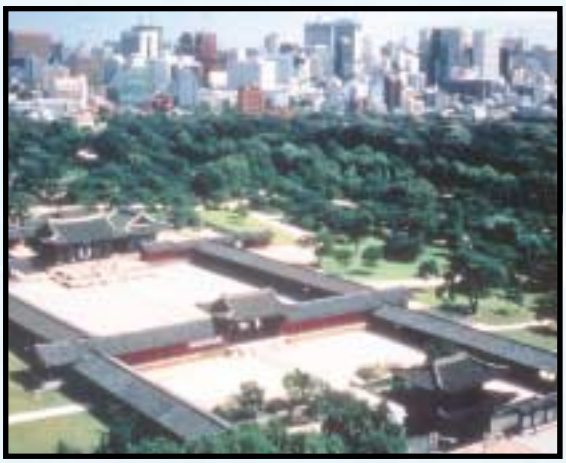
CONTROLLED RELEASE SOCIETY
Volume 18 • Number 3 • October 2001

NEWSLETTER



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Key Delivery Issues for the Therapeutic Use of Antisense Oligonucleotides

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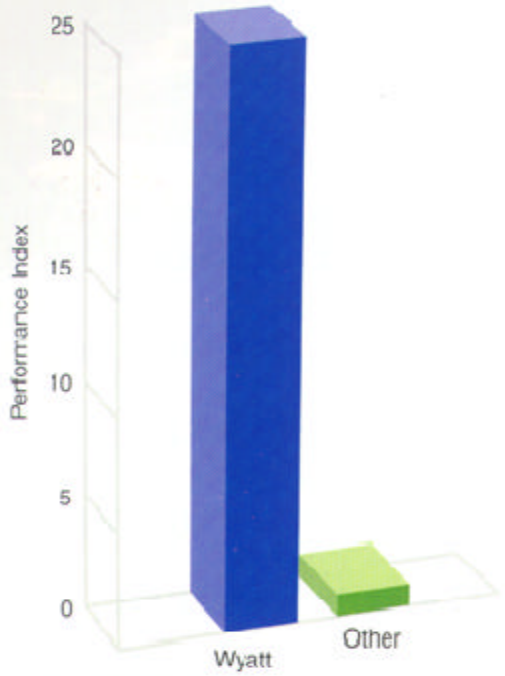

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inthisissue

On the cover –

The COEX World Trade Center in Seoul, Korea, is the site of the CRS 2002 Annual Meeting.

Editors
David Friend & Bozena Michniak

Managing Editor
Rosealee M. Lee

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

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

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

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journal of controlled release **highlights**

By David Friend

The most recent issue of the *Journal of Controlled Release* (Volume 75, no. 3) features a wide range of excellent papers. Since I at one time worked with guar gum, I found the paper by Soppimath et al. stimulating. They report the preparation of spherically shaped cross-linked hydrogels of polyacrylamide-grafted guar gum. By using different amide and carboxyl group derivatives, these so called microgels were responsive to pH and ionic strength of the external medium. In another paper, Han et al. discuss the preparation and evaluation of poly(L-lactic acid) microspheres containing recombinant epidermal growth factor for treatment of chronic gastric ulcers. Finally Sung Wan Kim and coworkers present a paper on the use of a new plasmid (pRIP-IL-4) in which the expression of IL-4 is driven by the rat insulin promoter for pancreas specific and glucose responsive expression.

from the **editor**

By David Friend

It is my pleasure to announce that Professor Bozena Michniak has joined me as co-editor of the Newsletter. I have known Bo for many years having had the opportunity to collaborate with her on a transdermal project. She has a Ph.D. in Pharmacology from Leicester Polytechnic, UK. After postdoctoral appointments with Profs. N. Bodor and B. Barry, she joined the faculty at the College of Pharmacy, University of South Carolina. In 1998 she became a full Professor and Director of the Transdermal and Topical Drug Delivery Laboratory. In 2000, she joined the University of Medicine and Dentistry of New Jersey and also became a graduate faculty member at the College of Pharmacy, The State University of NJ-Rutgers, and Director of the Drug Delivery Laboratory of the NJ Center for Biomaterials. Her research interests include novel dermal penetration enhancers, their mechanism of action, and topical and transdermal formulations. Her group has also developed a novel organtypic human skin model which allows similar drug permeability to human skin.

Why a co-editor? Well, simply I need the help. As indicated in the last issue, we are aggressively expanding the scope of the Newsletter. To that end, our goal is to publish four issues per year (up from three). We have also added two new articles: 1) a patent review in each issue where a different topic is covered, and 2) an article on significant issues facing a given controlled release product area such as transdermal drug delivery. The theme of the latter articles will be on the promise, innovation and challenges facing any given area. The patent watch has for many years been on the field of transdermal drug delivery. Agis Kydonieus has faithfully assembled an annual review of the field. Now we would like to expand this column to include a range of topics, including:

- Gene delivery
- Oral delivery including peptide delivery, extended release, and targeted release
- Injectable microcapsules
- Consumer and diversified products: fertilizers, foods/nutrition, flavors/fragrances, materials/modeling, cosmetics, personal care, and new processing
- Veterinary and agriculture
- Diagnostics
- Vaccine delivery
- Tissue engineering
- Drug targeting
- Biodegradable/bioresporbable polymers
- Inhaled or nasally administered products

We are looking for volunteers to take over each of these topics (or others, if appropriate). Please contact either of the Editors or the Administrative Office if you are interested. In the next issue, we will publish the first 'Innovation, Challenge, Promise' article.

Finally, I again encourage the CRS membership to submit letters to the editor. I hope most of you will find the Newsletter a welcome addition to your mail (if not, write a letter to the editor).●

fromthepresident

By Kinam Park

Richard Guy - A Labor Dog President!

The 28th Annual Meeting of the Controlled Release Society (CRS) held in San Diego in June 2001 was the largest CRS annual meeting ever with almost 2,000 participants. This was a quantum increase in attendance as compared to the then most successful CRS annual meeting in Paris last year. The only sad thing in San Diego was that Richard Guy, who could still be the lame duck president of CRS at the meeting, had to leave for family reasons before the symposium began. It was Richard Guy who spent countless hours handling the never-seen-before amounts of work of CRS. He showed true leadership during probably the most difficult time in CRS history. Richard Guy is a good example showing how hard the Board of Directors work for the CRS members behind the scene. (You are right. It is the Board of Directors excluding me). Even in his final days, Richard Guy was not the lame duck president, but he was truly a labor dog president! The current Board of Directors includes Sandy Florence, Jim Anderson, Susan Cady, Joe Fix, Mitsuru Hashida, and Martyn Davies. Martyn received a baton from Robert Gurny who had served CRS for more than a decade as the Scientific Secretary.

• • • • •

Drug Deliveryman in TIME

Bob Langer was featured in TIME magazine as one of America's best scientists. He was labeled as a drug deliveryman (and also as a pharmaceutical postman), and this indicates that drug delivery research has reached the status of an independent scientific discipline. The drug delivery research was once regarded as a supporting actor in a movie. But the ever-increasing importance of drug delivery has established the area as a stand-alone scientific field. New drug delivery technologies are developed without any particular drugs in mind, and the seemingly useless chemical entities become useful drugs or drugs become more useful with the drug delivery technologies. It is time that the drug deliveryman should play a leading role, for example, in a movie entitled "Indiana Langer and the Raiders of the Lost Chip."

• • • • •

New Executive Director on the Block

CRS will continue playing a principal role in efforts to advance, promote, and disseminate science & technology of controlled drug delivery. While the Board of Directors, with input from the Board of Scientific Advisors and CRS members, is setting the goals and directions of the society, it is the Executive Director that handles the daily activities of CRS. Rosealee Lee assumed the Executive Director position of the CRS early this year and has been joined by Paul Stone, Assistant Executive Director. Rosealee and her team did an outstanding job in carrying out the most successful annual meeting in San Diego. Her enthusiasm and new ideas for CRS have been growing every day, and many of them have already been translated into new programs in the CRS home page as well as the daily activities at CRS Headquarters. CRS members should feel totally free to contact her either by phone or by e-mail for any matter as long as it is related to the CRS. There are some things a scientific organization can't provide. But for everything else there is Rosealee Lee.

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Starship CRS

The long journey that CRS is taking into the future is very similar to that of the Starship Enterprise. This is not because the current president of CRS looks like or behaves like Captain Kirk. This is simply because the missions of CRS are very similar to the missions of Starship Enterprise.

Mission 1. To explore new polymers and hydrogels

One of CRS' missions is to explore strange, new polymers and hydrogels for further advancement in drug delivery technologies. Drug delivery technologies would not exist without polymers and hydrogels, and development of polymers and hydrogels with new functional properties will be critical to the continued advances of the drug delivery discipline. CRS provides annual forums to discuss these advances. Continued participation by CRS members in exchanging ideas at annual meetings is critically important for the rapid growth of the CRS.

Mission 2. To seek out new dosage forms

The ultimate goal of developing drug delivery technologies is to develop dosage forms that bring good things to the patients' life. CRS also has been the center of developing new dosage forms and delivery devices that bring convenience to numerous people through the years. CRS will continue playing the leading roles in the years to come. CRS has been supporting various symposiums and workshops on the subjects in conjunction with other scientific organizations as well as national

institutions. Please suggest your ideas on symposium and workshop topics to CRS Headquarters.

Mission 3. To boldly go where not many have gone before

Unlike many other prominent, international scientific organizations that hold their annual meetings only in the U.S.A., CRS recognizes the importance of globalization and started annual meetings in various countries throughout the world. Because the advances in drug delivery technologies are the results of research efforts of CRS members throughout the world, it is prudent that the annual meeting is held in different places of the world. The CRS Annual Meeting in 2002 will be held in Seoul, Korea, shortly after the conclusion of the World Cup soccer event. This will be a great opportunity for researchers to meet many new scientists from Asia who have different ways of thinking and solving problems. This will also be a great occasion for companies to expand their business opportunities in Asia not only in the drug delivery area but also in the consumer & diversified products. According to Wall Street, the next engine for the growth of world economy is in Asia.

• • • • •

Whole new world

The Starship CRS is currently heading to Seoul with a speed of ultrasound. Please tighten your seat belt and enjoy the ride. Please mark on your calendar July 20-25, 2002, which will be the time for you to get out of the routine and jump into a whole new world. You will see that it's not a small world after all. ●

United Kingdom and Ireland Chapter of the Controlled Release Society (UKICRS) *By Duncan Craig*

The UKICRS represents the Controlled Release Society in the United Kingdom and Ireland, thereby encompassing the whole of the British Isles. The last year has seen a number of exciting developments for us, including a change in chair following the standing down of Dr. Tony D'Emanuele. Tony led the chapter through a number of important changes over the two years of his tenure, not least of which being the establishment of a very detailed website that may be found at http://www.pharmweb.net/pwmirror/pw9/ukcrs/pharmweb91.html. We are all deeply grateful to him for his very substantial contribution to the group.

The mainstay activities of the UKICRS have been the organisation of a one-day meeting in January of each year and the collaboration with the Royal Pharmaceutical Society of Great Britain in holding sessions at the annual British Pharmaceutical Conference (BPC). The last twelve months have been no exception, with a well-attended, one-day meeting (105 delegates) being held at Kings College, University of London earlier this year, coordinated by Dr. Jayne Lawrence. Among other eminent speakers, we were delighted to welcome the Chair of the CRS, Professor Richard Guy, as an invited presenter.

Committee members: Rupi Pannu (Secretary); Ali Rajabi-Siahboomi (Treasurer); David Brayden; Julie Cahill; Martyn Davies; Jayne Lawrence; Caitriona O'Driscoll; Karen Lewis; Snjezana Stolnik; Ijeoma Uchegbu; Neena Washington; Clive Wilson; Jane Worlock

We also ran two sessions at the BPC 2000 in Birmingham, a meeting hailed by the British pharmaceutical science community as being of exceptionally high quality. We reiterate our congratulations to the Science Chairman and UKICRS Committee Member, Professor Martyn Davies, for his outstanding and successful efforts in organising this meeting. This relationship with the Pharmaceutical Society and its scientific wing, the Academy of Pharmaceutical Sciences, is to continue in September of this year with two sessions organised by the UKICRS in collaboration with the Science Chairman, Professor Peter York. These sessions are entitled *Delivery Challenges for Respiratory Disease* and *Drug Delivery to Solid Tumours* organised by Dr. David Brayden and Dr. Snjezana Stolnik Trenkic. We are very fortunate to have attracted a range of internationally recognized speakers to present at these sessions, including Dr. Douglas Lowrie, Dr. Len Seymour and Dr. Philip Low, amongst others.

We are also organising a one-day meeting on January 17, 2002, entitled *Oral Delivery of 'Difficult' Drugs*, to be held at Astra Zeneca in Loughborough, UK, with Dr. Karen Lewis and Dr. Rupi Pannu coordinating the event. While the programme is still being organised, the speakers are to include the forthcoming CRS President, Professor Sandy Florence and Professor Christos Reppas from the University of Athens, with topics including novel surfactant delivery systems, enhanced absorption of poorly soluble drugs, melt extrusion technology and the prediction of *in vitro/in vivo* correlations.

We are also about to issue our latest newsletter, compiled and edited by Dr. Neena Washington and Dr. Ijeoma Uchegbu which will contain details of both our past and forthcoming activities. The newsletter will be freely available from our website and we hope that as many of you as possible will have a chance to view it.

Finally, we have commenced a dialogue with Professor Ruth Duncan and Professor Clive Wilson with regard to CRS 2003 to be held in Glasgow, Scotland. The UKICRS has assured them that they can rely on our full and enthusiastic support to make this an outstanding conference. Overall, therefore, we remain an extremely busy organisation and would like to thank the many individuals who have helped to keep the chapter a thriving and ongoing concern. ●

Editor's Note: Professor Duncan Q. M. Craig is Chair of the UKICRS.

Key Delivery Issues for the Therapeutic Use of Antisense Oligonucleotides

By Gregory E. Hardee & Richard S. Geary

Understanding the complex pharmacokinetic behaviors that antisense oligonucleotide drugs display in vivo *is critical to making therapeutic agents form this class of molecules. Non-specific protein binding plays a significant role in gross drug distribution and ultimately in intracellular trafficking of oligonucleotide drugs. Delivery system design for these therapeutic agents should account for this process, with respect to how and where it may be manipulated to advantage.*

Introduction

End of the beginning, next hurdles

After many years of intense effort to answer the fundamental questions necessary to create a new technology, antisense oligonucleotide therapeutics are advancing in the clinic (Fig.1). Nonetheless, because of the newness of the technology many unanswered questions remain (Crooke 1999). The objective of this article is to review some of the progress in understanding the unique delivery challenges posed by these molecules and successes to date, and to stimulate thinking regarding the next set of challenges. By way of background, antisense molecules function by binding to targeted mRNA, and through various mechanisms discussed elsewhere, prevents translation of the encoded protein. The specific targeting required for activity is accomplished through Watson & Crick base pairing i.e.; specificity is achieved through complementary sequence and does not rely on secondary structure.

Appearance at the site of action

Distribution from the central compartment

Phosphorothioate oligonucleotides in circulation are largely bound to plasma proteins(>96%), a property that reduces renal filtration and results in extremely low urinary excretion (<1% excreted over 24 hr in man at clinically relevant doses, Glover 1997). This high-capacity protein binding becomes saturated only at supra-therapeutic doses (15-20 mg/Kg) administered by rapid intravenous infusion. Intravenously administered antisense oligonucleotides follow the distribution pathway: clearance from the systemic circulation, accumulation by organs/tissues, cellular uptake, migration within the cell, binding to the target mRNA, and finally metabolic length reduction and subsequent elimination. Plasma protein-bound oligonucleotide readily dissociates, allowing a great majority of intact oligonucleotide to broadly distribute into tissues shortly after intravenous injection, a phenomenon observed in multiple species including mice, rats, dogs and monkeys (Geary 2001; Dvorchik 2000). The distribution of this extensively plasma protein-bound drug (predominantly albumin, K_D 5-30*m*M) to reservoirs of lower-capacity, but higher-affinity in tissues, including intercellular matrix and cell surfaces, appears to be governed by the relative amounts of accessible protein, their binding avidity and perfusion dynamics. One would expect highly perfused tissues to initially accumulate the majority of an

(continued on page 7)

Route	Dosage Formulation	Target	Lead Indication	Preclinical	Clinical Phase 1	2	3	Market
Intravitreal	Sol. for Inj.	HCMV, IE-2	CMV Retinitis	X	X	X	X	X
IV Infusion	Sol. for Inj.	PKC-a	Lung Cancer, NSCLC	X	X	X	X	
IV Infusion	Sol. for Inj.	ICAM-1	Crohn's Disease	X	X	X	X	
IV Infusion	Sol. for Inj.	Bcl-2	Lymphoma, leukemia	X	X	X	X	
IV Infusion	Sol. for Inj.	PK A	Cancer	X	X	X		
Topical	Cream	ICAM-1	Psoriasis	X	X	X		
Enema	Solution	ICAM-1	Ulcerative Colitis	X	X	X		
SQ Infusion	Sol. for Inj.	HCV, IRES	Hepatitis C	X	X	X		
IV Infusion	Sol. for Inj.	H-ras	Pancreatic cancer	X	X	X		
IV Infusion	Sol. for Inj.	Raf	Ovarian cancer	X	X	X		
IV Infusion	Sol. for Inj.	DNA MeTase	Cancer	X	X	X		
Oral	Tablets	TNF-a	RA	X	X			
Topical	Cream	TNF-a	Psoriasis	X	X	X		
SQ	Sol. for Inj.,	PTP-1B	Diabetes	X	X			
Intravitreal	Sol. for Inj.	c-raf	Diabetic Retinopathy,	X	X			
Pulmonary	Aerosol	Aden A1 R	Asthma	X	X			
Parenteral	Stent	c-myc	Cardiovascular Restenosis	X	X	X		

X = 1st Generation Chemistry
X = 2nd Generation Chemistry

Figure 1. Developmental Progress of Antisense Therapeutics

Focus on Consumer and Diversified Products

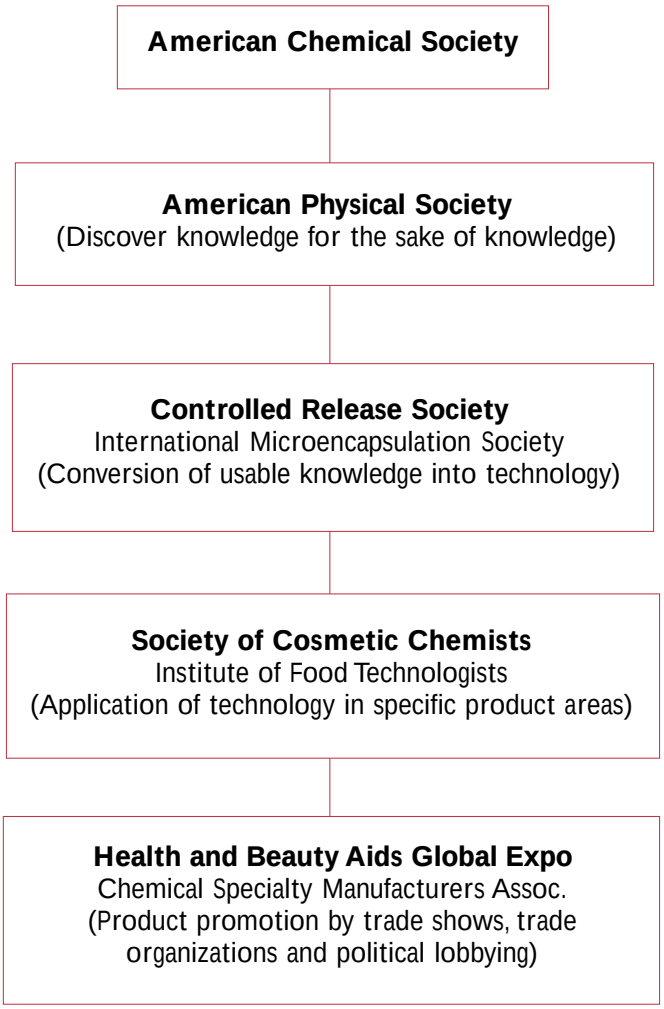
The "Orphan Products" Gang

By Ron Versic

We're actually the Consumer and Diversified Products sub-Committee of the CRS, or C&DP. A few years ago, one of our members kindly referred to us as the committee of "orphan products." Why?

We're the folks that bring you carbonless paper, Scratch'n'Sniff fragrances, visual effects in cosmetics and the Orkin Man. Yes, he uses time released pesticides with lovely names like Kill Master Two® and Knox Out®. He's been to your house—right?

How did we get into the CRS and why do we think we belong here? Actually, the friendly pesticide folks started the CRS. As recently as 1983, the CRS's 10th anniversary, 9 out of the 23 sessions were organized by the predecessors of C&DP. That's 38%. The percentage continued to decline until C&DP was reactivated within the CRS in the mid-1990s.



To see how C&DP fits into the CRS, and why we're a little different from the pharmaceuticals folks, please take a look at the hierarchy (flow) chart.

The chart shows the flow of knowledge into technology, then into products and finally into product marketing. Each of the organizations in the hierarchy has its proper and reasonably well defined role in the process. This is the way new products get to market by converting knowledge (information intelligently organized) into the technology that produces "8-hour relief," "30-day guarantee" and "long lasting."
This author's observation is that the pharmaceutical folks tend to cluster around the top two levels of the hierarchy and the C&DP folks tend to cluster around the middle two. That overlap at level two in the hierarchy brings us together. Such generalizations are often bad, but take a look sometime at the poster sessions and abstracts. The academics and students associate with the pharmaceuticals and the industry people associate with the C&DP. And, everyone seems to avoid the lowest level of the hierarchy — political lobbying, ugh!

None of this is right-or-wrong, good-or-bad. It just shows some differences. Fortunately, we all belong to and fit well within the CRS. There is a sameness and a valuable learning process going on here. For some reason there is the perception within the C&DP community that the pharmaceutical folks are much better funded and consequently they generate and exploit better the knowledge from the top tier organizations in the hierarchy. The C&DP folks often attend the CRS with the aim of converting the controlled release technology from pharmaceuticals to C&DPs. It has actually happened both ways: ethylcellulose microencapsulation for polar liquids and for potassium chloride; and, water based gels for drugs and room fresheners.

Such are the opinions of the author, which in no way express the opinions of anyone else. But now you may know how C&DP got here, what we're doing, and where we are going. ●

Editor's note: The author has been a CRS member since 1986, and recently organized a Workshop on C&DP in San Diego, designed to convert all those pharmaceutical folks into formulators of toothpaste, eye shadow and packaged foods.

(Scientifically Speaking
continued from page 5)

oligonucleotide dose, in fact, we see the highest oligonucleotide concentrations in liver and kidneys but not the lung and cardiac muscle. This data suggests that there is more than just perfusion directing accumulation.

Rapid clearance from plasma without much excretion in urine and feces suggests that oligonucleotides rapidly and broadly distribute to tissues. This clearance for plasma is non-linear, slowing as dose increases. This data suggests that at least some portion(s) of this pathway are saturable (Figs. 2a & 2b). Indeed, studies of increasing doses in rats show distribution of phosphorothioate oligonucleotides between organs, cells, and even within cells, that changes with dose (Geary 1997; Graham 1998; Lorenz 2000). Plasma concentrations of oligonucleotide can be measured days or weeks after a dose indicating that, after distribution, an equilibrium between plasma and tissue is established.

This equilibrium provides the long terminal phase seen in the plasma concentration-time profile (Fig. 3). The estimated terminal elimination rates in plasma correlate well with rates of elimination from whole tissue. When reasonable (non-saturating doses) are utilized *in vivo*, we can find evidence that tissue elimination rate is directly correlated with pharmacodynamic response (Zhang 2000; Yu 2001). Understanding these dynamics and the fortunate situation that laboratory animals predict these behaviors in man, allows accurate assignment of clinical dosing regimens (Fig.4).

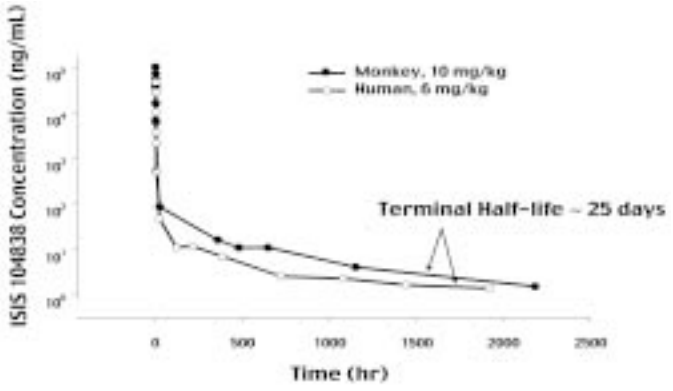


Figure 3. Comparison of Terminal Elimination of 2'-'MOE

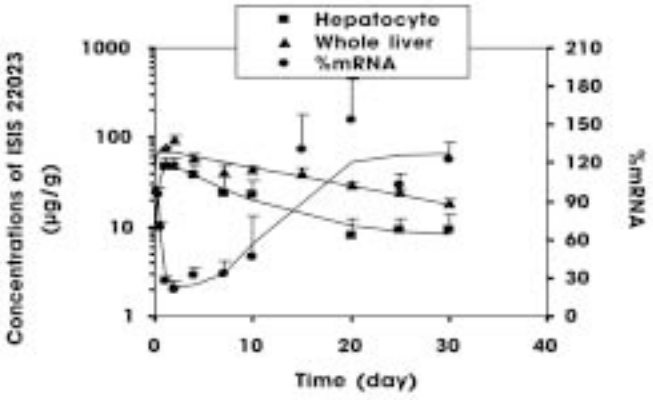
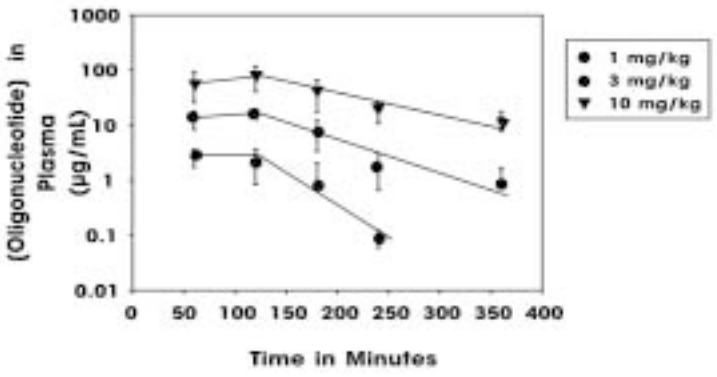
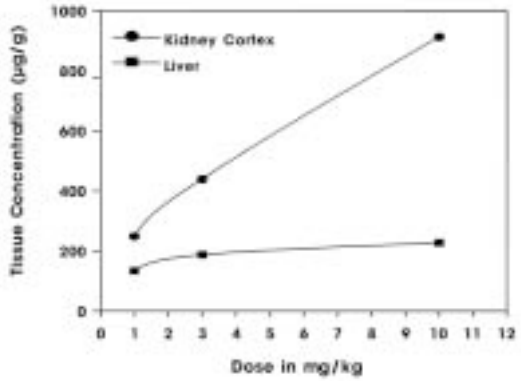


Figure 4. PK/PD correlation indicates the importance of oligonucleotide concentration in the cell and its duration of action over time.





Figures 2a and 2b. Nonlinearity in Plasma Pharmacokinetics are a Reflection of Saturable Distribution Pathways

Cellular Uptake

Based largely on *in vitro* data, multiple mechanisms of cellular uptake have been described for oligonucleotides. Both energy dependant and non-energy dependant uptake have been demonstrated in cell culture, and further, these have been shown to differentially predominate according to cell type. A substantial body of evidence teaches us that cell uptake *in vivo* is different from cell uptake *in vitro*. Certainly from the quantitative point-of-view, little is understood at this time about the relative contributions of these various mechanisms to total *in vivo* cellular uptake. For example, it has been postulated that cellular uptake in kidney and liver may be a function of scavenger receptor binding and uptake. However, scavenger receptor knock-out mice exhibit nearly equivalent kidney and liver uptake as normal mice (Butler 1999).

Recently an alternative mechanism for cell uptake has been proposed. It is postulated that cellular uptake may be a function of a protein binding "shuttle" that is consistent with the non-sequence dependent, non-specific protein binding characteristics of oligonucleotides. Further, that oligonucleotides transfer to higher-affinity proteins down an affinity gradient providing passage across lipoidal membranes using membrane bound proteins to shuttle oligonucleotide to intracellular proteins and ultimately, the highest affinity binding site – the cognate mRNA (Lorenz 2000). Several papers provide preliminary evidence for the

(continued on page 8)

Report on the FDD/CRSNZ Conference

By Nigel Davies

The first conference of the New Zealand Chapter of the Controlled Release Society was held in conjunction with the Fourth Annual Formulation and Drug Delivery conference held in Dunedin, in February 2001. The University of Otago through its emerging research theme of Formulations and Drug Delivery and the Controlled Release Society primarily sponsored the conference. 80 participants from academia, industry and Crown Research Institutes attended the two-day symposium. The Scientific Programme consisted of 14 invited lectures from national and international speakers, 5 submitted presentations and a poster session. Talks were divided between 6 sessions entitled Formulation and Delivery of Vaccines, Particulate Delivery Systems, Controlled Release of Bioactives, New Markets/Product Development and Advanced Formulation Technologies and Submitted Papers. The CRS sponsored invited speaker was Dr. Phil Green from BD Medical Systems who gave two talks relating to Vaccine delivery and the need for new delivery systems. Other international invited speakers were Dr. Bill Thiel of the Victorian College of Pharmacy, Monash University, Australia, who discussed his experiences on the development of a pulsatile release veterinary implant for antigen delivery; Dr. Greg Russell-Jones of Biotech Australia who talked on the use of vitamin B12 to improve the oral absorption of peptides and proteins; Dr. Elke Walter of the Swiss Federal Institute of Technology who talked on microparticle-mediated transfection of non-phagocytic cells; Prof. Meir Bialer of the Hebrew University Jerusalem who discussed new criteria for bioequivalence evaluation of controlled release products; and Prof. Wang of Nanjing Pharmaceutical University who outlined current developments in Pharmaceuticals in China. The annual meeting of the New Zealand Chapter of the Controlled Release Society was held at the end of the first day where it was decided to retain the existing committee for a further year. ●

Editor's Note: The New Zealand Local Chapter is featured on the CRS Global Community web page. To learn more about this exciting chapter, visit www.controlledrelease.org/global/index.htm.

(Scientifically Speaking... continued from page 7)

cellular uptake described by this model through the identification of non-specific, cell surface binding proteins in the 30-80 kDa range (Loke 1989; Hawley1996). Other evidence suggests that each cell type may have its own mix of mechanisms for uptake, some pinocytotic dominant and others shuttle dominant (Fig. 5). It is important to note here that cell uptake appears to be sequence independent until the final binding to the target mRNA.

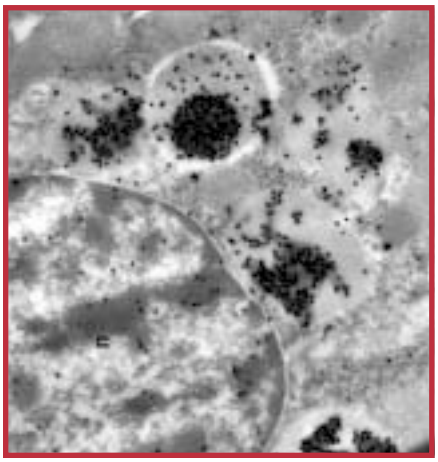


Figure 5. Electron photomicrograph of rat kidney (Proximal tubule) 24-hr post dose showing (gold immunostained) endosomal and cytoplasmic distribution of a deoxy-phosphorothioate oligonucleotide.

Delivery Strategies

Modulating Whole Body Distribution

Altering distribution and optimizing delivery to target tissues has been pursued along three lines: altering the chemical structure of the oligonucleotide, non-covalently associated formulations and changes in route of administration. Over the past decade, a wide variety of modifications to the basic DNA structure have been made in order to produce effective antisense molecules (Fig. 6). Of these, the best-studied are the phosphorothioate oligodeoxynucleotides and RNA/DNA

(continued on page 9)

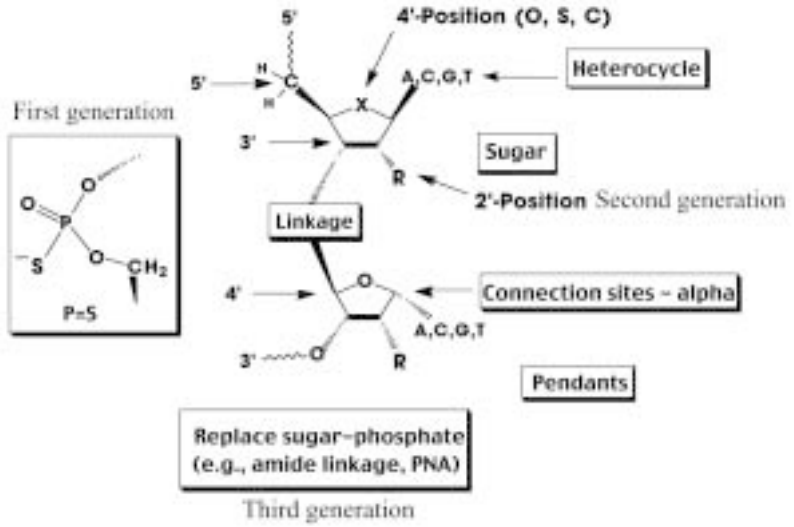


Figure 6. Medicinal Chemistry is being used to modify oligonucleotides at various sites, typically the backbone and/or the sugar to alter the native biological stability and trafficking patterns.

(Scientifically Speaking continued from page 8)

chimeras. The latter are attractive since they have greater *in vivo* stability and higher binding affinities to mRNA than the deoxyphosphorothioates, and importantly, maintain RNaseH activity for the intended destruction of the target mRNA. Also, they appear to follow the same rules of shuttling and distribution established for the phosphorothioate oligodeoxynucleotides. The critical factor in tissue delivery and uptake for both of these antisense chemistries is the nonspecific protein binding to both the plasma and cellular proteins. This binding has the end result of the avoidance of renal clearance and therefore efficient delivery to peripheral tissues (Geary 2001). On the other hand, preclinical data for oligonucleotides that have been modified to reduce sulfur in the backbone (e.g., phosphodiester chimeras) show significant decreases in plasma protein binding, increases in urinary excretion leading to decreased distribution to tissue and, as a matter of course, cells.

Formulation targeting that achieves gross alteration in whole body distribution by passive means has been achieved by liposomal encapsulation of oligonucleotides. The increased circulation times of these materials and the leaky vasculatures associated with infection, inflammation and certain tumor physiologies are considered to be factors that facilitate accumulation at these sites. For example, liposome-encapsulated and unencapsulated ISIS-2503, a 20-mer-phosphorothioate oligodeoxynucleotide directed to Ha-ras, was administered to rhesus monkeys by intravenous infusion (Yu 1999). The plasma and tissue concentrations of oligonucleotide demonstrate that Stealth® liposomes protect the oligonucleotide from nucleases in blood and tissues, slow tissue uptake, and slow the rate of clearance from the systemic circulation. The same formulation administered in the rat, tumor-xenograft model showed an approximate 4-fold increase in the amount of intact drug in the whole tumor. This accumulation was correlated with the amount and duration of tumor growth suppression (Figure 8). Presumably upon distribution to the

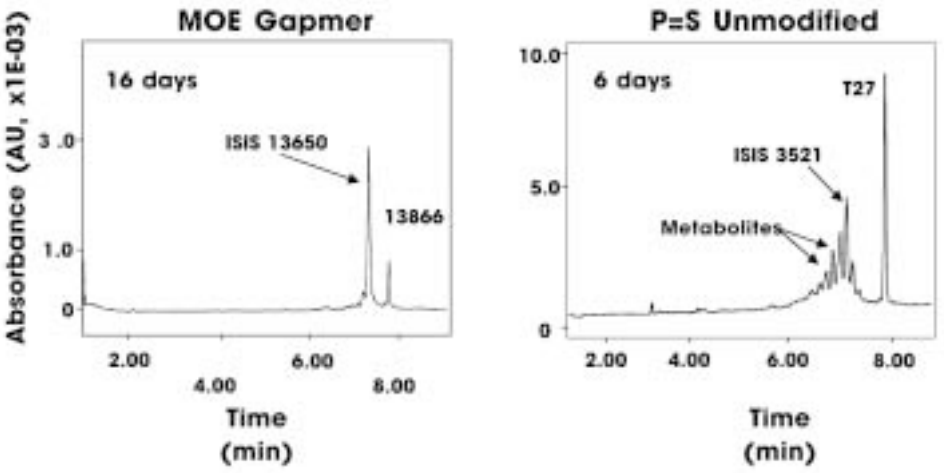


Figure 7. Capillary Gel Electrophoresis Illustrates the Relative Stability of Modified Oligonucleotides

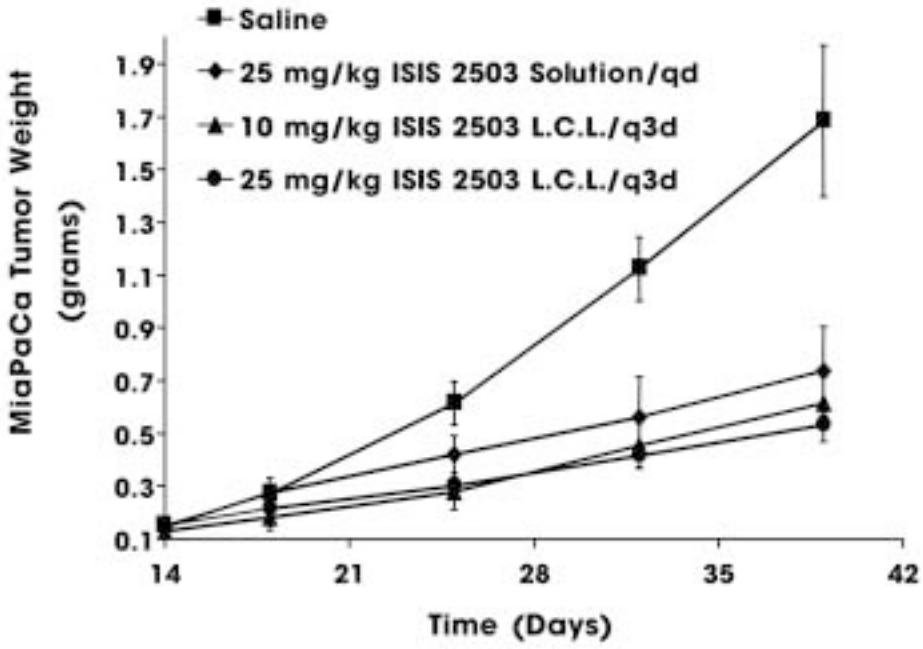


Figure 8. Suppression of tumor xenograft growth correlates with whole organ accumulation (deoxy phosphorothioate).

tumor, the oligonucleotide was released from the liposome to the extracellular matrix where it entered the uptake pathways described earlier.

Modulating Cellular Trafficking

Depending on the mechanism of uptake, oligonucleotide may be found either associated with protein in the cytosol or enclosed within an endosomal compartment where it may encounter conditions that increase the likelihood of degradation by depurination or nuclease digestion. In one example, facilitating endosomal escape with specifically designed formulations greatly enhanced gene knockdown in macrophages (Mathew 2000). Admittedly the relative importance of endosomal escape *in vivo* remains to be determined; however, facilitating release of oligonucleotide through formulation or chemical modifications remains an interesting approach.

(continued on page 28)

awardingexcellence

Henry Brem and Alejandro Zafforoni

Robert Gurny

Jeffrey L. Cleland

Saghir Akhtar

The Controlled Release Society was proud to present *Awarding Excellence* at the 28th International Symposium on Controlled Release of Bioactive Materials, June 23 – 27, 2001, in San Diego, California. The following is the impressive list of the 2001 award winners. Congratulations to all and good luck to everyone in Seoul, Korea, 2002 where we will present the award winners in a new and electrifying format! Stay tuned for more details in future issues of this newsletter.

Founders

Henry Brem from Johns Hopkins University was presented the 2001 Founders Award, the Society's most prestigious award, for his outstanding contributions in the science and technology of controlled release. Henry was presented a crystal award, $10,000 and grant-in-aid to attend the San Diego symposium. The award was sponsored by CRS and ALZA.

Nagai Innovation

Alejandro Zafforoni, who founded the ALZA Corporation, was awarded the 2001 CRS-Nagai Innovation Award for his exceptional contribution of a successful and innovative controlled release product or technology. Alejandro was presented a silver struck medal, $3,000 and grant-in-aid to attend the San Diego symposium.

Distinguished Service

Robert Gurny from the University of Geneva was presented the 2001 Distinguished Service Award for his long-standing exceptional commitment and service to the Controlled Release Society. Robert received a global award, $3,000 and grant-in-aid to attend the San Diego symposium.

Young Investigator

Jeffrey L. Cleland from Genentech and Saghir Akhtar from Kuweit University were awarded the 2001 CRS Young Investigator Award for their outstanding research contributions for a younger member of the Society. Jeffrey and Saghir were each presented a silver-struck medal, $1,000 and grant-in-aid to attend the San Diego symposium.

Eurand

Four awards were given out for outstanding contributions relating to novel approaches in oral drug delivery. All winners received special plaques, award checks and grant-in-aid expenses to attend the San Diego symposium.

Ranier H. Muller from the Free University of Berlin was awarded the 2001 Eurand Career Achievement in Drug Delivery Awards. Jean Paul Remon from Ghent University was awarded the 2001 Eurand Senior Prize. Isidora Caraballo from the University of Seville, and Fabiana Quaglia from the University of Naples were awarded the 2001 Eurand Junior Prize.

Capsugel

Farid A. Dorkoosh, Keiji Itaka, Maryellen Sandor and Jun Wang were winners of the 2001 CRS-Capsugel Graduate/PostDoc Award on their research of Innovative Aspects of Gastrointestinal Drug Absorption. Maryellen Sandor from Brown University was selected as the final winner. She was presented a plaque, $1,000, travel expenses, and grant-in-aid to attend the San Diego symposium.

Jorge Heller

Elka Touitou from the Hebrew University of Jerusalem, was awarded the 2001 Jorge Heller *Journal of Controlled Release* Outstanding Paper Award. Elka was presented a plaque, $1,000 and grant-in-aid to attend the San Diego symposium. The award was sponsored by CRS and Elsevier Science, B.V.

Outstanding Papers

Karin Kellner from the University of Regensburg was awarded a 2000 Graduate Student Paper Award. Karin was presented a plaque and grant-in-aid to attend the San Diego symposium. CRS and 3M Drug Delivery Systems sponsored this year's award.

Scott Sershen from Rice University was awarded a 2000 Graduate Student Paper Award. Scott was presented a plaque and grant-in-aid to attend the San Diego symposium. CRS and Cyngus sponsored this year's award.

Ronald A. Siegel, from the University of Minnesota, was awarded the 2000 Outstanding Pharmaceutical Paper Award. Ron was presented a plaque and grant-in-aid to attend the San Diego symposium. CRS and Ethypharm sponsored this year's award.

Leonid Margulis from Pfizer Global Research and Development was awarded the 2000 Outstanding Veterinary Paper Award. Leonid was presented a plaque and grant-in-aid to attend the San Diego symposium. CRS and Thorn BioScience sponsored this year's award.

Ranier Helmut Muller, Domineik Henrist for Jean Paul Remon, John Fraher of Eurand, Fabiana Quaglia, and Isidora Caraballo

Farid A. Dorkoosh

Keiji Itaka

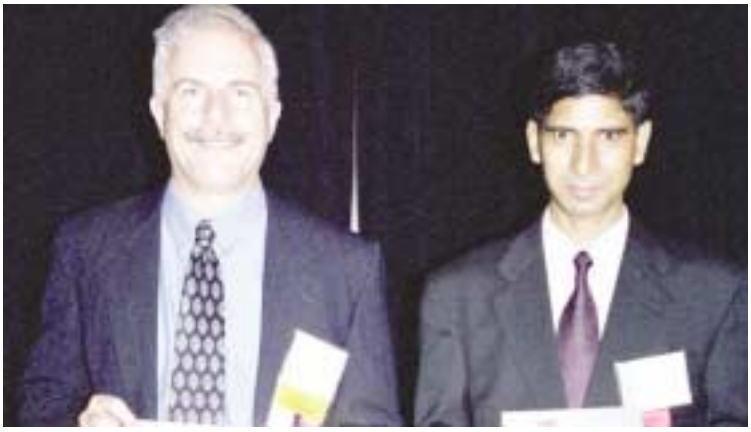
Roland Daumesnil from Capsugel & Maryellen Sandor

Jun Wang

Karin Kellner

Scott Sershen & Jennifer West

Nava Dayan & Elka Touitou



Ronald A. Siegel & Gerry Misra

Leonid Margulis & Richard Darrington

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Gold Level

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Donors

InterAg

3M Drug Delivery Systems

Aquaculture Pharmaceuticals and Biologicals

By Zezhi J. Shao

Although there are over 100 aquatic species being cultured worldwide, the development and commercialization of new medicines for the treatment of aquatic diseases are rather scarce. Officially, there are only five FDA approved products available for use in the finfish and shellfish industry to-date. This situation is contributed by a variety of factors ranging from lack of sponsor interest, concern over environmental impact from new chemical entities, and the relatively small market of aquaculture products (typically less than $25 million U.S.). Like many other animal-farming industries, the aquaculture field is further species-diversified into the culture of shrimps, samonids (Atlantic salmon, Rainbow trout), flat-fish, carp, shellfish (mussels and oysters), as well as ornamental fish. Targeting each potential species requires individualized field trials for that species, typically at multiple sites. Such trial runs, coupled with product development programs, are cost-prohibitive for most pharmaceutical companies.

The very nature of intensive farming practice, as well of disease-causing pathogens, contributes to the morbidity and mortality of farmed fish. Common fish diseases include non-infectious diseases (i.e., gas-bubble disease), infectious diseases (causes by bacteria, parasites, and viruses), and stress-mediated infections (opportunistic pathogen invasion). A notorious bacterial pathogen in the salmon industry is *Aeromonas salmonicida* which causes a severe septicemic disease, furunculosis. A common challenge with antibacterial treatment of such a disease is the formation of causative resistant bacteria, which re-infect healthy fish.

To combat various fish diseases, a two-prong approach is currently employed by the aquaculture industry, i.e., pharmaceutical agents and biological vaccines, with the latter being a more cost-effective measure. The primary means of drug administration include water treatment, incorporation in feed (medicated feed), and by injection. Commonly used pharmaceutical agents include anesthetic agents (tricaine methanesulfonate, benzocaine, AQUI-S, sodium pentobarbital, etc.) and chemotherapeutic agents (oxytetracycline, sulfadimethoxine/ormetoprim, formalin, sulfamerazine, etc.).

Premix represents a typical aquaculture pharmaceutical product and the successful development of which containing a novel chemical entity has unique challenges for formulators and analysts alike. Ph. Eur. contains a separate monograph on premixes for medicated feedingstuffs for veterinary use; and therefore premixes are considered a separate pharmaceutical entity from powders/granules for other uses. A good premix product must possess elegant physical characteristics (free-flowing, dust free, no segregation) and superb chemical stability. However, an elegant and stable premix is only a job-half-done, because in many countries a premix and its medicated feed require separate registration. Additional work on the medicated feedingstuffs can be demanding and include the demonstration of mixing/coating homogeneity, compatibility with typical feed ingredients, stability of the medicated feed, and the absence of segregation of the active from feed upon shipping/vibration.

Efforts in the early 1970s led to the development of fish vaccines against several bacterial strains, i.e., *V. anguillarum*, *A. salmonicida*, *V. salmonicida*, *V. ordalii*, etc. Adjuvants such as aluminum salts, glucan, and mineral oil are used in the vaccine formulations to improve their potency. A number of these vaccines can be given via the immersion method, which lends to their popularity. Anti-viral vaccines, on the other hand, are more challenging to develop since attenuated or avirulent forms of the virus is regarded as unacceptable due to residual virulence. The recent advancement in recombinant DNA technology, however, has made it possible to overcome this hurdle, as evidenced by the availability of an anti-IPN (infectious pancreatic necrosis) vaccine in Norway.

As for the future, research efforts are being focused on the oral delivery of vaccines through the formulation of biodegradable microspheres and enteric-coated beads. In addition, the extension of new drug delivery and processing technologies to the aquaculture formulation arena will undoubtedly result in safer and more efficacious pharmaceutical and biological products in the future.●

patentwatch: Transdermal Update

By Agis Kydonieus and Tapash K. Ghosh

In the year 2000 there were 296 pertinent patents/patent applications published, although there could be substantial duplication due to the fact that the patents we obtained were from several patent offices. There were 62 US patents, 121 PCT/WO, 10 EP, 43 Japanese, 47 German and 13 other. So there is an upswing in patent activity, with the total number being the highest since 1993, the year that I started recording patent activity. Lohmann had the highest number of patents (39) as it did in 1999 and 1998 and they were mainly in the area of device development. Following Lohmann were Hisamitsu (21) mainly in iontophoresis, Alza (18), Cygnus/J&J (11), Nitto (11), Sekisui (7), 3M (6), R&R Ventures (5), Watson (4) and Noven (4).

The breakdown according to categories was methods (196), enhancers (49), iontophoresis (44), and irritants/countersensitizers (7). The methods patents were broken down into two categories, devices (128) and applications (68). The device patents have inventive spirit in the method, component or process used to prepare the transdermal device. In the application, patents the inventive spirit is mainly the identification of a drug to be used transdermally in a therapeutic application. No real enhancer system or device innovations are disclosed in these applications.

Despite the great patent activity, no new chemical entities were approved in 2000 as drugs in transdermal form. No new information was obtained on transdermal products already being developed, e.g., buspirone, ritalin, and insulin. The Becton Dickinson transdermal group was sold and is now operating under the name Vyteris. 3M announced that it completed phase I clinical trials with testosterone and signed an agreement with Purdue Pharma to develop a fentanyl patch. At the end of the year, there were four transdermal products awaiting approval in the U.S. An estradiol/progesterone patch from Watson (additional endometrial protection trial needed), and an estradiol/norethindrone acetate patch (Estralis) from Noven, both for control of postmenopausal vasomotor symptoms. A third patch containing ethinyl estradiol and norelgestromin (Ortho Evra) developed by Cygnus/Ortho is awaiting FDA approval for contraception. The fourth product is an iontophoretic patch (E-trans Fentanyl) developed by Alza/Crescendo for the control of breakthrough pain.

Listed below some of the more interesting patents are discussed.

COUNTERSENSITIZERS/ANTI-IRRITANTS

Iontophoretic delivery to control adverse side effects (Novartis) US6018679
Irritation and other harmful effects are eliminated for drugs and other ingredients which form a depot in the skin after iontophoretic or passive delivery. The process involves a reverse phase iontophoretic delivery to remove the irritants from the skin depot and into an electrode away from the skin. The process takes place after the passive or iontophoretic delivery of a drug is completed.

Dermatological composition to protect skin (Kramer) DE19725405A
A dermatological formulation containing thiocyanate and urea is claimed for promoting the defense mechanism of the skin against physical and chemical irritations. It is claimed that the formulation not only prevents skin damage but also aids in the healing and repair process.
Interlenkin-4 production inhibitors (Kao Corp.) JP2000086529A
An interlenkin-4 (IL-4) production inhibitor is obtained as the steam distillate of Eucalyptus globulus myrtaceae. This IL-4 inhibitor is permeable through the skin and is stable and safe. It can be used as a skin external agent to prevent and remedy skin inflammation and allergic reactions.

ENHANCERS

Transdermal administration of cytokines (PharmaDerm Labs) US6165458
The permeation of a cytokine (peptides) is increased by covalently attaching to it at least one fatty acid moiety. The conjugate, e.g., interferon/fatty acid is shown to have substantially higher cutaneous permeation relative to the cytokine alone.

Transdermal delivery and analyte extraction (Elecsys Ldt) US6148232
A device for ablating the stratum corneum is described, which includes a plurality of electrodes which are attached to the skin. Applied energy through the electrodes, controlled by the magnitude of the current, the first time derivative of the current, and time, causes ablation of the stratum corneum, thus facilitating the passage of substance through the ablated area.

Device for enhancing transdermal permeation (Alza) US6083196, US6050988, WO9748442A, WO9748440A and WO9828037A
A device is claimed consisting of a sheet member having a plurality of microprotrusions extending from the bottom edge of the sheet, so as to be perpendicular to the skin and penetrate the skin when the device is applied onto the skin. The drug reservoir, on top of the sheet member, is incompressible so as to transmit the applied force and maintain the microprotrusions.

Combination of electric field with ultrasound (MIT) US6041253
The transport of drugs during sonophoresis can be further enhanced by treatment with iontophoresis or electroporation. This approach provides for higher fluxes with lower ultrasound intensities and better control of the flux, than when the ultrasound is applied in the absence of electric field.

Transdermal protein delivery with sonophoresis (MIT) US6018678
It is claimed that low frequency ultrasound (20 KHz) enhances transdermal administration of proteins and peptides. *In vitro* and *in vivo* tests with insulin (6000D), gamma interferon (17000D) and erythropoeiting (48000D) are shown.

Transdermal administration of high molecular weight drugs (American International Diagnostics) US6024975
A polymeric enhancer, polyvinylpyrrolidone at between 7 and 35% of the amount of drug is shown to increase the permeations of proteins and peptides (up to 25000D). The drug concentration is at least 15% by weight of the formulation and it includes such drugs as calcitonin and insulin.

Liposome transdermal delivery of proteins (Idea AG) US6165500
Amphiphilic liposomes (transfersomes) of specific minuscule droplet size are shown to penetrate through human skin and carry along proteins and peptides such as insulin. The lipid to surfactant ratio is critical in optimizing the rate of permeation of protein and other high molecular weight drugs, including insulin, prostaglandine E1 and hydrocortisone.

(continued on page 17)

Reflection, Nomination, Election

By Richard Guy

A dubious perk of being CRS' immediate past president is that one inherits the chairmanship of the Nominations Committee. Why dubious? Primarily because the participation of all but a few individuals in the nomination process has been sadly the norm, which has meant that the chair must work quite hard to generate the list of candidates necessary for next year's slate. Secondarily because, as a result of point number one, the chair is often the brunt of criticisms relating to 'clique mentality', favoritism, and frank stupidity (as in "how could you have possibly nominated so-and-so?").

So, with a view to reversing these characteristics, I am taking the opportunity of this Newsletter to broadcast a general appeal to the membership to reflect on what you would like to see in your officers, to nominate the names of individuals whom you believe will serve the needs of CRS's membership and, most importantly, to vote and elect the next generation of leadership. I would point out, if you decline to participate in the democratic process in this way, that it is hardly "cricket" to subsequently complain if the newly elected representatives are not to your taste.

The Nominations Committee therefore actively solicits your input and welcomes all suggestions, whenever possible supported by some persuasive justification for your proposals. This year, we need to fill the post of Vice-President (i.e., an individual who will be President in 2004-05) and to elect three members of the Board of Scientific Advisors (one from Europe, 2 from North America).

I look forward to your input and I promise that the Committee will consider carefully and fairly all suggestions received. Thanks.

Nominations may be forwarded to Richard Guy (richard.guy@pharm.unige.ch). Deadline for nominations is November 5, 2001.

statisticallyspeaking

2001 Symposium & Workshop in Review

By Paul M. Stone

The 28th International Symposium on Controlled Release of Bioactive Materials in San Diego, California was a hugely successful event for CRS. We had a record 2,000 attendees, but this is just one of the mind boggling numbers from the 2001 event--and it really was an event. The following are some telling numbers which depict the impressive size and scope of CRS.

35%	More attendees than the previous record
2,100	Contributing abstract authors
400	Multiple abstract authors
690	Poster Sessions
96	Podium Presenters
86	Poster Picks
315	Workshop Attendees
320	Soapbox Attendees
105	Exhibit Booths

Incredible science resulted in record breaking attendance at the Symposium.

These numbers tell nothing of the high quality of science that was presented, which was the most significant reason for the monumental increase in attendance. If you didn't attend, you not only missed the incredible science but also the countless new friends and networking opportunities. There isn't a number big enough to measure the value of these relationships. The Society's future events in Seoul, 2002 and Glasgow, 2003 promise more of the same. ●

Rise in Litigation

A dramatic increase in clinical trials is being closely paralleled by a rise in litigious claims that have the industry re-examining its policies and procedures for testing new drugs and treatments. "Heightened scrutiny of clinical research practices, from both oversight agencies and the industry itself, comes at a time when clinical trials are growing dramatically in number and complexity," said Jill Wadlund, life sciences casual manager at Chubb & Sons, Chubb Group Insurance Companies. Sponsors of clinical research face a wide range of ethical and regulatory considerations as they conduct trials overseas, employ new methods to recruit volunteers, and enter into close financial relationships with researchers. All these factors leave researchers who neglect the safety of participants vulnerable to significant risks and potential liabilities.

Though the confidential nature of legal records makes it hard to quantify the precise extent of this litigation trend, Wadlund said several high-profile lawsuits from Pennsylvania to Seattle make it clear that legal activity in the field is growing. "The biotech industry is well aware of its rapidly increasing economic and social significance, and well aware that a potential crush of litigation could darken its bright future fairly quickly," said Leslie A. Pratt, principal and leader of the Health Sciences Research Compliance Group at Ernst & Young.

Platt and Wadlund agree there are several preventative steps biotechnology companies can take, including:

- Adopting best practice standards for all research regulatory requirements, ranging from conflicts of interest and informed consent to good clinical practices, ensuring organizational compliance that continually exceeds the minimum federal standards;
- Creating an integrated compliance system based on best practice compliance;
- Responding rapidly to all compliance issues with effective measures to resolve problems on a system-wide basis;
- Making continuous compliance improvements based on benchmarking and measurement to best practice goals; and
- Utilizing best practice compliance to enhance organizational value, leading to higher intellectual property value and more research funding. ●

(Patent Watch
continued from page 15)

Transdermal delivery of testosterone (3M) US6132760
A matrix pressure sensitive adhesive is presented containing testosterone and an enhancer comprising a terpene and a fatty acid derivative. Terpenes disclosed include alpha terpineal, pinene, d-limonene, carveal, menthone, menthol, citral and others.

Transdermal administration of calcium channel blockers (U of Rhode Island) US6106856
Transdermal formulations containing dihydropyridine calcium antagonists (calcium channel blockers) such as nifedipine, nimodipine and nitrendipine are described. These agents are dispersed 1-20%, in a liquid composition containing 0.1 to 50% cis-oleic acid, 0.1 to 97% dimethylisosorbide dispersed in a propylene glycol base.

IONTOPHORESIS

Iontophoretic device with a membrane electrode assembly (Sanofi) US6064908
A standard iontophoretic device is described with a donor electrode, a counter electrode and a generator of electricity. The donor electrode, however, is composed of two elements, the primary electrode containing the active principle and a second reservoir element containing a neutral electrolyte. The two elements are separated by a dicarboxylic polyamide polymer membrane with MW up to 300,000D, containing 35-90% by weight polyamide sequences, and being selectively permeable to molecules of sizes smaller than a chosen threshold. The device improves the efficiency of drug delivery.

Liposomal delivery by iontophoresis (BioZone Labs) US6048545
The method claimed delivers drugs that are encapsulated in unilamellar, multilamellar or multivesicular liposomes. The liposomes are applied directly to the skin and iontophoretic delivery (1 to 3 milliamperes) is initiated and lasting from 1 to 15 minutes. The anesthetic lidocaine is shown as the drug of choice.

Sequential iontophoretic delivery (Novartis) US6032073
An iontophoretic system for the administration of at least two drugs is disclosed. The reservoir comprises a drug storage layer and a transfer means, which is arranged in the form of a separating layer connected to both the reservoir and the skin. Physical separation of the drugs are provided that render possible sequential administration.

Intraocular iontophoretic delivery (Optisinvest) US6154671
The device contains a drug reservoir with an electrode facing the eye tissue lying at the periphery of the cornea. The return electrode is placed in the partly closed eyelid. The current density is less than 10 mA/cm^2 and the duration between half and ten minutes.

Iontophoretic delivery from drug suspension (U of Oklahoma) US6119036
A conducting silicone matrix is described incorporating a suspension of a drug in ionized and non-ionized phases in an emulsion of hydrophobic polymers, e.g., a concentrated aqueous suspension incorporated in a silicone matrix with a silicone surfactant. During iontophoresis the drug in individual globules concentrates in the distal site, increasing the concentration of drug near the skin. The device is current efficient and provides a drug reservoir that can last for several days.

Iontophoretic electrode structure (Hisamitsu) US6104951
An electrode structure is disclosed comprising both a polarization electrode and a non-polarization electrode, electrically insulated from each other, wherein the electrodes can be switched back and forth during iontophoresis. The preferred polarization electrode material is titanium (iron, aluminum, platinum, carbon), the preferred non-polarization material is silver/silver chloride (copper) and the insulating material is polyethylene terephthalate. The delivery of drugs is very effective without irritation.

Fail-safe iontophoretic system (Becton Dickinson) US6029083
An apparatus is disclosed able to send current through a patch, an error detection unit and a control circuit that controls the current generation. When errors are detected by the error detection unit, the control circuit stops the current and disables itself. The error detection unit is able to detect at least one of the following: low battery voltage, reference voltage failure, clock failure, current over-voltage, excess time-current product, expired patch installed and incorrect patch installed.

Iontophoretic delivery with dipeptide buffer (Alza) WO9924015A1
A formulation is provided comprising an aqueous solution of a drug and a dipeptide buffer comprising a polypeptide chain having an isoelectric pH at which the dipeptide carries no net charge. The dipeptide has a minimum of 2 pKa's which are within 3.5 pH units, and the pH of the solution is within 1 pH unit of the isoelectric pH. These buffers minimally compete with the drug for carrying electric charges, and they protect peptides and proteins (hGH) with minimum degradation.

Iontophoretic formulation with vasodilator (Drug Delivery Systems) EP555510A
An iontophoretic formulation is claimed containing a protein drug such as insulin and a second agent such as a vasodilator, which induces the skin to produce endogenous compounds to dilate the vascular system. This formulation allows the administration of insulin for an extended period of time without decay in the delivery rate, which is the case with other iontophoretic systems.

METHODS/DEVICES

Transdermal patch to prevent ovulation (Ortho) US6071531
Transdermal methods and formulations are described to prevent ovulation in women as well as to impart female hormone replacement therapy. The patch delivers 17-deacetyl norgestimate alone on in combination with ethinyl estradiol, in sufficient amount to prevent ovulation in women. An ethinyl estradiol/17-deacetyl norgestimate patch is presently awaiting approval at the FDA.

Electromagnetic injection device (Boehringer Mannheim) US6074360
A method for delivering drugs through skin is disclosed whereby forces by electromagnetic repulsion are generated which accelerate the payload (drug) to be injected at a velocity sufficient to inject the drug through the skin and into the subcutaneous tissue. An electromagnetic force generating device and a transdermal injection device are also claimed.

Enhancer tolerant pressure sensitive adhesive (National Starch) US6077527
A pressure sensitive adhesive for transdermal drug delivery is claimed which is tolerant to plasticization by skin penetration enhancers. The adhesive is an acrylic copolymer comprising a) 40% monomers with Tg of –90 to 0 ^{0}C, b) 0-15% monomers with Tg of 0 to 250 ^{0}C, C) 10-60% substituted acrylamides and methacrylamides, d) 0.2% monomers containing a reactive hydrogen and e) 0.01 to 2% of a chelated metal alkoxide crosslinker.

(continued on page 27)

Controlled Release Society in collaboration with the Korean Society for Biomaterials present

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Corporations interested in releasing their potential in the chemical and biological delivery market at the largest international conference dedicated to the advancement of medicinal, agricultural, veterinary, cosmetic, and household chemical and biological delivery systems are encouraged to contact CRS today. 2002 exposition is nearing sell-out status, so don't delay.

Abstract submission deadline is January 15, 2002

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Join researchers from more than 50 countries as they share timeline research in podium and poster sessions. The scientific program will feature mini-symposia focusing on drug delivery systems for cardiovascular, diabetic and neoplastic disease treatment and emerging fields of oral drug delivery (sponsored by Eurand). Scientific sessions will spotlight two tracks: (1) controlled release and delivery of bioactive materials, and (2) consumer and diversified products.

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onsored by the Society For Biomaterials, U.S.

the Japanese Society of Drug Delivery Systems

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Consumer and Diversified Products Track

Applications of Controlled Delivery in Food, Flavor and Nutraceuticals

Applications of Controlled Delivery in Personal Care and Diversified Products

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Smart Polymers and Innovative Materials

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WASHINGTON, DC — The American Pharmaceutical Association (APhA) has named Ronald T. Borchardt, PhD, editor of the *Journal of Pharmaceutical Sciences (J Pharm Sci)*. Borchardt succeeds William I. Higuchi, PhD, who is stepping down after more than seven years as editor. The appointment becomes effective as of July 1, 2001.

"Having a scientist of Ron Borchardt s stature at the helm of *J Pharm Sci* gives APhA great confidence that the journal will remain the premier international journal of the pharmaceutical sciences," said John A. Gans, PharmD, Executive Vice President of APhA.

The several month selection process leading to the appointment of Borchardt involved input from more than 50 individual pharmaceutical scientists worldwide as well as from APhA s Academy of Pharmaceutical Research and Science, the Publications Board of the American Association of Pharmaceutical Scientists, and the Board of Pharmaceutical Sciences of the International Pharmaceutical Federation.

Borchardt is the Solon E. Summerfield Distinguished Professor of Pharmaceutical Chemistry at the University of Kansas, in Lawrence, Kansas. He was awarded a bachelor of science in pharmacy by the University of Wisconsin — Madison in 1967. After receiving his PhD in medicinal chemistry in 1970 from the University of Kansas — Lawrence and pursuing postdoctoral training at the National Institutes of Health, Borchardt joined the faculty at the University of Kansas — Lawrence in 1971 and has remained there ever since. From 1983 — 1998, he served as the Chairman of the Department of Pharmaceutical Chemistry.

During his academic career, Borchardt has received numerous awards and honors for his teaching and research. Last March at APhA s 148th Annual Meeting and Exposition in San Francisco he received APhA s Research Achievement Award in the Pharmaceutical Sciences. He received the Distinguished Pharmaceutical Scientist Award from the American Association of Pharmaceutical Scientists in 1997, the Volwiler Research Achievement Award from the American Association of Colleges of Pharmacy in 1998, the Host-Madsen Metal from the International Pharmaceutical Federation in 1999, and the Millennial Pharmaceutical Scientist Award from the International Pharmaceutical Federation in 2000.

Borchardt is the author or coauthor of 450 scientific publications and 410 abstracts, and he has held editorial appointments on several peer-reviewed journals. Before his appointment as editor of *J Pharm Sci*, he served as one of the journal s associate editors. In addition, he is the current president of the American Association of Pharmaceutical Scientists.

J Pharm Sci was launched by APhA in 1912. Borchardt becomes the 13th editor of the journal. *J Pharm Sci* was published until 1940 as the *Journal of the American Pharmaceutical Association* and then, through 1960, as the *Journal of the American Pharmaceutical Association, Scientific Edition*. John Wiley and Sons has published the journal on behalf of APhA since January 2000. The online edition of *J Pharm Sci* is available via Wiley InterScience at http://www3.interscience.wiley.com.

Journal of
Pharmaceutical Sciences

ON THE LEADING EDGE OF PHARMACEUTICAL RESEARCH...

membersrelease:
Strategic Governance

By Rosealee Lee

Dedicated leadership is integral to the future of CRS. The responsibility of that leadership is ultimately up to you, the members of CRS. That's a tough job, given our global expanse and multi-disciplinary nature. As evidenced by the strong history of CRS leadership, it's also a job that you as members have taken very seriously. So it is with great respect that I am taking this opportunity to thank you for your dedication, thoughtful nomination and selection of CRS leaders.

The recent June annual meeting in San Diego marked the end of the 2000-2001 governing year. The year will be remembered as one of great change and growth. On behalf of all CRS members, thanks to Richard Guy who expertly steered us through the year as president. June was also time to bid "au revoir" to Robert Gurny who guided CRS for many years, most recently as Scientific Secretary from 1987 to 2000. Thanks also to Susan Cady who in June completed her first term as Treasurer. Her commitment to CRS is so great that she chose to stand for election a second term, and won. Finally, thanks to the Board of Scientific Advisors (BSA) members who completed their term on that distinguished board in June. We are grateful to Jean-Pierre Benoit, Jeffrey Cleland, Lisbeth Illum, Kazunori Katoaka, Abraham Rubenstein and Ian Tucker for the energy they gave CRS during their three-year term as BSAers. The 2001-2002 governing year has begun, and newly-elected leaders have assumed their positions. Kinam Park, the new president of CRS is aiming the Society at the future expertly and is dedicated to refining the strategies that will ensure relevancy of our society to its members. James Anderson joined the Board of Directors as Vice-president. His insights and leadership skills are a great addition to the CRS board. Joseph Fix joined the Board of Directors as Member-at-large. Joe is already hard at work. His industrial perspective lends keen insight to issues that the board will face in the coming years.

The BSA welcomed its newly-elected members listed at right in July. At the July BSA meeting, BSAers accepted the challenge of increased involvement in CRS committees and opinion polls throughout the year, reviewed and refined the feedback on CRS's future that had been recruited from current and past CRS leaders. This important session laid the groundwork for a new CRS strategic plan.

Thank you to the many members who have given feedback relative to CRS goals and initiatives. Please continue to contact Paul Stone or me with your insights and frank discussion. The benefit that you gain from being a CRS member, like anything else in life, accrues in direct proportion to your level of involvement.

So members, we've only just begun the new year and already I am asking for your involvement. Read Richard Guy's (now Nominations Committee Chair) article on page 16 and nominate individuals for leadership positions in the 2002-2003 governing year.

Strategic governance is at the core of CRS initiative, and connecting your day to day professional needs with the goals and future of CRS is the next challenge The Board of Directors will meet later this year to develop a new strategic plan. Board members will be guided by input from individual members, the BSA and CRS committees. They will be answering tough questions and working to ensure the future of the controlled release and development community. Take a moment to be involved in this dynamic strategic planning process by visiting the web site at www.controlledrelease.org/releasing/ and let the Board of Directors know the challenges you face in performance of your job and development of your career. This input will ensure that the strategic plan that is developed will be relevant to your future.•

Richard Guy turns the presidential gavel over to Kinam Park.

Kinam Park honors Richard Guy's term with a commemorative gavel award.

2001-2002 Volunteer Leaders

President: Kinam Park

President-elect: Alexander T. Florence

Vice President: James Anderson

Scientific Secretary: Martyn Davies

Treasurer: Susan M. Cady

Member-at-large: Joseph A. Fix

Member-at-large: Mitsura Hashida

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inthenews

News from the controlled release and delivery global community

Avigen Begins Testing of Its Liver Delivery of Hemophilia B Gene Therapy

Avigen, Inc. that the first patient was treated in a second Phase I clinical trial using its gene therapy product for hemophilia B, a blood clotting disorder caused by a deficiency of Factor IX. In this trial, patients with hemophilia B will receive Avigen's adeno-associated virus (AAV) vector containing the Factor IX gene, Coagulin-B, via infusion into the hepatic (liver) artery. In a previous human clinical trial, Avigen and clinicians have tested delivery of the Factor IX gene via intramuscular injection of Coagulin-B and the data have shown it to be safe and well tolerated in all patients treated. "We are very excited about the new Factor IX liver trial, because the liver is the normal site of clotting factor production. Preclinical data from the hemophilic dog model show the Avigen vector to be safe and well tolerated when administered into the liver, and able to provide long-term expression of therapeutic levels of the clotting factor," said John Monahan, President and CEO of Avigen. To help complete its research and development on Coagulin-B, Avigen recently signed collaboration with Bayer Corporation, a worldwide healthcare and life sciences company with a long-term commitment to develop better products to serve the hemophilia community. Under the collaboration, Bayer will help Avigen conduct late phase clinical trials for Coagulin-B and take part in the regulatory approval processes in various countries, including the European Union and the United States.

Baxter Healthcare Acquired Cook Pharmaceutical

Baxter Healthcare Corporation completed its $219 million acquisition of Cook Pharmaceutical Solutions, formerly a unit of Cook Group Incorporated. The process of integrating Cook Pharmaceutical Solutions is underway and Baxter anticipates a seamless transition for its customers and its approximately 300 new employees. Joel Tune, general manager of Baxter's Global Drug Delivery business said, "The acquisition of Cook Pharmaceutical Solutions broadens the range of products and services we can offer our global pharmaceutical company partners and supports our strategy of becoming a complete provider." The acquisition of Cook Pharmaceutical Solutions expands Baxter's portfolio of medication delivery products and its capability to offer contract manufacturing, a full range of quality control, analytical and microbiological services, as well as validation and other assistance to its pharmaceutical company customers in regulatory submissions.

BTG Acquires Oral Vaccine Delivery Technology

BTG, the global technology commercialization company, acquired Bilosomes, a new oral vaccine delivery vesicle that protects antigens from the digestive process and can also act as a powerful immunological adjuvant. BTG is now seeking to license this technology and develop it further. Bilosomes include bile salts in their formulation, which stabilize the vesicle preparation and prevent premature release of the antigen. Bilosomes deliver the antigen directly into the mucosal tissue and as a result smaller quantities of antigens are required to be effective, both cellular and humoral immune responses can be induced, and a wider range of antigens, including smaller and generally weaker antigens, can be delivered. Commenting on the technology, Dr. Geoffrey Porges, BTG's Executive Vice President for Health, Medical and BioTechnologies said: "Vaccines are currently one of the fastest growing areas in bio-pharmacy and there is a real need for delivery systems and adjuvants that can improve and enhance oral vaccination. Bilosomes have shown great potential in experiments so far and we look forward to exploring this further." The technology has been tested using influenza and measles antigens but has many possible applications in the oral delivery of both human and veterinary vaccines. Bilosomes were developed by Professor James Alexander and Dr. James Brewer at the University of Strathclyde, UK.

Eos to Merge with Pharmacopeia

The merger of Pharmacopeia, Inc. and Eos Biotechnology, Inc. is valued at $197 million, based upon Pharmacopeia stock value and cash at the time of merger. The transaction unites Eos' drug target identification and validation expertise and therapeutic antibody development skills with Pharmacopeia's integrated small molecule drug discovery capabilities. Eos brings leading edge, genomics-based drug discovery technology and expertise to the combined company, to merge with Pharmacopeia's expertise in experimentation, computation, and informatics products. The combined company will have the full spectrum of drug discovery capabilities from target discovery and validation, through lead discovery, enhancement and optimization. The combined technologies will create a platform for the identification and validation of drug targets and the discovery of small molecule and therapeutic antibody treatments for cancer, angiogenesis, inflammation and other diseases.

Gemin X's Antiviral Program Gets $ Boost

Gemin X received a CDN $350,000 Industrial Research Assistance Program (IRAP) contribution from the National Research Council of Canada. This is the maximum amount obtainable from IRAP and is the second IRAP contribution Gemin X has received for this amount. The latest will be used to fund Gemin X's novel antiviral program that uses apoptosis to target and destroy cells latently infected with viruses such as Herpes.

Gene Therapy Drug Enters Clinical Trial Phase

The Heart and Vascular Research Institute (HVRI) began a clinical trial of a new agent designed to stimulate angiogenesis in patients who suffer from Peripheral Arterial Disease (PAD) in their legs. The drug, a Del-1 gene medication called VLTS-589 was developed by Valentis, Burlingame, CA to stimulate the development of smaller peripheral arteries to increase blood flow to affected areas.

Genetic Models Acquired

Charles River Laboratories International, Inc. acquired Genetic Models, Inc. (Gmi). Charles River paid $4 million in cash to acquire all Gmi stock which had revenues of approximately $2.5 million in the year 2000, and no outstanding debt. Gmi's novel research models are used to find new treatments for disease conditions such as diabetes, obesity, cardiovascular disease, and kidney disease. The acquisition will fit nicely into Charles River's research and development for new drugs, devices and therapies, as well as their portfolio of biomedical products.

Integrating Genomics with Chemical and Bioassay Data

Psychiatric Genomics, Inc., a genomics-based drug discovery company adopted SciTegic™, Inc.'s data pipelining system, Pipeline Pilot™. Psychiatric Genomics will use this technology to augment their proprietary approach to gene-based psychiatric research and drug discovery in the area of data analysis, chemistry and bioinformatics. "This data pipelining approach allows us to efficiently integrate genomics with chemical and bioassay data," said Michael G. Palfreyman, Ph.D., D.Sc., President and CSO of Psychiatric Genomics.

Microcide Pharmaceuticals and Althexis Form Integrated Drug Discovery and Development Organization

Microcide Pharmaceuticals, Inc. and The Althexis Company, Inc. signed an agreement to merge their businesses in a stock-for-stock exchange. Concurrent with the merger, the combined entity will receive $60 million in private equity funding, and Mark Skaletsky will become Chairman and CEO of the Company. The agreement will unite Microcide's discovery platforms, including its VALID Microbial Genomics technologies, with Althexis' proprietary target validation system, known as ACTT, and will accelerate Microcide's multiple drug development programs in infectious disease by applying Althexis' Structure-Based Drug Design (SBDD) technology to lead optimization. George H. Miller, Ph.D., Senior Vice President, Research and Development at Microcide and Manuel Navia, Ph.D., co-founder and Executive Vice President at Althexis, commented in a joint statement: "The greatest challenge today in drug discovery is being able to take advantage of the greatly expanded array of potential therapeutic targets. By combining the two companies' capabilities in target validation and screening, lead identification and

(continued on page 24)

optimization through structure-based drug design, we can better address this unprecedented opportunity to develop novel potent drugs more efficiently and with less risk."

New Technology

News of a new infinite-affinity antibody platform technology to permanent bind antibodies and radioactive carriers to potentially deliver effective treatment for a variety of cancers was released by Lexrite Labs. The new binding technique, developed by the company's founders, creates antibody-ligand pairs that exhibit an infinite level of affinity because the antibody and ligand become covalently bound to each other. In essence, the antibody recognizes and permanently binds to a radioactive carrier or other therapeutically active molecule and forms a permanent chemical bond, which can thereby deliver the maximum amount of therapy directly to a tumor cell while sparing healthy tissues. Potential applications include not only targeted delivery of radiation therapy but also biosensing, bioanalytical detection and improved targeting of effector molecules to specific cells of interest for imaging or therapy.

Origen and Embrex Awarded $4.7 Million

Origen Therapeutics, Inc. and Embrex, Inc. have been awarded an Advanced Technology Program (ATP) grant totaling $4.7 million from the National Institute of Science and Technology (NIST), a division of the U.S. Department of Commerce. The four-year grant will help fund a project, with a proposed budget of $9.7 million, for development of technology aimed at the large-scale production of poultry utilizing avian embryonic stem (ES) cells and *in ovo* technology. "This grant is intended to advance one of the first commercial applications of non-human embryonic stem cell technology, which we believe will confer benefits for animal health, consumers, and poultry producers," said Robert J. Etches, Ph.D., Vice President of Research at Origen. "For example, this technology could aid in the rapid propagation of flocks of disease resistant chickens as well as chickens of uniform size and meat quality desirable to the poultry industry and consumers." "By coupling high-density culturing of avian embryonic stem cells with Embrex's *in ovo* delivery technology, it may be possible to produce entire flocks of chickens with desired traits without the dilution of performance traits via traditional multi-generation, multi-year breeding programs," stated Catherine A. Ricks, Ph.D., Vice President, Research and Development for Embrex.

Schering-Plough to Fund Additional Research at Microcide

Microcide and Schering-Plough Animal Health amended their research collaboration and license agreement for research in antibiotic resistance. This joint research program is focused on the discovery and development of improved veterinary antimicrobial drugs using Microcide's state-of-the-art technology and knowledge of bacterial efflux pumps and other resistance mechanisms. Under the terms of the basic agreement announced in November 2000, Schering-Plough Animal Health has worldwide rights to products resulting from the collaboration. Microcide received an upfront payment and receives research support payments over a two-year period and milestone and royalty payments on products emerging from the collaboration. "Efflux pumps in bacteria eject antibiotics and thereby limit their effectiveness," said George H. Miller, Ph.D., Senior Vice President for Research and Development at Microcide. "This additional financial support will allow us to apply state-of-the-art pharmacodynamic modeling in our collaboration." "We believe this additional research will accelerate and enhance our ability to achieve novel veterinary products," said Jim Rurka, President and CEO of Microcide. "Our scientific knowledge of efflux resistance mechanisms, and the means to overcome them, continues to grow and is opening up new opportunities to add value to established antibiotic and antifungal therapies."

Swiss Court Rules In Favor of Biogen, Upholds Injunction Against Serono

The Swiss court upheld its injunction prohibiting Serono from publicizing misleading claims against AVONEX (Interferon beta-1a), Biogen's drug for the treatment of multiple sclerosis (MS). The court determined Serono's claims were false and misleading to doctors and people with MS and presented the prospect of causing irreparable harm. Serono is now prohibited from publicizing misleading claims of the superiority for Rebif®. Unfortunately, the seriousness of Serono's misleading claims presented throughout Europe required Biogen to take legal action in the courts. Serono's claims were based on data never submitted to, or reviewed by, appropriate regulatory authorities. In related legal actions, a court in Lausanne, Switzerland rejected Serono's request for a preliminary injunction against Biogen. And a court in Hamburg, Germany issued two separate injunctions against Serono: one prohibiting superiority claims based on the company's comparative study; a second prohibiting promotional claims misrepresenting patients' chances of remaining relapse-free on Rebif®.

Taisho Invests in Quark

Taisho Pharmaceutical Co. Ltd of Japan made an equity investment in Quark Biotech Inc. (QBI). QBI and Taisho are currently collaborating on scientific research projects to discover the genes that cause kidney disease and to develop a therapeutic treatment for the cause of the disease, rather than just affecting the symptoms. QBI and Taisho have already completed initial feasibility studies and achieved milestones. Financial terms were not disclosed; however, we do know that QBI will receive royalties on sales of the projects developed from the companies' collaboration, as well as milestone payments. Taisho will retain worldwide development, manufacturing and marketing rights on the products and QBI will have an option to co-market certain products in the U.S. and E.U. countries.

Vyrex Receives Patent

Vyrex Corporation was awarded a U.S. patent for claims covering Water Soluble Pro-Drugs of Propofol. The claims cover treatment of diseases, states or conditions associated with the nervous, cardiovascular and respiratory systems. Vyrex's Chairman, Sheldon S. Hendler, Ph.D., M.D.; and principal inventory commented, "Propofol is the drug active of the world's leading anesthetic with sales in excess of $750 million annually. The present delivery form of propofol, however, is associated with some problems, including causing pain at the site of injection, elevating serum lipid levels, susceptibility of propofol to oxidation and the possibility of microbial contamination which could lead to infection. Vyrex has developed the water soluble pro-drugs of propofol covered by the patent in order to overcome these problems. In addition, recent studies suggest propofol's potential effectiveness in a wide variety of other applications, ranging from the treatment of nausea of cancer chemotherapy to the treatment of severe itching of chronic renal failure as well as for the treatment of migraine headaches. The currently marketed delivery forms of propofol are unsuitable for applications beyond its sedative-hypnotic use. Vyrex has developed the water soluble pro-drugs of propofol covered by this patent in order to expand the potential clinical applications of propofol into these promising new areas as well as for its sedative-hypnotic use."

XenoPharm to Profile Bristol Myers Squibb Compounds

XenoPharm Inc. will evaluate developmental compounds for Bristol Myers Squibb Company using proprietary assays. Under the collaborative agreement, Bristol-Myers Squibb will provide to XenoPharm an unspecified number of compounds and XenoPharm will test the ability of these compounds to induce the expression of drug metabolism enzymes typically found in the liver. Financial terms were not disclosed. XenoPharm's mission is to apply its proprietary XenoSensor technology, the Steroid X receptor (SXR), Constitutive Androstane Receptor (CAR) and the Cytochrome P-450 3A4 (CYP3A4) gene promoter, to improve the safety profiles of existing and developmental medicines. XenoPharm was established through exclusive licenses to several technologies. Collectively these technologies allow for the high throughput analysis of compounds to determine their ability to induce the gene expression of key liver and intestinal genes, primarily the CYP3A4 gene, involved in absorption, deposition, metabolism, excretion and toxicity (ADMET) of many drugs. In addition, each of the core technologies has been developed into a humanized mouse that will be used as a more predictive model for pre-clinical drug development. XenoPharm's objectives are to provide the technology to the pharmaceutical industry and use the technologies to develop its own drugs. ●

Memoirs of an Iowa Farm Girl on

Travel to Korea

By Rosealee Lee

We are a global society. Aided by high-speed travel and communications the size of our world is smaller than ever before. Our businesses are global and our science is global. Yet there are some who are reticent to take that next global stride. We have all heard comments like, "Why is the CRS meeting in Korea?" and "Korea is too far". I confess to taking a negative position on travel to Korea until a few months ago. It is because of my original attitude and my being an Iowa farm girl, that Kinam Park, President of CRS, asked me to write a series of three articles about travel to Korea. As he so eloquently stated recently, "Rosealee, if an Iowa farm girl can like it in Korea, anyone can." Okay, it wasn't a compliment was it? But it got me thinking, and he's right. For readers outside the U.S., Iowans are known for their stubbornness that is frequently perceived as close-mindedness. It's true that although I enjoyed my first trip to Korea, I was looking for my U.S. culture to be in Korea and it wasn't. I was looking for American cuisine and it was, but I was extra "safe" because of the can of tuna and the crackers in my suitcase. I was anticipating the problem of not being able to read or converse in my language and I found I could. I was looking for the Korean people to be just like us in the U.S., and even strangers were much more gracious and polite.

Doksugung Palace, one of several of the Choson dynasty's jewels, is located in the heart of Seoul.

First let's address the question, "Why Korea?" Beside my obvious retort, "Why not?" a quick study of the Korean pharmaceutical market and record of the research community is reason enough. Add to that the number of CRS members in Korea and affiliated societies in Korea who are supportive and participatory in the meeting, including the Korean Society For Biomaterials who are in direct collaboration with CRS for the event, and the reasons for meeting in Korea begin to mount.

The question, "Why should I go to Korea?" also deserves attention here. You should go to Korea because the meeting is there, your colleagues are there and it's a great place. The cultural lore and artistic flair of the country and its people are spellbinding. If you continue to read these articles, I know you'll agree, so if you're absolutely dead set against going, please stop reading now. If you're still with me, let's continue . . .

If you are not already doing business in Korea, get with it. The Korean business and financial climate has never been more favorable. Japan and other Asian countries will also be well represented at the meeting. The annual meeting will be a global summit of controlled release and delivery science. Session tracks include traditional CRS bioactive materials and consumer/diversified products tracks, along with sessions organized by the Japanese Society of Drug Delivery Systems, Society For Biomaterials U.S., and the Surfaces in *Biomaterials* Foundation.

Yes, I agree with the statement, "It's a long distance." I, too, wish they could move it closer. But frankly, I'm beginning to look forward to plane rides where the phone doesn't ring, someone waits on me, I get to nap, have a couple of drinks, watch a movie and catch up on some reading. So, my respectful response is that with a little bit of planning, the plane trip can be the first part of your good time.

International travelers are greeted in Seoul with a new, world-class airport that, in my opinion, outclasses any the U.S. has to offer. Korea is a peninsula stretching southward from the center of the northeast coast of Asia. The peninsula has a land area of approximately 220,000 km and a coastline dotted with some 3,400 islands. Enjoy the beautiful natural environment during your visit. The landscape is traditionally referred to as *geumsu gangsan* or "a golden tapestry of rivers and mountains." Koreans value this environment and as a nation have fostered a vibrant culture thoroughly adapted to their natural surroundings.

"I don't know the Korean language" is not a problem. The only problem I have with the Korean language is that I miss its melodic nature when I return home. Signage and public information throughout Seoul are displayed in English, including street signs, subway signs and menus. This is just one of the many ways that the Korean people welcome international travelers. English is a required course in Korean schools, so it comes as no surprise that Koreans understand English. Sometimes, however, if they are not in contact with English-speaking people for a long time, they do not trust themselves to speak it. They always, however, understand it. Seung Jin Lee, Program Co-chair of the 2002 annual meeting told me this, but my Iowan upbringing made me go out and test it. So, I stopped strangers on the street and asked them for directions. There was always the glint of recognition in their eyes, but occasionally when an individual was not comfortable responding with words, they answered with gestures. It was on one of the test "treks" on the street that I realized how enormously welcoming and friendly the Korean people are.

The graciousness of the Korean people is founded in their culture and woven in their history and religious diversity. Want to know more? Visit www.vistikorea.or.kr/english/index.html or watch for the next issue of CRS newsletter. Information about hotel options in Seoul (accommodations are not expensive and are "world-class city" quality), ground transportation (taxi fare is much cheaper than in the U.S.) and food options (you can spend as little or as much as you want, with far greater selection) will be discussed next time. In the meantime, annyeong (goodbye).

Tripitaka Korean woodblocks preserved in the Haeinsa temple archives.

2000 Best Year Ever for Biotech

2000 was the best year ever for biotech, according to the *Integration: Ernst & Young's Eighth Annual European Life Sciences Report 2001*. While the European biotech industry raised more than $5.5 billion, an amount greater than the sums raised in the previous five years combined, companies must still continue to integrate to build the R&D mass necessary to compete on the global market.

"To sustain its growth, the European biotech community has a critical need for size and critical-mass," said Scott Morrison, National Director of Life Sciences, Ernst & Young LLP and co-author of the last three editions of Ernst & Young's annual U.S. Biotechnology Industry Report. "While European biotech broke previous records for capitalization and IPOs, the U.S. biotech community is pulling away as a result of its greater financial strength." Europe has more biotech companies than the U.S., the U.S. market share is far greater, with companies having average revenues of $18 million, compared with $6 million in Europe. In all, the European public biotech industry is only slightly larger than the U.S.-based Amgen. The average market capitalization of a U.S. public biotech company is almost 60 percent greater than that of the average European one, giving U.S. companies a better opportunity to dominate their niche within a chosen sector. "To garner market share, European firms will rely on horizontal integration. This activity will pull together threads that lie within other companies (i.e., new or complementary technology, solutions to technological challenges or development capabilities not held in-house) to provide the infrastructure necessary to meet the growing demand for new products," said Morrison.

While the European biotech market looks horizontally at integration to strengthen its market share, European biotech is also subject to U.S. financial and regulatory influences. "The top ten U.S. biotech companies out-capitalize the top ten European companies by about four to one. One reason for the imbalance in direct investment is the relative infancy of European biotechs. Many European technologies are still too early [of a] stage to attract attention," added Morrison.

In 2000, U.S. companies were able to attract some $23 billion in follow-on financing. European companies were slow to react to the bull market, scooping up a mere $2.4 billion. Europe's share of the total monies raised by the industry has failed to rise above 10 percent, hindering growth. "It very much was a case of the 'haves and the have-nots', with a number of major U.S. players including Celera, Abgenix, Human Genome and Millennium raising substantial sums of money, much of it European. In an attempt to counter financing trends and appeal to U.S. investors, more European companies are listed on both a European index and the Nasdaq. Last year, eight of the top ten European biotech firms had dual listings, compared with one the previous year.

In Europe, investors tend to keep companies on a short leash and drip feed funds. As a result, companies are consolidating to create a bigger R&D capability to fill product pipelines and to help garner parity with the U.S. biotech industry by meeting the drug needs of "big pharma."

European biotech companies have a strong drug discovery pipeline, with approximately 278 products in clinical trials. Additionally, the European regulatory approval process can be more lenient in many respects, and while seemingly an advantage for European biotech, it can cause problems down the road in bringing products to market in the U.S. Because European biotech study protocols and results do not necessarily satisfy the U.S. Food and Drug Administration, the FDA rulings against drug approvals are more detrimental to European biotech companies due to their size. Average U.S. market capitalization is approximately $1.2 billion compared to $0.7 billion for Europe, making drug approval delays more difficult for European biotech companies' long-term financial survivability.

The rising number of biotech-to-biotech mergers makes the European industry increasingly more financially secure. Last year, the proportion of biotech-biotech alliances increased from 16 percent to 34 percent, creating an opportunity for biotech companies to retain as much value as possible before having to deal with big pharma.

"The large disparity between the European and U.S. industries in company size and the amount of funding to which they have access means that a majority of the biotech winners will come from the U.S., even though the U.S. has a smaller number of biotech companies," said Morrison. "Integration is the key for the European biotech companies to demonstrate continued growth and to offer substantial contributions to life sciences." Cross-border mergers and acquisitions have increased with many U.S. companies looking to Europe and Canada to obtain technologies at values significantly lower than comparable opportunities in the U.S. ●

Hydrophilic/hydrophobic transdermal matrix (Ortho) US6162456
Homogeneous blends of hydrophobic and hydrophilic polymer are shown to increase the permeation of drugs when compared to that of matrices of either polymer alone. Hydrophilic polymers useful with the invention include cellulose derivatives, polyvinyl alcohols and polyacrylamides. Hydrophobic polymers should be immiscible with the hydrophilic polymers and include polysiloxanes, polyisobutylene and polyurethanes. Drugs presented include alprazolam and nicardipine as well as the enhancer propylene glycol monolaurate.

Extrudable transdermal compositions (J&J) US6072100
Water soluble thermoplastic compositions are described for the transdermal delivery of drugs including analgesics, antihistamines, anesthetics, fungistats and antiacne agents. The compositions contain 10-40% water soluble polymers such as hydroxypropyl cellulose and polyethylene oxide, 30-80% plasticizers such as glycerin, propylene glycol and polyethylene glycol and up to 10% drug. Specific drugs disclosed include benzalkonium chloride, bacitracin, polymyxin, neomycin, salicylic acid, benzoyl peroxide and retinoic acid.

Administration of Calcitonin (Toyo Jozo) JP4074133A
A transdermal composition is described for the delivery of calcitonin comprising at least two permeation enhancers, bile acid salts and protease inhibitors. Enhancers disclosed include glucosides and pyrrolidones. Protease inhibitors include soybean trypsin inhibitor, ovo inhibitor, cattle spleen trypsin inhibitor, bestatin, gabexate, benzamidine and others.

Prevention of Drug Crystallization (Lohmann) DE4429664
A transdermal system for estradiol and other crystallizable drugs is claimed which discloses the incorporation into the formulation of a water-binding substance, preferably calcium sulfate to prevent crystallization of estradiol. The calcium sulfate absorbs water and prevents the formation of estradiol semihydrate which would crystallize out; this allows for storage stable saturated conditions to be maintained and improved drug administration.

Prevention of Liquid Drug Crystallization (Alza) WO9720550A
The crystallization of liquid drugs that are capable of crystallizing, such as scopolamine, is prevented by heating to predetermined temperature each film or laminate containing a dispersion of the drug, immediately following the formation of the film or laminate. Other drugs disclosed include nicotine, secoverine and benztropine.

Transdermal Delivery of Peptides and Prokins (U of Ben-Gurion) WO9853847A
Transdermal formulations containing peptides or proteins to be administered also contain acceptable oxidizing agents and/or buthionine sulfoximine. These agents serve to oxidize reducing agents such as glutathione and thus prevent inactivation of the protein. Preferred proteins are those containing S-S bonds such as insulin.

METHODS/APPLICATIONS

Drugs in many therapeutic categories were presented including:

- Alzheimers/Dementia: deoxypeganin (DE19906977C1), isoxazole (DE19501022C).
- Asthma/Allergy: ketotifen (WO200001384A1 and JP4182425A), fenoterol (DE19908787A1), azelastine (JP10182463A), loratidine metabolite (US6165498).
- Antidepressant: rolipram (DE3943385A).
- Anifungal: tolnaflate (JP4316517A), benzimidazole (US6077528).
- Antiinflamatory/Analgenic/Pain: marijuana (US 6139866), cannabis (US6113940), piroxicam (KR9832546A), cetyl myristoleate (WO200064436A1), morphinium nicotinade (WO200041683A2), niflumic acid (WO200038681A1), nimesulide (NZ299500A), ascorbic acid (WO200009121A1), capsaicin (JP5105628A), indomethacin (WO9918955A1 and JP2935113B), capsacinoid and dextrorphan (WO9853825A), diclofenac (WO9951212A2), buprenorphine (US6090405 and WO200035456A1), fentanyl (US6139866 and JP200044476A).
- Antipsychotic/schizophrenia: risperidone (WO9631201A), nicotine (DE19847715A1), fluphenazine (DE19918105C1).
- Antitussive (cough): dextromethorphan (WO9739742A).
- Antiviral: acyclovir (US6162459), alpha interferon (WO9966906A1).
- Cancer/Nausea: granisetron (WO200047208A1), lerisetron (US6136807), methotraxate (WO9831369A), serotonin receptor antagonist (nausea) (WO9825592A).
- Cardiovascular: nicorandil (JP3261722A), noradrenaline re-uptake inhibitor (JP2000072662A), fenoldopan (WO200004886A1), angiotensin II receptor antagonist (WO20048634A1).
- Contraception/PMS/Sexual Disfunction: sildenafil (DE19834505A1), estradiol plus norethisterone (DE19828274A1), 3- ketodesogestrel (WO9404157A), estradiol (EP430491A), non-5 alpha reducible androgen (WO9913812A1).
- Lipid Lowering Compounds: lovastatin (DE19541260A).
- Irritable Bowel Syndrome: isoxazolyl (FR2792529A1).
- Parkinson's Disease: selegiline (HU9700608A), pergolide (DE196266221A), levodopa (JP2000038338A), biperiden (US6146656).
- Smoking Cessation: bupropion (EP1051971A1), nicotine (WO200037058A1 and WO9501766A).
- Thromboxane Suppression/Platelet Aggregation Inhibition: aspirin (US6071896), phenylalanine (WO9513825A), amidine (WO9933458A1).
- Urinary Incontinence: oxybutynin (DE19812413C1 and JP6145052A), tolterodine (DE29923242 and WO200012070A1).

Effect of Administration Route

It is not surprising that local administration can dramatically effect the amount of drug that accumulates in a particular tissue. Data from the pulmonary, intraocular, rectal and topical routes of administration indicate that local delivery of oligonucleotides impacts their "cellular bioavailability". For example, a topical formulation of an anti-ICAM-1 oligodeoxynucleotide, ISIS 2302, effectively inhibited, TNF-α induced, expression of ICAM-1 when applied to human skin transplanted on SCID mice. The reductions in ICAM-1 mRNA in skin were dose-dependent and sequence-specific. Whereas, intravenous administration of the drug did not reduce ICAM-1 mRNA expression in skin (Mehta 2000). Quantitatively, the topical application of a 2% oligodeoxynucleotide cream results in > 1000-fold greater concentration of total oligodeoxynucleotide in epidermis than that seen after an intravenous dose of 2 mg/kg. This difference is even greater if only intact (full-length) material is considered - as drug administered by the topical route is less prone to metabolism. Even when we consider the deeper dermis, the topical route was able to deliver > 100-fold of intact drug (Fig. 9). Taken together, these results establish that delivery systems providing significant concentrations of oligonucleotides in target tissues can result in specific pharmacological effects. Given the gross tissue levels achieved in these studies, it is reasonable to assume that an excess of sequestered oligonucleotide exists in the structures of the skin. As this article suggests for all oligonucleotide delivery systems, a greater understanding of the cellular trafficking extant to this application will be required to make further advances in potency.

Closing Remarks

There is little doubt that oligonucleotides will find use as therapeutic agents. It is proposed that the development of novel formulations and delivery routes will facilitate success of the technology in a wider variety of tissues, cells and targets. Such advances will be made possible through fundamental understanding of oligonucleotide biopharmaceutics and pharmacodynamics. Hopefully this article has stimulated some thought that will further advance these therapeutic goals. ●

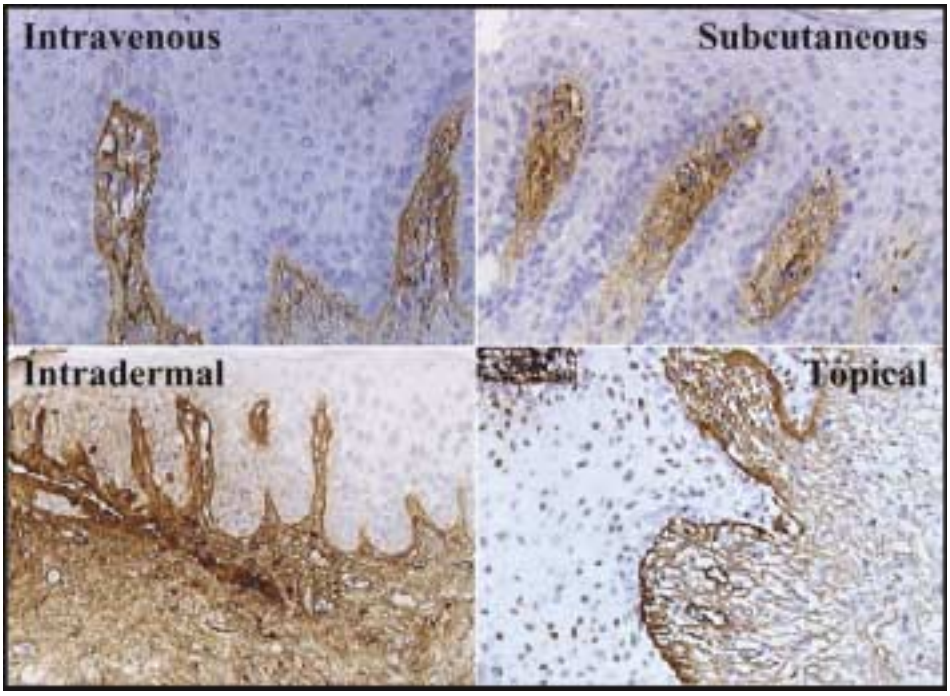

Figure 9. For Dermal Applications Cellular Accumulation is Altered by Administration Route (Oligonucleotide stained brown)

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Next issue deadline
November 16, 2001