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46th Sysmex Scientific Seminar

Lecture Guide

Future Prospects for Cardiovascular Disease Research

June 8 2024 Sat.

Seminar details

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Intent

The Sysmex Scientific Seminar, now in its 46th year, is an academic seminar with a long history, which has been held on cutting-edge research topics such as cancer, immunology, and genomics, with a focus on hematology. In the field of cancer, basic research has progressed, causative genes have been identified, molecular targeted therapy has become possible, and prognosis has improved significantly. In the field of cardiovascular diseases, it is expected that the advancements in genomic and omics research will clarify the causes and pathophysiology of these diseases and develop new diagnostic and therapeutic methods. In diseases caused by single gene abnormalities, such as familial hypercholesterolemia, cardiomyopathy, and hereditary arrhythmias, genome analysis will determine diagnosis and treatment methods, enabling personalized medicine. Genetic factors also play a major role in cardiovascular diseases that are related to other factors, such as myocardial infarction and atrial fibrillation, making it possible to predict the risk of disease onset and provide prevention and early intervention. In order to extend healthy life expectancy in Japan, basic research on genomics, immunity/inflammation, metabolism, and aging in cardiovascular diseases is expected to be promoted to develop biomarkers, new testing methods, and preventive measures.

This seminar has been attended by not only physicians but also clinical laboratory technologists and many other healthcare professionals, including those from overseas. We hope that this seminar will provide a good opportunity to discuss and deepen understanding of the future prospects of cardiovascular disease research.

Kenichi Hirata
Division of Cardiovascular Medicine, Kobe University Graduate School of Medicine
Sysmex Scientific Seminar Planning Committee

Program (Lecture: 50 mins / Q&A: 15 mins)

*all times are JST

10:00 ▼ 10:05

Opening Address

Yutaka Yatomi

Chairperson of Sysmex Scientific Seminar planning committee

10:05 ▼ 11:10

The Future of Cardiovascular Medicine

Issei Komuro, M.D., Ph.D

Vice President, International University of Health and Welfare /
Specially Appointed Professor, Department of Frontier Cardiovascular Science, Graduate School of Medicine,
The University of Tokyo

11:10 ▼ 12:15

How Can We Prevent Cardiovascular Aging?

Tohru Minamino, M.D., Ph.D

Professor and Chairman, Department of Cardiovascular Biology and Medicine,
Juntendo University Graduate School of Medicine

12:15 – 13:35 Break

13:35 ▼ 14:40

Precision Medicine for Primary Dyslipidemias and Atherosclerotic Cardiovascular Diseases

Hayato Tada, M.D., Ph.D

Assistant Professor, Department of Cardiology, Kanazawa University Hospital

14:40 – 14:55 Break

14:55 ▼ 16:00

Addressing Unmet Needs in the Cardiovascular Area by Industry-Academia Collaboration:
Establishment of a Novel Method to Assess HDL Functionality

Ryuji Toh, M.D., Ph.D

Associate Professor, Division of Evidence-based Laboratory Medicine, Kobe University Graduate School of Medicine

16:00 ▼ 16:05

Closing Address

Kenichi Hirata

Planner of the 46th Sysmex Scientific Seminar

Free-of-charge Webinar

* All registrants will have free access to the seminar textbook
(download link will be sent via e-mail)

The Future of Cardiovascular Medicine

Issei Komuro, M.D., Ph.D
Vice President, International University of Health and Welfare /
Specially Appointed Professor, Department of Frontier Cardiovascular Science,
Graduate School of Medicine, The University of Tokyo

Summary

As Japan becomes a super-aged society, the disease structure is changing, and the number of patients with cardiovascular diseases such as heart failure and atrial fibrillation that develop with age is rapidly increasing. In particular, heart failure, the terminal manifestation of all cardiovascular diseases, has become a major problem, with the number of patients and deaths increasing. Although progress has been made in the treatment of heart failure with both pharmacological and non-pharmacological therapies, most therapies are limited to symptomatic treatments such as cardioprotection and cardiac replacement, and molecular targeted therapies based on the pathogenesis of the disease, such as those for cancer, have not been developed. Cardiovascular disease is an "ultra-complex system" in which genetic and environmental factors are intricately intertwined, making it difficult to elucidate the pathogenesis. Heart failure, in particular, is an even more challenging problem because not only do numerous genetic and environmental factors play a role in its pathogenesis, but it is also a dynamic problem that must ultimately be solved through the contraction and relaxation of the heart. However, recent advances in data science have made it possible to analyze the pathogenesis of cardiovascular diseases, including heart failure, with more information than any other disease.

Future of Cerebrovascular and Cardiovascular Disease

Japan has become a hyper-aged society and the disease structure has changed dramatically. The number of patients with cardiovascular diseases such as stroke, heart failure, and atrial fibrillation, which tend to increase with age, has risen drastically. While cancer has been the leading cause of mortality in Japan for over four decades, when limited to the elderly population, the number of deaths from cerebrovascular and cardiovascular diseases (CVDs; stroke and cardiovascular diseases combined) are comparable to that from cancer. The average life expectancy of Japanese men and women rank among the highest in the world, currently 81 and 87 years, respectively, and are still increasing. However, there is a gap of 9 years for men and 12 years for women between the average life expectancy and the healthy life expectancy, which is the life span in which people can live independently without medical restrictions, and the number one cause is cardiovascular disease. Among the various types of disorders in CVDs, the most problematic is HF. There are approximately 1.2 million patients with HF currently in Japan, and this number is expected to keep rising until at least the year 2035. HF is at the top of the mortality list among cardiac diseases.

Regarding HF treatment, numerous large-scale clinical studies have been conducted for the past 30 years or so, demonstrating prognostic improvement with four drugs: angiotensin converting enzyme inhibitors/angiotensin II receptor antagonists, beta blockers, and mineralocorticoid receptor antagonists. More recently, four new HF drugs with different action mechanisms have become available one after another. Also, non-pharmacotherapeutic approaches specific to CVD treatment, such as catheter- and device-based therapies, have progressed considerably. Despite such major advances in HF therapy, the survival rate of HF patients remains far lower than the average all-cancer survival rate because all the HF therapies available are symptomatic, rather than pathology-based treatment of the cause.

In response to the major problems described above, the government enacted Cerebrovascular and Cardiovascular Disease Control Act in 2018, and following this, the National Plan for Promotion of Measures Against Cerebrovascular and Cardiovascular Disease was formulated in 2020. This Plan has three major goals in accordance with the three basic principles of the Act. The first goal is to “spread awareness of prevention measures and accurate information on CVD.” The Japanese public are largely

familiar with cancer, whereas only a few people have a correct understanding of CVD. It is significant for the public to learn about CVD including its prevention measures, since this disease is highly preventable. The Japanese Circulation Association was established in 2021 for the purpose of educating as many people as possible about CVD, and promoting linkage with patients suffering from this disease.

The second goal is to “improve the system for providing services related to health, medical care, and welfare.” This goal includes the promotion of health checkups, improving emergency transport systems, securing medical care systems, and providing patient support, rehabilitation, consultation support, palliative care, treatment-work balance and employment support, and measures to take against CVD from childhood or young adulthood onward. Especially for HF, guidance and management after hospital discharge are important, and it is impossible for specialists alone to provide sufficient support. The Certified Heart Failure Educator system was thus introduced in 2020 by the Japanese Circulation Society.

The third goal is to “promote research on CVD.” As stated before, many CVD therapies remain symptomatic, and pathophysiology-based treatment has yet to become available. To achieve pathophysiology-based molecular targeted therapy, like in cancer treatment, the mechanisms of CVD onset need to be uncovered first. It is essential to elucidate the molecular mechanisms of CVD development via genome and/or omics analysis, and verify the findings obtained using CVD models. AI-IoT-mathematical models, which have been attracting attention from various fields, can be broadly applied in the area of cerebrovascular and cardiovascular conditions, where numerous types of diagnostic devices are used. It is our hope to acquire a vast amount of clinical information in a burden-free manner from patients using wearable and/or non-contact devices, and to accomplish rapid and proper diagnosis, prevention, and treatment with the assistance of AI and other technologies.

Glossary

Angiotensin-converting enzyme (ACE) inhibitor:
An antihypertensive drug. By inhibiting angiotensin-converting enzyme (ACE), it suppresses angiotensin II production and lower blood pressure.

Angiotensin II receptor inhibitor:
An antihypertensive drug. By antagonizing angiotensin II and preventing it from binding to its receptors, It lowers blood pressure by inhibiting angiotensin II's vasoconstrictive and other effects.

Beta-blockers:
Blockade of β1 receptors expressed in the myocardium suppresses cardiac function and reduces blood pressure by decreasing blood output.

Mineralocorticoid Receptor Inhibitors:
By binding to mineralocorticoid receptors, these agents inhibit the action of aldosterone secreted by the adrenal glands, thereby reducing tubular reabsorption and lowering blood pressure. Also called aldosterone antagonists.

How Can We Prevent Cardiovascular Aging?

Tohru Minamino, M.D., Ph.D
Professor and Chairman, Department of Cardiovascular Biology and Medicine,
Juntendo University Graduate School of Medicine

Summary

The incidence of lifestyle-related diseases increases with age and, as a result, is the underlying pathology for the development of ischemic heart disease and stroke. These diseases, which shorten healthy life expectancy, can be viewed as part of the traits of aging, as they are commonly observed in many elderly people. In other words, the ultimate target for treatment of these diseases may be the mechanisms that regulate life span itself. In this current situation, research on the mechanisms of aging and lifespan has made tremendous progress in the last 20 years. There are many theories on the mechanisms of aging, one of which is the "cellular aging hypothesis". This hypothesis proposes that aging and metabolic stresses such as overeating cause the accumulation of senescent cells in various tissues, which in turn cause tissue damage and impair tissue regeneration through the secretion of inflammatory molecules, resulting in organ and individual cells aging. In fact, we have shown that the accumulation of senescent cells in blood vessels, heart, and visceral adipose tissue is involved in the onset and progression of atherosclerosis, heart failure, and diabetes, respectively. Furthermore, it has recently been shown that senescent cell removal (senolysis) ameliorates pathological aging traits. In this article, we would like to discuss the possibility of anti-aging therapies targeting senescent cells (seno-antigen, seno-anergy-related molecules).

Cellular senescence and age-related diseases

Cells have a limited capacity for proliferation; after a certain number of cell divisions, they irreversibly undergo cell cycle arrest. In addition, in the event of irreparable genome damage, the cells involved stop dividing and become senescent through activation of the p53/p21- or the p16-dependent cellular senescence pathway. This is considered one of the tumor suppressive mechanisms. We have proceeded with our senescence research on the basis of a cellular senescence hypothesis: senescence on the cellular level plays a role in the expression of some organismal senescence phenotypes, especially those of pathological senescence with age. Our studies showed the involvement of senescent cell accumulation in the genesis and progression of atherosclerosis and insulin resistance by demonstrating the accumulation of senescent vascular cells in human atherosclerotic lesions and accumulated senescent cells' exhibition of various dysfunctional vascular traits (e.g., decreased nitrogen oxide production or enhanced expression of inflammatory molecules)[1)2)]. Senescent cell accumulation was also noted in the visceral fat of obese mice and patients with type 2 diabetes; in them, a senescence-associated secretory phenotype (SASP) factor, in addition to p53/p21 signaling activation, triggered chronic inflammation and induced insulin resistance. These phenotypes were ameliorated by depletion of adipocyte-specific p53, pointing to the crucial involvement of senescent cell accumulation in adipose tissue in the onset and advancement of type 2 diabetes[3)]. Additionally, we found that in the condition of heart failure (HF), activation of myocardial, vascular, and macrophage p53 signaling in the cardiac tissue was involved in the genesis and progression of HF, that the cardiac function was further negatively regulated by HF-associated activation of p53 signaling in adipose tissue, and that these vicious cycles were moderated by the depletion or suppression of adipose tissue-specific p53[4)5)].

The above results indicate that p53-dependent senescence signaling activation plays a role in pathological senescence, and that suppression of this activation may potentially inhibit the onset and progression of age-related diseases such as atherosclerosis, HF, and diabetes. However, since p53-targeted antisenescence therapy is likely to promote tumorigenesis, different therapy strategies need to be developed.

Senolysis

Meanwhile, Baker et al. from Mayo Clinic College of Medicine produced transgenic mice to enable p16-positive senescent cell clearance via drug-induced apoptosis, and reported that senescent cell elimination ameliorated various senescence phenotypes in experimental progeroid mice and aged mice, with a potential for lifespan extension. The key point here is that the senolysis strategy was shown to possibly suppress, not only not induce, tumorigenesis. It was also noted that senescent cell clearance by senolytics might extend aged mice's lifespans, in addition to improving various senescence phenotypes, and conversely that introducing a small quantity of senescent cells into aged mice promoted pathological senescence phenotypes, shortening their lifespans. However, many of the senolysis reported to date are nonspecific, targeting the apoptosis resistance of targeted senescent cells, leaving concern over potential side effects. While a particular cellular senescence state has been reported to play an important physiological role, currently available senolytics are likely to act on all types of senescent cells. Against such a backdrop, we identified a seno-antigen that was expressed in a senescent cell-specific way, and successfully developed a senolytic vaccine targeting this antigen[6]. The effects of senolytic vaccination therapy were noted, including improvement in obesity-associated atherosclerosis and dysglycemia, improvement in frailty in aged mice, and lifespan extension in progeroid mice. These results suggest that health span extension may be achieved by the development of senescent cell-targeted treatment.

Glossary

p53/p21:
One of the cancer suppressor genes. In cellular senescence signaling, p53 induces p21 expression, leading to cell cycle arrest and cellular senescence.

p16:
A cancer suppressor gene. p16 induces cell cycle arrest and cellular senescence. It is rarely functional in normal cells, but is expressed and induces cellular senescence when abnormal cell proliferation or canceration is observed. In cancer cells, p16 mutation and functional inactivation are observed.

NO production:
Nitric oxide (NO) acts on smooth muscle in the tunica media of blood vessels to dilate them. Lack of NO causes blood vessels to stiffen, leading to atherosclerosis.

Senescence-associated secretary phenotype (SASP) factor:
Senescent cells secrete a variety of inflammatory proteins into the extracellular space. This phenomenon is called senescence-associated secretory phenotype, and the group of secreted proteins is collectively called SASP factor.

Apoptosis induction:
The induction of genetically programmed cell death (apoptosis) in cells.

Frailty:
A condition that falls between the healthy state and the state requiring long-term care, in which physical and cognitive functions have declined, but with appropriate intervention and support, it is possible to maintain and improve the functions of daily living.

Reference (as of November 2nd, 2023)

1) Minamino T, Miyauchi H, Yoshida T, et al. Endothelial cell senescence in human atherosclerosis: role of telomere in endothelial dysfunction. Circulation. 2002; 105 (13): 1541–1544.
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4) Sano M, Minamino T, Toko H, et al. p53-induced inhibition of Hif-1 causes cardiac dysfunction during pressure overload. Nature. 2007; 446 (7134): 444–448.
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doi: 10.1038/s43587-021-00151-2.

Precision Medicine for Primary Dyslipidemias and Atherosclerotic Cardiovascular Diseases

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Summary

Arteriosclerotic diseases are a major cause of death not only in Japan but also worldwide, and overcoming them is extremely important. Dyslipidemia, the greatest risk factor for atherosclerotic diseases, is an inherited trait, and genetic research has been conducted for its prevention and treatment. Dyslipidemia is not only a risk factor for atherosclerotic diseases, but also a cause of them. In this lecture, I would like to introduce genomic medicine as medical treatment and research, focusing on familial hypercholesterolemia (FH), the most appropriate and frequent monogenic disease related to this topic. I will also discuss the current efforts towards ultra-precision personalized medicine for similar primary lipid disorders and atherosclerotic disease. Additionally, I will present the current status and future developments of ultra-precise personalized medicine based on genetic polygenic risk scores.

Significance of the genetic diagnosis of familial hypercholesterolemia

What is the significance of the genetic diagnosis of familial hypercholesterolemia (FH), which can be deemed a model disorder for understanding the association between dyslipidemia and atherosclerotic cardiovascular disease? Some may question whether clinical diagnosis is sufficient. To answer this question, we performed clinical diagnosis (based on family history, Achilles tendon thickening, and other factors), plus genetic analysis of individuals with marked hyper low-density lipoprotein (LDL) cholesterolemia (LDL-cholesterol [LDL-C] ≥180 mg/dL). They were classified into four groups based on FH clinical diagnostic criteria and FH-causing gene mutation status, and evaluated for odds ratios for coronary artery disease (CAD) risk. Intriguingly, compared to "clearly non-FH" subjects - despite having LDL-C levels ≥180 mg/dL - who neither met any clinical diagnostic criterion for FH nor carried any FH-causing mutation, those with either an FH clinical sign (e.g, Achilles tendon thickening) or a single FH mutation had significantly increased odds ratios for CAD risk, and even higher odds ratios in the presence of both an FH clinical sign and an FH mutation[1]. These results indicate the additive utility of genetic diagnosis as well as the importance of clinical diagnosis of FH.

Polygenic risk scores based on numerous common single nucleotide variants (SNV)

In general, the effect of a common single nucleotide variant (SNV) alone on a disease is very small, which almost nullifies the clinical significance of evaluating each variant separately. Now genome-wide association studies, which have been actively conducted since 2007, have identified numerous SNVs associated with CAD risk. In 2016, we discovered that a polygenic risk score (PRS) composed of 50 CAD-associated SNVs provides information more useful than and independent from family history in CAD risk prediction[2]. Research in this field progressed further, and a study utilizing SNV information from 6.6 million individuals found that surprisingly 8% of the population had more than three times higher odds ratios for CAD risk (clinically highly significant in terms of risk stratification)[3]. To our great interest, these polygenic high-risk individuals are reported to be difficult to identify from conventional risk factors, such as blood pressure and LDL-C levels. Namely, clinically significant high-risk subgroups like the one accounting for 8% of the population are only detectable using PRS that take numerous relevant SNVs into account. It has been evident from analysis of extreme phenotype patients with early-onset myocardial infarction (MI) at age <55 years that FH mutations contribute to a certain degree to this phenotype. More recent analysis has found an association between early-onset MI and both FH mutations and polygenic state,

being equivalent in the magnitude of early-onset MI risk, but the latter association was 10 times more prevalent[4]. To emphasize, as opposed to clinical diagnosis of FH, which is relatively readily established based on tendon xanthoma, family history, LDL-C levels, and other factors, high-risk cases harboring many common SNVs like the above are too difficult to identify clinically for any skilled expert at the present time.

What is even more interesting regarding the PRD for CAD is that the magnitude of reduction in relative and absolute risks with statin treatment is larger (the benefit of statin is greater) in cases of higher PRD, in other words, genetically unlucky cases[5]. In a nutshell, high genetic risk for CAD can be (partly) canceled by statins. It is also known that even in a group of high genetic risk individuals, CAD odds ratios can be altered considerably through lifestyle changes[6]. These research results can be summarized as follows: lifestyle changes can possibly cancel (part of) high genetic risks. Reviewing the association between CAD and acquired factors (e.g., drug therapy or everyday habits) and genetic/congenital factors, half of the CAD phenotype-causing variants are, as mentioned at the outset, inherited (i.e., congenital factors), which means that the other half are acquired, deriving from drug therapy, lifestyle, and so forth. In conclusion, phenotypes like those of CAD, to which inherent and acquired factors contribute equally, can be ameliorated to a large extent by early management, including examination for genetic factors and provision of pharmacotherapy and lifestyle alteration guidance.

Glossary

High Frequency Gene Polymorphism:
A genetic variant that is highly prevalent in a given population. SNV (Single Nucleotide Variant) is a single nucleotide variation in a nucleotide sequence.

Polygenic:
Polygenic refers to the involvement of multiple genes, and the Polygenic Risk Score is a method of assessing the incidence of disease that takes polygenicity into account.

Tendon Xanthoma:
An enlargement of the Achilles tendon or tendons of the limbs due to abnormally high cholesterol.

Statins:
Drugs that lower blood cholesterol by inhibiting HMG-CoA reductase, which is necessary for cholesterol synthesis in the liver.

Variance:
Refers to differences, variances or variations.

Reference (as of November 2nd, 2023)

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Lecture 4

Addressing Unmet Needs in the Cardiovascular Area by Industry-Academia Collaboration:

Establishment of a Novel Method to Assess HDL Functionality

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Summary

In Japan, where the population is aging at a rate unparalleled in the world, the extension of healthy life expectancy is an urgent issue. As a countermeasure against cardiovascular disease, which is a major cause of conditions requiring long-term care, we have been working with Sysmex Corporation to develop a method to evaluate high-density lipoprotein (HDL) function, although hypo-HDL cholesterolemia is one of the residual risks of cardiovascular disease after LDL cholesterol lowering therapy. Recently, it has been suggested that HDL is important not only in quantity but also in quality. However, there is no established method to assess HDL function, which has been a barrier to the development of HDL-targeted prevention and treatment strategies. Therefore, we have proposed the cholesterol uptake capacity (CUC) as a new clinically applicable HDL functional index, and have demonstrated its clinical usefulness. Recently, we have completed a fully automated measurement system with high reproducibility, which enables high-throughput evaluation of CUC and provides an environment in which real-world evidence can be established. At the same time, the company is also working on the development of new biomarker discovery and testing methods, utilizing the know-how cultivated through past industry-academia co-creation. In addition, accurate understanding of the current situation is essential in disease control. We are conducting the KUNIUMI registry on Awaji Island, Hyogo Prefecture, with the aim of understanding the issues involved in the treatment of heart failure in a super-aging society.

High-density lipoprotein quality assessment required in addition to quantity

Cerebrovascular and cardiovascular disease is the major cause of the need for long-term nursing care in the Japanese population. Our country, which has transformed into a super-aging society at a globally unprecedented rate, faces an urgent challenge of counteracting cerebrovascular and cardiovascular disease and overcoming the aging issue to achieve healthy lifespan extension. Intervention studies using lipid-lowering drugs, such as statins, have shown that the onset and recurrence of coronary artery diseases can be prevented by decreasing low-density protein cholesterol (LDL-C) levels. Meanwhile, with the cardiac event avoidance rate using statins remaining at only around 30%, it is necessary to eliminate risks remaining in LDL-C level-controlled individuals. In this setting, the significance of intervention in high-density lipoprotein (HDL) has not been established.

Many epidemiological studies have demonstrated that reduction in the HDL-C level is a cardiovascular disease risk factor. However, higher HDL-C levels are not always accompanied by longevity. Multiple studies have reported stunning results that very high levels of HDL-C rather increase the cardiovascular disease risk. A report from Denmark exhibited a U-shaped association between HDL-C levels and death rates of all causes. In Japan, an EPOCH-Japan (Evidence for Cardiovascular Prevention from Observational Cohorts in Japan) study found an increase in cardiovascular disease death risk with HDL-C at ≥90 mg/dL. More recently, a study on patients recruited from the UK Biobank and those from a US biobank showed that HDL-C levels at ≥80 mg/dL were associated with higher mortality risk in patients with coronary artery disease[1].

As shown above, unlike in the case of “the lower, the better” LDL-C concentrations, HDL-C, while a quantitative measure of HDL, is only a snapshot of the process of the reverse cholesterol transport, where HDL plays a leading role. While HDL has diverse antiatherogenic effects in addition to absorbing cholesterol, its effect as the “good” player is lost in the presence of certain conditions such as chronic inflammation or diabetes. HDL should therefore be assessed for its quality in addition to quantity, but the absence of an established HDL functionality assay poses a great hurdle for HDL research.

Cholesterol uptake capacity: a new measure for HDL functionality

HDL collects cholesterol from peripheral tissues and transports it to the liver (reverse cholesterol transport system). Since cholesterol is not used as a source of energy and is expelled only by the liver and steroidogenesis organs, the reverse transport system is essential for homeostasis. Cholesterol "efflux" capacity is an ex vivo metric of the first step of the reverse cholesterol transport system. This capacity has been shown to be more useful than the HDL-C level for cardiovascular event risk stratification[2]. However, reports on this efflux capacity have only been available from limited cohort studies, since the conventional quantification method for this capacity involves the use of radioisotope labels and cells, and requires complicated manipulative techniques. Aiming for a clinically applicable HDL functionality assessment, through industry-academia cooperation, we have developed a new assay system for HDL functionality, which we have termed "cholesterol uptake capacity" (CUC), and demonstrated its utility in the secondary prevention of cardiovascular events[3][4]. More recently, we have launched a fully automated CUC assay system based on a chemiluminescence immunoassay, in place of fluorescence detection, a methodology with a high throughput of 33 tests per hour[5]. We are now ready to proceed to establish real-world evidence of the significance of monitoring HDL in terms of functions. Further development is awaited.

We are also exploring new biomarkers and testing methods, capitalizing on the know-how that we have built up via industry-academia collaboration. Since it is essential in combatting a disease to accurately know its current status, we have started a prospective observational study to identify what challenges exist in treating heart failure in our super-aging society using a registry of residents of Awaji Island, Hyogo (KUNIUMI Registry)[6][7]. In this study on patients from the Registry, we aim to validate the utility of new biomarkers and testing methods and promote the expeditious clinical application of such tools.

Glossary

EPOCH-JAPAN:
A project initiated in 2005 as a MHLW (Ministry of Health, Labor, and Welfare) Science Research project, with the aim of obtaining evidence to serve as a foundation for public health measures in Japan. It is a collaborative study integrating 17 cohort studies in Japan.

Steroid synthesizing organ:
Organs and tissues in the body that synthesize steroid hormones. The adrenal cortex, in particular, uses cholesterol to synthesize steroid hormones.

Isotope:
Radioactive isotope. Elements with equal atomic number and different mass numbers.

Reference (as of November 2nd, 2023)

1) Liu C, Dhindsa D, Almuwaqqat Z, et al. Association Between High-Density Lipoprotein Cholesterol Levels and Adverse Cardiovascular Outcomes in High-risk Populations. JAMA Cardiol. 2022; 7 (7): 672–680.
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