Open Letter to Calico and Cynthia Kenyon – Comments on Research Directions

*(**Calico Labs** is a new Google company formed to perform aging research.)*

Congratulations on your appointment as Research Director for the Google Calico Labs, a very substantially funded cutting-edge "research and development company whose mission is to harness advanced technologies to increase our understanding of the biology that controls lifespan." From the stellar cast already involved we can expect outside-the-box thinking and innovation that is badly needed in this area.

I think we agree that aging is purposely "programmed" because possession of a biological function that *causes and controls* aging creates an evolutionary advantage. My recent article *Modern Evolutionary Mechanics and Resolving the Programmed/ Non-programmed Aging Controversy [1]* describes why it is no longer possible to produce a plausible science-based evolutionary argument that programmed mammal aging is less likely than non-programmed aging and empirical evidence supporting the general existence of aging programs is steadily increasing. The current question, central to Calico's mission, therefore concerns the nature of the aging program in humans.

It seems reasonable to assume that the aging function would share characteristics common to other biological functions like digestion or reproduction such as genes, gene products, signals, receptors, coordination of activities between tissues and systems, etc. Further, many functions possess the ability to adjust their operation based on temporary internal or external conditions that affect the optimum operation of the function. It is widely agreed that local or temporary conditions (e.g. predation, famine, overcrowding, or changes in the organism's reproductive parameters) can affect the optimum lifespan for an organism and that therefore an aging function would likely have the capability for *regulating* lifespan in response to the detection of those conditions. Substantial research, some conducted by your lab at UCSF, has confirmed the existence of just such lifespan regulation. Finally, it seems very likely, that like many other mammal functions, the aging function would be coordinated by *blood signals*. Pro-aging signals could direct that tissues exhibit their aging phenotype and/or anti-aging signals could direct receiving tissues to exhibit a youthful phenotype. Substantial evidence that this is indeed the case has already been found [2].

Especially in a non-programmed context, telomere shortening has been popular as a simple cell-level aging mechanism that causes deterioration and simultaneously provides a "clock" attribute to at least grossly explain observed gradual deterioration. However, as explained above, in a programmed context, an organism-wide mechanism similar to the one that controls reproductive functions is much more likely. Reproductive functions are controlled by a complex mechanism that involves detection of external cues (e.g. planetary cycles in determining mating seasons). Nobody doubts that if we wanted to, we could delay or advance puberty or other reproductive function. If aging is mediated by a similar complex mechanism, many paths to intervention would exist. Experiments to distinguish between proposed aging mechanism concepts are

therefore essential. E.g. would changing external cues (like changing day/night period) affect aging in animals?

Harold Katcher [UMD] has proposed that *heterochronic plasma exchange (HPE)* could be used to investigate plasma signals associated with aging in humans or other mammals and possibly to even perform therapeutic anti-aging treatments in humans [3]. Plasma in an older individual would be replaced by plasma from a young individual thus reversing the signal situation for some period.

This approach has some potentially major advantages:

- Plasma exchange is a recognized medical treatment and equipment and procedures for performing it already exist thereby potentially allowing human experiments to be rapidly performed. Positive human results would have direct medical research impact and defuse the common objections "mice are not humans," "worms are not humans," etc. HPE could potentially end the interminable programmed vs. non-programmed argument and correct the current situation in which a major fraction of investigators are looking in the wrong places.

- HPE does not require that we understand the details of the aging mechanism. We do not have to understand the cell-level mechanisms that implement the aging phenotype. Nor do we have to understand the details of the upstream mechanisms (clock(s), detection of external or internal conditions that affect optimum lifespan, etc.). We do not have to *a priori* understand which blood components are involved, what tissues are generating the signals, or even if signals are assertive or inhibitory or both. HPE would be a tool for answering these questions.

Best wishes for major success for yourself and Calico! Millions of baby-boomers salute you!

Theodore C. Goldsmith, Azinet LLC November 7, 2014

[1] Goldsmith TC. Modern evolutionary mechanics and resolving the programmed/ non-programmed aging controversy. Biochemistry (Moscow). 2014 79(10) 1290-99. Full text: http://www.azinet.com/aging/programmed-aging-controversy.pdf

[2] Conboy IM, et al. Rejuvenation of aged progenitor cells by exposure to a young systemic environment. Nature 433, 760-764 (17 February 2005) | doi:10.1038/nature03260;

[3] Katcher HL. Studies that Shed New Light on Aging. Biochemistry (Moscow), 2013, Vol. 78, No. 9, pp. 1061-1070. Full text: http://protein.bio.msu.ru/biokhimiya/contents/v78/pdf/bcm_1061.pdf

[4] Goldsmith T. The Evolution of Aging, 3rd edition. 2014 Azinet Press Annapolis ISBN 9780978870959