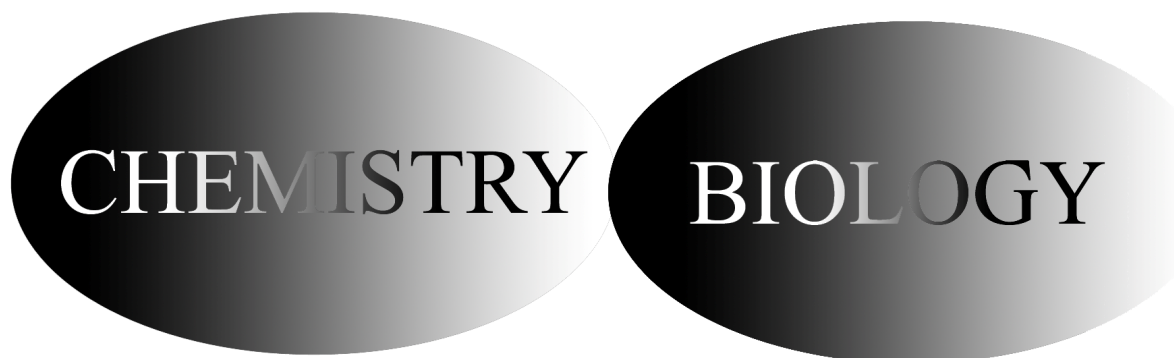


Chmielewski Group Literature Abstracts



February 2008

Contributing Editors:

Marcos Pires (*Science/Nature and Nature subdivisions*)

Brandon Gaddis/Iris Geisler (*JACS*)

Jee Yeon Lee (*PNAS*)

Dawn Ernenwein (*ACS Chemical Biology/Chem Biol & Drug Design*)

Dave Przybyla (*Angewandte Chemie*)

Hilda Namanja (*Chem & Bio*)

Nicole O'Neil (*Org Lett*)

Nature

Self-healing and thermoreversible rubber from supramolecular assembly

Nature **451**, 977-980 (21 February 2008)

Philippe Cordier¹, François Tournilhac¹, Corinne Soulié-Ziakovic¹ & Ludwik Leibler

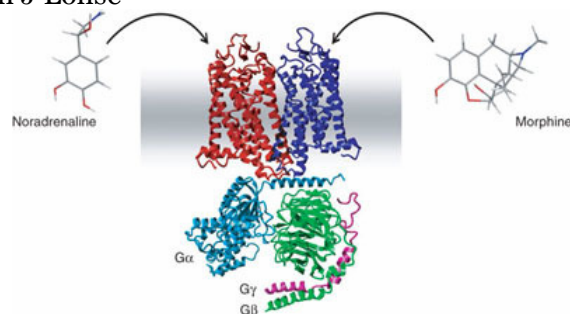
Rubbers exhibit enormous extensibility up to several hundred per cent, compared with a few per cent for ordinary solids, and have the ability to recover their original shape and dimensions on release of stress^{1, 2}. Rubber elasticity is a property of macromolecules that are either covalently cross-linked^{1, 2} or connected in a network by physical associations such as small glassy or crystalline domains^{3, 4, 5}, ionic aggregates⁶ or multiple hydrogen bonds^{7, 8, 9, 10, 11, 12, 13, 14, 15, 16}. Covalent cross-links or strong physical associations prevent flow and creep. Here we design and synthesize molecules that associate together to form both chains and cross-links via hydrogen bonds. The system shows recoverable extensibility up to several hundred per cent and little creep under load. In striking contrast to conventional cross-linked or thermoreversible rubbers made of macromolecules, these systems, when broken or cut, can be simply repaired by bringing together fractured surfaces to self-heal at room temperature. Repaired samples recuperate their enormous extensibility. The process of breaking and healing can be repeated many times. These materials can be easily processed, re-used and recycled. Their unique self-repairing properties, the simplicity of their synthesis, their availability from renewable resources and the low cost of raw ingredients (fatty acids and urea) bode well for future applications.

Nature Chemical Biology

Conformational cross-talk between alpha2A-adrenergic and mu-opioid receptors controls cell signaling

Nature Chemical Biology **4**, 126-131 (2008)

Jean-Pierre Vilardaga^{1,2}, Viacheslav O Nikolaev^{3,4}, Kristina Lorenz³, Sébastien Ferrandon^{1,2}, Zhenjie Zhuang^{1,2} & Martin J Lohse



Morphine, a powerful analgesic, and norepinephrine, the principal neurotransmitter of sympathetic nerves, exert major inhibitory effects on both peripheral and brain neurons by activating distinct cell-surface G protein-coupled receptors—the mu-opioid receptor (MOR) and alpha2A-adrenergic receptor (alpha2A-AR), respectively. These receptors, either singly or as a heterodimer, activate common signal transduction pathways mediated through the inhibitory G proteins (Gi and Go). Using fluorescence resonance energy transfer microscopy, we show that in the heterodimer, the MOR and alpha2A-AR

communicate with each other through a cross-conformational switch that permits direct inhibition of one receptor by the other with subsecond kinetics. We discovered that morphine binding to the MOR triggers a conformational change in the norepinephrine-occupied α_2A -AR that inhibits its signaling to G_i and the downstream MAP kinase cascade. These data highlight a new mechanism in signal transduction whereby a G protein-coupled receptor heterodimer mediates conformational changes that propagate from one receptor to the other and cause the second receptor's rapid inactivation.

Science

Single-Molecule Cut-and-Paste Surface Assembly

Vol. 319, no. 5863, pp. 594 - 596

S. K. Kufer,¹ E. M. Puchner,¹ H. Gump, ¹ T. Liedl,² H. E. Gaub

We introduce a method for the bottom-up assembly of biomolecular structures that combines the precision of the atomic force microscope (AFM) with the selectivity of DNA hybridization. Functional units coupled to DNA oligomers were picked up from a depot area by means of a complementary DNA strand bound to an AFM tip. These units were transferred to and deposited on a target area to create basic geometrical structures, assembled from units with different functions. Each of these cut-and-paste events was characterized by single-molecule force spectroscopy and single-molecule fluorescence microscopy. Transport and deposition of more than 5000 units were achieved, with less than 10% loss in transfer efficiency.

PNAS

High-resolution structures of HIV-1 reverse transcriptase/TMC278 complexes: Strategic flexibility explains potency against resistance mutations

PNAS | February 5, 2008 | vol. 105 | no. 5 | 1466-1471

Kalyan Das*, , Joseph D. Bauman*, , Arthur D. Clark, Jr.* , , Yulia V. Frenkel* , , Paul J. Lewi , Aaron J. Shatkin* , , Stephen H. Hughes, and Eddy Arnold

TMC278 is a diarylpyrimidine (DAPY) nonnucleoside reverse transcriptase inhibitor (NNRTI) that is highly effective in treating wild-type and drug-resistant HIV-1 infections in clinical trials at relatively low doses (25–75 mg/day). We have determined the structure of wild-type HIV-1 RT complexed with TMC278 at 1.8 Å resolution, using an RT crystal form engineered by systematic RT mutagenesis. This high-resolution structure reveals that the cyanovinyl group of TMC278 is positioned in a hydrophobic tunnel connecting the NNRTI-binding pocket to the nucleic acid-binding cleft. The crystal structures of TMC278 in complexes with the double mutant K103N/Y181C (2.1 Å) and L100I/K103N HIV-1 RTs (2.9 Å) demonstrated that TMC278 adapts to bind mutant RTs. In the K103N/Y181C RT/TMC278 structure, loss of the aromatic ring interaction caused by the Y181C mutation is counterbalanced by interactions between the cyanovinyl group of TMC278 and the aromatic side chain of Y183, which is facilitated by an 1.5 Å shift of the conserved Y183MDD motif. In the L100I/K103N RT/TMC278 structure, the binding mode of

TMC278 is significantly altered so that the drug conforms to changes in the binding pocket primarily caused by the L100I mutation. The flexible binding pocket acts as a molecular "shrink wrap" that makes a shape complementary to the optimized TMC278 in wild-type and drug-resistant forms of HIV-1 RT. The crystal structures provide a better understanding of how the flexibility of an inhibitor can compensate for drug-resistance mutations.

A chemical method for fast and sensitive detection of DNA synthesis in vivo

PNAS | February 19, 2008 | vol. 105 | no. 7 | 2415-2420

Adrian Salic*, and Timothy J. Mitchison

We have developed a method to detect DNA synthesis in proliferating cells, based on the incorporation of 5-ethynyl-2'-deoxyuridine (EdU) and its subsequent detection by a fluorescent azide through a Cu(I)-catalyzed [3 + 2] cycloaddition reaction ("click" chemistry). Detection of the EdU label is highly sensitive and can be accomplished in minutes. The small size of the fluorescent azides used for detection results in a high degree of specimen penetration, allowing the staining of whole-mount preparations of large tissue and organ explants. In contrast to BrdU, the method does not require sample fixation or DNA denaturation and permits good structural preservation. We demonstrate the use of the method in cultured cells and in the intestine and brain of whole animals.

Precise engineering of targeted nanoparticles by using self-assembled biointegrated block copolymers

PNAS | February 19, 2008 | vol. 105 | no. 7 | 2586-2591

Frank Gu*, , Liangfang Zhang*, Benjamin A. Teply*, , Nina Mann*, Andrew Wang , , Aleksandar F. Radovic-Moreno, Robert Langer and Omid C. Farokhzad

There has been progressively heightened interest in the development of targeted nanoparticles (NPs) for differential delivery and controlled release of drugs. Despite nearly three decades of research, approaches to reproducibly formulate targeted NPs with the optimal biophysicochemical properties have remained elusive. A central challenge has been defining the optimal interplay of parameters that confer molecular targeting, immune evasion, and drug release to overcome the physiological barriers in vivo. Here, we report a strategy for narrowly changing the biophysicochemical properties of NPs in a reproducible manner, thereby enabling systematic screening of optimally formulated drug-encapsulated targeted NPs. NPs were formulated by the self-assembly of an amphiphilic triblock copolymer composed of end-to-end linkage of poly(lactic-co-glycolic-acid) (PLGA), polyethyleneglycol (PEG), and the A10 aptamer (Apt), which binds to the prostate-specific membrane antigen (PSMA) on the surface of prostate cancer (PCa) cells, enabling, respectively, controlled drug release, "stealth" properties for immune evasion, and cell-specific targeting. Fine-tuning of NP size and drug release kinetics was further accomplished by controlling the copolymer composition. By using distinct ratios of PLGA-b-PEG-b-Apt triblock copolymer with PLGA-b-PEG diblock copolymer lacking the A10 Apt, we developed a series of targeted NPs with increasing Apt densities that inversely affected the amount of PEG exposure on NP surface and identified the narrow range of Apt

density when the NPs were maximally targeted and maximally stealth, resulting in most efficient PCa cell uptake in vitro and in vivo. This approach may contribute to further development of targeted NPs as highly selective and effective therapeutic modalities.

Collagen fibril architecture, domain organization, and triple-helical conformation govern its proteolysis

PNAS | February 26, 2008 | vol. 105 | no. 8 | 2824-2829

Shiamalee Perumal, Olga Antipova, and Joseph P. R. O. Orgel

We describe the molecular structure of the collagen fibril and how it affects collagen proteolysis or "collagenolysis." The fibril-forming collagens are major components of all mammalian connective tissues, providing the structural and organizational framework for skin, blood vessels, bone, tendon, and other tissues. The triple helix of the collagen molecule is resistant to most proteinases, and the matrix metalloproteinases that do proteolyze collagen are affected by the architecture of collagen fibrils, which are notably more resistant to collagenolysis than lone collagen monomers. Until now, there has been no molecular explanation for this. Full or limited proteolysis of the collagen fibril is known to be a key process in normal growth, development, repair, and cell differentiation, and in cancerous tumor progression and heart disease. Peptide fragments generated by collagenolysis, and the conformation of exposed sites on the fibril as a result of limited proteolysis, regulate these processes and that of cellular attachment, but it is not known how or why. Using computational and molecular visualization methods, we found that the arrangement of collagen monomers in the fibril (its architecture) protects areas vulnerable to collagenolysis and strictly governs the process. This in turn affects the accessibility of a cell interaction site located near the cleavage region. Our observations suggest that the C-terminal telopeptide must be proteolyzed before collagenase can gain access to the cleavage site. Collagenase then binds to the substrate's "interaction domain," which facilitates the triple-helix unwinding/dissociation function of the enzyme before collagenolysis.

A virocidal amphipathic α -helical peptide that inhibits hepatitis C virus infection in vitro

PNAS | February 26, 2008 | vol. 105 | no. 8 | 3088-3093

Guofeng Cheng*, Ana Montero, Pablo Gastaminza*, Christina Whitten-Bauer*, Stefan F. Wieland*, Masanori Isogawa*, Brenda Fredericksen, Suganya Selvarajah, Philippe A. Gallay, M. Reza Ghadiri, and Francis V. Chisari

An amphipathic α -helical peptide (C5A) derived from the membrane anchor domain of the hepatitis C virus (HCV) NS5A protein is virocidal for HCV at submicromolar concentrations in vitro. C5A prevents de novo HCV infection and suppresses ongoing infection by inactivating both extra- and intracellular infectious particles, and it is nontoxic in vitro and in vivo at doses at least 100-fold higher than required for antiviral activity. Mutational analysis indicates that C5A's amphipathic α -helical structure is necessary but not sufficient for its virocidal activity, which depends on its amino acid composition but not its primary sequence or chirality. In addition to HCV, C5A inhibits infection by selected flaviviruses, paramyxoviruses, and HIV. These results suggest a model in which C5A

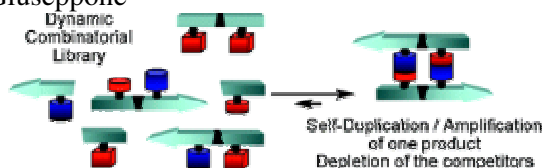
destabilizes viral membranes based on their lipid composition, offering a unique therapeutic approach to HCV and other viral infections.

Journal of the American Chemical Society

Self-Duplicating Amplification in a Dynamic Combinatorial Library

J. Am. Chem. Soc., 2008, 130 (6), 1826 -1827

Shengguang Xu[†] and Nicolas Giuseppone

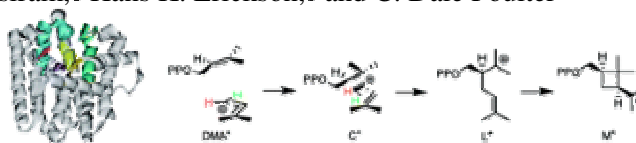


A dynamic combinatorial library has been designed to produce a set of constituents among which one is able to self-complementarily direct its duplication. The overall molecular distribution in the library evolves along both kinetic and thermodynamic biases, leading to the amplification of the species that reproduces most efficiently and to the depletion of the other competitors.

A Common Mechanism for Branching, Cyclopropanation, and Cyclobutanation Reactions in the Isoprenoid Biosynthetic Pathway

J. Am. Chem. Soc., 2008, 130 (6), 1966 -1971

Hirekodathakallu V. Thulasiram,[†] Hans K. Erickson,[‡] and C. Dale Poulter

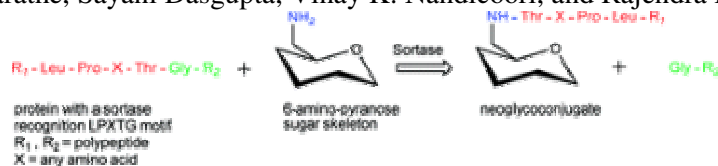


Four reactions-chain elongation, cyclopropanation, branching, and cyclobutanation-are used in nature to join isoprenoid units for construction of the carbon skeletons for over 55 000 naturally occurring isoprenoid compounds. Those molecules produced by chain elongation have head-to-tail (regular) carbon skeletons, while those from cyclopropanation, branching, or cyclobutanation have non-head-to-tail (irregular) skeletons. Although wild type enzymes have not been identified for the branching and cyclobutanation reactions, chimeric proteins constructed from farnesyl diphosphate synthase (chain elongation) and chrysanthemyl diphosphate synthase (cyclopropanation) catalyze all four of the known isoprenoid coupling reactions to give a mixture of geranyl diphosphate (chain elongation), chrysanthemyl diphosphate (cyclopropanation), lavandulyl diphosphate (branching), and maconellyl and planococyl diphosphate (cyclobutanation). Replacement of the hydrogen atoms at C1 or C2 or hydrogen atoms in the methyl groups of dimethylallyl diphosphate by deuterium alters the distribution of the cyclopropanation, branching, and cyclobutanation products through primary and secondary kinetic isotope effects on the partitioning steps of common carbocationic intermediates. These experiments establish the sequence in which the intermediates are formed and indicate that enzyme-mediated control of the carbocationic rearrangement and elimination steps determines the distribution of products.

Peptide-Sugar Ligation Catalyzed by Transpeptidase Sortase: A Facile Approach to Neoglycoconjugate Synthesis

J. Am. Chem. Soc., 130 (7), 2132 -2133, 2008.

Sharmishtha, Uttara Marathe, Sayani Dasgupta, Vinay K. Nandicoori, and Rajendra P. Roy

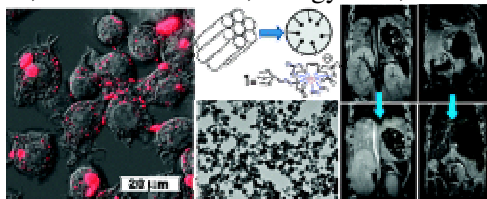


Glycoconjugate synthesis involving sugar and polypeptide remains a formidable challenge. Here we report a novel enzymatic method involving an unprecedented sortase-catalyzed transamidation reaction for site-specific engineering of sugars into native proteins. We show that sugars appended with a 6-aminohexose moiety can be efficiently ligated to peptides and proteins encoded with a LPXTG sortase recognition sequence. This robust reaction provides an elegant and simple approach for generating neoglycoproteins with an amide-linked sugar moiety at the carboxy terminus.

Mesoporous Silica Nanospheres as Highly Efficient MRI Contrast Agents

J. Am. Chem. Soc., 130 (7), 2154-2155 2008.

Kathryn M. L. Taylor, Jason S. Kim, William J. Rieter, Hongyu An, Weili Lin, and Wenbin Lin

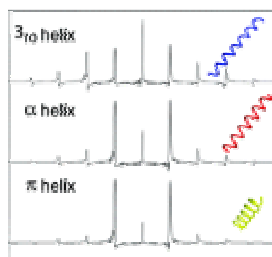


Mesoporous silica nanoparticles (MSNs) containing a hexagonal array of one-dimensional channels with diameters of 2.4 nm were synthesized using a surfactant-templated, base-catalyzed condensation reaction. After extraction of the template, the highly porous 75 nm nanospheres were coated with a Gd-Si-DTTA complex to give MSN-Gd particles that exhibit very high MR relaxivities. The MSN-Gd nanoparticles were characterized using SEM, TEM, TGA, BET, PXRD, and DCP, and the relaxivities were determined on both a 3.0 T and a 9.4 T MR scanner. The MSN-Gd particles exhibit very high MR relaxivity on a per Gd basis and even more impressive MR relaxivity on a per nanoparticle basis, owing to the ready access of water molecules through the nanochannels of the MSN-Gd particles and a high payload of Gd centers. The in vivo efficacy of these particles as MR contrast agents was further demonstrated with monocyte cells and mouse models. Both T1-weighted and T2-weighted signal enhancement can be obtained at doses much lower than what is currently being used. In vitro MTS assay and in vivo mouse studies indicated no acute toxicity of the MSN-Gd nanoparticles. This work thus demonstrates the design and synthesis of highly efficient nanoparticulate MRI contrast agents based on MSNs and suggests the potential of using these new hybrid nanomaterials for early disease diagnosis.

Determination of Peptide Backbone Torsion Angles Using Double-Quantum Dipolar Recoupling Solid-State NMR Spectroscopy

J. Am. Chem. Soc., 130 (7), 2202-2212, 2008.

Manish A. Mehta,* Matthew T. Eddy, Seth A. McNeill, Frank D. Mills, and Joanna R. Long

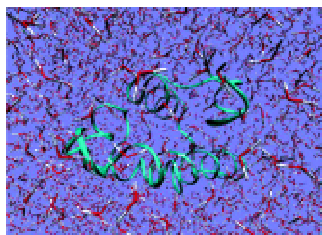


Several approaches for utilizing dipolar recoupling solid-state NMR (ssNMR) techniques to determine local structure at high resolution in peptides and proteins have been developed. However, many of these techniques measure only one torsion angle or are accurate for only certain classes of secondary structure. Additionally, the efficiency with which these dipolar recoupling experiments suppress the deleterious effects of chemical shift anisotropy (CSA) at high magnetic field strengths varies. Dipolar recoupling with a windowless sequence (DRAWS) has proven to be an effective pulse sequence for exciting double-quantum (DQ) coherences between adjacent carbonyl carbons along the peptide backbone. By allowing this DQ coherence to evolve, it is possible to measure the relative orientations of the CSA tensors and subsequently use this information to determine the Ramachandran torsion angles ϕ and ψ . Here, we explore the accuracies of the assumptions made in interpreting DQ-DRAWS data and demonstrate their fidelity in measuring torsion angles corresponding to a variety of secondary structures irrespective of hydrogen-bonding patterns. It is shown how a simple choice of isotopic labels and experimental conditions allows accurate measurement of backbone secondary structures without any prior knowledge. This approach is considerably more sensitive for determining structure in helices and has comparable accuracy for β -sheet and extended conformations relative to other methods. We also illustrate the ability of DQ-DRAWS to distinguish between structures in heterogeneous samples.

Protein Sequence- and pH-Dependent Hydration Probed by Terahertz Spectroscopy

J. Am. Chem. Soc., 130 (8), 2374 -2375, 2008

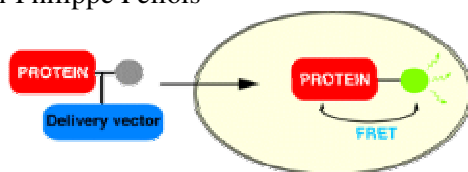
Simon Ebbinghaus, Seung Joong Kim, Matthias Heyden, Xin Yu, Martin Gruebele, David M. Leitner, and Martina Havenith



Abstract: protein itself have received more attention because they are easier to probe. Here we use terahertz (far-infrared) spectroscopy to directly probe the effect of mutations and solvent pH on the solvent shell-protein interaction. We study absorption spectra of the 80 residue viral protein , a five helix bundle, in the 2.1-2.8 THz region. We find that the wild type at pH 7 has a much more pronounced effect on long-distance solvation water than mutants replacing a single polar glutamine side chain with aromatic residues (tyrosine, histidine). This is true both in the context of enhanced and decreased helix stability (via alanine and glycine substitutions). Bringing the wild type and mutants closer to the unfolding transition by lowering the pH likewise reduces the long distance solvation effect. Thus terahertz spectroscopy can be used to probe both local and global solvation dynamics around proteins.

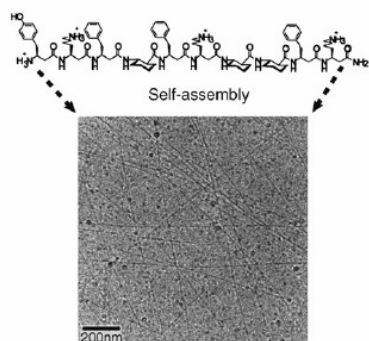
Real-Time Fluorescence Detection of Protein Transduction into Live Cells

J. Am. Chem. Soc., 130 (8), 2398 -2399, 2008.
 Ya-Jung Lee, Silpi Datta, and Jean-Philippe Pellois



We describe a protein probe with multiple fluorescence signals that can unambiguously detect protein translocation into live cells. When combined with fluorescence microscopy, this unique probe design allows for the first time the investigator to visualize and distinguish intact and degraded proteins with high spatial and temporal resolution. Thus, by using this approach, one can now compare the mechanisms and measure the efficiency of different delivery vectors, a prerequisite for the rational design of protein transduction systems with superior properties.

Angewandte Chemie



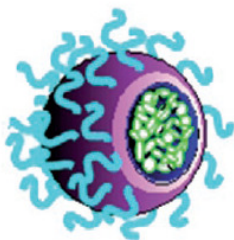
More than a pretty phase: A class of helical β -peptides has been discovered that form lyotropic liquid-crystalline (LC) phases in water. The β -peptide sequence strongly affects the mode of assembly and ultimately whether a LC phase is formed. For a non-globally amphiphilic β -peptide that can form a LC phase, cryo-TEM revealed thin fibers several micrometers in length, consistent with Onsager theory.

Nanostructured Materials

W. C. Pomerantz, V. M. Yuwono,
 C. L. Pizzey, J. D. Hartgerink,*
 N. L. Abbott,*
 S. H. Gellman* _____ 1241–1244

Nanofibers and Lyotropic Liquid Crystals
 from a Class of Self-Assembling
 β -Peptides

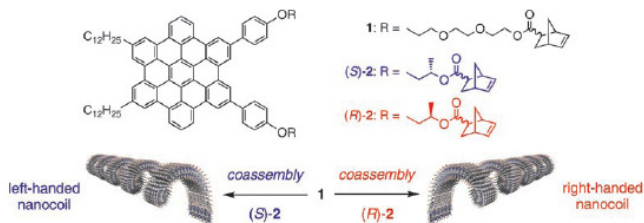
A new concept for fabricating nanocarriers carrying free DNA for gene delivery to overcome the intracellular dissociation barrier of cationic polymer/DNA complexes is presented. Free DNA plasmids (shown in green) are encapsulated in a nanocapsule core, which is protected by a hydrophobic membrane (purple) with a poly(ethylene glycol) outer layer (blue). The nanocapsules can release free DNA into the cells and have high in vitro and in vivo transfection efficiency.



Gene Delivery

P. Xu, S.-Y. Li, Q. Li, E. A. Van Kirk, J. Ren,*
 W. J. Murdoch, Z. Zhang, M. Radosz,
 Y. Shen* _____ 1260–1264

Virion-Mimicking Nanocapsules from pH-
 Controlled Hierarchical Self-Assembly for
 Gene Delivery



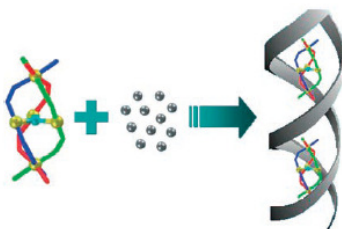
One-handed military discipline: The hexabenzocoronene (HBC) derivative **1** can coassemble with the chiral HBCs (S)- or (R)-**2** to yield graphitic nanocoils (see picture). Self-assembly of **2** alone gives noncoiled fibrous assemblies. A sergents-and-soldiers effect leads to the

formation of one-handed nanocoils. These can be covalently stabilized by post-surface ROMP of the pendant norbornene groups to give a uniform cast film. Upon doping with I_2 , this film becomes electroconductive without any detectable morphological disruption.

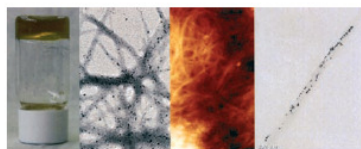
Helical Coordination Polymers

J.-Z. Hou, M. Li, Z. Li, S.-Z. Zhan, X.-C. Huang, D. Li* _____ 1711–1714

Supramolecular Helix-to-Helix Induction: A 3D Anionic Framework Containing Double-Helical Strands Templated by Cationic Triple-Stranded Cluster Helicates



All wrapped up: Supramolecular polymeric helices were fabricated by using cluster helicates as templates. The helicity of the template (see picture; gold spheres: Ni or Zn; blue spheres: O), upon hydrothermal treatment with CuSCN (gray spheres), is transferred to the strands of the resulting copper-based coordination polymer, which is wrapped around the helicate units in the final product.



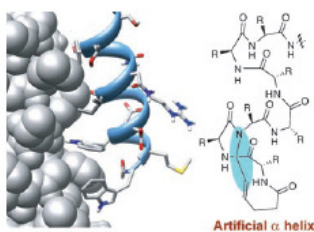
Functionalized gold nanoparticles with complementary H-bonding groups can control the secondary structure of xerogel fibers formed by a molecular conductor thanks to their incorporation into the nanowires, which show metal-like conductivity once doped without the need for annealing. The picture shows a photograph of the xerogel, TEM images of Au particles in the gel and a single fiber, and an AFM image revealing the texture of the gel.

Supramolecular Nanocomposites

J. Puigmartí-Luis, A. Pérez del Pino, E. Laukhina, J. Esquena, V. Laukhin, C. Rovira, J. Vidal-Gancedo, A. G. Kanaras, R. J. Nichols, M. Brust, D. B. Amabilino* _____ 1861–1865

Shaping Supramolecular Nanofibers with Nanoparticles Forming Complementary Hydrogen Bonds

Inhibition with a twist: An artificial α helix obtained by replacing an N-terminal main-chain i and $i+4$ hydrogen bond with a carbon-carbon bond (see structure) inhibits gp41-mediated cell fusion. This work suggests that hydrogen-bond-surrogate-derived helices may provide a general class of scaffolds for the generation of leads against viral entry.



α -Helix Mimetics

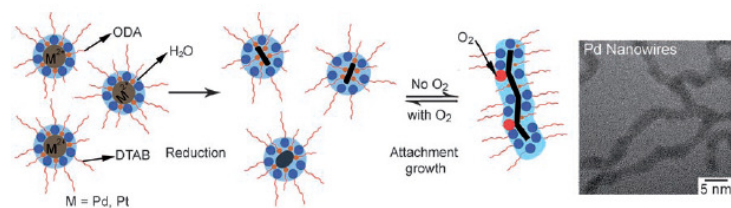
D. Wang, M. Lu, P. S. Arora* _____ 1879–1882

Inhibition of HIV-1 Fusion by Hydrogen-Bond-Surrogate-Based α Helices

Metallic Nanowires

X. Teng, W.-Q. Han,* W. Ku,
M. Hückler ————— 2055 – 2058

Synthesis of Ultrathin Palladium and
Platinum Nanowires and a Study of Their
Magnetic Properties



Thin and wiry: Ultrathin palladium and platinum nanowires with widths of 2.4 ± 0.2 (Pd) and 2.3 ± 0.2 nm (Pt) and lengths of over 30 nm are synthesized by a modified phase-transfer method (see

picture). Both nanowires show ferromagnetic properties and unusual shifts in their hysteresis loops at low temperature. ODA = octadecylamine, DTAB = *n*-dodecyltrimethylammonium bromide.

ACS Chemical Biology

How the “Melting” and “Freezing” of Protein Molecules May Be Used in Cell Signaling

ACS Chem. Biol., **3** (2), 89–91

Dennis Bray^{†,*} and Dudley Williams

The motile response of *Escherichia coli* bacteria to attractants and repellents is one of the best-understood examples of a signal transduction pathway. A number of recent studies suggest that the receptors in this system undergo major changes in both their degree of structural order and their state of aggregation in the membrane. We discuss the thermodynamic basis for this effect and argue that the “freezing” or “melting” of protein structure may be the language of signaling.

Reprogramming the Translation Initiation for the Synthesis of Physiologically Stable Cyclic Peptides

ACS Chem. Biol., **3** (2), 120–129

Yuki Goto, Atsushi Ohta, Yusuke Sako, Yusuke Yamagishi, Hiroshi Murakami[†], and Hiroaki Suga

The initiation codon dictates that the translation initiation event exclusively begins with methionine. We report here a new technology to reprogram the initiation event, where various amino acids and those bearing $N\alpha$ -acyl groups can be used as an initiator for peptide synthesis. The technology is built upon the concept of genetic code reprogramming, where methionine is depleted from the translation system and the initiation codon is reassigned to the desired amino acid. We have applied this technology to the synthesis of an antitumor cyclic peptide, G7–18NATE, closed by a physiologically stable bond, and it is also extended to the custom synthesis of its analogues with various ring sizes. Significantly, cyclization occurs spontaneously upon translation of the precursor linear peptides. To demonstrate the practicality of this methodology, we also prepared a small cyclic peptide library designated by 160 distinct mRNAs. Thus, this technology offers a new means to prepare a wide array of *in vivo* compatible cyclic peptide libraries for the discovery of peptidic drug candidates against various therapeutic targets.

Chemistry and Biology

An Engineered Protein Tag for Multiprotein Labeling in Living Cells

Volume 15, issue 2 , 22 February 2008, Pages 128-136

Arnaud Gautier, Alexandre Juillerat, Christian Heinis, Ivan Reis Corrêa Jr., Maik Kindermann, Florent Beaufils and Kai Johnsson

The visualization of complex cellular processes involving multiple proteins requires the use of spectroscopically distinguishable fluorescent reporters. We have previously introduced the SNAP-tag as a general tool for the specific labeling of SNAP-tag fusion proteins in living cells. The SNAP-tag is derived from the human DNA repair protein O6-alkylguanine-DNA alkyltransferase (AGT) and can be covalently labeled in living cells using O6-benzylguanine derivatives bearing a chemical probe. Here we report the generation of an AGT-based tag, named CLIP-tag, which reacts specifically with O2-benzylcytosine derivatives. Because SNAP-tag and CLIP-tag possess orthogonal substrate specificities, SNAP and CLIP fusion proteins can be labeled simultaneously and specifically with different molecular probes in living cells. We furthermore show simultaneous pulse-chase experiments to visualize different generations of two different proteins in one sample.

Chemical Biology and Drug Design

Rhodanine Derivatives as Selective Protease Inhibitors Against Bacterial Toxins

Chem Biol Drug Des 2008; 71: 131–139

Sherida L. Johnson¹, Li-Hsing Chen¹, Rebecca Harbach¹, Mojgan Sabet², Alexei Savinov¹, Naomi J. H. Cotton¹, Alex Strongin¹, Donald Guiney² and Maurizio Pellecchia

In this study, we analyzed a series of rhodanine derivatives, as potential inhibitors of bacterial toxins, namely the proteases anthrax lethal factor and the botulinum neurotoxin type A. Conducting an extensive structure–activity relationship study on rhodanine derivatives, we profiled their selectivity against the two bacterial toxins and two related human metalloproteases using in vitro assays. In addition, we examined initial in vitro ADME-Tox properties of selected compounds and their ability to protect lethal factor-induced cell death of macrophages. These data allowed the selection of one additional drug candidate for which preliminary in vivo efficacy studies against anthrax spores were conducted. Integration of these results with our structure–activity relationship studies provides a framework for the development of potential drug candidates against anthrax and botulinum.

A Structural Informatics Study on Collagen

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Sorana D. Bolboacă^{1,*} and Lorentz Jantschi²

The study integrates knowledge resulting from structure–activity relationships analysis of amino acids with respect to the characterization of $\alpha 1$ and $\alpha 2$ type I collagen chains. Specifically, 15 amino acids and 14 properties were investigated and their structure–activity relationship models were obtained. The models were integrated into a web application and were used to predict the properties of a set of six amino acids. The

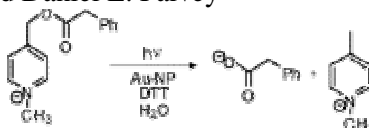
similarities in $\alpha 1$ and $\alpha 2$ type I collagen chains has been investigated starting from the observed and predicted properties of amino acids by using two-step cluster analysis screening.

Organic Letters

Photorelease of Carboxylic Acids Mediated by Visible-Light-Absorbing Gold-Nanoparticles

Org. Lett., 10 (3), 457 -460, 2008.

J. Brian Borak, Susana López-Sola, and Daniel E. Falvey*



Visible-light-absorbing citrate-stabilized gold nanoparticles and tryptophan-dithiane-conjugate-stabilized gold nanoparticles have been used to mediate electron transfer between dithiothreitol (DTT), a good electron donor, and an N-methylpicolinium ester in aqueous solution. Quantitative yield of the free carboxylate has been obtained with quantum yields of release, Φ_{rel} , ranging from 0.5 to 4.5.

Supramolecular Helix of an Amphiphilic Pyrene Derivative Induced by Chiral Tryptophan through Electrostatic Interactions

Org. Lett., 10 (4), 645 -648, 2008.

Jinchong Xiao, Jialiang Xu, Shuang Cui, Huibiao Liu, Shu Wang, and Yuliang Li



An amphiphilic pyrene derivative (PyDNH₃) bearing positively charged ammonium cations has been synthesized and characterized. Self-assembly of PyDNH₃ in the presence of chiral tryptophan derivatives was investigated in ethanol/water by optical and chiroptical spectra, indicating the formation of helical aggregates. Scanning electron microscope (SEM) images showed the formation of ring-shape structures.