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Twenty years of transgenic animals: Are some inventions SO important as to NOT be entitled to full patent protection?

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Abstract

Transgenic animals have been known for 30 years but the first transgenic mammal patent dates from 1988. This first patent, for the Oncomouse which has been created to be susceptible to developing tumors, has generated large revenues for its licensee, DuPont. Equivalent patents were only granted in Canada and Europe after litigation and amendment of the patent. DuPont has strictly enforced its patent rights but this has led to debate over whether it is impeding research.

Keywords: Transgenic animals; Transgenic mammals; Oncomouse; Oncogene; DuPont; Harvard mouse; Patenting organisms

1. Introduction

April 12, 2008 marks the 20th anniversary of the first patent granted on a non-human mammal. The patent described a mouse carrying an activated oncogene sequence that led to its superhero-sounding name: Oncomouse. Over the life of the patent, the Oncomouse has certainly proved to be super at generating licensing revenue for DuPont, which owns the patent and has licensed the patent strictly. What effect did this patent have at the time it was granted? And what effect has it had in the ensuing 20 years? This article will discuss the status of patenting living beings when the Oncomouse patent was granted, as well as the details of the Oncomouse patent, and the effects the Oncomouse patent has had on the patenting and commercialization of transgenic mammals.

2. Transgenic animal technology

The idea of a transgenic animal originated in the 1970s. All living organisms contain genetic material in the form of DNA or RNA. This genetic material (called the genome) carries the instructions for making the proteins necessary to keep the organism alive and growing. Each segment of the organism's genetic material that codes for a protein is called a gene. The cell contains its own machinery for reading its genetic material and synthesizing proteins.

The concept of transgenic animals uses the cell's own machinery to the scientist's advantage. The scientist creating the transgenic organism introduces a segment of DNA that codes for a protein foreign to a host cell (called a transgene) somewhere into the host cell. As the host cell's normal mechanisms for producing proteins from its genome (called translation) continue to function, the cells that were inoculated with the foreign gene will also make the proteins encoded by the transgene, making the host organism transgenic.

Two well-known types of transgenic animals are knock-ins and knock-outs. A "knock-in" organism has a transgene inserted into a specific portion of its genome, allowing for over-expression of the transgene product. "Knock-outs," by contrast, have had genes inactivated by insertion of mutated genes into the host genome. "Knock-ins" and "knock-outs" have been highly useful for studying diabetes, cancer, heart disease, and other common maladies.

The insertion of the transgene into the host organism's genome results in the vast majority of cells not containing

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the transgene. However, for the process to be successful, the transgene must be passed onto its progenitor cells. If only one generation of cells produced the transgene product of interest before dying, there would be no useful yield of product.

The first published transgenic animal was described by Gordon et al. at Yale in 1977 [1]. Building on the work of Jaenisch and Mintz [2], who showed that DNA placed into mouse blastocysts could be found in the resultant offspring, Gordon and his colleagues genetically transformed mice embryos by microinjecting DNA. Although only two of the 78 embryos showed DNA sequences homologous to those injected (suggesting successful insertion of the transgenic material), the experiment served as an enticing proof of principle.

Building on Gordon's success, other scientists perfected the technology further. In subsequent years, transgenic mice were created containing human globin genes [3,4]; rabbit globin genes; the chicken transferrin gene; and a functionally rearranged immunoglobulin gene. Palmiter et al. took the technology a step further, creating a transgenic mouse containing the rat growth hormone gene fused to a heavy metal-inducible metalothionein promoter sequence (promoter sequences facilitate the translation of genes); a thymidine kinase gene fused to a metalothionein promoter sequence; and the human growth hormone gene fused to a metalothionein promoter sequence.[1]

3. Development of the Oncomouse

In the late 1980s, Drs. Timothy Stewart from University of California, San Francisco, and Philip Leder of Harvard College successfully bred a mouse into whose genome they had inserted an activated oncogene sequence by microinjection. The activated oncogene sequence makes the mouse susceptible to breast cancer by expression of the oncogene sequences in mammary tissue. Transgenic mice that were susceptible to developing tumors were quite valuable for many reasons:

- Because of the size of the mice and their hypersensitivity to developing tumors, much less material would be needed not only to test the potential carcinogenicity of test compounds, but also to test their ability to treat tumors. This decreased the costs and time involved with basic research.
- The mice will develop the tumors faster because of their predisposition to develop tumors. This also led to faster and less expensive research.
- The information gained from testing compounds in these mice should be more relevant to humans because both are vertebrates. This is important because, before mice, the best indicator of a compound's ability to cause cancer was an indirect measure called its mutagenicity, discussed below.
- This system will test the carcinogenicity of a compound, rather than its mutagenicity. The original test for a compound's ability to trigger mutations in genomic DNA, called the Ames test, involved treating bacteria with increasing amounts of a compound until mutations were seen in the bacterial colonies.
- The transgenic animals could serve as sources of transformed cells, offering another avenue for testing compounds. These cells could be induced or down-regulated whenever an inducible promoter sequence was present in the oncogene sequence.

4. Genesis of the Oncomouse patent

Drs. Stewart and Leder applied for and received a patent on this technology in April 1988. The abstract of their patent (US 4,736,866) described "a transgenic non-human eukaryotic animal whose germ cells and somatic cells contain an activated oncogene sequence (namely a c-myc oncogene, claim 6) introduced into the animal, or an ancestor of the animal, at an embryonic stage." The '866 patent specifically excluded humans from the scope of its 12 claims, but otherwise was quite broad; it covered "any transgenic animal...that contains in all its cells an activated oncogene that had been introduced into it or an ancestor at an embryonic stage." Claim 2 discloses a chromosome within the transgenic animal including an endogenous coding sequence that is "substantially the same" as the oncogene sequence, but that is inserted into the transgenic animal genome at a site different from the endogenous sequence (claim 3), and that is controlled by a different promoter sequence than that of the endogenous sequence (claim 4). The '866 patent also claims the use of an inducible (claim 5) viral promoter sequence (claim 7) to control transcription of the transgene, such as MMTV (claim 8) or RSV (claim 9), or alternately, a synthetic promoter sequence (claim 10). This would ostensibly allow for the non-infringing use of a bacterial promoter sequence or some other non-viral promoter sequence (assuming it was not synthetic) in a similar transgenic technology.

While claim numbers 11 and 12 claim the use of a rodent, specifically a mouse, as a host for the transgenic technology, the abstract immediately preceding the claims section also discusses the use of "any species" for the transgenic technology, such as a primate. Because of the complexity of the primate genome compared to a rodent genome, despite its usefulness because of its similarity to the human genome, this technology would probably require a substantial amount of effort to develop. In fact, transgenic rats have only just recently been developed.

Soon after receiving the '866 patent in 1988, Drs. Stewart and Leder granted an exclusive license to DuPont, who had funded their research. Later, Harvard College applied

[1] These first attempts at creating transgenic animals were not commercialized as extensively as the Oncomouse, perhaps because, as "proofs of principle," it was more technically feasible to start with genes that were easier to manipulate and insert into the mouse genome.