# Chem 689: Medicinal Chemistry Of Small Molecules Binding Protein Surfaces

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## A. Learning Objectives

Bioorganic and medicinal chemistry converge in the study of *small molecules binding protein surfaces*. This course is designed for any student of biological or organic chemistry who is interested in understanding, and possibly exploiting, the impact of binding protein surfaces. At the end of the class, student will understand key approaches that may be used to observe and quantify small molecules binding to proteins, and how they are applied to form molecules to target cell surface receptors and protein-protein interactions.

## B. Course Outline

The course begins with a one lecture introduction illustrating how the exploding field of monoclonal antibodies (mAbs) binding proteins is having a profound impact on diagnostics, imaging, and targeted therapeutics, particularly for disruption of protein-protein interactions. As it breaks ice and steams towards previously unconquered areas, mAb research leaves a trail of methodological approaches and validated targets for medicinal chemistry that organic chemists may then tackle with small molecule binding agents.

Analytical techniques to investigate small molecules binding to proteins are outlined. These include colorimetric, fluorescence-based outputs that may be applied to ELISA and various cellular assays. Fundamentals of blotting assays, SPR, ITC, particularly useful NMR techniques (STD, HMQC, HMBC), and photoaffinity labeling are covered.

Two lectures will be dedicated to combinatorial syntheses and screens to illustrate how split-and-mix and positional scanning can be used to find small molecules that bind unknown cell surface receptors.

Following this I plan five lectures on some of the most compelling protein-protein interaction targets in modern medicine. These include PCSK9•LDLR (heart disease), PD-1•PD-L1 (cancer immunotherapy), and uPA•uPAR (metastatic spread of cancer, circulating tumor cells). Throughout the emphasis is on the protein science, and approaches that have or could be used to find small molecule binders.

## C. Textbook

None, though I might recommend Patrick's *An Introduction To Medicinal Chemistry,* Mike Williamson's *How Proteins Work*, and Whitford's *Proteins: Structure and Function* as useful but non-essential references.

## D. Lecture And Homework Format

### Lecture Content

Topics for each lecture are shown in the "Tentative Schedule" table below, with some possible reading for some of the lectures.

## E. Schedule

| Lecture | topics that will be covered | possible reading<br>(I am still working on this) |
|---|---|---|
| 1 | Introduction: mAbs Show The Impact Of Binding Protein Surfaces<br>Diagnostics • Histology • Therapeutic Index and Actively Targeted Imaging and Therapeutic Agents • Targeted PET • Targeted MRI • Comparison Of mAb And Small Molecule Targeting Agent • Disruption Of Protein-protein Interactions | *Key ref: TiPS.,* 2000, **21**, 266<br><br>*Non-essential refs:*<br>*Expert Opin. Drug Discov.*, 2014, **9**, 1-12 |

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|---|---|---|
| 2 | Analytical Techniques To Investigate Molecules Bound To Protein Surfaces.<br>1. Detection based on electronic transitions.<br>Colorimetric Assays • Methods Involving Fluorescence and Bioluminescence (FACS, fluoromelt • FRET, TR-FRET, FP, BRET Detection Of Pyrophosphate) $\alpha$-screens • Z-Factors • ELISA • Cellular Assays<br>(Detection of Live Cells, Cell Survival Assays, Growth and Differentiation, Migration and Adhesion) • Blotting Assays | *Key refs: Bioorg. Med. Chem.,* 2012, **20**, 1979-1989<br>Bioorg. Med. Chem. Lett., 2015, **25**, 3079–3086<br>*Non-essential refs:*<br>*On assays: J. Chromatography B*, 2005, **829**, 1-25<br>*On the fragment approach: Quarterly Reviews of Biophysics*, 2012, **45**, 383. |
| 3 | Analytical Techniques To Investigate Molecules Bound To Protein Surfaces.<br>2. Detection based on other effects.<br>Surface Plasmon Resonance (SPR) • Isothermal Calorimetry (ITC) • NMR<br>(STD, HMBC and HSQC) • The Fragment Approach Via X-ray and NMR • Photoaffinity Labeling | Important to understand solid phase peptide syntheses for next section, see an undergrad book and https://youtu.be/_ajfhzhBB2U<br>*Key ref on combinatorial methods with peptides: Chem. Rev.* 2014, 114, 1020−1081. Concentrate on the methods not the results.<br>*Non-essential refs:*<br>Houghten *et* al, Drug *Discovery Today*, 2000, **5**, 276 and *Proc. Natl. Acad. Sci.*, 1985, **82**, 5131-5 |
| 4 | Combinatorial Syntheses. 1<br>Phage Display • T-Bag and Can Methodologies • Houghten's Creation And Deconvolution Of Mixtures • Split-syntheses • Peptoids • Identification and Tagging In Split Syntheses | *Non-essential refs:*<br>*Selective binding of cells to beads*: *ACS Chem. Biol.*, 2015, acschembio.5b00592<br>Excellent *in situ* click example: Heath *et al*, *Nature Chem.*, 2015, **7**, 455<br>*Libraries of fluors:* Chang, *Acc. Chem. Res.*, 2014, **47**, 1277-1286; and, *Angew. Chem. Int. Ed.*, 2015, **54**, 2442 –2446 |
| 5 | Combinatorial Screens. 2<br>Targeting Unknown Cell Surface Receptors (quantum dots for labeling cells) • *In Situ* Click Chemistry To Optimize Affinity • Targeting Particular Cell Types With Libraries Of Fluors | *ACS Chem. Biol.*, acschembio.5b00592<br>*Nat. Chem.*, 2015, **7**, 455<br>*Acc. Chem. Res.*, 2014, **47**, 1277 |
| 6 | Pharmacokinetics<br>Adsorption (oral, injection) • Distribution (BBB) • Metabolism (phase 1 and 2) • Excretion (importance of drug $t_{1/2}$ in blood) • Ames test | Patrick, *An Introduction To Medicinal Chemistry 5 th edition* |
| 7 | Interesting PPI Targets 1: PCSK9•LDLR<br>Therapeutic Rational • Structure • Strategies To Assay Small Molecules That Disrupt | *J. Biol. Chem.*, 2014, **289**, 942<br>*Chem. Biol.*, 2014, **21**, 284 |
| 8 | Interesting PPI Targets 2: PD-1•PDL-1<br>Therapeutic Rational • Structure • Strategies To Assay Small Molecules That Disrupt | *Structure*, 2015, j.str.2015.09.010<br>*Angew. Chem. Int.*, 2014, **53**, 2286 |
| 9 | Interesting PPI Targets 3: uPA•uPAR<br>Therapeutic Rational • Structure • Strategies To Assay Small Molecules That Disrupt • Relevance To The Epithelial-mesenchymal transition (EMT) In Generation Of Circulating Tumor Cells | *Theranostics*, 2013, **3**, 487<br>*Angew. Chem. Int.*, 2016, **55**, 3642 |
| 10 | Interesting PPI Targets 4: NEDD8•NAE<br>Therapeutic Rational • Structure • Strategies To Assay Small Molecules That Disrupt | THIS LECTURE WILL ONLY BE GIVEN IF TIME *ALLOWS*<br>*Nat. Rev. Mol. Cell Biol.*,2015, **16**, 30 |