Project: Identification of novel functional and molecular targets for cardiac glycosides beyond the heart Na/K ATPase: focus on estrogen-dependent cancer inflammatory microenvironment
Applicant: Bolego Chiara

General assessment of scientific quality and innovation

Reviewer n. 1

Project aimed at expanding on NKA inhibitors and their use in tumour therapy. Use of CGs as anti-angiogenesis agents already claimed in 2006 in a patent application. Further studies on interactions of tumour microenvironment and tumour-associated macrophages of great interest.

Reviewer n. 2

Project related to anticancer therapy with digitoxin. In principle, the project seems interesting but reviewing literature I found that part of this project (at least tasks 1 and part of tasks 2 and 3) appears already carried out and published this year by the team (article in Biochem Pharmacol. August 2018). Therefore, the project is not fully novel.

Reviewer n. 3

A potential for re-purposing drugs with the well-known pharmacology for the treatment of incurable diseases is an attractive proposition. In this respect, the anti-cancer effects of cardiac glycosides are certainly interesting. Understanding whether it is a direct effect on cancer cells or on neovascularisation or as suggested here, on tumour-associated macrophages would be needed if this group of drugs is to be used in oncology. Acute and chronic toxicity of CGs might however be a problem in re-purposing these drugs.
While the generic nature of CG makes them inexpensive, it is also likely to result in limited interest of the big pharma and thus funding streams.
Project involves local and regional but not international collaboration.

Reviewer n. 4

The project is fairly scientifically significant, original and innovative. CG as anti-cancer are not new
It is built on a departmental know-how and has a significant impact for future development. It has perspective for international collaborations, applications, networking and the character of start-up research that can attract in the future competitive and non-competitive funds
Project question: Cardiac glycosides as anti-cancer drugs (tumor microenvironment and in vivo). Effect in angiogenesis. Is FAK (non receptor tyrosinekinase) a target? Affect the migration and growth of estrogen-dependent tumor cells but not normal cells.

Assessment of scientific plan

Reviewer n. 1

Scientific plan well written, with detailed methods and timeline. Possible additional activities also specified. Travel costs are high.

Reviewer n. 2

No list of references is given. The project makes reference to other CGs than digitoxin but they are not specified.
A young postdoctoral fellow is proposed to be hired to perform experiments but not for the whole project duration. No clear profile and activities described for this fellow.

Reviewer n. 3

The projects background indicates a focus on tumour associated macrophages, but experiments lean towards tumour cell analysis – this is unclear. Also, applicants already identified a direct effect of CGs on FAC signalling but makes relatively little use of this mechanism in the study. The in vivo study may be hampered by the lack of digitoxin data – a preliminary study suggested in the contingency plan would make sense.
High travel costs compared to overall expenditure – why?

Reviewer n. 4

The objectives and hypotheses are clearly presented and the plan is realistically feasible. Research methods, materials, work packages and timeline are not completely appropriate and in agreement with deliverables. The project supported by adequate human resources
Task 1: 8 months is too long.
One ovarian carcinoma cell line, and two breast cancer. Why these cell lines and no others? Why SKOV3, cell line full of mutations.
Task 2: Anoikis assay: why? Which controls?
Task 3: Assess the phosphorylation of purified recombinant FAK kinase (from Merck), why? Should be downstream. Not in the cellular environment.

Task 4: is the cancer model subcutaneously injected with OC cells a good model for ovarian cancer? Why don´t they inject intraperitoneal directly? Explain.

Competence and expertise of the applicant.

Reviewer n. 1

The applicant has expertise in inflammation but she got involved in research in oncology only recently. This notwithstanding, her long-standing experience in research and inflammation guarantee she can efficiently lead the project.

Reviewer n. 2

The PI is a very experienced researcher in the project field. Good publication level and good impact. Previous work published in the project topic

Reviewer n. 3

These are very appropriate and very good.

Reviewer n. 4

The competence and expertise of the applicant are appropriate and sufficient for the proposed project
The CV ends in 2007 in Milan. Until now?

Competence and expertise of the research team.

Reviewer n. 1

The team members are researchers with appropriate and complementary expertise in cancer to move the project forward.

Reviewer n. 2

The team is composed by two additional experienced researchers in cancer research, who provide complementary skills.
No international collaboration described in the project.

Reviewer n. 3

This project involves local and regional collaborators with overlapping and complementary expertise of a high standard but not international collaboration.

Reviewer n. 4

The research team brings complementary expertise to the project. The project is not involved in international research collaborations that can significantly contribute to the success of the project.

Overall assessment

Reviewer n. 1

Off-target activities of cardiac glycosides are known from quite some time. The project will result in incremental knowledge on the topic. However, the aim of specific repositioning CGs for the treatment of specific tumours is valuable. Risk analysis and contingency plan appear weak.

Reviewer n. 2

The project has already been partially carried out and published.

Reviewer n. 3

This project is based on an interesting discovery and has a potential to add to the anti-cancer *instrumentarium*. But it veers from the aims of TAM analysis into the cancer cell effects and between the in vitro analysis of mechanisms into the in vivo study with a drug with a poorly established pharmacology. It's outcome is therefore risky.

Reviewer n. 4

Digitoxin repositioning interesting.
They want to submit later on a proposal to study ocular haemangiomas, then why do they use OC here as a model? Why is the postdoc not sent out for six months abroad to do additional experiments?

Valutazione Commissione Interna

Il progetto di ricerca è ben strutturato nella sua organizzazione e si identificano in maniera chiara gli obbiettivi finali. La tematica affrontata si va a collocare in un'area farmaceutico/farmacologica di particolare interesse scientifico come quella del riposizionamento dei glicosidi cardioattivi in ambito oncologico. Appropriato il profilo scientifico del proponente e chiaro il suo personale contributo nello svolgimento dell'attività scientifica prevista dal progetto. Adeguati e complementari i profili scientifici dei partecipanti anche se che non emerge la presenza di un partenariato (accademico e/o industriale) ampio per dare un respiro internazionale al progetto.

Sono state evidenziate alcune criticità che vengono qui di seguito riassunte: a) alcune attività previste dal progetto, in particolare quelle in parte descritte nelle sezioni 2 e 3, sembrerebbero già state documentate in recenti pubblicazioni scientifiche; b) alcuni dettagli sperimentali relativamente all'investigazione meccanicistica dei glicosidi cardioattivi selezionati per lo studio sia in vitro che in vivo non vengono riportati con la giusta chiarezza; c) la bibliografia così come riportata nel progetto risulta estremamente difficile da poter essere consultata/utilizzata; d) non si evince chiaramente quali nuove e concrete opportunità farmaceutiche/terapeutiche possano emergere da questo studio; e) il profilo ed il ruolo della posizione di post-dottorato acquisibile nel progetto non sono chiaramente descritte.

Project: Preclinical characterization of new TMA analogues as CFTR modulators

Applicant: Chilin Adriana

General assessment of scientific quality and innovation

Reviewer n. 1

The proposal is a technology-oriented project. The scientific innovation relies on the compounds previously identified by the applicant. Activities that will be carried out are routinely applied in drug discovery projects.

Reviewer n. 2

The project is scientifically significant, original and innovative, it is apparently not built on a departmental know-how. It has a significant impact for future development, but perspectives for international collaborations, applications, networking are not described. The project has possibly the character of start-up research that can attract in the future competitive and non-competitive funds. This project is a follow up of previous research of the group where they developed TMA derivatives with potential for cystic fibrosis treatment without the side effects of TMA. The project aims to characterize the pharmacokinetic behaviour and metabolic stability of the compounds.

Reviewer n. 3

This is a follow up form the last year project. It is understood that TMA analogues with a potential to act as CFTR modulators have now been synthesised and results have been published. This project focuses on their characterisation, formulation and pre-clinical studies. Project builds on departmental expertise and have some potential for future development and collaborations. However, the potential for international collaborations suggested in the last year proposal is not reflected in this application. It is not clear why. Also, the external funding is not clearly delineated.

Reviewer n. 4

TMA active in CFTR but mutagenic, so found derivatives now in vivo tox ADME.

Assessment of scientific plan

Reviewer n. 1

The objective and the tasks are clearly presented. Project activities can be completed in the two-year time frame.

Reviewer n. 2

The compounds are not described in detail in the application. You have to go to the literature to identify them. Some parts of the work plan are vaguely described.
Workplan and timeline appear feasible and well organized.
Three young researchers and a PhD student to be enrolled but the funds to hire him/her are not specified and not allocated in the budget.

Reviewer n. 3

The project follows the logical developmental path from the synthesis of new derivatives to their evaluation. Its cost is very high, and it is not clear whether it will deliver return on this investment.
The project mentioned employing a PhD but this post is not financed here. Experiments are to be undertaken by the team members.

Reviewer n. 4

The objectives and hypotheses are clearly presented, the research plan is realistically feasible and research methods, materials, work packages and timeline are appropriate and in agreement with deliverables. The project is supported by adequate human resources.
Comments on the modifications in the lactone ring and the benzene ring but there is no figure with the formula.

Competence and expertise of the applicant.

Reviewer n. 1

The applicant has long-standing experience in the medicinal chemistry of the class of compounds that will be studied. Therefore, she will be able to provide an important support to team activities and bring forward the project.

Reviewer n. 2

The merits and scientific expertise of the applicant are appropriate and sufficient for the proposed project
The applicant is a well-experienced researcher in the field and the project is based on her previous work. She has a good publication record and experience as project leader.

Reviewer n. 3

Very appropriate for this proposal.

Reviewer n. 4

The merits and scientific expertise of the applicant are appropriate and sufficient for the proposed project.
Long time expertise

Competence and expertise of the research team.

Reviewer n. 1

Team members have the complementary expertise to move the project forward. No international collaborations is in place on the objectives of the project.

Reviewer n. 2

The research team brings complementary expertise to the project. International research collaborations that can significantly contribute to the success of the project are not described.
The team is composed by several mid-aged researchers with complementary expertise in the needed tasks.
No international collaboration involved.

Reviewer n. 3

There is a complementarity in the team. The experiments are to be undertaken by the team members with a possibility of a PhD to be involved but funding for this post not identified. It is surprising that successful synthesis of these derivatives is not driving any international collaborations.

Reviewer n. 4

The research team brings complementary expertise to the project. International research collaborations that can significantly contribute to the success of the project are not foreseen.

Overall assessment

Reviewer n. 1

The proposed activities can be regarded as a lead optimization process of a typical drug discovery process. This is a very important step toward the nomination of a preclinical development candidate. As such, however, the project has limited scientific innovation.

Reviewer n. 2

Strengths: Follow up of previous successful research with solid results and several publications. Clear workplan and feasible timeline. Complementary team of mid-aged researchers.
-Weaknesses: No funds allocated for PhD student. No international collaboration.

Reviewer n. 3

Clearly, the Applicant demonstrated perseverance and capability to achieve goals. This is a follow up from the last year project. The TMA analogues have now been synthesised and results have been published. This project focuses on their characterisation, formulation and pre-clinical studies. While it remains to be demonstrated that this project can attract significant external funding and international collaborations, it has been advanced since the last year and therefore could receive funding to help it achieving its potential. However, the requested funding is very high and has not been justified sufficiently.

Reviewer n. 4

Promising preliminary results in cells. Publications. Very clear.

Valutazione Commissione Interna

Così come già riportato nella relazione conclusiva dello scorso anno, la tematica affrontata in questo progetto di ricerca si va a collocare in un'area terapeutica, come appunto quella relativa al trattamento della fibrosi cistica, di grande interesse scientifico e con importanti ricadute socio-sanitarie. Il progetto di ricerca è ben strutturato nella sua organizzazione e si caratterizza primariamente per una profilazione farmacologica preclinica e formulativa di analoghi della TMA precedentemente sintetizzati e caratterizzati da un punto di vista della loro potenziale efficacia terapeutica. In questo senso il ruolo del proponente nelle attività di ricerca è prevalentemente rivolto al coordinamento delle attività descritte. Adeguati e complementari i profili scientifici dei partecipanti anche se che non emerge la presenza di un partenariato (accademico e/o industriale) ampio per dare un respiro internazionale al progetto.
Sono state evidenziate alcune criticità che vengono di seguito riassunte: a) alcune delle attività previste dal progetto, in particolare quelle legate alla profilazione metabolica e ADMET, sono descritte in maniera eccessivamente generica che, in mancanza della struttura dei composti presi in esame, rende difficile apprezzare l'impegno temporale e la strategia metodologica utilizzabile; b) in alcune sezioni, la bibliografia così come riportata nel progetto risulta mancante o estremamente difficile da poter essere

consultata/utilizzata; e) nell'organigramma è previsto il reclutamento di un dottorando di ricerca, il cui ruolo nel progetto, ma soprattutto la copertura finanziaria della borsa corrispondente, non sono chiaramente descritti. Qualora questa posizione non fosse ricopribile non è evincibile quale unità di personale supplirebbe nell'esecuzione delle attività assegnate al dottorando di ricerca, o quali attività previste non potrebbero essere portate a buon fine; d) non si evince chiaramente per quali ragioni la via di somministrazione inalatoria non sia stata presa in considerazione.

Project: Molecular mechanisms involved in musculoskeletal disorders in oncological patients treated with tamoxifen: basis to develop promising treatments to prevent disability and improve quality of life
Applicant: Montopoli Monica

General assessment of scientific quality and innovation

Reviewer n. 1

The project aims at addressing specific side effects of tamoxifen in oncology patients. The topic is clearly described. However, the literature references appear not up to date, and articles' titles and journals are not reported. Citing more recent literature would have helped having a more comprehensive picture.

Reviewer n. 2

The project is scientifically significant, original and innovative, it is apparently not built on a departmental know-how. It has a significant impact for future development, but perspectives for international collaborations, applications, networking are not described. The project has possibly the character of start-up research that can attract in the future competitive and non-competitive funds. This project combines in vitro and in vivo study of the side effects of TMX on mitochondrial dysfunction and its effects on musculoscheletal problems associated to TMX treatment of cancer.
I did not find previous work published by the applicant in the topic covered.

Reviewer n. 3

The project is scientifically significant, original and innovative and it is built on a departmental know-how. It has a significant impact for future development, but perspectives for international collaborations, applications, networking are not described. The project has the character of start-up research that can attract in the future competitive and non-competitive funds. Estrogen Receptor + patients under tamoxifen therapy, present musculoskeletal disorders. ERs express in mitochondria,: TMX treatment affects scheletal muscle and interaction with physical exercise. Effect of TMX in muscle; mitochondria genotyping to predict response; mitoprotection for TMX side effects.

Reviewer n. 4

There is a noticeable absence of recent citations on the subject of ER and TMX on muscle and bones, which severely affects my enthusiasm for this project as being "cutting edge" and that it will attract external funding. For example: Review on oestrogen receptor in skeletal muscle homeostasis (https://onlinelibrary.wiley.com/doi/pdf/10.1111/apha.12341). Tamoxifen in mitochondria (https://www.nature.com/articles/s41419-018-0607-9). Furthermore, tamoxifen has been used as a treatment in the chronic muscle disease with inflammation (Duchenne MD) model (https://www.ncbi.nlm.nih.gov/pubmed/23332367). Just this paper can shed some light on the proposed experiments. I am not sure the proposal is built on in the departmental expertise.

Assessment of scientific plan

Reviewer n. 1

Objectives are clearly presented. The applicant refers to compounds that could protect mitochondria but does not provide examples. In Task 4, it is not clear which compounds the team will test in combination with tamoxifen.

Reviewer n. 2

The objectives and hypotheses are clearly presented, the research plan is realistically feasible and research methods, materials, work packages and timeline are partially appropriate and in agreement with deliverables.
The project is supported by adequate human resources.
No list of references in the state of the art is provided.
Some parts of the work plan, especially Tasks 3 and 4 are not well described and are difficult to understand.
Especially Task 4 is not properly described. Mitoprotector agents are not described.
Compounds to be tested as protectors are not described.
Deliverables and milestones are confusing.
The project does not involve any fully dedicated young researcher but includes funds for hiring one.
The budget is vaguely defined. Includes funds from associated grant.

Reviewer n. 3

The objectives and hypotheses are clearly presented, the research plan is realistically feasible and research methods, materials, work packages and timeline are appropriate and in agreement with deliverables. The project is more or less supported by adequate human resources.

Which compounds are going to be selected in task3? How? Ar and ERs inhibitors…. Explain. Mitochondria protection.
Task4: "a dose response analysis…" where? Cells, mice?
Tasks are not clearly assigned to the collaborators.

Reviewer n. 4

The experiments proposed will provide answers to some of the questions but they not always built on the existing and published knowledge. The selection of targets to be analysed is not explained sufficiently. Moreover, PCR analysis of MMPs is insufficient as it is the activities not transcript levels of these proteases that are important and the two often not correlate.

Competence and expertise of the applicant.

Reviewer n. 1

The background of the applicant is appropriate for leading the proposed project.

Reviewer n. 2

The merits and scientific expertise of the applicant are very good and they are appropriate and sufficient for the proposed project
The applicant is a bright young researcher with good potential. Good publication rate. Experience as PI.

Reviewer n. 3

The merits and scientific expertise of the applicant are appropriate and sufficient for the proposed project

Reviewer n. 4

The applicant has an excellent track record and works in the appropriate area

Competence and expertise of the research team.

Reviewer n. 1

The team members have complimentary expertise. It is not clear, however, the role of one of the member (AF), who appears to be only the contact point with a researcher (Milena Fini) not directly part of the team. Team members work in different Institutions and this could affect a smooth progression of activities. No international research collaborations are in place.

Reviewer n. 2

The team is composed by two assistant professors and a group leader of different Italian universities. The researchers seem to provide complementary expertise.
No international collaboration involved.

Reviewer n. 3

The research team brings complementary expertise to the project. The project is not involved in international research collaborations that can significantly contribute to the success of the project.

Reviewer n. 4

The assembled team is very good and appropriate for the task. It involves mostly local and no international collaborations.

Overall assessment

Reviewer n. 1

The project will address an unmet medical need for patients receiving tamoxifen. If the team manages to identify molecular mechanisms related to TMX side effects, this could trigger new efforts in the field. Careful planning and networking necessary as team members work in different Institutions.

Reviewer n. 2

Strengths: The IP is a young researcher with good potential and good scientific production. The project is based on collaboration by several groups from different Italian universities.
Weaknesses: No previous results published in the topic. The project seems to be new. The work plan is vaguely described in tasks 3 and 4. No international collaboration mentioned.

Reviewer n. 3

(-) last part is not described how it will be done. Assignment of tasks to collaborators?
In the abstract: 1) TMX effect in vitro in vito. 2) potential of patients´mitochondria genotyping to predict their response to therapy. 3) mitroprotection as a new strategy. Objectives and 3 not foreseen in the tasks.

Reviewer n. 4

This is a difficult proposal to evaluate. It comes from an accomplished researcher who assembled a very good team of collaborators. However, the proposal is vaguely described, does not take the latest data into consideration and the methodology fails to convince.

Valutazione Commissione Interna

Il progetto di ricerca risulta essere nel complesso ben strutturato e identifica in modo pertinente gli obbiettivi finali, presentando alcuni elementi di innovatività (come appunto il ruolo del tamoxifene nell'omeostasi mitocondriale) pur collocandosi in un'area terapeutica tradizionalmente ad elevatissima competitività, come appunto quella oncologica. Appropriato il profilo scientifico del proponente anche se non emerge in maniera chiara il suo personale contributo nello svolgimento dell'attività scientifica prevista dal progetto. Adeguati e complementari i profili scientifici dei partecipanti anche se che non emerge la presenza di un partenariato (accademico e/o industriale) ampio per dare un respiro internazionale al progetto. Da sottolineare, che la maggior parte delle attività ricerca previste sembrerebbero essere sostenute dalla rete di collaborazioni che il proponente ha instaurato.
Sono state evidenziate alcune criticità che vengono di seguito riassunte: a) alcune attività previste dal progetto, in particolare quelle riconducibili alle sezioni 3 e 4, non vengono riportare con la giusta chiarezza e completezza descrittiva; b) si riscontra una parziale incoerenza tra alcuni degli obbiettivi riportati nel riassunto del progetto, le metodologie descritte nelle diverse sezioni e gli obbiettivi finali auspicati alla conclusione del progetto; c) la descrizione dell'utilizzo del finanziamento è poco dettagliata; d) il profilo ed il ruolo della posizione di borsista acquisibile nel progetto non sono chiaramente descritte; e) non si evince chiaramente quali nuove e concrete opportunità farmaceutiche/terapeutiche possano emergere da questo studio.

Project: Interplay between muscle and brain metabolic homeostasis in Hereditary Spastic Paraplegia diasease: Drosophila as a tool for new targets and drugs discovery
Applicant: Genny Orso

General assessment of scientific quality and innovation

Reviewer n. 1

The aims are to improve the knowledge on a set of rare genetic diseases and, possibly, finding tool compounds that could be further developed. This is an innovative and challenging project, with high potential for future development, collaborations, and application for competitive funds. Rationale of the project well presented with many references.

Reviewer n. 2

The research proposed tackles the molecular and biochemical mechanisms of a rare disease (HSP) using a combined gene transcription and biochemical approaches.
Lack of HSP treatment makes the project very attractive. Good potential for future development of results in case of identification of active compounds.
Interesting use of Fruit Fly as model of HSP.

Reviewer n. 3

Question of the project: Which is the influence of muscle in neurodegeneration in Hereditary Spastic Paraplegia using Drosophila as a model? Lipid droplets turnover/biogenesisin HSP models is a problem in neurodegerneration? Search for small molecules with activity in the identified metabolic pathways. Influence of autophagy.
Many mentions to Drosophila as a good model for HSP, but no reference. Is it??
Are there supportive preliminary results?
If there is a perspective for international collaborations is not mentioned.

Reviewer n. 4

This is a scientifically significant and interesting project targeting an orphan and under-researched pathology. Understanding these complex abnormalities could lead to therapies and also help our understanding of several important cellular mechanisms. The project suggests using an innovative approach and an interesting animal model. Therefore, it has a significant developmental potential, also for impact. Proposal exploits existing collaborations and should lead to the development of further collaborations. It also has potential to attract significant future funding. It is not clear to me whether there is a departmental know how in this area, but the applicant has all the relevant knowledge and the project is clearly of the start-up nature.
However, the project appears over-ambitious.

Assessment of scientific plan

Reviewer n. 1

The objectives and hypotheses are clearly presented. There are many planned activities, and deliverables appear challenging considering the timeframe of the project and the resources allocated. Task 4, although interesting, appears somewhat unrelated to the previous ones. It is not clear where NGS and screening will be performed.

Reviewer n. 2

Objectives are mixed in some parts with the state of the art at are not clearly presented.
The objectives appear very ambitious but I am unable to evaluate of they can be fulfilled for such a small project. Contingency plan is well described.

Reviewer n. 3

The costs will be definitively higher. Task4: For compounds is foreseen 5000 EUR. The metabolic collection of Selleckchem costs 9456 $ only one plate with 100 compounds. They have a max of 513 small-molecules.
Enzo does not offer a metabolic collection itself, they will have to choose the compounds.
Not described if it is the main project of the student (Barbara Napoli) or a secondary project. In fact it is not told if this is her PhD project.

Reviewer n. 4

All the aspects of the project are described relatively well. Unfortunately, it is unfocussed, which makes it unrealistic. While the methods are presented and I am confident the applicant and the team are fully capable of undertaking this work successfully, I fear that they try to achieve too much. Generation of mutant flies with a selective downregulation of spastin and REEP1 in muscle, neuron and glia, RNAseq analysis and

subsequent investigations of pathways and finally drug screening would require time and effort and also money.
It is not clear how many replicates will be used for RNAseq and too few replicates may invalidate these data, and thus the starting point of this project. If minimum 3 replicates are used for muscle and brain in each mutant the cost will be significant. It appears that co-applicants, who are senior scientists, will perform bioinformatics analyses. This might be a bottleneck.
There is a PhD student involved, who will presumably undertake the bulk of experimental work.

Competence and expertise of the applicant

Reviewer n. 1

The applicant's background is suitable to lead the project. She has previous experience and relevant publications in the field.

Reviewer n. 2

The PI has previous expertise working with fly models of HSP and identifying an active compound. Good level of publications, some of them in outstanding journals but none yet as corresponding author.

Reviewer n. 3

Broad experience in Drosophila as a model.
No own project until now.
No first author publication between 2009 (yet a Nature) and 2016. There will be publications out of this project?

Reviewer n. 4

This aspect is excellent.

Competence and expertise of the research team

Reviewer n. 1

The team is composed of researchers with complementary experience that allows addressing all the work packages. No international research collaboration is in place.

Reviewer n. 2

The team involves two experienced researchers from other Italian universities who bring the complementary expertise. A PhD student directly involved in the experiments.
A related international grant covers part of the funding but interaction with this grant is not specifically described in the application.

Reviewer n. 3

Senior collaborator, Prof. Ferri the publications are not really related.
Dr. Vantaggiato, good experience in transcriptional profiling (NGS).
No international research collaborations.

Reviewer n. 4

The team is excellent, members bring complementary expertise. The team is national and so internationalisation would be desirable.

Overall assessment

Reviewer n. 1

Research topic interesting and offering opportunities to clarify mechanisms important for other pathologies. Risk analysis and contingency plan addressed. Milestones appear challenging. The timeframe for completing the proposed activities may be short. Money appears not enough to perform all activities.

Reviewer n. 2

Strengths: Innovative and original project. PI has previous experience in this type of research. Very experienced team and a young researcher directly involved. Clear objectives and deliverables.
Weaknesses: Objectives appear ambitious for such a short project. Risky project with many difficulties. Possible International collaboration not clearly described in the project.

Reviewer n. 3

(+) Novelty.
(-) Task1 not well described (UAS-GAL4 system); which starting material to perform next generation sequencing? Project not easy to read for not Drosophila experts, for example "The effects of compounds will be monitored every day until the eclosion", why? When is eclosion happening? A graphic would have been helpful. On the contrary, Fig. 3 does not give information**.** In the written application, English spelling-check should be performed. See intro. Besides Fig.2 which should be Fig. 1 is not explained: enzymes, acronyms etc. Sense?
"Drosophila models of HSP genes have been extensively used in the last years to decipher the main mechanisms of neurodegeneration" No reference when it has been extensive. Only one Drosophila reference

For me it is not clear an alternative if the milestones are not working.
The funding will be short at least for Task 4.
No foreseen international collaborations.

Reviewer n. 4

It is a very impressive proposal based on an excellent idea and great preliminary data. The applicant is a world-class scientist with expertise in this area. I would support this project fully if it were focussed and abovementioned points regarding the work packages were explained.

Valutazione Commissione Interna

Il progetto di ricerca è ben strutturato nella sua organizzazione e si identificano in maniera chiara gli obbiettivi finali. Pur essendo caratterizzato dalle peculiarità di introdurre a livello dipartimentale il modello della Drosophila come nuovo approccio di screening farmacologico, le finalità della ricerca nella loro scansione temporale, nella richiesta di risorse umane ed economiche appaiono eccessivamente ambiziose. Indubbio il valore dell'approccio scientifico/metodologico da un punto di vista dell'attrattività da parte di altri gruppi di ricerca e da realtà industriali operanti nell'ambito bio/farmaceutico.
Appropriato il profilo scientifico del proponente e chiaro il suo personale contributo nello svolgimento dell'attività scientifica prevista dal progetto. Anche se i profili scientifici dei partecipanti al progetto sono di ottimo livello, risulta difficilmente enucleabile, almeno per alcuni di loro, il loro reale ruolo ed il loro contributo all'interno delle attività previste dal progetto. Inoltre, non emerge la presenza di un partenariato (accademico e/o industriale) ampio per dare un respiro internazionale al progetto stesso.
Sono state evidenziate alcune criticità che vengono di seguito riassunte: a) in alcune sue parti, il progetto perde di chiarezza e completezza descrittiva; b) non viene descritta la competenza nell'effettuare una accurata analisi bioinformatica per una descrizione robusta delle profilazioni genetiche riportate nel progetto; c) il finanziamento assegnabile al progetto è assolutamente inadeguato rispetto agli obbiettivi enumerati nel progetto; d) non si evince chiaramente quali nuove e concrete opportunità farmaceutiche/terapeutiche possano emergere da questo studio.

Project: Application of hydrogen exchange mass spectrometry in molecular medicine - Probing protein structure and dynamics in protein systems of biopharmaceutical interest
Applicant: Spolaore Barbara

General assessment of scientific quality and innovation

Reviewer n. 1

This is a technology-driven project. The aim is to implement a technique that is already described in the literature and applied at several Institutions. This technique could definitely help progressing other projects in the department, but it cannot be considered original and innovative.

Reviewer n. 2

Challenging project that is aimed to incorporate a new powerful technique such as HDX-MS to characterize conformational dynamics of several proteins of therapeutic interest from the own lab or through external collaborations. No international collaboration is described in the project to support the application. Potential for future industrial collaborations is mentioned.

Reviewer n. 3

This application is firmly anchored in the departmental know how, exploits the existing equipment, proposes very interesting targets for analyses and exploits well-defined collaborative links. Therefore, it has all the making of a project that can attract further funding and international collaborations.

Reviewer n. 4

The project is scientifically significant, original and innovative, it is built on departmental know-how, has a significant impact for future development, perspective for international collaborations, applications, networking and the character of start-up research that can attract in the future competitive and non-competitive funds.

Assessment of scientific plan

Reviewer n. 1

The objectives and plans are clearly presented. Tasks are applications of the technique to different research fields.

Reviewer n. 2

Workplan details are scarce.
The project involves testing a large number of proteins and may be quite challenging considering the available human power allocated to the project and the relatively limited experience of the participants in the technique.
A postdoc with experience in HDX-MS will be hired for 1 year.
Clear workplan and deliverables.

Reviewer n. 3

This is not my area of expertise but I asked for a confidential input from an expert and understand the scientific plan to be very good.

Reviewer n. 4

The objectives and hypotheses are clearly presented; the plan is quite realistically feasible, the research methods, materials, work packages and timeline are appropriate and in agreement with deliverables and the project is supported by adequate human resources . The project proposes that the Postdoc will start in January and will have established the methodology already for February… Milestone 1-time period seems a bit short for that.

Competence and expertise of the applicant

Reviewer n. 1

The applicant has the scientific and technical expertise for leading the project.

Reviewer n. 2

The applicant has a reasonable record of scientific publications in the field of the project and a high citation rate. She made a postdoctoral period with Carol Robinson, one of the leading experts in Mass spectrometry of proteins, but she has not carried out recent specific research with the technique. She is experienced in protein research.

Reviewer n. 3

This is very appropriate for the project and the applicant is a very productive researcher with a significant track record.

Reviewer n. 4

Expertise in MS. Several publications in the last years (4 in 2018).

Competence and expertise of the research team

Reviewer n. 1

The team appears rather small: the main players will be the applicant and a post-doc that will be recruited. Other researchers seem to be involved just as supplier of specific proteins that will be studied with the technique.

Reviewer n. 2

The team is composed by two highly experienced researchers of the same university, who bring complementary experience. Other collaborations external to the Padova Univ. are involved.
No international collaboration is involved.

Reviewer n. 3

The team assembled is complementary and very appropriate. Potential for re-training in the right environment to be funded from this project.

Reviewer n. 4

International research collaborations will be established and a stay of the postdoc abroad also. The research team bring complementary expertise to the project, but at the moment the project is not involved in international research collaborations that can significantly contribute to the success of the project.

Overall assessment

Reviewer n. 1

The proposal appears as a technology-driven project that aims at implementing in the Department an already established technique. The availability of the technique could definitely help the progression of other research projects active in the Department, and allow establishing international collaborations and contacts with companies.

Reviewer n. 2

Strengths: Very powerful technique to incorporate to the Department expertise. Availability of the instrumentation at the Department. Highly experienced team in the systems of study. Based on previous published results.
Weaknesses: New technique in the group. Heterogeneity of the systems of study. The project relies upon training of a postdoc to be hired for one year. No international collaboration explicitly mentioned.

Reviewer n. 3

This project has a potential to fulfil the expectations of this grant scheme: It is scientifically original; the innovation builds on the departmental resources and expertise; can be impactful in terms of publications, further funding and new collaborations both academic and industrial.

Reviewer n. 4

Collaborative project that will strengthen the know-how in the department, with possibility of international collaborations and contacts with the industry.
Publications potential.

Valutazione Commissione Interna

Il progetto di ricerca è ben strutturato nella sua organizzazione e si identificano in maniera chiara e convincente gli obbiettivi finali. La sua peculiarità è quella di introdurre a livello dipartimentale una nuova tecnologia nell'ambito della spettrometria di massa basata sullo scambio idrogeno/deuterio (HDX) che potrebbe essere particolarmente attrattiva sia per le attività di ricerca di altri gruppi di ricerca a livello dipartimentale, extra-dipartimentale e di realtà industriali che operano in ambito bio/farmaceutico. Appropriato il profilo scientifico del proponente e chiaro il suo personale contributo nello svolgimento dell'attività scientifica prevista dal progetto, anche se non appare documentata una sua specifica competenza nell'ambito dell'implementazione e utilizzo della tecnologia HDX. Adeguati e complementari i profili scientifici dei partecipanti, anche se che non emerge la presenza di un partenariato (accademico e/o industriale) ampio per dare un respiro internazionale al progetto.
Le criticità intrinseche a questo progetto sono essenzialmente due: a) la necessità dell'implementazione strumentale per poter effettuare le attività previste dal presente progetto; e b) l'acquisizione di una persona che possa essere formata o, preferibilmente, che già lo sia in questo specifico ambito di lavoro.

Project: Novel curcumin analogues as inhibitors of amyloid ß-induced neuroinflammation in Alzheimer's disease
Applicant: Zusso Morena

General assessment of scientific quality and innovation
Reviewer n. 1
The proposal aims at exploring the involvement of microglia in the pathogenesis of AD. This is a new avenue of research that deserves being pursued. If encouraging results are obtained, the project has good perspectives for establishing collaborations and attracting competitive and non-competitive funds.
Reviewer n. 2
This is a very interesting and ambitious project based on previous research of the applicant on the effects of curcumin and derivatives on microglia activation and its impact in neurological disorders. It has a very good potential for future development and may have a high impact in AD research.
Reviewer n. 3
It is a high risk project dependent on the preparation and identification of curcumin derivatives that are better than those already available and even tested in clinical trials. Therefore, it is not very original and innovative. For example:
New approaches and formulations are being trialled: Sabinsa C3 complex, Meriva and Longvida.
Curcumin derivative has been described:
https://www.alzheimersanddementia.com/article/S1552-5260(16)32416-5/fulltext
Curcumin clinical trial: https://alzres.biomedcentral.com/articles/10.1186/alzrt146 showed no difference but another is underway: https://clinicaltrials.gov/ct2/show/NCT01811381?term=Frautschy&rank=1.
Project is based on departmental know-how but whether it can attract external funding is highly uncertain.
Reviewer n. 4
The project is not particularly original and innovative, but it is built on departmental know-how, has a significant impact for future development, perspective for international collaborations, applications, networking and the character of start-up research that can attract in the future competitive and non-competitive funds.
Assessment of scientific plan
Reviewer n. 1
The hypothesis and objectives are clearly presented. The timeline for the first year appears stretched. Activities will be conducted at three Universities; therefore, a proper planning and networking are needed. Risks reasonably outlined in the contingency plan.
Reviewer n. 2
Clear state-of-the-art. Previous results support the hypotheses and objectives. Clear objectives. A figure is missing illustrating the curcumin modifications approaches. A fellowship included in the budget to hire a young researcher.
Reviewer n. 3
The objective and hypothesis are presented clearly and are realistic but there is no fall-back plan if new derivatives do not offer an improvement over the existing compounds.
Reviewer n. 4
They mention that they will do amino acid derivatives of curcumin, but they do not explain why? Probably to use the amino acid transporter and go through the BBB. Not known until Task4 (not mentioned in Intro).
Task1 indicates modifications in curcumin, but there is no formula of curcumin.
“Brain levels and metabolism of the studied compounds will be measured… REF” Will be helpful a two sentences explanation of how. “percentage of Iba-1- and GFAP-stained area in cortical and hippocampal regions” not explained.
Bibliography: To indicate also the title is of help.
Competence and expertise of the applicant
Reviewer n. 1
The expertise of the applicant is in the field of the proposed project. She received several grants, including a PRID. Therefore, she is perfectly qualified to lead the program.
Reviewer n. 2
Competent young researcher with a strong recent publication record and demonstrated experience in the project topic.
Reviewer n. 3
Dr. Zusso is an excellent expert is in the field of molecular neuropharmacology but not in the synthesis and derivatisation of compounds. Therefore, the Applicant would be perfectly suited to investigate molecular mechanisms of action and effects of pharmacological compounds. But the project relies on the successful synthesis of new moieties, which would be entirely dependent on the co-applicants. The emphasis on the analysis of existing new compounds, that might perhaps be obtained through collaborations, would be a more attractive proposition.
Reviewer n. 4
Expertise with models of neuroinflammation.
Competence and expertise of the research team
Reviewer n. 1
Team members have complementary expertise. Although no international collaborations are in place, there is the potential to start new ones.

Reviewer n. 2
The applicant has merged a team composed by two experienced researchers from other Italian universities and a young researcher from the same department. No international collaboration is mentioned.
Reviewer n. 3
The team is well suited to undertake the project but see above.
Reviewer n. 4
Very good complementary team.
Overall assessment
Reviewer n. 1
The application aims at addressing a possibly important component of AD pathogenesis. The project has the potential to establish international collaborations, and attract funds. Proper planning and networking are needed as three Universities are involved in the project.
Reviewer n. 2
Strengths: Very interesting innovative project based on previous results of the team. Complementary and collaborative team. Very active and pushing PI. Potential for internationalization. Weaknesses: Highly competitive topic.
Reviewer n. 3
It is a high risk project building on the already exploited idea of curcumin analogues. Given that it relies heavily on the generation of new drugs, which are of uncertain quality/properties, preliminary data would be helpful but I appreciate it is a bit of a chick and egg situation.
Reviewer n. 4
If there is no derivative working there is no foreseen a plan B.

Valutazione Commissione Interna

Il progetto di ricerca risulta essere, nel complesso, ben strutturato e identifica in modo pertinente gli obbiettivi finali, anche senza presentare particolari elementi di innovatività, in particolare per quanto riguarda la scelta di utilizzare, in questa sperimentazione, la curcumina e i suoi analoghi. Dall'altro canto, indiscutibile la ricaduta che questi studi potrebbero avere in un'area terapeutica particolarmente rilevante, come appunto la patologia neurodegenerativa di Alzheimer. Appropriato il profilo scientifico del proponente e chiaro il suo personale contributo nello svolgimento dell'attività scientifica prevista dal progetto. Adeguati e complementari i profili scientifici dei partecipanti, anche se che non emerge la presenza di un partenariato (accademico e/o industriale) ampio per dare un respiro internazionale al progetto. Da sottolineare che una parte rilevante delle attività di ricerca previste sembrerebbero essere sostenute dalla rete di collaborazioni che il proponente ha instaurato.
Sono state evidenziate alcune criticità che vengono di seguito riassunte: a) alcune attività previste dal progetto, in particolare quelle riportate nelle sezioni 1 e 4, non vengono riportare con la giusta chiarezza e completezza descrittiva. Apprezzata sarebbe stata la presenza di alcuni schemi/figure che avrebbero facilitato la comprensione di alcuni aspetti meccanicistici cruciali riportati nel testo; b) scarso rilievo è stato posto alla profilazione ADME/Tox dei candidati, con particolare riferimento alla permeazione della barriera emato-encefalica; c) il profilo ed il ruolo della posizione di borsista acquisibile nel progetto non sono chiaramente descritte; d) non si evince chiaramente quali nuove e concrete opportunità farmaceutiche/terapeutiche possano emergere da questo studio.