Multi-Omics Research Trends in Sepsis

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Multi-Omics Research Trends in Sepsis: A Bibliometric, Comparative Analysis Between the United States, the European Union 28 Member States, and China

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Abstract

''-Omics'' research is in transition with the recent rise of multi-omics technology platforms. Integration of ''-omics'' and multi-omics research is of high priority in sepsis, a heterogeneous syndrome that is widely recognized as a global health burden and a priority biomedical funding field. We report here an original study on bibliometric trends in the use of ''-omics'' technologies, and multi-omics approaches in particular, in sepsis research in three (supra)national settings, the United States, the European Union 28 Member States (EU-28), and China. Using a 5-year longitudinal bibliometric study design from 2011 to 2015, we analyzed the sepsis-related research articles in English language that included at least one or multi-omics technologies in publicly available form in Medline (free full texts). We found that the United States has had the lead (almost one-third of publications) in the inclusion of an ''-omics'' or multi-omics technology in sepsis within the study period. However, both China and the EU-28 displayed a significant increase in the number of publications that employed one or more types of ''-omics'' research ($p < 0.005$), while the EU-28 displayed a significant increase especially in multi-omics research articles in sepsis ($p < 0.05$). Notably, more than half of the multi-omics research studies in the sepsis knowledge domain had a university or government/state funding source. Among the multi-omics research publications in sepsis, the combination of genomics and transcriptomics was the most frequent (40.5%), followed by genomics and proteomics (20.4%). We suggest that the lead of the United States in the field of ''-omics'' and multi-omics research in sepsis is likely at stake, with both the EU-28 and China rapidly increasing their research capacity. Moreover, ''triple omics'' that combine genomics, proteomics, and metabolomics analyses appear to be uncommon in sepsis, and yet much needed for triangulation of systems science data. These observations have implications for ''-omics'' technology policy and global research funding strategic foresight.

Keywords: sepsis, funding sources, bioeconomy, research policy, multi-omics

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Introduction

''-Omics'' technologies are key drivers for personalized medicine and modern public health, enabling effective screening and prevention programs, early diagnosis, precision treatments, and minimization of costs (Brand et al., 2016). ''-Omics'' research is currently in transition, further broadening the scope of its available technology base. Most notable in this context is the recent rise of multi-omics technology platforms in postgenomic medicine and integrative biology research. In an era where knowledge is being increasingly conceptualized as a public good, ''-omics'' technologies are contributing to a shift in the culture of science toward greater sharing of data. These changes are relevant in enhancing public confidence in science and have been also suggested to foster the innovation capacity of the biopharmaceutical industry (Evangelatos et al., 2016; Taichman et al., 2017).

The impact of ''-omics'' technologies on public health goes beyond their applications in medicine, being also conveyed by their economic and social externalities as a major pillar of the knowledge-based biotechnology innovation (Hafen et al., 2014; Jiménez-Sánchez and Philp, 2015). This fact underlines the significance of ''-omics'' in the field of global competition for economic growth and sustainability.

While ''-omics'' technologies, such as genomics, allow for systems-scale analyses, their separate focus on certain biological molecules (e.g., genome, proteome, and metabolome) also results in knowledge silos across molecules that are not isolated in a living organism, but work, instead, in concert. Such modularity, related to the singular use of ''-omics'' technologies, may result in piecemeal data and barriers toward real-life applications, such as precision medicine (Collins, 2010; Varmus, 2002), unless multi-omics methodologies are employed. On the business front, despite unprecedented global revenues of the ''omics''-based biotechnology industry, signs of slowing growth may suggest that this wave of initial success may have reached its peak (ey.com 2015), and that newer models, which better mimic real-life biology, such as multi-omics diagnostics, should be taken into account in business development.

This is especially relevant for complex diseases and syndromes, such as sepsis, where the disruption of the pathophysiological homeostasis is often caused by numerous, intertwined, subcellular biological events. Integration of data generated by various ''-omics'' technologies sheds light on such disorders within the different ''-omics'' regimes, allowing for precision diagnosis and targeted treatment (Langley and Wong, 2017; Sweeney et al., 2016). In this sense, integration of research efforts (either in terms of ''-omics'' data generated by single ''-omics'' technologies or in terms of multi-omics approaches) has a significant impact on the daily clinical practice; thus, the degree of integration may be considered a potential qualitative indicator of scientific performance on multiple levels, ranging from the researchers and the scientific journals to the research institutes and the (supra)national settings.

Although the need for integration of data generated by single ''-omics'' technologies has long been established and relevant strategies have been developed (Kohl et al., 2014), the discovery and exploitation of the appropriate data sources remain decisive challenges associated with data integration (Weidman and Arrison, 2010). In that sense, research that employs more than one ''-omics'' technologies and spans multiple layers of the ''-omics'' cascade (i.e., multi-omics research) is an important step toward integrated biology.

However, integration of ''-omics'' research faces significant hindrances. In a recent survey among researchers, funding was considered a crucial issue and funding priorities were also identified (Gomez-Cabrero et al., 2014); notwithstanding, the optimal ways to ensure that funding leads to multi-omics research remain elusive. With the new administration in the United States intending to downsize the 2018 National Institutes of Health (NIH) budget by 18.3%, or ~$5.8 billion, optimizing investments in research has become critical. Moreover, given that a $10 million increase in public (NIH) funding results in a net increase of 2.3 patents in the biopharmaceutical sector (Azoulay et al., 2015), this intended downsizing noted above may have wide-ranging implications for the research and innovation capacity of the United States in the knowledge-based biotechnology innovation (Katz and Wright, 2017).

Maintenance and optimization of the NIH budget under fiscal constraints have long been a fiercely debated subject (Loscalzo, 2006). Previous efforts have attempted to analyze medical research funding in different national contexts and correlate it with the created commercial (such as patents) or academic (such as publications) value (Moses et al., 2015). The relationships between federal and nonfederal (such as university) funding sources have also been studied, with results indicating that public funding has far-reaching effects in the biomedical sector.

As an end result of numerous, disorganized, activated pathways at multiple levels from the genome to the phenome, the septic syndrome has devastating consequences for patients and their families, and comprises a major public health concern (Shankar-Hari et al., 2016). The impact of sepsis on public health and the knowledge-based biotechnology innovation is not mediated solely by its effects on biomedicine. Septic infections affecting agriculture as well as livestock and fish farming also underline the relevance of sepsis for the knowledge-based biotechnology innovation. The septic syndrome requires, due to its systems impact and heterogeneity, a broad research agenda, employment of multiple ''-omics'' approaches in many different settings (e.g., from critical care units to fish farms), and commensurate funding (Skibsted et al., 2013). These attributes render sepsis a representative model for the study of research trends and inferences in the field of multi-omics research.

To the best of our knowledge, no previous effort has tried to capture research trends in multi-omics research among countries and possible associations with funding sources. We report here an original study on bibliometric trends in the use of ''-omics'' technologies, and multi-omics approaches in particular, in sepsis research in three (supra)national settings, the United States, the European Union-28 Member States (EU-28), and China.

Materials and Methods

Using a 5-year longitudinal bibliometric study design from 2011 to 2015, we analyzed the sepsis-related research articles that included at least one or multi-omics technologies. As we intended to provide a dynamic measure of ''-omics'' and multi-omics research in sepsis over time, we opted for a

longitudinal study over a cross-sectional one (Ployhart and Vandenberg, 2010). Our aim was to establish associations as a baseline for future research. While we did not employ modeling that considers lag times between the rise of multi-omics research and its applications in sepsis (Taris and Kompier, 2014), our longitudinal 5-year analysis offered new insights. The starting year for this analysis, 2011, relates well to the year 2010 when the need for multi-omics approaches began to be recognized.

The research was based on data mining with the use of specific search terms and MeSH strategy in the Medline database (supplemental material on methodology). All retrieved articles in ''-omics'' related research in sepsis published in the Medline database from January 2011 to December 2015 were reviewed by the authors (N.E., P.B., and C.K.), and those rendered suitable were included in the analysis.

To be included in the analysis, the articles had to be freely accessible (free full texts), written in the English language, and employ one or multi-omics'' technologies in sepsis-related research. Viral infections were included only in cases where they primarily (and not as complication of their course) lead to sepsis.

As our study focused on comparisons between (supra)national entities and countries, the selection bias of working with free full texts from Medline is uniform, and hence, does not have an impact on the methodological integrity of the study. Notably, there was a statistically significant and strong correlation between the total number of articles with ''-omics'' research in sepsis with the number of free full text articles with ''-omics'' research in sepsis through this period of time, (Supplementary Fig. S1). This means that free full text research articles were a key driver of ''-omics'' research in sepsis during the study period, further supporting our study design and focus on free full text articles.

The included articles were reviewed in detail by the authors (N.E., P.B., and C.K.) so as to further group them as ''-omics'' research, multi-omics research, and in regard to the source of research funding.

Insofar as the designations for multi-omics research are concerned, several methodological issues should be considered. For example, transcriptomics research is often preceded by manipulations of the genome (such as, for example, reverse transcriptase polymerase chain reaction and generation of complementary DNA [cDNA]). However, we chose to include an ''-omics'' technology as a distinct part of a research effort only when it clearly represented a separate step in an integrated methodological approach.

In addition, while genomics or transcriptomics relies almost exclusively on the use of certain methods, such as sequencing (Heather and Chain, 2016), this is not the case with proteomics and metabolomics. The large-scale study of the proteome and/or the metabolome may be conducted with an array of different technologies (such as mass spectrometry, immunoassays, and hybrid technologies) (Altelaar et al., 2013; Holmes et al., 2008). As a result, the classification of a methodological approach as proteomics and/or metabolomics was based not on the technology used, but rather on the conceptual framework of the research. For the same reason, the classification of the articles was performed manually (i.e., we thoroughly reviewed the articles), rather than with the use of a text mining tool, which might have been able to identify keywords and search terms, but not conceptual frameworks.

We categorized the articles as originating from the United States, the EU-28, China, or any other country based on the main affiliation of the first author. Although some authors may have conducted their research within the context of a visiting scholarship or a similar setting in a country other than hers/his, we do not consider the magnitude of the related bias to be significant for our analysis. The same assumption applies for the bias related to the selection of the English language as an inclusion criterion.

We considered the funding sources as originating from governmental or state institutions (e.g., NIH and governmental departments), or from universities, be they private or public. All other sources of funding were considered nongovernment and nonuniversity. Many of the other sources correspond to nonprofit organizations (e.g., foundations and nongovernmental organizations). Our grouping of the funding sources into three main categories, (1) government/state, (2) university, and (3) other, allowed us to have a perspective beyond public/private dichotomies, focusing on the organizational setting of the funding source (only government/state, only university, or nongovernment/state and nonuniversity). This, we believe, offers deeper insights that are relevant for future organizational policies in regard to multi-omics research funding.

In this study, it should be noted that, due to the relatively low number of multi-omics studies in every single year, we performed a pooled analysis of the multi-omics research studies along funding sources for the whole period of the study (January 2011 to December 2015). Finally, we should note that our analysis of the included research studies for their funding has focused on single sources, such as only government/state or only university, so as to be able to draw more robust conclusions. We recognize, however, that studies with multiple sources of funding warrant further research in the future in terms of the impact of funding source on multi-omics research use.

Results

In all, 1426 articles were retrieved for the years 2011–2015. Of those, 513 were unsuitable for inclusion in the analysis (336 not related, 117 reviews, 2 case reports, and 37 others, e.g., double entries). The results from the analysis of the remaining 913 articles are depicted in Figures 1–3 as well as Tables 1 and 2.

We found that the United States has had the lead (almost one-third of publications) in inclusion of an ''-omics'' or multi-omics research in sepsis within the study period. However, both China and the EU-28 displayed a significant increase in the number of publications that employed one or more types of ''-omics'' research ($p < 0.005$) (Table 1), while the EU-28 displayed a significant increase especially in multi-omics research articles in sepsis ($p < 0.05$) (Table 2). The percentages of studies with one or more ''-omics'' (Fig. 1) or multi-omics (Fig. 2) in the sepsis knowledge domain across different supranational regions are additionally shown. More than half of the multi-omics research studies in the sepsis knowledge domain had a university or government/state funding source (Fig. 3).

The total number of publications with multi-omics research increased significantly over time (from 29 in 2011 to 80 in 2015, Table 2). The combination of genomics and transcriptomics was the most frequent (40.48%), followed by

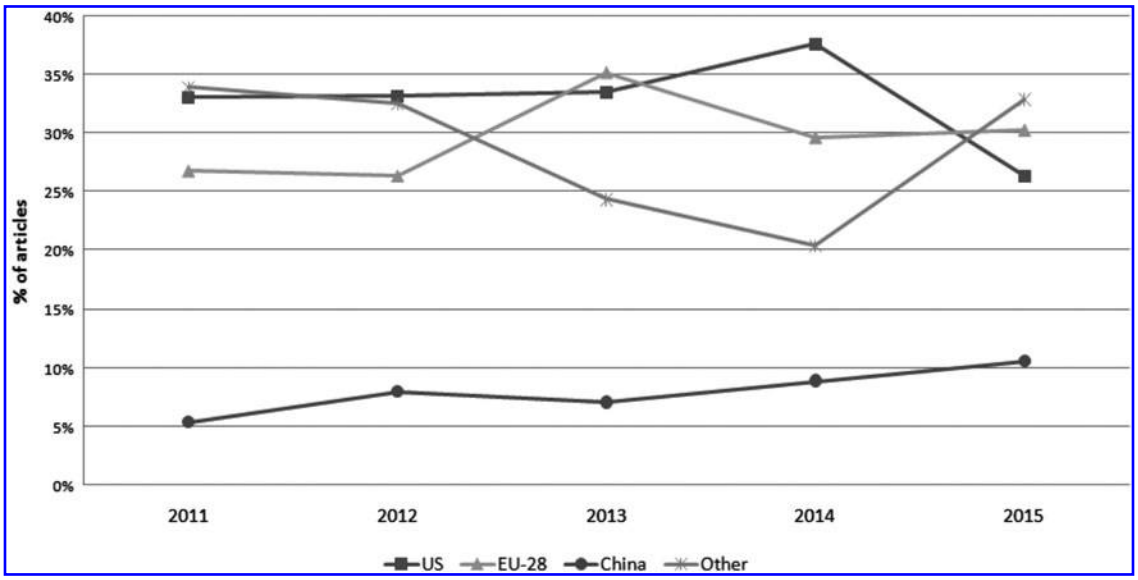

FIG. 1. Research publications that contain at least one or more ''-omics'' technologies in sepsis-related research from year 2011 to 2015, in each of the following geographical regions: the United States, the EU-28, China, and other regions. The data in each country/region and year are expressed as percentage (%) of total number of research studies with at least one or more ''-omics'' technologies in sepsis research in a given year. EU-28, European Union-28 Member States.

genomics and proteomics (20.4%), genomics, transcriptomics, and proteomics (13.8%) and transcriptomics and proteomics (9.3%). All other combinations of multi-omics efforts (for example, proteomics and metabolomics) were below 4%. Each year, with the exception of 2015, almost 40% of the articles presenting multi-omics research came from the United States (range 23.7–45.3%), whereas almost one-fourth of the articles originated from the EU-28 (range 22.6–27.9%, Fig. 2). On the other hand, the contribution of China in the multi-omics field in sepsis was around 10% (range 4.6–15.5%, Fig. 2).

The EU-28 showed a significant increase in the number of published articles with multi-omics over time (Table 2). On the contrary, China and the United States display a subtle and not constant increase of the number of such articles, which is not considered statistically significant (Table 2).

As far as the type of funding source is concerned, of the 913 articles included in the analysis, 416 received funding from a single source (government/state, university, and other), while the rest received funding from multiple sources. Of the former, 285 articles presented single ''-omics'' research efforts and 131 presented multi-omics studies. According to the pooled analysis of multi-omics research for the years January 2011–December 2015, 87.8% of the articles presenting multi-omics efforts over the years 2011–2015 received government/state

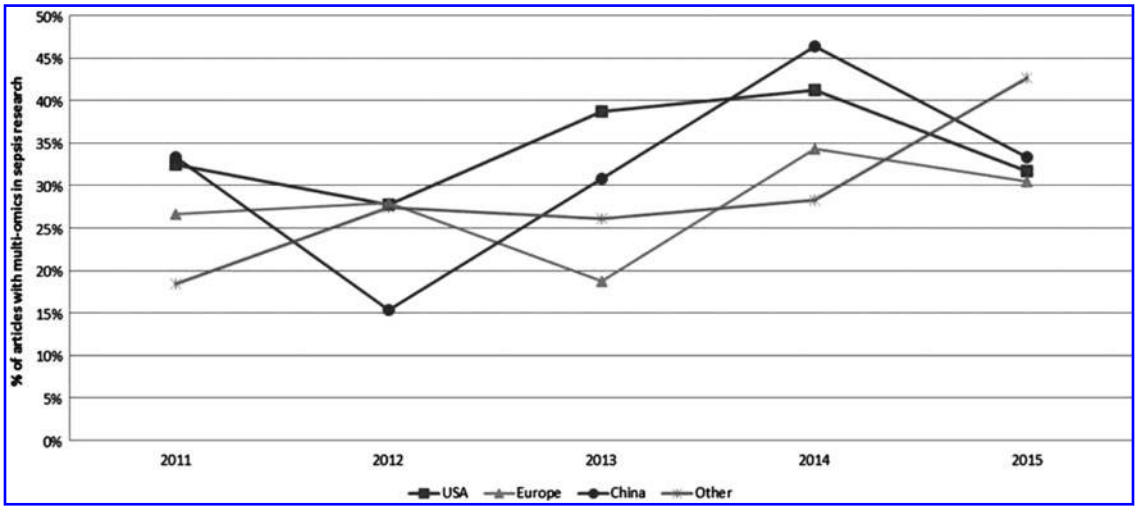

FIG. 2. Research publications that contain at least two or more (**multi-omics**) technologies in sepsis-related research from year 2011 to 2015, in each of the following geographical regions: the United States, the EU-28, China, and other regions. The data in each country/region and year are expressed as percentage (%) of total number of research studies with multi-omics technologies in sepsis research in a given year.

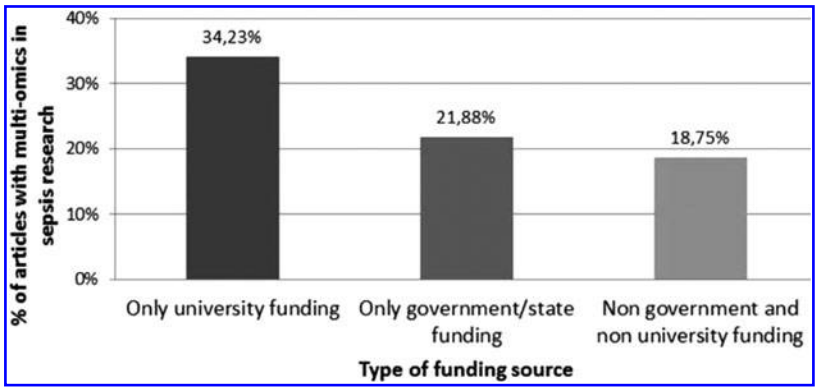

FIG. 3. Percentage of multi-omics research in sepsis according to the source of funding, pooled across years 2011 to 2015, and expressed in three organizational funding categories: (1) only government/state funding, (2) only university funding, be it public or private, and (3) other = nongovernment and nonuniversity. Note that more than half of the multi-omics studies originated from government/state or university funding scheme.

funding (115/131 articles, in comparison with university and nongovernment/state and nonuniversity funding, Fisher's exact test, $p = 0.047$).

On the other hand, more than a third (34.2%, Fig. 3) of the publications with (exclusively) university funding focused on multi-omics. On the contrary, only one-fifth of the articles with only government/state funding and less than one-fifth of those with nongovernment/state and nonuniversity funding resulted in multi-omics (21.9% and 18.7%, respectively, Fig. 3).

Discussion

Context for the study

One of the main reasons for the aforementioned relative underperformance of ''-omics'' in terms of both their clinical significance and contribution to knowledge-based biotechnology innovation is the extensive reliance on reductionism. Indeed, despite its groundbreaking contributions in the early days of molecular biology, excessive reductionism has underestimated the complexity of biological systems and the effects of emergent properties that have evolved over evolutionary time (Kim, 1999). Relying on simple causal chains and giving explanatory weight to single (mostly structural) factors, reductionism overlooks the functional complexity of biological systems and ignores the evolutionary insights into the reciprocal interactions between genes, organisms, and their environment (Van Regenmortel, 2004).

Furthermore, the perception of knowledge in modular terms has led to the uncritical adoption of research and business models from other sectors (most notably from the Information and Communication Technology industry), which cannot be readily applied to biomedicine. Developing a piece of intellectual property, such as, for example, a cDNA of a certain gene (Kesselheim et al., 2013), to secure financial profits through licensing or other business arrangements, may work well in the semiconductor sector, but is not that effective in biomedicine, where what matters most is the integration of pieces in an articulated whole (Buescher and Driggers, 2016; Pisano, 2006).

The first period of research in the era of genomic medicine, a period of ''normal science'' in the Kuhnian sense (Kuhn, 1996), has revealed these restrictions of reductionism and the existence of many levels in the ''-omics'' cascade between the genome and the phenome (Ebrahim, 2012; Houle et al., 2010). Although the boundaries among these different ''-omics'' regimes are often overlapping, genomics, epigenomics, transcriptomics, proteomics, and metabolomics are considered the main ''-omics'' layers that coproduce, along with environmental influences, the final phenotypes and their dynamic temporal and spatial variations.

In an era of fiscal constraints, funding of the various ''-omics'' technology platforms noted above and the related research needs to be rationally allocated to ensure generation of results that contribute to both public health and the

Table 1. Number of Research Publications That Contain One or More ''-omics'' Technologies in Sepsis-Related Research from Year 2011 to 2015

No. of publications with one or more ''-omics'' research in sepsis	*2011*	*2012*	*2013*	*2014*	*2015*	*Spearman's correlation coefficient*
United States	37	54	62	85	60	$R = 0.497$, $p = 0.184$
EU-28	30	43	65	67	69	$R = 0.861$, $p = 0.023$[a]
China	6	13	13	20	24	$R = 0.949$, $p = 0.005$[a]
Other	38	53	45	46	75	$R = 0.555$, $p = 0.149$
Total	111	163	185	226	228	$R = 0.9323$ $p = 0.008$[a]

The bibliometric analysis is based on the Medline database and focused on the open-access (free full text) publicly available research studies in English language. Results of the Spearman's correlation coefficient.

[a]Statistical significance.

EU-28, European Union-28 Member States.

Table 2. Number of Research Publications That Contain Two or More (Multi-omics) Technologies in Sepsis-Related Research from Year 2011 to 2015

No. of publications presenting multi-omics research in sepsis	*2011*	*2012*	*2013*	*2014*	*2015*	*Spearman's correlation coefficient*
United States	12	15	24	35	19	$R = 0.355$, $p = 0.289$
EU-28	8	12	12	23	21	$R = 0.821$, $p = 0.034$[a]
China	2	2	4	13	8	$R = 0.596$, $p = 0.126$
Other	7	14	13	13	32	$R = 0.669$, $p = 0.091$
Total	29	43	53	84	80	$R = 0.908$, $p = 0.012$[a]

The bibliometric analysis is based on the Medline database and focused on the open-access (free full text) publicly available research studies in English language. Results of the Spearman's correlation coefficient.
[a]Statistical significance.

knowledge-based biotechnology innovation (Fragoulakis et al., 2017). Integration of data derived from ''-omics'' technologies is considered crucial for the extraction of biological meaning and the apprehension of biological systems as a whole (Joyce and Palsson, 2006). This becomes ever more important in the era of Big Data, where technological developments allow us to integrate biological data with the so-called personomics, to pave the way from precision medicine to personalized medicine (Ziegelstein, 2017).

In this context, multi-omics research efforts, which involve more than one ''-omics'' regimes, are more likely to put research results in biological context, compared to studies that involve only one of the ''-omics'' layers that extend from the genome to the phenome. This is of particular interest for sepsis, which has been recognized by the World Health Organization as a global health concern and a priority research area for both funding bodies and commissioned research (Reinhart et al., 2017).

Key observations

Our data indicate that, over the years 2011–2015, the United States had the lead in ''-omics'' related research in sepsis, producing almost one-third of the relevant publications. This finding confirms that, contrary to the hypothesis of the so-called ''European Paradox,'' up to now, the EU-28 has underperformed in the scientific research, at least in the field of ''-omics'' research in sepsis (Dosi et al., 2006). However, over the same period, there is a tendency for an increase in the number of publications originating from the EU-28 and China, which was proven to be of statistical significance and was stronger for China. At the same time, the situation in the United States does not seem to follow a similar trend. These results may indicate that investment in this research area has already been a priority for the EU-28 and China at a time where the United States is planning a downsizing of public research funding. These findings suggest that this quantitative lead of the United States may change in the future.

Furthermore, almost 40% of the publications presenting multi-omics research during this period, with the exception of 2015 where EU-28 takes the lead, came from the United States, whereas almost one-fourth of the publications originated from the EU-28. Notably, however, only the EU-28 showed a significant increase in the number of published articles with multi-omics over time, whereas both China and the United States failed to attain a similar tendency. These results show that, although the United States had the lead in multi-omics research (i.e., the % of research efforts employing more than one ''-omics'' regimes), the situation changed in 2015 in favor of the EU-28, which, importantly, tends to increase its multi-omics research efforts at a statistically significant rate.

On the other hand, although China also increased the number of (and, presumably, the investment in) ''-omics'' publications in sepsis, the qualitative characteristics (in terms of multi-omics approaches) of its research did not display a similar trend. This finding confirms that, despite China's demonstrated strength in high-quality primary research as the second largest country contributor to the Nature Index, the country still underperforms in selected subject areas, such as biology and medicine (Tang and Du, 2016). Our results are in line with the findings of a recent bibliometric study on China's contribution to sepsis research.

Although this study did not focus on ''-omics'' research, it still confirmed that, overall, the United States has been the main contributor with the highest number of publications, citations, and h-index. Furthermore, it demonstrated that, despite the notable increase in the number of scientific publications, the quality of China's research in sepsis was relatively low (Zhang et al., 2017).

Using these results for benchmarking, further research in sepsis as well as in other research areas, such as cancer, is needed to confirm this trend, which suggests that the EU-28 is taking the lead in the multi-omics research in sepsis and may profit from the expected benefit of such approaches.

Research funding has always been a fiercely debated subject (Vaesen and Katzav, 2017) and relevant research has shown the advantages of public funding in terms of commercial and academic outcomes. In the case of sepsis, an analysis of the UK investments in sepsis research has shown that public and philanthropic institutions accounted for the majority of the awarded funding. However, it should be noted that this study did not differentiate between ''-omics'' and other forms of research in sepsis (Fitchett et al., 2014).

To our knowledge, no attempt has been made to correlate the qualitative characteristics of ''-omics'' research (in terms of multi-omics approaches) with funding sources. The data presented in this study show that the vast majority of articles with multi-omics received government/state funding and that the latter was associated at a significantly higher frequency with multi-omics research when compared to university or nonstate/government and nonuniversity funding sources. These findings indicate that the planned reduction of public funding in the United States could undermine the use of multi-omics approaches in sepsis research in the United States and, eventually, their competitive economic advantage.

On the other hand, when studying the percentages of only government/state, only university or nongovernment/state and nonuniversity funding associated with multi-omics research (e.g., what percentage of the total single university funding for ''-omics'' research in sepsis was used for multi-omics research), we found that funding channeled through universities is better associated with multi-omics compared to funding channeled through government/state or other institutions (Fig. 3). These results suggest that although the majority of multi-omics research funded from single sources relies on government/state funds, funding channeled through universities may lead more often (as a percentage) to multi-omics research efforts. Further research is needed to find out which are the best channels of funding when it comes to ''-omics'' and multi-omics research in sepsis.

Admittedly, correlating funding sources with scientific output requires taking into account several parameters. In bibliometric terms, an increase in the number of publications in a research field may not necessarily be the result of an increase in funding alone, but rather may represent a recognition from the research community of the importance of this field. However, by focusing on the correlation of multi-omics approaches in sepsis with funding sources, we highlight the importance of different channels of funding (e.g., state/government sources vs. university) for the scientific output.

The impact of ''-omics'' sepsis research on public health is manifold and becomes obvious if we take into account, for example, the multitude of septic infections affecting livestock and intensive fish farming. Furthermore, it should be noted that ''-omics'' are horizontal technologies that transcend nominal categories. Therefore, developments in sepsis-related ''-omics'' research have an impact on the knowledge-based biotechnology innovation that extends beyond their medical applications. The use of ''-omics'' technologies for biodegradation (with the use of microbial colonies) of chemical and industrial waste and their function as innovation platforms, with biopatents based on ''-omics'' technologies being already a reality (Yadav et al., 2012), are examples of such effects.

Although the generation of value does not solely rely on the underlying technological developments, but rather is a bidirectional process between the latter and the corresponding sociopolitical frameworks (Birch, 2017), ''-omics'' technologies radically transform the research and economic landscape in biomedicine. Based on the above, an eventual change in the research landscape is anticipated to have a major impact on both public health and the new, biotechnology-driven economy.

In all, our results indicate that the quantitative and qualitative (in terms of multi-omics approaches) lead of the United States in the field of ''-omics'' research in sepsis is at stake, with both the EU-28 and China rapidly increasing their research efforts and, presumably, their share in the new knowledge-based biotechnology innovation. Although derived by the study of ''-omics'' research trends exclusively in sepsis, our findings may have implications for (supranational) research policies and can be used as a benchmark case for similar studies in other areas of ''-omics'' research.

Conclusions and Outlook

Being a prerequisite for the elucidation of the (patho)biological pathways underlining the septic syndrome, adoption of multi-omics approaches is important for both public health and the innovation capacity of the biotechnology industry. Our results indicate that the majority of multi-omics research efforts were funded by government/state sources. Whether this is also the case in other areas of ''-omics'' research remains, however, to be seen. To this direction, analysis of funding sources in other research areas, such as complex disease or common types of cancer, would confer valuable additional information.

Although the United States has currently the lead in multi-omics research in sepsis, this could rapidly change if government/state funding will be decreased, as planned by the current administration. With the EU-28 steadily increasing the quantity and quality (in terms of multi-omics approaches) of its research capacity at a statistically significant rate and China displaying a similar trend, these developments could undermine the lead of the United States in ''-omics'' research, with consequences for both public health and its position in the new economy, which extensively relies on the knowledge-based biotechnology innovation, therefore triggering adoption of appropriate research policy measures.

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Author Disclosure Statement

The authors declare that no conflicting financial interests exist.

References

Altelaar AF, Munoz J, and Heck AJ. (2013). Next-generation proteomics: Towards an integrative view of proteome dynamics. Nat Rev Genet 14, 35–48.

Azoulay P, Graff Zivin JS, Li D, and Sampat BN. *Public R&D Investments and Private- Sector Patenting: Evidence from NIH Funding Rules*. NBER working paper no. 20889. Cambridge, MA: National Bureau of Economic Research, January 2015, Revised January 2017. www.nber.org/papers/w20889.pdf, Accessed January 11, 2018.

Birch K. (2017). Rethinking value in the bio-economy: Finance, assetization, and the management of value. Sci Technol Human Values 42, 460–490.

Brand A, Evangelatos N, and Satyamoorthy K. (2016). Public health genomics: The essential part for good governance in public health. Int J Public Health 61, 401–403.

Buescher JM, and Driggers EM. (2016). Integration of omics: More than the sum of its parts. Cancer Metab 4, 4.

Collins F. (2010). Has the revolution arrived? Nature 464, 674–675.

Dosi G, Llerena P, and Labini MS. (2006). The relationships between science, technologies and their industrial exploitation: An illustration through the myths and realities of the so-called ''European Paradox.'' Res Policy 35, 1450–1464.

Ebrahim S. (2012). Epigenetics: The next big thing. Int J Epidemiol 41, 1–3.

Evangelatos N, Reumann M, Lehrach H, and Brand A. (2016). Clinical trial data as public goods: Fair trade and the virtual knowledge bank as a solution to the free rider problem—A framework for the promotion of innovation by facilitation of clinical trial data sharing among biopharmaceutical companies in the era of omics and big data. Public Health Genomics 19, 211–219.

ey.com. (2015): www.ey.com/Publication/vwLUAssets/EY-beyond-borders-2016-financial-performance/$FILE/EY-beyond-borders-2016-financial-performance.pdf, Accessed January 11, 2017.

Fitchett JR, Head MG, and Atun R. (2014). Investing in sepsis research: Systematic analysis of UK public and philanthropic funding 1997–2010. JRSM Open 5, 2054270414538954.

Fragoulakis V, Mitropoulou C, Katelidou D, van Schaik RH, Maniadakis N, and Patrinos GP. (2017). Performance ratio based resource allocation decision-making in genomic medicine. OMICS 221, 67–73.

Gomez-Cabrero D, Abugessaisa I, Maier D, et al. (2014). Data integration in the era of omics: Current and future challenges. BMC Syst Biol 8 Suppl. 2:I1.

Hafen E, Kossmann D, and Brand A. (2014). Health data cooperatives—citizen empowerment. Methods Inf Med 53, 82–86.

Heather JM, and Chain B. (2016). The sequence of sequencers: The history of sequencing DNA. Genomics 107, 1–8.

Holmes E, Wilson ID, and Nicholson JK. (2008). Metabolic phenotyping in health and disease. Cell 134, 714–717.

Houle D, Govindaraju DR, and Omholt S. (2010). Phenomics: The next challenge. Nat Rev Genet 11, 855–669.

Jiménez-Sánchez G, and Philp J. (2015). Omics and the bioeconomy: Applications of genomics hold great potential for a future bio-based economy and sustainable development. EMBO Rep 16, 17–20.

Joyce AR, and Palsson BØ. (2006). The model organism as a system: Integrating ''omics'' data sets. Nat Rev Mol Cell Biol 7, 198–210.

Katz IT, and Wright AA. (2017). Scientific drought, golden eggs, and global leadership-why trump's nih funding cuts would be a disaster. N Engl J Med 376, 1701–1704.

Kesselheim AS, Cook-Deegan RM, Winickoff DE, Mello MM. (2013). Gene patenting-the supreme court finally speaks. N Engl J Med 369, 869–875.

Kim J. (1999). Making sense of emergence. Philos Stud 95, 3–36.

Kohl M, Megger DA, Trippler M, et al. (2014). A practical data processing workflow for multi-OMICS projects. Biochim Biophys Acta 1844(1 Pt A), 52–62.

Kuhn TS. (1996). *The Structure of Scientific Revolutions, 3rd ed.* Chicago, IL: University of Chicago Press.

Langley RJ, and Wong HR. (2017). Early diagnosis of sepsis: Is an integrated omics approach the way forward? Mol Diagn Ther 21, 525–537.

Loscalzo J. (2006). The NIH budget and the future of biomedical research. N Engl Med 354, 1665–1667.

Moses H 3rd, Matheson DH, Cairns-Smith S, George BP, Palisch C, and Dorsey ER. (2015). The anatomy of medical research: US and international comparisons. JAMA 313, 174–189.

Pisano G. (2006). *Science Business: The Promise, the Reality, and the Future of Biotech*. Harvard Business School Press, Boston, MA.

Ployhart, RE, and Vandenberg RJ. (2010). Longitudinal research: The theory, design, and analysis of change. J Manage 36, 94–120.

Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, and Finfer S. (2017). Recognizing sepsis as a global health priority—A WHO resolution. N Engl J Med 377, 414–417.

Shankar-Hari M, Phillips GS, Levy ML, et al. (2016) Sepsis Definitions task force. developing a new definition and assessing new clinical criteria for septic shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 315, 775–787.

Skibsted S, Bhasin MK, Aird WC, and Shapiro NI. (2013). Bench-to bedside review: Future novel diagnostics for sepsis - a systems biology approach. Crit Care 17, 231.

Sweeney TE, Wong HR, and Khatri P. (2016). Robust classification of bacterial and viral infections via integrated host gene expression diagnostics. Sci Transl Med 8, 346ra91.

Taichman DB, Sahni P, Pinborg A, et al. (2017). Data sharing statements for clinical trials: A requirement of the International Committee of Medical Journal Editors. JAMA 317, 2491–2492.

Tang X, and Du J. (2016). The performance of China's biomedical innovation: A scientometric analysis. Sci China Life Sci 59, 1074–1082.

Taris TW, Kompier MAJ. (2014). Cause and effect: Optimizing the designs of longitudinal studies in occupational health psychology. Work Stress 1, 1–8.

Van Regenmortel MH. (2004). Reductionism and complexity in molecular biology. Scientists now have the tools to unravel biological and overcome the limitations of reductionism. EMBO Rep 5, 1016–1020.

Vaesen K, and Katzav J. (2017). How much would each researcher receive if competitive government research funding were distributed equally among researchers? PLoS One 8;12, e0183967.

Varmus H. (2002). Getting ready for gene-based medicine. N Engl J Med 347, 1526–1527.

Weidman S, and Arrison T. (2010). Steps toward large-scale data integration in the sciences: Summary of a workshop. Natl Res Council Natl Acad, pp.1–33.

Yadav D, Anand G, Dubey AK, Gupta S, and Yadav S. (2012). Patents in the era of genomics: An overview. Recent Pat DNA Gene Seq 6, 127–144.

Zhang K, Zhao J, Chu L, et al. (2017). China's growing contribution to sepsis research from 1984 to 2014: A bibliometric study. Medicine (Baltimore) 96, e7275.

Ziegelstein RC. (2017). Personomics: The missing link in the evolution from precision medicine to personalized medicine. J Pers Med 7, pii: E11.

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Abbreviations Used

cDNA = complementary DNA
EU-28 = European Union-28 Member States
IP = intellectual property
MeSH = medical subject headings
NGOs = non-governmental organizations
NIH = National Institutes of Health
RT-PCR = reverse transcriptase polymerase chain reaction
US = United States
WHO = World Health Organization

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3. Jean-Louis Vincent, Yasser Sakr. 2019. Clinical trial design for unmet clinical needs: a spotlight on sepsis. *Expert Review of Clinical Pharmacology* **12**:9, 893-900. [Crossref]
4. Pedro Palma, Jordi Rello. 2019. Precision medicine for the treatment of sepsis: recent advances and future prospects. *Expert Review of Precision Medicine and Drug Development* **4**:4, 205-213. [Crossref]
5. Niklas Bruse, Guus P. Leijte, Peter Pickkers, Matthijs Kox. 2019. New frontiers in precision medicine for sepsis-induced immunoparalysis. *Expert Review of Clinical Immunology* **15**:3, 251-263. [Crossref]
6. M. KOHOUTOVÁ, J. DEJMEK, Z. TŮMA, J. KUNCOVÁ. 2018. Variability of Mitochondrial Respiration in Relation to Sepsis-Induced Multiple Organ Dysfunction. *Physiological Research* S577-S592. [Crossref]