Telomere – The Twilight to Immortality

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Abstract
Besides forming a very important component of the chromosome, the telomeres have extremely significant modes of action and functions, right from maintaining a basic infrastructure and integrity of the chromosome vis a vis the other chromosomes, telomeres are responsible for the cell divisions and replicative senescence of the cell.

The number of mitotic divisions which a cell will go through in its life span while passing through the cell cycle is governed in turn by these telomeres, the crux of the entire functioning of these chromosomal components suggests that they are the ticking clocks of the cell and when they diminish or are worn out so does the cell reach it’s senility at the fag end of it's replicative life- resulting fate being - the cell is sent to it’s grave yard (the final destination).

Clinical implications include- regulation of cell life spans, regulating the cell’s replicative behavior and it’s utility in forming cells which usually are impossible to divide or replicate, telomeres regulate the cloning process, the telomeres play a major role in predicting the fate of a neoplastic cell and finally enhancing the life span of a single cell, the organ, the body as a whole by enzymes which expand the telomeres – the telomerase.

Historical Aspects
The earliest known renderings of human chromosomes were the drawings, published in 1882 by the German microscopist Walter Flemming while observing dividing nuclei from epithelial cells.

The first accurate count of the human chromosomes was achieved in 1956 by J.H.Tijo and Albert Levan, when they added PHA (Phyto Haemagglutinin) to the lymphocytes obtained from peripheral blood, to stimulate cell division, then added colchicines to arrest at the metaphase, fixed and stained and photographed the ‘X’ shaped objects of different sizes-which were in fact double chromosomes united at the centromere, which would form two complete sets of normal single chromosomes for the two daughter cells. They described 22 pairs of autosomes and one pair of sex chromosomes, XX or XY.

Early studies by Hermann Muller and Barbara McClintock showed that the ends of chromosomes are capped by a structure called the telomere to prevent chromosome fusions (Muller, 1938); (McClintock, 1941).2

In the 1970’s, as the mechanisms behind DNA replication were becoming better understood, it became clear that DNA polymerase, the enzyme responsible for DNA replication, could not fully synthesize the 3’ end of linear DNA. In 1972, James Watson called this the end-replication problem (Watson, 1972).3 At about the same time, in a Moscow subway station, Alexey Olovnikov also recognized Watson’s problem in an analogy between the track that represented the DNA and the train that represented DNA polymerase.

Yet Olovnikov went further to propose that the end-replication problem would result in telomere shortening with each round of replication and that this mechanism could be the cause of replicative senescence or RS (Olovnikov, 1971 and 1973).4,5 Soon after, studies by Leonard Hayflick and colleagues found that the nucleus controls Replicative senescence (RS). (Wright and Hayflick, 1975);6 (Hayflick, 1994).7

The Telomeres
Each eukaryotic chromosome consists of a single molecule of DNA associated with a variety of proteins.

The DNA molecules in eukaryotic chromosomes are linear; i.e., have two ends. (This is in contrast to such bacterial chromosomes as that in E. coli that is a closed circle, i.e. has no ends.)

The DNA molecule of a typical chromosome contains
• A linear array of genes (encoding proteins and RNAs) interspersed with
• Much noncoding DNA.

Included in the noncoding DNA are
• long stretches that make up the centromere and long stretches at the ends of the chromosome, the telomeres.

Telomeres (Fig. 1) are crucial to the life of the cell. They keep the ends of the various chromosomes in the cell from accidentally becoming attached to each other.

The telomeres of humans consist of as many as 2000 repeats of the sequence 5’ TTAGGG 3’.

5’...TTAGGG TTAGGG TTAGGG TTAGGG TTAGGG TTAGGG 3’

3’...AATCCC AATCCC AATCCC AATCCC AATCCC AATCCC AATCCC 5’

Fig. 1: Showing the position of telomeres in the chromosome (T.A. Sciences online-Introduction to Telomere Science)
transcribing a partly distinct set of genes. They also become unresponsive to triggers that would normally stimulate them to divide. Though these growth arrested cells can live on in the body for years, once they have reached this state, they do not under normal circumstances, replicate themselves. They are said to have reached their Hayflick limit (named for the discoverer of the arrested state).

Introduction to Telomerase

Because sperm and egg cells are themselves descended from progenitor cells, if there were no mechanism for replacing lost telomere, then all organisms with linear chromosomes (eukaryotes) would be condemned to quick extinction due to Hayflick limits in their reproductive tissues. Instead, there are a number of mechanisms in nature that counteract the natural tendency of telomeres to erode over time.

Vertebrates, including mammals, use a remarkable enzyme dubbed ‘telomerase’. This hybrid molecule, part protein, part RNA, is capable of slowing telomere erosion, halting erosion altogether, or lengthening telomeres beyond those in the parent cell.

The genes that produce telomerase are found in every potentially replicating cell in the body, including cells at their Hayflick limits, but the genes that produce telomerase are inactive in the great majority of our cells, for the vast bulk of our lives. Those genes are active across the body only in early fetal development. After that point, telomerase is only found in a few special tissues such as antibody producing immune cells, cells that replenish the gut lining, and sperm producing cells.

A telomere is a repeating DNA sequence (TTAGGG) at the end of the body’s chromosomes. The telomere can reach a length of 15,000 base pairs. Telomeres function by preventing chromosomes from losing base pair sequences at their ends. They also stop chromosomes from fusing to each other. However, each time a cell divides, some of the telomere is lost (usually 25-200 base pairs per division). When the telomere becomes too short, the chromosome reaches a “critical length” and can no longer replicate. This means that a cell becomes “old” and dies by a process called apoptosis.

The Molecular Genetics

As the cell divides, and moves into the cell cycle for mitotic activity, the chromosomes are copied by enzyme molecules. The two chromosomes which are read and copied by these molecules are not only mirror images to themselves but, the newly formed daughter chromosomes will also be mirror images to their progenitors. But the enzyme molecules that do the duplicating are unable to completely reproduce the tips of the chromosomes. As a result, the duplicate chromosome or the newly formed chromosome is necessarily slightly shorter than the original, at their ends (arm tips) lacking a small amount of the original telomere sequence. The missing DNA does not measurably affect cellular functioning until enough cell divisions have occurred that the telomeres on at least one of the chromosomes in the cell become critically short.

The entire situation of chromosomal replication can be explained as in Fig. 2

In summation though the replicated templates are true copies of the parent chromosome strand yet the template fall short of the exact match at the 5 clock end, finally resulting in slightly shorter strand (incomplete strands), this part which is shortened is the part of the telomere.

Cells with critically short telomeres alter their character by

Fig. 2: DNA polymerase and RNA primer to initiate synthesis. The result is the “end-replication problem” in which sequence is lost at each round of DNA replication. (Author: Dr. John W. Kimball, Kimball’s biology pages, online)

Fig. 3: The products of two genes are required to reconstitute basic telomerase activity; the RNA component, hTR, which includes the template for synthesis of telomere DNA, and the protein catalytic component, hTERT, which has reverse transcriptase activity. Nature Clinical Practice Oncology 1, 88-96 (30 November 2004)

Fig. 4: Telomerase adds telomere repeats to the 3’ end of DNA strands. It is an enzyme that adds telomere repeat sequences to the 3’ end of DNA strands. By lengthening this strand, DNA polymerase is able to complete the synthesis of the “incomplete ends” of the opposite strand.

Telomerase

- Is a ribonucleoprotein.
- Its single sRNA molecule — called TERC (“TElomere RNA Component”) — provides an AAUCCC (in mammals) template to guide the insertion of TTAGGG.
- Its protein component — called TERT (“TElomere Reverse
Transcriptase”) — provides the catalytic action.

• Thus telomerase is a reverse transcriptase; synthesizing DNA from an RNA template.

Fig. 3 shows formation of telomerase

Telomerase is generally found only in

• The cells of the germline, including embryonic stem (ES) cells;
• Unicellular eukaryotes like Tetrahymena thermophila;
• Some — perhaps all — “adult” stem cells and “progenitor” cells enabling them to proliferate;
• Cancer cells.

When normal somatic cells are transformed in the laboratory with DNA expressing high levels of telomerase, they continue to divide by mitosis long after replicative senescence should have set in. And they do so without any further shortening of their telomeres. This remarkable demonstration reported by Bodnar et. al. provides the most compelling evidence yet that telomerase and maintenance of telomere length are the key to cell immortality.

Telomere shortening is now considered the main causal mechanism of Replicative Senescence and telomere length is the molecular clock that counts the CPDs cells endure (reviewed in Wright and Shay, 2001). Although it was previously known that telomere shortening occurs in each subcultivation (Harley et al., 1990), the key finding relating the telomeres to RS was made in 1998 by scientists at Geron Corporation.

Telomerase is a reverse-transcriptase enzyme that elongates the telomeres and thus corrects the normal telomere erosion (Greider and Blackburn, 1985). It has two components: an RNA component (Feng et al., 1995) and a catalytic subunit (Nakamura et al., 1997). Telomerase activity was shown in immortal cell lines (Counter et al., 1992). But the definitive breakthrough came when it was shown that expression of the catalytic subunit of human telomerase (hTERT) in retinal pigment epithelial cells or foreskin fibroblasts avoids RS (Bodnar et al., 1998). Human diploid fibroblasts or HDFs immortalized with hTERT divide vigorously, do not show increased staining for SA β-gal, and do not show signs of transformation (Jiang et al., 1999); (Morales et al., 1999). Even expression of hTERT in old HDFs appears to reverse the loss of function characteristic of senescent cells (Funk et al., 2000). It appears that ectopic hTERT expression is sufficient to restore telomerase activity in human cells (Counter et al., 1998).

Telomere and Telomerase

Well as per the above mentioned scenarios it is but naturally evident that the existence of telomere and telomerase go hand in hand without the action of telomerase enzyme the end of the Chromosome (telomeres) will carry out their normal fate and continue shortening, until and unless acted upon by these enzymes which prolong and add telomeres to the preexisting ones. This at the end results in prolonged cell survival and alters the destined life span of the cell.

The basic functions and telomere property

• Telomeres allow cells to distinguish chromosome ends from broken DNA
  • If DNA is broken there are two options after the cell cycle is stopped: Repair or Death
    • Repair can occur in two ways:
      • Homologous Recombination (HR) -- Error-free but need homologue nearby
      • Non-homologous end-joining (NHEJ) -- Error-prone but saves chromosome from degradation
  • Telomeres prevent chromosome fusions by NHEJ
  • Fusion-bridge-breakage cycles leads to genomic instability which in turn can result in cell death or neoplastic transformation
• Telomeres are specialized structures that are essential for protecting chromosome ends and ensuring chromosome stability
• Telomeres also provide a mechanism for “counting” cell divisions

Telomerase the key to replicative immortality

• Enzyme (reverse transcriptase) with protein + RNA subunits
• Adds telomeric repeats directly to 3’ overhang (uses its own RNA component as a template)
  • Vertebrate telomere repeat: TTAGGG
  • Vertebrate telomerase RNA template: AATCCC
• Overcomes telomere shortening/end replication problem
  • Added back to somatic cells
  1. Prevents telomere shortening
  2. Prevents replicative senescence
  • However cells that express telomerase still undergo
Ca TRF1 complex
- TANK (altered in some tumours)
- TRF1 (altered in some tumours)
- TRF2 (altered in some tumours)
- POT1 (altered in some tumours)
- PTOP
- RAP1
- TIN2 (altered in some tumours)

Cb TRF2 complex
- ERCC1 (Xeroderma pigmentosum)
- MRE11/NBS1/RAD50 (Nonogen breakage syndrome, Atadá telangloctasia like disorder)
- ATM (Ataxia telangiectasia)
- KU86
- PARP2
- WRN (Werner syndrome)
- BLM (Bloom syndrome)

Cc Telomerase
- TERT (aplastic anaemia, altered in tumours)
- TERC (Dyskeratosis congenita, aplastic anaemia, altered in tumours)
- DKC1 (Dyskeratosis congenita)

Fig 5: The components of the telomere repeat binding factor 1 (TRF1) (Ca) and 2 (TRF2) (Cb) complexes and the telomerase enzyme (Cc) are shown. The human diseases in which expression of these components has been shown to be altered are indicated. Nature Reviews Genetics 6, 611-622 (August 2005)

Telomeres and Cellular Aging
Normal cells are finite and do not endlessly replicate while the malignant cells have got an infinite potential to replicate.

Multiple invitro experiments have shown that the cells of newborn are rather in their Budding stages with tremendous potential to revolve around the cell cycle and undergo mitotic activity when placed in required culture media, so much as to divide almost a 100 times. But yes at the fag end they to have a limitation of potential and finally their rate of mitosis begins to decline (to less than once every two weeks). Where as cells of Septuagenarians, would manage only a couple of dozen mitoses before they ceased dividing and died out.

This phenomenon is called replicative senescence (RS).

Lacunae – Blaming the telomeres
Finally the telomeres and their relationship with replicative senescence is one spectrum of viewing cellular aging and if we were to include other parameters into account for cellular aging then telomeres per se cannot be the only regulating index or replicative senescence cannot be the final frontier in accountability regarding cell aging process. There are other parameters like cell metabolism, internal milieu of the cell, enzymatic regulations, free radicals hits, anti oxidant shield, etc. which also can be accounted for cell aging prolongation or shortening.

Hence following points should also be taken into account
- Telomere contributes to aging only if replicative senescence contributes to aging and therefore, telomerase will prevent aging and/or restore youthfulness.
- Telomerase protects against replicative, but not other forms of cellular senescence as mentioned above.
- Telomere length is neither the only nor the ultimate timekeeper of cells (reviewed in Blackburn, 2000). During telomerase-immortalization of human cell lines, several researchers noticed that immortalized cells had shorter telomeres than growth arrested controls (Ducray et al., 1999); (Zhu et al., 1999). Surprisingly, these immortalized cells featured less chromosome fusions, which are the most noticeable outcome of short telomeres (Hande et al., 1999). Most, not all, human somatic tissues have no detectable telomerase activity. In the bone marrow, hematopoietic cells express telomerase. Telomerase activity is higher in primitive progenitor cells and then downregulated during proliferation and differentiation.

Telomerase activity has been detected in some normal human somatic proliferating cells: for instance, in skin cell, immune system cells, and colorectal tissues. A decline in telomerase activity was reported in blood mononuclear cells with age. Human germ cells have been found to express hTERT.

Telomeres, Telomerase and Disease
The diagrammatic sketch in Fig. 5 shows the diseases which can be directly or indirectly attributed to telomere or telomerase malfunction and also pin points or zero’s in on the exact genetic targets which have resulted in such a catastrophic outcome.

There is a definite linkage between the various components of the telomere both in terms of structural integrity and functioning of the telomere components and their correlation with disease development both congenital or acquired.

The TRF-1 complex basically contains set of telomere components which deal with cell replication steps and alteration in their fusions and at times in structure indirectly altering their function can lead to abnormal cell proliferation leading to cell proliferation and tumor formation.

The TRF-2 complex basically involves syndromes or disorders pertaining to DNA repair defects, that is DNA repair genes are affected resulting in Chromosomal breakage syndromes like – Bloom’s syndrome, Ataxia telengiectasia, Fanconi’s anemia,
Xeroderma pigmentosa and Werman’s syndrome.

Finally the telomerase complex regulates disease like Dyskeratosis Congenital, aplastic anemia.

**Telomerase and Cancer**

Science has learned much about cancer since the so called ‘War on Cancer’ began. One of the most striking discoveries has been that cancer is rarely if ever the result of a single mutation. Generally, several complimentary mutations must occur in the same cell to produce an ever growing tumor, which then experiences further changes, producing a cancer (Fig. 6).

In order to grow large enough to capture our attention, some particular cell must have at least two mutations.

The two hit Hypothesis states, primarily a cell must be genetically damaged such that it becomes insensitive to the signals that would normally tell it to stop dividing. The product of the first mutation will be a small colony of growth arrested cells, each of which contain the changes by that first mutation.

This primary mutation not only causes altered cell morphology, cell physiology and certain permanent detrimental genetic change with the cells internal milieu but also trigger a reproduction cascade which otherwise would not have taken place. The result being production of reproduction capable progeny of mutant cells. But, in spite of being prone to reproduce endlessly, these cells will be dormant because their newly produced short telomeres will have arrested the machinery of cell division. And that is where the process will end, unless one of those cells is unlucky enough to receive further genetic damage.

The second hit or genetic damage takes place in the area of the telomerase gene. If the gene required to prevent telomerase from being produced is damaged, in such a situation abundant, excess and instant telomerase is suddenly available, then the reproducitvely-prone, previously growth-arrested cell, will resume the growth juggernaut. But this time, there are no built in limits to be reached. With a propensity to grow, and telomerase maintaining the telomeres, a dangerous cascade is well under way. This is the beginning of a tumor.

As we have seen from the above mentioned discussions, intensive studies and experiments world over that the normal cultured human cells have a limited replication potential in culture.

Most cancers arise from somatic cells. But one of the crucial features that distinguishes a cancer cell from a normal somatic cell is its ability to divide indefinitely. It turns out that most (85–90%) cancer cells have regained the ability to synthesize high levels of telomerase throughout the cell cycle, and thus are able to prevent further shortening of their telomeres.

On the molecular front the entire phenomenon of tumor cell hit hypothesis can be further elaborated.

The ectopic expression of the catalytic subunit of hTERT results in immortalization of human cells if telomeres are

**Fig. 6**: Carcinogenesis vol.26 no.5 pp.867–874, 2005

**Fig. 7**: Telomere length vis a vis cell doublings. Nature Reviews Cancer 8, 167-179 (March 2008)
Fig. 8: Relation of telomere length with age in years. Nature Reviews Cancer 8, 167-179 (March 2008)

Fig 9: the telomerase enzyme is targeted at various levels beginning from the telomerase genes, the genetic transcripts, Holoenzyme assembly, telomere interaction.

Normal cells in culture replicate until they reach a discrete point at which population growth ceases. This is termed mortality stage 1 (M1 stage) and is caused by the shortening of a few telomeres to a size that leads to a growth arrest called cellular senescence. This stage can be bypassed by abrogation of the function of p53 and pRB human tumor suppressor genes.

The cells then can continue to proliferate with further decreases in telomere length until another check point termed mortality stage 2 (M2 stage) or crisis stage. The growth arrest in the M2 stage is caused by balance between the cell proliferation and cell death rate. At this stage, when most of the telomeres are extremely short, end-to-end fusions and chromosomal breakage-fusion cause marked chromosomal abnormalities and apoptosis.

Under rare circumstances, a cell can escape M2 and become immortal by stabilizing the length of its telomeres. This occurs through the activation of the enzyme telomerase or an alternative mechanism of telomere lengthening.

**Telomeres and Cell Doublings**

As shown in Fig. 7 in normal occurring somatic cells there is the telomere independent and dependent pathway of cell replication, maturation and senescence arrest.

In the telomere independent pathway, the cells are inhibited from further proliferation by the microenvironment and or by differentiation program arrest.

In case where there is a transformation mutagenesis and defective malfunction of the p53 along with activation of CDK 4 then the cells are not sent to the grave yard but are rather...
activated and go in for innumerable repetitive cell cycles of mitogenesis attaining immortality there by cancerous changes.

In the telomere dependent mechanism it is the telomerase which disappears or are critically shortened in such scenarios there is genomic instability and cell death takes place, in such critically shortened telomeres due to genetic mutagenesis if in case the telomerase are activated then the cells again seek a potential immortal pathway and are transformed to cancerous cells.

**Telomeres and Age in years**

As shown in Fig. 8, Germ cells have a switched on telomere with a life long elongated telomere length. Next in line are the stem cells where the telomerase is transiently on and slow reduction in the length of telomeres takes place resulting in prolonged life span of the stem cells.

In normal somatic cells the telomerase is transiently switched on and then off resulting in clonal expansion of two different cell lines which finally reach point of absolute differentiation, replicative senescence and no further replication eventually die off.

In the above described chart there can arise situations like mutagenesis in the somatic cells resulting in growth dysregulating mutations ultimately giving rise to clonal cells which become immortal, due to telomerase activation and reelongation of telomeres.

**The Cancer Therapeutics**

In recent times an array of extremely calculative and precisely devised strategies have evolved with intense experimentation and research to have a singular aim and objective the aim being to inhibit telomerase action and the objective to have minimally reduced cancer cells Fig. 9.

Currently, strategies aimed at selectively treating the cancers from telomerase positive cells involve modulation of TERT (Telomerase Reverse Transcriptase) function or length of telomeres by antisense strategy, dominant negative mutants or pharmacological agents.

The use of nucleoside analogs (e.g., AZT) has been attempted to interfere with human telomerase activity with an aim to treat cancers. The methods disclosed in the prior art administering nucleoside analogs to modify telomerase activity, however, are not satisfactory or are not suitable in a clinical setting because their clinical utility is limited by a low therapeutic ratio, i.e., the ratio of toxic dose to effective dose.

Perhaps agents that prevent the expression of the gene for telomerase — or prevent the action of the enzyme — will provide a new class of weapons in the fight against cancer. But

- if telomerase activity — however brief — is essential for all cells, we had better be careful, and
- if lack of telomerase hastens replicative senescence, it may also hasten the aging of the tissues that depend on newly-formed cells for continued health — a tradeoff that may not be worth making.

To conclude researchers hope to target the enzyme telomerase to treat cancer Fig. 9. Telomerase synthesizes telomeres, which occur on the ends of chromosomes. Telomerase actually consists of a complex of proteins and RNA. One of the proteins is the enzyme reverse transcriptase, which uses the RNA as a template to reconstruct the telomere. Defective reverse transcriptase can interfere with this process and kill the cancer cells.

**Telomerase and Transplanted Cells**

One approach to gene therapy is to

- Remove cells from the patient,
- Transform them with the gene for the product that the patient has been unable to synthesize,
- Return them to the patient.

One problem with this approach is that the cells — like all normal somatic cells — are mortal. After a series of mitotic divisions, they die out.

If their cells could be transformed not only with the therapeutic gene but also with an active telomerase gene, This should give them an unlimited lifespan.

Yet there is always a risk that can these transplanted cells have a risk of developing into cancer cells once the telomerase is activated. Perhaps not. The cells described by Bodnar et. al. in the 16 January 1998 issue of Science have continued to grow in culture and have been subjected to a number of tests to see if they have acquired any properties of cancer cells in culture.

The results are encouraging. While these cells continue to divide indefinitely as cancer cells do,

- They still show contact inhibition as normal cells do when grown in culture.
- They do not grow into tumors when injected into immunodeficient mice (as cancer cells do).
- They are still fussy about their diet — unable to grow on the simple media that supports cancer cells in culture.
- They still retain a normal karyotype; something that cancer cells seldom do.

However, studies with whole animals — transgenic mice that express abnormally high levels of TERT — reveal that they do suffer an elevated incidence of cancer.

**Telomeres and Cloning**

The now-famous sheep Dolly was cloned using a nucleus taken from an adult sheep cell that had been growing in culture. The cell donor was 6 years old, and its cells had been growing in culture for several weeks.

What about Dolly’s telomeres? Analysis of telomere length in Dolly’s cells reveals that they were only 80% as long as in a normal one-year-old sheep. Not surprising, since the nucleus that created Dolly had been deprived of telomerase for many generations.

Does this mean that Dolly is doomed to a shortened life? She seemed healthy at first and even had babies of her own. But medical problems — probably unrelated to her telomeres — ended with her being euthanized at a relatively young age 3.

But her short telomeres do add another question to the debate about cloning mammals from adult cells.

**Conclusion**

In oncology, the best advantage of telomerase is that they help identify the malignancy causing cells and as a result the malignant cell which are telomerase positive can be separated out. Telomerase positive cells can be easily identified and can be genetically modified hitting the cancer causing genes. Modified telomerase, telomere activity and their docking together
ultimately can inhibit the proliferative activity of the cells which cause malignancy.

If telomerase activation of telomeres by mutations are a prerequisite to cancer, then why hasn’t natural selection eliminated this land mine from our cells? If short telomeres are the reason we grow old, then why not activate telomerase across the body and stay young? As should be clear at this point, there is a built in trade-off that we have no means of escaping. Increasing resistance to cancer necessarily comes at the cost of accelerating our decline with age. Slowing the aging process would necessarily expose us to increased propensity for cancer.

At any given moment the body of an adult human is composed of roughly 10 trillion cells. Nearly all of those cells could spawn a deadly tumor with the right mutations. The system of finite, eroding telomeres provides us that ability to repair and maintain our tissues for a substantial period, and help prevent malignant transformations but the flip side of the coin is that we are condemned to grow old. As bad as that may seem, however, it is the lesser of two evils. If our telomeres did not erode, and therefore did not provide a failsafe mechanism to catch runaway mutants, then we would likely be overrun by tumors before we ever got the chance to reproduce.

The medical fraternity and all its human consumers are today standing at the dawn of new era and, as we humans have finally found the Achilles’ heel! what remains as matter to see is whether we with our gray matter can ever proclaim the ability to conquer mortality, until then we are standing in the twilight zone of immortality via a vis Death.

References