Original Article

SCNT Method and the Application for Patent Eligibility on Cloned Animals

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Abstract: Patents recognize economic right and are important for both individual and social economic benefit. Nonetheless, mere economic right does not eliminate the requirement for moral assessment when adjudicating intellectual property claims, especially in the case of claims associated with applications of biomedical technology [e.g., somatic cell nuclear transfer (SCNT) methods]. This is so for applications for patent in the case of live-born animal clones, as governed in the setting of the judicial system of the USA. Here recent federal court decisions in the USA are reviewed, and the ethical ambiguities of this judicial review are engaged in light of the current prohibitions on human reproductive cloning. It is concluded that the legal proscription of patents on animal clones bodes well for human accountability to present and future generations in the event of human reproductive cloning.

Keywords: SCNT; intellectual property; live cloned animals; human reproductive cloning; US federal court decisions

Introduction:

> "Patents cannot issue for the discovery of the phenomena of nature…"
> ---U.S. Court of Appeals for the Federal Circuit

According to positive law, a patent is a legal entitlement to intellectual property that is intended "to promote creation," i.e., to provide an incentive to invention[1]. "A patent confers the right on the holder to prevent anyone else from using, making, selling or distributing their invention. No one else will be able to make use of the invention, during the term of the patent, without obtaining the right from the patent holder…An invention, which is eligible for a patent usually has to be something that is new, useful and not obvious. It can be an improvement on an earlier device or process, or it can be a completely new invention." Patents are important for both individual and social economic benefits. As Audrey Chapman put it, "Intellectual property regimes seek to balance the moral and economic rights of creators and inventors with the wider interests and needs of society. A major justification for patents and copyrights is that incentives and rewards to investors result in benefits for the society" [2]. But, of course, mere economic right is not sufficient to outweigh the need for further moral evaluation

associated with claims to intellectual property, despite whatever may be said about the scientific grounds or legal basis for adjudicating intellectual property claims.

Consider the question of application for patent in the case of live-born animal clones, in the setting of the judicial system of the USA. A decision issued on 08 May 2014 from the United States Court of Appeals for the Federal Circuit affirmed an earlier decision of the Patent Trial and Appeal Board (hereafter, "Board") that live-born animals cloned by way of the somatic cell nuclear transfer method (SCNT)—including here cattle, sheep, pigs, and goats—are themselves not patentable, in which case a scientist using the method is not eligible for a patent claim on the animals[3]. This decision has ethical implications related to deliberation about and resolution of the moral status of cloned animals.

The Legal Background: The ruling from the Federal Circuit Court (FCC) is not surprising, given the decision from the U.S. Supreme Court (USSC) in "Association for Molecular Pathology et al. *v*. Myriad Genetics, Inc., et al.," issued on 13 June 2013[4]. In the Myriad case, the USSC recognized that Myriad's "principal contribution" in its scientific research was to uncover "the precise location and genetic sequence of the BRCA1 and BRCA2 genes" (i.e., the genes involved in breast cancer oncogenesis). Referencing *Diamond v. Chakrabarty* (447 U.S. 303), the USSC considered the central question whether Myriad's research involved a legitimate claim on a "new and useful…composition of matter" (both *novelty* and *utility* being essential elements of claim eligibility for what is supposedly "a nonnaturally occurring manufacture or composition of matter") or instead a claim on "naturally occurring phenomena." The former clearly has to be (1) "a product of human ingenuity 'having a distinctive name, character [and] use" and (2) an action that is new "with markedly different characteristics from any found in nature."

If Myriad's argument were successful, then it would have a right "'to exclude others from making' its patented composition of matter under the Patent Act." Anyone who did so would infringe the patent and thus be legally liable. The USSC reasoned that although Myriad "found an important and useful gene," it nevertheless "did not create or alter either the genetic information encoded in the BRCA1 and BRCA2 genes or the genetic structure of the DNA." At issue here is the legally governing taxonomy, in this case what counts as "a product of nature" in contrast to an "invention," the latter characterized by the manufacture of "something new."

Delivering the opinion of the USSC, Justice Clarence Thomas clarified that Myriad's petition required the USSC "to resolve whether a naturally occurring segment of deoxyribonucleic acid (DNA) is patent eligible under 35 U.S.C. §101 by virtue of its isolation from the rest of the human genome." The USSC also considered the question of patent eligibility of "synthetically created DNA known as complementary DNA (cDNA), which contains the same protein-coding information found in a segment of natural DNA but omits portions within the DNA segment that do not code for proteins." Justice Thomas held that, "a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but that cDNA is patent eligible because it is not naturally occurring." For the purpose of entitlement to patent, *discovery* (no matter how "iterative" the research process), in short, does not entail *invention*. That said, however, it is noteworthy that the USSC left open the question whether "scientific alteration of the genetic code," i.e., "DNA in which the order of the naturally occurring nucleotides has been altered," presents a different inquiry…"

In the FCC's opinion, an animal cloned by way of SCNT "is an exact genetic replica of the adult mammal from which the somatic cell nucleus was taken." At issue in the earlier Board decision was whether the claimed clone "may be called a composition of matter or a manufacture." This disjunction is not clearly dispositive so as to represent accurately the ontological status of such an animal, since the former refers to a naturally occurring *substance* while the latter refers to human agency and an action that manipulates a natural substance in a *process* of manufacture. Thereby, one distinguishes conceptually two distinct categories, viz., substance and process. According to the applicable federal statute (35 U.S.C. § 101), both a "composition of matter" and a "manufacture" are allowable categories of "subject matter" for a patent claim to be issued. But, there are exceptions to eligibility—(1) "laws of nature," (2) "natural phenomena," and (3) "abstract ideas." Thus, a "naturally occurring organism" falls into the category of natural phenomena and is, therefore, not patentable.

In oral argument before the FCC, counsel for Roslin Insitute emphasized the idea of infringement on a patent claim in the case of a production of a clone of a clone, accounting for "obvious" phenotypic presentation that differentiates individual animals. However, the main point for substantiating the patent claim was the fact of "time delay" in the process of production, i.e., the time frame from donor to copy/clone produced, which then ostensibly allows the claim that the clone is an *invention* and, therefore, eligible for patent against infringement on the manufactured "product." But, the FCC insisted on the fact of genetic identity (*genetically* donor = clone, despite individuation of donor and clone and time delay) as controlling for the purpose of argument, rather than the factor of time delay privileged in argument by Roslin. DNA, according to the USSC decision in Myriad, is not patentable subject matter; in which case, an animal having genetic identity (i.e., identical DNA, such as a clone has) is thereby not patent eligible.

The Scientific Ambiguity: The foregoing legal determinations presuppose a reasonably clear conception of what counts as an organism and what is meant by 'naturally occurring.' This seems, at least *prima facie*, to be a matter of *scientific* proposition and only thereafter a legal definition, since it is the science of biology and not positive law that is to govern the validity of an empirical claim that is then taken up into legal discourse for a purpose such as that of adjudication of patent claims. But, then, the scientific claim itself presupposes an *ontological commitment* as to the *being* of the organism, which is by no means clear for either theoretical or experimental biologists. And, where "ontological status" of an organism is ambiguous, more often than not there is associated ethical ambiguity about the morally permissible disposition of the organism in question.

Indeed, Stephen Talbott correctly reminds that, "biologists have gone on for decades using the language of meaning while remaining content never to *reckon* with it… [5]." As Pepper and Herron notes yet more basically, "Among biologists, there is no general agreement on exactly what entities qualify as 'organisms' [6]." In fact, given the ambiguity of the concept among biologists, rather than speak of "organism" in terms of distinct categories, Pepper and Herron construe organisms to be "continuously variable." To put the point differently, as Talbott explains, "Because every local activity of the organism must find its meaningful place within the encompassing activity of a striving, developing, self-transforming whole, there can be no fixed syntax, no mechanical constancy of relations among the parts."

The above claim is meaningful also in terms of a position advanced by philosopher of biology Michael Ruse, who has considered the status of organisms so as to be understood in three senses—ontological, methodological, and epistemological[7]. By 'ontological' Ruse means "the ultimate status of the entities of the organic world;" by 'methodological' he "refers to the question of organization;" and by 'epistemological' he intends that sense that "refers to the relationship between theories," e.g., "in particular whether the theories of the biological sciences can be shown to be logical consequences of the theories of the physical sciences."

Bearing Ruse's distinctions in mind, consider, for example, Schneider and Grosschedl (2007) observing that, "The clarification of the cause-and-effect relationship of nuclear organization and the function of the genome represents one of the most important future challenges. Further experiments are needed to determine whether the spatial organization of the nucleus is a consequence of genome organization, chromatin modifications, and DNA-based processes, or whether nuclear architecture is an important determinant of the function of the genome[8]." Surely, this question of cause-effect relationship remains unanswered in the case of the somatic cell that is used by an investigator in the context of SCNT method. Such an investigator is aware of the nuclear architecture of the somatic cell, understands to some degree the spatial organization of the nucleus of this cell in relation to the whole of the cell, removes the nucleus in view of any number of empirical claims about that cell's genome organization, chromatin modifications, and DNA-based processes, etc. Indeed, there would be no SCNT method were it not for the hypothesis at the base of this method that assumes much of this without, however, being precisely clear as to cause-effect relations and determinants.

Randall Prather reminds us that when Hans Spemann first described the concept of cloning, "He wanted to test the theory that cells become irreversibly differentiated because they inherit an unequal amount of 'nucleoplasm' and thus are not totipotent," otherwise understood as the concept of "nuclear equivalence[9]." Subsequent research has continued investigations of "nuclear remodeling" and reprogramming by way of transfer of nuclei into the cytoplasm of oocytes, the operating assumption being that "structure confers function," i.e., there is an "exchange of proteins between the donor cell nucleus and the oocyte cytoplasm" which then "remodels the chromatin such that the nucleus is reprogrammed to behave as though it were a pronucleus [10]."

In their original paper outlining the experiment that resulted in Dolly, Wilmut *et al*., explained the purpose of their method: "an opportunity to investigate whether cellular differentiation to that stage [of fertilization of a mammalian egg] involved irreversible genetic modification[11]." The Dolly experiment investigated "whether normal development to term is possible when donor cells derived from fetal or adult tissue are induced to exit the growth cycle and enter the G0 phase [i.e., quiescence] of the cell cycle [of replication] before nuclear transfer." For these scientists, the experiment confirmed that, "differentiation of [an adult cell] did not involve the irreversible modification of genetic material required for development to term." Further, for them the results "indicate[d] that nuclei from a wide range of cell types should prove to be totipotent after enhancing opportunities for reprogramming by using appropriate combinations of these cell-cycle stages." Finally, the authors opined, "Birth of the lamb shows that during the development of that mammary cell there was no irreversible modification of genetic information required for development to term. This is consistent with the generally accepted view that mammalian differentiation is almost all

achieved by systematic, sequential changes in gene expression brought about by interactions between the nucleus and the changing cytoplasmic environment [12]."

One may, therefore, ask: Is it reasonable to assert that an *un-manipulated* "natural state" somatic cell (a) counts as an organism and that (b) it is naturally occurring, consistent with the evidential empirical claims of cell biology? Surely, such a cell is naturally occurring. But, whether it counts as an organism *in and of itself* depends on meaning in use. Cell biology identifies its domain of investigation, viz., cell structure and cell function, premising "the cell" as "the fundamental unit of life." From the perspective of cell biology, a single cell *can* count as an organism, e.g., when one has in mind a unicellular entity[13]. In the context of SCNT, a somatic cell is taken from a multicellular organism, yet it can be said that this cell has its own "physiological independence" or "physiological discreteness" for the purpose of cell biology, even as a cell is "physiologically integrated" with the multicellular organism from which it is extracted. One can consider, thus, whether a somatic cell that is to be used for the purpose of SCNT counts as a "unitary organism" (in the sense articulated by Santelices) or as a "paradigm organism" (in the sense expressed by Wilson) [14], [15].

Either way, it seems that, "Many of the commonly used organism criteria are in fact descriptions of various boundaries on functional integration," so that "The essence of the organism syndrome is *a discrete package of functional integration*." A somatic cell would then, in this sense, be construed as such a discrete package. The latter proposition, taken as probably true, therefore yields a practical definition for 'organism': "a complex structure of inter-dependent and subordinate elements whose relations and properties are largely determined by their function in the whole[16]." But, when one examines reports of ongoing DNA studies, the discourse suggests ongoing dynamics further complicating the question of definition[17]. In the latter discussion, at issue is what contemporary science understands from the *genetics*, of course; but also, what they do not understand currently from the *epigenetics* in organismal development.

Thus, Talbott comments, "The activity of individual genes reflects the choreography of chromosomes, which reflects the larger choreography of the nucleus, which reflects the choreography of the cell and organism as a whole. Who, then, is sculpting whom?" Accordingly, there is ample reason for us to say, as Talbott summarizes, that biological research informs us of "the importance of organismal context, and of the organism's plasticity, and of its dynamism, and of the complexity of its interweaving process, and of the causal ambiguity of our explanations." What this means in terms of the taxonomy at issue, is that, "Organisms cannot be fully elucidated in terms of the definitive lawfulness so satisfactory to the physicist—a lawfulness lend in itself to the application of mathematics and other reduced 'skeletons' of language[18]." "Organisms," properly understood, "are revealing themselves as intentional wholes not governed by any particular parts[19]." Thus, despite the technologies with apparent successes of SCNT method in the case of animal cloning, "Epigenetics and the organism's almost unfathomably complex and intricate skill in managing its genes" require us to reconsider and disabuse ourselves of "the notion that DNA embodies a linear code that spells our destiny"—or, indeed, the destiny of any other biological organism at whatever level of organization and complexity.

But, once a somatic (diploid donor) cell (e.g., a mammary epithelial cell with complete genome of the individual animal, e.g., a Finn Dorset ewe as in the case of Dolly the sheep) is "manipulated" by way of the SCNT method, with the cell's nucleus and genetic content

extracted (enucleated at metaphase II), and the cell nucleus and genetic content transferred into another cell (i.e., into the recipient cytoplasm of an unfertilized ovum from which its own haploid nucleus has been removed, e.g., as in the case of the ovum taken from a Scottish Blackface ewe for the Dolly experiment), and then these two cells juxtaposed and subjected to an electric pulse to fuse them and start cell division, then it may be said that a *process* of *manufacture* surely occurs thereby. It is a process of *asexual* reproduction that contrasts to "normal mammalian sexual reproduction," with the otherwise natural process of "sperm-mediated fertilization…subverted in SCNT [20]."

The scientist in this case manipulates what is a naturally occurring composition of matter and alters it according to the intent of the SCNT method. Rather than a natural substance that is a naturally occurring composition of matter, one now has a substance the *material composition* of which has been altered by way of SCNT method in a way that does not occur naturally. This is why one says the clone is both novel and useful. It is reasonable to assert, then, that the "product" from the SCNT method is no longer *in se* "naturally" occurring, even if it cannot be said (as a matter of contrast) that this is an "artificially constructed life form" such as pertains to genetic engineering techniques of synthetic biology. The latter allows for a distinction of "synthetic DNA" and "natural DNA," thus a distinction of a synthetic or semi-synthetic "artificial" life-form and a natural life-form[21].

It is, therefore, important to ask the question (the implicature of which is legal, ethical, and scientific): Does the fact of *mixture* of naturally occurring cell components constitute an "invention?" The SCNT *method* itself is already patented, of course; so, this is not at issue in present case as reviewed by the USSC and the FCC. What is at issue is whether the end product of a SCNT application, viz., *the live-born cloned animal* (as distinct from the manipulated/altered somatic cell)—is the "equivalent" of an invention even if it remains a composition of matter. If the method of SCNT merely *discloses* "a secret of nature," e.g., discloses the natural mechanism of genetic replication despite the alteration/substitution of the nucleus as a cell component, then this is not an invention *per se* but only a disclosure of the way nature operates at the level of the cellular organism.

Under the applicable statute in the USA, as noted above, such disclosure is not patentable—"patents cannot issue for the discovery of the phenomena of nature." Indeed, the building blocks of the animal clones involved in the patent application are still the "natural DNA" codified in the base-pairs ("chemically joined nucleotides") of cytosine-guanine (C-G) and adenine-thymine (A-T); and not, e.g., a composition such as results from the most recent "artificial DNA" base pair of "X-Y" that has been added to these natural base-pairs to create a new genetic content and, thus, a new synthetic life-form. The latter product of synthetic biology may count ontologically, legally, and, insofar as any ethical issue arises, as an invention rather than as a process of human ingenuity that merely duplicates a natural process.

Given the contrast, it is not surprising that the Board "concluded that the claimed subject matter was ineligible for patent protection" under the defined statute, "because it constituted a natural phenomenon that did not possess 'markedly different characteristics than any found in nature.'" Arguably, then, the distinction here provides a central criterion by which to determine what counts as "manufacture"—simply, an item of manufacture must be markedly different in characteristics from those characteristics found in a naturally-occurring entity. Where the two are "identical" or "substantially identical," or are "produced by identical or substantially identical processes"—each of these predicates by no means transparent in its

meaning—then there is no legitimate patent claim for the item produced, even if the prior item (e.g., the donor animal) is a naturally occurring animal. Moreover, the FCC (as did the Board) accounted for prior artificial cloning methods, viz., embryotic nuclear transfer and *in vitro* fertilization, to hold that the cloned animals were both "anticipated" and "obvious," despite the difference in method (SCNT), and thus indistinguishable from a product issued from these methods.

Ethical Ambiguities at Issue: Given the foregoing overview of legal and biological elements of the question before the courts in the USA, the judgments taken, while important generally for *animal* cloning *per se*, can also be considered presumptively guiding in any moral question involving human reproductive cloning, just in case researchers should be inclined to translate such results into the clinical setting of human reproduction (including here any goals associated with human fertility by way of *in vitro* technologies and associated prospects of genetic enhancement).

We may be reminded that Stanford University Nobel laureate Joshua Lederberg has already (in 1966) written in favor of human reproductive cloning. Commenting on the scientific desideratum of a "new evolutionary theory needed to model a self-modifying system that makes imperfect plans for its own nature," Lederberg championed the goal of human eugenics against "the cultural process" that "poses contradictory requirements of uniformity (for communication) and heterogeneity (for innovation)" and, thus, an impediment to eugenic goals [22]. "Humanistic culture rests on a definition of man which we already know to be biologically vulnerable," Lederberg observed. "Inevitably," therefore, so he opined, "biological knowledge weighs many human beings with personal responsibility for decisions that were once relegated to divine Providence." Commenting on "tempered clonality," Lederberg anticipated that "we would at least enjoy being able to observe the experiment of discovering whether a second Einstein would outdo the first one." Indeed, taking a global perspective on the implications of developments in molecular biology, specifically "any conceivable program of calculated eugenics," Lederberg asked: "Western culture and its limited population is being succeeded by a much broader world culture. Is there much point in setting eugenic standards relevant only to a small minority of the world's population even as we watch the unprecedented breakdown of intercultural barriers?"

Writing in 1994, and accounting for developments in the period since Lederberg's contribution to the periodical literature on the subject, John A. Robertson allowed that, "The idea of splitting off cells from embryos to clone human beings sounds so bizarre and dangerous that one would think the practice should not be permitted [23]." Yet, at that time Robertson argued that such cloning promised to be ethically acceptable. Noting that the scientific procedures had not succeeded with mammals (and only with frogs at the time) and appeared "highly unlikely to be accomplished in even the mid-range future," even so, were scientists so inclined, Robertson remarked, "If this form of cloning were possible, scientists could fabricate as many copies as one wished of any available human genome, *subject only to the limits of uterine or artificial gestation*" (emphasis added).

Accounting for various uses of cloning, Robertson argued that, this scientific enterprise was "neither so harmful nor so novel that all research and development should not stop until the ethics of the practice are fully aired, or that governmental restrictions on cloning research or applications are needed." That, of course, changed with the production of Dolly (1996-1997); and the near-term prospect of human reproductive cloning moved the matter center-stage as a

matter of public policy and government regulatory intervention. Leon Kass and James Wilson, surveying the scene of public opinion at the time, underscored the fear: " 'I a child and Thou a lamb,' despite our differences, have always been equal candidates for creative making, only now, by means of cloning, we may both spring from the hand of man playing at being God [24]."

Granted, at our point in time, applicable national and international regulatory instruments continue to proscribe human reproductive cloning. In June 1997, following President Bill Clinton's ban on federal funding that might support human cloning research, the US National Bioethics Advisory Commission recommended a moratorium on reproductive human cloning[25]. Any legal decision to permit patenting in the case of human reproductive cloning would contradict international commitments to "democratic principles of dignity, equality, and mutual respect of men," as stipulated in the Preamble of UNESCO's constitution and as reiterated in the Universal Declaration on the Human Genome and Human Rights (1997) hereafter UDHGHR)[26].

So long as rights recognized under international law are considered to be "human" rights (thus distinguished in principle from social, political/civil, economic, cultural rights) reproductive human cloning would entail a morally problematic situation: viz., in the case where "patented" "human clones" may not be recognized ontologically to have the status of the naturally occurring human being and so be *diminished in moral status* so as not to be permitted a claim to the ordinary human entitlements of dignity, equality, and mutual respect. The United Nations Convention on Biological Diversity of 1992 anticipated the probability of ongoing scientific research and developments in biomedical technology so as to emphasize the genetic diversity of humanity, with the expressed injunction that there must be no interpretation of a social or political nature that would call into question "the inherent dignity" or "the equal and inalienable rights" of "all members of the human family[27]." The introduction of a "human clone" into the natural human population that now expresses this genetic diversity would presumably add to that diversity but also raise any number of moral and political questions.

Clearly, a human clone having the *legal* status of a *patented entity* would have neither inherent dignity (intrinsic worth, rational nature, etc.) nor equal and inalienable rights such as the naturally occurring human being has—and, importantly, has not only as a matter of conventions of law (thus civil right) but as a matter of natural right. Patenting in the case of human reproductive cloning would open the door to prospective discrimination against human clones in any number of ways, contrary to Article 2(b) of the UDHGHR that, "dignity makes it imperative not to reduce individuals to their genetic characteristics and to respect their uniqueness and diversity." Here, 'uniqueness' may not be interpreted negatively so as to authorize or justify the reductive argument according to which a human clone would be identified merely or primarily genetically. Hence, research integrity is a matter of anticipation (e.g., the moral virtue of prudence, having forethought that precludes vice on the side of scientific excess or scientific deficiency) as well as currently permitted practices under both national and international regulations. The UNDHGHR (Article 10) aptly stipulates that, "No research or research applications concerning the human genome, in particular the fields of biology, genetics and medicine, should prevail over respect for the human rights, fundamental freedoms and human dignity of individuals or, where applicable, groups of people." Thereby, developments in human genetics may not proceed merely for the sake of advancing knowledge and must maintain the scientific integrity so expressed in

the declaration. Therefore, as Article 11 of the Declaration states the point explicitly: "Practices which are contrary to human dignity, such as reproductive cloning of human beings, shall not be permitted."

The judicial assessments in the USA, deliberating and deciding on the question of patenting of animal clones, provide important barriers to human reproductive cloning research. Thereby, they safeguard the long-standing and time-honored moral and legal commitment to human dignity that would otherwise succumb to hubris or to posit of merely instrumental ends. It is meritorious indeed that, were human reproductive cloning to be permitted, as a matter of moral and legal principle patenting of human clones would be proscribed even more so, ensuring human accountability to present and future generations.

Author's contribution:
Author developed the conceptual idea, data collection, data analysis and manuscript writing.

Conflict of Interest: Declared none.

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