Epigenetic Reprogramming of Aging: a new paradigm to fight aging

Tapash Jay Sarkar, Marco Quarta, Gary C Hudson, Sergio Ruiz, and Vittorio Sebastiano

Turn Biotechnologies, 110 Pioneer Way, Mountain View, California, USA • www.turn.bio

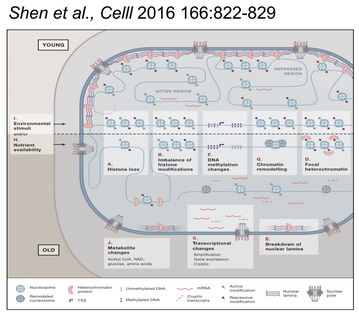
1. Abstract

Aging is characterized by a gradual loss of function occurring at the molecular, cellular, tissue and organismal levels. At the chromatin level, aging is associated with the progressive accumulation of epigenetic errors that eventually lead to aberrant gene regulation, stem cell exhaustion, senescence, and deregulated cell/tissue homeostasis. The technology of nuclear reprogramming to pluripotency, through over-expression of a small number of transcription factors, can revert both the age and the identity of any cell to that of an embryonic cell by driving epigenetic reprogramming. Recent evidence has shown that transient transgenic reprogramming can ameliorate age-associated hallmarks and extend lifespan in progeroid mice (Ocampo et al., 2016). However, it is unknown how this form of 'epigenetic rejuvenation' would apply to physiologically aged cells and, importantly, how it might translate to human cells. Here we show that transient reprogramming based on non-integrative mRNA technologies reverses hallmarks of physiological aging of human fibroblasts and endothelial cells, ameliorates disease phenotypes in osteoarthritis, and restores youthful regenerative response to aged, human muscle stem cells, in each case without abolishing cellular identity. Our method of transient cell reprogramming paves the way to a novel, potentially translatable strategy for *ex vivo* cell rejuvenation treatment. In addition, this approach holds promise for *in vivo* tissue rejuvenation therapies to reverse the physiological manifestations of aging and the risk for the development of age-related diseases.

2. Background and Rationale

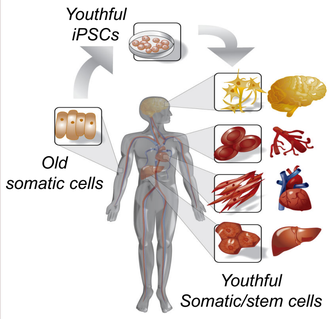
1) Aging is an Epigenetic Process (for the most part at least!) Question: Can it be Reprogrammed?

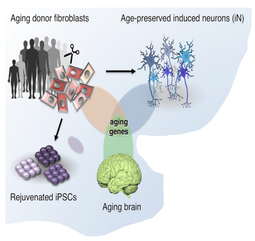
Shen et al., Cell 2016 166:822-829



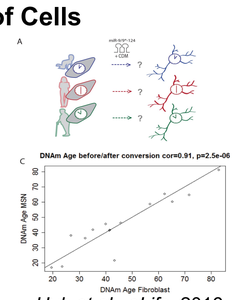
Adapted from Kazutoshi Takahashi, and Shinya Yamanaka. Development 2013;140:2457-2461

2) Reprogramming to Pluripotency (but not Direct Reprogramming) Can Revert the Function and the Age of Cells





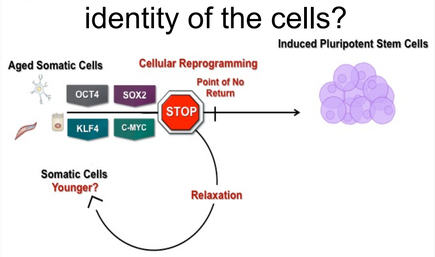
Cell Stem Cell 2015 17, 705-718



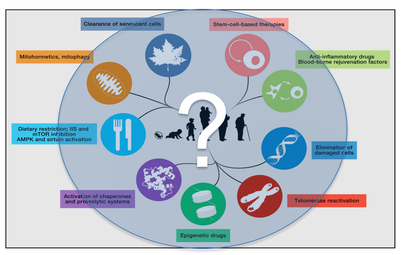
Huh et al., eLife 2016

3. Working Hypothesis

Question 1: Can tightly controlled Epigenetic Reprogramming (Transient Reprogramming) "reset" the age of the cells w/o affecting the identity of the cells?

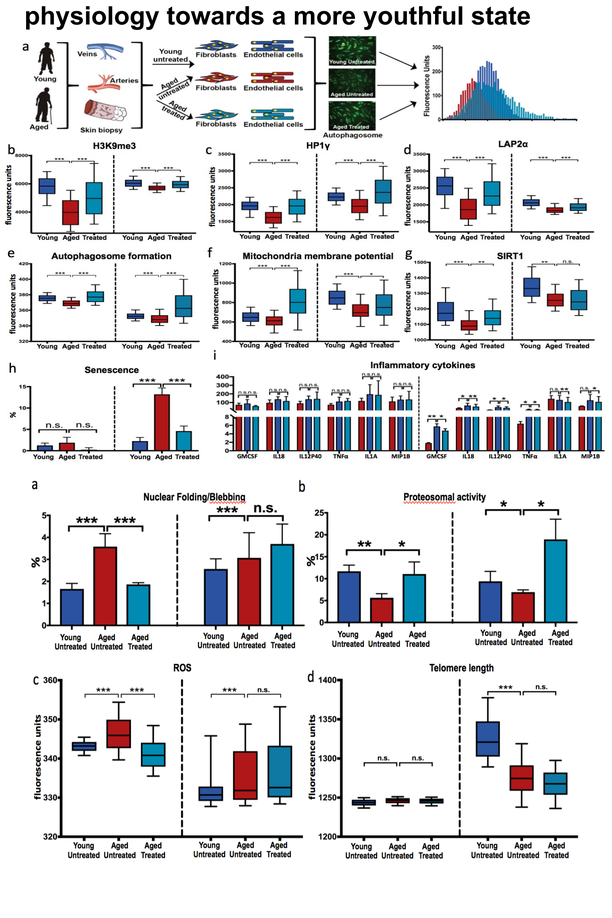


Question 2: How many different hallmarks of aging can Transient Reprogramming affect at once?

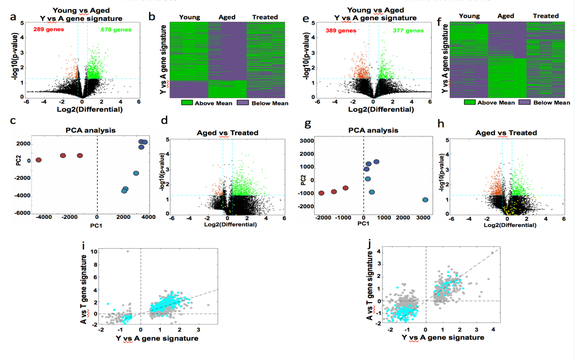


Results (1)

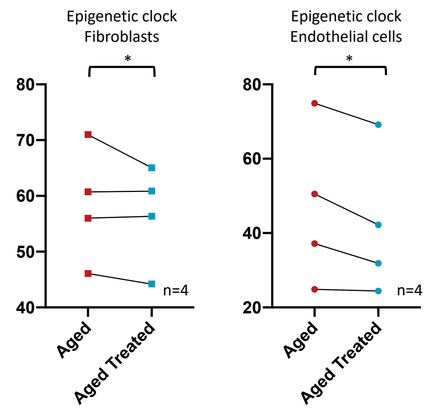
A) Transient reprogramming reverts aged physiology towards a more youthful state



B) Transient reprogramming rejuvenates cells without affecting cell identity

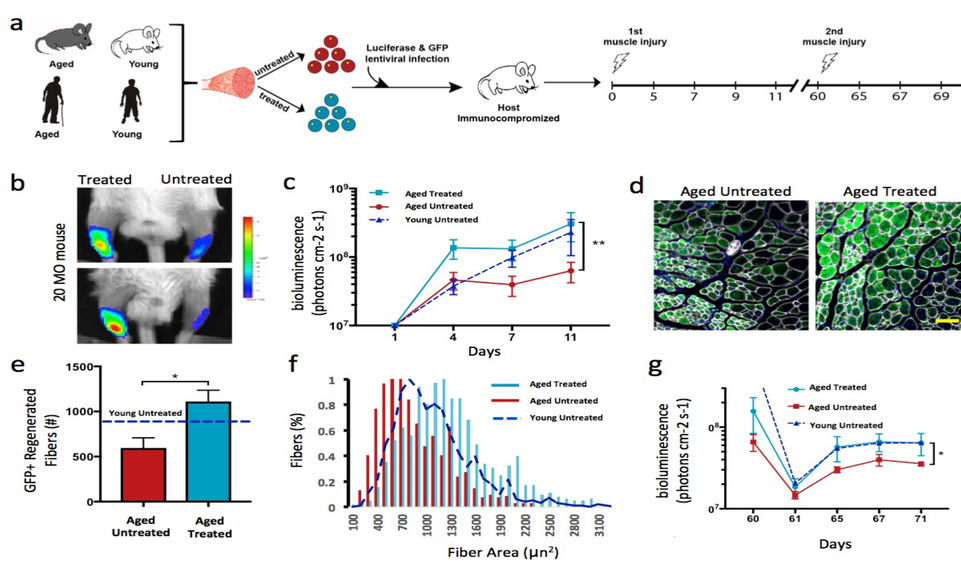


C) Transient reprogramming-based age "reset" is epigenetic

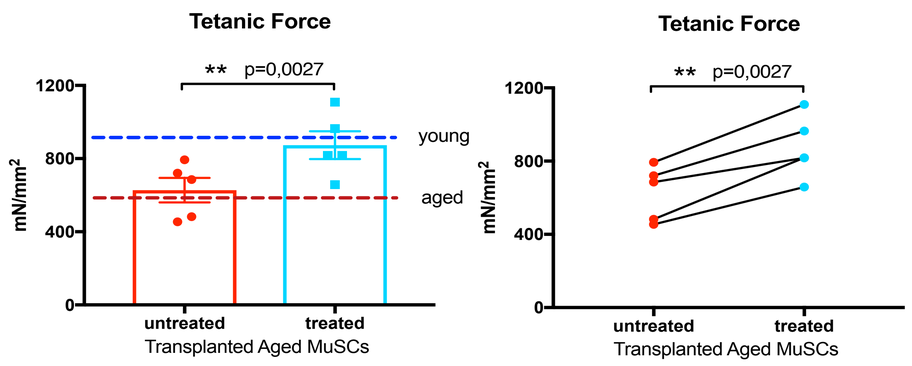


Results (2)

ERA promotes rejuvenation of Muscle Stem Cells

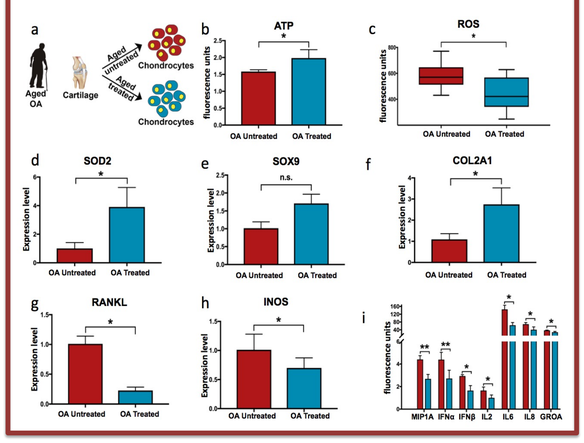


ERA as a treatment for Sarcopenia

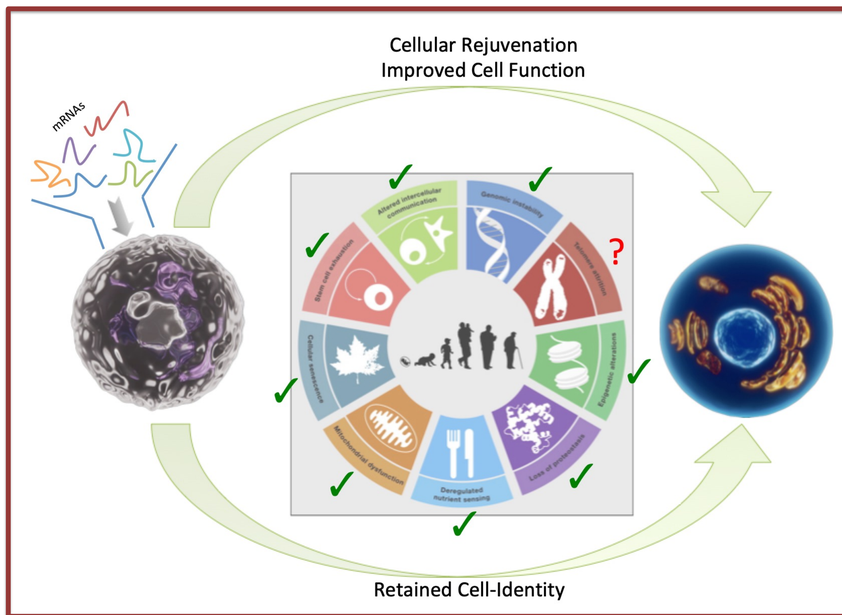


Results (3)

Transient Reprogramming promotes functional amelioration of OA chondrocytes



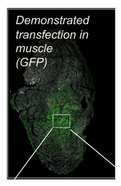
4. Summary of Results

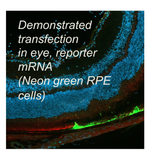


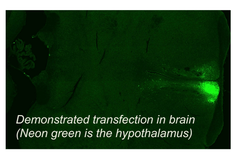
Turn Bio: Present & Future Efforts

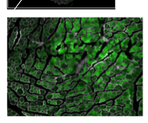
Direct reprogramming of aged cells in vivo, including muscle, the eye and the hypothalamus has been achieved

turn.bio









- **Reprogramming cells reverts aging phenotype**
- **Turn.bio offers a demonstrated platform technology that can reprogram both somatic and stem cells ex vivo**
- **We are working towards practical in vivo reprogramming using a combination of novel approaches that offer great translational promise**
- **We are ready to move to preclinical and tox studies in primates**

Founding Investors Methuselah Foundation METHUSELAH FUND