最終講義

NAGOYA UNIVERSITY GRADUATE SCHOOL OF MEDICINE

私にとって勇気ある知識人とは何か
― 鉄が語る発がん機構 ―
Cultivating Courageous Intellectuals

名古屋大学大学院医学系研究科 生体反応病理学
名古屋大学 低温プラズマ科学研究センター
東海国立大学機構 低温プラズマ総合科学研究拠点

豊國　伸哉

2026年3月13日（名古屋大学医学部 第4講義室）

私の略歴

1961年　島根県松江市生まれ、父は京都大学農学部出身で水工学の研究者であったため、松江市・大阪府枚方市・京都府宇治市・愛媛県松山市と多彩な転校経験を味わった

1979年　愛光高校卒業（第21期生）共通一次テスト第1回（上田龍三先生・村上善則先生）

1985年　京都大学医学部卒業（軟式テニスクラブ、西医体・全医体 準優勝）

1985～87年　天理よろづ相談所病院 初期研修医（上田裕一先生）

1991年　京都大学大学院医学研究科 修了（医学博士・病理学）

1990～92年　米国 FDA, CDRH (Rockville, MD)で博士研究員

1992～2008年　京都大学大学院医学研究科病態生物医学（病理学教室第1講座）助手・講師・准教授

2008年7月～　名古屋大学大学院医学系研究科 生体反応病理学　教授

昭和５４年度入学

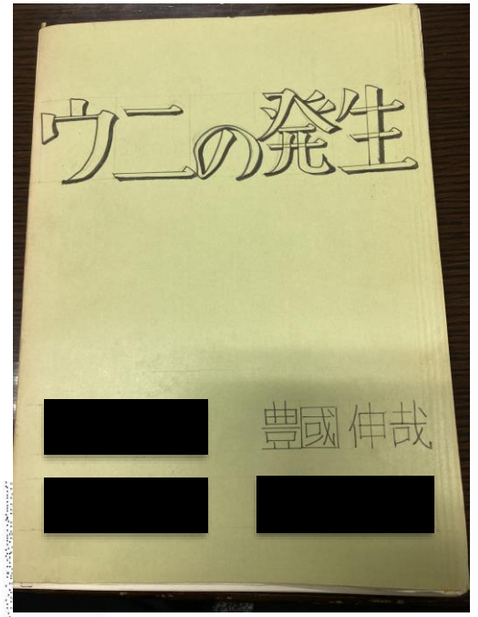
京都大学医学部名簿

30 豊國伸哉 (愛光)

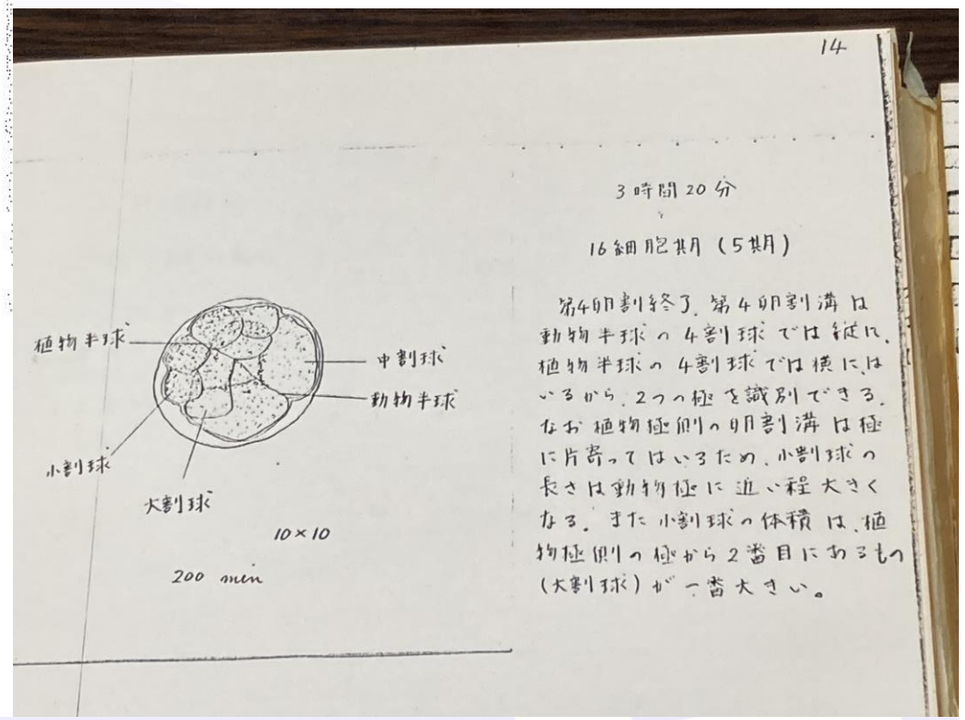
〒606 (075)
① 左京区 [redacted]

〒790 (0899)
② 松山市 [redacted]

歎石の「坊っちゃん」で有名な四国の松山から来ました。性格を自分で評すれば少々内気だが明朗であるといったところです。特技は軟式テニスで、医学部のクラブに入っています。趣味はクラシック、ポップス、読書、映画、ですが、近頃はクラブに忙しくて映画を見に行けないのが残念です。将来は出来れば「基礎」をやろうと思っています。



京都大学白浜臨海実験所
S54.11.21～24



NAGOYA UNIVERSITY
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OF MEDICINE

「勇気ある知識人」

― 名古屋大学 学術憲章・教育の基本方針 ―

2000年

研究者にとっての「勇気」とは何か

- 流行ではなく、自分の問いに忠実であること
- データと形態を最後まで信じ抜くこと
  ― セレンディピティーはその先に現れる
- 異なる分野から得た発想を自分の領域で実際に試してみること

なぜ「鉄」なのか

Iron Meteorites (Viena)

- 生命に必須の元素
- 酸素と共に進化を支えた
- しかし同時に、強い毒性を持つ

NAGOYA UNIVERSITY
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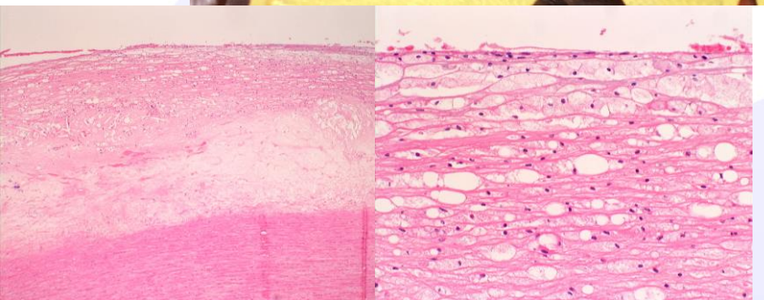
本日の話

1. 病理学との出会い
2. 鉄と発がん機構
3. フェロトーシスという概念
4. 理論から実装へ ― 名古屋大学における学際融合 ―

病理学との出会い
―「形態を読む」学問―



山邉 博彦 教授

杉山 武敏 教授

岡田 茂 教授

翠川 修 教授
（飯島 宗一 総長
と従兄弟関係）

形態は、最初の仮説である

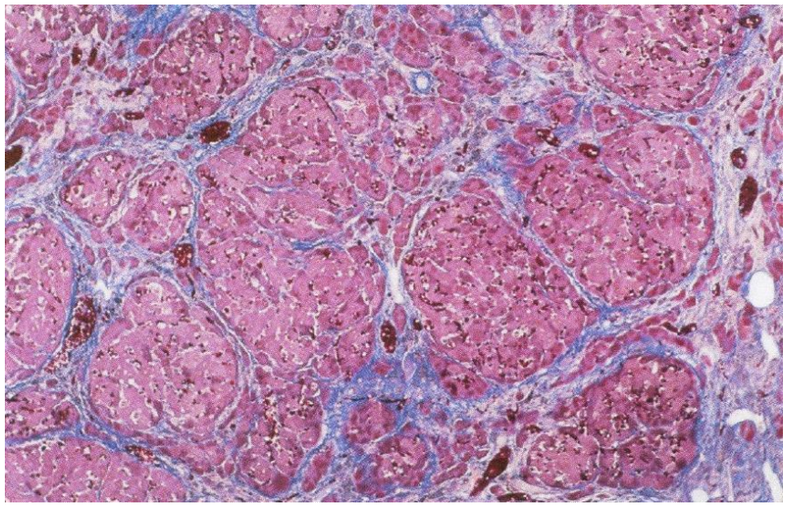
- 分子は後から追いつく
- 形態は嘘をつかない・すべてを総括している
- 形態は永久に記録が残る
- 病理学は仮説生成学

最初の研究テーマ：金属毒性

- 派手ではない
- しかし生命に本質的
- 病理学的に「見える」現象

Cu-NTAモデル
― 金属キレート化合物の生体毒性 ―

- 初めての第一著者論文
- キレート化の意義
- 金属と生体反応の関係



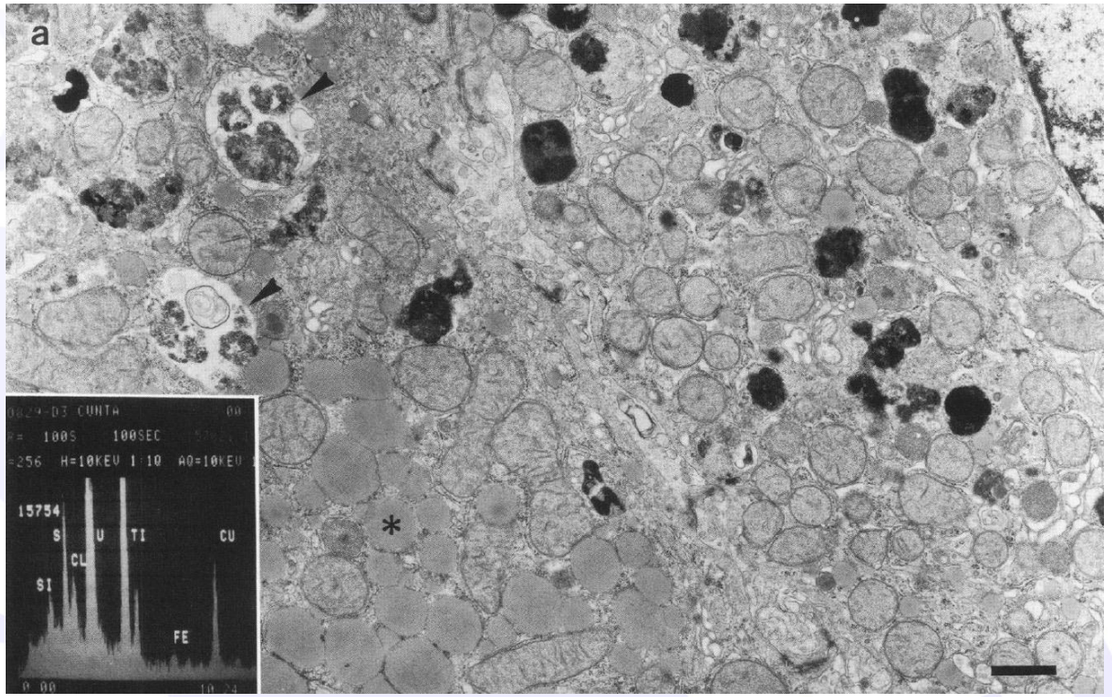
American Journal of Pathology, Vol. 134, No. 6, June 1989

Cirrhosis of the Liver Induced by Cupric Nitrilotriacetate in Wistar Rats

An Experimental Model of Copper Toxicosis

Shinya Toyokuni, Shigeru Okada, Shuji Hamazaki, Makio Fujioka, Jia-Li Li, and Osamu Midorikawa
From the Department of Pathology, Faculty of Medicine, Kyoto University, Sakyo-ku, Kyoto 606, Japan

tions of Fe-NTA.[7–12] Acute renal tubular necrosis, mid
nal coagulation necrosis of the liver, and central nerv
system abnormalities were observed by repeated in
peritoneal injections of aluminum nitrilotriacetate.[11,1
this study we induced liver cirrhosis by repeated intrap
toneal injections of cupric nitrilotriacetate in rats.



昭和末期～平成初期：私の研究の出発点

- 英語のワードプロセッサー(Word Star)ができたばかり、原稿はIBMの電動タイプライターをNEC 9801に接続して打っていたので、原稿50頁を一通り打つのに半日を要した
- 論文投稿は航空便、4部をアメリカに航空便で送るのに1万円くらいかかったのを覚えている
- 論文の受け取りの葉書がくるのに3週間、審査には最低3ヶ月くらいを要していた
- 葉書でリプリント請求
- 学会口頭発表はすべて写真屋に持ち込んで現像したスライドの投影

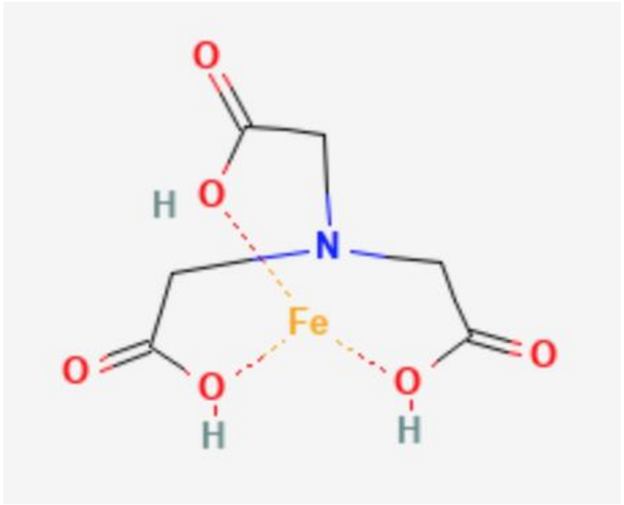
- 情報も少なかったが、雑音も極めて少なかった
- 当時はキャンパス内に不夜城の研究室もたくさんあった

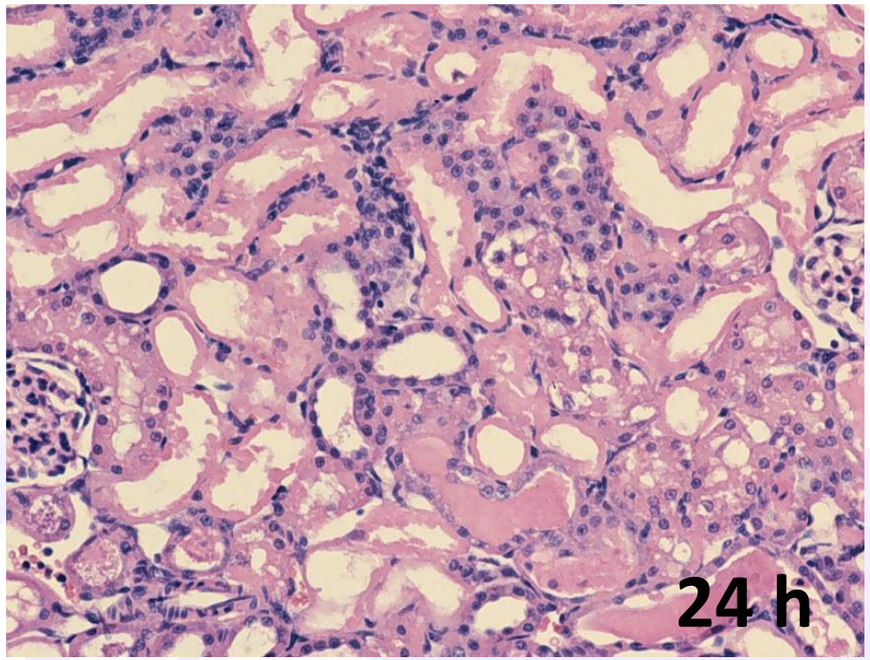
漠然とした将来への不安

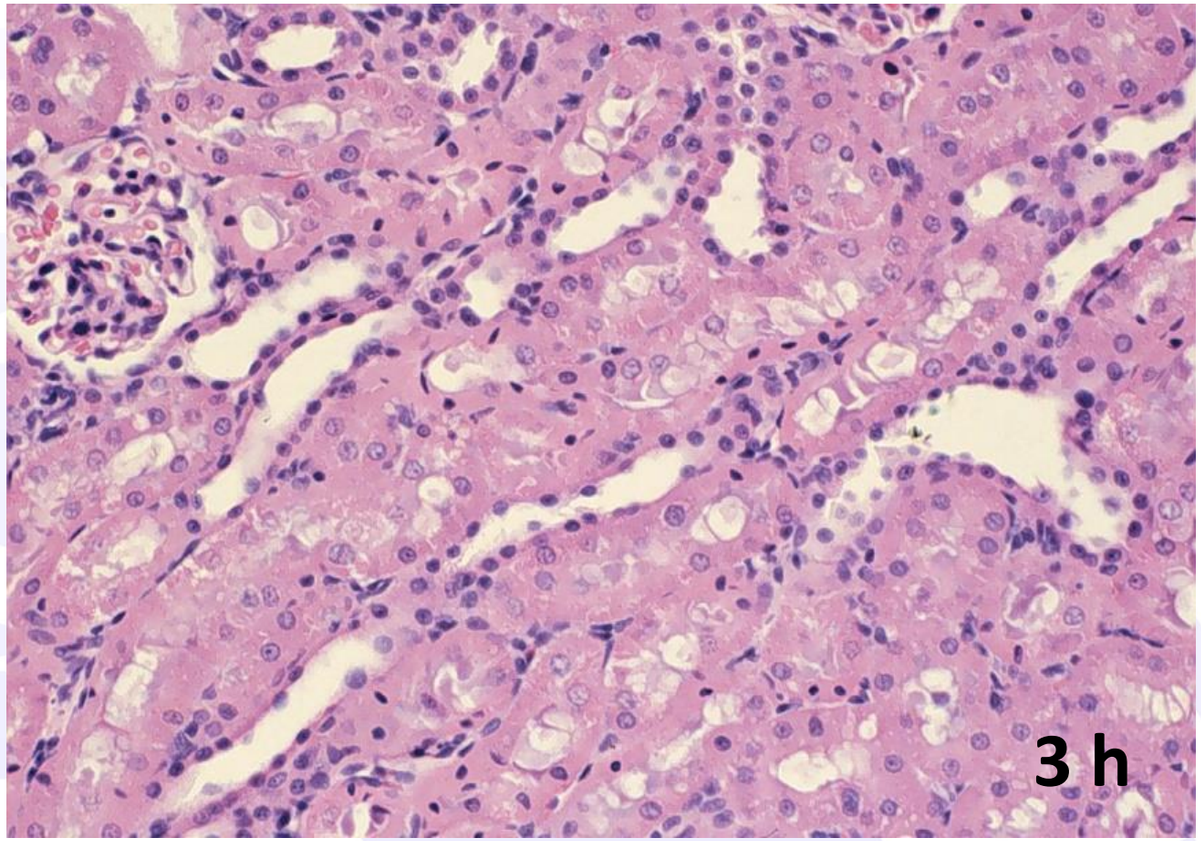
- 流行ではない
- すぐに引用されない
- これで研究を継続できるのか
- 次に何をしたらいいのか

Fe-NTAとの出会い

- 鉄という必須元素
- 腎近位尿細管という標的
- 強烈な病理変化

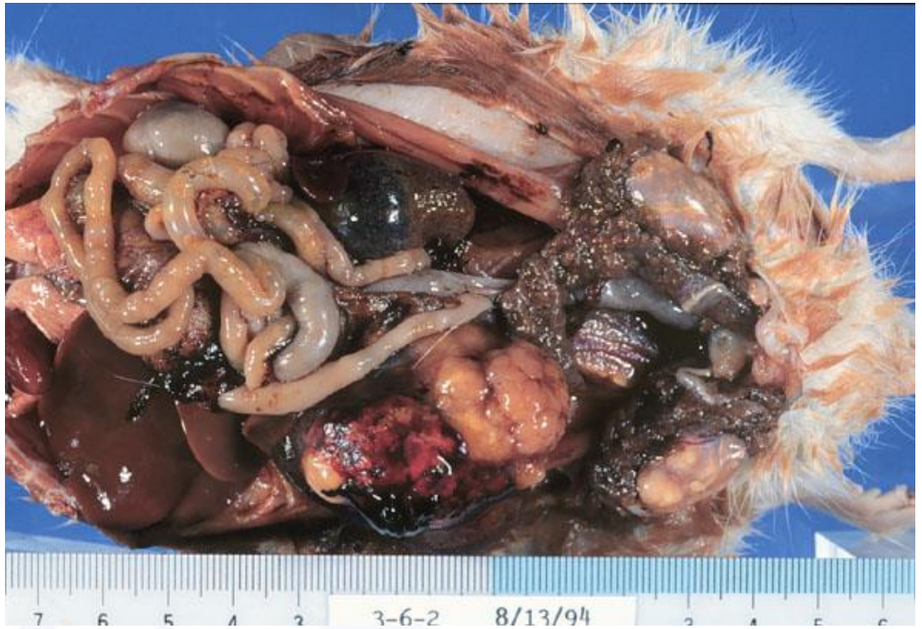


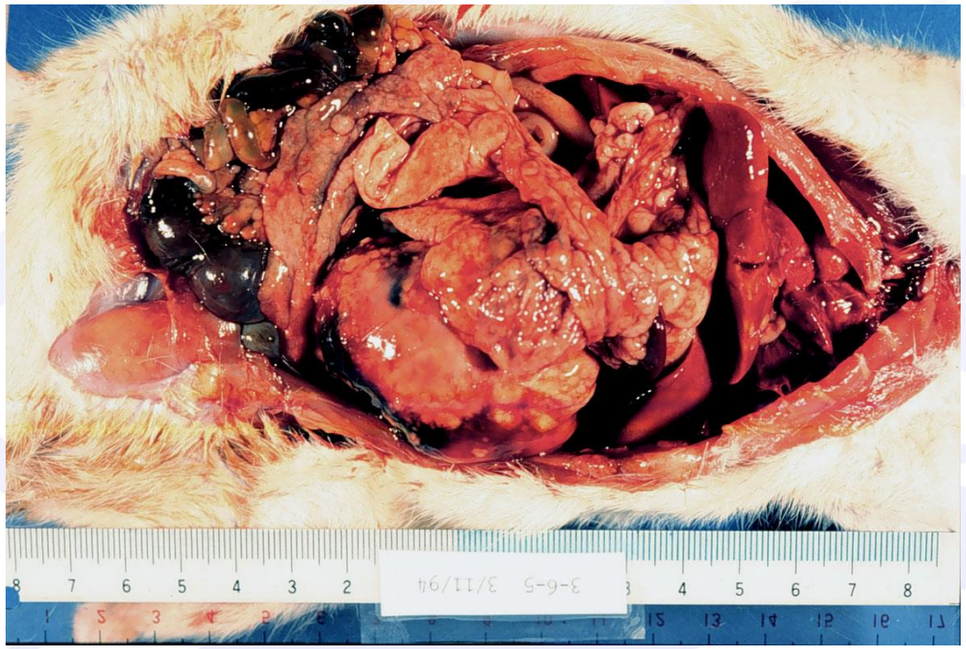


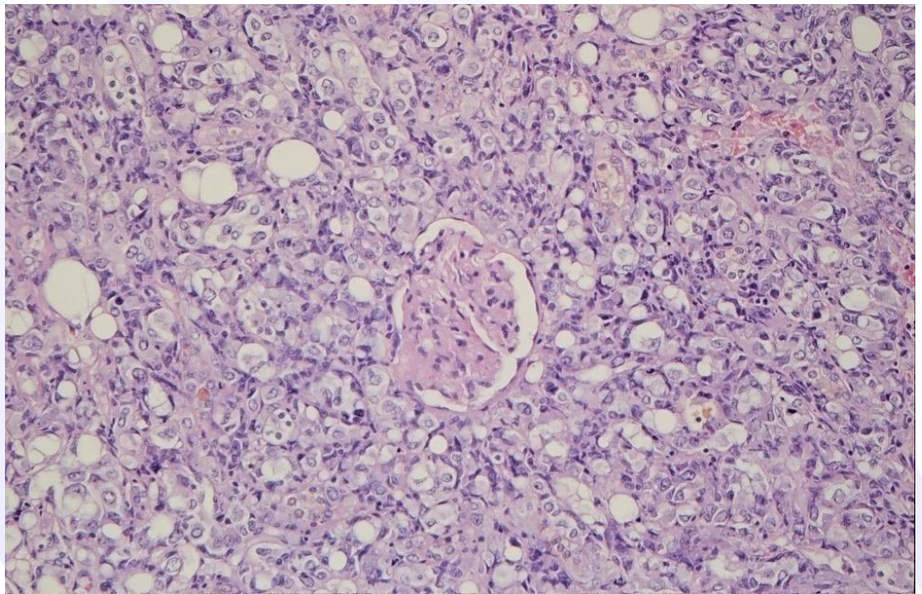


Fe-NTA腎発がんモデル

- 急性傷害 → 耐性 → がん
- in vivo Fenton反応
- 「時間」を含む病理モデル







セレンディピティー

Shigeru OKADA

NAGOYA UNIVERSITY GRADUATE SCHOOL OF MEDICINE

› Am J Pathol. 1979 Jun;95(3):663-73.

Induction of diabetes in animals by parenteral administration of ferric nitrilotriacetate. A model of experimental hemochromatosis

M Awai, M Narasaki, Y Yamanoi, S Seno

PMID: 377994 PMCID: PMC2042322

3ヶ月の糖尿病モデルを1年以上観察することにより、腎発がんモデルを発見

› J Natl Cancer Inst. 1986 Jan;76(1):107-13.

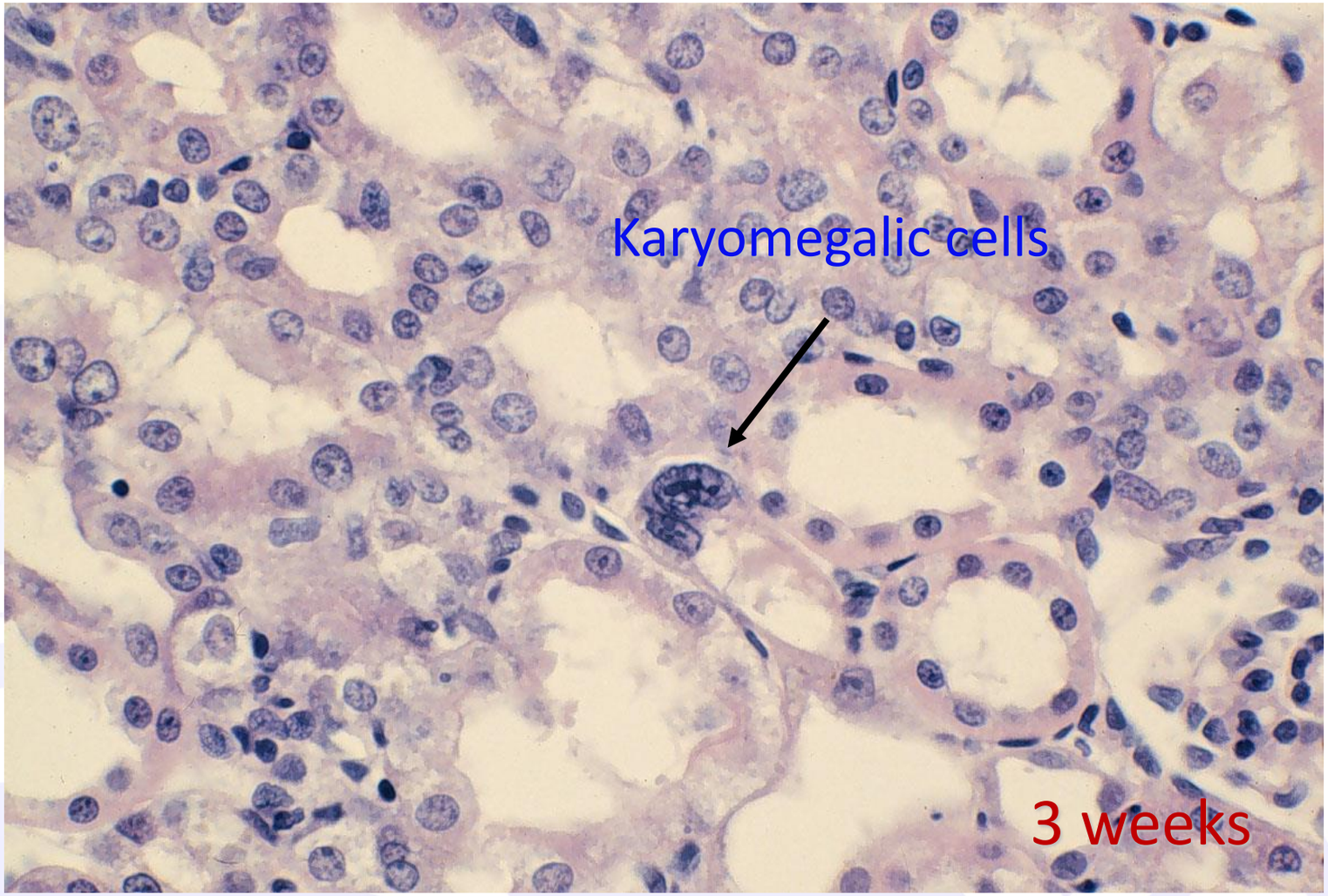
Nephrotoxicity and renal cell carcinoma after use of iron- and aluminum-nitrilotriacetate complexes in rats

Y Ebina, S Okada, S Hamazaki, F Ogino, J L Li, O Midorikawa

PMID: 3455733

病理が示した連続性

- 壊死
- 再生
- 耐性獲得
- 発がん



若手研究者へのメッセージ①

「どんなテーマでも、新しい思想があれば世界に届く」

ここまでの要点

- 病理学的思考が出発点
- 金属が生体に与える影響を問い続けた
- 流行よりも一貫性を選んだ

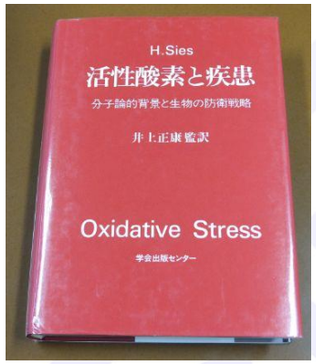
次に見えてきた現象

- Fe-NTAによる傷害は一過性ではない
- 時間をかけて質が変わる
- 何が細胞を変えているのかを知りたい

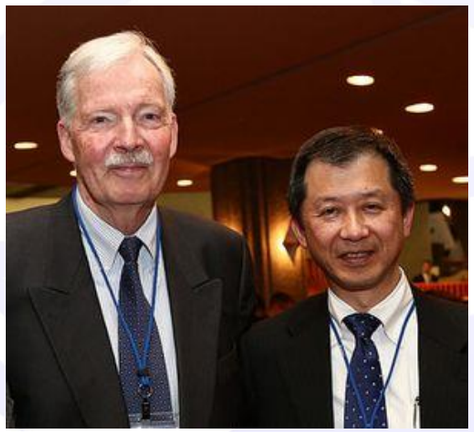
フリーラジカル・活性酸素・酸化ストレス

NAGOYA UNIVERSITY GRADUATE SCHOOL OF MEDICINE

- 酸化ストレス Oxidative Stress　Helmut Sies 1985
- 日本フリーラジカル学会・日本過酸化脂質/フリーラジカル学会（八木國夫教授・早石 修教授が立ち上げに関与）吉川敏一 教授（現　日本酸化ストレス学会 SFRR Japan）
- Society for Free Radical Research International (SFRRI)
- International BioIron Society (IBIS)
- International Redox Network 淀井淳司 教授（京都大学ウイルス研）



1985



Helmut Sies

Toshikazu Yoshikawa

http://www.louis-pasteur.or.jp/greeting/

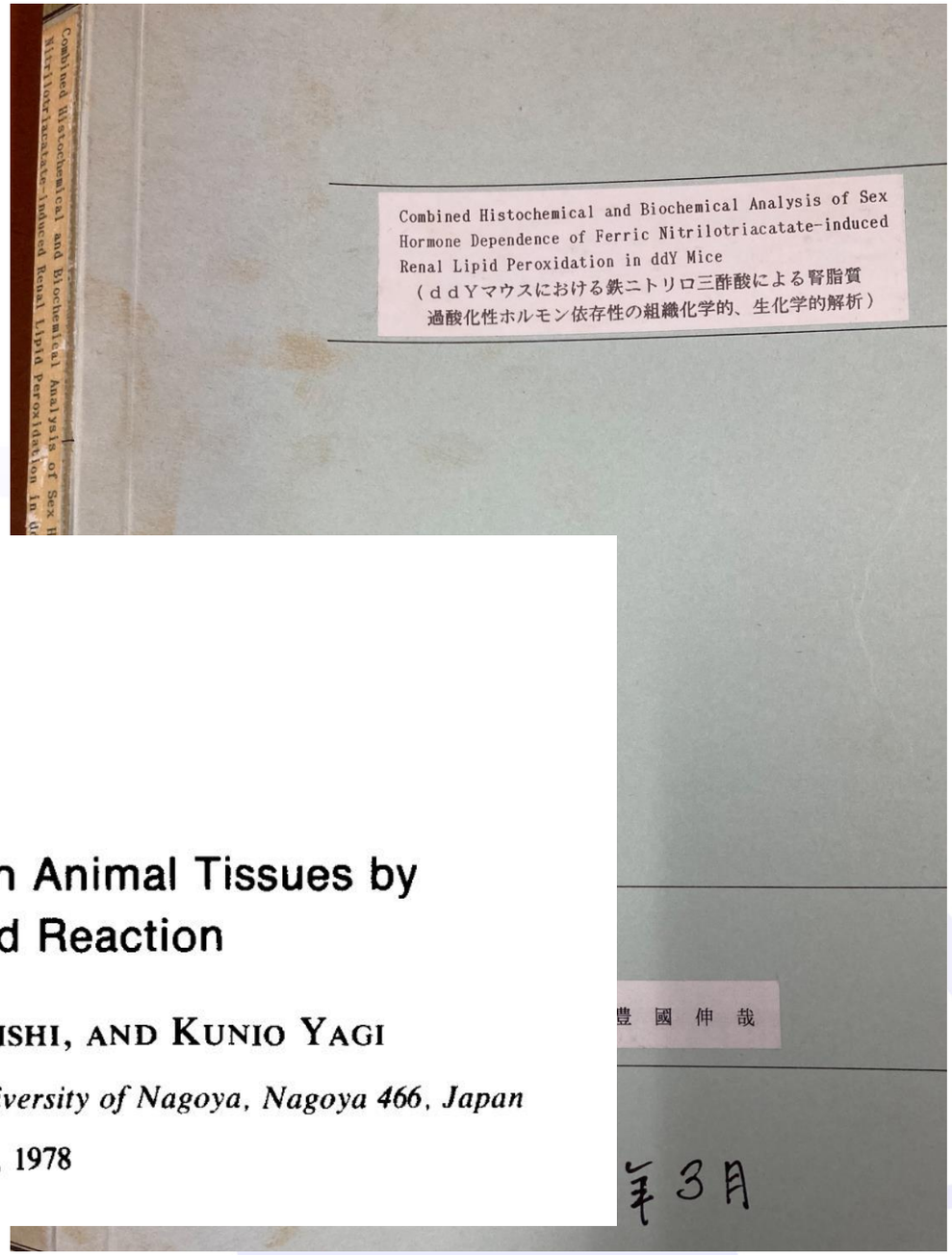
Junji Yodoi

https://kyoto-u.academia.edu/JunjiYodoi

脂質過酸化

- 鉄依存的に起こる
- 細胞膜脂質が標的
- 極めて再現性が高い

Co



ANALYTICAL BIOCHEMISTRY 95, 351–358 (1979)

Cited 24,269 times

Assay for Lipid Peroxides in Animal Tissues by Thiobarbituric Acid Reaction

HIROSHI OHKAWA, NOBUKO OHISHI, AND KUNIO YAGI

Institute of Biochemistry, Faculty of Medicine, University of Nagoya, Nagoya 466, Japan

Received July 20, 1978

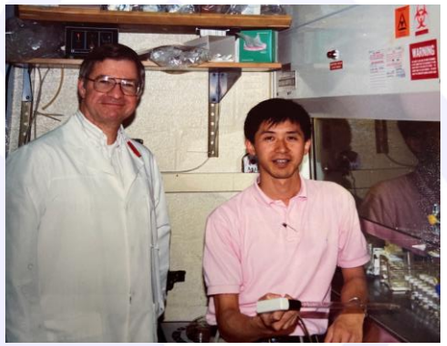
副産物ではなかった

- 傷害の中心に位置
- 傷害部位と完全に一致
- 発がん部位と重なる

米国FDAへの留学 1990-92（留学のメリット）

- 英語環境にどっぷり浸れる
- 新たな研究ネットワークの構築
- 日本を外から眺められる
- 新たな技術に触れることができる
  （reference managerを知った）

Jose-Luis Sagripanti, FDA

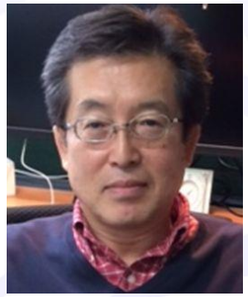


Jim Strickland, NCI, NIH

4-hydroxy-2-nonenal（HNE）

- 脂質過酸化（アルデヒド）の代表的生成物
- 高い反応性
- 組織内で検出可能（見える化が重要）

Earl Stadtman, NIH



Koji Uchida, Nagoya Univ

https://irp.nih.gov/catalyst/21/1/the-stadtman-legacy

留学中の出会い

アルデヒドとタンパク質のアミノ酸残基との反応（マイケル付加反応）

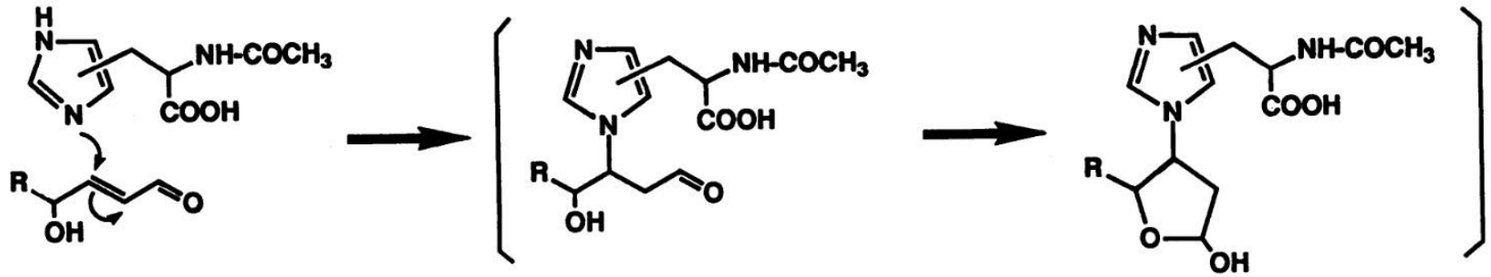


FIG. 4. Proposed mechanism for formation of HNE-histidine adducts.

油（アルデヒド）を抗原として認知可能な分子へ転換

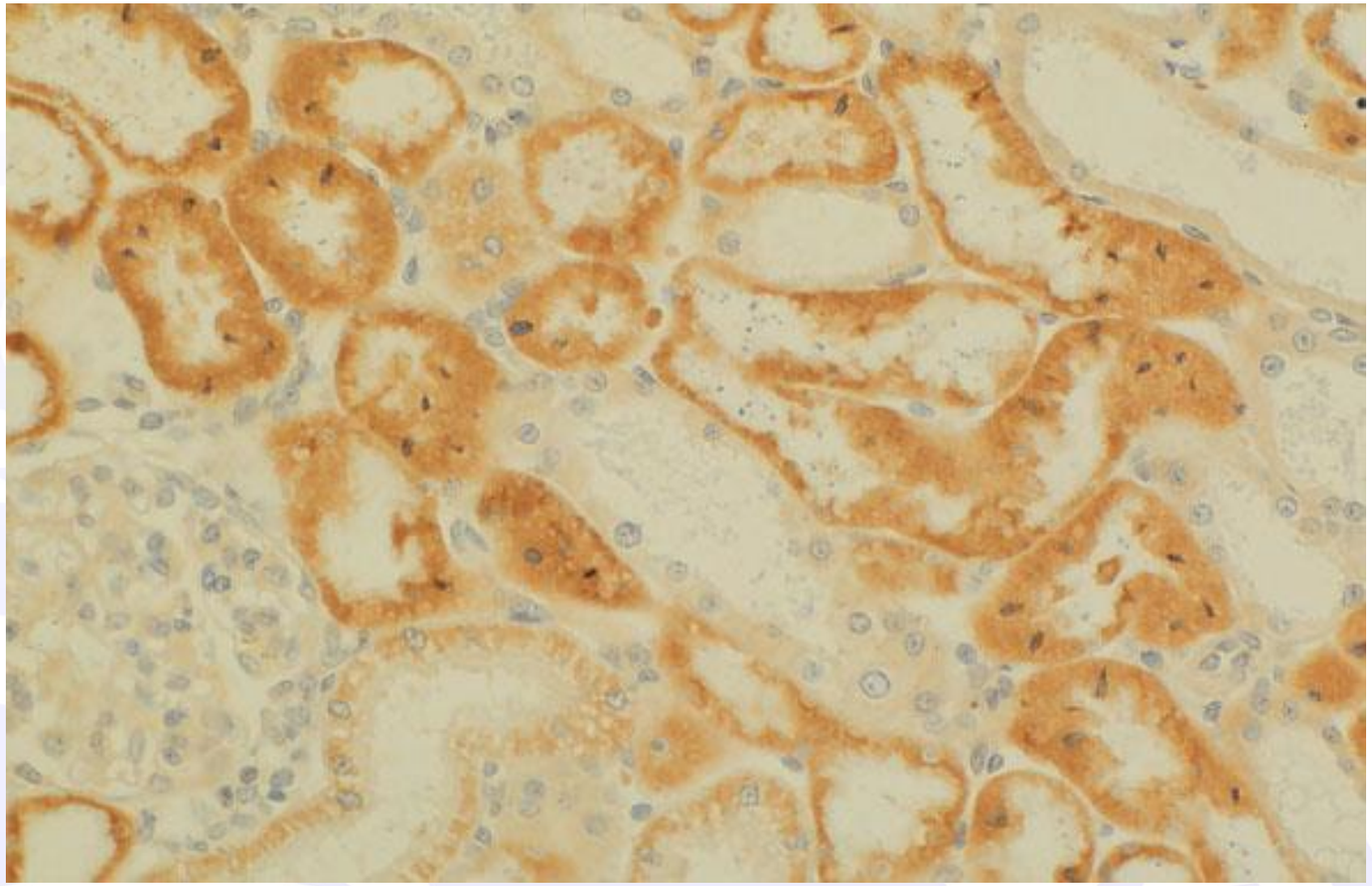
PNAS 1992

PNAS論文（1994）

- HNE修飾タンパク質の局在
- 病理と分子の接続
- 国際的な可視性

FFPE specimens

Formalin-fixed paraffin-embedded



HNEによる可視化

- 免疫組織化学
- 傷害部位と一致
- 時間依存性

Free Radical Biology & Medicine, Vol. 22, No. 6, pp. 1019–1027, 1997

0891-5849/97 $17.00 + .00

ELSEVIER

PII S0891-5849(96)00489-3

Original Contribution

INDUCTION OF A WIDE RANGE OF C_{2-12} ALDEHYDES AND C_{7-12} ACYLOINS IN THE KIDNEY OF WISTAR RATS AFTER TREATMENT WITH A RENAL CARCINOGEN, FERRIC NITRILOTRIACETATE

SHINYA TOYOKUNI,* XIAO-PING LUO,† TOMOYUKI TANAKA,* KOJI UCHIDA,‡ HIROSHI HIAI,* and DENIS C. LEHOTAY†

*Department of Pathology and Biology of Diseases, Graduate School of Medicine, Kyoto University, Sakyo-ku, Kyoto 606, Japan; †Department of Clinical Biochemistry, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8; and ‡Laboratory of Food and Biodynamics, Nagoya University, School of Agriculture, Nagoya 464-01, Japan

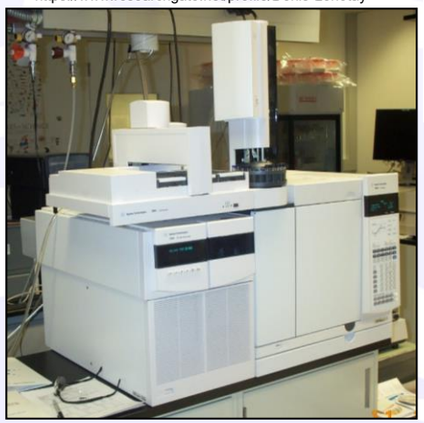
(*Received* 11 *July* 1996; *Revised* 10 *September* 1996; *Accepted* 10 *September* 1996)

Abstract—An iron chelate, ferric nitrilotriacetate (Fe-NTA), induces renal proximal tubular necrosis associated with lipid peroxidation and oxidative DNA damage that finally leads to a high incidence of renal cell carcinoma in rodents. In the present study, we investigated what kinds of C_{2-12} saturated and unsaturated aldehydes and C_{7-12} acyloins, metabolites of saturated aldehydes, are produced in the kidney and liver within 24 h after single ip administration of 15 mg Fe/kg of Fe-NTA, or after repeated (1 or 3 wk) in administration of 5–10 mg Fe/kg of Fe-NTA. Amounts

HNE as most sensitive marker

Denis C Lehotay

https://www.researchgate.net/profile/Denis-Lehotay



FEBS 15105

FEBS Letters 359 (1995) 189–191

The monoclonal antibody specific for the 4-hydroxy-2-nonenal histidine adduct

Shinya Toyokuni[a,*], Naoki Miyake[a], Hiroshi Hiai[a], Maiko Hagiwara[b], Shunro Kawakishi[b], Toshihiko Osawa[b], Koji Uchida[b]

[a]*Department of Pathology, Faculty of Medicine, Kyoto University, Sakyo-ku, Kyoto 606, Japan*
[b]*Laboratory of Food and Biodynamics, Nagoya University School of Agriculture, Nagoya 464-01, Japan*

Received 19 December 1994

Abstract **Monoclonal antibodies directed against proteins modified with the major membrane lipid peroxidation product, 4-hydroxy-2-nonenal, have been established and characterized. The monoclonal antibodies specific for HNE-modified proteins were raised by immunizing mice with a HNE–keyhole limpet hemocyanin conjugate. The resulting five monoclonal antibodies (mAbs HNEJ-1–5) recognized HNE-modified bovine serum albumin (BSA), but not native BSA in Western blot studies. Of the five mAbs, HNEJ-2 exhibited the highest affinity for HNE-modified proteins and a much higher affinity for the HNE–histidine adduct than the HNE–lysine or HNE–cysteine adducts. mAb HNEJ-2 did not cross-react with proteins that had been treated with other aldehydes, such as 1-hexenal, 2-hexenal, 4-hydroxy-2-hexenal, 2-nonenal, formaldehyde, or glutaraldehyde. These results suggest that the major epitope recognized by mAb HNEJ-2 is the Michael addition-type HNE–histidine adduct.**

Key words: Reactive oxygen species; Lipid peroxidation; 4-Hydroxy-2-nonenal; Histidine; Monoclonal antibody

Ehrlich ascites tumor cells. HNE also exhibits genotoxic and mutagenic effects, as well as inhibitory effects on cell proliferation [2]. In a model system using Ehrlich ascites tumor cells, more than 80% of HNE are metabolized to non-toxic compounds, either by oxidation or reduction, within 10 min after exposure. However, a fraction (approximately 1–6%) of HNE is covalently bound to proteins [3]. It has been proposed that HNE exerts the cytotoxic effects via its facile reactivity with proteins. We have previously established that the imidazole nitrogens of the histidine residue is one of the major targets of HNE reactivity, in addition to the ε-amino group of the lysine residue and the sulfhydryl group of cysteine residue [4].

We have recently raised a polyclonal antibody against HNE-modified proteins, and showed that epitopes recognized by this polyclonal antibody are present in oxidized cultured hepatocytes [5], atherosclerotic lesions of human aorta [6], renal proximal tubules of rats treated with a renal carcinogen, ferric nitrilotriacetate [7], and human renal cell carcinoma [8]. However, polyclonal antibodies recognize multiple epitopes and

Hiroshi Hiai

8-OHdGによる可視化

Hiroshi Kasai

Toshihiko Osawa

NAGOYA UNIVERSITY GRADUATE SCHOOL OF MEDICINE

Int. J. Cancer: **57,** 123–128 (1994)
© 1994 Wiley-Liss, Inc.

Publication of the International Union Against Cancer
Publication de l'Union Internationale Contre le Cancer

DNA BASE MODIFICATIONS IN RENAL CHROMATIN OF WISTAR RATS TREATED WITH A RENAL CARCINOGEN, FERRIC NITRILOTRIACETATE

Shinya TOYOKUNI[1,4], Toshiaki MORI[2,3] and Miral DIZDAROGLU[3]

[1]*Department of Pathology, Faculty of Medicine, Kyoto University, Sakyo-ku, Kyoto 606, Japan;* [2]*Division of Radiation Chemistry, Research Institute for Advanced Science and Technology, University of Osaka Prefecture, Sakai 593, Japan; and* [3]*Chemical Science and Technology Laboratory, National Institute of Standards and Technology, Gaithersburg, MD 20899, USA.*

Ferric nitrilotriacetate (Fe-NTA) causes renal proximal tubular necrosis, a consequence of iron ion-mediated free-radical-associated damage, that finally leads to a high incidence of renal adenocarcinoma in male rats and mice. We have investigated the levels of typical hydroxyl radical-induced DNA base modifications in renal chromatin of male Wistar rats treated with a single or repeated administrations of Fe-NTA. Five pyrimidine-

whether they are the typical ·OH-induced products of DNA and to determine whether these DNA lesions can be accumulated after chronic exposure to Fe-NTA.

MATERIAL AND METHODS

Animals

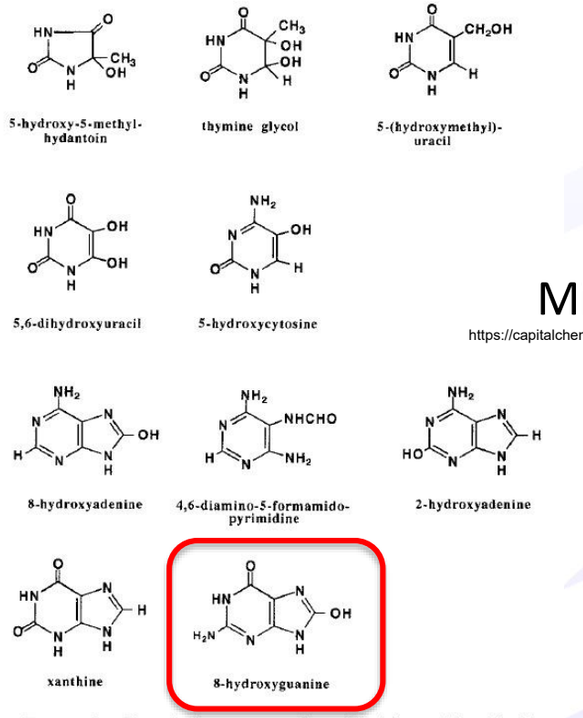
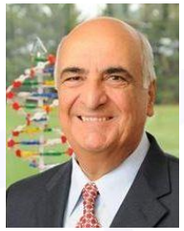


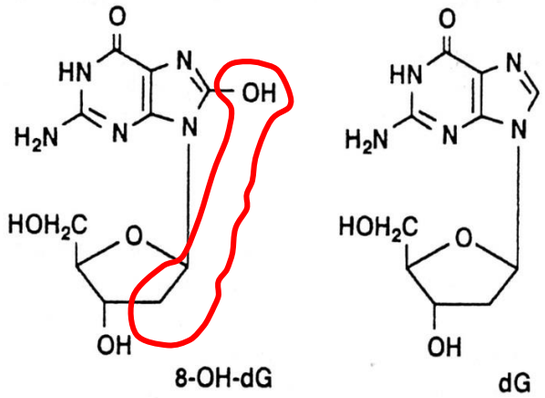
FIGURE 1 – Chemical structure of modified bases identified in renal chromatin of rats.

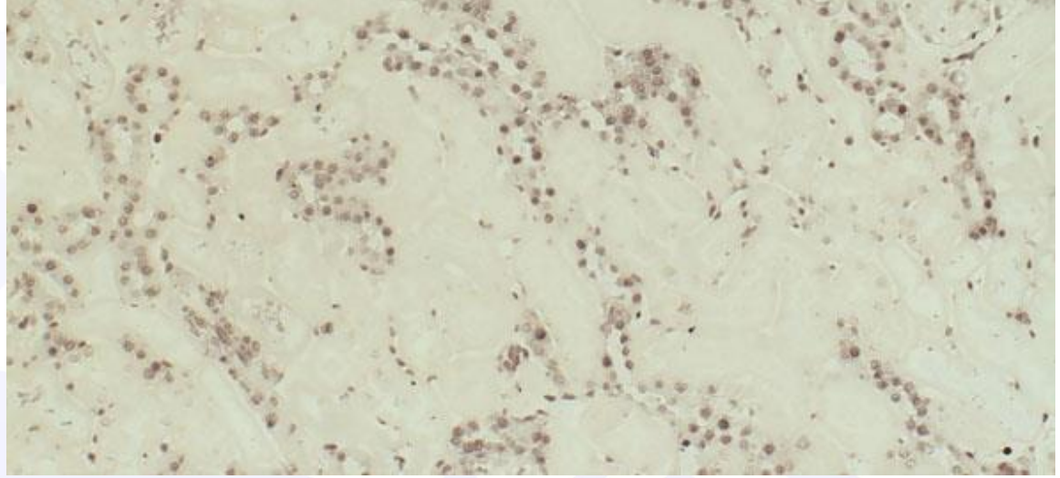


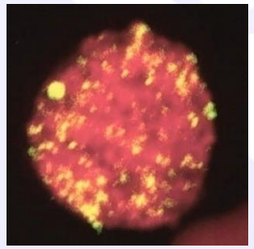
Miral Dizdaroglu

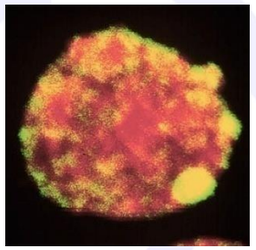
https://capitalchemist.org/wp-content/uploads/2017/12/CC_Apr_2012.pdf

N45.1









8-OHdG as most sensitive marker

Lab Invest 1997

病理が先に見ていたもの

- 鉄依存性 Iron-dependence
- 脂質過酸化 Lipid peroxidation
- 特定の細胞死様式 Specific cell death mode

フェロトーシス Ferroptosis という名前

Eradicate *Ras*-transformed cells: Erastin

- 概念化は2012年 (Dixon and Stockwell, Cell)
- 現象はそれ以前から存在
- 病理は概念を待たない

Pathology International

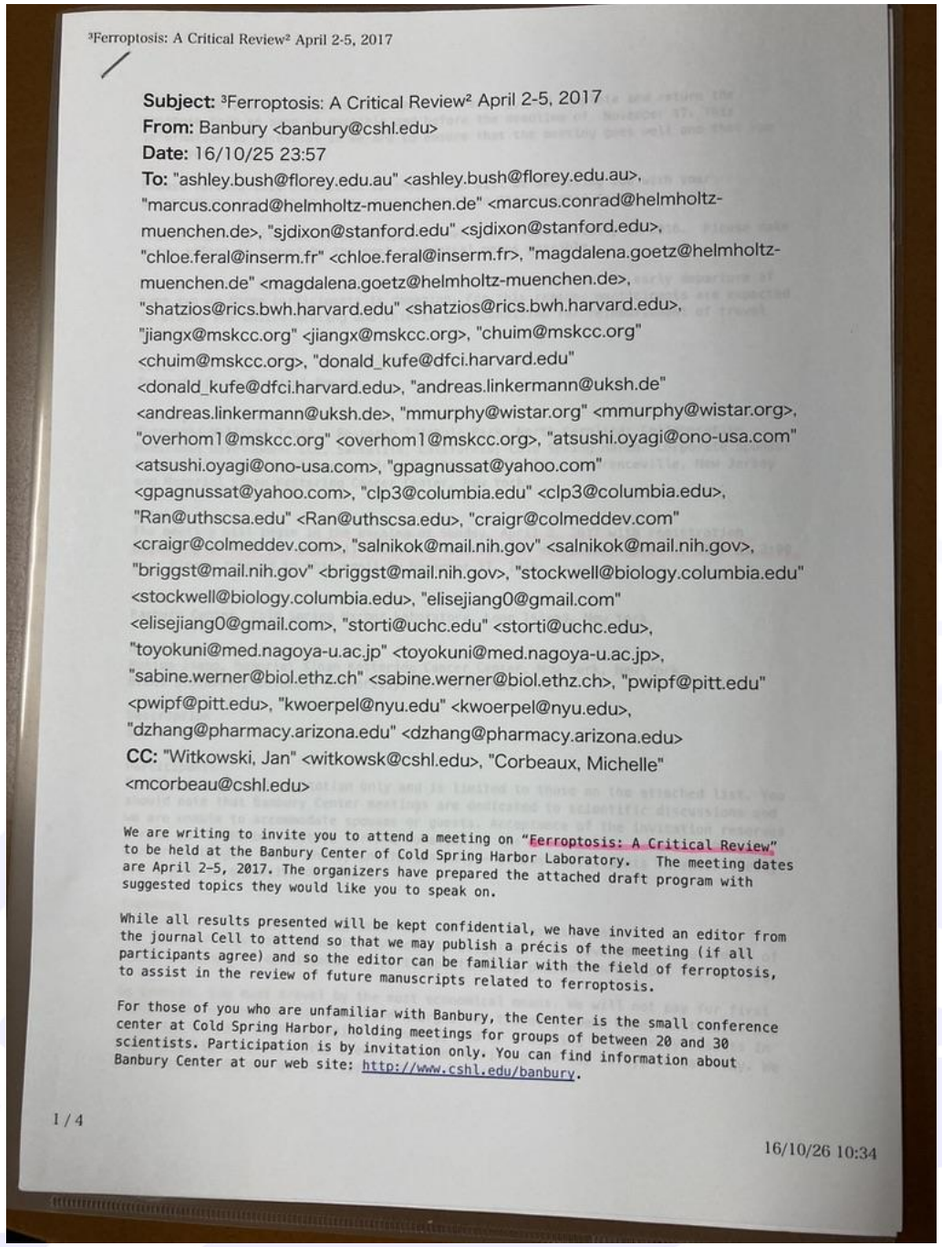
Pathology International 2016; **66**: 245–259 doi:10.1111/pin.12396

Review Article

The origin and future of oxidative stress pathology: From the recognition of carcinogenesis as an iron addiction with ferroptosis-resistance to non-thermal plasma therapy

アメリカから1通の電子メール

NAGOYA UNIVERSITY GRADUATE SCHOOL OF MEDICINE



³Ferroptosis: A Critical Review² April 2-5, 2017

Subject: ³Ferroptosis: A Critical Review² April 2-5, 2017
From: Banbury <banbury@cshl.edu>
Date: 16/10/25 23:57
To: "ashley.bush@florey.edu.au" <ashley.bush@florey.edu.au>, "marcus.conrad@helmholtz-muenchen.de" <marcus.conrad@helmholtz-muenchen.de>, "sjdixon@stanford.edu" <sjdixon@stanford.edu>, "chloe.feral@inserm.fr" <chloe.feral@inserm.fr>, "magdalena.goetz@helmholtz-muenchen.de" <magdalena.goetz@helmholtz-muenchen.de>, "shatzios@rics.bwh.harvard.edu" <shatzios@rics.bwh.harvard.edu>, "jiangx@mskcc.org" <jiangx@mskcc.org>, "chuim@mskcc.org" <chuim@mskcc.org>, "donald_kufe@dfci.harvard.edu" <donald_kufe@dfci.harvard.edu>, "andreas.linkermann@uksh.de" <andreas.linkermann@uksh.de>, "mmurphy@wistar.org" <mmurphy@wistar.org>, "overhom1@mskcc.org" <overhom1@mskcc.org>, "atsushi.oyagi@ono-usa.com" <atsushi.oyagi@ono-usa.com>, "gpagnussat@yahoo.com" <gpagnussat@yahoo.com>, "clp3@columbia.edu" <clp3@columbia.edu>, "Ran@uthscsa.edu" <Ran@uthscsa.edu>, "craigr@colmeddev.com" <craigr@colmeddev.com>, "salnikok@mail.nih.gov" <salnikok@mail.nih.gov>, "briggst@mail.nih.gov" <briggst@mail.nih.gov>, "stockwell@biology.columbia.edu" <stockwell@biology.columbia.edu>, "elisejiang0@gmail.com" <elisejiang0@gmail.com>, "storti@uchc.edu" <storti@uchc.edu>, "toyokuni@med.nagoya-u.ac.jp" <toyokuni@med.nagoya-u.ac.jp>, "sabine.werner@biol.ethz.ch" <sabine.werner@biol.ethz.ch>, "pwipf@pitt.edu" <pwipf@pitt.edu>, "kwoerpel@nyu.edu" <kwoerpel@nyu.edu>, "dzhang@pharmacy.arizona.edu" <dzhang@pharmacy.arizona.edu>
CC: "Witkowski, Jan" <witkowsk@cshl.edu>, "Corbeaux, Michelle" <mcorbeau@cshl.edu>

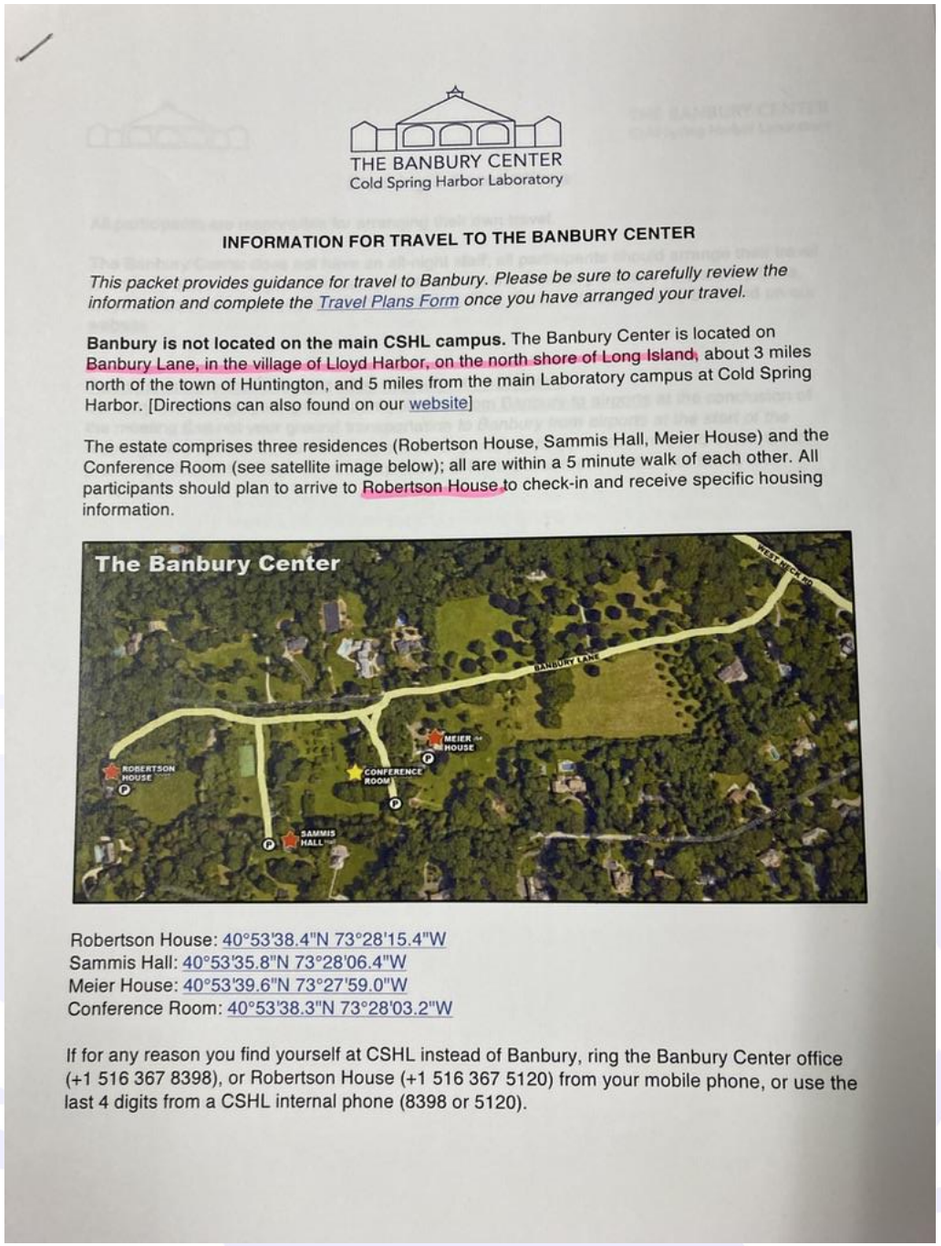
We are writing to invite you to attend a meeting on "Ferroptosis: A Critical Review" to be held at the Banbury Center of Cold Spring Harbor Laboratory. The meeting dates are April 2-5, 2017. The organizers have prepared the attached draft program with suggested topics they would like you to speak on.

While all results presented will be kept confidential, we have invited an editor from the journal Cell to attend so that we may publish a précis of the meeting (if all participants agree) and so the editor can be familiar with the field of ferroptosis, to assist in the review of future manuscripts related to ferroptosis.

For those of you who are unfamiliar with Banbury, the Center is the small conference center at Cold Spring Harbor, holding meetings for groups of between 20 and 30 scientists. Participation is by invitation only. You can find information about Banbury Center at our web site: http://www.cshl.edu/banbury.

1 / 4

16/10/26 10:34



THE BANBURY CENTER
Cold Spring Harbor Laboratory

INFORMATION FOR TRAVEL TO THE BANBURY CENTER

This packet provides guidance for travel to Banbury. Please be sure to carefully review the information and complete the Travel Plans Form once you have arranged your travel.

Banbury is not located on the main CSHL campus. The Banbury Center is located on Banbury Lane, in the village of Lloyd Harbor, on the north shore of Long Island, about 3 miles north of the town of Huntington, and 5 miles from the main Laboratory campus at Cold Spring Harbor. [Directions can also found on our website]

The estate comprises three residences (Robertson House, Sammis Hall, Meier House) and the Conference Room (see satellite image below); all are within a 5 minute walk of each other. All participants should plan to arrive to Robertson House to check-in and receive specific housing information.

Robertson House: 40°53'38.4"N 73°28'15.4"W
Sammis Hall: 40°53'35.8"N 73°28'06.4"W
Meier House: 40°53'39.6"N 73°27'59.0"W
Conference Room: 40°53'38.3"N 73°28'03.2"W

If for any reason you find yourself at CSHL instead of Banbury, ring the Banbury Center office (+1 516 367 8398), or Robertson House (+1 516 367 5120) from your mobile phone, or use the last 4 digits from a CSHL internal phone (8398 or 5120).

フェロ（2価鉄）トーシス（剥離）：触媒性2価鉄依存性の制御性壊死で脂質過酸化を伴うもの

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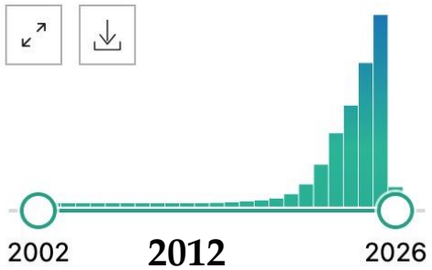
RESULTS BY YEAR

8527 (24115 on Jan 17, 2026)



Dixon et al.

Leading Edge

Primer

Cell

Ferroptosis: A Regulated Cell Death Nexus Linking Metabolism, Redox Biology, and Disease

Brent R. Stockwell,[1,2,*] José Pedro Friedmann Angeli,[3,29] Hülya Bayir,[4] Ashley I. Bush,[5] Marcus Conrad,[3] Scott J. Dixon,[6] Simone Fulda,[7] Sergio Gascón,[8,28] Stavroula K. Hatzios,[9,10] Valerian E. Kagan,[11] Kay Noel,[12] Xuejun Jiang,[13] Andreas Linkermann,[14] Maureen E. Murphy,[15] Michael Overholtzer,[13] Atsushi Oyagi,[16] Gabriela C. Pagnussat,[17] Jaesun Park,[18] Qitao Ran,[19] Craig S. Rosenfeld,[12] Konstantin Salnikow,[20] Daolin Tang,[21,22] Frank M. Torti,[23] Suzy V. Torti,[24] Shinya Toyokuni,[25] K.A. Woerpel,[26] and Donna D. Zhang[27]

[1]Department of Biological Sciences

[2]Department of Chemistry

Columbia University, 550 West 120th Street, MC 4846, New York, NY 10027, USA

evelopmental Genetics, Helmholtz Zentrum München, Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH),

many

f Critical Care Medicine, Safar Center for Resuscitation Research and Center for Free Radical and Antioxidant Health,

ittsburgh and Children's Hospital of Pittsburgh, Pittsburgh, PA, USA

stitute of Neuroscience and Mental Health, The University of Melbourne, Parkville, VIC, Australia

f Biology, Stanford University, Stanford, CA, USA

xperimental Cancer Research in Pediatrics, Goethe-University Frankfurt, German Cancer Consortium (DKTK),

ankfurt, German Cancer Research Center (DKFZ), Heidelberg, Germany

milians University of Munich, Physiological Genomics, Biomedical Center (BMC), Planegg-Martinsried, Germany

f Molecular, Cellular and Developmental Biology and Department of Chemistry, Yale University, New Haven, CT 06511, USA

ences Institute, Yale University, West Haven, CT 06516, USA

ee Radical and Antioxidant Health, Departments of Environmental Health, Pharmacology and Chemical Biology, Chemistry,

ology, University of Pittsburgh, Pittsburgh, PA, USA

Medicinal Development, LLC, Sausalito, CA, USA

Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA

of Internal Medicine III, Division of Nephrology, University Hospital Carl Gustav Carus at Technische Universität Dresden,

nany

olecular and Cellular Oncogenesis, The Wistar Institute, Philadelphia, PA, USA

USA, Lawrenceville, NJ 08648, USA

Cell (Oct 5, 2017)

Cited 6127 times

1st International Meeting on Ferroptosis (Banbury Center, Cold Spring Harbor Laboratory, NY, USA; April 2-5, 2017)

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Cold Spring Harbor Asia Ferroptosis Meeting in Japan

Iron, Reactive Oxygen Species & Ferroptosis in Life, Death & Disease, AWAJI, JAPAN

Awaji Yumebutai Conference Center, JAPAN

November 15-20, 2026
Abstract deadline: September 4, 2026

Organized by:

Quan Chen, Nankai University
Marcus Conrad, Helmholtz Zentrum München
Xuejun Jiang, Memorial Sloan Kettering Cancer Center
Hozumi Motohashi, Tohoku University
Brent Stockwell, Columbia University
Shinya Toyokuni, Nagoya University

https://www.csh-asia.org/?content/2871

World longest hanging bridge over the sea

研究は「当てる」ものではない

- 流行を追わない
- 現象を追い続ける
- 名前は後からついてくる

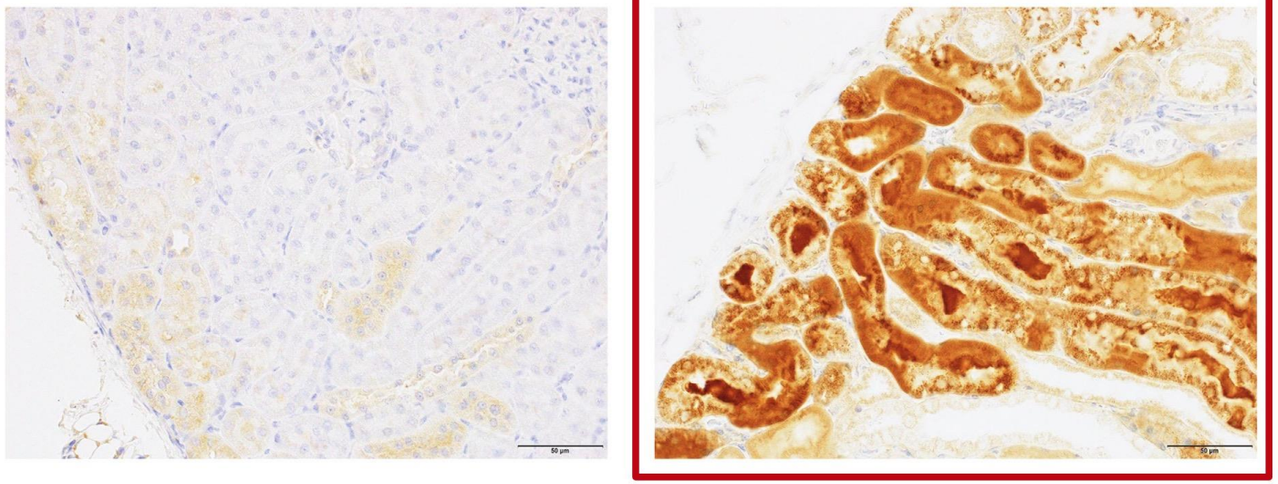
次の問いへ

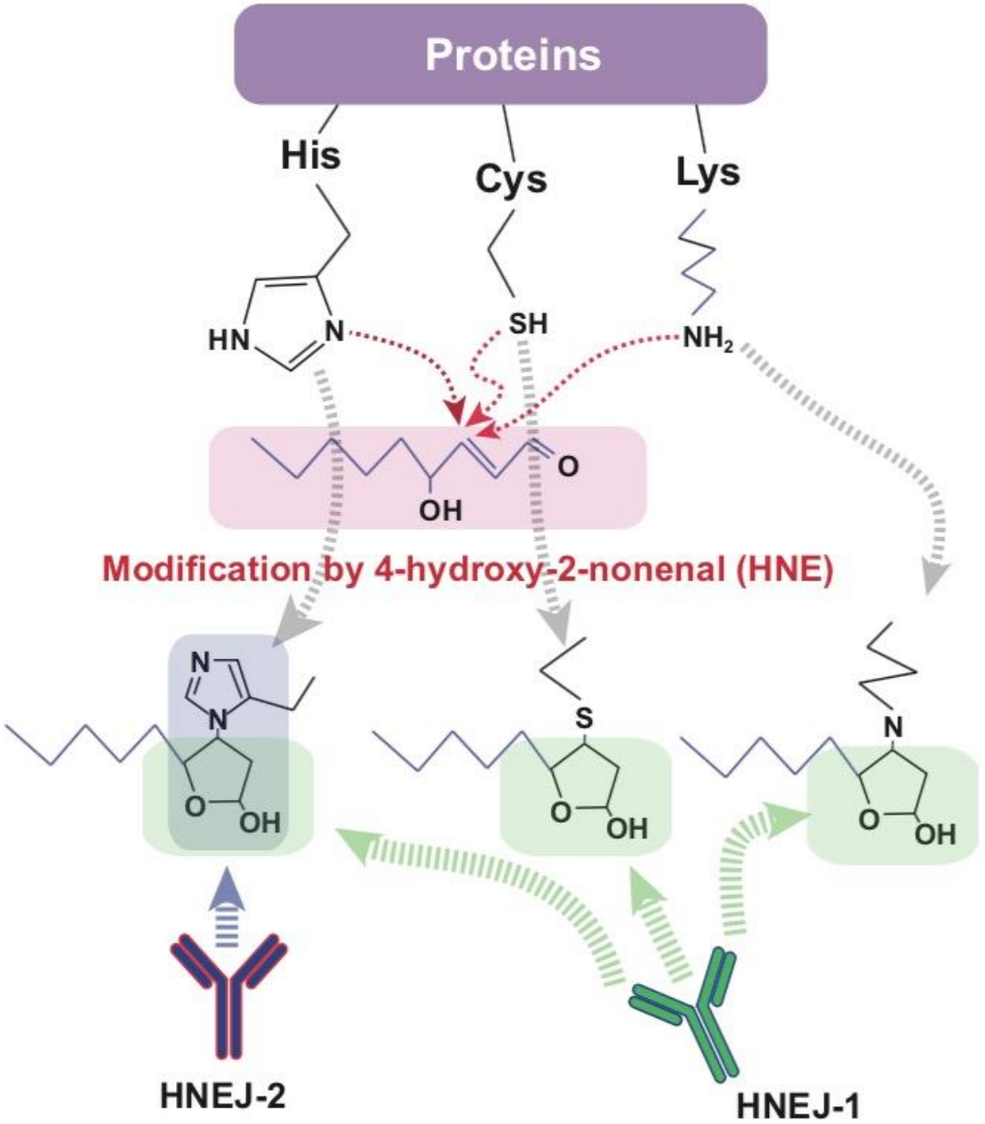
- 鉄依存性細胞死は制御できるか
- 生理的な役割はあるのか
- がん治療に使える新たな方法はあるのか

フェロトーシスの定義への挑戦

- 鉄依存性
- 脂質過酸化を伴う
- 制御性壊死

HNEJ-1





研究科内の共同研究

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Redox Biology 67 (2023) 102890

Contents lists available at ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox

Retinal ferroptosis as a critical mechanism for the induction of retinochoroiditis during ocular toxoplasmosis

Kazuhisa Yamada [a,1], Akira Tazaki [b,1], Nanako Ushio-Watanabe [c,1], Yoshihiko Usui [d], Atsunobu Takeda [e], Masaaki Matsunaga [f], Ayana Suzumura [a], Hideyuki Shimizu [a], Hao Zheng [g], Nanang R. Ariefta [c], Masahiro Yamamoto [h], Hideaki Hara [i], Hiroshi Goto [d], Koh-Hei Sonoda [e], Koji M. Nishiguchi [a], Masashi Kato [b], Yoshifumi Nishikawa [c], Shinya Toyokuni [g,j], Hiroki Kaneko [a,*]

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[b] Department of Occupational and Environmental Health, Nagoya University Graduate School of Medicine, Nagoya, 466-8550, Japan
[c] National Research Center for Protozoan Diseases, Obihiro University of Agriculture and Veterinary Medicine, Obihiro, 080-8555, Japan
[d] Department of Ophthalmology, Tokyo Medical University, Tokyo, 160-8402, Japan
[e] Department of Ophthalmology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
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[g] Department of Pathology and Biological Responses, Nagoya University Graduate School of Medicine, Nagoya, 466-8550, Japan
[h] Department of Immunoparasitology, Research Institute for Microbial Diseases, Osaka University, Suita, Osaka, Japan
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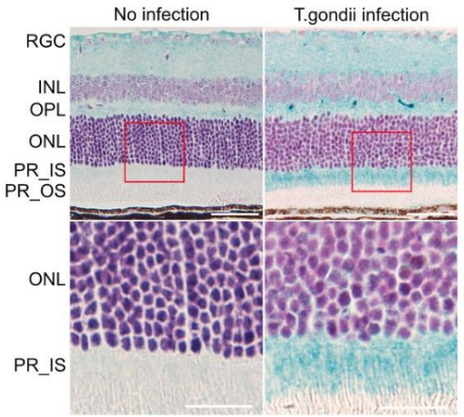
[j] Center for Low-Temperature Plasma Sciences, Nagoya University, Furo-Cho, Chikusa-ku, Nagoya, 464-8603, Japan



Photoreceptor-Inner Segment

Free Radical Biology and Medicine 228 (2025) 33–43

Contents lists available at ScienceDirect

Free Radical Biology and Medicine

journal homepage: www.elsevier.com/locate/freeradbiomed

Silicone oil, an intraocular surgical adjuvant, induces retinal ferroptosis

Hideyuki Shimizu [a], Hiroshi Tanaka [b], Akira Tazaki [c], Kazuhisa Yamada [a], Ayana Suzumura [a], Junya Ota [a], Nanako Ushio-Watanabe [d], Hao Zheng [e], Keiko Kataoka [f], Hideaki Hara [g], Yoshifumi Nishikawa [d], Tsutomu Yasukawa [h], Kiyoshi Suzuma [i], Hiroko Terasaki [a,j], Koji M. Nishiguchi [a], Masashi Kato [c], Shinya Toyokuni [e], Hiroki Kaneko [a,k,*]

[a] Department of Ophthalmology, Nagoya University Graduate School of Medicine, Nagoya, 466-8560, Japan
[b] Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, 602-0841, Japan
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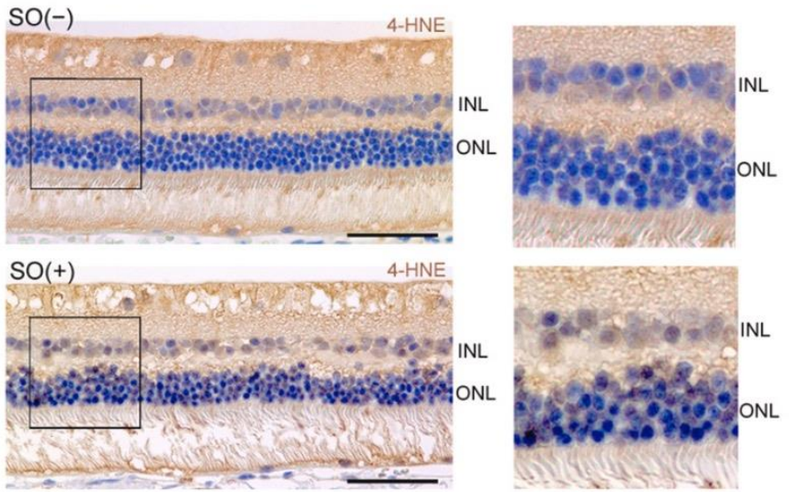
[f] Department of Ophthalmology, Kyorin University School of Medicine, Tokyo, 181-8611, Japan
[g] Department of Biofunctional Evaluation, Molecular Pharmacology, Gifu Pharmaceutical University, Gifu, 501-1196, Japan
[h] Department of Ophthalmology and Visual Science, Nagoya City University Graduate School of Medical Sciences, 467-8601, Japan
[i] Department of Ophthalmology, Kagawa University Faculty of Medicine, 761-0793, Japan
[j] Institutes of Innovation for Future Society, Nagoya University, Nagoya, 466-8550, Japan
[k] Department of Ophthalmology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, Shizuoka, 431-3125, Japan



日本眼科学会 学術奨励賞

Inner Nuclear Layer

Outer Nuclear Layer

病理像が示すフェロトーシス

- 特定細胞集団が標的
- 壊死の1つであり、アポトーシスとは明確に異なる
- 再現性の高い組織像

なぜ「鉄」なのか

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Earth Science and Life

Wikipedia

13.8 bY Big Bang
4.6 bY Earth
3.8 bY First Life

シアノバクテリア
GOE:大酸化事変
鉄鉱石・硫酸産生菌・
火山活動

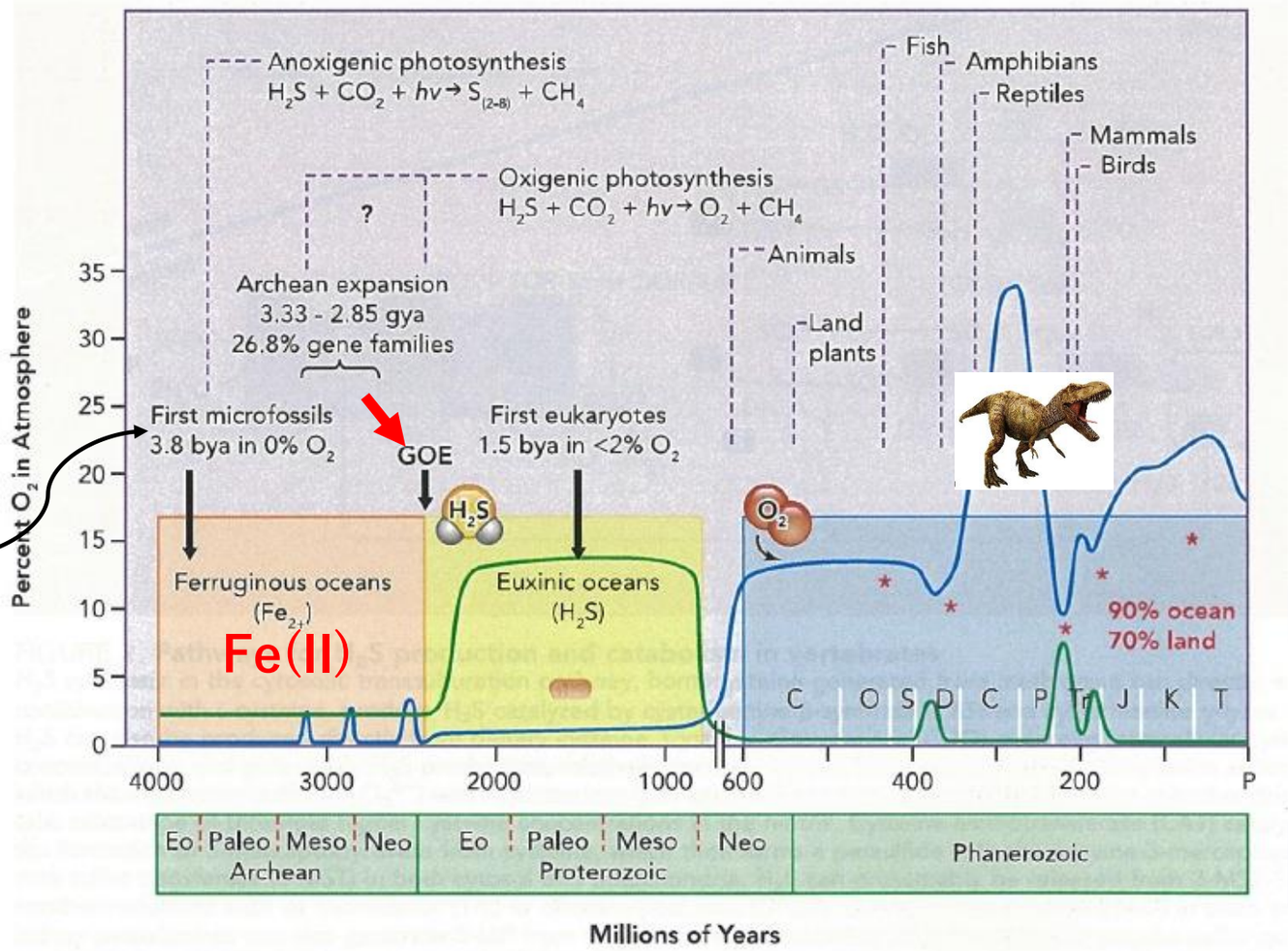


FIGURE 1. **Time line of evolution relative to atmospheric oxygen (O_2, blue line) and oceanic H_2S (orange line)**
Other than possibly a few "whiffs," atmospheric O_2 was essentially nil from the onset of life ~3.8 billion years ago (bya) until the great oxidation event (GOE) 2.3 bya, the latter correlating with a substantial rise in H_2S. Eukaryotes first appeared 1.5 bya in anoxic and sufidic (euxinic) oceans and developed for hundreds of millions of years until O_2 production by oxygenic cyanobacteria and plants oxidized the H_2S and Fe^{2+} ~0.6 bya, essentially eliminating sulfide as an energy source. Mass extinctions (*) were often associated with a fall in ambient O_2 and increase in H_2S, perhaps providing a biological filter for descendants that retained some degree of tolerance to hypoxia and sulfide.

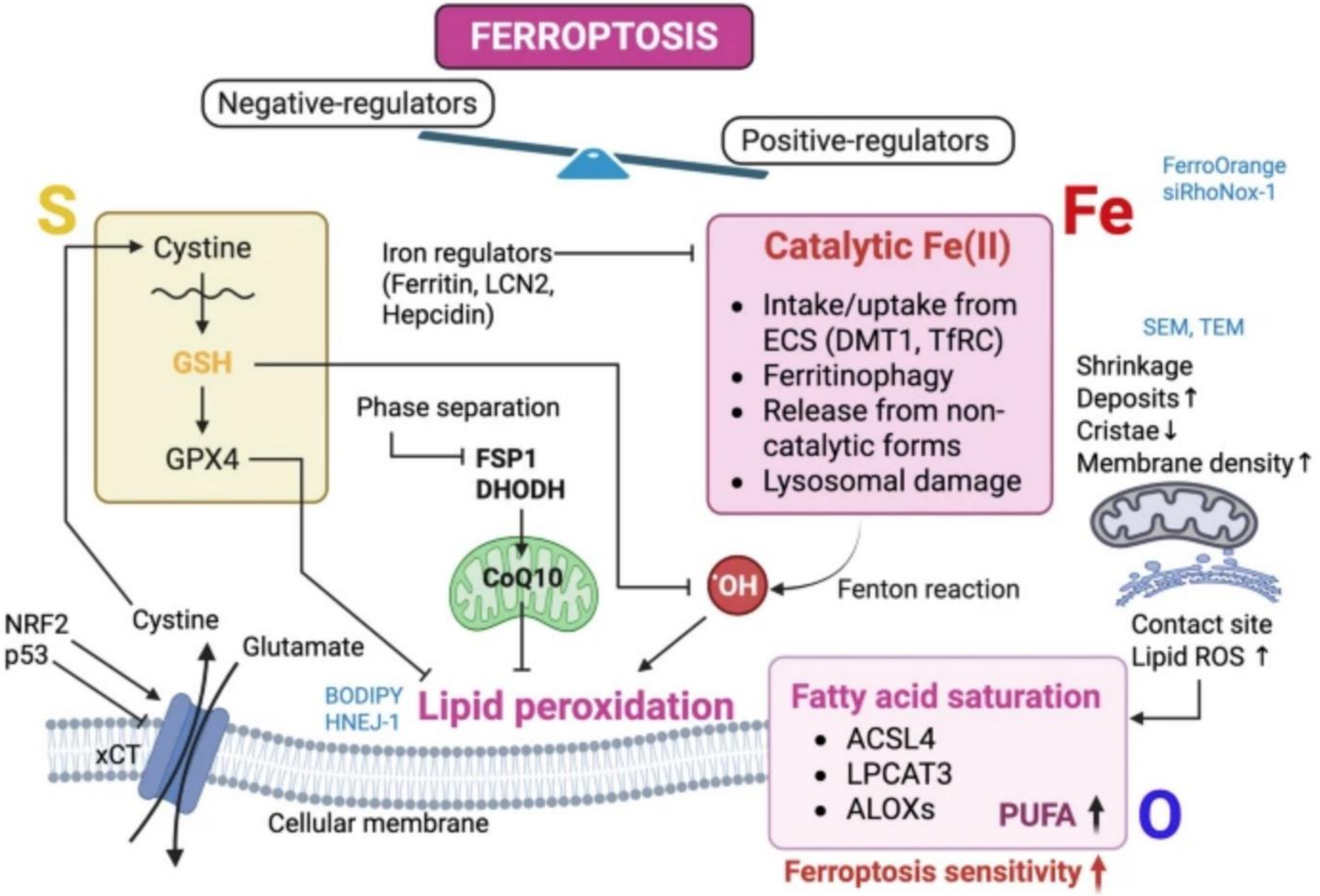
EVOLUTION
Fe>S>O

O2

H2S

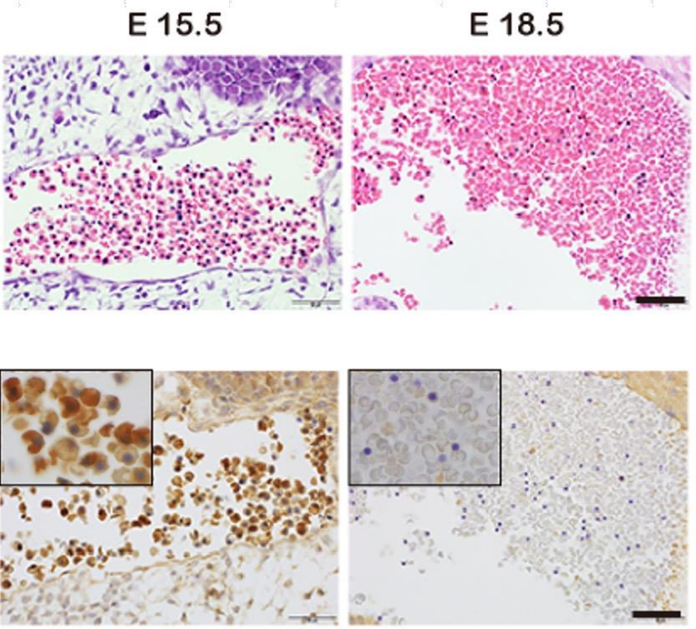
Olson KR and Straub KD. Physiology 2016

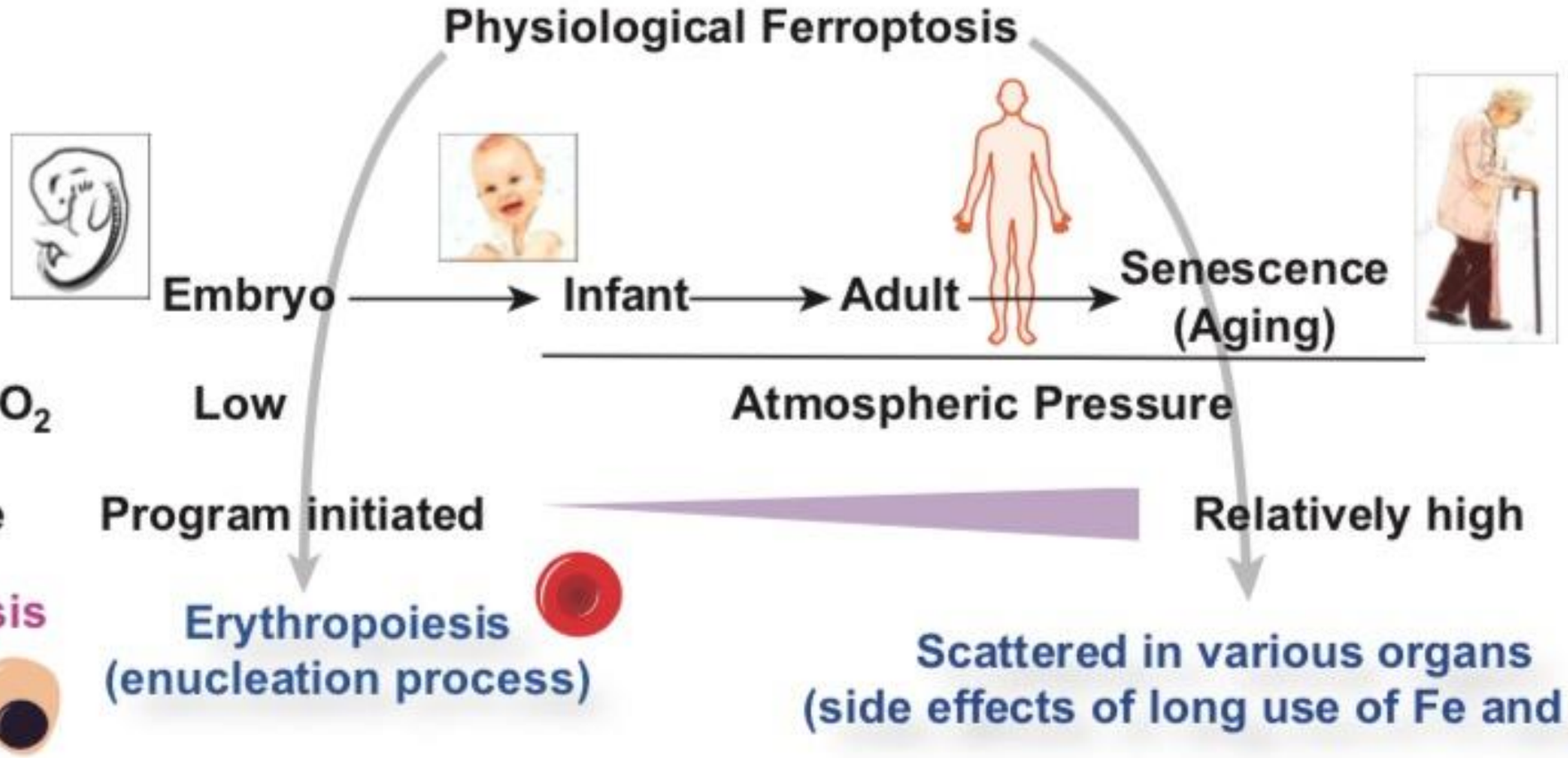
フェロトーシスの概念



Toyokuni S *et al.* Cell Mol Life Sci **2025**

生理的フェロトーシス





Zheng *et al.* Redox Biol 2021

病理は概念を待たない

- 現象は先に存在する
- 概念は後から整理される
- 名前は最後につく
- だから正確な記録が重要

フェロトーシス研究の位置づけ

- 新しい概念
- しかし新しい現象ではない
- 病理学の延長線上にある

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研究は「現象」から始まる

- 流行を追わない
- 現象を追い続ける
- 概念は後からついてくる
- 社会的な問題に自らの視点で取り組む

Shigetada Nakanishi

https://www.kyoto-u.ac.jp/ja/archive/prev/news_data/h/h1/news7/2009/091214_1

新規コンセプト
やり尽くしている
社会への還元（税金）

鉄発がんの標的遺伝子問題

- 標的遺伝子があるかどうかがわからない

Oncogene (1999) 18, 3793–3797

http://www.stockton-press.co.uk/onc

SHORT REPORT

High incidence of allelic loss on chromosome 5 and inactivation of *p15*^{INK4B} and *p16*^{INK4A} tumor suppressor genes in oxystress-induced renal cell carcinoma of rats

Tomoyuki Tanaka[1], Yoko Iwasa[1], Shohei Kondo[1], Hiroshi Hiai[1] and Shinya Toyokuni*,[1]

[1]*Department of Pathology and Biology of Diseases, Graduate School of Medicine, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan*

Table 1 Pathological feature, LOH pattern on chromosome 5, and genetic alteration and methylation of p15^{INK4B} and p16^{INK4A} genes in Fe-NTA-induced rat renal cell carcinoma

Case	Histological grade	Invasion and metastasis[a]	Microsatellite markers on chromosome 5					*p15*[d]	*p16*[d]
			Mgh5[b]	Mit9	Mgh6	Mit11	Mit6		
1	1	LN	W[c]	W	W	W	NI	-	met[d]
2	1	-	-	-	-	-	NI	-	-
3	1	-	LE[c]	LE	LE	LE	LE	-	-
4	1	-	LE	LE	LE	LE	LE	-	-
5	1	-	LE	-	-	-	-	-	-
6	1	-	W	W	W	W	W	-	-
7	1	-	-	-	-	-	-	-	-
8	2	-	LE	NI	NI	NI	LE	LOH[d]	met
9	2	-	W	NI	NI	NI	-	-	met
10	2	-	LE	NI	LE	-	-	-	-
11	2	-	LE	NI	LE	NI	LE	met	LOH, met
12	2	pancreas, peri	W	W	W	W	NI	-	LOH, met
13	2	liver, peri	LE	-	-	-	-	LOH	LOH

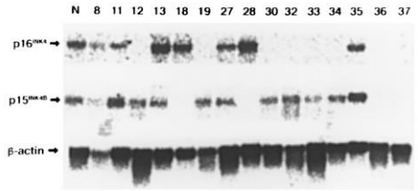

Figure 4 Northern blot analysis of *p15* and *p16* in the Fe-NTA-induced RCCs. Case numbers correspond to those of Table 1. Poly(A)$^+$ RNA (8 μg) was loaded to each lane, and the visualization was done with BAS2000 (Fiji Film, Tokyo, Japan). The exposure time was 48 h for *p15* and *p16* while 3 h for β-actin

Oncogene 1999

Hiroshi Hiai

Forward Genetics
(positional cloning with microsatellite markers)

⇕

Reverse Genetics

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RESEARCH ARTICLE OPEN ACCESS

Fenton Reaction Induced Cancer in Wild Type Rats Recapitulates Genomic Alterations Observed in Human Cancer

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Shinya Akatsuka[1], Yoriko Yamashita[1], Hiroki Ohara[1], Yu-Ting Liu[2], Masashi Izumiya[3], Koichiro Abe[3,4], Masako Ochiai[3], Li Jiang[1], Hirotaka Nagai[1,2], Yasumasa Okazaki[1], Hideki Murakami[5], Yoshitaka Sekido[5], Eri Arai[6], Yae Kanai[6], Okio Hino[7], Takashi Takahashi[8], Hitoshi Nakagama[3], Shinya Toyokuni[1]*

1 Departments of Pathology and Biological Responses, Nagoya University

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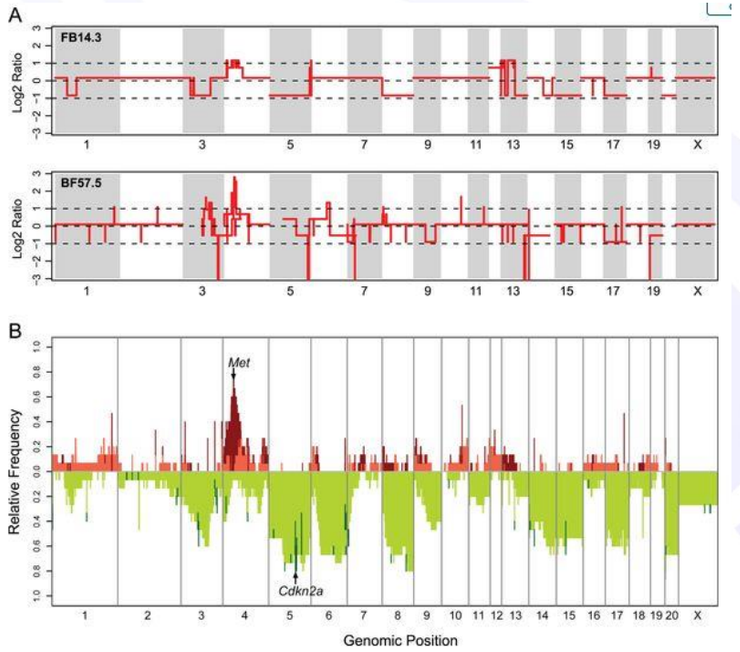
Jump to
Abstract
Introduction



PLOS One 2012

aCGH

Hitoshi Nakagama

Fe-NTA誘発腎がんの主な標的遺伝子はc-Met増幅とp16ホモ欠損

アスベストの中皮腫発がん問題

- 発がん機構が明らかでない
- 白石綿（クリソタイル）には発がん性があるのか
- 標的遺伝子があるかどうかがわからない

Nature 12/16/2010

Asbestos scandal

Irresponsible policies could cause an epidemic of malignant lung disease.

Viewed through an electron microscope, asbestos fibres look like thin glass straws, some no more than a fraction of a micrometre wide. If inhaled, they penetrate the soft alveoli of the lungs and the membranes that line the chest cavity. And there they stay. Over

sends the mineral have little or no protection. Asbestos exported from Canada and other countries including Russia, Brazil and Kazakhstan is routinely mixed into building materials and consumer products, prized for the same durability that makes it troublesome for living tissue. Owing to the long time between exposure and the onset of disease, 30 years or more, the asbestos trade in North America and elsewhere is creating an epidemic that may take decades to peak and subside.

The minerals industry has long tried to convince regulators that white asbestos — or chrysotile — is safe when handled properly. It argues that only the already controlled forms — blue and brown asbestos, known collectively as amphibole — are of concern.

To support this, industry advocates point to scientific data and studies.


毎日新聞 (夕刊)

クボタ社員ら

"石綿死"10年で51人

工場周辺住民も2人

アスベスト（石綿）を関連病の発症が増し、過去10年間で51人が死亡していたことが分かった。石綿水道管を長年製造してきた大手機械メーカー「クボタ」（本社・大阪市浪速区）の社員（退職者含む）や出入り業者の間で、がんの一種「中皮腫」や肺がんなど石綿人も中皮腫を発症し、うち2人が死亡していたことが、民間団体「関西労働者安全センター」（大阪市中央区）の調べで判明した。石綿関連がんの潜伏期間は約20～50年と出した石綿使用の原則禁止措置を受け、石綿使用でも発症者数が急激に増加するとみられる。発症者への対応や救済が今後大きな課題となりそうだ。

同社は昨年10月に国が

毎日新聞 6/29/2005

NAGOYA UNIVERSITY GRADUATE SCHOOL OF MEDICINE


川崎医科大学
大槻剛己 教授


兵庫医科大学
中野孝司 教授

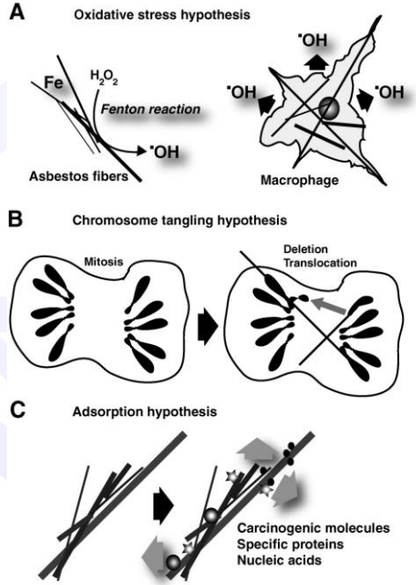

愛知県がんセンター
関戸好孝 副所長

科学技術振興調整費：重要課題解決型研究等の推進（2006-2010）

ROS (frustrated phagocytosis, Fe)

Histone

Hemoglobin



Journal of Pathology
J Pathol 2012; **228:** 366–377
Published online 2 August 2012 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/path.4075

ORIGINAL PAPER

Iron overload signature in chrysotile-induced malignant mesothelioma

Li Jiang,[1] Shinya Akatsuka,[1] Hirotaka Nagai,[1,2] Shan-Hwu Chew,[1] Hiroki Ohara,[1,2] Yasumasa Okazaki,[1] Yoriko Yamashita,[1] Yutaka Yoshikawa,[3] Hiroyuki Yasui,[3] Katsuya Ikuta,[4] Katsunori Sasaki,[5] Yutaka Kohgo,[4] Seishiro Hirano,[6] Yasushi Shinohara,[7] Norihiko Kohyama,[8] Takashi Takahashi[9] and Shinya Toyokuni[1]*

アスベスト発がんの標的遺伝子はp16・白石綿も発がん性高い

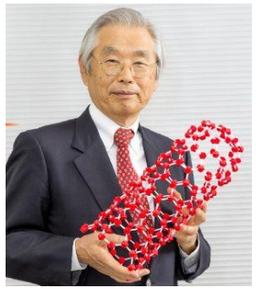
カーボンナノチューブの発がん性問題

- 発がん性があるかどうかがわからない

Hirotaka Nagai

NAGOYA UNIVERSITY GRADUATE SCHOOL OF MEDICINE

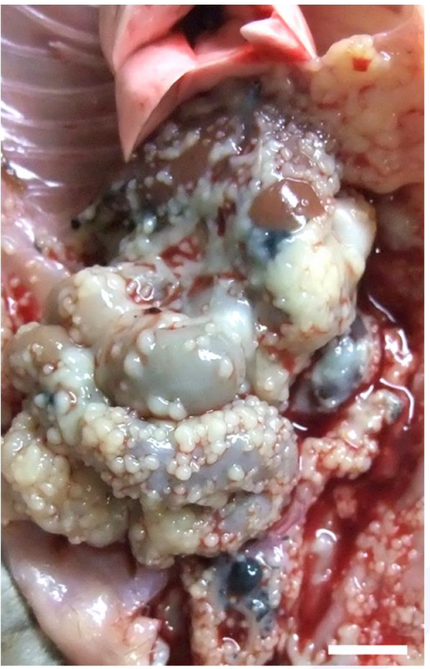
PNAS PLUS



飯島澄男教授

篠原久典教授

https://www.sangyo-times.jp/article.aspx?ID=624

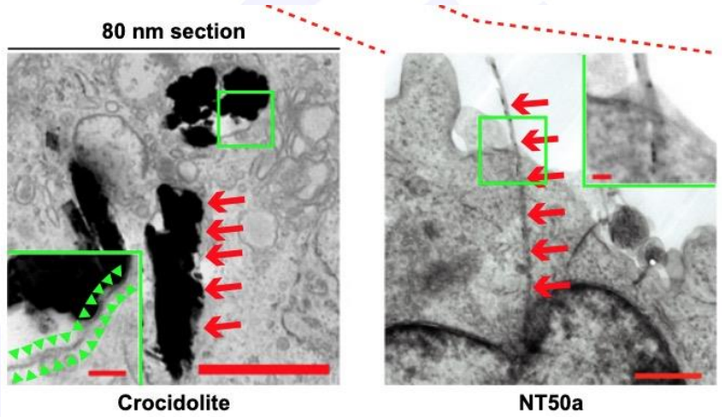


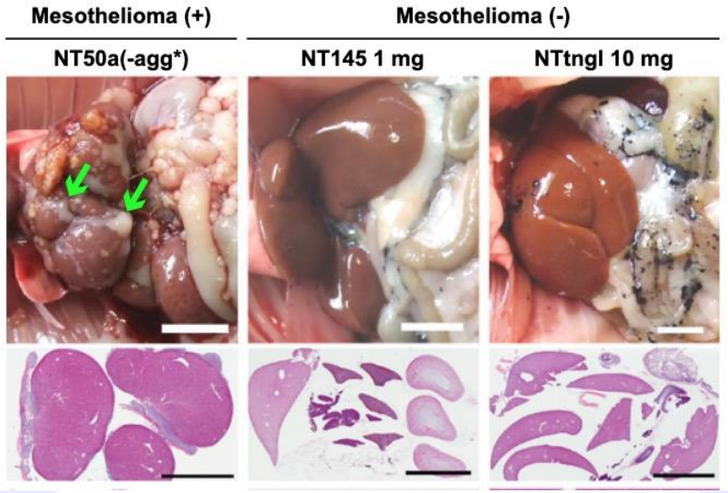
Diameter and rigidity of multiwalled carbon nanotubes are critical factors in mesothelial injury and carcinogenesis

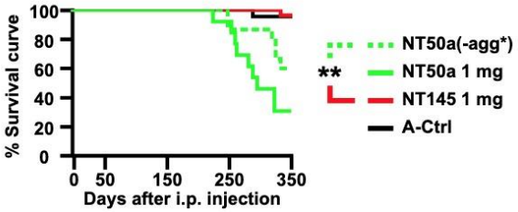
Hirotaka Nagai[a,b], Yasumasa Okazaki[a], Shan Hwu Chew[a], Nobuaki Misawa[a], Yoriko Yamashita[a], Shinya Akatsuka[a], Toshikazu Ishihara[a], Kyoko Yamashita[a], Yutaka Yoshikawa[c], Hiroyuki Yasui[c], Li Jiang[a], Hiroki Ohara[a], Takashi Takahashi[d], Gaku Ichihara[e], Kostas Kostarelos[f], Yasumitsu Miyata[g], Hisanori Shinohara[g], and Shinya Toyokuni[a,1]

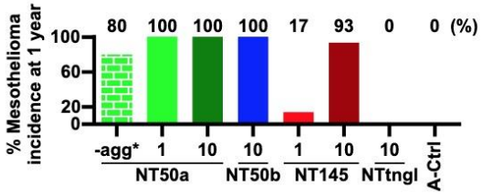
[a]Department of Pathology and Biological Responses, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Japan; [b]Department of Pathology and Biology of Diseases, Kyoto University Graduate School of Medicine, Kyoto 606-8315, Japan; [c]Division of Analytical and Physical Chemistry, Department of Analytical and Bioinorganic Chemistry, Kyoto Pharmaceutical University, Kyoto 607-8414, Japan; Departments of [d]Molecular Carcinogenesis and [e]Occupational and Environmental Health, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Japan; [f]Nanomedicine Laboratory, Centre for Drug Delivery Research, School of Pharmacy, University of London, London WC1N 1AX, United Kingdom; and [g]Department of Chemistry and Institute for Advanced Research, Nagoya University, Nagoya 464-8602, Japan

Edited by David A. Tirrell, California Institute of Technology, Pasadena, CA, and approved October 19, 2011 (received for review June 22, 2011)









標的遺伝子はやはりｐ16であった

CREST

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CREST「細胞外微粒子」2019-2024 事後評価会

細胞外微粒子に起因する生命現象の解明とその制御に向けた基盤技術の創出
「細胞外微粒子」（研究総括：馬場　嘉信）

細胞外微粒子への生体応答と発がん・動脈硬化症との関連の解析

名古屋大学大学院・医学系研究科　生体反応病理学　豊國　伸哉（研究代表者）

名古屋大学大学院・医学系研究科　循環器内科学　室原　豊明

和歌山県立医科大学・医学部　大町　遼

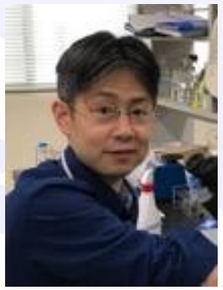
立命館大学薬学部　免疫微生物学　中山　勝史

名古屋大学大学院・医学系研究科　ウイルス学　佐藤　好孝

物質材料研究機構・国際ナノアーキテクトニクス研究拠点　岡本　章玄

Yoshinobu Baba



https://seikagaku.jbsoc.or.jp/10.14952/SEIKAGAKU.2023.950184/data/index.html

CREST 豊國チームの主な業績

blood® Regular Article

RED CELLS, IRON, AND ERYTHROPOIESIS

CD63 is regulated by iron via the IRE-IRP system and is important for ferritin secretion by extracellular vesicles

Izumi Yanatori,[1] Des R. Richardson,[1,2,*] Herschel S. Dhekne,[3] Shinya Toyokuni,[1,4,*] and Fumio Kishi[5]

[1]Department of Pathology and Biological Responses, Nagoya University Graduate School of Medicine, Nagoya, Japan; [2]Centre for Cancer Cell Biology and Drug Discovery, Griffith Institute for Drug Discovery, Griffith University, Nathan, Brisbane, QLD, Australia; [3]Department of Biochemistry, Stanford University School of Medicine, Stanford, CA; [4]Center for Low-Temperature Plasma Sciences, Nagoya University, Nagoya, Japan; and [5]Kenjinkai Healthcare Corporation, Yamaguchi, Japan

KEY POINTS

- CD63 is involved in EV secretion from cells and is shown herein to be regulated by iron via the IRE-IRP system.
- Iron-loading increased secretion of CD63$^+$ EVs containing iron-loaded ferritin.

Extracellular vesicles (EVs) transfer functional molecules between cells. CD63 is a widely recognized EV marker that contributes to EV secretion from cells. However, the regulation of its expression remains largely unknown. Ferritin is a cellular iron storage protein that can also be secreted by the exosome pathway, and serum ferritin levels classically reflect body iron stores. Iron metabolism–associated proteins such as ferritin are intricately regulated by cellular iron levels via the iron responsive element-iron regulatory protein (IRE-IRP) system. Herein, we present a novel mechanism demonstrating that the expression of the EV-associated protein CD63 is under the regulation of the IRE-IRP system. We discovered a canonical IRE in the 5′ untranslated region of *CD63* messenger RNA that is responsible for regulating its expression in response to increased iron. Cellular iron

RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Yanatori et al, page 1490

CD63 orchestrates ferritin export

Suzy V. Torti and Frank M. Torti | University of Connecticut Health Center

In this issue of *Blood*, Yanatori et al[1] demonstrate that the vesicular protein CD63 is regulated by iron and facilitates the secretion of iron-laden ferritin into extracellular vesicles, suggesting that CD63 may enable the transfer of iron-rich ferritin among cells.

Yanatori et al. Blood 2021

nature nanotechnology

Article https://doi.org/10.1038/s41565-023-01363-w

Carbon nanotube recognition by human Siglec-14 provokes inflammation

Received: 5 October 2021

Accepted: 28 February 2023

Published online: 6 April 2023

Check for updates

Shin-Ichiro Yamaguchi[1,2,12], Qilin Xie[2,3,12], Fumiya Ito[2,4], Kazuki Terao[1], Yoshinobu Kato[1], Miki Kuroiwa[1], Satoshi Omori[5], Hideo Taniura[6], Kengo Kinoshita[5,7,8,9], Takuya Takahashi[3], Shinya Toyokuni[2,4,10], Kota Kasahara[2,3,11] & Masafumi Nakayama[1,2]

For the design and development of innovative carbon nanotube (CNT)-based tools and applications, an understanding of the molecular interactions between CNTs and biological systems is essential. In this study, a three-dimensional protein-structure-based in silico screen identified the paired immune receptors, sialic acid immunoglobulin-like binding lectin-5 (Siglec-5) and Siglec-14, as CNT-recognizing receptors. Molecular dynamics simulations showed the spatiotemporally stable association of aromatic residues on the extracellular loop of Siglec-5 with CNTs. Siglec-14 mediated spleen tyrosine kinase (Syk)-dependent phagocytosis of multiwalled CNTs and the subsequent secretion of interleukin-1β from human monocytes. Ectopic in vivo expression of human Siglec-14 on mouse alveolar macrophages resulted in enhanced recognition of multiwalled CNTs and exacerbated pulmonary inflammation. Furthermore, fostamatinib, a Syk inhibitor, blocked Siglec-14-mediated proinflammatory responses. These results indicate that Siglec-14 is a human activating receptor recognizing CNTs and that blockade of Siglec-14 and the Syk pathway may overcome CNT-induced inflammation.

Yamaguchi et al. Nature Nanotechnol 2023

NAGOYA UNIVERSITY GRADUATE SCHOOL OF MEDICINE

nature communications

Article https://doi.org/10.1038/s41467-024-48055-0

Fatal COVID-19 pulmonary disease involves ferroptosis

フェロトーシス検出抗体(HNEJ-1)の利用

Received: 18 August 2023

Accepted: 18 April 2024

Published online: 20 May 2024

Check for updates

Baiyu Qiu[1,11], Fereshteh Zandkarimi[1,2,11], Anjali Saqi[3,11], Candace Castagna[4], Hui Tan[1], Miroslav Sekulic[3], Lisa Miorin[5,6], Hanina Hibshoosh[3], Shinya Toyokuni[7,8], Koji Uchida[9] & Brent R. Stockwell[1,3,10]

SARS-CoV-2 infection causes severe pulmonary manifestations, with poorly understood mechanisms and limited treatment options. Hyperferritinemia

Collaborative efforts among Columbia Univ (NY, USA), Nagoya Univ and Univ Tokyo

Qiu et al. Nat Commun 2024

エクソソームと鉄代謝の問題（CREST 2019-2024: 馬場嘉信 領域代表）

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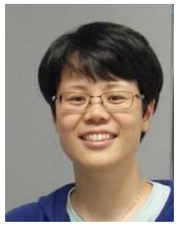
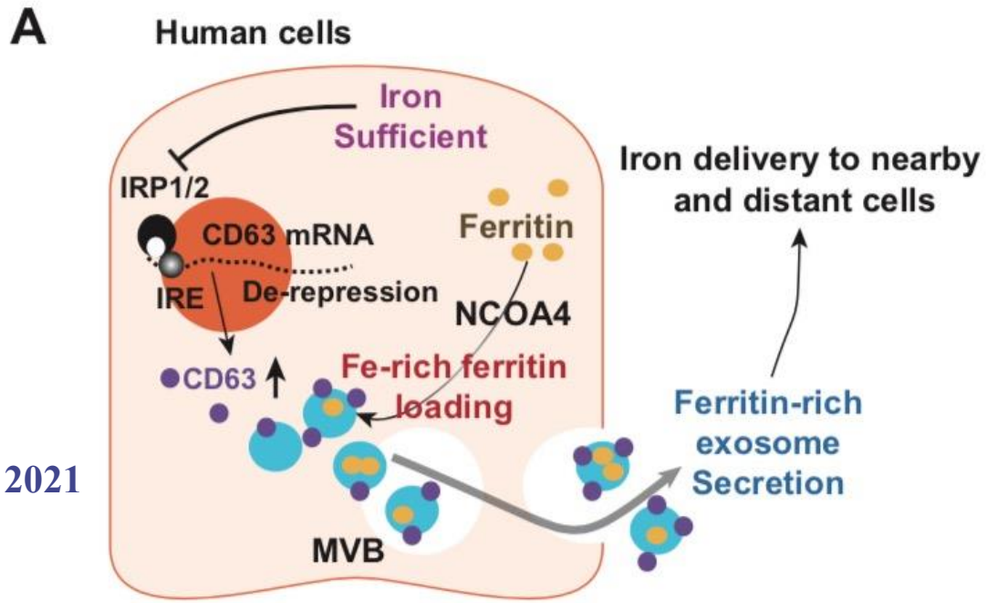
- 細胞外微粒子と細胞内微粒子をつなぐ仕事

生理的

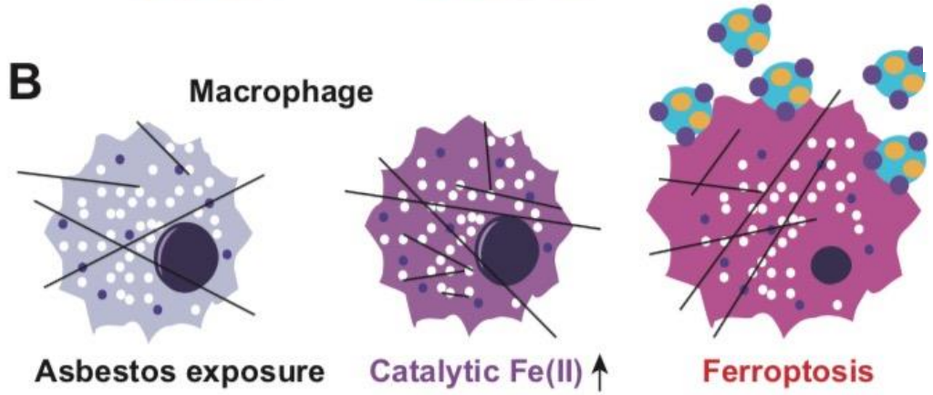


Yanatori *et al.* Blood 2021



アスベスト曝露病態

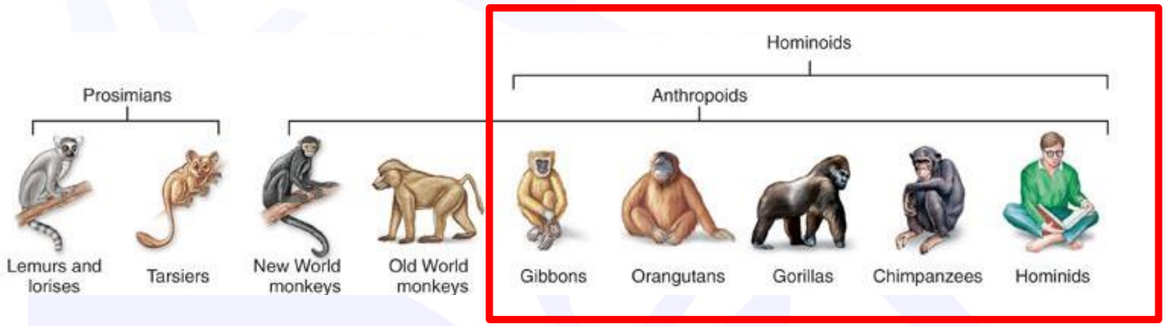
Ito *et al.* Redox Biol 2021



フェロトーシス

鉄代謝関連遺伝子に特有な転写後調節を担うIRE配列が CD63 mRNA の5’ 非翻訳領域に存在

- 余分な鉄を鉄の足りない自己細胞にのみ送達



- アスベスト繊維を貪食したマクロファージはフェロトーシスを起こし、分泌されたCD63+フェリチン含有エクソソームは発がん標的である中皮細胞が受け取り、酸化的DNA傷害をひきおこす

遺伝疾患への応用(BRCA1/2)

NAGOYA UNIVERSITY GRADUATE SCHOOL OF MEDICINE

- マウスモデルではBrca1/2ともに表現型が出ない

https://plaza.umin.ac.jp/model

支援申請
申請から支援までの流れ・公募要領
モデル動物作製支援
病理形態解析支援
生理機能解析支援
分子プロファイリング支援
新たに追加された注目の支援
研究機関別採択実績

Tatsuhiko Imaoka
(Brca1 Mutant)
https://www.qst.go.jp/site/iqls/22512.html

Tomoji Mashimo
(Brca2 Mutant 作成)
https://www.cbms.k.u-tokyo.ac.jp/labs/mashimo/

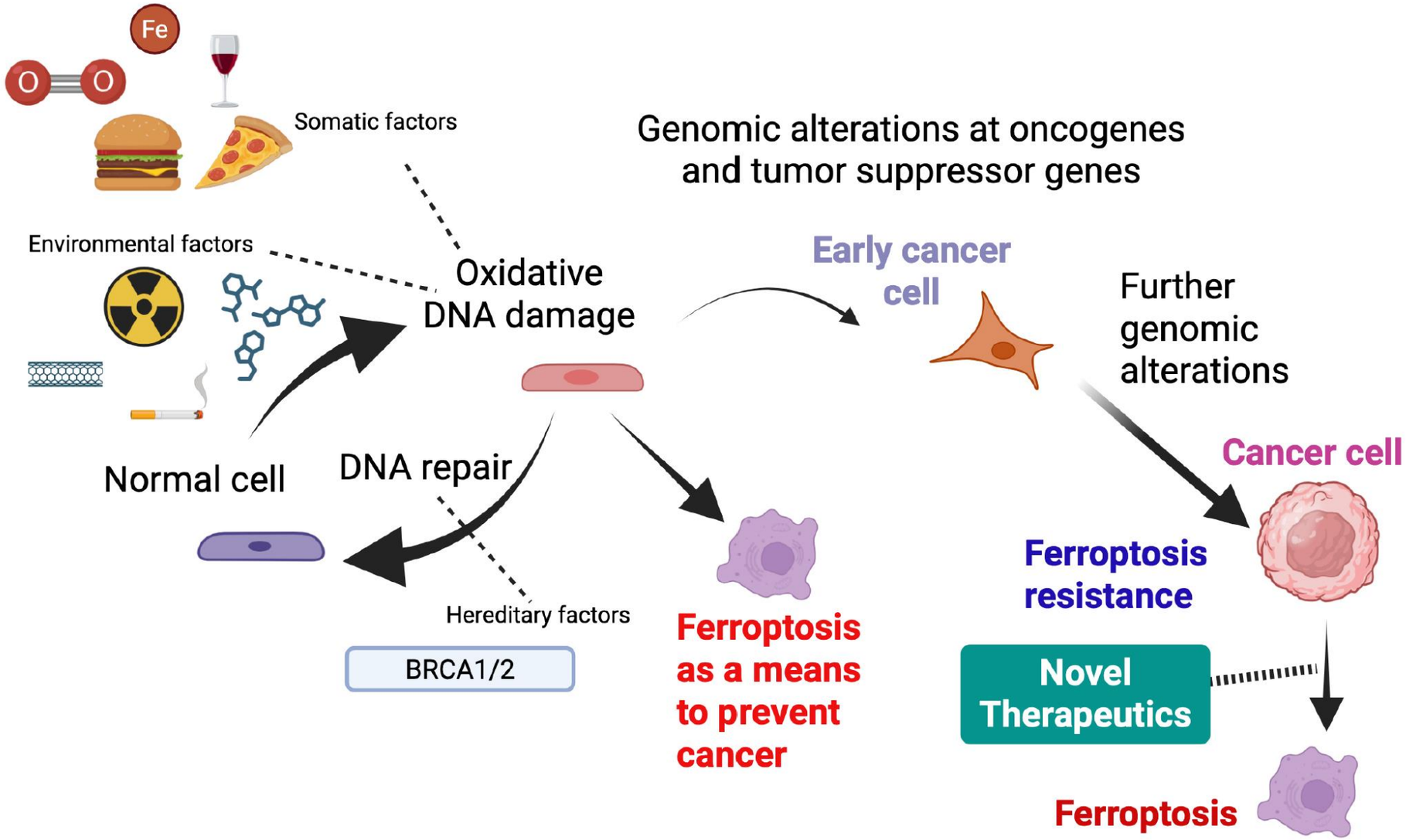
https://www.anim.med.kyoto-u.ac.jp/nbr/default_jp.aspx

京都大学

- では、ラットがあるじゃないか

表現型	Brca1 Mutant Rat	Brca2 Mutant Rat
鉄代謝異常	あり	あり
自然発がん	変わらず	増加
Fe-NTA 誘発腎がん	促進 (C-Myc 増幅)	変わらず(フェロトーシス感受性が高い)
男性不妊	？	あり
女性不妊	CPA+OLP に感受性高い	あり

発がん過程におけるフェロトーシスの理解



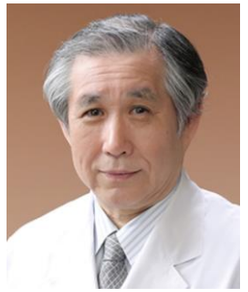
次の段階へ

- フェロトーシスは制御できるか
- 人為的に誘導できるか
- 理論を「実装」できるか

理論から実装へ

- フェロトーシスの理解
- 次の問い：操作できるか
- 基礎から応用への必然的な流れ

低温プラズマという選択
― 工学と医学の交差点 ―



Fumitaka Kikkawa

https://www.kishokai.or.jp/philosophy/fukuriji.html

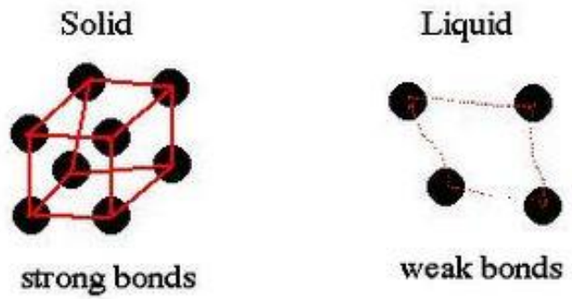
Masaru Hori

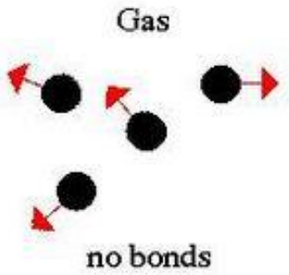
NAGOYA UNIVERSITY GRADUATE SCHOOL OF MEDICINE

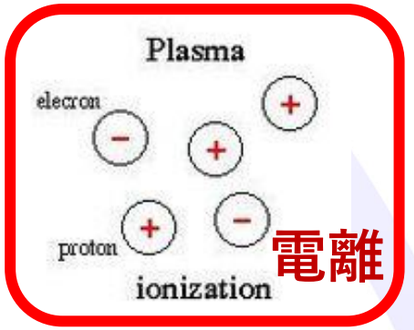
- 薬剤ではない
- 化学反応を超えた「場」の制御
- 鉄・酸素・ラジカルを同時に扱える

2012-2016　新領域研究「プラズマ医療科学創成」

名古屋大学
プラズマ研究所
Since 1961







低温プラズマの主要な本質の1つはラジカル

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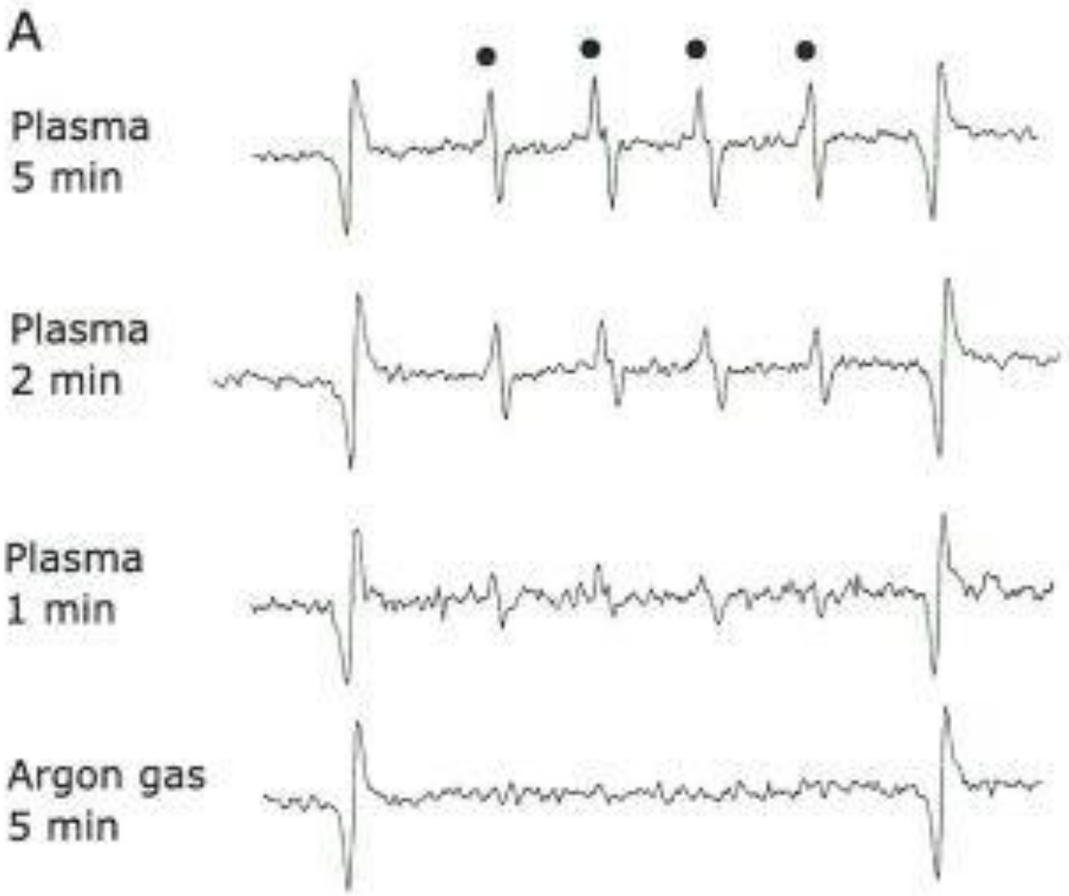
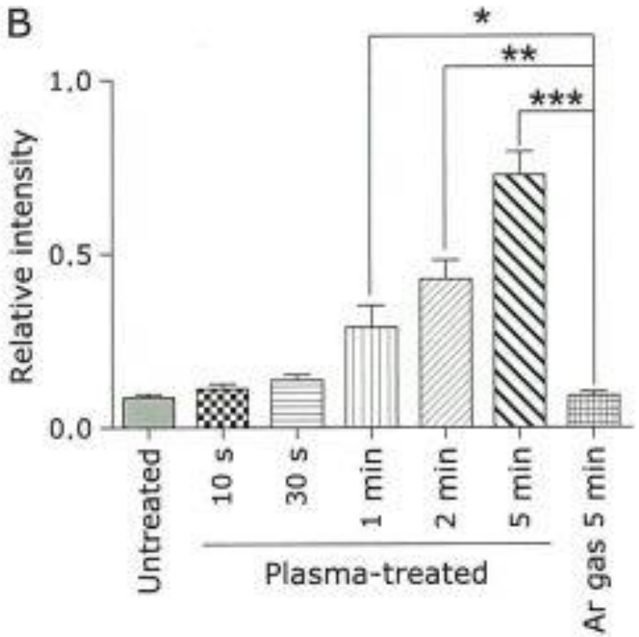


電子スピン共鳴



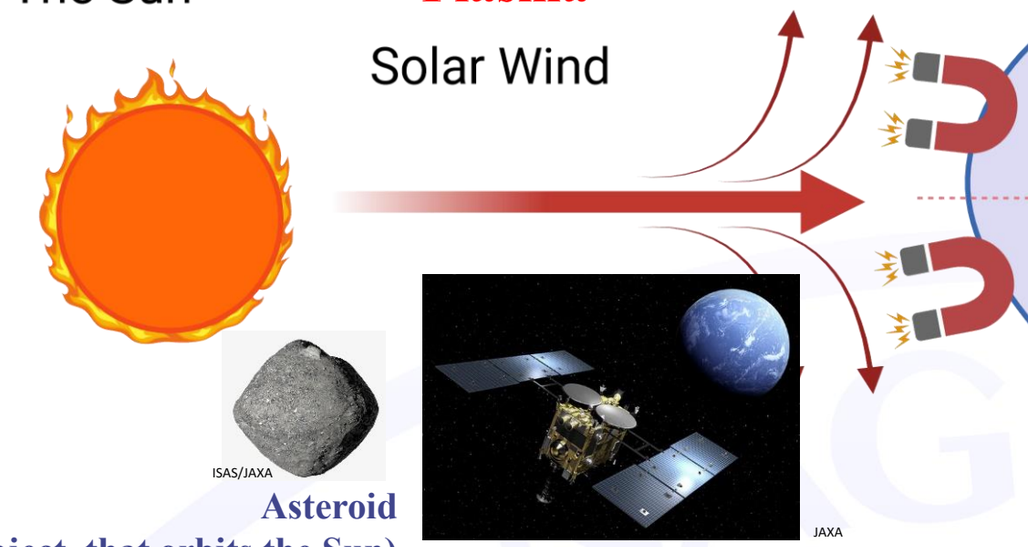
3,3,5,5-tetramethyl-1-pyrroline-N-oxide (M4PO)

Yasumasa Okazaki

J Clin Biochem Nutr 2014

地球上の生命体に対する鉄の最大の意義

NAGOYA UNIVERSITY GRADUATE SCHOOL OF MEDICINE



Asteroid
(small rocky object that orbits the Sun)

Hayabusa Project

nature communications

Article

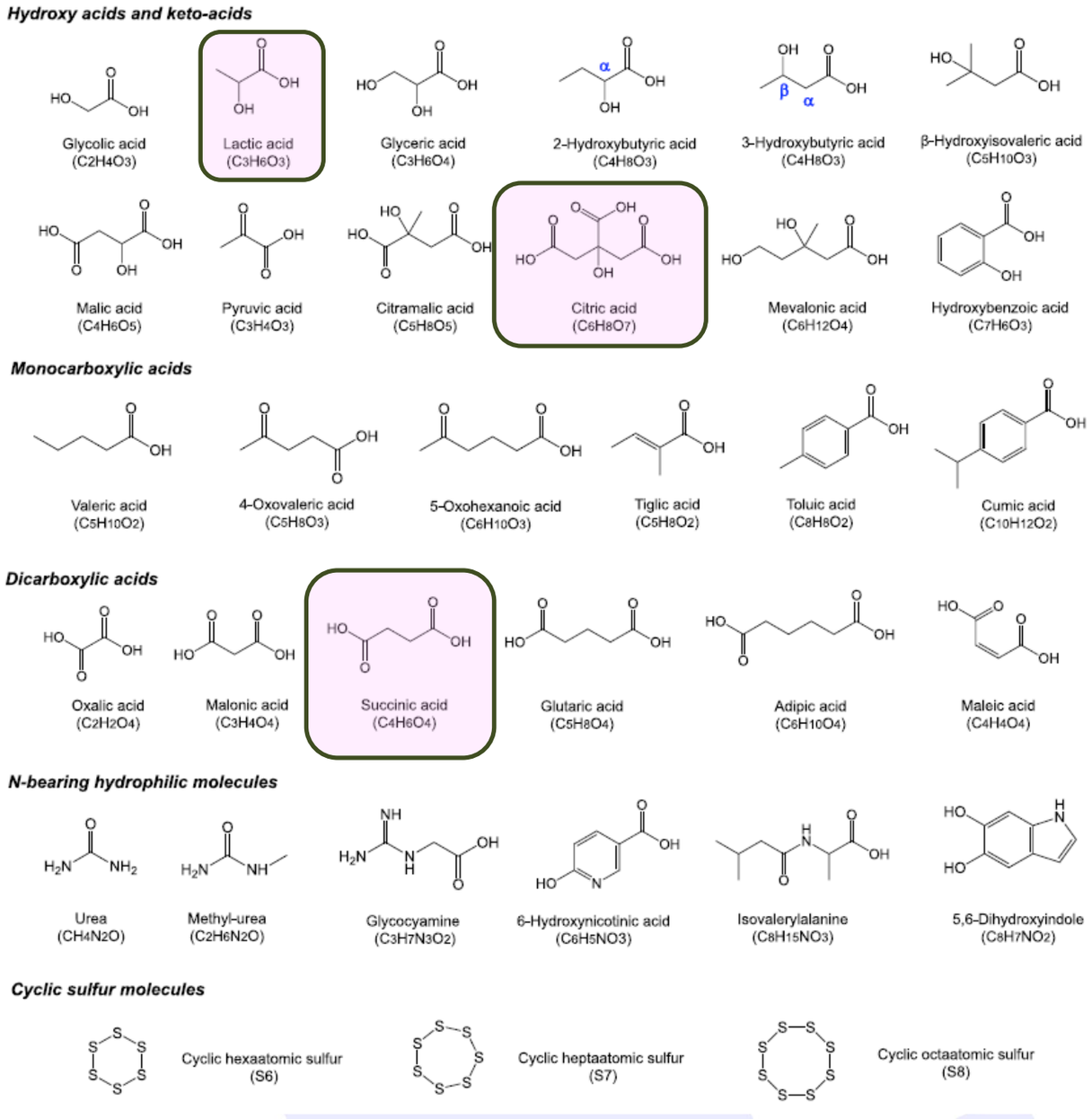
https://doi.org/10.1038/s41467-024-49237-6

Primordial aqueous alteration recorded in water-soluble organic molecules from the carbonaceous asteroid (162173) Ryugu

Received: 16 September 2023

Accepted: 29 May 2024

A list of authors and their affiliations appears at the end of the paper



東海国立大学機構における拠点形成

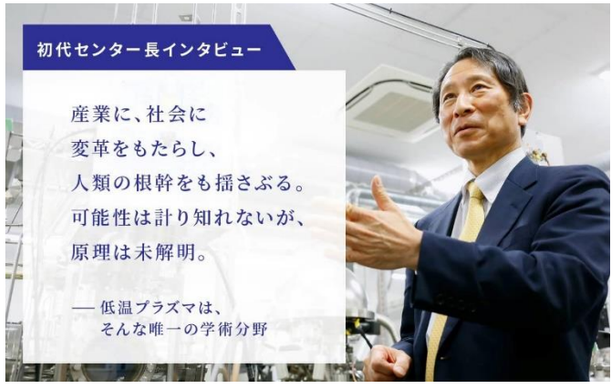
NAGOYA UNIVERSITY GRADUATE SCHOOL OF MEDICINE

- 医学 × 工学 × 農学 x 理学 x 薬学 x 獣医学
- 学際融合を制度として実装
- 若手が挑戦できる研究環境
- 東海国立大学機構の**起爆剤**

大野 哲靖 教授
拠点長

https://c-arp.gifu-u.ac.jp/member/

上坂 裕之 教授
副拠点長



Masaru Hori

MAKE NEW STANDARDS. 東海国立大学機構

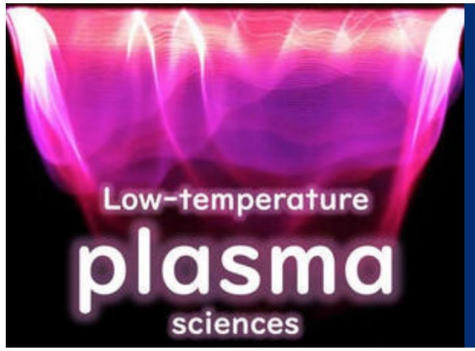
Tokai National Higher Education and Research System ▶ 交通アクセス ▶ お問い合わせ ▶ English ▶ 寄附する

機構の概要　大学の紹介　情報公開　サイト内検索

ホーム > 教育・研究支援 > 低温プラズマ総合科学研究拠点

低温プラズマ総合科学研究拠点

- 糖鎖生命コア研究拠点（iGCORE）
- 健康医療ライフデザイン統合研究教育拠点
- 航空宇宙研究教育拠点
- 低温プラズマ総合科

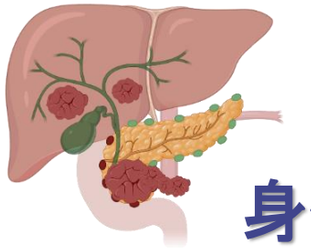


低温プラズマ総合科学研究拠点

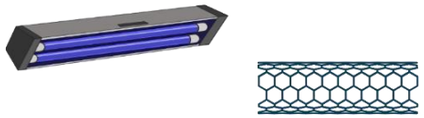
がんにおける鉄の意義

Human Cancers

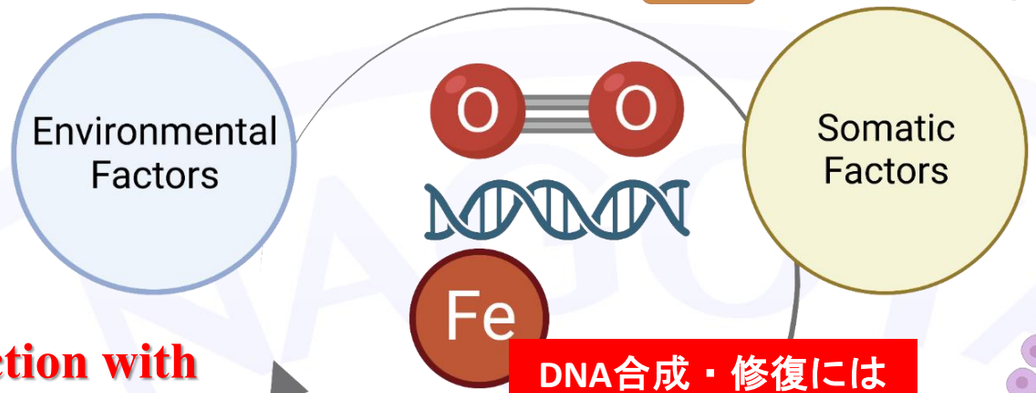
がんはゲノムの病気



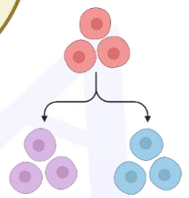
身体要因

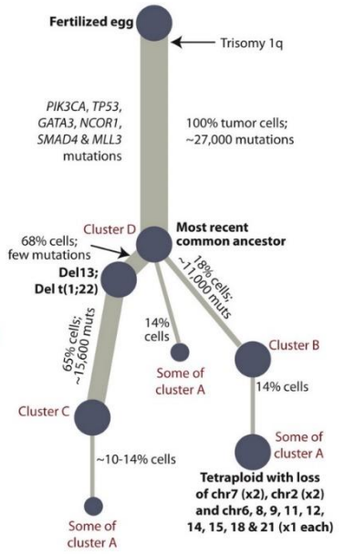


環境要因



DNA合成・修復には鉄が必要



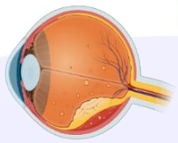


がんの系統樹
全ゲノム解析によるクローンの増殖

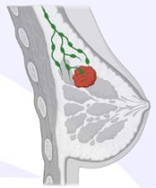
Nik-Zainal Cell 2012

Iron Addiction with Ferroptosis-resistance

Iron: good or evil?



RB



BRCA1/2

遺伝要因

Detection of catalytic Fe(II) with novel turn-on fluorescent probes

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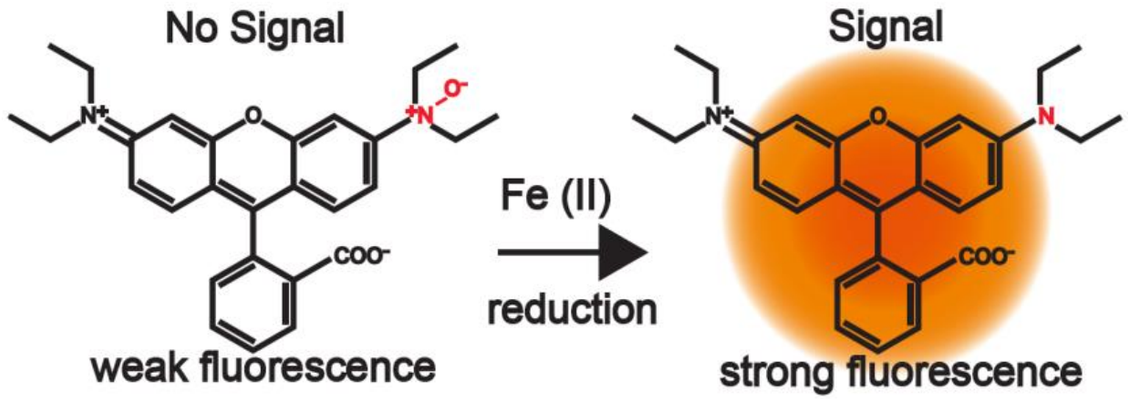
https://www.horiba.com/jpn/company/about-horiba/three-business-fields/fluorescent-probe/

岐阜薬科大学

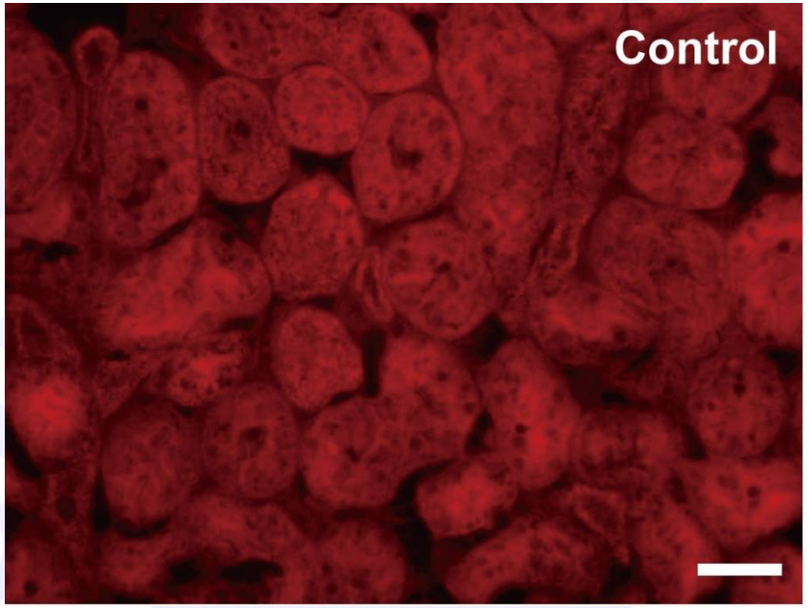
Tasuku Hirayama

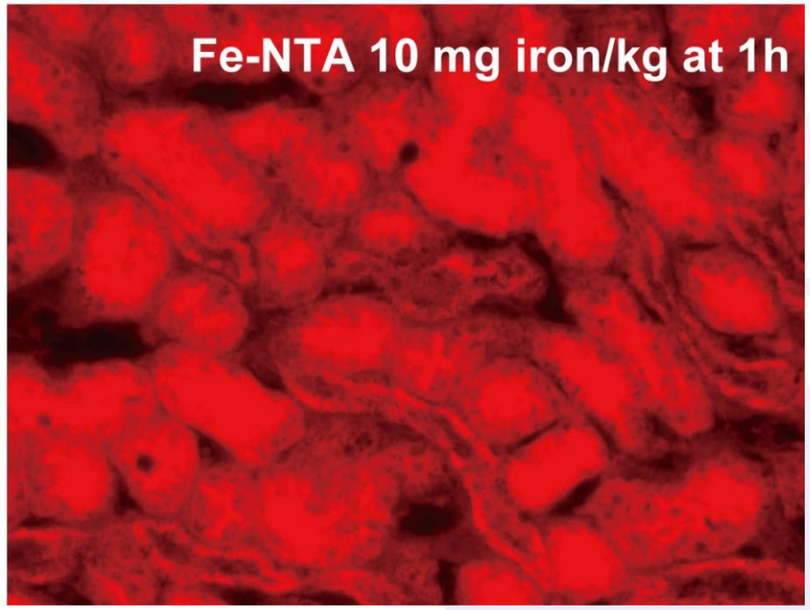


Hirayama T, *et al.* highly selective turn-on fluorescent probe for iron (ii) to visualize labile iron in living cells." *Chemical Science* 4.3 (2013): 1250-1256.

Mukaide *et al.,* Free Radic Res 2014

Cultured cell or frozen section





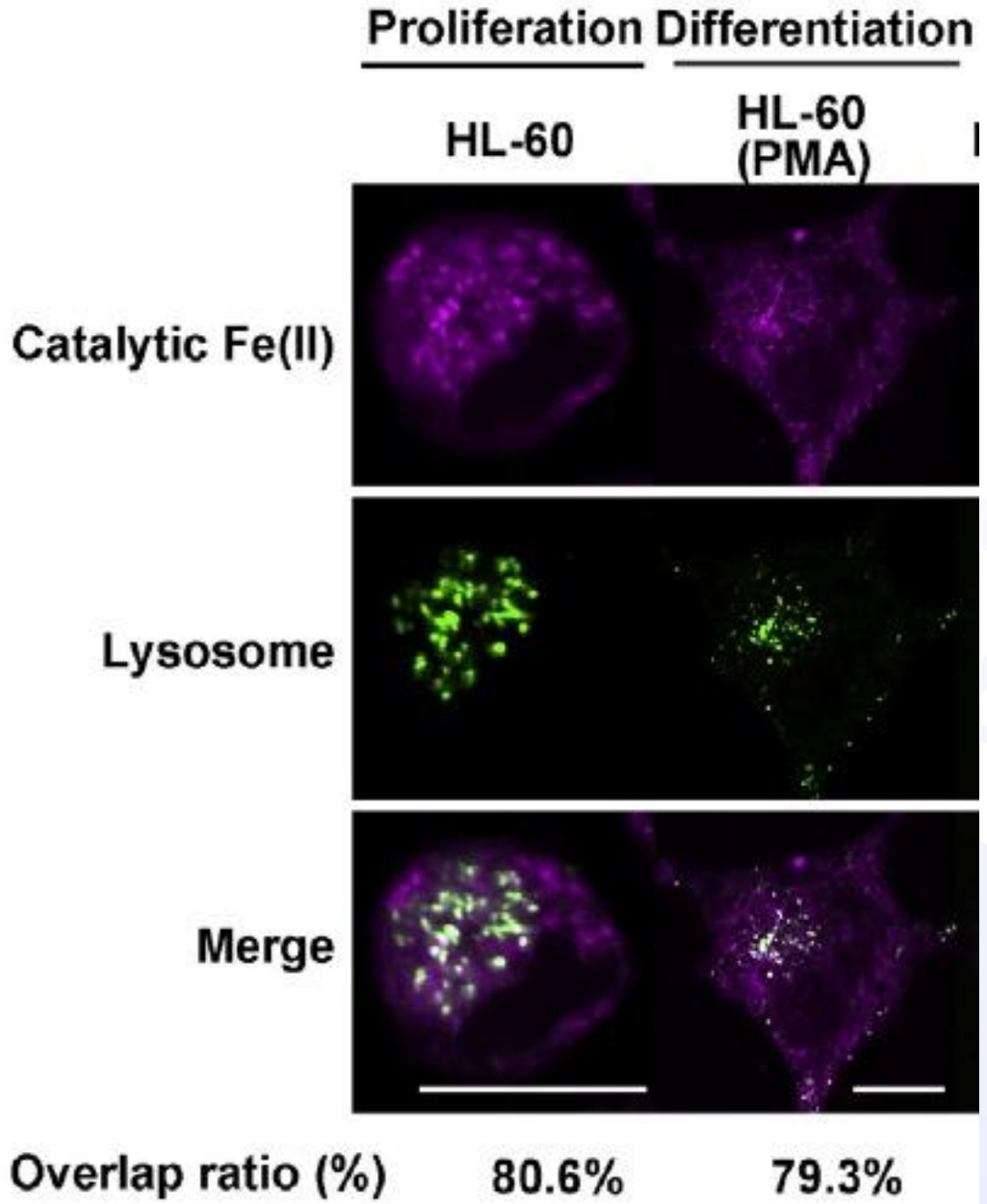
FerroOrange

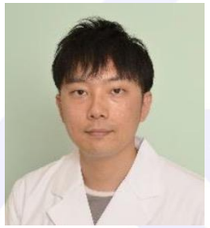
Time-lapse analysis

Organelle-directed probes are available

Cancer cells have higher levels of catalytic Fe(II)

NAGOYA UNIVERSITY GRADUATE SCHOOL OF MEDICINE





Fumiya Ito

BBRC 2016

FEBS 14981

FEBS Letters 358 (1995) 1–3

Hypothesis

Persistent oxidative stress in cancer

Shinya Toyokuni[a,*], Keisei Okamoto[a], Junji Yodoi[b], Hiroshi Hiai[a]

[a]*Department of Pathology, Faculty of Medicine, Kyoto University, Sakyo-ku, Kyoto 606, Japan*
[b]*Department of Biological Responses, Institute for Virus Research, Kyoto University, Sakyo-ku, Kyoto 606, Japan*

Received 10 November 1994; revised version received 28 November 1994

Abstract DNA of cancers such as renal cell carcinoma and mammary invasive ductal carcinoma, is persistently exposed to more oxidative stress than that of adjacent nornal tissue. We suggest that the concept of 'persistent oxidative stress in cancer' may open up a new research area, explaining part of the characteristic tumor biology of cancer such as activated transcription factors and proto-oncogenes, genomic instability, chemotherapy-resistance, invasion and metastasis.

Key words: Reactive oxygen species; Oxidative DNA damage; Tumor biology; Mutation; Transcription factor

It is reasonable to suppose that membrane lipids near the ROS generation site are the most severely damaged.

The metabolism of ROS in cancer cells is a research area that has not been intensively pursued. The first important question is whether cancer cells produce larger amounts of ROS than non-neoplastic cells or whether the antioxidant system of cancer cells is suppressed. There is evidence favoring both mechanisms. Large amounts of hydrogen peroxide are reportedly produced in vitro without exogenous stimulation in several human carcinoma cell lines, including malignant melanoma, colon carcinoma, pancreatic carcinoma, neuroblastoma, breast carcinoma and ovarian carcinoma [10]. A flavoprotein and/or a nucleoside oxidase may be involved in the mechanism of H_2O_2

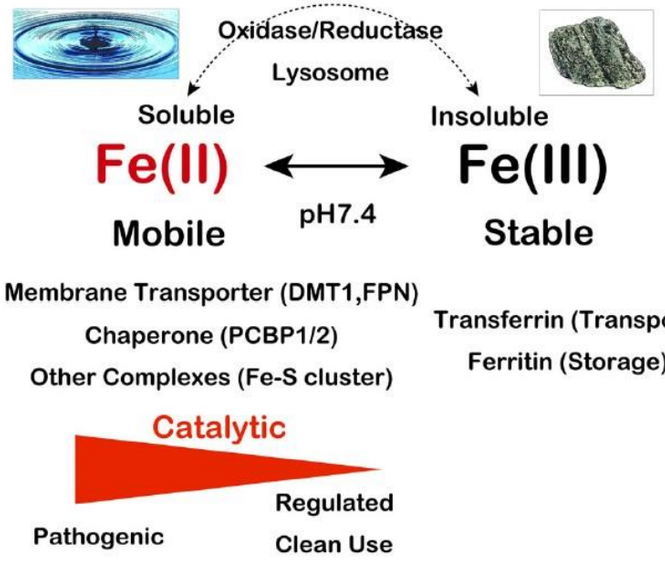
Cited 1535 times
(Google scholar)

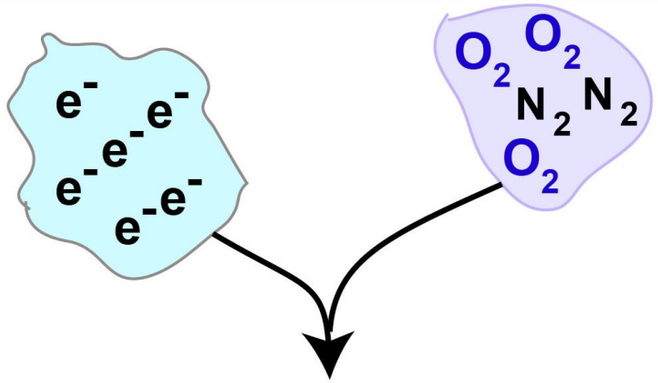
Table 1
Content of 8-hydroxy-2′-deoxyguanosine in human carcinoma (multiple case study)

Organ	Histology	Control	Tumor	*n*; statistics	Method	Reference
Breast	Invasive ductal carcinoma	4.13 ± 0.43	40.1 ± 11.1	(5; $P < 0.01$)	GC/MS	[33]
Lung	Squamous cell carcinoma	11.2 ± 2.3	25.5 ± 7.0	(5; $P < 0.05$)	GC/MS	[13]
Liver	Hepatocellular carcinoma	1.57 ± 0.21	2.29 ± 0.38	(11, 18; $P = 0.174$)	HPLC/ECD	[34]
Kidney	Renal cell carcinoma	3.60 ± 0.20	5.56 ± 0.41	(31; $P < 0.0005$)	HPLC/ECD	[9]

The amount of 8-hydroxy-2′-deoxyguanosine per 10^5 deoxyguanosine in DNA is shown by means ± S.E.M. Some of the data were modified for unity. All the samples except those from [34] are paired samples from the same patient. The patients were all heavy smokers [13]. Control liver samples were from patients with metastatic liver tumors [34]. GC/MS, gas chromatography with mass spectrometry; HPLC/ECD, high performance liquid chromatography with electrochemical detector.

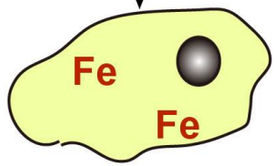
低温プラズマの細胞への作用





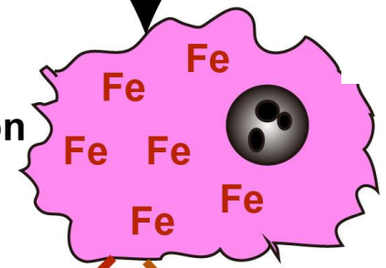
Biological/Medical fluids

$\cdot OH$ H_2O_2 NOx Various peroxides



Non-tumorous cell

Fenton reaction



Lipid peroxidation

Cancer cell

Non-toxic
or even proliferation

Ferroptosis

Apoptosis

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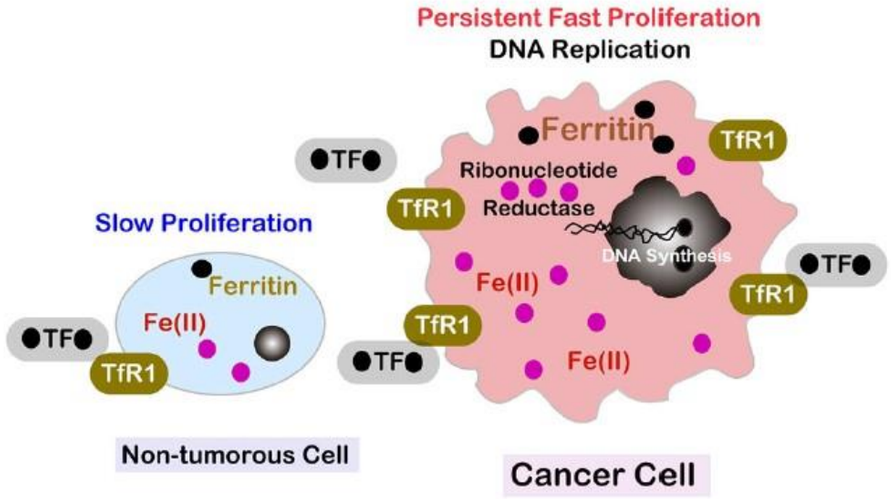
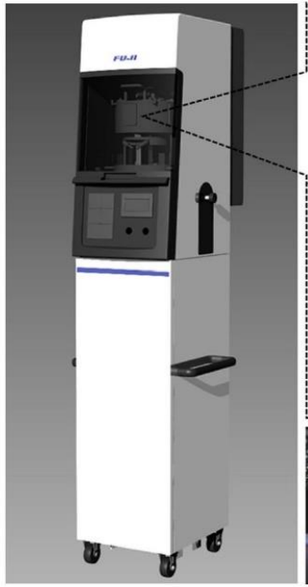
OF MEDICINE

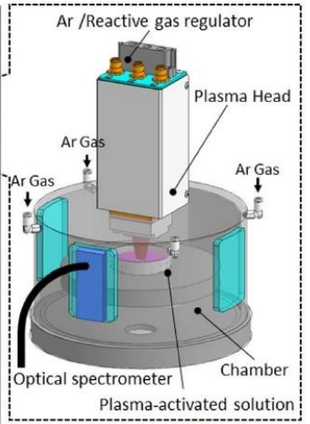
- 直接照射
- 間接照射
  (via liquid)

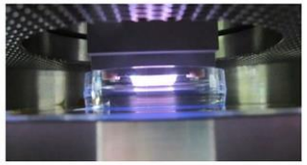


Proof of Concept

低温プラズマ活性化乳酸リンゲル液 (PAL) は
悪性中皮腫細胞特異的にフェロトーシスをおこす







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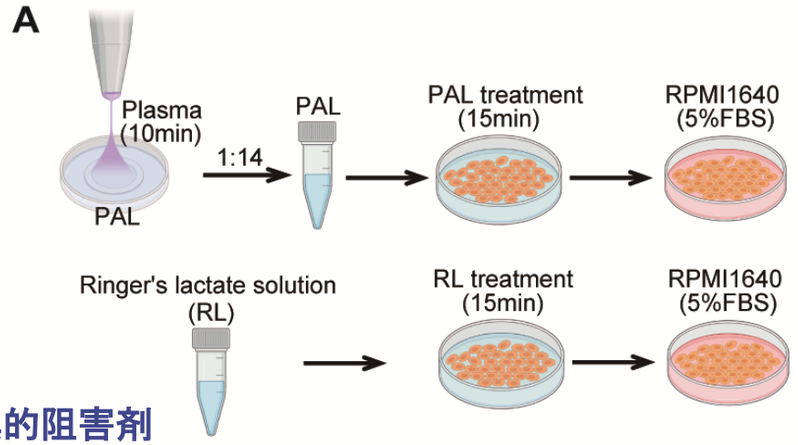
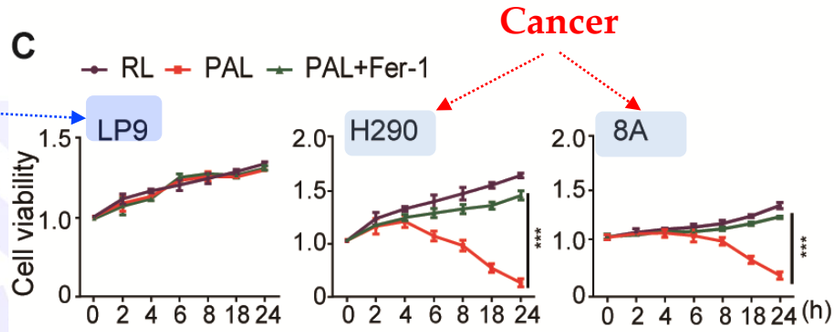
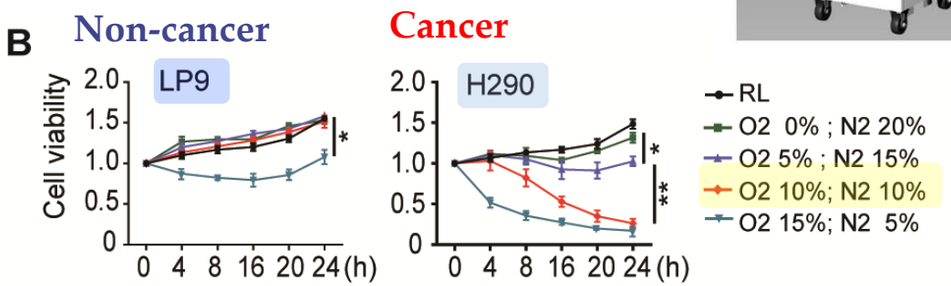
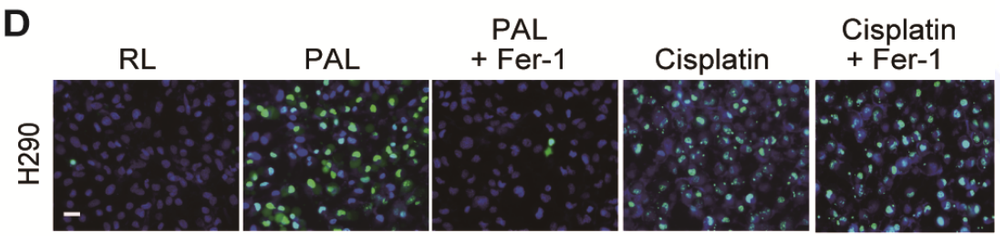
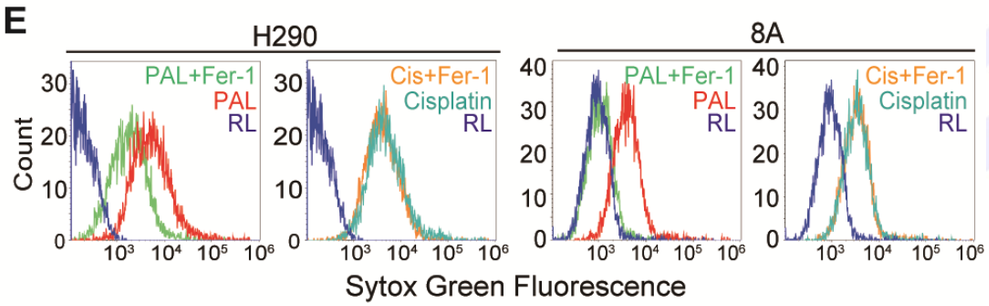


Fer-1: Ferrostatin-1
フェロトーシス特異的阻害剤

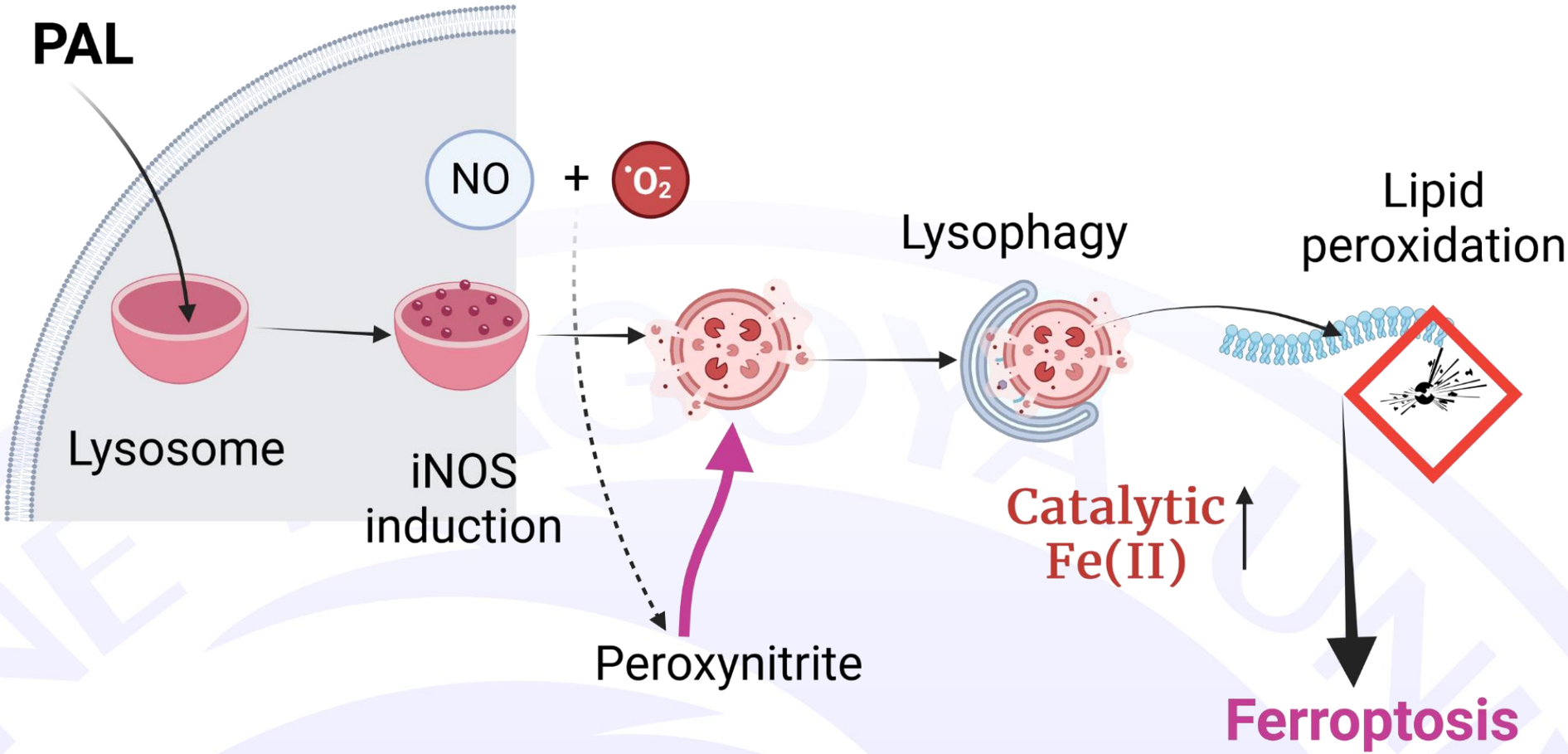








PAL により中皮腫細胞がフェロトーシスを起こす分子メカニズム



Jiang *et al.* Redox Biol 2021

研究は個人で始まり、環境で育つ

名古屋大学という研究環境

- 医学系研究科 分析機器部門・動物実験施設 の卓越性
- 医学・工学・農学・理学の距離の近さ
- 学際融合が「日常」にある
- 若手に裁量がある

Ecotoxicology and Environmental Safety 298 (2025) 118327

Contents lists available at ScienceDirect

Ecotoxicology and Environmental Safety

journal homepage: www.elsevier.com/locate/ecoenv

Terrestrial iron sulfide minerals induce distinct regulation of intracellular redox homeostasis and iron assimilation

Qinying Lyu [a], Yui Kouketsu [b], Akira Tazaki [c,d], Masashi Kato [c,d], Yashiro Motooka [a], Shinya Toyokuni [a,e,f,*]

[a] Department of Pathology and Biological Responses, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Japan
[b] Department of Earth and Planetary Sciences, Nagoya University Graduate School of Environmental Studies, Furo-cho, Chikusa, Nagoya 484-8601, Japan
[c] Department of Occupational and Environmental Health, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Japan
[d] Activity of the Institute of Innovation for Future Society of Nagoya University, Japan
[e] Center for Low Temperature Plasma Sciences, Nagoya University, Furo-cho, Chikusa, Nagoya 464-8603, Japan
[f] Center for Integrated Sciences of Low-temperature Plasma Core Research (iPlasma Core), Tokai National Higher Education and Research System, Furo-Cho, Chikusa-ku, Nagoya 464-8603, Japan

拠点形成の本当の意味

- 大きな研究費のためだけではない
- 学際的な「場」を維持するため
- 次世代のための投資

人材育成という研究

- テーマよりも思考法（柔軟性・異なる視点）
- 技術よりも姿勢（問題意識と解決を心から望むこと）
- モチベーションの維持と向上

指導で大切にしてきたこと

- 現象を自分の目でみる
- データの再現性が第一、解釈はあと
- 原理の異なる複数の方法で真偽を確かめる（形態 x 生化学的方法論 など）
- 流行を鵜呑みにしない
- テーマはできるだけ本人の好きなことを
- 論文化の際にはもう一ひねり(新たな論理の構築)できないかを常に考える
- 博士になったら、年1本は第 I 著者の論文を書く

学位授与（博士48名・修士5名）

学位授与（医学博士）

（当時の官職にかかわらず、豊國伸哉が指導教官・責任著者のものをあげている。臨床科名のないものは病理学専攻である。）

【京都大学医学研究科】

服部ゆかり（皮膚科）、岡本圭生（泌尿器科）、田中智之、西山泰由、Soon Chan Um（形成外科）、井原　裕（糖尿病内科）、松井美萌（皮膚科）、近藤昌平（消化器外科）、赤塚慎也、李　文華、白瀬智之、蒋　麗、劉　玉婷、Dutta Khokon Kumar、吉原美奈子、胡　茜、永井裕崇（MD・PhDコース）、大原浩貴

（合計18名）

【名古屋大学医学系研究科】

真野由起雄（産婦人科）、周　珊瑚（修士課程より）、小林浩晴（産婦人科）、舟橋諭美（修士課程より）、山下享子、向出貴裕、Dilnur Alkin、服部有香（産婦人科）、王　越、石　蕾、伊藤文哉（修士課程より）、森　正彦（産婦人科）、李　光華（修士課程より）、王　申奇、大原悠紀、石田千晴（産婦人科）、平光志麻（産婦人科）、佐藤康太郎（口腔外科）、林　祥太郎（産婦人科）、程　真（日本の医師国家試験合格）、羅　亜光（日本の医師国家試験合格）、李　賛、鄭　好、孔　穎怡、曽根原玲菜（産婦人科）、田中秀明（産婦人科）、可世木　聡（産婦人科）、本岡大社、呂　沁穎（修士課程より）、前田勇貴

（合計30名）

修士課程のみ

賈　霆涵

（1名）

失敗した研究・進めなかった研究

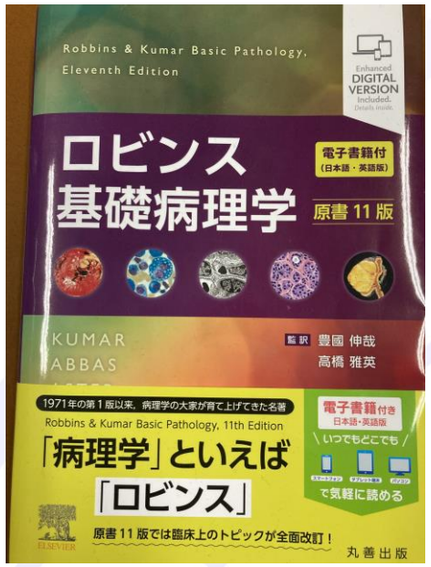
- 成功談だけではない
- 撤退も判断
- 失敗は蓄積され、やがて成功を生み出す
- 記録を残す
- 3回やってだめなら、仮説が間違っている

研究者の孤独

- 最終判断は一人
- 評価されない時間
- それでも考え続ける

名古屋大学での17年9ヶ月

- 教育
- 研究（国際学会発表 155/297、国内学会発表 262/812）
- 診療（病理診断）
- 大学運営（名古屋大学 低温プラズマ科学研究センター・東海国立大学機構 低温プラズマ総合科学拠点・医学図書館・Nagoya J Med Sci・JACME審査員・入学試験）



「ロビンス基礎病理学」丸善出版

第8版～第11版　監訳

- 論文の引用は絶対的な評価ではないが、研究の励みにはなる
- 自分の論文をどんどん引用すべき

H-index 89

私の名古屋大学における足跡

- 八木國夫・小澤高将（脂質過酸化・酸化的DNA損傷）
- 飯島宗一（翠川　修）
- 森 尚義・高橋雅英・中村栄男（病理学）
- 飯島澄男・篠原久典（カーボンナノチューブ）
- 堀 勝・大野哲靖（低温プラズマ）
- 榎本 篤・加留部謙之輔（病理学）

若手研究者へのメッセージ

「問いを持ち続けられるかどうかが、すべてを決める」
「研究はある意味マラソンであるし、オセロゲームでもある」

ここまでのまとめ

- 研究は個人の問いから始まる
- 環境が問いを育てる
- 人材育成は未来への投資

生命進化と鉄・酸素

- 鉄は生命に必須
- 酸素は効率（長寿化）と危険をもたらした
- 両者の共存が生命を進化させた

がんは例外か、必然か

- 感染症克服による長寿
- 酸化反応の蓄積（Exposome）
- 鉄と酸素を長期間使用した副作用！

鉄が語る発がん機構

- 鉄依存性傷害
- 脂質過酸化
- フェロトーシス耐性獲得による発がん

科学は未完成である

- すべては途中経過
- 次の問いが生まれる
- 次の世代が続ける

次世代に託したい問い

- 鉄依存性細胞死の人為的制御
- 生理的フェロトーシス
- 生命誕生・進化とフェロトーシスの関連
- 社会実装のあり方

低温プラズマ医療としての社会実装計画

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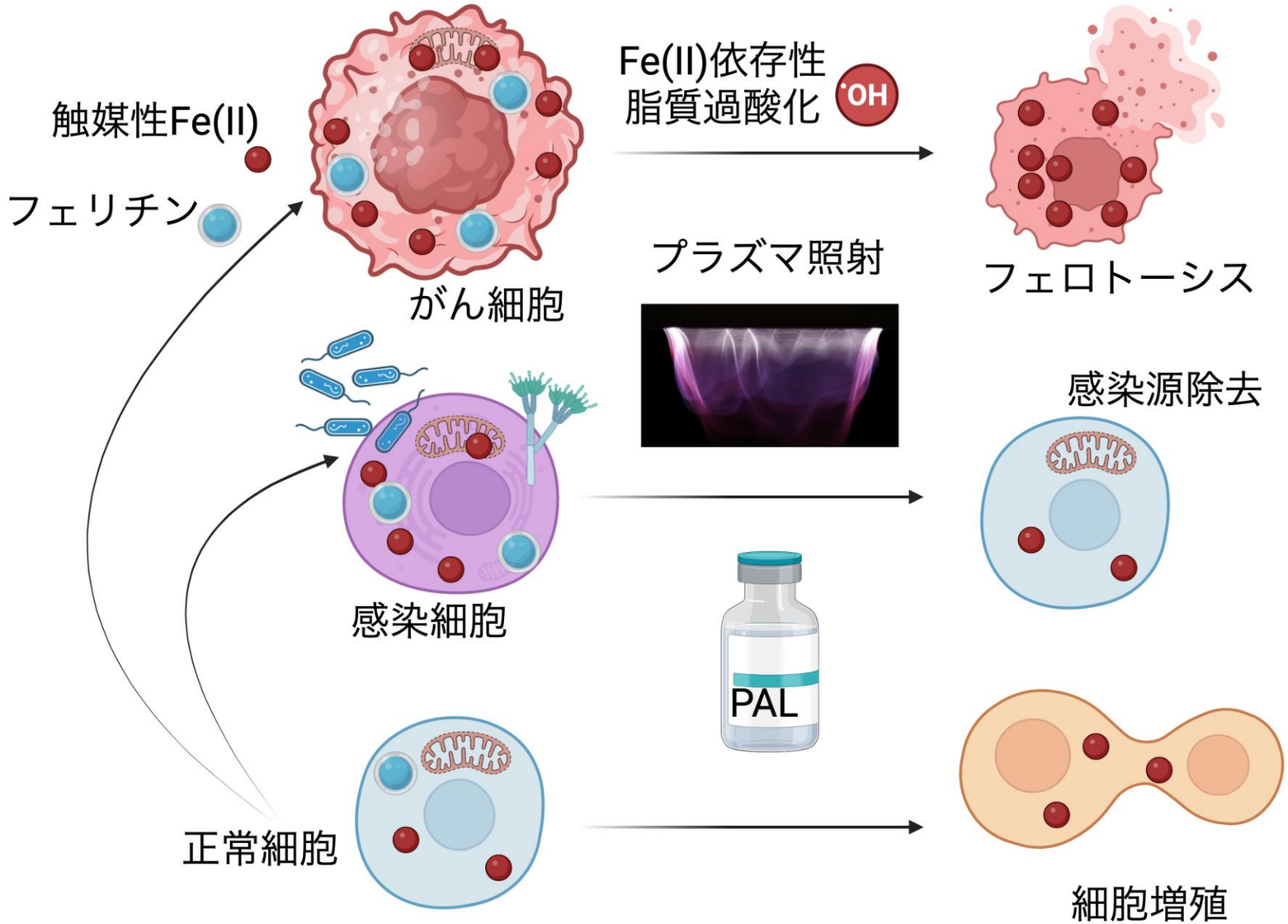
東海国立大学機構の1つの突破口



- 口腔癌術後
- 放射線照射後口内炎
- 薬剤性顎骨壊死

Kotaro Sato

Hideharu Hibi

- 創傷治癒

Kae Nakamura

Masaaki Mizuno

https://www.u-toyama.ac.jp/outline/overview/officer/2025vice-mm/

若手研究者へ

「流行ではなく、自分の目で見た現象を信じてほしい」

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医学部学生・研修医のみなさんへ

- すべてを理解しなくていい
- 何か一つ、心に残ればいい

病理医・研究者へ

- 病理学は強い
- 正確な記録が重要
- 現象から逃げない
- 分野を越えて考える

同窓生・来賓の皆さまへ

- 名古屋大学の価値
- 教育と研究の連続性

共に歩んだ仲間たち

- 共同研究者
- 教室員・同窓会・同門会
- 学生・若手研究者・同級生
- 所属学会

日本病理学会（病理専門医）、日本酸化ストレス学会 (SFRR Japan)、日本癌学会、日本鉄バイオサイエンス学会 (JBIS)、日本生化学会、日本分子生物学会、日本がん予防学会、日本微量元素学会、発がん病理研究会、分子予防環境医学研究会、SFRR International、International BioIron Society、ISPlasma、International Conference on Plasma Medicine (ICPM)

コロナ渦の東京レジナビ参加（日本病理学会リクルート委員会）

SFRR Austrasia-Japan, Sydney, Australia 2013

Cold Spring Harbor Asia, Ferroptosis, Awaji, Japan 2022

SFRR Asia, Seoul, Korea 2022

Young-Joon Surh, Barry Halliwell

CREST・細胞外微粒子、熊本

基礎医学セミナー発表会

鶴舞公園　花見

教室旅行　伊勢神宮

China-Japan Asbestos Symposium, Qingdao, China 2019

ICPM, Nagoya, Japan 2017
Alexander Friedman, Masaru Hori

日本微量元素学会･学会賞受賞 2022

Manabu Fukumoto, Tatsuaki Tsuruyama
（京大病理同窓）

発がん病理研究会、鳥羽 2019

Yuzuru Ikehara

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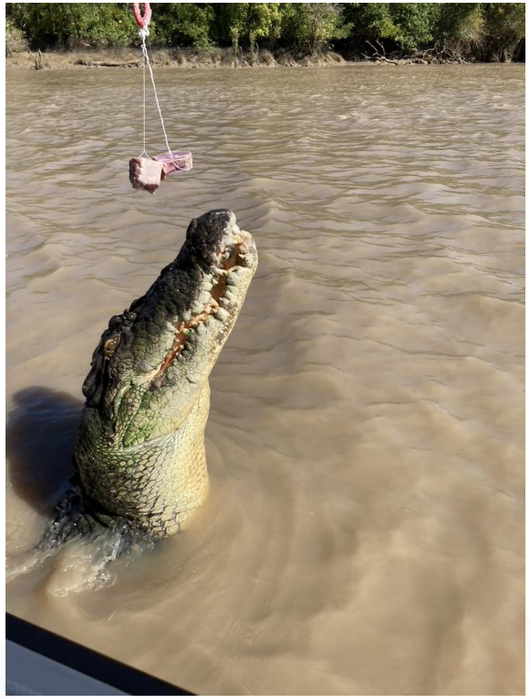
ICPM, Bratislava, Slovakia 2016

SFRR Asia, Chiang Mai, Thailand 2015
Junichi Fujii, Mike Davies

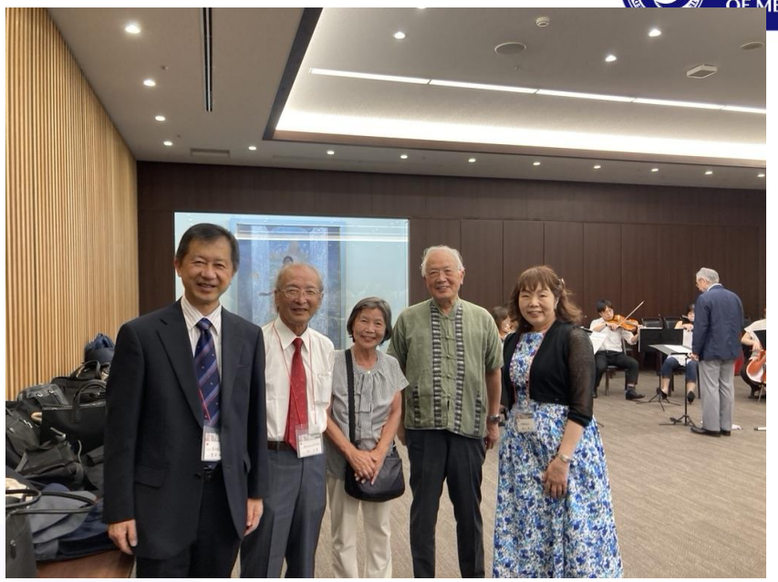
Chiang Mai University, Thailand

病理学会カンファレンス、犬山 2017

Des Richardson



Conference Tour, IBIS, Darwin, Australia 2023



日本鉄バイオサイエンス学会、岡山 2023

先端モデル動物支援プラットフォーム、琵琶湖 2024 (AdAMS)

SFRRI, Punta del Este, Uruguay 2023

Marcus Conrad

第113回日本病理学会総会、名古屋 2024

Hirotaka Nagai

Helmut Sies

SRRRI, Galway, Ireland 2025

三澤伸明 技官 退官記念祝賀会

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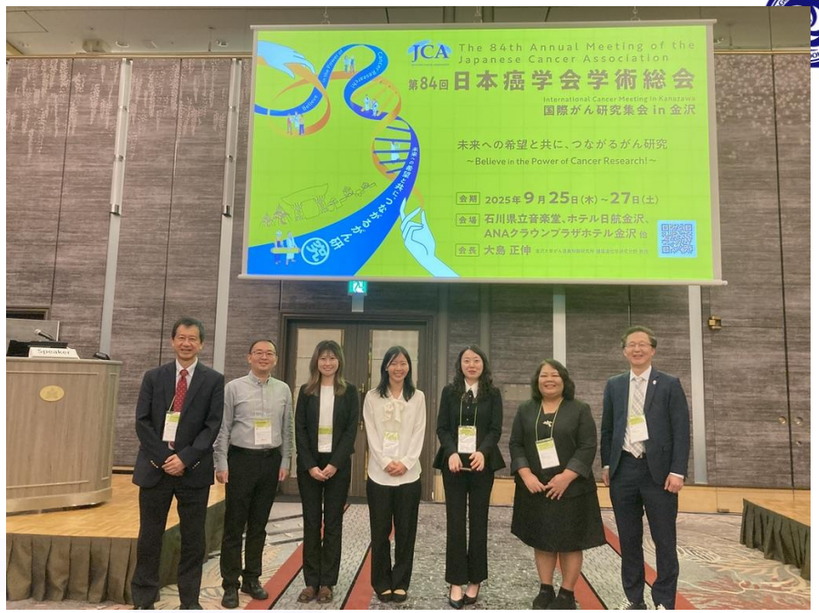
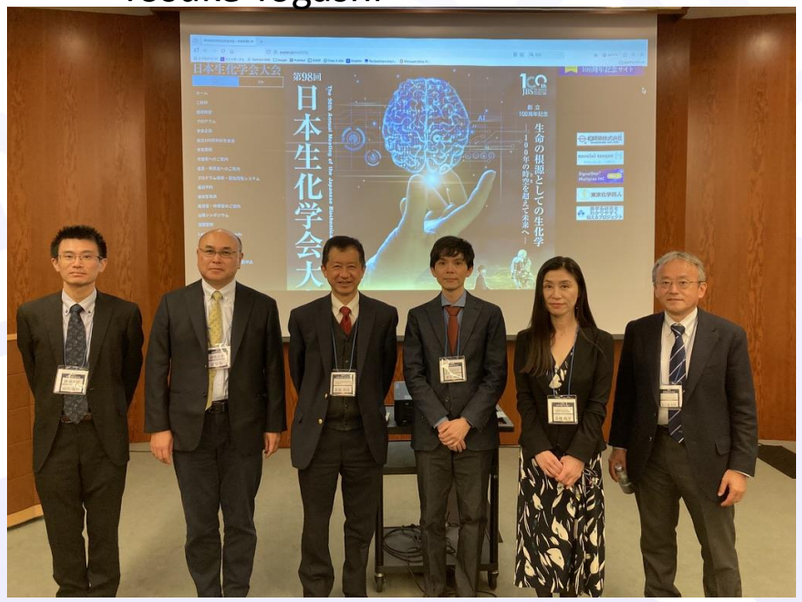
名大 MIRAI GSC 高校生の受入れ

軟式庭球部仲間の再会
Yosuke Togashi

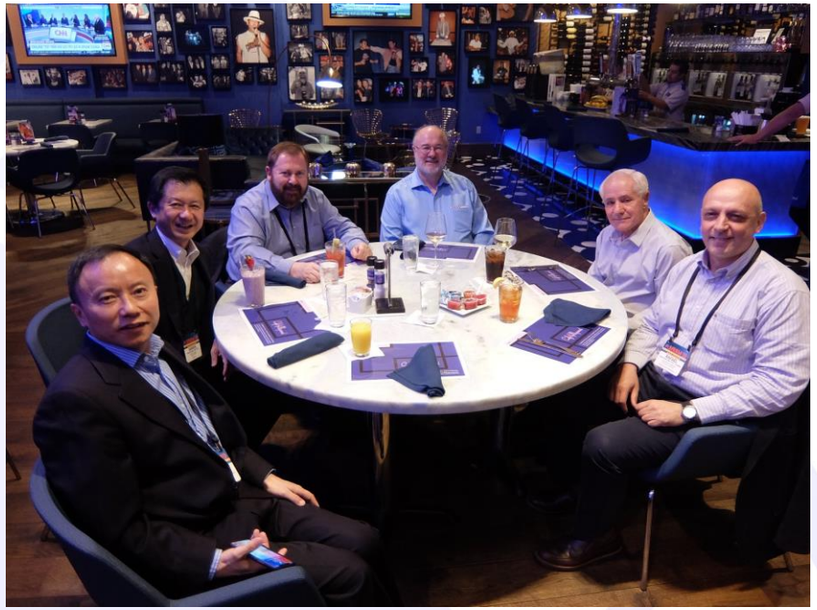


日本癌学会・レドックス シンポジウム (International session)

名古屋大学医学部 卒業式



日本生化学会・フェロトーシス シンポジウム

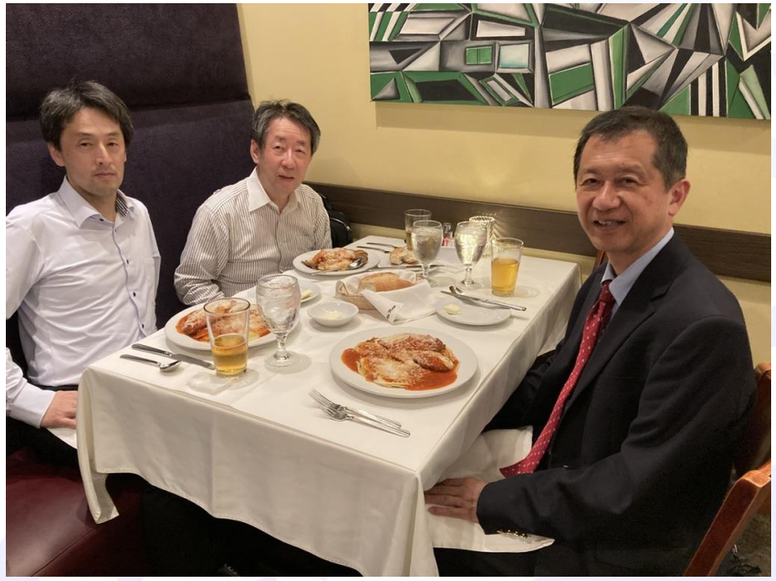


FRBM, Editor Meeting, Las Vegas, NV, USA

教室旅行　京都

SFRR India, Mumbai, India 2020

SFRR Korea, Jeju, Korea 2025



Pacifichem2025, Honolulu, HI, USA

Redox Biology 170 JSPS Meeting, Tokyo

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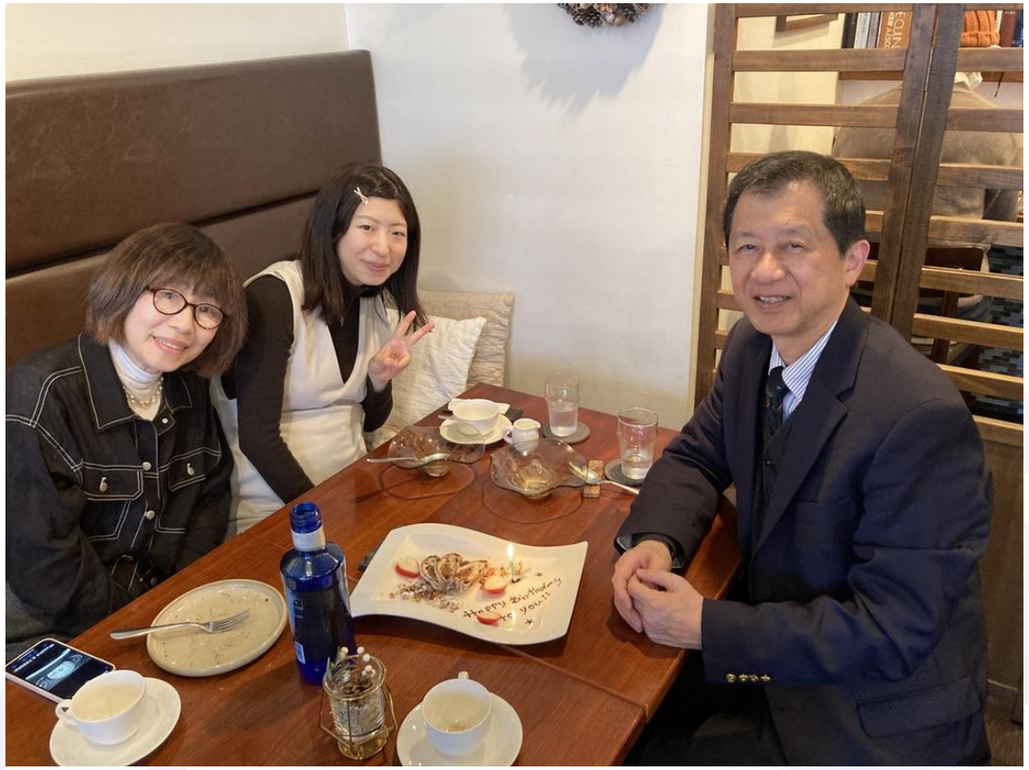
家族への感謝



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本当に伝えたかったこと

「研究は、姿勢で決まる」（自らが信じているかどうか、外から信用されるか）

「英語で発信しなければ意味はない」（自分のアイデアをもっと海外に発信しよう！）

「まずは興味あるトピックの論文の査読を定期的にやろう」（自分のセンサーの感度を上げよう！）

勇気ある知識人とは何か

- 現象から逃げない
- 流行に依存しない（独自性）
- 時代の変化に柔軟に対応
- できるだけ視野を広げて考える
- 新しいことをやってみる
- 異分野の研究者から学ぶ
- 次世代に問い（ワクワク感）を渡す

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次の世代へ

未来の「勇気ある知識人」へ

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この道のりで出会ったすべての方々へ、心からの感謝を込めて。

With heartfelt gratitude to everyone I have met along this journey.

4月からは一宮市民病院に病理専門医として週4日勤務しながら、若手研究者のサポートをします
名古屋大学低温プラズマ科学研究センターでは客員教授として活動します