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editorial

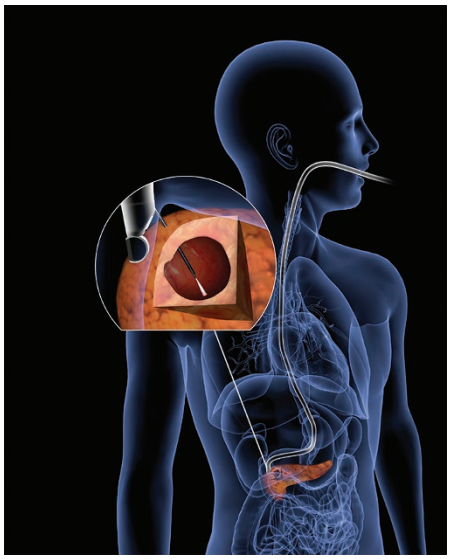
Brighter cancer probes

The early detection of cancer demands translatable light-emitting or light-collecting probes with unprecedented levels of sensitivity and specificity.

Diagnosing solid tumours using non-ionizing light in a minimally invasive manner can be achieved in essentially three ways: by shining light on suspected malignant tissue and analysing the reflected light, by means of a reporter probe that lights up only when taken up by tumours, or through the detection of tumour biomarkers captured from bodily fluids such as blood or urine. Endoscopy and laparoscopy are routinely used in hospitals to examine (and biopsy) tissue, yet detection of potentially abnormal tissue relies on the physician's experience. Fluorescent probes that target endogenous tumour biomarkers or nanoprobes that accumulate in tumours do not require knowledge of the location of a tumour or it being surgically accessible, yet the probes require stringent safety and efficacy requirements before they can reach the clinic. Instead, analysing a patient's blood or urine for cancer biomarkers involves less risk, but requires *a priori* knowledge of which biomarkers to look for. Irrespective of the advantages and disadvantages of all these approaches, they all benefit from research geared towards increasing their sensitivity (so as to minimize the proportion of missed tumours) and specificity (to avoid misdiagnosing healthy patients). Eight technological advances representative of the three approaches for diagnosing tumours are included in this focus issue on cancer diagnostics.

The best clinically available method for the identification of malignant pancreatic cysts is endoscopic ultrasound-guided fine-needle aspiration, yet its specificity is only ~50%. Lev Perelman and colleagues (article no. 0040) describe a fibre-optic probe, compatible with routine endoscopic-aspiration procedures (see image), that distinguishes weakly scattered photons from cancer tissue over the more broadly diffuse photons from healthy tissue. In a double-blind prospective study of 25 patients, the technique achieved an overall accuracy of 95% in cysts with definitive diagnosis (benign, precancerous or cancerous).

Probes at the nanoscale can be designed to target tumours and to emit light at wavelengths that can effectively penetrate tissue and be detected by sensors outside the body. This is the main advantage of nanoparticles that emit in the near-infrared spectral range, in particular in the short-wavelength infrared region. As demonstrated by Moungi Bawendi and collaborators (article no. 0056), suitably functionalized quantum dots with indium arsenide cores enable functional imaging, such as intravital imaging of blood flow in the tumour margin of a glioblastoma, at unprecedentedly high spatial resolution, deep penetration and fast acquisition speeds. To translate this technology into the clinic, however, heavy-metal-free versions of the bright emitters will be needed. At the molecular scale, biocompatible near-infrared probes can be designed to successively respond to tumour acidity and hypoxia and amplify the detection sensitivity while doing so, as shown by Xiqun Jiang and colleagues (article no. 0057). Their highly tumour-specific and ultrasensitive probe detected metastatic tumour nodules as small as 1 mm in the livers of mice.



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High specificity can also be achieved by fluorescent probes that target an endogenous biomarker. Ka-Leung Wong and co-authors report that a rationally designed small peptide inhibitor of the dimerization of an oncoprotein of the Epstein–Barr virus fluoresces on binding to the oncoprotein after intratumoural injection and inhibits the proliferation of tumours associated with the virus (article no. 0042). The specific accumulation of probes in tumours can also be augmented via functionalization with tumour-penetrating ligands. As shown by Sangeeta Bhatia and colleagues (article no. 0054), nanoparticles optimized with the right amount and type of ligands (tumour-penetrating peptides and tumour-protease-cleavable fluorescent peptides) delivered intravenously can detect tumours smaller than 2 mm in an orthotopic model of ovarian cancer. Because fluorescent peptides cleaved by tumour proteases filter through the kidneys into the urine, detection involves a simple urine test.

In urine, the low amounts of microRNAs and other nucleic acids secreted by cancer cells are difficult to detect by point-of-care diagnostics. Daniel Heller and collaborators (article no. 0041) show that a carbon-nanotube–DNA complex with a miRNA-capture domain can sense, via blue shifts in fluorescence, miR-19 spiked into urine down to concentrations of 1 nM, and at 100-pmol levels when the sensors were implanted in the intraperitoneal cavity of live mice. Direct detection of biomarkers in biofluids can also be achieved through signal enhancement by antibody-conjugated plasmonic nanoparticles, as Ye Hu and colleagues (article no. 0021) show with a rapid and inexpensive ultrasensitive sensor chip for capturing extracellular vesicles (EVs). By using only 1 μl of blood plasma from cancer patients, the assay quantified a biomarker (identified via proteomic analyses of the content of the EVs) for pancreatic adenocarcinoma that outperformed the standard clinical biomarker. And to isolate nanoscale EVs, including exosomes, Si-Yang Zheng and co-authors (article no. 0058) took advantage of the spontaneous insertion of biotin-labelled lipid nanoprobes into vesicle membranes to isolate the vesicles in two steps and just 15 minutes via biotin–avidin binding on avidin-tagged magnetic beads. Downstream analyses of the content of the EVs allowed the authors to detect genetic mutations in plasma samples of non-small-cell lung-cancer patients.

As discussed by Catherine Alix-Panabières and Klaus Pantel in a Comment (article no. 0065), analysing exosomes alongside circulating tumour cells (CTCs) will further the understanding of metastasis. In fact, such 'liquid biopsies' provide an example of how biological understanding steered the clinical focus for interventional decisions from CTC counts to CTC-derived biomarkers in what was a decade-long process. The early detection of cancer can never come too soon. ❐