

Medical Detection Dogs Unit 3 Millfield Greenway Business Park Great Horwood Milton Keynes MK17 0NP

T 01296 655888 E operations@medicaldetectiondogs.org.uk

www.medicaldetectiondogs.org.uk

Patron: HRH the Duchess of Cornwall

Canine Olfactory Detection of Human Cancer: Research Summary

In 2004 we completed a study published in the **<u>British Medical Journal</u>** (BMJ) (Willis CM, Church SM, Guest CM, Cook WA, McCarthy N, Bransbury A, Church MRT, Church JCT. Olfactory detection of human bladder cancer by dogs: proof of principle study. BMJ 2004 329: 712.) The study provided the first proof that dogs could identify a unique odour or 'odour signature' that was associated with cancer. This was the first clinically robust trial to be completed and published in the world.

Since our BMJ and more recent Journal of Cancer Biomarkers publication, there have been a number of promising publications from around the world investigating the potential of dogs to detect human cancer by odour. Dogs with their incredible sense of smell can detect the minute odours now understood to be associated with many cancers. Specialist dogs trained to detect cancer volatiles can provide valuable information that will assist in the development of new ways to detect and diagnose cancer.

In a recent study Cornu et al (2011) evaluated the efficacy of prostate cancer detection by a trained dog, on human urine samples. After a learning phase and a training period of 2 years, the dog's ability to discriminate urine from cancer patients from control urine was tested in a double-blind procedure. The dog correctly selected the cancer samples in 30 of 33 cases. Of the three cases wrongly classified as cancer, one patient was rebiopsied and a PCa was diagnosed. The sensitivity and specificity were both 91%. The authors concluded that dogs can be trained to detect the odour signature of PCa by smelling urine with a significant success rate.

A Japanese study by Senoda et al (2011) on colorectal cancer using breath and faecal samples showed equally promising results. Sensitivity was at 0.97 with a specificity of 0.99 for faecal samples, while sensitivity was at 0.91 with a specificity of 0.99 for breath samples. The accuracy of canine scent detection was high even for early cancer. Canine scent detection was not confounded by current smoking, benign colorectal disease or inflammatory disease. The authors concluded that a specific cancer scent does indeed exist and that cancer-specific chemical compounds may be circulating throughout the body. These odour materials may become effective tools in colorectal cancer screening.

In 2006 in the USA, McCulloch et al evaluated the ability of trained dogs to distinguish exhaled breath samples of 55 lung cancer patients from those of 83 healthy controls. Among lung cancer patients and controls, overall sensitivity of canine scent detection compared to biopsy-confirmed conventional diagnosis was 0.99 and overall specificity 0.99. Additional evidence of a dog's ability to detect lung cancer from a breath sample was published by Ehmann et al. (2012) who found that sniffer dogs can identify lung cancer with an overall sensitivity of 71% and a specificity of 93%. The authors anticipated that a robust and specific volatile organic compound (or pattern) is present in the breath of patients with lung cancer.

In an additional study in 2006, McCulloch also tested the dog's ability to distinguish exhaled breath samples of 31 breast cancer patients from those of the 83 healthy controls. Dog handlers and experimental observers were blinded to the identity of breath samples, obtained from subjects not previously encountered by the dogs during the training period. Among breast cancer patients and controls, sensitivity was 0.88 and specificity 0.98.

Whilst these studies show huge promise there is still a long way to go. Much of this work has been with one dog and on a very limited number of samples. In some cases there has been repeated use of controls in testing and controls have been from younger healthy individuals and not from aged matched symptom matched individuals. This would result in much higher accuracy levels from the dogs that may not be replicated in clinical setting. Further research is required with a larger group of dogs, much larger sample sizes and robust double blind testing with age matched symptoms matched controls. This can be done but requires funding as ethics and patient consent must be passed and all sample collection can be a lengthy process. However the value of studies such as these to follow up this initial proof of principle studies would be invaluable.

The charity is working in conjunction with Professor Karol Sikora, scientists and medical statisticians in the detection of prostate cancer from human breath and urine. There are massively powerful reasons for such a study. Prostate cancer is a major killer and the current test, the prostate specific antigen test [PSA], is so unreliable that many GP's are reluctant to use it. If dogs can sniff prostate cancer from a urine sample the chances are high that from the results of the dogs' sniffing research, a test can be developed that is far superior to the PSA test. The results would indicate the existence of a potential odour signature of prostate cancer that may correspond to one or, more likely, multiple VOC's. These molecules should then be assessed by specific gas chromatography/mass spectrometry analysis.

We are working with colleagues in Italy (MDD .I) and have already developed our knowledge and have the opportunity to work on samples in a true clinical setting. During the trip, we also had the opportunity to work our dogs on samples in a hospital in Trento run by the chairman of MDD.I. This was a fantastic experience and we were able to ascertain from the samples provided, that both our cancer detection dogs Daisy and Lucy were able to indicate bladder, prostate and two types of renal cancer from urine samples. During our first trip we were asked to screen a sample from a patient who had a recent biopsy of the prostate that had been negative. There were concerns due to this patient's fluctuating PSA. Both dogs indicated positively on this sample. The clinician observing this response recalled the patient back for a second 21 needle biopsy. This second biopsy revealed cancer.

This opens the question of whether in the shorter term (prior to the development of an electronic system) dogs might be used as a second-line screening using a regulated process, similar to that used by DSTL, a UK agency for the UK Ministry of Defence. This is the RASCO system, Remote Air Sampling for Canine Olfaction, and is used for the detection of explosives in cargo. In this system odour collected on specialist filters by drawing air form the cargo is presented to the dog for detection in a separate working environment. Please see Appendix 1.

The PSA's high false positive rate could be complimented by a canine urine screening service that demonstrated a low false positive rate and higher accuracy. Second line screening of this nature is already in place in Tanzania where rats are used for the second-line screening of human TB.

APOPO offers second-line screening to partner hospitals, which has increased new case detection rates of TB in partner hospitals and DOT centres by over 30 percent. The APOPO rat detection technology meets the seven top priorities required for a diagnostic method, as determined by the TB diagnostic group of the World Health Organization.

These developments together with additions to our team supported by Professor Karol Sikora will give our project impetus and lead to further discoveries in the potential of this work. In addition, specialist dogs trained to detect cancer volatiles can provide valuable information that will assist in the development of new ways to detect and diagnose cancer in the future. Hopefully with the knowledge the dogs provide, scientists will be able to develop an electronic system which can mimic the dog's nose and open the way for new noninvasive methods of screening for cancer. Following our 2004 study scientists have been investigating this potential

and a recent publication reported success in the development of a nano –sensor for cancer detection. Please see Appendix 2. Although some of the claims stated in this article are yet to be proven, it is a clear indication of the progress that has been made.

With regard to further studies, we have now have a collaborative team including clinicians, Giles Cunnick (Breast Surgeon) and Alan Makepeace (Oncologist) and are preparing to do an MDD proof of principle study into the detection of breast cancer from a breath sample. We are currently preparing an ethics proposal for this project and will then proceed with the collection of samples from patients and controls. In broad terms the proof of principle study will be similar to the original BMJ paper. For guidance on how the study will be conducted please refer to the BMJ article regarding the bladder cancer study.

This study will be conducted on very similar lines. We propose that a proof of principle study is completed with a minimum of 4 dogs some of which may be dogs previously trained to sniff cancer from urine. We will use computer software to enable the dogs to be rewarded after detection of a sample. This system has already been used successfully in our other odour detection studies. Dog training and testing would take an estimated 8 months. Careful records will be kept on computer and video tape.

All this existing evidence opens the door of VOC detection for cancer diagnosis and suggests that the conditioned dog should be used in the near future to validate candidate molecules emerging from metabolomic screening. The results provide a new insight in the field and further work with more dogs is now required to further investigate and validate this work. If an electronic nose with sufficient accuracy can be developed for GPs to use in the surgery the benefits will be truly vast.

Dr Claire Guest BSc(Hons) MSc. HonDSc.