循環器治療薬の最前線SPRINT試験とミトコンドリア病治療薬MA-5

臨床実習前特別講義：4年生最終講義 20151201

循環器治療薬の最前線

- SPRINT: Systolic Blood Pressure Intervention Trialについて
  - N Engl J Med 2015;373:2103-16
- オーキシン（植物ホルモン）から誘導した合成化合物のミトコンドリア病治療薬MA-5について
  - Tohoku J Exp Med. 2015 July;236(3):225-32.
  - J Am Soc Nephrol. Published online 2015 Nov 25.
  - tohokuuniv-press20151126_01web

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分子薬理学分野（旧第二薬理学講座）
柳澤輝行（昭和51年卒、昭和55年大学院修了）

昭和47年より、薬理学教室にて学んだ。

東北大学

SPRINT: Systolic Blood Pressure Intervention Trialについて

20151201

- SPRINT: Systolic Blood Pressure Intervention Trial
  - フラミンガム研究、framinghamheartstudy
  - 高血圧患者、120mmHg未満か140mmHgか？
  - SPRINT試験対象者
  - Medications（1.8剤から3剤へ）
  - 一次評価項目も全死亡率も3/4に
  - 治療に伴う有害事象は約2倍

東北大学

Framingham Heart Study

A Project of the National Heart, Lung, and Blood Institute and Boston University

Cardiovascular Disease (10-year risk)

(based on D'Agostino, Vasan, Pencina, Wolf, Cobain, Massaro, Kannel. 'A General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study')

Outcome

CVD (coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, heart failure)

Duration of follow-up

Maximum of 12 years, 10-year risk prediction

Population of interest

Individuals 30 to 74 years old and without CVD at the baseline examination

Predictors

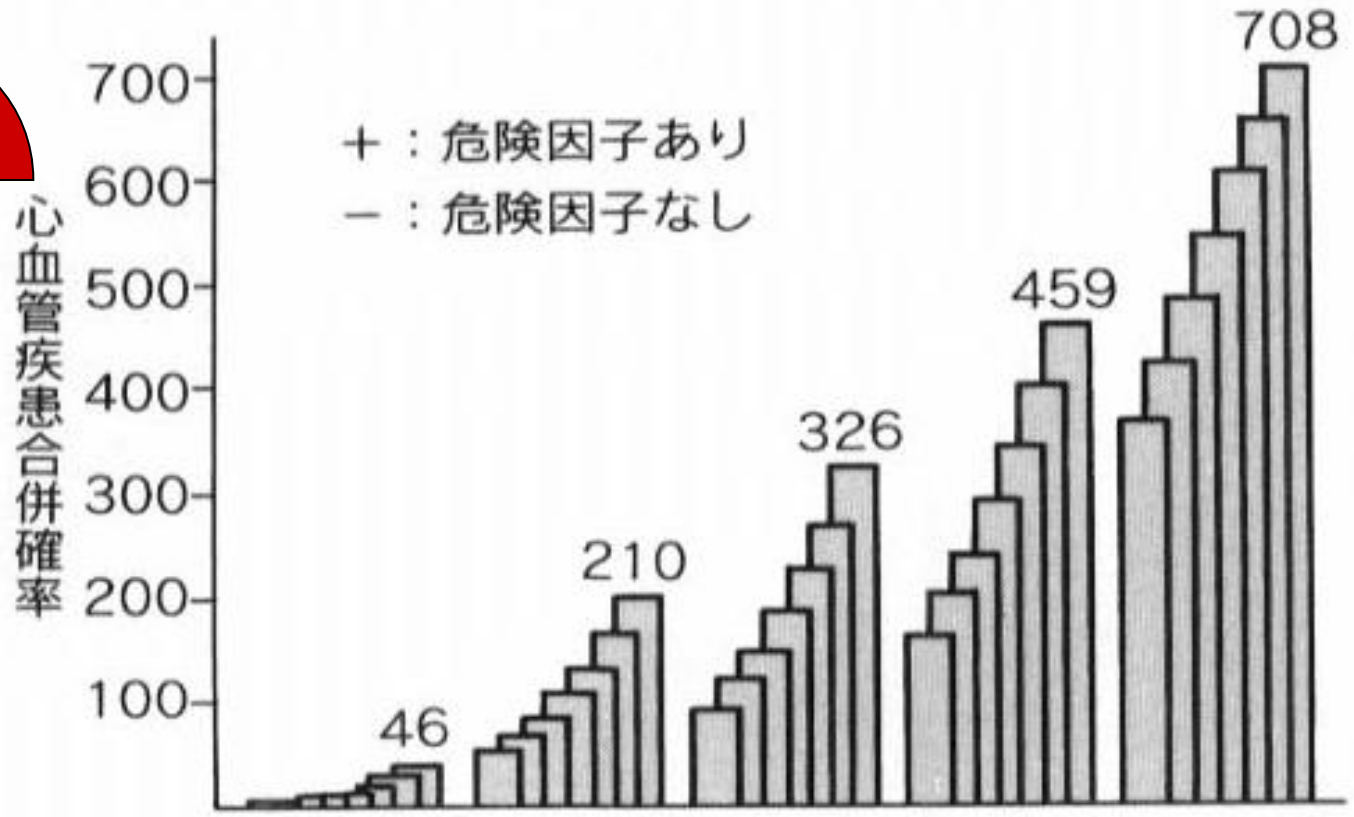
- Age
- Diabetes
- Smoking
- Treated and untreated Systolic Blood Pressure
- Total cholesterol
- HDL cholesterol
- BMI replacing lipids in a simpler model

Risk Score Calculators

https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php

心血管合併症に対する危険因子の影響
（40歳男性千人、18年間）フラミンガム研究

脳
心
腎



収縮期血圧	105～195	105→195	105→195	105→195	105→195
コレステロール値 (mg/dL)	185	335	335	335	335
耐糖能低下	－	－	＋	＋	＋
喫　煙	－	－	－	＋	＋
ECG左室肥大	－	－	－	－	＋

http://cvdrisk.nhlbi.nih.gov/

National Heart, Lung, and Blood Institute

Risk Assessment Tool for Estimating Your 10-year Risk of Having a Heart Attack

The risk assessment tool below uses information from the Framingham Heart Study to predict a person's chance of having a heart attack in the next 10 years. This tool is designed for adults aged 20 and older who do not have heart disease or diabetes. To find your risk score, enter your information in the calculator below.

Age:	65 years
Gender:	○ Female ◉ Male
Total Cholesterol:	145 mg/dL
HDL Cholesterol:	65 mg/dL
Smoker:	◉ No ○ Yes
Systolic Blood Pressure:	120 mm/Hg
Are you currently on any medication to treat high blood pressure.	◉ No ○ Yes

Calculate Your 10-Year Risk

http://cvdrisk.nhlbi.nih.gov/

Monday, November 30, 2015

Information for Health Professionals

- Clinical Practice Guidelines
- Heart & Vascular Information
- Lung Information
- Blood Information
- Sleep Information
- Interactive Tools and Resources
- Education Campaigns
- National Education Programs
- Continuing Education Opportunities
- Health Observances

Information about your risk score:

Age:	65
Gender:	male
Total Cholesterol:	145 mg/dL
HDL Cholesterol:	65 mg/dL
Smoker:	No
Systolic Blood Pressure:	120 mm/Hg
On medication for HBP:	No
Risk Score*	7%

Means 7 of 100 people with this level of risk will have a heart attack in the next 10 years.

* Your risk score was calculated using an equation. Other NCEP products, such as printed ATP III materials, use a point system to determine a risk score that is close to the equation score.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group

N Engl J Med 2015; 373:2103-2116 | November 26, 2015 | DOI: 10.1056/NEJMoa1511939

Comments open through December 2, 2015

Background: The most appropriate targets for systolic blood pressure to reduce cardiovascular morbidity and mortality among persons without diabetes remain uncertain.

Methods : We randomly assigned 9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes, to a systolic blood-pressure target of less than 120 mm Hg (intensive treatment) or a target of less than 140 mm Hg (standard treatment). **The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes**.

SPRINT試験対象者

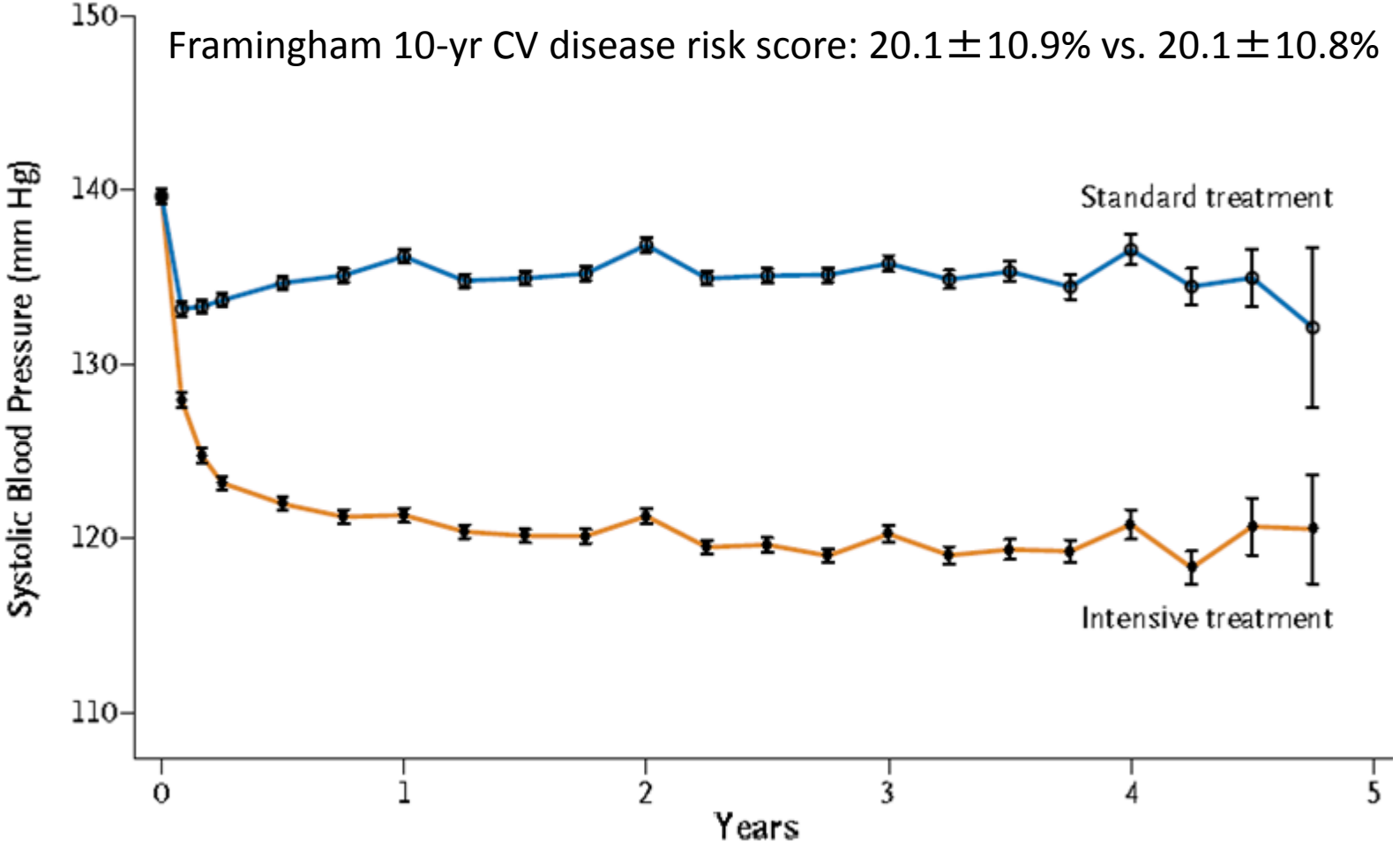
対象	●収縮期血圧130～180mmHg ●50歳以上 ●以下の心血管疾患リスク因子が1つ以上ある ●心血管疾患の既往(脳卒中は除く)　●慢性腎臓病の既往(多嚢胞性腎症は除く)　●フラミンガムリスクスコアによる10年間の心血管疾患発症リスクが15%以上※　●75歳以上
除外項目	糖尿病、脳卒中の既往

※フラミンガムリスクスコア：年齢や性別、血中脂質レベル、血圧、糖尿病歴、喫煙歴などの冠危険因子を用いて今後10年以内の心血管イベント発症のリスクを評価する指標

日経メディカル（20151203）より改変

SBP in the Two Treatment Groups over the Course of the Trial.

Framingham 10-yr CV disease risk score: 20.1±10.9% vs. 20.1±10.8%



No. with Data									
Standard treatment	4683	4345	4222	4092	3997	3904	3115	1974	1000
Intensive treatment	4678	4375	4231	4091	4029	3920	3204	2035	1048
Mean No. of Medications									
Standard treatment	1.9	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Intensive treatment	2.3	2.7	2.8	2.8	2.8	2.8	2.8	2.8	2.8

Medications（1.8剤から3剤へ）

- Chlorthalidone
  - loop diuretics (for participants with advanced chronic kidney disease)
  - β-adrenergic blockers (for those with coronary artery disease)
- Amlodipine
- ACE-I
- Azilsartan or Azilsartan + chlorthalidone

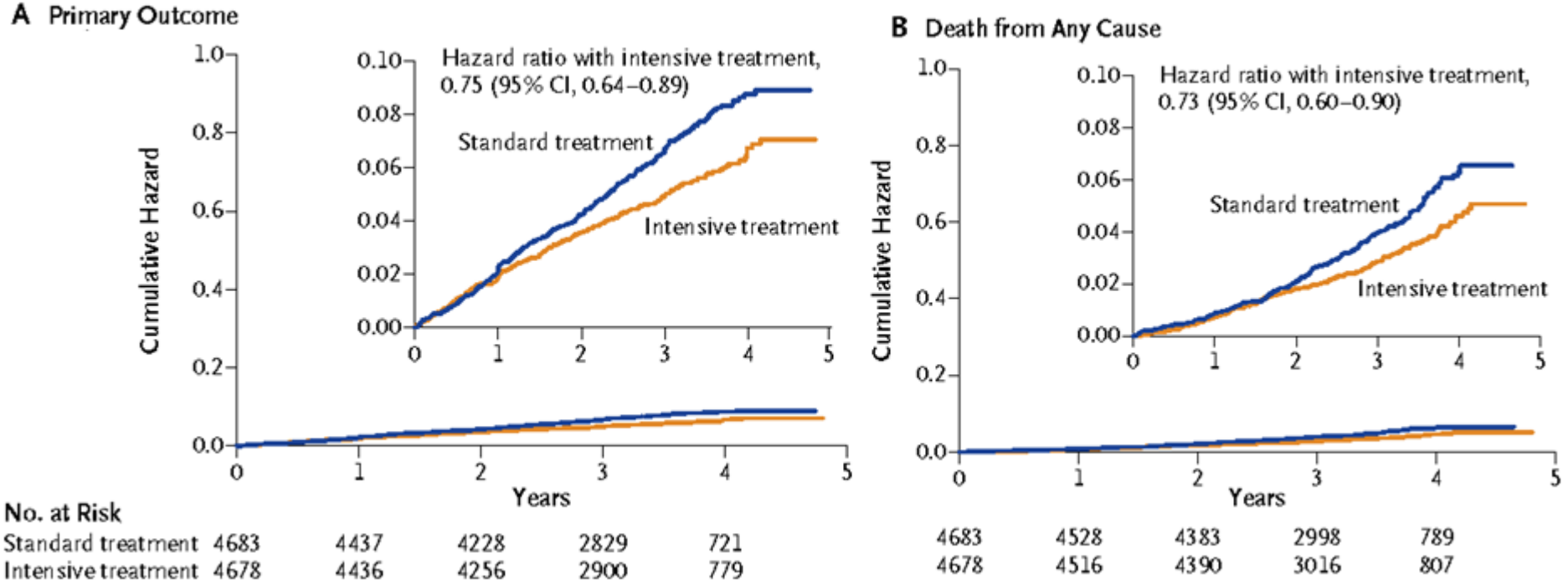
Utilization of Antihypertensive Medication Classes at Most Recent Visit

	Intensive (N=4678)	*Standard (N=4683)*
Number of agents		
Average	2.7 (1.2)	1.8 (1.1)
0	125 (2.7)	530 (11.3)
1	493 (10.5)	1455 (31.1)
2	1429 (30.5)	1559 (33.3)
3	1486 (31.8)	807 (17.2)
4+	1137 (24.3)	323 (6.9)

Utilization of Antihypertensive Medication Classes at Most Recent Visit

	Intensive (N=4678)	*Standard (N=4683)*
ACE-I or angiotensin II antagonist	3580 (76.7)	2582 (55.2)
ACE inhibitors	1729 (37.0)	1320 (28.2)
Angiotensin II antagonists	1854 (39.7)	1264 (27.0)
Renin inhibitors	1 (0.0)	1 (0.0)
Diuretics	3127 (67.0)	2006 (42.9)
Thiazide-type diuretics	2562 (54.9)	1557 (33.3)
Aldosterone receptor blockers	405 (8.7)	185 (4.0)
Other potassium-sparing diuretics	144 (3.1)	119 (2.5)
Alpha-1 blockers	482 (10.3)	258 (5.5)
Beta blockers	1919 (41.1)	1440 (30.8)
Central alpha-2 agonists or other centrally acting drugs	107 (2.3)	44 (0.9)
Calcium channel blockers	2667 (57.1)	1654 (35.4)
Dihydropyridines	2465 (52.8)	1463 (31.3)
Non-dihydropyridines	218 (4.7)	199 (4.3)
Direct vasodilators	340 (7.3)	110 (2.4)

Primary Outcome and Death from Any Cause.



At 1 year, the mean systolic blood pressure was 121.4 mm Hg in the intensive-treatment group (ITG) and 136.2 mm Hg in the standard-treatment group (STG).

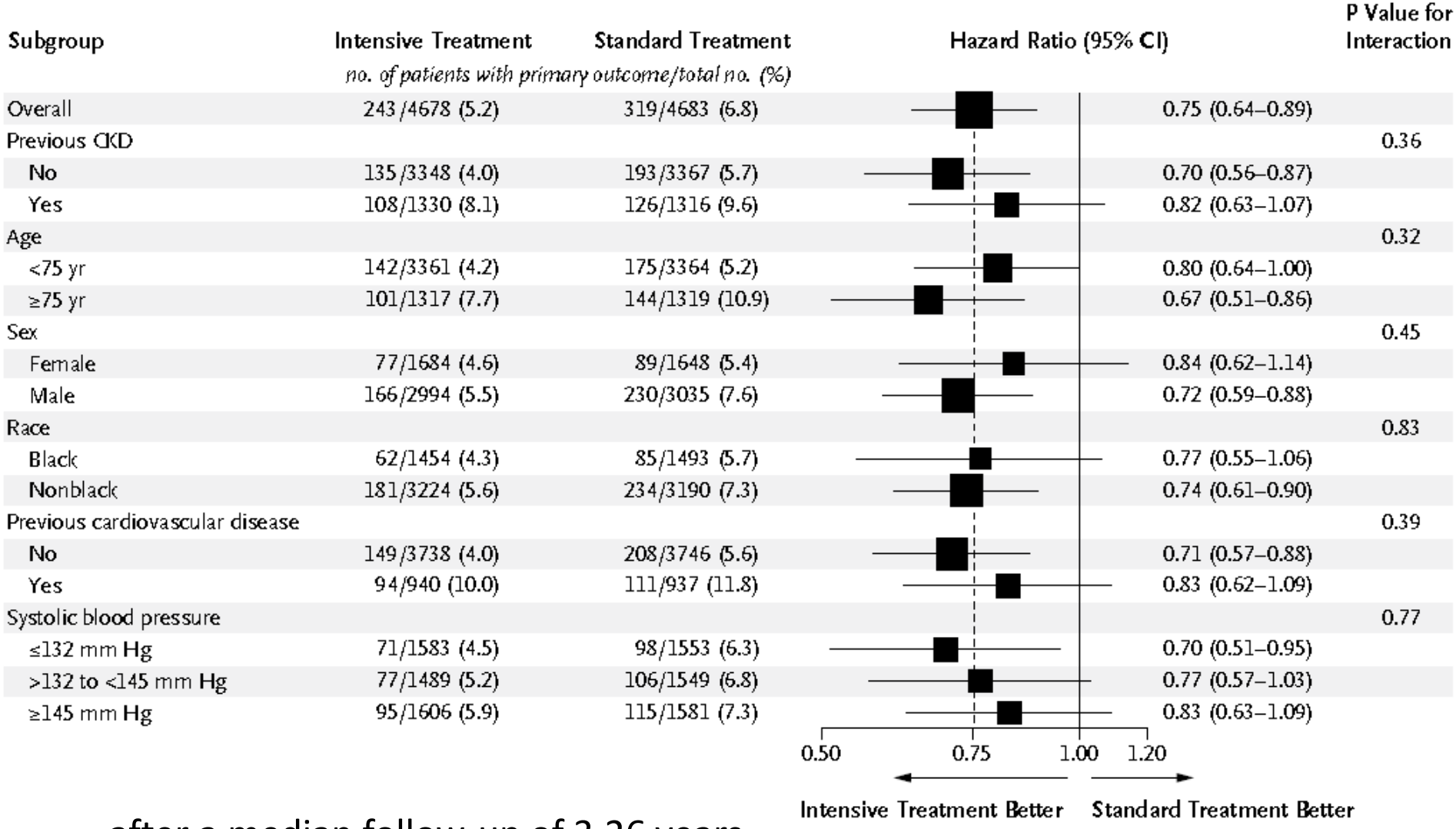
The intervention was stopped early after a median follow-up of 3.26 years owing to a significantly lower rate of the primary composite outcome in the ITG than in the STG (1.65% per year vs. 2.19% per year; $P<0.001$). All-cause mortality was also significantly lower in the ITG (1.04% per year vs. 1.40% per year; $P=0.003$).

一次評価項目も全死亡率も3/4

	治療群	ITG 120mmHg	STG 140mmHg	ハザード比(95%CI)	P値
主要評価項目	複合心血管病発症率 (%/年)	1.65	2.19	0.75 (0.64-0.89)	＜0.001
副次評価項目	心筋梗塞	0.65	0.78	0.83 (0.64-1.09)	0.19
	急性冠症候群	0.27	0.27	1.00 (0.64-1.55)	0.99
	脳卒中	0.41	0.47	0.89 (0.63-1.25)	0.50
	心不全	0.41	0.67	0.62 (0.45-0.84)	0.002
	心血管死	0.25	0.43	0.57 (0.38-0.85)	0.005
	全死亡	1.03	1.40	0.73 (0.60-0.90)	0.003

日経メディカル（20151203）より改変

Forest Plot of Primary Outcome According to Subgroups.



after a median follow-up of 3.26 years

Causes of Death

Cause of death	Overall	Intensive	Standard
CVD Death	102	37	65
__CHD Death coronary heart disease	50	18	32
__Stroke	17	8	9
__Sudden cardiac death	13	2	11
__CHF	17	8	9
__Not cardiac but other cardiovascular	5	1	4
Non-CVD Death	192	90	102
__Death from kidney disease	2	1	1
__Death related to dialysis procedure	1	0	1
__Other cardiac/non-ischemic	2	0	2
__Cancer	101	49	52
__Accident/Injury/Suicide/Homocide	14	4	10
__Other noncardiac, nonstroke death	72	36	36
Undetermined	71	28	43
__Unclassifiable	35	13	22
__Not yet adjudicated	36	15	21
Total	365	155	210

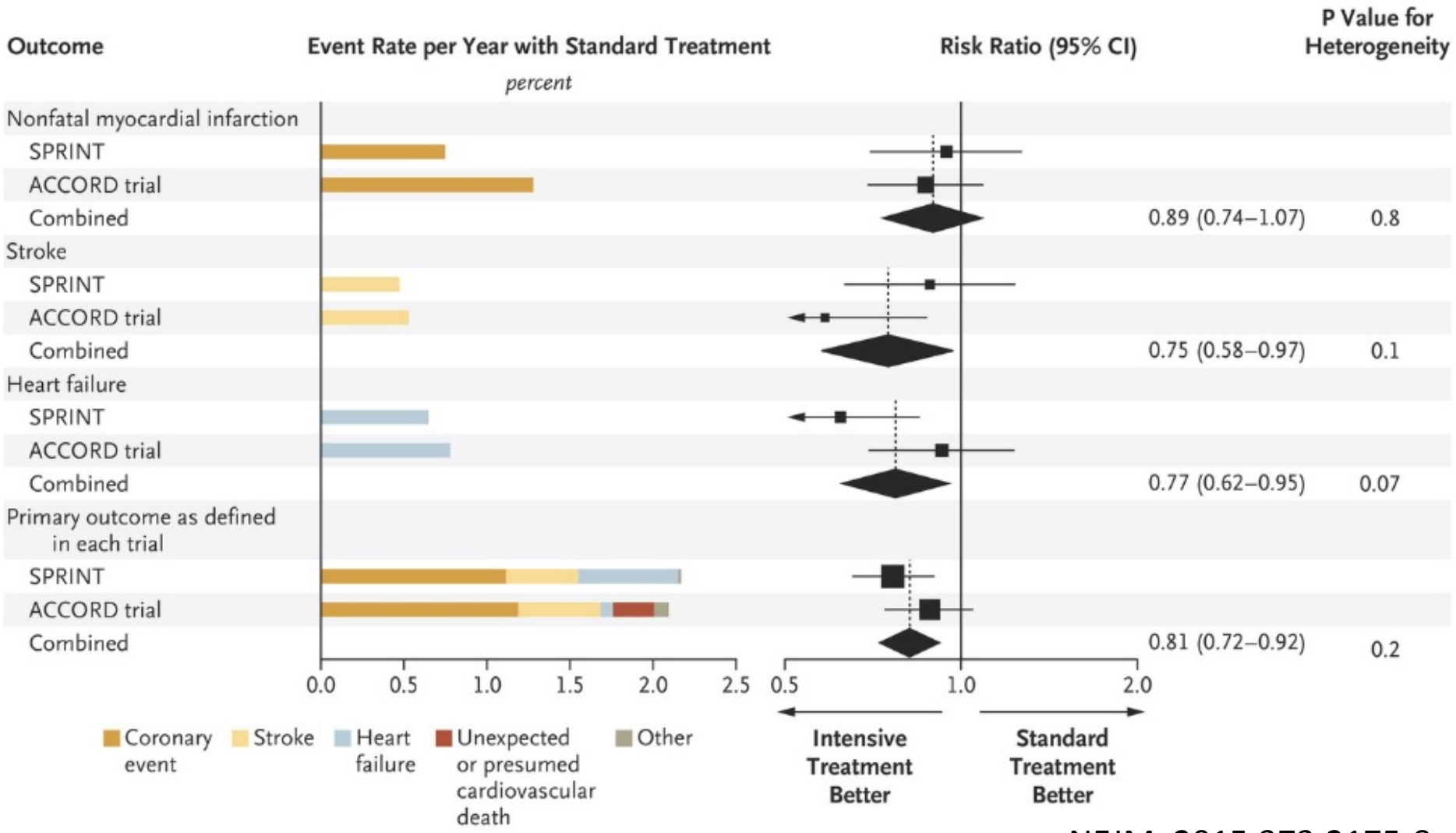
治療に伴う有害事象は約2倍

Rates of serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure, but not of injurious falls, were higher in the ITG than in the STG (1072 (22.9%) vs. 554 (11.8%); hazard ratio, 1.94 (<0.001) from Table S5).

Table S5. **Serious Adverse Events and Conditions of Interest** Classified as Possibly or Definitely Related to the Intervention

	Intensive (N=4678)	Standard (N=4683)	
	no. of patients (%)	no. of patients (%)	Hazard Ratio (P Value)
Serious Adverse Events[1]	220 (4.7)	118 (2.5)	1.88 (<0.001)
Conditions of Interest			
SAE Only			
Hypotension	83 (1.8)	37 (0.8)	2.52 (<0.001)
Syncope	64 (1.4)	28 (0.6)	2.15 (0.006)
Bradycardia	34 (0.7)	24 (0.5)	1.28 (0.44)
Electrolyte abnormality	69 (1.5)	48 (1.0)	1.58 (0.05)
Injurious fall[2]	19 (0.4)	13 (0.3)	1.99 (0.21)
Acute Kidney Injury or Acute Renal Failure[3]	88 (1.9)	34 (0.7)	3.14 (<0.001)
ER Visit or SAE			
Hypotension	125 (2.7)	58 (1.2)	2.24 (<0.001)
Syncope	94 (2.0)	44 (0.9)	2.13 (0.005)
Bradycardia	51 (1.1)	29 (0.6)	1.68 (0.05)
Electrolyte abnormality	93 (2.0)	62 (1.3)	1.61 (0.02)
Injurious fall[2]	36 (0.8)	23 (0.5)	2.22 (0.05)
Acute Kidney Injury or Acute Renal Failure[3]	96 (2.1)	36 (0.8)	3.13 (<0.001)

Outcomes Data from SPRINT and the ACCORD Trial and Combined Data from Both Trials



NEJM. 2015;373:2175-8.

Systolic Blood Pressure Intervention Trial (SPRINT)

Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial; **T2DM**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group

N Engl J Med 2015; 373:2103-2116 | November 26, 2015 | DOI: 10.1056/NEJMoa1511939

Comments open through December 2, 2015

Conclusions: Among patients at high risk for cardiovascular events but without diabetes, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause, although significantly higher rates of some adverse events were observed in the intensive-treatment group.

臨床実習前特別講義：4年生最終講義

20151201

昭和47年より、薬理学教室にて学んだ。
おかげで、ハリソン内科書を早くに知り、
学生時代からのNEJMの生涯購読者

- オーキシン（植物ホルモン）から誘導した合成化合物のミトコンドリア病治療薬MA-5について
  - 河北新報の紙面
  - Tohoku J Exp Med. 2015 July;236(3):225-32.
  - J Am Soc Nephrol. Published online 2015 Nov 25.
  - tohokuuniv-press20151126_01web

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●主要論文のアブストラクト

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河北新報
2015年(平成27年)11月27日(金曜日) 社会 16版 (30)

幼少期から重い障害 遺伝子異常の指定難病

ミトコンドリア病に治療薬

脳卒中、筋力低下など多様な症状が現れる指定難病「ミトコンドリア病」の治療薬を開発したと、東北大大学院医学系研究科の阿部高明教授（腎臓高血圧内科）のグループが26日、発表した。新薬の効果はマウスの実験で既に確認しており、3年後の臨床使用を目指す。

東北大院・阿部教授グループ

ミトコンドリア病は遺伝子の異常が原因で、エネルギーを生み出すことが困難になる病気の総称。幼少期から重い障害が起き、患者数は国内に700人程度いるとされる。これまで効果的な治療法がなかった。

グループは、腎臓病患者の腎臓に蓄積された血液から、骨髄の造血作用を刺激する物質を発見。化学合成で治療薬「MA−5」を生成した。細胞内の小器官ミトコンドリアのタンパク質と結合し、エネルギーを生み出す働きを取り戻すこともできる。

臨床使用18年にも

正常な働き促す

ミトコンドリア病のマウスにMA−5を投与した実験では、心臓と腎臓で機能の改善が確かめられた。ヒトの患者の皮膚片を使った実験でも、MA−5の投与でミトコンドリアの活性化を確認した。

グループは2018年ごろの薬事承認を目指し、16年度にも治験に入る。阿部教授は「MA−5は異常なミトコンドリアだけに効き、正常なものには毒性がない。幼くして亡くなる患者もいる。一刻も早く薬を届けたい」と話した。

ミトコンドリア病

ATPの枯渇（低酸素・虚血）
酸化ストレスによる細胞死

緊急性が高いが、治療薬が無い希少疾患

ミトコンドリア病

Leigh 脳症：
MELAS：
Leber病：
Kearns Sayre症候群：

ミトコンドリア機能異常

エネルギー代謝異常

活性酸素↑ 酸化ストレス↑

細胞・臓器
エネルギー産生低下
機能異常

細胞死

Tohoku J. Exp. Med., 2015, **236**, 225-232

Mitochonic Acid 5 (MA-5), a Derivative of the Plant Hormone Indole-3-Acetic Acid, Improves Survival of Fibroblasts from Patients with Mitochondrial Diseases

Takehiro Suzuki,[1,2,*] Hiroaki Yamaguchi,[3,*] Motoi Kikusato,[4,*] Tetsuro Matsuhashi,[5,*] Akihiro Matsuo,[1] Takeya Sato,[6] Yuki Oba,[1] Shun Watanabe,[1] Daichi Minaki,[7] Daisuke Saigusa,[8] Hiroko Shimbo,[9] Nobuyoshi Mori,[10] Eikan Mishima,[1] Hisato Shima,[1] Yasutoshi Akiyama,[1] Yoichi Takeuchi,[1] Akinori Yuri,[11] Koichi Kikuchi,[1,12] Takafumi Toyohara,[1] Chitose Suzuki,[1] Masahiro Kohzuki,[10] Jun-ichi Anzai,[7] Nariyasu Mano,[3] Shigeo Kure,[5] Teruyuki Yanagisawa,[6] Yoshihisa Tomioka,[11] Masaaki Toyomizu,[4] Sadayoshi Ito,[1] Hitoshi Osaka,[13] Ken-ichiro Hayashi[14] and Takaaki Abe[1,12,15]

Mitochondria are key organelles implicated in a variety of processes related to energy and free radical generation, the regulation of apoptosis, and various signaling pathways.

Mitochondrial dysfunction increases cellular oxidative stress and depletes ATP in a variety of inherited mitochondrial diseases and also in many other metabolic and neurodegenerative diseases. Mitochondrial diseases are characterized by the dysfunction of the mitochondrial respiratory chain, caused by mutations in the genes encoded by either nuclear DNA or mitochondrial DNA.

We have hypothesized that chemicals that increase the cellular ATP levels may ameliorate the mitochondrial dysfunction seen in mitochondrial diseases.

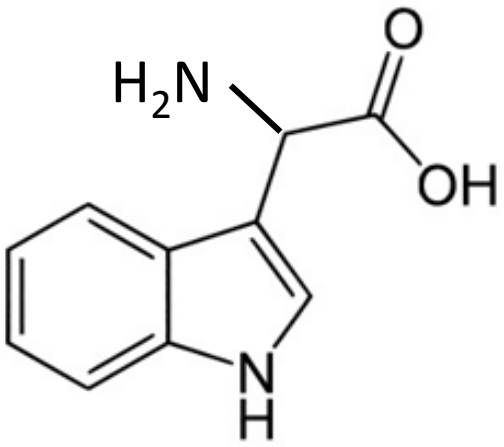
To search for the potential drugs for mitochondrial diseases, we screened an in-house chemical library of indole-3-acetic-acid analogs by measuring the cellular ATP levels in Hep3B human hepatocellular carcinoma cells.

We have thus identified mitochonic acid 5 (MA-5), 4-(2,4-difluorophenyl)-2-(1H-indol-3-yl)-4-oxobutanoic acid, as a potential drug for enhancing ATP production. MA-5 is a newly synthesized derivative of the plant hormone, indole-3-acetic acid.

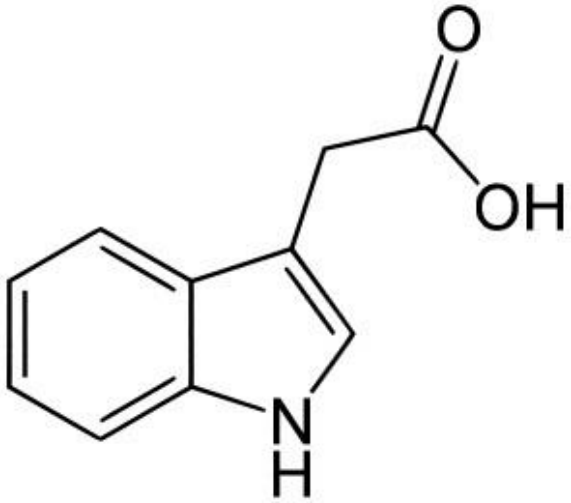
Importantly, MA-5 improved the survival of fibroblasts established from patients with mitochondrial diseases under the stress-induced condition, including Leigh syndrome, MELAS (myopathy encephalopathy lactic acidosis and stroke-like episodes), Leber's hereditary optic neuropathy, and Kearns-Sayre syndrome.

Auxin (indol-3-acetic acid)

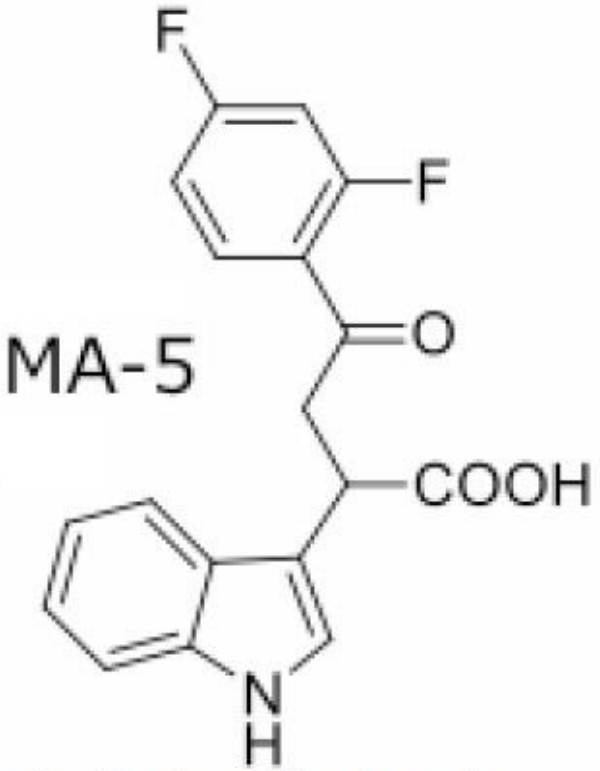
In patients with renal failure, many uremic toxins are accumulated, such as indoxyl sulfate and *p*-cresyl sulfate (Toyohara et al. 2010). Unexpectedly, we also found the accumulation of indole-3-acetic acid (IAA), a plant hormone auxin, in uremic patients (Toyohara et al. 2010). IAA regulates growth and essential for plant's life cycle and body development, but IAA is synthesized in the mouse liver and kidney (Gordon et al. 1972) and intestinal anaerobes (Chung et al. 1975). In addition, IAA increased the growth of mouse and human fibroblasts (Abu Sinna 1983), although the precise role and mechanism has not been clarified. We are therefore interested in the bioactive properties of IAA.



トリプトファン



植物ホルモン
オーキシン auxin
インドール−3−酢酸
(IAA: indole−3−acetic acid)



MA-5

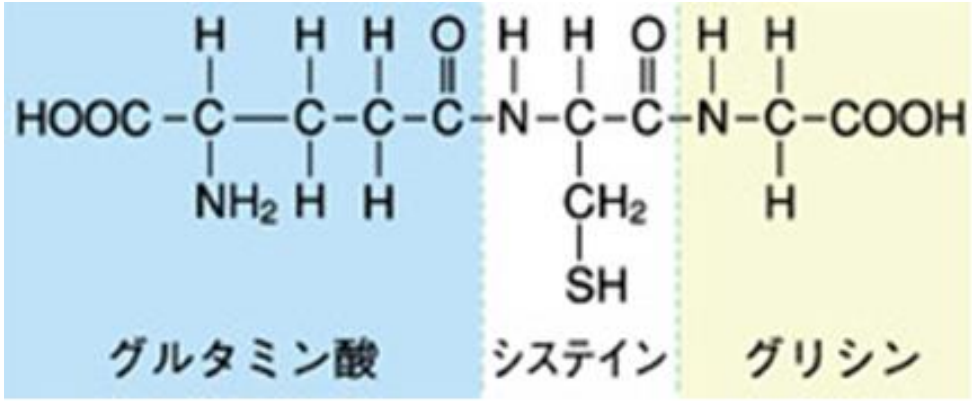
Mitochonic Acid 5 (MA-5), 4-(2,4-difluorophenyl)-2-(1H-indol-3-yl)-4-oxobutanoic acid

細胞内タンパク質のSH基を適当な酸化状態に保つ

グルタチオン

Glutathione (GSH)

2GSH ⇔ GSSG＋2H

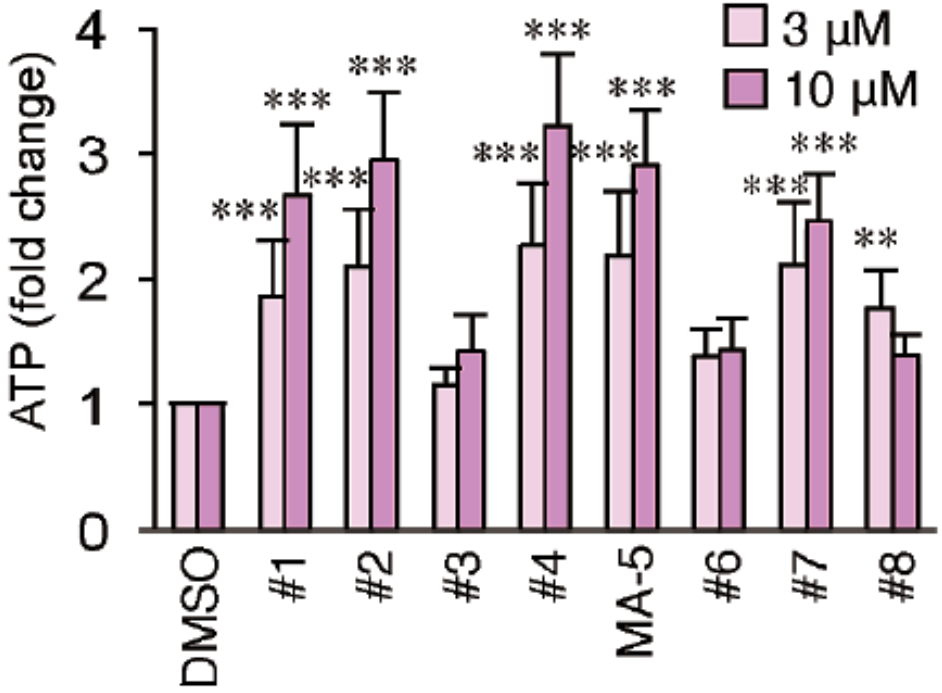


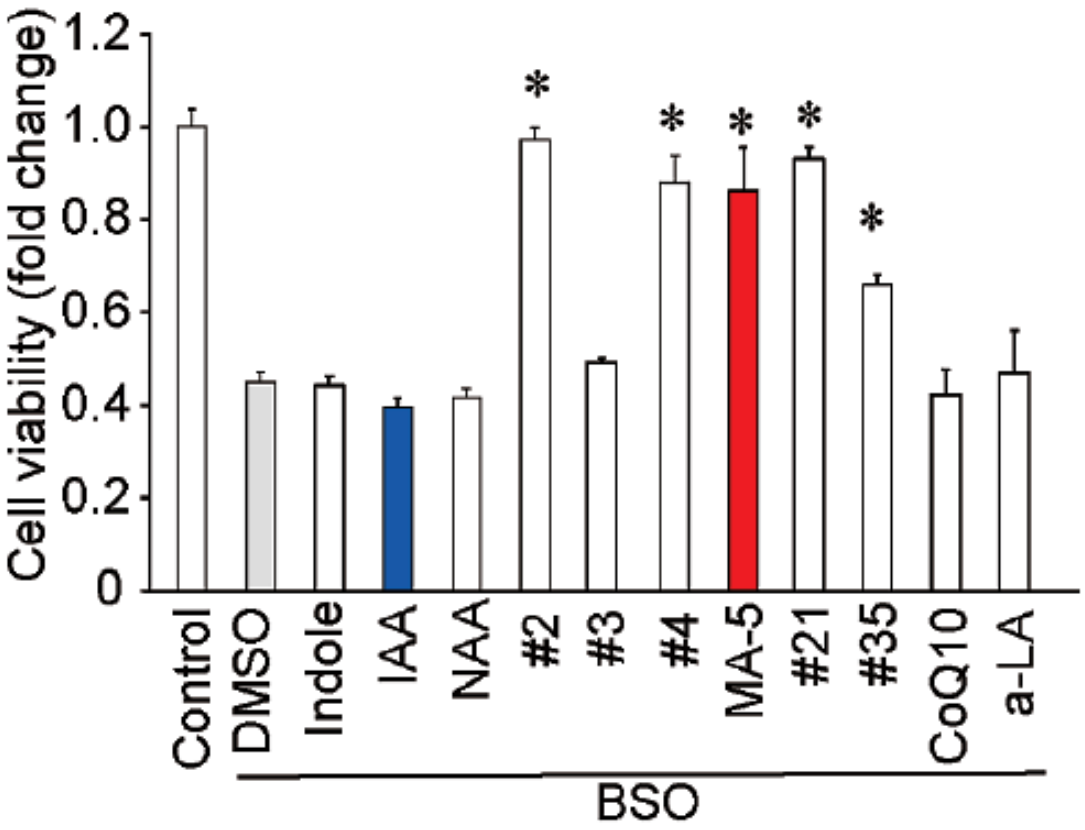
Mitochonic acid (MA-5)

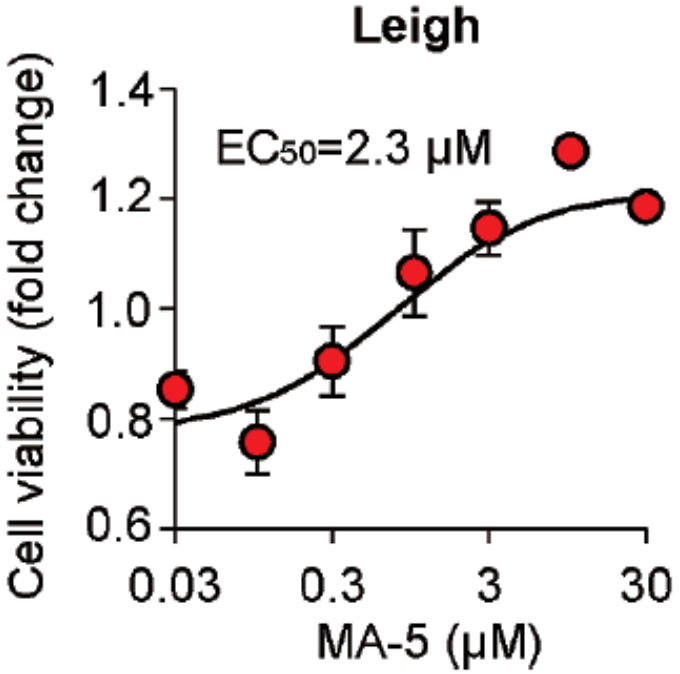
Here, we screened an in-house chemical library of IAA analogs (Hayashi et al. 2012) and found that derivatives of IAA significantly increased the cellular ATP level in Hep3B human hepatocellular carcinoma cells, including mitochonic acid (MA)-5, 4-(2,4-difluorophenyl)-2-(1H-indol-3-yl)-4-oxobutanoic acid (Hayashi et al. 2012). Moreover, MA-5 improved the survival of fibroblasts established from patients with mitochondrial diseases probably increasing the ATP level independently of the membrane potential or OXPHOS complexes. Our finding changes the focus on searching drugs for mitochondrial and neurodegenerative diseases.

細胞障害試薬、L-buthionine-(S,R)-sulfoximine (BSO, glutathione synthesis inhibitor, 100 μM)

MA-5 increases ATP and the survival of fibroblasts from mitochondrial diseases. EC_{50} = 2.3 µM







Tohoku J. Exp. Med., 2015, **236**, 225-232

Mitochonic Acid 5 (MA-5), a Derivative of the Plant Hormone Indole-3-Acetic Acid, Improves Survival of Fibroblasts from Patients with Mitochondrial Diseases

The improved survival was associated with the increased cellular ATP levels.
Moreover, MA-5 increased the survival of mitochondrial disease fibroblasts even under the inhibition of the oxidative phosphorylation or the electron transport chain.
These data suggest that MA-5 could be a therapeutic drug for mitochondrial diseases that exerts its effect in a manner different from anti-oxidant therapy.

BRIEF COMMUNICATION www.jasn.org

J Am Soc Nephrol 27: ccc–ccc, 2015. doi: 10.1681/ASN.2015060623

Mitochonic Acid 5 Binds Mitochondria and Ameliorates Renal Tubular and Cardiac Myocyte Damage

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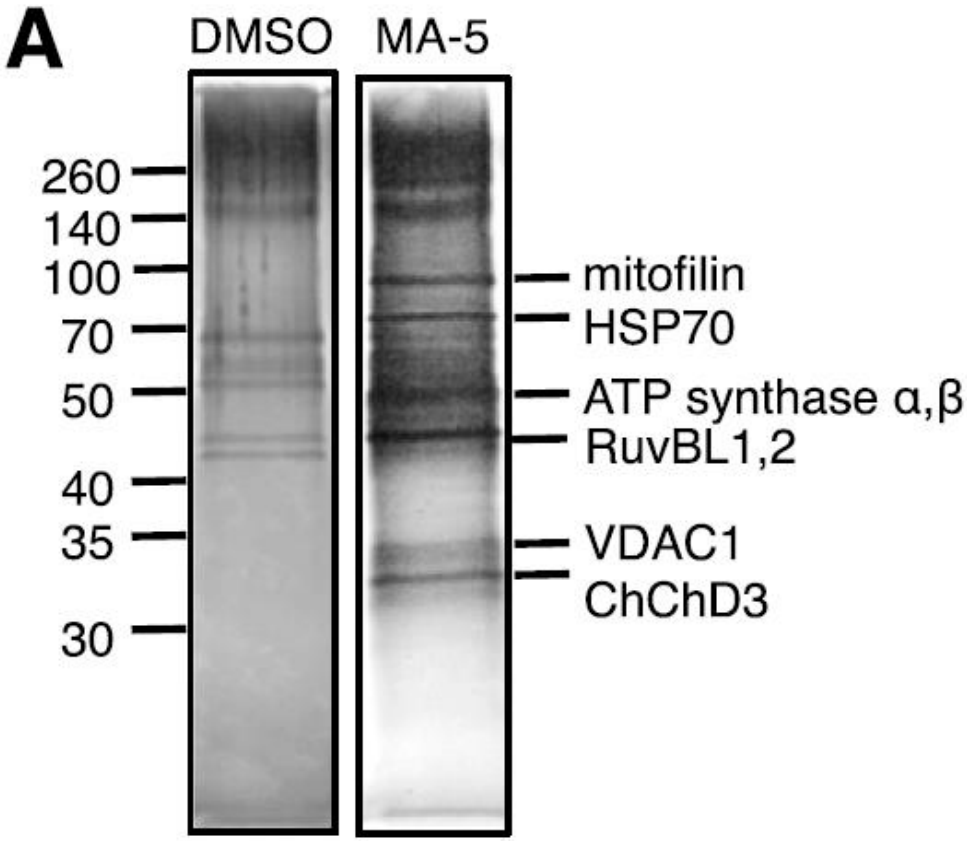
Mitochondrial dysfunction causes increased oxidative stress and depletion of ATP, which are involved in the etiology of a variety of renal diseases, such as CKD, AKI, and steroid-resistant nephrotic syndrome. Antioxidant therapies are being investigated, but clinical outcomes have yet to be determined.

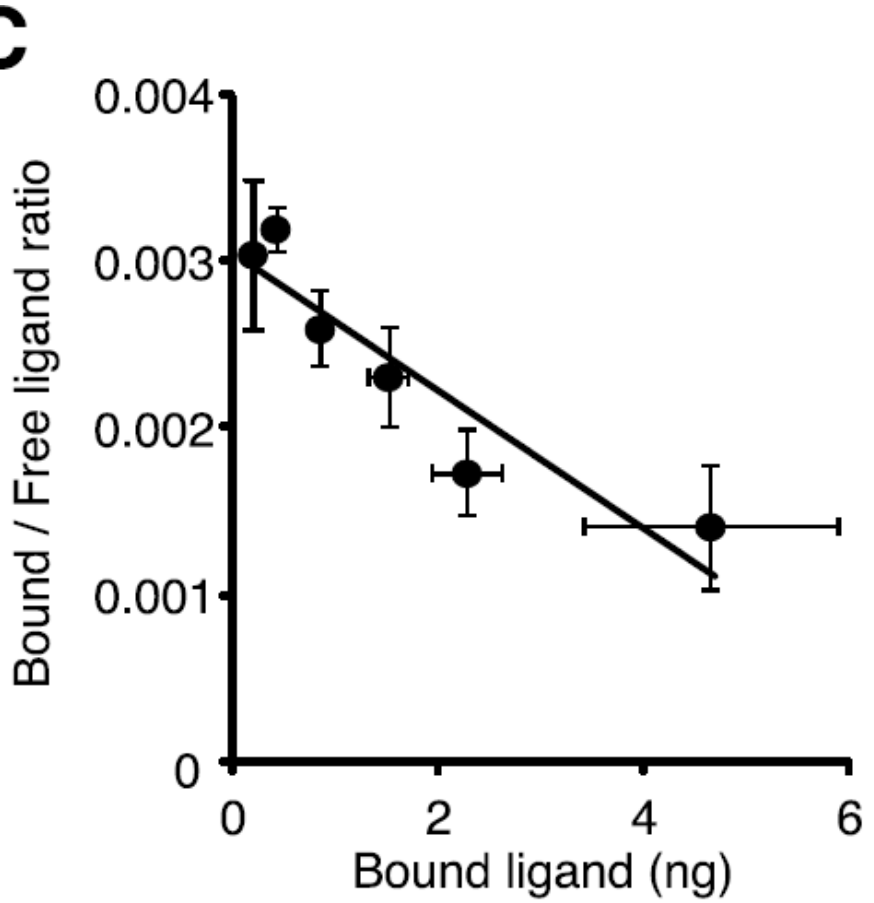
Recently, we reported that a newly synthesized indole derivative, mitochonic acid 5 (MA-5), increases cellular ATP level and survival of fibroblasts from patients with mitochondrial disease. MA-5 modulates mitochondrial ATP synthesis independently of oxidative phosphorylation and the electron transport chain.

Here, we further investigated the mechanism of action for MA-5. Administration of MA-5 to an ischemia-reperfusion injury model and a cisplatin-induced nephropathy model improved renal function.

In *in vitro* bioenergetic studies, MA-5 facilitated ATP production and reduced the level of mitochondrial reactive oxygen species (ROS) without affecting activity of mitochondrial complexes I-IV.

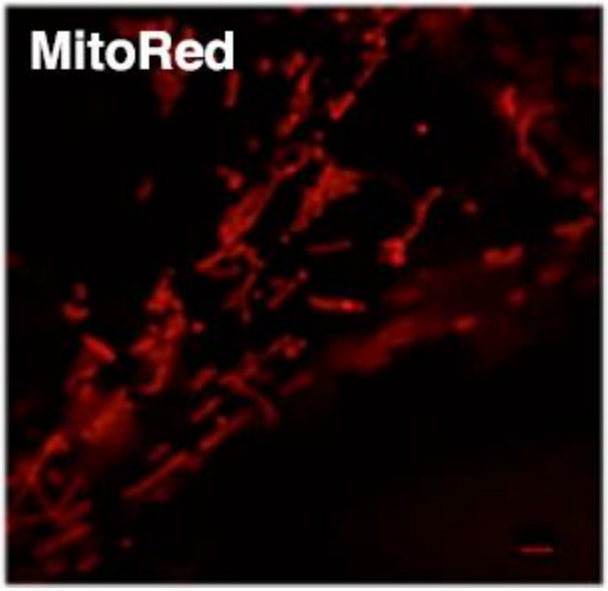
MA-5 binds with mitofilin

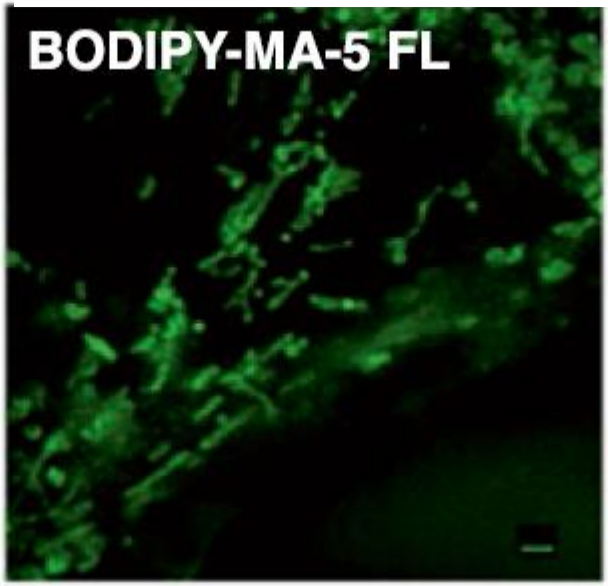


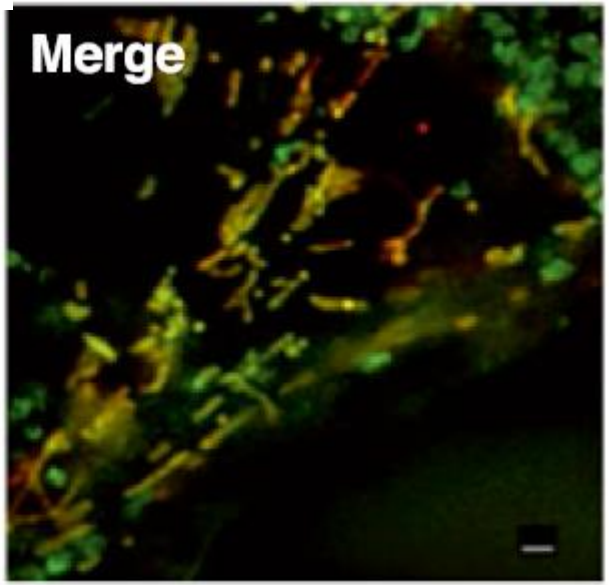


Mitofilin forms a core complex in the mitochondrial inner membrane organizing system (MINOS)

BODIPY-MA-5 FL







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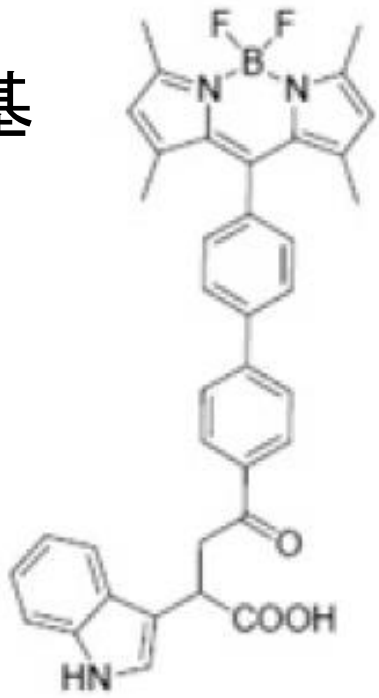
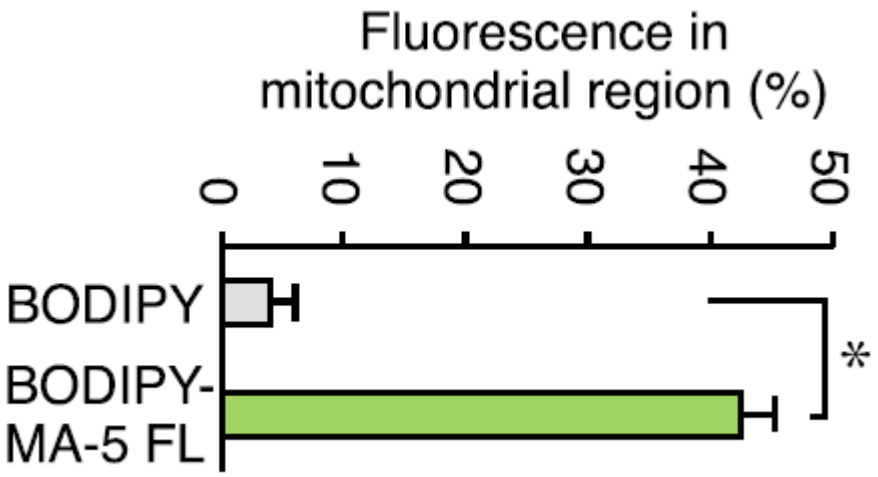
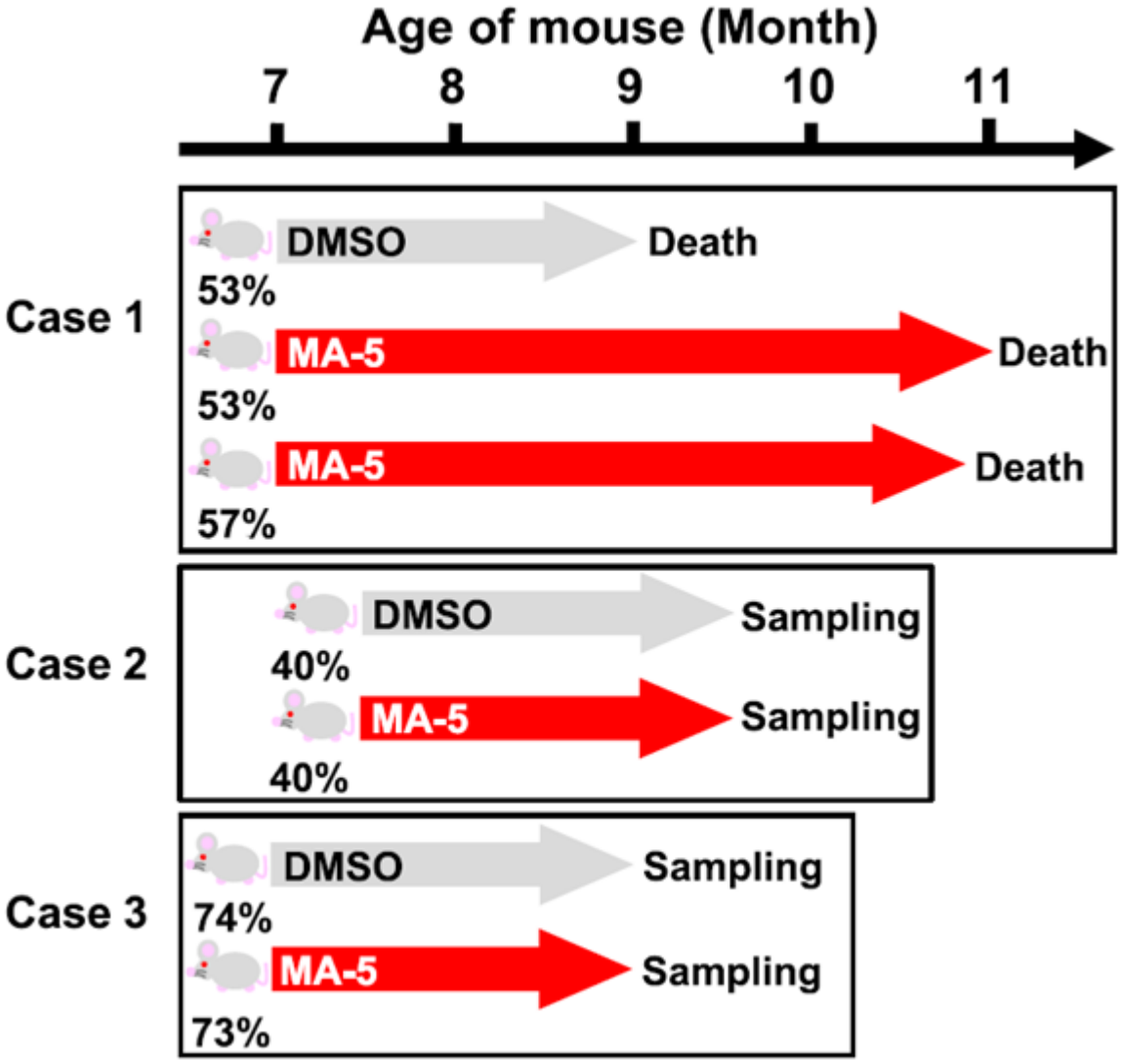


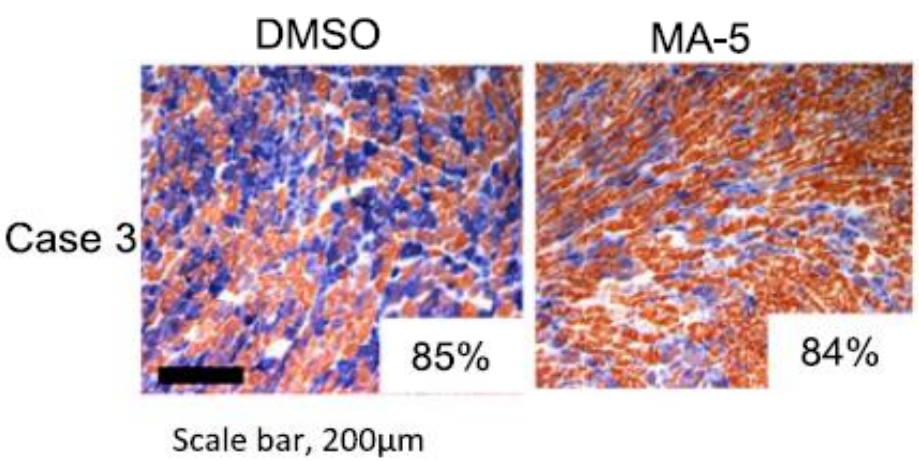


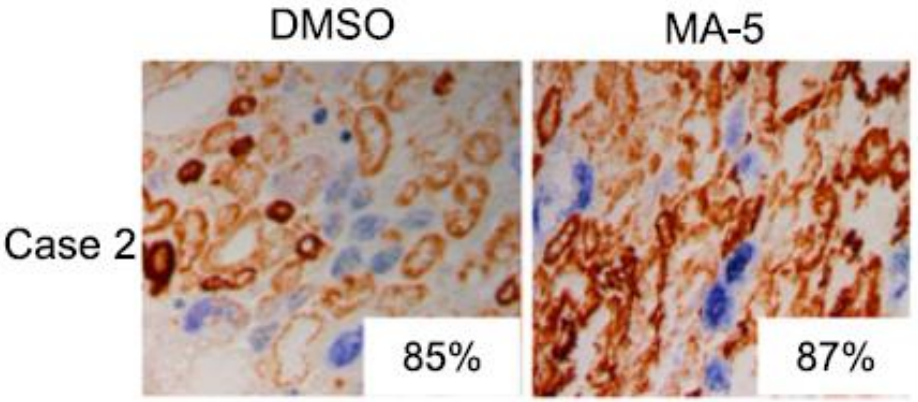
MA-5 improved respiration of cardiac and renal cell in **Mitomice**

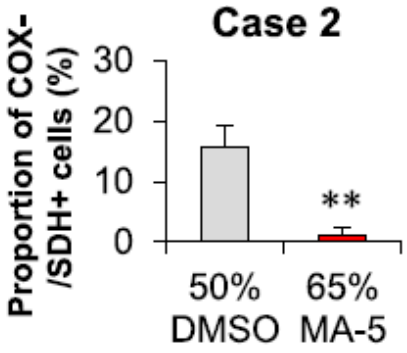


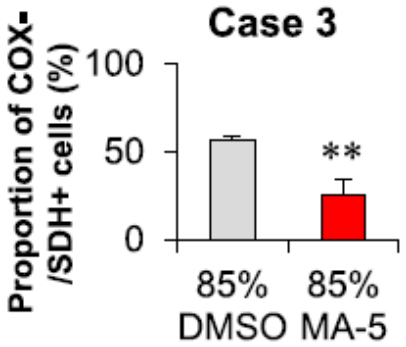
A mitochondrial disease model (Mitomice with mitochondrial DNA deletion that mimics typical human mitochondrial disease phenotype)

MA-5 improve respiration in Heart & Kidney



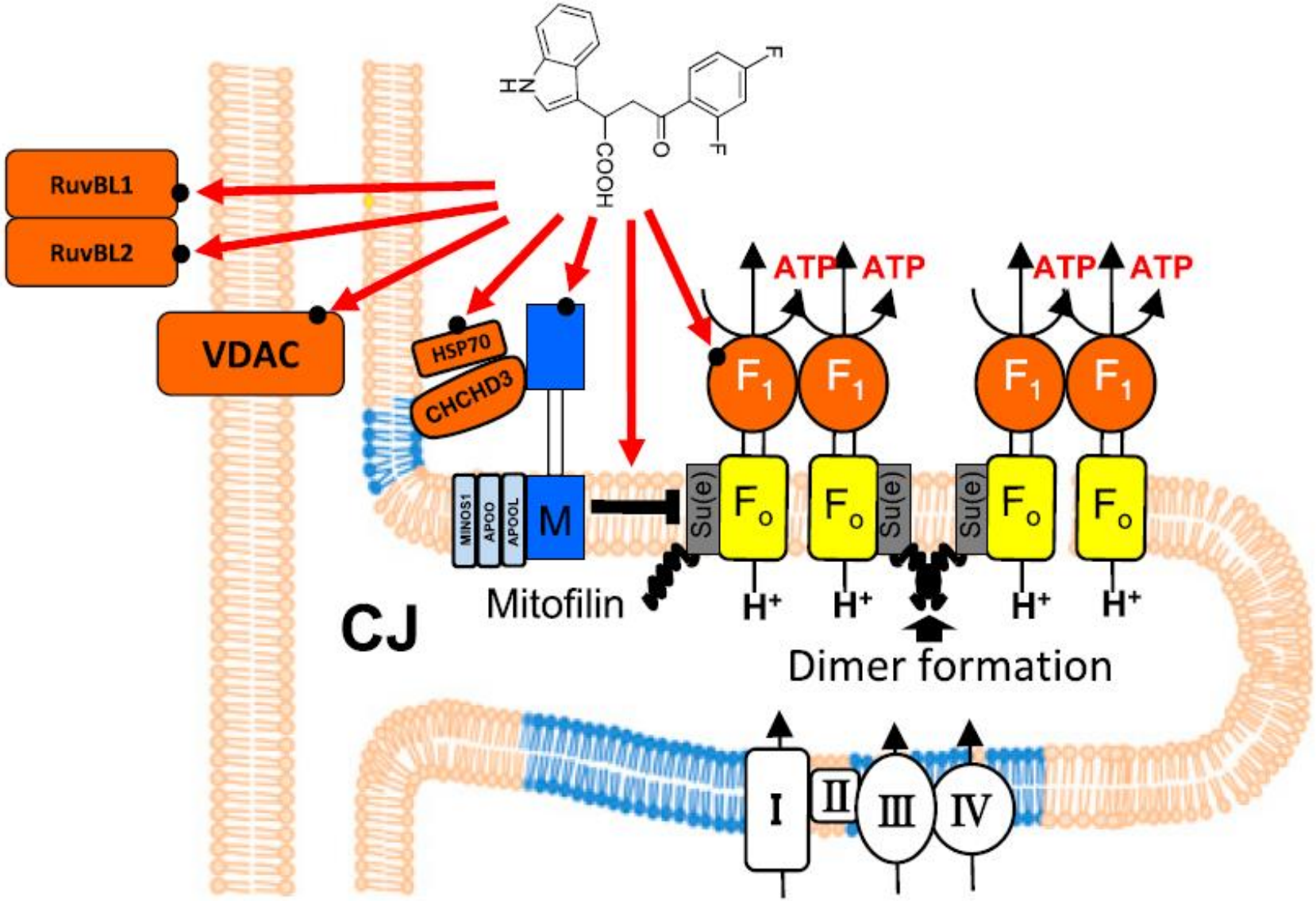






Succinate dehydrogenase (SDH) and COX activity were assessed by immunostaining of the heart tissues (Left) and SDH (right) of the kidny tissues from Mitomice

Schematic model of the action of MA-5. MA-5 interacts with mitofilin and modifies the MINOS complex.



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Mitochonic Acid 5 Binds Mitochondria and Ameliorates Renal Tubular and Cardiac Myocyte Damage

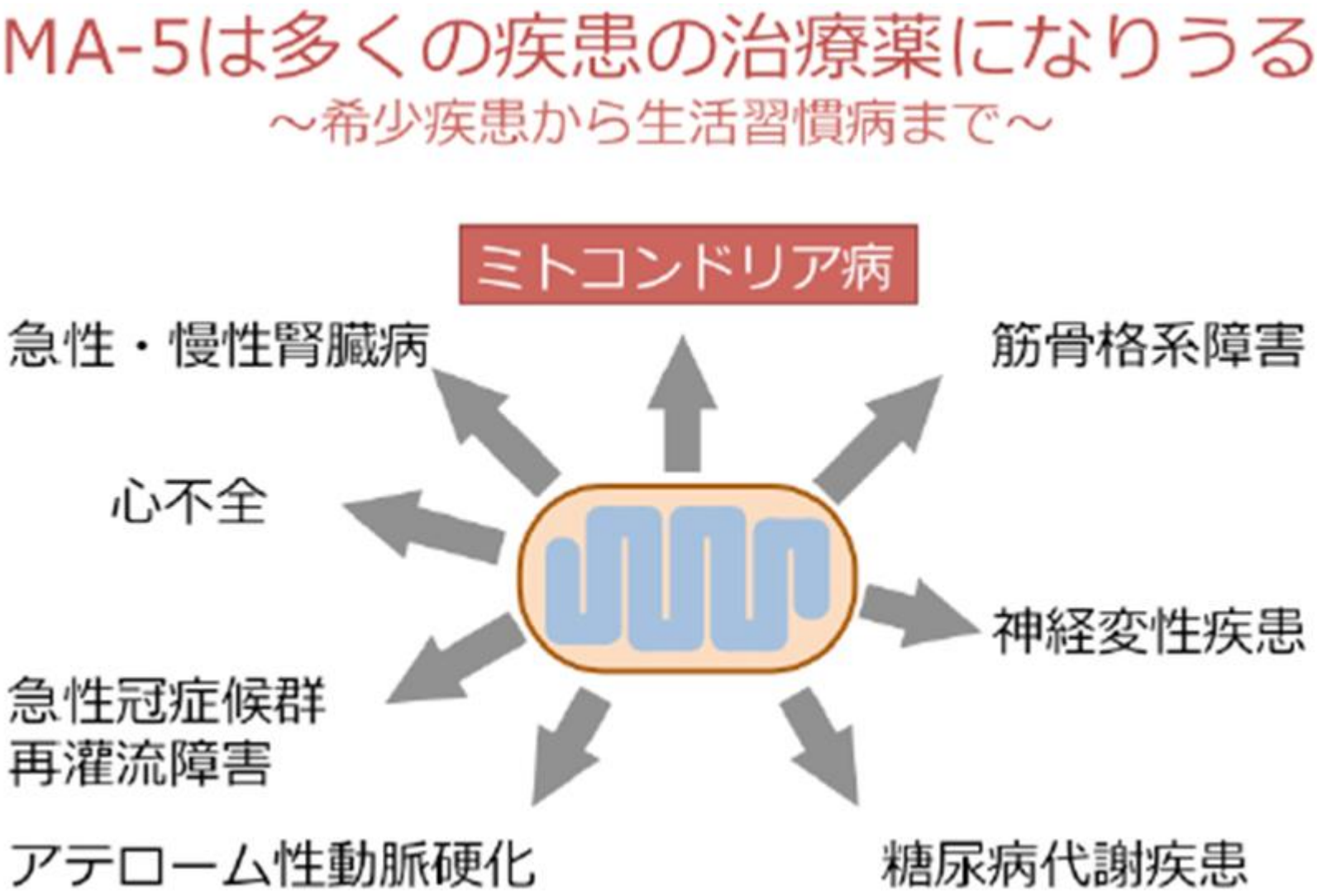
Additional assays revealed that MA-5 targets the mitochondrial protein mitofilin at the crista junction of the inner membrane. In Hep3B cells, overexpression of mitofilin increased the basal ATP level, and treatment with MA-5 amplified this effect.

In a unique mitochondrial disease model mouse, MA-5 improved the reduced cardiac and renal mitochondrial respiration and seemed to prolong survival.

These results suggest that MA-5 functions in a manner differing from that of antioxidant therapy and could be a novel therapeutic drug for the treatment of cardiac and renal diseases associated with mitochondrial dysfunction.

MegaBuster from an orphan drug

極めて少数の難病治療から多数の一般病治療薬へ



サプライズがありました。花の色は黄、紫、赤オレンジ色で、それぞれ窒素（硝酸薬）、カリウム、カルシウムだそうで、NKハイブリッド、細胞内Ca濃度の象徴として炎色反応の色を選んでくれたのです。なんと知的で細やかな学生であることよ。彼らを教えることができたことを感謝して、大学を去れます。