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DIALOGUE

A collective roadmap for spatiotemporal omics in combating infections

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This dialogue explores the transformative potential of spatiotemporal omics in reshaping the future of infectious disease research. Experts Zhihua Ou, Ziqing Deng, George Fu Gao, Andrea Cossarizza, Wenhong Zhang, and Aldo Tagliabue discussed the integration of multi-omics technologies to obtain high-resolution, dynamic, and spatiotemporal insights into disease pathogenesis. The conversation highlighted the key technical barriers that must be addressed for the broad application of spatiotemporal omics. Strategic research priorities were outlined, with a focus on diseases with high global burden and an emphasis on a "One Health" framework. The dialogue underscored the need to prioritize omics technologies based on specific biological questions and clinical goals. Major challenges in translating basic discoveries into clinical applications, such as data standardization, interdisciplinary collaboration, and ethical considerations, were also examined. Finally, the experts proposed strategies for the newly established SpatioTemporal Omics Consortium (STOC) Infection Working Group to foster international collaboration through cultivating a shared vision, developing interoperable platforms, and securing sustainable funding to effectively integrate global scientific talent and resources for substantive innovations.


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George Fu Gao


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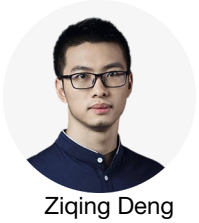
Ziqing Deng

Ou: Good morning, distinguished colleagues and esteemed experts. With the growing integration of multi-omics technologies to resolve the spatial and temporal complexity of disease pathogenesis, we seek to advance the application of cutting-edge spatiotemporal omics in infectious disease research. To achieve this goal, we must pool our collective wisdom (Figure 1). Dr. Deng, the spatial transcriptomics technologies developed by BGI Research (China), including spatial enhanced resolution omics-sequencing (Stereo-seq) and spatial enhanced-resolution single-cell sequencing (Stereo-cell), have unveiled considerable novel insights into cancer and developmental biology. From a technical perspective, how do you think spatiotemporal omics will benefit research in infectious diseases?

Deng: Firstly, I would like to explain the phrase "spatiotemporal omics", as it may be interpreted differently depending on the research scenarios. In a narrow sense, spatiotemporal omics specifically refers to the spatial transcriptomics technologies that can quantify thousands of RNA molecules while simultaneously preserving their spatial coordinates in the tissue. Some of these technologies, such as Stereo-seq, can reach single-cell or even subcellular spatial resolution. In contrast, the broadly defined spatiotemporal omics encompasses research that integrates multi-omic technologies and time-series observations. The goal is a holistic, dynamic understanding of how cellular states and interactions change over space and time. Here, I would like to focus on the broad perspective of spatiotemporal omics. This means integrating multiple omic technologies, including single-cell transcriptomics, spatial transcriptomics, genomics, proteomics, and metabolomics, to elucidate the pathogenesis of infectious diseases. Spatiotemporal omics technologies drive a paradigm shift in the study of host–pathogen interactions, moving research beyond bulk tissue analysis to a high-resolution, multi-dimensional framework. This enables the characterization of localized immune responses, cell–cell communication patterns, and specific cellular reservoirs responsible for pathogen persistence and cell clusters associated with tissue remodeling during infection. Based on matched multi-omics data, we will be able to dissect the key factors driving disease pathogenesis across multiple biological layers—from genetic traits and gene regulatory networks to gene expression profiles, ligand–receptor signaling pathways, and protein and metabolite dynamics. This comprehensive approach will enable us to identify key molecular pathways driving disease phenotypes, ultimately facilitating the discovery of novel biomarkers and therapeutic targets.

Ou: This sounds really exciting. However, the utilization of spatiotemporal technologies remains limited in infectious disease research. What technical barriers remain to be solved?

Deng: Indeed, significant technical barriers still impede the broad adoption of spatiotemporal technologies. Achieving true single-cell or subcellular resolution across tissue sections remains technically demanding, especially for tissues collected during acute infections that are largely composed of damaged or dying cells with low RNA content. Furthermore, integrating multimodal data (transcriptomic, proteomic, and epigenomic) from the same sample requires intricate project design and is usually resource-intensive. Moreover, detecting the low-abundance pathogen signals against the dominant host background is challenging, even with unbiased capture strategies. In some research scenarios, custom pipelines must be established for co-detection of microbial and host signals, such as enrichment of pathogen nucleic acids or removal of the cell wall of bacteria and fungi to facilitate RNA release. Addressing these technical challenges demands additional time and resources. Another obstacle is the requirement for advanced computational tools to accelerate analysis of the large volumes of sequencing data and to extract core scientific insights from the massive datasets. Moreover, when working with high-risk pathogens—especially those that must be handled in biosafety level 3 or 4 (BSL-3/4) containment—preparing samples for omics studies remains

Figure 1. Group photo
From left to right: Ziqing Deng, Wenhong Zhang, George Fu Gao, Andrea Cossarizza, Aldo Tagliabue, Zhihua Ou.

difficult because of biosafety constraints. Finally, most omics technologies are too costly for routine use in ordinary laboratories, significantly limiting their adoption and dissemination.

Ou: Thank you for your thorough answer. Prof. Gao, given the multitude of challenges in infectious diseases, how should we prioritize our research sequence? Which specific diseases or scientific questions represent the most strategic and feasible breakthrough points for launching a large-scale research initiative?

Gao: The issue you mentioned is very important in practical decision-making. Establishing priorities for infectious disease research requires a multidimensional and systematic evaluation, centered around five core elements. First, disease burden and public health impact, which encompass incidence, mortality, and socioeconomic costs, diseases such as tuberculosis and human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) remain high priorities. Second, epidemic and outbreak potential necessitate a focus on high-consequence pathogens and emerging infectious diseases (e.g., "Disease X″) to mitigate the risk of global pandemics. Third, gaps in response capabilities call for prioritized investment in areas lacking effective vaccines, therapeutics, or diagnostic tools, such as antimicrobial-resistant (AMR) bacteria, which are emphasized by the World Health Organization (WHO). Fourth, equity needs require a deliberate allocation of resources to neglected diseases that disproportionately affect impoverished regions and vulnerable populations. Fifth, technical feasibility urges researchers to leverage breakthrough opportunities offered by emerging technologies like mRNA vaccines and genomics.

Current strategic priorities include the following areas: First, addressing AMR challenges through the development of novel antibiotics and alternative treatment strategies. Second, combating major persistent threats such as tuberculosis, HIV/AIDS, and viral hepatitis by advancing new vaccines and shortened therapeutic regimens. Third, enhancing preparedness and control of emerging infectious diseases by developing rapid-response platform technologies. Fourth, fostering interdisciplinary efforts in areas such as broad-spectrum vaccines, point-of-care testing (POCT), and pathogenic mechanisms. Finally, the priority-setting process must adhere to the "One Health" framework, integrating human, animal, and environmental health, and employ transparent and inclusive mechanisms to ensure that research investments align with global public health needs while remaining scientifically feasible.

Ou: Thank you for sharing your insights. Our future omics research should be strategically framed around these key points. Prof. Cossarizza, given the availability of diverse omics technologies, do you think there should be a prioritization in their application? How do you assess the relative strengths and limitations of these technologies in both deciphering the mechanisms of infectious diseases and advancing clinical translation?

Cossarizza: It is crucial to prioritize the use of specific platforms, particularly when sample numbers are limited, resources are constrained, or budgets are tight. Not all platforms provide equally informative data for every scientific or clinical question; the choice should be guided by the specific immune mechanism or biological process under investigation, the type and amount of available material, and the ultimate goal—whether mechanistic insight or clinical translation. For example, if the focus is on the functional state of T cells during viral infection, conventional, spectral, and mass cytometry can quickly generate interesting and useful data. In this context, approaches that combine cell sorting, single-cell RNA sequencing (scRNA-seq) with protein profiling, such as cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq), are particularly informative, as they enable simultaneous characterization of transcriptional programs and surface marker expression, allowing a highly detailed identification of activated, exhausted, or senescent cells. Conversely, if the goal is to understand immune cell metabolism and its role in inflammation, metabolomics or lipidomics should take priority. Indeed, recent mass cytometry data show that metabolic patterns in vaccine-induced, antigen-specific T and B cells can vary among patients with chronic autoimmune diseases, depending on their therapeutic regimens.

Clearly, each technology has its strengths and limitations. Genomics allows identification of host or pathogen variants but offers limited functional information. Transcriptomics captures dynamic gene expression but does not always reflect protein production or post-translational modifications. Proteomics, high-parameter conventional cytometry, spectral cytometry, and mass cytometry provide functional insights at the protein level but often require larger cell numbers. Epigenomics reveals regulatory programs and immune memory but demands significant computational expertise. Finally, spatial technologies excel at mapping immune responses in tissue contexts, such as lungs infected by influenza, but they are costly and offer lower single-cell resolution compared to traditional scRNA-seq. From a clinical perspective, integrating these approaches is essential. A striking example comes from studies of the immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): by combining scRNA-seq, mass cytometry, and proteomic analyses, researchers identified subpopulations of T cells and myeloid cells associated with severe disease, providing predictive biomarkers of clinical outcomes. Similarly, integrated studies of vaccination, such as with Bacille Calmette-Guérin (BCG), have shown that monocyte epigenetic and metabolic programs reveal "trained immunity," offering novel avenues for therapeutic intervention.

In conclusion, I think that there is no single "universal" platform. Prioritization should be guided by the biological question, the resolution needed, and the anticipated clinical impact. A thoughtful, integrated approach—starting with the technologies most likely to yield actionable insights—enables better dissection of immune mechanisms and accelerates translation to the clinic.

Ou: Thanks for your valuable experience. Now I would like to ask Prof. Zhang, how can we systematically promote the application of basic discoveries from spatiotemporal omics into clinical diagnostics, vaccine development, and precision therapies? What could be the main barriers?

Zhang: Spatiotemporal omics has provided unprecedented resolution for infectious disease research, enabling the visualization of dynamic host–pathogen interactions across time and space. To systematically translate these discoveries into clinical

diagnostics, vaccine development, and precision therapies, coordinated efforts are needed on three fronts. First, establish cross-disciplinary translational platforms. Basic omics studies often remain at the single-cell or spatial transcriptomic level, while clinical practice focuses on actionable biomarkers and therapeutic targets. Integrating basic research, clinical samples, data algorithms, and validation models will allow scientists and clinicians to share resources, bridging the gap between discovery and clinical application. Second, align omics discoveries with unmet clinical needs. For infectious diseases, priorities include early detection of pathogen, stratification of host response, characterization of immune evasion, tissue injury, and repair mechanisms. Precisely aligning temporal and spatial sampling can transform molecular findings into diagnostic markers, vaccine candidates, and therapeutic targets with true clinical relevance. Third, build high-quality longitudinal clinical cohorts. Infectious diseases are highly dynamic and heterogeneous; systematic multi-timepoint, multi-tissue sampling is essential to map disease trajectories and immune responses, forming a foundation for personalized diagnostics and targeted interventions.

The major barriers may include the following three areas. Firstly, limited comparability of data and samples: variations in sampling time, anatomical position, and analytical platforms hinder standardization and cross-center integration. Secondly, challenges in cross-disciplinary collaboration: effective translation requires sustained co-development among bioinformatics, clinical, immunological, and pharmacological teams, rather than isolated cooperation. Thirdly, lagging ethical and regulatory frameworks: spatiotemporal omics involves high-dimensional and privacy-sensitive data, yet mature systems for data security, algorithm transparency, and traceability remain lacking—posing challenges for clinical translation and regulatory approval.

Ou: Indeed, these obstacles cannot be overcome by isolated efforts. Today, we're glad to witness the establishment of the SpatioTemporal Omics Consortium (STOC) Infection Working Group—initiated by BGI Research, Beijing and jointly led by Prof. Gao and Prof. Cossarizza—which has already drawn more than 50 experts from 40 institutions in 13 countries, signaling the field's growing commitment to spatiotemporal omics. How can we effectively integrate dispersed top scientific talent, clinical resources, and technological platforms to achieve substantive interdisciplinary and cross-institutional collaborative innovation? Do you have any suggestions?

Cossarizza: I think that integrating top scientific talent, clinical resources, and advanced technological platforms is both a logistical and conceptual necessity. The immune response is orchestrated across multiple layers—diverse cell types, signaling pathways, and tissue-specific organization—and no single lab or discipline can capture this complexity. Insights emerge when mechanistic immunologists, computational biologists, and clinicians collaborate closely, leveraging high-dimensional technologies such as single-cell transcriptomics, conventional, spectral, and mass cytometry, spatial proteomics, and metabolomics within coordinated workflows and centralized computational pipelines. During SARS-CoV-2 research, multi-omics analyses across patient cohorts revealed rare immune cell populations and transcriptional states invisible to conventional approaches. Cytometry and scRNA-seq identified exhausted and hyperactivated T-cell subsets, while proteomics and cytokine profiling captured systemic inflammatory circuits. Integration with clinical outcomes yielded predictive biomarkers of disease severity and immune protection. Studies of vaccination, such as the BCG vaccine, further highlighted how epigenetic and metabolic reprogramming of monocytes and T cells can be unveiled only through integrated multi-omics approaches.

Effective collaboration and integration of talent require not only infrastructure but also a culture and an incentive structure that promotes interdisciplinary dialogue and full international engagement. Standardized protocols, shared databases, and consortium meetings ensure that teams across different countries contribute synergistically. Mechanistic hypotheses generated at the bench can be rapidly tested against clinical data, while patient outcomes inform and refine experimental design, creating a dynamic, iterative process. Integration, therefore, is less about physical co-location and more about building an ecosystem where talent, technology, and clinical insight flow seamlessly across borders and disciplines. When such an ecosystem is established, the benefits are substantial: it enables the resolution of immune heterogeneity, identification of rare or tissue-specific cell populations, and rapid translation of mechanistic insights into clinical interventions. The multi-center, multinational efforts during the coronavirus disease 2019 (COVID-19) pandemic provide a prime example, demonstrating how international collaboration and the integration of expertise and technology can transform both our understanding of immunity and our ability to develop effective therapies and vaccines.

Ou: Yes, the working group must nurture an interdisciplinary network of experts and foster collaborative efforts centered on the core challenges. Prof. Gao, what's your opinion?

Gao: I believe an effective integration depends on three priorities. First, the establishment of a shared vision and a coordination framework among researchers and policymakers worldwide is of pivotal importance. That means agreeing on common scientific priorities and creating an inclusive structure that ensures all partners—whether from academic, clinical, technological, or governmental domains—have a voice in shaping the agenda. Without a unifying vision, even the best resources risk remaining fragmented and underutilized. Second, more efforts are needed to establish interoperable platforms. Data integration from multiple sources is often the bottleneck in collaborative science. If we can standardize approaches to data sharing, metadata annotation, and analytical pipelines, clinical observations, omics datasets, and technological advances can be combined in a way that accelerates scientific discovery and clinical translation as well. Third, innovation rarely comes from going it alone; instead, it more often thrives on cross-disciplinary exchange. This goes beyond occasional meetings. Sustained opportunities for interactions between experts of diverse disciplines, such as joint workshops, exchange programs, and collaborative funding, would drive genuine breakthroughs by enabling the serendipitous emergence of "sparks of wisdom", a term that also serves as the name of our small meeting room. Finally, I would like to emphasize the

importance of equity and sustainability. In order to make collaboration meaningful, all institutions, regardless of geography, disciplines, or resources, should have equitable access to platforms, data, and leadership opportunities. And we must think beyond single projects by building infrastructure and training programs that will sustain collaboration over time. In short, how to integrate dispersed expertise efficiently is the key. If we can align around shared goals, create systems that enable seamless collaboration, and foster a spirit of trust and reciprocity, I think this working group can achieve truly substantive innovation.

Ou: Great! An equal ecosystem with a shared vision and standardized tools for collective innovations. Your insights will surely benefit the future development of the STOC Infection Working Group. How can we establish long-term and sustainable funding channels? Prof. Tagliabue, do you have any suggestions?

Tagliabue: The advent of the first omics era, triggered by recombinant DNA technology, made it possible to develop the hepatitis B vaccine in the 1990s and sparked a renaissance in vaccinology over the following decades. This came thanks to the funding of several institutional donors such as the World Bank and the Bill & Melinda Gates Foundation (BMGF). Additional support came from Global Alliance for Vaccines and Immunization (GAVI), which initially focused on countering the three leading infectious killers—HIV, tuberculosis, and malaria—especially in developing countries. The recent pandemics exposed both our fragility in confronting infectious diseases and our lack of readiness for global health crises. This situation led to the creation of Coalition for Epidemic Preparedness Innovations (CEPI), which aims to accelerate vaccine development against emerging diseases and expand manufacturing capacity for safe, effective vaccines. The World Bank, BMGF, GAVI, and CEPI should therefore be among the first funding bodies informed of the STOC Infection Working Group and its high potential for fighting infections. To this end, a dedicated expert subgroup should be formed within the STOC Infection Working Group to engage these global funders and secure sustained support for the initiative.

Ou: Yes, we must take action as soon as possible to make the STOC Infection Working Group visible to funding authorities. How can we maintain openness and sharing in international collaboration while safeguarding national interests in critical technologies and data security?

Tagliabue: The geopolitical variations in the last decades and the profound revolution that occurred in science and economy globally have created a new world where Asia has assumed a co-primary role with the United States of America and Europe. But infections "have no borders" and the experience of the past pandemics has demonstrated how devastating the damage in terms of mortality can be and how large the economic loss can be. Maintaining openness and sharing in international collaboration while safeguarding national interests in critical technologies and data security may not be that difficult. A potential good model could be that of the Framework Programmes for Research and Technological Development of the European Union. These programmes (abbreviated FP1 to FP9) are created by the European Union/European Commission to support and foster research in the European Research Area (ERA). The funding programmes began in 1984 and continue to the present day. The latest, Horizon Europe (FP9), has a budget of 95.5 billion Euros to be distributed over 7 years. The specific objectives and actions vary between funding periods. In FP6 and FP7, the focus was on technological research. In Horizon 2020 (FP8), the focus was on innovation, delivering solutions to end users that are often governmental agencies. Although primarily aimed at the 27 European Union (EU) member states, the schemes are open worldwide for training and funding, and both academic and industrial partners can participate through public–private partnerships (PPPs); many critical issues have thus already been examined and resolved. Engaging the STOC Infection Working Group in a dialogue with the European Commission could be beneficial.

Ou: Thank you all for your invaluable insights—they will guide the future of the STOC Infection Working Group. Let us work together to resolve these challenges, advancing spatiotemporal technologies for infectious disease research, accelerating scientific discovery, and ultimately contributing to more effective prevention and control of infectious diseases worldwide.

AUTHOR CONTRIBUTION

Zhihua Ou: conceptualization, writing – original draft, writing – review & editing. **George Fu Gao:** writing – original draft, writing – review & editing. **Andrea Cossarizza:** writing – original draft, writing – review & editing. **Wenhong Zhang:** writing – original draft, writing – review & editing. **Aldo Tagliabue:** writing – original draft, writing – review & editing. **Ziqing Deng:** writing – original draft, writing – review & editing.

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DECLARATION OF COMPETING INTERESTS

The authors declare that they have no competing interests. Professor George Fu Gao is the founding editor and Editor-in-Chief of *hLife*.