FEATURE ARTICLE

How Not to Die?

Modern gerontological answers to an ancient puzzle

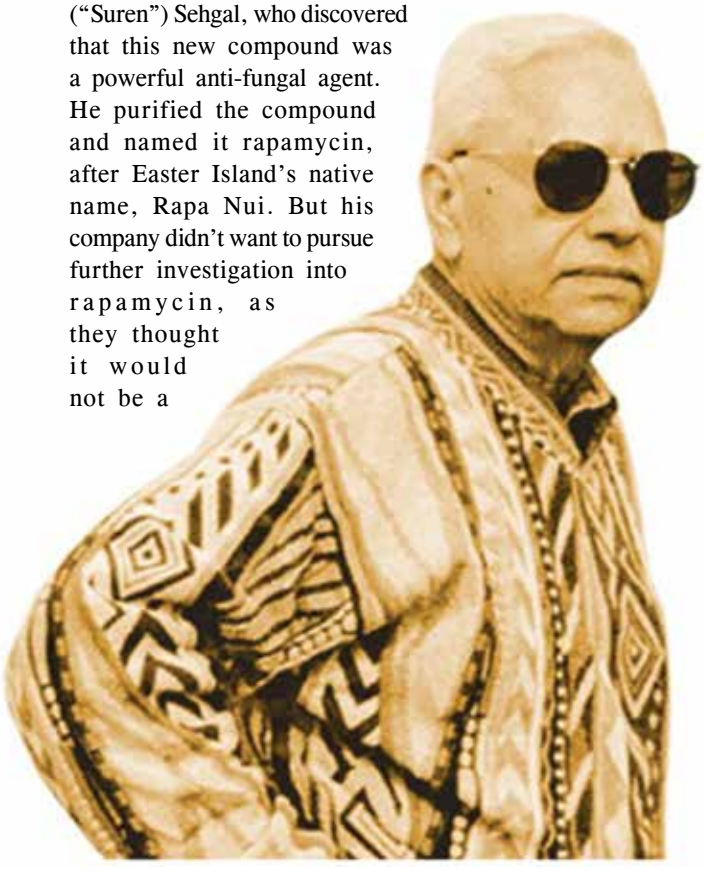
Farogh Gibraiel

EVER since Qin Shi Huangdi, the first emperor of unified China, had heard about a mountain in the midst of the eastern sea, inhabited by immortals who possessed the "herbs of everlasting life", he became obsessed with finding the elixir of eternal life. He sent several expeditions in search for this mythical mountain. Sadly, the people sent on the search missions never came back. The emperor died in 210 BC, with his dream unfulfilled.

Of course, he was not alone in sharing such a fantasy. It is said that Alexander the Great, had once set out on a similar mission to find for himself what the Persians refer to as the "fountain of life". He failed obviously; we know that because he died! The idea of *Amrit* (nectar of immortality) is described in ancient Indian scriptures too, the search for which never really ceased. Call it what you like, Amrit or fountain of life, the quest for this *elixir vitae* that grants "eternal life" or "eternal youth" has been the dream of mankind, since the dawn of civilization.

Perhaps, Huangdi and Alexander were not looking at the right places; that's why their missions failed. However, there was an expedition that came close to success. In 1964, a joint expedition by the Canadian Research Council and the Centers for Disease Control (CDC) was sent to an isolated island in the middle of the Pacific, known as Rapa Nui, Isla de Pascua or the Easter Island. Scientists gathered soil samples from this Island and analysed them at Ayerst Laboratories, a pharmaceutical company in Montreal. They isolated a compound from a rare strain of bacteria *Streptomyces hygroscopicus*.

One of the scientists at Ayerst Laboratories was the mycologist Dr. Surendranath ("Suren") Sehgal, who discovered that this new compound was a powerful anti-fungal agent. He purified the compound and named it rapamycin, after Easter Island's native name, Rapa Nui. But his company didn't want to pursue further investigation into rapamycin, as they thought it would not be a productive exercise. In 1983, they decided to shut down their Montreal lab and destroy all "nonviable" samples, including rapamycin.



Dr. Suren Sehgal, discoverer of rapamycin

However, Dr. Sehgal successfully "smuggled out" a few vials of the bacteria from the lab and stashed them in his freezer at home to pursue further research which led him to discover that rapamycin was not just an anti-fungal agent, it also suppressed the immune system, and therefore can be used as a drug for transplant patients.

Thirty-five years later, in 2009, a large National Institute of Health-funded study established that rapamycin and its derivatives helped mice live longer. Male mice on rapamycin lived 9 percent longer. The females' lifespan was extended by 14 percent.

Rapamycin acts on what is called the mechanistic Target of Rapamycin (mTOR) complex, a set of genes that acts as the cell growth regulating kinase. When mTOR is blocked, it can push cells into a life-extending survival mode. However, there's one catch: Rapamycin suppresses the immune system. Giving such a drug to older patients, whose immune systems are often already diminished, would make them vulnerable to life-threatening infections, defeating the purpose.

However, a breakthrough came on Christmas Eve 2014. Novartis conducted its first study on a derivative of rapamycin called everolimus. This study was conducted with volunteers in Australia and New Zealand, and it showed that everolimus boosted the immune response of elderly patients by around 20 percent, when administered in limited doses. This "first human aging trial" was a success.

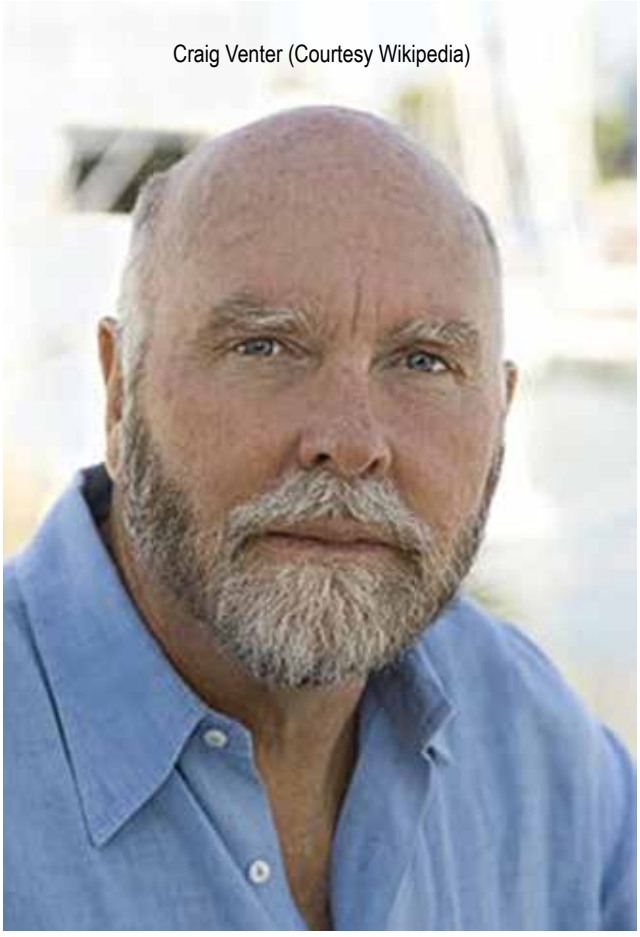
This sounds like a very promising success story. But Rapamycin is not the only potential candidate for an anti-ageing drug. There are many other molecules and therapies in the race, with their own stories.

Hacking the Code of Life

Today, gerontologists are fairly certain that prolonging life is a very real possibility, so much so that you can literally bet your money on it! If you think it's a tall calim, ask Dr. Anthony Joon Yun, a Korean-American physician and the founder of the Palo Alto Institute in California. In 2014, he announced the $1 million Longevity Prize as an incentive to encourage scientists from all over the world to "hack" the code that regulates our lifespan. In his own words, "I have the idea that aging is plastic, that it's encoded. If something is encoded, you can crack the code. If you can crack the code, you can *hack* the code!"

When the *Time* magazine published its cover story, "Google vs. Death", in the September of 2013, it created a lot of buzz in the scientific community. It was the story on Google's new company *Calico*, built in a $1.5 billion partnership with the drug company AbbVie, with the goal to focus on "health, well-being, and longevity", in the words of Google founder Larry Page. But *Calico* is not the only company in the field. Many other entrepreneurs have taken up the initiative to fight ageing.

Craig Venter, the man behind the "Human Genome Project", has started his own venture under the name Human Longevity Inc. His firm plans to sequence the genomes of



Craig Venter (Courtesy Wikipedia)

40,000 people per year and use the data to find keys to human health, which inevitably includes ageing.

Unity Biotechnology Inc., a biotech firm dedicated to halting or even reversing ageing diseases, recently announced the closing of a $116 million Series B financing, some of which came from Amazon's founder Jeff Bezos, Mayo Clinic and WuXi Pharmatech.

Let us look at the different strategies, other than those involving Rapamycin, which scientists have been working on.

Calorie Restriction and Red Wine

The most well-known strategy to extend an animal's lifespan is Calorie Restriction (CR) or Dietary Restriction (DR). Discovered about 70 years ago, CR involves reducing the calorie intake of an animal by 30-40 % compared to its normal caloric intake. It is thought to lower metabolic rate and cause the body to generate fewer damaging free radicals.

CR delays or prevents age-related diseases and extends lifespan in species ranging from yeast to primates. Evidence that Calorie Restriction (CR) retards aging and extends median and maximal lifespan was first presented in the 1930s by McCay *et al*. Since then, similar observations have been made in a variety of species including rats, mice, fish, flies, worms, and yeast. Although not yet definitive, results from the ongoing calorie-restriction studies in monkeys also suggest that the mortality rate in calorie-restricted animals will be lower than that in control subjects.

But radical dieting for calorie restriction is not a reasonable idea to increase lifespan among humans, for two reasons, firstly because CR has shown to affect fertility of the organism in many cases, secondly because the person would most likely die of starvation, if not of aging. So we need to find alternatives.

To begin with, we need to ask the question: If calorie restriction is the cause, then what is the effect? In other words, what does calorie restriction do specifically to enhance lifespan?

As bizarre as it may sound but the answers to these questions might lie in the red wine! Well, to be precise, an ingredient of the red wines is a bit of more interest here.

Red Wine, Extending Life? Not Quite.

Resveratrol, a phytoalexin polyphenol that is found naturally in the grape skins and is present at low concentrations in red wine, has shown diverse health benefits ranging from reducing the risk for heart disease and increasing human lifespan.

It was discovered that resveratrol somehow "mimicked the lifespan-extending effects of caloric restriction" for several model organisms, including yeast, worms, flies, and fish. It would have been great if this molecule produced similar effects in humans. However, reality is never that simple. It would require a person to drink 1000 bottles of red wine per day to expect something close to life-extension. Even consuming resveratrol concentrated in the form of a pill has not proved to be a feasible endeavour.

So, what does resveratrol do specifically to enhance the lifespan?

Red wine, extending life? Not quite.

The "Resveratrol-Sir 2" Affair

In September 2003, Konrad Howitz, director of biochemistry at Biomol Research Laboratories and David Sinclair, Professor in the Department of Genetics at Harvard Medical School, published the results of their study showing that resveratrol acts as an activator of Silent information regulator 2 (Sir2) proteins, or sirtuins. It was a remarkable discovery. The variants of these sirtuins are present in all organisms studied so far, from yeast to humans.

Sinclair and his team had already established the link between sirtuins and ageing. When an extra copy of the *SIR2* gene was added to the yeast *S. cerevisiae*, the formation of extra chromosomal rDNA circles was repressed which led to a 30 percent extension in the cell's lifespan. This explained how *SIR2* could act as a longevity gene in yeast. Interestingly, very soon it was discovered that extra copies of the *SIR2* gene could also extend the lifespan of roundworms by as much as 50 percent!

Mammals possess seven types of sirtuins, SIRT1 to 7. Sinclair's team has shown that resveratrol targets SIRT1 directly at moderate doses and hits other targets at higher ones. But, irrespective of dose, SIRT1 is required for resveratrol's benefits. We just have to find the lowest effective dose of resveratrol.

Resveratrol or calorie-restricted diet extended the lifespans of yeast, worms or flies by about 30 percent, only if they possess the *SIR2* gene. Moreover, a fly that overproduces Sir2 has an increased lifespan that cannot be further extended by resveratrol or calorie restriction. The simplest interpretation is that calorie restriction and resveratrol each prolong the lives of fruit flies by activating Sir2. Resveratrol-fed flies do not suffer from the reduced fertility often caused by calorie restriction.

The promising results of these studies led David Sinclair to found his start-up firm Sirtris Pharmaceuticals for developing drugs based on resveratrol. This start-up company was bought in 2008, by GlaxoSmithKline in a $720 million deal.

Prof. David Sinclair, discoverer of resveratrol-sirtuins connection

The Long-living Jews

There is a historically isolated and culturally insular population from Eastern and Central Europe, known as the Ashkenazi Jews. It has been observed that these Jews unusually tend to live longer and suffer from less cardiovascular problems compared to other populations. The secret of this interesting group of people could help us pin-point the longevity genes responsible for ageing.

Researchers at Yeshiva University's Albert Einstein School of Medicine examined 477 Ashkenazi Jews, looking for factors that may have contributed to their longevity. They observed that the Ashkenazi Jews who have crossed the age of 95, are more likely to possess a genetic variant that down-regulates insulin-like growth factor 1 (IGF-1). Studies suggest that such mutations could be responsible for delaying old age.

Experiments conducted by Andrzej Bartke, a biologist at the Southern Illinois University School of Medicine in


Ashkenazi Jews – tend to live longer

Springfield, on mice have shown that the disruption of *IGF1* has caused an increase in the lifespan of mice by 30 to 40 percent. Some scientists are of the opinion that Sir2 which regulates the low metabolic state of calorie restriction may be part of the IGF-1 pathway.

The complex interlinked dynamics of calorie restriction, Siruins, IGF1 and many other 'longevity genes' presents itself like a puzzle before scientists, that needs to be solved if any serious progress can be made in fighting ageing.

The Truth is Never Simple

So are we really going to invent the ultimate "longevity pill"? Just pop in this pill to put an end to all the misery of old age, and wipe out the term 'age-limit' from the dictionary of our life! Is it so simple to achieve this pure idealism? As goes the saying, "the truth is rarely pure and never simple."

"The field has been over-focused on overhyped claims of longevity," says Johan Auwerx, a researcher at the Federal Institute of Technology in Lausanne, Switzerland. "The field needs to calm down".

The claim of Sirtuin relation to long life does not appear to hold good. David Gems, a geneticist at University College London, studied the *C. elegans* worm that was expressing Sirtuin and mated it with normal nematodes. He observed that the new young nematode worms did not live longer than normal "despite being overloaded with Sirtuin". That's when he began to get suspicious about this whole thing. He says that there are a lot of rumours going around and he doesn't want to get involved. "No, I don't want to work on this. Somebody else can clean up this mess," he said in an interview. "A lot of other people have wasted a lot of time."

On the other hand, MIT's Leonard Guarente insists on the link between Sirtuins and longer life. "We absolutely do not agree that there is a serious question about whether sir2 (Sirtuin) extends life span in worms," he said. "I think the whole thing is a tempest in a teapot."

There is another tempest cooking up somewhere else. There is an apparent clash between the candidate anti-ageing drugs themselves. The claims of resveratrol have been attacked by the advocates of Rapamycin. Matt Kaeberlein, a leading American biogerontologist at the University of Washington says, "The difference between rapamycin and resveratrol is that rapamycin really works as advertised and resveratrol doesn't. If you look at the data, you have to agree," he insists.

Whatever may the case be, one thing is clear: To sort out this whole life-extension business, we need more data, more evidence.

A Long Road Ahead

According to WHO's Global Health Observatory (GHO) data, "Global average life expectancy increased by 5 years between 2000 and 2015, the fastest increase since the 1960s."

A recent study by Imperial College, London, suggests that the life expectancy at birth will cross the 90-year mark by 2030. Indeed the advancements in medical science and increased access to better healthcare services are enhancing the quality of life. Resveratrol and rapamycin are the two substances that represent the first efforts by scientists to translate anti-ageing research from the laboratory to the clinic. Both have successfully proven their roles, in enhancing the lifespan and reducing ageing effects in multiple model organisms.

But there is quite a lot of scepticism going around in the scientific community. We may be on the right track but cannot simply ignore the sceptics' comments just because we don't want to. There is a lot of work that needs to be done, before anyone can be confident enough to launch a "longevity pill" in the market.

To be realistic, the goal is not to achieve immortality; the goal is to eliminate age-related diseases. The focus of serious researchers in this field is not to extend the life-span, rather to maximize the "health-span" of people.

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