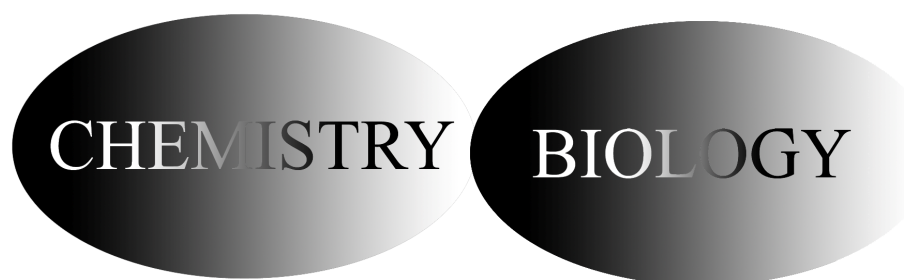


Chmielewski Group Literature Abstracts



June 2007

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 Biotechnology

Improved antimicrobial peptides based on acyl-lysine oligomers

Nature Biotechnology **25**, 657 - 659 (2007)

Inna S Radzishovsky¹, Shahar Rotem¹, Dmitry Bourdetsky¹, Shiri Navon-Venezia², Yehuda Carmeli² & Amram Mor

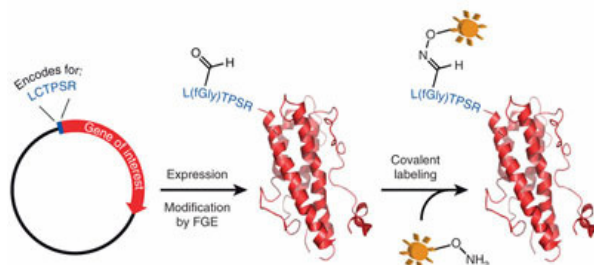
We describe peptidomimetic oligomers that show rapid, nonhemolytic, broad-spectrum bactericidal properties in mice and do not induce the emergence of resistance. The oligomers contain acyl chains, which prevent the formation of stable secondary structure. This design appears advantageous over conventional antimicrobial peptides with respect to in vivo efficacy and safety, and may provide a convenient platform for the development of peptide antibiotics.

Nature Chemical Biology

Introducing genetically encoded aldehydes into proteins

Nature Chemical Biology **3**, 321-322 (2007)

Isaac S Carrico^{1,3,4}, Brian L Carlson^{2,4} & Carolyn R Bertozzi

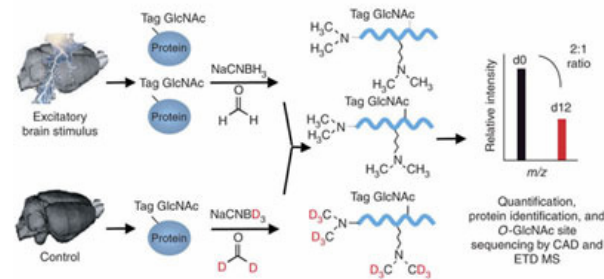


Methods for introducing bioorthogonal functionalities into proteins have become central to protein engineering efforts. Here we describe a method for the site-specific introduction of aldehyde groups into recombinant proteins using the 6-amino-acid consensus sequence recognized by the formylglycine-generating enzyme. This genetically encoded 'aldehyde tag' is no larger than a His6 tag and can be exploited for numerous protein labeling applications.

Probing the dynamics of O-GlcNAc glycosylation in the brain using quantitative proteomics

Nature Chemical Biology **3**, 339-348 (2007)

Nelly Khidekel¹, Scott B Ficarro², Peter M Clark¹, Marian C Bryan¹, Danielle L Swaney³, Jessica E Rexach⁴, Yi E Sun⁴, Joshua J Coon³, Eric C Peters² & Linda C Hsieh-Wilson



The addition of the monosaccharide beta-N-acetyl-D-glucosamine to proteins (O-GlcNAc glycosylation) is an intracellular, post-translational modification that shares features with phosphorylation. Understanding the cellular mechanisms and signaling pathways that regulate O-GlcNAc glycosylation has been challenging because of the difficulty of detecting and quantifying the modification. Here, we describe a new strategy for monitoring the dynamics of O-GlcNAc glycosylation using quantitative mass spectrometry-based proteomics. Our method, which we have termed quantitative isotopic and chemoenzymatic tagging (QUIC-Tag), combines selective, chemoenzymatic tagging of O-GlcNAc proteins with an efficient isotopic labeling strategy. Using the method, we detect changes in O-GlcNAc glycosylation on several proteins involved in the regulation of transcription and mRNA translocation. We also provide the first evidence that O-GlcNAc glycosylation is dynamically modulated by excitatory stimulation of the brain in vivo. Finally, we use electron-transfer dissociation mass spectrometry to identify exact sites of O-GlcNAc modification. Together, our studies suggest that O-GlcNAc glycosylation occurs reversibly in neurons and, akin to phosphorylation, may have important roles in mediating the communication between neurons.

Nature Methods

A semisynthetic epitope for kinase substrates

Nature Methods - 4, 511 - 516 (2007)

Jasmina J Allen¹, Manqing Li², Craig S Brinkworth^{3, 7}, Jennifer L Paulson^{3, 7}, Dan Wang⁴, Anette Hübner⁵, Wen-Hai Chou⁴, Roger J Davis⁵, Alma L Burlingame³, Robert O Messing⁴, Carol D Katayama², Stephen M Hedrick² & Kevan M Shokat

The ubiquitous nature of protein phosphorylation makes it challenging to map kinase-substrate relationships, which is a necessary step toward defining signaling network architecture. To trace the activity of individual kinases, we developed a semisynthetic reaction scheme, which results in the affinity tagging of substrates of the kinase in question. First, a kinase, engineered to use a bio-orthogonal ATPbold gammaS analog, catalyzes thiophosphorylation of its direct substrates. Second, alkylation of thiophosphorylated serine, threonine or tyrosine residues creates an epitope for thiophosphate ester-specific antibodies. We demonstrated the generality of semisynthetic epitope construction with 13 diverse kinases: JNK1, p38alpha MAPK, Erk1, Erk2, Akt1, PKCdelta, PKCepsilon, Cdk1/cyclinB, CK1, Cdc5, GSK3beta, Src and Abl. Application of this approach, in cells isolated from a mouse that expressed

endogenous levels of an analog-specific (AS) kinase (Erk2), allowed purification of a direct Erk2 substrate.

Science

Restriction of an Extinct Retrovirus by the Human TRIM5 Antiviral Protein

Science Vol 316, Issue 5832, 1756-1758, 22 June 2007

Shari M. Kaiser,^{1,2} Harmit S. Malik,³ Michael Emerman

Primate genomes contain a large number of endogenous retroviruses and encode evolutionarily dynamic proteins that provide intrinsic immunity to retroviral infections. We report here the resurrection of the core protein of a 4-million-year-old endogenous virus from the chimpanzee genome and show that the human variant of the intrinsic immune protein TRIM5 can actively prevent infection by this virus. However, we suggest that selective changes that have occurred in the human lineage during the acquisition of resistance to this virus, and perhaps similar viruses, may have left our species more susceptible to infection by human immunodeficiency virus type 1 (HIV-1).

HIV-1 Proviral DNA Excision Using an Evolved Recombinase

Science Vol 316, Issue 5833, 1855-1857, 29 June 2007

Indrani Sarkar,^{1*} Ilona Hauber,^{2*} Joachim Hauber,² Frank Buchholz

HIV-1 integrates into the host chromosome and persists as a provirus flanked by long terminal repeats (LTRs). To date, treatment regimens primarily target the virus enzymes or virus-cell fusion, but not the integrated provirus. We report here the substrate-linked protein evolution of a tailored recombinase that recognizes an asymmetric sequence within an HIV-1 LTR. This evolved recombinase efficiently excised integrated HIV proviral DNA from the genome of infected cells. Although a long way from use in the clinic, we speculate that this type of technology might be adapted in future antiretroviral therapies, among other possible uses.

PNAS

Kinetics and thermodynamics of amyloid formation from direct measurements of fluctuations in fibril mass

PNAS | June 12, 2007 | vol. 104 | no. 24 | 10016-10021

Tuomas P. J. Knowles^{*,†}, Wenmiao Shu^{*}, Glyn L. Devlin^{*,‡}, Sarah Meehan[§], Stefan Auer[§], Christopher M. Dobson^{§,¶}, and Mark E. Welland

Aggregation of proteins and peptides is a widespread and much-studied problem, with serious implications in contexts ranging from biotechnology to human disease. An understanding of the proliferation of such aggregates under specific conditions requires

a quantitative knowledge of the kinetics and thermodynamics of their formation; measurements that to date have remained elusive. Here, we show that precise determination of the growth rates of ordered protein aggregates such as amyloid fibrils can be achieved through real-time monitoring, using a quartz crystal oscillator, of the changes in the numbers of molecules in the fibrils from variations in their masses. We show further that this approach allows the effect of other molecular species on fibril growth to be characterized quantitatively. This method is widely applicable, and we illustrate its power by exploring the free-energy landscape associated with the conversion of the protein insulin to its amyloid form and elucidate the role of a chemical chaperone and a small heat shock protein in inhibiting the aggregation reaction.

Engineering nanoscale order into a designed protein fiber

***PNAS* | June 26, 2007 | vol. 104 | no. 26 | 10853-10858**

David Papapostolou[†], Andrew M. Smith^{‡,§}, Edward D. T. Atkins[¶], Seb J. Oliver^{||}, Maxim G. Ryadnov[†], Louise C. Serpell[‡], and Derek N. Woolfson

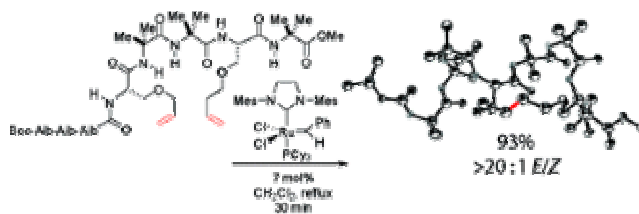
We have established a designed system comprising two peptides that coassemble to form long, thickened protein fibers in water. This system can be rationally engineered to alter fiber assembly, stability, and morphology. Here, we show that rational mutations to our original peptide designs lead to structures with a remarkable level of order on the nanoscale that mimics certain natural fibrous assemblies. In the engineered system, the peptides assemble into two-stranded α -helical coiled-coil rods, which pack in axial register in a 3D hexagonal lattice of size 1.824 nm, and with a periodicity of 4.2 nm along the fiber axis. This model is supported by both electron microscopy and x-ray diffraction. Specifically, the fibers display surface striations separated by nanoscale distances that precisely match the 4.2-nm length expected for peptides configured as α -helices as designed. These patterns extend unbroken across the widths (≥ 50 nm) and lengths (>10 μm) of the fibers. Furthermore, the spacing of the striations can be altered predictably by changing the length of the peptides. These features reflect a high level of internal order within the fibers introduced by the peptide-design process. To our knowledge, this exceptional order, and its persistence along and across the fibers, is unique in a biomimetic system. This work represents a step toward rational bottom-up assembly of nanostructured fibrous biomaterials for potential applications in synthetic biology and nanobiotechnology.

Journal of the American Chemical Society

Facile and *E*-Selective Intramolecular Ring-Closing Metathesis Reactions in 3_{10} -Helical Peptides: A 3D Structural Study

***J. Am. Chem. Soc.*, 2007, 129 (22), 6986 -6987**

Amie K. Boal[†], Ivan Guryanov[‡], Alessandro Moretto[‡], Marco Crisma[‡], Erica L. Lanni[†], Claudio Toniolo[‡], Robert H. Grubbs[‡], and Daniel J. O'Leary

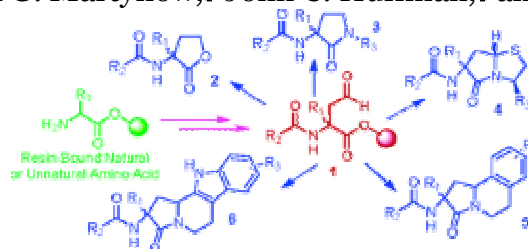


The ring-closing metathesis reaction can be used to cross-link allylated serine residues situated at the i and $i + 3$ positions in 3_{10} -helical peptides containing the helicogenic amino acid, α -aminoisobutyric acid (Aib). An octapeptide with the sequence Boc-Aib-Aib-Aib-Ser(Al)-Aib-Aib-Ser(Al)-Aib-OMe was found to undergo a facile and $>20:1$ E -selective ring-closing metathesis (RCM) reaction catalyzed by the Grubbs second-generation catalyst to yield an 18-membered macrocycle. The formation of this cross-link does not significantly disturb the peptide's native 3_{10} -helicity, as judged by an X-ray diffraction study of the acyclic diene, the E -olefin RCM product, and its hydrogenated derivative. A heptapeptide system with the sequence Boc-Val-Ser(Al)-Leu-Aib-Ser(Al)-Val-Leu-OMe also underwent an efficient RCM reaction, albeit with diminished E -selectivity. It is apparent from these studies that a minimal, RCM-derived, macrocyclic constraint can be readily incorporated into 3_{10} -helical peptides.

Solid-Phase Synthesis of Multiple Classes of Peptidomimetics from Versatile Resin-Bound Aldehyde Intermediates

J. Am. Chem. Soc., 2007, 129 (22), 7077 -7088

William L. Scott,*† Jacek G. Martynow,† John C. Huffman,‡ and Martin J. O'Donnell

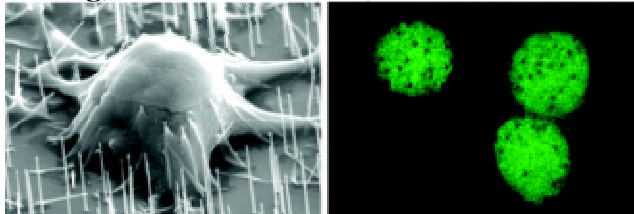


A wide variety of highly substituted lactam containing peptidomimetic scaffolds are prepared by solid-phase synthesis from a single, versatile class of resin-bound aldehyde intermediates (1). These include monocyclics 3, bicyclics 4, tricyclics 5, and tetracyclics 6. The key intermediate 1 is readily synthesized from resin-bound natural or unnatural α -amino acids. The synthetic procedures permit the construction of a large diversity of substitution patterns for ready use in combinatorial chemistry. In every case, the release of final products from resin is by a cyclitive cleavage process. Since this depends on successful completion of multiple intermediate synthetic steps, the products are often quite pure, even though previous steps involve only a filtration workup. The mild conditions for many of these synthetic procedures offer the promise of using this chemistry in peptide fragment condensations to produce modified peptides, at either the N-terminus or C-terminus, or as individually assembled peptide segments with a wide variety of conformationally restricted peptidomimetic linkers at the point of juncture.

Interfacing Silicon Nanowires with Mammalian Cells

***J. Am. Chem. Soc.*, 2007, 129 (23), 7228 -7229**

Woong Kim,[†] Jennifer K. Ng,[‡] Miki E. Kunitake,[‡] Bruce R. Conklin,^{*‡} and Peidong Yang

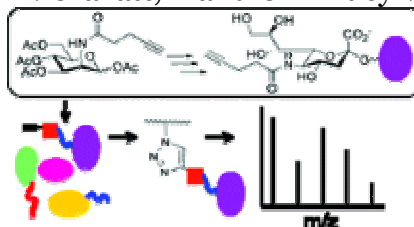


We present the first demonstration of a direct interface of silicon nanowires with mammalian cells such as mouse embryonic stem (mES) cells and human embryonic kidney (HEK 293T) cells without any external force. The cells were cultured on a silicon (Si) substrate with a vertically aligned SiNW array on it. The penetration of the SiNW array into individual cells naturally occurred during the incubation. The cells survived up to several days on the nanowire substrates. The longevity of the cells was highly dependent on the diameter of SiNWs. Furthermore, successful maintenance of cardiac myocytes derived from mES cells on the wire array substrates was observed, and gene delivery using the SiNW array was demonstrated. Our results suggest that the nanowires can be potentially utilized as a powerful tool for studying intra- and intercellular biological processes.

Tailored Glycoproteomics and Glycan Site Mapping Using Saccharide-Selective Bioorthogonal Probes

***J. Am. Chem. Soc.*, 2007, 129 (23), 7266 -7267**

Sarah R. Hanson,[†] Tsui-Ling Hsu,^{†‡} Eranthie Weerapana,[†] Kuniyuki Kishikawa,[†] Gabriel M. Simon,[†] Benjamin F. Cravatt,^{*†} and Chi-Huey Wong



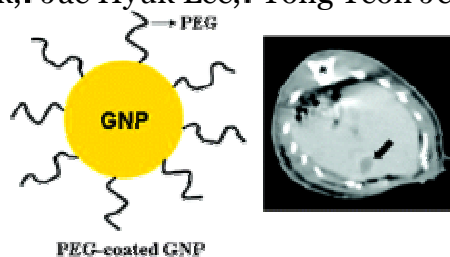
Protein glycosylation is an important post-translational modification of proteins that has profound effects on structure and function. However, the complex and non-templated nature of glycans has been a barrier to studying many of their basic features, especially on a proteome-wide scale. Here, we introduce a glycoproteomic method, glycoprotein identification and glycan mapping (GIDmap), that tailors the isolation of specific glycoprotein subpopulations based on display of metabolically inserted alkyne sugar probes that can be selectively manipulated using the bioorthogonal Cu(I)-catalyzed [3 + 2] azide-alkyne cycloaddition. This saccharide-selective glycoprotein immobilization allows for subsequent manipulation and analysis of peptides and glycopeptides by liquid chromatography-tandem mass spectrometry. The power of GIDmap was demonstrated by mapping over 200 N-linked glycosylation sites from glycoproteins isolated from prostate cancer cells treated with an alkyne sugar derivative of *N*-acetylmannosamine. Overall, GIDmap is a robust method that will greatly aid in

inventorying glycoproteins and mapping glycosylation sites, in addition to providing specific information about saccharide content and glycan behavior.

Antibiofouling Polymer-Coated Gold Nanoparticles as a Contrast Agent for in Vivo X-ray Computed Tomography Imaging

J. Am. Chem. Soc., **129** (25), 7722 -7723, 2007

Dongkyu Kim,[†] Sangjin Park,[†] Jae Hyuk Lee,[‡] Yong Yeon Jeong,^{*‡} and Sangyong Jon

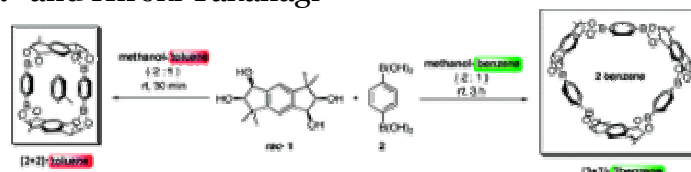


Current computed tomography (CT) contrast agents such as iodine-based compounds have several limitations, including short imaging times due to rapid renal clearance, renal toxicity, and vascular permeation. Here, we describe a new CT contrast agent based on gold nanoparticles (GNPs) that overcomes these limitations. Because gold has a higher atomic number and X-ray absorption coefficient than iodine, we expected that GNPs can be used as CT contrast agents. We prepared uniform GNPs (~30 nm in diameter) by general reduction of HAuCl_4 by boiling with sodium citrate. The resulting GNPs were coated with polyethylene glycol (PEG) to impart antibiofouling properties, which extends their lifetime in the bloodstream. Measurement of the X-ray absorption coefficient in vitro revealed that the attenuation of PEG-coated GNPs is 5.7 times higher than that of the current iodine-based CT contrast agent, Ultravist. Furthermore, when injected intravenously into rats, the PEG-coated GNPs had a much longer blood circulation time (>4 h) than Ultravist (<10 min). Consequently, CT images of rats using PEG-coated GNPs showed a clear delineation of cardiac ventricles and great vessels. On the other hand, relatively high levels of GNPs accumulated in the spleen and liver, which contain phagocytic cells. Intravenous injection of PEG-coated GNPs into hepatoma-bearing rats resulted in a high contrast (~2-fold) between hepatoma and normal liver tissue on CT images. These results suggest that PEG-coated GNPs can be useful as a CT contrast agent for a blood pool and hepatoma imaging.

Boronic Esters as a System for Crystallization-Induced Dynamic Self-Assembly Equipped with an "On-Off" Switch for Equilibration

J. Am. Chem. Soc., **129** (25), 7760 -7761, 2007

Nobuharu Iwasawa* and Hiroki Takahagi

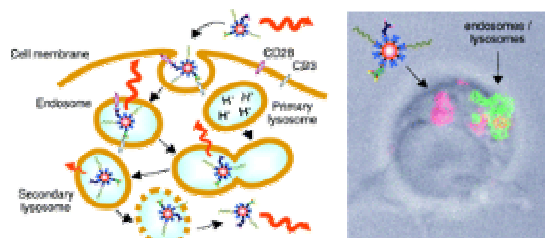


We report dynamic self-assembly utilizing boronic ester formation with special emphasis on the following six points: (1) two kinds of host molecule are constructed spontaneously with benzene or toluene as the guest molecule under neutral conditions simply by mixing a di(boronic acid) and a bis(1,2-diol) in methanol; (2) the precipitation process is essential for this selective preparation of host molecules; (3) recognition of the enantiomers of bis(1,2-diol) is achieved during host formation in this system; (4) it is possible to freeze or free the conversion between the two host molecules, thus enabling formation of complexes that cannot be prepared under thermodynamic conditions typical for such self-assembly; (5) naphthalene and triphenylene are even more efficient guest molecules in this system; and (6) almost complete separation of naphthalene and 1-methylnaphthalene is achieved utilizing this guest-induced precipitation process.

Luminescent Silica Nanobeads: Characterization and Evaluation as Efficient Cytoplasmatic Transporters for T-Lymphocytes

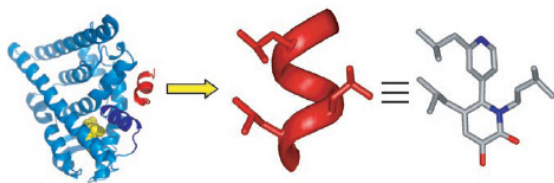
J. Am. Chem. Soc., **129** (25), 7877 -7884, 2007

Massimo Bottini,*†‡ Fabio Cerignoli,† David M. Mills,† Federica D'Annibale,‡ Marilisa Leone,† Nicola Rosato,| Andrea Magrini,‡ Maurizio Pellecchia,† Antonio Bergamaschi,‡ and Tomas Mustelin



We report the fabrication and characterization of neutravidin-conjugated silica nanobeads doped with a ruthenium-complex luminophore and functionalized with antihuman CD3, antihuman CD28, and an acid-sensitive polymer. We observed that the nanobeads were readily delivered into Jurkat T leukemia cells by endocytosis, transported into lysosomes and subsequently into the cytoplasm as revealed by pH-sensitive luminescence. Since signs of cytotoxicity were not observed, the reported nanobeads could be an excellent and nontoxic building block for efficient intracellular transporters.

Angewandte Chemie



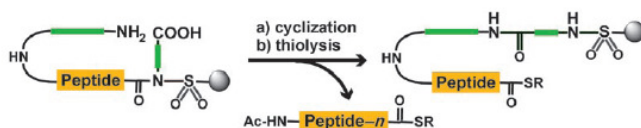
The short and curlies: A new α -helix mimetic based on a pyridylpyridone scaffold has been developed to bind to the estrogen receptor (ER) by mimicking the key leucine side chains of coactivator

LXXLL boxes (L = leucine, X = any amino acid). These inhibitors compete with coactivator peptides for the surface of the ER and act as small-molecule inhibitors of the ER-coactivator interaction.

α -Helix Mimetics

J. Becerril, A. D. Hamilton* 4471–4473

Helix Mimetics as Inhibitors of the Interaction of the Estrogen Receptor with Coactivator Peptides



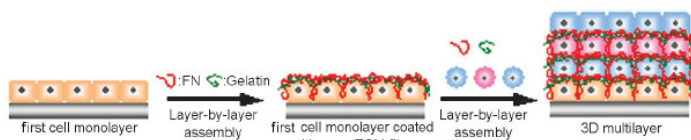
Separating the wheat from the chaff: A cyclization–thiolysis sequence adds a new property to sulfonamide safety-catch resins. Activation of the sulfonamide is used to introduce a carboxy group for subsequent macrocyclization. Truncation

products are noncyclic and hence washed away following thiolytic ring opening. Only the full-length peptide thioesters are detached, usually in pure form, in the final step.

Peptide Synthesis

F. Mende, O. Seitz* 4577–4580

Solid-Phase Synthesis of Peptide Thioesters with Self-Purification



Layer it on: Cellular multilayers were fabricated by preparing nanometer-sized extracellular matrix (ECM) films (6-nm thick) with fibronectin (FN) and gelatin on the surface of each cell layer. The four-

layer cellular architecture was well organized and self-standing. Xenogenic human bilayer architectures similar to blood vessels were prepared by fabrication of the nanofilms on cell surfaces.

Cellular Multilayers

M. Matsusaki, K. Kadowaki, Y. Nakahara, M. Akashi* 4689–4692

Fabrication of Cellular Multilayers with Nanometer-Sized Extracellular Matrix Films

ACS Chemical Biology

Mitomycin–DNA Adducts Induce p53-Dependent and p53-Independent Cell Death Pathways

ACS Chem. Biol., 2 (6), 399–407

Ernest K. Boamah^{†,‡}, David E. White^{†,‡,§}, Kathryn E. Talbott[†], Nicoleta C. Arva[†], Daniel Berman[†], Maria Tomasz[□], and Jill Bargonetti

10-Decarbamoyl-mitomycin C (DMC), a mitomycin C (MC) derivative, generates an array of DNA monoadducts and interstrand cross-links stereoisomeric to those that are generated by MC. DMC was previously shown in our laboratory to exceed the cytotoxicity of MC in a human leukemia cell line that lacks a functional p53 pathway (K562). However, the molecular signal transduction pathway activated by DMC–DNA adducts has not been investigated. In this study, we have compared molecular targets associated with signaling pathways activated by DMC and MC in several human cancer

cell lines. In cell lines lacking wild-type p53, DMC was reproducibly more cytotoxic than MC, but it generated barely detectable signal transduction markers associated with apoptotic death. Strikingly, DMC's increased cytotoxicity was not associated with an increase in DNA double-strand breaks but was associated with early poly(ADP-ribose) polymerase (PARP) activation and Chk1 kinase depletion. Alkylating agents can induce increased PARP activity associated with programmed necrosis, and the biological activity of DMC in p53-null cell lines fits this paradigm. In cell lines with a functional p53 pathway, both MC and DMC induced apoptosis. In the presence of p53, both MC and DMC activate procaspases; however, the spectrum of procaspases involved differs for the two drugs, as does induction of p73. These studies suggest that in the absence of p53, signaling to molecular targets in cell death can shift in response to different DNA adduct structures to induce non-apoptotic cell death.

High-Throughput, Microarray-Based Synthesis of Natural Product Analogues via in Vitro Metabolic Pathway Construction

ACS Chem. Biol., **2** (6), 419–425

Seok Joon Kwon[†], Moo-Yeal Lee[‡], Bosung Ku[†], David H. Sherman[§], and Jonathan S. Dordick

The generation of biological diversity by engineering the biosynthetic gene assembly of metabolic pathway enzymes has led to a wide range of “unnatural” variants of natural products. However, current biosynthetic techniques do not allow the rapid manipulation of pathway components and are often fundamentally limited by the compatibility of new pathways, their gene expression, and the resulting biosynthetic products and pathway intermediates with cell growth and function. To overcome these limitations, we have developed an entirely in vitro approach to synthesize analogues of natural products in high throughput. Using several type III polyketide synthases (PKS) together with oxidative post-PKS tailoring enzymes, we performed 192 individual and multienzymatic reactions on a single glass microarray. Subsequent array-based screening with a human tyrosine kinase led to the identification of three compounds that acted as modest inhibitors in the low-micromolar range. This approach, therefore, enables the rapid construction of analogues of natural products as potential pharmaceutical lead compounds.

Chemistry and Biology

The Tumor Inhibitor and Antiangiogenic Agent Withaferin A Targets the Intermediate Filament Protein Vimentin

Volume 14, Issue 6, 25 June 2007, Pages 623-634

Paola Bargagna-Mohan, Adel Hamza, Yang-eon Kim, Yik Khuan (Abby) Ho, Nirit Mor-Vaknin, Nicole Wendschlag, Junjun Liu, Robert M. Evans, David M. Markovitz, Chang-Guo Zhan, Kyung Bo Kim and Royce Mohan

The natural product withaferin A (WFA) exhibits antitumor and antiangiogenesis activity in vivo, which results from this drug's potent growth inhibitory activities. Here,

we show that WFA binds to the intermediate filament (IF) protein, vimentin, by covalently modifying its cysteine residue, which is present in the highly conserved α -helical coiled coil 2B domain. WFA induces vimentin filaments to aggregate in vitro, an activity manifested in vivo as punctate cytoplasmic aggregates that colocalize vimentin and F-actin. WFA's potent dominant-negative effect on F-actin requires vimentin expression and induces apoptosis. Finally, we show that WFA-induced inhibition of capillary growth in a mouse model of corneal neovascularization is compromised in vimentin-deficient mice. These findings identify WFA as a chemical genetic probe of IF functions, and illuminate a potential molecular target for withanolide-based therapeutics for treating angioproliferative and malignant diseases.

Specific Inhibition of p300-HAT Alters Global Gene Expression and Represses HIV Replication

Volume 14, Issue 6, 25 June 2007, Pages 645-657

K. Mantelingu, B.A. Ashok Reddy, V. Swaminathan, A. Hari Kishore, Nagadenahalli B. Siddappa, G.V. Pavan Kumar, G. Nagashankar, Nagashayana Natesh, Siddhartha Roy, Parag P. Sadhale, Udaykumar Ranga, Chandrabhas Narayana and Tapas K. Kundu

Reversible acetylation of histone and nonhistone proteins plays pivotal role in cellular homeostasis. Dysfunction of histone acetyltransferases (HATs) leads to several diseases including cancer, neurodegeneration, asthma, diabetes, AIDS, and cardiac hypertrophy. We describe the synthesis and characterization of a set of p300-HAT-specific small-molecule inhibitors from a natural nonspecific HAT inhibitor, garcinol, which is highly toxic to cells. We show that the specific inhibitor selectively represses the p300-mediated acetylation of p53 in vivo. Furthermore, inhibition of p300-HAT down regulates several genes but significantly a few important genes are also upregulated. Remarkably, these inhibitors were found to be nontoxic to T cells, inhibit histone acetylation of HIV infected cells, and consequently inhibit the multiplication of HIV.

Quantitative Comparison of the Relative Cell Permeability of Cyclic and Linear Peptides

Volume 14, Issue 6, 25 June 2007, Pages 671-677

Yong-Uk Kwon and Thomas Kodadek

Cyclic peptides are of considerable interest as potential protein ligands. It has been postulated that cyclic molecules might be more cell permeable than their linear counterparts due to their reduced conformational flexibility. We report a study that tests this hypothesis by using a quantitative, reporter gene-based assay that measures the relative cell permeability of steroid conjugates of molecules of interest. We demonstrate that cyclic peptides are, in fact, not generally more permeable than their linear counterparts.

Chemical Biology and Drug Design

Hydrophobic Interactions in Complexes of Antimicrobial Peptides with Bacterial Polysaccharides

Chem Biol Drug Des 2007; 69: 405–412

Hsin H. Kuo^{1,2}, Celine Chan^{1,2}, Lori L. Burrows³ and Charles M. Deber

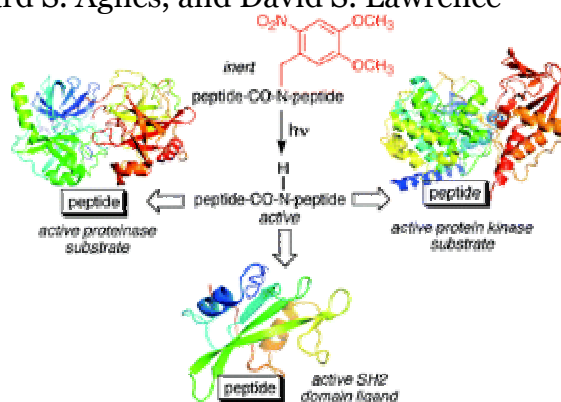
Biofilms of *Pseudomonas aeruginosa* are responsible for chronic lung infections in cystic fibrosis patients, where they are characterized by overproduction of the exopolysaccharide alginate and are recalcitrant to treatment with conventional antibiotics. Cationic antimicrobial peptides (CAPs) are potential alternatives for the treatment of multi-drug-resistant *P. aeruginosa*. However, alginate in *P. aeruginosa* biofilms has been proposed to bind these peptides through hydrophobic interactions, consequently reducing their activity [Chan et al., *J Biol Chem* 2004; 279: 38749–38754]. Here we perform biophysical analyses of the interactions of alginate with a series of novel peptide antibiotics (α -CAPs) of prototypic sequence KK-AAAXAAAAAXAAWAXAAA-KKKK (where X = Phe, Trp or Leu). The hydrophobic interaction interface in alginate was investigated by examining (i) the effects of polysaccharide composition with respect to d-mannuronate and l-gulonate content; (ii) glycan chain length; (iii) α -CAP Trp fluorescence; and (iv) 1-anilinonaphthalene-8-sulfonate fluorescence. The results show that, while M and G residues produce equivalent effects, hydrophobic interactions between alginate and α -CAPs require a minimal glycan chain length. Peptide interactions with alginate are deduced to be mediated by hydrophobic microdomains comprised of pyranosyl C–H groups that are inducible upon formation of α -CAP–alginate complexes due to charge neutralization between the two species.

Organic Letters

Photochemically-Activated Probes of Protein-Protein Interactions

Org. Lett., 9 (12), 2249 -2252, 2007.

Sandip K. Nandy, Richard S. Agnes, and David S. Lawrence

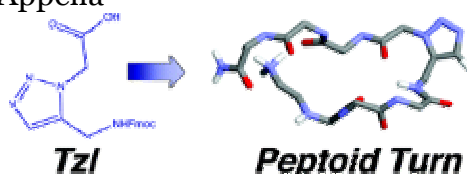


The activity of light-activatable ("caged") compounds can be temporally and spatially controlled, thereby providing a means to interrogate intracellular biochemical pathways as a function of time and space. Nearly all caged peptides contain photocleavable groups positioned on the side chains of key residues. We describe an alternative active site targeted strategy that disrupts the interaction between the protein target (SH2 domain, kinase, and proteinase) and a critical amide NH moiety of the peptide probe.

Introduction of a Triazole Amino Acid into a Peptoid Oligomer Induces Turn Formation in Aqueous Solution

Org. Lett., 9 (12), 2381 -2383, 2007.

Jonathan K. Pokorski,[§] Lisa M. Miller Jenkins,[†] Hanqiao Feng,[‡] Stewart R. Durell,[†] Yawen Bai,[‡] and Daniel H. Appella

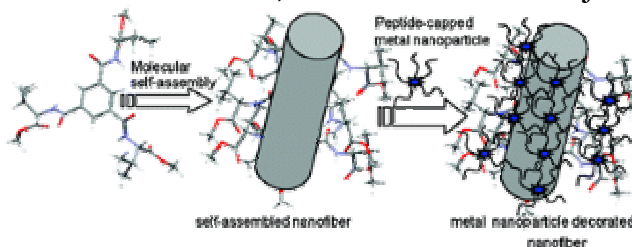


Peptoids are a non-natural class of oligomers that are composed of repeating N-substituted glycine units and are capable of folding into helices that mimic peptide structure and function. In this letter, we report the concise synthesis of a 1,5-substituted triazole amino acid (Tzl) and its subsequent incorporation into a short peptoid. The Tzl amino acid was shown to induce turn formation in aqueous solution, thus expanding the structural repertoire available to peptoid chemists.

Decoration of Au and Ag Nanoparticles on Self-Assembling Pseudopeptide-Based Nanofiber by Using a Short Peptide as Capping Agent for Metal Nanoparticles

Org. Lett., 9 (13), 2489 -2492, 2007.

Partha Pratim Bose,[†] Michael G. B. Drew,[‡] and Arindam Banerjee



The surface of a nanofiber that is formed from a self-assembling pseudopeptide has been decorated by gold and silver nanoparticles that are stabilized by a dipeptide. Transmission electron microscopic images make the decoration visible. In this paper, a new strategy of mineralizing a pseudopeptide based nanofiber by gold and silver nanoparticles with use of a two-component nanografting method is described.