



Talking 'omics

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"I remember seeing an elaborate and complicated washing machine for automobiles that did a beautiful job of washing them. But it could do only that, and everything else that got into its clutches was treated as if it were an automobile to be washed. I suppose it is tempting, if the only tool you have is a hammer, to treat everything as if it were a nail."

Abraham H. Maslow (1966). *The Psychology of Science*. p. 15.

The philosophy and psychology that determines our interests and what we do on a daily basis is fascinating, to me at least. As a general (non-interventional) cardiologist with an interest in acute cardiac care I enjoy teasing my interventional colleagues by accusing them of one-dimensional management and belittling their skills with the phrase "to a man with a hammer everything looks like a nail." However, to confine such criticism to the ocular-stenotic reflex is itself belittling. As Wikipedia attests, the concept of distorting one's view towards a nail, if holding a hammer, is known as the "Law of the instrument." The concept is delightfully embodied by the French transmutation of "*formation professionnelle*" to "*déformation professionnelle*." Although perhaps a little unfair, I believe a scientific hypothesis, especially when much has already been invested, can also act like a hammer. You may ask what this has to do with the current issue of our journal.

This issue is devoted to the "omic" discovery technologies. Inherently these technologies do not rely on a hypothesis and therefore provide an unbiased report of variations in gene sequence (genomics), RNA abundance (transcriptomics), protein abundance or modification (proteomics) or metabolite concentration (metabolomics) that are associated with a particular disease (phenotype). As a result, endeavors using these techniques are often likened to "fishing trips" since it is unknown at the start of the journey what will be caught, if anything. This criticism is becoming less valid as sophisticated bioinformatic approaches are used to analyze, organize and visualize the huge amount of data these techniques generate. To extend the fishing trip analogy, increasingly, modern bioinformatic approaches combine with improved machinery and computing power to effectively trawl through the data and capture a more complete shoal rather than an individual fish. Thus, by their nature the 'omic techniques bear little, if any, resemblance to the man with the hammer.

Nonetheless, it could be argued by confining an investigation of a particular disease to one 'omic technology, investigators are in effect using a hammer. This is exactly the point made in the Basic Article about 'omic technologies by Manuel Mayr et al. Using cardiac fibrosis as the example, it is clear the proteome is determined by the transcriptome. However, this relationship need not be the simple linear relationship between mRNA transcript and the protein it encodes. Rather some RNA species can have more wide-ranging effects on multiple mRNAs and therefore proteins, providing an introduction into the exciting and rapidly evolving world of microRNAs. In the past, combining genomics and transcriptomics has enabled novel insights into gene regulation [1]. What Manuel Mayr is proposing is a wider extension of such

technologies to embrace the spectrum from genetic code to metabolic substrate. A generic term often used for such integration of unbiased information at multiple levels is “systems biology.”

The topic of systems biology is further elaborated in the Main Clinical Article by Grainger et al. Here the main focus is on metabolomics, the measurement of small molecules that are products of metabolism. As Grainger points out the advantage of this approach is that it incorporates the influence of environment. In contrast, genetic information is fixed at conception (meiosis). While this is probably true for most diseases relevant to the cardiovascular system, it is not true of diseases where clonal proliferation of cells is important. A nice example of how metabolomics can provide information not directly dependent on genotype is illustrated by the recent high-profile studies on vascular risk prediction. These studies are nicely summarized by Grainger and have concluded that a major proportion of vascular risk is both indicated and determined by circulating choline metabolites that are produced by the bacteria we carry in our colons.

Thankfully, the metabolic imaging article brings us back to the heart! Eykyn et al. provide an introduction to an extraordinarily powerful MRI technique that allows visualization of the fate of a single atom in a cardiac substrate. The technique of dynamic nuclear polarization uses science fiction-like quantum physics to line up spins on asymmetric stable isotopes, in most cases carbon-13. In the case illustrated by Eykyn pyruvate is labeled with ^{13}C on its first carbon. The spin of this atom is then aligned/polarized at absolute zero before rapid warming and injection in the circulation. The fate of ^{13}C can then be tracked by its chemical shift according to whether it remains in pyruvate, or the pyruvate flows through competing metabolic pathways to convert its first carbon atom to CO_2 , HCO_3^- , lactate or alanine. The only caveat is that once the pyruvate has been warmed, spin alignment/polarization decays with a half-time of 30s! As is apparent from the article, experiments of this type must be as immensely expensive as they are powerful.

For this issue of *Heart and Metabolism*, we have veered from our usual New Therapeutic Approaches. Instead we have focused on the topic of personalized medicine and how cheap sequencing can provide genetic information that informs the therapeutic approach. Luisa Mestroni provides an extremely thorough review that ties together threads of information from varied cardiac therapies where response is determined by genotype. This article provides a glimpse of the cardiologist of the future where a DNA sequencing machine accompanies the ECG machine, to provide an index of cardiac repolarization and the arrhythmia risk of medication.

Finally, the Case Report and Hot Topics focus on the measurement and prevention of myocardial ischemic injury. At the end of this exciting issue they bring us back down to earth. We have amazingly sensitive ways to measure myocardial infarction. Unfortunately, despite enormous effort and expense, we have not found all the ways to totally control it. Perhaps those hammer-wielding interventional cardiologists found the right nail after all? •

Reference

1. Heinig M, Petretto E, Wallace C, Bottolo L, Rotival M, Lu H, Li Y, Sarwar R, Langley SR, Bauerfeind A, Hummel O, Lee YA, Paskas S, Rintisch C, Saar K, Cooper J, Buchan R, Gray EE, Cyster JG; Cardiogenics Consortium, Erdmann J, Hengstenberg C, Maouche S, Ouwehand WH, Rice CM, Samani NJ, Schunkert H, Goodall AH, Schulz H, Roeder HG, Vingron M, Blankenberg S, Münzel T, Zeller T, Szymczak S, Ziegler A, Tiret L, Smyth DJ, Pravenec M, Aitman TJ, Cambien F, Clayton D, Todd JA, Hubner N, Cook SA (2010) A trans-acting locus regulates an anti-viral expression network and type 1 diabetes risk. *Nature* 467(7314):460–464