

POLYMERS IN DRUG DELIVERY

May 20, 2010

1:00 PM to 6:30 PM (registration begins at 12 noon)
Rutgers University, Busch Campus Student Center – Multipurpose Room/Fireside Lounge

Sponsored by NJACS Polymer Topical Group
Cosponsored by the Controlled Release Society

Organized by Kathryn Uhrich (Rutgers-Chemistry) and
Ron DeMartino (Polymer Therapeutics LLC)

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| 12:00-1:00 | REGISTRATION | | |
| 1:00-1:10 | WELCOME AND GENERAL INTRODUCTIONS (KE Uhrich & R DeMartino) | | |
| | Speaker | Affiliation | Title |
| 1:10-1:50 | Aruna Nathan | Johnson & Johnson | <i>Novel Polyesters for Drug Delivery Applications</i> |
| 1:50-2:30 | Narayan Variankaval | Merck | <i>Macromolecules in Drug Development: Vignettes from the Pharmaceutical Industry</i> |
| 2:30-3:10 | Vladimir Trubetskoy | Roche | <i>Polymer Conjugates for Systemic Delivery of siRNA</i> |
| 3:10-3:45 | BREAK AND POSTER VIEWING | | |
| 3:45-4:25 | Prabhas Moghe | Rutgers University | <i>Polymers as Multimodal Therapeutics for Cardiovascular Medicine</i> |
| 4:25-5:05 | Emmanuel Dimotakis | L'Oreal | <i>Delivery of Actives in Cosmetics</i> |
| 5:05-5:10 | CONCLUSION OF ORAL SESSION (KE Uhrich & R DeMartino) | | |
| 5:10-6:30 | POSTER SESSION (Robert Falcone) | | |

Contacts:

Technical/Symposia: Kathryn Uhrich (keuhrich@rutgers.edu)

Poster Submission: Robert Falcone (rpf2@njit.edu)

Exhibits/Commercial Posters: Nicole Harris (nicole.harris@sunchemical.com)

General Information: Willis B. Hammond (wbhammond1@verizon.net)

Speakers

Dr. Aruna Nathan

Manager of R & D

Johnson & Johnson

Novel Polyesters for Drug Delivery Applications

Biography of Speaker:

Dr. Aruna Nathans received his BSc in chemistry from Madris University (1987) and his Ph. D. in polymer chemistry from Rutgers University (1992). Following 3 years as a Post Doctoral Fellow at Harvard – MIT Division of Health Sciences and Technology, where he worked in tissue engineering and drug delivery, he took a job with Bristol Myers Squibb (94-98). In 1998 he moved to Johnson & Johnson and is now the Manager of R & D.

Dr. Narayan Varian

Research Fellow

Merck Research Laboratories, West Point, PA

Macromolecules in drug development: Vignettes from the pharmaceutical industry

Polymers are ubiquitous in the pharmaceutical industry. This talk will focus on two main areas in which polymers play a major role in enabling the delivery of drugs – (i) design of oral solid dosage forms to increase bioavailability and improve physical stability and (ii) design of delivery systems for sterile parenteral applications such as ocular and IV delivery. The physics and chemistry of polymers that enables the design of these systems will be highlighted through case studies and examples from internal Merck experience and from the literature.

Biography of speaker

Narayan Variankaval is currently a Research Fellow at Merck Research Laboratories, West Point, PA and head of the Materials Science group within Pharmaceutical R&D. The group is responsible for all aspects of solid-state characterization of drug products including solid and liquid dosage forms. His research interests are in amorphous systems of pharmaceutical importance, novel means of improving bioavailability and strategies to improve workflows in early-stage salt selection processes. He has numerous publications and patents to his credit and has given several invited presentations around the world. He holds MS (1998) and PhD (2001) degrees in Polymer Science and Engineering from the Georgia Institute of Technology, Atlanta, GA, where he was an Office of Naval Research Fellow at the Molecular Design Institute. He also holds a B. Tech. in Chemical Engineering from Anna University in India.

Vladimir Trubetskoy

Roche Madison

Polymer Conjugates for Systemic Delivery of siRNA

Abstract

RNAi therapeutics represent a promising new approach to treat a broad variety of conditions connected to aberrant protein expression. Hepatocytes are a particularly attractive target cell type for siRNA delivery due to their role in expression of vital proteins. Here we describe Dynamic PolyConjugates (DPC), a novel polymer-based system for systemic delivery of siRNA to hepatocytes in vivo. DPC feature a new class of membrane-active polymers, a reversible poly(ethylene glycol) coating and active N-acetyl galactosamine-mediated targeting to the liver cells.



Short Biosketch for Rutgers Univ.

Vladimir S. Trubetskoy, Ph.D.
Currently Senior Principal Scientist (Imaging and Formulation)
at Roche-Madison

Vladimir Trubetskoy received MS in Polymer Chemistry from Moscow State University, PhD in Biochemistry at National Cardiology Research Center (Moscow, Russia) with Professor Vladimir Torchilin. He studied drug delivery using liposomes.

He has received his postdoctoral training at the Center for Imaging and Pharmaceutical Research at Massachusetts General Hospital where he was involved in design of particulate contrast media for imaging of blood pool and lymphatic system.

Vladimir Trubetskoy joined Mirus Corporation (now Roche-Madison) in 1996 where he was involved in design of polymer-based systems for nucleic acid delivery.

He is a co-author of 44 research papers and co-inventor on 32 US patents.

Prabhas V. Moghe
Department of Biomedical Engineering
Department of Chemical and Biochemical Engineering
Rutgers University, NJ
moghe@rutgers.edu

Polymers as Multimodal Therapeutics for Cardiovascular Medicine

Few existing therapeutic strategies address the local management of atherogenesis within the vascular walls and related inflammation. There is a critical need to develop integrative approaches to locally intervene in the cascade of atherogenesis, which arises from the accumulation of highly oxidized low-density lipoproteins (LDL) within the walls of blood vessels.

Our laboratory in collaboration with Kathryn Uhrich has been investigating the possibility of engineering nanoscale biomaterials for inhibiting cholesterol accumulation and the related inflammation. A generation of 15-20 nm polymeric amphiphilic micelles was designed whose surface features such as surface anionic density; amphiphilicity; and nanoscale architecture can be systematically varied. We report that such *nanolipoblockers* can systematically block scavenger receptor binding to highly oxidized LDL, and thus inhibit the uptake of the most atherogenic form of LDL as well as reverse the formation of the foam cell phenotype and reduce cytokine secretion. A multimodal strategy of depleting cellular cholesterol content was examined by using the amphiphilic nanopolymers as drug delivery carriers. The nanopolymers were found to primarily target inflamed cells due to enhanced scavenger receptor expression. Further, the nanopolymers markedly enhanced the intracellular delivery of a model drug, a liver-X receptor agonist, which binds to nuclear receptors and upregulates channels for cholesterol efflux, further depleting cells of any accumulated cholesterol. The in vivo efficacy of the polymers and polymer-encapsulated agonist was then tested. The polymeric therapeutics lowered intimal levels of accumulated cholesterol and inhibited macrophage retention relative to non-treated controls. Thus, this study highlights the promise of the coordinated use of bioactive polymer therapeutics for de-escalation of the athero-inflammatory cascade, which is integral to the management of vascular arterial disease and also features in a number of metabolic and neurodegenerative disorders.

BIOGRAPHY (4/2010)

Prabhas Moghe is a Professor of Biomedical Engineering and Chemical & Biochemical Engineering at Rutgers University. He is the Director of the joint Rutgers-UMDNJ graduate program in Biomedical Engineering. He also holds appointment as Adjunct Professor in the Division of Bioengineering of the Department of Surgery at Robert Wood Johnson Medical School, UMDNJ.

Dr. Moghe obtained his PhD. in Chemical Engineering from the University of Minnesota and pursued postdoctoral research in bioengineering at Harvard Medical School. His research interests are cell-interactive biomaterials for tissue engineering; cellular bioengineering; nanobiomaterials and nanobiotechnology. An elected Fellow of the American Institute of Medical and Biological Engineering (AIMBE), Dr. Moghe has received several awards/honors for his research accomplishments, including the NSF CAREER Award, the Johnson & Johnson Discovery Award, and Leadership in Diversity Award; and several teaching and mentoring awards. An author of over sixty journal publications and over 150 presentations, Dr. Moghe has trained over 25 PhD students to date. He currently directs an NSF IGERT training program on Integrative Science and Engineering of Stem Cells (www.igert.rutgers.edu), a NSF funded Nanoscale Interdisciplinary Research Team (NIRT), a Core NJCST project on 3-D scaffolds for human embryonic stem cell



engineering, a NIH NHLBI funded program on polymeric micelles for cardiovascular therapies, and a major core within a NIH/NIBIB-funded P41 program grant on Cell Profiling of Polymeric Biomaterials (www.resbio.org).

Dr. Moghe's research expertise is in cellular bioengineering and cell-interactive biomaterials, with applications ranging from fundamental design of cell-material interactions to regenerative therapies and nanomedicine. His research in nanobiomaterials and nanobiotechnology is focused along two distinct projects. In the first, the Moghe group, in collaboration with Dr. Kathryn Uhrich's laboratory, have developed self-assembled micellar nanoparticles with potential as "nanolipoblockers" to reduce atherosclerosis. In the second project, matrix-functionalized albumin nanoparticles are being investigated as biodynamic interfaces to promote tissue regeneration during wound repair; as well as for imaging and treatment of cancer. In the area of cell-biomaterial interactions, Dr. Moghe's team is combining new "high content" imaging of stem cell reporters with higher throughput platforms of combinatorially synthesized substrates, to accelerate the rational design of biomaterials "inductive" for strategic stem cell fates. In the area of stem cells, Dr. Moghe's lab has recently proposed a new approach to accelerated differentiation of human embryonic stem cells using engineered feeder cells and sustained self-renewal of stem cells using synthetically modified polymer scaffolds and humanized media conditions. One of the first NSF funded graduate training programs on stem cells in the U.S. was conceptualized and founded in September 2008 with Dr. Moghe as its principal investigator (www.igert.rutgers.edu).

Dr. Emmanuel Dimotakis

Associate Principal Scientist

L'Oreal USA in Clark, NJ.

Delivery Systems for Actives in Cosmetics

The principal delivery systems for actives in cosmetics will be reviewed. Different emulsions (classical, lamellar, nanoemulsions etc.) and vehicle systems (oleosomes, niosomes, microcapsules etc.) will be discussed. Vectorization and stabilization of actives as well as examples of cosmetic effects will be also presented.



Dr. Emmanuel Dimotakis is an Associate Principal Scientist with L'Oreal USA in Clark, NJ. He is managing the Materials Science Research Contracts of L'Oreal with Universities and Start Ups in N. America working very closely with Advanced and Applied Research in Paris and Development groups in the US.

He was previously a Sr. Staff Engineer in Materials Technology Operations of Intel (Chandler, AZ) in charge of pathfinding and roadmapping of microelectronic packaging polymers working very closely with suppliers in Asia and US. Prior positions include Scientist (Associate, I & II) and Black Belt (DFSS) with Sun Chemical (Carlstadt, NJ) and R&D Chemist with Merck KGaA (Savannah, GA).

E. Dimotakis did his postdoc in the Mater. Sci. & Engr. at the U of Illinois at Urbana-Champaign. He holds a MS in Chemical/Pharmaceutical Engr. (NJIT) and a PhD in Chemistry (Michigan State U)

POSTER ABSTRACTS

1. Analysis of Transport Mechanisms Governing the Efficient Tumor Penetration and siRNA Delivery by Tumor-Targeted PAMAM Dendrimers

Carolyn Waite

Rutgers University

Chemical and Biochemical Engineering

The inability of macromolecular drugs and nanoscale drug delivery systems to penetrate into solid tumors represents a major barrier to efficient drug delivery in these malignancies. A complex network of abnormal cells, extracellular matrix (ECM) proteins and a limited number of blood vessels within solid tumors render efficient diffusion of drug molecules particularly challenging. In this work, poly(amidoamine) (PAMAM) dendrimers presenting varying numbers of cyclic(RGD) targeting peptides were generated to facilitate siRNA delivery to malignant glioblastoma cells. The presence of RGD peptides on PAMAM dendrimers was found to enhance the penetration of siRNA cargo through an in vitro three-dimensional tumor spheroid model of malignant glioma in a manner that depends on the number of RGD peptides present. The mechanisms governing efficient nanoparticle transport including integrin-binding affinity and cell internalization kinetics were studied quantitatively in this work. Surface plasmon resonance (SPR) biosensor experiments showed that a decreased binding affinity to integrin protein receptors was observed with increasing RGD number. The effect of dendrimer functionalization with RGD on cellular internalization kinetics was also studied. This work provides a framework for the rational design of drug-delivery systems to balance cellular binding and internalization rates to facilitate efficient drug delivery into solid tumors.

2. TAT- Modified PEG-PEI Copolymers Complexed to splice modulating Oligonucleotides Increase Dystrophin Expression in Myostatin-blocked Musculature of Dystrophic Mice

Xiangying Guna, PhD

Department of Pathology-Anatomy & Cell Biology

Jefferson Medical College

Thomas Jefferson University

Splice modulating oligonucleotides (SMOs) are regarded as extremely promising therapeutics for treating Duchenne Muscular Dystrophy (DMD). However, a major limitation to their use is their poor delivery profile to muscle tissue in vivo. We previously established that copolymers made of poly(ethylene imine) (PEI) and poly(ethylene glycol) (PEG) along with the cell-penetrating peptide TAT (trans-activator of transcription) enhanced SMO transfection in skeletal muscle of dystrophin-null (mdx) mice, resulting in widespread distribution of dystrophin-positive fibers, and about 30% of normal levels of dystrophin expression. In an attempt to improve dystrophin expression, mdx mice crossed with myostatin-null mice (myostatin inhibits muscle growth) were used. We found that intramuscular injections of similar amounts of SMO produced nearly twice as much dystrophin normalized to muscle weight in myostatin-blocked mdx mice than in mdx mice. These data suggest that co-administration of SM!
Os and myostatin blockers have synergistic effects and represent a promising approach to treating DMD.

3. Surface-Engineered Targeted siRNA-PPI Dendrimer complexes for Efficient Intracellular and Intratumoral delivery

Oleh Taratula^{a,b}, Olga B. Garbuzenko^a, Paul Kirkpatrick^b, Ipsit Pandya^b, Ronak Savla^{a,b}, Vitaly P. Pozharova, Huixin He^b and Tamara Minko^a

a Department of Pharmaceutics, Rutgers, The State University of New Jersey, Piscataway, NJ.

b Department of Chemistry, Rutgers, The State University of New Jersey, Newark, NJ.

Low penetration ability of siRNA through the cellular plasma membrane combined with its limited stability in blood plasma, limits the effectiveness of the systemic delivery of siRNA for cancer treatment. In order to overcome such difficulties, we constructed a nanocarrier-based delivery system by taking advantage of the lessons learned from the problems in DNA delivery. In the present study, siRNA nanoparticles were first formulated with poly(propyleneimine) (PPI) dendrimers. To provide lateral and steric stability to withstand the aggressive extracellular environment, the formed siRNA nanoparticles were caged with a dithiol containing crosslinker molecules followed by coating them with PEG polymer. A synthetic analog of Luteinizing Hormone-Releasing Hormone (LHRH) peptide was conjugated to the distal end of PEG polymer to direct the siRNA nanoparticles specifically to the cancer cells. Our results demonstrated that this layer-by-layer modification and targeting approach confers the siRNA nanoparticles extracellular stability and intracellular bioavailability, provides for their specific uptake by tumor cells, accumulation of delivered siRNA in the cytoplasm of cancer cells, and the efficient gene silencing. In addition, *in vivo* body distribution data confirmed high specificity of the proposed targeting delivery approach which created the basis for the prevention of adverse side effects of the treatment.

4. Polymer Separation and Identification by GPC with UV and FTIR Detection

Qirong Wu, Yuri V. Il'ichev, Lori Alquier

Cordis Corporation, a Johnson & Johnson Company, McKean & Welsh Road, Spring House, PA 19477

Gel permeation chromatography (GPC) is widely used to separate polymers based on their hydrodynamic volume in solution. Multiple-detection GPC methods are becoming increasingly popular because they can provide absolute molecular weights, intrinsic viscosity, and other parameters not accessible for conventional analysis. In the present study, GPC analysis of synthetic polymers was performed by using an HPLC system equipped with a diode-array detector and an automated IR detection system. The latter detector offers a unique LC interface that removes mobile phase and acquires full absorption spectra in the mid-IR range for each component. Desolvated analytes are deposited onto a rotating IR-transparent disc. Multiple parameters of the FTIR-LC interface were tested and optimized by using poly(styrene) standards and poly(DL-lactide-co-glycolide) (PLGA) copolymers. The instrumental parameters were found to be inter-related, and they had a strong impact on polymer detection. Several PLGA copolymers of different composition were characterized and a limit of detection for PLGA was determined. The developed GPC-UV-FTIR method was also found to be efficient in identifying an unknown polymer in a complex mixture.

5. Facile Production of Multifunctional Nanoparticles for Difficult to Deliver Therapeutics: hydrophobic drugs, peptides, and siRNA.

Robert K. Prud'homme*

a, Chemical Engineering, Princeton University, Princeton, NJ, 08544 USA

Several classes of therapeutics are Nanoparticle formulations of hydrophobic drugs present unique opportunities for treatment of solid tumor cancers, for delivery of drugs by aerosol

administration, and as a route to novel vaccine adjuvants. The common requirements of these applications are precise control of particle size and surface functionality. For cancer therapy particles in the size range of 100-200 nm passively pass through defects in the vasculature in tumors and deposit by “enhanced permeation retention”. In addition to delivery, the ability to monitor the fate of the nanoparticles is also of important since anti-cancer agents are invariably toxic to healthy tissue. Our process --Flash NanoPrecipitation – a controlled precipitation process that produces stable nanoparticles at high concentrations using amphiphilic diblock copolymers to direct self-assembly enables the production of composite nanoparticles that enable simultaneous imaging and delivery. Uniform particles with tunable sizes from 50-500 nm can be prepared in an economical and scalable manner. The key to the process is the control of time scales for micromixing, polymer self-assembly, and particle nucleation and growth. The PEG protective layer creates long-circulating particles and the inclusion of PEG chains with terminal ligands allows drug targeting. The incorporation of gold nanoparticles, magnetic nanoparticles, or fluorophores into the composite particle enables imaging by x-ray, MRI, or confocal microscopy, respectively. The incorporation of up converting phosphor crystals into the composite nanoparticles enables a highly efficient form of photodynamic therapy. The use of hydrolytically unstable linkers enables the controlled release of single and multiple drugs from nanoparticles to enable “drug cocktails” in a way that has not been possible previously. The process enables the incorporation of imaging agents in addition to drugs. Examples presented will include fluorescent dyes for confocal microscopy, gold colloids for CAT Scan imaging, and SPIO colloids for MRI imaging.

6. Facile Production of Multifunctional Nanoparticles for Difficult to Deliver Therapeutics: hydrophobic drugs, peptides, and siRNA.

Robert K. Prud'homme, Suzanne D'Addio, Varun Kumar*

a, Chemical Engineering, Princeton University, Princeton, NJ, 08544 USA

Several classes of therapeutics are Nanoparticle formulations of hydrophobic drugs present unique opportunities for treatment of solid tumor cancers, for delivery of drugs by aerosol administration, and as a route to novel vaccine adjuvants. The common requirements of these applications are precise control of particle size and surface functionality. For cancer therapy particles in the size range of 100-200 nm passively pass through defects in the vasculature in tumors and deposit by “enhanced permeation retention”. In addition to delivery, the ability to monitor the fate of the nanoparticles is also of important since anti-cancer agents are invariably toxic to healthy tissue. Our process --Flash NanoPrecipitation – a controlled precipitation process that produces stable nanoparticles at high concentrations using amphiphilic diblock copolymers to direct self-assembly enables the production of composite nanoparticles that enable simultaneous imaging and delivery. Uniform particles with tunable sizes from 50-500 nm can be prepared in an economical and scalable manner. The key to the process is the control of time scales for micromixing, polymer self-assembly, and particle nucleation and growth. The PEG protective layer creates long-circulating particles and the inclusion of PEG chains with terminal ligands allows drug targeting. The incorporation of gold nanoparticles, magnetic nanoparticles, or fluorophores into the composite particle enables imaging by x-ray, MRI, or confocal microscopy, respectively. The incorporation of up converting phosphor crystals into the composite nanoparticles enables a highly efficient form of photodynamic therapy. The use of hydrolytically unstable linkers enables the controlled release of single and multiple drugs from nanoparticles to enable “drug cocktails” in a way that has not been possible previously. The process enables the incorporation of imaging agents in addition to drugs. Examples presented will include fluorescent dyes for confocal microscopy, gold colloids for CAT Scan imaging, and SPIO colloids for MRI imaging.

7. Fine-Tuning Biomaterial Degradation by Embedding Hydrolytic Enzymes

Manoj Ganesh & Richard A. Gross

NSF I/UCRC for Biocatalysis & Bioprocessing of Macromolecules,
Polytechnic Institute of NYU,
Six Metrotech Center,
Brooklyn, New York 11201

Bioresorbable materials with „tunable‘ lifetimes are needed to meet a continuously expanding range of biomedical applications. Control of polymer lifetime has relied on altering intrinsic properties of synthesized polymeric materials. However, development of new biopolymer compositions is hindered by time and cost constraints. Herein we show that a biomaterials bioresorption rate can be regulated by embedding an enzyme within a bioresorbable polymer matrix when that enzyme is active for matrix hydrolysis. Poly(ϵ -caprolactone) was selected as a model system since its use has been limited due to its slow hydrolytic degradation (years). *Candida antarctica* Lipase B (CALB) was surfactant paired to enable its dispersion throughout PCL films. By incorporating 1.6 and 6.5% w/w CALB in films, in vitro determined polymer lifetime was reduced from years to 1 and 17 days, respectively. *Embedded enzyme matrix hydrolysis* occurs by formation of multiple enzyme-surface interfaces throughout films. Films become highly porous and crystalline as degradation proceeds. The concepts developed herein are applicable to a wide range of accepted biomaterials and can greatly expand the range of applications for which they are useful.

8. Harnessing the Therapeutic Potential of Functionalized Nanoscale Amphiphilic Macromolecules: From Delivery Vehicles to Polymeric Ligands

Sarah M. Sparks^a, Nicole Iverson^b, Nicole M. Plourdec, Carolyn L. Waite^c, Alex M. Harmona,
Charles M. Roth^{b,c}, Prabhas V. Moghe^{b,c}, and Kathryn E. Uhrich^{a,b}

^aDepartment of Chemistry and Chemical Biology, ^bDepartment of Biomedical Engineering,
^cDepartment of Chemical and Biochemical Engineering, Rutgers University, Piscataway,
NJ 08854, keuhrich@rutgers.edu

Nanoscale amphiphilic macromolecules (AMs) are uniquely tunable polymers that self-assemble in aqueous media to form nano-sized micelles. Their ability to reach the nuclei of cells, non-cytotoxicity, and facile tunability make them ideal candidates for use in a variety of biomedical applications. Without modification, the parent polymers are capable of water-solubilizing hydrophobic drugs or even inorganic nanocrystals. However, with small modifications to alter the functional components of the polymer, many potential therapeutic options can be achieved. In one approach, AMs functionalized with acidic carboxylic acids results in bioactive polymeric ligands. These polymers inhibit the uptake of highly oxidized low-density lipoproteins by competitively binding scavenger receptors on macrophages, a process which uninhibited results in the escalation of cardiovascular disease. Alternatively, when functionalized with basic amines the resulting cationic polymers efficiently complex with and intracellularly deliver anionic nucleic acids for gene therapy. This poster will highlight the potential of functionalized AMs as a multifunctional therapeutic option for a wide range of diseases.

9. The Effect of Surfactant and Sonication on the Release and Bioactivity of Lysozyme from Electrospun Scaffolds

Tonye Briggs

Department of Biomedical Engineering
New Jersey Institute of Technology

Electrospun scaffolds are ideal for local delivery of growth factors in tissue engineering applications due to the high surface area-volume ratio of the fibers. However, maintaining the bioactivity of the released growth factor from electrospun scaffolds is a concern because of the risk of protein denaturation due to exposure to organic solvents in the polymer solution as well as the high voltage applied to the polymer solution in the electrospinning process. This study investigated methods of incorporating an aqueous protein solution of model protein lysozyme in an organic polymer solution comprised of a blend of polyethylene oxide and polycaprolactone for the purposes of electrospinning. The effect of the addition of the non-ionic surfactant, Span-80™, and the ultrasonication of the polymer solutions was characterized in terms of the lysozyme release kinetics and lysozyme bioactivity. Of the conditions evaluated in this study, Span-80/sonication, Span-80/no sonication, no Span-80/sonication, and control (no Span-80/no sonication), there were no differences in terms of lysozyme release within 14 days. However, the bioactivity of the released lysozyme from electrospun scaffolds of the Span-80/sonication condition was significantly higher than all other groups at 24 hours indicating the process of sonication and addition of Span-80 protects the protein from denaturation.

10. S. Bodnar³, J. Griffin², L. Gu¹, F. Halperin³, A.M. Harmon¹, I. Harper³, B.A. Langowski¹, L. Lavelle³, R. Rosario-Meléndez¹, S.M. Sparks¹ and K.E. Uhrich^{1,2}

*1Department of Chemistry and Chemical Biology; 2Department of Chemical and Biochemical Engineering. Rutgers, The State University of New Jersey. Piscataway, NJ 08854
3Sterile Process Technology. Johnson & Johnson. Raritan, NJ 08869*

Nanoscale amphiphilic macromolecules (AMs) and polyAspirin are two innovative polymer-based drug delivery systems that have been widely investigated for a variety of biomedical applications. However, for commercial use, these polymers must be sterilized. This work describes the physicochemical effects of exposure of AMs and polyAspirin to two forms of ionizing radiation, e-beam and Gamma, commonly used in biomedical sterilization processes. Changes in the physicochemical properties of the polymers upon dosing with 25 to 50 kGy of irradiation were evaluated. Preliminary data revealed that neither form of radiation resulted in significant impacts on structure or function of either of the polymer-based drug delivery. Therefore, this work highlights the promise of these polymer systems for further development into commercial drug delivery systems.

11. Bioactive-based Polyanhydride/PVP Physically Cross-linked Hydrogels

Authors: Renata Fogaça,^{1,2} Michelle A. Quimet,¹ Luiz H. Catalani,² and Kathryn E. Uhrich¹
*1Department of Chemistry and Chemical Biology, Rutgers University, Piscataway, NJ,
2University of São Paulo, Fundamental Chemistry, São Paulo, SP, Brazil*

Hydrogels are promising biomaterials for wound healing applications due to their unique ability to absorb large volumes of water or biological fluids without dissolving. To improve healing, bioactives are commonly chemically and physically incorporated into hydrogel networks. However, a partially biodegradable hydrogel that releases bioactive molecules upon hydrolytic degradation to allow controlled release of the drug would be advantageous. Therefore, bioactive-based polyanhydrides derived from ferulic acid, sinapic acid, *p*-coumaric acid, and salicylic acid

were synthesized and blended with poly(N-vinyl-2-pyrrolidone) (PVP) to produce hydrogels. The bioactives offer antimicrobial, anti-inflammatory, and antioxidant properties, which when formulated into biodegradable polymers, will achieve controlled release of the bioactive upon degradation, and cross-linking with PVP allows hydrogel formation. The polymer systems were physically cross-linked via hydrophobic interactions, as found using differential scanning calorimetry and fourier transform infrared spectroscopy. Porous structures were confirmed by scanning electron microscopy analysis of the hydrogels. In addition, the swelling ratios correlate with the polyanhydride content; a higher percentage of PVP produced hydrogels with higher swelling ratios. Additionally, the PVP/salicylic acid-based polymer hydrogels demonstrated the best swelling values as compared to the other polymers at the same ratios. This work highlights the potential of these systems for wound healing applications.

12. Selective Inhibition of Human Brain Tumor Cells through Multifunctional Quantum-Dot-Based siRNA Delivery.

Jongjin Jung¹, Aniruddh Solanki¹, Kevin A. Memoli¹, Ken-ichiro Kamei², Hiyun Kim¹, Michael A. Drahl¹, Lawrence J. Williams¹, Hsian-Rong Tseng², and Kibum Lee^{1*}.

¹Dept. of Chemistry and Chemical Biology, Rutgers University, NJ; ²Dept. of Molecular and Medical Pharmacology, UCLA, CA

The RNA interference (RNAi) using small interference RNA (siRNA) has delivered the promise to chemotherapeutic strategies. However, in order to harness the full potential of RNAi-based approach, it is necessary to monitor the localization and knockdown effect of siRNA, as well as to deliver them with high selectivity and maximum loading capacity.

Through Quantum Dot (QD)- based delivery vehicle, we demonstrated that siRNAs, RGD, and TAT peptides on the QD surface make it possible to transfer siRNA selectively to brain tumor cell (U87) among other control cells. At the same time, bright color of QD synchronized its position and the knockdown of the target gene, especially EGFP. We further showed that brain cancer cell (U87) death is induced by down-regulation of PI3K signaling pathway with siRNA against EGFRvIII (mutant epidermal growth factor receptor) as a proof-of-concept using the new delivery platform. We continue to develop various nanoparticle (NP) based platforms such as polymer, magnetic NP to accomplish the effective chemotherapy with siRNA and small drug molecules.

13. Synthesis of Opioid-based Poly(anhydride ester)s for Sustained Drug Delivery

Authors: Roselin Rosario-Meléndez and Kathryn E. Uhrich

Department of Chemistry and Chemical Biology, Rutgers University, Piscataway, NJ

Nalbuphine is an agonist-antagonist analgesic used to treat mild to moderate pain, has a half-life in plasma of 5 hours and its analgesic effect lasts between 3 and 6 hours. A novel poly(anhydride ester) that incorporates nalbuphine into its backbone was successfully synthesized. This polymeric version of nalbuphine could help to reduce frequent dosing and prolong its analgesic effect by controlling and sustaining the drug release. The synthesis of this polymer demonstrates that it is possible to incorporate opioids into a poly(anhydride ester) backbone. Current work involves the incorporation of morphine into a poly(anhydride ester) backbone to control morphine release and reduce abuse potential.

14. Amphiphilic Macromolecule-Lipid Complexes for Controlled Delivery of Chemotherapeutic Drugs

Authors: Melissa H. Lash, Alexander M. Harmon, Kathryn E. Uhrich
Department of Chemistry and Chemical Biology, Rutgers University, Piscataway, NJ

Chemotherapy drugs are generally insoluble in aqueous media, and therefore require solubilization by using nanocarriers. Historically, these nanocarriers exhibit adverse side effects and show low tolerability within their patients. Some nanocarriers also are unstable and exhibit an uncontrolled release of drug shortly after administration, limiting their efficacy. Nanocarriers that exhibit stability, controlled release and in vivo tolerability would be clinically advantageous. One specific chemotherapy drug is paclitaxel, a clinical formulation of a prescription chemotherapy in the form of Taxol. While Taxol is an effective drug for patients with breast, lung, and ovarian cancers, its carrier, composed of Cremophor EL and ethanol, causes patients extreme discomfort due to harsh side effects. This study investigates a different carrier for PXT, an AM-lipid complex, through an analysis of physicochemical properties, PXT release kinetics, and in vivo tolerability. The loading of PXT does not substantially alter the size of the nanocarriers. It can also be seen that PXT releases in a controlled fashion from AM-lipid nanocarriers, similarly to how it releases from Taxol. Over thirty days, Balb/C mice systemically treated with AM-lipids showed higher in vivo tolerability and Taxol treated mice. Based on these results, AM-lipid complexes show promise as a novel nanocarriers.

15. Ink-jet printed dosage formulations: Control of drug crystallinity and solubility via polymer substrate properties

Marlena Brown
Department of Biomedical Engineering
Rutgers University

This research utilizes ink-jet technology to deposit minute amounts of API onto polymer films creating new dosage forms with controllable architecture. The goal of this study is to establish the relationship between the API and polymer film properties, kinetics of the evaporation process, final stain morphology, and solubility properties of the fabricated dosage. The overall aim of this research is to develop scientific fundamentals which allow us to accurately create novel delivery systems where the final droplet structure exists as defined architecture with controllable release profile.

Through manipulation of substrate properties we can control the morphology of the API deposits and obtain variety of the API forms ranging from amorphous to crystalline structures. The data demonstrates that surface energy properties of the substrate and surface tension properties of the API solution have a direct affect on the final structure of the deposit and, in fact, determine spreading phenomena, evaporation kinetics, phase transition, crystal ordering, and amorphous structure. Control of droplet morphology is a significant attribute in the dissolution rate and potential bioavailability in vivo. Proposed technology will be the most useful for high potency drug formulations where high accuracy and control of the release profile are the most important.

16. Absorbable Polymers from functionalized Natural Products

Rao S Bezwada
Bezwada Biomedical LLC, 15-1 Ilene Court
Hillsborough, New Jersey, NJ 08844

In this poster, we will present absorbable polymers derived from functionalized natural products. These polymers were developed to incorporate therapeutic values of natural products in the polymer backbone. In the present study, natural molecules belonging to three different classes of

natural products i.e. Daidzein (a Isoflavone with antioxidant and hormonal activity), Isopimpinellin (a Coumarin with anticancer properties) and Capsaicin, an alkaloid with analgesic properties used in topical ointments were functionalized with safe and biocompatible molecules such as glycolic acid, lactic acid, p-dioxanone and caprolactone. These monomers are the building blocks of majority of biodegradable polymers used to make commercial medical devices. The resulting novel functionalized natural product monomers were then polymerized by condensation with diols to yield absorbable therapeutic polymers.

Synthesis and characterization of selected polymers will be presented. Key aspects along with potential applications of these absorbable polymers will be discussed.

17. Nitric Oxide and Drug releasing Absorbable Macromers and Oligomers for Biomedical Applications

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Nitric oxide (NO) is a vital biological molecule. It plays a significant role in diverse biological processes such as host defense, cardiovascular regulation, signal transduction, neurotransmission and wound healing. In addition, it helps reduce inflammation and regulate blood pressure by dilating arteries. Agents that release or generate NO locally have been proposed as systematic drugs to prevent and treat restenosis and thrombus formation.

In this paper, we will present NO and drug releasing macromers and oligomers wherein the rate of release of NO and drug molecule can be controlled. These macromers and oligomers comprise of a drug molecule and a NO releasing moiety linked to each other via a hydrolytically degradable linker. This linker comprises of repeat units derived from safe and biocompatible molecules such as glycolic acid, lactic acid, p-dioxanone and caprolactone, key components of all commercially available absorbable medical devices. The hydrolytic degradation rate of these NO and drug releasing macromers and oligomers is controlled by the number of repeat units in the linker as well as by the choice of the safe and biocompatible molecules from which the repeat units are derived. For example, NO and drug releasing macromers and oligomers comprising of degradable linker containing repeat units derived from glycolic acid will hydrolyze faster than the one comprising repeat units derived from p-dioxanone.

Key aspects along with potential applications of these NO and drug releasing macromers and oligomers will be presented. Synthesis and characterization of selected macromers and oligomers will be presented. *In Vitro* hydrolysis and the controllable hydrolysis profiles will be discussed during presentation

18. Improved Reproducibility of MW Measurements of Polypeptoids using an EcoSEC GPC System

Authors: Howard Barth, Consultant and Joe Machamer*, GPC Marketing Manager, Tosoh Bioscience LLC

There is considerable attention placed on the synthesis and characterization of polypeptoids, a new class of synthetic polypeptide analogues. Peptoids are peptide isomers that differ in the connectivity of the side chain. The resulting structure imparts proteolytic stability, may mimic polypeptide behavior and could have novel polymer properties for commercial use, as they are close in structure to nylon-type polyamides.

The EcoSEC GPC System and a set of TSK-GEL mixed-bed columns, both available from Tosoh Bioscience, were used successfully for obtaining high quality MWD data of a series of block poly-

β -alkylalanoids with HFIP as the mobile phase in under 15 minutes. The apparent MW averages based of PMMA calibration ranged from 27,000 to 49,000 for Mn and from 30,000 to 61,000 for MW with an average polydispersity of 1.20. Because of excellent flow rate and temperature control, and baseline stability of the EcoSEC GPC System, average MW values ranged from 0.2 to 0.3% relative standard deviation, a ten-fold reproducibility improvement as compared to SEC literature data of polyamides using a similar mobile phase system.

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19. **Polymer Drug Technology**

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Polymer Therapeutics creates polymers of ordinary drug molecules such as salicylic acid. These polymer drugs offer diverse fabrication options and can be made into powders, microspheres, fibers, films, coatings, sheets and molded articles. Our products have exceptionally high drug loads with uniform release rates. They can be used as part of a device, as a coating on a device or as the device itself. Using proprietary chemistry, we can optimize the physical properties (hard, soft, elastic, etc.) and the rate at which the polymer releases the drug (less than 1 week to over 2 years) all to the customer's specification.

The technology platform consists of producing polymers with the drug molecules in the backbone. The polymer breaks down *in situ* – delivering drug exactly where it is needed, while minimizing systemic drug exposure. The breakdown release rate does not depend upon the drug concentration leading to a more constant drug release rate than in other controlled release technologies. Products are salicylate based polymers that provide the well known anti-inflammatory, analgesic and antiseptic properties of aspirin (and diflunisal).