Arteriosclerosis, Thrombosis, and Vascular Biology

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Editorials

Scavenger Receptor A and CD36 Are Implicated in Mediating Platelet Activation Induced by Oxidized Low-Density Lipoproteins
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Brief Reviews

Nutrition and Cardiovascular Disease
Godfrey S. Getz, Catherine A. Reardon
Many risk factors for cardiovascular diseases are profoundly affected by diet. Although most of the information about nutritional risk factors and cardiovascular disease derives from studies in the developed world, the situation is rapidly evolving toward epidemic proportions in the developing world, leading to impending economic and health service burdens.

Intrinsic Pathway of Coagulation and Arterial Thrombosis
David Gailani, Thomas Renné
Deficiencies of the plasma proteases factor XII and factor XI are not associated with abnormal hemostasis in mice but prevent thrombus formation in arterial injury models. If factor XII or factor XI make similar contributions to thrombosis in humans, they could be therapeutic targets to treat or prevent thromboembolic disease.

PECAM-1: A Multi-Functional Molecule in Inflammation and Vascular Biology—ATVB In Focus
Abigail Woodfin, Mathieu-Benoit Voisin, Sussan Nourshargh
This review discusses multiple roles of PECAM in inflammation and vascular biology, focusing on the emerging complexities associated with its role in leukocyte transendothelial migration. The review also discusses potential interaction of PECAM-1 with other endothelial cell junctional molecules and the role of PECAM-1 in various vascular and inflammatory disorders.

Nitric Oxide and Mitochondrial Signaling: From Physiology to Pathophysiology—ATVB In Focus
Jorge D. Erusalimsy, Salvador Moncada
This review summarizes the evidence showing that binding of NO to cytochrome C oxidase elicits signaling events by which mitochondria modulate cellular defense mechanisms and adaptive responses. We also discuss instances in which the effects of NO on the electron transport chain might lead to mitochondrial dysfunction and pathology.

Emerging Concepts of Regulation of Angiotensin II Receptors: New Players and Targets for Traditional Receptors
Masaki Mogi, Masaru Iwai, Masatsugu Horiuchi
Recently, new evidence has accumulated showing the existence of several novel receptor interacting proteins and various angiotensin II receptor activation mechanisms such as dimerization and mechanical stretch-induced activation beyond the classical actions. In this review, these emerging concepts and a new insight into future drug discovery are discussed.
**Vascular Biology**

**Expression of HIF-1α in Injured Arteries Controls SDF-1α–Mediated Neointima Formation in Apolipoprotein E–Deficient Mice**

Ela Karshovska, Alma Zernecke, Guela Sevilinis, Andrea Millet, Mihail Hristov, Clemens D. Cohen, Holger Schmid, Florian Krotz, Haé-Young Sohn, Volker Klauss, Christian Weber, Andreas Schober

We studied the role of hypoxia-inducible factor (HIF)-1α in neointima formation after vascular injury in apolipoprotein E–deficient mice. Inhibition of injury-induced HIF-1α upregulation reduced the neointimal area and stromal cell–derived factor (SDF)-1α expression. This suggests a direct contribution of HIF-1α to SDF-1α–mediated neointima formation after vascular injury.

**A Novel Class of Prolyl Hydroxylase Inhibitors Induces Angiogenesis and Exerts Organ Protection Against Ischemia**

Masami Nangaku, Yuko Izuhara, Shunya Takizawa, Toshiharu Yamashita, Yoshiaki Fujii-Kuriyama, Osamu Ohneda, Masayuki Yamamoto, Charles van Ypersele de Strihou, Noriaki Hirayama, Toshio Miyata

We discovered 2 compounds (TM6008 and TM6089) that inhibited PHD and stabilized HIF activity. Local administration of TM6008 and TM6089 enhanced angiogenesis, and their oral administration stimulated HIF activity in transgenic rats expressing a hypoxia-responsive reporter vector. Oral administration of TM6008 protected neurons in a model of ischemic cerebrovascular disease.

**Macular Pigment Lutein Is Antiinflammatory in Preventing Choroidal Neovascularization**

Kanako Izumi-Nagai, Norihiro Nagai, Kazuhiro Ohgami, Shingo Satofuka, Yoko Ozawa, Kazuo Tsubota, Kazuo Umezawa, Shigeki Ohno, Yuichi Oike, Susumu Ishida

We investigate the effect of lutein on experimental choroidal neovascularization (CNV) and reveal that lutein inhibits CNV development together with inflammatory processes including NF-κB activation and subsequent upregulation of inflammatory molecules, providing molecular evidence of potential validity of lutein supplementation as a therapeutic strategy to suppress CNV.

**Local Delivery of Anti-Monocyte Chemotactic Protein-1 by Gene-Eluting Stents Attenuates In-Stent Stenosis in Rabbits and Monkeys**

Kensuke Egashira, Kaku Nakano, Kisho Ohtani, Kouta Funakoshi, Gang Zhao, Yoshiko Ihara, Jun-ichiro Koga, Satoshi Kimura, Ryuji Tominaga, Kenji Sunagawa

We created stents coated with 7ND gene, which attenuated stent-associated monocyte infiltration and neointima formation in rabbits, and showed long-term inhibitory effects on neointima formation in monkeys. No adverse effects of 7ND-eluting stents were noted. Therefore, 7ND gene-eluting stents might be useful for treatment of restenosis in humans.

**Novel Mechanism and Role of Angiotensin II–Induced Vascular Endothelial Injury in Hypertensive Diastolic Heart Failure**

Eiichiro Yamamoto, Keiichiro Kataoka, Haruo Shintaku, Takuro Yamashita, Yoshiko Tokutomi, Yi-Fei Dong, Shinji Matsuba, Hidenori Ichijo, Hisao Ogawa, Shohei Kim-Mitsuyama

We examined the mechanism and significance of angiotensin II (AII)-induced vascular endothelial injury. AII-induced vascular endothelial apoptosis and eNOS uncoupling were mediated by apoptosis signal-regulating kinase 1 and contributed to the exacerbation of vascular injury of salt-sensitive hypertensive rats with diastolic heart failure.

**IL-6 Deficiency Protects Against Angiotensin II–Induced Endothelial Dysfunction and Hypertrophy**

Laura I. Schrader, Dale A. Kinzenbaw, Andrew W. Johnson, Frank M. Faraci, Sean P. Didion

The role of IL-6 in endothelial dysfunction and oxidative stress produced by angiotensin II was investigated. IL-6 deficiency was associated with reductions in angiotensin II–induced endothelial dysfunction, vascular hypertrophy, and superoxide. Thus, IL-6 produced locally, within the vessel wall, contributes substantially to the vascular dysfunction produced by angiotensin II.

**Blocking Thrombospondin-1/CD47 Signaling Alleviates Deleterious Effects of Aging on Tissue Responses to Ischemia**

Jeff S. Isenberg, Fumimori Hyodo, Loretta K. Pappan, Momes Abu-Asab, Maria Tsokos, Murali C. Krishna, William A. Frazier, David D. Roberts

Decreased blood flow and wound healing are common in the elderly. Nitric oxide can increase both tissue blood flow and healing, but thrombospondin-1 limits responses to nitric oxide in aged mice. Blocking the thrombospondin-1 receptor CD47 restores blood flow and increases tissue healing.
Aortic Msx2-Wnt Calcification Cascade Is Regulated by TNF-α–Dependent Signals in Diabetic Ldlr−/− Mice
Ziyad Al-Aly, Jian-Su Shao, Chung-Fang Lai, Emily Huang, Jun Cai, Abraham Behmann, Su-Li Cheng, Dwight A. Towler
Type II diabetes (T2DM) promotes medial artery calcification, a significant risk factor for lower-extremity amputation. Using a murine disease model—the Ldlr−/− mouse fed high-fat diabetogenic diets—we identified that arterial TNF-α signaling activates osteogenic Msx2-Wnt gene expression programs that direct medial calcification during disease initiation.

RhoB Regulates PDGFR-β Trafficking and Signaling in Vascular Smooth Muscle Cells
Minzhou Huang, James B. DuHadaway, George C. Prendergast, Lisa D. Laury-Kleintop
Herein, we show that in vascular smooth muscle cells RhoB plays a critical role in trafficking and signaling by the platelet-derived growth factor receptor-β. Cells derived from RhoB knockout mice failed to proliferate in response to PDGF, and downstream signaling was compromised as reflected by reduced Akt and ERK1/2 phosphorylation.

Farnesoid X Receptor Ligands Inhibit Vascular Smooth Muscle Cell Inflammation and Migration
Yoyo T.Y. Li, Karen E. Swales, Gareth J. Thomas, Timothy D. Warner, David Bishop-Bailey
FXR is expressed in vascular smooth muscle cells. Here we show that in addition to antiproliferative properties, activation of FXR inhibits inflammation and migration of vascular smooth muscle cells. FXR may therefore be a novel direct target for vascular disease.

Epoxyeicosatrienoic Acids Regulate Trp Channel–Dependent Ca2+ Signaling and Hyperpolarization in Endothelial Cells
Ingrid Fleming, Alexandra Rueben, Rüdiger Popp, Beate Fisslthaler, Susanne Schrödt, Anna Sander, Judith Haendeler, John R. Falck, Christophe Morisseau, Bruce D. Hammock, Rudi Busse
Bradykinin-induced Ca2+ influx and Ca2+-dependent K+ channel activation in endothelial cells are potentiated by cytochrome P450 (CYP) expression and soluble epoxide hydrolase (sEH) inhibition. An epoxyeicosatrienoic acid–induced translocation of a TrpC6-V5 fusion protein to the endothelial cell membrane via a cAMP-dependent mechanism can account for these findings.

VEGF Induces Tie2 Shedding via a Phosphoinositide 3-Kinase/Akt–Dependent Pathway to Modulate Tie2 Signaling
Clarence M. Findley, Melissa J. Cudmore, Asif Ahmed, Christopher D. Kontos
Tie2 plays an important role in vascular remodeling. We demonstrate that soluble Tie2 shedding is induced by vascular endothelial growth factor (VEGF) in a phosphoinositide 3-kinase/Akt–dependent manner. These findings suggest a novel mechanism by which VEGF may inhibit Tie2-mediated vascular stabilization to promote angiogenesis and vascular remodeling.

Rosiglitazone Reduces Glucose-Induced Oxidative Stress Mediated by NAD(P)H Oxidase via AMPK-Dependent Mechanism
Giulio Ceolotto, Alessandra Gallo, Italia Papparella, Lorenzo Franco, Ellen Murphy, Elisabetta Iori, Elisa Pagnin, Gian Paolo Fadini, Mattia Albiero, Andrea Semplicini, Angelo Avogaro
The present study was designed to characterize the molecular mechanisms underlying the effects of rosiglitazone on hyperglycemia-induced ROS production in HUVECs. We demonstrate that rosiglitazone reduces glucose-induced oxidative stress through inhibition of NAD(P)H oxidase. This effect is not mediated by PPARγ but is dependent on AMPK activation and downstream PKC inhibition.

Activated Protein C Decreases Tumor Necrosis Factor–Related Apoptosis-Inducing Ligand by an EPCR-Independent Mechanism Involving Egr-1/Erk-1/2 Activation
Lee A. O’Brien, Mark A. Richardson, Sean F. Mehrbod, David T. Berg, Bruce Gerlitz, Akanksha Gupta, Brian W. Grinnell
We report that APC can suppress the proapoptotic mediator TRAIL by activating the ERK pathway to upregulate EGR-1, a negative regulator of TRAIL expression. The effect of APC was PAR-1– and S1P1-dependent, but independent of the endothelial protein C receptor, suggesting a mechanism to suppress injury in cells not expressing this receptor.

Statin Treatment and 3’ Polyadenylation of eNOS mRNA
Ioanna Kosmidou, Jeffrey P. Moore, Martina Weber, Charles D. Searles
We examined the effect of statins on eNOS mRNA polyadenylation, a process known to increase mRNA stability and translation. Statins increased polyadenylation in a time- and dose-dependent manner through a mechanism that appears to involve Rho-induced changes in the actin cytoskeleton.
Physical Inactivity Rapidly Induces Insulin Resistance and Microvascular Dysfunction in Healthy Volunteers
Naomi M. Hamburg, Craig J. McMackin, Alex L. Huang, Sherene M. Shenouda, Michael E. Widlansky, Eberhard Schulz, Noyan Gokce, Neil B. Ruderman, John F. Keaney Jr, Joseph A. Vita

Physical inactivity is associated with cardiovascular disease. We examined the effect of 5 days of bed rest on insulin resistance and vascular function in healthy subjects. Bed rest induced vascular dysfunction, insulin resistance, dyslipidemia, and increased blood pressure. Our findings provide insight into the pathogenesis of vascular disease in sedentary individuals.

Increased Enzyme Activity and β-Adrenergic–Mediated Vasodilation in Subjects Expressing a Single-Nucleotide Variant of Human Adenylyl Cyclase 6
Robert Gros, Stan Van Uum, Adam Hutchinson-Jaffe, Qingming Ding, J. Geoffrey Pickering, Robert A. Hegele, Ross D. Feldman

We examined the phenotypic characteristics of an adenylyl cyclase 6 (ADCY6 S674) variant in human subjects and isolated human mononuclear leukocytes and rat smooth muscle cells. Our data demonstrate that expression of this ADCY6 S674 variant is associated with enhanced adenylyl cyclase activity and enhanced cAMP-mediated regulation of contractile responses.

Hypoxia-Induced Mediators of Stem/Progenitor Cell Trafficking Are Increased in Children With Hemangioma

The pathophysiology of infantile hemangioma is unknown, yet there is evidence to suggest that stem/progenitor cells may contribute to their rapid proliferation. We investigated the mediators of progenitor cell mobilization and recruitment in children with hemangioma and demonstrate that growth may be linked to hypoxia and activation of vasculogenic pathways.

Atherosclerosis and Lipoproteins

Mapping, Genetic Isolation, and Characterization of Genetic Loci That Determine Resistance to Atherosclerosis in C3H Mice
Susanna S. Wang, Weibin Shi, Xuping Wang, Leandra Velky, Sarah Greenlee, Min T. Wang, Thomas A. Drake, Aldons J. Lusis

An F2 intercross between C57BL/6J and C3H/HeJ on the ApoE−/− background, fed on a chow diet and euthanized at 12 weeks, exhibited one significant QTL on chromosome 9, Ath29, and a suggestive QTL on chromosome 4, Ath8. Congenics for Ath29 confirmed the contribution of the locus to lesion development.

Induction of Oral Tolerance to HSP60 or an HSP60-Peptide Activates T Cell Regulation and Reduces Atherosclerosis
G.H.M. van Puijvelde, T. van Es, E.J.A. van Wanrooij, K.L.L. Habets, P. de Vos, R. van der Zee, W. van Eden, Th.J.C. van Berkel, J. Kuiper

HSP60-specific T cells contributing to the development of atherosclerosis can be counteracted by Tregs, which can be activated by oral tolerance induction to HSP60 and may produce IL-10 and TGF-β. This results in a beneficial effect on atherosclerosis and may provide a new therapeutic approach for the treatment of atherosclerosis.

IGF-1 Reduces Inflammatory Responses, Suppresses Oxidative Stress, and Decreases Atherosclerosis Progression in ApoE-Deficient Mice
Sergiy Sukhanov, Yusuke Higashi, Shaw-Yung Shai, Charlotte Vaughn, Jessica Mohler, Yangxin Li, Yoo-Hua Song, Jane Titterington, Patrick Delafontaine

Although insulin-like growth factor-1 (IGF-1) has been described to have pleiotropic effects in the vasculature, its role in the development and progression of atherosclerosis is obscure. Here we report that in ApoE-deficient mice fed a high-fat diet continuous infusion of IGF-1 suppressed progression of atherosclerosis potentially via antiinflammatory, antioxidant, and prorepair effects.

Defective Leptin/Leptin Receptor Signaling Improves Regulatory T Cell Immune Response and Protects Mice From Atherosclerosis
Soraya Taleb, Olivier Herbin, Hafid Ait-Oufella, Win Verreth, Pierre Gourdy, Véronique Barateau, Régine Merval, Bruno Esposito, Karine Clément, Paul Holvoet, Alain Tedgui, Ziad Mallat

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Leptin, a hormone that increases with obesity, was suggested to either accelerate or protect from atherosclerosis. Here, we identify a critical role for leptin/leptin receptor pathway in the modulation of the regulatory immune response in atherosclerosis, and suggest that alteration in regulatory immunity may predispose obese individuals to atherosclerosis.
Macrophage β3 Integrin Suppresses Hyperlipidemia-Induced Inflammation by Modulating TNFα Expression
Jochen G. Schneider, Yimin Zhu, Trey Coleman, Clay F. Semenkovich

The signals linking hyperlipidemia and the chronic inflammation characteristic of atherosclerosis are unknown. Here we demonstrate that the β3 integrin on macrophages suppresses diet-induced inflammation in hyperlipidemic mice by decreasing expression of TNFα. Promoting anti-inflammatory signaling mediated by the β3 integrin could represent a novel treatment strategy for atherosclerosis.

Hepatic PGC-1α Overexpression Induces Combined Hyperlipidemia and Modulates the Response to PPARα Activation
Christopher J. Lelliott, Anna Ljungberg, Andrea Ahnmark, Lena William-Olsson, Kim Ekroos, Anders Elmgren, Gunnar Arnerup, Carol C. Shoulders, Jan Oscarsson, Daniel Lindén

The effects of increased hepatic expression of PGC-1α or PGC-1β on PPARα activation, gene expression, and lipid metabolism were investigated. PGC-1β overexpression induced a combined hyperlipidemia and blunted the effects of PPARα activation on gene expression. Thus, inhibition of hepatic PGC-1β may ameliorate combined hyperlipidemia and improve the effects of PPARα activators.

Atherosclerosis Is Attenuated by Limiting Superoxide Generation in Both Macrophages and Vessel Wall Cells

We investigated the relative contribution of monocyte/macrophage versus vascular wall cell NAD(P)H oxidase to atherosclerosis using bone marrow transplantation from apoE<sup>−/−</sup>/p47phox<sup>−/−</sup> mice to apoE<sup>−/−</sup> mice and vice versa. Monocytes/macrophages and vascular wall NAD(P)H oxidases contribute equally to aortic superoxide production and atherosclerosis in apoE<sup>−/−</sup> mice.

Serum Matrix Metalloproteinase-8 Concentrations Are Associated With Cardiovascular Outcome in Men
Anita M. Tuomainen, Kristina Nyssönen, Jari A. Laukkonen, Taina Tervahartiala, Tomi-Pekka Tuomainen, Jukka T. Salonen, Timo Sorsa, Pirikki J. Pussinen

We evaluated the predictive value of serum MMP-8 (MMP-8) concentration for cardiovascular disease (CVD) events in a prospective sample of men without cardiovascular events. The results show a 3.0-fold increase in risk for CVD death in men with both elevated MMP-8 level and subclinical atherosclerosis.

Gamma-Glutamyltransferase Is Associated With Incident Vascular Events Independently of Alcohol Intake: Analysis of the British Women’s Heart and Health Study and Meta-Analysis
Abigail Fraser, Ross Harris, Naveed Sattar, Shah Ebrahim, George Davey Smith, D.A. Lawlor

In a meta-analysis of prospective population-based studies, GGT was associated with vascular events even among nondrinkers. ALT was also associated with these outcomes. Therefore it is possible that GGT reflects other biological processes such as oxidative stress or liver steatosis, or lifestyle behaviors that are linked to cardiovascular disease.

USF1 Gene Variants, Cardiovascular Risk, and Mortality in European Americans: Analysis of Two US Cohort Studies
Alexander P. Reiner, Christopher S. Carlsson, Nancy S. Jenny, J. Peter Durda, David S. Siscovick, Deborah A. Nickerson, Russell P. Tracy

A common haplotype of the gene encoding upstream transcription factor 1 previously associated with decreased susceptibility to familial combined hyperlipidemia is associated with lower cholesterol levels and decreased atherosclerotic risk in young adults, but with increased inflammatory markers and increased mortality in older adults.

Free Interleukin (IL)-18 Levels, and the Impact of IL18 and IL18BP Genetic Variation, in CHD Patients and Healthy Men
Simon R. Thompson, Daniela Novick, Carmel J. Stock, Julie Sanders, David Brull, Jackie Cooper, Patricia Woo, George Miller, Menachem Rubinstein, Steve E. Humphries

The effect of elevated IL-18 levels and the implications of variation within the IL-18 system genes were investigated. In both healthy and diseased individuals, IL-18, determined in part by common variation within IL18, was predictive of adverse outcomes, suggesting IL-18 may play a role in CHD development and postsurgery outcome.

Inflammatory Activation During Coronary Artery Surgery and Its Dose-Dependent Modulation by Statin/ACE-Inhibitor Combination
Alberto Radaelli, Claudia Loardi, Maria Cazzaniga, Giulia Balestri, Caterina DeCarlini, M. Grazia Cerrito, Elena Negro Cusa, Luca Guerra, Stefano Garducci, Danilo Santo, Lorenzo Menicanti, Giovanni Paolini, Arianna Azzellino, Maria Luisa Lavitrano, Giuseppe Mancia, Alberto U. Ferrari

CABG surgery triggers inflammation. Modulation of this response by statins/ACE-inhibitors (ACEI) was tested. Patients undergoing CABG were randomized to statin/ACEI treatment at standard (STD) or high doses (HiDo). Inflammatory mediators were assayed. Striking increases in inflammatory mediators were observed in the STD but not the HiDo group. CABG-related inflammatory response can be prevented by high doses of ACEI/statins.
Low C1-Inhibitor Levels Predict Early Restenosis After Eversion Carotid Endarterectomy
Concentrations of C1-inhibitor were determined in samples serially taken from patients who were followed up after carotid endarterectomy. Low C1-INH levels at 6-weeks postsurgery predicted the development of an early restenosis, indicating that it might be a marker in the identification of patients with high risk for early restenosis.

Soluble CD40 Ligand Predicts Ischemic Stroke and Myocardial Infarction in Patients With Nonvalvular Atrial Fibrillation
Domenico Ferro, Lorenzo Loffredo, Licia Polimeni, Filippo Fimognari, Paolo Villari, Pasquale Pignatelli, Valentin Fuster, Francesco Violi ................................................................. 2763
This prospective study provides evidence that enhanced plasma levels of sCD40L (>4.76 ng/mL) are predictive of cardiovascular events in patients with nonvalvular atrial fibrillation, thus suggesting that enhanced platelet activation may play a pivotal role in its clinical progression.

Thrombosis

Cardiac Glycosides Regulate Endothelial Tissue Factor Expression in Culture
Barbara E. Stähli, Alexander Breitenstein, Alexander Akhmedov, Giovanni G. Camici, Kushiar Shojaati, Nikolay Bogdanov, Jan Steffel, Daniel Ringli, Thomas F. Lüscher, Felix C. Tanner ................................................................. 2769
Inhibition of Na+/K+-ATPase by ouabain inhibited TNF-α–induced endothelial TF protein expression via a reduced protein translation. TF mRNA expression was not inhibited, and TF protein stability remained unaffected. This observation provides novel insights into posttranscriptional regulation of TF expression in culture.

Adiponectin Mediates the Suppressive Effect of Rosiglitazone on Plasminogen Activator Inhibitor-1 Production
Ruby L.C. Hoo, W.S. Chow, M.H. Yau, A. Xu, Annette W.K. Tso, H.F. Tse, Carol H.Y. Fong, Sidney Tam, Lawrence Chan, Karen S.L. Lam ................................................................. 2777
We demonstrated that rosiglitazone-mediated elevation of plasma adiponectin level is independently associated with the reduction in PAI-1 concentrations in diabetic patients. The suppressive effect of rosiglitazone on PAI-1 production was attenuated in adiponectin-deficient mice, whereas over-expression of adiponectin decreased PAI-1 production. Recombinant adiponectin inhibited PAI-1 expression in 3T3-L1 adipocyte.

Heritabilities of turbidimetric measures of structure/function were ≈0.30 in the Leeds Family Study. Clot structure/function was related to presence of the metabolic syndrome and number of metabolic syndrome components. Identification of the genetic and environmental factors influencing clot structure/function may further our understanding of factors predisposing to cardiovascular disease.

Letters to the Editor

A Comparison of Lupus Anticoagulant–Positive Patients With Clinical Picture of Antiphospholipid Syndrome and Those Without
Vittorio Pengo, Alessandra Biasiolo, Paolo Gresele, Francesco Marongiu, Nicoletta Erba, Fabio Veschi, Angelo Ghirarduzzi, Doris Barcellona, Armando Tripodi Web Site Feature ................................................................. e309–e310

A Highly Efficient Method to Differentiate Smooth Muscle Cells From Human Embryonic Stem Cells
Chang-Qing Xie, Jifeng Zhang, Luis Villacorta, Taixing Cui, Huarong Huang, Y. Eugene Chen Web Site Feature ................................................................. e311–e312


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