Mouse Cancer Models:  
Incorporation into 
Translational Research 
and Personalized Medicine
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.
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.
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.

• 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.
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

They are useful to screen leads

- Employ mouse tumor lines transplants in syngeneic immune-competent hosts
- Develop imaging approaches for \textit{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

Iterative medicinal chemistry
Optimize efficacy and pharmaceutical qualities

Target $\rightarrow$ Inhibitors $\rightarrow$ Validated hits $\rightarrow$ Leads $\rightarrow$ Drug candidate
How mouse models will contribute to human cancer prevention

- Drs. Eugene Gerner and Frank Meyskens used the APC\textsuperscript{\textit{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.
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.
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>
<thead>
<tr>
<th>Type of neoplasm</th>
<th>Wild-type (n = 100)</th>
<th>NF1+/− (n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neural crest tumors</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Soft tissue sarcomas</td>
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<td>8</td>
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<td>Pheochromocytoma</td>
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<td>6</td>
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<tr>
<td>Neuroblastoma/paragangioma</td>
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<td>Myeloid malignancies*</td>
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<tr>
<td>Poorly differentiated malignant tumors</td>
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<td>3</td>
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<tr>
<td>Other</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>51</td>
</tr>
</tbody>
</table>
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.
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?