

THIS WEEK



EDITORIALS

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Inside knowledge

The second phase of the Human Microbiome Project has provided insights into inflammatory bowel disease, type 2 diabetes and premature birth. Now, the third phase must be mapped out.

Twenty years ago, the human microbiome — or the community of microorganisms living in the body — was a fledgling field. Now, it is a flourishing area of research that integrates the basic and clinical sciences, and continues to attract large sums of public and private investment across the globe. One of the first large-scale initiatives was the US National Institutes of Health (NIH)-funded 10-year Human Microbiome Project (HMP), launched in 2007. One of its biggest initial revelations was that the taxonomic composition of the microbiota in the human body was not a reliable predictor of host phenotype, such as disease susceptibility. This was the impetus for a more comprehensive analysis of both the microbiome and the host, culminating in the second phase, the integrative HMP (iHMP). The key results of this project are published this week in *Nature* and *Nature Medicine*.

One of the *Nature* studies examines the gut microbiome of people with inflammatory bowel disease and finds that community composition and immune responses are significantly less stable in individuals with this disease (see page 655). In another study, the authors analysed human gut and nasal microbiomes during the onset of type 2 diabetes and show that microbial and host profiling can together predict insulin sensitivity status, despite high microbiome variability between individuals (see page 663). The third study found that in pregnant women, vaginal microbiome profiles before 24 weeks' gestation provide a marker for risk of premature birth, particularly among women of African ancestry (J. M. Fettweis *et al.* *Nature Med.* <https://doi.org/10.1038/s41591-019-0450-2>; 2019).

A major strength of all three studies is their unprecedented depth and breadth of molecular data for both the host and the microbiota. Another is their longitudinal design, which provides important insights into how host–microbiota interactions change over time.

So, what lies ahead now that the second phase of this major project has come to an end? Many questions about the basic biology of the microbiota remain, including what drives its variation over time and between populations and geographic regions. Ultimately, the goal is to translate such findings into clinical interventions — a monumental challenge. This will require close multidisciplinary collaboration. For example, the microbiology community on its own is unlikely to identify the animal models that are most appropriate for investigating a particular medical condition, or to establish the minimum criteria for substantiating claims of causality.

Multidisciplinary efforts require time and sustained funding to foster innovative ideas and drive translational research. A field this big and mature would benefit from a central agency or a dedicated institute to foster the necessary multidisciplinary collaborations and to focus on standardization, including data sharing and best practices, as well as on the ethical, regulatory and societal implications of such studies. As Lita Proctor, former HMP coordinator at the US National Human Genome Research Institute, discusses on page 623, there are lessons to be learnt from other disciplines such as ocean sciences.

To build on the achievements of the microbiome community so far, strong leadership and coordination are a priority. There are encouraging signs that the field is moving in this direction. ■

In from the cold

A Google-funded project to reproduce claims of bench-top nuclear fusion kindles debate.

Thirty years ago, claims of 'cold fusion' hit the headlines, promising a solution to the apparently impossible dream of producing cheap and clean energy using little more than standard bench-top apparatus. From the outset, it sounded too good to be true. Fusion of atomic nuclei is typically associated with high-energy astrophysical environments (the Sun, for example). So when researchers at the University of Utah in Salt Lake City asserted in early 1989 that they had induced the process by passing an electric current through a simple electrochemical cell, it drew scepticism straight away. The phenomenon — even if real — seemed ephemeral and had little to no theoretical basis. Many groups failed to repeat the findings. The episode is now largely remembered as a case study in confirmation bias (see page 601). Discussions of the phenomenon are relegated to the fringes of mainstream scientific discourse, and for years it has received little serious attention.

Until 2015, that is, when Google convened and funded a group of around 30 researchers spanning several laboratories to take another look (see page 611). After all, absence of evidence is not the same as evidence of absence. Society's need for cheaper and cleaner sources of energy is more pressing than ever, and, if cold fusion were possible, it could be a disruptive technology with a world-changing pay-off.

The goals of the Google team were simple to state, but challenging to execute: to develop a series of rigorous experiments and reproducible protocols that would tightly constrain the conditions under which cold fusion can be realized; and, if the team could detect the phenomenon, to develop a definitive reference experiment that would benchmark it for the wider academic community to scrutinize and verify. The programme is described for the first time in a Perspective, a technical opinion piece (C. P. Berlinguette *et al.* *Nature* <https://doi.org/10.1038/s41586-019-1256-6>; 2019).

The team found no evidence whatsoever of cold fusion.

Is that the final nail in the cold-fusion coffin? Not quite. The group was unable to attain the material conditions speculated to be most conducive to cold fusion. Indeed, it seems extremely difficult to do so using current experimental set-ups — although the team hasn't excluded such a possibility. So the fusion trail, although cooling, is not

yet cold, leaving a few straws for optimists to clutch on to.

The question now is whether it is even worth continuing this research. Here, the message is more nuanced. The project has produced materials, tools and insights — such as calorimeters that operate reliably under extreme conditions, and techniques for producing and characterizing highly hydrided metals — that could benefit other areas of energy and fusion research. But whether the spin-off benefits alone justify continued efforts and investment in pursuit of a probable pipe dream is another matter. Opinions are split.

So what do we take home from a multi-year failed experiment? First, that the programme has been conducted with rigour and attention to detail — we can have confidence in the results. Second, although the work provides no support for fringe groups that continue to insist that cold fusion exists, it does bring this research area back into the light of harsh scientific scrutiny. And, by doing so, the project might help responsible research in this general area to become less taboo, even if the chances of achieving cold fusion still look extremely remote. ■

Beyond retraction

Retracting a manuscript can be an opportunity to revisit the topic afresh.

Readers of this week's *Nature* might well have a justified feeling of déjà vu. In 2017, we published a modelling paper by Hamish Pritchard entitled 'Asia's glaciers are a regionally important buffer against drought', and today we publish a remarkably similar-sounding manuscript by the same author (H. D. Pritchard *Nature* 569, 649–654; 2019). *Nature* is effectively republishing a retracted paper. Why?

Shortly after the original publication, sharp-eyed readers noticed a major error in the incorporation and interpretation of a previously published estimate of glacial mass imbalance. An Editorial Expression of Concern (*Nature* 550, 548; 2017) followed, but because the error affected several aspects of the work, Pritchard retracted the paper, at our suggestion. In doing so, he became free to go back to the drawing board and do his modelling afresh.

Because, editorially, we continued to be interested in the topic, we were open to resubmission of this work, with the caveat that its significance and relevance to *Nature*'s readership would be re-evaluated at that time.

The original paper found that glaciers in the high mountains of Asia provided enough water to meet the basic needs of 136 million people; the republished paper is consistent with these results, but includes a range of estimates of those affected that has an upper limit of 280 million people. After extensive review by the referees, all of whom were familiar with the earlier issues surrounding the work, the revised paper is now published.

Such a case — in which a paper's conclusions become even more compelling after retraction and revision — is rare. The process and outcome, however, highlight the range of reasons for retraction. At one extreme lies clear fraud. Somewhere along the continuum are honest mistakes. At the other extreme is the reality of modern research, in which a complex mix of inputs, models and analysis might yield errors for which a quick correction is not sufficient. Today's unprecedented (for *Nature*) case teaches us to look beyond the 'retraction' label, and to keep an open mind lest we erase significant new discoveries. ■

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