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Where to from here?

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It is a plain fact that we are doing research in a need-to-cure-world. When our understanding of a disease pathology is a work in progress, it is often wise to focus on specific aspects of the disorder, gain an understanding of its components that will be assembled in a conceptual framework, and proceed to a therapy based approach [1]. Thus, before envisioning a cure for addiction, let us critically analyze whether our attempts to understand this exceedingly complex phenomenon using animal model systems *atleast nearly reflect the human condition*. To study a given scientific hypothesis, choices of model/model organisms are essential and options can be many. The model setting is complex. Frequently, responses connected to drug/addiction do not occur equally between humans (intraspecies variability) and variation in such responses between species can be even more diverse (interspecies variability). Additionally, when addressing "addiction" we have a multifactorial setting of intricate, imperfectly understood human behavior mechanisms e.g. craving, executive control that ideally would be mimicked in animal models. Realistically, the latter may only be possible in part. Thus, there exists a plethora of real and potential model systems and experimental approaches attempting to essentially address the same questions. The following thoughts (both scientific and opinions) are largely, inspired by Dr. Andrey Ryabinin's talk entitled "New hopes from evolutionary approaches to animal models of alcoholism and addiction" in the First International Conference and Exhibition on Addiction Research & Therapy in Las Vegas, USA (Aug 20-22, 2012).

Is it time to call a spade a spade?

Animal models have long been our means to experimentally address clinically relevant pathologies within the complexities of an in vivo setting and have been an integral part of many important achievements. The field of addiction biology is no exception. There are many different models addressing multiple parameters of drug addiction from drug preference to oral-drug-self administration to conditioned place preference/aversions tested in various organisms viz. chimpanzee, rat, mice, chicken, sheep, drosophila, zebrafish, C. elegans, honeybee etc. [extensively reviewed: [2-4]]. At the same time, let us not forget that any experimental organism cannot be *truly* counted as a "model organism" [5]. Clearly, the validity of ensuing scientific studies depends entirely on the model, how it is manipulated and the human relevance of its end-point measures.

Apparently, for each experimental approach, the most suitable animal must be selected on a *case-by-case basis*. Imprecise, biased selections will not only yield inaccurate conclusions but confuse literature/future studies etc. In modern science, "Scientific Validity" often takes a beating vis-à-vis reliable extrapolations of findings obtained in animal of a different species to humans. For instance, some animals, such as C57BL/6J strain of mice have high preference for alcohol. Importantly, C57 mouse have a far higher clearance rate for alcohol (109 mg/dl/h) as against human (23 mg/dl/h) [6,7] and thus the former averts any acute toxicity despite consuming a large dose of alcohol. In light of this issue, two important critical remarks come to mind: (i) "Does preference without toxicity constitute a model for alcoholism?" [8] (ii) "What is the medical relevance if ingestion of a substance as a food or flavor doesn't result in any harm?" [7]. This is not an off-topic view. It stresses the fact that generalizations cannot be made about alcoholism across given species of mice and humans. In other words, simple alcohol toxicity and biochemical measures dependent on metabolic profile in such models need to be cautiously approached. However, it does not preclude to study other relevant aspect such as "why these animals drink more?" which can address *partially* "why certain humans drink more?" [9]. Why partially? Because this model can address consequences of genetic background but not environmental interactions such as lifestyle, work and peer pressure. In short, it is not just the choice alone but the "*right*" choice of model should be the key buzzword to study a relevant hypothesis that can steer the field forward.

If animal research has taught us anything, it's time to care about how wrong it can be

Animal models can, in many settings, functionally reflect the human condition in addiction studies. However, as a budding independent researcher, one of my biggest pet peeves is assimilation of reports employing vastly diversified animal models to study the same aspect of addiction. Often, results emanating from such studies are not interpreted within the limits of specific model and each may claim to have provided invaluable science related to the problem in question. So, how does one approach such conflicts? Recently, Dr. Foster Olive in his Keynote talk at the 1st International Conference and Exhibition on Addiction Research & Therapy, highlighted that despite numerous successful experimentation on animals addressing different modalities of treatment of drug addiction ranging from individual and group therapy to biologically based therapies, has disappointingly made little progress. Following are couple of critical reasons for the increased drug attrition in clinical trials (i) poor predictive animal models (ii) majority of the pre-clinical findings resulted from improper choice of model/model organism and comprising critical ingredients for a given aspect of addiction (as discussed below). Dr. Mark Mattson who is a professor of neuroscience at Johns Hopkins and a leading scholar of degenerative brain conditions in one of his lectures quotes that "I began to realize that the 'control' animals used for research studies throughout the world are couch potatoes". In other words, mice housed and tested under standard laboratory conditions are left with nothing to do but leading a cushy lifestyle of just eating and sleeping. This raises a straightforward question as to what extent the data obtained from addiction studies involving psycho-social behaviors from such animals in enriched conditions can be comparable to the true addiction phenomenon.

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It is reasonable to attempt and resolve a research problem in experimentally accessible model/model organism, but if it has poor predictive power the rationale of the model needs to be questioned openly. For instance, the relevance of postnatal day (PD) rat/mouse model, one of the widely used models to study FASD (Fetal Alcohol Syndrome Disorder) related brain abnormalities during third trimester of pregnancy (occurs in *utero* in humans) is potentially challengeable. The general justification is that third trimester human equivalent of brain development is postnatal in rat and mouse. FASD is a devastating disorder afflicting the innocent fetus due to ingestion of toxic doses of alcohol by pregnant mothers thus, the cause for the effect is entirely dependent on maternal system. However, the response of fetal brain in a PD rat/mouse model of FAS is isolated, (i.e.), maternal-fetal interaction is disregarded. Thus, it appears that we are attempting to establish a fact at the expense of "*grand compromising*" another fact. Another instance, where animal models that are used to study binging stage of addiction cycle suffers from a major drawback in that there is a lack of definite criterion as to what constitutes a typical drug binge. Typically, in many studies, a very high, toxic dose as applied in acute studies is used in each session of the binging paradigm. For example, in actual settings, alcohol consumption in one session of binge is not the same as that of the other session (i.e.): blackout level consumption in one session of the binge and a moderate level consumption in the other, which is a less considered detail. Dose selection is further complicated by choice of animals. Generally, rodents are shown to have aversion for taste or odor due to disagreeable after effects that are a classical response of memory trace [10-12]. Many of the rodents either not consume ethanol to intoxicating blood alcohol levels due to aforementioned classical memory conditioning [13,14] or consume more alcohol due to genetic influences [9]. Thus, many voluntary drinking binging models that could be influenced by taste aversion or genetic influence would offer only little more than less information with respect to drug self-administration in human setting. This presses the need for appropriate template for binging without which precise understanding of the concept would be an impending impasse. Solely from a scientific perspective, it is difficult to suggest a replacement option at this juncture; nevertheless, a detailed sub microscopic consideration of more than just one factor would help us reach favorable depth in the field.

Cutting-edge research: Does it mean "Cutting off feet to fit the shoes rather than picking the shoes that fit"?

Unlike yesteryear's, researchers can certainly improve the understanding of a problem lot better nowadays if they couple the benefit of ease availability of resources and technical advancements with avoidance of oversight in selecting a model/model organism and experimental design. For example, it is well known that activation of HPA axis has been shown to play a critical role in cocaine addiction and alcohol stress [15,16]. However, the genetic manipulation model involving components of HPA axis, and studying alcohol, cocaine dependence would have to be approached and interpreted extra carefully. This is because any interference of HPA axis components can lead to subtle disturbances that can upset normal lifestyle and induce non-specific noisy changes that fall outside the actual disease/condition under investigation which inturn can affect the response of original stressor itself. Fruit flies (*Drosophila melanogaster*) that dine on toxic, rotting and fermenting fruits are gaining popularity as a model to study alcoholism. They have a robust enzymatic system for detoxifying alcohol and in fact, high alcohol content ranging from 5% to 15% is a natural habitat for them. Flies and mammals exhibit several similarities at the behavioral, neurochemical and molecular level. But, a basic question that persists is that whether Drosophila have distinguished HPA axis? It has been proposed that pars intercerebralis/corpora cardiaca in complex of insects is the verterbrate equivalent of hypothalamus-pituitary [17]. This is due to conserved properties between the two on (a) gross anatomical and (b) functional commonalities with respect to secretion of similar neuropeptides that regulate energy metabolism, growth, water retention, and reproduction. However, it is not clear as to what extent does these functional similarities represent true homologies? [18,19]. Though many studies have documented toxic responses of alcohol in flies [20-22], a recent report shows that flies can afford to drink for their living at the same time use alcohol as medicine to kill endoparasitoid wasps parasites [23]. Also the flies prefer more alcohol when they are infected with these parasites just to deter and kill them. Considering this along with HPA axis being the home of alcoholism [24], one has to adhere extra responsibility in avoiding any *comparisons per se or short-sighted interpretations* made out of alcohol studies in flies with other animal models and/or to human addiction.

Traditional whole body knockout (KO) animals can be powerful and highly useful models to study different aspects in an addiction setting. However, we now know that such model systems are fraught with potential problems of specificity. So, when a specific gene is globally disrupted from the animal, it is difficult to establish the role of a single anatomical region and its associated functions. Further, as these specific knockouts or gene alterations are engineered at the time of conception, a protein of same family or other and/or isoform could compensate for the gene that is targeted, which is unnoticed in several illustrations. In other words, subtle changes are always expected by insertion or deletion of target genes [25-27]. Over and above studying any addictive phenomena in such background and interpreting the data in purview of single organ/region/circuit/function in isolation is imprecise at best. Thus, unless it is a specific cell/organ specific knockout which does not influence the non-targeted organs, the results might not offer any new reliable information about the disease, vulnerability or the intended science. Further, in many instances of animal research of addiction, where molecular/signaling/any functional aspects are studied, the influence of genetic background in the same model organism is often less considered. Genetic background has been suggested to influence biological processes affecting cell signaling and cellular organization [28]. In fact, earlier studies have revealed that C57BL/6 mice (alcohol preferring) possess higher delta-receptor density and lower kappa-opioid receptor density in nuclear accumbens than do DBA/2 mice (alcohol avoiding) [29,30]. This differential endogenous opioid activity among these two strains has been suggested as one of the prime reasons for difference in alcohol preference of one strain over the other. Given the importance of genetic background influencing phenotypic outcome, structure and functional correlations, it is clear that if we have to obtain a profound understanding of both disease and non-disease associated phenotypes, it is critical to include this profile in our model/design framework. In addition, there is another potential issue with the usage of controls. For instance, in in *utero* Fetal Alcohol Syndrome (FAS) models, the widely recognized pair-feeding control procedure is used to match food intake with ethanol-consuming animals wherein the pregnant dams are usually starved for a significant period during treatment. Essentially, these pair-fed controls are weak in precisely matching for ethanol's effects on absorption and utilization of nutrients. To worsen this, the reduced ration is suggested to induce a mild prenatal stress [31] which could disrupt some of the normal prenatal programming of endocrinological, physiological (including HPA axis and related functions), behavioral, cognitive aspects etc. Thus, the subtle yet critical, mild starving stress factor needs to be accounted before arriving at final end-point for ethanol stress, which is quite often overlooked. Importantly, some of the key "higher order" cognitive

and behavioral responses is uniquely human and mimicking that in animal models is one of the many seemingly insurmountable issues. Further, with the science behind enigma of prefrontal cortex (PFC – region involved in congnitive control) equivalent regions among different species is yet to be completely cracked, addressing human cellular changes with respect to finer cognitive, behavioral functions in response to an addictive drug in animal models is highly challenging. All of these are further compounded by the existence of practical issues such as productivity, time pressures to publish and acquire grant-related funding; one can readily slip into safe mode of booting up research in an *easily accessible model organism* without fully evaluating the validity of the model. Thus, before pushing the technological boundaries to extract the knowledge it is very critical that appropriate steps are taken to keep the spurious artifacts minimized and strengthen the inferences. To an extent, this is possible if required set of guidelines starting from model organism selection to experimental models are developed and enforced by the related addiction agency. Is this possible? Well, let us recollect John Dewey's quote: "Every great advance in science has issued from a new audacity of the imagination".

Are we picking flowers when we want fruits? Is it time for a paradigm shift?

It is reasonable to understand that "All change is not growth; all movement is not forward" (Ellen Glasgow). At the same time, it is equally sensible that, until better predictive models are available, existing animal models for research and testing must not be criticized [32]. With that being said along with considering current economic climate and resources, how are we going to pull the strings and drive the field forward? Firstly, with the progress we have made thus far in a specific area of addiction, along with applying newer technical advancements we should reevaluate and attempt to create a more meaningful, tractable and reasonable working model. Along these lines, with the guidance of legion of senior scientists from a relevant field of addiction along with clinicians, anatomists, geneticists, pathologists, pharmacologists, molecular biologists, psychiatrists etc., appropriate "less-than-optimal unified animal model" that is most closely aligned to humans to study a specified element of addiction process (e.g.: a unified animal model for studying a particular aspect of (i) FASD (ii) nicotine dependence etc.) needs to be devised. Well, it is difficult to prove that one animal model is better than the other. The simple fact is that each and every model organisms has its own advantages and disadvantages and each of them is capable of reflecting only minor component of real phenomenon. At the same time, does it mean that working in many different model organisms to prove the same concept which generate no consensus but apparent and expected species specific effects going to strike gold? In my view, the answer is maybe, Yes and No. Despite limitations in all model organisms, *a near-perfect* model/model organism selection would be a strainer, filtering out unnecessary chaotic observables while allowing relatively a better understanding. It is not that need for a favorite model/model organism is suggested but a process that can streamline the efforts and facilitate a good question to be answered in more meaningful way. Indeed, there are efforts in place to develop and devise improved, *near-perfect models* to understand the concept of addiction. However, encouragement as similar to proposals aiming at identifying molecular targets for therapeutic intervention or developing new magic therapies is highly desirable.

"Think big and start small"-Can this oft-repeated modern day mantra be a kickstarter?

Kudos to addiction researchers who have untiringly attempted to develop or modify available animal models. As yet, none of the current models used in addiction field are satisfactory or closely comparable to human system. Not that we are unsuccessful or the previous studies should be underrated. The very reason for us to be where we are today in the scientific advancement is due to the knowledge contributed from existing experimental findings. With the understanding and acceptance of certain models/model organisms suited for addressing specific questions, the need of the day in the field of addiction is a research refinement to standardize models and setting a guideline for selection of appropriate model/model organisms to study a relevant aspect. However, the major challenge is to break the "status quo" and understand the "big picture".

In order to understand the big picture of a topic, would the idea of "Unifying concepts" put forth by National Science Education Standards work? Only time will tell, however, the encouraging aspect of this concept is that it is applicable and accessible to all areas of science. It comprises of 5 big ideas: (1) Systems, order, organization (2) Evidence, models, explanations (3) Constancy, change, measurement (4) Evolution and equilibrium (5) Form and function. Banishing the few expected hurdles wouldn't it be refreshing to get a head-start with focusing on point 1 and point 2 and work towards constructing a *"less than-ideal, unifying animal model" to study a specific aspect of a addiction phenotype?* Further, wouldn't be great if the related addiction agencies could enforce the set guidelines of model framework alike mandatory pre-flight safety demonstrations? But in this case, instructing the researchers (be it starters or experienced) to strictly listen to instructions prior to take-off. I hope this will be extremely beneficial in flying high and land safely.

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