Presidential Symposium
Getting to Cure – The Challenging Road to Disease Modification and Prevention for Epilepsy

Symposium Chair:

Amy Brooks-Kayal, M.D.

Saturday, December 5, 2015
Convention Center – Grand Ballroom AB

8:30 – 11:45 a.m.

GENERAL INFORMATION

Accreditation

The American Epilepsy Society is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Credit Designation

Physicians

The American Epilepsy Society designates this live activity for a maximum of 30.75 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Physician Assistant

AAPA accepts certificates of participation for educational activities certified for *AMA PRA Category 1 Credit*™ from organizations accredited by ACCME or a recognized state medical society. Physician assistants may receive a maximum of 30.75 hours of Category 1 credit for completing this program.

Jointly provided by AKH Inc., Advancing Knowledge in Healthcare and the American Epilepsy Society.

Nursing

AKH Inc., Advancing Knowledge in Healthcare is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity is awarded 30.75 contact hours.

Nurse Practitioners

AKH Inc., Advancing Knowledge in Healthcare is accredited by the American Association of Nurse Practitioners as an approved provider of nurse practitioner continuing education. Provider Number: 030803. This program is accredited for 30.75 contact hours which includes 8 hours of pharmacology. Program ID #21547

This program was planned in accordance with AANP CE Standards and Policies and AANP Commercial Support Standards.

Pharmacy

AKH Inc., Advancing Knowledge in Healthcare is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Select portions of this Annual Meeting are approved for pharmacy CE credit. Specific hours of credit for approved presentations and Universal Activity Numbers assigned to those presentations are found in the educational schedules. Criteria for success: nursing and pharmacy credit is based on program attendance and online completion of a program evaluation/assessment.

If you have any questions about this CE activity, please contact AKH Inc. at service@akhcme.com.

International Credits

The American Medical Association has determined that non-U.S. licensed physicians who participate in this CME activity are eligible for *AMA PRA Category 1 Credits*™.

CME/CE Certificates

For those attendees who wish to claim CME or CE, there is an additional fee. Registrants can pay this fee as part of the registration process. Those who do not pre-purchase the credit will also have the ability to pay this fee at the time they attempt to claim credit. Fees for CME increase after January 16 and are a one-time charge per annual meeting.

The evaluation system will remain open through Friday, February 26, 2016. Evaluations must be completed by this date in order to record and receive your CME/CE certificate.

Member Fees:	$50 through January 15, 2016 $75 January 16 – February 26, 2016
Non-member Fees:	$75 through January 15, 2016 $100 January 16 – February 26, 2016

Attendance Certificate/International Attendees

A meeting attendance certificate will be available at the registration desk for international meeting attendees on Tuesday, December 8.

Policy on Commercial Support and Conflict of Interest

The AES maintains a policy on the use of commercial support, which assures that all educational activities sponsored by the AES provide in-depth presentations that are fair, balanced, independent and scientifically rigorous. All faculty, planning committee members, moderators, panel members, editors, and other individuals who are in a position to control content are required to disclose relevant relationships with commercial interests whose products relate to the content of the educational activity. All educational materials are reviewed for fair balance, scientific objectivity and levels of evidence. Disclosure of these relationships to the learners will be made through syllabus materials and the meeting app.

Disclosure of Unlabeled/Unapproved Uses

This educational program may include references to the use of products for indications not approved by the FDA. Faculty have been instructed to disclose to the learners when discussing the off-label, experimental or investigational use of a product. Opinions expressed with regard to unapproved uses of products are solely those of the faculty and are not endorsed by the AES.

OVERVIEW
Epilepsy care has focused on symptomatic treatment, that is, control of seizures. Modification of disease progression, underway in other clinical areas, has not been a focus of epilepsy research until recent years. Translation from the bench to the clinic requires collaboration among scientists, clinical researchers and clinicians. This symposium will address the development of clinical trials for diseasemodifying therapies including issues which can adversely impact successful outcomes.

LEARNING OBJECTIVES
Following participation in this symposium, learners should be able to:

- Recognize role of treatments which can result in disease modification and be aware of research into such treatments
- Collaborate on the development of appropriate studies to evaluate potential disease-modifying treatments

TARGET AUDIENCE
Basic: Those new to epilepsy treatment or whose background in the specialty is limited, e.g., students, residents, general physicians, general neurologists and neurosurgeons, other professionals in epilepsy care, administrators.

Intermediate: Epilepsy fellows, epileptologists, epilepsy neurosurgeons, and other providers with experience in epilepsy care (e.g., advanced practice nurses, nurses, physician assistants), neuropsychologists, psychiatrists, basic and translational researchers.

Advanced: Address highly technical or complex topics (e.g., neurophysiology, advanced imaging techniques or advanced treatment modalities, including surgery.)

Agenda
Chair: Amy Brooks-Kayal, M.D.

Introduction:Why make the Journey: The Need for DmaP Therapies for Epilepsy
Amy Brooks-Kayal, M.D.

Picking Your Route: How Do We Identify and Validate Targets for Disease modification?
Manisha Patel, Ph.D.

Beginning the Journey: The Path to Phase I
Rajesh Ranganathan, Ph.D.

The Road Less Traveled: Novel Approaches to Successful Translation of Disease-modifying Therapy
Kate Dawson, M.D.

Detours and Misdirections: Cautionary Tales of Translation Failures
Emily Sena, Ph.D.

Getting to Cure: A Path Forward for Disease-modifying Therapy for Epilepsy
Robert Pacifici, Ph.D.

Conclusions
Amy Brooks-Kayal, M.D.

Education Credit
2.25 CME Credits

Nurses may claim up to 2.25 contact hours for this session.

Nurse Practitioners may claim 1.5 hours of pharmacology for this session.

Pharmacy Credit
AKH Inc., Advancing Knowledge in Healthcare approves this knowledge-based activity for 2.25 contact hours (0.225 CEUs). UAN 0077-9999-15-035-L01-P. Initial Release Date: 12/5/2015.

The American Board of Psychiatry and Neurology has reviewed the Getting to Cure – The Challenging Road to Disease Modification and Prevention for Epilepsy Symposium and has approved this program as part of a comprehensive program, which is mandated by the ABMS as a necessary component of maintenance of certification.

Commercial Support Acknowledgement
Supported in part by educational grants from Acorda Therapeutics and Supernus Pharmaceuticals, Inc.

FACULTY/PLANNER DISCLOSURES
It is the policy of the AES to make disclosures of financial relationships of faculty, planners and staff involved in the development of educational content transparent to learners. All faculty participating in continuing medical education activities are expected to disclose to the program audience (1) any real or apparent conflict(s) of interest related to the content of their presentation and (2) discussions of unlabeled or unapproved uses of drugs or medical devices. AES carefully reviews reported conflicts of interest (COI) and resolves those conflicts by having an independent reviewer from the Council on Education validate the content of all presentations for fair balance, scientific objectivity, and the absence of commercial bias. The American Epilepsy Society adheres to the ACCME's Essential Areas and Elements regarding industry support of continuing medical education; disclosure by faculty of commercial relationships, if any, and discussions of unlabeled or unapproved uses will be made.

FACULTY / PLANNER BIO AND DISCLOSURES
Amy Brooks-Kayal, M.D. (Chair)
Amy Brooks-Kayal, MD is Professor of Pediatrics, Neurology & Pharmaceutical Sciences, Co-director of the Translational Epilepsy Research Program, and Chief & Ponzio Family Chair of Pediatric Neurology at the University of Colorado and Children's Hospital Colorado Dr. Brooks-Kayal trained at Johns Hopkins, University of Pennsylvania and Children's Hospital of Philadelphia (CHOP). She joined the University of Colorado in 2008 after 13 years on the faculty at UPenn and CHOP. Her area of clinical focus is pediatric epilepsy. Her research focuses on regulation of neurotransmitter systems during epilepsy and epileptogenesis and preclinical development of disease modifying therapies. Dr. Brooks-Kayal is the current President of AES.

Amy Brooks-Kayal, M.D. discloses receiving support as a Consultant for Pfizer Neuroscience; spouse is President of SPI Pharma (no medications related to epilepsy); Stock Ownership in Johnson & Johnson; Honoraria form several universities for visiting professor lectures.

Kate Dawson, M.D.
Dr. Kate Dawson is Vice President, US Medical at Biogen, and is an Instructor/Neuroscientist at MGH/Harvard Medical School. She joined Biogen in 2004. In 2006, she became the Global Medical Lead on the BG-12 program with oversight of the Ph 3 clinical trials. More recently she led the Global Medical Neurology group and currently leads the US Medical Team. Dr. Dawson completed her Neurology Residency and Neuromuscular Fellowship at Massachusetts General Hospital and became

the Director of the Neuromuscular Fellowship Program, Attending Physician in the Neuromuscular Diagnostic Center at MGH. She received her Medical Degree from Albert Einstein College of Medicine. She serves on the Board of Directors of the Biogen Foundation.

Katherine Dawson, M.D. discloses receiving support as Salary from Biogen; as a Patent Holder – inventor on Biogen patent; Stock Ownership from Biogen; serves on the Board of Directors of the Biogen Foundation (focused on STEM education.)

Robert Pacifici, Ph.D.
Robert Pacifici is the Chief Scientific Officer of CHDI Foundation, a private, nonprofit organization that works with a global network of scientists to accelerate therapeutics development for Huntington's disease. Previously he was the Site Director and Chief Scientific Officer at the RTP Laboratories of Eli Lilly where he oversaw the company's global screening and quantitative-biology efforts. Prior to Lilly, Pacifici was Vice President of Discovery Technologies at Xencor, a biotechnology company that develops protein therapeutics. At Amgen for nearly ten years, Pacifici held positions of increasing responsibilities including leadership for their automation, high throughput screening, and information technologies groups.

Robert Pacifici, Ph.D. has indicated he has no financial relationships with commercial interests to disclose.

Manisha Patel, Ph.D.
Dr. Manisha Patel received her Ph.D. in Pharmacology and Toxicology at Purdue University and post-doctoral training in Neuroscience at Duke University. She is currently a Professor in the Department of Pharmaceutical Sciences at the University of Colorado Anschutz Medical Campus. Her laboratory conducts basic and translational research to understand the metabolic basis of epilepsy and develop neuroprotective therapies. She has served on numerous AES committees and taskforces. She is currently the chair of AES's Research and Training Council.

Dr. Patel discloses receiving support as Salary form Aeolus Pharmaceuticals Consultancy; Intellectual Property Rights/Patent Holder from the University of Colorado IP; Consulting Fees from Aeolus Pharmaceuticals; Stock options from Aeolus Pharmaceuticals; Honoraria from NIH, universities, private foundations for grant review; Serves as a Reviewer of Grants for NIH, AES, Cystic Fibrosis Foundation (spouse)

Dr. Patel does intend to reference unlabeled/unapproved uses of drugs or products in her presentation: Catalytic antioxidants, salicyclamine.

Rajesh Ranganathan, Ph.D.
Rajesh Ranganathan is VP of science and regulatory advocacy at PhRMA and leads PhRMA's continuing science advocacy efforts to promote effective, efficient, and innovative drug discovery and development. Rajesh was formerly the Director of the Office of Translational Research at the National Institute for Neurological Disorders and Stroke where he was responsible for leading the Institute's efforts to more quickly and effectively convert basic and translational research results into new therapeutics. He moved into this role after serving as the senior advisor to the Director of the National Institutes of Health (NIH) in the area of translational medicine. Rajesh has BA degrees in biology and chemistry and PhD in Biology from MIT.

Rahesh, Ranganathan, Ph.D. has indicated he has no financial relationships with commercial interests to disclose.

Emily Sena, Ph.D.

Dr Emily Sena is a postdoctoral researcher specialised in the validity of preclinical studies. Her research interests are in the use of systematic review and meta-analysis of preclinical studies to increase the understanding of critical facets of translational medicine and developing new hypotheses for testing in the laboratory. She has an interest in assessing for the presence and impact of publication bias in the life sciences, and also leads a consortium tasked with establishing the framework to undertake international multicentre preclinical animal trials.

Emily Sena, Ph.D. discloses being a Scientific Member of the University of Edinburgh's Annual Welfare Ethical Review Board.

CME Reviewer

Lara Jehi, M.D.

Dr Lara Jehi is an adult epileptologist, the head of the Outcomes Research Program, and the Director of Research at the Cleveland Clinic Epilepsy Center. Her interests have focused on understanding and improving outcomes of epilepsy treatment. She serves as the Associate Program Director of the Clinical Research Unit at Cleveland Clinic within the auspices of the NIH-funded Clinical and Translational Science Collaborative, is serving in leadership roles on many educational committees within the American Epilepsy Society and American Academy of Neurology, and is a reviewer for the Epilepsy Study Section at NIH. She has authored several original manuscripts, editorials and book chapters and spoke at multiple national and international meeting.

Dr. Jehi has indicated he has no financial relationships with commercial interests to disclose.

Ignacio Valencia, M.D.

Ignacio Valencia, M.D. is an Associate Professor of Pediatrics and Neurology at St. Christopher's Hospital for Children, Philadelphia, PA. He received his MD from Rosario University in Bogota, Colombia and residencies in adult and pediatric neurology at Rosario University and St. Christopher's Hospital for Children respectively. Dr. Valencia completed a Fellowship in Epilepsy and Clinical Neurophysiology at Children's Hospital in Boston. He is now pediatric neurology fellowship program director.

Dr. Valencia has indicated he has no financial relationships with commercial interests to disclose.

Paul Levisohn, M.D. (Medical Content Specialist, AES)

Dr. Levisohn is a member of the faculty of the section of Pediatric Neurology at The University of Colorado School of Medicine and Children's Hospital Colorado Neuroscience Institute, having joined the faculty over 15 years ago following a similar period of time in the private practice of pediatric neurology. His academic career has focused on clinical care for children with epilepsy with particular interest in clinical trials and on the psychosocial impact of epilepsy. Dr. Levisohn is currently a consultant on medical content for CME activities to staff of AES. He is a member of the national Advisory Board of EF and has been chair of the advisory committee for the National Center of Project Access through EF.

Dr. Levisohn has indicated he has no financial relationships with commercial interests to disclose.

AKH STAFF / REVIEWERS

Dorothy Caputo, MA, BSN, RN (Lead Nurse Planner) has indicated she has no financial relationships with commercial interests to disclose.

Bernadette Marie Makar, MSN, NP-C, APRN-C (Nurse Planner) has indicated she has no financial relationships with commercial interests to disclose.

John P. Duffy, RPh, B.S. Pharmacy (Pharmacy Reviewer) has indicated he has no financial relationships with commercial interests to disclose.

AKH staff and planners have nothing to disclose.

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PHYSICIANS

Physicians can claim CME credit online at **https://cme.experientevent.com/AES151/**

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How to Claim CME Credit

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Contact Experient Customer Service at: 800-974-9769 or **AES@experient-inc.com**

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The National Association of Boards of Pharmacy (NABP) requires that all pharmacists and pharmacy technicians seeking CE credit have an ID number issued by NABP. Pharmacy CE providers, such as AKH Inc., Advancing Knowledge in Healthcare, are required to submit participant completion information directly to NABP with your ID number and birth information to include month and date (not year) as a validation to this ID number. If you do not have an ID number (this is not your license #), go to: www.MyCPEmonitor.net

Nursing and Pharmacy credit (per session) is based on attendance as well as completion of an online evaluation form available at:

WWW.AKHCME.COM/2015AES

THIS MUST BE DONE BY JANUARY 15, 2016 TO RECEIVE YOUR CE CREDIT.
We cannot submit credit to NABP after this date.
If you have any questions, please contact AKH at service@akhcme.com.

DISCLAIMER

Opinions expressed with regard to unapproved uses of products are solely those of the faculty and are not endorsed by the American Epilepsy Society or any manufacturers of pharmaceuticals.

Why Make the Journey? The Need for Disease Modifying and Preventative therapies for Epilepsy

Amy Brooks-Kayal, MD
University of Colorado
Children's Hospital Colorado
President, AES

December 5, 2015

AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Disclosure

Grants from NIH, CURE, DOD

Member- NINDS Advisory Council

Pfizer- consultant at symposium on new therapy development

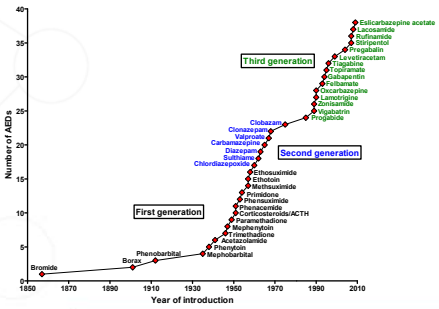
Learning Objectives

- Understand what is meant by disease modifying and preventative therapies for epilepsy and why we need them
- Appreciate the multiple challenges associated with development of disease modifying therapies for neurological disorders
- Learn from the successes and failures in translation experienced in other neurological diseases

What is "Disease Modification"?

- "Treatments or Interventions that affect the underlying pathophysiology of the disease and have a beneficial outcome on the course of the disease"
- How is it different from a "Prevention" or "Cure" (and aren't those what we want)?
- Do we need it?
- Why don't we have it?
- How do we get it?
- Why are there speakers from MS, Stroke and Huntington Disease at our epilepsy meeting?

There are 30+ anti-seizure medications, why do we need "disease modifying" therapies for epilepsy?

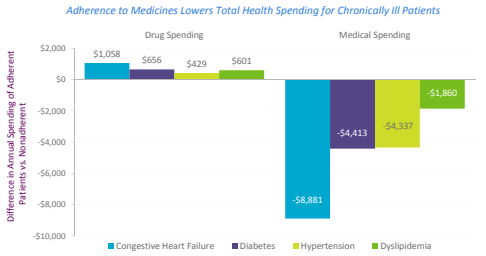


"Houston- we (still) have a problem"

- 1 in 26 people will have epilepsy during their lifetime
- 3 million people in US; 65 million worldwide have epilepsy
- More people die every year from epilepsy related causes (50,000/yr) than die from breast cancer
- Epilepsy costs $15.5 billion in direct and indirect costs (lost or reduced earnings) each year (CDC)
- >1/3 people with epilepsy have cognitive or neuropsychiatric co-morbidities that decrease their quality of life
- Epilepsy has a greater negative impact on HRQOL than most chronic diseases

- All current medications for epilepsy symptomatically treat seizures & only do it fully in 2/3 of patients
- None of our treatments target "non-ictal" symptoms of epilepsy such as depression, anxiety, cognitive and memory dysfunction
- All of our medications have unacceptable side-effects in some patients
- None of our current medications change the course of the disease or prevent/reduce progression
- We have no treatment that reduce the risk of epilepsy in patients at risk for developing epilepsy due to brain injuries such as TBI, stroke, HIE or

Effective Disease Modification can Reduce Medical Spending



Roebuck MC, Liberman JN, Gemmill-Toyama M, et al. Medication adherence leads to lower health care use and costs despite increased drug spending. *Health Affairs.* 2011;30(1):91-99.

Why don't we have disease modifying therapies for epilepsy- what are the challenges?

Identifying and validating your target for "rationale therapy"

- Hundreds of cellular and molecular changes have been shown to occur in neurons, glia, BBB/vasculature, etc during epileptogenesis- which do you choose?
- Is it causally related to epilepsy?
- Could it be compensatory or inconsequential?
- What are the adverse effects? Will "correcting" the target makes seizures better but cognition, mood or behavior worse?

Why don't we have disease modifying therapies for epilepsy- what are the challenges?

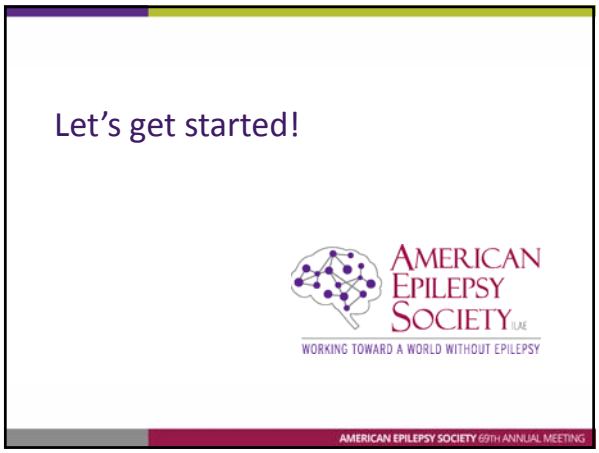
- Target identification is just the start, then you need to find a way to engage your target and change it
- PK/PD, ADME, toxicology and side effects (off- and on-target) lead to many failures
- Preclinical studies are expensive and time consuming, and clinical studies exponentially more so
- Response in animals doesn't always predict efficacy in humans
- We have no validated biomarkers to help us identify patients at greatest risk or predict response
- FDA labeling will be tricky
- Level of industry interest

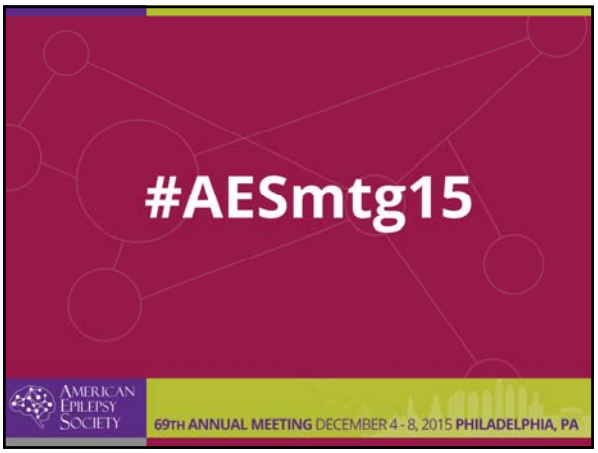
How do we get disease modifying therapies?

- Get a good map!
- Understand that therapy development is a team sport, and recruit the best players
- Shamelessly pilfer knowledge from other neurological disorders with more experience with it (like MS, Stroke and HD)
- Be persistent (and patient), it is a long road, but we can get there with the best guides

Our Guides for this Adventure…..

- Manisha Patel, Ph.D., University of Colorado: "Picking your Route: How do we identify and validate targets for disease modification?"
- Rajesh Ranganathan, Ph.D., PhRMA - "Beginning the Journey: The Path to Phase I"
- Kate Dawson, MD, Biogen: "The Road less Traveled: Novel approaches to successful translation of disease-modifying therapy"
- Emily Sena, PhD., The University of Edinburgh- "Detours and Misdirections: Cautionary tales of Translation Failures"
- Robert Pacifici, PhD, Chief Scientific Officer, CHDI Foundation "A Path Forward for disease-modifying therapy for Epilepsy"


Let's get started!
AMERICAN EPILEPSY SOCIETY
WORKING TOWARD A WORLD WITHOUT EPILEPSY
AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING


#AESmtg15
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Picking Your Route: How Do We Identify and Validate Targets for Disease Modification?

Manisha Patel, Ph.D.
Professor
Department of Pharmaceutical Sciences
University of Colorado Anschutz Medical Campus

December 4, 2015

AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

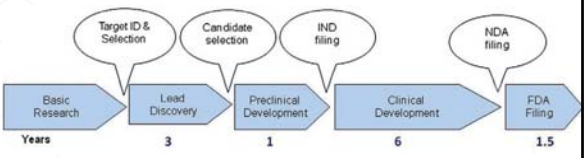
Disclosure

Name of Commercial Interest	Aeolus Pharmaceuticals
	Role: Consultant

Learning Objectives

- Define and provide examples of "target identification", "target validation" and "target engagement"
- Explain how basic science discoveries can lead to the identification and validation of a therapeutic target
- Provide an overview of the early stage preclinical process from target identification to potential lead candidates

Definitions



Target: Broad term applied to a range of biological entities such as proteins, genes and RNA. A good target needs to be efficacious, safe, meet clinical and commercial needs.

Target validation: A range of techniques that confirm the "validity" of an identified target from *in vitro* tools through the use of animal models.

Target engagement assays: Assays that test whether a pharmacologically relevant compound concentration "engages" the intended target.

Br J Pharmacol. 2011 Mar; 162(6): 1239–1249.

Target identification and validation

Impact on Clinical Care and Practice

- Acquired epilepsy is an important clinical challenge in need of novel targets for therapeutic intervention
  - What aspect of the disease should we target?
  - What is the rationale to target reactive oxygen species (ROS) and metabolic dysfunction?
- How can we validate this target?
  - Does genetic modulation of the target precipitate disease?
  - Does pharmacological modulation of target modify disease?

What aspect of the disease should we target?

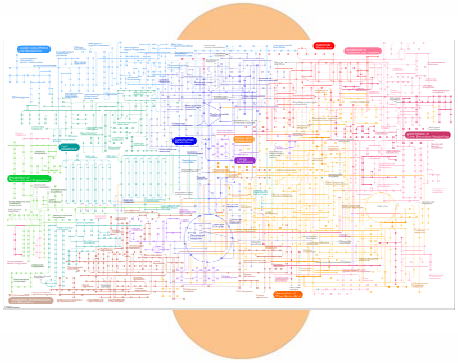
- Epileptogenic injury and its consequences
- Epileptogenesis
- Chronic epilepsy and/or Comorbidities

Picking your pathway

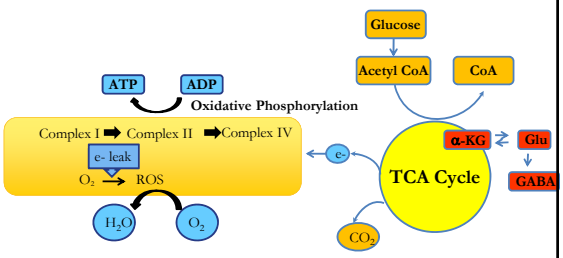
- Clues from disease pathogenesis
  - Rational discovery
- Screening
  - Targeted or untargeted

Personal journey into redox and metabolic control: A road less travelled in epilepsy

The case of metabolic dysfunction in epilepsy



Integrated metabolism



Oxidative stress: one example of a modifiable target

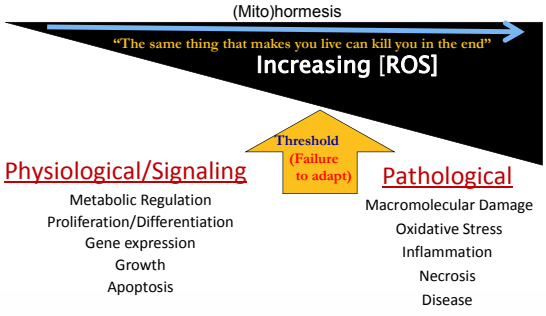
What is the rationale?

- The brain is uniquely vulnerable to oxidative damage
- Epileptogenic injury and seizures increase reactive oxygen species (ROS) production
- Oxidative stress is sufficient to cause epilepsy

Target identification and validation

- Is oxidative stress produced during disease process?
- Is oxidative stress sufficient to cause disease?
- Does antioxidant treatment ameliorate disease outcomes?
- Does metabolic therapy (i.e. ketogenic diet) alter the target?

Most drug targets have useful and harmful roles



Epileptogenic Injury (SE)
Oxidative stress
Cellular dysfunction
Neuronal Injury
Epilepsy development Cognitive dysfunction
Target Sources? Mechanisms?
Biochemical Consequence?
Cellular Consequence?
Disease Outcomes?
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Does epileptogenic injury increase production of ROS? If so, what is the time course?
Brain Injury
Epilepsy
Spontaneous seizures
Cognitive dysfunction
Kainate or Pilocarpine
Acute
Latent
Chronic
Time Points 3hr 8hr 24hr 48hr 1wk 3wk 6-12 wk
Disease Outcomes
Y-maze
Video EEG
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Assessment of target engagement

Challenges of ROS measurement:
- Evanescent , unstable and interchangeable species
- Compartment-specific measurement
- Lack of good markers

Approach: Surrogate markers of oxidative damage or redox environment (e.g. glutathione or GSH)
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What are the cellular sources of ROS production?
Status Epilepticus
Activation of Nox2
Extracellular ROS
Inflammation
Mitochondrial respiration
Mitochondrial ROS
Mitochondrial Dysfunction
Two major cellular compartments of seizure-induced ROS production
Mitochondria: Key mediators of seizure-induced ROS
Liang et al., 2000; Patel et al., 2005; Jarrett et al., 2008
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Evidence for oxidative stress in a chemoconvulsant model of epilepsy
Nucleus
H_2O_2
GPx
H_2O
GSH
GSSG
GR
NADP+
NADPH
GSSG
GSH
Mitochondrion
GSH/GSSG
% Control
CON 8hr 24hr 48hr 7d 21d 6 wk
Time After Kainate
Ryan et al., 2014
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Epileptogenic Injury (SE)
Oxidative stress
Cellular dysfunction
Neuronal Injury
Epilepsy development? Cognitive dysfunction?
Target Sources? Mechanisms?
Biochemical Consequence?
Cellular Consequence?
Disease Outcomes?
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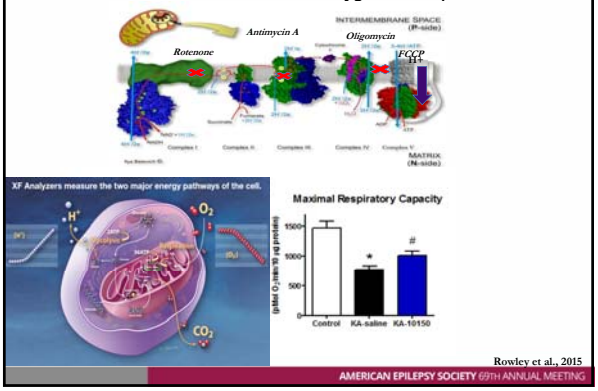
What is the cellular consequence of ROS production?

Decreased Mitochondrial Oxygen Consumption

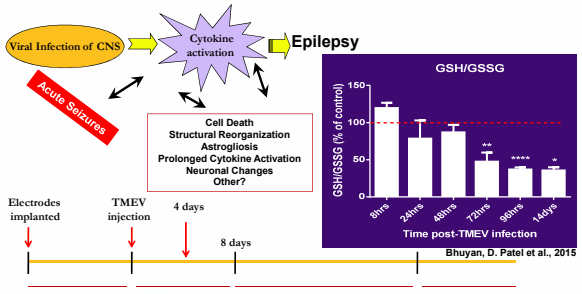


Rowley et al., 2015

Is oxidative stress specific to chemoconvulsant models or generalizable?

Oxidative stress in a model of infection-induced epilepsy

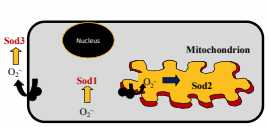
TMEV (Theiler's murine encephalomyelitis virus) - natural enteric pathogen of mice



Bhuyan, D. Patel et al., 2015

Target validation using genetic models

Does overexpression or deficiency of the target modulate disease outcomes?



$O_2^{\cdot-} + O_2^{\cdot-} + 2H^+ \xrightarrow{SOD} O_2 + H_2O_2$

Protein (gene)	MW	Location
CuZn SOD(*sod1*)	32,000	Cytosol
Mn SOD(*sod2*)	80,000	Mitochondria
EC-SOD(*sod3*)	135,000	Extracellular

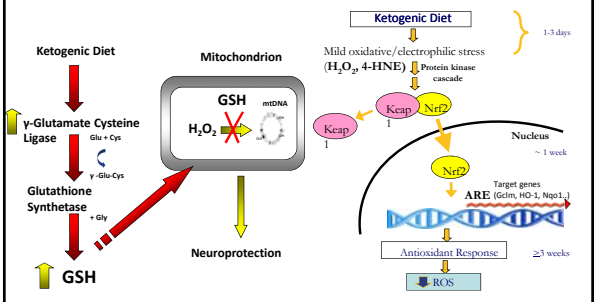
Neuronal death as end point:Sod2>Sod3>>>Sod1

- Sod2 overexpression inhibits KA-induced neuronal death
- Sod2 heterozygous knockout mice show exacerbation of KA-induced neuronal death
- Sod2 homozygous knockout mice show spontaneous seizures and neuronal death

Liang et al., 2000; 2004; 2012

Target validation using a metabolic therapy

Ketogenic diet



Jarrett et al., 2008

Milder et al., 2010

Does pharmacological modulation of target (i.e. ROS) modify disease?

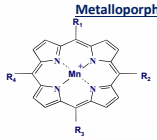
Choice of small molecule antioxidants

- **Direct Antioxidants**
  - Free radical scavengers (SOD/$O_2^{\cdot-}$)
  - Non radical scavengers (Catalase/H_2O_2)
- **Indirect Antioxidants**
  - Inhibitors of cellular sources of oxidants (chelators/metals, apocynin/Nox)
  - Inducers of cellular antioxidants (sulforaphane/Nrf2 targets-GSH)

Desirable properties of compounds

Catalytic Antioxidants	Neurological Diseases
Efficacy (high rate constant with ROS)	Efficacy, potency
Stability	Stability
Safety	Safety
Favorable pharmacokinetics	Favorable pharmacokinetics
Cell and mitochondria permeable	Blood-brain-barrier permeability
Non-antigenic	Oral bioavailability
Non-toxic metabolites	

Metalloporphyrin small molecule enzyme mimetics



- Perform one and two electron transfers which gives them both SOD and catalase-like properties.
- Capable of targeting four major species: $O_2^{\cdot-}$, H_2O_2, $ONOO^-$, lipid peroxides

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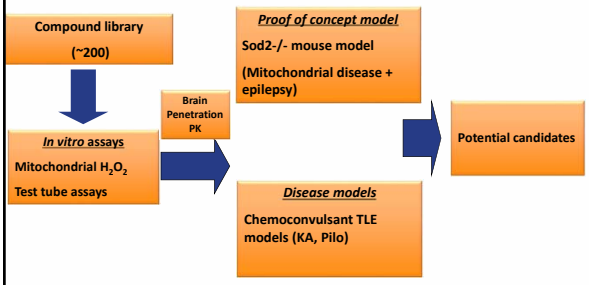
Therapeutic screening



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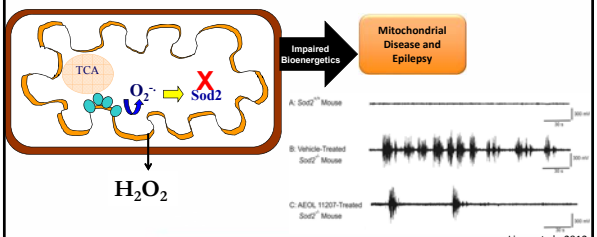
Mouse model of mitochondrial dysfunction and epilepsy
Proof of concept study

- Mutant mice lacking Sod2 develop mitochondrial disease and epilepsy
- Treated with vehicle or antioxidant drug starting day 5
- Advantage: Relatively cost-effective



Liang et al., 2012

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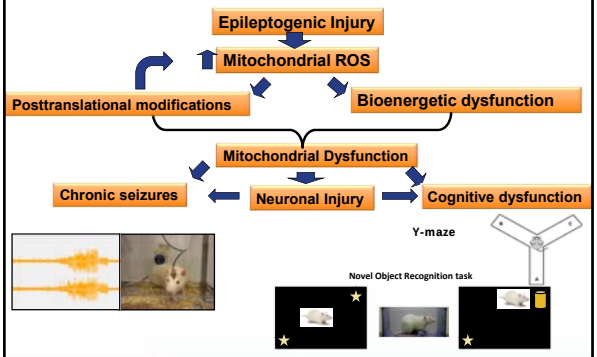
Does drug treatment modify disease outcomes in epilepsy model?



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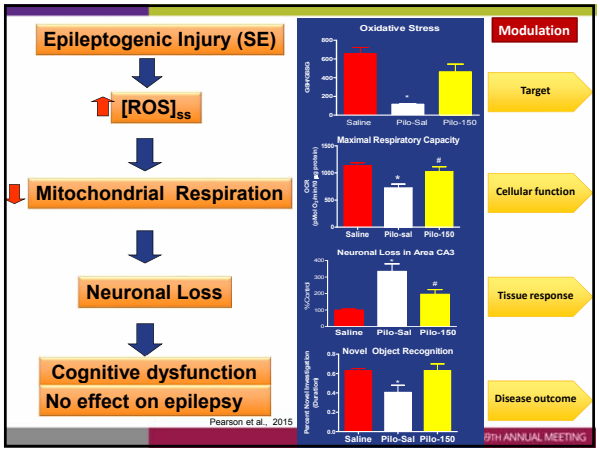

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Target identification and validation

- **Is oxidative stress produced during disease process?**
  - ✓ Time-dependent oxidative stress in animal models of TLE
- **Is oxidative stress sufficient to cause disease?**
  - ✓ Oxidative stress in Sod2 mutant mice develop epilepsy
  - ✓ Epilepsy in mitochondrial Sod2 deficient mice rescued by antioxidant treatment
- **Does antioxidant treatment ameliorate disease outcomes?**
  - ✓ Neuronal death
  - ✓ Mitochondrial dysfunction
  - ✓ Cognitive impairment
- **Does metabolic therapy (i.e. Ketogenic diet) improve redox status?**
  - ✓ Ketogenic diet corrects redox deficits observed in epilepsy models

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Acknowledgements

Lab members

Past lab members:
Stuart Jarrett PhD
Julie Milder PhD
Kristen Ryan PhD
Derek Drechsel PhD
Pablo Castello PhD
Shane Rowley PhD

Collaborators:
Brian J. Day Ph.D. (NJH)
Yogi Raol Ph.D. (UCD EEG Core)
UCD Behavior Core
Karen Wilcox Ph.D. (Utah)

Grant Support: NINDS (RO1NS039587-14), NIH-OD (UO1NS083422), AES/EF, MJFF, CURE, Skaggs Scholars Program.

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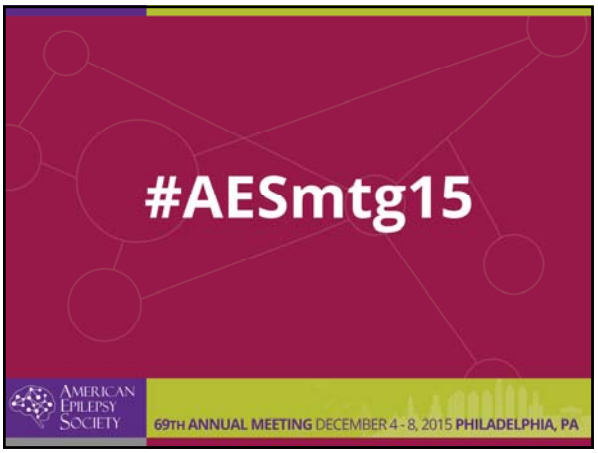


Beginning the Journey: The Path to Phase I

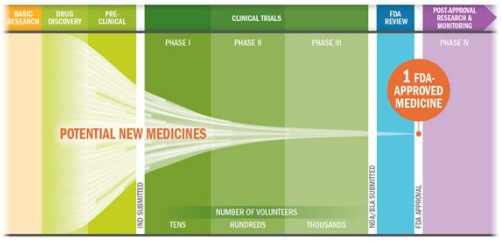
Preclinical stages of drug discovery and development

Rajesh Ranganathan, Ph.D.
VP Science and Regulatory Advocacy
PhRMA

Dec 2015

Drug Discovery and Development Process

From drug discovery through FDA approval, developing a new medicine on average takes at least 10 years and costs $2.6 billion.* Less than 12% of the candidate medicines that make it into phase I clinical trials will be approved by the FDA.



Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

*The average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be $2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

PhRMA adaptation based on DiMasi JA. Cost of developing a new drug. Tufts Center for the Study of Drug Development (CSDD). R&D Cost Study Briefing.

Disclosure

Current Role:

Vice President, Science and Regulatory Advocacy, Pharmaceutical Researchers and Manufacturers of America (PhRMA)

PhRMA is a non-profit/trade association, representing the country's leading innovative biopharmaceutical research companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives.

>7,000 Medicines in Development Globally

Biopharmaceutical researchers are working on new medicines for many diseases.

Selected Diseases	Medicines in Development*
Cancers	1,813
Cardiovascular disorders	599
Diabetes	475
HIV/AIDS	159
Immunological disorders	1,120
Infectious diseases	1,256
Mental health disorders	511
Neurological disorders	1,329

*Defined as single products which are counted exactly once regardless of the number of indications pursued

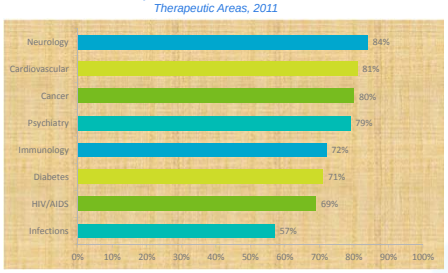
Learning Objectives

- The path from drug target to clinical candidate
- Appreciation of differences between drug and biologics
- Complexity of decision making at each step

Potential First-in-Class Medicines in the Pipeline

An average of 70% of drugs across the pipeline are potential first-in-class medicines.

Percentage of Projects in Development that Are Potentially First-in-Class Medicines in Selected Therapeutic Areas, 2011

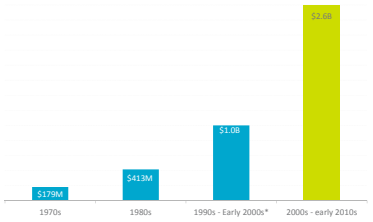


- Analysis Group. Innovation in the biopharmaceutical pipeline: a multidimensional view.

Drug Development Costs Have Increased

- **According to a 2014 study, it costs an average of $2.6 billion to develop one new**

The Average Cost to Develop One New Approved Drug—Including the Cost of Failures (Constant 2013 Dollars)



Tufts Center for the Study of Drug Development (CSDD). Cost of developing a new drug. Briefing. Boston, Mass.: CSDD, November 2014. Accessed March 2015.

7

Low molecular weight compounds / small molecules

- **Target space:**
  - "Drug-ables": Enzymes, ion channels, receptors & transporters
  - Protein – protein interactions (intra- & extracellular)
  - More? – depends on chemical matter and ability to assay
- **Opportunities:**
  - Inhibitors and activators possible, allosteric mechanisms
  - Hit upstream or downstream of targets not otherwise tractable
  - Many delivery options: Oral, IV, inhaled, etc
- **Hurdles on way to clinic:**
  - Potency and specificity, physicochemical properties, PK / ADME, toxicology / side effects (off- and on-target), mutagenicity, other
  - Every molecule is different – experience can guide - no perfect rules

10

Retail Spending on Prescription Medicines Is a Small Share of Total US Health Care Spending

2013 Health Care Dollar

PhRMA analysis of CMS data. National health expenditures by type of service and source of funds, CY 1960-2013. Baltimore, Md.: CMS; 2013. http://www.cms.gov/Research-

8

Approaches to hit finding

- **Patent "Busting"**
  (making use of existing patent literature for synthesis of novel chemotypes)
- **Structural Biology/Chemistry**
  in combination with CADD (Computer Aided Drug Design)
- **HTS**
  High-Throughput Screening (of chemical compound libraries)
- **FBS**
  Fragment Based Screening (of small fragment libraries)
- **Peptidomimetic**
- **HTD**
  High Throughput Docking (of large compound libraries)
- **Combinations of approaches**

11

You picked a target – now choose a therapy

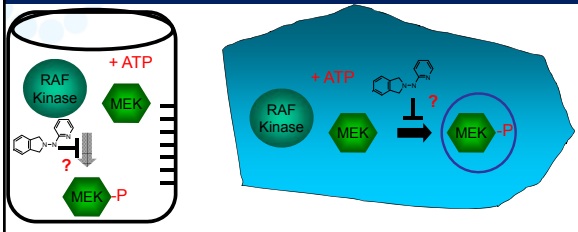
Multiple possibilities for therapeutic agents – different features

- **Low molecular weight / small molecules**
- **Antibodies**
- **Proteins**
- **siRNAs**

} Biologics

9

Biochemical vs. Cell Based Screens

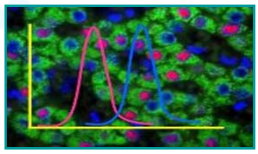


Biochemical
- Target protein usually recombinant, pure (Good and Bad)
- Cellular permeability unclear

Cell Based
- Can focus to hit a specific target
- Permeability info provided
- Cytotoxicity can be determined

12

HCS (High Content Screening): Imaging



Principle:
- Fluorescent detection of proteins at the subcellular level to spatially monitor cell functions/movements
- Most common fluorophore is Green Fluorescent Protein (GFP) which can be expressed as a fusion protein with the target of interest
- Fluorescent stains can be used to detect and localize cellular structures as reference points

Targets screened:
- **GPCRs**
- **Transcription factors**
- **Kinases**
- **Signalling pathways**

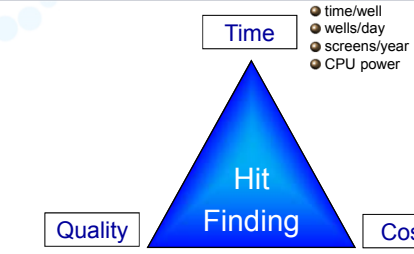
Detection labels:
- **GFP (Green Fluorescent Protein)**
- **Antibody staining of fixed cells (with commercial fluorophores)**

Detectors:
- **ArrayScan (Cellomics)**
- **InCell 3000 (GE Healthcare)**
- **Opera (Evotec Technologies)**
- **Acumen Explorer (TTP Labtech)**

Detection format:
- **96/384 well microtiter plates**

13

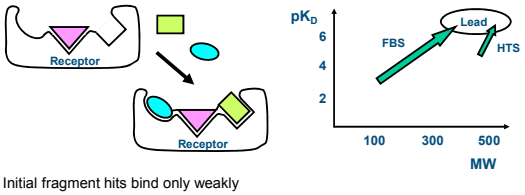
"Magic triangle"



16

Fragment - based screening

- Identify small ligands („fragments") with few but good interactions → combine fragments → higher efficacy, potency



- Initial fragment hits bind only weakly
  - Need sensitive and robust detection method (biochemical assay, mass spectrometry, NMR, X-ray crystallography
  - Need follow-up strategies to increase affinity

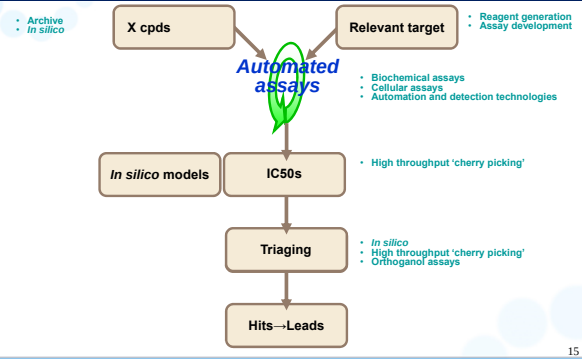
14

Validating and prioritizing 'hits'

- HTS hits require validation
  - IC$_{50}$ determination in HTS assay format
  - IC$_{50}$ in orthogonal assay format
  - Competition and kinetic studies
- Confirmation of chemical identity
  - What is the purity?
  - Is it the correct mass as registered?
- Classification and prioritization based on chemical and commercial tractability

17

Hit finding



15

When is a "hit" not a hit?

Potential pitfalls of biochemical / biological screens

- Unspecific interactions of compounds with the target protein
  - High concentrations of compound (~10 μM) used in HTS to increase chances of finding weakly active hits
  - Low solubility of many compounds at higher concentrations
- Chemical reaction of compounds with the target protein
- Interactions with the assay format (e.g. fluorescent or colored compounds, detergents, …)

18

Important Hit-to-Lead consideration

- Specific interaction with the relevant target (protein, pathway, cellular phenotype)
  - Non-covalent, reversible binding to target (exceptions exist …)
  - Time-independent IC_{50}/K_i
- Evidence for Structure-Activity-Relationships (SAR)
  - Activity varies with modifications of scaffold
- Initial assessment of weaknesses and liabilities
  - PK, Tox…
- Ability to address liabilities
  - Improvements should be readily measured
  - Deficiencies should be addressable by medicinal chemistry

19

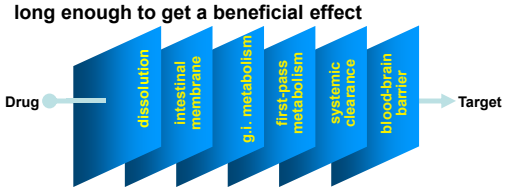
Multiple Parameters to consider during medicinal Chemistry optimization

- Pharmacokinetic Properties
  - Absorption, Distribution, Metabolism, Excretion Properties
  - Oral Bioavailability (in most cases …)
- Potency
  - Affinity to target (including in plasma, blood …)
  - Functional effect in cellular systems
  - Effect in animal models
- Phys.Chem. Properties
  - Solubility
- Side Effects, Toxicity
  - Selectivity for target versus related proteins
  - Selectivity against unrelated proteins (cardiac ion channels etc.)

20

Good in vitro efficacy ≠ good drug

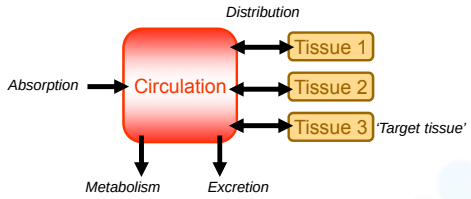
- **The body has many barriers to prevent a drug candidate getting to site of action and to stay there long enough to get a beneficial effect**



21

Early assessment of Metabolism and Pharmacokinetics

- Pharmacokinetics is the study of what the body does to an administered drug over time
- Pharmacodynamics is the study of what an administered drug does to the body over time



22

Metabolism and Pharmacokinetics

- **Physicochemical parameters**
  - Solubility (pH profile, intrinsic), pKa, logP
- **Permeability**
  - PAMPA, Cellular models (Caco-2, MDCK)
- **Stability in biological systems**
  - Blood, liver fractions (in vivo PK prediction), singly expressed metabolising enzymes (e.g. CYP3A4), other tissues (e.g. lung, gut, kidney…)
  - Species comparisons
- **Metabolic pathways**
  - Analysis of samples from stability studies to identify major routes by LC/MSMS
  - Trapping experiments (GSH) to assess formation of reactive metabolites
- **Distribution in blood**
  - Blood to plasma ratio, plasma protein binding
- **Drug/Drug Interaction potential**
  - CYP450 inhibition, time dependant CYP inhibition, CYP induction (PXR activation)

23

Studies lead up to an IND

Toxicology
- 2 week in vivo rat study
- Single rising dose dog study (TK/tolerability)
- CV Safety in telemetrized dog at highest tolerated dose

PK/ADME
- Bioavailability in at least two species (rats, dogs, monkeys)
- PK/PD in efficacy species
- Metabolic profile in at least two species and in vitro human

Pre-Formulation
- Early salt screening
- Solubility and stability assessment
- Tox formulation development

Biomarkers
- PD biomarker is available and has been used to establish PK/PD relationship in animals
- Biomarker assay is ready for transfer to clinical use

IND: Investigational New Drug

24

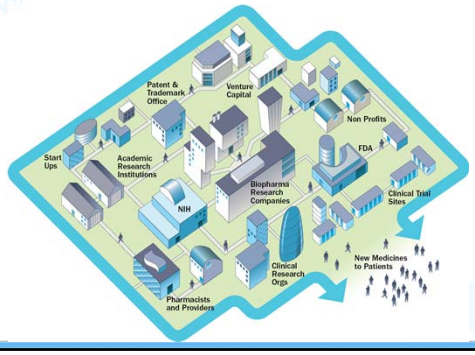
Why do projects fail?

- Top 5 reasons for project failure
  - Brown D. (2007) Drug Discovery Today 12; 1007-1012

Reason for failure	Description
Target mechanism	The chosen target mechanism fails in animal or clinical studies
Lead molecule	There may be either total failure to find a lead that can be optimized or 'hits' are selected as leads that later prove nondrugable
Drug safety	The final drug candidate selected from the lead series fails to pass regulatory toxicology requirements at IND stage
Clinical ADME	Adverse events or poor pharmacokinetics are observed in clinical trials that were not predicted by animal studies
Clinical efficacy	Failure to demonstrate the efficacy expected from animal studies or results from earlier smaller clinical trials

25

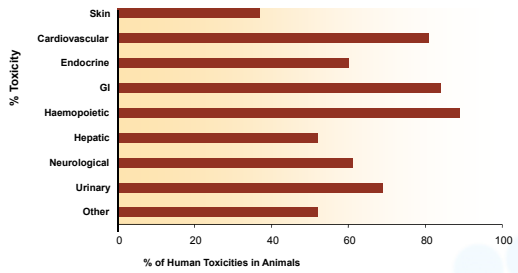
A Dynamic R&D Ecosystem as the Engine to Make Innovative Medicines for



28

Animals are not humans

Percentage concordance between animals and human toxicities



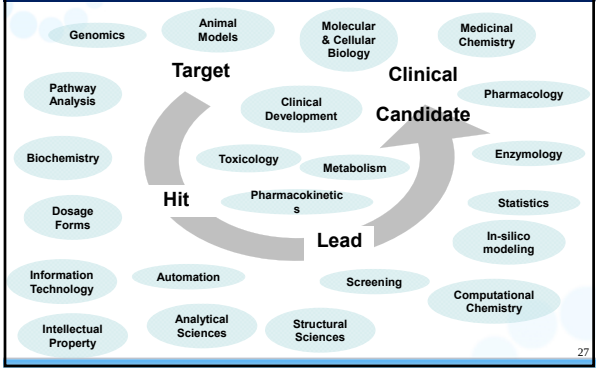
NRDD 3: 226 (2004)

26

If time permits

29

Drug Discovery: It takes a village (nay, army)



27

You picked a target – now choose a therapy

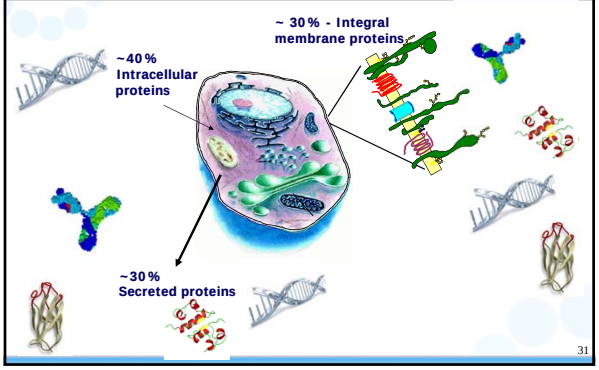
Multiple possibilities for therapeutic agents – different features

- **Low molecular weight / small molecules**
- **Antibodies**
- **Proteins**
- **siRNAs**

} Biologics

30

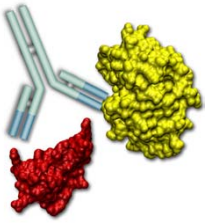
What is Biologics Target Space?



31

When Challenges are Tractable using Antibodies?

1. Getting to inaccessible targets



Problems intractable to low molecular weight compounds are accessible to antibodies (e.g., protein-protein interactions)

2. Antibodies represent the opportunity to provide a differentiated profile vis-à-vis specificity and toxicity

34

Why Use Biologics?

- **Can target biological mechanisms intractable to LMW drugs**
  - Antibodies can block soluble factors
    - Anti-VEGF or Anti-TNFα
  - siRNAs can inhibit transcription factor function
  - Therapeutic proteins are effective agonists
  - Therapeutic proteins and antibodies are ideal for targeting protein-protein interactions
- **Biologics may solve problems that LMW drugs cannot and offer both activation and inhibition of selected targets**

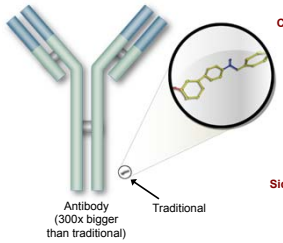
32

Therapeutic proteins

- **Natural proteins where the function cannot be mimicked**
  - Pre-recombinant technologies
    - Peptides
      - Insulin (51 aa)
        - Extracted from animals (porcine or bovine)
      - Calcitonin (32 aa)
        - Synthesized (72 step, 2 year chemical synthesis)
  - Recombinant proteins
    - Molecular biology enables large proteins to be prepared in large amounts
      - Erythropoietin (508aa)

35

Antibodies Vs. Low Molecular Weight (LMW) Chemical Drugs: some key differences



	Antibody	LMW drug
Drug Character-istics	• Parenteral administration • Dosed weekly-monthly • Physician administered	• Often orally administered • Dosed hourly to daily • Self administered
Target	• Extracellular mechanisms • Good at protein interactions	• Any druggable target • Enzymes/receptors/channels
Side effects	• Specific action low off target toxicity	• Less specific can inhibit multiple mechanisms

33

Therapeutic proteins: Challenges

- **Immunogenicity**
- **Half-life**
- **Post-translational modifications**
- **Delivery**

36

siRNA Therapeutics

- **Rationale**
  - Natural mechanism that is catalytic
  - Highly specific
  - Can target any mRNA and thus protein target
    - Drugging the undrugable
- **Challenges**
  - Delivery and formulation
  - Activation of the immune response

37

Therapeutic RNAi - Challenges

- **RNAi Mechanism**
  - Selection of potent siRNAs amenable to modification
  - Competition with endogenous RNAi activity
- **Delivery & Pharmacokinetics**
  - Cellular uptake and intracellular trafficking
  - Tissue targeting
  - Circulation/retention time
- **Toxicology**
  - Off targets
  - Innate immune stimulation
  - Delivery vehicles

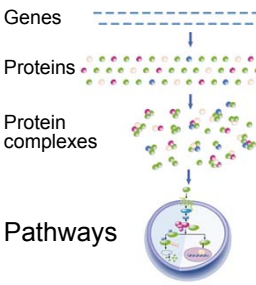
38

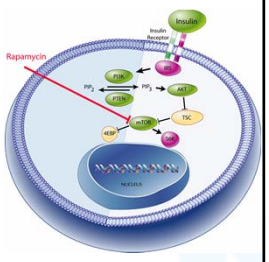
Appendix

39

Focus on pathways – "New Grammar"

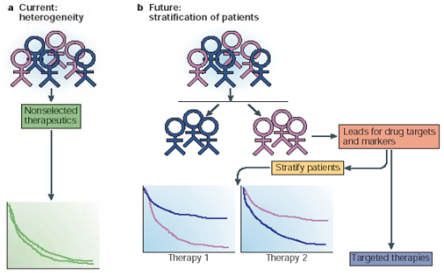
- Genes function through pathways
- Pathways are collections of targets: Drugs target key pathway nodes





40

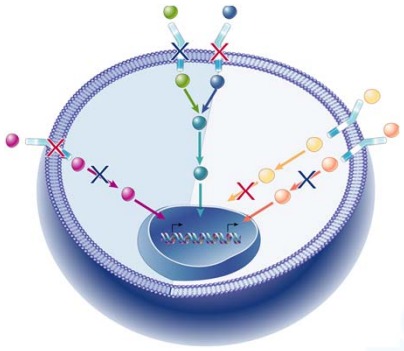
Patient stratification



From Mischel et al. Nature Reviews Neuroscience, 2004

41

Pathways: A Rational Approach to Drug Combinations



42

The Road Less Traveled: Novel Approaches to Successful Translation of Disease-modifying Therapy

Katherine Dawson, MD
VP, US Medical Biogen

December 5, 2015

AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Disclosure

- Dr. Dawson is an employee of and holds stock in Biogen
- This presentation does not offer continuing education credit.

Learning Objectives

- Understand the parallels between multiple sclerosis (MS) and epilepsy development challenges
- Understand development plan of delayed-release dimethyl fumarate (DR-DMF), an approved disease modifying therapy for relapsing MS (RMS)
- Provide examples of ways to address challenges in developing disease modifying treatments for RMS

State of the Art: Epilepsy

- Treatments do not fully control seizures in 1/3 of patients, and have substantial side effects
- Nothing to prevent epilepsy in high-risk patients, nor cure once begun
- Epilepsy-associated comorbidities without specific therapies
- Preclinical models need to aid translation of findings into clinically testable and relevant interventions
- Large gaps in understanding the pathophysiology of epilepsy in animals and humans leads to lack of clarity on clinical trial design

Dr. Richard Maslin (1969) "There are few areas of scientific inquiry which have spawned more inadequate studies and unwarranted recommendation than that of the therapy of multiple sclerosis. The history of this disorder is one of a long and continuing series of false claims of a cure for this disease."

McFarlin, N Engl J Med, 1983 Jan 27;308(4):215-7

Mc Farlin's complaints: Still True

Why therapeutic claims in MS still lead to controversy

- Cause of MS is unknown
- No good laboratory biomarkers for the disease
- MS varies among patients
- Symptoms worsened by fever, infection, activity and emotional components
- Placebo effects occur in clinical trials
- Disease is variable, chronic and most often doesn't shorten life expectancy, and medications with significant side effects are not given early, when such treatments might be most effective

Dale E. McFarlin, MD Head Neuroimmunology, NIH, NEJM, 1983; 308:215-217 January 27

Why new MS therapies are needed

400,000 persons with MS in the US
- 200,000 treated, 50,000 stopped therapy, 150,000 untreated*
- 14% of RRMS patients discontinue within 5 years[1,2]

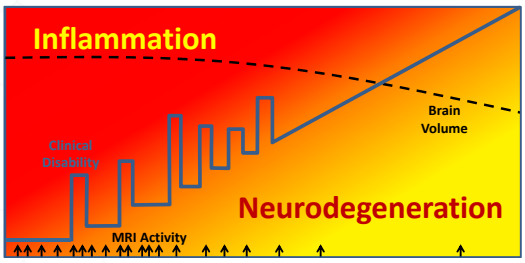
Among CNS disorders, most frequent cause of permanent disability in young adults

Significant unmet need for multiple sclerosis (MS) therapies
- Approved therapies all immunomodulatory
- ~30-67% relapse reduction[1-4,6]
- ~30-42% disability progression[1-4,6]
- Injection and infusion related side effects, adverse drug reactions, and fear of self-injection[1-5]

[1]IFNB MSSG. *Neurology*. 1993;43:655-661; [2]Johnson KP et al. *Neurology*. 1995;45:1268-1276; [3]Jacobs LD et al. *Ann Neurol*. 1996;39:285-294; [4]PRISMS. *Lancet*. 1998;352:1498-1504; [5]Mohr DC et al. *Ann Behav Med*. 2001;23:125-132; 6 Polman et al NEJM 2006; 354: 899-910

7

Multiple Sclerosis Pathophysiology



adapted from Spain *et al. BMC Medicine* 2009 **7**:74

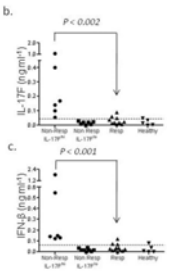
8

Predictive Biomarker?

T helper type 1 and 17 cells Determine Efficacy of IFN-β in Multiple Sclerosis and Experimental Encephalomyelitis

Robert C. Axtell[1], Brigit A. de Jong[1,2,3], Katia Boniface[4], Laura F. van der Voort[3], Roopa Bhat[1], Patrizia De Sarno[2], Rodrigo Naves[2], May Han[1], Franklin Zhong[1], Jim G. Castellanos[1], Robert Mair[1], Athena Christakos[1], Ilan Kolkowitz[1], Liat Katz[1], Joep Killestein[3], Chris H. Polman[3], René de Waal Malefyt[4], Lawrence Steinman[1,*], and Chander Raman[1,*]

- Identify responders and non-responders to IFN-β therapy
- Mice with TH1-EAE benefit from IFN-β treatment with reduction in levels of disability, while mice with TH17-EAE do not respond and disease worsens
- Using pre-treatment cytokine profiles, classified 26 patients into Responders (R)/Non-responders (NR). 2 years on therapy, median relapse rate R 0, NR 2



Nat Med. 2010 April ; 16(4): 406–412. doi:10.1038/nm.2110.

9

Unfortunately, Not Yet

Neurology
American Academy of Neurology

Serum IL-17F does not predict poor response to IM IFNβ-1a in relapsing-remitting MS

S.E. Bushnell, PhD, Z. Zhao, MS, MMed, [...], and R. Medori, MD

- Validation cohort included 54 good responders (GR) and 64 poor responders (PR) selected from 762 subjects with RRMS from the IM IFNβ-1a dose comparison study (Avonex study C94-805).
- Median pre-treatment and post-treatment serum IL-17F levels were not statistically significantly different between GR and PR, and serum IL-7/IL-17F ratios were also not predictive of response status
- Replicate aliquots from the Stanford study showed good correlation to their original cohort (r = 0.77)

Neurology. 2012 Aug 7;79(6):531-7: Bushnell SE, Zhao Z, Stebbins CC, Cadavid D, Buko AM, Whalley ET, Davis JA, Versage EM, Richert JR, Axtell RC, Steinman L, Medori R..

10

What about animal models of MS?

Experimental autoimmune encephalomyelitis is a good model of multiple sclerosis if used wisely

David Baker[a,*], Sandra Amor[a,b]

[a]Neuroimmunology Unit, Blizard Institute, Barts and the London School of Medicine & Dentistry, Queen Mary University of London, 4 Newark Street, London E1 2AT, United Kingdom
[b]Pathology Department, VU Medical Centre, Free University of Amsterdam, The Netherlands

Received 21 January 2014; received in revised form 1 May 2014; accepted 5 May 2014

EAE is not a useful model for demyelinating disease ☆

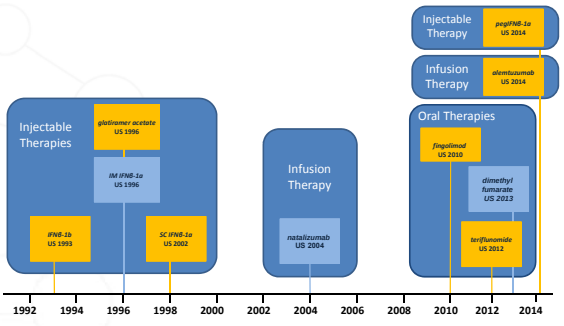
Peter O. Behan[a,*], Abhijit Chaudhuri[b]

[a]Institute of Neuroscience and Psychology, University of Glasgow, Glasgow G12 8QQ, United Kingdom
[b]Department of Neurology, Queen's Hospital, Rom Valley Way, Romford, Essex RM7 0AG, United Kingdom

Received 6 February 2014; received in revised form 2 April 2014; accepted 17 June 2014

11

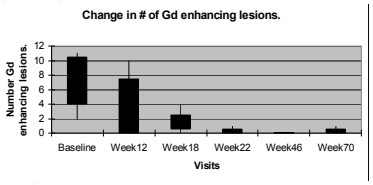
MS disease modifying therapy approvals



12

Fumaric Acid Therapy Has Shown Efficacy in Immune Disorders

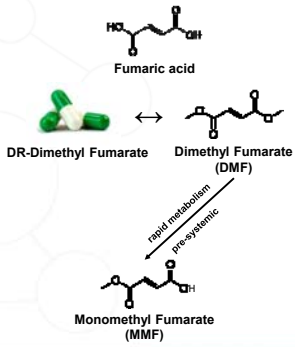
- Orally bioavailable
- Successfully used for long-term treatment of psoriasis[1-3]
- Significantly reduced gadolinium-enhancing (Gd+) lesions in 10 patients with relapsing-remitting MS[4]



[1]Nieboer C, et al. *Dermatologica.* 1990;181:33-37; [2]Altmeyer PJ, et al. *J Am Acad Derm.* 1994;30:977-981; [3]Mrowietz U, et al. *Br J Dermatol.* 1998;138:456-460; [4]Schimrigk K, et al. *Neurology.* 2005;64(Suppl 1):A392. Abstract S46.003.

13

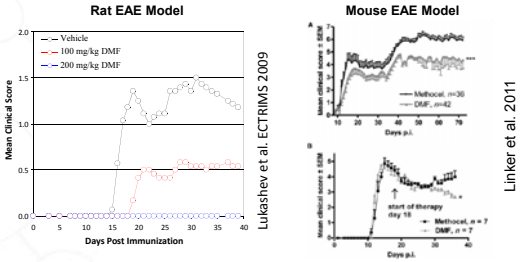
DR-DMF and Fumarates



- Fumaric acid is a naturally occurring molecule essential for oxidative respiration (Krebs, Citric Acid Cycle)
- DR-DMF contains dimethyl fumarate (DMF) formulated into enteric-coated oral microtablets contained in a capsule
- DMF is rapidly converted pre-systemically to monomethyl fumarate (MMF)
- MMF is the relevant fumarate species for in vitro studies

14

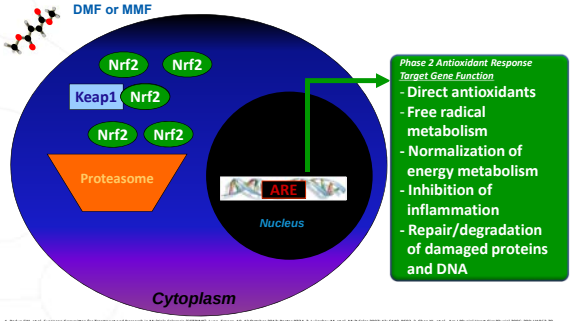
The Effects of DMF in Rodent Models of MS: Experimental Autoimmune Encephalomyelitis



- DMF improved behavioral and motor function (clinical score) in rodent experimental autoimmune encephalomyelitis (EAE), a preclinical MS animal model
- Treatment worked prophylactically and therapeutically

15

Potential Mechanism for DMF-Dependent Activation of the Nrf2 Pathway



Regulatory Pathway for MS

Primary endpoints must be clinical

- Relapse rate, disability progression as measured by EDSS
- MRI as proof of concept or support of primary endpoints only

Phase 3 trials of at least 2 years duration required

- Placebo controlled, superiority
- Confirm efficacy and safety profile

Active comparator trial required for EU

EMEA Guideline on Clinical Evaluation of medicinal products for the treatment of multiple sclerosis, 1 June 2007

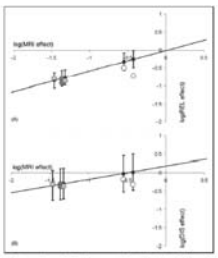
17

MRI Effect Predicts Clinically Relevant Outcomes

Magnetic resonance imaging as surrogate for clinical endpoints in multiple sclerosis: data on novel oral drugs[1]

MP Sormani[1], L Bonzano[2,3], L Roccatagliata[2,3] and N De Stefano[4]

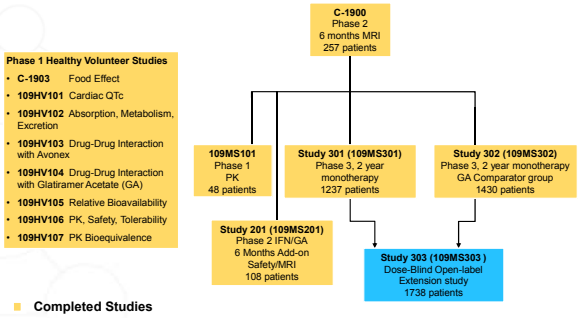
- Predicted clinical treatment effect from MRI-observed effect demonstrated strong correlation with observed effect on relapses and disability across trials [a,b]
- Association of these outcomes seen across therapies with distinct mechanisms of action
- MRI may, with additional validation, serve as a surrogate for clinical endpoints in confirmatory studies



1.Sormani MP, et al Multiple Sclerosis Journal,17(5) 630–633. a.Sormani et al, Ann Neurol 2009, 65: 268-275. b. Sormani et al, Neurology Epub 2010 June23

18

MS Clinical Development Plan for BG-12 (DR-DMF)



19

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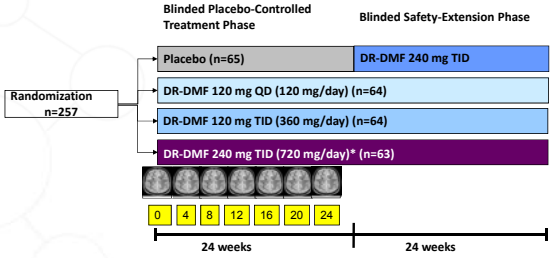
Delayed-Release DMF: Phase 2 Study



Primary endpoint:
Total number of new Gadolinium-enhancing (Gd+) lesions on MRI scans performed at Weeks 12-24

Kappos L et al. *Lancet* 2008;372(9648):1463-1472

20

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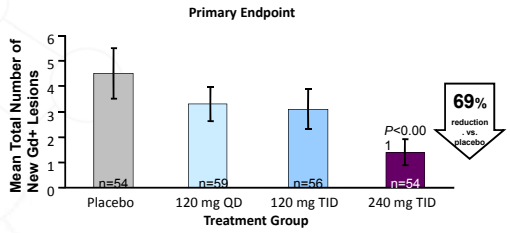
Phase 2 New Gd+ Lesions (Weeks 12 to 24)



- Common AEs associated with DR-DMF: headache, GI symptoms and flushing; infections similar incidence across groups;
- Similar proportion of SAEs in placebo and active arms
- Reversible ≥3X ULN transaminases in 8 patients receiving DR-DMF

Kappos L et al. *Lancet* 2008;372(9648):1463-1472

21

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Ethics of placebo-controlled clinical trials in multiple sclerosis

A reassessment

- International group of clinicians, ethicists, statisticians, regulators and representatives from the pharmaceutical industry convened and concluded that trials can still be done ethically with patients with relapsing MS for which treatments exist, but with restrictions. Should only be offered with rigorous informed consent if subjects refuse to use current therapies, have not responded to them, or these treatments are not available to them.
- Balance study subject burden and risk, scientific rationale and interpretability of outcomes.

Polman CH et al, Neurology 2008;70:1134–1140

22

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Phase 3 Studies for DR-DMF (BG-12) in Multiple Sclerosis

- Trials 109-MS-301 (DEFINE) and 109-MS-302 (CONFIRM) meet regulatory requirements
- Placebo design addressed by:
  - Eligibility for rescue based on relapse (after first year) or disability (any time)
    - Study provided IM INFβ rescue
  - Require signing Informed consent regarding available treatment options at study entry and upon confirmed disease activity
- Phase 3 studies: 35 countries, 5 continents, ~200 sites/study, 1200-1400 subjects

23

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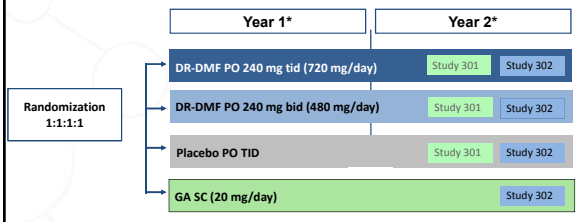
Clinical Summary: Phase 3 Studies 301 and 302



Same visit schedules, efficacy and safety assessments and endpoints

*30-day, post–last dose of blinded study treatment safety assessments conducted for those not entering Study 303. Double-blind only for DR-DMF and placebo; rater-blinded for all arms.

24

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Clinical Summary: Phase 3 Key Study Design Elements

- Two, 2-year, parallel group clinical trials
- DR-DMF 240 mg BID and TID superiority versus placebo
- Blinding: Treating and Examining Neurologists, INEC*, pre-visit study drug held
- Protocol specified definitions of relapse and disability progression

Primary and Secondary Endpoints in Phase 3 Studies at 2 years

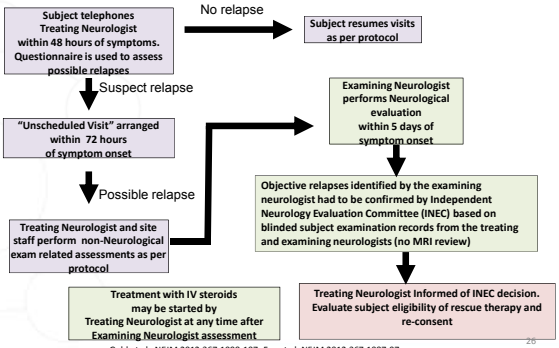
109MS301	109MS302
Primary Endpoint	
Proportion of patients who relapsed	Annualised Relapse Rate
Secondary endpoints (listed in descending rank order)	
Number of new or newly enlarging hyperintense T2 lesions	
Number of Gd-enhancing lesions	Number of new T1 hypointense lesions
Annualized relapse rate (Primary endpoint in Study 302)	Proportion of patients who relapsed (Primary endpoint in Study 301)
Time to 12-week confirmed disability progression	

*Independent Neurology Evaluation Committee

25

Gold et al., NEJM 2012;367:1098-107. Fox et al, NEJM 2012;367:1087-97

Relapse Evaluation



26

Gold et al., NEJM 2012;367:1098-107. Fox et al, NEJM 2012;367:1087-97

Blinding Procedures

Study staff blinded to subjects' randomized treatment

- To maintain blinding, separate neurologists were responsible for
  - Efficacy assessments
  - Treating relapses and other disease symptoms

Flushing is a common occurrence following DR-DMF administration

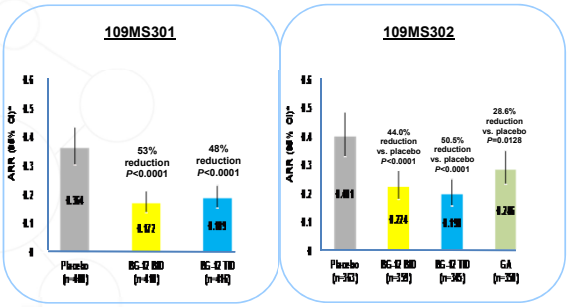
- To maintain blinding, patients were instructed not to take medication less than 4 hours before study visits

Study treatment was only dispensed by a pharmacist or medically qualified staff member

27

Gold et al., NEJM 2012;367:1098-107. Fox et al, NEJM 2012;367:1087-97

Annualized Relapse Rate at 2 Years



*ARR calculated with negative binomial regression, adjusted for baseline EDSS score (≤2.0 vs >2.0), baseline age (<40 vs ≥40), region, and number of relapses in the 1 year prior to study entry.

28

Gold et al., NEJM 2012;367:1098-107. Fox et al, NEJM 2012;367:1087-97

Clinical Summary: Efficacy Conclusions

- Results on relapses and all MRI secondary endpoints were robust, consistent and clinically meaningful, and statistically significant
- Clinically meaningful treatment effect on disability progression
- Both 240 mg BID and TID doses were efficacious and demonstrated similar and acceptable safety and tolerability
  - Recommended dose is 240 mg BID: lowest dose exhibiting a positive benefit-risk profile
- Robust, positive results on relapses and disability support DR-DMF's classification as a Disease Modifying Treatment for relapsing MS

29

Gold et al., NEJM 2012;367:1098-107. Fox et al, NEJM 2012;367:1087-97

Phase 3 Safety Summary: DR-DMF versus placebo

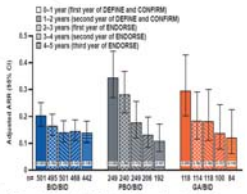
- Incidence of adverse events (AEs), serious AEs (21%, 18%, and 16% in the placebo, DR-DMF BID, and DR-DMF TID treatment groups, respectively), discontinuations, and withdrawals was similar across the 3 treatment groups
- Overall, there were no new safety signals and no increase in infections or serious infections
- DR-DMF treatment resulted in increased incidence of:
  - Flushing, gastrointestinal, and skin symptoms, liver enzyme elevations (ALT), low lymphocyte counts, microalbuminuria/proteinuria
- Increased incidence in discontinuations due to flushing and GI AEs
- Comprehensive clinical database at time of filing
  - 2468 MS patients exposed (maximum 4+ years)
  - 1578 patients ≥ 1 year, 1056 patients ≥ 2 years
  - 3588 person-years of exposure

30

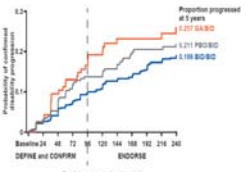
Gold et al., NEJM 2012;367:1098-107. Fox et al, NEJM 2012;367:1087-97

Persistent Effect of Earlier Treatment on Disease Course in Phase 3 Extension (ENDORSE)

Annualized relapse rate by yearly interval



Proportion of patients with 24-week confirmed disability progression by EDSS at 5 years



Hutchinson M et al, Presented at ECTRIMS, 7-10 October 2015, Barcelona, Spain P 543

31

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What is next for DR-DMF? Radiologically Isolated Syndrome (RIS) Study

Sponsored Research Agreement collaboration between RIS Consortium and Biogen

•RIS established via MRI criteria:

- Ovoid, well-circumscribed, and homogeneous CNS white matter foci with or without involvement of the corpus callosum
- T2-hyperintensities measuring > 3mm^2 and fulfilling 3 of 4 Barkhof-Tintoré criteria for dissemination in space
- Not consistent with a vascular pattern
- Have characteristic appearance of demyelinating lesions, but don't account for clinically apparent neurological impairments

•Objective: To complete the first randomized, controlled trial to study the efficacy of extending the time to a seminal acute or progressive demyelinating event in a cohort of RIS patients receiving either DR-DMF or placebo

•Primary Outcome: Time to the first acute or progressive neurological event resulting from CNS demyelination from randomization into the trial.

Okuda D et al, Presented at ECTRIMS, 7-10 October 2015, Barcelona, Spain P 1165

32

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What's next for MS at Biogen - Repair and Remyelination Studies: Anti-Lingo-1

- LINGO-1 is a CNS-specific membrane glycoprotein and suppressor of oligodendrocyte differentiation and myelination
- Anti-LINGO-1 (BIIB033) is a first-in-class human monoclonal antibody directed against LINGO-1
- RENEW (NCT01721161) was designed to:
  - Determine the efficacy/safety of anti-LINGO-1 for CNS remyelination after a first episode of Acute Optic Neuritis
  - Establish proof of biological activity
  - Primary endpoint: MOA for remyelination: Improvement in optic nerve conduction latency by full-field visual evoked potential [FF-VEP]
  - Secondary endpoints: MOA for neuroprotection: Change in retinal thickness, Change in low-contrast letter acuity

Cadavid D et al, Presented at AAN; 18–25 April 2015; Washington, DC. P7.202

33

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Summary

- Some challenges faced in developing a disease-modifying treatment for epilepsy are similar to those for MS
- Disease modifying studies are achievable but may require collaboration with regulators, clinicians, and sponsors to agree on valid endpoints that are clinically meaningful
- Studies will likely require longer follow up and larger sample sizes to demonstrate an effect on the underlying disease
- Use of placebo as the comparator appropriate as long as there is clinical equipoise and include design elements assure use of placebo is ethical.

34

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#AESmtg15

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69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Why new MS therapies are needed

- 400,000 persons with MS in the US
  - 200,000 treated, 50,000 stopped therapy, 150,000 untreated*
  - 14% of RRMS patients discontinue within 5 years[1,2]
- Among CNS disorders, most frequent cause of permanent disability in young adults
- Progressive disability phase usually occurs 10-20 years after disease onset[3]
- Median time to needing walking assistance - 28 years, earlier studies 16 years[4]

1 O'Rouke and Hutchinson Mult.Scl. 2005; 11: 46-50 2 Rio et al, Mult.Scl. 2005; 11: 306-309. 3. Tremlett H, Paty D, Devonshire V, Neurology. 2006;66(2):172. 4. Runmarker B, Andersen O, Brain. 1993;116 (Pt 1):117
*Biogen Idec internal data

36

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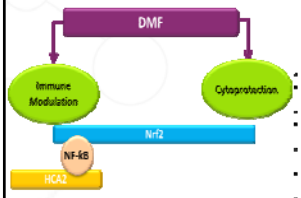
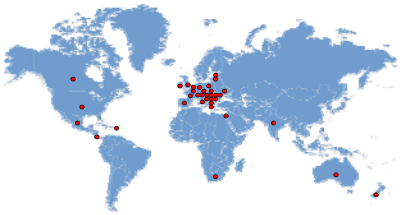
The Potential Mechanism Of Action Of DMF



1. Rakai KW, et al. European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), Lyon, France, 10–13 October 2012: Poster P724. 2. Lukashev M, et al. Mult Scler 2007; 13: S149, P503. 3. Chan JG, et al. Am J Physiol Heart Circ Physiol 2006; 290: H1832-70. 4. Tecfidera (dimethyl fumarate) delayed-release capsules. Prescribing information. Biogen Idec; 2013. 5. Fumaderm (dimethyl fumarate and ethyl hydrogen fumarate salts). Prescribing information. 2012. Available at: http://www.fumaderm.de/pdf/fachinfo_en.pdf. Accessed 5 September 2012. 6. Scannevin RH, et al. J Pharmacol Exp Ther 2012; 341: 274-84. 7. Li DK, et al. Mult Scler 2011; 17: 1037-44. 8. Arnold HM, et al. Neurology 2012; 78: P02.127. 9. Arnold HM, et al. Mult Scler 2011;17: S232, P918. 10. Sanofi. A study comparing the effectiveness and safety of teriflunomide and interferon beta-1a in patients with relapsing multiple sclerosis (TENERE). 2013. Available at: http://clinicaltrials.gov/show/NCT00883337?sort accessed 2 April 2013].

DR-DMF Phase 3, 2-year, Studies: 35 Countries on 5 Continents



DEFINE

198 sites, 28 countries
1234 patients

CONFIRM

200 sites, 28 countries
1430 patients

http://clinicaltrials.gov/ct2/show/NCT00420212?term=bg+multiple+sclerosis+define&rank=1. Accessed August 16, 2011.
http://clinicaltrials.gov/ct2/show/NCT00451451?term=bg+multiple+sclerosis+confirm&rank=1. Accessed August 16, 2011.

Detours and Misdirections: Cautionary Tales of Translation Failures

Emily Sena, PhD
Centre for Clinical Brain Sciences, University of Edinburgh
@camarades_

December 05, 2015

Disclosure

I have nothing to disclose.

Learning Objectives

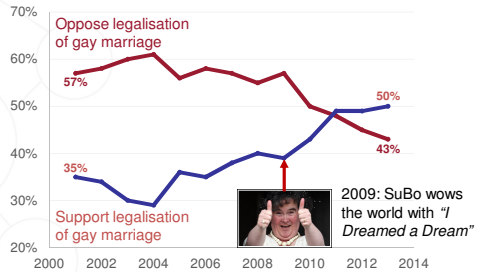
- Translational failure
- Internal validity of experiments
  - Reporting of measures to minimise bias
- Construct validity of experiments
- Reporting bias

Why do we do meta-analysis of animal studies?

- Preclinical studies are often performed with the purpose of improving human health
- Used in preclinical research to:
  - assess the quality and range of evidence
  - identify gaps in the field
  - assess for publication bias
  - try to explain discrepancies between preclinical and clinical trial results
  - inform clinical trial design
- Fundamental differences:
  - Many small (10s) animal studies
  - Fewer large (100s/1000s) clinical trials
- Hypothesis-generating tool

Correlation vs Causation

I'm not saying Susan Boyle caused Americans to support gay marriage



But Susan Boyle happened and then support of gay marriage increased

Outline

- Translational failure
- Internal validity of experiments
  - Reporting of measures to minimise bias
- Construct validity of experiments
- Reporting bias

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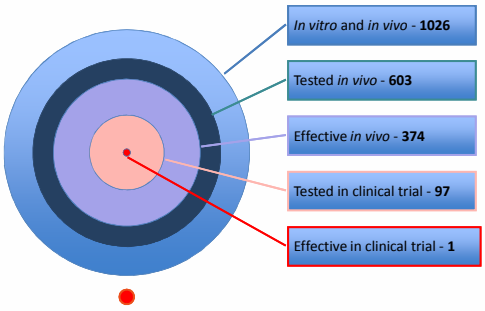
Hypotheses

- In the life sciences there are perverse incentives (publication, funding, promotion) to produce positive results with little attention paid to their validity
- In the use of animal disease models, pressure to reduce the number of animals (cost, time, ethics, feasibility) results in studies either being underpowered or of unknown power
- These factors combine to compromise the utility of animal models and contribute to translational failure

1026 interventions in experimental stroke

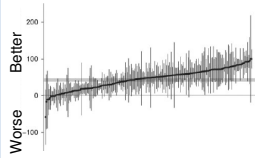


O' Collins *et al.* 2006

Animal data in stroke

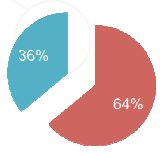
- There are huge amounts of often confusing data
- Systematic review can help to make sense of it
- If you select extreme bits of the evidence you can "prove" either harm or substantial benefit
- Investigating the sources behind this variation may be helpful in translation

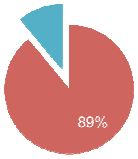
Hypothermia: a systematic search identified 222 experiments in 3353 animals



Van der Worp *et al Brain* 2007

Failure to replicate published pre-clinical academic results





BAYER

AMGEN

Outline

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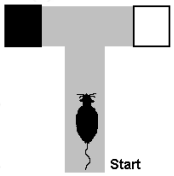
You can usually find what you're looking for …

- 12 graduate psychology students
- 5 day experiment: rats in T maze with dark arm alternating at random, and the dark arm always reinforced
- 2 groups – "Maze Bright" and "Maze dull"

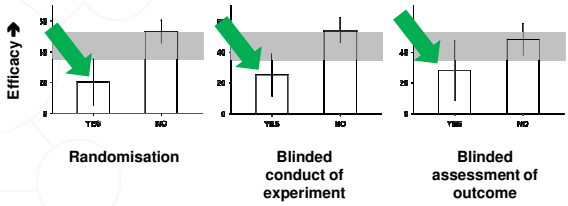


Group	Day 1	Day 2	Day 3	Day 4	Day 5
"Maze bright"	1.33	1.60	2.60	2.83	3.26
"Maze dull"	0.72	1.10	2.23	1.83	1.83
Δ	+0.60	+0.50	+0.37	+1.00	+1.43

Rosenthal and Fode (1963), Behav Sci 8, 183-9

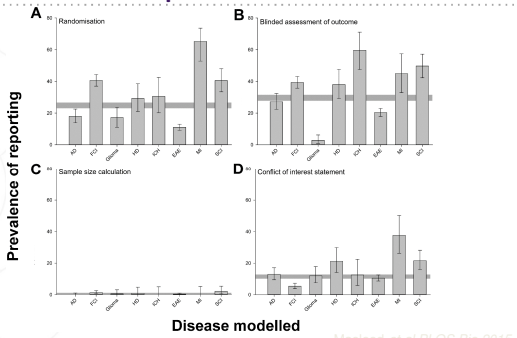
Internal Validity:
Lessons from NXY-059

Infarct Volume
- 11 publications, 29 experiments, 408 animals
- Improved outcome by 44% (35-53%)



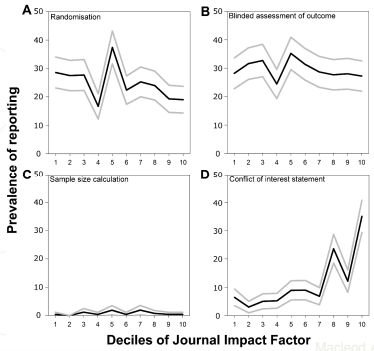
Macleod *et al*, 2008

How do models of neurological disorders compare?



Macleod *et al PLOS Bio 2015*

Reporting of risk bias items by decile of journal impact factor



Macleod *et al PLOS Bio 2015*

Outline

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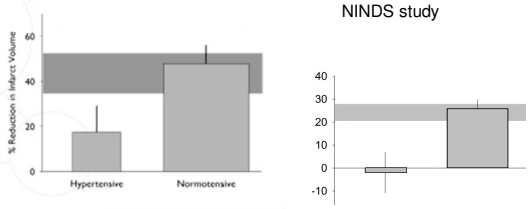
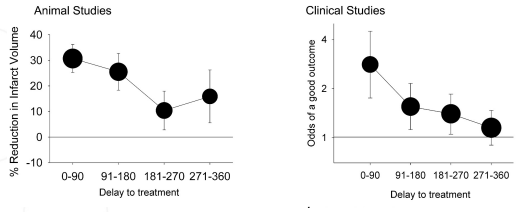
The wrong model
Hypertension and NXY-059 and tPA

NXY-059
- 7% of animal studies
- 77% of patients in the (neutral) SAINT II study

tPA
- 9% of animal studies
- Specifically exclusion criterion in (positive) NINDS study



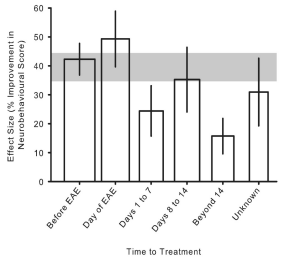
Validation of animal models
Clot busting treatment for stroke



External Validity:
Time to Treatment in EAE

- Median: 0 days (IQR -11 to 4)
- 1% did not report time of administration

Before EAE	48%
Day of Induction	22%
After EAE	30%
Day of Symptom Onset	2%



Outline

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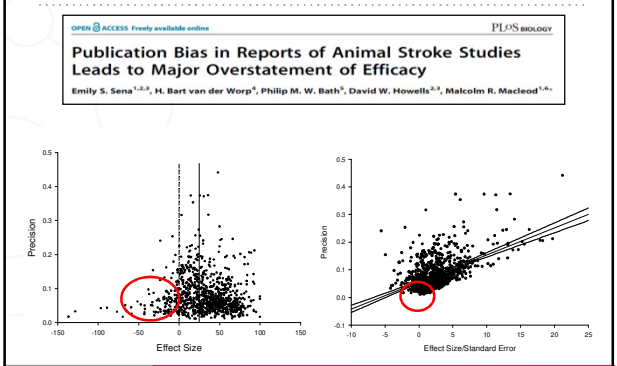
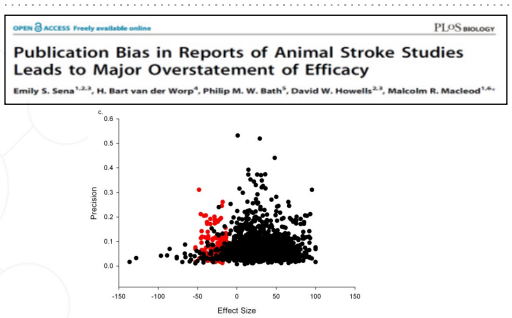
Reporting bias

- Neutral and negative studies
  - Publication bias
  - Time lag bias
- Selecti
- Vibrati
  - Selec





Overall efficacy was reduced from;
32% (95% CI 30 to 34%) to **26%** (95% CI 24 to 28%)

Publication bias in experimental stroke

- Trim and Fill suggested **16%** of experiments remain unpublished
- Best estimate of magnitude of problem
  - Overstatement of efficacy **31%**
- Only **2%** publications reported no significant treatment effects

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Publication bias

20% - 32%

	n expts	Estimated unpublished	Reported efficacy	Corrected efficacy
Stroke – infarct volume	1359	214	31.3%	27.5%
EAE - neurobehaviour	1892	505	33.1%	15.0%
EAE – inflammation	818	14	38.2%	37.5%
EAE – demyelination	290	74	45.1%	30.5%
EAE – axon loss	170	46	54.8%	41.7%
AD – Water Maze	80	15	0.688 sd	0.498 sd
AD – plaque burden	632	154	0.999 sd	0.610 sd

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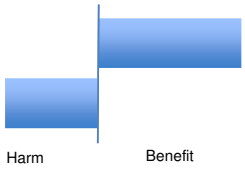
Different patterns of publication bias in different fields

	outcome	observed	corrected	
Disease models	improvement	40%	30%	Less improvement
Toxicology model	harm	0.32	0.56	More harm



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Key messages

- *In vivo* studies which do not report simple measures to avoid bias give larger estimates of treatment effects
- Most *in vivo* studies do not report simple measures to reduce bias
- Publication and selective outcome reporting biases are important and prevalent
- You cannot assume rigour, even in Journals of "impact"
- You can only find these things out by studying large numbers of studies
- Any experimental design can be subverted; what's important is knowing how to recognise when this has happened

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Improvement strategies – Internal validity

- Journals
  - ARRIVE reporting guidelines
  - LANDIS transparency guidelines
  - NPG publication policy
  - Audits and RCTs to improve uptake of these
- Funders
  - Emphasising rigour in grant award
- Institutions
  - Audit of performance
  - CPD opportunities for scientists

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Improvement strategies – external validity

- Scientists
  - Develop better validation of animal models
    - Targeted experiments (ALZ.org)
    - Systematic review of hundreds of experiments comparing models, outcome measures
- Design clinical trials to test where efficacy has been shown in preclinical studies

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Improvement strategies – reporting biases

- Journals
  - Are you the Sunday Sport, the Daily Mail or a journal of record?
- Funders
  - Withhold 10% of grant pending publication
  - Support new publication models
- Institutions
  - Encourage rapid publication anywhere, not vanity publishing in journals of the highest "impact"
  - On appointment panels, look at the work, not where it was published

How can we increase the chances of translational success?

- Systematically review the available data
- Conduct further *in vivo* experiments if indicated
- Design your clinical trial accordingly
- Develop tools to allow rapid, living systematic reviews

Thanks to.....

- Edinburgh
  - **Malcolm Macleod**
  - Kieren Egan
  - Hanna Vesterinen
  - Gillian Currie
  - Zsanett Bahor
  - Robert Stewart
- Melbourne
  - David Howells
  - Ana Antonic
  - Peter Batchelor
  - Taryn Wills
  - Sarah McCann
- Stanford/Ioannina
  - John Ioannidis
  - Kostad Tsilidis
  - Orestis Panagiotou
  - Eleni Aretouli
  - Vangelis Evangelou
- Utrecht
  - Bart van der Worp
- Translators
- NHS R&D methodology program
- Chief Scientist Office
- NC3Rs

#AESmtg15

AMERICAN EPILEPSY SOCIETY

69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Getting to Cure: A Path Forward for Disease-modifying Therapy for Epilepsy

Robert E. Pacifici, Ph.D.
Chief Scientific Officer
CHDI Foundation / CHDI Management Inc.

Presidential Symposium: Getting to Cure
The Challenging Road to Disease Modification and Prevention for Epilepsy

December 5th, 2015

CHDI
Accelerating therapeutic development for Huntington's disease

AMERICAN EPILEPSY SOCIETY
69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Disclosure

Nothing to disclose

CHDI Foundation is a privately-funded, not-for-profit biomedical research organization devoted to a single disease – Huntington's disease. Our mission is to develop drugs that will slow the progression of Huntington's disease and provide meaningful clinical benefit to patients as quickly as possible. To achieve this CHDI manages a diverse portfolio of research projects through a novel virtual model that encourages scientific collaboration to more directly connect academic research, drug discovery and clinical development. This helps bridge the translational gap that often exists between academic and industrial research pursuits, and which adds costly delays to therapeutic development. Our activities extend from exploratory biology to the identification and validation of therapeutic targets, and from drug discovery and development to clinical studies and trials.

Learning Objectives

- Meaningful Therapies
  - At the onset of a drug discovery effort what steps can be taken to ensure that
    - It will benefit the particular disease you are interested in treating
    - The treatment will be more impactful that current standard of care
- Human phenomenology
  - How can we leverage observations made in the population we seek to treat to inform our drug discovery efforts
  - How do we go beyond simple observational studies to probe specific aspects of a complex disease
- Mechanistic Hypothesis
  - What are the advantages and risks of developing highly granular mechanistic hypothesis to guide your drug discovery efforts?

What is CHDI…exactly?

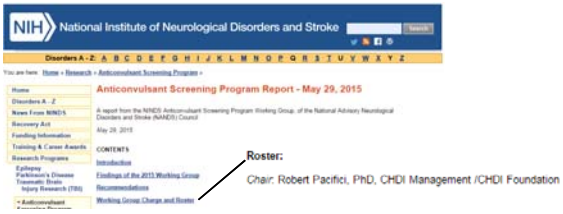
A not-for-profit drug discovery organization
- Motivated by TIME not MONEY
- No COMPETITORS only COLLABORATORS
- Fully integrated research: discovery-translational-clinical

Foundation funded
- All funds from private donors (~$80MM/yr)
- Driven by drug candidates
- Not by hype, press releases, or trial initiations

Exclusively dedicated to Huntington's disease
- Removes serendipitous indications discovery
- Unambiguous continuity, focus, passion
- IP, legal, business terms all designed to protect our primary indication (allows others)

Utilizing the "virtual" or outsourced model
- Approximately 70 internal FTEs across three sites (NY, NJ, & LA) covering all scientific and G&A competencies
- No internal wet-labs. All experimentation is done externally via collaborative partners and contract research organizations. Circa 600 FTE
- Select the "best-of-the-best"; yet fungible

Who am I, and why am I here?



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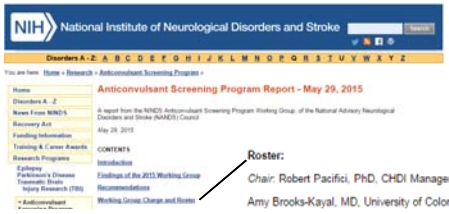
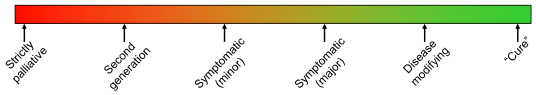


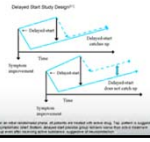
Anti Seizure →
- Disease Modification
- Antiepileptogenesis
- Drug resistance
- Specific sub-types
- Comorbidities

Concepts of disease modification & relevant therapies

Two separate, but related, issues

- Validation
  - Is our understanding of the biology around a target, pathway, mechanism sufficiently compelling that it's modulation would specifically (not exclusively) ameliorate disease (at a given stage)?
- Meaningful Therapy
  - Can we *a priori* predict how patients will benefit from this drug if successful?





7

Concepts of disease modification & relevant therapies

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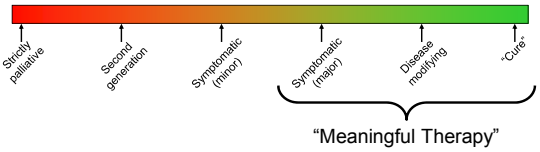
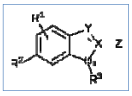


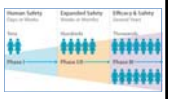
8

The Main Sources of "Risk" for any Therapeutic Program



Chemistry or Compound Related
- Potency, Solubility, Selectivity, PK & ADME
- CMC: Synthesis, Stability, Formulation
- Intellectual Property

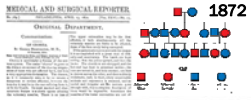
Clinical or Trial Related
- Outcome measures
- Trial design: subjects, timing/stage, length
- Statistics: power, calculations



Biology or Target Related
- On-mechanism toxicity & robustness
- Tractability & Pharmacology
- Validation / Disease association

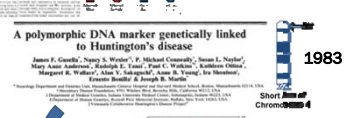
9

Genetics give us our first therapeutic strategy



1872

Century



1983

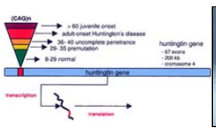
Decade

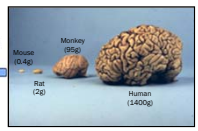
- Monogenetic disorder with autosomal dominant inheritance
- Enables: genetic testing, preimplantation genetic diagnosis, and the creation of various rodent models
- First cohort of targets and drug candidates emerge

10

Monogenic Disorder: A double-edge sword?

Perhaps trying to recapitulate *en toto* what happens in a big wrinkled human brain over 40 years in a rodent expressing a single transgene in a few weeks is…naïve!



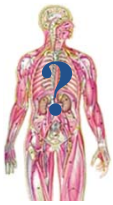


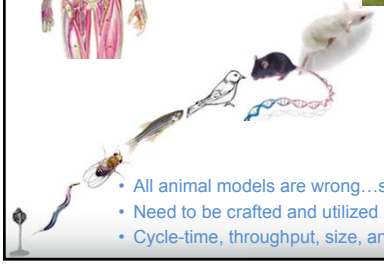
Courtesy of Dr. Russ Lonser

- Developed a robust "industrialized" testing paradigm
  - Synthesis, formulation, PK, broad outcome measures, stats…
- Tested over 30 compounds nominated from peer-reviewed

11

Monogenic Disorder: A double-edge sword?

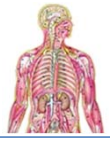




- All animal models are wrong…some are useful
- Need to be crafted and utilized 'fit for purpose'
- Cycle-time, throughput, size, and validity all matter

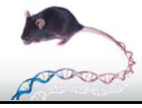
12

A new strategy: Using Humans as models of Humans



Experimental medicine studies involving affected individuals must be part of the iterative drug discovery process. There is nothing more precious to a drug hunter than information derived from the patient population they ultimately seek to treat.

Having a mechanism-based hypothesis is critical for translational research. Without a mechanism there is no way to eliminate unfruitful lines of investigation or to turn faint signals of efficacy into stronger ones.

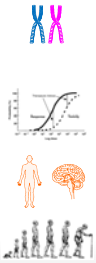


There is no such thing as a "good animal model of HD" or a "bad animal model of HD." Animals simply cannot model HD in its entirety. Rather their utility is in modeling certain aspects of the disease.

13

Everyone that has HD has the mutated gene
Everyone that has the mutated gene has HD

- Protein of unknown function, but the most proximal perturbation
- Stands to reason that eliminating the insult could be beneficial



What to Target?
- Mutant Htt, but what about the wild-type allele?

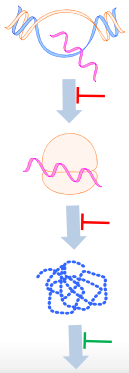
How Much to Suppress?
- Need to define a therapeutic window

Where to Treat?
- Striatum, cortex, periphery

When to Intervene?
- Symptomatic or pre-manifest

14

A variety of modalities, approaches, and companies



Large number of collaborative partnerships
- Academics
- Biotechnology companies
- Multinational "Big Pharmas"
- Nonprofit foundations

15

PK/PD: Don't go to the Clinic Without It!

Pharmacokinetics	Target Engagement	Biochemical Engagement
What dose, route, and frequency is needed so the drug will reach the needed tissues at a high enough concentration for a long enough period of time?	How can we measure that the drug has properly bound to the its cognate target *in situ*?	Can we verify that the drug elicited the desired biochemical effect to the desired extent?
Drug never achieved levels above EC50	Not bound to receptor ligand domain or enzyme active site.	Target is constitutively activated or irreparably impaired
New compound New route New dose	New compound New target	New target New mechanism

16

CHDI's Huntingtin Lowering Pharmacodynamic Biomarker Task Force

- Goal
  - Develop PD biomarkers of (Huntingtin) HTT lowering to support upcoming HTT lowering clinical trials
  - Should demonstrate that the delivery of a HTT lowering agent to the CNS does in fact lower the amount of HTT protein in the CNS
- Strategy
  - Assessed potential biomarkers that could be developed quickly
  - Hosted 3 workshops with internal and external experts
    - Imaging
    - Biochemical
    - Physiological
  - Prioritized biomarkers by both scientific rationale and feasibility
  - Established the criteria for a good PD biomarker
  - Began PoP studies in animals and feasibility in HDGECs

17

Criteria for a HTT-lowering PD biomarker

- Biological plausibility
- Technological feasibility
- Measurable in Humans
- Repeatable within subjects

Key in selection

- Reliably measured in HDGEC
- Signal metrics: dynamic range, variance
- Measurable in preclinical HD animal models

Gathering data, if not already available

- **PoP: Changes in response to central lowering of HTT in preclinical animal models**
- **Changes in response to a HTT lowering intervention in HDGEC**

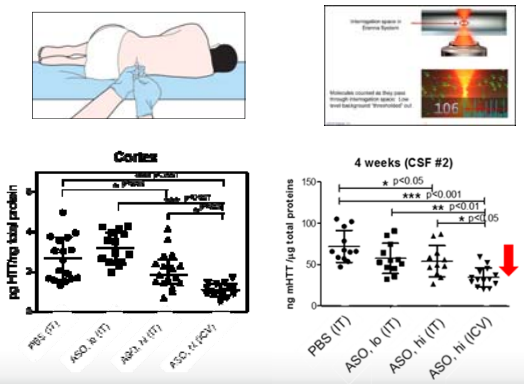
18

Prioritized HTT-Lowering PD Biomarker Domains

Biomarker Domain	Description
HTT Protein in CSF	*Ultra-sensitive method to measure HTT itself in CSF*
PET Imaging	*Brain receptors for which there are PET ligands and changes with HD*
PET Imaging HTT	*De novo development of a ligand to HTT aggregates*
CSF Proteomics: Static & Kinetic	*Kinemed in vivo isotopic labeling and ex vivo analysis*
qEEG	Non-invasive measure of altered electrical activity in the brain
MR Spectroscopy	Non-invasive measure of energetic metabolites in brain ROI

19

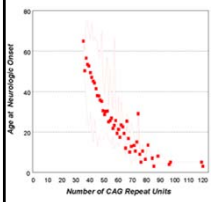
HTT Protein Measurement in CSF



20

The polymorphic gene provides another clue

- Inverse correlation between $(CAG)_n$ and age of motoric onset



21

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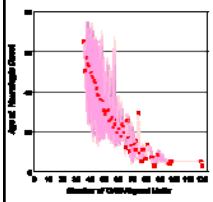
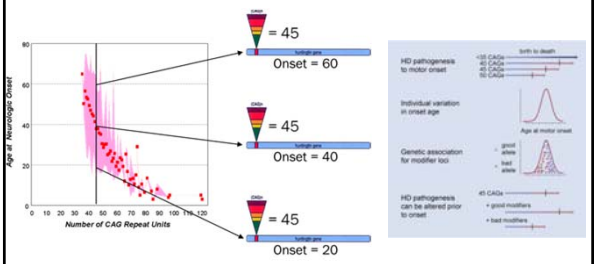


22

The polymorphic gene provides another clue

- Inverse correlation between $(CAG)_n$ and age of motoric onset
- Outliers driven by heritable factors: modifier genes!



23

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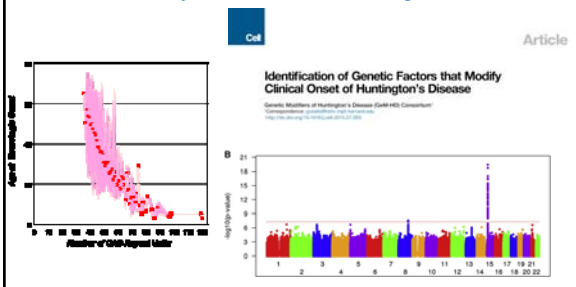


24

Energetic dysfunction's early link to Huntington disease

- Phenotypic observations in human HD patients
  - Weight loss
  - Increased lactate levels
  - Measurable deficits in complex II and creatine kinase
  - Inverse correlation of $(CAG)_n$ to ATP/ADP ratios

- Chemical lesions or "exo-toxins" mimic neurodegenerative diseases
  - Mildewed sugar cane poisoning of children in China
  - Mitochondrial poisons like 3-nitroproprionic acid selectively kills MSNs and produces an HD-like phenotype
  - Evidence from other diseases: MPTP and Rotenone produce PD-like
- Genetic lesions or mutations that cause neurodegenerative diseases
  - Leigh's syndrome and other "mitochondriopathies" have a differential effect on the basal-ganglia
  - Familial ALS is caused by mutations in the ROS detoxifying enzyme SOD1
  - Friedreich's Ataxia (another triplet repeat disease) energetic issues
  - Parkinson mutations like PINK1 also tie into mitochondrial function

25

CoQ_{10}: It doesn't work…and we don't know why.

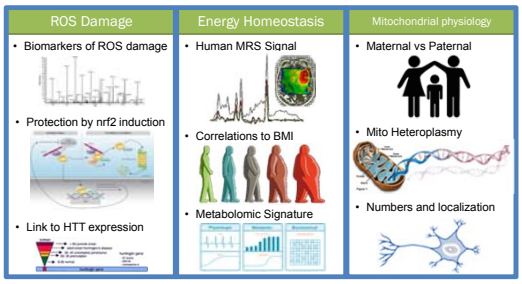
Announcement of 2CARE Early Study Closure

The National Institute of Neurological Disorders and Stroke (NINDS) stopped its study of coenzyme Q_{10} for the treatment of Huntington's disease (HD) on July 14, 2014. The study (2CARE), conducted by the Huntington Study Group (HSG), was stopped for futility. The NINDS and the HSG acted on the recommendation of the study's independent Data and Safety Monitoring Board (DSMB). Following the most recent DSMB review of the study data, an interim analysis was conducted that showed that, given the current data, it would be very unlikely (less than a 5 in 100 chance) to see a statistically significant benefit of active treatment (coenzyme Q_{10}, 2400 mg/day) over placebo at the scheduled end of the trial. The DSMB also noted a higher number of deaths in the coenzyme Q_{10} group (7%) in comparison to the placebo group (4%); most of these deaths appeared to be related to HD, which is a severe, progressive neurological disorder. Although this number may have been due to chance, and was not statistically significant, the DSMB noted it in their decision. Site investigators and coordinators have informed participants of the study closure and have encouraged each participant to schedule a final visit to the clinic.

- Must understand pathology to a high degree of granularity
- All (interventional) trials should advance the field; even if they fail
- Strong mechanistic hypothesis connects benchtop to bedside
- Some "observations" need to be generated *de novo*

26

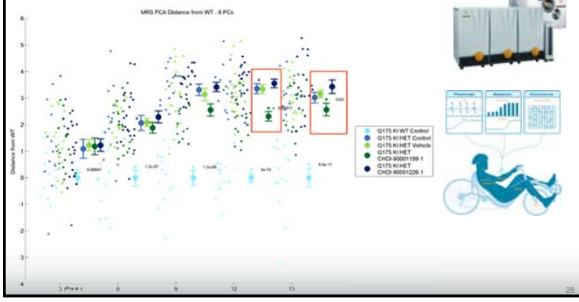
"Hybrid" observational studies generate new hypotheses



27

MRS Based Experimental Medicine: Tailored to a mechanistic hypothesis

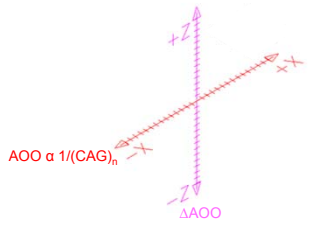
- Live, central, energetic 'signature' from HD rodent models
- Reversible with HTT lowering
- Sets up for a poignant non-invasive human study

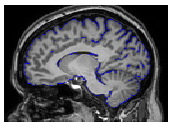


28

Do IPSC's give us a window to human phenomenology?

- Inverse correlation between (CAG)n and age of motor onset
- Outliers from curve driven my modifier genes
- Do IPSCs allow us to leverage another human observation?





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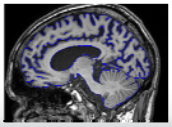
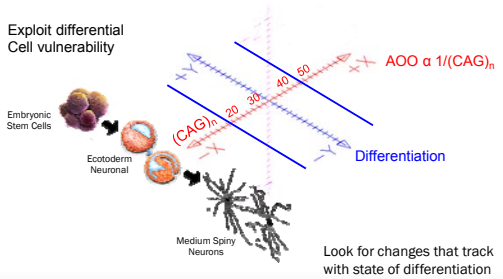


Huntington's Disease

29

Do IPSC's give us a window to human phenomenology?

Exploit differential Cell vulnerability



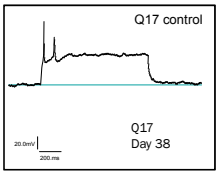
Look for changes that track with state of differentiation

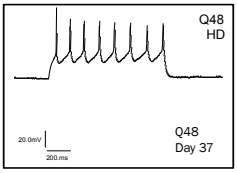
30

(CAG)n Dependent Electrophysiological Phenotype in IPSC derived neurons

Major difference between activity monitored to date

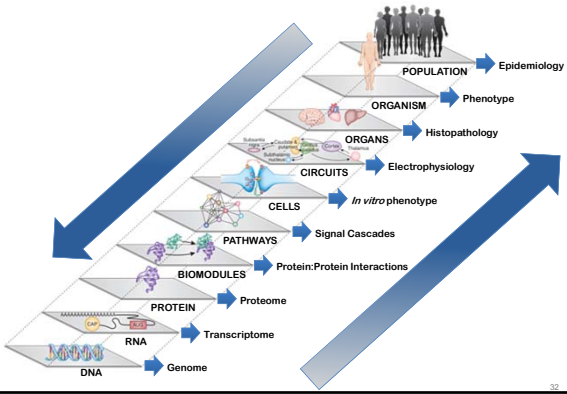
- HD cells are more excitable exhibiting more spontaneous activity
- Induced activity results in multiple Action potentials whilst stimulus is applied





31

We must strive to build continuity in the "Network of Networks"

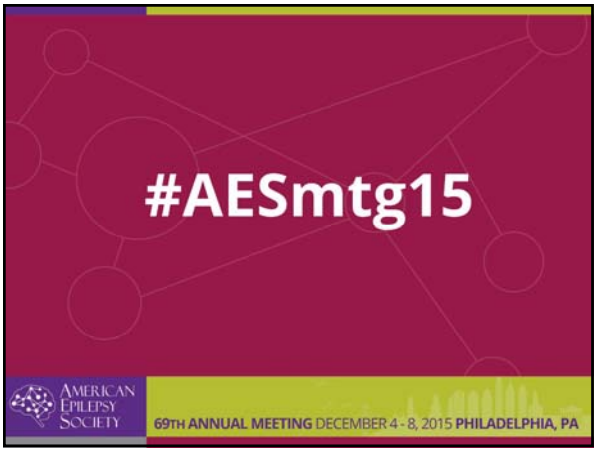


32

Take Away Messages

- Meaningful Therapies
  - More realistic in the near term
  - Clearer regulatory path for approval
  - Not mutually exclusive with "cures"
- Human phenomenology
  - There is nothing more valuable to a drug hunter than an observation made in the population they seek to treat
  - Genetics provide a strong unbiased way of focusing efforts
  - Experimental medicine can uncover new and poignant disease features
- Mechanistic Hypothesis
  - Needs to be sufficiently granular
  - Allows you to connect from benchtop to bedside
  - Enables shorter and informative interventional studies with pharmacodynamics biomarkers

33



Getting to Cure: the challenging road to disease modification and prevention for epilepsy.

Amy Brooks-Kayal, MD
University of Colorado
Children's Hospital Colorado
President, AES

December 5, 2015

What have we learned about disease modifying therapies?

- People with epilepsy need them
- Identifying and validating your target(s) are essential
- The path isn't simple: complex decision making is needed at each step
- Many good targets don't turn into useful therapies due to
  - Inability to "drug" it
  - Toxicity
  - Poor pharmacokinetics
  - Failure to demonstrate efficacy expected from animal studies or results from earlier smaller clinical trials
- Drug Development is a team sport

What have we learned about disease modifying therapies?

- Clinical trials for disease modifying studies are achievable but will require
  - longer follow up, larger sample sizes and more complex studies to demonstrate an effect on the underlying disease
  - collaboration with regulators, clinicians, and sponsors to agree on valid, clinically meaningful endpoints
- Developing a surrogate biomarker that correlates with clinically meaningful endpoints is an important way to make disease-modifying drug development feasible

How can we increase the chances of translational success?

- Translation failures are common but may be reduced by
  - Systematic reviews of available data
  - More extensive preclinical experiments potentially including multicentre studies with improved internal and external validity and increased rigor in reporting
  - Appropriate design of clinical trials
- Leveraging observations made in the population we seek to treat should inform our drug discovery efforts
- Specific mechanistic hypotheses may enable shorter and informative interventional studies with pharmacodynamic biomarkers

Let's get it done!

AMERICAN EPILEPSY SOCIETY
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