REVIEW ARTICLE

From human proteome to cross-functional personalized medicine

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Abstract

Personalized medicine has led the technological revolution in proteomics into a new phase where appreciation of the values and virtues of the human being are paramount. Thus we must not forget that the two main reasons for personalized medicine are both acknowledgment of the person's dignity and a tailored diagnosis and treatment of each patient, taking into account not only genes and proteins but also the person's social background and environment.

Key words: personalized medicine, human proteome and values, human dignity.

Introduction

Technoscience or "big science", which includes genomics, proteomics, nanotechnology and others, has represented a significant scientific advance during the 20th century aided by technology. Research requires large economic resources and access to complex equipment.[1,2] Technoscience offers real and potential benefits such as solving the global food crisis, advances in biomedicine, biotechnology, telecommunications as well as being responsible of the current technological environment we currently live in.

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Technoscience is the core of medicine in the 21st century and has become a daily practice. Biomedical technoscience includes names suffixed by "-omics," which group terms that describe the new areas within biological sciences. They refer to the study of macromolecules such as DNA and proteins. **Genomics,** the science of the genome, has as its purpose to analyze the genome of living things and identify their genes, function and products (the proteins). **Proteomics,** the science of proteomes, studies the proteins from an organism. **Phenomics** is the name given to the science that attempts to integrate the information provided by all these areas of study into a holistic picture of the complete organism–its phenotype (Figure 1).

These state-of-the-art areas have a direct impact on our conception and understanding of diseases. They change paradigms, focuses and methodologies from different areas of knowledge and affect scientific reflection.

Once the human genome was deciphered, medical research has focused on the analysis

of the human proteome and epigenetics, which includes the expression, structure, folding, interaction and function of proteins as well as the influence of the social background and environment that may in turn produce diseases (Figure 1).

Of human diseases, 95% result from social and environmental changes and not from genetic alterations. Therefore, genomics is surpassed and a new state-of-the-art area known as personalized medicine (PM) has evolved, including the human proteome project, far more complex because it is specific for each person and depends on social and environmental factors.[3,4]

The proteins are action macromolecules essential to develop and understand PM; with 20 different amino acids in their primary structure they can acquire variable three-dimensional structures. There are >100,000 different proteins that carry out diverse biological functions, such as enzymes, receptors, hormones, antibodies and others.

The structure-function relationship is one of the key subjects of study in protein research. There are two obstacles in protein science: a) folding and refolding of natural proteins and b) the need to find new biocatalysts unavailable in nature or the improvement of natural proteins.

The current challenge is to learn lessons from nature and be able to imitate and recreate the natural phenomena in laboratory, understand them, control them and, potentially, perfect them or re-design them. A polypeptide just synthesized depends on its amino acids sequence and the cellular microenvironment (containing other proteins, lipids, salts, etc.) to transform into a well-folded and active protein.

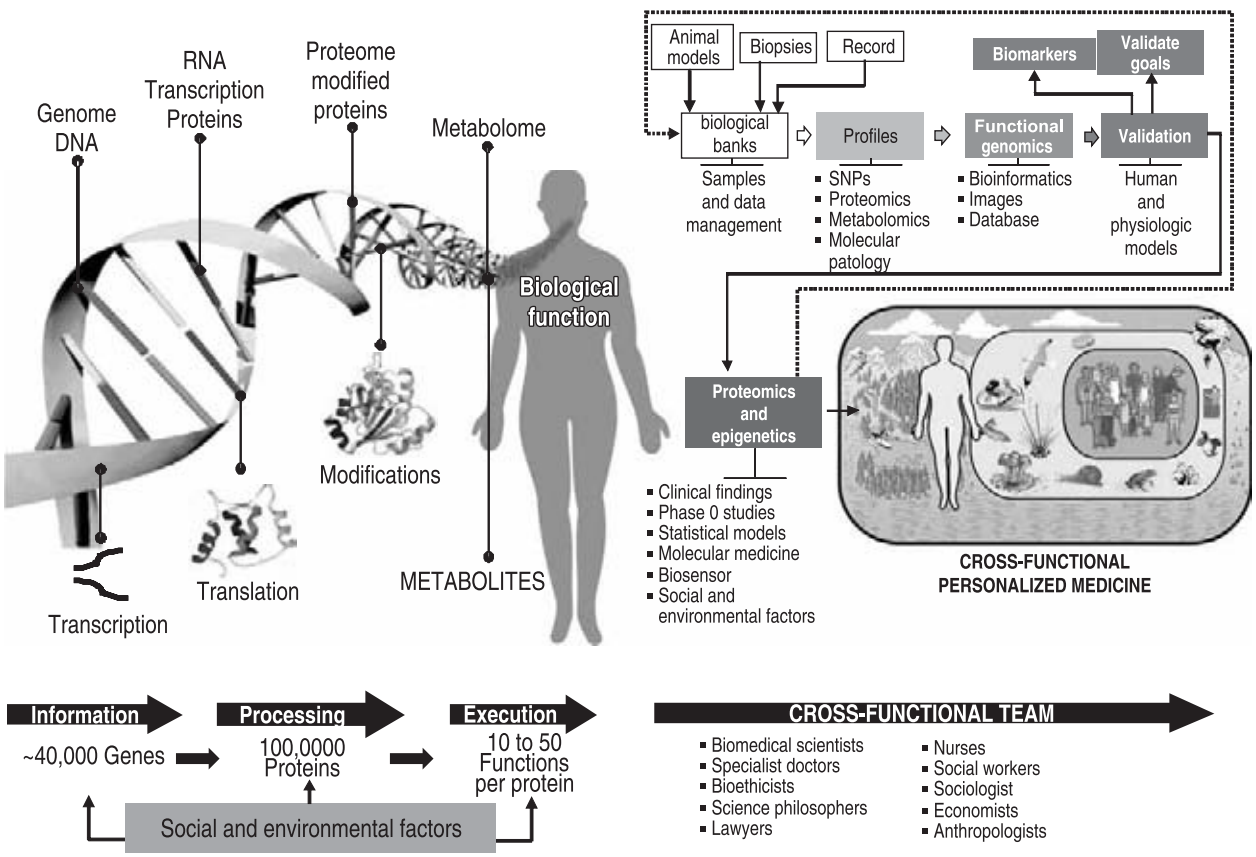

Figure 1. Personalized cross-functional medicine.

Proteomic techniques have a high performance; they analyze in quantitative and systematic ways large-scale biological samples of proteins and associated peptides from different pathophysiological conditions. They represent an essential tool to understand the relative abundance of proteins in complex biological samples. It is an ideal path to find biomarkers and new therapeutic targets (Figure 1).

New technologies allow rapid advances to identify proteins functions. For instance, powerful analytic techniques such as mass spectrometry, which identifies and classifies the molecules based on their mass have been used to identify small protein networks that work together to carry out a specific function. Through specialized genetic analysis using yeasts, protein associations are being identified and this may produce important advances to understand their function. Also, computational algorithms are used to analyze protein sequences, trying to identify proteins that have been developed together and therefore are involved in the same cellular process (Figure 1).

Misfolding and agglutination of misfolded proteins that escape from strict cellular control are study areas of proteomics. Protein agglutination has been associated as a common factor for a number of diseases[5,6] known as conformational diseases (CD) whose pathophysiological bases are protein alterations in size, form, folding or conformation[7,8] such as neurodegenerative diseases (Parkinson's disease,[9] Alzheimer's disease[10]), chronic diseases (diabetes mellitus,[11,12] hemodialysis-associated amyloidosis,[13] and prostatic amyloidosis[2]). These diseases are highly disabling and represent a great social and economic burden.[14]

The agglutination and aggregation of misfolded proteins is highly toxic for living cells.[15-18] Why do naturally soluble proteins unfold? What is the mechanism misfolded oligomers follow that initiates cellular dysfunction? Which are the intracellular conditions that affect natural proteins and induce their agglutination? The answers for these questions will revolutionize 21st century medicine. Proteomic studies include not only identification and quantification of proteins but determine their localization, modification, interaction, activities and, most importantly, their function.

Biomedical technoscience changes diseases' paradigms. We are able to generate biomolecular signatures and identify phenotypes. These individual genetic-proteomic profiles that condition the health/disease balance and their relationship with epigenetic and clinical data lead to PM (Figure 1).[19]

We are able to determine predisposition to a disease, generate opportune diagnoses, and offer short-, medium- and long-term prognoses. We have developed noninvasive methods to detect diseases and monitor therapeutic response. Therapeutic responses can be predicted and we are able to design an *ad hoc* treatment for each patient.

Characteristics of PM multiply their power as well as the involved techniques (nanotechnology, *in vitro* accelerated evolution, etc.), multiply their resources (biorobots, nanoarrays, etc.), their products (biosignatures, bioprofiles, vaccines, drugs, biological weapons, etc.), and control life (life-cycle control, aging control, disease control and personal improvement, etc).

We are in the golden age, which implies enthusiasm and concern. Knowledge bears power and in medicine this represents the difference between life and death. Here biotechnology and bioethics converge to know "what is" and "who the human being is."

We need to reach a personalized cross-functional medicine, which represents the acknowledgment of a patient as a person who can be loved (Figure 1). The term "cross-functional" is plentiful in large global economic groups, through cross-functional workgroups or cross-functional strategies.

Cross-functional workgroups are teams that work in a common project and have seemingly

distant academic and professional backgrounds (biomedical scientists, humanists, specialist physicians, scientific philosophers, anthropologists, lawyers, social workers, psychologists, nurses, economists, and others).

The objectives of cross-functional models are as follows:

1. Knowledge harmonization (strengthening of evidence-based medicine and value-based medicine)
2. Holistic and panoramic vision of research projects
3. Medical, scientific and technological personalization (humanization)

The challenge is to comply with these objectives and this requires that specialist physicians and biomedical scientists acquire a solid scientific and humanistic formation (strengthen evidence-based medicine and value-based medicine) to understand with vision and perspective the person, life, suffering, disease and death. They should look for their own moral improvement.

Healthcare professionals (physicians, nurses, biomedical scientists, psychologists, social workers, etc.) face ethical dilemmas continuously and discover self-realization through *discernment with conscience and choice freedom*.

This implies that healthcare professionals should:

KNOW who the human being is and the formal principles in ethical decision-making

DESCRIBE clear and simple ways to facilitate putting into practice the respect for personal dignity and formal principles in daily clinical practice and in biomedical research

RECOGNIZE ethical dilemmas in medical care and biomedical research

DESIGN strategies to express the maximum potential of human development

IMPLEMENT mechanisms for analysis, reference, discussion and discernment of ethical dilemmas in daily clinical practice as well as in research and in teaching

CONSOLIDATE discussion groups among researchers from humanistic and bioscience areas

Cross-functional PM calls for acknowledgment of the human being, but who is the human being? Boecio's metaphysical definition has been used as the base for person's analysis and definition: *Persona est rationalis naturae individua substantia* (the person is the individual substance of rational nature).[20]

Boecio uses two etymologies for the term *person*. The Greek etymology where *person* derives from *prosopon*, "*face or mask*" and the Latin etymology, which is derived from the verb *prosono*, "sound with force or to resonate". The term "person" expresses dignity or perfection and is the origin of all personal characteristics.

A role or a mission is always played in theatre and real-world representations. Person is a mask, the mask is what the actor places before him and through which he speaks, allowing his voice to sound through it. This guarantees a true unit and shows the audience a unique and unmistakable face, a semblance we should represent and adopt.

A person experiences himself as a finite unit, singular, alone, unchangeable, immediate and a being; on the other hand, the person realizes its indissoluble absoluteness and unconditionality.

According to Forment, these are a person's characteristics:

1) Maximum perfection: person refers to the maximum level of perfection, dignity, nobility and improvement, highly above its own nature.

The highest and most basic perfection is its individual being. St. Thomas [Aquinas] synthesizes: "Person is the most perfect thing in the whole nature".[21] "It is the most noble thing of all nature"[22] and, therefore, the most clearly existent, the most real thing, the most individual thing, the most different thing, the truest thing, the best thing and the most beautiful thing.

2) Identical and unalterable dignity: the own being explains a person's dignity, having its permanency, present time and identical grade character. During a human life, person's attributes change themselves or in different aspects. Even at certain times they are potential and not always present as during intra-uterine life. The above-mentioned does not occur with personal constituent. From conception to death, the human being is always a person and to the same degree. There are no "categories" of human beings related with person.

3) Person's universality: personal reality is found in all humans. Humans are always acting persons under any circumstances, independent of their qualities, relationships or accidental determination and other conditions such as biological, psychological, cultural and social, etc.

4) Personal equality: every human is a person to the same degree as everyone else. As for persons, all human beings are equal, even with the greatest differences in their individual nature. Therefore, they hold identical and inviolable human/natural rights. As human beings, we are different in our perfection level. As persons we are absolutely the same in perfection and dignity.

5) Maximum individuality: contrary to all other individual entities, the human person is a unique individual, not capable of being replicated or replaceable.

Cross-functional PM appropriates a person's dignity, to perfect us as human beings. This implies the rebirth of virtues or maxim ethics where the principles of bioethics are surpassed. While technology becomes more powerful, healthcare personnel must become more virtuous to avoid treating the patient as an object and resolve the ambivalence created by the power of knowledge.

Cross-functional PM imposes a context: the need to specialize and cross-functionality, provide patient care through a team, involvement of several specialist teams in the same process, the need to involve non-healthcare personnel for integral care of the patient and inter-institutional care. All of these imply a high level of complexity in healthcare relationships. Financing models for healthcare require the intervention of professional players who are far from the clinical context.

We consider, as Pellegrino and Thomasma,[23,24] that only preserving the ideal of medicine as a profession dedicated to improve a patient's life, to this singular **person** at the clinic, our interests can be sufficiently safeguarded when we are ill.

Cross-functional team member characteristics

Loyalty: To patient's integral care service.

Benevolence: "To want patient's well-being". All acts should be aimed at patient's well-being.

Abnegation: To assume required sacrifices to guarantee patient's well-being. Personal interests such as wealth, prestige and power are subordinated to the ultimate purpose of medicine, which is patient well-being.

Compassion: "Suffer with, suffer together". Compassion is the care that bears empathy and consideration for the patient.

Humility: To recognize knowledge has limits and admit ignorance when necessary.

Justice. Egalitarian justice requires that all persons bear their rights, receive what is owed to them (therapy alliance) and that equal cases receive the same treatment. The professional should adjust to

the specific needs of the patient, even when those needs exceed what is "owed" in the strict sense.

Prudence: The right reason used in deliberating and acting is a virtue of discernment and moral liberation. This plays a central role in medical ethics. This does not produce infallible professionals but predisposes us to choose in a reasonable and thoughtful way, looking for the most effective resources to treat our patients because the ultimate goal of medicine is the integral care of every patient.

Cross-sectional PM allows the physician to access powerful technology, enabling him to discover the world, not only in its reality but in its potentiality and in its inexhaustible possibilities. This bears the creation of new ethical dilemmas because knowledge is no longer an end in itself and becomes a tool that can affect the lives of persons bearing ethical challenges during professional activities.[25-28]

We need to define the role of high-technology medicine in connection with persons. Technique viewed as practice configures the person's instrumental relationship with the world and represents the continuation and empowerment of human beings. High-technology medicine generates new action possibilities and new personal development possibilities. Biomedical technoscience demands to be supplemented and to refer to a global anthropology where its function is defined together with other human dimensions.

It has been proven that there is interdependence between technological progress and human sociocultural changes.[29,30] An essential question is still open and its answer will define the future of our species. What combination of human values will be required to guarantee the survival of human kind during this millennium?[31,32]

High-technology medicine produces deep discussions among scientists, technologists, philosophers, economists, politicians and society in general because it increasingly influences our life: our bodies, our person, our family, our environment and the perception of right and wrong.[33,34]

During the last decades, a growing interest has been developed on a systematic reflection about our species interventions over living things, a reflection that holds a specific purpose that is difficult to reach: to identify values and norms that guide our acts, science and technological intervention over life and biosphere.[35]

The highly specialized characteristic of medicine, science and technology in the 20th century (with its neutral vision) has generated important debates around the questions: is science free of moral and non-moral values or is science neutral?[36]

Are there ethical commitments within scientific research or should research remain neutral on right and wrong? Do ethical problems arise only when scientific knowledge is applied?[37] These are open questions and their answers have fundamental implications in our conception of science, scientific knowledge and their value. We think frequently about science and technology as *pure and isolated knowledge* that does not obey interests, values and human passions. We forget persons act intentionally and they perceive, believe, think, imagine, wait, want, love, etc. Therefore, we should consider their idiosyncrasies and weaknesses, including their assets that impact and have direct influence over their scientific work and reports, findings, creations, hypotheses, their location and their relationship with the scientific community (epistemic community), their role as a cooperative or antagonistic epistemic subject.[38]

The relationship between cross-functional PM and values is a central vector from scientific and technological progress in 21st century medicine. Science is defined by its cognitive goals that imply ethical and human values[39] such as *philia* or affection for knowledge, *thauma* or state of astonishment and wonder, *aletheia*, which is the truth and the alertness when looking for knowledge. The main goal of scientists is *to know to be*. Science's neutrality has been surpassed and we

know biomedical technology axiology depends on a complex value system:[1]

1. Epistemic values (based on scientific knowledge) such as verisimilitude, empiric adaptation, precision, rigor, coherence, duplicable observations, measurements and experiments.
2. Typical values from technique and technology include innovation, functionality, efficiency, effectiveness, usefulness, applicability, reliability, simplicity, speed, flexibility, robustness, durability, versatility, ease of integration with other technologies, etc.
3. Economic values such as knowledge appropriation, resource optimization, good management of scientific enterprises, benefits, profitability, etc.
4. Ecological values (the risks of technoscientific innovations) such as health, biodiversity, sustained development, etc.
5. Human, political and social values (based on the incidence of new technologies over daily life and society) such as intimacy, privacy, autonomy, stability, security, publicity, multiculturalism, etc.
6. Fundamental ethical values such as life, human dignity, conscience freedom, respect for beliefs, tolerance, respect for animals, minimization of suffering during experimentation, the right to dissidence and difference, honesty, etc.

Biomedical technoscience is an activity that describes, understands and explains the world but also transforms it; therefore, it requires value integration. The best can rise only after a critical and holistic reflection, generating the right actions and creating well-being. We should discuss the moral and social responsibility of scientists and technologists in cross-functional PM.

The evaluation of technologies is a recent research area with two axiological dimensions: internal axiological dimension and external axiological dimension. According to Olive,[40] the internal axiological dimension is defined "by the group of values and purposes as well as criteria to judge valuable results from technique application." This is an internal evaluation specific to each technique. External axiological dimension is the external evaluation of results and their applications. It is centered in the achievement of desirable goals from the perspective of the evaluating community through a discussion of needs, necessities and purposes of affected human beings. This is the case of health technologies evaluation (HTE), defined as the evaluation of safety, effectiveness and efficiency of medications, work teams and procedures used in healthcare services for diagnosis, treatment and rehabilitation of patients.[41] This is a cross-functional area where several disciplines converge such as economics, social sciences and medicine.

The challenge during the new millennium is to harmonize knowledge and humanize science in general and in medicine in particular through the creation of cross-functional team works of humanist and natural science specialists to create the science/technology culture demanded by our current society. The high-specialization characteristic of 20th century science that generated important scientific and technological advances has highlighted the urgent need to create humanist and natural science specialists work teams that together will create new laws that will rule over biotechnology and biomedicine. These new rules will demand that science, philosophy and ethics understand the civilization direction and guarantee its transit; in summary, a contemporary and humanist moral philosophy that serves as an ontological substrate and new postgraduate programs that train new generations of biomedical and medical scientists. This will be a new generation of physicians with a

panoramic view beyond short-term goals and superficial clarity whose investigations and interests are in equilibrium between opening new paths and consolidating knowledge, remaining at the edge of knowledge where scientific and technological achievements are accompanied by philosophical and ethical values, a characteristic and essential manifestation of the human person.[42]

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