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Human photosynthesis, the ultimate answer to the long term mystery of Kleiber's law or $E = M^{3/4}$: Implication in the context of gerontology and neurodegenerative diseases*

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ABSTRACT

Kleiber's Law or $E = M^{3/4}$ is a mathematical expression known since 1932 that outlines the relationship between mass (biomass) and the use of energy. It is compelling because it supports a long standing observation that larger animals appear to use energy more efficiently than smaller ones. For example, an elephant's weight is 200,000 times of a mouse, but uses only about 10,000 fold energy; thus a cat, having a mass of about 100 times of a mouse, only spends roughly 33 fold energy. In other words, the bigger you are, the less energy per gram of tissue you actually need to stay alive. Many facts pertaining to animal size call for a rational explanation. This paper takes into account that the fascinating relationship between mass and energy use for any living thing is governed strictly by a mathematical universal formula across all living species, operating in the tiniest of bacteria to the biggest of whales and sequoia tress. For the first time, we report a capacity for the mammal eukaryotic cell to split, break or dissociate water molecules through melanin. Even though $E = M^{3/4}$ was discovered eight decades ago, no proper satisfactory explanation exists. Nevertheless, our multiyear detailed study on the "Human Photosynthesis" or first found in the human retina and later in all eukaryotic cells, may finally unravel this mystery, namely, the bigger you are the more surface area you have to absorb electromagnetic radiation and the more potential exists to use that electromagnetic radiation spectra to perform work. We propose a future application of this theory in the context of human diseases, especially age-related disorders, such as retinopathy, cerebrovascular and Alzheimer disease and these implications may not only foster a better understanding of the pathobiology of these devastating diseases but also develop much more effective therapies in the foreseeable future.

Keywords: Human Photosynthesis; Kleiber's Law; Geriatrics; Gerontology; Cardio- and Cerebrovascular Diseases; Neurodegeneration; Alzheimer Disease; Retinopathy

1. INTRODUCTION

When we try to find the rules that govern animal functions, we tend to think in terms of chemistry [1], thinking

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our knowledge, on water, salts, proteins, enzymes, oxygen, energy and so on, a whole word of chemistry [1]. However, the physical laws are equally important as they determine rates of diffusion, the transfer of heat, force and momentum; the strength of structures; the dynamics of locomotion and so on. Physical laws provide opportunities and possibilities, impose constraints and set limits to what is physically possible [1]. The same laws of chemistry and physics may apply to animals, which must live within the boundaries set by those laws. Body size has profound consequences for structure and function and the size of an organism is of crucial importance to the question of how it manages to survive. It is considered that life is the most complex and diverse physical phenomenon in the universe, manifesting an extraordinary diversity of form and function over an enormous scale from the largest animals and plants to the smallest microbes and subcellular units. Despite this, many of its most fundamental and complex phenomena scale with size in a surprisingly simple fashion [2]. The metabolic rate scales as the 3/4 power of mass over 27 orders of magnitude, from molecular and intracellular levels up to the largest organisms, are good examples of this. The smallest shrew, when fully grown, is only one-tenth the size of a mouse, or one-millionth the size of an elephant; however, the elephant don't eat a million times more than the shrew. For example, the Etruscan Shrew has a weight of 2 g, and requires 1.428 g daily of food, in contrast, an adult elephant consumes 140 to 170 kg of food a day, only 100,000 times more than the shrew. Organisms themselves span a mass range of over 21 orders of magnitude, ranging from the smallest microbes (10 - 13 g) to the largest mammals and plants (108 g). Despite these extraordinary amazing diversity and complexity, many of the most fundamental biological processes manifest an extraordinary simplicity when viewed as a function of size, regardless of the class or taxonomic group being considered. Scaling with size typically follows a simple power law behavior of the form: Y = Yo Mb. where Y is some observable biological quantity, Yo is normalization constant, and M is the mass of the organism. An additional simplification is that the exponent b, takes on a limited set of values, which are typically simple multiples of 1/4. Among the many variables that obey these simple quarter-power allometric scaling laws are nearly all biological rates, times, and dimensions; they include metabolic rate ($b \approx 3/4$), lifespan ($b \approx 1/4$), and heart rate ($b \approx 1/4$), DNA nucleotide substitution rate ($b \approx 1/4$), lengths of aortas and heights of trees ($b \approx 1/4$), radii of aortas and tree trunks ($b \approx 3/8$), cerebral gray matter ($b \approx 5/4$), densities of mitochondria, chloroplast and ribosome's ($b \approx -1/4$), and concentrations of ribosomal RNA and metabolic enzymes ($b \approx -1/4$). The best-known of these scaling laws is for basal metabolic rate, which was first shown in 1932 by Max Kleiber, author of the thesis "The Energy Concept in the Science of Nutrition", who came to the conclusion that the 3/4 power of body weight was the most reliable basis for predicting the basal metabolic rate (BMR) of animals and for comparing nutrient requirements among animals of different sizes. Subsequent researchers showed that the whole-organism metabolic rates also scale as M3/4 or Kleiber's law, in nearly all organisms, including animals (endotherms, ectotherms, invertebrates, and vertebrates), plants, and unicellular microbes [3]. This simple 3/4 power scaling has now been observed at intracellular levels in isolated mammalian cells down through mitochondria to the oxidize molecules of the respiratory complex, thereby covering fully 27 orders of magnitude [4]. The enormous size differences (**Table 1**) among living organisms are not easily conceptualized, *i.e*. the total difference between the smallest and largest organism—blue whale is 10^{21}, an hypothetical giant organism larger than the blue whale by the same ratio, 10^{21}; would be 100 times the volume of the earth.

Young, *i.e*., smaller organisms, respire more per unit of weight than older or larger ones within the same species, once the organism is out of the amniotic fluid. Inside the uterus the fetus breathing is slow, e.g. 20 - 30 per hour versus 20 to 40 per minute after birth. Traditionally, this has been explained by the overhead costs of growth, furthermore, some authors state that small adults of one species respire more per unit of weight than large adults of another species because a larger fraction of their body mass consists of structure rather than reserve, and structural mass involves maintenance costs where reserve mass does not.

However when we analyze Kleiber's law from the point of view of Human Photosynthesis, we see this is not the issue. The exponent in Kleiber's law, a power law where a mathematical relationship exists between two quantities, has been a matter of dispute for several decades. It is still contested by a diminishing number as be-

Table 1. Each step represents a 1000-fold difference in mass. Modified from Schmidt-Nielsen, Knut [18].

Organism	Mass	
Mycoplasma	<0.1 pg	$<10^{-13}$ g
Bacterium	0.1 ng	10^{-10} g
Tetrahymena	0.1 µg	10^{-7} g
Amoeba	0.1 mg	10^{-4} g
Bee	100 mg	10^{-1} g
Hamster	100 g	10^{2} g
Human	100 kg	10^{5} g
Blue whale	>100 tons	$>10^{8}$ g

ing 2/3 rather than the more widely accepted 3/4. Given the fact that this law is concerned with the capture, use, and loss of energy by a biological system, the system's metabolic rate was at first taken to be 2/3, because energy was thought of mostly in terms of heat energy, thus metabolic rate was expressed in energy per unit time, specifically calories per second. Given the fact that this law is concerned with the capture, use, and loss of energy by a biological system, the system's metabolic rate was at first taken to be 2/3, because energy was thought of mostly in terms of heat energy, thus metabolic rate was expressed in energy per unit time, specifically calories per second. This misconception was based on the wrong belief that energy and biomass evolve from the food we ingest. Two thirds therefore expressed the ratio between surface area (length^2) and volume (length^3) of a sphere, with the volume of the sphere increasing faster than the surface area, with increases in radius. This surface area-to-volume ratio gave the metabolic rate of a particular organism as proportional to its mass raised to the power of 2/3. This was purportedly the reason why large creatures lived longer than smaller ones, that is, it was thought that as they got bigger they lost less energy per unit volume through the surface, as radiated heat. Regardless of the exponent, 2/3 or 3/4, what has not yet been considered is the fact that a bigger surface, sphere, or mass, gives an organism better capability to absorb the electromagnetic radiations of diverse wavelengths, an unexpected and yet existing source of energy in chlorophyll-lacking living organisms. The concept of metabolic rate itself was poorly defined and difficult to measure. It seemed to concern more than just the rate of heat generation and loss.

Prevailing understanding of an organism's metabolic/respiratory chain was based entirely on blood-flow considerations. And yet, the equation has shown to be relevant over 27 orders of magnitude, extending from bacteria, which do not have hearts, to whales or forests. Therefore, to assume that this is due to how resources are distributed through hierarchical branching networks it is not a good explanation, given that the role of fractal capillary branching is not demonstrated as fundamental to the exponent 3/4.

2. BLOOD FLOW AND METABOLIC EFFICIENCY (ME)

The theoretical models are also relevant to things without blood flow, like bacteria and corals. Attempts to understand the metabolic rate of a multi-cellular organism (field metabolic rate, which includes the activity of the organism) are expressed in terms of the product of average basal metabolic rate and number of cells. This, plus capillary terminal size invariance, leaves the equation open to the criticism that it cannot possibly account for spikes in metabolic rate needed for motor activity that requires significant amount of blood mass. In plants the exponent of mass is close to 1[1]. Mathematically, this is not possible since the implication is that ME is greater than 100% in the case of plants and between 89 and 100% in mammals. Efficiencies like these are not found in nature. Further, Kleiber's law, as originally formulated, was based upon the idea that metabolic energy was entirely related to measurements of heat generation and loss. On the other hand, trying to explain part of Kleiber's law with blood flow is doomed by the invariant size of capillaries, which is the same in leaves and mammals.

The term *calories* is used for the measurement of heat energy. Undesirably this leads to the idea that thermogenesis is part of metabolism, a mistake in spite of the fact that it was Kleiber's original treatment, and it also does not consider that metabolism is about chemical energy, but not heat energy. For this reason the whole pictures are further confused when the idea of respiratory metabolism is introduced refining and limiting the definition of metabolism, making oxygen consumption and synthesis of adenosine three phosphate (ATP) its ultimate factors. When considering metabolic rates of cells in vitro, data from studies of oxygen consumption suggest that the exponent is not only far less than 3/4, but even becomes negative for things less than one gram in size. Furthermore, this model excludes glycogenesis from metabolic consideration since glycogenesis is not included in the respiratory chain, and is itself a reduction reaction not strictly dependent upon the proximity of certain molecules and atoms delivered by capillaries and vibrating from Brownian motion. Energy is required for glycogenesis, and blood does not deliver energy, just the ingredients for endergonic reactions. The energy comes from redox coupling, what ME is all about. The value of ME amends these problems, and describes the metabolic rate in watts. Metabolic rate becomes the rate at which a biomass recharges so that its degeneration is prevented, and its organization is perpetuated.

ME is a ratio of the rate of reduction reactions necessary for the maintenance, growth, replication and behavior of the biomass, to the rate of availability of energy captured and expended by that biomass. ME is a statement of redox coupling efficiency as well. The value of ME consequently excludes thermogenesis as part of metabolism. A graph of Kleiber that includes ME, with ME as the X axis, metabolic rate as the Y axis, and a different curve for each mass, reveals a picture of the relation of biomass to metabolic rate that suggests all of evolution took place at less than 45% ME.

The organism determines ME, and that ME is the same

for it and for its cells. If we put a limit in the considerations of metabolism to strictly electrochemistry and then, if metabolic rate (MR) is taken as the recharge rate in watts of an electrolytic biomass, then MR is directly related to the longevity of that biomass. The resultant equation suggests that for living things operating at over 25% ME, the organism lives longer than its cells. What this indicates is that the organism has a source of new cells that are not initially a part of it, undifferentiated stem cells for example, especially in creatures over one gram mass. Therefore in our knowledge aging appears to be the result of antagonism between BMR (basal metabolic rate or each cell) and FMR (field metabolic rate or the entire organism), given fluctuations in ME. These fluctuations most likely are driven predominantly by alterations in the denominator of the ratio ME, where that denominator represents the availability of food sources.

3. RESTING ENERGY EXPENDITURE

The relationship between resting energy expenditure (REE) (kJ/d) and body mass (M) (kg) is a cornerstone in the study of energy physiology. Kleiber formulated the now classic equation: $REE = 293M^{0.75}$. The biological processes underlying Kleiber's law have been a topic of long standing interest and speculation [5]. All living mammals expend energy for the maintenance of the resting energy expenditure (REE), the thermic effect of feeding, and for physical activity. REE is usually the largest portion of total energy expenditure. Kleiber's law is one of the most important and best-known laws in bioenergetics [6-8].

4. LIFE AND ENERGY

Living beings are capable of not only generating order from disordered matter but also replicating themselves with great fidelity. In both cases, there are two important requirements, the energy and the building blocks or carbon chains. The metabolisms of living organisms are intricate. They utilize molecular mechanisms that are quite delicate, very fine-tuned yet robust to the vicissitudes of life and to the environment. We need to center on tracking the flow of available energy in living systems since this common thread illuminates an underlying simplicity.

Since to be able to access available external energy is a necessary condition for producing as well as for maintaining a dynamic system, all living systems are out of thermodynamic equilibrium with their surroundings. Life requires a carefully "*balanced imbalance.*"

Available energy in biology comes mainly in several forms: photon, chemical, electrical and mechanical strain. This type energy is also called high-grade energy. It has to be conserved or utilized in living systems but not completely lost as heat to the surroundings for metabolism to function. In fact, available energy is converted from one form to another in most metabolic processes, although never with 100% efficiency [**Figure 1**]. Living matter on a large scale has a well-defined pressure, density, temperature and chemical composition. In short, it is in a thermodynamic state or steady state. Although there are statistical negligibly small fluctuations, isolated single molecules have to be described by the laws of classical or quantum mechanics in contrast. In a volume of a mitochondrion at pH 8, there is only a single proton present on the average. Therefore, the transfer of a single proton across the membrane changes pH appreciably. This highlights the fact that all thermodynamic properties of such small systems undergo appreciable fluctuations in space and time requiring constantly energy and energy dotted with certain characteristics as delimited range of fluctuation, chemical in nature, enough all time for the hundreds or thousands of reactions that occur incessantly into the cell or whole organism.

Thermodynamic states of matter can be fully described by thermodynamic variables including the total volume, temperature, pressure, density, available energy, chemical composition and concentrations of the chemical components, and in mammals and human being also included amount of light or photonic energy. More important is when energy is transformed into heat [**Figure 1**], which can't be recovered by living systems.

5. MELANIN IS A UNIQUE COMPOUND AS A CANDIDATE OF PRIMORDIAL CATALYSIS

Melanin appears to be a candidate for primordial catalysis. The reluctance to accept melanin as biologically active substance was based on its stability [9]. Here we have outlined our understanding how the melanin has significant powerful and more activities that's given the unique features. The detailed evolution of a reaction depends on its environment in a complex manner. Here it will be referred to simply as the reaction pathway. Within a given environment, ΔG (the change in free energy) depends only on the reactants and the products regardless sis in nature prior to the proteins evolution [**Figure 2**]. the path. Therefore ΔG is treated as discreet variable; otherwise if it were treated as a continuous variable, the result would exceed our abstraction capability.

The speed of a chemical reaction relies on its detailed path. In ordinary reactions, a great simplification results from postulating a transition state that constitutes the bottleneck for the reaction. The transition state is produced

$$2H_2O \leftrightarrow 2H_2 + O_2 + 4e^-$$
$$\downarrow$$
Energized state
$$\downarrow$$
Work performances

Figure 1. Schematic drawing of how energy is degraded into heat as a result of splitting of water. This reaction is reversible.

by local, microscopic fluctuations within the thermodynamic state in this approximation. However these microscopic fluctuations depend of the energy as first requirement and of the result of it over the present matter in second term. For a given a set of reactants, many reaction paths are possible usually. However, the one with the fastest rate predominates. A crucial observation is that the reaction rate is determined by the "***activation***" free energy of the transition state, ΔG†, and not by the final ΔG of the reaction. In particular, some reaction paths can generate a large amount of heat, *i.e*. have a very large negative ΔG, while some other reaction path with a much smaller negative ΔG and different reaction products can be a faster reaction [**Figures 1** and **2**]. That is the case when the transition state energy ΔG† of the second reaction is lower, and/or its crossing probability is larger than those for the first one. A similar argument can be given for generalized reactions if a bottleneck for the reaction can be identified.

6. CATALYSIS IN BRIEF

Catalysis, defined in the broadest possible way, including any change in the reaction path caused by the catalyst, encompassing the change of speed of a given reaction, and including changes in the products, has as a prerequisite for the catalyst to be able to influence a chemical reaction that a high-grade energy be exchanged among the catalyst and the reactants; or, expressed even more precisely, the catalyst has to interact with the reactants in order to influence the reaction. Thus quantitative predictions can be obtained only by solving the microscopic equations of classical or quantum mechanics, respectively. Catalysts provide a local environment to the reac-

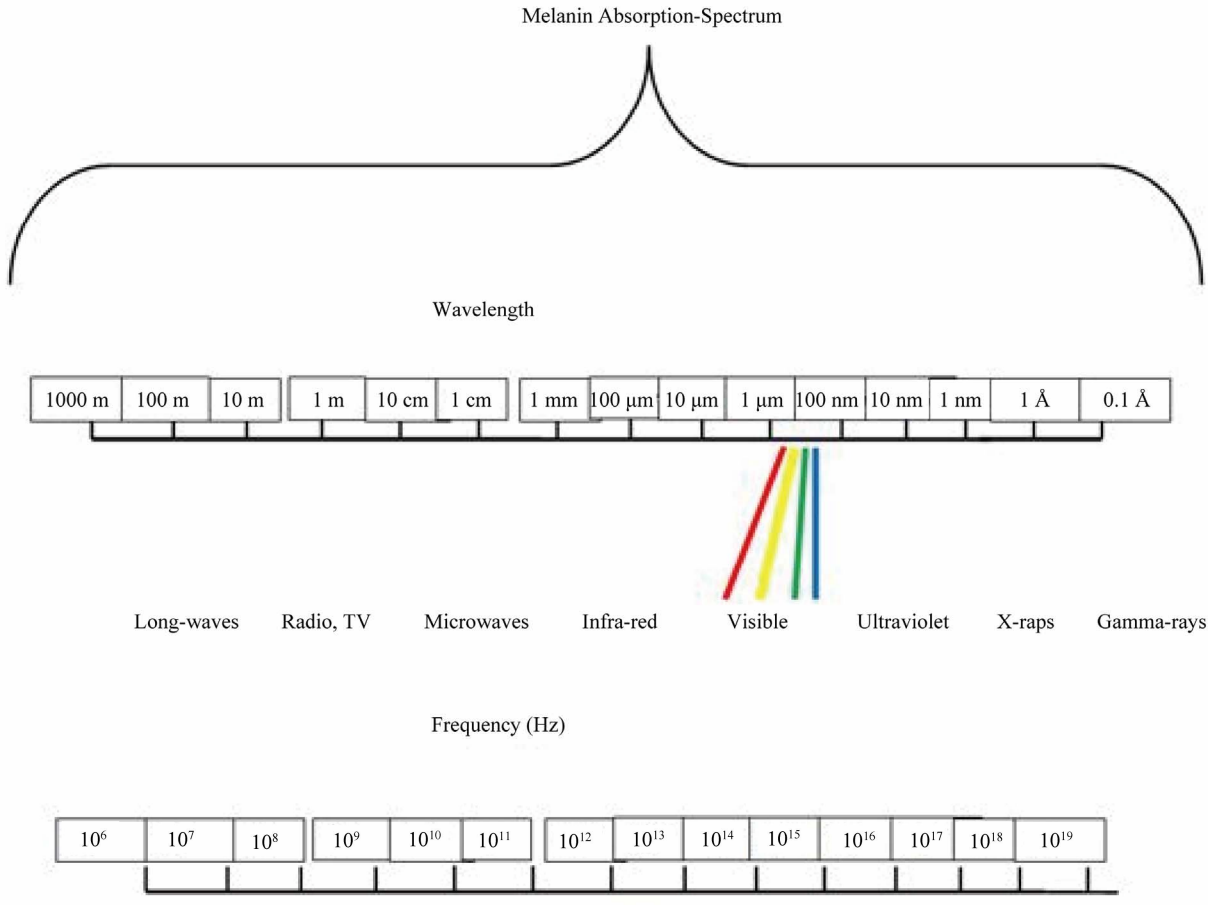

Figure 2. Schematic drawing melanin absorption spectrum. Explanation in the text.

tion. This is a valid description as long as the reactants are in their macroscopic and thermodynamic states. The reactants are then in local equilibrium before the reaction: they have a local ΔG, a local pH and some chemical groups have locally varying pK. Moreover, if reactants, e.g. both the substrates and the products of the enzyme reaction, are at steady state before reaction, a catalyst cannot change this equilibrium. It has been widely accepted that the equilibrium may be between at least two substances, e.g. a substrate and a product, and its disbalance triggers the reaction that can be catalyzed with a catalyst including the melanin that does for water dissociation and reformation. The result of this reaction is a ΔG after the reaction with a different local ΔG, etc. Moreover, during these intermediate stages (dissociation and reformation) ΔG is never depend on catalysts but only on reactant concentrations or ΔGs (**for the detailed information regarding the definition see: See Biological Catalysts—Enzymes Section**). This apparent relationships is resolved if ΔG of binding the reactants and of unbinding the products is properly added. The resulting ΔG is independent of the catalyst, as it should be, and melanin is not an exception. The importance of catalysis for biology is that catalysts can significantly influence the pathway for accomplishing a biological task. For example, catalysts are able to influence on the speed of the change the path of a reaction in such a way that available energy is sequestered during the reaction and, channeled into new products possibly. By selecting a reaction pathway, catalysts most likely can change the fraction of the available energy, G, in each of the steps, while keeping the sum of ΔG constant for all steps in the sequence. In such reactions, even when a catalyst does not change the dissipated fraction of ΔG it's most likely able to change the speed of the reaction that most likely able to temporarily holds some of the available energy during one part of the reaction, releasing it in a later part of the reaction. The fundamental mechanism of coupled reactions, ubiquitous in metabolism, is the exchange of high-grade energy between the exoergic and the endoergic components. We can state quite generally that the channeling of a reaction along a pathway of low heat loss, by enzymes, is the most important way high-grade energy that were is utilized in biology. We could consider melanin as a kind of enzyme whose relevance has not yet been taken into account in the sequence of the life, or in other words in any biochemical pathway.

7. EMERGENT LAWS

Emergent laws It is widely accepted that a living system exists by itself, regardless of the laws of physics and chemistry, but is subject to, judging by the experience of human on the well-established laws of physics and chemistry [10]. The rules that govern biological systems have to be described and understood on several distinct layers or levels. On each level a set of rules, appropriate to that level, has to be established. These properties have been called emergent behavior. Emergent laws of biology have to be established in addition to the laws of physics and chemistry [11]. In the utilization of available energy by living systems, as the driving force of life, we can consider three levels: macroscopic, mesoscopic and microscopic. At the macroscopic level, thermodynamics is valid and fluctuations are negligible. The concepts of free energy and of reversible and irreversible processes are well defined. The equations of motion are reversible at the level of microscopy and quantum chemistry, therefore thermodynamic concepts do not make sense anymore. The level being considered to explore the energetic of the basic metabolic processes is the mesoscopic level. It is between quantum chemistry and cell biology and can be used to describe energy utilization in a physically, chemically and biologically meaningful way.

8. BIOENERGETICS AND METABOLISM

Metabolism represents the net of chemical and physical events or processes. It is seems to be that the metabolism is the basis of creation, which take place within an organism and enable its emergence, continued growth and functioning. Living organisms are closed systems from a thermodynamic point of view. However they are open systems from a ***"cosmic"*** thermodynamic point of view since they constantly exchange materials and energy with their surroundings. The engines of life that keep metabolism going are fueled by available energy. In plants and animals, this energy comes from light or from sources someway or other linked with the light. In the case of human beings there is a deep-seated belief that energy and building blocks come from food. Deciphering the capability of melanin to split the water molecule breaks the ground of bioenergetics. We could say that human beings are autotrophic organisms, as plants are. Almost all reactions in metabolism are catalyzed. This is true even for molecular motion, protein folding and other generalized reactions in living systems, in brief and based on the utilization of available energy.

9. BIOLOGICAL CATALYSTS—ENZYMES

The fundamental mechanism of enzyme action is a transient, reversible exchange of high-grade energy between the enzyme and the reactants. That lowers the relative free energy of the transition state ΔG† are not dependent of the viability of the enzymes. However, we cannot differentiate among the various ways this is accomplished:

by lowering the transition state, unbinding the reactants and ***"pre-organizing"*** the enzyme itself. It is especially important that key steps in bioenergetics involve the reversible exchange of high-grade energy between uphill and down-hill between the chemical substances. Moreover, exchanges of the energy on the upper and the lower levels during the chemical reactions always involved at the same substances and same reagents during the chemical reaction. Such ***"coupled reactions"*** appeared to be the backbone of the biosynthesis. At this point, it is convenient to extend the definition of catalysis to a situation when the exoergic and the endoergic reactions are carried out consecutively. The exoergic (define) reaction then ***"charges"*** the enzyme involved on the formation of the high-grade energy and the endoergic reaction is driven by the accelerated action of the ***"energized"*** enzyme. Only the net difference, between the two ΔG's, is dissipated as heat and at the end of the cycle, the enzyme is reusable. In order to make each step spontaneous, ΔG has to be negative at each step separately. The great flexibility enables selection of ***"suitable"*** catalysts by evolution. We note that many biochemical cycles, e.g. the citric acid cycle and the Calvin cycle are now included in our definition. Also, those different enzymes have different efficiencies during the reactions and mostly cases dependent on the amount of the enzymes that exists in the media [12,13]. Heat generated during metabolism is not able to be reconverted into available energy by living beings today. However, some organisms seem to benefit from the generation of heat. For example: **i)** Flowers have hot plates to evaporate attractants. **ii)** Insects (e.g. the bumblebee) produce heat in futile cycles so that they can take off in the cold. **iii)** Bears waking from hibernation heat up their body by uncoupling electron transport [13].

10. A FRAMEWORK OF LIFE

The emergent set of rules compatible with the basic laws of physics, even though they cannot be derived from these basic laws, explain the functioning of living matter and form the framework for catalytic energy utilization, providing the link between biology on one side and physics with chemistry on the other. These rules are as follows: **1)** Dynamic systems require an input of external energy to move away from thermodynamic equilibrium and a continuous input of external energy to maintain a position away from equilibrium. We now know that in both, plants and animals, that continuous input comes from the sun, directly or indirectly. **2)** Dynamic, changing and evolving systems can stay out of equilibrium only if they do not degrade all of the available energy into heat during chemical changes. In order to achieve that, the fastest chemical reactions have to precede on paths that unlikely have a relatively small negative ΔG. **3)** A catalyst interacting with its reactants can exchange high-grade energy with the reactants and thereby alter the fastest path of the reaction. The sign of this transient energy exchange can be either positive or negative with respect to the catalyst, and when it is positive, the catalyst gets transiently energized. In the simplest coupled reactions, the energy is transmitted to another reactant and the net result is an activated molecule. The conserved high-grade energy from this step is then available to the organism for other uses. In more complex, and more common, coupled reactions, the temporarily unlikely stored high-grade energy in the catalyst. However, continues reaction or adding the catalyst most likely becomes as an available sources to possibility drive another reaction uphill. This ability is a "***built in***" feature of catalysis, and follows from the transient "***exchange***" of high-grade energy between catalyst and reactants, as discussed here. Therefore, the energy released during water dissociation and reforming of the water molecule is used in many ways by the eukaryotic cell. **4)** Catalysts provide a very large range of possibilities for selecting and varying chemical reactions. An enzyme with unperfected specificity allows evolution to work, and it is actually the prime vehicle of evolution. As a consequence, evolution selects catalysts that are best suited for a specific task in living systems. Replication and evolution are consequences of this relative simple framework, and as such they are also emergent properties of biological systems. The new discovery needed to understand the workings of life, is centered in the fact that the main source of energy in the animal eukaryotic cell is the water, in contrast with the ancient belief that energy and building blocks come from food.

11. DOES MELANIN ACT AS HUMAN CHLOROPHYLL?

Twenty-one years have passed since we began to study treatments for the three main causes of blindness; and our results were astonishing: Melanin has the amazing capability to dissociate the water molecule. Briefly, the reaction could be described as a following:

$$2H_2O \leftrightarrow 2H_2 + O_2$$

The human "*photosystem*" is composed of Light/Melanin/Water, arranged in order of abundance in nature. Melanin has the capability to harvest visible and invisible light, and with that energy melanin capable to break the water molecule into the hydrogen and oxygen. By analogy with plant photosynthesis, we call this ability of the Melanin as a "*Human photosynthesis*". The difference with photosynthesis in plants is crucial:

$$2H_2O \rightarrow 2H_2 + O_2$$

One main function of Chlorophyll is splitting a water molecule, however is unable to reform the water molecule from the hydrogen and oxygen. Therefore, the reaction in mammal including in human photosystem is bidirectional or called reversible, whereas in plants is unidirectional (or non-reversible). In addition, it has been well documented that the chlorophyll only absorbs 400 (blue) and 700 (red) nanometers of wavelength. In contrast, melanin absorbs the full electromagnetic spectrum. Therefore, mammals any photosynthesis is clearly different and much more efficient when compared to plants. The unexpected finding that the eukaryotic cell has the capability to harvest photonic energy and use it to break the water molecule by means of a photosystem composed of Light/Melanin/Water, in order of abundance in nature, explains clearly the longstanding observation that animals with greater size require less energy to sustain life, and furthermore, seen their lifespan increased significantly. In our knowledge that the organism is acting like a biological antenna; therefore, if the body in question has more surface area or a larger mass, has greater probabilities to catch energy in enough amounts to sustain life, or highly complex biochemical reactions interlaced between them, that always have energy as a first requirement. Therefore, we speculate that the unsuspected capacity of eukaryotic cell to split the water molecule through the photosystem composed by LightMelaninWater could be the competitive unifying principles.

12. IMPLICATION OF THE MELANIN PRECURSOR AS A ALTERNATE SOURCES FOR MELANIN IN THE CONTEXT OF HUMAN DISEASES

Melanin, a substance also known chemically as polihydroxyindol, has unique properties. In addition, to protecting tissues from various wavelengths of light, it has been found to generate electricity using self-renewing photoelectrochemical cells containing melanin, which separate the hydrogen atoms from water and then bring the atoms together again. The principle implies that melanin captures photonic energy and transforms it into chemical energy, similarly to the photosynthesis process as the absorption of photons from electromagnetic radiation, which brings about an ionic event. It is chlorophyll, which is accepted as the only substance widely disseminated in nature that is capable of delivering hydrogen to a plant cell. No other substance has been known to function in animal eukaryotic cells in the same way. Results obtained using melanin confirm that plants may not be the only organism capable of carrying out photosynthesis and maybe mammals can as well. We can extrapolate that melanin is to the animal kingdom what chlorophyll is to the plant kingdom. Structural similarities include the four nitrogen atoms in the center of both molecules. In the case of melanin, it would appear that it may be more reactive per gram of protein, since chlorophyll has only one center of reaction, while melanin has hundreds of centers of reaction per gram of the substance [3]. One drawback to using chlorophyll, which is more abundant, has the ability to split the water molecule in order to obtain hydrogen for energy purposes. However, once chlorophyll is taken out of the leaf of a plant, it becomes permanently inactive 20 seconds later. Many research institutes, such as The University of California, have been trying to improve chlorophyll's activity level outside of plants without success. Melanin functions for years in contrast when taken out of the system. Further research is necessary to perfect the technology and determine the function for time period. Melanin extracts energy from water by separating and reuniting the hydrogen atoms from the oxygen atoms. The reaction below outlines that two water molecules, plus melanin, in the presence of photons of electromagnetic radiation (symbolized by the sun), gives us two hydrogen molecules, an oxygen molecule and four electrons. However, when the reaction goes from right to left, the hydrogen and oxygen atoms reunite, giving us water and electricity, since the melanin does not undergo change but simply catalyzes the reaction without any deterioration to its molecule. The reaction proceeds in both directions and, being complementary reactions, one exergonic and the other endergonic, a cycle is established which lasts for years, as the melanin does not deteriorate. The melanin captures photonic energy and uses it to extract the hydrogen molecule from water. The time needed to recollect the energy required to split the water molecule is 3×10^{-12} seconds. The presence of light and melanin is a source of energy used by the human body for sight. Interestingly, the fetal eye, 35 days into pregnancy, is completely full of melanin, and perhaps may provide energy to oculars tissues. In the comparative figures below, a voltmeter registering zero current can be seen, when the recipient does not contain a melanin solution and 300 milivolts or as much as 470 milivolts when the concentration of melanin is increased. Moreover, once the cell is sealed, the cell does not require recharging in any way [**Figure 2**]. Initially, 30 mL of melanin produced 400 mV and 10 uA. The LED was lit with a cell containing 500 mL and produced 500 mV and 200 uA. Currently, our facility capable to produce about 200 liters of melanin daily. The modules we used for above demonstration consisted of ten 500 mL cells and can power other devices. Each cell currently produces 600 mV and 200 mA, that is (one thousand times more) than the 200 uA we

achieved previously [**Figure 2**].

13. EXPLORING THE ROLE OF MELANIN IN UNDERSTANDING AND TREATMENT OF HUMAN DISEASES

As we described in previous section the discovery of human photosynthesis, or the unexpected capability of melanin to split the water molecule, radically changes this widely accepted concept: Metabolism drives the interaction between energy and the building blocks that our body takes from the food we ingest, because metabolism is not an energy producing system, it solely represents the interplay between the building blocks obtained from food and our energy requirements; requirements that our organism takes from water. With the main aim to understand and unravel the three main causes of blindness in humans, we dedicated more than 15 years of continued studies into their mechanisms of human diseases including cardio- and cerebrovascular disease, neurodegeneration and other human diseases [14]. In addition, in 2002, we were able to reach an unexpected conclusion that at least in the human retina the main sources of the energy appeared to be water, but not ATP as accepted in current biology and medicine. Our primary working hypothesis consisting on the following that in any cell in mammals including human body, independently of its function, needs water not only as solvent and /or vehicle, but as a main energy source . The explanation of how an eukaryotic cell could dissociate or break the water at the body temperature still unknown, but it is very significant and obvious that melanin appeared to be as a chlorophyll of the mammals or animal in general [15]. Moreover, as we described in the detail that both substances are able to split and/or dissociate, or break the water molecule to the oxygen and hydrogen [**Figure 1**]. The unsuspected capacity of melanin to initiate at room temperature a biochemical reaction that in laboratory conditions requires 2000˚C is awe-inspiring. As an analogue, we appointed it as human photosynthesis. But in comparison, our photosynthesis is much more efficient than that of vegetables because chlorophyll only uses between 400 and 700 nm of light wavelength. In comparison, the human version of chlorophyll is capable of absorbing light through the whole electromagnetic spectrum. Furthermore, evidence indicates that melanin can absorb any form of energy, even gravitons, and that the energy that when human photosynthesis is turn down in an abrupt manner, hemorrhage and edema ensued in any part of our body, while when turned down in a chronic form, then fibrosis developed. In this work, we will show some striking examples of the therapeutic results of the pharmacologic modulation of human photosynthesis in various diseases (cardio- and cerebrovascular diseases, neurodegeneration, kidney, liver, lung, and human eye diseases) and their significant preventive results. The potential pharmacologic modulation of human photosynthesis offers a potentially powerful opportunity to open new and very efficient ways to treat several diseases, represents a an important are of study in the epidemiological point of view [14]. Namely, we have found that the mitochondria in neurons as well as all brain cellular compartments (glia and vessels wall cells) are a primary target of brain damage due to their high-energy demand and susceptibility to oxidation, which leads to energy failure, and results in cognitive impairment and memory decline [14]. Moreover, mounting evidence indicates that targeting mitochondria with antioxidants and potentially using melanin as an alternative energy source may offer a powerful treatment, which may be capable of restoring cell integrity and eliminating damage in the brain, resulting in significantly restored cognitive function and spatial memory. Further, deleted mtDNA positive signals in the damaged mitochondria of neurons, vascular endothelium and perivascular cells, indicates these cells and structures are targets of damage as well. Moreover, brain microvessels with atherosclerotic lesions revealed endothelium and perivascular cells that stained positively and in clusters when probed with wild and deleted mtDNA probes. These mtDNA deletions were associated with increased amounts of immunoreactive GRK-2, AbPP, 8OHG, and COX in the same cellular and subcellular compartments. Our In situ hybridization data, using mitochondrial DNA (mtDNA) probes for human wild type, 5 kb deleted and mouse mtDNA, together with immunocytochemistry using antibodies against AßPP, 8-hydroxyguanosine, the three isoforms of nitric oxide synthase (neuronal, inducible and endothelial specific NOS), GRK-2 and cytochrome c oxidase (COX) demonstrated that treatment with mitochondrial antioxidants [Acetyl-L-Carnitine plus alpha Lipoic Acid (ALCAR+LA)] was protective [14]. In addition, ApoE4 associated factors reduce CBF gradually to create brain hypoperfusion when compared to WT and the differences in CBF are greatest as animals age from 6-week to 12-month, ant this is a key factor in diminished cellular metabolism and energy for cellular functions. We measured age-dependent effects of the human ApoE4 on cerebral blood flow (CBF) using ApoE4 transgenic mice compared to age-matched wild-type (WT) mice by use of [^{14}C] iodoantipyrene autoradiography. The CBF changes associates structural damage in young and aged microvessel endothelium of ApoE4 animals extended to the cytoplasm of perivascular cells, perivascular nerve terminals and hippocampal neurons and glial cells. Moreover, mitochondrial structural alteration coexists and mitochondrial DNA overproliferation and/or deletion in all brain cellular compartments. Most

likely, further, complex of these alteration can lead to blood brain barrier (BBB) failure and breakage during the development of AD [14]. In contrary to this observation the animals that received mitochondrial antioxidants treatment showed an absence of any cellular or subcellular abnormality in brain cellular compartments. Spatial memory and temporal memory tests showed a trend in improving cognitive function in agedrats and ApoE4 mice fed selective mitochondrial antioxidants ALCAR & R-alpha-Lipoic acid [14]. While looking for alternate energy sources, we became aware of a biologic protein melanin possessed a striking ability to create energy by melanin, a substance also known chemically as polihydroxyindol, has unique properties that most likely able to reverse cellular energy deficits, in mitochondria, or correct paucities in energy metabolism. One role of melanin is protecting tissues from various wavelengths of light. However, it also serves as a sensing compound for primitive life forms, even a major constituents of eyes in cephalopods [8]. The principle implies that melanin captures photonic energy and transforms it into chemical energy, similarly to the photosynthesis process as the absorption of photons from electromagnetic radiation, which brings about an ionic event. The unexpected finding that the eukaryotic cell has the capability to harvest photonic energy and use it to break the water molecule by means of a photosystem composed of Light/Melanin/Water, in order of abundance in nature, may explain an observation that animals with greater size require less energy to sustain life, and furthermore, seen their lifespan increased significantly. How this is accomplished involves melanin extracting energy from water by separating and reuniting the hydrogen atoms from the oxygen atoms. Briefly, two water molecules, plus melanin in the presence of photons of electromagnetic radiation, gives us two hydrogen molecules, an oxygen molecule and four electrons [**Figure 1**]. However, when the reaction goes in the other direction, the hydrogen and oxygen atoms reunite, giving us water and electricity, since the melanin does not undergo change but simply catalyzes the reaction without any deterioration to its molecule. The reaction proceeds in both directions and, being complementary reactions, one exergonic and the other endergonic, a cycle is established which lasts for years, as the melanin does not deteriorate. The melanin captures photonic energy and uses it to extract the hydrogen molecule from water. The time needed to recollect the energy required to split the water molecule is 3×10^{-12} seconds. One drawback is the need for a particular wavelength of light to incident on the melanin from the reaction to occur. In animals, melanin is a source of energy used by the body primarily for sight or to protect from UV photo damage and UV irradiation [15]. Interestingly, the fetal eye, 35 days into pregnancy, is completely full of melanin, and perhaps may provide energy to ocular tissues, giving credence to our quest for an energy source for tissues other than brain. How the melanin can be as source of ATP, which would be available for systemic use. Our research has met with some skepticism, since the concept that photosynthesis implies it occurs only in plants. However, in March 2007, the article "Ionizing Radiation Changes the Electronic Properties of Melanin and Enhances the Growth of Melanized Fungi", was published by Dr. Ekaterina Dadachova and her colleagues at the Albert Einstein College of Medicine, New York [15]. This article is very important, because, finally, an independent research team has made findings that are compatible with our theory that melanin has the ability to carry out photosynthesis, also reaching this conclusion by observing the biological effects of melanin. This is explainable in the sense that melanin is accepted to be ***"intractable"*** [16], which refers to the fact that it has been impossible to discern the chemical structure of melanin.

14. IMPLICATIONS OF THE MELANIN PRECURSOR IN THE TREATMENT OF NEURODEGENERATIVE DISEASES

It is widely accepted that neuronal energy crisis, cerebral hypometabolism and vascular hypoperfusion are major and potentially treatable contributors to the loss of functioning in patients with Alzheimer disease (AD). As we described in the previous section, recently we have found an unexpected capacity for melanin to dissociate water and aid in deriving energy in the process. We hypothesize that melanin can be used as a new and more effective therapeutic approach in the treatment of AD patients. In addition, recent report from our group [14] demonstrated the E4 isoform of apolipoprotein E (ApoE) is involved in cardiovascular and cerebrovascular disorders and is the most prevalent risk factor for late onset or sporadic AD. Taking into the account this fact we have also determined the long-term effect of combined treatment (medications and non-pharmacological interventions) in the clinically depressed/demented and AD patients with cardiovascular risk. This study applies the vascular dementia paradigm to ApoE4 Tg+ mice in order to analyze the effects of selective mitochondrial antioxidants ALCAR+LA on the cerebral blood flow (CBF), neuropathology, brain and vessel ultrastructural abnormalities and behavior. We have also compared these results with our ongoing clinical study of clinically depressed and/or demented seniors with cardiovascular disease symptoms. Patients receive ALCAR+LA, Omega-3-6-9 from Fish, Flax and Borage Oils, Coenzyme Q-10, and Melanin analogues QIAPI-1, along with a

combination of multivitamins and trace elements (selenium) and dietary changes as part of our recently developed brain activation program [19-22]. The effects of treatment were analyzed by using MMSE and a continuous visual learning task [19-22].

We have found that ApoE4 associated factors gradually reduced CBF and created brain hypoperfusion when compared to wild-type (WT). The differences in CBF were the greatest in animals aged 6-weeks to 12 months. Transmission electron microscopy (TEM) with colloidal gold immunocytochemistry and in situ hybridization using human and mouse DNA probes showed structural damage and mitochondrial DNA overproliferation and/or deletion in young and aged microvessels endothelium of ApoE4 animals, extending to the cytoplasm of perivascular cells, perivascular nerve terminals, hippocampal neurons, and glial cells. Spatial and temporal memory tests showed a trend towards improving cognitive function in ApoE4 Tg+ mice that were fed selective mitochondrial antioxidants ALCAR+LA [14]. Patients that received combination of selective mitochondrial antioxidant plus the Melanin analogue (QIAPI-1) both in combination with our recently developed brain exercising program. Results from this pilot study showed that patients who received the combination of mitochondrial antioxidants and QIAPI-1 presented the maximum significant cognitive improvement at the end of 24 months of treatment [19-22]. The maximum significant cognitive improvement was seen with the combined treatment in MMSE, attention, memory, naming, construction, clock drawing, verbal fluency, and Ruff Frontal Fluency tests [19-22]. In addition, this group also showed that rest of the tests no signs of decreases and/or decline below base line for the entire period of the treatment. Our clinical results showed that patients who received integrative treatment with mitochondrial antioxidants, selenium and QIAPI-1 exhibited the most significant cognitive improvement at the end of 36 months of treatment [19-22]. This study demonstrated that the further examination of the potential pharmacologic modulation of brain hypometabolism by using human photosynthesis compounds such as selective mitochondrial antioxidants and Melanin analogue represents a completely new and more effective strategies to treat Alzheimer and/or other dementia types. Therefore, this pilot study demonstrate that further expanding this study to large group of patients able to provide much more accurate and conclusive background regarding new and more effective treatment strategies which based on the brain hypometabolism and neuronal energy crisis theory to fight against for these devastative diseases [19-22]. Future the perspective of human photosynthesis, that provide one great unifying principle; it is no accident, therefore, that many biological networks exhibit area-preserving branching, even though different anatomical designs exploit different hydrodynamic principles. In our knowledge, we could and must divide nutrition in two parts: Energy (absorbed from the electromagnetic spectrum, visible and invisible) and building blocks taken from the meals ingested. If we expressed the concept in other words then we have: Glucose is only a source of biomass, water is the source of energy. Based on our current knowledge most likely Kleiber's law obeys the general characteristics of electromagnetic radiations and their physicochemical interaction with melanin and water. Therefore, the discovery of the Human Photosynthesis, or more exactly, animal or mammals photosynthesis is the ultimate explanation for the long-standing mystery of Kleiber's law. Our hypothesize is that most likely this presents a step forward in the better understanding why the size of living subjects is of such fundamental importance that able to provide not only new knowledge for the better understanding of the fundamental biological process but also more effective and successful treatment strategies against many devastating diseases in the near future [14,19-22].

15. CONCLUSION AND FUTURE PERSPECTIVES

Evolution by natural selection is one of the few universal principles in biology, written by West, Brown and Enquist in an article published on June 4, 1999 [8]. Evolution has shaped the structural and functional design of organisms in two important ways. First, they said, it has tended to maximize metabolic capacity, because metabolism produces the energy and materials required to sustain and reproduce life. And yet, the discovery of ***"Human Photosynthesis"***, or the unexpected capability of melanin to split the water molecule, radically changes this widely accepted concept: Metabolism drives the interaction between energy and the building blocks that our body takes from the food we ingest, because metabolism is not an energy producing system, it solely represents the interplay among the building blocks obtained from food and our energy requirements; requirements that our organism takes from water. West, Brown and Enquist also wrote that metabolic capacity has been maximized ***"by increasing surface areas where resources are exchanged with the environment"***. Under the principles of ***Human Photosynthesis*** this enunciate is correct: the larger the surface is, the more exchange there is with the environment; that exchange is also applicable to light, or in a more descriptive way, to electromagnetic radiations, visible and/or invisible pathways.

The second important achievement evolution has brought, as cited by West, Brown and Enquist, is the tendency to maximize internal efficiency by reducing dis-

tances over which materials are transported and hence the time required for transport. And a further consequence of evolution is the incredible diversity of body sizes, which range over 21 orders of magnitude, from 10 - 13 g (microbes) to 108 g (whales). So, what are the consequences of a change in size? Are there upper and lower limits to the size of living organisms? Mycoplasma or pleuropneumonia-like organism (PPLO) is the smallest organism we know that is able to live and reproduce by itself in an artificial medium. It is so small, that, if the aqueous contents of the cell are at neutral pH, there will be, on the average, no more than two hydrogen ions inside the cell. Because the macromolecules that carry the metabolic and genetic functions are essential, and their size probably cannot be reduced, the Mycoplasma cell well represents an ultimate lower limit for the size of a living organism. A fundamental problem to understand, West, Brown and Enquist say, is how to exchange surfaces and transport distances change, or scale, with body size. In particular, a longstanding question has been why metabolic rate scales as the 3/4-power of body mass. Biological scaling can be described by the allometric equation Y = YoMb, whereas Yo varies with the trait and type of organism, b characteristically takes on a limited number of values, all of which are simple multiples of 1/4. The question has been why the exponents of the diameters of tree trunks and aorta scale as M3/8 rates of cellular metabolism and heartbeat as M-1/4, and whole organism metabolic rate as M3/4, are multiples of 1/4 rather than 1/3 as expected on the basis of conventional Euclidean geometric scale. The answer is quite simple: a larger surface area gives more capability for electromagnetic absorption, a principle similar to that of antennas. Proposed models was based on fractal-like architecture of the hierarchical branching vascular networks that distributes resources as molecules that eventually will go into endergonic reactions, within organisms accurately predict scaling exponents that have been measured for many structural and functional features of mammalian and plant vascular systems, however it is very difficult to fit with the ubiquitous 3/4-power scaling of metabolic rate in diverse kinds of organisms with their wide variety of network designs, and especially in unicellular algae and protests, which have no obvious branched anatomy. However, a more general model was based on the geometry rather than hydrodynamics, and maximizing metabolic capacity by means of the rate at which energy and material resources are taken up from the environment. This is equivalent to maximizing the scaling of whole-organism metabolic rate, B, that is limited by the geometry and scaling behavior of the total effective surface area, a; across which nutrients (e.g. glucose) and energy (sunlight in animals and plants) are exchanged with the external or internal environment. The effective surface area is "maximally fractal" and the network structure is volume-filling. It is in this sense that organism has exploited a fourth spatial dimension [17] by evolving hierarchical ***fractal-like*** structures to maximize resource acquisition and allocation. By understanding the harnessing of solar energy by animals, the trend of evolution towards an effective surface is clearly valued. Future the perspective of human photosynthesis, that provides one great unifying principle; it is no accident, therefore, that many biological networks exhibit area-preserving branching, even though different anatomical designs exploit different hydrodynamic principles. Although living things occupy a three-dimensional space, their internal physiology and anatomy operate as if they were four-dimensional. Quarter-power scaling laws are perhaps as universal and uniquely biological as the biochemical pathways of metabolism, the structure and function of the genetic code, and the process of natural selection. The vast majority of organisms exhibit scaling exponents very close to 3/4 for metabolic rate and 1/4 for internal times and distances. These are the maximal and minimal values respectively, for the effective surface area and linear dimensions for a volumefilling fractal-like network. On the one hand, this is testimony of the power of natural selection, which has exploited variations on this fractal theme to produce the incredible variety of biological form and function. On the other hand, it is testimony to the severe geometric and physical constraints on metabolic processes, which have dictated that all of these organisms obey a common set of quarter-power scaling laws, dictated mainly by the absorption of radiation or size of the wavelength absorbed, that is why it seems like general behavior or rather a general law. By the early 1930s, physics was a mature science abounding in universally applicable laws mainly because the matter of study of Physics exhibit a behavior and characteristics that are constant in more or less degree. In comparison organism biology was overwhelmingly descriptive and lacked quantitative expressions that could apply to a broad range of animals or plants because the living thing seems to have a wide diversity. In 1932, Max Kleiber changed all that when he published a paper on "Body size and metabolism" in Hilgardia which included a graph plotting the log of the body weight of mammals against the log of their basal metabolic rate (BMR). Although this initial data set was rather limited, it contained mammals ranging from rats to steers, a range of body weights spanning three orders of magnitude. As BMR measures energy expenditure at rest, in a post-absorptive state (digestion increases metabolism) and in a thermo neutral environment, it conveys fundamental information about animal's nutrition needs and allows fascinating intra- and site-specific comparisons. Hundreds of BMRs are now available for both cold and warm-blooded (exo-

thermic and endothermic) species, and they confirm Kleiber's 3/4 laws across 21 orders of magnitude, from unicellular organism to whales. Even more, Knut Schmidt-Nielsen has concluded that the 3/4 slope is representative for all ectotherms. And the explanation from the point of view of Human Photosynthesis is quite simple: the 3/4 slope obeys to the nature of light absorbed, visible and invisible, because melanin has the capacity to absorb all kinds of energy, the totality of the electromagnetic spectrum, even gravitons. From now on, we could and must divide nutrition in two parts: Energy (absorbed from the electromagnetic spectrum, visible and invisible) and building blocks taken from the meals ingested. If we expressed the concept in other words then we have: Glucose is only a source of biomass, water is the source of energy. Fractal geometry has given us an added dimension, allowing us to understand a bit more of the general principles of biology, however, what is really important for all living beings is optimizing the absorption of photonic energy. All living thing obey the rules of scaling discovered by Max Kleiber [5], and in turn Kleiber's law obeys the general characteristics of electromagnetic radiations and their physicochemical interaction with melanin and water. Therefore the discovery of the Human Photosynthesis, or more exactly, animal or mammals photosynthesis is the ultimate explanation for the longstanding mystery of Kleiber's law. We theorize that, most likely this presents a step forward in better understanding why the size of living subjects is of such fundamental importance that is not only able to better understanding many human diseases but more effective treatment strategies against for these devastating and incurables diseases [14,19-22].

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