

Merchants shall be expelled from the Temple: the PRGF® (Plasma-Preparation Rich in Growth Factors)-Endoret® case

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Dear Sir

We recently published in *Muscles Ligaments and Tendons Journal* a classification of platelet concentrates (commonly termed Platelet-Rich Plasma - PRP or Platelet-Rich Fibrin - PRF) for topical and infiltrative use in orthopedic and sports medicine¹, based on previous research works and consensus articles developed by several experts in the field in various clinical disciplines²⁻⁴.

Following the publication of our article, Anitua et al. submitted a letter to the Editor, complaining that they were not cited enough and about the way the technique, commercially termed PRGF® (Plasma/Preparation Rich in Growth Factors) or Endoret®, had been described shortly in our independent classification review article. In the form and in the content, these authors are aggressively attacking our scientific credibility. We will answer in a point by point fashion to their

letter. We thank Prof. Nicola Maffulli and the Editorial Board of *Muscles Ligaments and Tendons Journal* to have allowed us to reply to Anitua et al.'s letter.

What is the Biotechnology Institute? Who are Anitua et al.?

First, readers should be aware that Dr. Eduardo Anitua et al. are not independent researchers. The Biotechnology Institute (BTI, Vitoria, Spain) is a dental implant company that manufactures and markets the PRGF®/Endoret® system. Dr. Anitua is the Founder, President and Scientific Director of BTI, and the owner of PRGF® patents. This dental implant company has the specificity to use the fashion of platelet growth factors products as a theme to develop its credibility. Most coauthors of Dr. Anitua are his employees.

These authors rarely disclosed all their conflicts of interest since the beginning of the PRGF® story⁵. In most articles from this group, no disclosure of interest was clearly spelled, even though, in this case, the conflicts of interest cannot be bigger. After a few conflicts that highlighted this reality⁵, these authors were also using the affiliation "Eduardo Anitua Foundation for Biomedical Research", while it is obvious that this entity is heavily conflicted by commercial interests like BTI. We will voluntarily not cite any references from this group for the reason explained further in this letter, but they are easy to find on Pubmed and in other electronic databases.

Most publishers and journal reviewers appear to have not noticed these obvious undisclosed major conflicts of interest, and have not sanctioned this behaviour for the past 15 years. Anitua's group is heavily conflicted in all research related to PRGF®/Endoret® and dental implants (by definition), but Dr. Eduardo Anitua, as leader of the group, hides most time his conflicts of interest and even declares himself as an independent voice (using explicit declarations in many articles: "*The authors report that they have no conflicts of interest*"). In a recent letter to the *New England Journal of Medicine*, Dr. Anitua declares himself as "*being employed as researcher at BTI, the developer of plasma rich in growth factors*". There is clearly here a major omission in this wording.

The key of trust in Science is transparency. The world of medical research tries to reduce the influence of conflicts of interest to avoid distorted versions of reality. Per definition, through their undisclosed conflicts

of interest, Anitua et al. are introducing strong bias in PRP research: this may impact the use of platelet concentrates for surgical and infiltrative use during years, particularly in sports medicine. Their aggressive letter is the best illustration of their behavior and the confusion they are promoting.

Three basic recommendations to use against Merchants sneaking into the Temple

When we were young scientists, our mentors taught us that Ethics and Reputation are the most valuable things for a Scientist. Reputation is something that you take a life to build, and one second to lose. We also remember that in the past – before the time of mass publications – it was said that people with proven records of unethical publishing shall be banned from the Community of Scientists and banned from publishing for several years, or the whole scientific literature will lose its credibility. For this reason, we have to always push for this clear and honest disclosure of interest in all scientific publications and even lectures. As a logical consequence of this situation of undisclosed conflicts of interests, the only solution appears to boycott these authors. We wish to put forward several recommendations to our community:

1) We recommend that scientists boycott the citation of all articles from this group. Each time we are citing the articles of Anitua et al. – by ignorance of their real identity and commercial profile or to criticise their articles – we are, in reality, giving them citation points and reinforcing their credibility. This is the classical trap of the modern social network, where the simple fact of citing someone gives him a legitimacy he may not deserve. For this reason, we did not cite any articles of the Anitua's group in this letter. Actually, it is frequent in the Academic world to simply ignore the articles that do not deserve respect or interest. If someone wants to cite PRGF®-Endoret®, we suggest that colleagues cite this letter, the classification article we published in MLTJ¹ or some other independent items referring to this product or this ethical issue ^{2,3,5-8}.

2) We recommend to all international journals receiving submissions from this group to reject it for a significant period, given this long history of absence of fair disclosure of interest in most of their articles. It is the duty and responsibility of reviewers – the guardians of the Temple – to identify and neutralize unethical players.

3) We also recommend that all manuscripts about PRGF®-Endoret® or the BTI products in general (even if not signed by Eduardo Anitua's group) shall be considered with a lot of suspicion (particularly concerning their links with BTI and the source of funding of the study) prior to be published in peer-reviewed journals.

About the comments raised by Anitua et al.

We took the time to answer point by point to the statements of Dr. Anitua and his employees.

1) Anitua et al. are somehow complaining to not have been cited enough in our review classification. For the previously explained ethical reasons, we do not believe in many articles published by the group related to Dr. Anitua, and it is our right, as independent scientists, to refuse to cite articles from this group, to refuse to give them any legitimacy. Moreover, we have been perfectly honest, as the editorial of this special issue of MLTJ⁹ acknowledged Mikel Sanchez as a pioneer of PRP in orthopedics, even though his credibility may clearly be compromised by his association with Dr. Anitua's behaviour. Finally, we point out that the use of the PRP techniques is much older than what authors are often claiming^{10,11}, and other independent honest teams were publishing on the use of PRP in sports medicine at the same moment (the Swedish group of Per Aspenberg particularly) and with less debatable results¹².

2) Anitua et al. are complaining that the PRGF®-Endoret® protocol was described as not ergonomic and approximate, particularly given the use of several steps of pipetting during the production process of the PRGF®. They are also claiming that pipetting would be somehow a natural step for the production of platelet concentrates for surgical use. We disagree with their claims.

Regardless of that we define ergonomics, PRGF® method is not ergonomic, particularly in comparison to other easier methods¹³. PRGF®-Endoret® is a protocol mainly based on pipetting. No doubt pipetting is a common laboratory tool, but it is not comfortable for workers¹⁴, and does not fit well an operating theatre. Personnel using PRGF®-Endoret® must spend considerable time and effort pipetting to separate from each centrifuged tube the three indistinguishable plasma fractions. Other techniques are much easier, better designed and allow to work well and quickly (the definition of ergonomics). It appears obvious that the PRGF®-Endoret® protocol is not ergonomic and is approximate.

However, we could have been more detailed in our description, and we should have added that PRGF®-Endoret® system is also not practical, not user-friendly, extremely operator-dependent, and finally not reproducible. We strongly recommend all our readers to take an opportunity to have a demonstration of the PRGF®-Endoret® system (and to compare it with a simple system such as L-PRF system - Leukocyte and Platelet-Rich Fibrin)^{6,13}, in order to form their own opinion – which cannot be seriously different from ours. We thank Anitua et al. for giving us the opportunity to detail our field observation through this correspondence.

3) Anitua et al. are claiming that their company only published 37.5% of the articles about PRGF®, and that the remaining would be coming from independent teams. We disagree with these claims. Following our own statistics in the double-indexed literature, including the review articles (which are part of the global communication strategy and also need disclosure of interest) and discarding the articles using wrongly the acronym PRGF to refer to other products, the BTI

company men have directly produced 55% of the total PRGF® articles. A dozen of articles were produced by teams known as really independent (including us), and showing mixed results for PRGF®. For all other items, many names are coming repetitively, particularly a significant series produced by some teams sponsored and strongly associated with Dr Anitua's business. If we include just a few teams already well known as commercially connected with BTI, we reach already 80% of this international literature. And this literature is always showing excellent results for PRGF®, and mostly with an absence of clear disclosure of interests. International scientific publishing nowadays, this is really magic.

As BTI has been publishing mostly without clear disclosure of interests for years, the logical scientific conclusion is that this behavior may have been extended to affiliated researchers. This situation reinforces our previous third recommendation, that all articles referring to PRGF®-Endoret® or even to the BTI products in general (even if not authored by Anitua's group) shall be considered with suspicion. Articles about PRGF® from other groups than Anitua may not be as independent as it seems. We thank Dr Anitua to offer us the opportunity of this correspondence to clarify this situation.

4) Finally, Anitua et al. did a series of aggressive comments of little interest and sometimes without sense, but we will try to answer it clearly.

- Anitua et al. claimed that PRGF® membranes and clots are stable 7-8 days, and that leukocytes must be filtered to avoid the membrane resorption. This is not true *in vivo*, this is not true *in vitro*. Independent studies have shown that, in the best conditions *in vitro*, PRGF® membranes are completely dissolved after 4 days, while products from the L-PRF family can stay more than 7 days *in vitro* (in fact, it can stay in culture for at least one month)^{6,7,15}. Actually, the massive presence of leukocytes in L-PRF¹⁶ is advocated to explain that L-PRF membranes are so durable¹⁵, in comparison with PRGF® membranes⁶. Both were compared *in vitro* by our group. The statements from Anitua et al. are propagandist verbiage.

- PRP solutions have indeed the advantage to be liquid before activation, and the speed of polymerization mostly depends on the kind and quantity of activators, conditions of application, etc. We do not perceive any omission in the general wording we used.

- All dentists can easily confirm that PRP fashion has been globally abandoned in oral and maxillofacial surgery, particularly in comparison with L-PRF techniques. If they simply walk through a dental congress, readers can make their own opinion: a scientific reference is not always needed to spell an obvious field observation.

- Finally, Anitua et al. reopened shortly the debate about the function of leukocytes in platelet concentrates. For years, their business communication was built on the absence of leukocytes in PRGF®. They also claimed that macrophages would be the turntable of the healing process. This is actually a very surprising, limited and inaccurate vision of the im-

mune system. On the contrary, our article was briefly outlining the complexity of this leukocyte equation¹⁷ and the role of lymphocytes as regulators of the inflammatory and healing process - this is actually why we call some of these cells Bregs (Regulatory B cells) and Tregs (Regulatory T cells)¹⁸. There is actually a significant body of literature supporting this key role, for example that T cells can instruct monocytes/macrophages to down regulate key proinflammatory cytokines in certain conditions¹⁹; moreover, regulatory B cells utilize a number of suppressive mechanisms to regulate and restrain the inflammatory process, particularly through the production of Interleukin 10 (IL-10) and the secretion of other cytokines to regulate the immune responses mediated by T and innate cells^{18,20,21}. These aspects of lymphocyte function are influencing the effects of PRP/PRF, as it is commonly accepted by the scientific community²²⁻²⁵, particularly in some products (such as L-PRF) presenting a majority of lymphocytes in their composition^{15,16}. This aspect would benefit from more intense investigation. Immunology is a very complex science that requires careful statements and an open and sincere scientific mind.

We will conclude this part of our reply as Dr. Anitua and Employees concluded their own letter: they wrote that "Playing scientist is not a game, it is a hard journey". They are right, "playing scientist" is obviously not a game, it seems to be Dr. Anitua and Employees' profession and business, and it is a hard journey for them. For us, Science deserves better than people "playing scientist". Science deserves respect, honesty, transparency, humility, intelligence, some efforts, and a little bit of humour in front of a letter such as the one they wrote.

Perspectives and Conclusion

Whatever the opinions about the PRGF®-Endoret® relevance, it remains only one kind of PRP among many others. From our experience in the oral and maxillofacial community, the use of PRGF® remains scarce. Evolution and natural selection are a natural process for techniques also, and it is difficult to consider that PRGF® can survive in front of less expensive, more user-friendly and efficient methods such as L-PRF^{26,27} or recent versions of L-PRP. The main problems are the collateral damages provoked by Dr Anitua and his employees, as these frequent undisclosed conflicts of interests may impair the credibility of the whole topic for the future.

We shall remember that most PRPs were abandoned in oral and maxillofacial surgery, given their mixed and controversial results^{28,29}, and they even became a source of jokes in the dental community, given the commercial fashion and magic of growth factors. It took many years for credible alternative techniques to get over the PRP reputation failure. The PRGF®-Endoret® case of undisclosed conflicts of interest can only provoke the same kind of distrust in the field, starting by discrediting the scientific literature and

leaving a major ethical and scientific loss of credibility for all stakeholders in the field.

However, Anitua et al. gave us this open-access opportunity to transform their aggression letter into a new hope. Our classification article and this answer letter will serve as the basis of the Ethical rules of the PACT (Platelet & Advanced Cell Therapies) Expert Community of the POSEIDO Academic Consortium (Periodontology, Oral Surgery, Esthetic & Implant Dentistry Organization)³⁰, and it will be freely available through the platform of the POSEIDO Foundation to all our members in 39 countries (www.poseido.net). The PACT Forum Civitatis was designed to avoid this kind of commercial interferences to happen in our community, and the opportunity offered by this correspondence is ideal.

At the end, what will remain from the PRGF®-Endoret® technique? What will be the legacy in the field for Anitua et al.? Without the Trust of their Community, their works will remain a whisper. Much Ado About Nothing. A Human Comedy, but a Tragedy for the concepts of Ethics in publishing. Obviously, there is a crucial role for industry in research, but contributing to distorted versions of reality through undisclosed conflicts of interest it against patients, against scientists and against all Humanist values that Science holds.

P.S.: By the way, Dr. Anitua et al. forgot again to disclose their huge conflicts of interest in their insulting letter. This omission is in itself a fraud. There cannot be any better illustration for our answer.

Disclosure of interests

The authors have no conflict of interest to report.

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