It Takes 30

a blog from the Department of Systems Biology @ Harvard Medical School

- About
- Publications

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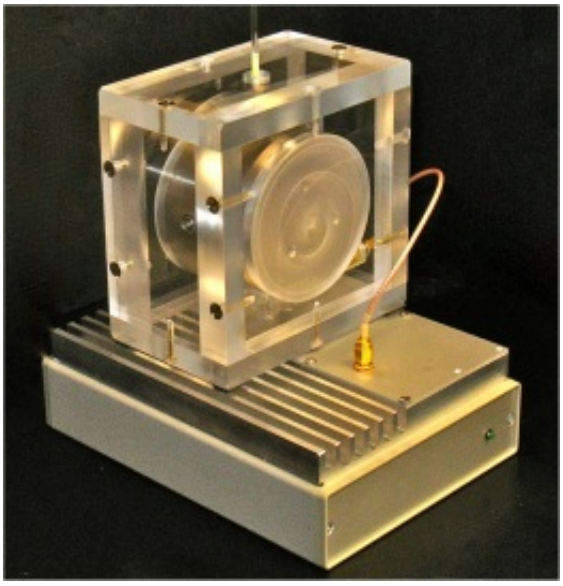
Miniaturizing medicine

You've probably seen NMR machines at some point during your career. They usually have their own room, often with an extra-high ceiling to allow the operator to insert the sample without bumping his or her head. So it may surprise you to know that a miniaturized NMR machine that you can literally hold in the palm of your hand has now been developed by Ralph Weissleder's group. And yes, there's an app for that: the instrument is operated via a smartphone, making it possible to use NMR analysis of clinical samples literally at the bedside (Haun et al. 2011. Micro-NMR for rapid molecular analysis of human tumor samples. *Sci Transl Med* **3**, 71ra16, doi:10.1126/scitranslmed.3002048).



The world's smallest NMR machine, so far

The Weissleder lab and their collaborators have been working on this miniaturized NMR machine and the imaging reagents required to use it for several years now; Ralph brought a prototype to our faculty lunch meeting about a year ago. The goal is to use NMR as a sensitive way of detecting specific markers on very small samples of cells from patients who may or may not have a malignant tumor. The device uses a miniaturized magnet to create the field inducing the magnetic resonance, solenoidal microcoils to detect the signal with high sensitivity, and tiny fluid channels, embedded in polydimethylsiloxane beside the microcoils, into which the sample is injected. The whole device has a footprint of 10cm square. The other part of the magic is in the imaging reagents. These are magnetic nanoparticles that can be linked to a variety of monoclonal antibodies via some clever chemistry that allows the linking to be done in the presence of whole blood (for more details, come to Neal Devaraj's Pizza Talk at 12.30 today). Using this system, it's possible to get a reliable measurement of the level of a specific marker from just ~200 cells. And the measurement is amazingly quick: it takes under an hour.

To understand how important that is, you need to know about the current state of the art. Right now, if you're unfortunate enough to be suspected of having a malignant tumor, the first thing your doctor will want to do is a biopsy. This might involve sticking a needle into the suspicious lump to remove a fragment of tissue, which can then be submitted for histology. If the fragment is large enough, it might also be sent for immunohistochemical analysis to get a better sense of which biomarkers the suspected tumor is expressing. But because current techniques require several cubic mm of tissue, the pathologist working on your sample will have to make careful choices about which markers to look for. Usually your doctor will get a report in about 3 days, but it can take over a week. And usually the result will be "yes, that does (or no it doesn't) look like cancer" — not a characterization of the molecular nature of the tumor. Whatever the politicians who declare "war on cancer" might imagine, cancer is not a single disease, and two cancers that look the same under histology may have very different responses to treatment. So an easy, quick way of getting detailed information about the tumor on a molecular level would be a huge boon to those who are trying to figure out how to treat it.

How many NMR-based tests can you do with an average biopsy? The least invasive and painful type of biopsy you can do is a fine-needle aspirate, basically drawing up a small number of cells into a 22-gauge needle. Haun et al. show that a sample like this contains about 2500 tumor cells, enough for 12 assays using their system. The authors chose 9 important biomarkers to test in a small clinical trial of 70 patients, using 50 patients to work out how best to use the NMR data, and then another 20 as an independent test of their results.

For the first 50 patients, the authors took their biomarker measurements and the eventual clinical diagnosis from conventional testing, and asked which biomarker, or combination of biomarkers, showed the best combination of sensitivity and specificity. No single biomarker did a perfect job of distinguishing the patients with malignant tumors from those whose tumors turned out to be benign; elevated levels of MUC-1 were the best predictor of malignancy, with overexpression of two receptor tyrosine kinases, EGFR and HER2, also doing well. After a bit of mathematical fiddling, Haun et al. found that a weighted combination of four markers, MUC-1, EGFR, HER2 and EpCAM, would give highly (96%) accurate predictions of an eventual diagnosis of malignancy. They then tested this four-marker panel in 20 new patients, and made their own diagnoses. They got every one right, which is amazing. It's especially amazing since they also show that there's considerable variability in the levels of biomarkers you detect from the same tumor if you sample multiple sites. Perhaps using four markers at once gives a more robust result.

This is not just a faster, cheaper method of doing what we can already sort-of do, though. First, it's actually more accurate than the current state of the art. And second, because each analysis uses such a small portion of the sample, you can look at many markers in addition to the four used to detect malignancy. For example, Haun et al. looked at the cell cycle progression marker Ki-67, which gives you a measure of how fast the tumor cells are dividing. They found that there was a significant difference between the levels of

Ki-67 in cells from patients who were showing a good response to their treatment and those from patients who were responding poorly. So perhaps Ki-67 could be used as an early marker of responsiveness. Characterizing the immune cells in the sample as well as the tumor cells may also turn out to be important. And third, of course, the instrument also has the coolness factor of running from a smartphone, which has led some to compare it to the medical devices available on the future voyages of the *USS Enterprise*. Maybe it's not quite that magical… but it's an amazing step forward towards being able to look in detail at what's actually happening in a patient's body.

Haun JB, Castro CM, Wang R, Peterson VM, Marinelli BS, Lee H, & Weissleder R (2011). Micro-NMR for Rapid Molecular Analysis of Human Tumor Samples. *Science translational medicine, 3* (71) PMID: 21346169

Imaging, Systems pharmacology

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