Foreword

The PhD program in Molecular Biomedicine is offering a number of positions with or without fellowship, linked to specific research projects. Only fellowship **10** is not linked to a specific project, and the successful candidates will have the option to choose one of several available projects spanning the various topics of the PhD program. Brief descriptions of all the available projects are provided below.

In their application, candidates may indicate their preference for any of the available projects/fellowships in the motivation letter, and will be asked to express their preference during the interview.
These preferences will be considered by the board, but please note that such preferences are **NOT binding.** The positions/fellowships will be assigned by the Selection Committee and the Board of Teachers according to their judgement.

Positions with fellowship

1 – Dr. Giuditta Di Lorenzo (AREA, Trieste)
Molecular and immunological strategies for Flavivirus intervention

Flaviviruses represent an escalating global health threat, with millions of annual infections transmitted via mosquito and tick bites. Due to the lack of universal antivirals and challenges in vaccine development, including antibody-dependent enhancement (ADE), there is an urgent need for advanced therapeutic and preventative strategies.
This PhD project aims to increase our knowledge on the immunoprofile of flavivirus proteins and develop the next generation of neutralizing antibodies, vaccines, and antiviral peptides against these arboviruses.
The successful candidate will leverage a multidisciplinary toolkit ranging from AI-driven antigen design to innovative delivery systems. Depending on the candidate's expertise and project evolution, the research will focus on one or more of the following areas:

- Immune mapping and discovery: identifying and characterizing high-potency neutralizing monoclonal antibodies to define the "blueprints" of protection.
- Structural dynamics: investigating how amino acid substitutions trigger "viral breathing," affecting stability and how the virus hides from or reveals itself to the immune system.
- Rational design: utilizing Artificial Intelligence and computational modeling to design synthetic antigens and antiviral peptides with enhanced stability and broader cross-reactivity.
- Biotechnological interventions: Developing innovating delivery systems to express therapeutic molecules, providing a novel avenue for controlling virus transmission at the vector and host level.

2 - Prof. Eugenio Fornasiero (DSV)
Modeling antisense oligonucleotide therapy in Phelan McDermid Syndrome

SHANK3 haploinsufficiency is considered the primary cause of Phelan-McDermid syndrome (PMS), a rare neurodevelopmental disorder. The absence of effective therapies for PMS underscores the urgent need for targeted treatment strategies. The broad range of deficits caused by SHANK3 haploinsufficiency presents a significant challenge to traditional biochemical pathway-based therapeutic approaches. A critical question

remains whether the pathology is reversible in adults. Interestingly, studies in mice have demonstrated that re-expressing the SHANK3 gene in adulthood improves synaptic protein composition, spine density, and neural function. While some behavioral deficits appear irreversible in adults, early postnatal intervention has been shown to improve pathological outcomes. These findings suggest that restoring normal Shank3 levels could be a viable therapeutic approach for PMS patients. In PMS, the presence of the remaining SHANK3 allele presents an opportunity to use antisense oligonucleotides (ASOs) to restore Shank3 expression to physiological levels. Through a collaboration we have already developed two SHANK3-specific ASOs designed to restore Shank3 expression to physiological levels. With this PhD project, the candidate will carry out a preclinical evaluation of the patient-specific ASOs and will receive full training in a broad panel of techniques, ranging from molecular biology, in vivo assays, behavioral testing and advanced human cellular models.

3 - Prof. Lorenzo Cingolani (DSV)

Modulating Brain Connectivity in Neurodevelopmental and Epileptic Disorders using Advanced Electrophysiology and In Vivo Imaging

This project aims to develop innovative approaches to selectively modulate dysfunctional neural circuits using remote magnetic stimulation. Focusing on neurodevelopmental and epileptic disorders, particularly fragile X syndrome, the research will investigate how alterations in synaptic connectivity and network excitability contribute to circuit dysfunction. The work is carried out within the European SynMech initiative (Horizon EIC Pathfinder), a multidisciplinary effort to develop next-generation mechanogenetic strategies for restoring brain function.

The candidate will investigate how magneto-mechanical stimulation influences synaptic transmission and neuronal activity by combining patch-clamp electrophysiology, calcium imaging and multi-electrode array recordings. The work will explore mechanisms of circuit dysfunction at both the cellular and network levels, with the possibility of extending towards in vivo studies of brain dynamics.

The project builds on recent advances in synaptic mechanogenetics, an emerging strategy that combines the spatial precision of optogenetics with the flexibility of remote magnetic control. The laboratory offers a highly collaborative and international research environment, with strong interactions across Italy, Germany and the Netherlands. The PhD candidate will receive advanced technical training, and opportunities to contribute to high-impact research at the interface of neuroscience, biophysics, and neurotechnology.

4 - Dr. Maria Passafaro (CNR, Pavia) and prof. Lorenzo Cingolani (DSV)

Investigation of molecular and functional mechanisms in neurodevelopmental disorders and the use of mechanogenetics to restore neuronal damage

Synaptic dysfunction has been demonstrated to underlie severe neurological symptoms in neurodevelopmental disorders caused by genetic mutations. In particular, alterations in synaptic structure and function are key determinants of disrupted neuronal communication and circuit imbalance in conditions such as autism spectrum disorders (ASD) and intellectual disability (ID). This project, in the frame of European SynMech initiative (Horizon EIC Pathfinder) aims to investigate whether synaptic function and brain circuit activity can be restored through mechanogenetic stimulation. This innovative approach will be tested both in vivo, using established animal models of ASD, and in vitro, employing human induced pluripotent stem cell (iPSC)-derived neurons obtained from patients carrying disease-relevant genetic mutations. We will take advantage of well-characterized preclinical models that recapitulate key features of ASD, alongside patient-specific neuronal cultures, to assess the translational potential of this strategy. Specifically, we will determine whether targeted mechanogenetic stimulation is able to rescue synaptic

deficits and restore functional neuronal connectivity. To achieve this, we will combine advanced imaging techniques with electrophysiological recordings, enabling a comprehensive evaluation of synaptic structure, function, and network activity. These integrated approaches will allow us to establish whether mechanogenetic stimulation can effectively reverse synaptic impairments across different experimental systems.

5 - Prof. Stefan Schoeftner (DSV)
R-loop mediated genome instability in cancer therapy response

R-loops are three-stranded nucleic acid structures composed of an RNA:DNA hybrid and a displaced single-stranded DNA loop. In cancer cells, pharmacological induction of R-loops can trigger transcription–replication conflicts that promote genome instability and lead to the accumulation of cytoplasmic DNA. This, in turn, activates innate immune pathways and reshapes the tumor microenvironment. Modulating R-loop formation in highly proliferative cancer cells may therefore represent an innovative strategy to enhance therapeutic responsiveness.
This PhD project will employ cancer cell models to investigate R-loop regulators and molecular pathways that regulate R-loop formation and resolution, with particular attention to metabolic circuits altered by Fasting-Mimicking Diets (FMDs). FMDs have recently been shown to potentiate anticancer therapies and reduce treatment-related toxicity by transiently inducing a fasting-like metabolic state through controlled nutritional restriction. Experimental findings obtained in cellular systems will be validated by R-loop mapping and the use of patient-derived material to identify clinically relevant mechanisms linking R-loops, metabolism, and therapy response within the tumor microenvironment.
The project is part of the EU-funded Interreg Italia–Austria grant *NuCaT*, carried out in collaboration with Austrian research partners. Relevant publications from the research group include: DOI: 10.1038/s41467-026-69479-w; DOI: 10.1038/s41467-022-29907-z; DOI: 10.1016/j.dnarep.2025.103859

6 - Prof. Roberta Bulla (DSV)
Hereditary angioedema: insights into the role of endothelium, pregnancy complications and tumor development
Abstract not available yet

7 - Prof. Pasquale Sacco (DSV)
Investigation of cardiac fibrosis and tissue regeneration via controlled softening of the extracellular matrix microenvironment

Cardiovascular diseases are a big problem for people's health in Europe today. They cost the European economy 282 billion Euros every year. After an injury, the adult human heart cannot repair itself. However, it is known that certain types of fish, such as Zebrafish, can regenerate their hearts after a temporary softening of the tissue. SOFTEN is an ambitious project that proposes the innovative idea of copying the temporary softening ability of the cardiac extracellular matrix that the Zebrafish exploits to regenerate its heart. So, first, the Applicant's group will use recent discoveries to develop hydrogel networks that can be made softer or harder. The second focus is to use these biomaterials as a model for heart tissue, suitable for 2D and 3D cultures of heart muscle cells to help us understand more about heart tissue scarring and how the heart can regenerate. To achieve these milestones, methods from different scientific areas will be used, like material design, polymer chemistry and in vitro cellular and molecular biology.

8 - Dr. Gustavo Baldassare (CRO, Aviano)

Evaluation of the role of epigenetic transcriptional alterations in the progression of gynecological tumors

Tumor heterogeneity—both inter- and intra-tumoral—represents a major obstacle to effective treatment, driving drug resistance, recurrence, and poor clinical outcomes. Increasing evidence implicates dysregulated epigenetic programs and RNA splicing as critical, yet underexplored, mechanisms underlying cancer plasticity and therapeutic escape.

To address this, we will leverage patient-derived tumor samples and integrated multi-omics approaches to identify key genetic, epigenetic, and post-transcriptional alterations associated with resistance to platinum-based chemotherapy and PARP inhibitors.

In parallel, we will establish advanced 2D and 3D culture systems, including patient-derived organoids (PDOs), to model tumor behavior and drug response, enabling functional interrogation of candidate molecular drivers through targeted perturbations. These studies will be complemented by in vivo preclinical models, including patient-derived xenografts (PDX) and immune-competent systems such as syngeneic models, to evaluate therapeutic efficacy and monitor tumor evolution under treatment pressure.

By integrating these approaches, we will map clonal dynamics, identify resistant populations, and uncover key signaling, epigenetic, and splicing-related pathways sustaining resistance.

Ultimately, this work aims to inform the development of more effective, personalized therapeutic strategies for patients with gynecological cancers.

9 - Dr. Barbara Belletti (CRO, Aviano)

Use of patient-derived models to study therapy resistance in luminal breast cancers

Our project aims to elucidate the mechanisms underlying tumor heterogeneity and driving therapy resistance in luminal breast cancer. To address this complexity, we will analyze patient-derived tumor samples using integrated multi-omics approaches to define molecular fingerprints and identify alterations associated with resistance to endocrine therapy and CDK4/6 inhibitors.

In parallel, we will employ advanced 2D and 3D culture systems, including patient-derived organoids (PDOs), to model tumor behavior and drug response. Particular emphasis will be placed on signaling network rewiring, focusing on the crosstalk between EGFR and estrogen receptor (ER) pathways, a key determinant of therapeutic response and endocrine resistance.

These studies will be complemented by preclinical in vivo models, including patient-derived xenografts (PDX) and immune-competent systems such as syngeneic models. A central component of the project is the implementation of an in vivo clonal evolution framework to longitudinally track tumor dynamics under therapy. By integrating lineage tracing with molecular profiling, we will identify resistant clones and characterize their adaptive trajectories.

Overall, using this integrated approach we aim to uncover critical mechanisms of resistance and support the development of more effective, personalized therapeutic strategies for patients with luminal breast cancer.

10 – Multiple possible projects (see below)

11 – Prof. Giannino Del Sal (ICGEB)
Aging, tissue stress, and cell competition in early phases of tumor Development

Aging is characterized by a progressive loss of tissue homeostasis, leading to a functional decline at the organism level, and it represents the major risk factor for a broad range of pathologies, including cancer and neurodegenerative disease. The maintenance of tissue homeostasis relies on the precise spatiotemporal regulation of cell signaling in response to macro- and micro-environmental stress stimuli. This regulation ensures proper tissue organization, cell-cell interactions and communication among organs. However, during aging these regulatory mechanisms become impaired. Aging-associated conditions such as chronic inflammation and alterations of the extracellular matrix, contribute to tissue remodeling and generate an environment more susceptible to disease onset.
Within aging tissues, cells progressively accumulate (epi)genetic alterations that can affect their fitness. These changes can trigger competitive interactions for nutrients and space, ultimately promoting survival and expansion of the fitter cell populations. However, aging-associated alterations (e.g., inflammation and remodeling of the extracellular matrix) can promote the survival and expansion of clones of cells carrying pathological alterations. For example, cells expressing oncogenic proteins, such as mutant p53, may gain a selective advantage contributing to the earliest stages of tumor development.
This project aims to investigate the key pathways that regulate stress responses and control cell competition during aging, using diverse organism and cellular models. It will also examine how these pathways contribute to tissue remodeling in the early phases of aging-related diseases, with a particular focus on cancer and neurodegenerative pathologies.

Positions without fellowship

SB1 - Prof. Enrico Tongiorgi (DSV)
Characterization of neurotrophic factors as a mechanism of action in the treatment of Rett syndrome
Rett syndrome is a neurodevelopmental disorder affecting 1:10.000 females and representing the second cause of mental retardation world-wide. 95% of the cases are caused by a mutation in the MeCP2 (methyl-CpG binding protein 2) gene localized on X chromosome. MeCP2 is involved in the control of BDNF expression and clinical trials for the Rett syndrome treatment have explored the possibility to target BDNF, aiming at increasing its levels.
It is therefore important on one side to better investigate the molecular details of the role of BDNF and other neurotrophic factors in the disease progression, and on the other side to develop better pharmacological strategies aimed at curing the disease. Currently, one of the limitations is due to the availability of effective protocols to produce recombinant BDNF for pharmacological applications.
This project aims at optimizing a novel methodology for the stable recombinant expression of mature BDNF in Chinese Hamster Ovary (CHO) cells. Also, the molecular characterization of the produced protein will be carried out, including the biophysical and structural characterization along with biological function assays, to better describe the molecular picture of the interaction of neurotrophic factors with endogenous binding partners. The protocols will be also extended to another neurotrophin of the family, NGF (Nerve Growth Factor), heavily involved in different degenerative diseases.

Finally, the project also includes the quantification via ELISA of BDNF, CNTF and GDNF from the sera of patients with Rett syndrome undergoing treatment with mirtazapine within the clinical trial denominated MirtaRett.

SB2 - Prof. Eugenio Fornasiero (DSV)
Towards Molecular Diagnosis of Hereditary Spastic Paraplegia through Integrative Multi-Omics

Hereditary spastic paraplegia comprises a heterogeneous group of rare neurological disorders characterized by progressive degeneration of the corticospinal tracts, with onset ranging from childhood to adulthood. Despite the widespread implementation of whole-exome and whole-genome sequencing, more than 50% of patients remain without a definitive molecular diagnosis, particularly in the presence of variants of uncertain significance. This diagnostic gap highlights the limitations of DNA sequence–based analyses alone and hampers mechanistic understanding and the development of targeted therapeutic strategies.
The aim of this PhD project is to elucidate the molecular mechanisms underlying unresolved cases of hereditary spastic paraplegia through integrative multi-omics approaches. The central hypothesis is that functionally relevant alterations at the levels of gene regulation, protein expression, epigenetic modification, and cellular metabolism contribute to disease pathogenesis but are not readily detectable at the genomic sequence level. The project will involve integrated analysis of transcriptomic, quantitative proteomic, and, where appropriate, metabolomic data generated from patient-derived cells, combined with advanced bioinformatic pipelines and in silico modeling to prioritize candidate genes, variants, and dysregulated biological pathways. This project will provide interdisciplinary training in molecular biomedicine, functional genomics, bioinformatics, and cellular neurobiology, and will contribute to the development of advanced diagnostic strategies.

SB3 - Prof. Flavio Rizzolio (CRO, Aviano)
Development and Validation of Advanced Organoid-Based Models for Precision Medicine in Colorectal Cancer
Abstract not available yet

SB4 - Prof. Claudio Tiribelli (FIF, Trieste)
Application of Omic Technologies for Innovation in Clinical Diagnostics
Abstract not available yet

RE1 - Dr. Gustavo Baldassare (CRO, Aviano)
Solid tumor characterization: Integrating clinical and molecular data to improve the efficacy of personalized therapies

Solid tumors exhibit extensive molecular and clinical heterogeneity, which limits the effectiveness of standard treatments and challenges the implementation of precision oncology. This project aims to characterize solid tumors by integrating clinical data with multi-layered molecular profiling to improve patient stratification and therapeutic outcomes. We will analyze patient-derived tumor samples using genomics, epigenomics, transcriptomics, and proteomics to identify actionable alterations, molecular subtypes, signatures and biomarkers predictive of therapy response or resistance. These data will be systematically integrated with clinical parameters, including treatment history, response rates, and disease progression, to uncover clinically relevant patterns and refine patient classification.

By combining molecular insights with clinical evidence, this project seeks to define robust predictive models and actionable signatures that can guide personalized treatment decisions. Ultimately, the goal is to enhance the efficacy of targeted therapies, reduce overtreatment, and improve clinical outcomes for patients with solid tumors through a more precise and integrative approach to cancer characterization.

Available projects for fellowship 10

Successful candidate will choose one of these projects/positions

Investigating the reciprocal crosstalk between cancer cells and microenvironmental cells during tumor initiation and progression. Biological impact and therapeutic opportunities
Prof. Licio Collavin (DSV) and Prof. Gianni Del Sal (ICGEB)

During cancer initiation and progression, the tumor microenvironment undergoes profound changes, reflecting a complex and dynamic crosstalk between genetically mutated cancer cells and non-mutated stromal cells. This reciprocal interaction is a major determinant of cancer aggressiveness, significantly influencing metastatic potential and responses to both conventional and immunological therapies.
Using animal models and a range of tissue culture techniques, we study transformed cancer cells and the signals they release, as well as the effects of cancer-derived signals on the molecular and functional identity of stromal cells, including immune cells, with the ultimate objective of identifying novel biomarkers and potential drug targets that may eventually be translated into the clinic.

Molecular Biomarkers of Physiological Decline During Physical Inactivity and Simulated Microgravity: Inter-individual and Sex-specific Variability
Prof. Gianni Biolo (DSM)

Prolonged muscle unloading, such as bed resting or long duration space flight, induces rapid and heterogeneous alterations in metabolic homeostasis, including early insulin resistance and initial changes in muscle function and mass. However, the timing of onset and the inter-individual variability of these responses remain poorly characterized, limiting the ability to identify individuals at higher risk of accelerated physiological decline. This project aims to identify early metabolic biomarkers of physiological deterioration during experimental bed rest and space flight in the international space station, focusing on molecular signatures that precede overt functional and body composition changes. A translational human approach will be applied using controlled bed rest protocols combined with comprehensive metabolic phenotyping. These analyses will be integrated with targeted metabolomics and endocrine biomarkers. Stable isotope tracer techniques will be used to assess early changes in muscle protein metabolism, while imaging methods (DEXA, MRI) will monitor body composition dynamics. A key objective is the identification of predictive biomarker signatures capable of stratifying individuals according to their susceptibility to inactivity-induced metabolic decline, with particular attention to sex-specific differences and inter-individual variability.

Structure/function studies on the antimicrobial and immunomodulatory activities of Host Defence Peptides (HDP)
Prof. Alessandro Tossi (DSV) and prof. S. Pacor (DSV)

The human cathelicidin LL-37, plays an important role in healing both as direct antimicrobial agent and immune signaling molecule. Its activity is based on a complex interplay of intra- and intermolecular interactions that determine its oligomerization and affect subsequent interaction with microbial or host cell membranes, leading to concentration-dependent cytotoxicity or receptor-modulation. It depends on the physiological environment and varies markedly in other primate orthologs, significantly altering their activity. The project continues an ongoing systematic investigation of the effects of rational, minimal variations in ortholog sequences on oligomerization and activity, to establish a comprehensive model for structure-activity relationships. The successful candidate will apply a broad range of biochemical and biophysical techniques, including peptide design, solid phase automated synthesis and purification of peptides, structure prediction and spectroscopic determination, microbiological assays, flow cytometry studies on both bacterial and host cells, and various types of biophysical interaction and oligomerization assays, working in DSV and CNR-IC and availing of an international collaboration with a group at Split University. In that context, a separate aspect of the project concerns the study of HDPs from helminths, which have interesting properties due to the complex life-cycles of these parasites, involving stages in different hosts with which they must coexist.