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Title: METHODS AND PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF MYOCARDIAL INFARCTION

Abstract: The present invention relates to methods and pharmaceutical compositions for the treatment of myocardial infarction. In particular, the present invention relates to a method of treating myocardial infarction in a subject in need thereof comprising administering to the subject a therapeutically effective amount of F4-neuroprostane (F4-NeuroP).
METHODS AND PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF MYOCARDIAL INFARCTION

FIELD OF THE INVENTION:
The present invention relates to methods and pharmaceutical composition for the treatment of myocardial infarction

BACKGROUND OF THE INVENTION:
Myocardial infarction (MI) or acute myocardial infarction (AMI), commonly known as a heart attack, occurs when the blood supply to part of the heart is interrupted causing some heart cells to die. This is most commonly due to occlusion of a coronary artery following the rupture of a vulnerable atherosclerotic plaque. The resulting ischemia and oxygen shortage, if left untreated for a sufficient period of time, can cause damage and or death of heart muscle tissue. Accordingly, in clinical situations of myocardial infarction, the immediate goal is to restore blood flow to the patient as quickly as possible. If blood flow is restored within a suitable time period, tissue damage can be averted. However, a significant delay in restoring blood flow leads to a second condition known as ischemia-reperfusion injury that can develop gradually after an ischemic event and may cause irreversible damage to tissues. Clinical examples include cardiac contractile dysfunction, arrhythmias and irreversible myocyte damage (heart cell death) following myocardial infarction. Accordingly, several methods for the cardioprotection after myocardial infarction have been investigated. For example, current therapies aimed at improving contractile function often involve the use of inotropic agents (e.g., calcium, dopamine, epinephrine, ephedrine, phenylephrine, dobutamine). However inotropic drugs have been reportedly associated with increases in intracellular calcium concentration and heart rate, which may be potentially harmful, especially in hearts with impaired energy balance. Thus the limited successful for cardioprotection is limited by a relatively small number of therapeutic targets. The present invention fulfills this need by providing a new therapeutic target for the cardioprotection.

SUMMARY OF THE INVENTION:
The present invention relates to a method for the treatment of myocardial infarction or acute myocardial infarction (AMI), in a subject in need thereof comprising administering to said subject a therapeutically effective amount of F4-neuroprostane (F4-NeuroP).
DETAILED DESCRIPTION OF THE INVENTION:

The present invention relates to a method of treating myocardial infarction in a subject in need thereof comprising administering to said subject a therapeutically effective amount of F4-neuroprostane (F4-NeuroP).

As used herein, the term "subject" denotes a mammal, such as a rodent, a feline, a canine, and a primate. Preferably, the subject according to the invention is a human.

As used herein, the terms "treating" or "treatment" or "alleviation" refers to therapeutic treatment, wherein the object is to prevent or slow down (lessen) the targeted disease. A subject is successfully "treated" for a particular disease, if after receiving a therapeutic amount of the F4-neuroprostane according to the invention; the subject shows observable and/or measurable reduction in or absence of one or more signs and symptoms of said disease. In a particular embodiment the treatment is a prophylactic treatment. The term "prophylactic treatment" as used herein, refers to any medical or public health procedure whose purpose is to prevent a disease. As used herein, the terms "prevent", "prevention" and "preventing" refer to the reduction in the risk of acquiring or developing a given condition, or the reduction or inhibition of the recurrence or said condition in a subject who is not ill, but who has been or may be near a subject with the disease. It is also to be appreciated that the various modes of treatment or prevention of medical conditions as described are intended to mean "substantial," which includes total but also less than total treatment or prevention, and wherein some biologically or medically relevant result is achieved.

In some embodiments, the method of the present invention is particularly suitable for the treatment of acute myocardial infarction. In some embodiments, the method of the present invention is particularly suitable for the treatment of ST-segment elevated myocardial infarction. In particular, the F4-neuroprostane compound is suitable to prevent deleterious effect (arrhythmias, cell death following the release of noxious substances after an ischemia etc) caused by coronary angioplasty. In particular, in a subject who has experienced a myocardial infarction, the F4-neuroprostane compound is suitable for preventing cardiac arrhythmias and for reducing the infarct size.

In some embodiments, the method of the present invention is performed sequentially or concomitantly with a standard method for treating myocardial infarction. Typically, standard
methods include percutaneous coronary intervention or thrombolysis. The term "percutaneous coronary intervention (PCI)" means coronary angioplasty which is a therapeutic procedure to treat the stenotic (narrowed) coronary arteries of the heart found in coronary heart disease. The term "thrombolysis" means the administration of thrombolytic agents. Currently available thrombolytic agents include reteplase (r-PA or Retavase), alteplase (t-PA or Activase), urokinase (Abbokinase), prourokinase, anisoylated purified streptokinase activator complex (APSAC), and streptokinase.

In some embodiments, the present invention relates to a method of treating myocardial infarction in a subject in need thereof comprising the steps consisting of i) restoring blood supply in the cardiac ischemic tissue, and ii) administering to said subject a therapeutically effective amount of the F4-neuroprostane compound to reduce infarct size and/or prevent cardiac arrhythmias, where steps i) and ii) are performed sequentially or concomitantly.

As used herein, the term "F4-neuroprostane" (F4-NeuroPs) has its general meaning in the art and refers to the class of lipid oxidation metabolites derived from docosahexanoic acid (F4-isoprostanes: a novel class of prostanoids formed during peroxidation of docosahexaenoic acid (DHA). Nourooz-Zadeh J., Liu E., Änggard E., Halliwell B., Biochem. Biophys. Res. Com., 1998, 242, 338.; Regiochemistry of neuroprostanes generated from the peroxidation of docosahexaenoic acid in vitro and in vivo. Yin H., Musiek E., Gao L., Porter N. & Morrow J.. J. Biol. Chem. 2005, 280: 2600). In particular, F4-NeuroPs include but are not limited to 4-F4-NeuroPs, 7-F4-NeuroPs, 11-F4-NeuroPs, 10-F4-NeuroPs, 14-F4-NeuroPs, 13-F4-NeuroPs, 17-F4-NeuroPs and 20-F4-NeuroPs (Figure 1). F4-NeuroPs may be synthesised through any method well known in the art. Typically, the compounds may be synthesised by the method described in: The handy use of Brown's catalyst for a skipped diyne deuteration: application to the synthesis of a d4-labelled-F4t-neuroprostane. Oger C., Bultel-Ponce V., Guy A., Balas L., Rossi J-C., Durand T., Galano J-M. Chem. Eur. J. 2010, 16, 13976. In a particular embodiment, the F4-NP is 4-F4t-NeuroP. In a particular embodiment, the epimers of configuration (S) of the allylic hydroxyl or F4t-NeuroPs with a (S) absolute configuration of the allylic hydroxyl are used.

According to the invention, the F4t-NeuroP is administered in a therapeutically effective amount. By a "therapeutically effective amount" is meant a sufficient amount of the F4t-NeuroP to treat the target disorder or disease at a reasonable benefit/risk ratio applicable to any medical
treatment. It is understood that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed, the age, body weight, general health, gender and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of the compound at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. In particular, the compositions contain 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 250 and 500 mg of the active ingredient for the symptomatic adjustment of the dosage to the subject to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, in particular from 1 mg to about 100 mg of the active ingredient. An effective amount of the drug is ordinarily supplied at a dosage level from 0.0002 mg/kg to about 20 mg/kg of body weight per day, especially from about 0.001 mg/kg to 7 mg/kg of body weight per day.

The F4-neuroprostane of the invention is typically combined with pharmaceutically acceptable excipients, and optionally sustained-release matrices, such as biodegradable polymers, to be administered in the form of a pharmaceutical composition. "Pharmaceutically" or "pharmaceutically acceptable" refer to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to a mammal, especially a human, as appropriate. A pharmaceutically acceptable carrier or excipient refers to a non-toxic solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, transdermal, local or rectal administration, the active principle, alone or in combination with another active principle, can be administered in a unit administration form, as a mixture with conventional pharmaceutical supports, to animals and human beings. Suitable unit administration forms comprise oral-route forms such as tablets, gel capsules, powders, granules and oral suspensions or solutions, sublingual and buccal administration forms, aerosols, implants, subcutaneous, transdermal, topical, intraperitoneal, intramuscular, intravenous, subdermal, transdermal, intrathecal and
intranasal administration forms and rectal administration forms. Typically, the pharmaceutical compositions contain vehicles which are pharmaceutically acceptable for a formulation capable of being injected. These may be in particular isotonic, sterile, saline solutions (monosodium or disodium phosphate, sodium, potassium, calcium or magnesium chloride and the like or mixtures of such salts), or dry, especially freeze-dried compositions which upon addition, depending on the case, of sterilized water or physiological saline, permit the constitution of injectable solutions. The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including sesame oil, peanut oil or aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. Solutions comprising compounds of the invention as free base or pharmacologically acceptable salts can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms. The antibody can be formulated into a composition in a neutral or salt form. Pharmaceutically acceptable salts include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. The carrier can also be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetables oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminium monostearate and gelatin. Sterile injectable solutions are
prepared by incorporating the active antibody in the required amount in the appropriate solvent with several of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms, such as the type of injectable solutions described above, but drug release capsules and the like can also be employed. For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, sterile aqueous media which can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage could be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion. Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The invention will be further illustrated by the following figures and examples. However, these examples and figures should not be interpreted in any way as limiting the scope of the present invention.

FIGURES:

**Figure 1**: Biosynthesis of $F_{4t}$-neuroprostanes

**Figure 2**: In vivo effects of 4-F4t-NeuroP on ischemia/reperfusion period. (A) Typical examples of heart slices in control and after 4-F4t-NeuroP injection. (B) Effect of pericardial infusion of 4-F4t-NeuroP on the ratio infarction/area at risk determined by quantification of the area from heart left slices. (C) Typical echography acquisition of fraction area change (upper)
and ejection fraction (lower) (expressed in percentage) before and after I/R in animals control or treated with 4-F4t-NeuroP. 7 animals have been studied in each condition. *(P<0.05) vs Control.

**Figure 3.** Effect of 4-F4t-NeuroP on electrical properties after ischemia/reperfusion period. (A) Representative trace of ECG with occurrence of an extrasystole. (B) Mean number of extrasystoles in basal condition, during the 30 minutes of ischemia and after 3h of reperfusion in the different conditions indicated. (C) Trace of ECG parameters measured in table 2. (D) Mean of Q-T interval in different conditions.

**Figure 4.** Timeline of the experimental protocol. Study was divided into a baseline phase, a pre-ischemic phase with intracardiac injection of 4-F4t-NeuroP or vehicle, an ischemia phase (30 minutes), and a reperfusion phase (24h). Hemodynamic data were collected during baseline phase and at the end of the reperfusion before sacrifice (see text for details). Quantification of arrhythmias was performed using the continuous electrocardiogram data obtained during coronary occlusion (ischemia) and during the first 120 min of reperfusion. Finally, area at risk and infarcted area were assessed at the end of the protocol (24h of reperfusion).

**EXAMPLE:**

**Material & Methods**

**Animal experiments**

Five-week-old male Wistar Kyoto rats weighing 120-140 g (Janvier, Le Genest-Saint-Isle, France) were randomly assigned into two groups 1) seven rats received infusion of vehicle (0.9% saline solution), 2) seven rats received final infusion of 1 DM (0.03mg/kg) of 4-F4t-NeuroP (Figure 2). The animal protocol was conducted according to the procedures conformed to European Parliament Directive 2010/63/EU and council on the protection of animals was approved by our institutional animal research committee (CEEA-LR-12096). Investigators were blinded to treatment when measurements were performed. Rats were housed in single cages in a room under regulated temperature and hygroscopic conditions (23±1°C, 45±10% humidity, light-dark schedule of 12h: 12h ad libitum feed).
In the surgical procedure, the rats were anesthetized by pharmacological injection of a mixture of ketamine (90 mg/kg) and of xylazine (6 mg/kg) and ventilated 60 times per min with a volume-cycled respirator. A control of the heart rate was realized by the temporary pose in subcutaneous of a telemetric transmitter ECG. After 20 min stabilization following completion of surgery, a medial sternotomy was performed to expose the heart and pericardial. Treatments (4-F4t-NeuroP or vehicle) were administrated as intracardiac injection (200 µl) of the prepared solution equivalent to 10 times the concentration to reach the final concentrations matching in cellulo experiments [1]. The control animals received the same volume of the saline solution plus the equivalent amount of the substrate vehicle (saline solution 0.9%). 20 minutes after treatments, the left coronary artery was ligated at 1-2 mm from its origin (5-0 silk suture; Tyco Healthcare) to induce ischemia. After 45 min of occlusion, the ligation was removed and the left coronary artery was reperfused.

Finally, the animals had a suture with points separated from the various muscular coats to close the surgical zone and subcutaneous injection of 0.01 mL buprenorphine solution (0.3 mg/mL) for post-operative analgesia was administered.

**Measurements of infarct sizes and risk areas**

At the end of reperfusion (24h), the left coronary artery was reoccluded and patent blue dye (5%) was injected in the left atrial appendage to verify the ischemic area (area at risk). Subsequently, all animals were killed by KCl injection (3M), and the hearts were then cut into 5 to 6 cross-sectional slices of 1 mm thickness to quantify infarction sizes. Slices were then incubated with 1% triphenyltetrazolium chloride in phosphate buffer (pH 7.4) at 37°C for 20 min. Triphenyltetrazolium chloride forms a red formazan derivative when reacting with viable tissue, whereas necrotic tissue is pale white. The morphology of infarct size and area at risk of the left ventricle were quantified by using ImageJ® software 1.46r (National Institutes of Health).

**Electrocardiograms acquisition and analyses**

In parallel to surgical approach (Figure 2), the rats were monitored with ECG recordings by using a signal transmitter-receiver (RPC-1; DSI) connected to a data acquisition system (IOX2; EMKA Technologies) as previously described (17). Arrhythmias (ventricular extrasystoles: ESV) and ECG parameters (RR, PR, QRS, and QT interval) were collected continuously over 24 h at a sampling rate of 1,000 Hz. ECG signals were digitally filtered between 0.1 and 1,000 Hz and analyzed manually to detect arrhythmias before surgery, during
ischemia and over 3 h of reperfusion in animal treated with the vehicle (saline solution 0.9%,
i.e. injected), or 4-F4t-NeuroP. ECG acquisition and analyses respected the Lambeth
conventions for the housing of animal to determination of arrhythmic events. ECGs were
analyzed with Ponemah 5.2 Physiology Platform (Data Sciences International, Saint Paul, MN).

Echocardiography
Transthoracic echocardiography was performed with a Vevo 2100 high resolution
imaging system (Visualsonics Fujifilm, Toronto, Canada) equipped with a 2.1MHz transducer
as previously described (17). A first echocardiography was performed 2 days before the I/R
surgery, and a second one 24 hours after the myocardial reperfusion (Table 1).

Preparation of cardiomyocytes
Cellular experiments were performed on freshly isolated left ventricular myocytes from
the non-infarcted free wall (excluding the border zone) that were enzymatically isolated. In
brief, the heart was removed, washed and the aorta was cannulated to a modified Langendorff
system.

The heart was then perfused with a Ca2+ free physiological Tyrode solution (116
mmol/l NaCl, 6 mmol/l KC1, 4 mmol/l NaHCO3, 1.5 mmol/l KH2PO4, 1.7 mmol/l MgCl2, 21
mmol/l HEPES, 20 mmol/l taurine and 12 mmol/l glucose, pH 7.15) containing a permeant
protease inhibitor (E-64, 10 µmol/L, E8640, Sigma-Aldrich, St-Quentin-Fallavier, France) at
constant flow perfusion rate. After enzymatic treatment (20 min) with type IV collagenase
(Worthington, Entraigues, France) solution, a part of the left ventricle was removed and minced
to separate the cells. The isolated myocytes were re-suspended in a sterile enzyme-free Tyrode
solution, and the Ca2+ concentration of the ventricular cell suspension was gradually increased
to 1 mM by the addition of CaCl2 in five sequential steps 100, 100, 300 and 500 µM with 10
min intervals in between. Prior to treatments, freshly isolated cardiomyocytes were maintained
in a physiological solution (140 mmol/L NaCl, 4 mmol/L KC1, 1 mmol/L MgCl2, 5 mmol/L
HEPES, 1.8 mmol/L CaCl2 and 11 mmol/L glucose, pH 7.4) at 37°C for 30 minutes.
Cardiomyocytes with obvious sarcolemmal blebs or spontaneous contractions were not used.

Only cardiomyocytes with clear edges were selected and were used within 1-6h following
isolation.

Results:
The present invention shows that the 4-F4t-NeuroP has an effect on the ratio infarction/area at risk as determined by quantification of the area from heart left slices. Inventors have also shown that 4-F4t-NeuroP has an effect on electric properties after ischemia/reperfusion period.

REFERENCES:

Throughout this application, various references describe the state of the art to which this invention pertains. The disclosures of these references are hereby incorporated by reference into the present disclosure.


Regiochemistry of neuroprostanes generated from the peroxidation of docosahexaenoic acid in vitro and in vivo.

CLAIMS:

1. A method of treating myocardial infarction in a subject in need thereof comprising administering to the subject a therapeutically effective amount of F4-neuroprostane (F4-NeuroP).

2. The method of claim 1 is suitable for the treatment of acute myocardial infarction.

3. The method of claim 1 is suitable for the treatment of ST-segment elevation myocardial infarction.

4. The method of claim 1 comprising the steps consisting of i) restoring blood supply in the cardiac ischemic tissue, and ii) administering to said subject a therapeutically effective amount of the F4-neuroprostane compound to reduce infarct size and/or prevent cardiac arrhythmias, where steps i) and ii) are performed sequentially or concomitantly.

5. The method according to any of preceding claims wherein the F4-neuroprostane is selected from the group of 4-F4-NeuroPs, 7-F4-NeuroPs, 11-F4-NeuroPs, 10-F4-NeuroPs, 14-F4-NeuroPs, 13-F4-NeuroPs, 17-F4-NeuroPs and 20-F4-NeuroPs.

6. The method according to any of preceding claims wherein said F4-neuroprostane is an epimer of configuration (S) of the allylic hydroxyl or F4-NeuroPs with a (S) absolute configuration of the allylic hydroxyl.
A

![Graph: Infarcted area/area at risk (normalized area %)]

- **○**: Individual data
- **□**: Mean ± SEM

Control vs 4-F₄₃-NeuroP 1μM

Figure 2A

B

![Images: Before IR and After IR with FAC and EF values]

- **FAC = 73%** (Before IR)
- **FAC = 50%** (After IR)
- **EF = 75%** (Before IR)
- **EF = 60%** (After IR)

Figure 2B

SUBSTITUTE SHEET (RULE 26)
Figure 3
INTERNATIONAL SEARCH REPORT

PCT/EP2016/079307

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/5575 A61P9/10

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC (IPC)

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, SCISEARCH, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance

“E” earlier application or patent but published on or after the international filing date

“L” document which may throw doubts on priority claim(s) or one which is cited to establish the publication date of another citation or other special reason (as specified)

“O” document referring to an oral disclosure, use, exhibition or other means

“P” document published prior to the international filing date but later than the priority claimed

“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle of theory underlying the invention

“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

“A” document member of the same patent family

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<td>JÉRÔME ROY ET AL: &quot;Nonenzymatic lipid mediators, neuroprostanes, exert the anti arrhythmic properties of docosahexaenoic acid&quot;, FREE RADICAL BIOLOGY AND MEDICINE, vol. 86, 1 September 2015 (2015-09-01), pages 269-278, XP055273551, US ISSN: 0891-5849, DOI: 10.1016/j.freeradbiomed.2015.04.014</td>
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