Realities at the leading edge of research

Good practice and proper conduct in research pay off, scientifically and economically

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When the Wright brothers set out to invent a flying machine at the end of the nineteenth century, they knew they were facing quite a challenge. Not only was it a daunting task to accomplish powered flight but also to overcome the ideology, morality and sensibility of their time, when most people believed that human flight was neither possible nor natural. Science fiction author Arthur C. Clarke once commented on such major advances in science technology that "Any sufficiently advanced technology is indistinguishable from magic." Even after they accomplished their first flight, lasting 59 seconds on 17 December 1903, the Wrights still found it hard to convince their fellow countrymen and everyone else around the world of their breakthrough achievement.

But the Wright brothers' success is not only notable for what was achieved—the first powered flight—but it should also be remembered for how it was achieved. First, the Wrights did background research and gathered all available information about flying machines. As they owned a newspaper—*The Evening Item*—they had already seen photographs of German flight pioneer Otto Lillenthal flying a glider in 1895. They also came across photos taken by Alexander Graham Bell of Samuel Pierpont Langley, the third secretary of the Smithsonian Institution, launching an unmanned flying machine over the Potomac River near Washington, DC, USA, in 1896.

Furthermore, and unlike most of their peers, the Wrights believed that the problem of flight could be solved through proper balance and experience—just as learning how to ride a bicycle. These problems,

they assumed, could ultimately be solved only through experimentation and drawing on the experiences of others. On 30 May 1899, Wilbur Wright wrote to the Smithsonian in Washington, DC, to find references on the state of the art in 'heavier-than-air flight' (Tobin, 2003). After critically reading articles suggested by Langley's assistant, Wilbur Wright later wrote: "Those who tried to study the science of aerodynamics knew not what to believe. Things which seemed reasonable were often found to be untrue, and things which seemed unreasonable were sometimes true" (Carson, 2003). Last but not least, the brothers meticulously documented their experiments using both written notes and photography (Fig 1). In this way they were able to return to earlier attempts and also to answer any questions about the authenticity of their experiments. In hindsight, the Wrights' procedures are a perfect model for how science should be done today.

More than 100 years after the Wrights' success, many researchers in all fields of science still perform their work following the same procedures the Wrights used: critically review available knowledge on the art, perform carefully planned experiments and document the results. If anything, such care has become even more important in the past century. Scientific research today is a complex and increasingly interdependent global network that requires researchers to rely on the published reports of others, many of which are of varying quality. In many areas, such as medical research or information technology, both academic and commercial researchers collaborate to

turn discoveries into new products and bring them to market. Few universities commercialize their own research, although most have technology transfer offices and many have established incubators for new business. Some medical centres are even moving towards conducting early-stage clinical trials on their own. Yet interconnectedness between academia and industry will remain a fundamental requirement for the development of new consumer products, which puts even more emphasis on mutual trust and proper conduct in research.

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In fact, all researchers, even those who are self-funded, have an ethical duty to conduct and document their research properly. US researchers who receive government funding also have a legal requirement under the Bayh–Dole Act to protect their intellectual property to allow the commercialization of their results (Bayh–Dole Act, 1980). Privately funded research, such as that conducted at the Bell Laboratories and the Cetus Corporation, have also led to Nobel Prize-winning research and important products: the integrated circuit and the polymerase chain reaction (PCR). Consequently, it does not matter whether it is academic, government or privately funded research or investments, or whether it takes place in the USA, Europe or Japan. What matters is that scientists adhere to world-class standards

Fig 1 | Orville Wright and Dan Tate launching the Wright 1902 glider. Pilot, Wilbur Wright; photo, George Spratt. Courtesy of Special Collections Archives, Wright State University (Dayton, OH, USA).

in conducting and documenting their work. The public, governments and private investors have a right to expect such proper conduct from scientists. Otherwise, how do they know that the vision in which they are investing is likely to come true?

Recent cases at Enron (Houston, TX, USA), ImClone (New York, NY, USA), Elan Pharmaceuticals (Dublin, Ireland), Texas Tech University (Lubbock, TX, USA) and many others demonstrated that investors must indeed be careful about where they put their money, even when they invest in well-established enterprises. In some of these organizations people allegedly misrepresented or even lied about their work, their results and the implications. Some have pleaded guilty or have been found guilty in court. These cases have all had a negative impact on public confidence in the validity of research findings and the ethics of those who receive public and private investments (Berry, 2003). Similar high standards must apply when searching for private funds to develop research findings into commercial products. Everyone should now realize that when a researcher is looking for external sources to invest in his or her modern 'flying-machine', investors will demand

competent documentation of the discoveries, how they were conducted and any potential conflicts of interest.

Of course, breakthrough advances do not come without controversies. The threat of future litigation is yet another reason to ensure that research is conducted and documented properly from the very beginning. For instance, the owners of the telephone, the aeroplane and PCR all endured extended litigation to protect patent rights on their inventions. Alexander Graham Bell was eventually able to claim his patent right on the telephone over similar patents by Elisha Gray and Philipp Reis because he provided superior documentation over his competitors (Fig 2). The bound laboratory notebooks of Bell and assistant Thomas Watson are now available through the US Library of Congress (Bell, 1876).

So how can investors, both private and public, identify true excellence in research and researchers and make decisions on grants or business investments? How do they avoid investing in the programmes of ethically challenged scientists or hucksters—super-salespeople—who focus on excitement and emotion

over details? How do they deal with researchers who feign indignation should anyone have the temerity to question their findings? It is not uncommon for some scientists to attack the questioner or avoid questions when someone gets too inquisitive. The heated exchanges that often occur in scientific circles make it even harder to separate truth from fiction.

A recent case at Johns Hopkins University in Baltimore, MD, USA, illustrates that such thinking is still present. In 2002, George A. Ricaurte and co-workers published results indicating that the abuse of ecstasy leads to reduced dopamine levels and could therefore cause Parkinson's disease (Ricaurte *et al*, 2002). However, the authors had to retract their findings from both *Science* and the *European Journal of Pharmacology* when it became clear that they could not verify their results and that they had inadvertently used methamphetamine instead of ecstasy in the trials. When questioned by the media about this mix-up, Ricaurte responded: "We're scientists, not chemists. ... We get hundreds of chemicals here—It is not customary to check them" (Revill, 2003). The case demonstrates that even world-renowned researchers must be vigilant

Fig 2 | Diagrams of Alexander Graham Bell's instrument for the improvement of telegraphic transmission, March 1876. © Bettman/Corbis.

about properly verifying and documenting their work. Indeed, all researchers should be ready and willing to produce data in such a way that their claims can be backed up by verifiable results. The only sensible way to deal with risks on the cutting edge of science is to 'trust but verify'.

Researchers who want their work to benefit society must also seek intellectual property (IP) protection. Not only does this give an additional stamp of quality to their findings but it is also a prerequisite for the further development of medical products that can be mass-produced and brought to

market. Those who believe that all research results should be freely available to the public may not be considering the realities of bringing innovations to market. Research advances without strong IP protection have little hope of attracting investors or of quickly reaching the market as treatments for patients. Robin Warren and Barry Marshall's discovery that *Helicobacter pylori* is a leading cause of stomach ulcers initially suffered from this predicament. Although the researchers made this conclusion in the 1980s, they neglected to patent their findings. Without patent protection, drug companies were hesitant to capitalize on their finding, and instead continued to market profitable but less effective remedies, according to a recent interview with Mayo Clinic officials. In fact, it took many years for antibiotics to become an accepted treatment for stomach ulcers (Landers, 2003).

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Of course, many researchers are also striving for other forms of recognition, such as funding, publications, tenure, promotion, editorships, review-board seats, patents, power and prestige. To accomplish any of these goals, ethical researchers must comply with private-sector standards—sponsorship, authorship and accountability standards—as well as government regulations. In the USA, many agencies such as the Environmental Protection Agency, the Food and Drug Administration (FDA), the Federal Trade Commission, the National Institutes of Health (NIH) and the Securities and Exchange Commission (SEC) regulate the research, development and marketing of drugs and biologics. Throughout the world, other countries have similar regulatory agencies, for instance the European Agency for the Evaluation of Medicinal Products (EMA), and the Therapeutic Goods Administration in Australia. Because regulations change regularly, it is important for researchers and research organizations to monitor such developments at relevant domestic and international agencies. For instance, the SEC and the FDA recently

announced new measures to protect investors from misleading statements about the status of experimental drugs under review by the FDA (US Securities and Exchange Commission, 2004).

We would like to highlight the importance of conflicts of interest (COI) in research and publication and the proper documentation of scientific findings for the quality and acceptance of scientific research. Of course, many other concerns must be considered, including: the tracking and reporting of adverse events; advertising and promotion; animal welfare; clinical trial design; corporate governance; data selection; drug labelling; good manufacturing practices; human research participant protections; privacy and confidentiality of health information; and regulatory filings (Watkins & Platt, 2003).

The goal of all COI policies is to ensure that any conflicts are disclosed and managed in a way that maintains public

confidence in research findings. It is important to remember that sometimes even the perception of COI can harm this confidence. However, the goal is not to eliminate all conflicts. It is beneficial and necessary for researchers to collaborate where appropriate, regardless of their institutional affiliation—corporate, academic or government. But there must be standards for disclosure, and there must be limitations on ties between personal gain and research results as well as review and oversight by disinterested parties (Kennedy, 2004).

The strictest conflict of interest rules are generally enforced at the world's patent and trademark offices and at some governmental agencies, such as the FDA and the NIH. In addition, many organizations have taken a proactive approach and issued more stringent guidelines for their members. The Association of American Universities (AAU), for example, recommends that its 62 member institutions require researchers to disclose all financial interests in their research, including equity, consulting fees

and royalty payments (Association of American Universities, 2001). Unlike the FDA and NIH, there is no threshold level for AAU disclosure.

COI policies for most major institutions are available on the Internet, and can be replicated easily at other organizations (Table 1). What is generally unknown, however, is how many and what type of exceptions to COI rules, if any, exist at each institution. A recent investigation of NIH records by the *Los Angeles Times*, for instance, suggests that the NIH granted COI exceptions to many of its own scientists during the past decade (Willman, 2003).

Many scientific journals and government publications also have standards for disclosure and have tightened these in recent years in response to public concerns about conflicts of interest. Although some prominent world-class scientific journals, such as *Nature* and *Science*, do not require

Table 1 | Selected examples of conflict of interest rules

	Requires disclosure	Exemptions	Additional information
AAU	Yes. All individuals engaged in research should disclose on an annual basis all financial interests related to university research. Financial interest should also be disclosed in studies referred to in oral presentations and written publications.	None	Disclosures include interests related to all studies whether federally funded or not.
EMEA	Employees: yes. Must disclose any direct/indirect financial or other interest in drug industry.	None	Must suppress conflicts to remain employed.
ICMJE	Authors and peer reviewers: yes	None	Editors must not have financial/non-financial interest in papers reviewed.
US FDA	Employees: yes. Non-employee investigators: yes	Employees: 1. No financial arrangement where study outcome may be affected. 2. No proprietary interest in product being tested. 3. No significant interest in the sponsor of the study. Non-employees: 1. Equity investment \$50,000; payments from sponsor \$25,000.	
US NIH	Employees: yes. Non-employee investigators: yes.	Employees: 1. Salary and royalties from applicant institution with recusal. 2. Income from seminars, lectures or teaching engagements. 3. Income from advisory committees or review panels. Non-employees: 1. Equity investment \$10,000; or 5% ownership in a single entity; or salary royalties \$10,000 from a sponsor.	
US PTO	Employees: yes. Non-employee applicants: yes.	Employees: 1. \$25,000 of stock/bond holdings in a single company. 2. Holding only in mutual funds.	

each author of a publication to state his or her individual contribution, other journals already demand greater disclosure. The International Committee of Medical Journal Editors (ICMJE), consisting of 586 member journals including *JAMA*, *The Lancet* and the World Health Organization journals, recommends that authorship credit should be given only when three criteria are met: each author makes substantial contributions to conception, design, data acquisition and/or analysis, helps to draft or revise the article, and is responsible for final publication approval (International Committee of Medical Journal Editors, 2003). We believe that this additional higher standard of disclosure permits a better analysis of the quality and integrity of the report, paper or article.

As with authorship requirements, there are also different standards for reporting potential conflicts of interest. The ICMJE recommends that both authors and peer reviewers should disclose all potential conflicts of interest, financial or otherwise. Decision-making editors must have no personal, professional or financial involvement in any issues that they might judge. Some journals require disclosure of conflicts, but allow financial influences that do not exceed US\$10,000 or 5% ownership in a company with related interests. There are publications that adhere to more rigorous standards of conduct; however, it is not always clear which ones are which. More effort is needed in this area to ensure that the public knows about such conflict of interest policies and supports them.

Aside from these issues in the greater area of scientific funding and publishing, scientists themselves have a responsibility to ensure that their work adheres to stricter standards, particularly when it comes to documenting their experiments and results. Working at the cutting edge of discovery, the Wright brothers understood that they had to record every step on their way to powered flight. Equally, researchers need to know about competing theories and insights developed by others. The US Patent and Trademark Office (PTO), for instance, assigns responsibility to inventors for the complete knowledge of prior art, including all relevant publications on their research topic.

The example of Kary Mullis's discovery of PCR is a warning to those who think that proper documentation is not important. When working at Cetus Corporation, Mullis had an excess of synthetic DNA oligonucleotides on hand at a time when they were so expensive that most molecular biologists could barely afford them (Mullis, 2002). His need to justify this excess inventory pushed him to consider using more than one oligonucleotide per experiment, leading him to discover a method for DNA amplification. This solved a major problem for genomic research and earned Mullis a Nobel Prize. However, Mullis struggled at first to get his research published because most of his peers did not grasp its significance. He was only credited as the sole inventor for PCR after a lawsuit established that he had conducted and documented the earliest DNA amplification experiments at Cetus. Without solid documentation, Mullis, like the Wright brothers, might never have received the credit he deserved.

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Unfortunately, there are examples where scientists did not live up to the Wright brothers' standard. In 2002, Bell Labs investigated its first case of scientific fraud in the 77-year history of the multi-Nobel Prize-winning laboratory. Jan Hendrik Schön, a Bell Labs researcher working on superconductivity, had 25 published papers called into question, including several in *Nature* and *Science*. An independent committee found that his laboratory records were not maintained systematically and that he had deleted virtually all original electronic data files. His most significant experimental results were not witnessed by any co-author or colleague. The investigation committee also found that Schön had committed scientific misconduct in 16 cases without the knowledge of his co-authors (Lucent Technologies, 2002). According to rules of good scientific practice, Schön's raw data should have been backed up and

stored for 10 years, and a colleague should have signed his notebook to state that he or she had read and understood the records (Max Planck Society, 2000). This case clearly reveals the need for scientists to share their data. It also demonstrates that even world-class research institutions are not exempt from dishonest behaviour, and that all stakeholders must be vigilant in documenting and authenticating scientific findings. As Wayne T. Hockmeyer, CEO of MedImmune, a biotech company in Gaithersburg, MD, USA, once said, "If it is not in your notebook, I don't want to hear about it."

As science is predicated on reproducibility, there needs to be clear, concise and complete documentation of the research performed. This documentation should adhere to globally accepted performance standards created by peer organizations and international standards organizations. Beyond the laboratory, we are now in a world of 24-hour news cycles and Internet publishing. This means that the lay press and the public must also be convinced quickly about the validity of scientific findings. To appeal to the public, and particularly to investors, scientists and research organizations should therefore adopt systems that measure and document their compliance with regulations and best-practice performance standards. At a minimum, such a system should clearly document each step taken in the research process and its results and should make sure that every experiment was performed in relation to both government requirements and to recognized best-practice performance standards. If documented properly, such a system can enable those who are using it correctly to move to the front of the line for decisions on funding, patents and publication. Just as importantly, a system of documentation excellence will ensure public confidence in scientific exploration, making it more likely that funds will flow into the discovery of the next 'flying-machine'.

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Careful scientists who document their ideas and experiments are a powerful force in society. Society benefits when scientists show proper diligence. For instance, one of the advances made by the Wrights was their construction and use of a wind tunnel to measure the lift of different wing configurations. This innovation allowed them to construct and test over 200 airfoils in a few months in the same way that PCR allows the amplification of hundreds of different DNA sequences in a few hours. The Wright brothers ultimately received credit for their invention of wing warping, as did Mullis for PCR. Both were immeasurably helped in this regard by their proper documentation of findings.

Both discoveries led to great breakthroughs. In just 100 years, the jet aeroplane has become one of the most complex manufactured machines on Earth, containing over one million parts. Equally, molecular biology would not have advanced to today's levels without PCR. Yet both the Wright brothers and Mullis initially found it difficult to convince their peers and the public about their invention and the implications it would have for society and science. What helped them to get public recognition was the fact that they performed their research according to high-quality standards with proper documentation of every step of the discovery process. Without it, they might have found it even more difficult to convince the world of the importance of their invention. As Arthur C. Clarke once said, "New ideas pass through three periods: It can't be done. It probably can be done, but it's not worth doing. I knew it was a good idea all along!"

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The views expressed herein are those of the authors and do not necessarily reflect the views of Ernst & Young LLP.

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doi:10.1038/sj.embor.7400137