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Research Article

Potential and Mentality of Genius and inspiration and milestone breakthroughs: longevity, diseases and Beyond

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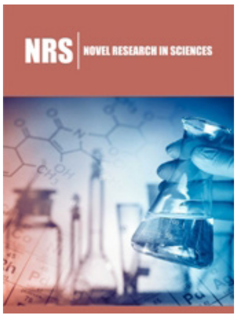

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Abstract

This conceptual study focuses on the evolving field of potential and the mentality of genius, inspiration and milestone breakthroughs alongside lines of stories of scientific life of, longevity, aging-related diseases and beyond. It aims to help promote government strategy, fostering apprenticeships, and renewing ideas about the role of family, hardship, war, paradigm shifts and religion in developing genius and inspiration that will help make more groundbreaking discoveries in China.

First, this essay reviews some of the factors that help stimulate, develop and inspire the leading scientists and researchers of the future. It then turns to some examples of inspired genius, before turning to my personal journey into the world of scientific research of longevity, aging-related diseases (e.g. Alzheimer's diseases, Huntington's diseases, cancer, Osteoarthritis (OA)) and beyond. We finish with some conclusions about how to inspire the prizewinning scientists of tomorrow' China, even the world.

Factors Fostering Genius and Inspiration

Numerous factors appear to be important in developing the brilliant scientists who make breakthrough discoveries. Here, we give only a brief review of each for reasons of space, as large amounts of literature could be written on each one.

Education system

The role of the education system is undeniable in inspiring and developing genius. In many cases, the interest of pupils in various topics is dependent on whether they like the personality of the teacher. The teacher should take responsibility for figuring out the areas in which each pupil shows the most talent. If necessary, teachers can show students who dislike particular topics by showing the links to related topics they enjoy more. Within the education system, more emphasis could be put on creativity and exploration rather than memorization and rote learning; indeed, this is one of the characteristics of the modern Western education system that China as 2nd largest economy could do well to adopt. Education could also do its part to value and encourage the use of the imagination, especially if we consider the example of Dr. Albert Einstein, who developed the theory of relativity that linked the seemingly unrelated dimensions of space and time after imagining what would happen if he could chase and catch a beam of light. Indeed, Einstein is famous for saying that "Imagination is more important than knowledge. For knowledge is limited, whereas imagination embraces the entire world, stimulating progress, giving birth to evolution. It is, strictly speaking, a real factor in scientific research."

Family, religion and tradition

Family, religion and tradition combine for foster a climate of learning, curiosity and exploration. Religion often emphasizes the importance of sacred texts and holy writings, which, in turn, encourages literacy and a love of reading. An excellent example is provided by Orthodox Jewish families and the tradition of honoring sacred texts by baking sugar cookies in the shape of the alphabet, which are given to young children to encourage them to learn to read. This encourages children become excited about reading, which starts them on a lifelong journey of high-quality learning. At a wider social level, in Europe, the Protestant Reformation and the desire to provide copies of the Bible to the common people in everyday language stimulated the development of the printing press pioneered by Gutenberg.

One can also see the importance of family culture in how sometimes a family can have Nobel laureates in several generations. For example, both Dr. Marie Curie and her daughter, Dr. Irene Joliot-Curie[1], were awarded the Nobel Prize in Chemistry (in 1911 for Marie; in 1935 for Irene). Similarly, Dr. Arthur Kornberg was awarded the Nobel Prize in Physiology or Medicine in 1959 and his son, Dr. Roger Kornberg, was awarded the Nobel Prize in Chemistry in 2006 [1]. One could, of course, debate whether this is a matter of nature (inheriting DNA predisposing one to genius) or nurture (growing up in a climate of enquiry and research). If a family "tradition" of research and scientific enquiry does not exist, potential genius can be stimulated and inspired through apprenticeships and mentors.

One of my friends was lucky to follow the 1987 Nobel Laureate in Chemistry, Dr Jean-Marie Lehn[1], for his doctoral degree. Lehn originally became very interested in chemistry when he was 15 or 16 years old. In particular, he liked to play with natural molecules such as chlorophylls, which he extracted from plants. His parents allowed him to set up a small and very primitive chemistry lab in the cellar, where he separated chlorophylls on paper and distilled various mixtures.

Government policy

Fast developing countries like China are eager to have more Chinese researchers awarded the Nobel Prize, they will contribute more to the whole world; but it has yet to create a climate that fosters the potential of genius and inspiration needed to make milestone breakthroughs. This will probably only occur if the government makes a paradigm shift away from a focus on ranked officers, officially awarded research evaluation systems and a focus on SCI publication citations. Official policy needs to support and promote lifelong interest and curiosity, as well as lifelong or decades-long practice in the field. Any hindrance to interest and curiosity could be harmful for science and original research in China.

In the recent annual Chinese Medical Association conference on rheumatology, I made a presentation emphasizing that milestone discoveries and groundbreaking research is crucial for our history. We move through the time dimension one step at a time, continually solving problems as we make one discovery after another. We can view the effects of original discoveries as a binary: yes or no, recognizing the pioneers and leaders rather than those who repeat the findings of others without any originality or innovation. Many of us will fail during our quest and the process is risky but it is worth it for the good of society overall. Researchers can save many more lives than clinical doctors; for example, a top cancer surgeon would have to up to 100 years and rescue one patient every three days to save the lives of 10,000 cancer patients at most. The research who makes a breakthrough in checkpoint immunotherapy for cancer can save many more. Understanding the principle and making the required shift in policy may be challenging but it is important. Interestingly, after vacillating about the value of SCI citations while, China's Ministry of Science and Technology (MOST) just turned to yes–no research innovation strategy rather than a SCI-led research approach after the COVID-19 outbreak [2].

As a metaphor for a supportive research environment, consider totipotent or multipotent stem cells and the unique function of differentiated cells. Stem cells have a democratic system of gene expression but the final direction of each cell depends on its niche. The stem cell is dynamic and none is solely dominant.

Countries like China could learn from its neighbors. Japan increases its list of Nobel laureates every year, but their well-designed advanced science and technology strategy and their well-organized lobbyist system seems to have a function in producing these impressive results. The 2018 Nobel Laureate in Physiology or Medicine, Prof. Tasuku Honjo studied checkpoint inhibitor therapy and won the first Nobel Prize awarded for cancer therapy for many years[1]. You will find him very nice and dedicated to his research, at least I felt so as I talked with him. He values having time to be accessible to patients and hear them tell him, "You saved my life." This feedback from others is his greatest pleasure, allowing him to know what he has done is really meaningful. His discovery may save patients dying from one particular line of lethal cancer forever.

Luck

Luck and serendipity (making discoveries by chance) have always played a role in scientific and technological research and will probably continue to do so. Consider the example of the chemist Dr August Kekulé, who discovered the structure of the benzene ring after a mysterious dream of a snake biting its own tail. Sometimes, it appears as if a supernatural force outside nature exists and inspires researchers, though we do not fully understand this force and how it works. Nevertheless, chance discoveries would not be made if the mind of the scientist has not been prepared and trained by studying the work of others. Sir Isaac Newton may have been inspired by apples falling in his orchard, but without the prior studies of Kepler and, before him, Galileo, Newton would not have discovered the principles of gravity, no matter how many apples fell on his head.

Difficulties

Paradoxically, encountering difficulties and challenges may inspire researchers to explore new avenues or ways to overcome the problems. For example, the 2011 Nobel Laureate in Physiology or Medicine, Prof. Shinya Yamanaka, was unable to use human embryonic stem (ES) cells in research because of the ethical laws applying to stem cell research in Japan regarding the use of human embryos[1]. He thus concentrated on nuclear reprogramming and generate ES-like pluripotent stem cells from somatic cells, whereas other scientists who did not face these legal barriers concentrate on researching how ES cells were differentiated into somatic cells. As another example of difficulty leading to inspiration, controversy once raged as to whether light was a particle (as maintained by Einstein and Newton) or a wave (as maintained by Maxwell). This controversy inspired de Broglie [1]to postulate the dual nature of light in his 1924 PhD thesis.

Examples

Switzerland is a country that boasts 28 Nobel laureates to date despite having a population of less than 8 million. Taking them as our example, we could adopt the Swiss model, where some Professors have lifelong contracts and academic independence, which would allow them to speak the truth fearlessly. This system enables researchers to devote themselves to science and the quest for truth. In addition, Swiss researchers do not have to compete for top administrative posts to get the resources needed for research, unlike their counterparts in China. Instead, we could be like my Swiss supervisor, who preferred to be lower in the administrative hierarchy and focused instead on his research.

The 2016 Nobel Laureate in Chemistry Prof. Jean-Pierre Sauvage explained how when he was working on his PhD thesis in 1967, he was inspired by his supervisor, Prof. Jean-Marie Lehn[1]. Sauvage stated that he was particularly inspired by the way that Lehn was accessible to his students and engaged them in stimulating discussions, reducing the traditional hierarchy between postdoc student and supervisor to a minimum[1]. Sauvage explained that this style of relationship within a research team was something that he tried to replicate, as it led to fruitful discussions where all team members, including graduate students, were able to state their opinions without being held back by the norms of a traditional hierarchy.

A History of Inspired Genius

Like many other longest historic countries e.g. India, Egypt, and *etc,* China has a long history of medical research and in particular the benefits of traditional Chinese medicine are well known worldwide. We could draw on this heritage and other factors to produce more Nobel laureates and other prizewinning researchers. Looking at the stories of successful Chinese scientists illustrates how inspiration can come from many sources, including hardship as well as tradition and national heritage.

The 2015 nobel laureate in physiology or medicine: tu youyou

The first Chinese medicine Nobel laureate, TU Youyou (屠呦呦；TU: in capital hereafter, family name; Youyou, corresponding to "first name " in Western culture)**,** claims that her name was the first thing that inspired her to the discovery of artemisinin, which is effective in the treatment of malaria[1]. Her name was taken from an anthology of ancient Chinese poems from 2000 years ago[《诗经》：呦呦鹿鸣，食野之蒿] and a line that can be translated as "The deer sing "Youyou" as they feed on the wild *Qinghao* [*Artemisia annua*]." She mentioned to she was also motivated to choose medical research for her advanced education and career after suffering tuberculosis in her youth, stating that, "If I could learn and have (medical) skills, I could not only keep myself healthy but also cure many other patients." When reading a classic work of traditional Chinese medicine, Ge Hong's A Handbook of Prescriptions for Emergencies (肘后备急方), she noticed one particular sentence" "A handful of *Qinghao* immersed in two liters of water; wring out the juice and drink it all" (青蒿一握，以水二升渍，绞取汁，尽服之) describing the use of *Qinghao* for alleviating malaria fevers. This unique way of using *Qinghao* inspired her with the idea that heating during extraction might destroyed the active component and therefore that high temperatures might need to be avoided in order to preserve the herb's active principle. Ge Hong's handbook also gave instructions to "wring out the juice." This suggested that the leaf of Qinghao might be one of the main components prescribed. She designed experiments in which the stems and leaves of Qinghao were extracted separately at a reduced temperature using water, ethanol and ethyl ether. Then her "Sample No. 191" provided a breakthrough in the discovery of artemisinin. This ethyl ether extract of Qinghao showed 100% effectiveness in inhibiting malaria parasites in rodents.

The father of hybrid rice

Prof. YUAN Longping（袁隆平**,** is a famous rice scientist from my hometown who was nominated for the Nobel prize. He was motivated by seeing people dying of starvation and he made lifelong efforts to breed better rice varieties and became known as the "father of hybrid rice" for his discoveries in rice genetics and hybridization. In honor of his contribution and efforts, a minor planet in space (planet 1996SD1, #8117) has been named "Yuan Longping"[2]. We are calling him as another Chinese "TU Youyou" in hybrid rice field (Figure 1).

The 1957 Nobel Laureates in Physics Profs. YANG Zhenning（杨振宁）and LI Zhengdao（李政道）**,** seem to be partly inspired by patriotism. During the post-invasion period of anti-Japanese sentiment, Nankai University, Peking University and Tsinghua University unified into one university and collaborated closely. Professors and students were inspired by patriotism and many developed strong talent and even genius. Profs. Yang Zhenning, Li Zhengdao became Nobel laureates[1], though they eventually moved to United States. However, Prof. Yang Zhenning has now returned home to China. As one of famous alumna, he distributed the Certificate of Bachelor degree to us in our graduation ceremony thirty years ago. Patriotism has also **in** part motivated Prof. ZHANG Tingdong（张亭栋）one emeritus Professor among my current colleagues in the first clinical college of Harbin medical university, who was the first to apply arsenic trioxide (ATO) to treat acute promyelocytic leukemia patients in response to a call "The huge leap courageous to explore everything"（大跃进）by Chairman Mao to explore both integrative traditional Chinese and Western medicine. Patients receiving his novel ATO treatment responded and survived for up to 45 years. It was considered a great discovery worthwhile of The Shaw Prize or other great prizes, with which many researchers have performed in-depth science [3]. We continue to be exploring its novel medical application [4-7].

Figure 1: YUAN Longping's dream lying in the rice field.

The father of artificial fish propagation

Prof. ZHONG Lin（钟麟）, the former director of Pearl River Fisheries Research Institute (PRFRI), where I had the privilege of working, is known as the "father of fish artificial propagation". He was motivated to excellence by a negative experience of being looked down on by others during his stay in Hong Kong. He was ambitious, intelligent, persistent and diligent, and wanted to prove himself to be as good as others, and thus devoted himself to the lifelong pursuit of aquaculture, especially artificial fish propagation. The same as Prof. ZHANG Tingdong's in response to a call "The huge leap courageous to explore everything" (大跃进) by Chairman Mao, although most, if not all, researchers had given up on exploring the artificial fish propagation, he continued to study every aspect carefully. One day, a storm broke and the rain that poured into his small home-made fish propagation pond produced water currents. The current stimulated the young fish to develop into mature carp, which eventually produced eggs that were finally fertilized. In 1970s, the WHO asked him to educate people worldwide about his techniques at the PRFRI. We are calling him as another Chinese "TU Youyou" in fish breeding field (Figure 2).

Figure 2: Fishpond for artificial propagation(Courtesy from DRTAN.net).

My Personal Journey

My family name is ZHANG. The character for ZHANG (张) includes the character for "arrow "(弓), reflecting how my ancestors are believed to have developed the bow and arrow for hunting. Although Zhang is one of the most common family names in the world, no Zhang has ever been king, emperor or any other top ruler over the 5000 years of China's history. However, Heng ZHANG invented the ZHANG-heng seismograph(张衡地动仪), and Dr Zhongjing ZHANG （张仲景）developed recipes for traditional Chinese medicine for catching -cold（伤寒论）namely, "Treatise on Febrile Diseases; Treatise on Fevers; Discussion of Cold-Induced Disorders, the plague, and *etc.*" which are now among exceptional ones good as anti-SARS-CoV2 remedies and to treat COVID-19 patients. One could say that creativity, discovery and similar pursuits are in our DNA rather than the quest for political power (Figure 3).

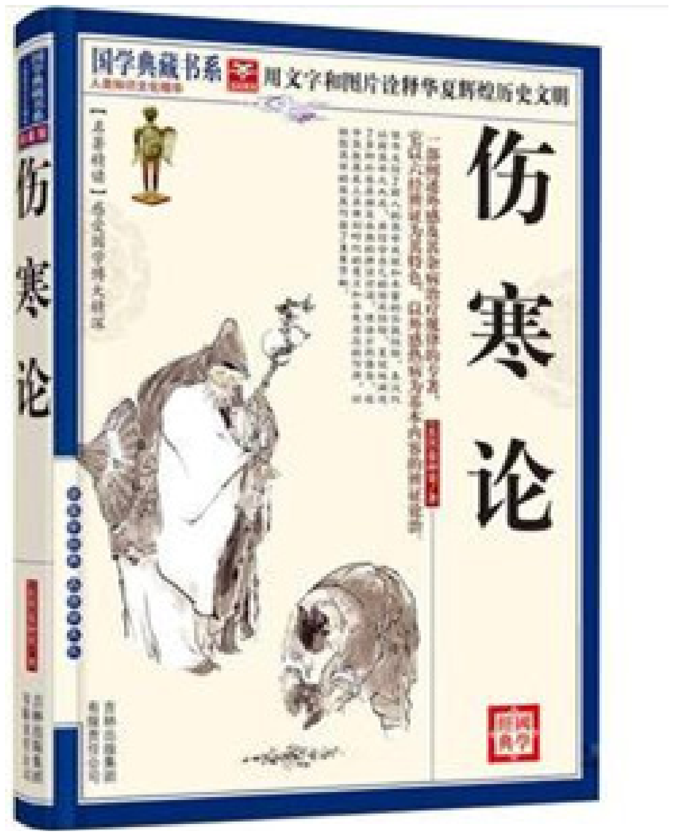


Figure 3: 伤寒论Treatise on febrile diseases, fevers, cold-induced disorders and the plague.

I was raised in a part countryside in China, which my aunt described as being so remote that "not even birds would want to nest there." However, it is known as the "Hometown of Rice and Fish", as it is located in the low-lying land in the Dongding Lake (洞庭湖) area. Dongding Lake is the second largest freshwater lake in China, and it is home to the world's oldest rice paddies, as well as being reputed to be where dragon boat racing originated. This area has inspired not only developments in agriculture but also literature and the arts. It was there in my childhood that the seeds of inspiration were first sown when I tried planting apple seeds in the soil and growing them successfully. My early explorations of how apple trees grew encouraged me to explore development and ageing. In light of this, I have done my best to ensure that my own sons are educated in surroundings that support and encourage them in their own journeys. I am happy to say that my eldest son won the gold medal at his school as part of their volleyball team. For the first time, his school obtained the gold medal at national competition games. He also gave the commencement address at their school. His hobbies include soccer, swimming and piano. After his junior middle school, he was recommended to enter a special and highly competitive talented class program that was aimed to prepare young people to compete for admission to famous universities, although this achievement of program was not publicly announced. I hope that after three years of hard work and dedication, he will be able to follow in my footsteps to the University of Toronto or Harvard University.

When I was working on my bachelor dissertation, i.e. "Identification of huge pears in greater Tianjin area ". Because pear trees are mostly grafted in North China, so I was assigned to perform only histology first. However, as I had experience in growing successfully the seeds of apple on soil, I proposed to work on plant chromosome karyotype analysis and managed to identify 4-ploid pears by growing them to seedlings. My supervisor showcased my work to an academician visitor to the lab. My bachelor dissertation also involved writing a review on the topic of ageing and longevity**.** At that time, most people believed in the multiple gene hypothesis of ageing. I kept the topic in mind until my PhD program. One side project I investigated was aging, although my lab mostly focused on either epigenetics or Hox genes [8,9]. I also initiated a genome-wide RNAi screen with a modified T-vector, which it has blue-white selection and turned out even better than first reported genome-wide RNAi screen in the world by Dr. Julie Ahringer 's lab. We observed and reported how TOR deficiency more than doubled the lifespan in the nematode *Caenorhabditis elegans* [10]. Within the field of longevity research, for *Nature's* 150-year anniversary, it was obviously at a point included in the 20 milestone discoveries in ageing research during the past 80 years (Figure 4) [10-14]. mTOR is also the master regulator for autophagy, the discovery for which Dr Yoshinori OHSUMI was awarded the 2016 Nobel Prize in Physiology or Medicine[1], , who co-authored in the article of autophagy-related gene 1 homolog in multicellular organisms nematode, *i.e.* UNC-51/ULK1(Unc-51 like kinase 1) initial cloning and identification completed in my PhD supervisor Prof. Fritz Mueller lab[12]. Dr. Mueller lab first cloned TOR in multicellular organism nematode, however, another pioneer in research into yeast TOR, Prof. Michael Hall, was awarded the Lasker Award in 2017) (Figure 4).

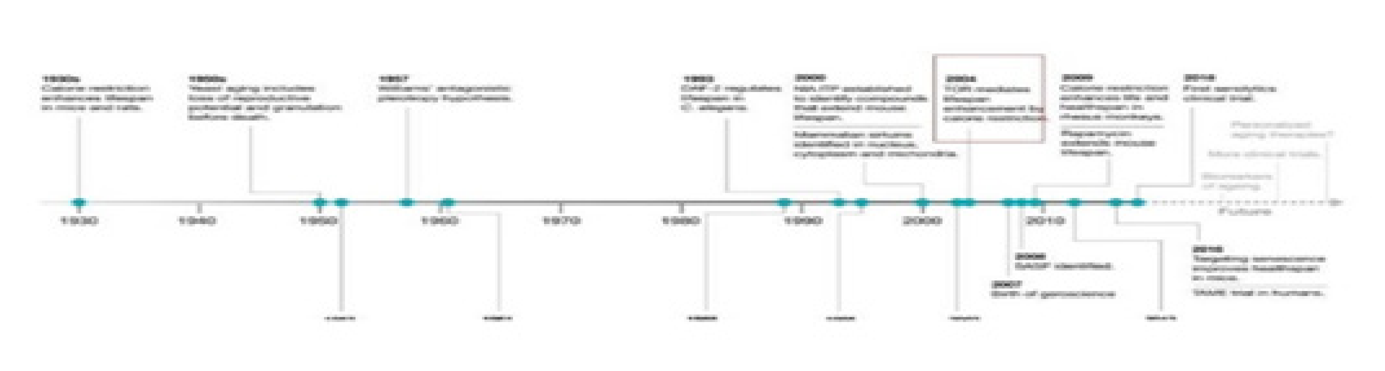


Figure 4: Twenty Milestones for ageing and longevity research during the past 80 years.

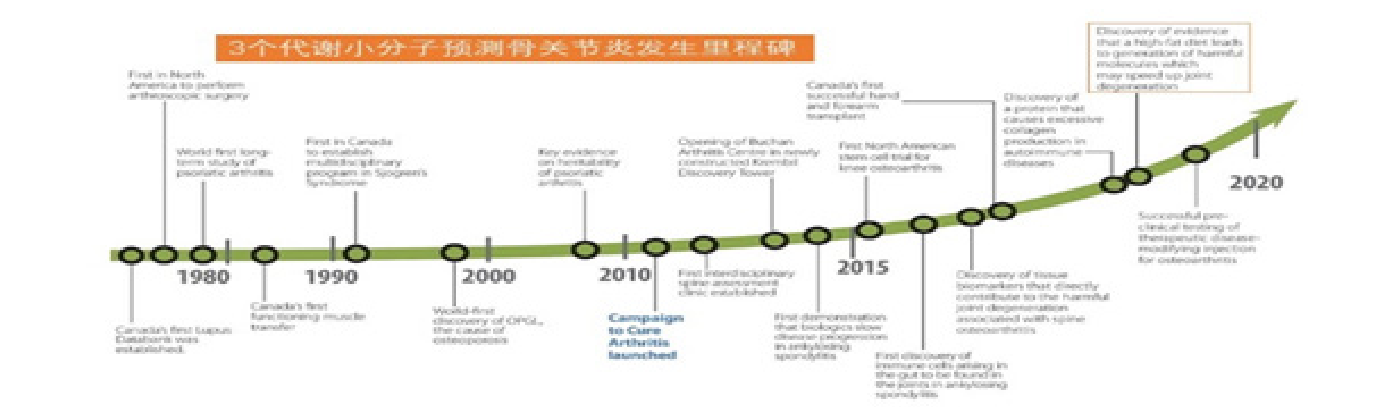
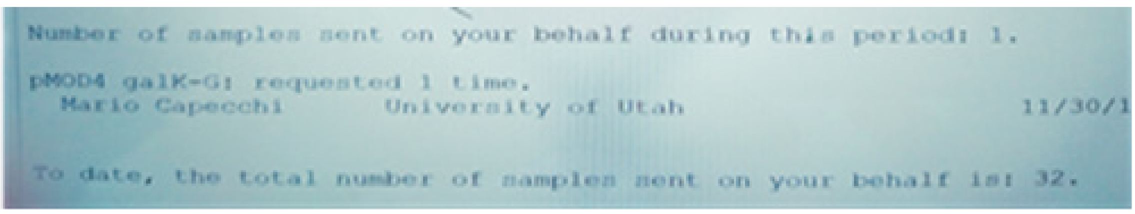


Figure 5: Twenty research milestones during the past 50 years at Toronto Western Hospital.

A recent report from my lab on metabolism and osteoarthritis [13] was included in the milestones of Toronto University Health Network (UHN), Toronto Western Hospital (TWH) (red box in Figure 5).

Over a decade ago, although many labs had given up, as well as some of my colleagues in my lab, I succeeded in the probably-earliest development of a *C. elegans* tissue ChIP. Based on this, we obtained 2 out of 20 poster awards during the 2003 UCLA *C. elegans* international meeting [8,9]. The vulval precursor cells (VPCs) are spatially patterned by a LET-23/EGF receptor-mediated RAS inductive signal and an Alzheimer's diseases-related LIN-12/Notch-mediated lateral inhibition signal. The lateral signal has eluded identification, so the mechanism by which lateral signaling is activated has not been known. Dr. Vellai in our lab was the first one having identified the first potential ligand for LIN-12, and then we and another lab confirmed together show that lag-2 is functional for the lateral signal during the period while several famous teams including one Nobel laureate lab have claimed opposite conclusions [9,14]. Besides, we observed that transcriptional control of Notch signaling by a HOX and a PBX/EXD protein during vulval development in *C.elegans.* Moreover, we reported in detail the Mi-2 nucleosome-remodeling protein LET-418 is targeted via Ras signaling pathway LIN-1/ETS to the promoter of lin-39/Hox during vulval development in C. elegans [8]. Later, Dr. Grreenwald lab computationally identify ten genes that encode potential ligands for LIN-12, and show that three of these genes, apx-1, dsl-1, and lag-2, are functionally redundant components of the lateral signal [14].

Later, the 2006 Top50 American, Prof. Richard Young of the Whitehead Institute, MIT (named as one of the Top 50 Americans in 2006) gave me a job invitation[15]. About 10 years ago, I developed a process for fosmid DNA recombineering, which made it easy to clone DNA fragments of 50–60 kb or longer [15,16]. Many requests came to our lab as a result, including one from Nobel Laureate Dr. Mario Capecchi[1] (Figure 6).


Number of samples sent on your behalf during this period: 1.

pMOD4 galK-G: requested 1 time.
Mario Capecchi University of Utah 11/30/1

To date, the total number of samples sent on your behalf is: 32.

Figure 6: Frequent requests for my cloning plasmid from Addgenes.

So far, millions of OA patients have no truly effective therapy [17-19]. Our life system has evolved several master regulators or"capacitors"such as chromatin binding protein Mi-2 [19,20], HSF1/Hsp90, mTOR and Vitamin D receptor [4,15] alongside their focused endogenous regulatory network to protect human from "catastrophes" as "Dam"controls the flood. As an instructor in Harvard medical school, particularly I and others found that mTOR and its directs autophagy to play a vital role in longevity and aging-related complex diseases, *e.g.* OA, cancer, neurodegenerative diseases cardioviscular diseases (CVD). Inspired by those, The National Institutes of Health (NIH) initiated TAME [11]: namely around 800 from totally elderly 3000 volunteers with distinct diseases (diabetes, cancer, neurodegenerative diseases, CVD) are testing disease-delaying or anti-aging clinical trials by using metformin therapy. Our hypothesis: aging is in part due to the accumulation of "metabolic garbage" and the autophagy is the unique mechanism to clear off them and recycles the nutrients. The exercise and fasting may activate autophagy. Therefore, we could propose to have us along with right protocols for exercise or fasting to keep our joint healthy [17-19].

The cancer cell attractors theory provides an amazing understanding of carcinogenesis and natural explanation of punctuated clonal expansions of tumor progression. The next-generation notion of atavism of cancer is impressive but more evidence is needed. Besides, the mechanisms that the ectopic expression of some germline genes result in somatic tumors such as melanoma and brain tumors are emerging but more stuides are awaited. Cancer could be triggered by cells undergoing abnormal cell attractor transitions, and may be reversible with "cyto-education" with a distinct reprogramming at a sytsem level Including epigenetics and immune system.From mammals to model organisms like *Caenorhabditis elegans* and *Drosophila melanogaster*, one example is the versatile Mi-2β/nucleosome remodeling and histone deacetylation complexes along with their functionally related chromatin remodeling complexes (CRCs), i.e., the dREAM/Myb-MuvB complex and Polycomb group complex, which are likely master regulators of cell attractors. The trajectory that benign cells switch to cancerous could revert the navigation of embryonic cells converging from a series of intermediate transcriptional states to a final adult state, which is demonstrated by gene expression dynamics inspector assays and some cross-species genetic evidence. The involvement of CRCs in locking cancer attractors may help find the intervention recipes of perturbing genes to achieve successful reprogramming. Consequently the reprogrammed cancer cell may function in the same way as the normal cells [20]. Latest effective cancer immunotherapy might provide a novel micro-niche to significantly reprogram cancer attractors too (Figure 7).

Figure 7: Metaphorical Dam and the "capacitor" for life span and health-span in human.

Lastly, we have studied the regulation of Heat Shock Factor 1 (HSF1), a key protein in control of the heat shock response and the regulator of HSP90, and a participant in aging, carcinogenisis, and neurological health [21-23]. As the mechanisms involved in the intracellular regulation of HSF1 in good health and its dysregulation in disease are still incomplete, we investigated the role of posttranslational modifications in such regulation [21]. We further found that HSF1 regulates one of the major pathways of protein quality control and is essential for deterrence of protein-folding disorders, particularly in neuronal cells, including Huntington's diseases [22, 23].

Based aforementioned underlying mechanisms for autophagy (the 2016 Nobel Prize in Physiology or Medicine to Yoshinori Ohsumi for his discoveries of mechanisms for autophagy) and (m) TOR(the 2017 Lasker Basic Medical Research Award to Michael Hall), the"capacitor(s)"of vitamin D receptor and heat-shock response and epigenetics system(Michael Grunstein has been jointly awarded the 2018 Lasker Basic Medical Research Award along with C. David Allis. He laid the groundwork for understanding the role of nucleosomes and their modifiable tails in gene expression), plus the circadian rhythm(the Nobel Prize in Physiology or Medicine 2017 was awarded jointly to Jeffrey C. Hall, Michael Rosbash and Michael W. Young "for their discoveries of molecular mechanisms controlling the circadian rhythm.") , we hereby may put together for one: for living happier, longer, healthier and more youthful alongside longer lifespan and health-span as I have proposed in some conferences and publications:"早上好，冷水澡； 一半一半一半，一带一（路），千百万(公园)；阳光一刻，早起早睡！"，namely, people may have a every good morning along with half-hour or so morning run, then taking 2-minutes brief-cold water first included bath; in general, they should have exercise regularly every other day (for 3 or 4 days per week, almost half week) and half-hour effective exercise (half hour) every time and half dosage of foods with vegetables and fruits rather than meals of full of meat and sugar alone for routine dinner for most people, making exercise together with one companion like mutual help in " one belt and one road", to open hundreds of gardens and parks for Chinese to have sport medicine in China, a moment of one quarter sunshine bath for natural vitamin D, getting up early and going to Based aforementioned underlying mechanisms for autophagy (the 2016 Nobel Prize in Physiology or Medicine to Yoshinori Ohsumi for his discoveries of mechanisms for autophagy) and (m)TOR(the 2017 Lasker Basic Medical Research Award to Michael Hall), the"capacitor(s)"of vitamin D receptor and heat-shock response and epigenetics system(Michael Grunstein has been jointly awarded the 2018 Lasker Basic Medical Research Award along with C. David Allis. He laid the groundwork for understanding the role of nucleosomes and their modifiable tails in gene expression), plus the circadian rhythm(the Nobel Prize in Physiology or Medicine 2017 was awarded jointly to Jeffrey C. Hall, Michael Rosbash and Michael W. Young "for their discoveries of molecular mechanisms controlling the circadian rhythm.") , we hereby may put together for one: for living happier, longer, healthier and more youthful alongside longer lifespan and health-span as I have proposed in some conferences and publications:"早上好，冷水澡；一半一半一半， 一带一（路），千百万(公园）；阳光一刻，早起早睡！" ，namely, people may have a every good morning along with half-hour or so morning run, then taking 2-minutes brief-cold water first included bath; in general, they should have exercise regularly every other day (for 3 or 4 days per week, almost half week) and half-hour effective exercise (half hour) every time and half dosage of foods with vegetables and fruits rather than meals of full of meat and sugar alone for routine dinner for most people, making exercise together with one companion like mutual help in " one belt and one road", to open hundreds of gardens and parks for Chinese to have sport medicine in China, a moment of one quarter sunshine bath for natural vitamin D, getting up early and going to bed early for a normal circadian rhythm.

Conclusion: A Vision for the Future

Let us imagine how the future of research in China could be. For example, our lab settings could be designed to promote lifelong interest and curiosity. Upstairs, we would have museums, full of specimens of animals and plants, and open to the public. These would be attractive for children and others. In front of the lab, we would have a botanical garden. Our labs could be open to the public, safety permitting, and we would have a culture that would allow us to stop work if a child came in and asked to see what happens in laboratories in institutes of zoology. We would show her/him what we were observing via fluorescent microscopy and explain to her/him how much fun science can be. Besides, in annual open science demonstrations, we can showcase and carefully explain our projects and our progress to all local visitors. We could also emphasize the importance of "citizen science" where members of the public are encouraged to contribute to scientific research in various ways, such as collecting data on wildlife, pollution and more, and even assisting in mapping and modeling via gaming platforms. In China, we may catch up with or even surpass better it in that this majority has come true during my stay for my PhD program in Institute of Zoology, University of Fribourg, Switzerland.

There are other ways the public can connect with and support scientific research. When you contribute to patients and society, they will return the favor in the form of donations. For example, Harvard University receives billions of dollars or so annually as donations and endowments. The PI in the lab neighboring my former lab at Harvard Medical School was researching a rare disease and a millionaire came to his lab and pledged to donate one million dollars every year. My colleague had dinner with the philanthropist and took them on a tour of the lab to chat with the other lab members.

Self-donation is new idea and is one we applied in the Arthritis Program at TWH. The goal is to improve the knowledge on osteoarthritis. Fundraising efforts to support arthritis research were needed to improve care for arthritis patients. Each staff member in orthopedic pledged to donate $125,000 over 5 years toward stem cell therapy for osteoarthritis, for a collective gift of $1.25 million. The donations will help researchers to explore the frontiers of osteoarthritis and make more discoveries. Last year, the TWH surgeons – now 12 of them – renewed their commitment with new gifts totaling $1.5 million. To date, the Campaign to Cure Arthritis has raised $50 million – double the original target. This concept could easily be applied elsewhere.

In closing, with sufficient funding, the freedom to research within a niche, extensive collaboration networks, and private and government supporters, as well as systematic encouragement from religion, family and the education system to stimulate young people's interest and curiosity, especially China becomes prosperous but we will expect to be well on the way to Chinese scientists being awarded more Nobel Prizes in the various scientific fields and contribute more to the world together with other scientists worldwide.

As for new manuscript, I would like to say YES when it is ready in near future. However, it is crucial for both journal and authors to improve the quality of journal!!

References

1. https://www.nobelprize.org/prizes/
2. Biography of Yuan Longping. 2018. Edited by QU J. volume 1(1)
3. Chen Z, Chen SJ (2017) Poisoning the Devil. Cell 168(4): 556-560.
4. Wang W, Li C, Zhang Z, Zhang Y (2019) Arsenic Trioxide in Synergy with Vitamin D Rescues the Defective VDR-PPAR-gamma Functional Module of Autophagy in Rheumatoid Arthritis. PPAR Res 2019: 6403504.

5. Zhang J, Zhang Y, Wang W, Zhang Z (2019) Potential molecular mechanisms underlying the effect of arsenic on angiogenesis. Arch Pharm Res 42(11): 9 62-76.

6. Zhang J, Zhang Y, Wang W, Li C, Zhang Z (2018) Double-Sided Personality: Effects of Arsenic Trioxide on Inflammation. Inflammation 41(4): 1128-1134.

7. Zhang J, Li C, Zheng Y, Lin Z, Zhang Y, Zhang Z (2017) Inhibition of angiogenesis by arsenic trioxide via TSP-1-TGF-beta1-CTGF-VEGF functional module in rheumatoid arthritis. Oncotarget 8(43): 73529-7346.

8. Guerry F, Marti CO, Zhang Y, Moroni PS, Jaquiéry E et al. (2007) The Mi-2 nucleosome-remodeling protein LET-418 is targeted via LIN-1/ETS to the promoter of lin-39/Hox during vulval development in *C. elegans*. Dev Bio 15: 306(2): 469-479.

9. Takács-Vellai K , Vellai T, Chen EB, Zhang Y, Guerry F, et al. (2007) Transcriptional control of Notch signaling by a HOX and a PBX/EXD protein during vulval development in *C. elegans*. Dev Biol 302(2): 661-669.

10. Vellai T, Takacs-Vellai K, Zhang Y, Kovacs AL, Orosz L, et al, (2003) Genetics: influence of TOR kinase on lifespan in *C. elegans*. Nature 26(6967): 620.

11. Campisi J, Kapahi P, Lithgow GJ, Melov S, Newman J, et al. (2019) From discoveries in ageing research to therapeutics for healthy ageing. Nature 571(7764): 183-192.

12. Ogura K, Wicky C, Magnenat L, Tobler H, Mori I, et al. (1994) Caenorhabditis elegans unc-51 gene required for axonal elongation encodes a novel serine/threonine kinase. Genes Dev 8(20): 2389-2400.

13. Datta P, Zhang Y (2017) High-fat diet-induced acceleration of osteoarthritis is associated with a distinct and sustained plasma metabolite signature. Sci Re 7(1): 8205.

14. Chen N, Greenwald (2004) The lateral signal for LIN-12/Notch in *C. elegans* vulval development comprises redundant secreted and transmembrane DSL proteins. Dev Cell 6(2): 183-192.

15. Hochbaum D, Zhang Y (2011) DAF-12 regulates a connected network of genes to ensure robust developmental decisions. PLoS tGene 7(7): e1002179.

16. Zhang Y, Nash L, Fisher AL (2008) A simplified, robust, and streamlined procedure for the production of *C. elegans* transgenes via recombineering. BMC Dev Biol 8: 119.

17. Zhang Y , Vasheghani F , Li YH, Blati M , Simeone K , et al. (2015) Cartilage-specific deletion of mTOR upregulates autophagy and protects mice from osteoarthritis. Ann Rheum Dis (7): 1432-1440.

18. Vasheghani F , Zhang Y , Li YH , Blati M , Fahmi H , et al. () PPARγ deficiency results in severe, accelerated osteoarthritis associated with aberrant mTOR signalling in the articular cartilage. Ann Rheum Dis 74(3): 569-578.

19. Ye Z,Z, Zhang ZY, Li ZG, Huang CB, Zhang Y, Toward wiping out osteoarthritis in China.

20. Zhang Y, Moriguchi H (2011) Chromatin remodeling system, cancer stem-like attractors, and cellular reprogramming. Cell Mol Life Sci 68(21): 3557-3571.

21. Zhang Y, Calderwood SK (2014) Autophagy, protein aggregation and hyperthermia: a mini-review. Int J Hyperthermia 27(5): 409-414.

22. Murshid A , Chou SD, Prince T, Zhang Y, Bharti A, Calderwood SK (2010) Protein kinase A binds and activates heat shock factor 1. PLoS One 5(11): e13830.

23. Zhang Y, Murshid A, Prince T, Calderwood SK (2011) Protein kinase A regulates molecular chaperone transcription and protein aggregation. PLoS One 6(12): e28950.

