sharma
Pam Sobotka
Akinori Suginaka
Jung Jin Sun
Sarah Tao
Sydney Ugwu
Evan Unger
David Velasquez
Svetlana Velkovska
Maria Vicent
Chun Wang
Stephen Wohlert
David Wotherspoon
Patti Wyszynski
Hiroyuki Yamamura

WOMEN IN THE PHARMACEUTICAL SCIENCES – *N*ot *M*any of *T*hem

By Ijeoma Uchegbu, Department of Pharmaceutical Sciences, University of Strathclyde, 27 Taylor St, Glasgow G4 0NR, United Kingdom.

"BREAK GLASS"
Tunde McKay | 2003

We are not there yet but we are inching our way slowly past the glass ceiling. We are creeping past in small numbers and without much fanfare. This was the verdict of a recent straw poll of women pharmaceutical scientists of all ages and seniority from both academia and industry. Despite the fact that women crowd the lower rungs of the scientific career ladder and rarely make it all the way to the top, all twelve respondents to a straw poll of thirty six female pharmaceutical scientists stated that they would give a nineteen year old female scientist-hopeful nothing but encouragement. The "thinning out" of women starts early on the career ladder and then women literally disappear. A look at a typical United Kingdom pharmacy department shows that seventy percent of first year students are female, just under half of pharmacy PhD students are female, and the proportion of females remains more or less the same into the post doctoral years, yet only one in five holders of pharmacy chairs are female. In the United States a recent AACP Institutional Report publication found that while a third of assistant deans were female, only one in six associate and full deans were female. The same report also found that only one in six full pharmacy professors were female and furthermore, to add insult to injury, female full professors typically earned 90% of a male full professor's wage!

Are women reluctant to speak out about sexism in the work place? You bet they are. Most respondents chose to remain anonymous and only senior scientists were able to articulate their frustration with the status quo. It seems that only when you have arrived are you able to say that the journey has been hard! Baroness Susan Greenfield, one of the most visible female scientists in the United Kingdom and a Professor of Pharmacology at the University of Oxford recently wrote in the British Guardian Newspaper about being "ignored" and "patronised" as a young scientist. In a uniquely personal account Professor Greenfield spoke of successful women suffering from "imposter syndrome" – a fear that someone else could do the job better. So there you have it, two sides to the problem. On one hand we feel frustrated when we do not arrive at the pinnacle of our careers and on the other hand there is a feeling of inadequacy when we eventually achieve recognition. Time to change things? I think so.

From our poll, the good news was that all respondents were really passionate about working in science: phrases like "doing something useful", "making a difference", "enjoying the challenge of research" peppered their responses, and none of the women had any immediate plans to leave the profession. This is a heartening thought, as, despite an acknowledgement that seniority eludes a large majority of women scientists, women, like all scientists, are deeply in love with their craft. One respondent, not only had no immediate plans to leave the profession but actually said that she had "many more dreams and goals for the future". This love affair with science and the failure of so many committed and indeed talented women to achieve more, is an area that we should be concerned about, regardless of our gender.

Three issues, our respondents thought were limiting the development of women scientists are family commitments, a lack of acceptance by colleagues, and women's reticence at self-promotion.

Despite the fact that most respondents thought that women's lack of status in the scientific professions could be attributed, in part, to competing priorities from the family, most respondents were fiercely positive about the value their families brought to their professional output. Professor Oya Alpar of the School of Pharmacy, University of London – one of a handful of female Pharmacy professors in the United Kingdom said, "I am in favour of a balanced lifestyle. I feel that one can be a great parent and a great researcher. Family life without a career can also have its difficulties" and Dr Jayne Lawrence, a Reader at the School of Pharmacy, King's College London, while acknowledging that having a family means that one's attention is divided, stated firmly, "I would not swap my husband and children for the world". It seems that women do believe that you can have it all and are trying their utmost to do so.

However having a family does take women away from the research mill and in academia where a career defining track record is measured by dividing one's output by the number of years spent at the task; which for convenience simply evaluates one's CV with reference to one's date of birth; taking time out to have children can be costly although as a parent dare I say infinitely rewarding. The anointing of the great, soon to be great and would be great usually takes the form of a number of "Young Investigator Awards". These usually come from the learned societies who select individuals under the age of 35 or 40 and such selections serve as a short list to talent scouts. A look at one particular British list of past and present award winners shows that over the past 30 years (a total of 26 awards) only one such award was made to a woman! This may not be proof but if you plan to take a real (temporarily leave the profession) career break or a virtual (temporarily tone down your activities) career break it

Women continued on next page

Women continued from previous page

does mean that you miss out on the anointing process and have to look to other ways to make your mark.

As some women scientists will continue to have children, for the benefit of society, not to mention tomorrow's pensions, perhaps it might be an idea to alter the selection criteria such that career breaks are taken into account. For example using full time postdoctoral research years as an evaluation tool instead of age may then allow talented women to be selected for such awards.

In the United States where the tenure track system of the early years means that women must literally chose between a family and seeking the reward of tenure, the "tenure clock" system has allowed a year to taken off for childrearing or the care of dependant relatives without attracting any penalty. However in real terms such a year out is an expensive option which hits the pay packet directly. This is because science is such a fast moving field that it may be impossible to catch up once the year out is over.

"Got that promotion interview today. Wish me luck!"

Since the family is perceived to wield a major influence on the output of women scientists, having the right partner also helps. A supportive partner who nurtures, cooks, cleans and makes the tea is always a good choice so long as one is prepared to do the same in return. However there is a less controllable element that stalks the workplace corridors. This is the genderless sceptic. Yes, genderless, as women can be guilty of this too. Most of our respondents spoke of a lack of acceptance by their peers, juniors and seniors – or, sexism in old money. Women find tat it is harder for them to gain the respect and acceptance of their peers. After a recent promotion I had a male colleague approach me, ostensibly to offer his congratulations, who blurted out in utter disbelief "I had no idea that you were in line for this"! What do women have to do to be accepted? Well, you could try dressing and looking like a man. This is no joke as research in management science has revealed that middle-aged women in senior management positions deglamourise themselves in a subconscious attempt to gain acceptance and be taken seriously. Whether this works is anyone's guess.

Women are not the same as men and the jury is still out on the nature of these behavioural differences and how they affect the workplace dynamics. Never the less some women feel that because women are still the primary care givers within the family unit their management style is more inclusive and nurturing which ultimately leads to a happy and successful team. The legendary multi-tasking skills of women may also be put to good use. How many men do you know who can breast-feed an infant, write a research grant proposal, and watch a toddler at the same time? This skill, that most women take for granted, is also often used to carry out simultaneous multiple tasks in the workplace.

It is interesting to see that one respondent felt that older men with supportive stay-at-home partners were more likely to be sexist: One married respondent reported, "I was told that I should get less money because I have a man to support me"!! While another respondent observed that most of her successful male colleagues had supportive wives. For women getting a "wife" is not an option as this turns the problem full circle. Instead women believe that they have to do more - "work harder", "spend longer hours in the laboratory" in order to gain recognition.

Working with a friendly company also helps and respondents cited the management in companies such as AstraZeneca and Eli Lily as having gender-invisibility policies. Paid paternity leave and the promotion of women to the rarefied atmosphere of senior management were cited as examples of this gender-invisibility. Please don't all send your CV's at once!

A further limiting aspect to workplace positioning is that our respondents thought that women were perceived as being "less hard nosed" and "less thrusting". It appears that men are more likely to put themselves forward for prominent positions and be aware of their value in an organisation while women are reluctant to blow their own trumpets. If women are to succeed we probably have to change this. The rooftop is a good place to start ladies!

However it is not all doom and gloom. There are a few successful women out there and the American Association of Pharmaceutical Scientists has recently had a female president – Dr Dianne Burgess of the University of Conneticut. Furthermore all women who responded felt that the gender bias in the workplace was gradually, ever so gradually, being left in the past. Every respondent felt that things were improving and some attributed this to the legal framework set up in some countries to eliminate gender bias. The ball seems to be in our court and as my teenagers say women need to "get out more" and push themselves to the front of the queue, apply for the big jobs and seek more responsibility in the workplace because we all know, as that shampoo advert jingles, that we "are worth it".

From the President

By Prof. Alexander Florence,
University of London, School of Pharmacy

Recently I returned from Salt Lake City from the CRS Winter Meeting and the 11th International Meeting on Advanced Drug Delivery Systems and I must thank Sung Wan Kim, Jindrich Kopeck and James Anderson - founders and stalwarts of the Utah meeting - for agreeing to share billing with CRS. Our Scientific Secretary, Martyn Davies, and Past President Kinam Park joined them on the organising committee. CRS is an international society and is committed to holding its meetings worldwide. Having the annual meeting in Korea and the UK this year was part of this plan but it was nonetheless thought wise to provide a home-based forum for US members. There were about 300 delegates in Salt Lake City who heard an excellent programme of invited speakers and young presenters chosen for podium presentations from their poster abstracts, which I believe is an excellent way of promoting and recognising young talent.

For a Society such as CRS the annual meetings are vital, not only in providing a forum for the latest developments in the field, but in providing income for the Society. It is essential that the meetings are successful. Members in fact should feel some obligation to attend. It is still the main benefit of membership. We look forward, of course, in spite of the uncertainty in the world at present to a large turn-out of members old and new in Scotland. But what if in the future the paradigm changes? With modern methods of communication it may be that we need to restructure conferences. Perhaps no longer will plenary speakers need to attend in person when they can be shown in real time on screens and interact with the audience. Where are the electronic poster boards, with posters beamed directly from their places of origin? What about the standard format of scientific meetings, the hierarchy of plenary lectures, invited lectures, poster sessions and workshops? Has anyone ever evaluated these? How many posters are never read? How many poster presenters are challenged by the questions asked? In Universities modes of education delivery have changed drastically over the last decade. Perhaps it is time for Societies such as ours to hear from their members about radical new ideas for conferences. At meetings we should perhaps have more reflective lectures, as well as those putting forward the very latest research ideas and data. These contextual lectures would place recent advances in perspective. Just how far are we progressing with gene therapy, with penetration enhancement, with oral protein delivery? Are we sufficiently critical of what is presented as question time is often rushed. Should we schedule more time for debate: it is often the innocent, or less than innocent, question that reveals the Achilles heel of our work, or give us ideas for new experiments. Do we need more stimulation after the lights have gone up?

A Society is much more than a conference organization. It has to have a coherence and other purpose: to promulgate the science, to stimulate awareness of the discipline, to communicate with its world-wide membership. The CRS with its local chapters achieves the world-wide penetration. We re-invested in local chapters this year. On the educational side we are beginning to formulate plans. Mike Rathbone has agreed to chair an educational committee to look at ways of enhancing the educational role of CRS.

Prof. Alexander Florence, University of London, School of Pharmacy

There will be stimulation aplenty in Glasgow. In the last newsletter I extolled the virtues of the Scottish location and the City of Glasgow. A once industrial city building ships, steam engines and heavy machinery for the world, it more relies now on its business flair and its academic bases in its three Universities: Glasgow, Strathclyde and Glasgow Caledonian, respectively 15th, 18th and 20th century creations. The CRS is a modern creation: the meeting in Glasgow is its 30th, but there will be little looking back, though I pay tribute here to those who devoted so much time to nurturing the Society in its early days. A record number of abstracts have been submitted for presentation which bodes well for the meeting itself. As an educational endeavor local school children are being invited to a special session to hear about the exciting research carried out in our field, put across in a lively way. If any members are traveling with their families to Scotland and have children of an age who would like to participate in the "Intelligent Medicines" session at the meeting please let Ronda Thompson know at rthompson@controlledrelease.org

We have to communicate that passion we have for our subject.

I do hope that I and the local team headed by Clive Wilson can welcome you personally to the futuristic Scottish Exhibition and Conference Centre, on the banks of the River Clyde and later in the week, as a complete contrast, at the ancient Stirling Castle for what must be one of the most spectacular venues ever for a CRS banquet. Come to the 30th Anniversary meeting to present, question, debate, network and enjoy the experience.

IN THE NEWS

Clinical Trial of New Opioid Product Shows Pain Reduction In Chronic Low Back Pain
Penwest Pharmaceuticals Co. stated that the results of five studies on the investigational drug EN3202, an extended-release (ER) oral form of the opioid oxymorphone, jointly developed by Penwest and Endo Pharmaceuticals, were presented at the 22nd Annual Scientific Meeting of the American Pain Society (APS). Included in the presentations were pharmacokinetics studies for EN3202, a low back pain study for EN3202, an osteoarthritis pain study for EN3202, and two long-term safety studies in osteoarthritis pain and cancer pain for EN3202.

According to the American Chronic Pain Association, chronic low back pain is a debilitating condition that affects an estimated 36 million Americans. Low back pain also is the most common form of acute pain, is the fifth most common cause for all physician visits, and is responsible for direct health care expenditures of more than $20 billion annually.

A Decade-Long Drop In Young Physicians Concerns Pennsylvania Medical Society
As Baby Boomers Retire, Future of Patient Care at Risk According to Stats. An analysis of data from the U.S. Bureau of Health Professions, 2002 Area Resource File, shows that the percentage of physicians in Pennsylvania under the age of 35 dropped significantly between 1989 and 2000, says the Pennsylvania Medical Society.

According to testimony today before the Pennsylvania House Republican Policy Committee in Lancaster, this drop should worry the state as Pennsylvania residents grow older and more baby boomers retire.

"In 1989, more than 12 percent of all physicians in Pennsylvania were under the age of 35," said Michael J. Prendergast, MD, chair of the Medical Society's board of trustees. "Data for 2000 now shows that less than five percent of physicians in Pennsylvania are under the age of 35."

Dr. Prendergast adds that in 1989 Pennsylvania was ranked 12th in the country for percentage of young physicians. By 2000, that ranking dropped to 41st.

Joining Dr. Prendergast at the hearing was Jessica Ellerman, a senior pre- med student at Dickinson College in Carlisle, Pa., who was born and reared in Pennsylvania. Ellerman, an NCAA Academic All-American in cross country who maintains a 3.72 GPA, had dreamed of delivering babies one day, but now is rethinking her decision due to the liability insurance crisis.

"I had all intentions of pursuing the skills to become an obstetrician/gynecologist," Ellerman said. "But, as the liability insurance crisis developed, I learned that obstetricians/gynecologists tend to be sued more often. While I discovered that the majority of medical liability claims are often dropped, dismissed, or found in favor of the doctor, the thought of wrongly being sued made me rethink my goals."

Ellerman mentioned that she now plans to delay medical school to see if the liability insurance crisis is solved. While waiting, she says she'll work in research as she was recently offered a position in Europe.

The Pennsylvania Medical Society, located in Harrisburg, has been advocating for the patient-doctor relationship since 1848. Through its statewide 20,000-physician membership and its 1,400-member patient advisory board, the Society listens to concerns of both patients and doctors to improve the delivery of health care services in the state. To learn more about the Pennsylvania Medical Society visit its Website at www.pamedsoc.org.

Advanced Cell Technology Prevails in Cloning Patent Dispute
Patents Include Core Intellectual Property for Cloning From All Somatic Cell Types. Advanced Cell Technology, Inc. (ACT) has stated that judgment has been awarded in its favor in a patent interference with Infigen, Inc., of Deforest, Wisconsin, involving three key animal patents exclusively licensed by ACT from the University of Massachusetts. The Board of Patent Appeals and Interferences of the U.S. Patent and Trademark Office issued the judgment on March 18, 2003. The proceeding involved a challenge initiated by Infigen of U.S. Patent Nos. 5,945,577, 6,215,041, and 6,235,969 assigned to the University of Massachusetts and licensed exclusively to ACT.

The disputed patents cover the use of any proliferating somatic cell for the cloning of non-human animals. ACT's patented cloning methods have practical application

News continued on page 15

JCR *Highlights*

By D. R. Friend, Delsys Pharmaceutical Corporation

Volume 88 of the Journal of Controlled Release contains, once again, a range of interesting papers. A technique under investigation to enhance delivery of drugs through the skin is electroporation. Denet and Préat have published a paper on transdermal delivery of timolol using this method. Passive diffusion of timolol is too low to produce therapeutic plasma concentrations. Electroporation (application of a short high voltage pulses) increased transdermal transport of timolol by 1 to 2 orders of magnitude compared with passive diffusion.

Microfabrication techniques have recently found application in the field of drug delivery. Desai and coworkers present data on a novel oral delivery system for macromolecules. A unique feature of these small dose units is the ability to create asymmetric systems. Therefore, bioadhesive materials (e.g., lectins) can be coated on a single, flat side of the units. Also, a reservoir can be created such that release occurs in one direction only. Fabrication methods and bioadhesive data are presented indicating the potential for such a system to enhance oral delivery of macromolecules.

Shen and coworkers report a process called reversible aqueous lipidization to create formulations with enhanced oral bioavailability of salmon calcitonin (sCT). Polypeptides are chemically derivatized to create conjugates using a new method (performed in water). These derivatives are capable of regeneration of the parent active (polypeptide) in tissues or blood. In this paper, synthesis of a lipidized sCT is described along with pharmacokinetic and pharmacodynamic results in mice and rats. The oral bioavailability of this polypetide was increased 19 times compared with unmodified sCT.

SPOTLIGHT
Lym-Drug Products, LLC

By R. Travis McKee, M.S.B.E., Avanti Polar Lipids, Inc.

The simplest solution is usually correct. This adaptation of Occam's Razor may also best describe modern medicine's current approach to solving complex disease states; fighting disease with simple but innovative tools. As technology promotes medical care by introducing more homeostatic remedies, therapies requiring drawn-out, often painful and inconvenient treatments will become less effective as they become less tolerated in light of advancing alternatives.

Appropriately then, advancements in drug delivery are often crowned by establishing successful oral bioavailability. The advantages of oral drug delivery are infinite; *e.g.* it removes the necessity for taxing invasive treatments often requiring the assistance of trained personnel and increases patient compliance. For many agents, from chemotherapeutics to insulin, however, oral delivery is not supported by current technology. An innovative scientific collaboration will correct that.

In this issue, the Spotlight is focused on Lym-Drug Products, LLC; a company formed to explore the novel lipid complex Lym-X-Sorb™ - a revolution in oral drug delivery.

Enter Lym-Drug Products and Lym-X-Sorb™ (Lymphatic Xenobiotic Absorbability). Lym-X-Sorb™ was developed as an analogue to the basic products of fat digestion by David W. Yesair, Ph.D., president of Biomolecular Products, Inc., a Byfield, MA based developmental company. Dr. Yesair first described the physiologic arrangement between the principle products of fat digestion, lipids; specifically lysophosphatidylcholine (LPC), monoglyceride (MG) and fatty acid (FA)[1]. In the intestinal lumen, these lipids form a unique three-dimensional, non-liposomal monomeric unit that is absorbed in the jejunum. Once reconstituted into chylomicrons, these lipids are transported via the thoracic lymph and enter the systemic circulation thru venous blood at the juncture of the subclavian vein. When manufactured and formulated with a drug agent, the Lym-X-Sorb™ monomer shields the drug from the hostile environs of the stomach and the upper intestine by enveloping it in the void created among the acyl-constituents of the lipid anchors (Figure 1). Directing this "lipid glove" from the intestinal lumen to the lymphatic system is the body's underlying mechanism for fat absorption.

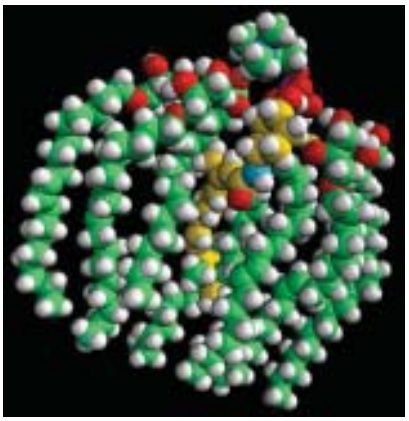


Figure 1, Monomer: The Lym-X-Sorb™ monomer complexed (in a conceptual model) with a molar equivalent of fenretinide (in yellow).

To explore the Lym-X-Sorb™ system, Dr. Yesair created Lym-Drug Products, LLC in 1998 and partnered with Walter A. Shaw, Ph.D., president of Avanti Polar Lipids, Inc., in 2002. The collaborative goal for Lym-Drug Products is to provide a lipid-based, non-liposomal oral delivery system that facilitates the therapeutic delivery of multiple drug candidates through the natural absorption processes of human digestion. One tool - the simplest solution.

Walter A. Shaw, PhD

David W. Yesair, PhD

As a lipid-based monomer, the Lym-X-Sorb™-drug complex is recognized in the intestinal lumen as a nutrient and therefore allowed to proceed into the thoracic lymph for systemic delivery; thus avoiding the liver and subsequent first pass metabolism. This recognition and metabolic by-pass greatly enhances the ultimate drug concentration in plasma. When examined at equivalent doses in beagle dogs, Lym-X-Sorb™-N-(4-hydroxyphenyl) (fenretinide) complexes demonstrated 3 to 4 times the peak plasma concentrations of current delivery systems. Human bioequivalence studies demonstrate 65mg doses of fenretinide complexed with Lym-X-Sorb™ present nearly identical plasma levels to 300 mg dosages via conventional corn oil delivery (5X the Lym-X-Sorb™ dose) (Figure 2).

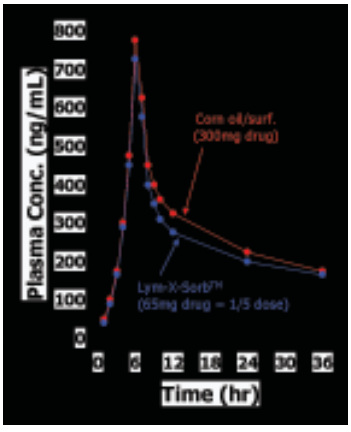


Figure 2, Bioequivalence Graph: Bioequivalence of Lym-X-Sorb™ vs. traditional oral delivery of fenretinide. The Lym-X-Sorb™ dosage was equally effective at 1/5th the dosage of current technology

Researchers have for years recognized the benefits of lymphatic delivery; sustainable high concentrations of drug (5-10,000 times higher in lymph than in plasma), slower transport enabling delivery duration, steadier delivery rate, expandable drug choice as advancing drug design produces an influx of highly lipophilic molecules and the inherent importance of the lymphatic system in immunity, fluid balance and metastasis[2].

Complexed with the drug of choice in a 1:1 molar ratio, the matrix forms stable particles 10 to 70 nm in size that are readily absorbed in the presence of sodium bicarbonate and bile salt (intestinal exocrines). The small and enveloping nature of the

***Spotlight** continued on page 21*

CRS' 30th Anniversary Annual Meeting

in Glasgow, Scotland, United Kingdom

By Prof. Martyn Davies, University of Nottingham

Well, who would have believed it? 921 abstracts received for Glasgow! I nearly fell off my chair when I was told by CRS Headquarters that the 30th Annual Meeting had attracted a record number of abstracts, 167 more than Korea last year and 250 more than San Diego in 2001, both very successful meetings! The number of abstracts and their countries of origin also highlighted the sustained globalisation of the Society with submissions received from all continents. Clearly, many CRS scientists from all across the world, were responding to the innovative science programs that were designed by the Science Program Chairs.

The invitation to a mid-winter break in Minnesota would not normally be my idea of fun, but the opportunity to put the final touches to the program at the CRS Headquarters with Clive Wilson (Program Chair for the Bioactive Sessions) and Jack Burger (Lead Program Chair for the C&DP Sessions) was an exciting prospect. We reviewed all the abstracts and were impressed by the quality of science across the diverse fields of controlled release activities and selected some of the higher ranked submissions for contributed talks in each session. This was a challenging task ably supported by the CRS Headquarters team, but I for one enjoyed the robust debates that were generated in the selection process.

From left: Prof. Martyn Davies, University of Nottingham
Dr. Jack Burger, Quest International
Prof. Clive Wilson, University of Strathclyde

Our pleasant sojourn in the bitterly cold Midwest (see photo) allowed us to reflect on the overall shape and scope of the meeting. As the Scientific Secretary I can only applaud the scientific program chairs for establishing such a vibrant and innovative scientific program and also for the introduction of new ideas and sessions to the meeting. A brand new concept entitled 'Pearls of Wisdom' will be held on Monday and Tuesday where lively interactive debates on topical issues in controlled release will be held and led by leaders in the field. A new out-reach Education Program for local school children will be held to promote the public understanding of controlled release science. This year sees a change to our Plenary Sessions; lectures will be spread throughout the meeting by leading international figures on subjects ranging from 'the challenge and opportunities for the treatment of cancer' to 'the design of new biomimetic materials'. The outward looking activities of the CRS have led us to embrace new disciplines and encourage interactions with other professional organisations as reflected in a day-long joint session organised between the UKI Chapter of the CRS and the Academy of Pharmaceutical Scientists from the UK.

As we sipped malt whisky in the wee small hours, our minds were transported to thoughts of what we believe will be an outstanding meeting in Glasgow in the summer with the rich culture and outstanding scenery of Scotland. I am sure this will be a meeting that many of us will remember for many years to come.

PEOPLE ON THE MOVE

University of Michigan's Victor C. Yang is AACP's 2003 Paul Dawson Biotechnology Award Winner

Victor C. Yang, Ph.D., Albert B. Prescott Professor of Pharmaceutical Sciences at the University of Michigan College of Pharmacy, has been selected by the AACP Board of Directors as the recipient of the 2003 AACP Paul Dawson Biotechnology Award and will be honored in Minneapolis, Minnesota, during the annual meeting awards banquet on July 22. The award, sponsored by Amgen Inc., consists of a double helix glass sculpture and a $10,000 cash prize. He will also present an address at a special session on July 21. Dr. Yang becomes the 11th winner of the Paul Dawson Biotechnology Award.

Dr. Yang has distinguished himself as an outstanding researcher in the areas of biotechnology-mediated diagnostics and drug delivery, excellence and dedication to teaching, and superb service to the University of Michigan and pharmaceutical sciences as a whole.

Standing out in his curriculum vitae is his pioneering work on electrochemical sensors for polyionic macromolecules such as heparin and protamine, his sensor-directed, protamine bioreactor-based, biofeedback system for clinical heparin removal, and his seminal "ATTEMPTS" approach for delivering enzyme drugs such as t-PA without their associated toxic effects. He received his Ph.D. in biochemistry and biophysics from Brown University in 1983.

Dr. Yang has published more than 130 peer-reviewed research articles and 3 edited books, he has 15 patents, 120 abstracts, and 144 presentations. With 144 presentations, many of them international, it is obvious that Dr. Yang is highly recognized as an expert in pharmaceutical biotechnology.

Since 1987, he has received over 9 million dollars of grant support, mainly from NIH and industries such as Medtronic. His research has recently moved into new areas, such as brain drug delivery systems for the treatment of Parkinson's and Alzheimer's diseases, protein and gene delivery for the treatment of various types of cancers, and the design of bioreactors for the treatment of autoimmune diseases such as immune thrombocytopenia purpura and multiple sclerosis..

Dr. Victor C. Yang, University of Michigan

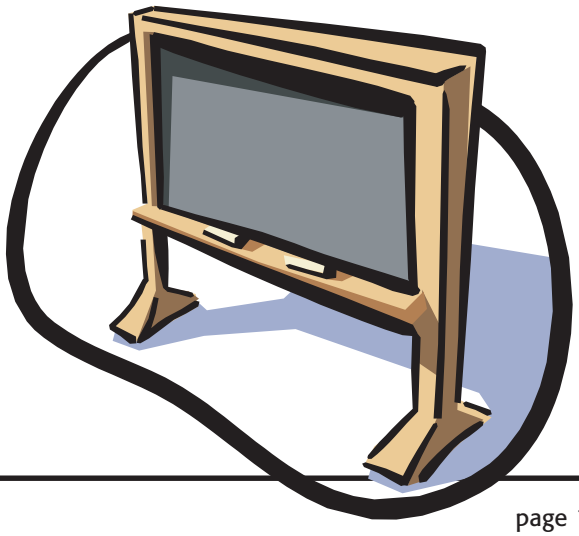
While teaching the professional physical pharmacy, biopharmaceutics, and biotechnology course, and actively participating in the Pharm.D. investigational course, Dr. Yang has mentored 13 Ph.D. students, 2 M.S. students, 21 postdoctoral fellows, 7 technicians, and 11 Pharm.D. students. It is laudable that 40% of Ph.D. students trained in Dr. Yang's laboratory have faculty positions at major universities.

Dr. Yang, who serves on the Board of Scientific Advisors of the Controlled Release Society is also on editorial boards of several scientific journals. He is the 2002 recipient of the Short-Term Invitation Fellowship for Research jointly selected by the US National Science Foundation (NSF) and the Japan Society for the Promotion of Science (JSPS) to conduct 60 days of research at the Tokyo Women's Medical University in Tokyo, Japan. He was also a University Guest Professor at Tianjin University, China in 2001.

Dr. Jindrich Kopecek (Utah), a prior winner of the Paul Dawson Biotechnology Award and chair of the review committee, noted that the committee was impressed with Dr. Yang's membership in the NIH Surgery and Bioengineering Study Section, and his influence over the future direction of biotechnology research.

Experience the wonders of science with your children!

Attend the
Intelligent Medicines:
The Future is Precision Session
on Saturday, July 19, 2003



PATENT WATCH Transdermal Update

By Agis Kydonieus, Samos Pharma, LLC &
Tapash K. Ghosh, Food and Drug Administration

The patents issued in the United States during 2002 are discussed in this review. There were 35 U.S. patents published that were pertinent to transdermal medication, a substantially smaller number than in previous years. Alza was awarded three patents in electrotransport and Sontra two in sonophoresis. Other companies with multiple patents included, J&J, Lohmann, Noven and L'Oreal.

The breakdown according to categories was methods/devices (10), enhancers (8), anti-irritants/countersensitizers (8) and electotransport (7). There was a substantial reduction in the number of enhancer and method patents and a surprising increase in the anti-irritant patents.

During 2002, several commercial activities of interest have taken place and some of them are discussed below:

In early 2002, the FDA requested additional clinical data from Watson Pharmaceuticals on its oxybutynin patch (Oxytrol™). Watson, resubmitted the application in August 2002 including clinical data from a Phase IIIb trial, which was also completed in 2002. At the writing of this Transdermal Update, Watson received approval (February 27) of the Oxytrol™ patch. Oxytrol™ is a transdermal oxybutynin patch for the treatment of overactive bladder with symptoms of urge incontinence, urgency and frequency of urination.

In June 2002, Noven Pharmaceuticals filed with the FDA for approval of a methylphenidate patch (MethyPatch™), and the new drug application was accepted by the FDA in August 2002. MethyPatch™ is indicated for the treatment of attention deficit hyperactivity disorder.

In June 2002, Vyteris, Inc filed with the FDA for approval of a lidocaine patch, using an iontophoretic transdermal delivery system. The indication for the lidocaine patch is for the reduction of pain associated with needle punctures of the skin.

In March 2002, Somerset Pharmaceuticals received a not approvable letter from the FDA for the selegiline patch (Emsam™), requesting additional efficacy data. Somerset is seeking approval for Emsam™ for the treatment of depression.

Evra™, the first birth control-patch (approved in 2001) was introduced in the United States by Ortho-McNeil. In August 2002 the patch was approved in Canada and in Europe. The patch will be marketed in Canada by Janssen-Ortho and in Europe by Janssen-Cilag.

Estradot™, developed by Noven, was introduced in Germany by Novartis. Estradot™, the smallest estrogen patch available, is marketed in the United States as Vivelle-Dot™ and it is indicated for the treatment of menopausal symptoms.

Transdermal gels are also being developed after the extraordinary success of Androgel™. In June 2002, Cellegy Pharmaceuticals filed with the FDA for approval of a testosterone gel (Tostrex™) for the treatment of male hypogonadism. Biosante Pharmaceuticals obtained the rights from Antares Pharma to develop and market a hormone-replacement gel (LibiGel-E/T™) for the treatment of female sexual dysfunction. LibiGel-E/T™ contains testosterone in addition to the traditionally used estradiol.

Below some of the more interesting patents are discussed.

COUNTERSENSITIZERS/ ANTI-IRRITANTS

Formulations and methods for reducing skin irritation (Hahn) US6455076
Compositions and methods are claimed for the inhibition of skin irritation attributable to chemical irritants by the application of aqueous soluble divalent tin cations. The concentration of the cations are between 10 mM and 3000 mM and more preferably between 250 and 500 mM. Irritants disclosed include lactic acid, salicylic acid, capryloyl acid, citric acid, tretinoin, benzoyl peroxide and others. Stannous chloride and stannous fluoride are presented as counter-irritants.

Powder composition comprising a skin irritation reducing agent (J&J) US6426092
A novel powder composition is claimed comprising skin irritation reducing agents trimethylglycine, scutellaria baicalensis extract, bisabolol and mixtures thereof. The powder can be used especially for treating prickly heat.

Therapeutic/cosmetic compositions comprising CGRP antagonists for treating sensitive human skin (L'Oreal) US6416760
Topically applied drug/dermatological/ cosmetic compositions are described containing an effective amount of at least one calcitonin gene-related peptide (CGRP) antagonist such as CGRP 8-37 or an anti-CGRP antibody. The compositions are well suited for therapeutic treatment of sensitive skin, mucous membranes, nails, etc., and particularly for reducing or avoiding the skin irritant side effects of bioactive agents such as alpha-hydroxy acids.

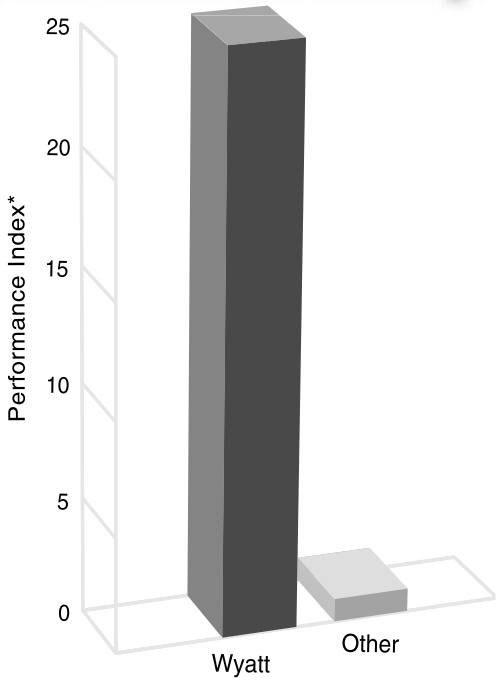
Use of complexes for the preparation of composition for the treatment of sensitive skin (J&J) US6352698
The invention relates to the use of at least two compounds chosen from components having a) anti-radical, b) anti-inflammatory, and c) anti-allergic activity. Anti-radicals are chosen from free radical scavengers, anti-lipoperoxides and stimulants of the endogenous production of enzymes which degrade free radicals. Anti-inflammatory compounds are chosen from inhibitors of prostaglandins, and inhibitors of the production of cytokines and leucotrienes. Anti-allergy compounds are chosen from inhibitors of lymphocyte proliferation, inhibitors of the internalization of HLA receptors and inhibitors of cytokines.

Active substances to enhance the skin's defenses (Kramer) US6346258
The invention pertains to a combination of active substances to enhance the skin's defenses against chemical and physical irritants. The topical agents comprise ionically bound and/or free thiocyanate ions and urea. The thiocyanate ions can be in the form of metal salts such as sodium, potassium and ammonium thiocyanates.

Electrode structure for reducing irritation to the skin (Nitto) US6336049
An electrode structure containing plural electrode elements each comprising an electrode and an electrolyte layer laminated onto it. The electrode of each element is electrically connected to a resistor that limits the current flowing through the electrode, the resistor having a resistance that is 1/5 to 5 times the resistance of the skin. This electrode structure keeps constant the

***Transdermal** continued on page 23*

Our macromolecular characterization has no peer.



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News continued from page 8

in the cloning of high-valued animals and for the introduction of genetic modifications into animals for a wide array of agricultural, animal science, companion animal, and human medical applications. ACT has licensed its cloning patents to Cyagra, Inc., of Worcester, Massachusetts, for agricultural applications, PPL Therapeutics, Limited, of Roslin, Midlothian, Scotland and Immerge BioTherapeutics, Inc., of Charlestown, Massachusetts, for xenotransplantation applications, GTC Biotherapeutics, Inc. of Framingham, Massachusetts, for the production of biopharmaceuticals in milk, and Genetic Savings and Clone of Sausalito, California, for the production of companion animals.

The Patent Office held that all of the claims of the interfering Infigen patent application were unpatentable because Infigen presented all of these claims more than one year after the ACT patent issued.

ACT's President and C.E.O., Michael D. West, Ph.D., stated: "We have felt strongly that our technology is unique, and we are very pleased with the Patent Office's decision, which confirms the value of ACT's intellectual property."

Advanced Cell Technology is a biotechnology company focused on discovering and commercializing the applications of cloning technology in human medicine and animal science.

Additional information can be found at http://www.advancedcell.com/.

Newly Published Data in Blood Confirm the Therapeutic Efficacy and Safety of Intercept Platelets

The first pathogen inactivation blood safety technology for platelets has been approved and is available for use in europe. The March 15 issue of the scientific journal Blood, the official journal of the American Society of Hematology, contains published data demonstrating that physicians in Europe can safely provide their patients with the added security of pathogen inactivated platelets while delivering the therapeutic benefits required of platelet transfusions. The pivotal European Phase III clinical trial data confirm the therapeutic efficacy and safety of the INTERCEPT Blood System for platelets, a new blood safety technology designed to protect patients by reducing the risk of transfusion-transmitted diseases such as HIV and hepatitis.

The study, known as the euroSPRITE trial, was one of the most extensive platelet transfusion clinical trials ever conducted in Europe in thrombocytopenic patients (patients with low platelet counts and at high risk for bleeding). The results were a determining factor in the INTERCEPT Blood System for platelets receiving European regulatory approval last year, making it the only pathogen inactivation system for platelets approved and available for use in Europe.

The study was designed to determine whether platelets treated with the INTERCEPT Blood System provided platelet transfusion support in preventing or stopping bleeding consistent with conventional medical practice. This included monitoring patients for bleeding and several secondary endpoints including acute transfusion reactions, as well as adverse events. The results showed that platelets treated with this new blood safety technology delivered comparable therapeutic benefits with no associated increase in patient adverse reactions.

"These results are particularly important as they indicate that platelets treated with the INTERCEPT Blood System offer the benefit of a prospective blood safety technology without compromising platelet performance or function," said Professor Dick van Rhenen, lead investigator and Director of Sanquin Blood Bank South West Region, Rotterdam, the Netherlands. "This is a significant advancement in the safety for patients undergoing chemotherapy, heart bypass surgery and other procedures that require platelet transfusions."

The randomized, double-blind and controlled trial compared conventional platelets with platelets treated with the INTERCEPT Blood System in 103 thrombocytopenic patients requiring repeated platelet transfusions for up to 56 days. The study included thrombocytopenic cancer and bone marrow transplant patients from four prominent medical centers in the United Kingdom, France, the Netherlands and Sweden.

The results of the euroSPRITE trial indicated that the platelets treated with the INTERCEPT Blood System were comparable in safety and efficacy to untreated platelets. In addition, both groups showed a comparable low incidence of bleeding, low numbers of red blood cell transfusions and low incidence of acute transfusion reactions. In this study, for specific patient groups the INTERCEPT Blood System also was used in place of gamma irradiation to inactivate white blood cells that can cause a fatal reaction in patients with damaged immune systems.

The INTERCEPT Blood System for platelets has been jointly developed by Cerus Corporation and subsidiaries of Baxter International Inc. With this technology, the two companies introduce a new, more comprehensive strategy for the protection of the blood supply by targeting a broad spectrum of pathogens associated with transfusion-transmitted diseases. The INTERCEPT Blood System for platelets uses a light-activated, nucleic acid- targeting compound that inactivates pathogens containing DNA and RNA, such as HIV and hepatitis B and C viruses, and prevents them from replicating. The technology also has been shown to inactivate emerging pathogens for which there are no current tests, such as West Nile Virus.

Clinical trials are underway for use of the INTERCEPT Blood System with plasma and red blood cells for transfusion, making it the only pathogen inactivation technology currently being developed for use with all primary blood components. The companies have begun the regulatory submission process for INTERCEPT Platelets in the United States.

The "ABOVE" MS Study Explores Effects of Increasing Dose and Frequency of Beta Interferon Therapy

Berlex Laboratories, Inc., the U.S. affiliate of Schering AG, Germany announced the start of a new clinical study to evaluate the effect of dose and frequency of beta interferon in patients with relapsing-remitting multiple sclerosis (MS). The study, known as "ABOVE" (Interferon beta-1a vs. Interferon beta-1b Observation of Efficacy), will compare the outcome of continuing once-weekly Avonex(R) (interferon beta-1a) versus changing to a high-dose, high-frequency regimen with Betaseron(R) (interferon beta-1b) for SC Injection.

Of the available disease-modifying MS treatments, beta interferons are the most studied and most widely used. These drugs are approved for use in patients with relapsing-remitting MS. Individually, the interferons may differ in their side effect and efficacy profiles, as well as dose and frequency and route of administration. Avonex is injected into the muscle once a week at a dose of 30 mcg, whereas Betaseron is injected under the skin every other day at a dose of 250 mcg.

"The ABOVE study will address several questions that previously have not been answered in full. For example, what are the effects of increasing the dose and frequency of beta interferon in relapsing-remitting patients who are on an established beta interferon regimen?" said Douglas S. Goodin, MD, a Professor of Neurology at the University of California, San Francisco and the lead investigator of the ABOVE study. "In addition, because ABOVE is such a large clinical trial that will be carried out for two full years, it will provide more complete answers to questions about the effect of neutralizing antibodies on interferon response and about differences in individual response patterns to interferon in patients with MS."

News continued on page 24

SCIENTIFICALLY SPEAKING

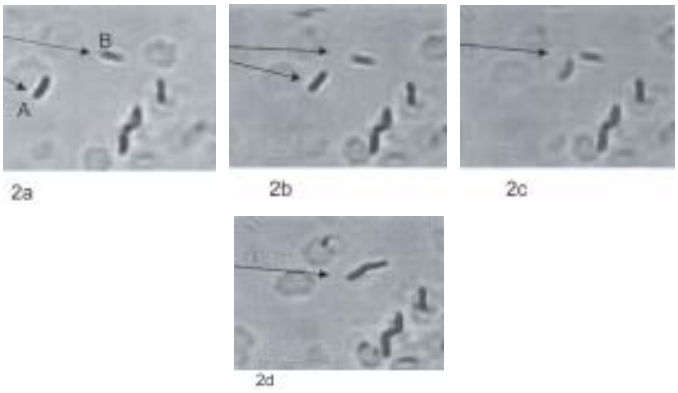
Sorbitan Monostearate Organogels and Amphiphilogels for Drug and Vaccine Delivery

By Dr. Sudaxshina Murdan
University of London, email: sudax.murdan@ulsop.ac.uk

Unlike their cousins hydrogels, organogels (gels where the fluid phase is an organic liquid) have been less widely studied and the literature is sparse, especially in the drug delivery field. Interest in these weird and wonderful systems is increasing however, and a number of novel organogels are being investigated, in an attempt to understand the basic science and to exploit their different characteristics. The gels are typically prepared simply by dissolving/dispersing the gelator in the hot solvent and cooling the resulting sol phase that sets to a semi-solid gel. Cooling the sol results in reduced solubility of the gelator in the solvent, and hence reduced affinity between solvent and gelator molecules. Consequently the gelator molecules self-assemble into aggregates, such as, rods, tubules, fibres, rope-like chains, ribbons, fan-like structures, which interact with one another and form a 3-dimensional network that immobilises the solvent. Potential applications of these gels include: media for reactions and for the purification of organic solvents, separation membranes, sensors, carriers for drugs, vaccines and thermotropic liquid crystals, tools to study the behaviour of membrane-bound proteins, etc.

In our laboratories, we have investigated the non-ionic surfactant, sorbitan monostearate, as an organogelator. Sorbitan monostearate gels a number of organic solvents such as alkanes (e.g. hexane, cyclohexane, octane, cis- and trans- decalins, hexadecane), the alkene squalene, long chain synthetic esters (e.g. ethyl oleate, isopropylmyristate) and vegetable oils (e.g. corn oil, olive oil, cottonseed oil). The gels are prepared by dissolving/dispersing the gelator in the hot solvent and cooling the resulting sol phase which sets to an opaque, white, semi-solid, thermoreversible gel. Cooling results in reduced affinities between the solvent and the surfactant, which leads to surfactant self-assembly into tubules, which join with one another and form a three-dimensional network (figure 1) that immobilises the fluid phase. The joining of tubules to form a network seems to be an active process, and tubules have been seen to move within the fluid phase towards other tubules and establish junction points (figures 2a-d). Tubule A unerringly migrated towards tubule B (figures 2a,b), over a period of a few minutes; once the tubule ends met (figure 2c), a few seconds was speant 'looking for the right position' until the apparently correct configuration was found and the tubules 'settled' into a junction point (figure 2d). The nature and the forces of attraction operating at junction points are not clear yet, but they can be destroyed by certain substances such as ethanol. When small amounts of ethanol are added to a hexadecane gel, the latter breaks into a suspension of tubules. Freeze-fracture microscopy, X-ray diffraction and SANS measurements on sorbitan monostearate organogels suggest that the tubules consist of bilayers of surfactant molecules. Thus polar regions in the bilayer (bounded by the surfactant headgroups) would alternate with nonpolar regions (consisting of surfactant tails).

Figure 1



Due to the presence of the polar regions, a certain amount of water can be incorporated within the organogel. The aqueous phase is present within the tubular network (figure 3); as a result, the electrical conductivity of the gel increases and X-ray diffraction measurements show an increased bilayer width (form 5.9 to 6.9nm). The aqueous phase can be a drug/vaccine solution, suspension or even complex liquids such as a vesicle suspension containing entrapped drug/vaccine. In the latter case, a multi-component system is produced, where the vesicles (with entrapped guest entities e.g. a fluorescent dye) are found within the tubular network of the gel (figure 4). This complex gel has been termed a vesicle-in-water-in-oil (v/w/o) gel. When injected intramuscularly in mice, the v/w/o gel exhibited a depot effect; a model antigen, entrapped within the vesicles, was released slowly and 40% of the administered antigen was still present in mice leg 48h following injection. The v/w/o gel also showed immunoadjuvant properties when administered intramuscularly and enhanced the primary and secondary humoral immune responses to haemagglutinin surface antigen (initially entrapped within vesicles).

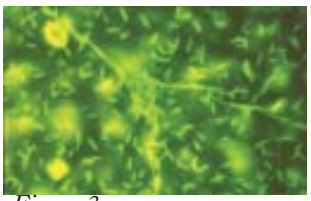


Figure 3

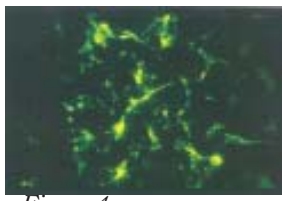


Figure 4

As well as gelling organic solvents, the non-ionic surfactant sorbitan monostearate also gels other non-ionic surfactants such as the Polysorbates , Brijs and the liquid sorbitan esters at concentrations as low as 5%w/w. Such systems, where one surfactant gels another surfactant, have been called 'amphiphilogels'. Prepared in the same way as organogels, the amphiphilogels are opaque semi-solids whose microstructures consist of tubular assemblies of the gelator in the fluid phase. Certain amphiphilogels are good solvents for a number of poorly water-soluble drugs such as cyclosporine, aspirin, paracetamol, ibuprofen and are being investigated as oral, dermal and transdermal drug delivery vehicles. When administered orally to

Scientifically Speaking *continued on page 20*

Report on the National Affairs Agenda

By Rosealee M. Lee, CEO, the ARDEL group & CRS AIMBE Representative

The CRS membership in AIMBE Council of Societies is proving to be a great member benefit. National affairs considerations of the more than 30,000 society members of the Council of Societies which include CRS, were the primary focus at the annual AIMBE event where participants met to draft the COS national affairs agenda. Participants utilized data from the recent COS survey from which almost 500 responses were received. Thanks to the CRS members who responded to the survey. Three working groups developed initiatives that will guide future COS national affairs activities. The three initiatives focus on "Government" (includes issues such as FDA, medical reimbursement, certification and issuance of credentials, etc.), "Education" (includes issues regarding education of the public and legislators, and school educational considerations), and "Funding" (focuses on federal research programs in medical and biological engineering). Following a brief period for review and comment by the working groups themselves, the agenda will be forwarded to voting representatives of the COS for comment. The complete agenda will then be forwarded to the AIMBE Board of Directors for approval.

Email AIMBENationalAffairs@convenemachine.com for more information about the national affairs agenda.

On Monday, February 24, the COS organized AIMBE's first Medical and Biological Engineers Day on Capitol Hill. Participants visited Congressional representatives and represented the AIMBE community on legislative issues of interest. Thanks to the individuals who took our message to the Hill!

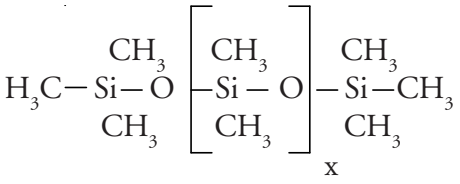
AIMBE is drafting plans to implement a Grants Workshop on the afternoon of June 24. Tentative plans indicate that there will be no charge for individual members of AIMBE COS societies to attend the Grants Workshop. One hour of the afternoon will be dedicated to preparations for AIMBE's second Medical and Biological Engineers Day on Capitol Hill which is scheduled for Wednesday, June 25. This workshop and the Hill visit are being planned in conjunction with the NIH BECON meeting (June 23 and the morning of June 24). "Talking points" given to participants of the Hill visit will incorporate the COS National Affairs Agenda. Please save the date! Watch your email and www.aimbe.org for more information as it becomes available.

CONSUMER & DIVERSIFIED PRODUCTS

Using Silicones for the Delivery of Actives in Personal Care Formulations

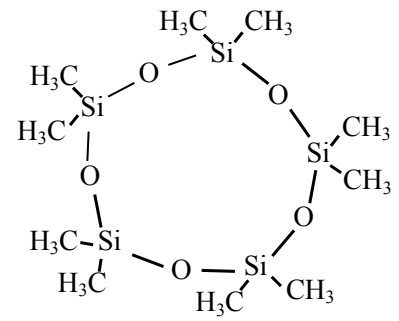
By Michael Starch, Associate Scientist,
Life Sciences Innovation Team, Dow Corning Corporation

Polyorganosiloxanes, popularly know as silicones, have been used in personal care products for over 50 years. They provide a combination of esthetic and functional benefits to products such as skin moisturizers, hair conditioners, cleansing products, color cosmetics, and antiperspirants. The term silicone encompasses a wide variety of different materials that range from low viscosity fluids to high molecular weight gums, and elastomers (crosslinked polymers). In the years prior to the later 1970's, silicones were generally used as additives at concentrations of 1-3%. At this level, silicones can reduce the stickiness of skin care formulations, improve spreading, lubricate, and improve gloss. The most popular silicone additive for personal care formulations is polydimethylsiloxane (PDMS), which is produced in a wide variety of viscosity grades that correspond to polymers with different chain lengths. In personal care applications, PDMS is referred to as "Dimethicone", which is the International Cosmetic Ingredient (INCI) name that is used in ingredient disclosure statements. The structure of Dimethicone is shown in the figure below:



Polydimethylsiloxane (Dimethicone)

In the mid-1970's, a new silicone was introduced to the personal care industry that changed the way that silicones are used personal care products. The silicone was cyclic PDMS, a group of material that are generally known by the INCI name "Cyclomethicone". The physical properties of cyclomethicone such as volatility depend on the ring size. The most popular cyclomethicone is the dimethyl cyclic pentamer that is composed of five dimethylsiloxane units as shown in the figure below. This material is most commonly referred to by its INCI name, Cyclopentasiloxane.



Cyclomethicone pentamer (Cyclopentasiloxane)

Cyclomethicones are non-polar cosmetic solvents that exhibit a combination of properties that make them very useful to the formulator. These properties include a pleasant non-greasy skin feel, lack of odor, and a low heat of vaporization. This latter property led to the use of cyclomethicone as vehicle for anhydrous antiperspirants. The first such product, Gillette's Dry Idea®, was brought to market in the late 1970's. Dry Idea is a low-viscosity (roll-on) formula where the active ingredient (e.g. aluminum-zirconium tetrachlorohydrate) is suspended in the cyclomethicone. Because of the low heat of vaporization of the cyclomethicone vehicle, such formulas do not cool the skin appreciably after application and this phenomenon gave rise to the product concept for Dry Idea. In fact, the esthetics of anhydrous antiperspirants based on cyclomethicone are so much better that the older formulations based on aqueous solutions of active ingredient that cyclomethicone-based antiperspirants have become the dominant product form in the U.S. market.

In a broad sense, the use of cyclomethicone as a vehicle for anhydrous antiperspirants was the first example of a silicone delivery system in personal care. In these products, the cyclomethicone "delivers" the active ingredients to the skin with superior esthetics. Later developments in antiperspirant actives increased the importance of an anhydrous formulation technology. The introduction of activated antiperspirant salts in the 1980's required the use of anhydrous formulations because exposure to water prior to application caused these salts to revert to their native (i.e. less active) form. Thus, cyclomethicone took on the added function of improving the shelf stability of activated antiperspirant salts.

Most silicones that are used in personal care are strongly hydrophobic and this in combination with their ability to wet and spread over virtually any substrate makes them useful as waterproofing treatments. There is a caveat however and that is the fact that silicone films are generally permeable to small molecules such as oxygen and water vapor. This limits the utility of silicones as water barrier coatings in situations where there is constant contact with water, as in most personal care formulations. If there is a gradient in osmotic pressure across a silicone film, water will generally pass through until the osmotic pressure is equalized.

Using Silicones to Increase Product Efficacy

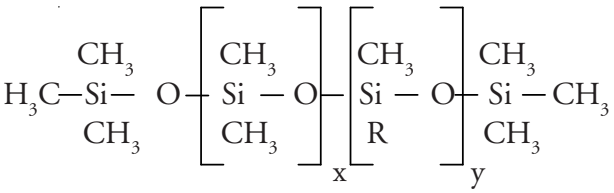
Another benefit of a delivery system is to increase the efficacy of active ingredients in a formulation. One product category where efficacy of the actives is critical is sunscreens, which are applied to the skin to protect it from the harmful effects of the UV radiation in sunlight. Sunscreen actives are usually oils that contain chromophores that absorb electromagnetic radiation in

***Products** continued on next page*

Products continued from previous page

the UV range. To function well, these actives must be delivered to the skin in a uniform coating that maintains it's uniformity as the formula dries and afterward. According to the FDA monograph on sunscreens, which are considered OTC drugs, the activity of a sunscreen formulation must be measured in-vivo by applying the formulation to the skin of human volunteers who are then exposed to controlled amounts of UV radiation from an artificial source. The performance of the sunscreen is rated according to the attenuation effect that is observed from the in-vivo test. The Sun Protection Factor (SPF) is the inverse of the attenuation factor, so for example if a sunscreen formulation reduces the UV exposure by 1/10, then it would be rated as with an SPF of 10. Because of the expense of in-vivo testing, the industry has developed in-vitro methods to estimate the SPF of a formulation. The in-vitro methods involve the application of the formulation to an artificial substrate such as 3M's TransporeÔ tape and measuring the UV transmittance using a specially designed spectrophotometer.

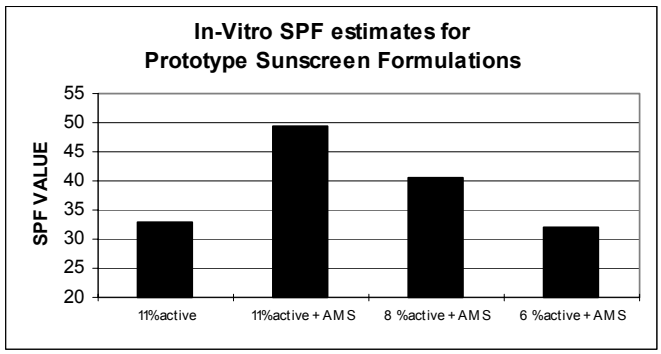
The relatively high cost of sunscreen actives and their potential to irritate the skin has led formulators to try and achieve the maximum SPF for the minimum amount of sunscreen active. It has been shown that a class of silicones known as alkylmethylsiloxanes (AMS) has the ability to increase the efficiency of sunscreen actives such as Octyl Methoxycinnamate. AMS is a variant of polydimethylsiloxane where some of the methyl groups have been replaced with higher alkyl groups such as cetyl (C_{16}) or stearyl (C_{18}), as shown below



examples: R = $-[CH_2]_{15}CH_3$ (Cetyl Dimethicone) or $-[CH_2]_{17}CH_3$ (Stearyl Dimethicone)

Alkylmethylsiloxanes

The introduction of long chain alkyl groups makes AMS more compatible with organic oils and also generally produces a solid wax. The melting point of the AMS waxes depends on the degree of substitution and the length of the alkyl chains. Melting points for AMS increase with the length of the alkyl chains. When Stearyl Dimethicone was included in a conventional oil-in-water emulsion sunscreen formulation, there was a significant increase in the SPF when these formulations were tested using an in-vitro method. The graph below shows SPF estimates for a series of formulations with different levels of sunscreen. The first bar shows the SPF estimate for the formulation with 11% active, but no AMS. Stearyl Dimethicone was added to the formula at a concentration of 4% and this increased the SPF significantly. Subsequent formulas were formulated with the AMS and lower levels of sunscreen active to determine what concentration would produce the same SPF as the original formulation with 11% sunscreen active. The results indicate that the sunscreen active concentration could be reduced to 6% and still provide the same SPF.



The reasons for the SPF increase that is observed when AMS is included in the formulation are not completed understood. The rheology of the formulation is thought to be a factor. Oil-in-water emulsion formulations with AMS exhibit a shear thinning effect and this means that the viscosity is reduced when the formulation is subjected to large shear forces as it is spread onto the skin or other surface. The viscosity of the formulations recovers rapidly as soon as the shear force is stopped and this is thought to help keep the droplets of sunscreen active fixed in place on the surface while the formulations dries. This effect would produce a more even distribution of sunscreen active and thereby increase its UV screening efficiency.

***Products** continued on page 22*

MEMBER RELEASE

The Members Have Spoken…
By Jaymie Griffin, CRS Newsletter Editor & Assistant Executive Director

CRS is excited to announce the results of the Readership Survey. Twenty-eight percent of the CRS membership responded, which is higher than the five percent average membership response rate. The results of the CRS Readership Survey, outlined below, reflect the highest and lowest percentages of each question.

	# Responses	Percent
1. The Newsletter serves its purpose to educate, inform and allow for networking of members.		
No response	2	0.58%
Agree	231	67.35%
2. The Newsletter could be improved by including more:		
No response	8	2.33%
Shorter well researched articles	204	59.48%
3. The Newsletter should be available to everyone online and not just CRS members.		
No response	1	0.29%
Agree	125	36.44%
4. Past issues of the Newsletter should be available to non-members and the current issue for CRS members only.		
No response	1	0.29%
Agree	132	38.48%
5. Do you prefer to receive the Newsletter in print, electronically, or both?		
No response	3	0.87%
In print	134	39.07%
6. Do you rely on the Newsletter for up-to-date information about the controlled release industry?		
No response	8	2.33%
Yes	216	62.97%

The editorial staff was delighted to see that an overwhelming number of members agree that the Newsletter serves its purpose to inform and allow for networking. The Newsletter Editors will strive to incorporate more, shorter and well-researched articles and more pharmaceutical press releases and drug delivery company business activities.

The majority of member responses indicate a preference for the printed version of the Newsletter, therefore, the Newsletter will remain online and in print. For the members that prefer their Newsletter electronically rather than in print, the membership application and renewal application have a section titled "Distribution Options", where a member can choose to receive the Newsletter and/or Final Program electronically or by direct mail.

Finally, this survey revealed that 62.97% of the membership relies on the Newsletter for up-to-date information about the controlled release industry. Up-to-date information is obtained by many different means, one of which is member input or involvement. Article submissions from members of the Controlled Release Society are not only welcome, but are a vital part of what makes this publication valuable to its members. It is a publication not only about the controlled release industry, but about its members as well, so please submit your articles to Newsletter@controlledrelease.org and be a part of what makes the Newsletter valuable to you, the member.

Scientifically Speaking *continued from page 16*

Beagle dogs, absorption of cyclosporine from the amphiphilogels was found to be similar to that from the commercially available formulation, Neoral®. Upon ingestion and dilution with the stomach contents, the gel is expected to form a fine dispersion which keeps the drug in a soluble form during its transit in the gastro-intestinal tract. The amphiphilogels have also shown promise as dermal delivery vehicles for dissolved and dispersed drugs. *In vitro* permeation studies have shown enhanced uptake of ovalbumin into full-thickness pig skin. The amphiphilogels are well tolerated when applied topically. *In vivo* studies in mouse revealed no significant irritation (measured by laser Doppler and by visual assessment of erythema) when the gels were applied to shaved mouse skin. Human volunteer studies on the irritation potential of these gels will commence shortly.

The author thanks Professor Gregory Gregoriadis, Professor Sandy Florence, Dr Tomas Andrysek, and Nadeen Jibry who have contributed to the work described above. The work on oral absorption of cyclosporine and the *in vivo* irritation studies will be presented at the next CRS annual meeting in Glasgow.

Spotlight continued from page 9

Lym-X-Sorb™ monomer serves to not only protect the drug from digestive degradation; it also protects the stomach and intestine from potential drug-induced cytotoxicity.

Because Lym-X-Sorb™ technology is based on digestive action, it has also proved effective in acting as a medical food. Lym-X-Sorb™ has proven an active agent in treating nutritional disorders by supplementing as a dietary fat; capable of delivering therapeutic essential fatty acid stores. This utilization of Lym-X-Sorb™ has been demonstrated in the treatment of cystic fibrosis where patients display compromised pancreatic function and have difficulty absorbing nutritional fat. In a one year double blind feeding study, the daily consumption of Lym-X-Sorb™ in comparison to triglyceride (24g lipid per 1.73 m^2 body surface) by cystic fibrosis patients significantly improved their energy intake, growth in terms of weight and height, lung function and plasma levels of linoleic/á-linolenic acid, vitamin E and retinal-binding protein[3]. One tool - the simplest solution.

Lym-X-Sorb™ is manufactured with Generally Recognized as Safe (GRAS) lipid materials in a range of molar ratios; 1:2:4 to 1:4:2, LPC: MG: FA respectively. This flexibility allows for improved solubility and stabilization of the drug compound. Feasibility trials have shown fenretinide, insulin, histrelin, â estradiol, nifedipin analogues, hydrochlorothiazide, McN-5703, capsaicin, diltiazen, renin inhibitors, hydrocortisone, cromolyn, pramoxine, buprenorphine, progesterone, cyclosporin A, metronidazole and gentamicin to be stable within the Lym-X-Sorb™ monomer.

Lym-Drug Products manufactures Lym-X-Sorb™ under an agreement with Avanti Polar Lipids, Inc., a bulk pharmaceutical facility specializing in the manufacture of lipid materials for industry and research. Avanti utilizes current Good Manufacturing Practices (cGMP's) and produces the largest number of lipid products with FDA submitted Drug Master Files in the US. Avanti is located in Alabaster, Alabama; just a few minutes from downtown Birmingham.

Lym-Drug Products is currently pursuing Lym-X-Sorb™ technology in clinical trials for cancer treatment with a number of biotechnology professionals in commercial and university settings. Working with colleagues at the University of Southern California and the Children's Hospital of Los Angeles, an NCI supported Rapid Access to Intervention Development (RAID) grant application has been submitted to support Phase I clinical trials of the Lym-X-Sorb™-fenretinide complex to pediatric patients with advanced neuroblastoma.

In 2001, a phase I, NIH supported Small Business Innovation Research (SBIR) grant was awarded to evaluate the Lym-X-Sorb™ complex and its palatability. Continuation of that work will be presented in a clinical Phase II application planned for submission in April 2003. Other ventures include the exploration of Lym-X-Sorb™ as a high caloric supplementation for HIV therapy, energy reserves and docosahexaenoic acid (DHA) delivery.

Lym-X-Sorb™ is a proprietary technology held by Biomolecular Products, Inc.; protected by seven US and worldwide patents/provisional applications and licensed to Lym-Drug Products, LLC and others. Additional patent protections are planned as new applications arise, guaranteeing future collaborators innovative security. Lym-Drug Products is focused on assisting the biotechnology industry with its drug delivery needs. By working closely with pharmaceutical and biotechnology companies eager to improve upon or implement an oral delivery program, Lym-Drug Products plans to lead the industry in therapeutic delivery.

One tool - the simplest solution. Utilizing innovative technology to fight disease by working with the body's inherent physiology, Lym-Drug Products is improving the benefits of oral drug delivery. As technology continues to offer drug candidates that fight disease and increase life expectancies, Lym-Drug Products will ensure they are absorbed expeditiously.

More information illustrating Lym-X-Sorb™ technology and how it can assist your organization may be found on Avanti's web site, www.avantilipids.com, or contacting BioMolecular Products, Inc. (978-462-2224).

References:

1. D.W. Yesair, Phosphatidyl choline and lysophosphatidyl choline in mixed lipid micelles as novel drug delivery systems. *Phospholipids*. Ed. by I. Hanin, G. Pepeu. Plenum Press, New York. (1990) 83-106.

2. C.J.H. Porter, W.N. Charman, Transport and absorption of drugs via the lymphatic system. Adv. Drug Delivery Rev. 50 (2001) 1-2.

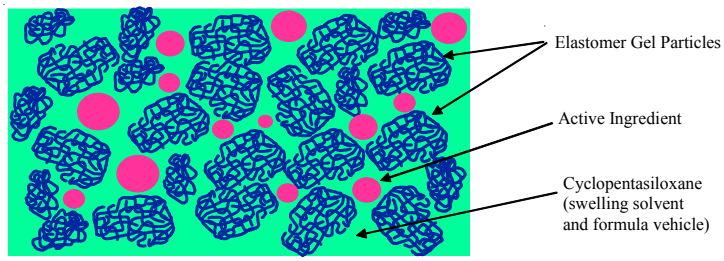
3. G. Lepage, D.W. Yesair, N. Ronco, J. Champagne, N. Bureau, S. Chemtrob, D. Berube, C.C. Roy, Effect of an organized lipid matrix on lipid absorption and clinical outcomes in patients with cystic fibrosis. J. Pediatrics 141, 2 (2002) 178-185.

Products continued from page 19

Another aspect of sunscreen performance that is of interest is resistance to removal by water. Consumers want sunscreen products that maintain their SPF after exposure to water and this presents a challenge to formulators because the same emulsifiers that are used to stabilize the formulation tend to re-emulsify the sunscreen active when the dried sunscreen film is exposed to water. This problem can be reduced by the incorporation of silicones, which increase the hydrophobicity of the dried sunscreen film. High viscosity Dimethicones are particularly useful for this purpose.

Delivery Systems Based on Silicone Elastomers

The development of silicone elastomers for personal care applications has expanded the possibilities for silicone applications in delivery systems. Silicone elastomers are essentially Dimethicones that have been crosslinked to produce an insoluble silicone polymer matrix. This matrix is typically swelled with a solvent such as Cyclopentasiloxane to produce gels. One of the most popular types of silicone elastomer is a paste that is made by shearing the swollen elastomer gel to produce a paste composed of gel particles. These swollen elastomer gel particles are very useful as thickeners and have a pleasant silky skin feel. They are used in unit dose skin care products (e.g. gelatin capsules) where the gel particles suspend the active ingredient in the silicone base. A schematic of how the silicone elastomer gel particles can stabilize a suspension of the active ingredient is given in the figure below. In addition to suspension of active ingredients in unit dose products, silicone elastomers have been used to thicken and suspend the active ingredients in anhydrous antiperspirants.

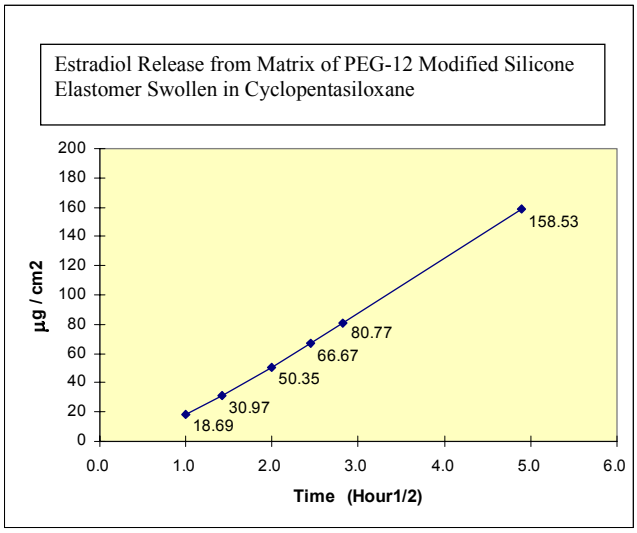


In formulations where the active ingredient is polar and therefore insoluble in the silicone matrix, it exists as a separate phase in the formulation. Release of the active occurs by one of two mechanisms. The active can be exposed when the formulation is sheared during application to the skin or when the vehicle evaporates. Evaporation of the vehicle (Cyclopentasiloxane) not only exposes the suspended active ingredient, but also causes the swollen gel particles to collapse. Thus, when a formulation such as the one depicted in the figure above is allowed to dry completely, the active is left behind together with a very small amount of dried elastomer powder. Unless there are nonvolatile oils (e.g. Dimethicone) in the formulation that can coat the particles or droplets of active ingredient there will be inhibition of activity.

When the active is completely insoluble in the silicone matrix, there does not seem to be any possibility for controlled release since the active cannot easily diffuse out of the formulation. However, it has been shown that modification of the silicone elastomer to increase its polarity facilitates controlled release of certain active ingredients. One such elastomer modification is the grafting of polyethylene glycols (PEGs) onto the elastomer backbone. Silicone elastomers with PEG substituents were prepared and blended with estradiol, cast into films, and measured for the release of the estradiol. The graph below shows the release of estradiol from this film of modified silicone elastomer. Another active ingredient that exhibits improved compatibility in PEG-modified silicone elastomer is tocopherol (Vitamin E). This suggests the possibility of controlled release forms of tocopherol, although this has not yet been demonstrated.

Estradiol Release from Matrix of PEG-12 Modified Silicone Elastomer Swollen in Cyclopentasiloxane

What's Next for Silicone Delivery Systems?



One topic of great interest to our customers is controlled release of fragrance. In response to this interest we have developed test methods to evaluate fragrance release rates from various types of formulations. Preliminary data indicates that silicone elastomers may be useful for extending the life of fragrances delivered from skin care formulations.

Other types of delivery systems based on silicones are also being investigated. There are silicone surfactants that are capable of forming vesicles that can entrap lipophilic actives such as Vitamin E (tocopherol). These vesicles are similar to liposomes, but are more robust and easier to produce. Other types of silicone surfactants can be used to prepare multiple emulsions that have the potential to segregate different water-soluble actives within the same formulation.

These are only a few examples of silicone delivery systems that are being developed for personal care applications. Given the wide variety of silicones that are available and increased understanding of how these materials modify the performance of active ingredients, it is expected that delivery systems will be a productive area for new developments by silicone suppliers and their customers for many years to come.

Transdermal continued from page 13

density of the current flowing to the skin, irrespective of the electrification method, and thus it is able in reducing the irritation due to electrification.

ENHANCERS

Process for limiting the penetration into the skin (L'Oreal) US6497888
A process and a composition are described for limiting the penetration into the skin of cosmetics or pharmaceuticals for topical application. The process involves the dispersion of vesicles in the base composition, with said vesicles comprising at least one ceramide of specific composition. Several such ceramides are disclosed including 2-(oleoylamino)octadecane-1,3-diol. The use in colorants and sunscreens are described.

Ultrasound enhancement of transdermal transport (Sontra Medical) US6491657
A device is claimed for enhancing transdermal transport, comprising an ultrasound transducer with ultrasound beam of specific diameter and energy and a chamber which channels the ultrasound beam, so that the beam has a substantially smaller diameter but retains at least 50% of the energy. This process allows for increase in skin permeability with lower skin adverse reactions.

Transdermal patch with controlled heating device (Zars) US6488959
A patch is disclosed which has a heating element secured to it. The heating element provides controlled heat to the patch and the patient's skin, thereby improving dermal drug administration. Fentanyl, nicotine and testosterone are disclosed as the drugs of choice and the optimum temperature of the heating element is between 42 and 44 ºC.

Dermal absorption promoting agent (Takasago) US6410034
Dermal absorption enhancer compositions are described comprising p-methane-3,8-diol and 1,3-butylene glycol. These enhancers are suitable for the administration of anti-inflammatory agents such as indomethacin, phenylbutazone, naproxen and ibuprofen.

Transdermal absorption from subcooled melts (LTS Lohmann) US6344211
A transdermal enhancer is disclosed which is a material that forms subcooled melts. Materials that form subcooled melts are understood to mean those whose melting points are above room temperature but which after a melting process, remain in the liquid state during cooling to room temperature. Enhancers of this type include levulic acid, glutaric acid monomethyl ester and dodecanol. The delivery of buprenorphine base with levulic acid is specifically claimed.

ELECTROTRANSPORT

Device for transdermal electrotransport delivery of fentanyl and sufentanil (Alza) US6425892
The fentanyl/sufentanil is provided as a water soluble salt, preferably in a hydrogel formulation, to be used in an electrotransport device. Analgesia is obtained by delivering fentanyl between 20 and 60 mg over a period of about 15 minutes. The process can be repeated up to 100 times per 24 hour period.

Iontophoresis, electroporation and combination patches for local delivery to body tissues (GPM Drug Delivery) US6424862
Patches for enhancing the delivery of drugs, plasmids, genes and other agents into the tissues are described. The patch devices provide an electrical driving force to deliver the drug to the desired tissues and cells, using iontophoresis only, electroporation only, or combined iontophoresis and electroporation. The invention is particularly applicable to the local delivery of drugs in procedures such as angioplasty, stent implantation, delivery of proteins to the heart and pericardium and delivery of plasmids and genes to cells.

Electrotransport adhesive for iontophoretic device (Alexgaard) US6347246
The invention provides for an electrically conductive adhesive hydrogel comprising from about 15 to 60% of cationic polymer prepared by the polymerization of monomers of specific formulas and from 5 to 40% water. In particular this polymer is useful in iontophoretic devices because it can function as a scavenger of hydroxyl ions generated during iontophoresis. A monomer useful in this invention is acryloxyethyldimethylbenzyl ammonium chloride.

Anhydrous drug reservoir for iontophoretic delivery (Alza) US6374136
A method is disclosed for forming an anhydrous reservoir layer of an electrode assembly. The method involves the dissolution of the active agent in a solvent, applying the dissolved active to the surface of a hydrophilic polymer filtration membrane, removing the solvent and placing the active agent/filtration membrane within the electrode assembly.

METHODS/DEVICES

Inhibition of crystallization in transdermal devices (Amarin) US6465005
Methods for the prevention of crystallization of hormone drugs when used in saturated or supersaturated conditions are disclosed. The crystallization inhibitors claimed are steroids, used in subtherapeutic levels, and include estrogens, progestogens, androgens and glucocorticoids.

Solubility enhancement of drugs in transdermal delivery (Noven) US6465004
A method for the prevention of recrystallization of an active in a pressure sensitive adhesive matrix is described comprising cellulose acetate butyrate with butyryl content of at least 30%. The cellulose acetate butyrate can be as high as 20% of the matrix composition.

Hydrophilic penetration agents for the treatment of onychomycoses (Novartis) US6455592
Topical formulations for onychomycoses are disclosed comprising an antifungal agent, a hydrophilic penetration enhancer and a solvent medium composed of water and a lower alkanol. Antifungal agents presented include terbinafine and naftifine. A large number of hydrophilic penetration enhancers are disclosed including glycols, glycol ethers, caprolactum, dimethylisosorbide and dimethyl acetamide, among others.

Matrix-type transdermal patch for steroid hormones (Rottapharm) US6440454
A matrix-type patch is disclosed containing estradiol and a progestagen which are dissolved in the matrix in an oversaturated solution. The matrix also contains from 1 to 5% activated silicon dioxide and less than 0.7% water (prevents crystallization). The silicon dioxide is activated by irradiation with an infrared source.

Method and devices for transdermal delivery of lithium (Emory U.) US6375990
A method and a device are disclosed for treating acute mania or bipolar disorder by delivering lithium ions at a constant rate. Iontophoretic delivery is used to provide blood lithium ion concentration levels between 0.6 and 1.4 mEg/L. The iontophoretic current density is in the range of 50 to 250 mu.A/CM^2 and pulse frequency between 1 and 10 kHz.

Matrix patches of hydrophilic drugs in hydrophobic pressure sensitive adhesives (Watson) US6365178
A method for manufacturing matrix patches is described, in which a hydrophilic salt form of a drug is dissolved into the aqueous phase of a dispersion of a hydrophobic pressure sensitive adhesive. Upon evaporation of the solvent, a film is obtained that has excellent physical stability and prevents recrystallization of the drug.

News continued from page 15

Betaseron(R) (Interferon Beta-1b) Gains Expanded FDA Labeling Approval for Treating Relapsing Forms of Multiple Sclerosis

Laboratories, Inc., the U.S. affiliate of Schering AG, Germany, and Chiron Corporation announced that the U.S. Food and Drug Administration (FDA) has approved new labeling for the multiple sclerosis (MS) treatment Betaseron(R) (interferon beta-1b) for SC Injection. The new labeling includes revisions to the clinical studies section to include data from two studies conducted in patients with secondary progressive MS. In addition, the indication section has been revised to now reflect that, "Betaseron is indicated for the treatment of relapsing forms of MS to reduce the frequency of clinical exacerbations." Relapses are repeat attacks during which new symptoms appear or existing symptoms worsen, followed by periods of recovery. Relapsing forms of MS include relapsing-remitting, the most common form, and secondary progressive MS with relapses.

"We are pleased with the FDA's approval of our label expansion. The enhanced labeling is testament to more than a decade's worth of research and clinical experience demonstrating the unsurpassed benefits of Betaseron use in treating MS," said Ayad Abdulahad, MD, PhD, Medical Director, CNS, of Berlex Laboratories. "We believe this important research — one of the largest data sets ever collected in MS — will enhance understanding of treatment options for the entire MS community."

"Betaseron's strong clinical results help ensure its continued growth, and this expanded label will increase treatment options for a broader population of MS patients," said Bruce Scharschmidt, MD, Vice President, Clinical Development, Chiron Corporation. "Chiron and Berlex are committed to further improvements to increase convenience and ease of use for patients."

The new labeling for Betaseron also includes updated safety information. In addition, a new patient Medication Guide will be available that provides information on Betaseron use.

Data Summarized in Clinical Trials Section

The expanded Betaseron label now will contain data from both the pivotal two-year study of 372 patients with relapsing-remitting MS and two secondary progressive MS trials involving more than 1,600 patients collectively. The first secondary progressive MS trial was a double-blind, placebo-controlled European study of 718 patients in 32 centers, and the second was a double-blind, randomized North American trial of 939 patients in 35 centers in the United States and Canada. Although the findings from these studies were discordant, the European study did meet the primary efficacy endpoint. Both secondary progressive studies showed that treatment with Betaseron significantly reduced the incidence of relapses and the amount and activity of brain lesions detected by magnetic resonance imaging (MRI).

Statement from the Royal Pharmaceutical Society of Great Britain

A response to comments by the Trade and Industry Secretary, Patricia Hewitt, about the Office of Fair Trading's recommendation that the control of entry regulations for UK community pharmacies be abolished.

Statement: Marshall Davies, President of the Royal Pharmaceutical Society of Great Britain said: "We are gratified that the Trade and Industry Secretary recognises the important contribution of pharmacies to the nation's healthcare, which was a[sic] not a focus of the OFT report.

"The unique status of community pharmacies as privately owned and financed businesses that support and deliver NHS services is inherently different from other enterprises' because of the need to serve the interests of patients and meet the requirements of the NHS."

Ranbaxy Gains FDA Approval to Market Amoxicillin and Clavulanate Potassium for Oral Suspension USP

Ranbaxy Pharmaceuticals Inc. (RPI), a wholly owned subsidiary of Ranbaxy Laboratories Limited (RLL), stated that RLL has received approval from the U.S. Food and Drug Administration to market Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 200 mg/28.5 mg (base)/5 mL and 400 mg/57 mg (base)/5 mL. The Division of Bioequivalence has determined the Ranbaxy formulations to be bioequivalent and, therefore, therapeutically equivalent to Augmentin(R) for Oral Suspension*, 200 mg/5 mL, and 400 mg/5 mL, respectively, of GlaxoSmithKline. Augmentin(R) has combined sales of $1.2 billion with total sales of $272.5 million in the suspension market (IMS - MAT: December 2002).

Amoxicillin and Clavulanate Potassium for Oral Suspension is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed as follows: Lower Respiratory Tract Infections, Otitis Media, Sinusitis, Skin and Skin Structure Infections, and Urinary Tract Infections. While Augmentin(R) is indicated only for these conditions listed above, infections caused by Ampicillin-susceptible organisms are also amenable to Augmentin(R) treatment due to its Amoxicillin content.

"We were delighted to make yet another dosage form of Amoxicillin available based on the skills and talents that are available through our parent company, Ranbaxy Laboratories Limited. This again demonstrates our depth and breadth of expertise to add to our expanding product portfolio, along with our commitment to bring generic alternatives to the U.S. healthcare system. We are adding yet another product that has clinical utility and value, and as such, will distinguish Ranbaxy in the years to come," according to Dipak Chattaraj, President and CEO of RPI.

Parker Hughes Engineers Anti-Viral Agent Against HIV

Scientists at Parker Hughes Cancer Center have designed and engineered a broad-spectrum recombinant anti- viral agent that is active against HIV. In a study to be published in the April issue of the journal Antimicrobial Agents and Chemotherapy, Parker Hughes Scientists report that PAP (recombinant pokeweed anti-viral proteins) show potent activity against HIV, including HIV strains resistant to major anti-HIV drugs.

There are an estimated 363,000 persons living with AIDS in the United States. Of those being treated with anti-HIV drugs some 80% will eventually develop drug resistance. For that reason scientists are working to develop agents that are effective against drug resistant strains of HIV. "We are cautiously optimistic that pokeweed antiviral proteins will provide the basis for salvage therapies for patients harboring highly drug resistant strains of HIV," said Dr. Fatih Uckun, MD, Ph.D., Medical Director of Parker Hughes Cancer Center. "Our goal is to provide hope to AIDS patients who find their hope is running out as they become resistant to currently available therapies," Uckun added.

Engineered non-toxic PAP may prove to be an effective vaccine against certain biological weapons. This is because a portion of PAP shares unique similarities to ricin, an exceptionally powerful toxin that is a much feared potential agent of biological warfare. Scientists theorize that vaccinating people with PAP might result in the deployment of antibodies that would protect the body against ricin.

"There is still much work to be done but PAP may prove to be the basis for an effective vaccine against ricin," Uckun said.

Reference: Antimicrob Agents Chemother 2003 Mar;47(3):1052-61. Structure-based design and engineering of a nontoxic recombinant pokeweed antiviral protein with potent anti-human immunodeficiency virus activity. Uckun FM, Rajamohan F, Pendergrass S, Ozer Z, Waurzyniak B, Mao C.

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Next issue deadline
August 29, 2003

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

eventcalendar

University of Minnesota Rheological Measurements Short Course
June 8-13, 2003
University of Minnesota
Minneapolis, MN, USA
giles@cems.umn.edu
www.cems.umn.edu/rheology
ph: +1 612-625-0880

American Society for Artificial Internal Organs ASAIO 49th Annual ASAIO Conference
June 19-21, 2003
Hilton Washington
Washington DC, USA
info@asaio.com
www.asaio.org
ph: +1 561-391-8589

Robert S. Langer, MIT: Advances in Controlled Release Technology: Polymeric Delivery Systems for Pharmaceuticals, Proteins, and Other Agents
June 23-27, 2003
Massachusetts Institute of Technology
Cambridge, MA, USA
professional-institute@mit.edu
http://web.mit.edu/professional/summer
ph: +1 617-253-2101

AO Foundation ECM IV: Bone Tissue Engineering
June 30 - July 2, 2003
Congress Centre
Davos, Switzerland
sonia.wahl@ao-asif.ch
www.aofoundation.org/events/ao/ecm/ECMIV
ph: +41-81-4142-541

Controlled Release Society 30th Annual Meeting and Exposition
July 19-23, 2003
Glasgow, Scotland
register@controlledrelease.org
www.controlledrelease.org
ph: +1 763-512-0909

American Society for Bone and Mineral Research
September 19-23, 2003
Minneapolis Convention Center
Minneapolis, MN, USA
asbmr@dc.sba.com
www.asbmr.org
ph: +1 202-367-1161

BMES: 2003 BMES Annual Fall Meeting
October 1-4, 2003
Renaissance Nashville Hotel
Nashville, TN, USA
www.bmes.org

OsteoArthritis Research Society International (OARSI) 2003 World Congress on Osteoarthritis
October 12-15, 2003
Berlin, Germany
oarsi@oarsi.org
www.oarsi.org
ph: +1 202-367-1177

Surfaces in *Biomaterials* Foundation presents BioInterface 2003
October 22-24, 2003
Savannah Marriott Riverfront
Savannah, GA, USA
member@surfaces.org
www.surfaces.org
ph: +1 763-512-9103

WCOI6: World Congress of Oral Implantology 6
March 5-8, 2004
Honolulu, Hawaii, USA
member@wcoi6.com
www.wcoi6.com
ph: +1 763-765-2300

Australian Society for Biomaterials 7th World Biomaterials Congress
May 16-21, 2004
Sydney Convention and Exhibition Centre
Sydney, Australia
biomaterials@tourhosts.com.au
www.tourhosts.com.au/biomaterials
ph: +612-9262-2277

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