THE MANIFESTO OF THE NEW PARADIGM IN MEDICINE

PIER MARIO BIAVA and ERVIN LASZLO

Abstract:

This article summarizes the scientific knowledge in the fields of quantum physics and of medical science about the origin and the nature of universe and of life. The recent discoveries in the field of biopsychic, genetic, epigenetic, neuroscience and psychosomatic describe universe and life as highly coherent systems where in-formation is a key factor and has a fundamental role in their origin. In this vision living systems are cognitive networks in a dynamic relationship with everything around them. Health in this context has to be considered a dynamic balance in a subject in which the information moves on in a correct way. On the contrary diseases have to be identified as pathologies of information, which can be classified in a new way, considering two different codes -semiotic and symbolic- of meaning.

Key words: Code, coherence, complexity, information, living system, meaning, sign, symbol

The application of the analytical method and the adoption of a research methodology centered on the progressive specialization of knowledge, produced in the context of scientific research, the acquisition of a significant amount of new knowledge, more refined and deeper than the past. It is however also highlighted a limit that has to be overcome to allow further progress of scientific knowledge. Medicine, psychiatry, psychology, biology, psychosomatic, neuroscience, genetics, if they were to remain too rooted into a logical-deductive and deterministic system based on the analysis of the object of study, they would no longer be able to respond to the fundamental question which moves science and humankind: what is life ? This happens because, as shown by the recent discoveries in the field of biology, epigenetics, psychosomatic and physics, the theoretical criteria and the methodology of research have to evolve to access an integrated, trans-disciplinary vision of what we call life. In the recent decades science overcame the strongly positivistic approach. The new recent discoveries demonstrated that life can be understood only in a complex and systemic vision, which recognizes that all parts of living systems are in relationship to each other to build what is called the network of life.

It is crucial in this regard to establish some key concepts that modern physics and the theory of complexity offer us to redefine the new paradigm

a) The properties of a system are not intrinsic properties of its component parts, but can only be understood in the context of the whole to which the system belongs.

b) According to the complexity paradigm, the properties of a system are destroyed when the system is analyzed in isolated parts.

c) In the study of atoms and subatomic particles - the building blocks of nature - quantum physics showed that these are linked in a complex network of relationships which constitute a unified whole.

d)These relationships, in the mathematical formalism of quantum physics, are expressed in terms of probability and the probabilities are determined by the dynamics of the whole system.

The study of the probability of connection does not allow the researchers to isolate an object of the network, because the same act of describing an infinitely small entity by an observer changes the reality of the observed phenomenon (Heisenberg's uncertainty principle).

The conclusion emerging from this reflection is that the researcher who is studying nature actually observes only the exposed part of his investigation method.

e) Gödel's theorem also hopelessly postulates the impossibility of building a formal system that is both complete and capable of describing all phenomena.

f) The development of quantum mechanics with the concept of entanglement has stressed the notion that a single synchronic mechanism seems to combine the microscopic world of particles, the macroscopic world of the universe with psychic individual and collective phenomena.

So a science of the human being wanting to put itself in its proper role, in particular medicine and psychology which deal with health and illness, has to consider these changes in general science.

The great technical progress of medical science, in particular centered on extremely sensitive diagnostic tools and accurate pharmacological and surgical interventions has necessarily to be complemented by a similar progress of means aimed at preserving and improving the health and physical and mental condition of human beings.

Asclepius, the ancient god of medicine, had two daughters: Panacea, who knew the remedies for diseases, and Hygeia, who knew the secrets to preserve health.

Modern medical science can not be limited to Panacea, but has to give space to what is Hygeia.

This type of deeply humanized medicine has to be put in relationship not only to the biological sciences, but also to psychology, psycosomatic and environmental sciences.

It appears therefore a conception of medicine characterized by a great level of complexity, in which the specialists are not just experts of medical, surgical and psychological "techniques", but also individuals who know all the complex aspects of human beings.

THE NEW VISION OF LIFE

You cannot solve a problem with the same kind of thinking that gave rise to it.

(A. Einstein)

In the light of new discoveries in the fields of physics, biology, epigenetic, neuroscience, psychology and psychosomatic, it is necessary for science, which so far has provided a fragmented picture of the world, bound by disciplinary aspects apparently unrelated, to look for a new paradigm. This paradigm has to unify the various disciplines, starting from what connects the physical universe to the living world, the living world to the social world, the social world to culture.

As for the Universe, recent discoveries bring out a non-local type of coherence, so in the field of quantum medicine it was discovered that the atoms and molecules within an organisms, as well as whole organisms and their environments, are linked together as the microparticles that originate in the same quantum state.

The living organism is therefore extraordinarily consistent: all its parts are connected with all others in a multidimensional, dynamic and instantaneous way. What happens in a cell or in an organ also happens in some way in all the cells and organs: a connection that recalls the kind of entanglement that characterizes the behavior of quanta in the microscopic kingdom.

The organism is also consistent with the world around it: what happens outside the body is connected in a consistent manner to the inside of the body. With this consistency our body is able to evolve in tune with its environment. Living organisms in fact communicate with the external environment and are consistent with their own internal environment through what 'was defined as "signification of the messages": this definition should be understood not metaphorically, but as a literal term.

This has been demonstrated by recent studies and researches carried out on cultures of tumor cells in vitro (P.M. Biava), conducted to test the hypothesis to see whether during organogenesis there could exist regulatory substances able to correct the alterations caused by carcinogens in stem cells, transforming them in cancer stem cells, which constitute, as widely demonstrated, the cells that are at the origin of the malignancy of tumors.

These researches led to identify specific stem cell differentiation factors that can slow or stop the growth of various tumors in vitro. This happens because stem cell factors of differentiation represent what is called "epigenetic code", a code that is able to regulate gene expression. Like an Orchestra Director, the epigenetic code determines the timing and the ways in which genes should be regulated, activated or repressed and silenced. So the demonstrated ability to regulate the expression of several genes in cancer cells has led Biava to sustain the hypothesis that the communication in biology involves the signification of messages. The possibility that the genetic and epigenetic codes function as codes of meaning, as was said, is not metaphorical, but real. In fact, it is well known that cell differentiation, which brings the totipotent stem cell to differentiate into different cell types (cells of kidney, lung, liver, brain, etc..), consists of a complex series of events.

During these events the epigenetic code determines, as said, the activation or repression of specific genes, so that at the end of the differentiation process every cell has the same genetic code. In this code, however, according to the different types of cells that constitute the various organs and systems, the activated or deactivated genes, are specifically different in the different cells types. Therefore the difference between the various types of cells is not genetic but epigenetic. The two codes, the genetic and epigenetic ones, after cell differentiation process, remain in any case tuned and use the same system to decode the messages: in this way the different types of cells, which constitute the various organs and systems of the body "speak" to each other using the same codes of "meaning". To say that a cell has the ability to understand the meaning of a message is the same as saying that molecules and all the factors of the microenvironment surrounding it carry

information and that cells process this information, decode, integrate and understand it not only in its form, but also in terms of message content. These messages therefore elicit responses that pass on information to all the other nearby or far away cells on the content of the processing and on any other messages that might need to be transmitted

This happens only when a cell is contextualized in a body and not when it isn't part of a context of an organism. Only the emerging of the identity of an organism, or a new-complex adaptive system makes it possible that all subsystems are functioning as a specific cognitive network . This occurs in all animal species, even in the most simple, or even in unicellular organisms, where it forms a new identity, a unit that functions as an organism.

So an organism is much more than the sum of its parts and we could define it as an organization, a network system. The context, therefore, assumes a great importance: it ensures that the various chemical or physical-chemical reactions occurring are not the expression of simple mechanical events and of a blind determinism, but of a subtle tuning with the environment.

The context addresses the information, thus allowing a single molecule to give place to different behaviors in different contexts. The information carried by molecules, however, is only a part of the information that arrives to the cells. Information coming from electromagnetic and sound waves in fact must be added.

At this regard, research carried out in this direction (Ventura C.) shows that electromagnetic waves of low frequency (50 Hz) and low intensity (0.6 milli Tesla) are capable of differentiating embryonic stem cells to cells of specific tissues. Furthermore, the cells, in different stages of differentiation, when placed in contact with biomaterials, perform a series of movements which are useful to them in order to decode in an intelligent way the form of that material and give rise to tissues which have the desired conformations. It was also possible to record sound waves emitted from yeast cells placed at different temperatures and at the moment of their degeneration and death.

Important information are also carried by the molecules of super coherent water , as many researches demonstrated (E. Del Giudice). Starting from this biological basis, it is necessary to recognize the presence at the origin of life of a element that is neither matter nor energy: this unifying element is information, which governs the evolution of each element of the Universe.

Information has different degrees of complexity and different levels of expression in the living world ranging from information to in-formation. Information means (in the standard theory of communication) the received message on some facts or events through a channel from a source: this information is what we perceive in the form of sign. It is characterized as local in the natural sciences and as individual in the research on consciousness.

On the other hand in-formation is defined as "that which gives form," a subtle connection, common to all living and non-living systems. This connection is characterized in the natural sciences as non-located and in consciousness research as transpersonal.

At the basis of the notion of information and in-formation the concept of coherence is fundamental. These premises lead to a redefinition of the human being on the following assumptions:

1) Life is not organized on principles such as linearity, causality and mechanism, but on principles such as complexity, information, coherence and analogy.

2) Life is complex and irreducible and cannot be adjusted through a breakdown of data (analysis) but through the awareness of the importance of information in life itself (meaning and synthesis).

3) The Universe is a highly coherent system where the in-formation is a key factor.

4) Organisms are cognitive networks in which information is at the origin and at the basis of life.

5) Any form of the living system is in a dynamic relationship with everything around it and, in a broad sense, with the universe.

In this context it is important to consider the crucial role of consciousness in the knowledge of the world in relationship with information and in-formation.

First of all, we have to remember that consciousness is not only a human phenomenon, but according to the point of view of the in-formed universe, consciousness is actually present in all the Universe, but not everywhere in the same way and at the same level of development. Consciousness evolves simultaneously with matter, of which we find the most complex form in the human being. At the biological level, cognition has been recognized (Maturana and Varela, aa) as common to all living systems. Cognition represents in fact the biological basis of the process of life, of which information represents, in addition to the matter and the energy, the objective basis to signify the messages. The living systems have different levels of knowledge of the world. In addition to knowledge, it has been identified in the living systems a primary consciousness arising when the cognitive processes are joined by a perceptive and emotional experience. This consciousness is probably present in mammals, birds and other vertebrates. Besides this primary consciousness there is another consciousness, defined secondary or self-consciousness, which includes the ability to use symbolic images, through which we can build the system of values and beliefs. In the cognition- self-consciousness continuum, if cognition expresses itself using an information code of signs, self-consciousness expresses itself using both a code of signs and of symbols. These concepts make us conceive a new model of the human being based on information and awareness, interpreting the individual as a complex information system beyond the interpretation offered by Psychoneuroendocrineimmunology (PNEI). The required complex-system thinking must recover the multidimensionality of the subject-object-environment relationship as the self-organization of information in interaction with the unconscious. The PNEI model is no longer sufficient to interpret the complexity of the living system and should be integrated into a broader model that views the human being as an informed psychosoma-system. After these preliminary observations it becomes extremely important to conceive a new paradigm in medicine which considers psychology and psychosomatic as integrant part of medicine and which could allowed a transdisciplinary dialogue between these sciences on the basis of the concept of information in its double code of meaning (signs and symbols).

Given the foregoing considerations, the diseases which affect the living systems have to be considered as an imbalance of information. To understand the causes and the nature of the different diseases we will continuously consider the two logics with which it is possible to decode the information, ie the sign and the symbolic logics.

The informed psychosoma is a true ecosystem that interacts with larger informational networks such as the world's ecosystem, social, cultural networks and information of all kinds, including artificial networks created by humans, it keeps its balance and its health if it is in tune with all these ecosystems.

The Manifesto of the new paradigm in medicine: the logic of life.

The "new medicine" hereby emerging, involves a deep transformation of the relationships between human beings and nature. This has inevitable consequences on medical studies and on the treatments of the different diseases with important changes in medicine towards an holistic vision.

1) In-formation is the connecting element between humans and nature and it represents the basis of life. In-formation is in fact "that which gives form," to life and to all the things of the universe, a subtle connection, common to all living and non-living systems. On the other hand information has also other different levels of expression, ranging from information to in-formation. Information means, as already said, the received message on some facts or events through a channel from a source: this information is what we perceive in the form of sign.

2) Health represents a dynamic balance in a subject in which the information moves on in a correct way.

3) Diseases have to be considered as an imbalance of information. In other words, diseases have to be identified as pathologies of information, that can be classified according to different types of disruption of information.

4) Disease is an event simultaneously individual and collective. It is individual when it is limited to an individual subject, but, given that all living beings are in a dynamic relationship with each other, the individual disease only reflects the reductive vision with which it is considered. So it would be more correct to define every disease as collective.

5) Diseases are pathologies of information which can affect the two codes- symbolic and semiotic- of meaning: the therapist must consider both, the semiotic as well as the symbolic, levels. When decoded, the languages of the two codes provide the correct information to the psychosoma.

6) The decoded information, in relationship to the two symbolic and semiotic codes of meaning, given back to the informed psychosoma in a precise and consistent manner , can bring the system back into a correct balance.

7) Considering this concept, it becomes necessary to create a new kind of therapist who knows very well the two codes of meaning and who is able to make an intervention which can correct the specific pathologies of information.

8) There is the necessity to create a new dictionary with a new terminology, new definitions of pathology and new classification of the different diseases.

9) It is also necessary to apply new therapies to different patients , which can be defined informational therapies. These therapies are based on the conditions described above, enabling a complex approach to the patient in which the pharmacological and non-pharmacological (biological substances) and complementary medicines may overlap and act harmoniously on the individual, taking into account the whole information network and the inseparability of the body-mind system.

10) informational therapies are therefore therapies that take into account the network of the organism, as an indivisible unity of body-mind in relationship with its environment. These therapies would usually be represented by natural and biological substances that restore the physiological conditions and health in the organism.

11) There is the necessity to create a New University which can prepare new therapists who know well the two codes- semiotic and symbolic- of meaning.

12) The studies and formation of the new therapists must consider the effective transdisciplinary integration in order to cooperate on this basis.

The article here enclosed is fundamental for the comprehension of the Manifesto of the New Paradigm in Medicine

Reprogramming of Normal and Cancer Stem Cells: Stem Cell Differentiation Stage Factors and Their Role in Controlling Tumor Growth, in Preventing Neurodegeneration and in the Treatment of Psoriasis.

Pier Mario Biava

Abstract

The term "cancer cell reprogramming" is used to define any kind of intervention aimed at transforming cancer cells into terminally differentiated cells. This review reports our personal contributions, aimed at reverting cancer cells into a normal phenotype. Our approach is based on the evidence that tumor development is suppressed by the embryonic microenvironment. On the basis of this rationale, experiments have been conducted using stem cell differentiation stage factors (SCDSFs) taken at different stages of development of Zebrafish embryos. SCDSFs induce a significant growth inhibition on different tumor cell lines in vitro, because of activation of cell cycle regulatory molecules, such as p53 and pRb. Treatment with these factors activates apoptosis and differentiation. A product prepared for human treatments, containing SCDF at very low doses, yielded favorable results in intermediate-advanced hepatocellular carcinoma with 20% of regression (2,4% of complete regression), 16% of stable diseases and with a significant improvement of survival and of performance status of the treated patient. A more recent clinical trial on 50 cases of hepatocellular carcinoma in intermediate-advanced stages demonstrated a grater rate (13,1%) of complete regression. In addition these factors used in a model to study the neurodegenerative processes, like the cells of Hippocampus of mice, demonstrated a significant prevention of neurodegenerative events induced by using high doses of NMDA. Finally some clinical trials demonstrated a significant improvement of psoriasis lesions after the treatment with stem cell differentiations stages factors, with reduction of cheratosis, eritema and of itching.

Introduction

Conventional medicine uses drugs to provide the right chemicals or to correct defective reactions. However, recent developments in medicine have provided insights regarding the biological treatments of a lot of diseases, ushering in an era of ground-breaking developments in the history of healing and therapies.

There is a growing awareness of the existence of sophisticated mechanisms that conventional medical science is reluctant to accept. There is evidence, for instance, that tumors are caused by an incomplete differentiation cycle in stem cells. The damaged stem cells produce equally damaged daughter cells, i.e. cells that are less differentiated than those of the organ in which they are located. Cells failing to reach maturity do not integrate with other cells and produce a growing tumor mass with the well-known negative effects. Maximum cell differentiation takes place in the developing embryo where a single egg cell can generate 252 different kinds of tissues. Special substances contained in small amounts in an embryo trigger differentiation by sending signals to the cells, and these complete their cycle by differentiating into the various organs and organ-systems that make up the developing organism. Those cells that do not complete the cycle are repaired, or when this is not possible, they are eliminated through apoptosis.

The most severe alteration of information and break in communication between cells occurs in tumors. Yet even in the case of tumors, it was demonstrated that it is possible to correct errors by providing accurate information to the malfunctioning cells, considered as mutant stem-cells. Conventional medicine uses chemotherapy and other treatments to kill the damaged cells. In the new medicine malignant or dysfunctional cells are reprogrammed rather than killed.

The same substances that induce differentiation in the embryo act on malignant tumor cells, making them differentiate and revert to normal functioning, or undergo programmed cell-death.

EXPERIMENTAL RESEARCHES AND CLINICAL TRIALS

The treatment of oncologic and degenerative diseases

Experiments carried out on various tumor cell lines showed a significative growth reduction of the treated lines due to the administration of Stem Cell Differentiation Stage Factors (SCDSFs) obtained at different stages of stem cell differentiation in the embryo of zebra fish.

Research conducted in order to establish which molecular events were involved in the control and regulation of cancer cell lines demonstrated transcriptional or post-translational regulation of key cell cycle molecules, such as p53 and pRb.

Research on apoptosis and differentiation processes showed that stem cell differentiation stage factors (SCDFs) induce caspase-3 activation, mainly through E2F-1 gene regulation thus hyper expressing c-Myc and activating a p73 dependent apoptotic pathway. Moreover, it was demonstrated a concurrent and significant normalization of the e-cadherin/β-catenin expression, with an e-cadherin rise.

Administration of SCDFs in an open clinical RCT conducted on 179 patients affected by intermediate-advanced hepatocellular carcinoma (hcc) resulted in 19.8% patients with disease regression (whom 2.6% with a complete regressions), 16% patients with stable disease and a significant increase in median overall survival. A subsequent analysis of 50 intermediate-advanced hcc patients showed 13.1% complete regressions.

SCDF showed also to significantly prevent neurodegenerative processes induced by strong doses of N-Methyl-D-Aspartate (NDMA) in rat hippocampus cell line.

Finally, clinical application of topic SCDF on psoriasis patients resulted in almost 80% of reduction or remission of the disease.

Basic data

Current medical literature acknowledges that embryonic micro-environment is able to suppress tumor development during cell differentiating processes (1,2). Administering carcinogenic substances during organogenesis leads in fact to embryonic malformations, but not to offspring tumor growth. Once the organogenesis has ended, administration of carcinogenic substances causes a rise in offspring tumor development (3,4,5). This data indicates we can consider cancer a deviation in normal development, that can be controlled by factors contained in embryonic microenvironment during the cellular differentiating period. Furthermore, it has been demonstrated that teratoma differentiates in normal tissues once implanted in the embryo (6).

Recently, it has been shown that implanting a melanoma in a Zebrafish embryo did not result in a tumor development, while it did in the adult specimen (7). Moreover, the injection of melanoma in Zebrafish extra-embryonic membranes originated Zebrafish's own neuronal cells. This demonstrates that cancer cells can differentiate in normal tissues when implanted in embryos (8).

Here we summarize several experiments conducted over the past 20 years in vitro as well as in vivo and finally clinical studies on cases of hepatocellular carcinoma at intermediate-advanced stage having administered factors extracted during stem cells differentiating processes.

Lastly, we report recent experiments that showed that stem cells differentiating factors (SCDFs) are able to prevent neurodegenerative processes in mouse hippocampus cell line and to significantly ameliorate psoriasis.

Materials and methods of both in vitro and in vivo experiments on different human tumor cell lines and patients selection for hcc clinical trials have already been illustrated.

Materials and methods of trials on psoriasis have already been published.

Materials and methods (hippocampal slices) used in the study on neurodegenerative prevention, which have never been published, were prepared as described in literature (9). In order to test the effects of SCDF, we exposed organotypic hippocampal slices to N-Methyl-D-Aspartato (NMDA) 50 μM and 300 microM in serum free medium and, to the treated group, also SCDF.

For each treatment neuroprotective activity of SCDF has been evaluated. To evaluate the cellular damage a fluorescence associated to propidio ioduro (PI) (5mg/ml) has been performed as already described in literature (10).

Quantitative analysis of cell mortality has been performed in CA1 area of hippocampus, compared to organotypic cells exposed to NMDA. Images have been acquired with an epifluorescence microscopy Zeiss Axiovert 200M (10x objective) and Cool Snap CCD camera. The same exposure periods have been performed for qualitative analysis.

Average fluorescence intensity has been measured after having traced CA1 correspondent area and mortality has been analyzed in terms of fluorescence intensity and area has been expressed in pixels.

Results of in vitro experiments on diverse human tumor lines

Seven different human tumor lines (multiforme gliobastoma, melanoma, hepatocarcinoma, kidney adenocarcinoma, colon, and breast adenocarcinoma, acute lymphoblastic leukemia) have been treated with factors taken from Zebrafish embryos in four different development stages: a) morula stage, characterized by merely multiplicatory events and therefore made of totipotent embryonic stem cells, b) medium-blastula/gastrula (50% epiboly), where the totipotent embryo stem cells differentiate into pluripotent ones, c) five somite stage and d) 20 somite stage, where important differentiation events, characterizing the intermediate and final embryo differentiation, take place. All cell lines have shown a significant slowdown in the growth curve when treated with factors drawn during the above-mentioned cell differentiation stages, with inhibition percentages ranging from 73% of the glioblastoma and 26% of the melanoma. No effects have been registered, except from a weak tumoral growth with factors extracted in the morula stage. This data confirms the intuition that during the differentiating stages networks of factors are present in the embryo and they are able to readdress tumoral cells towards a normal path. Those networks appear in the very first phases of the gastrulation, while they are absent in merely multiplicative stages (11).

Several studies were carried out in order to understand which molecular events were involved in tumor growth inhibition mechanisms. It has been shown that molecules that have a fundamental role in the cellular cycle regulation process, such as p53 and pRb, are involved through transcriptional and post-translational regulation events. More precisely, a p53 transcriptional regulation took place, highlighted by a considerable increase of the p53 protein's concentration in the cells of some of the tumor lines, such as the glioblastoma multiforme and the melanoma. This has been measured through cytofluorimetric as well as immune-histochemical method, after the treatment with cell differentiation factors (12).

The slowdown of tumor growth on other tumor lines, such as kidney adenocarcinoma, is due to a post-translational regulation of the retinoblastoma (pRb) protein, which leads to a change in the relation between such protein's phosphorylated and non- phosphorylated shape (13). It is widely known that the non-phosphorylated shape stops the cellular cycle, preventing the transcription of the E2F-1 gene, which is instead facilitated when the protein is phosphorylated.

Finally, apoptotic events as well as cell differentiation events were studied, in order to understand what are the consequences of the tumor cells regulation cycle ascribed to differentiation factors. The analysis was carried out on colon adenocarcinoma cells, highlighting the activation of an apoptotic pathway dependent on p73, as well as a cell differentiation pathway. Within colon tumor cells culture, a significant apoptosis increase, as well as a considerable increase in the e-caderine concentration (cell differentiation markers) have been highlighted (14). Therefore, the molecular mechanisms at the basis of the tumor growth slowdown, due to the treatment with SCDF can be summarized as follows: stop of the cell cycle in G1-S or G2-M phase, according to the tumor type, genetic damage repair and cell re-differentiation, or tumor cells apoptosis if reparation is not possible because of mutation gravity.

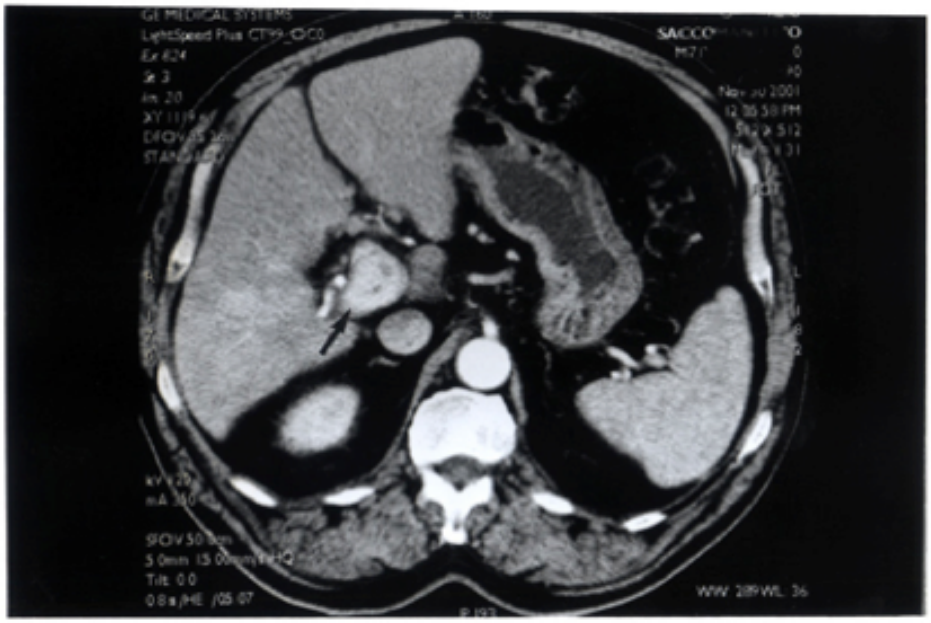
Results from clinical trial on intermediate-advanced hepatocellular carcinoma (hcc)

A randomized controlled trial conducted from January the 1st 2001 to April the 31st 2004 on 179 patients affected by hcc in intermediate advanced stage, for which no further treatment was possible, was performed administering a product fine tuned on the basis of above mentioned studies. The posology was 30 sublingual drops three times a day. The sublingual solution was chosen because the composition of the active fraction is made of low molecular weight proteins and micro-RNAs.

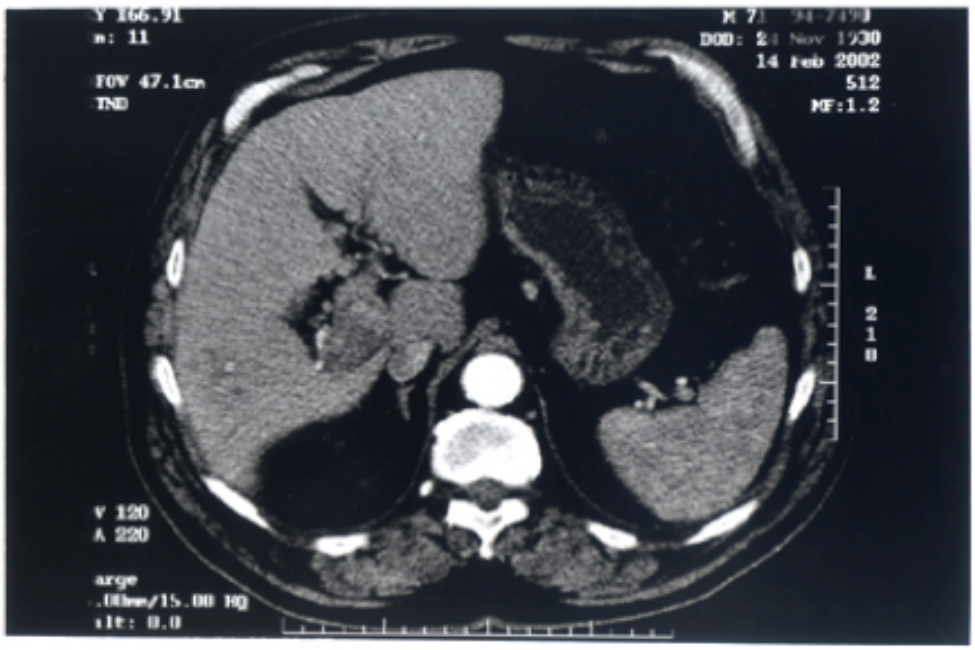
Objective tumor response median overall survival and performance status have been evaluated. Results showed a 19.8% patients who experienced a regression and 16% patients who experienced a stabilization with an overall survival of more than 60% of responsive patients after 40 months, against 10% of non responsive ones.

A wide improvement of performance status has been registered in a great majority of patients (82.6%), also in those who experienced a progression of the disease (15). A new recent study published on current Pharmaceutical Biotechnology on reprogramming normal and cancer stem cells, confirms the role of SCDF in determining complete response in primitive intermediate advanced liver cancer in 13.1% patients (16). Here below CT of some complete responses in hcc patients are reported: images show the liver before and after a 6 months treatment with SCDF. Moreover, images referring to survival curves of responsive patients are reported compared with no response patients.

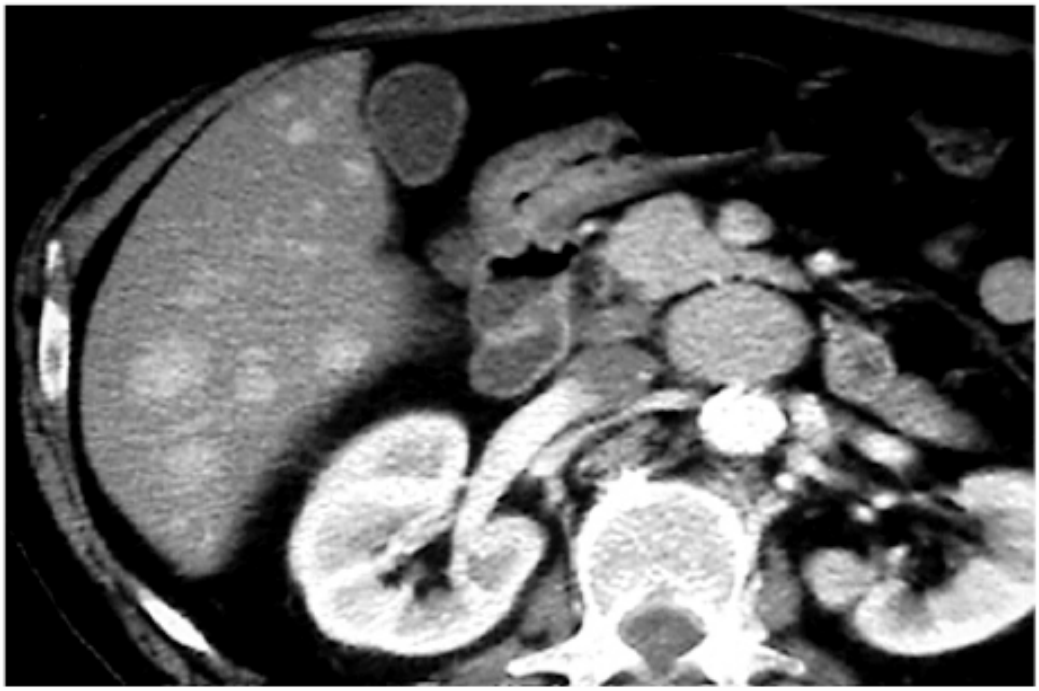
Spiral CT during the arterial phase prior to treatment with stem cell differentiation stage factors (SCDSF) shows an advanced HCC of the right lobe. Neoplastic hypervascularized areas are present in segment 7, and a hypervascularized thrombus (arrow) occupies the right portal branch and reaches the main trunk.



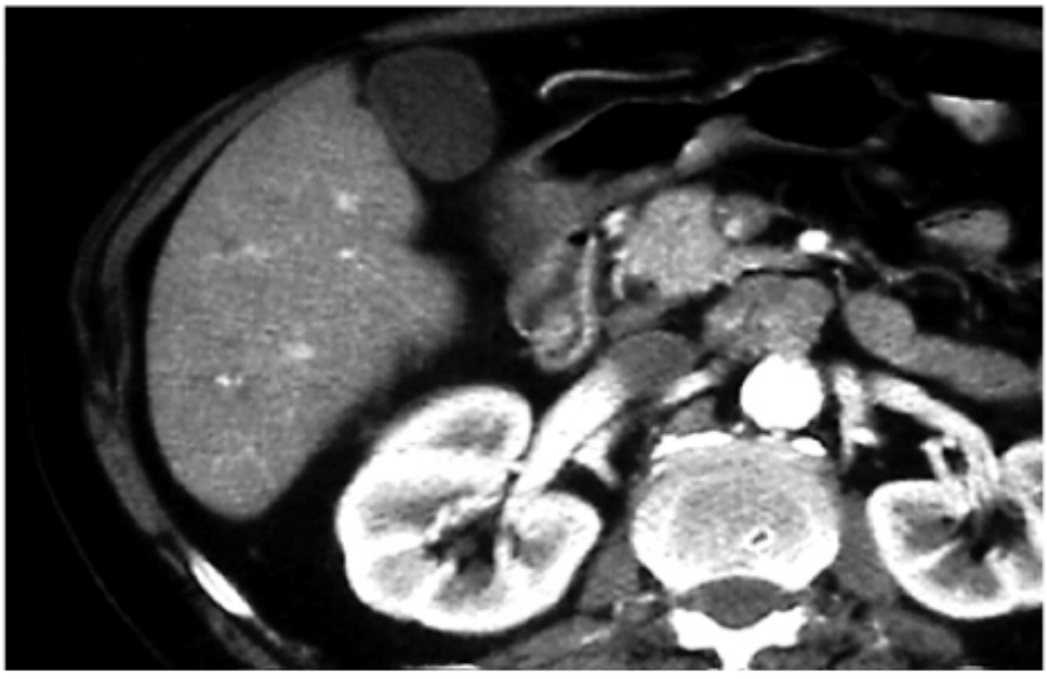
Spiral CT performed 6 months after treatment with SCDSF shows the shrinkage of portal thrombus and disappearance of HCC in the right lobe

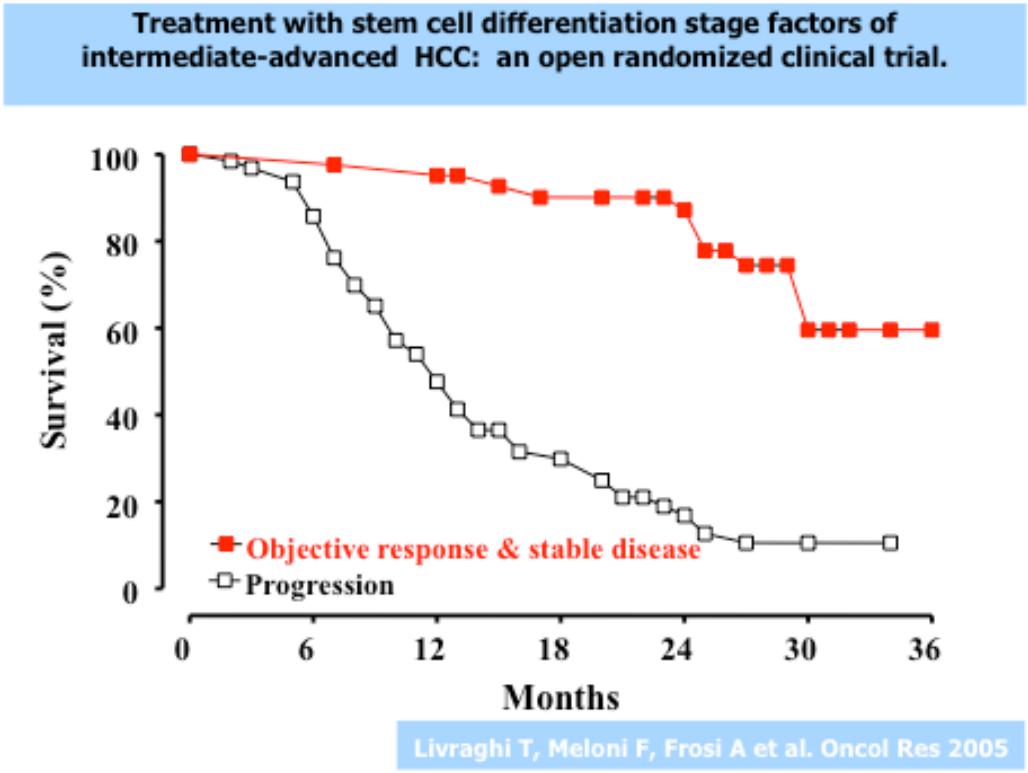


In another case, CT during arterial phase prior to treatment with SCDSF shows several nodules of HCC



CT performed 6 months after treatment with SCDSF shows the disappearance of neoplastic hypervascularization inside the nodules





Results of experiments on neurodegenerative diseases.

A first series of experiments has been conducted with the aim of determining the best experimental conditions for evaluating a presumed neuroprotective activity of Zebrafish extracts.

A one hour treatment with NMDA 50 µM has been chosen to induce a significant mortality in the experimental conditions studied. Organotypic hippocampal slices has been treated with NMDA 50 µM to induce mortality and after 24 hours has been performed a PI coloration.

After fixing, the CA1 area has been acquired and mortality has been analyzed as described in materials and methods.

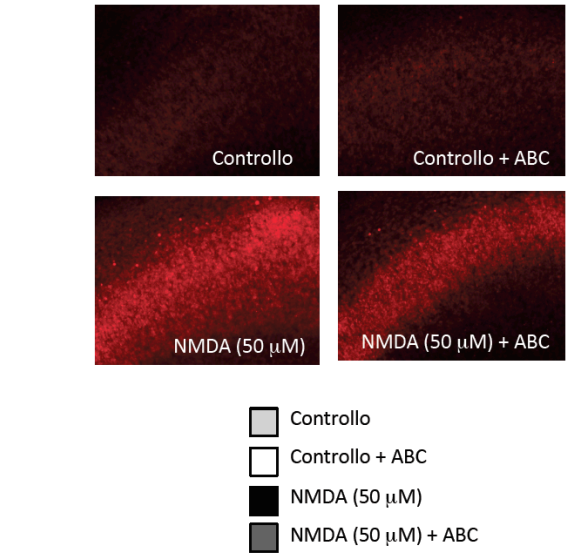
NMDA treatment increases mortality of 47%, if compared with the control group, in the CA1 area 24 hours after the administration.

Neuroprotective properties of extracts have been evaluated on organotypic hippocamapal slices exposed to different toxic stimuli (serum deprivation, NMDA 50 µM; 1h).

In the first series, potential neuroprotective effects of the extracts mix A (in medio-blastula/gastrula stage) B (in 5 somite stage) and C (in 20 somite stage) were evaluated.

The A+B+C mix was administered to NMDA group and to serum deprivation group with a further dilution of 1:100 and analysis were conducted after 24 hours.

Treatment with A+B+C extracts mix determined a reduction in neural mortality (p=0,005) induced by 1 hour serum deprivation. In the NMDA 50 µM group, A+B+C extracts mix determined a mortality reduction as well. (Figure 1).



Subsequently, potential neuro-protective activities of A or B or C were investigated. In this case too the experiment showed a reduction in mortality, overall for A extract; results are almost significant but not enough, neither in the NMDA group nor in the serum deprivation group. Thus, the whole informational set is needed to produce an effective result.

Results of clinical studies on psoriasis

Two clinical trials (17,18) were conducted to evaluate the efficacy in cases of psoriasis following the administration of a topic formulation of Zebrafish embryo extracts added with Boswelia serrata, 18-beta glicirretic acid, Zanthoxylum Alatum, 7-deidro-colesterolo, vitamin E. Results show 80% clinical objective improvements, with a reduction of keratosis and itch after 20-30 days from the beginning of the treatment.

Discussion and Conclusions

The use of stem cells differentiation factors in anticancer therapy has enabled us to build up a model of cancer corresponding to reality (19). In such a model the cancer cells are

considered undifferentiated cells, mutated, blocked in a multiplication phase between 2 stages of cellular differentiation.

Therefore, from this point of view, the cancer cells can be defined as" mutated stem cells", that according to their degree of malignancy , are considered blocked at a different phase of development. In support of this model it can be recalled that in tumors with an elevated degree of malignancy, such as acute lymphoblastic and myeloid leukemia, multipotent mutated stem cells are present, whereas in tumors with lower malignancy, such as chronic lymphocytic leukemia, cells not yet completely(entirely) differentiated are present, but towards a final differentiation.

In agreement with such a view, we recall the characteristics that cancer cells and stem cells have in common: tumoral cells present oncofetal antigens, maintained during the phylogenesis, (20) and specific receptor on the cellular membrane on which the stem cells differentiation factors probably act. It has already been mentioned above that such factors activate metabolic pathways of cellular differentiation, that lead the cells to differentiate or to die, as usually occurs in the embryo (the apoptotic events in the embryo are many) .

Furthermore, the cancer cells and the embryonic cells share common metabolic pathways: for instance APC/beta catenin/ TCF/Wnt pathway and the Hedgehog/Smoothened/ Patched pathway. The problem of stem cells is double: not only that they present genetic mutations, that are at the origin of malignancy, as is so far known; but also that there is perhaps a more important thing, an imbalance of the epigenetic code. The gene configuration and the metabolism of cancer cells is actually very similar to that of stem cells: both have active proto-oncogene and produce embryonic growth factors, present, as above emphasized, oncofetal antigens, they work with an aerobic metabolism: the difference between the cancer cells and stem cells is that tumoral cells, in contrast with normal stem cells are not able to complete their development and to differentiate because they have lost information, i.e. they experienced a mutation in their epigenetic code. The correction of the epigenetic code through the use of differentiation factors, transforms the cancer cells into normal cells.

It is now emerging more and more clearly that the regulatory DNA is responsible, via RNA, for the translation of proteins, so that the transcription factors, the microRNAs, the translational- and post-translational factors, play a fundamental role in the regulation of the genetic code thus in the regulation of the cellular life. In other words, epigenetic code is able to differentiate and regulate normal stem cells and cancer stem cells, deactivating genes that lead cancer stem cells to proliferate while activating new differentiating pathways.

Our studies have recently been confirmed by other researches performed by colleagues of the Children Hospital of Chicago, that at present are arousing profound interest (21). In particular such studies have confirmed that malignant melanoma reverts to a normal phenotype when it is in the environment of zebrafish embryo. On the other hand there has recently been a growing body of studies that highlighted that tumor malignancy is linked to the presence of tumoral stem cells (22) , which again, seem to be resistant to conventional therapy, such as chemo- and radiotherapy. In the last 4-5 years scientific works are so numerous that it is almost impossible to name all of them.

Here we mention only those researches that have demonstrated the presence of tumoral stem cell in glioblastoma (23,24,25), breast cancer (26,27,28,29,30,31), lung cancer (32,33,34,35), prostate (36,37,38), ovary cancer (39,40,41,42,43), liver cancer (44,45,46,47,48,49), stomach cancer (50,51,52,53,549, colon cancer (55,56,57), pancreas cancer (58,59,60,), head and neck cancer(61,62,63,64). On the other hand, it is known that

malingnancy of many haematological tumoral diseases is due to the presence of stem cells.

Regarding the interpretation of the results obtained following the treatment with the differentiation factors of stem cells for the prevention of the neurodegenerative and for the treatment of psoriasis, we can assume same reasons: the differentiation factors are epigenetic regulator, that, on the one hand prevent the processes the development of degenerative phenomena and on the other hand, regulate the processes of changed cellular multiplication, as it comes for instance, in psoriasis, where the multiplication of cells of the epithelial basal layer is five fold higher of that considered physiological: in this case we have demonstrated that the differentiation factors reduce the changed multiplication factors of the epidermal layers by normalizing it .

It is expected that the use of epigenetic regulation factors can be applied in a very large field regarding the prevention and treatment of degenerative diseases, not only of the nervous system, but also of the cardiovascular- osteoarticular system, diabete etc., also in degenerative medicine as anti-aging factors, so that by improving the general state of health of the elderly and in particular, with the available products for topic use that improve the state of the skin. The studies carried out with such factors, briefly mentioned in this article, led me to conceive a new model, that interpret the human organism as a cognitive system mind-body, of which all the regulation patterns of information are described.

In fact, the new model considers the human being as a complex cognitive system as envisaged in Psyconeuroendocrinology (PNEI). However, PNEI is inadequate. The latter has had a remarkable importance to clarify and to understand the numerous mechanism of adaptability and of behavior of the human organism towards the environment. Nevertheless, in the light of the latest studies in the bio-medical field the model on which is based the PNEI is no more sufficient to explain the complexity of human being and should be integrated in a larger model that interpret the human being as an informative integrated mind-body system.

This model differentiates from all the others in that it stresses the concept of information crucial to maintain the life. In fact, it is evident from all the arrays of experiments above reported , that the epigentic regulation factors are fundamentally regulation factors of the information, that circulates in the living system and that maintain health. They maintain the informative order, as they increase the negentropy and also the structural order of the system.

Health in the organism is a process of continuous renewal through the organization of the information that circulates in the system and expresses the functions and the phenomena of life.

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