Mouse Cancer Models:

Incorporation into Translational Research and Personalized Medicine

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Mouse Cancer Models: Incorporation into Translational Research and Personalized Medicine

- What is a mouse cancer model?

- Why use mouse models?

- How will they be used in cancer research?

  - Cancer genetics

  - Drug development

  - Therapy and prevention

  - Drug safety and toxicity

Mouse Cancer Models: Incorporation into Translational Research and Personalized Medicine

Mouse models of cancer are:

- Normal inbred laboratory mice and their crosses;

- Mice whose genomes are "engineered" with mutant genes to initiate spontaneous cancer development (GEMMs);

- Mice that are exposed to carcinogens to generate spontaneous tumors.

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Mouse Cancer Models: Incorporation into Translational Research and Personalized Medicine

Why do we use mouse cancer models?

- Mice and humans have very similar genomes;

- Mice are an intact mammalian system to bridge basic cancer cell biology and translational research;

- Laboratory mice, GEMMs, and humans have normal immune function;

- GEMMs have a natural history of cancer progression that is analogous to humans;

- GEMMs can represent the clinical course of human cancers;

- The genetics of mouse crosses can reflect the heterogeneity of human population genetics.
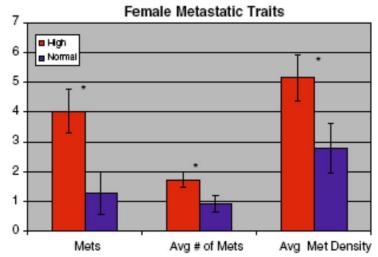
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How mouse models will contribute to human cancer genetics

- High dietary fat intake and obesity may increase the risk of susceptibility to certain forms of cancer.

- To study the interactions of dietary fat, obesity, and metastatic mammary cancer, Drs. Daniel Pomp and Kent Hunter crossed the M16i model of diet-induced obesity with the Polyoma MT breast cancer model.

- They fed the mice a very high-fat or a matched-control-fat diet, and measured growth, body composition, age at tumor onset, tumor number and severity, and pulmonary metastases.

- Animals fed a high-fat diet had decreased cancer latency, and increased tumor growth and pulmonary metastases.

Female Metastatic Traits

- They identified genome loci for 25 modifiers for mammary cancer and pulmonary metastasis, likely representing 13 unique loci, and novel diet/modifier interactions among most of the loci.
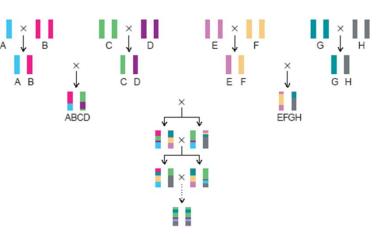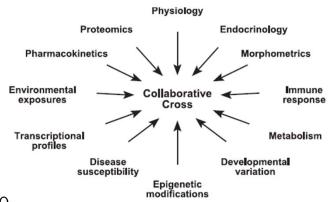
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How mouse models will contribute to human cancer genetics

- An international organization, the Complex Trait Consortium, is evolving a new mouse genetic resource consisting of strains that contain genomic contributions from a highly diverse set of 8 founder lines, including several wild strains.

- The top panel shows the breeding scheme for this "Collaborative Cross", a common genetic reference panel.

- The approximately 700 strains, once generated, genotyped, and cryo-preserved, will be a renewable resource to study multi-genic traits and the interactions among known disease genes, other genetic loci, and etiologic factors.

- As more researchers in many disease communities use the strains, phenotype them, and add the data to a public database, the value of the strains for everyone engaged in systems genetics research will greatly increase.
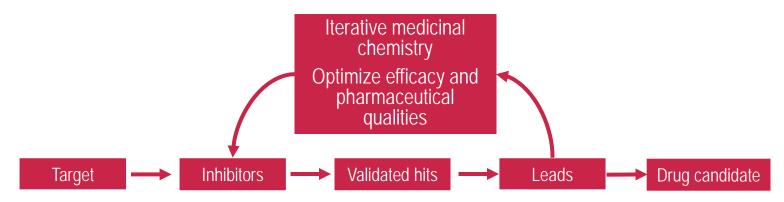
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How mouse models will contribute to drug development

Mouse models are a biological context for target selection

- Identify new targets
- Credential targets for efficacy
- Validate the roles of targets in disease biology
- Expose genetics of response and toxicity

Iterative medicinal chemistry

Optimize efficacy and pharmaceutical qualities

Target → Inhibitors → Validated hits → Leads → Drug candidate

They are useful to screen leads

- Employ mouse tumor lines transplants in syngeneic immune-competent hosts
- Develop imaging approaches for *in vivo* evaluation of leads
- Discover genetic determinants of response or resistance

They inform the use of candidate drugs

- Identify patient populations
- Select effective combinations and appropriate disease site and stage
- Test novel delivery approaches
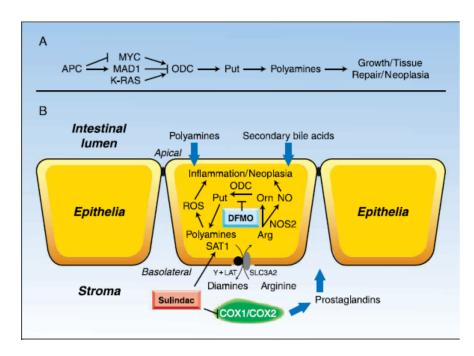- Identify & test surrogate endpoints

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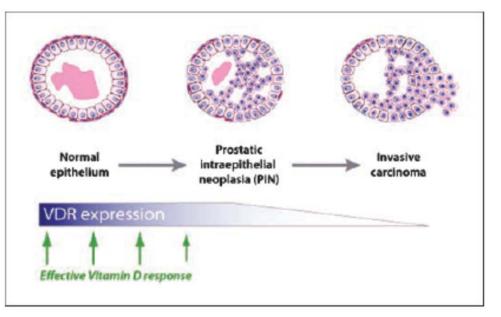
How mouse models will contribute to human cancer prevention

- Drs. Eugene Gerner and Frank Meyskens used the APC ^{min} mouse model of intestinal neoplasia to discover the details of interactions among the APC and c-MYC genes and polyamines in the intestinal lumen.

- They then used an iterative cross-species approach with mouse and human specimens to validate the observations from the mouse model.

- These studies, and epidemiological evidence for the role of polyamines in the development of colon adenomas, led them to evolve an effective approach for prevention of recurrent adenomas, tested in a randomized, prospective, placebo-controlled 3-year trial.

- The combination of sulindac and DFMO prevented occurrence of all adenomas in 70% of patients, and 90% of advanced adenomas.

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How mouse models will contribute to human cancer prevention

- Epidemiological studies implicate relative vitamin D3 deficiency as a significant risk factor for development of prostate cancer.

- Dr. Cory Abate-Shen and her colleagues tested the efficacy of vitamin D3 as a preventive agent in the Nkx3.1;Pten prostate cancer model, which undergoes cancer progression from PIN to adenocarcinoma.

- Sustained delivery of vitamin D3 to the mice resulted in significant reduction of PIN, and was maximally effective if it was given before appearance on PIN.

- Their findings predict that vitamin D3 will be optimally beneficial if delivered during early stage prostate carcinogenesis, when the vitamin D3 receptor is expressed in the prostatic epithelium.

- Delivery of vitamin D after cancer initiation may not be effective for preventing its progression.

Normal epithelium → Prostatic intraepithelial neoplasia (PIN) → Invasive carcinoma

VDR expression

Effective Vitamin D response

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How mouse models will contribute to drug safety and toxicity

- Dr. Kevin Shannon and his colleagues studied therapy-induced cancers in NF-1 mutant mice, a model of children with neurofibromatosis;

- The NF-1$^{+/-}$ mice were treated with radiation or cyclophosphamide, or both;

- Either treatment or the combination induced secondary malignancies, including myeloid leukemias, sarcomas, and breast cancer;

- This is a tractable system for mechanistic studies, comparing malignancies induced by various therapies, and conducting prevention studies;

- It is also an example of a translational system to study risks of using genotoxic therapy for NF1 patients.

Table 1. Tumor spectra in untreated and genotoxin-exposed mice according to genotype

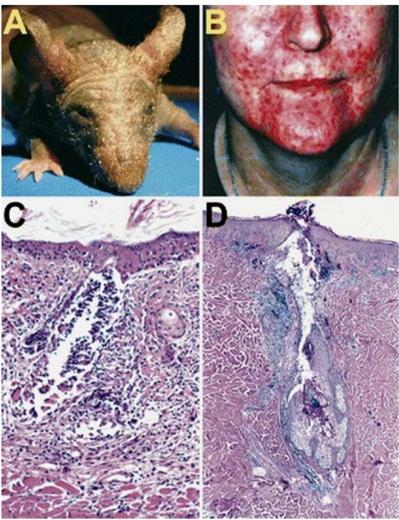| Type of neoplasm	Wild-type (n = 100)	Nf1$^{+/-}$ (n = 81)
Neural crest tumors	0	16
Soft tissue sarcomas	0	8
Pheochromocytoma	0	6
Neuroblastoma/paraganglioma	0	2
Myeloid malignancies*	4	17*
Breast cancer	0	4
Poorly differentiated malignant tumors	0	3
Other	13	11
Total	17	51

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How mouse models will contribute to drug safety and toxicity

- Dr. David Threadgill and his colleagues examined the histology of the skin and other organs in a mouse with an EGF-R gene with reduced activity (hypomorph).

- Shown here is histology of the effect of the genetic change on the mouse skin compared to the effect of an EGF-R inhibitor on a patient who has developed acneiform folliculitis.

- The changes in histology in many organs of this mouse indicate the toxicities of EGF-R targeted drugs , including cardiac, renal, digestive, neuronal, lung, and liver perturbations.

- Similar analyses of mice with altered expression of the targets of other clinical agents, such as COX-2, also presage the organ specificity of these agents.

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Discussion Topics

- How can the NCI ensure that the many mouse models and mouse genetics resources reach the goal of improving human health?

- How can the NCI promote integrated human/mouse research?

- Are there additional research areas for which mouse cancer models may be appropriate?

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