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Review Article

Improved Cancer Drug Development with Drug DISCO

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Abstract

Cancer drug development is inefficient, costly, and rarely leads to effective new drugs. Game-changing therapies that transform cancer care are the exception rather than the norm. As a solution, Drug DISCO (Development Incentivization Strategy in Comparative Oncology) is suggested as a means to re-position Comparative Oncology as a parallel and integrated approach to cancer drug development that includes dogs with spontaneous cancer during human clinical trials. This distinct approach recognizes the broader integrated/parallel value of Comparative Oncology for clinical development teams to use data from studies in the dog to answer questions as a means to optimize Phase II and Phase III human trials. This alternate focus will result in better definitions of dose, schedule, indication, and biomarkers of response of targeted therapies, and will collectively increase the chance of success in human trials beyond phase I studies. Ideally this will result in greater iteration within a drug development path rather than the existing binary succeed or fail approach. Drug DISCO also provides an opportunity to enhance the development of drugs that can prevent metastatic recurrence. Collectively we expect important therapeutic advances from this approach.

Cancer Drug Development is Difficult, Inefficient and Often Leads to Small Improvements in Outcomes

The field of cancer drug development is universally accepted to be one of the most challenging areas of drug development. This has been consistently endorsed by many perspectives in the field and directly supported by the fact that successful oncology drug approvals occur in less than 10% of drugs that enter the human clinical development path [1,2]. Even more striking is the late attrition for many of these failures, which results in disproportionately high financial costs for failure and the exposure of large numbers of patients to what will eventually be inactive drugs [3]. Furthermore, most approved drugs provide small improvements in outcomes [4]. Game-changing therapies that transform cancer care, such as checkpoint inhibitors in melanoma, are the exception rather than the norm. An analysis published in JAMA Oncology found that new cancer drugs provided an overall survival extension by an average of 3.43 months between 2003 and 2013 (43% increasing overall survival by 3 months or longer, 11% by less than 3 months, and 30% no increase) [5]. The authors concluded that "the added benefits of new cancer medicines vary widely across and within therapeutic indications." Lastly, with respect to the United States, this success assessment needs to be recognized against the backdrop of major funding initiatives, beginning with the National Cancer Act (or War on Cancer) in 1971 and continuing through to recent major funding initiatives to finding a cure for cancer in our lifetime. This begs the question, is a different approach needed?

Where are we Failing?

A closer dissection of these failures has been reviewed [6-8]. A synthesis of these reports reveals important and specific challenges in the cancer drug development path. First, there is a relatively high rate of successful human phase I trials (even more so in the setting of molecularly-targeted therapy) suggesting that conventional preclinical models are being effectively used to eliminate drugs associated with unacceptable acute toxicity risks [1]. Nonetheless, many other toxicities are not identified within the context of existing preclinical studies or phase I human clinical trials, resulting in late attrition due to toxicity, which disproportionately include chronic risks (e.g. neurotoxicity)

[9]. Similarly, the relatively small number of successful phase II human proof-of-concept clinical trials suggests that neither preclinical efficacy models, nor phase I human trials are sufficiently informative efficacy signals, and as such should be another area of improvement [10]. Finally, the largest and most costly failure is the agents that appear to be active in phase II, but then fail in phase III trials, or demonstrate minimal benefit in studies conducted after commercialization [11]. This suggests that conventional preclinical studies and human phase II trials are not sufficiently predictive of human phase III efficacy endpoints and/or that there is collectively insufficient data to inform the design of successful pivotal/phase III trials.

Based on the above, it is reasonable to prioritize the following two reasons as part of an agenda that seeks to improve cancer drug development:

- Prediction of chronic toxicities using conventional preclinical models and conventional human phase I trials.
- Failure to predict phase III success (importantly in the prevention of cancer recurrence or metastatic progression) using conventional preclinical models and conventional human phase II trials, which most often seek signals of measurable tumor shrinkage.

Why are we Failing?

Drug development requires substantial resources and time, which have been committed for decades and will continue to be committed. Some of the key areas leading to failure include:

Complex Biology

From the perspective of cell and molecular biology, it is simple and perhaps sufficient to explain our failure to be the result of the complexity of cancer biology. Cancer is a multifactorial disease characterized by cellular and molecular heterogeneity that drives the evolution of targets within cells and within distinct lesions [12]. Furthermore, our understanding of any differences that may exist between the tumor and the healthy cells of a patient is largely incomplete.

Genomics Data is Still in an Early Stage of Maturity

It is clear that cancer is a disease of dis-regulated genomics. It is therefore reasonable to conclude that a more complete understanding of genomics, and more specifically cancer genomics, would improve cancer drug development [13,14]. In the era of molecularly-targeted therapy, clear evidence in support of this can be seen from the recent approvals in human lung cancer, partially driven from an understanding of genomic subsets of this previously monolithic disease entity, and the potential serendipitous activity of novel immune-oncology assets in subsets of these patients [15]. A broader understanding of cancer genomes has been delivered through The Cancer Genome Atlas and other similar genomic characterization studies (i.e. Pediatric TARGET) [16-20]. These data, the dramatic reduction in the cost of genomic analysis and computing power, and the parallel genomic and biological annotation of human genes, has both fueled the field of precision medicine and delivered recent drug approvals in oncology. Additional evidence in support of how genomics and molecularly-targeted therapy has improved the cancer drug development path emerges from the observations of greater hints of clinical activity in phase I clinical trials using molecularly-targeted therapy compared to conventional cytotoxic therapy, and the resultant improvement in phase II successes [21,22].

Advances in Biology Are Needed to Keep Pace with Genomics in Order to Optimally Deliver Value

Challenges to the field of precision medicine, and more generally to molecularly-targeted therapy, must be addressed before this important and novel approach to cancer therapy will improve outcomes alone and will improve cancer drug development.

These challenges include, but are not limited to:

- **Cancer Evolution:** Describing the fact that most precision medicine platforms analyze patient tissue from a primary tumor resection, whereas most patients require therapeutics that target the evolution of molecular alterations that occur after the initial presentation and result in metastatic progression [23].
- **Cancer Geography:** Describing the fact that it remains unclear if molecular analysis of distinct portions of the same tumor may result in distinct therapeutic recommendations, and more specifically how to select the most valuable and informative portions of tissue for molecular analysis. Evidence from many genomic studies suggests that this problem of geographic heterogeneity is cancer-specific and will require studies in specific cancers to determine optimal biopsy recommendations for molecular analysis [24,25]. A reasonable solution to the problems of cancer geography and evolution may be delivered through the identification of cell-free circulating tumor DNA (liquid biopsy) and its potential value, rather than tumor biopsy as a substrate for genomic analysis of a cancer patient [26-28].
- **Context:** A critical but often ignored problem in the field of precision medicine is the growing understanding that specific genomic alterations in a given cancer influence the biology of that cancer in the context of that cancer [29,30]. More specifically this understanding applies to the therapeutic value of targeting these alterations, which can show benefit for one cancer type, but not necessarily others. For example, targeting BRAF at V 600E using a raf inhibitor has been shown to deliver favorable clinical responses in melanoma patients with that specific mutation, whereas targeting the same mutation in colon cancer with the same drug delivers no similar benefit [31-

33]. Therefore, the context in which a target exists determines its value as a therapeutic target. With this understanding, it is not surprising that there may be a biological challenge to the notion of targeting specific mutations across cancer histologies. Important hypotheses have been advanced and tested to explain context and drug target non-responsiveness [34]. Indeed, in the setting of BRAF at V 600E, a concurrent amplification of EGFR in colon cancer may explain the lack of response to raf inhibitors in human colon cancer [35,36]. It is likely that hypotheses to explain context will be cancer-specific and will not be overcome by further genomic analysis of cancers alone, but will require parallel cell biology and preclinical studies. Furthermore, since most experience with cancer genomics comes from the study of human epithelial cancers, it is likely that precision medicine rules derived from these cancers will not be necessarily applicable to non-human or even non-epithelial human cancers and vice versa. One thing is certain however; additional evidence will be accumulated with respect to this topic since there is an increasing use of basket trials earlier in oncology development and there is now regulatory precedent for pan-carcinoma approval or approval based on common biomarker versus tumor origination [37]. Nonetheless a priority should be placed on biological understanding of context

Misalignment of Needs and Strategy (Metastasis)

The late phase III attrition of cancer drugs resulting from lack of efficacy in phase III perhaps deserves our greatest discussion. Phase II clinical trials in oncology most often ask whether long-term clinical outcomes and improvements are delivered by a new therapeutic. However, long-term clinical improvements will most often occur when a therapeutic can effectively address the problem of cancer recurrence and metastatic progression. Recurrence and metastatic spread of cancer is the cause of 90% of cancer deaths [38]. Despite this being an unequivocal and unmet therapeutic need for most cancer patients, most preclinical assays and models and most phase II human cancer trials seek to identify drugs that will shrink an existing tumor (most often by targeting cell proliferation or inhibiting apoptosis) [39]. It is therefore reasonable to ask if this misalignment between drug discovery and the unmet therapeutic need may explain some of the lack of efficacy signal in phase III trials, despite phase II success or with less successful clinical outcomes with expanded use after approval. It is critical that this misalignment is addressed in more successful cancer drug development paths.

Two areas of misalignment relating to treating and preventing overt metastases are:

Treating Primary and Overt Metastatic Tumors Requires Different Strategies

Current therapeutic strategies for treating metastases are essentially based on preclinical models that test the impact of the drugs on the primary tumors. Metastasis arises from very few subpopulations of neoplastic cells that comprise the primary tumor [40-42], suggesting that the biology of metastases is different than their corresponding primary tumors [43].

Targeting Cancer Progression and Preventing Metastatic Recurrence Requires a Different Strategy Compared to Targeting Both Primary Tumors and Overt Metastatic Tumors

Since current therapeutic strategies are often based on preclinical models that test the impact of drugs on primary tumors followed by testing the drugs in humans for a similar effect on overt metastases, they fail to focus on modes of action that specifically target the major need: preventing cancer recurrence. Adding to the challenge of the drug discovery process is the role of the tumor microenvironment (comprised of resident stromal cells, infiltrating immune cells and the extracellular matrix) in metastatic progression and the subsequent evolution of malignancies promoting progression of the disease and potentially mediating multiple drug resistance [44,45]. Finally, preclinical models, and clinical trials need to be designed in a manner that can detect an agent's ability to prevent metastatic cancer recurrence.

Too Many Question Left Unanswered: Human Trials Do Not Encourage Iteration

A structural problem within the human clinical development path in oncology is the failure to answer as many important questions needed to optimize clinical development, which results in the requirement to increasingly guess rather than answer questions using parallel clinical or nonclinical trials. Within the understood complexity of cancer biology and therapeutic targeting, our failure to completely answer simple questions regarding dose schedule, target subpopulations, and appropriate selection of drug combinations, likely contribute to the existing drug development failures in oncology [46].

Failure to Use Preclinical Models Correctly

A common refrain in the setting of oncology drug development is the failure of mouse models to be predictive of response [47]. In most cases this critique is directed to simple heterotopic transplantable mouse models used in the drug development industry [48]. A reasonable response to this critique is the understanding that model systems of human disease do not necessarily fail themselves, but rather fail to answer questions (i.e. "predict") when the questions that have been asked of the model extend beyond the capacity of that model. Therefore, the failure of the mouse model of cancer is most often the result of our failure to correctly ask questions of that mouse model. For example, in the setting of cytotoxic chemotherapy, an important revision of the question "Is a given cytotoxic therapy active?" should be "Is a given

cytotoxic therapy active when administered with an understanding of the relevance of the exposure achieved vis-à-vis what can be achieved safely in humans?" [49]. Indeed, when translatable pharmacokinetic analysis of achieved exposures in mice is used to guide dosing in antitumor activity studies in mice, the correlation between responses in mice and humans is also quite high [50]. Furthermore, when overall responses of cytotoxic drugs in mice are correlated to responses seen in human clinical trials, the rate of prediction is impressive [51]. This however, suggests the need for multiple models of efficacy to collectively assess activity (rather than "cherry picking" specific model results).

In the setting of molecularly-targeted anticancer therapy, the correlation of response between mouse and human is also high when the question is focused on target modulation at appropriate pharmacokinetic exposures [52]. Beyond the commonly used transplantable mouse models, the use of genetically engineered mice and murine PDX models may be quite effectively used to answer early drug development questions regarding target modulation and resulting correlative biology and impact on tumor growth [53,54]. Related to the above discussion about cancer genomics and the issue of genomic context, it is reasonable and likely that such questions should be very specific to the molecular target and its "tested" context in that model system. Given the understood nascent and evolving evolution of cancer genomics, it is necessary to limit questions with such molecular cancer therapeutics in these mouse models to short-term endpoints, where the impacts of genomic evolution may be controlled. Unfortunately, in most cases, this limits the value of these mouse models since they often do not fully model the critical features of cancer recurrence, resistance, and metastasis, which collectively describe the "essence of the problem of cancer" in human patients [55]. Collectively, we would argue that it is important to understand and refine the questions that can be asked and answered within a given model and ask distinct questions in distinct models, where the questions are most appropriately asked. This understandably requires cancer drug development to include more than one model system and likely consider alternative models to improve the outcomes from of cancer drug development paths.

The Use of Drug DISCO to Improve the Cancer Drug Development Process and Success

Despite widespread recognition that pet dogs that naturally develop cancer provide a unique opportunity to improve the development path of new cancer drugs (referred to as Comparative Oncology), this modeling approach is perceived to be underutilized. Given the expanded awareness around the value and potential of Comparative Oncology, and expansion of current infrastructure, there is a significant opportunity to increase the use of an integrated/parallel and comparative approach to cancer drug development [56].

Comparative Oncology

In the setting of cancer drug development, Comparative Oncology involves the inclusion of dogs with naturally occurring cancer in clinical trials where novel cancer drugs are tested to answer questions that cannot be answered in conventional animal models of cancer or human clinical trials [57]. Comparative Oncology seeks to address many of the current shortcomings in oncology drug development through the study of these naturally occurring canine cancers as they share the same biological complexity and heterogeneity seen in human cancers [58-60]. Nonetheless, Comparative Oncology remains an uncommon component of most cancer drug development paths. This is despite significant investments in the field, such as the launch of the US NIH NCI-Comparative Oncology Program, as well as similar efforts and research by other institutions around the world [61-63]. Given the unquestioned need and the available translational and clinical infrastructure to deliver the promise of Comparative Oncology, there is an urgency to expand the use of a comparative and integrated cancer drug development path.

What is Drug DISCO?

When considering the promise of Comparative Oncology and its potential shortcomings, we now propose a strategic perspective to better deliver Comparative Oncology, referred to as Drug DISCO (Development Incentivization Strategy through Comparative Oncology; aka Comparative Oncology 2.0, overview shown in Figure 1).

Positioning Comparative Oncology in the Oncology Drug Development Path

This distinct approach recognizes the broader integrated/parallel value of Comparative Oncology for clinical development teams to use data from studies in the dog to answer questions as a means to optimize Phase II and Phase III human trials. This alternate focus will result in better definitions of dose, schedule, indication, and biomarkers of response of targeted therapies, and will collectively increase the chance of success in human trials beyond phase I studies.

Optimizing Comparative Oncology by Including Animal Health Industry in a Collaborative Model

This collaboration will allow greater exchange of assets between animal health and human health. This alignment will de-risk human R&D in many ways and has the potential to create new streams of investment (through animal drug development) to support these critical, parallel, and integrated translational studies. This disruption in cancer drug development will redefine roles and reduce costs for conventional animal health R&D and will provide early exits for human cancer drug development through the veterinary market.

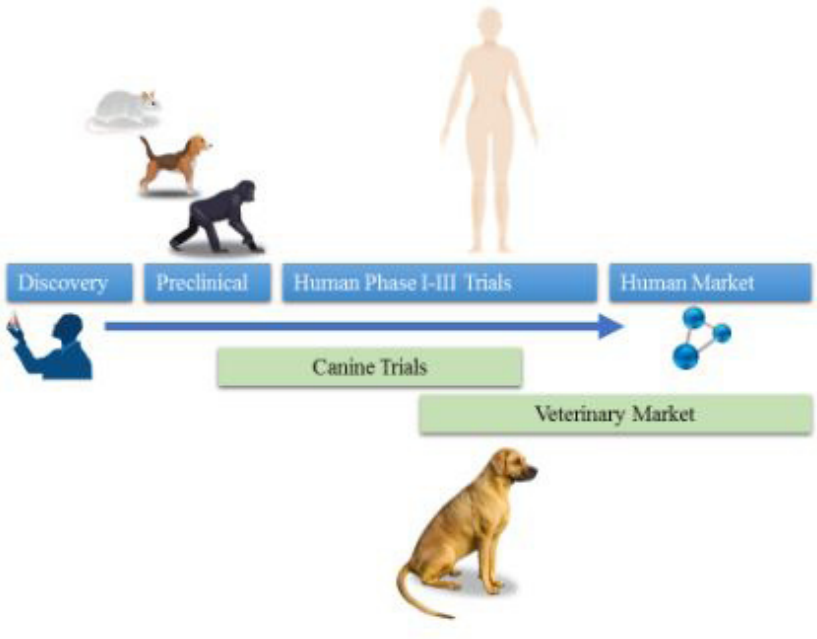

Figure 1: Drug-DISCO Overview.

Positioning Comparative Oncology in the Oncology Drug Development Path

A potential shortcoming in the use of Comparative Oncology may include a strategic pitfall that results from the current commonly held perspective that this approach is merely an additional preclinical strategy used late in drug discovery before human phase I entry. Within Drug DISCO we now suggest re-positioning Comparative Oncology as parallel and integrated research done with dogs with spontaneous cancer during human clinical trials. This distinct approach recognizes the broader integrated/parallel value of Comparative Oncology for clinical development teams to use data from studies in the dog to answer questions as a means to optimize phase II and phase III human trials. This alternate focus will result in better definitions of dose, schedule, indication, and biomarkers of response of targeted therapies, and will collectively increase the chance of success in human trials beyond phase I studies. Ideally this will result in greater iteration within a drug development path rather than the existing binary succeed or fail approach. This opportunity for greater iteration around unanswered questions will become more useful to those in cancer drug development rather than at the conclusion of cancer drug discovery efforts.

Optimizing Comparative Oncology by Including Animal Health Industry in a Collaborative Model

Repositioning of the dog as a parallel, rather than a preclinical model, offers additional opportunity through collaboration between human and animal health drug development communities [64,65]. This collaboration will allow greater exchange of assets between animal health and human health. This alignment will de-risk human R&D in many ways and has the potential to create new streams of investment (through animal drug development) to support these critical, parallel, and integrated translational studies. This disruption in cancer drug development will redefine roles and reduce costs for conventional animal health R&D and will provide early exits for human cancer drug development through the veterinary market. Such early exits may include "monetizing/value" events earlier than possible in a human-only drug development path and may fund ongoing iteration within the human development path.

What is Needed from Regulators

As collaborations form between animal health and human health drug development communities, there is a need for greater alignment between regulators in both fields. For example, where possible, closer alignment on CMC package reviews for human and animal health drugs will provide a greater rationale for collaboration and sharing of that agent from human health and vice versa. There is regulatory clarity on the design, conduct, and reporting of data from Comparative Oncology and other non-clinical studies within an existing human drug development path [66]. No further clarity on the methods of integration is needed.

An example of the value of regulatory clarity for the field of Comparative Oncology was provided on the record by the CDER-FDA at a recent meeting convened by the Institute of Medicine

[67]. At this meeting, a significant previously expressed, perceived risk, raised by human pharma regarding Comparative Oncology studies was addressed. This was addressed through a simple public statement that indicated that "Toxicity signals identified in these diseased models would be interpreted in context." This was understood to mean that if an unexpected adverse event was observed in a study involving pet dogs with cancer, that event would be interpreted in light of human tolerability data and any other tolerability data observed in nonclinical species. This simple comment has been sufficient to address the previous concern regarding adverse events seen in dogs that may impact the design and conduct of ongoing human clinical trials. The concept of an early exit from a human drug development path, for whatever reason, to a potential licensing agreement with animal health pharma, will not likely be a sufficient financial incentive alone for human drug development and not feasible within many animal health paths. Therefore, creative incentives from regulators to both communities may create greater value for such sharing and resulting collaborations.

What Else is Needed to Unleash Drug DISCO

Several factors have limited the use and value of Comparative Oncology studies in the past and some remain as obstacles for Drug DISCO:

- **Awareness:** There continues to be an inadequate awareness of the value and best application of Comparative Oncology within a human oncology drug development path. This issue requires ongoing effort, and has been previously addressed through high-impact publications, national meetings, and numerous interactions between Comparative Oncologists and human pharma [68-70]. An important advance to the field was provided through the endorsement of this concept by the National Institutes of Health and the National Cancer Institute's Comparative Oncology program [57]. Similar endorsements have come from many comprehensive cancer programs around the world, and more recently within human pharma companies [62].
- **Capacity to conduct canine patient trials:** Through the National Cancer Institute Comparative Oncology Program and other cooperative groups, canine cancer studies can be conducted efficiently with effective reporting of data in a timely manner. Nonetheless, related to the item of awareness there remains a need for cancer drug development teams to be aware and consider the time and cost impacts of Comparative Oncology studies as they design and de-risk more successful development paths.
- **Canine genomics and annotation:** An important advance to the field was delivered through the release of the first public canine genome in 2004 [71]. This genome has allowed a deeper use of biology within canine Comparative Oncology studies. There is nonetheless an ongoing need for the canine genome to mature through better genomic annotation. It is understood that privately held canine genomes exist and remain unshared, which limits the opportunity for initial deeper canine genomic annotation and the subsequent and more complex biological annotation of the canine genome. Especially in the context of targeted and molecular therapy, where cancer drug development will be target-based and less influenced by histological characterization of diseases, there is now a need for investigators to use in silico data to understand if a specific cancer gene alteration exists in a given dog cancer. Fortunately, through a recent RFP from the NIH and from the Animal Cancer Foundation, initial studies with canine cancer genomes have begun [72]. This will allow investigators to align models in dogs with human disease. As described above, until there are solutions to the problems of genomic evolution, geography, and context, it will not be reasonable to effectively deliver the above genomic translational modeling within Comparative Oncology studies nor as a therapeutic strategy within animal health without the needed biologic annotation of cancer genomes. Indeed, large studies are needed to better define the context of genomic alterations in dogs to allow appropriate drug matching. These data from dog studies may simultaneously inform questions of context in less common forms of human cancer where biological annotation similarly remains lacking (i.e. sarcoma).
- **Reagents:** As fields of drug development emerge, for example the recent interest in the field of immuno-oncology [73,74], there will be an ongoing need for biological reagents to be developed to allow optimal correlative biological endpoints to be included in Comparative Oncology studies. It is likely most efficient that such reagent development occurs on an as needed basis (e.g. the recent development of several canine immune checkpoint inhibitor antibodies and cellular immunology reagents needed for the development of canine CAR T cells) [75,76] rather than investing new funds for reagent development absent of a therapeutic mandate.
- **Metastasis:** The spontaneous development of metastasis as an outcome of cancer progression in canine cancers is likely the most valuable feature of the dog to improve both cancer drug development paths and deliver more effective therapies to humans. The development of biological correlates of metastatic progression (i.e. liquid biopsy) in dogs will further facilitate this important value of the Comparative Oncology approach to drug development that will ultimately improve patient outcomes by targeting metastatic progression.

How Drug DISCO will Improve Cancer Drug Development

An optimized and parallel/integrated comparative development path, through the implementation of Drug DISCO, will result in a greater number of successful phase II human trials. This is due to a better integration of patient selection, biomarker-optimization of dosing and schedule, and elimination of likely

inactive drugs. The advantage gained through better selection of agents to advance to human phase II trials has been modeled and previously reported [57,77,78]. There will be more successful phase III trials through the early identification of drugs that are able to prevent spontaneous metastatic progression in dog cancers. Animal health drug development will benefit from access to a greater number of drug licensing opportunities that have been de-risked through Comparative Oncology research studies in dogs.

In the context of preventing cancer relapse, Drug DISCO provides the unique opportunity to more accurately assess the anti-metastatic activity of a drug. Aligned with this use of Comparative Oncology, many clinical groups have embraced and recognized the need for novel phase II human clinical trial designs. Noteworthy of and related to the above is the Children's Oncology Group, with the design of human phase II clinical trials in osteosarcoma that prioritize endpoints related to metastatic progression. This may be complemented with parallel osteosarcoma dog trials, leveraged by the higher prevalence of osteosarcoma in pet dogs, and the similarities in the disease biology (including metastatic progression to the lung) between the species [79]. Collectively we expect important therapeutic advances from these new efforts to develop drugs that target metastatic progression.

Bringing on DISCO

Organizations that have developed expertise in Comparative Oncology can facilitate this approach by bringing interested human and animal health pharma/biotech companies together. This can create the connections between human and animal health drug development efforts, which are especially needed organizations where internal animal health and human health capabilities are not co-located. This approach will create synergy to leverage resources, de-risk drug development, and generate returns simultaneously within a human and animal health drug development path.

Concluding Remarks

Drug DISCO enables re-positioning Comparative Oncology as parallel and integrated research done with dogs with spontaneous cancer during human clinical trials. This distinct approach recognizes the broader integrated/parallel value of Comparative Oncology for clinical development teams to use data from studies in the dog to answer questions as a means to optimize phase II and phase III human trials. This alternate focus will result in better definitions of dose, schedule, indication, and biomarkers of response of targeted therapies, and will collectively increase the chance of success in human trials beyond phase I studies. Ideally this will result in greater iteration within a drug development path rather than the existing binary succeed or fail approach. This opportunity for greater iteration around unanswered questions will become more useful to those in cancer drug development rather than at the conclusion of cancer drug discovery efforts. Collectively we expect important therapeutic advances from these new efforts to develop drugs that target various cancer stages and metastatic progression.

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Conflict of Interest Statements

Samuel Stewart and Chand Khanna are employees of Ethos Veterinary Health. Dalit Barkan has a consulting agreement with Vuja De Sciences, Inc. and compensated with Vuja De Sciences equity. Richard Lampe is Co-Founder and executive at Vuja De Sciences, Inc., is employed by the company and holds stock in the company. David Warshawsky is Founder and CEO of Vuja De Sciences, Inc., is employed by the company and holds stock in the company. Ethos Veterinary Health and Vuja De Sciences have entered a Memorandum of Understanding to collaborate in cancer drug development.

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