RNAi Database sample wiki

Contents

- 1 Sample of the RNAi Database Dashboard
- 2 Overview
  - 2.1 Effector RNA molecules
- 3 Cellular Mechanism
- 4 Cancer specific Targets
- 5 **Intellectual property**
  - 5.1 Search Strategy
- 6 Interactive Taxonomy
- 7 **Top Players and Patenting Activity**
- 8 RNAi Database Dashboard
- 9 RNAi Sequence Dashboard
- 10 Experimental data comparison matrix
  - 10.1 **Patent Focus- Therapeutic Application**
  - 10.2 Qualitative Data from Patent Documents

Sample of the RNAi Database Dashboard

RNAi Database

Overview



RNA Interference Source

- **RNA interference (RNAi)**, is a technique in which exogenous, double-stranded RNAs (dsRNAs) that are complimentary to known mRNAs, are introduced into a cell to specifically destroy that particular mRNA, thereby diminishing or abolishing gene expression.
- This technology considerably bolsters functional genomics to aid in the identification of novel genes involved in disease processes and thus can be used for medicament and for delivery as therapeutics. Source
- RNA interference was known by other names, including post transcriptional gene silencing and quelling. Source

Effector RNA molecules

RNAi pathways are guided by small RNAs that include

SiRNA:

- Small interfering RNA (siRNA), sometimes known as short interfering RNA or silencing RNA, is a class of 20-25 nucleotide-long double-stranded RNA molecules.
- SiRNAs can also be exogenously (artificially) introduced into cells by various transfection methods to bring about the specific knockdown of a gene of interest. Source

miRNA:

- microRNAs (miRNA) are single-stranded RNA molecules of about 21?23 nucleotides in length, which regulate gene expression.
- miRNAs are encoded by genes from whose DNA they are transcribed but miRNAs are not translated into protein (non-coding RNA); instead each primary transcript (a pri-miRNA) is processed into a short stem-loop structure called a pre-miRNA and finally into a functional miRNA.
- Mature miRNA molecules are partially complementary to one or more messenger RNA (mRNA) molecules, and their main function is to down-regulate gene expression. Source

shRNA:

- A small hairpin RNA or short hairpin RNA (shRNA) is a sequence of RNA that makes a tight hairpin turn that can be used to silence gene expression via RNA interference.

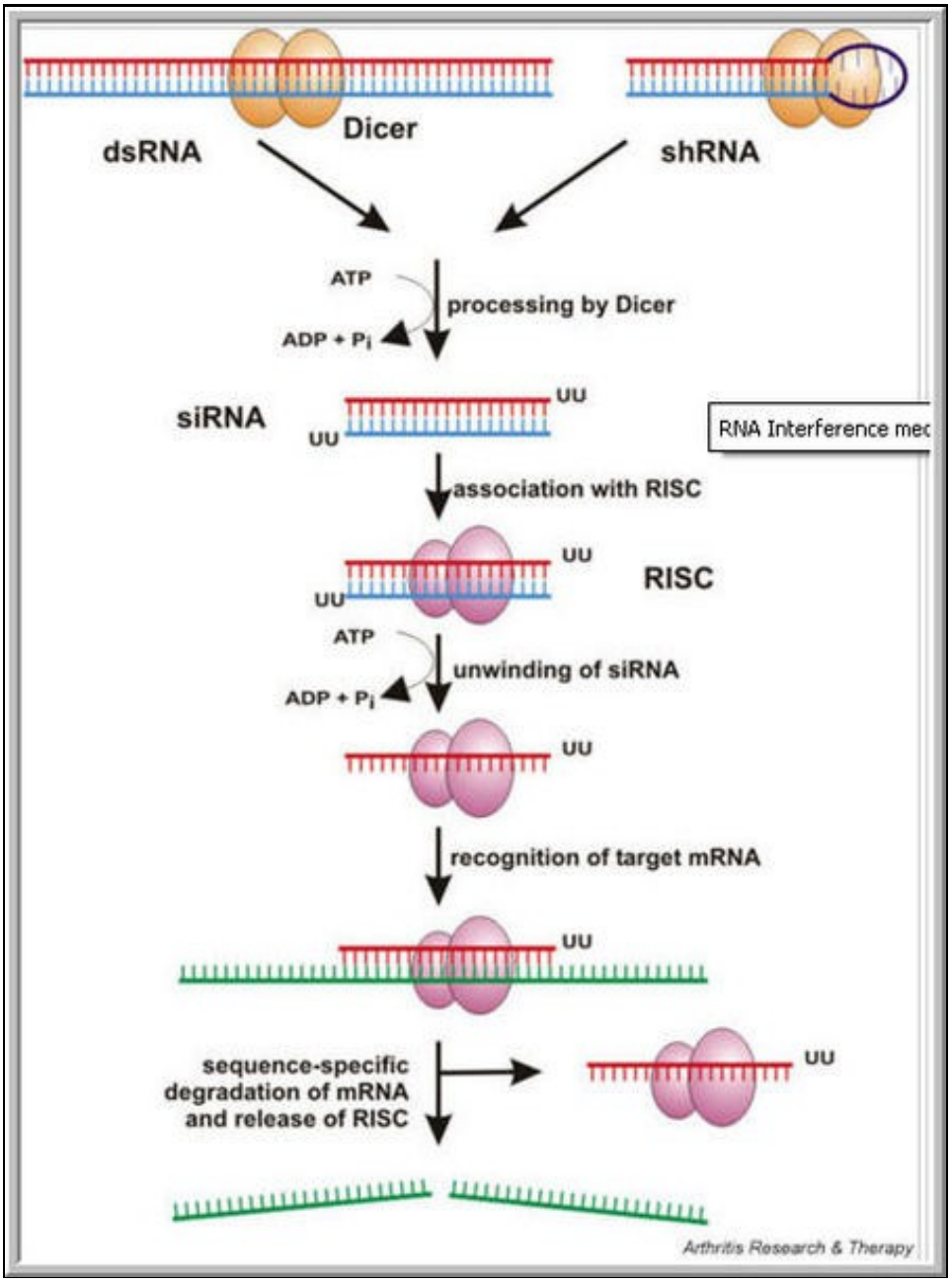
shRNA uses a vector introduced into cells and utilizes the U6 promoter to ensure that the shRNA is always expressed. This vector is usually passed on to daughter cells, allowing the gene silencing to be inherited. The shRNA hairpin structure is cleaved by the cellular machinery into siRNA, which is then bound to the RNA-induced silencing complex (RISC). This complex binds to and cleaves mRNAs which match the siRNA that is bound to it. Source

Others:

- In addition to miRNAs and siRNAs, other innate RNAi effectors have been identified.
    - One class of these is the Piwi-interacting RNAs (piRNAs). piRNAs seem to be uniquely expressed in the mammalian germline, particularly in the testes. The functional role of piRNAs is currently unclear, but a role in spermatogenesis is likely.
    - A number of other small RNAs associated with RNAi have been identified in different species, including trans-activating siRNAs (tasiRNAs), studied in plants and nematodes, and small scan RNAs (ScnRNAs), found in Tetrahymena. Source

Cellular Mechanism

The RNA interference pathway: Long double-stranded RNA (dsRNA) or small hairpin RNA (shRNA) is processed by Dicer to form a small interfering RNA (siRNA), which associates with RNA-induced silencing protein complex (RISC) and mediates target sequence specificity for subsequent mRNA cleavage leading to gene silencing.



RNA Interference mechanism Source

Cancer specific Targets

TABLE I. EXAMPLES OF RNAi AGAINST CANCER-PROMOTING GENES

PATHWAYS	TARGET GENE	CANCER	REF.
MAP kinase	K-Ras	Lung, ovarian, colon and pancreatic	17–19
	H-ras	Bladder, prostate	20
	Nras	Leukemia	21
	Nox1	Colon, prostate	22
	b-Raf	Melanoma	23–26
	Skp2	Melanoma	25
Viral oncogenes	E6/E7	Cervical, skin, head and neck	27–32
Mutations	Bcr-Abl	CML	33
Signaling	STAT3	Breast, laryngeal	34
	cSrc	Colon	35, 36
	PKC	Breast, prostate	20
Apoptosis	Bax		37
	Bcl-2	Lymphoma, leukemia	20, 38
Receptors	EGFR	Lung	39, 40
Growth factors	VEGF	Breast	41
Transcription factors	c-myc	Small cell lung carcinoma, breast	42
	n-myc	Small cell lung carcinoma, neuroblastoma	43

Abbreviations: MAP kinase, mitogen-activated protein kinase; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; PKC, protein kinase C.



Cancer specific Targets Source

Intellectual property

Search Strategy

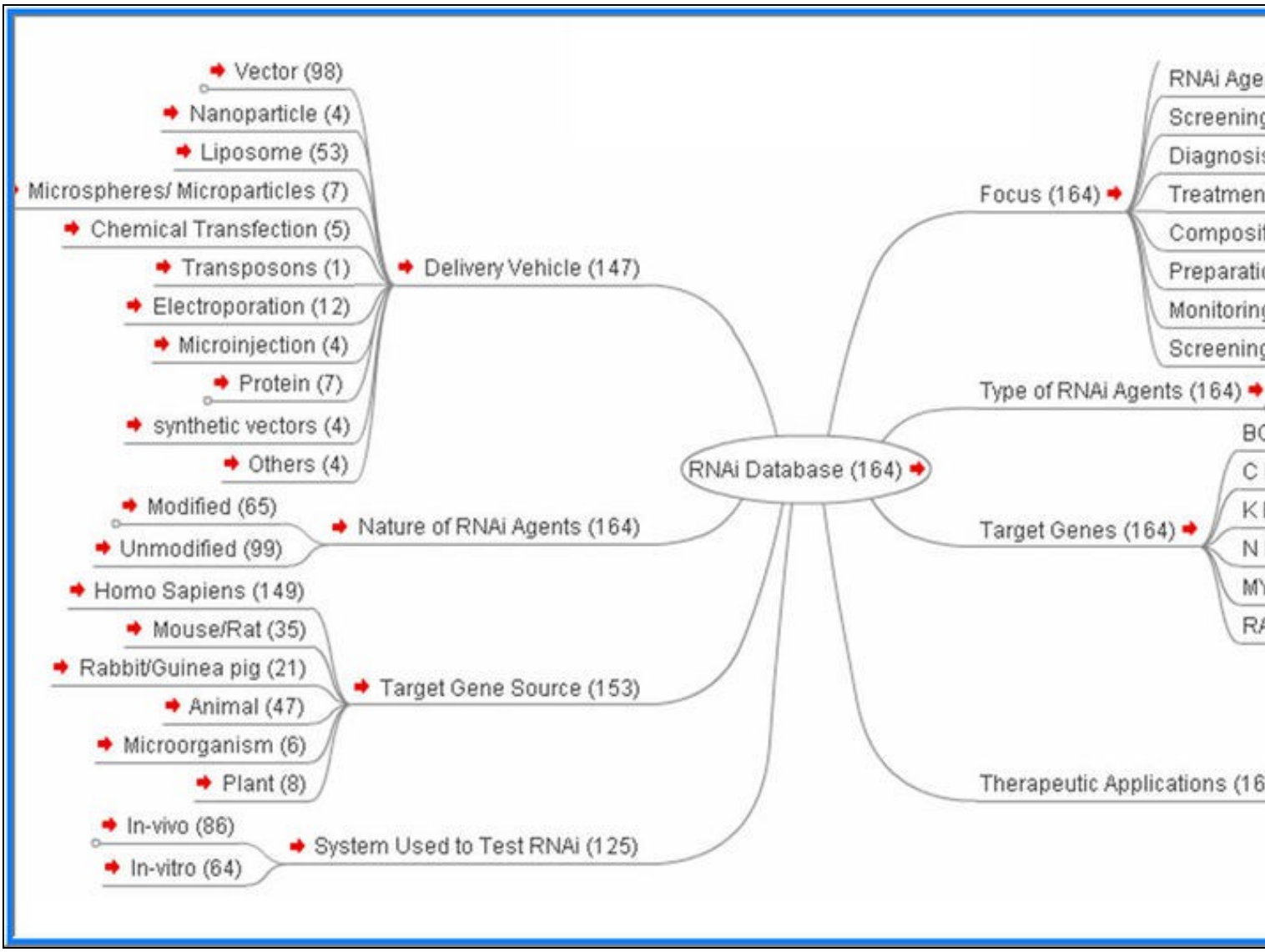
Effective search strategy ensures that all key words covering the technology are adequately covered. IPC class limitations help in removing the unwanted patents.

The search strategy was employed to extract patents disclosing RNAi agents against disease causing target genes. Table below summarizes an exemplary search strategy used to extract patents for BCL2, a target gene for curing cancer.

S.No.	Concept	Search scope	Query	No. of Hits
1	RNAi	Claims,Title, Abstract	(siRNA*1 OR (short ADJ1 interfering ADJ1 RNA*1) OR (short ADJ1 interfering ADJ1 nucleic ADJ1 acid*1) OR (short ADJ1 interfering ADJ1 NA*1) OR siNA OR siNAs OR (si ADJ1 RNA*1) OR (Small adj1 interfering adj1 RNA*)OR miRNA or (microRNA* or micro adj1 RNA*)OR shRNA or (small adj1 hairpin adj1 RNA*)OR piRNA or (Piwi adj1 interacting adj1 RNA*)OR tasiRNAs or (trans adj1 activating adj1 siRNA*) OR ScnRNAs or (small adj1 scan adj1 RNA*)OR RNAi or(RNA adj1 interference))	12729
2	IPC		a61k or c12q or c12n or c07k or c07h	1688146
3	**BCL2**	Full Patent Spec	(Bcl2 OR (Bcell ADJ1 CLL) OR (Bcell ADJ1 Lymphoma2) OR DKFZp781P2092) and Current IPC-R a61k or c12q or c12n or c07k or c07h	3890
4	BCL2 + RNAi +IPC		**1 AND 3**	**633 (293 unique records)**

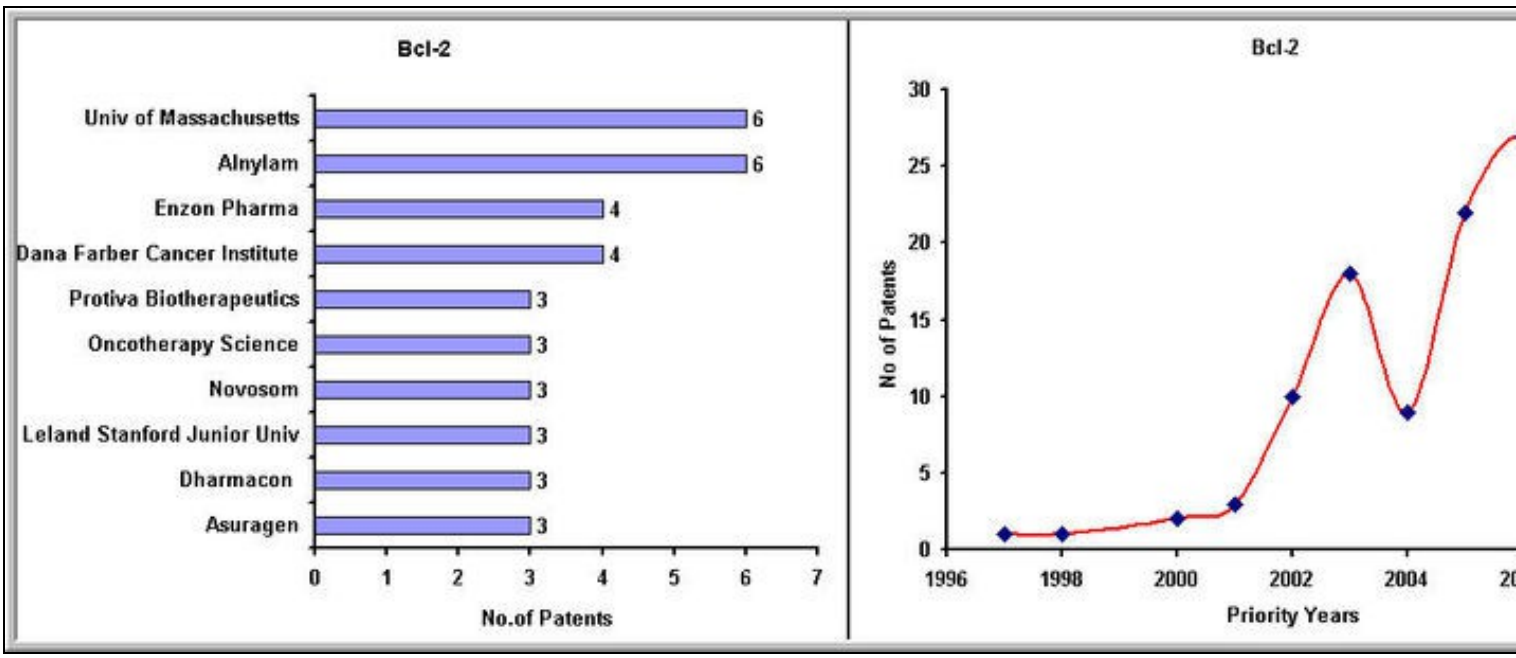
Interactive Taxonomy

Grouping specific elements into more general categories is conceptually easier and cleaner than is entertaining hundreds of specific elements separately. We categorize the information from analyzed patents and scientific literate into four levels of taxonomy which allow both ?bird?s-eye view? and ?in-depth views? of scientific technologies.



Interactive Taxonomy

Top Players and Patenting Activity

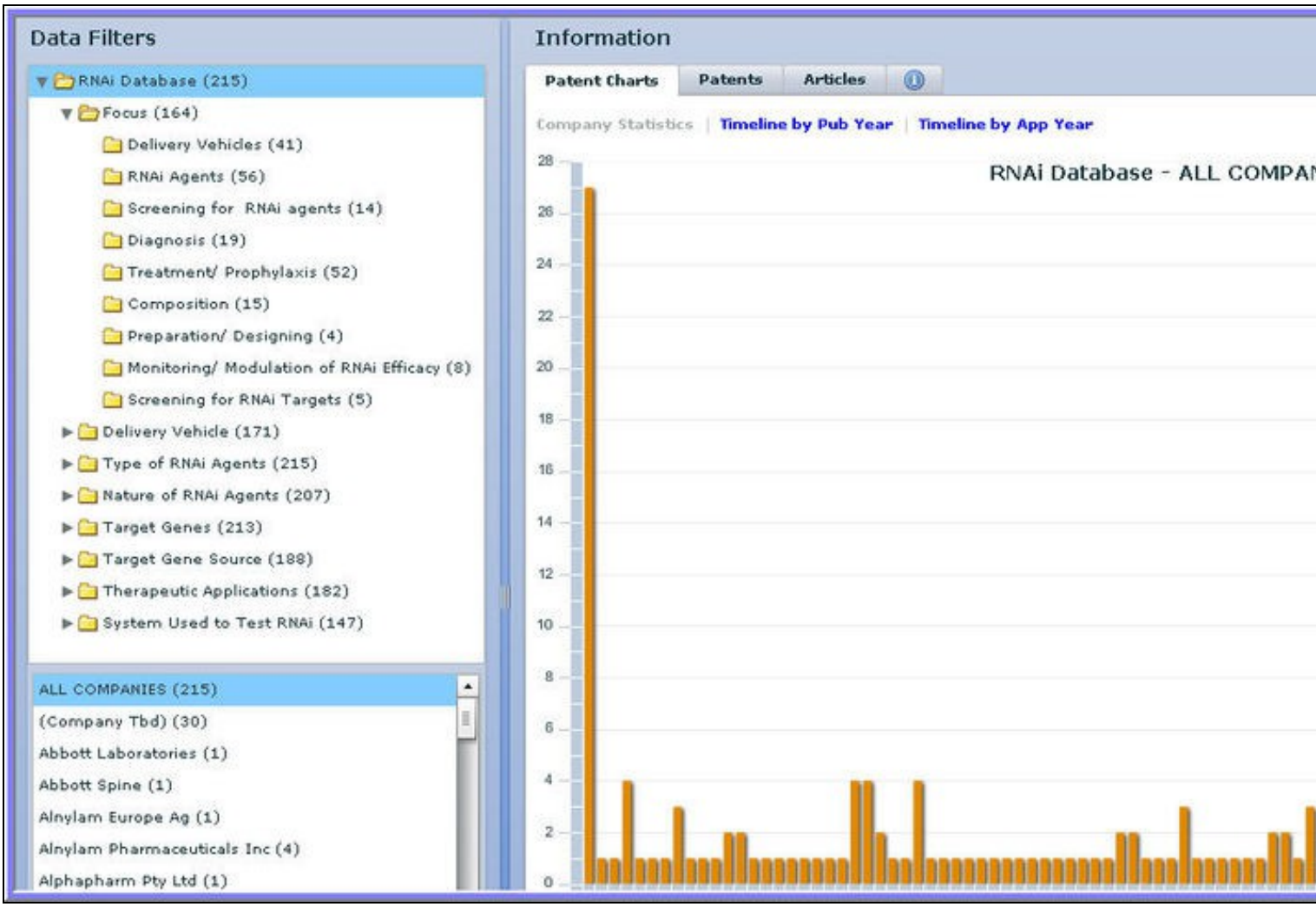


Bcl-2

RNAi Database Dashboard

RNAi database dashboard:

- Categorize and organize large sets of product, patent, and scientific literature
- Analyze client?s competitive position and that of key competitors
- Identify licensing opportunities
- Make build-vs.-buy decisions in new product areas
- Predict product features based on technology and market trends

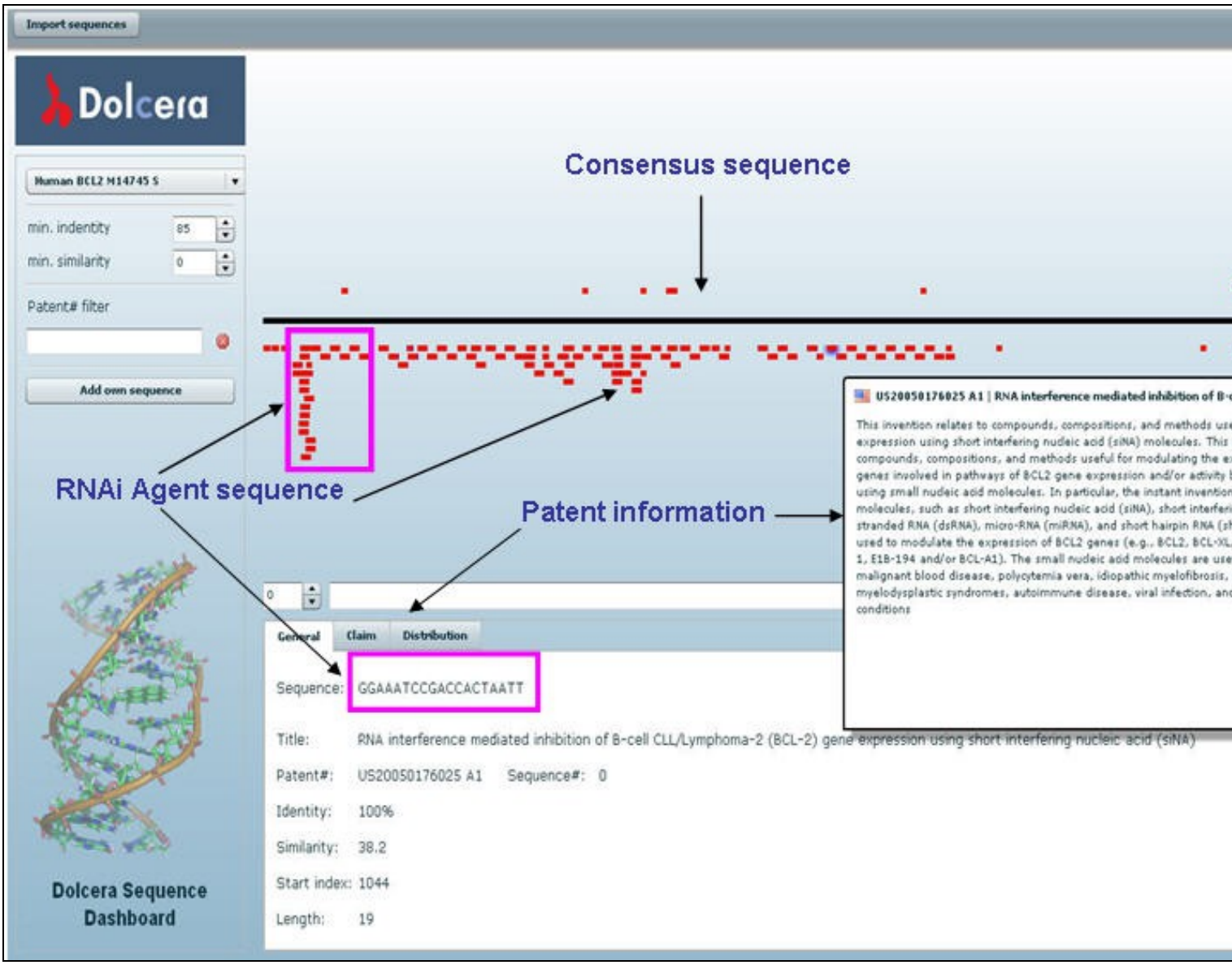


Patent Dashboard

RNAi Sequence Dashboard

Sequence dashboard allows comparison of siRNA agents extracted from patents and scientific literature to the consensus sequence. Since not all the documents disclose the target sequence, the consensus sequence has to be identified and used for sequence dashboard. For example for Bcl-2, consensus sequence is retrieved from NCBI having seq. id **M14745**.

The dashboard also depicts the associated information with RNAi agent on the click of your mouse such as patent number, patent title, length of RNAi agent (siRNA), identity score etc.



Sequence Dashboard

Experimental data comparison matrix

Experimental data may be qualitative or quantitative, each being appropriate for different investigations.

Quantitative data was captured from following RNAi experiments for patent focusing on therapeutic application and compared.

- % inhibition of target mRNA expression
- % encapsulation efficiency
- % transfection efficiency
- % tumor volume reduction
- % cell count reduction

More such comparison matrix can be prepared for patent having varied focus such as on delivery vehicle, nature of RNAi agents, target gene source, system used to test RNAi etc.

Patent Focus- Therapeutic Application

Sr. No.	Patent/Publication No.	Target gene		Experimental Details							R
		BCL-2	Others	Test Model	Inhibition of Target mRNA Expression (%)	Encapsulation Efficiency	Transfection efficiency Increase (%)	Tumor Volume Reduction (%)	Cell Count Reduction (%)	Other Remarks	
1	US20070298056A1	Yes		Human colon cancer (Caco-2) xenografts	No	No	No	90.08% Day 25 (Fig 2)	No	No	

			in nude mice						
2	US20080038296A1	Yes	In vivo (Mice)	No	No	No	61.29% Day 13 (Fig 3)	No	No
3	US20070258952A1	Yes	Human pancreatic carcinoma H79 xenografts	No	No	No	49.23% Day 25 (Fig 4)	No	No
4	US20070172847A1	Yes	Ramos cells	80% (Fig 4. B)	No	No	No	No	No

Ranking of patents can be done on the basis of focus of the study, experimental data disclosed, effectiveness of RNAi agent, type of model used to test the RNAi agent, etc.

Advantages:

- Information disclosure wise sorting available.
- Efficiency of different RNAi agent against target gene can be compared.
- Different models used to test cell line and the efficiency can also be compared.

Qualitative Data from Patent Documents

Experiments yielding qualitative data, mentioned below, can?t be compared but are equally important. We did not miss them!

- Gel electrophoresis
- Gel blots
- Tissue section* Cell staining
- RNAi agent construction

Patent/ Publication No.	Gel blots	Gel Electrophorosis	Tissue section micrograph	Cell staining micrograph	RNAi Agent Construction
US20080021205A1	Yes	_ _	_ _	Yes	_ _
US20070275465A1	_ _	Yes	_ _	_ _	_ _
WO2007013575A2	_ _	Yes	Yes	_ _	_ _
US20070081982A1	_ _	_ _	_ _	_ _	Yes
WO2007013575A2	Yes	_ _	Yes	_ _	_ _
US20050266561A1	_ _	_ _	_ _	_ _	Yes

*Mathematically incomparable data disclosed in patents