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February marks the first anniversary of the Humanimal Hub, and this issue we are pleased to celebrate our birthday in style by talking to Hub member Professor Matthew Breen from North Carolina State University. Matthew is well-known in the field of comparative genetics and oncology, particularly in canine urothelial carcinoma. He tells us a little about his comparative work in canine and human cancers, and about an exciting One Medicine project involving pet owners and their dogs in a nationwide citizen science program.

A Chat in the Collaboration Café

The data generated by your research is used to improve the outcomes for canine cancer patients and to also advance understanding of comparable cancers in humans. Could you tell Hub members what forms of cancer your research focuses on, and why you consider a One Medicine approach to be important?

Matthew: Over the past 20+ years our research has spanned numerous cancers that are common to dogs, including lymphoma, leukaemia, osteosarcoma, bladder and prostate, intracranial, soft tissue sarcoma, melanoma, and mast cell. As we started to investigate the genomics of these cancers it became apparent that many of the genomic aberrations we detected in canine cancers were shared with the corresponding human cancers.

HUB MEMBER PROFILES:

Professor Matthew Breen



Matthew Breen is Professor of Genomics and the Oscar J. Fletcher Distinguished Professor of Comparative Oncology Genetics at the North Carolina State University College of Veterinary Medicine.

Matthew's primary research over the past 30 years has focussed on genomics, genome mapping and the comparative aspects of canine cancer. Most recently, his research group are investigating the role of the dog as a sentinel species.

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Working in collaboration with colleagues focused on human oncology, we were able to develop tools that facilitated direct comparison of data and thus enhance our ability to tease out the key signatures associated with diagnosis and also prognosis. It is this cross species evaluation, i.e., a One Medicine approach, that provides opportunities to identify shared features suggestive of an ancestral mechanism of pathogenesis; it is the cancer associated with the changes, not the species.

Could you tell us a little more about your work with canine bladder and prostate cancers?

M: Most cases of canine bladder and prostate cancers (urothelial carcinoma, UC) are detected only after the dog has started to show clinical signs, which can be late in the course of disease. In addition, the clinical signs of canine UC are shared with other more common urinary tract issues, such as infection, polyps, prostatitis, and bladder stones. As a result, first line treatment commonly targets the clinical signs, usually involving antibiotic and/or anti-inflammatory medications. UC is only generally considered once clinical signs recur, by which time the cancer has had more time to advance. This series of events can delay the start of treatment targeted to the cancer.

If we can detect canine UC earlier in the course of disease, before clinical signs develop, and initiate appropriate treatments sooner, we may be able to provide better outcomes.

When a dog urinates, cells from the urinary tract, including those from any tumour, are shed. Our research identified genomic signatures that are shared by over 95% of dogs presenting with clinical signs of disease. One of these signatures, the presence of a V595E BRAF mutation, is detectable in the urine of 85% of dogs with canine UC. We therefore developed a way to detect the presence of this mutation using a non-invasive (free-catch) urine specimen as a liquid biopsy (Wiley et al, 2019).

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Access to urinary BRAF testing is now used widely to aid diagnosis of a UC in dogs with clinical signs, helping to avoid delays in initiating treatment for the cancer. In addition, the Urothelial Carcinogenesis group at NC State, in collaboration with colleagues at the University of Wisconsin and Duke University, are conducting a study to evaluate the role of urinary BRAF mutation testing for detection of canine UC in preclinical cases. By detecting cases even before clinical signs present, and then following the disease progression of these dogs, we are hoping to determine the timeline during which earlier intervention may be impactful.

From a comparative aspect, working with our colleagues at the Duke Cancer Institute, we are looking at canine UC cases as a model for human bladder cancer, which we propose will help to accelerate advances in human medicine.

Could you explain how genomics and genome mapping are used to identify those chromosomes which are involved in both human and canine cancers?

M: The process of identification of shared genomic changes has evolved with technology. We began our analysis of canine cancers by developing a series of molecular tools that allowed us to identify all dog chromosomes, and used these to investigate large numbers of patient specimens and identify the chromosomes recurrently involved in aberrations. By integrating the cytogenetic maps of human and dog we were able to determine, at low resolution, which regions of both genomes were comparable.

Once the canine genome had been sequenced, we were able to develop higher resolution tools to hone in on the specific regions of chromosomes involved, and then to the actual genes. Today we use a combination of molecular techniques to generate data, including cytogenetics, whole genome sequencing, whole exome sequencing, RNAseq, and targeted sequencing, etc.

In parallel, working with dog owners, we have accumulated thousands of pathology-verified and clinically annotated canine cancer specimens and now use our framework to discover and validate genomic changes. As these data are generated, our parallel studies of the corresponding human cancers allow us to identify shared changes. Using this approach our goal is to advance the ability for veterinary medicine to offer improved management of canine cancers, as well to provide our human oncology colleagues the opportunity to identify new opportunities to aid treatment of their own patients.

Your research on canine cancers also examines the impact of daily environmental exposures on animal health, adopting the dog as a sentinel species for human health. Could you tell Hub members more about this aspect of your research?

M: Cancers cannot all be explained by genetics alone, and our environment may also contribute to disease development. Quantifying our own exposures is a major challenge due to latency, meaning that it can take years before an exposure leads to disease.

Our dogs share our home environment and our external exposures. We breathe the same air, we drink the same water, we sometimes eat the same food, we sit on the same sofa, and when we are outside our dogs walk and play on the same ground that we do.



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The extent of our shared environment means that our dogs are perhaps the best sentinel species we have for exposure-related human disease. With a 6 to 8 fold shorter lifespan, shared clinical and biological behaviours, and closely related genomes, our dogs offer a similar opportunity to assess the longer-term health impacts on humans from our shared exposures.

For example, in our recent collaborative study with Dr Stapleton at Duke University (Wise et al, 2020), we demonstrated that the levels of chemicals detected by passive silicone samplers, as well as in the urine of dogs and their owners, was highly comparable.

This study, highlighted by National Geographic and the National Institute of Environmental Health Sciences, demonstrated that the household dog could be a valuable One Health model and potential sentinel species for examining how exposure to consumer product chemicals impact health. This project has now advanced to ask additional questions about our shared exposures.

The current research studies your lab is undertaking are looking at tens of thousands of dog owners across the US and both human and canine patients. In terms of broader international collaboration, how could Hub members from the human and veterinary medicine professions get involved?

M: We have worked with many thousands of pet parents over the years and one of the major findings is that many dog owners are very eager to become involved and contribute to research studies that have the potential to lead to longer and healthier lives for all dogs. Having worked with the dog owning community as collaborators for many years, we started a larger scale study to engage even more dog owners into our nationwide citizen science program.

As part of this program, we obtain biological samples and clinical information that will help us understand more about how dogs can guide research related to the environmental impact on our own health.

In the 20th Century we had canaries in the coalmines to warn of dangerous gases. In the 21st Century we have canines on the couch to warn us of potential daily exposures to hundreds of chemicals. Due to the COVID-19 pandemic and associated lockdowns, stay at home orders, and working from home, those of us with dogs have perhaps spent more time with them at home that at any other time in modern history. This means that 2020-2021 is the period during which the extent to which our shared daily household exposures has likely never been so great.

Our goal is also to expand this initiative to include dogs and their owners from other countries and so if anyone has interest in learning more, I think the Hub could be a great forum to begin the discussions.

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Who has most influenced your research work?

M: For over 20 years, my work has been most influenced by dog owners. Everyone I speak to who has a dog at home regards that dog as a member of their family. At the time that their beloved companion is facing serious health challenges, potentially even end of life, dog owners somehow have the courage to overcome their own distress and arrange for biological samples and clinical information to be sent to our lab so that we can include their dog to one of our studies.

I am constantly amazed by the community spirit - even when we cannot help their own dog, owners are eager to do what they can to help us with our research so that other families may not have to face a similar situation with their own dog in the future. It is very humbling for us to have the confidence of dog owners to make a difference, and this is what drives us each day.

Find Out More

Connect:

In addition to being Professor of Genomics and the Oscar J. Fletcher Distinguished Professor of Comparative Oncology Genetics at the North Carolina State University College of Veterinary Medicine, Matthew is a member of the North Carolina State Comparative Medicine Institute and the Centre for Human Health and the Environment, and is affiliated with the University of North Carolina (UNC) Lineberger Comprehensive Cancer Centre and the Duke Cancer Institute. Matthew is also a member of the Humanimal Hub, and can be contacted directly via The Hub.

Collaborate:

If you're interested in joining the discussion about expanding Matthew's research work (e.g., the Early Detection of Urothelial Carcinoma Clinical Trial and Environmental Monitoring Study) internationally, or if you want to explore other potential collaboration opportunities and would like to connect with Matthew, please get in touch directly on the Humanimal Hub, or via hub@humanimaltrust.org.uk.

Request for help: Student placement sought by Hub member

Can any of our Hub members help fellow Hub member Kerry Holtham?

Kerry is a second year BSc (Hons) Bioveterinary Science student at the University of Lincoln and is presently seeking a student placement opportunity commencing September 2021. This could either be a placement year or a period of shorter-term placements. She has work experience gained from veterinary surgeries, farms and bird gardens and is a keen apiarist, having represented the Harrogate and Ripon Beekeepers Association.

Kerry is looking for a student placement opportunity in the fields of clinical diagnostics, veterinary biopharmaceutical product development or disease pathology.

If any Hub members know of any potential opportunities, please do get in touch with us via hub@humanimaltrust.org.uk and we will connect you with Kerry.

Would you like a chat in the Collaboration Café?

Humanimal Hub wishes to say a huge thank you to Professor Matthew Breen for featuring in this issue of the Collaboration Café.

If you would like to have a Hub Chat with us in the Collaboration Café to tell us more about yourself, the work that you are doing and what sort of collaboration opportunities with Hub members you may be looking for, we'd love to hear from you!

Send the Hub Admin Team an email via hub@humanimaltrust.org.uk and we'll be in touch to sort out the rest!

Best wishes,
The Humanimal Hub Admin Team