3. 阿部弘太郎、廣岡良隆、砂川賢二、江頭健輔：特集　Small-vessel disease Small-vessel disease と肺高血圧症. 循環器内科　科学評論社　2012;71(2):119-124

＜新聞報道＞

2011 年 08 月 01 日 「ナノ DDS 技術による革新的低侵襲治療的血管新生療法の橋渡し研究」について、24 年度に医師主導型治験を開始する旨の記事が日本経済新聞に掲載された。

【研究成果の刊行物・別刷】

○をつけた論文の別刷あるいは資料を次のページ以降に添付します。

Anti-Inflammatory Gene Therapy for Cardiovascular Disease

Tetsuya Matoba and Kensuke Egashira*

Department of Cardiovascular Medicine, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan

Abstract: Inflammation in the vascular wall is an essential hallmark during the development of atherosclerosis, for which major leukocytes infiltrated in the lesions are monocytes/macrophages. Therefore, monocyte chemoattractant protein-1 (MCP-1) and its primary receptor CC chemokine receptor 2 (CCR2) are feasible molecular targets for *gene therapy* to inhibit monocyte/macrophage-mediated inflammation in atherogenesis. A mutant MCP-1 that lacks N-terminal 7 amino acids (7ND) has been shown to heterodimerize with native MCP-1, bind to CCR2 and block MCP-1-mediated monocyte chemotaxis by a dominant-negative manner. Gene therapy using intramuscular transfection with plasmid DNA encoding 7ND showed inhibitory effects on atherosclerosis in hypercholesterolemic mice, and neointima formation after vascular injury in animal models. Bare metal stents for coronary intervention were coated with multiple thin layers of biocompatible polymer with 7ND plasmid. The 7ND *gene-eluting stent* inhibited macrophage infiltration surrounding stent struts and in-stent neointima formation in rabbit femoral arteries and cynomolgus monkey iliac arteries. Finally, the authors describe new application of 7ND plasmid encapsulated in polymer nanoparticle (NP) that functions as gene delivery system with unique *in vivo* kinetics. NP-mediated 7ND gene delivery inhibited MCP-1-induced chemotaxis of mouse peritoneal macrophage ex vivo, which may be applicable for the treatment of atherosclerotic cardiovascular disease. In conclusion, anti-inflammatory gene therapy targeting MCP-1/CCR2 signal, with a novel NP-mediated gene delivery system, is a potent therapeutic strategy for the treatment of cardiovascular diseases.

Keywords: ??????????????????????????.

INTRODUCTION

Recent advances in interventional cardiology employing percutaneous coronary intervention (PCI) and other modalities of revascularization have ameliorated symptomatic cardiovascular diseases; however, atherosclerotic cardiovascular disease is still a major cause of death worldwide. In order to improve patients' prognosis, it is needed to develop therapeutics that intervene specific molecular mechanisms underlying disease pathogenesis. Widespread use of transgenic animals has provided various genetic models of human diseases including atherosclerotic cardiovascular disease. Pathological and biochemical analysis in animal models revealed functional consequence of each gene product, which led to basic concept of *gene therapy* to develop new therapeutics for cardiovascular disease. In this manuscript, the authors describe translational application of gene therapy using plasmid DNA for the treatment of atherosclerotic cardiovascular disease, focusing on the gene therapy targeting monocyte-mediated inflammation, and novel nanoparticle-mediated gene delivery system.

ATHEROSCLEROSIS

Recent studies suggest that the inflammatory response plays an important role in the development of atherosclerosis [1]. Chemokines are proinflammatory cytokines, and regulate migration and infiltration of leukocytes into tissues and subsequently cause their activation. During atherogenesis, major leukocytes infiltrated in atherosclerotic lesions are monocytes/macrophages for which monocyte chemoattractant protein-1 (MCP-1) is a primary chemokine that regulates migration and infiltration into the vascular wall. MCP-1 belongs to the CC chemokine subfamily and its primary receptor CC chemokine receptor 2 (CCR2) is dominantly expressed in monocyte and also in vascular endothelial and smooth muscle cells. The importance of MCP-1/CCR2 signaling in athrogenesis is evident from previous studies using genetically-modified mice. Gu *et al.* [2] analyzed atherosclerotic lesions in MCP-1-deficient mice crossed with LDL receptor-deficient mice that develop atherosclerotic lesions in the aorta when fed with high fat diet. Boring *et al.* [3] analyzed CCR2-deficient mice crossed with ApoE-deficient mice that also develop atherosclerotic lesions in the aorta. Both MCP-1/LDL-R double-deficient mice and CCR2/ApoE double-deficient mice developed less atherosclerotic lesions in the aortas. Thus, gene therapy targeting MCP-1/CCR2 signaling is a feasible approach for the treatment of atherosclerotic cardiovascular disease.

We have developed a gene therapy to block MCP-1 activity *in vivo* by using an N-terminal deletion mutant of MCP-1, called 7ND, which lacks the N-terminal amino acid 2 to 8. This mutant MCP-1 has been shown to heterodimerize with native MCP-1, bind to CCR2 and block MCP-1-mediated monocyte chemotaxis by a dominant-negative manner [4] Fig. (**1A**). Plasmid encoding 7ND was constructed by recombinant polymerase chain reaction using a wild-type human MCP-1 cDNA as the template and cloned into BamHI (5') and NotI (3') sites of the pcDNA3 expression vector (Invitrogen) [5] For gene transfer, we injected

*Address correspondence to this author at the Department of Cardiovascular Medicine, Kyushu University Graduate School of Medical Sciences, 3-1-1, Maidashi, Higashi-ku,Fukuoka 812-8582, Japan; Tel: +(81)-92-642-5360; Fax: +(81)-92-642-5374; E-mail: egashira@cardiol.med.kyushu-u.ac.jp

1566-5232/11 $58.00+.00

naked 7ND plasmid vector into skeletal muscles followed by electroporation, and demonstrated that 7ND protein was detectable in the circulating blood over 2 to 4 weeks and blocked monocyte chemotaxis induced by subcutaneous injection of recombinant MCP-1 [6] Fig. (**1B**). Based on these results, we investigated the effect of this gene therapy on the development and progression of atherosclerosis.

ApoE-deficient mice spontaneously develop hypercholesterolemia and atherosclerotic lesions in aortas. We injected with 7ND plasmid into hindlimb muscles of ApoE-deficient mice at 7 to 8 weeks of age, which have not developed apparent atherosclerotic lesions, and evaluate the effect of the transfection on atherogenesis after high cholesterol diet administration. Gene therapy with 7ND plasmid inhibited atherosclerotic lesions without affecting serum lipid concentration [5]. Furthermore, this strategy increased the lesional extracellular matrix content and accordingly, the plaque stability score. These results suggest that MCP-1 is associated with not only atherogenesis but alsoatheromatous plaquevulnerability. We also determined the effect of blockade of MCP-1 on progression of pre-existing atherosclerotic lesions in the aortic root in ApoE KO mice at 20 weeks of age. Gene therapy with 7ND also could limit progression of established lesions [7] In addition, blockade of MCP-1 improved plaque stability (i.e., containing fewer macrophages and lymphocytes, less lipid, more smooth muscle cells and collagen). This strategy decreased expression of CD40 and the CD40 ligand in the atherosclerotic plaque and normalized the increased gene expression of cytokines (MCP-1, RANTES, TNFα, IL-6, IL-1β, and TGF-β1) in the aorta. Suppression of MCP-1 and the other cytokine expression by 7ND gene transfer implies that MCP-1-mediated inflammation causes a vicious cycle to enhance inflammation in the vascular wall by activating lesional monocytes/macrophages. These data suggested that gene therapy with 7ND plasmid is an effective strategy to specifically intervene to MCP-1/CCR2 signaling for the treatment of atherosclerotic cardiovascular disease.

NEOINTIMA FORMATION

Restenosis after PCI consists major part of cardiovascular events in patients of advanced coronary artery disease who underwent PCI even after the introduction of drug-eluting stents (DES). The pathological mechanism of restenosis is undesirable growth of neointima that consists mainly from vascular smooth muscle cells. Drugs on DES inhibit not only vascular smooth muscle cell growth but endothelial cell growth and thus stent re-endothelialization, which causes adverse effects including late stent thrombosis [8]. Therefore, development of new treatment is needed that specifically inhibits undesirable neointima formation. Recent evidence suggests that PCI-induced vascular injury causes an inflammatory response that accelerates recruitment and activation of monocytes through expression of MCP-1 in vascular cells [9, 10]. Inflammation of injured vascular wall results in production of growth factors and other cytokines, which accelerates regrowth of vascular smooth muscle cells causing neointimal hyperplasia. Thus, anti-inflammatory therapy targeting MCP-1-mediated signaling may be an effective approach to treat clinical restenosis.

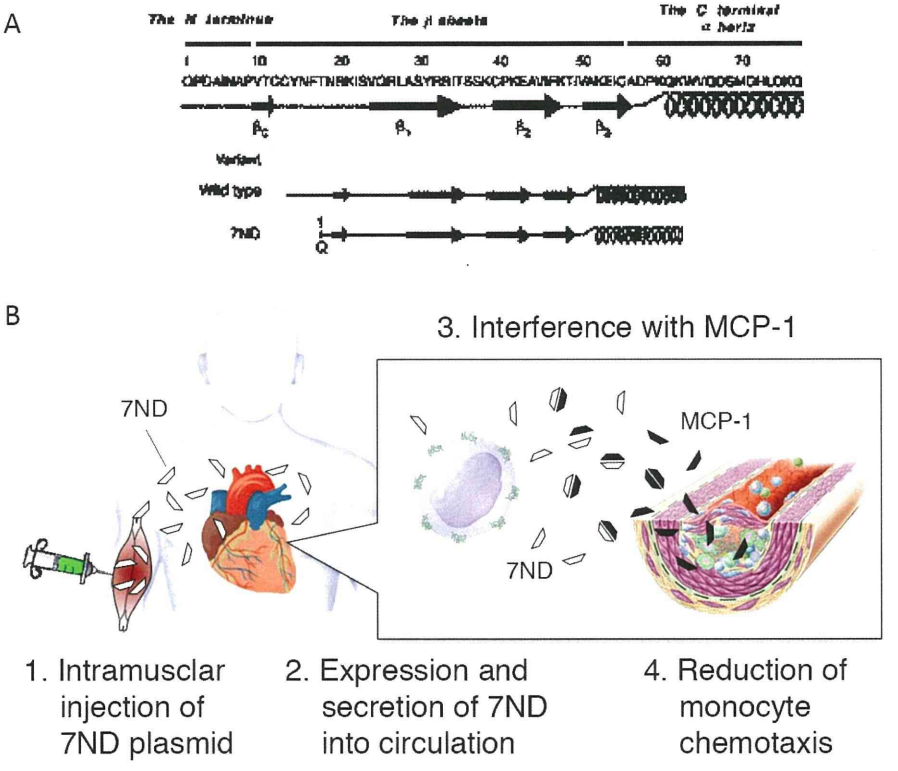

Fig. (1). A, N-terminal deletion mutant of MCP-1 (7ND) lacks the N-terminal amino acids 2 to 8, and acts as a dominant negative inhibitor for MCP-1. **B**, Therapeutic strategy of 7ND gene therapy consists of these 4 steps. 1) Intramusclar injection of 7ND plasmid. 2) Secretion of 7ND into circulation. 3) Interference with MCP-1 in a dominant-negative manner. 4) Reduction of monocyte chemotaxis, which inhibits inflammation in the vascular wall.

We have examined the effect of gene therapy with 7ND plasmid in animal models of vascular injury. Balloon-induced endothelial denudation in rat carotid artery causes neointima formation. Expression of MCP-1 and CCR2 in the injured artery was significantly higher on days 3, 7, and 28 than that in contralateral non-injured artery [11]. Three days before the balloon injury, rats were injected with empty plasmid or 7ND plasmid into hindlimb muscles. Gene therapy with 7ND plasmid reduced monocyte/macrophage infiltration and inhibited proliferation of neointimal cells [11]. Similar therapeutic effect was observed in another balloon injury model in carotid arteries of cynomolgus monkeys. The effect of 7ND gene therapy was confirmed in other animal models in which nonconstrictive polyethylene cuff was placed around the femoral arteries in mice and cynomolgus monkeys [12]. In these models, 7ND gene therapy suppressed infiltration of macrophage and proliferation of smooth muscle cell in the neointima 7-day after cuff placement. Cross-sectional intima/media ratio 28-day after cuff placement was significantly reduced by 7ND gene therapy. These data indicated that 7ND plasmid transfection into hindlimb muscles is a valid anti-inflammatory strategy to inhibit local inflammation in the vascular wall to prevent restenosis after PCI.

Based on these findings, we have formulated a stent coated with 7ND plasmid to examine the effect of local delivery of 7ND to inhibit neointima formation. A 15-mm-long stainless-steel balloon-expandable stent was dipcoated under sterile conditions with multiple thin layers of biocompatible polymer (polyvinyl alcohol [PVOH], GOHSENOL EG-05, Nippon GohseiInc). The polymer solution additionally contained either 7ND cDNA plasmid, plasmid encoding beta-galactosidase or polymer without plasmid as a control [13]. Gene transfer of beta-galactosidase by this gene-eluting stent system was confirmed in rabbit femoral arteries stented with β-galactosidase gene-eluting stent Fig. (**2A**). The 7ND gene-eluting stents inhibited macrophage infiltration surrounding stent struts 10 days after stenting in rabbit femoral arteries. In cynomolgus monkeys, 7ND gene-eluting stent or stent without plasmid was placed in the iliac arteries. After 6-month observation, in-stent neointima formation was significantly less in arteries stented with 7ND gene-eluting stents Fig. (**2B**). In these studies, the biocompatible polymer and plasmid DNA coating material used did not cause any adverse reactions during a 1-month observation period in rabbits and during a 6-month observation period in nonhuman primates. These findings suggest that anti–MCP-1 gene therapy via 7ND gene-eluting stents may be clinically relevant and further clinical trials are warranted.

NANOPARTICLE-MEDIATED GENE DELIVERY SYSTEM

Above described gene therapy using intramuscluar injection of 7ND plasmid was dependent on the expression of 7ND in the skeletal muscle and release into the circulation. Transduced 7ND protein was detectable in the plasma *in vivo*, which interfered MCP-1/CCR2 signaling to inhibit monocyte/macrophage chemotaxis into the inflamed vascular wall. Although intramuscular 7ND transfection showed no notable side effects, we have been developing nanoparticle-mediated plasmid gene transfer to raise the specificity of gene delivery and reduce possible off-target effects of extrinsic 7ND gene.

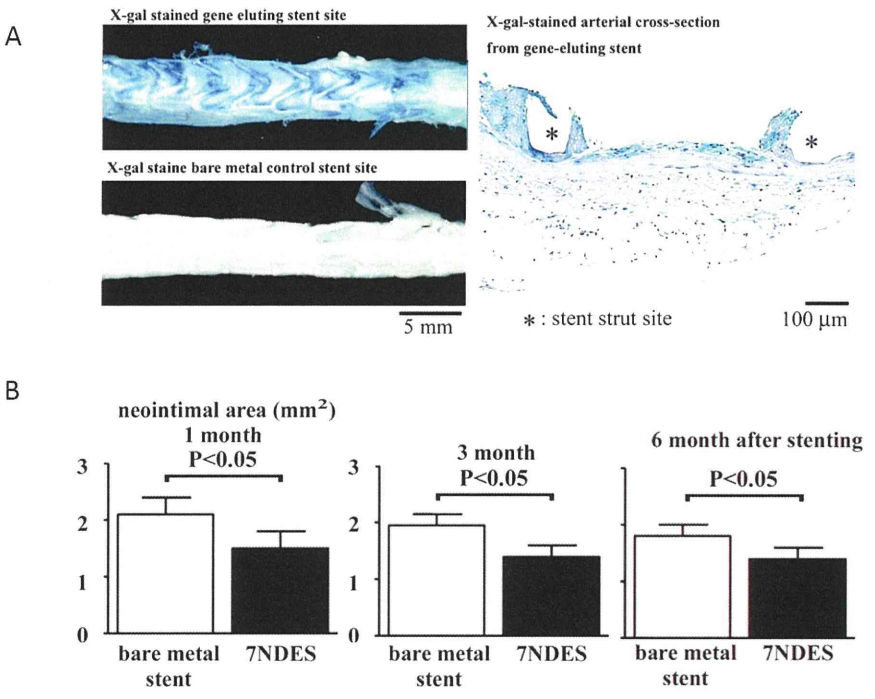

Fig. (2). A, Transgene expression in the rabbit iliac artery stented with gene-eluting stent. Left, Macroscopic image of the luminal surface of X-gal-stained iliac arteries stented with β-galactosidase gene-eluting stent (upper left) or bare stent (lower left). Right, a cross section of X-gal-stained artery stented with β-galactosidase gene-eluting stent. **B**, Inhibitory effect of 7ND gene-eluting stents (7NDES) on in-stent neointima formation in iliac arteries of monkeys.Neointima area at 1, 3, and 6 months after stenting (n=6 each).

We have employed poly lactic-co-glycolic acid nanoparticle (PLGA-NP) that is formed by emulsion solvent diffusion method as previously reported [14-18].

PLGA polymer is shown to be biocompatible and biodegradable. An average diameter of PLGA-NP was 200 nm. Fluorescein isothiocyanate (FITC, Dojindo laboratories, Kumamoto, Japan) containing PLGA-NP (FITC-NP) was prepared for the examination of *in vivo* distribution of nanoparticles. *In vivo* distribution of FITC-NP was examined after intravenous administered into C57Bl/6J mice from the tail vein. Two hours after injection, mononuclear cells that took FITC-NP into cytoplasm were observed in the peripheral blood. Flow cytometry showed that FITC-NP was taken up by CD11b+ monocytes Fig. (**3A**).

We prepared PLGA-NP containing 7ND plasmid (7ND-NP, content of 7ND plasmid 0.40 wt%) and PLGA-NP containing GFP plasmid (GFP-NP, content of GFP plasmid 0.32 wt%) using the same method and tested nanoparticle-mediated gene transfer in cultured mouse monocyte cell line J774A.1 (DS Pharma Biomedical, Suita, Japan). J774A.1 was maintained in RPMI 1640 medium containing 5% fetal bovine serum. For gene transfer, J774A.1 was incubated with 20 μg/mL GFP plasmid conjugated with conventional transfection reagent according to the manufacturer's protocol (Fugene®, Roche Applied Science) or GFP-NP that contained 3 μg/mL GFP plasmid for 1 hour and then, medium was changed. Twenty-four hours after GFP-NP treatment, RNA was extracted and reverse transcripted and gene expression was quantified by real time polymerase chain reaction (RT-PCR). GFP and GAPDH primer, which are mixed with probes as TaqMan® Gene Expression Assays, were commercially available and purchased from Applied Biosystems. RT-PCR showed equivalent GFP expression in cells after conventional gene transfer as well as nanoparticle-mediated gene transfer Fig. (**3B**). These results suggest that PLGA-NP-mediated delivery of plasmid DNA results the expression of the gene. Then we examined the effect of nanoparticle-mediated 7ND gene therapy on MCP-1-induced mocyticchemotaxis in murine abdominal macrophages ex vivo. Thioclycolate elicited macrophages were collected from abdominal cavity 4 days after injection of 7ND-NP or Empty-NP. Migration of macrophages was examined by Boyden's chamber method. Pretreatment with 7ND-NP significantly inhibited MCP-1-induced macrophage chemotaxis compared with Empty-NP Fig. (**3C**), suggesting the autocrine effect of 7ND in the macrophages themselves.

At the time of writing, we have been examining the effect of nanoparticle-mediated 7ND gene delivery on several vascular disease models based on the above results. Nanoparticle-mediated 7ND gene delivery haves shown inhibitory effects on monocyte/macrophage infiltration into atherosclerotic lesions, lesion progression, and plaque instability in hypercholesterolemic mice. Intravenous treatment of nanoparticulated 7ND plasmid significantly reduce total amount of plasmid DNA required, in compared with intramuscular injection of naked 7ND plasmid, in order to regulate monocyte/macrophage chemotaxis (unpublished observations, Egashira and Matoba). These findings support the concept of novel nanoparticle-mediated gene delivery system Fig. (**4**).

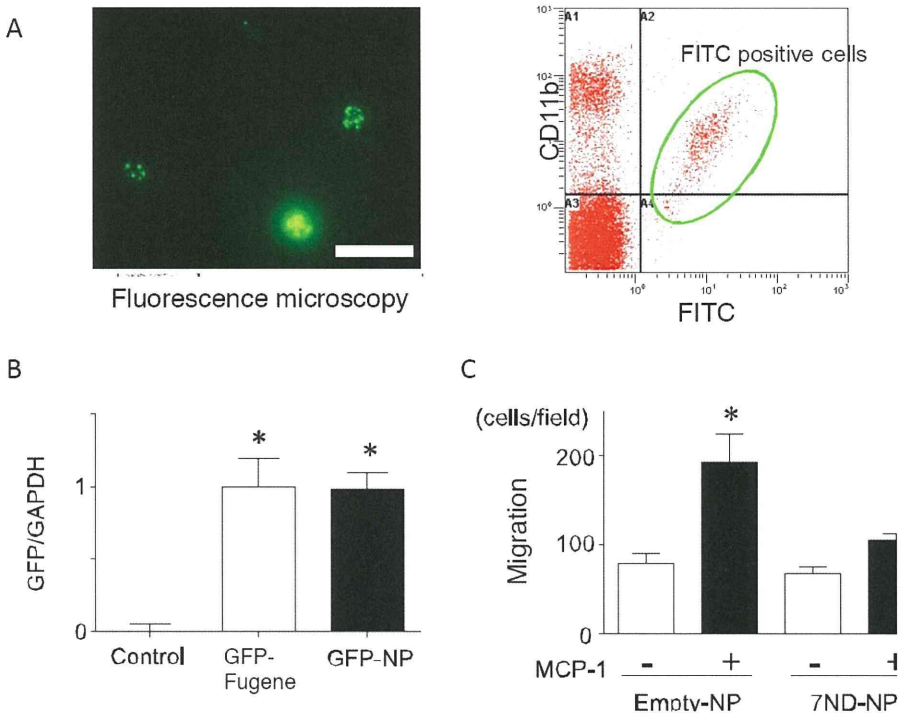

Fig. (3). A, Left, fluorescent micrograph of peripheral blood 2 hours after intravenous administration of FITC-NP. Scale bar indicates 50 μm. Right, flow cytometry showed that FITC positive cells presented CD11b+ monocytes. B, cultured macrophages (J774A.1) were incubated with Fugene-conjugated GFP plasmid (GFP-Fugene) or nanoparticulated GFP plasmid (GFP-NP) for 1 hour. RT-PCR showed GFP expression was comparable between two transfection methods. * $p<0.01$ vs control. C, chemotaxis of thioglycolate-elicited macrophages was suppressed by pretreatment with nanoparticulated 7ND plasmid. * $p<0.001$ vs control (Empty-NP, MCP-1(-)).

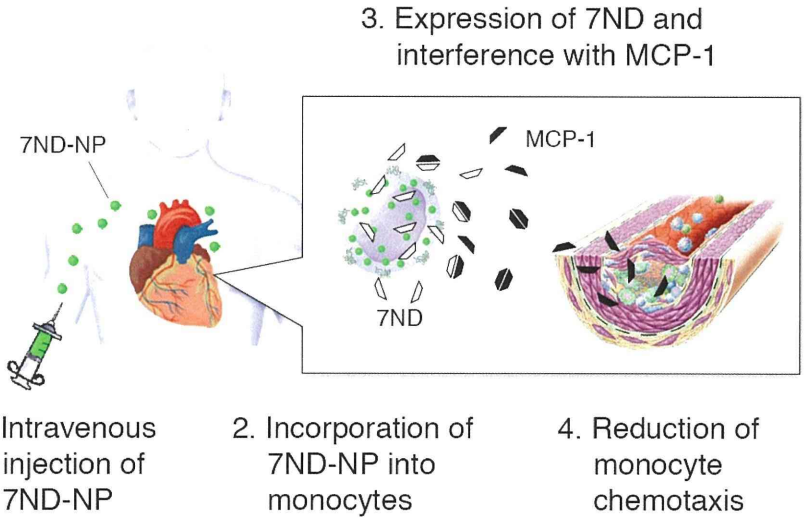

Fig. (4). Therapeutic strategy of nanoparticle-mediated 7ND gene therapy consists of these 4 steps. 1) Intravenous injection of nanoparticulated 7ND plasmid (7ND-NP). 2) Incorporation of 7ND-NP into peripheral monocytes. 3) Expression of 7ND and Interference with MCP-1 in aautocrine/paracrine manner. 4) Reduction of monocyte chemotaxis, which inhibits inflammation in the vascular wall.

SUMMARY

Monocyte/macrophage-mediated inflammation plays an important role in the development of cardiovascular diseases including atherosclerosis and vascular remodeling after injury. Gene therapy targeting MCP-1/CCR2 signals are potent therapeutic strategy, for which novel nanoparticle-mediated gene delivery system extendsthe efficacy of anti-inflammatory gene therapy to treat cardiovascular diseases.

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臨床評価　39巻2号　2011

九州大学　各拠点からの報告

「血管内皮細胞選択的ナノDDS技術」を活用した低侵襲ナノ医療の開発

The development of vascular endothelial cell selective nanotechnology based drug delivery system for less invasive nanotherapy

中野　覚[1)*1]　江頭　健輔[2)*2]
Kaku Nakano　Kensuke Egashira

1）九州大学大学院医学研究院循環器病先端医療研究開発学　准教授
Associate Professor, Department of Cardiovascular Research, Development, and Translational Research, Graduate School of Medical Sciences, Kyushu University

2）九州大学大学院医学研究院循環器病先端医療研究開発学　教授
Professor, Department of Cardiovascular Research, Development, and Translational Research, Graduate School of Medical Sciences, Kyushu University

1. 開発目標

試験物はピタバスタチン封入PLGAナノ粒子製剤，対象疾患は重症末梢動脈疾患（閉塞性動脈硬化症等）です（Table 1）．最終目標は本製剤を医薬品として市販化，医療として定着させることです（Table 2）．出口は医師主導治験によるPOC（proof of concept）取得です．出口に至る現時点での主なハードルはGLP基準の安全性試験，安定性試験の実施およびGMPでの製造です．現在，本製剤の安全性試験，薬物動態試験および筋注製剤の製剤設計と安定性試験を実施中です．GMP製造のためのスケールアップには既に成功し，GMP施設への技術移管も完了し，来年度（2011年度）は本格的に治験薬GMPの製造を開始します．

2. 開発スケジュール・知財確保状況

本年度（2010年度）末までに安定性試験および安全性試験の最終報告書が上がってくる予定です（Fig. 1）．治験薬の製造については昨年度（2009

Table 1　「血管内皮細胞選択的ナノDDS技術」を活用した，重症虚血性疾患に対する革新的低侵襲ナノ医療を実現するための探索的橋渡し研究ならびに臨床試験
— 平成22年度成果報告会 —

プロジェクト責任者：　江頭　健輔
（九州大学大学院医学研究院　循環器病先端医療研究開発学）
（NEDO橋渡し研究プロジェクトリーダー，スーパー特区分担プロジェクトリーダー）
プロジェクトマネージャー：　中野　覚
連携企業：　興和株式会社

試験物名称：ピタバスタチン封入PLGAナノ粒子製剤
対 象 疾 患：重症末梢動脈疾患（閉塞性動脈硬化症等）

*1　写真と筆頭著者は，発表者．
*2　プロジェクト責任者．

Table 2　開発目標

①開発の最終目標
ピタバスタチン封入PLGAナノ粒子製剤を医薬品として市販化
医療として定着

②当該プロジェクトの「出口」
医師主導治験によるPOC取得

③「出口」へ至る主なハードル
GLP基準の安全性試験と安定性試験の実施およびGMP製造
1. ピタバスタチン封入PLGAナノ粒子製剤（以下本ナノ製剤）のGLP基準安全性試験
2. 本ナノ製剤の筋注製剤の製剤設計と安定性試験
3. 本ナノ製剤の治験薬GMP製造

④「出口」へ至る現時点での到達点と解決策
1. 本製剤の安全性試験，薬物動態試験，および筋注製剤の製剤設計と安定性試験を実施中．GMP製造施設から治験施設への輸送を鑑み，冷凍保存（-20℃）で18ヶ月，冷蔵保存（4℃）で12ヶ月，の製剤安定性が確認された．
2. 本ナノ製剤製造のGMP製造のためのスケールアップに成功（本橋渡し研究プログラム）
3. GMP製造施設への技術移管完了，来年度は治験薬GMP製造開始

年度）より試作を開始しており，平成23（2011）年度中には医師主導治験を開始したいと思っています．最終的には平成33（2021）年度の市販を目指します．

3. 非臨床試験成績

マウス急性モデル，ウサギ慢性下肢虚血モデルにおいて，本製剤の有効性は既に実証し，国際的なトップジャーナルに既にアクセプトされました（Table 3）．

Table 3　マウスおよびウサギ下肢虚血モデルで本製剤の有効性を実証

Integrative Physiology/Experimental Medicine

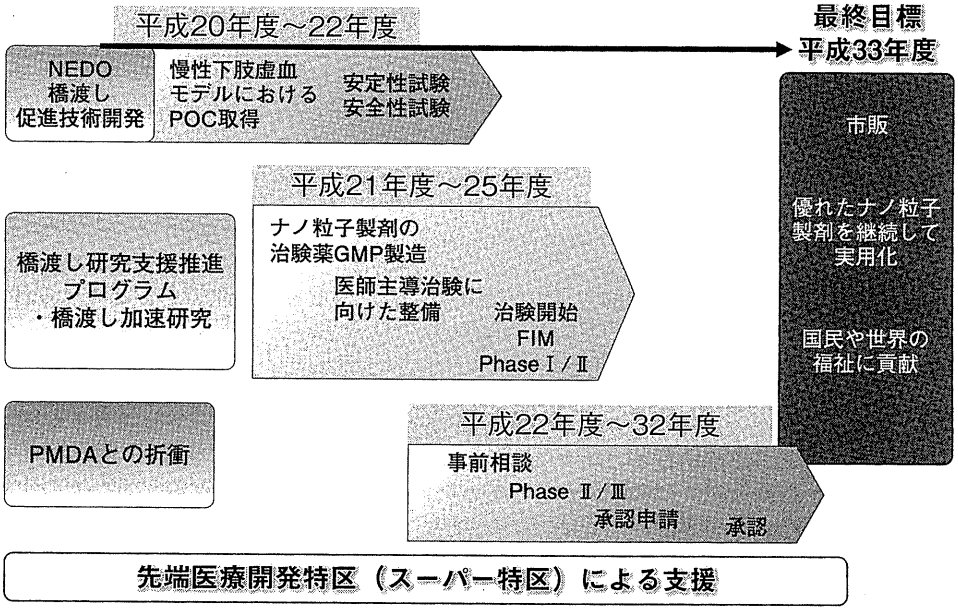
Therapeutic Neovascularization by Nanotechnology-Mediated Cell-Selective Delivery of Pitavastatin Into the Vascular Endothelium

Arterioscler Thromb Vasc Biol. 2009；29：796-801.

Nanoparticle-mediated endothelial cell-selective delivery of pitavastatin induces functional collateral arteries (therapeutic arteriogenesis) in a rabbit model of chronic hind limb ischemia

J Vasc Surg. 2010；52：412-20.

Fig. 1　開発スケジュール（ロードマップ）



また，霊長類であるカニクイザルの重症下肢虚血モデルを用い，単回投与群，3日間連続投与群，6日間連続投与群を設け，CTによる分子イメージングを行い，側副血行路数を測定しました．投与後8週では，溶媒対照群に比べて3日間連続投与群，6日間連続投与群において側副血行路数が有意に増加するという結果が得られました(Fig. 2)．

安定性試験は，本製剤の室温で6ヶ月まで影響ないという結果が得られています．また，GLP下で行った安全性試験では，ラット，イヌの筋肉注射でいずれも重篤な副作用は認められていません．安全性薬理試験も実施しましたが，特に問題となる副作用は認められませんでした．

4. 治験実施計画の概要・実施体制

医師主導治験で，first-in-manになります(Table 4)．試験デザインはまだ案の段階でfixしていませんが，筋肉内投与に関するPhase Ⅰ/Ⅱa臨床試験，安全性と用量設定を行うスタディを実施する予定です．単施設，用量漸増試験，現在1用量4症例，4用量として合計16症例を検討しています．

Fig. 2　スタチン封入ナノ粒子3日間および6日間連続投与により側副血行路（血管新生）が有意に発達（サル）

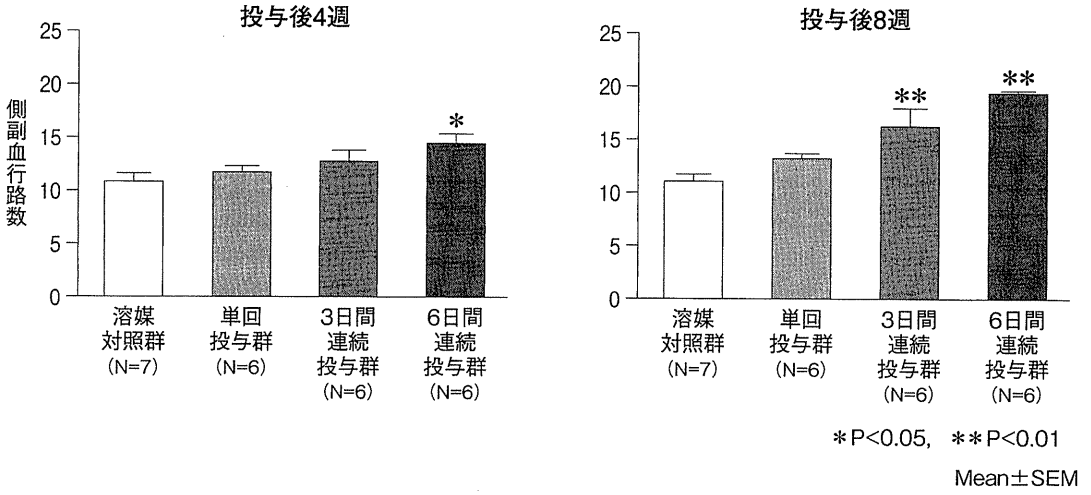


Table 4　臨床試験の概要（1/2）

①**試験の枠組み**　医師主導治験

②**試験の段階**　First-in-man

③**プロトコルコンセプト**

背景・Rationale：本ナノ製剤筋肉内投与によりピタバスタチンは血管内皮細胞選択的に送達されて薬効を発揮することが疾患モデル（ラット，ウサギ，霊長類）において明らかになった．全身経口投与と比較して格段に少ない用量(300分の1)で有効性を発揮した．これらの成果から，より効果的で且つ低副作用のナノ医療を実用化できると考えられる．ピタバスタチン経口製剤（リバロ錠，4mg/body/日）のヒトにおける安全性は確立．

試験デザイン：

1. 本ナノ製剤の筋肉内投与に関するPhase Ⅰ/Ⅱa臨床試験（安全性と用量設定）：単施設，用量漸増試験，1用量4症例，4用量として計16症例
2. 本ナノ製剤の筋肉内投与に関するPhase Ⅱb/Ⅲ臨床試験（POC試験）：偽薬対照・二重盲検・群間比較，ピタバスタチン封入ナノ粒子製剤筋肉内投与群と対照群の比較：1群20症例，計40症例

適格基準：重度の糖尿病性網膜症患者，担癌患者，透析患者を除外

主要／副次エンドポイントは（Table 5），救肢率，Fontaine分類の変化，Rutherford分類の推移，血行動態を考えています．治験実施計画書および治験薬概要書第1版が完成，治験薬GMP基準下での治験薬試作品が完成し，前臨床試験はすべて終了しています．臨床試験の障害は，適応基準を満たす患者さんのリクルートだと考えています．これを解決するため，先ほど内山麻希子先生が報告したシーズ[*3]を実施した米満吉和先生方の血管外科チームの協力を得る予定です．

「自ら治験を実施する者」は前原喜彦先生（九州大学消化器・総合外科学教授）です（Table 6）．以下Table 6に示すようなスタッフで実施を予定しています．

本ナノ粒子製剤について，興和株式会社と連携し九州大学病院高度先端医療センターの支援のもと治験を実施し，日本や世界の医療として定着させることを目指しています（Fig. 3）．

Table 5　臨床試験の概要（2/2）

主要／副次エンドポイント：
救肢率，Fontaine分類の変化，Rutherford分類の推移，血行動態

臨床試験の準備／進捗状況
医師主導治験実施計画書ドラフト完成，治験薬概要書ドラフト完成
治験薬GMP基準下での治験薬試作品完成，前臨床試験は全て終了

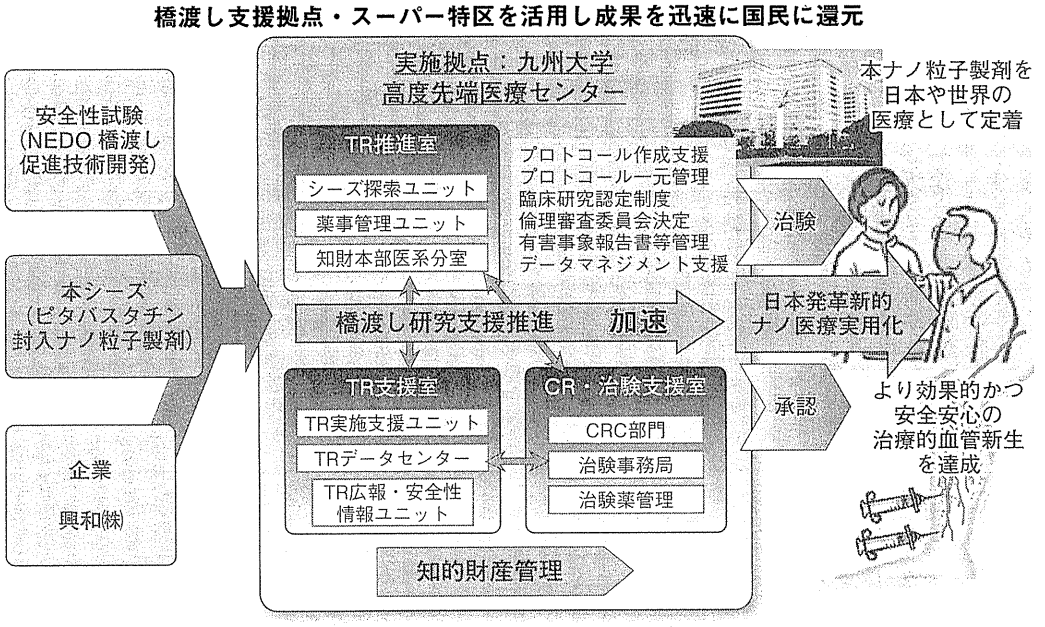
臨床試験の障害とその解決策（費用調達も含む）
障害：臨床試験の適応基準を満たす患者のリクルート
解決策：
①先行するシーズ（TR1：高性能国産新規RNAウイルスベクターによる虚血肢治療製剤の開発）を実施した血管外科チームの協力を得る
②循環器内科も患者の動員を支援

Table 6　医師主導治験実施組織編成表（H22.10.）

＜TR08＞	所属・責任者名	所属・担当者名
自ら治験を実施する者	消化器・総合外科学・前原喜彦	
プロジェクト責任者	循環器内科学・江頭健輔	
プロジェクトマネジメント	循環器内科学・中野　覚	
薬事	TR推進室・内山麻希子	—
データマネジメント	TR支援室・下川元継	—
統計解析	デジタルメディシン・イニシアティブ 岸本淳司	医療情報部・徳永章二
モニタリング	がん先端医療応用学講座・江見泰徳	—
CRC	高度先端医療センター・菊武恵子	高度先端医療センター 田中理子，中尾雅文
安全性情報管理	医療情報部・徳永章二	TR支援室・北島奈緒子
記録保存／文書管理	高度先端医療センター・中西洋一	—
メディカルライティング	—	—
信頼性保証／監査	呼吸器科・高山浩一	血液・腫瘍内科・馬場英司

[*3] 内山麻希子，米満吉和，松本拓也，岡崎　仁，吉田久美，中西洋一，前原喜彦．高性能国産新規RNAウイルスベクターによる虚血肢治療用バイオ製剤の開発．臨床評価．2011；39(2)：293-9.

Fig. 3　本橋渡し支援拠点における実施体制



＜質疑応答＞

清水　プロトコルと概要書が既に1版というのはGCP管理上少々問題があるのではと思いますが.

中野　第1版と申しましたが，第0.1版のドラフトです．現在，九州大学学内で米満先生方，専門家の先生方にレビューがようやく回った状況で，1版として確定したものではありません.

清水　多分今後苦労されると思いますが，版管理の状態をしっかりしておかないと，治験に行くときに監査で，第1版から全部記録があるかという話になってしまうので，0コンマ何版というのを導入されることを強くお勧めします.

中野　どうもありがとうございます.

福島　SOPは揃っていてGCPの適格性調査もクリアされているので，私は大丈夫だと思っています．1点確認したいのですが，九州大学でなぜ2つの下肢血管再生を行うのか皆さんひょっとして疑問に思われるといけませんが，私がお聞きしているのは，適応が違う．つまり先ほどの米満先生の開発されたウイルスベクターによるもの[*3]は間歇性跛行，より軽症のもので，先生のところはより重症のクリティカルなケースを対象にするというわけですね.

中野　はい，そうです.

福島　そういうことで，皆さんご理解いただければと思います.

*　　*　　*