MEDICINE

Life Cycle of Translational Research for Medical Interventions

From the initial discovery of a medical intervention to a highly cited article is a long road, and even this is not the end of the journey.

Despina G. Contopoulos-Ioannidis,[1] George A. Alexiou,[2] Theodore C. Gouvias,[2] John P. A. Ioannidis[2,3,4]*

Despite a major interest in translational research (*1*–*3*), development of new, effective medical interventions is difficult. Of 101 very promising claims of new discoveries with clear clinical potential that were made in major basic science journals between 1979 and 1983, only five resulted in interventions with licensed clinical use by 2003 and only one had extensive clinical use (*4*). Drug discovery faces major challenges (*5*–*8*). Moreover, for several interventions supported by high-profile clinical studies, subsequent evidence from larger and/or better studies contradicts their effectiveness or shows smaller benefits (*9*). The problem seems to be even greater for nonrandomized studies (*9*). Here, we present the results of an empirical evaluation of the life-cycle phases of translational research for selected medical interventions.

We examined key milestones in the life cycle of translational research for all the interventions claimed to be effective in at least one study that received over 1000 citations in the literature in 1990–2004, on the basis of the Web of Science. These are the most-cited papers in the literature of medical interventions (*10*). Because they have received the greatest attention, they provide easily identifiable scientific milestones. Citation counts are a widely accepted coinage of recognition. Of course, several blockbusters may go through an industrial discovery–testing–production process that does not involve any particular highly cited paper in the peer-reviewed literature. In these cases, it is not as clear-cut to isolate one or a few studies that are indisputable milestones in the translational process.

Of 49 articles with >1000 citations, we excluded articles where the intervention was ineffective, as well as those assessing management strategies rather than specific interventions, and we selected only the earliest article whenever two or more highly cited studies with >1000 citations had been published on the same intervention and indication. Thirty-two interventions for specific indications were thus evaluated, and we could place the milestone of when their first highly cited clinical study was published showing effectiveness (tables S1 and S2). We considered this an important time point in the translational process and estimated how long a time ("translation lag") it had taken from the initial discovery of each intervention to reach that point. Highly cited status does not necessarily mean that these interventions continue to be considered as effective as proposed in the original highly cited papers. By the end of 2006, the effectiveness of 19 interventions had been replicated by other subsequent studies (n = 14) or had remained unchallenged (n = 5), whereas the other 13 had been either contradicted (n = 5) or found to have had initially stronger effects (n = 8) when larger or better controlled subsequent studies were performed (table S1).

Translation Lag

To place each discovery in time, we identified the year when the earliest journal publication on preparation, isolation, or synthesis appeared or the earliest patent was awarded (whichever occurred first). Overall, the median translation lag was 24 years (interquartile range, 14 to 44 years) between first description and earliest highly cited article (see the chart, page 1299). This was longer on average (median 44 versus 17 years) for those interventions that were fully or partially "refuted" (contradicted or having initially stronger effects) than for nonrefuted ones (replicated or remaining unchallenged) (P = 0.004).

In a secondary analysis, we defined the time of discovery as the first description (publication or awarded patent) of any agent in the wider intervention class (those with similar characteristics and mode of action). Early translational work may be performed with different agents in the same class compared with those that eventually get translated into postulated high-profile clinical benefits. Analyses using information on the wider class of agents showed even longer translation lag, with median of 27 (interquartile range, 21 to 50) years and similar prolongations of the translation lag for refuted interventions.

Among the 18 nonrefuted interventions that had a highly cited randomized trial to support them, the median translation lag was 16.5 years (range 4 to 50 years) in the main analysis [22 years (range 6 to 50 years) considering the wider class]. The fastest successful translation occurred for indinavir (as part of triple antiretroviral therapy) and abciximab, both of which took only 4 years from their patenting to the publication of a highly cited randomized trial. Both of these fast successes involved multidisciplinary work spanning molecular to clinical research on protease inhibitors and integrins, respectively.

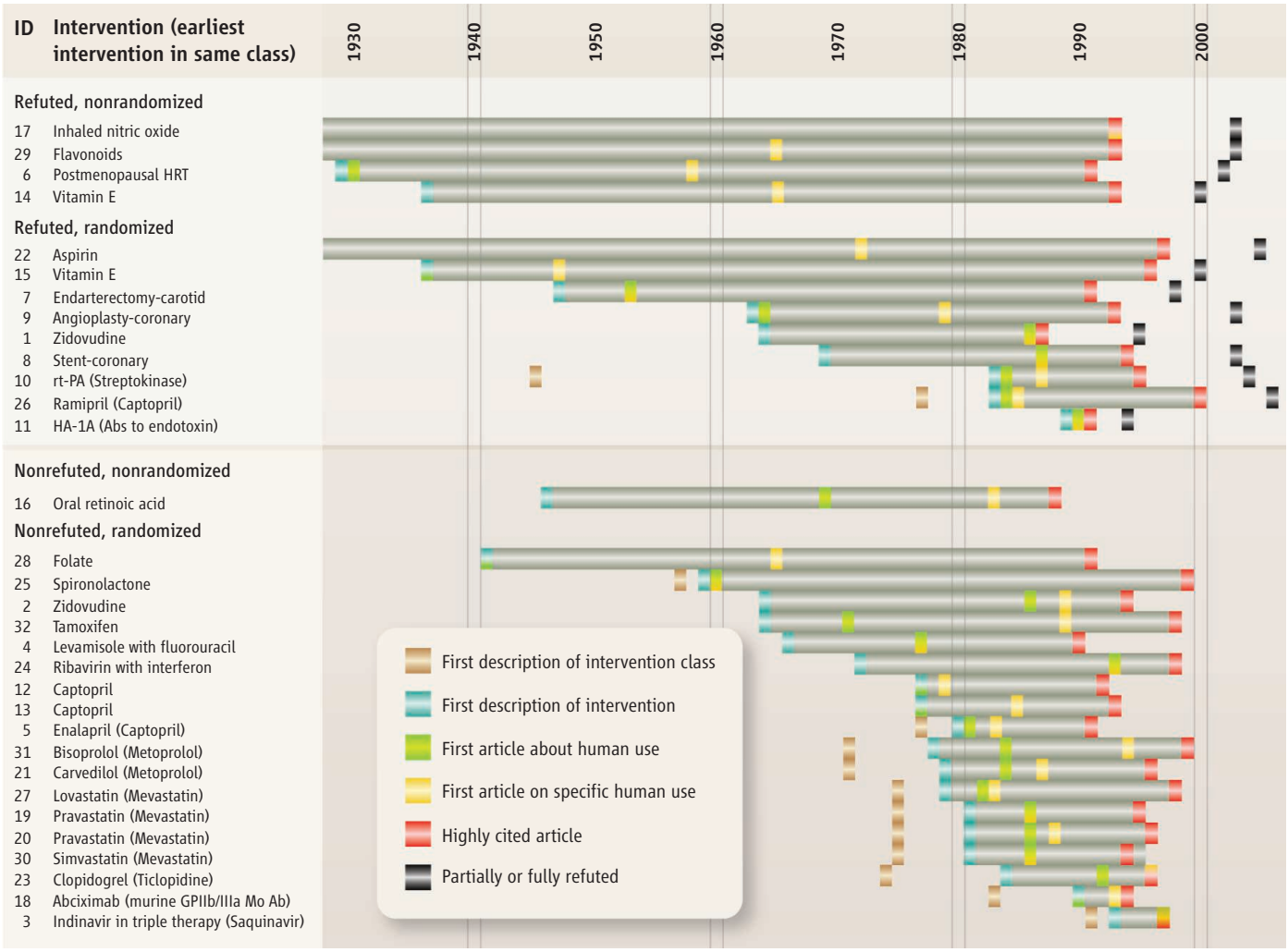
We also tried to identify the first published article that described the use of each intervention in humans and the first published article that described the use of each intervention in humans for the specific intervention described eventually in the highly cited study (*11*). There was a very large variability in the timing of the first human study and of the first human study for the specific indication (see the chart, page 1299). The range for the time from first discovery to first human use was 0 to 28 years. The range for the time from first discovery to first specific human use was 0 to 221 years.

We observed that most highly cited claims that were eventually refuted had a very slow translation history preceding them [e.g., flavonoids, vitamin E, and estrogens were already available for many decades before observational (nonrandomized) studies claimed implausibly large survival benefits in the 1990s]. We conclude that claims for large benefits from old interventions require extra caution as they are likely to be exaggerated. Given the considerable refutation rate of even the most highly cited interventions, extensive replication and confirmation of proposed treatment benefits are indicated. New drug discovery is probably essential for common diseases where the existing drug armamentarium has been already extensively screened. Conversely, for uncommon and neglected diseases, the existing drug options may remain largely untested, and old drugs may find interesting new uses (*12*–*14*).

[1]Department of Pediatrics, University of Ioannina School of Medicine, Ioannina, 45110, Greece, and Department of Pediatrics, George Washington University School of Medicine and Health Sciences, Washington, DC 20037, USA. [2]Clinical Trials and Evidence-Based Medicine Unit, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, 45110, Greece. [3]Department of Medicine, Tufts Medical Center, and Institute for Clinical Research and Health Policy Studies, Tufts University School of Medicine, Boston, MA 02111, USA. [4]Biomedical Research Institute, Foundation for Research and Technology–Hellas, Ioannina 45110, Greece.

*Author for correspondence (at the address in footnote 2). E-mail: jioannid@cc.uoi.gr; john.pa.ioannidis@gmail.com

Published by AAAS



Milestones for the 32 interventions. First description of agent in wider class, tan box (when the agent used in the highly cited article is not the same as the first described in its class); first description, cyan box; first human-use article, green box; first specific–human use article, yellow box; earliest highly cited publication, red box; realization of full or partial refutation (for contradicted or initially stronger effects), black box. Whenever two or more milestones coincide in the same year, the respective colors are superimposed on that box. Folate, flavonoids, and vitamin E were already in human use at the time of first description. Extending beyond the illustrated time range were the first description for nitric oxide in 1772 and its first human use in 1800; and the first description of flavonoids in 1898, aspirin in 1853, and of the wider class of antiendotoxins in 1896. Details for these interventions can be found in tables S1 to S5, listed by the ID number. Ab, antibody; GP, glycoprotein; HA-1A, human IgM monoclonal antibody against endotoxin A; HRT, hormone replacement therapy; mo Ab, monoclonal antibody; rt-PA, recombinant tissue plasminogen activator.

Recommendations for the Future

Our analysis documents objectively show the long length of time that passes between discovery and translation. As scientists, we should convey to our funders and the public the immense difficulty of the scientific discovery process. Successful translation is demanding and takes a lot of effort and time even under the best circumstances; making unrealistic promises for quick discoveries and cures may damage the credibility of science in the eyes of the public. The following are some recommendations for improving the system, based on our analyses:

• Discovery of new substances and interventions remains essential, but proper credit and incentives should be given to accelerate the testing of these applications in high-quality, unbiased clinical research and the replication of claims for effectiveness.

• Multidisciplinary collaboration with focused targets and involving both basic and clinical sciences should be encouraged.

• Proof of effectiveness for new interventions requires large, robust randomized clinical trials.

• Translational efforts for common diseases should focus more on novel agents and new cutting-edge technologies; for these ailments, it is unlikely that genuine major benefits from interventions already known for a long time have gone unnoticed.

References and Notes

1. E. A. Zerhouni, *JAMA* **294,** 1352 (2005).
2. F. M. Marincola, *J. Transl. Med.* **1,** 1 (2003).
3. J. P. Ioannidis, *J. Transl. Med.* **2,** 5 (2004).
4. D. G. Contopoulos-Ioannidis, E. Ntzani, J. P. Ioannidis, *Am. J. Med.* **114,** 477 (2003).
5. P. Cuatrecasas, *J. Clin. Invest.* **116,** 2837 (2006).
6. G. Duyk, *Science* **302,** 603 (2003).
7. B. Booth, R. Zemmel, *Nat. Rev. Drug Discov.* **3,** 451 (2004).
8. D. G. Hackam, D. A. Redelmeier, *JAMA* **296,** 1731 (2006).
9. J. P. Ioannidis, *JAMA* **294,** 218 (2005).
10. Methods and details for the collection and analysis of data are available as supporting material on *Science* Online along with its supplementary tables S1 to S5. These interventions included 18 drugs, two monoclonal antibodies, one hormonal therapy, four vitamins or food products, and three surgical or device interventions. Three drugs and one vitamin appear two times each in the list, as they were used for two different indications. For more information and references, see tables S1 and S2.
11. For more details, see Methods in the supporting online material and tables S3 to S5
12. C. R. Chong, D. J. Sullivan, *Nature* **448,** 645 (2007).
13. S. Zhu *et al.*, *Nature* **417,** 74 (2002).
14. J. D. Rothstein *et al.*, *Nature* **433,** 73 (2005).

10.1126/science.1160622

Supporting Online Material
www.sciencemag.org/cgi/content/full/321/5894/1298/DC1

Published by AAAS