HABILITATION THESIS - ABSTRACT

Genetic factors involved in the occurrence of hematological malignancies and hemostatic disorders

Dr. ADRIAN PAVEL TRIFA

UMF
UNIVERSITATEA DE MEDICINĂ ȘI FARMACIE
IULIU HAȚIEGANU
CLUJ-NAPOCA

This habilitation thesis, entitled "Genetic factors involved in the occurrence of hematological malignancies and hemostatic disorders" presents my achievements obtained after defending my PhD thesis, entitled " Genetic factors involved in the occurrence of the myeloproliferative neoplasms and their thrombotic complications", back in 2014. The first chapter of the habilitation thesis, entitled "Post-doctoral research regarding the contribution of the genetic factors to the occurrence of malignant and non-malignant hematological diseases" comprises three subchapters, reflecting my main interests, namely:

- Defining the genetic predisposition to myeloproliferative neoplasms
- Genetic factors involved in acute myeloid leukemia
- Genetic factors involved in hemostatic disorders

The second chapter, entitled "The steps taken in the professional evolution" points out my major achievements in the research, teaching, medical and humanitarian activities, as well as so far established collaborations on a local, national and international level . The third chapter, entitled "Future directions of professional development" forecast future directions in the research, teaching, medical and humanitarian activities, as well as future world wide collaborations.

Most of my work performed after my PhD reverberates around various blood disorders, including both malignant and non-malignant disorders. I was introduced to these conditions by Dr. Andrei Cucuianu in 2008, while I was still a forth year medical student. With this thesis, I want to thank this great man for enlightening my path.

I am a 35 years old geneticist, researcher, teacher and above all a humble human. Starting 2011, I am an Assistant Professor in the department of medical genetics, at the "Iuliu Haţieganu" University of Medicine and Pharmacy in Cluj-Napoca. In 2015, I obtained the degree of consultant in genetics, while in 2020 I became senior consultant in genetics. As soon as I became a consultant, I started working as a geneticist at "Prof. Dr. Ion Chiricuţă" Oncological Institute, Cluj-Napoca. I have a work experience of over 15 years in the field of research, addressing the involvment of genetic factors in various pathological and physiological conditions. While being still a second year medical student, I was welcomed to work in the research laboratory of the medical genetics department of the "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca. During my first 4 years in the department, I worked together with Assoc. Prof. Radu Popp on the genetic factors involved in infertility, which also made out the foundation of my graduation thesis. Around that time, we started a productive collaboration with the department of pharmacology and toxicology, initially consisting of two projects coordinated by Prof. Dr. Anca Buzoianu, in which we assessed the pharmacogenetics of antiepileptic drugs and oral anticoagulants. As a student I participated at numerous student and medical conferences, on a national and international level. The results which I presented herein were well received, therefore being frequently awarded with prizes. I was also named "student of the year" by the "Iuliu Haţieganu" University of Medicine and Pharmacy, for two consecutive times, in 2007 and 2008.

However, towards 2010, the year in which I graduated medicine, my interests gradually shifted towards what eventually became my main scientific preoccupation, translational research in the field of hematology. Initially, I started developing and implementing genotyping protocols for various somatic mutations involved in myeloid malignancies, such as *JAK2* V617F, *FLT3*, *KIT* D816V, and others, some even for the first time in Romania. At the beginning of 2009, I stumbled upon three articles describing the *JAK2* 46/1 haplotype, the first constitutional genetic factor predisposing to myeloproliferative neoplasms. Shortly after, I developed a genotyping protocol for *JAK2* 46/1 and analyzed it in a cohort of Romanian patients with myeloproliferative neoplasms. All these efforts led to my first 3 ISI articles as first author, published in Revista Română de Medicină de Laborator, Acta Haematologica and Annals of Hematology, respectively. The results I published herein came to the attention of the European working group on the molecular diagnosis in myeloproliferative neoplasms. Consequently, I was invited that year (2010) to share these results with them in their annual conference, held in Portugal. Upon

attending the conference, I was also invited to join the European working group on the molecular diagnosis in myeloproliferative neoplasms as a permanent member, which I accepted. Genetic factors involved in myeloproliferative neoplasms also represent the subject of my PhD thesis, which I deffended in 2014.

The genetic factors involved in myeloproliferative neoplasms, especially the genetic predisposition to these diseases, have represented the main focus of my post-doctoral research. I won my first national research grant as principal investigator in 2015. It dealt with the genetic variation at *JAK2*, *TERT*, *HBS1L-MYB11, MECOM* loci as a possible factor predisposing to myeloproliferative neoplasms. During that time, I also obtained another project, in which I studied the correlation between *JAK2* V617F allele burden and various clinical parameters of patients with myeloproliferative neoplasms. A third national project as a principal investigator I obtained in 2018 and it allowed me to analyse more in depth the genetic predisposition to myeloproliferative neoplasms. In my last project as principal investigator, obtained in 2020, I will assess the effect of additional somatic mutations in patients with myeloproliferative neoplasms.

Acute myeloid leukemia represents another major direction of my research, especially after my PhD. I developped this research area together with Prof. Dr. Claudia Bănescu, from the University of Medicine, Pharmacy, Science and Technology from Târgu-Mureș. The funds acquired through various research projects that we won, allowed us to study different somatic mutations and their relationship with clinical features of patients with acute myeloid leukemia. The genetic predisposition to acute myeloid leukemia was one of our major preoccupations. We analysed genetic polymorphisms involved in multiple patogenetic pathways, such as DNA stability and integrity maintenance, oxidative stress and inflammation, both as risk factors in the occurrence of acute myeloid leukemia and its' associated somatic mutations, as prognostic factors.

Further, I continued my research with the Department of pharmacology from "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, regarding the involvement of genetic factors in hemostasis, undertaking new correlations between *VKORC1* polymorphisms and the hemostatic balance, as well as the pharmacogenetics of new oral anticoagulants.

Regarding my publications, I published 66 articles so far, indexed in Pubmed, 44 of them after defending my PhD thesis. They were cited more than 850 times, generating a Hirsch index of 13 (ISI Web of knowledge), 14 (Scopus), and 17, respectively (Google Scholar).

Among the collaborations I established so far, I think the most relevant is the network of hematologists I have established in the last 12 years, starting from the Hematology Clinic from Cluj-Napoca, extending thereafter to numerous other hematology wards and clinics across the country, from Baia-Mare, Sibiu, Bucureşti, Oradea, Timişoara, Deva, Constanţa, Brăila, Târgu-Mureş, to Satu-Mare, and other. In all these years, I strived to develop diagnostic assays for various somatic mutations seen in hematological malignancies, together with research activities related to these diseases. As far as international collaborations are concerned, I think it is of utmost importance to mention my membership in the European Network of Experts in the Molecular Diagnosis of Myeloproliferative Neoplasms, comprising experts from 15 European countries. I have also obtained a fellowship at the Henri Becquerel Institute from Rouen, France, which allowed me to learn and implement innovative techniques for assessing molecular alterations specific for acute leukemia back in Cluj-Napoca. The collaboration with Prof. Gabriel Ghiaur, from Johns Hopkins University and Medical Center, USA, allowed me to apply and obtain a fellowship from the American Society of Hematology, that I will pursue in 2022.

The four projects I won as a principal investigator, numerous other projects in which I was investigator, the articles that I have published in significant journals, specifically those as principal author, the numerous local, national and international professional collaborations, the ability to coordinate and teach students to conduct research on their own, prove my independent researcher status, able to coordinate PhD students and research teams.

Regarding my future professional development, I strongly believe that the three components - scientific research, teaching and medical activity are interdependent. All of them should evolve together in defining my career.

Regarding research activity, I will continue to develop the concept of translational research in hematological malignancies. After obtaining the degree of PhD supervisor, I plan on increasing our research team. This expansion will allow me to develop new research directions, concerning also solid tumors, such as breast and ovarian cancer and melanoma. I also plan to study the genetic predisposition syndromes to various rare cancers. Obviously, this implies the development of a network of oncologists. In this matter, I will try to establish new connections and collaborations at local, national, and international level. I will support the participation of the members of our research team at different exchange programs and fellowships, within the country and abroad.

Regarding my teaching activity, I will encourage diminishing the overlapping of topics especially within molecular disciplines, in order to eliminate the redundancies, especially those related to fundamental genetic mechanisms. Most of our students are future clinicians, as such, in order for them to benefit from the knowledge acquired while studying medical genetics, I think this area should be more integrated in the context of clinical topics. Also, I will support the early involvement in our research team of students who show interest in translational research.

Regarding the medical activity, I will continue to develop molecular assays for mutations specific to hematological malignancies and solid cancers. I will strive to implement functional molecular boards, which is also one of my major goals. I will also continue to diagnose, assess and guide patients with various genetic diseases and to support them by every possible means, including financial aid, mostly offered through the non-governmental organization Noi pentru EI (NEI), in which I serve as president. It is the central philosophy of our organization that all patients that need genetic tests should benefit from free genetic testing.