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Regenerative Medicine Will Make Orthopaedic Implants Obsolete In Our Time

Orthopaedic Research Society First Annual Meeting Debate, San Diego, March 21st, 2017

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Abstract

The mission of the Orthopaedic Research Society is to promote and advance musculoskeletal research worldwide. With this in mind, the Annual Meeting Program Committee sought to establish a debate as a key component of the meeting. Our purpose was to provoke discussion on topics that are core to our mission and to engage all constituencies within the society by examining questions of broad relevance. To this end, the topic “Regenerative medicine will make orthopaedic implants obsolete in our time” was selected as the title of the inaugural debate. The arguments for and against the motion are presented in this perspectives article.

The debate in context

J Mark Wilkinson, Programme Committee Chair 2017, Professor, University of Sheffield, UK

Musculoskeletal disease has been the leading cause of chronic disability in the United States for every one of the last 14 years, with an annual healthcare spend approaching $300 billion. Despite the dominant burden of musculoskeletal disease on national healthcare economies, musculoskeletal research continues to receive a disproportionately small share of a diminishing governmental health research budget. The mission of the Orthopaedic Research Society is to promote and advance musculoskeletal research worldwide. This necessarily requires advocacy to address these disparities through various profile-raising initiatives.

It is with this backdrop that the Orthopaedic Research Society has introduced the 'ORS Debate' as a prominent feature of its Annual Meeting program. Our objective is to profile key questions within the musculoskeletal research agenda through discussion led by thought leaders in the field. The inaugural Debate was held at the 2017 Annual Meeting in San Diego, March 2017. The topic "Regenerative medicine will make orthopaedic implants obsolete in our time" was chosen to be of interest to the whole musculoskeletal research community and to reflect the vision of the ORS to help create a world without musculoskeletal limitations. We also wished to celebrate the value of musculoskeletal research from horizon scanning basic discoveries through clinically-applied research conducted within the timeframe funders may prioritize for translation to meaningful clinical impact.

The debate was aired in plenary session before a capacity crowd, with Dr Brian Johnstone, Past ORS President proposing the motion and Dr Josh Jacobs, Past ORS President and Past AAOS President opposing. The debate was chaired by Past-ORS President and JOR Editor Linda Sandell, who also acted to prevent any fist-fighting between the protagonists. This event introduced a new dimension to the Annual Meeting and also helped raise the profile of our mission *to advance musculoskeletal research worldwide* and our vision of *a world without musculoskeletal limitations*. Those of us who witnessed the event will be able to say "I was there…", but for those who missed this momentous occasion there follows a summary of the arguments outlined by Drs. Johnstone and Jacobs. We leave you to make up your own mind on the arguments…

Arguing for the motion:

Brian Johnstone, Professor, Oregon Health & Science University, Portland, OR

Overview

Amara's law states that we tend to overestimate the effect of a technology in the short run and underestimate the effect in the long run. I argue that regenerative medicine is a perfect example of such a technology. We have been busy overestimating its effects in the short run, with claims made that we have not been able to fulfill. The effect of the overestimation is to convince those comfortable with the status quo that they have nothing to worry about. The reality is that orthopaedic surgeons, and the orthopaedic industry, had better become smarter biologists soon, because we are underestimating the myriad of things that regenerative medicine will do in the long run.

Regenerative medicine – defined

The purpose of regenerative medicine is the repair, regrowth or replacement of damaged or diseased cells, tissues or organs. It differs from other fields of medicine by the array of disciplines it brings together and its ability to harness the body's innate healing capacity. Within Orthopaedics there is a tendency to see regenerative medicine as only tissue engineering, but it is much broader. What I want to first emphasize is that it includes gene therapies, cell therapies, tissue engineering and the production of artificial organs. At this point, if one stops to consider the array of potential therapies under those subheadings, it is hard for me to believe that regenerative medicine will not make plastic and metal implants obsolete in our time.

The Hype Cycle

It could be argued that those who voted against the motion at the start of the debate are following the Hype Cycle model of technology development. This model was developed by the research and advisory company Gartner [1] and is illustrated in figure 1 [2]. In the model, a technological development triggers significant media interest, but no products exist and the viability of the development to change the status quo is unknown. There is then a rapid rise in expectations, generally over-inflated. One could argue stem cell therapy, gene therapy, tissue engineering and all other buzzwords that fit under the regenerative medicine heading fit this description in their first decades. As the over-inflated expectations are dashed, the trough of disillusionment is reached, but an upward slope of enlightenment is then created by those researchers and companies that stay in the game, or join at this point with new ways of thinking about the initial exciting prospects. They will then reach the plateau of productivity.

The Hype Cycle is criticized since as well as being poorly named (it's not actually cyclical), it presumes each technology will have its day of glory in the end – there is no allowance for technologies that fail. Furthermore, as Michael Mullany points out in his retrospective on technologies once listed on the Hype Cycle, some technologies are simply not recognized until they are already in their plateau of productivity and were never over-hyped [3]. I have thoughts on both of these criticisms as they apply to regenerative medicine. With regard to

the possibility of failure, we are already starting to see regenerative medicine work, as I will discuss later, so the idea of failure is off the table. That regenerative medicine was not over-hyped is sadly not true – the proliferation of stem cell 'treatment' clinics that promise much but don't deliver, or deliver wrongly, is the perfect, if very sad, illustration of that. Thankfully, the FDA has recently begun to act to regulate over-hyped, and potentially dangerous 'snake oil salesmen' [4]. With all that stated there is perhaps a better model to use to argue for the motion – Amara's Law – of which Gartner's Hype Cycle is meant to be an illustration, but which is a better argument for my cause here if considered without the shortcomings of the Cycle example.

Laying down the (Amara) Law

Perhaps those who voted against the motion at the outset of the debate are guilty of what can be described as a self-deception: the deception of linear versus exponential thinking. This common problem is one that Roy Amara, scientist and futurist, used as the basis for what has become known as Amara's Law (figure 2). Put simply, his law states that we tend to overestimate the effect of a technology in the short run and underestimate the effect in the long run [5]. The Human Genome Project is a great example of how Amara's Law works. When it started and for many years of its progress, we overestimated what it was going to accomplish: reading the whole code would rapidly allow us to solve the challenges of complex diseases. That did not occur. However, we are now underestimating the long-term effect of having the complete code. We have not only developed a myriad of techniques for reading it faster and faster, but now use it as the basis of developing many applications not even dreamt of when it was conceived, as I will discuss later. This is all happening because we gained the ability to read, and then write and edit the genetic code.

A question of time

Perhaps it is the very phrase 'in our time' that led much of the audience to initially vote against the motion? However, I would note that it took 50 years from Themistocles Gluck's ivory hip in 1891 to Philip Wiles performing the implantation of the first metal hip replacement in the 1938 in London, England (with apologies to the other great scientists and surgeons that contributed to the development of the field in the 19th and early 20th centuries). Moreover, while the busy Dr Gluck implanted an ivory hinged knee device even earlier, in 1860, it would be 100 years until Bjorg Walldius used a metal knee implant in 1958. Thus, the argument against regenerative medicine does not consider the time and effort it takes to move some technologies to success. It took 50 to 100 years for orthopaedic implants to move from ivory to metal, and so it will be as we move from biology laboratory to biological therapies. However, to those present at the debate that thought I had now defeated my argument that implants will be obsolete 'in our time', I made the following point. *The majority of those attending an ORS meeting, and thus in the audience at the debate, are young researchers in their twenties. Therefore, 50-100 years is within their lifetimes given that science and technology continue to increase lifespan.* Thus, I asked those that initially voted against the motion because they believed that it would take longer than 'in our time' whether they were appropriately considering the age of the audience in which they sat?

Why the answer to the question in the motion has to be yes

I often frame a discussion of my own tissue engineering research with an introduction that includes an acknowledgement that joint prostheses present a high bar for regenerative medicine to get over, given their success and (possibly, or at least initially) cheaper cost. However, in preparing for the debate it struck me how little consideration I give to the negatives of joint replacement surgery. Search online for how long a knee or hip replacement lasts and the answer 'at least 20 years for 80-90% of people' is most commonly found. Note that means that up to a fifth of recipients get implants that don't last that long. For this reason, those suffering with degenerative joint diseases are told to hold off as long as they can before getting the surgery. So, now we are discussing these implants as therapies of last resort. Moreover, as illustrated in figure 4, the patient will have to endure years or even decades of pain and discomfort before getting one [6]. Not such a high bar after all.

Furthermore, if one looks at the success of knee implants more closely, the bar is even lower for that joint. Satisfaction with the outcome may be high due to the fact that the patient has been waiting many years in pain to get the operation and the decrease in pain score is appreciated. However, the persistence of pain after total knee arthroplasty has been documented in many studies and depending on the study, it is found that between 5-40% of patients report only minor to no improvement after total knee arthroplasty. Total joint arthroplasty is a great orthopaedic success story, but let's not think it's the long-term answer for mankind.

Climbing out of the box

One of the more recent trends in orthopaedics has been trying to make our clever regenerative medicine ideas into therapies that fit into the current version of an orthopaedic surgeon's operating procedures, space, and above all, time. The emphasis on 'simple', 'rapid' and 'minimally manipulated' has led to the growth of new treatments with the concomitant development of machines and one-time use gadgets that fit into the operating room. These types of treatments are also designed to be approved by the FDA with the lowest effort, and thus cost, since they are not subject to the lengthy process a 'drug' or similar therapy must undergo. But what if these therapies are just a huge distraction, distracting talented surgeon-scientists and their counterpart basic scientists and biomedical engineers from doing the really ground-breaking work that is needed? One can argue it is an industry hamstrung by the federal regulations or constrained by investment costs that is doing what they can to help, but it is entirely unclear whether the current 'simple', 'rapid' and/or 'minimally manipulated' treatments are really doing much for patients with skeletal tissue pathologies.

Before we go further, I need to make it clear that I'm not arguing that all regenerative medicine will by definition be hard to translate into the patient treatment setting. My point is rather that we should not be constrained in our thinking by the current model of how surgeons work to fix a patient with an orthopaedic pathology, or how the traditional orthopaedic industry that supports this process works. The industry and the practitioners of surgery lean heavily on technologies that have reached a plateau. I am arguing that we have

to transition from traditional engineering and metallurgy-based therapies to biology and biomedical engineering-based ones. To do that, we need to emphasize far more biology and biomedical engineering training for orthopaedists and staff our industries differently. I posit that the present model is holding us back.

Is that the cavalry I hear arriving?

For the last part of my argument, I pointed out that regenerative medicine is already having success in many fields of medicine, and highlighted examples of outside-the-box thinking that is getting us to new therapies. To illustrate how fast things are now moving, I told the audience we need look no further than the Plenary lecture at the 2017 ORS meeting, which was given by Professor Jennifer Doudna, a leading figure in the development of CRISPR/Cas9 technology for editing the genome. She pointed out how this had already begun to revolutionize the creation of genetically modified animal models, but had also been taken further to alter the genetic code for a myriad of other applications including regenerative medicine. What I didn't know at the time of the debate was how this technology had already entered our field, a fact I will return to later.

My next example considered the tortured path to success for 'gene therapy'. It is one of the best examples of the Amara Law, such that the very large area of 'disappointment' for gene therapy has recently been left behind, with its development curve rising into the area of 'amazement' due to approvals of treatments for diseases, including those previously thought to be untreatable. The first examples were the gene therapy for squamous cell carcinoma approved in China, and those for severe combined immunodeficiency and lipoprotein lipase deficiency approved in Europe. In the USA, T cells have been genetically engineered with chimeric antigen receptors (CARs) to recognize antigens on tumor cells and as this debate article goes to press, we have seen the FDA approve two CAR T cell therapies for forms of lymphoma and leukemia, respectively. Add the recent approval of gene therapy for an inherited disease, a rare form of childhood blindness, and you see that regenerative medicine is maturing.

To illustrate how this technology had already entered our field I gave the example of work by Professor Farshid Guilak and colleagues. Prof. Guilak and colleagues had genetically engineered stem cells to produce interleukin-1 receptor antagonist (IL1-RA). The cells can be used in tissue engineering cartilage for 'biological' joint replacements. Since the debate, Guilak et al have shown this same feat can be accomplished with the CRISPR/Cas9 technology I mentioned earlier such that the antagonist is only produced in an autoregulated, feedback controlled manner [7]. I didn't get to use this fascinating development in the debate but one can see that regenerative medicine has advanced from the relatively unsophisticated 'drill and fill' paradigm using simple scaffolds containing cells with limited differentiation potential for joint tissue repair. With the highly sophisticated, biocompatible, bioresorbable scaffolds that bioengineers can now create, delivery of sophisticated regenerative therapies that also address the underlying degenerative mechanisms in a joint is now possible. That such therapies can be advanced into the clinic within 50-100 years doesn't seem so implausible any more.

Summary

The debate was always going to be hard to win for those for the motion since metal and plastic orthopaedic implants are without question, a success story. What I attempted to do was show that even with their success some serious downsides remain. Furthermore, I argued that they had plateaued in terms of significant improvement, providing a stimulus for developing new technologies. That notwithstanding, I emphasized how people need to think more carefully, more inventively, and less linearly, when considering the future of our field. I hope I have captured the essence of the arguments I made in this retrospective rerun in print.

Arguing against the motion:

Joshua J. Jacobs MD, Professor, Rush University Medical Center, Chicago, IL

Overview

Regenerative medicine has great potential and has been invested with great hope. Fabricating complex biological structures to replace or restore diseased organs has been the holy grail for decades. While great strides have been made in this scientific discipline, there still are a dearth of evidence-based regenerative medicine solutions to musculoskeletal disease and injury. Furthermore, for orthopedic applications such as total joint replacement, there are no viable regenerative medicine alternatives at the present time. The question to be addressed in this manuscript is whether regenerative medicine approaches to joint replacement will, in our time, supplant the current approach of using metal, ceramic, polymeric and/or composite materials. In my opinion, the answer to this question is an emphatic “no”. Stated another way, implants fabricated from engineering materials will continue to be the standard of care for joint replacement and other orthopedic applications in our lifetimes.

Why vote against the motion?

The argument to support this position is twofold: (1) there are major limitations and unsolved technical challenges in the fabrication of biological replacements for end stage joint failure and (2) the contemporary clinical outcomes of total joint replacement with engineering materials are outstanding; contemporary total joint replacement is associated with high survivorships and excellent functional results due to steady, incremental improvements in implant materials and surgical technique. Furthermore, ongoing research into the biomechanics, biocompatibility, and materials science of total joint replacement promises further improvements in survivorship and functionality over the next decade. In other words, total joint arthroplasty with engineering materials has set a very high bar for performance that will be difficult for regenerative medicine approaches to exceed.

Limitations of Tissue Regeneration Approaches

One of the major limitations of regenerative medicine approaches is that pluripotent stem cells are viable for a relatively short period of time. Human IPS cells may be viable for up to

ten months and human mesenchymal stem cells for three to six months[8]. It is a major technical hurdle to overcome this barrier to success in current regenerative medicine strategies. Another important issue is that there is no evidence that regenerative medicine approaches will actually relieve the pain from end-stage degenerative joint disease. Our understanding of the causes of pain in this condition are incompletely understood; evidence suggests that these pain pathways are quite complicated[9]. While we have decades of experience documenting the dramatic improvement of pain with traditional joint replacements, we do not know if that is going to be case with regenerative medicine interventions.

Another general tactic in the regenerative medicine arena is to stimulate local pluripotent stem cells to regenerate diseased tissues. While this may be a promising approach, in joint replacement applications the enthusiasm is mitigated by the fact that there are very few endogenous mesenchymal stem cells that are identified in joint tissue. In other words, the number of cells simply may not be enough to be activated for tissue regeneration[10]. In addition, there has been recent concerns of malignant transformation of mesenchymal stem cell lines[11]. Regenerative medicine interventions have not completely characterized the risk of malignant transformation; extensive investigative work will be required to fully understand and mitigate this risk.

More Limitations of Tissue Regeneration Approaches

There is great complexity in the pathophysiological processes that lead to the necessity for total joint replacement. One particularly informative way to conceive of this is to consider end-stage joint disease as organ failure, akin to liver failure, heart failure or renal failure. According to Loeser et al: "The pathologic changes seen in OA joints include degradation of the articular **cartilage**, thickening of the subchondral **bone**, osteophyte formation, variable degrees of **synovial** inflammation, degeneration of **ligaments** and, in the knee, the **menisci,** and hypertrophy of the **joint capsule**. There can also be changes in periarticular **muscles**, **nerves**, **bursa**, and local **fat pads** that may contribute to OA or the symptoms of OA. The findings of pathological changes in all of the joint tissues are the impetus for considering OA as a disease of the joint as an organ resulting in **"joint failure"**"[12]. This pan-tissue involvement underscores the tremendous challenge in developing regenerative medicine techniques to treat end-stage joint failure; multiple discrete tissue types are involved and need to be addressed.

Some Other Limitations of Tissue Regeneration Approaches

Regenerative medicine approaches in and of themselves do not take into account the underlying pathomechanics of the disease process. That is, aberrant anatomy may lead to static and/or dynamic overloading and subsequent progressive degradation of native cartilage tissue. Such is the case in the pathogenesis of osteoarthritis associated with femoral acetabular impingement, developmental dysplasia of the hip, adjacent joint deformity, or constitutional genu varus or valgus. If the aberrant biomechanics, whether static or dynamic, are not corrected, tissue engineered constructs will likely be overloaded and degraded as was the native tissue.

The Coup de Gras?

On a more fundamental level, it is currently unclear whether regenerative medicine methodologies in general will be robust enough to recapitulate the complex molecular, morphogenic and biomechanical ontogeny that leads to the complex micro- and nano-structure of mature musculoskeletal tissues and surrounding vital structures. With advancements in developmental biology and the discovery of novel tools for studying and simulating these complex processes this is a possibility; however, I would argue that this advanced state-of-the-science is not feasible within our lifetimes. If not, can tissue engineered constructs that are fabricated with an incomplete understanding of this ontogeny be able to withstand cyclic physiological loads without long term degradation? I think not.

Total Joint Replacement: The Operation of the Century

There is a broad consensus that the development of total joint replacement has been the single greatest advance in the treatment of arthritis in the last century[13]. Until the later part of the 20th Century, individuals that were afflicted with end stage degenerative conditions of their hip or knee were condemned to a life of pain, deformity and limited function. While earlier approaches to mitigating the impact of severe osteoarthritis such as interposition arthroplasty, osteotomy, and arthrodesis resulted in marginal improvements in pain and function, the advent of the modern total joint arthroplasty has created an era in which the vast majority of patients experience a dramatic and long-lasting reduction in pain and improvement in function following these procedures.

Early in the history of arthroplasty, outcomes were compromised by a relatively high rate of failures due to aseptic loosening, periprosthetic joint infection (PJI) and osteolysis/wear. Our understanding of the science of implant fixation has improved dramatically such that modern fixation techniques can facilitate survivorships (with loosening as an end point) in excess of 95% at 20 years of follow-up (Figure 4)[14]. As fixation problems were solved and infection rates were reduced to their current level of <1%, wear related issues emerged as the major limitation to implant longevity. With introduction of alternative bearing surfaces, particularly highly cross-linked ultrahigh molecular weight polyethylene, wear-related failures are far less common due to a dramatic reduction in the polyethylene wear rate[15]. Data from national implant registries have documented the steady improvement in implant performance. For example, in the Australian Orthopaedic Association National Joint Replacement Registry, there is a continued reduction in the overall revision burden. In 2003, revisions comprised 12.9% of all hip arthroplasty procedures whereas in 2015 it was 9.6%[16] and in 2016 there was a further reduction to 8.9%, the lowest level ever reported by this registry[17]. Similar trends were observed in all knee arthroplasty procedures. Likewise, in the Swedish Hip Arthroplasty Register survivorships continue to improve and are quite high (Figure 5).[18] In fact, with good surgical technique utilizing modern bearing surfaces, aseptic loosening, wear and osteolysis have been nearly eliminated at 10 to 15 years postoperative.

There are some remaining challenges with modern total joint arthroplasty that, if successfully addressed, with further improve the survivorship and function while decreasing

the revision burden. Tribocorrosion, PJI, and instability continue to be responsible for a finite number of reconstructive failures, but there is active research in all of these areas that will further improve total joint arthroplasty outcomes. This research will likely include improved diagnostics; precision medicine approaches to implant selection and surveillance using biomarkers and various –omic tools; pharmacological strategies to arrest or retard implant loosening and osteolysis at an early stage; novel coatings to prevent PJI; robotic tools to optimize and customize implant placement and soft-tissue management; further optimization of tribocorrosion resistance of modern implant alloys; and advanced pre-clinical testing protocols, including computer modeling, to predict long term performance.

Summary

Total joint arthroplasty with engineering materials is the operation of the century. The operation is getting better and it is here to stay. Regenerative medicine approaches to total joint replacement are intriguing and alluring, but due to the myriad of issues discussed above, are unlikely to surpass the outcomes of total joint arthroplasty using engineering materials in our lifetimes.

References

1. https://www.gartner.com/technology/research/methodologies/hype-cycle.jsp
2. https://commons.wikimedia.org/w/index.php?curid=10547051
3. https://www.linkedin.com/pulse/8-lessons-from-20-years-hype-cycles-michael-mullany/
4. https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm286155.htm
5. Susan Ratcliffe, ed. (2016). “Roy Amara 1925-2007, American Futurologist”. Oxford Essential Quotations (4th ed.). Oxford University Press.
6. Losina et al. Arthritis Care Res (2015) 67(2):203-215. doi: 10.1002/acr.22412.
7. Brunger et al. Stem Cell Reports (2017) 8(5):1202-1213. doi: 10.1016/j.stemcr.2017.03.022.
8. Chen, D. Personal Communication.
9. Miller, R.E., Miller, R. J. and Malfait, A-M. Osteoarthritis Joint Pain: The Cytokine Connection. Cytokine 70:185-193, 2014.
10. Candela, M.E., Yasuhara, R., Iwamoto, M. and Enomoto-Iwamoto, M. Resident mesenchymal progenitors of articular cartilage. Matrix Biology 39:44-49, 2014.
11. Lee, H-Y. and Hong, I-S. Double-Edged Sword of Mesenchymal Stem Cells: Cancer-Promoting Versus Therapeutic Potential. Cancer Sci 108:1939-1946, 2017.
12. Loeser, R., Goldring, S.R., Scanzello, C. and Goldring, M.B. Osteoarthritis: A Disease of the Joint as an Organ. Arthritis Rheum. 64:1697-1707, 2012.
13. Learmonth, I.D., Young, C., and Rorabeck, C. The Operation of the Century: Total Hip Replacement. Lancet 370:1508-1519, 2007.
14. Della Valle, C.J., Mesko, N.W., Quigley, L., Rosenberg, A.G., Jacobs, J.J. and Galante, J.O. Primary Total Hip Arthroplasty with a Porous-Coated Acetabular Component. A Concise Follow-up, at a Minimum of Twenty Years, of Previous Reports. J Bone Joint Surg 91A:1130-1135, 2009.

15. Hopper, R.H. Jr., Ho, H., Sritulanondha, S., Williams, A.C. and Engh, C.A. Jr. Otto Aufranc Award: Crosslinking Reduces THA Wear, Osteolysis, and Revision Rates at 15-year Followup Compared With Noncrosslinked Polyethylene. Clin Orthop 476:279-290, 2018.
16. Australian Orthopaedic Association National Joint Replacement Registry 2016 Annual Report. Executive Summary, Page 7 https://aoanjrr.sahmri.com/documents/10180/275066/Hip%2C%20Knee%20%26%20Shoulder%20Arthroplasty
17. Australian Orthopaedic Association National Joint Replacement Registry 2017 Annual Report. Executive Summary, Page 7 https://aoanjrr.sahmri.com/documents/10180/397736/Hip%2C%20Knee%20%26%20Shoulder%20Arthroplasty
18. Garellick, G., Karrholm, J., Lindahl, H., Malchau, H., Rogmark, C. and Rolfson, O. The Swedish Hip Arthroplasty Register. Annual Report 2014, p. 91 https://registercentrum.blob.core.windows.net/shpr/r/Annual-report-2014-BJv-q8pil.pdf

Legend to figures

Figure 1: The Hype Cycle (reproduced from [2]).

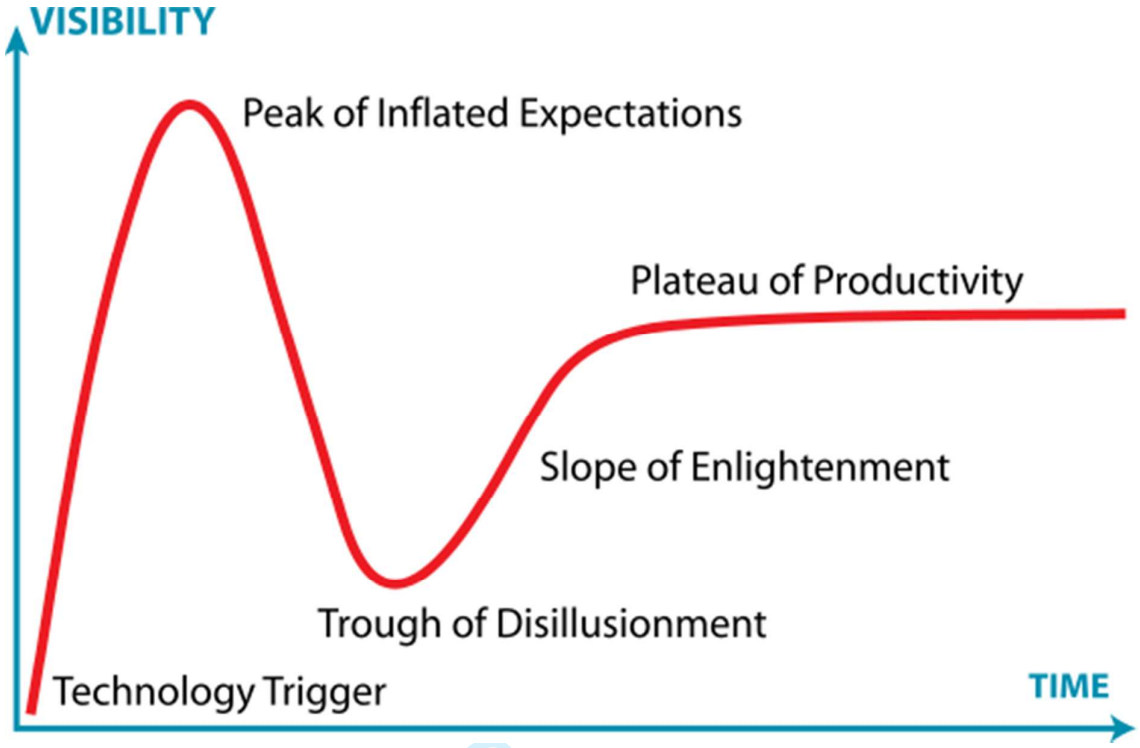
Figure 2: Amara's Law illustrated.

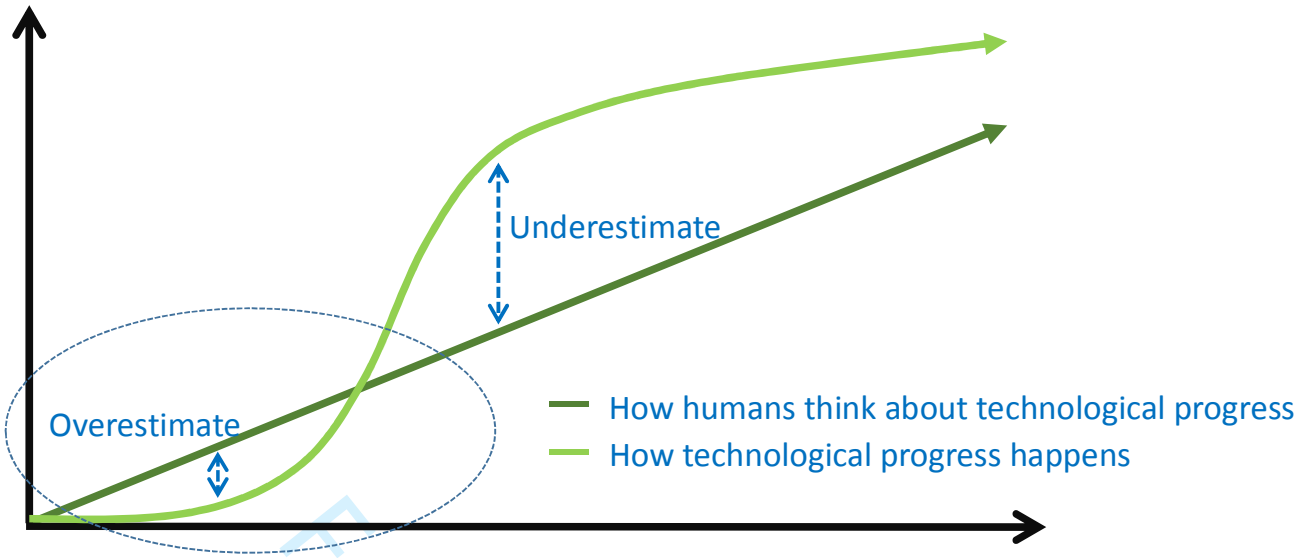
Figure 3: From diagnosis to total knee – a long time of suffering (reproduced from [6]).

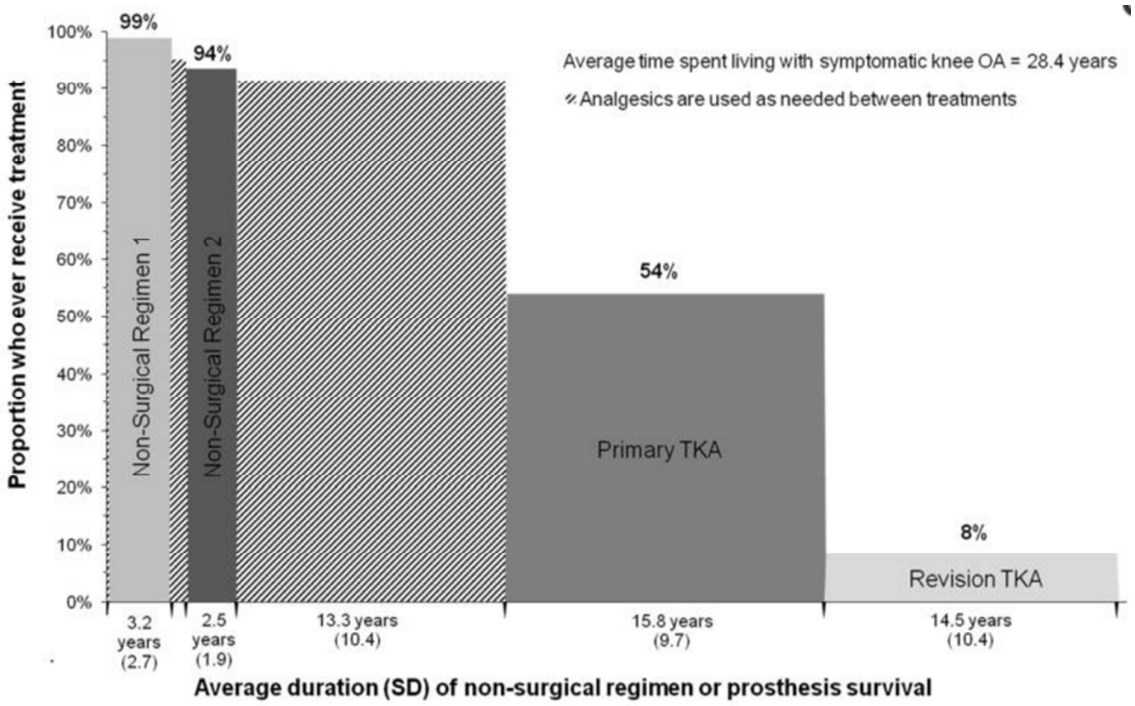
Figure 4A. Histological section showing the osseointegration of a modern cementless acetabular component.

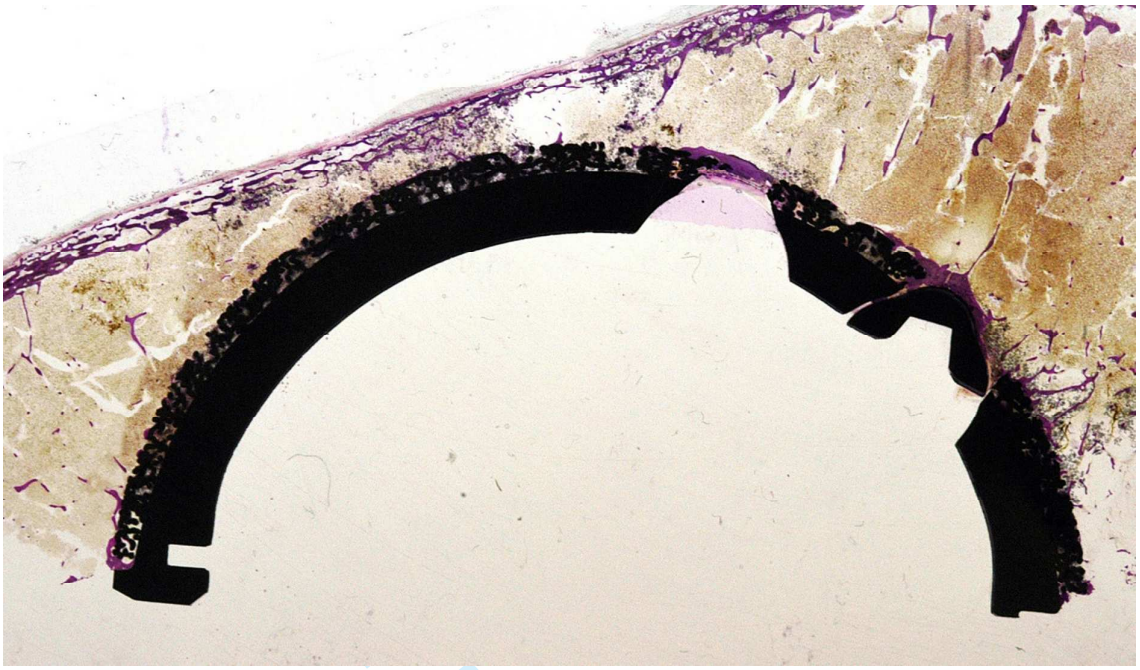
Figure 4B. Close up view of the cementless acetabular component showing mature remodelled lamellar bone at the osseointegration surface

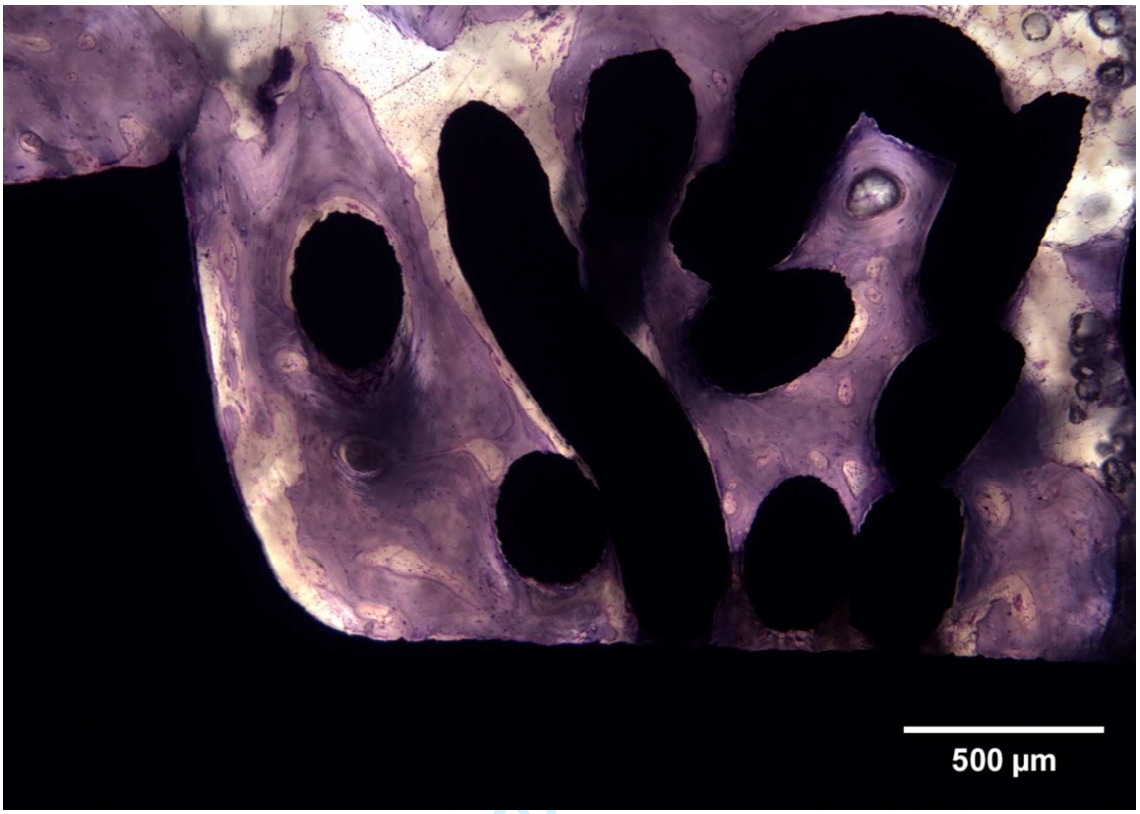
Figure 5. Survivorship of modern hip replacement components illustrated using data from a national register. Is it really likely that a regenerative medicine approach could reach this level of performance within our lifetime? I think not!

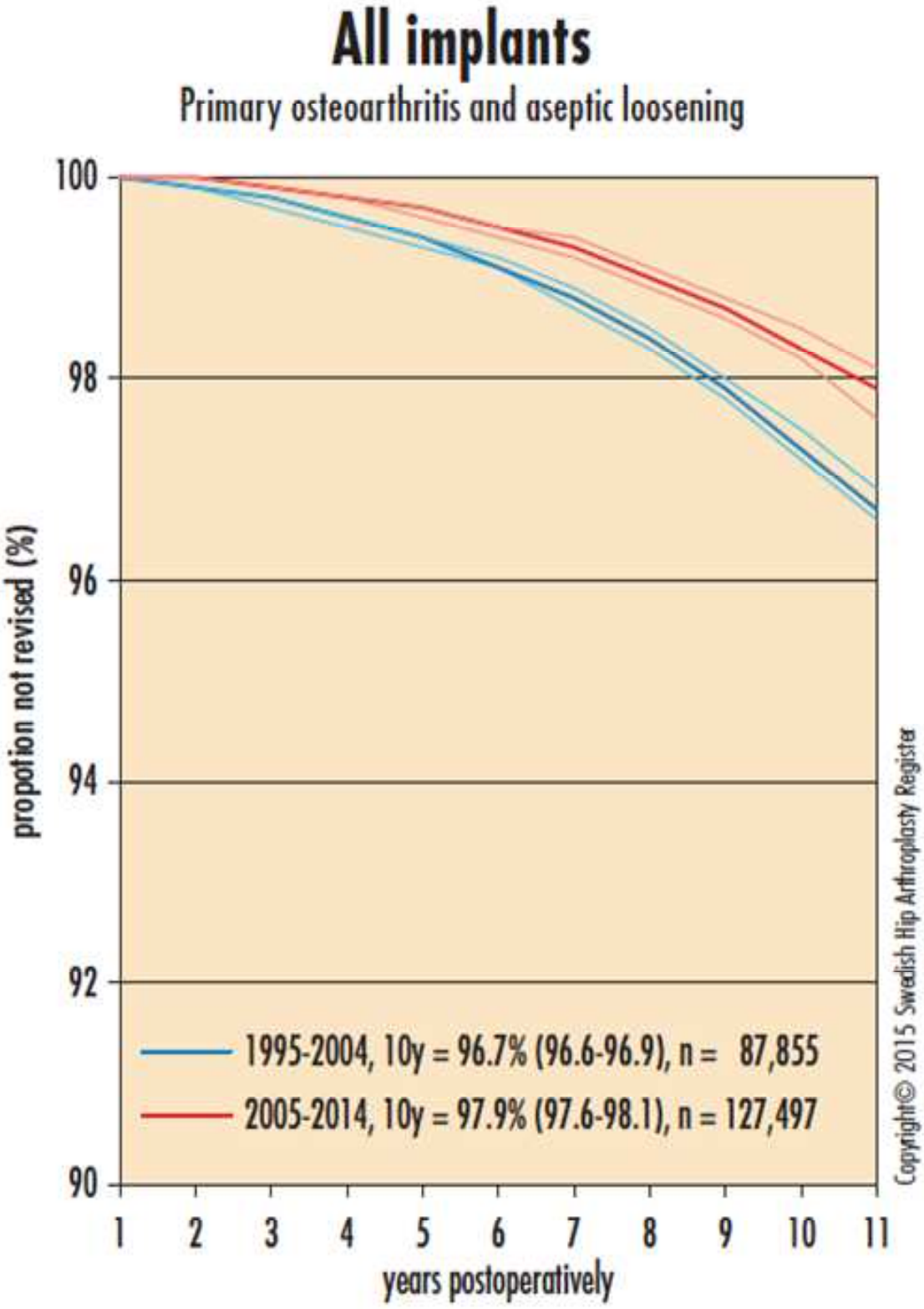

VISIBILITY
Peak of Inflated Expectations
Plateau of Productivity
Slope of Enlightenment
Trough of Disillusionment
Technology Trigger
TIME










All implants
Primary osteoarthritis and aseptic loosening
propotion not revised (%)
100
98
96
94
92
90
1995-2004, 10y = 96.7% (96.6-96.9), n = 87,855
2005-2014, 10y = 97.9% (97.6-98.1), n = 127,497
1 2 3 4 5 6 7 8 9 10 11
years postoperatively
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