

J: Plenary

* Invited paper

SESSION J1: Plenary I

Chair: Anil Patri
Monday Morning, June 27, 2011
Green Auditorium

9:20 AM *J1.1

Building Molecules to Image and Help Treat Cancer. E. S. Olson¹, T. A. Aguilera¹, T. Jiang¹, M. Whitney¹, J. L. Crisp¹, P. Steinbach¹, L. G. Ellies², Q. T. Nguyen³ and R. Y. Tsien¹; ¹HHMI and Department of Pharmacology, University of California-San Diego, La Jolla, California; ²HHMI and Department of Pathology, University of California-San Diego, La Jolla, California; ³HHMI and Department of Surgery, University of California-San Diego, La Jolla, California.

Activatable cell penetrating peptides (ACPPs) are polycationic cell penetrating peptides (CPPs) whose cellular uptake is minimized by a polyanionic inhibitory domain and then restored upon proteolysis of the peptide linker connecting the polyanionic and polycationic domains. Local activity of proteases able to cut the linker causes amplified retention in tissues and uptake into cells. Tumor uptake of ACPPs is up to 4 fold higher with a matrix metalloproteinase substrate (PLGLAG) as the linker than with a negative control composed of D-amino acids. Conjugation of ACPPs to macromolecular carriers such as PAMAM dendrimers prolongs pharmacokinetics and increases delivery of payload (Cy5 or Gd-DOTA or both in the same molecule) to tumor for far-red or MR imaging. The dual labeled dendrimer with Cy5 and Gd-DOTA enables whole body magnetic resonance imaging followed by fluorescence-guided surgery. Such fluorescence guidance improves tumor-free survival in two animal models. Thus the ability of ACPPs to deliver imaging and therapeutic payloads with enzymatic amplification to protease-expressing tissues in vivo offers clinical potential. Furthermore, we have used phage display to discover peptides that home to peripheral nerves. When these peptides are fluorescently labeled and injected intravenously, all the peripheral nerves become fluorescent for a few hours without apparent side effects. A custom-built multispectral fluorescence imager then permits the surgeon to overlay the fluorescence images of the tumor vs. the nerves on the traditional reflected-light color image continuously in real time. We believe such molecular fluorescence guidance will greatly improve surgical accuracy. Current efforts are aimed at further improvements in contrast, reduction in background signals, dual labeling for ratiometric and fluorescence lifetime detection, imaging of metastatic lymph nodes, targeted delivery of radiation sensitizers for post-surgical mop-up of small nests of tumor cells, and chemotherapeutic delivery.

SESSION J2: Plenary II

Chair: Eric Simanek
Monday Afternoon, June 27, 2011
Green Auditorium

3:20 PM *J2.1

Aqua Materials: Ultrahigh-Water-Content and Ultralow-Organic-Content Hydrogels by using Dendritic Molecular Binders. Takuzo Aida, ¹Department of Chemistry and Biotechnology, The University of Tokyo, Tokyo, Japan; ²RIKEN, Wako, Japan.

Here we report that water and clay (2–5%), upon mixing with a minute amount of a dendritic molecular glue carrying multiple guanidinium ion pendants (< 0.15%), quickly form a transparent hydrogel (Nature 2010, 463, 339–343). This material can be molded into shape-persistent freestanding objects owing to its high mechanical strength, and instantaneously self-heals when destroyed. Furthermore, it preserves biologically active proteins for catalysis. Prior to our discovery, no hydrogels have been reported to possess all these exceptional features.

SESSION J3: Plenary III

Chairs: Scott Grayson and Lars Pichler
Tuesday Morning, June 28, 2011
Green Auditorium

9:10 AM *J3.1

Bioinspired Synthesis of Complex Molecular Systems. Virgil Percec, Roy & Diana Vagelos Laboratory, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania.

Bioinspired synthesis involves the design and synthesis of programmed

primary structures that are instructed to undergo intramolecular and intermolecular self-assembly, self-organization and the other sequence of events involved in the emergence of complex molecular systems via the same principles as those used by complex biological systems. Since the mechanism of transfer of structural information is not understood, primary structures responsible for the creation of complex systems and functions cannot be designed. Complex systems are identified by what they do, display organization without a central organizing authority, and therefore are emergent, and also by how they may or may not be analyzed; they cannot be understood by analyzing their individual parts in isolation. The major features that characterize complex systems are adaptation or self-control, self-organization and emergence (1). Some also exhibit self-repair and memory. Therefore, complex systems cannot be designed or engineered. Examples of complex systems include social and political organizations, financial and economic systems, life, highways, the internet, the power grids, metabolic pathways, most biological systems, some molecular systems and selected chemical reactions. Complex systems are different from complicated systems that are not characterized by adaptation or self-control, self-organization and emergence and therefore, they can be understood in isolation, engineered and designed. Complex biological systems are emerging from biological macromolecules and molecules with a precise primary structure programmed to mediate the creation of a particular biological system. However, even in biological systems it is not yet understood how a primary structure is selected for a particular function. This lecture will discuss the elaboration of strategies and methods for the bioinspired synthesis of primary structures responsible for the emergence of selected examples of mimics of complex biological systems by using self-assembling dendrons and dendrimers as building blocks (1c,2,3,4,5). The lecture will also address the fundamental question: will the design and/or prediction of programmed primary structures that are responsible for the emergence of complex molecular systems be possible? Lessons learned from complex molecular systems may apply to all other complex systems. References (1) (a) Ottino, J.M. Nature 2004, 427, 399-399. (b) Caspar, D.L.D.; Klug, A. Cold Spring Harbor Symp. Quantit. Biol. 1962, 27, 1-24. (c) Rosen, B.M.; Wilson, C.J.; Wilson, D.A.; Peterca, M.; Imam, M.R.; Percec, V. Chem. Rev. 2009, 109, 6275-6540. (2) Percec, V.; Ahn, C.H.; Ungar, G.; Yeardey, D.J.P.; Moeller, M.; Sheiko, S.S. Nature 1998, 391, 161-164. (3) Percec, V.; Glodde, M.; Bera, T.K.; Miura, Y.; Shiyanovska, I.; Singer, K.D.; Balagurusamy, V.S.K.; Heiney, P.A.; Schnell, I.; Rapp, A.; Spiess, H.W.; Hudson, S.D.; Duan, H. Nature 2002, 419, 384-387. (4) Percec, V.; Dulcey, A.E.; Balagurusamy, V.S.K.; Miura, Y.; Smidrcal, J.; Peterca, M.; Edlund, U.; Hudson, S.D.; Heiney, P.A.; Hu, D.A.; Magonov, S.N.; Vinogradov, S.A. Nature 2004, 430, 764-768. (5) Percec, V.; Wilson, D.A.; Leowanawat, P.; Wilson, C.J.; Hugh, A.D.; Kaucher, M.S.; Hammer, D.A.; Levine, D.H.; Kim, A.J.; Bates, F.S.; Davis, K.P.; Lodge, T.P.; Klein, M.L.; DeVane, R.T.H.; Aqad, E.; Rosen, B.M.; Argintaru, A.O.; Sienkowska, M.J.; Rissanen, K.; Nummelin, S.; Roponen, J. Science 2010, 328, 1009-1014. (6) Rosen, B.M.; Peterca, M.; Morimitsu, K.; Dulcey, A.E.; Leowanawat, P.; Resmerita, A.-M.; Imam, M.R.; Percec, V. J. Am. Chem. Soc. 2011, 133, 5135-5151.

SESSION J4: Plenary IV

Chair: Mary Cloninger
Tuesday Afternoon, June 28, 2011
Green Auditorium

3:20 PM *J4.1

Design and Properties of New Dendrimer Types.

Jean Pierre Majoral^{1,2}, Cédric Rouxel³, Aurélien Hameau¹, Mireille Blanchard-Desce³, Anne-Marie Caminade¹, Nadia Katir^{1,2}, Abdelkrim El Kadib² and Mostapha Bousmina^{2,4}; ¹Laboratoire Chimie de Coordination, CNRS, Toulouse, France; ²Institute of Nanomaterials and Nanotechnology, (MASCIR), Rabat, Morocco; ³Chimie et Photonique (UMR 6510), CNRS, Rennes, France; ⁴Hassan II Academy of Science and Technology, Rabat, Morocco.

More and more applications of dendrimers are appearing in the literature covering many topics from biology, biomedicine, material sciences, catalysis ... As a consequence such an appealing field of research implies to diversify the nature and the composition of existing types of dendrimers but also to propose the preparation of tailored new types of dendrimers which might be able to open new areas of investigations. The properties and applications of some of these unprecedented dendrons, dendrimers and related "molecular asterisks" will be presented and discussed.

SESSION J5: Plenary V
Chair: Anil Patri
Wednesday Morning, June 29, 2011
Green Auditorium

8:30 AM *J5.1

Nanotechnology for Cancer Approaches in the Clinic.

James R. Baker, University of Michigan, Ann Arbor, Michigan.

Our group has developed a number of dendrimer-based targeted therapeutics for epithelial, lung and ovarian cancers. These macromolecules are actively targeted to tumors that over-express receptors for a number of receptors for small molecule ligands including folate, riboflavin, RGD and EGF. Our first generation therapeutics used a dendrimer scaffold combined with linking multiple targeting and therapeutic molecules to produce multifunctional combinatory therapeutics. Unfortunately, the complexity of these molecules prevented their entry into clinical trials. We have re-designed the platform using a simplified approach; polyvalent small molecule therapeutics which also act as ligands to target the nanoparticle and kill cancer cells. The revised scaffold still uses a dendritic polymer that is uniquely suited to biomedical applications in that it can be uniformly produced and yet has a diameter less than 10 nanometers. Our linker mechanism utilizes a more complex and extended linker to conjugate ligands, drugs and imaging agents to the dendrimer. The goal of this work is to develop several polyvalent therapeutics and imaging agents and advance these materials through preclinical animal efficacy and toxicity trials. If this approach is successful *in vivo*, it can facilitate the concept of targeting many small molecule drugs on nanoparticles to address varied tumor types with different genetic or enzymatic alterations associated with individual cancers. Thus, the polyvalent drug approach would yield common, interchangeable therapeutic platforms that transcend any single tumor type or cellular abnormality.

9:10 AM *J5.2

Pathways through a Molecular Forest: One Person's Journey.

George R. Newkome, Polymer Science, University of Akron, Akron, Ohio.

For nearly three decades, my collaborators and I have been wandering through a dendritic jungle and it has been fun dealing with the things that we have bumped into – for better or for worse! Watching the trees mature and then taking advantage of the fruits that they have produced. The use of a tree for Christmas has led to new thoughts on what is appropriate to see at Christmas time and what gifts should be under or in that tree. What does an ideal tree actually look like and is there such a thing as a perfect design for a tree? What happens when the trees lose their protective foliage, how does the environment react to or with the residue? Architecturally, our dendritic trees are simply fractal structures; thus, we should be able to create new alternative designs for different types of artificial trees. Although currently most tree-like macromolecular motifs are constructed by long and somewhat painful procedures, is it then possible to create a tree-like (fractal) structure in one day or less? Via stoichiometric self-assembly, can fractal super-structures be made? In 1982, this journey started for me and it has been pure fun – this lecture will demonstrate the different avenues leading to higher ordered fractal motifs and other things. Thanks to the National Science Foundation for fiscal support of these research endeavors.

SESSION J6: Plenary VI
Chair: Mark Grinstaff
Thursday Morning, June 30, 2011
Green Auditorium

9:00 AM *J6.1

Pushing Divergent Synthesis to the Limits: Synthesis of the Largest Molecule with Defined Structure.

A. Dieter Schlueter, Baozhong Zhang and Hao Yu; Department of Materials, ETH Zurich, Zurich, Switzerland.

Divergent growth is a key method in dendrimer synthesis.¹ Arguably the largest representative that was ever built this way is Caminade's and Majoral's 12th generation (G12) P-containing dendrimer with a theoretical molar mass of ~ 3 MDa.² The molar mass increase on going from G11 to G12 is ~1.8 MDa. Seeing both the enormous potential to built-up substantial covalent mass in a controlled fashion and the limitations that the use of dendrimers implies, we set out to apply divergent growth schemes to linear polymers. We here report on the synthesis of the largest ever made synthetic structure, a G5 dendronized polymer with a molar mass of ~200 MDa and a structure perfection of > 94%.³ The molar mass increase from G4 to G5 amounts to 100 MDa which is more than any polymerization can afford. Organic chemistry can thus effectively compete with polymer chemistry in regard to creation of molar mass. Further we discuss

which properties emerge from this systematic thickening of polymer chains and also where we expect the limits to be. 1. Buhleier, E., Wehner, W., Vögtle, F. *Synthesis* 155-158 (1978); Denkewalter, R. G., Kolc, J. F., Lukasavage, W. J., U.S. Patent, 4,360,646 (1979); Tomalia, D. A. et al. *Polym. J.* (Tokyo), 17, 117-132 (1985); Newkome, G. R., Yao, Z., Baker, G. R., Gupta, V. K. *J. Org. Chem.* 50, 2003-2004 (1985). 2. Lartigue, M.-L., Donnadiou, B., Galliot, C., Caminade, A. M., Majoral, J.-P. *Macromolecules* 30, 7335 (1997). 3. Zhang, B., Wepf, R., Fischer, K., Schmidt, M., Besse, S., Lindner, P., King, B. T., Sigel, R., Schurtenberger, P., Talmon, Y., Ding, Y., Kröger, M., Halperin, A., Schlüter, A. D. *Angew. Chem. Int. Ed.* 50, 737 (2011).

SESSION J7: Plenary VII and Award Ceremony

Chair: S. Thayumanavan
Friday Morning, July 1, 2011
Green Auditorium

11:00 AM *J7.1

Dendrons and Dendrimers: Window to a New Systematic Framework for Unifying and Defining Nanoscience.

Donald A. Tomalia, National Dendrimer & Nanotechnology Center, NanoSynthons LLC, Midland, Michigan.

“Science will continue to advance regardless of disputes over priorities, however, confusion and disagreement over common scientific language and standards can plunge a discipline into chaos. Such was the case for 19th century traditional small molecule chemistry, before the emergence of Mendeleev's Periodic Table of the Elements (1869)” P. Strathern.[1] A central paradigm and Mendeleev-like periodic system based on traditional chemistry first principles has been a missing link in the transformation of nanotechnology from an empirical to a predictive science. A nano-periodic system would assist in the a priori design, as well as defining critical risk/benefit boundaries related to the use and development of nanomaterials. Unique quantized dendrimer nano-features and periodic property patterns (i.e. dendritic effects) have provided a window to such a systematic nano-periodic framework for unifying nanoscience. Simple extrapolation of first principles (i.e. discrete valencies, stoichiometric compounds/assemblies and periodic property patterns), that underpin traditional small molecule chemistry, have been invoked in a proposed new nano-periodic concept for all well defined inorganic (Hard) and organic (Soft) nanomaterials[2,3] including dendrons/dendrimers. This lecture will describe a proposed Nanomaterials Classification Roadmap which categorizes all well defined nano-matter (i.e. dendrons, dendrimers, etc.) in the context of heuristic atom mimicry, as well as nano-element categories, stoichiometric compounds and assemblies. The unique quantized features of the soft-dendrimer/dendrimer nano-element category have provided many examples of nano-periodic property patterns and have been referred to as “dendritic effects” in the literature. These quantized nano-features/periodic property patterns are defined as a function of Critical Nanoscale Design Parameters (CNDPs) such as: (a) size, (b) shape, (c) surface chemistry, (d) flexibility, (e) architecture and (f) elemental composition. These CNDPs directly influence intrinsic physico-chemical properties as well as important functional/performance properties. The importance of these CNDPs has been recently demonstrated by Percec/Rosen et al.[4] in the first reported Mendeleev-like nano-periodic tables. These tables predict a priori self assembly modes of soft nano-element type dendrons with 85-90% accuracy as a function of their CNDPs and fulfills our predictive nano-periodic property pattern hypothesis. We propose this nano-periodic concept perspective as a first step toward more clearly defining the new emerging disciplines of synthetic organic/inorganic nano-chemistry, as well as providing a systematic framework for unifying nanoscience. References: 1. P. Strathern, Mendeleev's Dream (2000), Berkley Books, NY. 2. D.A. Tomalia, J. Nanoparticle Research (2009), 11, 1251. 3. D.A. Tomalia, *Soft Matter* (2010), 6, 456. 4. B.M. Rosen, V. Percec, et al., *J. Am. Chem. Soc.* (2009), 131, 17500.