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ORIGINAL ARTICLE

Sucrosomial® iron and folic acid supplementation is able to induce Il-6 levels variation in healthy trained professional athletes, regardless of the hemoglobin and iron values

La supplémentation en fer sucrosomial® et acide folique permet de induire une variation de les taux d'IL-6 chez des atlétes professionnels en bonne santé, quelles que soient leurs valeurs en hémoglobine et en fer

T. Bongiovanni[a], **G. Pasta**[a], **G. Tarantino**[b,*]

[a] *Football Medicine and Science Department, Parma Calcio 1913, Parma, Italy*
[b] *Pharmanutra S.p.A., Pisa, Italy*

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KEYWORDS
Interleukin-6 ;
Sucrosomial® iron supplementation ;
Inflammation

Summary
Objective. — Inflammation plays a fundamental role in the healing process after a trauma. Recent data have suggested that interleukin-6 (IL-6) plays a key role in iron metabolism after stress response.
Equipment and methods. — To study the correlation between iron metabolism and inflammatory status in fifteen professional male athletes, a Sucrosomial® iron plus folic acid supplement was administered during the professional sport season and a prospective analysis of data was performed.
Results. — The healthy athletes who took the supplement did not show a significant increase in hemoglobin or iron parameters, compared to those who did not receive it. However, none of them started from deficit conditions. Interestingly, the athletes who received Sucrosomial® iron

* Corresponding author at: Pharmanutra S.p.A. Via Delle Lenze, 216/b, 56122 Pisa, Italy.
Adresse e-mail : g.tarantino@pharmanutra.it (G. Tarantino).

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had a significant lower IL-6 levels throughout the season (4.22 ± 3.7 pg/ml vs 6.9 ± 9.6 pg/ml, $P = 0.04$ and 6.3 ± 3.1 pg/ml vs 11.1 ± 7.7 pg/ml, $P = 0.04$). This is the first demonstration that Sucrosomial® iron plus folic acid supplementation in professional athletes is able to induce IL-6 levels variation during the season, regardless of the values of hemoglobin and serum iron.

MOTS-CLÉS
Interleukine-6 ;
Supplémentation en fer sucrosomial® ;
Inflammation

Résumé
Objectifs. — Chez les athlètes, l'inflammation joue un rôle fondamental dans le processus de guérison après un traumatisme. Des études récentes ont suggéré que l'interleukine-6 (IL-6) joue un rôle clé dans le métabolisme du fer après la réponse au stress. La carence en fer est au moins deux fois plus fréquente chez les athlètes par rapport aux personnes inactives.
Matériels et méthodes. — Pour mettre en évidence la corrélation entre le métabolisme du fer et l'état inflammatoire chez quinze athlètes masculins professionnels, nous avons administré un supplément d'acide folique et de fer Sucrosomial® pendant la saison sportive professionnelle et effectué un recueil et une analyse des données prospectives.
Résultats. — Les athlètes en bonne santé qui ont pris le supplément n'ont pas présenté d'augmentation significative des paramètres de l'hémoglobine ou du fer par rapport à ceux qui ne l'avaient pas reçu. Cependant, aucun d'entre eux ne présentait de déficit au début de l'étude. Il est intéressant de noter que les athlètes ayant reçu du fer Sucrosomial® ont présenté une variation significative du niveau d'IL-6 au cours de la saison (4,22 ± 3,7 pg/ml vs 6,9 ± 9,6 pg/ml, $p = 0,04$ and 6.3 ± 3,1 pg/ml vs 11,1 ± 7,7 pg/ml, $p = 0,04$). C'est la première démonstration que le supplément d'acide folique et de fer Sucrosomial® chez les athlètes professionnels est capable de induire une variation de les taux d'IL-6 pendant la saison, quelles que soient les valeurs d'hémoglobine et de fer sérique.

1. Introduction

Iron deficiency (ID) is the most prevalent nutrient deficiency in the world. According to the World Health Organization data, it affects up to 25% of the global population [1]. ID is associated with several impairments, including oxidative stress, damaged mitochondrial electron transport and altered protein synthesis. It can even compromise the process of erythropoiesis [2] resulting in impaired oxygen-carrying capacity and endurance performance [3].

The prevalence of iron depletion is at least double fold in athletes compared to inactive people, reaching 50% in both female and male athletes in some reports [4]. The increased prevalence of ID in athletes may be due to the combination of several factors. First, foot strike and impact can cause hemolysis [5]. Second, sweat but also hematuria and gastrointestinal bleeding are responsible for increased iron losses [6,7]. Third, inflammation due to training can be associated with an altered iron metabolism and its intestinal absorption [8].

Inflammation is a very complex physio-pathological process that aims at defending the body from internal and external insults. In the athletes, inflammation plays a fundamental role in the healing process after a trauma. However, when the inflammatory process is prolonged, self-initiated and self-sustained, it becomes harmful. In fact, a chronic inflammation worsens the reparative phenomena and favors further pathological processes, of a degenerative type. Moreover, an inflammation sustained over the years promotes the onset of numerous pathologies, in particular all pathologies related to atherosclerosis (myocardial infarction, stroke, etc.) and several neoplasia. Numerous data show that intense physical stress may promote inflammatory response, which depends on the duration of physical effort, with increased acute-phase cytokines, and an altered iron metabolism. Interleukin-6 (IL-6) is the major cytokine produced under conditions of intense physical stress [9]. Recent data have suggested that IL-6 is the main promoter of hepcidin, a liver produced hormone that plays a key role in iron metabolism. The inflammatory mediated rises in hepcidin ultimately result in rapid decreases in plasma iron concentrations, preventing the iron recycling from macrophages, iron release from liver and spleen stores and iron absorption at the gut level [5,10]. Thus, in such conditions commonly used oral iron supplements have lower absorption rate compared to physiological conditions, with unabsorbed iron leading to well-known and frequent gastrointestinal side effects [11].

Sucrosomial® Iron represents an innovative formulation of oral ferric pyrophosphate carried by a phospholipid bilayer membrane plus a sucrose esters of fatty acid matrix, that provides gastro-resistance and allows the iron to be highly absorbed at the intestinal mucosae [12—14].

Some data showed that Sucrosomial® Iron absorption does not seem to be affected by hepcidin levels [15,16]. Recently has been demonstrated that Sucrosomial® Iron

absorption doesn't induce any pro-oxidative effects and doesn't increase inflammatory markers (IL-6, Socs-3) after administration, compared to ferrous sulfate in vivo [17]. Therefore, Sucrosomial® Iron could be taken in consideration in cases of inflammatory conditions and in professional athletes undergoing intense training and physical stress. Interestingly, it has previously been shown that short-term supplementation could have unfavorable effects on iron metabolism [18]. However, there is no convincing data regarding prolonged supplementation in populations of healthy professional athletes.

To improve the knowledge of the correlation between physical stress, iron metabolism and inflammatory response and the effect of the supplementation with Sucrosomial® iron on these factors in a group of professional sportsmen, a retrospective analysis of prospectively collected data was performed.

2. Material and methods

2.1. Participants and Study Design

A prospective study design was used using blood data from routine blood tests taken from July 2017 to July 2018. Fifteen professional male athletes from an Italian national soccer team (mean ± standard deviation age 28.8 ± 1.3 years; height, 180.2 ± 4.5 cm; fat mass, 7.17 ± 0.9 kg; VO_{2max}, 52.2 ± 2.9 mL/kg^{1}/min^{-1}) were included in the study. All participants gave a written informed consent before participating in the study. Of them, 11 accepted to assume a Sucrosomial® Iron supplement (Sideral® Folico, Pharmanutra S.p.A.), 21 mg iron/day plus folate 400 mcg/day for 5 days a week, for a period of 18 weeks. Furthermore, 4 additional athletes were randomly excluded from supplementation and used as controls.

All included athletes underwent a standard medical examination by a sports medicine doctor and, at its conclusion, blood was drawn under aseptic technique from a vein in the cubital fossa. Blood samples were taken under standard conditions between 7 and 8 am after a 12-h overnight fast. After collection, the samples were immediately stored at a temperature of 4 °C. Within 10 minutes, they were centrifuged at 3000 g and 4 °C for 10 min. The analyses of hematological parameters were conducted immediately upon sampling.

Visit and blood sampling were repeated at 3 time points: T0 (pre-season sample), T1 (in-season sample), and T2 (after-season sample). T0 was performed just before iron and folate supplement assumption; T1 was performed after 18 weeks of iron and folate supplement assumption, for those that received Sideral® Folico. T2 was performed 10 weeks after the last dose of product supplementation.

Hematological parameters [RBCs (red blood cells), Hb (hemoglobin), Hct (hematocrit), MCV (mean cellular volume), MCH (mean cell hemoglobin), MCHC (mean cell hemoglobin corpuscular), RDW (red cell distribution width)] have been obtained by flow cytometry. The measurement of hs-CRP (high-sensitivity C-reactive protein) was taken by turbidimetric method, while ferritin and IL-6 were determined using chemiluminescent immunoassay technology. All the above parameters were measured at each time point for all the subjects enrolled in the study.

2.2. Statistical Analysis

Statistical analysis was performed using STATA version 14. Descriptive statistics are presented as mean ± standard deviation (SD). The statistical significance was determined on a probability level (P) of < 0.05. For comparison of mean between groups (exposed versus unexposed to iron supplement), independent sample Student t-test or nonparametric Mann—Whitney U—test were used, when appropriate (P between groups). Variations over time of the different parameters were evaluated by analysis of variance (ANOVA) for repeated observations, correcting with post-hoc Bonferroni test (P for trend).

3. Results

3.1. Iron Parameters

Considering the trend over time, serum ferritin increased in both treated (from 117.9 ± 60.4 to 135.7 ± 68.7 ng/mL) and untreated (from 119.2 ± 43.7 to 182.5 ± 30.5 ng/mL) groups over the study period, although the difference was not statistically significant (Table 1). Serum transferrin significantly decreased in the treated group only (from 244.6 ± 34.9 to 216.1 ± 31.5 mg/100 mL) over the study period. Moreover, transferrin saturation kept almost stable over time in both study groups.

However, considering differences between treated and untreated groups at the 3 time points, they did not significantly differ by serum ferritin, transferrin and transferrin saturation (Table 1).

3.2. Blood Count and Biochemical Parameters

Hb and RBC did not significantly change in both study groups over time, with mean values stable above 14 g/dl and 4.9 × 10^{6}/μL, respectively (Table 1). In the same way, no between-group differences of these parameters were observed at the 3 time points of the study (Table 1).

However, in the treated group, MCV, MCH, MCHC increased significantly from baseline measurement after iron supplementation. MCHC value increased also in untreated players. Concerning between-group analyses, MCV was slightly smaller in treated compared to untreated group. However, this difference is not likely to be associated with iron supplementation, since it was already evident at baseline (Table 1). WBC and platelet values did not significantly change in both treated and untreated groups from T0 to T2.

Vitamin B12 and folate increased significantly after Sideral® Folico supplementation, from 551.9 ± 211.1 to 969.0 ± 510.3 pg/ml and from 3.3 ± 1.2 to 5.7 ± 3.1 ng/mL, respectively. On the contrary, vitamin B12 and folate did not change significantly in untreated group over time.

Biochemical parameters (BUN, creatinine, transaminases, CPK) remained stable over time. Renal and liver function indices were similar between treated and untreated groups at baseline and after treatment, with the only

Table 1 Values are presented as mean ± SD.

Parameters	Sucrosomial® Ironsupplement	T0	*P* between groups	T1	*P* between groups	T2	*P* between groups	*P* for trend
Iron indices								
Serum ferritin (ng/mL)	Y	117.9 ± 60.4	NS	131.5 ± 67.2	NS	135.7 ± 68.7	NS	NS
	N	119.2 ± 43.7		150.8 ± 44.4		182.5 ± 30.5		NS
Transferrin saturation (%)	Y	33.0 ± 11.7	NS	33.4 ± 9.1	NS	32.5 ± 7.4	NS	NS
	N	42.7 ± 12.4		42.1 ± 13.7		42.8 ± 9.3		NS
Transferrin (mg/100 mL)	Y	244.6 ± 34.9	NS	230.0 ± 28.0	NS	216.1 ± 31.5	NS	**0.004**
	N	222.8 ± 25.2		210.3 ± 21.0		208.5 ± 6.4		NS
Biochemical parameters								
Hb (g/dL)	Y	14.9 ± 0.5	NS	14.9 ± 0.6	NS	15.0 ± 0.8	NS	NS
	N	14.8 ± 1.2		14.6 ± 1.0		15.7 ± 0.4		NS
RBC ($\times 10^6/\mu L$)	Y	5.1 ± 0.2	NS	5.2 ± 0.3	NS	5.1 ± 0.3	NS	NS
	N	4.9 ± 0.3		5.0 ± 0.2		5.2 ± 0.1		NS
WBC ($\times 10^3/\mu L$)	Y	6.0 ± 1.2	NS	5.9 ± 1.0	NS	5.8 ± 1.0	NS	NS
	N	5.9 ± 0.3		5.8 ± 1.0		5.9 ± 1.2		NS
HCT (%)	Y	45.6 ± 2.2	NS	45.7 ± 2.0	NS	43.6 ± 2.2	NS	**0.002**
	N	46.0 ± 3.2		45.3 ± 2.1		44.8 ± 1.7		NS
MCV (fL)	Y	85.5 ± 1.4	NS	87.2 ± 1.7	**0.01**	85.8 ± 1.8	NS	**0.005**
	N	87.2 ± 2.5		91.0 ± 3.5		86.4 ± 2.1		NS
MCH (pg)	Y	28.9 ± 0.6	NS	28.4 ± 0.7	NS	29.5 ± 0.5	NS	**0.001**
	N	29.6 ± 1.6		29.2 ± 1.4		30.2 ± 0.3		NS
MCHC (g/dL)	Y	33.4 ± 0.6	NS	32.6 ± 0.5	NS	34.4 ± 0.5	NS	**< 0.001**
	N	32.7 ± 1.0		32.1 ± 0.9		35.1 ± 0.5		**0.01**
RDW (%)	Y	11.9 ± 0.6	NS	11.7 ± 0.4	NS	11.6 ± 0.5	NS	NS
	N	12.1 ± 0.7		11.6 ± 0.3		11.0 ± 0.0		NS
PLT ($\times 10^3/\mu L$)	Y	233.8 ± 59.9	NS	237.4 ± 73.6	NS	205.2 ± 37.5	NS	NS
	N	218.3 ± 11.4		219.3 ± 22.0		192.5 ± 2.1		NS
Folate (ng/mL)	Y	3.3 ± 1.2	NS	5.7 ± 3.1	NS	4.4 ± 1.4	NS	**0.03**
	N	4.1 ± 0.9		3.8 ± 2.1		3.2 ± 0.1		NS
Vitamin B12 (pg/ml)	Y	551.9 ± 211.1	NS	969.0 ± 510.3	NS	579.9 ± 165.7	NS	**0.01**
	N	476.0 ± 238.1		626.8 ± 508.5		452 ± 38.2		NS
AST (U/L)	Y	24.7 ± 3.3	NS	27.2 ± 4.7	**0.04**	25.7 ± 7.3	NS	NS

Table 1 (*Continued*)

Parameters	Sucrosomial® Ironsupplement	T0	*P* between groups	T1	*P* between groups	T2	*P* between groups	*P* for trend
	N	25.3 ± 9.4		34.3 ± 7.8		21.0 ± 4.2		NS
ALT (U/L)	Y	26.2 ± 10.2	NS	24.4 ± 6.1	NS	22.1 ± 8.3	NS	NS
	N	19.0 ± 2.9		32.5 ± 11.7		19.0 ± 4.2		NS
BUN (mg/dL)	Y	24.1 ± 9.7	NS	22.9 ± 4.5	NS	20.7 ± 4.7	NS	NS
	N	21.0 ± 7.1		20.8 ± 1.7		20.0 ± 1.4		NS
Creatinin (mg/dL)	Y	1.0 ± 0.1	NS	1.0 ± 0.1	NS	1.0 ± 0.1	NS	NS
	N	1.0 ± 0.1		1.1 ± 0.1		1.0 ± 0.1		NS
CPK (U/L)	Y	243.8 ± 145.2	NS	287.4 ± 103.7	**0.03**	244.7 ± 144.1	NS	NS
	N	315.0 ± 51.0		518.5 ± 282.8		189.0 ± 73.5		NS
Inflammatory markers								
hsCRP (mg/dl)	Y	0.3 ± 0.3	NS	2.9 ± 3.6	NS	0.3 ± 0.5	NS	**0.04**
	N	0.2 ± 0.1		1.2 ± 1.2		0.1 ± 0.1		NS
IL-6 (pg/ml)	Y	6.9 ± 2.6	NS	4.22 ± 3.7	**0.04**	6.3 ± 3.1	**0.04**	NS
	N	6.2 ± 4.5		6.9 ± 9.6		11.1 ± 7.7		NS

Blood sampling were repeated at 3 time points: T0 (pre-season sample), T1 (in-season sample), and T2 (after-season sample). T1 was performed after the end of iron supplement assumption for those that received Sideral® Folico. Statistical significance difference ($P < 0.05$) between the group exposed and unexposed to Sideral® Folico supplement (*P* between groups) and of variations over time of the different parameters (*P* for trend) are indicated in **bold**. NS: not significant; Y: yes; N: no.

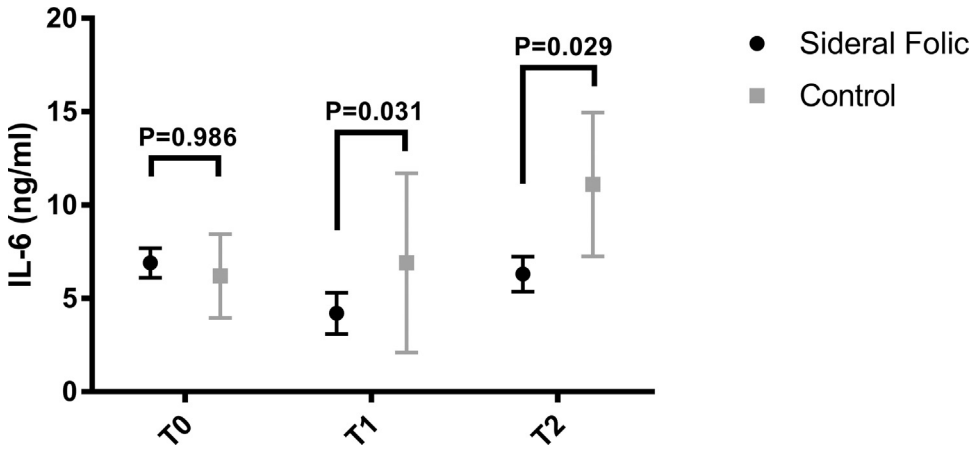

Figure 1 The IL-6 levels increase over the season in athletes that do not take the iron supplementation and remain low in athletes that received Sideral® Folico. The results are expressed in ng/ml and values are presented as mean ± SD. Statistical significance difference ($P < 0.05$) between the group unexposed compared to exposed to iron supplement.

exception of a modest elevation of AST in the control untreated group still in the range of normality (i.e. below 40 U/L) (Table 1).

3.3. Inflammatory Markers

There was a nonsignificant tendency to an increase in IL-6 in untreated group (Table 1, Fig. 1). In the group under supplementation, a different trend was observed: in T1, i.e. during the season and after the period of iron supplementation, IL-6 level was lower than at the baseline (before season), and turned again up to baseline value after season ended.

Therefore, while IL-6 values were similar between groups at baseline, they became significantly higher in untreated compared to treated group immediately after the end of treatment (T1). Interestingly, IL-6 levels were still greater in untreated than treated group longer after Sucrosomial® Iron supplement interruption and at the end of playing season (Table 1).

Differently from IL-6, CRP trends were similar in the 2 study groups, i.e. increasing in T1 and return back to baseline values at T2. However, this trend was statistically significant in treated group only. No difference was detected between treated and untreated players at the 3 time points (Table 1).

4. Discussion

Inflammation certainly plays a major role in tissue regeneration required in professional athletes that experienced a trauma [10]. It is well known that a pathophysiological process, that includes the homing of the different cell types involved in the tissue healing and the triggering of the reparative process locally, is fundamental to the recovery of injured professional players. However, a prolonged inflammation is dangerous and undesirable because it can only slow down or even stop the healing process [19]. An increase of some inflammatory markers can be seen not only after a trauma injury but even after intense training sessions. In this scenario, IL-6 plays a double-faced role [20,21]. In fact, this cytokine is certainly involved in the reparative process observed in muscular tissue after an injury and this cytokine is overproduced during intense exercise and prolonged stress, as a factor that promotes muscle hypertrophy required in the athlete. Furthermore, IL-6 is able to regulate and modulate muscle metabolism and this contributes to the ameliorating of the tissue repair. On the other hand, IL-6 can also have an extremely negative role. In fact, this cytokine has been associated with the loss of muscle mass in different experimental models. Assuming that there are elevated IL-6 circulating values in cancer cachexia, many research groups have shown that prolonged exposure to elevated IL-6 values can result in significant muscle mass loss [21].

To our knowledge this is the first demonstration that an oral iron and folic acid supplement relates to a IL-6 reduction in athletes during the sport season. Thus, regardless of the iron status and the incidence of sports injuries. In fact, we did not observe substantial differences between the control group and the treated group, in terms of ferritin, transferrin and hemoglobin levels. It is important to consider that these athletes had an optimized dietary intake and had no nutritional deficiency. Under normal conditions, the iron supplementation could not be expected to significantly alter iron metabolism. Furthermore, there were no significant injuries during the season. Since intense stress may increase IL-6 levels, regardless of the presence of pro-inflammatory external factors, it is possible to assume that the increase in IL-6 observed in the controls is due to normal exercise during the season. This increase in cytokine levels was not observed in athletes who received the Sucrosomial® Iron and folic acid supplement. This result is very important because it shows us that the positive effect of this supplement is independent of the iron status and, potentially, it can be suggested even in the absence of an established deficit. However, it has been shown previously that short-term iron supplementation during intensive endurance training could have some detrimental effects on iron metabolism [18]. Here we have highlighted that prolonged sucrosomial® iron supplementation during the sport season, has positive effects on the iron homeostasis, and a beneficial effect on inflammatory parameters. Prolonged exposure to IL-6 increases systemic

inflammation, increases the probability of muscle injury and worsens injury recovery [20]. Very recent and fascinating data show that blockade of IL-6 can have beneficial effects even in mouse models of muscular pathology [22]. We have demonstrated that Sucrosomial iron doesn't induce any IL-6 increase. This is probably due to the innovative sucrosome® coating that makes sucrosomial iron behave differently than conventional free iron salts. Clearly, in the case of latent iron deficiency anemia, the administration of the product determines additional beneficial effects on iron stores and hemoglobin levels. In fact, Sucrosomial® Iron supplementation can improve anemia and is better tolerated than other oral iron formulations, such as ferrous sulfate [23]. In our group of athletes there were no significant increases in hemoglobin, probably because they did not start from reduced values. We can hypothesize that supplementation may only increase hemoglobin when an iron deficiency or pre-existing anemia conditions are present.

There are some limitations in this study. First of all, the small number of athletes considered in the protocol does not allow for sufficiently valid data to express safe judgments. It is not possible to exclude, for example, that a larger number of findings could have shown an effect of the supplement even on hemoglobin levels. However, this is a pilot study, carried out on a single team of professional players. Given the results obtained, it is possible to design a larger study and with wider outcomes. A further limitation is that hepcidin levels were not evaluated, but this was not among the objectives of the research. It is possible that hepcidin and IL-6 levels are linked also in this population of sportsmen, as already shown, but the objective of the protocol was to focus on one of the main effectors of inflammation, IL-6. Finally, the small number of components of the analysis is not allowed to stratify groups homogeneously between owners and reserves. Probably, the different workloads can have a direct impact on IL-6 levels. However, starting from a real-life situation, it was not possible to extrapolate further subgroups in the analysis.

In conclusion, this is the first demonstration that Sideral® Folico supplementation in professional athletes is able to not increase IL-6 levels during the sport season. Although stronger data on a larger number of subjects is necessary, this evidence can be a starting point for all the professionals involved in the management of these athletes, a suggestion for the practical management of diet and supplements of professional athletes and a starting point for future studies.

Authors' contribution

TB, GP and GT participated in the design of the study, performed data analysis and reviewed the manuscript. GT and TB conceived the study, participated in its design and coordination and helped draft the manuscript. All authors read and approved the final manuscript.

Disclosure of interest

Germano Tarantino is Pharmanutra S.p.A. employee.

Tindaro Bongiovanni and Giulio Pasta have no competing interest.

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