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Translation takes time: Study shows how to measure it properly

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DUBLIN – The lag between the initiation of new research and the approval of targeted or biologic drugs for treating cancer can exceed 40 years, according to a newly published analysis that examines the relationship between the maturation of technologies and their potential to generate successful products.

To casualties of the early era of antibody development, the conclusion might appear obvious. The field spent billions of dollars on more than 200 failed clinical trials before getting it right. "Now they've totally fulfilled their promise. The easiest thing to develop is a monoclonal antibody," Fred Ledley, director of the Center for Integration of Science and Industry at **Bentley University**, in Waltham, Mass., told *BioWorld Today*.

What Ledley and his team – including first author Laura McNamee – have shown is that the time it takes for technologies to mature to the point where they can be translated into reliable products is predictable. It explains the time gap between the significant investments in basic research on cancer in the 1970s and the appearance of new drugs based on that work. "For around 20 years after massive amounts of money went into basic research – it really was a big deal – nothing happened," Ledley said. "The bottom line for us is it just takes time. We should have known it, and we can model it," he said. Ledley's group has previously published similar work on gene therapy and Alzheimer's disease. Research on modeling cardiovascular drug development is ongoing.

Ledley, a former Howard Hughes Medical Investigator and serial biotech entrepreneur, is corresponding author on the new study, which appeared in the March 27, 2017, issue of *PLOS One* under the title, "Modeling timelines for translational science in cancer; the impact of technological maturity." The team mapped the accumulation of knowledge in cancer, measured by the number of publications (> 2.7 million), against research funding and the timing of 138 cancer drug approvals across more than six decades.

Between 1950 and 1985, the group found no significant correlation between the number of new cancer drugs approved every year and the volume of publications – more than 700,000 – that appeared during that time. But their analysis demonstrated a significant correlation between approvals and cumulative publications between 1985 and 2012, an era in which cancer drug approvals increased substantially.

The group also conducted technology maturation analyses of 16 areas associated with cancer drug development, including anti-metabolites, alkylating agents, alkaloids (anti-microtubules), anthracyclines, recombinant proteins, estrogen/progesterone, topoisomerases, monoclonal antibodies, cancer immunology, oncogenes, protein kinases, apoptosis, genomics, epigenetics, systems biology, and synthetic biology. The latter three are still in an exponential growth phase and were too new to be tractable to assessment with the group's analytical model, Technology Innovation Maturation Evaluation (TIME), which traces the development of specific technologies from initiation to their becoming established. The former is defined by the "maximum exponential acceleration" of knowledge accumulation, the latter by the corresponding deceleration in publications.

"As long as you get unexpected things from your research it's very exciting," Ledley said. "When the results begin to be predictable, people move onto other things," he added. "At the point when results are predictable, that's the smart time to develop a drug," he said. In cancer, that means that the next wave of cancer therapeutics will come from areas that are now reaching their established phase, such as genomics, immunotherapy and gene therapy. It will take longer to develop innovations based on systems biology or synthetic biology.

Investment decisions around drug development are not solely determined by technological or scientific considerations, however. "What makes this very complicated, of course, is the financial side," Ledley said. "People make a lot of money by investing in the latest and greatest thing, long before there's a possibility of a drug getting out."

For established technologies, the average length of the growth phase, between initiation and becoming established, was 29 years. In some cases, initiation corresponded directly to well-known discoveries, such as monoclonal antibodies, which emerged from research on hybridoma technology, or recombinant proteins, which emanated from work on gene cloning. In other examples, the technology emanated from the convergence of several lines of research.

Given the very long time horizons involved in biomedical innovation, the present focus on accelerating regulatory approval processes that may only take nine months is, Ledley argued, misplaced. "There's not much mileage in the end stage," he said. In contrast, cutting 10 percent from the time taken for a particular technology to mature could speed the associated drug development process by several years.

Conversely, cutting basic research funding has long-term rather than short-term consequences. "There's a cost in that – it's not that the next year is bad, it's 20 years later when you don't get a drug out," Ledley said. Such an observation is germane, in the light of the current proposal from the Trump administration to cut the NIH annual budget by 18 percent. Ledley has already had some input into political debates on this theme, having testified before the House of Representative's Committee on Energy and Commerce in June 2014.

Ledley's group is part of a wider effort to understand and accelerate the translation process. "Basic and applied sciences are traditionally driven by investigator-initiated research and peer review, not evidence-based principles of innovation," the study authors noted. "Nevertheless, some of the initiatives undertaken to reimagine the path of translational science including formation of the National Center for Advancing Translational Sciences, efforts to improve collaboration, communication, and data sharing, and the Accelerating Medicines Partnership between non-profits, government and industry – could accelerate this maturation." Whether any of these efforts will have a voice in the present debate on science funding is an open question for now.