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【名誉会員寄稿文】

Unfinished Odyssey for Well Aging and Humanness

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Life is a Sail between Scylla and Charybdis

The first written epic of human kind, the Gilgamesh story in Mesopotamian myths tells us the recklessness and futility of pursuing immortality. Nevertheless, my lifelong ambition has been never changed but to reveal and manipulate the mystery of definiteness, limitation and mortality of life. When I read the famous Homer's Odyssey in high school days, the agony of Odysseus to sail between Scylla and Charybdis was not appealing to me. Only after grown up, the presence of perils and hazards in either side of life aroused me to ponder on its significance. And I come to realize what I could do at such a situation is nothing but to choose the some better. My journey of scientific research was not far from such a sailing. I have been enforced to sail between cumbrous questions of life and death, immortality and mortality, irreversibility and reversibility. Despite uncertainty ahead, I have marched pompously forward with the words of Ernest Hemingway in his famous book of Old Man and Sea, which has been always ringing a bell to my ears, "A man can be destroyed, but never defeated". In this essay, why, what and how of my voyage on aging research have been proceeded will be introduced in sequence of my life.

Dreams and Pains for Growing

My first and serious conflict was to determine what to do for my lifelong mission after graduation from Seoul National University Medical School (SNUMC) in 1973. In those days, frankly speaking, my country Korea was yet suffering from scars and aftermath of the Korean War, and the University was barely equipped with facilities and experts. Nonetheless, I had a belief that the basic fundamental approach for life should be essential and utmost requiring, for which Biochemistry would be the right direction, to which I must devote myself. Thereafter, my graduate days of *Sturm und Drang* began with dream and ambition. But the reality was not so simple. In the Department of Biochemistry of SNUMC, there were three professors of different expertise, while I was the only one assistant in the whole Department, who joined the Department for the first time after 15 years of vacancy as MD graduate. Thereby, my duty was to support all three professors together. Consequently from morning till night every day, I had to hurry and rush for this and that, assisting not only for teaching but for experiments. Professor Ki Young Lee, the founder of Korean Society of Biochemistry, worked for comparison of base ratio of nucleic acids from varying animals and plants; Professor Seung Won Kimm majored in enzymology and metabolic regulation; Professor Bum Suck Tchai carried out the nutritional survey for children. My ineludible participation into all of those works allowed me to glimpse and taste the varying technologies and ideas of versatile fields. Though those days were terribly busy, hard and complicated, yet to my memory it was a fortune to be able to learn and acquire the philosophy of comparison, change and care. Ever after, these principle influenced me strongly to have more integrative thinking and interactive concepts on science and human beings: compare of cancer and aging, young and old, city and country; change from normal to cancer, from young to old; care for sick, old and poor, which have been always lingering around in my mind and aroused me to be keen.

After graduate days, I had to admit to Korean Navy as a military medical officer for three years to do my military duty. During military period, my jobs were

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to optimize and modernize many protocols of training and living of military members, used to simply follow the hackneyed US military system, and to establish the marine research institute for healthcare and training system for crews of ships and submarines and to monitor the water pollution of sea and vessels. These totally unacquainted experiences led me to open eyes to diversity of strange and exotic worlds.

Then I crossed the Pacific to work as the postdoctorate fellow at Laboratory of Biochemistry, in NHLBI, NIH (National Heart Lung Blood Institute, National Institutes of Health), led by Dr. Earl Stadtman. In this laboratory, my eyes were clearly washed and the delights of research penetrated into my heart. My mission was to complete the unique and elaborate glutamine synthetase (GS) system for its nitrogen sensing and control mechanism in *E.coli* under Dr. Sue Goo Rhee's guidance. The GS system is consisted with glutamine synthetase(*glnA*), adenylyl transferase(*glnE*), PII protein(*glnB*), and uridylyl transferase(*glnD*). I could successfully clone and characterize the uridylyl transferase, the ultimate regulator of GS system. Through characterization of this enzyme, GS system could be completed and the mystery of genetic and metabolic regulation of nitrogen sensing and utilization could be figured out as the TriCyclic Cascade system (1, 2, 3, 4). These works led me to understand the harmony of genetic and metabolic control, the biological beauty of sensing and integrity, and the significance of relativity and ratio of biomolecules. This well balanced integration of signals of metabolism and genetics for amplification and efficiency to maintain and flourish the life enlightens me the holiness and grandeur of life.

Moreover, the days at NIH let me open my eyes to aging research, because Dr. Earl Stadtman was the right person who discovered the protein oxidation by oxidative stress and initiated the protein works in aging research. At that time, my mission was not directly related with protein oxidation, but I could join all the discussion with those members working at the front on aging related protein oxidation, protein stability and other aging-related projects. Therefore, I am deeply indebted to Dr. Earl Stadtman for my basic concept on aging and later aging research.

No Way but Cancer: Challenge to Multistep Carcinogenesis

Returning back to SNU in 1984, I was obliged to establish my own laboratory, since my professors were twenty and more years senior to me, preparing for retirement. With very limited resources, I was in terrible situation what to do and how to do, which forced me to decide the simple and clear target rather than elaborate but expensive works of beautiful biochemistry. Since I had done the survey and screening of the mutagens in Korean favorite foods for my PhD thesis works, cancer related projects were more convenient to me at that time. Moreover, the highest morbidity and mortality of the digestive organ cancers such as stomach cancer and hepatoma in Korean population provided me a good excuse for cancer research. I adopted *Ames* test for mutagen screening and carried out broad survey of raw and cooked food materials altogether (5, 6, 7). With this approach, I could discriminate the good and bad food materials and cooking process of Korean traditional diets. Thereby, it was natural for me to participate in nutrition and food societies as well as to be involved in the public health education. But my desire was not for screening but for mechanism.

As a Biochemist, the essential molecular mechanism is the goal to achieve. My works on cancer were extended to elucidate the mechanism of cancer generation, why cancer cells are immortal and how the normal cells can be transformed to gain the immortality. At that time, there were no idea at all on telomere and stem cell, and only primitive concept of oncogenes. I preferred the stepwise transformation, consisted with multi steps, rather than to the abrupt certain single step effect, because my hunch on life process was based on gradual stepwise changes as in metabolic pathway. I presumed that cancer must be similar not exceptional. I started the animal experiments with chemical-induced mammary cancer models, in which cancers could be readily induced by single *IV* or *per os* treatment of NMU (N-methyl nitrosourea) or DMBA (7,12 dimethyl benzanthracene) (8). With this model system, I tried to reveal the mechanism for multistep carcinogenesis of initiation, promotion and progression.

During the time, I was happy and fortunate to be acquainted with my dear lifelong Japanese master, Dr. Hirota Fujiki of National Cancer Center, who discovered so many tumor promoters, such as Okadaic acid, Teleocidin and Nodularin, etc. Later, he moved to Saitama Cancer Institute and then to Tokushima Bunri University. He kindly introduced me to the global cancer society and provided me with so many precious information and supports, which shall not be forgotten in my life. Together with him and Professor In Kyoung Lim, we organized Korea-Japan Cancer Research Group and later Korea-Japan Cancer and Aging Scientists Meeting until now for more than 30 years consecutively with 12 more biannual international conferences and Journal of Cancer

Research and Clinical Oncology meeting reports (9). It was the success of friendship between Korea and Japan and also between him and me along with all of our colleagues. Since from Dr. Fujiki's works, the importance of tumor promotion step was realized, I did follow the assumption that inhibition or blockage of this promotion step would be the best way for cancer prevention.

Thereby, I paid a special attention on the preneoplastic stage of carcinogenesis, because this step is prior to cancerous status, which might be in reversible state. It might be significant and of use to develop the tools and methods to adjust the carcinogenesis step back to normal status by intervening this stage. I tried to develop the markers and methods for identifying and to screen and test the blocking or inhibiting substances against preneoplastic changes or looking for any possibility of restoring or reversing the preneoplastic lesion (10). If cancer is one way program for immortality, at what stage of carcinogenesis, the immortality is gained? And for such changes, what could be the biochemical markers? I presumed that this kind of one way phenomenon must be based on certain biochemical irreversible mechanism, which was very intriguing to me.

During this period, thanks to my frontier experience of cloning and overproduction of genes with genetic engineering tools at NIH, I was invited to SNU Institute of Molecular Biology and Genetics as the founding member and also participated as one of the core organizers for the Korean Society of Molecular Biology (which later become Korean Society of Molecular and Cellular Biology), which is now the biggest and most active biological society in Korea.

Crosslinking as a Bridge of Cancer to Aging: From Immortality to Mortality

Dealing with preneoplastic lesion, I was preoccupied by the concept of biochemical switch on and off for biological reversibility. For the on/off mechanism, I supposed the requirement of some structural fixation of molecules for one way process, which must not be reversible. I picked up enzymatic crosslinking by transglutaminases (TGase) as the candidate mechanism for biochemical irreversibility, since it was known that the isopeptide linkage formed by TGase could not be degraded by any known proteolytic enzymes. At that time, proteasome and autophagy system were far beyond our knowledge. There have been already many reports of the increased non-enzymatic crosslinking of the biomolecules in aging, implicating their responsibility for degenerate change. However, I preferred the enzymatic crosslinking to non-enzymatic crosslinking, because enzymatic control needs not only the genetic but also metabolic regulation, while non-enzymatic mechanism would be totally dependent on random event. It was not conceivable at that time to me that the nature allows randomness to control the life process. With this enzyme as the target, a spectrum of works such as discovery and purification of new isozyme TGase 3 from human skin, and its relation with apoptosis, dystrophy, and exercise had been performed. For the research, I visited and met Dr. Ron Sooil Chung and Dr. Peter Steinert of NIH to get the information and for collaboration (11, 12).

Meanwhile, my group has obtained an interesting result that TGase activity is highly increased in aging tissues, while cancer and growing tissues have low activities of TGases (13). Increased activity of TGase with aging attracted me to concern about aging. Why and how enzymatic crosslinking activity is increased in aging? Is there any possibility to block aging by inhibiting this crosslinking activity? I was thrilled and decided to devote all my efforts to aging research. And at the same time, since I was in trouble with my personal abhorrence to develop transgenic or knockout mice for confirming oncogene effect, I was seriously looking for shifting the theme of my research, which would not require heavy genetic manipulation. In that aspect, aging research was much better and more agreeable to me than cancer research, and fortunately crosslinking TGase formed a bridge for me to cross cancer research to join aging research.

Thereafter, I started to participate in international aging research meetings and learned the Strehler's 4 principle of irreversibility, inevitability, degeneracy and universality for aging. The concept that lifespan can be defined by aging process attracted me strongly. If aging is the one-way program for mortality, what are the biochemical fixatives for aging process? And what would be the essential biochemical parameters to discriminate mortality and immortality, in other words, cancer and aging? For the question, I assumed the enzymatic crosslinking hypothesis of aging. The evidence that the TGase activity increases with aging would not suffice the theory. Thereby, TGase knock out or deletion experiment was expected to clarify the role of TGase in aging process. But it was not. Phenotypic defect was limited, indicating that TGase would not be sufficiently functional for aging. The results were very disappointing and pushed me back into labyrinth of aging. If not crosslinking, what would be the most significant pathognomonic change of cancer, normal and aging status?

It was Responsiveness, What matters: Operation of Switch for Mortality

After considerable perusal, I had to shift my target for aging research. And I decided to focus on the growth responsiveness of those different states. Why cancer cell grows fast, normal cell grows slow but aged cell does not grow? There have been already many studies on cell cycling activation and growth factor response, but most of the works used to emphasize only the differences in amounts of ligands and receptors or their affinity without any conclusive explanation. At this stage, I set up a hypothesis that there must be some generally operating system in aging process for control of growth factor response. For the candidate, three dimensional regulation for growth factor responsiveness was conjectured, which must be not ligand-specific but more general in action. Through screening of differential expression of genes between young and senescent cells, the receptor mediated endocytosis system was finally selected for targeting, which is one of the general signal regulatory mechanisms. Thereby, caveolin-1 was identified to increase with aging and to suppress a variety of growth factor signaling in general. Moreover, by knock down of caveolin-1, the biosynthesis of nucleic acids was reactivated in the senescent cells and the morphological restoration to young cell like shape was induced though in partial. Therefore, the role of caveolin-1 as one of the general masters via adjusting tyrosine kinase-mediated signal activation was suggested as the mechanism for aging-related hypo-responsiveness to growth factors (14, 15, 16, 17). Furthermore, the role of ampiphysin-1 in clathrin-mediated endocytosis was also discovered to be associated with aging-related hypo-responsiveness as well (18). With these data of the low efficient growth factor response by aging related alteration of receptor-mediated endocytosis, Gate Theory of Aging was proposed (19), in which the extrinsic signals for growth are controlled at the membrane level and the efficiency of signaling to switch on/off is dependent on the level of caveolin-1 or ampiphysin-1, which are aging-dependently altered.

In middle of struggling for mechanism of aging, I actively joined the international aging conferences and there I met many aging research Gurus such as Professor Denham Harmon, Dr. Kenichi Kitani, Professor Sataro Goto, Professor Byung Pal Yu, Professor George Martin and Dr. Jan Vijg and so on. With them, I had many opportunities to discuss the aging issues and to be blessed with so many wonderful ideas by those Gurus. And the Korea-Japan aging research exchange program was organized through Japanese Biomedical Gerontology Society and Korean Society of Gerontology since 2002 until now continuously with a purpose of friendship and encouraging young scientists for their international relationship. Again I realized to my heart the importance of lessons from Gurus and friends and the truth that science cannot be achieved alone. Let me remember some of my dear friends in Japan, especially of my same age, born in 1949, which I named the Members of 49ers Club, including Professor Yasuyoshi Ouchi, Professor Nobuyoshi Hirose and Dr. Naoki Maruyama. Every time we met together, none of us hesitated to drink and chat, and we never forgot to encourage each other. Though met by coincidence, but we marched forward with destiny. Yes, it is true that science requires friendship!

Since aging related hypo-responsiveness toward growth factors was explained in terms of membrane function, I was curious about aging dependency of the responsiveness toward stress in the next step. Therefore, a series of experiments were carried out to test and compare the young and old cells with an idea that old cells might be more vulnerable to toxic stress than young cells. However, surprisingly, the old cells showed the resistance toward UV stress and many other apoptotic stress such as oxidative stress, ER stress and oncogene stress (20). Up to that time, the concept that aging would provide the more liable state to death was prevailed. And I myself had been also in agreement with the idolum that aging means a state close to death, as spoken by Dr. Martin Heidegger in his book of "*Sein zum Tode*". But the experimental data showed the opposite pattern to my preoccupied concept. The old cells are actually more resistant to toxic and apoptotic stress than young cells. This resistant character of old cells toward toxic stress was again confirmed by *in vivo* experiment (21). Young and old animals were compared for apoptosis induction of liver tissues after peritoneal injection of MMS (methyl methane sulfonate), a DNA damaging agent, which resulted in high incidence of apoptosis in young organs but negligible incidence of apoptosis in old organs. These striking data that the senescent state is more resistant to toxic stress than young state *in vitro* and *in vivo* clearly elucidate the value of aging as survival strategy rather than death prone program. Aging is not for death but for survival!! This new concept revolutionized all of my previous preoccupied prejudiced ideas on aging as the inevitable, irreversible and degenerate path to death and redirected me to the new and eye-opening idea of possibility for survival, control and restoration of aging.

Thereafter, I tried hard to bring a light on the

nature of aging dependent hypo-responsiveness not only to growth factors but also to apoptotic factors. With many different models and tools, the common pattern of aging dependency toward extrinsic signals was identified as the peri-nuclear accumulation of down-stream signals (22, 23, 24). Why in aging, signals could not reach nuclei and be stocked in peri-nuclear zone? Through a variety of experiments, in the senescent cells, the reduced nucleocytoplasmic trafficking was confirmed as a general mode. In consequence, aging dependent formation of nuclear barrier was assumed and actually the general reduction in expression of nuclear pore complex genes was confirmed. Thereby, with these data, the Nuclear Barrier Hypothesis of Aging could be brought out to the world. In this hypothesis, the aging process would be initiated by formation of nuclear barrier, which was named as "Park and Lim's Barrier (25)". This barrier would limit not only the transport in and out of the nutrients and waste but also exchange of the essential components for life maintenance, resulting in restriction to living system and leading to the senescent state. This nuclear barrier together with membrane barrier in the senescent state are responsible for hypo-responsiveness not only toward growth factors but also apoptotic factors (26). In other words, the aging process is accompanied by reduced growth and enhanced survival at the same time. In summary, the cellular senescence has to tradeoff growth with survival. And this is the unique and clear molecular mechanism to explain the biological tradeoff phenomena. The biological significance of this Tradeoff Strategy of Senescence prerequisite the sincere operation of payment or sacrifice in life economy.

Aging Revolution by Centenarians: Not Somebody But Everybody

In 1996, I was nominated as Director to Aging and Physical Culture Research Institute of SNUMC and in 2002, to Aging and Apoptosis Research Center of Ministry of Science and Technology. Thereby, my mission should not be confined to basic science of aging but extended to human aging with wide open eyes and ears. In study of human aging, it is out of question that the longitudinal study would be essential and fundamental. The first Korean longitudinal study on aging, named "Seoul Longitudinal Study on Aging (SLSA)" project was launched. In the middle of the project, all of sudden, a big and serious question turned up. That was: if the functional decline follows aging, what would be the minimal function of life to maintain the humanness and quality of life? For the study, I presumed the age of 100 as the ultimate age for monitoring the minimum status of life. In turn, I organized a multidisciplinary team for study of centenarians for the first time in Korea, inviting experts from medicine, psychiatry, nutrition, family, social welfare, ecology, economy and anthropology. What I learned from our centenarian study can be summarized in a single phrase: "Centenarians are not so terribly degenerate but strong enough to maintain their life". It was a thunder to me that the simple number of years could not determine the fate of human beings (27, 28, 29, 30). How old a man may be, he could maintain his life! I had to change my prejudice that old man must be degenerate and obsolete. And I could be convinced that the longlive community might not be so gloomy as anticipated but there would be yet some sun light. Moreover, it becomes clear that the trend of population aging illustrates the generalization of centenarian phenomenon, implicating the coming world of centenarians not by somebody but by everybody. Longevity is now the common global issue for ordinary people in general.

It was a great and splendid success to work together with members from totally different training backgrounds for the same target of person and situation. Their respective own varying views on human longevity provided all of our members with the unexpected delights of knowledge on human aging. It was natural that our team, each in their own field, could initiate and lead the aging sciences and communities with new integrative and innovative ideas thereafter, which I am still proud of. And this collaborative works of multidisciplinary team led us to establish the Institute on Aging, SNU, which played a big role and contributed greatly to our aging society, thereafter.

Public Aging for Wellbeing and Longevity: Science for Human

Through this collaborative works of Korean centenarian study, I could propose a longevity model, named Park's Temple Model of Human Longevity, in which for achieving longevity, multi factors are required, as if building up a temple; base, pillars and rooftop factors. The base factors are many natural variables, such as genes, personality, gender, ecology, and culture: the pillar factors are individual personal variables, such as nutrition, exercise, participation and relation: the rooftop factors are social variables such as healthcare system, social safety networks and social overhead capitals. In other words, this model informs that for longevity, all the dimensions of human living should work together. As suggested in this model, I tried my best to recommend and advice many programs to

the public and community to prepare the coming aged society through persuading the local governments and the public to correct the individual lifestyles as well as the interactive relationship either personally or official campaign wise. Thereby, the GuGokSunDam longevity belt community was incorporated with my advice, consisted with 4 different counties of Gurye, Goksong, Sunchang, Damyang, which collaborated together for enhancing longevity culture and regional industrial development.

Furthermore, our Institute could design and develop several programs to lead the public to more healthy life such as exercise program of the elders and cooking program of the male seniors. For the exercise program, the Korean traditional dance-based exercise was prepared with simplicity, regularity and affinity principles. Thereby, a series of Woori-Chum Chejo have been developed. The dance exercise has acquired the nickname as Longevity Dance and became very popular in senior society. For the cooking program, since the male adults are traditionally not accustomed to cooking and suffered from isolation in old ages, the simple but graceful foods for the seniors have been designed, which were open to public for cooking class. And in order to let the male seniors to be proud, the title of Gold Cook was given to those who cook by themselves after age of 60. Now this campaign of cooking class for male seniors becomes very popular as well. And our Institute initiated several educational programs on issues of aging society for the public, such as University of 3rd Age for the retirement preparing group, MiniMed School for general and scientific medical knowledge spread, and The Advanced Leaders Program for Aging Science for leader training in variety of disciplines.

During this period, I have been actively involved in organization and extension of Korean Society of Gerontology and Federation of Korean Societies of Gerontology to successfully organize the Asia/Oceania Regional Congress of IAGG and the International Congress of IAGG.

Meditation for Immortality and Community: Emerging Issue of Transhuman and Posthuman

In 2011, I decided to retire from SNU after 33 years of service and temporally moved to Gachon University as Professor and Director of Lee Gil Ya Cancer and Diabetes Institute in order to revive and extend my science on aging, because after age of 60, it is almost impossible to get the grant and to recruit the students in Korea. But out of sudden in 2013, Samsung Electronics Co requested me to establish Well Aging Research Center in their globally-famous SAIT (Samsung Advanced Institute of Technology). Without any hesitation but with ambition, I joined SAIT and did my best to establish the world best aging institute in order to initiate a record-breaking and concept-revolutionizing works of integrating BT-IT-NT (Bio-Informatic-Nano Technology) for future aging community. But the project was suddenly closed by unexpected occasion, which I feel very sorry. Now, I am at DGIST as Chair Professor for New Biology and Well Aging Research Center. My last experience at globally leading IT industrial institute aroused me to have a new vision on the coming new world. Human being is no more restricted to pure biological being, but the interaction of man and machine is enforcing human longevity as well as welfare. Therefore, it is now inevitable to take the issues of transhuman and posthuman into our consideration. No more traditional concept of aging and being, but the groundbreaking concept of human becoming should be positioned in the center of our discussion and meditation.

Foundation and Organization

To look back the past, what I have done can be summarized as initiation, recruitment, activation, integration and marching together. I served as directors to Aging and Physical Culture Research Institute, WHO Collaborating Center for Physical Culture and Aging, Institute of Genetics and Molecular Biology, Aging and Apoptosis Research Center, Institute on Aging, SNU, Lee Gil Ya Cancer and Diabetes Institute, Gachon University, executive vice president to SAIT, vice dean of Student Affairs, SNUMC, Dean of Research Affairs, SNU and Presidents to Korean Society of Biochemistry and Molecular Biology, Korean Society of Molecular and Cellular Biology, Korean Society of Gerontology, Federation of Korean Societies of Gerontology, International Association of Biomedical Gerontology, International Society of Protein Crosslinking and Transglutaminases, and International Society of Sports Science. With these complicated busy jobs, my life has been always in rush and hush, but at any time, I dare to tell that I have done my best to promote and extend the organization that I was belong to.

Unfinished Sail Back and Forth for Tomorrow

My sail between Scylla and Charybdis is unfinished yet. Ever continuing pressure of choice restricted the space and time, but I must survive in the global scientific society, which forced me to tradeoff my other part of life with my family for never ending works. As a human being, the choice is inevitable, as suggested by Kierkegaard "*Entweder oder*". Choice of something

means sacrifice of other. In every situation of my life, I have tried to choose anything with principle of better world for more people, for which I do not repent, though many things have been forlorn. In my lifelong path, I have been preoccupied haughtily by an illusion that my destiny is to stand aloof in the position of lighthouse to lead the direction, notwithstandingly unfamiliar to myself. To retrospect, aging research, though started haphazardly with crosslinking mechanism for irreversibility, was the beginning of my destination for aging science. However, now I am truly realized that all the experiences from days of graduate days, throughout postdoc period until now together with all the scientific tools and ideas have been intertwined harmoniously for my aging science. Thereby, in all through my works, the lessons from my Professors of comparison, change, and care alerted me to consider the private aging and public aging together for the human beings. And biochemical beauty of harmony, integration and relativity always guided me to the wonder of life.

Now, it turns out nevertheless evident that the upcoming frightening progress in science and technology, exploded by informatics technology and tantalized by artificial intelligence, would swindle the basis of aging and longevity of human, who is no more being but becoming. The issues of immortality vs mortality, reversibility vs irreversibility, man and machine, nature and nurture are raised up imminently, which would definitely and heavily influence the human life span and quality of life. As a gerontologist, what to anticipate and how to confront the dizzy reality would be the biggest headache issue ahead. In this situation, I wish my successors and juniors do not lose the hope of better world coming and hold the courage to confront the changes to save our community for well aging. Longevity with happiness is the goal of well aging, for which I would not hesitate or be tumbled down but sail ahead. And in conclusion of my essay, I would like to remind the impressive words by French philosopher Voltaire "Paradise is where I am".

References

1. Chung HK, Park SC, Rhee SG (1984) Conformation-specific monoclonal antibodies to glutamine synthetase in Escherichia coli. J. Biol. Chem. 259(19), 11756-11762
2. Rhee S.G., Park S.C., Koo J.H. (1985) The role of adenylyltransferase and uridylyl-transferase in the regulation of glutamine synthetase in E. coli. Current Topics in Cellular Regulation 27, 221-232
3. Park SC, Kim IH, Kimm SW, Rhee SG (1988) Genetic control of glnD operon in Escherichia coli. Kor. J. Biochem. 20: 99-110
4. Kim IH, Kwak SJ, Kang JS, Park SC (1998) Transcriptional control of glnD gene is not dependent on nitrogen availability in E. col. Mol. Cells. 8, 483-490
5. Kimm SW, Park SC (1982) Evidences for the existence of antimutagenic factors in edible plants. Kor. J. Biochem 14(2) 47-59
6. Lee MS, Mo SM, Park SC (1987) Mutagenicity of pyrolytic products of Korean animal protein foods by Salmonella/mammalian-microsome test. Enivron. Mut. Carcinogen. 7:85-102
7. Lee MS, Mo SM, Kim JH, Park SC (1988) Mutagenicity of pyrolytic products of Korean animal protein foods by Salmonella/mammalian-microsome test. 2. Mutagenicity of varying customary cooked meats. Environ. Mutagens & Carcinogens 8: 105-125
8. Park SC, Kim EG, Park CY, Kim IH, Han JH, Tchai BS, Kimm SW, Song KY (1986) Promoter modifies carcinogenesis process-adenocarcinomas initiated by DMBA alone differ from those induced by DMBA and phorbol esters. Kor. J Biochem. 18, 85-89
9. Kim EG, Seimiya H, Chung J, Hoheisel J, Lim IK, Fujiki H, Park SC(2013) The eleventh Korea-Japan-Germany joint symposium on cancer and ageing research. J Cancer Res Clin Oncol. 139(6):901-4.
10. Song KY, Kim DY, Kim HC, Rha YH, Park SC (1990) Immunohistochemical and genetic changes in putative preneoplastic lesion in rat liver. J. Kor. Cancer Assoc. 22, 395-409
11. Kim HC, Lewis MS, Gorman JJ, Park SC, Girard JE, Folk JE, Chung SI (1990) Protransglutaminase E from guinea pig skin-isolation and partial characterization. J. Biol. Chem. 265, 21971-21978
12. Kim IG, Gorman JJ, Park SC, Chung SI, Steinert PM (1993) The dedeuced sequence of the novel protransglutaminase (Tgase 3) of human and mouse. J. Biol. Chem. 268, 12682-1690
13. Park SC, Yeo EJ, Hwang YC, Choi JY, Han JA, Park JS, Park, YH, Kim KO, Kim IG, Seong SC, Kwak SJ. (1999) Aging process is accompanied by increase of transglutaminase C. J. Gerontol (Biol), 54, 78B-83B.
14. Park WY, Park JS, Cho KA, Kim DL, Ko YG, Seo JS, Park SC (2000) Upregulation of caveolin attenuates epidermal growth factor signaling in senescent cells. J. Biol. Chem. 275(27):20847-20852.
15. Cho KA, Ryu SJ, Park JS, Jang Is, Ahn JS, Kim KT, Park SC (2003) Senescent pheonotype can be

reversed by reduction of caveolin status. J, Biol. Chem. 278(30), 27789-27795
16. Cho KA, Ryu SJ, Oh YS, Park JH, LeeJW, Kim HP, Kim KT, Jang IS, Park SC(2004) Morphological adjustment of senescent cells by modulating caveolin-1 status. J. Biol. Chem. 279, 42270-42278
17. Cho KA, Park SC (2005) Caveolin-1 as a prime modulator of aging: A new modality for phenotypic restoration? Mech. Age. Devel. 126(1) 105-1015.
18. Park JS, Park WY, Cho KA, Kim DI, Jhun BH, Kim SR, Park SC (2001) Down-regulation of amphiphysin-1 is responsible for reduced receptor-mediated endocytosis n the senescent cells. FASEBJ. 15(9) 1625-1627
19. Yeo EJ, Park SC (2002) Age-dependent agonist-specific dysregulation of membrane-mediated signal transduction: Emergence of the gate theory of aging. Mech. Ageing. Devel 123. 1563-1578
20. Yeo EJ, Hwang YC, Kang CM, Choy HE, Park SC (2000) Reduction of UV-induced cell death in the human senescent fibroblasts. Mol. Cell, 10(4), 415-422.
21. Suh Y, Lee KA, Kim WH, Han BG, Vijg J, Park SC (2002) Aging alters the apoptotic response to genotoxic stress. Nature Medicine 8. 3-4
22. Lim IK, Hong KW, Kwak IH, Yoon G, Park SC (2000) Cytoplasmic retention of pErk½ and nuclear accumulation of actin proteins during cellular senescence in human diploid fibroblasts. Mech Ageing Dev, 119(3), 113-130.
23. Ryu SJ, Oh YS, Park SC. (2007) Failure of stress-induced downregulation of Bcl-2 contributes to apoptosis resistance in senescent human diploid fibroblasts. Cell Death Differ. 14(5):1020-8.
24. Kim SY, Ryu SJ, Kang HT, Choi HR, Park SC (2011) Defective nuclear translocation of stress-activated signaling in senescent diploid human fibroblasts: a possible explanation for aging-associated apoptosis resistance. Apoptosis. 16(8):795-807
25. Park SC (2011) Nuclear Barrier Hypothesis of Aging as Mechanism for Tradeoff Growth to Survival. Advances in Experimental Medicine and Biology 720:3-13
26. Kim SY, Kang HT, Han JA, Park SC (2012) The transcription factor Sp1 is a master regulator for the senescence-associated functional nuclear barrier. Aging Cell. 11(6) 1102-1109
27. Choi YH, Kim JH, Kim DK, Kim JW, Lee MS, Kim CH, Park SC. (2003) Distribution of ACE and APOE polymorphisms and their relations with dementia status in Korean centenarians. J. Gerontol. (A. Biol. Sci Med Sci) 58(3) 227-231.
28. Park SC, Lee MS, Kwon IS, Kwak CS (2008) Environment and gender influences on the nutritional and health status of Korean centenarians. Asian J Gerontol Geriatr. 3. 8-14
29. Park SC (2012) Comprehensive approach for studying longevity in Korean centenarians. Asian J Gerontol Geriatric. 7: 33-38
30. Han JW, Park SH Kim DJ, Kim H, Choi YH, Lee JH Park SC, Chung JH(2016) Antibodies to the DNA-directed RNA polymerase II subunit RPB1 occur with highest frequency in centenariansImmunity & Ageing 13:8-10