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December 8, 2015

Comparative Oncology: A New "Breed" of Trial Set to Improve Clinical Success in Oncology

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Summary

Launching the Dawson James Comparative Biology and Veterinary Biotech Sector Universe

Our research indicates that few of our peers are looking at companies who specifically are adopting comparative biology approaches to clinical development for new drugs or to veterinary biotechnology as an emerging subsector of the biotech world. We are introducing a universe of companies that fit a distinct profile for this new sector as many of the therapies being explored through comparative biology trials or under development in veterinary applications of biotechnology are truly transformative. As such, they may offer unique solutions in the treatment of cancer, neurological diseases, degenerative diseases such as osteoarthritis, rare diseases and in regenerative medicine.

In coming weeks, we will expand on this initial universe of companies by adding various specialty "satellite" groups of companies to highlight selected therapeutic technologies, such as gene therapy, as well as bridging technologies and devices, such as imaging/visualization technologies, and molecular diagnostics that are being employed as enabling technologies by these companies. We will also feature selected indications, such as neuro-oncology, where these enabling technologies and comparative biology are coming together to offer potentially new treatment paradigms compared to traditional small molecule drug development. We believe that by identifying a suite of companies representative of this emerging sector, our investors may find potentially unique and undiscovered opportunities.

The initial universe that follows is comprised of three primary company sets: 1) veterinary biotech and animal health companies that are developing both animal and human biotech products, 2) veterinary companies developing products around biologics and other human-related drugs and devices and 3) human biotech companies who are uniquely utilizing comparative trial approaches in their clinical programs. We have included one or two companies that do not fit any of these categories, such as Trupanion (TRUP/$8.63/Not rated), because of collateral relevance to growing the market for veterinary biotech, the advancement of novel therapies for companion animals or by facilitating the use of comparative biology in the development of new human therapeutics. We view the following universe of companies as a "starter list" and will be fine-tuning this universe over time.

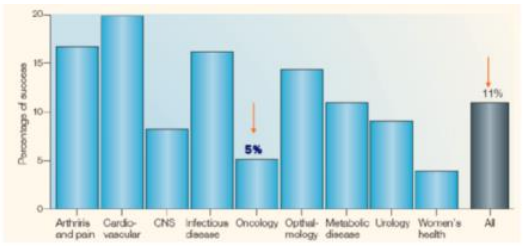
DAWSON JAMES COMPARATIVE BIOLOGY & VET BIOTECHNOLOGY SECTOR

Ticker	Security Name	Last Price	Chg	%Chg	CVol	YTD %Chg	Mkt Cap (MM)	EPS FY1	PE FY1	Div Yld
ABSCF	AB Science SA	13.82	0	0.00%	0	-2.47%	515	-0.55	--	0
NVET	Nexvet Biopharma PLC	3.57	-0.17	-4.55%	47,051	--	41	-1.89	--	0
ALQA	Alliqua BioMedical, Inc.	2.45	-0.07	-2.78%	44,643	-53.77%	68	-0.96	--	0
BIOG.B-OME	BioGaia AB Class B	301	2.5	0.84%	7,762	67.69%	5,218	7.15	42.07	1.66
PAHC	Phibro Animal Health Corporation Class A	32.71	0.6	1.87%	155,007	3.68%	1,283	1.7	19.22	1.22
PARN	Parnell Pharmaceuticals Holdings Ltd.	4.02	-0.13	-3.11%	7,470	-3.11%	53	-0.94	--	0
KIN	Kindred Biosciences, Inc.	3.79	-0.05	-1.30%	79,434	-49.13%	75	-1.49	--	0
ICCC	ImmuCell Corporation	7.44	0.06	0.81%	9,463	53.08%	23	--	--	0
NEOG	Neogen Corporation	58.22	0.46	0.80%	189,815	17.40%	2,176	1.07	54.33	0
OASM-OME	Oasmia Pharmaceutical AB	11.55	-0.1	-0.86%	100,566	-42.25%	1,219	--	--	0
PETX	Aratana Therapeutics, Inc.	5.77	-0.07	-1.20%	358,133	-67.62%	202	-1.79	--	0
POLXF	Polydex Pharmaceuticals Limited	2.1	0.1	5.00%	1,000	180.00%	6	--	--	0
VETO-PAR	Vetoquinol SA	41.2	-0.8	-1.90%	2,528	14.76%	490	2.22	18.52	0.95
ENTB	Entest BioMedical, Inc.	0.01	0	0.00%	0	-26.67%	1	--	--	0
RGS-ASX	Regeneus Ltd.	0.1	0	0.00%	5,000	-34.38%	22	-0.02	--	0
ANAC	Anacor Pharmaceuticals, Inc.	110.66	-1.16	-1.04%	684,399	243.13%	4,883	-1.28	--	0
NVC-TSE	Neovasc Inc.	5.46	-0.29	-5.04%	663	-29.09%	363	-0.49	--	0
CTIX	Cellceutix Corporation	1.63	-0.01	-0.43%	229,898	-62.87%	193	--	--	0
DPH-LON	Dechra Pharmaceuticals PLC	10.12	0.16	1.61%	47,504	20.98%	891	0.43	23.54	1.67
GNVC	GenVec, Inc.	2.29	-0.08	-3.54%	2,414,354	9.90%	39	-0.37	--	0
SCYX	SCYNEXIS, Inc.	6.99	0.2	2.94%	89,248	-29.96%	97	-2.59	--	0
DPH-LON	Dechra Pharmaceuticals PLC	10.12	0.16	1.61%	47,504	20.98%	891	0.43	23.54	1.67
ANIK	Anika Therapeutics, Inc.	43.3	1.01	2.39%	89,985	6.28%	634	1.84	23.6	0
TRUP	Trupanion, Inc.	8.63	0.18	2.13%	40,842	24.53%	244	-0.57	--	0
CYDY	CytoDyn Inc.	0.84	0.01	1.21%	22,858	-27.39%	77	--	--	0
ORNBV-HEL	Orion Oyj Class B	31.26	0.02	0.06%	206,361	21.30%	4,397	1.48	21.15	4.16
SAC-ETR	SANOCHEMIA Pharmazeutika AG	1.41	0	-0.35%	3,500	44.72%	18	-0.05	--	0
KPTI	Karyopharm Therapeutics, Inc.	16.75	0.37	2.26%	237,231	-55.25%	599	-3.21	--	0
SNTA	Synta Pharmaceuticals Corp.	0.41	0	-1.03%	1,421,265	-84.70%	56	-0.61	--	0
SRNE	Sorrento Therapeutics, Inc.	7.8	0.17	2.23%	297,686	-22.54%	295	-0.99	--	0
ONCS	OncoSec Medical Incorporated	3.01	-0.02	-0.66%	147,461	-67.98%	51	51	-1.72	--
JAGX	Jaguar Animal Health, Inc.	2.21	-0.19	-7.92%	7,614	--	18	18	-3.27	--
Private	Blaze Biosciences	Novel imaging agent used to define tumor margins during surgery, canine studies supported NIH grant								
Private	Susavion	Novel peptide immunotherapies, C-type and I-type lectins. Just initated canine trial for lead compound								
Private	Juvaris BioTherapeutics	Novel cancer vaccines based on cationic lipid/DNA complexes. Canine allogenic tumeor vaccine trial								
Private	MetaMorphix Inc.	Canine genetic testing								
Private	Protein Sciences	Novel vaccines. FluBlok (trivalent flu vaccine) is genetically produced vaccine using canine kidney cells								
Private	GeneQuine	Novel gene therapy directed against Il-1r for equine and human osteoarthritis								
Private	HealhGene	Novel veterinary oncology diagnostics								

Prices as of the close December 4, 2015

Introduction

It's no secret that recent years have seen an increase in the proportion of late stage clinical trials that fail to reach efficacy endpoints or succumb to unexpected adverse events. The high failure rate has resulted in a dearth of new treatments for a variety of major diseases and conditions in cancer, neurology, metabolism and other areas. It has also burdened the healthcare system, investors and patients with billions of dollars in unproductive capital and outright losses. In response to this challenge, the NCI Clinical Trials Working Group was launched in 2004. This group was charged with developing recommendations and an implementation plan to optimize the NCI clinical trials system.

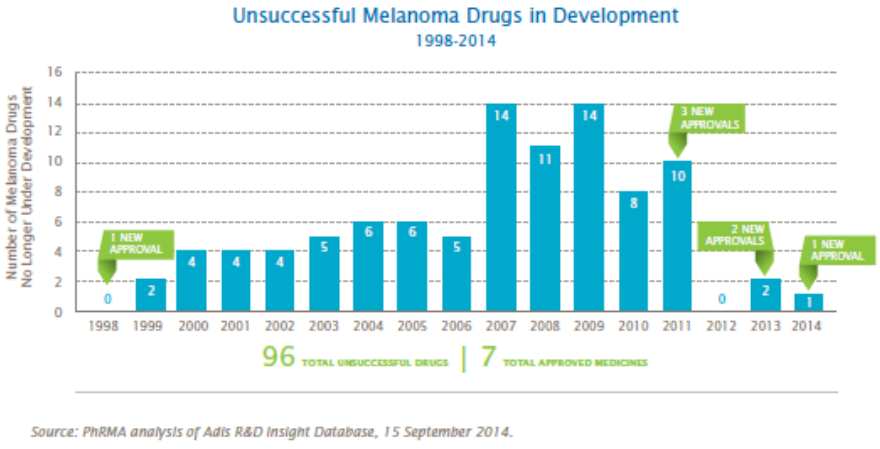


Data from 10 biggest drug companies from 1991-2000

As the chart, published by Kola & Landis in **Nature Reviews Drug Discovery** 2004 to the left indicates, the problem the NCI Clinical Trials Working Group was attempting to address was disproportionately related to the development of new cancer treatments. Since then, neurology has also proven to be a dramatic loser for drug developers, with over a 99% trial failure rate in Alzheimer's and other cognitive impairment indications.

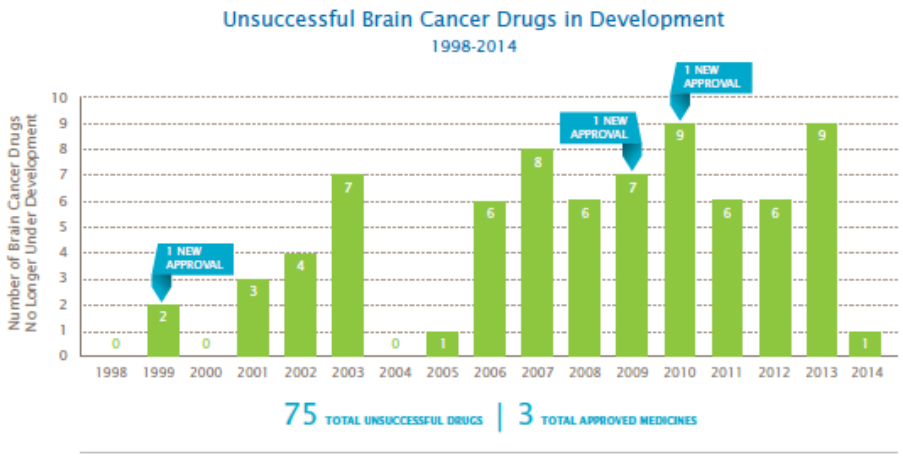
However, while improvements in the clinical process have been made since the formation of the Working Group, bringing new cancer drugs over the finish line has still proven as difficult as ever. In 2013, five of the top ten late stage trial failures were in cancer. These trials were in soft tissue sarcoma, metastatic melanoma, renal cell carcinoma and relapsing B-cell lymphoma. The list was topped by Sanofi's (SNY/$43.45/Not rated) failed metastatic lung cancer and resistant ovarian trials with iniparib, which caused a $525MM writedown for Sanofi. High profile failures continued in 2014 with Exelixis's (EXEL/$5.40/Not rated) failure with cabozantinib for prostate cancer, thus raising possible concerns for its partner, Roche's (RHBBY/$272.40/Not rated) probability of success in melanoma patients with the BRAFV600 mutation treated with a cobazantinib and Zelboraf cocktail. Pfizer (PFE/$32.80/Not rated) had three late stage cancer drug trial failures in 2014 with the same drug, dacomitinib, all announced on one day last January. Other Big Pharma were not unscathed. GlaxoSmithKline plc (GSK/$40.27/Not rated) failed in lung cancer with MAGE-A3 after its failure in a very long term trial for melanoma.

PhRMA's 2014 *Researching Cancer Medicines: Setbacks and Stepping Stones* publication brought out a few startling facts as to just how difficult it has been for cancer drug developers with an analysis of just three cancers that have proven elusive for treatment success: melanoma, brain cancer and lung cancer. PhRMA notes that since 1998, there have been 96 drug failures in melanoma and only 7 drug approvals. The statistics for brain and lung cancers aren't much better: 10 new approved lung cancer drugs against 167 drug failures from 1998 to 2014 and only three new drugs approved for brain cancer out of 75 trial failures. PhRMA defines trial failures as those trials that are discontinued, suspended or had no development reported. For melanoma, where only one drug was approved between 1998 and 2011, recent progress with immunotherapy directed treatments has finally begun to bring hope to late stage metastatic melanoma patients, but still in all, during this timeframe, there was a 14:1 failure to FDA approval success ratio.

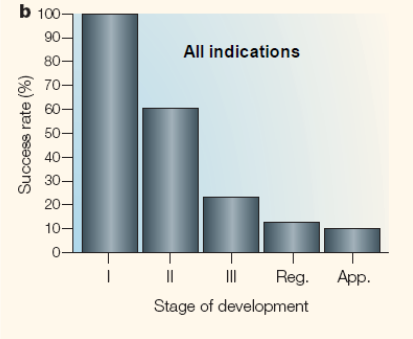


Source: PhRMA analysis of Adis R&D Insight Database, 15 September 2014.

The picture is similar for brain cancer where there have been only three approvals in over 15 years, a 25:1 failure to approval rate.



Source: PhRMA analysis of Adis R&D Insight Database, 15 September 2014.



Kola & Landis; Nature Reviews Drug Discovery 2004

A further and perhaps most important characteristic of these trial failures is the stage at which they fail. Again, as noted by Kola & Landis in their seminal paper, oncology drug failures occur at higher levels than the "All Indications" data. Over 70% of oncology trials *fail* to progress from Phase II to Phase III versus a 60% *success* ratio for trials as a whole, and 59% of those oncology drugs go on to fail in Phase III, where the cost of failure is at its highest.

In short, cancer treatment failures have significantly contributed to overall healthcare system costs—an issue that is becoming increasingly critical for the future as the World Health Organization is now predicting that the current incidence rate for cancer on a worldwide basis could rise by 60% to 22 million people in the next 20 years. Estimates from the National Institutes of Health and American Cancer Institute put the direct treatment costs associated with cancer at $86.6 billion annually in the US. The indirect costs which include costs associated with lost productivity due to premature death are pegged at an estimated $130 billion annually.

Known Challenges

The challenges in developing new cancer treatments are widely known. The sheer number of cancer variations has become daunting. It is now recognized that there are 120 discreet forms of cancer. The proliferation of cancer takes place in a highly complex biological system which doesn't lend itself to a single, direct approach. Cancer is highly adaptive, subject to genetic mutation and heterogeneity, and "personalized" through individual epigenetic events, immune system response and other internal "environmental" conditions as well as the external environment to which the individual has been or is exposed. Our better understanding and appreciation for cancer complexity and its plasticity is driving the need to create novel combination treatment strategies that include better and more specific diagnostics and the use of multiple approaches to treating cancer over time.

But Disconnected from Relevant Translational and Clinical Human Experience

While our understanding of the system biology and the "personalized" nature of cancer is continuing to expand, this knowledge is not being translated into the development of successful treatments. In almost every paper on the subject, the leading reasons why most oncology trials fail are that cancer is complex and heterogeneous, preclinical models are not adequately predictive, and the current translational/clinical pathway's linear and serial approach largely ignores opportunities to be informed at early points in the clinical process. Researchers

and clinicians both lay a root cause of failed clinical trials at the feet of the preclinical animal models which underpin virtually all dosage and treatment protocols for human trials. "The average rate of successful translation from animal models to clinical trials is less than 8%". (*Lost in Translation: Animal Models and Clinical Trials in Cancer Treatment*, Mak, et al, **American Journal Translational Research**, 2014).

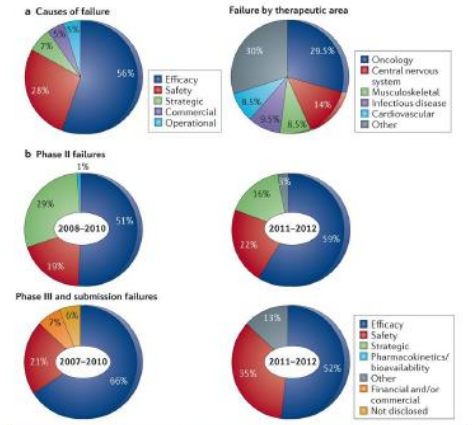


Figure 4: charts to show failure of drugs by cause and therapeutic area a) between Phase II and submission and b) individually for Phase II and Phase III (dates vary)[4]

Specifically, this lack of translation to human clinical experience is tied to the inability of these models to appropriately predict response in humans, as most preclinical work is performed in rodents specially bred to mimic particular human disease conditions. Furthermore, over time, ethical concerns have all but eliminated the use of primates, except in rare experimental cases, which provided a more biologically appropriate model.

This leap from mouse or rat to human is the conundrum facing drug developers, as the accompanying chart (*Trial Watch: Phase II and Phase III attrition rates 2011–2012* John Arrowsmith & Philip Miller, **Nat Rev Drug Discovery**, June 2013) illustrates. Developers are clearly not hitting the mark when the primary reasons for failure are unexpected adverse safety or tox profiles or lack of efficacy. While the data is this chart reflects research on trials conducted in 2000, more recent research published on this topic demonstrates that these very same factors continue as primary causes of trial failure. The primary reasons for approved drug attrition in 2000 were safety/tox issues and lack of efficacy, accounting for about 30% of failures each. By 2012, the percentage of failures due to lack of efficacy had risen to a 56% and while safety/tox remained just above 30%. The increase in the proportion of efficacy failures compared to safety/tox failures is likely reflective of a higher rate of Phase II "killed" programs because of unexpected adverse events, thus leaving efficacy as the primary contributor to Phase III trial failure.

Despite extensive specialty breeding programs to "humanize" it, the most commonly used preclinical animal, the mouse, still is a long distance from human biology as critical genetic, molecular, immunological and cellular differences exist between mice and man. As an example, of the 4,000+ genes common in mice and man, researchers have found that in looking just at transcription factor binding sites, between 41% and 89% of the analogous binding sites had significant differences between the species. In addition, the artificial breeding and environment of lab animals contribute to augmenting other types interspecies differences, and more importantly, the controlled environment adds potential non-natural responses. Here a just a couple of examples where the animal model was a predictive failure:

- TeGenero's immunomodulatory humanized anti-CD28 monoclonal antibody, TGN1412, caused catastrophic cytokine storm and organ failure in its Phase I human trials even though dosages used were approximately 500X lower than was found safe in animal models (**New England Journal of Medicine**, 2006; 355:1018-1028)

- Pathway molecules such as Hedgehog pathway antagonists failed despite seeming remarkable success in murine models for pancreatic and brain cancers. Infinity Pharmaceuticals (INFI/$8.09/Not rated) was developing IPI-926 (saridegib) for pancreatic cancer, myelofibrosis and chondrosarcoma when in January 2012, the company had to suspend it Phase II pancreatic cancer program because the death rate in the treatment group was exceeding the placebo arm.

Infinity had six drugs aimed at various cancer indications. Out of those six drugs, which underwent 18 trials, four programs have been completely suspended (Biomed Tracker). In a paper just published in the Journal of Clinical Oncology, vismodegib, another Hedgehog pathway antagonist, has also failed in a combination Phase II trial with gemcitabine "The addition of vismodegib to gemcitabine in an unselected cohort did not improve overall response rate, PFS, or OS in patients with metastatic PC. Our preclinical and clinical results revealed no statistically significant differences with respect to drug delivery or treatment efficacy using

vismodegib." (*Randomized Phase Ib/II Study of Gemcitabine Plus Placebo or Vismodegib, a Hedgehog Pathway Inhibitor, in Patients with Metastatic Pancreatic Cancer*, Catenacci et al, **American Society of Clinical Oncology**, 2015)

- Another example is matrix metalloproteases (MMPs), a family of zinc-dependent proteinases implicated in tumorigenesis. Animal models indicated a strong potential to use various MMP mediators to treat cancer and arthritis related diseases. Over 158 trials have been initiated (www.clinicaltrials.gov) employing an MMP inhibitor, but to date, only one MMP, doxycycline, has been FDA-approved.

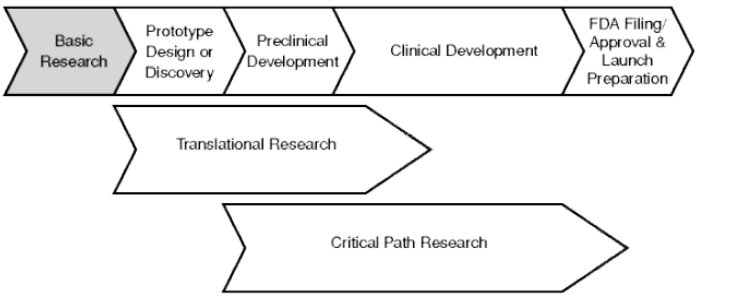
- Most recently, therapeutic cancer vaccines have also had failures in human clinical trials. In a recent review article in the American Journal of Translational Research (2014), it was reported that out of 23 Phase II/III clinical trials testing 17 distinct therapeutic anticancer vaccines, 18 of these studies had failed. A few high profile examples are Merck's (MRK/$53.64/Not rated) Stimuvax which failed a multi-thousand patient, 10 year phase III trial on non-small cell lung cancer, GlaxoSmithKline's (GSK/$40.27/Not rated) MAGE-A3 failed in both high profile, long-term phase III melanoma and non-small cell lung cancer trials, Vical's (VICL/$0.45/Not rated) Allovectin also failed a phase III metastatic melanoma trial, and GemVax & KAEL's (082270.KQ/24,850/Not rated) TeloVac failed a phase III pancreatic cancer trial. It has been suggested that most of the cancer vaccine trials have failed due to elevated levels of circulating immunosuppressive cytokines and varying behavior of immunological checkpoints encountered humans that was not found in preclinical studies with rodents.

In short, the limitations of traditional animal models are a central cause of clinical trial failure. Mak's *Lost in Translation* review of animal trials emphasizes this point in the research paper's summary: current animal studies seem to overestimate the likelihood that a treatment will be effective as a result of failed animal trials not being published; of highly cited animal research, little more than a third is followed by human trials and finally, of that one-third that enter into clinical trials, as few as 8% of compounds make it through Phase I trials.

Innovation or Stagnation: the FDA and National Cancer Institute Take on the Challenges

In 2004, the FDA undertook a mandate to address these challenges with the release of its landmark report, *Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*. The publication articulates core drivers of the widening gap between scientific discoveries that are unlocking biological clues to society's most intractable diseases such as cancer, Alzheimer's disease/cognitive impairment, or diabetes, and translation of this knowledge into innovative medical treatments. In this seminal publication, the FDA noted significant challenges facing the drug development industry and defined three areas of research support for medical product development: Basic research, translational research and a new term, Critical Path research. Clinical Path Research was defined as that research directed towards improving the product development process itself by establishing new evaluation tools. It provides the bridge from preclinical/translational research to final clinical development. A key component of Critical Path Research was aimed at strengthening the clinical research infrastructure.

Figure 5: Research Support for Product Development



Source: FDA: Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products

One result of enhancing critical research infrastructure has been the introduction of FDA and the European Medicines Agency (EMEA) guidelines for testing very small 'micro-doses' of drugs in humans under a "Phase

0" program. Drug protocols are limited to concentrations less than a one-hundredth of the therapeutic dose. Because the concentrations are so low, the drugs can be tested in a small number of human patients without the level of safety data normally required before a phase I study. These early 'Phase 0' studies collect human data quickly by showing how the drug is distributed and metabolized in the body, and whether it hits the right molecular target.

Establishment of the National Cancer Institute's Comparative Oncology Program (COP)

A second result from the FDA's Critical Path mandate was the development of a totally novel clinical trial infrastructure initiated by the NCI's Center for Cancer Research (CCR). The CCR recognized that the biological complexity and heterogeneity of cancer was not being adequately represented by the rodent tumor models commonly used in preclinical efficacy screening, nor was the complex systems biology between drug exposure and necessary biological changes in the tumor tissue or extracellular space easily modeled in murine cancers. "As a result, many key questions concerning pharmacodynamics, pharmacokinetics and toxicity were left unanswered before drug candidates were moved into early phase human studies. Spontaneous cancers in companion (pet) dogs in particular, offered a unique, and largely unexploited translational research opportunity for better informing early stage human trials." (**PLoS ONE** | www.plosone.org 1 March 2009 | Volume 4 | Issue 3 | e4972.)

The Comparative Oncology Program was formed in 2004 with the partnership of CCRs Pediatric oncology branch and veterinary oncologists at Colorado State University to assist with the integration of results from studies in companion dogs into the overall development and design of human trials. COP further coordinated the development of a variety of research tools to enable the integration of canine data into human trials. In 2008, the CCR established the Comparative Oncology Program (CCR-COP) and developed a clinical trial infrastructure capable of multi-center nationwide trials in tumor-bearing dogs using cancer drugs that are under development for human patients. This infrastructure, the Comparative Oncology Trials Consortium (COTC), integrates clinical trials in pet dogs with naturally occurring cancers into the development of new drugs, devices and imaging techniques for human cancers. The premise behind the Consortium is that by bringing in data from a large animal with similar naturally occurring cancer biology to humans, trial failures could be reduced, thus improving cancer treatment efficacy for both humans and animals.

The COTC designs and implements clinical trials in dogs with cancer with the goal of providing necessary translational data for novel therapies, techniques or devices for future cancer patients. Trials are executed at COTC member institutions, which currently include twenty veterinary teaching hospitals across the United States. Trials conducted by the COTC include several biological and clinical endpoints that define safety, biological and clinical activity of novel treatment agents that can be directly integrated into the design of human Phase I and II clinical trials. In addition, the COTC incorporates other key technologies into the clinical process including imaging and visualization and therapeutic devices. Under COP and the COTC, trials are specifically designed to address questions and challenges involved with conventional preclinical models and early stage human trials but are not readily answered with small animal preclinical models.

Our Companions Are More Like Us than We Think

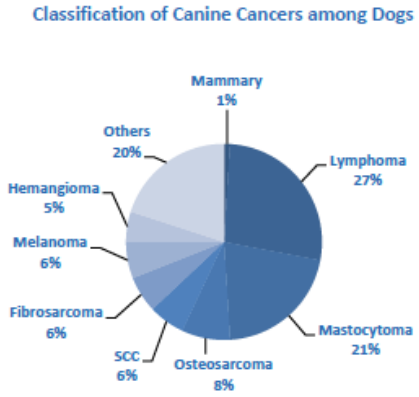
Companion animals, and dogs in particular, naturally develop many of the same cancers for which there are few or no successful treatments for humans. Canine cancers share most of the same cancer characteristics such as histological appearance, tumor genetics, biology, molecular targets, therapeutic response and recurrence and metastases as human cancers, and as such, clinical study in pets is being looked at as a more appropriate translational bridge to human oncology therapeutics for analysis of safety, tolerability and early signs of efficacy as compared to rodent models. Although not defined as such until the CCR-COP, comparative oncology has had a long history of bridging translational and human clinical research. Comparative oncology has contributed to advancing surgical techniques, such as limb sparing for pediatric sarcoma patients,

pioneering the use of hyperthermia and radiobiology in cancer treatment, and evaluating novel anti-cancer agents and delivery mechanisms, such as inhalation drug delivery and combination chemotherapy strategies. Large animal spontaneous cancer models can be a valuable addition to successful studies of cancer biology and novel therapeutic drug, imaging and device development.

The usefulness of dogs extends beyond the physiological characteristics of their naturally occurring tumors. Canine physiology, metabolism and drug distribution are all similar to those of humans. Environmental exposure also drives epigenetic changes in humans which contribute to majority of human cancers. Our pets live in the same environment as us and therefore can be reflective of these same environmental factors. Human familial susceptibility is mirrored by breed susceptibilities and like humans, dogs develop cancer with intact immune systems. This is in contrast to most rodent animal models where animals have been bred to be intentionally immunocompromised because of the need to accept the human tumor tissue or be a mimic of the disease under study. Further, canine genetic diversity is also a more realistic model of human patients. As such, the opportunity to assess drug exposures, toxicity and efficacy (therapeutic index) in a single large animal model whose lifespan is 1/7th that of humans, is highly informative for human trials.

The position of the dog within mammalian evolutionary tree also makes it an important channel for comparative analysis of the human genome in other diseases driven by genetic variation or dysfunction. High prevalence of specific diseases that affect certain breeds gives more direct indications of mutational defects underlying those diseases than may be apparent in humans. This makes genetic analysis of disease potentially more traceable in dogs than humans. Next to humans, the dog is the most intensely studied animal in medical practice, with detailed family history and pathology data. Using genetic resources developed over the past 15years, together with a third revision of its genome that was completed in 2011, researchers have already identified mutations in canine genes underlying ~25 Mendelian diseases in humans.

These genomic similarities may be enhanced in dogs, due to extensive canine selective breeding. Breed genetics have been highly preserved and have laid the basis for some breeds' increased susceptibility to certain cancers. In fact, there are very few human cancers that don't occur naturally in companion dogs as compared to other companion animals. Cancer susceptibility and the high degree of biological similarity between dog and human genomes have facilitated the comparison of canine genomes to the study the evolutionary genetic changes associated with human cancer. When molecular cytogenetic analysis of canine tumor cells was carried out from hematological malignancies, for instance, it was revealed that the ancestral chromosomal aberrations were preserved in comparable cancers of both human and dog. In some cases, specific genetic mutations such as in p53, are identical for both canine and human cancers. In other cases, the canine version of the human genetic alteration results in a different cancer.



Source: Oasmia Pharmaceuticals AB

COP in Practice

Like humans, our pets are living longer, and also like humans, the incidence of cancer in pets is rising. This fact alone makes the case that as we are becoming more likely to develop cancer, or be close to someone else with cancer, it is increasingly likely that our own pets or the pets of others close to us, will be in similar position. There is substantial synergy and mutual benefit, therefore, in the development of novel cancer treatments for both us and our canine companions.

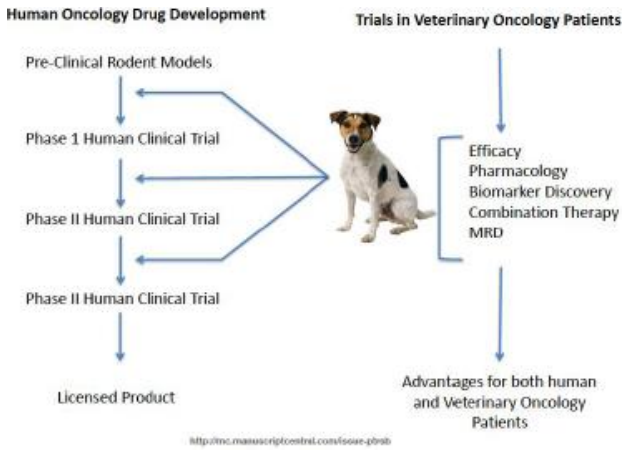
A couple of basic statistics:

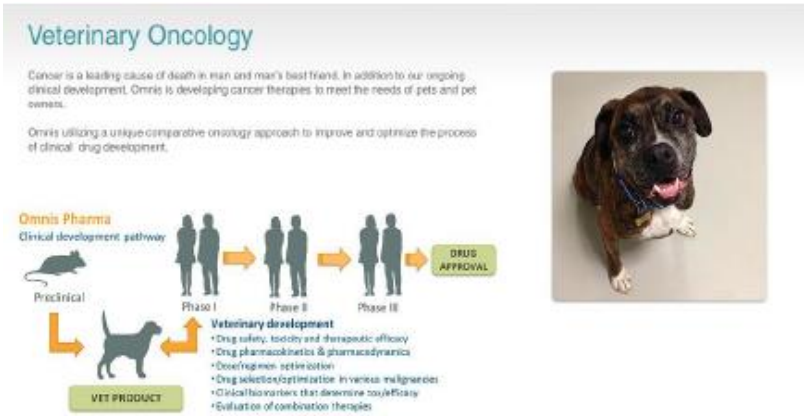
- 80 million pet dogs and 90 million pet cats in the US.
- Over 50% of dogs who live beyond 10 years develop cancer, and in some breeds, this incidence rate is far higher and younger dogs are also susceptible.
- 33% of dogs under 10 years old are diagnosed with cancer.
- Cancer kills 33% of pet cats.

(Source: Kastan, Duke University, NCI Institute of Medicine Comparative Oncology Workshop, June 2015)

In particular, comparative oncology studies are currently being conducted in sarcomas, lymphomas and other hematological malignancies, glioblastomas and to a lesser degree, in breast, prostate and lung carcinomas. These studies are employing novel drug delivery systems, novel immunotherapies and drug combinations that are not seen in human trials. They are being supported by new imaging and visualization technologies, novel devices and by molecular diagnostics that are also crossing the human/animal boundary. Important to the value of these trials in supporting FDA requirements, data is being accumulated under organizations such as the Canine Comparative Oncology and Genomics Consortium, the Pfizer-Canine Oncology and Genomics Consortium Biospecimen Repository and the Comparative Oncology Program Tissue Array Resource.

The Comparative Oncology Trial Consortium Model





Source: LeBlanc, et al, NCI Comparative Oncology Workshop, June 2015

The following case study illustrates how the comparative oncology consortium is put to work. The first trial completed under COTC guidance was a study designed to inform the next step decisions in the clinical development of an adeno-associated virus (AAV) phage delivery of tumor necrosis factor alpha (RGD-TNFα) to a V integrins target in tumor and tumor-associated vascular endothelium. The trial sought to reconcile the disparities seen between studies in tumor-bearing mice and that of human cancer patients of this family of anti-angiogenic and vascular-targeted agents.

COTC001: Evaluation of RGD Targeted Delivery of Phage Expressing TNF-alpha to Tumor Bearing Dogs

Sponsor: The National Cancer Institute

Purpose:This clinical trial sponsored by the National Cancer Institute (NCI) evaluates the safety and effectiveness of the phage-based delivery of an agent known as Tumor Necrosis Factor (TNF alpha). TNF alpha is known to kill cancer cells and the blood vessels that feed them. It is currently used in human cancer patients as an isolated infusion and efforts to find new ways to deliver it safely have been underway for some time. The NCI has developed a special way to deliver TNF-alpha specifically to blood vessels around tumors using a molecular approach based on a viral-like carrier (phage). Results of this trial in dogs will be used to inform the design and implementation of planned clinical trials in human cancer patients.

Participating Sites: Colorado State University; University of Missouri; University of Pennsylvania; University of Tennessee; University of Wisconsin

Study Numbers: 15-20 dogs will be enrolled in each study

Eligibility Requirements:

- Hisotogically confirmed, Measurable disease (<2cm), can be primary and/or metastatic disease
- Favorable performance status
- Naïve or recurrent disease
- Dogs must be more than 15kg
- Dogs cannot receive concurrent chemotherapy, radiation or angiogenesis for 4 weeks prior to study enrollment

Source: Center for Cancer Research (NCI) website

The comparative oncology approach allowed for the evaluation of both the anti-angiogenic agents and the novel gene delivery methods, which would not have been possible in an early stage human trial. Canine patients were treated for bone sarcomas and soft tissue sarcomas. The results of this trial provided a strong pre-clinical basis for the first-in-man cancer studies. The trial went on to demonstrate the successful targeted delivery of TNFα with the AAVP gene delivery system to tumor blood vessels of dogs with spontaneous cancer.

Although activity of RGD-TNFα had demonstrated efficacy in traditional small animal models, the comparative oncology approach provided unique information regarding the safety of RGD-TNFα that was not apparent from conventional animal safety studies. Since neither tumor nor tumor vasculature are present in healthy animals (i.e. purpose-bred rodent or research dogs), a safety assessment in these animals would likely under-report adverse events related to RGD-TNFα.

Study dogs euthanized due to disease progression, however, showed that RGD-TNFα targeted as desired to tumor vasculature but not blood vessels within normal visceral organs. Importantly, RGD-TNFα was not found in any of the control tissues analyzed or in the liver. This was a key finding as the presence of RGD-TNFα had been previously seen in the liver and spleen of rodents treated with RGD- TNFα. This seminal study provided for the immediate evaluation of agents in a naturally occurring setting that resulted in key information used to optimize the drug's protocol before entering human trials. The drug went on to becoming the first USDA

approved canine cancer vaccine, and in fact was the very first cancer vaccine approved in the US for any species. The vaccine, licensed to Merial, was developed by Vical from its DNA plasmid vaccine encoding human tyrosinase.

A second early case of a successful collaborative effort utilizing a comparative oncology approach was the collaboration between Pfizer and Sugen for the development and commercialization of the oral cancer drug toceranib phosphate (Palladia), which was developed by Pfizer for dogs, alongside the human version, Sugen's sunitinib (Sutent). Both drugs inhibit proteins called receptor tyrosine kinases. The comparative oncology research was let by Ohio State University to test the efficacy of receptor tyrosine kinases in companion dogs. Toceranib phosphate, which came to market in 2009, is the first and so far only cancer drug approved by the FDA specifically for dogs. Prior to its approval, veterinarians had no choice but to use the same chemotherapy and radiation therapeutics developed for people to treat canine cancers.

The COTC Approach is Working

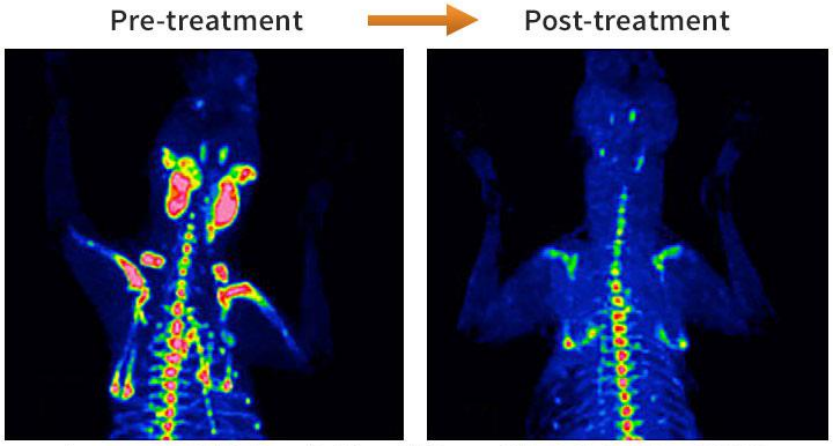
While Big Pharma companies such as Pfizer, Novartis and Bayer AG have been able to exploit their own captive animal health capabilities and organizations, a number or smaller biotechs are also leveraging the advantages comparative oncology studies bring to their translational and clinical development paths through partnering and internal comparative biology research. These COP innovators include human biotherapeutics companies such as Gilead Sciences, Inc. (GILD/$104.07/Not rated), Karyopharm Therapeutics (KPTI/$16.75/Not rated), Synta Pharmaceuticals (SNTA/$0.41/Not rated), Juvaris BioTherapeutics , Blaze Biosciences, Advaxis (ADXS/$11.81/Not rated), Sorrento Pharmaceuticals (SRNE/$7.80/Not rated), Oasmia Pharmaceutical AB (OASM/$4.01/Not rated), Protein Sciences, and Genelux Corporation, among others. On the animal health side, other innovative partnerships have also been initiated such as Elanco's development partnership with Anacor Pharmaceuticals (ANAC/$110.65/Not rated).

Comparative Oncology Case Studies

1. **Vanquish Oncology Inc.** University-driven comparative oncology research is leading to novel veterinary oncology treatments and technologies that are emerging as new stand-alone companies. In 2007, Dr. Timothy Fan at the University of Illinois, Urbana-Champaign began studying procaspase-activating compound-1 (PAC-1), a small molecule designed to convert procapase 3 into its active form, capase 3, to initiate apoptosis in cancerous cells in late stage human malignancies. As a single compound, it only demonstrated modest efficacy in early stage canine trials. However, in a Labrador patient whose MRI showed the dog suffered from meningioma, Fan treated the dog with a combination of oral PAC-1 and temozolomide. The canine trial, which demonstrated an effective novel combination therapy, also provided underlying drug dosing, toxicity profile and preliminary efficacy evidence for a novel drug combination trial in humans. The technology was spun out to Vanquish Oncology and the company is now recruiting patients for a Phase I human clinical trial using PAC-1 in the treatment of a range of advanced malignancies. (Procaspase Activating Compound-1 (PAC-1) in the Treatment of Advanced Malignancies www.Clinicaltrials.gov)

2. **Gilead Sciences and VetDC:** VetDC is pursuing a strategy of converting early stage human anti-cancer therapeutics into veterinary oncology products. VetDC was originally formed as a spin-out of the University of Colorado to commercialize the prodrug of Gilead's GS 9219, for canine oncology. University of Colorado conducted canine trials with the prodrug, rabacfosadine, a novel acyclic nucleotide analogue anti-proliferative agent aimed a refractory or relapsed lymphoma on Gilead's behalf. VetDC licensed rabacfosadine, now Tanovea™, from Gilead for use in animal cancer when GS 9219 failed in a Phase I/II human trial for

refractory CLL, NHL and multiple myeloma. The adjacent images are from VetDC's website (http://vet-dc.com/products/tanovea-for-lymphoma/) and demonstrate Tanovea's significant efficacy in canine lymphoma.



Lawrence, et. al.: **Veterinary Radiology & Ultrasound** Vol. 50, No. 6, 2009, pp 660-668

VetDC received MUMS status (Minor Use and Minor Species Animal Health Act of 2004 designation) for Tanovea in 2013. MUMS designation is an "Orphan Drug"-like status for veterinary products that allow products to be introduced to selected species dogs, cats, horses, cattle, pigs, turkeys and chickens for diseases that occur infrequently or in limited geographic areas and receive seven years marketing exclusivity). Vet-DC is currently awaiting FDA conditional approval for Tanovea.

In August 2013, VetDC acquired a second product from Pathway Therapeutics, Inc. This product is an orally available, dual-acting inhibitor of PI3K and mTOR proteins, now labeled as VDC-597. Oral administration of VDC-597 has been evaluated in animal studies as well as in a Phase I human clinical trial. VDC-597 demonstrated significant blood concentrations and bioactivity in both dogs and people at well-tolerated doses. These results suggest VDC-597 might become important new therapeutic option for animals suffering from certain cancers, including osteosarcoma, hemangiosarcoma, lymphoma and solid tumors. VetDC intends to expand the indications for VDC-597 to include many of these animal cancers.

3. **Oasmia Pharmaceuticals:** Oasmia Pharmaceutical AB brings the development of novel drugs for both human and veterinary oncology under one roof . The company specializes in manufacturing novel formulations of well-established cytostatics, such as paclitaxel, in combination with its proprietary water solubulizer micelle, XR-17, in order to improve efficacy, improve the side-effect profile and an expand therapeutic areas of use. Oasmia's lead canine product, Paccal Vet-CA1, is the first canine paclitaxel injectable. It has received conditional FDA approval for mammary carcinoma and squamous cell carcinoma. The company is expanding its animal product portfolio to include a new formulation of doxorubicin and utilizing the same technology for mirror products in human cancers.

Source: Oasmia Pharmaceuticals AB webpage 12012015 http://www.oasmia.com/pages.asp?c_id=6

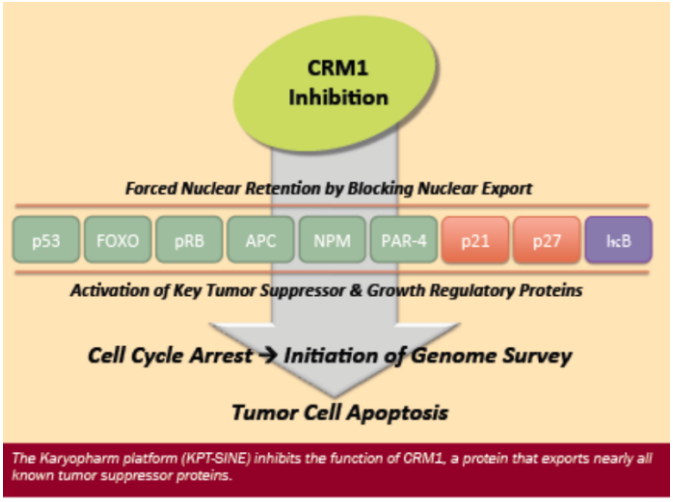
4. **Aratana and Advaxis:** Aratana is developing a variety of canine therapeutics in both cancer and non-cancer indications. Aratana has adopted human monoclonal antibody therapy strategies to develop and commercialize

two MAb's to treat canine B and T-cell lymphomas. Approximately 7% of all canine cancers diagnosed in the US annually are lymphomas. A number of breeds, including Golden and Labrador Retrievers, German Shepherd, Poodles, and Boxers are particularly susceptible to developing lymphoma.

Aratana and Advaxis established a partnership to extend the indications for Advaxis's human immunotherapy technology into veterinary applications. In 2014, Aratana exclusively licensed Advaxis's novel HER2/neu immunotherapy (AT-014, ADXS-cHER2) for canine osteosarcoma as well as three other immunotherapeutic candidates. About 8,000-10,000 dogs are diagnosed with osteosarcoma each year. The standard of care is amputation and radiation. The preliminary results of a Phase I AT-014 canine osteosarcoma trial conducted by the University of Pennsylvania were reported at the American College of Veterinary Internal Medicine (ACVIM) Forum in June 2015 and suggested that AT-014 was able to delay or prevent metastatic disease and prolong overall survival in dogs with osteosarcoma that had minimal residual disease following amputation and chemotherapy.

As noted in the Advaxis press related to the data, the canine experience with ADXS-HER2 will likely have important translational relevance for human patients with OSA as well as other HER2+ cancers, such as breast, gastric and esophageal. Advaxis initiated a Phase 1b dose-escalation study of ADXS-HER2 in humans with HER2+ solid tumors in September 2015. Once dosing is established in the human trial, Advaxis plans to work with Children's Oncology Group (COG) to launch a pivotal trial in human pediatric OSA in early 2016. ADXS-HER2 recently received Orphan Drug status by the EMEA and already has Orphan Drug status from the FDA.

5. **Karyopharm Therapeutics:** Karyopharm is conducting clinical trials in both dogs and humans by studying two separate molecules that act on the same target, Selinexor (KPT-330) and Verdinexor (KPT-335). Karyopharm is developing their technology around a family of compounds, referred to as CRM1, that mediate nuclear transport. CRM1 is instrumental in preventing the body's natural ability to fight tumors with intracellular mechanisms. Karyopharm CEO Michael Kauffman has been quoted as saying Karyopharm's canine trials were particularly valuable for understanding the side effects that can result from blocking CRM1. This understanding was developed from a canine lymphoma study which was used to support the identification of the adverse event profile and to optimize the dosing regimen for the sister human CRM1 drug, Selinexor. Kauffman notes that from a tolerability standpoint, knowing what KPT-335 does in dogs is immeasurably beneficial for humans because dogs are part of families, and family members can play an important role in observing and reporting how their pets are responding to treatments. Furthermore, having this sort of situational awareness concerning a pet's response to treatment is not possible with laboratory animals since they caged and in an very artificial situation. The canine clinical data of the toxicity profile of Verdinexor was used to set the drug regimen and toxicity supportive care protocols for Selinexor.



Source: Synergy: Animal Cancer Care and Research Program, University of MN, 2011

Evaluation of an anti-cancer drug (Verdinexor) in dogs with cancer (Lymphoma)

In cancer cells, the function of XP01 (a specific protein in the membrane) is critical to maintaining the uncontrolled growth and survival of these cells.

The novel compound Verdinexor is an inhibitor of XP01 that is given orally twice per week. Verdinexor has been studied in 2 separate clinical trials in dogs with lymphoma with over 75 dogs treated to date. Approximately 30-40% of dogs with both newly diagnosed and relapsed lymphoma appear to benefit from Verdinexor treatment.

The purpose of this study is to evaluate the biologic activity of Verdinexor when it is administered in combination with therapeutic doses of prednisone in dogs with lymphoma.

If you think your dog can participate in this clinical trial read more **here**!
Source: Ohio State University College of Veterinary Medicine, Clinical Trials Update, May 2015

Karyopharm is currently conducting over seven human clinical trials with Selinexor and Verdinexor. Karyopharm has submitted an NADA for oral Verdinexor in canine lymphoma and has already received MUMS (Minor Use and Minor Species Animal Health Act of 2004) designation.

6. **Genelux Corporation**: Genelux has developed a platform technology in cancer vaccines based on oncolytic viruses. Genelux made two different versions of its drug product and is currently conducting first -in-man human clinical trials in several solid tumors with GL-ONC1, the human version, and using the other, V-VET1 in dogs as part of a wide-ranging research strategy designed to yield cutting-edge cancer treatments for both man and pets. Its V-VET1 product is a genetically characterized replication-competent oncolytic vaccinia viral therapy. Genelux modified the vaccinia virus to boost its therapeutic ability with targeting and diagnostic capabilities.

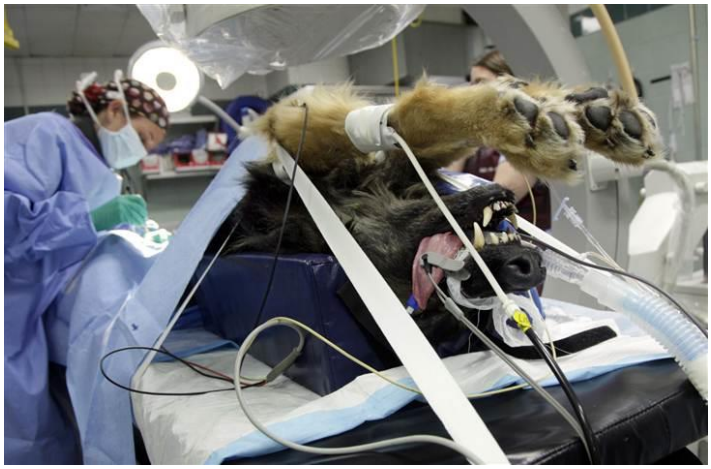
V-VET1 and GL-ONC1 are both administered systemically and are constructed to be able to locate, selectively enter and lyse cancer cells through the disruption of cancer cell replication, while leaving healthy tissues intact. The drugs also have light-emitting properties that allow oncologists to track their activity in the body using imaging technologies. The oncolytic process stimulates both innate and adaptive immune responses that target tumor-specific tissue destruction. Genelux launched a ground-breaking canine clinical trial with the CVS Angel Care Cancer Center in Carlsbad, California, in 2012. In an article published in **Xconomy** that year, Aladar Szalay, then CEO, explained the rationale of employing comparative oncology, *"Cancer as a disease in dogs is as significant as it is in humans," says Aladar Szalay, founder and former CEO of Genelux. "We expect that humans will benefit from the information we obtain from canines."*

Genelux's products are in the same class of drugs as Amgen's (AMGN/$161.43/Not rated) T-VEC, the first-in-class oncolytic viral therapy talimogene laherparepvec. Amgen received regulatory approvals by both the FDA and the EMEA for T-VEC in October 2015 for the dual-acting cancer vaccine/viral therapy for inoperable melanoma recurrent after initial surgery, thus opening the commercial door for other oncolytic viral therapies.

Why Now is the Time for Companion Animals and Veterinary Biotechnology

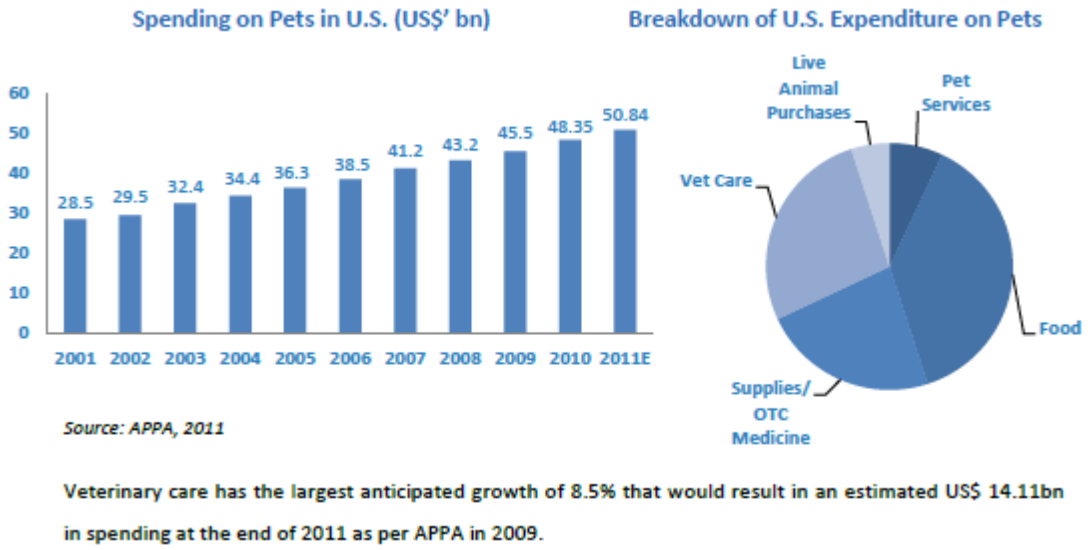
We believe there are several factors at play driving the emergence of a new era in veterinary medicine and igniting a vibrant veterinary biotech arena. First is the transformation from what was historically a distinct boundary between the human health and veterinary sectors into now, an evolving merger of human and veterinary biotechnology. This merging of vet and human therapeutics has been spurred by advances in veterinary science in a number of areas such as gene therapy, regenerative medicine and imaging, that are further developed or are already commercialized ahead of the human counterparts. For instance, stem cell therapy has become an almost routine treatment in horses for tendon repair and joint problems, but there is not yet a human standard of care stem cell product.

As the COP highlights, the costs and timeline associated with commercializing human biotech therapeutics are forcing more "out of house" collaborations and as such, promoting the interaction between human and veterinary researchers and physicians. An example of this new paradigm was the first joint symposium held by the Animal Medical Center of New York this fall where human surgeons were individually paired with their veterinary counterparts to discuss techniques and technologies on a 1x1 level. Similarly, cutting edge human therapy is moving into the veterinary suite as seen in this picture from the Animal Medical Center showing a canine patient receiving a radiation treatment.



Source: Pet Health on NBC News, July 20, 2010

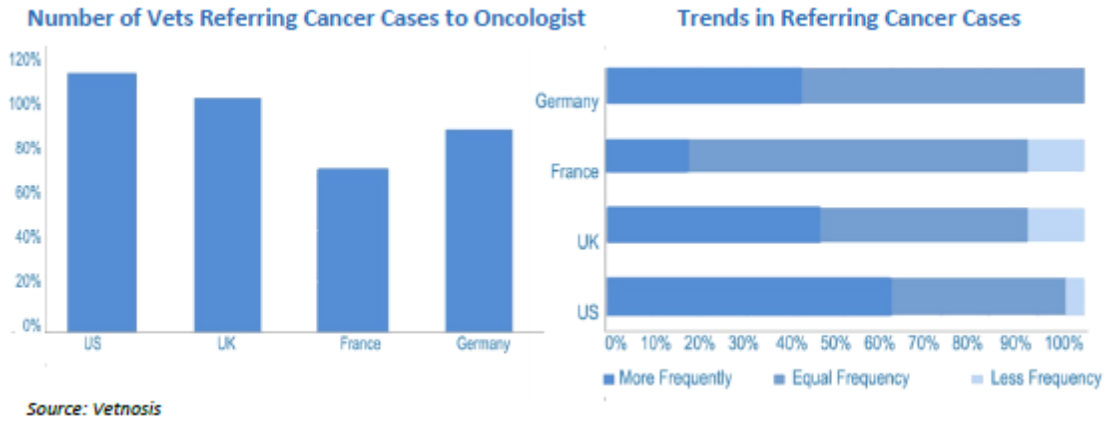
As the charts below indicate, demographics favor our view that veterinary care will be an increasing portion of the US household spending on pet care. For many, pets are the "children" in the household, and owners are willing to spend on advanced care when they learn there are treatment options.



Source: Oasmin Pharmaceuticals ECOFIN Global Coverage Initial Report, June 2011

Another important trend is the growing availability for pet health insurance. According to Trupanion, the US actually lags substantially behind Europe in the market penetration of pet health insurance with only about 5% of companion animals covered by a health plan in the US. This compares to a 25% penetration rate for pet health insurance in the U.K. We see increased market penetration of pet insurance in the US as becoming a major incentive for pet owners to opt for advanced therapeutics and treatments in an effort to extend or improve the life of their companion animal.

Finally, veterinary practice has increasingly become specialized, as the charts below indicate. It is becoming commonplace for the household vet to refer to a specialist, especially in the areas of cancer and orthopedics.



Source: Oasmin Pharmaceuticals ECOFIN Global Coverage Initial Report, June 2011

We believe the establishment of a Comparative Biology & Veterinary Biotechnology sector is a first among our peers. This distinct sector is remarkable in that many of the therapies being explored through comparative trials and in veterinary medicine are truly transformative and may offer unique solutions in the treatment of cancer, neurological diseases, degenerative diseases such as osteoarthritis, rare diseases and in regenerative medicine. Further, through the use of bridging technologies such as imaging/visualization technologies and molecular diagnostics as enabling technologies as well as the adoption of innovative devices in some of these new treatment paradigms, we think the breadth of technology represented in this sector may provide investors potentially unique and undiscovered opportunities.

For those interested in further information related to veterinary oncology clinical trials:
http://www.vetcancertrials.org/studies

Risk Factors

In addition to normal economic and market risk factors that impact most equities, and the common risks shared by the companies named in this sector and those in the biotechnology sector as a whole, we believe an investment in any of the Dawson James Comparative Biology Sector companies involves the following risks:

- **Regulatory risks** – the companies in the DJ Comparative Biology Sector are subject to regulatory review for their ongoing research and development activities and manufacturing operations with local, state and federal governmental agencies both in the US and Internationally.

- **Need to defend patents, trade secrets and other intellectual property** – Biotechnology companies rely heavily on intellectual property related to their technology and products. While larger companies may have adequate resources to defend their intellectual property, most of the smaller companies in the DJ Comparative Biology Sector would be materially and negatively impacted by intellectual property infringement or the loss of one or more patents.

- **Historical lack of profitability** – To date this year and in past years, most of the companies in the DJ Comparative Biology Sector have not operated on a profitable basis, and are not forecast to do so in the immediate future. Although companies typically have been able to raise funds from the capital markets, there can be no guarantee that any particular company will not be able raise additional operating capital in the future should losses continue.

- **Competitive Markets** – This universe of companies operate in a highly competitive marketplace, where speed to market, clinical results and other factors bear on a company's viability. There can be no assurance that any one company will be able to continue to market or later launch its products successfully in these competitive markets in the future.

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	Company Coverage		Investment Banking	
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Market Outperform (Buy)	16	67%	10	63%
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Market Underperform (Sell)	0	0%	0	0%
Total	24	100%	16	67%

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