

INNOVATORS & IDEAS: RESEARCH LEADER

Keqiang Ye: The C/EBP β /AEP pathway is the key driver for Alzheimer's disease (AD) and Parkinson's disease (PD) pathogenesis and its specific inhibitor attenuates AD/PD pathologies

© The Author(s), under exclusive licence to Genomic Press 2024

Brain Medicine; <https://doi.org/10.61373/bm024k.0010>

Keywords: α -Synuclein, Alzheimer's disease, Asparagine Endopeptidase (AEP), CCAAT/Enhancer Binding Protein Beta (C/EBP β), Parkinson's disease, positron emission tomography tracer.

Dr. Keqiang Ye is currently an endowed professor and Department of Biology Chairman at Shenzhen Institute of Advanced Technology (SIAT), China. Prior to this role, he held positions at Emory University in Atlanta, Georgia, USA, serving as an Assistant Professor (2001–2007), a tenured Associate Professor (2007–2010), and a Full Professor (2010–2021). He has received numerous professional honors, notably the Distinguished Scientist Award from the Sontag Foundation (2003) and the American Cancer Research Scholar Award (2004). His research focuses on neurodegenerative diseases, including molecular mechanisms in pathogenesis, early diagnosis, and drug development. With 265 published papers, including contributions to esteemed journals such as *Cell*, *Nature*, *Nature Medicine*, *Neuron*, and *PNAS*, among others, Dr. Ye has made significant strides in identifying novel compounds with therapeutic potential for treating neurological diseases, particularly Alzheimer's disease (AD). His work has led to the licensing of these drugs by pharmaceutical companies and their ongoing clinical development. Dr. Ye shares with our readers the highlights of his professional and personal journeys.

The Genomic Press Interview Part 1: Keqiang Ye – Life and Career

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

As a rotation graduate student at Emory, I discovered nscapine, a natural product, as an anticancer drug through a visual structural comparison of known microtubule inhibitors from the Sigma catalog. This discovery led to the publication of my first *PNAS* paper as part of my PhD thesis, and nscapine was licensed by a biotech company and progressed into clinical trials against prostate cancer. As a postdoc at Johns Hopkins University, I furthered my research by uncovering the role of PIKE GTPase in mediating nuclear PI3K signaling (*Cell*, 2000), PLC- γ 1's mitogenic effect via nerve growth factor (NGF)-triggered PLC- γ 1 nuclear translocation and PIKE activation (*Nature*, 2002 and featured as a research highlight by *Nature Reviews Molecular Cell Biology*, 2002;3:149). These exciting findings not only advanced scientific knowledge but also fueled my enduring passion for science and drug discovery.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channeled you toward that leadership responsibility?

As a faculty member at Emory, my lab dissected how neurotrophin-provoked nuclear PIKE/PI3K signaling promotes neuronal survival and published dozens of top-level papers (*Nature Neuroscience*, 2003; *Molecular Cell*, 2005; *EMBO Journal*, 2004, 2006; *Nature Cell Biology*, 2007, 2008). As a faculty member at Emory, my belief in dedicated work and



Figure 1. Keqiang Ye, PhD, Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, China.

a problem-solving approach has been crucial in shaping my leadership journey. I have always endeavored to maintain a holistic view of our research efforts, ensuring that I provide instructive guidance and support to students. Meanwhile, I work closely with my team, fostering a collaborative environment and guiding them through challenges. Over 20 years, positive feedback and notable achievements have further bolstered my faith in this approach. The identification of the small molecular TrkB agonist, 7,8-DHF, and its translational impact, including the FDA approval for R13 (a prodrug of 7,8-DHF) IND for Alzheimer's disease (AD) indication and the initiation of phase I clinical trials have supported our methods and leadership style.

Please share with us what initially piqued your interest in your favorite area of research or professional focus.

My lab discovered that AEP, an acidosis-activated protease, cuts SET, which is a DNase inhibitor during stroke, which can be antagonized by



PIKE (*Molecular Cell*, 2008). This finding was made by serendipity due to preparing the buffer at wrong pH values. My team disclosed that AEP, an asparagine endopeptidase, acts as a delta-secretase that cleaves APP, Tau, and α -Synuclein, promoting AD and Parkinson's disease (PD) pathogenesis.

What kind of impact do you hope to achieve in your field through your focus on your specific research topics?

Based on dozens of top-tier publications, I have put forward a conceptually novel theory that the C/EBP β /AEP pathway is the key driver for AD/PD pathogenesis and its specific inhibitor attenuates pathologies and restores cognitive or motor functions.

Could you tell us about your current scholarly focal points within your chosen field of science?

On the basis of this theory, our team has found that follicle-stimulating hormone (FSH), which drastically escalates after menopause, not only drives osteoporosis but also activates the aforementioned signaling pathway, preferentially instigating AD onset in women (*Nature*, 2022). This discovery sheds light on the perpetual puzzle of why women are more vulnerable to AD onset. Moreover, our team has successfully identified a long-awaited α -Synuclein PET tracer, F0502B, for PD diagnosis (*Cell*, 2023).

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences, that you uphold within your own research environment?

Proposing a hypothesis based on the principles of natural philosophy and addressing a question starting from the epidemiology and unbiased global findings or big datasets are the main habits!

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that you think warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?

To discover the master regulator driving the aging process that not only dictates the lifespan but also encodes different age-dependent diseases' onset and progression deeply stirs my scientific passion.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?

Reading books about history, war, philosophy, fishing, or playing Texas Hold'em POKER are the most preferred leisure moments.

The Genomic Press Interview Part 2: Keqiang Ye – Selected questions from the Proust Questionnaire¹

What is your idea of perfect happiness?

Perfect happiness would be the pleasure arising from internal spiritual peace.

¹In the late nineteenth century various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. Multiple other historical and contemporary figures have answered the Proust Questionnaire, such as Oscar Wilde, Karl Marx, Arthur Conan Doyle, Stéphane Mallarmé, Paul Cézanne, Martin Boucher, Hugh Jackman, David Bowie, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.

What is your greatest fear?

Dismal worrisome uncertainty.

Which living person do you most admire?

My postdoc mentor Dr. Solomon H. Snyder.

What is your greatest extravagance?

To enjoy leisure during the working day.

What are you most proud of?

To single out the key dominant feature from a gigantic tangled dynamic mess!

What is your greatest regret?

We have yet to be able to dissect the reproducible technical experimental details for TrkB receptor activation in primary neurons by its small molecular agonist.

What is the quality you most admire in people?

Dauntless courage and imagination.

What do you consider the most overrated virtue?

The relentless pursuit of perfection.

What is your favorite activity (physical or intellectual)?

Fishing!

Where would you most like to live?

Southern California or Shenzhen, China.

What is your most treasured possession?

Inherent ambition.

When and where were you the happiest? And why were you so happy then?

The first year (1993) when I came to Emory University (Atlanta, Georgia, USA) as a graduate student from China has been the happiest moment in my life. The lifestyle change was drastic and everything around me is so amazing!

What is your most marked characteristic?

Perseverance.

Among your talents, which one do you think gives you a competitive edge?

Imagination.

What is a personality/characteristic trait you wish you had?

Tolerance/patience.

What do you consider your greatest achievement?

To establish the theory that C/EBP β /AEP signaling is the single key driver for aging and age-related disorders.

What do you most value in your friends?

Honesty.

Who are your favorite writers?

Victor Hugo and Mao Zedong.

Who are your heroes of fiction?

The Monkey King.

Who are your heroes in real life?

Albert Einstein and Solomon H. Snyder.



What aphorism or motto best encapsulates your life philosophy? Money takes care of itself!

Keqiang Ye¹ 

¹Shenzhen Institute of Advanced Technology (SIAT), Chinese Academy of
Sciences, 518055 Shenzhen, Guangdong, China
✉ e-mail: kq.ye@siat.ac.cn

Publisher's note: Genomic Press maintains a position of impartiality and neutrality regarding territorial assertions represented in published materials and affiliations of institutional nature. As such, we will use the affiliations provided by the authors, without editing them. Such use simply reflects what the authors submitted to us and it does not indicate that Genomic Press supports any type of territorial assertions.



Open Access. This article is licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (CC BY-NC-ND 4.0). The license mandates: (1) Attribution: Credit must be given to the original work, with a link to the license and notification of any changes. The acknowledgment should not imply licensor endorsement. (2) NonCommercial: The material cannot be used for commercial purposes. (3) NoDerivatives: Modified versions of the work cannot be distributed. (4) No additional legal or technological restrictions may be applied beyond those stipulated in the license. Public domain materials or those covered by statutory exceptions are exempt from these terms. This license does not cover all potential rights, such as publicity or privacy rights, which may restrict material use. Third-party content in this article falls under the article's Creative Commons license unless otherwise stated. If use exceeds the license scope or statutory regulation, permission must be obtained from the copyright holder. For complete license details, visit <https://creativecommons.org/licenses/by-nc-nd/4.0/>. The license is provided without warranties.