

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID – ANNO 2021

COMMISSIONE ESTERNA

Project: NLRP3 inflammasome in Parkinson's disease: pharmacological modulation and impact of high fat diet on central and peripheral inflammatory processes

Applicant: Colucci Rocchina

General assessment of scientific quality and innovation - Assessment of scientific plan

- *Is the project scientifically significant, original and innovative?*
- *Is the project **built on a departmental know-how**? Has the project a significant **impact** for future development? Is the **plan realistically feasible**?*
- *Are the research **methods, materials, work packages, tasks, milestones and timeline** appropriate and in agreement with deliverables?*
- *Are the risk assessment and the contingency plan properly considered?*
- *This project has perspectives for **international collaborations, applications, networking**?*
- *Has the project the character of **start-up research** that can attract in the future competitive and non-competitive funds?*

Reviewer n. 1

The project is, on the whole, interesting and impactful for research and development in the field of etiological mechanisms associated with neurodegenerative diseases (in this case with specific interest in Parkinson's disease). The activation of the inflammasome and the gut-brain relationship, although already studied in recent years, are both of great interest and are a potential target for the treatment of patients. The ambition to combine basic science, pharmacological approach and lifestyle (preventive function) is a strong point, but along the description, it generates some inconsistencies and difficulties of understanding that penalize the overall meaning. Some objectives are, for example, not perfectly matching with the description of the experimental plan (which, moreover, is very concise and does not allow a clear understanding of the research activity). The amount of work seems to be somewhat higher than the duration of the project. Overall, it seems a bit unrealistic to do all this activity in the space of two years and with such a small budget. It would have been useful to understand if there were any support funds for the realization of the various phases.

Reviewer n. 2

While the proposal is based on a solid scientific background, its innovation and originality appear quite weak. The timelines are probably too long in view of the proposed activities. The use of a single compound in order to test a key hypothesis seems limiting the probability of success and this is underestimated in the risk assessment; why not considering compounds with different profiles, eg with respect to their absorption? Also, the use of natural extracts, whose composition is quite complex, seems out of the focus of the proposed research (mechanism understanding); it could be in case considered as a future and applicative expansion of the project.

Reviewer n. 3

This project is based on a significant problem and has the potential for impact and future funding. The proposal is well written and based on the hypothesis that Parkinson's disease may be associated with low grade inflammation. The aims work through the idea by exploring the expression of inflammasome components in periphery and central areas in a mouse model of PD and investigate this in the NLRP3 knockout mouse. The use of blueberry extract is questionable. The research plan is feasible, risks have been considered and contingency is presented. This holds good potential for further collaborations.

Competence and expertise of the applicant.

- *What are the **merits and scientific expertise** of the applicant?*
- *Are they **appropriate and sufficient** for the proposed project?*

Reviewer n. 1

Dr Colucci has an excellent curriculum, adequate for this type of studies, publications and previous studies confirm this opinion and justify the applicant's relevance for the following project. Dr Colucci's previous work experience is appropriate and well balanced for all the activities described.

Reviewer n. 2

The applicant has wide experience and scientific competence in the pharmacological area, sufficient to support the proposed activities. The project proposal appears though redundant for what concerns the description of the background information, while missing a general strategic view (eg exploration vs application, see above)

Reviewer n. 3

The main expertise of the applicant is in gut inflammation but also neurodegenerative diseases and she has an excellent track record in this area. The PI is appropriate for the study.

Competence and expertise of the research team.

- Does the research team bring complementary expertise to the project?
- Is the project involved in international research collaborations that can significantly contribute to the success of the project?

Reviewer n. 1

The team of collaborators, both internal and external, covers the different areas of the research and reveals, through the publications presented in the project, a proven theoretical experience inherent to the activity described. Also, as number of people, it seems to be well balanced for the duration and the amount that can be financed.

Reviewer n. 2

The team members have complementary experience with respect to the applicant and do represent a good network.

Reviewer n. 3

There is an international collaboration with UK (Lopez-Castejon). Bertinaria brings expertise in medicinal chemistry developing NLRP3 inhibitors. Pellegrini brings complementary expertise in gut inflammation and neurodegenerative diseases. An excellent team.

COMMISSIONE INTERNA

Prof.ssa Rocchina Colucci

Titolo del Progetto: *NLRP3 inflammasome in Parkinson's disease: pharmacological modulation and impact of high fat diet on central and peripheral inflammation processes*

Obiettivo: Caratterizzare il ruolo dell'infiammazione enterica mediata dall'inflammasoma NLRP3 sullo sviluppo della malattia di Parkinson mediante un modello murino indotto da rotenone su topi wild-type e NLRP2-KO. Un progetto molto simile è stato presentato dalla proponente nel 2020.

Punti di forza: Lo studio considera la possibilità di utilizzare farmaci (INF176) o sostanze di derivazione naturale nel modulare l'infiammazione enterica associata alla malattia di Parkinson. Il progetto mostra numerosi aspetti di innovatività. L'indagine valuterà l'effetto dei trattamenti proposti su numerosi parametri infiammatori e metabolici, oltre che sulla funzionalità del sistema nervoso. Il progetto risulta nel complesso ben strutturato ed è coerente con le linee di sviluppo del DSF. L'impatto del progetto sul Dipartimento può essere significativamente positivo. Il team è interdisciplinare e presenta anche una collaborazione internazionale. L'esperienza del PI appare adeguata. L'analisi dei rischi e le possibili soluzioni sono adeguatamente delineate. Nel complesso, il progetto presenta un elevato grado di fattibilità.

Criticità: Alcune parti dell'attività di ricerca non sono definite chiaramente. Nella descrizione dello studio, non è ben delineato il ruolo della *high fat diet* (HFD), nonostante questa sia indicata nel titolo, nell'abstract e nell'obiettivo del progetto. La HFD viene menzionata solo marginalmente nel Task 3. Non è definito chiaramente il *sample size* dello studio.

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID – ANNO 2021

COMMISSIONE ESTERNA

Project: New agents for multifaceted targeting of neurodegenerative diseases**Applicant:** Dalla Via Lisa**General assessment of scientific quality and innovation - Assessment of scientific plan**

- *Is the project scientifically significant, original and innovative?*
- *Is the project **built on a departmental know-how**? Has the project a significant **impact** for future development? Is the **plan realistically feasible**?*
- *Are the research **methods, materials, work packages, tasks, milestones and timeline** appropriate and in agreement with deliverables?*
- *Are the risk assessment and the contingency plan properly considered?*
- *This project has perspectives for **international collaborations, applications, networking**?*
- *Has the project the character of **start-up research** that can attract in the future competitive and non-competitive funds?*

Reviewer n. 1

The project submitted by Dr Dalla Via is extremely ambitious and has an important relapse. Reading the description, it is possible to realize that Dr Dalla Via is aware about the state of the art and the effort made to include many aspects of absolute importance within the project is certainly worthwhile. Unfortunately, the project reveals gaps in the construction and experimental plant. Although it is possible to understand the general purpose, it is sometimes vague in the explanations and presents parts, which in terms of shape or substance, seem not very related to each other. In particular, from the aims and background, it is difficult to understand the relationships between tau, Mao, kinases and their pluripotency in profoundly different pathologies such as AD and PD. The studies on the cellular patterns connected to them are not well described (we often talk about interesting preliminary results but then a clear explanation of them is not given). The description of WPs and tasks should also be a little more linear and exhaustive. The project is, as previously reported, very ambitious and can hardly be completed in 24 months and with the required budget (in this case it would be useful if this project is considered to support a larger and already funded project).

Reviewer n. 2

The proposed project is scientifically significant, feasible and original, while bringing a limited innovation in the field. A positive outcome would for sure trigger an extended research due to the very high medical need. All the required materials, methods and technologies are available to all the team members, while the risk assessment is in my opinion overestimating the probability of success for a number of Wps (ie the low risk of failure in the biological testing of new compounds).

Reviewer n. 3

The project has some originality and is quite well written. The commonalities between neurodegenerative diseases offer opportunities for intervention. Designing molecules targeting multiple proteins is key to the project. The research plan may not be completely feasible in the timeline as there is much characterisation to be done. Work packages are well described. Risks have been considered with contingencies suggested although there may be high risk if molecules do not have the required activity. There is already international collaboration and networking between other universities in Italy. Good potential for attracting further funding if the goals are realized.

Competence and expertise of the applicant.

- *What are the **merits and scientific expertise of the applicant**?*
- *Are they **appropriate and sufficient for the proposed project**?*

Reviewer n. 1

Dott.ssa Dalla Via has an excellent curriculum, her training process and her publications are of a high standard and very relevant to the project's themes.

Reviewer n. 2

The applicant has a large experience and competence in the areas of interest, with a specific know-how in the pharmacology of neurodegenerative disease and her expertise can well support the proposed testing activities

Reviewer n. 3

The applicant has expertise in natural product pharmacology. Track record is excellent and applicant is appropriate for the project

Competence and expertise of the research team.

- *Does the research team bring complementary expertise to the project?*
- *Is the project involved in international research collaborations that can significantly contribute to the success of the project?*

Reviewer n. 1

The group is very solid and with great knowledge and experience in biochemistry, cell biology, chemistry and pharmacology. Perhaps a reference with neurological knowledge is missing to have a greater translational impact. It is also true, however, that the present study aims only to provide proof of concept still distant from the approach on the patient and, even, from the planning of any in vivo studies.

Reviewer n. 2

The team appears well integrated and individual members have a solid know-how in their areas of competence. Also their publications show a high grade of collaboration at both national and international level

Reviewer n. 3

Di Paolo has expertise in amine oxidases, Cosconati brings expertise in kinase inhibitors, Taliani has medicinal chemistry expertise with targeting kinases. Hortensua Parra-Delgado (Mexico) brings natural products chemistry and is an established collaborator.

Prof.ssa Lisa Dalla Via

Titolo del Progetto: *New agents for multifaceted targeting of neurodegenerative diseases*

Obiettivo: Lo studio è orientato allo sviluppo di farmaci in grado di modulare processi di fosforilazione della proteina tau e dell' α -sinucleina, limitando la progressione di patologie neurodegenerative quali morbo di Parkinson e Alzheimer. Lo studio si focalizza sull'identificazione di molecole capaci di inibire la MAO-B e le chinasi GSK-3 β e DYRK1A, enzimi responsabili della iperfosforilazione patologica della proteina tau e dell' α -sinucleina. Nella sua fase iniziale, il progetto si basa sulla disponibilità di librerie di molecole, dalle quali verranno identificate quelle più promettenti quali inibitori di MAO-B e delle chinasi GSK-3 β e DYRK1A. Nell'ambito di una collaborazione internazionale, saranno valutati anche composti di origine naturale.

Punti di forza: Il progetto è ben strutturato, basato su di un solido *background* risultante dalla attività di ricerca del PI e dei collaboratori. Lo studio è coerente con le linee di sviluppo del Dipartimento e l'impatto del progetto sul DSF può essere significativamente positivo. Il progetto presenta un sufficiente livello di innovatività. Il progetto mostra numerosi aspetti di innovatività. Il team è multidisciplinare e presenta anche una collaborazione internazionale. Le collaborazioni esterne sono ben delineate e qualificate. L'esperienza del PI e dei collaboratori appare adeguata. L'analisi dei rischi e le possibili soluzioni sono adeguatamente delineate. Nel complesso, il progetto presenta un elevato grado di fattibilità.

Criticità: L'*abstract* descrive ampiamente il background, ma non adeguatamente gli obiettivi e le fasi di sviluppo del progetto. Manca una descrizione della *sample size* degli esperimenti programmati. Per alcuni aspetti, il progetto appare troppo ambizioso, con 7 WPs. Anche se il ruolo di coordinamento del proponente emerge in maniera chiara, numerose sono le attività sperimentali che verranno condotte al di fuori del DSF. La valutazione dei rischi è appena sufficiente.

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID – ANNO 2021

COMMISSIONE ESTERNA

Project: MODulation of Copper TRansport in ANTicancer Strategies (MOCTRANS)**Applicant:** Dolmella Alessandro**General assessment of scientific quality and innovation - Assessment of scientific plan**

- *Is the project scientifically significant, original and innovative?*
- *Is the project built on a departmental know-how? Has the project a significant impact for future development? Is the plan realistically feasible?*
- *Are the research methods, materials, work packages, tasks, milestones and timeline appropriate and in agreement with deliverables?*
- *Are the risk assessment and the contingency plan properly considered?*
- *This project has perspectives for international collaborations, applications, networking?*

Has the project the character of start-up research that can attract in the future competitive and non-competitive funds?

Reviewer n. 1

The project submitted by Dr. Dolmella focuses on the synthesis, characterization, validation (in vitro and in vivo) of chemotherapeutic compounds associated with copper in order to increase targeting selectivity and, consequently, improve the therapeutic index of chemotherapeutic compounds. The project is huge and encompasses all phases of research, chemistry, biochemistry, cell biology, pharmacology and medical imaging with PTE / SPECT. Overall, it is a well described project, even if there are some parts not totally clear such as the description of the appropriate animal models and the possible interaction with off-target (circulating - endothelial) cells. The division by task is well structured and the deliverables are consistent with the progress of the research. The big limitation of this project lies in the impossibility of managing such a complex amount of work in terms of time and with the means available. I sincerely consider it utopian to think of achieving so many goals in this context. Such a number of collaborators is also very large for this type of funding. It is therefore extremely risky in terms of investment. Maybe there are other funding, but anyway the time is too limited for accounting for the reasonable accomplishment of all activities.

Reviewer n. 2

My comments are the same I made last year, and I see a positive value in the proposed project. However, there are two simple additional comments/questions from my side: has any relevant data been produced in the last year by either the same team or others in the world? No additional reference has been reported or comment made in the proposal text. Also, while quoted in the text, it is not clear to me which will be the direct contribution of the existing international collaborators

Reviewer n. 3

The project is interesting and addresses a key problem thus could yield scientific impact. There seem to be several ideas within the project which makes it appear ambitious and feasibility is questioned. The goal is to make copper-based drugs for anti-cancer activity by targeting a copper transporter and development of radioactive imaging agents. The tasks are broken down and well described. Milestones and deliverables are indicated. Project has the potential for good impact for future funding. Risks are described with a detailed contingency plan.

Competence and expertise of the applicant.

- *What are the merits and scientific expertise of the applicant?*
- *Are they appropriate and sufficient for the proposed project?*

Reviewer n. 1

Dr Dormella demonstrates a reliable experience and he has appropriate publications for this project. Especially the chemical background is very robust. The works on PET / SPECT imaging agents and the part associated with copper-binding molecules are very much in line with the project.

Reviewer n. 2

The applicant has a solid know-how and experience in field of interest and is involved in a strong scientific network. For sure, he can well support the proposed activities

Reviewer n. 3

Applicant has the scientific expertise in med chem and computational chemistry and excellent track record.

Competence and expertise of the research team.

- Does the research team bring complementary expertise to the project?
- Is the project involved in international research collaborations that can significantly contribute to the success of the project?

Reviewer n. 1

The group is large, possessing a great experience and multidisciplinary. Interestingly, in the project the role of each "partner" for each task is well described. As previously reported it seems more appropriate to an international large project, but no doubts about the reliability and the robustness of the team.

Reviewer n. 2

The team is well structured and individual expertises well complement the applicant's competence and experience. It is not yet clear though how the international collaborators will be effectively involved in the proposed work.

Reviewer n. 3

Marzano brings cancer expertise, Santini (Camerino) brings expertise in metal chemistry, Bolzati (radiopharmaceutical expertise) Esposito (Padua) brings radioisotope expertise, Alafort (nuclear medicine). There is a detailed breakdown of the contribution of the team members to the research program.

COMMISSIONE INTERNA

Prof. Alessandro Dolmella

Titolo del Progetto: *Modulation of copper transport in anticancer strategies*

Obiettivo: Il progetto ha come obiettivo principale lo sviluppo di nuovi composti basati su complessi del rame, potenzialmente attivi quali agenti antitumorali, meno tossici rispetto agli attuali chemioterapici basati sul platino e con minori fenomeni di resistenza. Altre potenziali applicazioni dei risultati ottenibili da questo progetto, riguardano aspetti diagnostici dei complessi radioattivi del rame. Un progetto molto simile è stato presentato dal proponente nel 2020.

Punti di forza: Il progetto si colloca in ambito chemioterapico e diagnostico, è ben strutturato e sfrutta positivamente il solido *background* metodologico e di ricerca del PI e dei collaboratori. Lo studio è coerente con le linee di sviluppo del Dipartimento, ha un elevato grado di fattibilità e l'impatto del progetto sul DSF può essere molto positivo. Il ruolo dei collaboratori è molto ben delineato. Il team coinvolge altre istituzioni e Università in ambito nazionale. Non sono indicate collaborazioni internazionali. L'esperienza del PI appare adeguata. L'analisi dei rischi e le possibili soluzioni sono ben delineati.

Criticità: In alcune parti, il progetto è difficile da leggere e complessa risulta l'organizzazione delle attività sperimentali prospettate.

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID – ANNO 2021

COMMISSIONE ESTERNA

Project: Multiple sclerosis and TOLL-like rEceptor 4 signAling: linking eNteriC dysfunction to nEurodegeneration (TOLLERANCE)

Applicant: Giron Maria Cecilia

General assessment of scientific quality and innovation - Assessment of scientific plan

- *Is the project scientifically significant, original and innovative?*
- *Is the project **built on a departmental know-how**? Has the project a significant **impact** for future development? Is the **plan realistically feasible**?*
- *Are the research **methods, materials, work packages, tasks, milestones and timeline appropriate and in agreement with deliverables**?*
- *Are the risk assessment and the contingency plan properly considered?*
- *This project has perspectives for **international collaborations, applications, networking**?*
- *Has the project the character of **start-up research** that can attract in the future competitive and non-competitive funds?*

Reviewer n. 1

The project submitted by Dr. Giron is undoubtedly interesting. Although not entirely innovative, the idea of linking the role of toll like receptor 4 (and of the cascade of events associated with it) and its possible modifications as a binding element GUT / BAIN in the triggering / or exacerbation of MS, is certainly interesting and current. The study is well described in its background, accompanied by interesting complementary results and the clear division of WPs. The most difficult element to deduce is how the coordinator intends to integrate all the results obtained in the various WPs in order to define general results on mechanisms, functional and anatomical correlations, immediate impact and future developments. The text states that we want to aspire to the "definition of new neuroimmune signature", however this sentence is a bit too general and does not give a precise idea of how to order the enormous amount of work to be done. Some other technical details on the models should be revised or expanded, but I understand that this is a function of the space allowed.

Reviewer n. 2

The proposed project is scientifically significant and innovative, bringing some originality to the area of interest and is definitely feasible (being not an expert in the area and the related biology, my evaluation is clearly limited). The team is well structured, involves an international network and possesses a good know-how. All material, methods and technologies are available. A positive outcome could undoubtedly raise further interests and funds considering the unmet medical need. Looking at the risk assessment part, I wonder if the use of TLR4 agonists/antagonists could be integrated in the project tasks instead of being considered only as part of the contingency plan. There are indeed small molecules already available and characterised both in-vitro and in-vivo.

Reviewer n. 3

(no need to try to make an acronym from the title in my opinion). This is an interesting project with some originality investigating the impact of TLR4 on MS and the driver of the disease coming from the gut. It could be made more explicit the role of TLR4 here and the expectations arising from the work – does this present TLR4 as a future therapeutic target? The key ideas could be made more explicit. The schematics included are helpful. The project seems ambitious and there is a lot to do. This could have the potential for attracting further funding if expected outcomes are met.

Competence and expertise of the applicant.

- *What are the **merits and scientific expertise of the applicant**?*
- *Are they **appropriate and sufficient for the proposed project**?*

Reviewer n. 1

Dr Giron's publications are valuable and focused on the topic (in particular the relationship of the intestine, microbiota and inflammation). The percentage of first and last names that clearly delineate the leadership of the project is remarkable. The training and work experiences are also in line with what is required for a good coordination of the research project.

Reviewer n. 2

The applicant's expertise and competence are good and can definitely support the project progression

Reviewer n. 3

Expertise of the applicant is not well stated in the proposal. From the track record this seems to be gut-brain axis and enteric nervous system therefore the applicant does have the required expertise

Competence and expertise of the research team.

- *Does the research team bring complementary expertise to the project?*
- *Is the project involved in international research collaborations that can significantly contribute to the success of the project?*

Reviewer n. 1

The group is heterogenous, supporting the multidisciplinary activity and well complementary in each role. Great experience covering the whole area of the study and CV-publication lists high ranked.

Reviewer n. 2

The team is quite large, well integrated and international. I would consider the use of small molecules agonist/antagonist and therefore adding a medicinal chemistry competence to the team.

Reviewer n. 3

Team brings 4 others from DSF/DSB together but difficult to judge their expertise as not stated. There are international collaborators although their roles are unclear.

COMMISSIONE INTERNA

Prof.ssa Maria Cecilia Giron

Titolo del Progetto: *Multiple sclerosis and TOLL-like receptor 4 signaling: linking enteric dysfunction to neurodegeneration*

Obiettivo: Valutazione del ruolo del sistema nervoso enterico nella patogenesi della sclerosi multipla, mediante un modello sperimentale murino di patologia indotta da cuprizone.

Punti di forza: Il progetto è ben organizzato, ha un livello di innovatività elevato e sfrutta metodologie ben stabilite nel gruppo di ricerca del proponente e dei collaboratori. Lo studio è coerente con le linee di sviluppo del Dipartimento e l'impatto del progetto sul DSF può essere significativamente positivo. Nello studio sono coinvolte altre istituzioni e università anche in ambito internazionale. L'esperienza del PI è adeguata e il progetto si presenta fattibile. Sono stati presentati dati preliminari a supporto. L'analisi dei rischi e le possibili soluzioni sono adeguatamente delineate. Il progetto è corredato dalle autorizzazioni di OPBA alla sperimentazione animale. E' previsto un cofinanziamento del progetto.

Criticità: Come in tutti i progetti presentati, non è definito il sample size. Il modello sperimentale di Sclerosi Multipla murina, che utilizza il cuprizone, è soggetto a numerose variabili che potrebbero inficiare la rilevanza dei risultati del progetto.

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID – ANNO 2021

COMMISSIONE ESTERNA

Project: Development of small Molecules for the EGFR-ECD Targeting (MEETs): a new strategy for the early in vivo diagnosis of EGFR-overexpressing cancers

Applicant: Marzaro Giovanni

General assessment of scientific quality and innovation - Assessment of scientific plan

- *Is the project scientifically significant, original and innovative?*
- *Is the project **built on a departmental know-how**? Has the project a significant **impact** for future development? Is the **plan realistically feasible**?*
- *Are the research **methods, materials, work packages, tasks, milestones and timeline appropriate and in agreement with deliverables**?*
- *Are the risk assessment and the contingency plan properly considered?*
- *This project has perspectives for **international collaborations, applications, networking**?*
- *Has the project the character of **start-up research** that can attract in the future competitive and non-competitive funds?*

Reviewer n. 1

The project submitted by Dr. Marzaro aims at investigating the development of new peptides having a higher and more selective targeting against the EGFR extracellular domain. Although it is not so innovative (many groups are working on this topic) the project is well designed and correctly divided in four main pillars: Determination of binding sites, Library of Molecules targeting EGFR-ECD (MEETs), evaluate their efficacy and mechanism of actions, and provide elements for a possible proof of concept in vivo. Although the reaching of in vivo phase seems a little bit unrealistic, the project is consistent with the time, but the budget is too little to think to cover all kind of expenses. Anyway, it is really attractive and has a potential great impact maybe for future financed projects. Very easy to follow and to understand for the reader (reviewer)

Reviewer n. 2

The proposed project is scientifically significant and original with a good level of innovation, is feasible and can trigger future development in case of positive results, both from a drug discovery and adiaagnostic standpoints. All the required material, methods and technologies are available and well established within the international team. The risk assessment is well described, even though the risk of failure is a bit underestimated, also considering that the activity of the starting hits is not so high as assumed by the PI. Also, the selectivity of the future compounds will have to be carefully assessed due to the potential for off-target activities of the newly identified series. Finally, some comment should be made on the publication strategy: in view of the potential creation of a start-up initiative for clinical applications of the obtained results I wonder if any patenting activity will be considered by the team.

Reviewer n. 3

This project is original and built on preliminary data presented. There is potential for good scientific impact and the team have two lead compounds to work with. This is a well-planned project with good feasibility. The only issue may be completing the in vivo work in the timeframe. There is a good potential for attracting further funding. Risks have been identified and contingency is addressed.

Competence and expertise of the applicant.

- *What are the **merits and scientific expertise of the applicant**?*
- *Are they **appropriate and sufficient for the proposed project**?*

Reviewer n. 1

Dr Marzaro is younger than the other applicants, therefore his CV and his publication list is shorter. However, it fits the scopes of the project and it demonstrates a great scientific robustness. Academic and work experience are in line with the project requests.

Reviewer n. 2

The applicant's experience and competence in the medicinal chemistry area is good and more than sufficient in order to support this chemistry-driven proposed project.

Reviewer n. 3

The applicant has background in chemistry and pharm science and has worked on kinase inhibitors previously. The applicant has the required skills to perform the work.

Competence and expertise of the research team.

- *Does the research team bring complementary expertise to the project?*
- *Is the project involved in international research collaborations that can significantly contribute to the success of the project?*

Reviewer n. 1

The group of collaborators is of a good level in all components. The biomedical part appears to be a little more deficient than the chemistry, however the project is very focused on the study of the interactions of the MEETs with the target and therefore, all in all, this imbalance should not have a significant impact.

Reviewer n. 2

The proposed team is well integrated and include all the expertises required for the proposed activities, however it is worth noting that the team resides essentially within the same university apart from the part concerning the labelling activities. I wonder if other groups could bring a further and wider intellectual contribution.

Reviewer n. 3

There are 4 researchers from DSF added who bring skills and expertise in med chem, proteinchemistry, antitumour chemicals and polymers. One international collaborator.

COMMISSIONE INTERNA

Prof. Giovanni Marzaro

Titolo del Progetto: *Development of small Molecules for the EGFR-ECD Targeting (MEETs): a new strategy for the early in vivo diagnosis of EGFR-overexpressing cancers.*

Obiettivo: Sviluppo di MEETs che abbiano una migliore affinità e selettività per EGFR, da sottoporre a radiomarcatura con ¹⁸F, allo scopo di ottenere radiotraccianti specifici disponibili per via orale (¹⁸F-MEETs) per l'imaging in vivo e/o la diagnosi precoce dei tessuti EGFR-esposti.

Punti di forza: Il progetto risulta nel complesso ben strutturato, basato su di un solido *background* ed identifica in modo adeguato gli obiettivi finali. Il progetto mostra un elevato grado di innovatività ed è coerente con le linee di sviluppo del Dipartimento. Il team è interdisciplinare e comprende anche collaboratori internazionali. L'esperienza del PI appare adeguata. L'analisi dei rischi e le possibili soluzioni risultano ben delineate.

Criticità: Non sono evidenti particolari criticità e il piano proposto è pienamente coerente con le competenze del gruppo di ricerca, come chiaramente delineato dal previsto workpackage. Come in tutti i progetti presentati, non è definito il sample size, in particolare per le previste valutazioni *in vivo*.

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID – ANNO 2021

COMMISSIONE ESTERNA

Project: Interfering in the amyloid fibril formation against the progression of Parkinson disease (InterPD)

Applicant: Polverino de Laureto Patrizia

General assessment of scientific quality and innovation - Assessment of scientific plan

- *Is the project scientifically significant, original and innovative?*
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- *This project has perspectives for **international collaborations, applications, networking**?*
- *Has the project the character of **start-up research** that can attract in the future competitive and non-competitive funds?*

Reviewer n. 1

The project submitted by Dr. Polverino de Laureto concerns the selection and development of compounds with anti-amyloid properties of belonging to polyphenols and catechols. The state of the art and the rationale are well explained and the experimental plan is very clear. The three main purposes: Selection of molecules similar to catechols capable of improving bioavailability; 2) improve the chemical interaction with the target; 3) preventing the formation of toxic aggregates is consistent with the rationale and extremely important for the development of potential tools against neurodegenerative diseases such as parkinson's disease. The task division is well constructed, although perhaps it would be better to first evaluate the in vitro aggregation of the cytotoxicity studies in order to reduce the amount of unnecessary work. I really appreciated the consistency of the project with the time allowed (2 years and with the budget).

Reviewer n. 2

The proposed project is addressing a high unmet medical need and is scientifically significant, but innovation and originality are moderate. Materials, methods and technologies are available to the team members. There are though doubts about the feasibility of the project within the given timelines. The chemical starting point is indeed questionable (polyphenols are often hardly optimisable scaffolds) and this may generate a quite longer and extensive medicinal chemistry work than expected (the risk is indeed underestimated) also considering the plan to test the compounds against -Syn and its mutant.

Reviewer n. 3

The project is scientifically significant and original in that interfering with synuclein aggregates could be a new treatment for Parkinson's disease. Scheme of research presented is helpful. The project is well written in general and the tasks seem appropriate and supported by preliminary work demonstrating that the compounds can affect aggregation. This is likely to attract further funding so meets start-up criteria. Risks are discussed within the proposal although contingency plans not as well developed.

Competence and expertise of the applicant.

- *What are the **merits and scientific expertise of the applicant**?*
- *Are they **appropriate and sufficient for the proposed project**?*

Reviewer n. 1

The applicant has a consolidated experience and the publication list clearly highlights her relevant effort in biological, chemical and pharmacological areas. The expertise of Dr Polverino de Laureto perfectly fits the aims of the proposed project.

Reviewer n. 2

The applicant's expertise and competence is good even though focused on a small part of the proposed activities; this may in turn bring a limited strategic view to the project management

Reviewer n. 3

Pharmaceutical chemistry background of the applicant and an interest in aggregation states. Expertise in mass spectrometry methods. Excellent track record.

Competence and expertise of the research team.

- *Does the research team bring complementary expertise to the project?*
- *Is the project involved in international research collaborations that can significantly contribute to the success of the project?*

Reviewer n. 1

The collaborator and the internal group will be for granted an added value for the success of the project. They are well balanced (among chemist and biomedical research) covering all areas of the study.

Reviewer n. 2

Team members have good and complementary experiences and are well integrated in view of the proposed activities. Also, they represent a valid international network. However there has been a general overestimation of the probability of success by the team.

Reviewer n. 3

Team includes 5 other researchers from Padova, plus Tosi from Modena & Reggio Emilia. Minervini brings computational skills, Acquasaliente brings structural biology skills, Mattarei brings medicinal chemistry and chem biology, Spolaore brings expertise in conformational protein analysis. Bucciantini (Firenze) for cell biology.

COMMISSIONE INTERNA

Prof.ssa Patrizia Polverino de Laureto

Titolo del Progetto: *Interfering in the amyloid fibril formation against the progression of Parkinson disease (InterPD).*

Obiettivo: identificazione di un nuovo set di molecole con caratteristiche chimico-fisiche simili ai catecoli già studiati ma con proprietà farmacocinetiche e farmacodinamiche migliorate, in grado di interagire con α Syn e i suoi mutanti, impedendo la formazione di aggregati tossici.

Punti di forza: Il progetto, risulta nel complesso ben strutturato ed è coerente con le linee di sviluppo del Dipartimento. L'impatto del progetto sul DSF può essere molto positivo. Il team è interdisciplinare. Nel progetto non sono presenti collaborazioni internazionali. L'esperienza del PI appare molto idonea al progetto.

Criticità: Il piano proposto è coerente con le competenze del gruppo di ricerca, ed illustrato chiaramente nelle linee di svolgimento, ma appare carente nell'individuazione delle molecole di partenza da valutare e nella valutazione globale del rischio.

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID-J – ANNO 2021

COMMISSIONE ESTERNA

Project: Development of novel selective melatonin receptors ligands for autism spectrum disorder

Applicant: Comai Stefano

General assessment of scientific quality and innovation - Assessment of scientific plan

- *Is the project **scientifically significant, original and innovative**?*
- *Is the project **built on a departmental know-how**? Has the project a significant **impact** for future development? Is the **plan realistically feasible**?*
- *Are the research **methods, materials, work packages, tasks, milestones and timeline appropriate** and in agreement with deliverables?*
- *Are the risk assessment and the contingency plan properly considered?*
- *This project has perspectives for **international collaborations, applications, networking**?*
- *Has the project the character of **start-up research** that can attract in the future competitive and non-competitive funds?*

Reviewer n. 1

The project is very ambitious and challenging. The rationale is robust but some controversial opinions arisen from the etiological role played MT1/2 in ASD. The study in animal is interesting but, perhaps, the temporal window of two year is too short to cover all activities.

Reviewer n. 2

This proposed project is scientifically significant and partially innovative; it's based on a solid dept know-how and established experimental methodologies. Feasibility and timelines are appropriate, while some doubt remains on the risk assesment part, where the use of two compounds only appears limited considering the importance and the potential interest of this approach and future development; also the potential evaluation of full agonists is underestimated. The availability of a larger number of chemical tools (and therefore a larger collaboration panel) is feasible in the available time frame and highly recommended.

Reviewer n. 3

This is an original project which should generate scientifically significant data. The major goal is to understand the role of melatonin receptors in autism behaviours. The use of two partial agonists is rationalised based on their receptor selectivity but are these the only selective tools available? The research plan for studying behaviour is feasible and well described but the timeline shows the behavioural tests taking 16 months (I don't think it would take this long). The risks have been considered and some contingency plans are proposed. This project has the character of a good start-up project which will attract further funding if meeting the expected outcomes.

Competence and expertise of the applicant.

- *What are the **merits and scientific expertise of the applicant**?*
- *Are they **appropriate and sufficient for the proposed project**?*

Reviewer n. 1

The applicant has a sufficient experience to move on to this project. In particular, the neuropharmacological knowledge is greatly valuable.

Reviewer n. 2

The applicant has a solid scientific experience as certified by the relative CV, and is an expert in the field from the pharmacological standpoint and his competence and experience are appropriate for the proposed project.

Reviewer n. 3

Excellent track record and the applicant has the required expertise for this project.

Competence and expertise of the research team.

- Does the research team bring complementary expertise to the project?
- Is the project involved in international research collaborations that can significantly contribute to the success of the project?

Reviewer n. 1

The group is well balanced and reliable. Especially in the field of neurobiology.

Reviewer n. 2

The research team brings minimal complementarity to the project due to the evident lack on any medicinal chemistry expertise and also the international network seems quite limited.

Reviewer n. 3

The team brings strength to the methodology with their expertise in GPCR (Calò), neuropsychiatric disorders (Gobbi), animal models (Gregorio) and in-vivo electrophysiology (Cambiaghi). The roles of the team members are clearly described.

COMMISSIONE INTERNA

Dott. Stefano Comai

Titolo del Progetto: *Development of novel selective melatonin receptors ligands for autism spectrum disorder*

Obiettivo: Chiarire a livello preclinico il ruolo neurobiologico e psicofarmacologico dei recettori MT1 e MT2 della melatonina nei disturbi dello spettro autistico (ASD).

Punti di forza: Lo studio si propone di valutare, per la prima volta, dei ligandi selettivi dei recettori MT1 e MT2 come potenziali agenti terapeutici nell'ASD. I risultati ottenibili potranno avere un elevato impatto per un futuro sviluppo della ricerca traslazionale applicata all'ASD. Il progetto è scritto in maniera chiara, è ben organizzato e sfrutta positivamente le competenze del PI e dei collaboratori. Lo studio mostra chiaro carattere di innovatività ed è coerente con le linee di sviluppo del Dipartimento. Il team è interdisciplinare e presenta anche una collaborazione internazionale. L'esperienza del PI appare adeguata. L'analisi dei rischi e le possibili soluzioni sono chiaramente delineate.

Criticità: Non sono presenti particolari aspetti di criticità, anche se la trasferibilità dei risultati ottenuti in un modello murino di ASD all'uomo resta da determinare con attenzione.

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID-J – ANNO 2021

COMMISSIONE ESTERNA

Project: Development of long non-coding RNA-targeting therapeutics for the treatment of melanoma

Applicant: Groaz Elisabetta

General assessment of scientific quality and innovation - Assessment of scientific plan

- *Is the project **scientifically significant, original and innovative**?*
- *Is the project **built on a departmental know-how**? Has the project a significant **impact** for future development? Is the **plan realistically feasible**?*
- *Are the research **methods, materials, work packages, tasks, milestones and timeline appropriate** and in agreement with deliverables?*
- *Are the risk assessment and the contingency plan properly considered?*
- *This project has perspectives for **international collaborations, applications, networking**?*
- *Has the project the character of **start-up research** that can attract in the future competitive and non-competitive funds?*

Reviewer n. 1

Amazing project. Interesting, innovative, well written. Starting from a robust thought and moving by a step-by-step approach where the possible problems that can be encountered are well “weighted” and contingency plan is considered. The possibility of success are therefore high, and also unneeded “negative results” could be well exploited for the advancement of research into this topic.

Reviewer n. 2

The proposal is focused on the chemical optimisation of an innovative lead series, is scientifically significant. The plan appears feasible and of potentially high impact for future development; however it should probably involve some more human resources, due to high risk (in part underestimated) from both a synthetic and a biological point of view, with the consequent need for a larger exploration than expected. It's also worth noting that the reported reaction schemes are poorly reported and this created some difficulties in carrying out the required appropriate evaluation. Know-how, materials, technologies and methodologies appear appropriate. The project has potential for an increased application and collaborations as well as for raising further funds. Finally, some clarification is required for what concerns the publication strategy (eg patent vs scientific publications) in view of potential future exploitation of the obtained results.

Reviewer n. 3

This is an interesting project with the potential for future innovation in melanoma treatment. Some parts were challenging to understand and the references could be better presented in the document (in brackets). Also, the Figures are not good resolution in the document. The risks have been considered and some contingency is described. The work packages are outlined with deliverables and milestones and I believe the project to be feasible. The outcomes may have significant impact and attract future funding.

Competence and expertise of the applicant.

- *What are the **merits and scientific expertise of the applicant**?*
- *Are they **appropriate and sufficient for the proposed project**?*

Reviewer n. 1

The international experience and the CV is very valuable and assures that the applicant is able to coordinate the project.

Reviewer n. 2

The PI has high competence and technical expertise for the proposed tasks, as well as the required international network and experience to manage the proposed collaborations.

Reviewer n. 3

The applicant has the required expertise for the project to be successful.

Competence and expertise of the research team.

- Does the research team bring complementary expertise to the project?
- Is the project involved in international research collaborations that can significantly contribute to the success of the project?

Reviewer n. 1

The group is interesting even if a higher experience on the part related to the chemical development seems to be weaker.

Reviewer n. 2

The team is based on international collaborations and team members bring appropriate complementarity in terms of competence and experience. However an enlarged team, particularly from the medicinal chemistry point of view, would be more appropriate in view of the proposed objectives.

Reviewer n. 3

An international collaboration with KU Leuven is in place with 2 Professors Leucci and Herdewijn. These bring particular expertise in cellular testing of antisense oligonucleotides and experiments will be performed there.

COMMISSIONE INTERNA

Dott.ssa Elisabetta Groaz

Titolo del Progetto: *Development of long non-coding RNA-targeting therapeutics for the treatment of melanoma.*

Obiettivo: Sviluppo di nuove strategie terapeutiche per il melanoma basate sul targeting di lnc-RNA, mediante lo studio delle proprietà di oligonucleotidi sintetici come inibitori specifici di meccanismi di regolazione mediati da SAMMSON nelle cellule di melanoma.

Punti di forza: Il progetto è innovativo, ben organizzato e gli obiettivi sono delineati in maniera chiara. Il progetto presenta un buon grado di fattibilità. Lo studio è coerente con le linee di sviluppo del Dipartimento, con un buon impatto sul DSF. Il team presenta una collaborazione internazionale. L'esperienza del PI è adeguata. L'analisi dei rischi e le possibili soluzioni sono delineate in modo sufficientemente adeguato.

Criticità: In alcune sue parti, il progetto non è facile da leggere e i rischi sono significativi.

VALUTAZIONI ASSEGNI DI RICERCA DI DIPARTIMENTO DI TIPO B ARD-B – ANNO 2021

COMMISSIONE ESTERNA

Project: 3D models of ovarian cancer cells to shed light on chemoresistance

Applicant: Hyeraci Mariafrancesca

General assessment of scientific quality and innovation - Assessment of scientific plan

- *Is the project **scientifically significant, original and innovative**?*
- *Is the project **built on a departmental know-how**?*
- *Has the project a significant **impact** for future development?*
- *Are the **objectives and hypotheses** clearly presented?*
- *Is the **plan** realistically feasible?*
- *Are the research **methods, materials, work packages and timeline** appropriate and in agreement with deliverables?*
- *Has the project perspectives for **international collaborations, applications, networking**?*

Reviewer n. 1

In her research project, Dr Hyeraci aims at a 3D system of ovarian cancer cells to evaluate in a more realistic situation the capacity of action of compound derivatives of Pt. The one-year project starts from the assumption of developing and characterizing the 3D culture and then testing the efficacy of the aforementioned compounds both on toxicity but also on the interaction with specific transcripts and the role in inhibiting the so-called transition between epithelial and mesenchymal characterizing part of the resistance to many chemotherapeutic compounds. The project is, on the whole, interesting, but doubts remains, which, reading the text, is not easy to clarify. It is not in fact well understood whether the candidate has already developed this type of culture or should start the project from this point. It is in fact very unlikely to think of creating and standardizing a multi-cell 3D culture mimicking a tumor mass in 3 months. Another slightly hazy point is the choice of using, in the last period of the biopolymers project. It seems to me a little redundant and off topic. Perhaps it would be better to allocate a part of the project for data analysis. I also found the part describing the contingency plan not very comprehensive.

Reviewer n. 2

The proposed project is scientifically significant, while originality and innovation are limited. It is based on a solid know-how and experience in the field and may have a significant impact on future activities. Materials and methods and feasibility are adequate, while timelines could be probably shortened, and it is not clear how this project may bring to increased international collaborations. Finally, the application of the proposed technology to other topics (toxicity of biomaterial) decrease the focus of the project and appears not productive

Reviewer n. 3

The project is built on departmental know-how as it follows on from previous works. An important step in determining the anti-cancer effect is testing in 3D models therefore this represents an important pre-clinical step. In writing, don't overuse abbreviations eg cancer stem cells. It is better to add a short reference list at the end rather than add the whole citation in the text. One of the weaknesses is the lack of information regarding how many Plat (II) compounds will be tested in the project. As this is a one year project, it seems there is a lot to do in this time including establishing the 3D model therefore feasibility is questionable. The risks have not been well considered – what if the Plat(II) complexes have no effect on the cell viability of the spheroids? The final part mentions testing of biomaterials and biopolymers – this is a distinct idea and there are no details to be able to assess this fully.

Competence and expertise of the applicant.

- *What are the **merits and scientific expertise** of the applicant?*
- *Are they **appropriate and sufficient** for the proposed project?*

Reviewer n. 1

Dr Hyeracy has an excellent CV in particular considering her age. Interesting publications and participation to international and national symposia. Her expertise is appropriate and well fits the project requirement.

Reviewer n. 2

The applicant has a sufficient expertise and competence in the field of proposed research

Reviewer n. 3

The applicant has finished her PhD in 2020 and has the required skills for carrying out the project.

Competence and expertise of the supervisor and of the research team.

- *Does the research team bring complementary expertise to the project?*

Reviewer n. 1

The group including supervisor and the project team well integrate the skills and the formation of Dr Hyeraci. Maybe an expert on the cancer cell lines would have been important to make faster the process of data analysis.

Reviewer n. 2

The applicant is backed by experts who bring the required expertise to develop the project

Reviewer n. 3

The mentor is Prof Lisa Dalla Via and the team consists of Dr Ketì Vezzu and Dr Gioele Pagot as participants in research. It is not written how Dr Vezzu will contribute to the works.

COMMISSIONE INTERNA

Dott.ssa Hyeraci Mariafrancesca

Titolo del Progetto: *3D models of ovarian cancer cells to shed light on chemoresistance*

Il progetto risulta molto articolato, con possibili criticità nello svolgimento secondo il working plan; inoltre non appare completamente supportato da dati sperimentali preliminari. Il progetto si presenta con un discreto livello innovativo nell'ambito dello studio *in vitro* di modelli per la valutazione della chemioresistenza di cellule tumorali. Le competenze del richiedente e del gruppo di ricerca sono adeguate allo svolgimento del progetto. La presentazione del progetto al colloquio è risultata chiara, anche se sono emerse alcune criticità di tipo metodologico.

VALUTAZIONI ASSEGNI DI RICERCA DI DIPARTIMENTO DI TIPO B ARD-B – ANNO 2021

COMMISSIONE ESTERNA

Project: Transduceromics studies of the NOP receptor**Applicant:** Malfacini Davide**General assessment of scientific quality and innovation - Assessment of scientific plan**

- *Is the project scientifically significant, original and innovative?*
- *Is the project built on a departmental know-how?*
- *Has the project a significant impact for future development?*
- *Are the objectives and hypotheses clearly presented?*
- *Is the plan realistically feasible?*
- *Are the research methods, materials, work packages and timeline appropriate and in agreement with deliverables?*
- *Has the project perspectives for international collaborations, applications, networking?*

Reviewer n. 1

The project proposed by Dr Malfacini is very interesting and clearly illustrated. The use of the Trupath Approach is certainly a further strong point of the proposal. The experimental plan is robust and well balanced in time. The description of the endpoints is also very clear. The project does not aim to get straight to the production and development of new pharmacologically active agents, it could however be a good starting point for selecting some candidates. We can therefore say that, if the results are positive, it could give rise to future projects aimed at greater characterization (in vitro and in vivo) to evaluate factors such as PK / PD, toxicity and specificity of action. However, for a yearly project it seems to me that it is rational and well planned.

Reviewer n. 2

The project is scientifically significant and brings a good level of innovation with some element of originality; furthermore is based on a quite solid general know-how, even though the topic of research is relatively young. The risk assessment has not been completely explored and risk of failure is quite high, so some mitigation approach should be considered in advance. Materials, methods and technologies are available and appropriate. The results could open new and interesting path in the identification of selective and potent new therapeutics and this would also wider collaborations at both national and international level.

Reviewer n. 3

This project applies new technology to evaluate the NOP receptor and its G protein coupling preferences which has the potential to provide very interesting data that could attract further funding. The work is based on using a newly available set of plasmids for overexpression of all G proteins for a BRET-based study of signalling pathways. The project is clearly described although there could be more detail in the Tasks. The risks are not well addressed with a contingency plan if the BRET studies fail. How will BRET be measured (equipment?) – more contingency information needs to be added.

Competence and expertise of the applicant.

- *What are the merits and scientific expertise of the applicant?*
- *Are they appropriate and sufficient for the proposed project?*

Reviewer n. 1

The CV and the publications of the applicant are very interesting and they deserve to be carefully taken into consideration for the evaluation of the project. The knowledge and the skills are appropriate for this kind of study.

Reviewer n. 2

The applicant possess a solid competence and experience, obtained through an extended network and international working activities, and his know-how appears valid in view of the proposed project and objectives.

Reviewer n. 3

The applicant acquired his PhD in 2015 and has an excellent track record. He has sufficient expertise for

the project and has international experience which may help foster new collaborations.

Competence and expertise of the supervisor and of the research team.

- *Does the research team bring complementary expertise to the project?*

Reviewer n. 1

The supervisor and the research team is well balanced and seems to be perfect to support the applicant activities.

Reviewer n. 2

The required competence and expertise of members of the team are extremely valid in view of the proposed activities.

Reviewer n. 3

The mentor is Prof Calò who has great experience in this area. Other participants include Dr Orso (DPPS) and Dr Mattia Sturlese (DPPS) bringing expertise in molecular biology and computational modelling.

COMMISSIONE INTERNA

Dott. Davide Malfacini

Titolo del Progetto: *Transduceromics studies of the NOP receptor*

Il progetto inquadra nell'ambito della farmacologia molecolare ed ha come obiettivo principale lo studio del pathway del recettore NOP, un recettore GPCR. Lo studio in vitro risulta coerente con le linee di sviluppo del Dipartimento ed ha un rilevante impatto scientifico unito ad innovatività. La presentazione del progetto è stata molto chiara ed esaustiva e dimostra piena competenza del proponente, come pure adeguato è il profilo scientifico dei partecipanti. Non sono evidenti particolari criticità.

VALUTAZIONI ASSEGNI DI RICERCA DI DIPARTIMENTO DI TIPO B ARD-B – ANNO 2021

COMMISSIONE ESTERNA

Project: Modular PROTAC design for the degradation of Clostridium botulinum type A neurotoxin (BoNT/A)

Applicant: Ongaro Alberto

General assessment of scientific quality and innovation - Assessment of scientific plan

- *Is the project scientifically significant, original and innovative?*
- *Is the project built on a departmental know-how?*
- *Has the project a significant impact for future development?*
- *Are the objectives and hypotheses clearly presented?*
- *Is the plan realistically feasible?*
- *Are the research methods, materials, work packages and timeline appropriate and in agreement with deliverables?*
- *Has the project perspectives for international collaborations, applications, networking?*

Reviewer n. 1

The project submitted by Dr Ongaro is ambitious and with a strong impact. It is well described and it is clear that he knows the state of the art in an adequate manner. The chemical part and the studies in vitro for the development/selection of the most interesting molecules seem to be balanced to the duration and the type of the project. Some perplexity arises from the real possibility to carry out also the in vivo studies in a so relatively short interval of time. The effect of the selected compounds should need a deeper characterization in cells be deeper characterize, in particular the experiments related the functionality of these agents. The contingency plan is missing.

Reviewer n. 2

The proposed project is scientifically significant and innovative in the application of a quite established technology (PROTAC). The required synthetic chemistry know-how is present in the team and the potential impact of a positive outcome is high. The objectives are clearly expressed and required methods, materials and technologies are available. The project is amenable for further collaborations, particularly at an industrial level, in case of positive results. In order to mitigate the risk from the medicinal chemistry point of view, the plan could be extended to a larger number of linkers since the beginning.

Reviewer n. 3

This is a well written proposal with good originality and innovation. It has the potential for excellent impact in an area of urgent unmet clinical need. The objectives are clearly presented and the methods well detailed presenting this as a feasible project in the given timeline. The in vivo work is taking place in the collaborators lab and it is assumed that ethical approvals are in place so this can happen. Risks are considered and contingency is addressed. This project has an international collaboration and presents a good opportunity for networking and further funding applications.

Competence and expertise of the applicant.

- *What are the merits and scientific expertise of the applicant?*
- *Are they appropriate and sufficient for the proposed project?*

Reviewer n. 1

The CV is very interesting and well fits the topics of the project. In particular, the applicant is the first author of the 80% of published papers. This underline the relevant role of Dr Ongaro on this research.

Reviewer n. 2

The applicant has developed a good experience in the fields of synthetic and medicinal chemistry which appear appropriate to support the proposed work. Also, he has a good national and international network

Reviewer n. 3

The applicant has an excellent track record of chemistry projects since getting his PhD in 2017. He has the required expertise and skills to perform the project.

Competence and expertise of the supervisor and of the research team.

- *Does the research team bring complementary expertise to the project?*

Reviewer n. 1

The supervisor and the research team is well balanced and seems to be perfect to support the applicant activities.

Reviewer n. 2

The research team well complement the applicant's expertise and provide the required experience for the full pharmacological profiling of the newly synthesised compounds.

Reviewer n. 3

Mentor is Dr Andrea Mattarei (DPPS), a medicinal chemist. Other participants are Dr Marco Pirazzini and Dr Ivica Matak (Zagreb) bringing their expertise in neurotoxins and in in vivo testing.

COMMISSIONE INTERNA

Dott. Alberto Ongaro

Titolo del Progetto: *Modular PROTAC design for the degradation of Clostridium botulinum type A neurotoxin (BoNT/A)*

Il progetto è di notevole interesse scientifico e mostra un elevato livello di innovatività. Lo studio si presenta coerente con il piano di sviluppo dipartimentale. Le competenze scientifiche e tecniche del richiedente sono adeguate, come pure quelle dei partecipanti alla ricerca. Il progetto comprende anche collaborazioni internazionali. La descrizione della ricerca appare complessa e molto articolata, e qualche criticità potrebbe presentarsi in particolare nella valutazione finale *in vivo* dei composti selezionati. La presentazione è stata chiara ed esaustiva.

VALUTAZIONI ASSEGNI DI RICERCA DI DIPARTIMENTO DI TIPO B ARD-B – ANNO 2021

COMMISSIONE ESTERNA

Project: A novel biomimetic drug delivery nanovector for the treatment of primary and metastatic pediatric osteosarcoma

Applicant: Rampado Riccardo

General assessment of scientific quality and innovation - Assessment of scientific plan

- *Is the project **scientifically significant, original and innovative**?*
- *Is the project **built on a departmental know-how**?*
- *Has the project a significant **impact** for future development?*
- *Are the **objectives and hypotheses** clearly presented?*
- *Is the **plan realistically feasible**?*
- *Are the research **methods, materials, work packages and timeline** appropriate and in agreement with deliverables?*
- *Has the project perspectives for **international collaborations, applications, networking**?*

Reviewer n. 1

The project is very interesting and well structured. The applicant explains well the step-by-step process necessary to move from production to biological validation of the product. It seems quite innovative and having a great potential. Unfortunately, it is difficult to propose all this amount of work in one year. It seems that Dr Rampado should start from the synthesis of the nanocompounds and follow the characterization, the whole study on cells. Already these two phases would be more than sufficient adequate. I therefore think that, although the description is very pertinent and well done, the organization of the experimental plan is too ambitious for this kind of project.

Reviewer n. 2

The proposed projects is scientifically significant and innovative, particularly for nature of the tumor under consideration. The know-how is clearly present in the dept and the impact of a positive result would be relevant. The objectives are clear, while it not completely clear how to mitigate the potential lack of activity due to poor targeting; the risk mitigation through changes in the site of in-vivo administration seems indeed extremely empiric. Materials, methods, technologies and timelines are appropriate, providing the results are immediately supportive of the basic hypothesis. Also for this project, a positive outcome could be of interest for larger collaborations, particularly in the industrial setting.

Reviewer n. 3

The project seems innovative in its aim to use leukocyte-derived membrane proteins in nanovesicles to deliver drugs to osteosarcoma cancer lesions building on the work by others in different cancer models. It is ambitious in the time available so feasibility is questioned. Not only are LEUKOS to be characterised and loaded, 3D models of osteosarcoma are to be developed and an in vivo model also used. This may not be realistic in 12 months. Will resazurin work on the 3D models or should another viability method be better?

Competence and expertise of the applicant.

- *What are the **merits and scientific expertise** of the applicant?*
- *Are they **appropriate and sufficient** for the proposed project?*

Reviewer n. 1

The CV is interesting but reveals a limited experience (due to the youngest of the applicant) and is somehow unrelated to the project items.

Reviewer n. 2

The applicant has gained a good expertise, even though in a short time frame. His basic competence is wide and well described, supporting the proposed work

Reviewer n. 3

The applicant has the required skills for the project, both in cell biology and nanoparticle development and characterisation.

Competence and expertise of the supervisor and of the research team.

- *Does the research team bring complementary expertise to the project?*

Reviewer n. 1

The group supporting the project brings adequate complementary expertise to the project.

Reviewer n. 2

The team well complement the applicant's expertise and can definitely support the project work.

Reviewer n. 3

The mentor for the project is Prof Paolo Caliceti with expertise in liposomes and drug delivery, Dr Agostini brings expertise in 3 D models of tumours and drug delivery systems. An excellent team.

COMMISSIONE INTERNA**Dott. Riccardo Rampado**

Titolo del Progetto: *A novel biomimetic drug delivery nanovector for the treatment of primary and metastatic pediatric osteosarcoma*

Il progetto è originale e innovativo e risulta essere ben strutturato. Gli obiettivi sono stati presentati in modo chiaro, sia nel testo del progetto che dal proponente durante il colloquio. Il progetto è in linea con il piano di sviluppo dipartimentale. Per quel che riguarda la fattibilità, alcune criticità potrebbero emergere soprattutto per quel che riguarda la ricostituzione dei sistemi recettoriali in un sistema artificiale come i liposomi.

VALUTAZIONI ASSEGNI DI RICERCA DI DIPARTIMENTO DI TIPO B ARD-B – ANNO 2021

COMMISSIONE ESTERNA

Project: Evaluation of the synergistic effect (entourage effect) of cannabinoid and terpenoid on *in vitro* model of dysfunctional intestinal barrier, the anti-inflammatory and antioxidant activities of cannabis extracts and isolated compounds

Applicant: Sut Stefania

General assessment of scientific quality and innovation - Assessment of scientific plan

- *Is the project scientifically significant, original and innovative?*
- *Is the project built on a departmental know-how?*
- *Has the project a significant impact for future development?*
- *Are the objectives and hypotheses clearly presented?*
- *Is the plan realistically feasible?*
- *Are the research methods, materials, work packages and timeline appropriate and in agreement with deliverables?*
- *Has the project perspectives for international collaborations, applications, networking?*

Reviewer n. 1

The project is well written and clear. Some ideas are interesting but the goals are sometimes difficult to be understood. The topic is not so innovative and the experimental plan does not seem to consider of potential troubles during the different phases of the project.

Reviewer n. 2

Scientific significance, innovation and originality of the proposed project appear low- medium, and a number of questions have to be considered, in particular: are part of the indicated compound commercially available? Do we really need to extract them? How can we consider the cited compounds sufficient to study potential synergies and run comparison with the whole extracts? How can we exclude that activities of the whole extracts are due to undefined compounds/mechanisms? The risk assessment and the proposed mitigation have not been properly evaluated. So, the overall probability of success does appear very low; also the potential breakthrough is not clear being focused on increase of experience and crosstalk between research groups, more than an effective scientific result forming the basis for future and larger explorations and collaborations.

Reviewer n. 3

The project aims to characterise the activity of components of *Cannabis sativa* hypothesising that certain anti-inflammatory activity is due to active molecules acting together. This could be via other receptors than cannabinoid receptors. Whether this project will have a major scientific impact is not clear. What is the benefit of a simplified extract vs the whole extract? Is it simply to remove psychotropic side-effects? The tasks are well detailed, risks have been considered and contingency ideas presented.

Competence and expertise of the applicant.

- *What are the merits and scientific expertise of the applicant?*
- *Are they appropriate and sufficient for the proposed project?*

Reviewer n. 1

The CV and the publication of the applicant are enough robust for the coordination of the project. Maybe the expertise in the field of cannabinoids biology is a little bit weaker.

Reviewer n. 2

The applicant's expertise is sufficient to support the project, particularly for what concerns the required analytical methods and technologies. The experience in the specific area of cannabinoid research is instead limited.

Reviewer n. 3

The applicant has a PhD in related area and has the required skills for the project.

Competence and expertise of the supervisor and of the research team.

- *Does the research team bring complementary expertise to the project?*

Reviewer n. 1

The group demonstrates a relevant experience and interconnection to follow the applicant along the whole project.

Reviewer n. 2

The research team does appear to well complement the applicant's expertise in supporting the project activities, with a deep competence in terms of natural products.

Reviewer n. 3

The mentor is Prof. Dall'Acqua bringing natural product expertise and Dr Maggi has expertise in extractions, Prof. Montopoli has expertise in inflammation in the gut.

COMMISSIONE INTERNA**Dott.ssa Stefania Sut**

Titolo del Progetto: *Evaluation of the synergistic effect (entourage effect) of cannabinoid and terpenoid on in vitro model of dysfunctional intestinal barrier, the anti-inflammatory and antioxidant activities of cannabis extracts and isolated compounds.*

Il progetto è interessante e riguarda lo studio del possibile effetto farmacologico sinergico di cannabinoidi e terpenoidi isolati da *Cannabis sativa*. Il workflow è adeguatamente delineato e dettagliato. Tuttavia, lo sviluppo del progetto si presenta abbastanza complesso, specialmente nelle fasi di valutazione *in vitro* e nella successiva elaborazione multivariata dei dati, volta a stabilire un possibile sinergismo. La presentazione del progetto durante il colloquio non è stata molto efficace.