frontiers in Drug Discovery

FIELD GRAND CHALLENGE
published: 28 July 2021
doi: 10.3389/fddsv.2021.728469

Post-Pandemic Drug Discovery and Development: Facing Present and Future Challenges

Bruno O. Villoutreix *

Université de Paris, Inserm UMR 1141 NeuroDiderot, Robert Debré Hospital, Paris, France

Keywords: drug discovery, drug development, artificial intelligence, small molecules, biologics, admet, clinical trials

The history of drug discovery and medicine is as ancient as humanity with, according to numerous historians, the first evaluation of the medicinal values of some herbs as early as a few thousand years B.C. in China and in India. Indeed, the practice of Ayurveda, traditional Chinese medicines and the evidence of medicinal practice in Egypt have been documented thousands of years ago. Then in Greece, Hippocrates started to transform medicine from art to science. Intellectual contributions of many great minds from different countries developed over two thousand years gradually established the foundation of scientific medicine. Modern drug discovery started to emerge by the end of the 20th century. Today, this immense field of investigation is characterized by highly complex, time consuming, expensive (yet profitable), often unsuccessful, multidisciplinary processes carried out by a myriad of local, national and international public and private organizations. These players may have divergent interests, and are sometimes driven by concerns other than patients' health. Given the complexity of drug discovery and development as a field, any attempt to improve the odds of success requires humility, consideration of opposing views and escaping intellectual silos. Although history cannot always foretell the future, there are certainly some lessons to be learned from the past. Strong statements about exploring only some specific scientific areas, with most of the time substantial budget cuts to other disciplines or other departments, should be avoided. For instance, in 1999, it was suggested that the Human Genome Project would transform drug discovery by 2010 and that by 2020 significant improvements in patient care through tailored therapies (personalized medicine) would take place. While the human genome project might change everything in the future, translation to new drugs has been limited (Joyner and Paneth, 2019). The problem is obviously not the human project in itself but the fact that it was oversold, expectations were not realistic and the complexity of the human body in the health and disease states largely underestimated. Along the same line of reasoning but about technologies, J. Bezdek proposed in 1993 a curve showing how technologies tend to progress with time and in silico drug design strategies were analyzed with this approach (Van Drie, 2007). The "Bezdek phases" usually involve an overreaction to immature technology, a peak of hype, followed by despair because the results do not match the expectations. Eventually, after years of efforts, true user benefits are noticed. As today artificial intelligence is increasingly over-advertised in drug discovery and development, the Bezdek theory may apply, suggesting that a curious enthusiastic but cautious approach is advisable (Schneider et al., 2020). Related to this is the need of high quality data that are often missing or maintained confidential in health-related research (Scannell and Bosley, 2016; Bender and Cortés-Ciriano, 2021). Nowadays, while fashionable research topics appear unavoidable, decision makers, scientists and patients should keep in mind that hype cycles may turn out to hype bubbles and that such cycles can be detrimental to science (Rinaldi, 2012).

In the field of drug discovery and development, several different challenges seem to be awaiting us and the dramatic COVID-19 pandemic could be one catalyst accelerating the changes (Aghila Rani et al., 2021). Among the numerous challenges, some are briefly discussed below.

OPEN ACCESS

Edited and reviewed by:
José L Medina-Franco, National Autonomous University of Mexico, Mexico

***Correspondence:**
Bruno O. Villoutreix
Bruno.Villoutreix@inserm.fr

Received: *21 June 2021*
Accepted: *08 July 2021*
Published: *28 July 2021*

Citation:
Villoutreix BO (2021) Post-Pandemic Drug Discovery and Development: Facing Present and Future Challenges. Front. Drug. Discov. 1:728469. doi: 10.3389/fddsv.2021.728469

ENHANCING OUR UNDERSTANDING OF DISEASE BIOLOGY, CONSIDERATION OF PATIENT HETEROGENEITY AND MORE

This is a recurrent problem in the field and despite tremendous progress these last 30 years, we still have a limited understanding of disease pathology and progression, and of variability in disease presentation. As such, the list of unmet therapeutic and societal needs remains long while disease-severity and condition-severity have also to be considered in health-care priority setting. Early drug discovery research usually starts by the search of putative therapeutic targets and pathways that seem associated with a disease. The biological hypothesis is then tested on cellular and animal models that are, in numerous cases, too far away from human biology. Thus, these past decades, heavy reliance on often inappropriate surrogate biology, early in the discovery process, certainly contributed to many failures. For example, the difficulty in translating cancer research into therapeutics is well-known (de Bono and Ashworth, 2010). Some authors have reported that the average rate of successful translation from animal models (e.g., like following only the reduction of the tumor mass) to clinical cancer trials is less than 8% (Mak et al., 2014). In addition to the search of the right targets and pathways, the definition of a target patient population and a practical method to identify these cancer patients in a clinical context via appropriate biomarkers or companion diagnostics is required (e.g., stratified approaches). In part, related to these observations, Fojo et al. have examined the anti-cancer drugs approved by the FDA between 2002 and 2014 (Fojo et al., 2014). They found that the mean benefit was 2.5 months for progression free survival and 2.1 months for overall survival. Cancers are not only a genomic driven alteration but involve complex dysregulation including genetic, epigenetic, proteomic, metabolic, and structural alterations, with a lot of shedding systems.

In depth characterization of targets (e.g., proteins, nucleic acids, cell membranes…) and pathways using human-based systems as early as possible in the process should lead to the development of novel and better therapeutic agents in all disease areas. For some pathologies, following preclinical studies, phase 0 approaches which include microdosing could be highly valuable to further improve the quality of the drug candidates entering clinical development and to reduce attrition rates (Burt et al., 2020). For this to happen, patients and their carers should be empowered to contribute to the drug discovery process. Explanations about the process should be clearly provided, from the drug discovery steps (the pros and the cons of the different therapeutic agents including the costs) up to the clinical trial phases. With the emergence of new technologies during the COVID-19 crisis (thousands of clinical trials have been put on hold since the pandemic began), decentralized clinical trials powered by smart devices that are able to monitor patients automatically directly from home are gaining momentum. Such systems could definitively assist drug discovery and development beyond clinical trials.

CLINICAL SUCCESS: BETTER PREDICTION OF EFFICACY AND SAFETY

Related to the above, cutting-edge technologies are needed to improve our ability to predict the clinical success of a drug candidate. A significant amount of work is ongoing in an area that is often referred to as investigative toxicology (Beilmann et al., 2019). Humanized models, such as organ-on-a-chip, 3D bioprinting and organoid models, provide an environment in which cells behave more like they would in the human body, generating data that are more relevant than with the previously used methods. Gene editing technologies such as CRISPR/Cas9 should facilitate the development of more relevant animal disease models while patient-derived xenograft models, and various types of imaging approaches (e.g., to detect biomarkers) should help to predict the clinical effectiveness of candidate drug molecules. Stratified medicine and then personalized medicine or individualized medicine or precision medicine using many "omics" data (not only genomics) will also contribute, but such approaches are going to be unevenly distributed for many years to come, both in terms of diseases and geography. For these approaches to be fully successful, the general public will need reassurance on data confidentiality. In this context, collecting and curating high quality data should allow for the development of novel ADMET (absorption, distribution, metabolism, excretion and toxicity) in silico prediction tools that could use various types of algorithms, from machine learning, artificial intelligence up to approaches that take into account the tri-dimensional atomic structures of all the molecules in a dynamic state within a cell.

DIFFERENT THERAPEUTIC AGENTS ARE NEEDED

Although not exactly a challenge per se, this topic requires attention because of many misleading statements suggesting that "biologics" mean innovation. There is a wide variety of therapeutic agents including different types of small molecules (synthetic, natural products, nucleic acids, carbohydrates, short peptides, stapled peptides…) and of "biologics" (recombinant proteins, antibodies, often immunotherapies although some small molecules can also be used, siRNAs, cells, genes… and vaccines can also be listed in this category). Some treatments involve the combination of different therapeutic agents. In some cases, antibodies are combined with a small molecule (e.g., antibody-drug conjugate), in other situations, heterobifunctional small molecules composed of two active domains and a linker (proteolysis targeting chimera or PROTAC) can be designed. These drugs and drug candidates act via various molecular mechanisms (far from being understood in many cases) that can be monitored by using various advanced biophysical approaches and in silico simulation engines. Radiation therapy

and surgery are making important progress while cell and gene therapy are at the time of writing essentially in development. Drugs may be dosed intravenously, orally, topically, or by other routes of administration but oral administration (essentially small molecules) is the most convenient and patient's preferred route of administration (if possible). Biologics can possess outstanding qualities but, for the time being, they tend to be difficult or impossible to administrate orally although developments are ongoing in this area (Homayun et al., 2019). Biologics are generally much more expensive to develop, and/or produce, and/or store (e.g., in refrigerators, a problem in many countries) with treatment for one patient easily reaching over $100,000 per year and much more when it comes to gene therapy (at least at the time of writing). Although the price of biologics may drop in the coming years, this trend has not been observed thus far. Of course prices per se are of different nature than medical parameters, yet they have to be taken into consideration. It is important to note, although most people know, that the healthcare systems in most countries were about to collapse before the COVID-19 crisis (very high costs due to the prevalence of multiple chronic diseases, highly complex diseases. . .), and the pandemic may impact negatively for some years these already fragile systems. Thus, while working on drug discovery, drug accessibility and affordability cannot be ignored. When looking at drugs approved by the FDA from 2010 to 2019, it was found that a total of 289 concerned new molecular entities (NMEs, a drug product containing as active ingredient (and maybe soon active moiety) a small molecule), 89 biologics and 27 biosimilars (a molecule with no clinically meaningful differences from a reference product and highly similar to a reference product) (Brown and Wobst, 2021). In that study, it was observed that the proportion of approved biologics did not change over the past decade while the top five therapy areas considering both, NMEs and biologics, were oncology (25%), infectious diseases (14%), CNS disorders (12%), metabolic disorders (7%) and cardiovascular diseases (6%). From these observations, it is difficult to consider, from a pure scientific standpoint, that innovation concerns only "biologics". In fact, innovation is here very difficult to define because several meanings emerge from different perspectives. Innovation can be everywhere, on the therapeutic agent, on the putative target, on the mechanism, etc. For instance, a breakthrough innovation can come from small molecule drug repurposing strategies, it could be because the drug targets the drivers of a disease, or it could be a small molecule that inhibits protein-protein interactions (PPIs) like the Bcl-2 inhibitor venetoclax, an orally active anti-cancer drug approved by the FDA in 2016. Why this example is important in this context? Fundamental processes in living cells are largely controlled by several hundred thousands of PPIs and dysregulations of PPIs contribute to the pathogenesis of most diseases (Villoutreix et al., 2014). Also, infectious agents usually enter the host cells via PPIs as seen with the interaction of the SARS-CoV-2 Spike protein and the host angiotensin-converting enzyme 2 (ACE2) receptor. Most PPIs remain undrugged and in addition, PPIs have been largely considered to be undruggable by small molecules for the last 30 years. But, new types of chemistry are being developed that can be guided by artificial intelligence approaches allowing to explore unknown regions of the almost infinite chemical space with powerful algorithms and strong computer cluster or cloud. Now, if one considers cystic fibrosis, an inherited, multi-organ disease caused by mutations in the CF transmembrane conductance regulator (CFTR) gene, at present, only a combination of three small molecules (elexacaftor, tezacaftor, ivacaftor) improves lung function and the quality of life of some patients. Cell-based therapies and gene editing technologies (e.g., CRISPR/Cas9) could here be very valuable but so far, numerous problems remain unsolved (Allan et al., 2021). To face the global COVID-19 pandemic, various types of vaccines including mRNA-vaccines were developed in less than a year (in part due to studies carried out on SARS-CoV-1 since 2003 and then efforts on MERS). This is a triumph in the area of drug discovery, but other types of therapeutic agents (e.g., antibodies, small molecules, peptides) are urgently needed considering that new variants may partially escape the current vaccines and that it will take time to develop yet some other vaccines and because there are huge variations in the efficiency of vaccine roll-outs between countries and even within them with the associated persistent low vaccine coverage (increasing the risk of novel resistant mutations to appear). Further, some patients do not tolerate vaccines while others are against (anti-vax groups). All therapeutic agents are needed, not one category over the others and the notion of innovation with regard to therapeutic agents decoupled from commercial interests. Finally, we are scientists, not fortune-tellers, and as such, it is not possible to predict the type of therapeutic agents that might be needed to face future pandemics or any other upcoming major health crisis 20 or 50 years down the road.

DATA SCIENCE, MACHINE LEARNING AND ARTIFICIAL INTELLIGENCE

Data volume tends to grow exponentially spurred by numerous high-throughput technologies and numerous devices. Big data are often described by the following characteristics: Volume, Variety, Velocity, Veracity, Value and Variability. The value of data can only be realized if they are transformed to quality data and turned to knowledge and then to actionable knowledge. In theory, the right data passed through various types of algorithms should help gaining a better understanding of diseases, in identifying better targets and pathways, in designing better therapeutic agents, in planning better clinical trials, in assisting stratified and personalized medicine strategies, in generating new ideas and hypotheses and in increasing the quality of the new drugs while in some cases, in speeding up processes. Impressive results have been noticed, from fast and accurate image analysis of tissue samples up to the generation of novel molecules.

Along this line, modern data visualization technics are needed including multi-omics data visualization approaches. The rapid adoption of high-quality electronic health records should also play a major role here but there will be no "free lunch" (Kohane et al., 2021). For these to occur, data management frameworks have to be developed and in this context the FAIR (Findable, Accessible, Interoperable and Reusable) backbone or alike is required with clear data and AI ethical rules including transparency, security and privacy. As mentioned above, a trust-but-verify approach is required and in drug discovery and development, the human component will remain essential for many years to come (i.e., the human-in-the-loop model).

ASIDE FROM TECHNOLOGY AND SCIENCE, A STRATEGIC VISION IS REQUIRED

Bureaucratization of research, budget cut, constant reporting and meaningless meetings, among others, are exhausting people and slowing down projects. Clearly, the development of new and sustainable funding models with public and academic participations is urgently needed so as to be able to performing properly all the necessary steps. In academia, drug discovery is most often fragmented, organized around principal investigators that seldom want to partially lose control over their favorite targets or chemicals. Translational centers facilitating the interaction between clinicians, basic scientists and the practice community are certainly of interest. Efforts to break down silo mentality are needed and platforms that facilitate exchange of ideas and discussions among departments and the private sectors should be developed. Yet, given the wide range of disciplines and techniques that are required for cutting edge drug discovery and development, translational centers are certainly not enough and drug discovery networks should also be developed. In all situations, and independently of the selected organizational model, integration and better usage of sophisticated technologies are of outmost importance. In all cases, the skills and talents of the individuals along the value chain will have to be acknowledged. Open innovation models and various types of public-private partnerships to find and to develop new drugs have been used already but they are not so easy to maintain in the context of competition. However, these partnerships are important so as to utilize the strengths and expertise of all parties. Progress in drug discovery will also require proper education and training at the interfaces among disciplines and interactions with patients, the citizens and the society should be empowered. Drug discovery endeavors definitively require nurturing the appropriate mindset and culture of the different stakeholders so as to create trust and the appropriate ecosystem enabling the development of new medicines. The COVID-19 pandemic could here play a role and be a catalyst for changes in both, the academic and private sectors.

Over the past half-century, remarkable progresses have been made in drug discovery and development as a field. Yet if we consider novel knowledge about disease biology and the use of modern technologies and holistic approaches, by 2040, one would expect that many diseases will be better diagnosed, prevented, cured, or eventually managed in some cases with nonpharmacological interventions. It is my hope that this vision turns out to be true. Scientists and clinicians will work hard and continue to make contributions to Human health and welfare. Frontiers in Drug Discovery aims at stimulating exchanges in the field and welcomes high quality publications related to the topics mentioned above.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

REFERENCES

Aghila Rani, K. G., Hamad, M. A., Zaher, D. M., Sieburth, S. M., Madani, N., and Al-Tel, T. H. (2021). Drug Development post COVID-19 Pandemic: toward a Better System to Meet Current and Future Global Health Challenges. *Expert Opin. Drug Discov.* 16, 365–371. doi:10.1080/17460441.2021.1854221

Allan, K. M., Farrow, N., Donnelley, M., Jaffe, A., and Waters, S. A. (2021). Treatment of Cystic Fibrosis: From Gene- to Cell-Based Therapies. *Front. Pharmacol.* 12, 639475. doi:10.3389/fphar.2021.639475

Beilmann, M., Boonen, H., Czich, A., Dear, G., Hewitt, P., Mow, T., et al. (2019). Optimizing Drug Discovery by Investigative Toxicology: Current and Future Trends. *Altex* 36, 289–313. doi:10.14573/altex.1808181

Bender, A., and Cortés-Ciriano, I. (2021). Artificial Intelligence in Drug Discovery: what Is Realistic, what Are Illusions? Part 1: Ways to Make an Impact, and Why We Are Not There yet. *Drug Discov. Today* 26, 511–524. doi:10.1016/j.drudis.2020.12.009

Brown, D. G., and Wobst, H. J. (2021). A Decade of FDA-Approved Drugs (2010-2019): Trends and Future Directions. *J. Med. Chem.* 64, 2312–2338. doi:10.1021/acs.jmedchem.0c01516

Burt, T., Young, G., Lee, W., Kusuhara, H., Langer, O., Rowland, M., et al. (2020). Phase 0/microdosing Approaches: Time for Mainstream Application in Drug Development? *Nat. Rev. Drug Discov.* 19, 801–818. doi:10.1038/s41573-020-0080-x

de Bono, J. S., and Ashworth, A. (2010). Translating Cancer Research into Targeted Therapeutics. *Nature* 467, 543–549. doi:10.1038/nature09339

Fojo, T., Mailankody, S., and Lo, A. (2014). Unintended Consequences of Expensive Cancer Therapeutics-The Pursuit of Marginal Indications and a Me-Too Mentality that Stifles Innovation and Creativity. *JAMA Otolaryngol. Head Neck Surg.* 140, 1225–1236. doi:10.1001/jamaoto.2014.1570

Homayun, B., Lin, X., and Choi, H. J. (2019). Challenges and Recent Progress in Oral Drug Delivery Systems for Biopharmaceuticals. *Pharmaceutics* 11. doi:10.3390/pharmaceutics11030129

Joyner, M. J., and Paneth, N. (2019). Promises, Promises, and Precision Medicine. *J. Clin. Invest.* 129, 946–948. doi:10.1172/jci126119

Kohane, I. S., Aronow, B. J., Avillach, P., Beaulieu-Jones, B. K., Bellazzi, R., Bradford, R. L., et al. (2021). What Every Reader Should Know about Studies Using Electronic Health Record Data but May Be Afraid to Ask. *J. Med. Internet Res.* 23, e22219. doi:10.2196/22219

Mak, I. W., Evaniew, N., and Ghert, M. (2014). Lost in Translation: Animal Models and Clinical Trials in Cancer Treatment. *Am. J. Transl Res.* 6, 114–118.

Rinaldi, A. (2012). To Hype, or Not to (O) Hype. *EMBO Rep.* 13, 303–307. doi:10.1038/embor.2012.39

Scannell, J. W., and Bosley, J. (2016). When Quality Beats Quantity: Decision Theory, Drug Discovery, and the Reproducibility Crisis. *PloS one* 11, e0147215. doi:10.1371/journal.pone.0147215

Schneider, P., Walters, W. P., Plowright, A. T., Sieroka, N., Listgarten, J., Goodnow, R. A., Jr., et al. (2020). Rethinking Drug Design in the Artificial Intelligence Era. *Nat. Rev. Drug Discov.* 19, 353–364. doi:10.1038/s41573-019-0050-3

Van Drie, J. H. (2007). Computer-aided Drug Design: the Next 20 Years. *J. Comput. Aided Mol. Des.* 21, 591–601. doi:10.1007/s10822-007-9142-y

Villoutreix, B. O., Kuenemann, M. A., Poyet, J.-L., Bruzzoni-Giovanelli, H., Labbé, C., Lagorce, D., et al. (2014). Drug-Like Protein Protein Interaction Modulators: Challenges and Opportunities for Drug Discovery and Chemical Biology. *Mol. Inf.* 33, 414–437. doi:10.1002/minf.201400040

Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.