Research Ethics and Lessons from Hwanggate: What Can We Learn From the Korean Cloning Fraud

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Abstract
We review the Korean cloning scandal involving Woo Suk Hwang. We document the nature of the disaster and suggest reasons why it occurred. We highlight the general problems it raises for scientific research and offer 6 possible ways to improve practice based on this case: (1) better education of science students; (2) independent monitoring and validation; (3) guidelines for tissue donation for research; (4) foster debate of ethically contentious research in science journals; (5) develop an international code of ethical research practice; (6) foster public involvement in ethical review and debate through the web.

Appendix A, available as web only additional material, we include the information sheets and consent forms used by Hwang.

Science today is an international enterprise. Large multi-national companies and researchers collaborate across the globe. However, it is mostly at the national level that science is regulated and funded. This can result in a confusing patchwork of regulatory policy and ethical guidance which can retard the progress of science and fail to promote ethical behaviour. There are enormous personal and national drivers to succeed. The cocktail of pressure to succeed in the presence of patchy national regulation, ethical standards and
cultural norms can cause ethical controversy and scientific misconduct. A fine recent example is the Korean cloning scandal.

The Korean scandal starts with Woo Suk Hwang. Hwang was raised in South Chungcheong Province in a mountain town. He worked on a farm to finance himself through high school. His commitment to study was rewarded when he graduated from Seoul National University as a veterinary scientist. After gaining his PhD, Hwang worked as a veterinary researcher before his desire “to help solve some incurable human diseases” led him to therapeutic cloning using human embryonic stem cells. His early achievements included the creation of transgenic pigs to provide organs for transplant into humans; the cloning of a dairy cow in 1999; and in 2003 he claimed to have developed BSE-resistant cattle. But this, and most of Hwang’s early work, was unpublished and unverified.

**Part I The Korean Cloning Scandal**

Between 2001 and 2004, Hwang donated $250,000 to Ky-Young Park, a biologist at Sunchon National University. She undertook two projects for Hwang regarding the social impact of BSE-resistant cows (2001) and ethical guidelines and commercial use of bio-organs (2003). From 2002, Ky-Young Park had close connections with the Korean Government and often acted as unofficial mediator between Hwang and Roh Moo Hyun’s Government. Park became more influential in 2003 when she was made presidential advisor of science and technology.

Hwang became a scientific enigma and international celebrity on publication of ‘Evidence of a Pluripotent Human Embryonic Stem Cell Line Derived from a Cloned Blastocyst’, on which Park is a co-author. This was the first time anyone had offered proof of a cloned human blastocyst, let alone successfully extracted stem cells from it. However, *Nature* questioned the ethical framework under which Hwang’s research was conducted after an interview indicated that some oocytes used were donated by junior researchers. Hwang denied the allegation but voluntarily suspended this research until the Biosafety Act of 2003 came into effect in January 2005. Even so, the Korean Bioethics Association (KBA) asked Hwang to answer questions regarding his funding sources and recruitment of egg donors. In response, Hwang and Shin Yong Moon declared that they did not consider the KBA neutral because it advocated “restricting the pace of biomedical advancements”.

Between suspension of his research and the new Korean Biosafety Act becoming law, Hwang collaborated with Gerald Schatten, a primate researcher at the University of Pittsburgh. Using techniques for extrusion of oocyte DNA developed by Hwang, Schatten successfully cloned
the first monkey embryos. Though a live birth was not achieved, Schatten’s group developed embryos to the blastocyst stage from which it is possible to extract stem cells. The success was seen to be validation of techniques that Hwang developed for somatic cell nuclear transfer (SCNT).

On the 13 January 2005, Hwang’s research became the first to be approved under the new Biosafety legislation. Soon after resumption of his research, Hwang told Park and Schatten that four of six SC colonies he had created were infected with Fungi. Park oversaw implementation of preventative measures but did not officially report the incident. Allegedly, Schatten urged Hwang to publish anyway since SCs had “clearly been produced” and just five months later Hwang submitted his second groundbreaking paper ‘Patient-Specific Embryonic Stem Cells Derived From Human SCNT Blastocysts’ and Schatten was listed as second author.

On the 3 August 2005 Hwang and colleagues announced that they had created a cloned Afghan hound, Snuppy. Because canines produce very immature oocytes, many thought that cloning dogs would be more difficult than human cloning. Once again, the efficacy of Hwang’s techniques for cloning using SCNT appeared to be verified. However, the work was overshadowed by Schatten informing Science that Sung-Il Roh, a co-author on the 2005 human SCNT paper, had illegally traded ova. Schatten assured Science that none of the women who donated eggs for their papers had been reimbursed. But just days later Schatten broke links with Hwang claiming that he had been misinformed about consent issues surrounding the 2004 paper.

Hwang’s work and the research ethics underpinning it subsequently came under increasing scrutiny. Pressure for a formal investigation into Hwang’s research practices increased after submission of corrected tables for the 2005 paper and Roh’s admission that Hwang had unwittingly used 20 eggs that had been paid for. But pressure on Hwang was eased by Moon Il Park, Director and Chair of the Institutional Review Board (IRB) on Human Subjects Research and Ethics Committees at Hanyang University Hospital - the IRB found Hwang’s research not to be illegal or in violation of the Declaration of Helsinki. Moon Il Park initially reiterated his belief that none of Hwang’s team were oocyte donors, though he was later to correct this belief.

On November 22, Editor’s Notebook, a Korean investigative program by Munhwa Broadcasting Corporation (MBC), cast doubt on the claims by Hwang’s research team that most Korean people were admiring Hwang’s research and willing to donate eggs, raising
suspicions that there was illegal trade in eggs. The program resulted in great controversy in Korea. Significantly, MBC came under fire for reporting against the national interest. A number of companies, concerned about adverse publicity, withdrew commercial support. Subsequently, Hwang conceded that he had used eggs that were paid for and eggs donated by junior researchers. Moon Il Park concluded that the two junior researchers donated oocytes voluntarily and without coercion. The payment of ~$1,445 was for direct expenses and had no impact on the validity of the scientific conclusions.

On the 1 December 2005, MBC turned up the heat on Hwang, openly questioning the credibility of Hwang's research after obtaining samples of five patient-specific cell lines from Hwang’s lab. Independent DNA analysis indicated that one cell line did not match its supposed donor.

However, pressure was relaxed on Hwang as reports emerged that MBC had used threats to coerce incriminating statements about Hwang. MBC was forced to apologise for unethical journalism practices having “tricked [Sun Jong] Kim into believing that Korean prosecutors had begun an investigation.”

Following accusations regarding the validity of Hwang’s research on the Biological Research Information Centre’s (BRIC’s) website, Hwang informed Science that the 2005 paper included redundant images. The images were not in the original submission but submitted later by Schatten in response to a request for supporting evidence. In response to the weight of mistrust that surrounded Hwang’s research the University of Pittsburgh opened an investigation into Schatten’s role in the affair. An investigation by Seoul National University (SNU) quickly followed at Hwang’s request.

Scepticism abounded after Schatten expressed doubt as to the scientific value of the paper. Asking for his name to be removed from the paper, he stated that new information and re-evaluation of data “casts substantial doubts about the paper's accuracy.” This led Dr Ian Wilmut, who is credited with creating ‘Dolly the sheep’, to ask for independent verification of Hwang’s research. The situation was further muddied on 15 December, when Roh quoted Hwang as saying “there are no cloned embryonic stem cells!” Soon after, Hwang and Schatten requested that their paper was retracted because analysis had indicated their data “could not be trusted.” Hwang maintained that, though mistakes occurred, patient-matched stem cells were created and he would thaw lines for independent authentication. Hwang declared that patient-specific SCs were still “the proud technology of our nation.”
However, the initial investigations by SNU concluded that a large proportion of data from the 2005 paper had been fabricated. Results indicated that data came from only two cell lines rather than the eleven stated, it was soon verified that neither of these two lines were cloned via SCNT but derived from in vitro fertilisation embryos. The SNU concluded that both the 2004 and the 2005 papers were based on fraudulent data – the NT-1 cell line described in the 2004 paper appearing to be parthogenically derived. Snuppy, however, was a somatic cell clone of Tie and not simply highly inbred. Science retracted Hwang’s 2005 paper on 4 January 2006 and subsequently his 2004 paper. Additionally, two papers involving Sun Jong Kim and Sung Il Roh have been retracted. One because “upon re-examination of their work, the authors have found that the data in Figure 2A was intentionally fabricated” and the second (Biology of Reproduction DOI: 10.1095/biolreprod.105.046870) was withdrawn after it was shown to contain a photo that is the same as a picture from Hwang's 2005 Science paper.

Hwang was fired in March 2006 from his post as a professor at Seoul National University’s veterinary department. Prosecutors completed an investigation into the scandal in May 2006. Hwang was indicted on charges of fraud and embezzlement, as well as violation of Korean bioethics laws.

Hwang apologised for his part in the ‘Hwanggate’ scandal but insinuated that other researchers had sabotaged his work, suggesting that scientists at the MizMedi might have replaced cloned SCs with other cells. Hwang insisted that his lab was capable of producing patient-specific stem-cells and that they could reproduce their result in six months given a favourable research environment. In support of his claims, the SNU investigation panel stated that Hwang’s “team was in possession of technique[s for] creating cloned human blastocyst[s]”. However, Hwang saw initial cell colony formation as successful establishment of a cell line. Without further corroborating evidence the scientific basis for claiming success was “wholly lacking”. Subsequently, PD Notebook alleged that the junior researchers had been coerced into donating eggs – an allegation that has since been reiterated by the National Bioethics Committee.

It should be noted that, in any episode such as this, especially one occurring in a foreign country, which involves multiple allegations of misconduct, it is very difficult to arrive with certainty at the truth. However, it appears from the evidence available to us that Hwang's team neither possessed patient-specific embryonic stem cell lines nor the NT-1 embryonic SC line.
described in the 2004 paper. Data in both ground-breaking publications was fabricated as shown by the non-matching DNA profiles. The scenario of a rogue scientist operating to undermine Hwang’s research cannot explain the parthenogenetically derived cell line nor the fabrication of DNA profiles. Such acts require scientists to work complicitly to deceive those reviewing and publishing the paper. In March 2006 Hwang admitted to ordering researchers to fake data for the 2005 paper. This is difficult to comprehend given the SNU report that suggests Hwang was technically able to produce and in possession of cloned human blastocysts from SCNT. It is likely that this and the parthenogenically derived embryo were in themselves publishable. It is possible that Hwang submitted the 2005 paper believing that he would soon have the evidence to corroborate it. However, this does not appear to be the explanation for the 2004 paper which appears to be completely fabricated. And despite this, it does appear that Hwang successfully used SCNT to create Snuppy the dog, and Schatten appears to have successfully cloned a monkey.

Hwang rose from global obscurity to Scientific American’s ‘Research Leader of the Year 2005’ - exposure of “Korea’s Cloning King” as an alleged fraud rocked science. Though the scientific value of Hwang’s research is largely discredited, it still raises many important issues with respect to science policy and ethics, “as opponents of research on cloning make political capital from the scandal”. Hwang’s case highlights that sound transnational ethical oversight is required for reliable science. It appears Hwang was a good scientist operating in an environment that was conducive to misadventure. Hwang credited his ‘success’ to plentiful funds, abundant oocytes, and a supportive (mostly unregulated) political and legal environment. But these, together with ambition, also created an environment for disaster. Hwang met with many pressures but few constraints; the choices he made at each juncture made his decline inevitable. The Machiavellian desire for “community recognition and prestige” in modern science cannot be underestimated nor easily mitigated.

**How Common Is Research Misconduct?**

We do not know but it may be more common than many initially presume, particularly if one includes scientific misbehaviour (see Author Responsibility) as introduced by the University of Pittsburgh. In fact, there is evidence of systematic scientific misconduct even in heavily regulated research environments. In a survey of NIH researchers 1.5% admitted to falsifying or plagiarising data. Luk Van Parijs was recently fired by the Massachusetts Institute of Technology after admitting that he fabricated and altered research papers in order to support grant applications. Such is the pressure to publish that some researchers may start the publication procedure before they have results to support their assignations – believing that they can predict the outcome from their preliminary findings.
The problems of withholding results which are against researchers’ or funder’s interests, and subsequent publication bias have long been documented. Such misconduct continues. The authors of a 2000 Vioxx study failed to inform The New England Journal of Medicine that several patients had heart attacks while taking the drug. Additionally, an article on Celebrex in The Journal of the American Medical Association has been discredited because the authors submitted only 6 months of the 12 months of data they collected.

No aspect of the research process seems immune to fraud and misconduct. The results of this misconduct can be lethal. Paul Kornak altered patient medical records to facilitate their enrolment in drug trials from which they should have been omitted due to existing conditions. One patient died and Kornak was recently jailed for criminally negligent homicide.

Part II. Pressures Facilitating Misconduct

1. Funding and publication
Funding directs, if not dictates, science because without funding research cannot occur. Publication provides investors with information regarding the researcher’s capabilities and therefore there is great pressure to publish. Funding-advantage is gained from how far up the journal hierarchy one publishes. The Research Assessment Exercise in the UK implements selective funding for universities – but there is suspicion that the publishing journal is “given greater weight than the papers' content.” Ground-breaking papers are more likely to secure a major journal; attract more public and/or commercial interest and be favoured by investors. Researchers are likely to feel pressure to exaggerate their capabilities or the possibilities of their research. There is a fine line between exaggeration and deception.

The majority of funding comes from Governments, companies and private investors. Companies have a specific interest in the funding research that could improve their profit margins. Pressure from investors does influence research: an NIH survey revealed 15.5% of respondents admitted to altering their research approach under pressure from funding sources. Barnes investigated whether a scientist’s affiliation affected research conclusions. 106 passive-smoking review articles published between 1980 and 1995 were analysed; 37% concluded passive-smoking was not harmful. Of these 74% were written by tobacco-affiliated authors - only 2 tobacco affiliated researchers concluded passive smoking was harmful.
Barnes found to 95% confidence that conclusions related to the affiliation of the author. For this reason, many journals require disclosure of conflict of interest and author affiliations.

Hwang may have felt pressure from Government who funded his research. Since much of Hwang’s early research was unpublished it is interesting that he commanded such a sophisticated lab. Admittedly, his work was better known in South Korea than worldwide; but it is questionable that unsubstantiated claims of creating BSE-resistant cattle should secure ~$40 million in Government grants. Ky-Young Park was named as a co-author on Hwang’s 2004 paper because of her work into the socio-ethical concerns involved in cloning; however the SNU investigation determined that she made “no contribution.” The KBA has more than 50 listed members and is seen as the principle leader in bioethics policy in South Korea. Why did Hwang fund Park’s research (a botanist with no history of ethical study) instead of consulting the KBA? There is suspicion that Hwang ‘employed’ Park to further political support for his own research, in turn increasing his obligations to Government funders. Pressure on Hwang to succeed would be immense because the nationalistic ethos of South Korea would mean Hwang’s fame reflected well on the Government.

**Media and the general public**

Hwang “never shied away from the strong appeals to nationalism” that fuelled his rise to stardom. Soon after cloning his first cow, Hwang promised to "spread the Korean people's spirit by cloning the [holy] Mount Paektu tiger.” Revered by the public, Hwang was treated like a “rock star.” The government issued ‘Dr Hwang’ postage stamps depicting a paralyzed person walking again and textbooks were rewritten - one describing Hwang as a potential Nobel Prize winner.

![Postage Stamp](http://www.sciencemag.org/cgi/reprint/308/5729/1738a.pdf)

Hwang was a symbol of everything that South Korea stood for and desired, his picture was plastered on public transport and posters were released proclaiming he would change the world. South Koreans viewed Hwang as holding the hopes of the world, to further Hwang’s research was to further South Korea.
At the pinnacle of Hwang’s popularity a survey indicated that 30% of women would donate their ova to research and 45% of men wanted their partners to donate. The website www.ovadonation.or.kr was set-up in November 2005 for women to pledge their eggs to research. In seven days, 800 women had signed up and the message board was full of encouragement for Hwang. Kim Yong-Hae, a disabled 27 year old, wrote “Please don’t give up, doctor Hwang. Your research is my only hope. You should take all of my ova if they help”. Worshipped by so many people, Hwang [had] no choice but to accomplish even more as soon as possible so as to live up to the expectation of his fellow country people.

The media was crucial in stoking public reaction and stories about Hwang’s research and its implications for the future of humankind were commonplace. Irresponsible reporting and unfounded speculation by scientists bred misconception and false hope within the general public and probably led to extra pressure on Hwang to deliver results. Unfortunately, some scientists allow misconceptions to occur, as media attention brings fame and funding. Schatten’s said: “we will be able to make a person to have [sic] immunity against HIV... his somatic cells can be cloned to produce HIV-resistant cells”.

Following comments like these scientists and the media were looking for proof; one must either produce results or lose face.

Lax Implementation of Weak Ethical Policy

Investors
The Stem Cell Research Centre (SCRC) invested in Hwang’s 2004 paper. Hwang’s co-author, Shin Yong Moon, was the SCRC president and sat on its ethics committee which “prohibits the production of human embryos for stem cell research” 5. Thus, it is questionable whether Moon should have worked on the project and whether the SCRC should have donated. Similarly, it is problematic that the Government department that invested so heavily in Hwang was also his regulator. Park “received the report on the contamination from Hwang in January [2005], but did not report to the president [Roh Moo Hyun] directly” 9 - her failure to do so may have indicated to Hwang that he was politically immune and that the government wanted him to succeed at any cost. Park must have known that Hwang’s 2005 paper was compromised because the four infected SC lines were included, yet she did not expose nor publicly question Hwang. Because Park did not officially report the infection of Hwang’s cell lines or her intervention it was more difficult to uncover subsequent fabrications.

Research Ethics Committees
The Research Ethics Committees or Institutional Review Boards (IRBs) of Hanyang University and SNU both approved Hwang's research, and his proposal was quickly passed by the National Bioethics Committee (NBC). However, it appears numerous oversights were made. Following Hwang’s exposure, the NBC determined that Hwang failed to sufficiently protect donors because he provided insufficient information on the possible risks of donation and allowed 15 women to donate more than twice 38. By handing out ova-donation consent forms to junior researchers in his team, Hwang failed to comply with the Declaration of Helsinki because he did not act responsibly with a subject “in a dependent relationship with the physician” 38. Though Hwang is not a physician, the Declaration of Helsinki is seen as the ethical baseline standard for scientific research. Hwang’s actions could have been misinterpreted as a request for a donation.

Hwang’s somatic cell donors suffered from congenital hypogamma-globulinemia; spinal cord injury; or juvenile diabetes. Magnus and Cho, two ethicists who have provided commentary throughout the Hwang case, find it “easy to understand the value of SCNT experiments using somatic cells donated by individuals suffering from genetic disorders”. But they find it “difficult to understand why spinal cord injury patients [were] recruited” because their inclusion increased the likelihood of people inaccurately attributing therapeutic intent to the research (therapeutic misconception) 39. However, because none of the donors could feasibly benefit from the research there was no reason to enrol patients rather than healthy volunteers, especially if one were worried about therapeutic misconception. Somatic cell donors were only required to be unique from oocyte donors. The use of vulnerable groups without reason was also said to be unethical.
Acknowledging Hwang’s prominence, Magnus and Cho question how truly independent IRB members were. This is especially worrisome given allegations that Hwang nominated some IRB members and the NBC head, Yang Sam-Sung, tendered his resignation because of an undeclared conflict-of-interest. While reviewing Hwang’s research for the NBC Sam-Sung was providing legal advice to Hwang regarding the PD Notebook allegations. Evidence suggests that Hwang was aware of ethical issues following his 2004 paper and in January 2005 he consulted Dr Jung and together they devised some of the most ethically defensible protocols for research conduct. However, it now seems that Hwang ignored these protocols but he, and perhaps IRB members, knowingly gave the impression that they were being adhered to. Hyun and Jung’s concern was first raised by the discrepancy between the timeline for egg and somatic cell donations and the timeline necessary for Hwang to produce data for the March 15 article submission to *Science*. Hyun and Jung reported their “concerns immediately to a member of the Hanyang Hospital IRB and the leadership of the International Society for Stem Cell Research (ISSCR) and its bioethics committee” but no action seems to have been taken as a result. Jung and Hyun had to retract their paper about the ethical integrity of Hwang’s research.

Collaborating with Schatten meant Hwang’s research crossed numerous regulatory borders. From information provided by Schatten the Pittsburgh IRB resolved, using the Federal definition, that no human subjects were used; and because samples could not be traced back to the donor the research was exempt from full IRB review. However, South Korean organ sharing laws required that donors benefit preferentially if therapies are developed via research, thus at least one scientist should have been able to link samples to donors. Therefore, while Schatten was involved, Hwang’s research should have had full American IRB review. The USA National Research Council – Institute of Medicine now recommends all embryonic SC research have full IRB oversight. Part of the problem was that Pittsburgh allows their researchers themselves “to determine if their work constitutes human-subject research, a policy that disregards federal recommendations designed to safeguard people”. Miscomprehension or ignorance of South Korean law meant that Schatten’s assertion that the research did not involve identifiable people was false. Documented evidence now shows that one of the egg donors later worked in Schatten's Oakland lab.

Problems In Science Raised By Woo-Suk Hwang’s Research
Hwang’s research raises many general problems related to scientific research, related verification of results, the validity of peer review and authorship. However, here we concentrate on the ethical issues raised by this research.
**Journals**

Magnus and Cho argue that journals must be satisfied with the ethical conduct of researchers.\(^{45}\) Whether journals have the resources to evaluate the ethics of a paper is questionable. The Hinxton Group encourages journals to “require a statement from scientists that their research conforms to local laws and policies”\(^{46}\).

**Author Responsibility**

The ethical issues surrounding Hwang are still contentious and the number of authors on a single paper makes it unclear where responsibility lies. The link between publications and funding means it is common practice for anyone, even vaguely, involved with research to be a co-author. Additionally, lead authors may not be the most significant person in the research; as exemplified by the current case surrounding ‘Dolly the Sheep’ which has striking similarities to Schatten being second-author on Hwang’s 2005. For the last ten years, Dr Ian Wilmut has been widely credited with the successful creation of ‘Dolly’ via SCNT-cloning. However, a recent legal hearing forced him to admit that he was only the lead author because of a prior agreement and that Professor Keith Campbell deserved 66% of the credit.\(^{47}\) Additionally, it appears that much of the work was done by two technicians, Bill Ritchie and Karen Mycock, who because of their positions were not seen worthy of co-authorship – merely being acknowledged at the end of the paper.\(^{48}\)

There were 15 and 25 authors respectively on Hwang’s 2004 and 2005 papers. This makes it difficult to assign responsibility for misconduct. Journals are considering making authors detail their involvement in projects so they can ascertain whether authorship is valid and assign responsibilities.

It is also ethical misconduct to appear as an author when no significant practical or theoretical contribution has been made. The Pittsburgh investigation panel “We have no reason to doubt the Schatten’s statement to us that his major contribution to the paper was a suggestion that a professional photographer be engaged, so that Snuppy would appear with greater visual appeal. It is less clear that this contribution fully justifies co-authorship”\(^{50}\). The University of Pittsburgh panel found Schatten guilty of ‘research misbehaviour’\(^{51}\) and chided him for his failure to take greater steps to ensure the veracity of Hwang’s data.\(^{52}\) Schatten received $40,000 from Hwang, including $10,000 for appearing at a press conference.\(^{50}\) It may be that Hwang used Schatten to give credibility to his research in the west. As Dr Weissmann said: “Everyone wondered how Schatten got to be the senior co-author, but his vouching for Hwang made it a little more likely.”\(^{53}\).
Failure of Education and Monitoring of Research Conduct

Hwang’s research highlights the difference between gaining research approval and conducting research ethically. IRB approval does not ensure ethical practice. Hyun considers that originally Hwang’s team had very little ethical knowledge and on moving their focus from animals to humans they applied the same concepts in ethics as in science (Insoo Hyun, personal communication, Hinxton UK). A study of over 900 biotechnology researchers in South Korea found that 46% had not heard of the Helsinki Declaration; 39% had heard of it but did not know what it was; and 42% did not know about IRBs. Generally, there is little ethical education in science. Ethics is seen as integral to modern medical training; however degrees in biological sciences do not appear to have kept in touch with the ethical aspects associated with their fast-paced area. As the case of Hwang vividly illustrates, researchers with insufficient ethics education are a risk to themselves, their colleagues, their institution and to the scientific community and public in general.

International Co-ordination

Hwang’s research took place in South Korea with the approval of institutions required by South Korean law. Schatten was working out of America and no federal funding was used for the research; the creation of human stem cells under these conditions is not prohibited by either South Korean or USA law. However, the failure of Schatten and the Pittsburgh IRB to recognise that the Korean organ sharing law meant full IRB review was required demonstrates the difficulty of regulating international collaboration. Regulating SC research is a compromise between advancing knowledge and protecting national ethical standards, in which cultural diversity manifests itself as a patchwork of legal environments. Transnational variation in law can leave scientists uncertain about their legal standing when working internationally. Ambiguous use of technical language may discourage scientists from developing legal avenues of research. Alternatively, scientists working within the law may be the target of legal proceedings initiated by people who wish to challenge those ambiguities. The Hinxton Group calls for legal policy to be “clear and explicit” in order to maximise the potential for valid scientific research to be undertaken.

Donation

The South Korean ethos, in promoting altruistic donation, poses new questions for research participation. Excess IVF embryos are seen as the most ethically acceptable source of oocytes but whether they are suitable for all research is a controversial question. Excess IVF embryos currently have ethical and legal advantages for use in SC research because the woman is a patient, having given clinical consent for the IVF procedure. As a patient she is able to give research consent for any excess embryos to be used for research. However, some results
indicate that ‘fresh’ (non-frozen) oocytes are most productive for IVF. The same is probably true for therapeutic cloning. However, it is mostly stored oocytes from older donors that are available to researchers via IVF. To obtain ‘fresh’ oocytes Hwang enrolled patient family members, as in organ donation. Many suggest that oocyte donation and organ donation are equivalent. This maybe true when, and if, SC therapy becomes clinically viable. However, clinical viability is unproven and the argument invalid and may represent an extension of therapeutic misconception.

The use of altruistic donors raises serious ethical problems and is the subject of a current HFEA consultation. Women donating eggs purely for research expose themselves to not insignificant risks - studies put the risk of ovarian hyper-stimulation syndrome following oocyte procurement from 0.1% up to 8% only for the presumed future good of others. The BBC reported that by June 2005 five women in the UK had died of ovarian hyper-stimulation syndrome. Altruistic donors, especially with regard to organ donation, have their motives severely scrutinised and there are problems with coercion from family members.

Altruistic donors to research could be treated as research subjects or ‘Research Donors’, 45 given full information about the risks of the procedure and realistic estimates of its research value. Information sheets and consent forms used by Hwang dealt little with the risk of procurement [Web addition - Appendix A], though this is the only significant risk undertaken by participants.

One way to regulate the treatment of donors is through donor databases, as in organ donation. The donor database of the website www.ovadonation.or.kr may be the first step to such a system, but it is worrying because the details regarding donation are unclear - at least to these authors at this time given that only scant detail is available in English. The website could act as a depository which licensed researchers can use to approach women willing to donate. This would be advantageous in preventing women from donating more than the legal number of times and ensuring that a suitable time is left between procedures. The woman, once contacted, would become a ‘research donor’ and go through the IRB approved informed consent procedures. One risk of a publicly accessible database is that it could be used by a private ‘oocyte procurement’ company. Ambiguity surrounding the website highlights the need for regulation of not just research but tissue donation.

Possible Solutions
1. Education
Hwang’s case highlights the numerous threats to ethical integrity faced by scientists today. Good research is dependent on good ethics and education is the foundation stone to ensure that researchers understand their responsibilities. Ethics should be compulsory in biological degrees. It should deal with practical aspects of research: justifying the use of and working with vulnerable groups; informed consent and rights of participants. Those working with human subjects should take appropriate courses and satisfactorily demonstrate relevant knowledge. This education should be renewed every few years in light of the constant evolution of science.

2. Independent Monitoring and Validation
A scientific and ethical review committee without conflicts-of-interest should have been able to highlight the ethically questionable aspects of Hwang’s research proposal. Thus, ethical assessment independent of, and in an environment separated from, the researcher is essential. However, this assumes that Hwang’s proposal detailed the methods he intended to use. Without auditing research to ensure guidelines are adhered to scientists have free-reign once approved. Hwang was able to ignore the protocols he drew up with Jung - not even asking donors to sign IRB approved consent forms. Many now suggest on-site monitoring by IRBs is appropriate. Magnus and Cho suggest this IRB should be independent of that approving the research. Additionally, where applicable, suitable agencies could keep patient samples for independent analysis and ensure that cell lines are submitted to an international depository for validating.

3. Guidelines on Tissue Donation
Donors should be carefully and ethically selected; and currently, it would be ethically advantageous to use donors who would not benefit from prospective treatments. It may also be beneficial to set-up a donor register to ensure proper regulation of this aspect of research. Healthy donors should be protected by ethical guidelines, just as patients are in clinical research. Science should work towards reducing the misconceptions surrounding SC research.

4. Debate Ethically Contentious Research
The question of whether to publish unethical research has arisen before with reference to Nazi experiments. Many suggest that there should be limits on what is published. Much Nazi ‘research’ had no scientific value and was a simple disregard for human dignity; however, some was important. Dr Epstein used results of his research to help children recover from Noma (orofacial gangrene) - the scientific worth of unethical experiments should not be lost. To prevent distribution of scientific credit, unethical research could be published anonymously. If excessive time was spent debating a paper’s ethical quality originality could be lost and this would be disadvantageous to both journal and author.
Hwang’s case demonstrates the difficulty in assessing a paper’s ethics. Journals could review IRB and consent forms to inform their decisions and research auditing would support this. However, only with open debate following publication did details of Hwang’s research and its ethical questions become apparent. Journals should publish research such as Hwang’s because it would be ethically questionable to withhold valid data. But rather than censoring such research, by highlighting questionable legal or ethical areas journals could facilitate debate by lawyers and ethicists.

5. Establish an International Ethical Code of Practice

It seems unlikely that global consensus on SC research will soon be reached. To facilitate discussion, the ‘Hinxton Group’ calls for legal clarification with regard to SC research[ers]. There was consensus that scientists should be free to conduct ethically defensible research in a country where such research is legal. The group is developing a website where scientific and ethical protocols can be deposited so that collaborating scientists can conform to a common set of protocols appropriate to both jurisdictions and available to public scrutiny 46. The Group’s move toward documenting ethical and scientific policy in its global context is an important step towards establishing global standards of ethical review. What is perhaps urgently needed is a set of “gold standard” ethical procedures which has international credibility. The Declaration of Helsinki and other international guidelines articulate general principles but are poorly placed to address in detail rapidly emerging, complex areas of research, such as egg donation.

6. Foster Public Involvement through the Web

Much of the detail surrounding Hwanggate was first brought to the fore on online forums. For example, it was a post on the BRIC website that first addressed image duplication in Hwang’s 2005 paper. However, there was also much debate about “whether someone should inform Science” 15. Filing charges of scientific misconduct can be a dangerous business, as the press shows whistleblowers often pay a high price for their actions. This is largely because we feel that wrong-doing should be reported it, yet we are uneasy with the act of ‘abusing’ another’s trust to do so 61. Although whistleblowers have done a good deed in removing bad science from the public domain the knock on effects of their action damage not only the perpetrator but the organisation with which they are associated. The costs of whistleblowing can be high62,63. It is thus understandable, if not defensible, that companies are less likely to employ someone known to have been a whistleblower. The exposure of Hwang highlights a way in which this can be done effectively while protecting those acting in good faith – in the anonymous medium of the internet. A website, or ‘blog’, dedicated to discussion of dubious research practices would facilitate the exposure and hopefully reduce research misconduct. The exposure of Hwang took many posts to build momentum and gain credibility, and in this
way would prevent the website from being abused by bad-faith bloggers. The web is the new police and conscience.

Another form of novel ethical oversight using the internet and public involvement would be to make research protocols, patient information and consent forms publicly available on the net. Clearly, commercial interests would need to be protected and key parts of the research anonymised but it is possible in principle for the ethically relevant details to be disclosed without divulging details of novel substances or procedures. It is the risks and benefits which are important for the ethics, not the nature of the intervention or its commercial advantage or value.

**Concluding Comments**

Evidence suggests that Hwang was originally a pioneering scientist, and nuclear extrusion techniques he developed have furthered cloning research. However, the extreme pressures of his work environment complemented by lax implementation of ethical policy and his ambition led Hwang to make grossly unethical decisions that compromised his integrity. Hwang personifies the fact that good science requires good ethics.

No amount of education, guidance, review and oversight can stop a determined and talented person who wants to commit fraud. Good rules can detect bad cheaters, but not good cheaters. The vast majority of scientists are men and women of the highest integrity who sacrifice significant parts of their lives for the pursuit of knowledge to benefit others. Perhaps, we must also prepare ourselves for the next Hwanggate and protect the science that overall serves us so well.

Thanks to Ruth Faden for valuable comments.

**References:**

5. KBA. Korean Bioethics Association - Publications; 2004 22 May.
52. Gerber P. What can we learn from the Hwang and Sudbø affairs? 2006;184(12):632-635.
Appendix A:
The information sheets and consent forms used by Hwang have caused much concern amongst commentators, yet they have proved difficult to obtain. The following documents were taken from Schatten’s final submission of ‘Patient-Specific Embryonic Stem Cells Derived From Human SCNT-Blastocysts’ to *Science*. For those wishing to assess the standard of the translation the original Korean version of the consent form has been included. With thanks to Alison Murdoch.
We would like to request your permission to enrol you as a participant in a research study. This statement is to provide basic information and knowledge in regard to oocytes donation for therapeutic cloning research.

Neuronal tissues can be injured by various routes such as stroke, cerebrospinal injury by trauma, Parkinson’s disease, Alzheimer, encephalopathy, kinesio-neurosis, cerebrospinal lesion and more. These injuries may cause death/reduction of working nerve cells/tissues, leading to permanent brain damages and bodily disorders. Unfortunately, however, effective treatment methods for these conditions are rare, often with doubtful treatment efficacy. These conditions have posed significant social and economic burden, not to mention economic and psychological hardships for patients and their families. If an individual were paralysed from cerebrospinal injuries by trauma, which may occur especially among a young age group, the duration of medical and social dependency would span throughout the normal life expectancy. Therefore, the need for developing a novel and advanced therapeutic method cannot be emphasized too much for these individuals.

The new therapy for treating these degenerative diseases/tissue injuries could be found from the method whereby injured (nerve) cells are replaced by normal (nerve) cells, and stem cells can be an excellent candidates to be used to replace injured cells. Many scientists are actively conducting research to understand the characteristics of stem cells. Especially, stem cells called ‘cloned embryonic stem cells’ can re-generate damaged nerve cells when they are grown in large scale, differentiated to nerve cells, transplanted into a damaged nerve tissue. The ‘cloned embryonic stem cells’, since they are identical to the damaged cells, are less likely to suffer from immune rejection, opening a new path to the possible treatment/cure of the various diseases.

Although stem cell research is in its infancy, rapid technical and scientific development anticipates the actual clinical application in the near future. As one of the global leaders in the field of stem cell therapy/research, this research institute endeavours to address various diseases by researching cloned human embryonic stem cell lines through a technique called ‘somatic cell nuclear transfer (SCNT)’. The schematics of the SCNT process are described in the figure. The current research protocol aims to obtain human embryonic stem cell from the SCNT procedures, differentiate (grow to be a specific type of cells) into neuronal stem cells, and grafted (transplanted) into patients with neuro-degenerative diseases. The protocol also aims to test the feasibility of the efficacy and safety of the procedures. For this purpose, voluntary donation of somatic cells and oocytes is needed to obtain cloned stem cell lines. In order to help you make decisions for your voluntary participation, we would like to inform and explain in detail the study procedures. You have your right to refuse to participate, redraw from the study, and cancel the intention to donate.
oocytes at any time prior to the actual donation without any penalty or loss of benefits, which otherwise you are entitled to.

Information for Oocyte Donation for Therapeutic Cloning Research

This study utilizes human oocytes and somatic cells that are donated by you voluntarily. There is no direct benefit to you as a result of your participation in this study. No financial reward (in any form) will be provided. It is hoped that the information obtained from this study may help us better understand how the stem cells work. Oocytes donated herein can be used for the treatment of anonymous patient(s), who is (are) not related to you in any way. If oocytes are donated on behalf of your family member, the designated family member has the priority to receive the donation. However, any unused oocytes can be used for the treatment of anonymous patient(s), who is (are) not related to you.

You will be interviewed on your medical history upon enrollment, and several gynecological tests such as pelvic examination (manual examination of female reproductive organs) and ultra-
sound examination (ultrasonography) may be given. According to the legal/regulatory requirement, several laboratory blood tests such as hepatitis test, ADIS test, and syphilis test are required to determine whether you can participate in the study.

Information for Oocyte Donation for Therapeutic Cloning Research

In order to retrieve oocytes, you will undergo a procedure to induce ‘over-ovulation’ (normal ovulation is one per menstruation cycle) and collects many oocytes at once. ‘Over-ovulation’ refers to the procedure to speed up the growth of several ovarian follicles (where an oocyte is nurtured) by the hormonal injection. More specifically, the hormonal injection starts at 2 ~ 3 days after the onset of menstruation, and continued for 7 ~ 10 days. Matured ovarian follicles can be seen using ultrasonography, and doctor(s) will determine the exact timing of extraction procedures.

For the retrieval of oocytes, you may need to undergo general anesthesia (insensibility to general sensation with loss of consciousness). While you are unconscious, oocytes will be retrieved via needle under the guidance of ultrasound (a special vaginal probe resembling a tampon will be inserted into your vagina). During this retrieval process, you shall not feel any significant pain other than discomfort related to the general anesthetic procedures. The procedures are conducted typically in the morning. Therefore, you should not eat breakfast since anesthetics sometimes could cause vomiting in some people. Under the doctor’s observation, you may return home in 2 ~ 3 hours after the procedure.

We would like to emphasize that there could be unknown risks associated with this procedure. The major discomfort prior to the donation is related to the blood collection for several preliminary tests, which may cause pains, bleeding at a lesion site, vein infection or other types of general infection. In addition, during the over-ovulation procedures, injected hormones may bring known side effects or symptoms such as headache, nausea, hyper-sensitivity, blood clots, and flare at an injected site. During the oocyte retrieval, anesthetic agents that are injected for the general anesthesia may cause side effects such as nausea and vomiting. If you have not been sexually active, it is possible that ‘hymen’ (thin membrane near the vaginal opening; you may or may not have it regardless of your sexual history) could be damaged. If you found that you are pregnant or suspect possible pregnancy during any stages of participation, please inform the researchers as soon as possible, and stop the participation. Whenever suspicious or unusual symptoms occur, you may seek the help/medical attention from the physician-in-charge or clinical investigators immediately. There may be other side effects, although not described above or forecasted. If present, please report to your physician-in-charge immediately. All the procedures will be explain to you again when you are scheduled for meeting with initial consultation, and you may ask detailed questions for all the procedures at any point during this study.

In case you are donating ‘surplus’ oocytes for in vitro fertilization (in IVF procedure), there will
be no additional discomfort/procedures other than IVF procedure itself. In any circumstances, oocytes will not be collected in excessive amount against your intention, and oocytes can be donated only with the prior written intention/consent for the donation. Other than that, after the donation, equal right and rules applies to all donors.

**Information for Oocyte Donation for Therapeutic Cloning Research**

With the successful completion of this project, a new therapeutic cloning method may help others in the future. Accordingly, the potential benefits/commercial value, including the intellectual property, may rise from the outcome from this research. However, it is important to inform you that any immediate medical breakthrough cannot be promised by any means. In addition, we would like to inform you that you cannot reserve, file, or claim any right on the outcome of the research activities resulting from this donation.

During and after the study, all the medical records and identifiable information that are associated with you will be securely protected. If the experimental results are disclosed in academic journals, textbook, or other form of publications, the identity of the donor will be strictly classified and protected.

Your signature below indicates your willingness to participate in this study, and your authorization to gather, use and share with other researchers, both domestic and international, your private confidential health information under the strict legal guidance on the extent and method of use or release individual information for research purpose. However, you can withdraw from the study any time. If you are injured or affected by the side-effects during the course of the study, or if you have any questions about any aspect of the study, please contact the researcher-in-charge and other co-investigators at the number provided in this form. You will always receive help properly and immediately.

Biomedical and Biotechnology Research Team, Seoul National University Contact Number: 019-265-0209
Informed Consent Form for Oocyte Donation

난자 기증 동의서 (기증자가 임산과 혈연관계가 없을 때)

1. 본 동의서는 자료 목적의 증거보조생산을 위해 연구용으로 난자를 제공하는 데 대한 동의서입니다.

2. 본 난자기증은 전적으로 자의에 의한 정상의 판단에 따른 기증으로 어떤한 강요도 없었습니다.

3. 본인은 난자의 기증을 금전 등 어떠한 이익을 위해 간접적으로 제공임을 주지하나 이에 동의합니다. 단, 본인 기증을 위하여 소요된 외부 고용비, 시술비 등 심비에 관하여 제공될 수 있음에 명시하였습니다.

4. 본인이 기증하는 난자는 본인의 혈연관계가 없으며 서로 알지 못하는 객자에게 사용될 수 있도록 순수적이게 기록하였습니다.

5. 본인은 난자 기증 시 필요한 수술 및 과정에 대해 충분한 설명을 들었으며 그에 따른 임상 발생 가능범위에 대해서도 충분히 숙지하고 있습니다. 연구수행 후 적법한 절차에 의해 폐기함을 원칙으로 합니다.

6. 본인은 기증된 난자를 이용한 연구 및 결과물에 대하여 저작 재산권 또는 여타의 부가 가치가 입증될 수도 있음을 설명하였습니다. 그 외 경로 본인의 권리가 위반될 경우를 인정하고, 당사 이에 대한 권리를 주장할 수 있음을 인정합니다.

7. 본인은 본인으로의 관리 및 신상 정보 등 일체의 개인 정보가 보호될 수 있도록 설명하였습니다.

8. 본인은 난자의 제공전에는 언제든지 난자의 기증을 취소할 수 있음을 설명하였습니다.

본인은 이상의 내용을 준분히 인지하고 기증된 난자를 연구 목적대로 제공하는데 동의합니다.

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본 인: (성명/인) 주민등록 번호
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서울대학교 수의과대학 생물공학 연구팀
Informed Consent Form

Informed Consent for Oocytes* Donation
(In case of blood or familial relationship established between the donor and the recipient)

1) This informed consent form is to certify the volunteer subject’s willful consent to donate human oocytes with intention to produce human cloned embryos and embryonic stem cells for the purpose of researching their potential therapeutic applications.

2) I confirm that the donation of my oocytes for participation in this research is of my own will and entirely voluntary. No one has forced, persuaded, or recommended my participation.

3) I acknowledge and confirm that my participation in this research and donation of my oocytes is free of element of any financial reward or conflict-of-interest**.

4) I acknowledge and confirm that oocytes donated herein will be used for the patient(s) who is/are in blood or familial relationship to me with priority. However, any unused oocytes can be used for the treatment of anonymous patient(s), who is (are) not related to me in any way.

5) I confirm that the purpose of this research, the study procedures including the surgical procedures for oocytes retrieval, the possible risks, and discomforts relating to this research have been fully explained to me. I acknowledge that the embryos and oocytes, after the study end point, will be destroyed according to the manner as defined by the Korean legal codes***.

6) I acknowledge that the potential benefits/commercial value, including the intellectual property, of the outcome from the research was fully explained to me. I hereby agree that I do not will not reserve, file, or claim any right on the outcome of the research activities resulting from my donation.

7) I acknowledge that the act of this donation as well as my private information are entirely protected and will not be disclosed or divulged under any circumstances.

8) I acknowledge and confirm that I reserve my right to refuse to participate, redraw from the study, cancel the retrieval of oocytes at any time prior to the donation without any penalty or loss of benefits, which otherwise I am entitled to.

I confirm that I have read this consent form. All my questions have been answered including the alternatives to my participation in this research. My signature below indicates my willingness to participate in this research and authorization to use and share the donated oocytes for research.

Data:

Donor: __________________________ signature
Address:
NO. of Identification:

IRB member in charge: __________ signature
Researcher in charge: ________ signature

Translation Notes
* In Korean, the word ‘oocyte(s)’ is preferred choice of word over ‘human egg(s)’, and is commonly used.
* In Korean, plurality and singularity of certain object is often omitted and understood in the contexts.
** Conflict-of-interest (COI) describes a relationship, commitment or financial interest that could results in moral hazard and breach of ethical obligations.
*** Korean Legal Code refers to the bill and code for Korean Legal Codes for Biomedical Ethics and Safety - Code 7150**