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A second vaccine revolution for the new epidemics of the 21st century

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Non-communicable, chronic diseases are currently the major cause of death and disability worldwide, and many of these maladies have reached epidemic proportions. According to the World Health Organization (WHO) these disorders, including cardiovascular and respiratory diseases, diabetes, obesity and cancer, now account for about half of the global disease burden as well as deaths worldwide. The WHO identifies comparatively few risk factors, namely smoking, alcohol abuse, obesity, high cholesterol and high blood pressure, as the cause of many of these chronic conditions. A new class of medicines, based on vaccine approaches, are now in clinical trials and hold significant promise to treat both risk factors and their associated chronic diseases.

New epidemics

The population of the world is ageing. According to a United Nations report (http://www.un.org/esa/population/publications/worldageing19502050/), at the beginning of the 21st century there are ~600 million individuals worldwide aged 60 years and over. This number is predicted to increase more than threefold over the next 50 years. The increase in longevity, in both economically developed and developing countries, results from advances in several fields. Economic development, relative political stability, nutritional sufficiency and biomedical progress have all played their part in increasing the span of human lives. At the start of the 21st century, increasing lifespans present us with a new global challenge: epidemics caused by non-communicable, chronic diseases, many of which are coupled to specific risk factors associated with enforced or elected lifestyles or accompany the natural process of ageing. The WHO estimates that non-communicable disorders now account for some 59% of the 57 million deaths annually and almost half the global burden of illness. It is estimated that by 2020 this category of disorders will increase to over 60% of the global disease quota (http://www.who.int/chronic_conditions/burden/en/).

Risk factors for diseases have changed over the past century. Infectious diseases remained the major risk factor for premature death well into the 20th century. The most effective way to prevent such communicable diseases is vaccination. Indeed, vaccines against viral and bacterial pathogens have enormously contributed to the increased life expectancy we are currently enjoying. In our ageing society, infectious diseases are currently a limited threat but new risk factors are emerging. According to the WHO, these are smoking, alcohol abuse, obesity, high cholesterol and high blood pressure [1]. Given the outstanding success of classical vaccines to deal with the risk of infections, it seems a logical extension to use the same modality for the management of today's risk factors and chronic disease epidemics. This review will discuss such 'risk-managing' vaccines in clinical development and highlight their medical, sociological and economical characteristics.

Two approaches to preventive medicine

Disease avoidance or early intervention in the disease process is a major goal of preventive medicine. There are two approaches to achieve this: (i) through the correction of defective biological processes early in the disease process, perhaps even before symptoms are presented, and (ii) through the removal of major risk factors that are causal to the disorder. Effective management of chronic conditions might benefit most from addressing both arms of preventive treatment. Vaccines to address both approaches are now in clinical trials (Table 1) and the most advanced drug candidates are discussed below.

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TABLE 1

Ongoing clinical trials for vaccines in addictions and chronic diseases (limited to company-sponsored trials in non-cancer, non-allergy and non-infection indications)

Indication	Conjugated target	Carrier protein	Company	Clinical status
Addiction	Nicotine	Virus-like particles	Cytos	Phase II
Addiction	Nicotine	*Pseudomonas aeruginosa* exoprotein A	Nabi	Phase II
Addiction	Nicotine	Recombinant cholera toxin B	Xenova	Phase I
Addiction	Cocaine	Recombinant cholera toxin B	Xenova	Phase II
Hypertension	Angiotensin II	Virus-like particles	Cytos	Phase I/II
Cholesterol management	Cholesterol ester transferase	Tetanus toxoid	Avant	Phase II
Gastro-esophageal reflux disease	Gastrin 17	Diptheria toxoid	Aphton	Phase II
Obesity	Ghrelin	Virus-like particles	Cytos	Phase I/II
Psoriasis	Tissue necrosis factor	Virus-like particles	Cytos	Phase I/II
Hypertension	Angiotensin I	Keyhole limpet hemocyanin	Protherics	Under reformulation
Alzheimer's	Aβ-fragment	Virus-like particles	Novartis/Cytos	Phase I
Alzheimer's	Aβ-fragment	Not disclosed	Wyeth/Elan	Phase I

Early intervention

Intervention in early-stage disease, or even in pre-symptomatic individuals, will require high-throughput diagnostic tools and/or a proper understanding of heredity and the environment on disease predisposition, onset and progression. Such knowledge and tools are currently not available for many complex disorders and a better understanding of their biology is required. Nonetheless, the treatment of certain disorders early after onset of symptoms and before irreparable damage is suffered by major organs of the body is yielding benefits and saving lives. A notable success in the early diagnosis and treatment of diseases is provided by breast and cervical cancer screening programs. After 30 years of breast cancer screening, the benefits of these early intervention programs are clearly apparent in several countries with an average of a 24% reduction in mortality compared with non-screened populations [2]. The most effective mode of early intervention in terms of benefits to the population and healthcare economics is the vaccination against infectious diseases. It is therefore reasonable to propose that second-generation vaccines that manage risk factors and their associated chronic diseases will be used as first-line therapy in the medicine of tomorrow aimed at early intervention in disease and the most efficient use of valuable healthcare resources.

Vaccines addressing health risks of society

The most prominent chronic maladies are linked to common risk factors [1] that, once identified, should be easy to remove. In practice this is scarcely possible because in some cases personal habit and choice speak against healthy living, whereas for a significant number of people economic, educational or social constraints leave no opportunity for attaining a healthier lifestyle. In addition, genetic conditions might, for example, predispose individuals to hypertension or high cholesterol, leaving little room for improvement through a change in behaviour. The next sections will discuss some current and major health risks of our society and vaccines that might help address these factors. The vaccines discussed below all attempt to induce antibodies neutralizing either drugs of addiction or the endogenous molecules of the host that drive conditions such as smoking, hypertension, Alzheimer's disease or obesity. Vaccination against self molecules is a unique challenge and is discussed in Box 1.

Smoking: the global risk

Smoking is a global epidemic of enormous proportions: worldwide there are 1.2 billion smokers [3]. The cocktail of toxins in cigarette smoke attack every organ in the body and lead to greatly increased risks of cancer, cardiovascular and respiratory diseases (see the Surgeon General's Report 2004, The Health Consequences of Smoking; http://www.cdc.gov/Tobacco/sgr/sgr_2004/). These diseases represent a devastating burden to the individual and an enormous and avoidable cost to our healthcare systems. Although health campaigns, anti-smoking legislation and economic penalties are important devices in reducing the burden of smoking, they are insufficient for eliminating the problem, even in the most highly developed countries [4]. Personal choice and addictive habits are notoriously difficult to overcome. Nicotine-replacement therapy and other available medicines are not very effective and aid only up to 20% of smokers who elect for these therapies to 'kick their habit' successfully and avoid relapse [5,6]. The large and unsatisfied medical need combined with an underserved market makes smoking cessation an important area of focus for pharmaceutical and biotechnology companies. Several vaccines [7] are now in clinical development and a new low-molecular-weight therapy [8] was recently approved for marketing.

Vaccines for nicotine addiction

Nicotine, an alkaloid found in tobacco, is the principle substance in cigarettes driving addiction in the brain. The basis of vaccines against smoking addiction is to induce high levels of nicotine-specific antibodies that sequester the alkaloid in the blood and so prevent it from entering the brain. Hence, the therapy aims to remove the addictive potential of cigarettes. This concept is similar to that of heroin antagonists, such as Naltrexone, which are used to treat heroin-addiction [9]. As is the case for Naltrexone, such a therapy will not reduce withdrawal symptoms or craving, it will reduce the addictive potential of the drug and therefore prevent

BOX 1

Vaccination against self-molecules: a unique challenge

Conventional vaccines induce immune responses against foreign, pathogen-derived structures. By marked contrast, vaccination against self-molecules aims to induce a specific antibody response; however, an undesired self-specific T-cell response might also be generated, potentially causing organ damage resulting from infiltrating T cells [34]. Indeed, a vaccine in early clinical development against Alzheimer's disease has highlighted this issue [35]. By using low amounts of vaccines, avoiding adjuvant and using small peptides devoid of T-cell epitopes it might be possible to overcome this issue. In addition, the induced antibodies might themselves be harmful because they can neutralize potentially essential target molecules, generate harmful immune complexes and predispose cells to antibody-dependent cellular toxicity (ADCC). These safety issues have to be addressed on a case-by-case basis. Some general rules might apply nonetheless (Figure 1, main text). Avoiding membrane-bound target molecules eliminates the issue of ADCC and inducing antibodies against target molecules present at low concentrations reduces the potential for immune complex formation. Indeed, autoantibodies specific for various cytokines are frequently observed in healthy individuals without any signs of immune-complex disease [36]. Membrane-bound proteins are not ideal targets for a second reason because they generally induce B-cell tolerance, rendering it a difficult task to induce antibodies against such molecules. The problem is particularly prominent for membrane proteins expressed at high levels because B cells recognizing such proteins are usually deleted [37]. By contrast, B-cell tolerance can be overcome for membrane proteins expressed at low levels that cause reversible B-cell anergy [38] (Figure 1, main text).

The longevity of the antibody response induced by vaccination is one of the major advantages of such a treatment modality because it causes a long-lived therapeutic effect. However, long-lived antibody responses might also raise safety issues resulting from the potentially irreversible depletion of molecules targeted by vaccination. It is therefore important to note that self-specific antibody responses, including those against some of the molecules described in the main text, decline in animals (tumour necrosis factor (TNFα) [39], IL9 [40] and RANKL [41]) and humans (angiotensin [23,24] TNFα and ghrelin (M.F.B. unpublished) with a distinct half-life.

A further potential problem of the vaccine approach lies in the difficulties in reaching therapeutically beneficial antibody levels. For this reason, it is important to choose targets that do not have a narrow therapeutic window. Levels of monoclonal anti-TNFα antibodies vary, for example, between individuals by more than a factor of 100 despite overall good efficacy [42]. The variation of antibody levels upon vaccination is in a similar range. In addition, vaccination will never lead to the complete blockage of a particular molecule, because there will always be an equilibrium between free and antibody-bound molecules. Consistent with the law of mass action, a tenfold increase in production of a targeted molecule in response to a given physiological stimulus will result in tenfold increased levels of free molecules in vaccinated individuals, allowing limited physiological activity of the targeted molecule. Thus, although great care with the development of such vaccines and use in clinical studies is certainly warranted, there is currently no evidence for an undue risk, and as a consequence the regulatory authorities have approved the use of these experimental vaccines for exploratory clinical studies.

relapses. The main challenge in developing a vaccine against smoking addiction is the high amounts of antibodies required *in vivo* to block nicotine because affinities of antibodies against small molecules such as nicotine are low and peak concentrations of the alkaloid in the blood are relatively high [7]. In an exploratory Phase II clinical trial using nicotine coupled to virus-like particles for vaccination, it was shown that it is possible (i) to generate sufficient antibodies to sequester nicotine in the blood and (ii) to facilitate smoking cessation markedly in the 33% of immunized individuals in the clinical study who responded best to the vaccine ($p < 0.004$). Thus, a vaccine against nicotine holds promise to offer a significant improvement on current therapies for smoking cessation.

An interesting issue is whether a vaccine against nicotine addiction should be given prophylactically to younger members of society. This proposition invites an ethical challenge, but there are also practical issues in treating adolescents and young adults for years or even decades with multiple injections per year to maintain antibody titers at a high enough level for efficacy.

Obesity, an outsized problem

Genetic predisposition, nutrition and sedentary lifestyle have allied to create an obesity pandemic. More than one billion people worldwide are overweight and of these at least 300 million are diagnosed as clinically obese (http://www.who.int/dietphysicalactivity/publications/facts/obesity/en/). Many severe diseases including type 2 diabetes, hypertension, stroke, heart disease and osteoarthritis can be causally related to obesity. No effective medicines are available to manage this problem and instead many obese individuals resort to surgery, which bears its own risks. New safe and efficacious drugs are therefore needed [10].

Vaccines for obesity

Weight is essentially controlled by food intake and host metabolism. Appetite and food intake are regulated in part by peptide hormones produced either in the brain or in the periphery. Hormones produced peripherally often travel to the brain and act centrally. Because antibodies penetrate the blood–brain barrier only inefficiently, hormones produced in the periphery are better targets for therapeutic vaccination. By a similar mechanism as that discussed for nicotine vaccines, specific antibodies will sequester the hormone in the blood and block its entry into the brain. A prototype of an appetite-regulating hormone is ghrelin. Injection of ghrelin into mice or humans increases appetite [11] and reduced ghrelin levels correlate with reduced appetite [12]. Thus, blocking ghrelin by vaccine-induced antibodies might offer an effective and long-lasting therapy by reducing food intake.

Ghrelin is also an attractive target from a safety perspective because it is a soluble peptide present at low concentrations. It therefore represents a good candidate for a target molecule because it has a low potential to induce immunopathology (Figure 1, Box 1). Indeed, an N-terminal peptide derived from ghrelin coupled to a protein carrier has recently been demonstrated to attenuate weight gain in rats [13]. Furthermore, a Phase I/IIa study in 112 obese patients is ongoing to assess the safety and potential efficacy of a ghrelin vaccine consisting of an N-terminal peptide coupled to virus-like particles.

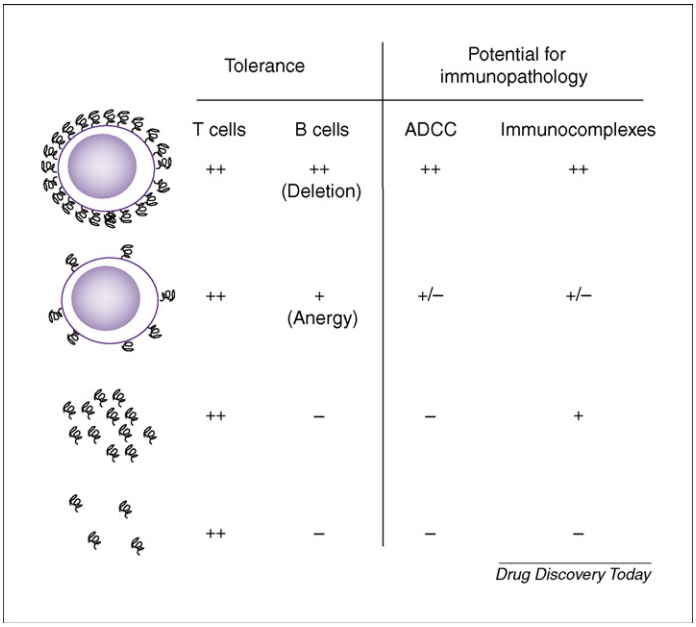

FIGURE 1

A summary of the general characteristics of membrane-bound versus soluble proteins for targeting by vaccination. As shown in the figure, abundant membrane-bound proteins are particularly difficult targets for vaccination because they usually induce B-cell tolerance, rendering it difficult to induce a response, and are particularly susceptible to destructive mechanisms, such as antibody dependent cellular toxicity (ADCC). + and − depict the magnitude of the tolerance and immunopathology. Rare soluble proteins as targets face the least challenges, because they do not induce B-cell tolerance and are unlikely to cause immunopathology resulting from ADCC or immune complexes.

The burden of cardiovascular diseases

Worldwide, hypertension affects around one billion individuals [14] and heart attacks and strokes kill ~12 million people every year [15]. Although there are several effective anti-hypertensive and cholesterol management drugs on the market [16,17], major hurdles to addressing these conditions are the early diagnosis of individuals at risk and, for those individuals receiving therapy, the problems associated with daily compliance and self administration of orally active drugs.

Vaccines for cholesterol management

The management of high cholesterol is possible at various levels. Enhanced elimination of low density lipoproteins (LDL; the major source of 'bad' cholesterol) is one strategy that is followed. There is good preclinical evidence that antibodies raised by vaccination against *Streptococcus pneumoniae* cross-react with LDL, leading to an increased removal of LDL from the bloodstream [18]. An alternative approach attempts to interfere with the metabolism of LDL [19]. Similar to LDL, high densitiy lipoprotein (HDL) also consists largely of cholesterol. In contrast to LDL, however, HDL is cardioprotective. Indeed, it is the ratio between LDL and HDL that determines the risk for cardiovascular complications. The enzyme cholesteryl ester transfer protein (CETP) converts HDL into LDL and therefore antibodies against CETP might increase the ratio of HDL/LDL [20]. A promising Phase II clinical trial has validated this strategy because it was shown that a vaccine based on a peptide containing a region of CETP coupled to a fragment of tetanus toxin significantly improved the HDL/LDL ratio in vaccinated individuals [20,21]. Moreover, targeting CETP seems safe because CETP-deficient individuals do not show any physiological abnormalities other than having increased HDL levels [22].

Vaccines for high blood pressure control

Blood pressure is regulated by various parameters. A key system for increasing blood pressure is the renin–angiotensin axis. Angiotensin-converting enzyme (ACE), which cleaves the angiotensin I precursor peptide into the biologically active angiotensin II, is a major target for classical drugs managing hypertension (ACE inhibitors). Angiotensin II receptor antagonists are a second class of powerful drugs that lead to a reduction in blood pressure in hypertensive patients. It is therefore not surprising that currently developed vaccines focus on the induction of antibodies against angiotensin I or II, thereby mimicking the action of ACE inhibitors or receptor blockers. There is good preclinical evidence that such an approach is feasible in hypertensive rats and Phase I clinical studies have indicated that such vaccines are well tolerated in healthy individuals [23,24]. Current vaccines under evaluation include angiotensin I or angiotensin II peptides chemically coupled to protein carriers or virus-like particles. Interestingly, the potential to induce hypotension by vaccination seems limited because ACE inhibitors and receptor blockers fail to reduce blood pressure below normal levels even at very high doses.

The diseases of ageing and early intervention

Alzheimer's disease is a degenerative disease of the brain characterized by memory loss and decline in other mental facilities and skills. The onset of Alzheimer's disease usually occurs after 65 years of age, although earlier onset is not uncommon. As life expectancy increases, the total number of people suffering from this disorder is expected to increase proportionally (International Alzheimer Society, http://www.alz.co.uk/research/statistics.html).

Vaccination for Alzheimer's disease

Vaccines against Alzheimer's disease aim to reduce plaque load in the brain of Alzheimer's patients. Current vaccination strategies focus on antibody responses against Aβ, the major constituent of the plaques. A first Phase II clinical study using Aβ1–42 formulated in the adjuvant QS-21 was able to demonstrate efficacy of the vaccine because those patients mounting an antibody response against fibrillar Aβ in plaques progressed with the disease much more slowly than those patients failing to respond with such antibodies [25]. Although these data are promising, the trial had to be discontinued because 6% of the vaccinated individuals developed a sterile meningoencephalitis. This side effect seems to be due to Aβ-specific T cells. Current vaccination strategies therefore aim to avoid such T-cell responses by using shorter peptides and no adjuvants (Box 1).

The timeframe for therapeutic vaccines

First-generation therapeutic vaccines to manage risk factors or established disease are advancing towards late-stage clinical trials. Within the next five years, the first wave of these new medicines, subject to their successful development and regulatory approval, will be available to manage diverse risk factors such as smoking, high blood pressure and elevated cholesterol. Thereafter, during

the second decade of the 21st century, vaccines to manage additional chronic conditions could be introduced.

Vaccines and patient compliance

Causal and disease-modifying medicines on the basis of chemical entities and recombinant proteins are also being developed by most of the world's pharmaceutical and biotechnology companies. These investigational drugs, when successfully introduced into the marketplace, offer the potential for significant health benefits for treating diseases. However, both of these therapeutic modalities face a significant hurdle, namely patient compliance. Already, patient compliance has been identified as a major hurdle to successful intervention in hypertension [26] and other chronic conditions such as elevated cholesterol, osteoporosis and asthma, where 50% or more of patients do not take their medicines as instructed by their doctors [27,28]. Poor compliance is a well-known problem in individuals suffering from benign symptoms of early-stage disease. Consequently, this will be a major barrier to the successful use of preventive medicines based on orally active drugs and injectable recombinant proteins. By contrast, a therapeutic vaccines-based approach promises to be more effective in achieving patient compliance because its therapeutic effect is expected to be longer lived, thus relieving the individual of the burden of daily and/or weekly drug administration.

Supply and distribution

Vaccination is a well accepted and economically viable approach to combat global epidemics in all countries, even the most underdeveloped, as witnessed by the eradication of smallpox in the 1970s. Through global disease eradication initiatives of the WHO and others, a significant investment has already been made in strengthening health service delivery systems for vaccines in many countries. Many thousands of health workers have been trained, millions of volunteers have been enlisted to support immunization campaigns and cold-chain transport equipment is available. Hence, the global network for the distribution and administration of vaccines is already established and operative and can also be utilized for the supply and distribution of therapeutic vaccines. Nevertheless, there are problems associated with the use of therapeutic vaccines, including the potential need for life-long periodic booster injections, and, perhaps more of an issue for the underdeveloped world, the need for sterility and single-use syringes as well as potential refrigeration issues. It will be a challenge but certainly not impossible to build up the logistics for this task.

The economics of vaccination

Risk factors and their consequences on health impose an economic burden on society. For example, obesity is estimated to consume 5% of the national health expenditure in the USA, equivalent to US$ 75 billion in 2003 (Center for Disease Control and Prevention (CDC) Press Release, http://www.cdc.gov/od/oc/media/pressrel/r040121.htm), whereas in other countries it is calculated as 2–3.5% of their annual medical expenditures [29]. Tobacco-related health care accounts for 6–15% of all annual healthcare costs. Hence the ability to address risk factors or manage their adverse consequences on health at an early stage will offer significant economic benefits [30,31].

It is difficult to put a price on human life. Nevertheless, health economists generally agree that if an intervention can save one year of life by preventing disease for less than US$ 50 000, it is cost effective (CDC: Screening to Prevent Cancer Deaths, http://www.cdc.gov/nccdphp/publications/factsheets/Prevention/cancer.htm). Currently, the cost of intervention with monoclonal antibody therapy presents a challenge for staying below this cost threshold. Indeed, the costs of monoclonal antibody therapies often prevents their choice by health providers as first-line therapy in chronic diseases. A case in point is in the treatment of rheumatoid arthritis where intervention with small-molecule therapy (methotrexate and steroids) is selected in preference to available antibody-based drugs, which might cost up to €12,000 per year per patient, even though antibody-based drugs offer superior therapy because they are disease-modifying and halt the progression of the disease [32]. Hence only new drugs that can compete with the cost of conventional treatments based on chemical entities can be placed as first-line therapy [33]. Vaccine-based approaches to preventive medicine therefore offer a better investment in economic terms than antibody products.

Preventive medicine and early intervention will probably require long-term drug treatment. In purely economic terms, infrequent booster injections of low dose vaccines will be sparing of both drug substance and healthcare resources versus therapeutic intervention based on frequently administered small molecules and recombinant proteins. The intermittent timing of vaccine dosing, perhaps a few times each year, fits well with a preventive approach to medicine, which does not overburden practioners while still enabling them the opportunity of monitoring changes in the health status of their patients.

Outlook

The favourable economics associated with vaccines, the worldwide acceptance of this therapeutic modality, and the existing global vaccines strategies and networks hold promise that therapeutic vaccines for chronic diseases will reach the broadest possible patient base worldwide. If the first-generation therapeutic vaccines fulfil their expectations in the ongoing clinical studies then a vaccines-based solution is on hand to meet the challenge of the chronic disease epidemics of the 21st century.

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