Chem 689: Biomedicinal Chemistry Of Small Molecules Binding Protein Surfaces

Room ILSB, Room1147, 11:10 – 12:25 pm, TR, 2021.
Professor Kevin Burgess, Room 301C, 845-4345, burgess@tamu.edu
Assistant: Andrea Scott, Room 2161 ILSB, ascott@chem.tamu.edu, Mon - Fri 1 – 5 pm

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. Prerequisites

Completion of sophomore organic chemistry. For undergraduates I will require a B grade or above in 227 and 227 sophomore organic chemistry. You do not have to be a chemistry major; in fact, the content may be interesting to biochemists, biologists, pre-meds, pharmacists, vets, and possibly bioengineers too.

C. Flexible Credit

This class can be two or three credit hours. In summary, students must decide at the beginning of the semester if you want to sign-up for a two or three credit option knowing that it is possible to change but only early in the course (I think up until about the fifth lecture).

In the first third I will teach some basic concepts in biomedicinal chemical research that everyone should know about. The only exam will be on that part, about 10 weeks into the semester.

The second third will feature lectures from me stressing applications of the basic principles from the first course-segment, applied to contemporary biomedicinal research directed at solving important problems. Students who want to stop at two credits will have given a 5 min ppt presentation to the class at that stage; they will then have more time for the last exam and finals in more demanding classes.

Students looking to accumulate 3 h of advanced chemistry credit probably want to sign up for 3 credit hours. The third and final credit will be a literature survey on a topic I will assign in consultation with the students, featuring a written report with citations. I will teach how to choose a literature topic in an exciting, narrow field that does not involve too many papers to review. For undergraduates, there is a possibility a student's presentation can be on this same topic. Graduate students selecting the three credit hour option might work out a plan with me to review around their new research project (assuming it involves a component of biomedicinal chemistry). I think that exercise might be an ideal way to begin a research career at TAMU. In that case I will help the student formulate a possible set of specific aims for his/her new supervisor to evaluate. Those literature reviews must identify and cite the most important developments in the field, and give a forward looking conclusion to predict where the area is going.

There will be no class room lectures for the last third of the semester, except I might organize less formal meeting for talks from the people who have not presented yet, and to check on the review process.

D. More Details About The Course Content

Studies of monoclonal antibodies (mAbs) binding proteins are having a profound impact on diagnostics, imaging, and targeted therapeutics, particularly for disruption of protein-protein interactions. For instance, mAb therapies have led to breakthroughs in treatment of heart disease, and in cancer immunotherapy. As research on mAbs breaks ice and steams towards previously unconquered areas, it leaves a trail of methodological approaches and validated targets that may be tackled using with *small molecule* binding agents.

Discovery of small molecule agents to bind proteins may be achieved via a range of different combinatorial methods. Initial hits are validated as leads via a range of analytical techniques including 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 also involved.

Parts of this course will be devoted to how small molecules can be used to target cell surface receptors to image (*eg* optical, photoacoustic variants photodynamic therapy, MRI, and positron emission tomography) or treat (*eg* photodynamic therapy). For example, how can split-and-mix and positional scanning combinatorial methods be used to find small molecules that bind unknown cell surface receptors?

There will be around 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), EGF•EGFR (cancer) and uPA•uPAR (metastatic spread of cancer, circulating tumor cells, and EMT). Throughout the emphasis is on the protein science, and approaches that have or could be used to find small molecule binders.

E. Textbook

None.

F. Lecture And Homework Format

Lecture Content

Topics for each lecture are shown in the "Tentative Schedule" table below, with the corresponding homeworks scheduled for each lecture.

Homework Format

Giving students too much homework and material to read is only marginally more effective as giving them nothing at all. This course is meant to be interesting, not arduous. Consequently, throughout, one homework will be set per lecture, and it will not be excessive.

Quizes

About 5 - 10 min in each lecture will be devoted to a quiz *on the previous lecture or a reading assignment from the previous lecture*. At least twelve quizzes selected at random will be graded out of 2 points, only the best ten scores for each student will count. These quizzes will be relatively straightforward. There will be no make-up quizzes.

Exam

An exam will be given on the material covered in lectures 1 – 6, tentatively on *Thurs Oct 14*, in the class period. It will consist of 10 questions like the ones used for the quizzes, 3 pts each.

Special Assignments: Class Presentations

Students will be asked to prepare 5 min presentations (about 10 ppt slides) on an aspect of the area (small molecules binding to protein surfaces) that was not covered in the course, and assigned by me. Depending on the class enrollment, I may ask students to be responsible for their own presentations or to work together in groups. I shall assess the talks out of 10 pts: quality of slides, 3 pts; effective delivery, 3 pts; and, level and accuracy of content, 4 pts.

The Course Will Be Graded On A Curve

TWO CREDIT OPTION	**THREE CREDIT OPTION**
10 quizzes (each 2 pts, 20 pts total)	10 quizzes (each 2 pts, 20 pts total)
presentation (10 pts)	presentation (10 pts)
exam, (30 pts)	exam, (30 pts)
-	literature report
total pts: 60	**total pts: 90**

G. Opportunities For Meeting KB

Catch me after class, email or call me, or email Andrea to arrange a meeting.

H. Detailed Schedule

yellow shading = first third of course cyan = second third of course

Lecture (date to be added)	tentative topics that will be covered	tentative study assignments for next class (this list is currently incomplete)
1	Introduction: mAbs Show The Impact Of Binding Protein Surfaces 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	*to study:* know about the Warberg effect, the structure of Abs, and the difference between monoclonal and polyclonal Abs
2	Analytical Techniques To Investigate Molecules Bound To Protein Surfaces. 1. Detection based on electronic transitions. Colorimetric Assays • ELISA • Methods Involving Fluorescence Chemiluminescence, and Bioluminescence, FACS, fluoromelt • FRET, TR-FRET, FP, BRET Detection Of Pyrophosphate) α-screens • Cellular Assays (Detection of Live Cells, Cell Survival Assays, Growth and Differentiation, Migration and Adhesion) • Blotting Assays	*to study:* fully understand CETSA and TR-FRET assays, *first talk: De novo* discovery of high-affinity peptide binders for the SARSCoV-2 spike protein Pentelute, *ACS Cent. Sci.* 2021, 7, 156−163.
3	Analytical Techniques To Investigate Molecules Bound To Protein Surfaces. 2. Detection based on other effects. Z-Factors • Surface Plasmon Resonance (SPR) • Biolayer Interference (BLI) • Isothermal Calorimetry (ITC) • NMR (STD, HMBC and HSQC) • The Fragment Approach • Photoaffinity Labeling	*to study:* Classic deconvolution approach: *Proc. Natl. Acad. Sci.*, 1985, **82**, 5131-5, and Z-factors for high throughput screening *second talk:* Assays involving selective binding of cells to beads: *ACS Chem. Biol.*, 2015, acschembio.5b00592
4	Combinatorial Syntheses. 1 Phage Display and Mirror Image Phage Display • T-Bag and Can Methodologies • Deconvolution Of Mixtures • Split-syntheses • Peptoids • Identification and Tagging In Split Syntheses	*to study:* what are DNA encoded chemical libraries and how they are used, types of gels (reducing, non-reducing *etc*) *third talk:* selection of DNA-encoded chemical libraries against endogenous membrane proteins on live cells. *Nature Chem.*, 2021, **13**, 77 - 88
5	Combinatorial Screens. 2 Targeting Unknown Cell Surface Receptors (quantum dots for labeling cells) • *In Situ* Click Chemistry To Optimize Affinity	*to study:* Western blots *fourth talk:* a recent (2020 – 1) application of *in situ* click chemistry
6	Peptidic Drug Design Secondary Structure Mimics • CLIPS • peptidic knots (cyclotides, knottins, defensins, metallothionines) • Miniproteins	*to study:* cyclotides, knottins, defensins, metallothionines *fifth talk:* J. Am. Chem. Soc. 2021, 143, 14287−14299
7	Dyes In Biomedicinal Chemistry Optical Imaging and NearIR2 Dyes • Common Concepts For Turn-on Fluors • pH Dysregulation In Solid Tumors and pH Sensitive Probes • Photoacoustic Imaging • Targeting Particular Cell Types With Libraries Of Fluors	*study for lecture 9:* difference between emission-based and excitation-based imaging with near-IR2 dyes *sixth talk:* Novel and cyclic peptide PCSK9 inhibitors from an mRNA display screen *J. Med. Chem.* 2020, **63**, 13796 - 13824
8	EXAM (in class). Only on 1 – 7. There will not be an exam on the rest of the course.	no talk or quiz

9	Interesting PPI Targets 1: PCSK9•LDLR Therapeutic Rational • Structure • Strategies To Assay Small Molecules That Disrupt PPIs	*to study:* assays used for small molecules that potentially perturb PCSK9•LDLR *seventh talk:* Live cell PNA labelling enables erasable fluorescence imaging of membrane proteins *Nature Chem.*, 2021 **13**, 15-23; s41557-020-00584-z
10	Interesting PPI Targets 2: PD-1•PDL-1 Therapeutic Rationale • Structure • Strategies To Assay Small Molecules That Disrupt	*to study:* assays used for small molecules that potentially perturb PD-1•PD-L1 *eighth talk:* critical comparison of new (*ie* 2019 – 21) small molecule inhibitors of PD-1•PD-L1
11	Interesting PPI Targets 3: PROTACs, NEDD8•NAE PROTACs • Therapeutic Rational For Disrupting NEDD8•NAE • Structure • Strategies To Assay Small Molecules That Disrupt	*to study:* differences between ubiqutination and NEDDylation
12	Interesting PPI Targets 4: uPA•uPAR Therapeutic Rational • Structure • Strategies To Assay Small Molecules That Disrupt • Relevance To The Epithelial-mesenchymal transition (EMT) In Generation Of Circulating Tumor Cells	*ninth talk:* the relevance of Forkhead Box proteins to EMT
13	Interesting PPI Targets 5: EGF•EGFR Therapeutic Rational • Structure • Strategies To Assay Small Molecules That Disrupt	*only if time allows*
14	Pharmacokinetics Adsorption (oral, injection) • Distribution (BBB) • Metabolism (phase 1 and 2) • Excretion (importance of drug $t_{1/2}$ in blood) • Ames test	*only if time allows*

I. Make-up Exams

There are no make-ups on quizzes: if one of the graded ones is missed then that will count as one of the two dropped grades. Ideally, there will be no make-up exam. If a student has to miss an exam because of an excused absence as designated in the official *Texas A&M University Regulations* (see below) he/she should:

(i) Before the exam, contact Andrea Scott with a reason. Ms Powers will document such emails/calls. Students who can anticipate an excusable absence should provide notification before the day of the exam. Notifications should be received absolutely no later than two working days after the exam, and then only in cases of extreme hardship.

(ii) Written explanations must then be submitted to Ms Scott at the earliest possible time, with supporting documentation. Written requests that are not received within two working days of the absence will usually be denied (see University Rules).

J. Legal Stuff

Copyright Notice. All handouts used in this course are copyrighted and may not be copied without my expressly granted permission. By "handouts", are all materials generated for this class, including but not limited to syllabi, quizzes, exams, lab problems, in-class materials, review sheets, problem sets or other materials. Tutors and tutoring services are expressly forbidden from copying any of these materials. Only students currently enrolled in the class may make a single copy of this material for their personal use.

Excused Absences. Absences of less than three days due to injury or illness will require that you provide either a physician's note affirming the date and time of visit related to the absence or the TAMU Explanatory Statement for Absence from Class form available at: http://shs.tamu.edu/forms.htm. You may use this form to document excused absences of less than three days. However, if you do not have a physician's note, please keep in mind that the information will be verified. Misinformation on the form or an inability to verify the information will lead to sanctions under the Aggie Code of Honor. Absences of three or more days due to illness or injury will definitely require a physician's note or other acceptable documentation. Appropriate documentation will be required for other excused absences. The University's policy has an absolute deadline (by the end of the second working day after the absence) by which you must notify the professor of any excused absence. Delays in notification usually raise some doubts about the validity of the excuse. Do not take this admonition lightly since some people receive zeros on exams each semester for failure to follow this University regulation. It is your responsibility of a student requesting an excused absence to contact the Prof, not his/hers to contact them, so e-mailing asking me to contact you is unacceptable. You must keep trying to contact me or Andrea to talk with me either in person or on the phone until you are successful.

Americans with Disabilities Act (ADA) Policy Statement: The Americans with Disabilities Act (ADA) is a federal anti-discrimination statute that provides comprehensive civil rights protection for persons with disabilities. Among other things, this legislation requires that all students with disabilities be guaranteed a learning environment that provides for reasonable accommodation of their disabilities. If you believe you have a disability requiring an accommodation, please contact Disability Services, currently located in the Disability Services building at the Student Services at White Creek complex on west campus or call 979-845-1637. For additional information, visit http://disability.tamu.edu.

"An Aggie does not lie, cheat, or steal or tolerate those who do." All TAMU students commit to uphold the Honor Code, to accept responsibility for learning, and to follow the philosophy and rules of the Honor System. Students will be required to state their commitment on examinations, research papers, and other academic work. Ignorance of the rules does not exclude any member of the TAMU community from the requirements or the processes of the Honor System.