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## Metabolites derived from radical oxidation of PUFA: NEO-PUFAs, promising molecules for health?

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### ABSTRACT

Oxidative stress plays a critical role in numerous pathological processes. Under these stress conditions, the free radical-catalyzed lipid peroxidation generates *in vivo* a large number of key products that are involved in many physiological and pathophysiological processes. Among these products are neuroprostanes, which arise from the peroxidation of docosahexaenoic acid (DHA), and isoprostanes, resulting from arachidonic acid (AA) and eicosapentaenoic acid (EPA) through the same peroxidation process. These non-enzymatic oxygenated metabolites newly appointed NEO-PUFAs have gained recognition as reliable markers of oxidative stress in neurodegenerative and cardiovascular diseases. Moreover, some of them display a wide range of biological activities. The ability to detect and measure these metabolites offers precious insights into the mechanisms of oxidative damage and holds potential therapeutic implications for various health conditions, including neurodegenerative diseases. This review focuses on the role of neuroprostanes as biomarkers for oxidative stress and related diseases, highlighting their potential applications in medical research and treatment.

### 1. Introduction

In 1956, Denham Harman proposed the idea that “aging and the degenerative diseases associated with it are attributed basically to the deleterious side attacks of free radicals on cell constituents and on the connective tissue” [1]. Since then, numerous findings have emerged connecting oxidative stress to the development of various human diseases, including vascular disorders, inflammatory ailments, cancers, and neurodegenerative conditions [2].

However, certain end-products of oxidative stress, particularly those originating from lipid peroxidation, are not only regarded as sensitive biomarkers of oxidative stress but also often exhibit potent biological activity [3].

The presence of multiple double bonds that are prone to peroxidation, makes polyunsaturated fatty acids (PUFAs), a crucial component of human body and particularly brain cells, vulnerable to the detrimental effects of oxidative stress [4]. Today, several classes of active compounds, resulting from peroxidation of different PUFAs, in other words,

Non-Enzymatic Oxygenated metabolites of PUFAs (newly appointed NEO-PUFAs), have been identified [5]. Following the discovery of prostaglandins, the enzymatic metabolites of arachidonic acid (AA), in 1930s [6], it was commonly believed for many years that NEO-PUFAs either had a deleterious impact or, at best, no significant effect on health. It was not until Morrow et al. [7] identified prostaglandin-like compounds, which they named isoprostanes, in the 1990s that research in the field of non-enzymatic NEO-PUFAs restarted, leading to the subsequent identification and isolation of other compounds such as phytoprostanes (PhytoPs) by Parchmann and Mueller [8] in 1998, isofurans (IsoFs) by Fessel and Roberts [9] in 2004, or dihomom-isoprostanes (dihomo-IsoPs) by VanRollins and colleagues [10] in 2008. Two different nomenclature systems for naming complex NEO-PUFAs were proposed by Taber [11] and by Rokach [12]. According to the latter, NEO-PUFAs are divided in classes based on  $\omega$ -carbon of fatty acid, which serves as the reference point. Roman numerals I-VIII refer the types of NEO-PUFAs. Noteworthy, this nomenclature is not approved by IUPAC. According to Taber's classification system, NEO-PUFAs are designated

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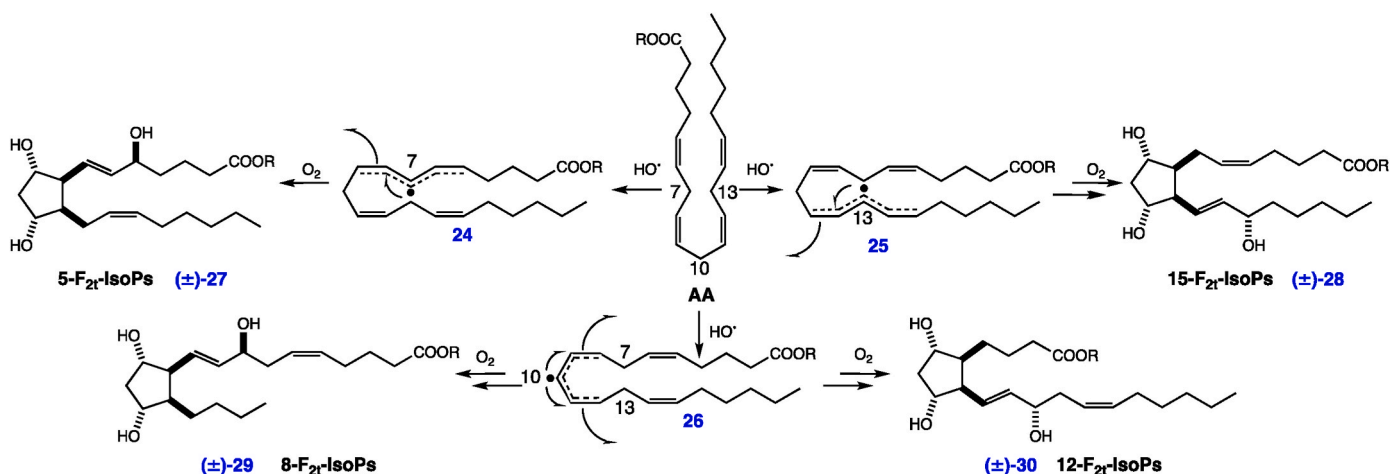


Fig. 1. Formation of isoprostanes (IsoPs) from AA, R = H, phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI).

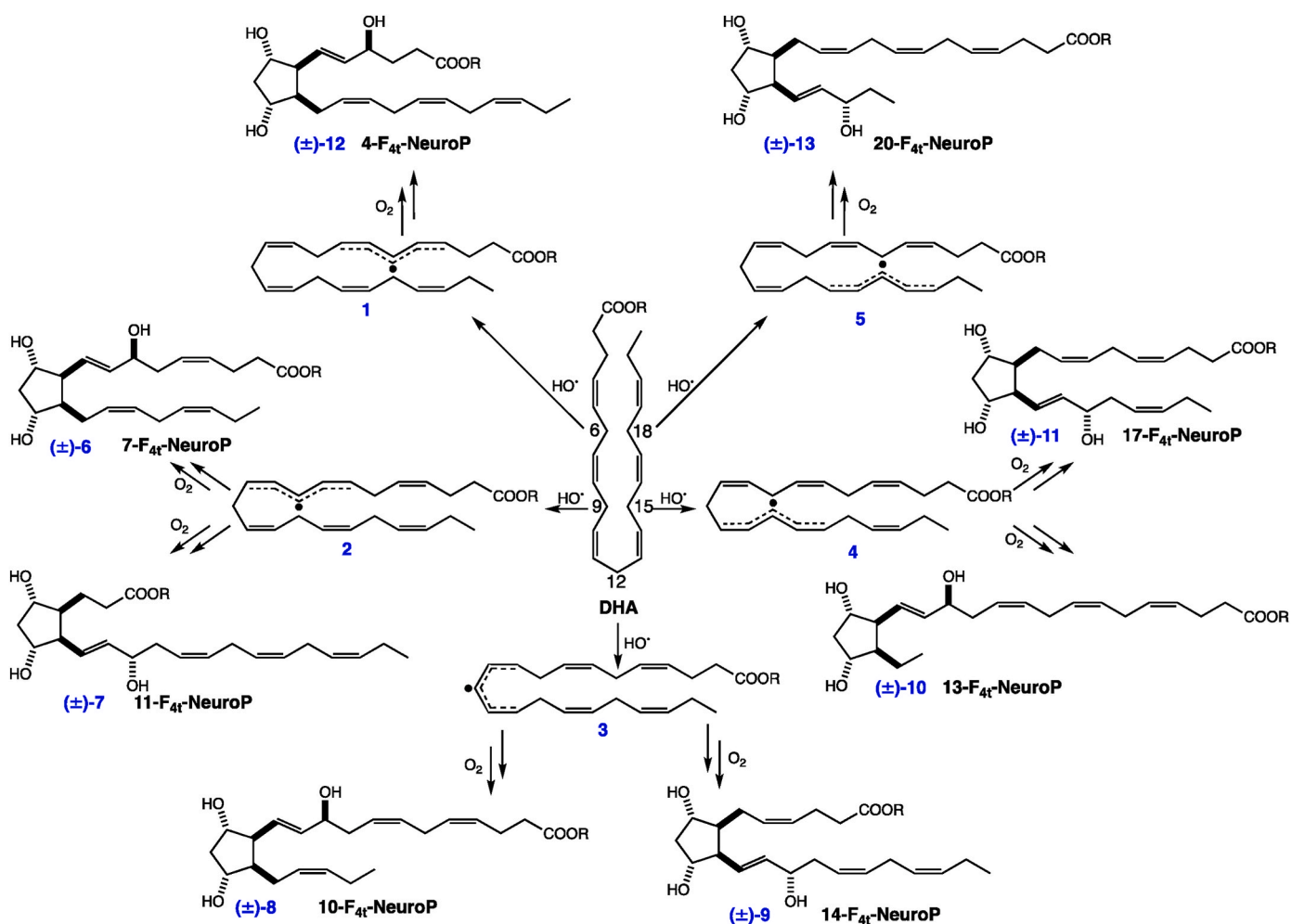


Fig. 2. Formation of neuroprostanes (NeuroPs) from DHA, R = H, phosphatidylcholine.

based on their precursor PUFA. Additionally, this system describes NEO-PUFAs by their ring substitution pattern (A-H, J), relative orientation of side chains, and the number of double bonds. This system, approved by IUPAC, will be used in this review.

### 1.1. NEO-PUFA from AA: F<sub>2</sub>-Isoprostanes

F<sub>2</sub>-Isoprostanes (IsoPs) are a class of NEO-PUFAs formed by the free radical-catalyzed peroxidation of arachidonic acid (AA). Unlike enzymatically derived eicosanoids, isoprostanes are generated, inside the membranes, through a complex series of reactions involving reactive oxygen species (ROS), which lead to the formation of a variety of

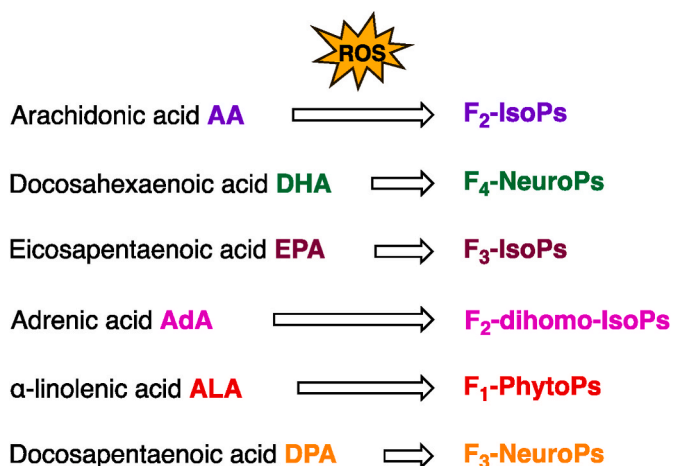


Fig. 3. ROS-mediated oxidation of Polyunsaturated Fatty Acids (PUFAs).

isomeric structures. As a result, their main structural difference compared to prostaglandins include the *cis*-relationship of the side chains and defined number of potential isomers. Besides, it is important to note that all these metabolites are produced *in vivo* as racemic mixture. According to the mechanism of peroxidation of AA proposed by Rokach and co-workers [13], the reaction begins with the abstraction of a hydrogen atom from one of the bis-allylic carbons of AA (C7, C10 or C13) by reactive oxygen species, such as hydroxyl radicals ( $\bullet$ OH). This step generates a radical intermediate (compounds 24–26). The radical

thus formed then reacts with molecular oxygen to yield a peroxy radical that undergoes a cyclization followed by trapping with an additional oxygen molecule to give bicyclic endoperoxide, which is eventually reduced to the final allylic alcohol (compounds 27–30) (Fig. 1).

### 1.2. NEO-PUFA from DHA: F<sub>4</sub>-Neuroprostanes

F<sub>4</sub>-Neuroprostanes (NeuroPs) were first described by Roberts and co-workers [14] in 1998. These are NEO-PUFAs formed non-enzymatically *in vivo* by the oxidative attack of free reactive oxygen species (ROS) on docosahexaenoic acid (DHA). According to the biosynthetic mechanism proposed by Yin and colleagues [15], a family of eight possible regioisomeric NeuroPs can be formed. These are derived from five different bis-allylic carbons (C6, C9, C12, C15, C18) of DHA. The biosynthesis of NeuroPs is initiated by hydrogen atom abstraction by HO $\bullet$  at one of these bis-allylic positions to give a resonance stabilized pentadienyl radical (compounds 1–5). Similar to IsoPs, NeuroPs (compounds 6–13) are then formed following the same steps of oxygen trapping, cyclization, and reduction (Fig. 2).

Interestingly, pentadienyl radicals resulting from hydrogen atom abstraction at the C9, C12, or C15 position of DHA give rise in each case to two different NeuroPs regioisomers: the 7/11-series (compounds 6, 7), 10/14-series (compounds 8, 9), or 13/17-series (compounds 10, 11), respectively. Meanwhile, hydrogen abstraction at the C6 or C18 position produces a single regioisomer: the 4-series (compounds 12) from the C6 position or the 20-series (compounds 13) from the C18 position. Furthermore, quantitative analysis *in vitro* and *in vivo* has demonstrated that both 4-series and 20-series are produced in greater amounts compared to other regioisomers [16]. Finally, just like IsoPs, NeuroPs

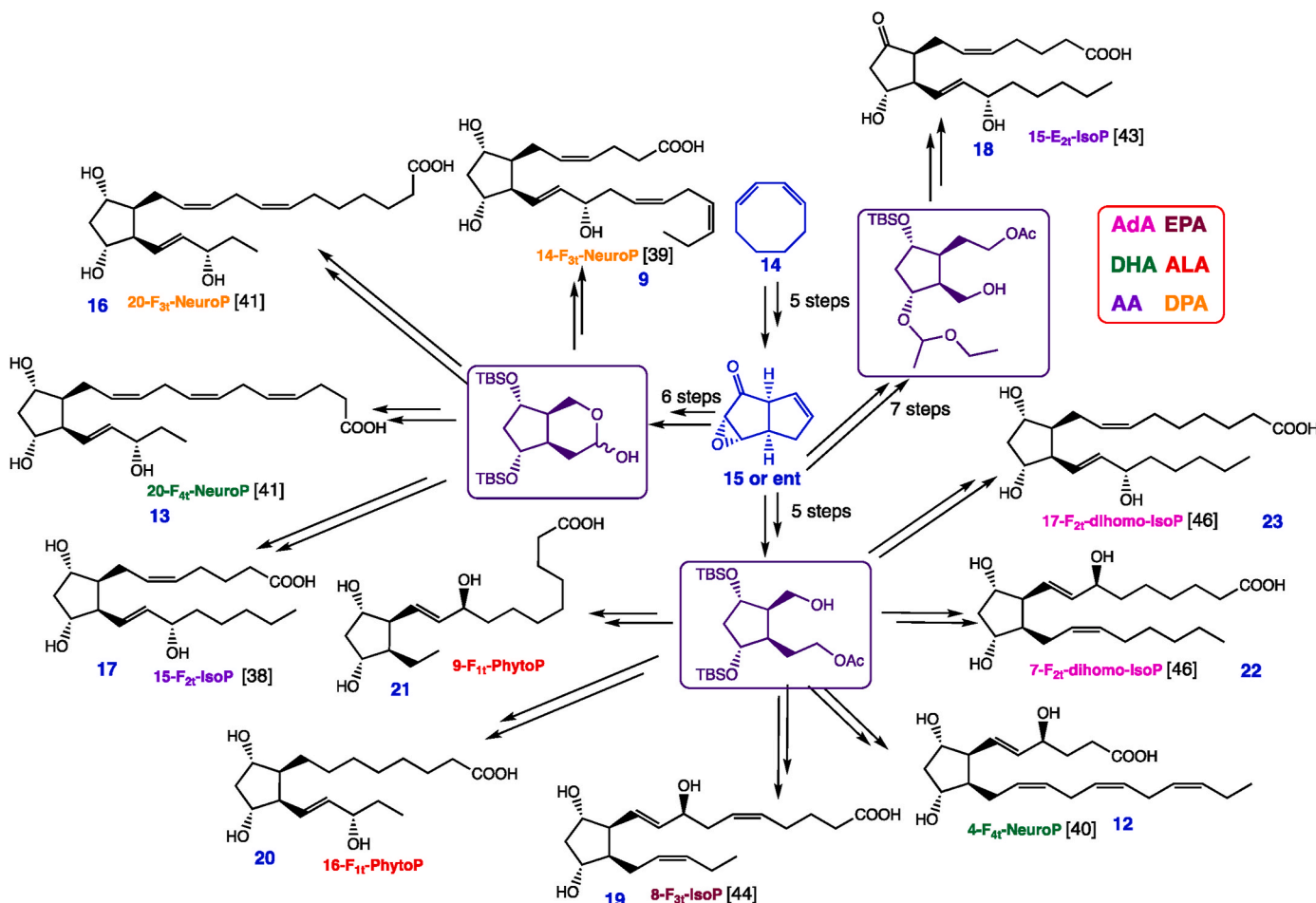


Fig. 4. Synthesis of AdA, DHA, AA, EPA, ALA and DPA metabolites from 1,3-cyclooctadiene 14.

are produced *in vivo* as racemic mixture, thus doubling the total number of possible products. In the end, it is remarkable how nature can convert such a simple molecule into a vast array of highly complex compounds.

### 1.3. NEO-PUFA from EPA, ALA, AdA, DPA: F<sub>3</sub>-IsoPs, dihom-IsoPs, PhytoPs, F<sub>3</sub>-NeuroPs

Similar to AA and DHA, other PUFAs such as eicosapentaenoic acid (EPA), adrenic acid (AdA),  $\alpha$ -linolenic acid (ALA), and docosapentaenoic acid (DPA) undergo oxidation through analogous metabolic pathways. EPA generates 6 regioisomeric F<sub>3</sub>-isoPs [17] while AdA yields 4 regioisomeric dihom-Isoprostanes (dihom-IsoPs) [10]. ALA and DPA oxidation produce 6 regioisomeric phytoprostanes (PhytoPs) [18] and 6 F<sub>3</sub>-NeuroPs, respectfully (Fig. 3).

### 1.4. Biological role of DHA

DHA, an  $\omega$ -3 fatty acid, plays a vital role in maintaining healthy brain function and development. In humans, it is a major component of brain tissue, where it is especially abundant in gray matter, accounting for about 40 % of the total PUFA population and nearly 50 % of the weight of neuronal membranes [19]. Additionally, DHA is highly concentrated in sperm, retinal photoreceptors, and brain synapses [20,21]. Given the abundance and significance of DHA in the human body, identification, isolation and quantification of DHA NEO-PUFAs offers unique biomarkers of oxidative stress in the central nervous system. It also provides potential new therapeutic compounds as some of these NEO-PUFAs have demonstrated promising beneficial biological effects [22–25]. This review explores the fascinating journey of DHA metabolites, the neuroprostanes, as well as other NEO-PUFAs. It covers nearly three decades of research, highlighting key developments in synthesis, diagnostic applications, and biological activities, some of which have yet to be fully elucidated. The work outlined in this review results from productive collaborations with chemists, biologists, and clinicians across the globe [26–30].

## 2. Chemical synthesis

Over the past 30 years, various methods of the total synthesis of NeuroPs and other NEO-PUFAs have been described [31–35]. Durand's group has developed three distinct approaches: one involving radical carbocyclization [36], another based on furan ring transformation [37], and a third utilizing a bicyclo-[3.3.0]-octene intermediate [38]. The latter is remarkable because the bicyclo-[3.3.0]-octene intermediate **15** (Fig. 4), prepared in five steps from commercial 1,3-cyclooctadiene **14**, serves as a versatile substrate for the synthesis of NeuroPs (compounds **9** [39], **12** [40], **13** [41], **16** [42]) as well as other NEO-PUFAs, such as IsoPs (compounds **17** [38], **18** [43], **19** [44]), PhytoPs (**20**, **21**), and dihom-IsoPs (compounds **22** [45], **23** [46]) (Fig. 4). Moreover, intermediate **15** can be synthesized in both enantiomeric forms, enabling access to each enantiomer.

To access the desired metabolites, lateral chains are introduced via Wittig or Horner-Wadworth-Emmons reactions using the corresponding phosphonium salts or phosphonates.

Fig. 4 outlines a non-exhaustive list of DHA, adrenic acid (AdA), eicosapentaenoic acid (EPA),  $\alpha$ -linolenic acid (ALA), arachidonic acid (AA) and docosapentaenoic acid (DPA n-3 or DPA n-6) NEO-PUFAs synthesized by Durand's group using this approach [33–41].

## 3. NEO-PUFAs as biomarkers

This review will focus on NEO-PUFAs as biomarkers in diseases and nutraceuticals will not be addressed.

The first NEO-PUFAs studied as biomarkers of oxidative stress, are the F<sub>2</sub>-IsoPs derived from AA [47,48]. They became the gold standard for evaluating oxidative stress *in vivo* in human [49] as well as in animal

models [50] because these molecules are chemically stable and can be detected in all analyzed biological fluids and tissues [51]. Since the 1990's, the 15-F<sub>2t</sub>-IsoP and other derivatives have been commonly used as the best available standard for measuring the extent of lipid peroxidation in most tissue fluids [52].

### 3.1. Central nervous system (CNS)

The brain is particularly susceptible to oxidative stress due to its high oxygen requirements for oxidative metabolism and its rich content of  $\omega$ -3 PUFAs, in particular DHA. One compelling example highlighting the biomarker role of NEO-PUFAs pertains to Rett syndrome (RTT) pathology [53]. This syndrome stems from a neuronal developmental disorder resulting from loss-of-function mutations in the methyl-CpG binding protein 2 (MECP2) gene which leads to autism in females [54], myocardial dysfunction (subclinical biventricular systo-diastolic myocardial dysfunction), and a 300-fold increased risk of sudden death [55]. In this study, increased oxidative stress was observed, which was manifested as significant lipid peroxidation in blood samples taken from RTT patients [53].

F<sub>4</sub>-NeuroPs emerge as significant biomarkers in RTT, with plasma F<sub>4</sub>-NeuroPs levels correlating with disease severity, neurological symptom severity, mutation type, and clinical presentation. Thus, F<sub>4</sub>-NeuroPs likely could play a role in the biochemical pathway from MeCP2 gene mutation to clinical manifestations, indicating the occurrence of a DHA oxidation process [56].

Additionally to F<sub>4</sub>-NeuroPs, clinical evidence indicates the involvement of F<sub>2</sub>-IsoPs in the underlying pathogenetic mechanisms of RTT [57]. Plasma levels of free F<sub>2</sub>-IsoPs are significantly elevated during the early stages of RTT compared to the later stages of typical RTT progression. Prior to 2011, it was believed that primary CNS damage in RTT primarily affected gray matter. However, the abundance of the precursor AdA in myelin and the heightened levels of F<sub>2</sub>-dihom-IsoPs suggest early and severe damage to white matter in the brain, which supports previous findings from brain MRI studies [57]. Therefore, F<sub>2</sub>-dihom-IsoPs could be considered early indicators of lipid peroxidation in RTT. Finally, the research group led by De Felice and Signorini has highlighted the potential importance of NeuroPs and dihom-IsoPs in sperm capacitation [58] and in various neurological diseases, including Krabbe disease [59] and cerebral adrenoleukodystrophy [60].

Furthermore, conditions such as aneurysmal subarachnoid hemorrhage (aSAH) and traumatic brain injury (TBI) are associated with severe CNS damage. Two case-controlled studies have demonstrated a significant elevation in cerebrospinal fluid (CSF) levels of IsoPs in patients with aSAH and TBI compared to their respective age- and gender-matched controls. Additionally, aSAH patients exhibited notably increased CSF levels of F<sub>4</sub>-NeuroPs and F<sub>2</sub>-IsoPs. In contrast, patients with TBI showed elevated CSF F<sub>4</sub>-NeuroPs levels, while F<sub>2</sub>-IsoPs remained similar to control levels [61]. These findings affirm that CNS injury, whether due to aSAH or TBI, leads to heightened oxidative stress. Given that DHA is a major PUFA in the brain, with further investigation, levels of F<sub>4</sub>-NeuroPs in CSF may serve as a more specific indicator of neurological dysfunction than F<sub>2</sub>-IsoPs.

Moreover, Hsieh et al. demonstrated a correlation between increased F<sub>4</sub>-NeuroPs levels in CSF of aSAH patients and poor neurological outcomes [62]. They suggested that F<sub>4</sub>-NeuroPs might offer greater utility than F<sub>2</sub>-IsoPs in CSF for predicting outcomes and interpreting the role of hemorrhage in aSAH. While Farias et al. observed increased F<sub>2</sub>-IsoPs levels during rat brain ischemia, they found that E<sub>2</sub>/D<sub>2</sub>-IsoPs were elevated to a greater extent, suggesting that the latter may serve as better markers of oxidative stress in brain ischemia [63].

Some studies also reported the importance of NeuroPs and dihom-IsoPs in Alzheimer disease (AD) and brain injury in newborn [64,65]. Recognizing the significant role of lipid peroxidation in AD, Garcıa-Blanco et al. (2018) hypothesized that corresponding NEO-PUFAs detected in urine samples could serve as potential biomarkers [66].

Through the analysis of urine samples from patients early diagnosed with mild cognitive impairment or mild dementia AD, their study revealed differences in total NEO-PUFAs (NeuroPs, IsoPs, IsoFs) between the control and clinical groups. Consequently, with further investigation, these NEO-PUFAs could have the potential to serve as early biomarkers for Alzheimer's disease, indicating the pro-oxidant condition of patients.

Finally, in 2021, this research group delved into studying the relationship between an oxidative stress, inflammatory biomarkers and cerebral lesion in newborns following an hypoxic-ischemic encephalopathy (HIE), a major cause of severe neurological disability and mortality in the perinatal period [67]. Remarkably, the identification of specific biomarkers associated with diagnosis and long-term outcome prediction, as a supplementary tool to standard evaluation, remains an unexplored territory in newborn critical care. To address this gap, they conducted a longitudinal study aiming to identify biomarkers of oxidative stress and inflammation in noninvasive urine samples from newborns with moderate/severe HIE, using liquid chromatography-mass spectrometry. Their findings unveiled significant differences in oxidative stress levels among neonates exhibiting distinct brain lesion patterns as detected by magnetic resonance imaging. Notably, there was an elevation in lipid peroxidation biomarkers (numerous NeuroPs, IsoPs) in newborns with cerebral lesions. This observation leads to the hypothesis that monitoring noninvasive lipid peroxidation biomarkers could contribute to the diagnosis and prediction of long-term outcomes, serving as a complementary tool to standard assessment methods. More recently, in 2023, Raffay et al. confirmed that NeuroPs in urine could serve as biomarkers for hypoxemia events in preterm neonate [68].

### 3.2. Pregnancy

In 2012, a study has quantified F<sub>4</sub>-NeuroPs, F<sub>2</sub>-IsoPs, and IsoFs in maternal plasma and cord blood of women with pre-eclampsia and those with normal pregnancies [69,70]. Pre-eclampsia is a pregnancy disorder that combines high blood pressure with the presence of protein in the urine. It results from a dysfunction of the placenta. Women with pre-eclampsia exhibited significantly elevated levels of maternal IsoFs and F<sub>4</sub>-NeuroPs, but no increase in F<sub>2</sub>-IsoPs. Cord blood levels of F<sub>4</sub>-NeuroPs were also found to be higher among neonates born to mothers with pre-eclampsia. Notably, cord blood levels of IsoFs were approximately five times higher than those detected in maternal plasma. This disparity could be indicative of the oxidative stress encountered during birth, wherein there is a transition from a relatively low intra-uterine oxygen environment to a significantly higher extra-uterine oxygen environment. Interestingly, maternal levels of F<sub>4</sub>-NeuroPs did not show a significant correlation with cord blood levels of F<sub>4</sub>-NeuroPs in both pre-eclamptic and normal pregnancies, suggesting that the origin of cord blood F<sub>4</sub>-NeuroPs may be independent of maternal plasma levels. In normal pregnancies, there was a negative association between birth weight and maternal levels of F<sub>2</sub>-IsoPs, IsoFs, and F<sub>4</sub>-NeuroPs suggesting them as potential markers in maternal blood at early stages of pregnancy relate to subsequent maternal, fetal, and neonatal complications.

In 2023, Ferreira et al. investigated whether gestational diabetes mellitus (GDM) associated with maternal obesity modifies the placental profile of F<sub>4</sub>-NeuroPs and F<sub>2</sub>-IsoPs [71]. Their results revealed that levels of F<sub>4</sub>-NeuroPs and F<sub>2</sub>-IsoPs were higher in obesity compared to lean controls. However, when obesity was further complicated with GDM, these levels decreased to levels similar to those of lean women. The lower content of F<sub>2</sub>-IsoPs suggests adaptive placental responses in GDM, which may attenuate oxidative stress. However, the quantification of arachidonic acid (AA) is necessary to confirm this hypothesis. Conversely, the reduced levels of placental F<sub>4</sub>-NeuroPs in GDM may indicate impaired DHA metabolism, which could potentially affect fetal development and offspring health but further experiments are needed.

Interestingly, these results were not correlated with differences in placental content of DHA, AA, and PUFAs status, nor with maternal diet or gestational weight gain. This suggests that, with further investigation, that NeuroPs and IsoPs could serve as potential biomarkers and predictors of altered placental fatty acid metabolism.

### 3.3. Obesity

Obesity is a chronic disease and a major cause of morbidity and mortality. Numerous evidence has linked this condition to inflammation and oxidative stress [72]. To assess the potential NEO-PUFAs as biomarkers in obesity, recently, Sarajlic et al., have measured an increase of pro-inflammatory markers 5-F<sub>2c</sub>-IsoP and 15-F<sub>2t</sub>-IsoP as well and a decrease of 14-F<sub>4t</sub>-NeuroP and 5-F<sub>3t</sub>-IsoP with age in urine sample from obese patients [73]. This study suggests that ω-3/ω-6 oxidation ratio may serve as an indicator of inflammation associated with obesity.

### 3.4. Cancer

Several pieces of evidence have suggested that prostate cancers may be associated with oxidative stress. This hypothesis was investigated by Barocas et al., in 2011, where urine was collected from men before biopsy and diagnosis. An increase in F<sub>2</sub>-IsoPs was highlighted in men diagnosed with high grade prostatic intra-epithelial neoplasia and prostate cancer [74]. This hypothesis was further explored by Brys et al., who measured high level of urinary 8-iso-PGF<sub>2</sub> in patients diagnosed with prostate cancer [75]. These results could suggest that F<sub>2</sub>-IsoPs found in urine may be a biomarker of oxidative stress in prostate cancer.

### 3.5. Renal function

End-stage renal disease is a condition in which the kidneys completely lose their ability to filter blood, requiring dialysis and a kidney transplant. However, after transplantation, there is an increased risk of allograft rejection, which leads to further graft loss and affects patient survival. It is therefore important to identify potential biomarkers that could reflect graft function after transplantation and predict the risk of rejection. In this regard, De las Heras-Gómez et al., showed a trend towards lower levels of 4-*epi*-4-F<sub>3t</sub>-NeuroP, *ent*-7(RS)-7-F<sub>2t</sub>-dihomo-IsoP, *ent*-7(S)-7-F<sub>2t</sub>-dihomo-IsoP and 15-F<sub>2t</sub>-IsoP in urine of renal transplant patients, which was associated with an improved kidney function [76]. In conclusion, with further investigation, these metabolites may serve as predictors of rejection.

### 3.6. Cardiovascular function

NEO-PUFAs has also been investigated as biomarkers in cardiovascular diseases such as atherosclerosis. This condition is a chronic inflammatory disease of vascular system associated with an increase of ROS and consequently lipid peroxidation. In 1997, Praticò et al., showed an increase of the content of two F<sub>2</sub>-IsoPs, 8-*epi*-PGF<sub>2α</sub> and IPF<sub>2α</sub>-I, in human atherosclerotic plaque compared to controls [77]. In 2023, Lefort et al. used a mouse model deficient in very-long chain acyl-CoA dehydrogenase (VLCAD), an enzyme which catalyzes the first step of beta-oxidation in the mitochondria to mimics the inherited VLCAD deficiency (VLCADD) causing a predisposition to neonatal arrhythmias [78]. Compared to controls (VLCAD<sup>+/+</sup>), VLCAD<sup>-/-</sup> mouse hearts exhibited lipid alterations characterized by significantly higher levels of F<sub>2</sub>-IsoPs (8-F<sub>2t</sub>-IsoP, 5-F<sub>2c</sub>-IsoP and 5-*epi*-5-F<sub>2t</sub>-IsoP) and lower levels of F<sub>4</sub>-NeuroPs (10-F<sub>4t</sub>-NeuroP, 20-F<sub>4t</sub>-NeuroP). This finding could suggest that, with further investigation, these NEO-PUFAs could serve as intriguing biomolecules for use as biological markers in the development of some cardiovascular pathologies.

Taken together, this non-exhaustive list of publications highlights some NEO-PUFAs as potential biomarkers in several diseases associated with oxidative stress. However, there is considerable evidence that some

of these NEO-PUFAs also display beneficial biological properties. This topic will be discussed in the next chapter.

#### 4. New bioactive lipids

Regarding their bioactivity, NEO-PUFAs are poorly studied, and the idea of attributing biological activity to these peroxidation products remains dogmatically difficult to accept. The lack of studies can be attributed to several reasons: 1- *In vivo*, the concentrations of these NEO-PUFAs may be low in the absence of supplementation, 2- NEO-PUFAs are not commercially available or are scarcely so, and they must be custom-synthesized, a skill possessed by few chemistry groups worldwide, 3- Enzymatic synthesis pathways quantitatively limit any other form of production of bioactive NEO-PUFAs.

##### 4.1. Biological activities of $\omega$ -6 NEO-PUFAs

F<sub>2</sub>-IsoPs as « degradation products » induced by oxidative stress have long been considered only as biomarkers in diseases [79–81]. It was not until the research of Morrow and Roberts that the biological activity of these NEO-AA began to be discussed. Indeed, the biological activity of 15-F<sub>2t</sub>-IsoP (also known as 8-epi-PGF<sub>2</sub> $\alpha$ ) has been studied in the rat kidney and has shown that an infusion into the peripheral vein or the intrarenal artery reduces the glomerular filtration rate and the renal blood flow, indicating that it is a potent renal vasoconstrictor [7].

Since then, investigations have uncovered the vasoconstrictive effects of IsoP from AA in numerous vascular beds (heart, liver, lung, kidney, smooth muscle, retina) via the thromboxane receptor (TP) [82]. Additionally, 15-F<sub>2t</sub>-IsoP can modulate platelet activity through the same receptor [83]. Furthermore, 15-E<sub>2t</sub>-IsoP, an other NEO-AA, acts as a vasoconstrictor via the TP [84]. It also serves as a ligand for the E-series of prostaglandin receptors (EP), contributing to bronchoconstriction in the lungs. Bendorf et al. demonstrated that 15-F<sub>2t</sub>-IsoP, 15-E<sub>2t</sub>-IsoP, and 15-A<sub>2t</sub>-IsoP inhibit VEGF-induced migration and tube formation of endothelial cells, thereby collectively inhibiting angiogenesis via activation of TBXA<sub>2R</sub> [85]. 15-J<sub>2</sub>-IsoP has been found to elicit an inflammatory response by inhibiting peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) activation and inducing RAW264.7 cell apoptosis in a PPAR $\gamma$ -independent manner [86]. Another cyclopentenone AA derivative, 15-A<sub>2</sub>-IsoP, exhibits anti-inflammatory effects by inhibiting the NF- $\kappa$ B pathway in lipopolysaccharide (LPS)-induced macrophages and human gestational tissues [87]. The overall picture of these cyclopentenone metabolites remains unclear, as recently highlighted for their prostaglandin equivalents, and is likely highly dependent on their structures [88].

##### 4.2. Biological activities of $\omega$ -3 NEO-PUFAs

Like  $\omega$ -6 NEO-PUFAs,  $\omega$ -3 NEO-PUFAs are also considered as biomarkers in diseases. But for many years, diets enriched with  $\omega$ -3 PUFAs have been associated with beneficial outcomes when given in diseases.

###### 4.2.1. Anti-inflammatory and anti-atherogenic properties

To assess whether  $\omega$ -3 NEO-PUFAs are beneficial in an inflammation context, Sethi's group in 1996 demonstrated that the reduction in monocyte adhesion to endothelial cells is only observed when the cells are exposed to previously oxidized  $\omega$ -3 PUFA [89], thereby challenging the role of  $\omega$ -3 PUFA themselves and the importance of considering their NEO-PUFAs in studies.

Also, a first study revealed that, unlike 15-F<sub>2t</sub>-IsoP derived from AA, 15-F<sub>3t</sub>-IsoP from EPA did not activate platelet aggregation but instead exerted an antiplatelet aggregating effect [90]. These initial data suggest that there is indeed a notable difference in activity between oxygenated products derived from  $\omega$ -3 and  $\omega$ -6 PUFAs, most likely linked to their structural differences [49].

In addition, endothelial cells treated with oxidized EPA revealed

inhibition of monocyte chemoattractant protein-1 (MCP-1) and endothelial nuclear factor- $\kappa$ B (NF- $\kappa$ B) through a PPAR-dependent pathway, supporting the anti-inflammatory effects of  $\omega$ -3 NEO-PUFAs [91].

Among NEO-EPAs, 15-A<sub>3t</sub>-IsoP revealed a potent biological activity by inhibiting the activity of enzymes involved in inflammation such as iNOS or COX-2 via NF- $\kappa$ B inhibition in mouse macrophages [92]. Thus, many observed effects of  $\omega$ -3 PUFA on inflammation may be due to their oxidized NEO-PUFAs, as well as their effects on oxidative stress. Indeed, 15-A<sub>3t</sub>-IsoP and 15-J<sub>3t</sub>-IsoP derived from EPA exhibit inflammatory activities [92]. They activate the NRF2 pathway (Nuclear factor erythroid 2-related factor 2) by inhibiting one of its negative regulators, Keap1 (Kelch-like ECH-associated protein 1) [93].

In 2017, Bosviel et al. conducted a dose-dependent and comparative study in human primary macrophages aiming to decipher the potential anti-inflammatory activity of NeuroPs (14-A<sub>4t</sub>- and 4-F<sub>4t</sub>-NeuroP) [24]. They observed that NeuroPs have anti-inflammatory properties with the highest dose (i.e., 10  $\mu$ M). Interestingly, the strongest effects were obtained with the 14-A<sub>4t</sub>-NeuroP, which caused substantial decreases of IL-6, TNF- $\alpha$ , MCP-1 mRNA. 4-F<sub>4t</sub>-NeuroP, also reduced these mRNA levels. Part of the anti-inflammatory properties of the NEO-DHA investigated could be linked to their activation of PPARs.

In contrast, NEO-PUFAs from DHA have been more extensively studied than EPA derivatives, with a greater emphasis on NeuroPs function. Just like AA-derived IsoPs, the group of Morrow and Roberts, pioneers in the *in vivo* identification of IsoPs/NeuroPs, also demonstrated biological effects of NeuroPs, particularly the A<sub>4</sub>/J<sub>4</sub>-NeuroPs. These DHA-derived cyclopentenones act as mediators of inflammation in murine cell line macrophages [94]. Similar to oxidized EPA NEO-PUFAs, 14-A<sub>4</sub>-NeuroP reduces the expression of pro-inflammatory mediators in these macrophages. This study confirmed that the inhibition of the NF $\kappa$ B pathway constitutes a mechanism of action for the NEO-PUFAs of EPA and DHA. Additionally, Majkova et al. demonstrated that A<sub>4</sub>/J<sub>4</sub>-NeuroPs down-regulated PCB77-induced MCP-1 expression and NRF2 activation in primary pulmonary endothelial cells [95].

In 2022, knowing the abundance of DHA in brain membrane phospholipids and this role in neurological functions Geng et al., examined the effects of 4-F<sub>4t</sub>-NeuroP on oxidative and inflammatory responses in microglial cells (primary and immortalized microglia (BV2)) treated with LPS [96]. They observed that the 4-F<sub>4t</sub>-NeuroP attenuated LPS-induced production of ROS in both primary and BV2 cells. This NEO-PUFA also attenuated LPS-induced inflammation through suppressing NF $\kappa$ B-p65 and levels of iNOS and TNF $\alpha$ . In addition, 4-F<sub>4t</sub>-NeuroP attenuated LPS-induced mitochondrial membrane potential loss in BV2 cells. In summary, these findings with microglial cells demonstrated neuroprotective effects of this 4-F<sub>4t</sub>-NeuroP and shed light into the potential of nutraceutical therapy for neurodegenerative diseases.

The anti-atherogenic effects of  $\omega$ -3 PUFAs, specifically EPA and DHA are well-established [97], yet the impact of dietary intake of fatty acid precursors on the quantity of newly synthesized NEO-PUFAs profiles remains unknown in specific tissues and animal models studied. Profiling such mediators could provide novel targets for future studies investigating the mechanisms of action of  $\omega$ -3 fatty acids. Researchers have focused on the inflammatory process resulting from atherosclerosis and the potential role of NEO-PUFAs. However, the initial observation was conducted for F<sub>2</sub>-IsoPs. In 2007, the *in vivo* study published by Saraswathi [98] demonstrated that fish oil feeding decreased the formation of pro-inflammatory F<sub>2</sub>-isoP, markers of oxidative stress. The increased white adipose tissue lipid storage in fish oil-fed mice was associated with reduced lipid accumulation in liver and decreased atherosclerotic lesion area. Taken together, these data highlight the specific role of dietary fish oil-mediated improvement in systemic lipid homeostasis and atherosclerosis. This hypothesis has been more recently investigated for NEO-PUFAs from  $\omega$ -3 fatty acids through an integrated approach combined with a DHA supplementation study in LDLR<sup>-/-</sup> (low-density lipoprotein receptor) mice prone to atherosclerosis [25].

Special attention was paid to non-enzymatic NEO-PUFAs due to DHA's susceptibility to free radical-mediated peroxidation and the heightened oxidative stress associated with plaque formation. Atherosclerosis-prone mice (*LDLR*<sup>-/-</sup>) received DHA over 20 weeks, displayed a dose-dependent reduction in atherosclerosis, triglyceridemia, and cholesterolemia. Moreover, Gladine et al. demonstrated in this atherosclerosis mice model (low-density lipoprotein receptor <sup>-/-</sup> or *LDLR*<sup>-/-</sup>) fed with  $\omega$ -6 or  $\omega$ -3 PUFAs enriched diet that the liver content of F<sub>4</sub>-NeuroPs was negatively correlated with atherosclerotic plaque extension but further experiments are required to confirm this correlation [25]. These results suggests that F<sub>4</sub>-NeuroPs could be potential biomarkers of DHA-associated atherosclerosis prevention.

#### 4.2.2. Antiarrhythmic properties

At the cardiac level, few studies have focused on the effects of peroxidized NEO-PUFAs on cardiac pathophysiology. In recent decades, there has been extensive documentation of the cardioprotective effects conferred by a diet enriched in  $\omega$ -3 PUFA, primarily attributed to EPA and DHA [99]. A significant prospective study highlighted that DHA and EPA supplementation notably reduces the incidence of sudden cardiac death in the months following a heart attack. This reduction has been attributed, at least in part, to a decrease in arrhythmias and systolic cardiac failure. Studies conducted on individual cardiac cells and animals have revealed that EPA and DHA can modulate the activity of ion channels, which are transmembrane proteins crucial for the heart's electrical activity. However, there is also speculation that NEO-PUFAs (from DHA and EPA) may contribute to these effects [100]. Indeed, research has demonstrated that some of DHA's impact on rat cardiac ion channels stems from a NEO-PUFAs.

Roy et al. have tested different F<sub>4</sub>-NeuroPs on isoprenaline-induced arrhythmias on murine isolated ventricular cardiomyocytes. Among them, the 4-F<sub>4t</sub>-NeuroP displays anti-arrhythmic effects (IC<sub>50</sub> ≈ 100 nM). The 4-F<sub>4t</sub>-NeuroP, showed dose-dependent antiarrhythmic properties *in cellulo* and *in vivo* in permanent myocardial infarction mice [22] or after ischemia/reperfusion event in rats [23]. At the cellular level, the mechanism of action can be explained by the Ryanodine Receptor (RyR2)/FKBP12.6 complex stabilization. In conclusion, the researchers proposed that in oxidative stress conditions, such as ischemic events, 4-F<sub>4t</sub>-NeuroP is product and then responsible for the antiarrhythmic properties of  $\omega$ -3 PUFAs.

#### 4.2.3. Anti-proliferative properties

Another study by same team revealed that DHA possesses anti-proliferative properties, which were inhibited by  $\alpha$ -tocopherol (an antioxidant) and enhanced by the pro-oxidant hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>). This confirms that DHA needs to be oxidized to exert its anti-proliferative effects [101]. They also found that certain F<sub>4t</sub>-NeuroPs exhibited antiproliferative effects on the human breast cancer cell line (MDA-MB-231), while no inhibitory effect was observed on a human mammary epithelial normal cell line (MCF-10A). These results suggest that NeuroPs aims to enhance stability against degradation, increase cellular availability, and control the release of bioactive fatty acids based on their lipophilic properties. Building on this study and the encapsulation methods used, Abawi et al., in 2023, demonstrated that integrating F<sub>4</sub>-NeuroP into liposomes with a fluid character enabled selective targeting of the metastatic prostate cell line (PC-3) *versus* fibroblast controls. A significant decrease in viability was observed for the PC-3 cancer line in the presence of F<sub>4</sub>-NeuroP fluid liposomes, whereas rigid F<sub>4t</sub>-NeuroP liposomes did not alter PC-3 cell viability. These findings confirm the antiproliferative role of F<sub>4</sub>-NeuroP and suggest that liposomes encapsulating 4-F<sub>4t</sub>-NeuroP or other related molecules may serve as promising drug carriers based on membrane fluidity [102].

In their 2021 study, Bilodeau et al. studied the relationship between NEO-PUFAs and tumor growth. They conducted experiments using immune-competent eugonadal and castrated C57BL/6 male mice

injected with TRAMP-C2 prostate tumor cells, while being fed diets rich in either  $\omega$ -3 or  $\omega$ -6 PUFAs [103]. Their findings revealed a significant inverse correlation between EPA and its NEO-EPA (F<sub>3</sub>-NeuroPs) and tumor volume. Conversely, F<sub>2</sub>- IsoPs showed a positive correlation with tumor volume. Notably, NEO-DHA (F<sub>4</sub>-NeuroPs) exhibited a specific increase in TRAMP-C2 tumors of castrated mice compared to those of eugonadal mice. The study concluded that the observed reduction in tumor growth under the  $\omega$ -3 diet regimen could be partially attributed to elevated levels of NEO-PUFAs.

#### 4.2.4. Neuroprotective properties

Jamil et al. investigated the ability of 5-F<sub>3t</sub>-IsoP to regulate glutamatergic neurotransmission [104]. This product could have significant pharmacological implications as glutamate serves as an excitatory neurotransmitter in several vertebrate retinal cells, as well as in ganglion cells. These researchers then examined the modulatory role of 5-*epi*-5-F<sub>3t</sub>-IsoP on potassium efflux associated with glutamate release from isolated bovine retina [104]. In this study, 5-*epi*-5-F<sub>3t</sub>-IsoP attenuates potassium efflux in a dose-dependent manner through mechanisms that are partially dependent on the activation of so-called "EP1-type prostanoic receptors." These results demonstrate a beneficial effect of this NEO-PUFA in attenuating the release of an excitatory neurotransmitter, as well as slowing the progression of ocular neuropathic diseases. In 2020, Lee et al. reported for the first time that native 4-F<sub>4t</sub>-NeuroP has a regulatory role in neurons for cell survival on human SH-SY5Y neuroblastoma cells [105]. They showed that 4-F<sub>4t</sub>-NeuroP can cross the blood brain barrier into rat brain tissue and alter brain  $\omega$ -3 and  $\omega$ -6 PUFA profiles, where anti-inflammatory and pro-resolvin lipid biomarkers were significantly elevated.

#### 4.2.5. Pro-fertility properties

Recently, F<sub>4</sub>-NeuroPs showed a biological activity in sperm function and was able to induce capacitation via increasing AMPK phosphorylation, and its role at ryanodine receptors is currently being explored [58]. Later, the same group investigated the biological role of 4-F<sub>4t</sub>-NeuroP on sperm capacitation (sperm hyperactivation and acrosomal reaction) *in vitro* [106]. After incubating swim-up selected human sperm with 7 ng of 4-F<sub>4t</sub>-NeuroP for 2 and 4 h, various parameters including motility, membrane mitochondrial potential, percentage of reacted acrosome, and chromatin integrity were evaluated. The results indicated an increase in progressive sperm motility and hyperactivation, suggesting that F<sub>4</sub>-NeuroPs could influence the physiological behavior of sperm. Mitochondrial functionality is closely linked to sperm quality. Finally, Moretti et al. reported that 4-F<sub>4t</sub>-NeuroP impacts human sperm, particularly affecting sperm capacitation mediated once again by a ryanodine receptor. In conclusion, a specific concentration of 4-F<sub>4t</sub>-NeuroP in seminal fluid may induce sperm capacitation through the modulation of ion channel activity present in sperm cells. Considering that infertile men often struggle with capacitation, these molecules could potentially assist in sperm preparation *in vitro* for some patients, thereby enhancing the success rate of assisted fertilization procedures.

#### 4.2.6. Other species

Recently, Roy et al. unveiled the presence of certain NEO-PUFAs (including NeuroPs and IsoPs) in the brain of rainbow trout, along with the modulation of brain lipid content by  $\omega$ -3 PUFAs such as DHA and EPA in a farmed fish species [107]. They observed that NEO-DHA (but not NEO-EPA) increased in brain tissues of rainbow trout having a diet enriched in  $\omega$ -3 PUFAs. In summary, this study represents the first documentation of NEO-PUFAs presence in fish brains and their regulation by dietary DHA and EPA levels, suggesting their potential as nutritional biomarkers but also potential biological activity in fish farmed. Given the known biological activities of  $\omega$ -3 PUFAs in mammals brain but also trout brain [108], further investigations are needed to fully characterize the impact of NEO-PUFAs on brain function and physiological effects in trout model.



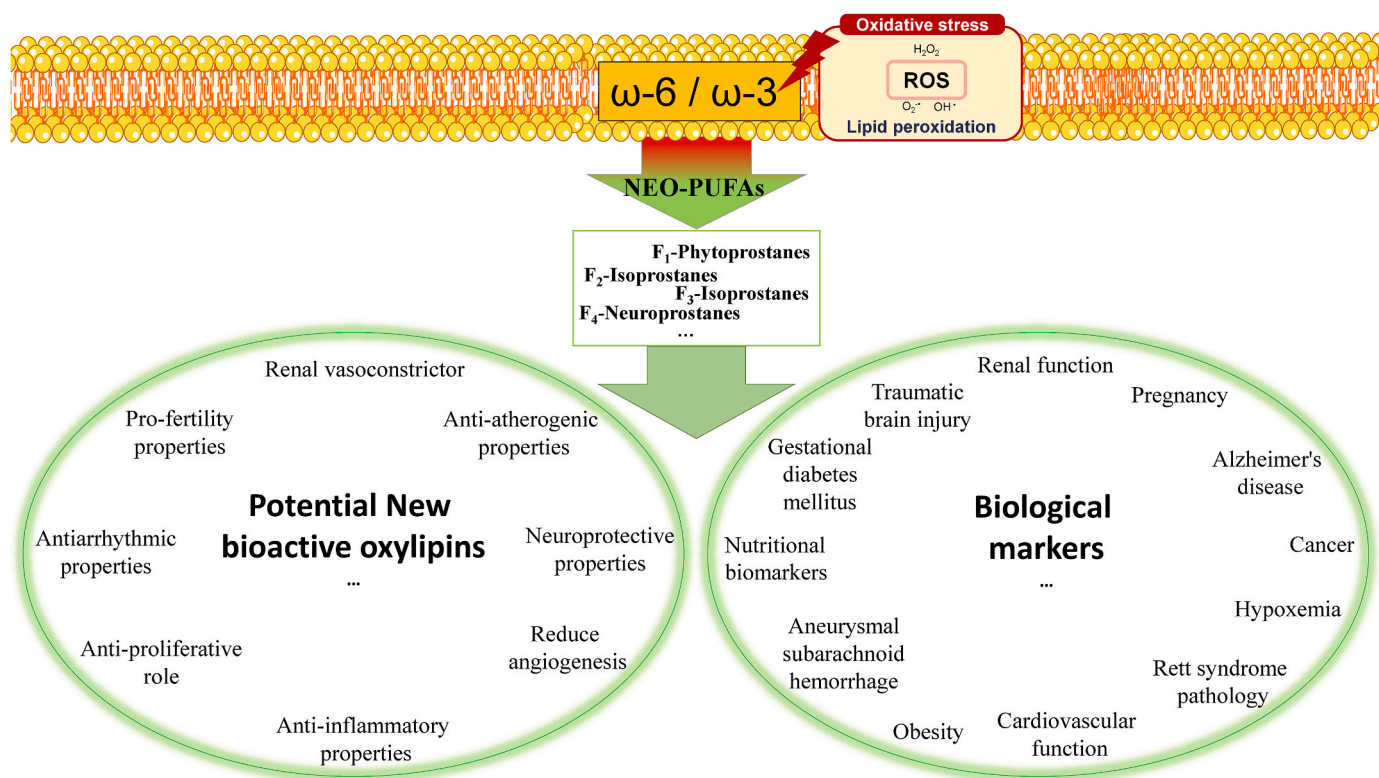


Fig. 5. Graphical abstract.

## 5. Conclusion

The free radical-induced autoxidation of PUFAs occurs in numerous pathophysiological conditions, ranging from cardiovascular disorders to cancers and neurodegenerative diseases (Fig. 5). Our understanding of these processes and their role still needs to be improved. However, leveraging our expertise in organic chemistry, we can contribute significantly to both clinical and basic research endeavors by developing new synthetic approaches and providing samples for biological and analytical investigations. Several innovative methods for the chiral synthesis of NeuroPs and other isoprostanoids have emerged. Some of these synthesized products hold potential as diagnostic and prognostic markers for patients, necessitating precise and accurate measurement. It is imperative even if dreamy at the moment to thoroughly ascertain the contribution of each unique NeuroP to tissue and organ damage within the intricate network of signaling molecules and mediators. Despite the considerable advancements in this field, there remains much to uncover, underscoring the critical importance of collaborations between chemists and biologists. Such interdisciplinary partnerships are paramount for pushing the boundaries of knowledge and driving progress in unraveling the complexities of PUFAs peroxidation-related diseases but also could allow the identification of key molecules displaying beneficial properties.

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## CRediT authorship contribution statement

**Anna Abramova:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Jamie Bride:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Camille Oger:** Visualization, Investigation, Writing – original draft.

**Marie Demion:** Visualization, Investigation, Writing – original draft. **Jean-Marie Galano:** Visualization, Investigation, Writing – original draft. **Thierry Durand:** Supervision, Visualization, Investigation, Validation, Writing – original draft, Writing – review & editing, Funding acquisition. **Jérôme Roy:** Supervision, Visualization, Investigation, Validation, Writing – original draft, Writing – review & editing, Funding acquisition.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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