

## Research Education

# INTELLECTUAL PROPERTY RIGHTS ISSUES FOR RESEARCH TOOLS IN BIOTECHNOLOGY RESEARCH

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**Abstract:** The research tools refer to the resources researchers need to use in experimental work. In Biotechnology, these can include cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry libraries, drug and drug targets, clones and cloning tools (such as PCR), method, laboratory equipment and machines, database and computer software. Research tools therefore serve as basis for upstream research to improve the present product or process. There are several challenges in the way of using patented research tools. IP issues with regard to research tools are important and may sometime pose hindrance for researchers. Hence in the case of patented research tools, IPR issues can compose a major hurdle for technology development. In majority instances research tools are permitted through MTAs for academic research and for imparting education. TRIPS provides a provision for exception to patent rights for experimental use of patented technology in scientific research and several countries including India have included this provision in their patent legislation. For commercially important work, licensing of research tools can be based on royalty or one time lump sum payment. Some patent owners of important high-end research tools for development of platform technology create problems in licensing which can impede research. Usually cost of a commercially available research tool is built up in its price.

**Key words:** Biotechnology; Research tools: Patent Rights; Experimental use; TRIPS.

## What are research tools?

Research tools are essential requirements for scientific work. They are intermediate tools needed to develop end product. The researchers are consumers of research tools because they necessarily require using research tools for their experiments. These can include cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry libraries, drug, and drug targets, microarray, clones and cloning tools (such as PCR), method, laboratory equipment and machines, database and computer software (NIH, 1998).

## Importance of research tools

Biotechnology involves use of living things in engineering, technology and medicine. Biotechnology covers the application of all biological systems, which comprises enzymes, organelles, animal/plant tissues or whole cells and microorganisms. Biotechnology majorly comprises several vital fields such as medical biotechnology, environmental biotechnology, agricultural biotechnology, microbial biotechnology. In medicine, biotechnology is mainly involved in drug production, pharmacogenomics, gene therapy and genetic testing.

Research tools in biotechnology are needed to carry out research to build the foundation for downstream research for the development of drug, pharmaceutical and medical treatment and

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help in diagnosing diseases. Likewise they may be used for development of improved crop varieties (resistance to biotic and abiotic stress, yields), to produce medicine (recombinant vaccines, therapeutics proteins or peptides) and to diagnose and treat diseases. Business of some biotech companies comprises developing research tools as for them research tools are the end products. Research tools facilitate development of new downstream product/technologies at a faster pace. They do not comprise final product available in the market. Research Tools are innovative in nature.

Research tools therefore serve as basis for upstream research to improve the present product or process. These are very important for technological advancement since they facilitate development of new products at a faster pace.

### IPR issues

In case of patented research tools, IPR issues may comprise a major hurdle for technology development although in majority instances research tools are permitted for academic research. For commercially important work, licensing of research tools will be an important method to solve this problem. The impact of patent protection on universities, government labs and nonprofit research organizations are different than that on commercial research organizations.

### Patenting of research tools in the field of biomedical sciences

Since licensing of research tool would increase cost of research, the research tool should be selected based on whether it is foundational research tool and if it is essential for further research and development (R&D) to develop innovative technology (Heller and Eisenberg 1998). There are some research tools that are non-rival in use. Such tools include microarray, PCR, combinatorial libraries etc. For maximization of social benefit, it is required that the research tools be made available to researchers on easy terms. In many instances it is seen that the patent holder charge higher royalty from commercial organization in comparison to universities and academic organization. Usually royalty elements

are built up in the cost of the reagents or devices. In some instances free access is allowed to the databases such as GenBank, NCBI, EMBL etc. In a few cases data sharing is also a viable option such as in case of EST's.

Research tools in drug discovery present an example of the difficulties in protecting intellectual property when technologies involve complex biological systems as research for drug discovery is often multidisciplinary. Broad patents in such cases have been considered to stifle research on development of useful drugs and are also seen to be vital for translation of research knowledge into useful products. Hence a thicket of patents on individual components of the system may restrict research as this would require obtaining multiple licenses on individual components of the system. This raises the question of substantial royalty. "Royalty stacking" (multiple royalties) thus can swamp the development costs of some therapies to the point where development would no longer be commercially feasible and becomes an impediment for R&D on drug discovery.

### Case Studies of patented biological research tools

**Polymerase Chain Reaction (PCR) and Taq polymerase:** PCR is also a foundational technology for molecular biology research. PCR has proven to be a versatile standard research tool for biologists. It has been used for targeted amplification of DNA or RNA sequences. This technique was invented by Kary Mullis in 1985 as result of the research carried out at the Cetus Corporation. Cetus sold the patent to Hoffman La Roche in 1991 for US\$300 million. The right to use the product was incorporated in the price of the product. The fee for PCR technique use is also centered on cost of taq polymerase. This might have negative effect on molecular biology research in academic institutions. To solve this problem, free access to technologies for research and educational purposes should be allowed, For example Roche allowed free access to PCR technology for research purposes. Cost of Taq polymerase often limited access of academic researchers to use the PCR-technology. This technique has diverse applications of vital importance including genotyping, cloning,

mutation detection, sequencing, microarrays, forensics, paternity testing, diagnostics and forensics.

**Recombinant DNA:** The r-DNA technology invented by Cohen and Boyer is a platform technology, which consisted of three patents: a process patent for making molecular chimeras, while second and third were for the proteins produced by prokaryote r-DNA and eukaryote r-DNA respectively that were granted during 1980-1988 to Stanford University and University of California San Francisco and the inventors S. Cohen and H. Boyer. The patents were licensed non-exclusively for inexpensive license fee so that the technology could be licensed extensively for its dissemination among molecular biology researchers as this know how was of pivotal importance and no other technologies for the same purposes were available at that time. This strategy resulted into tremendous number of licenses. This case is an apt example of early level technology licensing of an emerging technology and important research tool on a broad basis by universities from public funded research.

**Protein and DNA sequencing instruments:** Protein & DNA sequencing instruments: DNA sequencing includes methods and technologies that can be used to determine the order of nucleotide bases-adenine, guanine, cytosine, and thymine- in a molecule of DNA. Sequencing of nucleic acid strands, particularly DNA, has become increasingly important in a variety of advancing fields including medicine, agriculture, forensics and biological research. However, conventional gel techniques for sequencing nucleic acid strands are time-consuming and expensive.

Various techniques are known in the art for sequencing portions of DNA molecules that include:

- Chain termination methods with fluorescent dyes and gel electrophoresis.
- Membrane based methods
- Deposition of nucleic acid containing samples on substrates.

Depending upon the sequencing technique, the sequence of the nucleic acid sample can be

determined by measuring ionic responses to nucleotide addition or by measuring fluorescent emissions resulting from nucleotide addition.

Success of Human Genome project is also attributable to automated sequencing instruments. Leroy Hood's group at Cal Tech developed sensitive DNA & protein sequencers during 1970-1986. These instruments looked promising to revolutionize protein & DNA sequencing in minute quantities. Initially the companies were reluctant and apprehensive to invest funds into commercialize this know-how. Eventually ABI (Applied Bio-systems) licensed it on exclusive basis from Cal Tech. ABI is the leader in sequencing arena. LI-COR, Illumina, Life Technologies, Beckman, Coulter and Pacific Bioscience are other major players. These companies have prospered due to direct patent licensing and cross licensing, mergers and acquisitions.

Latest in this domain are high-throughput, cheaper, highly accurate and ultra fast Next Generation Sequencing (NSG) technologies. NSG encompass sequencing by several techniques such as synthesis including fluorescent in situ sequencing (FISSEQ) and pyrosequencing, sequencing by ligation including using polony amplification and supported oligonucleotide detection (SOLiD), sequencing by hybridization in combination with sequencing-by-ligation and nanopore technology, nanopore sequencing and other novel sequencing technologies using nanotransistor array, scanning tunneling microscopy and nanowire molecule sensors etc. (Lin *et al.* 2008). NSG has enormously impacted solving of complex biological problems. Various sequencing platforms have been launched by companies such as 454 Life Sciences/Roche Diagnostics (Genome Sequencer 20 System), Solexa (now Illumina Inc.) has a high throughput sequencing platform (Genome Analyzer system) and Affymatrix etc.

**EST's:** An expressed-sequence tag (EST) is part of a sequence from a cDNA clone that corresponds to an mRNA (Adams *et al.* 1991). It can be used to identify an expressed gene and as a sequence-tagged site marker to locate that gene on a physical map of the genome. The patenting of EST is controversial. It raised the issue about patenting research tools to an issue of access to

unpatented research tools. Like many other research tools, ESTs fulfill different roles. Patenting of ESTs have focused on the criteria of utility. ESTs are of limited value without substantial and nonobvious development. Based on EST's, the researchers may claim for the work they may not have actually carried out. A huge number of EST data has been generated by researchers from more than 250 organisms which is held in public or private collections. Some important collections are NCBI (dbEST) GenBank, EMBL etc. which provide free access to the researchers. Hence if patenting of EST's is again permitted then the research costs using EST's would rise. Hence data sharing for free access is a better option for researchers.

### **Why need patenting?**

Patents help Biomedical innovations by attracting investments in R&D. The research tools developed have increased the productivity of biomedical research. Relative merits of protection of inventions or their free distribution are a matter of debate. Protecting inventions through patents can act as an incentive for academicians and industry both with hope to get funding and financial gain. On the other hand, patent rights bestow rights of excluding others by patent holder to make end use the invention. This can result into higher costs of development and delay.

### **Research tools: implication and challenges**

The NIH Working Group noted that efforts to standardize license terms for research tools had experienced 'limited success' (NIH, 1998). To reach 'standardized terms' has become complicated due to the difference in nature and value of research tools on one hand and 'requirement' of patent holders on the other hand. The 'needs' of the users of research tools also contribute to difficulty in standardizing the terms of access to research tools across the broad spectrum of biomedical and biological research. Case-by-case negotiation for obtaining license/permission to use research tools may create administrative delays, which can slow down research (NIH, 1998). Researchers may also have to pay transaction costs for negotiations over access to technologies, which can be long and

complicated, imposing delays and administrative and financial impediments on research (NIH, 1998). Even if the total license fees can be kept low, one 'hold out' may be enough to cause a research project to be cancelled (Barton, 2002). Researchers may choose not to pursue research using patented research tools where they have to navigate complex sets of patents held by a number of different patent holders.

In the case of infringement by researchers, an injunction to prevent further infringement may be issued by the court. Damages or an account of profits will generally be relevant only where a product has been developed and commercialized. Most claims of infringement never reach the courts because the parties reach a settlement – possibly involving payment of a license fee (ALRC Report 99: S. No. 12, 2004). Thus we see that there are several challenges in way of use of using patented research tools. To circumvent these, universities and academic institutions can make and protect research tools since these are upstream technology. Some times researchers find it easier to make a simpler research tool than license it due to high cost and time delays licensing may cause.

### **Patentability of research tools**

**Legal basis:** Patent right is an exclusive, time bound right to its owner. This right prevents other parties from commercially exploiting an invention without permission of patent holder. India is a member of Paris convention, PCT, Berne Convention and Convention on Biodiversity and WTO but there are still some disputes over patenting of research tools. The Indian Patent Act, 1970 manages the patent protection in India. It has been amended three times in a period of five years from 1990 to 2005 to suit India's international commitments under TRIPS (Indian Patent Act 1970). TRIPS agreement is the international agreement on Trade-Related Aspects of Intellectual Property Rights. The provisions of TRIPS agreement provide adequate standards and principles concerning the availability, scope and use of trade-related intellectual property rights and effective appropriate means for the enforcement of trade-related intellectual property rights, taking into

account differences in national legal systems of the member countries. India became a signatory to the TRIPS agreement in December 1997.

The first amendment to Indian Patent Act was made in 1999 (came into effect in January 2000) after which exclusive marketing rights (EMR) and mailbox provisions were introduced for pharmaceutical and agricultural patents filed from January 1995. Second amendment of 2002 allowed patenting of microorganisms provided the patentability criteria were fulfilled. The third amendment of December 2004, which came into force from January 2005 to make the Indian Patent Act fully TRIPS compliant. The deletion of section 5 of Indian Patent Act, 1970 permitted product patents in the area of biotechnology, pharmaceuticals and chemicals.

According to TRIPS, inventions related to biotechnology are patentable. Patenting of genes or parts of DNA sequences are allowed in European Union (EU), Japan and US. Though genes or part of DNA sequences per se was not allowed in India until January 2005, but process involving recombinant DNA technology to produce protein was patentable subject matter. Product patent for genetic inventions, DNA or RNA are patentable subject matter following the third amendment of the Indian Patent Act (2005). Patenting of nucleic acid (DNA, RNA) and genes sequences is a wide term that passes on to the patenting of a process that involves identification, isolation of nucleic acids, protein and peptides. The genetic materials that can be patented include cDNA (complementary DNA) and SNPs (Single Nucleotide Polymorphs). Earlier genes, DNA sequences and ESTs (Expressed Sequence Tags) were also patentable but as per latest guidelines later are not patentable even on fulfilling the patentability criteria.

**Patentability criteria:** A patentable invention means any product or process, which is novel (novelty), not obvious to a person skilled in the art (inventive step) and capable of industrial application (utility). According to Indian Patent Act 1970, *"new invention means any invention or technology which has not been anticipated by publication in any document or used in the country or elsewhere in the world before the date of filing of patent application with complete specification, i.e. the subject*

*matter has not fallen in public domain or that it does not form part of the state of the art"* [Sec 2(1) (l) page no 5]. Also, *"inventive step means a feature of invention that involves technical advance as compared to the existing knowledge or having economic significance or both and that makes the invention not obvious to a person skilled in the art"*, (Sec 2(1)(ja) (Indian Patent Act, 1970).

In research tools, the genes or partial sequence of genes can follow the criteria of novelty because they are chemical entity, isolated and purified from the form in which they are found in nature (human body or any other organism) and involve a technical process. Hence novel cDNA sequence of a gene, peptide sequences, promoter, marker, novel cassette, construct, novel micro-organism (isolated/genetically engineered), vaccines, new viral strains are patentable. In addition, any *in vitro* process, method of protein purification, downstream processing, process using micro-organisms to obtain chemicals (novel fermentation product), PCR process, screening assays, novel techniques - RFLP, AFLP, ELISA, RIA, fingerprinting also fulfill the criteria of patentability.

The invention must have its utility means it should have industrial application. Research tools like genes or part of genes, SNPs, SSR, SCAR, ESTs all have a broad variety of applications. They are used in detection of disease, producing protein, genotyping, and biosensors development. Now days, most of the desired proteins are produced by cloning and over expressing the desired genes; these proteins may be hormones, blood factors, enzymes, antibodies, vaccines, antigens or structural proteins.

### Scope of patent law

A patent grant does not give one the right to make, use, sell and import an invention. In fact it gives the patent owner the right to exclude others from doing so for a period of twenty years [Indian Patent Act, 1970 section 53(1)]. Hence the patent is temporarily granted right that can be sold, licensed or assigned. Patent provides the patentee monopoly right and in turn the patentee has to disclose the details of the invention in patent document. This document is published in official gazette so that person skilled in the art can benefit

from the information disclosed. Disclosure of invention describing the invention should be disclosed in a way that any interested person skilled in the art can repeat it. Otherwise it would not serve as basis for further progress. Thus the patent system is based on the communal deal that wishes to balance between the profit-making benefits gained by the patent owner and that gained by the public through disclosure and encouragement of invention (Baldwin, 2007). In other words patent law stimulates technology progress by motivating one to be proactive to invent, to disclose and to invest.

The patents reward the patentee firstly for introducing a new technology to the society and secondly for contributing to economy. In turn, inventor gets reward from the people who benefit from the invention, depending upon the usefulness of the invention. The reward depends on the willingness to sell or commercial exploitation of the invention. Hence patent are important for disclosing knowledge in public domain so that it can prevent other scientist from investing their money and time in the same inventive activity again rather they can be utilized for a new invention and knowledge for the advantage of society (Prinz zu Waldeck und Pyrmont, 2008).

### **Exception for experimental use of patents for scientific research**

TRIPS provides for a provision for exception to patent rights for experimental use of patented technology in scientific research. This exception is contained in the Indian Patents Act, Section 47(3) and provides exemption to experimental use and/or scientific research:

*"Any machine or apparatus or other article in respect of which the patent is granted or any article made by the use of the process in respect of which the patent is granted, may be made or used, and any process in respect of which the patent is granted may be used, by any person, for the purpose merely of experiment or research including the imparting of instructions to pupils.(section 47(3))".*

The public policy objective behind this exception is to ensure that patent rights should not hinder research and education in the country.

### **Mechanisms to address the issue of access to Patented Research Tools**

#### *Changes in patenting policies*

Indian patent policy after the 2005 amendments became quite different. Now exchange of biological material and data takes place between institutions, companies, universities. Certain research tools serve as fundamental research platform for development of new technology.

#### *Access to upstream technologies*

**Licensing:** It could be royalty based exclusive or non-exclusive licensing.

**MTA:** Material Transfer Agreements for non-commercial use (for exchange of biological material such as vectors, gene constructs, proteins, oligonucleotides etc.)

**Cross licensing:** One can cross license a research tool in exchange of another patented know-how on reciprocal basis.

**Collaborative research:** Inclusion of terms allowing use of research tools belonging to the parties in collaborative research agreement can provide access to the research tools to the parties to the agreement.

**Compulsory License:** Compulsory license is the license issued by the government of a country without the consent of the patent owner under certain conditions. Indian government can issue a compulsory license under section 84 of Indian Patent Act when the *"reasonable requirements of the public with respect to the patented invention have not been satisfied or that the patented invention is not available to public at a reasonably affordable price, or that the patented invention is not worked in the territory of India."* [Indian Patent Act, 1970, Sec 84]. In most of the countries, as per the patent law, compulsory license can be issued by the governments in the situation where development of research field of public importance such as health care or agriculture are monopolized by a patent holder who is not allowing the patented R&D to reach the public. This hinders economic benefits of patents, increases R&D costs, which could be detrimental for technology development. Compulsory licenses must be combined with

some exemption, which gives its owner the right to exclude others in certain situations. If Universities or any publicly funded Institute desires to use an invention for educational or non-commercial purposes, it shall be protected by compulsory licensing and, hence, may always get a license. Though there would be no question about research tool at any rate if patent holders commercialize their invention and sell licenses to each one at suitable price.

### Free access and data sharing

Many a times researchers do not opt for formal intellectual property registration and allow others easy and free access for research purposes to their research tools and know-how by submission into appropriate publically held databases. This can be an option for academicians and researchers for easy access to research tools databases, for example, DNA, RNA and protein sequences, carbohydrates, protein structure, metabolic pathways, chemical components (ligands, small molecules), gene nomenclature database, antibody database etc. and many more which also allow wide dissemination of research tools. Online free to use open source software tools,

genome browsing software tools, sequence analysis tools are also extensively used. Data sharing cuts down the cost of research and can be used as a option for accessing information. Many of these do not have a cost element for access but do have several terms and conditions to which the user must agree before hand. One has to be careful while clicking 'OK' in such cases to be sure of the terms of usage allowed. To prevent unscrupulous users from data 'theft' and misuse the access to databases is often limited by 'click-wrap' agreements having specific terms of usage.

### Examples of Research tool patents in Biotechnology

Representative examples of patented research tools in biotechnology have been summarized in Table 1.

### Conclusions

Importance of research tools lies in their function for downstream research for development of new invention. They are the knowledge, which is either embodied in the instrument or disembodied in the techniques. Though the IPR

**Table 1**  
**Summary of Representative Biological Research Tool Patents**

<i>Sr. N.</i>	<i>Research Tool</i>	<i>Title of Patent</i>	<i>Details</i>	<i>Patent No.</i>	<i>Assignee/Inventors</i>
1.	Transparent Zebra fish	Transparent zebrafish and preparation method thereof. Patent Grant: 2014.	This invention relates to preparation of transparent zebrafish, Citrine, which can be used to: 1. Create various mutant lines, 2. Create novel transgenic zebrafish which express fluorescent proteins in specific organs for tissue label, 3. Observation of progression and expansion of various disease stages or physiological processes.	US8710294	National Tsing Hua University (Hsinchu, Taiwan)  Inventors: Huang and Chuang, 2014
2.	Microarray	Peptide microarray and method of use. Patent Grant: 2014	In this invention immobilized peptide microarray is provided which can be used for 1. Quantitative determination of protein-peptide interaction, 2. Epitope mapping, and 3. Drug screening.	US8728980	University of California. Oakland (CA).  Inventors: Wang and Zheng, 2014

*contd. table 1*

Sr. N.	Research Tool	Title of Patent	Details	Patent No.	Assignee/Inventors
3.	DNA sequences	Banana Promoters. Patent Grant: EP: 2014 US: 2015	This invention provides polynucleotide constructs that are useful: 1. For modulating transcription of a desired polynucleotide and/or 2. For construction of recombinant genes for plant transformation to enable expression of foreign or endogenous coding sequences in plants.	US9057072 EP2504442	Inverensiones Europas Nicaraguenses SA [Panama]; Katholieke Universiteit Leuven, K.U. Leuven R&D  Inventors: Swennen <i>et al.</i> , 2014
4.	Antisense sequences	Double-stranded oligonucleotides. Patent Grant: 2014	The invention provides optimized antisense oligomer compositions and improved method for making and using both in <i>in-vitro</i> systems as well as for therapeutic use.	US8815821	Life Technologies Corporation (Carlsbad, CA).  Inventor: Woolfe, 2014
5.	DNA labeling reagent	Reagents useful for synthesizing rhodamine-labeled oligonucleotides. Patent grant: 2014	The invention provides reagents that can be used to label synthetic oligonucleotides with rhodamine dyes or dye networks that contain rhodamine dyes	EP2001871	Applied Biosystems LLC  Inventors: Benson <i>et al.</i> 2014
6.	CRISPER (Clustered Regularly Interspaced Short Palindromic Repeats)	CRISPR-Cas systems and methods for altering expression of gene products	The CRISPR-Cas system allows effective genome editing. The invention provides for systems, methods, and compositions for altering expression of target gene sequences and related gene products. It also provides vectors and vector systems, some of which encode one or more components of a CRISPR complex, as well as methods for the design and use of such vectors.	US8697359	Broad Inst Inc [US]; And Massachusetts Inst Technology [US];  Inventor Zhang (2014)
7.	DNA sequencer	Devices and methods for sequencing nucleic acids. Patent grant: 2013	The invention provides device for measuring DNA with nano-pores sized to allow DNA to pass through the nano-pore. The capacitance can be measured for the DNA molecule passing through the nano-pore. The capacitance measurements can be correlated to determine the sequence of base pairs passing through the nano-pore to sequence the DNA.	US 8535512	California Institute of Technology.  Inventors: Walavalkar <i>et al.</i> 2013
8.	Genetic variants	BRCA2 mutations and use thereof. Patent Grant: 2013	The invention discloses genetic variants in the BRCA2 gene are disclosed which are useful as diagnosis biomarkers. DNA	US8476020	Myriad Genetics Inc. (Salt Lake City, UT)  Inventors:

contd. table 1



<i>Sr. N.</i>	<i>Research Tool</i>	<i>Title of Patent</i>	<i>Details</i>	<i>Patent No.</i>	<i>Assignee/Inventors</i>
			microchips or microarrays are also disclosed. This invention may be useful for identification of genetic variants that are associated with diseases.		Scholl et. el., 2013
9.	RNAi gene silencing	RNA interference using a universal target. Patent Grant: 2008	The present invention provides novel methods for manipulating levels of expression of gene products using RNA interference (RNAi). The methods disclosed can be used to: 1. Investigate gene function, 2. To create disease-resistant organisms, and 3. To treat disease.	US7422853	Myriad Genetics, Inc. (Salt Lake City, UT)  Inventors: Huang and Ley, 2008
10.	Enzyme Assay	Enzyme assay and use thereof. Patent Grant: 2008	An assay and kit for determining the activity of an enzyme such as kinase, ATPase and GTPase is disclosed. The assay and kit are useful in drug screening to select modulators of such an enzyme.	US7338775	Myriad Genetics Inc. (Salt Lake City, UT). Inventors: Ostanin et. al. 2008
11.	Next Generation Sequencing	Ultra-rapid DNA sequencing method with nano-transistors array based devices	This invention relates to a method of and apparatus for ultra-rapid nucleic acid sequencing where Carbon Nano Tube Field Effect Transistor has been used. Using the methods and apparatus of the invention, base sequences of different lengths of nucleic acid molecules in the solution can be determined ultra-rapidly and automatically by devices of stretching and driving and the nanotube transistors.	US20062464 97 (A1)	Huang, J.T.  Inventors: Huang and Tsai (2006)
12.	RNAi mediated gene silencing.	RNA interference mediated small RNA molecules. Patent Grant: EP: 2007 US: 2006	The invention provides novel agents capable of mediating target-specific RNA interference or other target-specific nucleic acid modifications such as DNA methylation with improved efficacy and safety compared to prior art agents.	European Patent No. 1407044  US7078196	Max Planck Gesellschaft, Europ Lab Molekularbiolog.  Inventors: Tuschl et. al., 2006
13.	Transgenic Zebra Fish	Cell-lineage specific expression in transgenic zebrafish. Patent Grant: 2002	This invention relates to transgenic zebrafish which have applications for study of: 1. Developmental process, 2. Relationship of cell lineages, 3. The assessment of the effect of specific gene and compounds on the development.	US6380458.	Medical College of Georgia Research Institute, Inc. (Augusta, GA) Inventor: Lin, 2002

Sr. N.	Research Tool	Title of Patent	Details	Patent No.	Assignee/Inventors
14.	ESTs	5' ESTs for secreted proteins expressed in brain. Patent Grant: 2001	Here the sequence of 5' ESTs derived from mRNA encoding secreted proteins are disclosed which may be used for : 1. Obtaining and expressing cDNAs and corresponding genomic DNAs useful in diagnostics, Forensics Gene therapy and Chromosome mapping, and 2. Generating upstream regulatory sequences and designing expression and secretion vectors.	US6222029	Gen Set SA, Serono Genetics Institute FR  Inventors: Dumas <i>et al.</i> , 2001
15.	Enzyme	Purified Thermostable Nucleic Acid Polymerase Enzyme from Thermotoga Maritima. Patent grant: 1997.	A purified thermostable enzyme derived from the eubacterium Thermotoga maritima and has a molecular weight of about 97 KD and has DNA polymerase I activity. Thermostable DNA polymerases are useful in many recombinant DNA techniques, especially nucleic acid amplification by the polymerase chain reaction (PCR).	US5624833	Hoffman La-Roche Inventors:: Gelfand <i>et. al.</i> , 1997
16.	Device for PCR	Apparatus and method for performing automated amplification of nucleic acid sequences and assays using heating and cooling steps. Patent grant: 1994	The patent discloses a method and an apparatus for automatically performing the polymerase chain reaction. This method is especially useful for performing clinical tests on the DNA or RNA from a fetus or other donor where large amounts of the DNA or RNA are not readily available and more DNA or RNA must be manufactured to have a sufficient amount to perform tests. This patent also covered the thermostable Taq polymerase enzyme from Thermus sps.	US5333675	Hoffman La-Roche Inventors: Mullis <i>et. al.</i> , 1994
17.	Competitive ELISA	Competitive ELISA for the detection of HTLV-III Antibodies. Patent Grant: 1987	This invention is a specific and sensitive method of detecting antibodies in test sera and is particularly useful for detection of human T-cell leukemia lymphoma virus type III (HTLV III).	US4661445.	The Department of Health and Human Services, USA Inventors: Saxinger and Gallo, 1987
18.	Animal model	Transgenic non-human mammals. Patent Grant: EP: 1986 US: 1988	The invention features a transgenic non-human eukaryotic animal preferably a rodent such as a mouse, which has been genetically	US4736866, EP0169672	Assignee: Harvard College Cambridge, MA  Inventors:

contd. table 1

Sr. N.	Research Tool	Title of Patent	Details	Patent No.	Assignee/Inventors
			modified to carry an activated oncogene. The animals of The invention can be used to: 1. Test a material suspected of being a carcinogen, 2. As source of cancer cell culture, 3. As a test system, to bacteria (used, e.g., in the Ames test).		Leder et. al., 1986
19.	Recombinant DNA Technique.	Process for producing biologically functional molecular chimeras. Patent Grant: 1980	The invention is concerned with the method and compositions for replication and expression of exogenous genes in microbes for the production of nucleic acids and proteins of medical and commercial importance.	US4237224	Stanford University & University of California.  Inventors: Cohen and Boyer, 1980
20	Cell Line	Cell lines Patent Grant: 1976	The invention relates to human epithelial heteroploid liver cell line has been developed having applications to provide cell cultures useful for supporting viruses for the preparation of various types of animal or human viral vaccines.	US3935066	Burroughs Wellcome Co. (Tuckahoe, NY)  Inventor: Kostadin, 1976

issues in use of patented research tools may pose certain difficulties due to issues of access due to monopoly enjoyed by patent rights, the research tools have played an important role for biotechnological/biomedical research for development of innovative foundational (platform) technologies.

*Note:* This is a review article. For specific issues the reader is advised to contact a patent attorney.

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### Abbreviations

IPR: Intellectual Property Rights; IP: Intellectual Property; HRD: Human Resource Development; PCR: Polymerase Chain Reaction; MTA: Material Transfer Agreement; TRIPS: Trade-Related Aspects of Intellectual Property Rights, R&D: Research and Development; NIH: National Institutes of Health; PCT: Patent Cooperation Treaty; WTO: World Trade Organization; EMR: Exclusive Marketing Rights; EU: European Union;

### References

- Adams, M. D., Kelley, J. M., Gocayne, J. D., Dubnick, M., Polymeropoulos, M. H., Xiao, H., Merril, C. R., Wu, A., Olde, B., Moreno, R. F., Kerlavage, A. R., McCombie, W. R., and Venter, J. C. (1991). Complementary DNA sequencing: expressed sequence tags and human genome project. *Science* 252, 1651-1656.
- ALRC Report 99 (2004). Genes and Ingenuity: Gene patenting and Human Health. <http://www.alrc.gov.au/sites/default/files/pdfs/publications/ALRC99.pdf>
- Baldwin, T. (2007). Ethics and patents for genetics diagnostic test. In Van Overwalle G (ed.). *Gene Patents and Public Health*. Bruylant Publishers, Brussels. pp 45-59.
- Barton, J. (2002). Research Tool Patents: Issues for Health in the Developing World. *Bulletin of the World Health Organization* 80, 121-125.
- Benson Scott C, Zou Ruiming N, Upadhyaya Krishna G, Kenney Paul M, Cassel Jonathan M. (2014). Reagents useful for synthesizing rhodamine-labeled oligonucleotides, European patent No. EP2001871 issued on July 16, 2014.
- Cohen, S. N. and Boyer, H. W. (1980). Process for producing biologically functional molecular chimeras. US Patent No. US4237224, Issued on December 2, 1980.
- Dumas, M. E. J.-B., Duclert, A. and Lacroix, B. (2001). 5' ESTs for secreted proteins expressed in brain, US Patent No. US6222029, Issued on April 24, 2001.

- Gelfand, D.H., Lawyer, F. C. and Stoffel, S. (1997). Purified Thermostable Nucleic Acid Polymerase Enzyme from *Thermotoga Maritima*, US Patent No. US5624833, Issued on April 29, 1997 29, 1997.
- Heller, M. A. and Eisenberg, R.S. (1998). Can Patents Deter Innovation? The Anticommons in Biomedical Research. *Science* 280, 698-701.
- Huang, J.T. and Tsai, C.H. (2006) Ultra-rapid DNA sequencing method with nano-transistors array based devices. US patent application No. US2006246497 (A1) on November 2, 2006.
- Huang, W-C. and Chuang, Y-J. (2014). Transparent zebrafish and preparation method thereof, US patent No. US8710294, Issued on April 29, 2014.
- Huang, L. and Ley, III. Herbert, L. (2008). RNA interference using a universal target, US patent No. US7422853, Issued on September 9, 2008.
- Indian Patent Act 1970 (amended) [www.ipindia.nic.in](http://www.ipindia.nic.in)
- Kostadin, A. (1976). Cell lines, US Patent No. US3935066, Issued on January 27, 1976.
- Leder, P. and Stewart, T. A. (1986). Method for producing transgenic animals European Patent No. EP 0169672, Issued on 19 January 1986.
- Lin, S. (2002). Cell-lineage specific expression in transgenic zebrafish, US patent No. US6380458, Issued on April 30, 2002.
- Lin, B., Wang, J. and Cheng, Y. (2008). *Recent Pat Biomed Eng.* 2008, 60-67.
- Mullis, K. B., Johnson, L., Leath, R. A., Wennberg, T.J., Mezei, L. M. and Widunas, J. T. (1994). Apparatus and method for performing automated amplification of nucleic acid sequences and assays using heating and cooling steps, US Patent No. US5333675, Issued on August 2, 1994.
- NIH (1998). Report of the National Institutes of Health (NIH) working group on research tools. [www.nih.gov/news/researchtools/#backgrnd](http://www.nih.gov/news/researchtools/#backgrnd).
- Ostanin, K. and Hunsaker, T. (2008). Enzyme assay and use thereof, US Patent No. US7338775, Issued on March 4, 2008.
- Prinz zu Waldeck und Pyrmont, W. (2008). Research Tool Patents after *Integra v. Merck* – Have they reached a Safe Harbor? *In Michigan Telecommunications and Technology Law Review*, volume 14, pp. 367-446.
- Saxinger, W. C. and Gallo, R.C. (1987). Competitive ELISA for the detection of HTLV-III antibodies, US Patent No. US4661445, Issued on April 28, 1987.
- Scholl, T., Ward, B. E., Deffenbaugh, A., Barbidge, L. and Noll, W. W. (2013). BRCA2 mutations and use thereof. US Patent No. US8476020, Issued on July 2, 2013.
- Swennen, R., Sagi, L., Remy, S., Smeijers, L. and Wiame, I. C. M. (2014). Banana Promoters, European Patent No. EP2504442, Issued on July 16, 2014.
- Tuschl, T., Elbashir, S., Lendeckel, W., Wilm, M. and Luehrmann, R. (2006). RNA interference mediating small issued on September 19, 2007 RNA molecules. US Patent No. US7078196, Issued on July 18, 2006 and European Patent No. EP1407044, issued on September 19, 2007, US patent No. US9057072, Issued on June 16, 2015.
- Walavalkar, S., Scherer, A., Tombrello, T.A. Rajagopal, A., Homyk, A.P and Garcia, E. Devices and methods for sequencing nucleic acids (2013). US patent No. US 8535512, Issued on September 17, 2013.
- Wang, W. and, Zheng, X. (2014). Peptide microarray and method of use. (2014) US patent No. US8728980, Issued on May 20, 2014.
- Woolfe, T. (2014). Double-stranded oligonucleotides, US patent No. US8815821, Issued on August 26, 2014.
- Zang, F. (2014). CRISPR-Cas systems and methods for altering expression of gene products, US patent No. US8697359 issued on April 15, 2014.