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Perspective

Delivering Innovation to Oncology Drug Development through Cancer Drug DISCO (Development Incentive Strategy using Comparative Oncology): Perspectives, Gaps and Solutions

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Abstract

The field of Comparative Oncology has historically sought to conduct clinical trials in dogs with naturally occurring cancer to answer drug development questions relevant to human Oncology that cannot be easily answered in conventional animal cancer models or in human clinical trials. This approach to delivering Oncology drug development innovation has produced several notable successes and has gained support from many groups within the human Oncology drug development community. However, widespread adoption of this paradigm has not yet occurred. As an immediate follow up to an international meeting of experts and stakeholders in the field at the Pre-Congress One Health committee meeting of the World Small Animal Veterinary Association (WSAVA) in Toronto, Canada in July 2019, we hypothesized that new commercial incentives for Comparative Oncology would jointly accelerate and optimize cancer drug development for humans and pet dogs by more closely aligning the human and animal health pharmaceutical/biotech industries. This enhanced animal and human pharmaceutical/biotech proximity will create new commercial transactions between animal health and human health companies, and will reposition Comparative Oncology canine trials as interspersed with, and parallel to, human development rather than merely as preclinical models. We refer to this new animal-human pharma proximity and the resultant outcomes (new commercial incentives and parallel repositioning of Comparative Oncology) as Drug Development Incentive Strategy using Comparative Oncology (DISCO). The gaps and solutions to implementation of Drug DISCO are provided herein as the first output of the WSAVA One Health committee meeting.

Introduction

The need for innovation in Oncology drug development is widely acknowledged. The average cost of development for a new anticancer drug exceeds $1 billion (US) and nine out of ten promising new drugs will fail [1-5]. An innovation proposed two centuries ago is now increasingly employed to address this need by studying spontaneous cancers in pet dogs, which are largely indistinguishable from many cancers that occur in humans and which are often treated in a similar fashion. Indeed, in the setting of drug development, this field of Comparative Oncology involves clinical trials for pet dogs with naturally occurring cancers designed to answer drug development questions that cannot be easily answered in either conventional animal models of cancer or in human clinical trials. The nature and value of these challenging drug development questions have been the focus of recent reviews [6,7]. Traction surrounding the scientific and translational value of answering these drug development questions within complex cancer models that embody the essence of cancer as a biological phenomenon (i.e. heterogeneity, recurrence, resistance, and metastasis) has led to a number of recent steps forward. These include the launch of the National Institutes of Health (NIH) National Cancer Institute (NCI)-Comparative Oncology Program and research supported by the extramural NIH and academic research centers around the world (Table 1), increased regulatory clarity surrounding this approach, and more recently the launch of Comparative Oncology programs by several human pharmaceutical and biotech companies [7,8]. This progress and promise has been reviewed and described previously [9-14]. Nonetheless, historically recognized barriers to realizing the potential of Comparative Oncology within the human drug

development path must still be addressed to allow this innovation to reach its full potential. These barriers are summarized in (Table 2).

Agency	Program
EU Framework Programmes	European University Grants/Fellowships
	ERC
	IMI
Japanese Assoc for Cancer Research	The Prince Hitachi Prize for Comparative Oncology
United States National Institutes of Health	National Cancer Institute (NCI) Comparative Oncology P30 Cancer Center Supplements[1]
	NCI Pre-medical Cancer Immunotherapy Network for Canine Trials (PRECINCT)[2]
	The Clinical and Translational Science Award (CTSA) One Health Alliance (COHA)[3]
	The Integrated Canine Data Commons (ICDC)[4]
	SBIR Contracts for Development and Validation of Non-Mouse Reagents to Enable Preclinical Development of Novel Therapeutics[5]
	Addition of a specific focus on comparative oncology to the standing NCI clinical trials R21[6]
Private Foundations	American Kennel Club[8]
	Animal Cancer Foundation[10]
	Blue Buffalo Foundation[9]
	Canines-N-Kids Foundation[11]
	Morris Animal Foundation[7]
	The Osteosarcoma Institute[12]
	V Foundation[9]

[1] https://www.frontiersin.org/research-topics/9729/emerging-translational-opportunities-in-comparative-oncology-with-companion-canine-cancers

[2] https://dctd.cancer.gov/NewsEvents/20190327_canine_immunotherapy.htm

[3] https://ctsaonehealthalliance.org/

[4] https://www.cancer.gov/news-events/cancer-currents-blog/2019/comparative-oncology-dogs-cancer-clinical-trials

[5] https://sbir.cancer.gov/funding/contracts/372

[6] https://grants.nih.gov/grants/guide/pa-files/PAR-19-356.html

[7] http://veterinarynews.dvm360.com/maf-cancer-initiative-seeks-raise-30-million

[8] http://www.akcchf.org/news-events/news/akc-canine-health-foundation-20.html

[9] https://www.petfoodindustry.com/articles/6765-blue-buffalo-funds-dog-and-human-cancer-research

[10] https://www.globenewswire.com/news-release/2017/10/24/1152566/0/en/Animal-Cancer-Foundation-Announces-1-Million-Gift-to-Inaugurate-Canine-Cancer-Genome-Project.html

[11] https://www.caninesnkids.org

[12] https://www.osinst.org

Table 1: Examples of Comparative Oncology Research Supported by the Extramural NIH and Academic Research Centers Around the World.

Barrier	Mitigation
Poor understanding of the value of comparative oncology	Continue to expand awareness within human cancer drug development communities
Inaccessible or cumbersome trial infrastructure	More widespread use of the facile approaches to conduct studies within an existing human development path
Limited funding	Fully incentivize stakeholders[1]
Limited availability of canine-specific clinical and biologic reagents	Biological reagents to understand canine disease-targets and develop biomarker and PD endpoints[2]
Aversion to disrupt existing human drug development path	Earlier preparation for investments towards comparative data

[1.] DRUG DISCO should deliver early revenue exits for human therapeutics in development. These very revenues could be used to both fund comparative oncology trials and also to incentivize needed creativity of therapeutic asset managers.

[2] Foundational grant funding should prioritize "toolbox development" projects which will lay the groundwork for future discoveries (i.e., annotated canine cancer tissue banks, cell lines and patient-derived xenografts).

Table 2: Comparative Oncology: Addressing Existing Barriers.

We now propose a new direction for the field of Comparative Oncology beyond the previously articulated scientific and translational value that will emerge through increasing the commercial proximity between human and animal pharma/biotech to effectively create mutually beneficial commercial interests valued by both animal and human pharma (Figure 1). The desired proximity and commercial incentives will also result in repositioning Comparative Oncology with questions that need answers during human clinical development, collectively described as Drug DISCO.

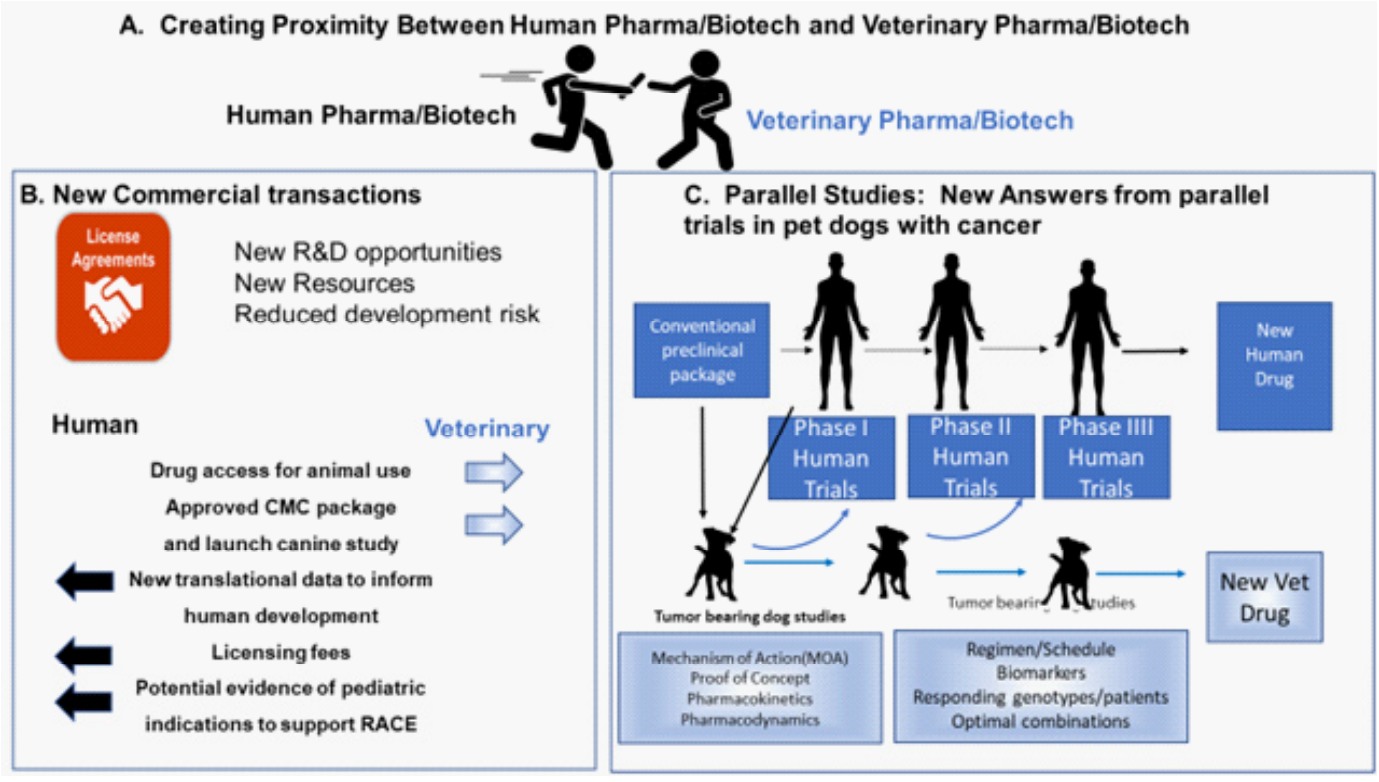

Figure 1: The DRUG-DISCO (Development Incentivization using Comparative Oncology) concept begins with **A:** New proximities developed between human pharma/biotech and animal health pharma/biotech. Increased Proximity will lead to **B:** New commercial

relationships and transactions between human pharma/biotech and animal health pharma/biotech. These transactions will likely include licensing agreements between parties for the development and future commercialization of a human pharma/biotech therapeutic agent for approval by the veterinary pharma biotech team. The licensing agreements will provide new revenues for the human therapeutic and can allow an early development exit for the human pharma/biotech and/or allow ongoing human drug development by the human pharma biotech. Initial studies conducted with the human therapeutic, in pet dogs with cancer will answer translational questions that will optimize ongoing human development; but may also create a commercial understanding of the value of this agent in the veterinary market and allow the animal health pharma/biotech to determine if a veterinary a regulatory development path towards an animal health approval should be considered. Ideally the terms of the transaction would also include payment for the transfer of an approved CMC package to the veterinary pharma biotech entity. As proposed in this text efforts to align FDA-CDER and FDA-CVM around CMC package approval would add value and incentivize these transactions for both parties. In addition to the new revenue from the licensing agreement, human pharma/biotech may benefit from the fact that pet dogs tend to develop cancers that are similar to human pediatric oncology patients (i.e. osteosarcoma) and the resultant translational data may be useful to human pharma/biotech as they plan a strategy for a RACE fast track FDA voucher, based on drug development in an orphan pediatric indication; more common in pet dogs. **C:** The secondary consequence of greater human and veterinary pharma/biotech proximity from DRUG DISCO is the repositioning of translational comparative oncology studies in parallel with the human clinical development plan. With this paradigm, drug development questions that are difficult to ask or answer in conventional preclinical models or human clinical trials are asked in parallel tumor bearing dog comparative oncology studies, as a means to design the best human clinical trials possible and improve the chances of a future human oncology approval.

Here, we highlight this novel perspective on Comparative Oncology suggested by Drug DISCO, and then address gaps with proposed solutions for its implementation (Table 3).

· Inefficiency in the transfer of therapeutics between human and animal health due to regulatory hurdles
· Limited veterinary oncology market data through the DISCO lens
· Minimal awareness of the animal health pharma approval/regulatory landscape
· Impediments to successful animal pharma/biotech-human pharma/biotech transactions
· Perceived risk of adverse events affecting human assets

Table 3: DRUG-DISCO: What gaps need to be addressed to unleash Drug DISCO.

This Drug DISCO gap analysis and our proposal will be implemented though new collaborations led by the One Health Committee of the World Small Animal Veterinary Association in the coming months. The new perspective of Drug DISCO (Development Incentive Strategy using Comparative Oncology; (Figure 1) has the following desired outcomes:

- Optimize design of human clinical trials through iteration within the drug development path using data from clinical trials in pet dogs that parallel extant trials in humans.
- Create new revenue streams and other potential values for human pharma/biotech from the transfer of agents into an animal health commercial path.
- Identify human path liabilities (lack of activity, off-target effects), and add translation answers (correlative biomarkers, optimal responder phenotypes/genotypes, activity against metastatic progression) necessary for optimal human Oncology therapeutic development.
- Increase the likelihood of success of new agents in phase II/III human clinical trials through the above mechanisms.
- Engender a self-funding mechanism to develop innovative Comparative Oncology translational data.
- A parallel outcome of Drug DISCO is the realization of the following animal health benefits:
- New data that will de-risk canine cancer drug development in animal health and deliver new approvals in the animal health industry.
- Lower risk and cost for Oncology research and development in the animal health industry.
- Delivery on the unmet needs of the veterinary commercial market in Oncology.

Having defined the needs, potential benefits, and desired outcomes of cancer Drug DISCO, we now describe existing gaps and solutions to unleash the power of this new drug development opportunity.

Drug DISCO gap/solution: New teams that explore and leverage incentives from aligned animal and human pharmaceutical industries in order to generate a self-funding development model and reposition canine cancer drug studies as parallel to human

In recent years, many leaders of the human pharmaceutical and biotech communities have recognized the costs and inefficiency of the conventional human Oncology drug development path and have been motivated to consider alternative innovative solutions [15,16]. Despite existing interest and investment in Comparative Oncology, a strategic pitfall of this approach results from its implementation primarily in the late stages of preclinical drug discovery often immediately prior to human phase I entry. This historical approach resulted in collaboration and alignment between human cancer drug discovery teams and those involved in Comparative Oncology toward the end of the discovery team's responsibility for an agent [17-20]. In the setting of Drug DISCO, new collaborations must be developed between drug development teams and the Comparative Oncology field to optimize the human drug development path with new sources of data from pet dog clinical trials that are uniquely aligned to optimize human phase II and Phase III trials (Figure 1). These new teams will share perspectives and vocabulary around trial designs in both species. This alternate focus on parallel/integrated drug development seeks to optimize Phase II/III human trials and will result from better definition of dose, schedule indication/biomarkers of response, drug-target mechanisms of action, and will collectively increase the chance of success in human Phase II and beyond. It is likely that these new teams will consist of DVM and MD clinician scientists supported by PhD drug discovery teams and commercial leaders. Such repositioning could result in a shift in the need for resources for Comparative Oncology from the tail end of conventional preclinical discovery budget, in what is a period of therapeutic candidate risk and diminished access to discovery team resources to the domain of newly formed clinical drug development teams.

This approach will de-risk human R&D in many ways. Drug development requires considerable resources and time; estimates for financial return on investment of R&D expenditures for 12 large pharmaceutical companies reportedly fell to a low point of 3.7% in 2016 [21-23]. This trend in falling financial returns, combined with the record-level high cost of bringing an asset to market has created a need for companies to embrace novel ways to unlock R&D productivity and deliver scientific breakthroughs. With respect to these challenges, when combined with greater human pharma and animal pharma proximity, Drug DISCO may deliver early revenue exits for human therapeutics in development and incentivize needed creativity among asset management teams and fund these critical, parallel/integrated translational studies.

Drug DISCO enables repositioning of Comparative Oncology as parallel/integrated research in dogs with spontaneous cancers during human clinical trials. This distinct, strategic approach leverages the broader value of Comparative Oncology and fosters the exchange of assets between human and animal pharma/biotech by including the animal health industry into this model. We anticipate that the increased commercial proximity between human and animal pharma/biotech will effectively create mutually beneficially transactions between these groups that will include: 1) new translational data that will improve human Oncology drug development and optimize the design of human Phase II and III trials; 2) creating new commercial exits for human Oncology assets; which may also add value through new pediatric indication data; 3) access to new Oncology drugs from human pharma/biotech to animal pharma/biotech; and 4) new animal health R&D opportunities and animal health pharmaceutical approvals for Oncology drugs. Ideally, positioning Comparative Oncology in parallel (and providing input to each step of drug development), rather than as a preclinical model, will circumvent several of the current challenges faced by traditional drug development modeling approaches in defining dose/schedule, indication, and biomarkers of response and will collectively increase the chances of success in phase II and III human clinical trials. In contrast to the binary 'succeed' or 'fail' approach in cancer drug development, Drug DISCO offers an alternative strategy and provides opportunity for greater iteration within the drug development path.

Drug DISCO gap/solution: Veterinary Oncology market data

In order for greater proximity between human pharma/biotech and animal pharma/biotech to generate mutually beneficial commercial transactions, deal makers on both sides need better market data for Oncology in animal health. Such data does not exist at this time but is being developed by a number of groups. The total accessible market in veterinary Oncology has not been assessed and requires better estimates of disease volume and price point that can only be defined within the context of a specific therapeutic and its ability to address a specific unmet need in the market. Fortunately, market assessment tools exist and can be used to create market and price point data in specific canine Oncology disease areas and make them available to users for purchase, subscription or through partnership. Companion animal market analysis and data has thus far focused on relatively lower price point and higher volume markets (i.e. antibiotics and parasiticides), and thus existing perspectives on the market must also evolve.

Drug DISCO gap/solution: Awareness of the animal health pharma landscape

The private equity markets have recognized veterinary medicine as a segment of the health care services industry and valued it accordingly; however, they have also recognized its key differences from other segments of the health care services market. Similarly, animal health pharma may be considered a unique segment of the greater pharmaceutical industry. An awareness of

the differences of this segment vis-à-vis risks/returns and regulatory timelines of animal health versus human approvals is necessary as part of the effort to create proximity between these market segments. Briefly, and for many reasons, animal health pharma approvals should deliver faster revenues with lower overall risk, but with lower returns than human pharma approvals. It is not true that animal health approvals are fast or easy; therefore, awareness and education within pharma commercial forums with adequate dialog is needed.

Drug DISCO gap/solution: Facilitate successful animal pharma/biotech-human pharma/biotech transactions

The recent successful transactions between animal pharma/biotech and human pharma/biotech, have been opportunistic and largely built on personal relationships. To scale these emerging transactions as part of Drug DISCO, it is possible that greater awareness by both communities alone will be sufficient, but possible that neutral third parties may be helpful to facilitate these planned new deals. Furthermore, when successful, these transactions should be showcased and branded as part of Drug DISCO in relevant human and animal trade journals. This awareness should be used to progressively refine future transactions and identify features of the best therapeutic agents and data packages for cross-species transfer.

Drug DISCO gap/solution: Risk of adverse events affecting human asset

In 2014 as a matter of fact and public record, the U.S. Food and Drug Administration Center for Drug Evaluation and Research (FDA-CDER) made it clear that safety signals uncovered in the study of new therapeutics in canine cancer clinical trials would be viewed in context and not take priority over human safety data or toxicokinetic studies in purpose-bred dogs. Indeed, CDER indicated that no such example has ever been recorded. Despite this public statement, an unwillingness by some human pharma groups to pursue Comparative Oncology data is still related to a perceived risk of uncovering an unexpected safety signal in these canine Comparative Oncology studies. A next step to provide assurance to these late adopting human pharma companies would involve the arduous task of new FDA guidance on this seemingly resolved question. It is reasonable to wonder if such a further step is needed under the public clarity of the existing CDER statement.

Drug DISCO gap/solution: Animal-human regulatory alignment

Of the components of a regulatory package, it is reasonable to expect closest alignment of regulatory interpretation to be on the topic of the FDA Chemistry Manufacturing and Controls (CMC) package. On the topic of CMC, the guidance documents describing the steps towards regulatory approval of a therapeutic within FDA-CDER (for the human market) and FDA Center for Veterinary Medicine (CVM) (for the animal health market) are similar; however, interpretation by these bodies is quite distinct and currently requires additional work by animal health pharma despite an existing and approved human CMC package to obtain a CVM approval. To facilitate the greatest exchange of therapeutic assets between human and animal pharma/biotech, closer alignment on CMC approval is necessary and is a reasonable expectation. This may be accomplished through a task force to work with members of FDA-CVM and FDA-CDER to create this alignment.

Conclusion

What will Oncology drug development look like post-Drug DISCO?

What do we desire and from whom?

Post Drug DISCO, the authors hope to see an environment for drug development in which contact between human pharma/biotech and animal pharma/biotech are much closer than they are currently. The number of transactions between human and animal pharma/biotech medicine should increase, most importantly, Comparative Oncology trials in pet dogs (or other species) with cancer must graduate from its current status as "another preclinical model" and become a process that can provide input into every needed step of the drug development process. Within the Drug DISCO approach, this broader inclusion of dogs in parallel with human clinical trials provides a distinct opportunity for development teams to integrate data generated from studies in the dog as a means to optimize phase II and III human trials.

The opportunity to optimize collaboration between human pharma/biotech and animal pharma/biotech will enhance the exchange of assets between these communities. This approach will facilitate early engagement and transactions between animal pharma/biotech and human pharma/biotech. Such engagement has the potential to create new streams of investment (through animal drug development) and provide early exits for human cancer drug development through the veterinary market. Thus, these transactions may fund ongoing iteration within the human development pathway.

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