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# The evolving landscape of single-cell genomics in CNS and PNS oncology

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Single-cell genomics has transformed neuro-oncology, revealing the cellular and molecular diversity of tumors across the central and peripheral nervous systems (CNS and PNS).[1–5] These approaches have highlighted intratumoral heterogeneity, identified the molecular programs driving malignancy and refined our understanding of the tumor microenvironment.[2] In recent years, this technology has been increasingly applied to tumors of the CNS and PNS, revealing complexities that bulk genomic method cannot capture.

This special issue of *Neuro-Oncology Advances* explores the transformative impact of single-cell technologies on the characterization of CNS and PNS tumors. It provides a comprehensive overview of current advancements, showcasing how single-cell genomics is reshaping our understanding of brain, spine, and peripheral nerve tumors. The goal of this special issue is to consolidate existing knowledge, foster collaborations, and guide future research that integrates single-cell analyses into neuro-oncology. Below is a summary of the articles included in this special issue, organized by category and highlighting their significance.

## Single-Cell Omics in Central Nervous System Tumors

- Gonzalez Castro et al.: Redefining the immune microenvironment of gliomas in the era of single-cell genomics.[6]
- Porter et al.: Single-cell advances in the investigation of the pathogenesis and treatment of brain metastasis.[7]
- Ellenbogen et al.: Current landscape of single-cell genomics in meningioma.[8]

Gliomas are the most common malignant primary brain tumors and are a major focus of single-cell genomics in neuro-oncology. Glioblastoma demonstrates significant intratumoral heterogeneity across malignant and non-malignant populations and is best characterized by single-cell and spatial methods that capture cellular diversity within the tumour and microenvironmental compartments. Non-malignant cells within the tumor microenvironment represent a large portion of the tumor, and single-cell genomics has improved our understanding of its complex cellular composition and interactions. In the first article of this supplement, Gonzalez Castro et al. synthesize recent findings, emphasizing the evolving understanding of glioma immune landscapes and their implications for immunotherapy.[6]

Similarly, single-cell technologies have expanded our understanding of brain metastases, which remain a major cause of morbidity and mortality in cancer patients. Like glioblastoma, brain metastases exhibit significant cellular heterogeneity and complex interactions with the surrounding microenvironment. In the second article, Porter et al. review how single-cell RNA-seq (scRNA-seq) and related modalities dissect tumor, immune, and stromal populations within metastases and clarify mechanisms of progression and treatment response.[7] These insights offer potential avenues for novel therapeutic strategies.

Meningiomas are the most common primary CNS tumors.[9] These tumors present substantial clinical heterogeneity, with some exhibiting aggressive recurrence despite surgical resection and radiotherapy. Single-cell and spatial transcriptomics have refined molecular subgrouping and resolved intratumoral heterogeneity beyond the resolution of bulk profiling. The third article of this supplement summarizes single-cell and spatial transcriptomic studies of meninigioma and highlights the unique cellular populations, regulatory networks, and microenvironmental interactions that drive meningioma behavior.[8] These advances deepen biological understanding and identify candidate therapeutic targets tailored to the molecular diversity of these tumors.

## Single-Cell Omics in Peripheral Nervous System Tumors

- Pari et al.: Single-cell multiomic techniques highlight the diverse composition and intercellular interactions of the vestibular schwannoma tumor microenvironment.[10]
- Gui et al.: Single-cell transcriptomic profiling of malignant peripheral nerve sheath tumors.[11]

Vestibular schwannomas (VS) are benign tumors originating from Schwann cells of the vestibulocochlear nerve and were historically considered molecularly homogeneous.[12] However, recent single-cell and multiomic analyses have challenged this notion, revealing substantial cellular diversity within these tumors.[13–15] Pari et al. highlight how single-cell transcriptomic and epigenetic profiling identify distinct Schwann cell subpopulations and complex interactions within the tumor microenvironment.[10] Their work reveals 2 molecularly distinct groups of VS: one characterized by an "injury-like" Schwann cell phenotype that is associatd with immune cell recruitment, and another composed of quiescent Schwann cells with reduced immune infiltration.These insights reshape the understanding of VS pathogenesis and may inform future therapies targeting specific microenvironmental interactions.

Malignant periphal nerve sheath tumors (MPNSTs) are aggressive sarcomas that exhibit significant molecular and cellular heterogeneity. Gui et al. explore how single-cell profiling deepens understanding of MPNST biology, revealing diverse cellular populations including neoplastic Schwann cell-like, malignant neural crest-like, immune, and stromal cells.[11] Comparative single-nucleus analyses of MPNSTs and their benign precursors highlight Schwann cell dedifferentiation into mesenchymal, stem-like state that underlies malignant transformation. This article synthesizes these findings, highlighting cellular plasticity within MPNSTs and pointing to potential therapeutic targets designed to halt or reverse malignant progression.

## Pearls and Pitfalls in Single-Cell Data Analysis

- Tirosh: Pitfalls in analysis and interpretation of single-cell RNA-seq data in cancer[16]

scRNA-seq and single-nucleus RNA-seq (snRNA-seq) have become essential tools in cancer research, enabling high-resolution analyses of cellular heterogeneity and the tumor microenvironment. The widespread adoption of these technologies has been supported by the development of specialized computational tools tailored for sc/snRNA-seq data. However, proper analysis and interpretation require significant expertise, as limitations in computational methods can lead to misleading conclusions.

This article reviews common pitfalls encountered in cancer sc/snRNA-seq analysis and interpretation, emphasizing recognition of data limitations, understanding the assumptions behind common analytical methods, and employing rigorous statistical approaches.[16] It discusses potential sources of error, including inaccuracies in statistical modeling, challenges in trajectory analysis, and the misapplication of single-cell RNA-seq signatures to bulk data. It also addresses pitfalls in inferring chromosomal aberrations such as somatic copy number variations and large-scale structural rearrangements from sc/snRNA-seq data, and the challenges these pose for accurately defining complex cell populations. By outlining these challenges and providing practical strategies to mitigate them, the review aims to guide researchers toward more robust, reproducitve analyses, ultimately promoting more reliable interpretations of sc/snRNA-seq data in cancer research.

## Conclusion

This special issue underscores the transformative impact of single-cell genomics in CNS and PNS oncology. As these technologies and analytical method continue to improve, the knowledge gained from single-cell analyses is shaping neuro-oncology, informing precision medicine approaches and the development of targeted therapies.

## Conflict of interest statement

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