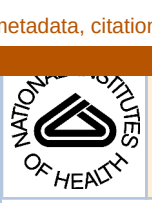

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The untapped potential of genetically-engineered mouse models in chemoprevention research: Opportunities and challenges

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Summary

The past decade has witnessed the unveiling of a powerful new generation of genetically-engineered mouse (GEM) models of human cancer, which are proving to be highly effective for elucidating cancer mechanisms and interrogating novel experimental therapeutics. This new generation of GEM models are well-suited for chemoprevention research, particularly for investigating progressive stages of carcinogenesis, identifying biomarkers for early detection and intervention, and pre-clinical assessment of novel agents or combinations of agents. Here we discuss opportunities and challenges for the application of GEM models in prevention research, as well as strategies to maximize their relevance for human cancer.

Introduction: Modeling cancer prevention in genetically-engineered mutant mice

Despite many recent advances, cancer remains a leading cause of death in the United States. While many patients have benefited from the development of new approaches for diagnosis and treatment; ultimately, the most successful strategy for eradicating cancer will entail discovery of more effective means for its prevention, early detection, and early intervention. While genetically-engineered mouse (GEM) models of human cancer can greatly augment prevention research, to date, these models have not been widely exploited for prevention research. Here we consider the progress, potential, and pitfalls of using GEM models for

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prevention research, concluding with a discussion of how we can best capitalize on these models in the future. For a more in depth discussion of GEM models in cancer prevention the reader is referred to (1).

GEM models of human cancer refer to mouse strains in which the genome has been manipulated to achieve gain- or loss- of oncogene or tumor suppressor gene function, respectively, the consequences of which are manifested in tumor phenotypes (2). Similar to chemically-induced rodent models, which historically have been widely used in prevention research, GEM models provide an opportunity to investigate carcinogenesis in the context of the whole organism. However, GEM models are distinct from chemically-induced rodent models, since their tumor phenotypes are induced by manipulating a specific gene or genetic pathway rather than induction with carcinogens and/or other cancer promoting agents. Thus, GEM models enable the assessment of specific molecular pathways for tumorigenesis in the context of the whole organism.

GEM models are also distinct from xenograft models, which are typically based on the propagation of human tumors and/or cell lines in immune-deficient mice. While xenograft models have the obvious advantage of being developed from human cancer cells, they are often derived from established tumors or cancer cell lines (and very often from advanced tumors or metastases), and therefore are unlikely to precisely model early events in carcinogenesis. Moreover, since xenografts are propagated in immunodeficient mice, they do not recapitulate the contributions of the tumor microenvironment, bacterial flora, or host immune system for carcinogenesis, which is of considerable concern as it is becoming increasingly apparent that these play critical roles in carcinogenesis, particularly at early disease stages (3–5).

However, critics of GEM models argue that their relevance for human cancer has not been established (6), and cite examples in which studies in mouse models have not been validated to human cancer (see below). On the other hand, proponents of GEM models contend that the problem is not that the models aren't relevant, but that the experimental parameters have not been designed in such as way as to effectively translate studies from mice to human cancer (7–9). Indeed, the applicability of prevention studies done in GEM models of human cancer will invariably be dependent on the *choice* of the model, the *design* of the experiment, and many other logistical issues. Ultimately, for studies in GEM models to be applicable to humans, the models need to be appropriately chosen such that their biological and pathological properties are relevant for the experimental question being asked and, conversely, the experimental design of the study should be analogous to design of prevention research in humans.

Accordingly, it is imperative to establish criteria for evaluating the relevance of a particular GEM model for a given experimental paradigm. Such criteria should include: (1) *Pathological analyses* — does the model display histological and pathological features in common with human cancer or a sub-type thereof? (2) *Disease evolution* — does the model recapitulate the stages of disease progression as occurs in humans? (3) *Tumor microenvironment* — does the model effectively recapitulate the contribution of host factors including the tumor stroma, bacterial flora, and immune response for cancer progression? (4) *Molecular pathways* — does the model display relevant genetic, genomic, epigenetic, and/or proteomic alterations that are known to be relevant for their human counterpart? (5) *Environmental factors* — do hormonal, dietary, or other factors affect disease progression in the mouse models in a similar way as they do in humans?

Notably, it is often the case that in the course of characterizing these criteria for GEM models, new insights emerge that are relevant for understanding the molecular and biological properties of the human disease. Thus, analyses of GEM mice have elucidated critical biological

mechanisms of tumorigenesis that provide new insights into human cancer, including as the critical role of telomere length in disease pathogenesis (10) and more recently the role of cellular senescence in tumor suppression *in vivo* (11). Similarly, comparative analyses of the molecular properties of mouse and human tumors have enabled the comprehensive analyses of global alterations in genomic pathways (12), as well as the identification of specific genes that are novel biomarkers of disease outcome in humans (13,14).

In the discussion that follows, we first provide a historical perspective on the types of GEM models that are available for prevention research (Table 1). Following which, we discuss past experiences using mouse models in prevention research and consider how these past experiences can impact the design of future studies. Finally, we consider opportunities for using GEM models as well as obstacles that need to be overcome to effectively capitalize on their application for prevention research.

The first generation: the oncomice

Historically, the first GEM models of human cancer were the transgenic models, the so-called "oncomice", in which a particular gene (most often an oncogene and in many cases SV40T antigen) was expressed in the mouse genome via a tissue-specific promoter, resulting in a cancer phenotype (reviewed in (15)) (Table 1). These oncomice provided some of the earliest GEM models for pancreatic, breast, prostate, and brain cancer, and their analyses over the past two decades have provided the foundation for many investigations of cancer mechanisms, and have been used in pre-clinical studies for both prevention and experimental therapeutics.

As is the case for all model systems, transgenic models have certain advantages as well as limitations. One of the major reasons transgenic models remain popular is their relative simplicity of design and propagation; these models provide a straightforward means of assessing the consequences of gain-of-function of particular genes for tumorigenesis. However, disease evolution may be dissimilar to that of most human cancers, since it is initiated by expression of an exogenous gene and typically not stoichastically. Furthermore, the generation of transgenic models is, by definition, dependent on the availability of suitable promoters, defined as those that achieve targeted expression in the appropriate cell types and in the appropriate spatial-temporal domains such that the resulting cancer phenotypes resemble their human counterparts. While this may seem a high bar to achieve, in practice several promoters have been effectively utilized for the development of transgenic models that recapitulate the progression and phenotypic features of their counterpart human cancer (15).

The second generation: loss-of-function of tumor suppressors

The next phase in the evolution of GEM models of cancer was based on targeted deletion of tumor suppressor genes in the germline (Table 1). Among the first of such models were those resulting in targeted deletion of *Trp53* and *Rb1*, which develop a spectrum of cancer phenotypes (2). Notably, their tumor spectrum was found to be dissimilar to the consequences of mutations of these tumor suppressor genes in human cancer, which has been offered as an indictment of the lack of relevance of these GEM mouse models for human cancer. However, subsequent studies have shown that gain of function mutations of *Trp53*, in contrast to null mutations, lead to more similar tumor phenotypes to human cancer (16,17), and have also shown that the occurrence of a retinoblastoma phenotype in *Rb1* mutant mice is dependent on alterations of other genes (18). Interestingly, although these and other germ-line mutant mouse alleles have been extensively utilized to investigate cancer mechanisms, to date they have not been widely used for cancer prevention studies.

Another potential limitation of germline mutant alleles is that they are more similar to inherited forms of cancer than sporadic forms, which are far more prevalent in humans. However,

improved technologies for manipulating the mouse genome have led to more sophisticated gene targeting approaches, wherein selected genes of interest are conditionally inactivated (or conditionally activated) in spatially- and temporally-restricted domains. These conditional models include those based on loss-of-function of tumor suppressor genes, such as *Trp53* and *Pten*, as well as gain-of-function of oncogenes, such as *Kras* (reviewed in(2)). Conditional gene targeting offers many advantages over traditional gene targeting in the germ-line, such as overcoming the problem of embryonic lethality, which often precludes analyses of homozygous germ-line deletion of tumor suppressor genes, such as *Rb1* and *Pten*. In addition, selective gene targeting to specific cell/tissue compartments often yields GEM models with a more restricted spectrum of tumor phenotypes, which are more suitable for pre-clinical studies.

The “next” generation of mouse models of cancer

Conditional models depend on having suitable approaches for achieving targeted gene deletion/activation in spatially- and temporally-restricted domains. Thus, what has truly revolutionized the application of such models for human cancer has been the tremendous advances in recent years for achieving highly restricted expression of Cre recombinase in tissue specific compartments using transgenic or “knock-in” approaches, as well as the potential to selectively regulate Cre activity using derivatives that are activated by tamoxifen or other compounds (7,19) (Table 1). Furthermore, technological improvements have enabled the introduction of Cre recombinase into specific tissue sites using adeno- or lentiviral approaches. For example, selective delivery of Cre recombinase via an adenoviral delivery into the lungs of a mouse allele harboring a conditionally-activatible Kras allele has led to the generation of a mouse model of lung cancer, which has provided new insights for stratifying human patients with lung cancer, has led to the identification of lung progenitor cells, and has been effectively used for pre-clinical studies for experimental therapeutics and prevention research (20–23).

Other important technological approaches include the utilization of systems in which gene expression can be turned on or off using tetracycline-regulated activators affecting the responsive promoters driving the transcription of a gene of interest (24), which has been applied to several organ systems, including lung, lymphoid and breast to study the roles of oncogenes in tumor maintenance and mechanisms of tumor recurrence (25,26). Other approaches for manipulating gene expression include targeted expression of the receptor to the TVA chicken virus in specific mouse tissues, thereby providing a means to transduce the target tissues with viruses that will express specific genes of interest (27), which has led to the generation of valuable models of CNS and other tissues (28). Moreover, as an alternative to gene targeting approaches, new technologies for the stable “knock-down” of gene expression *in vivo* by delivery of RNAi moieties are proving to be effective for developing mouse models of cancer (29,30). Finally, major technological advances in small animal imaging approaches, which now enable the effective visualization of tumors *in vivo* has made a huge impact on the effective utilization of GEM models and will surely be an asset for their application for cancer prevention (31).

In summary, a robust generation of GEM models is now available or in the pipeline, which are based on the restricted loss- or gain-of-function of gene expression in highly selective tissue-specific compartments and with precise temporal kinetics. Several of these models have already been validated to the human cancers they emulate, often to specific sub-types of the disease, and are now being exploited for the development of novel therapeutic approaches in academic and industrial settings. However, it is important to note that relatively few studies of cancer prevention have been done using this “next” generation of more sophisticated GEM models of human cancer. Thus, potential promise of GEM models for cancer prevention research remains largely unexplored.

Lessons from the past: successes or failures?

Although GEM models have been relatively under-utilized in prevention research, lessons from previous studies can help to assess their potential value for cancer prevention in future research. In particular, the colon is among the best-studied areas of prevention research in which mouse models have been employed extensively (32,33). This reflects in part, a long-standing tradition of prevention research in colon cancer, as well as the availability of a chemically-induced Apc^{Min} (multiple intestinal neoplasia) mouse model of the disease based on mutational loss-of-function of the *Apc* (Adenomatosis polyposis coli) gene, which is also mutated in the Familial Adenomatous Polyposis syndrome and many human colon cancers (32,33). Notably, while the Apc^{Min} model has been extensively used to gain insights into the mechanisms of colon carcinogenesis and for prevention research, the phenotype occurs mainly in the small intestines and is non-invasive, whereas a newer generation of GEM models that develop colon cancer should provide improved models for colon cancer prevention research (33,34).

Extensive epidemiological evidence has shown that individuals consuming a high-fat "Western-style" diet have a higher incidence of many cancers and that agents such as Vitamin D have a protective effect against cancer. Preclinical studies done in the Apc^{Min} model to investigate the consequences of a Western-style diet, including reduced calcium and vitamin D and increased fat, for colon carcinogenesis resulted in elevated cancer-rates in the mutant mice, in agreement with the epidemiological data (32,33). However, some subsequent prospective clinical trials did not confirm that altering dietary factors led to prevention of colon cancer (35), which led to concerns about the relevance of these pre-clinical studies in mice for human colon cancer. Skeptics of using mouse models for cancer prevention have offered these data as an indictment of the limited relevance of these models to human cancer.

However, proponents of mouse models have noted that the trial design and endpoints of the clinical trial were quite different than those of the epidemiological and pre-clinical studies, and have suggested that the discrepancy between these findings may reflect differences in experimental design rather than an actual differences in between the mouse and human situations. Indeed, examination of stratified groups in the polyp prevention trial revealed that the most compliant quartile showed a three-fold reduction in risk of advanced adenoma (36). Therefore, the data from the mouse models, which are inherently more homogenous and nearly 100% compliant, may recapitulate a sub-group of the human patients. This suggests that the findings in mouse models may be relevant when appropriate comparisons are made.

Indeed, while it is customary to consider the criteria of the best *model*, perhaps it may be more relevant consider the most appropriate model for the *experimental question*; surely any model, no matter how relevant, can be considered non-predictive if it is not used in the appropriate contextual framework. Importantly, since any model will undoubtedly have certain limitations, the issue is not whether a given model recapitulates every aspect of the human disease (which would be nearly impossible!) but rather whether it provides reliable information for the experimental question that is being addressed and whether the experimental design will ultimately lead to insights that will be applicable to human cancer.

The challenge of using GEM models for cancer prevention

So, why have GEM models been so underutilized in cancer prevention thus far? One important reason has been the need for model refinement; indeed, GEM models that are likely to be most effective for prevention research have come on board only recently. As discussed above, these "next generation" models more closely recapitulate the evolution of cancer progression, more effectively enable the interrogation of earliest disease stages, and provide valuable models for pre-clinical assessment. However, in addition, there remain important practical and scientific

issues that have hampered the use of GEM models in cancer prevention research and will continue to do so if not addressed.

One key problem is that prevention research requires the integration of multiple scientific perspectives. Improving ways of bringing together epidemiologists, basic scientists, mouse modelers, geneticists, bioinformaticians, and clinicians will be imperative for making real headway in cancer prevention. Unfortunately, communication between these multiple areas of research have been limited, particularly with respect to the potential application of GEM models for prevention research. An effective strategy to bridge this gap may be to establish consortia of prevention researchers, including those with the various complementary expertise noted above.

A second major problem is one of cost. Preclinical studies in mutant mice are expensive and difficult to recover from standard funding mechanisms. Although GEM models are now being increasingly utilized for experimental therapeutics by the pharmaceutical industry, most prevention research has been focused in academic settings and there has been little opportunity for cost-sharing with industry. One means of addressing the high cost of these research efforts would be to establish designated centers for conducting pre-clinical prevention studies that would bring together on a large-scale expertise in animal handling, pre-clinical design and implementation, *in vivo* imaging, pathology, genomics and pharmacology.

Another major stumbling block for virtually all studies using GEM models of cancer is the lack of sufficient numbers of pathologists that can critically evaluate GEM models relative to the human cancers they represent. While the involvement of pathologists will be key to the successful establishment of a concerted effort in applying mouse models to cancer prevention, the number of veterinary and academic medical pathologists available for such collaborative efforts is limited. In addition, the adoption of standardized morphologic nomenclature is needed to facilitate comparison of mouse models with human cancer (37,38). Close working relationships between veterinary and medical pathologists will be critical for assessment of the utility of these models

Finally, a significant impediment to the use of GEM models has been intellectual property issues. In particular, broad patents on the use of genetically-engineered mice for cancer studies have hampered pre-clinical testing of compounds using GEM models in academic and industrial settings (9,15). Fortunately, the recognition that GEM models may play a critical role in identifying compounds that are more likely to succeed in human clinical trials has begun to accelerate their use in both academic and industry settings (9).

Opportunities for using GEM models for cancer prevention

Despite these challenges, the future of GEM models for cancer prevention is very promising. The time is now ideal for exploiting a new generation of highly sophisticated mouse models to address critical issues in cancer prevention (Fig. 1). However, for this to be fully realized, careful consideration needs to be paid not only to the design of the models but also to the design of the experimental paradigms in which they are used. Moreover, there is a need to recognize and overcome the limitations of the model systems, as well as practical limitations that have hindered their effective use for cancer prevention research.

So, what are the major opportunities for using GEM models to augment prevention research (Fig. 1)? First of all, GEM models offer a unique opportunity to interrogate the earliest stages of carcinogenesis in the context of the whole animal. While premalignant lesions are often inaccessible in humans, they can be readily studied in GEM models, particularly with the benefit of new imaging modalities. Such studies in GEM models can facilitate our understanding of the molecular pathways that are deregulated in pre-invasive lesions in

humans, as well as provide models to test the consequences of targeting such pathways with chemopreventive agents. Indeed, it would be exceedingly difficult to identify the relevant pathways in premalignant or early invasive lesions in human cancer, considering their relative inaccessibility, the overall heterogeneity, and inability to study progression over time. However, once pathways and mechanisms have been identified in GEM models they can be readily assessed to evaluate their potential relevance for human cancer.

In addition, since most GEM models are developed from defined genetic alterations, carcinogenesis is relatively uniform and generally dependent on specific de-regulated pathways. Therefore, cancer phenotypes in mouse models tend to be relatively homeogenous, which can help to overcome the problem of biologic variation due to the tremendous genetic diversity in studying human cancers. As a consequence, GEM models can provide a filter for the identification of relevant molecular pathways for target validation as well as biomarker detection. An exciting recent application is the use of serum profiles from GEM models to identify potential biomarkers for early detection of human cancer (Hanash, S. and Depinho, R., personal communication)(39). Furthermore, analyses of tumor phenotypes in genetically-variant strains of mice can help to identify “risk” factors or “modifier” genes that influence tumor phenotypes (40), which would be exceedingly difficult to identify in humans.

Finally, appropriately designed pre-clinical studies in GEM models can provide an important resource for investigating the efficacy of novel chemopreventive agents, as well as the consequences of dietary, chemical, hormonal, and/or environmental influences on carcinogenesis. In particular, studies in GEM models can enable the initial testing of single agents, or evaluate the efficacy of combinations of agents, which have potential chemopreventive benefit, and can also provide initial insights into their toxicity limits and mechanisms of action *in vivo* (9,41). Moreover, GEM models offer a resource for investigating the consequences of environomental influences, such as the contribution of diet, the intestinal flora, or hormonal influences for carcinogenesis (42–44).

In summary, GEM models offer a unique opportunity for providing biological and mechanistic insights regarding the interplay between genetic and environmental factors that influence cancer initiation as well as pre-clinical models to test the consequences of targeting specific factors for alleviating carcinogenesis. While analyses of mouse models will never be a suitable replacement for human clinical studies, such analyses can surely aid in the refinement of such studies to the considerable benefit of the human population assuming that the appropriate models are used in the appropriate experimental paradigms.

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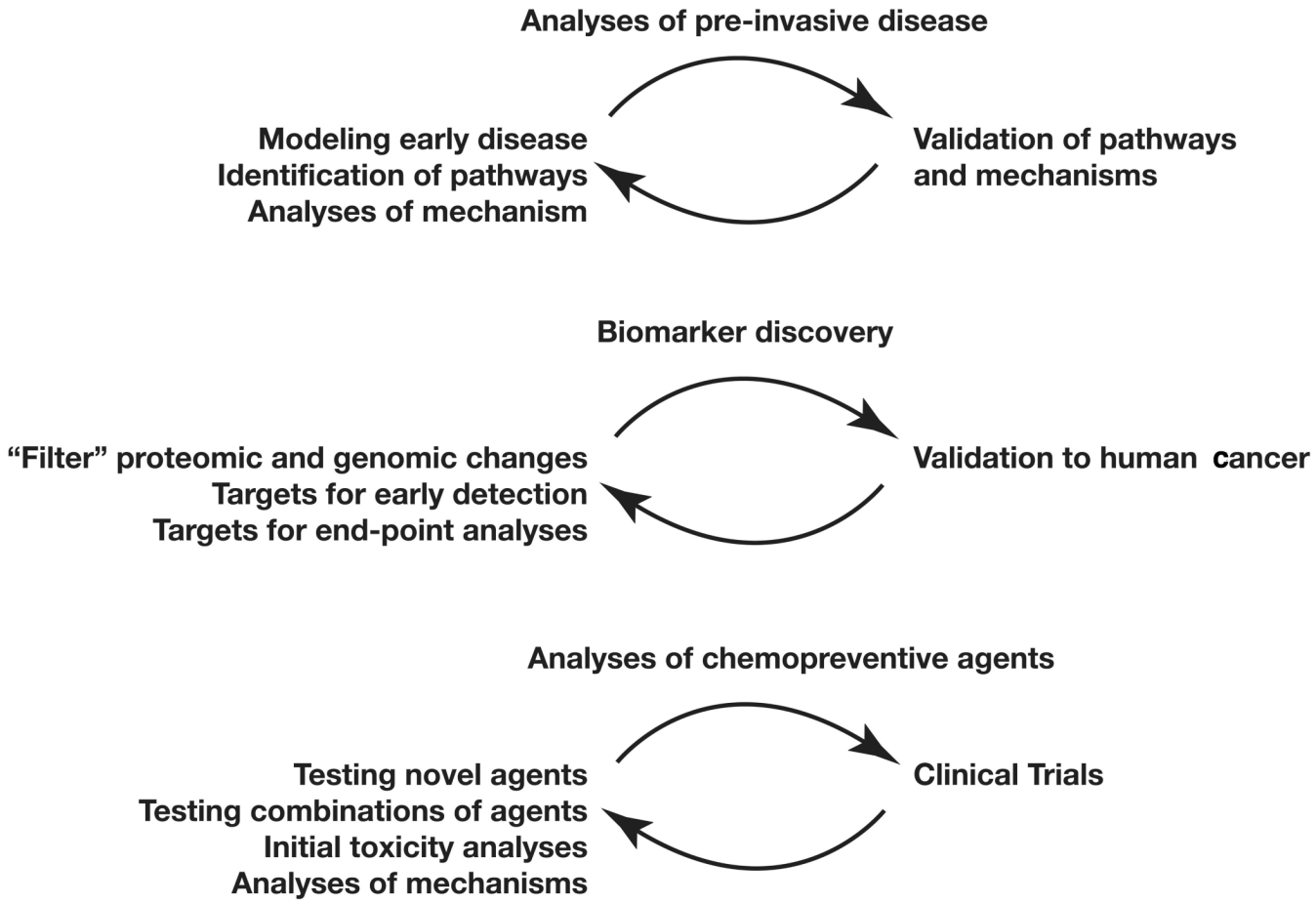

Figure 1.
Chemoprevention: From Mouse to Man

Table 1

Type of model	Common Uses	Advantages	Disadvantages
Transgenic	Gain of oncogene function	Ease and simplicity of design and use Classic models are still relevant	Forced expression may not model disease evolution Requires tissue-specific promoter
Germline deletion	Loss of tumor suppressor function	Initial insights of tumor suppressor function Classic models are still relevant	Model inherited rather than sporadic cancer Homozygous deletion often results in lethality
Conditional gene targeting	Gain or loss of function	Overcome embryonic lethality Tissue specific phenotypes	Require tissue-specific promoter expressing Cre Recombination often in many cells, not stochastic
Cre-inducible gene targeting			
Via Cre mouse alleles	Gain or loss of function	Control spatial, temporal, and extent of gene targeting	Require inducible Cre alleles Matings are complex
via viral delivery	Gain or loss of function	Viral delivery is stochastic and not directed to a specific cell type	Targeting multiple cell types can lead to heterogeneity
Tet-regulatable models	Gain or loss of function	Reversible spatial and temporal control of gene expression	Long-term investiment for multiple targeting alleles Matings are complex
TVA models	Gain of function	Stochastic spatial and temporal regulation	Need specialized mouse alleles for tissue of interestVirus infects replicating cells
RNAi gene silencing	Loss of function	Control levels of gene expression Can be reversible	Possible off target effects Technology is still in development