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Editorial

OMICS technologies and personalized vaccination in the COVID-19 era

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"I do not predict the future, but I observe it, because the future is here."
Gerd Leonhard

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The COVID-19 pandemic has powerfully brought the importance of vaccination in disease prevention back to the forefront. However, concerns remain about population groups that are undervaccinated, unresponsive, and/or have serious side effects. The presence of these groups represents a major health and economic burden on society that will become particularly difficult to address, especially in settings with limited public resources [1]. As recently stated, the core problem is that "vaccines do not save lives, vaccinations do" [2]. This means that the design of new vaccine candidates and the manufacturing of effective and safe vaccines may not be sufficient to meet the goals of a vaccination campaign; to reach approximately 100% immunization, it is crucial to understand the genetics, immunogenetics, and molecular mechanisms associated both with the inter-individual heterogeneity in vaccine-induced immune responses and with adverse side effects from vaccines. Based on these two assumptions, in 2007 a group of researchers from the Mayo Clinic (Rochester, MN, USA) coined the terms "vaccinomics" and "adversomics" [3]. The basis of vaccinomics and adversomics lies on the system biology approach, which integrates immunogenomics, proteomics, metabolomics, and bioinformatics to develop personalized vaccines at both the personal and population levels [4]. More recently, the system biology approach has been applied in conjunction with artificial intelligence and machine learning models [5]. On the other hand, reputable scientists claim the urgent need to develop universal coronaviruses vaccines broadly protective against all betacoronaviruses [6]. For this purpose, Anthony Fauci and his team prepared a list of ideal properties for a universal coronavirus vaccine [7]; among various properties indicated by the authors, the list includes vaccine safety for pregnant women, no limit in vaccine immunogenicity in persons with preexisting immunity, and the use of the vaccine in persons of all ages (universal). The purpose of a universal vaccine is challenging, especially because coronaviruses exhibit a high genetic diversity due to the generation of new genomes and homologous genetic recombination in multiple species. The question is: how could vaccinomics and universal vaccines be combined to reach 100% immunization coverage against all the coronaviruses? At first sight, the two visions are conflicting: vaccinomics is focused on tailored vaccines based on the individual molecular and immunological phenotype, while the universal vaccine is focused on the global immunization against all the coronaviruses by a unique vaccine. However, both visions are strategic; it is likely they could be realized with the substantial contribution of the system biology approach and, in particular, of metabolomics.

Recently, several articles have been published on the potentially extraordinary contribution that OMICS technologies can provide to this area of Medicine as well. One of them exhibits a strongly suggestive title, "OMIC Technologies and Vaccine Development: From the Identification of Vulnerable Individuals to the Formulation of Invulnerable Vaccines" [1]. The articles talk about how OMICS technologies, associated with bioinformatics tools, can be useful to identify new biomarkers of safety and immunogenicity for future studies on vaccines. This is in order to predict, prior to vaccination, the outcome of the vaccination itself in terms of efficacy and tolerability, providing highly predictive "signatures" of vaccine safety, immunogenicity and efficacy/protection, thus targeting personalized vaccine interventions in vulnerable populations [1, 8-10].

A further key concept refers to "systems vaccinology and big data" [11], where OMICS technologies, with their ability to capture the complexity of individuals and their immunological responses, may become real pillars of the future in this field, with a particular focus on the impact of the epigenome in the modulation of vaccination-induced memory in the innate or adaptive immune system [12]. Indeed, OMICS technologies capture the essence of global changes induced by vaccination and infection in the host, at the cellular and molecular level. For example, lipidomics and metabolomics identify infection-induced changes in lipids (free fatty acids, sphingolipids and lysophosphatidylcholines) and amino acids (tryptophan, serine and threonine), and unveil perturbations in the carbohydrate and bile acid pathways triggered by vaccination.

It is likely that the integration of metabolomics with other OMICS will improve knowledge in the molecular mechanisms associated with health and disease in humans [13]; furthermore, it is challenging to adjust/convert the ordinary pharmaceutical production pipelines to the so-called "multi-OMICS-guided customized production pipelines" for developing more effective and safe vaccines [14-16].

Very interesting is the work of McClenathan et al. aimed to identify metabolic biomarkers (by using an untargeted metabolomic approach and proton nuclear

magnetic resonance spectroscopy) for the prediction of adverse events after smallpox vaccination. Serum samples were collected from military personnel before and after smallpox vaccination. Basal pre- and post-vaccination samples from individuals who manifested clinically verified myocarditis or asymptomatic troponin elevation after vaccine were metabolically distinguishable before and after vaccination compared with both individuals who manifested only systemic symptoms and controls. Metabolomic profiles before and after vaccination differed substantially when an adverse event resulted. This study is the first describing the pre- and post-vaccination metabolic profiles of subjects who developed an adverse event after immunization, showing promise for the identification of predictive biomarkers [17]. These data are particularly important in light of what we are observing for COVID-19 in both adults and children [18, 19]. Another study evaluated, with metabolomics and transcriptomics, healthy young and elderly people immunized with the live attenuated herpes zoster vaccine Zostavax®. Networks associated with inositol phosphate, glycerophospholipids, and sterol metabolism were found to be closely related to immunity [20].

Two more metabolomic and transcriptomic studies involved the live attenuated vaccine against *Francisella tularensis* [21] and hantavirus (hemorrhagic fever) [22].

In a pilot study, the metabolomic composition of exhaled breath was characterized for early diagnosis and differentiation of influenza viral infection, as well as other types of respiratory viral infections [23].

Finally, it is worth mentioning a very recent Chinese preprint study (and therefore still under evaluation) [24], carried out on subjects vaccinated with Coronavax, an inactivated SARS-CoV-2 vaccine whose use was authorized by the WHO in the pandemic emergency. Several metabolites associated with the tricarboxylic acid (TCA) cycle and different amino acids and fatty acids metabolic pathways presumably linked to adaptive and innate immunity, differentiated vaccinated from unvaccinated subjects.

The impact of the microbiota on the vaccine response depicts an extremely fascinating chapter, for example towards the influenza vaccine [25, 26].

There are already studies in the literature demonstrating that the microbiota alters the immune response to rotavirus vaccination and suggesting further exploration and manipulation of the microbiome to improve the immunogenicity and safety of vaccines [27, 28]. These studies provide further evidence of the close interconnection between the metabolome and the microbiota, as we have previously reported [29, 30], and with particular regard to pharmacometabolomics [31].

Given that the individualized and predictive vaccinology requires the analysis of various human and viral variables, the development of a "universal" vaccine should be associated with the utilization of multi-OMICS-based strategies, combining data from genomics, proteomics, metabolomics, and metagenomics in conjunction with artificial intelligence algorithms and machine learning models. This challenge will be won if we are able to identify and track in the near future:

a. SARS-CoV-2 mutations;
b. new viral variants;
c. the individual's genetic background;
d. the molecular host response to vaccination;
e. vaccine immunogenicity, efficacy, and safety.

In conclusion, the application of OMICS technologies to vaccinations is crucial for several fundamental objectives:

1. to identify biomarkers predictive of vaccine efficacy/tolerability;
2. to assess and monitor the dynamics of COVID-19 cases, managing genomic surveillance;
3. to decipher the cellular transcriptomics response induced by the SARS-CoV-2 vaccination, with the aim to decipher mechanisms underlying risk factors.

Now we can rely on ideas, projects, technology, to face challenging objectives, such as the global immunization against SARS-CoV-2; however, the final success will depend not only on the science and scientists but even on the achievement of global policy strategies and adequate public health responses with available resources. United we stand, divided we fall.

Declaration of interest

The Authors declare that there is no conflict of interest.

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