Editorial

Cancer Research

The Half-Lives of Facts, Paradigm Shifts, and Reproducibility in Cancer Research

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The history of science documents how our perception of the natural world changes over time, and cancer research is no exception, having shifted profoundly as new information opened uncharted paths to empirical truths. Most illustrative of a seismic shift of our world-view is the Copernican revolution in 1543 that displaced the Earth from the center of the Ptolemaic universe to its proper place as one of eight planets that revolve around our sun (1). More recently, in the 1930s, the majority of U.S. doctors smoked cigarettes and anecdotally "prescribed" smoking to relieve stress (1). Against the force of profiteering tobacco companies, cigarette smoking was later unmasked as a major culprit of ill health and cause of cancer.

Thomas Kuhn coined the term "paradigm shift" to describe seismic shifts in concept when new empirical evidence carries us down the road not taken, reshaping our perception of fact (1). Epistemologic paradigm shifts are naturally subject to greater scrutiny, as they shake the foundation of our knowledge and disrupt the prevailing social fabric of science, woven around a deeply held belief. However, many pivotal, paradigm-shifting claims, such as cold fusion, polywater, or disruptive human stem cell technologies, were initially met with great amazement and fanfare, only later disproved as these claims were revealed to be sloppy science or frankly fraudulent. Scientific misconduct, whether falsification (such as manipulation of images) or fabrication (such as using a black marker pen to fabricate suppressed immune rejection of a skin graft on a white mouse) driven by whichever human desires or frailties, is the most serious scientific crime as it undermines public trust and leads costly additional research down dead-end paths. Plagiarism is intellectually dishonest and constitutes misconduct. The astounding claim 10 years ago of the ability to decode the genomic make-up of a patient's cancer and match it with the best chemotherapy was disappointingly founded on scientific misconduct, as concluded by the government's Office of Research Integrity (https://ori.hhs.gov). This misconduct was not just a crime against science, but it could also have caused significant harm to patients enrolled in a clinical study that was based on fabricated falsehood. Scientific integrity is a pivotal, profound responsibility of investigators and authors. The goal of *Cancer Research* (and all AACR journals) is to promote robust, hypothesis-driven science toward building our knowledge of cancer to impact clinical outcomes while actively guarding against scientific misconduct.

Aside from major cases of fraudulent scientific claims, there are ongoing concerns about reproducibility of cancer research at large. Several non–peer-reviewed commentaries claimed that over 50% of cancer research findings could not be replicated. This generated significant concerns and dialog among scientific professional societies and journals, culminating in part in the Reproducibility Project (https://cos.io/rpcb/). The project aims to select key studies in cancer research and to replicate them in consultation with the authors of the original studies. To date, many Reproducibility Project studies have been published and several lessons have been learned. First is the acknowledgement of biological variables, including the technical skills of the investigator and behaviors of model systems, such as cell lines that can morph over time from initial characteristics through passaging and tissue culture conditions. Mouse strains and housing environments and variation in reagents could collectively add noise to the results. Second, the choice of statistical methods to analyze studies is a critically important second lesson for reproducibility. The temptation for "p-hacking" or the biased selection of statistical analysis to reach the magical P value <0.05 must be avoided, particularly because the value of 0.05 is an arbitrary set point for statistical significance (2). The third lesson underscores the importance of system robustness, defined as the ability of a system to reproducibly respond to specific perturbations under different conditions. The more robust the system, the more likely is the reproducibility of the response under different experimental conditions. As such, key claims that shift our understanding of cancer science should be sufficiently robust to yield similar responses in different biological systems and contexts. In this regard, *Cancer Research* seeks to publish studies that utilize multiple cell lines under different conditions and, when relevant, the demonstration that these responses are also seen *in vivo*, particularly in immunocompetent hosts.

Facts, as Samuel Arbesman proposed, have regular, nonrandom half-lives (3). What was once fact is now vestigial in the current body of knowledge, decaying from prominence and popularity over time. In 1926, the Nobel Committee awarded the Physiology or Medicine prize to Johannes Fibiger for "his discovery of the *Spiroptera carcinoma*," a roundworm that purportedly caused cancer, only later to be disproved by definitive experiments illustrating that the roundworm caused metaplasia and not cancer. Remarkably, Irving Langmuir (chemistry Nobel laureate) pointed out in his talk at the General Electric research labs in 1953 on "pathological

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science" as an area of research driven by a collective belief and wishful thinking. One such example involves the purported existence of N-rays, which were elusive figments of imagination culminated from poorly designed experiments later proved to be false (https://www.cs.princeton.edu/~ken/Langmuir/langmuir.htm). "Facts" are displaced by new facts as old hypotheses are falsified by new evidence. As popularized by Karl Popper, the ability to falsify or disprove a hypothesis is a foundational principle for the advancement of science (4). It takes only one incompatible, well-founded scientific observation to disprove a hypothesis or an entire research field. Hence, it is critically important to disprove or falsify your hypothesis as quickly as possible with the best-designed experiment, to efficiently drive the aggregate knowledge of the field toward sustainable facts, and in the case of cancer research, improved clinical outcomes. The examination of an article for rigorous controls is, therefore, a major duty of referees and editors of *Cancer Research*, ensuring that the advancement of our knowledge is on firm technical grounds.

Although we anticipate that some current cancer "facts" will be refined or displaced by paradigm-shifting moments, it is our collective responsibility as investigators, authors, manuscript referees, and editors to ensure that manuscripts submitted to and published by *Cancer Research* are based on rigorous, well-controlled studies that are robust and have the highest probability of being reproducible.

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The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

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