Course Objectives

• Logistics
• Expectations
Schedule/Website

https://hopecenter.wustl.edu/

https://hopecenter.wustl.edu/?page_id=11922
Lessons from previous years
Comments on genetic studies

A Hexanucleotide Repeat Expansion in C9ORF72 Is the Cause of Chromosome 9p21-Linked ALS-FTD

**Hypothesis:** ALS-FTD is a genetic disease and a heritable element can be identified at chromosome 9p21
Exome Sequencing Reveals DNAJB6 Mutations in Dominantly-Inherited Myopathy

**Hypothesis:** Some muscle diseases have a genetic etiology, we hypothesize that exome sequencing will identify a genetic cause.
Patient phenotyping

• Clinical Neurology is a science in itself
Two papers of same family

Linkage of Familial Dilated Cardiomyopathy with Conduction Defect and Muscular Dystrophy to Chromosome 6q23


Etiology of Limb Girdle Muscular Dystrophy 1D/1E Determined by Laser Capture Microdissection Proteomics

ANN NEUROL 2012;71:141–145
Laser microdissection

Sequencing identifies known desmin mutations in this family
Desmin is on chromosome 2q35 not 6q23
Imaging techniques in neurologic disease

• CT scan
• MRI
MRI based Diffusion Tensor imaging
PET/SPECT imaging
PET base PIB imaging
Functional MRI

- BOLD contrast (blood-oxygen-level dependent)
Functional connectivity
Functional connectivity
Translational Neuroscience

• Definitions
To the Editor:

“Studying Aging, and Fearing Budget Cuts” (Feb. 22) points out that research on aging is seriously underfinanced, but overlooks the reasons.

A major factor is the overemphasis on so-called translational research, which seeks to translate laboratory findings into clinical applications, at the expense of basic research. The push for translational studies by the National Institutes of Health, Congress and our universities is shortsighted and damaging.

We do not even know the normal function of proteins that cause neurodegenerative diseases like Alzheimer’s. Moreover, several recent clinical trials to test drugs for dementia are not based on solid scientific evidence. Before we can find rational treatments for these diseases, more resources must be directed to basic studies.

Moses V. Chao

New York

The writer is a professor in the molecular neurobiology program at New York University School of Medicine.
Therapy development

- Basic
- Translational
- Clinical
Where do drug companies get leads?
Believe it or not: how much can we rely on published data on potential drug targets?

Florian Prinz, Thomas Schlange and Khusru Asadullah

- Bayer HealthCare
- Internal study with 23 labs and 67 projects
- 70% Oncology
- Outcomes of drug target discoveries
c)

- Inconsistencies (65%)
- Not applicable (3%)
- Literature data are in line with in-house data (21%)
- Main data set was reproducible (7%)
- Some results were reproducible (4%)

<table>
<thead>
<tr>
<th>Inconsistencies</th>
<th>Not applicable</th>
<th>Literature data are in line with in-house data</th>
<th>Main data set was reproducible</th>
<th>Some results were reproducible</th>
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</thead>
<tbody>
<tr>
<td>Model reproduced 1:1</td>
<td>Model adapted to internal needs (cell line, assays)</td>
<td>Literature data transferred to another indication</td>
<td>Not applicable</td>
<td></td>
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<tr>
<td>In-house data in line with published results</td>
<td>1 (7%)</td>
<td>12 (86%)</td>
<td>0</td>
<td>1 (7%)</td>
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<tr>
<td>Inconsistencies that led to project termination</td>
<td>11 (26%)</td>
<td>26 (60%)</td>
<td>2 (5%)</td>
<td>4 (9%)</td>
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Raise standards for preclinical cancer research

C. Glenn Begley and Lee M. Ellis propose how methods, publications and incentives must change if patients are to benefit.

Researchers at Amgen could only reproduce 6/53 published studies (11%)
Academic labs can reproduce the studies

<table>
<thead>
<tr>
<th>Journal impact factor</th>
<th>Number of articles</th>
<th>Mean number of citations of non-reproduced articles*</th>
<th>Mean number of citations of reproduced articles</th>
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<tr>
<td>&gt;20</td>
<td>21</td>
<td>248 (range 3–800)</td>
<td>231 (range 82–519)</td>
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<tr>
<td>5–19</td>
<td>32</td>
<td>169 (range 6–1,909)</td>
<td>13 (range 3–24)</td>
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Results from ten-year retrospective analysis of experiments performed prospectively. The term ‘non-reproduced’ was assigned on the basis of findings not being sufficiently robust to drive a drug-development programme.

Why discrepancies?

• Unrelated to journal quality
• Unrelated to previous claims regarding the target
• Unrelated to number of independent groups that had validated

• Other thoughts?