Imaging in **CNS** Drug Discovery and Development

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Editors

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Implications for Disease and Therapy

Springer

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Preface

The last decade has seen a loss of confidence in the big pharma model for the development of new drugs. Despite unprecedented development costs, only about 10% of molecules entering Phase I were registered as drugs between 1991 and 2000 (Kola and Landis 2004). More concerning for the industry is that a significant proportion of the molecules failed in late phase development, after major investments already had been made. Two problems dominated these late stage failures: lack of efficacy and unanticipated safety risks.

Several reasons for this high attrition are suggested by the observation that critical issues related to efficacy often were not answered early in development. For example: Does the molecule reach its target? Is there evidence for the desired pharmacological effect in vivo? What is the dose-response relationship? In cases in which some of this information was established in preclinical models, the models did not necessarily reflect the critical biology in humans or for the human disease. Drug development needs to incorporate approaches for more direct in vivo pharmacology in humans.

In addition, because so much of the safety evaluation either relies on short term outcomes in humans or preclinical studies using high compound concentrations, more slowly developing pathologies or pathologies idiosyncratic to humans or particular populations can escape detection until large numbers of patients are treated for long periods in Phase III studies. Better ways of bridging between preclinical toxicology and clinical toxicology studies are needed. More sensitive measures for toxicology are desired in clinical studies. Safety assessment also can benefit from in vivo physiological measures in humans.

The primary limitations of conventional clinical development for many current major disease targets (e.g., in CNS, metabolic and cardiovascular indications) relate to requirements for long periods of evaluation and the modest sensitivity of usual, clinically based measures of outcome. While these clinical measures of outcome may have ecological validity in terms of ultimate clinical impact, they typically are only indirectly related to pharmacology and rarely address toxicology in particular. A compelling new approach to addressing this challenge is the aggressive application early in development of experimental medicine approaches designed to test specific pharmacological or toxicological hypotheses. Using biochemical, structural, or physiological measures that report on changes reflecting distribution or

direct consequences of drug action, the kinds of critical questions posed above can begin to be answered translationally in a coordinated strategy extending from preclinical to clinical studies. The translational element involves initial qualification of biomarkers in preclinical experiments, where they can be related directly to a broad range of well-accepted outcomes. When combined with patient populations in which the disease mechanisms are well characterized, the interaction between pharmacology and disease mechanisms can be elucidated more powerfully in shorter studies with more precisely defined and sensitive measures of response.

Such short term biomarker measures of drug distribution of pharmacological response may or may not be predictive of ultimate clinical response for any indication. However, they constitute direct tests of the fundamental hypotheses that are driving development of a molecule. Strict criteria for progression can be defined, making proof of pharmacology a critical part of a decision to progress development from early stages.

While some may argue that there are many examples of useful drugs with activity in disease that was not well predicted by the initial pharmacological hypothesis, set against this is the sad prior (for a rigorous, Bayesian view of drug development): most molecules will fail to make suitable drugs. The prior probability of not developing a potentially important therapeutic molecule because of failure at an early, direct test of pharmacology is therefore low.

*Imaging in **CNS** Drug Discovery and Development* provides a primer to the emerging potential of imaging as a general biomarker particularly for CNS drug development. The Editors have gathered together an internationally respected group of experts. Both academic and industry leaders are included. Together, they have produced a unique volume introducing the major tools, approaches, and challenges.

Important themes of integration run through the book. The selection of chapter topics emphasizes the need to integrate clinical and preclinical investigations of pharmacology. Preclinical investigations provide a fundamentally important way of relating imaging measures directly to conventional pharmacological and neurobiological response indices. It is not just through biomarker qualification that preclinical imaging provides an important tool to drive more effective clinical investigations. Preclinical studies also provide an opportunity to more completely define response relations and to push the range of such studies over a broader range, providing hypotheses that can later be explored in human toxicologically focused investigations. Preclinical imaging also allows the similar measures used for candidate selection to be applied to the initial proof of pharmacology in humans. At the same time, applications of imaging to preclinical investigations address the three R's of *reduction*, *refinement*, and, by extension to the clinical studies, an emphasis on *replacement* of use of animals by human experimental medicine in drug development.

A second theme addressed very directly in the concluding section of the book is the importance of integration of imaging and other biomarker information to provide multivariate measures of response. The neurobiology of disease and related neuropharmacology are complex. There is increasing evidence that multivariate

approaches provide new ways of enhancing precision of outcome measures and sensitivity. Computational power now should not be limiting. It is imperative that we use the full range of data available more effectively.

Applications of imaging to drug development have been growing rapidly in number over the last few years. In this exciting environment, it would not be possible to create a volume that remains fully current with the state-of-the-art. The Editors therefore have included chapters from experts providing paradigmatic examples that establish a "blueprint" for a way forward. Key therapeutic areas that illustrate the major problems have been identified. The use of functional imaging-based measures to objectify subjective experience is described in the chapter on pain, illustrating how sensitivity to the range of responses to a complex illness can be captured powerfully by imaging. The description of initial studies with post-traumatic stress disorder highlights the role of imaging in diseases of mind. Examples also are chosen from disorders in which there is a more complete understanding of disease neurophysiology, such as addiction and anxiety, illustrating how knowledge of the underlying cognitive systems can be coupled with imaging to drive stronger pharmacological hypotheses. Finally, the discussion of plasticity highlights one of the most important characteristics of noninvasive imaging approaches: the potential to follow the dynamics of change over time.

Recent commentators have looked to major changes in industry structure as a solution to the problems of innovation and high attrition in pharma. *Imaging in **CNS** Drug Discovery and Development* is part of a fundamentally optimistic alternative future scenario: the idea that drug development can be made better by becoming smarter. Implicitly, the Editors make a strong case that, using a science-based strategy, the paradigm for drug development can be improved. All of us must hope that this promising path forward will have a substantial impact on getting better medicines to the right patients more quickly. This volume contributes substantially to accelerating this grand experiment.

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Reference

Kola I, Landis J (2004) Can the pharmaceutical industry reduce attrition rates? Nat Rev Drug Disc 3:711–715

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About the Editors

David Borsook, MD, PhD, trained in medicine and neurobiology at the University of the Witwatersrand, Medical School, Johannesburg, South Africa. He graduated in 1980. Following his internship, he trained in Neurology at Boston City Hospital and then was the first Pain Fellow at the Massachusetts General Hospital, Department of Neurology. He subsequently was the Director of the Pain Center at the Hospital from 1994 to 2004. He has completed doctoral studies in Neurobiology and later started the Pain Imaging Program in the Department of Radiology at Massachusetts General Hospital. In 2002, he led an effort to cofound a Biotech – Descartes Therapeutics Inc., with his colleague Lino Becerra PhD to use imaging in drug development, where he was Senior Vice President and Chief Scientific Officer. He currently directs an integrated imaging program – Pain & Analgesia Imaging Neuroscience (P.A.I.N.) Group at three Harvard Medical School Affiliated Hospitals, Massachusetts General Hospital, McLean Hospital and Children's Hospital Boston. A component of this is a consortium of pharmaceutical and academic centers involved in the evaluation of fMRI in drug development known as ICD (Imaging Consortium for Drug Development). He has participated in a number of NIH meetings on future directions of pain research. His research is supported by grants from the National Institutes of Health, Foundations and Pharmaceutical Companies interested in the use of imaging in defining pain phenotype. He has published over 85 papers that include various aspects of pain, imaging in pain, and analgesia.

Dr. Lino Becerra, PhD, is Lecturer in Psychiatry at Harvard Medical School, he has co-appointments in the Departments of Psychiatry at McLean Hospital and Massachusetts General Hospital (MGH), and Radiology at MGH. He is the Director of the Imaging and Analysis Group at the Brain Imaging Center, McLean Hospital; and Co-Director of the Imaging Consortium for Drug Development (ICD) and the Pain Imaging and Analgesics Neuroscience Group (P.A.I.N. Group) at the same institution. Dr. Becerra was a cofounder of Descartes Therapeutics Inc., a biotech company dedicated to the development of drugs for chronic pain patients. His research interests are focused on the optimization of functional imaging for its utilization in drug development, in particular for chronic pain. Translational aspects of drug development through the study of preclinical and clinical early phase trials with the aid of

neuroimaging have been his main interest. Dr. Becerra is the author of over 50 publications, reviews, and book chapters appearing in journals such as *Neuron*, *Neuroscience*, *Journal of Neuroscience*, *Journal of Neurophysiology*, *NeuroImage*, and *European Journal of Pain*. He is a reviewer for these Journals, as well as for *Biological Psychiatry* and *Archives of General Psychiatry*.

Edward Bullmore, MD, PhD, trained in medicine at Oxford and St Bartholomew's Hospital, London, graduated in 1985. Following a period of further medical training as a Lecturer in Medicine at the University of Hong Kong (MRCP 1989), he started specialist training in psychiatry at St George's Hospital, London, and then at the Bethlem Royal & Maudsley Hospital as a registrar from 1990 (MRCPsych 1992). From 1993, he was supported by the Wellcome Trust as a Research Training Fellow (then as an Advanced Research Training Fellow 1996–1999) at the Institute of Psychiatry in London, where he completed doctoral studies on statistical analysis of magnetic resonance imaging data (PhD 1997). In 1999, he moved to the University of Cambridge as a Professor of Psychiatry and since 2005 he has been Clinical Director of the Behavioural & Clinical Neurosciences Institute at Cambridge. Also since 2005, he has combined his academic roles with a 50% secondment to GlaxoSmithKline as Vice-President for Experimental Medicine and head of GSK's Clinical Unit in Cambridge (CUC). His research in Cambridge has been supported by grants from the National Institutes of Health (Human Brain Project), the Wellcome Trust and the MRC; he has published more than 200 papers on various aspects of neuroimaging, neuroscience, and psychiatry. In 2008, he was elected a Fellow of the Academy of Medical Sciences.

Richard Hargreaves, PhD, trained at Chelsea College, London University in the UK where he obtained a First class honors degree in pharmacology. After completing his doctorate through the Physiology Department at King's College London University UK, he joined Merck's Neuroscience Research Center in Harlow UK in 1988 where he occupied positions of increasing seniority. Richard led the discovery biology teams that contributed to the development of MAXALT® (rizatriptan) for the treatment of migraine and EMEND® (aprepitant) and IVEMEND® (fosaprepitant), novel agents that advance the protective pharmacotherapy of acute and delayed chemotherapy-induced nausea and vomiting and postoperative nausea and vomiting. In 1999, Richard moved to the USA to establish and lead a worldwide imaging research strategy for Merck Research Laboratories. Since that time, he built a Global Multimodality Imaging Group that supports decision making in drug discovery and development across Merck's key therapeutic areas. A key component of this imaging strategy has been the use of precompetitive initiatives to combine expertise and share the costs of developing and characterizing new imaging tools and technologies that can be used to improve the evaluation of the safety and efficacy of novel drug candidates. Richard was awarded the 2007 Gary Neill Award for "Innovation in Drug Development" by the American Society of Clinical Pharmacology and Therapeutics (ASCPT) for his work on imaging in drug discovery and development. In February 2008, he was named Worldwide Head of Basic Research, Neuroscience for Merck Research Laboratories.

Part I
Background

The Challenges and Opportunities

David Borsook, Edward Bullmore, Lino Becerra, and Richard Hargreaves

Introduction

The global burden of neurological disease is high (Macdonald et al. 2000) and is expected to continue to increase dramatically in the future, given the increase in the elderly population. This medical need is reflected in the intense research and development activity; in the USA alone, there may be as many as 300 neuroscience drugs in development. Between 2003 and 2005, the global market for CNS therapies grew by nearly 20% (~10% of the total pharmaceutical sales) (Market Trends 2007; Palmer and Stephenson 2005) and is predicted to expand to nearly $64 billion by 2010. In addition, new insights into the complex interplay between peripheral and central mechanisms involved in metabolic diseases (Elmquist and Flier 2004; Theander-Carrillo et al. 2006; Obici et al. 2002) have revealed new CNS therapeutic targets for drug development. Drug development is an expensive venture with the average costs of developing a new chemical entity exceeding $800 million. Therefore, with such a large number of opportunities in the CNS field, there is a pressing need to find ways to improve the speed and reduce the cost of decision making, so that only the best molecules and hypotheses are taken into consideration in the later stages of drug development. It is important to identify likely "losers" early and make clear 'no go' decisions, and to identify likely winners quickly and enable them to increase their probability of success in development. New CNS imaging technologies have become a focus of attention as they provide fast, efficient and objective ways to evaluate the direct wanted and unwanted effects of centrally acting drug candidates on the brain. Indeed, imaging is now an integral part of most conferences on CNS drug development, and the pharmaceutical industry has invested in internal and external imaging programs to support CNS drug discovery (for current reviews see (Borsook et al. 2002; Borsook et al. 2006; Wise and Tracey 2006; Matthews and Honey GD Bullmore 2006)).

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Failure: A Driving Force for Improved Approaches

In 2006, the number of drugs discontinued for peripheral and CNS disease (including the treatment of a range of neurological disorders, including chronic pain, Alzheimer's disease, Parkinson's disease, multiple sclerosis, epilepsy and anxiety) is significant (>50%) (Collins 2007). Unlike many other therapeutic areas, there is a paucity of scientifically validated and clinically qualified biomarkers predictive of central activity, and this contributes to the low probability of success for novel CNS drug discovery and development programs directed against unprecedented targets. The prolonged timelines, the expense, and the uncertainty of decision making in CNS therapeutic evaluation also raises the distinct possibility that drugs are "put on the shelf" with missed opportunities because the initial indications explored were misdirected. Clearly, new indications could be rationally explored if functional insights into the effects of a drug on CNS circuits could be objectively assayed.

New Approaches and Indications

Many CNS drugs have been found serendipitously from astute clinical observations in humans that have spawned drug development programs. A more rational approach is to use neuroimaging techniques to define the disease condition in humans first. In addition, while there is a focus on developing drugs with specific MOA, the hypothesis driven mechanism of action (MOA) approach to drug development may have limited utility as many successful CNS therapeutics have no clear primary MOA, and others may provide benefit through actions at multiple sites. In such cases, looking at the functional CNS fingerprints of active drugs and using them, much like RNA expression profiling, to identify novel therapeutics is a rational and mechanistically unconstrained approach. Clearly, new chemical entities have specific effects on a disease process. In addition, by assaying the direct effects of a drug on CNS function through the mapping and interpretation of the specific circuits affected, it may be possible to evaluate new indications for specific drugs.

Integration of Processes in CNS Drug Development

The key theme for this book is whether and how neuroimaging could improve the success rates in CNS drug development. The neuroimaging approaches considered in the chapters that follow cover four main areas: (1) *Functional Imaging*; (2) *Anatomical Imaging;* (3) *Molecular Imaging*; and (4) *Chemical Imaging.* (Beckmann et al. 2001; Rudin et al. 2003; Silva and Chandra 2006; Beckmann et al. 2007). Obviously, it is appreciated that neuroimaging is not a stand-alone answer to all the challenges of CNS drug discovery; it needs to be carefully integrated with traditional

and emerging biomarker driven decision making processes (Gomez-Mancilla et al. 2005). The key challenges to overcome have some commonality with other therapeutic areas, and some are unique to neuroscience:

1. *Discovery and Development Hurdles*: Drug development for CNS disorders faces issues similar to those that are encountered by other therapeutic areas: increasing development costs; development of novel drug targets with unproven therapeutic potential; and health care systems and regulatory agencies demanding more compelling demonstrations of the value of new drug products.
2. *Clinical Testing*: Clinical testing remains the core area for the registration of any new drug. Traditional clinical trial methods are expensive and difficult, and they frequently fail. Many CNS disorders are chronic, slow processes manifested by highly subjective and context dependent signs and symptoms are late onset (exceptions degenerative disorders) with ill-defined or undefined pathophysiology. Thus, patient populations selected for treatment trials using clinical criteria are inevitably heterogeneous, and dependence on traditional endpoints results in early proof-of-concept trials being long and large, with very poor signal to noise.
3. *Integration of New Technologies*: With the relative failure of preclinical models, more focus is being placed on accessing information from human "material", including human surrogate models, genetics, proteomics tissue samples and imaging. Biomarkers are being targeted as part of the decision-making process as a means of rationalizing CNS drug development and reducing the cost of failure.

Chasing the Ideal: Can Neuroimaging Help?

Figure 1 summarizes the questions that could potentially be addressed with the help of imaging datasets. It is important to note, however, that for many approaches, there is still some way to go before their potential benefits and limitations in the context of drug discovery decision making are determined. Failure in drug development has been suggested (Hurko and Ryan 2005) to result from making poor choices in several crucial areas: recognition of differences between animal assays and human disease, selection of doses sufficient to test clinical hypotheses, selection of objective surrogate models to obtain proof of biology, specific measures of disease, selection of subjects for proof of clinical concept testing, and sensitive and early detection of therapeutic response. Developing imaging strategies that may help evaluations in these domains may impact the speed and cost effectiveness of CNS drug development significantly.

Animal–Human Translation

Non-invasive functional imaging allows specific insights into drug and disease phenotype in humans that can be used to select and align preclinical CNS models and

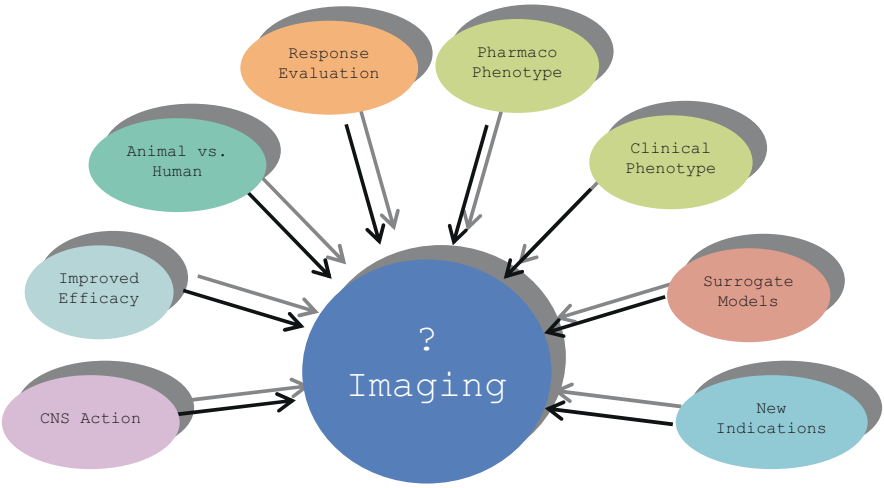

Fig. 1 Profiling disease state and drug effects: objective measures

characterize effective and ineffective drug therapies, thereby improving early decision-making on novel candidates. Insights garnered during preclinical development can sometimes be "lost in translation", and drug candidates that look excellent in the laboratory, fail in early phase clinical trials. Improvements in our ability to translate from animal to human or vice versa will advance traditional approaches where animal models are often developed with no clear path to evaluating their equivalence in the human condition. Such a notion of course implies that the "language of translation" is the pattern of activations across the neuro-circuitry of the brain.

CNS Target Engagement and Dosing

Direct measurement of CNS target engagement by drug candidates is critical for CNS drug discovery and development. PET molecular imaging can confirm that drugs reach their target in sufficient amounts at safe and well tolerated doses to make clinical studies worthwhile and to reject hypotheses with certainty if data are negative. It is important to remember, however, that occupancy is not efficacy; knowing target engagement allows rational dose selection for clinical proof of concept testing trials. PET radioligand binding studies do not, however, provide any insight into the functional aspects of a particular drug. Functional imaging has advanced from PET based tracer studies using [18F] FDG glucose metabolism and 15O – water cerebral flow to using a range of functional MRI techniques (rsfMRI, BOLD, ASL) with different experimental designs. These fMRI techniques can provide data on dose-responsiveness by studying increasing activation (or deactivation) in specific brain regions of interest, particularly those hypothesized to be involved

in the desired therapeutic action (for example, activation in the periaqueductal gray in pain, or the hippocampus or amygdala in anxiety).

Human Surrogate Models

Activation in specific brain circuits defines the behavioral consequences of a drug effect or disease process. Patterns of neuro-activation and their changes are, therefore, potential markers of disease state or drug efficacy. An objective evaluation of the CNS processing involved in disease states in humans will allow for a top down approach to the evaluation of drug effects on disease state for most functional CNS diseases. Thus, functional neuroimaging provides an objective readout of CNS activity (neuroinformatics) that can inform neurobehavioral studies of CNS disorders and provide a novel framework to evaluate therapeutic hypotheses rapidly.

The use of healthy human subjects for the evaluation of a drug may provide information about safety and tolerability, but may not provide helpful information about efficacy for a particular condition. Having appropriate healthy surrogate models or markers for the evaluation of a drug for efficacy would, of course, be extremely helpful. In the early stages of CNS drug development, the delivery of potential therapeutics and their actions are often studied in healthy individuals with normal neurocircuitry. Whilst this can have great value in ensuring target engagement and proof of biochemical mechanism, these studies usually create baselines for the study of disease states and their therapeutic modulation – the holy grail of targeted CNS therapies. In some cases, it is difficult to recapitulate key aspects of psychiatric or neurological disease in healthy individuals, but their use is a rapid step toward the development of paradigms for patients.

Clinical Phenotype

Objective indices of clinical phenotypes (anatomical, functional or chemical) would be highly useful in clinical trials, as well as in standard clinical practice for disease evaluation. Many CNS diseases evolve slowly, and their clinical manifestations may therefore, post-date changes that may have been taking place slowly over months or years. An ability to evaluate a CNS brain state using imaging may open novel prediction and prevention approaches in drug development. In a number of fields of CNS disease, there appears to be some reason to believe that imaging markers of a clinical phenotype could have real utility. Today, anatomical imaging is perhaps the most advanced in terms of brain measures in disease states such as multiple sclerosis and Azheimer's disease (see Alzheimer's Disease Neuroimaging Initiative, http://www.loni.ucla.edu/ADNI/). Interestingly too, it has recently been shown that chronic pain may affect brain function and structure (gray matter loss) and here, neuro-imaging may provide novel markers for the development of therapies

modifying new disease rather than symptomatic therapies. Using neuro-imaging to provide a clinical phenotype and monitor its progression will enable the selection of the most appropriate patients for clinical trials, especially in CNS neurodegenerative disorders, and will hopefully lead to smaller cohorts being needed to power pivotal long-term outcome studies.

Pharmaco-Phenotype

Some drugs may have the best efficacy in patients with a particular genetic constitution. Targeting drugs to subpopulations (enriched in terms of clinical phenotype or genotype) may show enhanced benefit-risk. A "pharmaco-phenotype" defined by neuroimaging may assist in the enrichment of trials or help with individualizing therapy in groups of subjects when used as a means of differential diagnosis.

Challenges in Adopting Neuroimaging Technologies

The adoption of imaging technologies requires evidence based data. While imaging holds the promise of accelerating and improving success rates in CNS Drug Development, it is clear that there is still much work to be done to define the utility, reproducibility, and harmonization of imaging protocols, data capture and analysis that are so critical to its use in decision making, particularly in longer term studies that use it to monitor progression of neurological disease. Nevertheless, we have seen revolutionary progress in the scientific validation and clinical qualification of many new neuro-imaging approaches. This book is an effort to understand the current and potential use of imaging technologies in drug development, supporting the path of bringing safe and effective medicines to patients and providing them better quality of life.

References

Beckmann N, Mueggler T, Allegrini PR, Laurent D, Rudin M (2001) From anatomy to the target: contributions of magnetic resonance imaging to preclinical pharmaceutical research. Anat Rec 265:85–100

Beckmann N, Kneuer R, Gremlich HU, Karmouty-Quintana H, Ble FX, Muller M (2007) In vivo mouse imaging and spectroscopy in drug discovery. NMR Biomed 20:154–185

Borsook D, Ploghaus A, Becerra L (2002) Utilizing brain imaging for analgesic drug development. Curr Opin Investig Drugs 3:1342–1347

Borsook D, Becerra L, Hargreaves R (2006) A role for fMRI in optimizing CNS drug development. Nat Rev Drug Discov 5:411–424

CNS Market Trends, 2007 to 2010 : Key Market Forecasts and Growth Opportunities. 2007 Urch Publishing:

Collins SD (2007) Discontinued drugs in 2006: central and peripheral nervous system drugs. Expert Opin Investig Drugs 16:1743–1751

Elmquist JK, Flier JS (2004) Neuroscience. The fat-brain axis enters a new dimension. Science 304:63–64

Gomez-Mancilla B, Marrer E, Kehren J, Kinnunen A, Imbert G, Hillebrand R, Bergstrom M, Schmidt ME (2005) Central nervous system drug development: an integrative biomarker approach toward individualized medicine. NeuroRx 2:683–695

Hurko O, Ryan Jl (2005) Translational research in central nervous system drug discovery. NeuroRx 2:671–682

Macdonald BK, Cockerell OC, Sander JW, Shorvon SD (2000) The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. Brain 123(4): 665–676

Matthews PM, Honey GD Bullmore ET (2006) Applications of fMRI in translational medicine and clinical practice. Nat Rev Neurosci 7:732–744

Obici S, Zhang BB, Karkanias G, Rossetti L (2002) Hypothalamic insulin signaling is required for inhibition of glucose production. Nat Med 8:1376–1382

Palmer AM, Stephenson FA (2005) CNS drug discovery: challenges and solutions. Drug News Perspect 18:51–57

Rudin M, Allegrini MT, PR BD, Rausch M (2003) Characterization of CNS disorders and evaluation of therapy using structural and functional MRI. Anal Bioanal Chem 377:973–981

Silva MD, Chandra S (2006) MRI in preclinical drug development. Methods Mol Med 124:299–322

Theander-Carrillo C, Wiedmer P, Cettour-Rose P, Nogueiras R, Perez-Tilve D, Pfluger P, Castaneda TR, Muzzin PSchurmann A, Szanto I, Tschop MH, Rohner-Jeanrenaud F (2006) Ghrelin action in the brain controls adipocyte metabolism. J Clin Invest 116:1983–1993

Wise RG, Tracey I (2006) The role of fMRI in drug discovery. J Magn Reson Imaging 23:862–876

Imaging of CNS Systems: Importance for Drug Development

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Introduction

During the twentieth century, society has experienced enormous benefits from advances in health care with a dramatic prolongation of life expectancy and life quality. While these improvements can be attributed in part to public health measures such as clean water, reduced smoking, preventive medicine, vaccination, and a reduction in the spread of infectious disease in the first half of the century, a dramatic increase in the availability of novel, efficacious and safe drugs has played a cardinal role in the latter half of the century. During this time, the pharmaceutical industry, along with academic, government-sponsored research, has materialized chemical and biological innovation contributing to all aspects of disease management, including diagnosis, prognosis and therapy. However, the pace of such medical innovation, as judged by successful approvals of new drugs, has significantly declined over the past two decades despite exponential increases of investments in research and development (Feuerstein et al. 2008; Pangalos et al. 2007).

One factor contributing to this inverse relationship between escalating drug development costs and successful new drug approvals can be attributed to the continued decreasing probability of successful transition through critical proof of concept studies in early clinical development (Feuerstein, 2007). Another contributing trend over the past decade has been the greatly increased public and political scrutiny with regard to adverse events for both marketed products and investigational drugs, resulting in an increased risk aversion by regulatory agencies around the world and an increasing demand for larger and longer late stage clinical trials. Finally, as generic drugs have become increasingly available, new investigational therapies face tougher developmental hurdles, and a greater need to demonstrate clear superiority or differentiation with regard to safety or efficacy compared to existing therapies.

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In this increasingly challenging environment, the key objective of translational medicine is to help improve the success rates of investigational drugs in clinical development. In order to accomplish this goal, translational medicine employs biomarkers to aid in the understanding of (1) the relevance of the drug target to human disease (2) the drug interaction with the target (3) the consequences of target modulation by the drug (pharmacodynamics) in respect to efficacy and safety (4) patient selection for the best medical outcome and (5) new disease biomarkers. The use of such evidence-based biomarkers can increase confidence during early development, improve the ability to prioritize clinical drug candidates across a broad portfolio and yield better and more cost effective decision making for the advancement of compounds through the development process. For convenience and to achieve a uniform lexicon for the wide array of potential biomarkers, we group biomarkers into the following categories (see Fig. 1):

1. Target Validation Biomarkers provide scientific evidence on the role of the target in human diseases and its potential to be exploited in drug discovery and development campaigns.
2. Target-Compound Interaction Biomarkers provide evidence on the physico–chemical interaction of the drug with its intended target.
3. Pharmacodynamic (PD) Biomarkers report on the biological consequences of drug action in the exposed organism or patient. These include biomarkers of efficacy and safety.

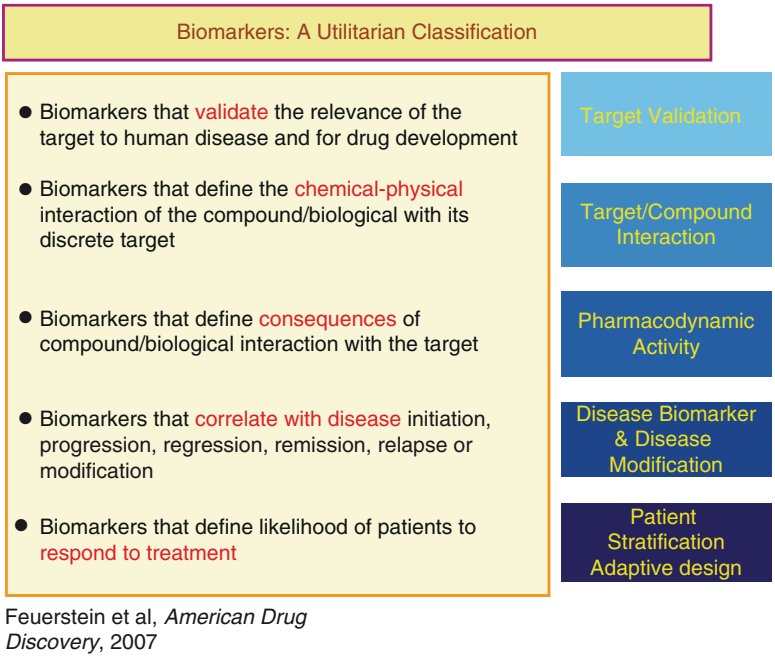

Fig. 1 Classification of biomarkers according to utility

4. Disease biomarkers report on elements of disease progression, regression, severity etc and provide guidance on whether a drug has the potential to fundamentally alter or modify the disease process.
5. Patient Selection, Stratification Biomarkers provide information about those patients most likely to respond (or not respond) to the treatment. Such biomarkers provide an opportunity to stratify patients for risk of disease progression and potentially enable shorter trials with higher event rates and earlier outcome assessments.

In this context, the use of imaging in drug development for CNS disorders is of particular importance, given the relative inaccessibility of the brain to a direct sampling of cells, tissues, or fluids *in vivo*. Imaging techniques offer non-invasive approaches to assess systematically both the structural and functional integrity of the CNS and can be applied to all of the biomarker categories previously defined. Furthermore, imaging techniques established in humans are now feasible in many of the key animal models that serve drug discovery and development (rodents and nonhuman primates), allowing a closer alignment of imaging biomarkers across species and an improved congruency between the laboratory and clinical settings. Some relative advantages and limitations are summarized in Table 1.

Table 1 Comparison of imaging technologies commonly used in humans for studies of drug effects on the central nervous system

Technique	Advantages	Limitations
Computed tomography (CT)	Readily available Noninvasive Can assess vasculature	Only provides structural Information Radiation exposure limits
Magnetic resonance imaging (MRI)	Multiple applications Structural imaging T1, T2, FLAIR, DWI, PWI Diffusion tensor imaging Functional imaging (regional blood flow) Metabolite measurement Cerebrovascular assessment Noninvasive Good spatial resolution	Cannot be used for ligand binding Temporal resolution limited to ~ 7 s for fMRI Sensitive to motion artifacts Some subjects cannot tolerate confinement in magnet Cost and bed-side limitation
Positron Emission Tomography (PET)	Can be used for Blood flow Metabolism Ligand binding	Requires administration of radioactivity Requires access or proximity to cyclotron, radiochemistry lab Limited temporal resolution Chemistry limitation in ligand preparation
Single Photon Emission Computed Tomography	Can be used for Blood flow Ligand binding More widely available than PET	Only semi-quantitative Limited spatial and temporal resolution Chemistry limitation in ligand preparation

Note: EEG and MEG are not considered here. Combinations of the above techniques are often used (e.g., PET and MRI, PET and CT) to take advantage of complementary features.

In the following sections, we will describe examples of imaging-based biomarkers as they have been applied in drug discovery for diseases of the CNS. These include both "neurologic" diseases such as Alzheimer's disease (AD) and stroke, characterized by macroscopic alterations in brain structure, and "psychiatric" disorders, including schizophrenia and mood disorders, that are manifest chiefly by alterations in thought, mood, and behavior. We will demonstrate the use of target-compound interaction biomarkers in the development of symptomatic therapies of AD, disease and disease modification biomarkers in developing disease modifiers in AD, patient-selection biomarkers for acute stroke and stroke recovery treatment, and pharmacodynamic and disease biomarkers in schizophrenia and Major Depressive Disorder (MDD).

Imaging Biomarkers for Target–Compound Interaction in Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disease and the most common cause of age-related dementia. It is characterized clinically by a gradual deterioration of intellectual abilities concomitant with dramatic alterations in personality, affective regulation, and behavior (Bozeat et al. 2000). In its more advanced stages, AD is typified by severe and wide-ranging cognitive deficits, including gradual but inexorable memory loss, difficulty in learning, loss of language skills, impairment of judgment, a decline in the ability to perform routine tasks, and ultimately, disorientation and loss of interpersonal contact. The neurodegenerative nature of the disease eventually leads to the failure of other organ systems and death.

Treatments for AD address short-term improvement and stabilization of cognitive and functional deficits. The scientific rationale for the first symptomatic therapies was based on research showing profound degeneration of ascending cholinergic pathways from the basal forebrain to the hippocampus and cerebral cortical areas and led to symptomatic treatment strategies, aimed at boosting cholinergic function (Araujo et al. 1988; Bowen et al. 1983; Davis et al. 1982). For the cholinergic agents, imaging approaches using PET have been useful in demonstrating target engagement and pharmacodynamic activity. For example, one PET study demonstrated that donepezil treatment (3–5 mg per day) reduced AChE activity in the cerebral cortex of AD patients concomitantly with the patient's symptomatic improvement (Shinotoh et al. 2001). Similar PET studies demonstrated that donepezil (5 and 10 mg per day, 5 weeks) inhibits cortical AChE activity by 27% in the AD brain (Kuhl et al. 2006).

Preclinical studies have reported that specific 5-HT_{1A} receptor antagonists improve learning and memory in animal models, and several compounds have been advanced into clinical testing in AD patients (Schechter et al. 2005). In the early clinical development program, PET or SPECT imaging using specific radioligands for these target receptors provided information about the degree and duration of receptor occupancy (RO) as a target-compound interaction biomarker for confirming CNS target engagement. For example, in the early development of lecozotan, a 5-HT_{1A} antagonist, a PET study was conducted to assess the 5-HT_{1A} RO of the drug in healthy, young, elderly and AD subjects (Raje et al. 2008) (Fig. 2). This work

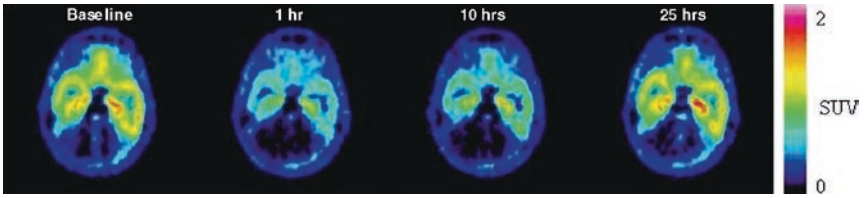

Fig. 2 [^{11}C]-WAY-100635 uptake in human temporal cortex. The scans were taken before and at different times (hours) after administration of 5 mg of lecozotan IR formulation to a young healthy subject. 5HT$_{1A}$ receptor occupancy of lecozotan, calculated based on uptake, serves as a biomarker of target-compound interaction, thus demonstrating CNS target engagement. *SUV* standardized uptake value. Figure courtesy of Dr. Sageeta Raje, Wyeth Research, Collegeville, PA

allowed a clear understanding of the relationship between lecozotan 5-HT$_{1A}$ RO and drug plasma concentrations and enabled the development of a PK/PD model which predicted peak 5-HT$_{1A}$ RO of 70–76% following a total daily dose of 10 mg. The PET data and PK/PD modeling work helped to guide the dose selection for the subsequent clinical studies in AD patients to further examine the efficacy and safety of lecozotan. This example illustrates the power of neuroimaging approaches to guide better decision making with regard to dose selection (Feuerstein et al. 2008). Several PET ligands are available for labeling the 5-HT$_{1a}$ receptor (e.g., [^{11}C]-WAY-100635), however, for newer targets, few PET or SPECT ligands are available. Furthermore, not all targets are suitable for imaging with PET or SPECT, depending on their level of expression in regions of interest in the brain relative to the surrounding areas(Ametamey and Honer 2007; Pimlott 2005). Importantly, the process of developing and validating radioligands for human use can be laborious, often taking 2 years or longer. Thus, once a molecular target has been validated as promising, it is highly desirable that PET/SPECT ligand development takes place in parallel to the drug discovery program in order to provide sufficient lead time for use in early clinical studies.

Imaging Biomarkers of Disease and Disease Modification in Alzherimer's Disease

Disease modification in AD refers to the ability of a drug to slow or halt the disease process by, for example, modulating the deposition of beta amyloid or the hyperphosphorylation of tau. The majority of disease modifying investigational drug treatments target either the production of beta amyloid by inhibiting beta (Hussain et al. 2007) or gamma secretase(Best et al. 2007), or the enhancement of beta amyloid clearance by active or passive immunization(Solomon 2007).

Several neuroimaging approaches have been explored in AD and some may hold promise as biomarkers of disease progression. Independent studies have shown that progressive brain atrophy, as measured by serial MRI, can be detected longitudinally in AD patients (de Leon et al. 2006; Jack et al. 1998; Xu et al. 2000). Changes in

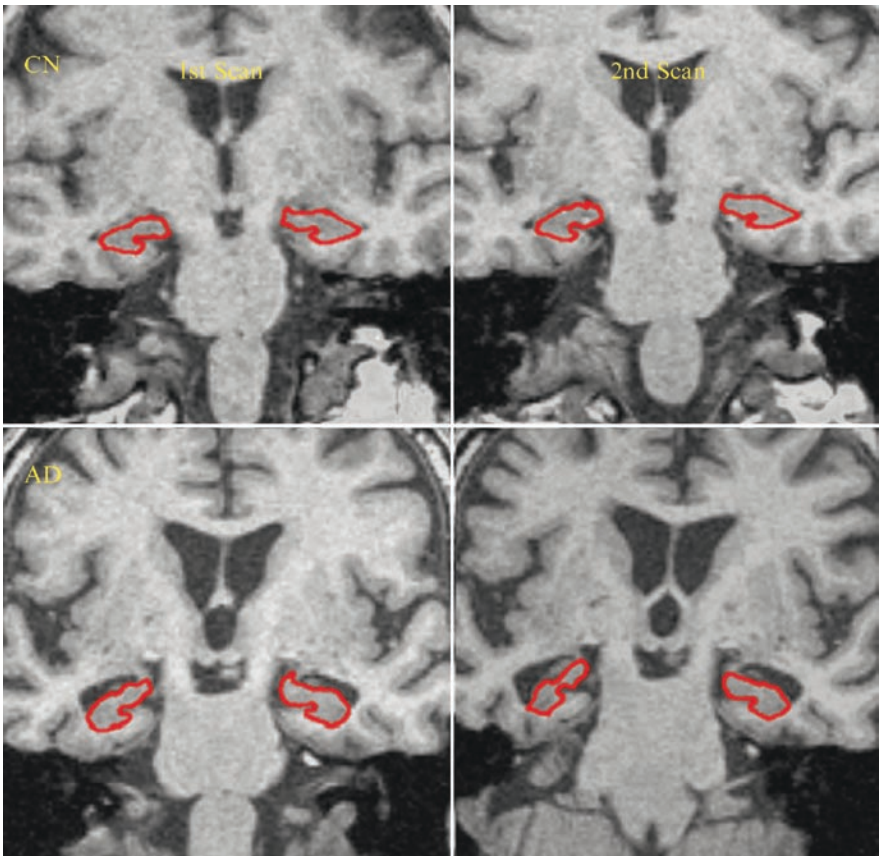

Fig. 3 Hippocampal atrophy detected in AD patients. Two MRI scans 1 year apart in the same individuals are shown. Hippocampi are indicated by the red trace on coronal sections. Marked atrophy (reduction of hippocampus area) is observed in an AD patient compared to an age-matched control subject. The area of hippocampus can be quantified as a biomarker of disease progression. Figure courtesy of Dr. Michael W. Weiner, University of California, San Francisco, CA

MR-based regional changes (hippocampus, entorhinal cortex, and corpus callosum) may be even more specific to the pathological process of AD than global (whole brain and ventricles) brain volume measures (Fox et al. 2005; Jack et al. 2003) (Fig. 3). These studies consistently show loss of brain volume in AD patients that is at least twice the rate of loss seen in age-matched control subjects. These imaging biomarkers have been piloted in several clinical trials with candidate disease modifying agents. For example, volumetric MRI measures of whole brain atrophy and hippocampus atrophy have been measured in clinical trials with anti-amyloid immunotherapy as well as small molecule amyloid modulators (Fox et al. 2005).

FDG-PET (fluorodeoxyglucose positron emission tomography) is an imaging method that provides a global measure of brain glucose metabolism.

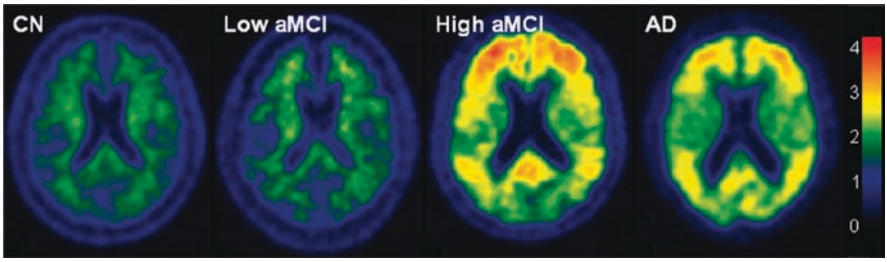

Fig. 4 Amyloid deposits detected with ^{11}C-PIB PET. Increased retention of PIB signal in cortical and temporal areas is observed in AD patients and subset of amnestic MCI patient compared to cognitive normal controls. The global PIB retention ratio can be used as a biomarker of amyloid plaques and may have potential as a biomarker of disease progression and therapeutic activity of amyloid-targeting agents. Figure courtesy of Dr. Chester A. Mathis, University of Pittsburgh, Pittsburgh, PA

In patients with AD and mild cognitive impairment (MCI), the cerebral metabolic rate for glucose (CMRgl) reductions in the posterior cingulate, parietal, temporal, and prefrontal cortex are correlated with dementia severity and progression (Mega et al. 1997; Mosconi et al. 2005). Molecular imaging also promises to provide specific information about the neuropathology of AD. The most advanced PET imaging ligand, the Pittsburgh Compound-B (PIB), is a thioflavin derivative that appears to be relatively selective for Aβ plaques (Klunk et al. 2004; Klunk et al. 2005) (Fig. 4). A few other amyloid imaging ligands have been reported, including ^{18}F-FDDNP, a PET ligand that binds both amyloid plaques and neurofibrillary tangles (Rowe et al. 2007; Small et al. 2006). Indeed, FDDNP studies in AD and MCI patients have found binding in areas of the brain with amyloid deposits and an increased signal at longitudinal follow-up(Small et al. 2006).

For any of the briefly described neuroimaging measures to qualify as a validated biomarker of AD disease progression, a correlation with clinical symptoms over a period of time needs to be demonstrated. In this regard, a consortium of academic, industry and government investigators have embarked on the Alzheimer's Disease Neuroimaging Initiative (ADNI), a large longitudinal neuroimaging and biomarker study of MCI and AD patients(Mueller et al. 2005). In addition to the identification of the most robust imaging biomarkers for disease progression, ADNI is also expected to deliver standardized protocols and methods for the evaluation of neuroimaging biomarkers in large-scale, multicenter studies.

Imaging Biomarkers of Patient Selection in Stroke and Cerebrovascular Disease

Stroke is the leading cause of disability in adults, and represents a growing unmet medical need, particularly as the population ages. In most cases, thromboembolism is the primary event leading to cerebral infarction, and thrombolysis with tissue