Universitatea *Transilvania* din Braşov

HABILITATION THESIS

Summary

Adult and pediatric asthma and related co-morbidities – from research to clinical practice and purposeful education

Domain: Medicine

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The habilitation thesis "Adult and pediatric asthma and related co-morbidities – from research to clinical practice and purposeful education" is the epitome of the scientific and academic activity in the last 12 years and encompasses the major scientific, professional and academic achievements, with the main research focus on adult and pediatric asthma and its co-morbidities.

The challenges in asthma research, management and education are both difficult and interesting. I tackled them with enthusiasm, tenacity, and dedication to develop new methods of analysis and provide new solutions to keep up with the ever-changing threats. My scientific, professional and academic development in the last 12 years reflects the profound implication in the asthma management directions outlined below, with notable achievements

a. ***Research and development programmes focusing on prevention, disease mechanisms and biomarkers, personalised approaches and development of new treatments curing the disease.***

b. ***Integrative management of asthma patients*** *at a global level including next generation guidelines largely applicable at all levels and in any country, registries for asthma, improved access to early diagnosis and quality treatment, environment and co-morbidities control, patient and general public education, cost-efficient use of resources and patient-centered care models*

c. ***Recognition of asthma as a major health problem*** *by the society and policy makers, with emphasis on the huge economic burden, decreased quality of life and impact of the child development into a healthy adult valuable for the society*

d. ***Strategic partnership between all stakeholders*** *(patients and caregivers, doctors and allied health, pharmacists, teachers, governments and policy makers, academia and pharmaceutical/devices industry) resulting in a* ***community approach to a community problem targeting*** *asthma*

Part I *presents the scientific, professional and academic achievements*

Research activity*, described in* ***Chapter 1****, focused mainly on:*

1. *the description and validation of pediatric and adults asthma phenotypes, endotypes and biomarkers;*
2. *endotype driven asthma treatment and new potential curative approaches;*
3. *tackling environment (infections, pollution), lifestyle (diet, exercise) and asthma co-morbidities (allergic rhinitis, obesity, food allergy);*
4. *asthma prevention and control;*
5. *development and implementation of new models for cost-efficient disease management.*

I published 58 papers with 2567 citations and h-index 18 in ISI Web of Science and 8590 citations in Google Scholar (4644 since 2012) with h-index is 20 and i-10 index 32.

Chapter 1.1 describes my contribution to the field of asthma phenotypes and endotypes. Defining the relation phenotype – endotype - biomarkers has a been a constant research theme since 2009 and is reflected by 12 papers with a total of 268 citations in journals with high impact factor, by lectures, oral communications and posters presented at top level international meetings and by the ongoing PN II research project aiming to endotype patients with non-eosinophilic asthma.

My research in this area brought forward several key findings summarized below:

1. *The necessity to link the key pathogenic mechanism (endotype) with a clinical phenotype of asthma.*
2. *The validity of the endotype should be demonstrated by longitudinal replication across different populations while predicting meaningful differences among individuals; should reflect the diseases' biology, natural history and predict response to treatment; should be easily applicable and useful in daily clinical practice and cost-efficient*
3. *The concept of simple versus complex endotype, using the type 2 asthma as the prototype for a complex endotype. Three main pathways (IL-5, IL-4/IL-13 and IgE driven endotypes) are described, supported by targeted interventions in asthma*
4. *The concept of endotype variability due to external or internal factors modulating the expression of endotype*
5. *The response to a targeted intervention in asthma which may vary between individuals or for the same individual in relation to the outcome measures - the so called dissociated effect*
6. *A stepwise approach to classify asthma incorporating precision (or deep) phenotyping, longitudinal data such as exacerbation rate, fluctuation analysis of lung function or exhaled NO, based on the author's previous original research together with identification of novel causal pathways with corresponding biomarkers (endotype-driven asthma classification) and translation of biomarkers into pathways-specific diagnostic tests*
7. *Several major unmet needs in asthma endotyping such as profiling the non-type 2 asthma and the resident cell compartment of asthma (the epithelial-mesenchimal trophic unit - EMTU) were tackled by the author.*
8. *Endotype-driven treatment of asthma was described for type 2 asthma and non type 2 asthma (neutrophilic, microbiome and EMTU driven) and for the obese asthma phenotype*
9. *Linking the endotype driven disease classification and management with the concept of precision medicine in asthma*
10. *The importance of describing and validation new phenotypes, such as epigenetic phenotypes, or neurophenotypes together with developmental endotypes addressing disease inception and progression highly needed for the outset of early prevention and disease modifying strategies as part of the 4Ps of precision medicine*

Chapter 1.2 focuses on the research on asthma biomarkers. Being closely linked to asthma phenotypes and endotypes the biomarkers research line of the author complemented the achievements in describing disease phenotypes and endotypes acknowledged by the worldwide scientific community through highly cited research papers, invited reviews, lectures and oral communications. In 2010 the author published a pioneering research on serum IL-17 as a biomarker of severe asthma followed by the recent demonstration on serum IL-5 and IL-13 as the best predictors for the blood eosinophilia phenotype in adult asthmatics. Several key concepts on biomarkers are introduced such as the relation to an endotype (the biomarker can be

a marker or the fundamental mechanism itself), validity (reproducible, easily measurable and affordable) and relevance (pathway specific and related to the relevant clinical end points)

Chapter 1.3 *describes the author contribution to novel targeted treatments for asthma such as quilizumab and allergen immunotherapy (AIT). AIT has the potential of modifying the fundamental, underlying disease mechanisms and shows sustained clinical effect. The author recently evaluated the benefits of AIT in several review paper and two international consensus documents and is leading the Task Force of International Guidelines on AIT in asthma developed by the European Academy of Allergy and Clinical Immunology (EAACI)*

Chapter 1.4 *describes the contribution to the implementation of precision medicine principles for asthma as a compelling continuation of the phenotypes, endotypes and biomarkers field pioneered by Ioana Agache since 2009. As recognition of the achievements in the field the author was included in two prestigious Expert Panels reuniting the major scientific academies in the field of Asthma and Allergy – EAACI, European Respiratory Society (ERS), European Rhinologic Society and the American Academy of Allergy, Asthma and Immunology (AAAAI).*

Chapter 1.5 *focuses on the contributions regarding asthma co-morbidities. As a major co-morbidity of asthma, allergic rhinitis (AR) represented a special focus of the research, from international guidelines (ARIA) authorship to epidemiology of the disease and risk factors, new treatments for AR evaluated both in randomized control trials and real-life scenarios and new models of care. As Secretary of the EAACI Asthma Section I initiated and chaired a Task Force on life style and asthma that produced several consensus documents and position papers based on systematic reviews derived data. As a member of the Expert Panel of EAACI Food Allergy and Anaphylaxis Guidelines I brought my expertise on asthma in relation to food allergy and anaphylaxis. I led the Task Force on Food Allergy and Anaphylaxis Management in the Community and was part of the Food Allergy Prevention and Epidemiology Task Forces. As a member of the GA²LEN-DARE projected funded by EU under the 6th Framework Programme Ioana Agache evaluated the evidence for viruses and bacteria in asthma exacerbations.*

Chapter 1.6 *provides insights into the author's contribution to asthma management plans and new models of care. This research direction was approached in the chapter "Best buys for asthma prevention and control" from the Global Atlas of Asthma, where I was both Editor in Chief and co-author. The author describes 10 key points to be tackled by an efficient asthma management plan.*

Better asthma diagnosis is a prerequisite of an efficient management plan. My research focused on the in vivo and in vitro diagnosis of allergies and asthma, leading an EAACI Task Force focusing on provocation tests in asthma and allergic diseases and being co-author of the EAACI guidelines for molecular diagnosis in allergy.

The standard of care for asthma and allergic diseases within a primary care setting has a strong influence on disease prevention and control, quality of life, and patient satisfaction. The level of knowledge of asthma and allergic diseases and the accessibility to regular follow-up are essential. I led an EAACI Task Force on Allergy and Asthma Management in Primary Care aiming to deliver the best care pathways for the general practitioners as part of the integrated management of asthma and allergic diseases

The low public health priority of asthma due to the importance of other illnesses and to the lack of awareness of the general public and policy makers is an important barrier to efficient implementation of asthma management plans. Two recently published papers highlight my activity in increasing awareness on asthma and allergic diseases in order to ensure proper funding for research and efficient management of these diseases.

Chapter 2 describes the professional developments of the author.

A brief career overview is presented in chapter 2.1 from graduation and PhD thesis Magna cum Laudae to a successful researcher pathway (58 papers with 2567 citations in ISI Web of Science and 8590 citations in Google Scholar; h-index 18 in ISI Web of Science, 20 in Google Scholar and i10-index 32), membership of the Expert Panels for several international guidelines and consensus documents, editorship and co-authorship of several books and Atlases, highly respected reviewer and Associate Editor, Vice-President and President Elect of the European Academy of Allergy and Clinical Immunology (EAACI). Developing a unique combination of abilities such as being a compassionate medical doctor, a good teacher and top researcher was the main goal of my career development. The PhD thesis highlights are presented in chapter 2.2 together with involvement in national and international research projects as a support and as a continuation of the PhD thesis. Leadership of national research programmes (PN-II-RU-TE-2014-4-2303 – Endotypes of Non-Eosinophilic Asthma - ENDANA) and partnerships in EU projects: COST actions (COST BM 1201: Early Origins of Chronic Lung Disease) and GA2LEN program, DARE – diary card piloting and validation, are described in details with aims and deliverables. The author was an invited expert for the European Asthma Research and Innovation Partnership (EARIP) project and is a member of the AIRWAYS ICPs consortium. Chapter 2.3 describes the professional development and national and international recognition describing the achievements as member in Steering Committees and editorial boards for the development of international guidelines, consensuses and statements, the editorial activity, authorship of books and monographs, the activities as a reviewer and lecturer at prestigious international meetings. Leadership and managerial skills are developed in chapter 2.4

Chapter 3 describes the academic development from 1996 to present from Junior Assistant Professor at Transylvania University from Brasov to Associate Professor. Through my academic career I focused on engaging students in the learning process and motivating them to practice high level critical thinking skills, while promoting meaningful learning experiences. A new teaching approach based on the interactive teaching styles incorporating a multitude of goals beneath a single roof was implemented. Another new approach was the creative scientific research to improve students' perception of academic success. The students were stimulated to approach a task-oriented behavior, exactness and consistency in the scientific quest while respecting the ethic principles of research. Proactivity, personal responsibility, vision, and discipline were enforced as basic principles of creative scientific research. A high quality research environment was ensured in order to develop research strengths of the student with the dissertation as a key opener for future career development

Part II elaborates on the evolution and development plans for career development

My career achievements in the last decade offer me a forefront position in translating bench-to-bedside innovations while offering the best education and research training.

Building on the results from the PN-II-RU-TE-2014-4-2303 project, Endotypes of Non-Eosinophilic Asthma (ENDANA) project my future research plans for non-eosinophilic asthma focus on validation of the subendotypes both through therapeutic targeted intervention and by longitudinal evaluation of the stability of the clusters described. The same approach will be undertaken for type 2 asthma subendotypes using and unbiased approach such as topological data analysis, Bayesian network analysis and longitudinal evaluation. Expansion of endotype and biomarkers research into the pediatric asthma population is also anticipated. Expected benefit is translation of endotype research into bedside, clinically meaningful decision protocols for selecting a targeted intervention into a given asthma patient and for a better prognosis of disease evolution.

In parallel my research plans focus on biomarkers and endotypes for allergen immunotherapy, international guidelines and consensus documents development and implementation, Mobile Health/Allergy 2.0 and 3.0 and development of protocols for educational intervention in the community for asthma management

We have a moral duty to promote high standards of both undergraduate and postgraduate medical education. I will continue to offer medical students and healthcare professionals (HCP) purposeful training to reflect changes in practice, changes in the needs of patients and the service, and changes in society's expectations of the way HCPs work.

Both as clinician, researcher and teacher I will continue to develop a wide-ranging competencies portfolio encompassing clinical update, research and scientific writing, multidisciplinary context of patient care, ethical practice, communication, management and behavioral skills, team building, information technology, audit, and appropriate attitudinal change to ensure improved outcomes and satisfaction for my patients, my students and my colleagues

In June 2017 I will take over the Presidency of the European Academy of Allergy and Clinical Immunology (EAACI), with a 2-year mandate. Besides the international recognition I aim to facilitate the cooperation between international and national societies as a scaffold for local adaptation and implementation of guidelines and cutting-edge research, best practices and efficient health policies and advocacy for promoting asthma as a major health problem.

I plan to develop in the next 4 years a new educational portfolio for students and young HCPs that facilitate both professional and career development with a clinical and a research track. The concept of purposeful education including key-concepts such as work-experience and social service will be introduced. New tools facilitating interactive learning, such as such as tutorials for the faculty master programmes and doctoral school, multidisciplinary learner programmes, interactive brainstorming, buzz-sessions, Think-Pair share, incident process, etc. are envisaged. Being certified for my English literacy for teaching purposes I will actively support the creation of a new Department with English teaching for foreign students.

Building the community feeling for students and teachers with increased engagement in shaping the academic landscape and the organizational culture is also a priority.

Both PhD coordination and achieving full professorship are envisaged in order to progress with my academic activity in the next 2 years. Through my involvement in coordination of doctoral thesis I will continue to support the young doctors to perform their own researches and to communicate the results of their research in the national and international scientific environment. Early career researches should be strongly supported in preparation of their doctoral thesis through cooperative projects developed with colleagues from related disciplines.