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Building dialogues between clinical and biomedical research through cross-species collaborations

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Abstract

Today, biomedical science is equipped with an impressive array of technologies and genetic resources that bolster our basic understanding of fundamental biology and enhance the practice of modern medicine by providing clinicians with a diverse toolkit to diagnose, prognosticate, and treat a plethora of conditions. Many significant advances in our understanding of disease mechanisms and therapeutic interventions have arisen from fruitful dialogues between clinicians and biomedical research scientists. However, the increasingly specialized scientific and medical disciplines, globalization of science and technology, and complex datasets often hinder the development of effective interdisciplinary collaborations between clinical medicine and biomedical research. The goal of this review is to provide examples of diverse strategies to enhance communication and collaboration across diverse disciplines. First, we discuss examples of efforts to foster interdisciplinary collaborations at institutional and multi-institutional levels. Second, we explore resources and tools for clinicians and research scientists to facilitate effective bi-directional dialogues. Third, we use our experiences in neurobiology and human genetics to highlight how communication between clinical medicine and biomedical research lead to effective implementation of cross-species model organism approaches to uncover the biological underpinnings of health and disease.

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Keywords

Undiagnosed Diseases Network; Model Organisms Screening Center; Interdisciplinary collaborations; Neurological Research Institute; *Drosophila* Zebrafish

Introduction

Recent technological advances in the life sciences such as sophisticated genetic technologies, including CRISPR-mediated genome editing, optogenetics, and super high-resolution microscopy allow detailed dissections of biological function in health and disease [1–3]. Although these techniques are still evolving, the discoveries resulting from their biological application are invaluable to the practice of modern medicine. However, the ability to efficiently diagnose and treat many complex human conditions remains limited due to insufficient knowledge regarding biological mechanisms and the relationship to human phenotypes. This is of particular concern to the field of neuroscience, where the increasing prevalence of chronic neurological disorders means that the vast majority of people in the world will be affected by neurological conditions during their lifetime [4]. These conditions include depression, schizophrenia, intellectual disability, epilepsy, autism spectrum disorders, Friederich's ataxia, multiple sclerosis, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. For many complex human disorders the genetic diagnoses often remain elusive, disease mechanisms are incompletely understood, therapeutic interventions are limited, and cures are rare. Critical steps to solving these challenges are well-designed biological studies in animal models. Mechanistic insights from biological studies in model organisms often provide invaluable information to guide and facilitate the development of diagnostic strategies and therapeutic interventions. Similarly, insights from the human condition are integral to the development of appropriate animal models of disease and the interpretation of biological discoveries. In this regard, humans have an important role as a model organism. Therefore, there is a tremendous need to identify and implement strategies to facilitate the bi-directional exchange of ideas and information between clinical medicine and biomedical research.

The Human Genome Project (HGP) illustrates a interdisciplinary biomedical research effort with wide-ranging impact on medicine and science [5, 6]. As the inaugural exemplar of a large-scale, multi-disciplinary, and international biological research effort, the HGP encountered many technical and communication challenges. The primary challenge was to reach a consensus for developing the best practice strategy to tackle the operation of sequencing across 20 centers in six countries. This challenge was solved by opening dialogues between the centers, as well as the private and public sectors, which ultimately resulted in a consensus strategy to coordinate sequencing efforts and accelerate construction of the human genome [6]. Subsequently, other large-scale efforts such as the International Haplotype Map (HapMap) [7], Model Organism Encyclopedia of DNA Elements (modENCODE) [8, 9], Encyclopedia of DNA Elements (ENCODE) [10], and the 1000 Genome Project [11] were implemented to systematically catalogue and organize the structural and functional categories of the human and selected model organism genomes.

The success of these large-scale research efforts effectively ushered in a new era of modern medicine and biomedical research.

The trial and error efforts of the HGP [5], HapMap [7], modENCODE [8, 9], ENCODE [10], and 1000 Genome [11] projects established many practice strategies that centers on the central theme of improved scientific communication [6, 12]. First, develop a compelling vision that appeals to the best and brightest minds in medicine, science, and technology. This is crucial for building stellar interdisciplinary teams who conduct exemplary large-scale science, encouraging international participation, and building public support. Second, ensure that the process remains driven by rigorous and solid scientific judgment and encourage continual discussions regarding the direction and long-term goal of the project. Third, publicly release data and technical resources rapidly, prior to publication, to the entire scientific community, given that quick transmission of information promotes the best interests of science and the general public [6, 13]. Fourth, encourage innovation and facilitate open discussions with technology developers to create new instrumentation and approaches that can have wide-ranging impact on the broader scientific community while also benefiting the general public.

Implementing these strategies ensured the success of many large-scale research consortiums and paved the way for the rise of whole exome sequencing (WES) or whole genome sequencing (WGS) as components of the biomedical research scientist's and clinician's armamentarium. In 2011, the Baylor Genetics Laboratory (BGL) became the first diagnostic laboratory to offer WES as a clinical test [14]. With regards to neurological disorders, the WES genetic diagnosis rate is reported to be ~36%, which exceeds prior traditional molecular approaches such as chromosome studies with a diagnostic rate of 5–10% and chromosomal microarray analysis with a diagnostic rate of 15–20% [15]. However, identifying the genetic cause of a human disorder is only the first step toward understanding disease mechanisms. The critical next step for translation of these human genetic findings into clinical applications is to decipher protein functions and determine how genetic alterations lead to human disease [16, 17]. It is at this critical step, that well-designed model organism research in animals such as the fruit fly (*Drosophila melanogaster*), zebrafish (*Danio rerio*), and mouse (*Mus musculus*) affords assessment of the biological impact of human genetic alterations in a living organism and may provide important insights for clinical applications of the biological findings. Therefore, in order to accelerate scientific investigations, the current era of biomedical research calls for the development and utilization of new modalities of communication strategies to foster bidirectional dialogues between bioinformaticians, human geneticists, model organism biologists, clinicians, and patients. Furthermore, many of the strategies identified from the large-scale genomics endeavors remain applicable to establishing effective collaborations between basic and clinical researchers at either the levels of large-scale consortiums or smaller groups of investigators.

Three principle challenges faced in developing collaborations between clinical medicine and biomedical research include proximity to collaborators, resource and data accessibility, and a "language barrier. First and foremost, the physical and intellectual distance between research scientists and clinicians hamper interdisciplinary communications. Physical proximity to

clinical and research scientists across diverse disciplines affords the opportunity to participate in seminars, conferences, and small group meetings where investigators are likely to encounter clinical cases or biological studies of interest. Academic clinical case conferences that involve both clinicians and basic scientists demonstrate significant success in improving diagnosis and treatment [15]. To encourage bi-directional dialogues between research scientists and clinicians we argue that the development of interdisciplinary research institutes, fostering joint participation in research consortia and scientific meetings, as well as online resources, patient registries, and video-conferencing technologies promote discussions and mutual educational opportunities by allowing research scientists, clinicians, and patients to share insights and resources from around the world. Second, another barrier is formed by the lack of the accessibility and transparency of human or model organism databases and resources. Again, these barriers are broken down when scientists, bioinformaticians and clinicians collaborate. Third, a “language barrier” occurs due to specialized training resulting in a “medical dialect” and a “scientific dialect” with unique terminology, acronyms, and jargons, which make it difficult for research scientists and clinicians to comprehend the meaning and the impact of discoveries outside their respective disciplines [18]. The result of this “language barrier” means that laboratory-based basic research scientists are often ill equipped to recognize the potential impact of their research findings in clinical medicine. Similarly, clinicians are poorly equipped to recognize the role of fundamental biological studies in advancing diagnostic modalities or therapeutic approaches. The strategies to overcome language barriers should include the development of skills in science communication and engagement with the public, developing the ability to effectively relay scientific and medical information in a language accessible to a diverse audience, and public outreach activities.

The goal of this review is to provide examples of strategies to enhance the dialogues between clinical medicine and biomedical research, to examine the impact of interdisciplinary collaborations on elucidating human diseases through model organism studies, and to inspire basic research scientists to reach out to translational or clinical scientists and clinicians through the viewpoint of our experiences with elucidating complex neurological disorders (Figure 1). First, we discuss examples of efforts to foster interdisciplinary collaborations on institutional and multi-institutional levels. Second, we explore collaborative strategies and tools that clinicians and research scientists can utilize to bridge the “language barriers” and facilitate dialogues. Third, we highlight how bi-directional communication between clinical medicine and biomedical research lead to effective implementation of cross-species approaches to improve our understanding of health and disease.

Collaborative efforts bridging clinical medicine and biomedical research

To improve the understanding of biological pathways relevant to disease pathogenesis, it is important to identify the genetic cause, perform functional analysis of the genetic alterations, and determine disease mechanisms in relevant model organisms. This process depends upon integrating findings regarding the human condition with biological discoveries in model organisms. This integration facilitates the translation of human genetic findings and biological discoveries into clinical applications. There already exists a number of large-scale

government-funded public research initiatives that bridge clinical and basic research scientists, as well as research institutes and relatively smaller-scale research initiatives supported by disease-specific private foundations and advocacy groups, which will be explained in greater detail [19–21].

The ability to determine the genetic causes, for heritable disorders with Mendelian traits (i.e. phenotypes associated with specific gene alleles) is critical for establishing a genotype to phenotype correlation, identifying critical molecular and cellular pathways, characterizing neural circuit perturbations, and ultimately developing targeted therapeutics. In order to surmount the challenge that ~50% of disorders with Mendelian traits continue to lack a genetic diagnosis, the NIH established the Centers for Mendelian Genomics in 2011 [22]. The CMGs created the necessary interdisciplinary and international collaborative framework and infrastructure to perform large-scale WES analysis in affected individuals and their relatives for the discovery of the genetic basis of “unsolved” Mendelian traits. As of January 2015, the CMGs formed partnerships with 529 investigators from 261 institutions in 36 countries, acquired 18,863 WES samples from 8,838 families, and identified genetic variants in 375 genes that were not previously associated with human disease [22]. A key factor to the success of the CMG research endeavor is the diverse partnerships developed between clinicians, physician-scientists, and biomedical research scientists across the world. The CMGs developed these partnerships by actively seeking interdisciplinary collaborators, recruiting investigators to submit appropriate clinical cases for research-based whole exome sequencing through the CMG, and providing the administrative and financial infrastructure to coordinate these partnerships and data. For example, our research group collaborates with the CMG located at our institution, Baylor College of Medicine (BCM), and utilizes fruit fly animal models to examine the potential association between human genetic alterations with a disease phenotype and elucidate the biological mechanisms. The regular CMG meetings are video-conferenced, which allow clinical and basic science investigators at various external sites to review clinical information, discuss new research findings, and plan research collaborations. Through these meetings, investigators are able to maintain dialogues throughout the CMGs and collaborators around the world. The partnership between the clinicians, human geneticists, and molecular geneticists in the CMG with our basic science laboratory resulted in the rapid identification of three genes where genetic alterations were not previously recognized to cause neurodevelopmental and neurodegenerative disorders [23–25].

Another recent effort to advance our understanding of human diseases through interdisciplinary collaborations and enhanced communication between clinicians and research scientists is the establishment of the Undiagnosed Diseases Program (UDP) and subsequently the Undiagnosed Diseases Network (UDN) by the National Institutes of Health (NIH). In 2008, the UDP was established to provide a definitive diagnosis for seriously and chronically ill individuals with mysterious conditions, uncover new biological pathways, and advance medical knowledge [19, 26]. A large impetus for the formation of the UDP was the technological advances of the Genomic Era that provided an unprecedented ability to annotate and sequence the human genome and heralded the promise of precision medicine [27]. Over the intervening years, the UDP expanded into the current seven UDN clinical-sites, two sequencing centers, a metabolomics facility, and the UDN Model Organisms

Screening Center (MOSC). UDN patients benefit from the incorporation of comprehensive standardized clinical evaluation with advanced diagnostic testing including WES, WGS, RNA-sequencing (RNA-seq), metabolomics, and *in vivo* functional assessment in model organisms through the MOSC [26]. The MOSC is comprised of both fruit fly and zebrafish investigators who integrate cutting edge high-throughput *in vivo* assessment of candidate gene variants with simultaneous in-depth clinical phenotyping by UDN clinicians. Our research group serves as the principal site for the UDN MOSC where we coordinate frequent regular meetings, both in person and by video-conferencing, with the clinical and research investigators, review and analyze the human genetic findings for UDN cases submitted to the MOSC for functional analysis, as well as conduct the fruit fly animal studies for the UDN. Findings from our functional fruit fly studies are transmitted to the clinical sites for real-time discussion of the findings, interpretation of the relevance to the human condition, and designing subsequent animal model studies based on clinical insights. The synchronized bench and bedside investigations between the UDN clinical sites and the MOSC demonstrate great potential for accelerating the genetic diagnosis of complex disorders and determining disease mechanisms *in vivo* [28–30].

In addition to public initiatives like the CMG and UDN, are interdisciplinary research institutes founded on the principal that improving the understanding and treatment of human disorders requires effective bi-directional communication between scientists and clinicians. Such research institutes foster the growth of interdisciplinary collaborations both within and across institutes. Examples of successful interdisciplinary institutes include the Broad Institute at Harvard and Massachusetts Institute of Technology [31], and the Jan and Dan Duncan Neurological Research Institute (NRI) at Texas Children’s Hospital [21]. As we are members of the NRI, we can easily expand upon its concept and development. The NRI was established in 2010 to foster collaboration and communication among bioinformaticians, model organism biologists, systems neuroscientists, molecular biologists, human geneticists, and physician-scientists with the goal to catalyze progress in basic and translational research related to developmental and aging-related neurological disorders [21]. The interdisciplinary focus at the NRI is facilitated by and facilitates collaborations between hospitals and laboratories located in a large medical center, the Texas Medical Center [32–34]. A key component to the success of the NRI vision is the effective utilization of model organisms, such as fruit flies and mice, to study the development and function of the nervous system, as well as the pathogenic mechanisms underlying complex neurological disorders. This strategy is key to the discovery or co-discovery of the genetic basis of many disorders and understanding the mechanisms of disease. Frequent interactions and collaborations between clinical medicine and biomedical research at the NRI fostered our understanding of several diseases including Fragile X syndrome, Angelman syndrome, Rett syndrome, *MECP2* duplication syndrome, myotonic dystrophy, Parkinson’s disease, Alzheimer’s disease, Spinocerebellar ataxia type 1, Friederich’s ataxia, amyotrophic lateral sclerosis, Leigh syndrome, Charcot-Marie-Tooth, other inherited ataxias, neuropathies, lysosomal storage disorders, epilepsies, and syndromic neurodevelopmental disorders [21, 28, 35–42].

Finally, key partners in the growth of interdisciplinary disease-oriented biomedical research for neurological disorders are the private foundations that are often established by affected families or individuals who strive to uncover disease mechanisms and develop novel

therapeutics. Although they are individually smaller in scope than the larger-scale government-funded and interdisciplinary research institute initiatives discussed above, the cumulative efforts from advocacy groups and private foundations represent a powerful impetus for advancing research endeavors. Foundations such as Citizens United for Research in Epilepsy (CURE), Epilepsy Foundation, International Rett Syndrome Foundation (IRSF), Simon's Foundation Autism Research Initiative (SFARI), Friedreich's Ataxia Research Alliance (FARA), Cure Friederich's Ataxia (CureFA), National Ataxia Foundation (NAF), Muscular Dystrophy Association (MDA), and many others are instrumental in both financially supporting the expansion of disease-oriented biomedical research and bringing patients, clinicians, research scientists, and model organisms together to the frontlines of modern medicine [43–48].

Collaborative outreach strategies and tools for clinicians and research scientists

The Online Mendelian Inheritance of Man (OMIM) database reveals that for the ~8,000 known or suspected heritable disorders, only ~50% have an identified genetic cause with a known molecular basis [49]. However, this is likely an insufficient estimate as disease-causing alterations in new genes are discovered daily in rare patients and only about 30–35% of all patients with suspected genetic causes are diagnosed by current methodologies. The ability to provide *in vivo* functional significance to genetic alterations is critical to confirming the genetic diagnosis. Therefore, the development of outreach strategies and tools form a powerful foundation for deciphering the genetic causes and pathogenic mechanisms of human disease.

The growing population of data scientists and bioinformaticians are constantly building and enhancing technological tools to improve collaboration and data sharing of large sets of genomic data between clinicians and research scientists. What was once an esoteric collection of genetic and human phenotypic data is now organized into easy to consume and quick to access databases and websites that offer clinicians and scientists an unprecedented access to vast amounts of information. Databases such as Matchmaker Exchange [50] and GeneMatcher [51] greatly facilitate the transfer of human genetic data from bedside to bench. Matchmaker Exchange hosts collections of genetic information gathered from around the world and aims to address the challenges of finding genetic causes for patients with rare diseases. Through Matchmaker Exchange, patients, clinicians and scientists can upload or research their disease or genes of interest in order to gather information and connect with other individuals with similar interests. In contrast, GeneMatcher is directed more to research scientists by linking investigators with a shared interest in the same gene through a web-based platform for information exchanged and streamlined procedures. As we describe later, these tools are critical for improving our understanding of protein dysfunction in relationship to human disease.

Building on the success of GeneMatcher, the development of other web-based resources such as MARRVEL and Gene2Function seeks to integrate human genomic databases with known disease associations and biological information from model organisms. MARRVEL

is a platform to allow model organism researchers the ability to determine the evolutionary conservation of human genes and evaluate whether gene variants may have potentially deleterious effects in the human population [29]. Gene2Function also integrates gene conservation with human disease annotation, OMIM and disease associations from genome-wide association studies (GWAS), and peer-reviewed studies on PubMed [52]. The information integrated by Gene2Function is searchable by either gene or disease. Together, web resources such as MARRVEL, Gene2Function, and others improve data accessibility and provide a solution to surmounting the technical “language barriers” between medicine and science.

For clinicians and patients, the website PatientsLikeMe allow individuals with chronic illnesses to connect with others suffering from similar ailments [53]. Many similar patient-driven web resources have adopted the idea of crowd-sourcing for biomedical research such as providing healthcare outcome measures and disease progression data [54]. In fact, forums like PatientsLikeMe may soon become an even more significant resource for researchers and clinicians alike to foster communication directly with patients in order to better understand the disease trajectory of rare disorders as well as recruiting patients for future clinical trials. Patient registries are another excellent resource for the study of human disease as they are a powerful tool for understanding the disease course, examining treatment efficacies, determining clinical outcomes, and measuring quality of care [55]. International initiatives to develop and collate patient registries for rare and common diseases include the European Platform for Rare Disease Registries (EPIRARE) Project [56], Cross Border Patient Registries Initiative (PARENT) Joint Action [57], and International Rare Diseases Research Consortium (IRDIRC) [58].

This is not an exhaustive review of available web-based data tools, social media platforms, and patient registries but these selected examples serve to highlight different types of online resources that streamline the dialogues between patients, clinicians, and research scientists. The combined findings from human genomics and well-established model organisms such as the fruit fly (*Drosophila melanogaster*), zebrafish (*Danio rerio*), and mouse (*Mus musculus*), provide an invaluable resource for deciphering the pathogenesis of many complex human conditions.

Fruitful cross-species collaborations

In this section, we provide examples of our experiences as research and physician-scientists in utilizing model organism studies to build collaborations with clinical medicine for understanding the disease-causing mechanisms in neurological disorders. Traditional phenotype-dependent gene discovery is challenging for disorders that lack strong unique features to stratify the affected individuals and nearly impossible for sporadic disorders with rare occurrence. This is relevant to biologically and genetically heterogeneous neurological conditions such as autism spectrum disorders, schizophrenia, Alzheimer’s disease, and others. Fortunately, many of the technological advances of the Genomic Era provided new genome sequencing strategies, such as WES, to determine a genetic diagnosis that does not require a constellation of strong unique features to unify a group of affected individuals. The application of WES and WGS to the study of human disease greatly enhances the ability to

detect candidate disease-causing genetic alterations, but *in vivo* studies are often required to determine the likelihood that the genetic alterations are pathogenic. Therefore, we recognized early on that identifying clinical collaborators and building research networks with investigators and clinicians at both our local medical center as well as nationally and internationally is key for conducting model organism studies with a high degree of biological and pathological relevance.

Both forward and reverse genetic approaches between human disease phenotypes and model organism analysis are effective in ultimately providing and supporting a genetic diagnosis. The forward genetic analysis approach utilizes information regarding the consequences of perturbing specific genes in model organisms to guide the discovery of genetic alterations in the human homologs that are relevant to human disease (model organism genotype to human phenotype approach). In contrast, the reverse genetic analysis approach utilizes human disease phenotype and human gene alterations of interest to promote the study of their homologs in model organisms and assess the *in vivo* consequences of the gene variants (human phenotype to model organism genotype approach). Through these forward and reverse genetic approaches, the fruit fly, zebrafish, and mouse are the three most widely used model organisms for biomedical research of human disease because their genomes are comprehensively sequenced and amenable to sophisticated genetic manipulations, and each of these model organisms provide unique qualities relevant to different areas of concern for the study of biological mechanisms in health and disease (Figure 1). For example, zebrafish morphology and development provide critical insights into many aspects of vertebrate developmental biology and is well suited for large-scale *in vivo* drug screening. Furthermore, the similarities between the mouse and human genomes allow for the detailed dissection of the genetic basis of many human disorders that make mouse models amenable to the discovery and preclinical testing of new drug therapies. Finally, approximately 65% of human genes have a fly homolog and the fruit fly is a simple eukaryote that is convenient for fast and high-throughput *in vivo* studies of conserved gene regulation, protein function, and pathogenic mechanisms [25]. These assets and properties formed the basis for the development of the MOSC focusing on fruit fly and zebrafish models, as well as our collaborations with mouse biologists to further confirm or investigate our findings in a mammalian model.

Dissecting human disease pathogenesis through fruit fly biology

Among these three model organisms, the fruit fly is well suited for ascertaining the genetic diagnosis for human disorders due to conservation of protein function in evolution, short lifespan (~3 months), ability to rapidly proliferate in large numbers, cost-effectiveness, and the largest arsenal of genetic tools for precise manipulation of the genome and nervous system [59]. One example of how our research group utilizes web-based resources like Genematcher and research initiatives like the CMGs to identify clinical collaborators began with the identification that *Nardilysin* (*dNRD1*) mutations cause neurodegeneration in a fly genetic screen [23]. Nrd1 was found to be critical in the folding of α -ketoglutarate dehydrogenase (Ogdh), a rate-limiting enzyme in the Krebs cycle. The recognition that loss of dNRD1 function is deleterious to neuronal survival raised the possibility that loss of Nrd1 function in humans may similarly contribute to neurodegeneration. Since *NRD1* was not

previously recognized to be a disease-associated gene, we reached out to clinicians around the world through Genematcher [51] and identified a patient with a potentially pathogenic variant in *NRD1*. Concurrently, we collaborated with our local CMG colleagues who analyzed the CMG human sequencing databases and identified an individual with homozygous variants in *OGDHL* (*OGDH like*). Hence, both patients were identified through our global and local outreach efforts to clinicians and human geneticists and both patients exhibited neurodegenerative phenotypes with microcephaly and severe developmental delay. This example illustrates how a basic biological finding in the fruit fly prompted basic scientists in our research group to connect with clinicians and identify a new genetic cause for a devastating childhood neurologic disorder [23].

Another example from our research group of how clinicians are able to connect to basic research scientists through the UDN MOSC to diagnose rare disorders is the discovery that *Early B-cell Factor 3* (*EBF3*) mutations were found in individuals with a unique neurodevelopmental disorder [28]. *EBF3* is an atypical helix-loop-helix (HLH) transcription factor associated with many neurodevelopmental processes across multiple model organisms [60]. Since *EBF3* mutations were not previously associated with human disease, we performed *in vitro* cell-based assays and *in vivo* fruit fly studies to confirm the pathogenicity of the candidate *EBF3* mutations. The MOSC reached out to our clinical and research scientist colleagues at our institution's Center for Mendelian Genomics and the Baylor Genetics Laboratory to identify other individuals with similarly damaging *EBF3* gene mutations and similar clinical phenotypes. This example illustrates how the efficient diagnosis of a new human neurodevelopmental disorder through functional studies of genetic alterations in the fruit fly occurred through a continual dialogue between clinicians and model organism biologists. In addition, through the use of Genematcher and large-scale research initiatives, two other international collaborations concurrently discovered that *EBF3* mutations cause a unique neurodevelopmental syndrome [28, 61, 62].

Together, these and other recent examples [63, 64] highlight that diverse resources and research initiatives are beginning to transform our understanding of health and disease by opening dialogues between clinicians, human geneticists, and model organism biologists. Importantly, the recent growth of using fruit flies to model human disease has promoted our ability to rapidly confirm the pathogenicity of genetic alterations and determine the biological pathways that can now be tested in vertebrate models and human cells.

Zebrafish and mouse models for deciphering vertebrate neurobiology in health and disease

Studies of molecular and cellular mechanisms of health and disease in fruit flies is a useful adjunct to the analysis of developmental processes, neural circuit function, and behavior in vertebrate models such as zebrafish and mouse. Rather than providing an exhaustive survey of the literature, our goal is to provide an overview of the role of zebrafish and mouse models in the study of human disease and to briefly highlight how communication between clinicians and research scientists were integral to the success of these studies.

Zebrafish is well suited for the study of vertebrate development due to its amenability to visualizing developing organs *in vivo*, ~80% conservation of human disease genes, transient

genetic assays, genome-editing abilities, and amenability for small molecule drug screens [65–68]. Large numbers of developmentally synchronized, genetically homogenous zebrafish can be screened in microtiter plates to allow for rapid evaluation of a variety of compounds and dosages in parallel as well as monitoring for toxicity and adverse side effects *in vivo* [66, 69]. The zebrafish blood brain barrier functions similarly to the human blood brain barrier and thus unlike traditional cell culture based drug screens, this method confers the benefit of discovering drugs that are more relevant for human neurological disorders [70]. In fact, some zebrafish small molecule screens targeted to specific neurological disorders have led to drugs currently in clinical trials. One example is a chemical that was identified that partially ameliorated the muscle phenotype in dystrophin-null zebrafish models of the progressive muscle wasting disorder Duchenne's muscular dystrophy, which currently is a terminal illness with no effective cure [71, 72]. These zebrafish chemical screen findings were further examined in a mouse model of Duchenne's muscular dystrophy and found to similarly ameliorate the muscle phenotype in a mammalian animal model [73]. Such discoveries have great potential for translation into clinical applications for Duchenne's muscular dystrophy by connecting basic research and clinical scientists through international clinical trial networks and patient registries such as the Translational Research in Europe-Assessment and Treatment of Neuromuscular Diseases (TREAT-NMD), Muscular Dystrophy Association, and the Registry of Muscular Dystrophy (Remudy) [47, 74].

With regards to mammalian animal models, the similarities between the mouse and human genomes, evolutionarily conserved behavioral traits, relatively easy to maintain in a laboratory setting, and genome-editing abilities led to mice becoming the gold-standard for the mammalian model. These strengths are invaluable for studying the cascade of biological events in a mammalian system after newly identified genetic alterations are established as pathogenic in high-throughput animal models such as fruit flies or zebrafish. One example illustrating how biological findings in mice can guide the identification of previously unrecognized neurological disorders in humans is the bench-side discovery that increased levels of the transcriptional modulator methyl-CpG-binding protein 2 (MeCP2) due to an extra copy of the human *MECP2* gene was deleterious to neurological function and behavior in mice [75, 76]. At the time, only MeCP2 loss of function was known to be associated with a neurologic condition in humans called Rett syndrome [77]. However, prompted by the discovery in mouse models that both loss and gain of MeCP2 is damaging to neurologic function, the research scientists reached out to clinicians and human geneticists at several institutions, as well as clinical diagnostic laboratories. This led to the identification of a syndromic neurodevelopmental disorder in humans due to duplication or triplication of the *MECP2*-containing genomic region [78, 79].

The successful translation of model organism studies into clinical applications hinges upon the ability of basic scientists and clinicians to recognize the translational potential of biological studies in model organisms. Such recognition depends upon strategies to communicate clinical insights and model organism discoveries across disciplines. Physical proximity between hospitals and research institutes play a prominent role in bridging clinical and research scientists. However, model organism biologists in other research centers who may not have the benefit of physical proximity to facilitate in-person discussions may

identify collaborators through web-based resources, private disease foundations, or advocacy groups.

Concluding remarks

Discoveries from dynamic interdisciplinary collaborations between clinicians, physician-scientists, and basic biologists are rapidly transforming our understanding of the biological mechanisms of health and disease. The establishment of interdisciplinary research institutes like the Broad Institute and the NRI, formation of biomedical research consortiums like the UDN to combine clinical medicine with basic science for the diagnosis of rare disorders, integration of human phenotypes with large disease-oriented WES data sets from the CMG, as well as the growing list of web-based databases, patient advocacy groups, disease-specific foundations, patient forums, and social media platforms have changed the landscape of modern medicine and biomedical research. These diverse research initiatives and resources ensure that the ability to initiate discussions and collaborations between clinicians, bioinformaticians, model organism biologists, and other research scientists are increasingly at our fingertips.

In this review, we provide a brief summary of our experiences during these interdisciplinary collaborations and our application of model organisms to the study of human disease. We recognize that aspects of our experiences reflect the unique close physical proximity we share with patients and clinicians by virtue of the central location of our institute in a large medical center. This physical proximity facilitates in-person discussions that breakdown the language barrier between medicine and science and creates opportunities for research scientists to learn about interesting clinical cases. The lack of physical proximity is a significant barrier for scientists and clinicians to reach out to the each other in pursuit of these human disease oriented biological studies. However, the increasing availability of web-based resources such as Matchmaker, Genematcher, PatientsLikeMe, MARRVEL, and Gene2Function and technologies such as video-conferencing promote the development of close intellectual proximity between scientists and clinicians around the world.

Our research group connects with investigators both near and far through our neighboring institutions in the medical center and through these web-based resources. In our experience, the vast majority of clinicians and their patients were supportive of participating in research studies. The clinicians are instrumental partners and intermediaries in human disease studies. They are integral to communicating the goals and design of the research studies to the patients, aiding in the recruitment of their patients to the studies, providing essential human findings, and relaying the scientific discoveries directly to the individual patient. Furthermore, by maintaining dialogues between clinicians and research scientists, we are increasingly better equipped to surmount the barriers between medicine and science. In our experience, we find that clinicians are more eager to reach out to research scientists and model organism biologists for collaborative studies. Similarly, scientists are better able to communicate their scientific endeavors and discoveries to clinicians. The end result is mutually beneficial collaborations between medicine and science that advance our ability to diagnose, treat, and potentially cure many complex human disorders.

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Figure 1. Resources to facilitate dialogues between clinical, biomedical, and model organism research scientists

This illustration highlights available resources that can be used to develop interdisciplinary dialogues that combine the strengths of the expert clinician, basic and clinical research scientists, and model organism biologists. These resources are divided into three categories: research initiatives (orange box), patient-driven initiatives (green box), and web-based resources (blue box). The utilization of these resources facilitate bi-directional dialogues between medicine and science, which advance our understanding of human disease through studies in animal models such as fruit fly, zebrafish, and mouse. First, incorporate clinical phenotypes with comprehensive genetic sequencing and model organism studies to identify the phenotype to genotype relationship. Second, conduct *in vivo* functional studies that effectively utilize the strengths of various model organisms to comprehensively determine basic biology and mechanisms of disease pathogenesis. Third, translate the information obtained from interdisciplinary collaborations into clinical applications and optimize therapeutic interventions.