University of Medicine and Pharmacy
”Carol Davila” Bucharest

Habilitation Thesis

Translational Neurosurgery – Transdisciplinary Vision
Connecting Scientifical Research and Clinical Practice

Abstract

Associate Professor Ligia Gabriela TATARANU

University of Medicine and Pharmacy ”Carol Davila” Bucharest

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ABSTRACT OF THE HABILITATION THESIS

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Title: Translational Neurosurgery – Transdisciplinary Vision Connecting Scientifical Research and Clinical Practice

Applicant: Associate Professor Ligia Gabriela TĂTĂRANU, MD, PhD

This Habilitation Thesis addresses my postdoctoral activity, between 2007 and 2023. The Habilitation Thesis is composed of three sections:

1. Scientific, academic, and professional activity
2. Scientific achievements and publications
3. Academic career advancement and development plan of action.

Section 1:

It generically presents the most important research field and the principles of translational medicine, which would essentially translate into a faster transfer of the results of fundamental biomedical research to concrete methods of diagnosis and treatment, in an interdisciplinary approach "from bench to bed", that defines translational neurosurgery.

The priority areas in both research and practice were: Neuro-Oncology (primary brain tumors, intracranial metastases, meningiomas, sellar and parasellar pathology), Neurosurgical techniques: Intracranial endoscopy, Vascular neurosurgical pathology, Neurotraumatology, Infectious neurosurgical pathology, Multidisciplinary neurosurgical pathology.

I presented the national research projects (won through competition) – 6 projects, as well as international – multiple project with 6 sections, in collaboration with Karolinska Institutet & University Hospital Stockholm (Sweden), international clinical trials – 3. I was the project manager in 2 national projects: "The stem cells in the diagnosis and treatment of brain tumors

- the role of growth factor receptors" (2007-2010) and " Effective strategies for increasing the ambient quality in operating rooms " (2012-2015).

A summary of the research activity results follows: published books and chapters, of which 2 by international publishers; articles published in specialized journals (85 articles between 1994 – 2023, 66 articles between 2007 – 2023, of which 32 ISI indexed articles, being the main author in 14 of them, 2 award-winning articles, Hirsch index H=11); communications at congresses (160 communications between 2007-2023, of which 36 abroad, in 27 countries).

I presented the way I integrated myself into the professional-scientific community, as a member of the medical societies of neurosurgery, neurology, surgery, oncology, endocrinology, rhinology, and neurological rehabilitation. I was elected as vice president of RSN for 3 terms, I was the secretary of RSN, as well as member or secretary/president of several organizing committees and scientific committees of some international congresses.

The thesis also includes a summary of my academic / teaching activity, over a period of 27 years at U.M.F. "C. Davila". As an assistant lecturer, lecturer and associate professor, I carried out the whole range of didactic activities, from practical work to teaching courses, in all academic segments in the university: students, resident doctors in the specialty of neurosurgery, as well as CME courses at a postgraduate level. I was a lecturer at international neurosurgical courses. I supported the professional training of students, resident doctors and young specialists, I attracted and guided them to publish articles in experienced collectives.

Professionally, on the medical-surgical level, I presented the course of training, starting with the residency program, obtaining the diploma of "Atestation de Formation Specialisée" at the Faculté de Médecine de L'Université de Caen (France) in 1996, graduating as a specialist doctor, and later as a senior consultant neurosurgeon. I have completed international specialization courses as well as management courses. I obtained the overspecialization certificate in "Functional and stereotaxic neurosurgery". I presented the neurosurgical practice experience, embodied in the performance of approximately 4,500 surgeries over the period of 2013-2023.

Section 2:

The thesis summarizes the scientific results over the period of 2007-2023, structured by fields, as they materialized in the published books and articles, with particular emphasis on those that appeared in ISI or IDB-indexed journals. I have grouped the subjects of major interest as follows:

- Primary brain tumors: A major concern of our research team has been to investigate cellular vulnerabilities in gliomas in general, and high-grade gliomas and glioblastomas (which are the best study models) in particular. A number of molecular targets possibly influenced by certain treatments have been identified. We focused on projects with high potential for rapid translation into medical practice, respectively: identification of specific membrane receptor alterations, identification of changes in intracellular signal transduction pathways, evaluation of the effect of certain substances or radiotherapy on glioma cell lines, determination of the effect of immunotherapy in gliomas.
- Intracranial metastases: Intracranial metastases represent the most common type of intracranial tumors, and currently their frequency continues to increase. It is estimated that approximately 20-40% of patients with a primary neoplasm will develop brain metastases. About 15% of cases present with neurological symptoms before the systemic neoplasm is diagnosed. Approximately 10% of cases with brain metastases do not have the primary neoplasm identified. That is why I was concerned with the study of surgical treatment techniques in intracranial metastases and research directions for the development of new medical therapies in neuro-oncology.
- Meningiomas: Although in the vast majority of cases, they are benign tumors, there are also atypical and anaplastic meningiomas, with aggressive biological behavior and increased risk of recurrence. Important research has been done and is still ongoing to identify the type of clinical behavior of the tumor and its malignant potential, as well as to discover new therapeutic possibilities. Currently, the treatment of these extraneuraxial tumors is essentially neurosurgical, aiming at the total excision of the meningioma and its insertion, without superimposed neurological deficits. However, the anatomical location of the meningioma sometimes makes its complete resection impossible, with the occurrence of recurrence. The study of meningiomas preoccupied me throughout my career, the results of research in this field being communicated through a series of articles.
- Sellar and parasellar pathology: The neurosurgical department where I work, is a sellar and parasellar neurosurgical pathology reference center, which gave me the opportunity to operate approximately 80-100 pituitary tumors/year and

represented an important advantage in specific research. In order to establish the best therapeutic options and obtain the best results in the surgical treatment of pituitary tumors, we have conducted extensive clinical studies on these types of tumors.

- Intracranial endoscopy: Introducing new intracranial endoscopy techniques in our clinic has been one of my career priorities. Thus, in 2000, an intracranial neuroendoscopic intervention was carried out for the first time nationally, in the 3rd Neurosurgical Department of "Bagdasar-Arseni" Emergency Clinical Hospital. Another national first was the realization of the first endoscopic transnasal transsphenoidal approach to the sellar region. I have published 2 books and 3 articles summarized in this chapter of the thesis.
- Vascular neurosurgical pathology: Vascular neurosurgery has always represented an interesting, cutting-edge field, requiring rapid risk assessment, adaptation to specific pathological conditions, good intensive therapeutic support, advanced diagnostic technology, special surgical skills, and appropriate instrumentation. Over the years we have analyzed surgical anatomy, pathophysiological findings, refinement of diagnostic imaging, and the evolution of therapeutic options in the field of vascular neurosurgery, the study materializing itself in a series of articles.
- Neurotraumatology: Although from an academic point of view, the most challenging area of research is to elucidate the molecular and biochemical mechanisms involved in the neural response to trauma and to discover methods to induce and optimize nerve recovery, much remains to be done also in terms of the pragmatic neurosurgical approach.
- Infectious neurosurgical pathology: Brain abscesses are rare neurosurgical conditions, but they can be life-threatening. There is controversy regarding the therapy of brain abscesses, and clinical trials are not numerous. That is why we considered it appropriate to conduct a clinical analysis on this subject.

Section 3:

Academic/teaching career advancement and development plans: Editing a neurosurgery guide that integrates the accumulated experience of Romanian neurosurgery personalities, from various university centers, to provide resident doctors and young specialists with the basic notions of neurosurgical clinical practice. In addition – the editing of a basic neurosurgical

techniques guide which will be useful in the preparation for board exams and senior consultant exams for neurosurgeons. The editing of neurosurgery courses for students, which also contain suggestive case presentations, considering that neurosurgery will be integrated as a way of training students in U.M.F. "C. Davila" Bucharest. Diversification of activities with the students' Neurosurgery Club - theoretical presentations, case presentations, and workshops.

Continuing the tradition – CME courses in neurosurgery nationally, ANCA conferences, workshops. Expanding collaborations with universities of international prestige (the University of Edinburgh is a reference center in translational medicine).

Professional career advancement and development prospective: the approach of complex neurosurgical cases, with the implementation of new innovative technologies in neurosurgery - especially in the field of intracranial tumors, skull base tumors and neuroendocrine pituitary tumors. Implementation of the transsphenoidal endoscopic approach in the daily practice of the clinic.

Plans for the advancement and development of the scientific research activity: Continuation of research in the field of neuro-oncology. I am interested in the molecular biological changes of the neoplastic cells of high-grade gliomas and glioblastomas, changes that can constitute a biological target for specific therapeutic agents, for immunotherapy or for counteracting the therapeutic resistance of malignant brain tumors. It is also of interest to study potential biomarkers in primary malignant brain tumors, especially those that can be detected by liquid biopsy.

The development of research on neuroendocrine pituitary tumor cell lines, being known that, although these tumors are mostly benign, about 40–50% are invasive in the neighboring structures, and about 10% have aggressive biological behavior, with rapid growth, multiple recurrences, and resistance to conventional treatment. Further publication in ISI-indexed high impact factor journals. Some topics of interest would be: "Combining immunotherapy and targeted therapies to induce an enhanced therapeutic effect in brain tumors", "Molecular targeted therapies and image-guided precision medicine for malignant diseases". Based on my own experience, I intend to write scientific papers, as : “Systematic retrospective review and Guidelines for the Treatment of adults with metastatic brain tumors”, “Systematic retrospective review and Guidelines on the primary management of Patients with nonfunctional pituitary adenomas”.

The present work on this thesis gave me the opportunity to make a full review of my post-doctoral activity, to systematize the results, and to establish better-defined directions for my future work and development.