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Letter

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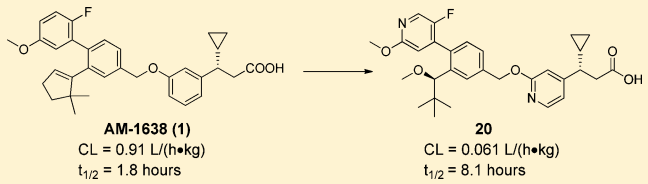
Improving the Pharmacokinetics of GPR40/FFA1 Full Agonists

Xiaohui Du,* Paul J. Dransfield, Daniel C.-H. Lin, Simon Wong, Yingcai Wang, Zhongyu Wang, Todd Kohn, Ming Yu, Sean P. Brown, Marc Vimolratana, Liusheng Zhu, An-Rong Li, Yongli Su, Xianyun Jiao, Jiwen (Jim) Liu, Gayathri Swaminath, Thanhvien Tran, Jian Luo, Run Zhuang, Jane Zhang, Qi Guo, Frank Li, Richard Connors, Julio C. Medina, and Jonathan B. Houze

Departments of Therapeutic Discovery, Metabolic Disorders, Pharmaceutics, and Pharmacokinetic and Drug Metabolism, Amgen Inc., 1120 Veterans Boulevard, South San Francisco, California 94080, United States

Supporting Information

ABSTRACT: We recently reported the discovery of a potent GPR40 full agonist AM-1638 (**1**). Herein, we describe our efforts in improving the drug-like properties of the full agonists through the systematic introduction of polar groups in the C-, D-, and A-rings. This led to the discovery of new GPR40 full agonists with significantly improved pharmacokinetic propeties. Compound **8** and **20** also showed potent in vivo efficacy in oral glucose tolerance tests in mice in addition to the improvement in properties.



KEYWORDS: *GPR40, FFA1, full agonist, insulin secretagoue, type 2 diabetes*

Type 2 diabetes is characterized by impaired glucose homeostasis due to insulin resistance and insufficient secretion of insulin from the pancreas.[1] Consequently, blood glucose increases and is a major risk factor for microvascular and macrovascular complications including retinopathy, nephropathy, neuropathy, and accelerated cardiovascular disease.[2−4] Treating type 2 diabetes remains a significant medical need to this day.

GPR40 (FFA1) belongs to Class A of the G-protein coupled receptor (GPCR) family. It is primarily expressed in pancreatic islet β-cells and also in enteroendocrine cells. GPR40 is not only involved in direct potentiation of glucose-stimulated insulin secretion in pancreatic islet β-cells but also stimulates GLP-1 release from enteroendocrine L-cells.[5] The dual mechanism of action provides a compelling rationale to develop GPR40 agonists as glucose-dependent insulin secretagogues for the treatment of type 2 diabetes.[6−8] Consequently, it has attracted interest from many in the pharmaceutical community.[9−11]

We previously described a GPR40 full agonist AM-1638 (**1**)[12,13] (Figure 1), which displayed superior antidiabetic efficacy in several rodent models. However, AM-1638 (**1**) is very lipophilic and has unsatisfactory physicochemical properties such as a calculated CLogP of 9.3. AM-1638 (**1**) exhibits clearance of 0.91 L/(h·kg) and a half-life of 1.8 h in rat. We hoped to reduce the CLogP and improve the pharmacokinetic profile of this class of GPR40 agonists by introducing polarity throughout the structure including the C-ring, D-ring, and the A-ring.[14,15]

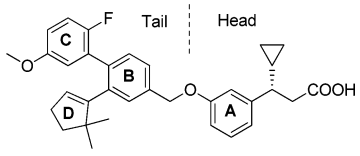


Figure 1. GPR40 full agonist AM-1638 (**1**).

An aequorin assay[13] was used to evaluate the potency of newly synthesized GPR40 agonists. GPR40 couples primarily to G_q and elicits a calcium response. The assay was performed with cells stably overexpressing the GPR40 receptor to examine the extent of calcium release upon activation by the synthetic GPR40 agonists.

To introduce polarity into the C-ring of AM-1638 (**1**), we decided to explore the use of pyridine as a replacement for the phenyl group. This strategy has been applied in a different GPR40 scaffold by Ulven et al.[16] Methoxy-pyridines were employed as the C-ring with the ring nitrogen at the ortho, meta, and para positions relative to the B-ring (Table 1).[17] The *ortho*- and *meta*-pyridines (compounds **3** and **4**, Table 1) were investigated with the *tert*-butyl group in place of the D-ring. Both **3** and **4** were less potent as compared to their nonpyridine analogue **2**. This strategy was revisited after the more potent dimethyl cyclopentenyl D-ring was discovered. Compound **5** with a 2′-fluoro-5′-methoxy pyridine C-ring maintained both the potency and efficacy in the aequorin assay compared to AM-1638 (**1**), while lowering the CLogP by 0.7 unit. Subsequently, the 2′-fluoro-5′-methoxy pyridine C-ring was combined with the best head groups and the 2,2-dimethylcyclopentyl D-ring to evaluate its impact on pharmacokinetic profile (Table 2).

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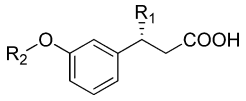
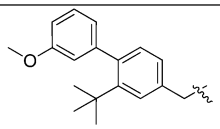
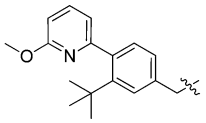
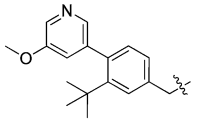
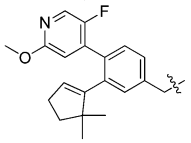
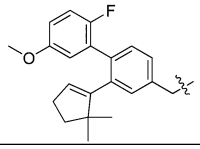
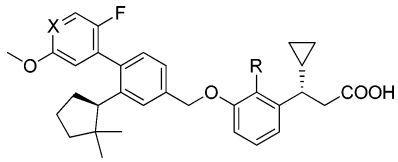
Table 1. Replacing the C-Ring with Various Methoxy Pyridines



Compound	R_2	R_1	Aequorin (0.01% HSA) EC_{50}[a] (nM)	Aequorin (0.01% HSA) E_{max}[b] (%)	CLogP[c]
2			370	94	8.4
3			3700	61	8.0
4			30000	72	7.4
5			120	100	8.6
1			161	100	9.3

[a]Mean of at least two runs; mean standard deviation is ±14%. [b]% Maximal efficacy compared to AM-1638 (**1**). [c]Calculated from ChemBioDraw Ultra 12.0 by CambridgeSoft.

Table 2. Methoxy Pyridine Replacement Improved the Pharmacokinetics of the GPR40 Agonists



Compound	X	R	Aequorin (0.01% HSA) EC_{50}[a] (nM)	Aequorin (0.01% HSA) E_{max}[b] (%)	CL Intrinsic[c] Human μL/(min.mg)	CL Intrinsic[c] Rat μL/(min.mg)	Rat PK[d] CL (IV) L/(h•kg)	Rat PK[d] $T_{1/2}$ (IV) (h)	Rat PK[d] F (PO) (%)	CLogP[e]
6	C	H	76	101	52	219	0.7	2.0	34	9.3
7	N	H	68	95	21	67	0.10	3.5	34	8.6
8	N	F	93	102	15	52	0.17	4.6	98	8.7

[a]Mean of at least two runs; mean standard deviation is ±14%. [b]% Maximal efficacy compared to AM-1638 (**1**). [c]Metabolic stability in clearance intrinsic: CL intrinsic (μL/min/mg) = {ln 100 − ln[(conc. after the metabolic reaction)/(conc. at initial 1 μM) × 100]}/[30 min]/[0.25 (mg/mL) human or rat liver microsomes] × 1000 at 37 °C. [d]IV dose: 0.5 mg/kg. n = 2; PO dose: 2.0 mg/kg. n = 3. [e]Calculated from ChemBioDraw Ultra 12.0 by CambridgeSoft.

Compound **7** with the 2′-fluoro-5′-methoxy pyridine C-ring showed improved metabolic stability, clearance, and half-life compared to its 2′-fluoro-5′-methoxy phenyl C-ring analogue **6**. The addition of a fluorine atom onto the headgroup resulted in

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compound **8**, which further increased the half-life (4.6 h) and oral bioavailability (98%) compared to those of compound **7** while maintaining good metabolic stability. Both **7** and **8** have lower CLogP values due to the pyridine C-ring.

Given the excellent pharmacokinetic profile of compound **8**, it was dosed in high fat fed/STZ type II diabetic mice.[5] Compound **8** demonstrated a dose-proportional decrease in blood glucose levels with comparable efficacy at 30 mg/kg compared to a maximally efficacious dose of 60 mg/kg AM-1638 (**1**) during an oral glucose tolerance test (Figure 2). Compound **8** also stimulated dose-dependent GLP-1 release, reconfirming the dual mechanism of action of GPR40.[18]

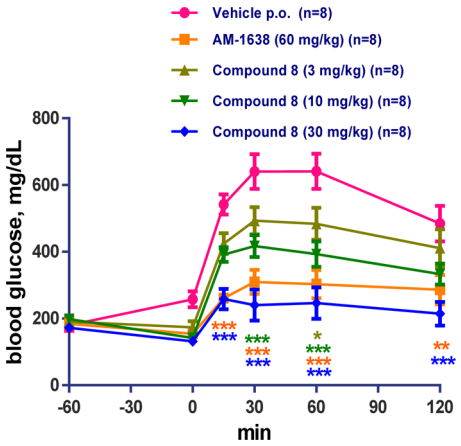
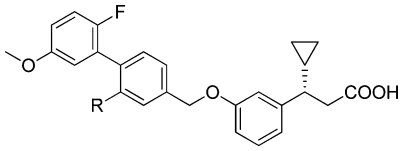


Figure 2. In vivo results of dosing compound **8** in a HF/STZ type II diabetic model in mice. Compound **8** lowered blood glucose in a dose-dependent manner. Statistical significance compared to vehicle treatment is denoted by *($p < 0.05$), **($p < 0.01$), ***($p < 0.001$), and ****($p < 0.0001$), as determined by two-way ANOVA, and is color-coded to the treatment in the figure legends.

Polar groups were also evaluated at the D-ring (Table 3). Compound **9** had a less lipophilic neopentyl group replacing the 2,2-dimethylcyclopentyl group. However, it displayed higher clearance in rat. The addition of a fluorine to the neopentyl group was tolerated in compound **10**. A methoxy replacement of the fluorine (compound **11**) further reduced the CLogP to 7.7 and led to a reduced clearance and a longer in vivo half-life in rats compared to those of compound **6**. Ethoxy replacement (**12**) did not significantly change the potency or DMPK profile compared to that of compound **11**. Constraining the ethoxy dimethylpropyl group into a dimethyltetrahydropyran D-ring (**13**) led to a decrease in potency. Compound **14**, a diastereomer of **11**, suffered a 10-fold loss in potency thus indicating the importance of the methoxy-bearing stereogenic center. These agonists suggested that the methoxy dimethylpropyl group in compound **11** could be a good functionality to combine with the best findings in other areas of the GPR40 molecules.

Seeking additional areas to introduce polarity, we also investigated into the A-ring (Table 4). Among the analogues with 2,2-dimethylcyclopentyl group as the D-ring, introducing an additional pyridine as the A-ring significantly lowered the clearance to 0.086 L/(h·kg) and extended the half-life to 9.7 h (compound **15**). Substitution at the benzylic position of the pyridine A-ring was explored. Exchanging the cyclopropyl group to an ethyl group (**16**) was less advantageous and resulted in a nearly 1.5-fold increase in clearance. Trimming the cyclopropyl group down to a methyl (**17**) led to a 3-fold drop in potency.

Table 3. Polar Group Introduction at the D-Ring



Compound	R	Aequorin (0.01% HSA) EC_{50}[a] (nM)	Aequorin (0.01% HSA) E_{max}[b] (%)	Rat PK (IV)[c] CL L/(h•kg)	Rat PK (IV)[c] $T_{1/2}$ (h)	CLogP[d]
6		76	101	0.7	2.0	9.3
9		88	102	1.2	1.2	8.6
10		105	100	n/a		8.2
11		147	105	0.28	3.5	7.7
12		114	101	0.32	3.9	8.0
13		227	96	n/a		7.6
14		1410	98	n/a		7.7

[a]Mean of at least two runs; mean standard deviation is ±14%. [b]% Maximal efficacy compared to AM-1638 (**1**). [c]IV dose: 0.5 mg/kg. n = 2. [d]Calculated from ChemBioDraw Ultra 12.0 by CambridgeSoft.

Replacing the D-ring of **15** with the methoxy dimethylpropyl group led to compound **20** with the lowest clearance of 0.061 L/(h·kg) among the compounds shown in Table 4. In addition, compound **20** has a long half-life (8.1 h) and good oral bioavailability of 54%. The improved pharmacokinetics correlated well with the improved CLogP value (6.0) of compound **20**, which is more than 3 units lower than that of AM-1638 (**1**).

To further confirm that these compounds are full agonists and that the signaling of the receptor is indeed through G_q that results in accumulation of IP_3, an upstream signal preceding calcium release, we performed an IP_3 assay on transfected A9 cells stably overexpressing the GPR40 receptor. While the aequorin assay was performed on cells that express low levels of the FFA1 receptor, the IP_3 assays were performed on cells stably expressing the FFA1 receptor at high levels. This accounts for the increased potency shift in IP_3 assay compared to aequorin assay. The use of different expression level of receptor helps to delineate if the compound is a true full agonist or not. All compounds in Table 4 were confirmed to be full agonists in both the aqeuorin and the IP_3 assays. Compound **20** has the same potency (162 nM) as AM-1638 (**1**) (161 nM) in aequorin assay, but it is much more potent in IP_3 assay (0.6 nM) than AM-1638 (**1**) (13 nM).

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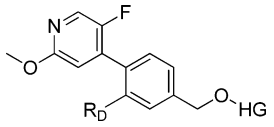
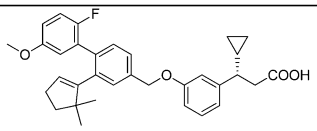
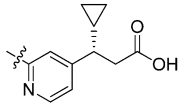
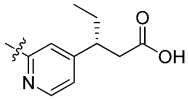
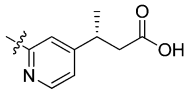
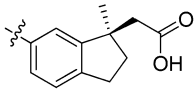
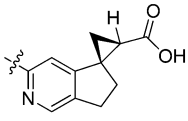
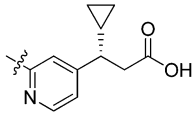
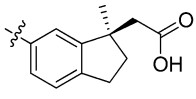
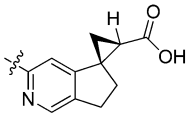
Table 4. Polar and Constrained Groups Introduction at the Head Group



Compound	R_D	HG	Aequorin (0.01% HSA) EC_{50}[a] (nM)	Aequorin (0.01% HSA) E_{max}[b] (%)	IP_3 (0.3% HSA) EC_{50}[c] (nM)	IP_3 (0.3% HSA) E_{max}[b] (%)	Rat PK[d] CL (IV) L/(h•kg)	Rat PK[d] $T_{1/2}$ (IV) (h)	Rat PK[d] F (PO) (%)	ClogP[e]
1			161	100	13	99	0.91	1.8	15	9.3
15			108	110	1.7	100	0.086	9.7	37	7.6
16			150	99	6	102	0.15	8.2	83	7.7
17			281	136	19	100	n/a	n/a	n/a	7.2
18			128	100	3.4	100	0.45	3.7	10	8.8
19			249	98	22	97	0.26	3.6	58	7.2
20			162	94	0.6	100	0.061	8.1	54	6.0
21			235	106	6.7	101	0.25	4.0	21	7.1
22			250	85	370	122	1.7	1.2	n/a	5.6

[a]Mean of at least two runs; mean standard deviation is ±14%. [b]% Maximal efficacy compared to AM-1638 (**1**). [c]Mean of at least two runs; mean standard deviation is ±10%. [d]IV dose: 0.5 mg/kg. n = 2; PO dose: 2.0 mg/kg. n = 3. [e]Calculated from ChemBioDraw Ultra 12.0 by CambridgeSoft.

A few of the constrained head groups[15] were combined with the findings in the C-ring and D-ring to form compounds **18**, **19**, **21**, and **22**. They generally showed improved clearance over AM-1638 (**1**) with the exception of compound **22**; however, they did not show superiority over compounds **15** and **20**.

Compound **20** had a desirable combination of potency, CLogP, and pharmacokinetics. It was scaled up for further studies through the synthesis shown in Scheme 1. Dimethyl 4-hydroxyisophthalate **23** was converted to triflate **24**. Subsequent palladium-catalyzed Suzuki coupling with (5-fluoro-2-methoxypyridin-4-yl) boronic acid yielded biphenyl **25**. Selective hydrolysis of the less-hindered ester in **25** resulted in compound **26**, and subsequent reduction of the carboxylic acid in **26** led to alcohol **27**. *tert*-Butyl lithium addition to the ester in **27** generated ketone **28**. Then it was converted to diol **29** through reduction of the ketone in **28** followed by chiral separation. The benzylic alcohol in **29** was selectively protected as a TBS ether, and then the secondary hydroxy group in **29** was protected as a methyl ether. After deprotection of the TBS group in **30**, the benzylic alcohol in **31** was converted to a bromide **32**, which would be used to couple to headgroup **38**.

To synthesize headgroup **38**, 2-fluoroisonicotinaldehyde **33** was condensed with Meldrum's acid to generate compound **34**. 1,4-Addition of cyclopropyl magnesium bromide to **34** and

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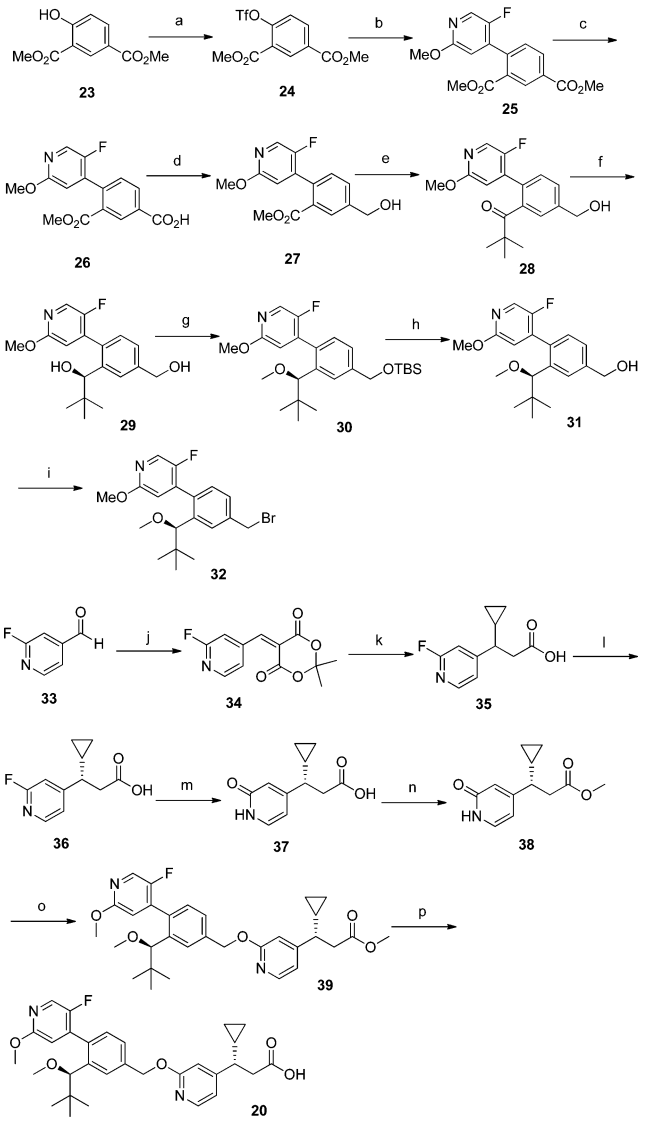
Scheme 1[a]



[a]Reagents and conditions: (a) $PhN(Tf)_2$, Et_3N, CH_2Cl_2, 88%; (b) (5-fluoro-2-methoxypyridin-4-yl)boronic acid, $Pd(PPh_3)_4$, K_2CO_3, DMF, 90 °C, 90%; (c) KOH, THF, MeOH, H_2O, 99%; (d) BH_3·THF, 90%; (e) *t*-BuLi, THF, 80%; (f) $LiAlH_4$, THF, then chiral separation with 4% IPA in hexanes on Chiracel-OD column, 44%; (g) (*i*) TBSCl, DMAP, Et_3N, 90%; (*ii*) MeI, NaH, DMF, 73%; (h) TBAF, THF, 100%; (i) NBS, PPh_3, 90%; (j) Meldrum's acid, HOAc, piperidine, benzene, reflux, 68%; (k) (*i*) cyclopropylMgBr, THF; (*ii*) DMF, H_2O, 95 °C, 84%; (l) chiral separation on chiral IC column with 50 g/min IPA +0.2% DEA and 50 g/min CO_2 on Thar 350 SFC, 45%; (m) aq. HCl, 100 °C, 96%; (n) MeOH, H_2SO_4, reflux, 89%; (o) **32**, Ag_2CO_3, toluene, 83%; (p) LiOH, THF, MeOH, H_2O, 87%.

decarboxylation generated acid **35**, which was chirally separated to obtain the desired enantiomer **36**. The fluoro-pyridine in **36** was hydrolyzed to form pyridone **37**. Esterification of compound **37** led to headgroup **38**. Coupling of **38** with tail group **32** facilitated by silver carbonate formed the O-alkylated compound **39**, and it was subsequently hydrolyzed with lithium hydroxide to give compound **20**.

The in vivo efficacy of compound **20** was demonstrated in a BDF-DIO model[19] in mice (Figure 3). At a low dose of 0.3 mg/kg, it lowered the blood glucose significantly during an oral glucose tolerance test. At 3 mg/kg, it showed comparable

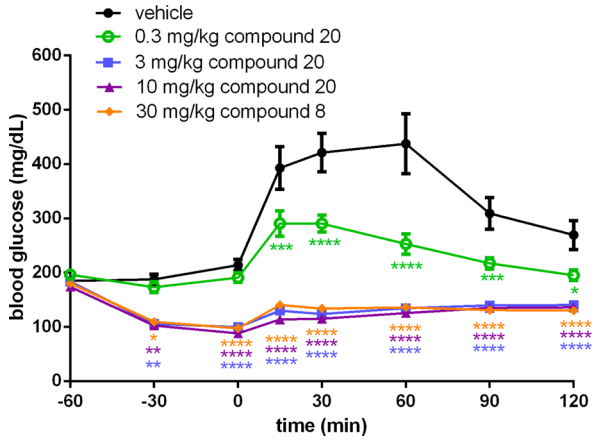


Figure 3. Compound **20** showed glucose-lowering effect in a BDF-DIO model in mice. Statistical significance compared to vehicle treatment is denoted by *($p < 0.05$), **($p < 0.01$), ***($p < 0.001$), and ****($p < 0.0001$), as determined by two-way ANOVA, and is color-coded to the treatment in the figure legends.

glucose-lowering effect similar to that of compound **8** at 30 mg/kg. Though compound **20** had no further increase in efficacy from 3 to 10 mg/kg, the blood glucose levels were not dropped lower into a hypoglycemic range. This result indicates that targeting GPR40 might provide a potential advantage as diabetes therapeutics in terms of hypoglycemic control. The potent in vivo efficacy of compound **20** is consistent with its potent in vitro activity as well as its superior pharmacokinetics.

In conclusion, lipophilicity oftentimes correlates with high metabolism and poor oral absorption. Our strategy of improving the lipophilicity of the GPR40 agonists through introducing polar groups in the C-ring, D-ring, and A-ring led to the discovery of a number of compounds with improved pharmacokinetics compared to AM-1638 (**1**). The improved pharmacokinetics generally correlated well with lowered calculated CLogP values. In addition, compounds **8** and **20** displayed potent glucose-lowering efficacy in mouse models.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and data for compounds, biological assay procedures, in vivo procedures, and GLP-1 release data for compound **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*(X.D.) E-mail: xdu@amgen.com.

Notes

The authors declare no competing financial interest.

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