Attenuation of neointima formation through the inhibition of DNA repair enzyme PARP-1 in balloon-injured rat carotid artery

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Zhang, Chunxiang, Jian Yang, and Lisa K. Jennings. Attenuation of neointima formation through the inhibition of DNA repair enzyme PARP-1 in balloon-injured rat carotid artery. Am J Physiol Heart Circ Physiol 287: H659–H666, 2004. First published March 25, 2004; 10.1152/ajpheart.00162.2004.—Increased oxidative stress is a major characteristic of restenosis after angioplasty. The oxidative stress is mainly created by oxidants such as reactive oxygen species (ROS), which are assumed to play an important role in neointima formation after angioplasty. DNA is a sensitive target for oxidants; however, oxidative DNA damage remains a poorly examined field in the pathogenesis of restenosis. In the present study, we demonstrated that the expression of the oxidative DNA damage marker 7,8-dihydro-8-oxo-2′-deoxyguanosine (8-oxo-dG) was increased in rat carotid arteries after balloon injury. It reached its peak at 14 days after injury and still kept high expression at 28 days after injury. The immunostaining of 8-oxo-dG was present predominantly in the neointima. In response to oxidative DNA damage, PARP-1 is similar to that of 8-oxo-dG. Daily injections of the PARP-1 inhibitor PJ34 (5 mg·kg⁻¹·day⁻¹ ip) attenuated neointima formation by ~40% at 7, 14, and 28 days after balloon injury. Treatment with PJ34 inhibited leukocyte infiltration and improved both anatomic (reendothelialization) and functional (endothelial function) recovery of endothelial cells after balloon injury. In conclusion, levels of oxidative DNA damage and the DNA repair enzyme PARP-1 are increased in vessels after balloon injury. Inhibition of PARP-1 attenuates neointima formation through inhibition of leukocyte infiltration and improvement of endothelial cell recovery after balloon injury. Targeting of the DNA repair enzyme might be a therapeutic strategy for restenosis.

angioplasty; DNA damage; oxidative stress; restenosis

THERE IS A GROWING BODY OF EVIDENCE suggesting that oxidative stress plays a very important role in the pathogenesis of cardiovascular diseases such as atherosclerosis, hypertension, diabetic cardiovascular complications, and restenosis postangioplasty (1, 14, 16, 45). Indeed, reactive oxygen species (ROS), which are the main creators of the oxidative environment, are significantly increased under pathological conditions in the above-mentioned cardiovascular diseases (15). Both basic and clinical studies have shown promising effects of antioxidants against cardiovascular diseases (28, 35). However, few studies have addressed the molecular physiological mechanism underlying this oxidative hypothesis.

Recent studies indicate that ROS can interact with isolated or cellular DNA to cause DNA strand breaks and/or base modifications (8, 32). Significant oxidative damage to DNA induced by ROS has been suggested to contribute to the pathogenesis of inflammatory cardiovascular diseases such as atherosclerosis (2, 4, 8, 10, 32). In this regard, one recent report showed that the level of the well-established oxidative DNA damage marker (3) 7,8-dihydro-8-oxo-2′-deoxyguanosine (8-oxo-dG) was increased in the thoracic aorta of cholesterol-fed rabbits (26). The same result was also found in human atherosclerotic lesions (27).

In response to oxidative DNA damage, cells have developed several defense systems to remove DNA damage (9, 13, 23). A major repair mechanism for oxidative DNA damage is the base excision repair pathway. The most important enzyme involved in base excision repair is the nuclear enzyme poly(ADP-ribose) polymerase-1 (PARP-1) (41). Although an elevated level of PARP-1 was found in the vascular wall under inflammatory cardiovascular disease conditions such as atherosclerosis and diabetic cardiovascular complications (26, 27, 38), the physiological role of PARP-1 is still unclear. Recent studies suggest that, in addition to DNA damage repair, PARP-1 has several other important effects. For example, pronounced activation of PARP-1 induces an energy-consuming, futile repair cycle that eventually leads to cell injury. PARP-1 inhibitors and PARP-1 deficit have been shown to diminish brain damage after cerebral ischemia, protect myocardial injury in heart ischemia, reduce renal ischemia-reperfusion injury, and prevent the development of diabetes (12, 25, 30, 31). In addition, several recent reports indicate that PARP-1 plays a very important role in the development of endothelial dysfunction in both diabetic and aging animals (29, 36). Furthermore, PARP-1 participates in inflammatory response by regulating inflammatory cell infiltration (24).

Since the birth of coronary angioplasty in 1977, percutaneous transluminal coronary angioplasty (PTCA) and peripheral artery angioplasty (PTA) have become widely adapted for use in the treatment of coronary and peripheral artery diseases. More than 1.5 million patients receive PTCA or PTA every year in the world. However, PTCA and PTA remain limited by restenosis, which occurs in 30–60% of patients despite a successful procedure (33). Although the advent of coronary stents has reduced the incidence of restenosis, the problem still occurs in 20–30% of stented vessels (33). Thus restenosis after angioplasty is not only important clinically but also for its impact on health care costs.

Although the notion is widely held that ROS and oxidative damage play an important role in restenosis (1, 40), few studies...
have addressed the molecular physiological mechanism underlying the oxidative stress hypothesis of restenosis. Herein, we detected, for the first time, the oxidative DNA damage marker 8-oxo-dG and its repair enzyme PARP-1 in vessels after balloon injury. The results indicated that 8-oxo-dG and PARP-1 were increased after balloon injury. Treatment with a potent PARP-1 inhibitor, PJ34, reduced leukocyte infiltration, improved both anatomic and functional endothelial cell recovery, and reduced neointima formation.

MATERIALS AND METHODS

Materials. Mouse anti-rat CD45 and PARP-1 antibodies were purchased from BD Biosciences. Mouse anti-8-oxo-dG antibody was from the Japan Institute for Control of Aging. Mouse-monoclonal anti-poly(ADP-ribose) antibody was purchased from Tulip BioLabs. Normal control mouse IgG was from Pharmingen. PJ34 was from Calbiochem. Peroxidase conjugated anti-mouse IgG was purchased from Sigma. The Vectastain ABC kit and DAB kit were from Vector Laboratories. A cGMP enzyme immunoassay kit was purchased from Biotrak Amersham. All other materials were purchased from Sigma.

Animals. Sprague-Dawley rats (weight: 250–300 g; Harlan Breeding Laboratories; Indianapolis, IN) were used in the study. The animals were maintained at constant humidity (60 ± 5%), temperature (24 ± 1°C), and light cycle (6 AM to 6 PM) and were fed a standard rat pellet diet. All protocols were approved by the Institutional Animal Care and Use Committee of the University of Tennessee and were consistent with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Pub. No. 85-23, Revised 1985).

Vascular injury model and animal treatment. Carotid artery balloon injury was induced as described previously (7). Briefly, rats were anesthetized with ketamine (60 mg/kg)-xylazine (5 mg/kg). Under a dissecting microscope, the right common carotid artery was exposed through a midline cervical incision, and blood flow to the site of surgical manipulation was temporarily interrupted by ligation of the left common, internal, and external carotid arteries with vessel clips. A 2-Fr Fogarty catheter (Baxter Edwards) was introduced through an arteriotomy in the external carotid artery and advanced to the proximal edge of the omohyoid muscle. To produce carotid artery injury, we inflated the balloon with saline and withdrew it six times from just under the proximal edge of the omohyoid muscle. To produce carotid artery injury, we inflated the balloon with saline and withdrew it six times from just under the proximal edge of the omohyoid muscle. After injury, the external carotid artery was permanently ligated with a 6-0 silk suture. The clips at the common and internal carotid arteries were released and the blood flow was restored.

Animals were divided into two groups. Group 1 was treated with PJ34 (5 mg · kg⁻¹ · day⁻¹ ip), which was dissolved in 0.5 ml PBS.

Fig. 1. Expression of the oxidative DNA damage marker 7,8-dihydro-8-oxo-2'-deoxyguanosine (8-oxo-dG) in uninjured and balloon injured rat carotid arteries. A: representative photomicrographs of immunohistochemical stains of 8-oxo-dG in uninjured and balloon-injured rat carotid arteries at 1, 4, 7, 14, and 28 days after balloon injury. Normal mouse IgG was used as a control IgG. B: quantitative analysis of 8-oxo-dG expression in the vascular wall after balloon injury.
Group 2 was treated with the vehicle (0.5 ml ip PBS, pH 7.4) as a control.

Vessel harvest and preparation. The animals were anesthetized with an overdose of pentobarbital (200 mg/kg). For vascular function assessment, the injured left carotid arteries were excised and cleansed of fat and adhering tissue. The uninjured right carotid arteries were also excised as uninjured controls. The vessels were then cut into individual ring segments (2–3 mm in width) and suspended from a force-displacement transducer in a tissue bath. For planimetric analysis of reendothelialization, the rats received an intravenous injection via the femoral vein of 0.5 ml of 0.5% Evans blue dye 30 min before they were killed. For morphometric analysis and immunohistochemistry, the right atrium was dissected quickly, and an 18-gauge catheter connected to the perfusion system was inserted in the left ventricle. All animals were perfused for 2 min with saline, followed by fixation with 10% buffered formalin for another 5 min at physiological pressure. The treated segment of right carotid artery and contralateral untreated segment of the left carotid artery were removed and embedded in paraffin. Six serial sections (5 μm thick), sectioned at equally spaced intervals, were stained with hematoxylin and eosin (H-E) staining for morphometry, and three additional sections (5 μm thick) were used for immunohistochemistry.

Vascular function assessment. Isometric tension was measured in isolated carotid artery ring segments of rats as described (46, 47). Ring segments were bathed in Krebs-Henseleit (K-H) solution. The vessels were contracted to 50–60% of their maximal capacity (50–60% of KCl response) with phenylephrine (3 × 10⁻⁷ M). When tension development reached a plateau, ACh (10⁻⁹–3 × 10⁻⁶ M) was added cumulatively to the bath to stimulate endothelium-dependent relaxation.

Measurement of tissue cGMP content. To further determine the functional recovery of endothelium cells, the vessel segments were collected after the maximal dose of ACh. Vessel segments of injured carotid arteries without ACh and SNP were used as basal controls. The samples were snap frozen in liquid nitrogen and stored at −30°C after in vitro vascular function measurement. Tissues were homogenized in a 10-fold volume of 6% trichloroacetic acid at 2–8°C and centrifuged at 2,000 g for 15 min at 4°C. The supernatant was collected and washed four times with water-saturated diethyl ether. Measurement of cGMP was performed with a cGMP enzyme immunoassay kit (Biotrak, Amersham) according to the manufacturer’s recommendations. Values for cGMP were standardized by tissue protein (in mg).

Planimetric analysis of reendothelialization. Planimetric analysis of the photograph of the harvested carotid arteries stained with Evans blue dye to identify the remaining endothelium-denuded site was performed with a computerized sketching program (Scion Image CMS-800) by one technician who was blind to the treatment regimen. The initially denuded area was defined as the total surface area between the carotid bifurcation and the edge of the omohyoid muscle. The reendothelialization area was defined macroscopically as the area that was not stained with Evans blue.

Morphometric analysis for neointimal formation. Morphometric analysis was performed in sections stained with H-E via a computerized image analysis system (Scion Image CMS-800) as described in our previous study (48). Six sections (5 μm thick) sectioned at equally spaced intervals of injured carotid arteries were used. The medial area was calculated by subtracting the area defined by the internal elastic lamina (IEL) from the area defined by the external elastic lamina (EEL), and the intimal area was determined by subtracting the lumen.

![Fig. 2. Expression of the oxidative DNA damage repair enzyme poly(ADP-ribose) polymerase (PARP)-1 in uninjured and balloon injured rat carotid arteries.](AJP-Heart Circ Physiol: Vol. 287: August 2004: www.ajpheart.org)
area from the area defined by the IEL. Finally, the intimato medial area ratio (I/M) of each section was calculated. The average I/M of the six sections was used as the I/M of this animal.

**Immunohistochemistry.** To test the oxidative DNA damage and DNA repair enzyme after balloon injury, 8-oxo-dG and PARP-1 were detected by immunohistochemistry in uninjured arteries and injured arteries at 1, 4, 7, 14, and 28 days after balloon injury. To test whether the effect of PJ34 on neointima formation is related to infiltration of inflammatory cells, immunohistochemistry with anti-CD45 antibody, a common biomarker for leukocytes, was performed in carotid arteries at 1, 4, 7, and 14 days after balloon injury using the method described in our previous study (49). To test the PARP-1 activity, the PARP-1 product poly(ADP-ribose) (PAR) was determined in rat carotid arteries (22). Normal control mouse IgG was used as a control. Immunohistochemistry was performed in paraffin-embedded sections. Mouse anti-8-oxo-dG, PARP-1, CD45, and PAR antibodies were used as primary antibodies. Peroxidase-conjugated anti-mouse IgG was used as a secondary antibody in combination with the Vectastain ABC system. A DAB kit was used to develop the positive reaction as a brown color. Positive cell expression in the vascular wall was quantitatively analyzed by a computerized image system and was expressed as the percent area occupied by positive cells.

**Statistics.** All data are presented as means ± SE. Dose-response profiles for different experimental conditions were analyzed and tested to determine differences in relaxation responses using the SigmaStat statistical analysis program. Unpaired observations were assessed by one-way ANOVA and multiple-range tests. A P value of <0.05 was required for significance.

**RESULTS**

**Oxidative DNA damage after balloon injury.** As shown in Fig. 1, there was no immunoreactivity for 8-oxo-dG in the normal, uninjured rat carotid artery. In contrast, strong 8-oxo-dG immunostaining was found in carotid arteries after balloon injury. 8-oxo-dG was present predominantly in the neointima and, to a lesser extent, in the media. After balloon injury, the expression of 8-oxo-dG was increased quickly and reached its peak at 14 days after injury. Although the 8-oxo-dG immunostaining began to decline 2 wk after injury, there was still strong immunostaining in the neointima of the vessel 28 days after balloon injury.

**Expression of PARP-1 after balloon injury.** In response to vascular injury and oxidative DNA damage, expression of PARP-1 was increased after balloon injury. As shown in Fig. 2, there was no immunoreactivity for PARP-1 in normal uninjured vessels. However, PARP-1 was found in vessels after balloon injury. PARP-1 was located predominantly in the neointima and, to a lesser extent, in the media. The time course changes of PARP-1 after balloon injury was similar to the expression of 8-oxo-dG. It peaked at 14 days after injury and was still expressed in the vascular wall 28 days after balloon injury.

**Effect of PARP-1 inhibitor on neointima formation after balloon injury.** To test the role of PARP-1 in neointima response after balloon injury, daily injections of PJ34, a potent PARP-1 inhibitor, were used. As shown in Fig. 3, PJ34 attenuated neointima formation by ~40% at 7, 14, and 28 days after balloon injury. The specificity of PJ34 for the PARP-1 pathway was well documented in previous reports (37, 39). To further confirm that the effect of PJ34 on neointima formation is related to the reduction of PARP-1 activity in the balloon

![Fig. 3. Effect of PJ34 on neointima formation after vascular injury. A: representative photomicrographs of the hematoxylin-and-eosin-stained section of uninjured rat carotid arteries and balloon-injured rat carotid arteries from vehicle-treated and PJ34-treated groups 14 days after balloon injury. B: neointimal-to-medial area ratio (I/M) of balloon-injured rat carotid arteries at 1, 4, 7, 14, and 28 days after balloon injury in arteries from vehicle- and PJ34-treated rats. *P < 0.01 vs. the vehicle-treated group.](https://ajpheart.physiology.org/doi/10.1152/ajpheart.00520.2003)
injury model, PAR formation in the vascular wall was determined. As shown in Fig. 4, there was no PAR staining in uninjured vessels. In contrast, strong PAR immunostaining was shown in balloon-injured arteries. PJ34 at the treated dosage (5 mg·kg⁻¹·day⁻¹) effectively inhibited PAR formation at every observed time point. It should be noted that a dose lower than 5 mg·kg⁻¹·day⁻¹ cannot totally block the PAR formation. A dose of 10 mg·kg⁻¹·day⁻¹ had a similar effect on PAR formation, whereas a dose higher than 20 mg·kg⁻¹·day⁻¹ induced unexpected side effects such increasing the rate of thrombosis after balloon injury (data not shown). Therefore, a dose of 5 mg·kg⁻¹·day⁻¹ was used in our study.

Effect of PARP-1 inhibitor on leukocyte infiltration after balloon injury. As shown in Fig. 5, in vehicle-treated carotid arteries, the infiltrated leukocytes were significantly increased after balloon injury. Leukocyte infiltration in adventitia reached a peak between 1 and 4 days after balloon injury (Fig. 5A). After that, the CD45 staining was reduced gradually in adventitia. However, in neointima, the CD45 staining reached a peak at 7 days after balloon injury (Fig. 5A). There was still CD45 immunostaining in the neointima at 14 days after balloon injury. The leukocyte infiltration in the whole vascular wall is shown in Fig. 5B. PJ34 did not change the pattern of leukocyte infiltration after balloon injury. However, PJ34 significantly decreased leukocyte infiltration at every detected time point.

Effect of PARP-1 inhibition on endothelial cell recovery after balloon injury. Several recent reports indicate that PARP-1 plays a very important role in the development of endothelial dysfunction. It is well known that endothelial dysfunction is induced by the impairment of the nitric oxide (NO) pathway, which plays an important role in endothelial cell regeneration (reendothelialization) and neointima formation after angioplasty. To test the role of PARP-1 in endothelial cell recovery, daily injections of PJ34 were used. The rats were killed at 14 days after balloon injury. Endothelial cell anatomic recovery was evaluated by the area of reendothelialization. Endothelial cell functional recovery was measured by endothelium-dependent relaxation. As shown in Fig. 5A, there was no difference in the total denuded area between the vehicle- and PJ34-treated groups; however, the reendothelialized area of the PJ34-treated group was much higher than that in the vehicle-treated group (P < 0.05). Consistent with the anatomic recovery, the endothelial function was improved after a 2-wk treatment with PJ34 (Fig. 6B). These results suggest that PJ34 accelerates both anatomic and functional recovery of endothelial cells after balloon injury.
Effect of PARP-1 inhibition on NO bioavailability after balloon injury. To test whether the PJ34-induced acceleration of anatomic and functional recovery of endothelial cells after balloon injury is related to NO bioavailability, tissue cGMP content was measured in carotid arteries 2 wk after balloon injury. As shown in Fig. 7, although the basal levels of cGMP in balloon-injured arteries were lower than those in uninjured arteries, the difference was not significant (P > 0.05). In contrast, the agonist (ACh)-stimulated cGMP content of carotid arteries was significantly lower in balloon-injured arteries than in uninjured arteries (P < 0.001). Furthermore, the agonist (ACh)-stimulated cGMP content was higher in the PJ34-treated group than that in the vehicle-treated group (P < 0.01). The result suggests that NO signaling plays a role in PJ34-induced vascular effects after balloon injury.

DISCUSSION

Restenosis after angioplasty is a complex process. Although the cellular events involved in restenosis are evident, the molecular mechanisms that are responsible for restenosis are still unclear. Recently, more and more evidence suggests that oxidative stress plays an important role in restenosis (1, 40). It is well known that oxidative stress after angioplasty is mainly induced by ROS such as superoxide, hydrogen peroxide, hydroxy radical, and peroxynitrite. ROS have been implicated in a variety of distinct cellular processes, including initiation of gene expression and promotion of cell proliferation, hypertrophy, growth arrest, and/or apoptosis (18, 20). Many molecular targets, including DNA, are involved in ROS-induced cellular responses. In general, DNA damage resulting from attack by ROS includes base modifications, sugar damage, DNA strand breaks, abasic sites, and DNA protein-cross-links (42). Oxidation of 2′-deoxyguanosine by ROS results in the formation of 8-oxo-dG, which is one of the most abundant products of DNA oxidative damage and is an established ROS-induced DNA damage marker (6, 27). In the present study, we demonstrated that 8-oxo-dG in vessels was increased after balloon injury. 8-oxo-dG was present predominantly in the neointima and, to a lesser extent, in the media. The result indicates that ROS-induced DNA damage is a molecular characteristic after angioplasty.

Several defense systems, including DNA repair enzymes, to remove DNA damage are developed in cells in response to oxidative DNA damage (23). There are several mechanisms involved in enzyme-induced DNA repair: base excision repair, transcription-coupled repair, global genome repair, mismatch repair, translesion synthesis, homologous recombination, and nonhomologous end-joining. Among them, base excision repair is the major pathway for repair of oxidative DNA damage (23). PARP-1 is a nuclear enzyme that is activated by DNA damage induced by ROS to participate in DNA repair. Recent reports have demonstrated that PARP-1 is the most important enzyme involved in oxidative DNA repair (11, 13). We demonstrated that, consistent with DNA damage, PARP-1 was significantly increased after balloon injury. The time course change of PARP-1 was similar to that of the DNA damage marker 8-oxo-dG. The results indicate that DNA damage and repair occur concurrently after angioplasty.

The physiological role of PARP-1 is still unclear. In response to DNA damage, PARP-1 catalyses the synthesis of PAR from its substrate β-NAD⁺, and this polymer is co-
valently attached to several nuclear proteins and PARP itself. As a result, PARP converts DNA breaks into intracellular signals that activate DNA repair programs (11). However, in addition to DNA damage repair, pronounced activation of PARP-1 can cause cell dysfunction, apoptosis, or necrosis by NAD(+) and ATP depletion (5, 11, 17). PARP-1 inhibitors and PARP-1 deficient have been shown to diminish ischemia induced cardiovascular damage and prevent the development of diabetic vascular complications. In the present study, we found that oxidative DNA damage and PARP-1 expression in rat carotid arteries was significantly increased after balloon injury. To further investigate the role of PARP-1 in the vascular proliferative response after angioplasty, daily injections of PARP-1 inhibitor PJ34 were applied. We found that PJ34 at a dose (5 mg·kg⁻¹·day⁻¹ ip) that can effectively inhibit PARP-1 activity (Fig. 5) attenuated neointima formation at every measured time point. The result indicates that pronounced activation of PARP-1 increased neointima response after balloon injury, although the detailed mechanisms need to be further investigated.

Leukocyte infiltration is one of the main cellular events involved in neointima formation after angioplasty. Recent reports suggest that PARP-1 participates in the inflammatory response by regulation of leukocyte infiltration (11, 24, 17). To determine whether leukocyte infiltration is involved in the PARP-1 inhibitor-induced inhibitory effect on neointima formation, we measured leukocyte infiltration in rat carotid arteries after balloon injury in PJ34- and vehicle-treated animals. We demonstrated that PJ34 inhibited leukocyte infiltration at every time point. The results indicate that regulation of inflammatory cell infiltration is one of the mechanisms of the PARP-1 inhibitor-induced effect on neointima formation.

Anatomic and functional recovery of endothelial cells after balloon injury plays an important role in the regulation of neointima formation (43). Endothelial cell recovery is related to NO signaling. Recent reports have suggested that PARP-1 plays a very important role in the development of endothelial dysfunction (29, 36). We hypothesized that PARP-1 may play a role in endothelial cell recovery after angioplasty. To test this hypothesis, the PARP-1 inhibitor PJ34 was used. Our results showed that PJ34 improved both anatomic and functional recovery of endothelial cells after balloon injury. The PJ34-induced effect on endothelial cell recovery was related to an increase in NO bioavailability.

Recent reports suggest that bone marrow-derived progenitor cells modulate both vascular reendothelialization and neointimal formation after angioplasty (34, 44). In addition, PARP-1 is a survival factor for progenitor cells (19). PARP-1 inhibition is able to improve the effectiveness of neural stem cell transplantation in experimental brain trauma (21). Therefore, the effect of PARP-1 on bone marrow-derived progenitor cells after angioplasty and the possible role of this effect in PJ34-induced attenuation of neointima formation should be further studied, although no direct evidence was provided in the present study.

In conclusion, oxidative DNA damage and repair occur simultaneously after angioplasty. Inhibition of the pronounced activation of the DNA repair enzyme PARP-1 reduces neointima formation. The PARP-1 inhibitor-induced attenuation of neointima formation is related to the reduction of inflammatory cell infiltration and improvement of both anatomic and functional recovery of endothelial cells after balloon injury. Targeting of the DNA repair enzyme might be a therapeutic strategy for restenosis.

There are two limitations of this study. First, the results are mainly from the pharmacological inhibition of PARP-1. Overexpression by gene transfer and PARP-1 deficit by gene knockout are needed for further study. Second, the best therapeutic window and dosage of the PARP-1 inhibitor should be determined.

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REFERENCES

INHIBITION OF PARP-1 ATTENUATES NEOINTIMA


