



Will biomedical innovation change the future of healthcare?

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Healthcare costs in all industrial nations have increased and payors are starting to look at new ways to contain costs and at new funding models. The business model of pharmaceutical companies is also undergoing rapid changes – potentially disruptive new modalities, such as RNAi, therapeutic vaccines, and cell therapy are emerging, R&D costs have increased year on year, pressures on drug pricing and the efficacy and safety of medicines are mounting. Change is therefore inevitable and already ongoing in healthcare systems and pharmaceutical companies alike. This paper presents several major forces which could drive different future scenarios including: R&D costs, the source of payments for medicines and the emergence of new modalities.

Introduction

Fundamental, 'disruptive', changes to industries can come if mature technologies are replaced by newer ones, such as digital cameras replacing traditional film photography, or internet news threatening paper-based newspapers. In all cases the technology is discovered some 10–20 years before the disruptive change is forced upon the industry. During this period the technology is refined and improved, often combined with other new technology before the case becomes compelling. In the meantime, most of the established practitioners continue to conduct business as usual and actually offer resistance to the new technology. Biomedical innovation is no exception, and new technologies are currently advancing at a rapid pace. For example medical progress has accelerated for some orphan diseases and cancer owing to protein/antibody therapeutics. Other new and potentially much more disruptive technologies are emerging, which could transform healthcare. For instance, new vaccines are undergoing tests today, which, if effective, could cure Alzheimer's disease, smoking and prevent HIV/AIDS, or Malaria. Therapeutic vaccines (directing immune responses against host targets), RNAi and cell therapy are new technology platforms – in fact, they are novel modalities –

that are currently in early clinical trials. These innovations are happening at a time when pharmaceutical companies are questioning and restructuring their business models to improve R&D efficiency and success rates. So far, of all the possible new modalities, only protein therapeutics are mature enough to have become a mainstream approach in big pharmaceutical companies. Yet they are currently too costly to displace small molecule drugs routinely. RNAi, therapeutic vaccines, cell therapy and other new entrants are a more fundamental alternative to traditional small molecule therapeutics in that they, if successful as cures, could compete with or even replace small molecule drugs. This paper speculates about possible future outcomes two decades into the future, which is a similar timescale to the period from inception to medical impact for a conventional drug discovery and development programme. It would seem pertinent to consider what impact the success of such novel modalities might have on all the participants in the healthcare system: patients, healthcare providers, society and pharmaceutical players. Against a current backdrop of high R&D costs, mainly symptomatic management of most major diseases by mainly small molecule medicines, increasingly unsustainable Western healthcare systems and the emergence of drug rationing/uninsured patients, we ask the question how biomedical innovations might change the future of

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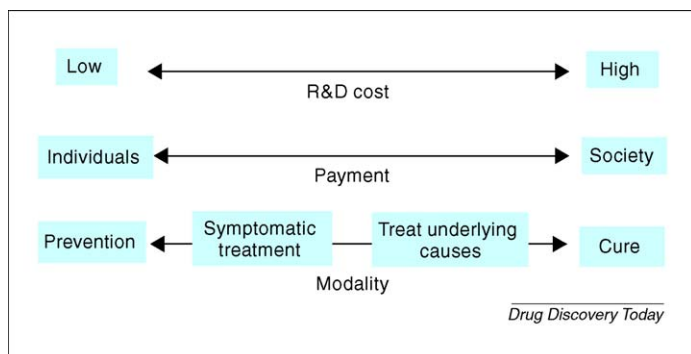


FIGURE 1

Spectrum of future outcomes for patients, healthcare providers/purchasers of medicines and pharmaceutical companies. R&D costs might continue to rise, or they might decrease depending on a range of cost drivers. Payment for medicines might in the future be left to individuals, or become a societal responsibility or a mix of both. Therapies might continue to be predominantly symptomatic treatments (middle). On the other hand, break-through biomedical advances might lead to cures, or preventions.

healthcare. We present several major forces in existence today (Fig. 1) which could drive different future scenarios.

- (1) the cost of R&D that pharmaceutical companies experience, which could be substantially higher or lower than today,
- (2) the willingness of individuals versus society to provide the requisite resources to buy therapies in the future and
- (3) the level of research into, and successful emergence of, new treatment modalities.

Current drivers for change

R&D cost

The cost of producing a medicine is determined to a large extent by the failure rate and associated sunk costs during drug development, but also, to a lesser degree, the efficiency of the R&D process itself. At one end of the spectrum, which defines the current state, the R&D process is long, resource consuming and prone to high failure rates. Attrition is mainly because of incomplete understanding of the pathophysiology and complexity of human disease (resulting in 'picking the wrong target' and leading to failures because of lack of clinical efficacy), and the limitations of current state of the art predictive toxicity screening (a cause of failures due to safety issues) [1]. A third cause of failure is of commercial nature: inability to achieve differentiation over existing treatment, particularly in follow-on drugs, can lead to costly late stage attrition. Finally, the frequently occurring mismatch between what traditional small molecule chemists consider 'druggable' target space and targets that are thought to be central in disease processes is also a cause of failure. This is exacerbated by the fact that many diseases, for example cancer, cannot be addressed through modulation of a single mechanism and increasingly the single drug/cure scenario will be harder to fulfil. The high failure rates and associated empirical learning processes are the most important drivers of R&D costs. Future drivers of high cost scenarios are expensive new modalities that will be described more fully later on in this paper.

Payment structure

The payment structure for healthcare is determined by government policy and cultural attitudes to healthcare. Currently, in

Western Countries, there is a shared responsibility for health-care cost between individuals, markets and society. This partnership is influenced by social, economic and political factors. In some countries, such as the UK, there is a societal expectation for universal healthcare, whilst in others, personal responsibility is emphasised. For example, vaccination programmes for infectious diseases tend to be a societal responsibility (in most countries), whereas elective treatments are largely at the discretion of the individual. The ever-increasing demand for more resources of all healthcare systems to fund newly emerging expensive therapies and technologies is, however, putting pressure on existing payment structures, leading to overt or covert rationing. This pressure is opening the way for potential new future funding models.

Emergence of new modalities that improve or transform care

At present, the majority of therapies are based on small molecule drugs and many of these are not able to prevent or cure disease, but rather alleviate symptoms and stop disease progression. Prevention of disease is currently only possible in some indications, most prominently in infectious diseases, and mainly through vaccines. Thus, the technical limitations of small molecules and the limited scope of current preventative therapies are drivers for new and improved modalities and technology platforms.

The ability to: (a) prevent, (b) address the underlying causes of or (c) even cure disease, all of which would transform the future of healthcare, is intimately linked to biomedical knowledge and effective drug discovery platforms. See Fig. 1.

Diabetes is an example of such transformational impact of new modalities:

- Without treatment, severely diabetic patients (Type 1) invariably die.
- Once insulin (a biological 'replacement' therapy) became available, the underlying causes (insulin resistance or deficiency) could be addressed by injecting insulin. Although a chronic treatment and, therefore, strictly speaking not a cure, injecting exogenous insulin reverts the disease back to near 'normal'.
- Stem cell therapy holds the potential to replace insulin-producing cells, thus providing a cure for the disease and avoiding the significant morbidity associated with incompletely controlled blood sugar levels.
- By contrast, small molecule sulfonylurea drugs merely stimulate insulin production and are ineffective once a patient's pancreas is unable to produce insulin. They are an example of disease modulators.
- Similarly, therapeutic vaccines hold the potential to slow or stop insulin-producing beta cell death and reduce levels of host proteins associated with poor glucose control (disease modulation).

Biomedical and technological advances leading to new modalities

Biomedical and technological progress is such today that we can expect, with some confidence, that new treatment modalities will become available on the market within the next decade or two. Some of these have huge potential as 'disruptive' technologies, with the potential to be vastly more efficacious than small

TABLE 1

Emerging technology platforms/modalities

<i>Technology platform</i>	First clinical or commercial prototype (year)	Current utility of platform
Gene therapy	Adenosine deaminase (ADA) gene deficiency replacement (1990)	Limited due to cancer risk arising from early vectors
Protein/enzyme/hormone replacement (synthetic)	Humulin, Eli Lilly (1982)	Widespread, many therapeutic classes
Therapeutic antibodies (murine)	OKT-3, J&J (1986)	Discontinued due to immunogenicity
Therapeutic antibodies (chimeric)	Campath, Cambridge University/Millennium (2001)	Widespread, several therapeutic classes
Therapeutic antibodies (humanised)	MabThera, Roche (1997)	Widespread, many therapeutic classes
Therapeutic antibodies (human)	Humira, Abbott (2002)	New, emerging platform
Antisense	Vitravene, Isis (1998)	Very limited due to delivery issues and off target effects
RNAi	No approved drug yet – several clinical trials	New, emerging platform, many stability, specificity and delivery issues still to be resolved
Therapeutic vaccines	M-Vax, Avax Technologies (2000)	So far limited utility, many agents for cancer, Alzheimer's asthma and diabetes still in Phase 3, due to efficacy and safety issues
Cell therapies, haematopoietic stem cells	First allogeneic bone marrow transplant, Sloan-Kettering, NY (1973)	Widespread clinical use
Cell therapies, human embryonic stem cells; induced pluripotent stem cells	No approved drug yet – many clinical trials planned	First human embryonic stem cell therapy (Geron) trial in 2009. New emerging platform
Cell therapies, human adult stem cells	No approved drug yet – several late stage clinical studies ongoing, for example graft versus host disease by Osiris (Prochymal)	New emerging platform

The first clinical application of each modality is listed. It should be noted that first entrants rarely display their full potential and the utility of each modality cannot be assessed on that basis. Rather, we assessed each modality on the current state of knowledge about its clinical benefits and breadth of use.

molecule drugs. Early success with some biologicals, most notably cancer drugs (antibodies, protein therapeutics *inter alia*) already indicate such a trend towards more targeted, albeit more expensive, treatments. Second and third generations of such biologicals are already being developed, to address deficiencies, for example delivery, safety and manufacturing issues. The future will most probably see other modalities emerge if technical limitations can be overcome (e.g. delivery issues) (Table 1).

In addition to the advances made with the above-described new modalities, there continues to be substantial progress in understanding disease mechanisms, for example the elucidation of the respective genetic origins of various forms of cancer, or of some hereditary diseases. Together, these two major trends (new

technology platforms and improved disease understanding, enabled by vastly improved information systems) have the potential to combine in the pursuit of addressing the underlying causes of disease or even cures. Several examples of how successful this can exist today, mainly for life-limiting or life-threatening orphan diseases, such as SCID, Hunter's disease and other 'niche indications' (see Table 2). There is good reason to believe that if these areas became commercially attractive to merit significant R&D investment many more transformative therapies could emerge. This is due to the potential increase, through expanding the medical opportunity space, in known 'good drug targets', that is targets that are causative of disease and tractable by an established modality.

TABLE 2

Summary of potentially transformative therapies approved by the FDA (www.fda.gov) over the past decade

<i>Disease</i>	Drug	FDA approval date	Manufacturer	Platform
Hunter's syndrome	Elaprase (idursulfase)	2006	Shire	Protein (enzyme replacement)
Pompe disease	Myozyme (alglucosidase alfa)	2006	Genzyme	Protein (enzyme replacement)
Severe primary IGF-1 deficiency	Increlex (mecasermin)	2005	Tercica	Protein (hormone replacement)
Maroteaux-Lamy syndrome	Naglazyme (galsulfase)	2005	Biomarin	Protein (enzyme replacement)
Acromegaly	Somavert (pegvisomant)	2003	Pharmacia & Upjohn (now Pfizer)	Protein (hormone antagonist)
Hereditary tyrosinaemia	Orfadin (nitisinone)	2002	Swedish Orphan	Small molecule enzyme inhibitor
Rheumatoid arthritis	Enbrel (etanercept)	1998	Immunex	Protein (tumor necrosis factor receptor/TNF antagonist)

Example: SCID

SCID manifests itself as severe immunodeficiency from birth, requiring isolation of such patients from pathogens (bubble boys). The underlying causes of SCID range from ZAP-70 deficiency, JAK-3 kinase, adenosine deaminase (ADA), recombina-activating genes (RAG), to Artemis gene mutations [2]. Recently, gene therapy for SCID has been successful, resulting in several cures, but carries a high risk of inducing leukaemia [3]. Unfortunately, in other diseases, gene therapy has not, so far, been successful and the safety concerns around gene therapy, even in a life-limiting disease such as SCID are currently considered prohibitive [4] for a mainstream therapy. Nevertheless, this platform exemplifies the huge potential that new technology harbours, which in some circumstances can exceed that of traditional small molecule chemistry-derived medicines.

Example: Hunter's syndrome

Hunter's disease is characterised by a defect in a single enzyme, iduronate-2-sulfatase. This insight, combined with the availability of modern protein therapeutic R&D platforms has allowed Shire, a pharmaceutical company, to launch Elaprase (idursulfase) in 2006 (www.fda.gov). Elaprase is a replacement for the missing or defunct natural enzyme that limits the life expectancy of Hunter's syndrome sufferers (patients usually die in early adulthood). This treatment has not been available long enough to understand how it will impact life expectancy and whether chronic medication will fully address the underlying causes of the condition. If successful, it could transform Hunter's disease in the same way that insulin treatment transformed diabetes.

Outlook for new modalities to transform healthcare

Biomedical progress has always been incremental, with the occasional quantum leap every few decades. Biologicals have already provided a huge step forward in addressing the underlying causes of disease (Table 2) through providing replacements for missing endogenous hormones and proteins. New emerging modalities, such as cell therapy, might go even further and provide cures by repairing or replacing damaged tissues. Vaccines have the potential to prevent some diseases, or cure others.

Preventative vaccines

Gardasil (Merck) and Cervarix (GlaxoSmithKline) are two commercial vaccines that both work against human papillomaviruses (HPV). Vaccination against HPV (or rather a mix of HPV types) is expected to prevent up to 70% of all cervical cancers. Whilst cervical cancer is relatively rare, with just under 3000 cases per year in the UK (www.cancerresearchuk.org), and the cost/benefit of HPV vaccination not entirely clear, the economic case for vaccinating entire populations against common and costly diseases seems overwhelming. For example, today there are 40 million people infected with HIV, the vast majority with no, or limited, access to antiviral therapy. Those on retroviral drugs experience side effects and growing drug resistance, which means that at some stage in a patient's therapy, treatment options run out. Thus, a vaccine could prevent numerous deaths, as well as reduce the overwhelming economic costs of the current HIV epidemic. A vaccine to prevent HIV has, so far, proven elusive, with many clinical failures. The latest example, Merck's AIDS

vaccine V520, was stopped in Phase 2 clinical studies in 2007 because of lack of efficacy, most probably associated with the type of immune response induced [5]. Nevertheless, the potential for preventive vaccines exists and poses a realistic future scenario. For instance, a Malaria vaccine (Mosquirix (RTS,S/AS02D), GSK) has recently shown some efficacy in Phase 2 [6]. A phase 3 study in 16,000 children has started in May 2009.

Therapeutic vaccines

Commercial R&D into therapeutic vaccines for cancer, Alzheimer's disease and other indications are at an early stage; for example clinical studies of vaccines against beta-amyloid (ACC-001, Elan/Wyeth) have been conducted in Alzheimer's disease. In addition to beta-amyloid, other proteins, such as tau might be important in the progression of this disease.

There is one marketed therapeutic vaccine available for cancer (M-vax, a melanoma vaccine). Encouraging levels of efficacy have been observed in several clinical studies (AngQb, Hypertension, Cytos; NicVax, Smoking Cessation, Nabi; GVAX, Cancer, Cell Genesys). This indicates that our increasing knowledge in how to manipulate the immune system offers exciting prospects for future therapies. The potential for therapeutic vaccines to have a lower cost base and infrequent simple administration, that assists with patient compliance, positions therapeutic vaccines as an attractive alternative for managing disease.

RNAi

Most approaches towards debilitating and life-limiting diseases today that are attempting to provide cures (or at least superior efficacy at disease modulation) use protein therapy platforms (Table 2). Other, newer, technologies are emerging, such as RNAi. In mouse models, HBV infection can be long-term suppressed by systemic siRNAs [7]. Whilst several clinical trials of siRNAs in a range of disease indications are ongoing, and many more in the pipeline, there is still inconclusive evidence whether RNAi can be delivered and targeted as clinical therapeutic agents. In January 2008, Alnylam Pharmaceuticals published data that the RNAi therapeutic ALN-RSV01 showed efficacy in a small Phase 2 experimental RSV infection study (GEMINI study) (<http://www.reuters.com/article/press-release/idUS134636+23-Jan-2008+BW20080123>), although there is uncertainty whether this was due to reduced gene expression. So far, no further evidence has emerged that clinical efficacy can be achieved consistently and selectively across a larger population. Furthermore, similar to other new modalities, delivery issues remain an unresolved issue for wider therapeutic use of RNAi.

It is becoming increasingly clear that degenerative diseases such as osteoarthritis, heart disease, Alzheimer's disease, diabetes, osteoporosis, and cancer are influenced by both genetic and environmental factors that impact at the gene transcription level [8,9]. Thus, not just cancer, but a range of degenerative disorders might be amenable to epigenetic modulation as a therapy. DNA and histone methylation/demethylation and acetylation/deacetylation mechanisms are currently considered some of the more important intervention points to modulate gene transcription. Although non-selective small molecule drugs, most prominently, histone deacetylase inhibitors (HDAC inhibitors), exist, selective and specific intervention in DNA expression via small molecules was up until recently thought to be very difficult. There are some

examples of successful traditional small molecule intervention at the transcriptional level, such as modulators of various nuclear hormone receptors (e.g. Mifepristone (an antagonist of glucocorticoid and progesterone receptors), Tamoxifen (an estrogen receptor modulator) and Bortezomib (a nuclear factor kappa B inhibitor)) and some antibiotics (e.g. some aminoglycosides and macrolides) that regulate gene transcription [10–12]. Traditional small molecule drug discovery in this area is difficult and hampered by the complexity of the targets (i.e. large protein complexes) or by the difficulty to achieve selectivity over a large number of rather similar isoforms of DNA/histone-modulating enzymes [13].

Cell therapy

Another emerging platform is cell therapy. Autologous and allogeneic stem cell treatment in the form of bone marrow transplants (e.g. for leukaemia patients) has been established as a therapy for decades and, in many cases, combined with chemo/radio-therapy, provide cures. What is new today is the emergence of new technology that allows the expansion and differentiation of progenitor cells to transplant larger quantities of specific cell types either from human embryonic cell lines, from adult stem cells or from induced pluripotent cells. These efforts are still in their infancy, although some early clinical results with autologous bone marrow stem cells in patients with cardiovascular disease are encouraging [14,15]. The earlier example of diabetes indicates the potential for cures that this modality holds.

Current barriers to change

High risk R&D process

Economic realities and pipeline attrition are barriers for the emergence of significant numbers of truly curative medicines on the market. For example, if an early R&D portfolio starts with a 50:50 split between high risk novel modalities and lower risk projects, such as small molecule projects with tractable targets that have a clear link to disease (and where maybe even an exciting marketed drug already exists), and if the lower risk projects 'survive' at a five to ten times higher rate to market then it is easy to see that the medicines brought to market will predominantly be lower risk, incremental advances on established modalities. This holds true even if the R&D funding for each cohort is equal and each receives similar management attention. Of course, this means that lower risk approaches, particularly for blockbuster diseases, yield better returns on investment. The dilemma for all stakeholders involved is that few of these incremental advances are likely to address future challenges by transforming the future of healthcare, although some, such as the lipid lowering statins, have done just that, resulting in a significant decrease in the number of deaths from heart disease and stroke [16,17].

Insufficient resources

Many current trends point to the tantalising possibility that if only the funds required to conduct R&D on the types of therapies and modalities described above (e.g. Table 2) could be increased by input from more stakeholders, many more diseases, including degenerative disorders, but also orphan diseases, would be conquered. Additional, tractable, targets might become available, niche diseases could become commercially more attractive, if

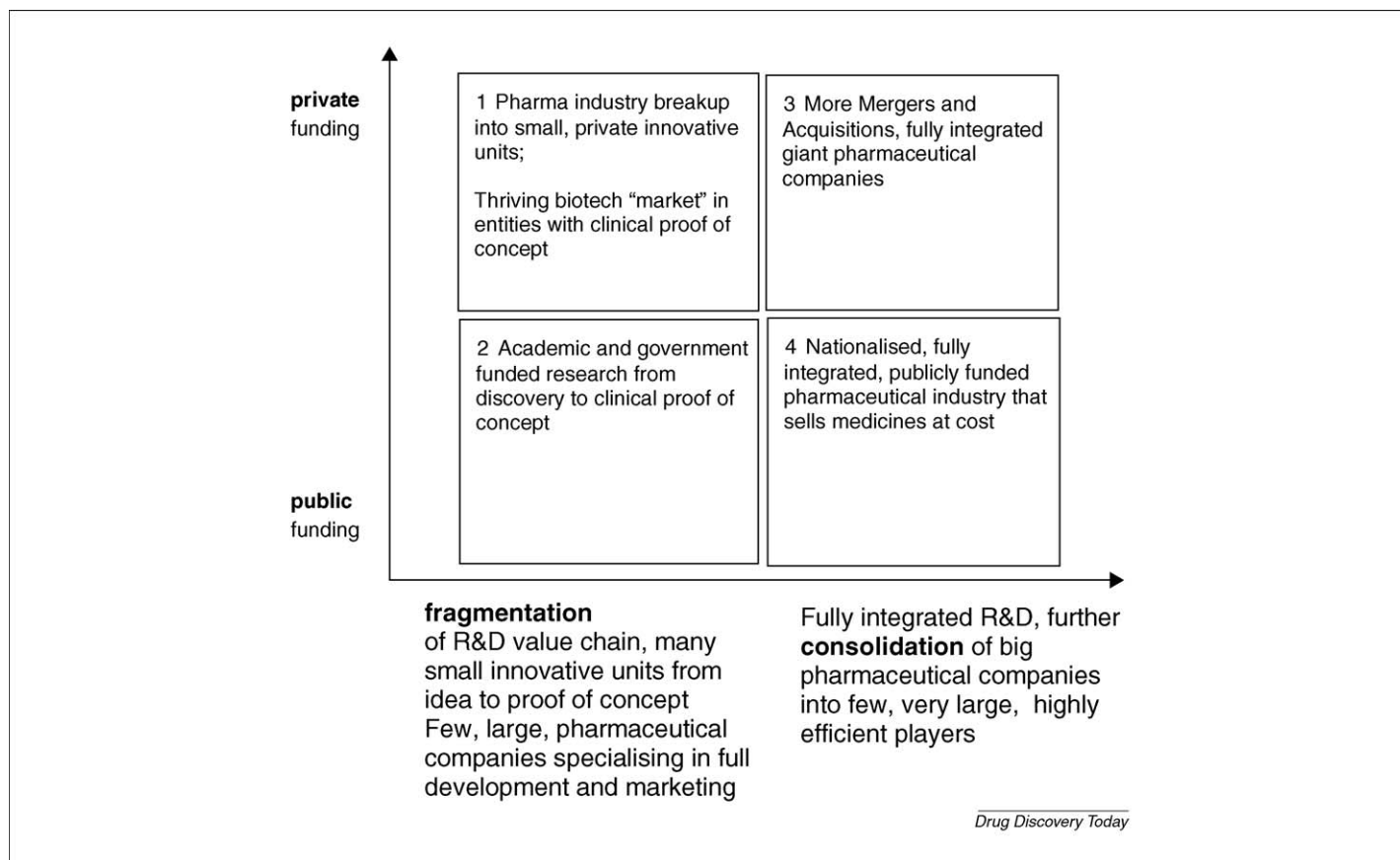
return on investment can be guaranteed, or R&D costs co-sponsored. These areas tend not, however, to get much commercial funding, because the patient numbers are too low and the R&D costs too high to generate any return on investment. Although there is philanthropic and 'not-for-profit' investment into neglected and orphan diseases, the effort is fragmented and usually lacks the R&D experience and focus that large pharmaceutical companies can bring. Furthermore, smaller research institutes or biotechnology firms rarely have the funds to conduct Research AND Development. In economic terms, this is a misalignment of funding opportunities in that early, academic and discovery work often gets funded, only to stall at the expensive development stage – or worse, patients are denied new drugs that emerge on the market place. By contrast, R&D into areas of higher patient numbers, but sometimes lesser medical need is conducted by large companies because the funding model is integrated and a market opportunity is evident.

The willingness of commercial companies to risk R&D funds in niche indications depends on the likelihood to recoup the cost of the initial investment. There is a trend today towards a greater degree of cost consciousness by payors, so some significant political intervention or societal demand would have to take place to allow pricing models that would make niche indications commercially attractive in the current industry structure. This dilemma was played out in full in the UK recently, where commercial return, pricing of a medicine and societal forces favouring the patient came into conflict. Lucentis (ranibizumab, Genentech), a drug that prevents blindness in wet age-related macular degeneration (AMD) was 'rationed' in the UK. The national institute for health and clinical excellence (NICE), which provides guidance on cost-effectiveness of new drugs to NHS payors took the view that, at £10,000 for each eye treated, patients would have to wait for the first eye to go blind before receiving treatment. This decision was reversed, but only after Novartis (who co-market the drug with Genentech) agreed to cap the costs at 14 injections (www.nice.org.uk).

Other drugs currently rationed are high cost, life-prolonging cancer drugs, including Avastin, Herceptin and Sutent. These drugs have triggered a political debate (and recent go-ahead) for co-payments by patients in the UK. This move contradicts the founding principles of the NHS in the UK (free at the point of delivery), but implicitly acknowledges that denying medicines to needy patients on the basis of cost is not a solution to the problem. It is conceivable that such co-payment could open up the medical insurance market and attract significant additional funding beyond taxation, thus placing many more life-saving drugs in the reach of patients. In the US, such constraints exist also; the varying degrees of insurance cover (ranging from no cover to gold plated), limits access to drugs for those unable to buy into the required insurance systems that provide these drugs.

The future of healthcare

The future of healthcare will demand cheaper or better, but most certainly more cost effective therapies (defined as the benefit–price ratio). Some emerging new modalities hold the potential for lower cost and therefore lower prices, particularly if administration and compliance is simple. This scenario is delivered by infrequently administered, low dose therapeutics, such as vaccines or stem cells.

**FIGURE 2**

Potential future structural changes to the pharmaceutical industry. To reconcile the dilemma between promoting biomedical innovation in high need diseases and managing the cost of novel medicines, four extreme future industry structures are conceivable. Structure 1 would enable private enterprise and innovation, favouring many small, flexible, private research units. These would compete with each other in a free market for drugs with clinical proof of concept data or platform technologies. Structure 2 would use taxpayers' money to fund innovation in a large number of small government laboratories up to proof of concept. Structure 3 would see few, very large, private pharmaceutical companies continuing to fight increasing R&D costs. Structure 4 would be a nationalised publicly funded pharmaceutical industry. Structures 1 and 2 could sell clinical proof of concepts to either public or private full development specialist organisations. Innovation potential based on existing skills distribution (defined as chances of producing successful new therapeutic entities): structure 1 > 2 > 3 > 4.

Given the pressures on healthcare budgets, biomedical innovation alone will not drive a brighter future for healthcare. Even though many transformational therapies are already emerging on the market place, many are either not affordable to all patients (e.g. targeted cancer therapies, protein therapeutics), do not attract sufficient funding to progress all the way through the R&D process (e.g. many orphan diseases) or subject to other commercial barriers. We believe that a new finance model is necessary either to fund publicly or to co-fund R&D into high medical need areas (Fig. 2, structures 2 and 4) or by accepting high drug prices as a necessity and pay for these in new ways. These could include increased general taxation, cradle-to-grave general insurance, general health savings systems (similar to state pensions) or some other means. Changes to the structure of the industry might also be conceivable to fund high risk, or commercially unviable areas. In such a scenario, the pharmaceutical value chain might break up into Research at the front end, served by an array of small- to mid-sized research or biotechnology companies taking the new drugs as far as early clinical development to ascertain a degree of confidence in efficacy and safety (Fig. 2). Full-scale Development in this scenario could be publicly funded, possibly concentrated in very few specialised development companies. These would buy up

potential medicines at competitive market prices from the private research companies once they have proven early clinical efficacy. Successful products would be made available to patients at cost. In either scenario, society pays for the creation of novel and effective medicines, either by directly funding the expensive development stage, or indirectly through risk-premiums for innovation in the pricing of the medicine.

Conclusion

In our paper we work from the assumption that as a society we want to have access to new life-saving drugs. For a patient, it is irrelevant how those medicines get discovered, as long as they are available in times of need. The cost of bringing drugs to market might reduce somewhat through biomedical advances and greater efficiencies, but are unlikely to ever be insignificant. Yet the cost of bringing drugs to market is a major barrier in the availability of drugs to patients with 'niche' diseases. A cost-sharing model might be a possible way forward in that in any future scenario, the overall cost and risk is merely distributed differently between patients, companies and payors and the timing of the payment differs (upfront funding of R&D versus later payment of a price premium of the marketed medicine).

Indication	Inderal, propranolol: 1960-70s Patient numbers	Tekturna, aliskeren: 2007 Patient numbers
Hypertension -	107 (uncontrolled) monotherapy plus diuretic	2,730 treated monotherapy 2,776 treated plus hydrochlorothiazide 1,797 treated plus valsartan
Angina pectoris	32	
Atrial fibrillation	10	
Migraine	62	
Essential tremor	9	
Hypertrophic subaortic stenosis	13	
Pheochromocytoma	3	

Drug Discovery Today

FIGURE 3

The rising complexity, limitations and cost of full development. Comparison of patient numbers and approved indications of cardiovascular experimental drugs in the 1970s versus today.

We argue the case that emerging new modalities (i.e. platform technologies such as protein and antibody therapeutics, therapeutic vaccines RNAi and stem cells) hold enormous potential to reduce the existing unmet medical need by accessing disease areas with known, but neglected drug targets or by making undruggable areas potentially drugable (e.g. stem cells). Table 2 demonstrates that novel modalities can treat diseases where small molecules may not be suitable (e.g. enzyme replacement). A huge opportunity space exists, but R&D efforts are mainly directed towards a commercially attractive subset of this space.

R&D into such novel modalities is risky and expensive, with the pharmaceutical industry currently shouldering the burden of huge R&D outlays (Fig. 3) before reimbursement and profit. Not surprisingly, the companies require the maximum return on their investment and will be reluctant to conduct R&D into areas without clear commercial potential. Similarly, early, novel technologies and modalities that carry high risks will not always be moved to a stage where they can prove whether or not they will be successful. Sometimes, the initial investment might be made by small players, but they rarely have the funds to bring a medicine all the way to market without a major partner – and those partners are increasingly looking to reduce the cost of their R&D operations and are more and more selective in the partnerships they fund, even at the risk of being locked out.

Greater partnership between all the participants could mean society, in the form of government and healthcare sector partici-

pants align available funds better along the R&D value chain, and share some of the risks of drug development earlier. Could proof of concept (Phase 2a) studies provide for reimbursement and the drugs then be developed under government funding to full clinical use and priced accordingly? Considering this scenario indicates a better return for discovery/early development pharmaceuticals and a substantially lower cost of the eventual medicine.

It is an ongoing dilemma that the resources required to bring such transformational biomedical innovation to patients requires two fundamentally different organisational models rather than the current one size fits all.

For break-through innovations to emerge, a multitude of small, flexible units, such as biotechnology or small pharmaceutical units might be better suited to generate novel technologies, platforms and modalities, identify superior drug targets and prove clinical efficacy and safety in small patient studies. Some of these platforms and modalities could lower R&D costs and healthcare costs overall. These units are not, however, able to fund full development and usually cannot bring drugs to market on their own. Currently, many such small players exist, in the form of biotechnology companies, or as Research Units within larger pharmaceutical companies. But their research is of high risk, many companies are completely unsuccessful and disappear as entities after a few years. This is only to be expected, given the risk profile and often single project portfolios. The rare successes stem from the large and diverse numbers of such units that increase the likelihood of

an occasional positive outcome. These rare events can bring fundamental change to an industry, as shown by the rise of Genentech from a small biotechnology company to a very large pharmaceutical company through the success of their early biological drugs.

By contrast, the cost of full development drives companies to consolidate and increases scale to generate efficiencies, which can reduce the focus on, diversity of and funding for, more risky innovations at the front end.

Thus, despite huge investment in biomedical research and development, advances in therapy and clear links to increased patient survival, a large funding gap for modern therapies remains and the existing funds are not well aligned to ultimately benefit all patients whether they suffer from a commercially unviable disease or a 'blockbuster' illness. Unless a way can be found to reduce the cost of R&D and/or the willingness increases to fund such therapy through novel means the current inequalities in healthcare around the world will remain. Efforts to solve this conundrum are made currently by the Pharmaceutical industry, Regulators and

Governments. For instance, Drug Registries are often publicly funded and provide valuable clinical data that support the R&D efforts of commercial and not-for-profit companies alike; but to harness the full potential of biomedical innovation to transform healthcare requires a more systematic and fundamental agreement on how R&D should be structured, sponsored, funded and directed by all three stakeholders. We hope that our paper will be the vehicle to open a wider debate.

Conflict of interest

All authors declare a conflict of interest for being employed by Pfizer, a major pharmaceutical company, and holding stocks and shares in the company.

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