



Submitted by Dr. Steven M. Carr

The July/August edition of *Bio Business* includes, on page 7, a short item on the July 2013 US Supreme Court (SCOTUS) unanimous decision rejecting the attempt by Myriad Genetics to patent the DNA sequences of the naturally-occurring breast cancer associated BRCA1 & 2 genes [18 US 192 (2013)]. The item incorrectly refers to cDNA as 'composite DNA' rather than 'complementary DNA.' In the context of bio-business, the difference is not insignificant.

SCOTUS in essence recognized that BRCA genes are 'products of nature' and thus on accepted principles not patentable. Such genes include expressed exon and intervening intron regions, as well as upstream and downstream promoters, enhancers, and other paraphernalia by which genes get things done. The BRCA1 gene region in vivo extends over 117,000 base pairs.

In contrast, complementary DNA (cDNA) is a laboratory artifact, made in vitro by isolating the expressed messenger RNA (mRNA) transcribed and processed from the original gene, and 'reversing' the Central Dogma to make a DNA copy from mRNA. cDNA is in a certain sense a 'composite' molecule, since it is equivalent to what would be obtained by joining widelyseparated exon sequences.

Non-scientists including members of the biotech industry have gotten sidetracked by the notion that a "composite" cDNA sequence is indistinguishable from the naturally-occurring gene sequence in my cells. By implication, it then seems SCOTUS has left open the possibility that someone could still patent "my gene" and no-one could tell the difference. This of course fails to differentiate the patentable process of creating an artificial DNA from the result that the sequence resembles a non-patentable 'real' one.

The SCOTUS decision explicitly leaves open several questions, particularly the patentability of cDNAs as synthetic sequences created literally from scratch. As has been recognized in the scientific literature ("Nature," 18 June 2013), cDNAs in and of themselves are unlikely to attract much patent interest, because (1) the method is "well understood, widely used, and fairly uniform" and hence not a strong candidate for protection, (2) the necessary information to make a cDNA is typically in the public domain, for example BRCA sequences are in GenBank, and (3) cDNAs are generally of commercial interest only as one of many analogous components in a comprehensive diagnostic test, in which case the test itself is likely the patentable IP.

These questions extend to other synthetic DNAs, such as the short (<50 base pair) oligonucleotides ("oligos") incorporated as probes into microarrays. For example, the "ArkChip" is a platform for simultaneous "re-sequencing" of complete mitochondrial DNA (mtDNA) genomes from multiple species ("Laboratory Focus," March 2009). In this application, the sequences of the oligos are implicit in known species-specific reference mtDNA sequences in the public domain (GenBank). Fabrication of oligos on the microarray is by a patented, proprietary photolithographic method. The license agreement with the manufacturer prevents a third party from buying microarrays made from to a commissioned design. However, there is nothing to prevent "reverse engineering" of a homologous microarray for an identical or similar species set. For example, our microarray includes a human mtDNA sequence, based on a different but homologous sequence used in a microarray that the manufacturer markets commercially.

In our microarray, a synthetic reference sequence, based on a natural sequence but 'tweaked' by modification of a few or many nucleotides to improve signal uniformity (and co-incidentally create an artificial sequence that does not exist in nature), might also be patentable. Where a gene sequence of clinical interest exists in multiple allelic forms, assembly of an artificial consensus sequence comprising the most common nucleotide at each variable position would be involve "creation, invention, and discovery," the important desiderata for patent protection.

Later in the same month at the SCOTUS decision, Myriad filed suit against competitors who have marketed BRCA tests of their own, based on so-called NextGen sequencing methods ("Cancer Discovery," September 2013). The competitors point out that these are novel biotechnologies that do not employ any synthetic DNAs protected by Myriad's patents. Myriad asserts patent protection of DNA preparation and post-sequencing bioinformatic methods at either end of the sequencing pipeline. Though these methods might be considered generic enough to obviate patent protection, future court decisions may turn on fine points of the broad claims implicit in patent law.

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