



Editorial: ImmunoPhysics and ImmunoEngineering

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Editorial on the Research Topic

ImmunoPhysics and ImmunoEngineering

The immune system comprises a collection of specialized cells, tissues, and organs that protect the organisms against pathogens and can survey cancer cells. Immune responses are precisely coordinated events that take place in complex, specialized tissue microenvironments. For an integrated view of innate and adaptive immune responses at the molecular level, we ideally need a better understanding of how immune cells communicate and fulfill their tasks *in vivo*, following events spatially and temporally. Conventional biochemical and genetic methods consider the cell as an individual entity and ligand/receptor pairs as isolated systems. Often, the data obtained refers to the average behavior of a pool of cells and/or receptors removed from their real-life context. The use of new technologies, particularly real-time imaging approaches, is showing us that biological responses are very dynamic and extremely dependent on the context in which they take place and are therefore much more diverse than we initially thought. The combination of these new approaches is radically transforming and enriching immunology, as demonstrated by the increasing number of publications in which physical and/or engineering tools are applied to study the immune response. Whilst scientists are often questioned for the discipline their research is best framed in, we rather think that one scientific discipline cannot be reduced to the terms of another. However, defining and naming cross-disciplinary fields sets our minds on common ground and helps establish a fluent communication to eventually produce groundbreaking, beautiful pieces of science. For instance, ImmunoPhysics was probably first coined by Prof. Morikis a couple of decades ago (<https://www.biophysics.org/profiles/dimitrios-morikis>); nevertheless, ImmunoPhysics has not become widely regarded as a discipline, despite the continuously growing body of research that requires physical approaches to resolving immunological questions. Hence, with this special issue, we wanted to open a scientific platform compiling ImmunoPhysics and ImmunoEngineering research breakthroughs and future perspectives. Sadly, towards the end of this fascinating journey Prof. Morikis passed away; thus now, with this special issue, we would also like to pay tribute to his fundamental contributions to the field.

The qualitative and quantitative knowledge-advancement resulting from the application of physical and engineering methods and techniques in immunology is unarguable. Coordinated advances in physics and engineering technologies are revolutionizing our research strategies, contributing qualitatively, and quantitatively to breakthroughs in the understanding of immune system function and its regulation in health and disease. Probably, the overarching goals

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of ImmunoPhysics and ImmunoEngineering are to facilitate the development of therapeutic interventions to more precisely modulate and control the compromised immune response during diseases; but whereas ImmunoPhysics study and assess the physical basis of the immune response, ImmunoEngineering pursues its control and prediction. Possibly the greatest challenge for the growth of these fields is the establishment of fluent communication between physicists or engineers and immunologists. For this purpose, in this special issue, we aimed to provide a broad and interdisciplinary forum for researchers to present their personal views on the field, point to future challenges, and show their latest empirical or theoretical observations or method developments, with biomedical implications *in vivo*, *in vitro*, and *in silico*. Initially, we eagerly sought contributions employing highly advanced static or dynamic quantitative techniques spanning from conventional to super- or ultra-resolved microscopy in space and time to unravel protein clustering [1–8] or to disentangle the involvement of actin cortex dynamics and its mechanics in T-cell activation and synapse formation [9–15]; we also welcomed contributions applying steady and non-equilibrium quantitative fluorescence spectroscopic approaches to resolve receptor protein oligomerization and lipid-protein interactions and dynamics [16, 17] that can be applied to resolve immune-relevant events [18, 19]. Investigations employing systems immunology approaches, including quantitative and high-throughput assessment of the immune status and mathematical modeling of immune interactions [20–25] were also sought after; finally, we were also keen to include breakthroughs in the design or utilization of engineered tools and methods with applications to T-cell biology or immunotherapy [26–31].

Overall, we were gratefully surprised by the broad scope of approaches we were exposed to. For instance, in relation to the application of biophysical tools, including advanced light microscopy and electron microscopy methods, to better understand the molecular mechanisms of immuno-biological processes, we received two reviews: one describing the most used fluorescent microscopy approaches dealing with the polarized secretory intracellular traffic during the immune synapse (Calvo and Izquierdo), and another describing how techniques able to resolve elements at the nanoscale have contributed to the fundamental understanding of the immune synapse (Shannon and Owen). We also received three original articles, one showing a new developed method to track soluble mediators in the B-follicle at the single-molecule level (Miller et al.), another about possible artifacts occurring during chemical fixation in T cells (Pereira et al.), and another revealing novel structures in the podosomes formed at the dendritic cells employing correlative light and electron super-resolution microscopy (Joosten et al.). Regarding the use of *in silico* simulations and mathematical modeling of immune interactions and quantitative approaches to resolving lymphocyte dynamic immune-related events, we received four contributions: one resolving a structural model for the transmembrane domain of the B-cell receptor with molecular simulation (Friess et al.), another integrating experiments and theory to better understand the dynamics of the T-cell receptor and the cognate peptide

of the major histocompatibility complex (Buckle and Borg), a third employing molecular dynamics and electrostatic studies to evaluate the importance of two proteins of the membrane attack complex in the initial steps of the formation of the complement system (Zewde et al.), and a fourth employing mathematical models to predict the fate of a naïve T cell during migration and recirculation (de la Higuera et al.). We also received articles dealing with the study of the cognate interaction between antigen-presenting cells and T cells, where the roles of different proteins were investigated, such as the protein kinase C during polarized exosome secretion (Herranz et al.), TCR interplay with CD3/CD6 (Meddens et al.), and with CD28 (Xia et al.) during the immune synapse. We also include reviews dealing with the plastic cellular morphological changes during early activation, upon triggering, and during the immune synapse, involving perspectives spanning from the highly dynamic, very sophisticated, and complex reorganization of receptor kinases and phosphatases at the plasma membrane (Pérez-Ferreros et al.; Glatzová and Cebecauer; Junghans et al.), and its associated lipids (Baumgart et al.; Pettmann et al.; Gawden-Bone and Griffiths) to the full cytoskeletal reassembly (Martín-Cófreces and Sánchez-Madrid.) The current increasing interest in the role of mechanotransduction in T-cell biology also received attention, with contributions dealing with the application of different biophysical tools to reveal cellular forces or molecular sensing to understand the correlation between the highly coordinated forces exerted by cells with their chemical sensing and activation processes (Kolawole et al.; Harrison et al.; Brockman and Salaita; Rossy et al.). Also, some contributions showed how the application of systems immunology and protein and lipid engineering could help predict lymphocyte receptor recognition patterns (Hammerschmidt et al.; Gorby et al.; Nieto-Garai et al.; Hörner et al.). Finally, contributions are also included on how building sophisticated mimetic *in vitro* models, for instance by means of microfluidics, novel substrates, and hydrogels, can help to unravel the complexity of immune molecular events at the single-cell level (Benard et al.; Sinha et al.; Weiden et al.).

Overall, the greatest reward was to continuously receive contribution requests, even after the closure of the submission period and to observe that the number of manuscript views and downloads is continuously increasing. We truly believe that, thanks to the 30 contributions comprising this Research Topic, we have fulfilled our aim of editing an article collection that stimulates and facilitates a scientific forum for physicists, engineers, and immunologists, filling the cross-disciplinary gap, increasing awareness, and maximizing discussion and dissemination of ideas and methodologies in this nascent field. The next challenges in the ImmunoPhysics and ImmunoEngineering fields will probably be related to mechanobiology, immuno-oncotherapy, and the engineering of the tumor immunological niche. Correlating the highly coordinated forces exerted by cells with their chemical sensing and activation process is seemingly very challenging but eventually scientifically rewarding. Furthermore, immunotherapy is now widely considered to be one of the best approaches to treatments for certain types

of advanced cancer, and immune evasion is now recognized as a hallmark of cancer. The physical understanding of the immunological synapse underpins checkpoint therapies, and immunoengineering of T-cell specificity is the basis of CAR-T therapies. However, there is still much to learn about the physical mechanisms that differentiate responders and non-responders to these powerful therapies. We still have much to learn about engineering the tumor immunological microenvironment. One future goal of ImmunoPhysics could be to construct an accurate *in vitro* model tissue environment, where advanced microscopy and spectroscopy, force microscopy, and eventually optical and magnetic tweezers would enable measurement and manipulation of key physical parameters to improve

fundamental understanding, ultimately leading to applications in improved immunotherapies.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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

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