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Synthetic Evidence of the Amadori-Type Alkylation of Biogenic Amines by the Neurotoxic Metabolite Dopegal

Martin J. Wanner, Ed Zuidinga, Dorette S. Tromp, Jan Vilim, Steen Ingemann Jørgensen, and Jan H. van Maarseveen*

Van’t Hoff Institute for Molecular Sciences, University of Amsterdam, Science Park 904, 1098 XH Amsterdam, The Netherlands

Supporting Information

ABSTRACT: The neurotransmitter metabolite 3,4-dihydroxyphenylglycolaldehyde (dopegal) damages neurons and the myocardium by protein cross-linking, resulting in conglomerations and cell death. We investigated this process on a synthetic scale, leading to the discovery of an Amadori-type rearrangement of dopegal in the reaction with several amino acids and neuropeptides. This alkylation also occurs with neurotransmitters, suggesting an influence of dopegal on neurochemical processes. The rearrangement occurs readily under physiological conditions.

Monamine oxidase (MAO) is known to catalyze the metabolism of the tyrosine-derived neurotransmitters dopamine 1, epinephrine 5, and norepinephrine 6 with the formation of 3,4-dihydroxyphenylacetaldehyde 2 (dopal) and 3,4-dihydroxyphenylglycolaldehyde 7 (dopegal), respectively (Scheme 1). Further metabolic transformation of these highly reactive aldehydes takes place via reducing (AR/ALR) or oxidizing (ALDH) enzymes arriving at the much less harmful alcohols or acids. When these enzymatic detoxification processes become less efficient, the residing catecholaldehydes give rise to unwanted reactions, eventually leading to protein alkylation and cross-linking.1,2 Neurodegenerative diseases such as Parkinson’s or Alzheimer’s diseases, as well as cardiovascular diseases, are associated with the presence of these reactive aldehydes.3 Meanwhile, knowledge about protein alkylation by the dopamine-derived aldehyde dopal (2) is growing, but the exact reaction mechanism of this process is not completely established.4 Oxidation of the catechol part of dopal 2 to a strongly electrophilic ortho-quinone with reactive oxygen species (ROS) likely plays an important role in irreversible protein alkylation.5

In the early stages of protein alkylation, Schiff’s bases 3 are readily formed in the reaction between the aldehyde of dopal and the lysine side chain amine residues (Scheme 1). The imines thus obtained equilibrate to conjugated enamines 4, a type of intermediate that is frequently observed during Pictet−Spengler reactions.6 In general, under aqueous conditions, imine/enamine adducts are not stable and swiftly hydrolyze to the starting compounds. Recently, a successful identification by mass spectroscopy of some of these imine/enamine intermediates derived from dopal (2) and some small amines was reported.5b The properties of dopegal (7) have not been studied in detail due to the limited stability and availability of this highly reactive aldehyde.7 Dopegal (7) contains an additional α-hydroxyl substituent compared to dopal (2), and this hydroxyl group plays an important role in the reactivity. While dopal requires an additional oxidation step of the catechol part to acquire irreversible reactivity with proteins after Schiff’s base formation, the α-hydroxyl substituent in...
dopegal actually presents a higher oxidation level, giving rise to direct irreversible alkylation of proteins as will be shown (Scheme 1).

The Amadori rearrangement is a well-known process that starts with imine formation in the reaction of primary amino substituents in proteins with reducing sugars such as ribose and glucose (Scheme 2). Initially, an imine is formed, which slowly tautomeres to the enamine and, after reprotonation, relatively stable \( \alpha \)-aminoketones are formed. The Amadori rearrangement is most known because this occurs during food preparations at elevated temperatures. Under physiological conditions, this reaction also takes place slowly and leads after further oxidation of these Amadori products to so-called advanced glycation end products (AGEs), which are harmful in many biological systems. Enhanced glucose levels as in diabetes mellitus-2 stimulate the process and result in irreversible damage to tissues and organs.

The responsible sugars contain an \( \alpha \)-hydroxylaldehyde part that resembles the glycolaldehyde part of dopegal. Nevertheless, the remarkably high reactivity of dopegal toward amines, and in particular, toward lysine residues in proteins, has never been recognized as an Amadori-type rearrangement. In a recent publication, a fast reaction between enzymatically synthesized dopegal and the therapeutical dipeptide \( \text{β-Ala-His} \) was mentioned without giving the structure of the reaction product. Therefore, the sequestration of neural dopegal is essential to protect proteins and tissues from alkylation. As a possible solution, amines that are more nucleophilic toward dopegal than the target lysine residues in proteins could be of therapeutic interest. To gain further understanding of this neurochemistry, we started a synthetic project by reacting dopegal with biologically relevant primary amines and amino acids such as \( \text{β}-\text{alanine} \) and lysines, as well as dipeptides and a series of more complex biogenic amines.

The production of dopegal (7) by chemical or enzymatic methods is troublesome, and the limited commercial availability hampers extensive synthetic research. Recently, a one-step preparation of the acetal precursor 13 from catechol (11) and glyoxal dimethyl acetal (12) was described, as an intermediate in a short synthesis of hydroxytyrosol (Scheme 3). The authors described a partial hydrolysis of acetal 13 with aqueous acetic acid and demonstrated a clean conversion to hydrated dopegal in D\(_2\)O solution (50% conversion after 3 days at 60 °C). We upscalled the alkylation of catechol with glyoxal dimethyl acetal to multigram quantities and obtained dopegal precursor 13 readily in pure form by direct crystallization. Complete hydrolysis of the dimethyl acetal in 13 was effected with 1 equiv of TFA in D\(_2\)O, at a concentration of 0.1 M (16 h at 40\(^\circ\)C). Under these conditions, dopegal (7) is almost entirely present in its hydrated form and contains only 5% of the free aldehyde, together with small amounts of its dimer as a complex mixture of several diastereomers. This dimer is formed reversibly, and the ratio of monomer/dimer is concentration-dependent. To obtain dopegal free from water and acid, the aqueous hydrolysis mixture was freeze-dried. However, in the solid residue, we could not detect the free aldehyde either by NMR, both in DMSO and D\(_2\)O, or by IR (no carbonyl absorption in the solid state), indicating that dopegal is completely converted to its cyclic dimer upon concentration. In the literature, a comparable dimerization of the phenyl analogue of dopegal, i.e., mandelaldehyde, is described, in support of our observations. These properties are different from previously synthesized dopegal, which was reported to display aldehyde signals in both NMR and IR spectra. In solution, the dimer is in equilibrium with its (hydrated) monomer but still shows the aldehyde-derived reactivity in further chemistry. After storage of the freeze-dried dopegal for several months, analysis by NMR spectroscopy did not show any decomposition.

With dopegal in hand, in multigram amounts in a stable form, the condensation reaction with several amines was conducted (Table 1). These condensation reactions proceeded readily in water under ambient temperatures (rt to 40 \(^\circ\)C) and at reasonable rates with reaction times ranging from 4 to 24 h, depending on the basicity and nucleophilicity of the amines. A pH range from 6 to 8 proved to be optimal. Above pH 8, the darkening of the solution became stronger due to side reactions that always occur when working with these types of catechols. Slightly acidic conditions (pH 4–6) were also effective, so the acidic aqueous solutions obtained from the TFA-catalyzed hydrolysis can be used directly for condensation reactions, adding one equivalent of a base resulted in a pH range of 7–8. Amino acids preferably react with freeze-dried, acid-free dopegal, which results in a pH of around 7 (entries 1–7). The condensation products were isolated by direct crystallization from the reaction mixtures or were obtained by trituration or precipitation after evaporation of the reaction solvents.

The \( \alpha \)-aminoketones 14–17 derived from \( \text{β-Ala}, \text{Gly-Gly}, \text{Ac-Lys} \), and \( \text{Gln} \), respectively, were obtained in good yields (entries 1–4). It should be noted that proteins that are targeted by dopegal contain lysine-rich areas that can be considerably more nucleophilic than isolated Ac-Lys (entry 3).
Cysteine condenses with dopegal in a different way and produces a diastereomeric mixture of catechol-substituted thiazolidines, which is a well-known reaction with aldehydes. Although the formation of this type of thiazolidine is reversible, the thiazolidine adducts with dopegal were stable. Carnosine is a naturally occurring dipeptide that is abundant in the brain and displays a variety of positive effects as an antioxidant, and more importantly, as an antiglycant, preventing the formation of AGEs from sugars and protecting against neurodegenerative diseases such as Alzheimer’s disease. Carnosine and the common neurotransmitters GABA and phenethylamine reacted smoothly, providing α-aminoketones, respectively, as solids in pure form. The Amadori products derived from the very important neurotransmitters dopamine and serotonin were prone to follow-up reactions and could not be obtained in pure form. As can be concluded from the 1H and 13C NMR spectra, dopamine-derived aminoketone was obtained in >80% purity. LCMS analysis showed that, most probably, a follow-up Pictet–Spengler reaction of dopamine-derived aminoketone with dopegal occurs, followed by further oxidation reactions. Both dopamine and serotonin are discriminated from the other neurotransmitters by their highly π-nucleophilic catechol or indole moieties. Also, histamine behaved differently, and although the reaction took place, we could not obtain the Amadori product in pure form. Finally, also of pyridoxamine, which is under investigation for the depletion of glucose in diabetes mellitus, the Amadori product was isolated in pure form, albeit in a low yield.

Because the aromatic ring of the catechol part within the condensation products is conjugated with the carbonyl group, the stability of the catechol part is strongly increased toward oxidation as compared to precursors such as dopamine, dopal, and dopegal. Some reactivity still remains in the α-aminoketones as condensation in methanol with phenyl acetaldehydes readily yields pyrroles. A representative example of the reactivity of the catecholaldehydes is the condensation of dopamine-derived aminoketone with dopal (2) at a neutral pH to give pyrrole (43% yield) without the use of oxidants and or catalysts.

Table 1. Reaction of Dopegal with Amines

| entry | H₂N-R | product | number (yield %) | entry | H₂N-R | product | number (yield %) |
|-------|-------|---------|-----------------|-------|-------|---------|-----------------|
| 1     | bAla  | Ar-N-CO₂H | 14 (60)         | 7     | GABA  | Ar-N-CO₂H | 20 (53)         |
| 2     | Gly-Gly | Ar-N-CO₂H | 15 (65)         | 8     | phenelethylamine | Ar-N-CO₂H | 21 (66) |
| 3     | Ac-Lys | Ar-N-CO₂H | 16 (55)         | 9     | dopamine | Ar-N-CO₂H | 22'        |
| 4     | Gln   | Ar-N-CO₂H | 17 (72)         | 10    | histamine | Ar-N-CO₂H | 23*         |
| 5     | Cys   | Ar-N-CO₂H | 18 (55)         | 11    | pyridoxamine | Ar-N-CO₂H | 24 (27) |
| 6     | bAla-His (carnosine) | Ar-N-CO₂H | 19 (68)         |       |        |        |                 |

Ar = catechol. Isolated yield. Conditions: H₂O (0.1 M), 1:1 ratio, 20–40 °C, 18 h. The product was contaminated due to follow-up side reactions. By LCMS analysis, the Pictet–Spengler products of dopamine-derived aminoketone with dopegal were detected. The product could not be isolated in pure form.

Scheme 4. Pyrrole Formation

The isolation and characterization of pure pyrrole is a further structure proof of the starting aminoketone (vide supra). Pyrrole could also be obtained by a one-pot, two-step condensation of dopamine with dopal with dopamine in a 1:1:1 ratio, at a neutral pH, albeit in a lower yield. This type of bis-aryl pyrroles and their further oxidized metabolites are well-known bioactive natural products, e.g., the lamellarines and ningaline. Bax et al. described an interesting, related pyrrole-forming reaction, whereby 2 equiv of dopal react with Ac-Lys under oxidative conditions, suggesting a mechanism for cross-linking processes in AD-related synuclein aggregation.

In summary, we have unraveled an efficient amine alkylation process with the endogenous neurotoxin dopegal in the absence of an external oxidant. This Amadori-type rearrangement, which is actually an intramolecular redox reaction, is much faster than the natural Amadori reaction of amino acid.
residues in peptides with sugars. The resulting catecholaminoketones are not known in the literature, and further (oxidative) conversion into harmful AGE-like derivatives cannot be ruled out. The potential value for these compounds can be found in the application as biomarkers for the accumulation of dopegal in biological systems. Finally, our scalable synthesis of dopegal enables its further use in neurobiochemical studies, which will be carried out in due course.

**Experimental Section**

**General Information.** All reactions concerning catechol derivatives were performed with degassed solvents and under argon to minimize darkening. Reagents and precursors were purchased with the highest purity (usually >98%) from Sigma-Aldrich and Fluorochem and used as received. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254). SilicaFlash P60 (particle size 40–63 μm) was used for silica column chromatography. NMR spectra were recorded on Bruker DRX-500, -400, and -300 MHz instruments and was used for silica column chromatography. NMR spectra were machine.

**Ionization method.** IR spectra were recorded on a Bruker Alpha FTIR (a solution of 3,4-bis((tetrahydro-2H-pyran-2-yl)oxy)benzaldehyde)

2.1 Hz, 1H), 6.48 (dd, 2H); 13C{1H} NMR (400 MHz, DMSO-6.84 (d, 1H), 4.07 (s, 2H), 3.79 (d, 2H); 11C(C) NMR (101 MHz, DMSO) δ 195.5, 174.1, 151.9, 145.9, 127.3, 121.5, 115.8, 115.3, 53.9, 44.9, 33.9; HRMS (FD⁺) m/z calcd for C₈H₈O₄ [M⁺] 168.0418, found 168.0419 (monomer).

3-(3,4-Dihydroxyphenyl)-2-oxoethylamine)alpropanic Acid (14) from β-Ala. Dopegal (70.6 mg, 0.42 mmol) was added to a solution of β-alanine (35.6 mg, 0.40 mmol) in water (1.5 mL), and the resulting solution was stirred at 40 °C for 18 h. Cooling to room temperature, filtration and washing with water (3×), and with a mixture of isopropyl/diethyl ether, (1/1) gave 14 (52.3 mg, 0.218 mmol, 54%) as a beige solid: mp=239–241 °C; IR 3358, 3300–2400, 1608, 1602 cm⁻¹; 1H NMR (400 MHz, DMSO-d₆) δ 7.38 (m, 2H), 6.84 (d, J = 8.0 Hz, 1H), 4.14 (2H), 2.86 (t, J = 6.6 Hz, 2H), 2.38 (s, J = 6.6 Hz, 2H); 13C(C) NMR (126 MHz, DMSO-d₆) δ 195.5, 174.1, 151.9, 145.9, 127.3, 121.5, 115.8, 115.3, 53.9, 44.9, 33.9; HRMS (FD⁺) m/z calcd for C₁₁H₃NO₅ [M + H⁺] 240.0876, found 240.0871.

(2,3-Dihydroxyphenyl)-2-oxoethylglycylglycine (15) from Gly-Gly. Dopegal (75.6 mg, 0.45 mmol) was added to a solution of glycylglycine (52.8 mg, 0.40 mmol) in water (1 mL), and the resulting solution was stirred at 40 °C for 18 h. After cooling, the precipitated product was filtered and washed successively with water (0.5 mL), isopropan, and ether to give 15 (73.7 mg, 0.261 mmol, 65%); mp=232–234 °C; IR 3333, 1665, 1589 cm⁻¹; 1H NMR (400 MHz, DMSO-d₆) δ 8.18 (t, J = 5.8 Hz, 1H), 7.35–7.33 (m, 2H), 6.83 (d, J = 8.1 Hz, 1H), 4.07 (s, 2H), 3.79 (d, J = 5.8 Hz, 2H), 3.28 (s, 2H); 11C(C) NMR (101 MHz, DMSO-d₆) δ 195.1, 171.8, 170.4, 151.7, 145.8, 127.1, 121.3, 115.7, 115.0, 54.2, 51.2, 41.4; HRMS (FD⁺) m/z calcd for C₉H₃N₂O₅ [M + H⁺] 283.0925, found 283.0930.
**Note**

1-(3,4-Dihydroxyphenyl)-2-(phenethylamino)ethan-1-one (21) from Phenethylation. A solution of phenethylamine (484 mg, 4.0 mmol) in methanol (2 mL) was mixed with doperol 7 (4 mL of a 0.1 M solution in 0.1 M TFA, 0.40 mmol) and stirred at 45 °C overnight.

Evaporation of the solvents and trituration with isopropanol gave 23 (TFA-salt, 81.3%, 0.266 mmol, 66%): mp 179–181 °C; IR 3400, 1676, 1669 1605 cm⁻¹; ¹H NMR (400 MHz, DMSO-δ) δ 10.24 (broad, 1H), 9.58 (broad, 1H), 9.02 (broad, 2H), 7.49–7.34 (m, 4H), 7.29 (m, 3H), 6.91 (d, J = 8.2 Hz, 1H), 4.70 (s, 2H), 3.22 (t, J = 8.3 Hz, 2H), 3.09–2.93 (m, 2H), ¹³C{¹H} NMR (126 MHz, DMSO-δ) δ 190.8, 159.9, 158.7, 152.8, 146.1, 137.6, 129.1, 129.1, 127.3, 125.9, 122.2, 115.8, 115.2, 52.2, 48.3, 31.9; HRMS (FD⁻) m/z calcd for C₁₀H₁₀NO₂ [M − H⁺] 272.1281, found 272.1278.

2-(3,4-Dihydroxyphenyl)-1-(3,4-dihydroxyphenyl)-ethan-1-one (22) from Dopamine. A solution of dopamine-HCl (151.6 mg, 0.8 mmol), ascorbic acid (352.2 mg, 0.20 mmol), and doperol 7 (123.9 mg, 0.81 mmol) in a mixture of degassed water (3 mL) and methanol (1 mL) was purged with argon for 30 min. Sodium hydroxide (840 mg, 10 mmol) was added; degassing was continued for 10 min. The reaction flask was wrapped in aluminum foil, and the reaction mixture was stirred at rt for 72 h. The precipitate was collected, washed with water (3 times) and a 1/1 mixture of isopropanol and diethyl ether. The brown product 21 (157.6 mg, 0.521 mmol, 65%) was stored at 4 °C: mp 183–192 °C; IR 3400–2500, 1645, 1589 cm⁻¹; ¹H NMR (400 MHz, DMSO-δ) δ 7.79–7.35 (m, 7H, 7H, 7H), 7.18 (s, 1H), 7.08 (d, J = 8.0, 2H, 2H), 3.98 (s, 2H), 2.73 (t, J = 7.3, 2H), 2.58 (t, J = 7.3 Hz, 2H), ³¹P{¹H} NMR (100 MHz, DMSO) δ 120.0, 147.0, 146.0, 133.9, 131.9, 129.1, 128.5, 128.4, 128.3, 128.2, 127.8, 127.5, 126.2, 121.9, 124.9, 124.8, 123.4, 123.3, 123.2, 122.8, 121.7, 117.2, 115.9, 115.3, 62.5, 52.0, 45.6, 37.7, 25.9, 22.7, 21.3; HRMS (FD⁻) m/z calcd for C₁₃H₁₂NO₂ [M + H⁺] 304.1180, found 304.1182.

2-((1H-Imidazol-4-yl)methyl)amino)-1-(3,4-dihydroxyphenyl)-ethan-1-one (23) from Histamine. NaHCO₃ (40 mg, 0.44 mmol) was added to a solution of histamine dihydrochloride (7.36 mg, 0.4 mmol) and doperol 7 (740 mg, 0.42 mmol) in water (2 mL). After stirring at 40 °C overnight, the dark reaction mixture was acidified with 2 M HCl (1 mL) and evaporated to dryness. The residue was coevaporated 3 times with methanol, redissolved in methanol (ca. 2 mL), and filtered to remove inorganic salts. Evaporation of the filtrate and triturating the residue with mixtures of ethanol, isopropanol, and diethyl ether gave 24·2HCl (67.0 mg, 0.20 mmol, 50%) as a dark, waxy solid: IR 3500–2500, 1674, 1596 cm⁻¹; ¹H NMR (300 MHz, DMSO-δ) δ 14.57 (s, 3H), 10.38 (s, 1H), 9.64 (s, 1H), 9.37 (s, 2H), 9.09 (s, 2H), 8.24 (s, 1H), 7.56 (s, 1H), 7.41 (m, 2H), 6.93 (d, J = 8.6 Hz, 1H), 4.99 (s, 1H), 4.69 (s, 2H), 3.3–3.4 (m, 2H), 3.25–3.11 (m, 2H), ¹³C{¹H} NMR (101 MHz, DMSO-δ) δ 190.3, 189.7, 152.7, 147.6, 147.1, 134.2, 129.1, 129.8, 125.8, 125.5, 122.3, 117.2, 115.9, 115.3, 62.5, 52.0, 45.6, 37.7, 25.9, 22.7, 21.3; HRMS (FD⁻) m/z calcd for C₁₃H₁₂NO₂ [M + H⁺] 262.1186, found 262.1189.

1-(3,4-Dihydroxyphenyl)-2-(((3-Hydroxy-5-(hydroxymethyl)-2-methylpyrrolidin-4-yl)amino)ethan-1-one (24) from Pyridoxamine. NaHCO₃ (57 mg, 0.44 mmol) was added to a solution of pyridoxamine dihydrochloride (96.4 mg, 0.4 mmol) and doperol 7 (73.9 mg, 0.44 mmol) in water (2 mL). After stirring at rt overnight, the dark reaction mixture was evaporated, acidified with 2 M HCl (1 mL), and evaporated to dryness. The residue was coevaporated with water (1 mL), redissolved in water (0.5 mL), and kept in the fridge overnight. The crystalline products were isolated by filtration and washed successively with a few drops of ice-cold water with isopropanol and diethyl ether to give 25 (42.1 mg, 0.108 mmol, 27% in 2 crops): mp 142–148 °C; IR 3500–2500, 1674, 1589 cm⁻¹; ¹H NMR (400 MHz, DMSO-δ) δ 10.37 (br, 1H), 9.64 (br, 2H), 8.27 (s, 1H), 7.41 (m, 2H), 6.94 (d, J = 8.8 Hz, 1H), 4.82 (s, 2H), 4.74 (s, 2H), 4.48 (s, 2H), 2.70 (s, 3H), ¹³C{¹H} NMR (101 MHz, DMSO-δ) δ 190.2, 154.1, 152.7, 146.0, 143.0, 140.2, 134.3, 130.5, 125.6, 122.1, 115.8, 115.2, 87.6, 52.5, 41.7, 16.0; HRMS (FD⁻) m/z calcd for C₁₃H₁₄NO₂ [M + H⁺] 319.1289, found 319.1306.

4-((1-(3,4-Dihydroxyphenyl)-1-phenylpyrrole)-3,4-diylibis(benzene-1,2-diol) (25). A mixture of 22 (60.6 mg, 0.2 mmol) and dopal 2 (33.5 mg, 0.21) in 1.5 mL of MeOH (degassed with argon)
was stirred in the dark for 42 h under O_{2}-free conditions. Evaporation and flash chromatography (DCM/MeOH 90/10 and 87/13) were performed quickly. Product 25 (36.4 mg, 0.0869 mmol, 43%) was obtained after drying (0.1 mbar, 40 °C) as a colorless glass, turning red/brown upon standing. A one-pot reaction of the three components in a 1:1 mixture of methanol and water, with 48 h intervals, gave 25 in a slightly lower yield: 1H NMR (500 MHz, DMSO-d_{6}) δ 8.63 (bs, 6H), 6.72 (s, 2H), 6.69−6.64 (m, 2H), 6.63−6.56 (m, 4H), 6.51 (dd, J = 8.1, 2.1 Hz, 1H), 6.44 (dd, J = 8.1, 2.1 Hz, 2H), 3.99 (dd, J = 9.0, 6.6 Hz, 2H), 2.96−2.78 (m, 2H); 13C{[1H]} NMR (126 MHz, DMSO-d_{6}) δ 145.5, 145.2, 144.1, 143.5, 129.9, 128.5, 122.3, 119.8, 119.8, 119.3, 116.6, 116.0, 116.0, 115.8, 50.8, 37.1; HRMS (FD^+)/m/z calc for C_{2}H_{12}NO_{6} [M^+] 419.1363, found 419.1355.

## ASSOCIATED CONTENT

- Supporting Information: The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.9b01948.

1H and 13C NMR spectra of all new products and intermediates; LCMS traces of the aminoketones 14−24 (PDF).

## AUTHOR INFORMATION

**Corresponding Author**

*E-mail: j.h.vanmaarseveen@uva.nl.

**ORCID**

Jan H. van Maarseveen: 0000-0002-1483-436X

**Notes**

The authors declare no competing financial interest.

## DEDICATION

We dedicate this contribution to the memory of Prof. Gerrit-Jan Koomen, who sadly passed away on January 16, 2019 as a consequence of Alzheimer’s disease.

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