Junior Research Associate Scheme 2022 - Student Application Form

JRA projects can take place on campus or online as long as you follow the government and University Covid guidance in place at the time. Due to the pandemic, it is possible that projects will have to be undertaken remotely if the situation changes before summer. Please ensure you include in your application how you would adapt to online research and supervision, should that be required.

Before completing this form, please ensure you have read and understood the Conditions of Award and Further Information for the Junior Research Associate Scheme 2022 (JRA), and have read the applicant guidance on the website carefully.

When completed, this form should be sent to undergraduate-research@sussex.ac.uk along with the following documents:

1. **Academic CV** - this should focus on your academic experience and be no more than two sides of A4. It must include all modules and grades.
2. **Academic Reference**
3. **Proposed Research Supervisor Statement**

Both the Academic Reference form and the Proposed Research Supervisor Statement form can be downloaded from the JRA Application Pack webpage. If your referee or supervisor does not want to disclose their statement to you, they can be sent separately to undergraduate-research@sussex.ac.uk.

The submission deadline is **12:00 noon on Monday 28th March 2022**. Incomplete and/or late applications will not be accepted.

If you need further information or have any queries please email undergraduate-research@sussex.ac.uk.

1. About you

Are you a First Generation Scholar? (delete as appropriate) *NOTE: This is not a selection criterion*			
Name:		**Student registration number:**	
Year of study:	2	**School of study:**	Life Sciences
Department/Subject Area:	Chemistry		
Email:		**Telephone:**	
Address:			

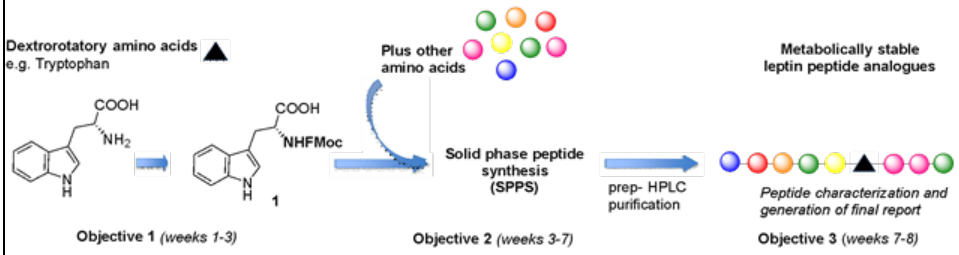
2. About your research

Name of your proposed supervisor:		**Name of your Mentor, if you have one:** *Your mentor is usually a PhD student or Postdoc who offers additional support. If not known now, their details can be added later.*	
School of your proposed supervisor:	Life Sciences		
Full title of your research:	Synthesis of metabolically stable leptin peptide analogues towards novel therapeutics for Alzheimer's disease.		
Research Summary: *Must be short and non-technical; max 150 words*	Alzheimer's disease (AD) is a hidden epidemic affecting an ever-growing proportion of the population. As there is no cure, and very few medications to treat the symptoms, research into AD is paramount. Neuroscientist collaborators have released findings about the naturally occurring protein, leptin, in our bodies. This protein, or better yet, small segments of it (called peptides), have shown promising effects of supporting nerve cell function and preventing their degradation – a cause of AD.		

	This project aims to delve into the use of peptide-based therapeutics as a potential treatment for AD. By synthetically altering the leptin peptide segments, the goal is to create an orally available drug that will not be metabolised by the digestive system – the biggest challenge facing these therapeutics. Existing and previously unexplored leptin-peptides show promising potential towards this goal. A leptin-peptide lead has already been explored; however, this project aims to branch from current research by studying structure-activity relationships and hopefully discovering an analogue that makes this structure stable enough to be administered orally. This is an issue that must be overcome to treat AD in tablet form.
Online delivery: *Outline how the JRA research and supervision will be undertaken virtually, either as the expected mode or the fall-back if Covid rules change and online research and supervision is required. Max. 100 words*	If required, this research project can be undertaken digitally, without any laboratory work conducted. The initial plan for synthesising leptin-peptide analogues in the laboratory will not be performed. Instead, a project based on computational modelling of leptin analogues will be used. Training on using necessary programs will be undertaken and weekly pre-scheduled group and supervisor meetings will be attended. Please see research statement for details of the digital project.
Motivation: *What is your motivation for undertaking a JRA research project? How will it benefit you / your future plans?* *Max. 200 words*	With the growing demand for renewable energy, potent medical cures and technological advancements, the idea of becoming a researcher is more alluring to me than ever. The possibility that I could contribute even in the tiniest way to the progression of human knowledge inspires me to push my education to the maximum. Since a young age, my dream has been to become a chemist. Having grown up in a medical family, my interests have always lied in why certain diseases occur and how to stop them on a molecular level. Seeing how something as slight as 3D molecular orientation could have such a huge effect, is fascinating. The precision and perfection of chemistry is something I've always admired. At university, my passion for accomplishing my dream has led me to achieve top marks in all my modules, with particular success in organic chemistry. The possibility to partake in research so early on in my chemical career is a dream come true. I endeavour to remain in the academic research domain for the foreseeable future and actively work towards a master's degree and a PhD. For me, the JRA scheme would be the first step towards my future career. I am certain it will galvanise my passion for research and further inspire me to achieve the best results possible so that I may spend my future researching. I was fortunate enough to partake in some research experience in Dr Erica Mancini's lab and I believe my experience there and the JRA scheme will cement my future in academic research.
Full Research Proposal/Statement: *Max. 1,500 words*	*Guidance note: We understand that in some disciplines it is necessary for the supervisor to write the research proposal. If this is the case and your proposal is supervisor-led, please add an additional section (max. 200 words) with your own comments to reflect on the importance of the research, the wider context, and why you feel the research needs to be undertaken.* Alzheimer's disease (AD) is the most common cause of dementia, affecting approximately every 6 in 10 people with dementia in the UK[1]. This epidemic has affected 46.8 million people world-wide, with numbers of cases expected to triple by 2050. Since there is no cure and very few successful therapies to alleviate the symptoms, research into AD is of critical

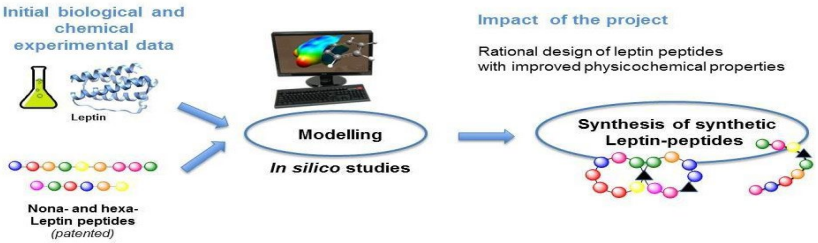
	importance. This project aims to explore peptide-based therapeutics as a potential novel path towards the treatment of Alzheimer's disease. Peptide-based therapeutics are an exciting prospect in medicinal chemistry, offering many advantages over the use of full-length proteins. They are highly selective, potent, have low toxicity and are easily synthesised. However, in their native state, these molecules can demonstrate low *in vivo* stability and retention and present challenges regarding oral administration as they are easily metabolised. Leptin is a large, naturally occurring peptide, involved in key physiological processes. These include the regulation of energy balance (hunger inhibition) and neuroprotection. Co-investigating neuroscientists at the University of St Andrew's have recently discovered, in laboratory AD models, that leptin can prevent nerve cells from dying and also support their function[2]. However, small fragments of this hormone (rather than the entire molecule) can achieve the desired effect, without the shortcomings of using leptin. The challenge, however, is that neither leptin, nor the peptide fragments can be administered orally due to metabolism in the digestive system. Herein lies the pressing need to develop these pharmacophores into more stable and patient-friendly drugs. These discoveries provide a thrilling opportunity to study the structure-activity relationships of these peptides. By adjusting the bioavailability, bioactivity and synthetic stability of these pharmacophores, the goal of developing novel orally available therapeutics for AD comes ever closer. In medicinal chemistry, the balance between hydrophilicity and lipophilicity of a drug is crucial. The target must be hydrophilic enough to diffuse into the bloodstream after oral administration, and lipophilic enough to cross the blood-brain-barrier (BBB) where the actual treatment of the neurons involved in AD occurs. The difficulty lies in finding the "Goldilocks" molecule containing the right pharmacophores, lipophilicity, hydrophilicity, potency, toxicity and ability to withstand digestive metabolism. These considerations need to be acknowledged when synthesising leptin-peptide analogues. This project involves the design and synthesis of novel and previously unexplored leptin-peptide derivatives. Dextrorotatory amino acids such as tryptophan, incorporated into the peptide analogues will hopefully show both improved affinity and selectivity towards biological targets, as well as enhanced stability against degradation. The focal point of this research is to synthesise a series of analogues of the key hexa- and nona-peptides, including unnatural amino acids. This will produce a library of analogues of the amino acids that we can further modulate to conformationally lock the peptide. This library will include branched amino acid analogues and dehydroalanine and halotryptophan analogues that can be further modulated through conjugate addition or cross-coupling reactions respectively (Figure 1). These synthetic leptin peptides will be computationally modelled and tested in biological studies as part of the research program within this group.

In this line of synthesis, various modern synthesis methods are required, including the use of a state-of-the-art microwave assisted peptide synthesiser and purification methods (normal and reverse phase chromatography). Various analytical techniques will also be used to confirm the identity of any products formed.



The possibility that one day Alzheimer's disease could be treated with a series of tablets, or better yet, prevented fully via medical intervention is certainly an exhilarating thought! We as a species know so little about the source of consciousness that makes us who we are, and what oftentimes causes our demise too. Research into this disease will not only help us understand what causes this degenerating ailment but also help us understand more about the anatomy and physiology of our brain. Our brain is the least understood organ in our body, so any research relating to neurology is of utmost importance. After all, the capabilities of our brains are what has made us the apex species in the animal kingdom after millennia of evolution.
If COVID-19 has taught us anything, it's how researchers' work is of utmost importance. We are evolving faster than medicine and natural science so it is paramount that scientists keep up with our anatomical and physiological changes and find solutions for what society deems "the unsolvable". Any progress in the diagnosis and treatment of Alzheimer's disease creates hope and excitement for our future.

<u>Remote Project</u>
For this project, Density Functional Theory will be used. Emphasis will be placed on computing physio-chemical properties and studying the critical points within leptin-peptide analogues. A focal point will be synthesising hexa- and nona- leptin peptides based on recent patents from collaborators. Infrared spectroscopy and 1D NMR will be used to analyse the structure and symmetry of the optimised leptin-peptides under investigation[3]. The data generated will help improve the physio-chemical properties of the analogues, while also creating a map of said properties. This will provide evidence on how to further optimise previously used leptin-peptide analogues. The DFT calculations will be conducted using Gaussian16 software on the Apollo2 high-performance computing cluster at the University, which will be accessed remotely.



(1) What is Alzheimer's disease? - Alzheimer's Research UK https://www.alzheimersresearchuk.org/dementia-information/types-of-dementia/alzheimers-disease/ (accessed 2022 -03 -31).

	(2) Malekizadeh, Y.; Holiday, A.; Redfearn, D.; Ainge, J. A.; Doherty, G.; Harvey, J. A Leptin Fragment Mirrors the Cognitive Enhancing and Neuroprotective Actions of Leptin. *Cereb Cortex* **2017**, *27* (10), 4769–4782. https://doi.org/10.1093/CERCOR/BHW272. (3) Güntert, P. Automated NMR Structure Calculation With CYANA. *Methods Mol Biol* **2004**, *278*, 353–378. https://doi.org/10.1385/1-59259-809-9:353.
Widening Participation Statement (Optional): *Max. 250 words See the JRA website for guidance on writing a WP statement.*	***Guidance note:*** *The JRA scheme seeks to benefit students from any background and group. We particularly want the JRA to be accessible to students who might not otherwise be exposed to research experience or to consider a career in academic research. If you are from an underrepresented group or face barriers to a positive student experience, this is a space to provide additional information in support of your application. This may include, but is not limited to, specific ethnic minority groups, students with a disability, mature students, care experienced students, estranged students and those with caring responsibilities (including student parents), forced migrant students, students from Gypsy, Roma and Traveller communities, students from military service families, First Generation Scholars, LGBTQ+ students, and commuter students.*
Ethical Approval *Does this research require ethical approval? If you are unsure, please refer to Sussex's self-assessment checklist. If your project does require ethical approval, it will be your responsibility to ensure such approval is attained before the JRA project commences.*	N/A
Fieldwork *Does your research involve fieldwork away from the university campus? Any students wishing to undertake off-campus fieldwork must ensure that they attain ethical approval for the proposed fieldwork and must subsequently complete the necessary risk and insurance applications. If your fieldwork takes you outside of the UK, you will need to apply for insurance cover. For more information on the University's insurance policy, please consult the University's Travel Risk Assessment webpages. (Note: this does not involve*	N/A

trips to museums and archives).	

If you have any questions regarding this form please email undergraduate-research@sussex.ac.uk