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Newsletter

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Yvonne Perrie
Aston University, School of Life and Health Sciences
Aston Triangle, Birmingham, U.K.

Gavels, Grumping, and the FBI—Blame It on the Editor

Dear Reader,

At the beginning of this year, the *CRS Newsletter* Editorial Team started on the ambitious task of increasing our number of issues from five to six. This was in response to feedback from the CRS membership survey that noted the *CRS Newsletter* as one of the key features of CRS membership. Obviously, the Editorial Team was delighted with this great feedback but slightly nervous about the task at hand. However, as we send issue 5 to press, it is great to see it's jam-packed full of news and reports. We have plenty of photos from the meeting; although looking at the front cover, I can't help but wonder what Diane plans to do with that gavel. We also have Scientifically Speaking articles on tumour targeting and nanoemulsification, a Spotlight article on the next generation of PEGylation, plus reports from our Local Chapters and our Vet Group.

As one of the editors of the *Newsletter*, I would love to take some credit; however, it all comes down to CRS members, who really do make the job of editor painless and fun. It's definitely much easier than being involved with the peer-review process (as an editor, reviewer, or author), where I'm often bemused by the grumpy tones in review correspondence. I can't help but ponder where the grouchy vibes emanate from. Perhaps it is due to heavy workloads, too many reviewer requests, or too much mind-numbing paperwork (that few people read). Or, is it the fact that peer-review is still often "blinded," where the authors are known to the reviewers but not vice versa? There are journals looking to address this, e.g., *PLoS ONE* identifies the reviewers at the time of decision, if the reviewer is willing. This is very progressive of *PLoS ONE*, but it doesn't seem to have spread throughout the research community yet.

Whether this would tame the more uncouth comments, it is not clear. However, responding to such reviews often takes high levels of self-restraint. Whilst we may wish we could reach for the gavel and wield it against such comments, generally we bite our tongues, but not all of us. For example Candace Sams, author of *Electra Galaxy's Mr Interstellar Fellar* (it's a rom-com in case you wondered), decided to start a comment threat on Amazon against a negative review her book received. Whilst it's now been deleted from Amazon, its legacy continues on various websites. In brief, after a review described her book as "a sad excuse for romance, mystery, and humor," she responded, "Authors rarely have full editorial control; rarely do they have even 'scant' control over their covers or the language used in dialogue or even sequencing of scenes…. These are ultimately controlled by editorial staff." Basically she blamed the editors. She also added she was reporting people on the thread to the FBI. All seems a bit odd to me, and I am not sure this would help in responding to reviewers comments.

Therefore, I do hope you enjoy this issue of the *CRS Newsletter*. If you don't, please do let us know but don't reach for the gavel—just e-mail me (and not the FBI ☺).

Best regards,

(a non-grumpy) Yvonne Perrie ■

Mark A. Tracy
Alnylam Inc.
Cambridge, MA, U.S.A.

In my column in the previous issue of the *CRS Newsletter*, I highlighted several "firsts" for CRS that were introduced at our annual meeting in Portland, OR, in July. I would like to dedicate this column to telling you more about one of those important "firsts"—the creation of a new level of membership in the Society, designated Fellow of the CRS (FCRS), and the establishment of the CRS College of Fellows. This is now the most prestigious level of membership in the Society and is one of the highest honors our Society can bestow upon our members. The creation of the Fellow level of membership and the College of Fellows is a significant event for the CRS and represents an important milestone for both the Society and our field as we recognize as a group, formally and in perpetuity, those members who have been instrumental in defining and building our field of delivery science and technology and our Society.

In Portland, I was honored to have had the opportunity to present the FCRS certificates to the inaugural class of Fellows. The founding members of the College of Fellows include past presidents, treasurers, scientific secretaries, members-at-large, and recipients of select current and former awards, including the Founders, Nagai Innovation, Career Achievement, and Distinguished Service Awards. The inaugural class reflects very well the high level required for election as a Fellow, which is based on highly distinguished leadership and sustained contributions to the fields under the CRS umbrella. A total of 72 Fellows make up the inaugural class. Their names are listed on page 5 in this issue. It was particularly memorable for me to see this group of members who have contributed so profoundly to CRS gather together at the induction ceremony to receive the FCRS award. There is a nice photo of the group in attendance at the Portland meeting. As you can see, there were lots of smiles that day. Congratulations to the founding class!

The creation of the College of Fellows was the result of a two-year award review and planning effort championed by Martyn Davies and myself during our consecutive terms as CRS vice president. I am particularly grateful to Martyn, Past-Presidents Diane Burgess and Lisbeth Illum, and the Board of Directors and staff for supporting this effort and making the College of Fellows a reality. The College of Fellows is a key part of our

broader vision to enhance our recognition of and connections with our distinguished members who have and will continue to play an important role in who we are, what we do, and where we go as a Society. The College of Fellows personifies, collectively, the highest achievement of our members. Our Fellows represent a valuable resource for CRS as leaders, ambassadors, and advocates for the CRS and our field. Importantly too, the Fellows are role models for our members, especially young scientists. In my opinion, the College of Fellows is, in essence, the nucleus of the CRS family.

Moving forward, a College of Fellows Selection Committee has been established, with Past-President and Fellow Gary Cleary as chair. The job of this committee is to seek nominations and select up to five new Fellows each year. Thank you Gary for taking on this important role. The annual selection process will provide us with the capability to continually strengthen the College of Fellows and recognize distinguished and sustained contributions to delivery science and technology and the CRS on an ongoing basis. Look for a call for nominations for next year's class later this year. I look forward to seeing the College of Fellows grow and develop over the coming years.

Mark A. Tracy ■

Inaugural CRS College of Fellows

Congratulations to the 2010 Class of CRS Fellows. Below is a list of the inaugural class of CRS Fellows and their accomplishments.

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Richard Baker (1981-1982)
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Alexander T. Florence (2002-2003)
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George Janes (1980-1981)
Hans E. Junginger (1994-1995)
Thomas H. Kissel (1998-1999)
Jindrich Kopecek (1995-1996)
Agis Kydonieus (1983-1984)
Robert Langer (1991-1992)
Vincent H. Lee (1992-1993)
Danny H. Lewis (1982-1983)
Zack Mansdorf (1984-1985)
Randall J. Mrsny (2006-2007)
Tsuneji Nagai (1996-1997)
Kinam Park (2001-2002)
Nicholas A. Peppas (1987-1988)
Joseph R. Robinson* (1990-1991)
Theodore J. Roseman (1986-1987)
Lynda M. Sanders (1988-1989)
Ronald A. Siegel (1997-1998)
Vladimir P. Torchilin (2005-2006)

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Martyn Davies (2001-2007)
Robert Gurny (1986-2001)
Zack Mansdorf (1980-1982)
Theodore J. Roseman (1982-1984)
Lynda M. Sanders (1984-1986)

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Susan Cady (1998-2004)
Robert Koestler (1982-1992)
J. Montemaro (1978-1982)
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Joe Fix (2001-2004)
Mitsuru Hashida (2001-2003)
Elka Touitou (2007-2010)
Ian Tucker (2006-2009)
Clive Wilson (2004-2007)

Founders Award Winners

Gordon Amidon (2003)
James Anderson (1997)
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Henry Brem (2001)
Nate Cardarelli (1982)
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Alexander Florence (2009)
Barrett Green* (1986)
Gregory Gregoriadis (1994)
Frank W. Harris (1983)
Mitsuru Hashida (2005)
Jorge Heller* (2006)
William Higuchi (1987)
Allan Hoffman (2007)
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Yasuhisa Sakurai (1996)
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Alejandro Zaffaroni (1988)

Nagai Innovation Award Winners

Khaled Greish (2008)
J. Milton Harris (2005)
Robert Langer (2002)
Danny H. Lewis (2004)
Hiroshi Maeda (2003)
Shirui Mao (2009)
Hiroaki Okada (2000)
Teruo Okano (2006)
John S. Patton (2007)
Hajime Toguchi (2000)
Alejandro Zaffaroni (2001)

Career Achievement Award Winners

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William Charman (2006)
Bob Davis (2003)
Lisbeth Illum (2007)
Nicholas A. Peppas (2002)
Ian Wilding (2005)

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Robert Gurny (2001)
Colin Pitt (2005)
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Michael Rathbone (2007)
Theodore J. Roseman (1996)

**Deceased*

A Look Back at the CRS Annual Meeting & Exposition

Connections. Education. Inspiration. These are what attendees came away with from the 37th CRS Annual Meeting & Exposition in Portland, OR. It was a time for gathering information, collaborating with other scientists, and taking home new ideas. And, most importantly, it was a time for making connections that will grow in the months and years to come.

A number of attendees arrived in Portland a day early to participate in the three premeeting CRS Educational Workshops and a Young Scientist Workshop. The majority, however, were finalizing their travel plans and getting their first glimpses of the beautiful city of Portland. The meeting really kicked off with the brand new CRS Innovation Sunday. The day was filled with sessions, workshops, and forums that focused on taking innovative science into the commercial sector. Participants were able to network with developers from entrepreneurial start-ups, venture capital firms, mid-sized and major pharmaceutical companies, and academia. CRS Partnering was launched, connecting participants in valuable one-on-one appointments. Sunday programming culminated in the third annual State of the Industry keynote, offering the latest statistics, trends, and drivers of the industry, along with the projected future of drug delivery.

The lifeblood of the meeting is truly the science. It was exciting to watch this meeting come together. As always, the call for papers was issued in November, and boy did the members of CRS respond! There was a great turnout of submissions that covered a wide breadth of topics that were used to create the podium and poster sessions. Topics ranged from nanoparticles to diagnostics, drug delivery methods to tissue engineering, and everything in between.

Even before the conclusion of the 2009 meeting in Copenhagen, CRS volunteers jumped into the task of arranging the outstanding lineup of plenary speakers and topics, as well as creating the various mini-symposia, workshops, sessions, roundtables, focus groups, and networking events for the 2010 program. It was these sessions, as well as the podium and poster sessions, that fueled discussions throughout the meeting. It was exciting to see attendees gathering in the hallways to discuss what they had just heard in the last session, exchanging business cards for future collaborations, and parting as friends.

There was also plenty of programming for young scientists. Workshops included Improving the Solubility of Poorly Soluble

Drugs; True Stories: Career Development; and Team Working and Motivation. Those who fell into the young scientist category were also invited to participate in the CRS Mentorship Program, which kicked off the 2010–2011 year at the annual meeting. About 40 protégés were matched with mentors during the Mentor/Protégé Meet and Greet. It was a huge success!

And, let's not forget the fabulous networking events! The first day of programming concluded with the Grand Opening Exposition and Welcome Reception, where meeting attendees were able to regroup and connect with colleagues. Exhibitors were the centerpiece of the evening, and the event was the capstone for the inaugural CRS Innovation Sunday. Monday evening offered a more relaxed night. Many attendees took this time to go out with people they had met at the meeting to see the beautiful city of Portland. Young scientists, however, were invited to attend the sold-out Networking Night at BridgePort Brewing Company. This was an event designed to allow young scientists to meet outside of the meeting. Those in attendance enjoyed good drinks, tasty foods, and informative tours of the brewery. Top that with great connections, and it was an event not to be missed. Tuesday concluded with a magnificent Closing Banquet at the Portland Art Museum, which featured the passing of the presidential gavel from Diane Burgess to Mark Tracy. It was an elegant evening with a sit-down dinner and festive music. Dinner was closely followed by the After Party, where attendees were found cutting a rug on the dance floor, doing crazy antics for the flip-book makers, and solidifying friendships that were made during the meeting.

As 2010 comes to an end, be sure to touch base with those who you met, not only in Portland, but also the friends you have made throughout the year. Through our personal and professional ties and events like the CRS Annual Meeting we continue to gain fresh ideas and new perspectives. Looking ahead to 2011, start planning for how you are going to stay current. Whether through satellite meetings, LinkedIn forums, chapter meetings, or the next CRS Annual Meeting & Exposition, stay connected with your colleagues and peers, informed on the latest science, and inspired by CRS. ■

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or contact Debby Woodard at +1.651.994.3817 or dwoodard@scisoc.org

TSPO Ligand—Platinum(II) Complexes Useful for Selective Tumor Drug Delivery[1]

Denora Nunzio, Laquintana Valentino, Franco Massimo, Latrofa Andrea, and Giuseppe Trapani[2]
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Introduction

The expression of peripheral-type benzodiazepine receptors, recently named "translocator protein TSPO," selectively increases in many tumor types, such as brain, colon, breast, prostate, and ovary (1,2). Moreover, TSPO-specific ligands induce apoptosis and cell cycle arrest in cancer cells (2,3). For these reasons, TSPO ligands have been widely explored as carriers for receptor-mediated drug delivery. We have selected a ligand with nanomolar affinity and high selectivity for TSPO, (2-(4-chlorophenyl)-8-amino-imidazo[1,2-*a*]-pyridin-3-yl)-*N,N*-di-*n*-propylacetamide (compound 3) (4), in order to prepare platinum adducts that are structural analogues to picoplatin, *cis*-($PtCl_2(NH_3)$(2-picoline)) (AMD0473, compound 4), a platinum analog currently being studied in an advanced clinical investigation (5). Therefore, the aim of this study was to evaluate TSPO ligand-anticancer drug complexes as an approach for the selective delivery of the antineoplastic agent cisplatin to tumor cell lines. To this end, two new Pt complexes, 1 and 2 (Figure 1), have been prepared and evaluated for their receptor binding affinity, as well for their cytotoxicity on human and rat glioma cell lines.

Results and Discussion

Synthetic Procedures. The new TSPO ligand-cisplatin complexes, 1 and 2, were prepared using the synthetic procedures reported in our recent paper and summarized in Figure 2 (6). Briefly, complex 1 was synthesized by direct reaction of compound 3 with $K(PtI_3(NH_3))$. The reaction was performed in absolute ethanol by refluxing for 24 hr, and the resulting product (compound 1) was purified by column chromatography on silica gel. The dichloride derivative compound 2 was prepared by substitution of chloride for iodide. The dehalogenation reaction was performed with $Ag(CF_3SO_3)$ in acetone. The triflate derivative, $(Pt(O_3SCF_3)_2(NH_3)$[(2-(4-chlorophenyl)-8-amino-imidazo[1,2-*a*]-pyridin-3-yl)-*N,N*-di-*n*-propylacetamide]) was then treated with LiCl, first in acetone (in which the Pt complex is soluble but LiCl is not soluble) and then in EtOH (in which the Pt complex is not soluble but LiCl is soluble). Both compounds 1 and 2 were fully characterized by elemental analysis (ESI-MS) and by 1D ^1H (acetone-d_6) and ^{195}Pt (DMF-d_7) and 2D (^1H-^{15}N)-HSQC, TOCSY, and NOESY experiments (DMF-d_7).

Stability Studies. Stability studies were carried out on compound 2, which is strictly analogous to picoplatin. Stability was assessed by monitoring the signals falling in the aromatic region of the spectrum. After 6 days in isotonic buffered solution at pH 7.4 and 37°C, there was no formation of new sets of signals. Furthermore, there was no detection of free ammonia, which would have appeared at approx. 6.5 ppm. Moreover,

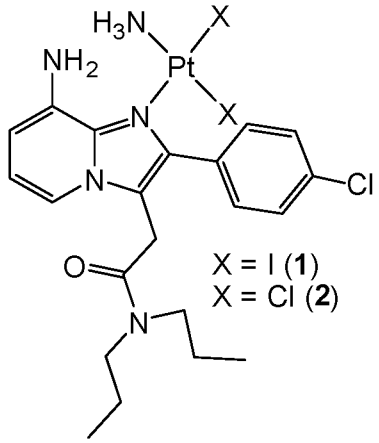

Figure 1. *Structures of the TSPO ligand-Pt complexes 1 and 2.*

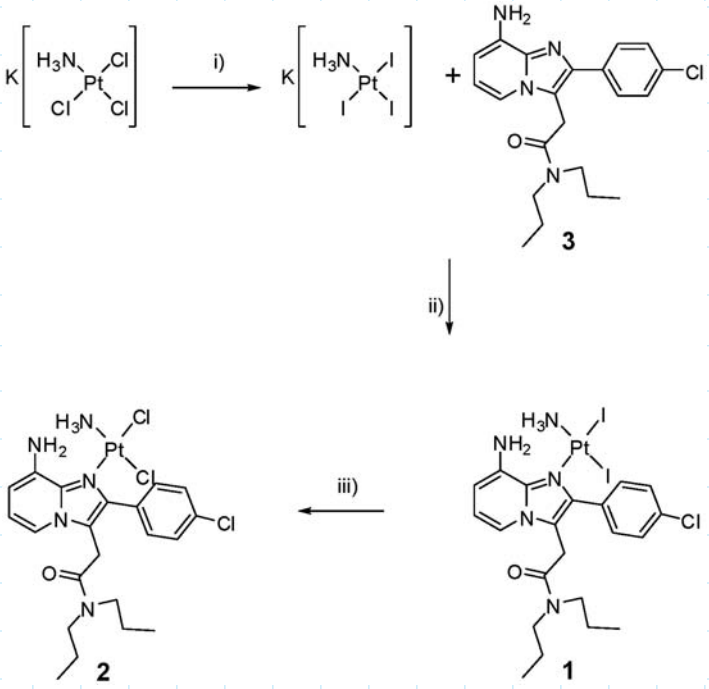

Figure 2. *Synthesis of compounds 1 and 2.* ***i)*** *EtOH/H_2O (50:50, vol/vol), KI, 50°C;* ***ii)*** *EtOH abs, reflux 24 hr;* ***iii)*** *Ag(CF_3SO_3) in acetone, LiCl EtOH/acetone. The TSPO ligand compound 3 was synthesized by a previously reported procedure (4).*

[1] CRS Italian Chapter Award.

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compound 3 remained coordinated since the addition of free compound 3 into the NMR tube led to a new set of signals belonging to the free ligand. We concluded that the chloride concentration used in our experiment was sufficiently high to prevent aquation, as is the case for cisplatin in the bloodstream.

Before antitumor platinum drugs reach DNA in the nucleus of tumor cells, they may interact with various sulfur-containing substrates, such as glutathione (GSH). Therefore, compound 2 at a concentration of 33 m*M* was mixed with GSH at a physiologically relevant concentration of 5 m*M* at 37°C. As shown in Table 1, the observed half-life was 23.9 ± 0.6 hr for compound 2 compared with the half-life of 1.5 ± 0.1 hr found for cisplatin. This 15-fold improved stability of compound 2 over cisplatin implies stability in solutions containing sulfur donors, a feature that confirms the similarity of this compound to picoplatin.

Radioligand Binding Assays. The affinity of compounds 1 and 2 for TSPO and the central-type benzodiazepine receptors (CBRs) was assessed by measuring their ability to prevent binding to the rat cerebral cortex of [^{3}H]-1-(2-chlorophenyl)-*N*-methyl-*N*-(1-methylpropyl)-3-isoquinoline carboxamide ([^{3}H]-PK11195) and [^{3}H]-5-(2-fluorophenyl)-1-methyl-7-nitro-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one ([^{3}H]-flunitrazepam), respectively. The binding data presented in Table 1 clearly demonstrate that both compounds 1 and 2 are endowed with high affinity and selectivity for TSPO at the nanomolar level.

Table 1. Affinities of compounds 1, 2, and 3 for TSPO and central benzodiazepine receptors (CBR) from rat cerebral cortex and the stability of compound 2 in the presence of GSH

	IC_{50} (n*M*)		Stability in presence of
Compound	**TSPO**	**CBR**	**5 m*M* GSH, $t_{1/2}$ (hr)**
1	18	>10^5	–
2	12.65	>10^5	23.9 ± 0.6
3	1.6	>10^5	–
Cisplatin	–	–	1.5 ± 0.1

Cytotoxicity Assays. Table 2 summarizes the cytotoxicity of compounds 1 and 2 against human SF188 and SF126 and rat C6 and RG2 glioma cells selected for their high expression level of TSPO. Compounds 1 and 2 were extremely effective and, in some cases, even better than cisplatin. The cytotoxic activities of cisplatin and compounds 1 and 2 were also determined against cisplatin-sensitive A2780 and cisplatin-resistant A2780cisR human ovarian carcinoma cell lines, commonly used to test cytotoxic activity of cisplatin analogues. As shown in Table 2, compounds 1 and 2 were effective against both A2780 and A2780cisR cell lines.

Cellular Uptake. To examine the cellular uptake, C6 glioma cells were exposed to a concentration (1 μ*M*) close to IC_{50} of compounds 1 and 2 and cisplatin for a short (4 hr) and a long (24 hr) time, and the intracellular platinum was measured by inductively coupled plasma mass spectrometry. Interestingly, the results presented in Table 3 suggest that the uptake of compounds 1 and 2 was approx. 155- and 224-fold greater than that of cisplatin after just 4 hr of incubation and became approx. 33- and 58-times greater than that of cisplatin after 24 hr. The observed increase in cancer cell accumulation of compounds 1 and 2 was likely due to both the increased lipophilicity of the platinum complex, leading to enhanced transport across the cellular membrane, and to the selective target of tumor cells that was TSPO-mediated.

Treatment of C6 Glioma Cells with Cisplatin and Compounds 1 and 2. Treatment of C6 glioma cells with cisplatin and compounds 1 and 2 induces mitochondrial and nucleus morphology modification. Nuclear morphological changes

Table 2. Cytotoxicity of compounds 1 and 2 and cisplatin against a panel of tumor cell lines

	IC_{50} (m*M*)					
Compound	**SF188[a]**	**SF126[a]**	**C6[a]**	**RG2[a]**	**A2780[b]**	**A2780cisR[b,c]**
1	1.50 ± 0.46	1.47 ± 0.65	1.14 ± 0.75	1.53 ± 0.6	6.38 ± 1.09	5.39 ± 1.11 (0.8)
2	3.67 ± 1.46	2.57 ± 0.58	1.73 ± 0.06	2.93 ± 0.7	3.56 ± 0.90	3.95 ± 0.75 (1.1)
Cisplatin	1.80 ± 0.92	1.87 ± 0.15	0.73 ± 0.51	3.07 ± 0.8	2.94 ± 0.43	9.17 ± 0.43 (3.1)

[a] Cells were seeded at a density of approx. 1,000–2,000 cells/well into 96-well microtiter plates. Following overnight incubation, cells were treated with a range of drug concentrations (0.03–10 μ*M*). Data are means ± SD of three independent experiments performed in duplicate.
[b] Cells were seeded in 96-well plates at a density of approx. 10,000 cells/well and incubated at 37°C in a humidified atmosphere with 5% CO_2. Cells were incubated in the presence of different concentrations of the tested compounds (0.1–50 μ*M*) for a period of 72 hr.
[c] Resistance factor, defined as IC_{50} (resistant)/IC_{50}(sensitive), is given in parentheses.

Table 3. Uptake by C6 glioma cells of cisplatin and compounds 1 and 2

Uptake by C6 glioma cells (μmol Pt/L)[a]	**Cisplatin**	**1**	**2**
After 4 hr of treatment	0.0015 ± 0.0003	0.2254 ± 0.0173	0.3257 ± 0.0123
After 24 hr of treatment	0.0073 ± 0.0011	0.2409 ± 0.0171	0.4235 ± 0.011

[a] Cells were seeded in 60-mm tissue culture dishes at a density of approx. 30,000 cells/cm^2.

Scientifically Speaking Nunzio continued on page 14

during apoptosis are very distinct and are characterized by convoluted nuclei with cavitations and clumps of chromatin abutting to inner regions of the nuclear envelope between the nuclear pores. Cisplatin–DNA adducts cause a variety of cellular responses, such as replication arrest, transcription inhibition, cell-cycle arrest, DNA repair, and apoptosis. Furthermore, TSPO ligands act on mitochondria, exerting pro-apoptotic activity. Therefore, we analyzed the structure of the mitochondrial network and nuclei in C6 cells treated with cisplatin and compounds 1 and 2. MitoTracker Red and DAPI dyes were used as mitochondria- and nucleus-specific markers, respectively. Figure 3 shows representative images of control C6 glioma cells in which the typical nucleus and tubular interconnected mitochondrial network are evident. In contrast, cells treated with 10 μ*M* cisplatin, compounds 1 and 2 exhibited morphological alteration of the organelles and nucleus after 24 hr (data not shown) and 48 hr of incubation. In particular, cells treated with cisplatin and compounds 1 and 2, the nuclei and mitochondria appeared fragmented, with MitoTracker Red diffused in the cytosol. Interestingly, inside the treated cells, the

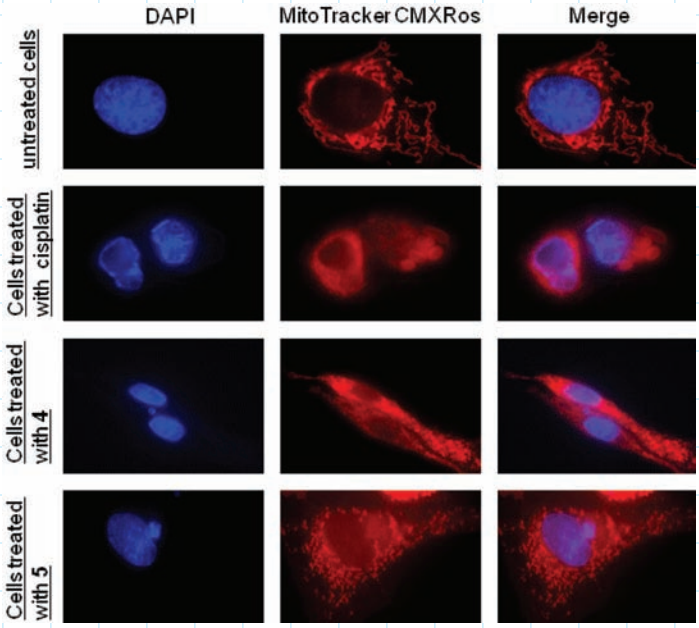

Figure 3. *Morphological analysis of the mitochondrial network structure and nucleus in C6 glioma cells. Cells seeded (approx. 100,000 cells/well) onto 24-mm coverslips were treated with 10 μ*M *compound 1 or 2 or cisplatin at 37°C in a 5% CO_2 atmosphere. Mitochondrial structure was evaluated 24 hr (data not shown) or 48 hr after incubation of cells with 25 n*M *MitoTracker Red CMXRos and with 1 μg of DAPI per mL. As a control, mitochondria of untreated cells are shown. Images are representative of 3 independent experiments in which more than 10 cells were examined.*

presence of nearly circular fluorescent structures started to appear, and their number and dimension increased at 48 hr of incubation, suggesting that the origin of these structures is related to nuclear fragmentation. Therefore, it can be concluded that compounds 1 and 2, like cisplatin, are able to induce apoptosis in cancer cells.

Conclusions

The TSPO ligand complexes 1 and 2 were characterized by 1) high affinity and selectivity for TSPO; and 2) high cytotoxicity for glioma and other human tumor cell lines. Moreover, the two compounds were equally cytotoxic against cisplatin-sensitive A2780 and cisplatin-resistant A2780cisR human ovarian carcinoma cell lines. Interestingly, the uptake of the new complexes by C6 glioma cells was much greater than that of cisplatin. Therefore, the new compounds appear to be very promising for further evaluation with brain tumors (and any type of TSPO-overexpressing tumor), with the hope that "receptor-mediated" drug targeting can lead to an improved clinical effect.

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Low-Energy Nanoemulsification to Design Veterinary Drug Delivery Devices

Thierry F. Vandamme[1] and Nicolas Anton, University of Strasbourg, Faculty of Pharmacy, Laboratory for the Design and the Application of Bioactive Molecules, Illkirch cedex, France

Similar to the research and developments that led to the design of new pharmaceutical products more adapted for different diseases in humans, there are different challenges for developing new drug delivery devices intended for animals. These comprise

- The design of biological sensors at a microscopic scale adapted for pets and stock animals
- The development of new animal products based on economic, societal, and technological issues
- The treatments of diseases such as diabetes, hypertension, skin atrophy, and cancer in pets and stock animals
- Significant cost-savings for the development of drug products for animals
- The development of efficient technologies to improve "classical" therapeutic treatments

The strategy commonly used in food industries for poorly soluble drug delivery is based on the use of premix, which is not optimized for different animal species or even for animals of different weights. The novelty of the present work lies in proposing a simple method that allows the adaptation of the exact amount of drug to different animal species and/or different body weights.

In this context, we propose to design veterinary drug delivery devices using a nanotechnology (1–3) involving low-energy nanoemulsification methods. Specifically, this technology can be used in the veterinary field to encapsulate and deliver poorly water-soluble drugs through oral or parenteral routes (Figure 1). Simple in composition and formulation, these formulations can be easily adapted for the veterinary field. There are several advantages to this technology:

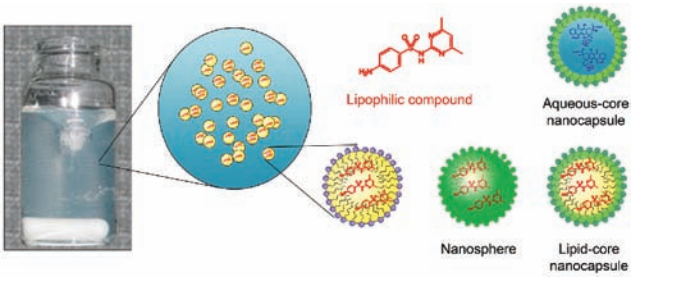

Figure 1. *Nanoemulsions and nanoparticulate (nanosphere, lipid-core nanocapsule, aqueous-core nanocapsule) systems formulated through low-energy nanoemulsification technology.*

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- It is powerful and leads to great intrinsic suspension stability
- It can be easily adapted to nanoparticle morphologies
- It can easily incorporate drugs
- The size and polydispersity can be controllable at leisure
- It is a solvent-free method and uses excipients intended for specific administration routes such as oral and parenteral

As illustrated in Figure 2, the nanoemulsification process results from contact between two liquids at a controlled temperature followed by fast diffusion of the surfactants and/or solvents from the organic phase to the aqueous phase and improvement of nanoemulsification and generation of spontaneous emulsion droplet sizing in the nanometric range. Low-energy nanoemulsification is a powerful process for generating stable nanodispersion of lipophilic compounds in an aqueous media at low energy costs. In addition, a great deal of the interest in nanoemulsion for such applications comes from the high degree of stability in suspension over several months. This stability is a consequence of the extremely small size of the nanoemulsion droplets, which makes the Brownian particles not as sensitive to

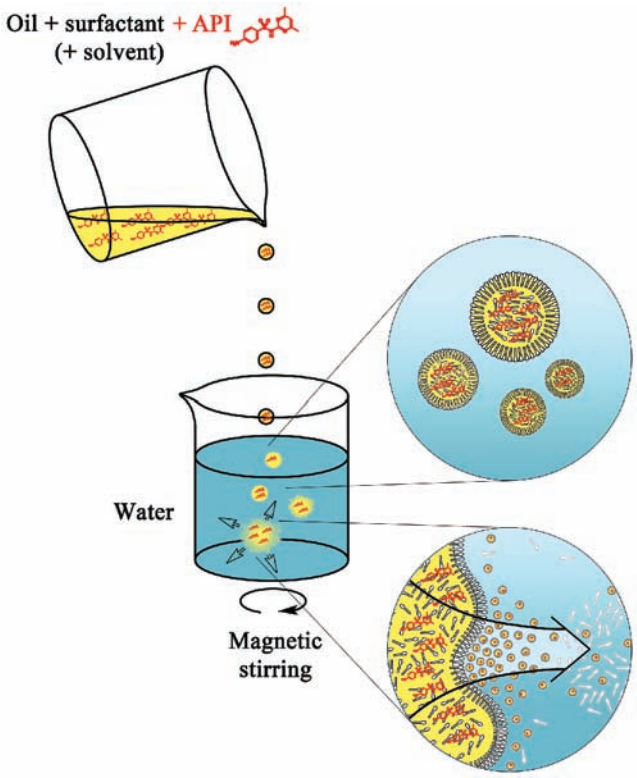

Figure 2. *Nanoemulsion generating process.*

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Scientifically Speaking Vandamme continued from page 17

the gravitational effect and, thus, to the subsequent destabilization processes such as flocculation (and coalescence) of concentrated droplets. Only Ostwald ripening (diffusion of the disperse phase through the bulk phase) acts in the destabilization of nanoemulsion droplets, which is very low and therefore very interesting for our intended applications.

As examples to illustrate this concept, we can mention the formulation of nanoemulsifications of ketoprofen (1 wt%) as a drug model, using a mixture of a glyceride like Labrafac CC or Solutol HS15 (Figure 3). By using different ratios (SOR) of these two compounds, i.e., the ratio of the weight of surfactant and oil, nanoemulsions can be spontaneously formed that have different diameters and a low polydispersity index. For example, by choosing a SOR of 50%, the size of the droplets of the nanoemulsions will be around 100 nm and have a polydispersity index of 0.2. Also, from Figure 3, we can conclude that the sizes and quality of nanoemulsions are preserved between loaded and empty droplets. Furthermore, the process is simple and allows easy industrial scale-up.

Similar results can be obtained using another drug model such as sulfamethazin, an antibacterial drug model solubilized in a mixture of tetraglycol, vitamin E acetate, and Cremophor ELP (Figure 4). In this case, by choosing a SOR of 40%, the droplets of the nanoemulsions will be around 50 nm, and the polydispersity index will be lower than 0.2.

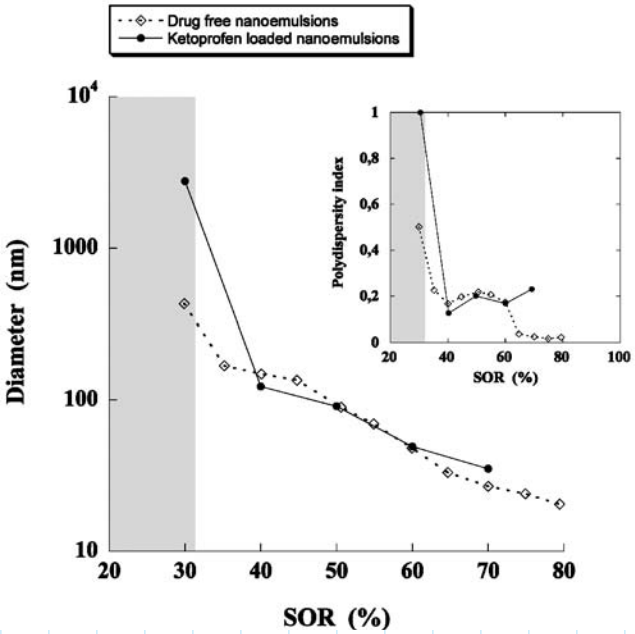

Figure 3. *Nanoemulsions formulated with low-energy spontaneous emulsification. Surfactant = Solutol HS15; oil = Labrafac CC. Hydrodynamic diameter and PDI (inset) are plotted against the surfactant oil weight ratio (SOR). Nanoemulsions encapsulating the drug (ketoprofen) are shown with the filled circles and compared with a formulation of "empty" nanoemulsions (open diamonds). The gray parts indicate that the criteria of PDI quality are not met; the suspension cannot be considered a nanoemulsion. Relative standard deviations are comprised for empty nanoemulsions between 1.3 and 0.1% and for loaded nanoemulsions between 3.8 and 2.2%.*

This low-energy method means that the energy yields are extremely favorable to industrial scale-up, since the emulsification method does not need any mechanical mixing. This point is all the more important for veterinary applications, since the order of magnitude of the number of simultaneous administrations are significantly different from the potential ones for humans. The two phases (organic and aqueous) once mixed have to be homogenized, and this stage of formulation is the only one, requiring a given (but low) amount of energy. This stage can be performed following automated *in situ*

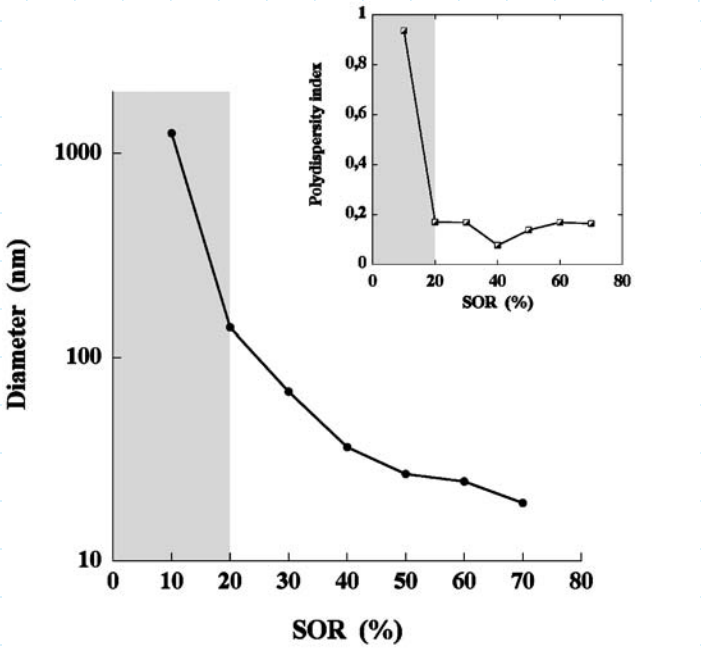

Figure 4. *Encapsulation of sulfamethazin in nanoemulsions formulated with low-energy spontaneous emulsification, using tetraglycol as a co-solvent. Hydrodynamic diameter and PDI (inset) are plotted against the surfactant oil weight ratio (SOR). Surfactant = Cremophor ELP; oil = vitamin E acetate. Relative standard deviations are comprised between 1.6 and 0.07%. Oil/co-solvent weight ratio = 1. The gray parts indicate that the criteria of PDI quality are not met; the suspension cannot be considered a nanoemulsion.*

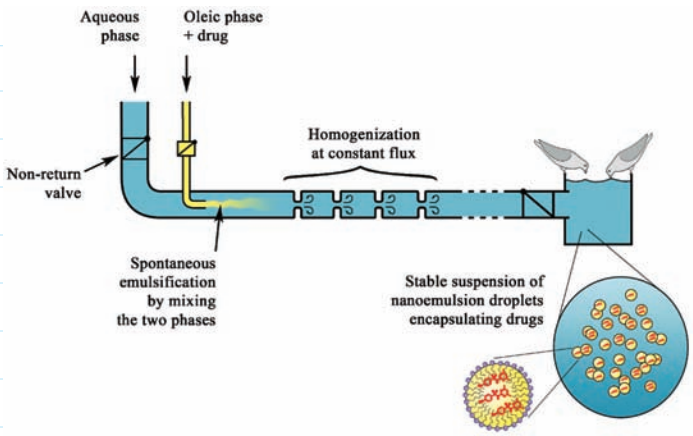

Figure 5. *Schematic design of automated* in situ *emulsification and delivery of drugs (red) in nanoemulsions (yellow) into beverages of breeding animals.*

emulsification and delivery of drugs in nanoemulsions, which can easily be realized, as illustrated in Figure 5.

The two immiscible phases are brought into contact through a system of two pipes and at constant flux. The proper functioning of the system is ensured by the two non-return valves before the emulsifying chamber. Once the emulsification is initiated, the homogenization is performed in the next homogenization chamber, with liquid turbulence that is induced by the successive changes in the liquid velocity created by the successive bottlenecks in the pipe. The homogeneous dispersion of drug-loaded nanoemulsions is finally transported toward the drinking trough.

In conclusion, such a technology would also appear to be appropriate for the administration of one or several drugs simultaneously, either by adding a pipe or by adding a commutation system. The choice of oil and surfactant for the nanoemulsification must be done following the envisaged route of administration and also considering the function of the solubilities of the different molecules involved in large-scale delivery of drugs. In addition, one can imagine that one formulation developed can have multiple applications, which either can be used for different animal species or can be adapted to animals with different weights (by changing the automated dosage instructions).

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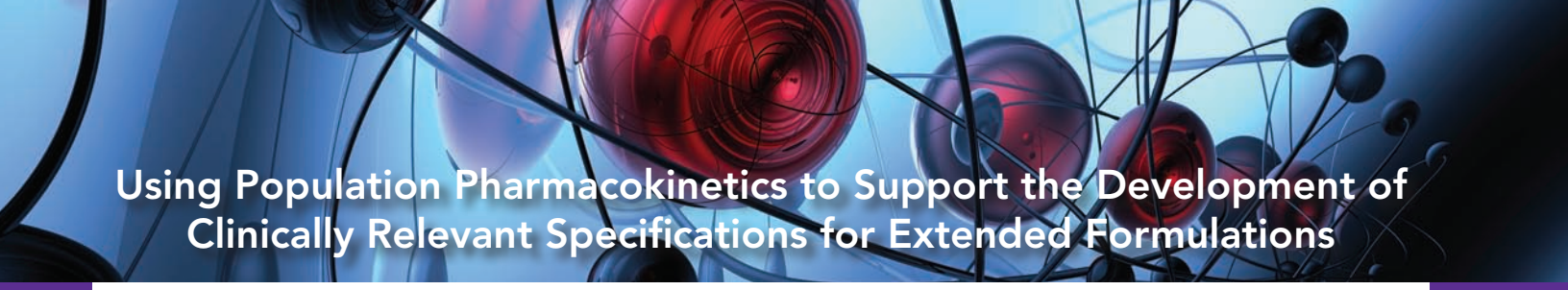

Using Population Pharmacokinetics to Support the Development of Clinically Relevant Specifications for Extended Formulations

A workshop co-sponsored by the American Association of Pharmaceutical Scientists and the Controlled Release Society.

Saturday, November 13, 2010 • 8:30 a.m. – 5:00 p.m.
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To be held immediately prior to the FIP Pharmaceutical Sciences World Congress 2010 in association with the AAPS Annual Meeting.

The Quality by Design (QbD) paradigm is ushering in new approaches for achieving a streamlined, knowledge-based process for generating products optimized to meet patient needs. Development of a Quality Target Product Profile (QTPP) can help maximize the likelihood of achieving the therapeutic objective by linking critical product quality attributes (CQAs) to the desired *in vivo* performance. In this workshop, we will discuss developing a QTPP through PK/PD modeling and simulation approaches that will enable linking CQAs to clinical outcome. Through the integration of population PK/PD models established on the basis of clinical trial data, this integrative approach could ensure the establishment of *in vitro* drug dissolution/release methods that link to the desired *in vivo* product performance, thereby providing dissolution/release criteria that are consistently informative and clinically relevant.

Who should attend?

Bench and clinical scientists involved in the development or regulation of modified release formulations and the optimization of dosing strategies.

Speakers include:

Introduction and objectives. *Marilyn Martinez, FDA*

Quality by Design: Impact on drug development and its global applications. *Terrance Ocheltree, FDA*

Design space and product specifications: A risk assessment approach. *Raafat Fahmy, FDA*

Quality Product Target Profile: Integrating product *in vivo* performance in a patient population with product design. *Arzu Selen, FDA*

Development of oral drug delivery platforms based upon patient GI characteristics. *Kevin Johnson, Intellipharm, LLC, and John Crison, Bristol-Myers Squibb*

A nonlinear mixed effects IVIVC model for multi-release drug delivery systems. *Adrian Dunne, Johnson & Johnson and University College Dublin*

The use of therapeutic drug monitoring to identify the relationships between optimized dosing strategies (input function) versus patient characteristics (covariates): Using this information to develop a target for *in vivo* product release characteristics. *Roger Jelliffe, University of Southern California*

The development of mechanistic population pharmacokinetic models to support the development of targeted release characteristics from modified release dosage forms. *William Jusko, University at Buffalo*

The use of modeling and simulation to target dosing strategies and predict optimal *in vivo* product release characteristics in a pediatric population. *Jeffrey Barrett, Children's Hospital of Philadelphia*

Integrating target *in vivo* performance characteristics into product design and specifications. *Maria T. Cruanes, Merck & Co., Inc.*

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Polysialylation: Next Generation to PEGylation

Gregory Gregoriadis[1] and Sanjay Jain
Lipoxen plc, London Biosciences Innovation Centre, London, U.K.

Introduction

Advances in genomics and proteomics have culminated in the discovery of a vast array of protein and peptide drug candidates. Many of these are on the market, for instance interferon alpha 2b, erythropoietin, granulocyte colony-stimulating factor (GCSF), and a variety of monoclonal antibodies employed in the treatment of cancers and other diseases. Hundreds of others are undergoing clinical trials. There is a need, however, to improve such protein and peptide drugs, as their effective use is often compromised by limitations inherent in their molecular structure. Thus, depending on their structural characteristics, injected protein and peptide drugs can be degraded by plasma enzymes, lost through the kidneys, removed by the reticular endothelial system (RES), or complexed with pre-existing antibodies. As a result, drugs are cleared from the circulation rapidly, before they can act optimally (1).

A number of approaches have been proposed for the protection of protein and peptide drugs from the vagaries of the biological milieu. They include changes in the amino acid sequence of the drugs to reduce biodegradation, fusion with other proteins or glycosylation to improve their half-life in the body, entrapment in nanoparticles such as liposomes for protection and targeted delivery, and conjugation with polymers, notably methyl polyethylene glycol (PEG). PEGylation offers significant advantages in terms of pharmacokinetics (Pk) and pharmacodynamics (Pd), and indeed, a number of PEGylated drugs, such as asparaginase, alpha 2a and 2b interferons, tumour necrosis factor, erythropoietin, growth hormone antagonists, GCSF, and anti-VEGF aptamer, are now in clinical use. In spite of its advantages over other systems, however, PEG is far from ideal. It is not biodegradable, and it accumulates intracellularly (1). With drugs administered chronically or in large doses, accumulated PEG could create a storage disease. Moreover, PEG can be immunogenic when coupled to proteins, and it activates complement (1).

Polysialylation: Nature's Way

An alternative approach to the circumvention of problems encountered by therapeutic proteins and peptides is the use of polysialic acid (PSA) (Figure 1A). PSA, an alpha 2-8–linked polymer of sialic acid, is a normal constituent of the body in the form of NCAM (neural adhesion molecule), modulating cell-to-cell contact inhibition in a variety of situations. For instance, PSA-NCAM facilitates neural tissue development and, as a component of cancer cells, promotes their metastasis. Interestingly, it appears that certain bacteria, through evolution, have hijacked PSA to coat themselves with it, thus succeeding in foiling the body's defences by avoiding interaction with host complement. This remarkable stealth mechanism of non-recognition was "hijacked" in turn in the early 1990s by proposing (2) that the unique ability of PSA to fend off external insults could be used to improve the Pk and Pd of therapeutic molecules or systems, as illustrated in Figure 2. It was reasoned (2) that the highly hydrophilic PSA (Figure 1B) would form a watery "cloud" around the therapeutic when coupled to it (Figure 1C) and, thus, prevent or reduce contact with proteolytic enzymes, opsonins, neutralizing antibodies or receptors on phagocytic cells. This would allow therapeutics to retain their

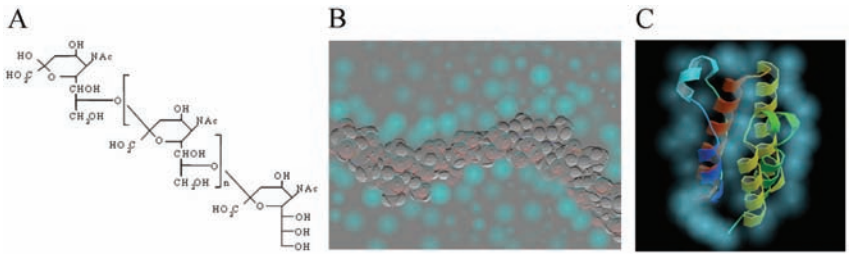

Figure 1. *Polysialic acid shown as a chemical structure (**A**); schematically with water molecules (blue circles) around it (**B**); and schematically as a "cloud" surrounding a protein conjugated to the polymer (**C**).*

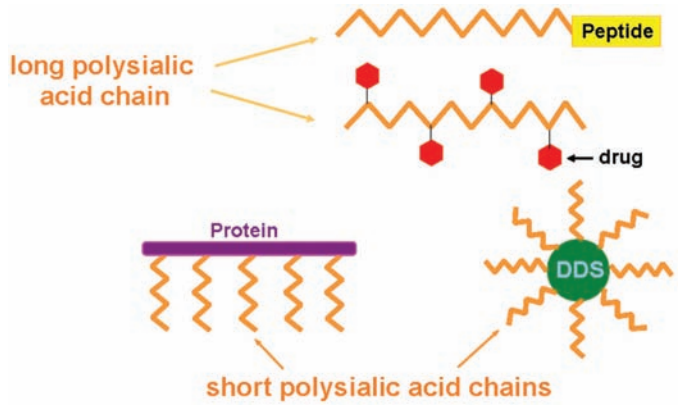

Figure 2. *Schematic representation of polysialylated constructs. DDS and "drug" denote drug delivery system and small molecular weight drug, respectively.*

[1] Lipoxen plc, London Biosciences Innovation Centre, 2 Royal College Street, London, NW1 0NH. E-mail: gregoriadis@lipoxen.com.

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integrity and activity, reduce loss (of shorter peptides) through the kidneys, and interfere with clearance from blood effected by the RES or pre-existing antibodies, thus prolonging the presence of therapeutics in the body in an active form, in turn reducing the frequency of injections (3,4). Figure 3 shows examples of polysialylation-mediated improvements in the stability, activity, clearance rate, and target accumulation of therapeutics. Additional advantages of PSA are its inert nature, ensuring complete lack of toxicity and immunogenicity. With regard to immunogenicity, efforts to raise IgG antibodies against PSA by coupling it to protein carriers such as tetanus toxoid or heamocyanin have failed spectacularly (3,4).

Work at Lipoxen plc, a biotechnology company founded by GG in 1997 as a spin out of the London School of Pharmacy, has established procedures for the production of PSA by *Escherichia coli* K1 at an industrial scale. The PSA is practically endotoxin free and can be fractionated to yield a spectrum of PSA molecular weights (1–120 kDa) of narrow size distribution (polydispersity < 1.10). Conjugation of PSA with a protein or peptide therapeutic can occur through the use of a wide range of chemistries that activate either the non-reducing end of PSA or

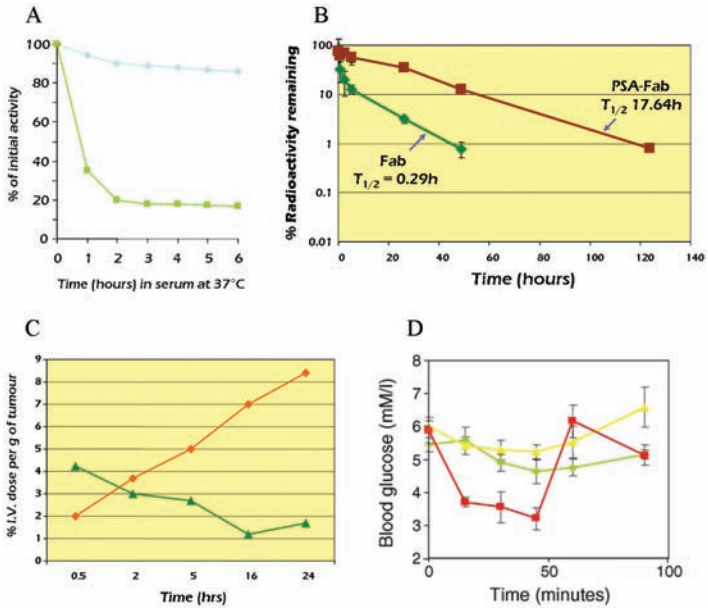

Figure 3. *Properties of polysialylated drugs.* ***A,*** *Stability of plain (blue) and polysialylated (green) asparaginase exposed to serum at 37°C.* ***B,*** *Clearance of plain (green) and polysialylated (red) Fab injected intravenously into mice bearing solid tumours. There was a 60-fold increase in the half-life of Fab (from 0.29 to 17.6 hr).* ***C,*** *Uptake by tumour tissue of plain (green) and polysialylated (red) anti-tumour Fab injected intravenously into tumour-bearing mice.* ***D,*** *Mice pre-immunized with insulin were injected subcutaneously with plain (yellow) and polysialylated (red) insulin. Control, intact mice (green). Note occurrence of hypoglycaemia upon injection of PSA-insulin.*

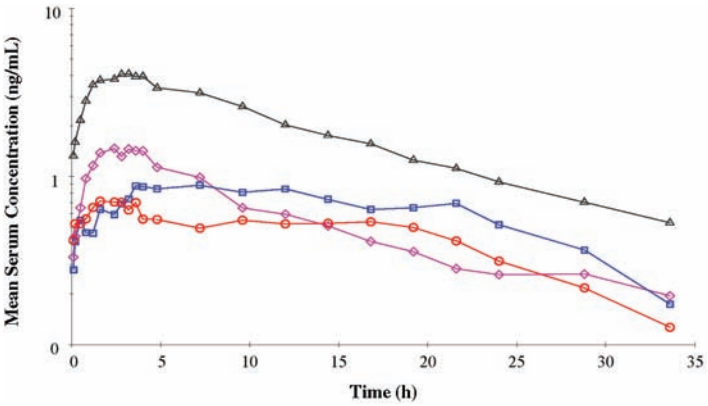

Figure 4. *Clearance patterns after s.c. injection of 0.5 µg/kg (circles), 1.5 µg/kg (squares), 3.0 µg/kg (rhomboids), and 4.5 µg/kg (triangles) of polysialylated EPO in human volunteers. Number of blood reticulocytes were increased up to about 20 days (not shown).*

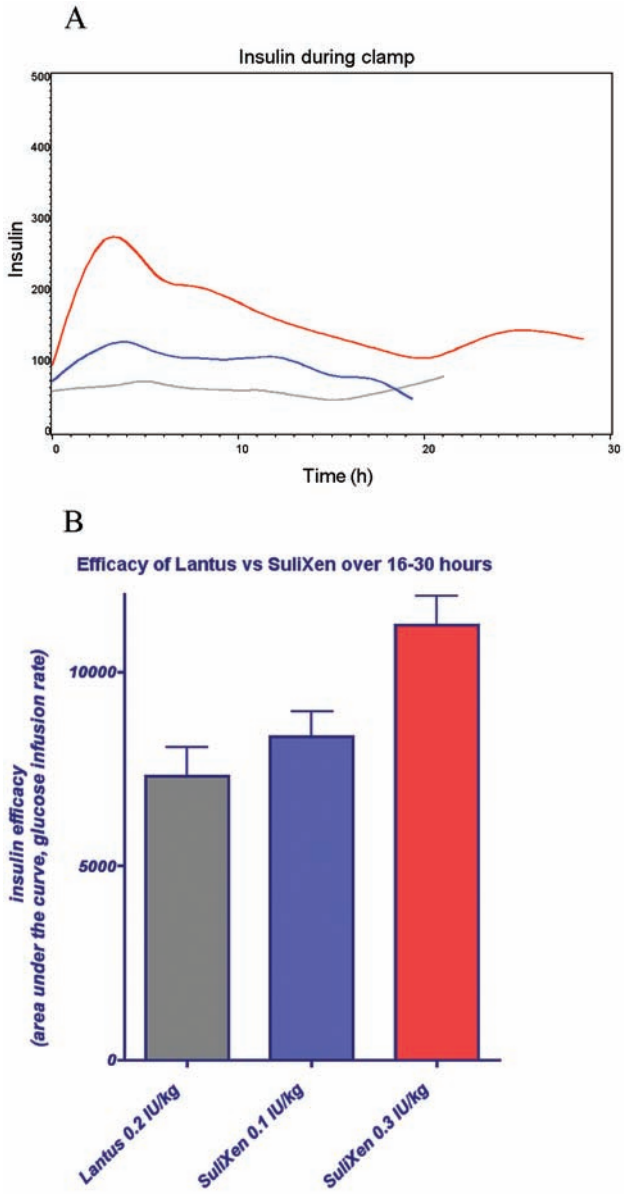

Figure 5. *Human volunteers were infused with glucose, using the clamp procedure to maintain normal glucose values following subcutaneous injection with 0.3 IU/kg (red) or 0.1 IU/kg (blue) of polysialylated insulin and 0.2 IU/kg of Lantus insulin (gray).* ***A,*** *Values over time (hours) denote insulin levels in blood.* ***B,*** *Areas under the curve of patterns in* ***A****.*

the reducing end of the polymer. Activated PSA can then be linked to chosen sites on therapeutics. Typically, such sites include the epsilon or terminal amino groups of proteins or peptides. Alternatively, activated PSA can link to terminal sugar moieties on glycoproteins, especially when glycons are located away from the active sites of the therapeutic so its inactivation is avoided. Protein or peptides coupled to one or more PSA chains of a molecular size deemed to be optimal for a given therapeutic retain much of their activity. Polysialylation as a way to improve the Pk and Pd of therapeutics has been exemplified in "proof of principle" *in vivo* studies with numerous active molecules. They include asparaginase, catalase, insulin, a variety of insulin analogs, beta galactosidase, erythropoietin, GCSF, growth hormone, antibodies, Fab and Fc fragments, DNAse, and Factor VIII, as well as other molecules confidentially investigated for partners.

Clinical Studies

In collaboration with the Serum Institute of India, a Phase I clinical trial with polysialylated recombinant human erythropoietin (ErepoXen®) was carried out with remarkable success, demonstrating not only complete safety but also prolongation of the protein's Pk and Pd compared with intact erythropoietin, suggesting monthly injections (Figure 4) instead of two to three injections per week, as is currently the case with erythropoietins in clinical use. Results from an ongoing Phase II trial with dialysis patients look promising. A Phase I clinical trial with polysialylated recombinant human insulin (SuliXen®), carried out successfully in Russia, has also demonstrated complete safety, as well as prolongation of activity, suggesting a once-a-day injection (Figure 5). These studies were preceded by similarly successful studies in mice (5), as well as cats and dogs, in collaboration with a pharmaceutical industry (unpublished). Moreover, our ongoing collaboration with Baxter Healthcare has already produced promising preclinical results with polysialylated Factor VIII.

Conclusions

Studies at Lipoxen have provided ample evidence that polysialylation is a next generation approach to improving the Pk and Pd of therapeutic proteins and peptides. Polysialylated therapeutics not only retain much of their activity, they also exhibit prolongation of pharmacological function in the body. In contrast to PEG, PSA is biodegradable and non-immunogenic. Clinical studies in progress with polysialylated erythropoietin and insulin support the notion that polysialylation is a credible alternative to PEGylation, likely to become in due course the mainstay of optimal drug delivery.

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Vet Activities at the 37th CRS Annual Meeting & Exposition in Portland, Oregon, U.S.A.

Michael Rathbone[1]
School of Pharmacy, Griffith University, Australia

The Veterinary Committee had a very busy and productive annual meeting in Portland, OR, with well-attended and interesting sessions. In a Pearls of Wisdom session titled "Of Mice and Men: Can Parenteral Product Specifications Be Extrapolated Across Species?" Prof. Diane Burgess (University of Connecticut, U.S.A.) and Dr. Marilyn Martinez (CVM, FDA, U.S.A.) debated interspecies differences in IVIVC. Ramesh Panchagnula (Pfizer Animal Health, India) moderated the session and was faced with the difficult task of separating the arguments of the debaters. At the end of the day, Marilyn and Diane conceded that neither was more convincing than the other, and the debate was declared a draw.

Profs. Mike Rathbone (Griffith University, Australia) and Jim Riviere (North Carolina State University, U.S.A.) co-chaired the vet track scientific session for 2010. The session attracted a good number of attendees, as the topic was of general interest to both human and animal drug product developers. The session covered the prediction and application of IVIVC for veterinary species and included presentations on the topics of dogs as models, GastroPlus® absorption, pharmacokinetic and pharmacodynamic simulation software, and transdermal penetration models. Prof. Mark Papich (North Carolina State University, U.S.A.) talked on an extensive evaluation he had conducted that examined literature evidence for the potential application of IVIVC for drugs in veterinary species. His interesting presentation was followed by Dr. Marilyn Martinez, who gave an authoritative presentation discussing the *in vivo/in vitro* relationships for oral dosage forms in dogs. Marilyn provided an extensive overview and large amount of supporting data that provided the audience with insight into the issues and challenges of treating this group. The use of GastroPlus® models in veterinary research and development was expertly discussed by Assoc. Prof. Steven Sutton (University of New England, U.S.A.). The session closed with an informative presentation by Prof. Jim Riviere on the use of *in vitro* dermal penetration models to estimate *in vivo* absorption of topical dosage forms. The session included a roundtable discussion during which presenters were bombarded with a myriad of questions.

Dr. Marilyn Martinez discusses the in vivo/in vitro *relationships for oral dosage forms in dogs during the vet track scientific session.*

The Vet Committee activities were concluded at the Vet Get Together, at which Dr. Keith Marotti (Pfizer Animal Health, U.S.A.) provided an overview of his many years of experiences with the challenges, opportunities, and technological innovations in drug and vaccine delivery for animal health. One of Keith's roles within Pfizer is the assessment of new technologies, and some of his talk reflected on his extensive personal experiences relating to the dos and don'ts of presenting your new technology to a big pharma company.

Overall, the veterinary members of CRS were treated to a variety of high-quality informative, educational, and social experiences this year at the 37th CRS Annual Meeting & Exposition in Portland. ■

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Consumer and Diversified Products

Charles Frey
Coating Place, Inc., Verona, WI, U.S.A.

This article summarizes selected patents from the U.S. Patent collection database that were issued between January 1 and June 30, 2010. Patents were selected based on use or potential use of the technology for controlled release or delivery in consumer and diversified product areas such as food, nutritional, cosmetic, household, personal care, agricultural, industrial, and other non-pharmaceutical applications. The reader is referred to the U.S. Patent Office website (http://patft.uspto.gov/) for more detail on the patents.

Controlled Release Compositions (Dow Corning Corporation, U.S.A.); U.S. Patent 7,674,764

This patent involves the use of cyclopolysiloxane as an inclusion structure for controlled release of components such as fragrances, sunscreens, vitamins, or biocides from products such as hair shampoo, shower gel, antiperspirant, deodorant, laundry detergent, hard surface cleaners or polishes, fabric softener, air freshener, or tumble drier sheets.

Compounds for Controlled Release of Active Molecules (Firmenich SA, U.S.A.); U.S. Patent 7,723,286

This invention relates to the field of perfumery. It concerns compounds comprising at least one β-oxy or β-thio carbonyl moiety capable of controlling the release of a perfuming molecule such as an α- or β-unsaturated ketone, aldehyde, or carboxylic ester. The present invention concerns the use of the compounds in perfumery, as well as the perfuming compositions or perfumed articles such as solid or liquid detergents, fabric softener, cologne, aftershave, soap, shower or bath gel, mousse, oil or salt, hygiene products, hair-care products, body-care products, deodorant, antiperspirant, air freshener, cosmetics, fabric refresher, ironing water, paper, wipes, or bleach.

Beneficial Agent Delivery Systems (Michigan Molecular Institute, U.S.A.); U.S. Patent 7,723,285

An improved fragrance delivery system capable of providing controlled release of fragrance molecules in various consumer products is claimed. The system is composed of a hyperbranched silyl hydroxyl polymer having covalently bound fragrance moieties that are releasable in the form of fragrance molecules. Certain embodiments comprise globular polymer particles in which unbound fragrance molecules are occluded, absorbed, and/or adsorbed. Certain other embodiments incorporate fragrance monomer units, which achieve reduced residuals upon complete release of the fragrance. Examples of applicable products include deodorants, skin-care products, laundry detergent compositions (both liquid and granular), household cleaning compositions, fabric softeners, hair-care products (including shampoos and conditioners), air fresheners, cosmetic preparations, and personal cleaning products (such as soaps and bath gels). Utilization in other beneficial applications, such as tanning agents, is mentioned.

Sustained Release Air-freshening Device (Ashland Licensing and Intellectual Property, LLC, U.S.A.); U.S. Patent 7,651,763

This invention involves an improved means for distributing a fragrance by employing an oligomeric system made by the Michael addition of β-dicarbonyl donor compounds to mixtures of hydroxyl-functional acrylates and multifunctional acrylate receptor compounds to store and release a fragrant material in a controlled fashion over an extended period of time. The novel UV-curable, liquid oligomeric composition incorporates a butadiene backbone in the UV-curable, oligomeric composition. The UV-curable, oligomeric composition can be cured in the presence of a fragrance and an optional carrier solvent for the fragrance. The cured residue of the UV-curable, oligomeric composition is used in various applications as a controlled release air freshener. The method of cure inhibition can be utilized to create internal areas of high and low cross-link density to further control the release rate. The presence of the isocyanate-capped polybutadiene helps to overcome the shrinkage, brittleness, and cracking deficiencies typical of other systems.

Multiple Emulsions (Wacker Chemie AG, Germany); U.S. Patent 7,722,891

The preparation of storage-stable multiple emulsions is described in this patent. This is achieved with the use of surfactants at less than 0.1 times the critical micelle concentration and silica dispersants. The multiple emulsions have numerous uses, including controlled release of active substances from a dispersed phase.

Methods, Devices, and Coatings for Controlled Active Agent Release (SurModics, Inc., U.S.A.); U.S. Patent 7,709,049

This invention relates to methods, devices, and controlled release coatings, wherein active agent release rate from a coated device or material is determined by coating material deposition rate. Although the specific mechanism is not committed, it is suggested that the faster release from a rapidly applied coating is the result of an entrained solvent that modifies the coating structure.

Electrochemical Dispenser (M&R Consulting Services, U.S.A.); U.S. Patent 7,681,809

This invention is a device for achieving a controlled low emanation rate of small volumes of liquid solutions, such as single- or multi-component solutions, fragrances, or pheromones for pest and insect management or fragrance enhancement. The device uses electrochemical generation of a gas to displace a liquid solution of the active from a bladder. The gas generator is capable of releasing gases such as hydrogen, oxygen, and carbon

Patents continued on page 26

Patents continued from page 25

dioxide at extremely small, pre-determined, and adjustable rates. An economic advantage over current technology is claimed.

Gelled Biopolymer-based Foam (FMC Biopolymer AS, Norway); U.S. Patents 7,671,100; 7,671,101; 7,671,102; and 7,674,837

This series of patents discloses gelled biopolymer-based foams. The gelled foams comprise a cross-linked biopolymer, preferably alginate, an optional foaming agent such as hydroxyl propyl methyl cellulose, and a plasticizer. The foams are soft and pliable and have high absorbency. They are used as wound-dressing materials, controlled release delivery systems, cell culture, barrier media for preventing tissue adherence, and bioabsorbable implants. They also have various personal care applications, especially in oral hygiene, and can be used in food applications.

Thermo-gelling Composition (Kimberly-Clark Worldwide, Inc., U.S.A.); U.S. Patent 7,658,947

This invention describes a new thermo-gelling composition made with methylcellulose and citric acid that gels near body temperature. This composition may be formulated with an effective amount of a treating agent, which may be a medicinal agent, cosmetic agent, moisturizer, adjuvant, nutritional agent, of other ingredients for controlled release through the mucosal tissues, body surfaces, or subcutaneous injection. The composition may also be used as a replacement for the soft tissues of the body, as in, for example, the foot cushion and cartilage repair.

Soy-based Thermosensitive Hydrogels for Controlled Release Systems (United States of America, as represented by the Secretary of Agriculture, U.S.A.); U.S. Patent 7,691,946

Biopolymeric hydrogels are prepared by means of a ring-opening polymerization of epoxidized vegetable oils followed by chemical hydrolysis. Recovered hydrogels have properties similar to Pluronic RTM-type surfactants and have a plurality of potential end-use applications, including controlled release of food additives and pharmaceutical ingredients.

Nanoparticles from Chitosan (University of Debrecen, Hungary); U.S. Patent 7,740,883

Methods are disclosed for preparing cross-linked core and core-shell nanoparticle polymers from chitosan. The process involves amidation with mono-, di-, tri, or poly-carboxilic acids to form the nanoparticles, and the use of vinyl and other functional carboxylic molecules to control surface characteristics. The final products may be used in controlled release, superabsorbent, and biomaterials like enzyme immobilization.

Biodegradable Oxidized Cellulose Esters (University of Iowa Research Foundation, U.S.A.); U.S. Patent 7,662,801

This invention relates to the preparation of a series of oxidized cellulose esters suitable for use as a drug carrier in the development of biodegradable controlled and/or sustained release pharmaceutical, agricultural, and veterinary compositions, such as films, compacts, microspheres, and pellets. The esters are prepared by acylation of oxidized cellulose having at least 3% carboxyl groups. The resulting oxidized cellulose esters are soluble in aqueous alkaline solutions, water, and a variety of organic solvents. The products are suggested as a less-expensive alternative to biodegradable materials such as poly(lactide-co-glycolide) copolymers.

Biodegradable Carrier and Method for Preparation Thereof (DelSiTech Oy, Finland); U.S. Patent 7,727,543

This invention describes production of a biodegradable silica xerogel carrier for preservation and/or controlled delivery of biologically active agents such as infecting or transfecting viruses. The carrier is made from water and silane using acid or base as a catalyst. Silica xerogel material can be pharmaceutically acceptable, and it can be used as a medicine.

Transgenic Plants with Controlled Distribution of a Trait to Progeny (ICON Genetics GmbH, Germany); U.S. Patent 7,642,404

This patent describes a process to produce transgenic multi-cellular plants or parts expressing a trait of interest for hybrid seed production. The process involves producing first and second plants or cells with heterologous nucleotide sequences in the first and second loci of a homologous chromosome pair, respectively. Hybridization of the first and second plant or cells generates progeny exhibiting the functional trait of interest due to binding between a protein or polypeptide encoded by a first heterologous nucleotide sequence and a protein or polypeptide encoded by the second heterologous nucleotide sequence. The invention provides a process of producing hybrid seeds for agriculture.

Controlled Release Fertilizer Material and Process for Production Thereof (Agrium Inc., U.S.A.); U.S. Patent 7,713,326

A controlled release fertilizer material is described that is composed of a particulate plant nutrient surrounded by a coating that is the reaction product of a mixture of an isocyanate, an epoxy resin, or mixtures of both with an active hydrogen-containing compound selected from the group, consisting of a thiol ester composition, a hydroxy thiol ester composition, a cross-linked thiol ester composition, or mixtures of the compounds.

Algae-resistant Roofing Granules with Controlled Algaecide Leaching Rates, Algae-resistant Shingles, and Process for Producing Same (CertainTeed Corporation, U.S.A.); U.S. Patent 7,687,106

Algae-resistant roofing granules are formed by coating mineral particles with a formulation of clay-silicate binder, metal oxide algaecide, and small, organic, pore-forming particles. When coated particles are heated to cure the binder, the organic, pore-forming particles pyrolyse to form pores. Release of the algaecide is controlled by the resulting porous structure of the coating. ■

REGISTER NOW TO ATTEND

CRS Product Development Forum – Poorly Soluble Drugs
January 27–28, 2011
Doral Golf Resort & Spa, Miami, Florida, U.S.A.

Call for Papers open until October 29, 2010.
Registration and housing deadline is January 4, 2011.

Who should attend? People from all fields involved in the development of receptor targets; drug discovery; ADME; pre-formulation (and formulation); human physiology; and in-vitro, in-silico, and in-vivo models and clinical trials (including special populations). Don't miss this opportunity to hear about the latest innovations in poorly soluble drugs.

PROGRAM

The program consists of a single track on day one and two tracks on day two.

Thursday Morning

Poorly Solubles from Concept to Patient

Plenary – *Pros & Cons of BSC in Drug Discovery*
Gordon Amidon, University of Michigan, U.S.A.

Human GI Physiology
- *General Human GI Physiology*, Clive Wilson, Strathclyde University, Scotland
- *Lipid Digestion and Absorption*, Frederic Carriere, CNRS Laboratoire, France
- *Dosage Form Behavior in the GI Tract*, Werner Weitschies, University of Greifswald, Germany
- *Site-Specific Drug Absorption*, Amnon Hoffman, Hebrew University of Jerusalem, Israel

Thursday Afternoon

Plenary – *Formulation Strategies for Delivering Poorly Soluble Actives*
Marcus Brewster, Johnson & Johnson, U.S.A.

***In-Vivo* Studies of Absorption of Poorly Soluble Actives**
- *Different Species GI Physiology and Relevance to Man*, Speaker to be announced.
- *In Vivo Aspects of Food Effect*, Speaker to be announced
- *Predicting Drug Dissolution and Absorption in the Colon*, Bertil Abrahamsson, AstraZeneca, Sweden
- *Intestinal Drug Absorption*, Hans Lennernas, University of Uppsala, Sweden
- *Models of Lymphatic Transport*, Caitriona O'Driscoll, University College Cork, Ireland

Friday Morning

Plenary – *Formulation Strategies with Emphasis on Class 4 Compounds—Good Case Stories*
Vincent Lee, The Chinese University of Hong Kong, China

Solution/Semi-solid Formulation Approaches
- *Cyclodextrins and Inclusion Complexes*, Rene Holm, Lundbeck, Denmark
- *Lipid-based Drug Delivery Systems*, Colin Pouton, Monash University, Australia
- *Mesopourous Silica*, Randy Mellaerts, Katholieke Universiteit Leuven, Belgium
- *Erosion-based Drug Delivery*, Daniel Bar-Shalom, University of Copenhagen, Denmark
- *Preclinical Models for Drug Absorption*, Patrick Augustijns, Katholieke Universiteit Leuven, Belgium
- *Facilitating Formulation Development of BCS II/IV Drugs through Oral Absorption Modeling Tools*, Filippos Kesisoglou, Merck, U.S.A.
- *Extrapolating from In Vitro or Preclinical Studies to Clinical Studies*, Speaker to be announced
- *Expedient Development of an Amorphous Formulation for Maximum Exposure and Phase I Trials*, Maria Cruanes, Merck, U.S.A.

Friday Afternoon

Plenary – *Lipolysis Modeling and Food Effect*
Anette Mullertz, University of Copenhagen, Denmark

***In Vitro* Methodologies**
- *Physical Chemical Dissolution*, Jukka Rantanen, University of Copenhagen, Denmark
- *Assessing Dissolution and Permeability of Poorly Soluble Actives*, Peter Langguth, University of Mainz, Germany
- *Solute Carrier Transporters in Drug Absorption and Drug–Drug Interactions*, Jim Polli, University of Maryland, U.S.A.

Mid- to Late-State Development (Phase II and Beyond)
- *Pediatric Formulations*, Speaker to be announced
- *Changing a Formulation in Late Development*, Pat Crawley, GlaxoSmithKline, U.S.A.
- *Special Populations—Special Concerns*, Speaker to be announced
- *Biopharmaceutics and Quality by Design—Perspectives from FDA*, Arzu Selen, U.S. Food and Drug Administration, U.S.A.

For Exhibit and Sponsorship Opportunities contact Debby Woodard at +1.651.454.7250. To submit an abstract, register, book your hotel room, and view the complete program visit www.controlledreleasesociety.org.

New CRS Member Benefits

The CRS Board is continually looking for ways to add value to your membership. This past year alone CRS has added new local and student chapters that help you to connect to other professionals in your region, as well as a LinkedIn group that gives you the opportunity to talk with people around the globe about issues that are important to you. We are also in the process of redeveloping the CRS website to make the information you need more accessible and easier to find. In addition, starting in 2011, as a CRS member you will receive a subscription to *Drug Delivery and Transitional Research*, the brand new official journal of the Controlled Release Society. The journal will be published bimonthly and provide yet another way in which CRS can help you stay current on the latest research and trends.

Owned by CRS and published by Springer Science+Business, LLC, the direction and development of the journal will be led by Editor-in-Chief Vinod Labhasetwar (Cleveland Clinic) and Associate Editors Kensuke Egashira (Kyushu University) and Justin Hanes (The Johns Hopkins University). The journal will provide high-quality research exclusively focused on transitional aspects of drug delivery, including such topics as designing and developing novel drug delivery systems, with a focus on their application to disease conditions; preclinical and clinical data related to drug delivery systems; short- and long-term biocompatibility of drug delivery systems; nanomedicines; and other state-of-the-art technologies. In addition to original full-length papers, communications, and reviews, the journal will publish editorials, reports on future meetings, research highlights, and announcements pertaining to CRS activities.

Do you have research that should be featured in *Drug Delivery and Transitional Research*? We would love to see it! Visit http://www.editorialmanager.com/ddtr/ for submission instructions and to submit your manuscript. The publication of the first issue is planned for January-February 2011. Submit your research early to be considered for the inaugural issue. ■

Welcome New CRS Members

Firouz Asgarzadeh
Sujin Cho
Bernd Fiedler
Robert D. Gleim
Matthew B. Greene
Bill Grubb
Donghyun Hong
Keith Hurley
Eun Hye Jo
Yun-Sik Kim
Eugene Lee
James A. Matriano
Brian R. McMillan
Carlos A. Miranda Alvarez
Shyamala P. Pillai
Byung Joo Song
Karunakar Sukuru
You-Yeon Won
Shirley Yang
DongHyuck Yoo

CRS Chapters—Reaching Around the Globe

Expand your local network.
Become involved in a CRS Chapter.

Argentina Local Chapter
Australian Local Chapter
Canadian Local Chapter
Germany Local Chapter
Greek Local Chapter
India Local Chapter
Israeli Local Chapter
Italy Local Chapter
Korea Local Chapter
New Zealand Local Chapter
Nordic Local Chapter
Peoples Republic of China Local Chapter
Slovenia Local Chapter
Spain-Portuguese Local Chapter
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Student Chapter Hebrew University of Jerusalem
Student Chapter Illinois
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Join a Chapter in Your Region

www.controlledreleasesociety.org/main/chapters

Controlled Release Society Germany Local Chapter Holds Convention

Olivia M. Merkel[1]
Philipps-Universität Marburg, Department of Pharmaceutics and Biopharmacy, Marburg, Germany

The 2010 Annual Convention of the Controlled Release Society (CRS) Germany Local Chapter was held March 24 in Saarbrücken, Germany. The 2010 convention was organized by 2009 Vice President Jun.-Prof. Marc Schneider (Saarland University), and for the first time, the event was embedded in the International Conference and Workshop on Biological Barriers, which is held biannually. The convention brought together internationally recognized scientists from industry and academia. Keynote speakers included Prof. Ijeoma Uchegbu (University of London), Prof. Tejal Desai (University of California, San Francisco), Prof. Udo Bakowsky (University of Marburg), and Prof. Hamid Gandehari (University of Utah). In addition, doctoral students and post-docs from Germany, England, Ireland, Poland, and Russia exhibited their work in short podium presentations. An additional highlight was the Galenos Euro-Ph.D. Award Ceremony, during which four newly graduated doctorates received their diplomas. This report covers recent advances in controlled release drug delivery presented at the convention, as well as information on decisions made by the local chapter during its business meeting.

Keynote Addresses

New Polymers for Bioavailability and Solubility Enhancement. Ijeoma Uchebu provided an overview of nanomedicines for both drug and gene delivery, with an emphasis on polymeric carriers such as poly-L-lysine, modified polyethylenimines, poly(propylenimine) dendrimers, poly(amino acids), and ammonium palmitoyl glycol chitosan. In one part of her talk, she presented promising results concerning solubilization of hydrophobic drugs into polyelectrolyte nanoparticles. Later, she reported on intravenous gene delivery with dendritic poly(propylenimine) vectors, leading to almost exclusive tumour targeting in an orthotopic tumour model that is visualized by SPECT imaging.

Nanostructured Particulate Drug Carriers for Advanced Drug Delivery. Tejal Desai (Therapeutic Micro and Nanotechnology Laboratory, UC San Francisco) shared her extensive experience in the field of bioadhesive drug delivery devices. She drew comparison between gecko setae, which allow geckos to stick to walls, and synthetic silicon nanowires produced by vapour deposition. She explained the mucoadhesive characteristics of these drug delivery systems, showing specific interactions with the gastrointestinal mucosa that lead to greater residence time, which was investigated *in vitro* and in a canine model.

Novel Ultrasound Active Liposomal Formulations in Diagnostics and Therapeutics. Udo Bakowsky's talk was given by his collaborator, Andreas Becker, who introduced the audience to high-intensity focused ultrasound (HIFU) techniques. The background of ultrasound imaging was explained with respect to microbubbles as carriers of contrast agents. Andreas explained the principles of the measurements and optimization of different liposomal microbubble formulations with regard to defined stability.

Polymeric Nanocarriers. Hamid Gandehari took up the theme of the very first lecture. The seminar covered PAMAM dendrimers for oral delivery of chemotherapeutics, recombinant polymers, i.e., polypeptides, stimuli-sensitive hybrid particles, bi- and monocyclic RGD-peptides for multivalency, and recombinant silk elastin-like polymers that form hydrogels at body temperature, allowing insight into Hamid's experience with polymer nanomedicines. Dendritic polymers were shown to interact with tight junctions, which leads to opening of the latter and explains the high efficacy of these polymers.

Local Chapter Meeting

During the business meeting, all members of the CRS Germany Local Chapter were invited to practice their determination in the Society. The acting executive board was re-elected unanimously. The suggestion to organize the 2011 meeting in Jena, with Prof. Dagmar Fischer as current vice president and president elect in 2011, was most welcome. Topics discussed included the creation of a website for the local chapter and establishment of a register of members for circulation of news and meetings, as well as reminders concerning membership fees.

Galenos Euro-Ph.D. Award Ceremony

The Galenos Euro-Ph.D. program supports students in the field of advanced drug delivery that spend at least 12 months of their practical training in a research institute abroad. It offers networking with other fellows and well-recognized researchers and advances the Ph.D. training of fellows in workshops. Training in presentation techniques is also offered, and one oral presentation at an international conference is mandatory to receive the diploma after graduation. Three of the awardees who received their diploma in Saarbrücken gave their presentation within the framework of the CRS chapter day.

Poster Session

During the poster session, students and post-docs from all over the world presented a vast amount of data in posters of 188 accepted abstracts. The posters had already been mounted in the morning and could be viewed all day. From their active participation, it was obvious that the CRS local chapter meeting is an excellent opportunity for young researchers to present their data in posters and short presentations. Local food was served for lunch and during the poster session, and the participants were invited to stroll among the posters with a glass of wine. The poster session also allowed for networking and an exchange of experiences inspired by the lectures and posters. ■

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Drug-Device Combination Products: Delivery Technologies and Applications

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University of Brighton

Drug-Device Combination Products: Delivery Technologies and Applications
Edited by A. Lewis
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CRC Press/Woodhead Publishing Ltd.
www.woodheadpublishing.com/en/book.aspx?bookID=1515

In recent years there has been considerable interest in the development of drug-delivery combination products to improve the efficacy of medical implants, reduce post-operative complications, and reduce the need for longer term revision surgery. This book provides the first comprehensive and authoritative text on this developing field by drawing on the recent development, clinical evaluation, and commercialisation of a range of drug-device combination products.

The first part of this book provides a detailed overview of the field: the introductory chapter outlines the importance and impact of the development of both drug-enhanced medical devices and device-based drug delivery systems in the fields of medical device technology and drug delivery. This is followed by contributions that consider the advantages, challenges, and opportunities of achieving controlled release of drugs through devices and the new opportunities presented through the development of nanotechnology in the field.

The second part of the book focuses on specific applications of drug-delivery combinations and, through contributions from leading experts in different fields, provides up-to-date insight to the state-of-the art in 1) the development of combination devices for reducing complications associated with medical catheters; 2) the future of drug-eluting cardiovascular stents; 3) the development of chemoembolisation technologies; 4) antibiotic-loaded bone cements; 5) antibacterial dental restorative materials; 6) bioactive collagen wound dressings and bone-graft substitutes; and 7) drug-device combination products for ocular applications. These contributions highlight the important role that drug-device combinations are playing in, for example, reducing postoperative infection and inflammation, enhancing postoperative tissue repair, and providing local site-specific, controlled drug delivery to combat localised disease. These contributions also highlight the challenges that such systems present with respect to achieving effective controlled release of the active agents employed in such devices.

The final section of this text is devoted to the regulatory challenges of developing drug-device combination products for the clinic. This includes two very informative contributions on the regulation of drug-device combination products in Europe and the United States, not only outlining the regulatory requirements in these different global markets, but providing an extensive reference base that is an invaluable resource for anyone considering the development of products for these markets. The contribution on the safety and efficacy issues in designing products, using drug-eluting stents as a case study, is complemented by a wider consideration of the requirements for preclinical testing of drug-device combination products. These contributions not only highlight the types of consideration that must be given to the design of preclinical testing, but also emphasises the potential challenges and limitations of the use of *in vitro* models for predicting longer term performance *in vivo*. Finally, this section includes an informative contribution on the sterilisation of drug-device combination products. This is an area that needs to be given early consideration in the development process given that a drug-device combination may require a completely different sterilisation process than the device alone to avoid, for example, drug degradation and/or modification to the drug-carrier matrix. The challenges and opportunities of using ionising radiation for the sterilisation of drug-device combination products are discussed in detail with reference to their potential effects on both the pharmaceutical agents and polymeric materials from which device and/or coatings are often fabricated.

The editor should be congratulated on the spectrum of contributors that has ensured that this foremost text will be of value to those seeking to develop, evaluate, and commercialise new combination products in the industry and clinic, as well as researchers in the medical device and drug delivery fields. A key strength of the text is the inclusion of detailed sources of further information and key references that direct the reader to the latest up-to-date information on individual topics. Although presently available only in hardback, the publication of this text as an e-book will also provide educators with a useful resource to ensure that the next generation of clinical, material, biomedical, and pharmaceutical scientists has the appropriate skills and interdisciplinary knowledge to provide the clinical and industrial workforce to support the development of future generations of controlled release systems for drug-device combination products. ■

[1] Professor of biomedical materials.

In the News

Compiled by Steven Giannos
Industrial Editor

August 2010

MonoSol Rx Announces FDA Approval of Reckitt Benckiser's Suboxone® Sublingual Film for Treatment of Opioid Dependence

PRNewswire: August 31, 2010 – WARREN, NJ – MonoSol Rx, the developer of PharmFilm® technology and a drug delivery company specializing in film pharmaceutical products, has announced that its partner, Reckitt Benckiser Pharmaceuticals Inc., a wholly owned subsidiary of Reckitt Benckiser Group plc (LSE: RB), has received approval from the U.S. Food and Drug Administration (FDA) to market Suboxone® (buprenorphine HCl/naloxone HCl dihydrate) sublingual film for the treatment of opioid dependence.

This is the second U.S. marketing authorization for a prescription product based on MonoSol Rx's PharmFilm® technology. Suboxone® sublingual film delivers a convenient, quick-dissolving therapeutic dose of buprenorphine, a partial opioid agonist, and naloxone, an opioid antagonist. The drugs rapidly absorb under the tongue to ensure compliance.

A. Mark Schobel, president and CEO of MonoSol Rx, stated, "We are very pleased to announce the approval of Suboxone® sublingual film and disclose our important relationship with Reckitt Benckiser. Following the FDA approvals of Suboxone® sublingual film and Zuplenz® oral soluble film, both within the past two months, the agency has clearly accepted our proprietary PharmFilm® technology as a viable prescription drug dosage form."

"The success of Suboxone® sublingual film through our collaboration with Reckitt Benckiser is another example of the significant value our PharmFilm® technology delivers to leading pharmaceutical companies, and further validates the commercial potential of film drug delivery for this industry. We look forward to working closely with Reckitt Benckiser to prepare for the launch. Upcoming royalty and supply revenues under this agreement are expected to support our pipeline and provide further confirmation of the acceptability of PharmFilm® for future partners."

Suboxone® sublingual film was developed under a previously undisclosed collaboration between MonoSol Rx and Reckitt Benckiser Pharmaceuticals Inc., in which Reckitt Benckiser's Suboxone® products were formulated utilizing MonoSol Rx's PharmFilm® technology. Under the worldwide agreement, MonoSol Rx will manufacture Suboxone® sublingual films, and Reckitt Benckiser will leverage its existing Suboxone® sales force to market the product. MonoSol Rx is eligible to receive pre-launch milestone payments, development fees, supply payments, and royalties on net sales.

Shaun Thaxter, president of Reckitt Benckiser Pharmaceuticals Inc., said, "We are pleased that our positive working relationship with MonoSol Rx has resulted in FDA approval of Suboxone® sublingual film. The development of Suboxone® sublingual film through our exclusive agreement with MonoSol Rx reinforces our commitment to our addiction therapy franchise and to its development. During clinical studies, Suboxone® sublingual film was shown to be faster dissolving than Suboxone® sublingual tablets, and patients preferred the film. Our partnership with MonoSol Rx, represents a strategic business opportunity which will contribute to the longevity of Suboxone® in the U.S."

InspireMD Becomes a Supporting Organization in the Growing Stent for Life Initiative

PRNewswire: August 30, 2010 – STOCKHOLM, SWEDEN – The Stent for Life (SFL) Initiative celebrated its first year anniversary at the ESC 2010 Congress in Stockholm. InspireMD Ltd., a medical device company engaged in the development and commercialization of MGuard novel stent systems, has joined the SFL Initiative as a supporting organization. The SFL Initiative aims to improve patient access to the life-saving indications of PCI and, thereby, reduce the mortality and morbidity of patients suffering from acute coronary syndromes.

InspireMD Ltd. is a medical device company that engages in the development and commercialization of MGuard, a novel net protective stent system that is specifically designed to treat thrombus-loaded lesions in the cases of acute coronary syndrome, acute myocardial infarction, or saphenous vein grafts. "We are delighted to become part of the SFL initiative," stated Ofir Paz, CEO of InspireMD. "We are convinced that increasing the use of primary PCI in STEMI patients is the most important advancement in our field today and we focus our efforts on providing the best products and solutions to support this noble initiative."

SFL was initiated one year ago during the European Association of Percutaneous Cardiovascular Interventions (EAPCI) General Assembly at the ESC Congress 2009 in Barcelona. The Initiative is a unique European platform for interventional cardiologists, government representatives, industry partners, patient groups, and patients to work together and, by shaping the healthcare systems and medical practices, ensure that the majority of ST elevation myocardial infarction (STEMI) patients will have equal access to the life-saving indication of percutaneous coronary intervention (PCI).

Industry partners, such as InspireMD, actively support the project goals. This support may include participating in defining strategy, as well as providing expertise such as project

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management, local analysis, patient awareness, promotion, funding, and investment planning.

Bend Research Receives Patent for Preparation of Spray-dried Drug Dispersions Using Pressure Nozzles

PRNewswire: August 30, 2010 – BEND, OR – Bend Research Inc. (www.bendres.com), a leading independent drug-formulation development and manufacturing company, has received a new U.S. patent covering a process for making spray-dried solid amorphous dispersions of drugs using pressure nozzles. The patent, which adds further protection to the company's spray-dried dispersion (SDD) technology, can be used to make solid amorphous dispersions with larger particle sizes and minimal fines (e.g., small particles). By spray-drying with a pressure nozzle, relatively large droplets are formed that dry to form dense particles with good properties for making solid dosage forms, such as tablets.

"This patent is an important addition to our spray-drying patent portfolio," said Bend Research President and CEO Rod Ray. "Customers come to Bend Research for the quality of our science, engineering, and clinical-supply manufacture, and our ability to move fast. Having patents that protect intellectual property offers them another key benefit by adding value to the formulations our scientists and engineers produce."

The patent, which is titled "Method for Making Homogeneous Spray-dried Solid Amorphous Drug Dispersions Using Pressure Nozzles," was assigned Patent No. 7,780,988 by the U.S. Patent and Trademark Office. The inventors are Bend Research employees Ron Beyerinck, Rod Ray, Dan Dobry, and Dana Settell. The patent covers a spray-drying process for producing solid amorphous dispersions from drugs with low aqueous solubility and polymers. In many cases, the resulting formulations increase the amount of drug that is orally absorbed when administered to a patient.

The patent addresses a common problem encountered using conventional spray-drying processes: they often produce small particles, including numerous very small particles known as "fines." As a result, solid amorphous dispersions produced using conventional processes often have poor flow characteristics and are difficult to collect efficiently and formulate into solid dosage forms. The technology covered by this patent makes it possible to produce larger particles with fewer fines, improving particle flow characteristics and collection efficiencies and simplifying downstream handling and processing.

The patent is one in a growing of number of formulation- and process-related patents associated with Bend Research's SDD technology. The SDD technology has successfully enabled the advancement of hundreds of compounds from preclinical studies to several large Phase III clinical trials.

Alexza's Staccato Nicotine Licensed to Cypress Bioscience

PRNewswire: August 26, 2010 – MOUNTAIN VIEW, CA – Alexza Pharmaceuticals, Inc. (Nasdaq: ALXA) has licensed its Staccato nicotine technology to Cypress Bioscience, Inc. (Nasdaq: CYPB). The Staccato nicotine technology is a novel electronic multidose delivery system designed to help people stop smoking. Staccato system is intended to improve on a well-validated smoking cessation approach by delivering nicotine via inhalation, mimicking the nicotine effects of smoking without the harmful side effects associated with cigarettes.

"The Staccato system is a broad technology platform and Alexza has more Staccato-based product candidates than we can currently afford to develop on our own. In early July, we outlined our strategy to advance Staccato-based product candidates into development through self-funding and through collaborations," said Thomas B. King, Alexza president and CEO. "Today's announcement of the licensing of our Staccato nicotine technology to Cypress, along with our recently announced plans to advance AZ-007 (Staccato zaleplon) into Phase 2 clinical development, are examples of our execution of this dual-tracked development strategy."

For more information about Alexza, the Staccato technology, or the company's development programs, please visit www.alexza.com.

Vyteris and Georgia Tech Enter into Exclusive Agreement for Transdermal Drug Delivery Technologies

Marketwire via Comtex: August 24, 2010 – FAIR LAWN, NJ – Vyteris, Inc., developer of the first FDA-approved active transdermal patch and a leader in alternative drug delivery technology, has announced an agreement with the Georgia Tech Research Corporation of the Georgia Institute of Technology (Georgia Tech) granting Vyteris the option to exclusively license Georgia Tech's patented thermal ablation and microdevice fabrication technologies for transdermal drug delivery.

The thermal ablation technology is designed to selectively enhance skin permeation to allow delivery of therapeutic drugs of high molecular weight, including peptides and proteins, through the skin, eliminating the need to inject or infuse such drugs with hypodermic needles. The microdevice fabrication technology provides a novel method to manufacture microstructures for drug delivery, using mild conditions that do not harm encapsulated drugs. Vyteris plans to work closely with Georgia Tech to identify therapies that would be appropriate for the application of the new technologies.

Georgia Tech's proprietary thermal ablation and microdevice fabrication technologies were developed by Dr. Mark R. Prausnitz (professor of chemical and biomedical engineering at Georgia Tech), a leader in developing energy- and microneedle-based transdermal delivery systems. Dr. Prausnitz has received major research awards from the National Science Foundation, Controlled Release Society, Wallace H. Coulter Foundation, Sigma Xi Scientific Research Society, *Technology Review Magazine*, and American Society for Engineering Education.

Dr. Prausnitz commented, "Transdermal drug delivery, in addition to doing away with painful needles, can empower patients to better control their medication schedule, improves drug efficacy in many cases, and offers the promise of reduced healthcare costs. The thermal ablation-based transdermal delivery systems may be beneficial to improving the lives of patients around the world. Our agreement with Vyteris is an important step toward bringing Georgia Tech's advanced transdermal drug delivery technologies to patients in need."

"This is a significant inflection point for Vyteris that we believe enhances the Company's current transdermal capabilities by providing access to these innovative technologies from Dr. Prausnitz' laboratory," said Haro Hartounian, president and chief executive officer of Vyteris, Inc. "Georgia Tech's thermal ablation and microdevice fabrication technologies are potentially complementary to our active transdermal smart patch technology, and may allow Vyteris to deliver a much broader range of therapeutic drugs through the skin. We look forward to working with Dr. Prausnitz and his team in advancing these combined drug delivery technologies toward clinical testing." For more information, please visit www.vyteris.com.

FibeRio Technology Corporation Developing New Nanofiber Technology

PRNewswire: August 16, 2010 – EDINBURG, TX – The University of Texas – Pan American (UTPA) has launched a start-up company that may revolutionize manufacturing. FibeRio Technology Corporation is perfecting a new technology called ForceSpinning to create the microscopic nanofibers used to produce everything from traditional textiles and personal care products to medical supplies and aerospace materials, with potential applications ranging from tissue engineering to drug delivery.

Nanofibers, which are about 1,000 times smaller than the diameter of a human hair, are currently made with a process called electrospinning, which uses an electrostatic charge to create ultra-fine fibers from polymers used in common plastics. ForceSpinning technology, a concept developed by UTPA mechanical engineering Profs. Drs. Karen Lozano and Kamal Sarkar, employs centrifugal force to push materials through tiny openings to create the nanofibers. A wider variety of materials, including metals and ceramics, can be used with ForceSpinning technology, making it more versatile and cost-effective than electrospinning.

FibeRio will develop and manufacture ForceSpinning machinery for commercial applications. The company is projected to generate $234 million in revenue by 2014 and create 110 jobs.

NextWave Pharmaceuticals and Tris Pharma Enter into CNS-focused Development and Commercialization Agreement

PRNewswire: August 12, 2010 – CUPERTINO, CA, and MONMOUTH JUNCTION, NJ – NextWave Pharmaceuticals and Tris Pharma, both privately held companies, have announced a new collaboration agreement to enhance NextWave's CNS product portfolio utilizing Tris Pharma's unique drug delivery technology for liquid and solid formulations. Tris has reacquired the rights to non-CNS products, including all the OTC products previously licensed to NextWave Pharmaceuticals.

NextWave will commercialize NexiclonXR (clonidine) extended-release tablets and suspension, which is the first ever 24-hr liquid extended release product approved by the FDA. NexiclonXR has been cleared for marketing by the U.S. FDA and will be introduced to wholesalers and pharmacies by NextWave in the second half of 2010. NextWave and Tris will also collaborate on the development of three additional CNS products, with an option to expand development to additional products. All products under the agreement incorporate Tris' OralXR+ technology for delivery of suspension or solid dosage forms, which provides up to a 24-hr delivery profile in taste-neutral formulations.

"Long acting products that do not require swallowing remains an unmet need of the industry. With our products, we intend to focus on this unique opportunity. We are excited to work with Tris to bring these unique and important products to patients, especially the pediatric, adolescent, and adult populations," stated Jay Shepard, chair and CEO of NextWave. "Given our experience in this marketplace and the convenience and clinical benefits provided by this technology, we are convinced these products will make a significant impact on the lives of patients and caregivers."

"The CNS market, especially pediatric CNS, is an ideal application of the OralXR+ platform. In the current paradigm parents need to persuade young children to swallow extended release pills; OralXR+ suspensions, chewable tablets and ODT's are child-friendly and long acting," commented Ketan Mehta, CEO of Tris Pharma. "The team at Tris has worked diligently in developing this important advance for physicians and patients. We are fortunate to work with a number of outstanding commercialization partners and appreciate the CNS expertise NextWave brings to these important therapies."

Agile Therapeutics Commences Phase III New Choice Study of AG200-15, Agile's Novel, Low-Dose Weekly Contraceptive Patch

Business Wire: August 11, 2010 – PRINCETON, NJ – Agile Therapeutics, Inc., a pharmaceutical development company specializing in women's healthcare products, has announced study initiation and dosing of the first patient in the company's pivotal, Phase III New Choice Study of AG200-15, Agile's lead contraceptive patch. AG200-15 is designed to effectively deliver a low dose of estrogen (ethinyl estradiol [EE]) in combination with levonorgestrel (LNG). The patch is applied once weekly for three weeks followed by a patch-free week.

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"We are pleased with the progress of our lead AG200-15 program and the initiation of the pivotal, Phase 3 NEW CHOICE Study. We anticipate enrollment into the study will be rapid, driven by women's desire for greater convenience and ease of compliance in their choice of contraception."

Agile's New Choice Study will enroll up to 1,500 women aged 17–40 at more than 100 sites throughout the United States. The study will compare efficacy and tolerability of AG200-15 to a low-dose, oral contraceptive. Women interested in participating in the study should visit www.newchoicestudy.com.

Dr. Marie Foegh, chief medical officer and vice president, clinical research and development, of Agile Therapeutics, commented, "AG200-15 has been designed to maximize both safety and tolerability for women, delivering EE at a dose which can provide a favorable bleeding profile. Clinicians in fact have long experience with both EE and LNG, which have been used in contraceptive products for over 25 years. AG200-15 also incorporates Agile's novel SKINFUSION™ delivery system, offering additional advantages, including good adhesion and minimized irritation."

Dr. Thomas Rossi, Agile president and CEO, stated, "We are pleased with the progress of our lead AG200-15 program and the initiation of the pivotal, Phase 3 NEW CHOICE Study. We anticipate enrollment into the study will be rapid, driven by women's desire for greater convenience and ease of compliance in their choice of contraception."

According to market research conducted on behalf of Agile with 105 OB/GYN physicians who are significant prescribers of contraception, 89% said they would be likely to prescribe AG200-15. Almost half said they would prescribe it immediately upon approval, demonstrating that physicians perceive a large need among their patients for the comfort and convenience of Agile's low-dose, weekly contraceptive patch. This physician data supports the findings of Agile market research with 1,500 women, in which nearly two-thirds of the participants said they would ask their doctor about AG200-15 if it were available to them.

Noven to Acquire Daytrana® Methylphenidate Transdermal System from Shire

Business Wire: August 10, 2010 – MIAMI, FL – Noven Pharmaceuticals, Inc. has entered into a product and trademark acquisition agreement with affiliates of Shire plc pursuant to which Noven will acquire global rights to Daytrana® (methylphenidate transdermal system) from Shire.

Daytrana®, developed and manufactured by Noven, was originally licensed globally to Shire in 2003 and was approved and launched in the United States in 2006. The product is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in patients 6–17 years old. Daytrana® should be used as a part of a total treatment program for ADHD that may include counseling or other therapies. Shire's net sales of the product in 2009 were $71 million.

The agreement provides that Noven will acquire substantially all rights and assets related to Daytrana®, including the product's new drug application, and will assume certain related liabilities. Shire will continue to commercialize the product through closing of the transaction, scheduled for October 1, 2010. Once transferred to Noven, Daytrana® will be marketed and sold by Noven Therapeutics, Noven's specialty pharmaceuticals marketing and sales unit, with U.S. promotion of the product expected to begin in March 2011. Noven Therapeutics currently promotes the oral prescription products Pexeva®, Stavzor®, and Lithobid® to psychiatrists and other target physicians in the U.S.

Jeffrey Eisenberg, Noven president and chief executive officer, said, "We are excited to add Daytrana® to the product portfolio of Noven Therapeutics. Since 2006, Daytrana® has been an important therapeutic alternative for patients with ADHD and their physicians. Applying the focused strategies and resources of Noven Therapeutics, we believe Noven will be well-positioned to continue to raise awareness of Daytrana®, with the ultimate goal of helping patients manage their ADHD."

Endo Pharmaceuticals Agrees to Acquire Penwest Pharmaceuticals and Submits NDA for New Formulation of Long-acting Oxymorphone Designed to be Crush Resistant

PRNewswire-FirstCall: August 9, 2010 – CHADDS FORD, PA – Endo Pharmaceuticals (Nasdaq: ENDP) has announced actions designed to advance the company's leadership and growth in pain management, including an agreement to acquire all outstanding shares of Penwest Pharmaceuticals (Nasdaq: PPCO) for $5.00 in cash per share, or an estimated enterprise value of approximately $144 million at the time of deal close. Penwest has been working with Endo since 1997 on the development and commercialization of OPANA ER and receives a royalty stream on net sales of the product.

"Our acquisition of Penwest sets the stage for maximizing the value of the OPANA franchise and for leveraging Penwest's drug delivery technologies and pipeline across our branded and specialty generics businesses for the benefit of patients," said Julie McHugh, chief operating officer, Endo Pharmaceuticals. "This transaction highlights the growth potential of Endo's core Pain Management franchise, enhances our earnings, and creates significant value for shareholders of both organizations."

Under the terms of the merger agreement, Endo will shortly commence an all-cash tender offer to acquire 100% of the outstanding common stock of Penwest Pharmaceuticals for $5.00 per Penwest share. The tender offer is expected to be completed in September 2010. Endo will acquire any Penwest shares that are not purchased in the tender offer in a second-step merger, which is expected to be completed during the fourth quarter of 2010, at the same price per share paid in the tender offer. The tender offer will be subject to certain closing conditions, including a minimum condition that not less than a majority of shares of Penwest common stock are tendered into the offer. Tang Capital Partners, LP, and Perceptive Advisors

LLC, shareholders of Penwest, and Jennifer Good, Penwest president and chief executive officer, who collectively own 38.6% of fully diluted common stock of Penwest, have committed to tender their shares in the tender offer. The transaction has been unanimously approved by the boards of directors of both companies.

Celsion's Phase III ThermoDox Heat Study Recommended as Priority Clinical Trial for HCC

PRNewswire-FirstCall: August 3, 2010 – COLUMBIA, MD – Celsion Corporation (Nasdaq: CLSN) has announced that the consensus recommendations of the National Cancer Institute (NCI) Clinical Trials Planning Meeting (CTPM) for hepatocellular carcinoma have been released and published in the August 2010 issue of the *Journal of Clinical Oncology*. In addition to evaluating the current standard of care, the NCI panel also recommended Celsion's Phase III ThermoDox Heat Study as a priority clinical trial for HCC.

"We are pleased this prominent panel of experts at the NCI Clinical Trials Planning Meeting have recognized the importance of our Phase III HEAT Study," stated Michael H. Tardugno, president and chief executive officer of Celsion. "Upon completion of the trial and eventual marketing approval, ThermoDox plus RFA will provide an additional therapeutic option for patients afflicted with HCC, a dreadful disease with high unmet medical need." Dr. Nicholas Borys, chief medical officer of Celsion commented, "This JCO article also reinforces the global importance of new therapies for HCC, and highlights the prominence of the ThermoDox program, which is now over 2/3rds enrolled in 75 global sites and 11 countries."

Celsion's global Phase III ThermoDox study for primary liver cancer plans to enroll 600 patients and is being conducted under an FDA special protocol assessment (SPA). The study is designed to evaluate the efficacy of ThermoDox in combination with radiofrequency ablation (RFA) when compared with patients who receive RFA alone as the control. The primary endpoint for the study is progression-free survival.

ThermoDox is a proprietary heat-activated liposomal encapsulation of doxorubicin, an approved and frequently used oncology drug for the treatment of a wide range of cancers, including breast cancer. ThermoDox is administered intravenously and in combination with hyperthermia has the potential to provide local tumor control and improve quality of life. Localized mild hyperthermia (39.5–42°C) releases the entrapped doxorubicin from the liposome. This delivery technology enables high concentrations of doxorubicin to be deposited preferentially in a targeted tumor.

Victory Pharma Completes Acquisition of Assets of MiddleBrook Pharmaceuticals

PRNewswire: August 3, 2010 – SAN DIEGO, CA – Victory Pharma, Inc. has completed the acquisition of substantially all of the assets of MiddleBrook Pharmaceuticals, Inc. (OTCQB: MBRKQ). Through the acquisition, Victory Pharma has expanded its product portfolio with the addition of anti-infective products MOXATAG and KEFLEX, as well as the PULSYS drug delivery technology platform. The product additions complement Victory's current products, such as NAPRELAN, which the company markets to primary care and specialist physicians.

"This acquisition reflects our strategy of leveraging our existing commercial infrastructure to expand our portfolio of marketed products," said Matt Heck, president and chief executive officer of Victory Pharma. "The addition of these products balances our portfolio nicely, as NAPRELAN's highest period of utilization is in the spring and summer, while MOXATAG's utilization peaks during the flu season. And we believe MOXATAG will substantially benefit from our management team's prior, successful experience marketing anti-infective products."

MOXATAG is the only FDA-approved, once-daily formulation of amoxicillin and is indicated for the treatment of tonsillitis and/or pharyngitis. MOXATAG utilizes PULSYS technology to deliver the drug at set intervals over a 24-hr period, whereas other amoxicillin products require dosing multiple times daily. Reduced dosing frequency can improve therapy compliance, which is potentially important given that patient non-compliance is widely recognized as the primary reason for antibiotic therapy failure, and non-compliant patients have been shown to have a 175% greater chance of infection recurrence.

Access Pharmaceuticals Furthers Clinical Development Program of Thiarabine in Patients with Hematologic Malignancies

PRNewswire-FirstCall: August 3, 2010 – DALLAS, TX, and NEW YORK, NY – Access Pharmaceuticals, Inc. (OTC Bulletin Board: ACCP) has initiated a Phase I/II dose-escalating study of its proprietary, anti-cancer drug, Thiarabine, a nucleoside analog for patients with hematologic malignancies (cancers of the blood). The primary objective of the study is to determine the maximum tolerated dose (MTD) in two different dosing schedules with various leukemias and lymphomas and recommended Phase II dose. The program is being led by Hagop Kantarjian, chair of the Department of Leukemia at the University of Texas MD Anderson Cancer Center in Houston.

The clinical development program follows previously conducted Phase I and II trials of Thiarabine in solid tumors, where myelosuppression (decrease in the production of blood cells), particularly lymphopenia (abnormally low white blood cell levels), was dose limiting. Access believes an agent that produces significant lymphopenia can be a strong active against lymphoproliferative disorders like acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), myeloma, and lymphoma.

"We are pleased to have Dr. Kantarjian lead our continued clinical development of Thiarabine," said David Nowotnik, Access Pharmaceuticals senior vice president for R&D. He

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continued, "The findings in preclinical and clinical studies to this point have given us a strong indicator that Thiarabine could be highly beneficial in treating patients with hematologic malignancies. The new Phase I/II trial at MD Anderson, one of the country's leading cancer centers, is the next step in our comprehensive plan to build on the strong set of data and clinical results that have been generated to date."

Thiarabine is a novel nucleoside analog with considerable potential for the treatment of cancer. Great interest has been shown in this class of molecules. Three nucleoside analogs have been approved in recent years, and extensive research continues to produce compounds with improved activity. In preclinical models, Thiarabine has exhibited significant activity, including regressions or cures, in six leukemia or lymphoma cell lines. The compound produced better activity than the approved nucleoside analogs, cytarabine, gemcitabine, and clofarabine. Two monotherapy Phase I studies were conducted with Thiarabine in patients with solid tumors. In the first Phase I study, of 26 patients with incurable advanced and/or metastatic solid tumors, 9 patients experienced stable disease; 7 of 27 patients in the second study achieved stable disease. Lymphopenia observed in these studies coupled with the excellent preclinical results in leukemia models indicate that Thiarabine is an excellent candidate for treating advanced hematologic malignancies.

Cornerstone Therapeutics Announces Collaboration with The Cough Company

PRNewswire-FirstCall: August 2, 2010 – CARY, NC – Cornerstone Therapeutics Inc. (Nasdaq: CRTX), a specialty pharmaceutical company focused on acquiring, developing, and commercializing significant products primarily for the respiratory and related markets, has entered into a license and development agreement with Alitair Pharmaceuticals, Inc., also known as The Cough Company. Under the terms of the agreement, Cornerstone has acquired a license to certain of The Cough Company's proprietary intellectual property, and the companies will collaborate in developing one or more products to treat respiratory diseases.

The Cough Company has a portfolio of patents pending that relate to its proprietary drug delivery system. This portfolio includes claims covering solid oral dosage formulations in a wide variety of therapeutic categories. Cornerstone intends to leverage this intellectual property to develop one or more proprietary, patent-protected cough and cold products.

"We view The Cough Company as an important partner in the continued development of our cough and cold franchise, which is a key aspect of our growth strategy," said Craig A. Collard, Cornerstone president and chief executive officer. "This collaboration has the potential to significantly enhance our pipeline, which already includes multiple innovative product candidates in the respiratory space."

"Cornerstone provides the respiratory marketing expertise which we believe will translate our development program into multiple commercial successes," said William Howard, president of The Cough Company. "We look forward to moving our platform forward with Cornerstone's support."

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SurModics and EGEN Announce Collaboration with Potential for Long-term Delivery of siRNA

PRNewswire-FirstCall: July 27, 2010 – HUNTSVILLE, AL – SurModics, Inc. (Nasdaq: SRDX), a leading provider of drug delivery and surface modification technologies to the healthcare industry, and EGEN, Inc., a privately held biopharmaceutical company focused on developing nucleic acid (DNA and RNAi) therapeutics for the treatment of human diseases, have executed a continuation of their feasibility collaboration focused on long-term controlled release of siRNA complexes. In work presented earlier this year at the Boston TIDES 2010 meeting, the companies disclosed more than 100 days of sustained release of siRNA nanocomplexes *in vitro*. Importantly, a high degree of gene knockdown was maintained, with little indication of degradation of the released complexes. The kinetics of siRNA nanocomplex release can be modulated by alterations in formulation, providing a broad range of extended release systems. In this work, EGEN's proprietary TheraSilence™ nanoparticles were used in combination with SurModics' proprietary Eureka™ DUET platform. Work is progressing to further optimize the combination of these technologies, leading to evaluation in relevant animal models.

Identification and characterization of mammalian siRNA mechanisms that control protein production has resulted in an important new area of research, opening up the potential to create entirely new classes of therapeutics that can specifically target the genes responsible for a variety of disease states. This breakthrough provides the ability to create siRNA-based drugs that can lead to innovative treatments for many of the most devastating diseases, such as cancer and genetic disorders.

Long-term siRNA delivery systems offer the potential of increased safety and efficacy, improved patient convenience (e.g., with less dosing or injections), enhanced compliance, and, ultimately, better therapeutic response. In general, the field of siRNA is not yet fully focused on long-term delivery, but it is expected that for many disease indications this will increasingly become a focus as siRNA-based products get closer to market.

"We are thrilled to be working with the team at EGEN and are excited about the compelling data generated to date. At SurModics, we like to maintain a balance of cutting-edge innovation. Many of our efforts are focused on creating new technologies and products for customers in the relative near-term. Others, however, like this extended release of siRNA, are ones where we intend to establish a leadership technology position for customers 2, 5, and 10 years in the future," said Arthur J. Tipton, chief scientific officer of SurModics.

Khursheed Anwer, president and chief scientific officer of EGEN, added, "The program with SurModics employs our TheraSilence™ technology for sustained delivery of therapeutic

RNAi. The extended release data generated from the collaborative work is impressive and warrants continuation of this exciting joint effort. A key mission for EGEN is to apply our broad-based RNAi delivery technology platform to create novel solutions for human diseases."

EGEN, Inc. is a privately held biopharmaceutical company focused on developing therapeutics for the treatment of human diseases, particularly cancer. The company specializes in the delivery of therapeutic nucleic acids (DNA and RNAi) aimed at specific disease targets via its proprietary TheraPlas™ and TheraSilence™ technologies. EGEN has a significant portfolio of functionalized, biocompatible synthetic delivery systems for use in combination with DNA, RNA, and other biomacromolecules for therapeutic applications. EGEN is located in Huntsville, AL, in the Hudson-Alpha Institute of Biotechnology. More information about the company can be found at www.egeninc.com

Titan Receives SBIR Grant to Investigate Long-term Treatment for Parkinson's Disease

PRNewswire-FirstCall: July 26, 2010 – SOUTH SAN FRANCISCO, CA – Titan Pharmaceuticals, Inc. (OTC Bulletin Board: TTNP) has announced that the National Institutes of Health (NIH) has awarded the company a grant under the Small Business Innovation Research (SBIR) program supporting the development of a long-term, non-fluctuating dopamine agonist treatment for Parkinson's disease. The first year award in the amount of $300,000 will be available to Titan starting August 1, 2010, and an additional $195,000 for the second year starting August 1, 2011, has been recommended subject to the availability of funds and satisfactory progress of the project. The grant will be administered by the National Institute of Neurological Disorders and Stroke (NINDS).

Parkinson's disease (PD) is a progressive disorder associated with the loss of dopamine-producing neurons in the brain. The cornerstone of symptomatic treatment for PD is dopamine-replacement therapy, and dopamine agonists such as pramipexole, ropinirole, apomorphine, and lisuride play a key part in the treatment of early, as well as advanced, stages of the disease. There is increasing evidence that maintaining continuous and stable blood levels of dopamine agonists may minimize the motor fluctuations and dyskinesias (involuntary movements) that are a debilitating side effect of the frequent oral administration of current dopamine-replacement therapies.

Titan's ProNeura technology can be used to develop a subcutaneous implant that provides round-the-clock delivery of dopamine agonists while maintaining a stable, non-fluctuating plasma drug level for six months or longer following a single treatment. The SBIR grant will cover all the external expenses for the initial evaluation of the non-clinical safety and efficacy of implant formulations of select dopamine agonists that are currently marketed for the treatment of PD. These studies will take approximately two years to complete, and the data will provide a basis for further development of potential product candidates that may alleviate the "on/off" motor fluctuations and treatment-related dyskinesias associated with current dopamine-replacement treatment regimens.

"We are very pleased by the award of this SBIR grant," said Sunil Bhonsle, president of Titan. "Long-term, non-fluctuating drug delivery using our ProNeura technology has been initially established with Probuphine® which is currently in Phase 3 clinical development for the treatment of opiate addiction, and this SBIR grant gives us an opportunity to investigate expanding the use of this technology," he noted.

"Parkinson's disease is a progressively debilitating condition and this support from NINDS will help us evaluate the possibility of alleviating some side-effects of current treatments, and hopefully make a meaningful difference for these patients," said Marc Rubin, executive chair of Titan.

ArmaGen Re-engineers Erythropoietin for Brain Penetration

PRNewswire: July 16, 2010 – LOS ANGELES, CA – Human erythropoietin (EPO) is a potent neuroprotective agent for multiple brain disorders, including stroke, brain and spinal cord injury, and Parkinson's disease. However, EPO drug development for the brain is limited, because EPO does not cross the blood-brain barrier (BBB). In acute stroke or brain injury, the BBB is intact in the early hours after the insult, when neuroprotection is still possible. Therefore, large-molecule biopharmaceuticals such as EPO must be re-engineered to enable BBB transport. ArmaGen Technologies has developed the BBB molecular Trojan horse platform technology for solving the BBB drug delivery problem and has used this technology to create a brain-penetrating form of human EPO. ArmaGen has successfully re-engineered human EPO as an IgG fusion protein that penetrates the brain following intravenous (IV) administration. Human EPO is fused to a genetically engineered monoclonal antibody (MAb) to the human insulin receptor (HIR). The HIRMAb acts as a molecular Trojan horse to ferry the EPO across the BBB via transport on the endogenous BBB insulin receptor. The HIRMAb-EPO fusion protein is a dual receptor-specific protein with low nanomolar binding constants for both the human EPO and insulin receptors. The HIRMAb part of the HIRMAb-EPO fusion protein cross-reacts with the Rhesus monkey insulin receptor. Therefore, brain penetration of the HIRMAb-EPO fusion protein was demonstrated *in vivo* in the adult Rhesus monkey following IV administration. EPO alone was shown not to cross the primate BBB. The brain uptake of the HIRMAb-EPO fusion protein in the Rhesus monkey was high, 2% injected dose/brain, and comparable to the brain uptake of small molecules. The plasma pharmacokinetics (PK) of the HIRMAb-EPO fusion protein differed markedly from the PK of EPO, which minimized any effect of the fusion protein on erythropoiesis. EPO-driven neuroprotection in human brain disorders is now possible with systemic administration of the HIRMAb-EPO fusion protein at doses that have minimal effects on erythropoiesis. The work was published in the June

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2010 issue of the *Journal of Pharmacology and Experimental Therapeutics*.

Nitto Denko and Quark Pharmaceuticals to Enter into Collaboration to Develop a Novel siRNA Anti-fibrotic Drug

PRNewswire: July 15, 2010 – OSAKA, JAPAN, and FREMONT, CA – Nitto Denko Corporation, Japan's leading diversified materials manufacturer, and Quark Pharmaceuticals, Inc., a world leader in the discovery and development of RNAi-based therapeutics, have announced the initiation of a collaboration and license agreement for the development of siRNA therapeutics for the treatment of fibrotic diseases.

The collaboration is designed to develop siRNA drugs using Quark's RNAi technologies and novel structures, providing freedom to operate in the siRNA intellectual property space, and Nitto Denko's drug delivery technologies for novel therapeutic concepts, currently owned by Nitto Denko. This refers to the concepts developed in a groundbreaking research by Prof. Yoshiro Niitsu (Sapporo Medical University, School of Medicine, Sapporo, Japan), as published in *Nature Biotechnology* (26(4): 431-442 (2008)). The collaboration will have an initial budget of double-digit million U.S. dollars to achieve the first IND for the U.S. FDA by early 2012.

"We are very pleased to collaborate with Nitto Denko in developing siRNA drugs. This collaboration is a perfect marriage between the core competencies of the two companies; we shall be using our technologies, intellectual property and capabilities to quickly bring drug candidates to clinical stage and Nitto will provide its delivery technologies and therapeutic strategy as well as their world-class capabilities in oligonucleotide production," said Daniel Zurr, Quark CEO.

Kageshi Maruyama, Nitto Denko officer, commented, "We are delighted to initiate this siRNA program. We believe siRNA is going to make a very important impact to the field of pharmaceuticals discovery and development. With its production facilities and extensive research, Nitto Denko is geared to have a very active participation in this market. We are pleased to work with Quark, we selected Quark due to the superior characteristics of its siRNA structure and chemical modifications, distinguished for the fact that [they] caused no immune response and look forward to utilizing this technology to create innovative medicines."

"I am very confident that siRNA drugs directed simultaneously to one or more specific target genes are the appropriate approach for therapies for a number of fibrotic diseases that are currently a totally unmet medical need," commented Prof. Niitsu. "Our research has demonstrated that the adequate siRNA, appropriately delivered to the liver caused regression of liver fibrosis and significantly prolonged survival time in siRNA treated animals. It is very likely that this approach is suitable to fibrotic diseases in other organs as well."

Quark Pharmaceuticals, Inc., a world leader in novel RNAi discovery and development, has the largest clinical stage siRNA pipeline in the industry. The company's fully integrated drug development platform spans therapeutic target identification to drug development. Quark's approach to delivery allows targeting of tissues and organs, including the eye, kidney, ear, lung, spinal cord, and brain. Quark is also committed to leveraging a broad research pipeline of siRNA drug candidates and novel siRNA structures to develop additional RNAi drug candidates. Quark is headquartered in Fremont, CA, and operates research and development facilities in Boulder, CO, and Ness-Ziona, Israel. Additional information is available at www.quarkpharma.com.

Biodel Reports Progress with Development of Glucose-regulated "Smart" Basal Insulin

PRNewswire-FirstCall: July 12, 2010 – DANBURY, CT – Biodel Inc. (Nasdaq: BIOD) has reported results of preclinical tests that demonstrated the potential of the company's glucose-regulated or "smart" basal insulin product candidate, BIOD620, to release insulin proportionally in response to changing glucose conditions. In an oral presentation at the 37th Annual Meeting & Exposition of the Controlled Release Society in Portland, OR, Nandini Kashyap, director of novel drug delivery at Biodel, described results of *in vitro* and *in vivo* studies with diabetic pigs that compared the use of BIOD620 to Lantus® (insulin glargine). BIOD620 is Biodel's proprietary injectable formulation of insulin glargine that has been designed to alter its insulin release profile in response to changing glucose concentration.

Six fasted diabetic pigs received a subcutaneous injection of 0.25 U/kg of BIOD620 or Lantus®. Their blood glucose was monitored every 15 min. Six hours after receiving their initial injection, they were fed 500 g of food as a glucose challenge. BIOD620 was able to reduce the elevated plasma glucose levels faster than the group receiving Lantus®. Furthermore, post-meal hyperglycemia was reduced more rapidly in the BIOD620 group than in the control group.

"Current basal insulins cannot respond to conditions that affect glucose levels, such as exercise and stress, and are often administered at inappropriately high doses. This study supports the hypothesis that BIOD620 released insulin in response to changing glucose conditions and is a truly self-regulating formulation that may translate to clinically relevant conditions," Kashyap noted. "We found that BIOD620 was able to manage plasma glucose levels more rapidly than basal insulin alone. Based on these findings, which we hope to test in clinical studies, we believe that BIOD620 insulin has the potential to be a significant improvement over basal insulin currently used by patients with diabetes mellitus."

Dr. Solomon Steiner, chief scientific officer of Biodel, commented: "We are excited about these results because they suggest we have developed a new form of basal insulin that adjusts automatically to changing glucose levels."

At the same conference, Biodel also reported findings from a preclinical study exploring the effect of disodium EDTA concentration in VIAject® (ultra-rapid–acting injectable human insulin) on the drug's speed of action in diabetic pigs. EDTA is one of two key excipients used in VIAject® that affect the rapid dissociation of insulin hexamers into monomers and the subsequent rapid absorption of insulin. In a poster presentation, Dr. Roderike Pohl and colleagues from Biodel described results of a study of eight diabetic pigs that showed that reduced amounts of EDTA produced lower insulin concentrations and less rapid absorption of insulin, although the duration of insulin action remained essentially the same regardless of the EDTA concentration. The authors concluded that the study demonstrated a systematic relationship between the concentration of EDTA and the speed of absorption, confirming that sufficient EDTA is required to achieve the ultra-rapid absorption profile and pharmacodynamic action of VIAject®.

Abstracts summarizing the oral presentation by Kashyap ("'Smart' Basal Insulin Formulation That Releases Insulin in Response to Blood Glucose Concentrations of Diabetic Swine") and the poster presentation by Dr. Pohl ("Effect of EDTA Concentration on Ultra-rapid Action of VIAject® in Diabetic Miniature Swine") are available on Biodel's website (www.biodel.com).

Fuisz Pharma Announces Acquisition of Key Anti-opiate Abuse Patent to Complement Its Anti-opiate Abuse Platform

PRNewswire: July 12, 2010 – MIAMI, FL – Fuisz Pharma has acquired a key issued patent (U.S. Patent 7,214,385, "Pharmaceutical Formulation Containing Dye" [invented by Dr. Thomas Gruber]). This patent covers the use of dyes and staining agents in pharmaceutical dosage forms as a method of preventing the improper use of opiate-derived drugs by visually demonstrating their misuse.

Fuisz Pharma President Joseph Matus Fuisz commented, "The technology described in the acquired patent is highly complementary to the anti abuse portfolio that we previously announced. Importantly, the Gruber patent enables us to offer strong, existing patent protection for our partners. We thus believe that this acquisition significantly enhances the value of our anti abuse platform and gives us a very strong IP position in the prevention of opiate abuse."

Fuisz continued, "This acquisition is also complementary to our next generation technology to aid and abet the absorption of all dosage forms including the ability to bring forth a very novel methodology to specifically play a critical role in the opiate agonist/antagonist pas de deux. This methodology is applicable to all dosage forms."

Fuisz Pharma is a private pharmaceutical technology company originated by the Fuiszes. The Fuiszes have made substantial contributions in drug delivery, including orally dissolving tablets and novel particle-coating systems at Fuisz Technologies, inventing and developing thin-film drug delivery technologies at Kosmos Pharma and MonoSol Rx, as well as independently developing extruded sheet technology, and have extensive experience working with big and specialty pharma. Fuisz Pharma is headquartered in Miami (www.fuisz.com).

Alexza Pharmaceuticals Updates Staccato Pipeline and Outlines Pipeline Development Strategy

PRNewswire-FirstCall: July 12, 2010 – MOUNTAIN VIEW, CA – Alexza Pharmaceuticals, Inc. (Nasdaq: ALXA) has selected AZ-007 (Staccato zaleplon) for the treatment of insomnia as the next product candidate to move forward into active development. This decision follows an Alexza technology and portfolio review during the first half of 2010. In addition, Alexza has created Addicere Therapeutics, Inc., a wholly owned subsidiary, to develop all applications of the Staccato technology for pharmaceutical uses of nicotine.

"As we started 2010, we deployed the vast majority of our efforts and resources on the pre-commercialization activities for AZ-004. Over the course of the first six months, we received notification of our PDUFA date, completed our first commercialization agreement and are continuing the work on commercial manufacturing scale-up for our lead program," said Thomas B. King, Alexza president and CEO. "We also completed a thorough analysis of our Staccato system-enabled pipeline of programs and potential new Staccato-based product candidates, in order to prioritize and select programs we could plan to self-fund and programs we could plan to develop through collaborations."

King continued, "Staccato zaleplon, as a self-funded development program, and Staccato nicotine, as a product/technology spin-out, are examples of our corporate strategy moving forward. We intend to capitalize on our internal resources to develop certain product candidates and to identify routes to utilize external resources to develop other product candidates. We look forward to continuing to expand our development pipeline in the coming months and years, as we execute this dual-tracked development strategy to take advantage of the strength and breadth of the Staccato technology platform."

Purdue Pharma L.P. Receives FDA Approval for Butrans (Buprenorphine) Transdermal System CIII

PRNewswire: July 1, 2010 – STAMFORD, CT – Purdue Pharma L.P. has announced that the U.S. Food and Drug Administration (FDA) has approved Butrans (buprenorphine) Transdermal System CIII for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time. Butrans Transdermal System is an analgesic product that delivers continuous release of medication for seven days.

"Healthcare professionals now have an important new option for appropriate adult patients suffering from moderate to severe chronic pain when an opioid may be needed to manage their

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pain," said Lynn R. Webster, medical director of the Lifetree Clinical Research and Pain Clinic in Salt Lake City, UT.

The active ingredient in Butrans Transdermal System is buprenorphine, a partial agonist at mu opioid receptors and an antagonist at kappa opioid receptors. Butrans is a Schedule III product. Butrans can be abused in a manner similar to other opioid agonists, legal or illicit. Working with the FDA, Purdue has developed a risk evaluation and mitigation strategy (REMS) for Butrans that includes a "Medication Guide, Elements to Assure Safe Use," such as healthcare provider training, and a timetable for submitting assessments of the REMS.

"We are very pleased with the FDA approval of Butrans and believe that it will be a valuable pain management option for healthcare professionals and patients," said John H. Stewart, president and CEO of Purdue Pharma L.P. "We are committed to improving the lives of patients in meaningful ways, including developing safe and effective therapies as well as offering educational tools and information that support their safe and proper use." ■

Do you have a great image of your science?

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The *CRS Newsletter* Editorial Board is inviting submission of images to be used on the cover for each issue of the *CRS Newsletter* in 2010.

Requirements
The image (photo, micrograph, etc.) must be an original, unpublished work that does not violate a third party's intellectual property rights. Images submitted for possible cover use must be no less than 7.375 inches (187 mm) wide × 10 inches (254 mm) deep at 300 dpi at the original image size. Acceptable file formats include tif, eps, and jpg.

Please send electronic copies of your images to the *CRS Newsletter* through our online dropbox at http://dropbox.yousendit.com/scisoc. Please include your e-mail address, the subject line "CRS Newsletter Cover," and a message that includes a short phrase that describes the image.

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See you next year for the

38th Annual Meeting & Exposition of the Controlled Release Society

July 30 – August 3, 2011
Gaylord National Resort and Convention Center
National Harbor, Maryland, U.S.A.

Where is Gaylord National?

Gaylord National stands on the shores of the scenic Potomac River in National Harbor, Maryland. National Harbor is a spectacular, new urban-waterfront community offering stunning views of Washington, D.C. and Old Town Alexandria and is a 15-minute drive to Washington, D.C.

When can I submit my abstract?

Submission opens November 2010. Check the CRS Annual Meeting website for updates.

FAST FACTS

What is the closest airport to Gaylord National?

Reagan National Airport (DCA) is just 15 minutes from Gaylord National. Washington Dulles International Airport (IAD) is approximately 45 minutes from Gaylord National.

FAST FACTS

When will advance registration and housing open?

March 2011. Check the CRS Annual Meeting website for updates.

FAST FACTS

How do I book an exhibit or sign up as a sponsor?

Please contact Debby Woodard at dwoodard@scisoc.org or call Debby at +1.651.994.3817.

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United States of America

Calendar of Events

2010

2010 NanoMedicine Summit – NanoMedicine: Bridging the Gap from Basic Research to Clinical Application

October 18-19
InterContinental Hotel and Bank of America Conference Center
Cleveland, OH, U.S.A.
www.nanomedicinesummit.org

CRS–AAPS Joint Workshop: Using Population Pharmacokinetics to Support the Development of Clinically Relevant Specifications for Extended Formulations

November 13
Morial Convention Center
New Orleans, LA, U.S.A.
www.controlledreleasesociety.org/main/meetings

FIP Pharmaceutical Sciences 2010 World Congress (in association with the AAPS Annual Meeting and Exposition)

November 14-18
Morial Convention Center
New Orleans, LA, U.S.A.
www.pswc2010.org/

2011

CRS Product Development Forum – Poorly Soluble Drugs

January 27-28
Doral Golf Resort and Spa
Miami, FL, U.S.A.
www.controlledreleasesociety.org

14th Industrial Symposium and 5th Trade Fair on Microencapsulation (organized by CRS, SwRI, and Bioencapsulation Research Group)

March 7-9
The Sheraton Gunter Hotel
San Antonio, TX, U.S.A.
http://impascience.eu/bioencapsulation/2011_San_Antonio

2011 Society for Biomaterials Annual Meeting

April 13-16
Orlando, FL, U.S.A.
www.biomaterials.org

2011 AAPS National Biotechnology Conference

May 16-19
Hilton San Francisco Union Square
San Francisco, CA, U.S.A.
www.aapspharmaceutica.com/NationalBiotech

38th Annual Meeting & Exposition of the Controlled Release Society

July 30-August 3
Gaylord National Resort and Convention Center
National Harbor, MD, U.S.A.
www.controlledreleasesociety.org/main/meetings

2012

9th World Biomaterials Congress

June 1-5
New International Exhibition & Convention Center
Chengdu, China
www.wbc2012.com

39th Annual Meeting & Exposition of the Controlled Release Society

July 14-18
Centre des Congrès de Québec
Québec City, Canada
www.controlledreleasesociety.org/main/meetings