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Integrating priorities at the intersection of cancer and neuroscience

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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Abstract

Cancer neuroscience is a rapidly growing multidisciplinary field that conceptualizes tumors as tissues fully integrated into the nervous system. Recognizing the complexity and challenges in this field is of fundamental importance to achieving the goal of translational impact for cancer patients. Our commentary highlights key scientific priorities, optimal training settings, and roadblocks to translating scientific findings to the clinic in this emerging field, aiming to formulate a transformative and cohesive path forward.

Introduction

Cancer neuroscience is an interdisciplinary field that focuses on the intricate relationship between the nervous system and cancer. Growing evidence supports the involvement of the central and peripheral nervous systems in the onset, development, and spread of cancer.[1–3] This unique area of investigation has seen remarkable growth over the past two decades, with scholarly articles mentioning both “cancer” and “neuroscience” witnessing a 22-fold increase from 2000 (216 articles) to 2023 (4,852 articles). This burgeoning interest has led to numerous special events, including the 2024 MD Anderson Cancer Neuroscience Symposium, which captured a broad spectrum of expert opinions about the field. At this pivotal moment, the field stands ready to harness its rapid growth to chart a path forward that is both cohesive and encompasses its diverse membership. This commentary seeks to synthesize the viewpoints of leading experts in the field that attended the symposium and responded to a survey, providing the broader scientific community with insights into the perspectives on the current state and future directions of cancer neuroscience. In addition, this survey and commentary incorporate the perspective of trainees (students and postdocs, 41.2% of attendees).

Defining cancer neuroscience: An emerging interdisciplinary field

Cancer neuroscience is an exemplar of multidisciplinary research, merging elements of cancer biology, bioengineering, pathology, developmental biology, immunology, neuroscience, psychiatry, bioinformatics, systems biology, and wound repair to create a rich tapestry of scientific domains within a single field. This integration has led to significant insights into the molecular and systemic mechanisms that drive cancer progression, particularly regarding nervous system components being integral to the tumor microenvironment (TME) in different cancers.

Cancer neuroscience is a term that captures a broad spectrum of research domains: (1) the role of the nervous system in regulating tumor onset, growth, and progression; (2) the adaptation of the nervous system to the tumor and tumor-derived substances; (3) the impact of cancer treatments on neuronal function; and (4) the parallels between normal neural development and the genesis of tumors (Figure 1). In essence, cancer neuroscience is defined as a discipline focused on deciphering the complex and evolving interplay between cancer and the nervous system, including the investigation of how cancer can cause neuronal dysfunction and, conversely, how the nervous system can influence cancer’s behavior, including its growth, invasiveness, and response to treatments.

However, as the field of cancer neuroscience is rapidly evolving, the scope of research into cancer-nervous system interactions continues to expand. For example, tumors have been shown to exploit the nervous system's signaling pathways, such as those involved in brain plasticity, to enhance their growth. The use of brain-derived neurotrophic factor by tumors to strengthen synaptic connections is a notable discovery, highlighting how cancer can hijack normal neural processes for its benefit.[4,5] Researchers also discovered that the role of tumor-infiltrating nerves extends beyond influencing the TME. For example, brain tumors form functional synapses with neurons that are subject to functional plasticity and potentially influence host behavior.[6–8]

Cancer neuroscience also continues to be energized by several unexpected discoveries. For example, researchers found that neural stem cells from the brain can migrate through the bloodstream and infiltrate prostate tumors outside the central nervous system (CNS), forming new neurons and contributing to cancer progression.[9] Additionally, the interplay between the microbiome and the brain-body axis (bidirectional communication between the periphery and the CNS) and the concomitant use of a new line of microbial-based therapies against cancer in clinical trials[10] are crucial areas of interest, enabling researchers to explore how the microbiome affects and is impacted by nervous system-cancer interactions. Likewise, mapping neural circuits that extend from the tumor to the brain using viral vectors injected into tumors that retrogradely label different areas of the CNS has opened new avenues for understanding cancer's influence on the brain-body axis. Exploring these neural circuits and understanding their effects offers the potential to develop neuromodulatory therapies that could dramatically improve patient outcomes. Thus, amidst the rapid growth of the cancer neuroscience field, it is paramount to systematically evaluate focus areas for future directions to ensure continued growth and success. These priorities can be distilled into three broad categories:

Multidisciplinary collaboration:

cancer neuroscience is at an inflection point where the complexity of ongoing scientific questions requires an influx of new perspectives and expertise to build upon those of early contributors to the field. Events like the Cancer Neuroscience Symposium and other collaborative platforms play a key role in developing and fostering multidisciplinary and cross-institutional networks of scientists to address the multi-faceted challenges and outstanding biological questions in cancer neuroscience. Furthermore, we recommend that the cancer neuroscience field establish a working group presence at scientific conferences and societies, like other subfields of cancer and neuroscience.

Diversification:

the field of cancer neuroscience is undergoing a "democratization," with numerous labs entering the field and making significant discoveries across various facets. Many questions arising in the field of cancer neuroscience cannot be optimally answered with existing neuroscience and cancer biology approaches. Hence, it is essential to continually welcome researchers from other fields, such as bioengineering, physics, pharmacology, immunology, and systems biology, to advance cancer neuroscience research. This diversification is critical for establishing rigorous standards to ensure the field's lasting impact. Alongside the need

for sustained multidisciplinary diversification, there remains a need to enhance global participation in the field. For instance, while the Cancer Neuroscience Symposium attracted many researchers across North America and Europe, there was very little representation from other parts of the world. In the coming decade, active recruitment of and collaboration with institutions and individuals in other parts of the world will be a priority.

Training and career development:

the advancement of cancer neuroscience also depends on the development of future scientists. Training interdisciplinary scientists in cancer neuroscience requires a comprehensive approach that integrates neuroscience and cancer biology through specialized courses, textbooks, and online resources. Training plans should aim to develop a variety of skills, such as (1) the ability to understand and learn the biology and tools of different fields, (2) the ability to integrate information from various research areas, and (3) openness to acknowledging what is not known. This training plan should also include a repertoire of tacit skills, such as (1) the ability to perceive and adjust to differences in communication styles and needs from different disciplines and (2) empathy for patients and an appreciation for their experiences with cancer.

Co-mentorship plays a significant role in this training, offering an effective way to provide expertise in both neuroscience and cancer biology. This approach helps trainees acquire diverse skills and knowledge, develop professional relationships, and engage in a supportive scientific community. Another advantage of co-mentorship is through a bystander effect; the trainee in cancer neuroscience serves as an ambassador of the field in both the neuroscience and cancer biology communities, specifically in labs that they are a member of, thereby bringing awareness and expertise into the field. Facilitating interactions between cancer and neuroscience labs will promote practical experience and the cross-fertilization of ideas, which is essential for the sustained growth of the cancer neuroscience field.

Translating cancer neuroscience

The untapped translational potential of cancer neuroscience is immense, and groundbreaking discoveries in recent years have culminated in scientists aspiring to translate their foundational biological findings into clinically relevant applications.[11] From a patient care perspective, it is increasingly recognized that treating cancer goes beyond targeting the tumor itself. Effective cancer treatment requires a comprehensive understanding of how the body and mind adapt to the disease, influencing disease progression and treatment response. Neurological disorders, such as pain, fatigue, and neurocognitive symptoms, are prevalent among cancer patients, often leading to treatment discontinuation and reduced quality of life. Thus, researchers are focused on developing strategies to mitigate cancer-related pain and dysfunction by studying the dynamic interactions between the TME and peripheral nerves. These efforts aim to enhance treatment adherence and reduce patient suffering, offering synergistic benefits when combined with conventional and targeted therapies.

However, significant barriers exist on the path toward achieving this goal. One significant challenge is the limited fundamental knowledge due to insufficient cross-disciplinary integration and a need for more scientists with dual expertise (Figure 2). There is a pressing

need to deepen our molecular understanding of how nerves influence both the disease process and the host to translate cancer neuroscience findings into clinical application. Another major barrier is the anatomical complexity and heterogeneity of the nervous system, which varies across different neurological sites in the body. Neuronal cell bodies are typically located outside malignant tissues, and the neurons that innervate tumors are part of extensive circuits that communicate with the brain, spinal cord, and ganglia. Manipulating one part of this circuit could inadvertently impact other parts of the pathway.

It is also important to recognize that the nervous system is composed of not only neurons but also glial cells that modify the behavior of neurons and directly influence tumor biology.[12,13] These glial cells influence the transmission of neural impulses, maintain and protect neurons, guide axonal growth within tumors, create invasive tracks for cancer cells to migrate along, support angiogenesis, and regulate anti-tumor immune responses. The heterogeneity among glial cells also contributes to the distinct properties of neuronal networks across various types of tissues. Furthermore, the specific contributions of neurons versus glia are not always clearly delineated, further complicating therapeutic targeting.

The field must develop methods to selectively target only the neurons and glia that promote cancer development and progression without unduly affecting other elements of the nervous system that perform critical physiological roles. This is particularly challenging as most neuromodulatory drugs have pleiotropic effects throughout many parts of the body. Techniques to improve specificity must identify molecules that are uniquely upregulated on tumor-innervating neurons, using a combination of specific viral vectors and transgenic tools; utilizing a combination of spatial and molecular targeting to the tumor (e.g., bispecific antibody-drug conjugates); and employing bioelectronic methods to precisely manipulate, stimulate, or inhibit specific neuronal circuit components. This approach may ultimately provide minimally invasive tools to stimulate nerves that inhibit malignancy while blocking those that promote cancer progression.

Another factor to consider when translating cancer neuroscience research to the clinic is the availability of existing drugs that target the nervous system for conditions such as neurodegenerative diseases, epilepsy, depression, and neuropathic pain. These existing drugs have already been characterized in clinical studies and databases (e.g., pharmacodynamics, pharmacokinetics, and toxicity), reducing the barriers separating drug discovery and clinical deployment. Therefore, repurposing these drugs for cancer treatment may be a promising and expedited pathway for translating cancer neuroscience knowledge into clinical oncology. However, the systemic effects of repurposed drugs still need to be carefully considered. Several groups have begun exploring the potential of repurposing neuromodulatory drugs to target cancer-nerve interactions. These groups found the use of a first-line antiepileptic drug (lamotrigine) inhibited neurofibromatosis type 1-associated optic pathway glioma progression in preclinical mouse models[14] and the use of a sympathetic neuronal signaling blocker (propranolol) inhibited the progression of a variety of cancers.[15]

Logistical and resource factors, including support from institutions and funding agencies, are crucial for advancing translational research in cancer neuroscience. Engaging large cancer centers and industry partners is essential for successfully translating biological

discoveries into clinical practice. Similarly, fostering communication and collaboration between researchers and clinicians is vital to ensuring that findings are effectively and meaningfully applied in the clinic and that patient-centric priorities are not overlooked. For example, researchers and clinicians must recognize the complexity of human cancers and patient factors and the limitations of our current models. Researchers must ensure their findings are cross-validated in robust orthogonal systems to strengthen the translatability of their research outcomes. Further, it is necessary to continue educating the biomedical community on therapeutically relevant cancer-nervous system interactions so that they can consider these discoveries when designing biomarker screening panels and clinical trials.

Finally, it is important to acknowledge that positive results in clinical trials are rare, and negative trials may be equally important as they refine scientific efforts, generate insights for new hypotheses, and guide future research and clinical practice. Recognizing the iterative nature of scientific inquiry is crucial for advancing translational findings in cancer neuroscience and improving patient outcomes. Emphasizing clinical trials and safety monitoring is paramount in this process, ensuring that new therapeutic approaches are rigorously tested and proven safe for patients before widespread clinical adoption.

Discussion

In the last decade, a synergistic convergence of the cancer and neuroscience fields has emerged, revealing overlapping topics that were once considered independent. The broad scope of research interests recognized within cancer neuroscience is poised to drive significant scientific and clinical breakthroughs. Harnessing the recent growth and momentum in the field is more crucial now than ever to understand how to advance as a unified yet multidisciplinary field. Collaboration and strategic planning are required to capitalize on this momentum and advance our understanding and treatment of cancer and cancer-associated disorders. We strongly advocate for establishing and systematically integrating robust platforms to facilitate cross-disciplinary and -institutional collaborations, focused working groups, technical and educational workshops, and resource sharing.

It is also essential to incorporate more trainee voices in shaping the future of cancer neuroscience, as they represent the next generation of leaders in the field. Interdisciplinary collaboration on specific cancer neuroscience projects emerged as the optimal training strategy from trainees and experts alike. Notably, there was a divergence in the second-most favored training strategy between trainees and non-trainees. Non-trainees selected dual training during the graduate and post-doctoral stages (e.g., cancer biology during graduate school and neuroscience during post-doc or vice versa), while trainees preferred formal co-mentorship under a cancer biology principal investigator (PI) and a neuroscience PI. Given this finding, we propose that institutions develop flexible training programs that incorporate co-mentorship opportunities across conventionally independent departments and make other accommodations for different stages of career development.

Translating cancer neuroscience knowledge to clinical applications is multi-faceted. First, as previously discussed, the field must address gaps in fundamental knowledge through collaborative research initiatives. Second, increased financial support should be provided

for such research. We recommend that organizations like the National Institutes of Health (NIH), National Science Foundation (NSF), Department of Defense (DoD), and other governmental entities with competitive scientific grant mechanisms play a role by offering targeted grants and funding opportunities that specifically address the challenges of cancer neuroscience. This involvement could include support for preclinical studies focused on the neurobiology of cancer and the development of technologies for manipulating neural circuits in the context of cancer. Moreover, fostering collaborations between academic institutions, clinical researchers, industry partners, and federal agencies could accelerate the translation of laboratory findings into clinical trials. Initiatives such as the BRAIN Initiative illustrate the potential impact of federal involvement in advancing neuroscience research. By extending similar support to cancer neuroscience, these agencies could help overcome translational barriers.

Our commentary aims to elucidate current perspectives on the present and future of the field, informed by the largest group of cancer neuroscientists surveyed to date. The high attendance rate at various events focused on cancer neuroscience, including the 2024 MD Anderson Cancer Neuroscience Symposium, indicates the engagement and enthusiasm among members of this field in collaboratively shaping a fruitful future. Regularly assessing the community's needs through surveys, as highlighted herein, will allow the field to unite in addressing important issues and allocate limited resources for maximal impact. Further, such field-wide coordination will help engage a broader audience, expand the cancer neuroscience workforce, and enhance the diversity of scientists in the field. Ultimately, we hope these insights inspire productive action and foster greater cohesion within the field, potentially serving as a model for other multidisciplinary disciplines.

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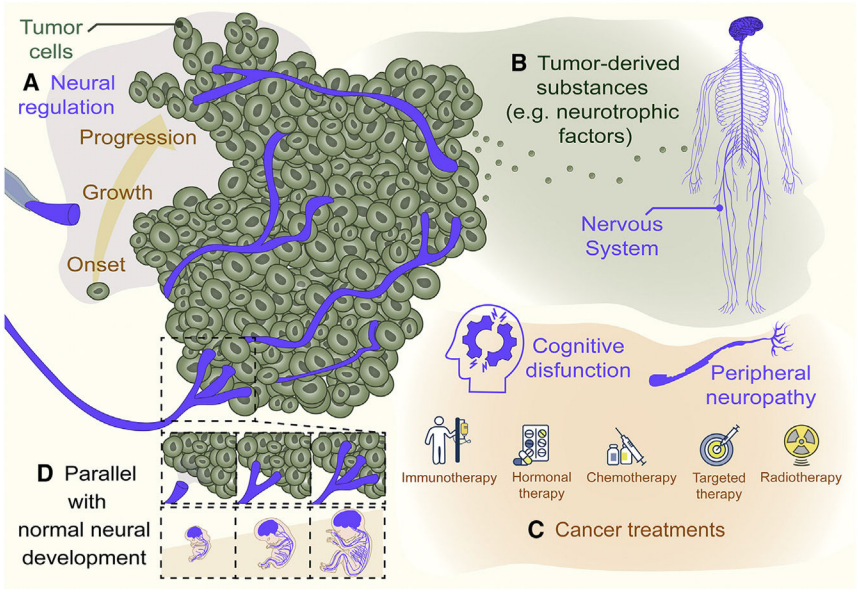

Figure 1. Broad spectrum of research domains included in cancer neuroscience

(A) The role of the nervous system in regulating tumor onset, growth, and progression; (B) the adaptation of the nervous system to the tumor and tumor-derived substances; (C) the impact of cancer treatments on neuronal function; and (D) the parallels between normal neural development and the genesis of tumors.

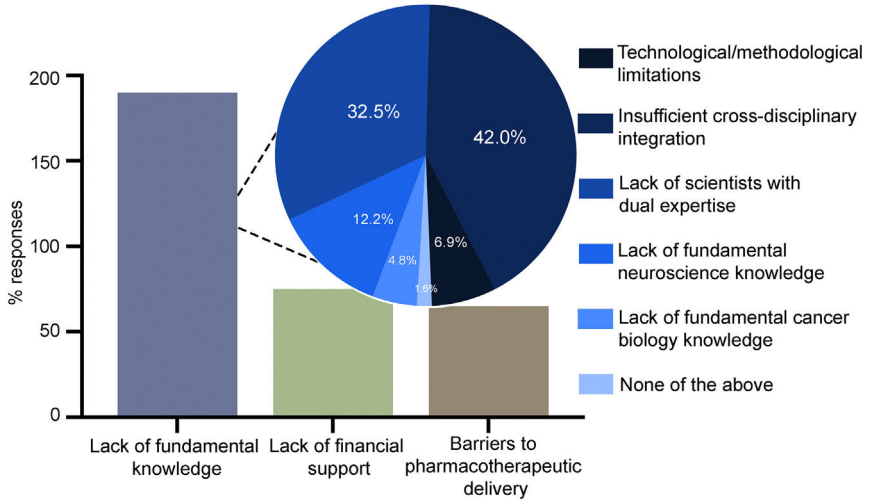

Figure 2. Barriers to translating cancer neuroscience knowledge to clinical applications

(Left) bar graph representing survey responses (n = 330) to the multiple-choice question "What is the primary barrier to translating cancer neuroscience knowledge to clinical applications?"

(Right) Pie chart representing survey responses (n = 188) to the multiple-choice question "If lack of fundamental knowledge, why?" from individuals who selected "Lack of fundamental knowledge" as the primary barrier to translating cancer neuroscience knowledge to clinical applications.