

Translational Research: An Industry Perspective

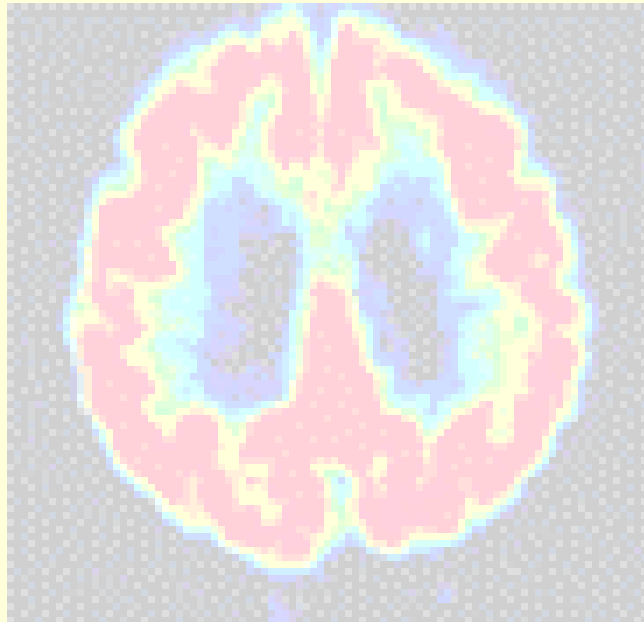
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August 4th 2005

Wyeth
Research

Today's presentation

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The challenge

The possibility

Summary

Translational Medicine has specific definitions and usage within the industry

The Industry's Definition of Translational Medicine:

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- Non-registrable clinical studies in humans
- Experimental studies to support human proof of concept

The Industry's use of Translational medicine:

- A tool to bridge the gap between preclinical and clinical studies
- Understanding the likely behavior of experimental medicines in humans
- Enabling cost-effective determination of efficacy and safety through the use of biomarkers and experimental studies in humans

Multiple challenges face the industry when developing novel therapies, including:

- Delays in reaching the market due to clinical delays and failures
- Loss of revenue associated with delays, and cost of failures
- Many diseases have very small markets with poor return on investment
- Regulatory agencies rely on precedent – many of today's medicines and diseases are unprecedented in the clinic
- The novel therapies arising from the human genome are unprecedented for everyone
- Many diseases are chronic versus acute

The disconnect between pre-clinical and clinical studies poses a significant challenge

Preclinical studies

- ✓ Produce a surfeit of candidates
- ✓ Focused, iterative experiments
 - ✓ 1000's of potential targets from genome sequence
 - ✓ combinatorial chemistry
 - ✓ high throughput screening
- ✓ Few ethical & regulatory constraints
 - ✓ complete control of experimental conditions
 - ✓ Direct measurements proximate to drug effects

Clinical studies

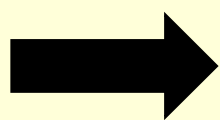
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- ✓ Rate limiting
- ✓ Large expensive studies
 - ✓ heterogeneous subjects for broad label
 - ✓ variable exposures for convenient dosing
- ✓ Ethical & regulatory restraints
 - ✓ Incomplete control of subjects & experimental conditions
 - ✓ Clinical & quality of life measures far downstream of drug effects

Pre-clinical studies offer a high degree of control and reproducibility

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- ✓ **Choose homogeneous subjects**
 - identical animals
- ✓ **Control lesion**
 - identical lesions
 - intervene at precisely known interval after insult
 - treat at earliest stages of pathophysiology
- ✓ **Tailored dosing**
 - mg/kg, avoid first pass metabolism
- ✓ **Make direct measurements of effect**
 - sacrifice animal to directly assess tissue damage



Little variance, small sample size, multiple iterations

However, despite their ease of use, pre-clinical models have a minimal use in drug development

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- Behavior of a compound in an intact organism cannot be predicted perfectly from interactions with isolated human molecules or cells *in vitro*
- Significant metabolic pathways in laboratory animals may be minor or redundant in humans
- Animal models are not identical to human disease

Clinical studies are more difficult because of ethical, regulatory & commercial constraints

- ✓ **Treat wide population – broad label**
 - variable subjects
 - concomitant medications

- ✓ **Treat naturally occurring disease**
 - lesions variable in severity, location, duration
 - intervene at unknown, variable interval after insult
 - treat only after disease advanced enough to be diagnosed

- ✓ **Convenient dosing**
 - oral, daily, fixed tablet size
 - variable exposure

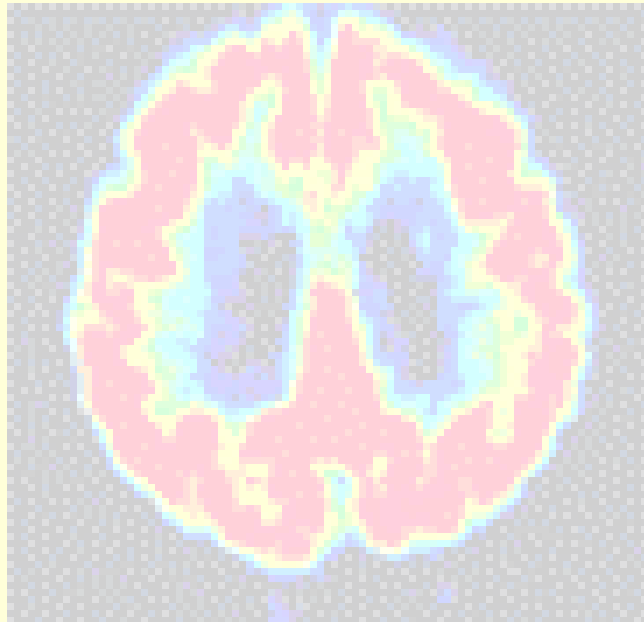
- ✓ **Make indirect measurements of effect**
 - noninvasive measurements
 - downstream clinical and quality of life measures

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 ***High variability, need large samples, limited revisions***

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Summary

Translational Medicine in an industrial setting can help manage the disconnect

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Small focused Translational Medicine studies...

- Demonstrate relevance of unprecedented target in humans before committing to traditional registration studies
- Begin biomarker discovery and validation while in discovery phase
- Exploratory IND's, minimal formulations to choose optimal compounds

Proof of Biology can be identified before traditional “registrable” Phase 2 to reduce risk

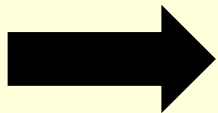
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- ✓ **Reduce subject variability**
 - stricter inclusion criteria than commercially viable label
 - crossover designs

- ✓ **Focused disease models**
 - challenge models in healthy volunteers
 - diseases with related mechanisms

- ✓ **Individualized dosing**
 - intravenous dosing
 - titrate to blood levels

- ✓ **Proximate measures of effect**
 - biomarkers, imaging



- ***Failure in P.O.B. is a NO GO decision***
- ***Advance to Phase 2 only if successful***

Our aim is to use these tools for internal decision making purposes only

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Successful Translational Medicine implementation should:

- ✓ Reduce risk associated with developing novel therapeutics
- ✓ Decrease cycle times
- ✓ Decrease late stage attrition by making better decisions earlier
- ✓ Reduce cost by reaching POC go/no-go decisions earlier

We can use Translational Medicine studies for internal decision making

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- What patients will respond to the drug? → Patient stratification biomarkers
- How much drug to give? → Pharmacodynamic biomarkers
- Does the drug have biological activity? → Biological activity biomarkers

Translational Medicine studies can help internal decision making through 3 key questions

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- **What patients will respond to the drug? → Patient stratification biomarkers**
- How much drug to give? → Pharmacodynamic biomarkers
- Does the drug have biological activity? → Biological activity biomarkers

The EGFR mutation in lung cancer is a well documented example of stratification biomarkers

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EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

J. Guillermo Paz, ^{1,2*} Paul A. Janne, ^{1,2*} Jeffrey C. Lee, ^{1,2*} Sean Tracy, ¹ Heidi Greulich, ^{1,2} Stacy Gabriel, ⁴ Paula Herman, ¹ Frederic J. Kaye, ² Neal Lindeman, ² Titus J. Boggon, ^{1,2} Kazuhiko Maeki, ¹ Hidefumi Sasaki, ⁷ Yoshitaka Fujii, ⁷ Michael J. Eck, ^{1,2} William R. Sellers, ^{1,2,4} Bruce E. Johnson, ^{1,2} Matthew Hayason ^{1,2,4}

Receptor tyrosine kinase genes were sequenced in non-small cell lung cancer (NSCLC) and matched normal tissue. Somatic mutations of the epidermal growth factor receptor gene (EGFR) were found in 15 of 56 sampled tumors from Japan and 1 of 81 from the United States. Treatment in the EGFR kinase inhibitor gefitinib (Iressa) causes tumor regression in some patients with NSCLC, more frequently in Japan. EGFR mutations were found in additional lung cancer samples from U.S. patients who responded to gefitinib therapy and in a lung adenocarcinoma cell line that was hypersensitive to growth inhibition by gefitinib, but not in gefitinib-insensitive tumors or cell lines. These results suggest that EGFR mutations may predict sensitivity to gefitinib.

Protein kinase activation by somatic mutation or chromosomal alteration is a common mechanism of tumorigenesis (1). Inhibition of activated protein kinases through the use of targeted small molecule drugs or antibody-based strategies has emerged as

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- Only 10% NSCLC patients respond well to Anti-EGFR Gefitinib (Iressa)
- The tumors of these patients carry high-frequency mutations in the EGF protein
- EGF protein drives lung cancer growth
- Iressa kills cancer cells bearing the mutation
- **However, some patients without mutation did respond to the drug – so caution is needed in interpretation of data**

Translational Medicine studies can help internal decision making through 3 key questions

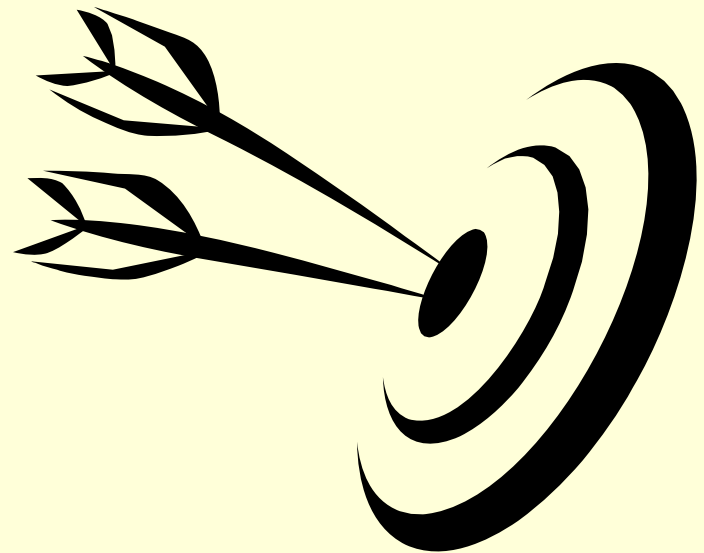
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- What patients will respond to the drug? —————> Patient stratification biomarkers
- **How much drug to give?** —————> **Pharmacodynamic biomarkers**
- Does the drug have biological activity? —————> Biological activity biomarkers

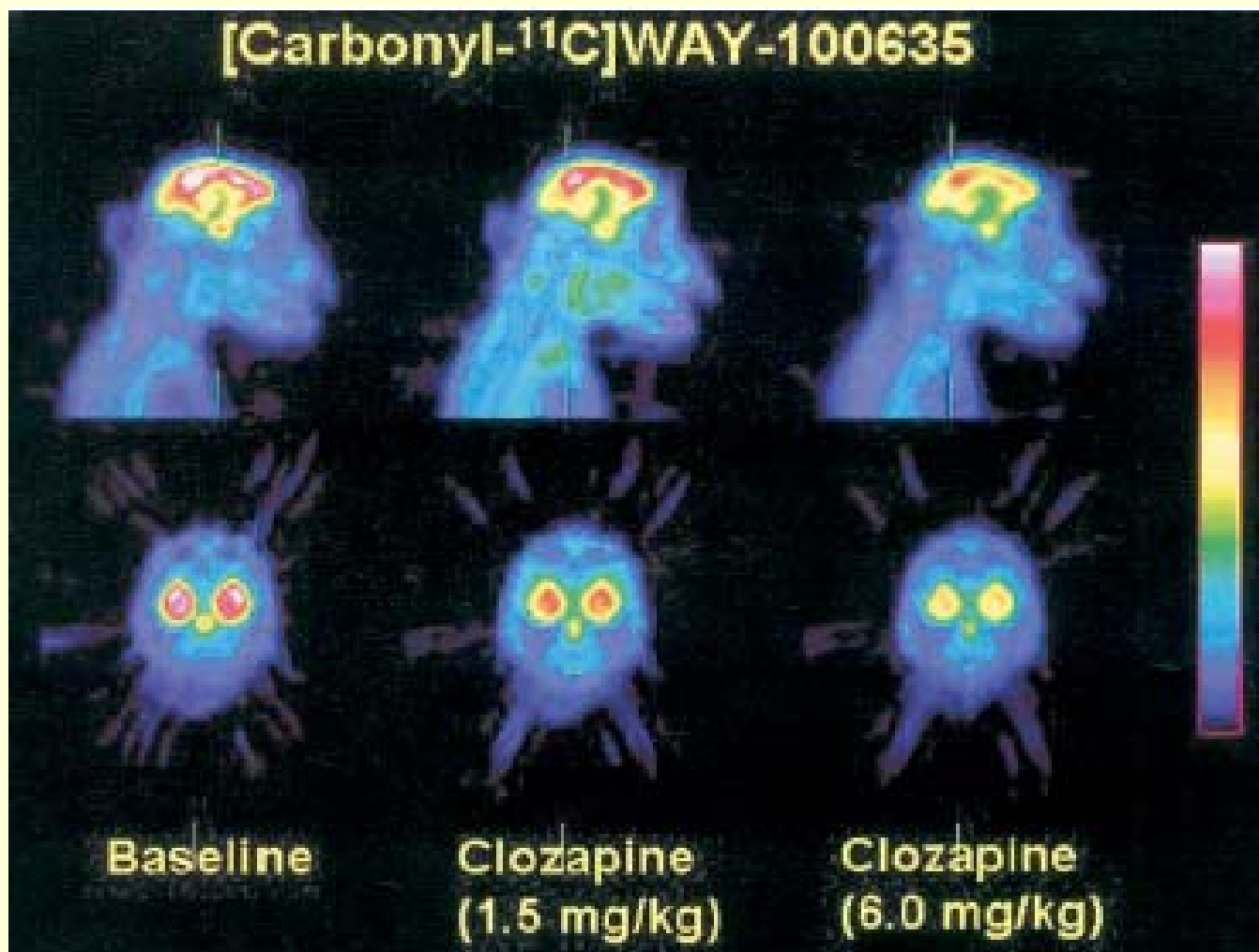
Historically many late stage clinical failures have been due to failure of drug to reach the target

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- Historically it was not possible to prove that drugs were getting to the target tissue
- Identifying drug in blood samples does not prove it has reached the target
- Especially problematic for neurological treatments which often have not crossed the blood brain barrier
- Pharmacodynamic markers prove drug target interactions



PET imaging demonstrates displacement of labeled ligand by cold drug



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Translational Medicine studies can help internal decision making through 3 key questions

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- What patients will respond to the drug? → Patient stratification biomarkers
- How much drug to give? → Pharmacodynamic biomarkers
- **Does the drug have biological activity? → Biological activity biomarkers**

Proof of clinical efficacy may take many years in chronic diseases

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- In chronic disease it may take over 10 years to prove efficacy using clinical criteria
- Not ethical to treat patients this long with non-efficacious drugs
- Not economically feasible to run 10 year phase 3 trials on all potential candidates
- Efficacy biomarkers offer a “quick-read” on the efficacy of novel drugs

For example, volumetric MRI distinguishes AD from other dementias

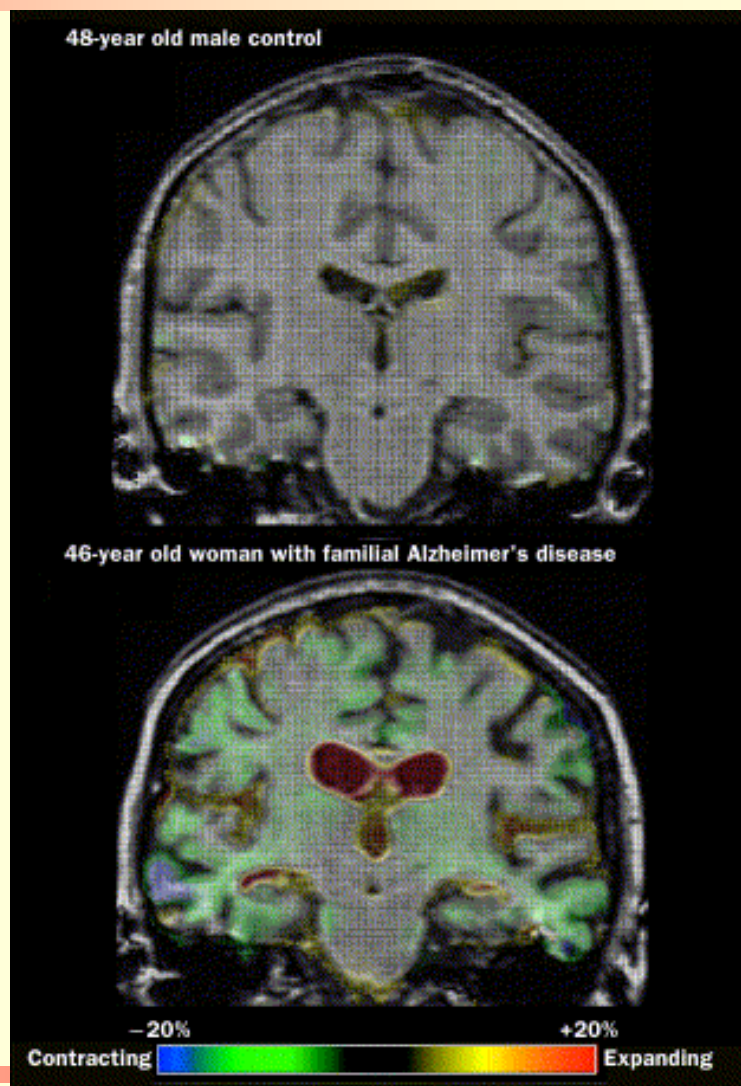
Rate of atrophy measured by serial scanning over one year completely separates Alzheimer patients from age matched controls

Pattern of atrophy distinguishes severe Alzheimer disease from other dementias

NIA study will extend MRI to earlier Alzheimer, compare with other modalities

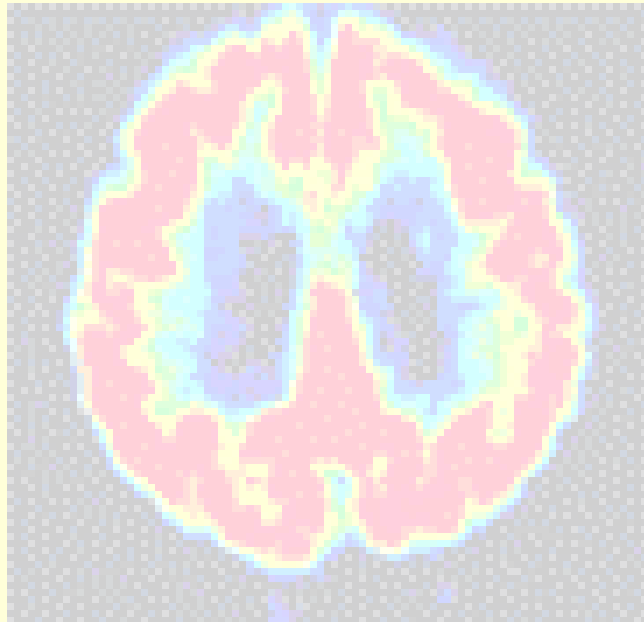
Normal
11 months

Alzheimer
14 months



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The challenge

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Summary

Translational Medicine allows for better internal decision making

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- Identify patients most likely to respond, before clinical trials
- Quantify drug-target interaction to guide dosing
- Early read from efficacy markers focuses resources on candidates most likely to be effective
- Use molecular knowledge of human disease to select targets

A number of issues remain for the successful implementation of Translational Medicine

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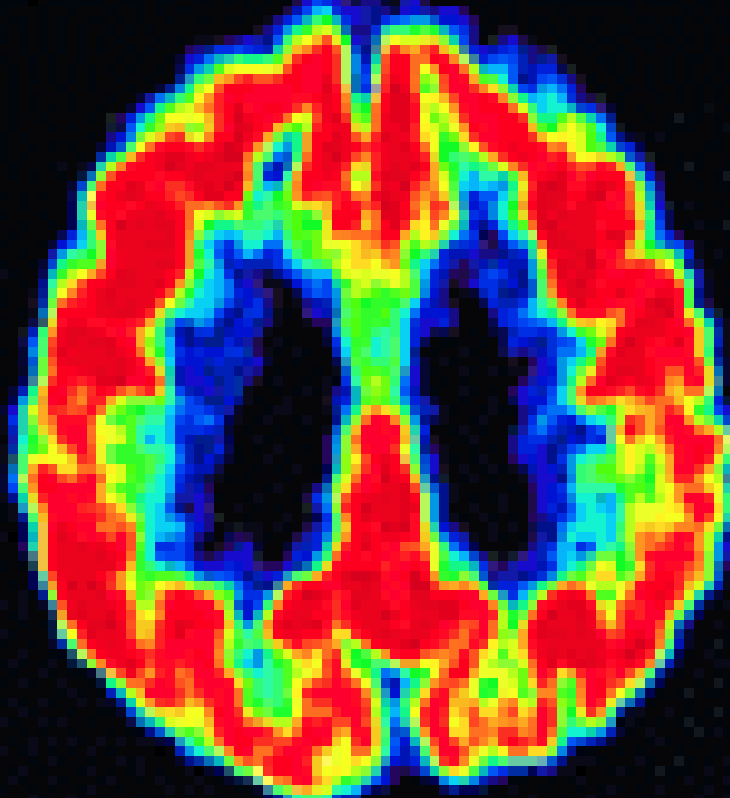
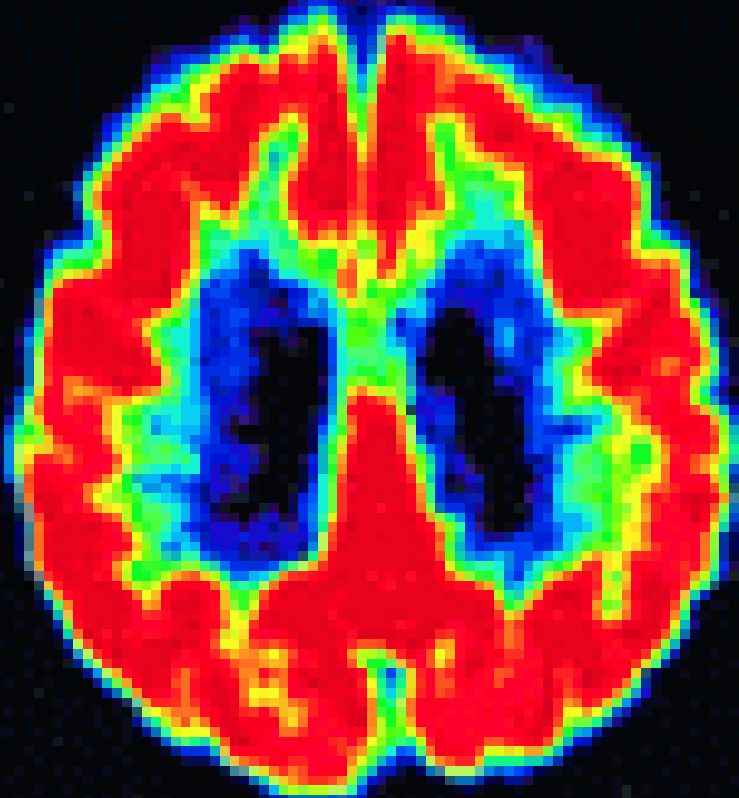
- Barriers interfere with the progress and utilization at all phases of the translational trial spectrum:
 - Too few patients
 - Sample collection differences
 - Non compatible data formats
- Guidelines are required to ensure maximum impact of such trials
 - Tissue Banking - National legislations, scope of analysis
- Guidelines need to be drafted for appropriate usage of individual patients genetic data
- Successful progress already made – Voluntary Genomic Data Submission - mechanism for discussing genomic data with FDA

Despite the promise of Translational Medicine, we must continue to be ethical

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We can not:

- ✓ Take shortcuts with patient safety
- ✓ Substitute unvalidated biomarkers for registrable endpoints of clinical efficacy and quality of life
- ✓ Delay development planning for novel targets until transition into development
- ✓ Lose sight of timelines and commercial objectives



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