Journal of Biotechnology 283 (2018) 115–119

Contents lists available at ScienceDirect

Journal of Biotechnology

journal homepage: www.elsevier.com/locate/jbiotec

The global role of biotechnology for non communicable disorders

Serena Zacchigna*, Mauro Giacca

International Center for Genetic Engineering and Biotechnology (ICGEB), Trieste, Italy

ARTICLE INFO

Keywords:
Non communicable disorders
Recombinant proteins
Diagnostics
Monoclonal antibodies
Cell therapy
Small nuclei acids

ABSTRACT

The World Health Organization (WHO) has tagged non-communicable diseases (NCDs) as one of the twenty-first century's major development challenges. NCDs account for over 15 million deaths annually and over 80% of those deaths occur in developing countries and among the poorest populations. Biotechnology presents unique opportunities to improve the early diagnosis and the treatment of NCDs. This review describes the major applications of biotechnology for a better clinical management of NCDs, i.e. the implementation of innovative diagnostic approaches and the production of innovative treatments, including those based on monoclonal antibodies, recombinant proteins, regulatory nucleic acids and cell-based therapies for regenerative medicine. In this context, it also examines the major challenges faced by biotechnology in developing countries.

1. Biotechnology for noncommunicable diseases (NCDs)

Noncommunicable diseases (NCDs), also known as chronic diseases, tend to be of long duration and are the result of a combination of genetic, physiological, environmental and behavioral factors. The main types of NCDs are cardiovascular diseases (like heart attacks and stroke), cancers, chronic respiratory diseases (such as chronic obstructive pulmonary disease and asthma), neurodegeneration (such as dementia and Parkinson's disease) and diabetes (G.B.D.R.F. Collaborators, 2016). These 4 groups of diseases account for over 80% of all premature NCD deaths. Each year, 15 million people die from a NCD between the ages of 30 and 69 years and over 80% of these "premature" deaths occur in low- and middle-income countries (http://www.who.int/mediacentre/factsheets/fs355/en/). The transition from infectious diseases to NCDs in developing countries has multiple causes, largely linked to economic development, including the consumption of food reach of fat, salt and sugar, sedentary life styles, tobacco, alcohol use and urbanization.

Biotechnology has revolutionized mankind since its existence in many sectors, particularly industry and agriculture, by improving quantity and quality of products. Every year, the number of commercial biotechnology products is increasing (Pertry et al., 2014) and medical industry is one of the most vital sectors of the economy worldwide. As also discussed later, biopharmaceuticals, generated by recombinant DNA technology, represent by far the fastest-growing part of the global pharma industry. Genetic manipulation and recombinant protein production is also instrumental for the development of novel diagnostic systems for genetic variations. A challenge for developing countries is to properly develop the human skills and infrastructure to ensure proper and effective domestic production. Thus, the concept of capacity building in the field of biotechnology represents a crucial requisite and a unique opportunity to improve the early diagnosis and the treatment of NCDs, particularly in developing countries.

2. Molecular diagnostics

The progress made in understanding the etiology and pathogenesis of a number of NCDs has illustrated that genetic factors and genetic predisposition are very important. Biotechnology has been and still appears instrumental to improve our capacity to detect disease-associated genetic variants, providing better prospects for screening, diagnosis, and early effective intervention.

For instance, genome-wide association studies (GWAS) have identified over 160 loci associated with CVD, adding major contributions to our understanding of the disease (Arking and Chakravarti, 2009). For many NCDs, genotyping could be exploited to determine susceptibility to the disease, predict the prognosis and optimize the treatment. The unraveling of novel genetic determinants provides early intervention, prevention and better management also for type 2 diabetes. For instance, carriers of a common variant in the gene encoding the transcription factor 7-like gene (*TCF7L2*) have a greater risk of developing diabetes (and/or progressing to diabetes from impaired glucose tolerance) compared to non-variant carriers (Meigs et al., 2008). While *CF7L2* could prove a promising biomarker for disease prevention for those with an elevated genetic predisposition to type 2 diabetes (Deacon et al., 2008), at present there is no clinical role for routine

* Corresponding author.
E-mail address: zacchign@icgeb.org (S. Zacchigna).

https://doi.org/10.1016/j.jbiotec.2018.07.043
Received 11 April 2018; Received in revised form 6 July 2018; Accepted 31 July 2018
Available online 02 August 2018
0168-1656/

screening for *TCF7L2*. *TCF7L2* variants might also serve as markers for tailoring customized therapeutic regimens. For example, *TCF7L2* polymorphisms have been associated with differential response to sulfonylurea treatment, although these effects appear too modest to actually guide care (Schroner et al., 2011). Genetic assays have been more successfully applied in pharmaceutical clinical practice for proper management of other NCDs. Pharmacogenomics and personalized medicine aim at using genetic information to make the best therapeutic choice by facilitating predictions about whether that person will benefit from a particular medicine or suffer serious side effects. One current use of pharmacogenomics involves people affected by various cancers. For instance, trastuzumab (Hereceptin), is a monoclonal antibody (see below) that works only in women with breast cancers having a particular genetic profile that leads to overproduction of the HER2 (Ahmed et al., 2015). Genetic testing is also recommended before administering chemotherapy based on mercaptopurine (Purinethol) to patients with acute lymphoblastic leukemia, as some genetic variants interfere with the ability to process the drug and can increase the risk of infection, unless the dose is adjusted according to the genetic profile (Lee and Yang, 2017). A similar dose tailoring approach, has been proposed for the blood thinning drug warfarin (Coumadin), which is included in the therapeutic regimen for various NCDs, although more research is needed to conclusively determine whether warfarin dosing based on the genetic information is better than the current trial-and-error approach (Tseng et al., 2018).

Thus, biotechnology-based diagnostics are offering a unique tool to properly control the onset and evolution of NCDs, allowing the identification of individuals at risk for a specific disease, leading to preventive or screening strategies for an individual or family members. At the same time, this information is paving the way to personalized medicine, as molecular diagnostics can identify sub-types of the same pathology, so that the treatment can be tailored to a precise patient.

3. Monoclonal antibodies

Over a century has passed since Shibasaburo Kitasato and Emil von Behring showed that the serum from human patients or horses, who had recovered from an infectious disease could be used to prevent and treat the disease in other people or animals, paving the way to the therapeutic use of antibodies. After more than 80 years, Köhler and Milstein developed an innovative strategy to produce endless amount of antibodies directed toward a known antigen (Kohler and Milstein, 1975), for which they shared the Nobel Prize in Physiology and Medicine in 1984. They showed that myeloma cells could be fused with B cells to create immortalized hybridomas, producing antibodies targeting a specific antigen. While the original protocol was not even subject of intellectual property, the following years witnessed an exponential increase in the development and clinical use of these biotherapeutics. The first licensed monoclonal antibody was Orthoclone OKT3 (muromonab-CD3), which was approved in 1986 for use in preventing kidney transplant rejection (Goldstein, 1987). Its use was, however, limited to acute cases due to major side effects (e.g. human anti-mouse antibody response) (Sgro, 1995). The humanization of monoclonal antibodies, achieved in 1988, eliminated the immune reactions elicited in some patients (Riechmann et al., 1988), and boosted their use for treating various diseases and conditions, including cancer, chronic inflammatory diseases, transplantation, infectious diseases and cardiovascular diseases (Li and Zhu, 2010). At present, there are over 40 monoclonal antibodies that have been approved for use in clinical practice, with many more currently being tested in clinical trials. The global value of the antibody market is approximately $20 billion per year (Liu, 2014), which is also part of the relative lack of commercial success. For instance, in leukemia treatment, one-year treatment with alemtuzumab costs approximately $52,000 (Shaughnessy, 2012). Thus, issues surrounding the cost of administration and the induction of side effects (e.g. fever-like symptoms at the first infusion) still need to be addressed in order for monoclonal antibodies to become fully commercially viable. Despite these drawbacks, there are various success stories and pharmaceutical companies have a major interest in developing new monoclonal antibodies for both therapeutic and diagnostic use. Among the best performing ones, there are i) rituximab, a monoclonal antibody specific for CD20, an antigen expressed by B-cell lymphoma cells, ii) cetuximab, which targets the EGF receptor on colorectal/neck cancer cells, and iii) trastuzumab, used for the therapy of NER2/Neu-positive breast cancer cells.

As medicine is progressing into the new era of personalized medicine, the clinical use of monoclonal antibodies to treat a spectrum of diseases is expected to explode. Thanks to the recent advances in genetic sequencing, current research in monoclonal antibodies currently aims at identifying novel targets and maximizing their efficacy for clinical use. Importantly, a balance has to be reached to reduce their side effects and overall economic costs, which somehow blighted their clinical and commercial success so far.

4. Recombinant protein drugs and biosimilars

Recombinant therapeutic proteins are a relevant class of medicinal drugs serving patients most in need of novel therapies. Recombinant protein drugs have been recently approved to treat a range of disorders, including cancer, infections, genetic and inflammatory/immune diseases. The manufacturing of therapeutic proteins is a multi-step and cumbersome process, much more complex compared to the one of a standard small-molecule drug. First. Protein therapeutics are usually orders-of-magnitude larger in size than small molecules. Second, they need to preserve their secondary and tertiary structure to be functional. Third, they cannot be produced by a chemical process and need a production system based on living cells (Lagasse et al., 2017). Multiple systems exist for protein production, including bacteria (e.g. *Escherichia coli, Pseudomonas* spp., *Serratiamas cescens, Erweniaher bícola, Lactococcus lactis* and *Bacillus subtilis*), fungi (*Saccharomyces cerevisiae*), Pichia, plants (tobacco plant, rape and transgenic potatoes), insects (*Spodoptra frugiperda*), mammalian cells (Chinese hamster ovary cells, baby hamster kidney cells) and transgenic animals. The choice of any of these systems affects the features of the final product and, possibly, also its post-translational modifications, which are essential for the biological activity. For instance, mouse NGF (mNGF) has been approved in China for the therapy of various neurodegenerative conditions, including Alzheimer's and Parkinson's disease, at the cost of approximately $1500 per milligram (Zeng et al., 2017). However, mNGF is less active than human NGF (hNGF) in human cells and major concerns exist about its possible immunogenicity (Paoletti et al., 2015). While attempts to produce hNGF have been made using bacteria, yeast, insect and mammalian cells (Negro et al., 1992; Nishizawa et al., 1993; Allen et al., 2001; Fan and Lou, 2010; Iwane et al., 1990), both the yield and the activity have been invariably low, prompting the use of salivary glands of transgenic animals as efficient bioreactors for the synthesis of therapeutically adequate hNGF (Zeng et al., 2017; Coulibaly et al., 1999).

Over 60 recombinant therapeutic proteins have been approved over the last 5 years by the FDA and EMA in the United States and Europe respectively (January 1, 2011, through August 31, 2016; "Purple Book" list of licensed biological products, including biosimilar and interchangeable biological products). Almost half of these are monoclonal antibodies, which have been discussed in the previous section, followed by coagulation factors and replacement enzymes. Others include biosynthetic insulins, peptide hormones, growth factors, interferons, interleukins, erythropoietin and protein antigens, used as vaccines (Tsiftsoglou et al., 2013).

There is no doubt that recently approved therapeutic proteins serve a wide spectrum of patient populations and are of benefit to public health in many medical disciplines, particularly oncology and hematology, but also cardiovascular disease, endocrinology, musculoskeletal