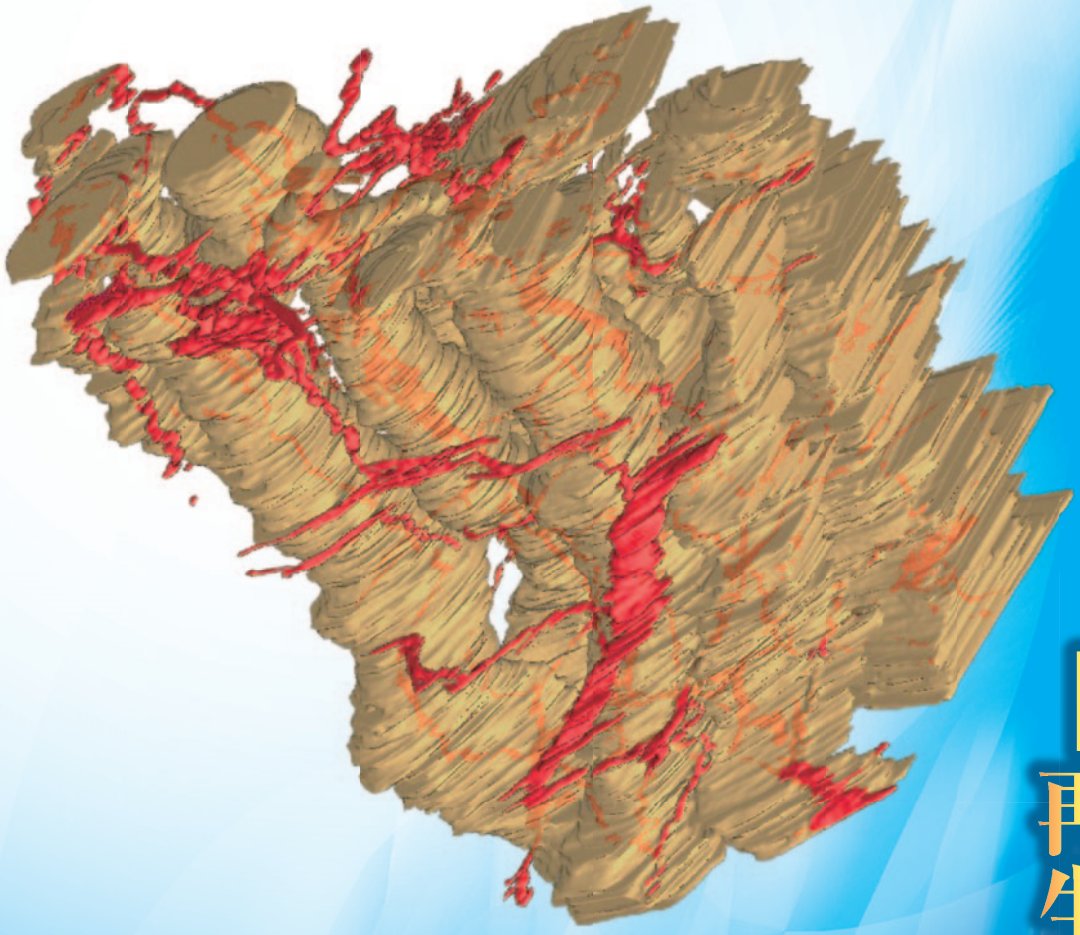
Japanese Society for Microcirculation

Iwate Medical University

第37回 日本微小循環学会総会

The 37th Annual Meeting of the Japanese Society for Microcirculation

—再生医学との関わり—



プログラム　抄録集

日時　2012年3月16日(金)・17日(土)

会場　盛岡グランドホテル

〒020-8501 岩手県盛岡市愛宕下1-10　TEL 019-625-2111

会長　藤村　朗（岩手医科大学 解剖学講座 機能形態学分野　教授）

■ 事務局 ■
岩手医科大学 解剖学講座 機能形態学分野
〒028-3694 岩手県紫波郡矢巾町西徳田2-1-1
TEL 019-908-8009
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http://www.jsmicrocirc.com/AnnualMeeting/37/

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2011年8月作成 (T)

ご　挨　拶

第 37 回日本微小循環学会総会を、平成 24 年 3 月 16 日（金）、17 日（土）の 2 日間にわたり、岩手県盛岡市の盛岡グランドホテルにて開催いたします。伝統のある本学会総会の会長を仰せつかり、名誉会員、理事、評議員をはじめとする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、基礎医学の双方が乗りいれ、理工学系、薬学、生物学の研究者が集い、微小循環を中心とした幅広い討論ができる貴重な学会であると思っております。

今回の学会を第 35 回の本総会でご指名いただき、第 36 回の総会終了後、岩手医科大学の移転作業終了時点で準備を開始する予定でおりました。ところが、3 月 11 日に東日本大震災が発生し、移転作業は中断、新しい建物の損傷、被災地での支援作業等が入り、一度はお断りしようかと考えましたところ、末松理事長をはじめ、多くの方々から暖かいお言葉をいただき、実際に準備に入れましたのが 7 月でした。すべてにおいて例年の学会より準備が遅れておりますことをお詫び申し上げます。

さて、本学会では臨床と基礎との融合を訴えてきていたように思います。常に臨床を見据えた基礎の立場を現在体現しているのが再生医学であると思います。生物の細胞や組織に備わっている再生能力をうまく利用して、障害を受けた組織や臓器を正常な状態に回復させることにより、病気の治癒へ導こうとするのが再生医学であり、このすべての現象に微小循環は重要な役割を持っていることになります。近年、再生医学の概念は多少変わってきているようですが、組織の再生に関わる微小循環を特別講演に組み込ませていただきました。活発な御討論をお願い申し上げます。

14 年前、本学会を岩手医科大学でお引き受けいたしました時期より今回は 3 週間ほど春に近付いているとはいえ、寒さは厳しく、また、年度末でお忙しい時期とは存じますが、本大会の趣旨を御理解のうえ、多数の方々のご参加とご協力を何卒よろしくお願い申し上げます。

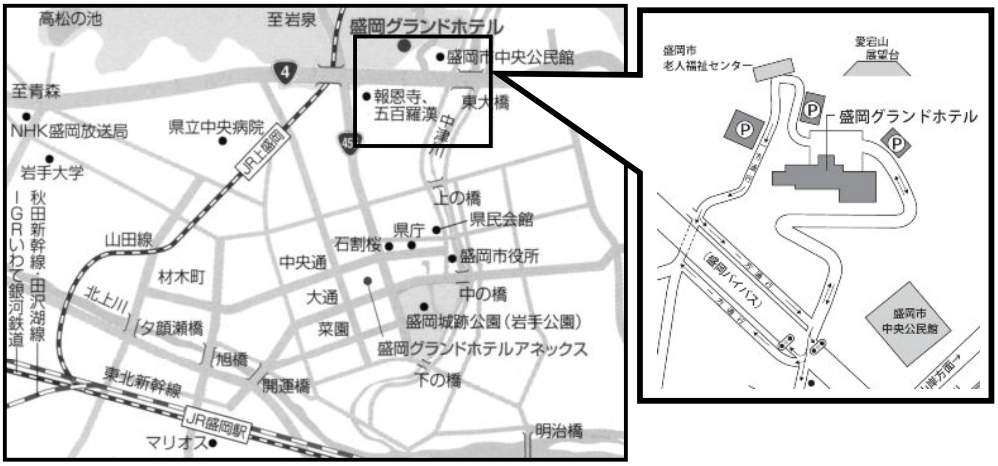
第 37 回日本微小循環学会総会
会長　藤村　　朗
岩手医科大学　解剖学講座　機能形態学分野　教授

日本微小循環学会総会の開催日および会長一覧
（＊印は「微小循環研究者の集い」）

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（慶應義塾大学医学部病理）	東　京　慶應義塾大学医学部
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10～11日	高木健太郎（名古屋市立大学本部）	名古屋　愛知県労働者研修センター
第５回＊	1980年２月９日	長嶋長節（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（東北大学抗酸菌病研究所）	仙　台　斎藤報恩会会館
第７回＊	1982年２月６～７日	岡　小天，中山　龍，新美英幸（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５～６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４～５日	関　清（東邦大学医学部内科）	東　京　こまばエミナース
第10回	1985年２月16～17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１～２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30～31日	三島好雄（東京医科歯科大学）	東　京　東京医科歯科大学
第13回	1988年５月20～21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20～21日	高橋和人（神奈川歯科大学口腔外科）	横須賀　神奈川歯科大学
第15回	1990年４月28～29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25～26日	鹿取　信（北里大学医学部薬理）	東　京　アルカディア市ヶ谷
第17回	1992年５月21～22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22～23日	磯貝行秀（東京慈恵会医科大学内科）	東　京　全共連ビル
第19回	1994年５月26～27日	大橋俊夫（信州大学医学部生理）	松　本　長野県松本文化会館
第20回	1995年４月20～21日	神谷　瞭（東京大学医学部医用生体工学）	東　京　東京大学山上会館
第21回	1996年２月23～24日	対馬信子（国立循環器病センター内科）	大　阪　千里ライフサイエンスセンター
第22回	1997年2月28～3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26～27日	野坂洋一郎（岩手医科大学歯学部）	盛　岡　盛岡グランドホテル
第24回	1999年２月26～27日	福内靖男（慶應義塾大学医学部内科）	東　京　日本海運倶楽部
第25回	2000年２月18～19日	時岡孝夫（明海大学歯学部解剖）	横須賀　神奈川歯科大学
第26回	2001年２月15～16日	梶谷文彦（岡山大学／川崎医大医用工学）	倉　敷　倉敷市立美術館
第27回	2002年２月21～22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13～14日	三浦総一郎（防衛医科大学校内科）	東　京　グランドヒル市ヶ谷
第29回	2004年２月19～20日	山本哲郎（熊本大学医学部分子病理）	熊　本　ニュースカイホテル
第30回	2005年２月23～24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10～11日	末松　誠（慶應義塾大学医学部医化学）	東　京　京王プラザホテル
第32回	2007年２月23～24日	吉川敏一（京都府立医科大学生体機能制御学）	京　都　ぱ･る･るプラザ京都
第33回	2008年２月21～22日	南谷晴之（慶應義塾大学理工学部生体医工学）	東　京　慶應義塾大学本部
第34回	2009年２月21～22日	馬嶋正隆（北里大学医学部薬学部）	東　京　北里大学白金キャンパス
第35回	2010年２月26～27日	棚橋紀夫（埼玉医科大学国際医療センター神経内科）	埼　玉　大宮ソニックシティー
第36回	2011年２月11～12日	小椋祐一郎（名古屋市立大学大学院学研究科視覚化学）	名古屋　名古屋市立病院大ホール
第37回	2012年３月16～17日	藤村　朗（岩手医科大学解剖学講座）	盛　岡　盛岡グランドホテル

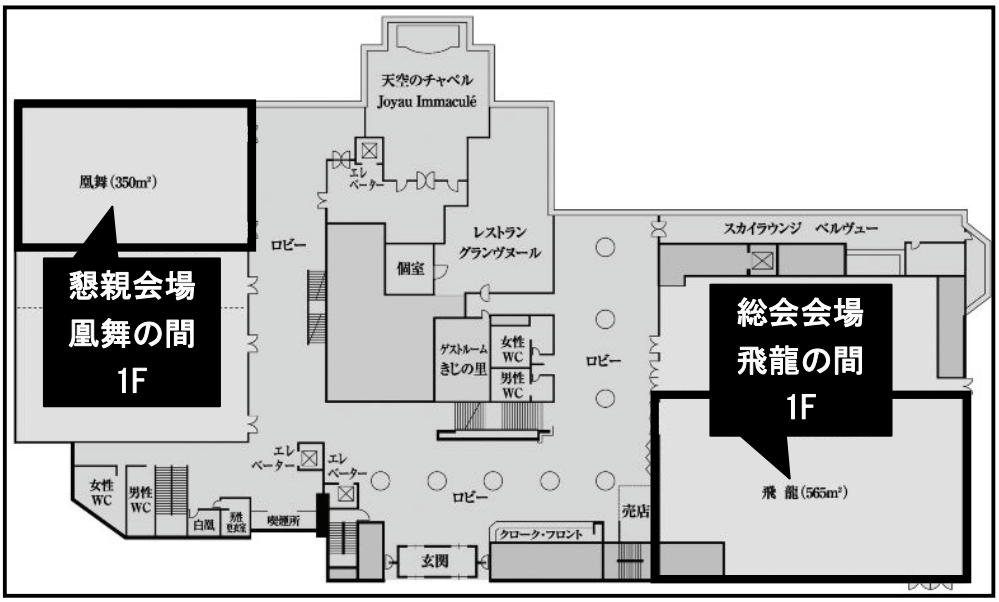
会場への交通案内・会場案内図

◆会場への交通案内



★　タクシー：盛岡駅前タクシーのり場より約 15 分
★　バス：盛岡駅前バスターミナル 11 番線
「盛岡山岸線」乗車→「中央公民館前」下車(約 15 分)、徒歩 5 分
★　自家用車：東北自動車道「盛岡南 I.C.」より約 20 分
★　自家用車：東北自動車道「盛岡 I.C.」より約 25 分

◆会場案内図



会場：盛岡グランドホテル　飛龍の間　(1F)

お知らせとお願い

■ 参加者へのご案内

1．会場
盛岡グランドホテル　飛龍の間

2．参加登録受付
場所：盛岡グランドホテル　1階　ロビー
日時：2012年3月16日（金）8時20分～17時00分
3月17日（土）8時20分～15時30分

3．受付方法・参加費
盛岡グランドホテル 1階 ロビーにて、当日登録用紙に必要事項をご記入の上、受付にお越しください。

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・抄録集費も含みます。

4．ネームカード
所属・氏名をご記入の上、会期中は必ず参加証をお付けください。

5．プログラム・抄録集
会員の方は学会より送付されましたプログラム・抄録集をご持参ください。
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円で頒布致します。

6．会場での呼び出し
会場内での呼び出しは行いません。掲示板をご利用ください。会場内ではサブスクリーンを使用してご連絡をすることもありますので、ご確認ください。

7．会場内でのご注意
会場内での撮影・録画・録音はご遠慮ください。携帯電話は、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．クローク
ホテルのクロークをご利用ください。

9．駐車場
車でお越しの場合は、ホテルの駐車場をご利用いただけます。詳しくはホテルフロントまでお問い合わせください。

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・監事会　　日時：3月15日（木）　18：00 ～ 19：30
　　場所：盛岡グランドホテル　祥雲（B1F）

評 議 員 会　　日時：3月16日（金）　11：40 ～ 12：15
　　場所：盛岡グランドホテル　飛龍の間

総　　会　　日時：3月17日（土）　13：00 ～ 13：30
　　場所：盛岡グランドホテル　飛龍の間

学会奨励賞授与式・意見交換・懇親会
　　日時：3月16日（金）　17：30 ～ 20：00
　　場所：盛岡グランドホテル　鳳舞の間

12. 学会入会申込み

年会費、登録および入会の受付は、総合受付の学会事務局デスクにて手続きをしてください。
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3,000円です。
＊巻末綴じ込みの入会申込書、変更届をご利用ください。また、入会の申し込みについては、下記にお問い合わせください。

◆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
The Japanese Society for Microcirculation
ＴＥＬ：03－5361－7101
ＦＡＸ：03－5361－7564
E-mail：js-micro@imic.or.jp

次回開催情報

第38回日本微小循環学会総会
会期：平成25年2月8日・9日
会場：都内予定
会長：西野　博一　先生
（東京慈恵会医科大学　消化器肝臓内科　教授）

■ 招待講演

＜特別講演＞

日　時：3 月 16 日（金）　13：30 ～ 14：45
場　所：盛岡グランドホテル　飛龍の間
演　題：「Elucidation of the molecular mechanisms underlying the ligand-controlled growth and differentiation of mesenchymal stem/progenitor cells: study on the establishment of novel cell therapy for construction of a vascular system」
講演者：石崎　明　先生（岩手医科大学 生化学講座 細胞情報科学分野 教授）
座　長：藤村　朗　先生（岩手医科大学 解剖学講座 機能形態学分野 教授）

■ ランチョンセミナー

＜ランチョンセミナー１＞

日　時：3 月 16 日（金）　12：30 ～ 13：15
場　所：盛岡グランドホテル　飛龍の間
演　題：「腫瘍血管における血管正常化／成熟化のインパクト」
講演者：高倉　伸幸　先生（大阪大学　微生物病研究所情報伝達分野 教授）
座　長：若林　剛　先生（岩手医科大学　外科学講座 教授）
（共催：中外製薬　株式会社）

＜ランチョンセミナー２＞

日　時：3 月 17 日（土）11：45 ～ 12：45
場　所：盛岡グランドホテル　飛龍の間
演　題：「電子線マイクロアナライザによる組織切片元素イメージング技術」
講演者：林　　広司　先生
（株式会社　島津製作所　分析計測事業部 X 線/表面ビジネスユニット　課長）
座　長：末松　　誠　先生（慶應義塾大学医学部　医学部長・医化学教室　教授）
（共催：株式会社　島津製作所）

＜イブニングセミナー＞

日　時：3 月 16 日（金）　16：00 ～ 17：00
場　所：盛岡グランドホテル　飛龍の間
演　題：「脳卒中と高血圧　―最近の話題から―」
講演者：棚橋　紀夫　先生（埼玉医科大学国際医療センター　神経内科　教授）
座　長：寺山　靖男　先生（岩手医科大学 内科学講座　神経内科・老年科分野　教授）
（共催：武田薬品工業　株式会社）

※ 3 月 16 日（金）のプログラム終了後、盛岡グランドホテル鳳舞の間にて意見交換会、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。
※懇親会終了後、盛岡グランドホテルより盛岡駅方面行のバスを運行いたしますので、ご利用ください。

◆総会事務局（お問合せ先）
岩手医科大学　解剖学講座　機能形態学分野
〒028－3694　岩手県紫波郡矢巾町西徳田２－１－１
ＴＥＬ：019－908－8009
ＦＡＸ：019－908－8010
E-mail：37jsm@iwate-med.ac.jp

■ 口演規定

【演者の方へ】

▶発表時間

各セッションの発表時間は下記の通りです。発表時間を厳守してください。
（発表開始に緑ランプ、終了1分前黄色ランプ、終了時赤ランプが点灯します）

シンポジウム	発表15分＋討論5分
学会奨励賞	発表10分＋討論5分
一般演題	発表 9 分＋討論3分

▶発表形式

1．発表はPCプレゼンテーションに限ります。

○発表形式はパソコン（Windows）です。Windows 7、office2003 ～2010をご用意します。
○発表データの受付は会場前「PC受付」で行います。発表30分前までにお越しください。
○使用ソフトはMicrosoft Power Point2003 ～2010に限らせていただきます。
○基本はデータでのお預かりとさせていただきます。USBフラッシュメモリまたはCD-Rでご持参ください。データのファイル名は、「演題番号＿演者名」を付けてください。
○動画がある場合またはMacintoshで発表する場合は、必ずご自身のコンピューターをお持ち込み下さい。
接続コネクターは、D-sub 15 pinタイプです。PCの外部モニター出力端子の形状をご確認ください。
変換コネクターが必要な場合はお持込みください。
ACアダプターも忘れずにお持込みください。
接続トラブルなどの場合に備え、バックアップデータを必ずお持ちください。
○発表時は、演台上にモニター、キーボード、マウス、レーザーポインターをご用意しております。
○お預かりした発表データは口演終了後、学会で責任をもって消去いたします。

2．PCプレゼンテーション原稿作成にあたっての注意事項

○「PowerPoint2003 ～2010」で作成してください。
○Windowsのみ使用可。
○フォントは画面レイアウトのバランスや文字化けを防ぐためOSに標準でインストールされているものでお願いいたします。下記のフォントを推奨いたします。
日本語；MSゴシック、MS明朝、MSPゴシック、MSP明朝
英　語；Century、Century Gothic、Arial、Times New Roman、Symbol
○解像度：XGA（1024×768ピクセル）です。このサイズより大きい場合、スライドの周囲が切れてしまいますので画像設定をXGAに合わせてください。
○「音」の効果は使用しないこと。

3．発表方法

○発表開始後の操作（マウス操作）は、各演者ご自身でお願い致します。
○発表15分前までに次演者席で待機してください。
○持ち込まれたPC本体は、口演発表後、PCオペレーター席にてご返却いたします。

【座長の方へ】

○15分前までに会場最前列の次座長席にお着きください。
○開始の合図が入り次第登壇し、セッションを開始してください。

【参加者の方へ】

○討論は、個別に行われます。
○討論者は、予め会場内の質問用マイクの近くでお待ち下さい。
○討論者は、氏名・所属を明確に述べた後、簡潔にご発言ください。
○追加発言や質疑応答のためのPCプレゼンテーションは受付いたしません。

日　程　表

	3月16日（金）	March 16 (Fri.)
8:00	参加受付　PC受付　8:20～	Registration　8:20～
	開会の辞	Opening Remarks
9:00	学会奨励賞候補者講演　9:00～9:30 Y-1, Y-2 座長:山本　哲郎	Applicants' Presentations for Young Investigators Award　9:00～9:30　Y-1, Y-2 Chair: Tetsuro Yamamoto
9:30	一般演題(1)　9:30～10:18 F-1～F-4　(脳、神経Ⅰ) 座長:鈴木　則宏	Free Paper(1)　9:30～10:18 F-1～F-4 (Brain, Nerve Ⅰ) Chair: Norihiro Suzuki
10:00		
10:30	一般演題(2)　10:20～10:56 F-5～F-7　(脳、神経Ⅱ) 座長:寺山　靖夫	Free Paper(2)　10:20～10:56 F-5～F-7 (Brain, Nerve Ⅱ) Chair: Yasuo Terayama
11:00	一般演題(3)　11:00～11:36 F-8～F-10　(消化器Ⅰ) 座長:沢　禎彦	Free Paper(3)　11:00～11:36 F-8～F-10 (Digestive organs Ⅰ) Chair:Yoshihiko Sawa
11:30		
12:00	評議員会　11:40～12:15	Council Meeting of JSMC 11:40～12:15
12:30	ランチョンセミナー(1)　12:30～13:15 LS1　高倉　伸幸 座長:若林　剛	Luncheon Seminar(1)　12:30～13:15 LS1　Nobuyuki Takakura Chair: Go Wakabayashi
13:00	(共催:中外製薬株式会社)	(Sponsored by Chugai Pharmaceutical Co., LTD.)
13:30	特別講演　13:30～14:45 SL　石崎　明 座長:藤村　朗	Special Lecture　13:30～14:45 SL　Akira Ishisaki Chair: Akira Fujimura
14:00		
14:30		
15:00	一般演題(4)　15:00～15:48 F-11～F-14　(脳、神経Ⅲ) 座長:吉田　晃敏	Free Paper(4)　15:00～15:48 F-11～F-14 (Brain, NerveⅢ) Chair: Akitoshi Yoshida
15:30		
16:00	イブニングセミナー　16:00～17:00 ES　棚橋　紀夫 座長:寺山　靖夫	Evening Seminar　16:00～17:00 ES　Norio Tanahashi Chair: Yasuo Terayama
16:30	(共催:武田薬品工業　株式会社)	(Sponsored by Takeda Pharmaceutical Co., LTD.)
17:00		
17:30	学会奨励賞・懇親会　17:30～	Award Ceremony / Reception 17:30～20:00
20:00		

Program at a Glance

	3月17日（土）	March 17 (Sat.)
8:00	参加受付　PC受付　8:20～	Registration　8:20～
9:00	一般演題（5）　9:00～10:00 F-15～F-19　（消化器Ⅱ） 座長：永田　博司	Free Paper（5）　9:00～10:00 F-15～F-19 (Digestive organs Ⅱ) Chair：Hiroshi Nagata
9:30		
10:00		
	シンポジウム　10:10～11:30 S-1～S-4	Symposium　10:10～11:30 S-1～S-4
10:30	座長：藤村　朗	Chair：Akira Fujimura
11:00		
11:30		
	ランチョンセミナー（2）　11:45～12:45	Luncheon Seminar（2）　11:45～12:45
12:00	LS2　林 広司	LS2　Hiroshi Hayashi
	座長：末松　誠	Chair：Makoto Suematsu
	（共催：株式会社　島津製作所）	（Sponsored by SHIMADZU CORPORATION）
12:30		
13:00	総会　　13:00～13:30	General Assembly of JSMC 13:00～13:30
13:30		
	一般演題（6）　13:45～14:45	Free Paper（6）　13:45～14:45
14:00	F-20～F-24　（癌、炎症）	F-20～F-24 (Cancer, Inflammation)
	座長：日比　紀文	Chair：Toshifumi Hibi
14:30		
	一般演題（7）　14:50～15:50	Free Paper（7）　14:50～15:50
15:00	F-25～F-29　（その他）	F-25～F-29 (Others)
	座長：矢田　豊隆	Chair：Toyotaka Yada
15:30		
	閉会の辞	Closing Remarks
16:00		
16:30		
17:00		
17:30		
20:00		

PROGRAM

Friday, March 16, 2012

Opening Remarks 8 : 55～9 : 00

President : Akira Fujimura

Applicants' Presentations for Young Investigators Award 9 : 00～9 : 30

Chair : Tetsuro Yamamoto

Y-1 **Watershed of the subcutaneous capillary lymphatic network at the midline of the body trunk**

Yoshinori Ando[1)], Shinji Furukawa[2)], Hiroyuki Miura[2)], Akira Fujimura[1)]

[1)]Department of Anatomy, Division of Functional Morphology, Iwate Medical University, [2)]Department of Developmental Oral Health Science, Division of Orthodontics, School of Dentistry, Iwate Medical University, Japan

Y-2 **Expression of autotoxin / lysophospholipase D in high endothelial venule-like vessel and its role on aberrant lymphocyte migration in inflamed intestinal mucosa**

Hideaki Hozumi, Ryota Hokari, Chie Kurihara, Hirokazu Sato, Kazuyuki Narimatsu, Shingo Sato, Toshihide Ueda, Masaaki Higashiyama, Yoshikiyo Okada, Chikako Watanabe, Kengo Tomita, Atsushi Kawaguchi, Shigeaki Nagao, Soichiro Miura

National Defense Medical Collage, Japan

Free Paper (1) Brain, Nerve I 9 : 30～10 : 18

Chair : Norihiro Suzuki

F-1 **Laser-induced thrombus formation in angiotensin II type 1a receptor-knockout 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 **Changes in diameter of cerebral microvessels and blood flow associated with potassium-induced cortical spreading depression in anesthetized mice**

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

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

F-3 **Measurement of change in RBC velocity and concentration evoked by whisker stimulation in awake and anesthesia mice**

Hiroyuki Takuwa[1)], Tetsuya Matsuura[1), 2)], Takayuki Obata[1), 3)], Hiroshi Kawaguchi[1)], Iwao Kanno[1)], Hiroshi Ito[1)]

[1)] Molecular Imaging Center, National Institute of Radiological Sciences, Japan, [2)] Faculty of Engineering, Iwate University, Japan, [3)] Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Japan

F-4 **Barrel Cortex Activity to Whisker Stimulation and CO2 Response Measured in Mice with Suppressed Neurvascular Coupling Induce by Prolonged Continuous Hypoxia**

Iwao Kanno[1)], Kazuto Masamoto[1),2)], Hiroyuki Takuwa[1)], Kyoko Yamazaki[3)], Hiroshi Kawaguchi[1)], Junko Taniguchi[1)], Yutaka Tomita[4)], Norihiro Suzuki[4)], Hiroshi Ito[1)]

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

Free Paper (2) Brain, Nerve II 10：20～10：56

Chair：Yasuo Terayama

F-5 **Effect of Clostazol on intramicrovascular behavior of platelets in murine brain after bilateral common carotid artery occlusion and reperfusion**

Takuya Fukuoka, Makiko Hirayama, Hajime Maruyma, Norio Tanahashi

Department of Neurology, Saitama Medical University Saitama International Medical Center, Saitama, Japan

F-6 **Immediate post-stroke administration of cilostazol alters profiles of various metabolic pathways in a mouse model of brain ischemia**

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

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

F-7 **CO-sensitive CBS/H_2S pathway mediates hypoxia-induced microvascular dilation in the brain**

Takayuki Morikawa, Mayumi Kajimura, Tomomi Nakamura, Takako Hishiki, Tsuyoshi Nakanishi, Yoshinori Yukutake, Makoto Suematsu

Department of Biochemistry, School of Medicine, Keio University, Tokyo, Japan

Free Paper (3) Digestive organs I 11：00～11：36

Chair：Yoshihiko Sawa

F-8 **Microcirculation changes of periodontal tissue after ultrasonic tooth preparation**

Masato Matsuo, Shun-Suke Takahashi, Shuta Sugiyama, Masaichi C-Lee
Kanagawa Dental College, Yokosuka, Japan

F-9 **Gingival Vascular Functions Are Altered in Periodontitis and/or Stroke Rodent Model**

Fumiaki Tokutomi, Satoko Wada-Takahashi, Shuta Sugiyama, Shun-suke Takahashi, Masaichi Chang-il Lee
Department of Clinical Care Medicine, Division of Pharmacology and ESR Laboratory, Kanagawa Dental College, Yokosuka, Japan

F-10 **A case series of 21 patients with gastric antral vascular ectasia: Clinical aspects and treatment with argon plasma coagulation**

Eisuke Iwasaki[1),2)], Hidekazu Suzuki[1)], Hiroyuki Imaeda[1)], Atsushi Nakazawa[2)], Nobuhiro Tsukada[2)], Toshifumi Hibi[1)]
[1)]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, [2)] Department of Internal Medicine, Saiseikai Central Hospital, Japan

Council Meeting of JSMC 11：40～12：15

Luncheon Seminar (1) 12：30～13：15

Chair：Go Wakabayashi

LS 1 Nobuyuki Takakura
Department for Signal Transduction, Research Institute for Microbial Diseases, Osaka University
（Sponsored by Chugai Pharmaceutical Co., LTD.）

Special Lecture 13：30～14：45

Chair：Akira Fujimura

SL **Elucidation of the molecular mechanisms underlying the ligand-controlled growth and differentiation of mesenchymal stem/progenitor cells: study on the establishment of novel cell therapy for construction of a vascular system**

Akira Ishisaki, PhD & DDS
Division of Cellular Biosignal Sciences, Department of Biochemistry, Iwate Medical University, Japan

Free Paper (4) Brain, NerveIII　15：00～15：48

Chair：Akitoshi Yoshida

F-11 **The expression of podoplanin and classical cadherins in the mouse choroid plexus**

Chiaki Kaji[1)], Miwa Tomooka[1)], Hiroshi Kojima[1)], Yoshihiko Sawa[2)]

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

F-12 **Effects of breathing method on the peripheral circulatory response and the brain blood flow in elders**

Miyuki Nishioka, Shinji Ishihama, Yukio Tanaka

Institute of technology, Division of advanced health science, Tokyo University of Agriculture & Technology, Japan

F-13 **Topical latanoprost increases retinal blood flow in the macular circulation**

Naomi Niwa, Tomoaki Hattori, Miho Nozaki, Yuichiro Ogura

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

F-14 **Ultra-widefield Fluorescein Angiography with Scanning Laser Ophthalmoscope**

Tomoaki Hattori, Shuichiro Hirahara, Miho Nozaki, Tsutomu Yasukawa, Munenori Yoshida, Yuichiro Ogura

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

Evening Seminar　16：00～17：00

Chair：Yasuo Terayama

ES Norio Tanahashi

Department of Neurology, Saitama Medical University Saitama International Medical Center

（Sponsored by Takeda Pharmaceutical Co., LTD.）

Award Ceremony / Reception　17：30～20：00

Saturday, March 17, 2012

Free Paper (5) Digestive organs II　9：00～10：00

Chair：Hiroshi Nagata

F-15 Development of in vivo imaging method and analysis of microcirculation of pancreatic islet in living animals

Chieko Ihoriya, Minoru Satoh, Atsunori Kuwabara, Tamaki Sasaki, Naoki Kashihara
Department of Nephrology and Hypertension, Kawasaki Medical School, Kurashiki, Japan

F-16 Involvement of ribosomal protein S19 oligomers in acute inflammation resolution

Tetsuro Yamamoto
Department of Molecular Pathology, Faculty of Life Science, Kumamoto University, Japan

F-17 Role of BTB and CNC homolog 1 (Bach1) in ischemia-reperfusion-challenged intestinal inflammation

Kazuhiro Katada[1)], Yuji Naito[1)], Tomohisa Takagi[1)], Takaya Iida[1)], Katsura Mizushima[1)], Kazuhiko Uchiyama[1)], Osamu Handa[1)], Hiroshi Ichikawa[2)], Akihiko Muto[3)], Kazuhiko Igarashi[3)], 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, [3)]Division of Biochemistry, Tohoku University Graduate School of Medicine, Japan

F-18 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-19 Thromboxane A2 receptor signaling promotes regeneration of the mouse liver during carbon tetrachloride-induced acute liver injury

Tsutomu Minamino[1), 3)], Yoshiya Ito[2)], Hirotoki Okubo[1)], Kanako Hosono[1)], Takehito Sato[1), 3)], Wasaburo Koizumi[3)], Masataka Majima[1)]
Departments of [1)]Pharmacology, [2)]Surgery, and [3)]Gastroenterology, Kitasato University School of Medicine, Kanagawa, Japan

Symposium　10：10～11：30

Chair：Akira Fujimura

S-1 **The mechanisms that lead endothelial cells to the gross anatomical architecture of vascular system for the brain stem**

Sumio Isogai, Eiji Kimura, Erina Saito, Jiro Hitomi
Department of Anatomy, School of Medicine, Iwate Medical University, Morioka, Japan

S-2 **How are the internal carotid arteries and vertebral arteries integrated during ontogeny?**

Eiji Kimura
Division of Human Embryology, Department of Anatomy, Iwate Medical University, Japan

S-3 **Diversity and variability of smooth muscle cells in arterioles; imaging analysis using a real-time confocal laser scanning microscope**

Tomoyuki Saino, Kazuki Masu, Makoto Matsuura, Yoh-ichi Satoh
Department of Anatomy, Division of Cell Biology, Iwate Medical University, Japan

S-4 **Intra-vital imaging of platelet production in living mammalian**

Shugo Kowata[1)], Sumio Isogai[2)], Jiro Hitomi[2)], Yoji Ishida[1)]
[1)] Hematology and Oncology, Internal Medicine, Iwate Medical University School of Medicine, JAPAN,
[2)]Anatomy and Human Embryology, Iwate Medical University School of Medicine, Japan

Luncheon Seminar (2)　11：45～12：45

Chair: Makoto Suematsu

LS2 Hiroshi Hayashi
Shimadzu Corporation Analytical & Measuring Instruments Division X-Ray/surface Business Unit
（Sponsored by SHIMADZU CORPORATION）

General Assembly of JSMC　13：00～13：30

Free Paper (6) Cancer, Inflammation 13 : 45～14 : 45

Chair : Toshifumi Hibi

F-20 **Reprogrammed cancer cells upregulate angiogenesis-related genes and downregulate tumor suppressor genes**

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

F-21 **Erc/mesothelin is a novel diagnostic biomarker for the mouse model of pancreatic ductal adenocarcinoma**

Chika Miyoshi, Hiroyasu Esumi
Cancer Physiology Project, Research Center for Innovative Oncology, National Cancer Center Hospital East, Japan

F-22 **Angiogenesis and Lymphangiogenesis in Hepatic and Pulmonary MALT lymphoma in *Helicobacter heilmannii*-infected Mouse: Effect of Eradication of Bacilli**

Masahiko Nakamura, Hidenori Matsui, Tetsufumi Takahashi, Kanji Tsuchimoto
School of Pharmaceutical Science, Kitasato University, Kitasato Institute for Life Sciences, Kitasato Institute Hospital, 3rd Department of Internal Medicine, Kyorin University, Japan

F-23 **Selective destruction of tumor vasculature by CAST (cancer stroma targeting) therapy**

Masahiro Yasunaga[1)], Shino Manabe[2)], Yasuhiro Matsumura[1)]
[1)]Investigative Treatment Division, National Cancer Center Hospital East, Chiba, Japan, [2)]Synthetic Cellular Chemistry Laboratory, RIKEN, Saitama, Japan

F-24 **MICROVASCULAR RICH PYOGENIC GRANULOMA OF THE DISTAL SMALL INTESTINE**

Kenro Hirata[1)], Hidekazu Suzuki[1)], Naoki Hosoe[2)], Hiroyuki Imaeda[2)], Mari Ueno[3)], Hiroko Murata[1)], Haruhiko Ogata[2)], Makio Mukai[3)], Toshifumi Hibi[1)]
[1)]Department of Gastroenterology and Hepatology, Keio University School of Medicine, [2)]Center for Diagnostic and Therapeutic Endoscopy, Keio University School of Medicine, [3)]Department of Pathology, Keio University School of Medicine, Japan

Free Paper (7) Others 14 : 50～15 : 50

Chair : Toyotaka Yada

F-25 **Cardioprotective Role of Hydrogen Peroxide and Angiotensin Type 1 Receptor Blockers during Acute Coronary Occlusion in Canine Native Coronary Collateral Microcirculation in Vivo**

Toyotaka Yada[1)], Hiroaki Shimokawa[2)], Osamu Hiramatsu[1)], Masami Goto[1)], Yasuo Ogasawara[1)], Fumihiko Kajiya[1)]
[1)]Department of Medical Engineering and Systems Cardiology, Kawasaki Medical School, [2)]Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Japan

F-26 Progressive dissociation of nephrin and podocin, glomerular slit membrane proteins, in distribution 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

F-27 Role of ThromboxaneA2 TP signaling in upregulation of PSGL-1 during recovery from ischemic condition

Hideki Amano[1)], Yoshiya Ito[1), 2)], Kazuhito Oba[1)], Shuh Narumiya[3)], Masataka Majima[1)]

[1)]Department of Pharmacology,[2)] Department of Surgery, Kitasato University School of Medicine, [3)]Department of Pharmacology, Kyoto University School of Medicine, Japan

F-28 Characterization of Ca^{2+} channels involved in endothelin-1-induced transactivation of epidermal growth factor receptor

Yoshifumi Kawanabe

Department of Neurosurgery, Otsu Municipal Hospital, Japan

F-29 The mechanism study of spironolactone-induced Ca^{2+} increase in rat testicular arteriole smooth muscle cells

Tomoyuki Saino, Yasunori Tamagawa, Yoh-ichi Satoh

Department of Anatomy, Division of Cell Biology, Iwate Medical University, Japan

Closing Remarks

Abstracts

SL

SElucidation of the molecular mechanisms underlying the ligand-controlled growth and differentiation of mesenchymal stem/progenitor cells: study on the establishment of novel cell therapy for construction of a vascular system

Akira Ishisaki, PhD & DDS

Division of Cellular Biosignal Sciences, Department of Biochemistry, Iwate Medical University, Japan

Previous studies have provided evidences for interactions between the fibroblast growth factor (FGF) family and transforming growth factor-β (TGF-β) super family signaling systems. FGF and bone morphogenetic protein (BMP) function reciprocally in the limb: FGF stimulates outgrowth of limb bud, and BMP inhibits the activity. In addition, BMP was identified as an antagonist of FGF-mediated tooth formation during the early stages of odontogenesis. However, it was remained to be clarified what kinds of molecular mechanisms underlay the reciprocal controls of organogenesis by FGF family and TGF-β super family. We examined to identify the signal-pathways induced by FGF family and TGF-β super family that reciprocally regulated the growth and differentiation of various progenitor cells or stem cells.

At first, we tried to find the molecular tools that inhibit intra-cellular signals activated by TGF-β super family. Smad6 and Smad7 appeared to prevent the ligand-induced activation of signal-transducing Smad proteins in the TGF-β super family. However, it was not clear which signals transduced by the pathway-restricted Smads (Smad1/5/8 or Smad2/3) the inhibitory Smads attenuate. We demonstrate that the ectopic expressions of Smad6 and Smad7 inhibited the BMP-induced Smad1/Smad5 phosphorylation in B lineage cells. Moreover, we found that the ectopic expression of Smad7, but not Smad6, inhibited the activin-induced Smad2 phosphorylation in the cells. Thus, Smad6 and Smad7 exhibit differential inhibitory effects in BMP- and activin-mediated signaling in B lineage cells.

Secondly, we investigated whether human umbilical vein endothelium-derived cells (HUVE-DCs) retain the potential to differentiate into smooth muscle cells (SMCs). Whereas HUVE-DCs cultured with FGF can be characterized as endothelial cells (ECs), when deprived of FGF, a significant fraction differentiates into SMC-like cells. Intriguingly, activin expression was upregulated in FGF-deprived HUVE-DCs; the inhibitory effects of exogenous follistatin and overexpressed Smad7 on the SMC-like differentiation confirmed that the differentiation was driven by the activin signal. Thus, in HUVE-DCs, maintenance of the EC phenotype and differentiation into SMC-like cells are reciprocally controlled by FGF and activin.

Thirdly, mesenchymal stem cell (MSC)-like activity of cells derived from the periodontal ligament (PDL) was identified by their capacity to form fibrous and osseous tissue and cementum. However, it remained to be clarified whether the cells had an ability to build the capillary network of blood vessels. We found that the swine PDL fibroblast cell line, TesPDL3 cells exhibited not only osteoblastic phenotype in response to BMP stimulation but also endothelial phenotype in response to FGF stimulation. Intriguingly, FGF inhibited the BMP-induced formation of mineralized nodules. Conversely, BMP inhibited the FGF-induced formation of tube-like structures. Thus, the commitment of differentiation of undifferentiated PDL fibroblasts into osteoblasts (OBs)-like cells or EC-like cells seemed to be reciprocally controlled by FGF and BMP. Further, we demonstrated that primarily cultured rat PDL fibroblasts under the stimulation with FGF have the ability to form EC-marker positive vessel-like structures in the type I collagen scaffold.

Here we propose a novel idea that the FGF-propagated fibroblastic lineage in the ligament tissue could be a candidate precursor for construction of a vascular system around damaged ligament tissue to facilitate its regeneration.

S-1

The mechanisms that lead endothelial cells to the gross anatomical architecture of vascular system for the brain stem

Sumio Isogai, Eiji Kimura, Erina Saito, Jiro Hitomi

Department of Anatomy, School of Medicine, Iwate Medical University, Morioka, Japan

The brain stem is supplied with blood by a pair of internal carotid and of vertebral arteries which are anastomosed by the *circlus of arteriosus* (of Willis) and the basilar artery. This anatomical patterning is highly conservative throughout the vertebrates. Padget described the detailed developmental process with the reconstruction from serial sections of a human (1947). Using the QH-1 monoclonal antibody as a maker for quail endothelium, Coffin and Poole (1991) investigated the endothelial origin and migration in cranial blood vessel development. Noden (1991) and Couly (1995) followed the developmental behavior of the mesodermal cells which vascularize the brain and head with the quail/chick transplantation technique. All authors had believed that the conserved anatomical architecture is generated by the angiogenesis mechanism so called "Remodeling" in their embryos.

We had used time-lapse multiphoton microscopy of living *Tg(fli1:EGFP)*^{y1} zebrafish embryos to examine how the vertebral vascular system for the spinal cord is generated in the early vertebrate trunk, and revealed that the basic patterning of the system is programmed by the genetic cues, but the flow dynamics plays an important role to determine the final arterial or venous identity and to maintain the functional system. Following this, we carry out the time-laps examination how the internal carotid vascular system is generated in the living embryos. Our images revealed that the precursor endothelial cells are directly laid down in situ, and migrate along the blueprint of prospective gross anatomical pattern without having "Remodeling" process. The reproducible phenomenon suggests that the patterning of the internal carotid system for the brain stem is tightly regulated by spatially and temporally defined genetic cues.

This results support our model combining genetic programming of overall vascular architecture with hemodynamic determination of circulatory flow pattern. Here, I introduce our study using time-laps movies on the vascularization for the brain and spinal chord, and present how arteries and veins are generated and integrated to form the functional blood circulatory system for the brain stem.

How are the internal carotid arteries and vertebral arteries integrated during ontogeny?

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Blood vessel formation is categorized into two phases; vasculogenesis and angiogenesis. The network model that blood flow determines the gross anatomical patterning of the vascular system among the early vascular plexus formed from mesoderm is proposed. However, the transgenic zebrafish line *Tg(fli1:EGFP)y1* in which the fluorescence of EGFP is strongly expressed in the endothelium was established and time-lapse multiphoton microscopy of living *Tg(fli1:EGFP)y1* embryos indicated the new model combining genetics programming of overall vascular architecture with hemodynamic determination of circulatory flow patterns in the blood vessel formation of trunk. The basic vascular plan of the brain is conserved throughout the vertebrate phyla, whereas how the gross anatomical patterning of cranial vessels is still poorly understood. There are two kinds of arteries supplying blood to the brain. The internal carotid arteries supply most of the cerebral hemispheres and the rest of circulation is provided via the vertebral arteries, and circles of arteries and the basilar artery (BA) anastomose these arteries. In this study, we carried out time-lapse studies of living *Tg(fli1:EGFP)y1* embryos to examine how the internal carotid arteries and vertebral arteries are integrated during ontogeny. To determine the source of the endothelial cells of this connecting portion, we performed additional time-lapse imaging with *Tg(fli1:EGFP)y7* zebrafish embryos, in which the expression of EGFP restricted in endothelial cells nuclei so that we can trace each endothelial cell. Our results clearly indicated the endothelial cells of 1st intersegmental arteries connected with those of the BA to integrate vascular systems of the brain and spinal cord. Furthermore the observation of the embryos treated with silent heart (*sih*) morphorino to suppress the blood circulation showed this process is not strongly influenced by the flow dynamics. These results coincide with the model supposed with the vessel formation in the trunk, combining the genetics and hemodynamics.

S-3

Diversity and variability of smooth muscle cells in arterioles; imaging analysis using a real-time confocal laser scanning microscope

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Intracellular Ca2+ concentration ([Ca2+]i) plays an important part in the regulation of cellular functions. Vascular smooth muscles are no exception to this rule. Arterioles play an important role in circulation in tissues. Given the important role of the resistance vasculature in the control of blood flow, we have investigated the alteration of intracellular calcium ion concentration in arterioles (external diameters < 100μm) against some modifying reagents. Arterioles were isolated from testis and brain of rats, then [Ca2+]i dynamics of arterioles was imaged by a real-time confocal laser scanning microscope (Nikon RCM/Ab). This time we show the results of the Ca2+ imaging studies using adenosine-5'-triphosphate (ATP) and Serotonin (5-hydroxytriptamine, 5-HT) in testicular and cerebral arterioles.

In the vascular wall, ATP is to be released, along with noradrenaline from sympathetic nerve terminals. The exposure of arteriole smooth muscle cells to extracellular ATP led to an increase in [Ca2+]i. The reaction of these muscles against ATP is different from arterioles between testis and brain ; The [Ca2+]i dynamics in testicular arterioles depend heavily on Ca2+ influx from extracellular space, whereas in brain arterioles it also takes part in the release from intracellular store (i.e. sarco/endoplasmic reticulum).

Serotonin is a well-known potent vasoconstrictor agent in several arteries. 5-HT elicited an increase in [Ca2+]i in most testicular arteriole smooth muscle cells. It was also noted that the reaction of these cells is different between testis and brain arterioles; the [Ca2+]i increase in testicular arterioles is depend on Ca2+ release from intracellular store, whereas in cerebral arterioles it plays a role in both the influx of extracellular Ca2+ and the release of Ca2+ from internal store. The [Ca2+]i increase in testicular arterioles is observed in any sizes of testicular arterioles, whereas in cerebral arterioles it was detected only large- and middle-sized (external diameters > 50 μm) arterioles.

These results indicate that the great variety of responsibility of the arteriole in different tissues. Namely, real-time confocal microscopy is a useful tool to investigate the structural and functional changes in living tissues, albeit a suitable tissue-preparation is important for the measurement.

Intra-vital imaging of platelet production in living mammalian

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Background and Purpose: Each megakaryocyte (MK) produces 1000-3000 enucleated platelets. The adult human produces approximately 1×10^{11}platelets per day and consumes in the day-to-day function maintaining vascular integrity and the other multiple functions. The derivation of blood platelets from bone marrow (BM) MKs has been known since 1906, and subsequent studies have led two different theoretical models, including platelet territory model and proplatelet model, for the mechanism of the in vivo platelet production. The final process of platelet production from MK, however, remains enigmatic, because there have been discrepancies over these models. In this study, to investigate the process of platelet production in intact BM, we studied mice skull BM by intra-vital microscopy.

Materials and methods: We used GFP-Tg mice which were anesthetized during time-lapse imaging by two-photon intra-vital microscopy. The protocol which focused on the MK protrusions in sinusoidal lumen was set. To support the morphological analysis from intra-vital imaging, we also observed fixed BM samples by scanning electron microscopy (SEM). All experiments were approved by Institutional Animal Care and Use Committees at Iwate Medical University.

Results: We successfully captured the clear time-lapse images of the process of platelet production in living mammalian BM. In intra-vital imaging study, BM MKs formed various size protrusions. These protrusions were released as various size strings into sinusoid, not discoid individual platelet. In SEM, we identified two types of protrusion determined by whether the protrusion contains platelet territory. Taken together protrusions principally consisted from two types, typical proplatelet without platelet territory, and thick protrusion with platelet territory.

Conclusion: *In vivo* BM MKs send and release the origin of platelets via two types of protrusion into vascular lumen, implying that individual platelet morphogenesis take place in the blood stream. Our results support the previous concepts of platelet production, not only proplatelet model, but also platelet territory model.

Y-1

Watershed of the subcutaneous capillary lymphatic network at the midline of the human body trunk

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Purpose & Methods: Most reports as to the network of subcutaneous capillary lymphatics in humans are about deep collecting lymphatics. The watershed at the midline of the body trunk is about collecting lymphatics running deep in the subcutaneous tissue and the network of capillary lymphatics existing in the dermis just beneath the epithelium remains poorly understood. As far as there was no interference with the student practice, we collected skin from a cadaver, stained lymphatics and observed (Approval number 01098).

Results & Conclusion: The networks of subcutaneous capillary lymphatics were observed in the subpapillary layer (SpL) and reticular layer (RL) of the dermis. The networks in these two shallow and deep layers were connected with each other by pre-collecting lymphatics and the lymphatic network in RL was connected with subcutaneous collecting lymphatics as previously reported. Valves were hardly recognized in the network of capillary lymphatics 10 μm in diameter in SpL, whereas they were present in the network of lymphatics 50 – 100 μm in diameter in RL and pre-collecting lymphatics were originated from around the valves and directed to the collecting venules in the deeper layer. We previously reported that there were arrays with a certain direction in the subcutaneous lymphatic network and they were presumed to be related with lymphatic flow. However, this study revealed that there was almost no valve that would determine the direction of lymphatic flow in the lymphatics network at least in SpL. Since the valves in the lymphatic network in RL were not placed to determine the lymphatic flow in the network, it was presumed that they played a role of a septum to let lymphatic fluid flow into the collecting lymphatics in the deep layer. Furthermore, there was no discontinuation in the lymphatic network in SpL or RL at the midline of the body trunk, and no watershed that resembled collecting lymphatics in the deep layer was observed. It was suggested that lymphatics just beneath the epithelium could potentially be used for collateral circulation in lymph drainage. Nevertheless, it has been reported clinically that efficiency is markedly poor. This point was also explained by the results of this study.

Y-2

Expression of autotoxin / lysophospholipase D in high endothelial venule-like vessel and its role on aberrant lymphocyte migration in inflamed intestinal mucosa

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Background: Aberrant leukocyte migration has been implicated in the pathogenesis of inflammatory bowel disease (IBD). Recently, lysophosphatidic acid (LPA) and its production enzyme, autotaxin (ATX)/ lysophospholipase D, are reported to play a critical role in lymphocyte migration to the second lymph organization. We have already reported that enhanced expression of ATX mRNA was observed in the high endotherium venule-like vessel in inflamed mucosa from IBD patients, and the degree of ATX mRNA expression was significantly elevated in the actively inflamed mucosa. This time, we investigated the involvement of ATX in the colonic inflammation using murine colitis model and cell line.

Method: In murine study, tissue samples were obtained from ileum of SCID mice transferred with CD4 cells of spleen, and colon of BALB/c mouse provided with drinking water containing DSS. Degree of expression of mRNA ATX was determined by using quantitative RT-PCR. Lymphocytes migration to the intestinal mucosa were evaluated by using intravitalmicroscopy. The inhibitory effect of ATX inhibitor on aberrant lymphocytes and activity of colitis were determined. To induce high endothelial venules in vitro, bEnd3 cell line was treated with TNF-alpha. Effect of ATX inhibitor on transendothelial migration of splenocytes through induced high endothelial vessels was studied by using transwell assay. Surface expression of adhesion molecules of transmigrated splenocytes were determined by flowcytometry.

Result: In both of mice models, degree of expression of ATX mRNA gradually increased as colitis developed and lymphocytes infiltration to intestinal mucosa increased. In both of mice models, lymphocytes migration to intestinal mucosa were increased. Administration of ATX inhibitor significantly ameliorated the colitis of each model mouse and decreased transmigration of splenocytes.

Conclusion: Enhanced expression of ATX in the active epithelium involves colitis through modulating lymphocytes migration to intestinal mucosa. Blocking of ATX ameliorates intestinal damage.

F-1

Laser-induced thrombus formation in angiotensin II type 1a receptor-knockout 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 angiotensin II type 1a (AT1a) receptor deficient 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 (control group, N=7) and AT1a receptor-knockout mice (AT1a knockout group, N=7) were anesthetized with chloral hydrate and inserted a catheter in their cervical vein. 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 AT1a knockout group (29%; P=0.043 vs control group, 6/21 vessels, vessel diameter 27.3±3.1μm). Thirty minutes after laser irradiation, the area of platelet thrombus was significantly larger in the control group (358±256μm^2) than in the AT1a knockout group (185±134μm^2; P=0.030 vs control group).

Conclusion: The present study suggested that the deficient of AT1a receptor inhibited the laser-induced thrombus formation in murine pial arteries.

F-2

Changes in diameter of cerebral microvessels and blood flow associated with potassium-induced cortical spreading depression in anesthetized mice

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Objective: We have already reported that potassium-induced cortical spreading depression (CSD) elicited transient enhancement of metabolism and suppression of red blood cell velocity in capillaries in spite of hyperperfusion in rats. The objective of this study was to measure the diameter of pial arteries and intraparenchymal capillaries, and examine the relationship with local cerebral blood flow (CBF) measured with laser Doppler flowmetry.

Methods: We used Tie2-GFP transgenic mice which emit fluorescence specifically in endothelial cells to visualize blood vessels (n=7). Under urethane anesthesia, a cranial window was made on the temporo-parietal region of the cerebral cortex. Diameter of microvessels was evaluated with the confocal laser-scanning microscopy and image analysis software ImagePro. Segments of pial arteries were classified as a main trunk (22-41 μm), a middle branch (13-23 μm) and a distal branch (7-16 μm) based on the branching pattern. DC potential and CBF were recorded at the nearest side of the cranial window simultaneously with measurement of vessel diameter.

Results: After administration of KCl on the brain surface through a burr hole posterior to the cranial window, CSD was repeatedly detected as a transient deflection of DC potential. First CSD elicited rapid vasoconstriction (-15.3±15.5 %) followed by gradual vasodilation (+11.1±14.9 %) in any segments of the pial arteries. Diametric changes were largest in the middle branches. CBF showed acute fall simultaneously with vasoconstriction and transient rise. After CSD, diameter of the pial arteries gradually returned to the baseline but slightly larger than the baseline (+7.3±7.0 %), whereas CBF showed long-lasting decrease by 30.6±12.2 % (post-CSD oligemia). Second and later CSD events were accompanied with transient CBF rise relative to inter-CSD level without significant diameter changes in the pial arteries. Diameter of the capillaries did not change significantly throughout CSD event.

Conclusion: Discrepancies between CBF response and diametric change in the cortical microvessels were observed during/after CSD. Integration of arterial responses in the distal regions may induce mixed changes in diameter of the proximal pial arteries. Capillary flow may be controlled, at least partially, by local mechanism other than diametric changes associated with CSD.

F-3

Measurement of change in RBC velocity and concentration evoked by whisker stimulation in awake and anesthesia mice

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Purpose: The mechanisms of regional hemodynamic response during neural activation including the concept of neurovascular coupling have been investigated using anesthetized rodent models. However, anesthesia significantly affects the physiological state including and regulation of cerebral circulation throughout the brain. The purpose of this study was to explore changes in hemodynamic characteristics during resting and sensory stimulation in awake animals as compared with those in anesthetized animals.

Methods: A total of 18 male C57BL/6J mice (20-30 g, 7-11 weeks) were used in this study. Changes in CBF, red blood cell (RBC) velocity and concentration in the somatosensory cortex to whisker stimulation were measured using laser-Doppler flowmetry in awake and anesthetized mice.

Results: The increase in RBC velocity observed during whisker stimulation was far higher than the increase in the RBC concentration under the awake condition ((RBC velocity: 18.4±7.5 %, RBC concentration: 1.7±2.9 %). 1.5% Isoflurane-induced anesthesia attenuated the increase in RBC velocity and concentration during stimulation (RBC velocity: 103.4±2.9%, RBC concentration: 1.4±1.0%), and the attenuation of increase in RBC velocity was quite large as compared to the change in RBC concentration. During the resting condition, significant differences in baseline CBF, RBC velocity and concentration between awake and anesthesia mice were not observed.

Conclusion: Isoflurane-induced anesthesia attenuated the evoked CBF that was mainly coursed by increase in RBC velocity during stimulation, indicating the decreased in energy demand in the brain as a result of the attenuation of neuronal activity with anesthesia might inhibit the evoked RBC velocity and concentration. The RBC measurement techniques in awake animals are likely useful for the investigation of the hemodynamic changes caused by changes in neural activity or other chemical factors like $PaCO_2$.

F-4

Barrel Cortex Activity to Whisker Stimulation and CO2 Response Measured in Mice with Suppressed Neurvascular Coupling Induce by Prolonged Continuous Hypoxia

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Objective: In order to examine possible explanation for suppression in neurovascular coupling (NVC) in prolonged continuous hypoxia model, cortical activity and vessel dilatory function were measured.

Material and Methods: C57BL/6J mouse was kept in a hypoxia chamber with 8% oxygen up to four weeks. A closed cranial window was made on the barrel cortex one week before the hypoxia. Cortical CBF responses to air puffs on whisker (10Hz for 20 sec) and to transient CO2 applications (5% for 20 sec per every 2min) were measured by LDF (n=2). Using separate prolonged continuous hypoxia mice, cortical activity to the stimulation was measured using multi-channel photodiode-array (12 x 12) and voltage sensitive dye (RH1691). All experiments were done in awake at 2 and 4 weeks of the hypoxia. Dynamic diameters of surface and parenchymal arteries at whisker stimulation were also measured at whisker stimulation using two-photon laser microscopy (TPLSM).

Results: CBF showed that CO2 response was preserved at 2 and 4 weeks of hypoxia. The barrel cortex neuronal activity was also preserved throughout before and after hypoxia. However, NVC response to whisker stimulation was reduced from 12.5% to 3.5%. TPLSM showed decreased dilation of the parenchymal artery from 11.8% to 2.3%.

Discussion: The present study showed that cortical neuronal function and vascular dilatory function were preserved even in the mice with suppressed NVC induced by the prolonged continuous hypoxia, suggesting that the hypoxia may cause malfunction in the pathway between the neuron and the vessel. Further study is needed to examine which component in this pathway is affected by the prolonged continuous hypoxia.

F-5

Effect of Clostazol on intramicrovascular behavior of platelets in murine brain after bilateral common carotid artery occlusion and reperfusion

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Introduction: Platelet behavior in cerebral microvasculature following vessel occlusion is not fully investigated. The purpose of this study is to investigate the effect of cilostazol on platelet behavior (rolling and adhesion) in murine cerebral microvessels following bilateral carotid artery occlusion and reperfusion using intravital fluorescence microscopy.

Methods: We used 18 C57BL/6J mice for the experment. 10 mice were used as control. In 8 mice, 10mg/kg of cilostazol was administered orally for 30 minutes before the experiment (cilostazol group). We induced bilateral carotid artery occlusion for 15 minutes using clip and reperfusion. A cranial window was prepared in the right parietal region. Platelets obtained from donor mice were labeled with a fluorescent dye (carboxyfluorescein iodoacetate succinimidyl ester; CSFE) *in vitro*. Labeled platelets were intravenously administered at 3 and 6 hours after reperfusion (3H, 6H) and then platelet behavior (rolling and adhesion) in the brain microvessels was observed. The number of platelet rolling and adhesion in the pial artery and vein were calculated.

Results: In cilistazol group, the numbers of platelet rolling were significantly inhibited in 3 or 6 hours after reperfusion compared to control ($P<0.05$), in pial veins; (3H;880±971/mm^2/30 sec, 6H; 1001±768, 3H Cilo; 85.6±185, 6H Cilo; 93.6±79.5) and in pial arteries; (3H;105± 98, 6H; 110±119, 3 H Cilo; 45.0±82.5, 6 H Cilo; 43.5±53.2). Similarly, the numbers of platelet adhesion were significantly inhibited in 3 or 6 hours after reperfusion compared to control ($P<0.05$), in pial veins; (3H;421±350, 6H; 804±685, 3H Cilo; 33.4±63.1 6H Cilo; 69.3±57.0) and arteries (3H;96±71, 6H;113±132, 3H Cilo; 12.1±36.3, 6H Cilo; 14.6±34). More platelets rolled and adhered to pial veins than to those in pial arteries ($P<0.05$).

Conclusions: Cilostazol inhibited platelet-endothelial intertaction following cerebral ischemia and reperfusion.

F-6

Immediate post-stroke administration of cilostazol alters profiles of various metabolic pathways in a mouse model of brain ischemia

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Background: Cilostazol, an inhibitor of phosphodiesterase3 (PDE3), is a unique antiplatelet drug as it has been shown to reduce the recurrence of vascular events without increasing the risk of bleeding complications, and to minimize post-stroke cognitive impairment. However, mechanisms underlining these beneficial effects remain elusive.

Purpose: The present study was, therefore, designed to examine 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 state was rapidly fixed by the *in situ* freezing to avoid autolysis of labile metabolites. Metabolites were then extracted from both contra- and ipsilateral hemispheres. A high-throughput metabolomics approach using capillary electrophoresis mass spectrometry (CE/MS) enabled us to assign and quantify approximately 150 water-soluble metabolites with a single sample preparation.

Results: Cilostazol treatment induced various changes in metabolic profiles in ischemic brain. First, 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. Second, 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. Finally, cilostazol treatment improved ischemia-induced attenuation of NAD^+ and decreased nicotinamide contents with dose-dependency in both hemispheres, indicating that cilostazol activated a salvage pathway of NAD^+ biosynthesis.

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 via NAD^+ elevation that may lead to beneficial therapeutic stratagem in cerebrovascular diseases.

Free Paper

F-7

CO-sensitive CBS/H2S pathway mediates hypoxia-induced microvascular dilation in the brain

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Objective: The main goal of the present study is investigate the role of gaseous mediators in the regulation of vascular and neural functions in the central nervous system. Brain generates a micromolar order of CO *via* heme oxygenase (HO) reactions and also generates H_2S *via* cystathionine β-synthase (CBS) reaction. Previous study from our laboratory using brain slice preparation indicates that a cascade of O_2-dependent events involving CO and H_2S productions play a role in hypoxia-induced microvascular dilation. To test this idea further *in vivo*, we visualized vascular responses under hypoxia in the CBS-null mouse and HO-2-null mouse cerebrum using two-photon laser scanning microscopy. Furthermore, we examined the effects of HO-2 deletion on hypoxic responses on cerebral energy metabolism.

Methods: After thinned skull window preparation, animals were mechanically ventilated with 21% O_2 balanced by N_2, and then challenged by hypoxia for 10% O_2. To visualize the cerebral microvasculature, a small bolus (~15 μL) of Q-dot 655 nanocrystals was injected. To determine the differences in the brain energy metabolism between wild-type (WT) and HO-2-null mice upon hypoxia, ATP, ADP and AMP were assayed using semi-quantitative imaging mass spectrometry.

Results: WT mice exhibited a rapid and robust dilation (>40% at 1 min) that became maximum within 10 min by hypoxia. On the other hand, such a dilation of pre-capillary arterioles was severely impaired by 50% in HO-2-null mice and lost completely in CBS-null mice, suggesting that the enzymes are necessary to initiate the acute vasodilatory response. Under normoxia, ATP amounts in the cortex were significantly greater in HO-2-null mice than in WT mice. After exposure to hypoxia for 1 min, the ATP contents in the cortex and hippocampus of WT mice were unchanged, while those of HO-2-null mice were decreased significantly by 50%. These results suggest that the HO-2/CO system is a determinant of basal energy metabolism and its tolerance against hypoxia in these regions.

Conclusion: Our data provide evidence that the CO-sensitive CBS/H_2S pathway mediates hypoxia-induced arteriolar dilation and regional ATP maintenance in the brain.

F-8

Microcirculation changes of periodontal tissue after ultrasonic tooth preparation

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Purpose: The purpose of this study was to examine the microcirculation changes in the periodontal tissue after tooth preparation. The conventional dental turbine and ultrasonic methods were examined as a way of tooth preparation. To evaluate invasion for gingival microcirculation, we investigated morphological and physiological differences between these preparations.

Materials and Methods: The preparations were performed on the premolars in Beagle dogs. A finishing line was created by a diamond instrument along the gingival margin with either a dental turbine or an ultrasonic wave. To visualize the changes in the gingival vasculature, a corrosion resin cast was used and visualization performed with a scanning electron microscope (SEM) and also to evaluate the effect of tooth preparation on gingival circulation, gingival blood flow at the same site with preparation was determined simultaneously by laser Dopplar flowmetry (LDF). These parameters were determined mmediately (0), 7 and 30 days after tooth preparation.

Results: Immediately after preparation using the dental turbine, blood vessel was destroyed by instruments. And resin leakage was seen, indicating that bleeding had occurred in the gingiva. Gingival blood flow at identical site with tooth preparation was significantly increased at immediately after tooth preparation. Seven days after the preparation, the blood vessels constructed glomerulus loops. On the other hand, immediately after preparation using ultrasonic waves, the vasculature appeared normal. Resin leakage was seen between the endothelium. Seven days after the preparation, vascular regeneration was nearly complete. No significant alteration was observed in gingival blood flow of preparation site for 30 days after preparation.

Conclusions: Our observations suggest that the use of the ultrasonic wave instrument caused minimum damage compared to the use of the dental turbine. Therefore, in terms of protecting the microcirculatory system in the gingival tissue during tooth preparation, the ultrasonic wave instruments would be useful tools in not only scaling and endodontic treatment, but also teeth preparation.

F-9

Gingival Vascular Functions Are Altered in Periodontitis and/or Stroke Rodent Model

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Purpose: In recent years, endothelial function has been estimated by plethysmography, which was verified reactive hyperemia of forearm. We reported that measuring of reactive hyperemia in the oral microcirculation could be estimated vascular endothelial function of general circulation same as plethysmography of forearm. Using by measuring reactive hyperemia in the oral microcirculation, we examined endothelial function and gingival blood flow on the oral microcirculation of lifestyle-related disease animal models such as periodontitis or stroke.

Method: Gingival blood flow was measured by using a laser Doppler flowmetry on Wistar Kyoto rats (WKY), *Porphyromonas gingivalis* (*P.g*) infection to WKY (WKY+*P.g*; periodontitis rodent model), Stroke-Prone Spontaneously Hypertensive Rat (SHRSP; stroke rodent model), and *P. gingivalis* infection to SHRSP (SHRSP+*P.g*; periodontitis and stroke animal model), respectively. To evaluate vascular endothelial and smooth muscle functions, reactive hyperemia was elicited by release of occlusive gingival compression for 1 min after acetylcholine (ACh) and nitroglycerine (NTG) were absorbed from gingival mucosa. Furthermore, relaxations of the posterior aortic ring preparations were measured as in vitro vascular responses in WKY, WKY+*P.g*, SHRSP and SHRSP+*P.g*.

Result: Gingival reactive hyperemia (GRH) was decreased in WKY+*P.g* compared to WKY. However, GRH was significantly increased in SHRSP+*P.g* compared to SHRSP and in SHRSP after treatment with ACh. In addition, GRH was significantly increased in WKY, SHRSP, and SHRSP+*P.g*, after treatment with NTG. The endothelium-dependent relaxation evoked by ACh, which was involved in nitric oxide (NO) from eNO synthase, to the ring preparations was attenuated in SHRSP compared to WKY, but not in SHRSP+*P.g*. This effect observed in SHRSP was recovered by pretreatment with superoxide dismutase.

Discussion: Our results suggested that alteration of endothelial function may occur in gingival tissue on both periodontitis and stroke rodent models. Oxidative stress induced by reactive oxygen species (ROS) could be related in vascular effects on both periodontitis and stroke. Therefore, it would be likely that the disruption of vascular function of oral microcirculation caused by the interaction between ROS and NO on periodontitis and/or stroke rodent model.

F-10

A case series of 21 patients with gastric antral vascular ectasia: Clinical aspects and treatment with argon plasma coagulation

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BACKGROUND: Gastric antral vascular ectasia (GAVE) is a rare but well-known cause of gastrointestinal bleeding. No practical criteria or simple index has been established for evaluating the risk of bleeding or the effect of therapy in patients with GAVE. Endoscopic treatment involving argon plasma coagulation (APC) has been considered as one of the best endoscopic therapeutic options for this condition. Here, we report the endoscopic and clinical features of GAVE and its response to endoscopic APC on the basis of a severity classification.

PATIENTS AND METHODS: The case records of 21 patients who were diagnosed with GAVE were retrospectively reviewed. The severity of GAVE was classified as the watermelon, diffuse, or macular type on the basis of endoscopic findings.

RESULTS: The average age of the patients was 69.5 (12.0) years (range, 34–91 years). All the patients had at least 1 comorbid condition: liver cirrhosis, 17 patients (hepatitis C cirrhosis, 13 patients; alcoholic cirrhosis, 3 patients; and primary biliary cirrhosis, 1 patient); esophageal varices, 14 patients; chronic renal failure (CRF), 10 patients; CRF requiring hemodialysis therapy, 5 patients; hypothyroidism, 2 patients; and active systemic lupus, 1 patient. Fourteen patients with anemia due to iron deficiency or GAVE-induced gastrointestinal blood loss were treated with APC. Of these 14 patients, 8 patients required blood transfusion. A sustained increase was observed in the mean post-treatment hemoglobin levels ($p < 0.001$). Although acute bleeding was well controlled, 9 patients experienced bleeding during the follow-up period (6–36 months). Refractory bleeding and APC retreatment were more frequent in the patients with watermelon-type GAVE than the other types. No remarkable procedure-related complications were identified.

CONCLUSION: GAVE is a serious condition in patients with chronic renal failure or liver cirrhosis and can cause either acute or chronic upper gastrointestinal bleeding. APC is a safe and effective endoscopic treatment modality for GAVE.

F-11

The expression of podoplanin and classical cadherins in the mouse choroid plexus

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Purpose: Podoplanin is a glycoprotein indirectly linked to classical cadherins through ezrin-actin networks and promotes the cadherin switch in some cancer cells. Recently, it has been reported that the overexpression of podoplanin occurs in high-grade malignancy brain tumors but there is no report examining the relation of podoplanin and classical cadherin in the normal brain. This study aims to investigate the expression of podoplanin and classical cadherins in the non-CNS tissue of the brain.

Materials and methods: Immunohistochemistry and the real time RT-PCR on the expression of gene and protein of podoplanin and classical cadherins were performed about the ICR mouse tissue.

Results and discussion: Immunohistochemistry showed that podoplanin was expressed on ependymal cells and choroid plexus epithelial cells at the ventricle side of cell surface and at the cell-cell junctions, and on retinal pigment epithelial cells and in the pia mater; P-cadherin between choroid plexus epithelial cells and endothelial cells at the basement membrane side of cell surface, and between retinal pigment epithelial cells; VE-cadherin on the PECAM-1 positive-choroid plexus endothelial cells of the fibrovascular core; and N-cadherin on the cell surface and at the cell-cell junctions of ependymal cells, and in the pia mater. The regions expressing podoplanin, P-cadherin, and VE-cadherin did not coincide. In real-time PCR analysis, podoplanin, and P- and N-cadherin mRNA amounts were larger in the ventricular wall with choroid plexus than in the abdominal aorta and cerebrum. In the RT-PCR analysis, the intensities of amplicon for VE-cadherin mRNA were the same for the abdominal aorta, cerebrum, and ventricular wall with the choroid plexus, suggesting that ependymal cells, choroid plexus epithelial cells, and glial cells under the pia mater have the ability to express podoplanin, and P- and N-cadherins.

Conclusion: Glial cells and retinal pigment epithelial cells may create barriers by podoplanin and classical cadherins as a rate-determining step for transmission of blood components.

F-12

Effects of breathing method on the peripheral circulatory response and the brain blood flow in elders

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1. Purpose: We reported that the control and regulation of muscle vascular tone are maintained well via the central nerve-sympathetic and myogenic coupling in Ki and Budo experts (2004). In Ki and Budo experts use the breath methods to reduce the stress and increase the relaxation. The purpose of this study is to investigate that the effects of the breathing method on the circulatory response and brain blood flow in elders.

2. Methods: 1) Subject: The subjects are the elder breathing method practitioners and the non-experienced elders. 2) Breathing Method: The Nishino breathing method (NBM) consists of three fundamental parts. The first is various breathing method (30min). The second is the slow moving body exercise for relaxation (30min). The third is Tai-ki for exchanging Ki energy with another person (30min). 3) Measurements: ①Mood and the degree of stress: The stress level was measured using the Lorish face scale method and the stress checklist (30 items) before and after the breathing method. ②Microcirculatory response: Peripheral vain size and hemoglobin were measured by ASTRIM in the finger tip on the several times in the experiment. ③the heart rate and respiration were monitored during the experiment. ④Brain blood flows were measured by near-infrared spectroscopy (NIRS) on the forehead during the experiment.

3. Result and discussion: The mean stress level was significantly reduced after the breathing method. Several subjects were observed that an increase in the peripheral vain size and the occurrence of vascular dilation was confirmed. Brain blood flows increased slightly in the experienced elders. It suggests that the changes of the brain blood flow concerned with the rich image. These results demonstrate that breathing method is able to reduce the stress and control the microcirculatory system in even elders.

F-13

Topical latanoprost increases retinal blood flow in the macular circulation

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Purpose: Retinal Function Imager® (RFI, Optical Imaging Ltd.) is a novel device offering a noninvasive diagnostic approach to retinal function assessment. The purpose of this study was to evaluate the effect of topical latanoprost on the retinal microcirculation using RFI in healthy volunteers.

Methods: Five healthy volunteers (mean age, 32.5 years) were recruited and microcirculation velocities at perifovea were quantitatively analyzed by RFI. Intraocular pressure (IOP), blood pressure (BP) were also measured. In a single-blind trial, all measurement was done before and after the instillation of latanoprost once a day for 2 weeks.

Results: One week instillation of latanoprost decreased IOP from 13.0 ± 4.3 mmHg to 10.0± 2.2 mmHg (p=0.05). Retinal arterial blood flow velocity significantly increased at 2 weeks after instillation of latanoprost (from 1.93± 2.0 mm/sec to 2.35± 0.30mm/sec, p=0.04). Retinal venous blood flow velocity also increased (from 1.85±0.30 mm/sec to 2.07± 0.24 mm/sec, p=0.08). There was no significant difference in BP and ocular perfusion pressure before and after instillation of latanoprost.

Conclusions: Our data showed that topical latanoprost significantly increased arterial blood flow velocity at perifovea in human eyes. These results suggested that RFI might be useful to evaluate blood flow velocity in the glaucoma patients, to assess the efficacy of topical glaucoma agent.

F-14

Ultra-widefield Fluorescein Angiography with Scanning Laser Ophthalmoscope

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Purpose: The ultra-widefield scanning laser ophthalmoscope (Optos 200Tx) provides retinal images of 200 degrees in a single capture which covers more than 80% of the fundus. The purpose of this study was to evaluate the usefulness of widefield fluorescein angiography in various retinal diseases.
Subjects: Color fundus imaging and fluorescein angiography were performed by Optos 200Tx (Optos, Scotland, UK) on patients at Nagoya City University Hospital. The patients had diabetic retinopathy, retinal vein occlusion, and uveitis.
Results: The widefield fluorescein angiograms allowed the detailed evaluation of microcirculatory changes in the mid-peripheral to the far peripheral retina. The assessment of capillary non-perfusion area in eyes with diabetic retinopathy and retinal vein occlusion was much easier than the conventional fundus camera. It was also useful to detect small neovascular vessels in the peripheral retina. Evaluation of peripheral lesions in eyes with uveitis was possible, which provided the useful information on the diagnosis and the treatment.
Conclusion: The ultra-widefield fluorescein angiography with Optos200Tx was very useful and provided the valuable information on the diagnosis and the treatment of ischemic and inflammatory retinal disorders.

F-15

Development of in vivo imaging method and analysis of microcirculation of pancreatic islet in living animals

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Backgrounds and Purpose: Hypertension and diabetes share a common basis of pathogenesis and thereby frequently develop concomitantly. Atherosclerosis and arteriolosclerosis develop and result in cardiovascular events in hypertensive patients. In such disease condition, deterioration of microvascular architecture and associated fibrosis are demonstrated even in pancreatic islets. These histological changes presumably impair the islet function and confer the susceptibility to development of diabetes. Some clinical studies have shown that the renin-angiotensin inhibitors delay onset of diabetes, independently of their antihypertensive effect. Islet afferent arterioles are demonstrated to be equipped with auto-regulatory mechanism and renin-angiotensin system is indicated to be involved in this mechanism. We hypothesized that angiotensin II directly regulate pancreatic islet microcirculation and thereby regulate insulin secretion. The aims of the present study are as follows; 1) to develop a novel technique to visualize pancreatic islet microcirculation in vivo, 2) to analyze the regulatory mechanisms of islet microcirculation, and 3) to evaluate the effect of angiotensin II and angiotensin type 1 receptor blocker (ARB) on islet circulation.

Methods: We have been already established the in vivo live-imaging method with two-photon laser microscopy and fluorescence probes to visualize microcirculation of kidney. We have applied this system to develop the novel in vivo imaging method of pancreatic islet microcirculation. To identify the islet beta-cells, we used Ins1-DsRed mouse, which have transgenic construct containing the Red Fluorescent Protein gene under the control of the mouse insulin 1 promoter. Angiotensin II or ARB were injected intravenously, and islets hemodynamic changes were observed.

Results: We have successfully developed the in vivo imaging method to visualize and analyze the microcirculation of islet in living mouse. Angiotensin II significantly contracted blood vessels of islet and decreased pancreatic islet blood flow in a dose-dependent manner. In contrast, ARB significantly induced vasodilation and increased islet blood flow.

Conclusion: We have elucidated that renin angiotensin system is involved in the regulatory mechanisms of microcirculation in pancreatic islets by novel in vivo live-imaging techniques.

F-16

Involvement of ribosomal protein S19 oligomers in acute inflammation resolution

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Purpose: The resolution of acute inflammation seems to be an active process as in the case of start. Major mechanisms of the inflammation resolution are apoptosis of infiltrated neutrophils and phagocytic clearance of the apoptotic cells by macrophages. We have been elucidating the extra-ribosomal function of ribosomal protein S19 (RP S19), and have revealed that the apoptotic cells generated the cross-linked RP S19 oligomers and released extracellularly; the RP S19 oligomers then recruited monocytes/macrophages in one hand and promoted the execution of apoptosis in the other. By these functions RP S19 oligomers synchronize the apoptosis and its phagocytic clearance. We currently made a hypothesis that the synchronization by the RP S19 oligomers would play a major role in the acute inflammation resolution, and experimentally examined this hypothesis.

Experimental procedures and Results: 1) We prepared a HL-60 transformant cells over-expressing Gln137Asn-RP S19 mutant which could not become the functional RP S19 oligomers, and made the mutant cells as well as the wild type cells to maturate *in vitro* to neutrophil-like cells. We respectively injected these neutrophil-like cells into the mouse skin, and comparatively examined their fates by means of histopathology. The wild type neutrophil-like cells quickly underwent apoptosis and were engulfed by infiltrated macrophages. On the other hand, the Gln137Asn-RP S19 over-producing neutrophil-like cells remained much longer in association to lacking the macrophage infiltration. 2) We induced mouse pleurisy by injecting carrageenin into a pleural cavity in the simultaneous presence of neutralizing antibodies against the RP S19 oligomers or of control IgG. When the RP S19 oligomers were neutralized, the neutrophil infiltration was greatly enhanced and prolonged; furthermore, the inflammation expanded into lung parenchyma. 3) We prepared a knock-in transgenic mouse in which the RP S19 gene was replaced by a Gln137Glu-RP S19 mutant gene, and induced the carrageenin pleurisy in the knock-in mouse. Basically the same phenomena as in the case of the RP S19 oligomer neutralization were observed.

Conclusion: Involvement of the cross-linked RP S19 oligomers in acute inflammation resolution was evidently shown.

F-17

Role of BTB and CNC homolog 1 (Bach1) in ischemia-reperfusion-challenged intestinal inflammation

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Purpose: The acute phase of intestinal ischemia-reperfusion (I/R) injury that occurs in various clinical settings is characterized by oxidative stress-related inflammation and leukocyte recruitment. Heme oxygenase (HO) and carbon monoxide, one of the by-products of heme by HO, have been shown to confer anti-inflammatory effects in intestinal I/R injury; however, the potential mechanisms of HO-1 transcriptional regulations including BTB and CNC homolog 1 (Bach1) in I/R-challenged intestinal injury remain unclear. In this study, we investigated the role of Bach1 on modulation of inflammatory responses in I/R-challenged intestinal injury.

Methods: To this end, mice (WT and Bach1 knockout) small intestine were challenged with ischemia by clamping superior mesenteric artery (SMA) for 45 mins. HO-1 inhibitor (SnPP) was used before induction of ischemia. Inflammatory responses in the small intestine was assessed 4h following reperfusion.

Results: Luminal inflammatory markers such as luminal protein/hemoglobin, tissue levels of TNF-alpha and KC, and subsequent PMN accumulation were significantly elevated in I/R-challenged small intestine of WT mice. The above changes were significantly attenuated in I/R-challenged small intestine of Bach1 knockout mice. Treatment with HO-1 inhibitor resulted in the reverse of these attenuations in I/R-challenged small intestine of Bach1 knockout mice. Immunohistochemical analysis showed that HO-1 protein was expressed in the macrophages of I/R-challenged intestinal mucosa in WT mice and further expressed in the small intestine of Bach1 knockout mice. These increases in HO-1 protein expression by IR induction and Bach1 deficiency were also confirmed by Western blot.

Conclusions: These findings indicate that deficiency of Bach1 gene resulted in attenuation of I/R-challenged intestinal injury via increase in anti-inflammatory macrophages and up-regulation of HO-1.

F-18

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

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Aims: Impaired liver repair and regeneration are linked to the extent of hepatic ischemia/reperfusion (IR) injury. Recent evidence suggests that vascular endothelial growth factor (VEGF) and its receptors are crucial for liver tissue repair after toxin-induced 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 (TK)-knockout mice (TK-KO) or their wild counterparts (WT) were subjected to 60 min 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. The mRNA expressions of growth factors in the liver tissues were determined by real-time RT-PCR.

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 TP-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, while there were no differences in the cells expressing F4/80 and Ly6B between the two genotypes.

Conclusions: These results indicate that VEGFR-1 signaling is involved in liver repair and regeneration during hepatic I/R through enhancement of growth factors and recruitment of macrophages expressing VEGFR1 and CD11b.

F-19

Thromboxane A2 receptor signaling promotes regeneration of the mouse liver during carbon tetrachloride-induced acute liver injury

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Aims: Prostanoids have been suggested to be involved in liver regeneration after partial hepatectomy. We thought that thromboxane A2 (TxA2) mediates liver recovery from the acute injury. The objective of the present study was thus to examine the role of TxA2 receptor (TP) signaling in liver repair after drug-induced acute liver injury.

Methods: Carbon tetrachloride (CCl4) (1.0 mL/kg, ip.) was used to induce acute liver injury in TP knockout mice (TP-/-) and their wild counterparts (WT). Serum samples and liver tissue for histology were analyzed on 0, 24, 48, 72, and 96 h after CCl4 administration. The hepatic levels of mRNA expression for growth factors were determined by real time RT-PCR. Liver microcirculation was assessed by *in vivo* microscopy.

Results: ALT levels in both groups with a peak at 24 h after CCl4, were declined thereafter. However, necrotic area in TP-/- was greater than WT. Sinusoidal perfusion in WT was impaired, and reached to the nadir at 48 h, and then recovered to 90% of pre-values. In TP-/-, the restoration of liver microcirculation was delayed. The numbers of proliferating cell nuclear antigen (PCNA) positive cells were peaked at 48 h in WT, while peaked at 72 h in TP-/-. The hepatic mRNA levels of IL-6, TNFα, and hepatocyte growth factor (HGF) in TP-/- were decreased when compared with WT. The numbers of infiltrating F4/80- and CD11b-positive cells in TP-/- liver were lower than WT. The expression of MCP-1 (monocyte chemoattractant protein-1) and its receptor CCR2 in liver from in TP-/- was reduced. The application of U-46619, a TP analogue, enhanced the levels of mRNA for MCP-1, CCR2, IL-6, TNF, and HGF from the isolated peritoneal WT-macrophages.

Conclusions: These results indicate that TP signaling may promote liver repair during CCl4-toxicity through restoration of liver microcirculation and enhancement of macrophage accumulation accompanied by expression of growth factors.

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Reprogrammed cancer cells upregulate angiogenesis-related genes and downregulate tumor suppressor genes

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Purpose: Reprogrammed cancer cells with pluripotency was reported and called as induced pluripotent cancer (iPC) cells. We previously reported that iPC cells repressed tumor suppressors. Here we investigated angiogenesis-related gene expressions and other tumor-related gene expressions of reprogrammed hepatoma cell (PLC/PRF/5).

Methods: PLC/PRF/5 cells were reprogrammed by induction of 4 factors (Oct3/4, Sox-2, Klf-4 and c-Myc) as previously reported. iPC cells were maintained in human ES cell medium supplemented with 4 ng/ml bFGF. Parental PLC/PRF/5 and iPC cells were plated in 12 well plates with ES medium without bFGF for RT-PCR analysis. Next day, the cells were treated with TGF-β (10ng/ml) and incubated for 48 h at 37 °C in a humidified 5 % CO_2 atmosphere. Total RNA was extracted and analyzed by real-time PCR. To determine cell growth rate, we performed MTT assay. Cells were plated in 96 well plates and were added MTT reagent at the indicated time points. To investigate tumorigenicity, we performed soft agar assay. Cells were suspended in DMEM containing 10 % FBS and 0.4 % low melting agarose, and plated onto solidified 0.6 % agarose containing DMEM in 6 well plates at a density of 2×10^4 cells per well. After incubating for 14 d at 37 °C in a humidified 5 % CO_2 atmosphere, phase contrast images were taken using a bright-field microscope.

Results: PLC/PRF/5 iPC cells generated by induction of 4 defined factors were round and flat in morphology and similar to human ES cells. We performed qRT-PCR to investigate their gene expressions. As a result, we found that reprogrammed PLC/PRF/5 iPC cells got increased expressions of immature status-related genes, and immature hepatocyte markers. We previously found that PLC/PRF/5 cells were capable to induce tumor suppressor Lefty expression prominently, which was only found in ES or iPS cells, upon TGF-β treatment. We also found that reprogramming cancer cells completely abolish induction of Lefty by TGF-β. As we expected, tumor suppressor expressions such as p53 and p16 were downregulated in PLC/PRF/5 iPC cells. In this study, we newly proved that their angiogenesis-related gene (VEGF, VE-cadherin and PECAM-1) expressions were increased significantly, and their growth and tumorigenicity were facilitated.

Conclusion: Reprogramming by induction of 4 defined factors could make hepatoma cells morphologically more ES cells-like and more immature than parental cells. This process may play important roles to repress tumor suppressor gene expressions and increase angiogenesis-related gene expressions. Reprogramming process is a new good model for cancer progression and may open new way to develop an effective cancer treatment.

F-21

Erc/mesothelin is a novel diagnostic biomarker for the mouse model of pancreatic ductal adenocarcinoma

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Purpose: Pancreatic ductal adenocarcinoma (PDAC) is one of most hard–to-treat cancer with the mortality rates almost identical to the incidence rate. The vast majority of patients present with incurable metastatic disease, and there remains a lack of both tests for early diagnosis, as well as effective therapies. Therefore the novel diagnostic biomarker and therapeutic agents are much required.

Erc/mesothelin is a glycoprotein expressed on normal mesothelial cells, and is also over expressed in several histological types of tumors including pancreatic adenocarcinomas. A soluble form of this protein has been detected in patient with ovarian cancer and malignant mesothelioma, and has prognostic value. Thus, we conducted a study on the potential diagnostic utility of Erc/mesothelin as a biomarker for the PDAC.

Methods: PDAC model mouse has been generated by pancreas specific type II receptor (*Tgbr2*) knockout, in the context of active *Kras* expression, using Cre-loxP system both driven by the endogenous *Ptf1a* (*pancreatic transcription factor-1a*) locus (Ijichi et al., Gene Dev 2006). Tumor tissue-bound and soluble Erc/mesothelin in PDAC model mouse was evaluated by immunohistochemistry and newly designed mouse Erc/mesothelin specific ELISA, respectively.

Results: Homozygous deletion of *Tgfbr2* with *Kras* expression developed well-differentiated pancreatic ductal adenocarcinoma with 100% penetrance with the median survival at day59. The histological features of these knockout mice recapitulated human PDAC. Expression of Erc/mesothelin in the tissue section of the PDAC mouse tumor was observed at the age of day35. Furthermore, marked increase in serum levels of Erc/mesothelin accompanying the tumor progression was detect as early as day28, which was 3 times higher than that of the basal level.

Thus, Erc/mesothelin may become a useful biomarker for the early detection of the PDAC, not only in mouse models but in patients of the pancreatic cancer.

F-22

Angiogenesis and Lymphangiogenesis in Hepatic and Pulmonary MALT lymphoma in *Helicobacter heilmannii*-infected Mouse: Effect of Eradication of Bacilli

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Background & Aims: We established the low-grade MALT lymphoma model in C57BL/6 mouse infection of *Helicobacter heilmannii* obtained from cynomolgus monkey (Infect. Immun. 75 (3): 1214-1222, 2007). After long term infection, we found the MALT lymphoma formation in the liver and lung in addition to gastric MALT lymphoma. Thus, the present study was undertaken to clarify the the influence of eradication of bacilli on the MALT lymphoma in the liver and lung.

Methods: We used an *Helicobacter heilmannii* 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. Half of the mice were treated with the combination of amoxicillin, clarithromycin and lansoprazole for the eradication of the bacilli. Macroscopic observations were carried out, and histochemical studies as well as PCR analysis of the bacteria of the Helicobacter species were performed. In addition, the histochemical characteristics of the microvascular network in the MALT lymphoma was investigated using monoclonal and polyclonal antibodies against CD31, podoplanin, VEGF-A, VEGF-C, Flt-1, Flk-1, Flt-4 and compared with the gastric MALT lymphoma.

Results: Nine months after the infection, small lymphocyte aggregates mostly composed of B cells were observed in the portal area of the liver as well as the gastric MALT lymphoma in about 50% of the infected mice. These lymphocytes were mostly centrocyte-like cells and lymphoepithelial lesion characteristic to the MALT lymphoma was also recognized. PCR and in situ hybridization analysis showed the existence of *Helicobacter heilmannii* not only in the fundic mucosa but in the liver and lung. After the eradication of the bacilli, the fundic glandular MALT lymphoma almost disappeared and the size of the MALT lymphoma in the liver and lung significantly reduced. The number of capillaries and venules decreased as well as VEGF, Flt-1, Flk-1, Flt-4 positive cells.

Conclusion: Long term infection of Helicobacter heilmannii in C57BL/6 mouse induced the low and high grade hepatic and pulmonary MALT lymphoma as well as gastric lymphoma. Eradication of the bacilli reduced the increased microvascular network in the hepatic and pulmonary lesion.

F-23

Selective destruction of tumor vasculature by CAST (cancer stroma targeting) therapy

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Background: Most human solid tumor forming hypovascular and stroma-rich tumor hinders the penetration of therapeutic monoclonal antibody (mAb) into the cells, and that leads failure of the conventional cell-targeting immunoconjugate strategy. To overcome this drawback, we developed anti-stroma targeting immunoconjugates as cancer stroma targeting (CAST) therapy.

Purpose: To evaluate anti-tumor vascular effect of CAST therapy in stroma-rich mouse cancer model.

Method: SN-38, a topoisomerase 1 inhibitor, was conjugated to a mAb to collagen 4 or fibrin, a plentiful component of the tumor stroma via ester-bond. Anti- collagen 4 or fibrin immunoconjugate was administered against pancreatic cancer xenotransplant model or chemical induced mouse skin cancer model. The change of tumor vessels was evaluated by immunohistochemical analysis or in vivo imaging visualized with FITC-dextran.

Result: Both anti-collagen 4 and anti-fibrin immunoconjugate were selectively extravasated from leaky tumor vessels, bound to the target molecules within the tumor stroma, from which effective sustained release of SN-38 occurred. The agent subsequently diffused throughout the tumor tissue causing marked arrest of tumor growth. In immunohistochemical analysis, besides damaged tumor cells, many collagen 4-positive round profiles corresponding to traces of destroyed vessels (empty sleeve) were observed. Moreover, in vivo imaging analysis showed discontinuation and irregularity comprising a mixture of narrowness and enlargement of the tumor vessels (but not normal vessels).

Conclusion: In addition to the direct tumor cell cytotoxicity, anti-stroma targeting immunoconjugates can destroy the tumor vessels selectively. Thus CAST therapy was validated as a new modality of oncological therapy, especially for refractory, stromal-rich cancers.

F-24

MICROVASCULAR RICH PYOGENIC GRANULOMA OF THE DISTAL SMALL INTESTINE

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Pyogenic granuloma is a hemorrhagic protruding tumor and lobular capillary hemangioma associated with secondary inflammation. Although it occurs most commonly on the skin and oral mucosa, its occurrence in the gastrointestinal tract is extremely rare. Recently, we experienced a case of pyogenic granuloma of the distal small intestine.

The patient was woman in her 80s who complained of bloody stool and severe anemia. Esophagogastroduodenoscopy, colonoscopy, capsule endoscopy, computed topography, and magnetic resonance imaging could not detect a significant bleeding focus. Double-balloon enteroscopy showed a freely bleeding, 10-mm protruding tumor of the ileum approximately 30 cm from the ileocecal valve, which was resected endoscopically. Histopathological analysis showed superficial erosion, proliferation of enlarged capillaries, and interstitial edema. In addition, F-VIII, CD31, and CD34, which are markers of the vascular endothelium, were positive. Based on these results, the patient was diagnosed as having pyogenic granuloma.

Pyogenic granuloma of the gastrointestinal tract is extremely rare, and only 9 cases in the ileum have been reported in Japan. Although it is a benign tumor, its growth is relatively rapid. Therefore, it is important to distinguish it from malignant tumors. Furthermore, because it is a vasculated tumor, it is sometimes accompanied by fatal anemia. Recurrence after resection has been reported in pyogenic granuloma of the skin and oral cavity; therefore, careful follow-up will be necessary. With the increased use of double-balloon enteroscopy or capsule endoscopy, the likelihood of identifying these cases will also increase. Moreover, it is important to consider pyogenic granuloma as one of the differential diagnoses in gastrointestinal bleeding.

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Cardioprotective Role of Hydrogen Peroxide and Angiotensin Type 1 Receptor Blockers during Acute Coronary Occlusion in Canine Native Coronary Collateral Microcirculation in Vivo

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***Purpose*:** We have previously demonstrated that endothelium-derived hydrogen peroxide (H_2O_2) is an endothelium-derived hyperpolarizing factor, playing a crucial regulatory role in canine coronary collateral microcirculation in vivo. However, the role of endogenous H_2O_2 in coronary collateral vasodilatation during myocardial ischemia before and after angiotensin type 1 receptor blockers (ARB) remains to be examined. In this study, we examined whether ARB enhances H_2O_2-induced vasodilatation during acute coronary occlusion in canine coronary collateral microvessels in vivo and if so, whether such beneficial effects of ARB acutely improves coronary collateral vasodilatation in diabetes mellitus (DM).

***Methods*:** Canine subepicardial native collateral small arteries (CSA ≥100 μm) and arterioles (CA <100 μm) were observed by an intravital microscope under cyclooxygenase blockade. Experiments were performed after LAD ischemia (90 min) under the following 6 conditions (n=5 each); (i) control, (ii) ARB (olmesartan, 10 μg/kg/min, 10 min, ic), (iii) ARB +catalase (H_2O_2 decomposer, 1000 U/ml, 5 min, ic), (iv) DM (alloxan 60 mg/ kg, iv, 1 week prior to study), (v) DM+ARB and (vi) DM+ARB+catalase.

***Results*:** Myocardial ischemia caused significant vasodilatation in both sized arteries (CA 17±4% CSA 6±1%) under control conditions. After ARB, the vasodilatation was significantly increased in both-sized arteries (CA 21±3%, CSA 9±1%, both $P<0.05$) compared with control, and was significantly decreased by catalase in CA (13±2%, $P<0.05$) but not in CSA (7±2%). DM significantly decreased the coronary vasodilatation compared with control in both sized arteries (CSA -4±1%, CA 2±1%, both $P<0.05$), whereas DM+ARB significantly improved the vasodilatation compared with DM in both sized arteries (CSA 1±1%, CA 7±1%, both $P<0.05$) and was significantly decreased by catalase in CA (-3±1%, $P<0.05$). DM+ARB also ameliorated oxidative stress and myocardial injury compared with DM, as assessed by plasma 8-hydroxydeoxyguanosine and troponin-T in the coronary sinus, respectively.

***Conclusions*:** ARB enhances H_2O_2-mediated dilatation of canine coronary collateral arterioles and improves coronary collateral vasodilatation in DM during myocardial ischemia in vivo.

F-26

Progressive dissociation of nephrin and podocin, glomerular slit membrane proteins, in distribution 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 all 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: To elucidate the mechanism of such leakage of larger molecules, we hypothesised that the structure of the glomerular slit membrane might be altered by diabetes even at the early stage of diabetes.

[Method] To test this, we dyed nephrin and podocin, the slit membrane components, by fluorescent antibody technique in early diabetic rats of from 1 to 3 months as well as normal control rats.

Results: We found homegenous staining of those proteins around the glomerular capillaries in the glomeruli of normal control rats. In contrast to this, we found heterogenous staining of those proteins in the glomeruli of diabetic rats. After quantifying distribution of those two proteins, we found that dissociation of the distribution of nephrin and podocin was significantly progressive with duration of diabetes.

Conclusion: This alteration of the glomerular slit membrane structure may be the attributing to the leakage of larger molecules at the early stage of diabetes.

F-27

Role of ThromboxaneA2 TP signaling in upregulation of PSGL-1 during recovery from ischemic condition

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Purpose: Thromboxane A_2 (TXA_2) is a prostanoid formed by thromboxane synthase using the cyclooxygenase product prostaglandin H2 as the substrate and known as a potent stimulator of platelet aggregation and smooth muscle constriction. Though TXA_2 had reported to induce angiogenesis, the cellular and molecular mechanisms of TP signaling in recovery from ischemic conditions are not fully elucidated. This study was aimed at investigating whether TP-dependent platelet adhesion contributes to angiogenesis in mice hind limb ischemia model.
Methods: The model of hind limb ischemia was made by ligated the femoral artery in the left limb. The microcirculation in the quadriceps muscles or the tissues adjacent to the femoral artery and vein was observed by TV monitor screen through a CCD camera. The expression of PSGL-1, P-selectin ligand, was analyzed by immunohistochemical and PCR analysis.
Results: *In vivo* microscopic studies revealed that the platelet-adherent microvascular density in the vasculature of both peri-femoral sites and muscle sites was suppressed in TP knockout mice ($TP^{-/-}$) compared with wild type mice (WT) ($P<0.05$). The selective platelets adhesion to the ischemic endothelial cells was significantly suppressed by injecting P-selectin neutralizing antibody in WT but not in $TP^{-/-}$. The expression of PSGL-1 was up-regulated in ischemic muscles, and was suppressed in $TP^{-/-}$ mice not in WT. Furthermore, the expressions of PSGL-1 on cultured HUVEC were enhanced by a throboxane analogue, U-46619, and cobalt chloride (CoCl2). Platelets contain the proangiogenic factors. Plasma levels in stromal derived factor-1 (SDF-1) and vascular endothelial growth factor (VEGF) were increased after ischemia, and antibodies against CXCR4 and VEGF blocked angiogenesis in WT but not in $TP^{-/-}$.
Conclusions: These results suggested that TP-signaling facilitates angiogenesis by P-selectin–mediated platelet adhesion bound to PSGL-1 on the vasculature at the ischemic sites, and that the adhered platelets supply proangiogenic factors to enhance angiogenesis.

F-28

Characterization of Ca^{2+} channels involved in endothelin-1-induced transactivation of epidermal growth factor receptor

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Purpose: This study demonstrates the involvement of Ca^{2+} influx through voltage-independent Ca^{2+} channels (VICCs) in endothelin-1 (ET-1)-induced transactivation of epidermal growth factor receptor protein tyrosine kinase (EGFR PTK).

Method: Measurement of EGFR PTK transactivation was performed using a Universal Tyrosine Kinase Assay Kit with monoclonal anti EGFR and anti phosphotyrosine antibody. Ca^{2+} channels involved in ET-1-induced EGFR PTK are evaluated by using Ca^{2+} channel blockers, LOE 908 and SK&F 96365 in rabbit internal carotid artery (ICA) vascular smooth muscle cells (VSMCs).

Results: ET-1-induced EGFR PTK transactivation was completely inhibited by AG1478, a specific inhibitor of EGFR PTK. In the absence of extracellular Ca^{2+}, the magnitude of EGFR PTK transactivation was near the basal level. Based on the sensitivity to nifedipine, a specific blocker of voltage-operated Ca^{2+} channels (VOCCs), VOCCs has minor roles in EGFR PTK transactivation. In contrast, Ca^{2+} influx through VICCs plays important roles in EGFR PTK transactivation. Moreover, based on the sensitivity to SK&F 96365 and LOE 908, VICCs consist of two types of Ca^{2+}-permeable nonselective cation channels (designated NSCC-1 and NSCC-2) and a store-operated Ca^{2+} channel (SOCC).

Conclusion: Ca^{2+} influx through VICCs plays essential roles in ET-1-induced EGFR PTK transactivation in rabbit ICA VSMCs.

F-29

The mechanism study of spironolactone-induced Ca^{2+} increase in rat testicular arteriole smooth muscle cells

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OBJECTIVE: A diuretic is any drug that elevates the rate of urination (diuresis). The antihypertensive actions of some diuretics are independent of their diuretic effect. Arterioles play pivotal roles in controlling blood supply in various tissues. We have previously reported that spironolactone (SP) induced intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) increase in rat testicular arteriole smooth muscle cells. However this Ca^{2+} increasing mechanism is not so clear. This time we have investigated the alteration of $[Ca^{2+}]_i$ in testicular arterioles with respect to SP and some other drugs using a real-time confocal laser scanning microscope.

METHODS: We isolated arterioles from testis of rats and soaked in Hepes-buffered Ringer's Solution (HR) (pH7.4). Connective tissues were digested by purified collagenase (100 units/ml) for 2 hours, then the specimens were loaded by Indo-1/AM (5 μM) for 2 hours at room temperature. They were placed on cover slides in chambers which were coated with Cell-Tak® and continuously perfused with HR containing some drugs. We used a real-time confocal microscope (Nikon RCM/Ab).

RESULTS: When SP (300 μM) was used as a stimulus, an increase of $[Ca^{2+}]_i$ in the smooth muscle cells was observed. This response was partially inhibited when extracellular Ca^{2+} was removed from perfused HR. In the presence of thapsigargin, stimulation by SP led to a small Ca^{2+} increase in testicular arterioles. U73122 failed to inhibit SP-induced increases in $[Ca^{2+}]_i$ and heparin (a potent IP_3 receptor antagonist) showed almost same as above. The protein kinase A inhibitor, H89, partially inhibited this increase, whereas, it had no effect using PKC inhibitor, GF109203X. When we used mifepristone, a glucocorticoid receptor antagonist, SP-induced Ca^{2+} increase was partially blocked.

CONCLUSIONS: In present study, we propose that the SP-induced dynamics of $[Ca^{2+}]_i$ can be caused by both a Ca^{2+} influx from extracellular fluid and Ca^{2+} mobilization from internal Ca^{2+} store, with the former being dominant. We suggested that this reaction may interact with G protein coupled receptors. And there is some possibility that SP is related to glucocorticoid receptors.

LS-1

腫瘍血管における血管正常化／成熟化のインパクト

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血管新生が、腫瘍組織から放出される血管内皮成長因子（vascular endothelial growth factor : VEGF）により誘導されるという事実から、そして内皮細胞の生存が VEGF により維持されていることから、VEGF あるいはその受容体を標的として血管新生を抑制し、内皮細胞の細胞死を誘導する治療法の開発が勢力的に進められ、VEGF の阻害による抗腫瘍効果が確認されるに至っている。元来、血管新生抑制剤の効果に関しては、血管を破綻させることによる低栄養状態から、腫瘍を休眠化させることに期待がもたれてきたのは事実である。しかし、マウス担がんモデルでは、血管新生抑制剤投与単独で腫瘍の増大が完全に停止したり、腫瘍がほぼ完全に消失するようなケースも見られるが、ヒトの場合 VEGF 阻害のみでは抗腫瘍効果がさほど認められず、抗がん剤との併用ではじめて腫瘍縮小効果がみられることが示されてきた。このことから、最近では腫瘍に対する血管新生抑制剤の効果というのは、「血管の破綻よりむしろ血管正常化による」というパラダイムシフトが生じてきている。

正常血管の管腔は主に２種類の細胞で構築されている。内腔は血管内皮細胞であり、それを外側から血管壁細胞と総称される血管平滑筋細胞あるいはペリサイト（周皮細胞）が覆い、血管構造を安定化している。内皮細胞間は種々の接着因子により密着しており、血管内から容易には分子や細胞が血管外に漏出しないようにしている。もちろんそのことで、血管内圧は高く維持され、組織深部への養分や酸素の透過性を可能にしている。一方で、腫瘍の血管には様々な異常が観察される。腫瘍内血管は透過性が亢進し、蛇行や拡張が観察され、一部嚢状を呈し、血管分岐も無秩序である。血管内皮細胞そのものも異常な形態を呈し、裏打ちする壁細胞も腫瘍中心部では非常にまばらで内皮細胞との接着も弱く、多くの領域で壁細胞の裏打ちが欠損している。これは、腫瘍内におびただしく動員されたマクロファージや間質細胞が分泌する VEGF を含む血管新生促進因子の過剰状態によりもたらされている。つまり、腫瘍内では、血管新生因子と血管抑制因子のバランスが促進因子の方に傾いており、壁細胞化を伴う血管の形成、つまり血管新生の終息過程が始まらない状態となっている。このような未成熟血管は内皮細胞間の接着も弱く、血管透過性が亢進し、腫瘍の間質に過剰な血管内成分が漏れ込み、この状態が続くとやがて血管内圧と腫瘍間質圧の差がなくなり、抗がん剤を投与しても血管内から間質まで透過することができなくなる。さらにはガス交換の不十分ながんでは低酸素が誘導され放射線療法にも抵抗性を示すようになる。

そこで、一旦血管新生抑制因子を投与することで、血管新生促進因子と抑制因子のバランスを平衡にし、血管構造を正常化させ、血管透過性をコントロールできるような血管に誘導する。引き続き、抗がん剤を投与して、腫瘍細胞を死滅させ血管新生促進因子を減少させる。これが血管正常化による治療のコンセプトである。血管を正常化すると低酸素状態が回復するために、低酸素状態では効果が十分でな

かった放射線治療の効果が高まり、癌細胞の細胞死を誘導する。一方、腫瘍の中の血管を正常化させるという概念は、腫瘍に酸素や養分を供給してしまうのではないかということが懸念されるという見方もある。そこで、我々は生理的な血管成熟化因子を同定して、本分子を用いた血管成熟化と他のがん治療法との併用によるコンビネーション治療が本当に有効なのかを解析した。

胎児期の血管形成は脈管形成（vasculogenesis）という過程に始まる。この過程では、中胚葉細胞から分化した、血管内皮細胞が管腔を呈するが、内皮細胞の周囲を取り巻く壁細胞の発生が十分ではなく、血管径は一様で、大中小の血管サイズの階層性はない。しかし、内皮細胞近傍に壁細胞が動員されると、徐々に血管の成熟化が生じ、血管構造の安定化、酸素養分の必要量に応じた血管径の適正化、余剰の血管の退縮、新しい血管の形成（発芽的血管新生）による血管密度の調節など、いわゆる血管リモデリングといわれる過程が生じて緻密な血管が形成されていく。内皮細胞に発現するレセプター型チロシンキナーゼ Tie2 は壁細胞から分泌される angiopoietin-1 (Ang1)により活性化を受けると、主に PI3K-Akt シグナル経路の活性化で、内皮細胞と壁細胞の直接的あるいはマトリックスを介した接着が誘導され、血管は構造的に安定化する。しかし、血管新生が開始している状態の内皮細胞では Tie2 の活性化は、ERK 経路の活性化により、内皮細胞の運動能の亢進による血管新生の亢進につながることが判明した。そこで、我々は Tie2 の下流因子で、血管が成熟化する過程に機能する実行分子の単離を行い、血管腔の拡大化、血管透過性制御にかかわる分子として apelin（アペリン）を同定した。アペリンは血管内皮細胞上の Tie2 が Ang1 により活性化をうけると分泌されるペプチドである。アペリンの受容体は 7 回膜貫通型の APJ である。この APJ は、我々の解析した限り、既存の血管には発現しておらず、血管新生が進行すると内皮細胞で発現が亢進してくることが判明した。確かに、APJ の発現は VEGF により誘導されることから、血管新生との密接な関係を想像させる。そして、このアペリンは内皮細胞上の APJ をオートクラインループによって活性化し、内皮細胞同士の集塊を形成することにより、血管径を拡大化して血流を増大する作用がある。また種々の血管透過性因子による VE-cadherin の細胞内移行を抑制して、血管透過性を制御する分子であることが判明した。つまりアペリンは血管新生過程における生理的な血管成熟化因子であると考えられた。

そこで、上記したように、アペリンは腫瘍内の血管を正常化／成熟化するか、そして血管成熟化が他のがん治療の効果を増強させるかを検討した。その結果、まずアペリンを過剰に発現させた腫瘍では、コントロールの腫瘍に比べ血管径が有為に拡大化し、血管透過性も制御され、血流の増大を反映して低酸素状態が軽減していた。そこで、担がんマウスに活性化した樹状細胞を静脈内投与してみると、アペリンを発現させた腫瘍中にはコントロールに比べ非常に多くの NKT 細胞が浸潤し、腫瘍細胞のアポトーシスを誘導して抗腫瘍効果を著しくもたらせた。つまり、生理的な血管成熟化因子が腫瘍血管の正常化を誘導して、他のがん治療の効果を高めるということが証明されたことになる。

LS-2

The Newest Pathological Inspection Method with EPMA

電子線マイクロアナライザによる組織切片元素イメージング技術

Shimadzu Corporation Analytical & Measuring Instruments Division

X-Ray/surface Business Unit　Product Manager Hiroshi Hayashi

体内に生存する金属元素は、様々な形で人の健康に影響を及ぼしている。しかし、健康の維持と深い関係にあることが明らかにはなってきたが、局在する器官やその組織分布などは不明な点も多い。従来の病理組織検査においてこれらの金属は、原子吸光法、組織染色法などで検査・測定が行われてきたが、分析者の技術に大きく依存する傾向がある。例えば、原子吸光法などに代表される機器分析法では、採取組織中の平均濃度を組織 1g あたりの金属元素 μg あるいは ng といった形で知ることはできるが、正常部位と異常部位の間で平均的に分布しているのか、それとも高濃度部位と低濃度部位に分かれているのかといったことを確認することは、非常に困難である。

また、組織切片を染色し光学顕微鏡で金属元素分布を観察するといった、従来から行われてきた組織切片染色法では、適切な染色法を用いれば病理組織的な異常部位の観察と局在部位の観察を同時に行うことができる。しかしながら、この方法は経験に基づく判断や評価、分析者の技術に依存する部分も多く、客観的な定量性について得られる情報は少ないと思われる。ただし、金属元素の分析だけでは得られない多くの知見を含んでいることも事実である。

一方、電子線マイクロアナライザ（EPMA）は微小部元素分析装置として様々な固体試料に対し幅広く利用されているが、生体試料においては、あまり積極的に使用されていない。その理由の一つに試料の調製技術が挙げられるが、組織病理学で一般的に用いられる薄切病理組織切片をスライドグラスではなくカーボン試料台に貼り付けるという単純な方法で経年変化に強く、電子ビームの熱的損傷にも耐えられる試料調製を行うことが可能であることが近年、我々の検討で明らかになってきた。この試料調製によって、電子線マイクロアナライザ（EPMA）での分析が実用的になり、その結果検体中の元素分布を直接的かつ定量的に知ることができる可能性が出てきた。

この分析手法はウィルソン病、超硬合金肺などすでにいくつかの具体的な病理診断に応用されてきている。

本セミナーでは、電子線マイクロアナライザ（EPMA）という元素分析装置による金属元素マッピング技術を紹介する。

脳卒中と高血圧　— 最近の話題から —

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埼玉医科大学国際医療センター副院長・神経内科　教授

脳卒中の 90%は 10 個のリスク因子で説明が可能とされている（INTERSTROKE study, 2010）。これらのリスク因子の中で、高血圧症が最も脳卒中の発症に強く関与している。脳卒中は脳出血、くも膜下出血、脳梗塞に大別されるが、病型別に関与の程度が異なり、脳出血が最も強く、次いで脳梗塞であり、くも膜下出血との関与は弱い。脳梗塞の中では、ラクナ梗塞との関与が最も強く、次いでアテローム血栓性脳梗塞であり、心原性脳塞栓症の関与は少ない。脳卒中予防のための血圧管理で重要なことは厳格な降圧であり、心血管イベントの抑制は降圧度によるとされている。現在、脳卒中の２次予防の降圧目標値は、140/90mmHg 未満と脳卒中治療ガイドライン 2009 では示されているが、130/80mmHg 未満、あるいは 120/80mmHg 未満などの目標値が適切ではないかとする議論がある。すなわち脳卒中発症に J curve 現象があるか否かの問題である。この問題を解決するため RESPECT 研究が進行中である。さらに、どの種類の降圧薬が脳卒中予防に有用であるか、脳保護作用についても多くのエビデンスが蓄積されつつある。現在、CCB, RAS 阻害薬、少量の利尿薬が脳卒中予防に推奨されている。RAS 阻害薬は、血管リモデリング改善作用、血管内皮機能改善作用、抗酸化作用、交感神経抑制作用、脳血流維持作用、血液脳関門維持作用、心房細動抑制作用、糖尿病新規発症抑制作用などを有しており注目されてきた。さらに近年は認知機能低下抑制作用も注目されている。RAS は ACE/AngⅡ/AT1 受容体軸により高血圧や臓器障害を促進する増悪因子と理解されてきたが、近年 ACE2/Ang-（1-7）/ MAS 受容体軸の存在と、その軸の活性化による臓器保護促進作用が明らかにされてきている。また新しい強い降圧効を有する ARB であるアジルサルタンが近日中に発売予定である。CCB については、抗酸化作用などの脳保護作用も報告されているが、強力な降圧作用と有し、受診時毎の血圧変動が少なく、脳卒中予防に優れているとする報告がある。また少量の利尿薬は代謝面での副作用も少なく RA 系阻害薬との併用により強力な降圧効果を示す。さらに食塩感受性高血圧症の多い日本人には有効な薬剤といえる。

日本微小循環学会

入会申込書

変更届

入会申込書（外国人用）

To:The Japanese Society for Microcirculation
Tel : 03-3359-0443 / Fax: 03-5361-7091
e-mail: js-micro@imic.or.jp

日本微小循環学会　入会申込用紙

	（姓）	（名）
氏名		
フリガナ		

生年月日（西暦）	年　月　日

所属機関

ﾌﾘｶﾞﾅ					
機関名					
部門名				役職名	
住所	〒				
電話・FAX	TEL		内線	FAX	
E-mail					

自宅住所

自宅住所	〒			
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E-mail				

研究分野	

送付先区分　☐所属機関　☐自宅

名簿掲載　☐所属機関　掲載承諾　☐自宅　掲載承諾　☐非承諾（※氏名のみ公開）

事務局記入欄	受付日	登録日	入金日	完了日	

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申請日	年　　月　　日
氏　名	

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機関名					
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役　職					
住　所	〒				
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E-mail					

自宅住所変更

住　所	〒			
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名義変更(※新姓をご記入ください)

氏　名	
フリガナ	

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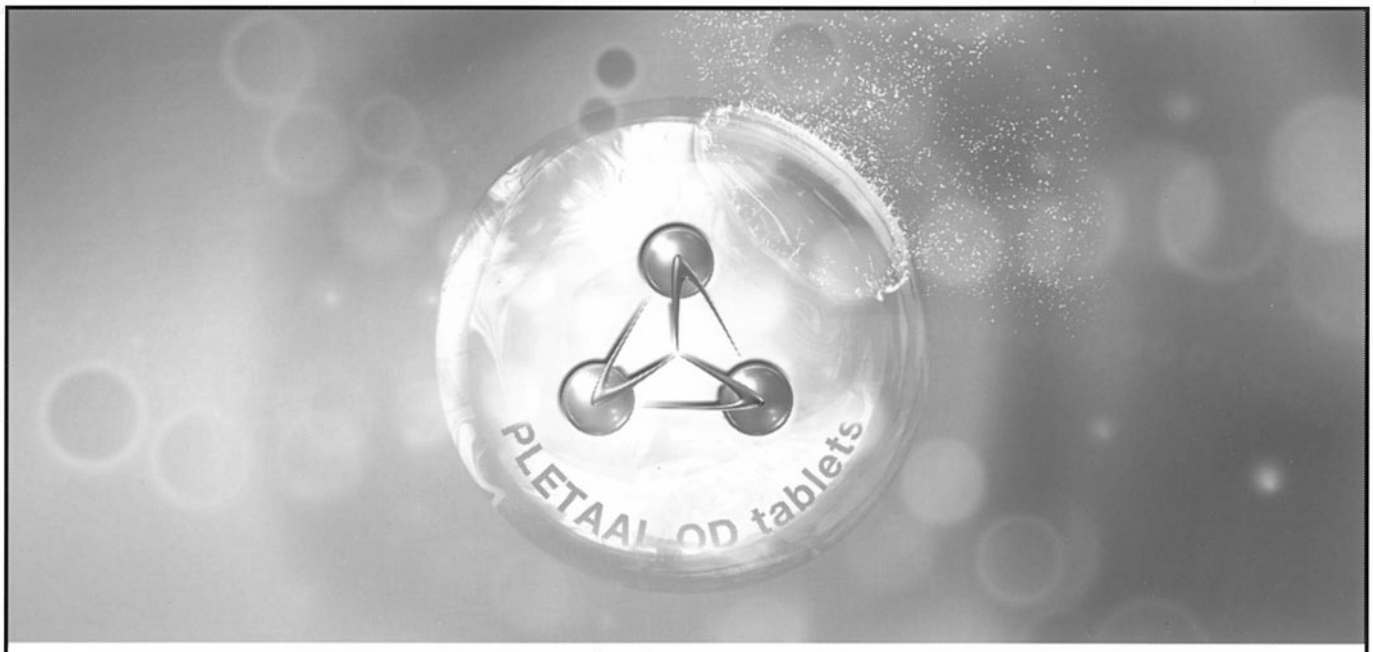

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大塚製薬株式会社
Otsuka 東京都千代田区神田司町2-9

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〒108-8242 東京都港区港南2-16-4　品川グランドセントラルタワー

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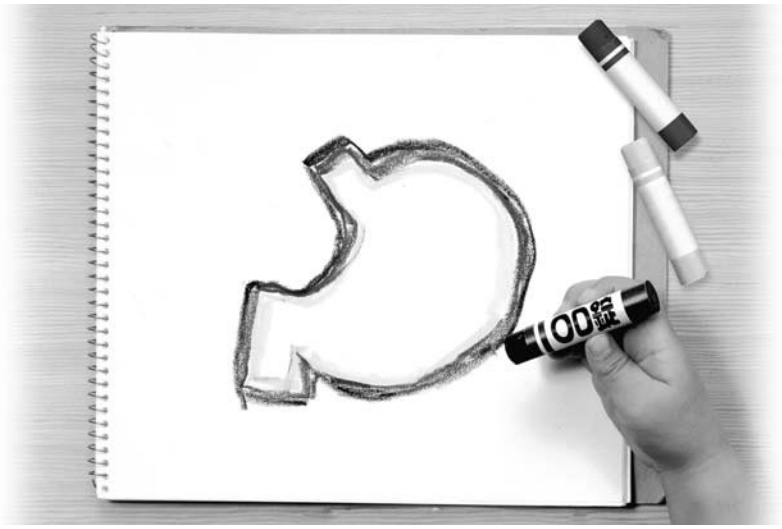

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2009年11月作成A4/2

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新発売

【禁忌】（次の患者には投与しないこと）
本剤の成分に対し過敏症の既往歴のある患者

【効能・効果】
中等度及び高度アルツハイマー型認知症における認知症症状の進行抑制
<効能・効果に関連する使用上の注意>
1. アルツハイマー型認知症と診断された患者にのみ使用すること。
2. 本剤がアルツハイマー型認知症の病態そのものの進行を抑制するという成績は得られていない。
3. アルツハイマー型認知症以外の認知症性疾患において本剤の有効性は確認されていない。

【用法・用量】
通常、成人にはメマンチン塩酸塩として1日1回5mgから開始し、1週間に5mgずつ増量し、維持量として1日1回20mgを経口投与する。
<用法・用量に関連する使用上の注意>
1. 1日1回5mgからの漸増投与は、副作用の発現を抑える目的であるので、維持量まで増量すること。
2. 高度の腎機能障害（クレアチニンクリアランス値：30mL/min未満）のある患者には、患者の状態を観察しながら慎重に投与し、維持量は1日1回10mgとすること（「慎重投与」及び「薬物動態」の項参照）。
3. 医療従事者、家族等の管理の下で投与すること。

【使用上の注意】
1. 慎重投与（次の患者には慎重に投与すること）
(1)てんかん又は痙攣の既往のある患者［発作を誘発又は悪化させることがある。］
(2)腎機能障害のある患者［本剤は腎排泄型の薬剤であり、腎機能障害のある患者では排泄が遅延する（「用法・用量に関連する使用上の注意」及び「薬物動態」の項参照）。］
(3)尿pHを上昇させる因子（尿細管性アシドーシス、重症の尿路感染等）を有する患者［尿のアルカリ化により本剤の尿中排泄率が低下し、本剤の血中濃度が上昇するおそれがある。］
(4)高度の肝機能障害のある患者［使用経験がなく、安全性が確立していない。］
2. 重要な基本的注意
(1)投与開始初期においてめまいが認められることがあるので、患者の状態を注意深く観察し、異常が認められた場合は、投与を中止するなど適切な処置を行うこと。
(2)通常、中等度及び高度アルツハイマー型認知症では、自動車の運転等危険を伴う機械の操作能力が低下することがある。また、本剤により、眠気、めまい等を催すことがあるので、本剤投与中の患者には自動車の運転等危険を伴う機械の操作に従事させないよう注意すること。
(3)他の認知症性疾患との鑑別診断に留意すること。
(4)本剤投与により効果が認められない場合、漫然と投与しないこと。
3. 相互作用 併用注意（併用に注意すること）
ドパミン作動薬：レボドパ等　**ヒドロクロロチアジド**　**腎尿細管分泌（カチオン輸送系）により排泄される薬剤**：シメチジン等　**尿アルカリ化を起こす薬剤**：アセタゾラミド等
NMDA受容体拮抗作用を有する薬剤：アマンタジン塩酸塩、デキストロメトルファン臭化水素酸塩水和物等
4. 副作用
国内における承認前の臨床試験において、1,115例中408例（36.6%）に副作用が認められた。主な副作用は、めまい4.7%（52例）、便秘3.1%（35例）、体重減少2.2%（24例）、頭痛2.1%（23例）等であった。
(1)**重大な副作用**
1)**痙攣**（0.3%）：痙攣があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。2)**失神**（頻度不明[注)]）、**意識消失**（頻度不明[注)]）：失神、意識消失があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。3)**精神症状**（激越：0.2%、攻撃性：0.1%、妄想：0.1%、幻覚、錯乱、せん妄：頻度不明[注)]）：精神症状（激越、幻覚、錯乱等）があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。
注）海外において認められている副作用のため頻度不明。

●本剤は新医薬品であるため、厚生労働省告示第97号（平成20年3月19日付）に基づき、2012年3月末日までは1回14日分を限度として投薬する。

●その他の使用上の注意等は製品添付文書をご覧ください。

NMDA受容体拮抗 アルツハイマー型認知症治療剤
メマリー®錠 5mg 10mg 20mg

劇薬、処方せん医薬品：注意－医師等の処方せんにより使用すること
一般名／メマンチン塩酸塩
薬価基準収載

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東京都中央区日本橋本町3-5-1

提携
メルツ ファーマシューティカルズ

2011年6月作成(1109)

効能・効果追加

新たなる選択

選択的DPP-4阻害剤 －糖尿病用剤－

薬価基準収載

グラクティブ®錠 25mg 50mg 100mg

シタグリプチンリン酸塩水和物錠

GLACTIV

処方せん医薬品注)

注）医師等の処方せんにより使用すること

〔禁忌(次の患者には投与しないこと)〕
(1)本剤の成分に対し過敏症の既往歴のある患者
(2)重症ケトーシス、糖尿病性昏睡又は前昏睡、1 型糖尿病の患者〔輸液及びインスリンによる速やかな高血糖の是正が必須となるので本剤を投与すべきでない。〕
(3)血液透析又は腹膜透析を要する患者を含む重度腎機能障害のある患者〔本剤の血中濃度が上昇する。(「薬物動態」の項参照)〕
(4)重症感染症、手術前後、重篤な外傷のある患者〔インスリン注射による血糖管理が望まれるので本剤の投与は適さない。〕

■効能・効果

2型糖尿病
ただし、下記のいずれかの治療で十分な効果が得られない場合に限る
①食事療法、運動療法のみ
②食事療法、運動療法に加えてスルホニルウレア剤を使用
③食事療法、運動療法に加えてチアゾリジン系薬剤を使用
④食事療法、運動療法に加えてビグアナイド系薬剤を使用
⑤食事療法、運動療法に加えてα-グルコシダーゼ阻害剤を使用
＊⑥食事療法、運動療法に加えてインスリン製剤を使用

■用法・用量

通常、成人にはシタグリプチンとして50mgを1日1回経口投与する。なお、効果不十分な場合には、経過を十分に観察しながら100mg 1日1回まで増量することができる。

〈用法・用量に関連する使用上の注意〉
本剤は主に腎臓で排泄されるため、中等度腎機能障害のある患者では、下表を目安に用量調節すること。(「慎重投与」及び「薬物動態」の項参照)

腎機能障害	クレアチニンクリアランス（mL/分） 血清クレアチニン値（mg/dL）※	通常投与量	最大投与量
中等度	30≦Ccr＜50 男性：1.5＜Cr≦2.5 女性：1.3＜Cr≦2.0	25mg 1日1回	50mg 1日1回

※：クレアチニンクリアランスに概ね相当する値

■使用上の注意（抜粋）

1. 慎重投与(次の患者には慎重に投与すること)
(1)中等度腎機能障害のある患者 (「用法・用量に関連する使用上の注意」及び「薬物動態」の項参照)
＊(2)他の糖尿病用薬(特に、インスリン製剤又はスルホニルウレア剤)を投与中の患者〔併用により低血糖症を起こすことがある。(「重要な基本的注意」、「相互作用」、「重大な副作用」及び「臨床成績」の項参照)〕
(3)次に掲げる低血糖を起こすおそれのある患者又は状態
1)脳下垂体機能不全又は副腎機能不全
2)栄養不良状態、飢餓状態、不規則な食事摂取、食事摂取量の不足又は衰弱状態
3)激しい筋肉運動
4)過度のアルコール摂取者
5)高齢者

2. 重要な基本的注意
＊(1)本剤の使用にあたっては、患者に対し低血糖症状及びその対処方法について十分説明すること。特に、インスリン製剤又はスルホニルウレア剤と併用する場合、低血糖のリスクが増加する。インスリン製剤又はスルホニルウレア剤による低血糖のリスクを軽減するため、これらの薬剤と併用する場合には、インスリン製剤又はスルホニルウレア剤の減量を検討すること。(「慎重投与」、「相互作用」、「重大な副作用」及び「臨床成績」の項参照)
(2)糖尿病の診断が確立した患者に対してのみ適用を考慮すること。糖尿病以外にも耐糖能異常・尿糖陽性等、糖尿病類似の症状(腎性糖尿、甲状腺機能異常等)を有する疾患があることに留意すること。
(3)本剤の適用はあらかじめ糖尿病治療の基本である食事療法、運動療法を十分に行った上で効果が不十分な場合に限り考慮すること。
(4)本剤投与中は、血糖を定期的に検査するとともに、経過を十分に観察し、常に投与継続の必要性について注意を払うこと。本剤を3ヵ月投与しても食後血糖に対する効果が不十分な場合、より適切と考えられる治療への変更を考慮すること。
(5)投与の継続中に、投与の必要がなくなる場合や、減量する必要がある場合があり、また、患者の不養生、感染症の合併等により効果がなくなったり、不十分となる場合があるので、食事摂取量、血糖値、感染症の有無等に留意の上、常に投与継続の可否、投与量、薬剤の選択等に注意すること。
(6)腎機能障害のある患者では本剤の排泄が遅延し血中濃度が上昇するおそれがあるので、腎機能を定期的に検査することが望ましい。(「用法・用量に関連する使用上の注意」、「慎重投与」及び「薬物動態」の項参照)
(7)急性膵炎があらわれることがあるので、持続的な激しい腹痛、嘔吐等の初期症状があらわれた場合には、速やかに医師の診察を受けるよう患者に指導すること。(「重大な副作用」、「その他の副作用」の項参照)
＊(8)インスリン依存状態の2型糖尿病患者に対する本剤とインスリン製剤との併用投与の有効性及び安全性は検討されていない。したがって、患者のインスリン依存状態について確認し、本剤とインスリン製剤との併用投与の可否を判断すること。
＊(9)速効型インスリン分泌促進薬、GLP-1アナログ製剤との併用についての有効性及び安全性は確立されていない。

3. 相互作用（抜粋）
本剤は主に腎臓から未変化体として排泄され、その排泄には能動的な尿細管分泌の関与が推察される。(「薬物動態」の項参照)

併用注意（併用に注意すること）

薬剤名等	＊糖尿病用薬(インスリン製剤、スルホニルウレア剤、チアゾリジン系薬剤、ビグアナイド系薬剤、α-グルコシダーゼ阻害剤、速効型インスリン分泌促進薬注)、GLP-1 アナログ製剤注)等)、ジゴキシン、血糖降下作用を増強する薬剤(β-遮断薬、サリチル酸剤、モノアミン酸化酵素阻害剤等)、血糖降下作用を減弱する薬剤(エピネフリン、副腎皮質ホルモン、甲状腺ホルモン等)

注)：「重要な基本的注意」の項参照

4. 副作用(抜粋)
＊国内で実施された臨床試験において、1,581 例中 181 例(11.4%)の副作用が認められた。主なものは低血糖症 63 例(4.0%)、便秘 17 例(1.1%)、空腹 9 例(0.6%)、腹部膨満 8 例(0.5%)等であった。また、関連の否定できない臨床検査値の異常変動は 1,579 例中 62 例(3.9%)に認められ、主なものは ALT (GPT) 増加 20 例 /1,579 例 (1.3%)、AST (GOT) 増加 12 例 /1,579 例 (0.8%)、γ-GTP 増加 12 例 /1,579 例 (0.8%) 等であった。(承認時)

(1)重大な副作用
1)アナフィラキシー反応　アナフィラキシー反応(頻度不明※)があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。(「禁忌」の項参照)
2)皮膚粘膜眼症候群 (Stevens-Johnson 症候群)、剥脱性皮膚炎　皮膚粘膜眼症候群(Stevens-Johnson 症候群)、剥脱性皮膚炎(いずれも頻度不明※)があらわれることがあるので、このような症状があらわれた場合には投与を中止し、適切な処置を行うこと。(「禁忌」の項参照)
＊3)低血糖症　経口糖尿病用薬との併用で低血糖症(グリメピリド併用時 5.3%、ピオグリタゾン併用時 0.8%、メトホルミン併用時 0.7%、ボグリボース併用時 0.8%)があらわれることがある。また、インスリン製剤併用時に低血糖症(17.4%)が多くみられている。特に、インスリン製剤又はスルホニルウレア剤との併用で重篤な低血糖症状があらわれ、意識消失を来す例も報告されていることから、これらの薬剤と併用する場合には、インスリン製剤又はスルホニルウレア剤の減量を検討すること。また、他の糖尿病用薬を併用しない場合でも低血糖症(1.0%) が報告されている。低血糖症状が認められた場合には、糖質を含む食品を摂取するなど適切な処置を行うこと。ただし、α-グルコシダーゼ阻害剤との併用により低血糖症状が認められた場合にはブドウ糖を投与すること。(「慎重投与」、「重要な基本的注意」、「相互作用」及び「臨床成績」の項参照)
4)肝機能障害、黄疸　AST(GOT)、ALT(GPT)等の著しい上昇を伴う肝機能障害、黄疸(いずれも頻度不明※)があらわれることがあるので、観察を十分に行い、異常が認められた場合には、投与を中止するなど適切な処置を行うこと。
5)急性腎不全　急性腎不全 (頻度不明※) があらわれることがあるので、観察を十分に行い、異常が認められた場合には、投与を中止するなど適切な処置を行うこと。
6)急性膵炎　急性膵炎(頻度不明※)があらわれることがあるので、観察を十分に行い、持続的な激しい腹痛、嘔吐等の異常が認められた場合には投与を中止し、適切な処置を行うこと。海外の自発報告においては、出血性膵炎又は壊死性膵炎も報告されている。(「重要な基本的注意」の項参照)
7)間質性肺炎　間質性肺炎 (頻度不明※) があらわれることがあるので、発熱、咳嗽、呼吸困難、肺音の異常(捻髪音)等が認められた場合には、速やかに胸部 X 線、胸部 CT、血清マーカー等の検査を実施すること。間質性肺炎が疑われた場合には投与を中止し、副腎皮質ホルモン剤の投与等の適切な処置を行うこと。
※：自発報告あるいは海外において認められている。

●その他の使用上の注意等、詳細は製品添付文書をご参照ください。

（＊2011年9月改訂）

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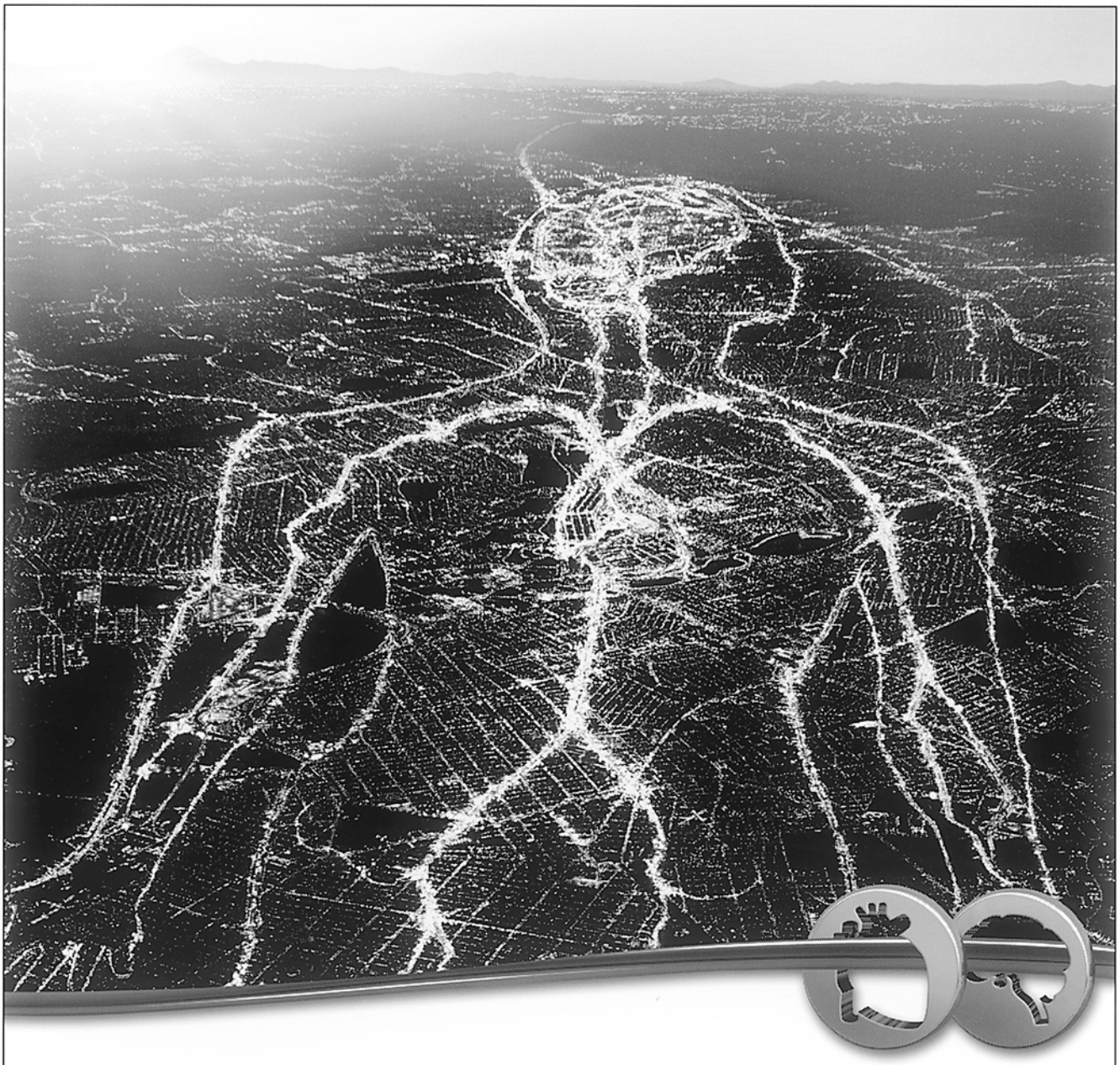

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(A4) 2009年4月作成

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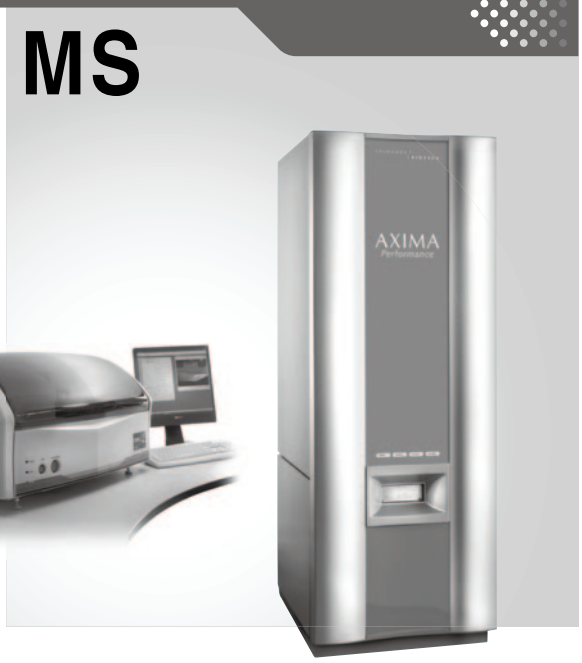

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2010年5月作成