# Sanjiv Sam Gambhir (1962–2020)

Physician-scientist who pioneered molecular imaging for the early detection of cancer.

With "What if… we could detect and measure molecular targets and biological processes non-invasively, in a living subject?", Sanjiv Sam Gambhir began the first exploratory steps into what would become the field of molecular imaging, first at the University of California Los Angeles and later at Stanford University. Sam — as he liked to be addressed — was driven by research that would tangibly help people with cancer. Trained in biomathematics and nuclear medicine, he was chair of radiology in the School of Medicine at Stanford University when cancer cut short his life at the age of 57.

Sam was never afraid to ask out-of-the-box 'what if' questions. He envisioned solutions without worrying about whether they were possible. His top-down approach to research was an invitation for everyone he mentored and collaborated with to brainstorm and co-develop technologies that would help realize his visions. Sam was the consummate collaborator. He believed in the power of strong interdisciplinary partnerships to tackle big challenges in early disease detection by using imaging technologies. He sought ways to motivate and engage, giving students and colleagues a greater sense of purpose to their work, and reminding everyone that helping patients was the ultimate goal. Sam took to heart his role as a mentor and was a champion for women in science and early-career researchers. His energetic and solution-driven mindset led to a succession of notable contributions to molecular imaging, nanomedicine and precision health.

"What if… we could image gene expression in vivo?" For decades, molecular biologists had employed enzymatic readouts for in vitro and cellular assays, and then turned to bioluminescence as a highly sensitive and versatile reporter system. Preclinical in vivo applications of bioluminescence soon emerged by cloning luciferase genes downstream of biologically interesting promoter regions in cells (for injection in vivo) or in transgenic mice. Bioluminescent reporters soon enabled the non-invasive optical imaging of gene expression in living subjects[1]. As a new assistant professor at the University of California Los Angeles, Sam challenged his group to take this concept a step further, and

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to develop reporter genes that could be used with positron-emission tomography (PET). Sam and his team initially repurposed mutated forms of the herpes simplex virus thymidine kinase to be expressed in cancer cells, and to act as a PET reporter gene when partnered with a specific F-18-radiolabelled probe such as fluorinated penciclovir[2].

"What if… we could use radiolabelled oligonucleotides to directly image gene expression in vivo?", Sam asked one of us (A.M.W.). We spent almost a year trying and failing, yet Sam continually offered his full support and the opportunity to try anything. Eventually, we found success by using engineered antibodies and fragments for imaging cell surface phenotypes in vivo. This strategy worked and led to the rise of immunoPET, enabling the highly specific detection of biomarkers for cancer and other diseases[3,4]. The approach is currently also being explored for the monitoring of immunotherapies and vaccines, for example therapies involving T cells with chimeric antigen receptors[5] or activated T cells for cancer vaccines[6].

"What if… we could image in different colours?" Sam grasped the challenges that biological complexity presented to the development of diagnostic strategies, and was among the early voices promoting multiplexing methods. He helped build technologies that allowed researchers to ask complementary questions, believing that no single assay, test or probe could capture the complete picture needed to understand, diagnose and treat diseases such as cancer. In particular, his laboratory pursued the development of several PET reporter genes, of luciferase–luciferin pairs for bioluminescence, and of multimodality imaging to combine diagnostic information from radioactive, bioluminescent and fluorescent imaging modalities. Sam also advocated for the development of label-free imaging technologies, such as Raman imaging, and led the development of surface-enhanced Raman scattering nanoparticles with multiplexing capabilities. His laboratory generated the first in vivo Raman image, and demonstrated the ability to unmix ten separate spectral signatures from a single image, all non-invasively, in a living subject[7]. Sam envisioned the technique's clinical translation by way of endoscopy, via the addition of a functional imaging accessory to clinical endoscopes used to screen the colon.

"What if… we could detect cancer at the earliest stages, long before a patient or physician notices signs or symptoms?" To tackle this problem, in 2009, Sam and Don Listwin founded the Canary Center at Stanford, which focused solely on developing innovative strategies for the early detection of cancer — a mission that became increasingly more personal for Sam after his wife's battle with breast cancer and the loss of their son to glioblastoma. Sam pioneered the integration of in vivo and in vitro diagnostic research under the same roof, bringing together specialists with expertise in molecular imaging, proteomics, bioinformatics, cell and molecular biology, and chemistry, and initiating collaborations that spanned the clinical, physical and engineering sciences. One of the initiatives led to the development of the MagWIRE, a flexible and biocompatible magnetic wire that can enrich and extract rare biomarkers, such as circulating tumour cells, directly from the bloodstream in vivo. Proof-of-concept work showed that the MagWIRE efficiently captured circulating tumour cells, with significantly higher enrichment compared with commercially available methods[8]. The MagWIRE brings the sampling directly to the body, increasing

the sensitivity of the assay by detecting a biomolecular signal continuously over time, and eliminating the restrictions imposed by a small tissue sample.

"What if… we could build ways of monitoring health and detecting disease, right in people's homes and daily lives?" Sam and his team developed a modular 'smart' toilet that analyses the user's excreta, which may allow the long-term monitoring of patients at home[9]. Sam was resolute in finding innovative ways to transform current healthcare systems from a reactive 'precision medicine' to a proactive 'precision health' — that is, shifting the emphasis to disease prevention and early detection, via risk-tailored longitudinal monitoring. Sam's vision of precision health entailed the use of non-invasive, low-cost, repeatable and clinically actionable methods integrated with artificial intelligence to model human health and disease. Devices such as the smart toilet and a smart bra (under development) are the building blocks of the 'smart home' that Sam dreamed about; a dream in which passive health monitoring provides early warning signs of disease before a person becomes a patient. ❐

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References
1. Contag, C. H. & Bachman, M. H. *Annu. Rev. Biomed. Eng.* **4**, 235–260 (2002).
2. Iyer, M. et al. *J. Nucl. Med.* **42**, 96–105 (2001).
3. Wu, A. M. et al. *Proc. Natl Acad. Sci. USA* **97**, 8495–8500 (2000).
4. James, M. L. et al. *J. Nucl. Med.* **58**, 1845–1851 (2017).
5. Simonetta, F. et al. *Clin. Cancer Res.* https://doi.org/10.1158/1078-0432.CCR-20-2770 (2020).
6. Alam, I. S. et al. *J. Clin. Invest.* **128**, 2569–2580 (2018).
7. Zavaleta, C. et al. *Proc. Natl Acad. Sci. USA* **110**, E2288–E2297 (2013).
8. Vermesh, O. et al. *Nat. Biomed. Eng.* **2**, 696–705 (2018).
9. Park, S. M. et al. *Nat. Biomed. Eng.* **4**, 624–635 (2020).