



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 53534

Title: Use of zebrafish embryos as avatar of patients with pancreatic cancer: A new xenotransplantation model towards personalized medicine

Reviewer's code: 03664719

Position: Peer Reviewer

Academic degree: FACS, FRCS, MD

Professional title: Professor

Reviewer's Country/Territory: United Kingdom

Author's Country/Territory: Italy

Manuscript submission date: 2019-12-31

Reviewer chosen by: Le Zhang

Reviewer accepted review: 2020-02-16 15:09

Reviewer performed review: 2020-02-17 16:08

Review time: 1 Day

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

The manuscript by Di Franco and colleagues analyses zebrafish embryos as a novel xenotransplantation model for pancreatic cancer patients. This is an interesting and relevant study. However, several concerns that should be addressed: 1. Xenotransplantation models are of interest, but the need has not increased 'exponentially'. There are other models such as for example patient-derived organoids. Further whole tumor genome sequencing has been another promising approach for personalized medicine. 2. Lederfolin is not a common English term. 3. What is meant by "exclusive treatment"? 4. How variable was the volume of the tumor and the number of tumor cells implanted? Could the authors provide estimates for this? 5. What was the reason for the 50% mortality rate at dpi2 in the model? 6. The effect of chemotherapy was assessed after 2 days. How valid is such a short duration time period? 7. The statistical analysis is difficult to follow, as multiple parameters are analysed. 8. It would have been important to compare this model to other established models, e.g. organoids. 9. There are several grammatical errors that should be corrected.



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 53534

Title: Use of zebrafish embryos as avatar of patients with pancreatic cancer: A new xenotransplantation model towards personalized medicine

Reviewer's code: 00225294

Position: Editorial Board

Academic degree: BM BCh, PhD

Professional title: Doctor, Professor, Senior Research Fellow

Reviewer's Country/Territory: Spain

Author's Country/Territory: Italy

Manuscript submission date: 2019-12-31

Reviewer chosen by: Le Zhang

Reviewer accepted review: 2020-02-14 07:09

Reviewer performed review: 2020-02-17 20:05

Review time: 3 Days and 12 Hours

Scientific quality	<input checked="" type="checkbox"/> Grade A: Excellent [] Grade B: Very good [] Grade C: Good [] Grade D: Fair [] Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing [] Grade B: Minor language polishing [] Grade C: A great deal of language polishing [] Grade D: Rejection
Conclusion	<input checked="" type="checkbox"/> Accept (High priority) [] Accept (General priority) [] Minor revision [] Major revision [] Rejection
Re-review	[] Yes [] No
Peer-reviewer statements	Peer-Review: [] Anonymous <input checked="" type="checkbox"/> Onymous Conflicts-of-Interest: [] Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

The authors are presenting a study for the use of zebrafish embryos as avatars for the analysis of potential therapeutic interventions in human pancreatic cancer patients. The proposal is well presented and discussed. The experimental protocol is described in detail and authors are transferring samples from patients to the embryos, followed by the test of several chemotherapeutic drugs. In addition to this, authors are comparing the avatar results with current data from the literature, after administration of several therapeutic drugs. This approach might accelerate the transfer to a 'personalized' medicine for the treatment of pancreatic cancer.



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 53534

Title: Use of zebrafish embryos as avatar of patients with pancreatic cancer: A new xenotransplantation model towards personalized medicine

Reviewer's code: 03656593

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Professor, Surgeon

Reviewer's Country/Territory: China

Author's Country/Territory: Italy

Manuscript submission date: 2019-12-31

Reviewer chosen by: Le Zhang

Reviewer accepted review: 2020-02-16 04:19

Reviewer performed review: 2020-02-21 11:19

Review time: 5 Days and 6 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

This is an interesting study. The authors developed a model to use zebrafish embryos as avatar of patients with PDAC, standardizing the protocol for the xenotransplantation of pancreatic tumor tissue, for the exposition of the xenotransplanted zebrafish embryos to the chemotherapy drugs, and for the evaluation of the effects of chemotherapy on the xenotransplanted tumor tissue. This model has some clinical significance and could service as a useful experimental tool. But the paper needs very significant improvement before acceptance for publication. My detailed comments are as follows: PDX and organoid are two of efficient model in vitro for chemotherapy screening. PDX and organiod both have restricted capability to passage and freeze the tumor tissue samples. The zebrafish model seems to lack of this function. It is more likely to be an one-off tool. Would the results on zebrafish model stand for the chemosensitivity of matched PDAC patients? Are there any supporting data? How do you prove it? The authors performed 4 kinds of chemotherapy on zebrafish models. And quantify the curative effect of chemotherapy by the reduced area of Dil on ImageJ. Would you provide the evidence of apoptosis of cancer tissue after treatment? In fig 2a, the right H-E staining image seemed that it was not from the left view field. And the images were not clear enough. In fig2, tumor tissue fragments were stained with CM-Dil, and fig2 seemed to indicate the success of transplanting PDAC tissue into zebrafish. I think H-E staining and Dil existence were unconvincing. Specific cancer cell markers should be stained with IHC. What's more, would the microenvirnment of tumor remain? How does it convert after transplanted on zebrafish? In fig3, seeing the relative area (a.u.) for POO2, although the mean value is higher in FOLFOXIRI group, the deviation of data in FOLFOXIRI group is smaller that the deviation in Gem+nab-P group. There was significant difference in Gem+nab-P group but no in FOLFOXIRI group, compared with control group. Would



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you provide the detailed SPSS statistical analysis file? As for table 6, i don't think those comparisons were logical. You can't compare your zebrafish survival data with those literature data representing the real clinical effective rate of chemotherapy on human being. This part of result should be deleted. Minor problems... 1/ page 8, "introduction" paragraph 1 line 3. The data about the median survival time and 5-year overall survival rate of PDAC should be update. 2/ page 8, "introduction" paragraph 1 line 3. The authors stated "The annual death rate for PDAC is almost equal to the incidence rate". Is there any references supporting this statement? 3/ page 8, line 13-14. The data about the rate of severe side effects and the specific chemotherapy regimens should be clearly stated. 4/ According to reference 6, the zebrafish model had been used to transplant PDAC tissue. And zebrafish model also was used on other cancer types. Is any similar studies performed on other cancer types towards personalized medicine, like breast cancer?



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 53534

Title: Use of zebrafish embryos as avatar of patients with pancreatic cancer: A new xenotransplantation model towards personalized medicine

Reviewer's code: 02544751

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Doctor, Professor, Surgeon

Reviewer's Country/Territory: Slovakia

Author's Country/Territory: Italy

Manuscript submission date: 2019-12-31

Reviewer chosen by: Le Zhang

Reviewer accepted review: 2020-02-14 11:18

Reviewer performed review: 2020-02-23 15:11

Review time: 9 Days and 3 Hours

Scientific quality	<input checked="" type="checkbox"/> Grade A: Excellent [] Grade B: Very good [] Grade C: Good [] Grade D: Fair [] Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing [] Grade B: Minor language polishing [] Grade C: A great deal of language polishing [] Grade D: Rejection
Conclusion	<input checked="" type="checkbox"/> Accept (High priority) [] Accept (General priority) [] Minor revision [] Major revision [] Rejection
Re-review	[] Yes [] No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous [] Onymous Conflicts-of-Interest: [] Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

Recension of manuscript No. 03714071: „ The use of zebrafish embryos as Avatar of patients with pancreatic cancer: A new xenotransplantation model towards personalized medicine, written by Gregorio Di Franco, Alice Usai, Matteo Palmeri, Matteo Bianchini, Desirée Gianardi, Niccolò Furbetta, Simone Guadagni, Luca Emanuele Pollina, Niccola Funel, Enrico Vasile, Alfredo Falcone, Vittoria Raffa, Luca Morelli“, which will be published in World Journal of Gastroenterology. The structure of manuscript is in keeping with the common required criteria. The topic of the work is very actual, because pancreatic cancer is a very aggressive malignancy with a poor prognosis. The response to chemotherapy treatment of patients with pancreatic ductal adenocarcinoma (PDAC) is difficult to predict and the identification of patients who most likely will benefit from aggressive chemotherapy approaches is crucial. Authors developed a simple, not expensive, diffusible zebrafish embryo model as avatar for patients affected by PDAC. Authors investigated the response of zebrafish xenografts to the chemotherapy options and authors analyzed the results by monitoring the fluorescent stained area. The described model appears to be an effective, usable and not expensive model for the xenotransplantation of pancreatic tumor tissue and for the evaluation of the efficacy of the different chemotherapy schemes available for the treatment of patients with PDAC. Work is clearly legible, brings summarizes new knowledge. The citations are actual and their format respect usual standards. This study could open a new frontier to personalized medicine because the results of the tests obtained in the present model in the xenotransplanted zebrafish embryos could reflect the clinical course of the patients' medical history, and such an approach might improve the evaluation of the patient's prognosis and the identification of the most appropriate individualized therapy. I recommend the manuscript to be published. Kosice, 21. February 2020 MUDr. Jana



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Katuchova, PhD. Professor of Department of Surgery University Hospital Košice
Slovakia



RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 53534

Title: The use of zebrafish embryos as avatar of patients with pancreatic cancer: a new xenotransplantation model towards personalized medicine

Reviewer's code: 00225294

Position: Editorial Board

Academic degree: BM BCh, PhD

Professional title: Doctor, Professor, Senior Research Fellow

Reviewer's Country/Territory: Spain

Author's Country/Territory: Italy

Manuscript submission date: 2019-12-31

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Reviewer performed review: 2020-04-14 08:57

Review time: 20 Hours

Scientific quality	<input checked="" type="checkbox"/> Grade A: Excellent [] Grade B: Very good [] Grade C: Good [] Grade D: Fair [] Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing [] Grade B: Minor language polishing [] Grade C: A great deal of language polishing [] Grade D: Rejection
Conclusion	<input checked="" type="checkbox"/> Accept (High priority) [] Accept (General priority) [] Minor revision [] Major revision [] Rejection
Peer-reviewer statements	Peer-Review: [] Anonymous <input checked="" type="checkbox"/> Onymous Conflicts-of-Interest: [] Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS



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The text has been significantly improved. Please check the version since the links to references appear in some parts of the text.



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Name of journal: World Journal of Gastroenterology

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Title: The use of zebrafish embryos as avatar of patients with pancreatic cancer: a new xenotransplantation model towards personalized medicine

Reviewer's code: 03664719

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Professional title: Professor

Reviewer's Country/Territory: United Kingdom

Author's Country/Territory: Italy

Manuscript submission date: 2019-12-31

Reviewer chosen by: Le Zhang

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Reviewer performed review: 2020-04-14 10:29

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
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Peer-reviewer statements	Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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Although some general concerns remain, the authors have satisfactorily answered most of the questions/concerns of the reviewers. I believe that this is an interesting and valid manuscript that has been strengthened by the additions/changes.