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COMMUNICATIONS ARISING

iPS Cells and Developmental Biology

A Revelation of Submission Manipulation and Neglect by *Nature*

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HIGHLIGHT

Revealed here are two submissions to *Nature* concerning some important problems in iPS research. These submissions were manipulated and then neglected by *Nature*.

ABSTRACT

Recently iPS reprogramming has become a hot research topic in the zoological world. However, from a botanical perspective, many of the concepts used in the animal cell research are misunderstandings. Unrealistic promises have been made that, if applied to clinical settings, will result in some avoidable risks. However, warnings against these misunderstandings and hyping have been ignored by *Nature*, as revealed in this Open Letter containing two submissions manipulated and neglected by *Nature*.

KEY WORDS

Stem cell, ESC, iPSCs, Induction, Reprogramming, Differentiation, Organ, Organogenesis, Niche, Cell therapy, Cancer, Medical, Ethical, Safety, Regeneration, Zoology, Botany, Warning, Neglect, Open letter

On February 2, 2009, I submitted a Correspondence to *Nature* entitled "Shedding a botanical insight onto zoological "reprogramming". On February 6, 2009, I received an E-mail from an editor of *Nature*; he said "Following your acceptance from Correspondence, please follow the links below to complete the two forms, one being the 'license to publish' form and the other the 'declaration of competing interests'." I submitted these two forms; both were received on Feb. 9.

But on March 17, I received an E-mail from another editor. She informed me that *Nature* was unable to publish the correspondence because it does not consider technical comments in this section of the journal.

Therefore, I rewrote the Correspondence as Communications Arising and submitted it to Nature on April 15. On April 29, I received an E-mail from an editor of *Nature*, who stated: "We notice, however, that it does not refer to a letter or article but rather to a piece we published in the front half of the magazine and therefore should be treated as Correspondence, not as Brief communication Arising. I have passed your submission to the front half team who should deal with it shortly."

However, until June 2, I did not receive any information on the submission from *Nature*. So I sent an e-mail inquiring what was going on. On June 4, I received a reply, stating: "Unfortunately there has been a misunderstanding due to my failure to explain myself correctly. Correspondence submissions generally refer to the articles we feature in the front half of Nature, while Brief Communications Arising refer to the letters and articles featured in the back half of *Nature*. I apologise for referring to Correspondence as 'front

half': I realise it must have caused confusion." And stating: "Unfortunately your submission was rejected by both Correspondence and Brief Communication Arising."

Later, I submitted on May 14, 2009 another Communications Arising entitled "Concerns over organ regeneration from dysfunctional niches". I was treated the same way as before with no response to my submission.

I should say that, before submitting these Communications Arising manuscripts to *Nature*, I sent them to the corresponding authors of the criticized Nature publications. However, on May 18, I received an E-mail from the author Dr. Birnbaum K. D. stating: "I don't think your brief communication represents a coherent argument. Of course you are free to submit to Nature. If the editors decide to pursue it, we will provide a detailed reply." This situation was reported to *Nature* after I submitted my manuscripts.

Frustrated with lacking basic responsibility from Nature, I decide to submit these Communications Arising manuscripts to other journals for publication. The revelation of the history of these manuscripts serves as a denouncement over the unprofessional and even unethical behaviors of *Nature* and its authors and editors.

Communications Arising submissions manipulated and then neglected by *Nature*:

1.
Shedding a botanical insight onto zoological "reprogramming"

Arising from: K. Okita1, T. Ichisaka & S. Yamanaka *Nature* 448, 313–318 (2007) and S. Yamanaka http://www.bio.pku.edu.cn/exchange/2008-09-14.164.html

From a recent lecture given by Shinya Yamanaka in the College of Life Sciences, Peking University[1] and an article in Nature[2], I learnt that induced pluripotent stem cells (iPSCs) are not as safe as embryonic stem cells (ESCs) because they have higher tendency to form cancers and cause offspring death. Yamanaka's statements seemed to concur with earlier criticisms[3]and also induced my thinking below.

The introduction of "pluripotence inducing factors" (PIFs) may cause a cell to change its "fate" in a manner similar to dedifferentiation, redifferentiation and transdifferentiation in plant tissue and organ regeneration. The consistently low efficiency of "induction" and the fact the stem cells are more easily "induced" by the same PIFs[4] suggest that some pre-existing pluripotent stem/progenitor cells (mother cells or initials in botanical term) are activated and then being selected out (based on some "stemness" markers) for further differentiation/cloning. Thus, these iPSCs are not "reprogrammed" from one type of cells to a different type of cells, even though the same iPSCs may be guided into the different differentiation paths (transdifferentiation or dedifferentiation and redifferentiation in botanical term).

Our long experience in studying plant tissue and organ regeneration led us to realize the cascade nature of cell differentiation [5,6]. Cell differentiation and dedifferentiation are two opposite reactions in various stages of this cascade marked with age, the differentiation is an aging process, but the dedifferentiation is a process that age reverting to zero. If a cell dedifferentiated into the stage which was equivalent to the differentiation stage of zygote, its age would be zero. A cell may stop at a stage of this cascade but the intermediate stage of differentiation/dedifferentiation is usually insurmountable. There is also a critical point after which the differentiation seemed irreversible. The last stage is programmed cell death (PCD), the critical point is during the process. Cell fate is determined by its positional information, and with the location change. A cell at any differentiation stage before the critical point can be dedifferentiated, and a cell dedifferentiated into any differentiation stage can redifferentiate to form an organ or embryoid, therefore, regenerated organs and embryoid could be at different age. But, the transdifferentiation only occurred between two types of cell that their differentiation stage and passed pathway were similar. According to this new theory , which developed the cell totipotency theory[6], in the cells before the critical point there is no change in genetic information involved in developmental program. Therefore, there is not "reprogramming". Now that there is no evidence showing disorder or loss of original developmental program, why is reprogramming required? In addition, the word "reprogramming" used in publications has different meaning[7,8], some of which means dedifferentiation (the stages dedifferentiated to were different) , redifferentiation, some of which means transdifferentiation.

So far, all reports on iPSCs are consistent with selection of pluripotent stem/progenitor cells, not

any "direct" "reprogramming" of "terminally differentiated" adult cells back to "undifferentiated" "embryonic" stem cells. Unless convincing evidence coming, I urge zoological stem cell researchers to refrain from using the yet unproven term of "direct" "induction" of "any" adult differentiated cell back into "embryonic" or "embryonic-like" stem cell. I also wish that cautions are exerted towards the claims of "successful" "reprogramming", because we even do not know the normal programming of organismal development.

Most likely, iPSCs are some incorrectly programmed stem cells (still iPSCs). Thus, the warnings given by News Feature "Stem cells: 5 things to know before jumping on the iPS bandwagon" [9] are still valid and should not be quickly forgotten.

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2.
Concerns over organ regeneration from dysfunctional niches

Arising from: G. Sena, X. Wang, H.-Y. Liu, H. Hofhuis & K. D. Birnbaum *Nature* 457, 1150–1154 (2009)

As botanists studying plant anatomy and development for long time[1-5] we wish to express some reservations on a claim that organ regeneration in plants does not require a functional stem cell niche[6].

In many detailed studies on plant regeneration (under the support of National Natural Science Foundation of China (NSFC))[1-5] we have observed some sequential events in plant regeneration. For example, after girdling the tree trunk to remove most of cambium cells (the lateral meristem which is located between xylem and phloem of root and stem of gymnosperm and dicotyledon) (Fig.1a, b), cells in surface layers of immature xylem cells (mainly xylem ray cells and occasionally a small number of cambium cells) dedifferentiated into callus, and then redifferentiated into periderm[1,3] (Fig. 1b, c, d, e, f, g). Cells in some layers of immature xylem cells bellow these surface layers transdifferentiated into phloem cells (Fig. 1b, c, d, e)[4]. And cells in the deep layers of immature xylem cells dedifferentiated into cambium cells (Fig. 1b, c, d, f, h, i). When the immature xylem was cultured as some explants *in vitro*, they dedifferentiated into callus, and then redifferentiated into shoot or root or embryoid[5]. These suggested that the fate of the immature xylem cells left on the girdled trunk surface changed with the location change.

Thus, a century-old botanical discovery (G Haberlandt 1902) seems to hold water that all cells in a plant are genetically "totipotent". Based on this theory, a cell may stop at any stage of a reversible differentiation/dedifferentiation cascade and be guided into some different differentiation/dedifferentiation paths. So the question for today's scientists is not whether organ regeneration in plants can happen even without a functional stem cell niche but if an organ is regenerated from a dysfunctional stem cell niche is normal and functional. Stem cell niche is not a special structure centered on stem cells, but position information on the location of stem cell[7,8,9]. Therefore, Sena et al's[6] or our results[1-5] demonstrated that position information (stem cell

niche) is essential for organ regeneration, and not the contrary.

The organs generated from niche-dysfunction stem cells all appeared abnormal (at least in their structures) as compared with the respective controls. As we leant from our own experience[1-5] and others' researches[10,11,12], although mesophyll cells cultured *in vitro* can transdifferentiate into xylem cells, the xylem cells are abnormal and have no function[12]. Thus, position information (stem cell niche) is essential for the regeneration of functional and normal organs.

Even though some organ abnormalities do not matter much for plant lives for which we care more about their original yields and re-generated yield, structural integrity and functional normality are very important for animal and even critical for human lives. For achieving that level of organ regeneration, we need not only a normal stem cell but also a normal niche to guide the proper developmental differentiation/dedifferentiation/transdifferentiation processes.

Thus, we feel it is inappropriate to overhype on the niche-free organ regeneration and even more dangerous to imply such success for iPSCs (induced pluripotent stem cells) in animal research. The plant cambium cultured *in vitro* as an explant does not form normal xylem and phloem[1,5,13]. The animal iPSCs inoculated *in vivo* into abdomen always developed into teratomas, instead of any normal organs. Putting the structural and functional normality out of mind to discuss niche-free organogenesis may not be a harmful thing for plants but may be a sure risk for animals including the most precious animal – the human being.

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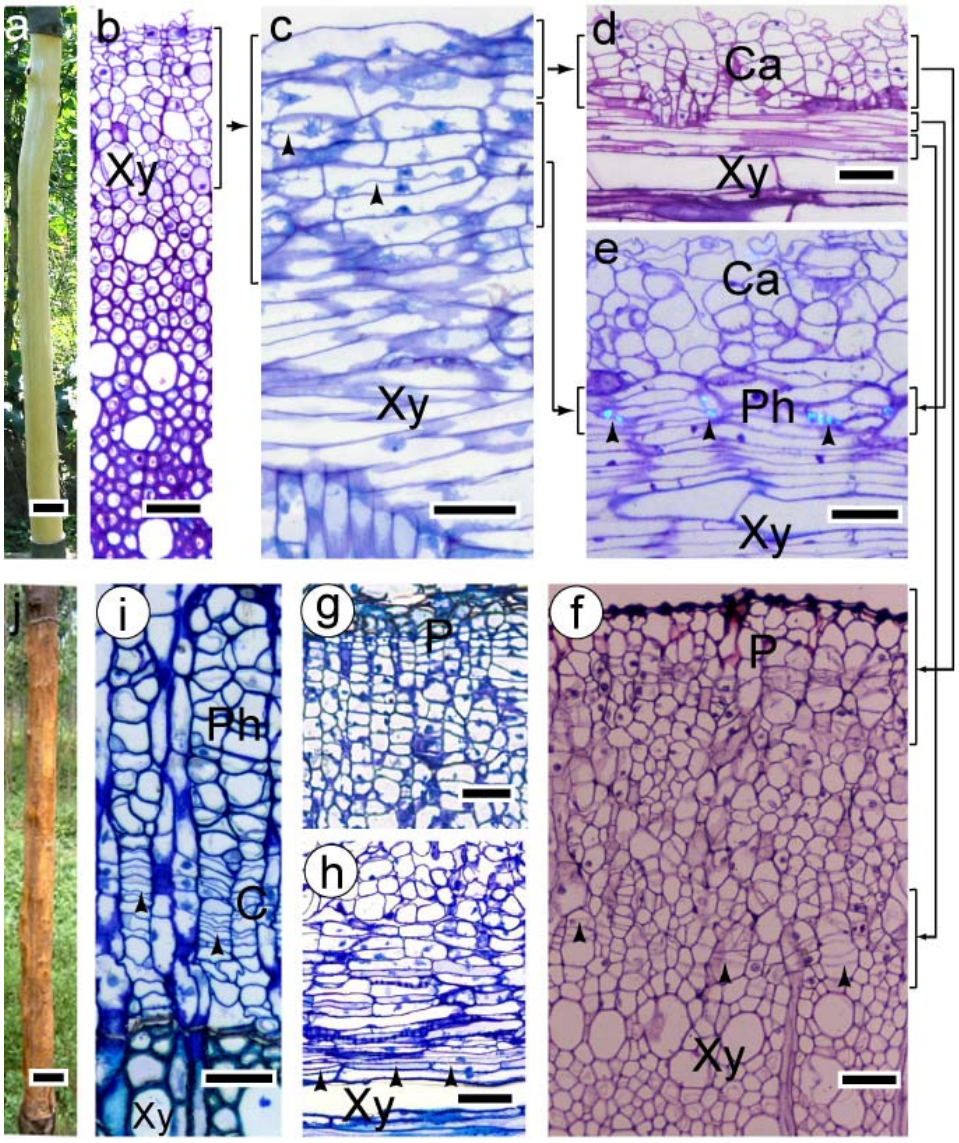

Figure 1. Regeneration after girdling in *Eucommia ulmoides* Oliv. showing the fate of the immature xylem cells left on trunk surface changing with the location change. (b-i) Cross-sections (b, f, i) or radial-longitudinal-sections (c, d, e, g, h) of a part from the trunk after girdling. Scale bar in (a) and j), 10 cm; in (b-i), 50 μm

Shown here is the out surface view of the just girdled trunk (a), the exposed surface of trunk (b) at 0 day after girdling (DAG), the dividing immature xylem axial cells in 2 DAG (c, arrowhead), the callus formation at 6 DAG (d), the generation of the sieve tube member at 10 DAG (e, the arrowheads indicate callose stained with aniline blue and observed under UV light by fluorescence light microscopy on sieve areas), the periclinal division of the vessel member (f, h, arrowhead) and periderm formed (f, g) at 14 DAG, and normal cambium formation and activity (i) with a recovered truck (j) at 30 DAG. The arrows between the figures indicate their developmental relation (C, cambium; Ca, callus; P, periderm; Ph, phloem; Se, sieve element; Xy, xylem.).