Small supernumerary marker chromosomes:
A legacy of trisomy rescue?

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Abstract
We studied by a whole genomic approach and trios genotyping, 12 de novo, nonrecurrent small supernumerary marker chromosomes (sSMC), detected as mosaics during pre- or postnatal diagnosis and associated with increased maternal age. Four sSMCs contained pericentromeric portions only, whereas eight had additional non-contiguous portions of the same chromosome, assembled together in a disordered fashion by repair-based mechanisms in a chromothripsic event. Maternal hetero/isodisomy was detected with a paternal origin of the sSMC in some cases, whereas in others two maternal alleles in the sSMC region and biparental haplotypes of the homologs were detected. In other cases, the homologs were biparental while the sSMC had the same haplotype of the maternally inherited chromosome. These findings strongly suggest that most sSMCs are the result of a multiple-step mechanism, initiated by maternal meiotic nondisjunction followed by postzygotic anaphase lagging of the supernumerary chromosome and its subsequent chromothripsis.

KEYWORDS
chromothripsis, evolutionary trade-off, maternal meiotic nondisjunction, small supernumerary marker chromosome (sSMC), whole genome paired-end sequencing (WGS)
For a long time, de novo nonrecurrent small supernumerary marker chromosomes (sSMC) have been considered pieces of chromosomes predominantly derived from the pericentromeric regions or, in rare cases, from acenric portions that have acquired a neocentromere. Accordingly, in terms of genetic counseling, these sSMCs were handled as copy number gains, with genotype–phenotype correlations based on the presence/absence of dosage-sensitive genes, although a prognosis remained challenging in prenatal diagnosis even if no known disease-genes were present. However, over time evidences accumulated showing that, except for the recurrent sSMCs with mirror duplicated genomic regions, including i(12p), idic(15), i(18p), and idic(22), de novo sSMCs are private rearrangements that may be more complex than previously estimated. Most of them, either recurrent or nonrecurrent, are characterized by: (i) increased maternal age at conception, and (ii) a mosaic condition with a normal cell line and a second one with the sSMC (Malvestiti et al., 2014). Seldom, segmental uniparental disomy (UPD) or UPD for the chromosome by which the de novo sSMC is derived has also been reported (see for a review Kotzot, 2001; Liehr et al., 2015). Even more rarely, fluorescence in situ hybridization (FISH) or array-comparative genomic hybridization (array-CGH) have documented some sSMCs as constituted by noncontiguous regions of the same chromosome or the terminal regions of two different chromosomes (Rothlisberger, 2000; Vetro et al., 2012). Moreover, at least in some of the recurrent sSMCs, trios genotyping supported the presence of three genotypes with two being of maternal origin (Conlin et al., 2012; Roberts, Maggouta, Thomas, Jacobs, & Crolla, 2003; Wandstrat & Schwartz, 2000).

Our study, approved by the institutional review board of Meyer Hospital in Florence, on 12 de novo nonrecurrent sSMCs (Table 1 and Supp. Table S1), all but one associated with developmental delay and/or phenotypic abnormalities (Supp. Table S1), brings together all previous observations, demonstrating by a whole cytogenomics approach that the primary driver for de novo SMCs is a nondisjunction at the maternal meiosis followed by a partial trisomy rescue of the supernumerary chromosome present in the trisomic zygote, through chromothripsis-like processes. Trisomy, which is the most frequent chromosomal abnormality in humans and the leading cause of spontaneous abortions, is essentially linked to chromosome mis-segregation at the maternal meiosis with the risk for a trisomic conceptus increasing with the increase of maternal age (Frasniak et al., 2014; Nagaoka, Hassold, & Hunt, 2012). Trisomy rescue, reported in no less than 1–2% of first trimester invasive prenatal diagnosis (Hahnenmann & Vejerslev, 1997; Kalousek & Vekemans, 1996) and considered responsible for most false positive results by noninvasive prenatal screening (Hartwig, Ambye, Sorensen, & Jorgensen, 2017; Van Opstal et al., 2018) may save some of the embryos otherwise fated to be spontaneously aborted, leading to confined placental mosaicism where the abnormal cell line theoretically is isolated to the placenta and missing from amniotic cells or other fetal tissues. A probably less frequent phenomenon is a partial trisomy rescue in which only a part of the original trisomic chromosome is eliminated while a part remains, more often in the form of a supernumerary marker, in mosaic with a normal cell line. Cases in which the initial full trisomy could be documented by direct villus analysis with the subsequent partial correction leading to the presence of a sSMC are few (Srebniak et al., 2011; Vialard et al., 2009).

More numerous are the cases in which the presence of the de novo sSMC is accompanied by maternal hetero/isodisomy of the homologous chromosomes (Ahram et al., 2016; Liehr et al., 2015; Melo et al., 2015), a situation that can only be explained by a partial trisomic rescue of the supernumerary chromosome of paternal origin, after a nondisjunction event at the maternal MI. The same applies to those sSMCs in which three different haplotypes at the level of the marker chromosome and biparental origin of the single nucleotide polymorphisms (SNPs) along the normal homologs are detected, with the only difference that the trisomic rescue occurred on one of the two chromosomes of maternal origin. It is well known that anaphase lagging accounts for trisomy rescue of the supernumerary chromosome (Ly & Cleveland, 2017; Nicholson et al., 2015) which is then trapped within a micronucleus where massive shattering occurs after disruption of the nuclear envelope exposing DNA to the cytoplasm (Liu et al., 2018; Zhang et al., 2015). As a consequence, the supernumerary chromosome is eliminated in one daughter cell, thus explaining the presence of the normal cell line. After the re-embedding of the micronuclear material into the main nucleus where DNA repair occurs (Ly et al., 2016), a second cell line containing a supernumerary chromothripsed chromosome would form, composed of only parts of the original supernumerary chromosome stitched together in a noncontiguous order. Depending on which of the three homologs undergo anaphase lagging, the remaining two may be in maternal hetero/isodisomy (loss of the paternal one) or of biparental origin (loss of one of the maternal ones). Trios genotyping (Supp. Tables S2, S3, and S4) in cases sSMC2.b, sSMC7.a, sSMC7.b, and sSMC1 detected maternal hetero/isodisomy of the normal homologs while the paternal origin of the sSMC could be demonstrated only in cases sSMC2.b, sSMC7.b, but was inconclusive in cases sSMC1 and sSMC7.a. This condition fits with a maternal meiosis I (mat-MI) nondisjunction, followed by chromothripsis of the supernumerary chromosome of paternal origin. Case sSMC8.a, with two different maternal haplotypes and a paternal one within the chromosome 8-derived sSMC region, and biparental SNPs along the two normal chromosomes 8, also indicates a mat-MI nondisjunction as the first event, in this case followed by chromothripsis of one of the chromosomes of maternal origin. In contrast, in cases sSMC18, sSMC2.a, sSMC17, and sSMC11, the marker region has the same haplotype as the intact maternally inherited chromosome, with biparental origin of the SNPs and/or microsatellites along the two homologous chromosomes (Table 1, Supp. Tables S2, S3, and S4). Since the markers we studied are from the pericentromeric regions of the respective chromosomes of origin, where cross-overs are not expected to occur, this finding indicates either a previous maternal meiosis II (mat-MII) nondisjunction or a postzygotic event. Indeed, in a number of cases of trisomy rescue (Butler et al., 2018; Chantot-Bastaraud et al., 2017) a mat-MII error has been documented. Similarly, the mechanism leading to the formation of the supernumerary i(12p), associated with Pallister-Killian syndrome, has been proven to be prezygotic and of maternal origin, presumably occurring at MII as demonstrated by the presence of three genotypes at the distal 12p region and only two at the pericentromeric one (Blyth et al., 2015; Conlin et al., 2012). The only case not compatible with a maternal meiotic nondisjunction is sSMC8.b, whose
<table>
<thead>
<tr>
<th>Case (mosaic)</th>
<th>Mat age (yrs)</th>
<th>SMC</th>
<th>Homolog. chr</th>
<th>Predicted timing</th>
<th>sSMC construction</th>
<th>Breakpoint characteristics</th>
<th>Mechanism</th>
<th>Final interpretation</th>
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</thead>
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<tr>
<td>sSMC1</td>
<td>35</td>
<td>Pat</td>
<td>Mat UPD (hetero/isodisomy)</td>
<td>MI</td>
<td>Single fragment (15.7Mb)</td>
<td>Not validated</td>
<td>seq[GRCh37]+der(1) (p21.1→p11.2)</td>
<td></td>
</tr>
<tr>
<td>sSMC2.a</td>
<td>35</td>
<td>Mat (single allele)</td>
<td>Biparental</td>
<td>MI or postzygotic</td>
<td>4 Fragments (2.7Mb+4.5Mb+254.6 kb+704.7 kb)/disordered</td>
<td>Insertion 2 bp (TA), microhomology of 3 bp</td>
<td>alt-NHEJ or MMBIR</td>
<td>seq[GRCh37]+der(2) (q11.1→q11.2:q12.2::q11.2→q12.1)</td>
</tr>
<tr>
<td>sSMC2.b</td>
<td>44</td>
<td>Pat</td>
<td>Mat UPD (hetero/isodisomy)</td>
<td>MI</td>
<td>2 Fragments (2.2Mb+38.7Mb)/disordered/ring</td>
<td>Blunt fusion</td>
<td>NHEJ</td>
<td>seq[GRCh37]+r(2) (q11.1→q11.2::q32.2→q36.3)</td>
</tr>
<tr>
<td>sSMC7.a</td>
<td>NA</td>
<td>Pat</td>
<td>Mat UPD (hetero/isodisomy)</td>
<td>MI</td>
<td>3 Fragments (4.4Mb+1.2Mb+6.7 kb)/disordered/ring</td>
<td>17 bp insertion (LINE-1), blunt fusion</td>
<td>alt-NHEJ or MMBIR</td>
<td>seq[GRCh37]+r(7) (q11.21→p11.2→q11.2)</td>
</tr>
<tr>
<td>sSMC7.b</td>
<td>39</td>
<td>Pat</td>
<td>Mat UPD (hetero/isodisomy)</td>
<td>MI</td>
<td>Single fragment (12.4Mb)/Ring</td>
<td>Not validated</td>
<td>seq[GRCh37]+r(7) (p22.1→q11.23)</td>
<td></td>
</tr>
<tr>
<td>sSMC7.c</td>
<td>38</td>
<td>NA</td>
<td>Mat UPD</td>
<td>MI</td>
<td>Single fragment (9.9Mb)/ring</td>
<td>Not involved in WGS</td>
<td>47,XX.+mar.arr[GRCh37]d</td>
<td></td>
</tr>
<tr>
<td>sSMC8.a</td>
<td>NA</td>
<td>Mat (two alleles)</td>
<td>Biparental</td>
<td>MI</td>
<td>3 Fragments (2.9Mb+4.4Mb/1.6 Mb)/disordered/ring</td>
<td>3 bp, 16 bp, and 34 bp of nontemplated insertions and microhomology of 2 bp</td>
<td>alt-NHEJ or MMBIR</td>
<td>seq[GRCh37]+r(8) (p11.2→q11.23::q12.1→q12::q12:q12)</td>
</tr>
<tr>
<td>sSMC8.b</td>
<td>35</td>
<td>Pat (single allele)</td>
<td>Biparental</td>
<td>postzygotic</td>
<td>Single fragment (46.7Mb)</td>
<td>Microhomology of 7 bp</td>
<td>alt-NHEJ or MMBIR</td>
<td>seq[GRCh37]+der(8) (p23.1→q12.1)</td>
</tr>
<tr>
<td>sSMC8.c</td>
<td>33</td>
<td>Pat</td>
<td>Mat or MII</td>
<td>MI or MII</td>
<td>3 Fragments (4.4Mb+8Mb+6.7Mb)/ring</td>
<td>Not involved in WGS</td>
<td>47,XX.+mar.arr[GRCh37]d</td>
<td></td>
</tr>
<tr>
<td>sSMC11</td>
<td>39</td>
<td>Mat (single allele)</td>
<td>Biparental</td>
<td>MI or postzygotic</td>
<td>14 Fragments (~9.1Mb in total)/disordered/ring</td>
<td>6 bp and 30 bp templated insertions, 11 bp, 13 bp, 14 bp, and 30 bp nontemplated insertions, 2 blunt fusions, 3 bp, and 8 bp microhomologies</td>
<td>NHEJ/alt-NHEJ/MMBIR-Alu mediated</td>
<td>seq[GRCh37]+r(11) (p11.2→q12.1:q12.1::p15.5:p15.4::p11.2×q12.1)</td>
</tr>
<tr>
<td>sSMC17a</td>
<td>39</td>
<td>Mat (single allele)</td>
<td>Biparental</td>
<td>MI or postzygotic</td>
<td>3 Fragments/disordered</td>
<td>36 bp insertion (LINE-1)</td>
<td>alt-NHEJ</td>
<td>seq[GRCh37]+der(17) (q11.2::p11.2→q12.1)</td>
</tr>
<tr>
<td>sSMC18b</td>
<td>24</td>
<td>Mat (single allele)</td>
<td>Biparental</td>
<td>MI or postzygotic</td>
<td>2 Fragments (74.4kb+7.5Mb)/ordered/ring</td>
<td>Microhomology of 4 bp, microhomology of 4 bp</td>
<td>alt-NHEJ or MMBIR</td>
<td>seq[GRCh37]+r(18) (q11.1→q12.3→q12.1)</td>
</tr>
</tbody>
</table>

The following abbreviations are used: NA (not available), homolog (homologous to the sSMC), chr (chromosome), mat (maternal), pat (paternal), UPD (uniparental disomy), MI (meiosis I), MII (meiosis II), NHEJ (nonhomologous end joining), alt-NHEJ (alternative NHEJ), MMBIR (microhomology mediated break induced replication), WGS (whole genome sequencing).

*aMaternal origin of sSMC17 was previously demonstrated (Vetro et al., 2012)

*bMaternal origin of sSMC18 and biparental origin of homologous chromosomes were previously demonstrated (Rothlisberger, 2000).

cPaternal origin of SMC was assumed although microsatellite data were inconclusive.

dSee table S1 for the detailed description of array-CGH analysis.
haplotype was paternal while the normal homologs were biparental (Table 1, Supp. Tables S2, S3, and S4). Thus, in this case, we have to assume a postzygotic nondisjunction of the paternal chromosome 8, followed by chromothripsis of the supernumerary 8, and recovery of its pericentromeric region.

Overall, we can conclude that the origin of the sSMC from a trisomy caused by maternal nondisjunction error at meiosis I, was directly demonstrated in four cases with hetero/isodisomy UPD (sSMC2.b, sSMC7.a, sSMC7.b, and sSMC1) and in one case (sSMC8.a) with two maternal alleles on the marker region, while in five cases (sSMC18, sSMC2.a, sSMC17, sSMC11, and sSMC8.c), the demonstration of a maternal meiotic error was indirect (Table 1). Remarkably, in all of these cases except for sSMC18 the maternal age at birth (Table 1) was increased (37.4 years on average), in agreement with a triggering event of maternal meiotic nondisjunction. To get further insight into the sSMCs structure and their breakpoint characteristics, we performed paired-end whole genome sequencing (WGS) (Supp. Table S5) in 10 out of the 12 cases, using Illumina TruSeq DNA PCR Free library, with DNA isolated from blood in 8 cases, abortive tissue in 1 case (sSMC2.b) and amniotic fluid in 1 case (sSMC11), and tried to confirm all possible breakpoints by PCR and Sanger Sequencing. Indeed, a full reconstruction of the sSMCs with Sanger confirmation of all the WGS breakpoints was successful only for sSMC18, while we failed to confirm 22 out of the total 60 WGS breakpoints. Anyway this analysis (Table 1, Supp. Table S6, and Supp. Figures S1–S13) revealed that the sSMCs in 7 out of 10 cases, in addition to the pericentromeric region, contained one or more additional segments from their corresponding chromosomes, which were disordered assembled, a finding highly suggestive of a chromothripsis event. Notably, previous CGH or SNP+CGH array investigations had highlighted a noncontiguous constitution only in four of these cases (Supp. Table S1 and S6). Among the 60 WGS breakpoints we identified within the duplicated regions (4 in sSMC18, 7 in sSMC2.a, 4 in sSMC2.b, 5 in sSMC7.a, 6 in sSMC17, 6 in sSMC8.a, 2 in sSMC8.b, 2 in sSMC7.b, 2 in sSMC1, 22 in sSMC11), we could fully characterize 19 fusion junctions (Supp. Table S6), which showed chromothripsis signatures such as blunt fusions (4: one in sSMC2.b and sSMC7.a, two in sSMC11), 2–8 bp microhomology (7: one in sSMC2.a, sSMC8.a, and sSMC8.b, two in sSMC11 and sSMC18), and 2–36 bp insertions (12: one in sSMC2.a, sSMC7.a and sSMC17, three in sSMC8.a, and six in sSMC11), indicating predominantly repair-based (NHEJ or alt-NHEJ) mechanism (Table 1). Similar sequence signature has been observed in rearrangements proposed to be formed by a replicative-repair mechanism, MMBIR (Carvalho & Lupski, 2016), which uses microhomology to restore a collapsed replication fork. On the other hand, in most of our cases, genotyping analysis on whole chromosome and not only on the duplication region showed that the duplication was the residual portion of the third chromosome rather than emerging through a microhomology-driven DNA synthesis. Among the insertions, two were Line-1 elements (sSMC7.a and sSMC17) and two were small insertions coming from distal portions of the same chromosome (sSMC11), while the remaining ones were nontemplated. Approximately 62% of the breakpoints detected by WGS were located in repeated regions and 20% of these repeats were LINE elements. Based on the Sanger sequencing data covering 400 bp downstream and upstream of the fusion junction we did not observe further de novo point mutations. In all but two cases (sSMC1 and sSMC7.b), the sSMC had one of the breakpoints falling within the centromeric alphoid sequences, which impaired the complete characterization of the breakpoint sequences. Only in case sSMC18 (Supp. Figure S1), in which the sSMC was constituted by the fusion of the two noncontiguous duplicated segments, 18b and 18d, we were able to identify both the two novel fusion junctions in spite one involved the alphoid sequences: BPI_18b(+)_18d(+)(chr18:18594804::chr18:41472065) and ring closure junction Ring_18d(+)_Alphoid(chr18:49040431::Alphoid DNA L1.84 of chromosome 18). Absence of telomere sequences, as demonstrated by metaphase FISH analysis using telomere specific (TTAGGG) PNA probes, supported its ring constitution. In case sSMC8.a (Supp. Figure S2), the initial SNP+CGH array indicated the marker as constituted by a single copy number gain at 8p11.21p11.1, while NGS data showed that the discordant reads, at the edge of the chr8:40082798-53561524 pericentromeric region, mapped also at two distally located additional copy number gains (fragments 8f at chr8:60002688-60002774 and 8d at chr8:55759348-55759565). Sanger confirmation allowed imputing the exact closure junction, thus indicating a ring structure, also supported by the TTAGGG FISH analysis. In case sSMC2.a (Supp. Figure S3), we identified four separate copy number gain regions with different levels of coverage, indicating triplication of fragment 2b (chr2:95326241-98026880), showing a 3–4x relative coverage, duplication of a fragment 2c (chr2:98058590-102613162), suggested by its 3x relative coverage, and mosaic duplications of fragments 2d (chr2:102613,162-102867861) and 2f (chr2:106555286-107260062), both having 2–3x relative coverage. Although discordant reads were detected only at the end of fragment 2c, a novel fusion junction was highlighted by Sanger, between fragments 2c and 2f (chr2:102613162::chr2:106555286), thus demonstrating their disordered orientation. In this case, the presence of duplication and triplication copy number gains, suggested the involvement of a chromoanasynthesis event as recently reported for a maternally inherited sSMC9 (Grochowski et al., 2018). In case sSMC11 (Supp. Figure S4), NGS analysis revealed an unexpected complexity compared to the initial array-CGH data in which a single de novo 9,1Mb pericentric duplication between 11p11.2 and 11q12.1 was detected. A second duplication at distal 11p (Supp. Figure S4) is a false, possibly related to the control DNA. Indeed the same duplication was shown in all the DNAs analyzed by array-CGH using this specific control DNA kit, including those of the mother and her partner. Coverage analysis after WGS revealed a series of duplicated portions spanning the entire 11p up to 11q12.1. Discordant reads at the breakpoints of each copy number gain region, revealed a total of 14 fragments, where 13 were stitched together in a disordered pattern. By Sanger sequencing, we could solve 8 out of the 12 novel fusions. A ring chromosome constitution was suggested by the absence of telomere sequence on sSMC11. Remarkably, we detected Alu–Alu mediated recombination at six fusion junctions (Supp. Figure S5). Involvement of Alu elements in constitutional chromothripsis was recently reported in a family (Nazaryan-Petersen et al., 2016).
Gene disruptions were detected in 29 out of 60 breakpoints (Supp. Table S6), 28 of them occurring within introns while one was exonic. Only in case sSMC11, a possible fusion gene was predicted as a result of the fusion of two truncated genes (PHF21A-SLC39A13).

As a whole, our data show that the trigger for the formation of de novo nonrecurrent sSMCs is a maternal meiotic nondisjunction followed by a postzygotic chromothripsis event, due to anaphase lagging and repositioning of one of the trisomic chromosomes within a micronucleus. It seems likely that the formation of the new chromosome after the massive shattering that occurred following anaphase lagging, depends on stochastic events, in the context however of some main limitations such as the propensity of the broken ends of the various fragments to integrate with each other, and the selection of more capable cells to survive and multiply in the presence of supernumerary chromosomal portions. Centric fragments (b and dbe in Figure 1) should be easily preserved as sSMC, provided that they assume a ring...
conformation to compensate for the absence of telomeric sequences at both ends. Indeed FISH analysis in sSMC18, sSMC2.b, sSMC7.a, sSMC8.a, sSMC7.b, sSMC11, sSMC7.c, and sSMC8.c, whose small size made it impossible if understand if they were linear or circular structures, demonstrated the absence of the telomeric sequences, thus supporting their ring conformation. In contrast, chromothripsed fragments equipped with both centromeric and telomeric sequences at one end only (ab in Figure 1), may be stabilized provided that they capture a telomeric region from another chromosome, thus forming a linear de novo derivative supernumerary marker chromosome (cases 3 and 4 in Vetro et al., 2012). Instead, the preservation of supernumerary interstitial acentric fragments (de in Figure 1) would require a neoacentromerization event as indeed demonstrated in some sSMCs (Klein et al., 2012) and their circularization (Figure 1). The case reported by Kato et al. (2017) of a de novo interstitial translocation derived by chromothripsis of a supernumerary chromosome present in a trisomic zygote, demonstrates that acentric interstitial fragments may also be captured by another chromosome (Figure 1). In contrast, chromothripsed fragments equipped with telomeric sequences but without centromere (f in Figure 1) may be captured by a nonchromothripsed chromosome which, by losing its distal portion, generates a de novo unbalanced translocation, as recently demonstrated for a number of them (Bonaglia et al., 2018).

In conclusion, our findings give account of all the peculiarities associated with de novo sSMC: maternal meiotic nondisjunction, which is the prelude to the formation of the sSMC, explains the increased maternal age reported in most de novo cases; anaphase lagging of the supernumerary chromosome and its subsequent insertion within a micronucleus that segregates to one of the two daughter cells, accounts for the mosaic condition with a normal cell line and a second one containing the sSMC; maternal (segmental) UPD occurs whenever the partial trisomy rescue affects the chromosome of paternal origin; chromothripsis explains why some sSMCs are formed by noncontiguous regions of a given chromosome. This multiple-step mechanism underlying the formation of most nonrecurrent de novo sSMCs identifies a link between numerical and structural chromosomal anomalies and indeed suggests investigating how frequently other structural anomalies such as some unbalanced de novo translocations and insertions may be the final result of a mechanism initiated by a trisomy (Bonaglia et al., 2018; Kato et al., 2017), passing through the elimination of the supernumerary chromosome by anaphase lagging and subsequent chromothripsis, as already anticipated (Janssen, van der Burg, Szuhai, Kops, & Medema, 2011). On the other hand, from the point of view of genetic counseling, the discovery of such a multiple-step mechanism reveals a bitter truth, that is that the prognosis for those sSMCs identified in prenatal diagnosis will be infeasible. Indeed within a chromosome formed by multiple pieces, disruption of higher-order chromatin organization such as topologically associating domains (Spielmann, Lupiáñez, & Mundlos, 2018) will occur. The final effect of altered gene dosage, potential for dysregulation and for formation of new genes by gene fusion (Spielmann et al., 2018), all in a mosaic state, will be a highly problematic cocktail.


SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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