

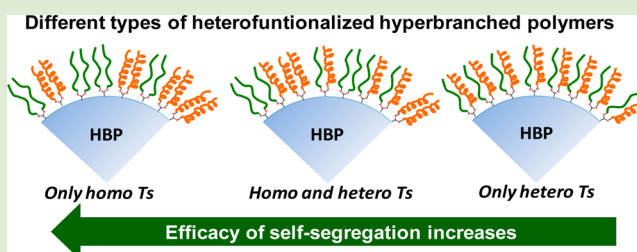
# Understanding Self-Segregation of Immiscible Peripheral Segments in Pseudodendritic Hyperbranched Polydithioacetals: Formation of Improved Janus Structures

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## S Supporting Information

**ABSTRACT:** Peripherally heterofunctionalized hyperbranched polymers (HBPs) undergo immiscibility-driven self-segregation of the outer segments to form Janus molecular entities (*Macromolecules* 2012, 45, 2348). In HBPs prepared via  $AB_2$  type self-condensation, single-step peripheral heterofunctionalization would lead to random distribution of the two types of terminal units, namely, homofunctionalized (homo-T) and heterofunctionalized (hetero-T) termini. Here, we examine the role of such hetero-T units on the self-segregation of heterofunctionalized pseudodendritic hyperbranched polydithioacetals. Three different heterofunctionalized HB dithioacetals bearing roughly 50 mol % each of docosyl (C-22) and MPEG-350 chains at the periphery were prepared: one of them carried a statistical distribution of homo-T and hetero-T units, and the other carried only two types of homo-T ( $-TR_1R_1$  and  $-TR_2R_2$ ) termini, whereas the third carried largely hetero-T ( $-TR_1R_2$ ) termini. Careful examination of DSC and SAXS data reveals that the self-segregation is most effective in HBPs devoid of hetero-T units; interestingly, however, it also showed that randomly heterofunctionalized HBPs self-segregated nearly as effectively.



Hyperbranched polymers (HBPs) are remarkable molecular entities that can be transformed into a variety of interesting structures by suitable modification of the nature of the peripherally located terminal segments; for instance, condensation polymerization of an  $AB_2$  monomer generates a HBP carrying numerous B-type functional groups, which can be PEGylated and thereby produce what has been often referred to as unimolecular micelles.<sup>1</sup> Such amphiphilic single-molecule entities have been explored extensively with regard to their self-assembly behavior,<sup>2</sup> as carriers of drugs,<sup>3</sup> imaging agents,<sup>4</sup> etc. Despite the intrinsic high dispersity of HBPs arising from the statistical nature of the polymer growth process, the *effective functional dispersity* in terms of their hydrodynamic size, especially in such amphiphilic HBPs, may be far smaller than expected because of the collapse of the hydrophobic core in a segment-selective solvent; this in turn would make these systems resemble multiarm amphiphilic star polymers.<sup>5</sup> Several studies have focused on the generation of amphiphilic HBPs using a variety of different methodologies;<sup>6</sup> recently, we developed some new single-step melt-condensation approaches to prepare peripherally “clickable” HB polyethers and polyesters that carry either propargyl or allyl terminal groups, which were readily clicked quantitatively using azide–yne or thiol–ene reactions to generate a range of core–shell type amphiphilic HBPs.<sup>7</sup>

*Heterofunctionalized HBPs* is a term that could be used to refer to systems where the terminal groups have been functionalized with more than one type of molecular segment. Recently, we showed that when two immiscible segments, such

as a long alkyl chain (C-22) and polyethylene glycol, monomethyl ether (MPEG-350) segments, are randomly clicked onto HB polyesters in a single step the resulting polymers demonstrated the ability to reconfigure and form Janus structures that further organize in the solid state to generate a lamellar morphology built-up of bilayers of the Janus molecular entities;<sup>8</sup> similarly, tripodal structures carrying three types of mutually immiscible segments were also shown to self-segregate, although with no readily discernible morphology.<sup>9</sup>

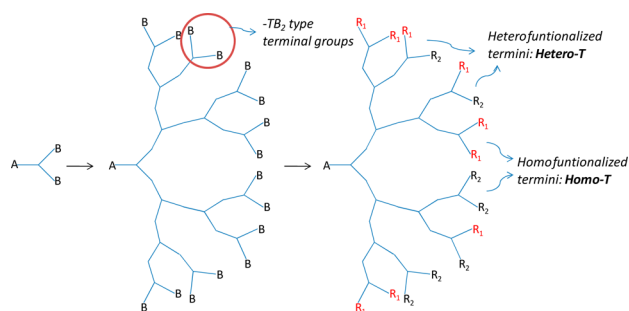
When a HBP is prepared by the self-condensation of an  $AB_2$  monomer, its periphery would carry primarily terminal groups of the type  $-TB_2$  (neglecting linear defects); when these peripheral B groups are reacted with two different segments, the resulting HBPs would bear three types of terminal units, namely,  $-TR_1R_1$ ,  $-TR_2R_2$ , and  $-TR_1R_2$ , as depicted in Scheme 1. In reality, HBPs additionally carry a significant fraction of linear defects (L) wherein only one of the B-groups has reacted, leaving the other unreacted; these would then be transformed to units carrying either  $R_1$  or  $R_2$  groups. Thus, in general, a total five different types of units can result upon transformation of the B-type end-groups in a HBP; of these, two would be homofunctionalized (homo-T), one heterofunctionalized (hetero-T), and the remaining monofunctionalized (mono-T). It may be expected that complete self-segregation of the two types of segments, namely,  $R_1$  and  $R_2$ , would be rather difficult in

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### Scheme 1. Formation of HBPs Carrying Different Types of Terminally Functionalized Units<sup>a</sup>



<sup>a</sup>For simplicity a defect-free HBP has been depicted; in general, linear defects carrying either  $R_1$  or  $R_2$  will also be present.

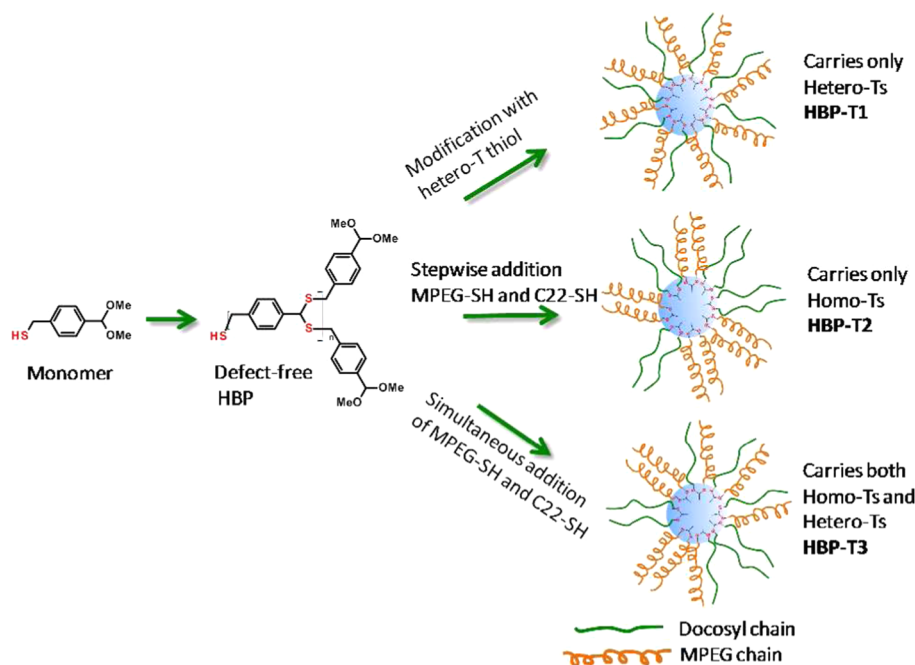
such randomly functionalized HBPs; however, as we showed recently,<sup>8</sup> Janus-type structures were indeed formed in HBPs wherein the terminal propargyl groups were randomly clicked with C-22 alkyl chains and MPEG-350. The feasibility of self-segregation, in the context of peripherally functionalized dendrimers, was recently examined computationally by Chute et al.,<sup>10</sup> and they arrived at the conclusion that dendrimers that carry only hetero-T units would not readily self-segregate to form Janus structures. Although this prediction appears intuitively reasonable based on the restricted conformational degrees of freedom possessed by hetero-T units, there are no experimental studies that have examined the role of various types of terminal units on the ability of dendrimers or HBPs to form Janus structures.

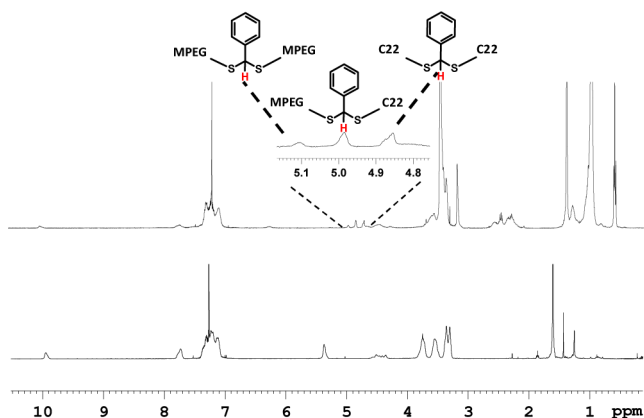
Recently, we reported a unique polymerization process wherein an  $AB_2$  monomer carrying a thiol and a dimethyl acetal underwent self-condensation, under acid catalysis, to yield a *pseudodendritic HB polydithioacetal* (see Scheme 2); a particularly useful feature of this HB polymer was the presence

of numerous dimethyl acetal terminal groups that could subsequently be transformed quantitatively by reaction with organic thiols.<sup>11</sup> We had shown that the primary reason for the absence of linear (L) defects in this HB polydithioacetal was the rapid irreversible transformation of the relatively labile monothioacetal intermediate to the dithioacetal; an important consequence of this feature of the reaction is that it also provides us a remarkable opportunity to create *heterofunctionalized HBPs that would be devoid of hetero-T units*. In the present study, we have utilized these pseudodendritic HB polydithioacetals to prepare different types of terminally heterofunctionalized HBPs and have examined the role of various types of terminal subunits in governing the self-segregation of the peripherally anchored immiscible segments; it is important to recognize here that, despite being defect-free, these structures are topologically distinct from dendrimers because of their highly unsymmetrical structure.

We first reacted the terminal dimethyl acetal groups of the pseudodendritic HB polydithioacetals (see Scheme 2) with both docosyl (C-22) thiol and MPEG-350 thiol (50:50 mol ratio) in a single step. The proton NMR spectrum of this sample, HBP-T3, clearly reveals the complete transformation of the terminal dimethyl acetal units, as evident from the disappearance of the methine proton peak at 5.4 ppm (Figure 1). Furthermore, from the integral intensities of the terminal methyl/methoxy peaks of the docosyl and MPEG segments, respectively, the composition of these segments was readily established; the total intensity of these two peaks also helped confirm the complete transformation of the dimethyl acetal segments. The most interesting and unexpected feature of the spectrum was the splitting of the dithioacetal methine protons after the heterofunctionalization; these appeared in the range 4.8–5.1 ppm (expanded in the figure) and were distinct from the methine protons belonging to the dendritic (D) dithioacetal units that appeared as a collection of broad peaks in the region 4.3–4.6 ppm, which is seen in this spectrum as a broad hump

### Scheme 2. Schematic Depiction of Three Different Strategies for the Preparation of Peripherally Heterofunctionalized Pseudodendritic HB Polydithioacetals



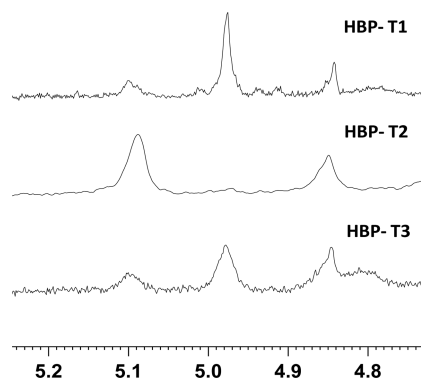


**Figure 1.** Proton NMR spectra of the parent HB polydithioacetal along with that of the single-step heterofunctionalized HBP (HBP-T3) carrying MPEG-350 and docosyl units. The peak at  $\sim 10$  ppm is due to the aldehyde protons resulting from inadvertent hydrolysis of the terminal dimethyl acetal units, and the peak at  $\sim 7.8$  ppm is due to the two aromatic protons *ortho* to the aldehyde.<sup>11</sup>

(Figure 1). This remarkable sensitivity of the peak positions of the dithioacetal methine protons to the nature of the attached groups provided us a unique opportunity to quantify the different types of peripheral units present in the HBP and thereby pose some interesting questions about their role in heterofunctionalized HBPs.

Careful examination of the region between 4.8 and 5.1 ppm revealed the presence of three distinct peaks, presumably associated with the three different types of terminal units, namely, the two types of homo-T units and one hetero-T (see Scheme 2). In order to confirm these assignments, we carried out a model NMR-tube reaction, wherein 4-nitrobenzaldehyde and dimethyl acetal were reacted with a 1:1 mixture of triethylene glycol, monomethyl ether (MTRIG) monothiol, and dodecyl (C-12) thiol in the presence of iodine as the catalyst;<sup>12</sup> from Figure S1 (Supporting Information), it is evident that as the reaction proceeds the dimethyl acetal peak at  $\sim 5.5$  ppm disappears, and three peaks appear in the region 4.9–5.4 ppm. The intensity ratio of these three peaks was roughly 1:2:1, suggesting that the center peak was due to the dithioacetal linked to one MTRIG and one dodecyl segment (as expected for a statistically random process); the downfield peak was assigned to the homo-T with two TRIG segments and the upfield peak to the homo-T carrying two dodecyl groups. The assignment was further confirmed based on model compounds, didocosyl dithioacetal (Figure S4, Supporting Information), which showed a single peak at 4.86 ppm and the model hetero-T molecule (carrying one MPEG and one docosyl) having a methine peak at 4.96 ppm (Figures S2 and S3, Supporting Information). On the basis of these observations, it was clear that HB polydithioacetals provide a unique opportunity to better understand the finer nuances of self-segregation of peripheral segments: first, it provides a pseudodendritic HBP carrying readily transformable peripheral dimethyl acetal units; second, since the monothioacetal is relatively unstable, sequential reaction of the terminal dimethyl acetal units using MPEG and docosylthiols should lead to HBP systems carrying only the two types of homo-T units and no hetero-T units; and, third and most importantly, the quantification of each of these three types of terminal units should be readily possible from their proton NMR spectra.

To obtain the sample that is devoid of the hetero-T units, the parent HB polydithioacetal was reacted sequentially; first with docosylthiol and subsequently with MPEG-350 thiol. It was found that the reactivity of MPEG thiols toward formation of dithioacetal is significantly lower than that of docosylthiol; therefore, a slight excess of MPEG was taken in the second step to ensure complete transformation of residual dimethyl acetal units. The proton NMR spectrum of this sample, HBP-T2, clearly reveals the absence of the central methine peak due to the hetero-T units (see Figure 2); based on the relative

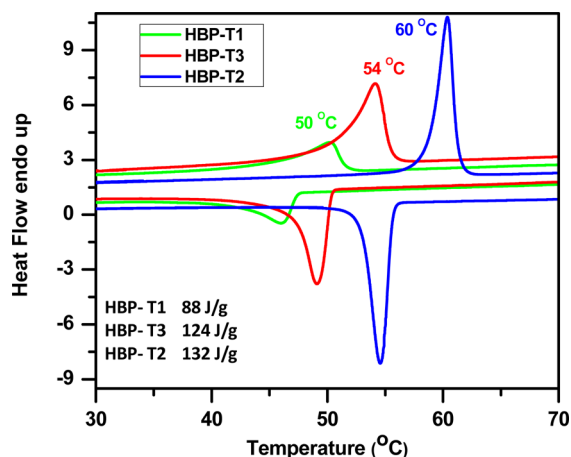


**Figure 2.** Expanded methine region of the proton NMR spectra of HBP-T1, HBP-T2, and HBP-T3. The most downfield peak at  $\sim 5.1$  ppm is due to a methine proton flanked by two MPEG units; the peak at  $\sim 4.96$  ppm is due to the methine proton attached to one MPEG and one docosyl unit; and the peak at  $\sim 4.85$  ppm corresponds to the methine proton attached to two docosyl units.

intensities of the peaks due to the two homo-T units, the peripheral composition was estimated to be 45:55 of docosyl and MPEG-350 units, respectively. It is important to recall here that the sequential reaction, in this specific system, leads to a HBP carrying only two types of homo-T's because of the rapid and irreversible transformation of the monothioacetal intermediate to the dithioacetal;<sup>11</sup> thus, no singly substituted terminal units would be formed, which would normally be expected if the reactivity of one B group of the terminal unit is unaffected by the other. The preparation of the third HBP that carries only the hetero-T units (HBP-T1) proved to be rather difficult; to achieve this we first prepared the hetero-T units separately from the dimethyl acetal precursor using a mixture of docosyl and MPEG-350 thiols, which yielded a statistical mixture of all three possible products (Scheme S1, Supporting Information). The product carrying a MPEG-350 and docosyl segments was chromatographically separated (see Figure S3, Supporting Information, for NMR); this compound was then hydrolyzed to yield the benzylthiol derivative, which was then used to cap the parent HB polydithioacetal. Despite several attempts, this process did not yield the final product in the desired purity; from the NMR spectrum (Figure 2), it is evident that the central methine peak at 4.96 ppm is the most intense peak, but peaks due to the other two are also present, although their intensities were considerably smaller. The mole fraction of the hetero-T units in this sample was estimated to be about 65 mol %; therefore, one might conclude that sample HBP-T1 is enriched in the hetero-T segments. Whereas HBP-T2 clearly exhibits only two types of methine protons implying that it contains no hetero-T units, HBP-T3 has a statistical distribution of all the three types of peripheral units, the majority of which is hetero-T units. HBP-T1, on the other

hand, carries primarily hetero-T segments along with a small but significant mol % of homo-T units. Despite our inability to prepare HBPs carrying only hetero-T units, we proceeded to compare the properties of these three distinct heterofunctionalized HBP samples. It is relevant to recall here that HBPs typically possess high dispersity in molecular weights; in addition, the present systems possess considerable variability in the relative amounts of different types of terminal groups and their distribution, all of which need to be considered while interpreting their macroscopic properties.

In order to compare the ability of the peripheral docosyl and MPEG segments to self-segregate, we first examined the DSC thermograms of the three samples; from Figure 3, it is evident

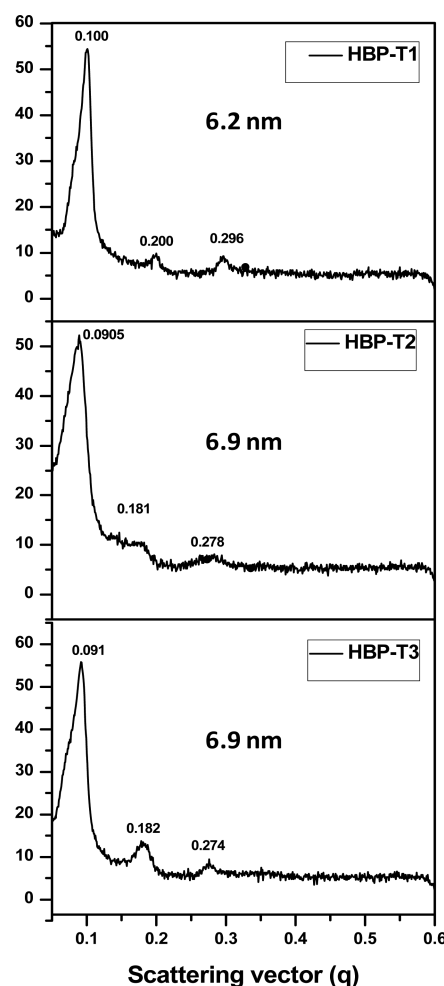


**Figure 3.** DSC thermograms of the three different peripherally heterofunctionalized polydithioacetals. The thermograms were recorded at a heating rate of 10 deg/min, and they represent the second scans; the reproducibility of the 2nd and 3rd scans was confirmed.

that a melting peak corresponding to the docosyl segment is seen in all three samples, although the transition temperatures were different. Furthermore, the sharpness of the peak also varied; the sharpest peak with the highest melting temperature was observed in the case of the sample devoid of any hetero-T units (HBP-T2), followed by the sample (HBP-T3) that was prepared in a single step leading to a statistically governed population of hetero-T units (~45 mol %), while the sample exhibiting the lowest melting peak was the one that contained the maximum mole fraction of hetero-T units (HBP-T1). Assuming that this melting transition is primarily arising from the crystalline phase formed by the self-segregated docosyl segments,<sup>8</sup> the enthalpy values were normalized with respect to the weight fraction of docosyl segments in the different samples, for better comparison; the normalized enthalpy values were also maximum (132 J/g) for the HBP-T2, followed by HBP-T3 (124 J/g) and then the HBP-T1 (88 J/g). It is clear that the sample carrying primarily hetero-T units (HBP-T1) does not self-segregate very effectively. Computational studies by Chute et al.<sup>10</sup> had indeed predicted that dendrimers that carry only hetero-T units at the periphery would not self-segregate; thus, while our studies based on hyperbranched polymers are broadly consistent with these predications, HBP-T1, carrying primarily hetero-T units, also shows a certain level of self-segregation of the peripheral segments. This is most likely to be a reflection of the presence of a finite amount of homo-T units in the sample, although one cannot rule out

contributions from the intrinsic topological differences between dendrimers and HBPs.

The small-angle X-ray scattering profiles (Figure 4) of the three HBP samples reveal the formation of a lamellar



**Figure 4.** SAXS profile of the different peripherally heterofunctionalized HBP samples; the data were collected at RT. The most intense peak represents the 001 reflection, while the two weaker peaks represent the 002 and 003 reflections, respectively.

morphology in all cases; the peaks corresponding to the 001, 002, and 003 reflections are clearly seen. One interesting observation is the significantly smaller spacing in the case of HBP-T1, which has primarily hetero-T units; the interlamellar spacing is 6.2 nm in the case of HBP-T1, while the spacing in the other two samples is 6.9 nm. Effective self-segregation of the alkyl and MPEG segments, and consequent crystallization of the alkyl segments, would cause the alkyl chains to adopt an extended all-*trans* conformation, which would explain the larger spacing in HBP-T2 and HBP-T3 samples. On the other hand, HBP-T1, which also exhibited a significantly lower melting temperature, exhibited a significantly smaller interlamellar spacing, both of which are consistent with the formation of less ordered crystalline domains by the alkyl chains.

In conclusion, we have synthesized, for the first time, heterofunctionalized HBPs with control over the nature of the placement of two immiscible segments, namely, C-22 alkyl chains and MPEG-350: one sample (HBP-T2) carries only two types of homofunctionalized terminal units; and the other



(HBP-T3) carries a statistically governed distribution of both homo- and heterofunctionalized terminal units; while the third sample (HBP-T1) carries primarily the heterofunctionalized terminal units. Comparing the properties of these three near-isomeric HBPs reveals that self-segregation of immiscible segments present on the periphery of the HBP best occurs in the sample that is devoid of hetero-T units, while in the sample that contains mostly hetero-T units, self-segregation is clearly more difficult; this is broadly consistent with the computational predications on dendrimers carrying only heterofunctionalized termini.<sup>10</sup> This can also be readily rationalized by recognizing that only a considerably smaller number of conformations of hetero-T segments would permit the collocation of the two immiscible segments. However, it also became evident that the HBP sample (HBP-T3) carrying a statistical distribution of all the three types of terminal units, the majority of which is of the hetero-T type, also appears to self-segregate reasonably well and form Janus structures; only a small difference in the quality of the self-segregated domains was discernible. Thus, contrary to intuition, randomly heterofunctionalized HBPs are clearly capable of self-segregation of peripherally located immiscible segments and provide an excellent alternative to generate Janus structures; therefore, given the simplicity of accessing such structures from readily available clickable HBPs,<sup>7</sup> several interesting properties could be imparted to these systems. The strong tendency for the long alkyl chains (C22) to crystallize, once colocalized, could be used to effectively stabilize the Janus structures; this could be exploited to create interesting molecular systems, such as for polar ordering of dyes, etc. Furthermore, computational studies of such statistically randomly functionalized HBPs would be of immense value to further understand the self-segregation process.

## ■ ASSOCIATED CONTENT

### Supporting Information

Detailed synthetic schemes and procedures, additional NMR spectral, and GPC data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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