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Of Mice and Men

Bridging the Translational Disconnect in CNS Drug Discovery

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Abstract

The tremendous advances in transgene animal technology, especially in the area of Alzheimer's disease, have not resulted in a significantly better success rate for drugs entering clinical development. Despite substantial increases in research and development budgets, the number of approved drugs in general has not increased, leading to the so-called innovation gap. While animal models have been very useful in documenting the possible pathological mechanisms in many CNS diseases, they are not very predictive in the area of drug development.

This paper reports on a number of under-appreciated fundamental differences between animal models and human patients in the context of drug discovery with special emphasis on Alzheimer's disease and schizophrenia, such as different affinities of the same drug for human versus rodent target subtypes and the absence of many functional genotypes in animal models. I also offer a number of possible solutions to bridge the translational disconnect and improve the predictability of preclinical models, such as more emphasis on good-quality translational studies, more pre-competitive information sharing and the embracing of multi-target pharmacology strategies.

Re-engineering the process for drug discovery and development, in a similar way to other more successful industries, is another possible but disrupting solution to the growing innovation gap. This includes the development of hybrid computational models, based upon documented preclinical physiology and pharmacology, but populated and validated with clinical data from actual patients.

The US FDA White paper *Innovation or Stagnation; Challenge and Opportunity on the Critical Path to New Medical Products* was intended to address the apparent dichotomy between increased research and development (R&D) budgets and decreased productivity in terms of the number of new innovative drugs approved.

Although rodent models have been used extensively for CNS drug discovery, their predictability is modest at best. The success rate of new CNS drugs entering phase I clinical development is only around 8%,[1] leading to huge losses of invested capital and resources. A majority of these failures are due to unexpected toxicity issues; however, an equally large fraction of the failures are due to an insufficient clinical response with an otherwise safe compound, because of dose mismatch or invalidated irrelevant targets.

The development in the mid-1990s of transgene mouse models, based upon certain genetic mutations observed in human patients, has

invigorated preclinical drug discovery, without much success in terms of innovative drugs.

Recent late-stage failures include AN-1792, tramisoprate, tarenflurbil (R-flurbiprofen), phenserine, MEM-1003 and leuprorelin (leuprolide) in the Alzheimer's disease field, and AC-104 and bifeprunox for schizophrenia.

This has led others to question the predictability of rodent animal models. A live discussion on the Alzforum website, called 'Mice on trial; issues in the design of drug studies',[2] recently gathered ideas and suggestions from many researchers working in the field of amyotrophic lateral sclerosis as to why so many drugs that work in animal models fail in the clinic. Similarly, clinical researchers in the field of spinal cord injury are questioning the face validity of animal models.[3] Of the 22 drugs shown to provide benefit in animal models of spinal cord injury, none of them worked in the clinical situation.

While others have identified managerial and economic roadblocks, this paper deals foremost with scientific and technical aspects.

Animal models are sometimes able to identify possible and innovative mechanisms, such as metabotropic glutamate receptor 2 agonism as a possible treatment for schizophrenia;[4] however, they are much less useful for the actual drug-discovery process. Some of the obvious problems include the genetic background of the mouse strain,[5] and genetic drift over generations in transgene animal models.[6] The former issue illustrates the effect of mouse genetic background on the resulting phenotype, while the latter reflects the potential loss of the specific phenotype after many breedings. Failure to recognize these problems can lead to false expectations of the predictability of the animal model to the human situation. This report deals with generic and inherent differences between the rodent and human physiology, which are not always very much appreciated in drug discovery.

In this paper, I discuss: (i) differences in pharmacological effects of the same compound on human versus rodent targets; (ii) differences in neurotransmitter wiring in human versus rodent brains; (iii) the absence of many relevant human functional genotypes in animal models; (iv) differences in drug and metabolism exposure; (v) difficulties in modelling the presymptomatic state; (vi) limitations in modelling the full human pathology; (vii) differences in placebo effects; and (viii) fundamentally different readouts in cognitive states (figure 1).

While all this might lead to a gloomy image of drug discovery and development, I also discuss some possible solutions to the translational disconnect that might ultimately result in lower attrition. These include: (i) the realization that many chronic diseases are imbalances of a network rather than the mismatch of a single target; (ii) the consequent emphasis on multi-target ligands in medicinal chemistry; (iii) better information exchange in pre-competitive peer-to-peer consortia; (iv) better integration of translational research in imaging and EEG; (v) addressing polypharmacy in early drug discovery; and, finally, (vi) reengineering the drug-discovery operation along the lines of other successful industries by incorporating the latest developments in mathematical modelling and computer power as an integral part of the whole R&D process (figure 2).

1. Aspects of Translational Disconnect

1.1 Different Pharmacology of Drug Candidates in Rodent and Human Targets

Because of the genetic similarity of human and rodent genes for different targets, it is tempting to assume that the pharmacology of a certain drug candidate is very similar for both the human and rodent target subtype. However, a recent study suggests that in the rhodopsin family of G protein-coupled receptors (GPCR), which includes most of the pharmaceutically interesting targets, only about 79% of the rat genes and 86% of the mouse genes have a one-to-one homologue with the human genes.[7]

Even the rodent-to-human homologue genes encoding GPCR have different sequences. We studied the reported affinity differences of the same compounds for the rodent and the human receptor subtype, using inhibition constant (K_i) determinations and receptor-binding profile data generously provided by the National Institute

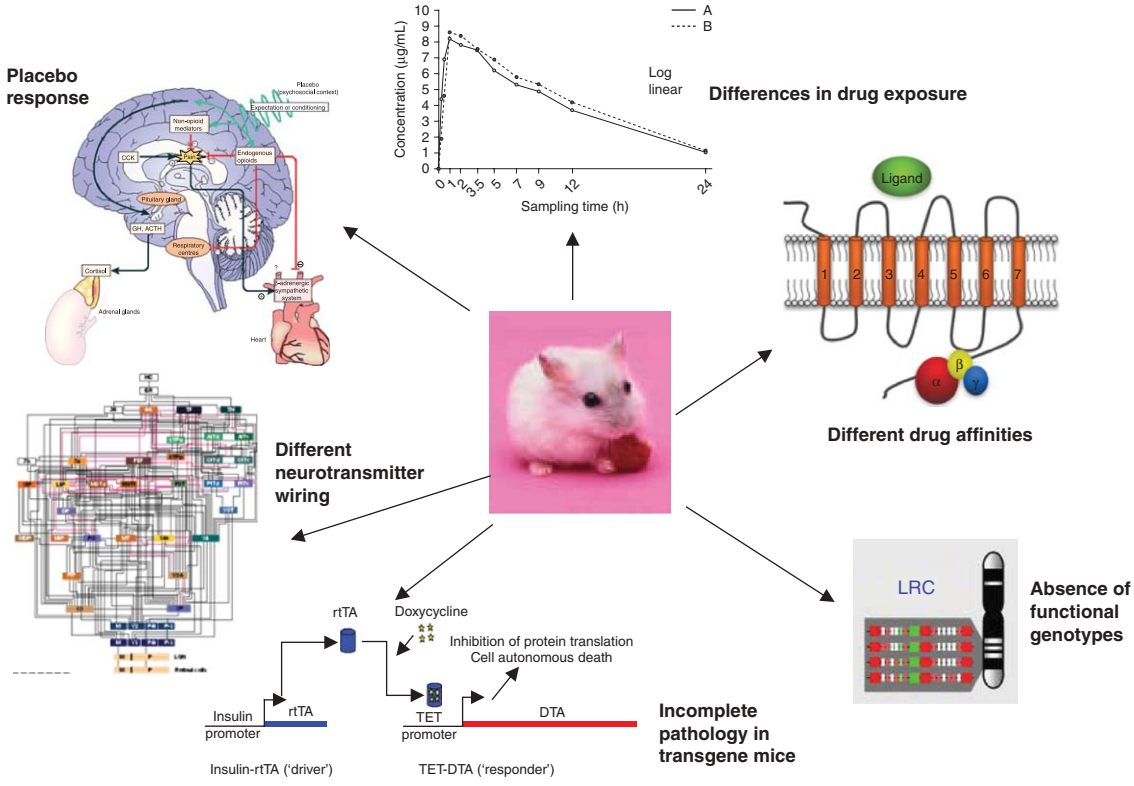

Fig. 1. Different under-appreciated limitations of rodent animal models in preclinical drug discovery and development. These include: differences in the pharmacology of drugs in human vs rodent targets; differences in neurotransmitter wiring; the absence of many relevant human functional genotypes in animal models; differences in drug and metabolism exposure; limitations in modelling the full human pathology; and differences in placebo effects. **ACTH** = adrenocorticotropic hormone; **CCK** = cholecystokinin; **DTA** = diphtheria toxin fragment A; **GH** = growth hormone; **LRC** = leukocyte receptor complex; **rtTA** = reverse tetracycline response transcriptional activator; **TET** = tetracycline on/oFF system for transgene animals.

of Mental Health's Psychoactive Drug Screening Program.[8] Briefly, in this study, reported binding affinity values for the same drug using the same radioactive tracer against the same rat and human receptor subtypes were compared. If the affinities were very similar, the ratio of maximal over minimal K_i would be close to 1. For a majority of receptor subtypes, average values for this ratio are <3, suggesting a close correlation between pharmacology at the rodent versus the human receptor. However, for some receptors, such as dopamine D_1 and D_4, serotonin 5-HT_{2A} and 5-HT_7 and muscarinic M_4, the ratio is much greater. For example, for the important D_1 receptor, the average ratio over 45 drug-tracer combinations was about 7, with some drugs showing >50-fold differences. Depending upon the absolute affinity of the neurotransmitter and compound, a factor of ≥4 could have significant biological consequences.

1.2 Different Neurotransmitter Wiring in Human and Rodent Brains

There is extensive literature on the distribution of specific receptor subtypes in the rodent and human brain. However, it is not very well recognized that the distribution of some neurotransmitter systems is considerably different between human (or primate) and rodent brains. This is very likely a consequence of the vastly different functions supported by the brains

of different species. For instance, the development of language has been speculated to be associated with the elaborate, functional, asymmetric development of right versus left hemispheres in the human brain, a lateralization that is only described for stress processing in rodent brains.[9]

Even at a more detailed level of the distribution of specific receptor subtypes, differences have been reported. Table I gives a few examples of reported differences between the human and rodent brain. Consequently, if novel therapeutic agents have intended or unintended effects at these receptor subtypes, the predictability of rodent models is likely to be limited.

1.3 The Absence of Key Functional Human Genotypes in Animal Models

It becomes increasingly clear that, despite a similar number of genes for humans and rodents, the expression of specific functional gene polymorphism can be dramatically different.

An obvious example is the apolipoprotein E (*ApoE*) gene in humans, the *ApoE4* polymorphism of which is an important risk factor for Alzheimer's disease,[16] with that polymorphism having the Arg at position 112 and 158. In contrast, rodents have only one *ApoE* version, which is slightly different. Mouse *ApoE*, like human *ApoE*, contains the equivalent of Arg-112 and Glu-255, but has a Thr-61 instead of the critical Arg-61, leading to a lack of *ApoE4* domain interaction, which makes it behave like human *ApoE3*, including preferential binding to high-density lipoproteins.[17] Simulating the biological effect of an *ApoE4* gene polymorphism in mouse models necessitates the development of complex transgene mice lines, possibly leading to confounding issues[18] and the demise of potentially important drug development programmes by pharmaceutical companies.

Another example is the human Val158Met genotype of catechol-*O*-methyltransferase (*COMT*), an enzyme involved in the breakdown of the important catecholamines dopamine and noradrenaline (norepinephrine). This genotype significantly influences working memory performance[19] and also the clinical effects of drugs that modulate dopamine and noradrenaline targets, such as olanzapine.[20] Rodents have only one *COMT* genotype[21] and a mouse *COMT* knockout (KO) model has been reported to address this possible confounding issue.[22] However, heterozygous *COMT* KO leads to a very distinctive phenotype that does not recapitulate the human changes. Failure to realize the possible effect of this functional genotype on the pharmacology of experimental drugs acting on dopaminergic and noradrenergic targets might lead to a lack of genotype-based patient stratification and, possibly, to a decreased signal in clinical trials.

1.4 Difficulties in Simulating Human Drug Exposure

Rodents are known to have fast metabolism of most exogenous drugs; therefore, it is difficult to simulate the same degree of exposure as in human clinical trials.[23] In many preclinical rodent experiments, drugs are tested acutely, which does not address neuroplastic changes induced by long-term treatment in patients; in fact, clinical benefit with antidepressant medications takes several weeks to develop. Such conditions are

Table I. Examples in which neurotransmitter wiring has been found to be different between human and rodent models. These differences might be important when the investigative drug either directly or indirectly affects this neurotransmitter circuit. This list is by no means exhaustive

Receptor subtype	Primate/human distribution	Rodent distribution	References
$mGlu_{1a}$	In cortex, both pyramidal and interneurons	Exclusively on interneurons in cortex	10
$mGlu_5$	In cortex, both pyramidal and interneurons	Exclusively on interneurons in cortex	10
NK_3	Cortical >> striatal expression	Striatal >> cortical expression	11,12
$5\text{-}HT_3$	Striatal >> cortical expression	Cortical >> striatal expression	13,14
$5\text{-}HT_6$	High density in ventral dorsal striatum	High striatal density in rats, but not in mice	15

5-HT = serotonin (5-hydroxytryptamine) receptor; **mGlu** = metabotropic glutamate receptor; **NK** = tachykinin receptor.

rarely tested in preclinical drug development, presumably because of cost considerations.

In addition, the metabolism of the parent drug in humans might be vastly different from that in animals, sometimes leading to the formation of unique active metabolites. Conversely, unique active metabolites might be formed in the rodent, without any equivalent metabolites in the human situation. These situations will very likely reduce predictability for the human situation. Efforts are already underway to address this issue by developing transgene animals with human-like metabolism, such as chimeric mice with humanized livers.[24]

An interesting study[25] dealt with measuring the exact receptor occupancy of antipsychotics, such as haloperidol, risperidone and olanzapine, in rat brains, using *ex vivo* radioactive tracer displacement techniques. Because of the fast metabolism in rats, the vast majority of dose regimens did not achieve the degree of D_2 receptor occupancy observed in the human situation, in terms of both the degree of blockade and length of exposure. Even slowly releasing drug implants at their peak concentration often did not achieve the degree of D_2 receptor occupancy observed in clinical trials. Although it is unclear what the consequence of these findings is in terms of clinical efficacy, it is likely that animal models might underestimate the degree of extrapyramidal symptoms.

1.5 Difficulties in Simulating the Presymptomatic State

Increasing evidence suggests that presymptomatic states are sometimes very different from the actual disease pathology state, because of attempts by the brain to compensate for the growing imbalance. As a particular example, minimal cognitive impairment (MCI) of the amnestic type (a prodrome of Alzheimer's disease) has been documented to have very different levels of cortical choline acetyltransferase, the enzyme that synthesizes acetylcholine. In contrast to the findings in Alzheimer's disease, in MCI patients this enzyme seems to be upregulated in an apparent attempt to compensate for the loss of cholinergic input.[26] Such changes in biochemistry have profound implications for treatment, leading to a failure of acetylcholinesterase inhibitors to modify the conversion rate from MCI to Alzheimer's disease.[27] The development of appropriate animal models for the presymptomatic state is almost as important as models for Alzheimer's disease pathology, as it becomes increasingly clear from recent clinical trial failures of amyloid-modifying interventions (tramiprosate and tarenflurbil) that amyloid pathology might best be treated in a presymptomatic state, as it is probably more upstream of the clinical symptoms.[28]

1.6 Difficulties in Recreating Full Human Pathology

Almost all animal models for CNS diseases display part, but not all, of the pathology, often leading to erroneous conclusions with regard to the extrapolation of preclinical data to the clinical situation.

A case in point are the transgene amyloid precursor protein models for Alzheimer's disease, which have dominated drug discovery without addressing the full Alzheimer's disease pathology (for a pertinent review of this animal model and its implications for the clinical situation, see Korczyn[29]). This approach was rightfully based upon the exciting discovery of the genes associated with familial Alzheimer's disease. However, scientists adhering to the β-amyloid hypothesis overestimated the impact of this 'familial' form of the disease in the general population and, most importantly, did not capitalize enough on the early onset of these dementia forms, suggesting that amyloid pathology likely plays the most important role in the early stages of the disease, a finding later confirmed by positron emission tomography imaging studies.[30]

In the field of psychiatry, 61 different animal models for 'schizophrenia' have been described,[31] 44 of these were based upon transgene technology; however, it is difficult to assess the predictability of these models for different patient populations. Although classical antipsychotics, such as haloperidol and clozapine, have been said to 'change the phenotype' in many of these models, there has been no systematic study of the effects of a wide variety of different antipsychotics (i.e. partial agonists or

glutamate modulators), including drugs that have shown negative results in clinical trials.

In addition, human pathology is often more subtle than is usually achieved in animal models, although gene dosage effects in heterozygous mice sometimes allow for a less exaggerated pathology. For instance, in the human striatum, the increase in free dopamine levels is, at most, 100% in schizophrenia patients compared with healthy individuals;[32] in many amfetamine models, free dopamine, as assessed by microdialysis, increases between 300% and 400% in mice.[33]

1.7 Placebo Effects in Animal Models

Increasing evidence suggests that the placebo response in psychiatric diseases is mediated by the subcortical reward circuitry, involving dopamine,[34] whereas the saline response in rodent models is usually associated with fear. The dopaminergic reward circuit is amenable to computer simulation[35] and there is increased effort to model the biophysical aspects of this model.[36] Such a significant placebo response, which might reduce the signal, is often observed in clinical trials for psychiatric disorders.

1.8 Unique Clinical Readouts in Humans

As some functions of the human brain have been developed exclusively to address social interactions and the concept of history and time, certain modalities unique to the human brain are not present in rodents. Besides the obvious lack of verbally mediated tasks, there are often more subtle differences.

A case in point is the recently reported lack of episodic memory in rodents.[37] In this cleverly designed study, rats were able to remember how long ago, but not when (i.e. at what time of the day) they learned to identify the location of previously encountered food with different saliencies.

Some cognitive deficits in schizophrenia include episodic memory,[38] as assessed by the Logical Memory and Visual Reproduction tasks of the revised Wechsler Memory Scale,[39] and the executive functioning in patients with MCI and Alzheimer's disease[40] are heavily dependent upon the preservation of cognitive effects. The lack of such modality in animal models might explain some of the clinical failures of cognition-enhancing drugs, as there is probably no direct correlation between some rodent cognitive readouts and their clinical counterparts.

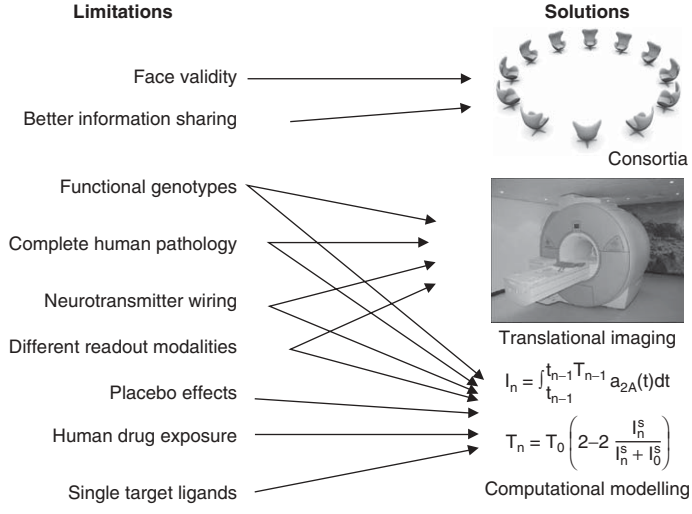

Fig. 2. Possible solutions to different types of limitations in animal models for drug discovery. Better information sharing and validation of preclinical assays can be achieved through peer-to-peer consortia; understanding the full human pathology and validation of preclinical efficacy models can be improved using better translational biomarkers, such as imaging and EEG; the effect of human-specific affinities, exposure, neurotransmitter wiring, readouts and genotypes can be assessed using computational models.

2. Possible Solutions to the Translational Disconnect

2.1 Recognition that Many Complex Diseases are Imbalances of Networks

In some therapeutic areas, such as oncology, evidence is mounting that the disease state is a system imbalance rather than a deficiency or overactivity of a single target. Concepts such as Highly Optimized Tolerance properties,[41] i.e. the diseased system is an abundantly redundant network and only very few nodes of this network are vulnerable targets, have been used in describing pathological states. Modulating irrelevant targets has little or no effect, as the system will adjust itself. For example, based upon this approach, predicting the sensitivity of different intracellular pathways in tumor cells with regard to proliferation became possible.[42] Modulating the activity of different pathways simultaneously has vastly larger effects than modification of a single pathway, and combined action against different pathways is anticipated to have a much larger beneficial effect.

In the area of CNS disease, there is an increasing understanding of the functional and structural connectivity between different human brain regions as a consequence of advances in non-invasive imaging.[43] For example, a default brain network in humans has been described, including its neurodevelopmental changes and possible relationships to cognitive changes.[44]

Additionally, network theory can be used to describe the changes in human brain network properties that are associated with specific psychiatric diseases. As an example, the changes in brain networks in schizophrenic patients seen with functional MRI (fMRI) studies are suggested to be due to deficits in local recurrent circuits.[45]

2.2 Embrace Multi-Target Ligand Medicinal Chemistry

A logical conclusion from the observations in section 2.1 would be to adapt medicinal chemistry efforts into developing multi-targeted drugs. In fact, many older drugs that have been found using functional tests affect many different receptors at clinically relevant doses, the consequences of which are not always very well understood. Examples include many antipsychotics, although the main action is thought to be limited to antagonism of the D_2 receptors.[46] However, recent meta-analyses[47] and large naturalistic studies, such as CATIE (Clinical Antipsychotic Trials in Intervention Effectiveness),[48] seem to indicate that there is more to clinical effects than D_2 receptor antagonism alone.

With the advent of molecular biology and the identification of unique targets, more recent drugs have been tailored to be very selective in order to limit adverse effects. At the same time, this has reduced their clinical efficacy.

Some efforts are ongoing to deliberately develop two- or three-target ligands.[49] Examples include BL-1020,[50] a combination of a D_2 receptor antagonist and a prodrug of the neurotransmitter GABA, which is currently in development for schizophrenia.

However, pursuing a 'lean' pharmacology increases the complexity substantially as the medicinal chemist cannot rely on the simple parameter of single-target potency to drive the chemistry synthesis plan as the multidimensional quantitative structure-activity relationship becomes increasingly complex. In addition, the relatively long feedback cycle of animal studies precludes the testing of many compounds, which makes this kind of drug discovery unattractive.

2.3 Better Information Sharing Through Peer-to-Peer Collaboration

It is often stated that you can learn as much from negative findings as from positive findings; however, the reporting of positive trials far outweighs the reporting of negative or failed clinical trials, very probably because of economic or investment reasons. In addition, trial data are considered by US law to be proprietary property of the sponsor. However, recent initiatives such as mandatory reporting of both trial initiation and trial results (see the ClinicalTrials.gov website[51]) are certainly steps in the right direction.

Since many drugs fail because of toxicity issues, simple tests that are predictive for the human situation are needed to identify possible

problems early in development. However, their validation is crucial to the large-scale acceptance of such tests by pharmaceutical and biotech companies. In fact, type II errors (false negatives) can be very expensive, because the development of potentially safe and effective drugs may be halted prematurely.

An interesting development in this regard is the construction of temporary consortia based upon peer-to-peer collaboration (see Cambridge Healthtech Associates[52]). The idea is to validate vendor-specific assays using compounds that have been halted in clinical development because of unexpected toxicity. The compounds would be provided by different pharmaceutical partners, thereby reducing the costs of validation through risk sharing and improving predictability because many different datasets with a large chemical diversity could be used. Another example is toxicokinetics optimization (see Cambridge Healthtech Associates[53]), where clinical drug exposure was calculated based on the full datasets from a wide variety of chemical structures provided by different pharmaceutical companies. This experimental pharmacokinetic profile was subsequently compared with an exposure calculated on simulated sparse datasets (i.e. subsets of the original data). Of the two algorithms evaluated, one was found to give robust and predictive effects. Such collaborations can help to identify and validate promising early toxicity tests at a fraction of the cost.

Such peer-to-peer consortia could also be used to determine face validity of animal models for clinical efficacy predictability. In such a construction, drugs with known clinical effects (for instance, on cognition) could be systematically tested in well defined preclinical animal models (for instance, the Morris water maze) and appropriate correlations could be determined.

2.4 Better Integration of Translational Techniques in Human Brain Imaging, Electrophysiology and Pharmaco-EEG

In many clinical situations, the type of sensory stimuli, such as faces, buildings and environmental factors, is very different from the kind of stimuli laboratory animals are experiencing. In addition, certain modalities such as verbal working memory or episodic memory simply do not exist in animal models.

It is therefore important to capitalize on translational research in the field of human brain imaging and electrophysiology. New advances in noninvasive imaging techniques have allowed the identification of both the neuronal circuits and the coding scheme of specific cognitive tasks, especially in the area of reward and neuro-economics.[54] For instance, using a novel multivariate analysis technique and high-resolution fMRI, activation patterns within specific brain regions, such as the fusiform area, can be identified for face versus non-face recognition; localized subregions highly selective to faces are spatially interdigitated with localized subregions highly selective to different object categories.[55] Such studies can then serve as a base for building computational models for noun understanding.[56]

Identifying similar brain-activation patterns in certain animal experimental paradigms could enhance the confidence of well defined outcomes in preclinical research, even when the tests are not identical.

Similarly, pharmaco-EEG measurements can identify the changes in EEG power spectra after drug administration;[57] being able to identify similar changes in animal models enables the prioritization of these models on the basis of face-validity. As an example, changes in sleep and EEG in the rat neonatal hippocampal lesion model were compared with observations in patients with schizophrenia.[58] Such studies enable us to better understand the limitations of, and to prioritize, different preclinical animal models.

In addition, non-invasive, evoked-response studies using new technology, such as high-resolution EEG or magnetoencephalography (MEG), can be used to identify possible responders to clinical treatment and open new windows on the underlying pathology and its response to treatment, which are more widely applicable than genetic studies. For example, MEG-measured activity in the anterior cingulate cortex in depressed patients after being shown fearful faces has been demonstrated to be positively correlated with treatment outcome of a fast-acting antidepressant.[59]

2.5 Use of Polypharmacy in Preclinical Animal Models

In clinical practice, polypharmacy is very common, especially in the elderly patient. For example, in advanced dementia, patients take an average of 6.5 medications, with a substantial fraction taking ten medications or more.[60]

Even in clinical Alzheimer's disease trials, many co-medications are allowed, such as insomnia drugs and, often, antipsychotics. In addition, clinical trials with amyloid-modulating agents are often performed against an existing acetylcholinesterase inhibitor as an active comparator.[61] Such co-medications can often interfere with the pharmacology of the investigative compound under study; yet, in preclinical animal studies, these co-medication studies are very rarely performed. For example, acetylcholinesterase inhibitors that are currently used in Alzheimer's disease, through their effect on the breakdown of acetylcholine, indirectly stimulate postsynaptic M_1 receptors, activating different intracellular processes and leading to the reduction of β-amyloid synthesis or tau phosphorylation.[62]

In the case of schizophrenia, antiepileptics and insomnia drugs are often allowed in clinical trials; these drugs acting on the GABAergic pathway might have a differential effect on part of the pathology,[63] possibly affecting the signal of the investigative drug under study.

2.6 Systems Biology and Computational Approaches

Systems biology, which aims to study the whole organism in an integrated view, might provide solutions to the innovation gap in identifying possible new, but often unknown, targets and validating biomarkers. However, this approach is limited by the enormous amount of data generated and the lack of robust approaches for identifying causality between the multitude of interacting processes. In order to use this information, one must not only gather and categorize data, but also integrate it in an interpretable context.[64] Also, very often, such approaches identify important pathways in a more qualitative way and are not always able to place the different target pathways in rank order or predict dose responses of certain therapeutic interventions.

Complementary alternatives to this are mechanistically based computational approaches, where existing knowledge is integrated in mathematical models. Obviously, such a modelling and simulation approach cannot identify novel unknown targets, but is more quantitative in predicting the outcome of certain interventions. Similar approaches have been proposed in other areas of medicine, notably inflammation, metabolism[65] and oncology.[66]

Given the legacy of computational neuroscience, starting with the seminal work of Hodgkin and Huxley,[67] it would be a logical extension to use this approach as a basis for implementing the effects of pharmacological modulation in a mathematical way. There are indeed efforts to integrate computational neuroscience into the field of systems biology, making this approach more attractive for CNS drug discovery.[68] In fact, dynamical neuropharmacology has been proposed as a way to evaluate the effects of pharmacological agents on theta oscillations in mathematical models of brain slices.[69] Such mathematical models are built on mechanistic data from preclinical models and include human patient data, such as relevant pharmacokinetic profiles, human-specific metabolites, pathology derived from imaging and EEG studies, and functional genotypes. The modulation of different receptors by certain drugs can be simulated through a calculation of the competition between the endogenous neurotransmitter and the drug and its metabolites, based upon the respective affinities and pharmacological activities. Subsequently, the effect of changed receptor activation levels on neuronal excitability, for instance, through phosphorylation of potassium ion channels, can be calculated from preclinical *in vitro* or *in vivo* data. A network model then allows us to evaluate the concomitant effect of many activities on the fine balance between excitation and inhibition. A 'humanized' pathological state is defined based upon the changes in receptor densities and neurotransmitter levels derived from imaging and postmortem studies. The model is validated by calculating the effect of

existing drugs, such as antipsychotics, on the in silico network and correlating this outcome with the reported clinical efficacy on, for instance, Positive and Negative Symptoms in Schizophrenia (PANSS) scale total scores.

These hybrid models, because they are much more translational, could address some of the limitations of animal models presented in this paper.

3. Conclusion

The successful development of new innovative drugs for chronic CNS diseases is in jeopardy and new paradigms need to be explored. The current drug-discovery paradigm is based upon detection of activity and toxicity in animal models; however, these models show a rather limited predictability for the clinical situation. This report presented a number of less appreciated and underestimated limitations of animal models that could explain, in part, the substantial number of failures in the clinic.

Ironically, target validation, which is the most important part of the whole drug-discovery process, does not always get the appropriate amount of attention or resources and is often solely based upon preclinical experiments or a very narrow window of information from the human clinical picture.

Some solutions to bridge the translational disconnect are proposed, such as organizational improvements, for example, information sharing, cost-sharing collaboration in precompetitive peer-to-peer consortia with other parties, and the better use of negative trial data, and technical improvements, e.g. better translation of biomarkers and endophenotypes between animal models and the clinical situation, and the introduction of realistic polypharmacy drug schedules early in drug discovery. However, I expect the biggest pay-off will come from conceptual improvements, such as the realization that chronic diseases like Alzheimer's disease and schizophrenia are imbalances of networks rather than mismatches of single targets, and that multitarget ligands may lead to significant clinical improvements. Such an approach necessitates fundamental changes in the drug-discovery concept, such as the change from the 'high selectivity' to the 'lean pharmacology' paradigm in medicinal chemistry and the realization that the best animal models only capture part of the pathology.

Re-engineering the drug-discovery process along the lines of other successful industries, such as aerospace and electronics, might be extremely helpful in this regard. Integrating computer modelling in drug discovery could be used to examine the consequences of many 'what if' scenarios, such as the effect of certain functional genotypes on the pharmacology of investigative drugs, exploration of the full dose response, the effect of allowed co-medications and the use of virtual patients in simulated clinical trials.

I believe that the integration of computational modelling as an essential part of the CNS drug-discovery process will contribute substantially to a better understanding of human biology and consequently to lower clinical trial attrition rates.

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