Life Science Project Titles 2012-2013

Biochemistry and Molecular Biology Subject Area

(with Drug Discovery and BSMS Subjects)

Life Science Projects 2012-2013

Faculty Name: Dr. John Armstrong

Room No: JMS3C18 **Email:** j.armstrong@sussex.ac.uk

Project Title/Area:

Invasive growth and differentiation in Fission Yeast

Course requirements:	No of places: 2

Further Information:

Fission yeast is usually considered a model single-celled eukaryote. However, we found that it can differentiate into elaborate multicellular structures which invade the growth medium. This switch in form is critical for infection for pathogenic fungi, which are much harder to study. We have identified groups of genes required for the process. The project will involve studying these by methods such as in vivo microscopy, and molecular genetics to understand the role of each, and hence to learn about this crucial process in pathogens.

Reference:

Dodgson, J., Brown, W., Rosa, C. A. and Armstrong, J. (2010) Reorganisation of the growth pattern of *Schizosaccharomyces pombe* in invasive filament formation. Euk. Cell **9**, 1788-1797.

Life Science Projects 2012-2013

Faculty Name: Dr. John Armstrong

Room No: JMS3C18 **Email:** j.armstrong@sussex.ac.uk

Project Title/Area:

Why are there so few treatments for fungal infections?

Course requirements:	**No of places: 4**

Further Information:

Fungal infections are an increasing problem in medicine and agriculture, but there are remarkably few ways of treating or preventing them. Why is this, and what can be done about it? Some questions which could be shared between projects:

1. What are the main and emerging fungal infections in humans?

2. What are the main infections in agriculture?

3. What sorts of treatments are currently in use?

4. Are any new approaches being developed?

5. Signalling molecules in fungi: could they be a new type of drug target?

These 'literature' projects will probably involve searching for sources of information beyond the normal places such as Pubmed (or Wikipedia).

Life Science Projects 2012-2013

Faculty Name: Professor Juan Pablo Couso

Room No: 4C14 **Email:** j.p.couso@sussex.ac.uk

Project Title/Area:

Coding potential of long-non-coding RNAs (Literature based)

Course requirements:	**No of places**: 2
Biochemistry or Biomedical degree	

Further Information:

The students will review literature on long-non-coding RNAs, focusing on the reasons to discard the possibility that they may actually encode short Open Reading Frames.

Life Science Projects 2012-2013

<table>
<tr><td colspan="2">Faculty Name: Professor Juan Pablo Couso

Room No: 4C14 Email: j.p.couso@sussex.ac.uk</td></tr>
<tr><td colspan="2">Project Title/Area:

Functional assessment of a smORF gene (experimental labwork)</td></tr>
<tr><td>Course requirements:

Genetics</td><td>No of places: 1</td></tr>
<tr><td colspan="2">Further Information:

The student will use population genetics techniques to assess the functionality of a Drosophila gene putatively encoding a small peptide in a small Open Reading Frame.</td></tr>
</table>

Life Science Projects 2012-2013

Faculty Name: Dr. Neil Crickmore

Room No: JMS 2B2 Email: n.crickmore@sussex.ac.uk

Project Title: Modelling the evolution of antibiotic resistance and pathogenicity in bacteria.

Course requirements: None	**No of places**: 1/2

Further Information:

In this project we are interested in the role that plasmids play in the evolution of pathogenic and antibiotic resistant bacteria. In many of these bacteria the factors required for pathogenicity or antibiotic resistance are encoded on a plasmid rather than on the chromosome. We will initially use molecular biological techniques to create recombinant bacteria that will be used to investigate what advantages there are to the bacterium in having these factors on plasmids. The information gained can potentially be used to model the spread of antibiotic resistance.

Life Science Projects 2012-2013

Faculty Name: Dr. Neil Crickmore

Room No: JMS 2B2 **Email:** n.crickmore@sussex.ac.uk

Project Title/Area:

Why do some insect toxins kill human cancer cells?

Course requirements:

None

No of places: 1/2

Further Information:

The bacterium *Bacillus thuringiensis* (Bt) synthesizes protein toxins that kill insects. In recent years some toxins have been isolated from this bacterium that have a similar sequence to the insect toxins but have reported toxicity towards human cancer cell lines. This project will use a combination of cell culture and protein biochemistry to try and establish whether this cancer cell activity is real, and if so why is it only found with certain toxins?

An additional non-lab project will also be available on this topic in which bioinformatic techniques will be used to compare and contrast the cancer killing toxins and related insect killing toxins in an attempt to define specificity determinants.

Life Science Projects 2012-2013

Faculty Name: Dr. Neil Crickmore

Room No: JMS 2B2 **Email:** n.crickmore@sussex.ac.uk

Project Title/Area:

Manipulating and understanding the mechanism of action of Bt toxins.

Course requirements:	**No of places:** 1/2
None	

Further Information:

The bacterium *Bacillus thuringiensis* synthesizes protein toxins that kill insects. This project will use molecular genetic and protein engineering techniques to better understand how the toxins work and how they might be improved.

Life Science Projects 2012-2013

Faculty Name: Dr. Neil Crickmore

Room No: JMS 2B2 **Email:** n.crickmore@sussex.ac.uk

Project Title/Area:

A global screen for Bt virulence genes.

Course requirements:

None

No of places: 1/2

Further Information:

Using transposon mutagenesis random Bacillus thuringiensis mutants will be created and then used to co-infect an insect host. Following pasaging in the insect, bacteria will be recovered and analysed in order to determine which genes are under or over-represented in the recovered population

Life Science Projects 2012-2013

Faculty Name: Dr. Neil Crickmore

Room No: JMS 2B2 **Email:** n.crickmore@sussex.ac.uk

Project Title/Area:

Finding new toxins from genomic sequencing data.

Course requirements:

None

No of places: 1/2

Further Information:

Many bacterial genomes have now been sequenced and the data deposited in public depositories. This project will develop bioinformatic procedures to attempt to identify new insecticidal toxins from this mass of data.

Life Science Projects 2012-2013

Faculty Name: Dr. Neil Crickmore

Room No: JMS 2B2 **Email:** n.crickmore@sussex.ac.uk

Project Title/Area:

Predicting non-target effects of insecticidal toxins.

Course requirements:

None

No of places: 1

Further Information:

Toxins from *Bacillus thuringiensis* are widely used to control insect pests of agricultural crops, either as a sprayable product or in the form of genetically modified plants. A large amount of data has been accumulated concerning the activity of these toxins against non-target insects. This project will build a database of known non-target effects and look for patterns between toxicity and toxin structure.

Life Science Projects 2012-2013

Faculty Name: Prof. Tony Moore

Room No: 4B16 **Email:** a.l.moore@sussex.ac.uk

Project Title:	**Project Type**: Wet lab
Overexpression, and characterisation of wild-type and mutated forms of a quinol oxidase in *E.coli*: a potential new drug target for pathogenic organisms.	Exp
Course requirements: Proteins–in-Action and/or Bioenergetics	**No of places**: 6

Possible Titles (please give if you can offer a number of projects within a specified area)

Further Information

Recent completion of a number of genome sequencing projects have revealed that a number of human pathogenic organisms (such as those causing trypanosomiasis and cryptosporidiosis & candidiasis) contain a novel enzyme that allows the organism to survive in the human host and that is not present in mammals (hence a drug target). We have recently identified the nature of this protein, have isolated the cDNA and constructed a number mutants in order to probe the structure-function of this enzyme. We have also designed a number of new inhibitors which we will be used to characterise the drug-binding region. Both wild-type and mutated forms of the enzyme will be overexpressed in *E.coli*, harvested and the protein characterised with respect to how changes to structure affect function and sensitivity to inhibitors both polarographically and spectrophotometrically. The possibility also exists to purify the protein to homogeneity and, should this prove successful, crystallisation trials will be undertaken. The project will provide experience in protein expression in *E. coli*; subcloning; western blotting, protein purification, bioinformatics and biophysical characterisation.

Life Science Projects 2012-2013

Faculty Name: Professor Simon Morley

Room No: 2C25 **Email:** s.j.morley@sussex.ac.uk

Project Title/Area:

The role for mTORC1 and Mnk signalling in regulating MGMT protein levels in brain tumour cells

Course requirements:	**No of places**: 4
Cell Regulation and Cancer	

Further Information:

Glioblastoma multiforme (GBM) is the commonest and most aggressive primary brain tumour. Combining radiotherapy with temozolomide (TMZ) chemotherapy improves survival, but virtually all patients experience disease recurrence. TMZ methylates DNA generating O^6-methylguanine which can be repaired by methylguanine methyltransferase (MGMT). MGMT is a "suicide" repair protein: each molecule binds irreversibly to a methyl group and then is destroyed by the proteasome. Human glioma cell lines with up-regulated MGMT levels exhibit resistance to TMZ. The capacity of the cell to remove O^6-methylguanine adducts thus depends on the steady state level of MGMT, which reflects the rate at which the cell can re-synthesise MGMT after incurring DNA damage.

Protein synthesis is carried out in three stages (initiation, elongation and termination), with the initiation stage of translation generally accepted as a major site of regulation of gene expression. This pivotal role reflects the regulated binding of mRNA to the ribosome, a process that modulates both quantitative and qualitative aspects of protein synthesis by recruiting specific mRNAs for translation. This step in the initiation of protein synthesis, often dysregulated under conditions of loss of growth control is facilitated by the assembly of initiation factors into a multiprotein complex known as eIF4F. In turn, the activity of the eIF4F complex is regulated by phosphorylation mediated by a number of cross-talking signalling pathways and by the inherent structural properties of the recruited mRNA.

We have recently shown that inhibition of mTORC1 signalling can reduce the steady state levels of MGMT protein in T98G cells without affecting mRNA levels, thereby potentially making them more sensitive to TMZ treatment. The role for Mnk1/2 signalling in this process is unknown. Using novel, cell-permaeable inhibitors of these pathways, we now wish to characterise such mechanisms of tumour-specific down-regulation of MGMT protein to enable effective treatment of the GBM subgroup defined by over-expression of the MGMT biomarker.

The work will involve tissue culture, preparation of cell extracts, affinity chromatography, SDS-gel electrophoresis, Western blotting, and cell imaging using fluorescence microscopy.

Life Science Projects 2012-2013

Faculty Name: Professor Simon Morley

Room No: 2C25 **Email:** s.j.morley@sussex.ac.uk

Project Title/Area:

What role can Mnk1/2 inhibitors play in the management of patients with malignant glioma?

Course requirements:	**No of places:** 2
Cell Regulation and Cancer	

Further Information:

Glioblastoma multiforme (GBM) is the commonest and most aggressive primary brain tumour. Combining radiotherapy with temozolomide (TMZ) chemotherapy improves survival, but virtually all patients experience disease recurrence. TMZ methylates DNA generating O^6-methylguanine which can be repaired by methylguanine methyltransferase (MGMT). MGMT is a "suicide" repair protein: each molecule binds irreversibly to a methyl group and then is destroyed by the proteasome. Human glioma cell lines with up-regulated MGMT levels exhibit resistance to TMZ. The capacity of the cell to remove O^6-methylguanine adducts thus depends on the steady state level of MGMT, which reflects the rate at which the cell can re-synthesise MGMT after incurring DNA damage.

Protein synthesis is carried out in three stages (initiation, elongation and termination), with the initiation stage of translation generally accepted as a major site of regulation of gene expression. This pivotal role reflects the regulated binding of mRNA to the ribosome, a process that modulates both quantitative and qualitative aspects of protein synthesis by recruiting specific mRNAs for translation. This step in the initiation of protein synthesis, often dysregulated under conditions of loss of growth control is facilitated by the assembly of initiation factors into a multiprotein complex known as eIF4F. In turn, the activity of the eIF4F complex is regulated by phosphorylation mediated by a number of cross-talking signalling pathways and by the inherent structural properties of the recruited mRNA.

The epidermal growth factor receptor (EGFR), also known as human epidermal growth factor receptor 1 (HER1), is an important regulator of cell growth and survival. It has been shown to play a key role in the pathogenesis of GBM. EGFR gene mutations can result in the production of mutant receptors such as the constitutively active EGFRvIII mutant, which activates Mnk1/2 to drive protein synthesis. One novel experimental approach designed to target malignant glioma cells is one which involves the use of Mnk1/2 inhibitors, such as cercosporamide, which prevents metastasis in model system. Is this a valid approach for GBM?

Life Science Projects 2012-13

Faculty Name: Dr Mark Paget

Room No: CRPC PC5.14 **Email**: m.paget@sussex.ac.uk

Project Title/Area

Site-directed mutagenesis of an RNA polymerase binding protein

Course requirements: None	**No of places**: 1

Further Information:

We have discovered an unusual RNA polymerase binding protein that interacts with a key subunit of the enzyme and activates transcription. This protein, RbpA, is only present in the actinomycete bacteria, including antibiotic producing *Streptomyces* and pathogens such as *Mycobacterium tuberculosis*. Site-directed mutagenesis will be used to alter key amino acids in this protein, and the effects monitored *in vivo*. Techniques – PCR-based mutagenesis, cloning, general microbiology

Life Science Projects 2012-2013

Faculty Name: Dr Mark Paget

Room No: CRPC PC5.14 **Email:** m.paget@sussex.ac.uk

Project Title/Area:

Promoter structure in *Streptomyces* bacteria

Course requirements: None	**No of places:** 1

Further Information:

In bacteria, RNA polymerase is directed to promoters by sigma factors, with each sigma factor contacting the -10 and -35 elements. Unlike *E. coli*, little is known about promoter structure and function in *Streptomyces*. Part of the problem is that whereas there are 7 sigma factors in *E. coli*, there can be more than 65 in *Streptomyces* species. The aim of this literature and bioinformatic-based project is to develop a database of *Streptomyces* promoters. The project will involve collation of promoters from a wide variety of sources: the literature, genome sequencing projects, and RNA sequencing data.

Life Science Projects 2012-2013

Faculty Name: Dr Mark Paget

Room No: CRPC PC5.14 **Email:** m.paget@sussex.ac.uk

Project Title/Area:

Are AT-rich genes silenced in *Streptomyces coelicolor*?

Course requirements:	**No of places: 1**
None	

Further Information:

There is evidence of extensive lateral gene transfer between bacteria, with such genes often recognised by their lower than native G+C content. Transferred genes therefore tend to contain rare codons, and it is generally accepted that poor expression of foreign genes is due to poor rates of translation. However, recent studies suggest that transcription of genes with lower than normal G+C content can be inhibited by chromatin-associated proteins that display a preference for AT-rich DNA. We have preliminary evidence that laterally transferred (low G+C) genes in *Streptomyces* are coated with a chromatin-associated protein. The aim is to test whether resynthesised genes with differing G+C content have different rates of transcription. Techniques – cloning, general microbiology.

Life Science Projects 2012-2013

Faculty Name: Dr Mark Paget

Room No: CRPC PC5.14 **Email:** m.paget@sussex.ac.uk

Project Title/Area:

The role of 6S RNA in *Streptomyces*

Course requirements:

None

No of places: 1

Further Information:

Small untranslated regulatory RNAs (sRNAs) are present in all kingdoms of life. In bacteria, although some have been known for many years, only recently has their widespread prevalence been realised. Genome-wide searches has led to the discovery of many sRNAs, for example up to 80 in *E. coli*. 6S RNA is a widespread in bacteria and binds to certain forms of RNA polymerase. Its role appears to be to sequester RNA polymerase during stationary phase, possibly leading to global changes in gene expression. Antibiotics are produced by the *Streptomyces* bacteria during stationary phase, when nutrients are exhausted. This project aims to investigate the possible link between 6S RNA and antibiotic production. This will involved the extensive characterisation of a constructed 6S RNA mutant. Techniques - DNA isolation, Southern blotting, basic microbiological techniques.

Life Science Projects 2012-2013

<table>
<tr><td colspan="2">Faculty Name: Dr Mark Paget

Room No: CRPC PC5.14 Email: m.paget@sussex.ac.uk</td></tr>
<tr><td colspan="2">Project Title/Area:

Genetic tools for Geobacillus thermoglucosidasius</td></tr>
<tr><td>Course requirements:

None</td><td>No of places: 2 (one literature-based)</td></tr>
<tr><td colspan="2">Further Information:

There is a pressing need to develop “second generation” biofuel technologies that efficiently utilise recalcitrant waste materials. One bacterium that has been commercially developed the thermophile Geobacillus thermoglucosidasius, which can produce ethanol from solid municipal waste. Although this organism can be genetically manipulated, there are currently a limited number of genetic tools. This project aims to develop new tools for genetic engineering, such as the use of new markers, or new vectors.
Techniques - DNA isolation, basic microbiological techniques.</td></tr>
</table>

Life Science Projects 2012-2013

Faculty Name: Dr. Prabha Parthasarathy

Room No: 5D21, JMS **Email**:P.Parthasarathy@sussex.ac.uk

Project Title/Area: Healthcare infections, antibiotic resistance and microbes

Course requirements: None **No of places**: 6

Further Information:

Project type: Literature review, collation and analysis of data in existing literature

Background

In the last two decades, research in the area of healthcare infection, antibiotic resistance and specific bacterial or fungal agents such as Methicillin Resistant *Staphylococcus aureus* (MRSA) , *Clostridium difficile*, Candida etc have been very popular. This is mainly because they are of great public health importance. Healthcare infections are infections that are commonly associated with various healthcare settings such as hospitals, nursing homes, long term care facilities etc. These infections are commonly caused by antibiotic resistant bacteria, which in turn are associated with poor outcomes in patients and a higher cost of hospitalisation. In the current situation, the number of resistant bugs is increasing, while there is a paucity of the number of available drugs that are available for treatment. More worrying is the spread of some of these agents into the community and worldwide. Bacteria such as MRSA have seen a constant change in the epidemiological pattern since it was first documented in 1961. Diagnostics are not well defined for many microbes. There is also an urgent need for better understanding of the host –pathogen interaction, which in turn drives the pharmaceutical industry towards developing newer antimicrobials and vaccines. Some multidrug resistant bacteria such as NDM-1 have spread globally within a span of couple of years and this in turn reflects the need for better surveillance systems. Many of these issues can be addressed by research. The project area will aim to look at where we stand with relation to some of these issues in this century.

The project work will mainly focus on

- Bacteria or fungi such as C.difficile, Methicillin resistant *Staphylococcus aureus (*MRSA), *Candida albicans*, Aspergillosis etc
- Clinically important and emerging mechanisms of multidrug resistance such as NDM-1, Extended spectrum beta lactamases (ESBL) etc.

Who would benefit

These projects are suitable for those with an interest in infectious diseases. Although there is no specific course requirement, knowledge of Medical Microbiology would be advantageous.

Specific project areas

The microbial and epidemiological study of healthcare infections and antibiotic resistance is vast. Hence, the project would focus on specific areas which are of current relevance in context to microbial agents/resistance mechanisms mentioned above. The study area could be specific to pathogenesis, epidemiology, clinical diagnostics, molecular typing or emerging therapies. Given below are some representative examples of potential project topics.

- Newer molecular typing methods in defining MRSA isolates.
- Comparative genomics and uses in the study of MRSA
- Community C.difficile. Is it an unrecognised problem?
- NDM-1: Global implications
- Diagnosis of invasive fungal infections with special emphasis on the role of galactomannan
- Virulence of community MRSA (CMRSA) strains
- Bovine mastitis and implications to humans with special reference to the problem of MRSA

Life Science Projects 2012-2013

Faculty Name: Dr Frances Pearl

Room No: JMS 4D15 **Email**:f.pearl@sussex.ac.uk

Project Title/Area:

Bioinformatics analysis of cancer-drug resistance mutations

Course requirements:	**No of places**: 2

Further Information:

All cancers arise as a result of the acquisition of a series of fixed DNA sequence abnormalities, termed mutations, many of which ultimately confer a growth advantage upon the cells in which they have occurred. A small subset of these mutations is acquired during drug treatment and can confer resistance of the cancer to the drug that it previously responded to. These drug resistance mutations can occur within the gene encoding the protein the drug was targeted to (direct resistance) or in a completely different gene and pathway (indirect resistance) that nonetheless allows the cancer cell to survive the drug.

This project will involve a bioinformatics and literature analysis to identify these mutations and assess their mode of action.

Life Science Projects 2012-2013

<table>
<tr><td colspan="2">Faculty Name: Dr. Roger Phillips

Room No: JMS 2c9 Email: r.g.phillips@sussex.ac.uk</td></tr>
<tr><td colspan="2">Project Title/Area:

Super resolution microscopy of fluorescent proteins in the drosophila polytene salivary gland cells.</td></tr>
<tr><td>Course requirements:

Developmental Biology</td><td>No of places: 1</td></tr>
<tr><td colspan="2">Further Information:

A bit of background on studies using fluorescent proteins in drosophila polytene salivary gland cells can be read in Yao J…and Lis J. NATURE Vol 442:31 August 2006.</td></tr>
</table>

Life Science Projects 2012-2013

<table>
<tr><td colspan="2">Faculty Name: Dr.Roger Phillips

Room No: JMS 2c9 Email: : r.g.phillips@sussex.ac.uk</td></tr>
<tr><td colspan="2">Project Title/Area:

The role of TFIIIH in Drosophila wing disc regeneration</td></tr>
<tr><td>Course requirements:

Developmental Biology</td><td>No of places: 1</td></tr>
<tr><td colspan="2">Further Information:

The Drosophila wing disc regeneration model is described in Smith-Bolton R et al, Dev Cell. 2009 June ; 16(6): 797–809.</td></tr>
</table>

Life Science Projects 2012-2013

Faculty Name: Dr Chrisostomos Prodromou

Room No: GDSC G4.02 **Email:** chris.prodromou@sussex.ac.uk

Project Title	**Project Type:**
Co-crystallization of Pih, Tah1 and Hsp90	Exp
Course requirements: none	**No of places**: 1

Further Information:

NOP17 (also known as PIH) is involved in pre-rRNA processing. It is known to associate with Spaghetti (Tah1p) and Hsp90. It has been implicated in the chromatin remodelling complex Ino80 and SWR-C.

The project will involve expression and purification of mouse Pih, Tah1 and Hsp90. We will investigate the interactions between these proteins by isothermal titration calorimetry and set up appropriate co-crystallizations.

Affects on the ATPase activity of Hsp90 will be determined as well as their Kd for binding to Hsp90. Techniques involved will protein expression, purification, crystallizatiobn, SDS-PAGE and immunoblotting, and ATPase assays.

Life Science Projects 2012-2013

Faculty Name: Dr Chrisostomos Prodromou

Room No: GDSC G4.02 **Email**: chris.prodromou@sussex.ac.uk

Project Title	**Project Type:**
Expression and co-crystillization of RuvBl1 and RuvBL2 with Pih	Exp
Course requirements: none	**No of places**: 1

Further Information:

RuvBL1 (RuvB-like 1) and its homolog RuvBL2 are evolutionarily highly conserved AAA(+) ATPases essential for many cellular activities. They play an important role in chromatin remodeling, transcriptional regulation and DNA damage repair. We aim to overexpress these proteins together with Pih, a co-chaperone of Hsp90, investigate their interactions and set up appropriate crystallization trilas.

Techniques involved will include protein expression, purification, crystallization, SDS-PAGE and immunoblotting, isothermal titration calorimetry and ATPase assays.

Life Science Projects 2012-2013

<table>
<tr><td colspan="2">Faculty Name: Dr. Mark Roe

Room No: 2R314A Email: M.Roe@sussex.ac.uk</td></tr>
<tr><td colspan="2">Project Title/Area:

X-Ray Crystallography of small molecule inhibitors of HSP90</td></tr>
<tr><td>Course requirements: Proteins In Action</td><td>No of places: 2</td></tr>
<tr><td colspan="2">Further Information:

These projects will involve the student crystallising the protein/inhibitor complex, collecting data, solving and refining the structure with a view to explaining the basis of binding of the inhibitor and exploring ways that the binding could be improved.</td></tr>
</table>

Life Science Projects 2012-2013

Faculty Name: Professor Louise C Serpell

Room No: Chichester2 315A **Email**: L.C.Serpell@sussex.ac.uk

Project Title/Area:

Structure and function of amyloidogenic proteins

Course requirements:	**No of places:**
PFF	2-3

Further Information:

Amyloid accumulates in the tissues in diseases including Alzheimer's disease and Diabetes type. Amyloid fibrils maybe formed from different peptides in vitro and we are able to study the mechanism of fibril formation, the fibril structure and also the potential pathogenic effect of fibrils in cell culture. In addition, amyloid fibrils are very stable fibrous protein structures and can be exploited for their potential to form strong polymeric materials.

These projects will involve exploring the structure and function of amyloidogenic peptides and require the use of biophysical techniques or imaging techniques to examine their assembly, structure or function.

Life Science Projects 2012-2013

<table>
<tr><td colspan="2">Faculty Name: Professor Louise C Serpell

Room No: Chichester2 315A Email: L.C.Serpell@sussex.ac.uk</td></tr>
<tr><td colspan="2">Project Title/Area:

Cellular changes related to Alzheimer’s disease</td></tr>
<tr><td>Course requirements:

None (PFF advantage</td><td>No of places: 2-3</td></tr>
<tr><td colspan="2">Further Information:

Alzheimer’s disease is related to changes in neuronal function and this may stem from changes in specific cellular functions in organelle systems. This project will involve research into the changes in either a) mitochondria or b) lysosomes, related to Alzheimer’s disease. This will involve electron microscopy of section tissue and cells or/and literature review focussed on aspect of Alzheimer’s disease</td></tr>
</table>

Life Science Projects 2012-2013

<table>
<tr><td colspan="2">Faculty Name: Professor Louise C Serpell

Room No: Chichester2 315A Email: L.C.Serpell@sussex.ac.uk</td></tr>
<tr><td colspan="2">Project Title/Area:

The use of self-assembling peptides as materials for bionanotechnology</td></tr>
<tr><td>Course requirements:

PFF</td><td>No of places: 1</td></tr>
<tr><td colspan="2">Further Information:

Amyloidogenic peptides assemble to form highly organised and stable fibrils. These have potential for uses as nanowires and materials. In this project, you will explore the possible methods for control and applications for these systems. Methods will include circular dichroism and electron microscopy as well as Xray diffraction.</td></tr>
</table>

Life Science Projects 2012-2013

Faculty Name: Professor Alison Sinclair

Room No: 3C19 **Email:** a.j.sinclair@sussex.ac.uk

Project Title/Area:

Explaining science to the public: unlocking the genetic material within viral genomes

Course requirements:

A background and interest in molecular biology is required.

Suited to Biochemistry, Molecular Genetics or Biomedical Science BSc programs.

No of places: 6

Further Information:

Visit a science Museum

Choose one exhibit

- Make note on the aims of the exhibit, the age group it is aimed at, the prior knowledge expected, whether there is a "hands-on" element to it, what materials it appears to be made of; what approximate size it is?
- Have a look at the text associated with it, are there acknowledgements, further sources of information, handouts?
- Take a photograph or make a sketch of the exhibit.
- Have a look to see if there's any on-line information associated with the exhibit, for example is there a QR code associated with it?

- Write a report on the exhibit encompassing the information that you collected (above). Including within this whether you think the exhibit reached its objectives, and what a layperson would understand from it.

- Decide on a specific area that you are going to design an exhibit for under the general theme of "unlocking the genetic material within viral genomes".
  - decide which age group you are aiming the exhibit at;
  - decide what prior knowledge you anticipate that the public would have;
  - decide whether it is going to be static, hands on or manned (for example at a science fair);
  - decide how long you anticipate people would spend at this exhibit;
  - choose the key points of information that you want to get across;
  - draw a diagram of the exhibit showing the scale;
  - show any text that you would put on the exhibit;
  - provide a CD for any sound, picture or video recordings that you would include within the exhibit;
  - if the exhibit is to be manned or unmanned but hands-on show a flow-diagram of how you think the public will interact with it;
  - suggest what types of materials might be suitable to build the exhibit with (ie what properties are required from the materials);
  - design an evaluation questionnaire to assess the educational value of the exhibit.

- We will hold project meetings and you will have deadlines for research reports, but you will be able to set your own timetable for the majority of your project work.

Life Science Projects 2012-2013

Faculty Name: Dr. Darren Thompson

Room No: 2R315B **Email:** d.thompson@sussex.ac.uk

Project Title/Area:

Transfer of metal ions between proteins

Course requirements:	**No of places:** 3

Further Information:

These projects involve the investigation of the transfer of metals between serum proteins. There is a combination of laboratory and literature based projects. The laboratory projects are investigating the possible roles copper carrying proteins such as ceruloplasmin and albumin play in the uptake of copper by the immune proteins C1 and SAP. This transfer will be examined under different physiological conditions and the acceptor molecules will be analysed for changes in their structure and function. The literature based project will take a larger look at the transfer of metal ions in biochemistry and how this effects protein structure and function

Life Science Projects 2012-2013

Faculty Name: Dr. Darren Thompson

Room No: 2R315B **Email:** d.thompson@sussex.ac.uk

Project Title/Area:

Cloning, expression, purification and characterisation of immune related proteins

Course requirements:	**No of places:** 2

Further Information:

C1 and Serum Amyloid P component (SAP) are currently being cloned within the lab. These projects will involve the various steps to produce active proteins and characterise them to compare with the data obtained for these proteins purified direct from human serum. These projects may involve laboratory work or a review of the literature on the cloning and expression of similar proteins

Life Science Projects 2012-2013

<table>
<tr><td colspan="2">Faculty Name: Dr. Darren Thompson

Room No: 2R315B Email: d.thompson@sussex.ac.uk</td></tr>
<tr><td colspan="2">Project Title/Area:

Structural changes that occur in C1 upon binding of copper</td></tr>
<tr><td>Course requirements:</td><td>No of places: 1</td></tr>
<tr><td colspan="2">Further Information:

This project involves studying the structural changes that occur in the protein C1 once the calciums that are required for structural integrity have been replaced by different metals</td></tr>
</table>

Life Science Projects 2012-2013

Faculty Name: Dr.Julian Thorpe	**Room No**: JMS 2C9	**Email:** j.r.thorpe@sussex.ac.uk

Project Title/Area: 'Utilising transmission electron microscopy (TEM) approaches to investigate and gain insights into the molecular pathogenesis of the neurodegenerative diseases'

Course requirements: None, but neuroscience background useful	**No. of places:** 3 (probably 2 lab, 1 critical review)

Further Information:

These projects would involve using TEM approaches to gain insights into the molecular pathogenesis of the neurodegenerative diseases - including Alzheimer's disease (AD), the frontotemporal dementias (FTDs), motor neuron disease (MND) and Parkinson's disease (PD) - utilising post-mortem human brain tissues and/or animal/cell models of disease. There is a broad range of potential tissues/cells available for study (or to be prepared for study); these include the SH-SY5Y neuroblastoma cell line and hippocampal neurons (with Louise Serpell and Kevin Staras, Sussex [cell models of AD]), mouse models of MND cortex and spinal cord (with Sherif El-Khamisy, Majid Hafezparast, Sussex, and Abraham Acevedo, MRC Harwell), post-mortem AD and FTD human brain tissues (with Nigel Cairns, Washington University School of Medicine, USA), and mouse models of PD substantia nigra tissues (with Robert Layfield, University of Nottingham and Simon Paine, Great Ormond Street Hospital, London). Immunogold labelling TEM* would be used to localise pathological and associated proteins-of-interest at the ultrastructural level and to assess their status, (re-)distribution and association with any pathologic inclusions within affected neurons, to gain insights into the molecular pathogenesis of these various diseases. The projects would be based in the Sussex Centre for Advanced Microscopy in Life Sciences. Please see the websites and references below for further background.

Relevant References and Websites

- http://www.sussex.ac.uk/lifesci/thorpelab/ (Thorpe Lab)
- http://www.sussex.ac.uk/neurodeg/ (Neurodegenerative Disease and Ageing Research Centre)
- http://www.lifesci.sussex.ac.uk/home/Julian_Thorpe/ad_cover.htm (for details of previous research and additional general background)
- http://www.lifesci.sussex.ac.uk/home/Julian_Thorpe/cover.htm (for fuller details of the TEM Lab here in Life Sciences, where the research project would be carried out)
- http://www.lifesci.sussex.ac.uk/home/Julian_Thorpe/immuno.htm (Immunogold labelling background)*

Soura V, Stewart Parker M, Williams TL, Ratnayaka A, Atherton J, Gorringe K, Tuffin J, Darwent E, RambaranR, Klein W, Lacor P, Staras K, Thorpe J, Serpell L (2012) Visualisation of colocalisation in Ab42-administered neuroblastoma cells reveals lysosome damage and autophagosome accumulation related to cell death. *Biochemical Journal* 441:579-590

Page T, Gitcho MA, Mosaheb S, Carter D,Chakraverty S, Perry RH, Bigio EH, Gearing M, Ferrer I, Goate AM, Cairns NJ, Thorpe JR (2011) FUS immunogold labelling TEM analysis of the neuronal cytoplasmic inclusions of neuronal intermediate filament inclusion disease: a frontotemporal lobar degeneration with FUS proteinopathy. *Journal of Molecular Neuroscience* 45: 409-421

Acevedo-Arozena A, Kalmar B, Essa S, Ricketts T, Joyce P, Kent R, Rowe C, Parker A, Gray A, Hafezparast M, Thorpe JR, Greensmith L, Fisher EMC (2011) A comprehensive assessment of the *SOD1G93A* low-copy transgenic mouse, which models human amyotrophic lateral sclerosis. *Disease Models & Mechanisms* 4: 686-700

Paine S, Bedford L, Thorpe JR, Mayer RJ, Bajaj N, Sheppard PW, Lowe J, Layfield R (2009) Immunoreactivity to Lys63-linked polyubiquitin is a feature of neurodegeneration. *Neuroscience Letters* 460: 205-208

Thorpe JR, Tang HHL, Atherton JM, Cairns NJ (2008) Fine structural analysis of the neuronal inclusions of frontotemporal lobar degeneration with TDP-43 proteinopathy. *Journal of Neural Transmission* 115: 1661-1671

Hashemzadeh-Bonehi L, Phillips RG, Cairns NJ, Mosaheb S, Thorpe JR (2006) Pin1 protein associates with neuronal lipofuscin: potential consequences in age-related neurodegeneration. *Experimental Neurology* 199: 328-338

Mosaheb S, Thorpe JR, Hashemzadeh-Bonehi L, Bigio EH, Gearing M, Cairns NJ (2005) Neuronal intranuclear inclusions are ultrastructurally and immunologically distinct from cytoplasmic inclusions of neuronal intermediate filament inclusion disease (NIFID). *Acta Neuropathol.* 110: 360-368

Thorpe JR, Mosaheb S, Hashemzadeh-Bonehi L, Cairns NJ, Kay KE, Morley SJ, Rulten S (2004) Shortfalls in the Peptidyl-Prolyl *Cis-Trans* Isomerase Protein Pin1 in Neurons are Associated With Frontotemporal Dementias. *Neurobiology of Disease* 17: 237-249

Thorpe JR, Morley SJ, Rulten SL (2001) Utilising the Peptidyl-Prolyl Cis-Trans Isomerase Pin1 as a Probe of its Phosphorylated Target Proteins: Examples of Binding to Nuclear Proteins in a Human Kidney Cell Line and to Tau in Alzheimer's Diseased Brain. *J. Histochem. Cytochem.*49: 97-108

Life Science Projects 2012-2013

Faculty Name: Dr. M.A. Titheradge

Room No: 2C15 **Email:** m.a.titheradge@sussex.ac.uk

Project Title/Area:

The role of asymmetric dimethylarginine (ADMA) and monomethyl arginine (MMA) as a risk factor in disease processes such as cardiovascular disease, renal dysfunction and diabetes.

Course requirements:	**No of places**: 2
Endocrinology and Disease	

Further Information:

Asymmetric dimethylarginine (ADMA), symmetric dimethylarginine (SDMA) and monomethylarginine (MMA) are naturally occurring amino acids that circulate in plasma and are excreted in the urine. They are formed by the enzymatic methylation of arginine residues within proteins by protein methyl transferases (PRMT). A number of PRMTs have been identified and fall into two classes. PRMT 1 form MMA and ADMA whilst PRMT 2 form MMA and SDMA. Upon proteolysis these methylated arginines are released into cells and subsequently into the circulation. ADMA is metabolised by the enzyme dimethylarginine dimethylaminohydrolase (DDAH), of which there are two isoforms, and is also excreted via the kidney. SDMA is not metabolised by DDAH

and it is thought that its only route of elimination is via the kidney. ADMA and MMA are potent inhibitors of nitric oxide synthases (NOS) whilst SDMA has been shown to have no effect upon these enzymes. NOS act upon arginine to produce nitric oxide (NO) and citrulline. The resultant NO induces vascular relaxation and also platelet adhesion and smooth muscle proliferation. By inhibiting NO production it is thought that increased concentrations of ADMA may contribute towards the atherogenic process and be a cardiovascular risk factor. A number of other studies have suggested that increased plasma ADMA concentrations are associated with renal dysfunction, diabetes, pre-eclampsia, pulmonary hypertension and insulin resistance and that this increase in ADMA is probably due to impaired metabolism by DDAH. The aim of these projects will be to take one of these diseases and investigate the potential roles played by ADMA and MMA in this disease using data obtained from the scientific literature.

Life Science Projects 2012-2013

Faculty Name: Dr Michelle West

Room No: JMS 3C20 **Email:** m.j.west@sussex.ac.uk

Project Title/Area:

How does the cancer-associated Epstein-Barr virus transcriptionally reprogramme host cells to drive their uncontrolled growth?

Course requirements:	**No of places**: 3
Biochemistry or Biomed Sci students only (unless students have appropriate biochemistry or molecular biology experience)	

Further Information:

Epstein-Barr virus (EBV) is causally linked with a number of human cancers and can infect and immortalise human B-cells *in vitro*. EBV immortalisation is accompanied by the expression of only nine viral proteins; six Epstein-Barr nuclear antigens (EBNAs 1, 2, 3A, 3B, 3C and LP) and three latent membrane proteins (LMP1, 2A and 2B). During immortalisation EBV directs transcriptional activation of genes that promote proliferation and prevent apoptosis, and repression of genes that inhibit cell growth and promote apoptosis. Host-cell gene transcription is reprogrammed through the concerted actions of the EBNAs with EBNA 2 and the EBNA 3 family of transcription factors (3A, 3B, 3C) playing key roles in this process.

Wet-lab projects

We have used chromatin-immunoprecipitation coupled to next-generation sequencing (ChIP-seq) to obtain information on how EBNA 2 and EBNA 3 proteins are targeted to the host genome to reprogramme gene expression. We have identified binding sites for these factors in the promoter and long-range enhancer regions of genes involved in the regulation of cell growth, signalling and apoptosis. The aim of these projects is to test the function of these transcriptional regulatory regions and determine the role of EBV proteins in regulating key cellular targets relevant to immortalisation.

You will use molecular biology techniques including DNA extraction, PCR, restriction enzyme digestion and ligation to create reporter plasmids containing regulatory elements from target genes. These reporter constructs will then be transfected into human cells in the absence and presence of EBNAs to determine how these regulatory elements are controlled by EBV-encoded factors.

Life Science Projects 2012-2013

Faculty Name: Dr Michelle West

Room No: JMS 3C20 **Email:** m.j.west@sussex.ac.uk

Project Title/Area:

Investigating the role of newly identified target cellular target genes in cancer promotion by Epstein-Barr virus.

Course requirements:	**No of places:** 3
Cell regulation and cancer in year 2	

Further Information:

Epstein-Barr virus (EBV) is causally linked with a number of human cancers and can infect and immortalise human B-cells *in vitro*. EBV immortalisation is accompanied by the expression of only nine viral proteins; six Epstein-Barr nuclear antigens (EBNAs 1, 2, 3A, 3B, 3C and LP) and three latent membrane proteins (LMP1, 2A and 2B). During immortalisation EBV directs transcriptional activation of genes that promote proliferation and prevent apoptosis, and repression of genes that inhibit cell growth and promote apoptosis. Host-cell gene transcription is reprogrammed through the concerted actions of the EBNAs with EBNA 2 and the EBNA 3 family of transcription factors (3A, 3B, 3C) playing key roles in this process.

We have used chromatin-immunoprecipitation coupled to next-generation sequencing (ChIP-seq) to obtain information on how EBNA 2 and EBNA 3 proteins are targeted to the host genome to reprogramme gene expression. We have identified binding sites for these factors in the promoter and long-range enhancer regions of genes involved in the regulation of cell growth, signalling and apoptosis.

Literature/data review projects

The aim of these projects is to research the function and deregulation of subsets of key cellular genes that we have identified as potential targets for EBV-encoded factors. Initial investigations will involve the analysis of expression data to determine whether any of the selected genes have been shown to be regulated by EBV-encoded factors. Further literature-based research will determine whether these genes have been reported to be deregulated in cancer cells and obtain information on how they are transcriptionally controlled.

Drug Discovery Subject Area

Faculty Name: Simon Ward **Email:**Simon.Ward@sussex.ac.uk

Room No: Biology lab of the Translational Drug Discovery Group (Lab 13 Chichester 2)

Project Title/Area: Drug discovery projects in Oncology

Course requirements: N/A	**No of places:** 3 (all Lab based)

Further Information:

The Translational Drug Discovery Group, in close partnership with colleagues across the Genome Damage and Stability Centre, and the Brighton and Sussex Medical School is working in the exciting field of oncology drug discovery. The group has two labs – medicinal chemistry and biochemistry & molecular pharmacology. The biochemistry lab will have three places available for projects in 2012-2013.

The Student will participate in a variety of ongoing drug discovery programs, with emphasis on enabling drug screening of targets from the Genome Damage and Stability Centre. The main core of the project will be the development of specific potency assays (using the standard SBS mircoplate format) to screen novel compounds against these specific biological targets.

The assay formats used could include Biophysical, Biochemical and Cell based measurements and will have to be validated using known pharmacological tools and proved to be robust and sensitive to inhibitors. Active compounds identified will be the starting point for structure activity based relationships, and for further targeted potency measurements.

The student will develop experience of the techniques such as fluorescence based measurements, mammalian cell culture, use of liquid handling systems, and data analysis and be exposed to an interdisciplinary team of chemists and biologists.

Brighton & Sussex Medical School Subject Area

Faculty Name: Prof. Florian Kern, BSMS

Room No: MRB.1.09 **Email**: f.kern@bsms.ac.uk

Project Title/Area:

Analysis of blood cell populations in Cytomegalovirus infection

/ T-cell immunology

Course requirements:	**No of places**: 1
Basic knowledge of immunology and white blood cell populations	

Further Information:

The project will involve practical flow-cytometry data analysis (existing data) and patient/health data in spread-sheet format. The student will learn to use FlowJo cytometry analysis software in order to analyse different subsets of activated T-lymphocytes. The aim of the project will be to present a summary analysis of data and its interpretation. The data will relate to the effect of

Cytomegalovirus infection on the immune system.

Life Science Projects 2012-2013

Faculty Name: Dr Sarah Newbury

Room No: 2.08, Medical Research Building **Email**: s.newbury@bsms.ac.uk

Project Title/Area

Role of RNA turnover in testis stem cells

Course requirements:

Biochemistry, Biomedical Science Molecular Medicine

No of places: 1

Further Information:

Stem cells have a vast potential in regenerative medicine for the replacement of defective tissue. They therefore offer a potential cure for injuries and also for degenerative diseases such as Alzheimers and Duchenne muscular dystrophy. We have recently shown that the conserved exoribonuclease Pacman/Xrn1, which is known to be involved in the cytoplasmic degradation of mRNA, RNA interference and degradation of microRNAs, is necessary for stem cell function in the testis of the fruit fly *Drosophila*. In common with mammals, self-renewing germline stem cells are critical for supplying cells which differentiate into sperm. Since the role of mRNA stability in controlling gene expression in stem cells has not been well studied, these results have uncovered a novel mechanism of gene regulation which is likely to be important in stem cells in other organisms.

The aim of the project is to analyse the effects of downregulation of *pacman* in the testis at the phenotypic and molecular levels to start to understand the molecular pathways regulated by *pacman* in stem cells.

Specific aims are:

(1) To use RNA interference to knock down the expression of *pacman* in stem cells, spermatogonia and somatic support cells (cyst cells) and analyse the phenotypic results.

(2) To investigate the effects of a new mutant of *pacman* on male fertility.

Techniques to be used include: Drosophila genetics, Immunocytochemistry, Western blotting, quantitative RT-PCR.

Life Science Projects 2012-2013

Faculty Name: Dr Sarah Newbury

Room No: 2.08, Medical Research Building **Email**: s.newbury@bsms.ac.uk

Project Title/Area:

Role of RNA turnover in growth and proliferation.

Course requirements:	**No of places**: 1
Biochemistry, Biomedical Science Molecular Medicine	

Further Information:

Imaginal discs are similar to stem cells in that they carry all he information required to make the adult tissue. Our recent work has shown that the 5' – 3' exoribonuclease *pacman* affects the growth and proliferation of wing imaginal discs that are destined to grow into the wing of the fly. The *Drosophila* imaginal disc provides an excellent model system to investigate growth and proliferation as many of the key signalling pathways are conserved in mammals. Our preliminary results suggest that *pacman* controls growth and proliferation via control of a histone deacetylation complex (the NuRD complex). Since histone deacetylases are involved in cancer our findings suggest a novel pathway to control cell proliferation which is relevant to human disease.

The aims of this project are:

1. To use RNA interference to knock down expression of *pacman* in different tissues and examine the phenotypic effects.

2. To examine the effect of *pacman* knockdown on expression of components of the histone deacetylation complex.

Techniques to be used include:

Western blotting, *Drosophila* genetics, RT-PCR, quantitative RT-PCR.

Life Science Projects 2012-2013

Faculty Name: Prof P Schmid & Dr Alice Shia

Room No: Trafford Centre **Email**: a.shia@bsms.ac.uk

Project Title/Area:

Epigenetic changes in cancer biology

Course requirements:	**No of places**: 2

Further Information:

Cancer initiation and progression can be driven by a number of changes. Recently, novel epigenetic changes have been described in various oncogenes and tumour suppressing genes that contribute to initiation and metastasis of cancer.

Epigenetics can be described as heritable changes in the phenotype that cannot be ascribed to the genome. The most common epigenetic change described is methylation of the cytosine base. The addition of a methyl group to this base at promoter regions of genes is expected to cause steric interference and disrupt the transcriptional regulation, causing repression of the gene.

Our laboratory has recently completed a large-scale microarray screen in a number of breast and lung cancer cell lines. We have identified a number of candidate genes involved in a variety of pathways that will need to be validated functionally and in patient samples as a prognostic or predictive biomarker.

The project student is expected to work in a laboratory for this project. They will work closely with the tutor to validate and confirm the role(s) of gene(s) involved in epigenetic changes as determined by a large-scale microarray screen. The student will be trained in techniques to extract nucleic acids (DNA, RNA & microRNA) and proteins from cell lines. The student will learn PCR, real-time quantitative PCR and Western blotting.

The student will be taught to analyse the data as per standard methods.

Life Science Projects 2012-2013

Faculty Name: Dr Simon Waddell

Room No: BSMS Teaching Building 3.07C **Email:** s.waddell@bsms.ac.uk

Project Title/Area:

The functional significance of small RNAs in bacteria

Course requirements: None	**No of places**: 1

Further Information:

The recent discovery of small RNA species in bacteria promises to transform our understanding of bacterial gene regulation and provides novel opportunities for therapeutic intervention. This literature review will describe the eukaryotic origins of this work, the principle investigations and the key techniques used to identify and characterise sRNA. The critique will also include an assessment of the likely impact of further advances in this field.