New Directions in Clinical Neuroscience

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Disclosures: None
Federal employee: Public filing of all financial interests
Impact of Research on Heart Disease

**Age-Adjusted Death Rates for Coronary Heart Disease, U.S., 1950–2007**

- **Actual**
- **Expected**
- **Peak**

- Almost 1.8M deaths expected in 2007 if rise had continued
- 1.5M deaths expected in 2007 if no decline from peak rate
- 1.1M deaths averted in 2007 due to decline from peak rate in 1968 (1.5M – 400K)
- 406,000 actual deaths in 2007

*Source: NHLBI Factbook, 2010*
Success Stories in Clinical Neuroscience

• Acute ischemic stroke – tPA within 3 hours of onset, 30% full recovery

• MS – treatments that slow progression and biomarker to track outcome

• Early Parkinson’s excellent response to DA agonists

• Mood, anxiety, and psychotic disorders – excellent response to meds and psychosocial Rx in subset

• DBS effects in Parkinson’s, tremor, refractory depression
But, there is still much to do....

- Diagnosis is by observation, detection is late, prediction is poor

- Etiology is unknown for many disorders; prevention is not well-developed for most disorders

- Treatment is trial and error – no cures, no vaccines.

**Bottom line:** Revolution in neuroscience, but... this revolution remains to be translated to better diagnostics, preventions, and cures
Brain Disorders are Chronic and Disabling

Burden of Disease: Lead Contributing Disease Categories to DALYs

1. Neuropsychiatric Disorders: 28.47
2. Cardiovascular Diseases: 13.94
3. Malignant Neoplasms: 12.57
4. Unintentional Injuries: 6.69
5. Sense Organ Disorders: 6.61
6. Respiratory Diseases: 6.57
7. Musculoskeletal Diseases: 3.84
8. Digestive Diseases: 3.31

Percent of Total DALYs; U.S. & Canada

Source: WHO 2008
Brain Disorders are Deadly

- Over 36,000 suicides per year in the U.S. (2009; CDC)
  - 90% related to mental illness (Mann, 2002)
  - More suicides than combat deaths in US Army (DoD, 2011)
  - 3rd leading source of mortality ages 15 - 24

- For context:
  - 17,000 homicides (2010)
  - 34,000 traffic fatalities (2010; NTSB)
  - < 20,000 AIDS deaths (2009, CDC)

Life expectancy reduced 8 years with serious mental illness (cardiopulmonary, metabolic, multiple conditions) (Druss et al., Medical Care, 2011)
### Economic Burden of Noncommunicable Diseases, 2011-2030

(trillions of US$ 2010)

<table>
<thead>
<tr>
<th>Country income group</th>
<th>Diabetes</th>
<th>Cardiovascular diseases</th>
<th>Chronic Respiratory diseases</th>
<th>Cancer</th>
<th>Mental Illness</th>
<th>Total</th>
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<tbody>
<tr>
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<td>0.9</td>
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<td>1.6</td>
<td>5.4</td>
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<td>4.8</td>
<td>8.3</td>
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</table>


US Annual Costs > $300B for SMI (Insel, AJP, 2008)
Prevalence = 5.4M in 2011
1 in 8 Americans > 65 y.o.
Prevalence projected to double by 2050

### Multi-level Scientific Approach: Our Toolbox

<table>
<thead>
<tr>
<th>Molecules</th>
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<td>imaging</td>
<td>ChR-2</td>
<td>Epidemiology</td>
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Genetics: Transforming Technologies
Sequencing Costs Drop Faster than Moore’s Law

Cost per Megabase of DNA Sequence

Moore’s Law

Cost per Mb

28,500X
Genetics – What Have We Learned?

- Genetic ≠ Inherited (spontaneous mutations are common)
- Genetic ≠ Causal (genes confer risk and resilience)
- Genetics may reveal pathways involved in risk and resilience
- Genetics provides a mechanism for experience to influence brain and behavior (epigenomics!)
- Genetics (genomics) is our most powerful tool for understanding individual variation (and that variation is huge!)
Transformative Technologies – iPS cells

Science 318, 1917 (2007)

Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells

Junying Yu,1,2,* Maxim A. Vodyanik,2 Kim Smuga-Otto,1,2 Jessica Antosiewicz-Bourget,1,2
Jennifer L. Frane,4 Shulan Tian,3 Jeff Nie,5 Gudrun A. Jonsdottir,3 Victor Ruotti,1
Ron Stewart,3 Igor I. Slukvin,2,4 James A. Thomson1,2,5


Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors

Kazutoshi Takahashi,1 Koji Tanabe,1 Mari Ohuchi,1 Megumi Narita,1,2 Tomoko Ichisaka,1,2 Kiichiro Tomoda,1
and Shinya Yamanaka1,2,3,4,*
1Department of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan
2CREST, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan
3Gladstone Institute of Cardiovascular Disease, San Francisco, CA 94158, USA
4Institute for Integrated Cell-Material Sciences, Kyoto University, Kyoto 606-8507, Japan

Map2, TH, DAPI

Dolmetsch lab, 2012
Disease in a dish for Rx screening

Personalized cell Rx

Transformative Technologies – iPS cells

_Nature_, Jan 19, 2012 vol 481
Cell Biology: dendrite dynamics in Timothy syndrome derived neurons

Source: Pasca and Dolmetsch
Optogenetics

Functional dissection of amygdala microcircuitry using optogenetic tools

Optogenetic reactivation of hippocampal neurons after fear conditioning.
Light-induced fear memory recall.

Tye and Disseroth, Nat Neurosci Rev 2012

Liu et al., Nature 2012
Mapping the Connectome: From DTI to DSI

Wedeen V.J, Science, 2012
Objective Measures

Activity, Sleep, EDA, EKG, EEG, Stereotypies, Temp.

Non-invasive 24/7 inexpensive phenotyping

MIT MEDIA LAB Roz Picard and colleagues
United States Flu Estimate

Google Flu Trends estimate

United States data

United States: Influenza-like illness (ILI) data provided by the U.S. Centers for Disease Control

From the Google Flu Trends web site: www.google.org/flutrends/
Crowd sourcing science: RNA nanostructure as a Rubik’s Cube
6,000 players worldwide; Social networks forming to compete
### Multi-level Scientific Approach: Our Toolbox

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- **Molecules**
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Where are we stuck?

• We don’t understand the biology of normal or abnormal brain development, function, and aging

• We arrive too late to preempt the major symptoms

• We are looking for home runs instead of base hits (and grand slams)
Drug development is slow and risky
Trends in Drug Development: Eroom’s Law

a Overall trend in R&D efficiency (inflation-adjusted)

- FDA tightens regulation post-thalidomide
- FDA clears backlog following PDUFA regulations plus small bolus of HIV drugs
- First wave of biotechnology-derived therapies

Scannell et al, NRDD, 2012
Trials to confirm or exclude “targets”; drugs as tools for fast fail
New Paradigm: Experimental Medicine

- Move quickly into humans
- Focus on Phase 0 – Phase 2a
- Fail quickly and often
- Target engagement (imaging, MOA)
- Precompetitive partnerships (biomarkers)
- Share data (especially failures)
New Targets?

Protective LOF mutations, Pathway targets, epigenetics

Cell replacement Rx, Plasticity agents

Circuit based Rx, rTMS, DBS

Combined Therapies

Cognitive training

Peer support
An epigenetic blockade of cognitive functions in the neurodegenerating brain

Johannes Gräff1,2,3, Damien Rei1,2, Ji-Song Guan1,2,3, Wen-Yuan Wang1,2,3, Jinsoo Seo1,2, Krista M. Hennig3,4, Thomas J. F. Nieland1, Daniel M. Fass3,4, Patricia F. Kao5, Martin Kahn1, Susan C. Su1,2, Alireza Samiel1, Nadine Joseph1,2,3, Stephen J. Haggarty3,4, Ivana Delalle5 & Li-Huei Tsai1,2,4

LETTER

doi:10.1038/nature10849
<table>
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<th>Disease</th>
<th>Target ID</th>
<th>Assay Dev.</th>
<th>HTS</th>
<th>Probe to Lead</th>
<th>Pre-Clinical</th>
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<th>Ph. I</th>
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<th>Clinic</th>
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Advancing Translational Science: Repurposing
The NCGC Pharmaceutical Collection: A Comprehensive Resource of Clinically Approved Drugs Enabling Repurposing and Chemical Genomics

Ruili Huang,* Noel Southall,* Yuhong Wang, Adam Yasgar, Paul Shinn, Ajit Jadhav, Dac-Trung Nguyen, Christopher P. Austin†

Small-molecule compounds approved for use as drugs may be “repurposed” for new indications and studied to determine the mechanisms of their beneficial and adverse effects. A comprehensive collection of all small-molecule drugs approved for human use would be invaluable for systematic repurposing across human diseases, particularly for rare and neglected diseases, for which the cost and time required for development of a new chemical entity are often prohibitive. Previous efforts to build such a comprehensive collection have been limited by the complexities, redundancies, and semantic inconsistencies of drug naming within and among regulatory agencies worldwide; a lack of clear conceptualization of what constitutes a drug; and a lack of access to physical samples. We report here the creation of a definitive, complete, and nonredundant list of all approved molecular entities as a freely available electronic resource and a physical collection of small molecules amenable to high-throughput screening.
### Informatics sources for NPC
- US FDA: Orange Book, OTC, NDC, Green Book, Drugs at FDA
- Britain NHS
- EMEA
- Health Canada
- Japan NHI

### Physical sources for NPC
- Procurement from >70 suppliers worldwide
- In-house purification of APIs from marketed forms
- Synthesis

<table>
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<th>In house</th>
<th>Procurement in process</th>
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<tr>
<td>US FDA</td>
<td>1635</td>
<td>182</td>
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<tr>
<td>UK/EU/Canada/Japan</td>
<td>756</td>
<td>177</td>
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<td>Investigational</td>
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<tr>
<td>Total Approved</td>
<td>2391</td>
<td>359</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>3319</strong></td>
<td><strong>4312</strong></td>
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</table>

**Drug plate composition**

- US FDA: 49%
- Canada/UK/EU/Japan: 23%
- Investigational: 28%
Rx depression in 3 hours instead of 8 weeks

Hamilton Depression Rating Scale

Time (Minutes)

Infusion

Response: 50% decrease in HAMD from baseline

Zarate et al. Arch Gen Psychiatry, 2006
Neuroscience: Lost in Translation?

NIH & FDA
Industry
Academia
Patients
Precompetitive Partnerships

ADNI
FNIH (Biomarkers Consortium)
NCATS (New Uses for Existing Drugs)
New Opportunities for Therapeutics

Revolutionary neuroscience:

Epigenetics
- New molecular targets
- Rapid treatments
- Circuit-based Rx
- Cognitive training
- Devices
- Combined interventions

Transforming Translation:

Precompetitive partnerships
- Experimental medicine
- Precision medicine
- Regulatory science
- Patient centered care
“We always overestimate the change that will occur in the next two years and underestimate the change that will occur in the next ten.”

--Bill Gates Jr.