Author’s response to reviews

Title: Safety of bioabsorbable implants in vitro

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Dear Editor; 20/10/2015

At the outset, I would like to express my gratitude to you and the reviewers for your invaluable efforts in reviewing our manuscript. In an attempt to fulfill the requests of the reviewers, we completely revised the discussion section as indicated and tried to expand this section to include citations of original articles which represented a surgical perspective.

Besides this, I would like to respond the other criticisms raised by the reviewer 2 in this rebuttal letter. The reviewer indicated that; “The team composition is incorrect: 5 authors belong to the Department of Orthopedic Surgery and one of Pharmacovigilance (chemist). Striking is the absence of authors from other disciplines such as biochemical or biologists.” We are of the opinion that we are being a bit underestimated by the reviewer 3 in terms of our background and expertise which definitely make us eligible to conduct molecular biology based and/or pharmacogenomic researches. Upon your request, I may provide you the certificates that certify our expertise along with the previously published articles that describe our similar projects. You may kindly search Ibrahim Yilmaz and Mehmet İsyar in Pubmed or Researchgate and find our previous studies.
Unfortunately, we witnessed that reviewer 3 used the term 'chemist' as a substitute for 'pharmacovigilance'. It may be our fault to be unable to clearly demonstrate what 'pharmacovigilance' means, but if only the reviewer could have conducted a quick research in google or Wikipedia, he or she would not have used this term. In Wikipedia, "Pharmacovigilance; also known as drug safety, is the pharmacological science relating to the collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products (The importance of pharmacovigilance. WHO. 2002). The etymological roots for the word “pharmacovigilance” are: pharmakon (Greek for drug) and vigilance (Latin for to keep watch). As such, pharmacovigilance heavily focuses on adverse drug reactions, or ADRs, which are defined as any response to a drug which is noxious and unintended, including lack of efficacy. The condition that this definition only applies with the doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological disorder function was excluded with the latest amendment of the applicable legislation). Medication errors such as overdose, and misuse and abuse of a drug as well as drug exposure during pregnancy and breastfeeding, are also of interest, even without an adverse event, because they may result in an adverse drug reaction (International Drug Monitoring The Role of National Centers. 2015)". In short, pharmacovigilance is a branch of clinical pharmacology not solely a 'chemist'. In clinical pharmacology education, many courses that are taught in the department of chemistry are also given. Furthermore, as a pharmacologist, during my education, I also had a course called 'pharmaceutical chemistry' which is not found in the curriculum of chemistry education. As a consequence, unlike a chemist, a clinical pharmacologist has the expertise and legal right to conduct methodological studies to analyze the implants designed for medical use.

Co-Author Ibrahim Yilmaz was graduated as a pharmacist from a School of Pharmacy after a 5 years of education. Following this, he gained expertise in Department of Clinical Pharmacology in School of Medicine for 4 years and was given the title of Clinical Pharmacologist. In our country, there are 250.000 medical doctors and 23.000 pharmacists. However, of these, only 7 pharmacists are known to proceed their education in a School for Medicine in Department of Clinical Pharmacology and he is one of them. Clinical Pharmacology, as its name implies, is a medical field of expertise and is classed along with the other disciplines of medicine. It gives the associated expert to not only the right to design an implant to be used in a human body, but also the right to analyze the impact of these implants on the tissues of a living host.

I hope my comments may be explanatory for the reviewer for making a clear-cut distinction between a clinical pharmacologist and a chemist.

In addition, reviewer 3 commented that “5.-This work is more appropriate for journals of basic research or biomaterials. Of 29 citations appear only 5 of clinical journals I suggest to authors to send this article to Journals as Biomaterials Research Journal or Journal of Orthopaedic Research, both in Biomed Central.” We would like to remind you that our team conducted another cytotoxicity analysis on chondrocytes and osteocytes using molecular biology methods and this work that also focused on a previously uninvestigated area was recently published in another surgery journal of BMC (Please refer to: Are biological agents toxic to human chondrocytes and osteocytes? Journal of Orthopaedic Surgery and Research 201510:118. DOI: 10.1186/s13018-015-0264-y© Isyar et al. 2015).
We kindly insist that our work merits being published in BMC Surgery Journal. You may think that our team is composed of six researchers with a medicine background (5 surgeons and one clinical pharmacologist), however, the previous projects of our team were investigating the molecular aspects of the diseases. You may have a look at the previous works conducted by Ibrahim Yilmaz below, and you may easily see that we did not need another team member to perform this molecular analysis.


Are the leading drugs to fight against Staphylococcus aureus really toxic to cartilage? Journal of Infection and Public Health. Accepted 07.2015.


Is it possible to increase the osteoblastic activity by using PLGA composites that are produced by calcium phosphate dibasic? 2nd International Conference on Tissue Science & Regenerative Medicine August 26-28, 2013. Raleigh-NC, USA.


Moderator Mehmet ISYAR “Are the leading drugs to fight against Staphylococcus aureus really toxic to cartilage?” 36th SICOT Orthopaedic World Congress, Guangzhou, China; 09/2015.

Can polymeric hydrogels containing nitric oxide manipulating agents improve osteoarthritic chondrocytes? 2nd International Congress on Stem Cell and Cellular Therapies 15-18, OP33; October 2015
We can not agree with the reviewers' opinion that this manuscript should be sent to biomaterial journals. Moreover, as an editor, if you approve publishing this manuscript in your journal, we believe that this research would reach a great number of researches worldwide and many surgeons would be inspired and encouraged to conduct similar molecular based pharmaceutic and pharmacologic researches. In our opinion, such studies would motivate many surgeons to keep the tissues they obtained from the surgical field in the Petri dishes for further research instead of sending them to medical waste department.

The significance of our research was pointed out in our cover letter as follows; “Further, studies in the literature mostly involved experimental animal models and models obtained from animal tissues. Besides, in studies using animal models, differences between human and animal tissues were highlighted, and thus, there would be differences in results. In the present study, because primary cell cultures obtained from human tissues were used, which is a first in the literature, we believe that the results were stronger.”

Please kindly find the manuscript of our study enclosed. We hope that our study would be considered to be published in your journal.

Best Regards.

Assist. Prof. M.D. Mehmet ISYAR
Istanbul Medipol University, School of Medicine
Department of Orthopaedic and Traumatology

Response to reviewers:

Reviewer 1.

Thank you for your criticism and contributions. We appreciate you for sharing your clinical experience regarding infections following use of implants made of polyethylene glycol (PEG) in anterior cruciate operations. As it is well known, PEG's are frequently used in a number of medical procedures (designation of surface active materials and etc.) to provide polymerization and preferred due to their high biocompatibility (Zhu W., et al. Amphiphilic biodegradable poly(CL-bPEG-b-CL) triblock copolymers prepared by novel rare earth complex: Synthesis and crystallization properties, European Polymer Journal. 2007;43,3522–3530.), and (Gates TA, et al. Biomechanical Analysis of a Novel Pedicle Screw Anchor Designed for the Osteoporotic Population. World Neurosurg. 2015;83(6):965-9.).

However, we did not use PEG 300 ( a PEG derivative ) in an attempt to design a surface active agent - as you indicated. We used is as an adjunct binding materials to promote polymerization of the designed PLGA and consolidate the weak crosslinking that occurred with chitosan (provision of increased binding by increasing the hydrophilic regions). PEG 300 used in our design is 1/50 mole/mole and it is usually neglected hence it is in trace amounts.
The design does not contain a high amount of PEG sufficient to cause an infection or a side effect. Furthermore, when we made a search in Pubmed using the keywords 'polyethylene glycole 300', 'anterior cruciate ligament' and 'infection', we retrieved no results.

If such a study has existed, we would cite it in the discussion and then point out to the visual and molecular analysis findings of our study which demonstrated that no infection occurred during the study. In case such an infection has occurred, the liquid broth in the cell culture would acidify and its color would turn into an orange color, which may be observed by even naked eyes. In addition we would observe dead cells in inverted light microscopy.

If you can check our results (ELISA, inverted and SEM images), you may observe the proliferation of the healthy cells. Anyway, we added a new paragraph into the discussion section for further explanation. I hope we could address your concerns.

I thank you on the behalf of authors for your keen efforts in reviewing our manuscript.

Best Regards.

Reviewer 3.

Thank you for your criticism and we tried to answer/comment your questions in discussion section.

Sincerely yours.

1.- There is no clear advantage of the new material in the analyzed factors which are exclusively in vitro: "more live cells and allowed more proliferation" Dear reviewer, within our analysis, you may kindly find the results of “Energy-dispersive X-ray spectroscopy (EDS) microanalysis’ which were presented with short and concise sentences. For you, I would like to point out the clear advantages one by for you, below. The first clear advantage, the presence of N and O atoms enables enhanced viability. ‘One of most important thing that, the PLGA prototype has more nitrogen atom numbers, which was the proof of viability’. This also seems to be a ‘clear’ advantage. Another clear advantage is the increased CD44 levels suggesting a superior osteoblastic activity, And one last clear advantage is increased viability and proliferation as determined by MTS ELISA tests and ESEM analysis.

2.- The authors write: "Regarding the use of implants in orthopedic trauma surgeries, the followings are expected: stabilized fixation, minimal surface contact, and causing no foreign body reaction or toxicity." They forget the pressure mechanical ability, strength and rigidity that is as important as the others. The authors have not done biomechanical studies that are essential to research new biomaterials. "Between lines 18 and 24 (First submission) we also pointed out that “ The actual limitation of the study was the lack of biomechanical tests of the implant. However, in this first pilot study, in vitro toxicity and viability tests were aimed, and subsequent studies were planned to be carried out regarding the animal experiments and experiments to present the biomechanical features”
This is a novel design and our future researches would investigate its biomechanical properties. But for the records, we may deduce from our findings that this novel design would have the required stability and strength. The stability of our prototype has unique stability when compared to its predecessors due to its C content. In the manuscript we stated that as; ‘Dense and shiny calcium zones showed that the PLGA prototype contained more carbon atoms compared to the control group, which was an indication of chemical stability’.

3.- The team composition is incorrect: 5 authors belong to the Department of Orthopedic Surgery and one of Pharmacovigilance (chemist). Striking is the absence of authors from other disciplines such as biochemical or biologists. We are of the opinion that we are being a bit underestimated by the reviewer 3 in terms of our background and expertise which definitely make us eligible to conduct molecular biology based and/or pharmacogenomic researches. Upon your request, I may provide you the certificates that certify our expertise along with the previously published articles that describe our similar projects. You may kindly search Ibrahim Yilmaz and Mehmet İsyar in Pubmed or Researchgate and find our previous studies.

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The work is focused on laboratory techniques and electron microscope that surgeons preferably not used.” If cell lines were used in this study, such a criticism would be meaningful. Who would harvest the osseous during total knee arthroplasty (femoral and tibial resection) ? In addition the authors team has a significant past experience regarding the molecular analysis of osseous tissue and has the expertise to recognize an osteocyte under ESEM. I was the chairman of the panel about the molecular based studies of osteochondral tissue (SICOT Orthopaedic World Congress, China, 2015)

4.- The results have no practical application and works in vitro and especially in vivo are needed to adopt a new biomaterial. Before conducting tests to assess the eligibility of a designed biomaterial implant, its pharmacodynamic characteristics should be investigated. The ability of the design to be biocompatible, biodegradable and etc. Should first be tested in vitro before proceeding to in vivo experiments. We also denoted that this study was performed to assess the in vitro characteristics of the design.

5.- This work is more appropriate for journals of basic research or biomaterials. Of 29 citations appear only 5 of clinical journals. Dear reviewer, we agree with you. We revised the discussion section of our manuscript according to your comments and added the recent publications with a high level of evidence from the field of orthopaedic surgery.

Best regards.

Reviewer 4.

We revised the discussion section according to your suggestions and we appreciate your kind efforts for criticising our manuscript.

Best regards.

Assist. Prof. M.D. Mehmet ISYAR
Istanbul Medipol University, School of Medicine
Department of Orthopaedic and Traumatology