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Protecting intellectual property rights in SELEX and aptamers

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Abstract

In an earlier article, the author explained the technology of a particular field of combinatorial chemistry—using artificial DNA/RNA sequences—aptamers—as the screening ligand, and the SELEX protocol for exposing an aptamer library to the desired target. In the present article the author explores the types of claims currently being sought and granted for this technology. He considers the relevant legislation, and sets out his views on the validity of various approaches to seeking effective patent protection in this emerging technology, and the ways that protection may develop. He also investigates the potential value of seeking registered design rights in this area.

Keywords: Aptamers; SELEX protocol; Combinatorial chemistry; Oligonucleotide ligands; Process patents; Product patents; Product-by-process patents; Design right; Binding footprint; Sequence claims; Homologous sequence claims; Structure claims

1. Introduction

In my previous article, the science behind SELEX and aptamer technologies was explained [1]. I briefly considered how they were defined for the purposes of patent protection. It was readily apparent from that discussion that patents for those technologies have already been liberally applied for and only slightly less promiscuously granted, particularly by the USPTO. However, the desire to acquire patents in this field can be readily understood when the value of such rights is considered. For example Gilead Sciences Inc licensed its SELEX™ processes to Archemix Corp. for $17.5 million, [1] in October 2001.

The present article focuses on the form and wording of the patents applied for to date and then briefly considers the possibility of using design rights to protect the three-dimensional structure of aptamers.

2. SELEX protocol patents

The history of SELEX patents goes back to the very beginnings of the technology in 1990, when Gold and Tuerk patented their discovery immediately after publishing it in *Science* [2]. The Gold group were also the first to coin the term SELEX. [2]

Since the first application, the patenting of refinements on the SELEX protocol (see Table 1 below) does not appear to have presented any great difficulties, although inevitably as the number of patents increases and the technology becomes more commonplace there will be increasing difficulties in generating variations in the protocol sufficient to escape challenges to their novelty or inventiveness or both.

There may, however, be greater difficulties in assessing to what extent "product by process" claims as envisaged under Article 64(2). [3] EPC will be applicable to patents for SELEX protocols. The problem being that the aptamers generated by a SELEX protocol against a particular target on one occasion will not or may not bear any sequence homology to those generated on another. Therefore, it would be impossible to identify with any certainty what the product of a SELEX protocol is (other than being an aptamer) in any way

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[1] Gilead also owns the "SELEX" trade mark.

[2] The term "aptamer" was first coined by the Szostak group who published their seminal work [3] only a month after the Tuerk and Gold paper.

[3] Article 64(2): If the subject-matter of the European patent is a process, the protection conferred by the patent shall extend to the products directly obtained by such a process.

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Table 1
Patented variations on the SELEX protocol*

SELEX protocol	Application	Related patents
Photo SELEX	Aptamers containing photoreactive groups capable of binding and/or photo cross-linking to and/or photo-activating or photo-inactivating a target molecule	US patent no. 5,763,177; US patent no. 6,001,577; US patent no. 6,291,184; US patent no. 6,458,539
Chimeric SELEX	Combination of aptamers generated from two parent libraries	US patent no. 5,637,459
Blended SELEX	Combination of aptamers with other non-oligonucleotide groups such as peptides	US patent no. 5,683,867; US patent no. 6,083,696
Counter-SELEX	Method for generating aptamers that can discriminate between highly related molecules, such as theophylline and caffeine	US patent no. 5,580,737
Solution SELEX	Method for high efficiency partitioning between oligonucleotide with high and low affinity for a target molecule	US patent no. 5,567,588
Chemi-SELEX	Method for covalently linking an aptamer to its target	US patent no. 5,705,337
Tissue SELEX	Method for generating aptamers capable of binding to complex tissue targets such as collections of cells e.g. Tenascin-C in diseased tissue	US patent no. 5,789,157; US patent no. 6,376,474; US patent no. 6,232,071
Parallel SELEX (not strictly based on SELEX but adopts many of the basic principles)	Process using oligonucleotide ligands to facilitate binding with other reactant molecules, which can then be screened against predetermined targets. The oligonucleotide bound to the selected reactant molecule can then be amplified for further rounds of selection	US patent no. 5,858,660
Transcription-free SELEX	Describes a method for ligating random fragments of RNA bound to a DNA template to form the oligonucleotide library. As there is no transcription step more diverse nucleotides can be incorporated	US patent no. 6,387,620

*Table 1 is not simply a review of US patents but reflects the commercial reality that US companies and inventors are attempting to appropriate the whole field of SELEX technology and in so doing have defined the terminology of those technologies.

appropriate to patentability. [4] As such it is possible that pure product by process claims will not be applicable to this technology, although the author accepts that the courts and the EPO may take the opposite view. However, the companies which own the rights to the SELEX protocols may well seek to exploit them by striking reach through agreements [5] with those wishing to license the technology and thereby partially avoid the problem.

3. Aptamer patents

3.1. General considerations

Whilst trying to separate aptamers from the SELEX technology by means of which they are produced is somewhat difficult, it is however necessary in order to consider how the approach to protecting the IP rights has changed in the space of a few years and needs to change further. The general trend has been to move away from patenting the SELEX means and towards trying to protect the aptamer end products, although many "method" form applications are still being filed (see [4,5], for example).

Claims for aptamers per se are unlikely to present inherent difficulties to the EPO or the USPTO. Whilst it could be argued that simply generating an aptamer for a particular characteristic, such as binding an identified target molecule, cannot really be inventive once the principles of SELEX are appreciated, this line of reasoning has been raised and dismissed before in relation to similar technologies.

A typical example of where such an argument has previously been found to be specious is the decision of an EPO Technical Board of Appeal [6]. In that case the main claim of the patent in question was for a method of preparing cultures of the yeast *Phaffia rhodozyma* producing high levels of the carotenoid astaxanthin by use of the non-specific mutagen *N*-methyl-*N*′ nitro-*N*-nitrosoguanidine. The claim was rejected by the examining division. Before the TBA the applicant, as an auxiliary request, sought a patent for its deposited strains of *P. rhodozyma* that had already been mutated by means of the described method and which displayed the desired enhanced astaxanthin production. The TBA allowed the auxiliary claim explaining that the prior art would have indicated to the skilled man the method of using of a non-specific mutagen and therefore broad claims to the products of such a process were obvious and as such unpatentable. However, the *successful results* of using such a method were in themselves inventive and therefore the deposited strains could be patented. The Board emphasised:

[4] In the sense that unless the product can be clearly identified it would be difficult to enforce the claim, particularly in an infringement action. However, this point will need to be decided by the EPO and the courts.

[5] By claiming a percentage on sales on any products generated using the protocol.