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Attorneys for Plaintiff RONGXIANG XU

SUPERIOR COURT OF THE STATE OF CALIFORNIA

COUNTY OF ORANGE – CENTRAL JUSTICE CENTER

RONGXIANG XU, an individual;

Plaintiff,

vs.

THE NOBEL ASSEMBLY AT KAROLINSKA INSTITUTET, a Swedish corporation, aka, NOBELFÖRSAMLINGEN and DOES 1-50, inclusive,

Defendants.

Case No. 30-2012-00615804-CU-DF-CJC

COMPLAINT FOR DAMAGES:
1. **DEFAMATION;**
2. **UNFAIR COMPETITION CAL. BUS. & PROF. CODE §§ 17200 et seq.; and**
3. **DECLARATORY RELIEF;**

UNLIMITED CIVIL:

DEMAND EXCEEDS $25,000

DEMAND FOR JURY TRIAL

Judge Sheila Fell

Plaintiff RONGXIANG XU alleges as follows:

GENERAL ALLEGATIONS

1. This is a complaint for libel. Plaintiff, who previously enjoyed a good reputation in the community, was defamed by a statement published by the defendants herein. A copy of the publication containing the defamatory statement is attached to this complaint as Exhibit "A".

2. The allegations of this complaint stated on information and belief are likely to have evidentiary support after a reasonable opportunity for further investigation or discovery.

3. Plaintiff Dr. RONGXIANG XU ("Dr. Xu" or "Plaintiff") is, and at all times herein mentioned was, an individual with his principal residence in Los Angeles County, California. Rongxiang Xu is the inventor of "the technology of awakening human somatic cell to turn to

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pluripotent stem cell and regenerating in situ new cell, tissue and organ of its own," the founder of "human body regenerative restoration science" and a renowned life scientist and medical scientist. A list of some of Dr. Xu's achievements and his background information is attached to this complaint as Exhibit "B."

4. Plaintiff is informed and believes, and thereupon alleges that Defendant THE NOBEL ASSEMBLY AT KAROLINSKA INSTITUTET, a Swedish corporation, aka, NOBELFÖRSAMLINGEN (hereinafter referred to as "the Nobel Assembly") is a corporation organized and existing under the laws of Sweden.

5. Plaintiff is ignorant of the true names and capacities of defendants sued herein as DOES 1 through 50, inclusive, and therefore sue these defendants by such fictitious names. Plaintiff will amend this Complaint to allege their true names and capacities when ascertained. Plaintiff are informed and believe, and thereon allege, that each of the fictitiously named defendants is responsible in some manner for the occurrences herein alleged and that Plaintiff' damages as herein alleged were proximately caused by their conduct.

6. DOES 1 through 50, inclusive, along with the Nobel Assembly shall hereinafter be referred to collectively as "Defendants."

7. Plaintiff is informed and believes, and thereon alleges, that at all times herein mentioned, each of the Defendants was the agent, servant and/or employee of each of the remaining Defendants, and that in doing the acts alleged in the Complaint, each of the Defendants was acting in the capacity of agent, servant and/or employee, and with the consent and ratification of the remaining Defendants. At all times relevant herein, each Defendant was acting with one or more of the other Defendants pursuant to a common scheme, course of action, enterprise or conspiracy. Each Defendant is therefore liable to Plaintiff for the events, happenings, and damages herein alleged by reason of the acts, conduct, and participation with one or more of the other Defendants.

8. Plaintiff is informed and believes, and thereon alleges, that the Nobel Assembly is responsible for selecting the Nobel Laureates in Physiology or Medicine. Plaintiff on information and belief, further allege that the Nobel Assembly is responsible for making press releases and

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publications in relation to the Nobel Prize in Physiology or Medicine.

9. On October 8, 2012, The Nobel Prize in Physiology or Medicine 2012 was awarded jointly to Sir John B. Gurdon and Shinya Yamanaka "for the discovery that mature cells can be reprogrammed to become pluripotent."[1] The announcement of the selection was reported, and continue to be reported by, essentially every major news organization and publication.

10. In an abstract published on its website made in conjunction with the selection, located at http://www.nobelprize.org/nobel_prizes/medicine/laureates/2012/advanced-medicineprize2012.pdf, the Nobel Assembly described the scientists' discovery. In the description, the Nobel Assembly claims that the scientists' discovery "represents a paradigm shift in our understanding of cellular differentiation and of the plasticity of the differentiated state." The abstract goes on to claim that: *"[t]ogether, Gurdon and Yamanaka have transformed our understanding of cellular differentiation. They have demonstrated that the usually very stable differentiated state can be unlocked because it harbours a potential for reversion to pluripotency. This discovery has introduced fundamentally new research areas, and offers exciting new opportunities to study disease mechanisms."* (hereinafter the "Statement")(Italics added).

11. Plaintiff is informed and believes, and thereupon alleges the Statement made by the Nobel Assembly is false. The Nobel Assembly states that the scientists who won the Nobel Prize "have transformed our understanding of cellular differentiation" because "[t]hey have demonstrated that the usually very stable differentiated state can be unlocked because it harbours a potential for reversion to pluripotency." Those scientists did not demonstrate as such. It was ten years earlier that Dr. Xu made that discovery when he was able to explain how his discovery unlocked a somatic cell's potential to revert to pluripotent stem cell in situ. The Nobel Assembly's use of the word "unlocked" compounds the falsity of the statement because it suggests that the scientists who won the Nobel Prize are harnessing an inherent ability of a somatic cell to revert to its pluripotent state through natural means that do not alter the cells integrity. On the contrary, the prize winners' method requires engineering of the somatic cell by mutating its DNA,

[1] "The Nobel Prize in Physiology or Medicine 2012". Nobelprize.org. 1 Dec 2012 http://www.nobelprize.org/nobel_prizes/medicine/laureates/2012/

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rather than unlocking the inherent abilities of the somatic cell's structure and composition. The Statement leads the reader of the Statement, especially in the scientific community, to believe that the scientists who won the Nobel Prize were the ones who unlocked the potential for reversion to pluripotency which enables a somatic cell to transform into a stem cell itself. If the Nobel Prize scientists' findings consisted of leaving a somatic cell intact and unmodified, such as Dr. Xu's finding, then the Statement would have been true and accurate. However, the Nobel Prize scientists' discovery actually consists of the creation of an altered cell having nothing to do with human body pluripotent stem cell. Dr. Xu's "human body regenerative restoration science" can be explained plainly as below: "human body regenerative restoration science" is not modern or traditional pharmaceutical science, not either genetic engineering and cellular engineering, but a new scientific system that achieved the procedure to awaken the innate regenerative potential of human body, nourish the regenerative cells with regenerative nutrients, facilitate the human body to regenerate new cells to replace and replenish the aged, diseased , damaged, apoptotic, mutated cells for the purpose of maintaining normal structure and function of its own tissue and organ as well as achieving healthy young state and longevity via its own regenerative mechanism.
The phenomenon of "reversion of a somatic cell to a pluripotent cell" described by the Nobel Prize in Physiology or Medicine 2012 is a small step of awakening somatic cell in the scope of the new system of "human body regenerative restoration science", because "reversion of a somatic cell to a pluripotent stem cell" is the innate ability of human body its own. For instance, there is such response to injury in somatic cells at wound site, however, the wound is repaired by fibrotic cells to form scar due to the lack of physiological regulation and nutrients. "Human body regenerative restoration science" has the techniques to regulate comprehensively the physiological environment and nutrients which facilitate the scar-less healing of the wound in the way of tissue regeneration by stem cells. Reversion of human somatic cells to pluripotent stem cells is the innate ability of human body, rather than something made artificially.

12. Plaintiff is informed and believes, and thereupon alleges the statement that "[t]his *discovery* has introduced fundamentally new research areas, and offers exciting new opportunities to study disease mechanisms" is also inaccurate. (Italics added). More specifically, the use of the

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term "discovery" is inaccurate. In 1962, Sir Gurdon demonstrated that the nucleus of the mature cell had not lost its capacity to drive development to a fully functional organism, but he never found a solution to the question of whether it would ever be possible to turn an intact cell back into a pluripotent stem cell". In 2000, by cellular cultivation, without any genetic engineering in a cell, Dr. Xu, for the first time in history, awakened intact mature somatic cells to turn to pluripotent stem cells in situ. This is only the very beginning step of in situ organ regeneration procedure achieved by Dr. XU as described in Exhibit B. About 6 years later, Dr. Yamanaka, in 2006, found an artificial in vitro approach to change an intact mature cell to an artificially altered cell by genetic engineering.

13. Plaintiff is informed and believes, and thereupon alleges that the Nobel Assembly has also partnered with Astrazeneca to publicize generally all the advances made by the scientists who won the Nobel Prize for Physiology or Medicine. Under these circumstances, the audience who will be exposed to the publication will include members of the scientific community and investors in the field of regenerative science.

14. Plaintiff is informed and believes, and thereupon alleges that members of the scientific community, especially in the area of regenerative science will understand that the Statement directly undermines the findings and accomplishments of Dr. Xu. Plaintiff is further informed and believes, and thereupon alleges that the Nobel Assembly did not reveal, acknowledge or discuss Dr. Xu's accomplishment in the field despite its knowledge of Dr. Xu's prior body of work and discoveries.

15. Plaintiff is informed and believes, and thereupon alleges that the Statement issued by the Nobel Assembly has caused confusion and misled the public as to the nature of the Nobel Prize scientists' discovery as several major articles have misinterpreted the scientists' discovery by also labeling the discoveries as unlocking a cell's unlimited potential. A National Public Radio's ("NPR") article (http://www.npr.org/blogs/health/2012/10/08/162496684/nobel-winners-unlocked-cells-unlimited-potential), stated "Nobel Winners Unlocked Cells' Unlimited Potential" and "The two scientists who won this year's Nobel Prize in Physiology or Medicine discovered that cells in our body have the remarkable ability to reinvent themselves. They found that every

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cell in the human body, from our skin and bones to our heart and brain, can be coaxed into forming any other cell." Such statements indicates that the general public have been misled by Defendants' Statement to believe that the Nobel Prize scientists have discovered a process in which every cell in our body can reinvent themselves and be induced to form any other type of cell themselves, which work has been actually achieved by Dr. Xu rather than the two Nobel prize winners who, in fact, did not coaxed or induced cells but modified or artificially reinvented cells. Through the mentioned statements in NPR's report, people would think the two Nobel prize winners induced the cells to reinvent and form any other type of cell themselves, while this should be credited to Dr. Xu.

16. Plaintiff is informed and believes, and thereupon alleges that under the facts and circumstances known to the scientific community, especially in the area of regenerative science and burn therapy, the Statement has specifically injured the Plaintiff's reputation, occupation and profession. The Statement has exposed him to contempt and ridicule as his accomplishments and achievements have been disparaged, questioned, diminished and discredited. Specifically, the Statement has also further discouraged others in the scientific community from associating or dealing with Dr. Xu as they now question Plaintiff's credibility in the discovery of the same.

17. This Court has personal jurisdiction over the Nobel Assembly as the above statement was continuously transmitted and made available throughout the United States, including this judicial district.

18. It should be noted that Dr. Xu has no interest in challenging the Nobel Prize, in discounting the work or discoveries of the scientists who won the Prize. Dr. Xu's main interest is in rehabilitating his dominant position as the owner, pioneer of the scientific achievement characterized in the publication at issue.

FIRST CAUSE OF ACTION FOR DEFAMATION (Libel Per Quod)

(Against all Defendants)

19. Plaintiff hereby restates and incorporates by reference paragraphs 1 through 17 above as though set forth in full herein.

20. Defendants' Statement was widely published and not privileged in any manner.

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21. Defendants' Statement was reasonably understood to concern Dr. Xu and was false.

22. Because of the fact and circumstances known to the readers of the Statement, it tended to injure Dr. Xu in his occupation, and expose him to contempt, ridicule and shame. The Statement also discouraged others from associating or dealing with him.

23. The Defendants failed to use reasonable care to determine the truth or falsity of the Statement.

24. Dr. Xu suffered harm to his business, profession and occupation including money spent as a result of the Statement.

25. The Statement has falsely tainted and damaged Dr. Xu's achievements in the eyes of the scientific community, business, potential investors. In addition, although Dr. Xu was the keynote speaker for several major international conferences, Dr. Xu will be less likely to be selected to promote his science.

26. The Statement was a substantial factor in causing Dr. Xu's harm.

SECOND CAUSE OF ACTION FOR VIOLATION OF BUSINESS & PROFESSIONS CODE § 17200, *et seq.*

(Against all Defendants)

27. Plaintiff hereby restates and reincorporates by reference Paragraphs 1 through 25 above, as though set forth in full herein.

28. Plaintiff is informed and believes and on that basis thereon allege, Defendants acts and omissions as described herein constitutes unfair and/or fraudulent business practices in violation of Section 17200 *et seq.* of the California Business and Professions Code and California common law.

29. As a direct and proximate result of Defendants' wrongful acts, Plaintiff has suffered and will continue to suffer substantial pecuniary losses and irreparable injury.

30. By reason of such wrongful acts, Plaintiff is and will be in the future, deprived of the profits and benefits described herein.

THIRD CAUSE OF ACTION FOR VIOLATION OF BUSINESS & PROFESSIONS CODE § 17200, *et seq.*

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(Against all Defendants)

31. Plaintiff hereby restates and reincorporates by reference Paragraphs 1 through 29 above, as though set forth in full herein.

32. Defendants' publication is ongoing, in that it remains prominently displayed on Defendants' website, which is viewed globally. Money damages will not make Dr. Xu whole for the injury occasioned by the continuing Statement. Unless enjoined by this Court, the false and damaging Statement will continue to be displayed.

33. An actual controversy exists between Plaintiff and Defendants in that Defendants have asserted and continues to publish the Statement and unless this Court issues declaratory relief, Defendants will continue to repeat such defamatory Statement.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff prays for Judgment as follows:

1. For special damages in an amount to be proven at the time of trial;
2. For general damages on behalf of Plaintiff;
3. A declaration that the defamatory Statement was untrue;
4. An injunction prohibiting Defendants from repeating such Statement and requiring Defendant to retract such Statement.
5. Costs of suit; and
6. For such other and further relief as this Court may deem just and proper.

Dated: December 2, 2012

ARDENT LAW GROUP, P.C.

By: _____
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EXHIBIT "A"

Mature cells can be reprogrammed to become pluripotent

The 2012 Nobel Prize in Physiology or Medicine is awarded to Dr. John B. Gurdon and Dr. Shinya Yamanaka for their discovery that mature, differentiated cells can be reprogrammed to a pluripotent stem cell state. This represents a paradigm shift in our understanding of cellular differentiation and of the plasticity of the differentiated state. Cellular differentiation appears as a unidirectional process, where undifferentiated cells mature to various specialised cell fates, such as neurons, muscle and skin cells. The prevalent view during the first half of the 20th century was that the mature cells were permanently locked into the differentiated state, and unable to return to a fully immature, pluripotent stem cell state. In 1962, John B. Gurdon radically changed this view by demonstrating that the nucleus from a differentiated frog intestinal epithelial cell was capable of generating a fully functional tadpole upon transplantation to an enucleated egg. This discovery shattered the dogma that cellular differentiation could only be a unidirectional process. Gurdon's discovery was the starting point for cloning endeavours in various organisms. However, the question remained whether an intact differentiated cell could be fully reprogrammed to become pluripotent. In 2006, by an astonishingly simple procedure, Shinya Yamanaka proved that introduction of a small set of transcription factors into a differentiated cell was sufficient to revert the cell to a pluripotent state. The resulting cells were called induced pluripotent stem (iPS) cells. Together, Gurdon and Yamanaka have transformed our understanding of cellular differentiation. They have demonstrated that the usually very stable differentiated state can be unlocked because it harbours a potential for reversion to pluripotency. This discovery has introduced fundamentally new research areas, and offers exciting new opportunities to study disease mechanisms.

Introduction

During normal development, cells proceed from the initial undifferentiated state of the egg and cells in the early embryo to a more specialised state. In the adult organism a range of differentiated cell types are required to execute the specialised functions performed in the adult body (Figure 1A). The fertilised egg and the cells in the early zygote are totipotent, in other words, they can give rise to all cell types in the embryo, as well as to extraembryonic tissues such as placenta. As development

progresses, cells at the blastocyst stage start to become distinguishable: the inner cell mass gives rise to the embryo proper, whereas the surrounding cells make up the trophoblast lineage and are the source of extraembryonic tissues. The cells in the inner cell mass are pluripotent, i.e. they can give rise to all somatic cells, as well as to the germ cell lineage: the cells destined to become gametes (eggs and sperm).

During this developmental journey, cells progressively become more restricted in their differentiation potential and as a consequence, they do not retain pluripotency. Most cells mature into fully differentiated cells, although stem cells with limited potency remain in certain locations in the body and serve as a source for cell replacement, for example in the bone marrow, intestine and skin. Differentiated cells are remarkably stable and as a rule they will not shift fate into other types of differentiated cells or revert to the type of undifferentiated cells that can be found in the early embryo. For this reason, the long-standing predominant view was that cells in the somatic lineage were permanently in a locked state, such that the journey back to a highly undifferentiated state was impossible. The insight that various differentiated cell types were endowed with a specific pattern of proteins suggested that differentiated cells may carry irreversible epigenetic modifications or genetic alterations that render induction of pluripotency impossible. Conrad Hal Waddington proposed an epigenetic landscape of mountains and valleys as a metaphor for development. In this landscape, undifferentiated cells, represented as marbles, reside on a mountain top. During differentiation they trickle down into energetically more stable valleys, where they come to rest as differentiated cells. The assumption was that it would be difficult to revert the differentiated cells back to the undifferentiated state by moving them back to the mountain top (Waddington, 1957) (Figure 1B). Despite the dogma, the notion that specialised cells could somehow be unlocked from their differentiated state and dedifferentiate was not entirely dismissed. Various strategies to experimentally address the problem were considered. For example, Hans Spemann (Nobel Prize in Physiology or Medicine 1935) entertained the idea of transferring nuclei from differentiated cells to an immature cytoplasmic milieu to test its developmental potential. He referred to this approach as a "fantastic experiment".

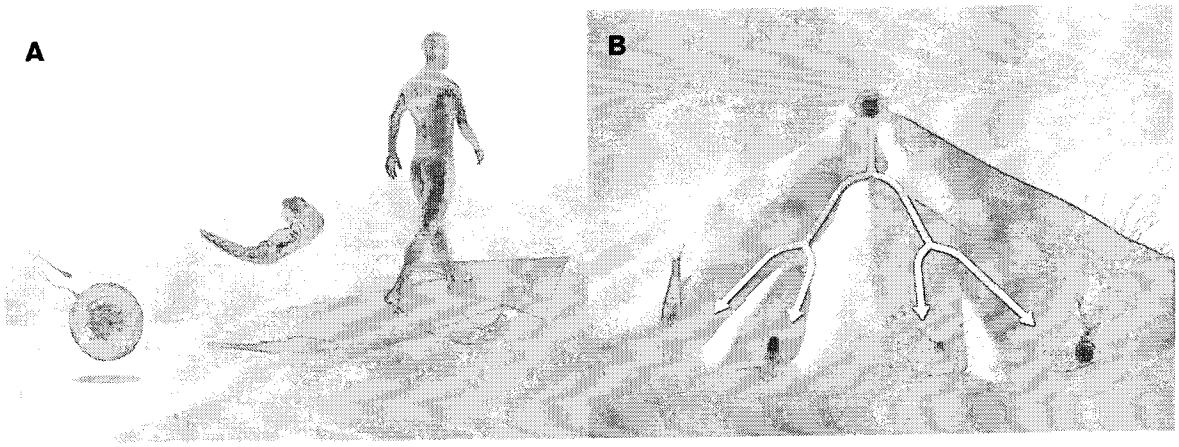

Figure 1 A, Normal development of a human from a fertilized egg illustrating the unidirectional process of maturation via the egg and embryo into an adult human. B, Waddington illustrated cellular differentiation as an epigenetic landscape in which cells are seen as marbles rolling down in valleys to reach their end-point destinations as differentiated cells. The metaphore nicely visualizes the unidirectional developmental process of normal development. Cells do not normally move back towards the top of the mountain to reach the undifferentiated state, and cells are not normally crossing into other valleys to develop into unrelated cell lineages.

Reprogramming a differentiated somatic cell nucleus

A direct attempt to test whether differentiated cells in the somatic cell lineage were endowed with a dormant dedifferentiation potential was first carried out by Robert Briggs and Thomas King, who developed a technology for transfer of somatic cell nuclei from undifferentiated and differentiated cells to an enucleated fertilized egg in the amphibian *Rana pipiens* (Briggs and King, 1952). Amphibians are particularly amenable to this type of experiments because of the large size of the egg and the extrauterine development of embryos. Briggs and King showed that an embryonic nucleus, when transferred to an enucleated egg, could indeed support development up to the tadpole stage. In contrast, when they repeated the procedure with nuclei from more differentiated cells, they failed to obtain developing embryos. Thus, they concluded that differentiated nuclei undergo irreversible changes during differentiation such that the capacity to promote development was lost (King and Briggs, 1955).

John B. Gurdon, who had trained in embryology with Michael Fischberg in Oxford, used a different amphibian, *Xenopus laevis* rather than *Rana pipiens*, to address the topic. In *Xenopus*, Gurdon could take advantage of a cell tracing system developed by Fischberg and colleagues (Elsdale et al., 1958) that allowed him to unequivocally distinguish the cells derived from transplanted nuclei from the cells of the host embryo. In a key study, Gurdon enucleated eggs by ultraviolet irradiation and found that when the eggs were transplanted with nuclei from differentiated tadpole intestinal epithelium, a

small number of swimming tadpoles were indeed generated (Gurdon, 1962) (Figure 2). He could also show that the efficiency of nuclear reprogramming could be greatly improved by performing serial transplantations. By this strategy, he showed that a rather large proportion of all intestinal epithelial cell nuclei could be reprogrammed (Gurdon, 1962). Gurdon concluded that differentiated somatic cell nuclei had the potential to revert to pluripotency. However, considerable time passed before his discovery gained broad acceptance in the scientific community. In subsequent experiments, Gurdon used nuclei from adult frogs to generate tadpoles, and conversely, embryonic differentiated nuclei supported development of adult frogs (Gurdon and Uehlinger, 1966; Laskey and Gurdon, 1970).

Gurdon's discovery was a fundamental paradigm shift, showing for the first time that the cell nucleus from a somatic differentiated cell was endowed with the capacity to drive development into a full range of somatic cell types and tissues after being placed in the cytoplasmic milieu of an egg cell.

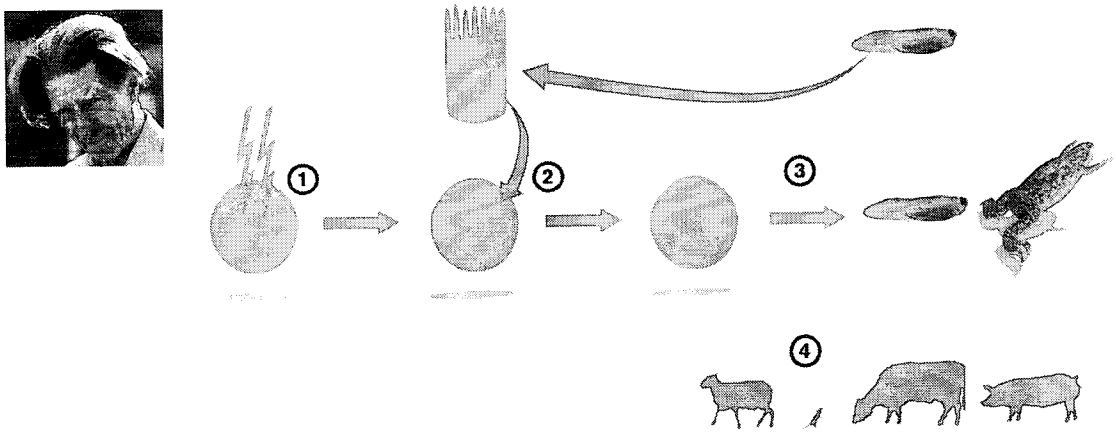

Figure 2 John Gurdon used UV light (1) to destroy the cell nucleus in a frog egg. He then replaced the egg nucleus with a cell nucleus from a differentiated intestinal epithelial cell from a tadpole (2). Many manipulated eggs did not develop but in several cases normal swimming tadpoles were generated (3). This showed that the genetic information required to generate the differentiated cells in a tadpole remained intact in the donor cell nucleus. Later studies have shown that also mammals can be cloned by this technique (4).

Further developments of reprogramming by nuclear transfer

Gurdon's discovery introduced a new research field of centered on somatic cell nuclear transfer (SCNT) as a method to understand reprogramming and how cells change as they become specialized. In 1997, the first cloned mammal, the sheep Dolly, was born after SCNT from an adult mammary epithelial cell into an enucleated sheep egg (Wilmut et al., Nature 1997). The experimental strategy by Ian Wilmut and Keith Campbell was based on Gurdon's work in *Xenopus*, but with additional technical adaptation. For example, one important modification was that nuclei used for

transplantation in mammals came from mammary gland epithelial cells induced to enter quiescence, which make them better suited to synchronize with the early developing embryo. Since the cloning of sheep in 1997, SCNT has now been used to clone a plethora of mammalian species, including mouse, cow, pig, wolf and African wildcats. By nuclear transfer of cell nuclei from B- and T-cells in the immune system, conclusive evidence was provided that a differentiated cell nucleus with rearranged immunoglobulin or T-cell receptor genes could indeed be reprogrammed to support the development of a mouse (Hochedlinger and Jaenisch, 2002).

Reprogramming of an intact somatic differentiated cell to become pluripotent

Gurdon revealed that a differentiated cell nucleus has the capacity to successfully revert to an undifferentiated state, with a potential to restart development. However an open question remained, namely, whether it would be possible to induce reversion of an intact differentiated cell to a highly immature state. Many scientists considered this impossible, or at the very least, that it would require very complex reorganization in the cell to unlock the differentiated state. Such was the scene when Shinya Yamanaka decided to approach the problem of reprogramming to pluripotency. Yamanaka, who had trained both in orthopaedic surgery and molecular biology, became interested in the pluripotent state in part by studying pluripotent embryonic stem (ES) cells, first cultured and characterised by Martin Evans (Nobel Prize in Physiology or Medicine 2007).

Yamanaka's laboratory focused on factors important for maintaining pluripotency in ES cells, such as ERas (Takahashi et al., 2003) and identified, in parallel with Austin Smith's laboratory, the pluripotency gene Nanog (Mitsui et al., 2003; Chambers et al., 2003). Yamanaka then embarked on the quest of inducing pluripotency in somatic cells. From his work and others, he knew a large number of transcription factors that were expressed in ES cells with either confirmed or suspected functions in the maintenance of the pluripotent state. Furthermore, ES cells were known to induce pluripotency in somatic cell nuclei after induced cell fusions between ES and somatic cells (Tada et al., 2001). Equipped with this information, Yamanaka selected a set of 24 ES cell transcription factors that he considered as candidates to reinstate pluripotency in somatic cells.

In a strikingly bold experiment, all 24 genes encoding these transcription factors were introduced in one step into skin fibroblasts and a few of them actually generated colonies that showed a remarkable resemblance to ES cells. The number of genes capable of inducing such colonies were reduced, one-by-one, to identify a combination of only four transcription factors (Myc, Oct3/4, Sox2 and Klf4) that were sufficient to convert mouse embryonic fibroblasts to pluripotent stem cells

(Takahashi and Yamanaka, 2006) (Figure 3). The pluripotent stem cells, which Yamanaka called induced pluripotent stem cells (iPS cells), appeared with a very low frequency, but could be selected for by expression of a neomycin/lacZ fusion gene (βgeo) inserted into the Fbx15 locus in the genome of the mouse from which the fibroblasts were obtained. The Fbx15 promoter is active in pluripotent stem cells, and activation of βgeo expression in the pluripotent stem cells results in G418 resistance. The iPS cells generated various cell types in teratoma assays and contributed to tissues in chimeric mice after injection in mouse blastocysts. However, iPS cell germ line transmission was not achieved in the first study (Takahashi and Yamanaka, 2006). However, a year later, Yamanaka's group, in parallel with Rudolph Jaenisch's and Konrad Hochedlinger's groups, refined the selection system (now selecting for activation of either the Oct4 or Nanog gene loci), and the resulting iPS cells showed germ line transmission (Okita et al., 2007; Wernig et al., 2007; Maherali et al., 2007). In 2007, Yamanaka's and James Thomson's laboratories were the first to produce human iPS cells (Takahashi et al., 2007; Yu et al., 2007). In the human iPS cell experiments, Yamanaka used the four factor combination from the 2006 paper (Myc, Oct4, Sox2 and Klf4), whereas Thomson used a somewhat different transcription factor combination (Lin28, Nanog, Oct 4 and Sox2).

Yamanaka's discovery of iPS cells represents a truly fundamental discovery, as it was the first time an intact differentiated somatic cell could be reprogrammed to become pluripotent. Yamanaka's discovery has opened up a completely new research field, and the astonishingly simple iPS technology is now used in a large number of laboratories around the world.

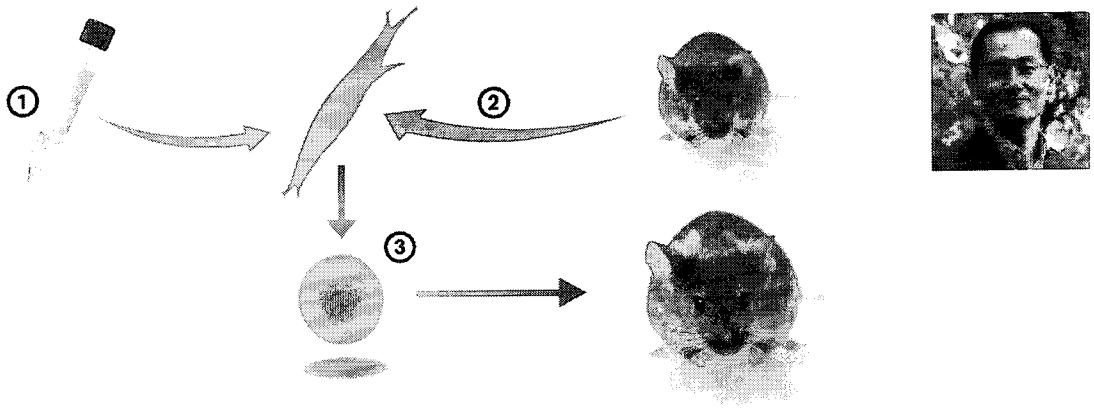

Figure 3 Starting from a collection of 24 different transcription factors (symbolised by the test tube); (1), Takahashi and Yamanaka (2006) demonstrated that a set of only four transcription factors (Myc, Oct3/4, Sox2 and Klf4) was sufficient to convert cultured mouse embryonic or adult fibroblasts (2) to become pluripotent cells capable of producing teratomas in vivo and contributing to chimeric mice (3). The pluripotent cells were called induced pluripotent stem cells (iPS cells).

Further developments of cellular reprogramming and its use in medical research

Since the initial discovery, the technology has been improved in several ways. For example, the pluripotency factors can now be delivered into the cell without the use of retroviral vectors, which integrate randomly in the genome and cause deregulation of nearby endogenous genes that may contribute to tumour formation. Non-integrating viruses, stabilised RNAs or proteins, as well as episomal plasmids, are now used for integration-free delivery of the pluripotency genes. In certain cell types fewer than four factors are required to induce pluripotency, for example adult mouse neural stem cells only require Oct4 for iPS cell induction (Kim et al., 2009). Similarly, small molecules have been shown, in certain cellular contexts, to substitute for some of the pluripotency factors (Li et al., 2009). Importantly, iPS cells meet the most stringent criteria for pluripotency, as they are able to generate all iPS cell-mice in tetraploid complementation tests, i.e., when the cells are introduced into a tetraploid 8-cell stage morula (Zhao et al., 2009). All these improvements, based on the original discovery by Yamanaka, have been important steps to make the iPS technology more efficient and useful.

Yamanaka's discovery, demonstrating that dramatic changes in the usually very stable differentiated state can be achieved, has also inspired research efforts to change the fate of cells without proceeding through a pluripotent state. Transdifferentiation experiments have a long history that goes back to imaginal disc experiments in *Drosophila* in the 1960s, followed by the use of single genes such as Antennapedia, MyoD, GATA1 or Pax5 to induce cell fate switches. In particular the discovery that MyoD could transdifferentiate 10T1/2 fibroblasts to myoblasts (Davis et al., 1987) showed that genes that carried out transdifferentiation could be systematically identified. Yamanaka's approach to systematically define a small set of transcription factors, rather than a single factor, has inspired a recent wave of transdifferentiation experiments using combinations of transcription factors. For example, exocrine cells convert to endocrine cells in the pancreas by introduction of three transcription factors (Zhou et al., 2008). Similarly, cardiomyocytes can be generated from fibroblasts *in vitro* by introducing three different transcription factors (Ieda et al., 2010), and a corresponding cell fate switch has recently been accomplished *in vivo* by using the same factors (Song et al., 2012; Qian et al., 2012). These examples provide evidence for transdifferentiation within a germ layer, but efficient transdifferentiation between germ layers can also be achieved. The transdifferentiation from fibroblasts (mesoderm) to neurons (ectoderm) (so called iN cells) was accomplished by expression of by three transcription factors (Pang et al., 2011).

Stem cells, including iPS cells, can potentially be used to replace diseased or lost cells in degenerative disorders including e.g. Parkinson's disease and in type 1 diabetes. Cell replacement therapy with iPS cells can allow autologous cell grafting that would be less prone to immune rejection. The improved methods for the generation of iPS cells will be important in these efforts. However, the possibility exists that currently used procedures for reprogramming may introduce mutations or other genomic abnormalities, which may render them unsuitable for cell therapy. The prospect of using pluripotent stem cells, including ES cells, in cell transplantation remains challenging for a number of additional reasons. Thus, although this is a very exciting and promising research area, further work is required to ensure that using cells originating from pluripotent stem cells in therapy is safe for patients.

Another, more imminent, area for medical use is to derive iPS cells from patients with genetic and other disorders and then use the iPS cells for *in vitro* differentiation to gain novel insights into the disease process or to produce cell-based platforms for toxicology testing or drug development (Onder and Daley, 2012) (Figure 4). iPS cells have been produced from a large spectrum of diseases, including amyotrophic lateral sclerosis (ALS), Rett syndrome, spinal muscular atrophy (SMA), α1-antitrypsin deficiency, familial hypercholesterolemia and glycogen storage disease type 1A. For cardiovascular disease, there are now iPS cell models for Timothy syndrome, LEOPARD syndrome, as well as type 1 and 2 long QT syndrome (Onder and Daley, 2012). In several of these iPS cell-based disease models, disease-relevant phenotypes are observed. For example, a progressive loss of motor neurons is observed in the iPS model for SMA. Moreover, Rett syndrome-specific iPS cells show reduced spine density after neuronal differentiation (Marchetto et al., 2010). Hepatocytic differentiation of iPS cells from α1-antitrypsin-deficient patients leads to elevated lipid and glycogen accumulation (Rashid et al., 2010). In vitro-differentiated iPS cell models can also mimic aspects of diseases with late onset, such as Alzheimer's disease (Israel et al., 2012), Spinocerebellar ataxia (Koch et al., 2011) and Huntington's disease (The HD iPSC Consortium, 2012). Progress has also been made when it comes to modelling diseases with complex genetics, such as schizophrenia (Brennand et al., 2011). However there are also diseases, for which it may be difficult to successfully mimic pathology in cultured iPS cell-derived cells. Furthermore, for some diseases, notably in the hematopoietic lineage, robust *in vitro* differentiation protocols for iPS cells are lacking, limiting progress in this area.

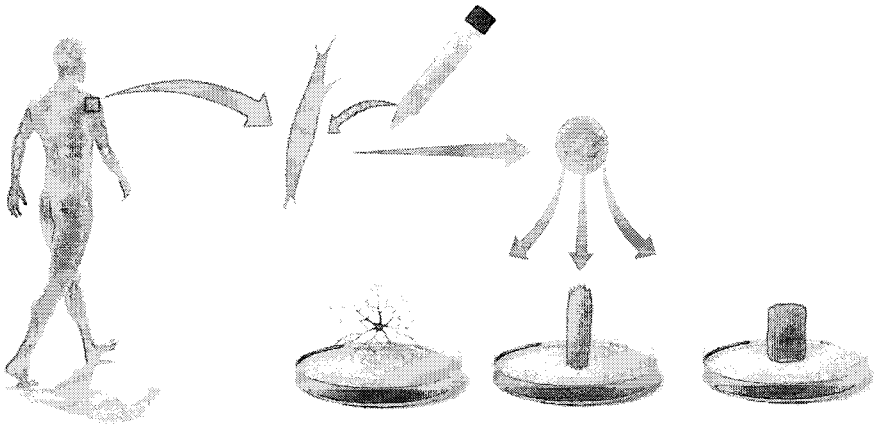

Figure 4 Differentiated cells can be obtained from a patient with a specific disease and reprogrammed to become iPS cells. The resulting iPS cells can then be in vitro differentiated to various specialised cell fates, such as neurons, cardiomyocytes or hepatocytes, and used to gain new insights into the disease process or as a cell-based platform to try to develop new disease therapies.

iPS cell-based *in vitro* differentiated cells are also increasingly used as screening platforms for development and validation of therapeutic compounds. In an iPS cell-based model for familial dysautonomia, a novel compound, kinetin, was identified, which could partially reverse the aberrant splicing of the IKBKAP gene that causes the disease (Lee et al., 2009). Similarly, in a Long QT syndrome iPS cell model, beta blockers and ion channel blockers proved effective in modulating the phenotype (Itzhaki et al., 2011). iPS cells are thus becoming valuable new tools to gain insight into disease processes and they are now used to test and validate new therapeutics. Furthermore, even diseases with complex genetics and late onset can be successfully modelled by this "disease in the dish" approach.

In summary, the concept that mature, differentiated cells can be reprogrammed to a pluripotent stem cell state is a paradigm-shifting discovery. This insight has influenced essentially all areas of medicine or physiology. The discoveries made by John Gurdon and Shinya Yamanaka clearly stand out as truly fundamental and have introduced an entirely new research field.

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EXHIBIT "B"

Exhibit "B" Background of Dr. Rongxiang Xu

Research and Achievement

Rongxiang Xu, in his study of burn treatment in 1984, discovered "regenerative cell" which was confirmed by subsequent studies to be keratin-19 positive stem cell (pluripotent stem cell). Dr. Xu accomplished the clinical systematic study of "in situ transformation of pluripotent stem cell from tissue cell (somatic cell), and in situ regeneration of new skin organ by the pluripotent stem cell" at deep burn wound site, and established the procedure of in situ regeneration of human tissue and organ by tissue cells. Based on this procedure, Dr. Xu achieved the in situ regenerative restoration and regenerative rejuvenation in varied tissues and organs. For instance, new skin was regenerated in situ without causing disability in the case of extensive deep burns; diabetic ulcers and surface body ulcers were healed via tissue regeneration; gastric ulcer was healed without scarring; severed distant finger regenerated new finger; skin scar was removed via regeneration; aged skin was turned back to young skin via regenerative restoration; aged and atrophic gastrointestinal villi of 60-year-old were restored to the state of 25-year-old; and so on. The new scientific system now entitled "human body regenerative restoration science" was then established by Dr. Xu. The accomplishment of clinical application of these core techniques consisted of the core contents of "human body regenerative restoration science" and has benefited people in 73 countries, e.g., burns regenerative therapy only, has helped 20 millions burns victims to restore normal skin. The all-inclusive technology of "human body regenerative restoration science" will soon benefit all the human beings.

Media Reports and Exclusive Interview

Newsweek, May 7, 1990, "A simpler way to save lives", reported the clinical study and practice of Dr. Xu. In this article, it was stated that "But if a new Chinese treatment fulfills its initial promise, much of modern burn therapy could be rendered instantly obsolete."

In 2003, Swedish Ministry of Education and Science and Sveriges Television had an exclusive interview with Dr. Xu.

International Conference and Lectures

In 2002, world conference on stem cell and regenerative medicine held in San Diego, USA, Rongxiang Xu was invited to be the key speaker to report the core technology and its application of human body regenerative restoration science.

In 2004, Dr. Xu gave a lecture on tissue regeneration under the special invitation of Stanford University.

In September 2012, the 17th world burns conference in the United Kingdom, Dr Xu's skin regeneration medicine became one of the most discussed topics among international experts and scientists attending the meeting.

Publications and Patents

Burns Regenerative Medicine and Therapy, Rongxiang Xu, 2004, Karger, Switzerland
In January 2004, Switzerland KARGER publisher (renowned publisher specializing in publications of medicine and physiology , also the publisher of many Nobel laureates' first books) published Dr. Xu's monograph *Burns regenerative medicine and therapy*, the comment on the back cover said that "Further, he demonstrates that ordinary cells can differentiate into varied organ tissues..." and "Burns specialists will learn of the new gold standard in burns treatment, and cell biologists of the potential of ordinary cells."

Human Body Regenerative Restoration Science, Rongxiang Xu, 2009, Chinese social science press

Patents:
US20030021850, US20060292692, US20080131528, US20080089945, US20120171298, US6991813, US8093048, US7972631, US7919123, US7550294, US7399492, US721127 6, US7074438, US6972195, US6685971 ; EP1439847,
EP0763362, EP0606786, EP1406643, EP2362777 ; CA 2464152 ; Japanese patents 4464133, 3126583, 3065530 ; Chinese patents ZL02102890.7, ZL200610000381.9, ZL200610093527.9, ZL200510123331.5, ZL02120138.2, ZL02105541.6, ZL95116651.4, ZL93100276.1.