THE IMPACT OF BIOINFORMATICS IN CLINICAL PRACTICES ON HUMAN CANCER

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ABSTRACT

Today's modern clinical medicine has been significantly enriched by a relatively new field of biological sciences called genomics-proteomics, which is based on sub-principles of genetics. This paper aims to present and elucidate the benefits of genomics-proteomics and project on how these new topics may support clinicians' diagnostic, prognostic and treatment decisions. It addresses the need for appropriate integration of various fields of science in order to correctly derive and implement these benefits. Furthermore, it attempts to demonstrate the way bioinformatics are applied in collaboration with traditional medical practices, to open new paths towards gene therapy and pharmacogenomics.

Keywords: cancer, genomics, proteomics, bioinformatics, clinical practice, gene therapy.

I. INTRODUCTION

The fields of genomics and proteomics, especially after the principal completion of the Human Genome Project (in 2003), generated a new basis for the application of modern medical practices. Due to the fact that human genetic variations are associated with many complex and life threading diseases, like cancer, the information hidden in data produced by genetic analyses is believed to be the key factor for the development of new and more effective diagnosis, prognosis and treatment mechanisms.

The efforts to use and apply genomics-proteomics to treat cancer may seem straightforward. Nevertheless, the behavior of cancer is dependent on many different genes, the way they interact, and the conditions they create to promote or suppress a disease. Although it is possible to identify a single gene that may signal a more aggressive type of disease, the analysis of a key set of genes expressed by the tumor can provide far more specific and reliable information. With oncogenomics it may be possible to individualize cancer assessment, which should dramatically improve the quality of treatment decisions.

The key to utilizing genomics in cancer is to determine which sets of genes and gene interactions affect different subsets of cancers. Studies can be performed that link response to therapy, or the likelihood of recurrence to the pattern of gene expression in tumors. These results can then be used to develop clinically validated services that provide the genomic profile of an individual's tumor, allowing clinicians to better understand what treatments are most likely to work for that patient or how likely a cancer is to recur. Towards this direction, further analysis has to take place to identify other suspicious factors that may lead to carcinogenesis. Recently, T.R. Colub and colleagues at Dana-Farber Cancer Institute in Boston, Massachusetts surprisingly discovered that even non-coding RNA species known as microRNAs (miRNAs) play an important role in cancer growth, Lu et al (1). This makes the analysis of genomic data even more complex and intriguing.

Bioinformatics now provide the ability to analyze genetic data and visualize the hidden genetic information, which will definitely put an added value to the traditional medical approaches applied today. The combination of the well established medical informatics with the new techniques of bioinformatics in a unified field, so called biomedical informatics, is expected to offer the clinician a new perspective in medical decision-making.

This paper addresses the use and potential of biomedical informatics focusing on the point of view of a clinician rather than an engineer. This perspective eventually reveals the value of integration among medical, technological considerations. *Section II* refers to the contribution of genomics-proteomics in today's clinical medicine, focusing on how ideas from the field of biological sciences are applied. *Section III* introduces principles of bioinformatics and explains how they correlate with the traditional medical informatics to assist clinicians' decision making for diagnosis, prognosis and treatment problems. *Section IV* provides examples of the latest advantages of genomics-proteomics and their valuable outcomes. It also reveals how technology can help clinical decision making, provided that a good and commonly accepted design strategy is followed. An explanation of how gene therapy will significantly contribute to today's clinical practices towards a more effective cancer treatment is also provided. The importance of this new path of therapy is pointed out through Pharmacogenomics and

their current applications. Several valuable gene based tests and drug treatments are presented.

II. GENOMICS-PROTEOMICS IN CLINICAL MEDICINE

It is widely accepted that any disease is influenced by a larger or smaller number of factors. These include on the one hand environmental factors such as toxins, radiation, infections, nutrition, age, stress and on the other hand the genetic predisposition that causes the human body to react to the environment in a certain way. Small changes in our genes can trigger, prevent, promote or alleviate diseases. Whether, when and how severely a person falls ill is determined by a combination of all these factors and proteins play a central role in mediating effects.

Recent analyses have generated several important facts and hypotheses, some of them being extensively studied today as presented in the following.

- Recently discovered genes, which assist the development of a disease, constitute a potential target for drugs. For example, in the past few decades biologists have discovered more and more oncogenes, i.e. cancer-promoting gene variants. Many anticancer agents act by restoring the correct function of the products of these genes (mostly proteins).
- Knowledge of the structure, i.e. the three-dimensional form, of a protein makes it possible to decide in advance whether a given substance has any potential use as a drug.
- If the genetic preconditions for a disease are known, a patient's individual risk can be determined and appropriate preventive action may be taken in advance.
- Many diseases are amenable to intervention at the gene level. For example, genes can be turned on or off by drugs.
- Drugs do not always have the same effects. The effect of a given drug can be too strong, too weak or absent altogether in people with the same symptoms. Moreover, adverse effects are always likely to occur. Our genes are at least partly responsible for these too; the discipline of pharmacogenetics investigates these relationships and attempts to foresee and ultimately prevent such problems.

The above considerations create many crucial questions that have to be answered in order to derive safe conclusions. The necessity to develop new sophisticated tools and techniques to assist the genomics-proteomics research is certainly a matter of time but a matter of life too.

III. BIOINFORMATICS: A PATH TO GENOMIC-BASED MEDICINE

Over the past decades, clinical medicine is supported by modern, highly sophisticated techniques that manage to derive convincing diagnosis/prognosis results for many complex diseases. These techniques accept as input data extracted from physical and laboratory examinations, which are combined with patient's history to design a specific treatment path, in association with population studies.

State of the art medical informatics has been already in use and offer clinicians the ability to search for specific information related to one disease or another. Such techniques are Biopsy, Lumbar Puncture and imaging methods like X-rays, Magnetic Resonance Imaging (MRI) etc., which are continuously being improved (e.g. functional MRI), Pavlidis et al (2). Other techniques used mainly for treatment, like Surgery, Radiotherapy, Chemotherapy, Immunotherapy, Stem Cell Transplantation are still the clinician's basic tools to face severe cancers, Castro et al (3). However, clinicians know that in many cases these tools are not enough though. Patients with the same symptoms many times react different to same drugs, as mentioned above, which leads to a wrong prognosis estimation. Several questions are born and efforts for more secure diagnosis results are definitely needed. This is the point where bioinformatics fit in and offer the opportunity to go deeper and derive even more accurate measurements based on genetic information.

Bioinformatics focus in discovering the functionality of genes and proteins and understand their interrelations. Even more, they attempt to detect their behavior under specific circumstances; for example measuring their expression levels under drug treatment, time etc. Figure 1 presents the relation between medical informatics and bioinformatics. It is obvious that, medical informatics are combined with bioinformatics to produce a more effective way to deal with diseases. This cooperation derives a new field, called biomedical informatics, which in turn provides remarkable effects in modern medical approaches underlying genomic based medicine.

It should be emphasized that bioinformatics do not strive to replace medical informatics, but rather enhance the information utilized and resolve uncertainties in clinical decision makings. Benefits of such a joint consideration include the following.

- Involve personalized aspects in pathogenesis and disease progression rather than be based on population-wise criteria, as usually done with medical informatics.
- Discover new types of disease subclasses that may result in the same symptoms (phenotype)

but having different genomic signatures (genotype)
- Resolve disease hypotheses with similar phenotype based on personalized genotype.

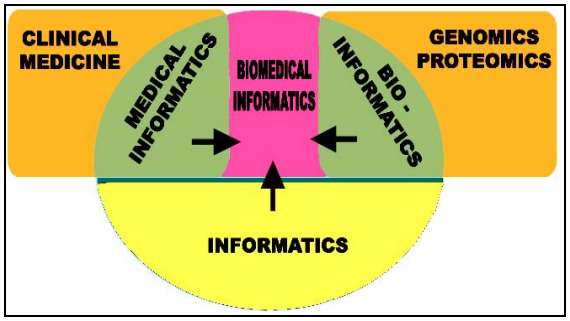

Figure 1. The interrelation between bioinformatics and medical informatics

A more detailed representation showing the way bioinformatics positively influence today's medical practices, is given in figure 2.

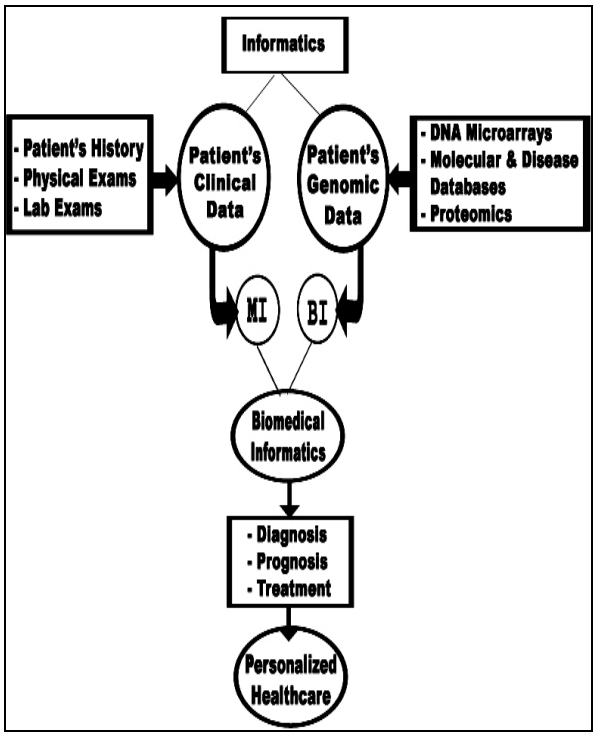

Figure 2. A schematic representation showing the synergy of bioinformatics with medical informatics towards personalized healthcare

As seen in this figure, the main reason for combining these two areas of informatics is not for deriving new tools and methods assisting clinicians' efforts, but for generating a new path that leads to personalized healthcare.

To understand the contribution of modern bioinformatics tools in medical practices consider a physician – clinician seeing a new patient who was recently diagnosed with breast cancer. The clinician desires to gather more information for this specific disease and especially genetic information of the TP53 tumor suppressor gene's mutation in breast cancer, to build up a more detailed image of this type of cancer. The physician could (even today!) explore the WWW to gather information in the following manner.

Step 1. The physician might first go to the National Center for Biotechnology Information (NCBI) web pages. The NCBI maintains a number of databases for biology and molecular medicine, which are integrated within the Entrez server.

Step 2. The Online Mendelian Inheritance of Man (OMIM), and/or the Human Gene Mutation Database (HGMD) resource contains a compilation of human genetic disorders, including automatic links to references in the literature and to the involved genes in the genetic databanks.

Step 3. The link to the protein sequence database is followed, and the detailed sequence of amino acids for this gene can be found. An algorithm can be run using this sequence to find all related sequences in the protein sequence databases, SWISS-PROT and PIR. The genetic databank, GENBANK, is then accessed from the protein sequence to see the detailed sequence of DNA bases that encode for the gene.

Step 4. The protein sequence entry is also linked to an entry in the Protein Data Bank, the database of three-dimensional structure.

Step 5. The information gathered should be easily combined with the clinical one to construct an analytic profile of the patient, based on this biomedical information. However, achieving this integration is far from reality today!

During the last decade and especially after the first announcement of the completion of the Human Genome Project by U.S. Department of Energy and the National Institutes of Health, modern bioinformatics have been amazingly improved. Gene expression levels are now easily derived for many different diseases and offer the opportunity to proceed with further analysis and gain valuable genetic knowledge.

Traditional bioinformatics techniques used for the specification of gene expression profiles include the following.

- FISH (Fluorescence in situ Hybridization)
- PCR (Polymerase Chain Reaction)
- Northern Blot Analysis
- SAGE (Serial Analysis of Gene Expression)

- Southern Blot Analyses
- Protein Truncation Test

It is only recently that DNA Microarrays have come into practice. Microarrays have an advantage over other methods, because in a single analysis they evaluate the expression of all genes that may be involved in a cancer case. By graphically depicting the degree to which each gene is active in the cancer, DNA Microarrays can generate a "genetic signature" for a particular cancer. This makes the identification of cancer subtype more precise. The ability to take a snapshot of a cancer's genetic signature may lead to a better understanding of how that cancer develops and how treatment can be individualized.

Besides this potential, the value of DNA Microarrays in clinical practice should be taken with appropriate caution. They provide high-resolution high-throuput information, but in a noisy and highly complicated form; to extract any useful conclusions from Microarrays in population studies, the size of samples should be unrealistically large. Genomic – proteomic data possess laboratory noisy elements that have to be "cleaned" in order to obtain accurate conclusions. Due to this fact, modern bioinformatics deal with several subtopics like: noise reduction (for example background subtraction from a DNA Microarrays image), normalization, feature selection (gene selection and/or dimensionality reduction), clustering and classification.

Thus, Microarrays should be combined with sources of lower resolution information extracted from medical informatics and be used as to support hypotheses by increasing posterior probabilities, or generate new-more detailed-hypotheses.

IV. RECENT ADVANTAGES OF GENOMICS – PROTEOMICS IN HUMAN CANCER

Some of the most common abnormalities detected in human cancer are the following:

- *Translocations*—the changing places of a gene from one chromosome with a gene on another chromosome;
- *Deletions*—a gene or sequence of nucleotides is missing in the DNA
- *Polymorphisms*—variations in nucleotide sequence

Tumor genesis involves an interplay between at least two classes of genes: *oncogenes* and *tumor suppressor* genes. Oncogenes are abnormally activated versions of cellular genes that promote cell proliferation and growth. Activated oncogenes thereby result in an exaggerated impulse for a cell to grow and divide. Tumor suppressor genes, on the other hand, are normal genes that act to inhibit tumor cell proliferation and growth. The inactivation of these genes results in tumor formation or progression.

The field of bioinformatics, with the latest advantages in technology, offers now the opportunity to examine alterations of these genes and derive valuable outcomes regarding tumor development and progression. More specifically, DNA Microarrays provide an accurate measurement of gene expression profiles of cancerous tissues. These data, after applying noise reduction and normalization methods, may be used to detect DNA sequence abnormalities and identify, with relative accuracy, new types or sub-types of already known and characterized tumors. Even more, they contribute in gene selection i.e. detection of new genetic markers (specific genes or groups of genes that mostly alter and determine the behavior of a tumor).

However, in order to attain meaningful results, useful in clinical practice, there is a great need for collaboration and integration among various fields of science. The goals of the study should be clearly set from a medical point of view, the design of experiments must be biologically valid and the technology tools must be correctly utilized, taking under consideration the incompleteness, size and uncertainty associated with the analyzed data.

After the completion of a DNA Microarray experiment an analytic table of genomic information is provided, where rows are genes and columns may be the samples of different tumors, or different patients, or even a tumor sample presented at different time phases. Figure 3 presents a sample of genomic data arranged in a table where the degree of gene alteration is measured using a climax of red to green. This analysis has reached a stage to be widely applied using two main technologies, the cDNA Microarrays (Stanford University) and the Oligonucleotide Microarrays (Affymetrix).

Latest applications of DNA Microarrays are encountered in several human cancer brain cancer, leukemia, breast cancer, ovarian cancer, prostate cancer etc. Some application examples are reviewed in the following.

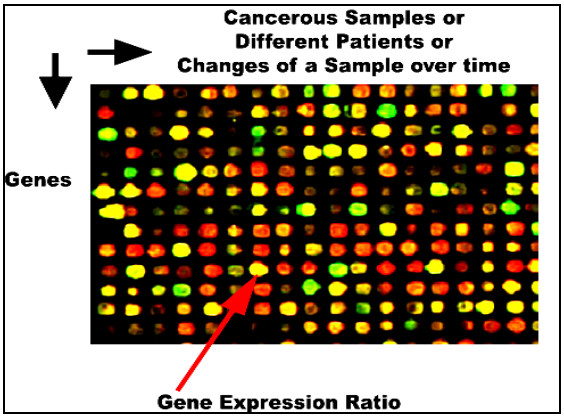

Figure 3. A sample Microarray image showing genes (rows) and samples (columns).

Example 1: A recent application of DNA Microarrays, Nutt et al (4), found that "gene-expression based classification of malignant gliomas correlates better with survival than histological classification". In this research, Microarray analysis was used to determine the expression of ~12,000 genes in a set of 50 gliomas, 28 glioblastomas and 22 anaplastic oligodendrogliomas. Supervised learning approaches were used to build a two-class prediction model based on a subset of 14 glioblastomas and 7 anaplastic oligodendrogliomas with classic histology. A 20-feature *k*-nearest neighbor model correctly classified 18 of the 21 classic cases in leave-one-out cross-validation when compared with pathological diagnoses. This model was then used to predict the classification of clinically common, but histologically nonclassic samples. When tumors were classified according to pathology, the survival of patients with nonclassic glioblastoma and nonclassic anaplastic oligodendroglioma was not significantly different ($P = 0.19$). However, class distinctions according to the model were significantly associated with survival outcome ($P = 0.05$). This class prediction model was capable of classifying high-grade, nonclassic glial tumors objectively and reproducibly. Moreover, the model provided a more accurate predictor of prognosis in these nonclassic lesions than pathological classification produced. These data suggest that class prediction models, based on defined molecular profiles, classify diagnostically challenging malignant gliomas in a manner that better correlates with clinical outcome than standard pathology does.

Other important diagnostic techniques already used in practice, like *in situ hybridization* that uses PCR or Southern blotting to measure the DNA sequence differentiations and *flow cytometry* that applies a laser beam to determine a large number of single cells in a sort time and detect their types, have proved their applicability in measuring the distribution of the oncogenes in a tumor. Studies based on these techniques, but also in DNA Microarrays, have already shown the importance of specific brain tumor genetic markers like the p53 gene, a tumor suppressor gene located on chromosome 17p13.1 that has an integral role in a number of cellular processes, including cell cycle arrest, response to DNA damage, apoptosis, angiogenesis and differentiation. The p53 gene is involved in the early stages of astrocytoma tumor genesis Levine et al (5). Another study, Collins (6), suggests that most of these abnormalities converge on one critical cell-cycle regulatory complex which includes the p16, cyclin-dependent kinase 4 (cdk4), cyclin D1 and retinoblastoma (Rb) proteins. Furthermore, epidermal growth factor receptor (EGFR) has been found over expressed in about 40% of adult primary glioblastomas and the PTEN (phosphatase with tensin homology) gene, which is located in chromosome 10q23.3, is mutated in approximately one-third of primary glioblastomas, Smith et al (7).

Example 2: Two important aspects concerning cancer treatment are class discovery and class prediction. Class discovery (clustering) refers to defining previously unrecognized tumor subtypes. Class prediction (classification) refers to the assignment of a particular tumor sample to already defined classes, which could reflect current state or future outcomes. For many tumor types, important subclasses are likely to exist but have yet to be defined by genetic markers. For example, prostate cancers of identical grade can have widely variable clinical courses, from indolence over decades to explosive growth causing rapid patient death.

Cancer classification is difficult because it relies on biological insights. Golub et al (8), proposed a method for subclass discovery using DNA Micro-array data (biology point of view) analyzed with established computer science and machine learning techniques (informatics point of view) like SOM (Self Organizing Maps) and various classifiers. The method was conducted to a leukemia data set, publicly available, and showed remarkable results especially in class discovery. The method proposed actually succeeded to distinguish the two well known types of leukemia, Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL). Authors subsequently obtained immunophenotype data and found three classes corresponding to: AML, T-lineage ALL, B-lineage ALL.

Another issue associated with the analysis of Microarrays is gene selection from the data provided. In a Microarray experiment, the expression levels of several thousands of genes are recorded, leading to problems of algorithmic instability where there are only a relatively low number of samples available. These kinds of problems relate to the so called "curse of dimensionality". It has been shown that selecting a small set of informative genes can lead to improved classification results as follows.

1. It can improve classification accuracy. Many studies have shown that gene selection prior to classification improves the classification accuracy.
2. It can reduce cost in clinical setting.
3. It could enable experts to get into the genetic nature of the disease and the mechanisms responsible for it.
4. It could finally improve the drug discovery process, resulting in more efficient drugs with less adverse effects and at a lower cost.

This approach was applied to 38 acute leukemia samples and lead to the selection of 50 genes out of 6817 total gene recordings. The 50 gene predictors derived, assigned 36 of the 38 samples correctly (either

ALL or AML) and the remaining two as uncertain. The 50 gene predictor was then applied to an independent collection of 34 leukemia samples and enabled correct prediction for 29 out of 34 samples. The success was notable because the collection involved a much broader range of samples, including samples from peripheral blood and bone marrow, childhood AML patients, and samples from different reference laboratories that used different sample preparation protocols. The overall prediction strengths were quite high at 73%. The average prediction strength was lower for samples from one laboratory that used very different protocol for sample preparation. This suggested that clinical preparation for such an approach should include standardization of sample preparation.

The list of informative genes used in the AML versus ALL predictor was highly instructive. Including CD11c, CD33, and MB-1, encode cell surface proteins for which monoclonal antibodies have been demonstrated to be useful in distinguishing lymphoid from myeloid lineage cells. Other genes provide new markers of acute leukemia subtype. For example the leptin receptor, originally identified through its role in weight regulation, showed high relative expression in AML. The leptin receptor was recently demonstrated to have antiapoptotic function in hematopoietic cells. Authors had expected that genes most useful in AML-ALL class prediction would simply be markers of hematopoietic lineage and would not necessarily be related to cancer pathogenesis. However, many of the genes encode proteins critical for S-phase cell cycle progression (Cyclin D3, Op 18, and MCM3), chromatin remodeling (RbAp48 and SNF2), transcription (TFIIEβ), and cell adhesion (zyxin and CD11c) or are known oncogenes (c-MYB, E2A and HOXA9). In addition, one of the informative genes encodes topoisomerase II, which was the principal target of the antileukemic drug etoposide. These data suggests that genes useful for cancer class prediction may also provide insight into cancer pathogenesis and pharmacology.

Example 3: Tumor genesis of breast cancer has been found to be directly related with two specific genes, the BRCA1 and BRCA2 (discovered in 1994), Ford et al (9). Based on this information, several studies on gene selection have been conducted with encouraging results. One such work was presented by Van't Veer et al (10), where research for gene selection was conducted on Microarray data for breast cancer. The data set consisted of 98 samples, 34 from patients who developed distant metastases within 5 years, 44 from patients who continued to be disease-free after a period of at least 5 years, 18 patients with BRCA1 germline mutations and 2 with BRCA2 carriers. Each sample was described with approximately 25,000 genes. Initially 5000 thousand genes were selected across the group of samples with the criterion of at least a twofold difference and a P-value of less than 0.01 in more than 5 tumors. The correlation coefficient of the expression of each of the 5000 genes was calculated and 231 were found to be significantly associated with disease outcome. These 231 genes were rank-ordered on the basis of the magnitude of the correlation coefficient. Subsequently, a class predictor was optimized by adding subsets of 5 genes from the top of this ranked list, evaluating its accuracy with the leave-one-out scheme. The accuracy improved until an optimal number of marker genes was reached, resulting at 70 genes. The classifier predicted correctly the actual outcome of disease for 65 out of 78 patients (83%), with respectively 5 poor prognosis and 8 good prognosis patients assigned to the opposite category.

The functional annotation of the selected genes provided insight into the underlying biological mechanism leading to rabid metastases. Genes involved in cell cycle, invasion and metastasis, angiogenesis and signal transduction are significantly up regulated in the poor prognosis signature (for example cyclin E2, MCM6, metalloproteinases MMP9 and MP1, RAB6B, PK428, ESM1, and the VEGF receptor FLT1). When evaluating all 231 genes initially selected, more genes become apparent (for example, RAD21, cyclin B2, PCTAIRE, CDC25B, CENPF, VEGE, PGK1, MAD2, CKS2, BUB1, etc).

V. GENE THERAPY & APPLIED PHARMACOGENETICS

Gene therapy relates to the introduction of genes into a person's DNA in order to treat tumours. Gene therapy is an emerging medical technique that involves the addition of DNA to the human genome in order to replace a defective gene or to provide a gene that the body can use to fight disease. This type of therapy mainly deals with the following topics:

- delivery of prodrug-activating genes that confer sensitivity to toxic metabolites.
- replacement of tumour suppressor genes that usually results in tumour apoptosis.
- delivery of genes resulting in suppression of angiogenesis.
- delivery of genes resulting in activation of host antitumor immune responses.
- antisense cDNA delivery to regulate negatively tumour-related protein.
- conditionally replicating viruses that selectively infect and destroy tumour cells.

Although these approaches significantly vary in strategy, they all share a common goal: *to deliver the therapeutic gene or virus efficiently and specifically to the targeted tissue.*

Gene therapy can be distinguished into two categories: *ex vivo*, in which cells are modified outside the body

and then transplanted back, and *in vivo*, in which genes are changed in cells that are still in the body. Several gene therapy approaches have been tested already as shown below:

- Immunotherapy: activation of the immune response against tumour cells.
- Conditioned cytotoxity: also known as 'suicide gene' approach and consists in the administration of toxic genes to destroy tumour cells.
- Phenotypic correction or mutation compensation: attempts to limit cancer cells by forcing tumour suppressor genes to over express or inactivate oncogenes.

The ex vivo approach was the first to be put into practice. In this approach, cells are removed from a patient's tumorous area and incubated with vectors (carriers) to introduce genes. Vectors are mechanisms that allow genes to be carried into the genome. Modified cells are then transplanted back into their host, where it is hoped that they will replace defective genes to correct protein problems.

For in vivo techniques, the challenge of inserting genes is greater. Here, vectors have a more difficult task to perform. They must deliver genes to enough cells as to have any effect, they have to remain undetected by the body's immune system and they must deliver genes into a precise spot on the genome for the body to properly produce desired proteins. Several applications have been reported in this area. One of them, elucidating the way gene therapy is applied, is the careful insertion of the Herpes virus simplex I thumidine kinase (HSV-tk) carrier directly into a glioblastoma multiforme (brain tumor) tissue (Figure 4). In general terms, this technique forces tumorous cells to suicide without destroying neighbor healthy cells. Another virus carrier also used is the Epstein–Barr virus.

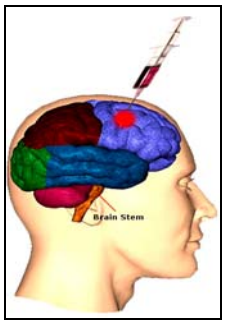

Figure 4. Insertion of virus carrier into the brain tumor

Most of the promise of pharmacogenomics remains to be fulfilled. However, the concept of using known genetic associations to prevent patients from taking drugs that would likely be ineffective or harmful is already available and used in clinical practice in certain specific arenas, thanks mainly to the steady progress made in pharmacogenetics over the past several decades.

There is now a commercially available diagnostic test measuring a patient's ability to produce the metabolic enzyme thiopurine *S*-methyltransferase (TPMT), which is essential for the metabolism of thiopurine medications used to treat acute lymphoblastic leukemia (ALL), the most common form of childhood cancer. Genetic testing gives clinicians the ability to classify ALL patients according to their TPMT genotype, which allows optimized dosing. Doses in patients with alleles rendering them deficient in TPMT (who are thus less tolerant of thiopurine medications) are reduced by as much as 95%. This means TPMT-deficient patients can tolerate the drug, yet enough is still metabolized to retain efficacy.

The breast cancer drug trastuzumab (trade name Herceptin), which is marketed in tandem with a diagnostic test, is often cited as an early indicator of the value of the concept. Trastuzumab is effective only in the 25-30% of breast cancer patients whose tumors over express the human epidermal growth factor receptor (HER2) protein. The drug was developed specifically to exploit that characteristic; it binds to HER2, which slows tumor growth. The diagnostic test measures HER2 expression in the tumor and is thus predictive of the potential efficacy of the drug; patients who do not over express HER2 are not given the drug, because it will not work.

Today, it is very difficult to predict which breast cancer patients may experience a distant recurrence of their disease. Genomic Health Inc. has developed Onco*type* DX to address this need. Onco*type* DX provides physicians and patients with a quantitative assessment of the individual likelihood of disease recurrence based on the expression of 21 genes in the tumor.

According to early release results recently, an oral mouthwash consisting of a genetically engineered virus that causes the common cold may help delay the development of oral cancer in high-risk patients, Rudin et al (11).

Furthermore, according to results presented in another study, Stupp et al (12), the chemotherapy combination consisting of Doxil® (doxorubicin HCL liposomal injection) and Temodar® (temozolomide) appears active in the treatment of glioblastoma.

Some currently available DNA-based Gene Tests that examine the individual's predisposition for specific tumor genesis are presented below:

- For Colon Cancer: Hereditary nonpolyposis colon cancer* (CA; early-onset tumors of

colon and sometimes other organs).

- For Luekemia: Fanconi anemia, group C (FA; anemia, leukemia)
- For Brain Cancer: Neurofibromatosis type 1 (NF1; multiple benign nervous system tumors that can be disfiguring; cancers)
- For Breast & Ovarian Cancer: Hereditary Breast Ovarian Cancer Syndrome, (BRCA1 / BRCA2), Peutz-Jeghers Syndrome, Ataxia Telangiectasia (A-T)

Researchers are also examining non-viral vectors such as nanoparticles that can deliver therapeutic genes. Scientists are also considering introducing an extra chromosome into cells. Alongside existing DNA, this additional chromosome could contain therapeutic genes. Introduced into the body as a large vector, it should not be targeted by the immune system.

CONCLUSIONS

Complex and life threading diseases, like cancer, forced today's medical practices to search for alternative ways promising more effective diagnosis, prognosis and treatment decision making. Genomics-proteomics and their valuable application through bioinformatics opened this path. Many believe that this new field of science will substitute the traditional clinical methods, and others that it will only enrich them. However, both schools emphasize the importance of applying genomics-proteomics principles in modern clinical medicine and prepare the way towards personalized healthcare.

Currently, a great percentage of clinical assays on gene therapy are used for cancer dealing topics and their efficiency is continuously assessed. All these efforts are pointed to one main goal. Make knowledge work, wherever this knowledge comes from.

In conclusion, we would like to emphasize some important points on the use of genomics-proteomics, which are becoming evident from this study. i) Bioinformatics cannot or should not replace medical informatics, but rather complement and support each other. ii) The design of a study must be carefully conducted and clearly directed towards a specific goal. iii) The collaboration and integration of clinical, medical, biology and technology experts is of utmost importance.

REFERENCES

1. Lu, J., Getz, G., Miska, E. A., Alvarez-Saavedra, E., Lamb, J., Peck, D., Sweet-Cordero, A., Ebert, B. L., Mak, R. H., Ferrando, A. A., Downing, J. R., Jacks, T., Horvitz, H. R., and Golub, T. R., 2005, Nature, 435, 834-838.

2. Pavlidis, N., Briasoulis, E., Hainsworth, J., and Greco, F. A., 2003, European Journal of Cancer, 39, 1990–2005.

3. Castro, M. G., Cowen, R., Williamson, I. K., David, A., Jimenez-Dalmaroni, M. J., Yuan, X., Bigliari, A., Williams, J. C., Hu, J., and Lowenstein, P. R., 2003, Pharmacology & Therapeutics, 98, 71-108.

4. Nutt, C. L., Mani, D. R., Betensky, R. A., Tamayo, P., Cairncross, J. G., Ladd, C., Pohl, U., Hartmann, C., McLaughlin, M. E., Batchelor, T. T., Black, P. M., von Deimling, A., Pomeroy, S. L., Golub, T. R., and Louis, D. N., 2003, Cancer Research, 63, 1602-1607.

5. Levine, A. J., Momand, J., and Finlay, C. A., 1991, Nature, 351, 453-456.

6. Collins, V. P., 1999, Seminars in Cancer Biology, 9, 267-276.

7. Smith, J. S., Tachibana, I., Passe, S. M., Huntley, B. K., Borell, T. J., Iturria, N., O'Fallon, J. R., Schaefer, P. L., Scheithauer, B. W., James, C. D., Buckner, J. C., and Jenkins, R. B., 2001, Journal of the National Cancer Institute, 93, 1246-1256.

8. Golub, T. R., Slonim, D. K., Tamayo, P., Huard, C., Gaasenbeek, M., Mesirov, J. P., Coller, H., Loh, M. L., Downing, J. R., Caligiuri, M. A., Bloomfield, C. D., and Lander, E. S., 1999, Science, 286, 531–537.

9. Ford, D., Easton, D. F., Bishop, D. T., Narod, S. A., and Goldgar, D. E., 1994, Lancet, 343, 692-695.

10. Van't Veer, L. J., Hongyue, D., Van de Vijver, M. J., He, Y. D., Hart, A. A., Mao, M., Peterse H. L., Van der Kooy K., Marton, M. J., Witteveen T. A. Schreiber, G. J., Kerkhoven R. M., Roberts C., Linsley, P. S., Bernards R., and Stephen F. H., 2002, Nature, 415, 530-536.

11. Rudin, C. M., Cohen, E. E. W., Papadimitrakopoulou, V. A., Silverman, J. S., Recant, W., El-Naggar, A. K., Stenson, K., Lippman, S. M., Hong, K. W., and Vokes, E. E., 2003, Journal of Clinical Oncology, 21, 4546-4552.

12. Stupp, R., Dietrich, P. Y., Kraljevic, O. S., Pica, A., Maillard, I., Maeder, P., Meuli, R., Janzer, R., Pizzolato, G., Miralbell, R., Porchet, F., Regli, L., de Tribolet, N., Mirimanoff, O. R., and Leyvraz, S., 2002, Journal of Clinical Oncology, 20, 1375-1382.