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The Role of Chemistry in Contribution to Biomedicine Recently

Dae Dong Sung*

Korea University Sejong Campus, Samse Medical Center, Korea

***Corresponding author:** Dae Dong Sung, Professor of Korea University Sejong Campus, Samse Medical Center, Sejong-si, 30019, Korea.

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Abstract

Background: *Recently, biomedicine has contributed greatly to extending human life and treating and preventing diseases. Biomedicine uses chemical tools to reveal the three-dimensional structure of cells and is responding to the treatment of chronic diseases.*

This review deals with how chemistry has contributed to the development of biomedicine.

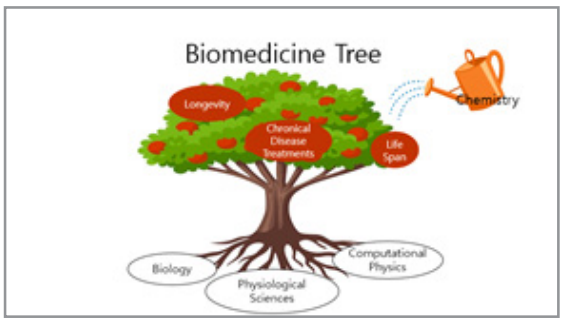
Results: *Biomedicine has made groundbreaking contribution to the mechanism of aging, the role of telomeres, and the development of new cancer treatments using immunity. These developments have been largely depended on physical chemistry, organic chemistry and quantum chemistry.*

Conclusions: *With the development of biomedicine, not only has it become possible to recognize aging mechanisms and epigenetic aging, but also new cancer treatments using immune cells within the body of patients, become possible. Chemical methods applied to biomedicine have become possible to apply to the cell systems at the atomic and molecule level in a more precise tool.*

Keywords: Biomedicine, Aging, Telomere, Chemistry, Epigenetic Aging, Immune Cells, Cancer Therapy.

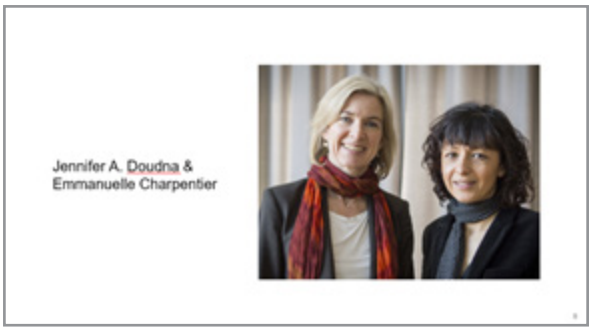
Background

Today, biomedicine is marking great progress with the help of chemistry [1]. Biomedicine has developed to understand the working principles of our body, how diseases appear and progress, and how to treat and prevent disease [2]. Recently, biomedicine has contributed greatly to the field of medical regeneration, life extension, development of new medicines, understanding aging mechanisms, and treating diseases related to aging [3, 4]. Biomedicine has made many advances with the help of biology, physiology, computer science, and chemistry [5]. Among them, chemistry has played a central role in the development of biomedicine [6]. Recently, biomedicine has made tremendous progress in understanding aging mechanisms, telomeres, and clustered regularly interspaced short palindromic repeats (CRISPR) [7].



Telomere – Life span

Elizabeth Blackburn
Carol Greider
Jack Szostak.



In this review, it will be uncovered the great advances made by chemistry in biomedicine.

Contribution of Chemistry to the Field of Life Extension

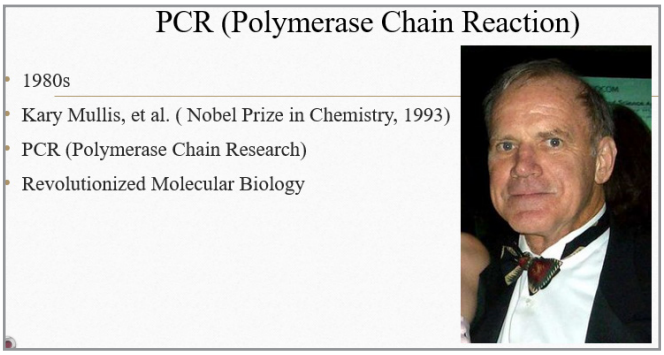
Extending life has been a long-cherished dream of mankind. Advances in medicine have made it possible to treat many diseases, and the average life expectancy has increased significantly. Recently, it is well known that chronic diseases related to diabetes, high blood pressure, dementia, and obesity accelerate aging [8]. Because aging is related to these chronic diseases, aging is defined as a disease. The scholar who preceded this claim is professor David Sinclair of Harvard Medical School [9]. His work takes us to the frontlines of research that is pushing the boundaries on our perceived incredible breakthrough. Aging is defined as a disease and laid the foundation for research to stop aging and extend life without disease [10].

From the aging studies the belief that humanity can do better and that everyone has the right to the best medical care and reprogramming cells in vivo. The aging theory has been developed based on the basis of changes in chromatin factor localization hypothesis, which proposes that epigenetic changes due to delocalization of chromatin factors in response to DNA damage may be a chief cause of aging [11].

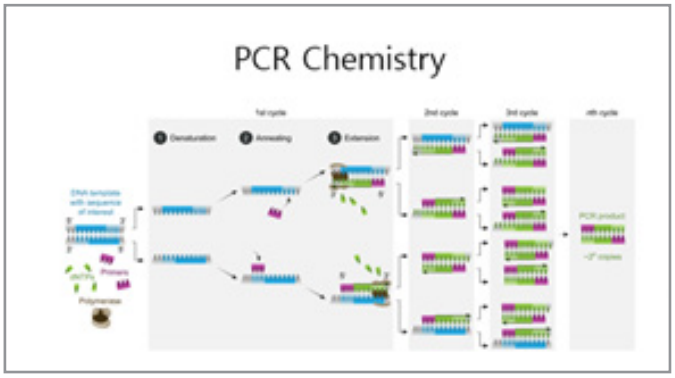
Epigenetics refer to changes in gene expression that do not involve modifications in DNA sequence and can be heritable through cell division. Such mechanisms are highly conserved among eukaryotes and can range from post-translational modifications in DNA or RNA, to changes in the 3D structure of chromatin, which is associated to proteins known as histones [12]. Epigenetic changes in gene expression can occur throughout cell differentiation and maturation, as well as in response to environmental stimuli. In humans, deregulation of epigenetic mechanisms has been associated to variety of cancers and autoimmune diseases, thus playing a key role in development. Eukaryote, any cell or organism that possesses a clearly defined nucleus. The eukaryotic cell has a nuclear membrane that surrounds the nucleus, in which the well-defined chromosomes [12]. Structure and composition of eukaryotic cells, the plasma membrane consists of proteins, carbohydrates and two layers of phospholipids. The phospholipids are arranged as the polar hydrophilic heads face the outside and inside of the cell. The structure of eukaryotic cell is being revealed with the help of molecular chemistry, especially three-dimensional molecular conformation programs [13]. Through the 3D molecular structure conformation tools, the structure of phospholipids, a component of eukaryotic cell, is being revealed continually. Density functional theory (DFT) is a quantum mechanical modeling method widely used in chemistry and condensed matter physics to study the electronic structure of molecules and solids. However, DFT is typically not used to predict protein structures. Proteins are large biomolecules composed of long chains of amino acids that fold into complex of the three-dimensional structures. The prediction of protein structure is challenging problem in computational biology and biophysics. While DFT can provide valuable insights into the electronic structure and properties of small molecules, it is generally not practical for predicting the three-dimensional structures of large biomolecules like proteins. Although DFT was used a tool to reveal simple molecular structures, it has been undoubtedly provided the basis for elucidating complex three-dimensional protein structures [14]. Instead, protein structure prediction methods typically rely on the physical organic chemistry that deals with the tools of molecular mechanics force fields, molecular dynamics simulations, and other computational techniques specially developed for studying biomolecular systems [15]. These methods of physical organic chemistry and quantum chemistry consider the interactions between atoms in proteins, such as van der Waals forces, electrostatic interactions, and hydrogen bonding, which play a crucial role in determining protein structure. Physical organic chemistry has been connecting between DFT to 3D protein structure.

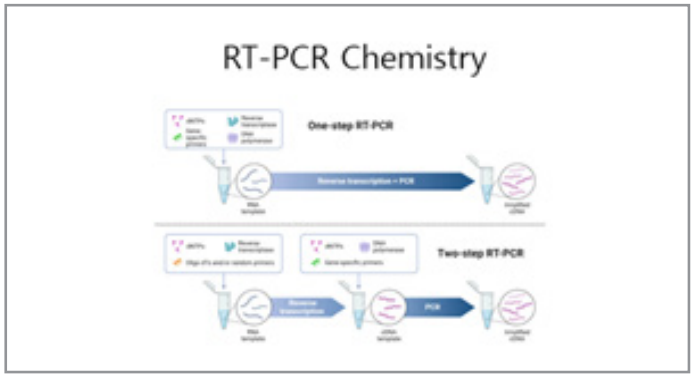
Contribution of Chemistry to the Field of Sequencing DNA and RNA of Protein

Recently, chemical knowledge has been widely used to identify the DNA and RNA sequencing of proteins [16].



While sequencing DNA gives a genetic profile of an organism, sequencing RNA reflects only the sequences that are actively expressed in the cells. To sequence RNA, the usual method is first to reverse transcribe the RNA extracted from the sample to generate cDNA fragments. The polymerase chain reaction (PCR) is a laboratory nucleic acid amplification technique used to denature and renature short segments of deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) sequences using DNA polymerase I enzyme, an isolate from Thermus aquaticus, known as Taq DNA.

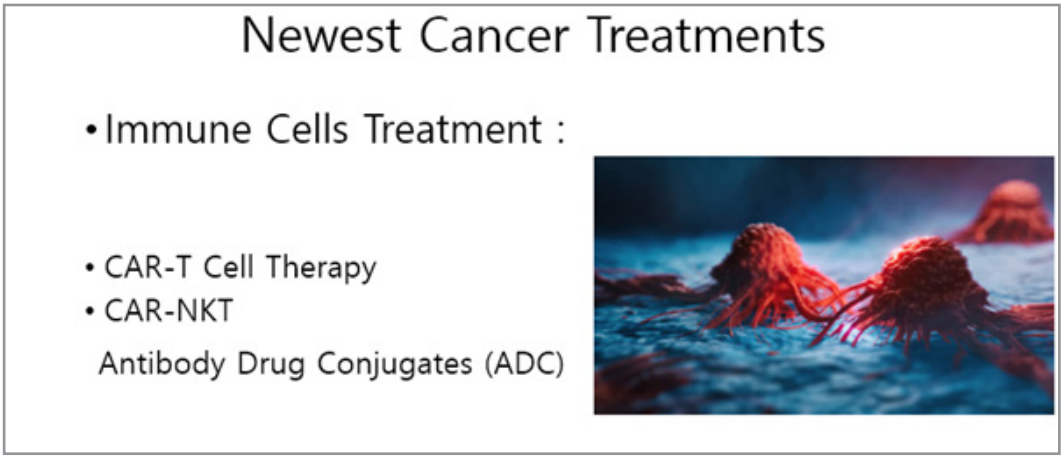




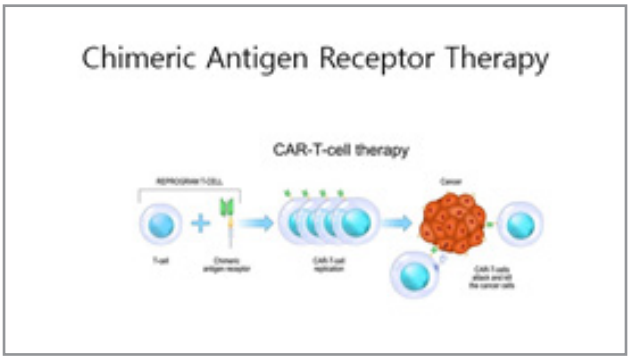
The Nobel Laureat, Kaly Mullis invented the process known as polymerase chain reaction (PCR), in which a small amount of DNA can be copied in large quantities over a short period of time [17]. By applying heat, the DNA molecule's two strands are separating and the DNA building blocks that have been added are bonded to each strand. With the help of the enzyme DNA polymerase, new DNA chains are formed and the process can be repeated. PCR has been of major importance in both medical research and forensic science. In particular, during Corona pandemic, PCR technology was a great help in eradicating the corona virus by allowing it to quickly identify the coronavirus by collecting the nasal phlegm of a patients infected with the coronavirus [18]. PCR is fundamental to many of the procedures used in genetic testing and research, including analysis of various samples of DNA and identification of infectious agents. PCR is now a common and often indispensable technique used in medical laboratory for a broad variety of applications. The majority of PCR methods rely on thermal cycling. Thermal cycling exposes reagents to repeated cycles of heating and cooling to permit different temperature-dependent reactions, especially DNA melting and enzyme-driven DNA replication [17]. PCR employs two main reagents-primers, which are short single strand DNA fragments known as oligonucleotides that are a complementary sequence to the target DNA polymerase. In the first step of PCR, the two strands of DNA double helix are physically separated at a high temperature in a process called nucleic acid denaturation. In the second step, the temperature is lowered and the primer bind to the complementary sequences of DNA [17]. The two DNA polymerase to enzymatically assemble new DNA strand from free nucleotides, the building blocks of DNA. As PCR progresses, the DNA generated is itself used as a template for replication, setting in motion a chain reaction in which the original DNA template is exponentially amplified. Nowadays, PCR has been developing real-time PCR [19]. This technique is based on the use of fluorescent reporter molecules in order to monitor the production of amplification products during each cycle of the PCR reaction. Unmodified fluorescent proteins can be visualized by fluorescence microscopy and can serve as probes of environments within living cells. Addition of targeting and retention sequences to fluorescent proteins can be exploited to highlight specific cellular organelles and to follow their dynamics. The fluorescent protein sequencing is developing based on fluorescence emission chemistry [20]. This technique is based on the fundamental origins of the emission color, that is, a theory that is being dealt with in physical organic chemistry as the local environmental variables around the chromophore, including the position of charged amino acid residues, hydrogen bonding networks and hydrophobic interactions within the protein matrix, can produce blue or red spectral shifts in the absorption and emission maxima of as much as 40 nm wavelength [21]. Larger spectral shifts, which distinguish the attributed to differences in the covalent structure and extent of π-orbital spectral classes, which have all been isolated from the sample, exhibit the potential to be useful in a variety of imaging scenarios.

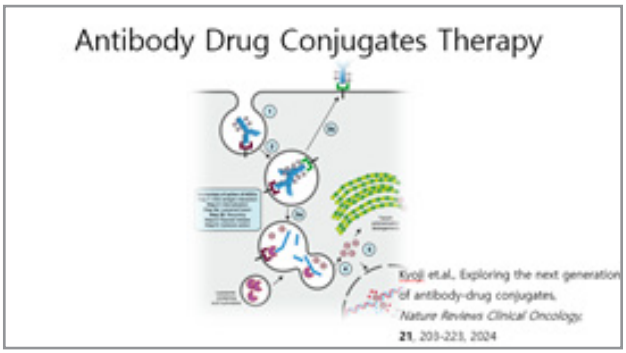
Contribution of Chemistry to the Field of Cancer Therapy

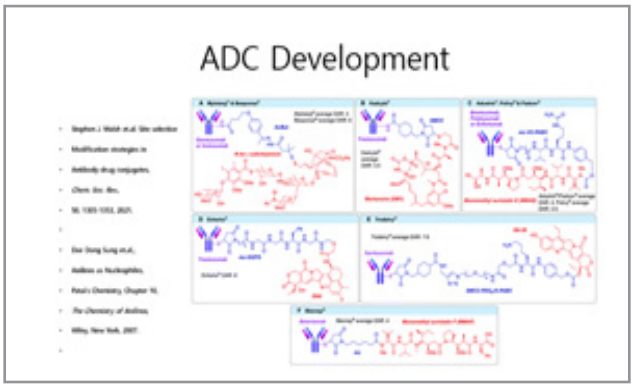
Cancer treatment has been a long-awaited project of mankind [21]. Cancer treatment began a long time ago with surgery, radiation therapy, progressed to chemotherapy, and now includes immunotherapy and heavy charged particle beam therapy [22].

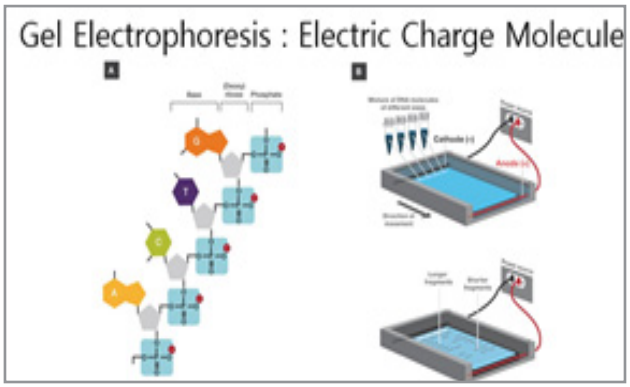


Through numerous trials and errors, cancer treatment has made remarkable progress. Recently, surgery, radiotherapy and chemotherapy have many side effects and now only applied to a few cancer patients. Nowadays, immunotherapy and heavy charged particle beam therapy are becoming common. These days, chemists are taking the lead in opening the way to completely treating cancer patients without side effects. Among them, a method to kill cancer cells using immune cells as T-cell, B-cell and natural killer cell within the human body has been developed [23].









In recent, over the past decade, immunotherapy that enlist and strengthen the power of a patient's immune system to attack tumors, has rapidly become what many call an important role of cancer treatment. That is because immune system boosting drugs have shown the ability to shrink and eradicate tumors in some patients with advanced cancer. These treatment responses can last for years in a small percentage of patients. Drugs called immune checkpoint inhibitors, for instance, are already in broad use to treat people with many types of cancer, including melanoma, lung, kidney, bladder, and lymphoma [24]. Among these immunotherapy treatments, chimeric antigen receptor (CAR)-engineered T cell therapy (CAR-T) has also generated substantial excitement among researchers and oncologists [25]. Although CAR-T cell therapy is not as widely used as immune checkpoint inhibitors, they have shown the same ability to eradicate very advanced leukemias and lymphomas and to keep the cancer at bay for many years. Since 2017, six CAR-T cell therapies have been approved by the Food and Drug Administration (FDA) [26]. All are approved for the treatment of blood cancers, including lymphomas, some forms of leukemia, and, most recently, multiple myeloma. Despite the excitement around theses therapies, they lead to long-term survival in fewer than half of the patient treated. They have also come under criticism for their cost, which, in the case of the most recently approved CAR-T therapy is more than $450,000. CAR-T cells are the equivalent of 'giving patients a living drug', explained [25]. The meaning of T cells which help orchestrate the immune response and directly kill cells infected by pathogens are the backbone of CAR-T cell therapy. Currently available CAR-T cell therapy is customized for each individual patient. They are made by collecting T cells from the patient and re-engineering them the laboratory to produce proteins on their surface called chimeric antigen receptors, or, CARs. The CARs recognize and bind to specific proteins, or antigens, on the surface of cancer cells. These receptors are 'synthetic molecules, they don't exist naturally'. After the revamped T cells are 'expanded' into the millions in the laboratory, they are then infused back into the patient. If all goes as planned, the CAR-T cells will continue to multiply in the patient's body and, with guidance from their engineered receptor, recognize and kill any cancer cells that harbor the target antigen on their surfaces. In recent, CD19-directed chimeric antigen receptor (CAR)-T cells has been reported to be achieved durable remissions in about 30% to 40% of relapsed/refractory large B-cell lymphomas. T-cell exhaustion and/or an immunosuppressive tumor microenvironment may contribute to CAR-T cell failure [27].

Pembrolizumab, an anti-PD1 immune checkpoint inhibitor, may reverse T-cells exhaustion after CAR-T therapy. In the process of detection of CARs with high specificity it is necessary the process of FluorokinesTM, as an efficient tool of fluorescent-labeled recombinant proteins, that enable highly specific detection of cell markers, CARs, immune checkpoint receptors, and more

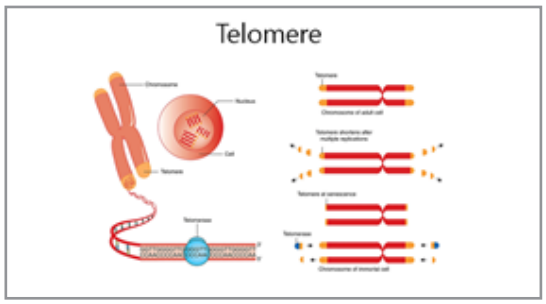
by flow cytometry. Fluorescent-labeled recombination prove has been developed by analytical chemists and physical chemists [28].

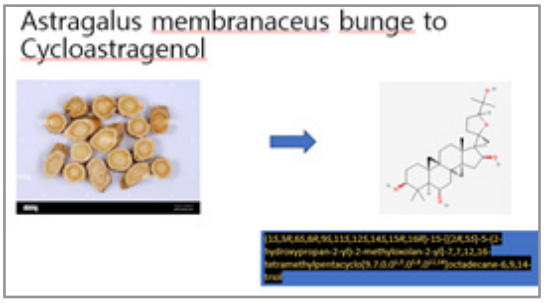
CAR-Natural Killer (CAR – NK) cell therapy is a more advanced treatment method than CAR-T for cancer immunotherapy. NKT cells are characterized by an invariant TCR α chain 18 in human and co-expression of NK markers [29]. NKT cells have demonstrated promising characteristics for the development of off-the-shelf cell therapy. They possess potent tumor-killing activity and can infiltrate tumors, and they bridge innate and adaptive immune response. In clinical studies, autologous CAR-engineered NKT (CAR-NKT) cells have relapsed or resistant neuroblastoma without causing noticeable toxicity or cytokine release syndromes. Antibodies and flow cytometry fluorochrome-conjugated specific for human CD45 is used in CAR-NKT therapy and clinical trials. Fluorescent dye has become an integral tool for protein expression in CAR-T and CAR-NKT therapies. Flow cytometers are using common lasers which are shown 488nm (blue), 405 nm (violet), 532 nm (green), 561 nm (green-yellow), 640 nm (red), and 355 nm (ultraviolet). The flow cytometry is based on photochemistry [30]. Nowadays, photochemistry is making a significant contribution to the research of CAR-T, CAR-NKT and clinical research in many hospitals. Following CAR-T and CAR-NKT, antibody-drug conjugates (ADC) treatment is emerging as a new cancer treatment method that is safer and has fewer side effects [31].

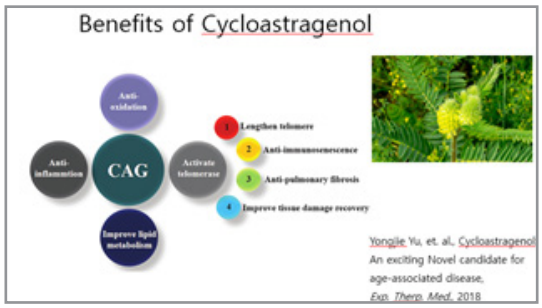
ADC has evolved to merge the high selectivity and specificity of monoclonal antibodies (mAbs) with the cytotoxic potency of attached payloads. ADC comprise a fast-expanding therapeutic modality designed to target cancer cells, sparing the adjacent healthy tissues [31]. ADC treatments are essentially tripartite pro-drugs consisting of an antibody tethered via a chemical linker to a given payload. After their administration, these agents circulate as inactive assemblies which are eventually catabolized via endogenous cleavage mechanisms at the intracellular compartment of the targeted cancer cell. Nowadays, linkers in ADC have been designed to tether the cytotoxic molecule to the antibody scaffold, regulating several prodrug parameters such as circulation stability, solubility, and aggregation propensity. These fields are supported by physical chemistry, especially, solvent properties, molecular spectroscopic chemistry. Cleavable linkers of ADC components, can be used an acid-labile likely, hydrazones, and protease-sensitive/peptide linkers. As an example of the first subgroup, ADC employs a bifunctional 4-(4-acetylphenoxy) butanoic acid part attached to the calicheamicin payload via hydrazone linkage. These techniques are supported by physical chemists and spectroscopic chemists.

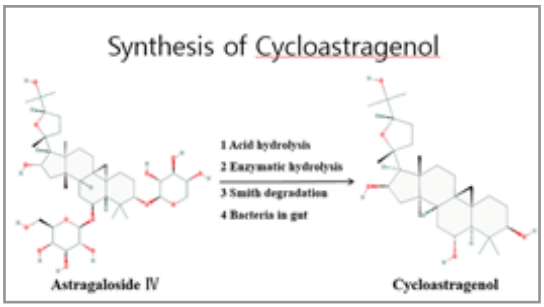
Contribution of Chemistry to the field of Telomere Length and Longevity

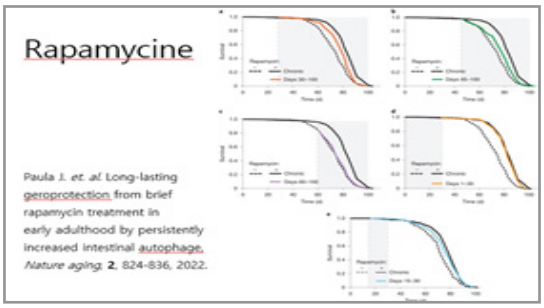
The length of telomeric DNA shortens with each cell division and when it reaches below a critical limit, the cell undergoes replicative senescence or apoptotic cell death [32]. Repetitive regions at the very ends of chromosomes are called telomeres, and they are found in a wide range of eukaryotic species, from human beings to unicellular protists.

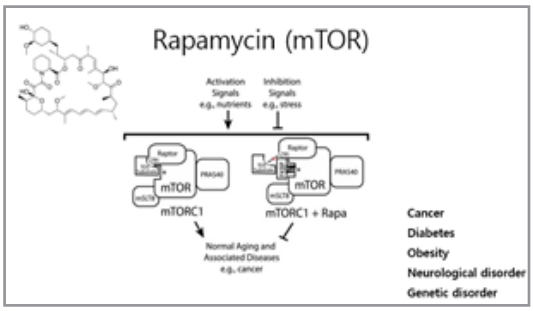


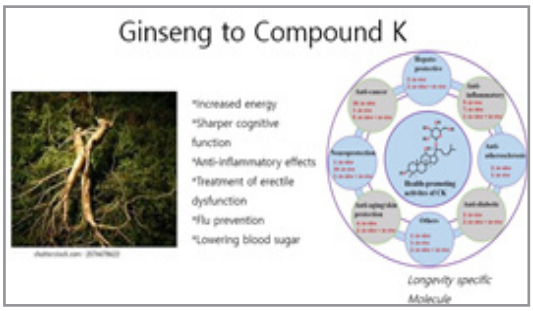


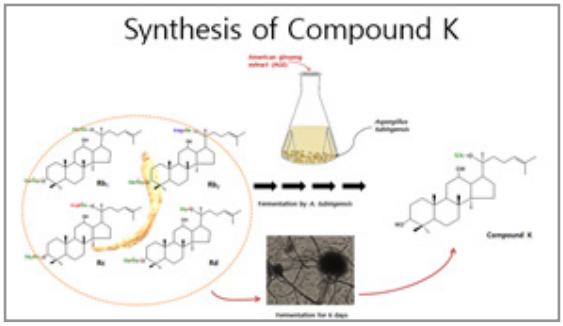












In the telomere effect, biochemists and Nobel Laureates, Elizabeth Blackburn, Carol Greider, Jack Szostak, explain that telomeres of our body cells, the tiny protective caps on our body DNA, dictate how fast we age: Longer telomeres keep our body cells youthful for longer and healthier life [33]. Telomerase adds complementary RNA bases to the end of the DNA strand. Once the end of the lagging strand template is sufficiently elongated, DNA polymerase adds the complementary nucleotides to the ends of the chromosomes; thus, the ends of the chromosomes are replicated. Telomeric dysfunction, is caused by shortening, deprotection or damage, and by DNA replication stress, triggers focal accumulation of activated DNA damage response (DDR) factors at telomere dysfunction-induced foci. Shortening of telomeres with each cell division, is caused by the 'end replication problem' and nucleolytic activities, eventually results in loss of protection, DDR activation and appearance of dysfunction-induced foci (TIF), causing cellular senescence or apoptosis. Cancer cells activate telomere maintenance mechanisms to counteract replication-driven telomere shortening. and gain replicative immortality. Most often this is achieved through the re-expression of telomerase, an enzyme that catalyzes the addition of telomeric DNA repeats, but a small part of cancers used to an alternative lengthening of telomeres. The techniques of re-expression of telomerase are developed by fluorescent chemistry of photochemistry [34]. Recently, the fluorescent chemists are developing faster and safer analysis techniques by incorporating molecular spectroscopic technology into telomerase enzyme analysis [35]. Advances are being made in new drugs that lengthen shortened telomeres from with help of extraction of natural products and with help of organic synthetic chemistry [36]. Efforts to restore the life clock at the end of DNA to a healthy state by increasing telomere length are continuing by synthetic organic chemists, physical chemists, and computational chemists. It can be increasing the length of telomeres at the end of DNA damaged by chronic disease by activating the telomerase enzyme. Among the candidate substances that activate telomerase, cycloastragenol, rapamycin, and compound K are known to play a role in extending already damaged telomere length [37, 38, 39]. Cycloastragenol increases telomere length contributing anti-immuno-senescence, anti-pulmonary fibrosis and improve tissue damage recovery [40]. Cycloastragenol is obtained by enzymatic reaction or acid decomposition of astragaloside IV extracted from astragalus roots [41]. In China and Korea, astragalus has been used to treat diseases for thousands of years [42]. Cycloastragenol was recently discovered by chemists to determine which ingredient in astragalus is effective in treating diseases. Chemists discovered that among the active molecules contained in astragalus extract, cycloastragenol, which is converted from astragaloside IV. Astragaloside IV is absorbed from the intestines of the human body and then converted into through an enzymatic reaction. However, it is very difficult to make cycloastragenol in the laboratory, and even if it is made in the laboratory, the amount is very small. Since the amount of cycloastragenol obtained at the laboratory is too small, with the technology of solvent chemistry among physical chemistry, a large amount of cycloastragenol can be obtained [43]. Rapamycin is another molecule that has been recommended to lengthen damaged telomeres [44]. It is known that rapamycin was discovered on Easter Island as an antibiotic produced by an aerobic Gram-positive soil bacterium, especially *Streptomyces hydroscopicus* AY B-994, and named in reference to the island's indigenous name Rapa Nui. Rapamycin shows acting both as a potent inhibitor of fungal cell growth and as an immunosuppressant and anticancer drug in humans [45].

Rapamycin was shown that is identified the highly conserved the mammalian target of rapamycin (mTOR) kinase [46]. mTOR is a kinase that in humans is encoded by a member of the phosphatidylinositol 3-kinase-related family of protein kinase. Following the discovery of mTOR, the field has been exploded with studies describing partners from the center of an intrinsic signaling network that controls virtually every aspect of growth and metab-

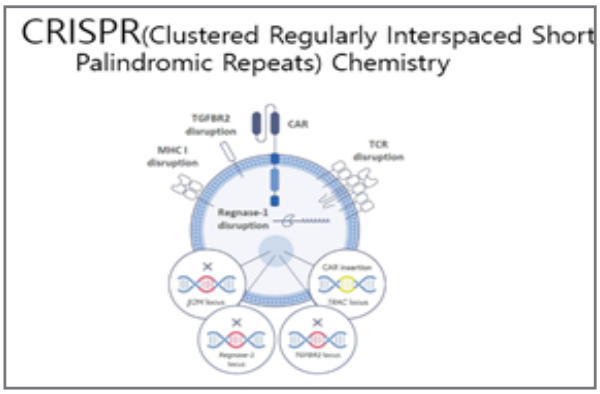
olism. Indeed, dysregulation of mTOR is involved in many human diseases, including cancer, and plays roles in aging as well as responses to environmental and nutritional stress. Rapamycin is currently well known as a molecule that increases the length of damaged telomeres [46]. Rapamycin is attracting attention as a drug that slows aging by increasing the length of telomeres damaged by various chronic diseases as long-lasting inhibition of aging from brief rapamycin treatment in early adulthood by persistently increased intestinal autophagy. The crystal structure of rapamycin shows to be bound to Tacolimus (FK506) binding protein 12 (FKBP12) and its binding domain in mTOR, the hydroxyl group is key for making the first generation of Rapalogs, pokes out from between the two. FKBP12, the 12-kDa FK506 binding protein, is a ubiquitous abundant protein that acts a receptor for the immunosuppressant drug FK506, binds tightly to interacellular calcium release channels growth factor β (TGF-β) type receptor [47]. In this process, the techniques of phosphate labeling and immunoprecipitation are using. For the phosphate labeling ^{32}P phosphate, the phosphorus isotope, fibroblasts, plated in dishes, were washed and preincubated containing dialyzed fluorescence correlation spectroscopy (FCS) [32]. Isotope chemistry and spectroscopic chemistry play a major role in tracking the process by which rapamycin increases immunity and also increases the length of the damaged telomeres in the human body [48].

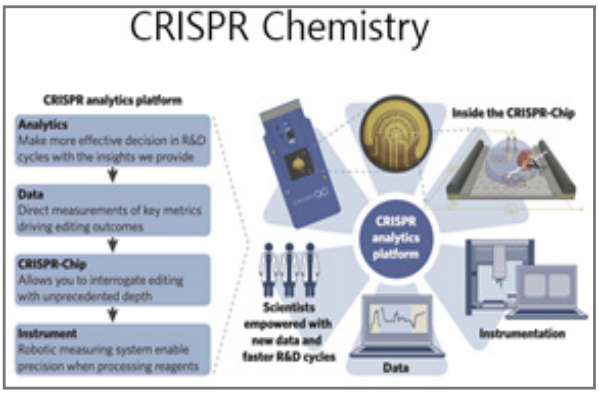
Compound K is another molecule that has been recommended to lengthen damaged telomeres [49]. It is known that compound K was discovered during research into how ginseng is absorbed in the intestines of human body. Ginseng has been used as a health supplement and medicine in Korea, Japan, and China for thousands of years [50]. Ginseng has long been known to have, revitalizing effect as increasing energy, sharper cognitive function, anti-inflammatory effects, treatment of erectile dysfunction, flu prevention and lowering blood sugar [51]. Compound K is turning out to be a more useful molecule in treating human diseases and maintaining healthy environment of human body as hepato-protective, anti-inflammatory, anti-atherosclerosis, anti-diabetic, anti-aging/skin-protection, neuroprotection and anti-cancer [52]. Recently, chemists discovered a precursor molecule that changes into compound K molecule among saponin molecules extracted from ginseng. Apart from the reaction in the human body, compound K can be obtained in the laboratory through a chemical reaction of Rb1, Rb2, Rc, and Rd saponin molecules [53].

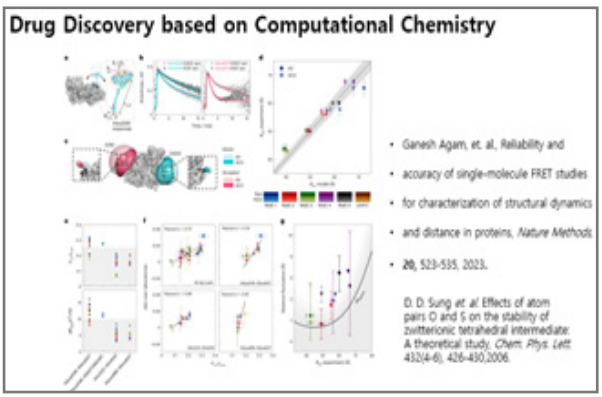
When making compound K from saponin molecules, Rb1, Rb2, Rc and Rd, confirmation knowledge is using a 420nm wavelength detection by using spectrophotometer, separation technique of various solvent systems, and determination tool of total phenol contents must be used. The techniques are provided by photochemistry and solvent chemistry [54].

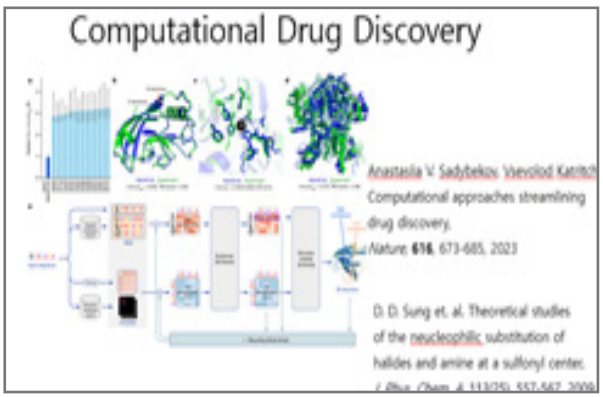
Contribution of Chemistry to the Field of Cell and Gene Therapy

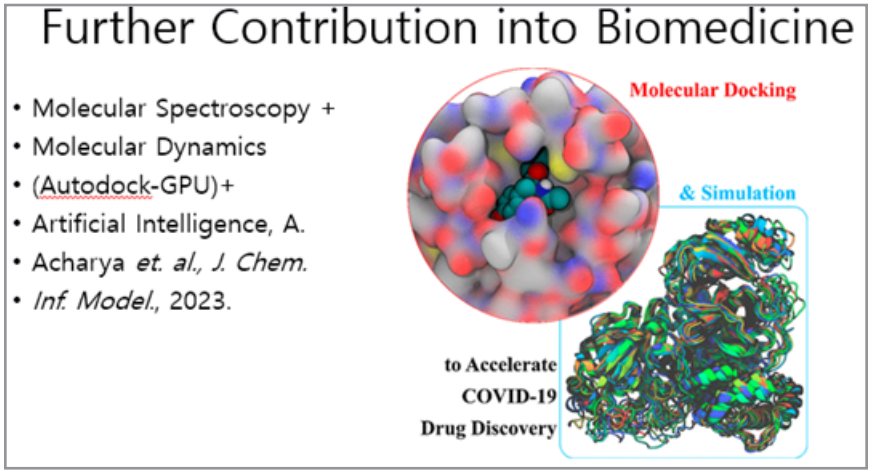
Cell and gene editing technologies have made a significant contribution to the development of biomedicine [55]. Cell and gene therapy technologies opened up the possibility of treating incurable chronic diseases by Nobel Laureat, Jennifer Doudna and Emmanuel Charpentier introduced as clustered regularly interspaced short palindromic repeats (CRISPR) [56].











CRISPR is based on the CAR chemistry treating, transforming growth factor β-receptor 2 (TGFBR2) disruption, major histocompatibility complex 1 (MHC1) disruption, Regnase-1 disruption, Engineering T-cells based on T cell receptors (TCR) disruption, β2M locus, CAR insertion, T-cell receptor α constant (TRAC) locus. In recently, a large and ever-expanding set of CRISPR-Cas systems now enables the rapid and flexible manipulation of genomes in both targeted and large-scale experiments [57]. CRISPR associated protein 9 (CAS9) is a programmable endonuclease that allows targeted cleavage of DNA in virtually any organism. Guided by a short RNA sequence, CAS9 binds onto the complementary genomic DNA and subsequently induces DSB. CAS9 contains two magnesium-dependent nuclease domains: an HNH domain that cleaves the complementary strand of DNA target, and an endonuclease domain named for an *E. coli* protein involved in DNA repair (RuvC) domain responsible for cleavage of the displaced noncomplementary DNA strand. When performing gene editing using CAS9, conformational calculation and quaternary structure theory are essential. The theory is based on the three-dimensional structure consisting of the aggregation of two of more individual polypeptide chains that operate as a single functional unit and the populate ensembles of conformational state. Protein dynamics and conformational changes based on quantum chemistry allow proteins to function as nanoscale biological machines within cells, often in the form of multi-protein complexes [58]. Numerous software tools and analytical methods based on chemistry, have been developed for the design and analysis of CRISPR-Cas experiments, including resources to design optimal guide RNAs for various modes of manipulation and to analyze the results of such experiments. It enables to make more effective decision in applying medicine as gene editing for patients and also enable to perform direct measurements of key metrics driving editing results. In order to treat chronic diseases that many scientists and medical researchers cannot yet treat, it is important to first identify the faulty gene protein structure. Quantum chemistry dynamics and three-dimensional molecular structure analysis techniques are being used more accurately reveal protein structures [59-63].

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Conflict of Interest

No conflict of interest is perceived by the author.

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