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White House Cancer Moonshot Task Force
Office of the Science & Technology Advisor
The White House
Washington, DC

September 30, 2016

Dear Dr. Carnival:

It is clear that the Moonshot initiative has already made an enormous impact in its short 6-month existence – particularly in placing the incredible unmet need that is pediatric cancer as a top priority. Congratulations on this significant accomplishment! We are heartened also to learn that you are working to ensure the Moonshot and its great promise transcends politics.

At the recent White House Briefing on Childhood Cancer, you asked participants to share ideas for the future of the Moonshot. We are delighted to weigh in. From the perspective of practicing pediatric and veterinary oncologists, immunologists, experts in genomics and translational research, we know we can do better for kids by incorporating promising new approaches into the pediatric cancer drug development continuum. Comparative oncology – studying spontaneous cancers and treatment in man's best friend to better understand cancer in children - can help us: 1) better understand pediatric cancer on the most fundamental level, and 2) accelerate the efficient development of new and better medicines for kids… (all the while helping man's best friend – a win-win). We offer some points to consider in support:

Shared Genes, Shared Cancers

At least 84% percent of dog DNA has human counter parts; and not surprisingly, canines develop many of the same cancers kids do. Importantly, all of these cancers are spontaneous. The domestic dog is a model system that not only has remarkable similarity at the genetic level to ourselves, but they also share our environment; we breathe the same air, drink the same water and are exposed to same environmental stressors.

Genomics research has identified shared genes involved with several pediatric cancers – including bone cancer, glioma, and lymphoma. These are providing some exciting insight into how such cancers develop. Like children, canines even exhibit fusion onco-proteins – a major focus in the Moonshot – but these are not currently well-characterized. Such studies have great potential to open the doors to new therapies much more quickly than if we are limited to conventional human research.

The purebred dog model in particular can be seen as the new "sentinel species," offering great potential for accelerating cancer gene discovery. Boxers have a very high risk of developing gliomas, while Rottweilers, Irish Wolfhounds and others are more likely to develop bone cancer. We can identify significant genetic features of these spontaneous cancers in a restricted genetic background, but also by comparing extended families, and then translating that data to humans.

Better, More Predictive Models

Within the Moonshot Recommendations, the Blue Ribbon Panel points to the inadequacies of today's mouse models and the need for better predictive models moving forward. We agree. The pet dog with cancer has an immune system that is more similar to the human patient than a mouse that is bred to have a deficient immune system so that cancer can be induced in

it to create "a model." It is widely known that such induced mouse models have limited predictive value. Their poor relevance to what actually occurs in human patients is driven by lack of heterogeneity, conformity of groups, an absence of comorbidities and an overall desire to reduce variables and thereby drive consistency of outcomes. The continued reliance of cancer research on artificial models is an important factor behind the high failure rates when translating to humans with spontaneous cancers that are inherently variable by nature.

Dogs, on the other hand, develop cancer spontaneously – like humans- in the presence of a natural [competent] immune system. They live with us, experiencing the same environmental insults. They can provide a unique opportunity to at least partially replicate the heterogeneity of human cancers, with respect to timeline of development, clinical presentation, existing comorbidities and, importantly, variability in therapeutic response.

More Efficient Implementation/Completion of Clinical Trials

As a rule, the barrier to implementation of a canine clinical trial is MUCH lower than for human (and particularly pediatric) studies. As we know, a major impediment to conducting meaningful pediatric trials is often the small number of geographically-dispersed patients, and the difficulty investigators face in accruing them. Many of the shared cancers are more prevalent in dogs than in kids – providing the necessary number of subjects in order to answer critical questions involving safety, dosing, and regimen. (For example, osteosarcoma afflicts an estimated 10,000 canine patients annually – versus ~400 kids). Comparative oncology centers and cooperative groups have developed to the point where they are now able to accrue patients fast enough to inform concurrent or planned human trials And the disease course for many shared malignancies is MUCH shorter in dogs, meaning that endpoints come much more quickly, and translatable data can be moved into children more rapidly.

Clinical trials in dogs also have more flexibility with regard to the rigid (Phase I-III) stages of typical of human studies. For example, it is possible to administer new therapies to dogs before standard of care, or when there is minimal residual disease (after surgery or radiation). In summary, clinical trial design in canine cancer patients allows for adaptive clinical trials – a more efficient and cost effective path towards FDA approval.

Means to Evaluate Immunotherapies in Kids

Immunotherapies offer great hope. The over-reliance on mouse models, however, limits the implementation of intelligent combinations of immune-modulating drugs. Mouse models do have value for preclinical proof-of-concept. However, the dog is a highly appropriate model for evaluating many of these particular strategies and can help select combinations more likely to help children.

Looking back to the future of Moonshot, if we want to accelerate the pace of drug development for pediatric cancers, we need models that can be quickly developed, rapidly accrue, have quick but meaningful endpoints, be conducted with budgets much less than previously required, and which can be used for testing modern immunotherapies. The dog model excels in ALL of these areas. Money invested in strengthening networks of veterinary clinical trial centers and in funding canine clinical trials, can only accelerate meaningful drug development.

This cannot be accomplished without a significant commitment of resources to comparative oncology, and particularly canine clinical trials. A better inclusion of canine patients within NCI's annual spending could potentially revolutionize the field of pediatric oncology, while having a minimal impact on conventional funding.

We encourage the Moonshot leadership to include comparative oncology explicitly in its future vision and recommendations. In that spirit, we have joined together to do our part, and are likewise committed to advancing this promising field for the benefit of our precious children and our four-legged best friends ... both ends of the leash. For more information, please contact Ulrike Szalay at uszalay@caninesnkids.org.

Again, we thank the Moonshot leadership for your important contributions, and wish you the best for a smooth transition.

Respectfully,

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