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ONE MOUSE, ONE PATIENT PARADIGM: NEW AVATARS OF PERSONALIZED CANCER THERAPY

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Abstract

Over the last few decades, study of cancer in mouse models has gained popularity. Sophisticated genetic manipulation technologies and commercialization of these murine systems have made it possible to generate mice to study human disease. Given the large socio-economic burden of cancer, both on academic research and the health care industry, there is a need for *in vivo* animal cancer models that can provide a rationale that is translatable to the clinic. Such a bench-to-bedside transition will facilitate a long term robust strategy that is economically feasible and clinically effective to manage cancer. The major hurdles in considering mouse models as a translational platform are the lack of tumor heterogeneity and genetic diversity, which are a hallmark of human cancers. The present review, while critical of these pitfalls, discusses two newly emerging concepts of personalized mouse models called “Mouse Avatars” and Co-clinical Trials. Development of “Mouse Avatars” entails implantation of patient tumor samples in mice for subsequent use in drug efficacy studies. These avatars allow for each patient to have their own tumor growing in an *in vivo* system, thereby allowing the identification of a personalized therapeutic regimen, eliminating the cost and toxicity associated with non-targeted chemotherapeutic measures. In Co-clinical Trials, genetically engineered mouse models (GEMMs) are used to guide therapy in an ongoing human patient trial. Murine and patient trials are conducted concurrently, and information obtained from the murine system is applied towards future clinical management of the patient’s tumor. The concurrent trials allow for a real-time integration of the murine and human tumor data. In combination with several molecular profiling

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techniques, the “Mouse Avatar” and Co-clinical Trial concepts have the potential to revolutionize the drug development and health care process. The present review outlines the current status, challenges and the future potential of these two new *in vivo* approaches in the field of personalized oncology.

Keywords

Genetically engineered mouse models; Mouse Avatars; Co-clinical trial; Personalized medicine, Xenograft models; Drug discovery

1. INTRODUCTION

Cancer is a highly heterogeneous disease characterized by multiple genetic lesions and aberrations in extensively interconnected signaling cascades. The inherent complexity of the disease has severely stymied drug discovery and development strategies with highest drug attrition rates for cancer therapies[1]. Indeed, rigorous attention to cancer prevention, early detection, and better therapy have reduced mortality and improved treatment regimens. However emergence of chemo-resistance and long-term survival for patients with advanced disease still remain a major challenge. In fact, only about 5% of the anti-cancer agents that go through preclinical testing get approved for use by the FDA[1]. To further exacerbate the situation, FDA approved drugs are being withdrawn or discontinued for several toxicity related issues[1]. By the year 2020, the direct/indirect cost of cancer is estimated to be at $300 billion dollars in the US alone[2]. Given the socio-economic burden of the disease, several *in vitro* and *in vivo* strategies are being developed in an attempt to combat cancer.

Amongst the large repertoire of *in vivo* systems used to study cancer, mouse models represent the most widely used system. The ease of genetic manipulation, short gestation period and low maintenance cost are some of the advantages associated with the use of murine systems[3]. The integration of vast amounts of information obtained from the Human and Mouse Genome Projects, respectively, has facilitated the genetic manipulation of mice to mimic human disease[4]. Use of sophisticated inducible tetracycline responsive systems, flippase-flippase recognition target system, inducible Cre systems and the Cre-LoxP technology allows temporo-spatial regulation of the genetic aberrations in ways that were impossible 10 years ago[4].

While these murine models have remained valuable to understand the molecular events driving oncogenesis, a limitation associated with the use of such inbred laboratory mouse models is the lack of heterogeneity that is inherent to human tumors. Intelligent use of conditional systems, inducible systems and chimeric mice has partially offset this limitation, however, improvements are yet to be made to address the issues of tumor heterogeneity and inter-patient variability in drug response observed in the clinical setting[3].

Several attempts are being made to address the limitations associated with the transition of scientific knowledge from the mouse to human disease. These attempts particularly aim at integrating the use of mouse models in personalized medicine. Two such initiatives in the field of cancer biology include the concept of Co-Clinical Trials and the use of “Mouse

Avatars". The Co-Clinical Trial Project primarily focuses on the use of genetically engineered mouse models (GEMMs) to guide patient therapy in ongoing human clinical trials[5]. On the other hand, "Mouse Avatars" represent a patient-derived tumor xenograft (PDTX) model to aid in the selection of appropriate chemotherapeutic agents[6]. This review outlines these recent advances and assesses their implications on future research.

2. MOUSE AVATARS

2.1 Introduction

A portion of a patient's tumor, obtained either by surgical resection or biopsy, is transplanted in immunodeficient mice, and allowed to propagate without any *in vitro* manipulation. Subsequent generations of mice are then used for drug testing purposes in an attempt to guide patient therapy[6] (Fig. 1). These systems are also referred to as personalized mouse models or patient-derived tumor xenografts models (PDTX). The application of this concept to drug efficacy and safety studies is referred to as 'xenopatient trials'[6].

2.2 The Approach

Sectioned patient tumor samples are implanted (subcutaneously or orthotropically) in immunodeficient mice. The generation of mice receiving the patient tumor transplant is referred to as F_0 or G_0. Subsequent generations are referred to as F_1, F_2, $F_3 \ldots F_n$ or G_1, G_2, $G_3 \ldots G_n$ respectively[7]. Successful implantation of the tumor depends on a number of factors including tumor type, site of transplantation and strain of mouse used and usually takes between 2-4 months[8]. Typically, the third generation (i.e F_3 or G_3) is used for drug testing purposes, although certain groups/institutions may use earlier generations for this purpose[6]. The generation of mice to be used for drug efficacy evaluation should be decided based on the similarity of the human and engrafted murine tumor rather than an arbitrary passage number[6]. The general approach with the use of such xenograft systems is outlined in Figure 1.

2.3 Current Status

Until recently, characterization of tumors at the molecular level was performed in the patient, which only gave tumor profile at one point in time, limiting our understanding of mechanisms of tumor metastasis and chemoresistance [3,9]. However, with the advent of "Avatars", where the tumor tissue is grown in many mice and harvested at different time points allows for understanding of the molecular changes driving metastasis and resistance to drug therapy[9,10]. Tumor profiling at the molecular level (of the genome, transcriptome, proteome and metabolome) at different time points with different treatments determines whether the molecular drivers, signaling pathways and metabolic fluxes of tumor growth and drug responses are comparable between the human and mouse tumors (Figure 2). Concordance between the engrafted murine tumors and the original patient tumors have been established in several cancer models such as non-small cell lung cancer (NSCLC), small cell lung cancer and pancreatic tumors amongst others[11,12,13].

These mice may also be used for biomarker development strategies. For example, research in *Kras* oncogene mutant colorectal cancer cell lines and PDTX models have identified activation of the Wnt pathway as a biomarker predicting resistance to AZD6244 (a mitogen-activated protein kinase kinase MEK1/2 inhibitor) therapy. The research suggests the use of combination therapy targeting MEK and the Wnt pathway effectors as a plausible pharmacological intervention strategy for these *Kras* mutant colorectal tumors[14]. Utility of these PDTX models to drug discovery, drug efficacy and biomarker studies is increasingly being recognized and is only going to grow at an exponential scale (see Table 1 for a representative list of PDTX models for different cancer types). Extensive research, over the years, has fueled commercialization of these xenograft models with various large and small companies providing ever more sophisticated services (Table 2). Commercialization of the PDTX models would help accelerate cancer research by eliminating the time and resources required for generation of xenograft models. Further, standard protocols designed and approved by a governing body such as NIH, NCI or the FDA maybe adopted to generate such PDTX models in the future. Use of uniform, approved protocols ensures that comparable standards are used to generate and evaluate PDTX models in different companies. This allows for reliable correlations to be made from the results obtained from multiple independent studies using these commercial models. These commercial models will not only benefit academic researchers but also serves as a resource for preclinical drug testing for pharmaceutical companies.

2.4 Recognizing the challenges facing the development of a personalized mouse

While the concept of having a personalized mouse to tailor individual drug therapy has shown some level of success, the technique does not come without its limitations and pitfalls. There are several scientific and non-scientific limitations associated with the use of this method.

Amongst the scientific limitations, first, patient tumor may not engraft in the mouse. . Second, depending on the type of cancer, engraftment efficiencies vary significantly, thereby not allowing the establishment of a standard operating protocol, which is essential in the clinical setting. For example, non-small cell lung cancer tumors are more likely to get implanted than prostrate tumors[15]. Third, subcutaneous or orthotopic implantation of the tumor does not accurately reflect the tumor microenvironment. Although implantation of the patient tumor along with stromal components may offset this problem, the murine stroma gradually replaces the human stroma and may lead to confounding results. Fourth, several tumors, that are known to metastasize in the patient, do not do so in the PDTX systems thereby severely hampering their applications to guide patient treatment[16]. Fifth, tumor propagation in the mouse may result in several genetic, pathologic, histological and micro-environmental niche changes that may not mirror the patient's tumor accurately[6,17,18]. Sixth, differential results seen in different immune-deficient mouse strains are another complicating factor. The immune-compromised nature of the mice make it impossible to study therapeutic agents that target the immune system[6]. Seventh, a major hurdle with the use of such systems is the evolving nature of human tumors. A patient's tumor continuously evolves and it may so happen that the tumor at biopsy (used to determine optimal

therapeutic regimes) is significantly different at the time when treatment is actually initiated based on murine data.

The most critical non-scientific limitation is the cost associated with maintaining such models. Development of these models entails the maintenance of 'live tumor banks'[6], mouse housing facilities and histopathological cores incurring high cost. Several companies are providing PDTX model generation and drug testing services to patients at a cost of tens of thousands of dollars. New York Times reported the case of a Ewing sarcoma patient who paid $25,000 to generate a mouse avatar [19]. However, this cost is not covered by health insurance. Moreover, the implantation, propagation and drug testing in mice are a time consuming process and many patients die before they can benefit from such xenograft systems. The emergence of several companies offering similar services is likely to lower the cost involved with the use of these avatars. However, quite a few patients from the middle and low-income groups will still not be able to make use of such personalized preclinical testing systems. Increased popularity of the "Avatar" systems also warrants the regulation of its use by a federally run centralized body similar to FDA or embedded within the FDA to regulate cost and streamline disparate practices with respect to health insurance. Such a regulatory body would oversee fair competition and uniformity of services offered by various commercial enterprises.

2.5 Customized adaptations to "Mouse Avatar" Systems

2.5.1 Validation of a PDTX model—A variety of molecular profiling techniques of the xenografted murine tumor and its comparison with a corresponding profile from the parent patient tissue can be used to validate a PDTX model and establish its capacity to faithfully mimic a patient's disease. Beijing Genomics Institute has recently launched a bioinformatics filtering tool called 'PDXomics' which helps eliminate any misreads due to contamination of host and murine xenografted tumors which is likely to be valuable for the validation of the models[20].

2.5.2 Applications to drug efficacy studies and chemoresistance prediction—Extensive bioinformatics and network analyses of the transcriptomic and proteomic data from the human and murine tumors can help identify metastatic pathways, drug targets and potential biomarkers[21]. Based on the drug targets identified, the mice with the transplanted tumors can be treated with a variety of chemotherapeutic agents to identify a rational combination for use in the human patient[7]. Biomarkers predicting drug response can be used to stratify the patient population for treatment purposes, thereby allowing for highly focused, personalized therapy that eliminates the use of agents that are likely inefficient or even toxic[7] (Figure 2). Continued drug treatment in the PDTX model may result in a relapse thereby enabling identification of potential resistance pathways. Such responses can serve as templates for what is expected in a patient following treatment. Further, the relapse observed in a mouse can be treated with multiple drugs, with the hope that some combination may work effectively for a given patient. Thus, at the time of a relapse in a patient, new therapeutic modalities would already be available.

2.5.3 Cryopreservation of xenografted murine tumors—One of the limitations associated with the use of xenograft systems is the increasing divergence between human and murine tumor characteristics as the tumor is continually passaged in mice[6]. Establishment of repositories that store frozen tumors from the F3 mouse generation will help offset this divergence. Such repositories also guarantee an unlimited supply of a specific patient's biopsy/tumor sample[15]. Storage of these xenograft systems will also facilitate in identifying and obtaining DNA lesions, aberrant transcriptomic (mRNA, miRNA and ncRNA), proteomic and metabolomics profiles as the technology for large scale deep sequencing and mass-spectrometry becomes accessible and cost-effective[6,22].

2.5.4 Establishment of a human tumor microenvironment in the xenograft model—Kuperwasser et al developed a new protocol for the generation of a xenograft model to study progression of breast cancer[23]. They generated "humanized mammary fat pads" in mice by injecting human mammary stromal and epithelial cells into the cleared murine mammary fat pad. Anatomical (ductal architecture) and physiological (production of milk in pregnancy) characteristics of this chimeric mouse fat pad was found to be similar to that of humans[23]. Such a system would help allow transplant of patient-derived tumors directly into the murine fat pad thereby ensuring a more accurate recapitulation of the human breast tumor. Similar strategies maybe applied to other cancer types to ensure that the human tumor grows in a more representative microenvironment in the mouse.

2.5.6 Use of humanized mice—The immune-compromised nature of the mice used for xenografting purposes presents several problems that must be addressed. The lack of an intact immune system in the mouse does not allow elucidation of the immune response to the tumor. Further, immunomodulatory agents cannot be evaluated for efficacy in such systems[24,25]. The emergence of different strains of humanized mice has indeed offset these problems. These humanized mice possess human immune systems thereby facilitating a better assessment of the tumor microenvironment and allowing the study of immune-modulatory agents for chemotherapy.

2.5.7 Comparing drug kinetics in PDTX models and human patients—A comprehensive study of drug pharmacokinetics and metabolism in the murine system and its concordance with human patients is warranted to ensure successful application of murine drug efficacy data to patients[25]. Several software suites allow for in-silico simulation, determination and comparison of pharmacokinetic parameters in different species. Cloe® PK is one such software from the company Cyprotex which allows pharmacokinetic predictions to be made for humans, rats and mice. Other such softwares are PK-Sim5® by Bayer Technology Services and GastroPlus™ by Simulations Plus Inc. The use of in-silico methods coupled with traditional pharmacokinetics and pharmacodynamics studies allow extrapolation of the results of murine testing to a clinical setup.

2.6 Future Prospects

The "Mouse "Avatar" system provides a means to test therapeutic regimens in an attempt to personalize cancer therapy. Despite inherent limitations, xenograft model in combination with other molecular biology techniques will prove useful(Figure 2). The utility of these

systems is enhanced in light of the finding that patient tumor derived cell lines have a significantly different expression pattern when compared to the original or the xenografted tumor[13] [7,25]. Furthermore, PDTX systems have already been successfully utilized for preclinical testing in a variety of cancers and is considered a superior modality [6]. Giovanella et al used colon cancer xenograft models as early as 1989 to establish the utility of DNA topoisomerase-I inhibitors[26], a practice which has evolved to encompass several other therapeutic agents, both approved and investigational[6]. Multi-institution studies allow for extensive genomic, proteomic and metabolomics characterization and successful application of these models to drug discovery endeavors[6]. One such study is the BEAUTY project initiated by Mayo Clinic which combines whole genome sequencing and the use of mouse avatars to guide therapy in breast cancer patients[27]. Taken together, the opportunity for patients and doctors to create mouse avatars and their utilization to guide therapy, assess drug responses to predict chemoresistance and attenuate drug toxicity in itself is a great leap in clinical medicine. Thus, xenograft systems are only going to get better as they are increasingly used in conjunction with molecular biology techniques and thus have tremendous potential to become a mainstream modality in the field of clinical oncology.

3. THE CO-CLINICAL TRIAL PROJECT

3.1 Introduction

A co-clinical trial refers to trials that are conducted simultaneously in GEMMs and human patients as part of the phase I/II trials for drug development[5]. The trial typically involves collection, comparison and integration of data obtained from analyses of the murine and human tumors. The data obtained include mutational background, single-nucleotide polymorphisms, responsiveness to therapeutic agents, tumor images, tumor RNA, protein and metabolic profiles[5]. The human tumor biopsy samples are also implanted and studied in immune-compromised NSG (NOD *scid* gamma) mice[5] (Fig. 3).

3.2 The Approach

The project aims at real-time integration of murine and human trial data in an attempt to improve clinical decisions and outcomes. The typical workflow involves the testing of a new drug entity (for a particular cancer) in the clinic and in all GEMMs developed for that cancer simultaneously (Fig. 3). Based on the response seen in each of the GEMM classes, the patient population is stratified[5]. Such a system helps in the identification of the genetic basis of therapeutic response (and hence lead to the development of biomarkers) and allow its translation, almost immediately, to the human patient cohort[5]. Analyses of the drug responses at the molecular level in these mouse models (due to the relatively short life span) will likely become a standard predictive tool defining the type of chemoresistance pathways a patient is predisposed to or already have when the drug is not working.

3.3 The need for co-clinical trials

Typically, drug safety and efficacy studies are carried out in animal systems prior to their introduction in human trials, which usually includes xenograft models, a relatively inexpensive and rapid means for assessment of drug efficacy. However, these systems have certain inherent limitations: first, they do not recapitulate the genetic aberrations that are

inherent to human tumors and second, the immunocompromized states of these mice do not provide a realistic tumor microenvironment[10]. GEMMs, on the other hand, are designed to carry genetic lesions seen in human tumors. However, the development of these models is typically time intensive[10]. It often takes a few years to develop and validate these models before any data can be obtained. Therefore, transition of this data to the clinical setting is slow and in most cases such a transition does not occur at all[5]. Since these GEMMs are primarily generated in academic institutions and research organizations, Material Transfer Agreements (MTA) between academia and industry are often time consuming[5]. The clinical transition of these models is further hampered by the unwillingness of pharmaceutical companies to delay phase I/II trials until data from these GEMMs is obtained[5]. All of these factors prevent the use of data obtained from GEMMs to help effectively design human clinical trials. Co-clinical trials have been introduced as an attempt to bridge this gap between academia and the pharmaceutical industry allowing for application of murine data to human trials. This “GEMM-to-human” strategy allows for real-time integration of murine and human data, thereby allowing better and timely clinical decisions to be made[5].

3.4 Conception of the Co-Clinical Trial paradigm

The idea of the GEMM-to-human transition was conceived by Pandolfi et al. during the study of fusion genes involved in Acute Promyelocytic Leukemia (APL). Briefly, APL is associated with defective hematopoiesis, particularly of the myeloid lineage, resulting in a block in differentiation at the promyelocytic stage. APL is associated with chromosomal translocations involving chromosome 17[28]. The group primarily studied two such translocations: the PML-RAR [29,30,31,32] and PLZF-RAR using GEMMs. Extensive studies on these GEMMs helped establish a combination of arsenic trioxide and retinoic acid as a treatment strategy for the PML-RAR subtype[33,34] and a combination of HDAC inhibitors and retinoic acid as therapy for the PLZF-RAR subtype[35,36,37]. These findings were then translated to human trials, wherein, complete remission was observed[38,39]. Interestingly, studies in human leukemia cell lines produced exactly opposite results[40]. The cell line based studies actually suggested that arsenic trioxide and retinoic acid interfere with each other’s action with the conclusion that the two agents should never be used in combination. This particular example of APL pharmacotherapy exemplifies the predictive nature of GEMMs, clearly indicating that these murine systems faithfully mimic human pathology and therapeutic response. Taking lead from the APL story, Pandolfi et al. conceptualized the Co-Clinical Trial with a long term goal of replicating the bench-to-bedside transition for several other cancers[5]. Concomitant trials in murine systems and humans would ensure that this transition occurs quickly.

3.5 An Application of the Co-Clinical Trial Concept to lung and prostate cancer

Non-small lung cancers (NSCLCs) represent a large subset of lung cancer characterized with poor prognosis. Wong et al designed and conducted a co-clinical trial for *Kras* (an oncogene) mutant lung cancers, a predominant molecular subtype of NSCLC[41]. Several therapeutic regimens have been tried in such *Kras* mutant tumors with few isolated success stories[42,43]. Significantly different clinical outcomes have been observed in patients harboring identical activating mutations in *Kras*. In order to address this, Wong et al

proposed to elucidate the effect of co-existing mutations in such *Kras* mutant tumors[41]. These tumors commonly show a concomitant loss of tumor suppressors[44] such as p53[45,46] and Lkb1[47]. A co-clinical trial was conducted using appropriate GEMMs and a genetically stratified patient population based on Kras, p53 and Lkb1 mutational status. The aim of the trial was to determine whether selumetinib (an inhibitor of the Ras signaling cascade) works synergistically with docetaxel (a standard of care chemotherapeutic agent) [41]. Studies in GEMMs identified that selumetinib synergizes with docetaxel in mice having only *Kras* mutations and those having both Kras and p53 mutations. However, mice harboring both *Kras* and *Lkb1* mutations were resistant to this combination[41]. The results obtained from murine studies were applied successfully to the patient population. Further, the study also identified the use of 18FDG-PET imaging as a biomarker to predict and track therapeutic response in patients[41].

Pandolfi et al. designed a co-clinical trial to study androgen-deprivation therapy (ADT) in cases of prostate cancer[48]. ADT represents a standard-of-care therapy for prostate cancer patients. However, it has met with limited success due to the emergence of castration-resistant prostate cancer (CRPC). In order to address the failures associated with ADT, the group designed GEMMs of CRPC. They identified that secondary loss of p53 and Zbtb7a genes in a PTEN-null background were responsible for the development of refractory tumors in mice[48]. These findings were independently confirmed using human prostate cancer patient samples and pre-existing comparative genomic hybridization databases. They also identified XAF1 (X-linked inhibitor of apoptosis protein-associated factor-1) and SRD5A1 (3-oxo-5-α-steroid 4-dehydrogenase 1) as biomarkers for monitoring response to standard ADT[48]. XAF1 is an inhibitor of apoptosis and was down-regulated in the CRPC mouse models and human patient prostate cancer samples. SRD5A1, on the other hand, is an enzyme that catalyzes the conversion of testosterone to its more potent form, dihydrotestosterone, and is known to be upregulated in CRPC[49]. Upregulation of SRD5A1 represents an alternative mechanism for the activation of androgen receptor signaling in cases of ADT. Taken together, the group established downregulation of XAF1 and upregulation of SRD5A1 as biomarkers of poor sensitivity to ADT, possibly predisposing to CRPC. Further, the co-clinical trial identified the utility of XIAP (X-linked inhibitor of apoptosis protein) and SRD5A1 inhibitors in sensitizing CRPC tumors to ADT[48]. The study predicts the therapeutic utility of a combination therapy in CRPC patients, wherein, the tumors demonstrate deregulation in the XAF1-XIAP and SRD5A1 pathways. In conclusion, the study advocates the genetic and molecular stratification of CRPC patients, guided by GEMMs, to better clinical outcomes.

3.6 Ongoing Co-Clinical Trials

The animal studies of an ongoing glioblastoma co-clinical trial were completed in early 2011[50]. In human glioblastoma, the PI3K/AKT signaling pathway is frequently up-regulated and is associated with a higher tumor grade and poor clinical outcomes[51]. Pitter et al. utilized GEMM of glioblastoma characterized by hyperactive PI3K/AKT signaling. The murine tumors were generated by a retrovirus-mediated over-expression of the platelet-derived growth factor receptor (PDGFR)[50]. The aim of the study was to study the effect of a combination of an AKT and mTOR inhibitor in suppressing tumor growth. Further, in

order to correlate therapeutic response with PTEN (a tumor suppressor gene frequently lost or mutated in gliomas) status, the PDGFR-driven tumors were generated in PTEN-intact and PTEN-deficient backgrounds. Combination therapy using perifosine (an Akt inhibitor) and CCI-779 (an mTOR inhibitor) demonstrated growth suppression in primary glioma cultures obtained from the GEMM described above, independent of PTEN status. These observations were further validated *in vivo* in GEMMs using immunohistochemical analyses, diffusion-weighted magnetic resonance imaging (DW-MRI) and immunoblotting techniques[50]. The preclinical studies demonstrate the utility of inhibitors against multiple components of the PI3K/AKT pathway and DW-MRI as a valuable imaging tool to monitor tumor growth during treatment. The human component of the co-clinical trial using combination therapy is currently being carried out at the Memorial Sloan Kettering Cancer Center (NCT01051557).

The Institute for Cancer Research and Treatment at Candiolo (IRCC), Italy, launched HERACLES, a co-clinical trial project for colorectal cancer, in August 2012. The murine portion of the co-clinical trial was conducted in PDTX models derived from 85 distinct patient samples. The murine study identified HER2 as an effective therapeutic target in metastatic colorectal cancers[52]. The human trial will involve the use of a combination of lapatinib (EGFR/HER2 dual inhibitor) or pertuzumab (HER2 receptor antagonist) and trastuzumab (HER2 monoclonal antibody) in patients with metastatic colorectal cancers harboring a HER2 gene amplification. The HER2 amplification will be assessed by immuno-histochemistry and silver in-situ hybridization. The trial is divided into two arms: HERACLES A for a combination of lapatinib and trastuzumab and HERACLES B for a combination of pertuzumab and trastuzumab. The trial is projected to end in July 2014[53].

3.7 Recognizing the Challenges facing Co-Clinical Trials

The renewed promise to cancer research brought about by the emerging Co-Clinical Trial concept is not without its tribulations. The design of predictive GEMMs is central to co-clinical initiatives. For each GEMM, it is important to determine whether the oncogenic progression is similar in humans and mice with respect to their life-spans. Application of this knowledge would be critical to the success of resource-intensive co-clinical endeavors. Further, human tumors accumulate several mutations, other than the driver mutations, over time. GEMMs are usually engineered based on driver mutations for a particular tumor type and therefore it would be critical to evaluate whether these murine models accrue mutations similar to those observed in human patients. In addition to the genetic mutations, it is critical that the mouse model also mimic the human tumor progression in terms of metastasis, angiogenesis and other changes in tumor microenvironment. Only once it is established that a particular set of GEMMs reliably mimic human disease can a project of such a large magnitude be initiated and successfully completed.

Simultaneous execution of pre-clinical trials in murine systems and phase I/II trials in humans requires a sustained and coordinated effort between academicians and clinicians. The process is extremely resource-intensive, requiring infrastructure for preclinical (murine) and clinical (human) trials. A mouse hospital, mouse imaging facilities, a mouse pharmacy, comparative pathology centers, a bioinformatics consortium are some of the facilities that would need to developed prior to the commencement of such a project[5]. The project would

also require personnel having expertise in the areas of mouse husbandry, genetics and biology, molecular biology and clinical oncology amongst others[5]. Further, a rigorous protocol is warranted to better coordinate various aspects of an undertaking of this magnitude. Another caveat to such an approach is the difficulty to obtain new drug entities, from pharmaceutical companies, in quantities that are sufficient to conduct both the murine and human trials. Material Transfer Agreements (MTAs) and pending patents on these new drug compounds complicate the availability of therapeutic agents[5].

3.8 Future Prospects

The Co-Clinical Trial concept prompts a rethink of the entire drug development and drug approval process. It aims to integrate several aspects of clinical trials thereby making the drug approval process more efficient in improving clinical outcomes. By combining both the GEMMs and xenograft models, this approach facilitates comprehensive analyses of the specific cancer and its progression, including responses and chemoresistance to existing and experimental drugs. In the case of APL, the GEMM-to-human transition took 18 years to achieve. The initiation and implementation of the Co-Clinical Trial Project will ensure that such transitions are quicker. The concept is resource-intensive; therefore it has to be implemented at a few centralized facilities where the expertise and resources exist. Once this is achieved, it has the potential to significantly contribute to both the health care and the pharmaceutical industry thereby helping to relieve the socio-economic burden of cancer.

4. CHALLENGES IN IMPLEMENTATION OF PERSONALIZED MEDICINE TO CLINICAL TRIALS

Several scientific, non-scientific and social challenges severely hamper the design, planning, execution and interpretation of clinical trials (Figure 4). Patient tumor heterogeneity, drug toxicity, radio-resistance, chemo-resistance and polypharmacy represent a few of the scientific challenges facing clinical trials. Inter-individual differences in patient tumors often confound the interpretation regarding the efficacy of the investigational agent. Systematic and comprehensive patient tumor profiling, as proposed by the co-clinical trial paradigm, would ensure better patient population stratification into trials. Also, PDTX models of an individual patient tumor sample would help anticipate differential outcomes upon treatment with the investigational agent. Frequently, patients enrolled in these trials are on several other concurrent medications – a factor that may potentially interfere with or confound the interpretation of the effects of the agent under investigation. Drug toxicity, radio-resistance and chemo-resistance represent common causes of increased patient drop-out rates from trials. It is expected that personalized therapy through the use of GEMMs and PDTX models has the potential to counter these problems. Apart from the scientific challenges, clinical trials represent a large resource-intensive endeavor with complicated regulatory aspects involved with every phase of the trial. The use of personalized medicine strategies necessitates genetic, protein and metabolic analysis for every patient, thereby significantly increasing the per-head cost of diagnosis and treatment. However, technological advances have allowed the price of whole genome sequencing to drop from $3 billion in 2003 to just a few thousand dollars today. Sophisticated systems and technological improvements will ensure successful implementation of economically feasible personalized medicine strategies

to a clinical setup. Further. only around half of all clinical trials conducted are actually published—these “invisible trials” may result in use of therapeutic agents that are ineffective or toxic[54,55,56]. Patient enrollment in clinical trials is a critical factor which determines the success of a clinical trial. Despite the large number of trials being conducted, only about 3% of oncology patients in the United States are enrolled in clinical trials[57]. Adequate enrollment will guarantee sufficient patient retention in the concluding stages of the trial. Insufficient patient retention often results in a small cohort of clinical data which is very unlikely to provide any conclusive evidence regarding the efficacy of the therapy under evaluation[57]. Often, clinical trial sponsors offer monetary compensation to physicians, nurses and medical personnel to recruit patients[58]. Such a practice may result in the recruitment of patients unsuitable for the trial thereby greatly increasing the patient drop-out rates during the course of the trial. Lack of knowledge of ongoing clinical trials, public misconceptions of clinical trials, hesitation of under-represented populations to enroll in trials, possibility of incurring costs not covered by insurance, administrative formalities associated with enrollment in clinical trials are some of the factors that discourage patient enrollment[57,59,60,61]. Although, the co-clinical and mouse avatar paradigm aim to address some of the scientific challenges facing clinical trials today – the social aspect remains largely unaddressed. In conclusion, combination of these newly emerging personalized models along with patient-support programs and advocacy groups is a step in the right direction for efficient clinical trials that will close the divide between clinical research and clinical practice.

5. CONCLUSIONS

The mouse avatar concept makes use of murine xenograft models to assess and guide therapy in cancer patients. It allows a quick assessment of the safety and efficacy profiles of an investigational drug or novel drug combinations. These xenograft systems are particularly useful in cases where patients are not eligible for clinical trials due to deteriorating health. PDTX models may also be used in cases where there are no ongoing clinical trial options for a patient. Research by several groups continue to demonstrate that there is an increase in robustness and accuracy of these systems in predicting clinical outcome when applied in combination with other molecular biology and bioinformatics tools.

The Co-clinical trial concept, on the other hand, advocates a more meticulous and comprehensive analysis of cancer. It makes use of both GEMMs and xenograft models to elucidate the molecular pathology and therapeutic response of tumors. Although resource intensive, it complements approaches of molecular and clinical oncology.

In conclusion, mouse avatars and co-clinical trials represent emerging applications of mouse modeling to the study of cancer. Although conceptually diverse, both these applications emphasize the need for tailoring therapeutic regimens based on individual molecular profiles of tumors. Awareness amongst patients, advocacy groups and the clinical professionals and, platforms such as academic, clinical and pharmaceutical conferences and meetings about these two approaches will give a new ‘avatar’ to the practice of clinical medicine, provided they become cost effective.

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List of abbreviations

FDA	The Food and Drug Administration
GEMMs	Genetically Enginereed Mouse Models
PDTX	Patient-Derived Tumor Xenograft
NSG	NOD *scid* gamma
MTA	Material Transfer Agreement
APL	Acute Promyelocytic Leukemia
HDAC	Histone deacetylase
NSCLC	Non-small cell lung cancer
18FDG-PET	18-Fluorodeoxyglucose-positron emission tomography

REFERENCES

[1]. Hutchinson L, Kirk R. High drug attrition rates-where are we going wrong? Nature Reviews Clinical Oncology. 2011; 8:189–190.

[2]. L.J. Yabroff KR, Kepka D, Mariotto A. Economic burden of cancer in the United States: estimates, projections, and future research. Cancer epidemiology, biomarkers and prevention. 2011; 20:2006–2014.

[3]. Cheon DJ, Orsulic S. Mouse Models of Cancer. Annual Review of Pathology: Mechanisms of Disease. 2011; 6(6):95–119.

[4]. Walrath JC, Hawes JJ, Van Dyke T, Reilly KM. Genetically engineered mouse models in cancer research. Adv Cancer Res. 2010; 106:113–164. [PubMed: 20399958]

[5]. Nardella C, Lunardi A, Patnaik A, Cantley LC, Pandolfi PP. The APL paradigm and the “co-clinical trial” project. Cancer Discov. 2011; 1:108–116. [PubMed: 22116793]

[6]. Tentler JJ, Tan AC, Weekes CD, Jimeno A, Leong S, Pitts TM, Arcaroli JJ, Messersmith WA, Eckhardt SG. Patient-derived tumour xenografts as models for oncology drug development. Nature Reviews Clinical Oncology. 2012; 9:338–350.

[7]. Jin KT, Teng LS, Shen YP, He KF, Xu ZZ, Li GL. Patient-derived human tumour tissue xenografts in immunodeficient mice: a systematic review. Clinical & Translational Oncology. 2010; 12:473–480. [PubMed: 20615824]

[8]. Morton CL, Houghton PJ. Establishment of human tumor xenografts in immunodeficient mice. Nat Protoc. 2007; 2:247–250. [PubMed: 17406581]

[9]. White, R.d.V. Can Mouse Avatars Guide Cancer Treatment? OncLive. 2013

[10]. Richmond A, Su Y. Mouse xenograft models vs GEM models for human cancer therapeutics. Dis Model Mech. 2008; 1:78–82. [PubMed: 19048064]

[11]. Fichtner I, Rolff J, Soong R, Hoffmann J, Hammer S, Sommer A, Becker M, Merk J. Establishment of Patient-Derived Non-Small Cell Lung Cancer Xenografts as Models for the Identification of Predictive Biomarkers. Clinical Cancer Research. 2008; 14:6456–6468. [PubMed: 18927285]

[12]. Rubio-Viqueira B, Jimeno A, Cusatis G, Zhang X, Iacobuzio-Donahue C, Karikari C, Shi C, Danenberg K, Danenberg PV, Kuramochi H, Tanaka K, Singh S, Salimi-Moosavi H, Bouraoud N, Amador ML, Altiok S, Kulesza P, Yeo C, Messersmith W, Eshleman J, Hruban RH, Maitra

A, Hidalgo M. An in vivo platform for translational drug development in pancreatic cancer. Clinical Cancer Research. 2006; 12:4652–4661. [PubMed: 16899615]

[13]. Daniel VC, Marchionni L, Hierman JS, Rhodes JT, Devereux WL, Rudin CM, Yung R, Parmigiani G, Dorsch M, Peacock CD, Watkins DN. A primary xenograft model of small-cell lung cancer reveals irreversible changes in gene expression imposed by culture in vitro. Cancer Research. 2009; 69:3364–3373. [PubMed: 19351829]

[14]. Tentler JJ, Nallapareddy S, Tan AC, Spreafico A, Pitts TM, Morelli MP, Selby HM, Kachaeva MI, Flanigan SA, Kulikowski GN, Leong S, Arcaroli JJ, Messersmith WA, Eckhardt SG. Identification of predictive markers of response to the MEK1/2 inhibitor selumetinib (AZD6244) in K-ras-mutated colorectal cancer. Mol Cancer Ther. 2010; 9:3351–3362. [PubMed: 20923857]

[15]. Garber K. From human to mouse and back: 'tumorgraft' models surge in popularity. J Natl Cancer Inst. 2009; 101:6–8. [PubMed: 19116380]

[16]. Mueller BM, Reisfeld RA. Potential of the Scid Mouse as a Host for Human Tumors. Cancer and Metastasis Reviews. 1991; 10:193–200. [PubMed: 1764764]

[17]. Sanz L, Cuesta AM, Salas C, Corbacho C, Bellas C, Alvarez-Vallina L. Differential transplantability of human endothelial cells in colorectal cancer and renal cell carcinoma primary xenografts. Laboratory Investigation. 2009; 89:91–97. [PubMed: 19002108]

[18]. Gray DR, Huss WJ, Yau JM, Durham LE, Werdin ES, Funkhouser WK, Smith GJ. Short-term human prostate primary xenografts: An in vivo model of human prostate cancer vasculature and angiogenesis. Cancer Research. 2004; 64:1712–1721. [PubMed: 14996731]

[19]. Pollack A. Seeking Cures, Patients Enlist Mice Stand-Ins. The New York Times. 2012

[20]. BioSpectrum. BioSpectrum Bureau; China: 2012. BGI launches tool for tumor xenograft research.

[21]. Garrido-Laguna I, Uson M, Rajeshkumar NV, Tan AC, de Oliveira E, Karikari C, Villaroel MC, Salomon A, Taylor G, Sharma R, Hruban RH, Maitra A, Laheru D, Rubio-Viqueira B, Jimeno A, Hidalgo M. Tumor engraftment in nude mice and enrichment in stroma-related gene pathways predict poor survival and resistance to gemcitabine in patients with pancreatic cancer. Clinical Cancer Research. 2011; 17:5793–5800. [PubMed: 21742805]

[22]. Jones S, Zhang X, Parsons DW, Lin JC, Leary RJ, Angenendt P, Mankoo P, Carter H, Kamiyama H, Jimeno A, Hong SM, Fu B, Lin MT, Calhoun ES, Kamiyama M, Walter K, Nikolskaya T, Nikolsky Y, Hartigan J, Smith DR, Hidalgo M, Leach SD, Klein AP, Jaffee EM, Goggins M, Maitra A, Iacobuzio-Donahue C, Eshleman JR, Kern SE, Hruban RH, Karchin R, Papadopoulos N, Parmigiani G, Vogelstein B, Velculescu VE, Kinzler KW. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. Science. 2008; 321:1801–1806. [PubMed: 18772397]

[23]. Kuperwasser C, Chavarria T, Wu M, Magrane G, Gray JW, Carey L, Richardson A, Weinberg RA. Reconstruction of functionally normal and malignant human breast tissues in mice. Proc Natl Acad Sci U S A. 2004; 101:4966–4971. [PubMed: 15051869]

[24]. Eckhardt SG. CHALLENGES TO PDTX MODELS IN DRUG DEVELOPMENT. Annals of Oncology. 2013; 24

[25]. Kopetz S, Lemos R, Powis G. The promise of patient-derived xenografts: the best laid plans of mice and men. Clinical Cancer Research. 2012; 18:5160–5162. [PubMed: 22912394]

[26]. Giovanella BC, Stehlin JS, Wall ME, Wani MC, Nicholas AW, Liu LF, Silber R, Potmesil M. DNA topoisomerase I--targeted chemotherapy of human colon cancer in xenografts. Science. 1989; 246:1046–1048. [PubMed: 2555920]

[27]. BEAUTY Combines Sequencing, Avatars. Cancer Discovery. 2012; 2:477.

[28]. Rowley JD. Chromosomal patterns in myelocytic leukemia. N Engl J Med. 1973; 289:220–221. [PubMed: 4514580]

[29]. Pandolfi PP, Grignani F, Alcalay M, Mencarelli A, Biondi A, Lococo F, Grignani F, Pelicci PG. Structure and Origin of the Acute Promyelocytic Leukemia Myl/Rar-Alpha Cdna and Characterization of Its Retinoid-Binding and Transactivation Properties. Oncogene. 1991; 6:1285–1292. [PubMed: 1650447]

[30]. He LZ, Tribioli C, Rivi R, Peruzzi D, Pelicci PG, Soares V, Cattoretti G, Pandolfi PP. Acute leukemia with promyelocytic features in PML/RARalpha transgenic mice. Proc Natl Acad Sci U S A. 1997; 94:5302–5307. [PubMed: 9144232]

[31]. Grisolano JL, Wesselschmidt RL, Pelicci PG, Ley TJ. Altered myeloid development and acute leukemia in transgenic mice expressing PML-RAR alpha under control of cathepsin G regulatory sequences. Blood. 1997; 89:376–387. [PubMed: 9002938]

[32]. Brown D, Kogan S, Lagasse E, Weissman I, Alcalay M, Pelicci PG, Atwater S, Bishop JM. A PMLRARalpha transgene initiates murine acute promyelocytic leukemia. Proc Natl Acad Sci U S A. 1997; 94:2551–2556. [PubMed: 9122233]

[33]. Rego EM, He LZ, Warrell RP Jr. Wang ZG, Pandolfi PP. Retinoic acid (RA) and As2O3 treatment in transgenic models of acute promyelocytic leukemia (APL) unravel the distinct nature of the leukemogenic process induced by the PML-RARalpha and PLZF-RARalpha oncoproteins. Proc Natl Acad Sci U S A. 2000; 97:10173–10178. [PubMed: 10954752]

[34]. Lallemand-Breitenbach V, Guillemin MC, Janin A, Daniel MT, Degos L, Kogan SC, Bishop JM, de H. The, Retinoic acid and arsenic synergize to eradicate leukemic cells in a mouse model of acute promyelocytic leukemia. J Exp Med. 1999; 189:1043–1052. [PubMed: 10190895]

[35]. Rego EM, Ruggero D, Tribioli C, Cattoretti G, Kogan S, Redner RL, Pandolfi PP. Leukemia with distinct phenotypes in transgenic mice expressing PML/RAR alpha, PLZF/RAR alpha or NPM/RAR alpha. Oncogene. 2006; 25:1974–1979. [PubMed: 16331271]

[36]. He LZ, Guidez F, Tribioli C, Peruzzi D, Ruthardt M, Zelent A, Pandolfi PP. Distinct interactions of PML-RARalpha and PLZF-RARalpha with co-repressors determine differential responses to RA in APL. Nat Genet. 1998; 18:126–135. [PubMed: 9462740]

[37]. He LZ, Tolentino T, Grayson P, Zhong S, Warrell RP Jr. Rifkind RA, Marks PA, Richon VM, Pandolfi PP. Histone deacetylase inhibitors induce remission in transgenic models of therapy-resistant acute promyelocytic leukemia. J Clin Invest. 2001; 108:1321–1330. [PubMed: 11696577]

[38]. Nasr R, de H. The, Eradication of acute promyelocytic leukemia-initiating cells by PML/RARA-targeting. Int J Hematol. 2010; 91:742–747. [PubMed: 20455087]

[39]. Warrell RP Jr. He LZ, Richon V, Calleja E, Pandolfi PP. Therapeutic targeting of transcription in acute promyelocytic leukemia by use of an inhibitor of histone deacetylase. J Natl Cancer Inst. 1998; 90:1621–1625. [PubMed: 9811311]

[40]. Shao WL, Fanelli M, Ferrara FF, Riccioni R, Rosenauer A, Davison K, Lamph WW, Waxman S, Pelicci PG, Lo Coco F, Avvisati G, Testa U, Peschle C, Gambacorti-Passerini C, Nervi C, Miller WH. Arsenic trioxide as an inducer of apoptosis and loss of PML/RAR alpha protein in acute promyelocytic leukemia cells. Journal of the National Cancer Institute. 1998; 90:124–133. [PubMed: 9450572]

[41]. Chen Z, Cheng K, Walton Z, Wang Y, Ebi H, Shimamura T, Liu Y, Tupper T, Ouyang J, Li J, Gao P, Woo MS, Xu C, Yanagita M, Altabef A, Wang S, Lee C, Nakada Y, Pena CG, Sun Y, Franchetti Y, Yao C, Saur A, Cameron MD, Nishino M, Hayes DN, Wilkerson MD, Roberts PJ, Lee CB, Bardeesy N, Butaney M, Chirieac LR, Costa DB, Jackman D, Sharpless NE, Castrillon DH, Demetri GD, Janne PA, Pandolfi PP, Cantley LC, Kung AL, Engelman JA, Wong KK. A murine lung cancer co-clinical trial identifies genetic modifiers of therapeutic response. Nature. 2012; 483:613–617. [PubMed: 22425996]

[42]. Douillard JY, Shepherd FA, Hirsh V, Mok T, Socinski MA, Gervais R, Liao ML, Bischoff H, Reck M, Sellers MV, Watkins CL, Speake G, Armour AA, Kim ES. Molecular predictors of outcome with gefitinib and docetaxel in previously treated non-small-cell lung cancer: data from the randomized phase III INTEREST trial. J Clin Oncol. 2010; 28:744–752. [PubMed: 20038723]

[43]. Mascaux C, Iannino N, Martin B, Paesmans M, Berghmans T, Dusart M, Haller A, Lothaire P, Meert AP, Noel S, Lafitte JJ, Sculier JP. The role of RAS oncogene in survival of patients with lung cancer: a systematic review of the literature with meta-analysis. Br J Cancer. 2005; 92:131–139. [PubMed: 15597105]

[44]. Weir BA, Woo MS, Getz G, Perner S, Ding L, Beroukhim R, Lin WM, Province MA, Kraja A, Johnson LA, Shah K, Sato M, Thomas RK, Barletta JA, Borecki IB, Broderick S, Chang AC, Chiang DY, Chirieac LR, Cho J, Fujii Y, Gazdar AF, Giordano T, Greulich H, Hanna M,

Johnson BE, Kris MG, Lash A, Lin L, Lindeman N, Mardis ER, McPherson JD, Minna JD, Morgan MB, Nadel M, Orringer MB, Osborne JR, Ozenberger B, Ramos AH, Robinson J, Roth JA, Rusch V, Sasaki H, Shepherd F, Sougnez C, Spitz MR, Tsao MS, Twomey D, Verhaak RG, Weinstock GM, Wheeler DA, Winckler W, Yoshizawa A, Yu S, Zakowski MF, Zhang Q, Beer DG, Wistuba MA II, Watson LA, Garraway M, Ladanyi WD, Travis W, Pao MA, Rubin SB, Gabriel RA, Gibbs HE, Varmus RK, Wilson ES, Lander M. Meyerson, Characterizing the cancer genome in lung adenocarcinoma. Nature. 2007; 450:893–898. [PubMed: 17982442]

[45]. Steels E, Paesmans B, Berghmans T, Branle F, Lemaitre F, Mascaux C, Meert AP, Vallot F, Lafitte JJ, Sculier JP. Role of p53 as a prognostic factor for survival in lung cancer: a systematic review of the literature with a meta-analysis. European Respiratory Journal. 2001; 18:705–719. [PubMed: 11716177]

[46]. Matsumoto S, Iwakawa R, Takahashi K, Kohno T, Nakanishi Y, Matsuno Y, Suzuki K, Nakamoto M, Shimizu E, Minna JD, Yokota J. Prevalence and specificity of LKB1 genetic alterations in lung cancers. Oncogene. 2007; 26:5911–5918. [PubMed: 17384680]

[47]. Gill RK, Yang SH, Meerzaman D, Mechanic LE, Bowman ED, Jeon HS, Roy Chowdhuri S, Shakoori A, Dracheva T, Hong KM, Fukuoka J, Zhang JH, Harris CC, Jen J. Frequent homozygous deletion of the LKB1/STK11 gene in non-small cell lung cancer. Oncogene. 2011; 30:3784–3791. [PubMed: 21532627]

[48]. Lunardi A, Ala U, Epping MT, Salmena L, Clohessy JG, Webster KA, Wang G, Mazzucchelli R, Bianconi M, Stack EC, Lis R, Patnaik A, Cantley LC, Bubley G, Cordon-Cardo C, Gerald WL, Montironi R, Signoretti S, Loda M, Nardella C, Pandolfi PP. A co-clinical approach identifies mechanisms and potential therapies for androgen deprivation resistance in prostate cancer. Nat Genet. 2013; 45:747–755. [PubMed: 23727860]

[49]. Chang KH, Li R, Papari-Zareei M, Watumull L, Zhao YD, Auchus RJ, Sharifi N. Dihydrotestosterone synthesis bypasses testosterone to drive castration-resistant prostate cancer. Proc Natl Acad Sci U S A. 2011; 108:13728–13733. [PubMed: 21795608]

[50]. Pitter KL, Galban CJ, Galban S, Saeed-Tehrani O, Li F, Charles N, Bradbury MS, Becher OJ, Chenevert TL, Rehemtulla A, Ross BD, Holland EC, Hambardzumyan D. Perifosine and CCI 779 Co-Operate to Induce Cell Death and Decrease Proliferation in PTEN-Intact and PTEN-Deficient PDGF-Driven Murine Glioblastoma. Plos One. 2011; 6

[51]. Chakravarti A, Zhai G, Suzuki Y, Sarkesh S, Black PM, Muzikansky A, Loeffler JS. The prognostic significance of phosphatidylinositol 3-kinase pathway activation in human gliomas. J Clin Oncol. 2004; 22:1926–1933. [PubMed: 15143086]

[52]. Bertotti A, Migliardi G, Galimi F, Sassi F, Torti D, Isella C, Cora D, Di Nicolantonio F, Buscarino M, Petti C, Ribero D, Russolillo N, Muratore A, Massucco P, Pisacane A, Molinaro L, Valtorta E, Sartore-Bianchi A, Risio M, Capussotti L, Gambacorta M, Siena S, Medico E, Sapino A, Marsoni S, Comoglio PM, Bardelli A, Trusolino L. A molecularly annotated platform of patient-derived xenografts ("xenopatients") identifies HER2 as an effective therapeutic target in cetuximab-resistant colorectal cancer. Cancer Discov. 2011; 1:508–523. [PubMed: 22586653]

[53]. HERACLES TRIAL Institute for Cancer Research and Treatment. 2012

[54]. Sample I. Big pharma mobilising patients in battle over drugs trials data. The Guardian, Guardian News and Media Limited. 2013

[55]. Couzin-Frankel J. Unmasking 'Invisible' Drug Trials. ScienceInsider. 2013

[56]. Doshi P, Dickersin K, Healy D, Vedula SS, Jefferson T. Restoring invisible and abandoned trials: a call for people to publish the findings. Bmj-British Medical Journal. 2013; 346

[57]. Frank G. Current Challenges in Clinical Trial Patient Recruitment and Enrollment. SoCRA SOURCE. 2004

[58]. Eichenwald K, Kolata G. Drug trials hide conflicts for doctors. N Y Times Web. 1999:1–34. [PubMed: 11648114]

[59]. N.I.o.H. National Cancer Institute. Cancer Clinical Trials: The In-Depth Program.

[60]. Ledford H. Translational research: 4 ways to fix the clinical trial. Nature. 2011; 477:526–528. [PubMed: 21956311]

[61]. English R, LY.; Griffin, R. Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary. The National Acdemies Press; 2010.

[62]. Fichtner I, Slisow W, Gill J, Becker M, Elbe B, Hillebrand T, Bibby M. Anticancer drug response and expression of molecular markers in early-passage xenotransplanted colon carcinomas. European Journal of Cancer. 2004; 40:298–307. [PubMed: 14728946]

[63]. Krumbach R, Schuler J, Hofmann M, Giesemann T, Fiebig HH, Beckers T. Primary resistance to cetuximab in a panel of patient-derived tumour xenograft models: activation of MET as one mechanism for drug resistance. European Journal of Cancer. 2011; 47:1231–1243. [PubMed: 21273060]

[64]. Julien S, Merino-Trigo A, Lacroix L, Pocard M, Goere D, Mariani P, Landron S, Bigot L, Nemati F, Dartigues P, Weiswald LB, Lantuas D, Morgand L, Pham E, Gonin P, Dangles-Marie V, Job B, Dessen P, Bruno A, Pierre A, De The H, Soliman H, Nunes M, Lardier G, Calvet L, Demers B, Prevost G, Vrignaud P, Roman-Roman S, Duchamp O, Berthet C. Characterization of a large panel of patient-derived tumor xenografts representing the clinical heterogeneity of human colorectal cancer. Clinical Cancer Research. 2012; 18:5314–5328. [PubMed: 22825584]

[65]. Dalerba P, Dylla SJ, Park IK, Liu R, Wang X, Cho RW, Hoey T, Gurney A, Huang EH, Simeone DM, Shelton AA, Parmiani G, Castelli C, Clarke MF. Phenotypic characterization of human colorectal cancer stem cells. Proc Natl Acad Sci U S A. 2007; 104:10158–10163. [PubMed: 17548814]

[66]. Zhu H, Zhou W, Hu J, Huang Z, Lao W, Huang X, He C. Suppressing the growth of rectal cancer xenografts derived from patient tumors by an adenovector expressing small hairpin RNA targeting Bcl-XL. J Gene Med. 2012; 14:761–768. [PubMed: 23169477]

[67]. Jin KT, Li GL, Cui BB, Zhang J, Lan HR, Han N, Xie BJ, Cao FL, He KF, Wang HH, Xu ZZ, Teng LS, Zhu TM. Assessment of a Novel VEGF Targeted Agent Using Patient-Derived Tumor Tissue Xenograft Models of Colon Carcinoma with Lymphatic and Hepatic Metastases. Plos One. 2011; 6

[68]. Jin K, Lan H, Cao F, Han N, Xu Z, Li G, He K, Teng L. Differential response to EGFR- and VEGF-targeted therapies in patient-derived tumor tissue xenograft models of colon carcinoma and related metastases. Int J Oncol. 2012; 41:583–588. [PubMed: 22581265]

[69]. Zhou W, Zhu H, Chen W, Hu X, Pang X, Zhang J, Huang X, Fang B, He C. Treatment of patient tumor-derived colon cancer xenografts by a TRAIL gene-armed oncolytic adenovirus. Cancer Gene Ther. 2011; 18:336–345. [PubMed: 21183948]

[70]. Ducker GS, Atreya CE, Simko JP, Hom YK, Matli MR, Benes CH, Hann B, Nakakura EK, Bergsland EK, Donner DB, Settleman J, Shokat KM, Warren RS. Incomplete inhibition of phosphorylation of 4E-BP1 as a mechanism of primary resistance to ATP-competitive mTOR inhibitors. Oncogene. 2013

[71]. Uronis JM, Osada T, McCall S, Yang XY, Mantyh C, Morse MA, Lyerly HK, Clary BM, Hsu DS. Histological and molecular evaluation of patient-derived colorectal cancer explants. Plos One. 2012; 7:e38422. [PubMed: 22675560]

[72]. Garrido-Laguna I, Tan AC, Uson M, Angenendt M, Ma WW, Villaroel MC, Zhao M, Rajeshkumar NV, Jimeno A, Donehower R, Iacobuzio-Donahue C, Barrett M, Rudek MA, Rubio-Viqueira B, Laheru D, Hidalgo M. Integrated preclinical and clinical development of mTOR inhibitors in pancreatic cancer. British Journal of Cancer. 2010; 103:649–655. [PubMed: 20664591]

[73]. Jimeno A, Rubio-Viqueira B, Rajeshkumar NV, Chan A, Solomon A, Hidalgo M. A fine-needle aspirate-based vulnerability assay identifies polo-like kinase 1 as a mediator of gemcitabine resistance in pancreatic cancer. Mol Cancer Ther. 2010; 9:311–318. [PubMed: 20103597]

[74]. Von Hoff DD, Ramanathan RK, Borad MJ, Laheru DA, Smith LS, Wood TE, Korn RL, Desai N, Trieu V, Iglesias JL, Zhang H, Soon-Shiong P, Shi T, Rajeshkumar NV, Maitra A, Hidalgo M. Gemcitabine Plus nab-Paclitaxel Is an Active Regimen in Patients With Advanced Pancreatic Cancer: A Phase I/II Trial. Journal of Clinical Oncology. 2011; 29:4548–4554. [PubMed: 21969517]

[75]. L.J. Walters DM, Adair SJ, Newhook TE, Cowan CR, Stokes JB, Borgman CA, Stelow EB, Lowrey BT, Chopivsky ME, Gilmer TM, Parsons JT, Bauer TW. Inhibition of the Growth of Patient-Derived Pancreatic Cancer Xenografts with the MEK Inhibitor Trametinib Is Augmented by Combined Treatment with the Epidermal Growth Factor Receptor/HER2 Inhibitor Lapatinib. Neoplasia. 2013; 15:143–155. [PubMed: 23441129]

[76]. Villarroel MC, Rajeshkumar NV, Garrido-Laguna I, De Jesus-Acosta A, Jones S, Maitra A, Hruban RH, Eshleman JR, Klein A, Laheru D, Donehower R, Hidalgo M. Personalizing cancer treatment in the age of global genomic analyses: PALB2 gene mutations and the response to DNA damaging agents in pancreatic cancer. Mol Cancer Ther. 2011; 10:3–8. [PubMed: 21135251]

[77]. A Combination of TH-302 and Radiation Reduced Human Pancreatic Tumor Growth in Hypoxic Xenografts. American Association for Cancer Research AACR Press Releases; Lake Tahoe, Nevada, USA: 2012.

[78]. Laheru D, Shah P, Rajeshkumar NV, McAllister F, Taylor G, Goldsweig H, Le DT, Donehower R, Jimeno A, Linden S, Zhao M, Song D, Rudek MA, Hidalgo M. Integrated preclinical and clinical development of S-trans, trans-Farnesylthiosalicylic Acid (FTS, Salirasib) in pancreatic cancer. Invest New Drugs. 2012; 30:2391–2399. [PubMed: 22547163]

[79]. Walters DM, Lindberg JM, Adair SJ, Newhook TE, Cowan CR, Stokes JB, Borgman CA, Stelow EB, Lowrey BT, Chopivsky ME, Gilmer TM, Parsons JT, Bauer TW. Inhibition of the Growth of Patient-Derived Pancreatic Cancer Xenografts with the MEK Inhibitor Trametinib Is Augmented by Combined Treatment with the Epidermal Growth Factor Receptor/HER2 Inhibitor Lapatinib. Neoplasia. 2013; 15:143–U207. [PubMed: 23441129]

[80]. Venkatesha VA, Parsels LA, Parsels JD, Zhao LL, Zabludoff SD, Simeone DM, Maybaum J, Lawrence TS, Morgan MA. Sensitization of Pancreatic Cancer Stem Cells to Gemcitabine by Chk1 Inhibition. Neoplasia. 2012; 14:519–525. [PubMed: 22787433]

[81]. John T, Kohler D, Pintilie M, Yanagawa N, Pham NA, Li M, Panchal D, Hui F, Meng FN, Shepherd FA, Tsao MS. The Ability to Form Primary Tumor Xenografts Is Predictive of Increased Risk of Disease Recurrence in Early-Stage Non-Small Cell Lung Cancer. Clinical Cancer Research. 2011; 17:134–141. [PubMed: 21081655]

[82]. Zhang JC, Zhang L, Su XY, Li M, Xie L, Malchers F, Fan SQ, Yin XL, Xu YP, Liu KJ, Dong ZW, Zhu GS, Qian ZL, Tang LL, Zhan P, Ji QS, Kilgour E, Smith PD, Brooks AN, Thomas RK, Gavine PR. Translating the Therapeutic Potential of AZD4547 in FGFR1-Amplified Non-Small Cell Lung Cancer through the Use of Patient-Derived Tumor Xenograft Models. Clinical Cancer Research. 2012; 18:6658–6667. [PubMed: 23082000]

[83]. Fiebig HH, Schuler J, Bausch N, Hofmann M, Metz T, Korrat A. Gene signatures developed from patient tumor explants grown in nude mice to predict tumor response to 11 cytotoxic drugs. Cancer Genomics Proteomics. 2007; 4:197–209. [PubMed: 17878523]

[84]. Nemati F, Sastre-Garau X, Laurent C, Couturier J, Mariani P, Desjardins L, Piperno-Neumann S, Lantz O, Asselain B, Plancher C, Robert D, Peguillet I, Donnadieu MH, Dahmani A, Bessard MA, Gentien D, Reyes C, Saule S, Barillot E, Roman-Roman S, Decaudin D. Establishment and characterization of a panel of human uveal melanoma xenografts derived from primary and/or metastatic tumors. Clinical Cancer Research. 2010; 16:2352–2362. [PubMed: 20371695]

[85]. Moestue SA, Borgan E, Huuse EM, Lindholm EM, Sitter B, Borresen-Dale AL, Engebraaten O, Maelandsmo GM, Gribbestad IS. Distinct choline metabolic profiles are associated with differences in gene expression for basal-like and luminal-like breast cancer xenograft models. BMC Cancer. 2010; 10:433. [PubMed: 20716336]

[86]. de Plater L, Lauge A, Guyader C, Poupon MF, Assayag F, de Cremoux P, Vincent-Salomon A, Stoppa-Lyonnet D, Sigal-Zafrani B, Fontaine JJ, Brough R, Lord CJ, Ashworth A, Cottu P, Decaudin D, Marangoni E. Establishment and characterisation of a new breast cancer xenograft obtained from a woman carrying a germline BRCA2 mutation. Br J Cancer. 2010; 103:1192–1200. [PubMed: 20877358]

[87]. Kabos P, Finlay-Schultz J, Li C, Kline E, Finlayson C, Wisell J, Manuel CA, Edgerton SM, Harrell JC, Elias A, Sartorius CA. Patient-derived luminal breast cancer xenografts retain hormone receptor heterogeneity and help define unique estrogen-dependent gene signatures. Breast Cancer Res Treat. 2012; 135:415–432. [PubMed: 22821401]

[88]. Fleming JM, Miller TC, Meyer MJ, Ginsburg E, Vonderhaar BK. Local regulation of human breast xenograft models. J Cell Physiol. 2010; 224:795–806. [PubMed: 20578247]

[89]. Romanelli A, Clark A, Assayag F, Chateau-Joubert S, Poupon MF, Servely JL, Fontaine JJ, Liu X, Spooner E, Goodstal S, de Cremoux P, Bieche I, Decaudin D, Marangoni E. Inhibiting aurora kinases reduces tumor growth and suppresses tumor recurrence after chemotherapy in patient-

derived triple-negative breast cancer xenografts. Mol Cancer Ther. 2012; 11:2693–2703. [PubMed: 23012245]

[90]. PH Cottu, TB.; Assayag, F.; Bièche, I.; Chateau-Joubert, S.; Fontaine, J-J.; Decaudin, D.; Slimane, K.; Vincent-Salomon, A.; Marangoni, E. Targeting the PI3K/mTOR pathway in patient-derived xenograft models of endocrine resistant luminal breast cancer. American Association for Cancer Research; San Antonio, Texas: 2012.

[91]. M-E Legrier, VY.; Beurdeley, A.; Stephant, G.; Le, Ven E.; Banis, S.; Lassalle, M.; Deas, O.; Cairo, S.; Judde, J-G. Early activation of IFN/STAT signaling in tumor cells of patient-derived triple negative breast cancer xenografts predicts tumor sensitivity to chemotherapy. American Association for Cancer Research; San Antonio, Texas, USA: 2012.

[92]. Serra V, Eichhorn PJA, Garcia-Garcia C, Ibrahim YH, Prudkin L, Sanchez G, Rodriguez O, Anton P, Parra JL, Marlow S, Scaltriti M, Perez-Garcia J, Prat A, Arribas J, Hahn WC, Kim SY, Baselga J. RSK3/4 mediate resistance to PI3K pathway inhibitors in breast cancer. Journal of Clinical Investigation. 2013; 123:2551–2563. [PubMed: 23635776]

[93]. Karam JA, Zhang XY, Tamboli P, Margulis V, Wang H, Abel EJ, Culp SH, Wood CG. Development and characterization of clinically relevant tumor models from patients with renal cell carcinoma. Eur Urol. 2011; 59:619–628. [PubMed: 21167632]

[94]. Yuen JS, Sim MY, Siml HG, Chong TW, Lau WK, Cheng CW, Huynh H. Inhibition of angiogenic and non-angiogenic targets by sorafenib in renal cell carcinoma (RCC) in a RCC xenograft model. Br J Cancer. 2011; 104:941–947. [PubMed: 21407223]

[95]. Hammers HJ, Verheul HM, Salumbides B, Sharma R, Rudek M, Jaspers J, Shah P, Ellis L, Shen L, Paesante S, Dykema K, Furge K, Teh B, Netto G, Pili R. Reversible Epithelial to Mesenchymal Transition and Acquired Resistance to Sunitinib in Patients with Renal Cell Carcinoma: Evidence from a Xenograft Study. Molecular Cancer Therapeutics. 2010; 9:1525–1535. [PubMed: 20501804]

[96]. Wu X, Zhang J, Zhen R, Lv J, Zheng L, Su X, Zhu G, Gavine PR, Xu S, Lu S, Hou J, Liu Y, Xu C, Tan Y, Xie L, Yin X, He D, Ji Q, Hou Y, Ge D. Trastuzumab anti-tumor efficacy in patient-derived esophageal squamous cell carcinoma xenograft (PDECX) mouse models. J Transl Med. 2012; 10:180. [PubMed: 22935382]

[97]. Oudard S, Legrier ME, Boye K, Bras-Goncalves R, De Pinieux G, De Cremoux P, Poupon MF. Activity of docetaxel with or without estramustine phosphate versus mitoxantrone in androgen dependent and independent human prostate cancer xenografts. Journal of Urology. 2003; 169:1729–1734. [PubMed: 12686819]

[98]. Raheem O, Kulidjian AA, Wu C, Jeong YB, Yamaguchi T, Smith KM, Goff D, Leu H, Morris SR, Cacalano NA, Masuda K, Jamieson CHM, Kane CJ, Jamieson CAM. A novel patient-derived intra-femoral xenograft model of bone metastatic prostate cancer that recapitulates mixed osteolytic and osteoblastic lesions. Journal of Translational Medicine. 2011; 9

[99]. Kortmann U, McAlpine JN, Xue H, Guan J, Ha G, Tully S, Shafait S, Lau A, Cranston AN, O'Connor MJ, Huntsman DG, Wang Y, Gilks CB. Tumor growth inhibition by olaparib in BRCA2 germline-mutated patient-derived ovarian cancer tissue xenografts. Clinical Cancer Research. 2011; 17:783–791. [PubMed: 21097693]

[100]. Bankert RB, Balu-Iyer SV, Odunsi K, Shultz LD, Kelleher RJ Jr. Barnas JL, Simpson-Abelson M, Parsons R, Yokota SJ. Humanized mouse model of ovarian cancer recapitulates patient solid tumor progression, ascites formation, and metastasis. Plos One. 2011; 6:e24420. [PubMed: 21935406]

[101]. Chaudary N, Pintilie M, Schwock J, Dhani N, Clarke B, Milosevic M, Fyles A, Hill RP. Characterization of the Tumor-Microenvironment in Patient-Derived Cervix Xenografts (OCICx). Cancers. 2012; 4:821–845. [PubMed: 24213469]

[102]. Hennessey PT, Ochs MF, Mydlarz WW, Hsueh W, Cope L, Yu WN, Califano JA. Promoter Methylation in Head and Neck Squamous Cell Carcinoma Cell Lines Is Significantly Different than Methylation in Primary Tumors and Xenografts. Plos One. 2011; 6

[103]. Keysar SB, Le PN, Anderson RT, Morton JJ, Bowles DW, Paylor JJ, Vogler BW, Thorburn J, Fernandez P, Glogowska MJ, Takimoto SM, Sehrt DB, Gan GN, Eagles-Soukup JR, Serracino H, Hirsch FR, Lucia MS, Thorburn A, Song JI, Wang XJ, Jimeno A. Hedgehog Signaling Alters

Reliance on EGF Receptor Signaling and Mediates Anti-EGFR Therapeutic Resistance in Head and Neck Cancer. Cancer Research. 2013; 73:3381–3392. [PubMed: 23576557]

[104]. Jin KT, Lan HR, Cao FL, Xu ZZ, Han N, Li GL, He KF, Teng LS. Antitumor effect of FP3 in a patient-derived tumor tissue xenograft model of gastric carcinoma through an antiangiogenic mechanism. Oncology Letters. 2012; 3:1052–1058. [PubMed: 22783390]

[105]. Liu Z, Zhao X, Mao H, Baxter PA, Huang Y, Yu L, Wadhwa L, Su JM, Adesina A, Perlaky L, Hurwitz M, Idamakanti N, Police SR, Hallenbeck PL, Hurwitz RL, Lau CC, Chintagumpala M, Blaney SM, Li XN. Intravenous injection of oncolytic picornavirus SVV-001 prolongs animal survival in a panel of primary tumor-based orthotopic xenograft mouse models of pediatric glioma. Neuro Oncol. 2013

[106]. Johansson M, Oudin A, Tiemann K, Bernard A, Golebiewska A, Keunen O, Fack F, Stieber D, Wang B, Hedman H, Niclou SP. The soluble form of the tumor suppressor Lrig1 potently inhibits in vivo glioma growth irrespective of EGF receptor status. Neuro Oncol. 2013

[107]. Wong JC, Tang G, Wu X, Liang C, Zhang Z, Guo L, Peng Z, Zhang W, Lin X, Wang Z, Mei J, Chen J, Pan S, Zhang N, Liu Y, Zhou M, Feng L, Zhao W, Li S, Zhang C, Zhang M, Rong Y, Jin TG, Zhang X, Ren S, Ji Y, Zhao R, She J, Ren Y, Xu C, Chen D, Cai J, Shan S, Pan D, Ning Z, Lu X, Chen T, He Y, Chen L. Pharmacokinetic optimization of class-selective histone deacetylase inhibitors and identification of associated candidate predictive biomarkers of hepatocellular carcinoma tumor response. J Med Chem. 2012; 55:8903–8925. [PubMed: 23061376]

[108]. Terziyska N, Castro Alves C, Groiss V, Schneider K, Farkasova K, Ogris M, Wagner E, Ehrhardt H, Brentjens RJ, zur Stadt U, Horstmann M, Quintanilla-Martinez L, Jeremias I. In vivo imaging enables high resolution preclinical trials on patients' leukemia cells growing in mice. Plos One. 2012; 7:e52798. [PubMed: 23300782]

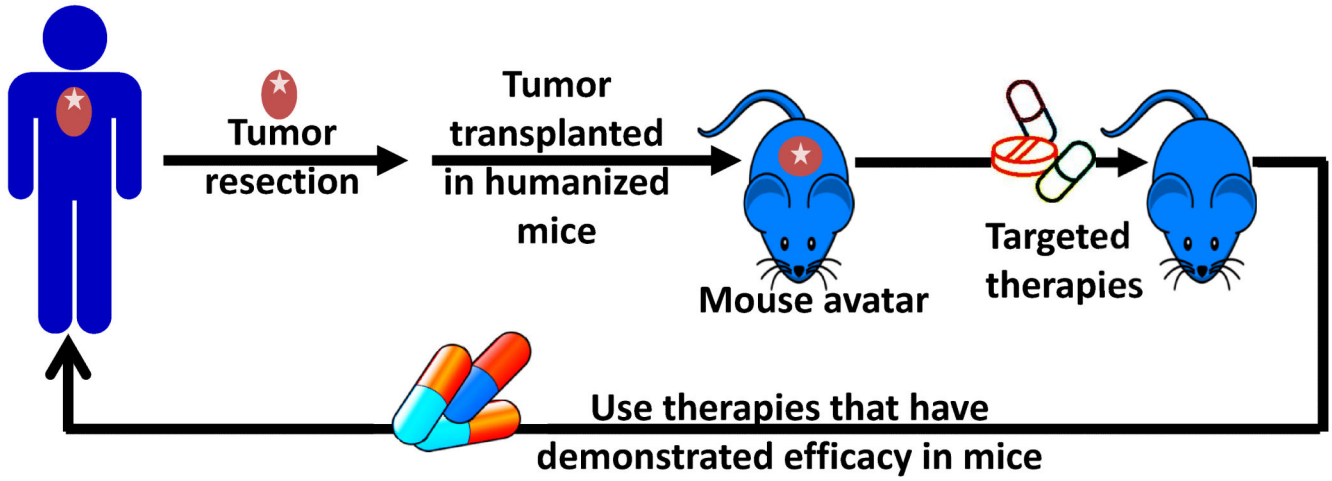

Figure 1. Concept of mouse avatars

Patient tumor samples, either resected or biopsied, are transplanted and propagated in immunocompromized mice. The mice with the implanted tumors are then used as an *in-vivo* system for drug testing. Several therapeutic agents are then tested, as cocktails in various combinations and concentrations, for efficacy and safety in these mice. Therapies that cause tumor regression in the murine system help build a clinical rationale that is then applied to the patient from whom the tumor sample was derived. Using this method, each patient would have an individualized *in-vivo* mouse, allowing for a large number of drug compounds to be evaluated for efficacy relatively quickly, resulting in the identification of a safe, targeted therapeutic regimen for the patient. The use of these mouse avatars would ensure that a patient is not given chemotherapeutic agents that are predicted to be ineffective or toxic as determined in the murine system.

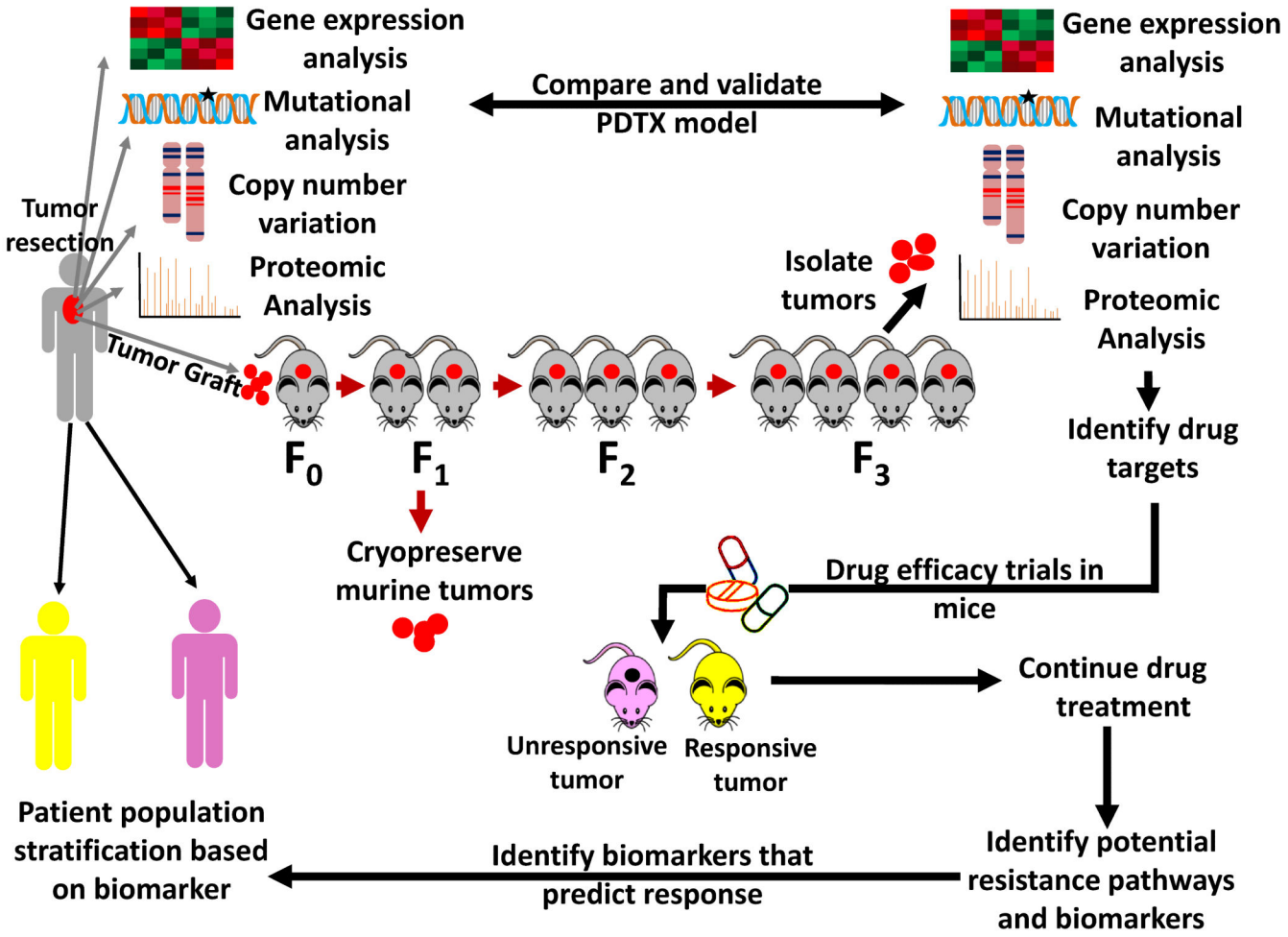

Figure 2. Development, validation, assessment and application of PDTX models to clinical oncology

The patient tumor is resected—a part of it is subjected to standard molecular profiling techniques and part of it is prepared for transplantation into immunocompromized mice. The patient tumor is analyzed for mutational status, copy number variations and is characterized at the nucleic acid and protein level using gene expression arrays and proteomics-based approaches. Another portion of the tumor is xenografted and propagated in immunocompromized mice through several generations (F_0…F_3). The propagated tumors are isolated from the F_3 generation and are characterized like the human tumors. The molecular profile of the human tumor is superimposed on the profile of the murine tumors. A high degree of concordance between the human and murine tumor profiles helps establish the mouse as a faithful model of the human cancer. Downstream bioinformatics analyses of data obtained after murine molecular profiling helps identify drug targets. Therapeutic agents against these targets are then evaluated for safety and efficacy in these F_3 mice. Comparative analyses of drug-sensitive and resistant tumors could result in the identification of biomarkers that predict therapeutic response. Validation of such biomarkers may then be used to stratify patient populations in clinical trials in the future. The mice having tumors that are drug-sensitive are treated continually with a that particular therapeutic agent to

anticipate and identify potential resistance pathways much before drug-resistance is observed in the clinical setting. Drugs efficacious in these resistant tumors are then determined and kept ready in case of emergence of resistance in the patient. In this way, PDTX models are useful not only for the identification of drug targets but also to determine predictive biomarkers and possible molecular changes and signaling pathways conferring resistance.

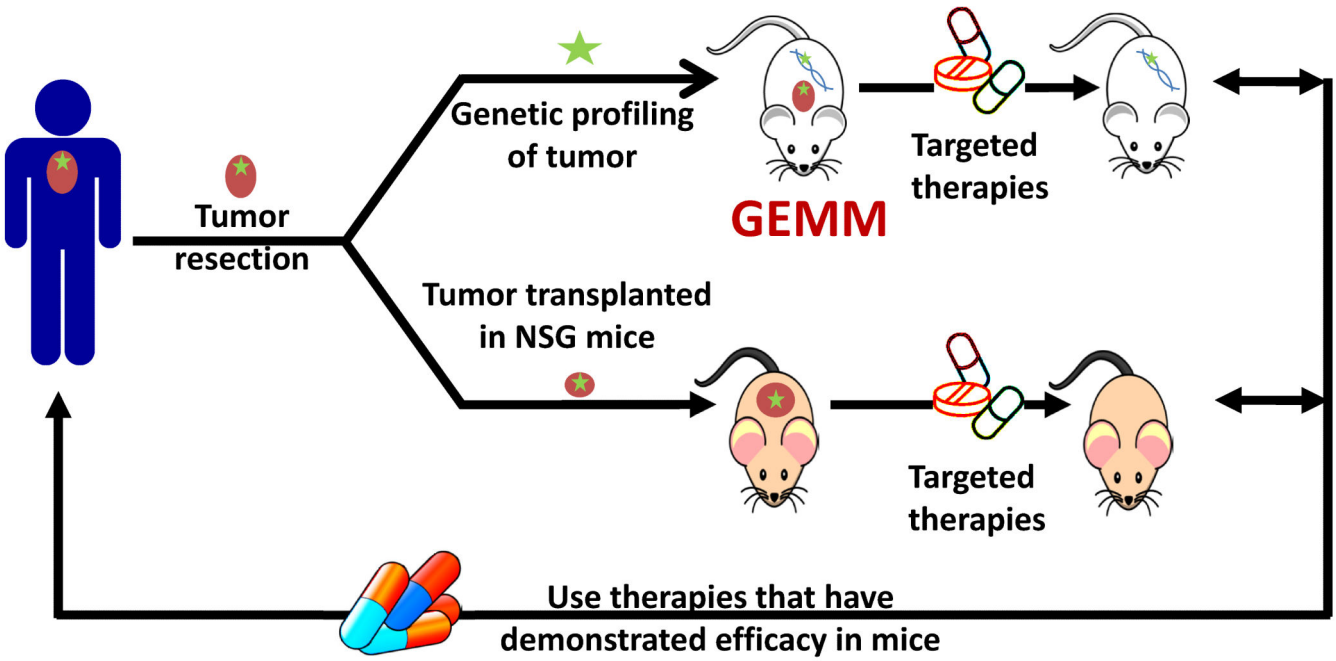

Figure 3. Concept of co-clinical trials

The concept of co-clinical trials advocates an integration of preclinical murine and clinical human trials in an attempt to accelerate the drug development and testing process. As part of co-clinical trials, both genetically engineered mouse models (GEMMs) that mirror a patient's tumor genotype and xenograft models for the transplantation and propagation of the patient's tumor are employed. Therapeutic agents that are efficacious in these mouse models are then applied to the patient population. This approach is complemented with standard molecular profiling and imaging techniques. Similar to the PDTX models, such a system allows for identification of biomarkers and potential resistance pathways. Although this concept seems more resource intensive when compared to the xenograft models, it allows for a more comprehensive approach towards clinical management of cancer. The use of GEMMs facilitates the identification of genetic modifiers, compensatory signaling pathways to therapeutic response and genetically-determined prognostic factors. This newly emerging concept attempts to bridge the gap between cancer biologists and oncologists and proposes a large-scale multi-centre collaborative approach to effectively treat cancer.

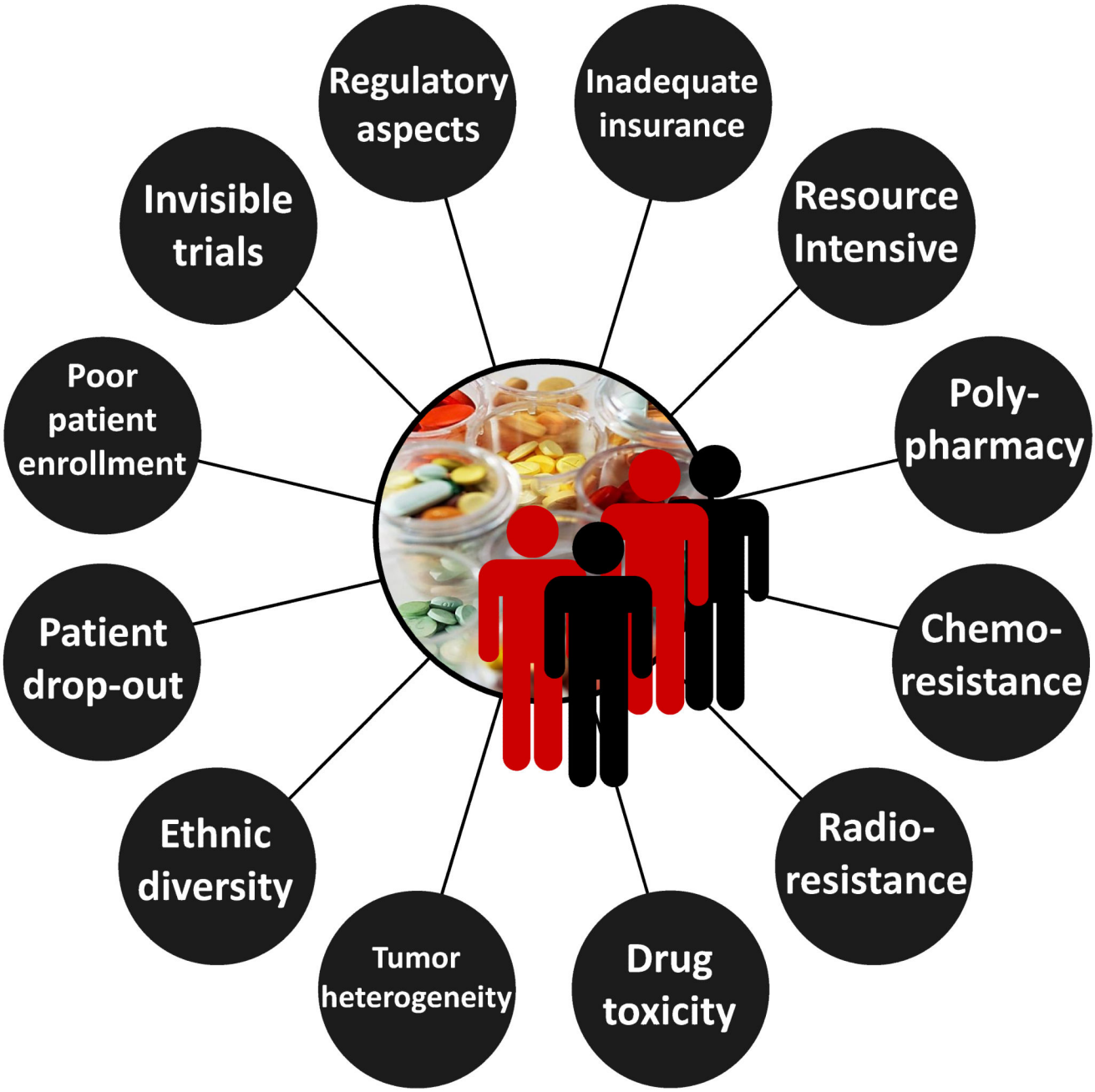

Figure 4. Challenges facing Clinical Trials

The figure outlines the various scientific, non-scientific and social problems that severely hamper the planning and successful execution of clinical trials.

Table 1
Existing PDTX models of different cancers and their therapeutic implications

Cancer	Significance
Colorectal cancer	• Use of 5-fluorouracil, oxaliplatin and irinotecan with concordant response rates in the PDTX models and patients[62] • 90% accuracy of the murine models in predicting cetuximab responsiveness in a genetically stratified subset, identification of biomarkers predictive of therapeutic response to cetuximab[63] • Identification of Her2 amplification as a genetic lesion in cetuximab-resistant colorectal tumors[52] • Establish correlation between Kras mutational status and resistance to cetuximab therapy[64] • Identification and characterization of a cancer-stem cell population in colorectal tumors[65] • Demonstration of efficacy of Bcl-XL targeting in rectal cancers[66] • Establishment of a model of colon cancer with lymphatic and hepatic metastasis, evaluation of efficacy of VEGF and EGFR targeting in the model[67,68] • Identification of activation of the Wnt pathway as a predictor of response to a MEK 1/2 inhibotor (AZD6244) in *Kras* mutant colorectal cancers[14] • Establish efficacy of an oncolytic adenoviral vector in combination with TRAIL gene therapy in a PDTX model of colon cancer[69] • Identification of the mechanism of resistance of Kras mutant colon cancer tumors to PP242, an mTOR inhibitor[70] • Establishment of 27 different PDTX models of colorectal cancer with a molecular profile similar to the human tumors[71]
Pancreatic cancer	• Lack of concordance between murine systems and human patients to mTOR inhibitors in patients with elevated p70 S6 kinase levels[72] • Demonstrated the utility of polo-like kinase inhibitors in gemcitabineresistant tumors, identification of cyclin B1 as a biomarker of polo-like kinase inhibitor response[73] • Use of gemcitabine and nabpaclitaxel to target tumor microenvironment with concordant responses in Phase I/II human trials[74] • Increased efficacy of MEK inhibitor trametinib in combination with EGFR/Her2 inhibitor lapitinib[75] • Demonstrated efficacy of mitomycin C in a gemcitabine-resistance pancreatic cancer guided by global genomic analyses[76] • Efficacious use of a hypoxia-activated prodrug TH-302 in combination with ionizing radiation in a PDTX model of pancreatic cancer[77] • Concomitant preclinical and clinical trials in PDTX models and patients demonstrating the effect of Salirasib, a Ras inhibitor, in pancreatic cancer[78] • Demonstrated efficacy of combination of trametinib (a MEK inhibitor) and lapatinib (a epidermal growth factor receptor/Her2 inhibitor) in panacreatic cancer PDTX models[79] • Demonstrated efficacy of AZD7762 (a Chk1 inhibitor) in sensitizing pancreatic cancer stem cells to gemcitabine[80]
Lung cancer	• Established a direct correlation between tumor engraftment capability in a mouse to the propensity of relapse in the patient[81] • Demonstrate the efficacy of AZD4547 in FGFR amplified NSCLC[82]
Melanoma	• Establishment of a gene set predicting response to standard chemotherapeutic agents[83] • Agreement in therapeutic response to temezolomide in uveal melanoma[84]
Breast cancer	• Development of models to study the role and implications of choline metabolism in ER and PR-positive breast cancers[85] • Development of a BRCA2 mutant model of breast cancer[86]

Cancer	Significance
	• Identification of a novel estrogen-regulated gene cancer/testis antigen 45 in a PDTX model of ER+ breast tumors[87] • Analysis of the effects and consequences of tumor engraftment at various locations in immunodeficient mice[88] • Determined the efficacy of aurora kinase inhibitors in a PDTX model of triple-negative breast cancers[89] • Establishment of endocrine resistant luminal breast cancer PDTX models, determined the utility of everolimus therapy in the said models[90] • Identification of IFN/STAT signaling as a predictor of therapeutic response to cyclophosphamide chemotherapy in triple negative breast cancer[91] • The Breast Cancer Genome Guided Therapy Study (BEAUTY Project) initiated by the Mayo Clinic combines whole genome sequencing and the use of mouse avatars to guide patient therapy[27] • Identified elevated levels of RSK3/4 as causative factors of resistance to PI3K inhibitors in breast cancer[92]
Renal cell carcinoma	• Development of PDTX models of renal cell carcinoma with both clear-cell and papillary morphologies which mimic patient tumors with respect to their molecular characteristics as well as response to sunitinib and everolimus therapy[93] • Demonstration of efficacy with tyrosine kinase inhibitor sorafenib[94] • Elucidation of resistance pathways in sunitinib-refractory tumors
Esophageal cancer	• Identified the efficacy of trastuzumab in Her2 positive tumors, demonstrated trastuzumab resistant in tumors with concomitant PI3KCA mutations[96]
Prostate cancer	• Establishment of hormone-dependent and hormone-independent models, assess efficacy of taxanes and estramustine phosphate in these models[97] • Establishment of a model of prostrate bone metastatic cancer[98]
Ovarian cancer	• Established a BRCA2 mutant ovarian cancer xenograft model, demonstrated selective efficacy of olaparib in BRCA2 mutant tumors[99] • Development of a humanized model of ovarian cancer with a profile consistent with the parent tumor[100]
Cervical cancer	• Characterization of tumor microenvironment in a xenograft model of cervical cancer[101]
Head and Neck cancers	• Comparative methylation microarrays to establish superiority of PDTX models over cell lines[102] • Demonstration of efficacy of a combination of EGFR and Hedgehog pathway inhibitors in PDTX models[103]
Gastric carcinoma	• Demonstrate efficacy of a VEGF inhibitor FP3 in a PDTX model of metastatic gastric cell carcinoma[104]
Bladder cancer	• Development of PDTX models of muscle invasive bladder carcinoma in NSG mice in collaboration with Jackson Laboratories[9]
Glioblastoma	• Demonstration of therapeutic effect of intravenous injection of an oncolytic picornavirus SVV-001 in PDTX models of pediatric gliomas[105] • Developed a drug-delivery methodology and demonstrated efficacy of a tumor suppressor Lrig1 in glioblastoma[106]
Hepatocellular carcinoma	• Pharmacokinetic optimization of HDAC1 inhibitors in PDTX models[107]
Leukemia	• Established a PDTX model of leukemia amenable to bioluminescent imaging[108]

Table 2
Currently available commercial services in relation to PDTX systems

Company/ Institution/ Organization	Services offered
Charles River Laboratories, Wilmington, Massachusetts, USA http://www.criver.com/products-services/drugdiscovery/oncology/patient-derived-xenografts	• PDTX models for a wide range of cancers • Lysates from xenografted tumors assayed for various cancer-related proteins • Genetic characterization of tumors for mutations
The Jackson Laboratory, Bar Harbor, Maine, USA http://jaxservices.jax.org/invivo/pdx.html	• PDTX models available for a variety of cancers in NSG mice • Gene expression and copy number variant analysis for the transplanted murine tumors • Cryopreservation of transplanted murine tumors
Oncotest GmbH, Freiburg, Germany http://www.oncotest.de/products-andservices/tumorcollection.html	• More than 325 established xenograft models • Murine tumor repository • Comprehensive profiling including chemosensitivity profiles to standard chemotherapeutic regimens, mutational analysis, gene and protein expression data, immunohistochemical analysis
Living Tumor Laboratory, Vancouver, British Colombia, Canada http://www.livingtumorcentre.com/PDC_Intro.html	• More than 150 established xenograft models • Cryopreservation of transplanted murine tumors • OVCARE core facility having more than 40 ovarian cancer xenograft models

Company/ Institution/ Organization	**Services offered**
Experimental Pharmacology and Oncology Berlin-Buch, Germany http://www.epoberlin.com/epo-tumormodels-xenografts.html	• Over 100 established models • Molecular data (gene expression profiles, mutations, protein expression), Response data (chemotherapy and hormone therapy) and patient data (patient status, drug-response, follow-up) available • Repository for tissue and nucleic acid samples
Oncodesign, Dijon Cedex, France http://www.oncodesign.com/assets/files/activities/Oncodesign_Tumorgraft_Models.pdf	• Availability of PTDX models in Chi® (humanized) mice • Most comprehensive collection of human colorectal cancer models
Taconic, Hudson, New York, USA http://www.taconic.com/wmspage.cfm?parm1=4064	• Several xenograft models provided in collaboration with Oncodesign • Over 50 colorectal cancer models available • Custom PTDX model generation services • Humanized super-immunodeficient CIEA NOG® mice available for model generation
Deshpande Laboratories, Bhopal, Madhya Pradesh, India http://deshpandelab.com/onco/AntiTumor/PDTX.html	• Provides contract research services in model generation, drug testing and pharmacodynamics/ pharmacokinetic profiling for a client's test samp
WuXi AppTec, Shanghai, China http://www.wuxiapptec.com/bio_oncology.html	• More than 400 established xenograft models • Molecular characterization (whole genome sequencing, gene expression and copy number variation) services • Cancer stem cell panels for PTDX models available

Company/ Institution/ Organization	**Services offered**
GenScript, Piscataway, New Jersey, USA http://www.genscript.com/Patient_derived_human_primary_tumor_models.html	• Panel of models for kidney, lung, colorectal, gastric, liver cancers
Champions Oncology, Hackensack, New Jersey, USA http://www.championsoncology.com/translationaloncologysolutions/superiority-overxenografts	• Models characterized by a high degree of genetic correlation (94%) with the original tumor • Champions TumorGraft TM platform for purposes of mouse avatar generation and drug testing • Provide personalized clinical oncology services to patients
Urolead, Strasbourg, France http://www.urolead.com/ips/products-and-services	• Over 40 characterized PDTX models for urological cancers (prostrate, kidney, bladder) • Repository for tumors, protein lysates, RNA and serum extracts • Access to clinical and pathological status of patients
Crownbio, Santa Clara, California http://www.crownbio.com/cancerbiology/in-vivopharmacology/hukemiatm-primary-patient-derivedblood-cancer-models	• HuKemia® platform for development and analysis of PDTX models of blood cancers
Molecular Response, San Diego, California http://pdxact.molecularresponse.com/	• Provide PDXact TM Precision PDX models including pre-characterized and custom made models • Offer pharmacological services drug testing services for PDX systems • Mutational analysis of murine tumors using IonTorrent TM Ion AmpliSeq TM Comprehensive Cancer Panel • Comparative histo-pathological analysis of the patient and engrafted murine tumors

Company/ Institution/ Organization	**Services offered**
XenTech, Paris, France http://www.xentech.eu/index.php?key=1_2_11_0_0_1&tpl=xentech	• Large collection of breast cancer PDTX models • Preclinical platform available for testing investigational agents
Pharmaron, Beijing, China http://www.pharmaron.com/Pages.aspx/Patient-Tumor-Derived-Xenograft-Models	• PDTX models of non-small cell lung cancer, small cell lung cancer, colorectal cancer, kidney, breast, ovarian, gastric, glioblastoma, esophageal, liver, prostrate, B cell lymphoma and ALL leukemias
Aveo Oncology http://www.aveooncology.com/r-d/humanresponse-platform/	• Proprietary Human-In-Mouse (HIM) Model for breast cancer