JAPANESE SOCIETY FOR MICROCIRCULATION

第38回
日本微小循環学会総会

The 38th Annual Meeting of Japanese Society for Microcirculation

プログラム・抄録集

会　期　2013年2月8日(金)～9日(土)

会　場　東京慈恵会医科大学　1号館3階講堂
（東京都港区西新橋）

会　長　西野 博一　東京慈恵会医科大学 内科学講座 教授
（第三病院消化器肝臓内科）

ご挨拶

第38回日本微小循環学会総会を、平成25年2月8日(金)、9日(土) の2日間にわたって東京慈恵会医科大学 (U1棟) にて開催させていただきます。伝統ある本学会総会を主催するにあたり、名誉会員、理事、評議員はじめ学会員の皆様に厚く御礼申し上げます。本学会は臨床医学系、基礎医学系、医療工学系、薬学系、生物学系などの幅広い領域の研究者が集い、微小循環研究に関して横断的に討論できる貴重な学会です。東京慈恵会医科大学の開催は、第18回総会 (会長：磯貝行秀教授) に続き20年ぶりで本学会をお世話させて頂くことになり、大変光栄に存じております。

今回の学会では、特別講演をHolger Gerhardt教授 (Vascular Biology Laboratory, London Research Institute, Cancer Research UK) にお願い致しました。Gerhardt先生はangiogenesisの分野で多くの業績を挙げられています。招待講演として、竹山宜典教授 (近畿大学外科肝胆膵部門) に「Pancreatic microcirculation and exacerbation of acute pancreatitis」のご講演をいただきます。また、教育講演として戸村道夫先生 (京都大学医学研究科) に「Approach to understand immune system based on spatiotemporal regulation of immune cells in the entire body」のご講演をいただきます。

多くの会員の皆様にご参加いただき、実り多い有意義な学会になりますように、努力する所存ですので、何卒よろしくお願い申し上げます。

第38回日本微小循環学会総会
会長　**西野　博一**
東京慈恵会医科大学内科学講座　教授

日本微小循環学会役員および総会の開催日 / 会長一覧

（＊印は「微小循環研究者の集い」）

理事長

末松　誠

名誉会員

朝倉　均　淺野　牧茂　石川　浩一　磯貝　行秀　大塩　力　大島　宣雄
織田　正也　梶谷　文彦　鹿取　信　神谷　瞭　神原　武　佐藤　信紘
所澤　剛　関　清　関　淳二　高橋　和人　田中　健蔵　対馬　信子
中山　龍　新見　英幸　野坂洋一郎　深田　栄一　福内　靖男　南谷　晴之

理　事

荒木　信夫　石川　眞美　大橋　俊夫　岡田　英吉　小椋祐一郎　梶村　眞弓
柴田　政廣　鈴木　則宏　鈴木　秀和　棚橋　紀夫　永田　博司　中村　正彦
西野　博一　藤村　朗　馬嶋　正隆　三浦総一郎　矢田　豊隆　山本　哲郎
吉川　敏一　吉田　晃敏

監　事

大久保千代次　寺山　靖夫

評議員

相磯　貞和　秋葉　保忠　天野　英樹　安藤　譲二　池本　卓　伊古美文隆
伊藤　和郎　伊藤　義彰　伊藤　義也　牛山　明　畝川美悠紀　大島　厚
大野　隆　岡部栄逸朗　荻原　達雄　長田　高志　河合　康明　河合　佳子
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鈴木　磨郎　関塚　永一　蘇原　泰則　高清水眞二　高橋　俊介　高安　正和
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船津　和夫　穂苅　量太　八月朔日秀明　本間　覚　前田　俊彦　松尾　雅斗
松原　明久　丸山　征郎　水野　嘉夫　水野　理介　南山　求　三好　千香
森下　鉄夫　柳　健一　矢吹　壮　山川　隆司　山口佳寿博　山口　三郎
吉田　憲正　和久井　信　渡辺　勳史　渡辺　嘉久

回数	開催年月日	世話人あるいは会長	開催場所	
第1回*	1976年2月14日	浅野 牧茂 (国立公衆衛生院)	東京	国立公衆衛生院
第2回*	1977年2月20日	影山 圭三 (慶應大学医学部病理)	東京	慶應大学医学部
第3回*	1978年2月11日	飯島 宗一・入沢 宏 (広島大学医学部病理)	広島	広島大学医学部
第4回*	1979年2月10日･11日	高木 健太郎 (名古屋市立大学本部)	瀬戸	愛知県労働者研修センター
第5回*	1980年2月9日	長島 長節 (杏林大学医学部生理)	東京	農林年金会館
第6回*	1981年4月18日	佐藤 春郎 (東北大学抗酸菌秒研究所)	仙台	斎藤報恩会会館
第7回*	1982年2月6日･7日	岡 小天・中山 龍・新見 英幸 (国立循環器病センター)	大阪	国立循環器病センター
第8回*	1983年2月5日･6日	竹重 順夫･村上 正浩･宮崎 道雄 (久留米大学医学部解剖)	久留米	石橋文化センター
第9回*	1984年2月4日･5日	関 清 (東邦大学医学部内)	東京	こまばエミナース
第10回	1985年2月16日･17日	砂田 輝武 (香川医科大学)	高松	高松国際ホテル
第11回	1986年2月1日･2日	林 秀男･神原 武 (熊本大学医学部病理･免疫アレルギー)	熊本	ニュースカイホテル
第12回	1987年1月30日･31日	三島 好雄 (東京医科歯科大学医学部外科)	東京	東京医科歯科大学
第13回	1988年5月20日･21日	松山 秀一 (弘前大学医学部眼科)	弘前	弘前市文化センター
第14回	1989年3月20日･21日	高橋 和人 (神奈川歯科大学口腔解剖)	横須賀	神奈川歯科大学
第15回	1990年4月28日･29日	所澤 剛 (秋田大学医学部病理)	秋田	秋田県総合保険センター
第16回	1991年4月25日･26日	鹿取 信 (北里大学医学部病理)	東京	アルカディア市ヶ谷
第17回	1992年5月21日･22日	大島 宣雄 (筑波大学基礎医学医工学)	つくば	筑波大学大学会館
第18回	1993年4月22日･23日	磯貝 行秀 (東京慈恵貝医科大学内科)	東京	全共連ビル
第19回	1994年5月26日･27日	大橋 俊夫 (信州大学医学部生理学)	松本	長野県松本文化会館
第20回	1995年4月20日･21日	神谷 瞭 (東京大学医用生体工学)	東京	東京大学山上会館
第21回	1996年2月23日･24日	対馬 信子 (国立循環器病センター内科)	大阪	千里ライフサイセンスセンター
第22回	1997年2月28日･3月1日	佐藤 信紘 (順天堂大学医学部内科)	東京	日本海運倶楽部
第23回	1998年2月26日･27日	野坂 洋一郎 (岩手医科大学歯学部口腔解剖)	盛岡	盛岡グランドホテル
第24回	1999年2月26日･27日	副内 靖男 (慶應大学医学部内科)	東京	日本海運倶楽部
第25回	2000年2月18日･19日	時岡 孝夫 (明海大学医学部解剖)	横須賀	神奈川歯科大学
第26回	2001年2月15日･16日	梶谷 文彦 (岡山大/川崎医大医用工学)	倉敷	倉敷市立美術館
第27回	2002年2月21日･22日	大久保 千代次 (国立公衆衛生院)	東京	国立公衆衛生院
第28回	2003年2月13日･14日	三浦 総一郎 (防衛医科大学校内科)	東京	グランドビル市ヶ谷
第29回	2004年2月19日･20日	山本 哲郎 (熊本大学医・薬学研究分子病理)	熊本	ニュースカイホテル
第30回	2005年2月23日･24日	織田 正也 (国際医療福祉大学内科)	東京	東京国際フォーラム
第31回	2006年2月10日･11日	末松 誠 (慶應大学医学部医化学)	東京	京王プラザホテル
第32回	2007年2月23日･24日	吉川 敏一 (京都府立医科大学･院･医学研･生体機能制御学)	京都	ぱ・る・るプラザ京都
第33回	2008年2月21日･22日	南谷 晴之 (慶應義塾大学・院・理工学研究科)	東京	慶應義塾大学 三田キャンパス
第34回	2009年2月20日･21日	馬嶋 正隆 (北里大学医学部薬理学)	東京	北里大学 白金キャンパス
第35回	2010年2月26日･27日	棚橋 紀夫 (埼玉医科大学国際医療センター神経内科)	大宮	大宮ソニックシティ
第36回	2011年2月11日･12日	小椋 裕一郎 (名古屋市立大学医学部眼科)	名古屋	名古屋市立大学病院大ホール
第37回	2012年3月16日･17日	藤村 朗 (岩手医科大学解剖学講座機能形態学分野)	岩手	盛岡グランドホテル
第38回	2013年2月8日･9日	西野 博一 (東京慈恵会医科大学消化器肝臓内科)	東京	東京慈恵会医科大学

会場への交通案内

※ご参加の方は病院の入口ではなく、上記『大学1号館入口』（病院の裏側）よりお入り下さい。

❑ 地下鉄をご利用の場合

都営三田線『御成門』A5出口 約3分
『内幸町』A3出口 約10分
日比谷線『神谷町』3出口 約7分
銀座線『虎ノ門』1出口 約10分
銀座線・都営浅草線『新橋』8出口 約12分
都営浅草線・都営大江戸線『大門』A2出口 約13分
丸の内線・千代田線・日比谷線『霞ヶ関』C3出口 約13分

❑ JRをご利用の場合

新橋駅下車 徒歩12分

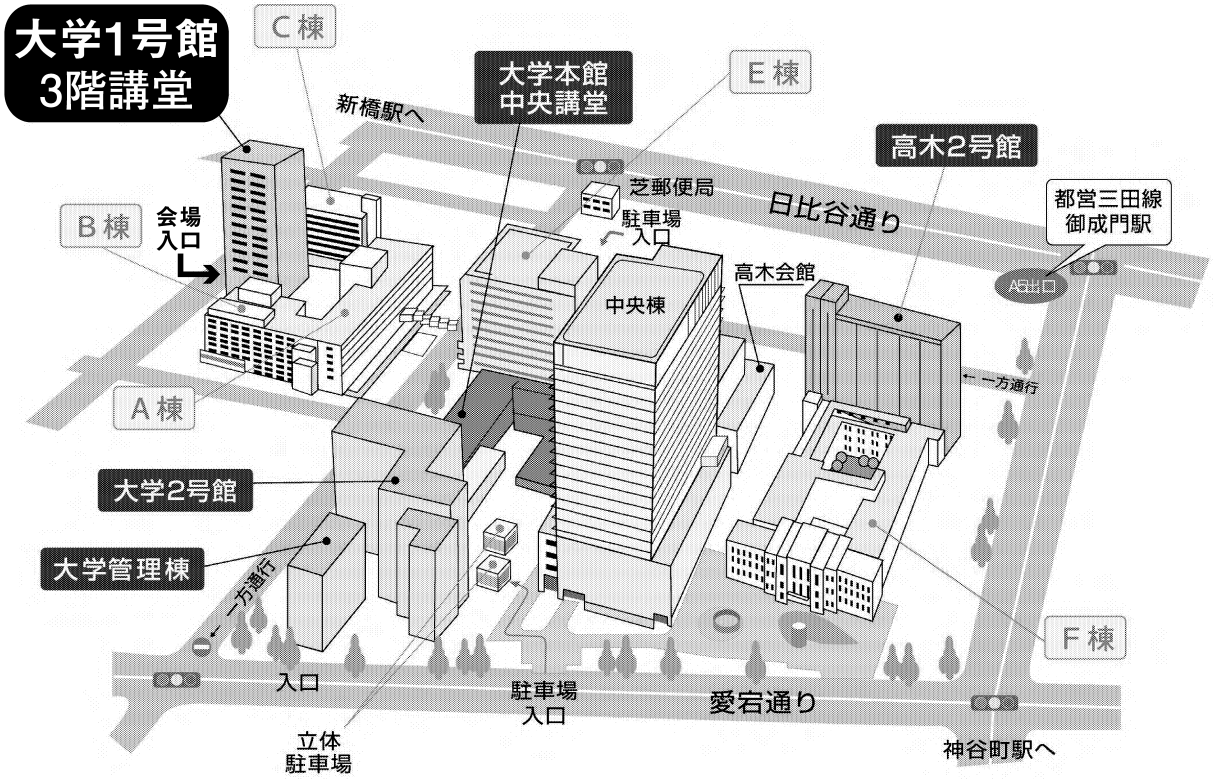
❑ バスをご利用の場合

東京駅丸の内南口（目黒駅経由）→等々力....『愛宕山下』または『慈恵会医大前』下車
目黒駅→新橋駅 ..... 『御成門』下車

会場案内図

東京慈恵会医科大学1号館 3階講堂

〒105-8461　東京都港区西新橋3－19－18
西新橋キャンパス　http://www.jikei.ac.jp/univ/access.html
施設案内　http://www.jikei.ac.jp/univ/access_s.html



お知らせとお願い

1. **会場**
   東京慈恵会医科大学1号館 3階『講堂』

2. **参加登録受付**
   東京慈恵会医科大学1号館 3階『講堂』の後方出口ホールにて行います。
   1日目：8：00～17：00
   2日目：8：00～14：00

3. **受付方法**
   東京慈恵会医科大学1号館 3階『講堂』受付にて、当日登録要旨にて必要事項をご記入の上、当日登録受付にお越しください。
   当日登録料
   参加費（会員）. 10,000円
   参加費（非会員）. 12,000円
   参加費（学生）. 5,000円
   懇親会費、プログラム･抄録集も含みます。

4. **ネームカード**
   所属・氏名をご記入の上、入場の際は必ず着用ください。
   ネームカードを着用されてないない方の入場は、ご遠慮願います。

5. **プログラム・抄録集**
   プログラム・抄録集は会期前に本学会会員に事前に送付いたします。
   プログラム・抄録集をお忘れの方、ご希望の方は、当日1部2,000円で頒布いたします。

6. **会場での呼び出し**
   会場内での呼び出しは行いません。受付周辺に伝言版を設置致しますので、ご利用ください。

7. **会場内でのご注意**
   会場内での録音・写真およびビデオ撮影は、著作権法に触れますので、固くお断りいたします。
   また、携帯電話およびポケットベルは、マナーモードに設定していただくか、電源をお切りください。

8. **会場内でのご飲食**
   会場内は禁煙ならびに飲食ならびに持ち込みも禁止しています。
   ご協力御願い致します。飲食は会場周辺の飲食店または病院内の飲食店をご利用下さい。

9. **駐車場**
   駐車場はございません。公共交通機関等をご利用ください。

10. **食事**
    会期中、ランチョンセミナーを開催いたします。
    お弁当をご用意しておりますが、数に限りがございますので、予めご了承ください。

11. 関連会議

理 事 会 ..... 2月7日(木) 16：00～17：30
三会堂ビル 2階『A会議室』(東京都港区赤坂1-9-13 財団法人農林水産奨励会)

評議員会 ..... 2月9日(土) 13：30～14：15　3階『講堂』

総　　会 ..... 2月9日(土) 14：15～14：45　3階『講堂』

学会奨励賞授与式 .... 2月8日(金) 18：30～　新橋愛宕山東急イン 新館1階

12. 学会入会申込み

会期中、新規入会・年会費受付デスクを設けております。
巻末綴じ込みの入会申込書・変更届をご利用ください。

なお、年会費は、役員は年額10,000円、評議員は年額7,000円、正会員は年額3,000円です。
また入会の申込みについては、下記にお問合せください。

◆ 日本微小循環学会事務局［お問合せ先］

〒160-0016　東京都新宿区信濃町35　信濃町煉瓦館5階
(財)国際医学情報センター内
TEL：03-3359-0443
FAX：03-5361-7091
E-mail：js-micro@imic.or.jp

次回開催情報

第39回日本微小循環学会総会

会 期：2014年2月7日(金)・8日(土)

会 場：北里大学 白金キャンパス薬学部コンベンションホール

会 長：中村 正彦
(北里大学薬学部 臨床医学 (大講座) 病態解析学)

❑ 特別講演

日　時：2月8日(金)　16：00～17：00
場　所：1号館 3階『講堂』
演　題：Branch or expand? Endothelial cell dynamics regulating vascular patterning
講演者：Holger Gerhardt
座　長：末松　　誠 (慶應義塾大学)

❑ 招待講演

日　時：2月9日(土)　11：00～12：00
場　所：1号館 3階『講堂』
演　題：Pancreatic Microcirculation and Exacerbation of Acute Pancreatitis
講演者：竹山　宜典 (近畿大学)
座　長：西野　博一 (東京慈恵会医科大学)

❑ 教育講演

日　時：2月8日(金)　13：15～14：15
場　所：1号館 3階『講堂』
演　題：Approach to understand immune system based on spatiotemporal regulation of immune cells in the entire body
講演者：戸村　道夫 (京都大学)
座　長：馬嶋　正隆 (北里大学)

❑ ランチョンセミナー 1

日　時：2月8日(金)　12：00～13：00
場　所：1号館 5階『会議室』
演　題：高血圧と臓器障害 ―重要臓器に刻印された日本人の記憶―
講演者：柏原　直樹 (川崎医科大学)
座　長：中村　正彦 (北里大学)
共　催：武田薬品工業株式会社

❑ ランチョンセミナー 2

日　時：2月9日(土)　12：15～13：15
場　所：1号館 5階『会議室』
演　題：機能性消化管障害と臓器微小循環
講演者：鈴木　秀和 (慶應義塾大学)
座　長：永田　博司 (けいゆう病院)
共　催：第一三共株式会社 / アストラゼネカ株式会社

❑ イブニングセミナー

日　時：2月8日(金)　17：00～17：45
場　所：1号館 3階『講堂』
演　題：Role of hydrogen sulfide in regulating metabolic systems and microcirculation
講演者：末松　　誠 (慶應義塾大学)
座　長：西野　博一 (東京慈恵会医科大学)
共　催：大塚製薬株式会社

※イブニングセミナー終了後、新橋愛宕山東急インにて学会奨励賞・懇親会を行います。
多くの皆様のご参加をお待ちしております。

❑ 口演規定

口頭発表について

1. データ・パソコン受付

メディア（USBフラッシュメモリ）持込みの方は発表の60分前までにPCセンターにご持参ください。
パソコンを持込みの方はPCデータ受付後、発表の30分前までに発表会場の左手前方のオペレーター席までパソコンをご持参ください。

2. 発表時間

一般演題発表：発表12分＋質疑3分　計15分
セッションは事前のご案内どおりの進行をお願いいたします。

3. 発表形式

パソコン発表のみとさせていただきます。スライドプロジェクターの用意はございません。
パソコン発表に際しては、下記の点にご注意ください。

【Windows】

1) USBフラッシュメモリ（以下メディア）、またはご自身のPCをお持込みください。
（インターフェイスのトラブルを避けるため、データ持込はメディアを推奨します。）
2) 会場ではWindows7、アプリケーションはPowerPoint2003/2007/2010のPCをご用意しております。
3) フォントは文字化けを防ぐため下記のフォントで作成してください。
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◆英　語（Century、Century Gothic、Times New Roman、Arial）
4) USBフラッシュメモリはWindowsで読み込み可能なもののみとさせていただきます。
5) データファイル名は「演題番号」「氏名」の順でつけてください。
【例】O-160　山田太郎
6) お持込みのメディアの中には発表データ以外は入れないでください。

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4) 動画や音声の再生はできません。
5) 発表終了後、パソコンは会場内で返却いたします。

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日程表

	2月8日（金）	February 8 (Fri.)
9:00	8：55～ 開会の辞	8：55～ Opening Remarks
	9：00 **学会奨励賞候補者講演1** Y-1～Y-4 座長：馬嶋　正隆 10：00	9：00 **Applicants' Presentations for Young Investigators Award 1** Y-1～Y-4 Chair：Masataka Majima 10：00
10:00	10：00 **学会奨励賞候補者講演2** Y-5～Y-7 座長：岡田　英吉 10：45	10：00 **Applicants' Presentations for Young Investigators Award 2** Y-5～Y-7 Chair：Eikichi Okada 10：45
11:00	10：45 **学会奨励賞候補者講演3** Y-8～Y-10 座長：鈴木　秀和 11：30	10：45 **Applicants' Presentations for Young Investigators Award 3** Y-8～Y-10 Chair：Hidekazu Suzuki 11：30
12:00	12：00 [5階 会議室] **ランチョンセミナー1** LS1　柏原　直樹 座長：中村　正彦 共催：武田薬品工業（株） 13：00	12：00 [5 Floor] **Luncheon Seminar 1** LS1　Naoki Kashihara Chair：Masahiko Nakamura Sponsored by Takeda Pharmaceutical Co., LTD. 13：00
13:00	13：15 **教育講演** EL　戸村　道夫 座長：馬嶋　正隆 14：15	13：15 **Educational lecture** EL　Michio Tomura Chair：Masataka Majima 14：15
14:00	14：15 **一般演題1** F-1～F-4［脳、神経］ 座長：鈴木　則宏 15：15	14：15 **Free Paper 1** F-1～F-4［Brain, Nerve］ Chair：Norihiro Suzuki 15：15
15:00	15：15 **一般演題2** F-5～F-7［脳、網膜循環、その他］ 座長：長岡　泰司 16：00	15：15 **Free Paper 2** F-5～F-7［Brain, Retinal Circulation, Others］ Chair：Taiji Nagaoka 16：00
16:00	16：00 **特別講演** SL　Prof. Holger Gerhardt 座長：末松　誠 17：00	16：00 **Special Lecture** SL　Holger Gerhardt Chair：Makoto Suematsu 17：00
17:00	17：00 **イブニングセミナー** ES　末松　誠 座長：西野　博一 共催：大塚製薬（株） 17：45	17：00 **Evening Seminor** ES　Makoto Suematsu Chair：Hirokazu Nishino Sponsored by Otsuka Pharmaceutical Co., LTD. 17：45
18:00	18：30～ **学会奨励賞・懇親会** 於：新橋愛宕山東急イン	18：30～ **Award Ceremony / Reception** at Shinbasi Atagoyama Tokyu Inn

Program at a Glance

	2月9日(土)	February 9 (Sat.)
9:00		
	9：00 **一般演題3** F-8～F-11［消化器、虚血・再灌流］ 座長：穂刈 量太 10：00	9：00 **Free Paper 3** F-8～F-11 [Digestive Organs, Ischemia, Reperfusion] Chair：Ryota Hokari 10：00
10:00	10：00 **一般演題4** F12～F15［癌、心臓・腎臓］ 座長：山本 哲郎 11：00	10：00 **Free Paper 4** F-12～F-15［Cancer, Heart, Kidney］ Chair：Tetsuro Yamamoto 11：00
11:00	11：00 **招待講演** IL 竹山 宜典 座長：西野 博一 12：00	11：00 **Invited Lecture** IL Yoshifumi Takeyama Chair：Hirokazu Nishino 12：00
12:00		
	12：15 **ランチョンセミナー 2** ［5階 会議室］ LS2 鈴木 秀和 座長：永田 博司 共催：第一三共(株) / アストラゼネカ(株) 13：15	12：15 **Luncheon Seminar 2** [5 Floor] LS2 Hidekazu Suzuki Chair：Hiroshi Nagata Sponsored by Daiichi Sankyo Co., LTD. Astrazeneca Co., LTD. 13：15
13:00		
	13：30 **評議員会** 14：15	13：30 **Council Meeting of JSMC** 14：15
14:00	14：15 **総 会** 14：45	14：15 **General Assembly of JSMC** 14：45
	14：45～ 閉会の辞	14：45～ Closing Remarks
15:00		
16:00		
17:00		
18:00		

Friday, February 8, 2013

8:55 – 9:00

Opening Remarks President : Hirokazu Nishino

9:00 – 10:00

Applicants' Presentations for Young Investigators Award 1 Chair : Masataka Majima

Y-1 **Effects of Prostacyclin on Isolated Porcine Retinal Arterioles: Cross-Talk between Nitric Oxide and Prostacyclin**

Shinji Ono, Taiji Nagaoka, Tsuneaki Omae, Takayuki Kamiya, Akitoshi Yoshida

Department of Ophthalmology, Asahikawa Medical University, Asahikawa, Japan.

Y-2 **Sphingosine 1-phosphate elicits constriction of isolated porcine retinal arterioles**

Takayuki Kamiya, Taiji Nagaoka, Tsuneaki Omae, Shinji Ono, Akitoshi Yoshida

Department of Ophthalmology, Asahikawa Medical University

Y-3 **Effect of Nitric Oxide on Increased Retinal Blood Flow in Response to Flicker Stimuli in Cats**

Takafumi Yoshioka, Taiji Nagaoka, Akitoshi Yoshida

Department of Ophthalmology, Asahikawa Medical University, Asahikawa, Japan

Y-4 **Ultra-wide field fluorescein angiography in patients with retinal vascular disorders**

Shuichiro Hirahara, Taneto Tomiyasu, Norihiro Suzuki, Ikuko Shimada, Satoshi Ota, Miho Nozaki, Munenori Yoshida, Yuichiro Ogura

Department of Ophthalmology and Visual Science, Nagoya City University Graduate School of Medical Sciences

10:00 – 10:45

Applicants' Presentations for Young Investigators Award 2 Chair : Eikichi Okada

Y-5 **Repeated 3D live imaging of microvascular-astroglia restructuring induced by hypoxia in mouse cerebral cortex.**

Kazuto Masamoto[1,2)], Hiroyuki Takuwa[2)], Takuma Sugashi[1)], Yukio Yamada[1)], Yutaka Tomita[3)], Miyuki Unekawa[3)], Haruki Toriumi[3)], Yoshiaki Itoh[3)], Norihiro Suzuki[3)], Hiroshi Ito[2)], Iwao Kanno[2)]

[1)]University of Electro-Communications, [2)]National Institute of Radiological Sciences, [3)]Keio University

Y-6 **Metabolic responses to mild hypothermia treatments after hypoxia-ischemia in newborn rats**

Toshiki Takenouchi[1)], Mayumi Kajimura[2,3)], Tsuyoshi Nakanishi[2,4)], Takako Hishiki[2,3)], Yoshiko Nagahata[3)], Tadao Sugioka[2)], Akiko Kubo[2)], Takayuki Morikawa[2)], Takao Takahashi[1)], Makoto Suematsu[2,3)]

[2)]Department of Biochemistry, School of Medicine, Keio University, Tokyo,
[3)]JST, ERATO, Suematsu Gas Biology Project, Tokyo, Japan,
[4)]MS Business Unit, Shimadzu Corporation, Kyoto, Japan,
[1)]Department of Pediatrics, School of Medicine, Keio University, Tokyo

Y-7 **Development of a Cell Culture Microdevice with Oxygen Gradient as a Model for Microvascular Environment**

Asako Sato[1)], Hideyuki Uchida[2)], Akira Miyayama[2)], Kosuke Tsukada[1,2)]

[1)]Department of Applied Physics and Physico-Informatics, Keio University,
[2)]Graduate School of Fundamental Science and Technology, Keio University

10:45 – 11:30

Applicants' Presentations for Young Investigators Award 3

Chair : Hidekazu Suzuki

Y-8 **Amelioration of NSAID-induced small intestinal lesions by Toll-like receptor 2 agonist through decreasing leukocytes migration to intestinal mucosa.**

Kazuyuki Narimatsu, Ryota Hokari, Yuuichi Yasutake, Hirokazu Sato, Chie Kurihara, Yoshikiyo Okada, Chikako Watanabe, Shunsuke Komoto, Kengo Tomita, Atsushi Kawaguchi, Shigeaki Nagao, Soichiro Miura

Department of internal medicine, National Defense Medical College, Saitama, Japan

Y-9 **Expression of toll-like receptors in glomerular endothelial cells under diabetic conditions**

Takata, S[1)], Uchiyama, T[1)], Tsuruga, E[2)], Hatakeyama, Y[2)], Ishikawa, H[1)], Sawa, Y[2)]

[1)]Department of Oral Growth & Development, Fukuoka Dental College,
[2)]Department of Morphological Biology, Fukuoka Dental College

Y-10 **Impaired blood flow recovery in streptozotocin induced Diabetes Mellitus mice by down regulation of VEGFR1TK signaling**

Kazuhito Oba, Hideki Amano, Takehito Sato, Fumihiro Ogawa, Koji Eshima, Shinichiro Okizaki, Hirotoki Okubo, Chie Kurashige, Mariko Kamata, Masayoshi Shichiri, Masataka Majima

Kitasato University

12:00 – 13:00

Luncheon Seminar 1

Chair : Masahiko Nakamura

Sponsored by Takeda Pharmaceutical Co., LTD.

LS1

Naoki Kashihara

13:15 – 14:15

Educational lecture

Chair : Masataka Majima

EL **Approach to understand immune system based on spatiotemporal regulation of immune cells in the entire body**

Michio Tomura[1)], Kenji Kabashima[1)], Osami Kanagawa[2)]

[1)]Kyoto University Graduate School of Medicine, [2)]RIKEN

14:15 – 15:15

Free Paper 1 [Brain, Nerve]

Chair : Norihiro Suzuki

F-1 **Effect of argatroban on laser-induced thrombus formation in murine brain microvasculature observed on intravital fluorescence microscopy**

Hajime Maruyama, Takuya Fukuoka, Norio Tanahashi

Department of Neurology and Cerebrovascular Medicine, Saitama Medical University International Medical Center, JAPAN

F-2 **Propagation of changes in diameter of pial arteries and cerebral blood flow following cortical spreading depression in anesthetized mice**

Miyuki Unekawa[1)], Yutaka Tomita[1)], Haruki Toriumi[1)], Takashi Osada[1,2)], Kazuto Masamoto[3,4)], Yoshiaki Itoh[1)], Iwao Kanno[4)], Norihiro Suzuki[1)]

[1)]Department of Neurology, Keio University, [2)]Department of Neurology, Tachikawa Hospital, [3)]Center for Frontier Science and Engineering, University of Electro-Communications, [4)]Molecular Imaging Center, National Institute of Radiological Sciences

F-3 **Deletion of HO-2 impairs an ability to maintain ATP and energy charge following acute cerebral ischemia**

Takayuki Morikawa[1)], Mayumi Kajimura[1,2)], Tsuyoshi Nakanishi[1,3)], Yoshinori Yukutake[2)], Yoshiko Nagahata[2)], Makoto Suematsu[1,2)]

[1)]Department of Biochemistry, School of Medicine, Keio University, Tokyo, [2)]JST, ERATO, Suematsu Gas Biology Project, Tokyo, Japan, [3)]MS Business Unit, Shimadzu Corporation, Kyoto, Japan

F-4 **Cerebral arteriolar responses and immediately after MCAO and reperfusion**

Mami Ishikawa[1,2)], Mayumi Kajimura[1)], Takayuki Morikawa[1)], Tomomi Nakamura[1)], Haruna Kamochi[2)], Akira Ebihara[2)], Gen Kusaka[2)], Yuichi Tanaka[2)], Makoto Suematsu[2)]

[1)]Department of Biochemistry, School of Medicine, Keio University, [2)]Department of Neurosurgery, Saitama Medical Center, Jichi Medical University

15:15 – 16:00

Free Paper 2 [Brain, Retinal Circulation, Others] Chair : Taiji Nagaoka

F-5 **Post-stroke administration of cilostazol changes metabolic profiles of ischemic brain in a mouse model**

Yasoo Sugiura[1,4], Mayumi Kajimura[1,2], Katsuji Hattori[1], Tsuyoshi Nakanishi[1,3], Takayuki Morikawa[1], Yoshiko Nagahata[2], Takako Hishiki[1,2], Makoto Suematsu[1,2]

[1]Department of Biochemistry, School of Medicine, Keio University, Tokyo,
[2]JST, ERATO, Suematsu Gas Biology Project, Tokyo, Japan,
[3]MS Business Unit, Shimadzu Corporation, Kyoto, Japan,
[4]Department of Pulmonary and Thoracic Surgery, Kanagawa National Hospital, Hadano

F-6 **Retinal angiography for small animals with ultra-wide-field scanning laser ophthalmoscope (Optos)**

Miho Nozaki, Shuichiro Hirahara, Tomoaki Hattori, Satoshi Ohta, Yuichiro Ogura

Department of Ophthalmology and Visual Science, Nagoya City University Graduate School of Medical Sciences

F-7 **Effects of the administration of anti-oxidants on ultraviolet B-induced leukocytes adhesion in the mouse dorsal skinfold chamber**

Akira Ushiyama[1], Chika Ohsawa[2], Shiori Fujita[2], Tomomi Suwa[2], Masako Ohsawa[1], Kazuyuki Ishii[2], Makishge Asano[1]

[1]National Institute of Public Health, [2]Meiji Pharmaceutical University

16:00 – 17:00

Special Lecture Chair : Makoto Suematsu

SL **Branch or expand? Endothelial cell dynamics regulating vascular patterning**

Holger Gerhardt

Vascular Biology Laboratory, London Research Institute – Cancer Research UK,
Vascular Patterning Laboratory, Vesalius Research Center, VIB3, Department of Oncology, KU Leuven

17:00 – 17:45

Evening Seminor Chair : Hirokazu Nishino

Sponsored by Otsuka Pharmaceutical Co., LTD.

ES **Role of hydrogen sulfide in regulating metabolic systems and microcirculation**

Makoto Suematsu

18:30 –

Award Ceremony / Reception at Shinbasi Atagoyama Tokyu Inn

Saturday, February 9, 2013

9:00 – 10:00

Free Paper 3 [Digestive Organs, Ischemia, Reperfusion] Chair : Ryota Hokari

F-8 **MALT Lymphoma Stem Cell and its Niche are related to Peculiar Microcirculatory Network in Helicobacter heilmannii-infected Mice Stomach**

Masahiko Nakamura[1)], Hidenori Matsui[2)], Tetsufumi Takahashi[1)], Kanji Tsuchimoto[1)]
[1)]School of Pharmaceutical Sciences, Kitasato University, Tokyo, Japan,
[2)]Kitasato Institute for Life Sciences, Kitasato University, Tokyo, Japan

F-9 **Role of VEGFR1 signaling in liver injury and repair following hepatic ischemia/reperfusion injury in mice**

Hirotoki Ohkubo[1,2)], Yoshiya Ito[2)], Tsutomu Minamino[1)], Kanako Hosono[1)], Masahiko Watanabe[2)], Masataka Majima[1)]
Departments of [1)]Pharmacology and [2)]Surgery, Kitasato University School of Medicine, Kanagawa, Japan

F-10 **Anti-inflammatory effects of carbon monoxide (CO) liberated by CO-releasing molecule on ischemia-reperfusion (I/R)-challenged intestinal injury in mice**

Kazuhiro Katada[1)], Yuji Naito[1)], Tomohisa Takagi[1)], Takaya Iida[1)], Katsura Mizushima[1)], Hiroyuki Yoriki[1)], Kazuhiro Kamada[1)], Kazuhiko Uchiyama[1)], Osamu Handa[1)], Nobuaki Yagi[1)], Hiroshi Ichikawa[2)], Toshikazu Yoshikawa[1)]
[1)]Department of Molecular Gastroenterology and Hepatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine,
[2)]Department of Medical Life System, Faculty of Life and Medical Sciences, Doshisha University

F-11 **Involvement of Cross-Linked Ribosomal Protein S19 Oligomers and C5a Receptor in Definitive Erythropoiesis**

Hiroshi Nishiura, Jun Chen, Umeko Semba, Tetsuro Yamamoto
Faculty of Life Science, Kumamoto University

10:00 – 11:00

Free Paper 4 [Cancer, Heart, Kidney] Chair : Tetsuro Yamamoto

F-12 **Development of CAST (cancer stromal targeting) diagnosis and therapy using anti-fibrin monoclonal antibody**

Masahiro Yasunaga[1)], Takashi Sugino[2)], Atsushi Tsuji[3)], Tsuneo Saga[3)], Shino Manabe[4)], Yasuhiro Matsumura[1)]
[1)]Investigative Treatment Division, National Cancer Center Hospital East,
[2)]Division of Pathology, Shizuoka Cancer Center, Shizuoka,
[3)]Diagnostic Imaging Program, Molecular Imaging Center, National Institute of Radiological Sciences,
[4)]Synthetic Cellular Chemistry Laboratory, RIKEN

F-13 **Reprogrammed cancer cells upregurate the expressions of angiogenesis-related genes and reactive oxygen species scavenging genes**

Akiko Saito, Hiromi Ochiai, Shoko Okada, Toshifumi Azuma
Department of Biochemistry, Tokyo Dental College, Japan

F-14 **Angiotensin Type 1 Receptor Blocker Enhances H_2O_2-induced Coronary Collateral Vasodilatation and Improves Microvascular Endothelial Dysfunction in Diabetes Mellitus and Endothelial H_2O_2 Production during Acute Coronary Occlusion in Canine Coronary Native Collateral Microcirculation in Vivo**

Toyotaka Yada[1)], Hiroaki Shimokawa[2)], Osamu Hiramatsu[1)], Masami Goto[1)], Yasuo Ogasawara[1)], Fumihiko Kajiya[1)]

[1)]Kawasaki Medical School, [2)]Tohoku University Graduate School of Medicine

F-15 **Wide inter-footprocess area in a rat at the early stage of diabetes**

Hiroshi Nakamoto[1)], Kazuhiko Nakayama[2)], Noriaki Emoto[2)], Fumihiko Kajiya[1)]

[1)]Department of Medical Engineering and Systems Cardiology, Kawasaki Medical School, Kurashiki, Okayama, JAPAN,

[2)]Clinical Pharmacy, Kobe Pharmaceutical University, Hyogo, JAPAN

11:00 – 12:00

Invited Lecture

Chair : Hirokazu Nishino

IL **Pancreatic Microcirculation and Exacerbation of Acute Pancreatitis**

Yoshifumi Takeyama, Takeshi Yasuda

Department of Surgery, Kinki University Faculty of Medicine

12:15 – 13:15

Luncheon Seminar 2

Chair : Hiroshi Nagata

Sponsored by Daiichi Sankyo Co., LTD. / Astrazeneca Co., LTD.

LS2

Hidekazu Suzuki

13:30 – 14:45

Council Meeting of JSMC
General Assembly of JSMC

14:45 –

Closing Remarks

Abstracts

Branch or expand? Endothelial cell dynamics regulating vascular patterning

Holger Gerhardt

Vascular Biology Laboratory, London Research Institute – Cancer Research UK,
Vascular Patterning Laboratory, Vesalius Research Center, VIB3, Department of Oncology, KU Leuven

Blood vessel patterning involves the iterations of sprout initiation, elongation, anastomosis, lumen formation and stabilization. Endothelial cells concurrently migrate, divide, select dynamic phenotypes and rearrange positions to allow organized branching morphogenesis. How exactly the cells orchestrate their behaviour remains poorly understood. Our recent work identified a regulatory network of VEGF-VEGFR and Dll4/Notch signalling as a key mechanism of pattern generation. Mosaic analysis in zebrafish and embryoid body sprouting assays illustrated a constant competition between cells for the leading tip cell position utilizing differential VEGFR levels. Computer simulations suggest that the coordination and timing of the competitive cell behaviour and Dll4/Notch signalling drives the angiogenic branching "pattern generator". Observations of emergent behaviour in computer simulations of pathological blood vessel growth driven by high VEGF levels, as in ischemia or tumour angiogenesis, now provide the first predictions for a mechanism of pathological vascular patterning, and possibly for organ specific branching adaptations. Studies into the dynamic regulation of Dll4 in vitro and in vivo indicate that high VEGF levels disrupt the "salt-and-pepper" pattern of Dll4 underlying branching morphogenesis. Instead, high VEGF levels promote contiguous Dll4 expression in clusters of adjacent cells that synchronize their behaviour, fail to rearrange and thus form vessel dilation domains leading to tortuosity. We propose that changes in the behaviour of the VEGF-Dll4-Notch feedback loop determine whether to branch or to expand a vessel during angiogenesis.

Further iterations of simulation and experimentation identified differential adhesion between endothelial cells as key determinant of dynamic cell rearrangements within the sprout. The pattern and endocytosis of VE-cadherin at individual endothelial cell junctions is highly differential between cells, under the control of VEGFR2 and Notch activity. We find that synchronization of Dll4/Notch signalling under pathologically high VEGF conditions halt cell rearrangements due to the loss of differential adhesion. Together, the identification of a phase transition in Dll4/Notch dynamics and the control of rearrangements by differential adhesion establish a novel mechanistic understanding of how endothelial cell signalling and behaviour is coordinated, determining whether to branch or expand new vessels during angiogenesis.

IL

Pancreatic Microcirculation and Exacerbation of Acute Pancreatitis

Yoshifumi Takeyama, Takeshi Yasuda

Department of Surgery, Kinki University Faculty of Medicine

Acute pancreatitis is a disease of autodigestion of the pancreatic gland by intrapancreatic activation of digestive enzymes due to several etiologies. In some cases, the severe damage of the gland, such as necrosis, or systemic spread of inflammatory response occurs, and severe acute pancreatitis (SAP) develops. The early pathophysiologic change in SAP is severe hypovolemia due to the increasing permeability of systemic vessels caused by the derangement of vascular endothelial cells. In fact, we have reported that plasma tissue factor which is the first mediator of extrinsic coagulation pathway is increased in the patients with SAP, indicating that the activation of coagulation pathway and derangement of vascular endothelial cells occur in SAP. It is anticipated that coagulo-fibrinolytic abnormalities affect microcirculation in the local pancreas, and that development and progression of pancreatic necrosis in acute pancreatitis is affected by microcirculatory derangements.

Acute necrotizing pancreatitis can develop in mouse by intraperitoneal injection of caerulein. To examine the effect of fibrinolytic system in the development of necrosis, this model of pancreatitis develops in α2 anti plasmin (α2 AP) deficient- and sufficient-mice. The ratio of the necrotic area was significantly lower in α2-AP deficient mice 24 h after induction of pancreatitis than in α2-AP sufficient mice. The serum levels of amylase and lipase were also significantly lower in α2-AP deficient mice after 24 h than in α2-AP sufficient mice. The immunoreactivity of von Willebrand factor (vWF) and vascular endothelial growth factor (VEGF) was detected only at the intra- and interlobular vascular endothelial cells in the pancreas from the α2-AP deficient mice 24 h after induction. These results suggest that activation of fibrinolytic system attenuates pancreatic necrosis by the acceleration of the vascular re-endothelialization via the enhanced VEGF activity.

Serum level of VFGF is significantly increased in the clinical acute pancreatitis, and animal model, and the levels of serum VEGF reflect the severity. In rat experimental SAP, intravenous administration of VEGF attenuates hepatic and renal failure, and blocks bacterial translocation. In SAP, apoptosis occurs in the majority of hepatocytes and renal tubules, and VEGF reduces the ratios of apoptotic cells. In the ileal mucosa, apoptosis occurs in mucosal epithelial cells resulting increasing permeability of the ileal wall. VEGF reduces apoptocsis and blocks bacterial translocation. Moreover, The immunoreactivity of vWF is reduced on the microvessels in the liver, kidney and ileum associated with SAP, and VEGF recovers the immunoreactivity ssignificantly.

In conclusion, microcirculation of the pancreas and the other systemic organs is damaged in SAP via vascular endothelial cell injury. Activation of fibrinolytic system may attenuate microcirculation injury via the action of plasmin and VEGF cascade.

EL

Approach to understand immune system based on spatiotemporal regulation of immune cells in the entire body

Michio Tomura[1)], Kenji Kabashima[1)], Osami Kanagawa[2)]

[1)]Kyoto University Graduate School of Medicine, [2)]RIKEN

Immune system is high-dimensional integrated system distributed in the whole body. Many kinds of, total 10^{11} of immune cells are regulated by receiving appropriate signals in appropriate places and move around the entire body. Although, there is no room for doubt that immune system consists of immune cell movement, we have no concrete information about immune cell movement under normal and pathophysiological conditions. Thus, we have been attempting to understand immune system by revealing spatiotemporal regulation of immune cells at the entire body level by "Visualization of immune response *in vivo*".

Photoconvertible protein, "Kaede"-transgenic (Tg) mice allow us to monitor cell-replacement and cell-movement between organs in the entire body by marking cells with color of Kaede from green to red with exposure to violet light.

When lymphocytes in inguinal lymph node (LN) was marked by photoconversion, we could monitor cell replacement in the photoconverted inguinal lymph node, and migration to down-stream axillary LN which directly connecting with inguinal LN by lymph vessel and distribution to other LNs *via* blood flow in a time dependent manner. By using this method, we have demonstrated that $CD4^+$T, $CD8^+$T and B cells recirculate in the entire body at their distinct rate (PNAS 2008). In addition, we also demonstrated that "Naive $CD4^+$ T cells recirculate through lymphoid organs to seek limited niche for interacting with [endogenous antigen derived peptide - MHC class II complex] to upregulate their function". Recirculation kinetics of T cell subsets were closly correlated with their interaction strength with endogenous antigens, and thus, memory phenotype and regulatory T cells recirculate slower than naive T cells (J. Immunol. 2010).

We applied Kaede-Tg system to monitor cell movement from skin to the draining (d)LN in the normal state. We found that dendritic cells (DCs) and $CD4^+$ T cells are major migrants from skin and $Foxp3^+$regulatery $CD4^+$T cells in skin also migrate to the dLN. DCs in skin work in sentinel to exogenous invasion and also meintenance of immune homeostasis. After migration to draining LN, skin-derived DC subsets stayed from 2 to 4 days and replaced by apoptosis without egrees of draining LN. Furthermore, after immunization of footpad, number of migratory DCs from immunized site to the dLN increased almost 100 times compared with that in normal state and continued for a long period, however migrated DCs in dLN replaced less than 24 houes. Thus, spatiotemporal regulation of DCs under immune response is like "Large supply and mass consumption", and rapid replacement of DCs would enable to control fine-tune of immune responses. In cutaneous contact hyper sensitivity (CHS) response, we found that "Activated regulatory T cells emigrating from CHS resion is responsible for termination of CHS reponse" (J. Clin. Invest. 2010).

I will summarize by showing data acquired by using Kaede-Tg system that immune cell movement in the normal state is more dynamic than that we have been thought, and when immune responses were elucidated, drastic changes, such as cell number increase, character and functional changes were induced to maintain immune homeostasis.

References

1) Kansen・Enshou・Men-eki, 38, 308-316 (2008). 41, 34-43 (2011).
2) Enshou to Men-eki, 19, p14-19 (2011).
3) Zikkenn-igaku-zoukan・Men-eki-kioku no seigyo to shikkan-chiryou, 2869-2876 (2011).
4) Zikkenn-igaku・29, 2607-2611 (2011).
5) Seika-gakkaishi 84, 152-202 (2011).

Y-1

Effects of Prostacyclin on Isolated Porcine Retinal Arterioles: Cross-Talk between Nitric Oxide and Prostacyclin

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Purpose: To investigate the vasomotor activity of prostacyclin (PGI_2) on porcine retinal arterioles.
Methods: Porcine retinal arterioles were isolated, cannulated, and pressurized without flow in vitro. Changes in diameter were recorded using videomicroscopic techniques. To confirm the role of the endothelium, we compared the responses before and after endothelial removal. To examine the involvement of endothelium-derived relaxing factor nitric oxide (NO), we assessed the responses in the presence of NO synthase inhibitor N^G-nitro-*L*-arginine methyl ester (L-NAME).
Results: The retinal arterioles dilated in a concentration-dependent manner in response to PGI_2. This vasodilation decreased significantly after the endothelium was removed. L-NAME significantly inhibited PGI_2-induced vasodilation comparable to denudation.
Conclusion: PGI_2 elicits vasodilation of the retinal arterioles mediated not only by the vascular smooth muscle but also the endothelium, suggesting that an endothelium-dependent component of PGI_2-induced vasodilation may be involved because of production of NO. We speculated that cross-talk between NO and PGI_2 may exist in the retinal circulation.

Y-2

Sphingosine 1-phosphate elicits constriction of isolated porcine retinal arterioles

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Purpose: Sphingosine 1-phosphate (S1P), a member of a large family of lipid metabolites called sphingolipids, induces a wide variety of biologic responses, i.e., immune responses, inflammatory processes, organ perfusion, and regulation of vascular tone in different organs through various high-affinity G-protein-coupled receptors (S1PR) 1-5. However, few reports have addressed the effect of S1P on the retinal circulation. We examined the effect of S1P to determine the signaling mechanisms involved in the retinal microvasculature.
Methods: Porcine retinal arterioles (internal diameter, 70-100 μm) were isolated, cannulated, and pressurized (55 cmH_2O) without flow in this in vitro study. Videomicroscopic techniques were used to record the changes in diameter in response to S1P.
Results: The retinal arterioles vasoconstricted in a dose-dependent manner (1 nM-10 μM) in response to S1P. This vasoconstrictive response to S1P was not attenuated after removal of the endothelium. Blockade of S1PR2 by the S1PR2 antagonist JTE-013 abolished the vasoconstrictive response to S1P, whereas the S1PR1 antagonist (compound 5) and the S1PR3 antagonist (suramin) did not affect the vasoconstrictive response. The Rho kinase inhibitor Y27632 (0.1 μM) significantly ($p<0.0001$) inhibited the effect of S1P-induced vasoconstriction.
Conclusion: S1P elicits vasoconstriction of the retinal arterioles via S1PR2 and Rho kinase.

Y-3

Effect of Nitric Oxide on Increased Retinal Blood Flow in Response to Flicker Stimuli in Cats

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PURPOSE. To investigate the role of nitric oxide (NO) in the increase in retinal blood flow (RBF) during flicker stimuli.

METHODS. Forty adult cats were used in this study. After anesthesia was induced with sevoflurane in each animal, laser Doppler velocimetry (LDV) was used to measure the vessel diameter (D) and blood velocity (V) simultaneously and calculate the RBF in the second-order retinal arterioles during flicker stimulation. In the first series of studies, the flicker frequencies and light intensities ranged from 2 to 64 Hz and 300 to 3000 lux, respectively. The durations of dark adaptation and flicker stimulation ranged from 0 to 30 minutes and 60 to 300 seconds, respectively. In the second series of studies, we injected phosphate-buffered saline (PBS) or N^G-nitro-L-arginine-methyl ester (L-NAME) into the vitreous and measured the D, V, and RBF during flicker stimuli 2 hours later.

RESULTS. Flicker stimulations from 2 to 32 Hz increased the RBF in the retinal arterioles. In contrast, flicker stimulation with 64 Hz did not affect the RBF. At 16 Hz, the increase in RBF was enhanced in response to light intensities of 300~3,000 lux, dark adaptation times of 0~30 minutes, and flicker stimulation times of 60~180 seconds. At 16 Hz, 3,000 lux, 30 minutes of dark adaptation, and 180 seconds of stimulation time, flicker stimulation resulted in a 51% increase in RBF over baseline in the PBS group (n=6) and an 11% increase in the L-NAME group (n=6), a difference that was significant ($P<0.0001$).

CONCLUSIONS. We confirmed that the LDV system allows evaluation of the flicker-induced increase in RBF in the retinal arteries in anesthetized cats. Our results suggested that NO plays an important role in the increase in RBF during flicker stimuli.

Y-4

Ultra-wide field fluorescein angiography in patients with retinal vascular disorders

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Purpose: To evaluate the fluorescein angiography(FA) findings of diabetic retinopathy(DR) and retinal vein occlusion(RVO) patients by using Ultra-wide field FA (UWFA) with Optos®200Tx.

Methods: The UWFA was performed on 154 eyes of 77 patients with DR (62 male, 15 female, average age; 60.2 years old), 32 eyes of 32 patients with branch retinal vein occlusion (BVO) (13 male, 19 female, 65.2), 11 eyes of 11 patients with central retinal vein occlusion (CVO) (3 male, 8 female, 67.0), and 12 eyes of 12 patients with RVO after photocoagulation (BVO 8 eyes, CVO 4 eyes). The fundus was divided to three zones - posterior pole, mid-periphery, and far-periphery. The location and size of capillary non-perfusion area (NPA) were evaluated in each zone.

Results: In DR patients, 126 eyes (82%) exhibited NPA. Forty five eyes (29%) had NPA in the posterior pole, 78 eyes (51%) in the mid-peripheral zone, and 41 eyes (26%) in the par-peripheral zone. Twenty-five eyes (16%)had NPA only in the mid-periphery, while 8 eyes (5%) showed NPA only in the far-periphery without any evidences of non-perfusion in the posterior pole and the mid-periphery. In BVO patients, 15 eyes (47%) exhibited NPA at the same quadrant where the vein occlusion existed. In 2 eyes (6%), the vessel leakage was found in the peripheral retina in the quadrant where vein occlusion did not exist. In CVO patients, NPA was found in 3 eyes (27%). The ratio of NPA to the whole image was calculated in order to quantify the degree of ischemia, which ranged from 1% to 81%. In post-photocoagulation RVO group, untreated NPA was found in 6 eyes (50%).

Conclusions: It was possible to evaluate the microcirculatory disturbance in the peripheral retina in DR and RVO by using UWFA. It might be possible to estimate the degree of ischemia in DR and RVO by UWFA semi-quantitatively as well as qualitatively.

Y-5

Repeated 3D live imaging of microvascular-astroglia restructuring induced by hypoxia in mouse cerebral cortex.

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Objective: A long-lasting exposure to hypoxia causes an adaptation of cerebral miscovasculature (e.g., an increase of vascular density and angiogenesis). In the present study, a spatiotemporal dynamics of the microvascular and astroglia restructuring in a process of the hypoxia-induced angiogenesis was characterized by using *in vivo* two-photon microscopy.
Methods: Tie2-GFP transgenic mice (N=12) in which endothelium had genetically expressed green fluorescent proteins (GFP) and C57BL/6J mice (N=4) were used for the experiments. The animals were anesthetized with isoflurane (1% in air), and sulforhodamine 101 (SR101, 10 mM in saline), a fluorescent marker of astroglia, was injected (8 μL/g i.p.). GFP-expressed microvessels (525/50 nm emission) and SR101-labeled astroglia or blood stream (610/75 nm emission) were concurrently imaged with two-photon microscopy (excitation at 900 nm). The image (1024 by 1024 pixels) was three-dimensionally captured up to a depth of 0.5-0.8 mm from the cortical surface with an in-plane resolution of 0.5 μm per pixel and a step size of 2.5-5 μm. After the completion of the initial imaging experiment, the animal was caged in a hypoxic room (8-9% or 10-11% oxygen), and follow-up imaging was performed repeatedly.
Results & Discussion: Hypoxic exposure predominantly caused a dilation of capillaries (< 7 μm in a diameter); 1.8 ± 0.5 and 1.4 ± 0.3 times increase of the diameter over 3 weeks for 8-9% and 10-11% oxygen conditions, respectively. At 1-2 weeks after the onset of hypoxia exposure, sprouting of a new vessel from existing capillaries was found. A mean diameter of the new vessels was 17 ± 7 μm, and their emergence rate was 15 vessels per unit volume. Astroglia soma slightly expanded after 2 weeks hypoxic exposure, whereas its processes wrapped an outside of the newly-developed vessels. No leakage of the fluorescent dye injected to blood stream was observed, which indicates a preserved blood-brain-barrier during hypoxia-induced angiogenesis.

Y-6

Metabolic responses to mild hypothermia treatments after hypoxia-ischemia in newborn rats

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Clinical trials found that after neonatal asphyxia, therapeutic hypothermia begun no more than 6 hours after birth improves long-term neurologic outcome. However, molecular mechanisms whereby lowering temperature achieves better outcomes remain unclear. To identify multifold macromolecular functions modulated by the temperature, we used non-targeted metabolomics approaches which made it possible to detect metabolic pathways responding to the treatment. Seven-day postnatal rats (male Sprague-Dawley) underwent unilateral common carotid artery occlusion followed by systemic hypoxia with 8% oxygen for 2.5 hours. Subsequently, pups were returned to 21% oxygen at either 38 °C (normothermia) or 30 °C (hypothermia) for 3 hours. Behavioral outcome was assessed with objective scale of posturing during this reoxygenation period. Brain metabolic state was then rapidly fixed by the in situ freezing to avoid autolysis of labile metabolites. Metabolites were extracted from both contra-and ipsilateral-hemispheres. With a high-throughput metabolomics using capillary electrophoresis mass spectrometry (CE/MS), contents of ~ 200 water-soluble metabolites in a single sample preparation were measured. Hypothermia caused not only decreases but also increases in metabolites. First, in the glycolytic pathway, the sums of metabolites upstream of 1,3-bisphosphoglycerate remained unchanged, while those of downstream were decreased, suggesting that glyceraldehyde 3-phosphate dehydrogenase (GAPDH) is an enzyme that is modulated. Second, metabolites such as carnitine, malonyl CoA, and branched-chain amino acids were increased, implying the existence of metabolic regulatory points that are activated rather than inactivated which may appear to be contrary to intuition of the effect of lowering temperature. Finally, metabolites with high energy phosphates including ATP, GTP, CTP, UTP, and creatine phosphate tended to increase by hypothermia. Our results suggest that mild hypothermia treatment is not the simple slowing of metabolism, but rather coordinated actions of multiple regulatory processes.

Y-7

Development of a Cell Culture Microdevice with Oxygen Gradient as a Model for Microvascular Environment

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Introduction: Diffusion of oxygen from microvessels and consumption in cells results in generation of oxygen gradient in tissues, which is also related to cellular functions *in vivo*. Mimicking the oxygen gradient for cellular experiments *in vitro* is important to clarify cellular mechanisms; however, the only way to produce hypoxic conditions at a constant level is using gas-controlled incubators. This is because currently no technique exists for creating oxygen gradient in cell culture dishes. In this study, we designed a microfluidic device to produce oxygen gradient mimicking the microcirculatory environment and estimated cellular oxygen consumption through theoretical and quantitative analyses.
Materials and Methods: The microfluidic device was made of PDMS, a polymer with high gas permeability, and was fabricated using photolithography. Microchannels for oxygen and nitrogen flow were created to generate the oxygen gradient on the PDMS surface. The oxygen gradient, which can be easily controlled by changing the size and location of gas channels, was estimated using a diffusion equation *in silico* and quantified using laser-assisted phosphorescence quenching. For cell culture experiments, HepG2 cells or HUVECs were cultured on the device for 6 hours with the oxygen gradient.
Results and Discussion: The measured oxygen gradient corresponded well to the simulated gradient, and the gradient in the presence of cells shifted to a lower pO_2 value compared to that in the absence of cells. This indicates that cellular respiration can be estimated by the amount of shift. RT-PCR showed an increase in VEGF expression according to the gradient. The changing profile of the oxygen gradient can mimic tumor hypoxic and organ-specific physiological conditions. These results suggest that our microdevice can generate oxygen gradient and can be used to study the mechanisms of cellular functions in both physiological and pathological conditions.

Y-8

Amelioration of NSAID-induced small intestinal lesions by Toll-like receptor 2 agonist through decreasing leukocytes migration to intestinal mucosa.

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Background: Although non-steroidal anti-inflammatory drugs (NSAIDs) are used widely in daily medical practice, it has been showed that NSAIDs induce more frequent small intestinal lesions as expected previously. Several aggressive factors are postulated in pathophysiology for intestinal lesions; impaired prostaglandin synthesis, increased membrane permeability, and increased migration of leukocytes to the intestinal mucosa with activation through Toll-like receptor (TLR) 4. Recently it has been reported that cross-tolerance occurs between TLR 2 and TLR 4 mediated signals due to modulation of the downstream common signaling pathways. In this study we investigated whether lipoarabinomannan (LAM), a ligand of TLR 2, could ameliorate NSAIDs-induced small intestinal ulcers through the interaction between TLR 2 and TLR 4 signaling.
Methods: Male C57BL/6 mice were used for this study. LAM (0.5mg/kg) was administered intraperitoneally five hours before the administration of indomethacin (IND, 10mg/kg). Four days later, small intestine was removed and total areas of ulcers and histological scores were evaluated. Mucosal MPO activity was determined and messenger RNA expressions of TNFα, MAdCAM, ICAM-1 and VCAM-1 were determined by quantitative RT-PCR.
In the study of leukocytes migration, splenocytes were fluorescence-labeled, and injected to recipient mice intravenously three hours after IND administration. Behaviors of leukocyte migration in small intestinal microvessels were observed by using intravital microscopy.
Results: Pretreatment with intraperitoneal LAM injection significantly attenuated the disease activity of IND-induced small intestinal lesions, accompanied with decreased MPO activity and mRNA expressions of TNFα and vascular adhesion molecules in the small intestinal mucosa. In addition, enhanced leukocytes migration by IND treatment was significantly attenuated by pretreatment with LAM.
Conclusion: IND-induced small intestinal lesions were successfully ameliorated by peritoneal treatment of TLR2 ligand through controlling leukocytes migration to the inflamed mucosa.

Y-9

Expression of toll-like receptors in glomerular endothelial cells under diabetic conditions

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In the diabetic nephropathy, the hyperplasia of both mesangium framework and glomerular capillary wall are found, and the advanced glycosylated endoproducts (AGEs) which formed by the nonenzymatic glycosylation and oxidation of the macromolecule under the hyperglycemia are thought to be the causative agent of the diabetic nephropathy. The AGEs have the immunogenicity and are recognized by the vascular endothelial cells with receptors for AGEs, called RAGE, and enhance the expression of several leukocyte endothelial adhesion molecules and cytokines, and allow mesangial cells to aggravate glomerulosclerosis by the hyperplasia of the extracellular matrix. Recently, we have immunohistochemically studied the expression of immunological molecules in the type 1 diabetes mice with streptozotocin-induced pancreatic islet destruction, and in KK/Ta-Jcl mice with the type 2 diabetes by high caloric bait. The confocal laser microscopy revealed that under the diabetic condition in both type 1 and 2 diabetic mice, PECAM-1 and VE-cadherin-possitive glomerular endothelial cells express toll-like receptors 2 and 4 which are not found in glomeruli with normal condition. The expression of TLR2 and 4 was not observed in glomerular epithelial podocytes and the mesangial cells, and was not in epithelial cells of blood vessels outside glomeruli. The expression is present for the whole cortex of kidney, furthermore, it revealed the expression of TLR2 in not only the glomerulus blood vessel but also the lumen side of the distal tubule epithelium unlike TLR4. It is thought that the expression of TLR occurs in glomerular capillaries under the long-term oxidative stress environment with AGE accumulation. Diabetic nephropathy by the glomerulosclerosis may be accelerated by pathogen-associated molecular patterns which invaded into the systemic circulation, being recognized to glomerular capillary endothelial cells through TLRs.

Y-10

Impaired blood flow recovery in streptozotocin induced Diabetes Mellitus mice by down regulation of VEGFR1TK signaling

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Impaired wound healing is a major clinical problem in patients with diabetes mellitus (DM). Vascular endothelial growth factor (VEGF) and its receptors promote angiogenesis. We hypothesized that the expression of VEGF receptors impaired in DM mice and that influenced recovery from ischemic condition.
6-8 weeks C57Bl/6 mice (WT) and VEGFR1-tyrosine kinase knockout mice (VEGFR1-TKKO) were used. Diabetes was induced by a single intraperitoneal injection of 150mg/kg streptozotocin (STZ). The model of hind limb ischemia was made by ligated the femoral artery in the left limb. The expression of VEGF receptor was analyzed by real time PCR analysis. Furthermore, flow cytometry analysis, immunofluorescent analysis and ELISA analysis were performed.
Compared to other receptors, the expression of VEGFR1 and hematopoietic maker was significantly suppressed following after 4 week after STZ injection ($P<0.05$). The expression of VEGFR1, not VEGFR2, in the ischemic muscle was significantly suppressed in DM mice ($P<0.05$). The hematopoietic marker, SCF, SDF-1 and pro-MMP-9 were significantly suppressed in DM mice ($P<0.05$). Furthermore, progenitor cells expressing $CXCR4^{+}VEGFR1^{+}$ cells were significantly suppressed in DM mice ($P<0.05$). In VEGFR1TKKO mice, there was no the blood flow recovery changes between control mice and DM mice ($P>0.6$).
These results suggested that DM suppress blood flow recovery from ischemic condition by down regulation of VEGFR1TK signaling.

F-1

Effect of argatroban on laser-induced thrombus formation in murine brain microvasculature observed on intravital fluorescence microscopy

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Purpose: Using a laser, we developed a technique to instantaneously induce thrombus formation in murine brain microvasculature. The purpose of this study was to observe the effect of argatroban on the process of laser-induced thrombus formation and platelet behavior in the brain microvasculature of mice using intravital fluorescence microscopy.
Methods: C57BL/6J mice (n=15) were anesthetized with chloral hydrate. Eight mice were given continuously argatroban (0.3 mg/h/mouse) injected into femoral vein during the experiment (argatroban group). Seven mice served as controls (control group). Their head was fixed with a head holder, and a cranial window was prepared in the parietal region. Platelets were labeled in vivo by intravenous administration of carboxylfluorescein succinimidylester (CFSE). Laser irradiation (1000 mA, DPSS laser 532 nm, TS-KL/S2; Sankei) was spotted for 4 seconds on pial arteries to induce thrombus formation. Labeled platelets and thrombus were observed continuously with a fluorescence microscope.
Results: After laser irradiation to the pial artery, the complete occlusion rate was significantly higher in the control group (60%, 12/20 vessels, vessel diameter 28.3±5.4μm) than in the argatroban group (20%, 4/20 vessels, vessel diameter 26.2±5.1μm). Thirty minutes after laser irradiation, the area of platelet thrombus was significantly higher in the control group (358±256μm^2) than in the argatroban group (153±94μm^2).
Conclusion: Argatroban significantly inhibited laser-induced thrombus formation in mice pial arteries.

F-2

Propagation of changes in diameter of pial arteries and cerebral blood flow following cortical spreading depression in anesthetized mice

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Background: Cortical spreading depression (CSD), a propagating phenomenon of depolarizing neurons and astroglia, affects cortical blood flow by unknown mechanisms.
Objective: To elucidate temporal and spatial response of the diameter of pial arteries and cortical cerebral blood flow (CBF) to propagation of CSD.
Methods: To visualize blood vessels, we used Tie2-GFP transgenic mice (N=12), in which specifically vascular endothelial cells emit fluorescence. Under urethane anesthesia and artificial ventilation, a cranial window was installed on the temporo-parietal region of the cerebral cortex. KCl (1 M) was applied on the brain surface through a burr hole posterior to the cranial window to elicit CSD. Diameter of pial arteries was measured with the confocal laser-scanning fluorescence microscopy and an image analysis software ImagePro. DC potential was recorded at both sides of the window along with CBF by laser Doppler flowmeter. Each confocal image was subtracted from the preceding one to visualize CSD wave as a propagating dark band where neuronal swelling was reported to alter the light intensity.
Results: Immediately after the first CSD wave arrived (90.8±59.7 s after KCl application), pial arteries constricted markedly and then dilated gradually in all mice, together with increase and decrease of CBF in a similar time course. As the CSD wave propagated, constricted region of the pial arteries moved even within a single artery. Among the repeated waves (n=34 in total), most CSD waves (n=30) moved in the direction straightly away from the application, whereas small number of waves (n=4) were presumed to turn around. The propagation of the region of arterial constriction coincided with that of CSD.
Conclusion: Diameter of pial arteries in each segment may be controlled by the local activity of neurons and astroglia neighboring the vessel during CSD.

F-3

Deletion of HO-2 impairs an ability to maintain ATP and energy charge following acute cerebral ischemia

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Brain generates a micromolar order of carbon monoxide (CO) *via* heme oxygenase (HO) reactions. Previous study postulated that HO-2 generates CO in an O_2-dependent manner and reserve the capacity to dilate cerebral arterioles upon hypoxia through a mechanism involving the ability of CO to inhibit an H_2S producing system. By acting as an acute O_2 sensor within the neurovascular unit, HO-2 contributes to the maintenance of cerebral ATP levels against acute global hypoxia (Morikawa *et al.*, PNAS, 109, 1293-1298). Here, we extended the idea and tested the hypothesis that the deletion of HO-2 exacerbates cerebral energy metabolism during acute focal brain ischemia. To this end, we conducted quantitative imaging mass spectrometry (Q-IMS) analysis for adenylates and lactate (Hattori *et al.*, Antioxid Redox Signal; 13, 1157-1167) to decipher local cerebral responses of energy metabolism from wild-type (WT) and HO-2-null mice that underwent a 60-min occlusion of the left middle cerebral artery (MCAO). In ipsilateral hemispheres, MCAO caused elevation of AMP, ADP, and lactate, and depletion of ATP in both WT and HO-2 null mice. Ischemic core area assigned by the ATP contents (<1.6 μmol/g tissue) was larger in HO-2-null than WT mice. Striking differences were found in the contralateral hemispheres, where the levels of ADP, AMP and lactate in HO-2-null mice were significantly higher than those in WT mice keeping a 30% higher ATP level than the HO-2 null. These results suggest that the HO-2/CO system plays key roles in protecting against ischemia not only at the regions of ischemic foci where the severe reduction of blood flow occurs, but it also protects even more effectively in the regions of trans-hemispheric diaschisis where only a subtle reduction of blood flow takes place.

F-4

Cerebral arteriolar responses and immediately after MCAO and reperfusion

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Aim: Penetrating and pre-capillary arteriolae regulate cerebral blood flow in parenchyma. It is difficult to investigate the mechanism accurately by measuring diameters of arteriolae on the cerebral surface, because the arterial flow on the cerebral surface is often kept by blood supply from collateral anastomoses, even when blood flow decreases in the parenchyma. We investigated responses of arteriolae within the parenchyma after the middle cerebral artery occlusion and reperfusion (MCAOR) and also observed astrocytes of GFAP-GFP mice in order to investigate responses of astrocytes after MCAOR, using two-photon laser scanning microscopy.
Methods: Anaesthetized GFAP-GFP mice (n=6) were equipped with cranial window after preparing MCAO with prone-thread model (Ishikawa et al, Stroke 1999). Using two-photon laser scanning microscopy, diameters of penetrating and pre-capillary arteriolae within parenchyma were measured after injecting Qdots and immediately after MCAO (15min) and reperfusion and astrocytes around these vessels were observed.
Results: During MCAO, the diameters of the arteriolae varied in each animal. The diameter of the penetrating arteriole increased from 13.4 +/- 6.5 μm to 15.1 +/- 7.8 μm within one minute after reperfusion and then decreased from that to 10.5 +/- 3.8 μm within 10 minutes after reperfusion. The diameter of the pre-capirally arteriole increased from 6.7 +/- 1.8 μm to 7.6 +/- 2.4 μm within one minute after reperfusion and decreased from that to 5.1 +/- 0.8 μm within 10 minutes after reperfusion. Fluorescent intensity of GFAP-GFP decreased during MCAO and increased after reperfusion, compared to pre-MCAO level.
Conclusion: With two-photon laser scanning microscopy and prone-thread MCAO model, the changes of arteriolar diameter and fluorescent intensity of GFAP-GFP mice were observed. Mechanisms of the microvascular responses should be further investigated.

F-5

Post-stroke administration of cilostazol changes metabolic profiles of ischemic brain in a mouse model

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Background and Purpose: Cilostazol, an inhibitor of phosphodiesterase3 (PDE3), has been suggested to minimize post-stroke cognitive impairment. However, mechanisms underlining these beneficial effects remain elusive. We, therefore, examined effects of cilostazol on biochemical characteristics of cerebral metabolism using mouse cerebral ischemia model *in vivo*.
Methods: Focal ischemia was induced by a left middle cerebral artery occlusion. Right after the induction of ischemia, either the cilostazol (30 mg/kg or 100 mg/kg) or vehicle was administered orally. At 60 min after the occlusion, metabolic processes were rapidly suspended by the *in situ* freezing to minimize autolytic changes. Metabolites were extracted and measured with high-throughput capillary electrophoresis mass spectrometry.
Results: Cilostazol treatment altered profiles of various metabolic pathways in the ischemic brain. First, it increased the total sum of metabolites belonging to glycolytic, Krebs cycle and pentose phosphate pathways in the contralateral hemisphere, suggesting an increased blood flow and/or a concomitant increase in the glucose uptake. Second, cilostazol treatment caused a marked decrease in NADH in both hemispheres, which may bring about attenuating acitvity of xanthine oxidase, an NADH-dependent superoxide producing enzyme. Finally, contents of cyclic AMP were dose-dependently increased in not only contralateral but also ipsilateral hemispheres suggesting that this PDE3 inhibitor was delivered to brain parenchyma even during ischemia.
Conclusions: These results indicate that cilostazol acts not only on the platelet to prevent thrombus formation *via* PDE inhibition, but also on yet identified receptors involving multiple metabolic remodeling that may lead to beneficial therapeutic stratagem in cerebrovascular diseases.

F-6

Retinal angiography for small animals with ultra-wide-field scanning laser ophthalmoscope (Optos)

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Purpose: Optos®200Tx is a confocal laser scanning ophthalmoscope with a parabolic mirror designed to obtain wide-field images of the retina, up to 200°, in one single image. And this image can be obtained without mydriasis in human. The purpose of this study is to evaluate the usability of ultra-wide field imaging (Optos®200Tx) for the rodent model of several eye diseases.
Methods: C57BL/6J male mice, 8-weeks-old and Brown-Norway male rats, 4-6 weeks old were used. Mouse model of laser-induced choroidal neovascularization was employed to test fluorescein angiography in Optos and regular fundus camera (angle at 50°) with 20D lens. Rat model of ischemic reperfusion was used to evaluate the leukostasis using acridine orange fluorography.
Results: All mice and rats were examined without any contact lens using Optos after mydriasis. For mouse fluorescein angiography, the choroidal neovascularization was clearly visible in one single image, and the venules and capillaries were also visualized by Optos. For rat acridine orange fluorography, Optos could not evaluate leukocyte rolling phenomenon and velocity, but could evaluate leukostasis in retina.
Conclusions: Theoretically, Optos®200Tx can capture wide-field fundus image through 2 mm diameter pupil. From our results, the Optos®200Tx may serve as a valuable tool to evaluate microvascular change and leukocyte in vivo in rodent model eye.

F-7

Effects of the administration of anti-oxidants on ultraviolet B-induced leukocytes adhesion in the mouse dorsal skinfold chamber

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OBJECTIVE: We previously demonstrated that ultraviolet B (UVB: wave length 280 – 315 nm) irradiation to mouse skin induced acute microcirculatory effects, i.e., vascular dilation, increase in vascular permeability and leukocyte-endothelial interaction, which was caused by reactive oxygen due to UVB. The objective of the present study was to evaluate effects of anti-oxidants such as vitamin E (VE) and green tea catechins (GTC) on leukocyte-endothelial interactions by UVB irradiation (UVBIR) using the mouse-dorsal skin chamber (DSC) as an experimental model.
METHODS: DSCs were installed to female hairless HR-1 mice by surgical procedure at least 72 hours prior to the experiment. We examined 4 experimental conditions; UVBIR only, anti P-selectin antibody treatment+UVBIR, VE administration+UVBIR and GTC administration+UVBIR. To visualize the leukocytes behaviors *in vivo*, a bolus of rhodamine 6G solution was injected into tail vein prior observation. Before and after UVBIR (240 mJ/cm^2) to the skin within the chamber, fluorescent images at the same microvasculature were recorded by using a fluorescence microscopy under conscious conditions. Off-line analysis of the leukocyte-endothelial interaction was done by counting numbers adhering and rolling leukocytes within venules for 30 sec per unit area. VE was administrated twice a day (25 μl/each) for 3 days and 1 hour before the UVBIR via feeding tube. Dissolved GTC in water (10mg/each) was administrated 1 hour before the UVBIR via feeding tube.
RESULTS: The mean value of rolling leukocytes number was significantly higher in the venules at 6 hours after UVBIR than that in pre-UVBIR. This increase was suppressed when anti-mouse P-selectin antibody was injected into tail vein prior to UVBIR. When VE or GTC was administrated prior to UVBIR, increase of rolling leukocytes number was also suppressed.
CONCLUSIONS: Our findings suggest that the administrations of anti-oxidants show the preventive effect on UVB induced leukocyte-endothelial interaction which is mainly mediated by P-selectin.

F-8

MALT Lymphoma Stem Cell and its Niche are related to Peculiar Microcirculatory Network in Helicobacter heilmannii-infected Mice Stomach

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Background & Aims: Although cancer and leukemia stem cells are indispensable in the initiation and enlargement of lesions, the gastric MALT lymphoma is thought to be polyclonal with the persistent infection of Helicobacter species and then change to monoclonal with genetic aberrations, and the participation of stem cells in the tumor formation remains to be elucidated. We performed a histochemical analysis in *Helicobacter heilmannii*-induced gastric and hepatic MALT lymphoma in the infected alone and eradicated after infection groups.
Materials and Methods: We used a Helicobacter heilmannii sample isolated from the stomach of a cynomolgus monkey and maintained in C57BL/6 mouse stomachs. Mucosal homogenates were used to inoculate C57BL/6 mice, which were then examined over 24 months. Macroscopic observations were carried out, and PCR analysis of the bacteria of the Helicobacter species was performed at intervals over the observation period. Histochemical analysis was performed using the gastric and hepatic MALT lymphoma with monoclonal and polyclonal stem cell-related antibodies against doublecortin-like kinase (DCAMKL1), Musashi-1, proliferating cell nuclear antigen (PCNA), CD44, CD133, as well as myofibroblast, endothelial, and pericyte markers.
Results: DCAMKL1, Musashi-1, CD144 positivities were not recognized in the early stage of the lymphoma formation but gradually found in the lymphocytes located in the marginal zone of the MALT lymphoma both in the gastric and hepatic MALT lymphoma. The well-developed microcirculatory network accompanied the stem cell rich area. The myofibroblasts were also distributed in these area, suggesting the formation of stem cell niche similar to that found in epithelial cells.
Conclusions: MALT lymphoma stem cells were found to exist in the marginal zone of the lymphoma, constituting the niche by the myofibroblast and microcirculatory components.

F-9

Role of VEGFR1 signaling in liver injury and repair following hepatic ischemia/reperfusion injury in mice

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Aims: Recent evidence suggests that vascular endothelial growth factor (VEGF) and its receptors are crucial for liver repair after acute liver injury through enhancement of macrophage recruitment. The objective of the present study was examined the role of VEGF receptor 1 (VEGFR-1) signaling in liver injury and repair during hepatic I/R in mice.
Methods: VEGFR1-tyrosine kinase knockout mice (TK-KO) or their wild counterparts (WT) were subjected to 1 h of partial hepatic ischemia followed by reperfusion. Sham-operated animals served as controls. Serum samples and liver tissue for histology were analyzed on 6, 24, 48, and 96 h after reperfusion. Mice were given anti-EGF neutralizing antibody intraperitoneal injection 6 h after reperfusion.
Results: ALT levels in WT with a peak at 6 h after reperfusion were declined thereafter. In TK-KO, the time course of changes in ALT levels was similar to that in WT, and the levels were higher. Necrotic area as indicated by histological assessment in TK-KO was greater than WT. The hemorrhagic area in TK-KO was higher than WT from 24 to 96 h. The proliferation of hepatocytes as evidenced by proliferating cell nuclear antigen (PCNA) stained positive cells in TK-KO was delayed when compared with WT. The hepatic mRNA levels of VEGF, VEGFR-1, and epidermal growth factor (EGF) were suppressed in TK-KO. The numbers of hepatic infiltrating cells expressing CD11b and VEGFR1 were reduced in TK-KO at 48 h as compared with WT. Treatment of WT with anti-EGF antibody delayed liver repair and reduced the recruitment of macrophages.
Conclusions: These results indicate that VEGFR-1 signaling is involved in liver repair and regeneration during hepatic I/R through enhancement of EGF and recruitment of macrophages.

F-10

Anti-inflammatory effects of carbon monoxide (CO) liberated by CO-releasing molecule on ischemia-reperfusion (I/R)-challenged intestinal injury in mice

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Introduction: It is well known that oxidative stress-related inflammation and leukocyte recruitments are characterized in the acute phase of intestinal ischemia-reperfusion (I/R) injury. Recently, carbon monoxide (CO) inhalation has been shown to activate NF-E2 related factor 2 (Nrf2) to protect ischemia-related injury. In this study, we therefore investigated the anti-inflammatory effects of water-soluble CO-releasing molecule (CORM-3) on I/R-challenged intestinal injury and the role of Nrf2 in CO-modulated protection.
Methods: To this end, mice (WT or Nrf2 deficient) small intestines were challenged with ischemia by occluding superior mesenteric artery (SMA) for 45 mins. CORM-3 (10 mg/kg) was intraperitoneally administered before induction of ischemia in WT mice. Inflammatory responses in the small intestine were assessed 4h following reperfusion by measuring luminal protein and hemoglobin, tissue levels of TNF-alpha and KC proteins (ELISA), polymorphonuclear neutrophil (PMN) tissue accumulation (MPO assay), HO-1/Nrf2 mRNA expression (RT-PCR), and Nrf2 nuclear/cytoplasm protein expressions (Western blot).
Results: Induction of I/R in WT mice caused significant increase in luminal inflammatory markers such as luminal protein/hemoglobin, tissue levels of TNF-alpha and KC, and subsequent PMN accumulation in the small intestine. The above changes were significantly attenuated by the treatment with CORM-3. Interesting to note that treatment with CORM-3 resulted in up-regulation of Nrf2 and HO-1. In another series of experiments, the above inflammatory markers were significantly deteriorated in I/R-challenged small intestine of Nrf2 deficient mice. The treatment with CORM-3 in Nrf2 deficient mice indicated partial improvements compared with WT mice.
Conclusions: These findings indicate that CO liberated by CORM-3 confers anti-inflammatory effects partially via up-regulation of Nrf2 and HO-1 in I/R-challenged intestinal injury.

F-11

Involvement of Cross-Linked Ribosomal Protein S19 Oligomers and C5a Receptor in Definitive Erythropoiesis

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We have previously reported the involvement of the C5a receptor and its ligand ribosomal protein S19 (RP S19) oligomers in the apoptotic cell clearance. According to an idea that molecular mechanisms of apoptosis would be partly utilized at the erythroblast maturation process in the definitive erythropoiesis, we performed a series of experiments to examine whether the RP S19 oligomers play an essential role in definitive erythropoiesis as a ligand of the C5a receptor of erythroblasts and macrophages. We found molecules functionally and immunologically indistinguishable from RP S19 oligomers in the extracellular fluid of porcine and guinea pig bone marrow. When an increased hematopoietic state was induced in guinea pigs by bloodletting, the bone marrow RP S19 oligomer concentration was concomitantly increased. However, when the RP S19 oligomers were immunologically neutralized or the C5a receptor was pharmacologically antagonised, hyper-erythropoiesis induced by bloodletting was prevented and the anaemic state was retarded in guinea pigs.
At meanwhile, we have established an *in vitro* erythroblastic island model using hemin-stimulated K562 cell-derived erythroblasts and THP-1-derived macrophages. The K562-derived erythroblasts expressed the C5a receptor, generated the RP S19 oligomers and organized an erythroblastic island-like structure with the macrophage-like cells. The macrophage-like cells helped the erythroblasts to become reticulocyte-like cells due to engulf the nucleus-containing pyrenocytes.

F-12

Development of CAST (cancer stromal targeting) diagnosis and therapy using anti-fibrin monoclonal antibody

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Background: Most human solid tumor forming hypovascular and stroma-rich tumor hinders the penetration of a monoclonal antibody (mAb) into the cells, and that leads failure of the conventional cell-targeting immunoconjugate strategy. To overcome this drawback, we developed cancer stroma targeting (CAST) therapy using anti-fibrin chimeric mAb, which reacted only with human or mouse insoluble fibrin, but not fibrinogen and soluble fibrin degradations.
Purpose: (1) Proof of pathophysiological specificity of fibrin in cancer. (2) Development of cancer-specific ImmunoPET imaging using anti-fibrin mAb.
Method: Immunohistochemical analysis of fibrin in various human tissues was conducted. Kinetics of fibrin in several non-malignant diseases of animal models was also examined. In addition, ImmunoPET probe composed of anti-fibrin mAb and zirconium (^{89}Zr) was developed and administered to the mouse bearing chemically induced spontaneous tumor.
Result: In immunohistochemistry of clinical samples and experimental animal models, almost all human cancer tissues from early to advanced stage showed positive fibrin deposition, but normal tissues not at all. Meanwhile, fibrin deposition was detected only at the onset of non-malignant diseases such as infarction, arthritis and trauma. PET/CT scan showed specific accumulation of ^{89}Zr-labeled anti-fibrin mAb on the fibrin-positive tumor-stroma in the mouse spontaneous tumor possessing abundant fibrin deposition, as in clinical human cancers.
Conclusion: We concluded that latent and prolonged fibrin deposition was the most specific characteristic of cancer. Moreover, fibrin-targeting CAST diagnosis and therapy may be applicable for various types of cancer.

F-13

Reprogrammed cancer cells upregurate the expressions of angiogenesis-related genes and reactive oxygen species scavenging genes

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Purpose: In previous report, reprogrammed cancer cells (called as iPC cells) got increased expressions of angiogenesis-related genes such as VEGF and VE-cadherin. Here we investigated the expressions of reactive oxygen species (ROS) scavenging genes in iPC cells.
Methods: The mRNA expressions of reprogrammed and parental cancer cells were determined by real-time RT-PCR. Antioxidant enzyme activities were performed with superoxide dismutase (SOD), glutathione S-transferase (GST) and glutathione peroxidase (GPx) assays. In vivo experiment, parental and iPC cells were resuspended in HANKS solution and were injected subcutaneously into NOD/SCID mice. We also investigated the effects of VEGFR and PDGFR inhibitor on angiogenesis in vivo.
Results and Conclusions: Reprogrammed cells got increased expressions of immature status-related gene, tumorigenicity and cell growth. Tumor suppressor gene expressions such as p53 and p16 were downregulated in iPC cells. Their angiogenesis-related gene (VEGF-A, VEGF-C, VE-cadherin and Ang2) expressions were increased significantly. In this study, we newly proved that their ROS scavenging genes (Atm, SOD and GST) expressions were increased. Also, these scavenging enzyme activities were increased. These results suggested that reprogrammed cancer cells may have effect on ROS levels.

F-14

Angiotensin Type 1 Receptor Blocker Enhances H_2O_2-induced Coronary Collateral Vasodilatation and Improves Microvascular Endothelial Dysfunction in Diabetes Mellitus and Endothelial H_2O_2 Production during Acute Coronary Occlusion in Canine Coronary Native Collateral Microcirculation in Vivo

Toyotaka Yada[1)], Hiroaki Shimokawa[2)], Osamu Hiramatsu[1)], Masami Goto[1)], Yasuo Ogasawara[1)], Fumihiko Kajiya[1)]

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Background: We examined whether an angiotensin type 1 receptor blocker (ARB) enhances hydrogen peroxide (H_2O_2, endothelium-derived hyperpolarizing factor)-induced vasodilatation and production during acute coronary occlusion in canine coronary collateral microvessels in vivo and if so, whether ARB acutely improves coronary collateral vasodilatation and endothelial H_2O_2 production in diabetes mellitus (DM). **Methods:** Canine subepicardial native collateral small arteries (CSA ≥100 μm) and arterioles (CA <100 μm) were continuously observed by an intravital CCD microscope under cyclooxygenase blockade. Experiments were performed during LAD ischemia (90 min) under the following 6 conditions (n=5 each); (i) control, C, (ii) ARB (olmesartan, 10 μg/kg/min, ic)+L-NMMA (NOS inhibitor, 2 μmol/min, ic), AL, (iii) ARB +L-NMMA+apamin+charybdotoxin (both are inhibitors of Ca-activated K (K_{Ca}) channels, 1μmol/L and 100nmol/L, ic), ALAC, (iv) DM (alloxan 40 mg/kg iv, 1 week prior to study) (v) DM+ARB+L-NMMA, DAL, and (vi) DM+ARB+L-NMMA+apamin+charybdotoxin, DALAC. Bradykinin was continuously and retrogradely infused into the diagonal branch of LCX during myocardial ischemia (85min). H_2O_2 production in myocardium was determined by quantitative measurement with an Amplex Red by ELISA. **Results:** Myocardial ischemia in C caused significant vasodilatation by bradykinin in CA (7±1%) but not in CSA (-2±1%). After AL, the vasodilatation was significantly increased in CA (15±5%) compared with C, and was significantly decreased by ALAC in CA (-6±6%). DM significantly decreased the coronary vasodilatation compared with C in both-sized arteries (CSA -8±1%, CA 2±1%), whereas DAL significantly improved the vasodilatation compared with DM in CA (7±2%) and was significantly decreased by DALAC in CA (-7±1%). Endothelial H_2O_2 production (μmol/L/mg protein) in DAL was significantly increased compared with C and DM and was significantly decreased by DALAC. DAL ameliorated myocardial injury compared with DM, as assessed by myocardial troponin-I, respectively. **Conclusions:** ARB enhances H_2O_2-mediated vasodilatation of canine coronary collateral arterioles and improves collateral vasodilatation, H_2O_2 production and myocardial injury in DM during acute coronary occlusion in vivo.

F-15

Wide inter-footprocess area in a rat at the early stage of diabetes

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Introduction: Previously, we reported that early diabetic rats are in a state of hyperfiltration. This is because creatinine clearance was increased in early diabetic rats. Supportively, afferent arteriolar diameters, efferent arteriolar diameters, renal blood flows and glomeular blood flow veclocities were increased in diabetic rats. We then visualised such hyperfiltration by multiphoton microscopy after administration of Texas Red conjugated dextrans of various molecular sizes. We quantitatively measured the intensities of the filtrate and compared them between control and early diabetic rats. We found there was a leakage of larger molecules of 40k and 70k Dalton dextrans from the glomeulri of early diabetic rats. The glomerular filtration function is already disturbed even in early diabetic rats. The size of 70k Dalton dextran is about 8 nm.
Purpose: We hypothesised that the structure of the glomerular slit membrane might be altered by diabetes even at the early stage of diabetes resulting in leakage of larger molecules. The purpose of this study is to examine whether or not there are structural changes in diabetic glomeruli.
Method: We induced diabetes by tail vein STZ administration (50 mg/kg) to Wistar rats. We examined rodent glomeruli (x 50,000) by electronmicroscopy in diabetic (up to 6 months) and control rats.
Results: Triangle interfoot-process area from the root of podocytes and the centre of the gap was compared between the control and diabetic rats after normalisation by gap length. Triangle area was significantly larger for diabetic rats than for controls ($p<0.01$).
Conclusion: In comparatively early diabetic rats, there was already structural widening of inter-footprocess area, which may be attributable to mild proteinuria.

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2) Pangratis N. Diagnostic investigation using vital capillary microscopy and dynamic capillaroscopy. Clin Hemorheol Microcirc. 1997: 17: 371-383.

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