

Scientist sues journal over truth and defamation

Online war between Shi V. Liu and *Nature* went into legal battle

TFCP

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US scientist Shi V. Liu has begun a legal proceeding against Nature Publishing Group (NPG) and its parent company Macmillan Publishers Ltd (Macmillan). The goal of this battle is to find answers for his dispute with *Nature* on the nature of iPSCs –“induced pluripotent stem cells” and legal assessment of his and *Nature*’s actions during the dispute.

The lawsuit charged “*Nature*” (used here as a collective term to include *Nature*, some of its editors, NPG and NPG’s parent company Macmillan) with “4D” actions. These “4D” actions spelled out as “DECEPTION”, “DEFAMATION”, “DISCRIMINATION” and “DISRUPTION” (more details will become available later).

Liu’s dispute with *Nature* on iPSCs began in July 2007 when he submitted a Communications Arising (CA) to *Nature*. In that CA he challenged the claims made in two research reports published in *Nature* (**448**, 313 and 318). The *Nature* publications¹ were heralded as firm confirmations for an earlier “discovery” made by a Japanese scientist Shinya Yamanaka. In 2006 Yamanaka reported in *Cell* (**126**, 663) “induction” of pluripotent stem cells from mouse embryonic or adult fibroblasts by introducing just four factors. However, that original “discovery” did not catch any big fire because the stem cell research field was still under a heavy cloud of the Hwang scandal. With the publication of these “twin” papers (one from the Yamanaka’s group and another from Jaenisch’s group in MIT of USA) the perception on iPSCs really changed greatly. After all, who can resist the lure of “simple switch turns cells embryonic” as headlined by *Nature* (**447**, 618, 2007)? Who would not appreciate the “engineered embryonic stem-like cells from normal mouse skin cells... without the use of donated eggs or embryos” as highlighted by *Nature* (**448**, 260, 2007)?

The emphasis that iPSCs are “indistinguishable” from embryonic stem cells (ESCs) by these *Nature* publications made iPSCs the much wanted “ethical” replacements for ESCs. Even White House was pleased with this “milestone” advancement in stem cell research. With a promise that cancer-free person-specific iPSCs can be efficiently generated from any normal adult cell looming over the therapeutic cloning and regenerative medicine field, the stem cell research underwent a seismic change and entered a new era, as declared by *Nature* (**451**, 135, 2008).

However, after carefully analyzing above *Nature* publications and other publications on iPSCs, Liu arrived at a different assessment on these cells. He believes that iPSCs are most likely originated from rare pre-existing stem cells or progenitors that were perceived as “stem cells”. The introduction of those “reprogramming factors” which are known oncogenes caused these stem cells to transform into cancer cells. These iPSCs thus should be distinct from ESCs. Indeed, some differences were already contained in the publications making the “indistinguishable” claim. However, those iPSCs researchers just did not recognize those differences and would not even admit the cancer nature of iPSCs.

Liu’s sharp vision on the true nature of iPSCs was based on his unique understanding of cell life (see details at <http://im1.biz/Aging.htm>) and cancer biology (<http://im1.biz/Cancer.htm>). In contrast to the conventional wisdom conveyed through the mainstream which claims that two cells derived from one cell are sister cells of the same daughter generation, Liu has firmly concluded that these two pairing cells are actually one pre-existing mother cell and one new born daughter cell. He believes that cell division is a wrong concept because no cell is actually divided but reproduced. With cell reproduction, a natural cell age difference exists between any two “paired”. This conceptual change actually ends a dichotomy in biology that most unicellular microorganisms are perceived as immortal while all multicellular macroorganisms are mortal. Liu’s pioneering study on aging in prokaryotic bacteria in the early 1990s₂ proved that indeed all life forms follow some same key life principles.

Liu even described in detail how cell aging is linked with aging at the molecular level and came up with a detailed prediction of a regular DNA segregation pattern in cell reproduction. Liu predicted that the older DNA template is always retained by the mother cell and the younger DNA template normally goes into the daughter cell during cell reproduction. Although such non-random segregation pattern has been observed before such as in some stem cells, its interpretation led to a wrong hypothesis of “immortal strand” and even the erroneous perception of stem cell immortality. Liu pointed out that stem cells are actually some older cells in a body of multicellular organism. They are mortal and susceptible to aging. As a matter of fact, the oldest DNA they contain may suffer more DNA aging even if they are not prone to replication mutations.

Liu outlined a cell-aging based roadmap for multicellular development and correctly identified the nature and developmental location of stem cells and the cell differentiation hierarchy. He also pointed out that some ASCs are actually the same ESCs lived into the adult age. Thus the real distinction between ASCs and ESCs is not that they are some different entities but the same entity under different age and functional status. In Liu’s view, a cell may change its differentiation status and functions, but its age cannot be

reversed. A stem cell may reproduce a daughter cell that is very similar to it but that does not mean a stem cell can be self-renewed (see details at <http://im1.biz/StemCell.htm> and <http://im1.biz/Aging.htm>).

From that fundamentally unique perspective on cell life and cell differentiation and development in multicellular life, Liu immediately sensed some unscientific nature of the claims made for iPSCs such as “turning back the developmental clock” and even reversing aging. Also, based on the repeated observations of very low “induction efficiency” for iPSCs and other indications of a “universal” activation of cell reproduction, Liu suspected that the so-called “induction” of “normal” differentiated cells into the pluripotent stem cells may be better explained by a mechanism of general activation of cell reproduction and then a selection of stem cells or even progenitors based on some “stemness” markers.

Liu sent his CA to Yamanaka first and got a formal response which included the following: “We agree that the origin of iPS cells may be tissue stem or progenitor cells co-existing in fibroblast cultures”. Yamanaka even declared that “We have never claimed that we generated iPS cells from terminally differentiated cells”, contradicting an earlier generalization made by a Commentary in *Cell* (**126**, 652, 2006) that “Takahashi and Yamanaka have successfully reprogrammed terminally differentiated cells to a pluripotent state”. Yamanaka’s response also proved that *Nature*’s characterization of the iPSCs as “engineered embryonic stem-like cells from normal mouse skin cells” is misleading because *normal* cells have been perceived as ordinary *differentiated* cells. Indeed, the popular mass media and laymen public got just that perception of any cell can be turned into a stem cell with that “induction” process.

Liu submitted his CA (with Yamanaka’s “agreement”) to *Nature*. *Nature* did not accept it as should be. Instead, *Nature* put Liu’s CA into a peer review process which resulted in the final rejection of Liu’s CA. Under such a circumstance, Liu published this CA (as submitted to *Nature*) in *Logical Biology* (**7**, 63, 2007). He also published others papers in *Logical Biology* (**7**, 69, 2007 and **7**, 73, 2007) to refute the review comments on his CA submitted to *Nature*. Liu sent copies of these publications to *Nature*, Yamanaka and other related parties for response. However, none of them offered any counter-argument over these PUBLISHED criticisms.

Since then, Liu has published a series of analyses on almost every original reports on iPSCs (see a list at <http://im1.biz/Cloning.htm>). Liu’s efforts caught attention of many researchers, especially from his popular blog in China (<http://blog.sina.com.cn/im1>). Some stem cell experts understood and even appreciated Liu’s insightful views. That appreciation even led Liu’s publication of a peer-reviewed review on iPSCs in *Stem Cells and Development* (17:391, 2008). That journal even published an Editorial (17:389,

2008) along with Liu's review and sent out notice to a wide readership suggesting Liu's review as a "must read" paper.

However, despite these published critical assessments on iPSCs, *Nature* and other top journals still presents an image of inducing embryonic-like cancer-free pluripotent stem cells from normal cells to the public. To overcome this deception in science, Liu began to confront *Nature* head-on by posting his views directly on the comment windows of different *Nature News* on iPSCs. Under the news "Stem cells: a national project" (*Nature* 451, 229, 2008) Liu began his series of comments with an open invitation to engage stem cell researchers into a constructive dialog or dispute (<http://www.nature.com/news/2008/080116/full/451229a.html>). However, so far no one have publicly answered Liu's invitation and expressed their counter-argument against Liu's criticisms. The silence and also the ignorance are both amazing. But, from his decade-long experience in running double-open new-generation scientific journals (<http://im1.biz>), Liu knows very well why scientists nowadays are unwilling to participate in any public debate (*Nature* 447, 1052, 2007).

Not to Liu's surprise, his courageous actions were not liked by all people. Actually some people even developed resentments towards him. Many of Liu's scientific comments were removed by the moderators of *Nature News*, as best exemplified by the incidences happened under *Nature News* "Stem cells: 5 things to know before jumping on the iPS bandwagon" (452, 406, 2008; <http://www.nature.com/news/2008/080326/full/452406a.html>). But some defamatory remarks on Liu were allowed and kept in *Nature News* even until today. These anonymous comments called Liu as "madman", "just plain neurotic" and "a nuisance" and trashed Liu's publications. They characterized the journals publishing Liu's view as "hilarity" and degraded Liu's supporters as "little fan club with this mockery of the scientific process". It is really unbelievable that an allegedly scholarly journal like *Nature* would allow such distasteful personal attacks running in a professional place.

Recently, *Nature* published an Editorial "It's good to blog" (*Nature* 457:1058, 2009). In response to *Nature*'s call that "there are societal debates that have much to gain from the uncensored voices of researchers" Liu posted several comments in the discussion forum "Science, journalism or public discourse?" (<http://network.nature.com/groups/naturenewsandopinion/forum/topics/4044>). These comments emphasized the value of blog in exposing scientific mistakes and even potential misconduct. However, Liu's comments were immediately removed. Later, many other comments supporting Liu's views were also removed. The moderator who is the publishing executive editor of *Nature* even concluded that "this forum discussion is being abused by a spammer who is using a range of pseudo-identities" and "They are all by the same user, using different false identities."

However, that conclusion of a single spammer contribution for all the deleted comments is simply untrue and was specifically challenged by a different person other than Liu. Comments criticizing *Nature's* censorship flew in. Under such situation, the moderator of *Nature* had to “lock” the blog from direct posting. However, during the locked period of more than three days, only one outside comment (submitted via email to the moderator) was posted which actually questioned the value of this censored blogging in *Nature*.

The disruption of normal blogging was stopped with a re-opening for direct posting. However, as soon as Liu's comment on the activities of this blog was posted, the blog was re-locked and Liu's comment removed. Liu's comment detailed many irregular actions by the moderator and pointed out the defamation nature of some comments against the alleged single “spammer” (such as calling him as a “pest”).

After this repeated disruption of normal blogging, *Nature's* publishing executive editor sent Liu an email which states “Please refrain from using Nature Network or any other part of nature.com. As you know, we have written to you to tell you that your comments on our websites are not welcome.” Why would *Nature* discriminate Liu? Does *Nature* have a right in suppressing Liu from expressing his scientific opinions and protest against personal attack on him?

It will be interesting to see how Liu's lawsuit against *Nature* goes. After all, there is no such precedent to such single individual scientist with relatively limited influence and means in terms of achieving a major impact in the scientific community and yet has dared to stand up against a powerful publishing house. However, it seems that the truth is on Liu's side because recent studies on iPSCs have shown observations that are more consistent with Dr. Liu's assessments. For example, higher “induction” efficiencies have been observed in several studies that started the “induction” from clearly identified stem cells (*Nature* **454**, 646, 2008; *PLoS Biol* **6**, e253; *Cell* **136**, 411, 2009). More and more studies now show distinctions between iPSCs and ESCs. Even the strongest defender of the “indistinguishable” claim now published a paper in *Cell* (**136**, 964, 2009) to show “Factor-free hiPSCs[are] more closely related to hESCs than to hiPSCs carrying the transgenes”. As to the cancer-free claim for some earlier “safe” iPSCs, none seemed to pan out. Yamanaka even showed some “abnormality” caused by his “safer” iPSCs as reported in a “note added in proof” to his *Science* paper and publicly “thanked” Liu for offering criticisms (*Science* **321**,641, 2008).

Now, the research on iPSCs is focused on how to silence, remove, or even avoid those oncogenic “inducing” factors. But Liu has predicted this is the only way that iPSCs can be made “safe” for therapeutic cloning and regenerative medicine. Liu even pointed out iPSCs research is a great detour because eventually people will come back to a realization that iPSCs are not the same as ESCs and even normal ASCs. Liu stated that those “inducing” factors may even be unnecessary if activation of cell reproduction and

isolating stem cells based on stemness marker is the true mechanism for the so-called “induction”. This is because there were already some successful ways to do so as exemplified by the pioneering study of a Chinese physician Rongxiang Xu. But Xu’s work has been largely ignored by the western scientists in the same research field.

Unfortunately, as the funding shifted towards the easy-to-do “induction” of pluripotent stem cells or transformation of normal cells into cancer cells, more and more research will be performed in this area and more and more publications will come out. Some people even used this phenomenon as an argument of the “success” of iPSC research. However, Liu asked people to relearn the “polywater” lesson. Hundreds research papers were published on “polywater”. But does “polywater” exist?

The credibility of Liu as an intelligent scientist seems unquestionable. Many of his “preliminary” discoveries such as bacterial aging, regular DNA strand segregation in cell reproduction, and stem cell mortality have been verified. Liu’s far-vision on the end of iPSCs may also come to a close view if the mainstream dam is broken.

But whether or not Liu’s ways of seeking truth and speaking out for the truth are acceptable to the mainstream of scientific society is still questionable. Some believed that he has gone too far or at least jumped at the gun too early. Some said his outspoken style is too harsh to normal scientists. But, when the mainstream scientific communication are dominated by some powerful peers who would not even allow expression of any alternative views, what can a normal scientist do? After all, Hwang’s stem cell deception was not caught by any expert reviewing his manuscript or spotted by any spinning article commenting on his publication. Hwang’s scandal might even not be exposed if it was not because of the internet blogging started from an anonymous post on a bulletin board maintained by "PD Notebook". So it is indeed good to (soundly) blog as stated by the recent *Nature* editorial and not good to block the blog as protested by Liu against *Nature*’s locking on a blog. 6

Nature published a correspondence from Liu in 2000 (403, 592) which stated “Debating controversies can enhance creativity” and even allowed for a reference to Liu’s pioneering effort in starting double-open (open access and open review) scientific journal called *Logical Biology* (<http://logibio.com>). Now when that openness led to some criticisms over *Nature*’s own publications and behaviors, Liu became “unwelcome” by *Nature*. Should this be tolerated by the scientific community or not? This should be clear in favor of the latter option if science and scientific truth are to be advanced.

Liu said that he is willing to sacrifice himself and become a victim in his war against top corruption in science. In his view, no one should be empowered with a dictatorship in science because science is a process of seeking truth, not a course of dictating dogmas. Before truth is known, every one has a right to seek truth. In front of truth, everyone is

equal regardless of his social status. However, what the reality is in today's scientific world? Today's scientific community is dominated by some dictators in science!

Let us hope a legal process can yield some right answers to the urgent societal questions regarding scientific research and communication. Let us wish justice will be fair to truth-seeking scientists no matter how "abnormal" his ways of seeking truth are.