[0004] In addition to diabetes, other spontaneously occurring diseases have been observed, such as cancer and autoimmune disease. Paoloni et al. describe the integration of the study of dogs with naturally occurring cancer with the study of human cancer biology to identify cancer-associated genes, study environmental risk factors, understand tumor biology and progression and evaluate and develop novel cancer therapeutics. (*Nature*, 8: 147-156 (2008)). The Canine Comparative Oncology and Genomics Consortium (CCOGC) is the result of many collaborative efforts to use the dog as a model of naturally occurring cancer for investigating cancer research in efforts to better both humans and dogs. *Nature Biotechnology* 24(9): 1065-1066 (2006). Examples of cancers that dogs naturally develop include: non-Hodgkin lymphoma, osteosarcoma, melanoma, prostate carcinoma, lung carcinoma, head and neck carcinoma, mammary carcinoma, and soft-tissue carcinoma. *Ibid.* Trials in pet dogs have been reported to help better define the safety and activity of new anticancer agents, assist in the identification of relevant biomarkers associated with the response or exposure to these anticancer drugs, and may allow rational development of combination strategies to improve the success of these new drugs in human clinical trials. *Ibid.* Candolfi et al describe the use of adenoviral-mediated gene transfer into dogs that spontaneously develop glioblastoma mutliforme (GBM) (Candolfi M et al, *Neurosurgery* 60: 167-178 (2007)). Paolini et al. reported that the Comparative Oncology Trials Consortium (COTC) evaluated a targeted AAV-phage vector delivering tumor necrosis factor (RGD-A-TNF) to αV integrins on tumor endothelium. *PLoS ONE* 4(3): e4972 (2009).

[0005] The invention described herein provides platform technologies for studying spontaneously occurring diseases that can be translated into therapeutic treatments and diagnostic methods.

[0006] All references cited herein, including patents, patent applications and publications, are hereby incorporated by reference in their entirety.

BRIEF SUMMARY ~~OF THE INVENTION~~

[0007] The ~~invention~~disclosure provides for platform technologies for investigating biological pathways, the effects (e.g., synergistic effects) of various combination of agents that affect biological and/or physiological pathways, underlying mechanisms of action, biological participants in complex physiological conditions and other parameters that can be useful for development of agents for treatment, diagnosis, or prophylaxis of various physiological

conditions and/or diseases. Such complex physiological conditions can include, but are not limited to, cancer, autoimmune disease, allergies, hypersensitivity, neurological diseases, hereditary genetic disorders, and infectious diseases.

[0008] Accordingly, in one aspect, there is provided a method for identifying a combination of anti-cancer agents with synergistic effects comprising: (1) administering two or more anti-cancer agents to a companion animal with a spontaneously occurring cancer; (2) monitoring the companion animal for a biological and/or physiological effect; and (3), identifying a combination of anti-cancer agents with synergistic effects when the biological and/or physiological effects are synergistic, wherein the anti-cancer agents comprise bisphosphonates and cationic CpG.~~the invention~~

[0008a] The disclosure provides for methods for identifying a combination of anti-cancer agents with synergistic effects comprising: (1) administering two or more anti-cancer agents to a companion animal with a spontaneously occurring cancer; (2) monitoring the companion animal for a biological and/or physiological effect; and (3), identifying a combination of anti-cancer agents with synergistic effects when the biological and/or physiological effects are synergistic. In one embodiment, the anti-cancer agent is selected from the group consisting of: bisphosphonates, platinum-based chemotherapeutics, inhibitors of the protein phospholipase D, alkylating agents, antimetabolites, anthracyclines, plant alkaloids, topoisomerase inhibitors, podophyllotoxins, antibodies, tyrosine kinase inhibitors, hormone treatments, soluble receptors, and antineoplastics. In another embodiment, the agents are clodronate and cationic CpG.

[0009] In another ~~aspect~~embodiment, the ~~invention~~disclosure provides for methods for identifying a treatment modality for treatment in humans comprising testing a combination of compositions in a companion animal with a spontaneously occurring disease and identifying the combination that has a higher probability of success in humans by comparing the results of the testing in the companion animal with a spontaneously occurring disease to the results of the testing in an animal without a spontaneously occurring disease.

[0010] In another ~~aspect~~embodiment, the ~~invention~~disclosure provides for methods of identifying an autoantigen associated an autoimmune disease comprising: (a) determining one more antigens in a companion animal with a spontaneously occurring autoimmune disease; (b) obtaining an antigen profile of the disease in the companion animal; (c) comparing the profile to a control companion animal that does not have the spontaneously occurring disease; and (d) identifying an autoantigen associated with autoimmune disease.

[0011] In another ~~aspect~~embodiment, the ~~invention~~disclosure provides for methods of targeting multiple antigens associated with or suspected of being associated with cancer in a human comprising: (a) administering one or more agents that is suspected of having anti-cancer effects to a companion animal with a spontaneously occurring cancer; (b) monitoring a biological or physiological effect of the agent in the companion animal; (c) identifying one or more

antigens in the companion animal for which the agent had a biological or physiological effect and (d) administering the same agent to the human if the agent has an anti-cancer effect in the companion animal.

[0012] In another ~~aspect~~embodiment, the ~~invention~~disclosure provides for methods of targeting multiple antigens associated with or suspected of being associated with an infectious disease in a human comprising: (a) administering one or more agents that is suspected of having effects against the infectious disease to a companion animal with a spontaneously occurring infectious disease; (b) monitoring a biological or physiological effect of the agent in the companion animal; (c) identifying one or more antigens in the companion animal for which the agent had a biological or physiological effect and (d) administering the same agent to the human if the agent has a beneficial effect in the companion animal. In one embodiment, the infectious disease is selected from the group consisting of influenza, septicemia (e.g., *Klebsiella pneumoniae* septicemia), bacterial infections (e.g., *Staphylococcus aureus*, other Staph infections, E. coli and enterococci), Pseudomonas aeruginosa, Leishmania infantum, Brucellosis, Coccidiosis, and *Salmonella enterica* Serovar Typhimurium.

[0013] In any of the aspects or embodiments ~~of this invention~~, the companion animal is a dog. The dog can be a purebred dog or a mongrel dog. The dog can have a homogeneous genetic background or a heterogeneous genetic background.

[0014] In any of the aspects or embodiments ~~of this invention~~, the companion animal is a cat. The cat can be a purebred or a mongrel. The cat can have a homogeneous genetic background or a heterogeneous genetic background.

[0015] Accordingly, in another ~~aspect~~embodiment, the ~~invention~~disclosure provides a companion animal model system for identifying a treatment modality for treatment in humans comprising a combination of compositions that have a higher probability of success for identifying the treatment modality than a standard model. In one embodiment, the combination of compositions comprises two or more antigens. In another embodiment, the combination of compositions comprises at least 1 antigen and an adjuvant. In another embodiment, the companion animal is a dog or cat. In another embodiment, the companion model system is a canine system and has a heterogeneous genetic background. In another embodiment, the companion animal is a purebred dog. In another embodiment, the companion animal is a mongrel dog.

[0016] In another ~~aspect~~embodiment, the ~~invention~~disclosure provides for methods for identifying an anti-cancer agent comprising: (a) procuring companion animal model system for testing the agent wherein the companion animal model system has a spontaneously occurring cancer; (b) administering the agent to the companion animal model system; (c) monitoring more than one cancer antigen in the companion animal model system for biological and/or physiological effects; and (d) identifying the agent as anti-cancer based on the biological and physiological effects. In one embodiment, the companion animal is a dog or a cat. In another embodiment, the cancer antigen is not a glioblastoma multiforme antigen.

[0017] In another ~~aspect~~embodiment, the ~~invention~~disclosure provides for methods of identifying an autoantigen associated an autoimmune disease comprising: (a) procuring companion animal model system wherein the companion animal model system has a spontaneously occurring autoimmune disease; (b) determining one more antigens to obtain a profile of the disease in the companion animal model system; (c) comparing the profile to a control companion animal model system that does not have the spontaneously occurring disease; and (d) identifying an autoantigen associated with autoimmune disease. In one embodiment, the companion animal is a dog or a cat. In another embodiment, the autoimmune disease is selected from the group consisting of diabetes, dilated cardiomyopathy, and discord lupus. In another embodiment, the autoantigen is not GAD65 or full-length IA-2, juxtamembrane domain (aa 605-682 of IA2). In another embodiment, the autoantigen is not myosin heavy chain, alpha cardiac actin, mitochondrial aconitate hydratase, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), or brain glycogen phosphorylase (GPBB).

[0018] In another ~~aspect~~embodiment, the ~~invention~~disclosure provides for methods of targeting multiple antigens associated with or suspected of being associated with cancer in a human comprising: (a) procuring companion animal model system for testing the agent wherein the companion animal model system has a spontaneously occurring cancer; (b) administering to the companion animal model system one or more agents that is suspected of having anti-cancer effects; (c) monitoring the effects of the agent on the companion animal model system; and (d) administering the same agent to the human if the agent has an anti-cancer effect in the companion animal model system. In one embodiment, the companion animal is a dog or a cat.

[0019] In another ~~aspect~~embodiment, the ~~invention~~disclosure provides for methods of targeting one or more antigens associated with or suspected of being associated with an infectious disease

comprising: (a) procuring companion animal model system for testing the agent wherein the companion animal model system has a spontaneously occurring infectious disease; and (b) administering to the companion animal model system one or more agents that is suspected of having an effect to combat the infectious disease; (c) monitoring the effects of the agent on the companion animal model system; and (d) administering the same agent to the human if the agent has an effect in the companion animal model system. In one embodiment, the companion animal is a dog or a cat. In another embodiment, the infectious disease is selected from the group consisting of influenza, septicemia (e.g., *Klebsiella pneumoniae* septicemia), bacterial infections (e.g., *Staphylococcus aureus*, other Staph infections, E. coli and enterococci), Pseudomonas aeruginosa, Leishmania infantum, Brucellosis, Coccidiosis, and *Salmonella enterica* Serovar Typhimurium.

[0020] In another ~~aspect~~embodiment, the ~~invention~~disclosure provides for methods of improving timing and/or cost for obtaining regulatory approval on an agent for a disease comprising: (a) identifying companion animal model system for the disease wherein the companion animal model system has a spontaneously occurring version of the disease; (b) administering the agent to the companion animal model system; (c) monitoring the animal for biological and physiological effects; (d) determining the effects of the agent on the disease and (e) documenting the effects of the agents on media that is suitable for submission to a regulatory agency. In one embodiment, the companion animal is a dog or a cat.

BRIEF DESCRIPTION OF THE FIGURES

[0021] Figure 1 depicts results which show that once weekly i.v. administration of 200 ul LC to C57Bl/6 mice with established s.c. MCA-205 (sarcoma) tumors produced significant inhibition of tumor growth.

[0022] Figure 2 depicts results which shows a dog with STS treated with a series of treatments with LC alone experienced significant spontaneous tumor regression beginning after the third LC administration.

[0023] Figure 3 depicts results which show that twenty-four hours after i.v. administration of LC in tumor-bearing mice, $CD11b^{+}/Gr\text{-}1^{+}$ MSC were enumerated in spleen, blood, and tumor tissues and that significant MSC depletion occurred in blood.

3. The method of any one of claims 1 or 2 wherein the companion animal is a dog.

4. The method of claim 3 wherein the companion animal is a purebred dog.