defects, and energy fluctuations induced by ions in the gating medium add up to the overall energetic disorder of these systems.

Such challenges appear to be overcome in the study by Kasuya and colleagues, where a positive temperature coefficient for the sheet resistance, revealing a metallic behaviour, is observed down to 20 K (Fig. 1a) when the areal carrier concentration in the organic conducting channel surpasses 4×10^{13} cm^{-2}, equivalent to a charge carrier every ten molecular units. Such a high concentration can be achieved thanks to the use of a liquid electrolyte dielectric, a strategy typically adopted to electrostatically increase the charge density in the organic channel[6]; in contrast, in most common non-electrolyte-gated organic field-effect transistors the carrier density usually does not exceed one carrier every 100 units. In the latter case, carrier interaction can be neglected, while in the scenario here proposed, where a record occupancy of 0.25 holes per molecule is also reached at the highest bias voltage reported, this cannot be assumed any more, leading to the emergence of a metallic state at high doping levels. It is the large carrier concentration that can also solve the apparent contradiction with typical carrier localization in organics. In fact, it is largely accepted that, by gradually filling the available density of states, carriers correspondingly occupy more delocalized states with respect to deep states, where carriers are typically localized within a single molecule[7]. The estimated hole mean free path corresponds (albeit under strong assumptions) to five unit cells: it is rather intriguing that the metal–insulator turning point is detected above an occupancy of one hole per ten molecules.

To explain why such behaviour was not observed in previous attempts using electrolyte gates in organic crystalline transistors, the researchers propose that the morphology of their organic channels, characterized by a molecularly flat crystalline layer insulated from the ionic liquid by an ordered, high-band-gap, alkyl-chains spacer (Fig. 1b), plays an essential role in reducing disorder in the system. As an example, high bias level, and therefore high carrier density, can be reached without triggering electrochemical reactions. A rather exciting feature of this work is that such fundamental observation is done in a solution-processed semiconductor, through an edge-casting method (Fig. 1c) — a method exploiting a blade to drag the meniscus of a semiconductor solution — on a plastic substrate, leveraging on coating procedures refined for years to achieve molecular control of films over large areas. Combined with the use of electrolyte gating, which in principle can be achieved also with solid electrolytes[8], this means that there is potential to endow flexible large-area surfaces with such striking electronic properties by means of low-temperature, scalable and cost-effective processing. At this stage it is natural to start envisioning the exploitation of 2DHGs in advanced organic transistor devices, mimicking the technology evolution path from GaAs-based metal–oxide–semiconductor field-effect transistors to high-electron mobility transistors[9]. Another inspiring perspective is to exploit this observation for highly sensitive biosensors[10]: what may appear as a technological limitation — that is, the use of liquid gating — can actually be seen as a distinctive trait for interfacing biological matter in aqueous environments.

How plausible are such appealing scenarios? It is difficult to tell at the moment. Clearly this observation is a first of a kind, achieved in highly controlled experimental conditions, and it already enables the exploration of its fundamental implications in condensed matter physics. Yet, further tests assessing the reproducibility and robustness of these observations using different organic materials and different architectures will be needed to devise how we can exploit these results for enhanced large-area devices operating at room temperature. Surely, the study by Kasuya and colleagues already shows that solution-processed molecular crystals on plastic foil can present remarkable electronic properties. This really brings us a step further in exploring what is achievable with organic semiconductors. If engineers are provided in future with extensive knowledge and know-how in the implementation of 2DHGs, we might be witnessing a further expansion of the capabilities of organic electronics. ❐

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Competing interests

The author declares no competing interests.

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CANCER DIAGNOSIS

A ‘Swiss army knife’ probe for metastatic cancers

A nanosensor probe that combines a tumour-targeting peptide, a diagnostic reporter and an imaging contrast agent enables early diagnosis, precision imaging, disease stratification and downstream therapeutic response monitoring of metastatic cancer.

Matthew Bogyo

Cancer is best described as a diverse collection of proliferative diseases that cause millions of deaths per year globally. While many new treatment approaches have helped to dramatically reduce the mortality caused by certain forms of cancer, there are many substantial hurdles that remain in our battle to effectively detect and treat these diseases.

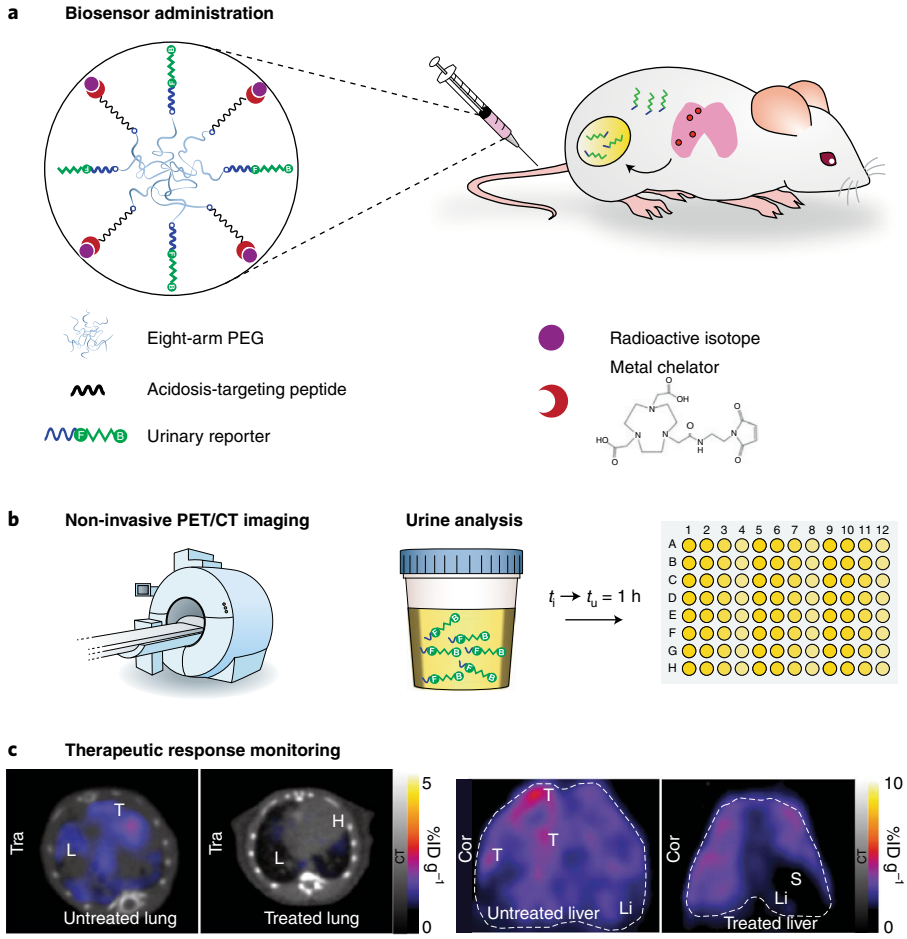

Fig. 1 | A multimodal imaging probe for detection and monitoring of metastatic cancers. **a**, The PRISM probe was developed from a tumour acidosis-targeting and insertion peptide, a urine reporter based on metalloproteinase activity in the tumour and a radioactive isotope. The probe is administered intravenously. **b**, This facilitated detection of tumour tissue non-invasively using urine analysis and positron emission tomography-computed tomography (PET-CT) imaging. t_i, time of sensor injection; t_u, time of urine collection. **c**, The probe was utilized to monitor the response of lung (left) and liver (right) metastasis to treatment with a chemotherapeutic drug. Images show transverse (Tra) and coronal (Cor) views. Location of tumour (T), spleen (S), heart (H), lung (L) and liver (Li) are indicated. Figure adapted with permission from ref. [5], Springer Nature Ltd.

One of the major ongoing challenges is the development of sensitive and accurate tests that enable both early diagnosis and effective tracking of disseminated, metastatic disease. Of particular importance is the ability to continuously monitor disease progression as well as response to treatment to ensure effective therapeutic outcomes. For the majority of solid tumours, the most effective intervention is surgical removal of the diseased tissue. For this strategy to be effective, it is essential to be able to identify the presence and precise location of a lesion to enable biopsy and subsequent surgical removal. This has been facilitated by advanced technologies that allow physicians to directly 'see' tumours with high sensitivity and spatial resolution. In general, diagnosis and subsequent image-guided treatment strategies are facilitated by completely different tools. Typically, diagnostic assays focus on biomarkers that can be sensitively detected from easily obtained samples such as blood and urine whereas image-guided interventions depend on advanced instrumentation and contrast agents. The development of an increasing number of clinically approved diagnostic tests and imaging techniques has led to improved outcomes for patients with cancer, yet there is still a pressing need for more effective tools to enable the detection of early-stage metastatic tumours. In most cases, these small lesions cannot be effectively diagnosed or imaged due to limitations in current state-of-the-art technologies.

An effective strategy to address some of the challenges for diagnosis and imaging of metastatic cancer has been to exploit enzymatic proteins, the activities of which are increased within the tumour microenvironment (TME). In particular, proteases have proven to be broadly effective cancer biomarkers due to the fact that they are expressed at elevated levels by cells within the TME of most types of cancer, including early metastasis. Furthermore, proteases are enzymes that catalyse the hydrolysis of peptide bonds and thus probes can be engineered using relatively simple peptide scaffolds to produce diagnostic signals in response to elevated protease activity. Several research groups have shown that inflammatory-cell-derived proteases such as lysosomal cathepsins are excellent biomarkers for virtually all types of solid tumour and thus are ideal for generating fluorescent signals to facilitate real-time detection of tumours during surgery[1,2].

In addition to enzyme activities that are elevated in the TME, there are other physiological differences that can be used for tumour targeting. Perhaps the most notable alteration in the TME relative to normal healthy tissues is the acidification that results from enhanced expression of proton pumps and increased metabolism inside a growing tumour. This results in a pH drop that can be exploited to drive the specific accumulation or activation of therapeutic or imaging agents. In particular, over two decades ago, work by Engelman and co-workers demonstrated that it is possible to design peptides that alter their biophysical properties in response to reduced pH, to facilitate membrane insertion into living cells[3]. This strategy has been refined to create so-called pH low insertion peptides (pHLIPs) for specific tumour targeting and delivery of attached payloads[4]. Writing in *Nature Materials*, Liangliang Hao, Sangeeta Bhatia and co-workers describe a veritable 'Swiss army knife' of molecular probes that combines pHLIP peptide targeting, protease activity reporters and molecular imaging contrast agents[5]. The resulting multifunctional, protease-responsive imaging sensors for malignancy (PRISM) probe facilitates early-stage diagnosis, longitudinal therapeutic response monitoring and subsequent real-time, non-invasive imaging of metastatic tumours (Fig. 1).

Starting from a platform technology developed by the Bhatia laboratory in which nanoparticles are loaded with peptides that are responsive to cleavage by proteolytic enzymes[6–10], the authors devised a method to attach pHLIP-targeting peptides and a positron emission tomography

(PET) radiotracer[5]. The result was a multifunctional probe that can accumulate within a tumour through the membrane insertion of the pHLIP peptide as a result of reduced pH in the TME. This accumulation enhances processing of the reporter peptide substrates by the tumour-associated protease, matrix metalloproteinase 9. Once cleaved, the resulting peptide fragments carrying a biotin and fluorescein label can be sensitively detected in the urine using a simple sandwich enzyme-linked immunosorbent assay (ELISA) readout. Finally, after positive diagnostic confirmation of the presence of tumours by the peptide reporters, the same probe can be loaded with a ^{64}Cu PET radiotracer to enable real-time imaging of the metastatic lesions. Furthermore, since the readouts are non-invasive, it is possible to carry out serial measurements over time to track changes in disease progression and response to therapy.

Hao and colleagues demonstrate the utility of the PRISM probe using multiple mouse models of metastasis of colorectal cancer. Specifically, they assessed metastasis in the lung and liver as these are locations where early-stage metastatic lesions are often difficult to detect. In addition to demonstrating that PRISM is valuable for diagnosis and imaging, the authors also establish that the probe is effective for tracking therapeutic response to a commonly used chemotherapy agent. Furthermore, since the same probe was used for both diagnosis and imaging, it was possible to correlate the size and density of metastatic tumours with the levels of recovered reporter peptides in urine to confirm the diagnostic value of the probe. The next big challenge for this technology will be demonstrating that it can be translated to the clinic and that this strategy has general utility in diverse types of cancer in humans. Ultimately, the results from these studies suggest that there is a bright future for the PRISM probe technology as a tool for early diagnosis and patient stratification, as well as for precise detection and treatment of disease. ❐

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Competing interests

M.B. is a founder and consultant for Akrotome Imaging Inc. and is a consultant at Vergent Bioscience. Both companies are developing optical contrast agents that target lysosomal cysteine protease for imaging tumours during surgery.