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Review

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.

Contents

1. 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

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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 an 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 bi-directional 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