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A Mouse Model Repository for Cancer Biomarker Discovery

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Abstract

Early detection of cancer using biomarkers obtained from blood or other easily accessible tissues would have a significant impact on reducing cancer mortality. However, identifying new blood-based biomarkers has been hindered by the dynamic complexity of the human plasma proteome, confounded by genetic and environmental variability, and the scarcity of high quality controlled samples. In this report we discuss a new paradigm for biomarker discovery through the use of mouse models. Inbred mouse models of cancer recapitulate many critical features of human cancer, while eliminating sources of environmental and genetic variability. The ability to collect samples from highly matched cases and controls under identical conditions further reduces variability which is critical for successful biomarker discovery. We describe the establishment of a repository containing tumor, plasma, urine, and other tissues from ten different mouse models of human cancer, including two breast, two lung, two prostate, two gastro-intestinal, one ovarian, and one skin tumor model. We present the overall design of this resource and its potential use by the research community for biomarker discovery.

Introduction

Despite enormous investment in research, cancer still ranks as the second most common cause of death in the U.S. Survival rates for those diagnosed with many of the most common cancer types have changed little over the past two decades [1]. Perhaps the most important reason why cancer treatment fails is that cancer is often diagnosed at a late stage, after it has metastasized. Treatment for metastatic cancer is much more difficult and less effective than is treatment of a localized tumor. If cancer is detected early, prior to metastatic spread, survival rates are vastly improved [1]. For this reason, early detection may be the most effective strategy for reducing the burden of suffering and death extolled by cancer.

One of the most promising methods for early detection is to identify molecular markers (or biomarkers) of disease in easily accessible tissues such as blood or urine. Ideally the presence of these biomarkers would predict the presence of a tumor with high sensitivity and specificity. This strategy is based on the assumption that the presence of a tumor results in reproducible changes in components in the blood, including proteins, DNA, or metabolites, prior to clinical diagnosis. This is not a new idea, for example circulating levels of CA125 or PSA, have been routinely used for years for ovarian and prostate cancer screening, respectively. However these tests are far from perfect, leading to unacceptably high false positive rates and over diagnosis [2;3]. The advent of genomic and proteomic technologies, has greatly increased the ability to monitor changes in gene and protein expression on a global scale and a growing number of studies have applied these technologies to biomarker discovery [4–7]. Despite these advances, and the awareness that early detection may be the most effective means to battle cancer, with one exception no cancer-related biomarker assays have been FDA approved that use these technologies [8]. This clearly illustrates the

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existence of major roadblocks in the pipeline from biomarker discovery to validation to clinical use. This in turn has prompted the National Cancer Institute to create the Early Detection Research Network whose mission is to improve the biomarker pipeline for early detection of cancer [9] http://edrn.nci.nih.gov/about-edrn/.

A major challenge in early detection research is in the discovery of potential biomarkers. The identification of trace levels of a signature protein or proteins which may signify disease within the vastly complex serum proteome is technically daunting. The plasma proteome is the most complex human derived proteome and plasma proteins range in concentration over twelve orders of magnitude with 99% of protein mass is represented by 22 of the most abundant proteins [10–13] Candidate biomarkers are likely to be very low in abundance making their identification by existing mass spectrometry methods technically challenging [14–16]. Identifying biomarkers in human samples is exacerbated by extensive genetic and environmental variability, both of which can significantly affect the serum proteome. Another roadblock is biomarker specificity. While many candidate cancer biomarkers have been found, most turn out to lack sufficient specificity to be useful [1]. Part of this failure can be attributed to the lack of high quality carefully matched samples from cancer cases and controls. Many potential cancer biomarkers turn out to be nonspecific markers of angiogenesis, fibrosis, inflammation, or other pathologies not specific to cancer.

Mouse models of cancer have been instrumental in understanding the genetic, molecular, and biological basis of human cancer. Mouse models have also been used extensively in translational research; for example, in cancer prevention, intervention, or therapy related research. However, to date, such models have not been widely utilized for early detection research. We argue here that mouse models represent a useful and under-utilized resource for cancer biomarker discovery and validation.

Mouse models of cancer recapitulate many critical features of the neoplastic evolution of human cancer [17]. The similarities extend through multiple layers, including genetics, biology, pathology, and etiology [18]. Practical advantages of using mouse models for overcoming some of the challenges in early detection research include the following. Mouse models are frequently inbred, eliminating genetic variability as a confounding variable. Mice can be kept under identical environmental conditions, eliminating environmental variability which could affect the plasma proteome. While reducing confounding sources of variability, mouse cancer biology and plasma proteome are as complex as their human counterparts, thus providing a realistic platform for biomarker discovery. In some mouse models, tumor development is highly predictable and easily monitored, and blood samples can be collected at any predetermined stage before or during tumor development. A given model can be used as an inexhaustible source of biospecimens permitting sequential use through a pipeline of discovery, followed by verification, and finally validation. The small ratio of tumor to plasma in mice compared to humans, increases the concentration of potential biomarkers in the plasma, facilitating detection. Perhaps most importantly, control, non tumor-bearing mice can be rigorously matched to experimental tumor-bearing mice so that any differences observed between cases and controls can be unambiguously attributed to the disease state of the experimental mice.

Several recent studies demonstrate the potential use of mouse models for cancer biomarker discovery. Unsupervised clustering of LC-MS derived peptide patterns from mouse plasma provided unambiguous discrimination of mice with or without cancer [19]. Mouse models can be used for both technology development and discovery of clinically relevant biomarkers [20]. By comprehensive shotgun proteomic profiling of tumor and normal tissue from a transgenic model of breast cancer, a large number of candidate biomarkers were identified. A number of these were confirmed to be elevated in tumor tissue by Western blot analysis.

For one candidate, osteopontin, an ELISA was available to quantify protein levels. Osteopontin, a previously identified biomarker in human breast cancer, showed increased abundance in both tumor tissue and in the plasma from tumor bearing mice. A subsequent cohort of mice showed that osteopontin levels were elevated in plasma as early as the hyperplastic “preclinical” stage of breast tumor development.

For proteins lacking reliable antibodies, semi-quantitative and quantitative MRM (multiple reaction monitoring) [21] was used to confirm additional candidates. One of these, the extracellular matrix protein Fibulin-2, was subsequently shown by SISCAPA (which can detect proteins in the ng/ml range [22]) to be elevated in plasma from tumor bearing mice. Thus this mouse model successfully identified Fibulin-2 as a novel, validated breast cancer biomarker. This was subsequently confirmed in an independent model of breast cancer using a different MS platform [23]. Moreover this illustrates that mouse models can be used to create a new pipeline for biomarker discovery and validation. The time for the use of mouse models in early detection has arrived.

A limitation for some laboratories attempting to engage in biomarker discovery is the availability of quality samples. We have developed a repository of tissues from ten different mouse models of human cancer which will be made available to the research community through an application process. In this manuscript, we describe the overall design and contents of the repository and procedures for obtaining samples. It is hoped that this repository will be used to accelerate biomarker discovery and validation so that the promise of early detection can be realized.

Description of Repository Contents

A mouse model biospecimen repository was established as part of the NCI Mouse Proteomic Technologies Initiative (http://proteomics.cancer.gov/programs/mouse/overview.asp) to provide samples in order to develop and standardize technologies that would improve the accurate measurement of peptides and proteins linked to cancer. Important goals of the initiative included standardization of methods of sample preparation, protein and peptide detection and analysis, and development of specimen reference standards. As part of this Consortium, plasma was used to development and evaluate multiple technologies to identify proteins associated with cancer [24]

Human samples are currently procured and processed at various clinical and research centers using a variety of protocols. In keeping with the goal of standardizing methods of sample preparation, we developed a standardized protocol for plasma and tissue collection, handling and storage in order to eliminate many of the discrepancies associated with multiple sampling methods [20] (http//www.proteomics.cancer.gov).

Inbred mouse strains contain pre-engineered cancer-inducing genetic mutations that initiate and promote tumorigenesis in a determined timeframe; thus minimizing heterogeneity, both in sample constitution and preparation. As a result, mouse models provide a rapid testing ground for developing standards and protocols that can be translated to human clinical proteomics. Ten different mouse models, including two breast, two lung, two prostate, two gastro-intestinal, one ovarian, and one skin were selected to represent a variety of solid human cancers. The mouse models were selected based on the following criteria:

1. Tumor bearing mice and their controls were isogenic, i.e. on similar inbred genetic backgrounds. The models were backcrossed a minimum of 8 times onto an inbred background. A relatively simple breeding strategy was preferred to obtain the desired genotypes, as complicated breeding schemes can introduce genetic variability.

2. To reliably obtain blood samples from mice with defined neoplastic conditions, the model exhibited highly predictable tumor development over a well defined time frame with high penetrance. It is critical to unambiguously correlate the plasma samples to the pathological and neoplastic state of the donor mice.
3. To correlate plasma proteomic features with a given neoplastic condition, models that develop tumors in more than one tissue type were excluded. This did not preclude the use of models that developed multiple independent neoplastic lesions in the same tissue.
4. Malignancy was a desired but not essential feature of the models. A combination of models that exhibited a range of pathological progression from benign adenomas to metastatic disseminated carcinomas was chosen. A strong argument in favor of using models that exhibited a range of progression features is that early detection, if it is to be useful, should be able to identify lesions at early stages. Every mouse that donated serum was examined for gross and histologic evidence of disease and categorized according to the degree of neoplastic progression.
5. Models that are well characterized in terms of the clinical course, biological behavior, and genetics were preferred over less well-studied models.
6. A single dominant genetic lesion, through either transgene expression or gene knockout, was preferred in order to make the tumors as uniform as possible. To more closely mimic human diversity in tumor etiology, multiple tumor models within a given tissue were used. This provides the benefit of comparing the plasma proteomic profile between two independent models of breast cancer, for example.

In addition to genetically engineered mouse models, we included two chemically induced tumor models, DMBA/TPA induced squamous cell carcinoma of the skin and urethane induced lung adenomas and adenocarcinomas. Both models have been extensively studied with respect to their genetics and biological phenotypes. Tumors from these models contain somatic mutations in *Hras* (skin) or *Kras* (lung) at high frequency. Mutations in the *Ras* gene are found in >30% of all human cancers, underscoring the relevance of these models. Genetically engineered models have a known, defined genetic lesion that drives tumor development. Models that express known human oncogenes e.g. Ras and Her2/Neu, or that inactivate known human tumor suppressor pathways e.g. Rb, APC, PTEN and p53 via the SV40 T antigen were used. Comparison of the plasma proteome from mice with tumors induced by chemicals vs. germline lesions and between similar tumors driven by different oncogenic pathways will highlight the limitations or robustness of potential biomarkers.

Table 1 summarizes all mouse models contained in the repository, including a common name of the model, the mouse strain, the target gene, tumor type (e.g., lung, mammary, etc.) and a representative citation providing details of the model. Each model is briefly described below.

Conditional Neu induced mammary cancer

HER2/Neu is overexpressed in >30% of breast tumors and is clearly implicated in cancer progression. This mammary cancer mouse model uses the tetracycline regulatory system to conditionally express activated Neu in the mammary epithelium of transgenic mice [25]. When induced with doxycycline, bitransgenic MMTV-rtTA/TetO-NeuNT mice develop multiple invasive mammary carcinomas, which metastasize to the lung. Tumors develop focally and with 100% penetrance and a latency of between 6 – 12 weeks. The tumors are invasive solid nodular carcinomas typical of Neu/ErbB2 initiated mammary tumors. Essentially all of these lesions regress to a clinically undetectable state following transgene deinduction. Corresponding controls were transgenic for MMTV-rtTA only, and were paired

and housed in the same cage with the experimental bitransgenic mice. Both mice received doxycycline (2mg/ml +5% sucrose) in the drinking water starting at 8 weeks of age. All mice were maintained on an isogenic FVB background and only females were used.

Polyoma Middle T induced mammary cancer (PyMT)

This model was designed to understand the biology of mammary cancer as it displays 4 distinct stages of tumor progression in a single tumor focus that mimics the stages of human mammary cancer [26]. The oncoprotein polyoma middle T antigen is driven by the MMTV LTR and restricted to the mammary epithelia. Hyperplasia is detected at 4 weeks of age and mice develop carcinoma with pulmonary metastasis by 14 weeks of age. All mice were maintained on an FVB background and only females were used.

SV40 T antigen-induced prostate cancer (TRAMP)

In this prostate cancer model, expression of T antigen is driven by the minimal regulatory element of the rat probasin gene (*PB-Tag*) to the secretory epithelial cells of the dorsal, lateral, and ventral lobes of the murine prostate [27;28]. TRAMP mice exhibit mild to severe epithelial hyperplasia as early as 10 weeks of age. 100% of the mice develop invasive carcinoma with a latency of between 18–25 weeks of age. These tumors exhibit profound cribiform structures, numerous apoptotic bodies and abundant nuclear abnormalities, features associated with malignant progression. 30% of TRAMP mice also demonstrate metastatic spread of these primary prostate epithelial tumors to distal sites including lymph node, lung, and kidney.

PTEN deletion-induced prostate cancer

The PTEN tumor suppressor is lost or mutated frequently in human tumors, particularly in prostate cancers. This model uses a conditional floxed PTEN allele whose deletion is controlled by probasin driven cre expression [29]. Controlled inactivation of PTEN in prostate leads to subsequent activation of the AKT pathway, which is also a central pathway in human cancer. To generate the prostate-PTEN deletion PTEN L/+, Pb-Cre+/− males were crossed to PTEN L/L, Pb-Cre −/− females. PTEN loss in these mice lead to shortened latency of PIN formation in the pre-existing prostatic ductules and acini, and progression to invasive and metastatic prostate cancer.

SV40 T antigen-induced ovarian cancer (MISIIR)

In this murine model of epithelial ovarian cancer, expression of both large and small T antigen is driven by a Mullerian inhibitor substance type II receptor (*MISIIR*) which directs expression to the ovary [30]. 100% of female *MISIIR Tag* transgenic mice develop bilateral epithelial ovarian cancer by 25 weeks. These tumors are poorly differentiated carcinomas and disseminate widely, invade the omentum and form ascites as do human ovarian carcinomas.

Mutant Apc models of intestinal neoplasia (Min and 1638N)

Apc is a tumor suppressor that is mutated in >80% of human colorectal cancer. The Apc^{min} mouse model contains a heterozygous germline mutation in the *Apc* gene and on a C57BL/6 genetic background, spontaneously develops adenomas of both the small intestine and colon at 100% incidence by 20 weeks of age [31]. An additional model, Apc^{1638N} spontaneously develop both adenomas and adeno-carcinomas of the small intestine and colon at 100% incidence, but with a longer latency of between 30–50 weeks of age [32;33]. The occurrence of malignancy in the Apc^{1638N} model will provide an important comparison with the benign lesions of the Min mouse model.

DMBA/TPA-induced squamous cell carcinoma (SKIN)

Skin tumors induced in mice with DMBA/TPA uniformly contain activating mutations in the H-ras oncogene. Tumors are induced with a single application of DMBA to the dorsal skin followed by repeated applications of TPA starting at 8 weeks of age [17]. Benign squamous cell papillomas appear by 8 weeks post-DMBA, which progress to malignant squamous cell carcinomas (SCC) beginning at 6 months. The skin tumors are highly uniform at both the histologic and genetic levels, and are easily monitored on the same animal through time. Conversion from benign to malignant lesions can be precisely quantified. Mice heterozygous for the tumor suppressor *p19/Arf* on a NIH01a background were used for the skin tumor model due to their reduced latency in developing papillomas and carcinomas compared to wild type mice [34].

Urethane-induced lung tumors

A single injection of urethane (1mg/kg) to A/J wild type neonatal mice (3 weeks of age) induces multiple broncho-alveolar adenomas with 100% incidence by 30 weeks of age [35]. These tumors contain activating mutations in the K-ras oncogene at codon 61. This model is commonly used for analysis of human non-small cell lung cancer.

Mutant EGFR induced lung tumors

To complement the chemically induced Kras model described above, we have included an inducible mutant EGFR transgenic model. These mice use the tetracycline regulatory system to direct expression of mutant EGFR to the lung. When induced with doxycycline, bitransgenic *CCSP-rtTA TETO-EGFR*^{L858R} mice express mutant EGFR in type II alveolar epithelial cells of the lung. [36] Focal hyperplasia is seen as early as 2 weeks after doxycyline treatment which progress to solid adenomas and adenocarcinomas. After 4 weeks on doxycycline, mice develop multifocal invasive adenocarcinomas of varying sizes, abnormal lung parenchyma, and sometimes accompanied by progressive thickening of the alveolar walls. These tumors regress completely following doxycyline withdrawal indicating a dependence on EGFR activation.

Mouse Husbandry—Care was taken to ensure that no systematic biases were introduced between cases and controls. Mice were closely matched with respect to age, sex, litter, cage status, and treatment protocols. To ensure environmental variability was minimized, nearly all the mouse models (9/10) were housed at the Fred Hutchinson Cancer Research Center to maintain uniformity in animal care and handling. All mice in the study were maintained with a 12 hr light dark cycle and access to food and water *ad libitum*. Experimental mice were monitored daily and any abnormal health or behavior noted. Case and control mouse pairs were housed together in the same cage and sacrificed back-to-back on the same day. All animal care and sample collection was performed by trained personnel utilizing a standard operating procedure as described below.

For all models, except the Conditional Neu model, a total of 25 pairs of mice (tumor bearing and control) were obtained at sacrifice to support technology development for biomarker discovery (e.g, a Discovery cohort). For the Conditional Neu model, more intensive breeding and sample ascertainment was performed and a “validation cohort” was obtained as well. A total of 250 pairs of mice were collected in total. An additional 50 pairs of mice were used to collect serial plasma samples from retroorbital sinus bleeds at 4 week intervals between induction to sacrifice, in order to monitor proteomic changes associated with neoplastic progression over time.

Collection of plasma and tissue—Based on the known clinical course of disease, mice were sacrificed at defined time points (e.g. when tumors were either visibly apparent or

predicted to be of specific size and progressive state) to obtain plasma and tissue samples. All mice were sacrificed between 10 and 3 pm by carbon dioxide asphyxiation. Whole blood was immediately collected by heart puncture using a 2ml syringe and a 22 gauge needle. Whole blood was immediately emptied from the syringe into K3EDTA coated 1.5 ml microcentrifuge tubes and spun in a refrigerated centrifuge at 4 °C for 5 min at 5000 rpm to remove cells. Plasma was collected, carefully avoiding cellular contamination. Between 0.3 to 0.6 ml of plasma was reliably obtained from each mouse. Samples were divided into 0.1 ml aliquots in cryovials and frozen in liquid nitrogen cooled tanks. All samples were barcoded and entered into the central database. For serial blood collection, 0.2 ml whole blood was collected in EDTA coated capillary tubes from the retroorbital sinus. These samples were processed as above to obtain plasma and frozen in 0.05ml aliquots in liquid nitrogen. No more than four bleeds per animal were taken, with a minimal interval of 4 weeks between bleeds.

Necropsy consisted of a visual examination of the external body surface, the thoracic, abdominal, and pelvic cavities and viscera. Tumor specific tissues and any organs or tissues with obvious gross lesions, including mammary, GI, liver, lung, kidney, gonads, pancreas, stomach, thymus, spleen, bladder, and lymph nodes were snap frozen in liquid nitrogen or fixed in neutral buffered formalin. A representative subset of tissues from each mouse model were embedded in paraffin, sectioned, stained with hematoxylin and eosin and examined microscopically by a veterinarian pathologist. The whole carcass of the tumor bearing animals were fixed in formalin in the event that further examination is needed for residual disease, micrometastatic lesions, or other pathological conditions.

All plasma and tissue samples for each individual mouse were designated with a unique identifying number and barcoded for easy extraction from the bank. All information regarding the mouse for which samples were obtained is available on a web based central database, and includes cage (includes litter and parental information), date of birth, date of sacrifice or serial bleed, general appearance and body weight. Digital photographs of any gross, neoplastic, or metastatic lesions are also stored on the site and available for inspection. The information recorded for all mice can be viewed by prospective investigators with permission.

Procedures for requesting specimens

The use of biospecimens from a mouse model repository may provide the proteomics community a means to develop and improve their technologies prior to undertaking costly human clinical studies. A primary goal of this mouse biospecimen repository is to provide sets of tumor and control tissue, plasma, and urine to accelerate the biomarker pipeline.

The repository contents, a summary of the current specimen availability, and specimen request forms may be found at http://www.proteomics.cancer.org. Requests for samples will be taken from investigators worldwide and will be reviewed on a quarterly basis. Researchers may request the use of any specimens contained in the repository. Table 2 summarizes the contents of the mouse repository including all tissues, plasma, and urine collected from each mouse model. Requests will be reviewed based on both scientific merit and the appropriateness of the volume of material requested. Scientific merit will be evaluated on the ability of the potential technological advance of the proposed work, the potential clinical utility, and funding sources for the work. All researchers must agree in principle to share their findings, conclusions, and potentially their data through the NCI CPTC program.

Conclusion

We have established a resource of biospecimens for use in technology development or validation of biomarkers for the early detection of cancer. The mouse model repository will provide researchers with plasma and tissue samples from both tumor bearing and non-tumor bearing control mice. Matched specimens of tissue and plasma from the same mouse will allow investigators to identify potential cancer specific proteins in the tissue followed by targeted proteomic approaches on the plasma. Proteomic analysis of plasma samples can complement both proteomic and genomic analyses performed on tissue samples. Mouse model samples contain all the biological complexity of human specimens making them potentially useful for identifying novel biomarkers and for evaluating new technologies. Use of this resource will accelerate the biomarker pipeline, from discovery, to verification, and validation of cancer specific markers.

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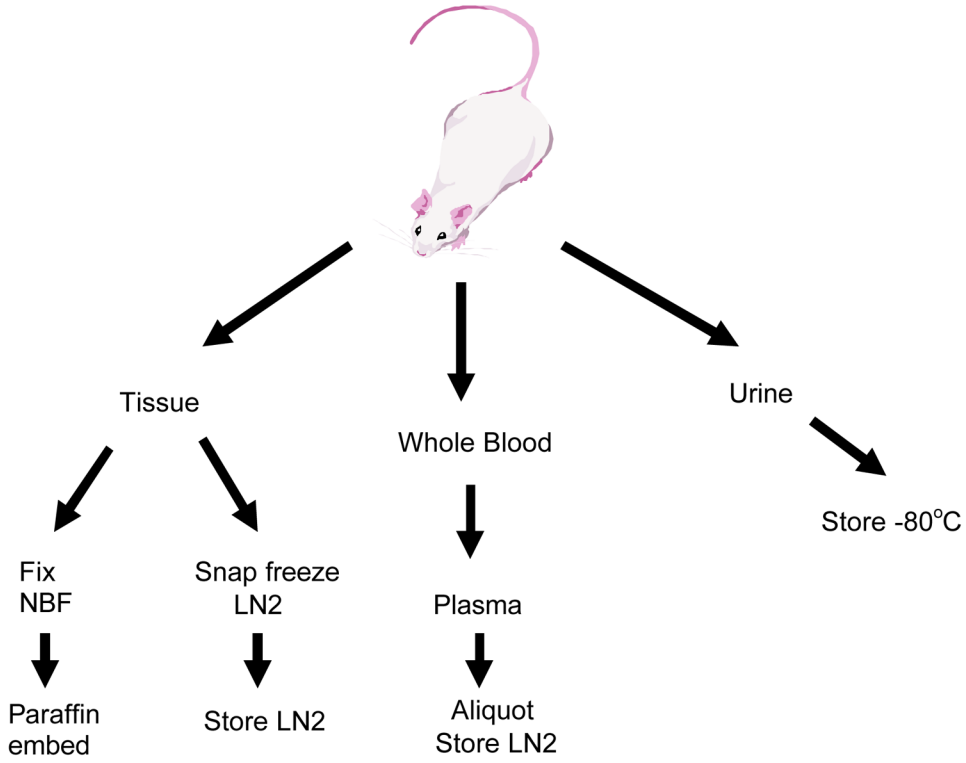

Figure 1.
Schematic of mouse model sample collection strategy.

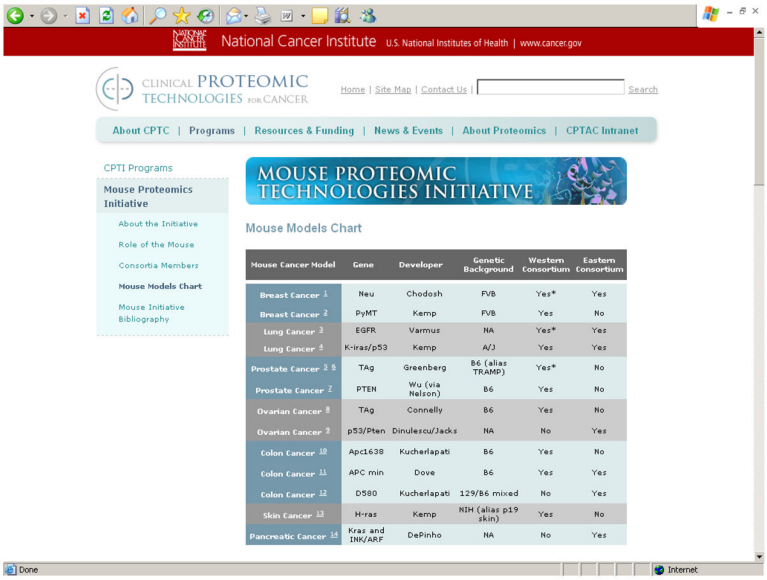

Figure 2.
NCI Proteomic Technologies Initiative Webpage

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Table 1

Summary of mouse models contained in the repository

Tumor type	Model common name	Primary genetic lesion	Penetrance	Latency (wks)	Strain	Metastasis	Citation
Mammary adenocarcinoma	Conditional Neu mammary	Doxycycline inducible MMTV-*Neu*	100%	6–12	FVB	Yes	Cancer cell, 2:451– 461, 2002
Mammary carcinoma Prostate adenocarcinoma	PyMT mammary	SV40-PyMT	100%	12–15	FVB	Yes	Amer. J. Path, 163: 2113–2126, 2003
	TRAMP prostate	SV40 *Tag* (*Rb* and *p53*)	100%	18–25	C57BL/6	Yes	Proc. Natl. Acad. Sci. 93: 3439–3443, 1995
Prostate adenocarcinoma	PTEN prostate	*PTEN*	100%	12–25	129	Yes	Cancer cell, 4:209– 221, 2003
Epithelial ovarian cancer	MISIIR ovarian	SV40 *Tag* (*Rb* and *p53*)	100%	15–25	C57BL/6	Yes	Cancer Res., 63: 1389–1397, 2003
GI adenoma	APC Min GI	Apc^{Min}	100%	12–20	C57BL/6	No	Science, 256, 668– 670, 1992
GI adenoma, adenocarcinoma	APC 1638N GI	Apc^{1638}	100%	30–50	C57BL/6	Yes	Proc. Natl. Acad. Sci. 91: 8969–8973, 1994
Skin papilloma, carcinoma	DMBA/TPA Skin	Hras p19*/Arf*	100% (PA) 80% (CA)	10–12 15–25	NIH01a	Yes	PLOS Biology, 2: 1138–1149, 2004
Lung adenoma	Urethane lung	Urethane induced *Kras1*	100%	15–30	A/J	No	Mol. Carcinog., 17:217–223, 1996
Lung adenocarcinoma	EGFR lung	*EGFR*	100%	9–12	B6/129	No	Genes & Dev.,20: 1496–1510, 2006

Table 2

Contents of mouse repository

Mouse model	Frozen and fixed tissues	Plasma 300–500ul	Urine (volume varies)	H&E slides Set = 1 tumor bearing and 1 control
Conditional Neu mammary	Mammary, lymph node, spleen, lung, liver, kidney, carcass	300 pairs	15 pairs	10 sets
PyMT mammary	Mammary, lymph node, spleen, lung, liver, kidney, carcass	25 pairs	9 pairs	5 sets
TRAMP prostate	Prostate, testes, pancreas, spleen, liver, lung, kidney, carcass	25 pairs	6 pairs	5 sets
Pten prostate	Prostate, testes, pancreas, spleen, liver, lung, kidney, carcass	25 pairs	0 pairs	5 sets
MISIIR ovarian	Ovary, pancreas, spleen, liver, lung, kidney, carcass	25 pairs	0 pairs	5 sets
Apc Min GI	Proximal, distal, medial SI, colon, pancreas, spleen, liver, lung, kidney, carcass	25 pairs	3 pairs	5 sets
Apc 1638N GI	Proximal, distal, medial SI, colon, pancreas, spleen, liver, lung, kidney, carcass	25 pairs	10 pairs	5 sets
Skin	Skin, carcinoma, papilloma, lymph node, lung, kidney, liver, spleen, carcass	25 pairs	0 pairs	5 sets
Urethane lung	Lungs, spleen, liver, kidney, carcass	25 pairs	11 pairs	5 sets
EGFR lung	Lung, spleen, liver, kidney, stomach, GI, bladder, pancreas, ovary or testes, carcass	25 pairs	0 pairs	5 sets