excluded from most trials of hepatocellular carcinoma for this reason.

In addition to the well-known prognostic indicators based on tumour burden, liver function, and presence of symptoms,[6] other evolutionary parameters that appear during follow-up should be considered in clinical trials for hepatocellular carcinoma. In that regard, progression pattern of the tumour during sorafenib treatment has been shown to be relevant. We recently showed that progression due to the development of a new extrahepatic focus or vascular invasion has the greatest effect on post-progression survival,[7] a finding that has been externally validated.[8] Further, some specific adverse events, such as early dermatological reactions, have been identified as predictors of improved survival and slower tumour progression during sorafenib treatment.[9] Therefore, trials in the second-line setting should consider these events to avoid risk of bias. Finally, if targeted therapy is meant to act on specific molecules or pathways it would be reasonable to select patients based on the identification of the molecular pathway to be modulated. This is the case in the phase 3 study assessing tivantinib as a second-line treatment (NCT01755767), in which patients can be included only if their hepatocellular carcinoma shows c-MET positivity by immunostaining; this design is based on the results of a randomised phase 2 study.[10] Disappointingly, although this approach is appealing, hepatocellular carcinomas present with substantial heterogeneity within the same nodule, across nodules, and during tumour progression, making one biopsy sample at a determined timepoint highly unlikely to provide an accurate tumour profile.

Major efforts should be made to advance our knowledge regarding the molecular mechanisms of cancer initiation and progression. These discoveries will be followed by further improvements in treatment options that would increase survival in advanced hepatocellular carcinoma. In conclusion, despite the negative result, ramucirumab has shown some signals of efficacy that deserve further evaluation.

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The erosion of research integrity: the need for culture change

During the past several decades, we have witnessed unprecedented advances in technology that have led to substantial improvements in the lives of patients with cancer. The ability to target driver mutations in tumours and the use of immune checkpoint inhibitors are two examples of great success in translational research. However, far more failures than successes occur in drug development: only about 5–15% of cancer drugs that undergo clinical development are ever approved by regulatory agencies.[1,2]

The success of drug development depends on robust and reproducible preclinical studies. Reports suggest that a high percentage of preclinical studies cannot be reliably reproduced.[3,4] Issues with data reproducibility have been highlighted by investigators in industry who are obligated to confirm studies done in academic

laboratories before initiation of a long and costly drug development programme. Causes for irreproducibility fit within a spectrum. On the benign side of the spectrum are issues with sloppiness, such as cell line contamination or inappropriate statistical analysis; at the other extreme is data falsification or even fabrication.

Research misconduct is defined by the US Office of Research Integrity as "fabrication, falsification, or plagiarism in proposing, performing or reviewing research, or in reporting research results". In oncology, our primary goal is to undertake research that will improve the lives of patients. With so much at stake, why would anyone commit research misconduct and mislead the cancer community? Investigators experience tremendous academic pressures. Funding is scarce, and even if an investigator is funded, they are unlikely to receive the full amount requested. The old adage of publish or perish is stronger than ever, and includes an overemphasis on publication in high-impact journals. The prestige associated with publication in high-impact journals can make an investigator a scientific celebrity. In a survey at my institute (University of Texas MD Anderson Cancer Center), and repeated at an American Association for Cancer Research meeting, roughly half of participants are aware of laboratories in which one cannot graduate without publication in a high-impact journal.[5] Nevertheless, publications with important scientific or clinical results are frequently not published in the highest impact journals. Seminal publications such as the initial description of the Kreb's cycle and the first reports of polymerase chain reaction were rejected by journals with the highest impact factors.[6]

For the **definition of research misconduct** see https://ori.hhs.gov/definition-misconduct

The accolades and rewards for publication in the highest impact journals result in perverse academic incentives.[7] This "impact factor mania", as described by Fang and Casadevall,[8] "is causing profound distortions in the way science is done that are deleterious to the overall scientific enterprise". In fact, these investigators have published studies showing that the higher the impact factor, the higher the retraction index.[9] Of course this retraction index can be due to many causes including increased scrutiny, but highlights the fact that work published in a journal with a high impact factor does not necessarily have high impact. A recent Nobel Prize winner stated that

Panel:* Suggested approaches to improve data reproducibility in preclinical studies

Publication requirements:

- Appropriate statistical analysis determined a priori
- Use of REMARK biomarker criteria
- Expanded methods sections
- Expedited data deposition to public databases
- Cell line identification confirmation
- Validation of reagents including antibody specificity
- Blinded assessments by at least two independent observers
- Pre-established inclusion and exclusion criteria
- Sign off by all coauthors that all relevant data, both positive and negative, have been submitted either in the manuscript or online
- Expanded materials and methods sections online
- Change the emphasis of the NIH biosketch (abbreviated CV) to highlight actual contributions to science and medicine
- Assessment of faculty candidates should include more than the number of publications in high-impact journals
- Sharing of unique resources (eg, cell lines and mouse models) with a standard single page material transfer agreement
- Journals should allow and encourage publication of negative results
- Journals should allow so-called imperfect data—biology is not all or none
- Mechanisms for online feedback on studies (eg, PubPeer, PubMed Commons) and allow commentary without the need for a subscription
- Reviewers of manuscripts should focus on the most relevant issues, and limit requests for additional studies that are not necessary for the underlying theme of the study
- Appropriately severe punishment for investigators found guilty of research misconduct (eg, ban such scientists from obtaining government funding for research)
- Provide academic security for people who report unethical behavior (so-called whistle blowers)
- The principal investigator should be responsible for keeping track of data in real time, so that deviations from the so-called perfect story are noted early; the principal investigator should be held responsible for the integrity of all data, and for inclusion of all relevant studies, whether they are negative or positive
- Journals should welcome publications validating or refuting previous publications
- Published articles should not be convoluted and should have a clear message; dense articles are difficult to review, probably leading to suboptimal reviews and requests for irrelevant experiments
- Allow submission of negative data in response to primary reviews of manuscripts; the temptation to selectively report positive data is probably highest when a paper is under revision

*Some have already been implemented.

he will no longer submit papers to high-impact journals because they "represent a tyranny that must be broken".[10] Of course, once you have been awarded the Nobel Prize, your tenure at a university is likely to be secure.

The challenges and academic pressures facing recent PhD graduates has probably contributed to an all-time low in the percentage of young investigators choosing a career in academia. Surveys show that only 14–18% of PhD graduates with training in biology and life sciences pursue an academic career.[11] Alternatives such as positions in industry, administration, or investment banking are less stressful and financially more secure than trying to establish and maintain an academic laboratory for the duration of a career. The sustainability of innovative cancer research is hindered by the present academic environment.

For the **surveys** see http://www.nsf.gov/statistics/sestat/

How do we fix the problem of data reproducibility? (panel). Let's go back to the spectrum and sloppiness. To the credit of several journals, some now have research checklists to complete for submission of a manuscript.[12] Additionally, publication of negative studies is encouraged by several publishing groups. However, more work needs to be done towards eradication of sloppy research. We should mandate cell line authentication, and statisticians should be involved early in design, interpretation, and review of experiments. At the other end of the spectrum, research misconduct is more complex; to address this issue, we need a complete culture change. We should avoid "impact factor mania" and sensationalised reporting practices and publicity. We should recognise that important contributions can be made without publication in high-impact journals. We should also appreciate the many contributions of faculty members and recognise and reward faculty for mentoring, teaching, counseling, organisation, and for being great role models.

The National Institutes of Health (NIH) should be credited for taking steps to de-emphasise "impact factor mania". The NIH biosketch (abbreviated CV) has been reformatted to stress contributions to science, and not simply allow for a listing of publications in high-impact journals. However, the US Government can do more. The Office of Research Integrity is responsible for oversight of the integrity of research supported, even in part, by the US Public Health Service. Even when investigators are found guilty of misconduct, penalties are often minimal. A strong reaction from the Office of Research Integrity and similar organisations from other countries would hopefully deter unethical behaviour by those who have deceived the public's trust and support (provided through taxes).

Additionally, we need to encourage publication of negative data. A quote from Albert Einstein graces the entrance to the National Academy of Sciences in Washington DC, USA: "The right to search for the truth also implies a duty; one must not conceal any part of what one has recognized to be true". Negative data can be as important as positive data, and publication of negative data will save investigators countless hours and money. Some journals do not favour publication of negative data for fear of decreasing their impact factor. Thus we inadvertently harm our own culture by allowing selective reporting of only positive data, or by penalising honest investigators who report negative or contradictory results.

It is time for a culture change. We owe our patients with cancer the truth.

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