第67回日本糖尿病学会年次学術集会
シンポジウム35

米国での留学経験と研究の継続

神戸大学大学院保健学研究科看護学領域老年看護学分野・高等学術研究院
山口裕子

米国での留学経験と研究の継続

山口裕子
神戸大学大学院保健学研究科

抄録

2020 年2 月-2021 年1 月の約1 年間米国に留学しビッグデータを用いた高齢者疫学研究(BaltimoreLongitudinal Study of Aging(BLSA)研究, Invecchiare in CHIANTI, aging in the Chianti area study (InCHIANTI study)研究)に従事した. BLSA 研究とは, 1958 年に開始した米国国内最長の前向きコホート研究である. InCHIANTI 研究とは, 1998 年に開始した主にイタリア・トスカーナ州フィレンツェ Chianti,Bagno a Ripoli 地区に住む高齢者を対象とした研究である. 留学先では, BLSA 及びInCHIANTI 研究にて収集したデータを用いて, 加齢と慢性疾患との関連に関する解析を行った. 帰国後も, 留学先の指導教官より指導を仰ぎながら米国での研究を継続して行っている. さらに, 現在は日本人糖尿病高齢者を対象としたビッグデータ解析による骨格筋低下に関連する栄養素の解明, フィリピンや台湾との共同研究による生活習慣病やサルコペニア予防に関する研究に取り組んでいる. 本シンポジウムでは, 留学に至るまでの経緯, 留学生活, 留学中に従事した研究, 現在取り組んでいる研究について紹介したい.

日本糖尿病学会
ＣＯＩ開示

発表者名：山口裕子

演題発表に関連し、開示すべきCOI関係にある企業などはありません。

平成30年度文部科学省科学技術人材育成費補助事業
ダイバーシティ研究環境実現イニシアティブ(先端型)事業
国際共同研究PI養成プログラム

- 在外研究機関：ジョンズ・ホプキンス大学
  (@メリーランド州ボルチモア)
- 受入教員：Prof. Richard D Semba
- 滞在期間：2020年2月-2021年1月

平成30年度文部科学省科学技術人材育成費補助事業
ダイバーシティ研究環境実現イニシアティブ(先端型)事業
国際共同研究PI養成プログラム

取り組み／目標	1)採用比率30%以上の恒常的達成	2)上位職登用比率（昇任比率）の向上	3)次世代を担う若手研究者の裾野拡大	4)ダイバーシティ環境の充実と学外への波及
(A)新しい人事ガバナンスシステムの構築	◎	○		
(B)国際共同研究PI 養成プログラムの実施		◎		
(C)国際人事交流プログラムの実施			◎	
(D)国際共同若手研究者養成プログラムの実施			◎	
(E)ダイバーシティ推進機構(仮称)の設置				◎
(F)ダイバーシティ基金の設置・ダイバーシティ共創ネットワークの構築	○	○	○	◎

- **事業期間**
  2018年-2023年

- **目的・概要**
  女性研究者の研究力の向上

- **達成目標**
  目標1：女性研究者採用比率30％以上の恒常的達成
  目標2：女性研究者昇任比率の向上
  目標3：次世代を担う若手女性研究者の裾野拡大
  目標4：ダイバーシティ環境の充実と学外への波及

- **海外派遣プログラム**
  国際共同研究PI養成プログラム
  国際人事交流プログラム
  国際共同研究若手研究者養成プログラム

国際共同研究PI養成プログラム

- **目的**
  女性研究者の上位職昇任に向けて優秀な女性研究者を海外の研究機関に派遣する。
- **対象者**
  准教授以下の女性研究者
- **期間**
  原則6か月以上
- **内容**
  研究代表者として国際共同研究を組織し、派遣先期間で研究を行う。
- **求められる成果**
  筆頭著者として、国際会議、国際ジャーナル等に研究成果を発表し、上位職へ昇任する。
- **支援内容**
  渡航費、滞在費、非常勤講師雇用費

渡航までのプロセス

Oct 2018-April 2019

- プログラムへの応募
- ホスト大学の決定

May 2019

- プログラム採択
- 受け入れ先大学との調整開始

June-Oct 2019

- PIとの面談
  (英語試験、研究内容等に関する相談)
- 事前学習

Nov 2019-Jan 2020

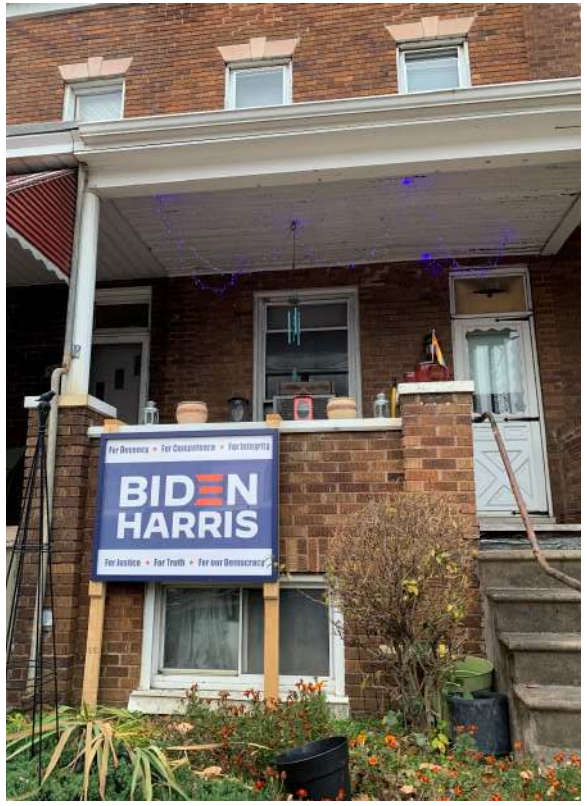
- 渡航準備

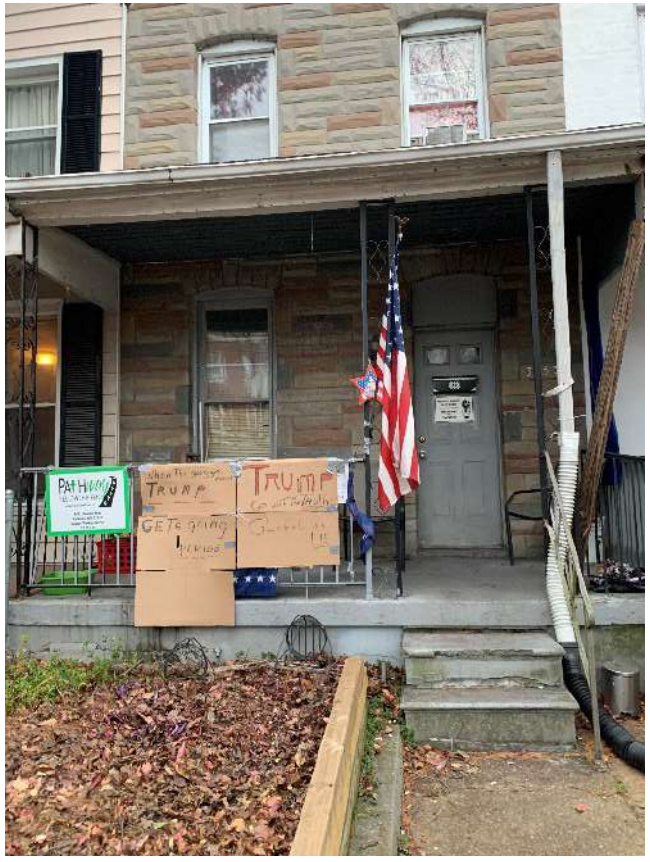
(Visa, house, public utilities, insurance, etc..)

Feb 2020
渡航

COVID-19 crisis

Black Lives Matter/ Election



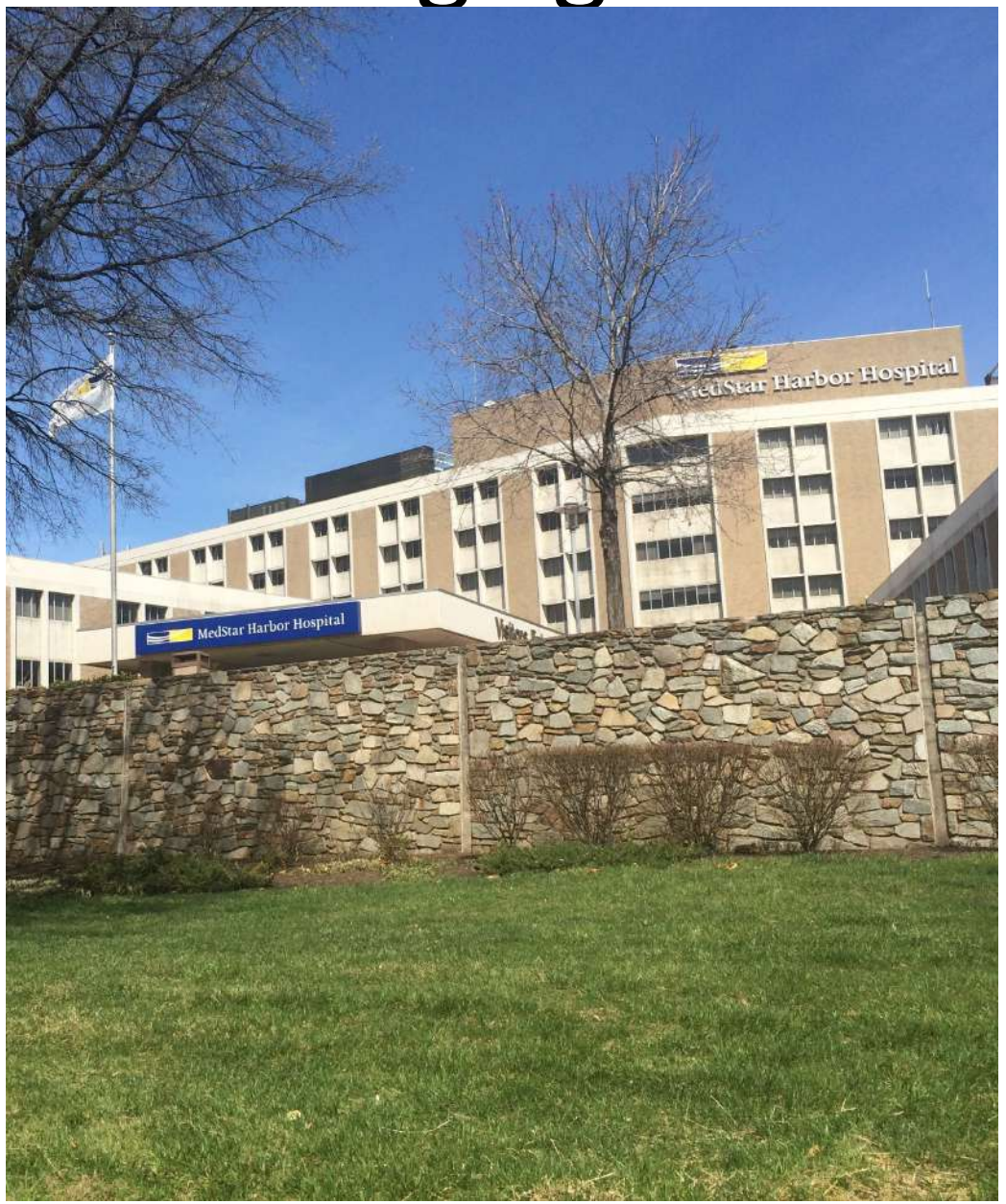


Weekly Schedule

- **Mon.** Journal club / PIとの個別ミーティング (at NIA)
- **Tue.** English for Second Language (ESL) class
- **Wed.**
- **Thrs.**
- **Friday.** Seminar (at NIA)

Johns Hopkins University

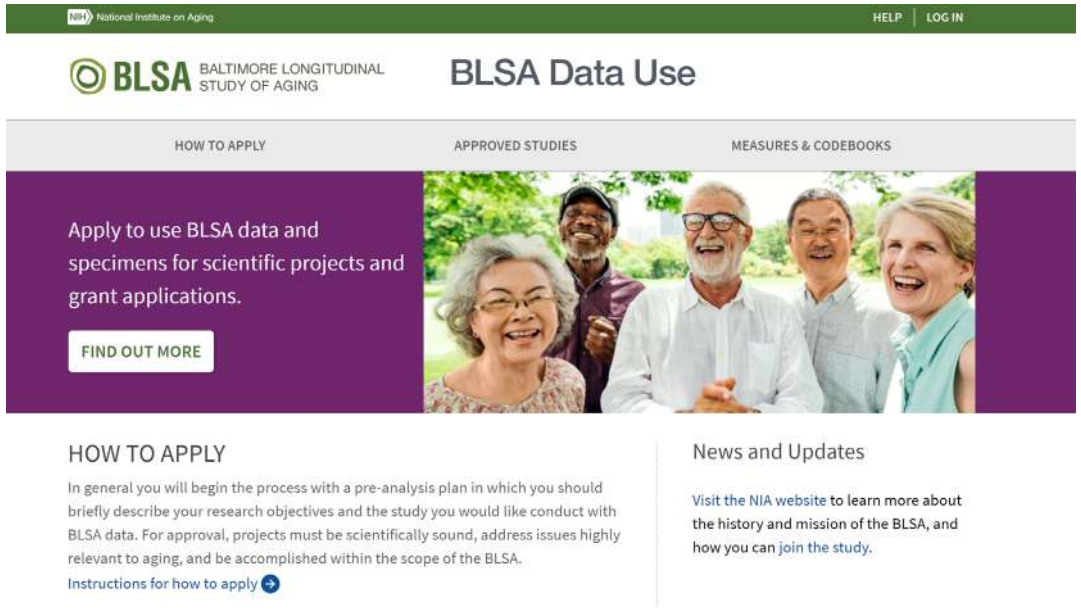
National Institute on Aging



研究活動

高齢者に関する長期縦断疫学研究

- Baltimore Longitudinal Study of Aging (BLSA)
- Invecchiare in CHIANTI, aging in the Chianti area study (InCHIANTI study)



1. リサーチプロトコール作成、IRB申請

2. データアクセス権の取得

3. データセット作成

4. データ解析

5. 論文執筆

とにかく
スピーディ！

Metabolome Analysis

The metabolome analysis comprises two main approaches: the directed analysis and the metabolic profile, as

Related terms:

Mass Spectrometry,
, Metabolomics
no Acids,
nd Solubility,
, Metabolite

About this page

Proteome Analysis

The concept of proteome analysis is defined as the separation, identification and quantification of the entire protein complement expressed by a genome, a cell or a tissue (Wasinger et al., 1995;

Related terms:

Amino Acids, Cereal, Antioxidant,
e,
omatography Mass
try
Mass Spectrometry,
Maize, Functional Food,
t

pics >

Cell

Leading Edge
Review

The Hallmarks of Aging

Carlos López-Otín,[1] Maria A. Blasco,[2] Linda Partridge,[3,4] Manuel Serrano,[5,*] and Guido Kroemer[6,7,8,9,10]
[1]Departamento de Bioquímica y Biología Molecular, Instituto Universitario de Oncología (IUOPA), Universidad de Oviedo, Oviedo, Spain
[2]Telomeres and Telomerase Group, Molecular Oncology Program, Spanish National Cancer Research Centre (CNIO), Madrid, Spain
[3]Max Planck Institute for Biology of Ageing, Cologne, Germany
[4]Institute of Healthy Ageing, Department of Genetics, Evolution and Environment, University College London, London, UK
[5]Tumor Suppression Group, Molecular Oncology Program, Spanish National Cancer Research Centre (CNIO), Madrid, Spain
[6]INSERM, U848, Villejuif, France
[7]Metabolomics and Cell Biology Platforms, Institut Gustave Roussy, Villejuif, France
[8]Centre de Recherche des Cordeliers, Paris, France
[9]Pôle de Biologie, Hôpital Européen Georges Pompidou, AP-HP, Paris, France
[10]Université Paris Descartes, Sorbonne Paris Cité, Paris, France
*Correspondence: mserrano@cnio.es
http://dx.doi.org/10.1016/j.cell.2013.05.039

Aging is characterized by a progressive loss of physiological integrity, leading to impaired f
and increased vulnerability to death. This deterioration is the primary risk factor for major h
pathologies, including cancer, diabetes, cardiovascular disorders, and neurodegenerativ
eases. Aging research has experienced an unprecedented advance over recent years, p
with the discovery that the rate of aging is controlled, at least to some extent, by genetic pathways
and biochemical processes conserved in evolution. This Review enumerates nine tentative hall-
marks that represent common denominators of aging in different organisms, with special emphasis
on mammalian aging. These hallmarks are: genomic instability, telomere attrition, epigenetic alter-
ations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular

老化のメカニズム？
バイオマーカ研究？
オミクス解析？

⇒プロトコール作成へ

al accumulation (by
tic stress tolerance
(Bower *et al.*, 2005) have
ave been numerous studies
biochemical roles for

t must be
y to get desired
largely influence
ıture and steady

resolving the

プロトコール承認→データアクセス権の取得→データセット作成

How to Apply (BLSA Data Use)

Submitting an Analysis Plan

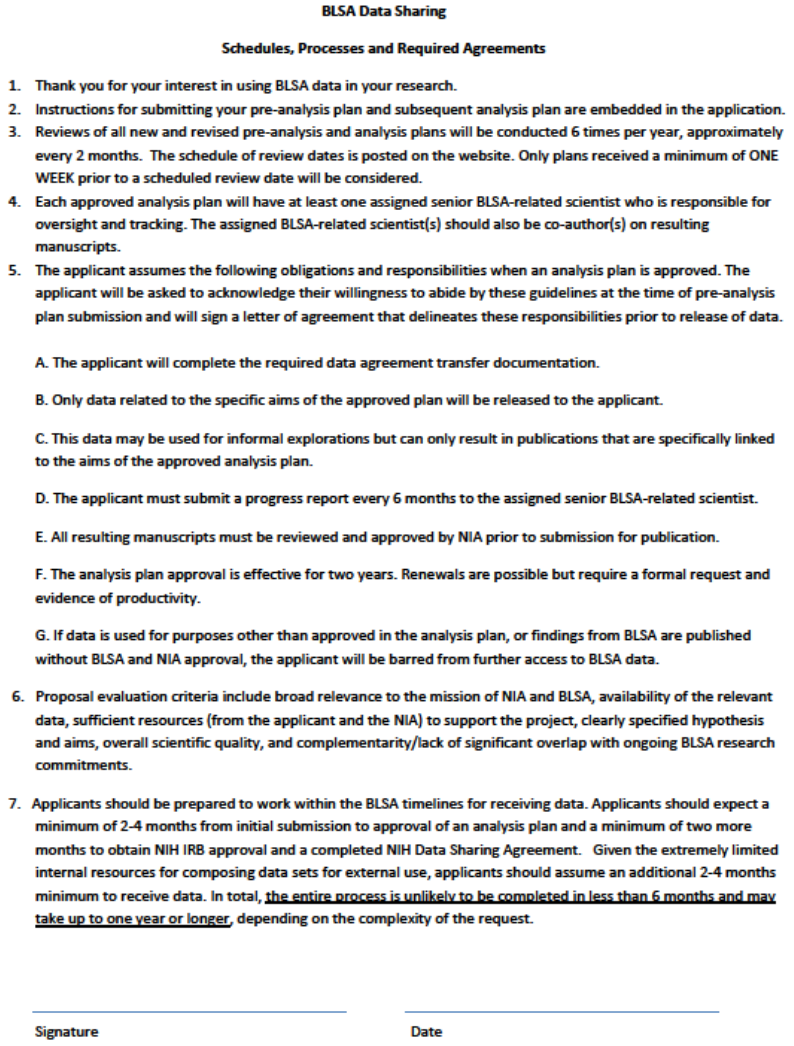
- If the Pre-Analysis Plan is approved, you will receive an email that requests a more extensive but concise proposal. The full proposal (called an Analysis Plan) should include a background and introduction that describes the status of the literature and the relevance of the problem to be addressed, as well as provide a strong rationale for using BLSA data and other BLSA resources if requested. In the objectives section, include at least one clearly stated hypothesis. Complete the statistical analysis section in accordance with the study hypothesis. Most importantly, provide a detailed description of the variables and all other materials needed from the BLSA. Include relevant references and attach an NIH-style biosketch for the proposed Principle Investigator.
- The required elements for a full Analysis Plan are provided on the form. Two to four months after submission, you will receive an e-mail stating whether your full Analysis Plan was accepted, rejected or whether revisions are requested. You may be asked to schedule a conference call to discuss any technical or administrative issues.
- The status of your submissions are displayed on the My Account and Status page.

General Guidelines for Submissions

- Be as descriptive and concise as possible.
- Complete all required fields on the submission forms.
- Attach any documents that support the current submission (e.g., previous publications, preliminary data).
- Attach an NIH-Style Biosketch for the anticipated lead author.
- You will be contacted by the BLSA team if any additional information is required to properly evaluate your submission.

BLSA Data Use Agreement

- By submitting an Analysis Plan, researchers are agreeing to the terms and conditions of use of BLSA data. The full agreement should be downloaded , read and signed by the researcher, and kept with study plan notes.



BLSA Data Sharing

Schedules, Processes and Required Agreements

1. Thank you for your interest in using BLSA data in your research.
2. Instructions for submitting your pre-analysis plan and subsequent analysis plan are embedded in the application.
3. Reviews of all new and revised pre-analysis and analysis plans will be conducted 6 times per year, approximately every 2 months. The schedule of review dates is posted on the website. Only plans received a minimum of ONE WEEK prior to a scheduled review date will be considered.
4. Each approved analysis plan will have at least one assigned senior BLSA-related scientist who is responsible for oversight and tracking. The assigned BLSA-related scientist(s) should also be co-author(s) on resulting manuscripts.
5. The applicant assumes the following obligations and responsibilities when an analysis plan is approved. The applicant will be asked to acknowledge their willingness to abide by these guidelines at the time of pre-analysis plan submission and will sign a letter of agreement that delineates these responsibilities prior to release of data.

   A. The applicant will complete the required data agreement transfer documentation.

   B. Only data related to the specific aims of the approved plan will be released to the applicant.

   C. This data may be used for informal explorations but can only result in publications that are specifically linked to the aims of the approved analysis plan.

   D. The applicant must submit a progress report every 6 months to the assigned senior BLSA-related scientist.

   E. All resulting manuscripts must be reviewed and approved by NIA prior to submission for publication.

   F. The analysis plan approval is effective for two years. Renewals are possible but require a formal request and evidence of productivity.

   G. If data is used for purposes other than approved in the analysis plan, or findings from BLSA are published without BLSA and NIA approval, the applicant will be barred from further access to BLSA data.

6. Proposal evaluation criteria include broad relevance to the mission of NIA and BLSA, availability of the relevant data, sufficient resources (from the applicant and the NIA) to support the project, clearly specified hypothesis and aims, overall scientific quality, and complementarity/lack of significant overlap with ongoing BLSA research commitments.

7. Applicants should be prepared to work within the BLSA timelines for receiving data. Applicants should expect a minimum of 2-4 months from initial submission to approval of an analysis plan and a minimum of two more months to obtain NIH IRB approval and a completed NIH Data Sharing Agreement. Given the extremely limited internal resources for composing data sets for external use, applicants should assume an additional 2-4 months minimum to receive data. In total, the entire process is unlikely to be completed in less than 6 months and may take up to one year or longer, depending on the complexity of the request.

Signature _____ Date _____

BLSA study
“What is aging?”への答えを明らかにすること目標に開始したアメリカ国内最長のコホート研究（1958年～）

Metabolomics (2021) 17:9
https://doi.org/10.1007/s11306-020-01762-3

ORIGINAL ARTICLE

Check for updates

Plasma metabolites associated with chronic kidney disease and renal function in adults from the Baltimore Longitudinal Study of Aging

Yuko Yamaguchi[1] · Marta Zampino[2] · Ruin Moaddel[2] · Teresa K. Chen[3,4] · Qu Tian[2] · Luigi Ferrucci[2] · Richard D. Semba[1]

Received: 4 August 2020 / Accepted: 16 December 2020

Abstract

Introduction Chronic kidney disease (CKD) is an important cause of disability and death, but its pathogenesis is poorly understood. Plasma metabolites can provide insights into underlying processes associated with CKD.

Objectives To clarify the relationship of plasma metabolites with CKD and renal function in human.

Methods We used a targeted metabolomics approach to characterize the relationship of 450 plasma metabolites with CKD and estimated glomerular filtration rate (eGFR) in 616 adults, aged 38–94 years, who participated in the Baltimore Longitudinal Study of Aging.

Results There were 74 (12.0%) adults with CKD. Carnitine, acetylcarnitine, propionylcarnitine, butyrylcarnitine, trigonelline, trimethylamine N-oxide (TMAO), 1-methylhistidine, citrulline, homoarginine, homocysteine, sarcosine, symmetric dimethylarginine, aspartate, phenylalanine, taurodeoxycholic acid, 3-indolepropionic acid, phosphatidylcholines (PC).aa.C40:2, PC.aa.C40:3, PC.ae.C40:6, triglycerides (TG) 20:4/36:3, TG 20:4/36:4, and choline were associated with higher odds of CKD in multivariable analyses adjusting for potential confounders and using a false discovery rate (FDR) to address multiple testing. Six acylcarnitines, trigonelline, TMAO, 18 amino acids and biogenic amines, taurodeoxycholic acid, hexoses, cholesteryl esters 22:6, dehydroepiandrosterone sulfate, 3-indolepropionic acid, 2 PCs, 17 TGs, and choline were negatively associated with eGFR, and hippuric acid was positively associated with eGFR in multivariable analyses adjusting for potential confounders and using a FDR approach.

Conclusion The metabolites associated with CKD and reduced eGFR suggest that several pathways, such as the urea cycle, the arginine-nitric oxide pathway, the polyamine pathway, and short chain acylcarnitine metabolism are altered in adults with CKD and impaired renal function.

Keywords Aging · Biomarker · Chronic kidney disease · Glomerular filtration rate · Mass spectrometry · Metabolomics

[目的]
血漿メタボロームを測定することで慢性腎不全及び腎機能低下に関連するバイオマーカを横断的に明らかにすること

[対象と方法]
BLSA 参加者616人を対象に、450種類の血漿メタボローム(アミノ酸，胆汁酸，脂肪酸，糖，ビタミン等)と慢性腎不全及び腎機能(推算糸球体濾過量; eGFR)との関連についてメタボローム解析を行った。

[結果]
参加者のうち12%が慢性腎不全であった。22種類がCKDと55種類がeGFRと有意な相関が認められた。

InCHIANTI study

イタリア人高齢者の運動障害に関する効果的な診断や治療法を解明することを目標に開始した高齢者疫学研究（1998年～）

THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Biological Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2021, Vol. 76, No. 7, 1192–1197
doi:10.1093/gerona/glaa324
Advance Access publication December 28, 2020

OXFORD

Original Article

Elevated Plasma Growth and Differentiation Factor 15 Predicts Incident Anemia in Older Adults Aged 60 Years and Older

Yuko Yamaguchi, RN, MHS,[1,*] Marta Zampino, MD,[2] Toshiko Tanaka, PhD,[2] Stefania Bandinelli, MD,[3] Yusuke Osawa, PhD,[4] Luigi Ferrucci, MD, PhD,[2] and Richard D. Semba, MD, MPH[1]

[1]Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. [2]National Institute on Aging, National Institutes of Health, Baltimore, Maryland, USA. [3]Azienda USL TOSCANA CENTRO, Geriatric Unit, Firenze, Italy. [4]Graduate School of Health Management, Keio University, Kanagawa, Japan.

*Address correspondence to: Yuko Yamaguchi, RN, MHS, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Smith Building, M015, 400 N. Broadway, Baltimore, MD 21287, USA. E-mail: yuko.yamayu@gmail.com

Received: October 7, 2020; Editorial Decision Date: December 16, 2020

Decision Editor: David Le Couteur, MBBS, FRACP, PhD

Abstract

Anemia is common in older adults and associated with greater morbidity and mortality. The causes of anemia in older adults have not been completely characterized. Although elevated circulating growth and differentiation factor 15 (GDF-15) has been associated with anemia in older adults, it is not known whether elevated GDF-15 predicts the development of anemia. We examined the relationship between plasma GDF-15 concentrations at baseline in 708 nonanemic adults, aged 60 years and older, with incident anemia during 15 years of follow-up among participants in the Invecchiare in Chianti (InCHIANTI) Study. During follow-up, 179 (25.3%) participants developed anemia. The proportion of participants who developed anemia from the lowest to highest quartile of plasma GDF-15 was 12.9%, 20.1%, 21.2%, and 45.8%, respectively. Adults in the highest quartile of plasma GDF-15 had an increased the risk of developing anemia (hazards ratio 1.15, 95% confidence interval 1.09, 1.21, $p < .0001$) compared to those in the lower 3 quartiles in a multivariable Cox proportional hazards model adjusting for age, sex, serum iron, soluble transferrin receptor, ferritin, vitamin B_{12}, congestive heart failure, diabetes mellitus, and cancer. Circulating GDF-15 is an independent predictor for the development of anemia in older adults.

Keywords: Anemia, Human aging, Proteomics, Senescence

[目的]
高齢者の貧血の発症に対するGDF-15タンパク質の影響についてプロテオーム解析により縦断的に明らかにすること

[対象と方法]
InCHIANTI studyに参加する60歳以上の高齢者708人を対象に、15年間の貧血の発症状況とGDF-15との関連についてコックス比例ハザードモデルにて解析した。

[結果]
15年間の追跡調査で貧血発症割合は25.3%であった。GDF-15タンパク質を第3四分位群と第1+2四分位群の2群に分けたときに、第1+2四分位群に比し、第3四分位群で有意に貧血発症のオッズが高かった(OR 1.15, 95%CI 1.09, *P*<0.001)。

留学先での研究経験を
どのように発展させているか？

- 国際共同研究の継続

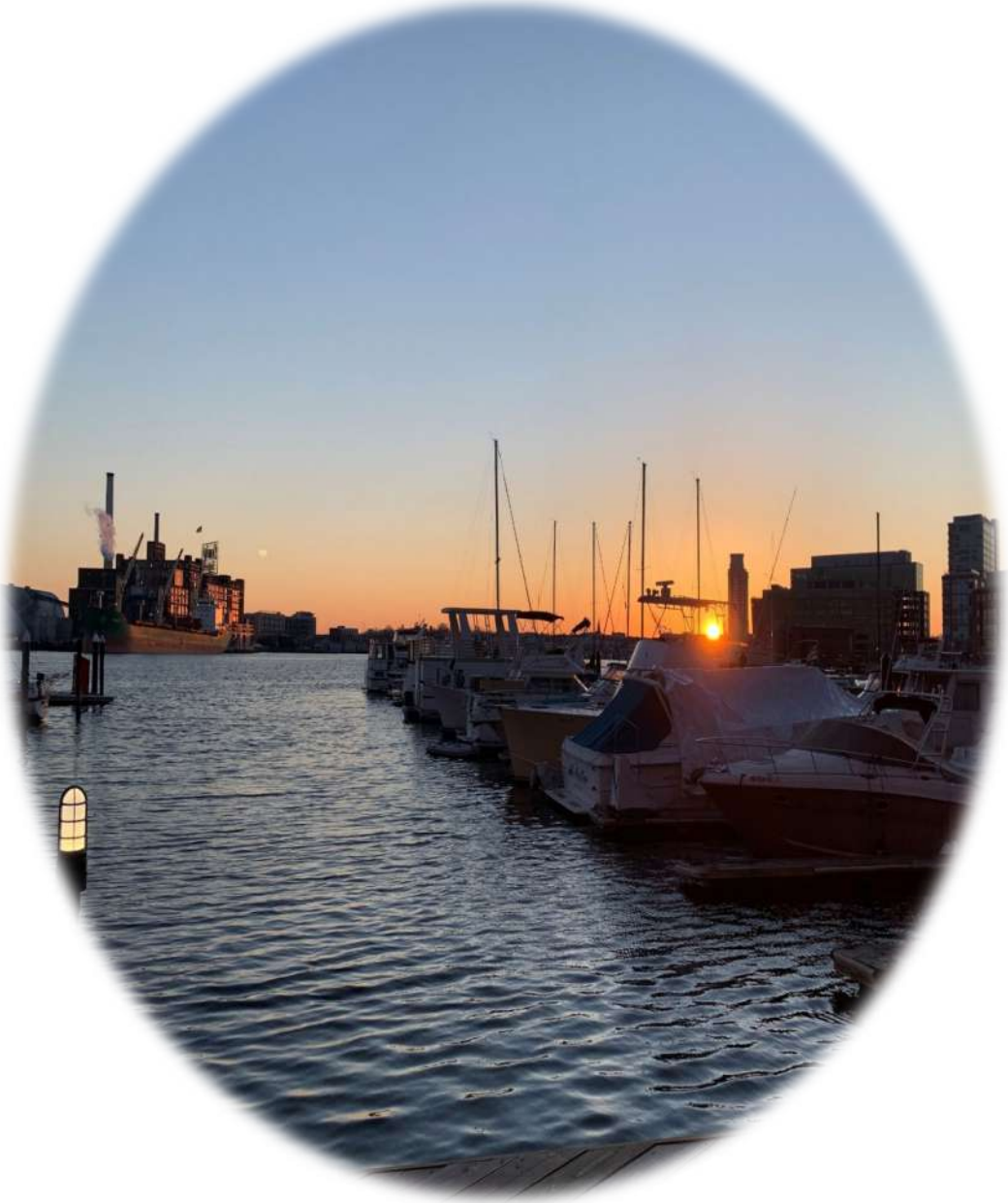
  高齢者の骨格筋低下と老化タンパクとの関連に関する研究

- 習得した解析手法等を生かしビッグデータを用いた高齢者研究を実施

  日本人糖尿病高齢者を対象とした骨格筋低下を予防する栄養介入策の解明に関する研究

最後に

- JHUには世界中から留学生や研究者が集まっており、多文化交流の機会を得た。刺激ある環境の中で友人たちと切磋琢磨することができた。
- 日本人研究者も数多く留学していたため、精神的に支えられた。
- 医師、統計学者、栄養士、社会心理学専門家等々様々なバックグランドを持った研究者とともに研究ができたことで、データを多角的にみる視点が養われた。
- コロナ渦で十分に会う機会は得られなかったが、Prof. Richard D Sembaには大変手厚くサポートしていただいた。一流の研究者たちと同じ時間を過ごし学べたことは大変貴重な経験であった。
- 留学中に得たスキルを棚卸しすることで、帰国後どのように自身の研究を発展させていきたいか、今後どのようなスキルを習得したいかを具体化させることができた。



ご清聴ありがとう
ございました