

# DECRETO RETTORALE

## Decree of the Rector n. 613 of 28/06/2024

Competition for awarding 1 research grant at the University of Udine

### DISCLAIMER:

The official and legally binding call for applications is in Italian only.

This document cannot be used for legal purposes and is only meant to provide information in English on the call for applications (Decree of the Rector n. 613 of 28/06/2024). Please refer to the official call published on: <https://www.uniud.it/it/albo-ufficiale>

Any change and integration will be made available on the above-mentioned web page. Therefore, no personal written communication regarding the examination date and/or competition results shall be provided to applicants.

### Annex 1

Call for applications for the award of 1 grant for the performance of research activities at the University of Udine on the topic "Characterising the ovarian tumour microenvironment: interference with epigenetic self-renewal circuits centred on OCT4 and its pseudogene" SSD: BIOS-10/A (principal investigator, Roberta Benetti)

Research grant funded by the resources of the project PRIN 2022 - Prot. n. 2022KWLYAL

### Art. 1

A selection proceeding is hereby announced for the award of 1 research grant at the University of Udine for the performance of the research activity identified in Annex A, which forms an integral and substantial part of this call. The research grant is linked to the research project on which it is based and is subject to the corresponding financial coverage.

The grant may be renewed with the winner in accordance with the provisions of Article 22 of Law no. 240 of 30 December 2010 (in the text prior to Leg. Decree no. 36 of 30 April 2022, converted with amendments by Law no. 79 of 29 June 2022) and the Regulations of the University of Udine for the awarding of research grants issued by Rector's Decree no. 182 of 31 March 2021, in the presence of a positive assessment by the scientific supervisor of the activity carried out by the research fellow, adequate scientific justification and related financial coverage, within the limits set out in Article 3, letters b) and c) below.

The research grant does not entitle the successful candidate to any rights as regards access to University roles.

Any personal communication to candidates relating to this selection will be sent exclusively to the email address indicated in the application form.

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### Art. 2

The activities covered by the research grant referred to in this call for competition and the admission requirements are indicated and described in Annex A. Failure to meet the admission requirements at the time of applying shall result in the **exclusion** of the candidate from the selection process.

Possession of a PhD qualification or equivalent qualification obtained abroad or, for the sectors concerned only, of a medical specialisation qualification accompanied by an adequate scientific production, constitutes a preferential requirement for the awarding of the grant envisaged for this selection, if it has not been mentioned as an admission requirement.

The Selection Board shall assess, for the sole purpose of admission to the competition, the suitability of any qualification obtained abroad, without prejudice to the assessment of the medical specialisation qualification to which Article 38, paragraph 3.1 of Legislative Decree 165/2001, as amended, and the relevant Community regulations apply.

The Board assesses the qualification obtained abroad based on the relevant documentation enclosed with the application to take part in the selection and may exclude the candidate if the submitted documentation does not provide sufficient elements for the assessment.

Candidates are therefore invited to enclose all documentation in their possession relating to their qualifications in order to provide the Board with sufficient elements to assess their position.

Candidates are admitted to the selection process subject to a reservation and their exclusion, for failure to meet the requirements, may be ordered at any time by reasoned decision.

### Art. 3

The research grant referred to in this call cannot be awarded to the following subjects:

- a) Employees of Universities and the entities referred to in Article 22(1) of Law no. 240 of 30 December 2010 (in the text prior to Leg. Decree no. 36 of 30 April 2022, converted with amendments by Law no. 79 of 29 June 2022).
- b) Recipients of previous research grants pursuant to Law no. 240 of 30 December 2010, for the maximum period allowed by the regulations, excluding the period in which the grant was received in conjunction with a PhD, up to the legal duration of the relevant course.
- c) Those who have already been awarded research grants and fixed-term researcher contracts pursuant to Law no. 240 of 30 December 2010 for a total of 12 years, even if not consecutive.
- d) Those who have a degree of kinship or relationship, up to and including the fourth degree, with:
  - The Rector, the Director General or a member of the Board of Directors of the University of Udine.
  - The principal investigator or a professor/researcher belonging to the department or structure of interest where the research grant activity takes place.

The research grant referred to in this call cannot be cumulated with the following:

- a) Awarded scholarships of any kind, except those granted by national or foreign institutions useful for supplementing, by means of stays abroad, the fellow's training or research activities.
- b) Other research grants.

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- c) Employment relationships, even if part-time, without prejudice to the provisions of the regulations for employees of public administrations.

The grant referred to in this call is also incompatible with simultaneous attendance of degree courses, master's degrees, and PhDs with scholarships and medical specialisation, in Italy and abroad.

Persons who have been convicted of a criminal offence resulting in disqualification from holding public office or inability to contract with the public administration as a secondary penalty are not eligible for selection.

### Art. 4

Applicants must submit, in the manner described in Article 5 below, the application to take part in the selection, duly signed in handwritten or digital form. An application without a signature will result in the **exclusion** of the candidate, except in the case of access through the use of the Public Digital Identity System (SPID) in which case the signature will not be necessary.

The application must be uploaded in its entirety (i.e., every page), **otherwise** the applicant will be **excluded** from the selection.

Applicants must enclose the following with their application for participation in the selection, **under penalty of exclusion**:

1. The professional scientific *curriculum vitae* in Italian or English or one of the additional languages, if any, indicated in Annex A, highlighting the candidate's aptitude for carrying out and implementing the research programme.
2. Copy of valid identity document or other identification document. Citizens of non-EU countries must enclose a copy of their passport.
3. Limited to citizens of non-EU states residing or authorised to reside in Italy, a copy of their residence permit or authorisation to reside in Italy.
4. For candidates who cannot provide a self-certification under the conditions set out below, documentation proving possession of the academic qualification required for admission to the selection. Possession of a higher academic qualification does not exempt the candidate from producing such documentation, which, if missing, will result in exclusion:
  - **Candidates who are Italian citizens or citizens of a European Union Member State** must submit a declaration in lieu of certification and, if necessary, a notarial deed regarding the academic qualification needed for admission (indicating the academic qualification, the academic institution awarding the qualification, the year it was awarded and the mark obtained) and the publications and other qualifications held, indicating for each one all the identification details necessary for the Board's assessment. **The application for participation counts as a declaration in lieu of certification of the declared academic qualification.** If the subject matter of the declaration is not clearly identified in terms of its nature, duration, time setting and institution concerned, the selection board will disregard it. The Administration reserves the right to carry out appropriate checks on the truthfulness of the content of the declarations made; in the event of a false declaration, the provisions of Article 76 of Presidential Decree no. 445/2000 and Articles 483, 485, and 486 of the Italian Criminal Code shall apply. The University will not take into account any certificates attached by candidates who are Italian citizens or citizens of a state belonging to the European Union.

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- **Citizens of a non-European Union State** must submit documents and qualifications in Italian or English or one of the additional languages, if any, indicated in Annex A, under penalty of exclusion from the selection or, as the case may be, non-assessment.  
Documents and titles, originally in a different language, must be accompanied by a translation, made by the candidate under his or her responsibility, into Italian or English or any other language indicated in Appendix A. With reference to the dissertation only, the translation may be limited to an extended abstract.
- **Citizens of a non-EU State regularly residing in Italy** may use declarations in lieu of certification only in respect of states, personal qualities or facts that can be certified or attested to by Italian public bodies, without prejudice to the special provisions contained in the laws and regulations governing immigration and the status of foreigners.
- **Citizens of non-EU states authorised to reside in Italy** may use the aforementioned declarations in cases where they are produced pursuant to international conventions between Italy and the declarant's country of origin.

Applicants may also enclose with their application for assessment purposes their publications and any other qualification deemed useful to prove their qualification in relation to the research programme described in Annex A and to certify any research activity carried out in public and/or private entities (with the indication of the starting date and duration). The submission modalities are similar to those indicated in point 4 of the previous paragraph.

Only the qualifications possessed by the candidate on the date of submission of the application for selection and presented in accordance with Article 5 will be assessed.

Any exclusion from the selection procedure due to lack of eligibility requirements, absence of mandatory documents, failure to sign the application to take part in the selection or submission of the application in a manner other than that provided for in this call will be communicated to the parties concerned exclusively by email to the email address indicated in the application to take part in the selection.

### Art. 5

Registration for this selection will begin on July 5, 2024 at 2:00 pm (Italian time) and will end on September 3, 2024 at 2:00 pm (Italian time).

The application to take part in the selection must be completed, under penalty of exclusion, using the appropriate online procedure, available at <https://pica.cineca.it/>.

For those who do not already have a user account, the procedure involves a registration phase for the applicant, and a subsequent phase for completing the application online.

Once completed, the application must be signed in the manner (handwritten signature, with attached identity document, or digital signature) described in the online procedure, under penalty of exclusion from the selection. The application does not have to be signed if the above-mentioned online procedure is accessed using the Sistema Pubblico di Identità Digitale (SPID - Digital ID Public System). In the case of a handwritten signature, the applicant must upload the application to the system in its entirety. The information entered in the application form shall constitute a declaration in lieu of certification and affidavit, pursuant to Articles 46 and 47 of Presidential Decree no. 445/2000.

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The qualifications referred to in Article 4 must be attached to the application in .pdf format. Individual files, in .pdf format, may not exceed 30MB in size.

It is not permitted to submit attachments to the application in the form of links to files residing on "online storage/file sharing" services or web pages. Reference may not be made to documents or publications submitted to this or other administrations or documents attached to the application for participation in another selection procedure.

The application for participation in the selection is automatically sent to the University of Udine with the final closure of the online procedure.

The University Administration:

- accepts no liability if it is impossible to read the submitted documentation in electronic format due to damaged files;
- does not accept or take into consideration qualifications or documents received in paper form or by any other means than those specified in this article.

The Administration accepts no liability in the event of incorrect indication by the candidate of his/her email address or in the event of failure or delay in communicating a change in the email address indicated in the application, nor for any digital transmission errors attributable to third parties, unforeseeable circumstances or force majeure.

Applicants are advised not to wait until the last few days before the deadline to submit their application. The University accepts no liability for any malfunctions due to technical problems and/or overloading of the communication line and/or application systems.

### Art. 6

The selection test takes place according to the modalities set out in Annex A.

The test will aim to ascertain the candidates' preparation, experience and research aptitude. It will consist of an assessment of the professional scientific curriculum, publications and titles submitted, and an interview, where applicable.

Failure of the candidate to attend the interview will be considered as withdrawal from the selection, whatever the cause.

Candidates who intend to avail themselves of the benefits provided for by Article 20 of Law no. 104 of 1992 (need for assistance, possible use of additional time for the performance of examination tests) in relation to their disability situation, must declare this and accompany the application with appropriate medical certification in order to allow the Administration to prepare in time the means and tools to guarantee the statutory benefits; failure to submit the medical certification exempts the Administration from any obligation in this regard.

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### Art. 7

The Competition Selection Board is identified in Annex A to this call, of which it forms an integral part. At its first meeting, the Board appoints the Chairperson and the Secretary taking the minutes, and establishes the criteria and procedures for assessing the qualifications and the interview, where applicable.

The results of the assessment must be made known to the parties concerned at the interview, where provided for.

The Board can attribute to the selection a total number of 100 points (one hundred hundredths). At the end of its work, the Board formulates the overall merit list based on the total marks obtained by each candidate and draws up the minutes of the competition operations.

The grant may be awarded, subject to the ranking list, to candidates who have obtained a minimum overall mark of 70/100 (seventy hundredths).

The Board's judgement is final on the merits.

The ranking list will be made public exclusively by publication on the University's official notice board; the outcome of the assessment will not be the subject of personal communication to candidates.

Those who do not declare their acceptance of the research grant and do not present themselves at the structure where the research activities are to be carried out to sign the contract by the deadline communicated by the same to the email address indicated by the candidate in the application shall forfeit their right to the research grant, except for health reasons or reasons of force majeure duly documented and promptly notified.

Candidates holding qualifications obtained abroad, if successful, must submit the following, if not already attached to the application:

- **For degrees issued by a country that is a party to the Lisbon Convention (<https://www.enic-naric.net/>), the following documentation:**
  - *Supplement* Diploma or similar certificate in English issued by the competent University.
  - "Certificate of Verification of Foreign Qualification - CIMEA" issued by CIMEA (Centre for Information on Academic Mobility and Equivalences) via the "*diplome*" service at <https://cimea.diplome.eu/udine/#/auth/login>
- **For degrees issued by a country not party to the Lisbon Convention (<https://www.enic-naric.net/>), one of the following options:**
  - Declaration of the on-site value of the qualification held and the certificate relating to the qualification with examinations and grades. The certificate in a language other than Italian or English must be accompanied by an official translation into one of those languages (certified by the competent diplomatic-consular authority or sworn at a court in Italy).
  - "Certificate of Comparability and Verification of Foreign Qualifications - CIMEA" issued by CIMEA (Centre for Information on Academic Mobility and Equivalences) via the "*diplome*" service at <https://cimea.diplome.eu/udine/#/auth/login>



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If the aforementioned documentation is not available at the time of the conclusion of the contract, the candidate must prove that he or she has requested it and submit it as soon as possible; if it is not submitted within six months of the start of the contract, the candidate will forfeit the contract and will be required to repay any related sums received to date.

### Art. 8

The research activity cannot be started before the contract defining the terms of the collaboration is signed.

The activity covered by the research grant must have the following characteristics:

- a) Be carried out in the context of the research programme covered by the grant and not be a purely technical support to the same.
- b) Close connection with the implementation of the research programme that is the subject of the relationship with the winner.
- c) Having a continuous and in any case temporally defined character, not merely occasional, and in coordination with the overall activity of the University.
- d) Performance in a condition of autonomy, within the sole limits of the programme prepared by the Head of the same, without predetermined working hours.

The research fellow is obliged to submit a detailed written report on the work carried out and the results achieved, together with the opinion of the scientific supervisor, to the reference structure within the deadlines laid down in the contract. The research fellow will also have to submit interim reports and time sheets if requested by the reference structure and/or the scientific supervisor.

The research fellow is bound to strict confidentiality regarding the data and information to which he/she becomes privy in the course of his/her research activity. At the request of the scientific coordinator, he/she will be required to sign an appropriate confidentiality agreement.

The industrial property rights to the results obtained by the research fellow in the performance of the research activity belong exclusively to the University, without prejudice to the moral right of the research fellow to be recognised as an author or inventor.

The University reserves the right to revoke this call for competition for reasons of public interest, should the research project and/or the financial backing on which the research grant is based cease to exist. Should these causes arise after the contract has been signed, the University may terminate the contract without notice.

### Art. 9

The following apply to the grant under this call:

- On tax matters, the provisions of Article 4 of Law no. 476 of 13 August 1984, as amended.
- On social security matters, the provisions of Article 2(26) et seq. of Law no. 335 of 8 August 1995, as amended.
- On compulsory maternity leave, the provisions of the Ministerial Decree of 12 July 2007.
- On sick leave, the provisions of Article 1(788) of Law No 296 of 27 December 2006, as amended.

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During the period of compulsory maternity leave, the allowance paid by INPS pursuant to Article 5 of the Ministerial Decree of 12 July 2007 is supplemented by the University up to the full amount of the research grant.

The grant will be paid in monthly instalments in arrears.

### Art. 10

The data collected as part of the procedure referred to in Article 5 is necessary for the proper management of the selection procedure, for the possible subsequent management of the research grant and purposes related to the management of the services provided by the University. The University of Udine is the Data Controller. At any time, the data subject may request access, rectification and, compatibly with the institutional purposes of the University, cancellation and restriction of processing or may object to the processing of his/her data. He/she can always lodge a complaint with the Italian Data Protection Authority. The full information is available on the University of Udine website in the "Privacy" section accessible from the home page [www.uniud.it](http://www.uniud.it) Direct Link: <https://www.uniud.it/it/it/pagine-speciali/guida/privacy>

### Art. 11

For any matters not expressly mentioned in this call, reference is made to the relevant regulations in force cited in the introduction and to the "Internal regulations for the award of research grants pursuant to Law no. 240 of 30 December 2010" of the University of Udine issued by Rector's Decree no. 182 of 31 March 2021.

### Art. 12

The official in charge of the proceeding is Dr. Sandra Salvador, Head of the Research Services Area of the University of Udine.

The reference office at the University of Udine is the "Area Servizi per la Ricerca - Ufficio Formazione per la Ricerca", Via Mantica 31 - 33100 Udine.

To request information on the call, please complete the following form available on the University of Udine website: [https://helpdesk.uniud.it/SubmitSR.jsp?type=req&accountId=universityofudine&populateSR\\_id=42105](https://helpdesk.uniud.it/SubmitSR.jsp?type=req&accountId=universityofudine&populateSR_id=42105)



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## Annex A

### Responsabile scientifico della ricerca / Principal investigator:

Nome e cognome / Name and surname: Roberta Benetti  
Qualifica / Position: Professoressa Associata / Associate Professor  
Dipartimento / Department: Medicina (DMED) / Medicine  
Area MUR / Research field: 05 - Scienze Biologiche  
Settore concorsuale e Settore scientifico disciplinare / Scientific sector: 05/BIOS-10; BIOS-10/A - Biologia cellulare e applicata

### Titolo dell'assegnio di ricerca / Topic of the research fellowship "assegnio di ricerca":

*I bandi sono consultabili dal sito dell'Ateneo, del MUR e di Euraxess / The calls are available on the University, MUR and Euraxess websites*

#### Testo in italiano:

Caratterizzazione del microambiente del tumore ovarico: l'interferenza con i circuiti epigenetici di auto-rinnovamento incentrati su OCT4 e il suo pseudogene.

#### Text in English:

Characterising the ovarian tumour microenvironment: interference with epigenetic self-renewal circuits centred on OCT4 and its pseudogene.

### Obiettivi previsti e risultati attesi del programma di ricerca in cui si colloca l'attività dell'assegnista di ricerca / Foreseen objectives and results of the research programme performed by the research fellow "assegnista di ricerca":

*I bandi sono consultabili dal sito dell'Ateneo, del MUR e di Euraxess / The calls are available on the University, MUR and Euraxess websites*

#### Testo in italiano:

L'EOC (epitelial ovarian cancer) è il tumore ginecologico più letale, con oltre 60.000 nuovi casi all'anno negli Stati Uniti e nell'UE. Metastasi, chemioresistenza e recidiva sono molto frequenti, con una sopravvivenza globale a 5 anni inferiore al 40% e tassi di mortalità costanti negli ultimi 20 anni. Studi recenti hanno rivelato l'elevata rilevanza del microambiente tumorale (TME) nella progressione dell'EOC. Il TME ha un forte valore prognostico, tuttavia le conoscenze sui percorsi che programmano un TME immunosoppressivo nelle cellule tumorali sono molto limitate.

OCT4 è un fattore di trascrizione dell'auto-rinnovamento, sensibile al dosaggio, che promuove la formazione del tumore. Nel nostro laboratorio di ricerca e altri gruppi abbiamo dimostrato che il fattore di trascrizione di auto-rinnovamento OCT4 guida l'aggressività dell'EOC. Recentemente abbiamo scoperto che l'espressione di lncRNA dagli pseudogeni murini mOct4P4 e umani hOCT4P3, altamente conservati, indirizza la iston metil transferasi SUV39H1 verso il promotore del gene OCT4 ancestrale, inducendo il silenziamento in trans. Di conseguenza, la progressione del tumore e la scarsa sopravvivenza dei pazienti sono legate a una bassa espressione del lncRNA hOCT4P3, il che indica una sua rilevanza clinica.

Con questo progetto, in collaborazione con l'Università di Trieste, vogliamo capire come le firme di espressione genica dipendenti da OCT4 programmino una TME favorevole al tumore e svelare il meccanismo dettagliato con cui l'IncRNA umano OCT4 pseudogene 3 (hOCT4P3) indirizza i complessi di silenziamento al promotore di OCT4 ma anche a geni bersaglio alternativi in tutto il genoma del tumore ovarico epiteliale.

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Nei primi mesi del progetto sono state eseguite analisi dell'espressione genica su una coorte iniziale di pazienti con cancro ovarico, consentendo la stratificazione dei pazienti in base all'espressione di OCT4 e rivelando una correlazione negativa dei livelli di OCT4 e hOCT4P3. Inoltre, è stato generato un pannello di vettori di espressione codificanti versioni di hOCT4P3 contenenti mutazioni negli elementi strutturali.

Nella fase futura del progetto, il/la candidato/a vincitore/trice del nuovo assegno sarà coinvolto per:

1. ampliare una collezione di campioni EOC stratificati per l'espressione di hOCT4P3 e OCT4 e definire i componenti della TME cellulare mediante IHC;
2. scoprire i meccanismi centrali della comunicazione tra cellule EOC e TME guidata da OCT4;
3. indagare l'impatto dei mutanti hOCT43, generati nella prima fase del progetto, sulla deposizione dei complessi di silenziamento;
4. mappare i siti target di hOCT4P3 lncRNA nel genoma dell'EOC e integrarli con i dati di espressione genica per comprendere il ruolo di hOCT4P3 nella modulazione dell'aggressività dell'EOC.

Il progetto proposto fonde due temi di ricerca di grande rilevanza scientifica e dettagliati di seguito: le vie che programmano la TME nell'EOC difficile da trattare e la dissezione di una nuova via di regolazione epigenetica dipendente da lncRNA che è risorta dal pool di pseudogeni.

a) Programmazione della TME dell'EOC mediante firme di auto-rinnovamento incentrate su OCT4 e hOCT4P3

Recentemente numerosi studi hanno dimostrato che la TME e il sistema immunitario contribuiscono in modo significativo alla progressione del tumore. I dati raccolti da ampie coorti di pazienti sottolineano l'importanza di eseguire una classificazione immunologica, il cosiddetto "immunoscore", con valore prognostico e potenzialmente predittivo per completare e implementare le informazioni ottenute dalla classificazione TNM.

I nostri dati preliminari mostrano che la presenza di cellule tumorali positive all'OCT4 è legata a una bassa conta di linfociti infiltrati (TIL) e a una scarsa sopravvivenza dei pazienti. Sulla base di questi dati ottenuti, un obiettivo centrale del/la nuovo/a assegnista sarà quello di caratterizzare la composizione cellulare della TME in una coorte allargata di pazienti con carcinoma ovarico e di collegare la composizione della TME con i livelli di espressione di OCT4 e hOCT4P3. Sulla base dei dati sull'espressione di OCT4 e hOCT4P3 in una coorte di pazienti con cancro ovarico generati in una fase iniziale del progetto, verranno supportati i dati IHC dai campioni tumorali. L'impatto dell'espressione di OCT4 nelle cellule tumorali sui componenti della TME sarà convalidato in vitro. Verificare in una coorte estesa di pazienti che le firme di espressione di OCT4 programmano una composizione immunosoppressiva del TME che porta a una scarsa sopravvivenza delle pazienti ha un'elevata rilevanza per una migliore stratificazione delle pazienti. Queste informazioni possono anche fornire informazioni aggiuntive per la selezione delle strategie terapeutiche attualmente disponibili che prevedono l'uso di inibitori del checkpoint immunitario. Ciò consentirebbe un uso migliore e più efficiente delle terapie antitumorali, migliorando le condizioni di vita dei pazienti ma anche riducendo l'onere economico derivante da terapie inefficaci.

b) Scoprire un nuovo paradigma di controllo epigenetico dei geni parentali da parte di pseudogene lncRNA

Il fattore di trascrizione OCT4 funziona in modo specifico dosaggio-dipendente; di conseguenza, molteplici meccanismi collaborano alla precisa espressione di OCT4 in diversi contesti biologici, tra cui l'EOC. Abbiamo recentemente dimostrato che questi meccanismi comprendono l'imposizione di complessi di silenziamento al promotore di OCT4 da parte di uno pseudogene conservato, che agisce in trans. L'obiettivo di questo progetto è quello di svelare il processo ancora enigmatico del riconoscimento del sito bersaglio e del reclutamento dei complessi di silenziamento e di dimostrarne la rilevanza biologica in un contesto clinicamente rilevante come quello dell'EOC. Sulla base di questi dati ottenuti, un obiettivo centrale del/la nuovo/a assegnista sarà di investigare l'impatto delle mutazioni dell'RNA sul reclutamento del complesso di silenziamento. Avendo identificato questi processi, gli lncRNA pseudogene hOCT4P3/mOct4P4 possono rivelare un nuovo paradigma della funzione degli lncRNA pseudogene che può essere esteso ad altre coppie gene/pseudogene. Ciò dimostrerà l'importanza dell'evoluzione degli pseudogene lncRNA in regolatori che invadono i circuiti di regolazione stabiliti per modellare e regolare l'espressione genica in organismi altamente complessi. I nostri

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dati indicano anche un meccanismo di targeting dipendente dalla sequenza. La comprensione del riconoscimento del sito bersaglio e del complesso di silenziamento può consentire di sviluppare strumenti ingegnerizzati basati su lncRNA che permettono di depositare silenziatori epigenetici nei siti bersaglio di interesse, influenzando così sull'espressione genica.

### Text in English:

EOC is the most lethal gynaecological cancer with > 60.000 new cases per year in the US and EU. Metastasis, chemoresistance and recurrence are highly frequent, resulting a <40% 5-year overall survival with death rates remaining constant in the past 20 years. Recent studies revealed high relevance for the tumor microenvironment (TME) in EOC progression. The TME has a strong prognostic value, however insights into pathways in cancer cells that program an immunosuppressive TME are very limited.

OCT4 is a dosage sensitive self-renewal transcription factor that drives tumor formation. We demonstrated that the self-renewing transcription factor OCT4 mediates EOC aggressiveness and poor patient survival. We recently found that lncRNA expression from the conserved processed murine mOct4P4 or human hOCT4P3 pseudogenes directs the repressive SUV39H1 HMTase to the promoter of the ancestral OCT4 gene, inducing silencing *in trans*. Accordingly, tumor progression and poor patient survival is linked with low hOCT4P3 lncRNA expression, indicating clinical relevance.

In the collaborative effort with the University of Trieste, we want to understand how OCT4 dependent gene expression signatures program a tumor-promoting TME, and unravel the detailed mechanism by which the human OCT4 pseudogene 3 (hOCT4P3) lncRNA targets silencing complexes to the OCT4 promoter but also to alternative target genes across the epithelial ovarian cancer genome.

In the first months of the project gene expression analyses were performed on an initial cohort of ovarian cancer patients allowing patient stratification according OCT4 expression and revealed negative correlation of OCT4 and hOCT4P3 levels. In addition, a panel of expression vectors encoding hOCT4P3 versions containing mutations in structural elements were generated.

In the future phase of the project the selected research fellow will:

1. expand the EOC specimen collection stratified for hOCT4P3 and OCT4 expression and define cellular TME components by IHC;
2. Unravel central mechanisms of OCT4 driven EOC cell – TME communication;
3. Investigate the impact of hOCT43 mutants, generated in the first phase of the project, on the deposition of silencing complexes;
4. Map hOCT4P3 lncRNA target sites across the EOC genome and integrate with gene expression data to understand the role of hOCT4P3 in modulating EOC aggressiveness.

The proposed project merges two research topics with high scientific relevance: stemness related pathways that program the TME in difficult to treat EOC and the dissection of a novel, lncRNA dependent epigenetic regulatory pathway that has resurrected from the pool of vertebrate pseudogenes.

### a) Programming of the EOC TME by self-renewing signatures centered on OCT4 and hOCT4P3

Recently numerous studies have shown that the TME and the immune system significantly contribute to tumor progression. Data collected from large patient cohorts underlines the importance of performing immunological classification, the so-called "immunoscore", holding prognostic and potentially predictive value in order to complete and implement information obtained from the TNM classification. Our preliminary data shows that the presence of OCT4 positive cancer cells is linked with low TIL count and poor patient survival. Based on these obtained data a central goal of the research fellow will characterize the cellular composition of the TME in an enlarged cohort of ovarian cancer patients and link TME composition with OCT4 and hOCT4P3 expression levels. Data on OCT4 and hOCT4P3 expression in a cohort of ovarian cancer patients generated in an early phase of the project will support IHC data from cancer specimen. The impact on OCT4 expression in cancer

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cells on TME components will be validated in cell models. Validating that OCT4 expression programs an immunosuppressive TME composition in an extended patient cohort has high relevance for a better stratification of patients. This information may provide additional information for the selection of currently available therapeutic strategies.

### b) Unravelling a novel paradigm of epigenetic control of parental genes by pseudogene lncRNA

The transcription factor OCT4 works in a dosage specific manner. Consequently, multiple mechanisms collaborate in the precise expression of OCT4 in different biological contexts including EOC. These mechanisms comprise a conserved OCT4 pseudogene lncRNA that deposits silencing complexes at the promoter of ancestral OCT4 gene *in trans*. The goal of this project is to unravel the still enigmatic process of target site recognition and silencing complex recruitment and demonstrate biological relevance in a clinically relevant setting of EOC. A central strategy is centered on the use of hOCT4P3 mutant versions, generated in the first phase of the project. The research fellow will investigate the impact of RNA mutations on silencing complex recruitment. Having identified these processes, hOCT4P3/mOct4P4 pseudogene lncRNAs may reveal a new paradigm of pseudogene lncRNA function that can be expanded to other gene/pseudogene pairs. This will demonstrate the importance of evolution of pseudogene lncRNAs into regulators that invade established regulatory circuits to shape and fine-tune gene expression in highly complex organisms. Understanding target site recognition and silencing complex recognition may allow to develop an engineered, lncRNA based tools that allow to deposit epigenetic silencers to target sites of interest thereby impacting on gene expression.

### **Struttura dell'Università di Udine presso la quale verrà sviluppata l'attività di ricerca / Department or other structure of the University of Udine where research activities will be carried out:**

Dipartimento di Medicina (DMED). / Department of Medicine.

### **Importo dell'assegno di ricerca (al lordo oneri carico assegnista) / Total grant gross for the research fellowship:**

€ 19.457,28

### **Durata dell'assegno di ricerca / Duration of the research fellowship "assegno di ricerca":**

12 mesi / months

### **Finanziamento / Financed by:**

La copertura finanziaria graverà sul progetto PRIN 2022 – "Reprogramming the ovarian tumor microenvironment by interfering with epigenetic self-renewal circuits centred on OCT4 and trans-acting OCT4 pseudogene lncRNA"; Prot. n. 2022KWLYAL. Decreto di finanziamento n. 1111 del 20/07/2023 - Settore LS4. Codice CUP G53D23005580006. Ministero dell'Università e della Ricerca (Finanziato dall'Unione Europea, NextGenerationEU - M4C2 Inv. 1.1).

### **Requisiti di ammissione / Minimum qualifications necessary:**

Possesso di un diploma di laurea vecchio ordinamento (ante decreto 3 novembre 1999 n. 509) o di laurea specialistica/magistrale (ex decreto 3 novembre 1999 n. 509 e decreto 22 ottobre 2004 n. 270) o titolo equivalente conseguito all'estero. / University degree obtained before Decree n. 509 of 3 November 1999 or specialistic/Master's degree (post decree n. 509 of 3 November 1999 and decree n. 270 of 22 October 2004) or equivalent degree obtained abroad.

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### Modalità di presentazione della documentazione oggetto di valutazione / Arrangements for the submission of documents:

La modalità di presentazione della documentazione oggetto di valutazione è specificata all'art. 4 del bando. / The way of presenting the documentation under evaluation is specified in art. 4 of the present notice.

Ai fini valutativi, i candidati potranno presentare le pubblicazioni e ogni altro titolo ritenuto utile a comprovare la propria qualificazione in relazione al programma di ricerca descritto nell'Allegato A, nelle seguenti lingue: / For evaluation purposes, candidates may present publications and any other qualifications deemed useful to demonstrate their qualification in relation to the research program described in Attachment A, in the following languages:

- Italiano / Italian
- Inglese / English

### Procedura selettiva / Competition procedure:

Valutazione per titoli e colloquio. / Evaluation of titles and oral exam.

I risultati della valutazione dei titoli saranno resi noti agli interessati nel corso del colloquio. / The evaluation of the qualifications will be disclosed to candidates during the interview.

Calendario del colloquio / Calendar of the oral exam	Modalità / Modality	Videoconferenza / Videoconference
	Data / Date	10 Settembre / September 2024
	Ora / Time	16:00 / 4:00 pm (Italian time)
	Luogo / Place	–

Per sostenere il colloquio i candidati devono esibire un valido documento di riconoscimento. / Candidates must come to the interview with a valid identity document.

Eventuali variazioni saranno rese note esclusivamente mediante pubblicazione all'albo ufficiale on line dell'Ateneo / Any change will be made public solely through publication on the University web site [http://web.uniud.it/ateneo/normativa/albo\\_ufficiale](http://web.uniud.it/ateneo/normativa/albo_ufficiale)

**Nota / Note:** Le indicazioni sulle modalità di svolgimento della prova in modalità telematica saranno inviate ai candidati con successiva email da parte del Presidente della Commissione. Ai fini dell'identificazione e a pena di esclusione dalla procedura selettiva, ciascun candidato è tenuto ad identificarsi prima che il colloquio abbia inizio, esibendo il medesimo documento di identità allegato alla domanda di ammissione al concorso. Il candidato deve risultare reperibile nella giornata e all'orario indicato sul bando. Il mancato collegamento, l'irreperibilità del candidato nel giorno o nell'orario stabilito o la mancata esibizione del documento identificativo, sono motivo di esclusione dalla procedura selettiva. La registrazione delle prove orali è vietata. L'Ateneo adoterà pertanto tutti i provvedimenti in suo potere per tutelare i soggetti coinvolti qualora venissero diffuse tramite internet – o altri mezzi di diffusione pubblica – video, audio o immagini della procedura selettiva. / Instructions on how the video interviewing will be conducted will be provided to candidates by the Chairman of the Examining Board via email. For identification purposes, each candidate is required to identify him/herself before the interview by exhibiting the



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same identification document attached to the application. Candidates must be available on the day and time established by the call for applications. Failure of the candidate to establish a video connection, the unavailability of the candidate on the day and/or time established or failure of the candidate to provide the required identification document are all grounds for exclusion from the selection procedure. Recording of the video interviews is prohibited. The University will adopt all the measures within its power to protect all personnel involved as a result of dissemination via the internet or via other forms of public dissemination, of videos, audios or other pictures of the selection procedures.

### Commissione giudicatrice / Examining Board:

Nome e Cognome	Qualifica	SSD	Università
<b>Membri Effettivi / Permanent members</b>			
Roberta Benetti	PA	BIOS-10/A	Università degli Studi di Udine
Gianluca Tell	PO	BIOS-08/A	Università degli Studi di Udine
Giulia Antoniali	PA	BIOS-08/A	Università degli Studi di Udine
<b>Membro Supplente / Temporary member</b>			
Teresa Gagliano	PA	BIOS-10/A	Università degli Studi di Udine