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**Educational Experience**

1993 Ph.D., Department of Biological Science, Seoul National University

1986 M.S., Department of Molecular Biology, Seoul National University

1984 B.S., Department of Molecular Biology, Seoul National University

**Professional Experience**

2020 – present Director, Cellular Degradation Biology Center (SRC), Seoul National University

2019 – Present CEO, AUTOTAC BIO Inc., Seoul, Korea

2013 – Present Professor, Department of Biomedical Sciences, Seoul National University

2010 – 2013 WCU Professor, Seoul National University

2008 – 2013 Associate Professor(Tenured), School of Pharmacy, University of Pittsburgh, USA

2002 – 2008 Assistant Professor, School of Pharmacy, University of Pittsburgh, USA

2000 – 2002 Senior Scientist and Key Staff, California Institute of Technology, CA, USA

1994 – 2000 Postdoctoral Fellow & Research Fellow, California Institute of Technology, CA, USA

**Selected Publications**

1. Ji, C.H., H.Y. Kim, M.J. Lee, A.J. Heo, D.Y. Park, S. Lim, S Shin, W.S. Yang, C.A. Jung, K.Y. Kim, E.H. Jeong, S.B. Kim, S.J. Lee, J.E. Na, H.M. Chi, J.I. Kang, H.T. Kim, Y.K. Kim, B.Y. Kim, **Y.T. Kwon**. (2022) The AUTOTAC chemical biology platform for targeted protein degradation via the autophagy-lysosome system ***Nat Comms.*** 13:904.
2. S.M. Shim, H.R. Choi, S.C. Kwon, H.Y. Kim, K.W. Sung, E.J. Jung, S.R. Mun, T.H. Bae, D.H. Kim, Y.S. Son, C.H. Jung, J. Lee, M.J. Lee, J.W. Park, and Y.T. Kwon. (2022) The Cys/N-degron pathway modulates pexophagy through the N-terminal oxidation and arginylation of ACAD10. ***Autophagy*** (accepted)
3. Lee, Y.J., J.K. Kim, C. Jung, Y.J. Kim, E.J. Jung, S.H. Lee, H.R. Choi. Y.S. Son, S.M. Shim, S.M. Jeon, J.H. Choe, S. Lee, J. Whang, K. Sohn, G.M. Hur, H.T. Kim, J. Yeom, E.J. Jo, and **Y.T. Kwon**. (2022) Chemical modulation of SQSTM1/p62-mediated xenophagy that targets a broad range of pathogenic bacteria. ***Autophagy*** (2022 Mar 22)
4. Heo, A.J., S.B. Kim, C.H. Ji, D. Han, S.J. Lee, S.H. Lee, M.J. Lee, A. Ciechanover, B.Y. Kim, and **Y.T. Kwon**. (2021) The N-terminal cysteine is a dual sensor of oxygen and oxidative stress. ***Proc. Natl. Acad. Sci. USA.*** 118:e2107993118
5. Ji, C.H, H.Y. Kim, A.J. Heo, S.B. Kim, S.H. Lee, G. Srinivasrao, S.R. Mun, H. Cha-Molstad, A. Ciechanover, C.Y. Choi, H.G. Lee, B.Y. Kim, and **Y.T. Kwon** (2019) The N-degron pathway mediates ER-phagy. ***Mol. Cell*** 75:1058-1072.
6. Zhang, Y., S.R. Mun, J.F. Linares, J. Ahn, C.G. Towers, C.H. Ji, B.E. Fitzwalter, M.R. Holden, W.Mi, X. Shi, J. Moscat, A. Thorburn, M.T. Diaz-Meco, **Y.T. Kwon**\* and T.G. Kutateladze\*. (2019) ZZ-Dependent regulation of p62/SQSTM1 in autophagy. ***Nat. Comms.*** 9:4373

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**The AUTOTAC chemical biology platform in drug development for targeted degradation via the autophagy-lysosome system**

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Targeted protein degradation (TPD) is the most recent of emerging modalities in drug discovery and development. TPD technology exhibits alternative and attractive pharmacological properties compared to those of conventional inhibition, offering an exciting new outlook on the vast majority of human proteome, ~80% of which is considered ‘undruggable.’ The current spectrum of degraders focuses on induced-ubiquitination of target substrate, exemplified by PROteolysis-TArgeting Chimeras (PROTACs). Here, we developed a general methodology by which given proteins are selectively recognized and delivered to macroautophagy for lysosomal degradation. This platform technology, termed AUTOphagy-TArgeting Chimera (AUTOTAC), employs a bifunctional molecule composed of a target-binding ligand (TBL) linked to an autophagy-targeting ligand (ATL). AUTOTAC simultaneously binds targets via its TBL and the ZZ domain of the otherwise inactive autophagy receptor p62/Sequestosome-1/SQSTM1 via its ATL, which activates p62 in complex with targets into an autophagy-compatible form. Targets are biologically inactivated and sequestered by autophagosomes, leading to lysosomal degradation. AUTOTAC compounds were successfully used to degrade oncoproteins (Ras, p53 aggregates, androgen receptor, estrogen receptor beta, and methionine aminopeptidase 2 etc) and degradation-resistant aggregates in neurodegenerative diseases such as Alzheimer’s disease (AD), Parkinson’s disease, and amyotrophic lateral sclerosis (ALS), some of which with low nanomolar DC50 values. Amongst these, the tau AUTOTAC ATC-102 under preclinical studies was demonstrated to degrade tau neurofibrillary tangles in the brains of AD mouse models, resulting in therapeutic benefits in locomotive activities, neuroinflammation, and lean body mass. We suggest that this technology provides a platform for selective degradation of cellular proteins in both research tool and drug development.

Keywords: N-degron pathway / targeted proteolysis / PROTAC / autophagy / lysosome