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Demand for medicines is growing around the world - yet innovation and the availability of more and better medicines may actually fuel this demand. How much reduction in medical need will we be able to afford? And who should pay for it?

Pharmaceutical R&D in the spotlight: why is there still unmet medical need?

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Huge amounts of money and knowledge have been poured into biomedical research for decades. Yet, in some disease areas next to no progress has been made in providing medical treatment. Importantly, it is not only neglected diseases where unmet medical need remains, but many diseases of 'rich' countries are also affected. Occasionally, new therapies exacerbate the medical need gap, such as in cancer. Our paper discusses some of the reasons why this might be and why all of society needs to find solutions to address unmet medical need.

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His wish in his work now is to have fun in the science and "to inspire another generation to take up the cudgel against disease".

Introduction

In the US alone, more than 50,000 biomedical PhDs and post docs are conducting basic, translational, or clinical research, which is funded by over $90 billion each year [1,2]. Worldwide that figure is about twice that. Not only is there a rich source of funding and talent for R&D, but also there is a phenomenal wealth of scientific substrate (drug targets) and scientific knowledge from which new therapies can be produced.

About 8000 potential drug targets for small synthetic molecules and protein/antibody therapeutics exist in the human genome [3]. Approximately 218 of those are already on the market [4] and roughly 100 are in advanced clinical development (http://www.iddb.com). An educated guess would predict that between the major pharmaceutical and biotechnology companies, another 500–800 mechanisms are being explored somewhere in the R&D continuum. Despite this wealth of substrate and information and despite a rising number of drugs on the market [5], the progress to reduce medical need and disease burden, not just in the developing world, but also in industrialized countries, seems agonizingly slow. The combined efforts of all public and private R&D efforts worldwide bring only around five drugs directed against completely novel mechanisms successfully to market each year [6]. Most drugs, whether first against a novel mechanism, or a follow-on entity, have had some therapeutic benefit, and some had phenomenal impact on mortality and morbidity, such as the lipid-lowering agents. However, in many diseases, the 'big cures' have not been discovered yet. Neurological damage (either as a result of accident or stroke), Alzheimer's disease, chronic heart failure, chronic obstructive pulmonary disease, many cancers,

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1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2007.08.013

obesity, and other chronic conditions have few or no treatment options. What could be the reason?

Some speculate that the 'low-hanging fruit', that is, those targets that are easily druggable and of disease relevance, has already been taken, leaving only difficult targets.

Other opinions point to the change in discovery paradigm in the mid-1990s and the move from whole animal screening to a reductionist approach, thus increasing attrition rates through flawed efficacy-safety–ADME relationships (since the main focus was on *in vitro* efficacy, which often could not be combined with required ADMET properties *in vivo*).

Another school of thought blames the shift from scientific freedom toward commercialism, unwieldy size, and process cultures by pharmaceutical companies [7]. The pharmaceutical industry also stands accused of channeling too much R&D investment into 'me too' drugs, that is, the pursuit of drugs against mechanisms that have already yielded a medicine.

Even the US Biotechnology sector, which consists of roughly 2600 firms, has been criticized for a diminishing appetite in risk taking [8].

Industry insiders will point to the shift in R&D portfolios from the better-served acute diseases (e.g. inflammatory pain) to those conditions where medical need is still unmet. These tend to be conditions of more chronic or difficult nature (e.g. Alzheimer's disease, heart failure, and stroke), and they tend to pose enormous 'translation' problems from preclinical models to human efficacy.

Any of the reasons stated above could account for a lack of progress in the significant number of indications of both high medical need and large epidemiological burden, for which few or no treatment options exist today. As if that was not enough, the limited, mainly philanthropic, pharmaceutical investment into neglected diseases (http://www.doctorswithoutborders.org/publications/opedsarticles/gillies_ft_05-24-2006.cfm) is thought to be a barrier to developing much needed treatment options for rare genetic disorders or diseases of the developing world, such as Malaria. We use the example of cystic fibrosis (CF) to exemplify the difficulties that such diseases pose for R&D and for society.

R&D costs and risks raise costs and leave gaps in the availability (and affordability) of new medicines

An analysis of the druggable genome [3] indicates that there is no shortness of quality R&D substrates, particularly since there are many more drug targets than genetic analysis would suggest. However, the risk associated with novel, druggable targets is substantial (which target should you choose and why?) and the investment in taking many targets forward until they fail, surpasses even the financial means of large pharmaceutical companies.

There are now several examples of genomic clinical rationale leading to substantially accelerated and successful drug discovery and development programmes. Among those are CCR5 receptor antagonists; the observation that human CCR5 receptor deletion conveys resistance to AIDS led to the development of Maraviroc. The finding that Philadelphia chromosome aberration leads to dysfunctional kinase activity in leukemia patients led to the development of bcr-abl kinase inhibitors, of which Gleevec is a marketed example, or that human Nav 1.7 dysfunction leads to lack of pain sensation, has led to an interest in development of Nav 1.7 blockers, which are currently in early stages of R&D. Despite these positive examples, the recent CETP inhibitor failure (torcetrapib, Pfizer), due to a safety finding despite an excellent genomic clinical rationale, is a point in case that careful project selection reduces, but does not eliminate risk, particularly if large clinical studies are required.

Limitations that impair the discovery of new medicines – medical need remains unmet

Why are there no drugs for stroke victims?

Around 50 neuroprotective drugs were tested between 1995 and 1999 in 74,000 patients [9], none of which demonstrated any efficacy, despite promising preclinical results. At an average cost of $8000 per patient in stroke trials [10], this equates to almost $6 billion in clinical trial costs alone, without even counting the discovery and preclinical costs.

In our own house, R&D colleagues explored several agents for the treatment of ischemic stroke, one of which was neutrophil inhibitory factor (NIF), a biological agent with a novel mechanism. This agent, which was supposed to limit reperfusion damage via blockade of neutrophil infiltration into sites of tissue damage, showed preclinical efficacy when tested in stroke models [11,12], but failed in patient trials. Other companies did not fare better with other neuroprotective mechanisms (e.g. NMDA antagonists, glycine site antagonists). Clearly, the limited understanding and complexity of the pathophysiological processes that leads to neurological damage after a stroke, the possible irreversibility of some of these processes, the limited understanding of primary pharmacology-driven side effects combined with nonpredictive animal models all contributed to these failures. Part of the difficulty may be differences in time window to treatment following infarct between animal models of instant treatment and the human clinical picture where most treatment may occur hours after a stroke. A compounding factor, almost certainly, has been the fact that PK/PD relationships from animal models to the human setting, including brain penetration, was poorly understood or not investigated. This meant that it has not been possible to separate whether the mechanism has not been tested in humans (because the compound did not reach the required concentrations) or whether the mechanism has been tested and simply does not work. At least now there are new clinical tools available, most notably imaging technologies. They can shed some light on receptor occupancy and possibly pharmacological drug effects in volunteers or patients to determine if the chemical entity has the required effects, even if proving efficacy of the target mechanism may require more extensive clinical testing.

The stroke example highlights the enormous risks involved in the pursuit of novel approaches in high medical need areas, particularly if the knowledge base is limited and no predictive preclinical models of efficacy exist that would allow a more empirical approach. The cost and complexity of definitive clinical studies is high and has made many pharmaceutical companies rethink whether to conduct R&D for stroke. Although the pathways involved in reperfusion injury are becoming clearer, and the tools and clinical designs have improved, there is at present still a knowledge gap that limits the R&D opportunities in this area. It seems unlikely that there will be a major breakthrough for stroke in the foreseeable future via targeted therapies. This does not rule out that some of the emerging technologies, such as stem cells, which

do not require a mechanism-based understanding of this disease, could bypass this gap in the future.

Why does oncology seem to fare better than stroke?

In contrast to stroke, there are now a range of targeted therapies emerging for various cancer indications, such as Gleevec and Mylotarg for leukemia, Herceptin for breast cancer, and others. Whilst the path to these successes has been thorny, it is becoming obvious that there could be many efficacious medicines to come in this field.

Unlike reperfusion injury, cancer has a clear genetic component, and indeed is caused by changes in gene function. Therefore, oncology is the ideal setting for targeted therapies, provided that cancer can be understood at the genetic and the pathway level. Therefore, the need for predictive preclinical models lessens, and the need to explore human genetic variations increases, paving the way for personalized medicines.

The number of clinical cancer studies is amazing: 3500 open and 15,000 closed cancer clinical trials are listed around the world (http://www.resresources.nci.nih.gov/database.cfm?id=1264). The national cancer institute (NCI) alone has a budget of $5 billion each year (http://www.plan.cancer.gov/plan_downloads.html). There are now (as of 2006) 650 medicines in development for cancer (http://www.phrma.org). A rise of 30% compared to 2005. Whilst a 'cure' for cancer is still an elusive goal, there has been a steady rise in life expectancy after cancer diagnosis, which, to a significant extent, is because of drug treatments. However, the success of R&D and the resulting availability of new therapies do not necessarily reduce the medical need gap as new drugs are added to existing regimens and the cumulative costs of therapy and longer life are starting to make some treatments unaffordable. In the UK, Velcade (bortezomib), for multiple myeloma, costs around $36,000 per patient (http://www.ukmi.nhs.uk/NewMaterial/Secure/BortezomibRGB.pdf). Yet this drug was not considered cost-effective by NICE, despite prolonging life by a median of six months versus dexamethasone (http://www.velcade.info/).

Shifting expectations – growing (rather than reducing) medical need through advances in therapy

The complex relationship between medical need and disease treatment can be illustrated by following the history of a disease and its impact on patients. Cystic Fibrosis (CF) is one of the most common genetic conditions and affects 1 in 2500 newborns. It is characterized by defective function of the pancreas and chronic obstruction and infection of the lungs. Originally, life expectancy was very short and the disease was viewed in the 1920s as congenital intestinal obstruction [13]. With improved diet, the pulmonary disorders became more dominant and contributed to the classification of CF. A clinical test, the sweat test, allowed more precise diagnosis in the 1970s. From the 1950s, CF was observed to be a classic Mendelian recessive disorder. The CF gene locus was identified in 1989. Over 1000 different mutations of the CFTR (cystic fibrosis transmembrane conductance regulator) gene have been identified, with the most common one, delta F508, accounting for around 70% of the cases [14]. CFTR is an ABC transporter (ATP-binding cassette transporter) and functions as a cAMP-regulated chloride ion channel. The tools to enable early diagnosis (such as genotyping) have played a part in the evolution of treatment. What was viewed as a fatal disorder of the very young, now has a median expectancy of close to 40 years, with patients surviving into their 50s. This trend is likely to continue. Treatment, though, is aggressive and time consuming. In the disease state, pancreatic enzymes are not released due to the thick mucus layer caused by the defective CFTR coded for by the gene. Pancreatic enzyme replacement therapy (PERT) replaces those enzymes [15]. The mucus layer in the lungs is daily disrupted by physiotherapy and the disposition to infection is counteracted by frequent courses of antibiotics. Treatment will occupy two to three hours of a patient's day and patients require constant medical support. Notwithstanding the ardour of treatment, patients can lead active or super-active lives; several patients have participated as marathon runners and so on. What is apparent is that medical need and, importantly, expectations of therapeutic benefit have changed. It is arguable that the accomplishment of treatment intervention and its impact on life expectancy has raised medical need. Even if this may seem an extreme definition, the medical need has changed from a short fatal disorder to a chronic debilitating (and costly) disease. The frequent use of powerful antibiotics, such as aminoglycosides (e.g. tobramycin) and macrolides (e.g. azithromycin), raises the possibility of inducing resistance. However, the discovery of CFTR, and accompanying disease-modifying genes, has opened the way for both traditional therapeutic discovery options [16,17] and the tantalizing prospect of gene therapy [14], or perhaps a combination of the two.

Moving to close this gap in medical need is very complex, in contrast to the existing therapeutic rationale. The large number of sequence variations lead to different outcomes for the CFTR mutations. Five classes of outcome [18] have been identified: defective protein synthesis, defective protein processing, defective protein regulation, altered conductance, and reduced CFTR level. The major delta F508 mutation results in the synthesis of a CFTR protein that is unable to fold correctly and is, therefore, largely retained and degraded in the endoplasmic reticulum. This defect in protein processing is also accompanied by abnormal exocytosis and recycling of the protein in the plasma membrane. Specific therapy aimed at this would need to correct protein folding and trafficking. Such a therapy would have little effect on the other classes of abnormalities, which all result in different degrees of CF, and are present in varying proportions in populations of different origins. For instance, defective protein synthesis is caused by stop-codon mutations, which cause the synthesis of inactive protein. Different strategies directed at delta F508 are clearly required. That this is druggable has already been exemplified: aminoglycosides show some activity *in vitro* and *in vivo* as they promote read-through of the stop-codon and synthesis of the protein.

CF represents an example disease as to why, despite the huge advance of medicine, there is still a huge and, arguably, growing medical need. The treatment of symptoms (diet, digestive enzymes, physiotherapy, and antibiotics) drives this widening gap. Although the disease is modified by a number of effects as outlined above, there is no doubt that correction of CFTR defects would attenuate or eliminate the severity of the disease in a large number of patients, even though the impact would vary with the patient origin. Although this is a single gene (and therefore medically attractive as a target for intervention), it has numerous mutations, leading to a variety of outcomes. Each outcome repre-

sents a different route that prevents functional CFTR protein being delivered to the plasma membrane. Each would require a different type of therapy with conventional medicine (delivery of a small or large molecule drug). Gene therapy is attractive, but remains a tantalizing prospect for the near future. Some narrowing of the gap can occur by use of existing medicines, as with all diseases. Inflammation is a part of the CF disease and NSAIDS, such as ibuprofen, has been successfully tried. In addition, research and understanding of medicines does not stop at the drug discovery or even the development stage. Only after extensive clinical usage will the best way to use a drug become clear; showing unexpected benefits or side effects that would not be seen in clinical trial. Azithromycin has been widely used as an antibiotic in CF. Gradually, as a result of clinical study, the drug has been recognized to have significant anti-inflammatory properties that benefit CF patients. These clinical results can also be reproduced in mutant mouse models of the delta 508 mutation [19]. These effects of azithromycin can be traced to inhibition of proinflammatory gene transcription [20] and increases in transepithelial electrical resistance by changing the processing of tight junctions [21] via effects on claudin-1 and -4, occluding, and JAM-A. These effects are likely to be missed in today's orthodox screening, where a single target is examined.

Market fragmentation and pricing make further reductions in medical need expensive

A major factor in making existing therapies available to reduce medical need is cost, as already mentioned in connection with cancer therapies. Although pricing has been cited as the major problem in making some of the new cancer 'miracle drugs' available to all patients, there is a bigger picture. The 'older' therapies are mainly generic, and therefore cheap. Even though most of these medicines have to be administered in a hospital setting, the costs of doctors, nurses, and hospital infrastructure tend not to be factored in when comparisons are made with targeted therapies. The newer agents are patent protected, which will automatically make them more expensive, because the price includes the R&D premium. However, that is not the whole story. The older drugs can and are used in a shotgun approach; because they are non-specific/selective, they are used in many cancer indications, thus reaching hundreds of thousands of patients. The newer drugs are selective, can often be taken on an outpatient basis, thus reducing hospital costs, and are as close to personalized medicine as can currently be produced by R&D. This also shows the dilemma of personalized medicine – in order to make a return on far fewer patients, manufacturers have to increase prices. Since there are now many different selective therapies, for example, Herceptin for breast cancer, Avastin for colon cancer, and so on, many therapies will be combinations of such new drugs for optimal efficacy. The total number of patients that need to be treated is no less, even though each manufacturer of selective therapies will reach fewer patients. Thus, the bill for cancer drugs in all developed economies is rising and will continue to rise, due to current population demographics and lifestyle. Whether prices have to be set at the level they are currently is a different matter, but even lower prices will only delay the inevitable; that is, Western healthcare systems will run out of money to pay for all patients and all therapies. There are those who predict a rise in personalized medicine, due to greater efficiency in R&D of such niche products, higher medical need, and easier or accelerated approval [22]. However, those who advocate that this represents the future may just find that there will continue to be a level of pricing necessary (to ensure return on investment) that will render these medicines unaffordable to many. For instance, HIV medicines, when initially developed, were quick to market and the R&D cost to develop them was relatively low. Today, HIV therapy R&D is as costly as any other R&D programme, due to rising safety hurdles and more complex clinical studies in what is now regarded (at least in the developed world) as a chronic, rather than deadly disease.

Societal value systems – how much is society prepared to pay for how much reduction in medical need?

Healthcare has become hugely more expensive. Even though drugs make up only about 10% of healthcare costs, they are the fastest growing component. Pharmaceuticals have contributed to the increased life spans of today's population in much of the Western World, yet the very extension of the life span brings with it a healthcare cost. There is a growing dilemma in the cost of innovative drugs. Some of these owe their discovery to modern advances in science. As the biochemistry of diseases, such as cancer, begins to be unravelled to an unprecedented degree, so the opportunity for drug discovery and personalized medicine opens up. What these new understandings show is that many new drugs will reach only a proportion of the patients suffering from the particular disease – as has already been outlined for CF. These drugs will require diagnostic tests to determine which drug will be of benefit to whom. Herceptin, which targets the HER-2 receptor in breast cancer, is an example of such a drug. This receptor is upregulated in about 20% of breast cancers. The drug shows excellent efficacy, although with some cardiotoxicity. The cost of a course of treatment is approximately $25,000. These costs can overwhelm healthcare budgets and also distort the apparent healthcare effort to be seen as focused on breast cancer rather than other cancers. In addition, the discovery of Herceptin, which treats the form of ductal breast cancer which previously had the worst prognosis, immediately raises a medical gap in the treatment of non-HER-2 breast cancers. As in the case example of CF, the more effective medicines are, the more that medical need becomes apparent. There is real need to define the place of medicines and healthcare in society and try to plan a way toward the future. Table 1 sets out some of the considerations that would need to be applied. Future medical need could mean a world in which the financial structure does not allow the cost of closing gaps in medical need, even though the tools, and indeed the medicines, are available. This world is not distant and some would argue that it is already here. Cancer therapies are becoming more expensive. Table 2 lists the prices and usage of several cancer medicines. Notable is that these treatments do not replace existing therapies, but are usually added on to a regimen incorporating existing drugs. In areas of high medical need, it is often impossible to proceed with placebo-controlled trials. New innovative therapies are often added to standard care and compared with standard care alone. In this paradigm, treatment gradually gets more complex and also more expensive. For example, in cancer care, the new-targeted therapies that would allow outpatient treatment are combined with inpatient chemotherapy. If the next generation

TABLE 1

Factors in driving medical need

Demand side drivers of medical need	Supply side drivers of medical need
Ageing population	Regional, country, and continental differences in regulation, pricing, control, and paying
Increasing patient numbers	Access to health care
Lifestyle changes	
Patient expectations	
Patient needs	
Cost of medicines	Pricing of the medicine; patent life
Cost of diagnostics	Pricing of diagnostic
Cost of other technologies	Pricing of other technologies (e.g. devices); cost of research and development; types of drugs discovered and developed by publicly owned pharmaceutical companies
Changes in perception of what constitutes disease (e.g. depression, high cholesterol, obesity, etc.)	Training of medical staff

TABLE 2

Increasing cost of cancer therapies

Cancer drugs	Mechanism	Approval date	Approximate costs per treatment course	Median survival versus standard care	Comment
5FU	Cytotoxic	1962	$63–263	12 months	Generic; usually in combination with leucovorin (to reduce side effects)
Methotrexate (Pemetrexed)	Antimetabolite (dihydrofolate reductase inhibitor)	1953	$100–200	5 months	Generic, usually in combination with 5FU
Irinotecan (Camptosar)	Cytotoxic	1994	$10,000	Up to 1 year longer	
Cetuximab (Erbitux)	Anti-EGF antibody	2004	$20,000–30,000	4 months	In combination with irinotecan
Bevacizumab (Avastin)	Anti-VEGF antibody	2004	$50,000 (capped)–100,000	5 months	In combination with 5FU

The cancer example used in this table is colo-rectal cancer (most of the agents in the table have multiple cancer indications with varying treatment regimens). It is probable that new innovative drugs will be added to these regimens rather than used in isolation, further driving up cost.

of cancer therapies uses a different mechanism will this paradigm still apply? Will we see courses of therapy costing $250,000? Undoubtedly such costs would fuel a huge gap in medical need.

Potential R&D solutions: better knowledge and new technologies to bring more medicines to market successfully

Better knowledge to improve success rates

This paper, so far, has focused on the risks associated with novel 'biology' and the difficulty of predicting efficacy. The flipside of this coin are those drug targets that are clinically established, or where there is high confidence that they will be efficacious. So why have these targets not been converted into useful medicines? The issue of druggability has been raised as early as the 1990s, when Chris Lipinski in his seminal article described the physicochemical properties (rules of five) required for oral absorption [23]. Since then, more and more concepts have been developed which allow the prediction of 'druggable' versus 'nondruggable' targets. Nearly all of these predictions center on the simple concept of a direct relationship between lipophilicity, molecular weight, and hydrogen bonding or polar surface area. Thus, as molecules increase in molecular weight, they either become highly lipophilic and insoluble (ineffective dissolution impairs bioavailability) or PSA and H-bonding groups render the molecule incapable of passing through a membrane, due to the energy cost of removing the water sheath. Small MW molecules can be absorbed by paracellular routes via the tight junctions of cells (aqueous pores), but the availability of this pathway is controlled by molecular size. The concept of druggability is perhaps better viewed as the probability of drug success. Within this term, not only the possibility of getting a small molecular weight ligand, or biological agent, is considered. Also included is the chance of gaining selectivity to the desired target and the safety implications of interacting with the target. Systems biology may eventually be the way targets are understood in terms of druggability. Thus, the road to success is not just one 'breakthrough', but a combination of findings.

Renin is a compelling target based on overall druggability, especially concerning probable efficacy and safety. However, many attempts failed to find a small molecular weight inhibitor. The history of failure was such that many scientists considered the target as nondruggable. Many of the early programmes produced renin inhibitors which were large peptide-like analogs, with ultra low oral bioavailability and therefore unsuitable as therapeutic entities [24]. Gradually companies terminated their research

TABLE 3

Drugs or phase 3 compounds with properties which would be defined as nondruglike, and the special circumstances that facilitate their appearance as drugs

Drug	Therapeutic class and indication	Molecular weight	H-bonding (total acceptors and donors)	Polar surface area (A^2)	Factors allowing progression of a drug
Cyclosporin	Macrolide – immunosupression	1202	23	324	Network of complex internal H-bond count renders molecules lipophilic in aprotic solvents (e.g. membrane lipid)
Erythromycin	Macrolide – antibiotic	734	19	194	Network of complex internal H-bond count renders molecules lipophilic in aprotic solvents (e.g. membrane lipid)
Doxycycline	Tetracycline – antibiotic	444	17	182	Network of complex internal H-bond count renders molecules lipophilic in aprotic solvents (e.g. membrane lipid)
Methotrexate	Folate antagonist – cancer and rheumatoid arthritis	454	20	211	Absorbed via reduced folate carrier (active transport)
Aliskiran	Renin inhibitor – hypertension	553	15	146	Low bioavailability offset by low intrinsic clearance and 0.6 nM potency
Montelukast	Leukotriene D receptor antagonist – asthma	586	6	96	Lipid target leading to lipophilic drug (cLogP 7.8), very high potency (0.1 nM) renders solubility not an issue due low dose
Torcetrapib	CETP inhibitor – hyperlipidemia	600	6	59	Lipid target leading to lipophilic drug (cLogP 8.2), spray dried formulation overcomes lack of solubility. Probable that high rate of membrane flux makes low aqueous solubility sufficient to allow complete absorption
Bosentan	Endothelin receptor antagonist – pulmonary hypertension	551	13	154	Properties close to those termed drugable, higher variation in PK than normal, but still allows effective therapy
Maraviroc	CCR5 receptor antagonist – antiviral (HIV)	514	7	63	Properties close to those termed drugable, higher variation in PK than normal and atypical plasma concentration curves. Slow offset of drug from the CCR5 receptor compensates

efforts until Novartis discovered, by chance, a hidden binding pocket, which allowed the structure-based design of high-affinity inhibitors [25,26]. These inhibitors moved much closer in terms of physicochemical properties to those deemed desirable. Nevertheless, the oral bioavailability of aliskiren is still low (3%) because of a low lipophilicity (MW 553, H-bond count 15, Table 3), however, the drug has a low intrinsic clearance (reflecting the low lipophilicity), that combined with its subnanomolar potency allows once a day dosing. After successful clinical studies, an NDA was filed in 2006 for the long-acting oral renin inhibitor, aliskiren (Rasilez, Novartis) (Figure 1) for the treatment of hypertension (http://www.novartis.com). Table 3 lists a series of drugs that fall outside the conventional rules governing the properties for oral therapies. In almost all cases, there is a series of factors or compromises that allow these compounds to become drugs or phase 3 candidates. Apart from the natural products or semisynthetic derivatives, which nature has 'discovered' over a timescale log orders away from conventional R&D, all the compounds have been 'hard won', often as a result of large investment in Research and Development over many years. The table with failed programmes would be much longer, but like renin some of these programmes will be revisited in future if the clinical rationale is compelling. The other problem is not only that the probability of overall success is lower, but that the probability that the compound will fall short of the actual 'product concept or patient needs' is higher.

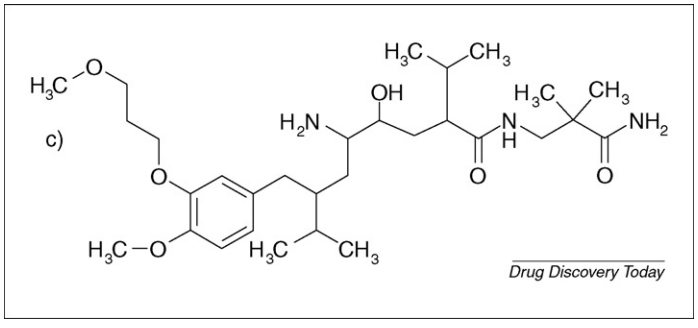

FIGURE 1

Chemical structure of the orally active renin inhibitor, aliskiren (IC_{50} = 0.6 nmol/L; human bioavailability 3%, $t_{1/2} \sim$ 24 hours).

Thrombin, like renin, has been a compelling biological target. There are no oral thrombin inhibitors (except the low therapeutic index drug warfarin) on the market today, despite programmes in almost all the major pharmaceutical companies. AstraZeneca

TABLE 4

'Barometer' of healthcare climate change (2005–2007)

Media headline	Country (source)	Issue	Comment	Wealth per adult in 2000 ($)[a]
'Fears over NHS cancer drug costs'	UK (The guardian)	Cost of new generation cancer drugs	Copayment by patients for new, nonreimbursed drugs only is not allowed by NHS	169,617
'Britain is sick man of Europe for providing cancer drugs'	UK (The independent)	Access to new cancer drugs – UK has lowest access and highest cancer death rate in EU	NICE acts as a gatekeeper, delaying NHS patient access to reimbursed novel drugs	169,617
'Alzheimer's drugs appeal refused'	UK (BBC News)	NICE determined existing drugs are not good value for moderate Alzheimer's disease	Alzheimer's drugs cost £2.50 per patient per day	169,617
'German Curbs on Drug Costs Rile Big Brands'	Germany (WSJ)	Reference pricing – reimbursement of patented drugs for which a generic class member exists	Germany creates a reimbursement ceiling for branded drugs based on generic class members (e.g. lipitor versus simvastatin)	109,735
'Americans get least bang for buck on health care'	US (The Globe and Mail)	The US healthcare system ranks poorly on measures of quality, access, efficiency, equity, and outcomes	US citizens spend twice as much on healthcare than other nations, yet have the highest number of uninsured	201,319
'Health Savings Accounts and high deductible health plans – why they won't cure what ails US health care'	US (The commonwealth fund[b])	Inefficiency of US healthcare system	Based on out of pocket payments – might drive focus on cost and quality of service	201,319
'Health Insurance Gap Surges as Political Issue – Democrats, Governors, Business Push Change, but Fixes Vary Widely'	US (WSJ)	Social divide	Number of Americans without health insurance rose by 1.4 million last year to 46.6 million (15.9% of the population)	201,319
'Japan's cancer refugees'	Japan (The Washington Times)	Japan denies access to latest drugs/treatment	Cancer death rates are rising in Japan	227,600
'Japan makes older people contribute toward their health care'	Japan (The Lancet)	Near-bankrupt medical insurance system	Patients aged 70 years and older will be required to pay 10% of their medical bills	227,600
'Chinese tycoon offers health care help'	China (USA today)	Divide between rural and city health provision is growing. Wide variations in quality	Social welfare costs are shifting from the state to employers and individuals. Commune medical co-ops that provided free and universal – health care were dismantled	3,885

$ values are not adjusted for purchasing power differences between nations.

[a] http://www.wider.unu.edu/research/2006-2007/2006-2007-1/wider-wdhw-launch-5-12-2006/wider-wdhw-press-release-5-12-2006.htm.

[b] http://www.cmwf.org/healthpolicyweek/healthpolicyweek_show.htm?doc_id=380493.

appeared to be successful with their thrombin inhibitor Exanta (ximelagatran) which was approved in Europe in 2004, but was withdrawn in 2006 mainly following liver damage reports (http://www.astrazeneca.com). Also cited in the decision not to approve the drug was the relatively short half-life and the risk of noncompliance compared with warfarin in an area critical for maintained therapy.

New technologies to improve drugability

Exanta and Rasilez represent examples of a tantalizing combination of high confidence in therapeutic potential – in areas of high medical need – with extreme chemical difficulty. To address this problem, new technologies are available today or are on the verge of becoming available, notably, the well-established protein and antibody therapeutics, the emerging field of RNA interference technology, and of course, stem cell therapies. The recent acquisition of Sirna Therapeutics (San Francisco) by Merck for $1.1 billion (http://www.merck.com) and the over 600 clinical stem cells studies listed in the clinical trials database (http://www.clinicaltrials.gov) are a clear indication of the enormous interest in finding alternative approaches for diseases where small molecule approaches have so far failed. Although other authors advocate a 'low risk' approach to drug discovery [27], advocating an increased focus on small molecule approaches and protein/antibody therapeutics, because they are 'known to work', there is a natural limit to both of these approaches. Proteins and antibodies cannot reach targets inside cells and some drug targets cannot be modulated by small molecules due to physicochemical properties of the binding sites. To truly address unmet medical need, additional modalities are needed. An increasingly significant approach is to conduct R&D into prophylactic and therapeutic vaccines. New delivery platforms are offering exciting prospects for vaccine-based medicines for formerly undruggable targets or indications. In addition, the potentially lower cost base of vaccine-based medicines might make them more affordable (and interesting as R&D options) in areas of lower commercial potential. Other alternative approaches, such as gene and antisense therapies, have run into significant problems and are less likely to provide a viable approach for difficult drug targets in the near future. Nevertheless, even for the more promising or established alternative approaches, the issue of drug delivery remains.

Conclusion

Drug companies today are struggling with many issues. Critics point to a lack of innovation and an obsession with commercial value as one of the reasons why the pharmaceutical industry has not delivered the cures that society expects. In this paper, we have pointed to the enormous financial investment that was and is being made by the public in the scientific foundations that are requisite for the development of knowledge around disease. Such knowledge may lead directly or indirectly to commercial drug discovery programs. Even more funds have been 'lost' by private enterprise through the pursuit of difficult diseases in high medical need areas such as stroke. Today, investments made by public and private organizations are starting to deliver new technologies and biomedical knowledge which could enhance or even provide an alternative to the traditional medicinal chemistry-based drug discovery. The huge potential that resides in such alternative approaches has already been demonstrated by antibody and protein therapeutics. Emerging technologies are therapeutic and prophylactic vaccines, based on new delivery platforms. They hold great promise in tackling diseases that are difficult to target and they also could reduce the cost of innovative new therapies. However, there are great risks associated with novel technologies, as the failures of gene therapy and antisense approaches have shown. Therefore, the question should not be 'why is there still unmet medical need?' but rather 'when will the basic knowledge generated by the new era of biomedical research be sufficient to allow incorporation into main-stream R&D efforts?' and 'can we, as a society, afford to close all medical need gaps?' The first question drives three fundamental mutually inclusive scenarios:

1. The need to find new mechanisms that will work safely, that is, where the drug target plays an exclusive, or dominant role in disease and modulating it does not cause major unwanted side effects (safe primary pharmacology).
2. The need to find the right compound, that is, molecules that have little or no off-target toxicities (safe secondary pharmacology).
3. The need to find alternative approaches where the above scenarios have reached their limitation (e.g. RNAi, antibodies, stem cells, and so on, where the disease mechanism (target, cell, or tissue) is not amenable to the traditional medicinal chemistry approach).

The second question goes to the heart of innovation. Who should pay for formerly life-threatening diseases that, through pharmaceutical innovation, become chronic, extend survival to months, sometimes years, or decades? This world is already here. The life expectancy for HIV and CF patients has increased by decades, but only if expensive treatments are provided. For oncology, the trend points in the same direction. Therefore, society needs to decide how scarce resources will be allocated. Will the enormous investments in R&D and academic research be wasted because the 'purchasing' healthcare systems cannot or will not match the innovation funds with purchasing budgets 20 years downstream? Will only those patients who can pay privately get innovative treatment? This is already a reality in the UK, as very recent articles (Table 4) in the press outline.

Will private health insurance provide a two-class system for the rich and the poor? This system exists in the US but is already breaking down even for the wealthier middle classes. Would levying higher taxes on society as a whole provide some kind of universal health insurance? This system exists in several EU countries, including Germany – and has also reached a threshold of viability. There are some emerging trends, most notably the policy offered by Western Provident Association (WPA) which offers insurance at annual premiums matched to age (e.g. £60 for a 60-year-old) to those under 65 against the cost of cancer treatment up to £50,000 worth of drug treatment. Except that familial cancers and those over 65 are excluded.

Perhaps the future will bring a low-cost 'universal insurance scheme', which provides means tested benefits for those unable to build a personal health fund, whilst those able to afford it pay into a personal 'health fund' over their working life time – akin to

personal pensions, to provide a safety net for future high-cost healthcare needs.

Novel vaccines to treat cancer or infectious diseases could reduce the cost burden on society. However, we live in a world today where even £2.50 a day for Alzheimer patients is considered a burden (Table 4). The better our medicines become, even if they reduce in price, the more demand will rise. Thus, we do not have one answer to this dilemma, but feel strongly that the skills and knowledge that were painstakingly built over decades of R&D, as well as the monumental public and private financial investment into pharmaceutical and academic innovation will be wasted if we cannot find the means to use the lifesaving therapies that science offers. Now is the time for all parties involved in healthcare to start to formulate an affordable strategy that benefits patients and innovators alike.

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