Bioorganic Chemistry (CHEM-GA 2884)

Spring 2017

Mondays & Wednesdays 12:30-2:00, BOBST LL151

Instructors: Paramjit Arora and Kent Kirshenbaum

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This graduate-level bioorganic/chemical biology course is primarily based upon recent articles in the chemical-biological literature and will use classical literature in the field as a reference frame. This course is taught from the perspective of an organic chemist with an emphasis on the thought process involved in making new discoveries and the insights gained from these discoveries. Physical organic and biophysical methods will be introduced as necessary. Undergraduate level Organic, Biochemistry and Physical Chemistry courses are required. This course works best when the "lectures" are conducted as discussions. Full student participation is expected during the lectures, which can only happen if everyone familiarizes himself/herself with the literature and lecture notes posted on NYU Classes prior to each lecture.

Textbook (Recommended): *Introduction to Bioorganic Chemistry and Chemical Biology* by Van Vranken and Weiss; Garland Science.
Link: http://www.garlandscience.com/product/isbn/9780815342144

Tentative Schedule

Week 1 (Jan 23, 25)	Chemical synthesis of biomolecules (PA)
Week 2 (Jan 30, Feb 1)	Synthesis of proteins: Native chemical ligation, nonnatural amino acid insertion (KK)
Week 3 (Feb 6, 8)	Structure and mimicry of biomolecules (PA/KK)
Week 4 (Feb 13, 15)	Structure and mimicry of biomolecules (PA/KK)
Week 5 (Feb 20, 22)	Presidents' Day/ Control of gene expression: transcription: epigenetics (KK)
Week 6 (Feb 27, March 1)	Midterm 1/Artificial control of gene expression: siRNA, CRISPR (KK)
Week 7 (Mar 6, 8)	Artificial control of gene expression: small molecules (PA)
Week 8 (Mar 13, 15)	Spring Break
Week 9 (Mar 20, 22)	Aptamers and Phage Display: Catalytic antibodies, RNA aptamers/enzymes, phage display, mRNA display, DNA display (PA/KK)
Week 10 (Mar 27, 29)	Protein activity control: kinase, protease and PPI inhibitors (PA)
Week 11 (Apr 3, Apr 5)	Identification of cellular targets: proteomics, ABPP (PA)
Week 12 (Apr 10, Apr 12)	Expanding the Genetic Code (KK)/ Midterm 2
Week 13 (Apr 17, 19)	Optopharmacology (Trauner)/GlycoConjugates (KK)/
Week 14 (Apr 24, 26)	GlycoConjugates (KK)/Metals in Biology (Buccella)

Week 15 (May 1, 3)	Small molecule and protein therapeutics (special lectures from pharma?)
May 8	**Final Exam**

Grading:
Two Midterm 20%each
Written Proposal 25%
Final 25%
Participation 10%

List of Useful Review/Reference Articles (Additional papers will be uploaded on Blackboard before every lecture)

The Beginning

Eigen M Self-organization of matter and evolution of biological macromolecules, *Naturwissenschaften*, 58: 465 **1971**
Orgel LE The origin of life - a review of facts and speculations *Trends Biochem Sci* 23 (12): 491- 495 **1998**
Joyce GF The antiquity of RNA-based evolution *Nature* 418: 214-221 **2002**
Szostak JW, Bartel DP and Luisi PL, Synthesizing life. *Nature* 409 387-390 **2001**
Issac R, Ham YW, Chmielewski J The design of self-replicating helical peptides *Curr Opin Struc Biol* 11: 458-463 **2001**

Peptide/Protein Engineering

Bryson JW, Betz SF, Lu Hs, Suich DJ, Zhou HX, O'Neil KT, Degrado WF Protein Design - A Hierarchical Approach *Science* 270 (5238): 935-941 **1995**
DeGrado WF, Summa CM, Pavone V, Nastri F, Lombardi A *De novo* design and structural characterization of proteins and metalloproteins *Ann Rev Biochem* 68: 779-819 **1999**
Smith CK, Regan L Construction and design of beta-sheets *Acc Chem Res* 30 (4): 153-161 **1997**
Kim PS, Baldwin RL Intermediates In The Folding Reactions Of Small Proteins *Annu Rev Biochem 59*: 631-660 **1990**
Dalal S, Balasubramanian S, Regan L Protein Alchemy: Changing Beta-Sheet Into Alpha-Helix *Nat Struct Biol* 4 (7): 548-552 **1997**

Protein Misfolding

Dobson CM Protein misfolding, evolution and disease *Trends Biochem Sci* 24 (9): 329-332 **1999**
Rochet JC, Lansbury PT Amyloid fibrillogenesis: themes and variations *Curr Opin Struc Biol* 10 (1): 60-68 **2000**
Bucciantini M, Giannoni E, Chiti F, Baroni F, Formigli L, Zurdo JS, Taddei N, Ramponi G, Dobson CM, Stefani M Inherent toxicity of aggregates implies a common mechanism for protein misfolding diseases *Nature* 416 (6880): 507-511 **2002**

Supramolecular Chemistry

Lindsey JS Self-Assembly In Synthetic Routes To Molecular Devices - Biological Principles And Chemical Perspectives - A Review *New J Chem* 15 (2-3): 153-180 **1991**
Cram DJ The Design Of Molecular Hosts, Guests, And Their Complexes (Nobel Lecture) *Angew Chem Int Ed* 27 (8): 1009-1020 **1988**
Lehn JM Supramolecular Chemistry - Scope And Perspectives Molecules, Supermolecules, And Molecular Devices *Angew Chem Int Ed* 27 (1): 89-112 **1988**
Breslow R Biomimetic Chemistry And Artificial Enzymes - Catalysis By Design *Accounts Chem Res* 28 (3): 146-153 **1995**
Breslow R, Dong SD Biomimetic Reactions Catalyzed By Cyclodextrins And Their Derivatives *Chem Rev.* 98 (5): 1997-2011 **1998**
Hof F, Craig SL, Nuckolls C, Rebek J Molecular encapsulation *Angew Chem Int Ed* 41 (9): 1488-1508 **2002**
Whitesides Gm, Simanek Ee, Mathias Jp, Seto Ct, Chin Dn, Mammen M, Gordon DM Noncovalent Synthesis - Using Physical-Organic Chemistry To Make Aggregates *Acc. Chem. Res.* 28 (1): 37-44 **1995**
Bowden NB, Weck M, Choi IS, Whitesides GM Molecule-Mimetic Chemistry And Mesoscale Self-Assembly *Acc. Chem. Res.* 34 (3): 231-238 **2001**
Niemeyer CM Nanoparticles, proteins, and nucleic acids: Biotechnology meets materials science *Angew*

Chem Int Edit 40 (22): 4128-4158 **2001**
Bong DT, Ghadiri MR Self-assembling cyclic peptide cylinders as nuclei for crystal engineering *Angew Chem Int Edit* 40 (11): 2163-2166 **2001**

Foldamers

Gellman SH Foldamers: A Manifesto, *Acc Chem Res* 31 (4): 173-180 **1998**
Hill DJ, Mio MJ, Prince RB, Hughes TS, Moore JS A field guide to foldamers *Chem Rev* 101 (12): 3893-4011 **2001**
Stigers KD, Soth MJ, Nowick JS Designed molecules that fold to mimic protein secondary structures C*urr Opin Chem Biol* 3 (6): 714-723 **1999**
Leininger S, Olenyuk B, Stang PJ Self-assembly of discrete cyclic nanostructures mediated by transition metals *Chem Rev,* 100 (3): 853-907 **2000**
Henchey, LK, Jochim AJ, Arora PS Contemporary strategies for the stabilization of peptides in the α-helical conformation C*urr Opin Chem Biol* 12: 692-697 **2008**
Yoo, B.; Kirshenbaum, K. Peptoid architectures: elaboration, actuation, and application. *Curr. Opin. Chem. Biol.* **2008**, *12*, 714-21.

Protein-Protein Interactions and Mimicry

Stites WE Protein-protein interactions: Interface structure, binding thermodynamics, and mutational analysis Chem Rev 97 (5): 1233-1250 **1997**
Conte, L.L., Chothia, C. and Janin, J., The atomic structure of protein-protein recognition sites, *J Mol Biol*, 285(5), 2177, **1999**
Bogan, A.A. and Thorn, K.S., Anatomy of hot spots in protein interfaces, *J Mol Biol*, 280(1), 1, **1998**
Zutshi, R., Brickner, M. and Chmielewski, J., Inhibiting the assembly of protein protein interfaces, C*urr Opin Chem Biol*, 2(1), 62, **1998**
Peczuh, M.W. and Hamilton, A.D., Peptide and protein recognition by designed molecules, *Chem Rev*, 100(7), 2479, **2000**
Cochran, A.G., Protein-protein interfaces: mimics and inhibitors, *Current Opinion in Chemical Biology*, 5(6), 654, **2001**
Gante J Peptidomimetics - Tailored Enzyme-Inhibitors *Angew Chem Int Ed* 33 (17): 1699-1720 **1994**
Hruby VJ, Li GG, Haskell-luevano C, Shenderovich M Design Of Peptides, Proteins, And Peptidomimetics In Chi Space *Biopolymers* 43 (3): 219-266 **1997**
Schneider JP, Kelly JW Templates That Induce Alpha-Helical, Beta-Sheet, And Loop Conformations *Chem Rev* 95 (6): 2169-2187 **1995**

Proteins & Enzymes

Kirby AJ Enzyme mechanisms, models, and mimics, *Angew Chem Int Ed* 35 (7): 707-724 **1996**
Khosla C, Harbury PB Modular enzymes, *Nature* 409 (6817): 247-252 **2001**
Koeller KM, Wong CH Enzymes for chemical synthesis, *Nature* 409 (6817): 232-240 **2001**

Catalytic Antibodies

Lerner RA, Benkovic SJ, Schultz PG, At The Crossroads Of Chemistry And Immunology - Catalytic Antibodies, *Science* 252 (5006): 659-667 **1991**
Mader MM, Bartlett PA Binding energy and catalysis: The implications for transition-state analogs and catalytic antibodies *Chem Rev* 97 (5): 1281-1301 **1997**
Hilvert D Critical analysis of antibody catalysis *Annu Rev Biochem* 69: 751-793 **2000**
Reymond JL Catalytic antibodies for organic synthesis, *Top Curr Chem* 200: 59-93 **1999**
Machajewski TD, Wong CH The catalytic asymmetric aldol reaction 39 (8): 1352-1374 **2000**

Molecular Imprinting

Wulff G Molecular Imprinting In Cross-Linked Materials With The Aid Of Molecular Templates - A Way Towards Artificial Antibodies, *Angew Chem Int Ed* 34 (17): 1812-1832 **1995**
Asanuma H, Hishiya T, Komiyama M Tailor-made receptors by molecular imprinting *Adv Materials* 12 (14): 1019-1030 **2000**
Davis ME, Katz A, Ahmad WR Rational catalyst design via imprinted nanostructured materials *Chem Materials* 8 (8): 1820-1839 **1996**
Ekberg B, Mosbach K Molecular Imprinting - A Technique For Producing Specific Separation Materials *Trends Biotechnol* 7 (4): 92-96 **1989**
Batra D, Shea KJ Combinatorial methods in molecular imprinting *Curr Opin Chem Biol* 7 (3): 434-442 **2003**
Haupt K, Mosbach K Molecularly imprinted polymers and their use in biomimetic sensors *Chem Rev* 100 (7): 2495-2504 **2000**

Polyketides

Carreras CW, Pieper R, Khosla C The chemistry and biology of fatty acid, polyketide, and nonribosomal peptide biosynthesis, *Top Curr Chem* 188: 85-126 **1997**
Cane DE, Walsh CT, Khosla C, *Biochemistry* - Harnessing the biosynthetic code: Combinations, permutations, and mutations, *Science* 282 (5386): 63-68, **1998**
Katz L . Manipulation of modular polyketide syntheses, *Chem Rev* 97 (7): 2557-2575 1**997**
Khosla C, Gokhale RS, Jacobsen JR, et al. Tolerance and specificity of polyketide synthases *Annu Rev Biochem* 68: 219-253 **1999**
Gokhale RS, Khosla C, Role of linkers in communication between protein modules *Curr Opin Chem Biol* 4 (1): 22-27 FEB **2000**

Non-Ribosomal Peptide Synthesis

Schwarzer D, Marahiel MA Multimodular biocatalysts for natural product assembly *Naturwissenschaften* 88 (3): 93-101 **2001**
Weber T, Marahiel MA Exploring the domain structure of modular nonribosomal peptide synthetases *Structure* 9 (1): R3-R9 **2001**

Inteins: Protein Ligation

Muir TW, Semisynthesis of proteins by expressed protein ligation, *Ann. Rev. Biochem.*72: 249-289 **2003**
Paulus H, Protein splicing and related forms of protein autoprocessing, *Annu Rev Biochem* 69: 447-496, **2000**
Camarero JA, Muir TW Biosynthesis of a head-to-tail cyclized protein with improved biological activity *J Am Chem Soc* 121 (23): 5597-5598 **1999**
Mootz HD, Muir TW Protein splicing triggered by a small molecule, *J Am Chem Soc* 124 (31): 9044-9045 **2002**

DNA and DNA-Protein General

Eschenmoser A Chemical etiology of nucleic acid structure *Science* 284 (5423): 2118-2124 25 **1999**
Patikoglou G, Burley SK Eukaryotic Transcription Factor-DNA Complexes *Annu Rev Bioph Biom* 26: 289-325 **1997**
Bewley CA, Gronenborn AM, Clore GM Minor Groove-Binding Architectural Proteins: Structure, Function, And DNA Recognition *Annu Rev Bioph Biom* 27: 105-131 **1998**
Nadassy K, Wodak SJ, Janin J Structural features of protein-nucleic acid recognition sites
*Biochemistr*y 38 (7): 1999-2017 **1999**
Ptashne M, Gann A Transcriptional activation by recruitment *Nature* 386 (6625): 569-577 **1997**

DNA/Small Molecule Interaction

Rajski SR, Williams RM DNA cross-linking agents as antitumor drugs *Chem Rev* 98 (8): 2723- 2795 **1998**
Grissom JW, Gunawardena GU, Klingberg D, et al. The chemistry of enediynes, enyne allenes and related compounds *Tetrahedron* 52 (19): 6453-6518 **1996**
Erkkila KE, Odom DT, Barton JK Recognition and reaction of metallointercalators with DNA *Chem Rev* 99 (9): 2777-2795 **1999**

DNA/Polyamides and Triple Helices

Dervan PB Molecular recognition of DNA by small molecules *Bioorgan Med Chem* 9 (9): 2215- 2235 **2001**
Frankkamenetskii MD, Mirkin SM, Triplex DNA Structures, *Annu Rev Biochem* 64: 65-95 **1995**
Thuong NT, Helene C Sequence-Specific Recognition And Modification Of Double-Helical DNA by Oligonucleotides *Angew Chem Int Ed* 32 (5): 666-690 **1993**

DNA/Zinc Finger Recognition

Wolfe SA, Nekludova L, Pabo CO DNA recognition by Cys(2) His(2) zinc finger proteins *Annu Rev Bioph Biom* 29: 183-212 **2000**
Beerli RR, Barbas CF Engineering Polydactyl Zinc-Finger Transcription Factors *Nat Biotechnol* 20 (2): 135-141 **2002**

Antisense, PNA & Unnatural Nucleobases

Uhlmann E, Peyman A Antisense Oligonucleotides - A New Therapeutic Principle *Chem Rev* 90 (4): 543-584 **1990**
Demesmaeker A, Haner R, Martin P, Et al. Antisense Oligonucleotides *Acc Chem Res* 28 (9): 366-374 **1995**
Hyrup B, Nielsen PE Peptide nucleic acids (PNA): Synthesis, properties and potential applications Bioorgan Med Chem 4 (1): 5-23 **1996**
Nielsen PE Peptide nucleic acid. A molecule with two identities *Acc Chem Res* 32 (7): 624-630 **1999**

Sugars

Dwek RA Glycobiology: Toward understanding the function of sugars *Chem Rev* 96 (2): 683-720 **1996**
Sears P, Wong CH Toward automated synthesis of oligosaccharides and glycoproteins *Science* 291 (5512): 2344-2350 **2001**
Seeberger PH, Haase WC Solid-phase oligosaccharide synthesis and combinatorial carbohydrat**e** libraries *Chem Rev* 100 (12): 4349 **2000**

Combinatorial Chemical Approaches

Thompson LA, Ellman JA Synthesis and applications of small molecule libraries *Chem Rev* 96 (1): 555-600 **1996**
Still WC Discovery of sequence-selective peptide binding by synthetic receptors using encoded combinatorial libraries *Acc Chem Res* 29 (3): 155-163 **1996**
Lam KS, Lebl M, Krchnak V The "one-bead-one-compound" combinatorial library method *Chem Rev* 97 (2): 411-448 **1997**
Schreiber SL Target-oriented and diversity-oriented organic synthesis in drug discovery *Science* 287 (5460): 1964-1969 **2000**
Ramstrom O, Lehn JM Drug Discovery By Dynamic Combinatorial Libraries *Nat Rev Drug Discov* 1 (1): 26-36 **2002**

DNA & RNA Selections

Osborne SE, Ellington AD Nucleic acid selection and the challenge of combinatorial chemistry *Chem Rev*

97 (2): 349-370 **1997**
Breaker RR In vitro selection of catalytic polynucleotides *Chem Rev* 97 (2): 371-390 **1997**

Phage & Ribosome Display and DNA Shuffling

Smith GP, Petrenko VA Phage display *Chem Rev* 97 (2): 391-410 **1997**
Roberts RW Totally in vitro protein selection using mRNA-protein fusions and ribosome display *Curr Opin Chem Biol* 3 (3): 268-273 **1999**
Stemmer WPC Rapid Evolution Of A Protein In-Vitro By DNA Shuffling *Nature* 370 (6488): 389-391 **1994**
Petrounia IP, Arnold FH Designed evolution of enzymatic properties *Curr Opin Biotech* 11 (4): 325-330 **2000**
Powell KA, Ramer SW, del Cardayre SB, Stemmer WPC, Tobin MB, Longchamp PF, Huisman GW Directed Evolution and Biocatalysis *Angew Chem Int Ed* 40 (21): 3948-3959 **2001**

Incorporation of unnatural amino acids

Mendel D, Cornish VW, Schultz PG Site-Directed Mutagenesis With An Expanded Genetic- Code *Annu Rev Bioph Biom* 24: 435-462 **1995**
Dougherty DA Unnatural amino acids as probes of protein structure and function *Curr Opin Chem Biol* 4 (6): 645-652 **2000**

Fluorescent Sensors

deSilva AP, Gunaratne HQN, Gunnlaugsson T, Huxley AJM, McCoy CP, Rademacher JT, Rice TE Signaling recognition events with fluorescent sensors and switches *Chem Rev* 97 (5): 1515- 1566 **1997**
Dugave C, Demange L Cis-trans isomerization of organic molecules and biomolecules: Implications and applications *Chem Rev* 103 (7): 2475-2532 **2003**
Tsien RY The green fluorescent protein *Ann Rev Biochem* 67: 509-544 **1998**
Zhang J, Campbell RE, Ting AY, Tsien RY Creating new fluorescent probes for cell biology *Nat Rev Mol Cell Bio* 3 (12): 906-918 **2002**
Niemeyer CM Nanoparticles, proteins, and nucleic acids: Biotechnology meets materials science *Angew Chem Int Edit* 40 (22): 4128-4158 **2001**
Chan WCW, Maxwell DJ, Gao XH, Bailey RE, Han MY, Nie SM Luminescent quantum dots for multiplexed biological detection and imaging *Curr Opin Biotech* 13 (1): 40-46 **2002**

Proteomics

Zhu H, Bilgin M, Snyder M Proteomics *Ann. Rev. Biochem* 72: 783-812 **2003**
Mann M, Hendrickson RC, Pandey A Analysis of proteins and proteomes by mass spectrometry *Ann. Rev. Biochem* 70: 437-473 **2001**
Lockhart DJ, Winzeler EA Genomics, gene expression and DNA arrays *Nature* 405 (6788): 827- 836 **2000**
Pandey A, Mann M Proteomics to study genes and genomes *Nature* 405 (6788): 837-846 **2000**

Chemical Genetics

Hung DT, Jamison TF, Schreiber SL Understanding and controlling the cell cycle with natural products *Chem Biol* 3 (8): 623-639 **1996**
Bishop A, Buzko O, Heyeck-Dumas S, Jung I, Kraybill B, Liu Y, Shah K, Ulrich S, Witucki L, Yang F, Zhang C, Shokat KM Unnatural ligands for engineered proteins: New tools for chemical genetics *Annu Rev Bioph Biom* 29: 577-606 **2000**
Bishop AC, Ubersax JA, Petsch DT, Matheos DP, Gray NS, Blethrow J, Shimizu E, Tsien JZ, Schultz PG, Rose MD, Wood JL, Morgan DO, Shokat KM A chemical switch for inhibitor- sensitive alleles of any protein kinase *Nature* 407 (6802): 395-401 **2000**

Koh JT Engineering selectivity and discrimination into ligand-receptor interfaces *Chem Biol* 9 (1): 17-23 **2002**
Visualization of biochemical networks in living cells Remy I, Michnick SW *P. Natl. Acad. Sci. USA* 98 (14): 7678-7683 **2001**