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Immunoinformatics: Pushing the boundaries of immunology research and medicine

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ABSTRACT

Immunology has come a long way, from its early religious beginnings thousands of years ago, to the explosion of immunological data in the 21st century. Thanks to discoveries in immunology, our world has seen tremendous progress in how we understand and treat disease. However, a lot of unmet clinical needs remain, which require focused, real-time collaboration at the clinical and scientific research forefronts. Moreover, the current exponential growth in the generation of research data makes it impossible to handle, analyze, visualize, and interpret such data without the use of advanced computational tools. We think immunoinformatics- a discipline at the intersection of immunology and computer science- will greatly increase efficiency in research productivity and disease treatment.

This perspective paper aims to emphasize the role of immunoinformatics toward pushing the boundaries of immunology research. It will also illustrate its clinical applications, including disease prevention, diagnosis, prognosis, treatment, monitoring, as well as in drug discovery.

We believe informatics approaches will be implemented increasingly more frequently in research. Thus, here we also discuss a set of fundamental prerequisites to facilitate the efficient and ethical integration of informatics in research and ensure immunological advancements provide maximum benefits to society.

1. Introduction

Immunology, as the scientific discipline we know it today, was born in the beginning of the 19th century with the discoveries of phagocytosis by Elie Metchnikoff, and neutralizing antibodies by Emil von Behring and Paul Ehrlich [1]. Nevertheless, the roots of immunology can be traced back to the earliest human civilizations, intertwined with our inherent need to heal disease.

Given our primal need to heal disease, it is not surprising that the ancient medical systems, along with their gods, arose independently in various parts of the world [2–4]. In ancient Egypt we see Sekhmet, goddess of healing and medicine [5]; in India we see the rise of Ayurvedic medicine [6]. In Mesopotamia we see Ningishzida, god of the underworld and patron of medicine [4]; Ixtlilton, god of medicine in Mesoamerica [7]; and lastly, god Asclepius, healer of men in Ancient Greece [3]. These deities highlight the importance of medicine in the ancient world, which was initially practiced using rudimentary tools (forceps, scalpels, bone saws), endemic plants, herbs, and animal parts such as brain and snakeskin [4–9].

Fast forward a few millennia, advancements in the field of immunology based on the scientific method have transformed the way we diagnose, treat, and prevent disease. The 21st century has seen an exponential growth in the generation of research data –with immunology being one of the fastest growing fields in the biological sciences [10–12]. Despite the high pace of scientific output however, we still fall short in our ability to fully exploit the data generated [13]. Nowadays, we appreciate that most diseases are complex and multifactorial, and expectations from research are higher and louder than ever before. For example, social media were inundated with people's disappointment in the lack of a vaccine or treatment, even at the onset of the COVID-19 pandemic. As unrealistic of a demand as this may sound, from a researcher's point of view, the reality is that we are expected to achieve more, faster. The fact that a variety of safe and efficacious vaccines against SARS-CoV-2 were distributed around the world only a year after the onset of the pandemic is both one of the proudest achievements of modern science and a testament to its potential. However, we don't have to face another pandemic for research to function at its peak level. While there are treatments for most common conditions nowadays, patients and clinicians

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are no longer satisfied with therapies that have serious side effects. On the other hand, rare diseases are left largely unaddressed in the scientific and the drug discovery process [14], which on average has become less efficient and more costly [15]. Importantly, we want to prevent the emergence of disease altogether, based on early risk factors [16]. These unmet clinical needs require us to establish "peak performance" practices routinely.

We believe that this will be achieved by better integration of informatics in immunology research.

2. Immunoinformatics applications

Immunoinformatics, or computational immunology, is a field that connects computer science and immunology by usage of computational resources and methods to handle and understand immunology data [17]. Informatics has been incorporated in many immunological topics, from disease prevention and diagnosis to drug discovery (Fig. 1). Current uses rely mostly on interpretation of wet-lab immunological results using computational methods, but many advances in the field have already allowed for purely data-driven, *in silico* discovery to take place using publicly available data, as we will highlight below.

2.1. Disease prevention

One of the key capabilities of immunoinformatics in disease prevention is mapping immune epitopes, which can be used for vaccine design, allergy prediction, disease understanding and host-pathogen interaction analyses [18].

Advanced prediction algorithms are necessary in reverse and structural vaccinology, in order to effectively characterize pathogenic epitopes and design vaccines faster and more efficiently [19]. With the use Artemis Comparison Tool (ACT), comparative sequencing of viruses can elucidate extensive mutations, insertions and deletions. This can help in designing T-cell epitope-based peptide vaccines, and multi-epitope mRNA vaccines, with the mRNA vaccine for SARS-CoV-2 [20] and Zika virus [21], being two recent examples. A most recent example of reverse vaccinology using computational methods is the *in silico* study on the T-cell and B-cell epitope prediction for the SARS-CoV-2 virus [22]. Here they used the screening server RANKPEP, which employs the position-specific scoring matrix (PSSM) [23], the BepiPred and Kolaskar & Tongaonkar Antigenicity servers [24], which use hidden Markov models and amino acid propensity scale methods, as well as the server *AllerTOP* to compute allergenicity of the predicted vaccine-antigen [25].

Adverse effects of vaccines are highly personalized, with pharmacogenetic studies having identified polymorphisms in *HLA* and other genes that lead to vaccine-induced immune responses to various diseases [26–28]. For example, macrophagic myofasciitis (MMF) is an intramuscular reaction against all vaccines containing aluminum hydroxide [29], and immunoinformatics analyses have been able to correctly classify MMF patients using F-FDG brain profiles [30]. Moreover, 5–10% of vaccines do not provide adequate long term antibody levels [31]. Machine learning (ML) algorithms and tools will allow for personalized vaccination to develop, and molecular dynamics will permit theoretical epitope experimentation through atomic motion within a molecular system, rather than using traditional wet lab methods [32].

Additionally, phylogenetic analyses can determine the evolutionary relationship between viral strains, which can help in epitope prediction.

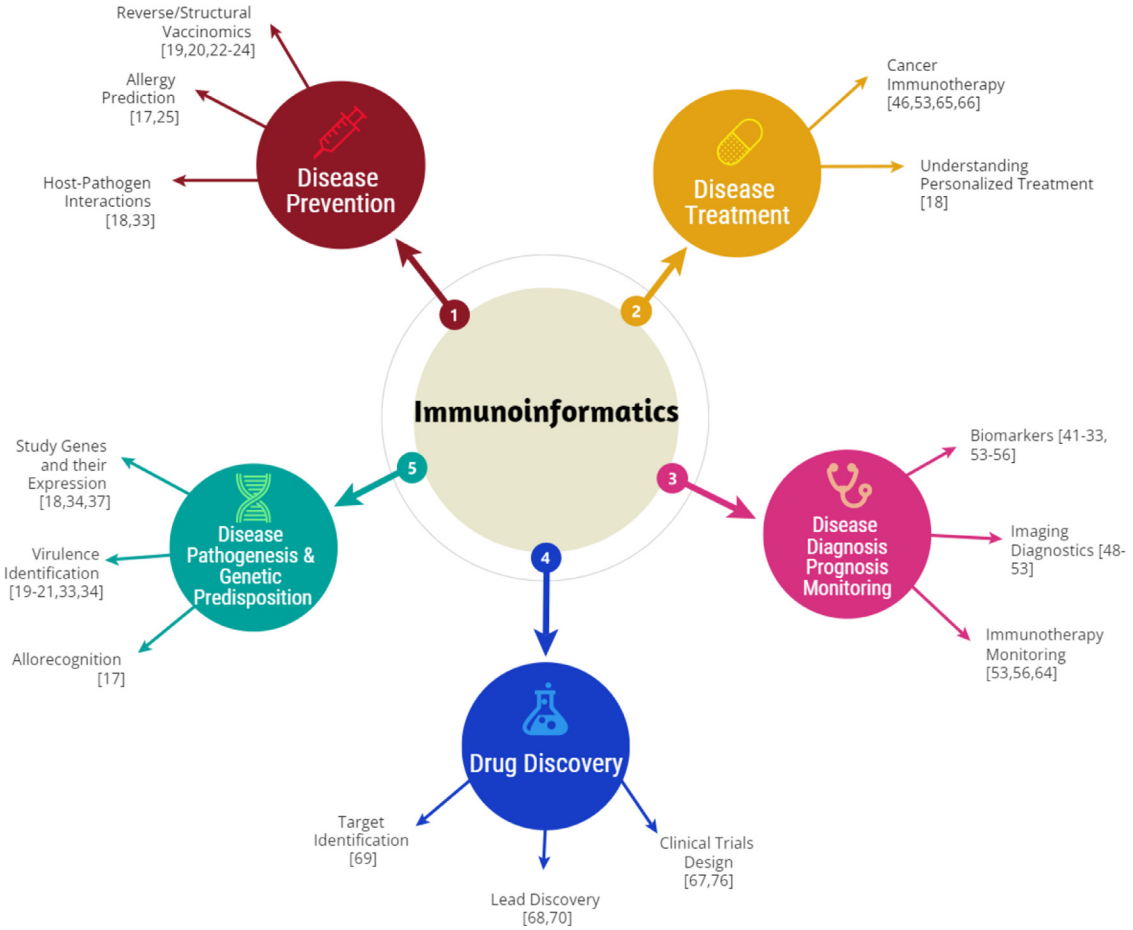

Fig. 1. Applications of immunoinformatics in medicine, drug discovery and research. Created with Venngage.com.

For example, evidence of horizontal gene transfer of two genes (*ORF8* and *ORF6*) was found in the HCoV-HKU1 strain of the SARS-Cov-2 virus, compared to the first Wuhan-Hu-1 strain, thus delineating the evolutionary trajectory of the virus [33].

2.2. Disease pathogenesis and genetic predisposition

Understanding host-pathogen interactions can answer questions regarding disease pathogenesis. Studies have indicated that *Herpes simplex* has gene products that are homologous to human proteins such as ApoE4 and Clusterin, which are implicated in Alzheimer's disease (AD), hinting at molecular mimicry as an underlying mechanism of AD pathogenesis following *H.simplex* infection [34,35]. These studies used resources such as the BepiPred server [36] in the Immune Epitope database [24,37]. Another team developed an algorithm called Compass, which uses single-cell RNA-seq and flux balance analysis to characterize cellular metabolic states and infer the pathogenic potential of Th-17 cells based on a metabolic switch [38].

Comprehending genetic predisposition to disease can direct people to take preventative measures, and thus reducing risk to developing the disease. Taking genotype datasets and using support vector machine (SVM) learning or random forest algorithms, disease prediction models have been created, linking single nucleotide polymorphisms (SNPs) to complex disease phenotypes such as celiac disease [39,40]. These cases highlight how informatics has become the foundation of contemporary omics studies, without which interpretation of data would not be possible.

2.3. Biomarkers for diagnosis, prognosis and monitoring

Biomarkers are invaluable in the clinical setting, and application of immunoinformatics on proteomic and immunomic data can accelerate biomarker discovery. Prognostic serum biomarkers for systemic lupus erythematosus (SLE) in the form of autoantibodies have been discovered [41,42], but initial evaluation tests do not offer pattern information for diagnosis. Using k nearest neighbor (kNN), an application was developed in order to accurately identify patients with SLE, thus benefiting them from an earlier and accurate diagnosis [43]. In another example, Galon *et al.* developed a methodology named Immunoscore, which allows quantification of the in situ immune infiltrate in colon cancer, a prognostic indicator that can be used in future clinical practice [44]. When Immunoscore is coupled with Artificial Intelligence (AI) such as ML, digital pathology-based cancer diagnostics can be accelerated, with more robust results [45]. Furthermore, a new procedure called FAUST (Full Annotation Using Shape-constrained Trees) was used to detect PD-1 expressing CD8+ T cell populations, making prognosis in a Merkel cell carcinoma anti-PD-1 trial possible [46].Moreover, with the aid of deep learning methods, an automated scoring of HER2 expression that can direct patients with breast cancer to the right targeted therapy has been developed, showing that computational approaches can facilitate clinical decision making [47].

Digitized whole slide imaging and AI have been used in disease diagnosis, monitoring [48,49] and detection, such as invasive ductal carcinoma [50]. Additionally, convolutional neural networks (CNNs) have been used at chest radiography, accurately identifying and classifying pulmonary tuberculosis [51]. A different representation learning approach, CellCnn, was used to reconstruct cell type-specific signaling responses and to identify diseased cell populations with HIV infection, as well as rare leukemic blast populations [52]. Lastly, imaging has been applied in predicting clinical outcomes of patients treated with immunotherapy [53].

Notably, a handful of diagnostic biomarkers have been developed and approved for diseases such as SLE and AD. However, most of them are not used clinically, because we do not understand their role in disease pathogenesis [54,55]. With ML tools and with precision medicine growing traction, it may be possible to salvage many of them [54].

2.4. Disease treatment

Autologous hematopoietic stem cell transplantation (AHSCT) replenishes the healthy immune cells pool following depletion of malignant or autoreactive immune cells [56,57]. Through clinical trials, AHSCT was demonstrated to effectively induce long-term remission in multiple sclerosis [58], type 1 diabetes [59], and other autoimmune diseases [58,60,61].

AHSCT, however, is a technology that is prone to failures, with cases of sepsis and viral reactivations [62]. For example, in rheumatoid arthritis, there is a gap between patient treatment with AHSCT and the positive response [63]. Discovery of robust and reproducible biomarkers, as well as adequately collecting, storing and assessing pre- and post AHSCT patient blood and bone marrow samples, will assist in immune monitoring [64]. In other words, biobanking will become crucial, assisting in AHSCT optimization, by enabling personalized treatment, depending on patient genetic and environmental background, thereby increasing AHSCT's utility. To this end, the integration of immunoinformatics in the analytical process is crucial.

Lastly, *in silico* research for epitope prediction in identification of cancer-specific neoantigens will assist in cancer therapeutics and immunotherapy. Efforts to create pipelines for this purpose have already been successful, with programs such as ProTECT that allow identification and ranking of tumor neoepitopes from patient data [65]. Prediction of tumor-associated neoantigens is another strategy for cancer therapeutics, with computational pipelines for somatic mutation calling and HLA-allele typing already established [66].

2.5. Drug discovery

Bringing a new therapeutic to market takes on average a decade and costs $2.5B [67], with cost of failure dominating the expenses [15]. This, coupled with a significant decline in drug discovery efficiency in the last 50 years [15], creates grand opportunities for informatics to improve the drug discovery pipeline. Advancements in computational methods along with ever-expanding databases for drug compounds, clinical records, and biomedical data [68,69] promise to enhance efficiency of drug discovery and development, and reduce risk of failure.

AI has been used in various phases of the pipeline, such as drug design [70–72] side effects identification in monotherapy or polypharmacy [73,74], and even excipient selection [75]. Furthermore, informatics can help identify the most appropriate participants in clinical trials, which is the costliest and most time-consuming part of the process [67,76]. For example, in some cases, exclusion rates of eligible patients who have comorbidities and use multiple medications can be as high as 80% [77]. Thus, matching most appropriate patients with a clinical trial using informatics will not only accelerate the testing process, but it will also enhance its success rate, by favoring an improved risk-benefit profile for the tested therapies. Ultimately, these informatics-aided approaches will lower the cost of drug discovery, while increasing the speed from inception to market, ensuring that more people have timely access to effective treatments at a potentially lower cost.

3. Future perspective

We are rapidly moving toward a world where immunology research is highly efficient, interconnected and democratized. At the center of this reality is the integration of informatics in every aspect of immunology. Based on current trends, we anticipate that in the future researchers around the world will routinely mine open access databases to test their hypotheses and use sophisticated, user-friendly tools, to design their bench experiments most effectively. Using informatics tools, the generated data will quickly turn into useful insights and effortlessly be deposited in the public repository for future use. In this paradigm, answering interesting immunology-related questions will no longer be a privilege of a few well-funded institutions, but a pursuit for anyone with

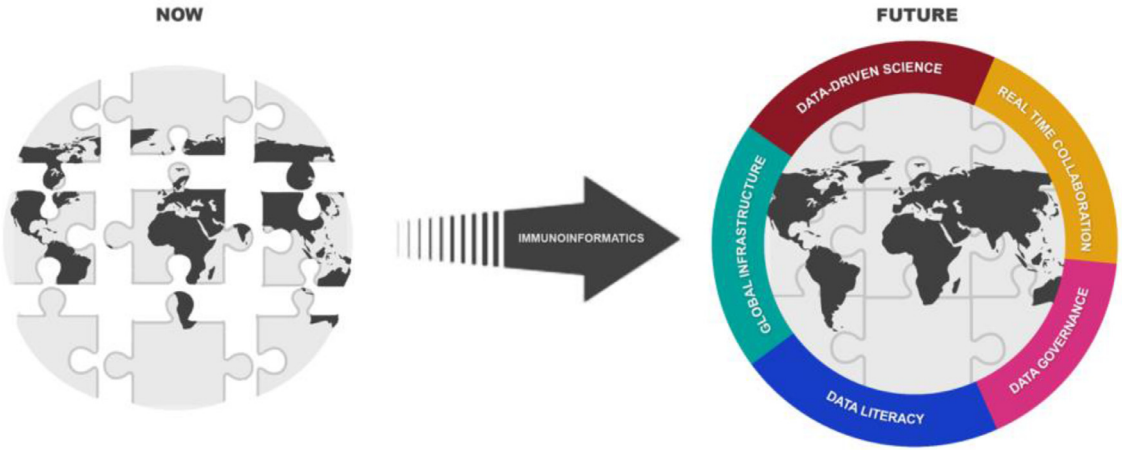

Fig. 2. Gearing toward an interconnected future of immunology research using informatics and enabled by five important elements; data-driven science, real time collaboration, data governance, data literacy and global infrastructure. Created with BioRender.com.

a computer and an internet connection [13]. As a result, immunology will be a familiar concept to the layperson, who will be open to routinely monitoring their immune system from personal data collected via wearable devices and personalized laboratory tests, which in turn will create more data for further research.

This real-time and democratized pursuit of immunology research around the globe, will propel biomarker discovery and the development of personalized vaccines, therapeutics, and disease management modalities at an unprecedented speed, at a much lower cost.

These are not exaggerated predictions of what immunology could become one day. In some sense, we are already there, as seen by the emergence of direct-to-consumer products and services that use AI and our biological data to improve our health. For example, in China, AI in health platforms are helping users manage their lifestyle to reduce chronic disease burden [78]. The company 23andMe estimates genetic predisposition to various diseases, based on one's DNA [79]. Similarly, an American company's mission "to make chronic illness optional", by recommending dietary supplements based on one's microbiome signature, is telling of the era we are headed toward [80]. To accelerate our progress toward this reality, we need to establish the five fundamental pillars below (Fig. 2):

1. *Data-driven science*. Currently, research is hypothesis-driven, which is limited by the deductive thinking of the human mind. Thanks to the abundance of research data, data-driven research will be possible, leading to the discovery of biological truths that would otherwise be unnoticed by the human eye. This data-driven approach better reflects the complexity of health and biological phenomena and could therefore be more relevant to discovery and clinical practice [13]. However, it requires a radical shift in the way we conduct basic research, from the established paradigm of: hypothesis–>wet lab experiment–> clinical translation, to: data analysis–>wet lab experiment–>clinical translation and potentially to: data analysis –> clinical translation [13]. Also, given the fundamental role of research data in the sustainability of data-driven science, we believe the mere generation of scientific data will be recognized as a worthy scientific achievement, thus broadening the definition of academic productivity and achievement. Indeed, the establishment of dataset journals, such as *Scientific Data (Nature)* and *Data in Brief (Elsevier)*, are a testament to these trends.
2. *Real-time interdisciplinary collaboration*. Scientific questions will be tackled simultaneously by several experts, resulting in efficient and clinically meaningful research output. Immunology researchers who are interested in understanding disease pathophysiology for example, will work in tandem with clinicians, statisticians, data scientists, and medical chemists at the same time. Thus, research will be conducted in large networks at improved efficiency and quality. Such large collaborations have already emerged in the form of interdisciplinary international consortia [81,82].
3. *Data governance*. Policies and principles adopted at the international level will provide a common framework for data labeling, storage, sharing, and mining, enabling full access and use of biomedical research data. An exciting initiative to this end is that of the National Institutes of Health (NIH), which guides and incentivizes researchers to produce datasets following principles that are FAIR (i.e. Findable, Accessible, Intraoperative, Reusable) [83]. We believe all countries should provide clear guidelines to standardize and streamline the lifecycle of research data and ensure that researchers adhere to ethical practices while making the most of the generated data.
4. *Data literacy*. Computational methods will be an integral part of immunology research; thus, everyone involved in a research network will sufficiently understand the fundamentals of data science and be kept abreast with computational tools and advancements that are relevant to their line of work. To this end, continuous improvement of data-relevant skills should be encouraged.
5. *Global infrastructure*. A large, networked community of researchers exchanging data in real-time requires the creation of a global public infrastructure that enables the storage, curation and mining of data for a wide range of users [13,84]. To prepare for this reality, research institutions and governments need to invest in the integration of advanced computational tools in biomedical research such as cloud and quantum computing, worldwide access to high-speed internet, and incentivize researchers to adopt new computational technologies that improve discovery efficiency.

4. Conclusions

With the exponential growth in immunology research and the advances in high-throughput technologies, we are faced with two contradictory challenges: On the one hand, the data deluge challenges our capacity to handle and capture value from data, thus necessitating the use of informatics in research. On the other hand, comprehensive, high-dimensional research data still need to be generated to improve existing computational tools [85]. Therefore, we believe the future of immunology is not a world where informatics overtakes bench work, but one where both disciplines are integrated (Fig. 2). We anticipate that this perspective will facilitate a growing dialog about the integration of informatics in immunology research to ultimately accelerate our progress toward disease prevention and medical care.

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