Tabriz University of Medical Sciences

AGING RESEARCH INSTITUTE NEWSLETTER

Tabriz University of Medical Sciences (TUOMS)

Editorial

AGING AND THE FUTURE

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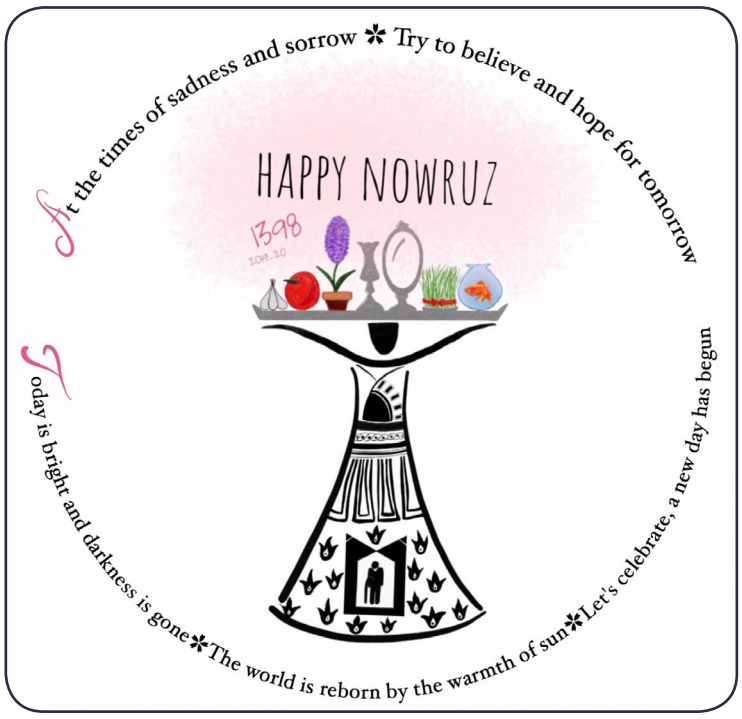
Aging is a journey into the future. It begins at conception and ends at an unpredictable moment in the future after a variable passage of time. Aging is a dynamic process, reined in by more or less balanced biological processes that are shared by all humans, although not to the same extent. The biological processes are the basis for the study of aging by biomedical methods. The methods allow the scientists of aging to determine and compute several measures that contribute to the average life times that characterize different populations of humans. It is well known that some groups can look forward to live to ripe old ages while others must accept somewhat more modest expectations.

Among the groups with different dynamics of aging are those of men and women. The genders have different lifetime expectancies that have risen significantly, also in the last four decades. In 1975, men on average lived 70 years, with the most common age at death of 74 years (modal age), while women on average lived 76 years, with the common age at death of 82 (modal age). In 2015, 40 years later, the life times had increased to an average for men of 77 years (modal age 85 years), and to an average for women of 81 years (modal age 89 years). Not only had the gap diminished but the drop-off after the modal peak had sharpened, as a sign that many shorter lifetimes had undergone a considerable prolongation, undoubtedly because some of the causes of early pathological aging had been eliminated. The question is now whether the curves of the numbers of deaths versus age will become increasingly skewed, as mankind perhaps approaches some absolute lifetime limit, with a sudden drop to zero deaths after, say, the ripe old age of 120 years, the highest age of death ever recorded for a human being, in that case a woman.

The averages of lifetime durations help the scientists understand the processes and the factors that influence the individual life expectancies and the averages help them predict how long different groups of people may live in the future. However, it is important to emphasize that the understanding collected by scientists also begs another question: We need to know what the goals are of the science of aging: Is the most important goal of this branch of science really no more than the prolongation of human lifetime expectancy at any cost? Assume for a moment that the science of aging could reveal and then inactivate all the mechanisms that end human lives in the course of aging. Considering the deteriorating conditions of the planet, and the effects of overpopulation, would such a program be embraced by reasonable people as consistent with the future of life in general? But there is also a biological issue: How did it come to pass that there is a lifetime limit in the first place? Here it may be worth to remember that some cells in our bodies are the direct descendants of the first cells on earth, even if all the atoms and molecules have been exchanged. Some cells never died. From the point of view of these master cells, the bodies that housed them through the ages were merely the temporary lodgings of these cells until they moved on.

The problem is that any alternative to live [cont.]



Designer and poet of above design "Happy Nowruz" are Hila Navadeshahla and Pooriya Sadeghi, Medical Students of TUOMS, respectively.

Mini Review

Is Vaccination Against Alzheimer's Disease Helpful?

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Abstract

Alzheimer disease (AD) is a major neurodegenerative disorder, which is characterized by a general decline in cognitive function. The number of cases of AD will increase as the number of elderly rises. The accumulation of amyloid beta (Aβ) and neurofibrillary tangles in the brain are believed to play a role in the progression of AD. Many drug treatments have been developed but there have been more failures than successes. Vaccination is considered the most cost-effective public health intervention. Immunization against Aβ in patients has been shown to reduce Aβ levels but failed to improve cognitive function. However, tau immunotherapy has been shown to decrease both phosphorylated tau and amyloid burden and improve cognitive function. Next generation of vaccines will advantage from concurrent Aβ and tau targeting.

Keywords: Alzheimer disease; Immunotherapy; β-amyloid; tau protein; Vaccination

Introduction

Alzheimer's disease is a destructive neurodegenerative disease [1]. AD is the most common form of dementia in the aging population and is characterized by a progressive loss of memory and a general cognitive decline [2]. Neurodegenerative diseases such as AD, Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) and prion diseases are progressively being recognized to have common cellular and molecular mechanisms [3]. These diseases involve the misfolding and aggregation of specific proteins into abnormal and toxic species [4].

The neuropathological features of AD include neurofibrillary tangles, deposition of β-amyloid (Aβ) in senile plaques, and neuronal loss [5]. Experiments with synthetic Aβ peptide and animal models have suggested that pathogenesis of AD involves soluble assemblies of Aβ peptides [6]. Parkinson's disease and Huntington's disease have similar amyloid origins and the risk of getting any of these diseases increases dramatically with age [7]. [cont.]

Editor-In-Chief's Message

Prof. Hassan Soleimanpour

Nowruz; the message of solidarity, union and sodality for all around the world

There is a deep message in the tradition of the ancient ritual and cultural events of Nowruz; a message about knowing the world and creation. Therefore, if we take a deep look at Nowruz, we will find the creation of the world in it.

Unfortunately, the start of this year and Nowruz coincided with the tragic event of flooding in our country, which caused feelings of grief in Iranians and all the people of the world. Expressing sympathy with our own fellow-countrymen, editorial board of Aging Research Institute Newsletter and I are grateful to all of our compatriots and countries helping the flood victims.

Fourtheremore, I am very pleased to take this opportunity to wish members of editorial board, all our independent expert referees, and all members of TUOMS a Very Happy Persian New Year. On behalf of the editorial board, we should like to express our gratitude to our contributing readership and our editorial team for their valuable contributions to the success of second issue of Aging Research Institute Newsletter.

Director of NSRC's message

Prof. Mehdi Farhoudi

Nowadays neurosciences as a multidisciplinary field makes a special position in the world; and related translational researches are one of important priorities of new generation universities. Neurosciences has extended in different levels such as molecular, cellular, human related and physics, and it has developed in many different fields including medical, cognitive, behavioral, psychological, sociological, imaging, computational, engineering, linguistic, mathematics, philosophy and physics.

Increasing and extending of human knowledge in every field may be as a potential value and makes us more familiar with secrets and wonders of world and God as creative of everything, but it is not enough. Nowadays and every day, the sciences are more valuable and important which are beneficial by making products and or technology to promote us for solving faced real problems in many domains such as prevention and or diagnosis/ treatment of a disease, improving a process to achieve neuroscience related health.

We hope that NSRC[1] can mobilize every related thoughts and abilities in the university, region, country, and abroad and find more supports to attain its final goal that is in a word, promotion of human health.

1. Neurosciences Research Center

Editorial [cont.]

forever is unclear. An alternative would have to address the issues of at what age(s) and under what circumstances the majority of people would be satisfied that they have lived full lives, after which any extension would be unreasonable and indeed undesirable. The context here is normal aging, as clearly different from the exigencies of abnormal aging to which other considerations obviously apply.

While we accept that abnormal aging is a challenge that must be met at all cost, the agreement is much less than universal when the topic is the future extensions of normal aging.

An important task may be for the scientists to discover the limits of normal aging if they exist and then to focus on the challenges of abnormal aging that are evident in a number of communities and countries around the world. The problem here of course is the possibility that the transition from normal to abnormal aging is so gradual that the change from one to the other is imperceptible such that we can never say with certainty that the process definitely has become abnormal and only now deserves the attentions of the researchers of aging.

As aging is indeed a journey into the future, it may be of value to explore more clearly how humans deal with the future challenges and how they choose which course to adopt for the coming journey into the future and what steps to take to adopt one particular future prospect over another. This is the task of the predictive brain and the mechanism of predictive coding that serves to satisfy the anticipatory urges of the humans to whom these brains belong. The power of anticipation may be the most important competence of the human brain.

Table 1: Measures of central tendency in age at death for men and women in 1975 and 2015 based on observed deaths (Note: IQR = Inter Quartile Range).

Men	Modal age	Average age	SD	Median age	IQR
1975	74	70.3	11.4	70.6	15.1
2015	85	76.5	13.2	78.6	17.4
Women	**Modal age**	**Average age**	**SD**	**Median age**	**IQR**
1975	82	75.6	11.9	77.0	15.5
2015	89	81.4	12.7	83.8	15.4

Table 1 shows three measures of central tendency for each gender - the mode, average, and median - and two measures of variability - the standard deviation and inter-quartile range. It shows an increase in all three measures and a widening in variability based on the inter-quartile range, which is 2.3 years greater for men and 0.1 years for women. The standard deviation also widens but the amount is the same at 1.8 years for both men and women. From Mayhew et al. 2018 with permission [1-4].

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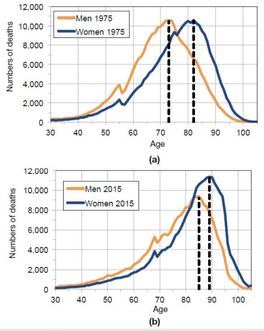

Figure 1: Charts showing the number of observed deaths by age and sex for England and Wales in (a) 1975 and (b) 2015 (hatched lines show the modal age at death). From Mayhew et al. 2018 with permission [1-4].

Neurosciences Research Center (NSRC)

The first steps for the foundation of Neurosciences Research Center (NSRC) of Tabriz University of Medical Sciences were taken by organization of a multidisciplinary research team in 2003 at Imam Khomeini Hospital. Overtime, with increment of research projects, the team decided to establish a research center. After, selection of founding board, and preliminary approval of Medical Sciences Universities Expansion Council, NSRC was finally established in 2006. Later in 2007, with the formation of NSRC`s research and policy councils, and also selection of Dr. Mahdi Farhoodi as director of the research center, the principle consent was issued from Ministry of Health and Medical Education (MOHME). Eventually, with increased cooperation of NSRC with other national/international research centers, admission of PhD students, and setting up of its well-equipped laboratories, NSRC achieved to get the definite consent of MOHME in 2009.

Currently, NSRC has numerous projects in cooperation with a wide range of local state and private universities, in various industrial, computational, basic sciences, clinical, diagnostic, and rehabilitation fields. NSRC has also accomplished the mission of expanding and deepening its international relations through working on some joint projects with the universities in Denmark, United States, United Kingdom, and Canada, which has led to publication of joint articles and designing research projects for PhD students.

NSRC is now working on conducting pre-clinical and clinical studies, and has succeeded to answer the ever-increasing demands of researchers by establishing specialized laboratories in the fields of motor and cognitive behavior, molecular neurobiology, surgery of laboratory animals, histopathology, electrophysiology, and cognitive evaluation and rehabilitation.

It has also paid special attention on conducting field studies and library researches, including disease registries or narrative and systematic reviews in recent years. Furthermore, in the last few years, by taking "aim-target" policies, the conducted researches of this center are mainly focused on brain vascular, and neurodegenerative diseases. For this reason, the modeling of Brain aging, Ischemia, Stroke, Alzheimer's disease, Parkinson's disease, and other cognitive diseases are developed in this research center.

In the field of education, NSRC hosts successful PhD and Post-Doc courses since 2010, and according to the quantitative and qualitative development of research projects in NSRC, this center is now working with junior and senior researchers in different grades, including MD, Parm.D., D.M.D., MSc, Medical Residency, PhD, and Post-Doc; and hopes to improve this potential by expanding its physical space as soon as possible.

It is also worth noting that one of the major achievements of this center is publish of "Journal of Experimental and Clinical Neurosciences" since 2014. This journal accepts original and review articles from local and international researchers.

Finally, despite all the existing restrictions, NSRC of TUOMS is one of the pioneering neurosciences research centers in Iran, according to annual evaluations; and hopes to maintain this position in the future as well.

Mini Review [cont.]

Alzheimer's disease therapy has been partially successful in terms of developing symptomatic treatments, although has also had several failures in terms of developing the disease-modifying therapies [8]. Acetyl-cholinesterase inhibitors (AChEIs) (donepezil, galantamine, and rivastigmine) are the basis of symptomatic treatment [9]. Low-affinity N-methyl-d-aspartate (NMDA) receptor antagonist (Memantine) has been shown to reduce l-glutamate excitatory neurotoxicity in AD [9]. Therapeutic inhibition of precursor protein synthesis with the use of RNA interference (RNAi) technologies are also being used in AD treatment [7]. Moreover, drugs that prevent protein hyperphosphorylation are also being tested, as well as drugs that induce chaperone expression. Finally, vaccines against aggregates are being developed [7].

Immunotherapy against β-amyloid

The presence of protective immunity against AD, which declines with age, supports the concept of preventive immune therapy or vaccination against this disease [10]. Vaccination against peptides specific to AD produces an immune response that could inhibit disease and symptom development [11]. Both active and passive Aβ immunotherapies have been shown to decrease cerebral Aβ levels and improve cognition in animal models of AD [12]. Vaccinations against Aβ peptide diminished amyloid deposition in a transgenic mouse model of AD and improved cognitive performance [13]. Furthermore, it has been shown in vitro that anti-Aβ antibodies can lead to disaggregation of Aβ fibrils, restoring Aβ solubility and consequently prevent neurotoxic effects on cell lines [14].

Vaccination of AD patients with Aβ42 induced antibodies that had a high degree of selectivity for the pathogenic target structures [15]. Some plaque clearance and modest clinical improvements were also observed in patients following immunization [12]. However, much more limited evidence in human studies supported the significant clinical benefits and it is becoming apparent that they may only be effective very early in AD [16]. In addition, in humans, dosing in the phase 2a clinical trial of the AN1792 Aβ vaccine was stopped when almost 6% of the immunized patients with mild to moderate AD developed meningoencephalitis [11, 12].

Immunotherapy against tau protein

Aggregation of hyperphosphorylated tau protein is a key characteristic of AD [17]. Some evidence shows that pathological tau species can travel from cell to cell and spread the pathology through the brain [18]. Pharmacological manipulation of tau protein in AD comprises tau protein kinase inhibitors, microtubule-stabilizing agents, tau aggregation inhibitors, active and passive immunotherapies, and inhibitors of tau acetylation [19]. Tau-targeted immunotherapies have recently shown potential for AD treatment [11, 19].

Immunization studies in animal models have shown that vaccination decreases intracellular levels of tau and phosphorylated tau and is associated with improved cognitive performance [20]. Moreover, phos-tau-vaccine has been shown to decrease the amyloid burden and improve cognitive impairment in the amyloid-AD-mice [21]. Full-length recombinant tau immunizations in the mouse have not shown any obvious side effect and some tau immunotherapies have now advanced from basic studies to phase 2 clinical trials [22]. Furthermore, the application of small molecules reducing tau aggregation is currently in Phase III clinical trials [17]. Recently, eight humanized tau antibodies and two tau vaccines have entered clinical trials either for AD or frontotemporal dementia (FTD) [18].

Dual Immunotherapy against AD

Both tau antigens and Aβ could be required for AD vaccines [23]. Information gained from the past studies has guided researchers to the development of second-generation Aβ-active immunotherapies, anti-Aβ monoclonal antibodies, and some immunotherapies targeting pathological tau [1]. Superior therapeutic efficacy for the next generation of vaccines will benefit from simultaneous targeting the most toxic species of Aβ and tau [16].

Conclusion

Prevalence of AD continues to grow as the longevity increases. Without effective therapies, the estimated population with dementia will reach 115 to 131.5 million by 2050 [17]. AD is currently incurable and treatments are only symptomatic. Vaccination against AD might be considered as an effective and cost-benefit treatment. Immunotherapy against Aβ although effectively removed Aβ plaques, it did not show significant improvement in cognitive function. Failures in improving cognitive decline by Aβ peptide vaccine and its side effects resulted in the commencement of extensive studies on tau immunotherapy. Efficacy data from tau vaccine clinical trials will be available by the end of [cont.]

Mini Review [cont.]

this decade [18]. Collectively, since the pathophysiology of AD is complex, the best clinical effect seems to be attained by simultaneously targeting of Aβ and hyperphosphorylated tau.

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Scholarly Article Critique by Student

Resveratrol in the Management of Rheumatoid Arthritis

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Incidence and prevalence of rheumatoid arthritis (RA) varies depending on the time and geographic areas. But every year relatively out of every 100,000 people, 41 are diagnosed with RA.[1] In recent years Resveratrol (3,4′,5-trihydroxy trans-stilbene) has attracted much attention to its anti-inflammatory, anti-proliferative, anti-oxidative, and analgesic effects in many studies.[2-7] Considering these effects, a group in Egypt studied the effect of Resveratrol as an adjuvant in the treatment of RA between July 2016 and June 2017, which is the first study conducted in this field. We would like to thank the authors for working on this admired article.

Khojah HM, Ahmed S, Abdel-Rahman MS, Elhakeim EH. Resveratrol as an Effective Adjuvant Therapy in the Management of Rheumatoid Arthritis: a Clinical Study. Clin Rheumatol. 2018 Aug;37

Khojah HM, et al. designed a randomized controlled clinical trial (RCT) including 100 RA patients (68 female, 32 male) followed up by the outpatient clinics of the Rheumatology and Rehabilitation Department of Assiut University Hospital, Assiut, Egypt. They were enrolled in a sequential manner to be randomly placed in either a test group or a control group. The test group received a daily 1g Resveratrol capsule with the conventional treatment for 3 months and the control group received conventional treatment. Assessing the clinical and biochemical markers of RA, Khojah HM, et al. found significantly decreasing of tender and swollen joint count-28, metalloproteinase-3 (MMP-3), undercarboxylated osteocalcin (ucOC), interluekine-6 (IL-6), tumor necrosis factor alpha (TNF-α), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) in Resveratrol treated patients. Therefore, this study suggests the addition of Resveratrol as an adjuvant in the treatment of RA patients. [8]

However, there are some points that should be considered in planning and performing this study:

1. In the selection of samples, inclusion and exclusion criteria are not exactly specified.
2. Selection of subjects for each invention or control group by sequential manner throughout the timeframe cannot be a systematic process of random allocation.
3. Because this study is randomized clinical trial, using placebo in control group could be better idea.
4. Blinding is not exactly specified.
5. Primary and secondary outcome(s) are not defined.
6. According to studies, RA over represents in women.[9] So, there is one question that how the effect of sex is controlled in this study.
7. What is the reason for using SEM instead of SD?
8. ANOVA cannot be appropriate statistical test for investigating pre-test variables.
9. Power of study (sample size estimation) is not determined.

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Student Letter

Aging and older adults: stereotypes and age discriminations in media

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Parallel to the growing rate of global population aging, age discrimination has turned to be a highlighted issue. Social status and dignity of the older adults owes much to the attitude paid by the community towards aged people and aging period [1]. Like other minorities, aged people are subjected to stereotypes, prejudices and discriminations. The stereotyping is a presuppositions by the collective mind of society, and due to oversimplified, hypothetical, exaggerated, and humiliating attributions to the members of a group, it prevents rational judgment and thinking. A touchstone in stereotyping is based on trivial information and clichés, often derived from the community or media.

Stereotypes are among important factors to degrade individuals/ groups identity [2, 3] and also decrease mental, moral and physical abilities of a group [3]. A great bulk of psychological problems experienced by older adults is due to the stereotypes in community, and therefore, aged people's position, dignity, capabilities and capacities are often neglected or trivialized. Of Stereotypes about older adults is that old age is a metaphor for general weakness, disorder, and dependency [4]. This metaphor often makes aged people to admit negative labeling.

According to the labeling theory, individuals' identity and behaviors can be affected by terminologies used to express or classify them. By accepting this axiom, older adults are more talented to a kind of self-fulfilling prophecy. In a way that although these beliefs may contain inaccurate information, only believing them, leads into the changes that make it real those inaccurate information.

The partiality and discrimination may have roots in consciousness or unconsciousness, and may be intentional or unintentional. Either in any case, it induces a negative image from aging and aged people. Age discrimination, fanaticism and prejudices toward aged people is a common issue in governmental, commercial, industrial, medical, and media professions and have become a prevalent problem in cultures and mass media [5-8] . The media can have a profound impact on the propagation of stereotyped thoughts or fighting against them, because they benefit from artistic-visual attractions and they can shape and direct public opinion [9].

The analysis of those themes used about aged people in media products can be an indicator of approaches paid by media toward age discrimination. By having a furtive glance at commercials, movies, TV shows and series content; it becomes clear that the themes used about older adults are either positive (successful, provident, experienced, and ...) or negative (white hair, wrinkles, loneliness, lack of care, socially isolated, depressed, disabled, motor limitation, being needy and independent, weakness, disease and incontinence of urine and feces, and need to use special diapers).

The role and position of mass media in directing collective minds and modifying or strengthening the stereotypes associated with minority groups in general and aged people in particular, highlights the need for more accuracy and control in producing and presenting minority-related subject matters in audiovisual media.

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International Projects (No.2)

Modulation of post-ischemic immune response of T lymphocytes to minimize ischemic brain injury in elderly patients with ischemic stroke

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CD4+CD25+ regulatory T (Treg) cells and Th17 cells play important roles in peripheral immunity. Immune responses are main elements in the pathogenesis of ischemic stroke (IS). The contribution of Th17 cells in IS patients has not been proved, and whether the balance of Treg/Th17 cells is changed in IS patients remains unidentified. In the present study, we studied Th17 and Treg cell frequency, cytokine secretion, expression of transcription factors, related to these cells differentiation, which is compared between IS patients and control group. Thirty patients with IS and 30 individuals as control group were enrolled in this study. The frequency of Th17 and Treg lymphocytes, the expression of transcription factors related to these cells, and the serum levels of associated cytokines were assessed by flow cytometry, real-time PCR, and ELISA, respectively. A significant reduction in proportion of peripheral Treg cell frequency and the levels of TGF-β and FOXP3 expression were observed in patients with IS compared with controls, while the proportions of Th17 were increased dramatically, and these effects were along with increases in the levels of IL-17A and RORγt expression in IS patients. These studies suggest that the increase in proportion of Th17 cells and decrease in Treg cells might contribute to the pathogenesis of IS. Manipulating the balance between Tregs and Th17 cells might be helpful for the treatment of IS. We have published an article with title Peripheral Th17/Treg imbalance in elderly patients with ischemic stroke in the Neurological


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Sciences journal (IF: 2.28) for the first part of our study. For the second part of the study, study of animals, we want to collaborate with Odense University.
In the next step we need mouse model of stroke to study the role of B cells in the inflammatory responses of T cells following stroke. For this purpose, two groups of mice with stroke MCAO (middle cerebral artery occlusion) will be used, a group as control group which have normal immune system and the second group has a defect in B cell called μMT/- (mice, which have a nonsense mutation introduced into the transmembrane exon of the IgM heavy chain resulting in the total deletion of B cells). In this study, after induction of ischemic stroke in two groups of mice, by middle cerebral artery occlusion with filament model the mice infarcted brain tissue volume measured by several staining methods, including Triphenyltetrazolium chloride and the level of the damaged area measured by using NIH image analyzer. T cell responses measured by immunological techniques. In our study: We focused here on the hypothesis that stroke can elicit a chronic, injurious B-lymphocyte-mediated response.
We hypothesized that: Modulation of inflammatory T cells in stroke patients by depleting of B cells might be improving ischemic brain injuries.

Top Article

Congratulations to Dr. Mehdi Yousefi, assistant professor of Immunology, TUOMS, on having his article entitled: "Application of hairpin DNA-based biosensors with various signal amplification strategies in clinical diagnosis" published in journal of Biosensors and Bioelectronics (IF=8.173) which has been selected as the top article of this issue.
To show greetings, Aging Research Institute has given him a special grant.