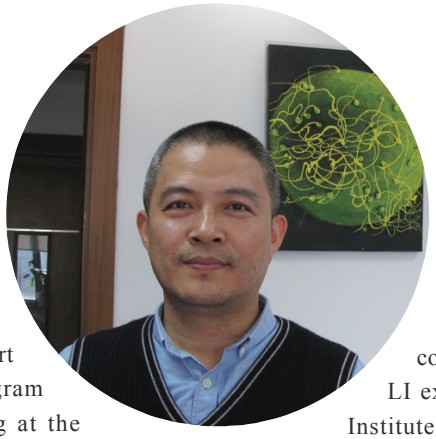
My "First Bucket of Gold"

By SONG Jianlan (Staff Reporter)



Dr. LI Jinsong, awardee of the 2014 Ho Leung Ho Lee Foundation Award for S&T Innovation, returned from the US in 2007, supported by the Hundred-Talent Program. (Photo by SONG)

Across students busy with their experiments among frames filled with tubes, reagent bottles and devices, at the depth of his lab the author found Dr. LI Jinsong, who just received the Ho Leung Ho Lee Foundation Award for S&T Innovation last November.

"With no doubt the stable support offered by the Hundred-Talent Program helped me greatly in my launching at the Shanghai Institute of Biochemistry and Cell Biology (SIBCB), Shanghai Institutes for Biological Science as a Principal Investigator (PI), exactly at the most difficult time in my struggle to transform my role from a postdoctoral research fellow to a PI," LI welcomed the author with a warm, candid smile. "It made it possible for me to focus on my research continuously for four years, working autonomously on the scientific topics chosen by me, and my work during this very time has laid a solid foundation for my later development."

LI returned to China in August 2007 after having worked for five years at Prof. Peter Mombaerts' lab at Rockefeller University, USA as a postdoctoral researcher. Before going to Rockefeller, he studied as a PhD student at the lab of Prof. CHEN Dayuan at the CAS Institute of Zoology in Beijing, and attended the work of the first cloned cattle in China, a sensational event at that time. As most oversea students, he found his first year at Rockefeller hard, but he overcame the difficulty soon and published a paper in 2004 in *Nature* as the first author, and worked on to publish some other papers in leading journals like *PNAS* and *Current Biology*.

Natural Choice

"Should I stay or go back home? For me the answer was natural," with a bright smile he shared his experience: "Go home. Of course." It did not take him much thought, either, to decide which research institution to join after coming back. "I graduated from CAS," LI explained: "I did my PhD at the CAS Institute of Zoology in Beijing. Naturally, I wanted to join a CAS institute when concluding my postdoctoral research in USA. At that point my target city was Shanghai, and hence talked to my wife that as long as I got a job in Shanghai we would come back home.

"As for which institute... Why hesitation? SIBCB is the Number One in the field," he asserted, illuminated with the pride for the institution, which made important contributions in the first successful artificial synthesis of crystalized bovine insulin in the world.

LI got to know the Hundred-Talent Program from another recruit of the Program, Dr. XU Guoliang, who returned earlier to join SIBCB and had already grown into a well-known biologist. XU told him the news that the institute was recruiting PIs supported by the program.

"I met him at a conference and had a good talk. He read my resume and sent it to members of the recruiting committee."

LI was not so confident of his application, however, given that his research interests were more "technique-oriented" compared with his to-be colleagues. To his great happiness, he made it. Given his strong background in stem cell research, LI was recruited by SIBCB as an effort to enhance its capacity in this discipline.

Now what seemed a bit intimidating to him was how to "survive" the intense competition at this top institute, without knowing what was waiting for him at this totally strange place.

"I heard that it would be tough to survive at this top-notched institute. What would add to this difficulty would

be the hardship to develop myself into an independent PI from a postdoctoral researcher. You don't need to worry too much as a postdoctoral fellow as long as you work properly at your experiments and papers; while working autonomously as a PI is totally different, as you are taking charge of the whole lab.

"But the sincerity held by then SIBCB Director, Prof. LI Lin, who is a CAS Member; Prof. LI Boliang, former Director of SIBCB; and prestigious biologist, CAS Member Prof. WANG Enduo cleared my worries. Through my interactions with them I realized that what had made SIBCB a top-notched institute was exactly the philosophy of working down to earth, and competing for excellence and innovation. On the other hand, junior scientists returning from overseas would receive very good support from the administration in terms of start-up funds, equipment purchases, experimental animals and student recruitment.

"More importantly, when the juniors run into difficulties in their professional development, the institute would always be ready to help. You are not fighting alone."

Growing Pains

Having to build his lab from scratch, LI did not make much progress in his scientific exploration during the first three years. It did not take him too much time, though, to establish the whole system for nuclear transfer, a technique to transplant somatic nucleus into enucleated oocyte. It is a demanding technique of critical importance – to date it is still the only approach available for cloning. What threw LI into frustration were the temporary setbacks in his research: he was working in an area not so familiar to most of his SIBCB colleagues, hence inevitably faced more difficulties and challenges, and sometimes even met with misunderstandings. What made it worse were the rumors among PhD students saying that what one could learn from his lab would be very limited, given the "technical" nature of the work. As a result, he found it very hard to recruit and hold students.

"Actually it was an under-evaluation of techniques," he argued: "In techniques lies science – in the process of solving technical problems you make interesting and important scientific discoveries. You see, quite a lot Nobel-winning achievements were firstly inspired by or closely connected to technical issues. On the other hand, techniques themselves are important for biological research; some innovative techniques could even bring about revolutionary changes to science.

"Mostly the institute focuses on research at a molecular level," LI continued: "as a contrast, my research interests looked more macroscopic and holistic – we explore on a cellular or organismal level. From the view of a student, it might not appear to be so 'advanced'," he laughed.

"But this difference might have been the reason why SIBCB recruited me; and this very difference has benefited both me and the institute. On the one hand I have learned a lot from my colleagues; on the other, my skills have offered something valuable to my colleagues, and this laid the basis for my later cooperation with them."

The value of this difference, however, was not well recognized until later. The most difficult time came in 2010 when the first mania faded out and results failed to make appearance after three years' anticipation. Thankfully, at this critical point his institute came for rescue.

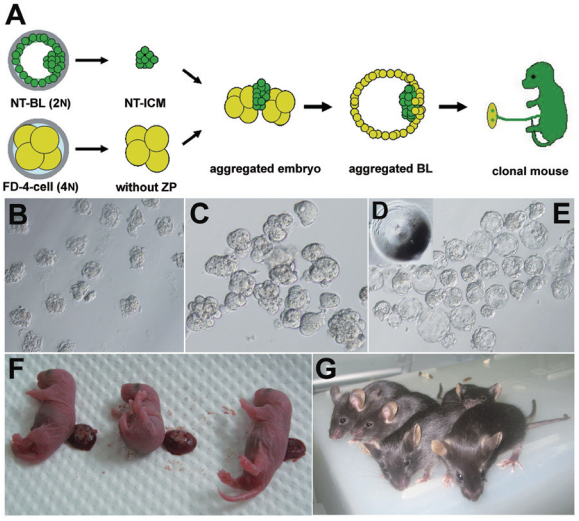
"The leadership of the institute and the administrative staff gave me very strong support. 'Carry on, Jinsong!' They told me: 'Every young PI could run into such problems and confusions at the early stage of their exploration. Hold on steadily and inspire your team with your own perseverance and aspirations. Everything will be fine!'" LI collected with emotions.

"I would never forget how Prof. LI Boliang helped me with my defense presentation for the 'Outstanding Young PI' Program," he collected. "Can you imagine what such a prestigious scientist had offered me? He kept working on my slides from 9 am till 12 am the next day, on the weekend! Nowadays when he attends my presentations at academic conferences, he would praise me of my slides: wonderful! But exactly it was he who gave me the most needed help in my early times!"

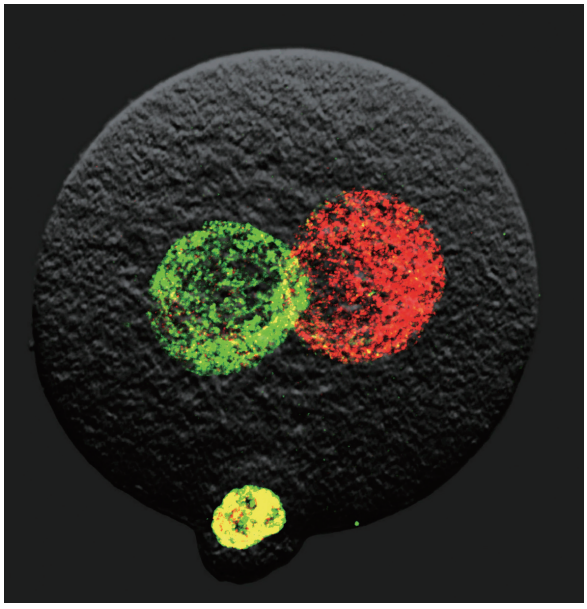
Encouraged by the strong support from the administration and predecessors, LI cheered up and managed to make a difference. "I personally taught my students experiment techniques, analyzed the data together with them, and groped for solutions. Eventually we saw the hope dawning."

Secured Survival

LI's subsequent accomplishment made a very good footnote for his argument on the importance of his "technical research". In 2011, his team detected an important reason causing low efficiency and poor success rates in somatic cloning of embryos via nuclear transfer: the abnormally reprogramed cells in trophoblast cell lineage. Later in the same year they successfully verified this discovery and published a paper in *Cell Stem Cell*, which marked his first important publication at SIBCB. This breakthrough marked a milestone in his career, securing his survival at SIBCB and heralding further up-coming discoveries: he published a work in *Nature* as a result from a cooperative research with



Milestone: LI's group revealed in *Cell Stem Cell* an important cause of poor success rates in nuclear transfer and embryonic cloning in 2011, marking his first important publication at SIBCB. This work secured his "survival" at this top institute and heralded further achievements. (Image by courtesy of Dr. LI, SIBCB)



A result from their first cooperative work with Dr. XU Guoliang, LI's group revealed the role played by a DNA dioxygenase named "Tet3" in reprogramming in the oocyte. This work led to the publication of their paper in *Nature* in 2011, and further developed into the latest result published in *Cell Stem Cell* in September 2014, in which they reveal that both paternal and maternal genomes undergo active de-methylation in the zygote. (Image by courtesy of Dr. LI)

the group of Prof. XU Guoliang in the same year, and since then the two have developed a close partnership in research.

"At that point I realized the importance of cooperation in science: it makes possible what otherwise impossible."

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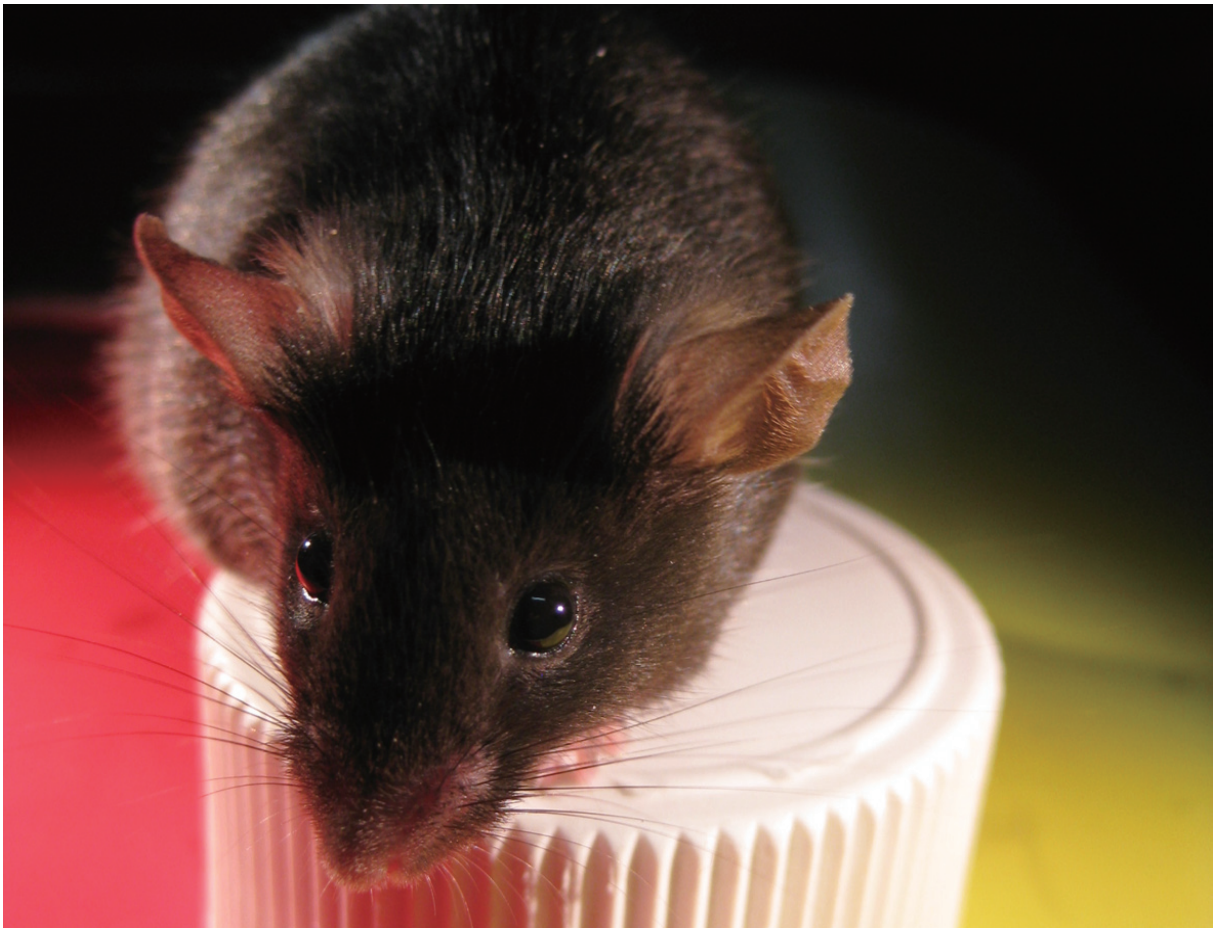
"We focus on embryonic and cell research, and we projected that our haploid cells might have significant applications in gene knockout experiments, therefore we needed to find a cooperator good at this. At that time only very few labs were capable of this, and XU's group was among the very few that were excellent at it," LI told the story how their cooperation began.

Generated from sperm-like cells cultured in vitro, this cute mouse hit the headlines in 2012. In cooperation with Dr. XU Guoliang's lab, Dr. LI Jinsong's team successfully established a haploid stem cell line from mouse androgenetic blastocyst, and verified that the stem cells reproducing in the cell line partially maintained sperm properties and could replace the role of sperms. Dubbed "artificial sperms", this work was published in Cell in the same year and listed in the annual Top 10 S&T Achievements of China. (Image by courtesy of Dr. LI)

This partnership yielded another important fruit in 2012: They managed to establish a haploid stem cell line from mouse androgenetic blastocyst. They successfully maintained a certain level of sperm properties in the cell line, and further verified that these stem cells could functionally replace sperms to "fertilize" oocytes: they produced healthy, fertile mice after being injected into mice oocytes. This cell line makes it possible to stably reproduce sperm-like cells *in vitro*, which would otherwise be impossible; and has offered a handy, reliable path to create genetically modified mice, and found wide applications in biological research.

"We called the offspring 'semi-cloned' mice, because in this 'cloning', it is not needed to get rid of the nucleus of the oocyte; only the 'cultured sperm' is cloned. This term also differentiates it from real fertilization – after all it is not fertilization."

LI's group is very good at some experiment skills valuable for other labs, like the highly accurate isolation and extraction of male and female genomes in zygotes. These techniques played important roles in their cooperation with XU's group, for example. In their latest work published in *Cell Stem Cell* in September 2014, they revealed a new scenario of de-methylation of the paternal and maternal genomes in mice zygotes: both of them experienced active de-methylation, rather than as what previously believed, only the paternal genome would de-methylate actively,



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while the maternal one would only go through the de-methylation passively.

"To directly observe the extent of de-methylation in parental and maternal genomes respectively, we need to divide and extract them accurately, and send them to Prof. TANG Fuchou at Peking University, another cooperator of ours, to do the DNA sequencing. To secure the accuracy, we need to capture the most favorable moment in wake of fertilization when the maternal pronucleus slightly expands and the parental genomes lie more noticeably apart, and isolate them respectively from the zygote under microscopy. This is very difficult, as the two genomes wind very closely together, in a distance very hard to detect – totally different from what is drawn in the schematic illustration, which is a little bit exaggerating," LI explained.

"In total, a student of mine alone performed over 10,000 operations of such," LI added with a subtle laugh: "Well, you can imagine the workload."

"Looking back I appreciate the steady trust given by my first PhD students. Some have done a very good job. YANG Hui, for example, published a paper in *Cell*, and a further one in *Nature*, which is also a result from our cooperative work with Dr. XU Guoliang. YANG Hui is now already a PI himself after returning from overseas; and we are still in close cooperation," LI smiled: "Thanks to their excellent work our lab is now developing in a virtuous circle: More outstanding students join in attracted by the renowned work by their predecessors, and hence more excellent work follow."

"Now whenever a young PI gets frustrated by their slow progress, I could be cited as an encouraging example: Don't worry, Jinsong had similar problems at first. And now, look, he's fine!!" LI laughed.

"I enjoy the atmosphere at SIBCB very much,"

LI commented when comparing his experience at Rockefeller and SIBCB: "I do not feel noticeable difference between them in terms of free exploration in academic research, close cooperation among colleagues and academic exchanges. We have lots of presentations and seminars on the campus every day; and the funding is sufficient."

Recalling his difficult time, LI still could not hold his gratefulness for the "first bucket of gold" offered by the Program. "They did not stipulate any pre-condition concerning your future results when offering the fund: Once they decide you are qualified for the fund after evaluating your ability and past work, they would totally trust you. This greatly helped me survive the first three years and lay down the foundation for my later development."

Biological "Shuttle Race"

LI has been working in the field of reprogramming of somatic cells and induction of pluripotent stem cells, a fascinating area of biology. "It is like a shuttle race in life," he explained: "Generally speaking it is almost impossible for certain types of somatic cells, like epithelial cells, to transform into another type, say liver cells, once they have been differentiated from stem cells.

"In some certain conditions, however," he continued: "through a biochemical process called reprogramming, the DNAs in the somatic cells can erase their epigenetic marks and return to an infant-like period, where they regain the totipotency or pluripotency to develop into any type of somatic cells, taking a restart into a brand new life, exactly like a 'shuttle race'. I would call this a shuttle race of life," LI smile.

"And what I have experienced at SIBCB is just like a 'shuttle race'," LI remarked when recalling his difficult yet rewarding growth from a postdoctoral researcher into a PI at SIBCB.

"It takes steady confidence and perseverance to pursue science exploration," LI concluded in the hindsight of his experience: "You must work down-to-earth in a somewhat acetic way, blazing a trail out of the brambles and thorns. Only the most courageous survive this sweet ordeal to smile on the victory."

"Exchanges with outstanding peers, who often open new horizons for you, could sparkle innovative ideas and lead to win-win cooperation," he continued: "Dr. XU is a perfect cooperator of mine. It is both a happy coincidence and predestination for me to have met him. We share the same research interests and common language, and we share the willpower needed for the long trek. We have been working like a relay team in the 'shuttle race' of life science to achieve the same goals.

"Similarly, my cooperation with another SIBCB colleague, Prof. LI Dangsheng has reaped a bumper harvest. Moreover, as the Editor-in-Chief of *Cell Research*, his strict, critical review of my papers from the perspective of an excellent science editor also gave a strong boost to my growth into a mature researcher," LI emphasized.

"I am lucky enough to grow with the Hundred-Talent Program. It was this program that has offered me 'the first bucket of gold' for my career home in China, and imprinted me with the brand of CAS – It is fortune for oversea Chinese scholars like me," LI said.