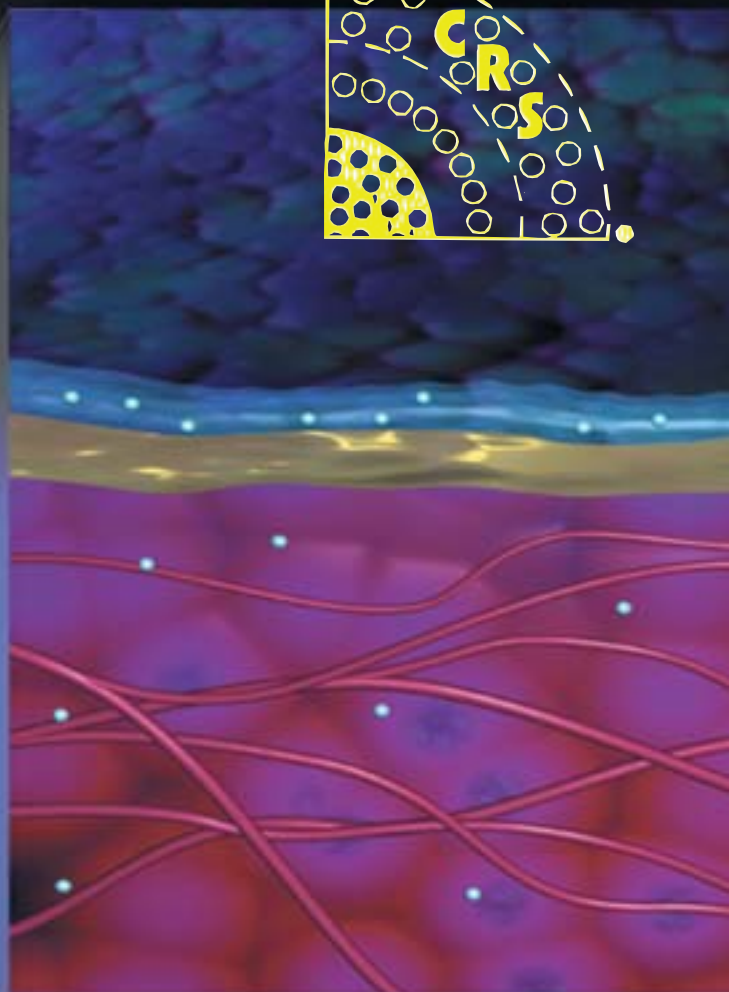
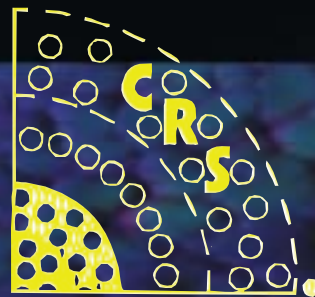


NEWSLETTER



Langer's Contributions are a Cornerstone of the Controlled Drug Delivery Industry

Transdermal Delivery of Drugs



Spotlight: Ratner Parlaying Enthusiasm, Creativity, and Science into a Heart



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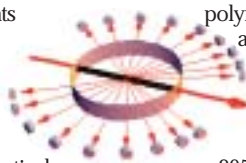
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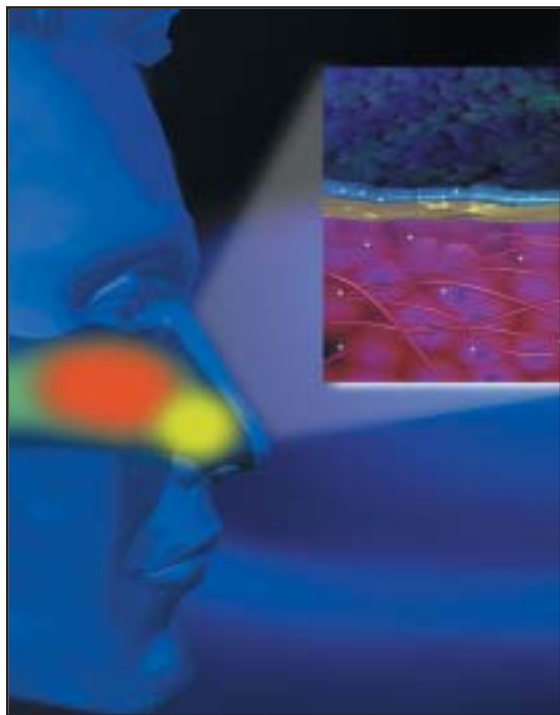
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Computer graphic depiction of human nasal passage with exploded view of potential nasal passage mucosal tissue receiving dispersed drug molecules. Photo courtesy of West Pharmaceutical Services, Inc., Drug Delivery Systems division. Reprinted with permission.

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Ahuja Receives Career Award

Dr. Alka Ahuja, Reader in Department of Pharmaceutics, Jamia Hamdard has been awarded The Career Award for Young Teachers by the All India Council for Technical Education (AICTE). Adjudged by a distinguished panel, this is a singular honour as she is the only teacher in the Pharmacy discipline to have received the award this year.

Under this award the council shall pay to the awardee her full salary and allowances for a period of three years. In addition, a research grant up to Rs. 3,00,000.00 (Rupees three lakhs only) will be given for securing technical services and for

strengthening the research facilities. She will be working on the project titled "Development of targeted low dose retentive system for oro-dental infections".

Dr. Ahuja has presented her research work in more than thirty conferences in India and abroad. She has published more than thirty five research articles in various national and international journals.

Dr. Ahuja has also authored a textbook of "Biopharmaceutics and Pharmacokinetics" and contributed an article on "Mucoadhesive drug delivery" in a book on Controlled and Novel Drug Delivery.



She has completed four major research projects funded by the University Grants Commission and AICTE. She has guided about 16 postgraduate students, and has four students working for their Ph.D program under her supervision.

A Gold medalist from the Panjab University and a recipient of the GP Nair Award instituted by the Indian Drug Manufacturers Association, Dr Ahuja has chosen Novel Drug Delivery Systems as her field of research.

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TRANSDERMAL DELIVERY OF DRUGS

Promise/Innovation/Challenge

By Agis Kydonieus

The "love affair" – Success

With the advent in the early eighties of the scopolamine and nitroglycerin transdermal patches, an innovative and exciting approach to drug delivery was introduced. The simplicity of the process and its advantages elevated transdermal drug delivery (TDD) into a "rock status" and produced a love affair with the pharmaceutical industry which continues to this day. For example, in the year 2000, 38 Japanese, 33 US, 12 German, 6 UK and 5 French companies filed for at least one transdermal patent. In all, companies from 15 different countries filed for TDD patents in the year 2000. As can be seen from Table 1, the patent output in the area continues to increase and it is safe to say that in the last decade over 2000 patents and patent applications were published pertaining to transdermal drug delivery.

| Table 1 | | | | | | | | |
|---|------|------|------|------|------|------|------|------|
| Transdermal Drug Delivery Patents & Patent Applications | | | | | | | | |
| | 1993 | 1994 | 1995 | 1996 | 1997 | 1998 | 1999 | 2000 |
| Methods | 60 | 81 | 146 | 143 | 139 | 131 | 132 | 196 |
| Chemical Enhancers | 63 | 60 | 57 | 93 | 61 | 51 | 48 | 42 |
| Physical enhancers | 29 | 29 | 32 | 46 | 35 | 20 | 40 | 51 |
| Anti-irritants/ Countersensitizers | 6 | 11 | 6 | 9 | 8 | 6 | 8 | 7 |
| Total | 158 | 181 | 241 | 291 | 243 | 208* | 228* | 296 |

*US and PTO/WO patents only

Attention to transdermal delivery is not misguided. TDD can impart impressive advantages to the delivery of therapeutic agents which include the reduction of side effects due to the optimization of the blood concentration-time profile, greater patient compliance due to the elimination of multiple dosing schedules, and reproducible and prolonged constant delivery rates. In addition, TDD can increase the therapeutic value of many drugs by obviating specific problems associated with the drug such as gastrointestinal irritation, low absorption, decomposition due to hepatic "first pass" effect, formation of metabolites causing side effects, and short half-lives necessitating frequent dosing.

TDD patches that have been commercially marketed in the USA and which solve some of the problems mentioned above include clonidine, estradiol, fentanyl, nicotine, nitroglycerin, scopolamine, and testosterone. Nitroglycerin used as a vasodilator has a 90% hepatic "first pass" effect, so it could not be used orally to prevent angina pectoris attacks. Its main use was as a sublingual tablet to abort an attack after it occurred. With the advent of transdermal medication, nitroglycerin is now used for the prevention of angina pectoris attacks. The transdermal delivery of the antihypertensive clonidine provides for a reduced side effect profile by lowering the daily dose required and eliminating peaking concentrations. Dry mouth and drowsiness, the two

most important side effects of clonidine, are substantially reduced by transdermal therapy. Reduction of side effects can also be accomplished for drugs that are substantially metabolized during the first pass through the liver such as estradiol. The elevation of the hepatic proteins that results from the oral administration of estradiol has been postulated to cause certain serious side effects of exogenous estrogens, including hypertension, hyperlipidemia, and hypercoagulability. Since the skin does not metabolize estradiol significantly, only 5% of the amount used in oral dosing is required for TDD, thus minimizing the side effects caused by the metabolite estrone.

The abrogation of these side effects together with the improved patient compliance afforded by TDD (e.g. clonidine and estradiol TDD systems are administered once per week) has made these products impressive commercial successes. Figure 1 shows the sales in the U.S. for some of the transdermal patches mentioned above compared to the total sales of all dosage forms. The performance of the transdermal patch products is impressive. The nitroglycerin patch reached \$250 million per year, 5 years after its introduction in 1982 and the fentanyl patch is rejuvenating a dying market of the oral fentanyl product. The performance of the clonidine and estradiol patches are equally as impressive.

*Parts of this article were excerpted (by permission from CRC Press) from the book "Biochemical Modulation of Skin Reactions: Transdermals, Topicals, Cosmetics", Agis Kydonieus and John Wille, eds., CRC Press, Boca Raton, FL., January 2000.

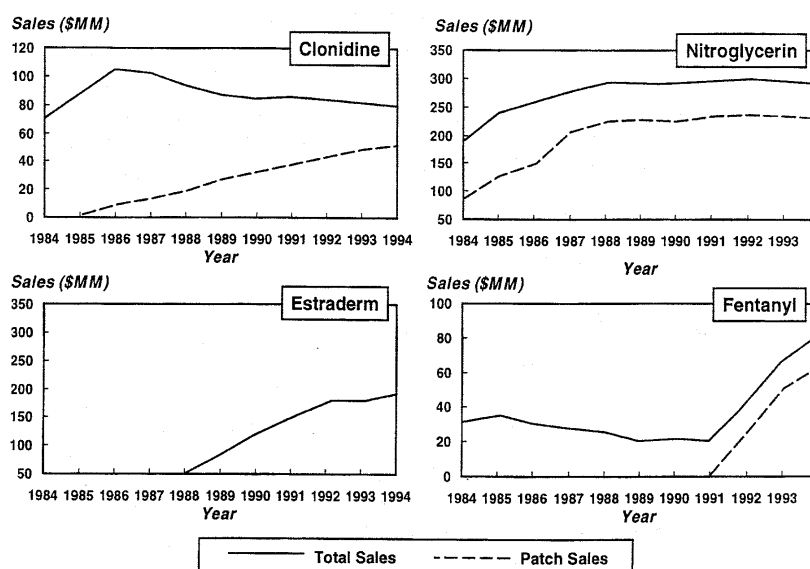


Figure 1 Sales of selected transdermal therapeutic systems.

(continued on page 4)

The “problem solving stage” – Drug Permeation

Soon after the introduction of the nitroglycerin patches, it was realized that the skin and especially the outermost layer, the stratum corneum, is an excellent barrier to almost all chemicals including drugs. The anatomy and biochemistry of skin clearly indicate that the lipid bilayers are perfectly stacked so as to exclude foreign substances (1,2). Mathematical modeling studies by Kasting and Cooper (3), Albery and Hadgraft (4), Berner and Cooper (5), Guy and Hadgraft (6) produced the same undesirable conclusion. Figure 2 shows the permeability of drugs through skin and graphically illustrates the difficulty that drugs have in permeating the stratum corneum.

Predictive Model for Skin Permeability

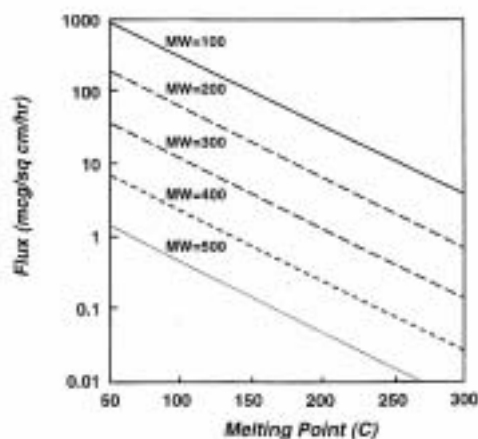


Figure 2 Berner-Cooper predictive model of skin permeability (logP (octanol/water) of 5).

Enter chemical enhancers! A chemical enhancer can be defined as a compound that alters the skin barrier function so that a desired drug can permeate the membrane at a faster rate. The chemical enhancer by its presence in the stratum corneum can also increase the permeation of a drug by increasing its concentration in the skin. Alcohols, amines and amides, amino acetates, sulfoxides, fatty acids, surfactants, urea and unsaturated cyclic ureas, terpenes, and many other chemicals have been patented and tested as chemical enhancers. Dozens of chemical enhancers are patented each year (see Table 1) and several books have been written summarizing the work and proposing mechanisms of enhancement (7,8,9). However, most of these agents cause skin reactions and hence their use is limited. The mechanism of action and the skin reactions caused by some penetration enhancers have been summarized (10). As a rule of thumb, a permeation enhancement of over two-fold will provide unacceptable irritation.

Enter electrophysical enhancing methods! There are several non-chemical methods that have been used to enhance drug permeation through skin. These include iontophoresis, electroporation, and phonophoresis (11,12,13).

Iontophoresis is a process that involves the transport of charged molecules, including proteins and peptides, into the skin by the passage of a direct electric current through an electrolyte solution containing the charged molecules to be delivered, using an appropriate

electrode polarity (13). Electroporation is another process presented recently to enhance skin permeation (14). Electroporation involves the application of a brief electric field pulse to create aqueous pathways in the lipid bilayers and thus enhance permeation. In contrast to iontophoresis where low current and long term application of electrical current are required, in electroporation the electric field pulses generate transmembrane potentials of 1 V but last only for 10 μ s to 10 ms. Phonophoresis, the application of ultrasound to increase the permeation of drugs through skin has also been experimentally investigated. The mechanism for permeation enhancement appears to be due to ultrasonic perturbation and decrease in the activation energy of the barrier membrane (15). Unfortunately all three methods suffer from irritation problems especially at energy levels that allow substantial penetration improvement (16,17,18,19).

Many other approaches have been patented including the use of microprotrusions to puncture the stratum corneum (US6083196, US6050988, US5964729, US5879326, US5843114), liposomes that are small enough to penetrate through the bilayers (US6165500, US5064655), and pulsed laser light to ablate the stratum corneum (US4775361). Methods for transdermal injection (needle-free) of drugs through the skin and into the subcutaneous tissue have also been patented. All of these depend on the generation of forces (electromagnetic repulsion, chemical reaction, laser initiated absorber explosion) to accelerate the payload to a velocity adequate to puncture the skin (WO9904838, RU2076746).

In the recent update of the patent literature for the year 2000 as many patents pertained to the delivery of proteins and peptides as they were to small molecules. The delivery of peptides through the skin will involve even more difficult skin reaction problems than the delivery of small molecules because the skin is a potent immunologic organ. Hence twenty years after the introduction of the first transdermal patch there are only seven drug entities that have been marketed in transdermal dosage form in the USA (scopolamine, nitroglycerin, estradiol, clonidine, nicotine, testosterone, and fentanyl).

The “reality check” – Sensitization

Most drug molecules, at least those containing amine groups are expected to be sensitizers to humans. For example, all of the antihistamines, antiasthmatics, CNS and beta blockers tested have been shown to be sensitizers. Peptides are expected to be even more potent sensitizers. The sensitization process is not totally understood and recently a hypothetical scheme (Figure 3) was presented which appears to explain why some biochemical modulators of the sensitization process appear to be effective (20).

In this figure, sensitization is depicted to the left, and the challenge reaction (generally applied 10 to 14 days after sensitization of human skin) to the right. Antigen (depicted as cross-hatched triangles) contacts with the epidermal surface during sensitization (Step 1) and is taken up by Langerhans cells (LC; Step 2). These normally freely motile cells traffic via dermal lymphatics (Step 3) and migrate to draining lymph nodes (Step 4). The perivascular dermal connective tissue at this juncture (to the upper left of draining node) may contain low numbers of naive CD4 T cells (CD4n) as well as mononuclear phagocytes and resting, nondegranulating mast cells (latter not shown). In the lymph node, the migrant antigen-containing LC

present processed peptide signals to the CD4n T cells (4), imparting antigen-specific memory (CD4_s; Step 5).

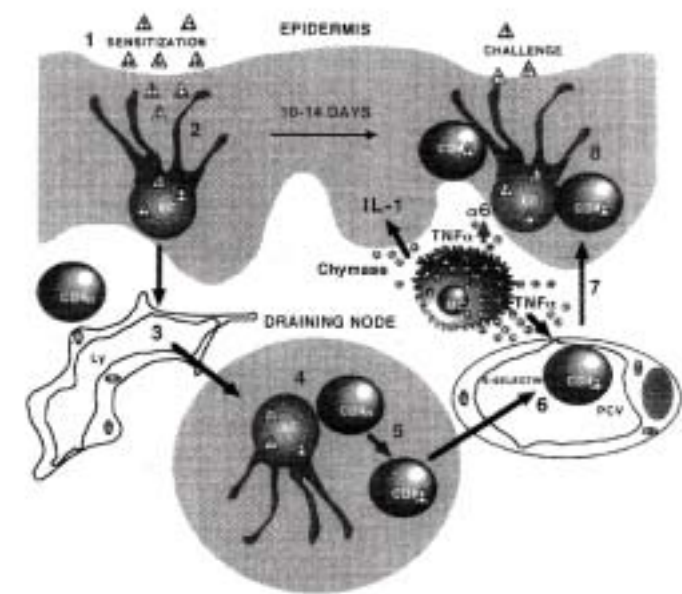


Figure 3: Hypothesis of processes involved in the induction and elicitation of the skin immune response

Upon entering the peripheral circulation, these newly formed CD4_s T cells constitute a small component of the total white blood cell population. During intranodal sensitization, experimental evidence in rodents suggests that another important event also may occur. This involves production of IgE-like, antigen specific molecules by a second, as yet undefined population of nodal lymphocytes which also receive peptide signals from the antigen-presenting LC. These antibodies circulate and eventually become bound to the membranes of dermal mast cells (MC) situated in the perivascular space of postcapillary venules (PCV).

Upon epicutaneous challenge by the same antigen, several events are now primed to occur. Mast cells may interact with antigen by virtue of cross-linking of surface molecules in an IgE-like fashion. This cross-linking results in mast cell degranulation in the perivascular space of superficial dermal PCVs. TNF-α acutely released from the liberated mast cell granules triggers endothelial activation, with induction of a cascade of leukocyte-endothelial adhesion molecules. One of these, E-selectin, promotes binding of CD4_s to the endothelial surface (Step 6), with subsequent diapedesis into the dermal matrix and ultimately, via adhesive and chemotactic gradients, into the epidermal layer (Step 7). Such endothelial activation and CD4_s recruitment may also be facilitated by cleavage of epidermal interleukin-1 (IL-1) into its active form by the mast cell granule serine proteinase, chymase. Small numbers of pioneer CD4_s T cells now located within the superficial dermis and epidermis interact with processed antigenic peptides (Step 8) presented by LC fixed within the epidermis as an apparent consequence of altered motility. This may result in part from TNF-α induced upregulation of LC cell surface integrins, such as α6, which promotes binding to basement membrane zone and soluble laminin. CD4_s T cells so stimulated produce and release a repertoire of TH1 cytokines which then drive the

inflammatory response, recruiting secondarily responding mononuclear cells. These events correlate clinically and histopathologically with the fully evolved delayed hypersensitivity reaction.

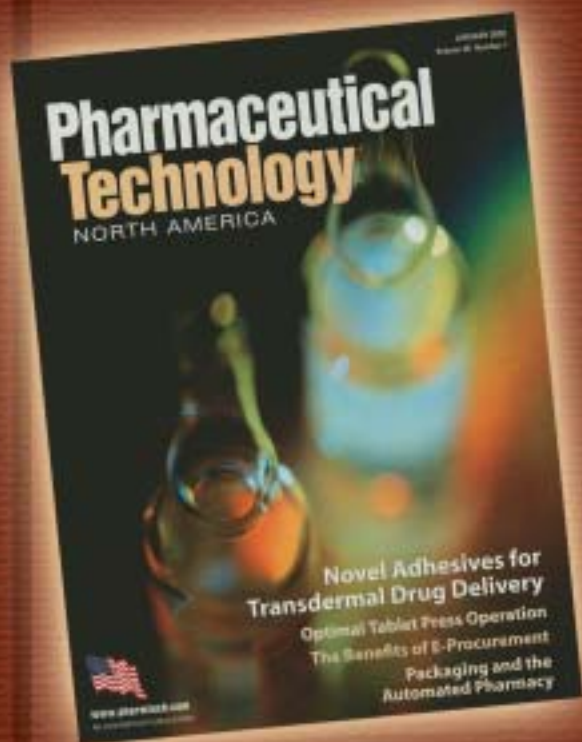
Dozens of chemicals have been presented in the patent literature as biochemical modulators of skin reactions and a general overview has been published (21). They are based on plant extracts, vitamins and antioxidants. Recently, biochemical modulators have been patented which are based on understanding the immunologic science of sensitization and interrupt some important steps of the sensitization process shown in Figure 3.

Steroids are well known for their anti-inflammatory and immunosuppressive properties, and formulations containing 0.5 and 1.0% hydrocortisone are standard remedies for treating skin irritation and inflammatory responses caused by allergens such as poison oak. However their ability to prevent irritation and the induction of sensitization had not been studied until recently (US5077054, US5000596, US5049387, US5118509, US5028431). Steroids, as well as steroid esters, were found to be suitable and they include hydrocortisone, hydrocortisone ester, betamethasone, betamethasone valerate, fluocinonide, and triamcinolone. In a human test on 80 volunteers (40 subjects each), dexchlorpheniramine maleate administered transdermally sensitized 16 subjects. When it was codelivered with 2% hydrocortisone, only two subjects were sensitized. In a separate experiment, it was shown that hydrocortisone did not affect the elicitation phase of sensitization – i.e., once sensitized, the presence of hydrocortisone did not prevent a skin reaction in allergic individuals (22).

U.S. Patents 4885154 and 5304379 pertain to methods and devices for the reduction of sensitization and irritation caused by transdermally delivered drugs, wherein one or more metabolic modulators is coadministered with the sensitizing or irritating drug. Metabolic modulators affect the enzymes in the skin and thus modify the metabolism of the drug, so as to inhibit the formation of reactive or irritating metabolites. Metabolic modulators that can modify monoamine oxidase activity include harmine, benzyl alcohol, tranlylcypromine, phenylhydrazine, 2-phenyl-1-ethanol, and cinnamyl alcohol.

| Table 2 Sensitization response to Propranolol and Modulation by Ammonium Chloride | | | | |
|---|-------------------------------------|-----|-----|-----|
| Time after Removal (Days) | Ammonium Chloride Concentration (%) | | | |
| | 0 | 2 | 4 | 8 |
| 0 | 0.7 ^a | 0.7 | 0.7 | 0.7 |
| 4 | 6.3 | 4.0 | 1.0 | 4.8 |
| 7 | 7.2 | 4.7 | 1.2 | 4.1 |
| 11 | 2.8 | 1.5 | 0.7 | 1.5 |

^aEvaluated using Minolta chromameter.
Adapted from US patent # 5120545



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Drug Delivery's New Target

By Guy Furness

My experience prior to becoming editor of PJB Publications' new newsletter, Scrip's Target, has been providing R&D information on the pharmaceutical industry in general. Since Target's launch in January however, I have immersed myself in drug delivery to the extent that I am now probably encapsulated to some degree, if not completely enteric-coated!

Two aspects of the world of drug delivery have struck me. First is the open-minded, scientific approach that the drug delivery community has adopted. The new technologies coming out of drug delivery research are frequently refreshingly simple and pragmatic. For example, achieving dual release by placing one capsule within another capsule, as with the system under development by Scottish company MW Encap. Another example is Alza's transdermal system that uses microprojections on a patch to painlessly, physically penetrate the keratinous layer of the skin for enhanced delivery. In oral delivery, even just changing the shape of tablets has been shown to alter gastric retention times.

In scientific research, the necessity to specialize and then specialize again in order to remain at the innovative frontier can lead to such a focus that the context of the problem, the reason that the research began, is lost.

In an interview in 1997, Alejandro Zaffaroni, who founded Alza, said he had been thinking for some time that medical science had been going down the wrong track. He believes that all the discoveries made since the invention of vaccines were small ones.

If he is correct, perhaps the reason for this wrong turn was that everyone had been looking so closely at the map they could only see where they were, albeit in detail, and not where they were headed. Drug delivery might be a step back from the map, in order to see more of the picture - the destination, or at least the next checkpoint.

The second aspect that struck me, as I became involved in reporting events in drug delivery, was the positive mood of progress and growth. It is not just a mood, the drug delivery sector is the fastest-growing sector of the pharmaceutical industry.

Global revenues from products incorporating drug delivery technologies are estimated by US analysts Friedman Billings Ramsey to have increased in 2001 to just over US\$12 billion.

During 2001, the share prices of drug delivery companies outperformed most of the general and healthcare indices, losing little or no value, when others lost in the teens or twenties per-cent.

In an environment that is becoming increasingly competitive, large pharmaceutical companies are now counting drug delivery as a central part of their R&D process. Drug delivery is where they have turned to give themselves the edge they now require to survive. Last year, Johnson & Johnson bought Alza, one of the original drug delivery companies, in a deal worth over \$10 billion.

Drug delivery has arrived. It has found its place as an independent sector within the healthcare industry and, some would argue, as an independent scientific discipline. The significance of drug delivery, to the researcher, businessman, shareholder and patient, is growing quickly and globally.

Because drug delivery has arrived in pharmaceutical development, Target has arrived in drug delivery. Its launch was a natural step for the publishers of Scrip World Pharmaceutical News.

While designing the newsletter, we took account of those things that are most important to the sector - from the laboratory bench, via the patent office and the clinic, through approval and to the market. The newsletter is technology focused, and split into sections. News about agreements is in its own section, for example, because deal-making is a key activity.

The publication aims to reflect some of the drug delivery sector's refreshing pragmatism back at the industry, with enough detail to inform while stepping back to provide a view of the whole picture.

Target's role, simply stated, is to enable its subscribers to keep abreast of the many changes taking place and new developments emerging from the drug delivery industry.

2002 Program Final

A record number of scientific abstracts were submitted to the 2002 Annual Meeting for review and consideration. Seven hundred seventy abstracts were accepted for podium or poster presentation. Martyn Davies, Scientific Secretary, Seung Jin Lee, Bioactive Materials Program Co-Chair, and James Paik, Consumer and Diversified Products Track Program Co-Chair, met in Minneapolis recently to finalize the 2002 scientific program. Together with Jared Switch and Ronda Thompson from ARDEL's Educational Services Department, sessions were formulated and placed within the three and one-half day session schedule. Visit www.controlledrelease.org/meetings/seoul/ to access the final program and create your personalized Egenda™. Your Egenda™, a schedule of the sessions you intend to visit each day of the meeting, can be printed or downloaded to your PDA. Plan NOW to attend the Annual Meeting in Seoul, Korea, July 20-25, 2002!



From left: Martyn Davies, Scientific Secretary, University of Nottingham, UK; James Paik, Consumer and Diversified Products Track Program Co-Chair, JSP Development, USA; Seung Jin Lee, Bioactive Materials Program Co-Chair, College of Pharmacy, Ewha Womans University, Korea; Ronda Thompson and Jared Switch, Educational Services Department, the ARDEL group, USA.

In the last quarter of 2001, 97 patents were found via the Derwent World Patent Index on encapsulation technologies for flavours and food additives and their application in food products. The geographical distribution of the patents was 32 from Europe (EP patents and specific patents from Germany, France, etc.), 17 from Japan, 10 US patents, 33 WO patents and 5 patents from the rest of the world.

SPRAY DRYING

Spray drying to convert liquids into powders was again the most patented technology. Approximately 15 patents were filed. Among them were the conversion of coffee extract into coffee powder, the spray drying of green essences after extraction from leaves, spray drying for the preparation of persimmon vinegar powder, spray drying of a slurry of denaturated protein and starch and using the resulting product for emulsification purposes, and spray drying of fresh milk to obtain a product with improved powder quality (Nestle, EP 1127494). Other patents in the area of spray drying were filed by **Daesang Foods** on water-soluble fermented soybean paste peptide seasonings (KR 2001019920) and by **Ogawa Koryo** (JP 2001224327) on a powdery acidic agent with a volume density of 0.40-0.95 g/cm³ prepared continuously by using a fluidizing spray drying pulvering machine. **Friedman** (WO 200162226) filed a patent on bitter taste masking products for nutraceuticals, by spray drying of a core compound (i.e. hydrophobic bioactive ingestibles) encapsulated in a homogeneous solid matrix. A combination of cyclodextrin

and spray drying to produce instant green tea containing powdered ginseng was patented by **Kang & Nou** (KR 2001035409).

COATING PROCESSES

Haarmann & Reimer (US 20010021404) filed a patent on the encapsulation of core materials (e.g. flavours or fragrances) by coating the spherical core with hydrophobic layer(s) and a modified cellulose layer in a fluidized bed. The modified cellulose layer has reversible gel formation when the temperature is increased. The idea is that the invention protects the encapsulated substances during heating at temperatures to greater than the flock point of the modified cellulose and to release it in a targeted manner during cooling. Application of the products of the invention are sauce powder, ready-to-use sauces, waffles or bakery goods. The preparation of capsules for use in foods, cosmetics, detergents and pharmaceuticals comprising the coating of particles of polyhydroxy compounds like starch with at least one mineral coating, in which each coating consists of a single mineral compound such as calcium phosphate, is patented by **Rhodia Foods** (WO 200141914). For the preparation of the capsules, a solid-phase process is used. Claimed application areas are energy drinks, diet drinks and food substitutes.

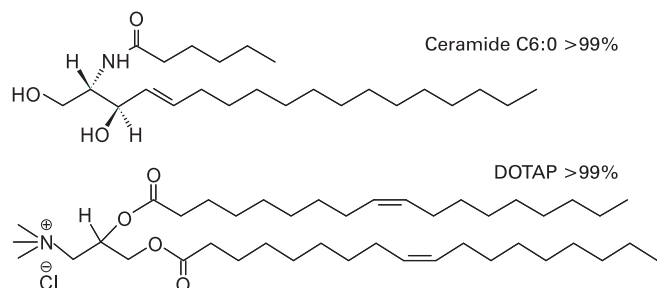
Fumaric acid particles of 70-140 micron with a coating having a melting point within normal baking temperatures are patented by **Balchem** (US 6312741) for imparting an acid environment to bread dough. According to the patent, the coated fumaric acid preserves the antimicrobial ingredients after baking without deleteriously affecting the bread dough before baking resulting in increased shelf life. Most probably, a high melting, hardened fat is used for the coating. In **Unilever** patent US 6312752, edible fat based, flavoured fat systems of 0.05-2.5 mm are made, consisting of a flavouring system, a bakery compatible fat, sugar and a filler material. The edible fat has certain, prescribed properties with regard to triglyceride composition. The coating process to form the edible fat based system is simple. At 40-70 °C, the bakery compatible fat is mixed with the dry ingredients of the composition followed by cooling the mixture in a direct heat exchanger to less than 40 °C, and firming the mixture obtained by cooling on a cooling belt to less than 25 °C. The fat based systems are used in bakery or snack products.

SIMPLE AND COMPLEX COACERVATION

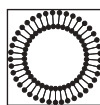
In the last quarter of 2001, a number of patents on coacervation appeared. Among them were EP 1123695 from **Unilever** on the manufacture of capsules containing water-insoluble keratin by complex coacervation. The amount of keratin in the encapsulation process can be varied to improve the breakage characteristics of the capsules. Although meant for personal care products like toothpaste, the process can also be used to encapsulate flavours. In JP 2001205075, **Shionogi** describes the manufacture of microcapsules via mixing of aqueous solutions of cellulose and copolymer followed by phase separation. **Henkel** filed three patents in the area of chitosan capsules, viz. DE 19962347, DE 19962350 and WO 200162376. In principle, the formation of chitosan microcapsules can be regarded as a simple coacervation process. The Henkel capsules are intended for cosmetic and dermatological compositions but the process can also be used for flavour encapsulation.

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MISCELLANEOUS

Freeze drying is claimed by Kurodera (JP 2001161348) as a method to obtain dry plant products from water-soluble saccharides and unicellular plants such as *Chlorella* for use as colouring agent, beverage and as nutritional food additive.

Plating of temperature and/or oxygen sensitive materials like lemon oil onto a solid carrier in an atmosphere inert to the sensitive material is patented by Balchem (US 6251478). After the plating step, the plated material is further encapsulated. The method can also be used for encapsulation of *Bifidobacterium* and enzymes like amylases and lipases. A patent for preparing an effervescent caramel product from a mixture of caramel, a water-soluble organic acid and a (bi)carbonate base, comprising feeding the ingredients to a bowl cutter which rotates the ingredients to an axis while simultaneously **granulating** the ingredients, was filed by Nestle (WO 200165906). The product gives an aerated texture and produces effervescence in contact with saliva in the mouth. Nestle also filed a patent on flavour encapsulation in high-boiled **sugar glass** for confectionery, beverages and functional products (WO 200174178). The encapsulation process is quite simple. It involves boiling of ingredients to give a syrup, heating and cooling of the syrup, adding the flavour, further cooling and particulating the resulting flavour containing product. A patent on an **apparatus** to produce sealed and filled capsules was filed by PVAXX Technologies (WO 200164421). It comprises a means of injecting and blow molding a source of polyvinyl alcohol composition into a mold cavity to form a capsule, a means of filling each capsule with a substance and a means of sealing each capsule. The PVA capsules, intended for people intolerant of gelatin, contain vitamins or nutrients.

Editors Note: Jack Burger is Senior Scientist at Quest International.

Langer's Contributions are a Cornerstone of the Controlled Drug Delivery Industry

Robert Langer of the Massachusetts Institute of Technology received the 2002 Charles Stark Draper Prize - a \$500,000 annual award and gold medallion, often referred to as "Engineering's Nobel Prize", from the National Academy of Engineering (NAE). Langer received the award for inventing medical drug delivery technologies that prolong lives and ease suffering of millions every year. His contributions are a cornerstone of the controlled drug delivery industry, a \$20-billion enterprise in the U.S. alone.

"Simply put, it gives me great satisfaction to see the things I do make other people happier and healthier," said Langer, the Germeshausen Professor of Chemical and Biomedical Engineering.

In 1974 Langer, new MIT chemical engineering Ph.D. in hand, had lucrative industrial job offers pouring in. He didn't take any of them. Instead he went to work in the lab of famous cancer researcher Dr. Judah Folkman.

"This job had a profound impact on what I ended up doing with my life," says Langer. "One of the great things about Dr. Folkman was that he believed almost anything was possible, and seeing his example was terrific for me."

"Simply put, it gives me great satisfaction to see the things I do make other people happier and healthier."

The general consensus at that time was that it was impossible to get large molecules, which were promising against cancer and other diseases, through plastic delivery systems in a controlled manner. Langer nevertheless discovered engineering principles that, for the first time, allowed a desired release of such medically important molecules from plastics. Soon thereafter, he excitedly detailed his findings before a distinguished audience of scientists. The response was both skeptical and critical. He was disappointed, but undeterred.

After that, Langer says he had nine straight grant requests rejected, one even questioning how an engineer could do this work when "he knows nothing about biology and even less about oncology." Langer turned



Robert Langer, recipient of the 2002 Charles Stark Draper Prize.

disappointment into resolve and, as the pharmaceutical industry took notice, his persistence began improving people's health.

Langer's creative engineering of polymer plastics now allows delivery of medicine in unique ways to difficult locations within the human body. One of his biodegradable polymer inventions broke a twenty-year drought in FDA-approved brain cancer treatments. It was the first such chemotherapy that could be delivered directly to the tumor site.

That success is just one of many for Langer. He has written about 700 papers, and 400 patents that are

licensed or sub-licensed to more than 80 companies - some launched on his ideas. Langer has a reputation for helping his students take their theses to the marketplace and says he's very proud of the students he has shepherded into professorships (more than 80 at universities around the world) and his undoubted impact on advancing chemical- and bio-engineering education.

"Bob Langer was chosen for the Draper Prize, both for the substance of his contributions and because he is a role model," says NAE President Wm. A. Wulf. "Notable is the large number of companies his students have created, and consequently the effective transfer of technology he has created into the private sector where it becomes available to all of us." ●

This is the last in a series of three articles on travel to the CRS Annual Meeting July 20-25, 2002, Seoul, Korea. As you will recall, the title phrase of these articles stems from a tongue-in-cheek comment made by Kinam Park, President of CRS. In the previous articles, we discussed the questions that you, the members, have asked about travel to Korea. Thank you for your kind comments about these articles. I am pleased that so many individuals will be coming to the Annual Meeting and that the information here, helped you to make your decision. (Readers may access the previous articles on-line at <http://www.controlledrelease.org/newsletter/index>.) Visit www.controlledrelease.org/meetings/seoul/korea.htm for supplemental tourist "must sees."

If for some reason you are still "on the fence" about attending the Annual Meeting, or you missed the articles in their original printing, allow me to summarize. Seoul has been the center of politics, economy, culture and transportation of Korea for six centuries. Seoul has preserved this heritage, and at the same time, has risen as a landmark of modernity, becoming a truly world-class city. The graciousness of the Korean people is founded in their culture and woven in their history and religious diversity. They speak English, and signs, menus, etc. are printed in English. Transportation to and within Seoul is simple to use and inexpensive. The Seoul airport is new and world-class. Hotel options are not expensive and are world-class (we really do intend to use the word world-class this much). Dining in Seoul can be as adventurous or as "back home" as you like and it can be as inexpensive as you desire. Since by now I am certain you are planning to attend the Annual Meeting in Seoul, I'll use the next few column inches sharing some of the wonderful things you can elect to experience during your visit.

History and architectural enthusiasts will be delighted in this city that has incorporated rich legacies with 21st century modernism. Seoul is home to thousands of years of history (dating back to 18 B.C.) that can be seen today in the form of well-preserved royal palaces, historical relics and cultural treasures. Visit the Dongdaemun and Namdaemun Gates, relics from the Joseon Dynasty. Seoul is home to five palaces: Gyeongbokgung, Changdeokgung, Changgyeonggung, Deoksugung, and Gyeonghuigung. The most imposing of these palaces is Gyeongbokgung. This palace is the oldest Joseon Dynasty palace, and is located in downtown Seoul at the north end of Sejongno

Street. The palace grounds include the National Museum of Korea and the National Folk Museum, where visitors can browse the unique cultural and historical traits of Korea and the life-style of olden days. Royal tombs include Hongneung and Seonjeongneung. Visitors will also want to visit

Seonggyungwan, the Confucian educational institution.



Gyeongbokgung Palace

Shopping enthusiasts will be delighted with Seoul's offerings. For art lovers, I recommend spending a day on Semcheongdonggil Street. A shuttle bus is offered on a circuit of art museums and well-known galleries around the area. The cost of a bus pass is K1,000 and available from the bus driver. Call 02-720-1020 for shuttle bus information. In addition to the famous art galleries on Semcheongdonggil Street, you will also find

Beomnyeonsa Temple, Korean Traditional Folk Dress Museum, the French Cultural Center, cafes, restaurants, and craft shops here.

Directly beneath the COEX Center, home to the CRS Annual Meeting, is the COEX Mall. COEX Mall has 400 retail stores, and is connected to the COEX Inter-Continental Hotel and the Grand Inter-Continental Hotel. COEX Mall also features Game Champ, an arcade with over 100 of the latest game machines, Megabox Cineplex with 16 screening rooms, and the 1.4-ha COEX Aquarium, showing more than 30,000 fish of 500 species.

For the ultimate in shopping, Itaewon is a special tourism zone, honeycombed with about 2,000 shops as well as jazz bars, nightclubs, and ethnic restaurants. Itaewon features almost 1,000 shops selling leather goods, bags, clothes, shoes, and tourist souvenirs. Itaewon's sidewalks are fringed with approximately 400 roadside stalls that sell accessories, hats, T-shirts, and much more. Taking a break during your shopping trip will be no problem in Itaewon since it is densely packed with diverse ethnic restaurants such as Italian, Swiss, German, Mexican, Indian, Pakistan, Thai, and more.

(continued on next page)

(Memoirs, continued from previous page)

The Han River runs through Seoul east to west. A river cruise should be on every CRS attendee's tour agenda. This is a great way to "see" Seoul. The river is crossed by 22 bridges and dotted with Hangang Riverside Parks. At last check, the cruise fare was approximately K7,000. Most cruises last an hour. For more information, contact the Cruise Service information office at 02-785-0392/3.

Namsan Park climbs the slope of Mt. Namsan. The park features Seoul Tower, a city landmark that presents an unobstructed panorama. Below the Tower are the octagonal pavilion Palgakjeong, a small zoo, a botanical garden, Namsan Public Library, and Patriot Ahn Choong Kun Memorial Hall. Meandering strolling paths and jogging courses through lush trees make this a perfect spot to visit. For an easy ascent of Mt. Namsan, take the cable car from the station at its foot. Some will prefer the steps leading past Namsan Botanical Garden to Palgakjeong Pavilion all the way up to Seoul Tower. The tower accommodates the Global Village Folk Museum, a 3-D theater, and Pulhyanggi Restaurant featuring mountain vegetable dishes plus performance of traditional arts. The tower also presents a fine nightscape. The northern foot of Mt. Namsan is dotted with cultural facilities. Among them is The National Theater. The National Theater's opera and dance companies provide colorful repertoire year-round. For information on programs during your visit, contact the theater by phone at 02-2264-8448 or on-line at www.ntok.go.kr. Visitors interested in learning the Korean traditional tea ceremony, cooking, and etiquette, will want to stop at Yejiwon. Learn more about Yejiwon by phone 02-2253-2211 or e-mail yejiwon@yejiwon.or.kr.

Join us in Seoul to celebrate the fabric of the past and promise of the future that is Korea.



Seoul Tower

Ricker Joins CRS

Mark J Ricker recently joined CRS as the Associate Executive Director. Mark has served the association community for approximately twenty years in CEO or associate CEO positions. He brings to CRS an extensive background in leadership, government relations, membership, communications, finance, and administration. He will work directly with Rosealee Lee to lead CRS initiatives and bring vision to the future of controlled release and delivery. Members may contact Mark via e-mail at mricker@controlledrelease.org, or by telephone +1 (763) 765-2311.



Mark Ricker, Associate Executive Director and Alexander Florence, President-Elect, make plans for the coming year.

Mark replaces Paul Stone who has served in the same position for the past year. Paul has decreased his assignment load at the ARDEL group to spend more time with his family. We wish him well and look forward to working with Mark.

“When a company decides not to exhibit at a show, it deprives buyers of a convenient way to assess its commitment and the level of service it provides to customers.”

**- Allen Konopacki
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spotlight: Ratner

Parlaying Enthusiasm, Creativity and Science into a Heart

By Rosealee M. Lee

Buddy Ratner was recently elected to the National Academy of Engineering (NAE). Election to this prestigious body is indeed a national honor and a large responsibility. The NAE is part of the National Academy of Sciences (NAS) that was created by the United States Congress in 1863. The purpose of the NAS is to advise the government in scientific and technical matters. The nation's leaders often turn to the institution for advice on the scientific issues central to policy decisions.

Many CRS members know Dr. Ratner as Professor of Bioengineering and Chemical Engineering at the University of Washington, USA. Others may recognize him as founding director of the National ESCA and Surface Analysis Center for Biomedical Problems (NESAC/BIO), or more recently as director of the University of Washington Engineered Biomaterials (UWEB), a National Science Foundation Engineering Research Center. UWEB is a consortium of 20 professors, 60 students and some 30 biomedical device companies that is revolutionizing the way biomaterials heal in medical implant applications. Dr. Ratner's work is internationally known and documented in the form of 13 patents, 175 refereed papers, 103 non-refereed papers, and 41 book chapters.

I recently had the opportunity to visit with Dr. Ratner about his election to NAE. Together, we took the time to discuss his career, his interests, and what drives him. When asked what drove him, Dr. Ratner replied that his criteria for each research project were that it must be fun, exciting and relevant. The opportunity to explore new territories and the ability to develop new ideas are central themes of his career. It therefore comes as no surprise that Dr. Ratner has been such a pioneer in our field.

Dr. Ratner cites the ability to reject his own hypotheses as integral to his research. The concept was nicely expressed by Konrad Lorenz, who loosely said, "Discard a hypothesis every morning before breakfast." Ratner states, "Hypothesis driven research is closely tied to the ability to reject your hypothesis. Your duty as a researcher is to

creative." With the students lucky enough to be taught creativity by Buddy Ratner, he shares the "tricks and tools" he has used, and his belief that people who are the most creative select careers in art, science, and literature. He also shares that there is no difference in the creative process that artists and scientists use to be creative. First, he

advises that students focus consciously on their creativity and consider it of value to free it. "It involves seeing the universe in a different way. Any artist will do this. Why not a scientist? You look at something that everybody else is looking at and see it in a whole new light; then attempt to communicate that." He teaches students to pick up a book – any book. "It doesn't matter what kind of book. Just go in the book and put your finger on a word. Then use that word to stimulate some

new ideas because you didn't

have that word in your head 10 seconds before. Now there's a new word in your head that can turn on and trigger something that is relevant to what you are trying to do. It's a pretty good trick, and it's easy. There are a lot of easy tricks that you can use regularly. New ideas come out."

Dr. Ratner believes it is important for scientists to have a broad view and an enjoyment of the breadth of scientific literature and ideas from different fields. "It is called being multidisciplinary. In my own

"Hypothesis driven research is closely tied to the ability to reject your hypothesis."



Using creativity, Buddy Ratner captures texture within his photography, just as he has used creativity in his science.

attempt to disprove your own idea. If you can't do it, then maybe the concept is good. By working diligently you find out what's right and what's not. Over the years I have had to discard key concepts that I have been working on. Interestingly, in leaving behind the old baggage, new horizons for intellectual travel open up."

His sense of creativity is an important element in everything he does. Dr. Ratner teaches creativity at the University of Washington, giving formal lectures on how to break out of molds and develop creative ideas. He explained his premise that everyone has creativity, and that, "one of the most deadly things you can do to your creativity is to say you are not creative, because as soon as that statement is made, you've put a block in your ability to be

career I started as a chemist but I finished my PhD working under a thesis advisor who was a chemical engineer. The combination of chemistry and engineering were the beginning. I quickly discovered that the tools of physics – the surface analysis tools such as ESCA and SIMS, were helpful. I had to hang around with physicists to learn how they worked, so that I could use their tools in a professional manner. So I picked up a lot of physics and physics approaches to things. By the early 1990's, I started to realize that modern biology was revolutionizing science. I immersed myself pretty thoroughly into a lot of the new ideas in biology and how we might use them. Being multidisciplinary enhances your creativity and ability to look at problems from new directions. That's where progress can be made. Plus, it's fun to try to integrate information coming from so many different directions!"

When asked how the election to the National Academy of Engineering will affect his work, Ratner replied, "It does seem like access to a national and international perspective will alter everything that I do. I will find myself dealing with some very large issues that potentially affect the entire community. In addition, I'll have the opportunity to advocate for controlled release, biomaterials, and bio-surfaces. Suddenly, what I do has greater impact and I think there is the possibility to make some advances, as well as raise the consciousness and recognition of our community."

Since childhood, Dr. Ratner has had a fascination with art and science. He was awarded the art medal in his public school and worked in creative photography

during his high school years. It was the Sputnik era and, "everybody was saying science was great." "There was not the least bit of cynicism about science and engineering at that point. The concept of the nerd had not surfaced yet, and science was considered a great career. The Soviets had put up Sputnik, the U.S. was in the race and it was almost patriotic to go into science. There were more opportunities in science than in

art, so I shifted in that direction." He still enjoys art and finds the art world very stimulating. "All of my creative energies are very nicely diverted into science which I find totally stimulating and creative. I can do my artistic creation in the scientific context."

When asked to identify one individual who had most influenced his career, Ratner replied that this influence had come from his father, Philip Ratner, who had consistently encouraged learning. Dr Ratner's father left high school early due to his father's illness and a need to support the family. Philip later finished high school, an accomplishment that Dr. Ratner was very proud of. Philip Ratner was an electrician who placed the value of education firmly in his son's value system. Following retirement, Philip worked at a department store helping to unload trucks. He stopped working at age 81. Philip Ratner passed away in January of this year at the age of 85. "Congestive heart failure is almost the normal end course in life in western civilization. It looked like he had some early symptoms of this, but congestive heart failure is something people live with and deal with for many years before they finally get to the end stage. He had just been diagnosed with it and went in to the hospital for an angiogram. He was told it was a relatively

safe test. The catheter induced a heart attack and a stroke. A triple bypass was done for the heart attack, the stroke was relatively minor

and he was recovering. What killed my father were device-centered infections – infections associated with catheters. Biomaterials killed my dad, and I will, sadly, always remember this cruel irony. It seems so trivial that one of the oldest organisms on this planet is still a threat and if one looks at the number of people that die from catheterization procedures, it is outrageous. This is something that biomaterials scientists



Dr. Ratner believes it is important for scientists to enjoy the breadth of scientific literature and ideas from different fields.

can and should address. I think that in the next few years of my career I am going to focus more of my energy on this simple problem that is hardly a simple problem. I think it is addressable with biomaterials engineering and I now have a personal reason why I will focus on this cause."

"While on the subject of my influences, there are a number of people I'd like to acknowledge. I started my Ph.D. thesis under Professor Dan Bradley at the Polytechnic Institute of Brooklyn. I learned about creativity in science from him. He passed away during the course of my thesis and I finished under Professor Irv Miller, at that time chair of Chemical Engineering. I got my engineering focus from working with Irv. I came to the University of Washington in 1972 to do a postdoc with Allan Hoffman – what better tutor could there be to continue my education in creativity and excitement applied to science and engineering? In 1972 I met another postdoc in the group, Tom Horbett. Tom demonstrates a superb recognition of quality in science and I've learned some of these ideas from him – he has been a friend and colleague for 30 years. Dr. Ron Thomas taught me ESCA and opened my eyes to surface science – I am

(continued on page 14)

grateful to him for his contributions to this facet of my career. There are so many others that have influenced me that by naming names, I'm sure I'd leave people out. However, two names do need to be mentioned. Professor James Anderson opened my eyes to the biological aspects of medicine and its interface with materials. A Ph.D. student who graduated from my group, Ann Schmierer, already a well-trained biologist when she arrived at the UW, opened my eyes to the revolution taking place in modern biology and was therefore a strong influence on the establishment of UWEB."

Dr. Ratner believes that he may now return to an earlier antibiotic project and perhaps take it forward into a marketable device. The project was a collaboration with Professor James Bryers from the University of Connecticut, Professor Tom Horbett and Connie Kwok who at the time was a Ph.D. student in Dr. Ratner's group. Kwok has since completed her Ph.D. and gone on to work with Guidant Corporation. The NSF Engineering Research Center on Biofilms at Montana State University contributed to the project. "For years there have been studies of imbedding polymers and plastics with antibiotics and watching them leach out, but there are new generations of exceedingly potent antibiotics and there are some concerns with them. Their effectiveness can be lost because the antibiotic leaches out quickly and any bacteria that survived can potentially reproduce into a more antibiotic-resistant strain. Also, the effective life of the device is reduced by unmodulated leaching, and these antibiotics are too expensive to allow them to pour out. So, our concept was to build on things we have done in the past. We have much experience with plasma deposited surface coatings and they have useful characteristics. We asked, could we load an antibiotic into a catheter and then put on to it what we would call in engineering terms, a rate limiting barrier, a very thin membrane that would slow down the release. What release rate did we want? Connie Kwok did some calculations in her thesis. The calculations showed that if you could get a certain release rate of this antibiotic right at the surface, you could develop a zone with 100% kill rate. By applying this plasma film coating the release time is greatly extended because the reservoir empties much more slowly. The release is "zero order" and the

device becomes effective locally against the bacteria without treating the whole body."

"I don't think this would be expensive to implement. When my dad developed these infections they were giving him antibiotics that cost \$200 per shot a few times a day and it still didn't save his life. Even if the catheter costs twice as much, I think health-maintenance organizations would see the economic value since this could eliminate antibiotic regimes and additional hospitalization. Biomaterial scientists can develop systems with reasonable economics that show great benefit to the health care system and save lives."

As the current president of the American Institute of Medical and Biological Engineering (AIMBE), Buddy Ratner believes AIMBE can have an impact on bioengineering aspects of today's healthcare system. "AIMBE is an organization focused on policy issues that deeply affect the bioengineering community, so I appreciate the opportunity to serve the community as President of AIMBE. AIMBE aims to impact healthcare through education on many levels. The economic advantages of improved, bioengineered devices would clearly be appropriate as a subject for AIMBE to address. I imagine that some day a catheter will come with a spreadsheet that says if a particular infection is found, you can get away with using the lowest cost therapy, but for another condition you might want to use a more expensive catheter because lower cost strategies may ultimately cost ten times more. There was a *New England Journal of Medicine* article that stated we lose thousands of people a year to catheter-related complications. It's addressable and a high priced, sophisticated technology is not necessarily involved. I think we can focus on the policy issues. I think the economic case has to be presented. One can't be totally naive about the importance of economics. Scientists or chemists are typically not introduced to economics. One of the characteristics of an engineer is that they are taught to integrate economic analysis in their work. An economic analysis should parallel technological development. It's an integral

part of the engineering field. I think it's very important and is something that should be taught and delivered to our students."

What lies ahead in controlled release? Ratner was recently asked to participate in a lecture series to address a futuristic perspective of biomaterials devices in dentistry. His report was recently printed in the *Journal of Dental Education*. In the report he presented a scenario that a dental implant might have a



Buddy Ratner has been playing guitar for 40 years as a "closet guitarist." The secret is out now.

reservoir with an antibiotic loaded in it. "Some years down the line, if the device became infected, the dentist might be able to just hit it with a dose of ultrasound to release this reservoir from the inside of the device. In fact, we have just had a lot of fun developing, and are in the process of working on an ultrasound-triggered drug delivery device that delivers all sorts of interesting things. It doesn't deliver anything until you hit it with a dose of ultrasound. It uses a focused ultrasound through the skin to enhance delivery. We call it a molecular switch. When you hit it with ultrasound, it opens up and closes back down again when the ultrasound irradiation is stopped. This idea could be used in a dental device, a heart valve, a vascular graft, and many other devices. Maybe reservoirs could be built into

these devices and if later-stage infection occurs, the physician, instead of having to explain the device to deal with the infection, might be able to just dose it with ultrasound.”

NSF Engineering Research Centers (ERCs) have been very important to Buddy Ratner and his work. UWEB, which Ratner directs is an NSF Center, “The NSF Engineering Research Center system has evolved a series of ideas that I think are very important, and all over the world other countries are adopting similar systems because there is so much potential to produce much more than the sum of the parts from the centers. The Engineering Research Center system gives you the funding, the long-term stability and the ability to make things happen in other domains that is not possible when you are just doing research — I really appreciate that. The three domains addressed by ERCs are technology research, industry, and education. The ERC system mandates that industry is involved in a major way and, in fact, industry is a partner in the endeavor. Also, one devotes a substantial portion of the funding and the energy of the center to education and outreach. There is an amazing synergy when you start to bring people from those three domains together. An NSF grant gives the resources, and the mandate to do this. Consider that the majority of the students go into companies. Also, even if we develop the cleverest thing in the world, unless a company adopts it and makes it into a product, it’s never going to help people. So, the ability to closely work with companies and understand how they think about marketing, and the introduction and development of products has been very important to me personally. In addition, to be able to integrate education through all parts of the program, to bring in undergraduates and have the undergraduates work with graduate students and to bring in high school students is a great benefit. At the moment, within our UWEB education effort we have a large number of high school science teachers who partake in the program. They are developing kits on biomaterials to take out into the school system. We have also just started a program with the African-American Academy of Seattle and we will be bringing middle-school kids in on the afternoons. What we’re thinking about is actually developing a group of young

African-American students who are excited about science and especially biomaterials. Hopefully, they will focus themselves on the University of Washington, and learning. Although we try very hard to recruit more diversity into our program, the applicants into our program simply are not a very diverse group. I am firmly convinced that much of the richness of science comes from diversity of ideas. Diversity of ideas comes from diversity of people and so I want to see a more diverse population within our students. This program with the African-American Academy is a way to maybe make this happen.” Thus, under Ratner’s leadership, and with funding from the ERC system, the potential to appropriately fuse the biomaterials research to industry needs and education/outreach is brought to fruition.

“Diversity of ideas comes from diversity of people and so I want to see a more diverse population within our students.”

The concept of mentoring is important to Dr. Ratner. “At this point I have mentored about 45 graduate students. Some are in academia; others have gone into medicine or dentistry, and the majority went into industry. I am still reasonably close with a very large fraction of them. I think I will always have a good feeling toward these people. The students have lots of opportunities because there are a many great professors at the University of Washington. They have lots of opportunities to choose great groups. When they do choose to work in my group, they obviously like the projects that are going on. Once they enter the group they are launched on a 5- or 6-year relationship that is pretty symbiotic for both student and professor. The student is there for training, mentorship, and to launch their career. The professor, on the other hand, tends to have grants and reputation at stake on the research that comes out of the group, much of which is generated by the student. There is an important symbiotic relationship and I have been fortunate in that generally it has led to very good relations with graduates from my group.”

Ratner is in year two of a ten year project funded by the National Institutes of Health to grow heart muscle and a ventricle. The project is part of the NIH Bioengineering Research Partnership Grant program. “I think one of the things I have always done well in my career is to partner with others and bring skills together to accomplish things. This is one of the most audacious projects I have undertaken in my career. It also has the potential for great significance and importance. What we said we would do is bring together a team of materials people and biologists and surgeons to grow a piece of living heart muscle in five years, and in ten years, make a living ventricle for the heart. The piece of heart muscle would be used to replace the scar on the wall of the heart of patients with a myocardial infarction. The surgeon would excise the scar and put in a piece of fresh muscle. An important thing about the heart muscle is that it doesn’t heal or regenerate at all. If it’s damaged, it dies and never heals, so that scar is a permanent liability on the heart and the surgeons would like to remove it and put in fresh heart muscle. To grow heart muscle we have to use this cell, the cardiomyocyte that has no ability to grow. It will live, function, and work, but it does not multiply or grow. So we have a major biological challenge in learning how to work with this cell or its precursors and to nurture or nudge it into a state where it will start multiplying or generating enough muscle or tissue. Then the challenge is that the heart is not just muscle; it is a very highly vascularized structure. The heart has tremendous demand for oxygen and lots of blood vessels must supply it. So you’ve got to get blood vessels in there. Then you’ve got to add electrical conduction to control the beating and electrical processes of the heart and, finally, the strength and toughness that comes from the extracellular matrix proteins. You’ve got to put this all together into a package that may be surgically useful. It is a tremendously exciting challenge. We’ve brought some new people into our program who are doing interesting kinds of materials science to make the new types of scaffolds we might need but also different types of biology to learn to manipulate the cells and control their differentiation and control their organization into tissue.”

(continued on page 23)

Amylin Pharmaceuticals Initiates Third Phase 3 Pivotal Trial Of AC2993 (Synthetic Exendin-4) in Type 2 Diabetes

Amylin Pharmaceuticals, Inc. initiated the third of three planned Phase 3 pivotal trials of AC2993 (synthetic exendin-4), a compound being studied as a potential treatment for people with type 2 diabetes. This study will evaluate the ability of AC2993 to improve glucose control in people with type 2 diabetes who are currently not achieving target blood glucose levels with a combination of metformin and sulfonylureas. This study is the third of three planned Phase 3 studies in the Company's "AC2993: Diabetes Management for Improving Glucose Outcomes" (AMIGO) development program. The AMIGO studies are aimed at demonstrating AC2993's ability to improve glucose control in people with type 2 diabetes who are currently not achieving target blood glucose levels with metformin and/or sulfonylureas. The first study was initiated in December 2001 to evaluate the effects of AC2993 when added to metformin alone. The second study was initiated in January 2002 to evaluate the effects of AC2993 when added to sulfonylureas alone.

AC2993 is a 39-amino acid peptide being studied for the treatment of type 2 diabetes. AC2993 has been shown in clinical studies to stimulate secretion of insulin in the presence of elevated blood glucose concentrations, but not during periods of low blood glucose concentrations (hypoglycemia). AC2993 has also been shown in clinical studies to reduce both post-meal and fasting blood glucose levels.

Antibiotic Technology Sparks PYROMANIA for BSKB

BSKB Medical Ventures, LLC., exclusively licensed the rights to commercialize a technology relating to a new class of potential antibiotics from California State University, Fullerton.

To exploit this technology, BSKB Medical Ventures recently established a new company, Pyro Pharmaceuticals, Inc. The licensed technology results from the research of Christopher R. Meyer, Ph.D., Associate Professor of Chemistry & Biochemistry.

"Dr. Meyer has identified a unique target that will be used to develop a novel class of antibiotics against a wide range of multi-drug resistant pathogenic microorganisms," says Alan M. Schechter, Managing Director of BSKB Medical Ventures and the Chairman & CEO of the newly formed company.

Boston Scientific Files for FDA Approval of Express™ & Express2™ Coronary Stent Systems

Boston Scientific Corporation filed an application with the U.S. Food and Drug Administration (FDA) for pre-market approval (PMA) of its Express™ coronary stent system and its Express2™ coronary stent system — rapid exchange and over-the-wire versions.

The Express stent — developed exclusively by Boston Scientific — is a laser-cut, balloon-expandable stent that features a new design concept called Tandem™ Architecture.

Tandem Architecture integrates short, thin Micro™ elements designed for flexibility and conformability, with long, wide Macro™ elements designed to enhance radiopacity. Combined, these elements are designed to create a structure that offers uniform vessel coverage and radial strength.

The Express2 stent system offers significantly greater flexibility and trackability compared to the original Express stent system that was launched in European and other international markets last September. The Company expects to launch the Express2 stent system in the United States in September and outside the United States in May.

Cancer Treatment Appears Effective Against HIV

A drug being tested as a cancer treatment also appears to be effective in the laboratory against HIV, say Stanford University Medical Center Researchers. The findings suggest the drug may benefit patients by targeting infected cells without harming the healthy cells the body needs to defend itself against disease. Plans are under way to test the drug in people with the HIV virus.

HIV devastates the body's immune system by taking over and killing a particular class of white blood cells known as CD4+ helper T cells. These cells coordinate the body's defense against foreign invaders. Without the normal array of T cells, HIV patients have weakened immune systems, leaving them susceptible to infections.

Stanford researchers have now found that low doses of the drug called motexafin gadolinium (or Gd-Tex) selectively kills HIV-infected T cells. "Gd-Tex worked in vitro," said Leonard Herzenberg, Ph.D., professor emeritus of genetics and senior

author of the study reported in the Feb 18 issue of the *Proceedings of the National Academy of Sciences*. "It selectively killed the HIV-infected cells when they were in a mixture with healthy white blood cells. And to our surprise, only the infected CD4+ T cells were killed."

Gd-Tex is now being tested in humans as a cancer treatment. The drug acts by accumulating in tumor cells and attacking the molecules that normally protect the cells from one type of stress. The cells therefore die more readily during radiation treatment.

Cardinal Health to Acquire Magellan Laboratories

Cardinal Health, Inc. will acquire privately held Magellan Laboratories Incorporated, a leading full-service contract pharmaceutical development organization.

Magellan has seven strategic divisions: Analytical, Inhalation, Microbiology, Structural Chemistry, Synthesis, Research and Bioanalytical, and Pharmaceuticals.

George L. Fotiadis, President and Chief Operating Officer of the Cardinal Health Pharmaceutical Technologies and Services segment, said, "Magellan's proven performance in pharmaceutical product development strongly enhances our service offering upstream to the manufacturer, allowing Cardinal Health to add more value earlier in the life of the molecule's development. From early stage drug development to commercial manufacturing on through to packaging — and for virtually every dosage form — this merger positions Cardinal Health as the most comprehensive product development service provider to the pharmaceutical and biotechnology industries." Alfred Childers, Ph.D., Magellan co-founder and President, Administration, added, "Together, our operations can provide a full spectrum of services — from pre-clinical services to commercial manufacturing. We can assist pharmaceutical and biotechnology firms in overcoming internal resource constraints while providing the highest quality of service to handle the development demands of their product pipelines. At the same time, smaller firms have shown an inclination to retain their intellectual property longer, often through Phase II and III, in order to maximize their business opportunity. Together, we can also meet this need exceptionally well."

Clinical Trials for HIV Break New Ground

The Institute of Human Virology (IHV) will open two innovative clinical trials this month. One of these trials will utilize a pharmaceutically-produced compound based on a naturally-occurring substance (called chemokines) that can block the HIV virus and halt the progression of AIDS, a Gallo discovery that was hailed by Science magazine in 1996 as one of that year's most important scientific breakthroughs.

The Schering-Plough Research Institute is the first to synthetically reproduce this compound (called SCH-C) — part of a new class of HIV therapies called entry inhibitors — and the Institute of Human Virology is one of three centers nationwide to offer the experimental drug to HIV patients.

"An underlying research emphasis at IHV is to use the body's natural ability to fend off infection and heal itself and to discover and utilize biological approaches to therapy and treatment that may be less toxic- and less costly — than drugs currently on the market," explains Dr. Robert Redfield director of the HIV's Division of Clinical Care and Research. "Schering-Plough has built upon these landmark discoveries to create a chemokine antagonist that blocks key receptors — or entry points of the virus. It's a new approach designed to actually block the HIV virus from getting into cells in the first place."

Unlike existing HIV drugs that work inside the cell and target viral enzymes involved in the replication of the virus, entry inhibitors work by blocking HIV before the virus enters the cell and begins its replication process.

Designer Plastics for Hairspray & Drugs

Research chemists at the University of Warwick have devised and patented a new process called Living and Controlled Radical Polymerisation which can cheaply and easily grow designer polymers (plastics). They have already used the process to produce a wide range of designer polymer designs that are now being tested by major companies for use in applications as diverse as hairspray, anti-obesity drugs and inkjet printer ink.

The research team has just been granted a patent on the process in Europe and the US and Professor Haddleton has now formed a spin out company called "Warwick Effect Polymers Ltd" (WEP) which has already begun to produce to-order designer polymers for high-value applications such as inkjet printer ink, hairspray and shampoo,

adhesives, pharmaceuticals, biomaterials, and medical devices for companies such as, Unilever, Procter and Gamble, BP Avecia, and GelTex Inc. WEP is now seeking partners to exploit the technology in licensing and joint venture agreements.

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Elan and Wyeth Suspend Alzheimer Treatment Trial

Elan Corporation and its partner Wyeth-Ayerst Laboratories have decided not to resume the trials of AN-1792, their new treatment of mild to moderate Alzheimer's disease.

The trials of the drug were suspended in January after four patients taking part in the study in France experienced signs of inflammation in the central nervous system. Since then, eleven additional patients were reported with similar symptoms.

Elan and Wyeth-Ayerst Laboratories say they will not treat any more patients with the drug. Instead they will test other potential treatments for Alzheimer's disease, first on animals and later on humans.

FeRx Granted Fundamental Japanese & European Patents

FeRx Inc. has received patents from both the Japanese and European patent offices, covering the composition of matter and method of manufacture of the company's novel Magnetic Targeted Carrier (MTC) technology.

MTCs are microparticles, composed of metallic iron and activated carbon, which serve as delivery vehicles for the site specific targeting, retention, and release of pharmaceuticals. The MTC technology

utilizes the physical force of a magnetic field, rather than a biological mechanism, for the targeted delivery of pharmaceutical agents to specific areas of the body.

Landmark Clinical Trial: Lescot Reduced Risk of Cardiac Events by 22% In Patients Undergoing First Angioplasty

NEOSeed™ Technology received FDA clearance for one of its core devices, the Dfiner™.

The Dfiner is a unique urethral imaging catheter with a Nitinol "umbrella" designed to wrap around the bladder neck and identify the position of the prostate in relation to the bladder. Its proprietary design enables the device to be viewed under both fluoroscopy and ultrasound. Increased visualization of the prostate and prostatic urethra can lead to a significant drop in the number of improperly placed brachytherapy seeds.

"The Dfiner will benefit both patients and physicians during the brachytherapy procedure by reducing the number of so-called 'cold spots' that result from lost brachytherapy seeds in the bladder," said Jerry Sanders, NEOSeed Chief Executive Officer. "The Dfiner, in addition to NEOSeed's other products, will allow doctors to continue effective brachytherapy treatment."

Lilly Receives Award for Therapeutic Breakthrough

Eli Lilly and Company received the Translational Medicine Award in recognition of Lilly's new biotech product, Xigris® (drotrecogin alfa (activated)). The award honors pioneering work in molecular medicine that leads to therapeutic advances for human diseases. Xigris also was recognized recently by Med Ad News as the Best New Medicine of 2001.

"Xigris is the first biologically targeted therapy for life-threatening severe sepsis, one of the most important unmet medical needs in all of medicine," said Kenneth R. Chien, M.D., Ph.D., director, UCSD Institute of Molecular Medicine. "Xigris has had a major clinical and scientific impact on an important human disease, which is why it was selected for this award."

Medinol Receives FDA Approval to Begin U.S. Clinical Trials of The Nirflex™ Stent

Medinol Ltd received U.S. Food Drug Administration (FDA) approval to begin recruitment for its Investigational Device Exemption (IDE) study in the US for its

(continued on page 19)

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next generation NIRFLEX™ stent. Last week, Medinol received CE-mark approval for introducing its pre-mounted NIRFLEX™ systems across Europe.

The FDA accepted the NIRFLEX™ as a continuation of the company's NIR™ stent, whose clinical data is owned by Medinol, thereby approving a simpler study of equivalence between the NIRFLEX™ and the NIR™. This study will begin in 12 US leading medical centers in May 2002.

Dr. Judith Richter, Medinol's CEO, said, "FDA approval of clinical studies on the NIRFLEX™ marks another important milestone in Medinol's charge back into the forefront of the global interventional cardiology market. We are very pleased with the momentum we are building towards delivering the profound benefits of the NIR™ family of stents to cardiac patients and cardiologists around the world."

The NIRFLEX™, Medinol's new coronary and peripheral stent, combines extreme flexibility, before and after deployment, with the optimal scaffolding traditionally associated with the NIR™ family of stents. The NIRFLEX™ was developed by Medinol and is the company's patented and exclusive property.

Merck to Expand Arcoxia® trade

Merck Co., Inc. plans to submit an expanded New Drug Application for Arcoxia® trade to the U.S. Food and Drug Administration in order to include new efficacy data that will better position the product to compete successfully in the coxib class, where there already are three entrants.

Accordingly, Merck announced the withdrawal of the original U.S. NDA for the investigational medicine.

Myriad, Abbott Form Drug Discovery Alliance

Myriad Genetics, Inc. has formed a drug discovery collaboration with Abbott Laboratories to identify novel genes and drug targets for the diagnosis and treatment of depression. The collaboration will merge Myriad's integrated drug target identification and validation technologies with Abbott's drug and diagnostic discovery and development expertise. The agreement provides Abbott with license rights and specifies an upfront payment to Myriad, plus guaranteed research funding and potential milestones totaling approximately \$34 million plus royalties.

"We are very pleased to be using our advanced biopharmaceutical technologies in collaboration with Abbott in our effort to discover the next generation of drugs to treat depression," said Peter Meldrum, President and CEO of Myriad Genetics, Inc. "The integration of drug target discovery with disease pathway discovery and functional validation provides Myriad with the ability to deliver to Abbott novel therapeutic targets with high potential to result in the safe and effective drugs that are needed to treat this important human disease."

Neoprobe Completes License for Lymphatic Agent

Neoprobe Corporation has completed an exclusive license agreement with the University of California, San Diego.

The license affords Neoprobe the rights to a proprietary compound developed by researchers at UCSD. The compound, which Neoprobe has designated Lymphoseek™, is being evaluated in clinical studies to determine its effectiveness in identifying lymphatic tissue in breast, and in melanoma cancer patients.

David Bupp, Neoprobe's president and CEO, said, "We are very pleased to have licensed Lymphoseek™ from UCSD. The initial clinical results from the Phase I clinical studies encouraged us to accelerate the Lymphoseek™ licensing activities. We will be working with the Phase I researchers to complete a submission package to the United States FDA to seek permission to begin the next phase of Lymphoseek™ clinical evaluation."

PenJet®; A New Kind of "Shot in the Arm"

Could the days of the dreaded needle be close to gone? PenJet®, received a US Patent for mixing a lyophilized (freeze-dried) drug with a diluent in a needle-less jet injector prior to administration.

"Pharmaceutical manufacturers will now be able to package their innovative lyophilized drugs in a needle-less, single use, inexpensive jet injector," said Thomas PI Castellano, PenJet® Corporation's CEO. "Although it has wide applicability for the needle-less delivery of a great many drugs, it is particularly relevant to the increasing number of highly potent, biotechnologically derived proteins that require lyophilization to maintain their required shelf life."

Rheumatoid Arthritis Trapped by Regeneron

Regeneron Pharmaceuticals, Inc.'s Phase Ib clinical trial for its Interleukin-1 Trap showed positive preliminary results.

Patients treated with the IL1 Trap experienced dose-dependent improvements in tender and swollen joints, and CRP (C-Reactive Protein) levels, as well as the composite ACR (American College of Rheumatology) measure of disease activity. "These results, while encouraging, must be interpreted cautiously because of the small numbers of patients, the short-term nature of the treatment, and the limited doses tested; however, we believe that the IL1 Trap has the potential to help patients with rheumatoid arthritis." Said Leonard S. Schleifer, M.D., Ph.D., Regeneron's President and CEO.

Ricerca and Siegfried Form Strategic Alliance

Ricerca, LLC, formed a strategic alliance with Siegfried Ltd. The two companies will collaborate on Active Pharmaceutical Ingredient (API) chemical development and manufacturing projects for their pharmaceutical industry clients.

According to the terms of the two-year, renewable agreement, Ricerca will provide process chemistry, development, scale-up, and API production services through Phase II of the clinical development program for their clients' projects. These projects may then be transferred to Siegfried for Phase III clinical trial and commercial API and dosage form manufacture.

Watson, Baxter to Co-Promote Ferrlecite®

Watson Pharmaceuticals Inc. entered into an agreement with Baxter Healthcare Corporation for the co-promotion of Ferrlecite® in the U.S. renal market. Ferrlecite®, the leading intravenous iron replacement product in the U.S., is indicated for the treatment of iron deficiency anemia in chronic hemodialysis patients receiving supplemental epoetin therapy.

"We are delighted to have entered into this co-promotion relationship with Baxter, one of the leading medical products companies in the world, with a highly respected sales force in the renal market," said Joseph Pap, Watson's CEO. "We are confident that the combined resources of Watson and Baxter will provide enhanced value for all of our Ferrlecite® customers."

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U.S. Patents 5120545 and 5149539 disclose methods for preventing induction of sensitization and treating the inflammatory response upon elicitation. The methods involve the co-administration to the skin or mucosa of a sensitizing drug together with an antigen processing-inhibiting agent. Events that lead to the association of the antigens with the cell surface of a class II MHC molecule are referred to as antigen processing. The above mentioned association is required for the occurrence of presentation of the antigen by the Langerhans cells to T cells. Presentation is required for both the induction and the elicitation step of the sensitization process. Antigen-processing inhibitors include ionophores and weak base compounds such as ammonium chloride. The processing inhibitors prevent the processing of the drug in the lysosome due to the increase of pH; thus the proteases in the lysosome are not able to chemically alter the drug into the required antigenic form for class II MHC association. Excellent data were obtained for two sensitizing drugs, propranolol and tetracaine. Over 90% reduction in inflammatory response to propranolol was obtained with a formulation containing 4% ammonium chloride (Table 2).

U.S. Patent 5843979 pertains to the use of mast cell degranulators to abrogate the induction step of delayed hypersensitivity in the dermal or transdermal delivery of drugs. The mast cell degranulators are also capable of inducing a state of immunological tolerance to the skin when the sensitizing agent is delivered prior to, or at the onset of, transdermal administration. cis-Urocanic acid and its analogs, capsaicin, chloroquine, an antihuman IgE antibody, compound 48/80, morphine sulfate, and substance P, are shown to be appropriate mast cell-degranulating agents. cis-Urocanic acid was able to reduce in balb/c mice the sensitization to DNCB, in a dose response fashion (23).

Ion channel modulators have been studied extensively, and they have been shown to modulate both the induction and elicitation steps of the sensitization response. The mechanism of modulation has not been elucidated. U.S. Patents 5686100, 5716987, 5618557 and 5912010 address the abrogation of sensitization, as well as pure irritation, by the use of ion channel modulators (24).

Skin reactions are the Achilles' heel which hinder the rapid progress in designing more transdermal drug delivery systems. However, in spite of the progress which has been made the last few years using the information gleaned from immunologic principles, much more work is needed to eliminate this major obstacle and allow TDD to enter the mainstream of drug delivery.

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Report on the 2nd Conference of the New Zealand Chapter of CRS • 20th -21st February 2002

By Thomas Rades

The second conference of the New Zealand Local Chapter of the Controlled Release Society was again held in conjunction with the Annual Meeting of the Formulation and Delivery of Bioactives Research Theme of the University of Otago, in Dunedin, New Zealand. This year a new venue for the conference was chosen; the Hutton Lecture Theatre in the recently renovated Otago Museum in Dunedin. The venue proved to be excellent and the organisers did a great job. The feedback from the more than 80 participants from academia and industry was very positive.

The conference kicked off with a session on *Protein Characterisation*. Invited speakers from the Department of Biochemistry at the University of Otago gave excellent overviews on modern characterisation methods for proteins (as drug targets and as new drugs): NMR (Dr. Catherine Day) and X-ray crystallography (Dr Sigurd Willbanks). These presentations were followed by Dr Natalie Medlicott from the New Zealand National School of Pharmacy in Dunedin who spoke about quantitative, chromatographic techniques for protein determination in formulations.

From proteins as bioactive molecules in the first session, attention then shifted to *Delivery Technologies* in the second session. Prof. Istvan Toth from the School of Pharmacy at the University of Queensland, Brisbane, gave an excellent invited talk about liposaccharides in drug delivery, which sparked a lot of interest. Other topics covered in this session included: Long term diabetes control with encapsulated porcine islets; delivery of immunocontraceptive vaccines for the control of possums in New Zealand; poly (ε-caprolactone) films impregnated with antimicrobial agents; and the effect of hydrophilic excipients on the release from silicone intravaginal delivery systems.)

The third and final session on the first day dealt with an increasingly important topic: the question of how research can be brought from the "*Bench to the Market*". Prof. John Tagg (Department of Microbiology, University of Otago) and Kelvin Moffat from BLIS Technologies discussed their experiences on the development from research on bacteriocin-like inhibitory substances to the formation of BLIS Technologies, a company which will bring their first product based on this research to the market in the near future.

The conference dinner was held at The Chalet Restaurant in the beautiful Glenfalloch Woodland Gardens. Glenfalloch is located on the Otago Peninsula and delegates enjoyed the scenic drive along the harbour from Dunedin.

The second day of the conference was almost completely devoted to *Vaccine Research*, a strength in New Zealand's Delivery and Formulation research, and already almost a tradition at the meetings of the Formulation and Delivery of Bioactives Research Theme of the University of Otago. In two sessions (one on

adjuvants and one on delivery issues) nine speakers from five different research centres in New Zealand and Australia presented results of their research. The topics included vaccination of cattle against bovine tuberculosis, enhancement of IgA levels in bovine milk, CpG DNA as an adjuvant component for new generation tuberculosis vaccines, continuous antigen delivery, slow release microcapsules, and poly(alkylcyanoacrylate) nanocapsules and liposomes as delivery systems for vaccine antigens.

The final session about *excipients* saw an exciting talk about mesoporous materials engineered by macromolecular surfactant-assembly templating by another invited speaker, Dr Steve Bagshaw, from Industrial Research Limited in Lower Hutt; a presentation about the use of spectroscopic characterisation methods in the characterisation of solid dosage forms by Dr Thomas Rades from the New Zealand National School of Pharmacy, and an overview about the various lactose qualities produced by Lactose New Zealand, presented by John Thomas.

A number of posters were also presented which covered diverse topics from treatment of xerostomia using emulsions to the use of enhancers to increase the permeability in the large intestine of the Australian brushtail possum.

The annual meeting of the New Zealand Chapter of the Controlled Release Society was held at the end of the first day. Dr Craig Bunt from InterAg, Hamilton, was unanimously elected as the new President. Our thanks goes to Dr Nigel Davies who retired as President. The newly elected Vice president is Dr Thomas Rades from the New Zealand National School of Pharmacy. Dr. Mike Rathbone from InterAg is Treasurer and Dr Bernie McLeod for AgResearch, Invermay is the Secretary. A student representative has also been elected and this position has been taken by Ms Arlene McDowell from the New Zealand National School of Pharmacy.

A new edition of the newsletter will contain summaries of some of the presentations given at the conference. The newsletter will be available electronically from the website of the New Zealand Chapter of the Controlled Release Society (<http://www.controlledrelease.org/chapters/newzealand>).

Please contact Dr Thomas Rades (thomas.rades@stonebow.otago.ac.nz) for further information about the meeting and Craig Bunt (crb@interag1.co.nz) about the New Zealand Chapter of the Controlled Release Society. The committee members are looking forward to the year ahead and further development of the New Zealand Chapter of the Controlled Release Society.

Editor's Note: Find out more about the New Zealand Chapter. Visit the CRS global portal at www.controlledrelease.org/global/index.htm.

Ratner has assumed a additional challenge in the form of a new corporation, Asemblon. Together with his wife, Cheryl Cromer-Ratner, they are spinning technological ideas off from the UWEB ERC. "An idea central to our ERC is that nature uses order and organization to deliver biological signals. In 1983, a seminal paper by Nuzzo and Allara showed that perfectly organized organic surface structures could be created by simply dipping a piece of gold in a dilute solution of n-alkyl thiols. This led to UWEB studies of self-assembling monolayers (SAMs) and the development of some technology around SAMs. Soon we realized that there are no reliable commercial sources devoted to producing these molecules. One of the goals of UWEB is to spin technology off into start-up companies. Also, I'd been teaching entrepreneurship ideas in my courses and encouraging the appropriate and symbiotic relationship between industry and academe. Here was an opportunity to start a business and practice what I've been preaching. Asemblon should open its doors very soon, selling a wide range of functionalized n-alkyl thiol molecules and other tools useful for self-assembly. Asemblon will also develop and patent new technology around self-assembly. Asemblon is looking closely at the rapidly evolving area of molecular electronics, but plenty of applications exist in medical diagnostics, biosensors, and biomaterials."

When asked if he considers the far-reaching effects of his work on future generations, Ratner replied, "If I'm doing something like this project to grow heart muscle, it's pretty obvious that success will have a tremendous impact and that's great. Ultimately, what I've always wanted to do, and the reason I have always focused on medical research in my work, is because as well as having scientific excitement, it will ultimately help people. A scientist could go into other things like electronics, — chips for example. Chips are great and you can make money from them. You can also get scientific excitement out of the work; but better Nintendos won't really help humanity.

In medicine, the potential benefits are obvious. You're helping people. That's how I think about it. On the other hand, there are a lot of projects we embark on, but rather than thinking about a paradigm shift to affect future generations, you think about it as a piece of science. You think about learning something new and working through a system. You get some interesting information and once you get this information it often makes other connections that lead to other things. Sometimes I think, 'hey, I wonder what's going on there and where might this lead? I wonder how we can explore this?' Almost inevitably, information comes out that is useful in other areas, it grows, and the work spreads — a tree of scientific ideas and possibilities."



Ratner enjoys comparing Washington State wines to wines of other areas.

Dr. Ratner is a member of the Controlled Release Society (CRS) and several other Societies. Of CRS, he stated that the society has made a very valuable contribution to the scientific community by developing a society that was truly international. He believes that CRS has taken advantage of the strength in numbers concept and the important economic benefit of having one society rather than multiple groups around the globe. He stated that his affiliations in professional societies have benefited his research and his career. He believes that when a new field evolves, professional societies should be responsive in making a home for that interest and encouraging its development.

Ratner has all too little time to pursue external interests, but he does make some time to relax. When asked how, Ratner stated "I have a number of external interests and never nearly enough time to pursue them. A lot of people know about my interest in wine. I'm pretty serious about wine and have a wine cellar. It's an important part of my life and actually a way to help relax too." He focuses on wines from Washington State and has nearly 600 bottles in his wine cellar. "I have quite an interesting collection of wines from Washington State going back many years. This is a very good wine-producing region. One of the things I enjoy is comparing the Washington State wines with wines of other areas and trying to understand the special characteristics that our local wines have. But, I do have a great liking for French Bordeaux wines. In fact, it often becomes my standard for comparison in wine tasting."

Dr. Ratner has been playing guitar for about 40 years and is admittedly, a "closet guitarist." "One of the things I do to relax is just pick up the guitar and play a tune. It makes me feel better and my wife seems to enjoy the sound, too."

Ratner is also interested in photography and has maintained that hobby since junior high school. "For a number of summers I got a job as a photography counselor in a camp in upstate New York. I got to teach photography and amazingly, they, paid me the whole summer to take pictures, which is something I enjoy. When I get out on my own, part of the synergy with all of the travel I do is that occasionally I can get an hour or two on my own to just look around places and take interesting pictures. I like to capture the textures of different places. Recently I had a meeting in Oaxaca, Mexico. The place was beautiful to the eye. It had so much texture, interesting colors and people, with wonderful light. I have never burned through so much film as I did there. I really enjoyed the place." ●

eventcalendar

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

American Association of Pharmaceutical Scientists Pharmaceutics and Drug Delivery Conference

April 22-24, 2002
Crystal City Marriott
Arlington, VA, USA
meetings@aaps.org
www.aapspharmaceutica.com
ph: 703-243-2800

Society For Biomaterials 28th Annual Meeting

April 24-27, 2002
Tampa Convention Center
Tampa, Florida, USA
registration@biomaterials.org
www.biomaterials.org
ph: +1-763-543-0908

SMi

Advances in Target Validation

April 29-30, 2002
The Hatton Conference Centre
London, UK
ghudson@smi-online.co.uk
www.smi-online.co.uk/target/asp
+44-(0)20-7827-6704

Institute for International Research 3rd Annual Chemistry Manufacturing and Controls

April 29 - May 1, 2002
Hilton Alexandria Old Town, Alexandria
VA, USA
skohen@iirusa.com
www.iirusa.com/cmc
ph: 888-670-8200

American Association of Pharmaceutical Scientists (AAPS) Co-Sponsored by CRS and AAVPT

AAPS Workshop on Collaboration in the Research and Development of Veterinary Pharmaceuticals

May 6-8, 2002
Anderson Center for Professional Education, St. Charles, IL, USA
meetings@aaps.org
www.aapspharmaceutica.com/meetings/index
ph: 703-243-2800

Max-Delbrück-Center for Molecular Medicine

Liposome Research Days Conference

May 21-24, 2002
Max-Delbrück-Center Berlin-Buch
Germany
mhensel@mdc-berlin.de
www.lrdi.org
ph: ++49-30-94063720

American Association of Pharmaceutical Scientists

Integration of Exposure Response Relationships in Drug Development and Regulatory Assessment

June 3-5, 2002
Crystal City Marriott
Arlington, VA, USA
meetings@aaps.org
www.aapspharmaceutica.com
ph: 703-243-2800

Biotechnology Industry Organization Bio 2002 International Convention & Exhibition

June 9-12, 2002
Metro Toronto Convention Centre
Toronto, Ontario
www.bio.org

National Institutes of Health

BECON 2002: Biosensors for Research and Medicine

June 24-25, 2002
Natcher Conference Center,
National Institutes of Health Bethesda,
MD, USA
www.nibib.nih.gov/becon/becon.htm

American Association of Pharmaceutical Scientists

National Biotechnology Conference

June 24-26, 2002
Sheraton San Diego Hotel & Marina
San Diego, CA, USA
meetings@aaps.org
www.aapspharmaceutica.com
ph: 703-243-2800

Gordon Research Conference Chemotactic Cytokines

July 7-12, 2002
Mount Holyoke College
www.grc.uri.edu

Gordon Research Conferences Drug Metabolism

July 14-19, 2002
Holderness School
Plymouth, NH, USA
www.grc.uri.edu

Gordon Research Conferences Chemotherapy Of Experimental/Clinical Cancer

July 14-19, 2002
Colby-Sawyer College
www.grc.uri.edu

Controlled Release Society 29th International Symposium on Controlled Release of Bioactive Materials

July 20-25, 2002
Seoul, Korea
register@controlledrelease.org
www.controlledrelease.org
ph: +1-763-512-0909

Surfaces in Biomaterials Foundation presents *BiolInterface* 2002

September 4-7, 2002
Fairmont Scottsdale Princess
Scottsdale, AZ, USA
kkazmierczak@ardel.com
www.surfaces.org
ph: +1-763-512-9103

CRS & NCI International Symposium & Exposition on Tumor Targeted Delivery Systems

September 23-25, 2002
National Cancer Institute
Rockville, MD, USA
www.controlledrelease.org
ph: +1-763-512-0909

BMES

2nd EMBS-BMES Joint International Conference

October 23-26, 2002
Westin Galleria & Oaks Hotel,
Houston, TX, USA
www.embs-bmes2002.org

American Association of Pharmaceutical Scientists 2002 AAPS Annual Meeting and Exposition

November 10-14, 2002
Metro Toronto Convention Centre
Toronto, Ontario
meetings@aaps.org
www.aaps.org

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events, log on to
[www.controlledrelease.org/global/
index.htm](http://www.controlledrelease.org/global/index.htm)

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