

ONCOMINE: A Cancer Microarray Database and Integrated Data-Mining Platform¹

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Abstract

DNA microarray technology has led to an explosion of oncogenomic analyses, generating a wealth of data and uncovering the complex gene expression patterns of cancer. Unfortunately, due to the lack of a unifying bioinformatic resource, the majority of these data sit stagnant and disjointed following publication, massively underutilized by the cancer research community. Here, we present *ONCOMINE*, a cancer microarray database and web-based data-mining platform aimed at facilitating discovery from genome-wide expression analyses. To date, *ONCOMINE* contains 65 gene expression datasets comprising nearly 48 million gene expression measurements from over 4700 microarray experiments. Differential expression analyses comparing most major types of cancer with respective normal tissues as well as a variety of cancer subtypes and clinical-based and pathology-based analyses are available for exploration. Data can be queried and visualized for a selected gene across all analyses or for multiple genes in a selected analysis. Furthermore, gene sets can be limited to clinically important annotations including secreted, kinase, membrane, and known gene–drug target pairs to facilitate the discovery of novel biomarkers and therapeutic targets. *Neoplasia* (2004) 6, 1–6

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Introduction

Gene expression profiling with DNA microarrays has emerged as a powerful approach to study the cancer transcriptome. More than 100 published studies have presented analyses of human cancer samples, identifying gene expression signatures for most major cancer types and subtypes, and uncovering gene expression patterns that correlate with various characteristics of tumors including tumor grade or differentiation state, metastatic potential, and patient survival [1–24]. Also, novel tissue

[25,26] and serum [27,28] biomarkers as well as potential therapeutic targets [29,30] have been identified using these genome-wide screens. These discoveries highlight the remarkable impact that DNA microarrays have had on cancer research; however, we argue that due to limitations of data availability and integration, the full potential of gene expression profiling with microarrays has not been realized. For most published microarray studies, which may comprise thousands of gene measurements across tens or hundreds of cancer specimens, the authors have presented one interpretation of their data and have reported on only a subset of genes that demonstrate their particular hypothesis. The complete microarray datasets are sometimes made available as supplementary data, but even if that is the case, the datasets often sit as cryptic text files, stored and processed in an unsystematic manner, and thus only useful to those with computational expertise. Although standards have now been set for recording and exchanging microarray data [31], and authors have been urged to provide their complete datasets upon publication [32], the full potential of cancer microarray data will only be reached when it is unified, logically analyzed, and made easily accessible to the cancer research community.

Here we describe our ongoing effort to systematically curate, analyze, and make available all public cancer microarray data via a web-based database and data-mining platform, designated *ONCOMINE* (www.oncomine.org). Our effort also includes centralizing gene annotation data from various genome resources to facilitate rapid interpretation of a gene's potential role in cancer. Furthermore, we are integrating microarray data analysis with other resources

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including gene ontology annotations and a Therapeutic Target Database. In this report, we describe microarray data collection and analysis, and data retrieval and visualization methods available at ONCOMINE, and demonstrate the potential for important discoveries.

Data Collection and Analysis

As the goal of this ongoing effort is to compile, analyze, and serve all public cancer microarray data, we identified all potential studies by literature searching, focusing on those that have generated gene expression profiles of human cancer tissue samples. We retrieved the complete datasets if available and, if not, we contacted the authors to request for the dataset. As of May 1, 2003, we cataloged information on 152 cancer microarray studies (catalog available at ONCOMINE), of which 40 studies were available and compiled—in total, 37,901,459 gene measurements from 3,762 microarray experiments. We processed and normalized each dataset independently by a single method (see Methods section) and mapped each microarray feature to Unigene build 159.

Although many analytical methods have been applied to microarray data, we chose differential expression analysis using *t*-statistics as a measure of differential expression, and false discovery rates [33] as a corrected measure of significance. To define potential differential expression analyses, we reviewed the samples in each dataset. Thirty-four datasets had samples corresponding to both classes of at least one comparison of interest including cancer *versus* respective normal tissue, high-grade (undifferentiated) cancer *versus* low-grade (differentiated) cancer, poor outcome (metastases, recurrence, or cancer-specific death) cancer *versus* good outcome (long-term or recurrence-free survival) cancer, metastatic cancer *versus* primary cancer, and cancer subtype 1 (e.g., estrogen receptor–positive) *versus* subtype 2 (e.g., estrogen–receptor negative). We conducted a total of 81 differential expression analyses, encompassing 939,117 gene/cancer hypotheses. The genes most differentially expressed in these analyses can be explored at ONCOMINE (see below).

GENE Module

Unifying cancer microarray data and then processing, normalizing, and analyzing all datasets by a single method allow for gene centric analysis. Typically, researchers use a single microarray dataset to identify a set of genes that are associated with a particular cancer type or subtype. With ONCOMINE, users can now assess and visualize the differential expression of a selected gene across all available datasets and differential expression analyses. After searching for a gene of interest, ONCOMINE lists all differential expression analyses in which the gene was included, and allows the user to select analyses of interest. For the selected analyses, the statistical results are provided and linked to graphical representations of the microarray data. To illustrate the value of gene centric analysis with ONCOMINE, we performed a search for ERBB2 (i.e., HER2/*neu*), an oncogene known to

be amplified in a subset of breast tumors and targeted by the antibody therapeutic, Herceptin [34]. We first looked at the expression of ERBB2 in breast cancer as per the study of Sorlie et al. [21]. We found that, as expected, ERBB2 is highly overexpressed in a fraction of breast cancer samples relative to normal breast samples ($P = .057$; Figure 1A). Next, we looked at ERBB2 expression in all “cancer *versus* normal” analyses. Interestingly, ERBB2 was significantly overexpressed in diffuse large B-cell lymphoma (DLBCL) relative to normal blood B-cells ($P = 1.2e-6$), in non small cell lung

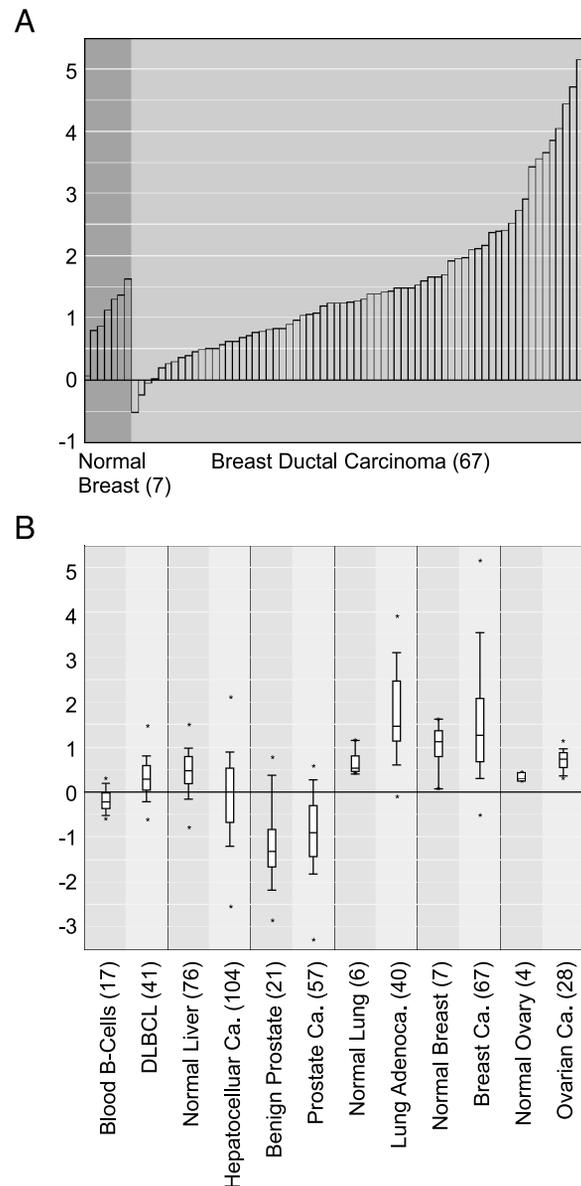


Figure 1. ERBB2 (*Her2/neu*) gene centric expression analysis as revealed by ONCOMINE. (A) ERBB2 is overexpressed in a subset of breast cancers relative to normal breast tissue ($P = .0567$). (B) ERBB2 is significantly overexpressed in DLBCL relative to normal blood B-cells ($P = 1.2e-6$), in non small cell lung cancer relative to normal lung ($P = 1.1e-5$), and in ovarian carcinoma relative to normal ovary ($P = 1.0e-5$), but not in hepatocellular carcinoma or prostate cancer relative to their respective normal tissue. Y-axis units are normalized expression values (standard deviations above or below the median per array). The number of samples in each class is given in parentheses. Adenoca. indicates adenocarcinoma; Ca. indicates carcinoma; DLBCL indicates diffuse large B-cell lymphoma.

cancer (NSCLC) relative to normal lung ($P = 1.7e-5$ and $P = 1.1e-5$), and in ovarian carcinoma relative to normal ovary ($P = 1.0e-5$), but not in the majority of other cancer types. Figure 1B depicts these analyses, along with selected others that were not significant, as a multidataset box plot for ERBB2. It is notable that the associations of Her2/*neu* with NSCLC and ovarian cancer as revealed by ONCOMINE have been documented by other independent studies [35], and clinical trials of Herceptin use for NSCLC are underway [36].

STUDY Module

The *STUDY* module provides a standard gene expression color map to visualize genes most differentially expressed in a selected analysis. Many of the differential expression analyses are analogous to those performed in the original publications; however, with ONCOMINE, they are centralized and apply a single, robust statistical method. Furthermore, some analyses available at ONCOMINE were not performed in the original publications, thus increasing the value of these microarray datasets. For example, Ramaswamy et al. published a report on multicancer type classification highlighting a focused gene set that can accurately classify tumor types of different origin [16]. Because the dataset also included respective normal tissue samples for many of the cancer types, we performed multiple “cancer *versus* normal” differential expression analyses, including pancreatic cancer *versus* normal pancreas—a hypothesis that was not testable from any of the other available datasets. A final point about the *STUDY* module: direct links are provided to the *GENE* module, so that if the gene of interest is identified by exploring a differential expression analysis, the user can quickly evaluate the gene’s expression in other differential expression analyses (as demonstrated below with prostasin).

Gene Ontology Integration

The focus of many cancer microarray studies is to identify potential therapeutic targets or diagnostic markers. Genes are usually considered as potential targets or markers if they are highly overexpressed in a particular cancer, and their molecular function or localization suggests that they might be amenable to pharmacologic inhibition or detection in serum or tissue. To provide a platform for the discovery of potential targets or markers that are overexpressed in cancer, we annotated genes with relevant gene ontology descriptors. Three ontology categories were created by combining gene ontology annotations from GO ontology consortium [37]: 1) membrane-bound, which could be targeted by antibody therapies; 2) kinase, which could be inhibited by small molecule kinase inhibitors; and 3) secreted, which could serve as serum biomarkers. Significantly overexpressed genes from each ontology category were present in nearly all analyses. The genes in a particular ontology category (e.g., membrane) that are most differentially expressed in a specific analysis (e.g., lung adenocarcinoma *versus* normal lung) can be explored at ONCOMINE. Furthermore, specific GO annotations (e.g., DNA binding) can also be used to filter differential expression analyses.

To demonstrate the utility of this approach, we will highlight an analysis using ONCOMINE to identify serum biomarkers for ovarian cancer. Ovarian cancer is in particular need of improved serum biomarkers to aid in early detection as it often presents late in the course of disease when treatment options are limited. Recently, a study was published suggesting prostasin as a potential serum biomarker for ovarian cancer [28]. The authors profiled a small number of ovarian cancer cell lines and found that prostasin was overexpressed relative to normal ovary cell lines and then used enzyme-linked immunosorbent assay to show that prostasin protein is found at high levels in the serum of ovarian cancer patients. Using the “secreted” filter in ONCOMINE, we looked for genes overexpressed in ovarian cancer based on a study by Welsh et al. [23], which had profiled 27 primary ovarian carcinomas. This search independently confirmed prostasin as one of the most highly overexpressed genes with a secreted annotation in ovarian cancer (Figure 2). Had this resource been available to the authors of the prostasin study [28], they could have avoided their microarray analysis of cell lines moving straight from ONCOMINE to validation studies. Of note, genes encoding five other secreted proteins were found to be more significantly overexpressed than prostasin (LIF, SPINT2, LGALS3BP, LYZ, and ECGF1), suggesting that more accurate biomarkers may exist. A gene centric analysis of prostasin revealed that this gene is also highly expressed in prostate cancer, as defined by two independent datasets, and a subset of lung cancers, suggesting a broadened role for this marker.

Known Therapeutic Target Integration

Based on the hypothesis that therapeutic agents are most effective in cancer types in which their targets are highly expressed (e.g., ERBB2 overexpression in breast cancer leads to Herceptin susceptibility), we sought to provide a platform to explore the expression of all known therapeutic targets in cancer, even those that are targeted in diseases other than cancer. We hypothesized that this platform may lead to novel drug target–cancer type associations, suggesting novel applications of therapeutic agents currently in use. We compiled a set of 148 known drug targets and their respective drugs by querying the Therapeutic Target Database [38] and by automated PubMed searches (see Methods section). Sixty-five of these targets were found to be significantly overexpressed in at least one differential expression analysis (data not shown).

Within the *STUDY* module, the user can apply the therapeutic target filter to identify the targets most overexpressed in a particular differential expression analysis. For example, we found that PTGS2, otherwise known as COX-2, is the most significant overexpressed drug target in bladder cancer relative to normal bladder tissue ($Q = 3.1e-15$; Figure 3A). COX-2 is the key enzyme in prostaglandin biosynthesis and is targeted by nonsteroidal anti-inflammatory medications such as aspirin. Unknown to us, COX-2 had previously been shown to be overexpressed in bladder cancer, and a COX-2 inhibitor, Celecoxib, was shown to inhibit

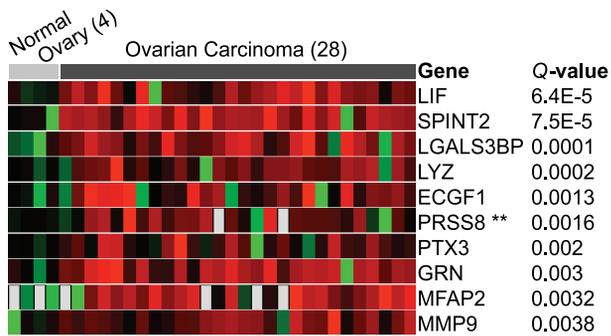


Figure 2. Genes encoding secreted proteins most significantly overexpressed in ovarian carcinoma relative to normal ovary samples as revealed by ONCOMINE. PRSS8, the sixth most significant gene, was previously shown to be an accurate serum biomarker for ovarian carcinoma [28]. Red signifies overexpressed relative to the mean normal value, black equally expressed, and green underexpressed. The number of samples in each class is given in parentheses.

bladder tumor formation in rats [39] and is currently in phase III clinical trials for the prevention of bladder cancer in humans [40]. Although this association was previously made, our coincidental finding supports the value of this approach.

The majority of hypotheses generated by this approach remain to be explored. For example, effective treatment strategies are desperately needed for pancreatic cancer, as current treatments have limited efficacy with survival rates less than 5% [41]. By applying the drug target filter, we found that ABL1 (Abl tyrosine kinase) is the most significant overexpressed drug target in pancreatic cancer relative to normal pancreas ($Q = 0.0097$; Figure 3B). Abl kinase is targeted by Gleevec, a small molecule inhibitor that has recently been approved for first-line therapy in chronic myelogenous leukemia [42]. Although the number of pancreatic samples in which ABL1 was overexpressed is small ($n = 8$), the association is novel and worth exploring. If further studies confirmed ABL1 overexpression and demonstrated its role in pancreatic carcinogenesis, perhaps Gleevec could be useful in its management. A gene centric analysis of ABL1 further revealed that it is overexpressed in glioblastoma ($P = .0012$) and medulloblastoma ($P = .0005$).

ONCOMINE Extras and Future Directions

To facilitate the rapid interpretation of a gene's potential role in cancer, ONCOMINE provides a centralized gene annotation resource, integrating information from other bioinformatics resources including Swiss-Prot, LocusLink [43], and Unigene, and providing direct links to Human Protein Reference Database (HPRD) [44] and SOURCE [45], and the pathway resources Kyoto Encyclopedia of Genes and Genomes (KEGG) [46] and Biocarta. An online tutorial is provided at the ONCOMINE website to demonstrate its functionality through a series of sample analyses. Future work will include the collection of additional microarray datasets as they become available, increased integration with other genome resources, and correlation-based analysis. ONCOMINE also serves as a platform to explore the "metasignatures" identi-

fied from the cancer microarray compendium, as described in our companion report (Submitted for publication).

In summary, ONCOMINE is a powerful platform for bioinformatic discovery that brings cancer microarray data and analysis capabilities to the fingertips of the cancer research community. We hope that this work and the continued support and development of ONCOMINE will stimulate further research and maximum access to and hypothesis generation from cancer microarray data, ultimately leading to the improved understanding of cancer and the development of novel diagnostic and therapeutic strategies.

Methods

Data Collection, Processing, and Storage

Microarray datasets were downloaded from public websites or provided by the authors upon request. The web

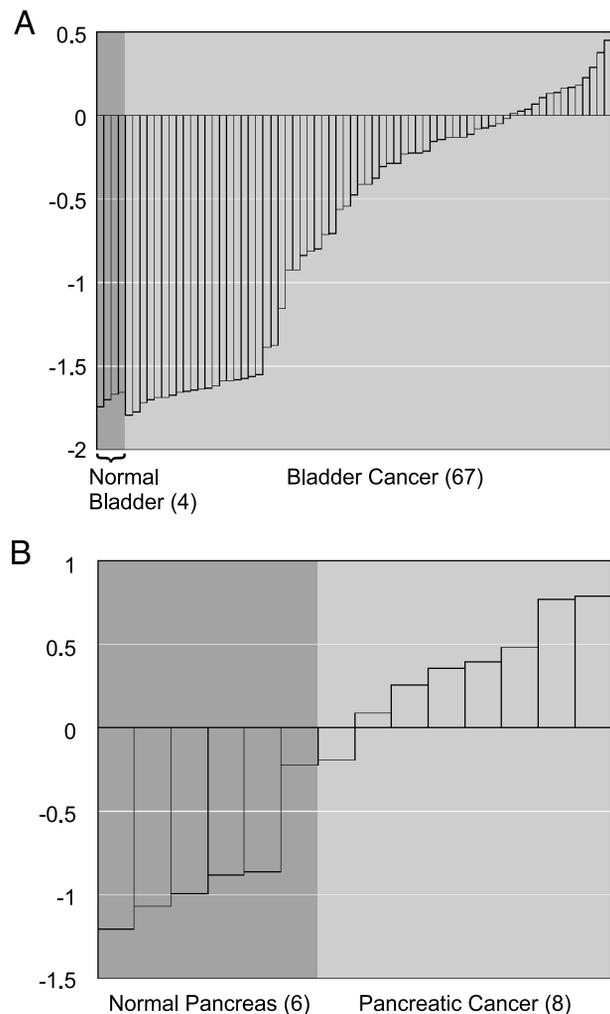


Figure 3. Therapeutic targets overexpressed in cancer as revealed by ONCOMINE. (A) PTGS2 (COX-2) is significantly overexpressed in bladder cancer relative to normal bladder samples ($Q = 3.1e-15$), confirming previous work that COX-2 is a potential target for bladder cancer. (B) ABL1 is significantly overexpressed in pancreatic cancer relative to normal pancreas samples ($Q = 0.0097$), suggesting that the Abl tyrosine kinase inhibitor, Gleevec, should be investigated for use. The number of samples in each class is given in parentheses.

addresses to download particular datasets are listed at ONCOMINE (www.oncomine.org). All data that were available from the authors were included in processing and analysis, except that negative values were not included. All data were log-transformed, median centered per array, and standard deviation normalized to one per array. Studies were named by the following convention: FirstAuthor_TissueTypeProfiled (e.g., Dhanasekaran_Prostate). To facilitate multistudy analysis, microarray features were mapped to Unigene Build 159. Data were stored in an Oracle 8.1 relational database.

Data Analysis

For each of the 40 microarray studies present in the database, we reviewed the samples profiled. Thirty-four studies had at least four samples corresponding to both classes of one analysis of interest and were further analyzed. Analyses of interest included cancer *versus* respective normal tissue, high-grade (undifferentiated) cancer *versus* low-grade (differentiated cancer) cancer, poor outcome (metastases, recurrence, or cancer-specific death) cancer *versus* good outcome (long-term or recurrence-free survival) cancer, primary cancer *versus* metastatic disease, and subtype 1 *versus* subtype 2. Following the assignment of samples to classes, each gene was assessed for differential expression with *t*-statistics using Total Access Statistics 2002 (FMS Inc., Vienna, VA). *t*-Tests were conducted both as two-sided for differential expression analysis and one-sided for specific overexpression analysis. For the purpose of whole study analysis, *P* values were corrected for multiple comparisons by the method of false discovery rates. Corrected *P* values are designated as *Q* values [33], where $Q = P^* n / i$ (n = total number of genes; i = sorted rank of *P* value).

Drug Target

Drug targets were defined by two methods. First, the Therapeutic Target Database [38] was queried for all targets that had a defined antagonist, inhibitor, or antibody. One hundred nine unique drug targets were identified. The targets were mapped to Unigene build 159 using gene names, symbols, and aliases as provided by SOURCE [45]. Second, all drug names present in the National Cancer Institute (NCI) clinical trials database (<http://www.nci.nih.gov/clinicaltrials/>) were subjected to automated PubMed searches, identifying articles with the drug name and the word “inhibitor” or “antibody” in the title. This list of titles was manually investigated for drugs and their specific targets (e.g., rituximab, CD20). Fifty-three unique targets were identified by this method. In total, 148 unique gene targets with specific drug inhibitors or antibodies were identified.

Gene Ontology

GO gene ontology [37] annotations linked to Unigene Cluster IDs were downloaded from SOURCE [45]. Three ontology categories were created by combining multiple annotations. The following annotations were part of the membrane-bound category: cell adhesion receptor, G-pro-

tein coupled receptor, plasma membrane, peripheral plasma membrane protein, transmembrane receptor, and transmembrane receptor protein tyrosine kinase. The following were in the kinase category: 1-phosphatidylinositol 3-kinase, cyclin-dependent protein kinase, diacylglycerol kinase, guanylate kinase, mitogen-activated protein (MAP) kinase, MAP kinase kinase, MAP kinase kinase kinase, nonmembrane-spanning protein tyrosine kinase, protein kinase, protein kinase C, protein serine/threonine kinase, protein tyrosine kinase, receptor signaling protein tyrosine kinase, transmembrane receptor protein serine/threonine kinase, and transmembrane receptor protein tyrosine kinase. Lastly, the following annotations were part of the secreted category: extracellular, extracellular matrix, and extracellular space.

ONCOMINE

ONCOMINE was developed using three-tier architecture. The back end consists of an Oracle 8i database for storing microarray data and statistics, and a series of key-indexed flat files for various biological databases. The middle tier, which handles application logic and core functionality, was developed with Python (www.python.org). The front-end client was implemented using ZOPE (www.zope.org). ONCOMINE is available at www.oncomine.org.

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