Introduction to Neurobiology of Disease

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Outline
1. Introduction:
   1. Neurological diseases:
      1. Epidemiology.
      2. Approach to the neurological patient.
   2. Biological basis of neurological diseases:
      1. A growing field.
      2. Recent advances.
2. Neurobiology of Disease at UI.
3. Why this course?

DALY = YLL + YLD.
DALY: disability-adjusted life years.
YLL: years of life lost because of premature mortality.
YLD: years of healthy life lost as a result of disability.

Source: World Health Organization

Neurological Disease on the Global Agenda

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Neurology

- Approaching the neurological patient:
  - History and physical.
  - Testing (structure, function)
- What is the neurologist trying to answer?
  - Where is the lesion?
  - What is the lesion?
  - Why did it happen?

Structural studies

- Pathology (biopsy/autopsy)
- Computerized tomography (CT)
- Magnetic Resonance Imaging (MRI)
  - MR Spectroscopy.
  - Diffusion tensor imaging (DTI).

Pathology

CT/MRI
Functional studies

- Electrophysiology:
  - EMG/NCS.
  - EEG.
  - Evoked potentials.
- Functional imaging:
  - fMRI.
  - PET/SPECT.
- Neuropsychology

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Recent advances

1. Animal models of neurological disease.
2. Protein quality control.
3. Advances in genetics—are they paying off?
4. RNA interference.
5. Cellular and molecular therapies.

Animal models

- Species: rodents, primates, worms, fish, flies...
- Generation:
  - Genetic models: transgenesis, gene targeting, conditional.
  - Environmental models.

Recent advances

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Animal models

- Express a transgene (foreign gene):
  - Conventional transgenesis.
  - Viral-mediated gene transfer.
  - Inducible systems.
  - YAC/BAC transgenics.
- Targeting of endogenous genes:
  - Knock out.
  - Knock down.
  - Knock in.
  - Conditional.
Recent advances

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Consequences

- Identification of many disease-linked genes.
- Redefinition of disease phenotypes.
- Pharmacogenomics.
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RNAi in neuroscience

1. Experimental tool to study neurological disease.
2. Role of endogenous RNAi (microRNA pathway) in neurological disease.
3. Therapeutic RNAi for neurological diseases.
Recent advances

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Molecular therapies

- Gene replacement.
- Gene silencing (RNAi).

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Patient care

Education

Research

Patient care

Education

Research

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   Diseases of the nervous system pose a significant public health and economic challenge, affecting nearly 1 in 3 Americans at some point in their life, with a cost exceeding $500 billion per year.

   The NIH Blueprint for Neuroscience Research is a collaborative and coordinated effort across 15 Institutes and Centers that supports research on the nervous system to accelerate the pace of discovery in neuroscience research.
• Goal: to translate this new understanding into clinical interventions that will reduce the public health burden of nervous system disorders and help to maintain a healthy nervous system throughout life.

• Translating basic scientific discoveries into clinical benefits would be significantly enhanced if bench scientists were both informed about the biology and clinical presentation/course of neurological diseases and engaged in addressing these challenges through their research.

• Integrating courses on the neurobiology of disease into basic neuroscience training programs throughout the nation would help to forge important links between basic and clinical science.

**“Translational Research”**

**GOAL**

Graduate Students

**Research proposal and exams**

• Effort:
  – 10% class participation.
  – 40% research proposal.
  – 25% midterm exam.
  – 25% final exam.

**Research proposal**

• Successful scientists write great grants.
• Writing a great grant takes practice.
• Great grant: A clear, compelling description of a logical set of experiments that test a biologically significant hypothesis.
Grant greatness

• “Clear, compelling description”
  – More is not always better (“If I had more time I would write a shorter letter” - Cicero)
• “Logical set of experiments”
  – The right methods to test your hypothesis(es) should lead to easily interpretable results
  – Expected outcomes aren’t the only possible outcomes
• “Biologically significant hypothesis”
  – Convincing the reader that the problem is important and that you are taking the right approach is more than half the battle

Proposal guidelines

• Proposal should address an important question regarding the neurobiology of a particular disorder or group of disorders
• Cannot be on your own research or that of your laboratory
• Cannot be a research project you worked on in a rotation laboratory, though it can be informed by a prior rotation
• Ideally centered on a disease discussed in course, though exceptions can be made with permission

Proposal guidelines (II)

• 10 page maximum length, single space text.
• Clearly stated, central hypothesis.
• Research described in 1-3 aims (2)
• Components:
  – Page 1: Abstract (200 words or less)
  – Page 2: Aims page (one page max)
  – Background/significance (2-3 pages)
  – Research design and methods (5-6 pages)

Research design and methods

• Typically organized into specific aims, with each aim testing a specific hypothesis.
• Organization of each aim:
  - Rationale for the experiments and chosen methodology.
  - Experimental design: with sufficient detail to show command of techniques.
  - Expected and alternative outcomes/potential problems.

Sites for grant writing help

NINDS website for grant writing:
http://www.ninds.nih.gov/funding/write_grant_doc.htm

All About Grants Tutorial:
http://www.niaid.nih.gov/ncn/grants/

Exams

• Dates and material:
  - Midterm: October 16th.
  - Final: December 16th.
• Primarily short answer questions.
• Will encompass course topics, including review articles provided.
• Systems, genetic, molecular, pathological and clinical elements all will be addressed in questions
• Focus will be on concepts and pathomechanisms rather than on details of disease