



Decree of the Rector n. 1558 of 16/12/2024

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. 1558 of 16/12/2024). 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 "New perspectives in proteolysis-mediated mechanism of transthyretin related amyloidosis: the role of mechanic forces" SSD: PHYS-06/A (principal investigator, Alessandra Corazza)

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.

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.
- 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 or, if available, a copy of the Italian identity document and of the valid residence permit.
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.
 - **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 January 16, 2025 at 2:00 pm (Italian time) and will end on February 17, 2025 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.

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.

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.diplo-me.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.diplo-me.eu/udine/#/auth/login>

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.

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 Direct Link: <https://www.uniud.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



Annex A

Responsabile scientifico della ricerca / Principal investigator:

Nome e cognome / Name and surname: Alessandra Corazza
Qualifica / Position: Professoressa Ordinaria / Full Professor
Dipartimento / Department: Medicina (DMED) / Medicine
Area MUR / Research field: 02 – Scienze fisiche
Settore concorsuale e Settore scientifico disciplinare / Scientific sector: 02/PHYS-06; PHYS-06/A - Fisica per le scienze della vita, l'ambiente e i beni culturali

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

Nuove prospettive per il meccanismo mediato da proteolisi dell'amiloidosi dovuta a transtiretina: ruolo delle forze meccaniche.

Text in English:

New perspectives in proteolysis-mediated mechanism of transthyretin related amyloidosis: the role of mechanic forces.

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'amiloidosi è la malattia associata all'accumulo tossico di aggregati fibrillari proteici nei tessuti del corpo. Ad oggi, più di 30 proteine che subiscono una conversione da una struttura solubile a una fibra insolubile sono state associate a diverse patologie come il morbo di Alzheimer e il morbo di Parkinson. Tuttavia, il meccanismo attraverso il quale queste proteine assumono un ripiegamento della catena polipeptidica anomalo e si aggregano in condizioni fisiologiche è tutt'altro che chiaro, impedendo così la scoperta di trattamenti appropriati e rendendo l'amiloidosi un grave problema di salute pubblica che coinvolge milioni di persone in tutto il mondo.

L'amiloidogenesi della transtiretina (TTR) wild type (WT) è la causa dell'amiloidosi sistemica che colpisce il 25% della popolazione di età superiore agli 80 anni. Inoltre, sono state identificate circa 100 varianti patologiche alcune delle quali sono associate a depositi fibrillari in particolari organi, anche se esiste una grande variabilità tra i pazienti. La maggior parte delle varianti di TTR mostra una stabilità ridotta ed è responsabile dell'insorgenza precoce di amiloidosi tessuto-specifica grave (cardiomiopatia e neuropatia amiloide). La TTR è un omotetramero costituito da un dimeri di dimeri. Ogni protomero è caratterizzato da un ripiegamento a β -sandwich formato da due fogli β a quattro filamenti e un'elica α lunga 7 residui. È noto che, per aggregare, il tetramero della TTR deve dissociarsi in monomeri che poi assumono un ripiegamento anomalo e fibrillano. La delucidazione del meccanismo di conversione amiloidogenica della transtiretina (TTR) è risultata tutt'altro che triviale e finora non è stata rivelata da alcuna caratteristica ovvia della struttura proteica nativa nonostante la cristallografia ad altissima risoluzione della WT e di diverse varianti amiloidogeniche. La maggior parte delle nostre conoscenze sull'amiloidogenesi da TTR deriva dal modello sperimentale di Kelly e colleghi in cui l'aggregazione della TTR in condizioni acide è innescata dalla dissociazione del tetramero e dal ripiegamento errato del monomero. Questo modello è stato fondamentale nello sviluppo del primo approccio farmacologico al trattamento dell'amiloidosi correlata a TTR (ATTR), che consiste nello sviluppo di stabilizzatori cinetici, come il tafamidis, che aumentano la stabilità cinetica del tetramero e prevengono la dissociazione e l'aggregazione. Più recentemente, sulla base di



diverse osservazioni che riportano la presenza di forme troncate di TTR nelle fibrille naturali, è stato proposto un modello più fisiologico di fibrillogenesi della TTR in cui la combinazione di forze biomeccaniche ed enzimi proteolitici specifici destabilizzano il tetramero e generano il frammento 49-127 altamente amiloidogenico. Il cosiddetto "meccanismo mecano-enzimatico" (MEM) della fibrillogenesi è comune alla TTR S52P più aggressiva e instabile così come alla WT e ad altre varianti amiloidogeniche più comuni della TTR.

Nell'ambito del modello di amiloidogenesi mecano-enzimatica proposto per l'ATTR, il nostro obiettivo è quello di chiarire il ruolo delle forze meccaniche nell'evento proteolitico che porta all'aggregazione proteica. Il gruppo di Bellotti ha dimostrato che il taglio proteolitico della WT e della variante V122I si verifica solo in presenza di stress meccanico, suggerendo un effetto cruciale delle forze sulla struttura e/o sulla dinamica della TTR. Vogliamo capire se e come le forze meccaniche possono modulare la dinamica delle proteine favorendo uno spostamento verso stati meno stabili più suscettibili alla scissione proteolitica. È prevista un'indagine molecolare dettagliata basata sulla spettroscopia NMR sull'impatto delle forze di taglio su diverse varianti della TTR presenti in natura al fine di ottenere informazioni con un dettaglio senza precedenti sul diverso comportamento delle varianti di TTR in condizioni di MEM nonostante la loro sostanziale somiglianza strutturale. Per raggiungere questo obiettivo, equipaggeremo lo strumento NMR con un apparato Rheo in grado di applicare forze di taglio al campione all'interno del magnete in modo da poter registrare in queste condizioni spettri NMR. Inoltre, i ligandi della TTR hanno dimostrato di essere in grado di inibire il MEM con diversa efficacia in diverse varianti. Si vuole quindi valutare l'effetto dei ligandi monovalenti sulla proteina in presenza di forze per chiarire se gli stabilizzanti influiscono sulla dinamica della proteina in condizioni di stress meccanico e se questo effetto dipende dalla variante specifica. Il progetto di ricerca può essere suddiviso in 2 obiettivi principali:

- **Obiettivo 1:** stabilire l'effetto delle forze di taglio sulla struttura e sulla dinamica della TTR alla risoluzione del singolo residuo.

Approccio: applicare un intervallo di intensità di forze di taglio sulla TTR marcata con ^2H - ^{15}N (WT, varianti omotetrameriche e tetrameri ibridi) utilizzando l'apparato Rheo-NMR e analizzare a livello di singolo amminoacido la risposta proteica.

- **Obiettivo 2:** indagare se gli stabilizzanti della TTR sono in grado di influenzare la plasticità della proteina sotto forze di taglio riducendo la propensione delle proteine alla scissione proteolitica.

Approccio: utilizzare la stessa metodologia dell'obiettivo 1 sulla TTR (wild type e varianti) stabilizzata da ligandi monovalenti a rapporti molari pari a 1:1 e 1:2.

Text in English:

Amyloidosis is the disease associated with the toxic accumulation of misfolded protein fibrillar aggregates in the body tissues. At present, more than 30 proteins which undergo a conversion from a soluble structure to insoluble fibres have been associated to different pathologies like Alzheimer's and Parkinson's diseases. However, the mechanism through which these proteins misfold and aggregate under physiological conditions is far from being unveiled, preventing the discovery of appropriate treatments and making amyloidosis a major public health issue involving millions of people worldwide.

Transthyretin (TTR) wild-type (WT) amyloidogenesis is the cause of systemic amyloidosis affecting 25% of the population over age 80. Moreover, approximately 100 pathogenic variants have been reported; some are associated with fibrillar deposits in particular organs, even though a great patients variability exists. The majority of TTR variants show a decreased stability and are responsible of the early onset of severe tissue-specific amyloidosis (amyloid cardiomyopathy and neuropathy). TTR is a homotetramer consisting of a dimer of dimers. Each protomer is characterized by a β -sandwich fold formed by two four-stranded β -sheets and a 7-residue long α -helix. It is well known that to aggregate TTR tetramer needs to finally dissociate into monomers which than misfold and fibrillate. Elucidation of the mechanism of amyloidogenic conversion of TTR has been challenging and hitherto has not been revealed by any obvious feature of the native protein structure despite very high-resolution crystallography of the wild-type and several amyloidogenic variants. Most of our knowledge on TTR amyloidogenesis derives from the experimental model by Kelly and colleagues in which acidic-mediated TTR aggregation is primed by tetramer disassembly and monomer misfolding. This model was pivotal in developing the first pharmacological approach to the treatment of TTR related amyloidosis (ATTR), represented by kinetic



stabilizers, such as tafamidis, that increase the kinetic stability of the tetramer and prevent disassembly and aggregation. More recently, based on several observations that truncated forms of TTR are present in natural fibrils, a more physiological model of TTR fibrillogenesis has been established in which the combination of biomechanical forces and specific proteolytic enzymes destabilize the tetramer and generates the highly amyloidogenic 49-127 fragment. The so called “mechano-enzymatic mechanism” (MEM) of fibrillogenesis is common to the most aggressive and unstable S52P TTR as well to the WT and other more common amyloidogenic TTR.

In the frame of the mechano-enzymatic amyloidogenesis model proposed for ATTR, we aim at elucidating the role of mechanical forces in the proteolytic event that leads to protein aggregation. Bellotti’s group has demonstrated that the proteolytic cleavage of WT and V122I TTR occurs only in the presence of mechanical stress, suggesting a crucial effect of forces on TTR structure and/or dynamics. We want to understand if and how mechanical forces can modulate protein dynamics promoting a shift towards less stable states more susceptible to proteolytic cleavage. A detailed molecular investigation of the impact of shear forces on different naturally occurring TTR variants based on NMR spectroscopy is envisaged in order to gain unprecedented insights into the different behavior shown by TTR variants under MEM conditions despite their substantial structural similarity. To reach this goal, NMR instrument will be equipped with a Rheo apparatus able to apply shear forces to the sample inside the NMR magnet allowing to record under these conditions NMR spectra. Moreover, TTR stabilizers demonstrated to be able to inhibit MEM with different efficacy in different variants. We want to assess also the effect of monovalent ligands on the protein in presence of shear stress to clarify if stabilizers affect the protein dynamics under mechanical stress conditions and if this effect depends on the specific variant. The research project can be divided into 2 main aims:

- **Aim 1:** establish the effect of shear forces on TTR structure and dynamics at single-residue resolution.
Approach: apply a range of shear forces on ²H-¹⁵N labelled TTR (wild type, homo-tetrameric variants and hybrid tetramers) employing Rheo-NMR apparatus and analyse at single amino acid level protein response.
- **Aim 2:** investigate if TTR stabilizers are able to affect TTR plasticity under shear forces reducing protein propensity to proteolytic cleavage.
Approach: use the same methodology as in Aim 1 on TTR (wild type and variants) stabilized by monovalent ligands at one and twofold molar ratios.

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:

€ 20.266,72

Durata dell’assegno di ricerca / Duration of the research fellowship “assegno di ricerca”:

12 mesi / months

Finanziamento / Financed by:

La copertura finanziaria graverà sui seguenti fondi:

- fondi dipartimentali - progetto PSR_2016_2018_DISM;
- fondi dipartimentali - progetto PSD_2022_2025_DAME_Interdip_AGEING, budget K, CUP G23C22002450006;
- fondi di ricerca libera della proponente, prof.ssa Alessandra Corazza (Codice U-GOV: RICLIB_CORAZZA).

**Research, Libraries and Third Mission Directorate
Research Education Office**

Directorate manager: Sandra Salvador

Office manager: Raffaella Medeot

Person in charge of the proceeding: Sandra Salvador

Drafter: Francesca Mion



HR EXCELLENCE IN RESEARCH





Requisiti di ammissione / Minimum qualifications necessary:

Possesso del titolo di Dottore di ricerca o titolo equivalente conseguito all'estero. / Possession of a Research doctorate or equivalent qualification obtained abroad.

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	In presenza / On site
	Data / Date	6 marzo / March 2025
	Ora / Time	14:30 / 2:30 pm (Italian time)
	Luogo / Place	Aula riunioni al 2° piano della sede di Piazzale Kolbe del Dipartimento di Medicina. / Meeting room on the 2nd floor of the Piazzale Kolbe headquarters of the Department of Medicine. Piazzale Kolbe, 4 - Udine

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



Commissione giudicatrice / Examining Board:

Nome e Cognome	Qualifica	SSD	Università
Membri Effettivi / Permanent members			
Giovanna Lippe	PO	BIOS-07/A	Università degli Studi di Udine
Gianluca Tell	PO	BIOS-08/A	Università degli Studi di Udine
Marina Comelli	RU	BIOS-07/A	Università degli Studi di Udine
Membro Supplente / Temporary member			
Valentina Rapozzi	PA	BIOS-07/A	Università degli Studi di Udine