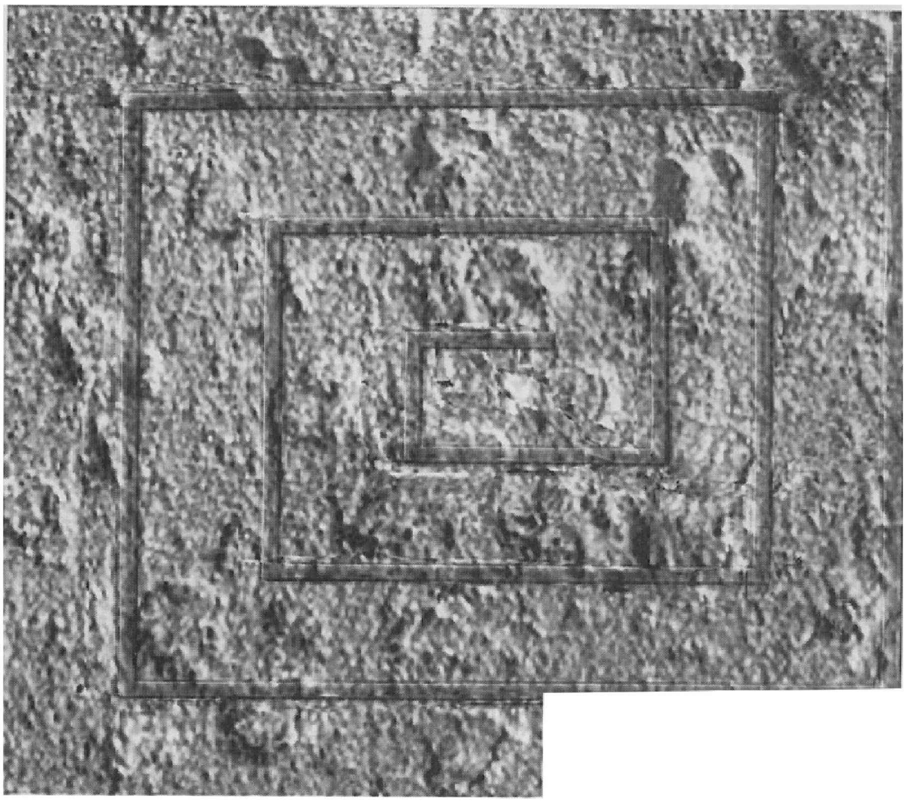

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Biotechnology, beginning with recombinant DNA toward a personalized medicine

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I would like to initiate this document by making a brief description of the term Biotechnology, hoping to not hurt the feelings of many other professionals better versed than I, on the details of this science, as the application of traditional and/or scientific knowledge to manipulate microorganisms, cells or even higher organisms, directed to supply goods and services to the daily growing human population. With almost 30-year-old, biotechnology, driven by the ability to transplant a gene from one organism into another to introduce novel functionality in the receiving organism, has evolved to reprogram cellular behavior or incorporate increasingly complex biosynthetic pathways (to produce novel metabolic products or to achieve greater system integration) or genetic regulatory constructs (to modulate the activity of recombinant genes in space and time) (Bhalerao, 2009). Biotechnology one of the riskiest industries has achieved a dynamic growth and unparalleled discovery, outstanding advances and contributions to human and animal medicine. This has mainly been possible throughout the exploration of diverse unicellular and multicellular genomes, the genes and the proteins they encode, and together with the development of dozens of technologies, reach every day a better understanding of cell biology, homeostasis and disease. Thus, biotechnology has established as an industry, where any bio-product can be patentable. Among the greatest technological advances that have fueled biotechnology research into a wide range of interesting areas that might have lead to new therapeutics and diagnostics are gene amplification (PCR) and protein engineering technologies, rapid genetic sequencing, automated liquid handling, protein analysis (Gas chromatography-mass spectroscopy, GCMS, Liquid chromatography-mass spectrometry, LCMS), plant and animal cell culture, real-time cell analysis, sample-preparation methods, fermentation technology, monoclonal antibody technology, microarrays and very important, high-speed computing (De Palma, 2005). The most successful uses of biotechnology so far have been the production of therapeutic drugs (biologics); genetically modified (GM) plants; and medical diagnostic tools such as DNA testing. Of note, developed countries own the industry, with an estimate of about 1,283 biotechnology companies only in the United States that employ more than 150,000 people in high value jobs, a record of sevenfold increase in the invested money from 45 billion USD in 1994 to 330 billion USD in 2001, and an increased rate in the number of issued patents. To mention, the number of patents issued per year increased almost 9-fold, from 518 patents in 1981 to 4,561 patents in 2001, and from 25 patents per year issued in the early 1990s to U.S universities, sharply rose to 174 in 1999 (Taylor and Cayford, 2003).

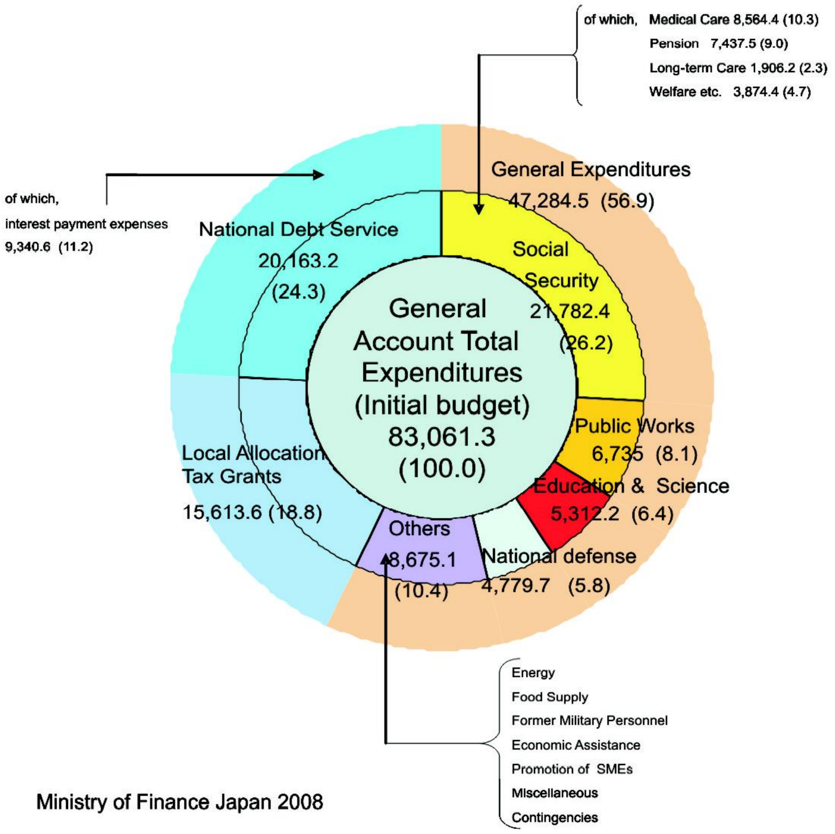
Diseases have been since them recognition, the main source of mortality in humans and animal species, particularly those subjected to intensive production. They not only originate from diverse alterations in the environment, including abundance of microbial and multicellular pathogens, and nutritional status of the host, but also by specific alterations in genes and the proteins they encodes, determining a novel phenotype, in other words, mutation. Therefore, motivation of insurers to pay for new medical treatments drives the demand for biotechnological products and services. Beginning with recombinant DNA in the late 1970's and earliest 1980's, a major biotechnology's breakthrough lead to the cloning and expression of several recombinant proteins, with profound impact on research and life sciences. Of note, Genetech, Inc, reported the production of the first human protein manufactured in bacteria in 1977, and this lead to replacement treatments like insulin (Humulin) in the treatment of type I diabetes mellitus (Johnson, 1983). Erythropoietin (Epogen) in anemia associated with chronic renal failure and patented by Amgen in 1989 (Eschbach *et al.*, 1987; Lin *et al.*, 1985), granulocyte-colony stimulating factor, G-CSF (Neupogen) in the treatment of neutropenia in cancer patients and hematopoietic stem cell transplantation to decrease the incidence of infection associated with some forms of chemotherapy (Nagata *et al.*, 1986; Souza *et al.*, 1986), and the human growth hormone (Protropin) in the treatment of its direct deficiency or in syndromes accompanied with shortness, wasting, obesity and renal transplantation (Gotherstrom *et al.*, 2007). It is worth to mention the production of recombinant interferon (rIFN) with today's more than ten products in the market place (among them are INFERGEN, AVONEX), rIFN has been widely used to treat cancer, autoimmune disorders included multiple sclerosis and viral infections (Nagata *et al.*, 1980; Takaoka *et al.,* 2003).

These advancements have lead to a greater understanding of biochemical diseases pathways and to an extensive search for biological agonists and inhibitors, with the generation of novel bio-drugs (targeted therapeutics) specifically targeting tyrosine kinase enzymes highly expressed and occasionally mutated in diverse cancers, including Imatinib for the treatment of malignances such as chronic myelogenous leukemia (CML), and gastrointestinal stromal tumors (GISTs) (Druker and Lydon, 2000; Deininger and Druker, 2003), Erlotinib for the treatment of metastatic non-small cell lung cancer and pancreatic cancer, mostly in combination with standard chemotherapy (Sordella *et al.*, 2004, Li *et al.*, 2007). In addition to and initially developed as promising scientific tools, today several monoclonal antibodies (mAbs), are considered the best hope for patients with cancer, autoimmune and cardiovascular diseases and infectious diseases. Among them, humanized monoclonal antibodies have been developed to target and inhibit the function of cell surface proteins highly expressed in tumor cells such as the vascular endothelial growth factor, VEGF (Avastin), which has anti-angiogenesis capacity used to treat metastatic colo-rectal cancer, and non-small cell lung cancer (Rini, 2007), mAb anti-HER2/neu receptor (Herceptin) for the treatment of breast cancer (Bange *et al.*, 2001; Hudis, 2007), and the mAbs Cetuximab (Erbitux) and Rituximab (Rituxan) generated against the epidermal growth factor and the CD20 molecule, respectively. They are used for the treatment of metastatic colorectal cancer and squamous cell carcinoma, and B-cell leukemias, impairing cell growth, proliferation and mediating antibody-dependent cellular cytotoxicity (Maloney *et al.*, 1997). Recently, the anti-IL-6R mAb (Tocilizumab) developed by professor Kishimoto at this institution (Nishimoto and Kishimoto, 2008), has been effective in the treatment of conditions where overproduction of IL-6 play a role in inflammatory autoimmune diseases, included rheumatoid arthritis (RA), and juvenile idiopathic arthritis (JIA) (Kishimoto, 2009). All of these bio-products together with the development of modularly designed production-scale fermentors and bioreactors have shortened considerably the fabrication time, and market time, making them efficient bio-processes.

With the completion of the human genome sequence the race for gene discovery and the cloning era decelerated, and the post-genomic era became imposed with a significant change in biotechnology, the era of functional genomics and systems biology. However, there is much skepticism than optimism in the new products and compounds the human genome will pave to develop. Even when it is widely accepted that only one in ten biotech companies is profitable, and the hopes to cure many infectious diseases and cancer are still far away, as are the hopes and promises of human embryonic stem cell therapy, this young industry is very optimist, and the perception is that many developments in near future, will provide a suitable economic and social environment, to accede a personalized medicine, with a greater impact than recombinant DNA. Today's race in technological development is focused on the construction and development of novel high-throughput sequencers with the aim to know many as possible individual genomes at low cost, and to achieve a personalized (targeted) therapy in the commercial arena. Nevertheless, many technologies have also experienced burst in this industry, included antisense, gene therapy and cancer vaccines, while others are considered promising in biotech, such as pharmacogenomics, biomarkers, fully humanized monoclonal antibodies, RNAi, protein therapeutics and structure-guided drug design (DePalma, 2005).

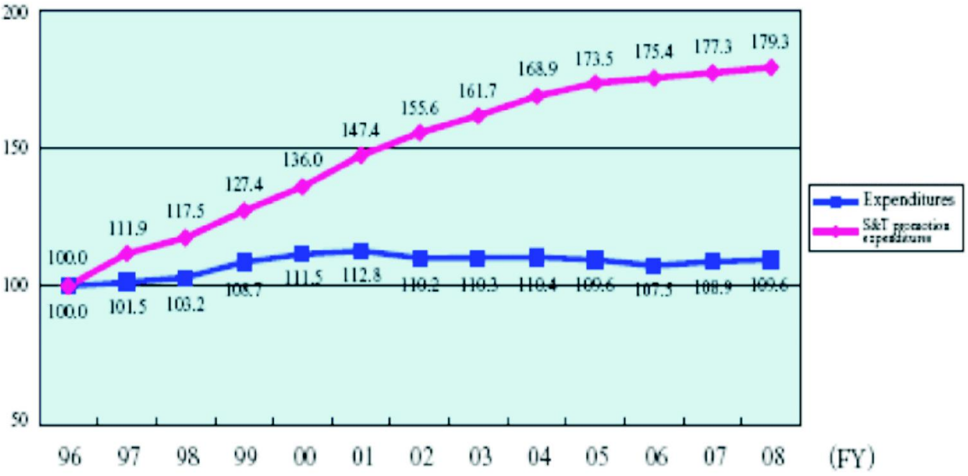
Since almost all of these developments are confined to developed countries, we could ask ourselves initial questions, where are we? and were do we want to go?. As an example, a country which has experienced dramatic economic, social and environmental changes associated with the World War II, Japan committed to achieve a new position, has been, thanks to his cooperative society's structure, made pioneering developments in science and technology. With as today's gross domestic income (GDI) of 83 trillions yen (Figure 1) and about 130 million people, this country, in spite of the severe fiscal conditions, lower government revenues, and a national debt of 20,163 billion Yen, has expanded its science and technology-related budget (Figure 2) with a 6.4 % of its total general account budget (Figure 1) on education and science (Ministry of Finance, 2008). Japan also has planed as for year-2008, strategically push ahead major technologies, such as R&D on next-generation super computers (14.5 billion Yen), space transportation systems (40.5 billion Yen) and important research projects where the country has a competitive edge, included regeneration medical research projects that make use of iPS cells (2 billion Yen). Also will provide generous supportive measures on basic research projects through expansion of Grant-in Aid for Scientific Research (Ministry of Finance 2008). It is worth to mention that a large portion of the research has long been translated to a better understanding of life, and the dramatic increase in the number of publications in high impact factor journals and outstanding technological advances promotes the creation of new institutions. Notably, in Osaka University, academic contributions have supported the acquisition of government's grants to pursue a World Premier International Immunology Frontier Research Center (IFReC), almost 2 years ago, which has planned to have expenses for about 1500-2000 million yen/year, and competitive research grants average of 1.066 billion yen for principal investigators compromised to unveil the whole picture of the dynamic immune system by employing a variety of imaging techniques to visualize cells within live animals (Akira, 2009).

Colombia, an agriculture country is waiting for a compromised investment to access, use and develop an already 25-years-old modern biotechnology. We should feel in peace with and proud of the huge diversity of our nation, after explore our environment deeply, revealing more of its nature as possible, looking for new genes, proteins and therapeutics with promising applications in disease prevention and treatment. Thus, Generating of novel, solid and cooperative, next generation of biotech enterprises with its original position of risk-taking R&D innovative status must to consider that survival, growth and thrive depends mainly on securing founding through patents, the cornerstone for biotech companies. Among the various areas in which Colombia's nature have great potential to reinforce human, animal and plant medicine, I would like to mention that pharmacogenomics, drug discovery, biopharmaceuticals, plant-made pharmaceuticals could be a central business. This task is still in our hands, we have not yet begun, and if we do not make decision today, tomorrow what was part of our nation's diversity will be sell in the stores not



Ministry of Finance Japan 2008

Figure 1. General account expenditures for FY2008 (Unit: billion yen, %)



Note: Changes in indexes of science and technology expenditures and general expenditures (100 for FY 1996). Ministry of Finance Japan 2008

Figure 2. Comparison of science and technology expenditures with general expenditures

by us but to us. The second question I would like to ask, are we really committed to get access to all of these technologies, to pursue original research, distinctive and useful for life science?. The situation is very critical in our country, as I already stated, modern biotechnology is evolving so fast, and today many high schools in developed countries, are setting biotechnology labs in order to offer to the students the opportunity to perform the most current bioscience experimentation, including bacterial transformation, manipulation and engineering bacterial plasmids, proteomics, and spectrophotometric analysis, thus preparing the students to engage in a global society with real-world science application. To my knowledge, in Colombia some high schools have already introduced gene amplification (PCR) and electrophoresis as a component of the daily science education, when many life science programs at universities have not incorporated these basic facilities for molecular biology, what can we expect in the next level of cell biology, confocal microscopy and fluorescent activated cell sorting, FACS; or in vivo cell imaging, included two-photon and multiphoton microscopy?. Finally, I would like to add something to all of these reflections, willing, cooperation, integration and commitment to common goals seems to be key drivers of progress.

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