[Frontiers in Bioscience, Landmark, 22, 982-990, January 1, 2017]

Third phase science: defining a novel model of research into human ageing

Marios Kyriazis[1]

[1]*ELPIs Foundation for Indefinite Lifespans, York Road, London TW10 6DR*

TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Discussion
3.1. The three phases of scientific inquiry
3.2. The patient in the context of the environment
3.3. Item-based, physical therapies
4. The alternative model
5. Conclusion
6. Acknowledgement
7. References

1. ABSTRACT

While the current paradigm of research into ageing relies heavily upon reductionist premises, and it has clearly not produced any of the dramatic benefits anticipated in our fight against ageing, the majority of scientists are hesitant, unable or unwilling to consider different or alternative models. In this paper I will discuss some of the shortcomings of a reductionist view of research aimed at finding treatments against ageing degeneration, and I will highlight several areas where proposed future treatments for basic age-related degeneration may be vulnerable to severe criticism. As an alternative model, I will attempt to present a different integrative concept of research which may result in a decrease of the impact of ageing, in participating humans. This model is based on a more inclusive worldview, examining the relationship between humans and their environment, the integration of humans with technology, and the biological consequences of an increasingly techno-cognitive ecosystem.

2. INTRODUCTION

History is littered with examples of people who tried to 'cure ageing' (1). From time immemorial scientists, alchemists, adventurers, philosophers, quacks and ordinary people have embarked on a quest to find an 'elixir of youth' which can lead to 'eternal life' or 'immortality'. In modern times, this quest continues but under the guises of more sophisticated terminology: 'rejuvenation biotechnologies' (2), 'stem cell therapies', (3) 'anti-senescence drugs' (4), and similar (5). This ideology, from the time of the Sumerian hero Gilgamesh to today's anti-ageing science, has one underlying common assumption: that it may be possible to eliminate age-related degeneration by treating it with a physical item such as an elixir, a drug, a pill, an injection, an intervention, a medical procedure (6). In other words, the entire model of research into ageing has been biased towards reductionism, and relies on a simplified ideal: thinking in terms of a physical object (7). This reflects an ancient predisposition of humans to believe in the value of individual therapies which can be given by a healer to the patient in order to effect a cure. This approach may be entirely wrong when it comes to treatments aimed, not at individual age-related conditions such as dementia, arthritis or the menopause, but at the underlying process of ageing itself (8). Although research has identified many drugs and supplements which can lessen some of the damage related to the passage of time, there is currently nothing that can eliminate this damage completely, and thus dramatically extend lifespan (9).

Therefore, perhaps now the time has come to consider a novel approach and a different way we approach this issue. Instead of searching for a drug, injection, procedure etc. in other words, something concrete, material, or tangible, in the hope that this will reduce the rate of age-related mortality, we should, instead, consider the abstract. Instead of continuing to see this subject in magnification (magnified cells, tissues, enzymes, DNA etc.), we should look at it in miniaturisation (in other words, 'zoom-out') (see video link https://www.youtube.com/watch?v=9XUaptg2Bl8). That is, we should examine how the human organism aligns itself in relation to society, the planet, the universe. With this in mind we may be in a better position to define a novel model of research by which humanity can become less sensitive to ageing.

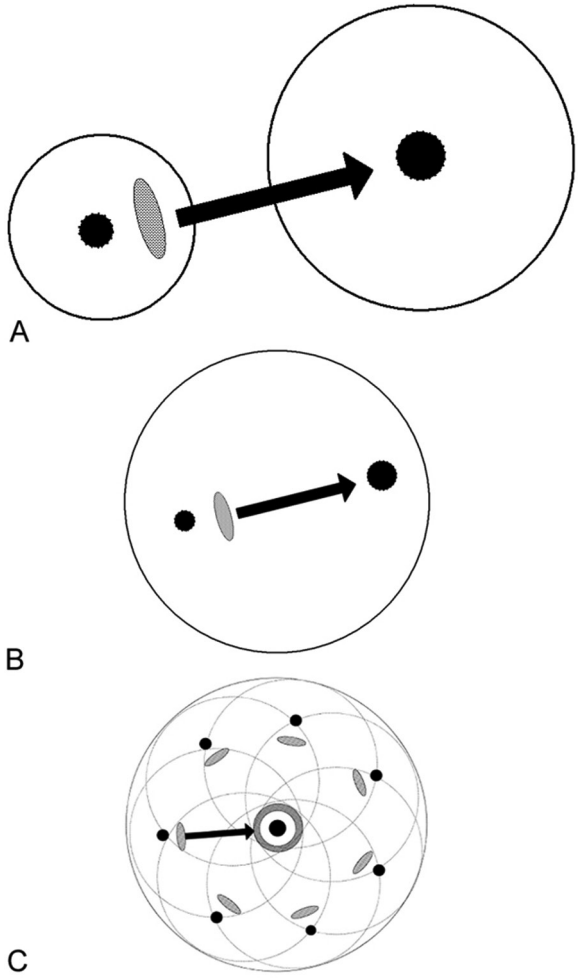

Figure 1. A. First Phase science: detached observer. B. Second Phase science: immersed observer. C. Third Phase science: Multiple Immersed Observers with multiple, interacting perspectives. Adapted with permission from (16).

3. DISCUSSION

3.1. The three phases of scientific inquiry

I posit that we need to move away from existing established models of research, and embrace more comprehensive narratives which reflect real life more closely. Until recent years, scientific inquiry was based principally on a reductionist 'First Phase science' model (10). This model was shaped by Descartes (11) among others, who envisaged a distinction between an objective world and a subjective one, with a detached observer separated from the object he was studying by a distinct mental barrier (Figure 1A). This model sees individual object-based therapies as well-defined objects that exist independently and are separate from the human patient. It soon became clear that this model cannot adequately be applied in complex situations, and thus the Second Phase science concept was developed. In Second Phase science, the observer is 'immersed' in the observation (Figure 2). The act of observation becomes a participating variable which may cause the system under study to react to this observation. Typical examples here include the reciprocal relationship between psychoanalysts and their patients, unblinded clinical trials, as well as therapeutic procedures which change and adapt according to the needs of the patient (12), so these interventions are shaped following feed-back from the patient himself. In Second Phase science the experience of reductionism persists, when the properties of the observed 'object' are reduced to individual elements which are expected to be valid across domains. This model is applied within the context of current research thinking, which believes that ageing is a process that can potentially (and mechanically) be reduced to individual components. However, this model is false because the rationale behind it is false. Ageing-related mechanisms adapt, change and respond to influences originating from the environment at large (13) and this includes not only biological, but also cultural, social and technological stimuli.

Here we need to take into account not just the individual patient and/or the individual therapist, but we also need to consider how these entities interact between them and with their environment. In this case, the Third Phase science model can appropriately be employed, a model of thinking that sees human beings as integral elements within a wider ecosystem (14) and it involves the study of adaptation to complex social situations (15). In Third Phase science, there are different interacting viewpoints which create more complexity and multi-dimensionality. The influences and viewpoints of the observer interact with those of other observers and result in a diversity of viewpoints which may form a more comprehensive overall picture (Figure 1C). In this model, the result is more dynamic, complex and integrative, representing a situation which is closer to a real-life situation. This model may describe the complexity of the human organism in much more accurate terms compared to the two other models of science. The model describes variable range correlations, when interactions at a local level may exhibit global effects, and also when global patterns affect local elements, a situation we typically encounter when we attempt to treat a complex organism in real life.

3.2. The patient in the context of the environment

One of the difficulties in using an object-oriented therapy is based on the phenomenon of emergence, or 'Nonadditive Determinism (17). This stipulates that the properties of a system are not predictable by the simple sum of the system's individual components (18). In addition, the separation of the observer from the object of the observation creates problems which become irrelevant when the object of the observation is examined within the context of its environment. In a classic experiment, the effects of the administration of

Table 1. Major predictors of non-adherence (33)

Item	Reference
Psychological problems - particularly depression, and also cognitive impairment which is common in older people who would be candidates for treatment with rejuvenation biotechnologies	(34)
Asymptomatic disease - which would be an issue in younger healthy people who enroll for the treatment	(35)
Side effects of the medication - likely to be several, as a wide range of therapeutic interventions will be deployed	(36)
Administrative issues - such as inadequate follow-up or discharge planning, poor relationship between patient and provider, missed appointments, lack of health insurance, and cost	(37)
Complexity of the treatment	(38)

amphetamine or placebo to nonhuman primates were examined and assessed (19). The assessment of each individual primate did not show any significant effects, but when each primate's position in the social hierarchy was considered, there were emergent effects. Amphetamine administration assessed in the context of the primates' social environment showed that there was amplified dominant behaviour in those primates who occupied high ranks in their society, and increased submissive behaviour in primates who were in the lower ranks of the social hierarchy.

Cacioppo and Berntson (18), discussed the principle of Reciprocal Determinism which identifies mutual influences between biological and social factors, influences which do not become evident when only the biological or only the social aspect of the behaviour is considered. This is a crucial element that needs to be taken into account when we want to devise suitable models for therapy of age-related degeneration. A biological approach alone is insufficient in making progress with regards to any appropriate interventions. Instead, the socio-cultural milieu of the target patient needs to be considered (20). The science of Social Genomics is a testament to the concept of a gene-society interaction, and it suggests that biological functions are inherently and mutually dependent upon the social environment (21).

The search for a single object (or multiple-object) therapies reflects an ideological narrative that has, inappropriately, been elevated to a universal paradigm which appeals to emotions more than it is grounded in science. It relies on the charisma of its proponents and it is not testable as an ideology, because with the failure of every proposed treatment, *ad hoc* counterarguments such as the issue of inadequate research funding is invoked, or other pretexts are put forward, which detract from the true reason of the failure.

3.3. Item-based, physical therapies

When I discuss the difficulties associated with the current model for seeking therapies against ageing, I refer specifically to therapies aimed at the background, continual process of ageing which leads to disease. Here, I define ageing as 'time-related dysfunction'. I fully acknowledge that certain current models of research may provide appropriate therapies for individual age-related conditions such as dementia, cardiovascular disease, age-related macular degeneration etc. My argument is about therapies used in order to eliminate age-related degeneration, thus radically extend lifespan and achieve what has been termed 'Negligible Senescence' (22) a situation whereby the age-related rate of human mortality tends to zero.

If we consider the case of individual drugs used against ageing, such as Rapamycin (23), metformin (24), and sirtuins (25) we immediately run into problems. For instance, pharmaceutical therapies have effects and interactions which are not easily predictable (8). The pharmacodynamics of complex therapies obey rules and principles based on non-linearity, which means that the output (the result of the treatment) does not necessarily depend on the input (the modality of the drug therapy). This system displays a chaotic behaviour which may be impossible to calculate (8). There are several other shortcomings associated with a physical–oriented approach to treating ageing. One such shortcoming, significant in my view, is the issue of non-compliance to a physical treatment, even if such a treatment existed. I quote from one of my papers (8):

> The fact that an effective therapy against ageing may theoretically be developed in the laboratory, does not necessarily align with the actual use of this therapy by the public. It is well known that non-compliance is a widespread problem in medicine (26) and, even in life-threatening conditions, the use of life-saving therapies can be suboptimal (27). For example, it was shown that only 75% of coronary heart disease patients take sufficient medicine for it to be effective (28). An example comparable to therapies for ageing rejuvenation is that of antiretroviral medication which can save a patient from certain death from AIDS. In this case, it was found that up to 37% of patient may be non-compliant (29). Another study shows that suboptimal adherence may be a problem in 50% of patients (30). Worsening compliance is proportional to the number of drugs taken (31). It is also inversely proportional to the number of times a patient has to take the therapy each day. If a patient has to take the medication once a day, the average compliance rate is 80%. This drops to 50% for those who have to take their medication four times a day (32). However, there are several other predictors of non-compliance, all of which add unknown variables to the problem (Table 1).

During the application of standard models of research, we often encounter the principle of Downward Causation. This cybernetic principle states that "all processes at the lower level of a hierarchy are restrained by and act in conformity to the laws of the higher level" (39). This means that we will be unable to calculate the effects of a treatment because of the inherent complexity and non-linearity of biological systems. Repairing or replacing a gene or molecule for instance (according to the current research model), will have unpredictable effects on the entire organism, effects that cannot be reduced to individual elements.

There are other problems associated with the existing model which is based on reductionist first and second phase science principles: These problems include the unpredictable multiplication of random errors in the repair process (the repair that is effected by the drug, even if such a drug existed). These random errors accumulate with each treatment session and affect the dynamical configuration of the cells and molecules in the organism (40). The science of Molecular Pathological Epidemiology asserts that there are multiple, inherently heterogeneous, interacting processes which may lead to a disease, and that these processes may affect individual patients in different unpredictable ways (41). Therefore the treatment modality must be tailored to the individual patient and cannot be developed as a generic, fit-all treatment (42).

Existing models of research into the ageing process (including rejuvenation biotechnologies) may be subjected to another conceptual obstacle. The aim of many medical biotechnologies is to develop advances in fault prediction and develop ways to mitigate the effects of any molecular, cellular or organ failure. However, due to the complexity of the human organism it may be difficult or impossible to predict and repair all possible faults in the system. It has been proposed (43) that a strategy of autonomous self-repair could be a better way of repairing a failing organism. Repairing a faulty element, or replacing a faulty gene may not give the expected result exactly because this particular gene or structure may be involved in processes which may give unpredicted end results.

According to the cybernetic Engagement Axiom (44), the capacity of a network of stakeholders to implement a plan of action depends strongly on the true engagement of these stakeholders in designing it. Designing action plans in order to address complex problems requires the engagement of the community of stakeholders in the design process. Disregarding the participation of the stakeholders is unethical and the plans are bound to fail (45). Currently held views about treating ageing do not make allowances for the proper application of the Engagement Axiom. They do not account for inclusion of the stakeholders (the patients), but passively offer treatments to recipient patients who just submissively accept the treatment offered.

It is important to highlight that the narrative of a single-object anti-ageing therapy shares several characteristics with mythical models of 'tales' instead of true science. Tales depend on the opinion of the proponent (the story teller) whereas science is objective. Tales contain suspense and mystery, and depend on the period context (in the Middle Ages the 'immortality elixir' was to be found in a chalice, in modern times it is a drug or a stem cell intervention), whereas science is based on universally valid principles that transcend time and place. There is certainly significant mystery and suspense shrouding the research in defining an 'elixir of youth' type therapy. Proponents of different treatments are often seen as cult-like figures who are:

- Characterised by great veneration and excessive devotion (e.g. Ray Kurzweil) (46)
- Considered to be unorthodox or extremist by conventional society, and have a simplified goal structure such to introduce something to everyone (e.g. SENSe) (47)
- Their messages are vague and fuzzy (e.g. Google Calico) (48), promising universal rejuvenation in return for funding the founder's efforts (49).

4. THE ALTERNATIVE MODEL

Due to the above issues, it is necessary to consider a different model of research that may be effective in reducing the impact of ageing. A model that is not based on searching for a physical item but on something more abstract and immaterial (50). Therefore, we return to the model based on third phase science, embracing a wider view of humanity (51). The interaction of modern humans with technology, and the changes in society and culture based on these interactions, are impacting on our biology and may be invoking mechanisms and pathways that can lead to improved health (52). I have argued elsewhere that our continuous integration within a techno-cultural environment (basically a 'human-computer merge') may enable certain mechanisms which are heavily dependent upon epigenetics (53) to operate in a way that shifts the allocation of repair resources from the germ-line to the soma, and thus promote a more effective somatic repair activity leading to a reduction of the rate of mortality due to chronic age-related degeneration (54).

We are currently experiencing a new stage in human evolution, an extension of 'gene-culture' coevolution (55, 56) when adaptations to our technological environment facilitate health and, at the same time, influence the evolution of the environment itself (57), characteristics which define the third phase science model. Social genomics principles are employed in order to study these interactions, from a joint point of view: biological and socio-cultural.

The fact that we are developing and will continue to develop a deeper relationship with technology, necessarily has an effect on our biology and brings some

hitherto unprecedented changes the human body (58). When we interact and merge with technology, then information and data from our environment are integrated in specific parts of the brain (such as the amygdala and prefrontal cortex) and up-regulate the stress response in neurons. These neurons generate stress response sensor molecules such as:
IRE-1 (59)

- PERK- (Protein kinase RNA-like endoplasmic reticulum kinase (60)
- ATF6 (activating-transcription-factor-6) (61)
- c-Jun N-terminal kinase 1 (JNK) (62)

which improve signaling and result in overall positive effects on our body, such as an increase in the rate of repairing damage associated with ageing. When we become indispensable agents (creative actors) within a high-level cognitive ecosystem, we initiate a series of upregulation sequences and involvement of certain evolutionary functions such as degeneracy (63), exaptation (64) including exaptation of transposable elements (65), adaptive response (an appropriate reaction to an environmental demand) (66, 67) and others, which cause our body to repair the ageing damage and thus completely avoid chronic degenerative diseases such as arthritis, heart disease, senile dementia, Alzheimer Parkinson etc. In this way, the life span will increase dramatically (68).

5. CONCLUSION

In this paper I have argued that any models purporting to manage the ageing process cannot be effective if these are based on discrete physical interventions. These interventions suffer all the shortcomings of a reductionist philosophy, fail to consider the human body as a complex adaptive system, and ignore emergent phenomena. Our experience suggest that ageing can be eliminated completely from certain human groups (20), but this is impossible to accomplish with bio-medical technologies or pharmaceutical interventions. Instead, the elimination of ageing must occur following certain events dependent on human evolution, the characteristics of natural laws, and the deepening interaction of humans with modern technology (69).

6. ACKNOWLEDGEMENTS

I would like to thank John Stewart, Michael Singer and Yiannis Laouris for general discussions during the preparation of this concept.

7. REFERENCES

1. I Stambler: A History of Life-Extensionism in the Twentieth Century, Rison Lezion, Israel (2014)
2. AD de Grey: Rejuvenation Biotechnology: The Industry Emerges, but Short-Termism Looms. *Rejuvenation Res* 19(3), 193-4 (2016) DOI: 10.1089/rej.2016.1846
3. IM Conboy, MJ Conboy, J Rebo: Systemic Problems: A perspective on stem cell aging and rejuvenation. *Aging (Albany NY)* 7(10),754-65 (2015) DOI: 10.18632/aging.100819
4. Y Zhu, T Tchkonia, T Pirtskhalava: The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. *Aging Cell* 14(4), 644-58 (2015) DOI: 10.1111/acel.12344
5. DM Huffman, MJ Schafer, NK LeBrasseur: Energetic interventions for healthspan and resiliency with aging. *Exp Gerontol*. pii: S0531-5565(16)30147-4 (2016) (doi not found)
6. L Demontis: Comparative Analysis of Medieval and Modern Scientific Research on Ageing Reveals Many Conceptual Similarities. *Gerontol & Ger Res* 4/3: 216, 1-4 (2015) DOI: 10.4172/2167-7182.1000216
7. M Kyriazis, A Apostolides: The Fallacy of the Longevity Elixir: Negligible Senescence May be Achieved, but Not by Using Something Physical. *Curr Aging Sci* 8(3), 227-34 (2015) DOI: 10.2174/1874609808666150702095803
8. M Kyriazis: The impracticality of biomedical rejuvenation therapies: translational and pharmacological barriers. *Rejuvenation Res* 17(4), 390-6 (2014) DOI: 10.1089/rej.2014.1588
9. BA Carnes, SJ Olshansky, L Hayflick L: Can human biology allow most of us to become centenarians? *J Gerontol A Biol Sci Med Sci* 68(2), 136-42 (2013) DOI: 10.1093/gerona/gls142
10. KC Bausch: The Theory and Practice of Third Phase Science, Social Systems and Design. *Transl Sys Sci* 1, 129-145 (2014) (doi not found)
11. R Harre: Cognitive Science: A Philosophical Introduction, Sage Publications London (2002)
12. AM Hall, PH Ferreira, CG Maher, J Latimer, ML Ferreira: The Influence of the Therapist-Patient Relationship on Treatment Outcome in Physical Rehabilitation. *Phys Ther*, 90,

1099-1110 (2010)
DOI: 10.2522/ptj.20090245

13. C Gershenson, N Fernández: Complexity and information: Measuring emergence, self-organization, and homeostasis at multiple scales. *Complexity* 18(2), 29-44 (2012)
DOI: 10.1002/cplx.21424

14. GS Metcalf (Ed). Social Systems and Design. Springer Ashland USA (2014)

15. G de Zeeuw: Three phases of science: A methodological exploration. Working paper nr. 7 of the Centre for Systems and Information Sciences, University of Humberside, ISBN 1 86050 025. (1996) http://www.cict.demon.co.uk/Threephases01.PDF
(doi not found)

16. KC Bausch, TR Flanagan: A Confluence of Third Phase Science And Dialogic Design Science (2012) https://www.gwu.edu/~uscs/docs/1112/ThirdPhaseScienceandDDS%20JRP.doc
(doi not found)

17. EA Necka, S Cacioppo, JT Cacioppo: Social Neuroscience of the Twenty-First Century. The University of Chicago, Chicago, IL, USA (2015)
DOI: 10.1016/b978-0-08-097086-8.56020-6

18. JT Cacioppo, GG Berntson: Social psychological contributions to the decade of the brain: doctrine of multilevel analysis. *American Psychologist* 47, 1019-1028 (1992)
DOI: 10.1037/0003-066X.47.8.1019

19. SN Haber, PR Barchas. The regulatory effect of social rank on behavior after amphetamine administration. In: Social Hierarchies: Essays toward a Socio-physiological Perspective. Ed: PR Barchas, pp119–132. Greenwood, Westport, CT (1983)

20. M Kyriazis: Opinion Paper: A Cognitive-cultural Segregation and the Three Stages of Aging. *Curr Aging Sci* 9, 81-6 (2016)
DOI: 10.2174/1874609809666151214104202

21. SW Cole: Social Regulation of Human Gene Expression: Mechanisms and Implications for Public Health. *Am J Public Health* 103 (S1), S84–S92 (2013)
DOI: 10.2105/AJPH.2012.301183

22. J Guerin: Emerging area of aging research: long-lived animals with "negligible senescence. *Ann N Y Acad Sci* 1019, 518-20 (2004)
DOI: 10.1196/annals.1297.096

23. SI Arriola Apelo, DW Lamming: An InhibiTOR of Aging Emerges From the Soil of Easter Island. *J Gerontol A Biol Sci Med Sci* 71(7), 841-9 (2016)
DOI: 10.1093/gerona/glw090

24. N Barzilai, JP Crandall, SB Kritchevsky, MA Espeland: Metformin as a Tool to Target Aging. *Cell Meta,* 23(6), 1060-5 (2016)
DOI: 10.1016/j.cmet.2016.05.011

25. A Camins, FX Sureda, F. Junyent, E Verdaguer, J Folch, C Pelegri, J Vilaplana, C Beas-Zarate, M Pallàs: Sirtuin activators: designing molecules to extend life span. *Biochim Biophys Acta* 1799(10-12),740-9 (2010)
DOI: 10.1016/j.bbagrm.2010.06.005

26. NK Choudhry, MA Fischer, J Avorn, JN Liberman, S Schneeweiss, J Pakes, TA Brennan, WH Shrank: The implications of therapeutic complexity on adherence to cardiovascular medications. *Arch Intern Med* 171, 814-822 (2011)
DOI: 10.1001/archinternmed.2010.495
DOI: 10.1001/archinternmed.2011.176

27. 27. WF Gellad, K Grenard, EA McGlynn: A review of barriers to medication adherence: a framework for driving policy options. RAND (2009). http://www.rand.org/content/dam/rand/pubs/technical_reports/2009/RAND_TR765.pdf (Retrieved September 4, 2016)
(doi not found)

28. CA Jackevicius, P Li, JV Tu: Prevalence, predictors, and outcomes of primary non-adherence after acute myocardial infarction. *Circulation* 117, 1028-1036 (2008)
DOI: 10.1161/CIRCULATIONAHA.107.706820

29. N Singh, C Squier, C Sivek, M Wagener, MH Nguyen, VL Yu: Determinants of compliance with antiretroviral therapy in patients with human immunodeficiency virus: prospective assessment with implications for enhancing compliance. *AIDS Care* 8(3), 261-9 (1996)
DOI: 10.1080/09540129650125696

30. F Puigventós, M Riera, C Delibes, M Peñaranda, L de la Fuente, A Boronat: Adherence to antiretroviral drug therapy. A systematic review. *Med Clin (Barc)* 119(4), 130-7 (2002)
DOI: 10.1016/S0025-7753(02)73341-1

31. RH Chapman, JS Benner, AA Petrilla, JC Tierce, SR Collins, DS Battleman, JS Schwartz: Predictors of adherence with antihypertensive and lipid-lowering therapy. *Arch Intern Med* 163, 1147-1152 (2005) DOI: 10.1001/archinte.165.10.1147

32. AJ Claxton, J Cramer, C Pierce: A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 23, 1296-1310 (2012) DOI: 10.1016/S0149-2918(01)80109-0

33. I Barat, F Andreasen, EMS Damsgaard: Drug therapy in the elderly: what doctors believe and patients actually do. *Br J Clin Pharmacol* 51(6), 615–622 (2001) DOI: 10.1046/j.0306-5251.2001.01401.x

34. EJ Lenze, MD Miller, MA Dew, LM Martire, BH Mulsant, AE Begley, R Schulz, E Frank, CF Reynolds: Subjective health measures and acute treatment outcomes in geriatric depression. *Int J Geriatr Psychiatry* 16(12), 1149-55 (2001) DOI: 10.1002/gps.503

35. EM Donadiki, R Jiménez-García, V Hernández-Barrera, P Sourtzi, P Carrasco-Garrido, A López de Andrés, I Jimenez-Trujillo, EG Velonakis: Health Belief Model applied to non-compliance with HPV vaccine among female university students. *Public Health* 128(3), 268-73 (2014) DOI: 10.1016/j.puhe.2013.12.004

36. S Malhotra, RS Karan, P Pandhi, S Jain: Drug related medical emergencies in the elderly: role of adverse drug reactions and non-compliance. *Postgrad Med J* 77(913), 703-7 (2001) DOI: 10.1136/pmj.77.913.703

37. JG Shepherd, E Locke, Q Zhang, G Maihafer: Health services use and prescription access among uninsured patients managing chronic diseases. *J Community Health* 39(3), 572-83 (2014) DOI: 10.1007/s10900-013-9799-1

38. GM Cochrane, R Horne, P Chanez: Compliance in asthma. *Respir Med* 93(11),763-9 (1999) DOI: 10.1016/S0954-6111(99)90260-3

39. DT Campbell: Downward Causation in Hierarchically Organised Biological Systems. In Studies in the Philosophy of Biology. Eds: FJ Ayala, T Dobzhansky Macmillan Publishers London, 179-186 (1974) DOI: 10.1007/978-1-349-01892-5_11

40. MR Stratton, PJ Campbell, PA Futreal. The cancer genome. *Nature* 458(7239), 719-24 (2009) DOI: 10.1038/nature07943

41. S Ogino, R Nishihara, TJ VanderWeele, M Wang, A Nishi, P Lochhead, ZR Qian, X Zhang, K Wu, H Nan, K Yoshida, DA Milner, AT Chan, AE Field, CA Camargo, MA Williams, EL Giovannucci: Review Article: The Role of Molecular Pathological Epidemiology in the Study of Neoplastic and Non-neoplastic Diseases in the Era of Precision Medicine. *Epidemiology* 27(4), 602-11 (2016) DOI: 10.1097/EDE.0000000000000471

42. A Nishi, DA Milner, EL Giovannucci, R Nishihara, AS Tan, I Kawachi, S Ogino: Integration of molecular pathology, epidemiology and social science for global precision medicine. *Expert Rev Mol Diagn* 16(1), 11-23 (2016) DOI: 10.1586/14737159.2016.1115346

43. C Bell, R McWilliam, A Purvis, A Tiwari: Concepts of self-repairing systems. *Measurement and Control* 46(6), 176-179 (2013) DOI: 10.1177/0020294013492285

44. A Christakis, Y Laouris: Harnessing the wisdom of the people. The tree of social action. Proceedings of the 3rd international conference of the Hellenic Society of systems sciences, Pireus, 26-28 May, (2007) (doi not found)

45. Y Laouris, R Laouri, A Christakis: Communication Praxis for Ethical Accountability: The Ethics of the Tree of Action: Dialogue and Breaking down the Wall in Cyprus. *Sys Res Behavioral Sci* 25, 1-16 (2008) DOI: 10.1002/sres.890

46. A Goldman: Ray Kurzweil says we're going to live forever. New York Times Magazine. 25 January 2013. http://www.nytimes.com/2013/01/27/magazine/ray-kurzweil-says-were-going-to-live-forever.html?_r=0 (accessed 31 August 2016) (doi not found)

47. http://www.bbc.co.uk/programmes/p0211msj

48. M Bergen: What's He Building in There? The Stealth Attempt to Defeat Aging at Google's Calico. Recode, (2015) http://www.recode.net/2015/12/28/11621734/the-stealth-attempt-to-defeat-aging-at-googles-calico (accessed 31 August 2016)
49. http://www.sens.org
50. M Kyriazis: Editorial: Novel approaches to an old problem: insights, theory and practice for eliminating aging. *Curr Aging Sci* 4;7 (1), 1-2 (2014)
(doi not found)
51. D Helbing: FuturICT-New science and technology to manage our complex, strongly connected world (2011). http://arxiv.org/abs/1108.6.131 (accessed 26 August 2016)
(doi not found)
52. M Kyriazis: Systems neuroscience in focus: from the human brain to the global brain? *Front. Syst. Neurosci* 9,7 (2015)
DOI: 10.3389/fnsys.2015.00007
53. M Kyriazis: Information-sharing, adaptive epigenetics and human longevity. http://arxiv.org/abs/1407.6.030 (2014) (accessed 20 August 2016)
(doi not found)
54. M Kyriazis. Reversal of informational entropy and the acquisition of germ-like immortality by somatic cells. *Curr Aging Sci* 7(1), 9-16 (2014)
DOI: 10.2174/1874609807666140521101102
55. MW Feldman. KN Laland: Gene-culture coevolutionary theory. *Trends Ecol Evol* 11, 453-7 (1996)
DOI: 10.1016/0169-5347(96)10052-5
56. M Chudek, J Henrich: Culture-gene coevolution, norm-psychology and the emergence of human prosociality. *Trends Cogn Sci* 15(5), 218-26 (2011)
DOI: 10.1016/j.tics.2011.03.003
57. M Kyriazis: Technological integration and hyper-connectivity: Tools for promoting extreme human lifespans. C*omplexity* 20, 5-24 (2014)
(doi not found)
58. M Kyriazis: Clinical Effects of a 'Human-Computer' Interaction. SSRN, June 21 (2016). http://ssrn.com/abstract=2798529
(doi not found)
59. M Levi-Ferber, H Gian, R Dudkevich, S Henis-Korenblit: Transdifferentiation mediated tumor suppression by the endoplasmic reticulum stress sensor IRE-1 in C. elegans. *Elife*. Jul 20, 4 (2015)
(doi not found)
60. R Chavez-Valdez, DL Flock, LJ Martin, FJ Northington: Endoplasmic reticulum pathology and stress response in neurons precede programmed necrosis after neonatal hypoxia-ischemia. *Int J Dev Neurosci* 48, 58-70 (2016)
DOI: 10.1016/j.ijdevneu.2015.11.007
61. A Yoshikawa, T Kamide, K Hashida, HM Ta, Y Inahata, M Takarada-Iemata, T Hattori, K Mori, R Takahashi, T Matsuyama, Y Hayashi, Y Kitao, O Hori: Deletion of Atf6α impairs astroglial activation and enhances neuronal death following brain ischemia in mice. *J Neurochem* 132(3), 342-53 (2015)
DOI: 10.1111/jnc.12981
62. JJ Riches, K Reynolds: Jnk1 activity is indispensable for appropriate cortical interneuron migration in the developing cerebral cortex. *J Neurosci* 34(43), 14165-6 (2014)
DOI: 10.1523/JNEUROSCI.3222-14.2014
63. L Seifert, J Komar, D Araujo, K Davids: Neurobiological degeneracy: A key property for functional adaptations of perception and action to constraints. *Neurosci Biobehav Rev* Aug 6, S0149-7634(16)30348-7 (2016)
(doi not found)
64. GV Glinsky: Mechanistically distinct pathways of divergent regulatory DNA creation contribute to evolution of human-specific genomic regulatory networks driving phenotypic divergence of Homo sapiens. *Genome Biol Evol* Aug 8. pii: evw185. (Epub ahead of print) (2016)
(doi not found)
65. FS de Souza, LF Franchini, M Rubinstein: Exaptation of transposable elements into novel cis-regulatory elements: is the evidence always strong? *Mol Biol Evo* 30(6), 1239-51 (2013)
DOI: 10.1093/molbev/mst045
66. B Pfeuty, Q Thommen: Adaptive Benefits of Storage Strategy and Dual AMPK/TOR Signaling in Metabolic Stress Response. *PLoS One* 11(8), e0160247 (2016)
DOI: 10.1371/journal.pone.0160247

67. V Tosato, J Sims, N West, M Colombin, CV Bruschi: Post-translocational adaptation drives evolution through genetic selection and transcriptional shift in Saccharomyces cerevisiae. *Curr Genet* Aug 4. (Epub ahead of print)) (2016) (doi not found)

68. M Kyriazis: The Indispensable Soma Hypothesis. (2016) https://figshare.com/articles/New_draft_item_The_Indispensable_Soma_Hypothesis/3079732 (doi not found)

69. M Kyriazis (ed). Re-thinking ageing: a cross-disciplinary perspective (Special issue). *Mech Ageing Dev* (2017) (in press) (doi not found)

Key Words: Ageing, Degeneration, Third Phase Science, Reductionism, Rejuvenation, Biotechnologies, Techno-Culture, Review

Send correspondence to: Marios Kyriazis, ELPIs Foundation for Indefinite Lifespans, York Road, London TW10 6DR, UK, Tel: 00447850 221796. E-mail: drmarios@live.it