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Research Article

Cancer Prevention Research

Methyl Selenocysteine: Single-Dose Pharmacokinetics in Men

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Abstract

The recently published report of the SELECT evaluation of selenium and vitamin E provided strong evidence that selenium 200 μg per day in the form of selenomethionine does not protect selenium-replete men against prostate or any other cancer. This seems to refute the result of the much smaller Nutritional Prevention of Cancer (NPC) trial of selenium. Because SELECT did not test the NPC agent, it is possible that the difference between the two trials stems partly from the use of different agents: selenomethionine in SELECT, and selenized yeast in the NPC trial. One of the organic selenium forms suspected of having strong chemopreventive effects, and which may have been present in the NPC agent, is methyl selenocysteine. This study characterizes the single-dose pharmacokinetics of methyl selenocysteine. *Cancer Prev Res; 4(11); 1938–44. ©2011 AACR.*

Introduction

Selenium is an essential nutrient (1); inadequate selenium nutrition has been associated with increased cancer vulnerability (2–6). However, the results of chemoprevention trials using different forms of selenium at supranutritional levels have been largely disappointing.

In the Nutritional Prevention of Cancer (NPC) trial, administration of 200 μg selenium per day in selenized yeast to nonmelanoma skin cancer patients was associated, after 7.4 years, with substantially decreased total cancer incidence, especially of the lung, colon, and prostate, and with decreased total cancer mortality (7–9). These endpoints were, to be sure, secondary to the primary endpoint of nonmelanoma skin cancer recurrence: supplementation actually increased recurrence (10). The association of selenium supplementation with decreased risk was especially marked for prostate cancer (8). In a large trial largely motivated by NPC, Karp and colleagues randomized more than 1,500 patients with resected non–small-cell lung cancer to selenized yeast or to placebo; the trial, designed for a 4-year treatment period, was halted after futility analysis showed that the endpoints of second primary tumors and progression-free survival were not likely to be different in selenium and placebo groups (11). In the much larger SELECT study, closed after subjects were followed for an average of 5.5 years, a 200 μg per day supplement of selenium in the form of selenomethionine (SeMet) had no impact on the incidence of prostate or any other cancer (12). Comparisons between the NPC and SELECT studies bring to light 2 differences of potential importance to the outcomes of the 2 studies. First, different forms of selenium were used in the 2 tria ls (7,12, 13): SeMet in SELECT, and selenized yeast in NPC. On the other hand, the agent of the randomized trial led by Karp and colleagues was selenized yeast (largely selenomethionine; ref. 11) and that showed no evidence of effectiveness. Another possible source of differences among these trials is that substantial numbers of the subjects in the NPC trial were close to being selenium deficient, whereas few of those in the lung cancer trial or SELECT were close to being selenium deficient; the mean baseline plasma selenium level of NPC participants was approximately 115 ng/mL and that of SELECT participants approximately 136 ng/mL (7, 8, 12).

The mechanisms by which selenium might inhibit carcinogenesis or otherwise serve as a chemopreventive agent are not known. It has been proposed, but not proven, that a key mechanism may be protection against oxidative stress (14–20). Selenium supplies important proteins that provide protection against oxidative stress (14, 21) so that those with inadequate selenium stores might be at increased risk; whether supranutritional doses of selenium would decrease oxidative stress further and thus protect against carcinogenesis is less clear.

Two major forms of selenium have been widely used in supplementation: SeMet and selenite. SeMet and selenite are metabolized to hydrogen selenide and then to methylselenol: both of these metabolites may exert chemopreventive activity (22–25). Hydrogen selenide is critical to the formation of selenoproteins (25, 26). Methyl selenol, with

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redox activity and possible effects on signaling, may be a key selenium metabolite in cancer prevention (21). SeMet is incorporated into cellular proteins in place of the sulfur-containing amino acid methionine. Given that methionine is common to all proteins, the displacement of a functionally important sulfur atom by selenium has the potential to alter protein structure and function. With continued ingestion, the pool of SeMet accumulates over time within the body; plasma levels increase, virtually without limit, even if toxicity develops (27). Selenite is nonorganic; approximately 35% of a single 200 μg dose is excreted in urine or feces within 12 days (22). In contrast, only approximately 15% of SeMet will have been similarly excreted within 12 days (23). Plasma selenium from these forms reaches a peak at approximately 8 hours and persists for up to 24 hours. Approximately equal amounts of selenium in selenite are recovered from urine and feces (22), whereas twice as much selenium in SeMet is recovered from urine as from feces. An unidentified selenium isoform present in the NPC yeast, possibly methyl selenocysteine (MSC), may have been at least partly responsible for its apparent effects (13).

MSC is water-soluble, absorbed in mammals from the gastrointestinal tract, and readily transformed to methylselenol (21, 24, 28). Methylselenol can be demethylated to yield selenide (29, 30) or methylated to yield dimethyl selenide and then released in the breath; methylated again, it yields trimethyl selenonium, which is excreted in urine. The role of selenium in cancer risk would be clarified by increased understanding of the pharmacokinetics of this methylated selenium compound. The purpose of this study was to characterize the toxicity and the pharmacokinetics of MSC in humans.

Methods

An Institutional Review Board–approved, phase I single-dose, dose-escalation pharmacokinetic/toxicity study of MSC was conducted at Roswell Park Cancer Institute (RPCI). Healthy male volunteers were recruited as subjects by public announcement in Buffalo, NY. After granting informed consent verbally and in writing, subjects were randomized, double-blinded, to receive either a single dose of MSC at 1 of 3 different concentrations or placebo. In the first wave, 5 patients received 400 μg of selenium and 1 received placebo; in the second wave, 5 patients received 800 μg of selenium and 1 received placebo; in the third wave, 5 patients received 1,200 μg of selenium and 1 received placebo. The intent of placebo group inclusion was to decrease the likelihood of participant reporting of inconsequential, subjective symptoms. The placebo arm experience is included in the results, although the statistical precision of estimates, with only 3 subjects, is very limited. Subjects were required to have normal hepatic, renal, and bone marrow functions as assessed by history, physical, and clinical chemistry analysis. They could not have given blood within 30 days of MSC administration, had to be 18 years or older, had to have an Eastern Cooperative Oncology Group (ECOG) performance status (31) of 0 or 1, and to weigh between 50 and 115 kg. Eligibility was restricted to males, because the most powerful effect of selenium was believed to be against prostate cancer. Subjects could not be taking prescription or nonprescription drugs, vitamins, or herbal supplements known to affect gastric acidity within 3 days of drug administration. Subjects arrived at RPCI at 7:00 AM on the day of their pharmacokinetic analysis after a fast beginning at 10:00 PM the previous night. After a brief review of concurrent medications, vital signs, and symptoms, subjects had an intravenous catheter placed in one arm. A baseline predose blood sample was drawn through the catheter, after which subjects ingested the assigned agent along with 8 ounces of water, under direct supervision. Subjects remained in hospital for 12 hours, returning at 24 and 48 hours. In each cohort of 6 men, 5 were randomized to MSC and 1 to placebo. Blood was drawn at baseline and at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 24, and 48 hours after dosing. Urine was collected within time spans of 0–4, 4–8, and 8–12 hours and at 12 and 24 hours. Subjects in the first, second, and third cohorts received 400, 800, and 1,200 μg of selenium in the form of MSC or placebo, respectively. All subjects in each cohort were treated and evaluated for toxicity before treating subjects on the next cohort. The occurrence of grade 2 or greater toxicity thought at least possibly due to drug was to preclude escalation to the next higher dose.

Methods: Statistics

Quantitative descriptors of subjects—age, race, baseline plasma selenium, toenail selenium, height, weight, and ECOG performance status (31)—were compared by means and SDs. Statistical significance of between-group differences was evaluated by one-way ANOVA. The statistical significance of category variation in race (white or nonwhite) among the treatment groups was considered by the χ^2 test. Baseline comparisons among the 4 different treatment groups showed no statistically or substantively significant difference in age, race, plasma or toenail selenium levels, height, weight, or ECOG performance status (Table 1). The ECOG score ranges from 0 to 5, with zero indicating that the subject is fully active and able to carry on all activities of daily living without restriction and 5 indicating death. That the mean ECOG score was zero means that subjects were in general quite healthy, experiencing no noteworthy limitations.

The pharmacokinetic parameters of maximum concentration (C_{max}) and area under the curve (AUC) were compared using one-way ANOVA, with $\alpha = 0.05$. Paired comparisons were used to evaluate the significance of mean differences of each treatment group from the placebo group. The pharmacokinetic program WinNonlin was used to estimate half-life for each dose-specific treatment group. Box-plot graphics were also used to describe in more detail differences in C_{max} and AUC. As the statistical power of the comparison of each group to the placebo patients is limited by the small number of placebo patients, interpretation of the findings is necessarily conservative.

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Table 1. Comparison of placebo and selenium groups at baseline

Characteristics	Study assignment (*n*)			
	Placebo ($n = 3$)	400 μg ($n = 5$)	800 μg ($n = 5$)	1,200 μg ($n = 5$)
Age, y	39 (17)	28 (8.0)	33 (14.1)	33 (14.5)
Race (% European American)	100	80	100	100
Plasma selenium, ng/mL	134 (3.8)	136 (17.1)	127 (18.8)	114 (14.3)
Toenail selenium, μg/g	0.89 (0.122)	0.94 (0.063)	0.90 (0.050)	0.99 (0.146)
Height, m	1.89 (0.091)	1.83 (0.140)	1.80 (0.084)	1.78 (0.124)
Weight, kg	103 (12.9)	97 (14.9)	82 (15.1)	98.9 (19.1)
ECOG performance status (0–5); ref. 39	0	0	0	0

NOTE: All values are mean (SD).

Toxicity was evaluated in all subjects. History was reviewed at baseline; physical examinations were conducted at baseline, at 12 hours, and at 1 week postdose. Vital signs were checked at baseline, at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, and 48 hours, and at 1 week postdose. Clinical laboratory studies, which included a hemogram, aspartate aminotransferase/alanine aminotransferase, total bilirubin, serum electrolytes with blood urea nitrogen and creatinine, and urinalysis, were conducted at baseline, 24 hours, and 1 week postdose. At 30 days postdose, subjects were contacted by telephone for toxicity assessments. All toxicities for all consented subjects were recorded and graded according to the National Cancer Institute's Common Toxicity Criteria (CTC) version 3.0.

Results

The primary endpoint of this study was toxicity. A total of 25 adverse events were reported in 18 subjects (Table 2); all were grade 1. We observed no association between assignment to MSC and the occurrence of adverse events, nor was any association between the dose of MSC and the occurrence of adverse events apparent.

Figure 1 describes the courses of mean plasma selenium concentration among subjects. Each subject's plasma selenium is expressed as a deviation from its baseline level. The most distinct concentration curve is for the 1,200 μg dose, although the curve of the 800 μg dose slightly exceeds that of the 400 μg dose and that of the 400 μg dose exceeds that of placebo. For those receiving MSC, maximum concentration times are similar, ranging between 3 and 5 hours for the 400 through 1,200 μg cohorts.

The pharmacokinetic parameter estimates of those curves are in Table 3. Mean C_{max} for the placebo group reflects values of 9, 10, and 11 ng/mL; 2 of these maximum values are seen near 24 hours, and the other at around 4 hours. The mean C_{max} increases in a dose–response fashion from 10 for placebo to 22.8, 30.75, and 63.2 ng/mL for 400, 800, and 1,200 μg dose subjects, respectively. Mean C_{max} for the 1,200 μg dose subjects is significantly and substantially greater than that of placebo subjects: approximately twice that of subjects who received the 800 μg dose. For those receiving MSC, mean C_{max} times are similar, ranging between 3 and 5 hours for the 400 to 1,200 μg

Table 2. Adverse events in subjects on study

MSC dose	Adverse event		
	Type	Grade[a]	Number of subjects
Placebo	Hypercholes -terolemia	1	1
	Hyperkalemia	1	1
	Elevated aspartate aminotransferase	1	1
400 μg	Anemia	1	1
	Hypernatremia	1	1
	Skin abrasion	1	1
	Blurry vision	1	1
	Hyperglycemia	1	1
	Headache	1	1
	Hyperkalemia	1	1
	Musculoskeletal pain	1	1
	Light headed (during blood draw)	1	1
800 μg	Dysgeusia	1	1
	Urinary frequency	1	1
	Hyperkalemia	1	1
	Diarrhea	1	1
	Sore throat	1	1
	Hypercholesterolemia	1	1
	Hyperglycemia	1	1
	Leukopenia	1	1
1,200 μg	Sore throat	1	1
	Bronchospasm	1	1
	Hypernatremia	1	1
	Hyperglycemia	1	1
	Headache	1	1

[a]NCI CTC version 3.0.

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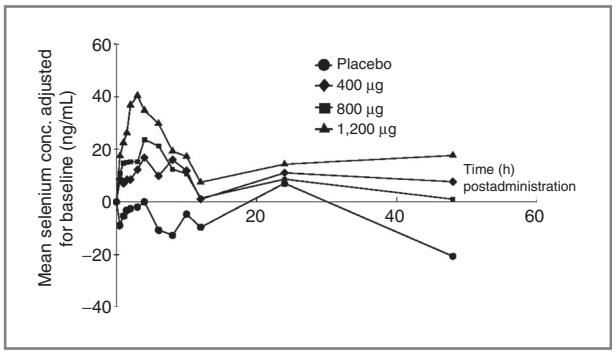

Figure 1. Mean plasma selenium concentration versus time by dose.

cohorts. The time of C_{max} for the 1,200 μg cohort is in fact the shortest.

Figure 2 describes in greater detail the pattern of C_{max} among the 4 treatment groups. In this box-plot graphic, the longest horizontal bar refers to the median, and the shorter bars to the 25th and 75th percentile values. The individual subject values are displayed with distinct symbols for the different doses. It can be seen that C_{max} increases substantially with increased selenium dose. The increase is not monotonic, however, as median C_{max} of the 1,200 μg dose is roughly 3 times that of the 400 μg dose, twice that of the 800 μg dose.

AUC values are also given in Table 3. The mean and median values for the 400 and 800 μg cohorts are greater than those of the placebo cohort, and their excesses over those of placebo statistically significant. However, the mean and median AUC of the 1,200 μg cohort are nearly twice those of the 800 μg cohort. It is not possible to derive convergent estimates of half-life for subjects receiving the 400 or 800 μg doses; for those who received 1,200 μg, however, half-life is estimated to be 29 hours (not shown). Figure 3 graphically describes this analysis: the AUCs of both the 400 and 800 μg doses are elevated, although the difference is slight; the elevation of the 800 μg dose is significantly greater than that of the placebo. On the other hand, the AUC for the 1,200 μg dose is significantly greater than that of placebo, nearly twice that of the 800 μg dose.

Figure 4 describes urinary concentration of selenium for subjects receiving each dose by interval of excretion. Because the baseline levels of subjects were in general below the level of detection, those concentrations are not expressed as deviations from baseline levels. Most of the urine values for subjects receiving placebo remain below the limits of detection, so these are not presented. The mean values of subjects who received 400 or 800 μg of selenium exhibit discernible peaks 4 to 8 hours postdose. Excretion among subjects who received the 800 μg dose is slightly higher than that of subjects who received 400 μg. For subjects receiving 1,200 μg selenium, the mean peak concentration is approximately twice that of subjects who received 400 or 800 μg doses; the maximum point of this excretion is seen 8 to 12 hours postdose.

Table 3. Pharmacokinetic parameter estimates

	C_{max}, ng/mL	AUC, ng h/mL
Placebo		
Mean (SD)	10.0 (1.00)	<0 (*x*)
Median	10.0	<0
CV%	10.0	–
400 μg		
Mean (SD)	22.8 (9.9)	427.1 (276.5)
Median	21.0	435.5
95% CI	(−25.5 to 51.1)	(−79.6 to 934.0)
800 μg		
Mean (SD)	30.75 (8.4)	567.5 (243.0)[a]
Median	30.5	648.75
95% CI	(−19.3 to 60.8)	(37.6 to 1,100)
1,200 μg		
Mean (SD)	63.2 (27.8)[a]	1,077.9 (203.3)[a]
Median	57.0	1,055.3
95% CI	(14.9–91.5)	(571–1,580)

[a]$P < 0.05$; determined by comparison of each dose group (400, 800, and 1,200 μg) with placebo group.

Discussion

These data represent a first examination of MSC as administered to humans. There was no evidence of toxicity.

A substantial body of preclinical data indicates that selenium is important to protection against oxidative stress (14–21, 29, 32–34). Selenium deficiency is also associated with increased cancer risk (22, 23, 35, 36); whether supplementation of those who are selenium deficient might decrease vulnerability to oxidative stress is not well known, as well as whether an agent that protects against oxidative stress would protect against carcinogenesis. SELECT suggests that among men who are selenium replete, selenium offers no such protection (12).

Preclinical toxicology studies of MSC—long and short term—have been conducted by the National Cancer Institute through the Division of Cancer Prevention (DCP) Rapid Access to Preventive Intervention Development (RAPID) Program (37). The studies conducted on rats and dogs showed dogs to be the most sensitive species. The no adverse effect level after 28 and after 90 days of dosing in dogs based on histopathologic and hematologic findings was 0.3 mg MSC/kg body weight per day (0.13 mg selenium/kg body weight per day); an equivalent value extrapolated to humans for a 70 kg person is 21,000 μg MSC per day, or 9,100 μg selenium per day. Single bolus doses of MSC were largely converted to excretory metabolites in breath and urine; even chronic high doses of MSC may lead to very modest tissue accumulations of selenium (34, 36). NCI DCP–sponsored genotoxicity studies with MSC were negative (37).

Selenium is a natural dietary constituent so that varying baseline concentrations were present in the plasma of

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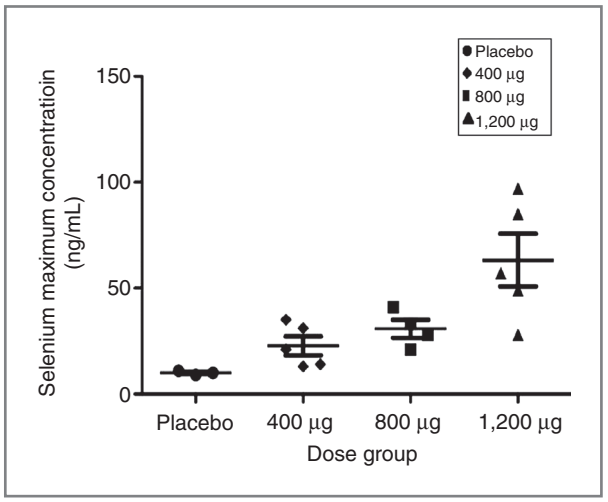

Figure 2. Selenium C_{max}* adjusted for baseline levels by dose group.

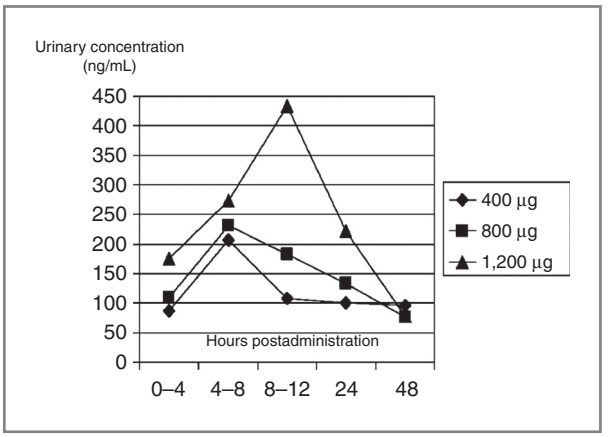

Figure 4. Mean urine selenium concentration both by selenium dose and by time postadministration.

subjects. To accurately gauge the pharmacokinetic parameters, we took these baseline values into consideration. It will be important to take a similar approach in future investigations. This factor, along with the single-dose nature of the study design and the relatively low doses investigated, limits the conclusions that can be drawn. However, these are inherent to the study of a first-time in-human chemopreventive agent and represent safeguards purposefully built into the design of the study. These factors notwithstanding, this study provides some important initial findings.

There was little difference in the pharmacokinetic parameters of the 400 and 800 μg doses. The values observed were clearly above those observed in the placebo cohort. There are important differences when the 1,200 μg cohort is compared with the other 2 MSC cohorts. Together, they are consistent with the possibility of saturation in metabolism and/or excretion. This is supported by the finding of a shorter time of maximum concentration in the 1,200 μg cohort; this time trends downward as dose increases, and it is coupled with a delay in the peak urinary excretion time. The time of maximum concentration for the 1,200 μg dose of MSC seems to be shorter than for SeMet (23), although it needs to be evaluated in a direct pharmacokinetic comparison.

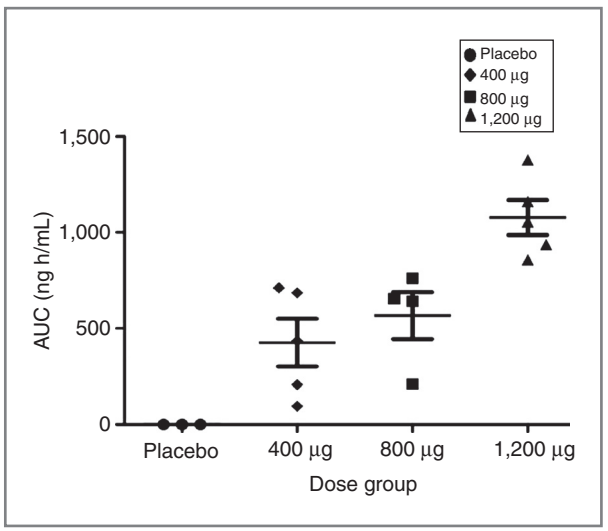

Figure 3. Selenium AUC adjusted for baseline levels by dose group.

The C_{max} and AUC for the 1,200 μg cohort are proportionally greater than the respective values for the 800 μg cohort. There are several potential implications to this for design of multidose studies. Specifically, given the possibility for accumulation, multidose studies should not exceed the 1,200 μg dose until additional information becomes available. This value is approximately one-eighth the value extrapolated from tests on the most sensitive nonhuman mammal. Second, this finding is not consistent with MSC moving into a large storage reservoir. This contrasts sharply with SeMet; as SeMet accumulates within essentially all proteins, the body provides a vast storage reservoir. This may explain why selenium concentration increases so directly with multiple doses of SeMet.

Preclinical research indicates that MSC provides a more efficient route than SeMet for the formation of methyl selenol, a metabolite that may impart a chemopreventive effect (24, 25, 35, 38). It will be important in the future to accurately speciate methyl selenol and related plasma selenium metabolites. This represents an evolving field, and work is actively progressing (30, 36). Once the technology is in place, it can be applied to stored samples. The major downstream protein products of selenium supplementation, selenoprotein P and glutathione peroxidase, which are the key and most abundant selenoproteins in plasma, can be readily evaluated. Indeed, given that the function of selenium resides primarily in the proteins to which it gives rise, a focus on these key selenoproteins may be highly informative (27). Analysis of these is under way.

The work by Ip and colleagues suggests that MSC might prove more physiologically relevant than SeMet or selenite.

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It has efficacy in preclinical prevention models, and it may therefore represent an important potential chemopreventive agent, if only for those who are selenium deficient (14, 21, 24–26, 28, 38). MSC is a close derivative of selenocysteine, which is referred to in the literature as the physiologic form of selenium (30). It is necessary for the synthesis of selenoproteins, and these proteins seem to be responsible for physiologic effects of selenium in humans.

The SELECT results leave little room for hope that selenium as SeMet will prove of chemopreventive efficacy for selenium-replete subjects (12). Whether supplementation will be of benefit to those who are not selenium replete is less clear. Moreover, the form of selenium administered in SELECT, SeMet, may have important limitations. It is important not to extrapolate without adequate evidence the findings of SELECT (i.e., SeMet) to all selenium compounds and all populations. Preclinical findings, as well as findings in humans now available through the current study, show in a corroborative fashion that there may be important differences between MSC and SeMet (21, 24–27). Taken together, prior studies and findings from this study support continued investigation of the role of MSC in cancer risk among humans.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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