CONTROLLED RELEASE SOCIETY

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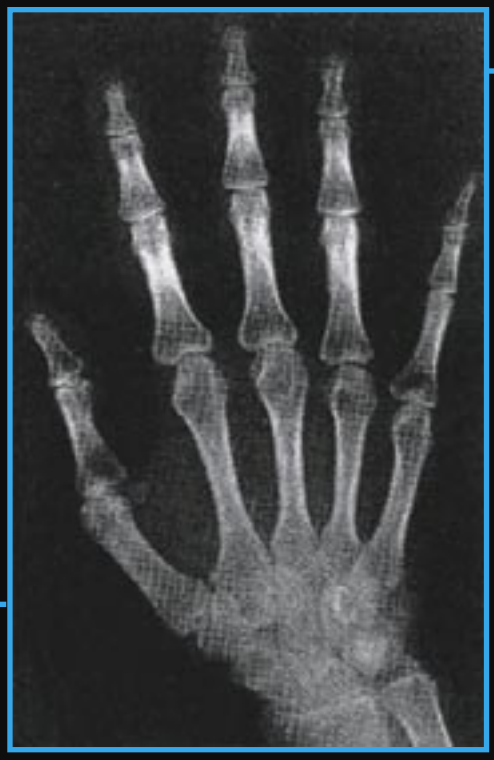
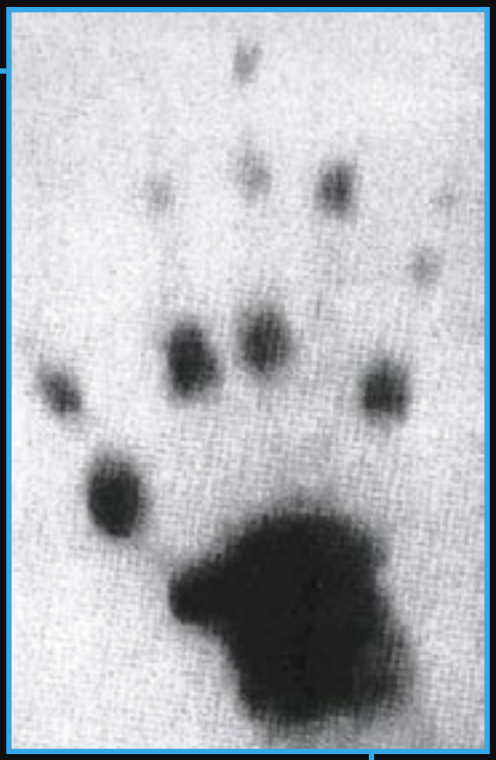
NEWSLETTER



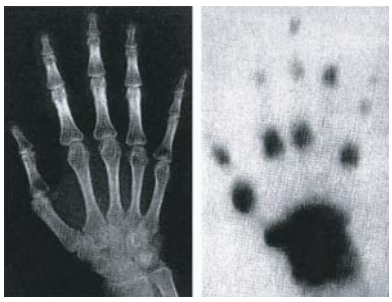


Dedicated to the science and technology of controlled release and delivery and promoting education by releasing science to deliver a better future.

CONTROLLED RELEASE SOCIETY
NEWSLETTER
Volume 22 • Number 1 • 2005

inthisissue

On the cover –



X-rays of hand gives structural imaging of hand however provides little insight into inflammation.

Image provided by Dr. Neena Washington, Co-Chair and presenter at the UKICRS "Imaging from Molecules to Man" One day symposia.

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

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FROM THE *Editors*

by Amy Lemmon
Managing Editor, U.S.A.

New Year resolutions are an incredible concept; an individual starts with good intentions and hopefully they are able to make life changing behavior. Personally, I quickly forget what I had planned to change and go back to my old ways (let's face it I don't even have the new year automatically etched into my mind until May).

Though New Years Day is famous to begin something new, why not reward yourself today by sharing you time and talents with the Controlled Release Society. In giving to the Society you are building the community among your professionals, and continue to make the Controlled Release Society the premier society. Here are a few thoughts on how you can make a difference:

- Volunteer for one of its outstanding committees: Awards, Consumer & Diversified Products, Education, Marketing, Meetings, Planning & Finance, Publications, and Veterinary. Go to http://www.controlledrelease.org/about/committees/index.cgi for more details.
- Attend the Annual Meeting in Miami, Florida, USA. Mark your calendar: June 18 – 22, 2005. Go to http://www.controlledrelease.org/meetings/miami/registration.cgi for more details and to register.
- Organize to recruit new members. Students? Graduate Assistants? Post Doc's? The person across the hall? Go to http://www.controlledrelease.org/membership/index.cgi for membership information.
- Submit your idea(s) for change. Email director@controlledrelease.org to share your ideas.
- Read each issue of this newsletter thoroughly.
    - o New items and technologies
    - o Educational and scientific foundation opportunities created by recent advances
    - o Personal profiles
    - o New patents

And most importantly, on behalf of the Editorial team, have a safe and successful 2005!

From the President

by Jennifer Dressman
Johann Wolfgang Goethe University, Germany

On behalf of the Board of Directors, I extend our very best wishes for the New Year to all CRS members. This year promises to be an active and progressive year for the CRS. We are actively building our educational initiatives with special programming planned for the Annual meeting. New this year, construction of the virtual library, which will be accessible to all members and is expected to be a rich source of information and visual aids. Further, through the efforts of our Local Chapter liaison, Ajit Singh, we will be establishing the infrastructure necessary to facilitate information sharing among the local chapters.

Another important area of activity for the Board has been ensuring that the Society stays in good financial health. With a strong financial base we can invest in the infrastructure and programs that are important to assisting members achieve their professional and research goals. Art Tipton and the Finance Committee are working hard to optimize our cost/benefit ratio, while Joe Fix and the Marketing and Development Committee are continuing their efforts to expand our sponsorship.

This year promises to be an active and progressive year for the CRS. We are actively building our educational initiatives with special programming planned for the Annual meeting.

Again this year we have a great program in place for the Annual Meeting (please visit the CRS website at www.controlledrelease.org for more details) and, due to the attractive and accessible location, we are looking forward to a record attendance. ***Please register soon for the Annual Meeting in Miami Beach, Florida from the 18th to the 22nd of June.*** Please remember, to make best use of your CRS member discount for registration you will need to register before the 22 of May. As most of you will have heard, Florida was pounded by several hurricanes in August/September of 2004. However, we are assured that our dates for 2005 are much too early for tropical storms to pose a threat to our meeting.

Especially strong this year at the Annual Meeting will be the Exhibition, with most of the important players in the drug delivery and controlled release fields represented. A new benefit for attendees is the availability of a lunch in the Exhibition area on both Monday and Tuesday. Please take the opportunity to lunch, browse the exhibits, surf websites or pick up email in the Internet Cafe, and visit the recruiting booths to find where the hottest jobs are being offered.

For those considering bringing the family to the Annual meeting, the convention hotel, the Fontainebleau Hilton, is an especially attractive destination, with a huge pool network and direct access to a gorgeous, sandy beach. Like last year, there will be a children's program available at the convention hotel.

We look forward to greeting you personally at the Annual meeting and wish you all a productive and successful New Year.

Jennifer Dressman ▪

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Scientifically Speaking

Formulation strategies in mucosal-adhesive drug delivery

by Hannah Batchelor
Aston University, U.K.

Hannah Batchelor

Introduction

Mucosal-adhesive materials have been used in a variety of formulations targeted to sites including the eye, oral cavity, nasal cavity, gastro-intestinal (GI) tract and the vagina. Adhesion of drug delivery devices to mucosal membranes leads to an increased drug concentration gradient at the absorption site and therefore improved bioavailability of systemically delivered drugs. In addition, bioadhesive dosage forms have been used to target local disorders at the mucosal surface (e.g. mouth ulcers) to reduce the overall dosage required and minimise side effects that may be caused by systemic administration of drugs.

The first recorded bioadhesive drug delivery formulation was described in 1947 when gum tragacanth was mixed with dental adhesive powder to apply penicillin to the oral mucosa; this was eventually to become Orabase® (Scrivener and Schantz, 1947).

Recent reports have suggested that the market share of bioadhesive drug delivery systems is increasing (Jasti et al. 2003). Table 1 lists some of the currently available bioadhesive drug formulations available within the UK.

Product	Company	Bioadhesive agent	Pharmaceutical form
Buccastem®	Reckitt Benckiser	Polyvinylpyrrolidone (PVP), Xanthan gum and locust bean gum	Buccal tablet
Corlan pellets®	Celltech	Acacia gum	Oromucosal pellets
Suscard®	Forest	Hydroxypropyl methylcellulose (HPMC)	Buccal tablet
Gaviscon Liquid®	Reckitt Benckiser	Sodium alginate	Oral liquid
Orabase®	ConvaTech	Pectin, gelatin	Oral paste
Corsodyl gel®	GSK	Hydroxypropyl methylcellulose (HPMC)	Oromucosal gel
Nyogel®	Novartis	Carbomer and polyvinylalcohol (PVA)	Eye gel
Pilogel®	Alcon	Carbomer	Eye gel
Timoptol-LA®	MSD	Gellan gum	Eye gel-forming solution
Aci-Jel®	Janssen-Cilag	Tragacanth, acacia	Vaginal gel
Crinone®	Serono	Carbomer	Vaginal gel
Gynol-II®	Janssen-Cilag	Sodium carboxymethyl cellulose and PVP	Vaginal gel
Zidoval®	3M	Carbomer	Vaginal gel

(MSD = Merck, Sharpe and Dohme; GSK = GlaxoSmithKline)

Readily accessible sites are utilised primarily within mucosal-adhesive drug delivery formulations, with the eye, oral cavity and vagina targeted via commercial formulations. The GI tract is a desirable site for bioadhesive drug delivery due to its propensity for drug absorption, although as yet there are no commercially available products within the UK that are designed to adhere to the GI tract. The nasal cavity has also been extensively examined as a site for bioadhesive drug delivery formulations as this is a growing market that is yet to be fully exploited (Koch, 2003).

Formulation strategies for mucosal-adhesive drug delivery systems

Mucosal-adhesive formulations generally use polymers as the adhesive component. These polymers are often water-soluble and when used in a dry form they attract water from the mucosal surface and this water transfer leads to a strong interaction due to this water transfer. These polymers also form viscous liquids when hydrated with water that increases their retention time over mucosal surfaces and may lead to adhesive interactions. Many theories have been proposed to explain the forces that underpin bioadhesion however, there is yet to be a clear explanation. As bioadhesion occurs between inherently different mucosal surfaces and formulations that are solid, semi-solid and liquid, it is unlikely that a single, universal theory will account for all types of adhesion observed. However, mucosal-adhesive polymers should possess certain physiochemical features including hydrophilicity, numerous hydrogen bond-forming groups, flexibility for interpenetration with both mucus and epithelial tissue and visco-elastic properties upon hydration.

In testing bioadhesive formulations, the test used should be appropriate to the particular system under development. This means that, as well as adhering, the bioadhesive formulation should be able to perform its designated function be it as a drug delivery device or as a protective agent. The nature of the biological substrate should be considered in test development, for example, adhesion to gastric mucosa would require a very different test to that of a topical adhesive device. Physiological conditions need to be considered and mimicked to produce an optimum testing system. In drug delivery systems, the main purpose of the bioadhesive system is to increase the efficacy of delivery of the drug in question. *In vivo* tests are the most appropriate situation used to reveal this required information. However, they are both costly and time consuming and for this reason, the majority of information available on bioadhesive drug delivery agents comes from *in vitro* tests. These simpler, routine tests have been developed to allow many different bioadhesive formulations to be tested, thus acting as a screening mechanism for candidate bioadhesive agents. In most cases, a simple test that is not influenced by physiological factors is more convenient than an *in vivo* bioavailability test. However, attempting to extrapolate data from such a test should be treated with caution, as the controlled environment may bear little relationship to the ultimate performance of the bioadhesive. Important considerations in the design of such tests include the residence time of the adhesive formulation and the adhesive interaction strength.

The main tests that have been used to monitor bioadhesion *in vivo* include gamma scintigraphy and transit studies with radiolabelled dosage forms. Pharmacokinetic data can be obtained in conjunction with these studies and represents the ultimate test for a bioadhesive drug delivery system. The limitations of the above test methods include the fact that the tests measure the retention or distribution of the dosage form yet not the clinical efficacy of the drug. Complexes that may form between the delivery matrix and drug must be accounted for and the way in which the delivery system affects the release of the drug.

Force of detachment tests are more commonly used tests available to assess the bioadhesive properties of many formulations. They are used to measure the forces involved in separating adhesive material

*(**Scientifically Speaking** continued on page 5)*

*(**Scientifically Speaking** continued from 4)*

from the tissue surface directly. Many different forms of this test have been described (Park & Park, 1990) although a lack of standardisation between test methods has given rise to non-uniform results.

It is very difficult to compare the relative merits of different polymers as bioadhesive agents as no test is all-encompassing and gives a result that is applicable to all situations. Some studies have been performed to rank bioadhesive polymers in order of their bioadhesive strength. Wong et al (1999a) used a chicken cheek pouch to simulate buccal delivery and ranked the following polymers in order of decreasing bioadhesive strength Carbopol > gelatin > sodium carboxymethyl-cellulose > hydroxypropylmethylcellulose > alginic acid = chitosan. Although a second study by Wong et al (1999b), showed the order to be sodium carboxymethyl-cellulose > xanthan gum > Carbopol. A further study used an *in vivo* periodontal model to show that the bioadhesive potential was ranked; xanthan gum > poly (ethylene oxide) > chitosan (Needleman et al, 1997). The polymers were ranked poly(acrylic acid) > sodium carboxymethylcellulose > hydroxypropylcellulose by Cvetkovic et al (1997) using an *in vitro* modified intestinal perfusion technique. These conflicting results show that there is discrepancy in the literature reports of the bioadhesive potential of polymers. The results show that according to the method used the bioadhesive potential can vary a great deal.

Solid bioadhesive formulations

Dry formulations achieve bioadhesion via dehydration of the local mucosal surface. Tablets that are placed directly onto the mucosal surface have been demonstrated to be excellent bioadhesive formulations, e.g. Buccastem® administered to the buccal mucosa. However, size is a limitation of tablets due to the requirement for the dosage form to intimate contact with the mucosal surface.

Bioadhesive microparticles offer the same advantages as tablets but their physical properties enable them to make intimate contact with a larger mucosal surface area, in addition, they can also be delivered to less accessible sites including the GI tract and upper nasal cavity. The small size of microparticles compared to tablets means that they are less likely to cause local irritation at the site of adhesion and reduces the uncomfortable sensation of a foreign object within the oral or nasal cavity.

Ocular inserts (solid devices, which are placed on the cornea or in the cul-de-sac of the eye) were introduced to the ophthalmic market 50 years ago. The earliest official record of a solid insert was described in the 1948 British Pharmacopoeia, it was an atropine-containing gelatin wafer. Ocular inserts offer many advantages over liquid formulations including longer retention times, accurate dosing, increased stability and shelf life. However, despite these advantages ocular inserts (eg Ocusert®) have not been widely used in ocular therapy. Combining an insert with a bioadhesive polymer offers additional advantages in that the device can no longer move freely over the surface of the eye thus minimising irritation and preventing loss of the device. A recent study has indicated that ocular inserts incorporating a bioadhesive polymer, thiolated poly(acrylic acid) are promising new solid devices for ocular drug delivery (Hornof et al 2003).

Bromberg et al (2001) described a conceptually novel periodontal drug delivery system (DDS) that is intended for treatment of microbial infections associated with periodontitis. The DDS is a composite wafer with surface layers possessing adhesive properties, while the bulk layer consists of antimicrobial agents, biodegradable polymers, and matrix polymers.

Bioadhesive lozenges may be used for the delivery of drugs that act topically within the mouth including antimicrobials, corticosteroids, local anaesthetics, antibiotics and antifungals. Conventional lozenges produce a high initial release of drug in the oral cavity, which rapidly declines to subtherapeutic levels, thus multiple daily dosing is required; a slow release bioadhesive lozenge offers the potential for prolonged drug release and once daily dosing with improve patient compliance. Codd and Deasy (1998) investigated bioadhesive lozenges as a means to deliver antifungal agents to the oral cavity.

Semi-solid bioadhesive formulations

Gel-forming bioadhesive polymers include cross-linked polyacrylic acid that has been used to adhere to mucosal surfaces for extended periods and provide controlled release of drugs. Gels have been widely used in the delivery of drugs to the eye, oral cavity and vagina. Advantages of gel formulations include their ability to form intimate contact with the mucosal membrane and their rapid release of drug at the absorption site. Limitations of gel formulations centre on their inability to delivery a measured dose of drug to the site, they are therefore of limited use for drugs with a narrow therapeutic window or for sites that are not readily accessible.

Flexible films may be used to deliver drugs directly to a mucosal membrane as they have the flexibility to form intimate contact with the membrane, they also offer advantages over creams and ointments in that they provide a measured dose of drug to the site. Bioadhesive films may be designed for use within the buccal cavity or for administration to the eye. Zilactin® (Zila) is a bioadhesive film used in the therapy of canker sores, cold sores and lip sores (www.zila.com).

Liquid bioadhesive formulations

The adhesion of liquid bioadhesive formulations has not been investigated to the same extent as solid mucosal-adhesive formulations. However, improved bioavailability from a mucosal-adhesive formulation would benefit from the drug being readily soluble in the adhesive vehicle as well as the prolonged retention at the site of absorption. Techniques used to assess the adhesion of liquids have varied a great deal and resulted in conflicting results within the literature. A model described by Batchelor et al. 2002 has been used to rank the adhesion of a range of liquids that have been reported to demonstrate adhesion to a mucosal surface previously. Figure 1 shows the percentage of the original dose that is adhered to porcine oesophageal tissue after 10 minutes of washing with to mimic conditions within the GI tract.

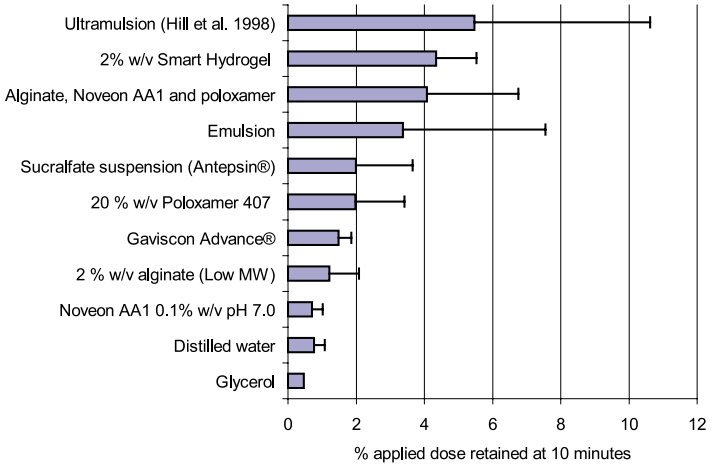

Figure 1. A comparison of the adhesive potential of a range of viscous liquids.

Viscous liquids may be used to coat mucosal surfaces either as protectants or as drug vehicles for delivery to the mucosal surface. Traditionally, pharmaceutically acceptable polymers were used to enhance the viscosity of products to aid their retention in both the eye and within the oral cavity. Indeed, artificial tears for the treatment of dry eye (e.g. Viscotears®, Novartis) are carbomer solutions that adhere on the surface of the eye providing a lubricated surface. Dry mouth is treated with artificial saliva solutions that are retained on the mucosal surfaces to provide lubrication, these solutions contains bioadhesive polymers including sodium carboxymethyl cellulose (e.g. Luborant®, Antigen; Saliveze®, Wyvern).

*(**Scientifically Speaking** continued on page 27)*

Pharm News

by Michael J. Rathbone
InterAg, New Zealand

Summaries of recent veterinary controlled release papers of interest

Medlicott NJ, Waldron NA, Foster TP. Sustained release veterinary parenteral products. ***Adv Drug Deliv Rev.*** **2004, 56(10):1345-65.**
Controlled release parenteral dosage forms have application in veterinary medicine. Systems that minimize the need for repeated injections while achieving therapeutic effects for extended periods offer benefits that make commercial development of these products desirable. While some products have already found commercial success, others will result from application of new controlled release technologies. This review highlights the formulation and technology challenges in developing some of these controlled release technologies into products. Further, examples of application of controlled release technologies in the veterinary field are discussed.

El-Zarkouny SZ, Cartmill JA, Hensley BA, Stevenson JS. Pregnancy in dairy cows after synchronized ovulation regimens with or without presynchronization and progesterone. ***Dairy Sci.*** **2004, 87(4):1024-37.**
Two experiments examined pregnancy after synchronized ovulation (Ovsynch) with or without progesterone (P4) administered via controlled internal drug release (CIDR) intravaginal inserts. In experiment 1, 262 lactating cows in one herd were in 3 treatments: Ovsynch (n = 91), Ovsynch + CIDR (n = 91), and control (n = 80). The Ovsynch protocol included injections of GnRH 7 d before and 48 h after an injection of PGF20. Timed artificial insemination (TAI; 57 to 77 d postpartum) was 16 to 20 h after the second GnRH injection. Cows in the Ovsynch + CIDR group also received a CIDR (1.9 g of P4) insert for 7 d starting at first GnRH injection. Control cows received A-I when estrus was detected using an electronic estrus detection system. Based on serum P4, 44.1% of cows were cyclic before Ovsynch. Pregnancy rates at 29 d (59.3 vs. 36.3%) and 57 d (45.1 vs. 19.8%) after TAI and embryo survival (75.9 vs. 54.5%) from 29 to 57 d were greater for Ovsynch + CIDR than for Ovsynch alone. In experiment 2, 630 cows in 2 herds received TAI at 59 to 79 d postpartum after 6 treatments. Estrous cycles were either presynchronized (2 injections of PGF2alpha 14 d apart; n = 318) or not presynchronized (n = 312). Within those groups, Ovsynch was initiated 12 d after second presynchronization PGF2alpha, and used alone (n = 318) or with CIDR inserts for 7 d (1.38 g of P4/insert, n = 124 or 1.9 g of P4/insert, n = 188). Before Ovsynch, 80% of cows were cyclic. Presynchronization increased pregnancy (46.8 vs. 37.5%) at 29 d after TAI, but CIDR inserts had no effect on pregnancy in experiment 2. Overall embryonic survival between 29 and 57 d in experiment 2 was 57.7%. Use of CIDR inserts with Ovsynch improved conception and embryo survival in experiment 1 but not in experiment 2, in part due to differing proportions of cyclic cows at the outset. Presynchronization before Ovsynch enhanced pregnancy rate.

*(**Pharm News** continued on page 11)*

Veterinary Controlled Release: Career Focus Profile of Dr. Craig Bunt, Senior Scientist, InterAg, New Zealand

Its 8am, raining and 4ºC. My client has been up since 5am and his biggest concern is to get 400 cows out to the paddock. One farm hand is helping the veterinarian and each additional hour the cows are in the yard costs the farmer in labour for the farm hand and cow pasture time (cows+pasture=milk=$). If this happened once a year the farmer would hardly notice, however this is almost a repeat of what happened last week when the veterinarian visited to administer the first part of a treatment to synchronise the cows for artificial breeding, starting with an intravaginal progesterone releasing insert and an oestradiol benzoate injection. Today's visit 8 days later is to remove the insert and to inject a prostaglandin. Tomorrow, the veterinarian will visit once more to inject oestradiol benzoate and the three days following that, the artificial insemination technician will visit. Sound like a scenario screaming out for controlled drug delivery?

Back in the early 1990s, New Zealand was a country with 3.5 million people and 60 million sheep and big Pharma was pulling out and relocating or concentrating to Australia. There were few options for the pharmaceutical scientist. New Zealand veterinary pharmaceutical companies and academic groups were, however, quietly conducting exciting and innovative controlled release research. These included work on injectable microcapsules, gastro retentive boli, patch-less transdermals and intravaginal inserts. It was initially targeted at New Zealand's unique needs such as cobalt and zinc deficiency in soils, livestock productivity and management. Since then, this research has resulted in a number of world first-to-market, innovative products. For more information, see the website of the New Zealand Local Chapter of the Controlled Release Society (www.controlledrelease.org/chapters/newzealand/).

Craig's career in veterinary controlled release can be traced back to a 1992 presentation by Dr. Keith Ellis in Sydney, Australia. Dr. Ellis presented a picture of a sheep and asked the audience "Where would you put a transdermal patch on this animal without having to shear a section of wool off and shave down to bare skin". Up until this point Craig had only paid attention to human pharmaceutics having a Bachelor of Pharmacy, and was at this time doing his PhD at the University of Otago on microencapsulation of living organisms. In 1995 Craig completed his Ph.D. and commenced employment with InterAg as a research officer looking at formulation of intravaginal progesterone inserts for oestrus synchrony of cattle.

In recent years Craig has worked with Prof. Billy Day, University of Missouri-Columbia on progesterone containing electronically controlled intravaginal inserts to control the estrous cycle in gilts (maiden pigs) and Prof. Keith McMillan, University of Melbourne, on progesterone containing poly (ε-caprolactone) intravaginal inserts cattle, results from which have been presented at CRS meetings over the last 8 years. Electronically controlled drug delivery has been a major focus of Craig's work over the last 7 years with the 2002 Controlled Release Society's Outstanding Veterinary Paper Award for the paper "Simultaneous sustained progesterone and pulsatile estradiol benzoate delivery from an electronically modulated bovine intravaginal insert" a particular highlight.

*(**Career Profile** continued on page 11)*

Deliver at a Distance: Ballistics for Wild Bison Live Brucella Vaccination

R. James Christie and David W. Grainger, Colorado State University,
Richard A. Hansen, SolidTech Animal Health, Inc.,
Rick Wallen, Yellowstone National Park,
Steven Olsen, National Animal Disease Center, U.S.A.

Recent Yellowstone National Park policy requires implementation of a plan to control the infection of brucellosis in indigenous populations of wild bison that live within the park. Contact, through mutual range areas, of bison with elk spread this disease beyond park jurisdiction. Of particular concern is the potential to infect cattle herds in Montana and Wyoming.[1] Approximately 40-50% of bison in Yellowstone Park test positive for brucellosis using standard serology tests. The disease, primarily transmitted through bacteria shed in fluids and placental tissues at abortion or during birth of infected calves, is characterized by infection through ingestion of the bacteria and eventual localization in reproductive, mammary gland, and lymphoreticular tissues in ruminant animals. Pathologic effects are primarily associated with localization in placental membranes and fluids surrounding the developing fetus. During late pregnancy, bacteria replicate in specific placental epithelial cells, causing late-stage, spontaneous abortion in domestic and wild bovids and ungulates.

A commercial cattle vaccine (www.coloradoserumcompany.com, RB51) is based on a live brucellosis strain that prompts cell-mediated immunity and antibody production (T- and B-cell priming) and is used to vaccinate female domestic calves, but also now with significant history in bison.[2] Calf-hood dosage is approx. 10^{10} CFU i.m., typically administered via a direct injection in holding pens. Importantly, this vaccine strain does not induce positive serologic responses on standard brucellosis surveillance tests, eliminating possible confounding screening results between cattle actually infected with those vaccinated. Additionally, multiple dosing (booster) is possible.

One possible solution to addressing the risk of brucellosis transmission from Yellowstone bison to other wild bison, wild elk, or domestic livestock is reliable vaccination of these herds to prevent spread of disease.[1] However, the National Park designation and environmental and wildlife management policy within the park place unique constraints on pursuing this solution. These include the live wild bison target, the need to leave natural herd behavior undisturbed by human presence, the "leave no trace" ethic mandating complete biodegradability for any vaccine vehicle and components, and safety issues regarding human casual exposure to residual vaccine or errant formulations (CDC recommends laboratory work with the live vaccine strain as a biolevel 2 pathogen). Details on desired vaccine properties in this context are listed in Table 1. These constraints indicate that a reliable ballistic-based vaccine formulation delivered from a distance of 50m or greater with accuracy to deliver i.m. without adverse incidents would be ideal. A biodegradable hydroxypropyl cellulose thermoplastically molded bullet delivery vehicle with either a 90- or 200-microliter payload compartment is commercially available (Biobullet™, SolidTech, Newcastle, OK). The requisite air rifle with back air canister is also available from the same vendor. However, disappointing recent vaccine protection performance of a compressed lyophilized RB51 vaccine payload to penned bison using this Biobullet™ delivery vehicle prompted our entry into revising the ballistic formulation to improve several technical delivery features for live vaccines.[3]

Table 1: Properties desired for remote vaccination of bison with Brucella live vaccine

- Live vaccine persists for approximately 12 weeks
- Induce strong cell-mediated immune responses to protect
- 'Clinically' safe, stable and reliable
- No adverse tissue localization/lesions post-vaccination
- Will not impair diagnostics-based field strain brucella detection
- Ballistics compatible: "leave no trace", 100% biodegradable
- Reliable sub-dermal delivery to bison from 50-100m range to thigh muscle
- Administration does not disturb normal herd behavior
- Rapid, inexpensive and convenient ballistic deployment and formulation for field personnel

Our answer to this unique parameter base in this formulation is to use hydrogel photopolymerization in the presence of the live vaccine formulation in reconstituted buffer in the bullet payload site. This produces a durable gel containing the live, viable RB51 *Brucella* strain at suitable dosages, and importantly, polymerized into the Biobullet™ payload compartment to resist displacement or dislodgement upon firing and impact.[4,5]

Hydrogel photopolymerization to encapsulate biological materials is a mature area of study with many examples. Live mammalian cells, proteins, and enzymes within polymer networks of many different chemistries are routinely reported.[6] Crosslinked polymer networks comprising polyethylene glycol (PEG) diacrylate esters were photopolymerized for the current application in the presence of aqueous reconstituted RB51 vaccine using a benzophenone photoinitiator. We demonstrated, consistent with other cell encapsulation reports, [6] that this strategy produced mechanically robust, swellable, benign gel environments, where the ultraviolet (<360nm) wavelengths used for polymerization and the photoinitiator were tolerated by the live, reconstituted RB51 bacteria without significant viability changes.[4] The 200-microliter payload compartment can be loaded with a gel matrix comprising ~ 10^{10} CFU of RB51, sufficient for bison dosing. One important distinction in the current releasing system is the need for rapid bacterial release. Since these RB51 organisms are non-motile and approximately 1-micron in size, matrix swelling to suitable mesh sizes sufficient for diffusion-mediated rapid, complete release proved difficult. Intrinsic PEG ester hydrolysis also proved too slow to permit degradation

(C&DP continued on page 21)

On the Move

by Kim Briggs
ELSEVIER, The Netherlands

This issue marks the 100th volume of the Journal of Controlled Release. The journal was born in 1984, and the first volume was published in September of that year. Perhaps a brief history of the genesis of the 8 *Journal of Controlled Release* would be of interest to our readers.

Early in 1984, I was asked by Dr. Danny Lewis, then the Controlled Release Society president, to investigate the possibility of starting a journal devoted to all aspects of controlled release of therapeutic agents for veterinary, agricultural, consumer products, and human therapeutics. Starting such a journal was a logical next step following the formation of the Controlled Release Society in 1978. After discussions with a number of publishing houses, it became clear that Elsevier would be best suited as the publisher, a decision that we have never regretted. Prior to launching the journal, Elsevier conducted an extensive survey to determine whether the scientific community felt the need for another journal. Due to an overwhelming positive response, the decision was made to launch such a journal, which we named the *Journal of Controlled Release*.

Since I felt that in addition to a demanding full-time job, launching a journal, acting as Editor-in-Chief and assuring its success was more than I was willing to take on alone, I asked a respected colleague and good friend Professor Jan Feijen to join me as founder and editor. To my immense relief, Jan agreed to do so. We decided that Jan would handle papers originating in Europe and I would handle papers originating in the Americas and elsewhere.

Once Jan and I had decided to work together we needed to work out the mechanics of getting the journal started. To do so, we met at the University of Utah, in Professor Sung Wan Kim's office, in a marathon session aided by generous portions of excellent scotch and in Jan's case, many, many, at least in my opinion, smelly cigars. Sung Wan was most helpful, by not only allowing us to use his office and supplying the scotch, but also by contributing valuable ideas. During that meeting, we also devised the logo that to this day adorns the journal.

In the 20 years that the journal has been in existence, there has been an enormous growth in the science of controlled release and, hopefully, the *Journal of Controlled Release* has mirrored that growth. Actually, Controlled Release is better viewed as Controlled Delivery since the delivery of the active agent to its site of action is critically important. Thus, had Jan and I possessed a crystal ball, we would have used the name *Journal of Controlled Delivery*. At various times we did consider changing the name, but that turned out to be so full of problems that we decided to keep the original name.

In keeping with the international nature the *Journal of Controlled Release*, and the Controlled Release Society, we approached the Japanese Society of Drug Delivery System (JSDDS) to see if they would honor us by making the *Journal of Controlled Release* their official journal, to which they readily agreed and on April 1, 1997 this became official. This was an important milestone and Professor Junzo Sunamoto became the first Japan/Far East editor.

After many years of acting as editors, both Jan and I decided that it was time to retire and let someone else take over. Jan made this decision in 1996 and I retired as editor in 1998. When Jan Feijen retired, we asked Professor Wim Hennink to assume the duties of European Editor and when I retired, we asked Dr. Colin Pitt to assume the duties of Editor-in-Chief. At that time, Professor Sunamoto asked to be relieved of his duties as the Japan/Far East editor, and Professor Tsuneji Nagai assumed that role. Professor Kazunori Kataoka is the current Associate Editor for Japan/Far East, having recently succeeded Professors Teruo Okano and Kozo Takayama in this capacity. This year, Professor Hennink has decided to step down and Professor Thomas Kissel will assume the duties of European Editor. In addition to these editors, Professor Vladimir Torchilin became the Review Editor and Professor Ronald Siegel became the Book Review Editor, taking over from Professor Lisa Brannon-Peppas.

The *Journal of Controlled Release* has enjoyed explosive growth. Starting with Volume 1 that consisted of only 325 pages, it has grown to its 2004 page budget of 3480 pages, slightly more than a 10-fold increase. To get a perspective of the volume of manuscripts that are processed on a yearly basis, the following statistics are of interest. In 2003, the total number of manuscripts submitted was 633. Of these, 166 were submitted from the Americas, 248 from Europe and 210 from Japan and the Far East. The acceptance rate in 2003 was 43%. In addition, 9 review articles were published. It is gratifying that a sufficient number of manuscripts are now received so that the editors can be highly selective and only accept high quality manuscripts.

There are a number of ways to judge the quality of a journal, and one of these is the ISI impact factor. An impact factor is calculated by dividing the number of citations to recent articles by the number of recent articles. In 1997, the *Journal of Controlled Release* had a relatively modest impact factor of 1.5, but the impact factor has steadily increased and in 2003 the impact factor was 3.3. Jan and I sincerely hope that this significant increase in the impact factor starting with 1998 is totally unrelated to our retirement as editors. An impact factor of 3.3 places the *Journal of Controlled Release* at the top of the list of comparable journals, a very significant achievement.

Since the inception of the *Journal of Controlled Release*, there has been an extraordinary evolution in the science of controlled delivery. One of the most significant developments deals with delivery of DNA and RNA. To recognize its importance and help attract high quality manuscripts dealing with this topic, a section entitled Gene Delivery was established in January 2001. This section has turned out to be very successful.

The two most important factors that will induce authors to send their best work to the *Journal of Controlled Release* is a high impact factor, and minimal delay in publishing the article. The latter has been aggressively pursued by the Editors and by Elsevier. While in 1999 the average production time was 28.5 weeks, the average production time decreased to only 14 weeks in 2003. And since articles in press are available on ScienceDirect, articles are available electronically in 12 weeks, or even earlier, after being sent electronically to Elsevier. Thus, if authors are prompt in returning revised manuscripts to the editors, they can have their manuscripts published in somewhat less than 6 months.

In our editorial for the first issue, we stated: *The success of a journal will clearly depend on the quality of the manuscripts contained within its covers, and the editors can only encourage the submission of high quality manuscripts and arrange for a critical and objective refereeing. Therefore, it is you, the authors, that will, in the last analysis, determine the ultimate quality of the journal.* Clearly, you, the authors, have done an outstanding job and the *Journal of Controlled Release* is now recognized as the leading journal dealing with all aspects of controlled delivery This editorial would not be complete without acknowledging the extraordinary contributions of Colin Pitt, the Editor-in-Chief, Wim Hennink, the European Editor, Junzo Sunamoto, Tsuneji Nagai, Teruo Okano, Kozo Takayama and Kazunori Kataoka, past and present Japanese/Far East Editors, David Friend, the former Associate Editor for the Americas, and the many, many reviewers who generously donated their time to provide the reviews without which it would not be possible to maintain the high standards that characterize the *Journal of Controlled Release*. On a personal note, Jan Feijen and I are enormously proud to have been instrumental in the creation of the journal.

Jorge Heller • E-mail address: jorgeheller2@aol.com.

SPOTLIGHT:

CHRONO THERAPEUTICS, INC.

by Guy DiPierro
Chrono Therapeutics, Inc., U.S.A.

Chrono Therapeutics, Inc. is developing the ChronoDose™ technology, a revolutionary medical device worn like a wristwatch for precise, programmable chrono-pharmacological drug delivery.

A significant focus of current research in drug delivery has been to determine the influence of a patient's circadian rhythms on drug efficiency. This research demonstrates that certain disease symptoms follow a daily pattern, with peak symptoms at certain times of the day. It is also widely acknowledged that hormones, neurotransmitters and other intra-body compounds are released in different amounts at different times of the day pursuant to daily patterns.

Research demonstrates that for certain diseases, drug effects can be optimized when administered in a defined (and most often varying) dosage at predefined times. By precisely timing the administration of drugs so that they reach peak levels when symptoms are likely to be at their worst, drug administration efficacy is greatly improved. Doctors have responded to this growing body of research by prescribing carefully timed drug administration regimens to optimize treatment, also known as chronopharmacology and chronopharmaceutics.

The continuing interest in chronopharmacology and chronopharmaceutics demonstrates the importance of biological rhythms to the dosing of medications. In response to this need, Chrono Therapeutics, Inc. is now developing a miniaturized drug delivery system for the precise, automated, time and dosage-controlled administration of drugs non-invasively through the skin. The ChronoDose™ system, worn like a wristwatch, can be pre-programmed to administer drug doses into the body automatically, at different times of the day, and with varying dose sizes. It automatically turns on and off to release drugs at preset times in preset amounts while asleep, or awake. The ChronoDose™ system is most effectively used to treat heart disease, depression, asthma, Attention Deficit Hyperactivity Disorder, hypertension, arthritis, and is also being commercialized for some "New to the World," over-the-counter applications.

The ChronoDose™ system represents the first true non-invasive chrono-pharmacological drug delivery device. While current passive transdermal applications are restricted to the dosage profile shown in Figure 1a, the automated ChronoDose™ system can be programmed for a variety of drug delivery patterns to achieve customized patient dosing regiments for optimal therapy (Figure 1b).

The ChronoDose™ system is capable of precisely tailored drug delivery where non-invasive, automated "time and dose precise" drug administration was previously impossible. The device can precisely control and vary the time of drug release and the amount of each dose by carefully controlling uptake rates thereby creating an easily set and fully automated pre-programmed dosage profile.

The system was developed on behalf of Chrono Therapeutics by its University Partners, the University of Basel, University of Applied Science of Solothurn (FHSO), and University of Applied Science of Basel (FHBB), and in association with the Director of New Product Development at Chrono Therapeutics, Dr. Hans Ludi, former Head of Product Development at Bayer Diagnostics.

FHSO's Head of MicroSolutions, Prof. Dr. Ing Wernher van de Venn, created components of the second prototype for *in-vitro* testing. Dr. van de Venn was honored with the Swiss Technology Award in 2002 and specializes in micro- solutions and micro-engineering. The first prototype was delivered by FHBB in August 2003 by Dr. Urs Bopp, and Dr. Daniel Gygax, micro-engineers. Dr. Hans Leuenberger, at University of Basel, began development by patenting the broad use of automated drug delivery systems.

Chrono Therapeutics, Inc. was created to commercialize drug-delivery devices with proven Chrono-Pharmacological advantages and broad, strong patent protection. It believes that Chrono-Pharmacology is the next major advance in drug delivery, and seeks to be on the cutting edge of this revolution. Chrono Therapeutics strategy is two-fold: quickly bring "new to the world" OTC applications to market; and rapidly merge existing medicines into improved therapies, with lower development costs, shorter time-to-market and less attrition. Chrono Therapeutics completed its first round of financing in February 2003.

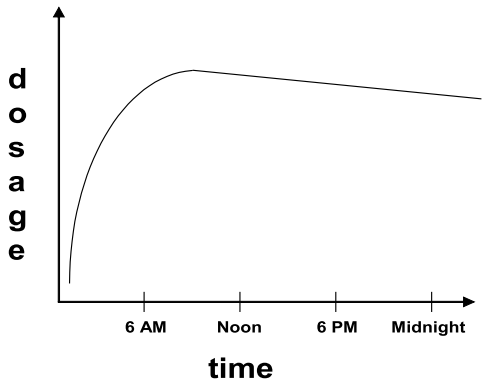

Figure 1a: Dosage Profile of Current Patch Products

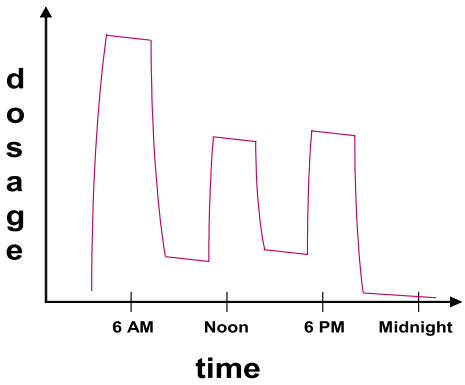

Figure 1b: Dosage Profile ChronoDose™ system

*(**Spotlight** continued on page 13)*

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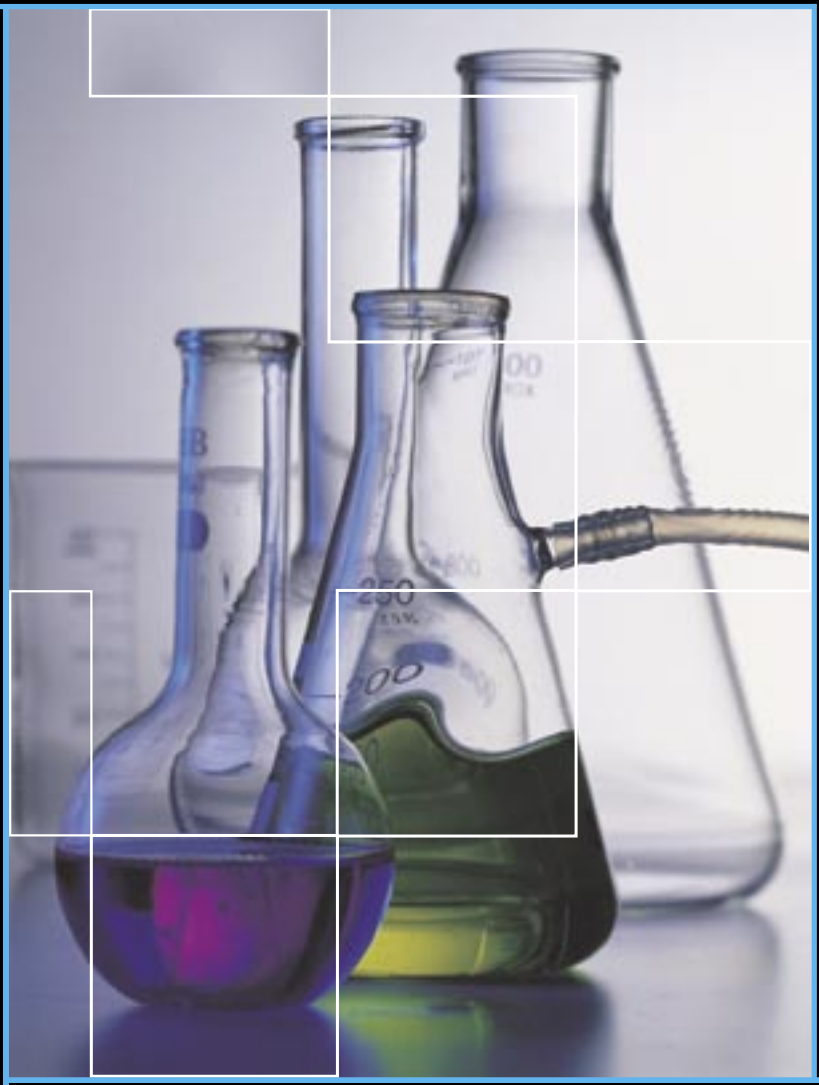

Plenary Sessions:

- **Angiogenesis in Cancer**
  M. Judah Folkman,
  Harvard University, U.S.A.
- **Nanotechnology**
  Sir Harold Kroto,
  University of Sussex, U.K.
- **Drug and Tissue Engineering: Past and Future**
  Robert Langer,
  Massachusetts Institute of Technology, U.S.A.

Workshops:

- **Colon Targeted Drug Delivery**
- **Drug Eluting Stents: Clinical Need and Technology Solution**
- **Micro and Nanoencapsulation: Formulation and Process**

Mini Symposia:

- **Bioinformatics Approaches to Drug Delivery and Targeting**
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*(**Pharm News** continued from page 6)*

Schmokel HG, Weber FE, Seiler G, von Rechenberg B, Schense JC, Schawalder P, Hubbell Treatment of nonunions with nonglycosylated recombinant human bone morphogenetic protein-2 delivered from a fibrin matrix.J.*Vet Surg.* 2004 Mar-Apr;33(2):112-8.
OBJECTIVE: To report the results of the treatment of nonunions with nonglycosylated recombinant human bone morphogenetic protein-2 (nglBMP-2) delivered from a designed fibrin matrix. STUDY DESIGN: Experimental trial in rodents and prospective clinical study in dogs and cats with nonunion fractures. ANIMALS: Twenty adult female, albino, Sprague-Dawley rats; 8 client-owned cats and dogs. METHODS: After development of a fibrin matrix and evaluation of nglBMP-2 in a rodent femoral defect model, 8 consecutive long bone nonunion fractures (no progression in healing in > or = 3 months), were treated using 300 microg nglBMP-2 in a liquid fibrin precursor, injected into the defect gap after fracture revision and stabilization, or through a stab incision into the fracture site. The fibrin matrix was designed to clot in the wound after 60 seconds and to release the nglBMP-2 continuously over several days. RESULTS: Using only fibrin gel, 7% of the rat femoral defect was filled with new formed bone compared with 79% defect filling using 2 microg nglBMP-2 (P=.006). Five and 10 microg nglBMP in fibrin resulted in union of all femoral defects with complete filling of the gap with new bone. Bony bridging and clinical healing was achieved in 7 patients within 24 weeks of administration of nglBMP-2. CONCLUSIONS: Application of nglBMP-2 in a functional matrix can induce bone healing. Controlled release of nglBMP-2 from a fibrin matrix mimics the natural fracture hematoma. CLINICAL RELEVANCE: nglBMP-2/fibrin can successfully replace a cancellous bone autograft in fracture treatment with an associated reduction in graft donor site morbidity and surgical time.

Moretto A, Tesolin L, Marsilio F, Schiavon M, Berna M, Veronese FM. Slow release of two antibiotics of veterinary interest from PVA hydrogels. *Farmaco.* 2004, 59(1):1-5.
Two antibiotics, tylosin tartrate and oxytetracycline hydrochloride, were entrapped in poly(vinyl alcohol) (PVA) hydrogels (MW 31,000-50,000) by a cryogen procedure obtaining a controlled release system suitable for veterinary application. It was found that at a low drug matrix loading (10 mg/ml), the *in vitro* release rate of both antibiotics could be reduced by a previous freeze drying of the gel, while no reduction in drug rate took place in heavily loaded matrices (300 mg/ml). When PVA hydrogels containing tylosin were administered to rats per os the drug could not be detected in the blood, but it was found in organs: liver, kidneys, and muscles, for up to 120 h. On the other hand, when the same amount of drug was administered orally as powder, no appreciable organ accumulation was detected, while the drug was found in faeces and urine. These data show that PVA hydrogels can be a suitable slow release system for tylosin administration. Oxytetracycline could also be quantitatively entrapped and released from PVA hydrogels, but once administered per os to rats, it was not detected in blood or organs.

Colazo MG, Kastelic JP, Mapletoft RJ. Effects of estradiol cypionate (ECP) on ovarian follicular dynamics, synchrony of ovulation, and fertility in CIDR-based, fixed-time AI programs in beef heifers. *Theriogenology.* 2003, ;60(5):855-65.
Estradiol cypionate (ECP) was used in beef heifers receiving a controlled internal drug release (CIDR; insertion = Day 0) device for fixed-time AI (FTAI) in four experiments. In Experiment 1, heifers (n = 24) received 1mg ECP or 1mg ECP plus 50mg commercial progesterone (CP) preparation i.m. on Day 0. Eight or 9 days later, CIDR were removed, PGF was administered and heifers were allocated to receive 0.5mg ECP i.m. concurrently (ECP0) or 24h later (ECP24). There was no effect of treatment (P = 0.6) on mean (+/-S.E.M.) day of follicular wave emergence (3.9+/-0.4 days). Interval from CIDR removal to ovulation was affected (P<0.05) only by duration of CIDR treatment (88.3+/-3.8h versus 76.4+/-4.1h; 8 days versus 9 days, respectively). In Experiment 2, 58 heifers received 100mg progesterone and either 5mg estradiol-17beta or 1mg ECP i.m. (E-17beta and ECP groups, respectively) on Day 0. Seven (E-17beta group) or 9 days (ECP group) later, CIDR were removed, PGF was administered and heifers received ECP (as in Experiment 1) or 1mg EB 24h after CIDR removal, with FTAI 58-60h after CIDR removal. Follicular wave emergence was later (P<0.02) and more variable (P<0.002) in heifers given ECP than in those given E-17beta (4.1+/-0.4 days versus 3.3+/-0.1 days), but pregnancy rate was unaffected (overall, 69%; P = 0.2). In Experiment 3, 30 heifers received a CIDR device and 5mg E-17beta, with or without 100mg progesterone (P) i.m. on Day 0. On Day 7, CIDR were removed and heifers received ECP as described in Experiment 1 or no estradiol (Control). Intervals from CIDR removal to ovulation were shorter (P<0.05) in ECP0 (81.6+/-5.0h) and ECP24 (86.4+/-3.5h) groups than in the Control group (98.4+/-5.6h). In Experiment 4, heifers (n = 300) received a CIDR device, E-17beta, P, and PGF (as in Experiment 3) and after CIDR removal were allocated to three groups (as in Experiment 2), with FTAI 54-56h (ECP0) or 56-58h (ECP24 and EB24) after CIDR removal. Pregnancy rate did not differ among groups (overall, 63.6%, P = 0.96). In summary, although 1mg ECP (with or without progesterone) was less efficacious than 5mg E-17beta plus 100mg progesterone for synchronizing follicular wave emergence, 0.5mg ECP (at CIDR removal or 24h later) induced a synchronous ovulation with an acceptable pregnancy rate to fixed-time AI.

Molento MB, Lifschitz A, Sallovitz J, Lanusse C, Prichard R. Influence of verapamil on the pharmacokinetics of the antiparasitic drugs ivermectin and moxidectin in sheep.*Parasitol Res.* 2004, 92(2):121-7.
P-Glycoprotein (P-GP) is a transport protein that participates in the mechanism of active secretion of different molecules from the

*(**Pharm News** continued on page 12)*

*(**Career Profile** continued from page 6)*

Veterinary controlled release offers exciting opportunities and challenges and while there is a trend for actives to translate from human to veterinary clinical indications, the same is often not the case for delivery technologies. Gastro-retentive technologies may be relatively new to the human field, but the veterinary pharmaceutical scientist has used and investigated density, physical lodgement and geometrical retention for many decades. Transdermal patches have been suggested as a means to avoid the sharp or large teeth of production animals, but the barrier to suitable patch adhesion presented by fur was overcome in part more than 20 years by patch-less technologies such as pour-ons. The first solvent-removal precipitation in-situ forming depot was indicated for dogs. The challenges now centre on issues associated with the development of products containing multiple actives and for long-term delivery of up to one year in a range of species. Craig is now focused on researching and protecting the intellectual property of a number of new controlled delivery technologies at InterAg. So far, Craig has had a rewarding and stimulating career in *in-situ* gelling, electronically controlled and polymer drug delivery in a unique specialised aspect of the veterinary pharmaceutical industry, namely controlled release. He also continues to contribute to the Society as Chair of the Veterinary Products Committee.

Email: craig.bunt@interag.co.nz ■

(Pharm News continued from page 11)

bloodstream to the gastrointestinal tract. The aim of the current work was to evaluate the effect of verapamil, a P-GP substrate, on the pharmacokinetic behaviour of the anthelmintics ivermectin and moxidectin in sheep. Thirty-two sheep were divided into four groups and treated orally with either ivermectin or moxidectin alone (200 micro g/kg) or co-administered with verapamil at 3 mg/kg (three times at 12 h intervals). Blood samples were collected over 30 days post-treatment and plasma was analysed to determine ivermectin and moxidectin concentrations by HPLC. The ivermectin peak concentration was significantly higher (P=0.048) after ivermectin plus verapamil, compared with the ivermectin alone treatment. Ivermectin plasma availability was significantly higher following co-administration (P=0.022). Verapamil had no effect on the kinetics of moxidectin. The significant alteration in the plasma disposition of ivermectin in sheep induced by verapamil, possibly due to interference with a P-GP-mediated elimination mechanism, may have an important impact on efficacy against resistant- or rate-limiting-parasites and on the persistency of its antiparasitic activity.

Mealey KL, Northrup NC, Bentjen SA. Increased toxicity of P-glycoprotein-substrate chemotherapeutic agents in a dog with the MDR1 deletion mutation associated with ivermectin sensitivity. *J Am Vet Med Assoc.* 2003; 223(10):1453-5.
Lymphoma was diagnosed in a 4-year-old spayed female Collie, and treatment with a combination chemotherapy protocol incorporating prednisone, L-asparaginase, vincristine, vinblastine, doxorubicin, and cyclophosphamide was initiated. The dog had signs of gastrointestinal tract toxicosis and myelosuppression after treatment with P-glycoprotein-substrate drugs (vincristine, vinblastine, and doxorubicin) even when dosages were reduced, but did not have signs of toxicosis after treatment with cyclophosphamide, a non-P-glycoprotein-substrate drug, even when administered at the full dosage. It was postulated that a deletion mutation in the canine MDR1 gene (deltaMDR1 295-298) could be responsible for the drug toxicoses in this dog. This mutation has been identified as the cause of a functional P-glycoprotein defect in Collies susceptible to the toxic effects of ivermectin, another P-glycoprotein-substrate drug. The MDR1 genotype of this dog consisted of 1 normal and 1 mutant MDR1 allele. Because P-glycoprotein contributes to renal, biliary, and intestinal excretion of P-glycoprotein-substrate drugs, it is possible that drug excretion was delayed in this patient, resulting in clinical signs of toxicosis.

Roulet A, Puel O, Gesta S, Lepage JF, Drag M, Soll M, Alvinerie M, Pineau T. MDR1-deficient genotype in Collie dogs hypersensitive to the P-glycoprotein substrate ivermectin. *Eur J Pharmacol.* 2003, 460(2-3):85-91.
Multidrug resistance (MDR) phenotypes in cancer cells are associated with overexpression of the drug carrier P-glycoprotein. The antiparasitic drug ivermectin, one of its substrates, abnormally accumulates in the brain of transgenic mice lacking the P-glycoprotein, resulting in neurotoxicity. Similarly, an enhanced sensitivity to ivermectin has been reported in certain dogs of the Collie breed. To explore the basis of this phenotype, we analyzed the canine P-glycoprotein-encoding MDR1 gene, and we report the first characterization of the cDNA for wild-type (Beagle) P-glycoprotein. The corresponding transcripts from ivermectin-sensitive Collies revealed a homozygous 4-bp exonic deletion. We established, by genetic testings, that the MDR1 frame shift is predictable. Accordingly, no P-glycoprotein was detected in the homozygote-deficient dogs. In conclusion, we characterized a unique case of naturally occurring gene invalidation. This provides a putative novel model that remains to be exploited in the field of human therapeutics and that might significantly affect tissue distribution and drug bioavailability studies.

Senel S, McClure SJ. Potential applications of chitosan in veterinary medicine. *Adv Drug Deliv Rev.* 2004, 56(10):1467-80.
Chitosan is a partially deacetylated polymer obtained from the alkaline deacetylation of chitin which is a glucose-based unbranched polysaccharide widely distributed in nature as the principal component of exoskeletons of crustaceans and insects as well as of cell walls of some bacteria and fungi. Chitosan exhibits a variety of physicochemical and biological properties resulting in numerous applications in fields such as waste and water treatment, agriculture, fabric and textiles, cosmetics, nutritional enhancement, and food processing. In addition to its lack of toxicity and allergenicity, and its biocompatibility, biodegradability and bioactivity make it a very attractive substance for diverse applications as a biomaterial in pharmaceutical and medical fields, where it has been used for systemic and local delivery of drugs and vaccines. It also has bioactive properties in its own right. This paper reviews current veterinary applications for chitosan including wound healing, bone regeneration, analgesic and antimicrobial effects. It also discusses the potential application of chitosan to drug and vaccine delivery in veterinary species. Given the restrictions imposed by financial and animal restraint considerations, especially in farming applications, the veterinary drug delivery areas most likely to benefit from chitosan are the delivery of chemotherapeutics such as antibiotics, antiparasitics, anaesthetics, painkillers and growth promotants to mucosal epithelium for absorption for local or systemic activity, and the delivery of immunomodulatory agents to the mucosal associated lymphoid tissue for induction or modulation of local immune responses. The properties of chitosan expected to enhance these functions are discussed, and the future research directions in this field are indicated.

Lamphear BJ, Jilka JM, Kesl L, Welter M, Howard JA, Streatfield SJ. A corn-based delivery system for animal vaccines: an oral transmissible gastroenteritis virus vaccine boosts lactogenic immunity in swine. *Vaccine.* 2004;22(19):2420-4.
Recombinant plant expression systems offer a means to produce large quantities of selected antigens for subunit vaccines. Cereals are particularly well-suited expression vehicles since the expressed proteins can be stored at relatively high concentrations for extended periods of time without degradation and dry seed can be formulated into oral vaccines suitable for commercial applications. A subunit vaccine candidate directed against porcine transmissible gastroenteritis virus and expressed in corn seed has been developed for oral delivery to swine. Here, we show that this vaccine, when administered to previously sensitized gilts, can boost neutralizing antibody levels in the animals' serum, colostrum and milk. Thus, this vaccine candidate is effective at boosting lactogenic immunity and is appropriate to pursue through large-scale field trials preceding commercialization.

Breathnach CC. Rudersdorf R. Lunn DP.
Use of recombinant modified vaccinia Ankara viral vectors for equine influenza vaccination. *Veterinary Immunology & Immunopathology.* 98(3-4):127-36, 2004.
Recombinant modified vaccinia Ankara (MVA) vectors expressing equine influenza virus genes were constructed and evaluated for use in equine vaccination. Two strains of recombinant MVA, expressing either hemagglutinin (HA) or nucleoprotein (NP) genes were constructed. Each influenza virus gene was cloned from A/equine/Kentucky/1/81 (Eq/Ky) into an MVA construction plasmid, and was introduced to the deletion III locus of the wild type MVA genome by homologous recombination. Recombinant viruses were plaque purified, and antigen expression was confirmed by immunostaining. Two ponies were primed by vaccination with 50 microg HA-DNA and two ponies were vaccinated with 50 microg NP-DNA using the

(Pharm News continued on page 32)

*(**Spotlight** continued from page 9)*

New Technology - Chrono Therapeutics has exclusive intellectual property rights to the ChronoDose system, and all related patents, pursuant to agreements between Chrono Therapeutics and its University Partners. We have a pre-eminent global umbrella patent, U.S. 5,370,635, and two patents pending that broadly protect automated transdermal systems. Next, pursuant to our extensive R&D contracts with the University, we have developed a groundbreaking new method for "time and dose" precise transdermal drug delivery. The University of Basel, Switzerland, located in Switzerland's highly regarded "BioValley" is our primary strategic partner. Together, with the University, we have filed a PCT utility patent application in Europe and in the USA to protect our novel technology and its use in combination with different types of drug delivery subcomponents. We believe our new technology will prove critical and indispensably valuable in time-dose precise applications. The ChronoDose system was tested at the University's Pharmacenter after carefully devising and implementing the testing parameters and the new technology has proven effective in initial testing.

These laboratory tests show that our New Technology significantly expands the capability of current, non-invasive drug delivery systems and achieved the initial objectives. These include: a) administer drugs more rapidly and with less lag time than current non-invasive systems b) accurately and precisely vary each and every dose (adjust delivery rates to predefined values), c) start and stop drug delivery accurately and with precision at predefined time points (accurate "on and off" dosing) and, d) achieve all of the above repeatedly and with the same degree of accuracy each time (i.e., multiple starts and stops to achieve any pre-programmed and optimized drug delivery profile that is therapeutically superior based on chronopharmacology).

Chrono Therapeutics, Inc. is developing the ChronoDose™ technology, a revolutionary medical device worn like a wristwatch for precise, programmable chrono-pharmacological drug delivery.

Suggested Reading:

Gothoskar, A. V., A.M. Joshi, A. M., & Joshi, N. H., Pulsatile drug delivery systems: A Review. *Drug Delivery Technology*, (4) 5

(http://drugdeliverytech.com/cgi-bin/articles.cgi?idArticle=250) Accessed 11/1/04(2004).

Journal of Controlled Release Highlights
Oct 2004

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

The following is a brief description of three papers accepted for publication in the *Journal of Controlled Release*. The first paper is by Li and Schwendeman. They report a mapping technique useful in measurement of the microclimate pH within poly(lactic-co-glycolic acid) (PLGA) microspheres. The issue of microclimate pH is important since it can limit the use of acid sensitive drugs with these polymers. The method is based on laser scanning confocal microscopic imaging. The technique was able to demonstrate the ability of acid neutralizing excipients, such as $MgCO_3$, to maintain a higher microsphere pH compared with microspheres without such excipients.

Holland, Tabata, and Mikos report on delivery of two growth factors from degradable oligo(poly(ethylene glycol) fumarate) hydrogels scaffolds for cartilage tissue engineering. The scaffold material is used to encapsulate gelatin microspheres, which contain the active agents. Depending on conditions and materials employed, the release of insulin-like growth factor-1 and transforming growth factor-β1 was sustained up to four weeks.

Microfabrication techniques can potentially address some current needs in the field of drug delivery and in their recent paper Li and a host of co-authors including Profs. Langer, Brem, and Cima, describe a microelectromechanical system (MEMS) with micro-reservoirs etched into a silicon substrate. Dissolution of drug from a microreservoir is controlled by the electrochemical dissolution of a gold membrane that covers the reservoir. This work reports the *in vivo* (rats) controlled dissolution of two tracer molecules and one chemotherapeutic agent, carmustine. The data presented demonstrate the ability of this MEMS device to deliver various compounds with defined temporal profiles locally.

Finally, I wish to mention Jorge Heller's editorial on the occasion of the publication of the 100th volume of the *Journal of Controlled Release*. This editorial covers the history of the Journal from the earliest planning days to the present (over 25 years). I had the honor of working with Jorge on the Journal and I extend my thanks to him for his hard work and dedication. Jorge's early vision has led to a truly successful enterprise covering the science and technology of controlled release. ■

Waterhouse J, An introduction to chronomedicine. *Drug Delivery Systems & Sciences*, (2) 45 (2001).

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Chapter Update

by Susie Berrill and Maura Kinahan
UKICRS Committee Members, U.K.

The UK and Ireland Controlled Release Society organised a mini-symposium on the theme of *'Imaging: from molecules to man'* at the British Pharmaceutical Conference in Manchester in September, 2004. Historically, imaging technologies have been used to help make diagnoses in individual patients in order to guide therapeutic decisions. However, in recent years, there has been a shift to a broader-than-diagnostic view of the value of routine imaging tools.

Dr Neena Washington (Astra Zeneca, UK) provided an overview of how medical imaging has evolved since the turn of the 20th century.

While scientific, regulatory and economic questions still need to be addressed, imaging technologies have the potential to increase efficiencies in many areas of drug research. A panel of international speakers addressed some of the exciting developments in this field which can support the drug discovery and development processes.

The morning session commenced with **Dr Kai Licha (Schering AG, Germany)**, who spoke of one approach to the great challenges of oncology, namely improved methods for early tumour detection. The use of cyanine dyes as contrast agents for in vivo optical detection of tumours using monoclonal antibodies to target receptors on the tumour cells has been extensively studied. However, the immunogenicity and the long plasma half-life of these molecules mean that they are not useful in practice. One approach to eliminate these problems is to use small tumour-targeting peptides. For example, many tumours have been shown to over express receptors for somatostatin. Dr. Licha presented on the in vivo diagnostic use of a peptide–dye conjugate consisting of a cyanine dye and the stable somatostatin analog octreotate as a contrast agent. When imaging mouse xenografts, indotricarbocyanine-octreotate accumulated in tumor tissue and tumor fluorescence was shown to rapidly increase and was more than threefold higher than that of normal tissue up to 24 hours after administration. The targeting conjugate was specifically internalized by primary human neuroendocrine tumour cells. This imaging approach, combining the specificity of ligand/receptor interaction with near-infrared fluorescence detection, may be applied in various other fields of cancer diagnosis. Additionally, this approach can help facilitate the drug discovery process for targeted cancer therapy.

Dr Anwar Padhani **from Mount Vernon Cancer Centre (London) and Synarc (San Francisco)** spoke about targeting tumours using MRI techniques capable of imaging vascularity. Dynamic contrast enhanced MRI (DCE-MRI) is a technique where the enhancement of a tissue or organ is continually monitored after the bolus intravenous administration of an exogenous contrast medium over a short period of time (i.e. minutes). The contrast medium diffuses into the extravascular-extracellular leakage space and DCE-MRI can then be utilised to highlight differences in the temporal contrast uptake patterns of healthy versus diseased tissues. DCE-MRI can also be applied as a biomarker to seek early biological evidence of antivascular pharmacodynamic action. Dr Padhani provided some "proof of concept" data in rodents where DCE-MRI was successfully used to identify a biologically active dose of intravenous combretastatin (CA4P) on the microvasculature of a carcinosarcoma over time. He also presented data where DCE-MRI was not an appropriate technique to identify targets for SU5416, an inhibitor in the tumour angiogenesis cascade. Dr. Padhani concluded that although DCE-MRI has been demonstrated as being a useful tool for the evaluation of treatment strategies to target some tumour vascularities, regulatory approval will depend mainly on improved QA procedures to allow for multi-centre comparisons.

Dr Neena Washington (Astra Zeneca, UK) provided an overview of how medical imaging has evolved since the turn of the 20th century. The focus with the various imaging techniques routinely available at the start of the 21st century such as magnetic resonance imaging (MRI) and positron emission tomography (PET) tends to be as anatomical diagnostic tools with some functionality. In recent years, the pharmaceutical industry has been considering how imaging techniques can accurately and economically monitor disease states, and how they can inform on the progression of a particular disease. In early 2004, the FDA published 'Imaging technologies tagged for FDA drug development initiative' (The Gray Sheet, 30(005), pp. 7 (February 2, 2004)) and a further FDA publication related to the subject was released in March 2004 ('Innovation or stagnation' FDA White Paper). These publications acknowledged that new and current imaging technologies could provide important biomarkers and surrogate endpoints to aid the scientific understanding of medicinal product development. However, the challenges that need to be addressed before these tools can be used routinely for such purposes include a greater understanding of the data generated including useful statistical treatment and the standardization of acquisition protocols.

Gamma Scintigraphy (GS) is one imaging technique that is used routinely to study the *in vivo* behaviour of dosage forms. Dr Washington provided data demonstrating the usefulness of GS by showing how a sustained release formulation of oxprenolol performed very differently *in vivo* between study subjects,

Dr Markus Rudin (Novartis Institute for Biomedical Research, Basel) spoke about scaling down imaging techniques to follow a drug's distribution and target binding in a live subject and to quantify its direct effect at a specific molecular target (e.g. receptor up- or down-regulation, activation or inactivation).

mainly due to differences in the dosage form transit times through the gastrointestinal tract. She posed the question whether or not GS has been superseded in the drug development field with the advent of seemingly more powerful imaging techniques. She concluded that GS is still a versatile, safe and economical means of helping to improve efficiencies in many areas of drug research.

Dr Markus Rudin (Novartis Institute for Biomedical Research, Basel) spoke about scaling down imaging techniques to follow a drug's distribution and target binding in a live subject and to quantify its direct effect at a specific molecular target (e.g. receptor up- or down-regulation, activation or inactivation). The prospect of having such tools available to the pharmaceutical industry just a few years ago seemed more wishful thinking than reality. However, the rapid development of enabling technologies with higher spatial resolutions and the advent of new imaging agents means that the use of imaging endpoints instead of time-consuming dissection and histology is fast becoming a reality. Additionally, advances in chemical, genomic and proteomic sciences have accelerated the development of more precise therapeutics aimed at specific molecular disease targets (e.g. Glivec™ to target BCR-ABL receptor tyrosine kinase). The choice of imaging modality in drug discovery and development depends on the specific question to be addressed. MRI can be used and for studying diseases of the central nervous system such as neurodegenerative disorders. PET has the sensitivity to monitor drug distribution, pharmacokinetics and pharmacodynamics, and for imaging specific molecular endpoints. A vast array of molecular endpoints can be visualized depending on the ligands and radionuclides used. This presentation emphasised that any developments in imaging techniques need to be quantitative, reproducible, safe, specific, sensitive, cost effective, and easily applied in clinical practice.

The assembled speakers and organisers of the symposia. From left to right: Dr. Neena Washington, Dr. Bill Vennart, Dr. Yvonne Perrie, Dr. Markus Rudin, Dr. Andreas Briel, Dr. Marc Berridge, Dr. Kai Licha, Dr. Anwar Padhani, Dr. Maura Kinahan, Dr. Susie Berrill, & Prof. Ken Miles.

The afternoon session commenced with a presentation from **Dr Andreas Briel (Schering AG, Germany)** on 'Ultrasonic Theranostics'. The term 'theranostics' is an amalgamation of therapy and diagnostics and describes a treatment strategy that identifies patients most likely to be helped or harmed by a new medication. Based on the results, a targeted drug therapy can be developed. Dr. Briel described the use of antibody-based microbubble conjugates as targeted *in vivo* contrast agents and drug delivery systems. The technology is flexible and can be used for functional diagnostics or for target specific delivery. The ultrasound contrast agent is a bubble surrounded by a surfactant coat of approximately 2 μm in size. Acoustic pressure on the microbubble will produce certain noise and as the microbubble ruptures it appears as a flash on the screen. If there is a high concentration of bubbles, many events can be observed. Counting of bubbles is the basis of functional imaging by ultrasound. The surface of the microbubbles can be modified using acidic groups and antibodies for targeted drug delivery. A further modification sees the incorporation of a drug into the internal void space of the bubble. The application of ultrasound causes the rupture of the microbubble allowing release of the drug to the targeted site. Dr Briel also discussed the application of this technique for gene delivery.

Dr Marc Berridge (Case Western Reserve University, Ohio, USA) presentation was entitled 'Drug delivery evaluation and dosage form development using positron emission tomography'. Historically, imaging has been achieved by computed tomography or CT scanning which provides cross-sectional images of the body. It is relatively non-invasive, and has very low short- and long-term risks (if the well-known potential hazards are avoided) and it can provide clinically relevant anatomic and functional information. By comparison, PET provides three-dimensional images which can be quantified. The images are obtained when an isotopic carbon atom is substituted on the drug molecule, and on decay, it produces gamma rays in all directions. This type of labeling requires full synthesis of the drug molecule with the isotopic substitution. After administration of the analogue molecule, the metabolic pathway can be observed using a PET scanner. Dr. Berridge showed some PET video clips of the path of inhaled drugs illustrating the deposition in the mouth, throat and lungs. The benefits of the spacer device in Azmacort™ developed by Kos Pharmaceuticals were illustrated and the deposition profiles was quantified, showing an increased lung deposition from 2.3% to 5% and reduced deposition in the mouth (64% down to 37%). Overall, a significant improvement in device performance was seen when using the spacer device with an inhaler. The path of the drug after deposition in the lung can also be monitored for up to 1 hour allowing the systemic delivery to be visualised. Images of the systemic delivery of a drug through the lung to the systemic circulation and ultimately the liver were also provided. Three dimensional video clips of the nasal drug delivery of Nasacort™ AQ Nasal Spray were also provided. In summary, PET is a valuable technique for product evaluation, formulation identification and a useful demonstration tool for marketing purposes.

*(**Chapter Updates** continued on page 30)*

Patent Watch

by Yvonne Perrie
Aston University, U.K.

Since our last Newsletter there have been several new Pharmaceutical patents granted relating to drug delivery and controlled release, a few of these have been highlighted below.

Aerosol Drug Delivery.
A system to support the delivery of diazepam through the inhalation route has been patented by Alexza Molecular Delivery Corporation (Palo Alto, CA) (US 6,805,853). Specifically it relates to aerosols containing diazepam. The invention is described as an aerosol comprising of particles containing at least 5% by weight of diazepam and typically, the aerosol is formed by heating a composition containing diazepam to form a vapour and subsequently allowing the vapour to condense into an aerosol. The device to achieve this will comprise: an element for heating the diazepam composition to form a vapour; b) an element allowing the vapour to cool to form an aerosol; and, c) an element permitting inhalation of aerosol. This company has also patented similar systems for the delivery of a range of drugs including anti-depressants (US 6,783,753), erectile dysfunction drugs (US 6,803,031), muscle relaxants (US 6,797,259), stimulants (US 6,780,399) and opioids (US 6,776,978) all through the inhalation route.

Vesicles and Particulates
Amersham Health, Inc (Princeton, NJ) has patented (US 2004197392) pH-sensitive liposome systems for application as contrast agents and medicaments. These liposomes, which could be prepared from various combinations of phosphoethanolamine and/or succinylglycerol analogues can entrap paramagnetic contrasting agents and remain pH sensitive in human blood. These liposomes are said to be suitable for *in vivo* detection of low pH areas including tumours or cardiovascular diseases (e.g. stroke and osteoporosis).

Advanced Inhalation Research Inc (Cambridge) (US 6,749,835) has patented a method for the formulation of spray-drying large porous particles suitable for pulmonary delivery. The method includes forming a mixture containing a carboxylate moiety (e.g. a carboxylic acid or salt thereof), a multivalent salt, a phospholipid, a solvent, and a therapeutic agent. The mixture, in the form of a colloidal suspension, is spray-dried to form particles having a tap density of less than about 0.4 g/cm^3. Preferred solvents that can be employed in the spray drying process include organic or organic-aqueous solvents.

Oral dosage forms
A table formulation which can give sustained release without an interfering food effect and which can be produced in a simple manner for all types of active compounds, in particular for poorly soluble active compounds have been patented by Bayer Aktiengesellschaft (US 6,805,881). The system relies on the combination of the hydrophilic polymer hydroxypropylcellulose (HPC) combined, in an amount from 40 -95% by weight, with the active compound. The active compound-polymer combination is converted into small particles such as pellets, granules or mini-tablets (max diameter 0.2 to 3.0mm). These sustained-release mini-particles can be administered as multiple-unit sustained-release dose forms (e.g. gelation capsules, sachets or tablets).

Ortho-McNeil Pharmaceuticals, Inc (Raritan, NJ) has been issued with a patent covering taste masked liquid pharmaceutical compositions (US 6,806, 256). This patent describes the application of artificial sweeteners to mask the taste of a bitter tasking pharmaceutically active agent.

Vaccines
A recently issued patent (US 6,803,042) to the U.S Army Medical Research Material Command (Fort Detrick, MD) outlines a system for oral or intranasal vaccines. The invention provides emulsions comprising a plurality of submicron oil-in-water droplets of a particle size in the range of 50 nm to 500 nm that effect enhanced immunogenicity of antigens incorporated intrinsically or extrinsically into the particles. Therefore the submicron emulsion particles of the invention can be used as vaccine adjuvants. The claimed novelty of this present invention is that it does not require use of any immunostimulatory mycobacteria or muramyl peptide-like additives for its submicron emulsion to be effective and effective adjuvant.

The US Army has also patented an Anthrax vaccine (US 6,770,379) which uses non-toxic proteins from *B. anthracis* and protects against infection with anthrax.

Aventis Pasteur SA (Lyons, France) has patented (US 6,780,421) an amphipathic compound which includes a sterol-derived lipophilic grouping bound to a cationic grouping (e.g. 3-.beta.-(N-(N'-N-'-dimethylaminoethane)carbamoyl) cholesterol) for use as an adjuvant in the delivery of a vaccine composition. The amphipathic compounds can be dispersed in water or in an aqueous buffer, and can yield a suspension of micelles or, when combined with a phospholipid (e.g. dioleoylphosphatidylethanol-amine or dioleoylphosphatidylch oline), will form liposomes. The administration of a liposomal composition of amphipathic compounds according to the invention combined with the antigen are said to increase the humoral type immune response, but also to induce specific cytotoxic T lymphocytes.

Gene Therapy.
A US patent (6,806,084) has been granted to The University of California (Oakland, CA) which describes methods and compositions for systemic introduction of exogenous genetic material into human cells in vivo. The patent claims novel methods (including cationic liposomes) and compositions are used to transfect multiple individual tissues. ■

IntheNews

compiled by Steven Giannos
Industrial Editor, U.S.A.

Drug Delivery Company Signs Licensing Agreement For Cystic Fibrosis Treatment

NewsRxGeneTherapy via NewsEdge Corporation : 11/3/2004 - Oriel Therapeutics announced that it has signed a development and licensing agreement with an undisclosed U.S.-based biotechnology company to develop a novel therapy for the treatment of cystic fibrosis. This therapy will be based on Oriel Therapeutics' proprietary dry powder inhalation technology incorporating the partner's proprietary compounds that represent a novel mode of action to improve airway function.

Cystic fibrosis is a genetic disorder that affects approximately 30,000 children and adults in the United States. The disease causes the body to produce abnormally thick, sticky mucus that clogs the lungs and leads to life-threatening infections and difficulty digesting food and nutrients. Traditionally, cystic fibrosis has been treated with nebulized products, which can take 30 minutes to administer and even longer for the treatment to take effect. In contrast, this therapy will be delivered as a dry powder in a single inhalation from a reloadable Oriel inhaler. This design allows for potentially quicker and easier administration of inhaled therapies.

Commenting for Oriel Therapeutics, CEO Paul Atkins said, "We believe that our technology has broad applicability across a wide range of powder formulations used to treat major pulmonary ailments including asthma, COPD and cystic fibrosis. This agreement to develop a novel therapy for treating cystic fibrosis is an exciting endorsement of the technology and we are delighted with this relationship."

New Canker Sore Treatment Heals Sores In 1-4 Days

NewsRxDrugs via NewsEdge Corporation: 10/29/2004 - Orahealth Corporation has introduced Cankermelts-GX, the only over-the-counter medication that heals canker sores in 1-4 days. The active ingredient in Cankermelts is Glycyrrhiza herbal extract (GX). GX has been found in clinical observations and double blind comparisons to shorten healing time to less than 4 days and typically 1 day. Using any other product or nothing at all, sores usually heal in seven to 14 days. The product also effectively heals other ordinary mouth ulcers, including denture sores and cuts from braces or biting your lip or cheek.

Cankermelts' patented delivery system, invented by Jeff Haley, chief scientist and founder of Orahealth, is a medicated disc, slightly smaller than a dime that adheres (within one to two minutes) inside the mouth on or near the sore. As the time-release medicine is delivered, the disc naturally dissolves over 2 to 6 hours. Cankermelts can be used comfortably during any activity, including sleeping and exercising and do not interfere with normal functions, such as swallowing, chewing or talking.

"We always take pleasure in doing business with local companies such as Orahealth, and it's gratifying to be the first retailer to carry a product that may soon be recognized throughout the nation as the leader for the treatment of canker sores," said John Weith, vice president of Merchandise for Bartell Drugs.

Formed in 2002, Orahealth Corporation is committed to providing the most effective medical treatments for healing and preventing canker sores and other ordinary mouth ulcers including denture sores and cuts from braces or biting your lip or cheek. The privately-owned company is based in Bellevue, Washington.

AXM Pharma Secures Exclusive Distribution Rights For Bioprogress Soluleaves In-The-Mouth Dissolving Film Oral Drug Delivery Technology For Prescription

NewsEdge Corporation : 10/28/2004 - AXM Pharma Inc has acquired the exclusive distribution rights in China to certain formulations of the Soluleaves oral drug delivery technology using dissolve-in-the-mouth films developed by BioProgress plc. The agreement includes the option to extend the distribution rights throughout Asia. The products will be manufactured by the BioProgress subsidiary BioTec Films LLC and will be distributed by AXM Pharma under the Sunkist brand and under AXM house brands. BioProgress plc through its BioTec films subsidiary in Tampa, FL, has successfully developed vitamin and nutritional products in this delivery mechanism and has several patents granted and in application for innovative processes which enable the delivery of pharmaceutical drugs in soluble film. The market for advanced drug delivery systems is expected to grow from $16.28 bn in 2000 to $27.35 bn in 2005 in the US. Market research at CIMA Labs shows that a significant percentage of consumers prefer orally dissolving drug delivery to conventional pills, tablets and liquids. AXM Pharma Inc, through its wholly owned subsidiary, Werke Pharmaceuticals Inc, is the 100% owner of AXM Pharma Shenyang Inc, a Wholly Foreign Owned Enterprise under the laws of the People's Republic of China.

Automated Drug Delivery

 Via NewsEdge Corporation : 10/27/2004 - Traditional methods of drug delivery require a caretaker or the patient themselves to administer the drugs when needed. All that can change with the advent of automated drug delivery systems. Researchers from the Georgia Institute of Technology, Atlanta, have developed micro-thin implantable films that hold and then release medication according to changes in temperature. A decade's worth of work in targeted drug delivery methods have shown the researchers that films assembled from microparticles allow more control over drug release than films made previously in monolithic form.

"We loaded insulin in layers of microgel films in the lab and released bursts of insulin by applying heat to the films," says Andrew Lyon, associate professor at Georgia Tech's School of Chemistry and Biochemistry. "They were extremely stable and could continue to release the drug for more than one month at a time." The film is envisioned as being part of a blood glucose monitoring system where if a high-blood sugar count is detected it will automatically release a specified dosage of insulin. Presently, the films release the drugs at 31°C, lower than the human body temperature, but efforts are under way to bring this up to a higher temperature. For more information, contact the Georgia Institute of Technology, 404-894-2000, www.gatech.edu/news-room.

New Gel Pill Could Mean An End To Injections

NewsRxDrugs via NewsEdge Corporation : 10/28/2004 - Scientists in India have developed a new gel that is taken orally and is capable of delivering drugs to manage diseases often requiring an injection. The research, published online September 20, 2004, in the journal Polymer International, suggests the gel could offer a painless way of treating diabetes, ulcerative colitis, Crohn's disease, bowel cancer, constipation and some infections, all of which require local drug delivery.

In these conditions, oral administration of medication cannot be achieved easily because highly acidic gastric fluid in the stomach contain enzymes that can break down the active drug before it reaches the target site. However, Dr. Sunil Bajpai and Seema Dubey from the Polymer Research Laboratory at Government Model Science College in Jabalpur, India, produced a polymer gel into which a drug may be simply loaded.

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The hydrogel system has been designed so that when swallowed by the patient, it passes through the stomach, retaining the majority of the drug by protecting it from the stomach acids. Fifty-six percent of the drug is released where it is needed - further down the gastrointestinal tract in the colon. It is deposited when the gel swells in response to the colon's alkaline pH.

"The terpolymeric hydrogel system studied by our team provides an alternative to the parenteral medication of insulin. It is now necessary to carry out *in vivo* studies of this hydrogel system so that it could be further modified to produce oral delivery pills," said Bajpai.

To test the gel, the scientists put vitamin B2 in the hydrogel in place of a drug and studied its releasing capacity in conditions simulating a human body, namely gastric (pH 1.0) and intestinal (pH 7.4) fluids at a body temperature of 37 degrees C, under various experimental conditions. This helped to predict the behavior of the vitamin-loaded gel in body conditions.

"This is important in a number of diseases and medical conditions. The new material developed in this research is simple, elegant, versatile, and performs well," said Dr. Malcolm Purbrick, industrial polymer science editor of Polymer International.

Bioresorbable Nanofibers May Be Drug Delivery Systems For Wound Healing

NewsRxAngiogenesis via NewsEdge Corporation : 10/8/2004 - Poly(lactide-co-glycolide) (PLAGA) nanofibers may be effective as antibiotic delivery systems to promote wound healing.

"Wound healing is a complex process that often requires treatment with antibiotics. This article reports the initial development of a biodegradable polymeric nanofiber-based antibiotic delivery system," researchers in the United States report.

"The functions of such a system would be (a) to serve as a biodegradable gauze, and (b) to serve as an antibiotic delivery system. The polymer used in this study was (PLAGA), and nanofibers of PLAGA which were fabricated with the use of the electrospinning process," wrote D.S. Katti and colleagues, University of Virginia, Department of Orthopedic Surgery.

"The objective of this study was to determine the effect of fabrication parameters: orifice diameter (needle gauge), polymer solution concentration, and voltage per unit length, on the morphology and diameter of electrospun nanofibers," the researchers stated.

"The needle gauges studied were 16 (1.19 mm), 18 (0.84 mm), and 20 (0.58 mm), and the range of polymer solution concentration studied was from 0.10 g/mL to 0.30 g/mL. The effect of voltage was determined by varying the voltage per unit electrospinning distance, and the range studied was from 0.375 kV/cm to 1.5 kV/cm," the researchers wrote.

"In addition, the mass per unit area of the electrospun nanofibers as a function of time was determined and the feasibility of antibiotic (cefazolin) loading into the nanofibers was also studied. The results indicate that the diameter of nanofibers decreased with an increase in needle gauge (decrease in orifice diameter), and increased with an increase in the concentration of the polymer solution," the researchers stated.

"The voltage study demonstrated that the average diameter of the nanofibers decreased with an increase in voltage. However, the effect of voltage on fiber diameter was less pronounced as compared to polymer solution concentration. The results of the areal density study indicated that the mass per unit area of the electrospun nanofibers increased linearly with time," the researchers wrote.

"Feasibility of drug incorporation into the nanofibers was demonstrated with the use of cefazolin, a broad-spectrum antibiotic. Overall, these studies demonstrated that PLAGA nanofibers can be tailored to desired diameters through modifications in processing parameters, and that antibiotics such as cefazolin can be incorporated into these nanofibers. Therefore, PLAGA nanofibers show potential as antibiotic delivery systems for the treatment of wounds," the researchers concluded.

Katti and colleagues published their study in the Journal of Biomedical Materials Research (Bioresorbable nanofiber-based systems for wound healing and drug delivery: Optimization of fabrication parameters. J Biomed Mater Res, 2004;70B(2):286-296).

For additional information, contact C.T. Laurencin, University of Virginia, Department Orthopedic Surgery, Charlottesville, VA 22903 USA.

Heat-Controlled Drug Implants Offer Hope For Future

NewsRxDiabetes via NewsEdge Corporation : 10/4/2004 - Researchers at the Georgia Institute of Technology have developed a material that may one day allow patients to forgo daily injections and pills and receive prescriptions instead through micro-thin implantable films that release medication according to changes in temperature. The research, detailing results from testing insulin release in the lab, appears in the September/October 2004 edition of the journal Biomacromolecules.

"We loaded insulin in layers of microgel films in the lab and released bursts of insulin by applying heat to the films. They were extremely stable and could continue to release the drug for more than one month at a time," said L. Andrew Lyon, associate professor at Georgia Tech's School of Chemistry and Biochemistry.

The results add to a decade's worth of work in controlled and targeted drug delivery. Lyon's use of films assembled from microparticles allows more control over drug release than films previously made in monolithic form.

The insulin tests, said Lyon, serve as proof of a concept that this method of drug delivery is worth further investigation. Currently, the films release their cargo at 31°C, 6 degrees below human body temperature, but Lyon's group is working on pushing the release point to a temperature slightly above that of the human body. Once implanted, the pharmaceutical-loaded films could be placed on chips with resistive heaters and scheduled to release drugs according to a time schedule or another trigger.

"One potential use is tying the implant to a blood glucose monitor using radio frequency (RF) technology," said Lyon. "When the monitor detects that a diabetic patient has low blood sugar, it could send a signal to the chip to heat the film and release insulin into the bloodstream."

Patients undergoing hormone therapy, chemotherapy or other treatments requiring periodic medication could conceivably get their dosages this way.

"Of course using these films to deliver medications in humans would require many more trials," said Lyon. "We believe we've taken an important step in new methods of drug delivery."

Carrington Subsidiary Receives $6 Million Biodefense Grant To Develop Nasal Flu Vaccine

PR Newswire via NewsEdge Corporation : IRVING, Texas, 10/5/2004 - Carrington Laboratories, Inc. (Nasdaq: CARN) today announced that its wholly-owned subsidiary, DelSite Biotechnologies, Inc., has been awarded a $6 million grant from the National Institute of Allergy and Infectious Diseases to develop an inactivated influenza nasal powder vaccine against the H5N1 strain commonly known as bird flu. The grant

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was awarded under a biodefense and SARS product development initiative and will fund a 3-year preclinical program utilizing the company's proprietary GelVac(TM) delivery system.

Commenting on the award, DelSite's president, Dr. Kenneth (Bill) Yates, said, "This award serves as an important milestone for DelSite because it allows us to begin development of our first vaccine product based on the GelVac(TM) delivery system, a vaccine that addresses the potential for pandemic outbreaks of H5N1 (bird flu), which has reportedly caused more than 30 deaths in Asia this year. We have assembled an excellent team of scientists for this project led by Dr. Yawei Ni, and we look forward to the opportunity that this grant provides for our company."

The company's GelSite(TM) polymer technology, which is the basis for the GelVac(TM) Nasal Powder vaccine delivery system, is a novel polysaccharide that turns from a powder to a gel upon contact with nasal fluids, resulting in controlled release and increased nasal residence time of vaccine antigens. The benefits of an intranasal powder vaccine could potentially eliminate the need for cold chain storage and the use of injections to immunize large populations and would be useful for stockpiling vaccine. This could be especially important in pandemic or biodefense situations.

Flexible Coils May Be A New Method Of Controlled Delivery Of Drugs To The Eye

NewsRxDrugs via NewsEdge Corporation : 10/5/2004 - A metallic coil coated with a hydrophilic, drug-containing polymer, may be better than eye drops for delivering drugs to the eye. "Delivery of drugs to the front-side of the eye is routinely done through eye drops. It is known that approximately 80% of each eye-drop is lost, as a result of rapid clearance of the tear fluid via the nasolacrymal canal," investigators in Netherlands report.

"Consequently, repeated administration through several droplets is usually necessary to achieve a desired effect, such as widening of the pupil prior to corneal surgery," wrote R.T. Pijls and colleagues, University of Maastricht, Medical Faculty.

"A new ocular drug delivery device was studied. The new device is believed to provide a basis for a more convenient and efficient method for ocular drug delivery. The device is a metallic coil with a hydrophilic, drug-containing polymeric coating. The coil is placed in the conjunctival fornix (under the lower eyelid) and the drug is slowly released by diffusion into the tear fluid," the researchers wrote.

"The capacity of the device could be increased by using the lumen of the coils as a depot for the drug to be released. Preliminary experiments with the new device were performed largely *in vitro* and *in vivo*. The latter experiments involved the release of a fluorescent dye and atropine (a potent mydriatic agent) in the eye of several healthy volunteers," they added.

"The first results obtained with the new device indicate its potential utility. More research and development work is required to define the optimal design of the coil in order to minimize the risk of irritation. Furthermore, the parameters that define the kinetics of the intraocular drug release must be defined and optimized with respect to the exact application," the authors concluded.

Pijls and colleagues published their study in the Journal of Bioactive and Compatible Polymers (Flexible coils with a drug-releasing hydrophilic coating: A new platform for controlled delivery of drugs to the eye?. J Bioact Compat Polym, 2004;19(4):267-285). For additional information, contact L.H. Koole, University of Maastricht, Medical Faculty, Center for Biomaterials Research, POB 616, NL-6200 MD Maastricht, Netherlands.

Micro- and Nanosystems Are Two New Approaches To Drug Delivery

NewsRxDrugs via NewsEdge Corporation: 10/1/2004 - Micro- and nanosystems are two new approaches to drug delivery. According to a study from Spain, "The conversion of novel therapeutics into medicines is frequently delayed by the lack of parallel investment in the 'enabling' field of drug delivery."

"During the past few years, a large number of new drug delivery technologies have been optimized to guide the potential drug specifically to the target where it is needed and to deliver it at an effective concentration and at the correct time, with safety and reproducibility," wrote G. Orive and colleagues, University of the Basque Country, Pharmacy Faculty.

The researchers concluded: "In this article, the use of micro- and nanosystems, pulsatile drug delivery systems, macromolecular conjugation and microfabricated systems together with their application in preclinical or clinical investigation will be discussed."

Orive and colleagues published the results of their research in Trends in Pharmacological Sciences (Techniques: new approaches to the delivery of biopharmaceuticals. Trends Pharmacol Sci, 2004;25(7):382-387).

For additional information, contact J.L. Pedraz, University of the Basque Country, Pharmacy Faculty, Pharmacy and Pharmaceutical Technology Laboratory, Vitoria-Gasteiz, Spain.

Ultrasound and Transdermal Drug Delivery Reviewed

NewsRxVaccines via NewsEdge Corporation: 9/29/2004 - Scientists review ultrasound and transdermal drug delivery in a recent issue of Drug Discovery Today.

"Transdermal drug delivery offers an attractive alternative to the conventional drug delivery methods of oral administration and injection. However, the stratum corneum acts as a barrier that limits the penetration of substances through the skin. Application of ultrasound to the skin increases its permeability (sonophoresis) and enables the delivery of various substances into and through the skin," investigators in Israel report.

"This review presents the main findings in the field of sonophoresis, namely transdermal drug delivery and transdermal monitoring," said Ilana Lavon and Joseph Kost at Ben-Gurion University of the Negev. "Particular attention is paid to proposed enhancement mechanisms and future trends in the field of cutaneous vaccination and gene delivery."

Lavon and Kost published their study in Drug Discovery Today (Ultrasound and transdermal drug delivery. Drug Discov Today, 2004;9(15):670-676). For additional information, contact Joseph Kost, Department of Chemical Engineering, Ben-Gurion University of the Negev, PO Box 653, Beer-Sheva, Israel. E-mail: kost@bgumail.bgu.ac.il.

Novo Nordisk Expands Licensing Rights to AERx(R) iDMS Inhaled Insulin Program From Aradigm and Obtains Full Development and Manufacturing Rights

PR Newswire via NewsEdge Corporation : BAGSVAERD, Denmark and HAYWARD, Calif., 9/28/2004 - Novo Nordisk (NYSE: NVO) and Aradigm Corporation (Nasdaq: ARDM) today announced an agreement giving Novo Nordisk full development and manufacturing rights to the AERx(R) insulin Diabetes Management System (iDMS) program. Under the agreement, Novo Nordisk will purchase manufacturing equipment and leasehold improvements currently utilized by Aradigm in the AERx(R) iDMS program for an estimated cash payment of USD 55 million. Novo Nordisk will assume all further responsibilities for AERx(R) iDMS development and funding. Aradigm will

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controlled release. We then incorporated degradable lactide and glycolide ester oligomers into the PEG, terminating with methacrylate polymerizable groups.[7] This permitted rapid gel degradation under simulated *in vivo* conditions, releasing 100% of loaded model fluorescent polystyrene 1-micron spheres from these degrading gels within days depending on the ester oligomer length and chemistry.

Bullet-loading of PEG gels with live organisms proceeds readily using either UV-initiated photopolymerization in situ in the payload compartment, or by using glass or polymer tubular molds ex situ, freeze-drying the tubes, removing the mold and cutting the glassy cylindrical gel to length to fit the payload dimensions. Figure 1 shows two hydroxypropyl cellulose Biobullet™ delivery vehicle prototypes: Fig. 1(A) is a tungsten particle-loaded bullet with a 200-microliter compartment, and Fig 1(B) is a shorter pure thermoplastic bullet with a 90-microliter compartment. The PEG hydrogel has been photopolymerized in situ into the back of each payload compartment (seen end-on). Placing the tungsten-particle loaded bullet (Fig. 1A) in buffer produces rapid dissolution of the bullet matrix, release of the cylindrical gel and substantial immediate gel swelling, shown in Figure 2. These bullets, loaded into the SolidTech commercial air rifle delivery system, actually retain substantial kinematic properties necessary for range and accuracy to target. Table 1 lists a desired range of 100m with >90% accuracy to a 4-inch circular target on a bison' hind thigh muscle area. This goal is currently not possible without additional metallic ballast in the thermoplastic bullet (hence, the black tungsten particle load in Figure 1B). However, use of metal ballast is currently prohibited since it is considered non-degradable. Therefore, current pure thermoplastic bullets, loaded with hydrogel, exhibit nearly identical mass and ballistic properties as commercial hydroxypropyl cellulose pellet-loaded controls in downrange velocity and range characteristics. Accuracy at 20m within 3 inches of the desired target is >85% in field conditions. This is currently too close range to be field-

Figure 1. *Commercial thermoplastic degradable Biobullet™s shown both side-on and end-on with PEG-hydrogel (arrow) photopolymerized into the payload compartments. (A) tungsten particle-loaded 200-microliter payload Biobullet™, and (B) smaller pure hydroxypropyl cellulose 90-microliter payload Biobullet™.*

Firing these gel-loaded bullets into model elk hide, ballistic gelatin and elk carcass at various distances produces reproducible intramuscular bullet delivery. Importantly, the gel payload remains intact within the bullet during both firing and impact. Bullet final resting positions in animal carcasses demonstrate rapid bullet dissolution and gel swelling, critical for RB51 vaccine rapid delivery.

We are currently working with USDA and NPS coworkers to report collaborative results where bullet RB51 formulations delivered via air rifle to penned bison in captivity are compared for protective effects (immunostimulation indices) to hand-vaccinated cohorts using conventional RB51 delivery.5 Eventual field testing in Yellowstone Park in wild bison is anticipated.

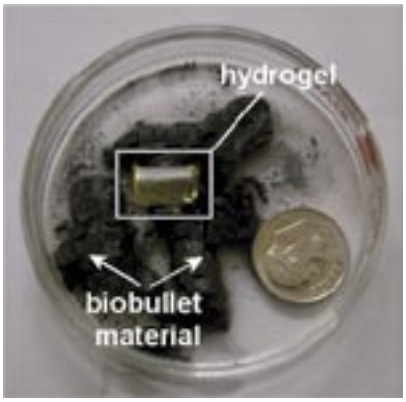

Figure 2. *Rapid dissolution of the black tungsten-loaded, gel-loaded bullet from Figure 1(A) in buffer at room temperature for 24 hours. The Biobullet™ has fragmented to small pieces while the intact photocrosslinked hydrogel* is released from the payload compartment and is observed in a swollen state (arrow and brackets). *The hydrogel portion of this image has been image-enhanced for visualization.*

Acknowledgements. Technical support from M. Dunfee and D. Findley, Colorado State University, T.J. Kreeger, Wyoming Game and Fish Department, and Mark Biel, Yellowstone National Park, is appreciated. Support from National Park Service contract 1200-99-009 is gratefully acknowledged.

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From the Education Committee

Need of Closer Alliances for Turning Nucleic Acids into Nanomedicines

by Ram I. Mahato and Ajit S. Narang
University of Tennessee Health Science Center , U.S.A.

Abstract
Recent advances in the exploration of physiological processes at the molecular level and the complete characterization of the human genome and the subsequent emergence of proteomics have given great hope for turning nucleic acids into therapeutics for the treatment of severe and debilitating diseases, which are not adequately treated with conventional small molecular weight and protein drugs. The success of nucleic acid-based therapeutics will be greatly enhanced if we would apply nanoscience and nanotechnology principles to overcome numerous biological barriers from the site of administration to the site of action. In this article, we highlight these issues and address the need for closer alliance among academia, pharmaceutical industries and scientific societies.

Introduction
After mission to the moon, human genome project has been one of the largest projects undertaken by the scientific community. Sequencing of the human genome along with significant advances in our understanding of molecular biology and disease pathophysiology, has led to the evolution of new therapeutic possibilities – whose development is a 21st century challenge to the pharmaceutical scientists. Most diseases are due to the absence or overproduction of a specific protein, leading to clinical manifestations depending upon the function of a particular protein in normal physiology. While most low molecular weight drugs act by modulating the function of some cellular proteins or DNA by specific binding; gene therapy approaches provide the patient's somatic cells with the genetic information necessary to produce specific proteins needed for treatment. The use of proteins as drugs presents problems with respect to unfavorable pharmacokinetic profiles, need for frequent administrations, poor oral bioavailability, physico-chemical instability, inappropriate concentration in the body and rapid hepatic metabolism and renal clearance. Although significant improvements in protein therapy can be made with nanotechnology, synthesis of a desired protein, or inhibition of an aberrant protein production, in the vicinity of diseased cells would be much more desirable specially for long-term therapy. Nucleic acid medicines fall under the two broad categories of *gene expression and gene silencing*. While the former is involved with plasmid and virus-based gene delivery to desired cells and tissues, the latter is involved with silencing gene expression – which may be achieved by inhibiting transcription (antigene) or translation (antisense and siRNA). Nucleic acid drugs are high molecular weight, hydrophilic compounds with

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Pharmaceutical Sciences Graduate Education in the Era of Nanotechnology, Pharmacogenomics, and Proteomics

by Uday B. Kompella
University of Nebraska Medical Center, U.S.A.

Advances in nanotechnology, pharmacogenomics, and proteomics are bringing new frontiers to pharmaceutical research and posing new challenges in providing a strong educational and scientific foundation to graduate students enrolled in the colleges of pharmacy, especially pharmaceutical sciences departments. After briefly defining the scope of these emerging disciplines, the purpose of this article is to share my personal opinions about the emerging trends in pharmaceutical science education and where we can potentially strengthen our graduate programs. I have not provided any clear resolutions to these issues because each graduate program has to utilize its own resources, and visions for the future to ensure that its graduate students are well trained. Although this article is written for graduate education in pharmaceutical sciences departments, several other programs including biomedical engineering and chemical engineering programs focusing on drug delivery also face these challenges. The opinions expressed in this article are mine and may not reflect those of the colleges I have been affiliated with over the years.

Emerging Technologies
Currently, there are at least three high-technology driven areas of research that are likely to make revolutionary contributions to the field of medicine. These include nanotechnology, pharmacogenomics, and proteomics. All these areas are driven by micro- and nano- machining technologies and computational science. While pharmacogenomics and proteomics rapidly advance the understanding of human biology by providing new diagnostic techniques and clinical targets for the treatment of diseases, nanotechnology is more products oriented and it is making advances in several non-pharmaceutical areas as well as in the pharmaceutical sciences.

Nanoscience: Nano- is currently among the most attractive prefixes, and it has been used to define many areas of science and technology - nanoscience, nanotechnology, nanoengineering, nanomedicine, nanobiology, and nanoimaging, to mention a few. If this trend is an indication of where this technology is headed, there will be nanopharmaceutics emerging in the near future. While the inclusion of the prefix nano- is currently paramount to the new wave of nanotechnology, related pharmaceutical research on nanoparticles has been ongoing for at least the past 3 decades, with the usual slow progression to the clinic. The quantum leap in nanotechnologies has been primarily in the fields of inorganic materials including the fabrication of 90 nm transistors that can

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be used on microchips, and the discovery that optical properties of materials such as gold are fundamentally different depending upon the particle size. Evolution of nanoscience at this stage has several pharmaceutical dimensions that have yet to be realized. Important areas of current research include the design of functional devices and a better understanding of the material properties and interactions at a nanoscale. If fundamentally new material properties are identified with applications in pharmaceuticals, it has the potential to lead to tremendous advances in the field. In the future, demonstrating the new biological properties of nanomaterials and the ability to integrate nanomachining approaches for economic large-scale manufacturing of drugs, drug products, and devices would be of critical importance. Such advances have the potential to revolutionize pharmaceutical characterization, analysis, dosage forms, and manufacturing.

Pharmacogenomics: Pharmacogenomics is at the interface of pharmaceutical sciences and genetics. Usually it refers to how different genes influence drug behavior. A related discipline, Pharmacogenetics refers to the study of inherited differences or variations in drug metabolism and response. For the purpose of this article, Pharmacogenomics includes pharmacogenetics. The pharmacogenomics field holds the promise that one day drugs might be tailored to suit each individual's genetic makeup.

Proteomics: Proteomics refers to the systematic study of proteins within a cell, tissue, or organism, with respect to their structure, regulation, and function. While human genome is estimated to contain 30,000 genes, the human proteome is estimated to contain 1-10 million proteins. Also, while the genome is static, proteins are mobile and participate in several reactions and undergo continuous changes. In addition, the protein composition and function varies between individuals, cell types, and even in the same cell under different stimuli. Thus, understanding proteomics is believed to be the key to better disease diagnosis and treatment.

Impact on Graduate Education

Desired qualities in a graduate student: One does not need a PhD to make significant scientific contributions to society. However, there is a purpose for graduate student education and training, which in general terms is to combine a high level of critical thinking, analytical abilities, experimental skills, and education to ultimately shape a scientist who is capable of generating new scientific knowledge and solving major scientific problems in his or her own area of expertise. There are several excellent books on what it takes to obtain a PhD. It is fair to say that obtaining a PhD is not for everyone. Table 1 lists some of the desired attributes in a graduate student. In the emerging multidisciplinary scientific world, for any scientist to infuse new scientific technologies into the pharmaceutical sciences, the importance of the fundamentals of mathematics, chemistry, biology, and physics are becoming more apparent. A biologist should be able to understand the language of a physicist to understand the applications and limitations of atomic force microscope and the language of bioinformatics so that pharmacogenomics and proteomics data can be interpreted correctly. To be able to conduct research at the cutting edge of science, one must fully understand the intricate physics and mathematics that govern a specific system. Similarly, an engineer fabricating nanomaterials should understand the intricacies of human physiology, pathology, and biocompatibility. While providing a solid foundation through coursework, graduate programs should also facilitate cutting edge research. It would be ideal if the faculty members possess a superset of the qualities listed for the graduate students (Table 2). Often it is common for a faculty member to be engrossed in his or her own research to an extent that they could be oblivious to the advances in other core areas of pharmaceutical sciences. Continuing education through faculty development or through personal initiatives, including attendance at scientific meetings is of paramount importance for every faculty member despite their multiple job commitments.

TABLE 1

Table 1. Desired attributes of a pharmaceutical sciences graduate student.

Desired attributes of a graduate studentt	Comments
A strong foundation in physical, chemical, biological, and mathematical principles.	This should be a pre-requisite and adequate measures should be in place to assess the incoming student in these fundamental areas.
A broad understanding of the discipline in which the graduate degree is being offered.	Adequate course work to cover the principles of the primary discipline (e.g., pharmaceutical sciences) is required.
An in-depth understanding in a sub-discipline encompassing the graduate research.	Advanced coursework in the sub-discipline is required.
Independent research (scientific publications is one of the measures).	Quality as well as the number of scientific publications is important. The more first authored publications, the better. Employers typically value publications. If the faculty member is funded by federal agencies, manuscripts are critical in demonstrating productivity for a grant renewal.
Drive and perseverance to excel in science, curiosity to be a lifelong learner and self-learning abilities, critical thinking skills, communication skills, and organizational skills	While all these factors are important, if there is no drive to excel upfront, it would be the hardest to instill. If the foundation is not strong enough, the critical thinking skills will suffer.

TABLE 2

Table 2. Desired attributes of a pharmaceutical sciences faculty member and some comments.

Desired attributes of a faculty member (primary measures)	Comments
Excellence in the qualities listed in Table 1 for graduate students	The faculty members need to find time to update their own understanding of fundamentals continuously.
Mentoring abilities	A mentor is someone who takes special interest in helping another advance in his/her educational, personal, and professional growth.
Research (grant sources, grant amounts, and number and quality of publications)	Grant money: The more the merrier, with the federal funding being the gold standard. Often this parameter weighs the most in faculty retention and promotion at the A-level Universities. Publications: The quality and numbers are important. But neither may retain or promote the faculty member at the A-level institutions in the absence of grant money. The publications are ultimately most responsible for the visibility and recognition of the faculty member and therefore, this is a personal core value for many faculty members.
Teaching (teaching load, teaching evaluations, and teaching awards)	Teaching loads typically escalate with time unless a faculty member assumes an administrative position or is able to negotiate for less - because of a greater time commitment on grants. While teaching is emphasized, it is not factored in as much into promotions at the A level institutions.
Service (level and quality of service- department, college, university, and scientific community, and service awards)	Typically service to the University counts the most. Service outside the University is what gets the faculty member most visibility and recognition.

Maintenance of primary discipline and integration of new technologies: Several years ago, the pharmaceutical sciences clearly encompassed preformulation and formulation, biopharmaceutics, pharmacokinetics (these three collectively referred to as pharmaceutics in general), pharmaceutical manufacturing or industrial pharmacy, pharmacology, and medicinal chemistry (including natural products chemistry) (Table 3). In general, over the years the pharmaceutical sciences departments have become

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more focused on pharmaceutics while the remaining areas have been diluted, especially industrial pharmacy and pharmacology. However, this is not a universal trend and there are several exceptions where the original structure has been retained.

The above core areas of pharmaceutical sciences are still ideal for the purpose of drug discovery and drug product development. The majority of pharmaceutical sciences graduates are absorbed into positions in industry, where there remains an inadequate supply of pharmaceutical scientists.

In whatever discipline the degree is awarded, it is critical that the student acquires a broad understanding of that discipline, including the key areas within their area of expertise (Table 3). If a student graduates with a degree in pharmaceutical sciences but does not know what bioavailability means, it would be a cause for concern. In the broadest sense, the fundamentals of the emerging areas can be fit into various courses offered at colleges of pharmacy (e.g., nanotechnology principles under drug formulation or product development courses; pharmacogenomics and proteomics as a part of pharmacology or pharmacodynamics). A simplistic and practical way to view emerging technologies is to view them as additional tools for pharmaceutical scientists. While a set of existing core courses can incorporate the established principles in the primary discipline, a set of electives can be offered by experts in a given emerging field to more fully train the graduate students in these specific areas. However, because the colleges have fewer and fewer faculty members with expertise in the core areas of pharmaceutical sciences a problem emerges and hence the core curriculum of a program suffers drastically, or at best, is lopsided. Thus, due to a lack of disciplined vision, programs may exist with a flavor of the emerging melting pot of disciplines, while lacking instruction in pharmaceutical sciences in the broadest sense.

Forces of nature in science – discipline in the era of multidisciplinary science: Often, a given field of science is lead by cutting edge technologies, which become the bandwagons for faculty members in that specific field. Such enhanced efforts have proved to be critical in providing solutions to existing problems. However, such efforts in a graduate program should not lose track of the core discipline, especially if the discipline has served its purpose well over the years, which I believe is true for the pharmaceutical sciences. In the process of catering to the emerging technologies, one needs to retain the focus on the fundamentals of ones discipline.

A few areas, which have seen a significant thrust along these lines in the field of pharmaceutical sciences, include controlled release, peptides and proteins, antisense oligonucleotides, and gene medicines. Such areas, which may have been at the leading edge of science at various times, contribute to pharmaceutical sciences by adding some fundamentals. Some of these contributions may be so substantial that a graduate course may be primarily based on such advances, as evident by the courses on controlled release offered in almost every pharmaceutical sciences department in the country. More often than not, it is the case that easily fixed problems are dealt with in a rapid manner while leaving the more serious problems unsolved (e.g., efficient non-invasive delivery of peptides and proteins). The resolutions to such serious problems occurs at a slow pace.

Graduate student training dilemmas:

Independent vs. co-dependent scientist: The trend today is of multidisciplinary science. This is understandable since most scientific endeavors have become application oriented for the federal government as well as private funding agencies who are under pressure to demonstrate tangible results. When I was in graduate school, "independent scientist" was the quality that was emphasized and rewarded for students as well as faculty members. For tenure or promotion purposes one paper could only be used towards the tenure of one faculty member; meaning the author had to be the principal contributor to be recognized for the work. Currently it is not uncommon to see resumes of academic investigators filled primarily with secondary-authored manuscripts. Through collaborations, a potentially wider reaching manuscript can be published. Also, at times, the issues addressed could be of a broader impact. This is a welcome trend keeping the public health at large in mind. However, when it comes to training graduate students to become experts in a specific scientific area, this approach should not undermine independent research.

Forces against graduate student training: The budgets for graduate programs in colleges of pharmacy have been flat over the years since there is no real incentive to provide more graduate student teaching assistantships. This is likely to get worse, given the declining number of undergraduate laboratory courses being taught, which is where the graduate students usually got their assistantships. This means that most of the students have to be supported with research assistantships from the beginning of graduate careers, which amounts to a lot of research responsibility even during the formative years when coursework is important.

Table 3. Desirable course areas for pharmaceutical sciences and emerging technologies.

Discipline	Course Areas
Pharmaceutical sciences: Study of drug design, development, and assessment.	Medicinal chemistry, pharmaceutical analysis, pharmacology, toxicology, preformulation, formulation, biopharmaceutics, pharmacokinetics, pharmacodynamics, and pharmaceutical manufacturing or industrial pharmacy
Nanotechnology: Design and study of materials at the nanoscale (< 100 nm).	Material science including material properties and interactions at nanoscale, material engineering at nanoscale, material visualization at nanoscale, and nanoscale biomaterial manufacturing
Nanomedicine: Application of nanomaterials and nanotechnologies for the diagnosis and treatment of diseases.	Biomaterial interactions with living systems in terms of disposition, compatibility, toxicity, and efficacy.
Pharmacogenomics: Study of how an individual's genetic factors affect the body's response to drugs.	Molecular biology, genetics, genetic variations in drug responses, individualized medicine, and statistics
Proteomics: Qualitative and quantitative study of the proteome under different conditions to understand biological processes.	Bioinformatics and computer science, enzyme kinetics, structural biology of proteins, functional biology of proteins, analytical techniques for proteins, mass spectrometry, and statistics.

TABLE 3

The Colleges and Universities are typically ranked by the level of their federal funding. Therefore, the recruitment of faculty is largely based on funding as opposed to the needs of the graduate or undergraduate programs. In addition, the faculty salaries in colleges of pharmacy are far below those for the industry counterparts, making it more difficult to recruit and retain faculty members with training in the core areas of pharmaceutical sciences.

Often, to be able to conduct multidisciplinary research, a faculty member may recruit a student from another discipline (e.g., chemical engineering student entering pharmaceutical sciences). Such a student has to be trained adequately in the biological aspects of the discipline as well prior to justifying his/her PhD degree in the pharmaceutical sciences. If the mentor takes

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poor cellular permeability, and suffer from rapid inactivation, degradation and clearance *in vivo*. Thus, the use of nucleic acids as drugs requires special considerations for their effective delivery.

Evolution of Nucleic Acid Nanomedicines

The progress of molecular biology in uncovering the genetic information of the nucleic acids, which form core of the central dogma of information transfer in living systems, has been catalyzed by the progress in information technology and evolving high-throughput, automated systems like the microarray analysis and DNA sequencing (Fig. 1). The rapid development and applications of the internet and computers has made possible widespread research at the speed of thought, in various applications of this information. Despite this unprecedented speed of progress, the clinical success in converting nucleic acids into prescribable pharmaceuticals has not been realized yet. Effective delivery of the genetic material into the cell and translocation into the nucleus, without causing immunostimulation is a major barrier. These problems can be effectively addressed by applying the principles of nanoscience and nanotechnology. This calls for a proactive role of the pharmaceutical scientists to take up this responsibility. Nanotechnology has been applied for delivery of small molecular weight drugs by encapsulation or reversible bonding on the surface of 10-100nm particles. The use of such nanoparticulate systems have been used for site-specific drug delivery to the desired disease target by passive or active targeting. The use nanoparticulate systems are limited for hydrophilic nucleic acid drugs due to their large size, strict conformational requirements and inherent instability. Nanoscale manipulation of these macromolecules must not adversely affect their stability and biological activity. Such manipulations are done through interaction with inactive, polymer, lipid and peptide-based carrier molecules, leading to significant alterations in the physico-chemical properties of the resulting systems. Additionally, small size of these complexes enables them to cross many physiological barriers that would otherwise hinder their access to their targets. Both biotechnology-derived and conventional small molecular weight drugs have their unique place in modern medicine. In some disease states, nucleic acid based therapeutics remains the best option, while in other cases one may be superior to another. An example of the former case is the modulation of insulin-secreting pancreatic islets for transplantation in type-I diabetes patients.

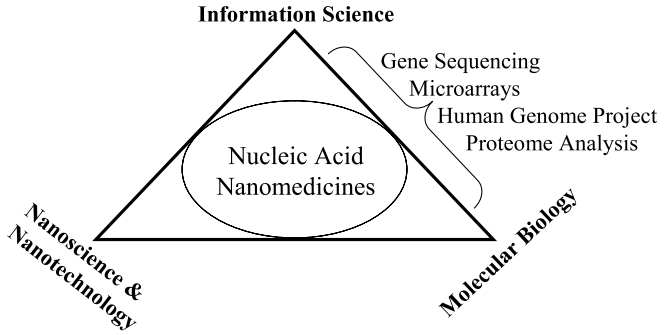

Figure 1. Evolution of nucleic acid nanomedicines from the research domains of molecular biology and nanoscience, catalyzed by the rapid progress in information science and technology.

Can Nanotechnology Make Gene Medicines a Reality?

The promise of nanotechnology to overcome physiological barriers to drug movement alter physico-chemical properties of the molecules, facilitate targeted delivery to the desired tissues, and to stabilize and prevent rapid clearance paves the way towards the desired systems for nucleic acid-based therapeutics. For efficient transfection to occur, vectors must be capable of condensing DNA into particles small enough to be taken up by the cells (typically <200 nm), protecting DNA from hydrolytic and enzymatic degradation; and delivering the DNA to the nucleus of the cell in a transcriptionally active form.[1] For example, we have been working on lipopolymers, which enhance the stability and delivery of plasmid DNA in vitro and in vivo.[1,2] These gene carriers bind to the multiple anionic charges on the duplex DNA by electrostatic interactions to form condensed, positively charged complexes, that provide enhanced stability from endogenous nucleic acid-degrading enzymes, and increase cellular internalization by interactions with the anionic cell surface.

Mother nature exemplifies the ideal nanoscale encapsulation and protection of nucleic acids and their specific targeting in the form of viral vectors. These vectors have been used extensively and are being evaluated in clinical trials. One good example of their application is type-I diabetes, where the insulin-producing pancreatic islet cells do not function properly. Islet transplantation can replace body's delicate machinery for glucose metabolism, but the transplanted islets are often fail to vascularize and are rejected by the host due to immune responses. Gene transfer to the islets for secretion of protective and vascular proliferative cytokines would help in better engraftment of the transplanted tissue so that physiological level of insulin can be produced.[3] We are working on adenoviral vectors for gene delivery to human islets. We have used recombinant adenoviral vectors with very high transfection efficiency.[4] We are currently working on surface modifications of these systems to incorporate enhanced targeting capabilities and reduced immunogenicity.

Commercial Challenges

Development as well as commercialization of nucleic acid-based nanomedicines is a daunting task. The transfer of these technologies from the academia to the industry and the clinic involves many challenges. Current gene expression and gene silencing technologies do not balance well on the two most fundamental requirements: safety and efficacy. Non-viral vectors are relatively safe but they are not efficacious while viral vectors provide high efficiency but with significant safety concerns. The eventual success of nucleic acid nanmomedicines will require patient acceptance and careful consideration of their social and economic consequences. Efforts are needed to develop novel systems that are efficacious, while also being safe and cost effective. In my laboratory at the University of Tennessee Health Science Center, we are working towards this end by generating hybrid systems of adenoviruses using nonviral technologies, to overcome their safety concerns.

Nucleic acid nanomedicines are being developed in the era of enhanced appreciation of the value of intellectual property – resulting in every technological advancement being patented. Scientific publications as well as patents have grown exponentially in these fields over the years. While this growing body of public knowledge provides an impetus to the development of science, complex intellectual property issues often hinder the commercial exploitation of emerging technologies. For example, patenting of different aspects of polymers, gene, gene delivery and gene expression systems, techniques for encapsulation etc by different groups working in multiple disciplines hinders the development of an integrated delivery system that utilizes these different features. Furthermore, rapid scientific advancements, although welcome in all aspects, tend to make the existing technology obsolete at a very rapid rate – sometimes faster than the industry may be able to recover and benefit from its investments in research and development. This creates a disincentive for the private companies to invest in fast growing, emerging technologies.

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maintain a long-term interest in the program through an adjusted royalty on future AERx(R) iDMS net sales.

Because of the expanded licensing agreement, Novo Nordisk has formed a new affiliate, Novo Nordisk Delivery Technologies, Inc. based in Hayward, California, which will assume the leases and operational overhead on two of Aradigm's current three buildings, and will offer employment to approximately 130 Aradigm employees who have been dedicated to iDMS. The companies have the option to continue collaborating in specific areas such as next-generation AERx(R) technologies. If needed, Novo Nordisk will provide certain contract manufacturing services to support other AERx(R) programs for up to three years.

"Novo Nordisk remains committed to the development of inhaled insulin. The AERx(R) iDMS is an excellent fit within our portfolio of insulin delivery systems," stated Lars Rebien Sorensen, president and chief executive officer of Novo Nordisk. "We are confident that the transition will be smooth, and that both companies will benefit from the new structure."

"We are pleased that Novo Nordisk has assumed a greater role in completing the development of the AERx(R) iDMS system," added Dr Bryan Lawlis, Aradigm's president and chief executive officer. "This agreement establishes two key components for Aradigm's future success: it confirms Novo Nordisk's commitment to the AERx(R) iDMS program, and it provides Aradigm the financial flexibility to accelerate the development of additional AERx(R) and Intraject(R) applications. In addition to the cash payment at closing, Aradigm will no longer be responsible for the expenditures associated with commercial scale-up and manufacturing of AERx(R) iDMS."

Finalization of the agreement is subject to customary closing conditions, including approvals from regulatory authorities, as well as approval from Aradigm common and preferred shareholders, which is expected at a special shareholder's meeting to be held later in 2004. The agreement is expected to close by the end of 2004. The transaction does not change Novo Nordisk's expectations for the financial results for 2004.

Pfizer to Purchase Drug Delivery Technology Venture From PA Consulting Group

PR Newswire via NewsEdge Corporation: NEW YORK and CAMBRIDGE, U.K., 9/22/2004 - Pfizer Inc and PA Consulting Group today announced the signing of a transaction in which Pfizer will purchase the remaining 90% ownership of Meridica Limited, a drug delivery technology company for $125 million and a contingent payment. The transaction is subject to normal conditions and is expected to close in the fourth quarter.

Meridica is a drug delivery technology company that designs and develops technologies for the pharmaceutical industry. It was established by PA Consulting Group, the management, systems and technology consulting firm, in May 2001 as part of the firm's venture program. In October 2003, Pfizer purchased a 10% interest in the company and licensed the rights to Meridica's dry powder inhaler.

Kelvin Cooper, Ph.D., Pfizer Senior Vice President, Worldwide Pharmaceutical Sciences, said: "The acquisition of Meridica strengthens Pfizer's presence in the growing allergy and respiratory therapeutic area, where there remains a high level of unmet medical need. Meridica has a proven-track record in developing technologically advanced drug delivery systems and its strength in this area will help Pfizer accelerate the development of allergy and respiratory product candidates in our pipeline."

Meridica's Chief Executive Officer, Dr Ian J Smith, said: "We are delighted to be joining such a successful, world-class pharmaceutical company. It is a tremendous endorsement of both Meridica's technologies and our committed and innovative staff. We are very excited about the future and our work in developing new products that will benefit millions of patients with respiratory disease."

Jon Moynihan, Executive Chairman of PA, said: "This deal with Pfizer is recognition of Meridica's major achievements, accomplished in a startlingly swift timeframe; its innovative technologies; and PA's wider venture program. The deal offers a healthy return to our shareholders, giving PA additional confidence to invest further in some of the promising new ventures that we have coming through at the moment. The future holds significant opportunity for Meridica and we wish our colleagues every success with Pfizer."

Biophan Technologies Names Drug Delivery Veteran John Lanzafame President of New Biophan Nanolution Division

ROCHESTER, N.Y.--(BUSINESS WIRE) - 9/16/2004 - Biophan Technologies, Inc. (OTC BB: BIPH), a developer of next-generation biomedical technology, has appointed biotechnology executive John Lanzafame to serve as president of the Company's Nanolution division, according to Biophan CEO Michael Weiner.

As Nanolution president, Mr. Lanzafame will oversee Biophan's development of advanced nanotechnology-based drug delivery devices and drug-elution technologies, patents, and products. Biophan estimates the market for these products and technologies at up to $40 billion. The Company will leverage its core competencies in nanoengineering, particularly its proprietary Nanoset nanomagnetic particle technology, as it develops next-generation drug delivery and drug-eluting devices.

Mr. Lanzafame has worked in several major aspects of the medical device industry in his 15-year career, including sales, marketing, research and development, and manufacturing. He most recently served as president of STS Biopolymers, a firm specializing in drug elution from medical device surfaces. STS Biopolymers was acquired by Angiotech Pharmaceuticals (NASDAQ: ANPI) for approximately $23 million in 2003. Angiotech is the supplier of the paclitaxel technology used on the TAXUS drug-eluting stent sold by Boston Scientific (NYSE: BSX).

Chemical Cages Deliver Drugs And Peer Into Cells

NewsRxCancer via NewsEdge Corporation: 9/14/2004 - As our understanding of biology increases, the tools of research become almost as important as the researchers wielding them. Currently, one of the major obstacles to research is actually getting inside of cells and tissue to see what is going on as it happens.

At the University of Pennsylvania, researchers are caging molecules - xenon, gene-blocking strands of antisense DNA and even therapeutics - to facilitate their entry into cells and enable researchers to observe nature's biochemical clockwork. Ivan Dmochowski, an assistant professor in Penn's department of chemistry, detailed the methods that his lab is developing for the next generation of imaging, at the American Chemical Society's 228th National Meeting in Philadelphia.

"We are developing techniques to control and study biomolecules within cells and living systems," Dmochowski said. "The most immediate payoff from this research will be in figuring out how proteins interact in real time inside living organisms as well as how diseases, especially cancer, progress through the body."

While magnetic resonance imaging has already become a useful tool for research, Penn chemists hope to extend the capabilities of MRI for monitoring multiple cancer markers simultaneously using the noble gas

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Gastric reflux of acidic material from the stomach into the oesophagus leads to damage of the oesophageal epithelium, bioadhesive liquids that coat the oesophagus after oral administration may be used to protect this mucosal surface from the damage caused by gastric reflux. Solutions of sodium alginate, a component of Gaviscon Liquid® (Reckitt Benckiser Healthcare), have been shown to adhere to oesophageal tissue for periods of up to 1 hour as well as offer protection from components of gastric reflux (Batchelor et al 2002; Tang et al 2004). In addition adhesive liquids that coat the oesophagus may be used to deliver drugs for the treatment of local disorders including motility dysfunction, fungal infections and oesophageal cancer (Batchelor et al 2004).

Sucralfate suspensions adhere directly to mucosal surfaces within the GI tract. This adhesion is not due to the presence of bioadhesive polymers but to acidification of the insoluble powder leading to the formation of an adhesive paste. Incorporation of a bioadhesive agent, however, has demonstrated enhanced in vitro adhesion of sucralfate formulation within the oesophagus (Dobrozi et al. 1999).

This type of formulation is liquid upon instillation and undergoes a phase transition to form a viscoelastic gel in response to a stimulus such as temperature, ionic strength or pH. Carbomers become more viscous upon increased pH. Poloxamers and Smart Hydrogel® (Advanced Medical Solutions) gel at approximately body temperature. Gellan gum and alginate both form gels in response to increased ionic strength. Gel-forming formulations are currently used for sustained ocular delivery, including Timpotal-LA® (MSD). Recent work has examined the oesophageal retention of Smart Hydrogel®, a liquid that gels in response to both high force and temperature with its gelling temperature at about 32 °C (Russell et al. 2004). The force involved in a swallow and the concomitant increase in temperature upon oral administration indicate that Smart Hydrogel® is well retained within the oesophagus.

Specific bioadhesives

Although much research utilises pharmaceutically acceptable polymers as bioadhesive agents, these systems lack specificity, which is especially important for orally delivered formulations that are targeted to sites within the gastro-intestinal tract. This lack of specific targeting results in polymers adhering to the first mucosal surface that is encountered, which in turn, may lead to problems such as those seen with tablets and capsules that adhere to the oesophageal mucosa causing localised tissue damage. Another issue with lack of specificity is that the formulation may interact with 'loose' mucus within the GI tract, be coated with this material and pass through the GI tract without coming into close contact with the absorbing mucosal membranes. Specific adhesion is demonstrated by a range of biological molecules that recognise and bind to specific target chemical structures on the surface of cells or within mucus. Specific targeting of bioadhesive particles to M cells has implications in oral vaccination strategies and has been reviewed by Jepson et al. (2004). Examples of molecules that exhibit specific adhesion include lectins, bacterial fimbrins and invasins. Incorporation of these molecules into bioadhesive formulations, including liquids, semi-solids and solids, provides additional specificity of targeting and may enhance the overall efficacy of the formulation.

Conclusions

Due to the large number of target sites for bioadhesive drug delivery there are many formulations that may be explored for drug delivery purposes. Currently solid dosage forms, oral liquids and gels applied to readily accessible sites including the eye, oral cavity and vagina are commercially successful. The future direction of bioadhesive drug delivery lies in vaccine formulations that adhere to the mucosal surface and result in mucosal immunity, this is especially relevant in nasal and oral vaccination programmes. Microparticulate bioadhesive systems are particularly interesting as they offer protection to therapeutic entities as well as the enhanced absorption that result from increased contact time provided by the bioadhesive component.

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xenon as an imaging agent. By encapsulating a single atom of xenon within a cage made of cryptophane, it can become a sensitive reporter of changes outside the cage. When the cage is "rattled" by a specific cancer protein, for example, the xenon molecule will emit a telltale signal that can be tracked by MRI.

"Based on this principle, our lab is generating new biosensors that we hope will identify biomarkers associated with cancers of the lungs, brain and pancreas," Dmochowski said. "Over time, we'll be able to use MRI to detect aberrant proteins that cause cancer in humans before the actual formation of a tumor."

Dmochowski and his colleagues are also exploring the use of ferritin, a large family of iron storage proteins that are integral to life, to smuggle items into cells. Since ferritin can move relatively easily into cells, the researchers are developing "greasy" ferritin-like cages that could be used for ferrying materials throughout the body. The protein cages have many interesting applications, including new agents for drug delivery, templates for forming metal nanoparticles and chemical probes for use in *in vivo* spectroscopic studies.

In order to understand the role of certain genes in embryonic development, the Dmochowski lab is studying how to use light to turn genes off. They have created caged antisense molecules - stretches of DNA that can clamp on top of working genes - that are released when their chemical cage is hit by ultraviolet or infrared light. "By uncaging these molecules, our goal is to alter protein expression within a particular cell and at a particular time during development," Dmochowski said. "It means that researchers could turn specific genes off like a switch in order to find out the nature of a gene by what happens when it does not work."

Needle-Free Anthrax Vaccine Shows Promise In Animal Studies

NewsRxBioterrorism via NewsEdge Corporation: 9/13/2004 - Researchers have developed a powdered form of an anthrax vaccine that could potentially be inhaled through the nose and eliminate the need for needle injections.

The new vaccine, which appears promising in preliminary animal studies, may offer a faster and easier way to protect the general population as well as soldiers on the battlefield in the event of a deadly bioterror attack, the researchers said.

The development, a joint project of BD Technologies and the U.S. Army Medical Research Institute of Infectious Disease, was described at the 228th national meeting of the American Chemical Society in Philadelphia.

The vaccine represents a growing pipeline of needle-free drug delivery technologies that are being developed for consumers, such as the FluMist intranasal vaccine currently sold to combat influenza. Considered the next-generation anthrax vaccine, the new formulation is based on an anthrax recombinant protective antigen (rPA) and can be formulated as a dry powder and self-administered through the nose using a novel, disposable powder delivery device, the researchers said.

The standard delivery for anthrax vaccination is through subcutaneous and intramuscular administration of a liquid formula using conventional needles and syringes, but this method has several drawbacks when employed for mass vaccination, including accidental needle-stick injury, the need for highly trained healthcare professionals and painful injections, the scientists said.

"Our intranasal powder vaccine discovery may provide a highly effective, more flexible, mobile and easy-to-use method of administering the anthrax vaccine in clinical and field settings," said the project's lead investigator, Vince Sullivan, PhD, a chemist with BD Technologies' Advanced Drug Delivery group in Research Triangle Park, North Carolina.

The vaccine has not yet been tested in humans, and additional animal studies are needed, but clinical trials could be possible within the next 2-3 years, investigators said. In laboratory tests using rabbits exposed to a lethal dose of inhalation anthrax, nasal immunization with the powder resulted in an 83-100% survival rate, similar to the protection offered by the injectable formulation, according to a key researcher on the project, Ge Jiang, PhD, a pharmaceutical scientist with BD Technologies.

Initial data indicate that the powdered formulation of the rPA antigen, a genetically engineered protein, is also more stable than the liquid version and can withstand wider temperature extremes, allowing it to be stockpiled for longer periods and in more extreme conditions without the need for refrigeration, the researchers said.

New Generation Of Polymer Nanoparticles For Drug Delivery Developed

NewsRxBlood via NewsEdge Corporation: 8/22/2004 - A new generation of polymer nanoparticles for drug delivery has been developed. According to recent research from France, "One of the main interests of using polymer nanoparticles as drug carrier systems is to control the delivery of the drugs including their biodistribution.

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"During the last decade, it was clearly demonstrated that surface properties of nanoparticles were the key factor which determined the in vivo fate of such a carrier. Thus, the purpose of this work was to develop a new method which allows the easy fabrication of nanoparticles with versatile surface properties using polysaccharides."

"This preparation was based on the use of a redox radical polymerization reaction applied for the first time to the emulsion polymerization of alkylcyanoacrylates in aqueous continuous media. The dispersion of nanoparticles was very stable," reported C. Chauvierre and coauthors.

"The nanoparticle surfaces were coated with polysaccharides and their characteristics can be modulated by the type and the molecular weight of the polysaccharides used during the synthesis. Interestingly," said researchers, "the biological properties of the polysaccharide immobilized on the nanoparticle surface can be preserved opening very interesting perspectives for such nanoparticles."

"This method also offers a new strategy for the design of modular biomimetic nanoparticles as drug carrier systems with multiple functions. One of the applications considered in this work was to use these nanoparticles coupled with hemoglobin as an oxygen carrier," Chauvierre concluded.

Chauvierre and colleagues published their study in Cellular and Molecular Biology (A new generation of polymer nanoparticles for drug delivery. Cell Mol Biol (Noisy-le-grand), 2004;50(3):233-239). For additional information, contact C. Vauthier, University of Paris 11, CNRS, UMR 8612, Faculty Pharmacy, Laboratoire de Physico-Chimie, Pharmacotechnie et Biopharmacie, 5 Rue JB Clement, F-92296 Chatenay Malabry, France.

Endo Licenses the Rights to Develop and Market Proprietary Sublingual Fentanyl Product From Orexo

CHADDS FORD, Pa., Aug. 18 / PRNewswire/ -- Endo Pharmaceuticals Inc., a wholly owned subsidiary of Endo Pharmaceuticals Holdings Inc. (Nasdaq: ENDP - News), announced that it has entered into an agreement granting Endo the exclusive rights to develop and market Orexo AB's (a privately held Swedish company) patented sublingual muco-adhesive fentanyl product (Rapinyl(TM)) in North America. Rapinyl(TM) is an oral, fast-dissolving tablet of fentanyl intended for the treatment of breakthrough cancer pain.

"We are delighted to add this novel proprietary product to our portfolio," said Carol A. Ammon, chairman and chief executive officer of Endo. "We believe that this product is an excellent strategic fit for us and reinforces our continued leadership position in pain management. The benefits of Rapinyl™ are believed to include both a fast onset of action and added convenience, which we believe will improve compliance in cancer patients who experience breakthrough pain."

"We are very pleased to be partnering Rapinyl™ with Endo Pharmaceuticals for the North American market," said Zsolt Lavotha, president and chief executive officer of Orexo AB. "Endo Pharmaceuticals is a market leader in pain management products, with a strong reputation for research and development as well as marketing and sales. We believe Endo Pharmaceuticals is the ideal partner to fully exploit the potential of Rapinyl™ in North America."

Rapinyl™ is based on Orexo's unique patented technology for sublingual administration. This novel pharmaceutical preparation is believed to provide rapid absorption of the active substance and a fast onset of action. Currently in Phase II clinical development, this product has demonstrated enhanced absorption characteristics and is intended for the management of breakthrough pain in opioid-tolerant cancer patients. Endo anticipates that it will commence Phase III clinical trials in 2005.

The agreement provides for Endo to make an up-front license fee payment of $10 million, in addition to other license fees and payments based on development and regulatory milestones, which may total up to $22.1 million through FDA approval of Rapinyl™'s New Drug Application. The agreement also provides for double-digit royalties upon commercial sales and may include sales milestones if defined sales thresholds are achieved.

Second Stage Ventures Inc. Acquires Rights To Innovative Drug Delivery System

Canada Newswire English via NewsEdge Corporation: LAS VEGAS, 8/17/2004 - Second Stage Ventures Inc. (OTC: SSVT) announced today that it has acquired the intellectual property rights relating to a non-invasive, drug delivery device that allows for the transdermal delivery of insulin and other large molecule drugs. The technology uses a standard transdermal patch along with a proprietary sonic applicator that deploys ultrasound in a unique combination of waveforms to introduce drug molecules through the skin that normally could not be effectively delivered transdermally.

The technology is appealing to pharmaceutical companies because it can potentially extend the patent life cycle of existing FDA approved drugs through the utilization of new drug delivery systems and affords them the means to effectively deliver new biopharmaceuticals and other drugs comprised of macromolecular proteins and peptides. It also is appealing to physicians who are seeking to deliver drugs more effectively, without side effects, and to patients, who are demanding pain-free, less complicated delivery systems. Additional research and development as well as FDA approval is required before the Company is able to market products based on the technology.

Second Stage Ventures acquired the rights, including a number of patents pending and other proprietary technology from Encapsulation Systems Inc., a private biotech firm based in the Philadelphia area for $20,500,000 of cash and securities (consisting of $2,500,000 in cash to be paid over three years and 12,000,000 common shares of Second Stage valued at $18,000,000) as well as a residual fee equivalent to 2.5% of the gross revenues generated by Second Stage through the commercial exploitation of the technology throughout the regulatory life of the underlying patents.

The Company is currently focusing its efforts on conducting additional Human Pilot Trials and plans subsequently to commence clinical trials in order to complete the testing requirements mandated by the FDA and global regulatory authorities.

Bruce Haglund, Chairman of Second Stage Ventures commented, "We are excited about the prospects for this technology and, in addition to our testing program, we are also exploring a number of strategic alliances with large pharmaceutical companies seeking to expand the market share for drugs that they are currently marketing." Mr. Haglund further added, "The market opportunity for needle-free delivery of insulin is very significant, and the urgency of bringing to market such a technology was evidenced in the recent meeting of the American Diabetes Association. Second Stage Ventures is uniquely positioned to make inroads into this large, high- growth market and to enhance shareholder value."

Second Stage Ventures Inc. ("Second Stage") is a development stage biotechnology company that is focused on the ongoing development, testing and eventual commercialization of a transdermal patch that has been designed to facilitate the efficient and needle-free delivery of heavy molecular drugs into the system. Second Stage will be seeking shareholder approval to change the name of the corporation to Dermisonics, Inc., a name that more accurately reflects both the nature of the company's business and its asset base. ■

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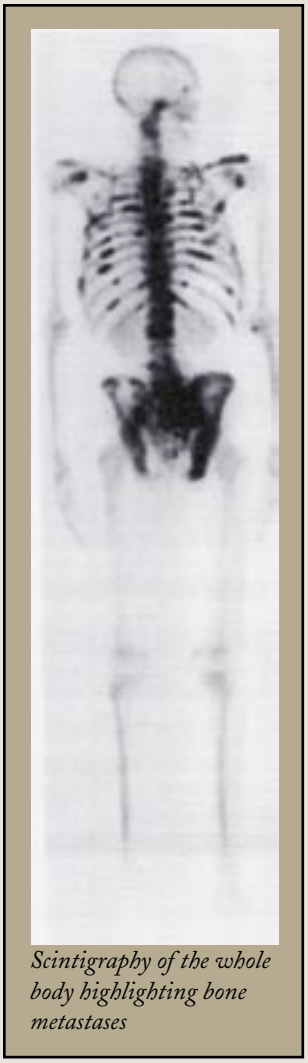
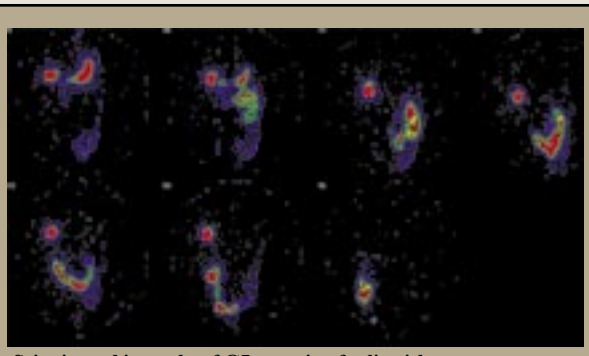


Scintigraphy of the whole body highlighting bone metastases

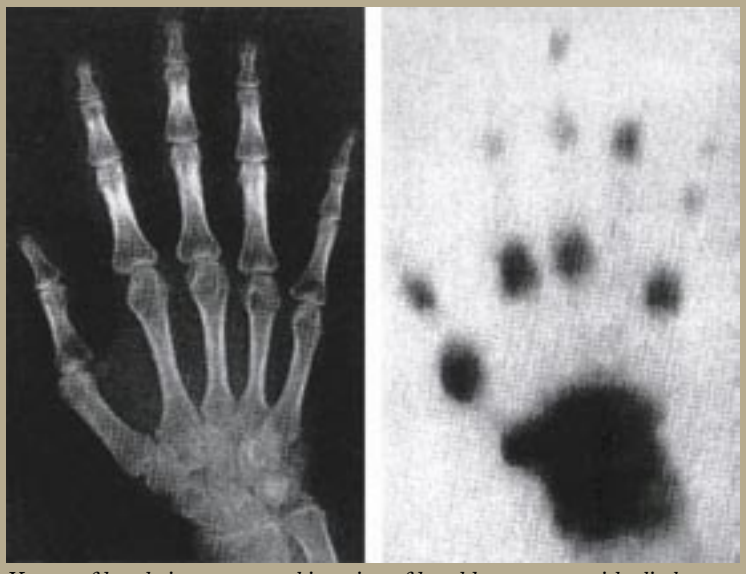
Professor Ken Miles (Brighton and Sussex Medical School, UK) presented on the bi-functional PET/CT imaging of drug targets in cardiovascular disease and cancer. CT was first discovered by Godfrey Hounsfield in 1973 who created the first clinical brain scanner and was awarded the Nobel Prize for his work in 1979. The CT scanner is now used to image the whole body in detail including arteries, bronchioles and more specifically structural abnormalities. However, one of the drawbacks of this technique in clinical diagnosis is that it may be difficult to diagnose malignant cancers. CT perfusion is the logical next step to assess a patient's condition quickly and to allow clinicians to prescribe appropriate treatment. CT perfusion analyses both arterial inflow and venous outflow. William Harvey published his findings on the circulatory system back in 1628 and proved that blood circulation through the body was continuous. CT perfusion allows a series of images to be taken after the administration of a contrast agent into the circulatory system. This imaging of blood flow can reveal problems in the flow to the brain that may indicate stroke. In combination with PET imaging, CT perfusion can be used to clearly indicate cancerous growths amongst other things. For example, HIF-1α hypoxia contributes significantly to the pathophysiology of major categories of human disease and the hypoxic nature of tumours results in a mismatch in flow and metabolism. This technique will soon be available as a routine clinical diagnosis tool in the UK as twenty PET/CT scanners will be available at NHS hospitals in the near future.

The final presentation of the day was by **Dr Bill Vennart (Pfizer, UK)** who discussed the topic of 'Clinical diagnosis to quantitative techniques in early drug development: can we do it?' Dr Vennart's talk was a brilliant round-up to the day's discussions. He discussed the problems in drug development and how the use of novel imaging techniques for diagnosis and in clinical trials can overcome these issues. The imaging techniques can be used to assess the safety and efficacy of a new molecule in the early phases of clinical trial and ensure targeted therapy. They are a powerful tool for metabonomics. The major benefit of using imaging techniques in the clinic is that it is quicker and cheaper to make early decisions on development compounds. Dr Vennart then illustrated his argument with various images showing quantitative measurements of disease progression by functional imaging. The versatility of the techniques in analyzing different diseases was demonstrated for pain assessment in rheumatoid arthritis, deep vein thrombosis and stroke to name but a few. In conclusion, he said it is possible to use quantitative techniques to aid early drug development and the industry should embrace the risks for the sake of the benefits involved. In time, some of these techniques could help make personalized medicine a reality.



Scintigraphic study of GI transit of a liquid

While scientific, regulatory and economic questions still need to be addressed, imaging technologies have the potential to increase efficiencies in many areas of drug research, particularly in pre-clinical drug development stage. Overall, it was agreed that the FDA initiative encouraging the use of imaging technologies to develop surrogate endpoints for drug submissions will help to consolidate the range of imaging techniques as important tools in the area of drug discovery and development. ■



X-rays of hand gives structural imaging of hand however provides little insight into inflammation.

*(**Nanomedicines** continued from page 25)*

Strengthening Industry Academia Alliance

The development of nucleic acid nanomedicines will also depend on the understanding and fostering of multidisciplinary intellectual environments in academic and corporate settings. While the academicians focus on developing the basic concepts and the science behind the technological advances, industrial scientists focus on technological development, with the goal of commercialization. American companies have been leaders in technological advances, in part by swiftly applying new leads from basic research in the universities, through collaborative projects as well as through the hiring of students and post-doctoral scientists. Collaborative alliances between the industry and the academia will play a key role in the development of these new therapeutic modalities. New developments need to be communicated and transferred rapidly across industry and academia to derive maximum benefit. As illustrated in Fig. 2, the Controlled Release Society, Inc. (CRS) can play a key role in enhancing scientific interaction between the two communities, by providing common meeting grounds, thereby acting as catalysts to scientific growth and technological advancement. Another important role for the CRS is to interface scientific and technological developments with the public at large, so that the laymen and young scientists and students develop a better understanding and appreciation of these newer avenues. This has an important role in helping not only to mobilize public support and young talent to the exciting new developments, but also in generating acceptance and enthusiasm in the public towards these new technological advances.

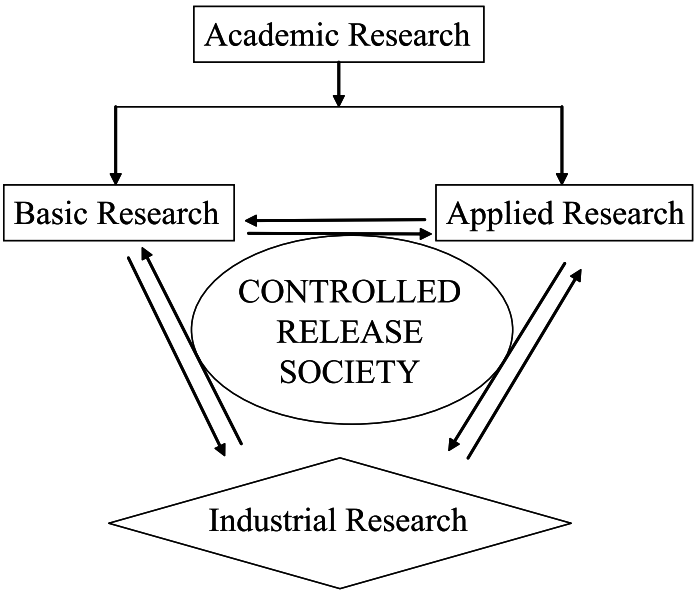


Figure 2. Interrelationship among academia, pharmaceutical industries and the Controlled Release Society, Inc.

Gearing-up Pharmaceutical Education

The United States faces the daunting challenge of attracting enough of the best graduate students to pharmaceutical sciences.[5] Development of nucleic acid nanomedicines requires technical knowledge and understanding of different fields that have traditionally grown independent of each other. While pharmaceutical sciences, by its very nature, encompasses the principles of a multitude of basic sciences; these emerging technologies require people with additional expertise in the newly developed and evolving disciplines, like molecular techniques and gene cloning, that have traditionally not been in the purview of pharmaceutical scientists. Such multi-disciplinary nature of discovery as well as development of these systems poses a bottleneck in the availability of broadly trained manpower for leading such projects. The current trends in the development of nucleic acid nanomedicines require some fundamental changes in our educational system. There is an urgent need to achieve the right balance between pharmaceutical specialization and interdisciplinary training in emerging nanoscience and nanotechnology disciplines. Education of students and budding pharmaceutical scientists towards a significant role in the development of molecular medicines of the future requires them to be trained in various disciplines.

There is an urgent need to prepare workforce for it by training budding pharmacists to learn more about molecular biology and pathophysiology. The CRS can play an active role in this evolution of pharmaceutical education by important role in addressing tremendous educational challenges by communicating the excitement and recent developments of nucleic acid nanomedicines, which will become a major factor in reinvigorating the nation's youth for careers in pharmaceutics and drug delivery. Educational development of graduate students in our laboratory at the University of Tennessee Health Science Center in Memphis is geared towards their multidisciplinary exposure.

Concluding Remarks

Despite early setbacks, there is no doubt that nucleic-acid based nanomedicines will eventually be prescribed as pharmaceuticals. In fact, there are already two marketed products: one is an antisense phosphorothioated oligonucleotide for the treatment of rhinitis (Vitravene®, Isis Pharmaceuticals, Inc.); and the other is an adenovirus encoding p53 gene for the treatment of cancer patients (Gendicine®, Shenzhen SiBiono GeneTech Co., Ltd., China). The inherent complexities of these systems provide an opportunity for multidisciplinary collaboration and co-operative efforts across industry and academia. The nucleic acid based medicines present enormous potential that has not yet been well utilized. The success of these emerging technologies heavily depends on the close alliance among academia, industry and scientific communities like the CRS, American Association of Pharmaceutical Scientists (AAPS), American Society of Gene Therapy (ASGT) and American Chemical Society (ACS). We hope that this review would provide an impetus to collaborative efforts between industry and academia, and will motivate young scientists and students to consider the most challenging and fast developing aspects of biomaterials and their use in turning nucleic acids into nanomedicines as their research careers.

Acknowledgements

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*(**Graduate Education** continued from page 32)*

the responsibility upon himself/herself, such activities add to their already limited time between teaching professional/undergraduate students, seeking grant money, and service (Table 1). Thus, the student from another discipline has to put in extra effort to excel in the coursework and research. In addition, a curricular system should be in place to ensure that the student will excel in his/her field upon graduation. Such a system while providing multiple opportunities for enhanced education should be flexible to accommodate students with varying backgrounds. While placing screens for the quality of graduate students is easy, it is more important even though harder, to institute educational measures that will bring the students to a higher level. The same applies for faculty development at a given institution.

Last but not the least, if the research productivity is the primary criteria for a faculty member, it can be best accomplished with research technicians and post-doctoral fellows as opposed to graduate students. Thus, there is a need for more resources and incentives to promote graduate student education and training.

Federal initiatives supportive of research and education: There are several federal initiatives to support research in the areas of nanotechnology, pharmacogenomics, and proteomics. Of these three, nanotechnology is probably the most supported in grant dollars based on its broadest impact and potential for multiple new commercial applications. In 2000, the US federal government introduced the National nanotechnology initiative under which, several federal agencies have been providing support. The National Science Foundation (NSF), the Department of Defense (DoD), and the Department of Energy (DoE) provide the most support (~200 million dollars each during 2004) for nanotechnology under this initiative, followed by NIH (~70 million dollars). The nanotechnology programs supporting research and education initiated by NSF include Nanoscale Science and Engineering Centers (NSEC) and Nanoscale Interdisciplinary Research Team (NIRT). In addition, the Integrative Graduate Education and Research Traineeship (IGERT) program established by NSF in 1997 is also supporting nanotechnology education initiatives. The NIH has initiated a nanomedicine roadmap to provide similar research and educational opportunities for improving healthcare. Additionally, several institutes of NIH including the National Cancer Institute have assigned top programmatic priorities for nanotechnology, pharmacogenomics, and proteomics. Besides these avenues, several programs at the University level are multidisciplinary (e.g., biomedical engineering) with faculty from different disciplines participating secondarily in the interdisciplinary program. Such programs are readily initiated and thrive more easily at a campus encompassing both medical and engineering disciplines. Thus, there are avenues to build multidisciplinary research and graduate educational programs in the newly emerging scientific areas.

Scientific associations such as the American Association of Colleges of Pharmacy (AACP), the American Association of Pharmaceutical Scientists (AAPS), and the Controlled Release Society (CRS) can further the graduate education and research by facilitating a national discussion among representatives of academia, government, and employers to assess the goals and conditions of graduate education, and resolve issues pertaining to graduate education at the national as well as global level.

Summary: As has always been the case, pharmaceutical sciences remain at the interface of biological sciences and physical sciences. Currently there is a growing need for an in-depth understanding at the level of molecular biology, genetics, informatics, and nano-engineering to make significant pharmaceutical advances. While infusion of scientists from other areas into pharmaceutical sciences is a feasible approach to make advances in emerging areas, there is a need for academic institutions to enhance pharmaceutical sciences by incorporating new fundamentals of basic sciences and engineering in order to empower the graduate students with education that is at the cutting edge. While each graduate student is ultimately responsible for his/her own learning, the institutes of higher education are responsible for providing the up to date environment through curricular planning and research training to ensure the sustained recognition and leadership of pharmaceutical scientists within the scientific community.

New drugs and drug products, the outcomes of the discipline of pharmaceutical sciences, are clearly the most tangible societal benefits among related disciplines. By incorporating new fundamentals from various basic sciences and engineering disciplines in a timely manner, pharmaceutical sciences should continually evolve to define the new age medicines. ■

*(**Pharm News** continued from page 12)*

PowderJect XR research device. Six and 10 weeks later, ponies were immunized with 2 x 10(9) infectious units of recombinant MVA encoding the homologous influenza antigen, equally divided between intramuscular and intradermal sites in the neck. A marked rise in influenza virus-specific IgGa and IgGb serum antibody titers was detected following administration of MVA boosters with both HA and NP antigens. Influenza virus-specific lymphoproliferative responses and IFN-gamma mRNA production were also strongly elicited by both antigens. This study demonstrates the facility with which recombinant MVA viruses expressing defined pathogen genes can be constructed, and provides preliminary evidence of the immunogenicity and safety of these vectors in the horse.

Woodland DL. Jump-starting the immune system: prime-boosting comes of age. Trends in Immunology. 25(2):98-104, 2004.
A major challenge for immunologists has been the development of vaccines designed to emphasize cellular immune responses. One particularly promising approach is the prime-boost strategy, which has been shown to generate high levels of T-cell memory in animal models. Recently, several papers have highlighted the power of prime-boost strategies in eliciting protective cellular immunity to a variety of pathogens and have demonstrated efficacy in humans. Coupled with recent advances in our understanding of the mechanisms underlying the generation, maintenance and recall of T-cell memory, the field is poised to make tremendous progress.

Vervarcke S. Ollevier F. Kinget R. Michoel A. stefaan.vervarcke@pharm.kuleuven.ac.be Oral vaccination of African catfish with Vibrio anguillarum O2: effect on antigen uptake and immune response by absorption enhancers in lag time coated pellets. Fish & Shellfish Immunology. 16(3):407-14, 2004.
The impact on antigen uptake and antibody response by the addition of absorption enhancers to Vibrio anguillarum O2 antigen was studied in oral vaccination trials of African catfish (Clarias gariepinus). Oral vaccination was achieved by feeding lag time coated pellets. The lag time coat prevents premature release of the encapsulated vaccine in the tank, before ingestion of the pellets by the fish. To monitor the antigen uptake, a competitive ELISA was used. The antibody response was measured using an indirect ELISA. Feeding of bacterin-layered pellets without absorption enhancers resulted in a rather low antigen uptake and antibody levels. The addition of absorption enhancers such as sodium salicylate, sodium caprate and vitamin E TPGS increased the serum antigen levels and specific antibody levels in the systemic circulation. Skin mucus antibody levels were higher after oral vaccination compared to the IP and control group. The addition of absorption enhancers in the oral groups further increased the antibody levels obtained in the skin mucus. ■

NEWSLETTER
CONTROLLED RELEASE SOCIETY
13355 Tenth Avenue North, Suite 108
Minneapolis, MN 55441-5554 USA

Issue 3 deadline
July 18, 2005

Calendar of events

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

American Chemical Society
Information:
(800) 227-5558, ext. 4508
or (202) 872-4508
Chemical and Biological Mechanisms in Toxicology
May 12-13, 2005
Crowne Plaza Union Square
San Francisco, California, USA

Wound Healing Society
Information: 1-888-434-4234
16th Annual Meeting
May 14-17, 2006
Doubletree Paradise Valley
Scottsdale, Arizona, USA

Canadian Society of Pharmaceutical Sciences 8th Annual Symposium Accelerating Drug Discover & Development
May 30 - June 2, 2005
Holiday Inn
Toronto, Ontario, Canada

American Chemical Society
Information:
(800) 227-5558, ext. 4508
or (202) 872-4508
Introduction to Polymers in Medicine
June 7-10, 2005
Virginia Commonwealth University
Richmond, Virginia, USA

Controlled Release Society
Information: 763-512-0909
32nd Annual Meeting & Exposition
June 18-22, 2005
Fontainbleau Hilton
Miami Beach, Florida, USA

8th US-Japan Symposium on Drug Delivery Systems
December 18-23, 2005
The Westin
Maui, Hawaii, USA

For complete calendar information, and to add your own events, log on to

www.controlledrelease.org/global