Interview

Maciej M. Mrugala, neuro-oncologist at Mayo Clinic and Mayo Clinic Comprehensive Cancer Center, Phoenix, Arizona, USA, boasts expertise in glioblastoma, neurofibromatosis Type 1, and CNS tumor guideline development. Reflecting on the research journey that has shaped his career, Mrugala shares emerging therapeutic strategies in neuro-oncology, and the practical challenges clinicians face when caring for patients with complex, rare, often fatal neurologic cancers.

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Q1 How did your early training in Warsaw, Poland, influence your approach to neurology once you began practicing in the USA?

While in medical school in Warsaw, I was involved in basic science research from my second year. I was very interested in biochemistry, as well as the central nervous system (CNS). I was studying detoxifying enzymes, specifically glutathione transferases in the brains of monkeys and then ultimately in the cerebrospinal fluid of human subjects. These experiences triggered my interest in clinical neuroscience and neurology in particular. Once I completed medical school, I was accepted through a scholar exchange program to complete a post-doctoral fellowship at the University of Massachusetts, Boston, Massachusetts, USA. I continued to work on the biological clock and circadian biology, as well as neural stem cells, and the data generated through this research led to my PhD thesis, which I defended at the Copernicus University in Toruń, Poland. Ultimately, I was accepted to the residency program in neurology at the University of Massachusetts.

Q2 What experiences at the University of Washington, Seattle, Washington, USA, and Seattle Cancer Care Alliance, Washington, USA, led you to prioritize research into devastating brain tumors like glioblastomas?

Following the completion of my residency, as well as my fellowship in neuro-oncology at the Massachusetts General Hospital and the Dana-Farber Cancer Institute, Boston, Massachusetts, USA, while earning the Master of Public Health at Harvard University, Cambridge, Massachusetts, USA, I took my first job at the University of Washington and Fred Hutchinson Cancer Research Center in Seattle, Washington, USA. I joined my mentor and dear

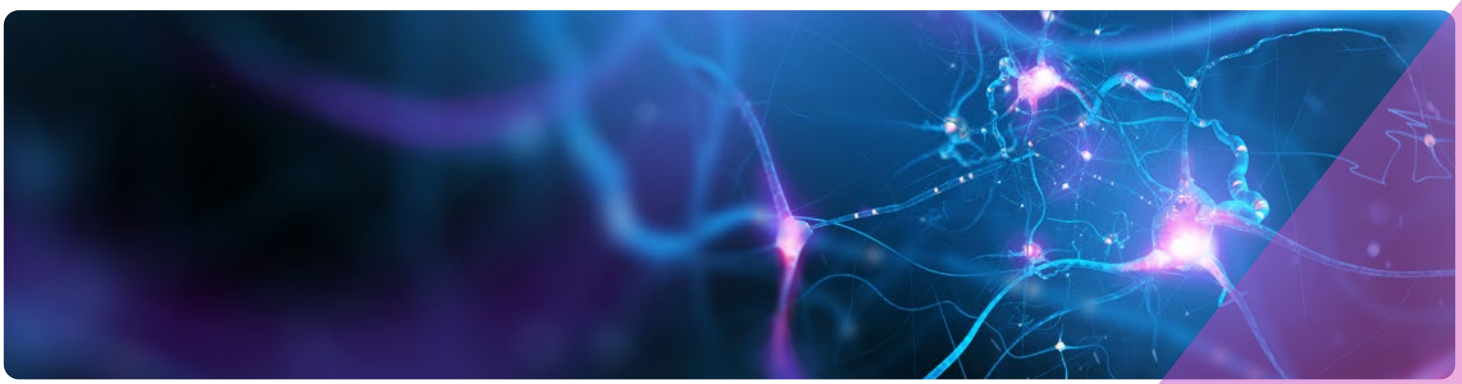
colleague Alexander Spence, Department of Neurology, University of Washington Medical School, Seattle, Washington, USA, and together we set the foundation to create the Alvord Brain Tumor Center, named after prominent neuropathologist Ellsworth (Buster) Alvord, who has worked at the University of Washington for many years and trained generations of clinicians. While at the University of Washington, I developed a specific interest in leptomeningeal carcinomatosis, a devastating complication of systemic cancer. We developed treatment protocols for patients suffering from these conditions, mostly those with metastatic breast and lung cancers. We identified a huge clinical need for this patient population and, given the large number of these patients being seen in Seattle, it provided the opportunity to develop and prioritize research opportunities in this space. In addition, we developed a unique protocol for the treatment of patients with glioblastoma using gene therapy (the first ever). The protocol was developed for patients with very poor prognosis: those with unmethylated *MGMT*. This was pioneering and translational work, done with the leadership of Hans-Peter Kiem and Jennifer Adair, Fred Hutchinson Cancer Research Center, that led us from the bench to bedside and allowed us to treat patients with this devastating condition with a novel, experimental therapy.

Q3 For clinicians considering tumor treating fields for recurrent glioblastoma, what key factors should guide their decision to recommend this therapy?

This particular therapy has now become a standard of care for this disease at many centers across the US. Given the nature of the therapy (a wearable device treatment), there are some challenges. One of the main factors is compliance with treatment, which is important and related to survival. Many patients, especially those with neurological deficits, might have a difficult time wearing the device and staying compliant. This is typically the main obstacle that limits the use of this technology on a wider scale. Clinical trials have shown that when this therapy is combined with a chemotherapeutic agent, the results are better. Discussing the treatment with patients, being open about possible challenges, and helping them throughout the journey is important and typically results in successful implementation of this modality.

Q4 Which immunotherapy or cell based strategies for glioblastoma are most poised to impact everyday practice, and what foundational knowledge should general neurologists develop now?

So far, immunotherapy has not been successful in the treatment of primary brain cancer, specifically glioblastoma. There are multiple ongoing clinical trials using this modality. There are several challenges associated with the biology of the immune system, specifically in the brain. Some of the more promising therapies that we have observed in clinical trials include CAR-T cells. This treatment modality may be known to neurologists from other applications, such as for patients with lymphomas and multiple myeloma. There have been several clinical trials in glioblastomas using CAR-T cells delivered directly into the tumor bed or into the spinal fluid, resulting in some very encouraging results. I hope that this technology, as well as other immunotherapy approaches in glioma, will be further developed and we will see success in the near future.



Q5 What practical steps can clinicians take today to incorporate cerebrospinal fluid (CSF) based diagnostics and targeted treatments for leptomeningeal metastasis?

Diagnosis of leptomeningeal metastases is frequently challenging. We usually use imaging as well as CSF analysis and clinical symptoms to make the diagnosis. CSF analysis typically incorporates cytology as well as assessment of the level of protein and glucose, which can indirectly indicate the presence of the condition. Cytology, while very specific, is unfortunately not very sensitive. Thankfully, we now have novel technologies such as circulating tumor cells and circulating tumor DNA, which can increase the sensitivity and specificity of testing. There are several commercially available assays that can aid clinicians in the diagnosis of this condition. Working with a local hospital laboratory, as well as external providers of this type of testing, can help clinicians seamlessly introduce them into the clinical workflow and use them on daily basis. We were successful in doing so at my institution, where we use them routinely.

Q6 What are the most critical gaps in care for adults with neurofibromatosis Type 1 (NF1) that practicing neurologists should be aware of?

I think that the most critical gap is access to multidisciplinary clinics that are comfortable with the diagnosis and management of patients with NF1. Thanks to the Children's Tumors Foundation (CTF), there is a network of designated and certified NF1 clinics that patients and physicians can identify within their geographic areas. It is highly recommended that patients with NF1 are consulted in those centers and, if possible, managed there as well.

I think another challenge is the transition of pediatric patients to adult medical care. Many of the younger patients with NF1 receive excellent care in local children's hospitals, but once they become adults, there is frequent fragmentation of care, with many patients lost to follow-up altogether. Creating a clear and easy pathway of transition from pediatric to adult care would help many patients and clinicians.

Q7 How do you, as a National Comprehensive Cancer Network (NCCN) panelist, approach guideline development when evidence is limited, and how can clinicians keep pace with these evolving recommendations?

NCCN guidelines for CNS tumors have been developed and expanded significantly over the last several years. While this increases the complexity of the guidelines, it also indicates how much progress in terms of tumor classification, as well as treatment approaches, has been made over the last decade. When I was starting as a panelist on NCCN guidelines, our CNS tumors guideline was very thin, with very limited options. This has thankfully changed. We try to find the best possible evidence to support the recommendations in the guidelines, and we heavily rely on published, Phase III, randomized clinical trials when available. If such evidence is not available, the panelists typically share their experience with particular diagnostic modalities or treatments, and the panel votes on the options. The recommendations have different categories: 1, 2A, 2B, and 3, with Category 1 associated with the highest level of evidence available and Category 3 where there is no consensus of the panel.

I think that clinicians should review NCCN guidelines on a regular basis, as they are updated annually. Even though I am on the panel, I frequently consult the guidelines myself to make sure I have the most up-to-date information regarding the diagnosis and treatment of specific tumors.

Q8 What qualities do you look for in neurology trainees who aspire to specialize in neuro-oncology, and what skills are currently under-emphasized?

Neuro-oncology is definitely a unique specialty, bringing together neuroscience and oncology. There is huge discovery potential and many opportunities for someone who would like to dedicate their time to research as well as clinical work. Taking care of patients with brain tumors is very rewarding, and because the landscape is changing and progress has been made, more treatment options are now becoming available. Patients with certain brain tumors can now be managed successfully, and frequently long term.

As for the skills, I think the ones I would consider to be the most important are: intellectual curiosity; the ability to deal with serious, frequently terminal diagnoses on a daily basis; a high level of empathy, compassion, and coping skills (that would allow for regeneration and recovery); and a positive, optimistic attitude and demeanor.

