CHM 696-D: Week 10

Instructor: Alexander Wei

Research proposals, Grantwriting, and the Peer review process

Research Grant Proposals

Single principal-investigator (PI) proposals:

- Unsolicited proposals: central hypothesis developed by PI

- Request for Proposals (RFPs): driven by specific program needs

Multi-investigator proposals: Lead PI, several "co-PIs"

- Centers: research and education activities developed around a single theme; can include outreach activities, industrial co-sponsorships

- Major Research Instrumentation: activities dependent on instrument access (e.g., transmission electron microscope with special capabilities)

Grant Proposals: Show me the money

Agencies which fund single-PI research proposals

- Federal funding agencies:

  3-5 year proposals;

  $250 K - $2 M

  (includes indirect costs)

  National Science Foundation (NSF)

  National Institutes of Health (NIH) – **RO1 proposal**

  Department of Energy (DoE)

  Department of Defense (DoD; CDMRP)

  Environmental Protection Agency (EPA)

- Non-profit organizations:

  1-3 year proposals:

  $50 K - $1 M

  (indirect costs restricted)

  American Chemical Society

  American Cancer Society

  American Heart Association

  Gates Research Foundation (developing world)

  Muscular Dystrophy Association

Research grants: Where the funds go

Major expenses (direct costs):

Personnel: approx. 80%

- PI salary (for academics): 1 month + 35% fringe benefits
- Grad. student RA + fringe (25K/year) + tuition remissions (10K/year)
- Postdoc. researcher (35K/year + 43% fringe benefits)

Supplies and expenses (S&E): approx. 10K/year-person

- chemicals, equipment, facilities use (TEM, NMR, etc.)

Capital equipment: variable (20-40K)

- lasers, spectrophotometers, potentiostats, microplate readers, etc.

Facilities and Administrative (F&A) (indirect costs):

54% of direct costs at Purdue, except equipment & tuition remission

1 student RA (35K) + S&E (10K) + F&A (18.9K) = **63.9K/yr**
1 postdoc (35K+15K) + S&E (10K) + F&A (32.4K) = **92.4K/yr**

The grantwriting process: Getting started

1. Develop an idea with an important (long-term) outcome

Examples: early diagnosis of cancer, pollution-free energy source

2. Contact program officer to seek advice

a) is the funding agency interested in this idea?

b) is my budget reasonable?

c) basic do's and don'ts for grant proposal submission

3. Construct a compelling research proposal

a) background of research problem (including prior efforts), and its significance: **what is the critical question?**

b) central hypothesis: **what is your main idea and innovation?**

c) research design and methods– **what do you plan to do?**

The hypothesis-driven research proposal

1. Background and significance

Purpose: to convince the reviewer that

(i) you are working on a significant problem;

(ii) there is not yet a satisfactory solution;

(iii) solving the problem will bring great benefits to science, society, or both

2. Central hypothesis

Purpose: to provide a clear statement of your goal– how your approach is different from others, and why it will solve the problem defined above.

Specific Aims (NIH-style proposal): Provide an outline of 3-4 "action items" which must be executed in order to address the central hypothesis.

Timeline: an outline describing order of events

*** Specific Aims do NOT need to be accomplished in series ***

2 or more complementary Aims can be initiated simultaneously

The hypothesis-driven research proposal

3. Research design and methods

Present research design in order of Specific Aims

Key points to consider:

(i) Provide sufficient detail in experimental design. Take nothing for granted! Does every step have a sound theoretical or experimental basis? Whenever possible, use literature precedence to back up your claims.

(ii) Established procedure vs. innovation: Unprecedented methods require more attention to detail– the risk is greater, so the payoff must be high.

(iii) Identify weaknesses or unknowns in your experimental design. **Be self-critical.** For any major unknown, do you have a sensible backup plan?

The technology-driven research proposal

“Solution looking for a problem”

Comments:

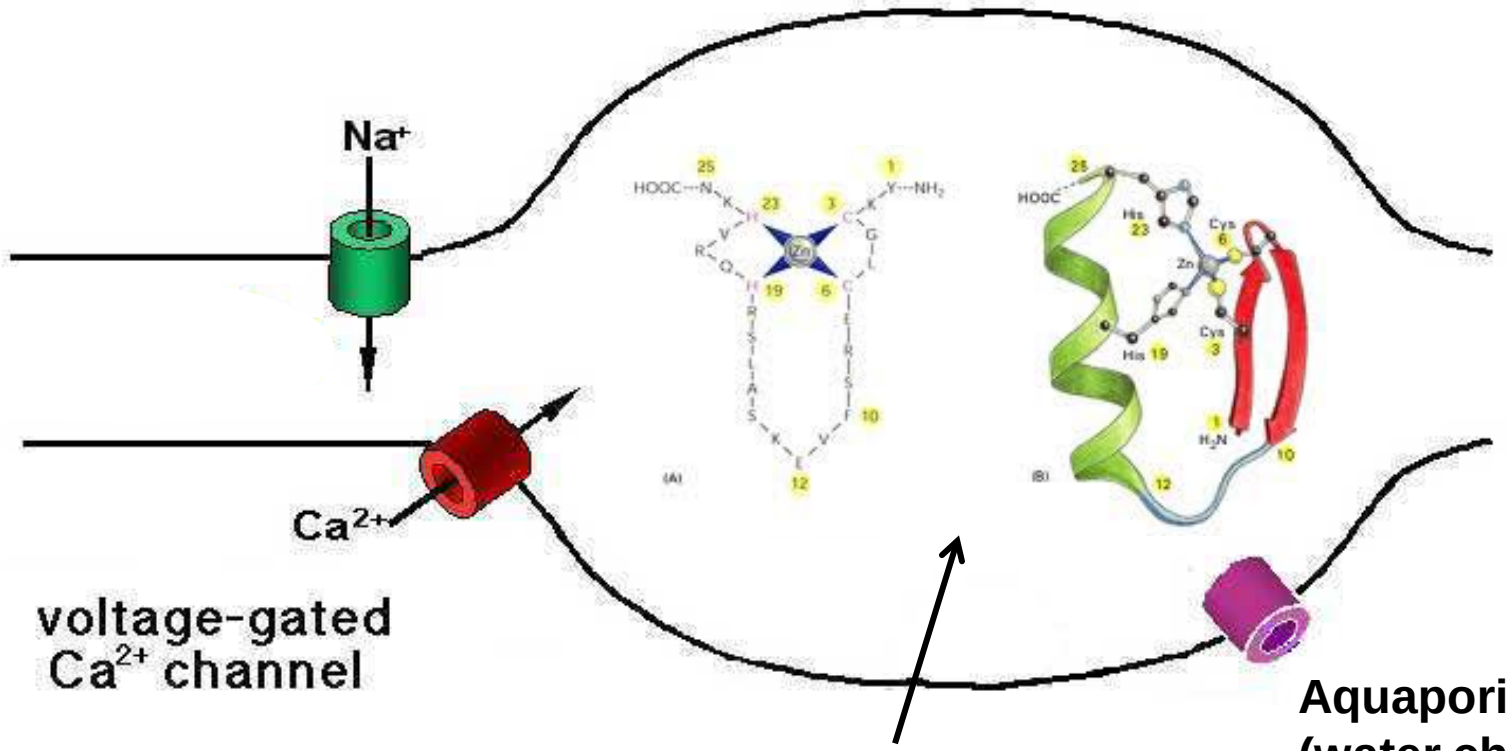
1) technology-driven proposals typically deliver improvements over existing capabilities: higher sensitivity, greater dynamic range, etc.

2) Addresses problems where advanced technical capabilities will enhance ability to address major research issue. For example:
   - high-throughput assays using DNA or protein microarrays
   - improved sensitivity for localization of biomarkers on tumor cells

3) Overlap between hypothesis- and technology-driven proposals exists; however, you must clearly define the goal of the research proposal.

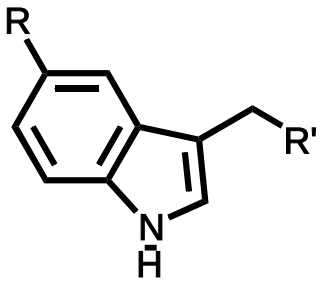
Hypothesis- vs. technology-driven research: Case 1

Research theme: ion transport into cells



Question: How do zinc ions get into cells?

Novel technology: SERS-active nanoprobe



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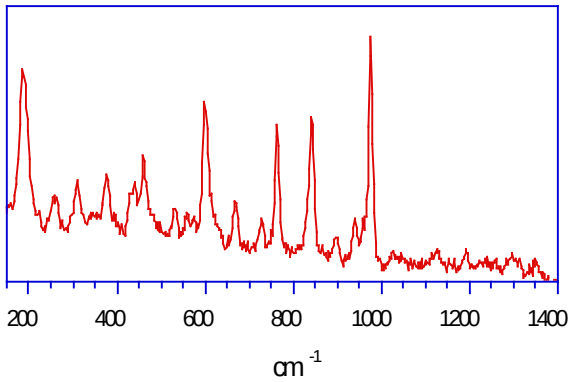
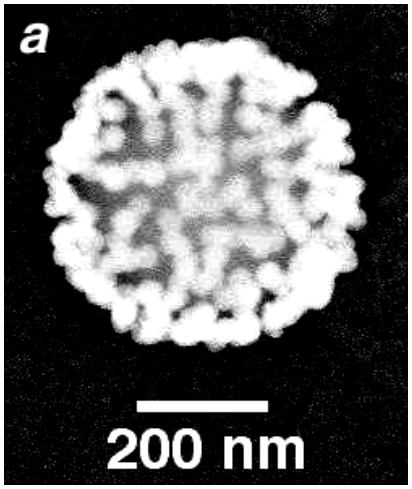
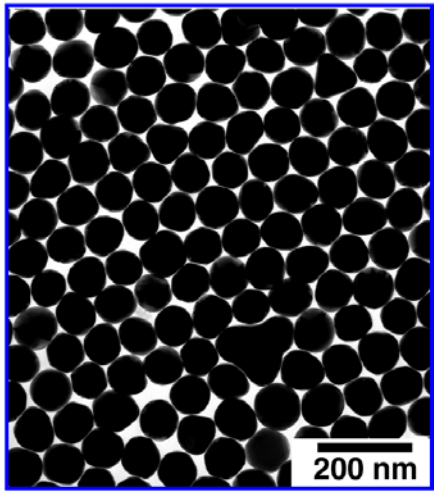


SERS spectrum = molecular "bar code"

works well in water





SERS-active receptor for metal ion detection:

nanostructured Au substrates: roughness ~ 10-200 nm

w/o Zn: 994 cm^{-1} **with Zn: 1020 cm^{-1}**

Zhao et al, *Langmuir*, *25*, 13833 (2009)

Hypothesis- vs. technology-driven research

Background 1: Zn ions are important for a variety of intracellular processes. It is unknown how Zn is transported into cells.

Background 2: Zn^{2+} and Ca^{2+} are very similar in size.

Background 3: Metal ions can be detected by synthetic receptors by a change in fluorescence or SERS activity.

(Critical question: How does Zn^{2+} get inside of cells?)

Central hypothesis: Ca^{2+} channels can mediate Zn^{2+} influx into cells, to micromolar levels.

Specific Aims:

- to develop a Zn-specific (nano)sensor with micromolar sensitivity;
- to deliver Zn nanosensors inside of cells;
- to accurately measure intracellular Zn levels using SERS;
- to correlate Ca channel activity with increases in intracellular Zn.

Hypothesis- vs. technology-driven research

Background 1: SERS is an exciting method for detecting molecules; Raman spectra can provide molecule-specific "bar codes."

Background 2: Au and Ag nanomaterials can be designed to enhance Raman scattering; single-molecule detection is possible

Background 3: SERS works well in water, and has been used for biological sensing and imaging.

(Critical question: Can we use SERS to detect ion uptake in cells?)

Central hypothesis: SERS-active nanoprobes can be designed to detect the influx of specific ions inside of cells.

Specific Aims:

- to develop a Zn-specific (nano)sensor with micromolar sensitivity;
- to deliver Zn nanosensors inside of cells;
- to accurately measure intracellular Zn levels using SERS;
- to correlate Ca channel activity with increases in intracellular Zn.

Hypothesis- vs. technology-driven research: Case 2

Research theme: neurotransmission

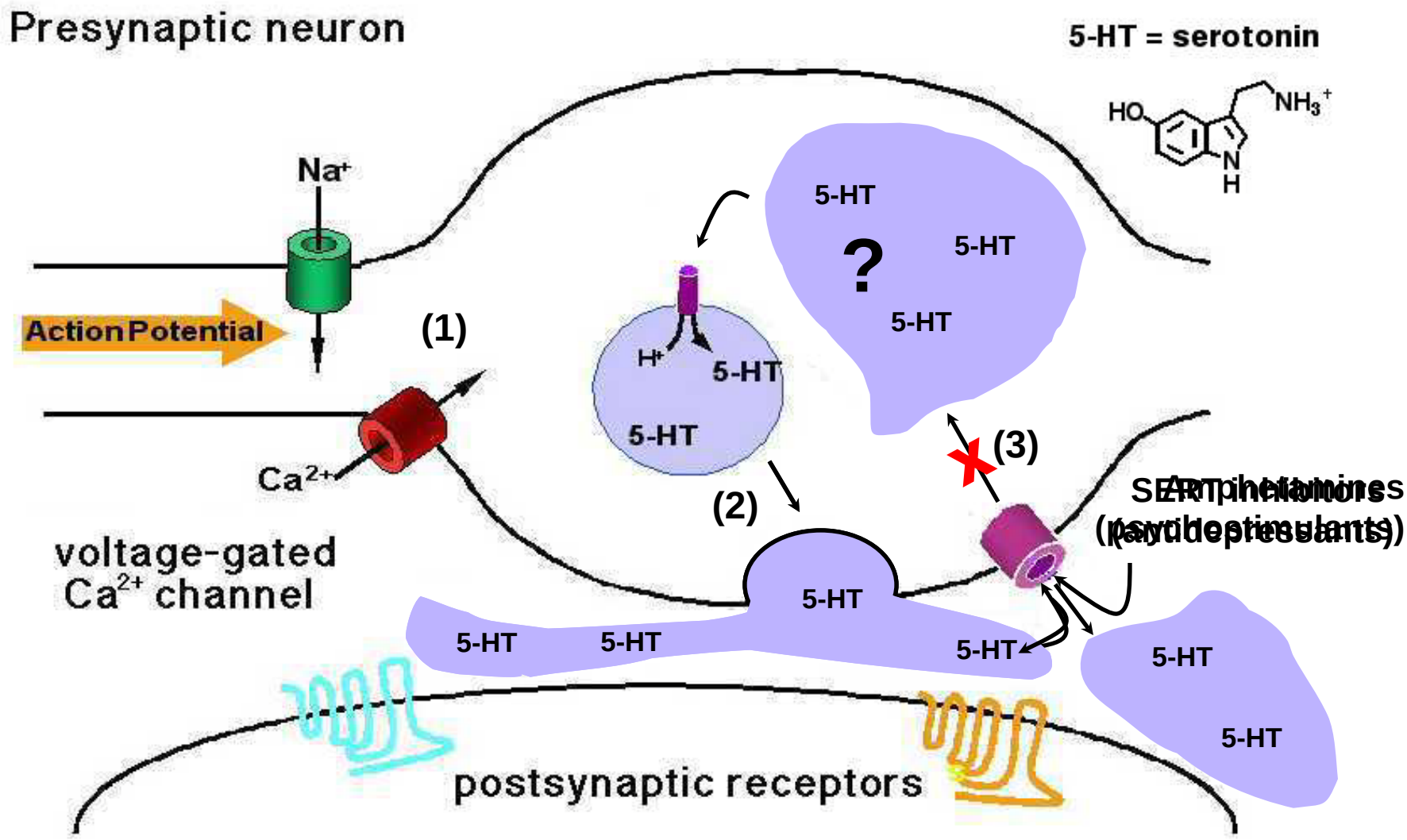
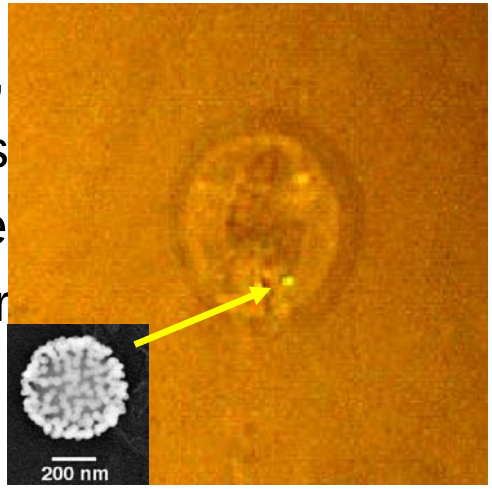


Illustration by Eric Barker (Purdue Univ., Mol. Pharmacology)

Hypothesis- vs. technology-driven research



Background 1: Serotonin reuptake is mediated by SERT, a regulatory transporter that can be inhibited by various

Background 2: It is unknown how serotonin is repackaged perhaps for lack of an appropriate intracellular sensor

Background 3: Molecules like serotonin can be detected in a manner by SERS.

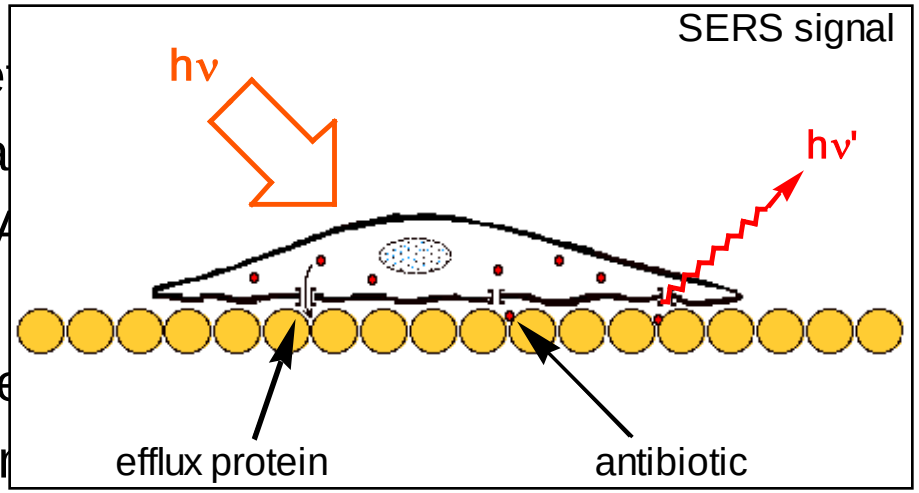
(Critical question: Is there any evidence for intracellular serotonin?)

Central hypothesis: SERT activity produces a transient spike in intracellular serotonin levels, prior to repackaging into vescicles.

Specific Aims:

- to optimize Au nanoparticles as SERS sensors for serotonin detection;
- to establish signal-response curves as a function of serotonin level;
- to deliver Au nanoprobes inside of cells (model neurons);
- to measure intracellular serotonin reuptake, with subsecond resolution.

Hypothesis- vs. technology-driven research



Background 1: SERS is a label-free me
on spectroscopic fingerprints (Rama
Background 2: Nanostructured Au and A
small amount of molecules, down to
Background 3: SERS works well in wate
toward biological sensing and imagi

(Critical question: can we use SERS to measure activity of single channels?)

Central hypothesis: SERS-active substrates can be designed with femtoliter cavities to detect molecular efflux from single cells.

Specific Aims:

- to design nanoporous Au substrates with ultrahigh SERS activity;
- to measure signal-response curves of serotonin, below micromolar levels;
- to grow cells with transporters (SERT) on Au substrates;
- to measure serotonin efflux upon treatment with methamphetamines.