

## A life dedicated to Alzheimer's disease research: in memory of Inge Grundke-Iqbal (1937–2012)

Cheng-Xin Gong · Alejandra del C. Alonso ·  
Jian-Zhi Wang

© Springer-Verlag Berlin Heidelberg 2012



Alzheimer's disease (AD) was first reported 106 years ago, but until the 1980s, little was known about the underlying disease mechanisms. Modern AD research had been driven mainly by two milestone discoveries made in the 1980s: (1) identification of amyloid  $\beta$  peptide as the major component of amyloid plaques and its precursor protein, and (2) identification of hyperphosphorylated microtubule-associated protein tau as the building block of paired helical

filaments (PHFs)/neurofibrillary tangles (NFTs). On 22 September 2012, the AD field lost a pre-eminent figure—Inge Grundke-Iqbal—who discovered hyperphosphorylated tau in Alzheimer PHFs/NFTs.

Inge Grundke-Iqbal was born in Osnabrueck, Germany, on 20 July 1937. After receiving a PhD degree in biology and biochemistry at Georg August University, Goettingen, Germany, in 1967, she started her research career as a postdoctoral fellow at the Max-Planck Institut fur Immunobiologie, Freiburg i. Br., Germany. In 1969, she moved to the USA and received further postdoctoral training at the University of Michigan, Ann Arbor, MI (1969–1970); the New York University Medical Center, New York, NY (1970–1972); and the Albert Einstein College of Medicine, Bronx, NY (1972–1974). In 1974, she was promoted to Assistant Professor in the Department of Pathology of the Albert Einstein College of Medicine, initiating her research focus on neuropathology and AD. In 1977, she moved to the New York State Institute for Basic Research in Developmental Disabilities (IBR), located in beautiful Staten Island, a borough of New York City. The institute, then under the direction of the late Henryk M. Wisniewski (also a pioneer of AD research), was an incubator of AD research and attracted many researchers in the field. It was here that she directed the Neuroimmunology Laboratory and, from 1997 to 1998, chaired the Department of Neurochemistry. She spent most of her time in her laboratory during her last 35 years, right up until the week before her death.

Inge Grundke-Iqbal embarked upon her career in AD research in 1974 in the Department of Pathology at the Albert Einstein College of Medicine together with her husband, Khalid Iqbal, who also is a world-renowned AD researcher. The department was directed by Robert D. Terry and was the most active AD research group in the world at that time. The biggest question in the AD field at

---

C.-X. Gong (✉)

Department of Neurochemistry, New York State Institute for Basic Research in Developmental Disabilities, 1050 Forest Hill Road, Staten Island, New York 10314, USA  
e-mail: chengxin.gong@csi.cuny.edu

A. C. Alonso

Biology Department, College of Staten Island, The City University of New York, 2800 Victory Boulevard, Staten Island, New York 10314, USA

J.-Z. Wang

Department of Pathophysiology, Key Laboratory of Neurological Diseases of the Education Committee of China, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China

that time was, what made up amyloid plaques and PHFs/NFTs, the hallmark brain lesions of AD described by Alois Alzheimer more than a century before. To address this question, Inge Grundke-Iqbal generated the first polyclonal antibody to PHF protein purified by SDS-PAGE of NFTs that Khalid Iqbal had bulk-isolated for the first time from autopsied AD brains. The anti-serum to PHF protein, which they subsequently identified as tau protein, not only stained NFTs in AD brain, but also reacted with a brain microtubule-associated protein. This anti-serum was the first antibody to PHFs/NFTs. In the early 1980s, the AD field believed that PHFs/NFTs were insoluble aggregates cross linked with  $\gamma$ -glutamyl- $\epsilon$ -lysine, whose protein nature could not be identified. The couple spent several more years intensively working, using several approaches, until finally their determination paid off, and they were able to demonstrate that some PHFs/NFTs are actually soluble and that they are made up of abnormally hyperphosphorylated tau. These seminal findings made at IBR, which broke the dogma that composition of PHFs/NFTs could not be studied, were supported by several other studies in the 1980s and opened a new avenue for AD research.

In addition to her seminal discovery of abnormally hyperphosphorylated tau as the protein subunit of PHFs/NFTs, Inge Grundke-Iqbal made numerous other contributions to the field of tau pathology, neurodegeneration and neuroregeneration. Together with Khalid Iqbal, she discovered that abnormal phosphorylation of tau precedes the formation of the NFTs and tau ubiquitination and that microtubule assembly is deficient in AD brain. They also identified, in collaboration with Heiko Braak and Eva Braak, neuropil threads as the third location of PHFs outside of NFTs and neuritic plaques. In the last 10 years, Inge Grundke-Iqbal's research interest was focused on neurogenesis and its potential for treating neurodegenerative diseases, such as AD. She discovered an 11-mer peptide derived from ciliary neurotrophic factor (CNTF) that can enhance neurogenesis and neuronal plasticity and improve cognition of normal adult mice and of transgenic mouse models of AD and Down syndrome. Very recently, she narrowed it down to a tetrapeptide. These new findings provide hope for using small peptide to promote neurogenesis and to treat neurodegeneration.

Behind most great discoveries in science is a unique combination of the talent and personality of the discoverers. Inge Grundke-Iqbal received a typical strict education and training in Germany and was very serious in all aspects of the science she was involved with. Working together with her for over 20 years, the present authors repeatedly witnessed her meticulousness with her research. She did not allow any doubt in her conclusions derived from experiments. This characteristic contributed to her persistence to uncover the truth of what makes up PHFs/NFTs,

despite ignorance of and skepticism over her and Khalid Iqbal's initial work.

During her scientific career, Inge Grundke-Iqbal authored/co-authored more than 200 scientific publications in prestigious journals and books. Her research contributions won her high recognition and honors. She received the New York State Governor's Award for Women of Distinction in 1994, the Lifetime Achievement Award for Research on Alzheimer's Disease at the International Alzheimer Congress in 2000, and the T.L.L. Temple Foundation Discovery Award for Alzheimer's Disease Research in 2001. She was also awarded an Honorary Professorship by Tongji Medical University, Wuhan, China in 2001, and by Nantong University, Nantong, China in 2011.

Together with Khalid Iqbal, Inge Grundke-Iqbal directed a large research group at IBR during the last 35 years. They trained many young scientists, many of whom have become independent investigators with major contributions of their own to the AD field. The present authors are among those fortunate enough to have received excellent training from Khalid Iqbal and Inge Grundke-Iqbal, enabling them to pursue success in their scientific careers. A life devoted to science is difficult but rewarding; it was Inge Grundke-Iqbal's inspiration that led the authors to fall in love with science and to devote their lives to follow her legacy. One common statement from everyone who received research training from or worked in Inge's and Khalid's group is that the group was like a second family and the lab like a second home. And Inge Grundke-Iqbal was the mother of that family. She was known to shed tears when any member of the group suffered personal problems. The love within this research family made it such a wonderful group to belong to, a heartbreak to leave, and the encouraging force for each member to pursue his or her research goals.

People who receive the most respect are those who not only make great achievements but also are generous and have big hearts for others, especially for the disadvantaged. Inge Grundke-Iqbal, together with Khalid Iqbal, co-founded a public, non-profit organization—the Promotion of Education in Pakistan (PEP) Foundation—in 1994. During the past 18 years, she donated her time and money and personally traveled many times to Pakistan to help young people there obtain a quality higher education. As a result of the PEP Foundation, led by Inge and Khalid, hundreds of Pakistani youth received higher education, which they otherwise would have been unable to receive.

Inge Grundke-Iqbal probably spent more time in her office and lab than in her home. She had an astonishingly rich life dedicated to AD research. Her legend inspired all those who had the privilege of working with her. She will remain in the memory of those who knew her, and her impact on science will continue into future generations that will benefit from her significant discoveries in AD research.