antiCODE: a natural sense-antisense transcripts database
Yifei Yin†1,2, Yi Zhao†2, Jie Wang3,4, Changning Liu2,4, Shuguang Chen1, Runsheng Chen*3 and Haitao Zhao*1

Address: 1Department of Liver Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, CAMS & PUMC, Beijing 100730, China, 2Bioinformatics Group, Institute of Computing Technology, Chinese Academy of Sciences, Beijing 100080, China, 3Bioinformatics Laboratory, Institute of Biophysics, Chinese Academy of Sciences, Beijing 100101, China and 4Graduate School of the Chinese Academy of Sciences, Beijing 100080, China

Email: Yifei Yin - yinyifei2005@yahoo.com; Yi Zhao - biozy@ict.ac.cn; Jie Wang - joyice_wang@hotmail.com; Changning Liu - lcn@ict.ac.cn; Shuguang Chen - csg959116@yahoo.com.cn; Runsheng Chen* - crs@sun5.ibp.ac.cn; Haitao Zhao* - dr_zht@yahoo.com.cn
* Corresponding authors  †Equal contributors

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Abstract
Background: Natural antisense transcripts (NATs) are endogenous RNA molecules that exhibit partial or complete complementarity to other RNAs, and that may contribute to the regulation of molecular functions at various levels. Though many natural antisense transcripts were discovered through their regulatory function on the expression of mRNAs [1,2], some global predictions of NATs in several species have also been published [3-10]. The first of these used mRNA data to predict natural antisense transcripts [4]. With the appearance of more draft genomes and full length cDNA data, the scale of NATs predictions has been extended. Several datasets, mainly based on full length cDNAs, have been published for mouse [8,11], rice [12] and Arabidopsis thaliana [7]. Since 2006, the trend in NATs prediction has turned to multi-species comparisons [6,13]. A number of published NATs have been validated by various experimental approaches, such as RT-PCR [10] and microarray [5], fur-
ther confirming that antisense transcript is a common occurrence in eukaryotic transcriptomes.

The background for the emergence of so much NAT data in recent years, is on the one hand the availability of more genomic and full length cDNA data, and on the other hand a growing realization of the important functions of natural antisense transcripts. Antisense RNAs may contribute regulatory activity at various levels, such as post-transcription [14,15], splicing [16,17], transport [18], and genomic imprinting [19,20], and have been shown to be involved in the control of developmental processes [21], adaptation to various stresses [22], and viral infection [23,24] through annealing to complementary sequences.

To facilitate research, previous publications have suggested a few classification systems for NATs. The most basic of these is the cis/trans system [4] in which an antisense transcript from the same genomic loci as the sense transcript is labelled a cis-NAT, whereas a trans-NAT is an antisense transcript expressed from a genomic locus different from that of the sense transcript. A second classification system is based on the overlapping position of the complementary pair, which will be divided into 5–6 categories according to their patterns of gene structure, e.g. depending on whether the pair overlaps at their 5’ ends, 3’ ends, completely, or in the introns [6,7,10,11]. A third classification system considers the respective coding potential of the complementary pair, and includes the categories coding-coding, coding-noncoding and noncoding-noncoding [8,13].

Up to present, a number of large-scale NAT data have been published and several functional studies of NATs have been carried out, however, thus far no database has been published and several functional studies of NATs have been carried out, however, thus far no database has been published and various nucleotide databases 

| Reference | Species involved in the predictions | The number of transcripts |
|-----------|-------------------------------------|--------------------------|
| [4]       | Human                               | 372                      |
| [5]       | Human                               | 2,667                    |
| [11]      | Mouse                               | 4,279                    |
| [12]      | Rice                                | 1,374                    |
| [10]      | Human                               | 5,880                    |
| [7]       | Arabidopsis thaliana                | 1,340                    |
| [8]       | Mouse                               | 37,562                   |
| [13]      | Human, mouse, rat, chicken, fruit fly, and nematode | 11,200 |
| [6]       | Human, mouse, frog, cow, fruit fly, worm, zebra fish and sea squirt | 21,266 |

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according to information in referenced papers. The second step was to classify the NAT pairs according to the coding/noncoding system, thus, all NAT pairs were sorted as coding-coding, coding-noncoding and noncoding-noncoding. In the third step, Blat [25] was used to classify the NAT pairs according to the 5/3/c/o system. Finally, we have removed redundant NAT pairs derived from different datasets.

**Website Features**
The three core functions of antiCODE database are browse, search and sequence alignment with Blast. Under the browse option, there are five sub-options – Pair ID, cis/trans, overlap, coding/noncoding, and species – by which users can browse all NAT pairs by pair ID, or NAT pair classes.

More specific lookups can be executed by the search function. Users can enter the exact gene accession number or clone ID to see whether a sequence of interest has a possible complementary transcript. If one is interested in NAT pairs relating to some particular condition, e.g. cancer, a relevant key word can be entered in the Text search frame under the search option.

If a sequence of interest cannot be found in the database or a user want to investigate whether some novel sequence possibly overlap with known NAT pairs, the Blast option will be very useful. Users just needs to paste her sequence in the sequence window, or load them into the Blast web page, and select the appropriate choices, such as expected number of hits (Figure 2), and then the Blast result will be returned.

After a NAT pairs of interest have been found, all information pertaining to the NAT pair, including annotation and map view links to other databases, affiliated classes, a simple description and references, will appear. More detailed annotations and comments can be obtained through the links to other relevant databases.

**Utility and discussion**
Recently, new technologies, such as microarray, SAGE, and MPSS have played prominent roles in the identification of NAT pairs. Before 2005 only EST (UniGene) and mRNAs had been used for NAT prediction. Later large scale full-length cDNA data emerged, based on which more than 1,000 rice NATs[12] were first reported, closely followed by mouse [8,11] and Arabidopsis [7] NATs. For NAT prediction in Arabidopsis [7] also MPSS data has been used, and in 2005, a new NAT dataset based on SAGE was reported in mouse [26]. In 2007, data [27] from whole-genome arrays was employed for NAT prediction in Arabidopsis. It is expected that along with the improvement in array technology, more transcripts from tillig microarrays will be used for future NAT predictions, hopefully resulting in an accurate and exhaustive set of NAT data.

**Conclusion**
The most recently released NAT datasets [9,26-28] have yet not been included in antiCODE, but will be included in the next release of the database. However, compared with other existing databases [29], antiCODE is presently the most comprehensive and integrated database for NAT pairs. The most distinctive features of antiCODE are as follows; (i) antiCODE includes almost all known natural antisense transcript (NAT) pairs from 12 eukaryotic model organisms, (ii) antiCODE provides substantial and compact information relating to NATs (e.g. accession number, clone ID, species, classification etc.), (iii) we have introduced a classification system based on the previous notions which should give users an immediate impression of the basic features of each NAT pair, (iv) a Blast service is provided, and (v) antiCODE provides a user-friendly interface and a convenient search option.
allowing efficient investigation and verification of natural antisense pairs from different species.

Availability and requirements
The antiCODE database and related resources can be freely accessed at its websites http://bioinfo.ibp.ac.cn/ANTICODE or http://www.anticode.org

Authors’ contributions
Yifei Yin and Yi Zhao carried out the design and the collection of data. Jie Wang carried for building the database. Changning Liu participated in the design of the study. Shuguang Chen helped to draft the manuscript. Runsheng Chen and Haitao Zhao participated in the design and coordination. All authors read and approved the final manuscript.

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