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Published in:
Expert review of medical devices

DOI:
10.1080/17434440.2019.1685869

Expert Review of Medical Devices

ISSN: 1743-4440 (Print) 1745-2422 (Online) Journal homepage: https://www.tandfonline.com/loi/ierd20

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To cite this article: Yijin Ren, Paul H. Fagette, Connie L. Hall, Herman Broers, David W. Grainger, Henny C. Van Der Mei & Henk J. Busscher (2019) Clinical translation of the assets of biomedical engineering – a retrospective analysis with looks to the future, Expert Review of Medical Devices, 16:11, 913-922, DOI: 10.1080/17434440.2019.1685869

To link to this article: https://doi.org/10.1080/17434440.2019.1685869

Accepted author version posted online: 28 Oct 2019.
Published online: 31 Oct 2019.

EXPERT REVIEW OF MEDICAL DEVICES
2019, VOL. 16, NO. 11, 913–922
https://doi.org/10.1080/17434440.2019.1685869

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PERSPECTIVE

Clinical translation of the assets of biomedical engineering – a retrospective analysis with looks to the future

Yijin Ren[a], Paul H. Fagette[a,b], Connie L. Hall[c], Herman Broers[d], David W. Grainger[e], Henny C. Van Der Mei[b] and Henk J. Busscher[b]

[a]Department of Orthodontics, University of Groningen and University Medical Center Groningen, W. J. Kolff Institute of Biomedical Engineering and Materials Science, Groningen, The Netherlands; [b]Department of Biomedical Engineering, University of Groningen and University Medical Center Groningen, W. J. Kolff Institute of Biomedical Engineering and Materials Science, Groningen, The Netherlands; [c]Department of Biomedical Engineering, The College of New Jersey, Ewing, NJ, USA; [d]Willem Kolff Foundation (Kampen, NL), Zwolle, The Netherlands; [e]Departments of Biomedical Engineering, and of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, Utah, USA

ABSTRACT

Introduction: Biomedical-engineering (BME) plays a major role in modern medicine. Many BME-based assets have been brought to clinical translation in the twentieth century, but translation currently stagnates. Here, we compare the impact of past and present scientific, economic and societal climates on the translation of BME-based assets, in order to provide the BME-community with incentives to address current stagnation.

Areas covered: In the twentieth century, W.J. Kolff brought kidney dialysis, the total artificial heart, artificial vision and limbs to clinical application. This success raises the question whether Kolff and other past giants of clinical translation had special mind-sets, or whether their problem selection, their training, or governmental and regulatory control played roles. Retrospective analysis divides the impact of BME-based assets to clinical application into three periods: 1900–1970: rapid translation from bench-to-bedside, 1970–1990: new diseases and increased governmental control, and the current translational crisis from 1990 onward.

Expert opinion: Academic and societal changes can be discerned that are concurrent with BME's translational success: mono-disciplinary *versus* multi-disciplinary training, academic reward systems based on individual achievements *versus* team achievements with strong leadership, increased governmental and regulatory control, and industrial involvement. From this, recommendations can be derived for accelerating clinical translation of BME-assets.

ARTICLE HISTORY
Received 17 July 2019
Accepted 24 October 2019

KEYWORDS
Translational medicine; valorization; biomedical engineering; medical technology; innovation; clinical impact; translational stagnation

1. Introduction

Valorization has become an integral part of science and engineering, and academic knowledge transfer is no longer optional anymore, but mandatory. Universities are viewed as key players in entrepreneurial innovation, following a worldwide paradigm shift in the overall scientific, economic and societal climate [1–3]. The academic discipline of biomedical engineering (BME) covers a vast spectrum of highly different disciplines. BME connects its centric fields and diverse disciplines through the application of engineering principles and design concepts with medicine and biology for health-care purposes, to produce a mission that is diagnostically, prophylactically and therapeutically focused. Traditionally, BME is positioned at the forefront of healthcare innovation. Typical BME areas of research include biomechanical, clinical, tissue, genetic and neural engineering, biomaterials and materiobiology, implant and device design, artificial organs and transplantation medicine, nanomedicine, bioinstrumentation, imaging diagnostics and robotic surgery, application of electromagnetic fields, lasers and ultrasound, and big data analysis [4]. BME therewith closes the gap between engineering and medicine and nowadays plays a crucial role in what is called 'healthy ageing', a *contradictio in terminis* meant to express the universal desire of human beings to enjoy a high quality of life for the longest possible period of time and then die within the shortest possible period of morbidity and decline from onset of disease till death (Figure 1). Whereas death hardly influences health-care costs, effective compression of the 'morbidity and decline period' reduces health-care expenditures, forming a growing economic burden in modern societies [5].

Downward clinical translation is defined as a process of moving basic academic research to clinical application. Others view clinical translation as an entrepreneurial process. Regardless of the exact definition, successful downward clinical translation of BME assets has occurred over the last 100 years, beginning slowly in the 1920s and more rapidly in the post-WWII period. This age of translation was arguably led by the Dutchman W.J. Kolff (1911–2009), bringing diverse innovations like kidney dialysis, the total artificial heart (TAH), artificial vision and limbs to clinical application [7]. BME sustained a high level of successful clinical translation apparently until the turn of the twenty-first century, that directly affected the 'morbidity and decline compression' (Figure 1). Notwithstanding ongoing technological advances in

CONTACT Henny C. van der Mei h.c.van.der.mei@umcg.nl Department of Biomedical Engineering, University Medical Center Groningen, Antonius Deusinglaan 1, Groningen, AV 9713, The Netherlands

Article highlights

- Retrospective analysis divides the impact of BME-based assets to clinical application into three periods: 1900–1970: rapid translation from bench-to-bedside, 1970–1990: new diseases and increased governmental control, and the current translational crisis from 1990 onward.
- Direly needed, direct involvement of clinicians in different stages of downward clinical translation decreases with risks of misdirected innovative efforts and waste of resources.
- Past successes of the multi-disciplinary teams in the age of the giants have led to multi-disciplinary education programs, but multi-disciplinary trained researchers do not replace the absence of clinicians in a team, nor does multi-disciplinary training provide specialists with the necessary deep knowledge and expert insight in their specific domain.
- While acknowledging the need for patient protection in human clinical trials, oversight should be more receptive and adaptive to needed innovation, risk-reward features of human introduction, and less antagonistic towards clinical translation.
- Clinical translation goes hand-in-hand with the progression of basic scientific knowledge, but making clinical translation central in guiding new developments, may have become a limiting factor for innovation.
- Partnering of industry and academia is needed for downward clinical translation, but industry must be more willing acknowledge academic importance to publishing, while academia must endorse the industrial responsibly of protecting important discoveries with patents.
- First signs of academic and societal changes can be discerned, including new violations of governmental oversight and human ethical constraints, that may herald the end of the current clinical translational crisis.

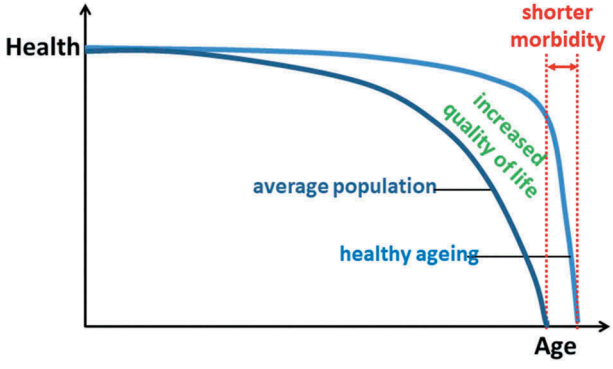

Figure 1. The goals of healthy aging and the challenges presented to BME are to elongate the human health-span, while compressing the period of morbidity and decline between the onset of disease till death (adapted from Hubert et al. [6]).

instrumentation, rehabilitation, medical device designs, new diagnostics and imaging capabilities, a series of articles in various medical journals [8–14] maintain that innovation has stagnated, and translation of BME assets from laboratory to bedside has diminished significantly, especially innovation and translation directly geared toward impacting disease, morbidity, and decline. The most cited evidence that translation is stagnating follows from the number of new truly innovative, first-in-class drugs coming to market from a high in the late 1980s and early 1990s, each following decade seeing less and less drug approvals [15]. Another measure is fewer patents for drugs and devices [16] in spite of more basic research, greater funding, larger databases, and genomic developments [17–21].

This reduction in medical innovation performance benchmarks of BME, raises the question whether Kolff and the other past giants of downward clinical translation had a special mind-set that allowed them to be more creative in translating assets of their research and development processes to clinical practice, whether it was the types of problems they worked on, the mono-disciplinary training of them and their team members or less governmental oversight and a more lenient regulatory system that allowed them to emerge as giants of downward clinical translation.

In order to answer these questions, we present a historical review of past innovations in biomedical engineering, how they transpired and were translated to accepted, routine clinical applications. Comparing the past with the present, recommendations are made on how to speed up downward clinical translation of BME assets.

2. A historical perspective

2.1. Introduction

A significant recognition of the importance of BME, based on its historical impact, was the foundation in 2000 of the National Institute of Biomedical Imaging and Bioengineering and the American Institute for Medical and Biological Engineering seeking to showcase BME assets, select global leaders as honorary Fellows, and advocate BME's leading role in medicine at governmental levels [22]. The impact of BME's contributions to clinical applications over the last century can be divided into three distinct periods each with their own context, motivations, and achievements (Table 1).

2.2. The age of the giants (1900–1970)

Translational medicine from 1900 to the 1970s represented a remarkable era in biomedical scientific progress when visionary and forceful personalities in research medical centers held sway over talented teams, driving their personal visions with determination, passion and unrelenting focus to clinical trials. Therefore, we call this period the 'age of the giants'. These 'giants' typically had access to financial support including governmental funding and conducted local clinical trials with relatively little oversight other than from their own ethical judgment or institutional policy.

Diabetes research produced an early multi-disciplinary team effort in the isolation and production of insulin. The Connaught Laboratories at the University of Toronto began work in 1920 and within 2 years produced the modern treatment for diabetes. In 1929, they began research into heparin, releasing a protocol based on bovine and porcine intestines within 6 years [23]. Tuberculosis research, as another example, consumed considerable efforts resulting in streptomycin in 1946.

Control of untreatable diseases emerged in the 1950s to loom large in the public domain, providing an optimism for improving human health unseen in previous times. Traditional children's diseases were eliminated with the 'baby shots' series. Salk's (1914–1995) efforts in treating polio earned him worldwide fame. Nine years of focused

Table 1. Three distinct historical periods of translating BME assets to clinical applications.

1900–1970 AGE OF THE GIANTS *Rapid translation from bench to bed side*	1970–1990 TRANSITION *New diseases and increased governmental oversight*	1990- present TRANSLATION IN CRISIS *Multidisciplinary-trained engineers work in teams on health-related problems*
ACCELERATORS and DECELERATORS		
- WWI and WWII - Visionary leaders with strong organizational abilities - Multidisciplinary teams of mono-disciplinary trained engineers and clinicians	- Evolving legislative and bureaucratic processes - Increased governmental funding and IRB oversight	- Emergence of biomedical engineering as a new academic discipline - Increasing health care costs consideration - Strong influence of human medical ethical committees - Societal resistance to animal use and approval for animal experiments becoming more difficult - Strong influence of regulatory agencies on application and marketing of innovations - Establishment of a modern health care system and new aging goals, including cost reduction - Negative clinical trial outcomes are often not published - Public-private partnerships act as translational catalysts
DISEASES and DISEASE CONTROL		
-Tuberculosis (streptomycin) -Diabetes (insulin) -Polio (vaccination)	-Cancer (diagnostics, chemo- and radiation therapies) -AIDS (immune therapy) -Antibiotic-resistant infections	-Compression of the morbidity and decline period from the on-set of disease till death -Gene therapies -More basic research on emerging diseases -Generic drug development
ROLE of BIOMEDICAL ENGINEERING		
-Dialysis delivery -Left ventricular assist devices -Heart valves -Heart lung-by-pass machines -Dacron vessel replacement -Total hip replacement -Dental implants	-Total artificial heart (TAH) -Refinement of medical devices utilizing new materials -New medical imaging techniques and devices	-Multi-disciplinary trained engineers become key-players in healthcare technology development -Transition of focus from organ systems to cellular and molecular levels -More advanced, basic research requirements -Development of *materiobiology*, aiming to control human biology using materials -Emphasis on supporting technologies like eHealth, 3D-printing, organs-on-a-chip -Big data analyzes to reveal factors influential on disease, morbidity and decline

research with a talented team resulted in Salk's 'killed' vaccine, delivered in three injections. Sabin followed with his attenuated vaccine more easily delivered on a sugar cube [24]. Kolff built the first clinically successful dialysis device in The Netherlands during WWII (1939–1945) [25]. His simple rotating drum design, based on cellophane tubing, was replicated in its original form and in the later robust Brigham-Kolff machine (1949). Results from these two designs between 1949 and 1953 prompted the medical community to accept dialysis as a viable treatment for acute kidney failure. Kolff emigrated to the USA in 1950 and designed a more user-friendly and less expensive dialysis design: the Twin Coil. Well into the 1960s, Baxter Travenol eventually produced the Twin Coil in the thousands. Kolff, who pursued dialysis designs to improve the treatment of kidney failure for the rest of his career, subsequently widened his interest into cardiovascular device development [26] with engineering teams from around the world. He controlled laboratories and funding with his strong personality and organizational skills. Kolff had an implicit faith in technology-based medical treatment. His entire career was devoted to device development, earning him the title 'the Father of Artificial Organs' [7].

Expertise in cardiothoracic and transplantation surgery advanced rapidly with the advent of the heart-lung bypass machine. Introduction of immuno-suppressant drugs in the 1970s allowed transplantation of hearts and kidneys. Lillehei (1918–1999) pioneered open heart surgery and trained an entire generation of surgeons at the University of Minnesota. Lillehei worked closely with a range of specialists, including electrical engineers [27]. Bakken produced a range of instruments and maintained others, when Lillehei asked him to design and build an external pacemaker for his patients. The first wearable external pacemaker began a new page in Bakken's career. He and his brother went from working in their garage to founding Medtronic [28]. Similarly, Houston became a center for cardiothoracic surgery in the 1960s. DeBakey (1908–2008) developed left ventricular assist devices (LVAD's), rotary pumps, Dacron vascular grafts, and other assist devices at the Baylor School of Medicine, USA [29]. He had a similar vision as Lillehei and Kolff: create multi-disciplinary teams of mono-disciplinary trained engineers and clinicians to work in concert and provide them with clearly defined, clinical problems to address.

The world would look different without total hip replacement brought to widespread clinical use and success by Charnley, who was as a British orthopedic surgeon convinced of the need to collaborate with mechanical engineers and materials scientists to overcome the wear and adverse tissue reactions resulting from the use of Teflon in his first prototypes [30]. In 1962, he implanted the first total hip arthroplasty using high molecular weight polyethylene but cautiously waited 10 years before announcing success [31]. Around the same time in the 1960s, Brånemark, in Sweden, developed osseo-integratable materials leading to dental

implants [32], arguably regarded as the largest innovation in modern dentistry. In all clinical innovations described above, multi-disciplinary teams were given considerable freedom along with funding and equipment, with their sole mission to resolve a compelling clinical problem.

Most early innovations arising from biomedical engineering were mechanical in nature and constructed from not too costly, readily available materials. Importantly, in the post-WWII period, the USA retained its manufacturing infrastructure intact, with considerable funds allocated for medical research, as opposed to a devastated Europe where most funds went to urgent, immediate clinical services. WWII contributed to significant advances in surgery, following a tradition that began in WWI and accelerated research into treating a wide range of diseases and rehabilitation procedures. Penicillin, for instance, was brought to clinical application in a record time of 15 years from its first discovery in 1928 to large-scale use in WWII, during which infection threatened the lives of many wounded soldiers. Public support of disease control developed strongly after 1945 and increased with each further success. Medical centers became more than a hospital; they were targeted by major philanthropic foundations, central or federal governments as focal points of biomedical research and development addressing diverse medical problems. Principal investigators in these early research centers maintained tight control over administration of treatment and oversight of research in their individual units, with rapid feedback coming back from clinical colleagues. This allowed multiple device prototypes to be developed, tried, refined or eliminated quickly and with considerable variation, in a manner unseen today. Kolff, for instance, reported 17 patients with advanced kidney failure between October 1942 and September 1945. Sixteen of these 17 patients died during, directly after or in the days after treatment with different prototypes of his kidney dialysis device. The first surviving patient #17, was a 67-year-old woman treated for 11.5 h. She made full recovery [7,25]. Accordingly, in the age of the giants, new BME assets resulted from multiple clinical trials after elimination of flawed designs and rapid refinement of prototypes to address daunting medical challenges, considered unsolvable before these innovations.

2.3. Transition: an end to the age of giants (1970–1990)

The 1970s through the 1990s were notable for increased governmental oversight of new treatments and technologies. Applicants for federal research funding were required to demonstrate not just a solution to an insurmountable clinical problem with a solid scientific/engineering basis, but also report approvals of institutional IRBs and precise methodologies on how clinical trials would be orchestrated, types of data collection and analyses, and how patients were protected against the risks of experimental therapies. Later, similar policies and requirements would be applied to increased oversight regarding preclinical animal testing. These changes led to a USA-initiated focus on downward clinical translation and a resulting perceived hostility toward regulatory bodies (i.e. US-FDA) and restrictive governmental oversight.

Although governmental oversite increased, this period continued production of significant devices and pharmaceuticals. For some, including Kolff, the Holy Grail of technological support for human health was a total artificial heart (TAH). Others fiercely resisted the thought of replacing parts of the human body by machine parts [7]. The many designs for a TAH and a wider array of LVADs were usually designed as a bridge to transplantation for desperate patients waiting for a donor heart. The TAH for these patients was a large, ungainly hospital-based, device often pneumatically powered to keep patients alive while awaiting a donor heart. Lighter, and later ambulatory, LVADs performed the same function and allowed patient mobility. The technological issues for developing a TAH independent of the hospital that allowed the patient to live a reasonably normal life were daunting. The energy supply system, valve failure, access ports, drivelines, and ubiquitous blood coagulation and infection issues were almost insurmountable challenges. Lastly, preexisting patient morbidities severely limited survival chances, as end-stage heart failure also meant concomitant, accompanying downstream organ failure [26,33].

At the same time, pharmaceutical development faced new challenges. A growing emphasis on cancer research and treatment, beginning in earnest in the late 1960s, with the rise of the American Cancer Society lobby and USA President Nixon's touted 'War on Cancer', saw the development of powerful new tools for research including genetic engineering for RNA replication and recombinant DNA. Monoclonal antibodies in conjunction with chemotherapy and radiation treatment allowed for individualized therapy in several cancer patients [34]. Major drug companies quickly assimilated all the latest imaging, computer, and polymerase chain reaction techniques into research and development pipelines. One appreciable success was the use of recombinant DNA to produce human insulin [35]. Another highly visible effort, led by the World Health Organization, resulted in the virtual elimination of smallpox by the end of the decade [36]. Other widely used drugs developed during this period, following the prevention and control approach, included statins [37] for cholesterol control and the equally important antihypertensive drugs [38].

The downside of these translational successes were not only the large expectations among the general public regarding 'better living through pharmacy', 'healthy aging reaching to old age', but also the costs associated with clinical application of BME assets. In order to reduce patient costs, the large-scale emergence and availability of generic drugs was promoted. The 1984 Drug Price Competition and Patent Term Restoration Act enabled generic drugs proven to exhibit identical bioequivalence to the patented, approved and exempt from repeating clinical trials. This significantly reduced the market entry costs, once exclusivity rights from a patented drug expired [39]. More drugs became available to more people at reduced costs through this pathway [40]. As a result, traditional and costly pharmaceutical research and development efforts would see less market exclusivity, return and market incentive to subsidize further risky development initiatives. Therewith, drug innovation and development incentives became limited. The greatest new product challenge to drug companies was the growing, almost epidemic, problem of antimicrobial and anti-tumor drug resistance. The natural selection that occurs in a changing environment including disease means that eventually, some type of resistance develops. Seventy-five years of antibiotic

treatment and overuse finally resulted in selection of naturally occurring antimicrobial-resistant pathogens, and a perceived end to the traditional antibiotic armada. This meant that drug companies, governmental research, and academic/medical institutions were forced to reconsider basic research and development all over again to re-address clinical problems thought to be solved decades prior [18]. However, antimicrobial drug development in this era no longer provided the attractive financial incentives of past years to balance development costs and risks of new antibiotics. Limited clinical first-in-class new antimicrobial offerings are a result.

Apart from poorly understood, emergent, threatening diseases without a cure taking over the medical innovation spotlight, these transition years witnessed increased governmental funding with accompanying patient and animal model ethical scrutiny. Human (e.g. IRB) oversight and regulatory complexity, both in the USA and Europe, defined the end of the transition period. The FDA had hegemony in the USA, based on a long institutional history and authority, dating from 1906. The European Union also implemented a series of legislative acts for drugs and devices beginning later in the 1980s. The Safe Medical Devices Act in the USA of 1990 was a reform of the original 1976 laws to provide greater public protection by requiring anyone who marketed medical devices to monitor and record their patient use and report all adverse events and failures to the FDA. Such new regulatory burden, established for proper patient protection, arguably also hindered the pace of product development and medical innovation.

Cynically, although Kolff might be considered as one of the most successful translators of BME assets to clinical application, he arguably also laid the foundation for the end of the age of the giants. His self-adapted 'freedom to operate' with new technologies implanted into desperate patients suffering life-threatening diseases, likely indirectly contributed to increased governmental and institutional oversight. This in turn slowed further rapid transitions of new ideas from bench-to-bedside and back. When in 1981, Kolff failed to obtain NIH funding for his TAH development, he went down his own path. Without NIH funding and oversight at that time, he took the risk of implanting the Jarvik-7 TAH heart into a terminally ill patient, gaining considerable notoriety in 1982 with the first TAH implantation into the elderly American dentist, Barney Clark, suffering end-stage organ failure associated with congestive heart failure [41]. However, this single, cavalier surgical event attracted considerable press attention.

A major ethical question raised after Dr. Clarks' death after living 112 days on the TAH, was how a single academic medical center could 'experiment' on a human patient in a terminal condition, with their basic patient rights protected only by the local institution. The ethical issues regarding the nature of such treatment are still being debated. Questions also arose over whether substantial amounts of money should be devoted to costly treatments of few and often terminally ill patients, that provided little chance of long-term success given the greater need for funding more widely applicable and affordable new treatments. These questions, both economic and ethical, fed into an already evolving legislative and bureaucratic process, in which NIH, FDA, and USA Public Health Service were given greater oversight with the aim of protecting all patients, regardless of federal biomedical research funding or patient's desperation and desire for treatment.

2.4. Translation in crisis (1990-present)

At the end of the transition period, engineering had become an essential component of the biomedical world and changed in response to increased public awareness and subsequent governmental funding of health care and research. Biomedical research occurred in the postwar period till 1990 with mechanical engineers bringing their expertise to disabled veterans with lost limbs. Electrical engineers were involved in heart-related matters with pacemakers. Computer engineers had a huge impact in relation to software development for computational modeling. In the early 1990s, an entirely new multidisciplinary field appeared: biomedical engineering [4,42] with growing academic interests, formal BME degrees, credentialing and research funding. Multi-disciplinary trained biomedical engineers working in teams on human health-related issues were distinct from predecessor, innovative teams of dedicated, mono-disciplinary trained specialists, each contributing their own expertise in multi-disciplinary teams, characteristic of the 'age of the giants'.

In the 1990s, a major transition occurred, prompting BME to focus on cellular and molecular technologies rather than solely operating on the level of organ systems, with the Human Genome Project and the Nobel Prize in Medicine for Mullis in 1993, rewarding his polymerase chain reaction technique, as some early prominent and enabling examples of new innovative tools. New techniques for manipulating and organizing molecular and cellular systems in biology exploded, with many future medical benefits promised. Further advances in bio- and nanotechnologies, tissue engineering, and artificial organs are ongoing, but require advanced basic research before translation to clinical application. These together have led to a new field within biomedical engineering named '*materiobiology*' [43]. Downward clinical translation of the assets of these new developments is performed under strong governmental oversight. Permission for validating preclinical animal studies is becoming more and more difficult to obtain, while moreover, animal use is under strong societal scrutiny. Human clinical trials are closely monitored and regulatory requirements for marketing new drugs and devices are sometimes close to impossible due to unrealistic requirements on clinical cohort sizes required for statistically significant benefit demonstration [44]. This scenario necessarily delays acquisition of translational evidence required to validate new medical technologies, increasing research and development costs that also impact health-care costs, promoting 'substantial equivalence' claims for incrementally different new drug and device introductions, emphasis on generic drugs instead of first-in-class breakthroughs. These scenarios taken together subsequently discourage commercial efforts to start new, higher risk innovation initiatives. Simultaneously, a growing geriatric global demography demands healthy aging, yet requires more and personalized healthcare, all raising health-care costs. Globally, large patient groups, especially in developing countries, lack access to the assets of biomedical engineering due

to their high costs. Orthopedic implants are not seldom used from one patient into another [45,46] or are locally produced [47], all to reduce costs and make them more widely available. New fields of BME such as eHealth, organ-on-a-chip, and 3D-printing are yielding cost-reductions without becoming visible as the new and spectacular advances like in the age of the giants, and lacking a clear impact on disease, morbidity and decline.

3. Comparing the past and present

3.1. Leadership, team efforts, and academic individualism

The age of the giants had brilliant, determined and undaunted leaders, with a cavalier attitude that was almost as important as their leadership ability in driving projects through the barriers of their times with self-adapted freedom to operate. Often stubborn, sometimes even ruthless, they drove themselves and their teams to overcome challenges to bring desperately needed aid and benefits to their patients. Downward clinical translation then was more important than innovative research that aims to publish high-impact papers, often promising clinical application, but in reality, representing nothing more than yet another scientific novelty.

University incentives and academic promotional systems nowadays more and more reward individual achievement based on published work and fund-raising, rather than team efforts aimed at translational research, more common to the age of the giants [8]. Also in academic medical centers, research is nowadays not always considered to be an economically viable activity due to the lack of renumeration for clinical staff time when conducting research compared to generating patient-driven clinical revenues. Innovative research, the foundation of any translational activity, is often viewed as disruptive to clinical care [12,48]. Nevertheless, clinicians are crucial for clear definition of the clinical problem to be solved, guidance and evaluation of new designs and solutions proposed. As a result, the direly needed, direct involvement of clinicians in different stages of downward clinical translation decreases with risks of misdirected innovative efforts and waste of resources [38,49–52].

3.2. Changes in academic training

The age of the giants was characterized by multi-disciplinary teams of mono-disciplinary trained specialists. A main educational question for a long time has been how to foster and institutionalize innovation and enhance the translational process [1,53,54]. Past successes of the multi-disciplinary teams in the age of the giants have inspired and stimulated development of diverse multi-disciplinary education programs. However, multi-disciplinary trained researchers do not replace the absence of clinicians in a team, nor does multi-disciplinary training provide specialists with the necessary deep knowledge and expert insight in their specific domain: *mono-disciplinary trained specialists know a lot about almost nothing, but a multi-disciplinary trained scientist knows almost nothing about a lot*. In modern medical education, the role of science and engineering in translational medicine is acknowledged by training physician-scientists or doctor-engineers, but without filling the deep knowledge and expert insight gap in absence of mono-disciplinary trained specialists [55–57].

3.3. Governmental oversight

With the accelerating influence on downward clinical translation of WWI and WWII during which rapidly saving lives was seemingly more important than human ethical considerations, the giants may have acted in a way that would nowadays evokes major ethical concerns. Yet one may wonder at the same time whether under present-day governmental oversight and without Kolff his self-adapted freedom to operate, kidney dialysis would have ever become the life-saving procedure it now represents globally. Governmental oversight of human clinical trials and animal experiments is indeed often portrayed as the single most substantial impediment to clinical translation. While necessarily acknowledging the compelling need for patient protection in human clinical trials, oversight should be more receptive and adaptive to needed innovation, risk-reward features of human introduction, and less antagonistic toward clinical translation [58].

3.4. Types of problems studied

Did the giants 'pick the low-hanging fruits', leaving current generations with clinical problems that are more difficult to solve? Whereas in hindsight, this is easily said, the problems of their times were most likely equally complex to solve and required knowledge that was beyond the horizon of scientific knowledge of the times. This illustrates how clinical translation goes hand-in-hand with the progression of the basic scientific knowledge, of which it cannot always be predicted whether and when it will turn to use for application. This realization begs the thought that making clinical translation important for obtaining research funding and central in guiding new developments may backfire and have become a limiting factor for innovation.

3.5. Regulatory requirements and market introduction

Industry is regarded as a necessary partner in fostering a focused path toward improved product development leading to clinical translation. Increased industrial cooperation, sharing of data and resources is essential [59,60]. This partnering is often beyond reach or realization for most academic researchers who generally know little about how and why industry decisions are made or can be leveraged for mutual benefit. Traditionally, universities have been the repository of basic research and initial innovative processes but not their maturation; industry must take over prototype development and testing for validation, regulatory approval, and eventual manufacturing, bringing the successful product to market in an economically feasible design, while assuming all risks at that level. For example, during the age of giants, Kolff developed his Twin Coil dialysis device exclusively at Cleveland Clinic and literally had to go shopping to find a manufacturer with a nearly final design. Moreover, the

decision to search for an industrial partner was taken out of his personal ambition to save the lives of his patients, and not by his scientific or personal financial ambitions or those of companies and their shareholders. Nowadays, many BME departments have industrial members who sit on their advisory boards and participate in senior design evaluation. Funding for industrially oriented undergraduate and graduate projects is a key part of this relationship. Therewith, industry has become a much bigger, key player than ever before in clinical translation. Given their economic incentives as a driver, industrial partnering requires greater protection for patients and attention to health-care costs than before. Regulation to ensure financial benefits and exclude risks for patients therefore had to increase compared to that in the age of the giants. For sure, this makes it (too?) easy to put the blame for stagnating clinical translation on regulatory agencies.

The venting of such regulatory complaints focuses almost exclusively on the USA FDA. Clinical trials currently stand out as a primary concern [61–63]. The FDA requires a significantly longer trial period than in the EU. Despite the overwhelming incentives to enter the dominant USA medical market, many companies instead opt to move first to overseas markets to receive initial product approvals. The key advantage to this strategy is that a new device or drug can first receive a European CE mark, certifying product human safety but not always clinical effectiveness, and allowing market authorization and entry with required post-market effectiveness surveillance [64]. Clinical trials in this case are simultaneous with marketing. By contrast, the FDA requires successful trials proving both safety and efficacy before market certification for any novel device; new trials are not always required for certain medical devices similar to appropriate predicates already approved for market (i.e. FDA 510k pathway). Certainly, inherent public dangers lurk for device/products that are unreliable or defective; hence, statistical clinical evidence must address such risks. Product safety might be sacrificed for speed but with a recognized higher risk to patients. The FDA is clearly risk-averse and a safety-driven protector of patient interests. In response to complaints and pressure from US Congress, the FDA has instead created an expedited access pre-market approval program for select medical devices that addresses serious patient medical conditions lacking other viable treatment options [65]. FDA's response to criticism has been to increase new application approval rates. Approval rates for devices increased by 12% in 2015, and an overall 30% increase from 2012 [66]. In a similar vein, the EU has not been exempt from the same criticism. Regulations that are over 20 years old are currently undergoing analysis for reform. Professional medical organizations are attempting to influence the legislative process for increased safety and a more streamlined testing and approval system [67–69].

The medical technology innovation relationship between academia and industry is tight, and often steered by industry with its greater financial possibilities. Yet, academia and industry partnerships seldom start from *de novo* partnering: the academic desire to publish as soon as innovation is evident is orthogonal to the industrial requirement for exclusivity provided by patenting and non-disclosure [70,71]. Public–private partnerships between industry and academia are emerging, but only after long discussion about rights and duties of the partners, alien to most scientists, but a popular intellectual playground for lawyers [60]. Successful partnering relies on industry becoming more flexible and willing to work in a risk-filled environment. Equally, academia must be more willing to reduce their importance attached to high-impact papers describing new innovation and endorse the value of first responsibly protecting important discoveries with patents and subsequent downward clinical translation [68,72].

4. Conclusion

Evaluating BME's historic contributions over the past 100 years by dividing it into three time periods as done here yields the conclusion that current stagnation in the downward clinical translation of the assets of BME occurs concurrently (Figure 2) with several academic and societal changes:

- Developments in biomedical engineering are no longer conducted by mono-disciplinary trained specialist under the leadership of highly visionary leaders, but by multi-disciplinary trained specialists.
- Academic reward systems are no longer based on achievements of a research group with a clearly visible leader but on individual academic achievements.
- Multi-disciplinary teaching has become the standard in academia, rather than in-depth mono-disciplinary education.
- Governmental oversight in the protection of patients (and preclinical test animals) has become much stricter.
- industry has become an indispensable partner in clinical translation, with interests that are not always compatible with those of their academic collaborators.

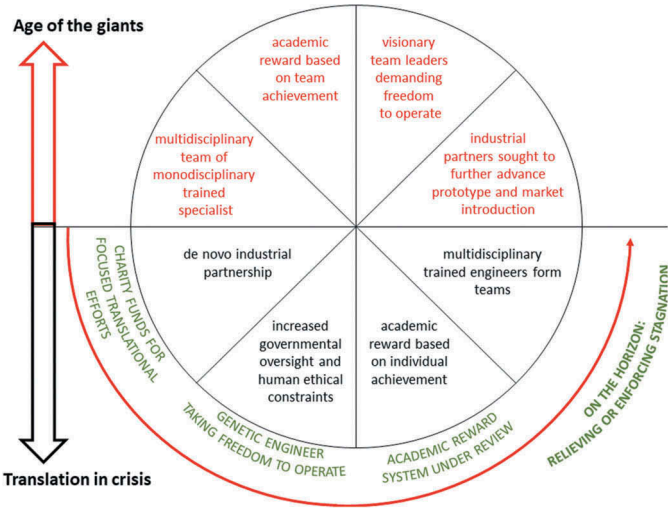

Figure 2. Academic and societal changes concurrent with the occurrence of the stagnation in downward clinical translation of BME assets to clinical application and recent events that may influence the duration of the translational crisis.

5. Expert opinion

It is impossible to conclude whether the above concurrency (Figure 2) may be extrapolated to state that these changes are causative the stagnation of the downward clinical translation of BME assets [73]. However, it would be within academic tradition and direct possibility, to start a thorough evaluation of the role of multi-disciplinary education programs, with as a possible outcome a return to in-depth, mono-disciplinary programs. Also, adapting an academic reward and promotion system based on academic team achievements rather than the current focus on performance evaluation of individual academicians might contribute to restoring translational balance. De-emphasizing high-impact publishing as the primary academic research metric would also facilitate more focus on clinical validation and intellectual property investments required for translation. Model changes in academic reward/promotional systems originating in The Netherlands might be a basis for such considerations [74]. Changing regulatory requirements and their impact on clinical translation must be addressed by jointly coordinated strategies from academia and industry, possibly supplemented by modern internet-based initiatives such as the Patient Innovation Sharing Solution [75] or the Euro-African Open Biomedical Engineering e-platform [76] for addressing individual patients needs. A recent trans-Atlantic consortium of scientists has provided published recommendations to change regulatory requirements, based on enrichment principles [77]. Lessening of governmental oversight and more flexible approaches toward required animal preclinical validation will require concerted efforts from academic and industrial stakeholders to improve downward clinical translation, but is currently at odds with societal developments [78]. Alternative preclinical validation models (e.g. 3-D tissue, or *in silico* models) represent a future path forward to assert safety and efficacy as an animal substitute, but not near term. New ways of working with nonprofit foundations, philanthropy, and charity funds have led to focused academic-industrial partnerships intent on solving urgent medical problems considered too risky for industry and commercial market places. Along these lines, the Dutch Kidney Foundation presented in 2018 the first prototype of a portable kidney dialysis system, developed within record time.

5.1. Five-year view

With the population of the world approaching almost 8 billion people, it is hard to believe that the current crisis in translating BME assets to clinical application can be attributed to a lack of sufficiently talented and visionary leaders. However, driven by their own and patients desperation for treatment, past giants of clinical translation broke governmental oversight barriers. Such self-adapted freedom to operate has been solidly declared undesirable, unethical and even illegal worldwide. However, with the continuing translational crisis, arguments are being raised that its consequences may exceed the risks associated with the cavalier behavior of past giants of clinical translation. Lack of ready permissions or routes for clinical translation may compel *post facto* seeking of forgiveness for clinical indiscretions in the name of new medical interventions. In this respect, it remains to be seen whether medical tourism to access unproven alternative therapies, or recent transgressions in human gene editing will be regarded by history as fraud, an exercise in researcher self-aggrandizement, narcissism and arrogance, trespassing of world-wide-accepted ethics (as is current judgment), or as an important stimulus for a new era of downward clinical translation proceeding at-risk and renegade of societal constraints.

In short, a number of diverse academic and societal changes are evident that might explain cause and effect for the current translational crisis in downward clinical translation of BME assets to clinical application. Simultaneously, the first signs of academic and societal changes can also be discerned, including new violations of governmental oversight and human ethical constraints that may possibly herald the end of the current clinical translational crisis.

Funding

This paper is not funded.

Declaration of interest

H.J. Busscher is director-owner of SASA BV, a consulting company. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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