Your time starts now — translation time lines for major ophthalmic discoveries

Key performance indicators for medical research do not always indicate the long-term success of a treatment

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Translation into reduced morbidity and mortality is the ultimate measure of success for medical research. However, this may take decades and often researchers are dead before the full impact of their research is realised. Gregor Mendel's research is an excellent example, with the most important publication in genetics remaining uncited for 30 years.[1] The key performance indicators for medical research are publications and their citations — the number of papers published in peer-reviewed journals, the number of times these publications are cited, and the impact factor of the journal in which they are published.[2]

How long does it take for a key publication to translate into new treatments that reduce morbidity and mortality? Some treatments evolve via gradual improvements. For example, bone marrow transplantation was first proposed in 1957,[3] but it was not until the 1980s that it became accepted treatment and successfully saved lives.[4] Patient survival improved over the following 25 years, with further incremental advances expanding the medical indications and increasing the numbers of patients who benefit.

Funding bodies need to be aware of realistic bench-to-bedside time lines if they are to effectively engage with medical researchers to achieve real advances in treatments. However, little research regarding this aspect of medical research translation has been conducted. Focusing on ophthalmology, I investigated the time line for translation for: anti-vascular endothelial growth factor (anti-VEGF) agents for age-related macular degeneration (AMD), the leading cause of blindness in developed countries;[5] the development of laser photocoagulation to treat diabetic retinopathy; intraocular lens (IOL) implantation for aphakia after extraction of cataract;[5] maternal rubella as the cause of congenital cataract, the most highly cited article in 160 years of ophthalmic literature;[6]and the lead-up to the use of penicillin, which was first used to treat ophthalmia neonatorum.[7]

> "Funding bodies need to be aware of realistic bench-to-bedside time lines"

Major research translations in ophthalmology

Anti-VEGF therapy for AMD

Treatment of AMD with anti-VEGF agents is one of the greatest advances in ophthalmology. In 1971, Judah Folkman proposed a blocking drug[8] against a vascular factor that had first been identified in 1945.[9] In 2002, a rare eye cancer was treated with an anti-VEGF antibody with dramatic success[10] and, in 2006, the ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-related Macular Degeneration) and MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD) studies showed the efficacy of anti-VEGF antibodies in the treatment of AMD.[11,12] This treatment was so successful that an editorial published in *The New England Journal of Medicine* described it as miraculous![13] A search of the Web of Knowledge indexing service showed that more than half the top 20 most frequently cited articles in ophthalmology journals from 2005 to 2010 relate to anti-VEGF treatments. Folkman died just after the fruition of 35 years of work.

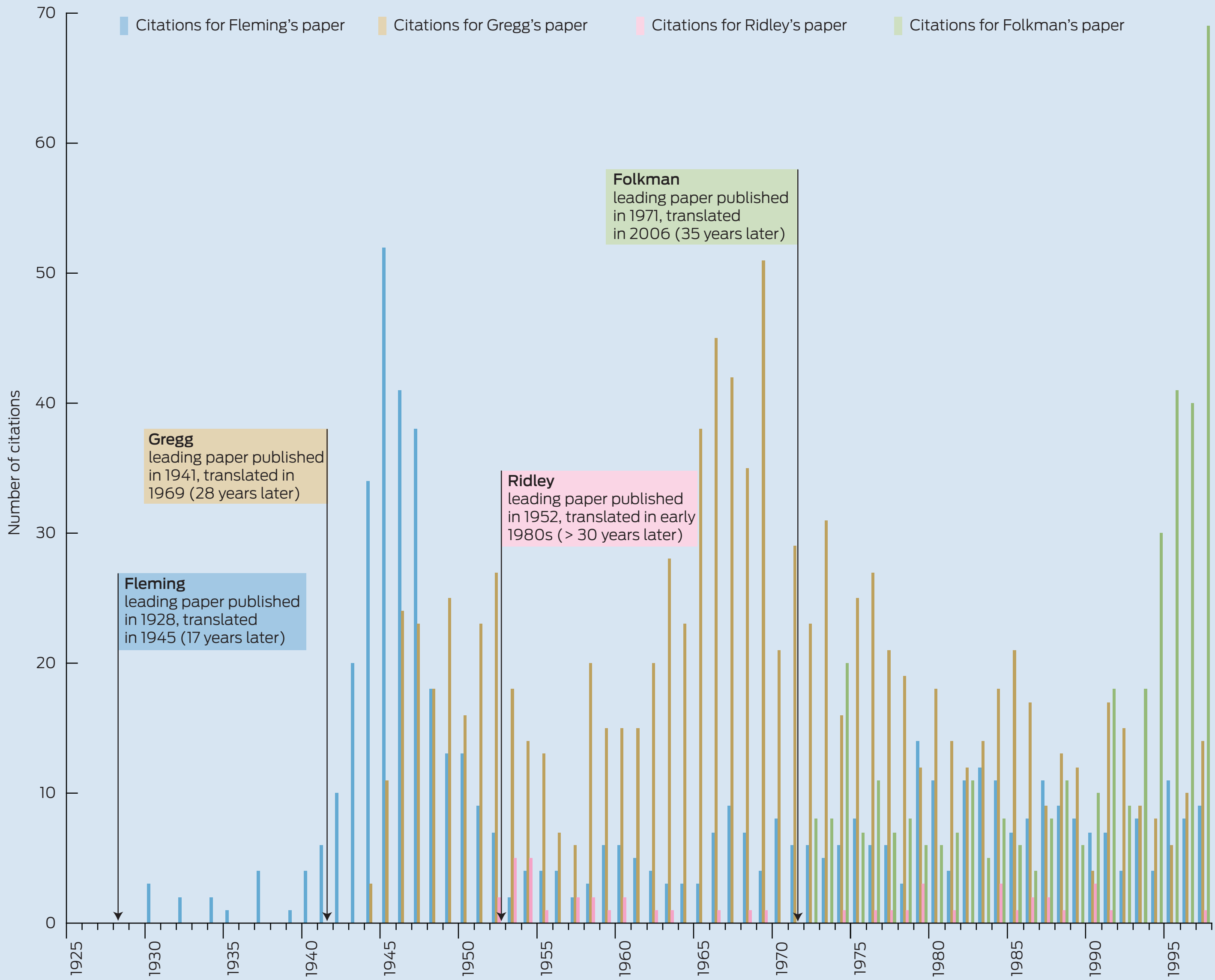
Lasers in ophthalmology, starting with diabetic retinopathy

Gerhard Meyer-Schwickerath first used sunlight coagulation to treat a retinal detachment in 1949.[14] He went on to develop the Xenon arc light coagulator in the 1950s.[15] The first functioning laser was developed in 1960[16] and laser's utility as a surgical tool was recognised in 1965.[17] The first major translation of laser in ophthalmology came in 1976, when laser treatment was shown to be effective for diabetic retinopathy in the Diabetic Retinopathy Study.[18] Other lasers, such as the Nd:YAG and excimer lasers, expanded the scope of treatment. The translation time line from 1949 to 1976 is 27 years, and from 1960 to 1976 it is 16 years.

IOL implantation after cataract extraction

IOL development began with the serendipitous observation of an injured World War II fighter pilot who had part of the perspex (polymethyl methacrylate) from his aircraft cockpit canopy lodged in his eyeball. The eye tolerated the perspex quite well. This led Harold Ridley to develop a perspex IOL, first implanted in 1949, but the initial work was unpromising.[19] Phakoemulsification, developed in the 1960s, provided a suitable method of cataract extraction to maximise the benefit of IOLs. Ridley met enormous opposition from the ophthalmic establishment. Because of high complication rates for inexperienced surgeons, Ralph Nader's consumer organisation, Public Citizen, campaigned against IOLs, wanting them banned by the United States Food and Drug Administration.[20] It was not until the early 1980s that IOLs became the standard of care — over 30 years after the first one was implanted.[21] Before IOLs, the standard was to operate on people when the better eye deteriorated to a visual acuity of worse than 6/60. With many refinements to IOLs, ophthalmologists now operate on people with mild visual loss, such as a visual acuity better than 6/12 (the cut-off for driving in many countries). Ridley was belatedly recognised for his work and perseverance with a knighthood at the age of 93 years.

Citations of leading ophthalmic discovery papers published during the 1900s*



* Data for after 1997 are not shown because citations of Folkman's paper increased exponentially, with over 400 citations a year since 2010, exceeding the scale of this graph. ◆

Vaccination for rubella embryopathy

Norman Gregg's 1941 paper reporting the association of maternal rubella infection and congenital cataract[6] is the most cited paper in an ophthalmic journal in over 160 years.[22] The impact of rubella embryopathy is enormous; major epidemics in countries such as the US in the 1960s affected tens of thousands of pregnancies.[23] Gregg was knighted in 1953 but died in 1966, before the final step in translating his discovery. The virus was isolated in 1962 and the rubella vaccine released in 1969, virtually eliminating this major health problem.[23] The translation time line from 1941 to 1969 is 28 years.

Penicillin for infections

In the case of penicillin, bread with a blue mould to treat suppurating wounds was a staple of folk medicine since the Middle Ages in Europe.[24] Alexander Fleming's famous observation in 1928[25] was rapidly followed when Cecil Paine used penicillin to (unsuccessfully) treat sycosis barbae in 1930. Paine then went on to treat ophthalmia neonatorum, a gonococcal infection in infants. He achieved the first recorded cure with penicillin on 25 November 1930. He then cured four additional patients (one adult and three infants) of eye infections, but failed to cure a fifth.[7] In the United Kingdom, 28.5% of children in schools for the blind in 1922 had been blinded by ophthalmia neonatorum; estimates from 1884 were 30%–41%.[26] The decline in cases of blindness due to ophthalmia neonatorum occurred before the widespread use of penicillin because of improved notification, Crede's prophylaxis (early treatment with asepsis and silver, such as Argyrol) and, in the 1930s, the use of sulphonamides.[26] Howard Florey read Fleming's work in 1938[28] and by 1941, with Ernst Chain and Norman Heatley, they had treated their first patient, Albert Alexander, who had been scratched with a rose thorn. His face and scalp were swollen, and his eye had been removed to relieve some of the pain from the periorbital cellulitis. Within 24 hours of being given penicillin, he began to recover. Unfortunately, when they ran out of penicillin he relapsed and died. By 1945, penicillin production was an industrial process for the allies of World War II. So 1928–1945 represents a relatively rapid 17-year translation time line. The even more rapid recognition of this translation came with the Nobel Prize in Physiology or Medicine being awarded to Florey, Chain and Fleming in 1945. The development of new antimicrobials and the race against microbial resistance continues today.

Citation rates for leading discovery papers

For each of these advances, I identified the leading paper that first described the discovery. Using the Web of Knowledge, I searched for citations of these papers (Box), which showed high citation rates for papers by Fleming,[25] Gregg[6] and Folkman[8] and peaks in citations before translation. Citations for Fleming's paper peaked early, Gregg's paper was cited consistently and citations of Folkman's paper increased exponentially. The paper by Ridley,[19] who had the longest and most persistent opposition to his work, had low citation rates. Unlike Mendel, however, Ridley lived to see the recognition and translation of his work. As Meyer-Schwickerath's leading paper was published in German,[14] it was difficult to identify citations. The sentinel laser paper[16] has been cited over 1000 times, mainly in literature on physics — not a true representation of a medical research translation metric.

Conclusion

Many other ophthalmic advances have led to major improvements in health care. The advance of spectacles for correction of refractive error, which has had the greatest overall impact on vision, took from classical times until the glass blowers of the Renaissance to be translated — over 1500 years! Many steps led to the diagnosis and prevention of glaucoma, but none is easily singled out. Treatments for trachoma, river blindness and vitamin A deficiency have had major impacts on prevention of blindness but are not universal.

Not all important research is driven by the need for translation to help humanity. Florey said

> People sometimes think that I and the others worked on penicillin because we were interested in suffering humanity. I don't think it ever crossed our minds about suffering humanity. This was an interesting scientific exercise, and because it was of some use in medicine is very gratifying, but this was not the reason that we started working on it.[28]

In reality, all translational research begins with "blue sky research", some of which may take decades to translate.

Research funders must consider the long-term view for translation of major advances in medicine. Numbers of publication citations indicate that a researcher is being productive, but they are not perfect key performance indicators for medical research. The Human Genome Project is only a decade old. Those who claim that it has failed to translate into clinical outcomes should look at real time lines for research translation. Then we can all look forward to the advances in health care that it will bring.

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