Follow-up questions from Chairman Mark Souder
to James F. Battey, M.D., Ph.D., Chair, NIH Stem Cell Task Force and
Director, National Institute on Deafness and Other Communication Disorders,
following March 6, 2006, hearing of
the Subcommittee on Criminal Justice, Drug Policy and Human Resources
entitled, "Human Cloning and Embryonic Stem Cell Research after Seoul:
Examining exploitation, fraud, and ethical problems in research"

1. Regarding the scientific process at issue in the Korean scandal:
   - Was it the process of somatic cell nuclear transfer, SCNT (a process for creating cloned embryos), that was supposedly achieved?

ANSWER:

Yes

   - Was it supposedly the same process that was used to create Dolly, the cloned sheep?

ANSWER:

Yes. Dolly, the cloned sheep was created by Somatic Cell Nuclear Transfer, which the Korean research used to create their embryos. The Korean researchers did not, however, propose to take their cloned embryos to live birth but rather to destroy them at an early developmental stage to derive stem cells from them. The first step, the cloning step, is the same, but the intended result is different.

   - And in this case, it was supposedly used to produce cloned human embryos for research purposes?

ANSWER:

Yes. By combining a patient's somatic cell nucleus and an enucleated (nucleus removed) egg, a scientist might create a cloned human embryo that can then be destroyed to harvest embryonic stem cells. Since the embryo is genetically virtually identical to the donor of the somatic cell nucleus, the resulting stem cells could be used to generate tissues that match that patient's body. This means, at least in theory, the tissues created are unlikely to be rejected by that patient's immune system. The researchers did not, however, seek to transfer the cloned embryo into a woman's uterus to develop to birth.

SCNT could presumably be used to accomplish either type of cloning.

2. The results in Korea, which we now know were fraud, were used to tout the promise of cloning for research, by advocates and politicians.
   - Any proof that SCNT has ever been successfully used to produce human embryonic stem cell lines?

ANSWER:

No.

3. The Korean studies were hyped as revolutionary advances. Even putting aside the issue of fraud here, are you concerned that the promise of embryonic stem cell research is being oversold by some advocates and politicians?

ANSWER:

Embryonic stem cell research has shown promise in the laboratory using animal models of human disease. There is the potential for treating diseases in humans. Scientists still have laboratory and clinical research that must be completed before that can be achieved, however. NIH is committed to studying all areas of stem cell research.

4. A common figure tossed around regarding the "promise" of embryonic stem cell research is that it can provide cures for 100 million people.

- Is there any scientific evidence to actually support that claim?

ANSWER:

It is unclear where this statistic came from. Human embryonic stem cell (hESC) research is a relatively new field of science, having been first reported by James Thomson at the University of Wisconsin in 1998. More basic research needs to be conducted in the laboratory before the full potential for treating diseases is clear.

5. Addressing the notion that embryonic stem cells can "become any kind of cell type in the body"

- Is that supported by evidence or current science?
- How many cell types have actually been achieved?

ANSWER:

Scientists report having differentiated embryonic stem cells into many different adult cell types. Some of these include: dopamine-producing nerve cells (the type lost in Parkinson's disease), insulin-producing cells, nerve support cells called glia, other types of nerve cells, blood cells, heart muscle, skeletal muscle, smooth muscle, cartilage, bone, liver, pancreas, sperm and eggs, fat cells, skin, the cells that detect sound in the inner ear, cells that line blood vessels, lung cells, and retinal cells of the eye.

Due to the pace of science, it is difficult to provide a complete list of all cell types derived from hESCs. However, the evidence thus far suggests that hESCs are able to become most, if not all, cell types in the body, under the proper culture conditions.

Another piece of evidence to support the pluripotency of hESCs is the teratoma test. Scientists verify that they have established a hESC line by injecting putative stem cells into mice that lack an immune system. Since the injected cells are not destroyed by the mouse's immune system, they survive and form a multi-layered benign tumor called a teratoma. Even though tumors are not usually a desirable outcome, in this test, the teratomas serve to establish the ability of a stem cell to give rise to all cell types in the body. This is because the teratomas contain cells derived from each of the three **embryonic germ layers** (explained below).

During normal development, the fertilized egg divides to produce cells that eventually make up three layers, called the **embryonic germ layers**. All cells in the body originate from one of these three layers (endoderm, mesoderm, and ectoderm). Teratomas formed by hESCs consist of gut epithelium (endoderm layer derivatives); cartilage, bone, smooth muscle and striated muscle (mesoderm layer derivatives); and neural epithelium, nerve ganglia, and stratified skin (ectoderm layer derivatives). The original injected cells' ability to produce cell types from all germ layers is evidence for pluripotency- the ability to form any cell of the body.

6. How much money was spent on human embryonic stem cell research in 2005? What portion of that went to the University of Pittsburgh researcher Gerald Schatten?

ANSWER:

In FY 2005, NIH-supported approximately $40 million in research involving hESCs. Of this amount, just over $1 million was in support of Dr. Schatten's projects on hESC.

7. University of Pittsburgh researcher Gerald Schatten is doing work on approved Bush stem cell lines as well as on primate embryos.

- How is Schatten's grant award categorized (as being all embryonic stem cell research, is the primate research categorized as something else)?

ANSWER:

In Dr. Schatten's center grant "Pluripotent Stem Cells in Development and Disease" the research is studying both human embryonic stem cells that are eligible for federal funding and non-human primate embryonic stem cells. In FY 2005, approximately 25% ($750,000) of the research focus of this project involves hESCs and 75% ($2,250,000) is devoted to non-human primate embryonic stem cells.

8. Where does Gerald Schatten's $16.1 million grant award fall in terms of how it compares to other large grant awards for all types of embryonic stem cell research?

ANSWER:

NIH awarded a grant (1P01HD047675-01A1) "Pluripotent Stem Cells in Development and Disease" to Dr. Schatten that totaled $16.1 million over 5 years. The portion of the

grant involving hESC research is $750,000 in FY 2005. Dr. Schatten's P01 grant is one of the larger hESC projects awarded by NIH in FY 2005; however, it is not the largest hESC research project. In FY 2005, NIH awarded $4.2 million to WiCell Research Institute to support the National Stem Cell Bank, plus there were eight other projects that were larger in hESC funding than Dr. Schatten's P01 grant.

9. How does Schatten rank in terms of NIH grant awards for ESCR in monkeys and the approved stem cell lines? How many grants has he been awarded? Is he the top single grantee for ESCR grants?

ANSWER:

Dr. Schatten is considered an expert in the field of non-human primate stem cell research, growth of human embryonic stem cells in culture, and non-human primate animal models. The P01 grant is unique in that it involves research involving both non-human primate and human embryonic stem cells; therefore, there are no other NIH-supported projects that have a similar scope. In FY 2005, Dr. Schatten received 3 individual NIH-supported grants that involve hESC research. The cumulative amount of hESC research funding of these grants was $1.1 million. Dr. Schatten is not the top single grantee for NIH-supported hESC research. In FY 2005, there were four other individual scientists who received more NIH funding for hESC research.

10. Gerald Schatten's successful grant application makes reference several times to Korean research.

- Was Schatten's grant contingent upon what was still viewed at the time of the grant application as successful Korean research in these areas?

ANSWER:

No. Dr. Schatten's grant award was not contingent on the stated work of the South Koreans, but instead was based on the results of work with monkeys eventually published in Developmental Biology in December 2004 as Simerly, et al., "Embryogenesis and blastocyst development after somatic cell nuclear transfer in non-human primates; overcoming defects caused by meiotic spindle extraction." That paper showed for the first time that cloned blastocysts can be developed in non-human primates – and most importantly, that unrelated nuclei were successful and transferred into different eggs. Dr. Simerly and other members of Dr. Schatten's lab were leaders of that work. The federal grant application in question was first submitted in 2003, then revised in November 2004 and reviewed by the National Institutes of Health a second time in April 2005. It did not cite the subsequently published (now withdrawn) Hwang Science '05 report. The federal grant application properly referenced the then-existing Hwang, et al., Science '04 article but did not rely on it as sole support for the importance of any of the application's numerous specific aims or even the only aim focused exclusively on deriving non-human primate embryonic stem cells by nuclear transfer (NT-nhpESC).

11. What are the 2005 figures for ESCR grant awards (i.e., how many grants, total dollar amount smallest grant award and largest grant award)?

ANSWER:

In FY 2005, NIH supported 154 individual research projects involving hESCs at the amount of approximately $40 million. In comparison, NIH supported approximately $199 million in human nonembryonic stem cell research in FY 2005. The smallest individual hESC project was a $2,000 effort to intramural scientists at NIH's National Human Genome Research Institute to conduct Genome Instability in Cancer Development. The largest hESC project was $4.2 million awarded to WiCell Research Institute to support the National Stem Cell Bank. In the FY 2005 listing of NIH hESC projects that we provided you after the hearing, some projects were shown with award amounts of less than $2,000. These projects were co-funded by multiple NIH Institutes/Centers (ICs) and the funding levels between the ICs differ.

12. In your oral testimony before the Subcommittee on March 7, 2005, you stated that you had finished a response to the Subcommittee's letter of October 8, 2002, within a "matter of weeks". The Subcommittee was seeking a "detailed report" providing comprehensive information on the medical applications of adult and embryonic stem cells as well as cells from cloned embryos and aborted fetuses. However, the Subcommittee did not receive a response to this letter seeking critical information until twenty months after it was sent, during which time the Subcommittee staff made numerous inquiries and additional Chairman's letters were sent.

You said in your testimony that although you had completed the letter in a matter of weeks, the extreme delay was caused by other officials in the agency. Please provide the names of all employees and/or officials who held up this letter, listing contact information for each person/office with how long they delayed the response and the reasons why. If you are unable to answer this question fully and completely, provide the Subcommittee staff with appropriate names and contact information for the appropriate official/s who can answer this question completely.

ANSWER:

In providing written information to Congress, it is critical that such information be as accurate and complete as possible. This therefore requires review within multiple channels of NIH and HHS to be cleared. We work to respond to inquiries as quickly as possible, and sometimes, additional time is required to collect, review, and summarize the scientific data, as in this situation. The delay was inappropriate, and it is critical that we be as responsive as possible.

13. In May of last year, Chairman Souder inquired with Secretary Leavitt about matters concerning your temporary resignation at the beginning of last year, then "unresignation" as the Chair of the NIH Stem Cell Task Force, while you were a job candidate to head the

California Institute of Regenerative Medicine, the California stem cell center established as the result of the state's controversial Proposition 71.

During the period of "resignation" you continued to make appearances and presentations on stem cell research. At the very least, this gives an appearance of impropriety, but we have concerns that this was a clear conflict of interest, and a violation of HHS's own ethics guidelines, which state the following:

- an employee may engage in outside activities that require the use of professional qualifications readily identified with his or her NIH position, provided his/her outside work does not create a real or apparent conflict of interest or interfere with regularly assigned official Government duties.

Based on information provided to the Subcommittee through a document request, it appears that HHS's own legal counsel advised you against continuing to speak on these matters during your extra-government job candidacy [documented in emails in the Subcommittee's possession]. As the Hwang scandal is demonstrating, it's clear that we have to be vigilant in guarding against impropriety among the leaders working in the field.

- Explain your justification for continuing to make stem cell presentations while at the same time, seeking a high profile job at the California Institute of Regenerative Medicine.

ANSWER:

When I stepped down as Chair of the NIH Stem Cell Task Force during my employment negotiations with the CIRM, I had already accepted several speaking engagements. I had a strong desire to honor these previous commitments. In the weeks that followed, I received invitations from other organizations to speak on stem cell research. Because of my subject matter expertise, I was the best qualified to deliver these talks. I wanted to continue to serve the NIH in this way. Hence, I requested approval from NIH Ethics Officials to accept these invitations, and approval was given subject to the parameters they laid out for me.

I note that the HHS guidelines that you refer to in your question address conflicts that may arise from performing outside activities. Regarding the advice from HHS legal counsel, I did not understand it to advise against giving the speeches. Rather, I understood it to explain parameters in which I was required to stay while delivering these speeches to avoid the appearance of a conflict. In every instance, I believe I adhered to the advice.

14. During the period of your "recusal" as head of the NIH Stem Cell Task Force, and while you were a candidate for the job to head the California Institute of Regenerative Medicine, you gave at least twelve presentations on stem cell research, including one at an investors' Conference for the California Biomedical Council, speaking on a panel listed in the conference brochure as "Opportunities in Stem Cell Research: organized in recognition of the importance of the California Stem Cell Research Initiative and to stimulate thinking about its likely impact on healthcare delivery and job creation."

You were also listed as a participant in the National Institute of General Medical Sciences workshop, "Human Embryonic Stem Cell Research: Recent Progress and Future Directions of NIGMS Grantees?" The purpose of this meeting was "to provide an opportunity for NIGMS grantees conducting human embryonic stem cell research to report on their recent progress, to exchange information, and to identify problems, challenges and opportunities associated with this emerging area of research."

Among the sixty-eight participants in this important stem cell research grantee meeting, you are the only Institute Director listed, and of sixty-eight research grantees participating in the meeting, ten are California-based. All of the California researchers' affiliated institutions would have been candidates for multimillion dollar grants from the California Institute of Regenerative Medicine at the time of this meeting. The California Institute of Regenerative Medicine has since awarded $15.9 million grants to California institutions represented at this workshop.

- Explain your justification for how this does not present a conflict of interest.

ANSWER:

As I understand the law, a conflict of interest would arise if I had participated personally and substantially in a matter that would have a direct and predictable affect on the financial interest of my prospective employer, the California Institute of Regenerative Medicine (CIRM). The matter in which I participated was the NIGMS workshop, not the awarding of grant money by CIRM to some of the workshop's participants. It is unlikely that the NIGMS workshop had any affect on CIRM's financial interest. Even if the workshop did affect CIRM's financial interests, I did not participate in that matter personally and substantially. My participation in the NIGMS workshop was limited to giving opening remarks as a substitute for NIGMS' Director, Dr. Jeremy Berg. (I agreed to this role long before I applied to CIRM.) After introducing the workshop, I left and did not return. These remarks strictly complied with the parameters given to me by ethics officials with respect to stem cell related presentations. Thus, my remarks did not create a conflict of interest with my employment negotiations with CIRM.

I note it is not unusual to have the Director of the sponsoring Institute be the sole Director to attend and address a workshop. As the substitute for NIGMS' Director at a NIGMS workshop, it was very reasonable for me to be the only NIH Institute Director present.