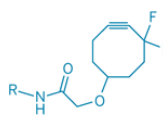


Chmielewski Group Literature Abstracts

CHEMISTRY

BIOLOGY

October 2007



R = fluorescent dye or biotin

Copper-Free Click Chemistry

Reagent for labeling biomolecules eliminates need for toxic metal catalyst A new reagent developed by chemistry professor [Carolyn R. Bertozzi](#) and coworkers at the University of California, Berkeley, eliminates the toxicity usually associated with a rapid and irreversible reaction strategy commonly known as "click chemistry" (PNAS). This tweak to remove copper catalysts makes the reaction, azide-alkyne cycloaddition, biologically friendly and thus useful for labeling biomolecules in cells. Copper-free click chemistry labels cell surface carbohydrates (green), which then move inside the cell. The reagent helps Bertozzi and her team study dynamic biochemical processes that are otherwise difficult to follow in real time. Bertozzi is particularly interested in studying glycosylation, the addition of sugar molecules to proteins. The reaction is tough to track because the sugar molecules, or glycans, are continuously recycled. "Most imaging of carbohydrates uses fixed systems," says Jeremy M. Baskin, a grad student in Bertozzi's lab and lead author of the report. "You can take a snapshot, but you can't make the equivalent of a movie." Azides make a handy tag for labeling biomolecules. They don't react with other molecules in the system, and they can be added to a range of biomolecules, including sugars, lipids, and proteins. Unfortunately, the two reactions most commonly used to affix fluorescent or other labels to azide-tagged biomolecules have limitations. The Staudinger ligation, which forms an amide bond between the azide and an ester-derivatized phosphine, is too slow. Azide-alkyne cycloaddition is much faster, but the conventional copper catalysts required are toxic to living systems.

Contributing Editors:

Stefan Hershberger (*Science*)

Marcos Pires (*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

Protein-based peptide-bond formation by aminoacyl-tRNA protein transferase

Nature **449**, 867-871 (18 October 2007)

Kazunori Watanabe^{1,3}, Yukimatsu Toh^{1,3}, Kyoko Suto¹, Yoshihiro Shimizu², Natsuhisa Oka², Takeshi Wada² & Kozo Tomita

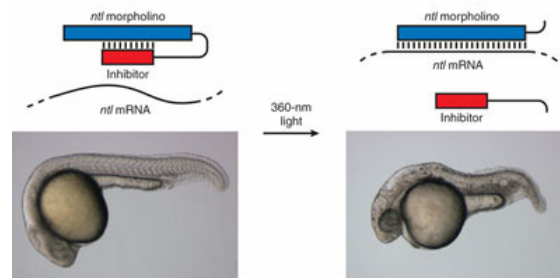
Eubacterial leucyl/phenylalanyl-tRNA protein transferase (LF-transferase) catalyses peptide-bond formation by using Leu-tRNA^{Leu} (or Phe-tRNA^{Phe}) and an amino-terminal Arg (or Lys) of a protein, as donor and acceptor substrates, respectively. However, the catalytic mechanism of peptide-bond formation by LF-transferase remained obscure. Here we determine the structures of complexes of LF-transferase and phenylalanyl adenosine, with and without a short peptide bearing an N-terminal Arg. Combining the two separate structures into one structure as well as mutation studies reveal the mechanism for peptide-bond formation by LF-transferase. The electron relay from Asp 186 to Gln 188 helps Gln 188 to attract a proton from the alpha-amino group of the N-terminal Arg of the acceptor peptide. This generates the attacking nucleophile for the carbonyl carbon of the aminoacyl bond of the aminoacyl-tRNA, thus facilitating peptide-bond formation. The protein-based mechanism for peptide-bond formation by LF-transferase is similar to the reverse reaction of the acylation step observed in the peptide hydrolysis reaction by serine proteases.

Nature Chemical Biology

Light-controlled gene silencing in zebrafish embryos

Nature Chemical Biology **3**, 650-651 (2007)

Ilya A Shestopalov^{1,3}, Surajit Sinha^{1,2,3} & James K Chen

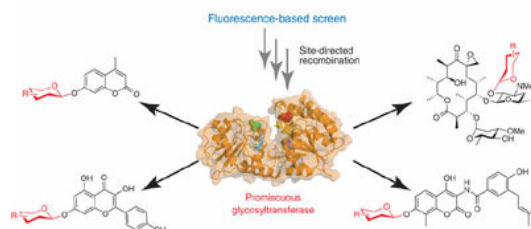


Functional genomic studies in zebrafish frequently use synthetic oligonucleotides called morpholinos that block RNA splicing or translation. However, the constitutive activity of these reagents limits their experimental utility. We report here the synthesis of a photoactivatable morpholino targeting the no tail (ntl) gene. This caged reagent permits spatiotemporal gene regulation in vivo and the photochemical generation of functionally mosaic organisms.

Expanding the promiscuity of a natural-product glycosyltransferase by directed evolution

Nature Chemical Biology 3, 657-662 (2007)

Gavin J Williams¹, Changsheng Zhang¹ & Jon S Thorson

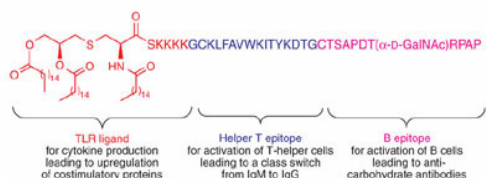


Natural products, many of which are decorated with essential sugar residues, continue to serve as a key platform for drug development¹. Adding or changing sugars attached to such natural products can improve the parent compound's pharmacological properties, specificity at multiple levels², and/or even the molecular mechanism of action³. Though some natural-product glycosyltransferases (GTs) are sufficiently promiscuous for use in altering these glycosylation patterns, the stringent specificity of others remains a limiting factor in natural-product diversification and highlights a need for general GT engineering and evolution platforms. Herein we report the use of a simple high-throughput screen based on a fluorescent surrogate acceptor substrate to expand the promiscuity of a natural-product GT via directed evolution. Cumulatively, this study presents variant GTs for the glycorandomization of a range of therapeutically important acceptors, including aminocoumarins, flavonoids and macrolides, and a potential template for engineering other natural-product GTs.

Robust immune responses elicited by a fully synthetic three-component vaccine

Nature Chemical Biology 3, 663-667 (2007)

Sampat Ingale¹, Margreet A Wolfert¹, Jidnyasa Gaekwad¹, Therese Buskas¹ & Geert-Jan Boons



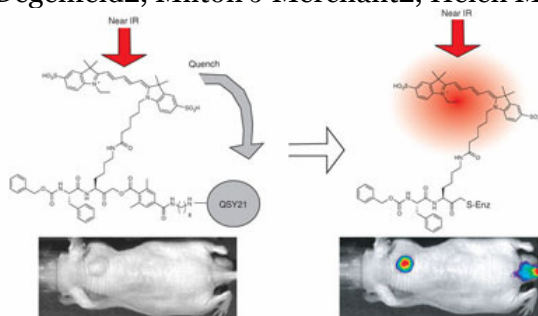
The overexpression of saccharides such as Globo-H, LewisY and Tn antigen is a common feature of oncogenic transformed cells. Endeavors to exploit this aberrant glycosylation for cancer vaccine development have been complicated by difficulties in eliciting high titers of IgG antibodies against classical conjugates of tumor-associated carbohydrates to carrier proteins. We have designed, chemically synthesized and immunologically evaluated a number of fully synthetic vaccine candidates to establish strategies to overcome the poor immunogenicity of tumor-associated carbohydrates and

glycopeptides. We have found that a three-component vaccine composed of a TLR2 agonist, a promiscuous peptide T-helper epitope and a tumor-associated glycopeptide can elicit in mice exceptionally high titers of IgG antibodies that can recognize cancer cells expressing the tumor-associated carbohydrate. The superior properties of the vaccine candidate are attributed to the local production of cytokines, upregulation of co-stimulatory proteins, enhanced uptake by macrophages and dendritic cells and avoidance of epitope suppression.

Noninvasive optical imaging of cysteine protease activity using fluorescently quenched activity-based probes

Nature Chemical Biology **3**, 668-677 (2007)

Galia Blum¹, Georges von Degenfeld², Milton J Merchant², Helen M Blau² & Matthew Bogoy



We have generated a series of quenched near-infrared fluorescent activity-based probes (qNIRF-ABPs) that covalently target the papain-family cysteine proteases shown previously to be important in multiple stages of tumorigenesis. These 'smart' probes emit a fluorescent signal only after covalently modifying a specific protease target. After intravenous injection of NIRF-ABPs into mice bearing grafted tumors, noninvasive, whole-body imaging allowed direct monitoring of cathepsin activity. Importantly, the permanent nature of the probes also allowed secondary, ex vivo biochemical profiling to identify specific proteases and to correlate their activity with whole-body images. Finally, we demonstrate that these probes can be used to monitor small-molecule inhibition of protease targets both biochemically and by direct imaging methods. Thus, NIRF-ABPs are (i) potentially valuable new imaging agents for disease diagnosis and (ii) powerful tools for preclinical and clinical testing of small-molecule therapeutic agents in vivo.

Nature Materials

In vivo imaging of hydrogen peroxide with chemiluminescent nanoparticles

Nature Materials **6**, 765 - 769 (2007)

Dongwon Lee^{1,5}, Sirajud Khajai^{1,5}, Juan C. Velasquez-Castano², Madhuri Dasari¹, Carrie Sun³, John Petros^{3,4}, W. Robert Taylor^{1,2,4} & Niren Murthy

The overproduction of hydrogen peroxide is implicated in the development of numerous diseases^{1, 2, 3, 4} and there is currently great interest in developing contrast agents that

can image hydrogen peroxide in vivo. In this report, we demonstrate that nanoparticles formulated from peroxalate esters and fluorescent dyes can image hydrogen peroxide in vivo with high specificity and sensitivity. The peroxalate nanoparticles image hydrogen peroxide by undergoing a three-component chemiluminescent reaction between hydrogen peroxide, peroxalate esters and fluorescent dyes. The peroxalate nanoparticles have several attractive properties for in vivo imaging, such as tunable wavelength emission (460–630 nm), nanomolar sensitivity for hydrogen peroxide and excellent specificity for hydrogen peroxide over other reactive oxygen species. The peroxalate nanoparticles were capable of imaging hydrogen peroxide in the peritoneal cavity of mice during a lipopolysaccharide-induced inflammatory response. We anticipate numerous applications of peroxalate nanoparticles for in vivo imaging of hydrogen peroxide, given their high specificity and sensitivity and deep-tissue-imaging capability.

Nature Nanotechnology

A virus-based single-enzyme nanoreactor

***Nature Nanotechnology* 2, 635 - 639 (2007)**

Marta Comellas-Aragonès¹, Hans Engelkamp¹, Victor I. Claessen¹, Nico A. J. M. Sommerdijk², Alan E. Rowan¹, Peter C. M. Christianen¹, Jan C. Maan¹, Benedictus J. M. Verduin³, Jeroen J. L. M. Cornelissen¹ & Roeland J. M. Nolte

Most enzyme studies are carried out in bulk aqueous solution, at the so-called ensemble level, but more recently studies have appeared in which enzyme activity is measured at the level of a single molecule, revealing previously unseen properties^{1, 2, 3, 4}. To this end, enzymes have been chemically or physically anchored to a surface, which is often disadvantageous because it may lead to denaturation. In a natural environment, enzymes are present in a confined reaction space, which inspired us to develop a generic method to carry out single-enzyme experiments in the restricted spatial environment of a virus capsid. We report here the incorporation of individual horseradish peroxidase enzymes in the inner cavity of a virus, and describe single-molecule studies on their enzymatic behaviour. These show that the virus capsid is permeable for substrate and product and that this permeability can be altered by changing pH.

Science

Target Protectors Reveal Dampening and Balancing of Nodal Agonist and Antagonist by miR-430

***Science* Vol 318, Issue 5848, 271-274, 12 October 2007**

Wen-Yee Choi,^{1,2} Antonio J. Giraldez,^{1,3*} Alexander F. Schier^{1*}

MicroRNAs (miRNAs) repress hundreds of target messenger RNAs (mRNAs), but the physiological roles of specific miRNA-mRNA interactions remain largely elusive. We report that zebrafish microRNA-430 (miR-430) dampens and balances the expression of the transforming growth factor- β (TGF- β) Nodal agonist *squint* and the TGF- β Nodal antagonist *lefty*. To disrupt the interaction of specific miRNA-mRNA pairs, we

developed target protector morpholinos complementary to miRNA binding sites in target mRNAs. Protection of squint or lefty mRNAs from miR-430 resulted in enhanced or reduced Nodal signaling, respectively. Simultaneous protection of squint and lefty or absence of miR-430 caused an imbalance and reduction in Nodal signaling. These findings establish an approach to analyze the in vivo roles of specific miRNA-mRNA pairs and reveal a requirement for miRNAs in dampening and balancing agonist/antagonist pairs.

Structure of a Thiol Monolayer-Protected Gold Nanoparticle at 1.1 Å Resolution

Science Vol 318, Issue 5849, 430-433, 19 October 2007

Pablo D. Jadzinsky,^{1,2*} Guillermo Calero,^{1*} Christopher J. Ackerson,¹ David A. Bushnell,¹ Roger D. Kornberg

Structural information on nanometer-sized gold particles has been limited, due in part to the problem of preparing homogeneous material. Here we report the crystallization and x-ray structure determination of a p-mercaptobenzoic acid (p-MBA)-protected gold nanoparticle, which comprises 102 gold atoms and 44 p-MBAs. The central gold atoms are packed in a Marks decahedron, surrounded by additional layers of gold atoms in unanticipated geometries. The p-MBAs interact not only with the gold but also with one another, forming a rigid surface layer. The particles are chiral, with the two enantiomers alternating in the crystal lattice. The discrete nature of the particle may be explained by the closing of a 58-electron shell.

Nanomechanical Basis of Selective Gating by the Nuclear Pore Complex

Science Vol 318, Issue 5850, 640-643, 26 October 2007

Roderick Y. H. Lim,^{1*} Birthe Fahrenkrog,^{1*} Joachim Köser,¹ Kyrill Schwarz-Herion,¹ Jie Deng,² Ueli Aebi

The nuclear pore complex regulates cargo transport between the cytoplasm and the nucleus. We set out to correlate the governing biochemical interactions to the nanoscopic responses of the phenylalanineglycine (FG)-rich nucleoporin domains, which are involved in attenuating or promoting cargo translocation. We found that binding interactions with the transport receptor karyopherin- β 1 caused the FG domains of the human nucleoporin Nup153 to collapse into compact molecular conformations. This effect was reversed by the action of Ran guanosine triphosphate, which returned the FG domains into a polymer brush-like, entropic barrier conformation. Similar effects were observed in *Xenopus* oocyte nuclei in situ. Thus, the reversible collapse of the FG domains may play an important role in regulating nucleocytoplasmic transport.

A Linear Pentapeptide Is a Quorum-Sensing Factor Required for mazEF-Mediated Cell Death in *Escherichia coli*

Science Vol 318, Issue 5850, 652-655, 26 October 2007

Ilana Kolodkin-Gal,¹ Ronen Hazan,^{1*} Ariel Gaathon,² Shmuel Carmeli,³ Hanna Engelberg-Kulka

mazEF is a toxin-antitoxin module located on many bacterial chromosomes, including those of pathogens. Here, we report that *Escherichia coli* mazEF-mediated cell death is a population phenomenon requiring a quorum-sensing molecule that we call the extracellular death factor (EDF). Structural analysis revealed that EDF is a linear pentapeptide, Asn-Asn-Trp-Asn-Asn. Each of the five amino acids of EDF is important for its activity.

PNAS

A functional single-molecule binding assay via force spectroscopy

***PNAS* | October 2, 2007 | vol. 104 | no. 40 | 15677-15681**

Yi Cao, M. M. Balamurali, Deepak Sharma, and Hongbin Li

Protein–ligand interactions, including protein–protein interactions, are ubiquitously essential in biological processes and also have important applications in biotechnology. A wide range of methodologies have been developed for quantitative analysis of protein–ligand interactions. However, most of them do not report direct functional/structural consequence of ligand binding. Instead they only detect the change of physical properties, such as fluorescence and refractive index, because of the colocalization of protein and ligand, and are susceptible to false positives. Thus, important information about the functional state of protein–ligand complexes cannot be obtained directly. Here we report a functional single-molecule binding assay that uses force spectroscopy to directly probe the functional consequence of ligand binding and report the functional state of protein–ligand complexes. As a proof of principle, we used protein G and the Fc fragment of IgG as a model system in this study. Binding of Fc to protein G does not induce major structural changes in protein G but results in significant enhancement of its mechanical stability. Using mechanical stability of protein G as an intrinsic functional reporter, we directly distinguished and quantified Fc-bound and Fc-free forms of protein G on a single-molecule basis and accurately determined their dissociation constant. This single-molecule functional binding assay is label-free, nearly background-free, and can detect functional heterogeneity, if any, among protein–ligand interactions. This methodology opens up avenues for studying protein–ligand interactions in a functional context, and we anticipate that it will find broad application in diverse protein–ligand systems.

Adaptations of guest and host in expanded self-assembled capsules

***PNAS* | October 9, 2007 | vol. 104 | no. 41 | 16000-16003**

Dariush Ajami and Julius Rebek, Jr.*

Reversible encapsulation complexes create spaces where two or more molecules can be temporarily isolated. When the mobility of encapsulated molecules is restricted, different arrangements in space are possible, and new forms of isomerism ("social

isomerism") are created: the orientation of one encapsulated molecule influences that of the other in the confined space. Expansion of a capsule's length is possible through addition of small-molecule spacer elements. The expanded capsules have dimensions that permit the observation of social isomerism of two identical guests, and they adopt arrangements that properly fill the host's space. The host also can adapt to longer guests by incorporating additional spacers, much as protein modules are added to a viral capsid in response to larger genomes. Arachidonic and related fatty acid derivatives act in this way to induce the assembly of further extended capsules having sufficient length to accommodate them.

3'-O-modified nucleotides as reversible terminators for pyrosequencing

PNAS | **October 16, 2007** | *vol. 104* | *no. 42* | **16462-16467**

Shundi Shi*, Dae Hyun Kim*, , Lanrong Bi*, , Nicholas J. Turr ,, and Jingyue Ju

Pyrosequencing is a method used to sequence DNA by detecting the pyrophosphate (PPi) group that is generated when a nucleotide is incorporated into the growing DNA strand in polymerase reaction. However, this method has an inherent difficulty in accurately deciphering the homopolymeric regions of the DNA templates. We report here the development of a method to solve this problem by using nucleotide reversible terminators. These nucleotide analogues are modified with a reversible chemical moiety capping the 3'-OH group to temporarily terminate the polymerase reaction. In this way, only one nucleotide is incorporated into the growing DNA strand even in homopolymeric regions. After detection of the PPi for sequence determination, the 3'-OH of the primer extension products is regenerated through different deprotection methods. Using an allyl or a 2-nitrobenzyl group as the reversible moiety to cap the 3'-OH of the four nucleotides, we have synthesized two sets of 3'-O-modified nucleotides, 3'-O-allyl-dNTPs and 3'-O-(2-nitrobenzyl)-dNTPs as reversible terminators for pyrosequencing. The capping moiety on the 3'-OH of the DNA extension product is efficiently removed after PPi detection by either a chemical method or photolysis. To sequence DNA, templates containing homopolymeric regions are immobilized on Sepharose beads, and then extension–signal detection–deprotection cycles are conducted by using the nucleotide reversible terminators on the DNA beads to unambiguously decipher the sequence of DNA templates. Our results establish that this reversible-terminator-pyrosequencing approach can be potentially developed into a powerful methodology to accurately determine DNA sequences.

A small-molecule therapeutic lead for Huntington's disease: Preclinical pharmacology and efficacy of C2-8 in the R6/2 transgenic mouse

PNAS | **October 16, 2007** | *vol. 104* | *no. 42* | **16685-16689**

David E. Housman,||, Aleksey Kazantsev*, Anne B. Young*, and Steven Hersch

Huntington's disease (HD) is a progressive neurodegenerative disease caused by a glutamine expansion within huntingtin protein. The exact pathological mechanisms

determining disease onset and progression remain unclear. However, aggregates of insoluble mutant huntingtin (mhtt), a hallmark of HD, are readily detected within neurons in HD brain. Although aggregated polyglutamines may not be inherently toxic, they constitute a biomarker for mutant huntingtin useful for developing therapeutics. We previously reported that the small molecule, C2-8, inhibits polyglutamine aggregation in cell culture and brain slices and rescues degeneration of photoreceptors in a *Drosophila* model of HD. In this study, we assessed the therapeutic potential of C2-8 in the R6/2 mouse model of HD, which has been used to provide proof-of-concept data in considering whether to advance therapies to human HD. We show that, at nontoxic doses, C2-8 penetrates the blood–brain barrier and is present in brain at a high concentration. C2-8-treated mice showed improved motor performance and reduced neuronal atrophy and had smaller huntingtin aggregates. There have been no prior drug-like, non-toxic, brain-penetrable aggregation inhibitors to arise from cell-based high-throughput screens for reducing huntingtin aggregation that is efficacious in preclinical *in vivo* models. C2-8 provides an essential tool to help elucidate mechanisms of neurodegeneration in HD and a therapeutic lead for further optimization and development.

Copper-free click chemistry for dynamic *in vivo* imaging

***PNAS* | October 23, 2007 | vol. 104 | no. 43 | 16787-16792**

Jennifer A. Prescher*, Scott T. Laughlin*, Nicholas J. Agard*, Pamela V. Chang*, Isaac A. Miller*, Anderson Lo*, Julian A. Codelli*, and Carolyn R. Bertozzi

Dynamic imaging of proteins in live cells is routinely performed by using genetically encoded reporters, an approach that cannot be extended to other classes of biomolecules such as glycans and lipids. Here, we report a Cu-free variant of click chemistry that can label these biomolecules rapidly and selectively in living systems, overcoming the intrinsic toxicity of the canonical Cu-catalyzed reaction. The critical reagent, a substituted cyclooctyne, possesses ring strain and electron-withdrawing fluorine substituents that together promote the [3 + 2] dipolar cycloaddition with azides installed metabolically into biomolecules. This Cu-free click reaction possesses comparable kinetics to the Cu-catalyzed reaction and proceeds within minutes on live cells with no apparent toxicity. With this technique, we studied the dynamics of glycan trafficking and identified a population of sialoglycoconjugates with unexpectedly rapid internalization kinetics.

Potent D-peptide inhibitors of HIV-1 entry

***PNAS* | October 23, 2007 | vol. 104 | no. 43 | 16828-16833**

Andrew P. VanDemark*, Annie Heroux, Christopher P. Hill*, and Michael S. Kay*,

During HIV-1 entry, the highly conserved gp41 N-trimer pocket region becomes transiently exposed and vulnerable to inhibition. Using mirror-image phage display and structure-assisted design, we have discovered protease-resistant D-amino acid peptides (D-peptides) that bind the N-trimer pocket with high affinity and potently inhibit viral entry. We also report high-resolution crystal structures of two of these D-peptides in

complex with a pocket mimic that suggest sources of their high potency. A trimeric version of one of these peptides is the most potent pocket-specific entry inhibitor yet reported by three orders of magnitude ($IC_{50} = 250$ pM). These results are the first demonstration that D-peptides can form specific and high-affinity interactions with natural protein targets and strengthen their promise as therapeutic agents. The D-peptides described here address limitations associated with current L-peptide entry inhibitors and are promising leads for the prevention and treatment of HIV/AIDS.

Probing polyproline structure and dynamics by photoinduced electron transfer provides evidence for deviations from a regular polyproline type II helix

PNAS | **October 30, 2007** | *vol. 104* | *no. 44* | **17400-17405**

Sören Doose*, Hannes Neuweiler, Hannes Barsch, and Markus Sauer

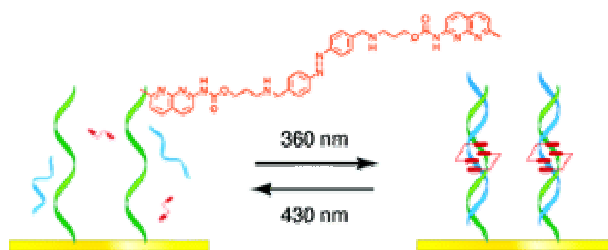
Polyprolines are well known for adopting a regular polyproline type II helix in aqueous solution, rendering them a popular standard as molecular ruler in structural molecular biology. However, single-molecule spectroscopy studies based on Förster resonance energy transfer (FRET) have revealed deviations of experimentally observed end-to-end distances of polyprolines from theoretical predictions, and it was proposed that the discrepancy resulted from dynamic flexibility of the polyproline helix. Here, we probe end-to-end distances and conformational dynamics of poly-L-prolines with 1–10 residues using fluorescence quenching by photoinduced-electron transfer (PET). A single fluorophore and a tryptophan residue, introduced at the termini of polyproline peptides, serve as sensitive probes for distance changes on the subnanometer length scale. Using a combination of ensemble fluorescence and fluorescence correlation spectroscopy, we demonstrate that polyproline samples exhibit static structural heterogeneity with subpopulations of distinct end-to-end distances that do not interconvert on time scales from nano- to milliseconds. By observing prolyl isomerization through changes in PET quenching interactions, we provide experimental evidence that the observed heterogeneity can be explained by interspersed cis isomers. Computer simulations elucidate the influence of trans/cis isomerization on polyproline structures in terms of end-to-end distance and provide a structural justification for the experimentally observed effects.

Journal of the American Chemical Society

Photoswitchable Molecular Glue for DNA

J. Am. Chem. Soc., **2007**, *129* (39), **11898-11899**

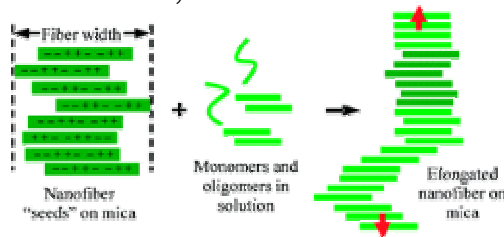
Chikara Dohno, Shin-nosuke Uno, and Kazuhiko Nakatani



DNA molecular glue is a small synthetic ligand that can adhere two single-stranded DNAs that do not spontaneously hybridize with each other. For reversible control of DNA hybridization by an external light stimulus, we have developed a photoswitchable molecular glue for DNA. The photoswitchable molecular glue, NCDA, consists of two guanine-recognizing naphthyridine moieties connected with a photochromic azobenzene unit. Azobenzene undergoes a reversible cis/trans isomerization by photoirradiation, which changes the relative orientations and positions of the naphthyridine moieties, resulting into photoswitching of NCDA binding to the DNA containing GG-mismatch. NCDA in the cis configuration binds to a GG-mismatch sequence and induces the formation of the DNA duplex. Using the photoswitchable binding property of NCDA, the hybridization event of two natural unmodified DNAs can be reversibly controlled by an external light stimulus.

Surface-Assisted Assembly of an Ionic-Complementary Peptide: Controllable Growth of Nanofibers

J. Am. Chem. Soc., 2007, 129 (40), 12200 -12210
 Hong Yang, Shan-Yu Fung, Mark Pritzker, and P. Chen



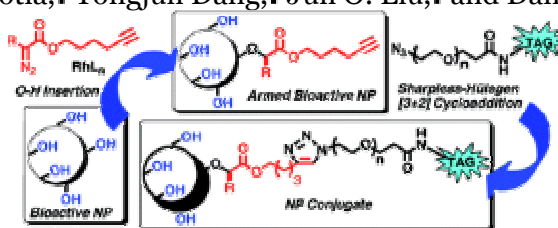
Numerous studies have shown that a surface can direct and regulate molecular assembly. In this study, the nanofiber growth of an ionic-complementary peptide, EAK16-II, on a mica surface was investigated under various solution conditions via in situ atomic force microscopy. In comparison to the assembly in bulk solution, nanofiber growth of EAK16-II on mica is surface-assisted and involves two steps: (1) adsorption of nanofibers and fiber clusters (from the bulk solution) on the surface, serving as the "seeds"; (2) fiber elongation of the "seeds" from their active ends. The nanofiber growth can be controlled by adjusting the solution pH since it modulates the adsorption of the "seeds" on mica and their growth rates. The amount of the adsorbed "seeds" decreases with increasing solution pH, while the growth rate under different solution conditions is found to follow the order pure water > 1 mM HCl > 1 mM NaOH > 10 mM HCl \approx 10 mM NaOH \approx 0. The pH-dependent nanofiber growth is due to the surface charge of the peptides and peptide assemblies in various solutions as indicated by ζ -potential measurements. A simple model was proposed to describe surface-assisted nanofiber growth. This study provides insights into the assembly of peptide/protein on a surface, which is essential to understand such physiological protein aggregation systems as

amyloid fibrillogenesis. In addition, the potential of this finding to construct biocompatible electrodes for biomolecular sensing is also discussed.

Activity Studies of Natural Products Employing O-H Insertions: An Expedient and Versatile Strategy for Natural Products-Based Chemical Genetics

J. Am. Chem. Soc., 2007, 129 (40), 12222 -12231

Satyamaheshwar Peddibhotla,[†] Yongjun Dang,[‡] Jun O. Liu,[†] and Daniel Romo

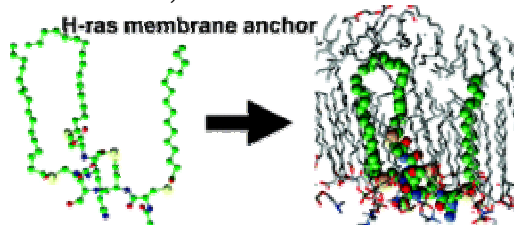


The identification of "druggable" targets is an immediate opportunity and challenge in the post-genomic era. Natural products are enduring tools for basic cellular studies and leads for identifying medically relevant protein targets. However, their use for these studies is often hampered by limited quantities and a lack of selective and mild monofunctionalization reactions. The development of selective methods that could simultaneously equip the natural product with a reactive group for subsequent conjugation to reporter tags and provide important structure-activity relationship (SAR) information, requiring only a knowledge of functional groups present in the natural product, could significantly decrease the time between bioactive natural product isolation and target identification. Herein, we report such a strategy that enables simultaneous arming and SAR studies of alcohol-containing natural products involving both chemo- and site-selective ("chemosite" selective) and site-nonspecific O-H insertion reactions with rhodium carbenoids derived from alkynyl diazo acetates. This strategy was applied to a diverse set of natural products, and general guidelines for predicting chemosite selectivity were formulated. A subsequent Sharpless-Huisgen [3 + 2] cycloaddition reaction with the appended alkyne allows for attachment of a variety of reporter tags. Using this strategy, we synthesized a novel FK506-biotin conjugate that enabled pull-down of the entire "immunosuppressive complex" including FKBP12, calcineurins A and B, and calmodulin. In addition, the potential for a chemoselective but site-nonspecific process was shown with both gibberellic acid methyl ester and brefeldin A using only achiral rhodium catalysts.

H-ras Protein in a Bilayer: Interaction and Structure Perturbation

J. Am. Chem. Soc., 2007, 129 (40), 12280 -12286

Alemayehu A. Gorfe,^{*†} Arneh Babakhani,[†] and J. Andrew McCammon

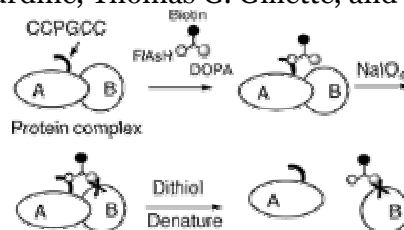


Ras GTPases become functionally active when anchored to membranes by inserting their lipid modified side chains. Their role in cell division, development, and cancer has made them targets of extensive research efforts, yet the mechanism of membrane insertion and the structure of the resulting complex remain elusive. Recently, the structure of the full-length H-ras protein in a DMPC bilayer has been computationally characterized. Here, the atomic interactions between the H-ras membrane anchor and the DMPC bilayer are investigated in detail. We find that the palmitoylated cysteines and Met182 have dual contributions to membrane affinity: hydrogen bonding by their amides and van der Waals interaction by their hydrophobic side chains. The polar side chains help maintain the orientation of the anchor. Although the overall structure of the bilayer is similar to that of a pure DMPC, there are localized perturbations. These perturbations depend on the insertion depth and backbone localization of the anchor, which in turn is modulated by the catalytic domain and the linker. The pattern of anchor amide-DMPC phosphate/carbonyl hydrogen bonds and the flexibility of Palm184 are important in discriminating between different modes of ras-DMPC interactions. The results provide structural arguments in support of the proposed participation of ras in the organization of membrane nanoclusters.

Label Transfer Chemistry for the Characterization of Protein-Protein Interactions

J. Am. Chem. Soc., 2007, 129 (41), 12348 -12349

Bo Liu, Chase T. Archer, Lyle Burdine, Thomas G. Gillette, and Thomas Kodadek

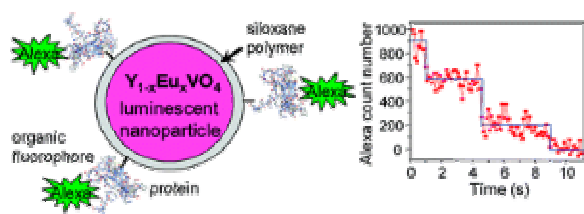


A new label transfer method is presented that overcomes most of the limitations of current systems. A protein of interest is tagged with a tetracysteine sequence (FlAsH receptor peptide (FRP)) that binds tightly and specifically to a chimeric molecule 3,4-dihydroxyphenylalanine-biotin-4',5'-bis(1,3,2-dithioarsolan-2-yl)fluorescein (DOPA-biotin-FlAsH). Upon brief periodate oxidation, the DOPA moiety is cross-linked to nearby surface-exposed nucleophiles. Boiling the products in excess dithiol dissolves the FlAsH-FRP interaction, resulting in transfer of the biotin tag to the partner proteins, allowing them to be identified by standard methods.

Counting the Number of Proteins Coupled to Single Nanoparticles

J. Am. Chem. Soc., 129 (42), 12592 -12593, 2007.

Didier Casanova,[†] Domitille Giaume,[‡] Mélanie Moreau,[‡] Jean-Louis Martin,[†] Thierry Gacoin,[‡] Jean-Pierre Boilot,[‡] and Antigoni Alexandrou

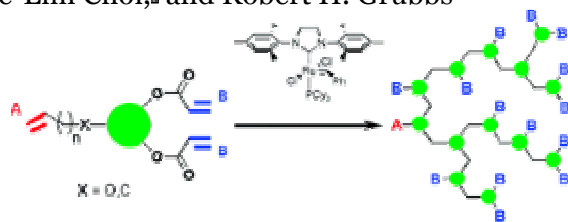


We implemented amine coating of lanthanide-ion doped oxide luminescent nanoparticles and coupling to a protein labeled with an organic fluorophore. We exploited the stepwise photobleaching of the organic fluorophores and their initial emission to count the number of proteins coupled to single nanoparticles. We thus precisely measured the distribution of the protein-nanoparticle ratio and showed that its maximum is different from the average ratio determined from ensemble measurements. The accurate quantification of the biomolecule-particle coupling opens up the possibility of selecting finely controlled conjugates.

Hyperbranched Macromolecules via Olefin Metathesis

J. Am. Chem. Soc., **129** (42), 12672 -12673, 2007.

Irina A. Gorodetskaya, Tae-Lim Choi,¹ and Robert H. Grubbs

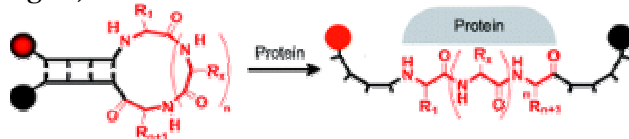


A facile route to hyperbranched polymers via acyclic diene metathesis is reported. Any molecule functionalized with two or more acrylate groups and one terminal olefin can serve as an AB_n monomer when exposed to an imidazolynylidene-based ruthenium olefin metathesis catalyst, due to the cross metathesis selectivity of this catalyst. For the polymers obtained by this method, both ¹H NMR spectroscopy and triple detector size exclusion chromatography conclusively indicate a branched architecture.

Dual-Labeled PNA-Peptide-Hybrids for Protein Detection

J. Am. Chem. Soc., **129** (42), 12693 -12695, 2007.

Stefanie Thurley, Lars Röglin, and Oliver Seitz*



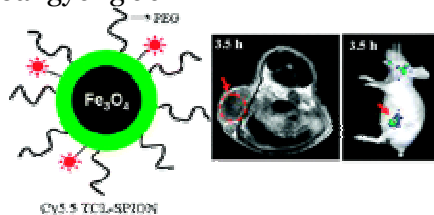
Probe molecules that report biomolecular interactions by changes of fluorescence properties are frequently used in drug screening, diagnostics, and cell biology. The predictability of nucleic acid-nucleic acid interaction has been a major driving force in the design of the powerful nucleic acid-based reporters that are available today. By comparison, the design of peptide-based probes that report on binding to (and dissociation from) specific protein targets by changes of fluorescence intensity is more challenging, owing to the lack of a universal peptide-protein recognition code. We herein introduce a new probe concept, in which protein binding is signaled by increases

of fluorescence. Hairpin peptide beacons (HPB) are dual labeled peptide probes designed to form stable hairpins in the absence of a protein target. HPBs are designed in analogy to DNA-targeted molecular beacons and consist of a central, protein specific peptide sequence flanked by two DNA-analogous self-complementary peptide nucleic acid (PNA) arm segments. Binding of the target protein to the peptide sequence induces a structural reorganization and results in opening of the closed structure. The accompanying separation of the terminally appended chromophores leads to increases of fluorescence. The particular advantage of the hairpin peptide beacons is the generic design which should be applicable to any protein that interacts with a peptide while allowing almost unrestricted access of interesting fluorophores. It is shown that hairpin peptide beacons signal the presence of the SH2 domain of the Src-kinase by more than 10-fold increases of fluorescence. Furthermore, the HPB concept has been used in the design of a noncleavable probe that reports on the activity of the protease renin. It is suggested that the reversibility of fluorescence signaling mediated by noncleavable probes may enable the continuous monitoring of both increases and decreases of protease activity.

Thermally Cross-Linked Superparamagnetic Iron Oxide Nanoparticles

J. Am. Chem. Soc., **129** (42), 12739 -12745, 2007.

Haerim Lee,[†] Mi Kyung Yu,[†] Sangjin Park,[†] Sungmin Moon,[‡] Jung Jun Min,[‡] Yong Yeon Jeong,^{*‡} Hae-Won Kang,[‡] and Sangyong Jon^{*†}



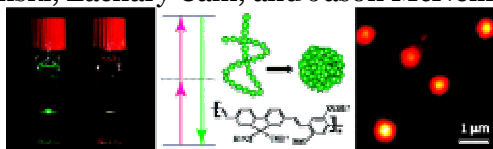
We report the fabrication and characterization of thermally cross-linked superparamagnetic iron oxide nanoparticles (TCL-SPION) and their application to the dual imaging of cancer in vivo. Unlike dextran-coated cross-linked iron oxide nanoparticles, which are prepared by a chemical cross-linking method, TCL-SPION are prepared by a simple, thermal cross-linking method using a Si-OH-containing copolymer. The copolymer, poly(3-(trimethoxysilyl)propyl methacrylate-*r*-PEG methyl ether methacrylate-*r*-N-acryloxysuccinimide), was synthesized by radical polymerization and used as a coating material for as-synthesized magnetite (Fe₃O₄) SPION. The polymer-coated SPION was further heated at 80 °C to induce cross-linking between the -Si(OH)₃ groups in the polymer chains, which finally generated TCL-SPION bearing a carboxyl group as a surface functional group. The particle size, surface charge, presence of polymer-coating layers, and the extent of thermal cross-linking were characterized and confirmed by various measurements, including dynamic light scattering, Fourier transform infrared spectroscopy, and X-ray photoelectron spectroscopy. The carboxyl TCL-SPION was converted to amine-modified TCL-SPION and then finally to Cy5.5 dye-conjugated TCL-SPION for use in dual (magnetic resonance/optical) in vivo cancer imaging. When the Cy5.5 TCL-SPION was administered to Lewis lung carcinoma tumor allograft mice by intravenous injection, the

tumor was unambiguously detected in T2-weighted magnetic resonance images as a 68% signal drop as well as in optical fluorescence images within 4 h, indicating a high level of accumulation of the nanomagnets within the tumor site. In addition, ex vivo fluorescence images of the harvested tumor and other major organs further confirmed the highest accumulation of the Cy5.5 TCL-SPION within the tumor. It is noteworthy that, despite the fact that TCL-SPION does not bear any targeting ligands on its surface, it was highly effective for tumor detection in vivo by dual imaging.

Conjugated Polymer Dots for Multiphoton Fluorescence Imaging

J. Am. Chem. Soc., **129** (43), 12904 -12905, 2007.

Changfeng Wu, Craig Szymanski, Zachary Cain, and Jason McNeill*

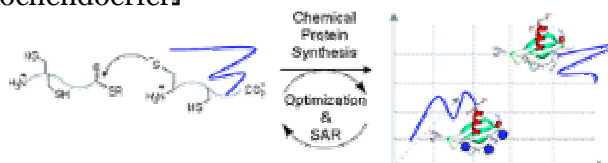


We report on the two-photon excited fluorescence of conjugated polymer dots (CPdots). As a new class of two-photon fluorescent probes, CPdots exhibit two-photon action cross sections as high as 2.0×10^5 GM, to our knowledge, the largest reported thus far for a nanoparticle. The cross section values are 3-4 orders of magnitude higher than those of conventional fluorescent dyes and an order of magnitude higher than those of inorganic quantum dots. Single particle fluorescence imaging was achieved using relatively low laser power.

A Chemical Approach to the Pharmaceutical Optimization of an Anti-HIV Protein

J. Am. Chem. Soc., **129** (43), 13153 -13159, 2007.

E. Neil Cagle, Maia Carnevali,[#] Alexander Lee, Di Song,[|] Ada Kung, James A. Bradburne, Xavier Paliard,[⊥] and Gerd G. Kochendoerfer[‡]



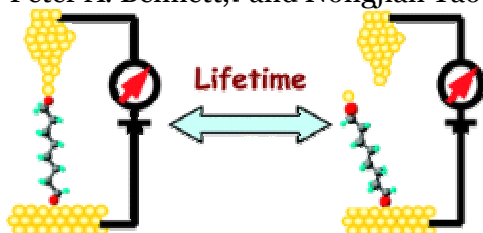
Chemical protein synthesis is important for dissecting the molecular basis of protein function. Here we advance its scope by demonstrating the significant improvement of the multifaceted pharmaceutical profile of small proteins exclusively via a chemical-based approach. The focus of this work centered on CCL-5 (RANTES) derivatives with potent anti-HIV activity. The overall chemical strategy involved a combination of coded and noncoded amino acid mutagenesis, peptide backbone engineering, and site-specific polymer attachment. The ability to alter specific protein residues, as well as precise control of the position and type of polymer attachment, allows for the exploration of specific molecular designs and resulted in novel CCL-5 analogues with significant differences in their respective biochemical and pharmaceutical properties. Using this approach, the complex-interplay of variables contributing to the noncovalent self-association (aggregation) state, CCR-5 specificity, in vivo elimination half-life, and anti-HIV activity of CCL-5-based protein analogues could be empirically evaluated via total

chemical synthesis. This work has led to the identification of potent (sub-nanomolar) anti-HIV proteins with significantly improved pharmaceutical profiles, and illustrates the increasing value of protein chemical synthesis in contemporary therapeutic discovery. These antiviral molecules provide a novel mechanism of action for the development of a new generation of anti-HIV therapeutics which are still desperately needed.

Single Molecule Junctions Formed via Au-Thiol Contact: Stability and Breakdown Mechanism

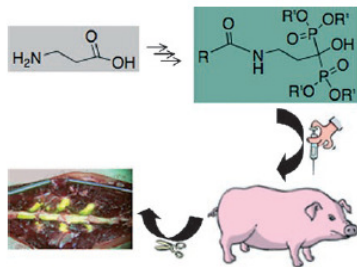
J. Am. Chem. Soc., 129 (43), 13225 -13231, 2007

Zhifeng Huang,[†] Fang Chen,[†] Peter A. Bennett,[‡] and Nongjian Tao



The stability and breakdown mechanism of a single molecule covalently bound to two Au electrodes via Au-S bonds were studied at room temperature. The distance over which a molecular junction can be stretched before breakdown was measured using a scanning tunneling microscopy break junction approach as a function of stretching rate. At low stretching rates, the stretching distance is small and independent of stretching rate. Above a certain stretching rate, it increases linearly with the logarithm of stretching rate. At very high stretching rates, the stretching distance reaches another plateau and becomes insensitive to the stretching rate again. The three regimes are well described by a thermodynamic bond-breaking model. A comparative study of Au-Au atomic point contacts indicates that the breakdown of the molecular junctions takes place at Au-Au bonds near the molecule-electrode contact. By fitting the experimental data with the model, the lifetime and binding energy were extracted. Both quantities are found to have broad distributions, owing to large variations in the molecule-electrode contact geometry. Although the molecular junctions are short-lived on average, certain contact geometries are considerably more stable. Several types of stochastic fluctuations were observed in the conductance of the molecule junctions, which are attributed to the atomic level rearrangement of the contact geometry, and bond breakdown and reformation processes. The possibility of bond reformation increases the apparent lifetime of the molecular junctions.

Angewandte Chemie



No fly in this oinkment: A targeted contrast agent allows real-time visualization of normal bones and hydroxyapatite crystals found in breast-cancer microcalcifications. Synthesis of the agent involves conjugation of a near-infrared fluorophore to methylester-protected pamidronate derivatives. Large-animal surgical models validate the effectiveness of the agent.

Contrast Agents

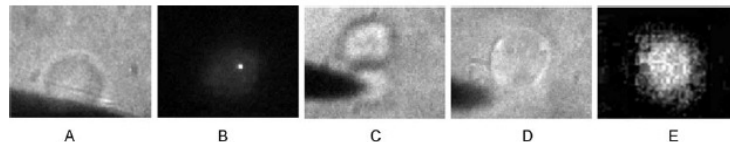
K. R. Bhushan, E. Tanaka,
J. V. Frangioni* _____ 7969–7971

Synthesis of Conjugatable
Bisphosphonates for Molecular Imaging
of Large Animals

Enzyme Catalysis

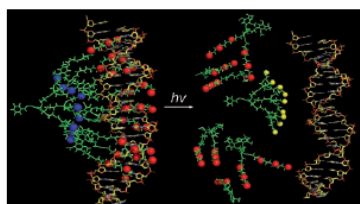
T.-M. Hsin, E. S. Yeung* _____ 8032–8035

Single-Molecule Reactions in Liposomes



Solitary confinement: Single-molecule reactions were initiated by trapping and fusing liposomes and monitored by fluorescence imaging. The pictures show: an optical image of the liposome containing the enzyme (A), a fluorescence image of one labeled enzyme molecule in the

liposome (B), an optical image of the enzyme and substrate liposomes prior to electrofusion (C), an optical image of the fused liposome (D), and a fluorescence image of the fused liposome after incubation (E).



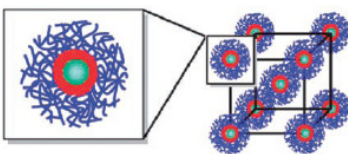
Catch and release: Multivalent dendrons that have *o*-nitrobenzyl-linked spermine surface groups bind DNA efficiently by multivalent interactions. Cleavage of the *o*-nitrobenzyl groups from the dendron framework, with short UV irradiation, results in a rapid release of DNA, which can be attributed to dendron degradation and charge-switching multivalency (see picture).

Controlled DNA Binding

M. A. Kostianen,* D. K. Smith,*
O. Ikkala _____ 7600–7604

Optically Triggered Release of DNA from
Multivalent Dendrons by Degrading and
Charge-Switching Multivalency

ABC gel: The triblock copolymer **PS-*b*-P2VP-*b*-PEO** undergoes simultaneous micellization and gelation, leading to high-storage-modulus materials that have fast responses to pH value, temperature, ionic strength, and shearing. The gel has a hierarchical structure (see picture) with spherical core-shell-corona micelles, which, in turn, pack closely into an ordered cubic structure.



Gels

N. Willet, J.-F. Gohy, L. Lei, M. Heinrich,
L. Auvray, S. Varshney, R. Jérôme,*
B. Leyh _____ 7988–7992

Fast Multiresponsive Micellar Gels from
Smart ABC Triblock Copolymer

ACS Chemical Biology

Signaling by Committee: Receptor Clusters Determine Pathways of Cellular Activation

ACS Chem. Biol., 2 (10), 652–655

Christopher W. Cairo

Receptor clustering is a common signaling mechanism for cell surface receptors. Exogenous ligands such as antibodies or synthetic analogues can be used to artificially induce clustering. New studies using defined synthetic ligands suggest that the spatial organization of these clusters attenuates signaling in one pathway but has no effect in another.

Metal Sensing by RNA in Bacteria: Exception or Rule?

ACS Chem. Biol., 2 (10), 656–660

Sabine Brantl*

Until 2006, it was believed that bacteria control their intracellular metal ion concentrations exclusively through metal-sensing proteins. However, the detection of the first riboswitch that uses a small ion, Mg²⁺, as ligand to regulate gene expression in *Salmonella* challenged this assumption. Now, the discovery and in depth characterization of a second metal-ion-sensing riboswitch that seems to be ubiquitously present in Gram-positive bacteria suggest that metal sensing by RNAs may represent a widespread mechanism.

Use of Docking Peptides to Design Modular Substrates with High Efficiency for Mitogen-Activated Protein Kinase Extracellular Signal-Regulated Kinase

ACS Chem. Biol., 2 (10), 665–673

Neychelle Fernandes[†], Denise E. Bailey[‡], David L. VanVranken[‡], and Nancy L. Allbritton*

The mitogen-activated protein kinase extracellular regulated kinase (ERK) plays a key role in the regulation of cellular proliferation. Mutations in the ERK cascade occur in 30% of malignant tumors. Thus understanding how the kinase identifies its cognate substrates as well as monitoring the activity of ERK is central to cancer research and therapeutic development. ERK binds to its protein targets, both downstream substrates and upstream activators, via a binding site distinct from the catalytic site of ERK. The substrate sequences that bind, or dock, to these sites on ERK influence the efficiency of phosphorylation. For this reason, simple peptide substrates containing only phosphorylation sequences typically possess low efficiencies for ERK. Appending short docking peptides derived from full-length protein substrates and activators of ERK to a phosphorylation sequence increased the affinity of ERK for the phosphorylation sequence by as much as 200-fold while only slightly diminishing the maximal velocity of the reaction. The efficiency of the phosphorylation reaction was increased by up to 150-fold, while the specificity of the substrate for ERK was preserved. Simple modular peptide substrates, which can be easily tailored to possess high phosphorylation efficiencies, will enhance our understanding of the regulation of ERK and provide a tool for the development of new kinase assays.

Chemistry and Biology

Allosteric Inhibition of the Protein-Protein Interaction between the Leukemia-Associated Proteins Runx1 and CBF β

Volume 14, Issue 10, 26 October 2007, Pages 1186-119

Jianxia Shi, Mohini Sridharan, Ryan Lilien, Bruce R. Donald, Nancy A. Speck, Milton L. Brown and John H. Bushweller

The two subunits of core binding factor (Runx1 and CBF β) play critical roles in hematopoiesis and are frequent targets of chromosomal translocations found in leukemia. The binding of the CBF β -smooth muscle myosin heavy chain (SMMHC) fusion protein to Runx1 is essential for leukemogenesis, making this a viable target for treatment. We have developed inhibitors with low micromolar affinity which effectively block binding of Runx1 to CBF β . NMR-based docking shows that these compounds bind to CBF β at a site displaced from the binding interface for Runx1, that is, these compounds function as allosteric inhibitors of this protein-protein interaction, a potentially generalizable approach. Treatment of the human leukemia cell line ME-1 with these compounds shows decreased proliferation, indicating these are good candidates for further development.

Chemical Biology and Drug Design

Important Changes in Biochemical Properties and Function of Mutated LLP12 Domain of HIV-1 gp41

Chem Biol Drug Des 2007; 70: 311–318

Yun Zhu[†], Lu Lu[†], Lijun Chao and Ying-Hua Chen

The human immunodeficiency virus type 1 gp41 possesses an unusually long and conserved cytoplasmic region. Mutations in the LLP12 domain in this region have been shown to significantly affect viral competence. It is likely that the impaired infectivity of this mutated virus involves certain biochemical aspects of the peptide LLP12. To test our assumptions, some important biochemical properties and functions of LLP12 domain were studied. The recombinant peptide LLP12 (LLP12 domain on gp41, including LLP1 and LLP2 domains) was prepared via bacterial expression system. Biochemical analysis directly demonstrated its multimeric potential and membrane-binding ability. Several arginine residues in this domain were observed to be extremely highly conserved. Interestingly, the LLP12 mutants constructed by substitution of these arginine residues with alanine (separate mutations in LLP1 or LLP2 or both) showed apparent decreases in their multimeric potential and membrane-binding ability. Comparing our results with independent data on human immunodeficiency virus from other researchers, it appears that both the multimeric state and the membrane affinity of the LLP12 domain of human immunodeficiency virus type 1 gp41 could be involved in viral competence and in the mechanism of human immunodeficiency virus type 1 Env-mediated cell fusion.

A Template-assembled Model of the N-peptide Helix Bundle from HIV-1 Gp-41 with High Affinity for C-peptide

Chem Biol Drug Des 2007; 70: 319–328

Weiming Xu and John W. Taylor*

The infection of target cells by HIV-1 is initiated by fusion of the viral and cell membranes, which is mediated by the viral glycoproteins, gp120 and gp41. After initial cell binding by gp120, the folding of gp41 to form a stable six-helix bundle structure is directly associated with membrane fusion. This helix bundle is composed of an α -helical trimer of gp41 N-peptide, with three copies of the α -helical gp41 C-peptide folded onto it in an antiparallel orientation. This report describes the synthesis and study of an N-peptide three-helix bundle structure, KTA-3N29b, that is assembled on a threefold symmetric template derived from Kemp's triacid. At neutral pH and in the presence of physiologic salt, KTA-3N29b, exists as a monomer with high helix content. Binding isotherms measured by circular dichroism spectropolarimetry indicate that KTA-3N29b binds three copies of the C-peptide native sequence, with a KD of about 260 nM. These features of KTA-3N29b demonstrate that this templated three-helix bundle serves as a functional model for the native N-peptide structure that will allow detailed studies of the folding and thermodynamic stability of the gp41 six-helix bundle, and may aid the future development of potent HIV-1 fusion inhibitors and immunogens.

Synthesis, QSAR and Calcium Channel Modulator Activity of New Hexahydroquinoline Derivatives Containing Nitroimidazole

Chem Biol Drug Des 2007; 70: 329–336

Hemmateenejad^{1,3}, Zahra Sepeheri¹, Masomeh Zalpouri¹, Taherh Behzadi¹, Mehdi Khoshneviszadeh¹, Najmeh Edraki¹ and Ahmad R. Mehdipour

The discovery that 1,4-dihydropyridine class of calcium channel antagonists inhibit Ca²⁺ influx represented a major therapeutic advance in the treatment of cardiovascular disease. In contrast to the effects of known calcium channel blockers of the Nifedipine-type, the so-called calcium channel agonists, such as Bay K8644 and CGP 28392, increase calcium influx by binding at the same receptor regions. Our goal was to discover a dual cardioselective Ca²⁺-channel agonist/vascular selective smooth muscle Ca²⁺ channel antagonist third-generation 1,4-dihydropyridine drug which would have a suitable therapeutic profile for treating congestive heart failure (CHF) patients. A series of unsymmetrical alkyl, cycloalkyl and aryl ester analogues of 2-methyl-4-(1-methyl)-5-nitro-2-imidazolyl-5-oxo-1,4,5,6,7, 8-hexahydroquinolin-3-carboxylate were synthesized using modified Hantzsch reaction. All compounds show calcium antagonist activity on guinea-pig ileum longitudinal smooth muscle and some of them show agonist effect activity on guinea-pig auricle. Effect of structural parameters on the Ca²⁺ channel agonist/antagonist was evaluated by quantitative structure-activity relationship analysis. These compounds could be considered as a synthon for developing a suitable drug for treating CHF patients.

Dihydropyridine Derivatives to Overcome Atypical Multidrug Resistance: Design, Synthesis, QSAR Studies, and Evaluation of Their Cytotoxic and Pharmacological Activities

Chem Biol Drug Des 2007; 70: 337–346

Ahmad R. Mehdipour^{1,2}, Katayoun Javidnia^{1,2}, Bahram Hemmateenejad^{1,3}, Zahra Amirghofran^{1,4} and Ramin Miri

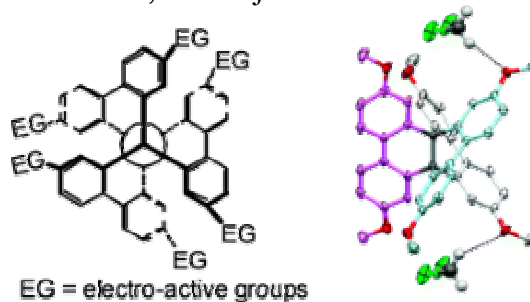
Multidrug resistance (MDR) is defined as resistance of tumor cells to the cytotoxic action of multiple structurally dissimilar and functionally divergent drugs commonly used in chemotherapy. Until now, there is no evidence for the effect of 1,4-dihydropyridines (DHPs) on atypical MDR, although there are some indications about the effect of DHPs on p-glycoprotein-mediated MDR. However, it was reported that a DHP derivative (Dexniguldipine) inhibited human DNA topoisomerase I through a non-competitive mechanism. Therefore, some derivatives of DHP were synthesized and their effect in reversing atypical MDR was evaluated. The results showed that two compounds were the potent reversals of atypical MDR. In addition, the intrinsic cytotoxicity of compounds was determined on four different cell lines. Furthermore, their Ca²⁺ channel blocking activity was evaluated and showed a clear structure-activity relationship (SAR) trend according to the moieties in C-4 position which confirmed the importance of C-4 moiety on Ca²⁺ channel blocking.

Organic Letters

Hexabenz[4.4.4]propellane: A Helical Molecular Platform for the Construction of Electroactive Materials

Org. Lett., 9 (21), 4091 -4094, 2007.

Paromita Debroy, Sergey V. Lindeman, and Rajendra Rathore

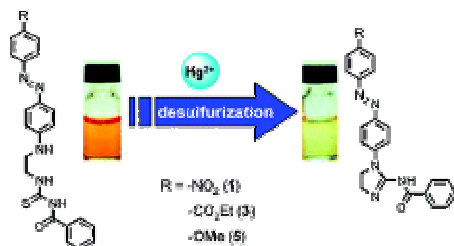


Helical hexabenz[4.4.4]propellane (a relative of hexaphenylethane) and its derivatives are synthesized and their structures are established by X-ray crystallography. Isolation and X-ray crystallographic characterization of a robust trication-radical salt of hexamethoxypropellane derivative confirms that its framework is stable toward oxidative (aliphatic) C-C bond cleavage. It is also demonstrated that propellane can be easily brominated at the 4,4'-positions of the biphenyl linkages for its usage as a molecular platform for the preparation of electroactive materials.

Selectively Chemodosimetric Detection of Hg(II) in Aqueous Media

Org. Lett., 9 (22), 4515 -4518, 2007.

Min Hee Lee,[†] Byoung-Ki Cho,[†] Juyoung Yoon,[†] and Jong Seung Kim



A new series of benzoylthiourea derivatives of 1, 3, and 5 were prepared, and their chemodosimetric behaviors toward metal cations were investigated in aqueous media at room temperature. Among various metal cations tested, exclusively Hg^{2+} ion responses to irreversible color changes of receptors, along with distinctive blue shifts in UV/vis spectra. The receptors can be applicable for the monitoring of Hg^{2+} ion in aqueous solution with a pH span 4-9.