Marie Curie ESR Handbook

Marie Curie Initial Training Networks (ITN)
Call: FP7-PEOPLE-2012-ITN

Decision-making within cells and **d**ifferentiation **e**ntity therapies

Registration Form for PhD Students 2013/2014

(Please fill in this form and had to your Research Project Lead so we have contact details)

Full name:

Student Registration number:

Home address:

Tel:

Project Supervisor (1):

Project Supervisor (2):

Term time address:

Tel:

E-mail address:

MARIE CURIE FELLOWS

Next Of Kin/Home Contacts

Your Details

Name: ……

Address: ……

……

……

Home phone no: .....

Mobile no: .....

E-mail (work): .....

Supervisor/Line Manager: .....

Next Of Kin Details

Name: ……

Address: ……

……

……

Phone no: ……

Relationship to you: ……

Please return to your Research Project Lead. This information is for institution use only e g; in cases of an emergency when you or your next of kin may need to be contacted. It will be kept by university/institution staff and will not be entered on publicly accessible files.

TABLE OF CONTENTS

1 LIST OF NETWORK PARTICIPANTS

Participant	Private sector	Country	Legal entity	Department	Scientist-in-Charge	Role Assoc. Partner
Full Network Partners (beneficiaries)						
1 - UBham		UK	The University of Birmingham	Immunity and Infection	Dr Geoffrey Brown	
2 -NUIG		Ireland	National University of Ireland, Galway	Regenerative Medicine Institute	Prof. Rhodri Ceredig	
3 - UBas		Switzerland	University of Basel	Department of Biomedicine	Prof. Antonius Rolink	
4 - UWroc		Poland	University of Wroclaw	Faculty of Biotechnology	Dr Ewa Marcinkowska	
5 – OTP	√	Ireland	Orbsen Therapeutics Ltd.		Dr Stephen Elliman	
6 – ICR		UK	Institute of Cancer Research, London	Haemato-Oncology	Dr Arthur Zelent	
7 - PRI		Poland	Pharmaceutical Research Institute, Warsaw	Chemistry and Analytical Departments	Prof. Andrzej Kutner	
8 – CTX	√	UK	Celentyx		Prof. Nicholas Barnes	
Associated Partners						
9 – UMDNJ		USA	New Jersey Medical School	Pathology and Laboratory Medicine	Prof. George Studzinski	Training visits, ITN Board
10 – HPR	√	UK	High-Point Rendel Ltd.		Martin Smith	Manage-ment courses, govern-ance, ITN Board

2 OVERVIEW OF THE ITN

The Marie Curie ITN programme:

Initial Training Networks aim to improve career perspectives of *early-stage researchers (ESRs)* in both public and private sectors, thereby making research careers more attractive to young people. They aim to work through trans-national networking through a partnership of public and private enterprises in the field. In particular, the networks aim to add to the employability of the recruited researchers through exposure to both academia and enterprise, thus extending the traditional academic research-training setting and eliminating cultural and other barriers to mobility.

The DECIDE ITN:

Our ITN has both scientific and therapeutic targets. DECIDE aims to advance understanding of normal blood cell development and why primitive cells fail to differentiate in acute myeloid leukaemia (AML). We will use the information gained to develop ways of alleviating the differentiation block in AML and so deliver new agents for use in differentiation therapy. This type of therapy aims to respond to the urgent need to devise milder treatments, especially for older and frailer AML patients. We have already identified a number of promising new therapeutic agents. Working across these two complementary areas will train our ESRs to understand the translation of new fundamental science into the development of new therapies.

The ITN brings together scientists who have made important advances in the fields of haematopoiesis and differentiation therapy, so will provide an excellent scientific training in these areas. Secondments by ESRs to participants who run centres of expertise in leading edge technologies will provide training in these. The time spent with private sector participants, and the courses they provide, will ensure that ESRs acquire the transferable skills they will need if they are to work well in, and build bridges between, commercial and publicly funded research organisations. ESRs will also receive management training. This research and training, which will develop our ESRs as versatile scientists, will involve the combined efforts of prestigious research institutes and universities, Poland's leading governmental pharmaceutical R & D institute, two successful biopharmaceutical companies and a leading management consultancy.

The DECIDE training objectives:

We aim to develop young researchers to be, first and foremost, purposeful thinkers who aspire to solve a major scientific problem who will then translate this new understanding into solutions to medical needs. There are two central aims. First, is to ensure that finished ESRs are highly skilled scientists: proficient in a variety of technologies and able to cross scientific disciplines. Second, is to ensure that ESRs acquire entrepreneurial aspirations coupled to the skills required to work across academia and industry and forge valuable links.

3 THE PARTNERS

DECIDE comprises partners from the UK, Switzerland, Poland and Ireland from academia and the private sector. Two associated partners - New Jersey Medical School, USA and High-Point Rendel Ltd, UK will also provide training opportunities. There are 12 ESR projects as listed below.

University of Birmingham – Dr Geoffrey Brown & Prof Antal Rot
(g.brown@bham.ac.uk; a.rot@bham.ac.uk)
- The Haematopoietic Repertoire: Chemokine Involvement and Interplay
- Verifying our New Model for Haematopoiesis

National University of Ireland, Galway – Prof Rhodri Ceredig
(rhodri.ceredig@nuigalway.ie)
- Monocytes: their Position in Haematopoiesis
- Mesenchymal Stem Cell Diversity and Support to Haematopoiesis

University of Basel – Prof Antonius Rolink
(antonius.rolink@unibas.ch)
- Early events in Haematopoietic Progenitor Cell Specification
- Lineage-Affiliated Specification Events

Orbsen Therapeutics Ltd., Galway – Dr Steve Elliman
(steve.elliman@orbsentherapeutics.com)
- Stromal Cells: their Roles in Haematopoiesis

Institute of Cancer Research, London – Dr Kevin Petrie & Dr Louis Chesler
(kevin.petrie@icr.ac.uk)
- New Retinoid-based Therapies for Acute Myeloid Leukaemia and Neuroblastoma

University of Wroclaw – Prof Ewa Marcinkowska & Prof Andrzej Kutner (Warsaw)
(ema@cs.uni.wroc.pl)
- Why do only Some Acute Myeloid Leukaemia patient's cells respond to Vitamin D_3?

Pharmaceutical Research Institute, Warsaw – Prof Andrzej Kutner & Prof Ewa Marcinkowska (Wroclaw)
(a.kutner@adm.um.edu.pl)
- Design and Synthesis of Vitamin D Analogs with Anti-Cancer Potential
- Synthesis and Evaluation of Vitamin D Analogs for Anti-Cancer Combination Therapy

Celentyx Ltd., Birmingham – Prof Nicholas Barnes
(N.M.Barnes@bham.ac.uk)
● Discovery and development of Novel Chemical Entities (NCEs) towards lead candidate status for the treatment of cancer

New Jersey Medical School, USA – Prof George Studzinski
(studzins@umdnj.edu) - Secondments for training in microRNAs

High-Point Rendel Ltd. – Martin Smith
(m.smith@hpworld.com) – Risk assessment and management training at the 1st ITN School

4 ESR PROJECTS

Each research project (RP) addresses a specific question tailored towards a PhD, and has been peer-reviewed by the Advisory Panel for scientific rigour and feasibility as a PhD project. ESRs will visit/be seconded to other laboratories to integrate RPs, for training methods, and to train university ESRs on biopharmaceuticals (at CTX, OTP or PRI). Each ESR will have joint university/biopharmaceutical sector supervision. Details of ESR RPs and planned collaborations, *via* secondments/visits, follow.

ESR Research Projects – work package (WP), secondment (S) and visit (V)

Work Package 1 A better understanding of Haematopoiesis

ESR1, RP1 @ *UBham (Lead supervisor Rot, and with Brown)* – The Haematopoietic Repertoire: Chemokine Involvement and Interplay

● Chemokines are secreted signaling proteins with characteristic structural features and broad range of pleiotropic activities. Chemokines are best known to induce directed migration of a variety of cells, including hematopoietic cells, thus directing their localization and trafficking in and out of the bone marrow. These effects are mediated by cognate cell membrane G-protein coupled chemokine receptors (GPCRs), which are expressed by defined subsets of hematopoietic lineages. However, chemokine signaling through their GPCRs also affects other responses by hematopoietic lineages including cell proliferation and differentiation.

Moreover, in addition to classical GPCRs, bone marrow cells express atypical chemokine receptors. These are serpentine membrane receptors with seven transmembrane domains structurally homologous to GPCRs but due to their lack of DRYLAIV consensus motive within the second intracellular loop, which is required for coupling to G-proteins, fail to induce classical signaling and downstream cellular responses characteristic of chemokine GPCRs. Despite their inability to mediate full spectrum of chemokine signaling, atypical chemokine receptors expressed in nucleated cells efficiently internalize chemokines and thus can influence chemokine availability and function as well as affecting signaling by the classical chemokine GPCRs.

Duffy Antigen/Receptor for Chemokines (DARC) is a minor blood group antigen and a promiscuous atypical chemokine receptor, which binds over 20 inflammatory CXC and CC chemokines. DARC is expressed exclusively by cells of erythroid lineages. Individuals of West African origin lack the expression of DARC on erythrocytes (Duffy-negative phenotype), a trait selected by their resistance to plasmodium vivax malaria, which uses DARC to invade erythrocytes. Recently we have generated a unique humanized DARC transgenic mouse strain, which recapitulates the expression pattern of DARC and its physiological consequences, e.g. neutropenia, that are characteristic of Duffy-negative West African individuals.

This project will study how inflammatory chemokines and their receptors expressed by the bone marrow progenitors contribute to the differentiation and proliferation of hematopoietic lineages and how the expression of DARC influences chemokine availability in the bone marrow and imprints lineage fate decisions on stem cells. Importantly, it will investigate how lack of DARC expression by the erythroid cells, as seen in Duffy-negative individuals, modifies the bone marrow homeostasis in physiology and pathophysiology.

The project will involve *in vivo* experimentation using knockout and humanized DARC transgenic murine strains, confocal microscopy, *in vitro* cell culture, gene expression arrays, FACS sorting and analysis and a multitude of functional assays of hematopoietic function.

Yr.1 - V to UBas (WP1); Yr.2 - V to NUIG (WP1); Yr. 3 - S to CTX (WP2)

ESR2, RP2 @ *UBham (Lead supervisor Brown, and with Toellner and Hughes)* – Verifying our New Model for Haematopoiesis

● The project aims to meet the need to revise textbook accounts of the generation of blood cells. We have provided a new, and highly regarded, model for blood cell development. The 30 year old 'classic' model of haematopoiesis states there are two families of cells, namely myeloid/erythroid and lymphoid. The model we favour refutes this viewpoint. We have proposed there is a series of pair-wise relationships between all lineage fates – a fate choice continuum. The project will test this model by examining various primitive haematopoietic progenitor cells to see whether there is a pattern to sub-sets of lineage potentials within single cells that fits with placing cell lineages adjacent in our pair-wise model. We will examine whether primitive progenitor cells can be divided into sub-sets with different sets of potentials by quantifying multiple mRNAs within single cells. Overt potentials of single cells will be studied using stromal cell-based cultures. If there are sub-sets of cells, we will make use of surface markers to sort them to examine their capacity to self-renew in culture.

Tasks and methodologies will include stromal-based cultures, single cell methods, FACS sorting of progenitors, lineage analyses, multiplex RT-PCR, and transcriptomics.

Yr.1 - V to UBas (WP1); Yr.2 - V to NUIG/OTP (in Galway, and WP1); Yr. 3 - S to CTX (WP2)

ESR3, RP3 @ *NUIG (Lead supervisor Ceredig, and with Brown)* – Monocytes: their Position in Haematopoiesis

● Monocytes are blood-borne myeloid cells capable of rapid differentiation into various cell types once they enter tissues. However, much controversy surrounds the nature of monocytes and an international nomenclature regarding subpopulations was only agreed in 2010. The project will investigate the differentiation plasticity of monocytes. At NUIG, we have a longstanding interest in mouse and human monocytes. Recently, we have shown that mouse and human monocyte cell lines and freshly-isolated cells express abundant transcripts for genes characteristic of stem cells and are capable of differentiating into foam cells and osteoclasts. Given the versatility of monocytes, the project will aim to provide a better understanding of *(i)* the position of monocytes in the pair-wise model and *(ii)* the differentiation plasticity of monocytes at the molecular level both in the forward (more mature) and reverse (stem cell-like) direction.

Tasks and methodologies will include FACS sorting, monocyte sub-sets, lineage analyses, transcriptomics, and systems'-biology/bioinformatics.

Yr.1 - V to UBas (WP1); Yr. 2 – S to OTP (WP1); Yr. 3 – V to CTX (WP2)

ESR4, RP4 @ *NUIG (Lead supervisor Ceredig, and with Elliman)* – MSC Diversity and Support to Haematopoiesis

● Mesenchymal stem cells (MSC) pose an enigma in that they support haematopoiesis, particularly early stages of lymphopoiesis, yet are also immunosuppressive for mature lymphocytes. At NUIG, there is considerable interest in characterising the properties of MSC, although to date this has not been studied using cloned MSC. We have a panel of mouse MSC lines which are immunosuppressive, and the project will focus on obtaining clones of fresh MSC directly from mouse bone marrow suspensions. To do so, we will make use of novel transgenic mice in which a fluorescent reporter gene is expressed in MSC so that MSC can be positively selected from bone marrow by FACS sorting. We have developed methods to improve the cloning efficiency of MSC and these will be applied to MSC freshly-isolated from bone marrow so that we can study the

capacity of cloned MSC to influence haematopoiesis and their immunosuppressive properties.

Tasks and methodologies include FACS cloning of MSC, transgenics, MSC biology, haematopoietic stem cell biology, lineage analyses, and multiplex RT-PCR.

Yr.1 – V to UBham (WP1); Yr. 2 – S to OTP (WP1) ; Yr. 3 – V to CTX (WP2)

ESR5, RP5 @ *UBas (Lead supervisor Rolink, and with Ceredig)* – Early Events in HPC Specification

● The project will examine early decision-making events during haematopoiesis by transcriptome profiling primitive haematopoietic progenitor cells. Early hematopoietic progenitors are present in the bone marrow. However, the numbers of these that can be isolated *ex vivo* are very low and therefore detailed molecular and developmental potential analyses are difficult to perform. Now we have generated a FLT3L transgenic mouse in which these hematopoietic progenitor populations are dramatically increased. Thus these mice have over 100 fold higher numbers of common myeloid precursors (CMP), common lymphoid precursors (CLP) and early progenitors with lymphoid and myeloid potentials (EPLM) in their bone marrow than non-transgenic littermates. By using these transgenic mice detailed molecular and developmental potential analyses are now very feasible.

Tasks and methodologies include FACS isolation of progenitor cells, cell transfer experiments, transcriptomics, systems-biology/bioinformatics, knock-out mice, multiplex RT-PCR, and single cell methods.

Yr.1 – V to UBham (WP1); Yr.2 – V to CTX (WP2); Yr. 3 – S to OTP/NUIG (WP1).

ESR6, RP6 @ *UBas (Lead supervisor Rolink, and with Ceredig)* – Lineage-Affiliated Specification Events

● The project will examine early decision-making events during haematopoiesis by transcriptome profiling primitive haematopoietic progenitor cells. Early hematopoietic progenitors are present in the bone marrow. However, the numbers of these that can be isolated ex vivo are very low and therefore detailed molecular and developmental potential analyses are difficult to perform. Now we have generated a FLT3L transgenic mouse in which these hematopoietic progenitor populations are dramatically increased. Thus these mice have over 100 fold higher numbers of common myeloid precursors (CMP), common lymphoid precursors (CLP) and early progenitors with lymphoid and myeloid potentials (EPLM) in their bone marrow than non-transgenic littermates. By using these transgenic mice detailed molecular and developmental potential analyses are now very feasible.

Tasks and methodologies include FACS isolation of progenitor cells, cell transfer experiments, transcriptomics, systems-biology/bioinformatics, knock-out mice, multiplex RT-PCR, and single cell methods.

Yr.1 – V to UBham (WP1); Yr.2 – V to NUIG (WP1); Yr. 3 – S to PRI (WP2).

Work @ *UMDNJ (Lead supervisor Studzinski)* – miRNAs: New Players in Cell Fate

● *Some ESRs will visit Studzinski (USA-NIH grant funded) for training in miRNA technologies and to integrate miRs with ITN work*. miR-223, miR-181, and miR-32 are important to myelopoiesis. miR-223 activation is required for ATRA-induced granulocytic differentiation of human cells in culture, and miR-223 targets TFs that are important to differentiation: C/EBPα (***link to work by ESR9, V in Yr. 2***), RelB, Mef2c and nuclear factor I/A. miR-181 family members target the cell cycle inhibitor $p27^{KIP1}$ and reducing miR-181a expression accelerated the initial stages of monocyte differentiation, suggesting that miR-181a can stabilize a cell fate decision by enhancing $p27^{KIP}$

expression. During monocyte differentiation miR-32 is up-regulated and enhances cell survival by decreasing the level of the pro-apoptosis protein Bim. miR-182 targets RARγ (***link to work by ESR8, V in Yr. 1***). **Innovation:** Inhibiting miR-181 and/or miR-32 expression may enhance the efficacy of current therapy of AML. Studzinski is also expert on agents that sensitize AML cells to 1,25-$(OH)_2D_3$ (***ESR9 to V in Yr. 2; ESR10 to V in Yr. 2, & ERS11 to V in Yr. 1***).

Visits: Yr.1 – V from ESR8 and ESR11; Yr.2 – V from ESR9 and ESR10

ESR7, RP7 @ *OTP (Lead supervisor Elliman, and with Ceredig)* – Stromal Cells: their Roles in Haematopoiesis

● Mesenchymal human adult tissue-derived Stromal Stem Cells (SSC) is a mixed population of plastic-adherent (PA) cells that can be isolated from bone marrow, placenta and adipose tissue. PA-SSCs secrete potent immune-modulatory, angiogenic and anti-microbial factors. Preclinical and clinical studies demonstrate that PA-SSC elicit potent immunomodulatory and angiopoietic responses *in vivo*. Current clinical trials are testing PA-SSC in 40 distinct autoimmune and ischemic diseases. To date, ~100 PA-SSC clinical trials have met safety endpoints, with several Phase 2/3 SSC efficacy trials close to conclusion. More notably in May 2012, the US-based biotech Osiris received market approval in Canada and New Zealand for a proprietary PA-SSC formulation (Prochymal) to treat specific cases of graft versus host disease (GvHD) – the world's first market approved allogeneic ("off-the-shelf") stem cell medicine.

ORB1 - from FP7 discovery to EMA compliant therapeutic: Here in Europe, recent EMA guidelines indicate that more stringent methods of SSC purification and characterisation are necessary for medicinal use. During the FP7 project, PURSTEM (ended April 2012), Orbsen advanced the state-of-the-art towards meeting these EMA criteria by developing the novel ORB1 antibody-based method for prospectively purifying SSC with class-leading levels of purity. ORB1 prospectively isolates comparable, equivalent $ORB1^{+ve}$SSC from multiple species' (human, horse, mouse and rat) tissues – a first for SSC technologies. Moreover, ORB1 may be used to isolate defined SSC from multiple tissues, including bone marrow, fat and placenta – reducing manufacturing dependence on a single, limiting tissue sources that require surgery to obtain. The FP7-funded discovery of ORB1 represents a novel, class-leading and tissue-independent cell isolation technology that enables the development of ORB1-based cell therapies. No equivalent cell technology is currently available. The therapeutic potential of the $ORB1^{+ve}$SSC is being evaluated in the EU FP7 REDDSTAR project (www.reddstar.eu) which will advance the $ORB1^{+ve}$SSC to a Phase 1b clinical trial. To inform the ORB1 route to the clinic we must define the role of $ORB1^{+ve}$stromal cells *in vivo*. To that end we are generating a series of ORB1 transgenic models in collaboration with Prof. Douglas T. Fearon at the University of Cambridge. The lineage-specific deletion of ORB1 protein and ablation of the $ORB1^{+ve}$stromal cells will enable the elucidation of the specific roles of this perivascular stromal cell in the homeostasis and pathologies of haematopoiesis.

Tasks and methodologies include transgenics, histology, FACS, cytometry, immunological assays, stem cell technologies, progenitor cell assays, RNA-seq transcriptomics,

Yr.1 – V to UBas (WP1); Yr.2 – S to NUIG (WP1); Yr. 3 – V to PRI (WP2)

Work Package 2: Pre-clinical development towards new Differentiation Therapies for AML

ESR8, RP8 @ *ICR (Lead supervisor Petrie, and with Chesler)* - New Retinoid-based Therapies for AML and Neuroblastoma

● The retinoid all-*trans*-retinoic acid (ATRA) possesses potent anti-cancer activity in acute promyelocytic leukaemia (APL) a subtype of acute myeloid leukemia (AML). Retinoid-based differentiation therapy is curative in APL with a complete remission rate of 94% and a long-term survival rate greater than 90%. Recently, we demonstrated a critical role for the histone H3 lysine 4 mono/di demethylase LSD1 as a negative regulator of the ATRA-mediated myeloid differentiation pathway. Treatment with LSD1 inhibitors (LSD1i) dramatically potentiated the pro-differentiative effects of ATRA with associated gene-specific increases in histone methylation, and greatly impaired engraftment of primary AML cells from patients in NOD.*SCID* gamma mice, suggesting that ATRA/LSD1i targets cancer-initiating cells. Combinatorial treatment also synergistically down-regulated expression of the MYC oncoprotein, which AML cells have been shown to be "addicted" to. This work identified LSD1 as an important therapeutic target and highlighted the potential for drugs targeting aberrant epigenetics in combination with retinoids.

Like AML, neuroblastoma (an aggressive neural crest-derived malignancy of infants and young children) can be considered to arise at least in part from a failure to properly implement developmental retinoid differentiation pathways. Another retinoid (13-*cis*-RA) is used to treat minimal residual disease in high-risk neuroblastomas, which are characterized by amplification of the *MYCN* oncogene. Also in common with AML, neuroblastomas with high levels of MYCN are addicted to its expression. A key downstream target of MYC oncoproteins in tumourigenesis is ornithine decarboxylase, the rate-limiting enzyme of polyamine biosynthesis and recent work suggest that agents that target the polyamine pathway show efficacy in high-risk, *MYCN*-amplified neuroblastoma. Lastly, LSD1 expression has been correlated with adverse outcome and is inversely correlated with differentiation in neueroblastomas.

This project will investigate the clinical potential of combinatorial use of retinoids with polyamine analogues, dual inhibitors of LSD1 and polyamine biosynthesis, as well as tranylcypromine analogs, in AML and high-risk neuroblastoma.

For this highly translational project, the researcher will utilize molecular biological techniques, including next generation sequencing and advanced imaging technologies, as well as xenografts and genetically engineered mouse models of neuroblastoma.

Yr.1 – V to UMDNJ (***miR training***, WP1); Yr.2 – V to UBas (WP1); Yr. 3 – S to CTX (WP2)

ESR9, RP9 @ *UWroc (Lead supervisor Marcinkowska, and with Kutner)* – Why do only Some AML patients' cells Respond to 1,25-$(OH)_2D_3$?

● There is an increasing need to devise milder treatments for older patients with acute myeloid leukaemia (AML), and other cancers. In AML, and other acute leukaemias, differentiation is impaired resulting in the accumulation of immature cells. One approach to treating acute leukaemia, termed differentiation therapy, is to find ways of alleviating the block in cell differentiation to allow cells to terminally mature. An agent that has be used to drive differentiation of a wide variety of cell types is vitamin D_3 (1,25-$(OH)_2D_3$) and recent work by Marcinkowska has recently identified a sub-group of AML patients that respond to vitamin D_3. The project will investigate why some patients' AML cells respond to vitamin D_3 whilst other patients' cells are unresponsive to the differentiating effects of vitamin D_3. This will involve examining vitamin D receptor expression, signaling events upstream and

downstream of this receptor, transcription factor-mediated events, and epigenetic regulation of gene promoters. The project will also examine the use of vitamin D_3-sensitizing agents to attempt to drive differentiation of resistant patients' cells.

Tasks and methodologies will include leukaemia cell differentiation, cellular signaling, transcription factor technologies, differentiation sensitizing agents, and microRNAs.

Yr.1 – S to PRI (WP1); Yr.2 – V to UMDNJ (WP1); Yr. 3 – V to UBham/CTX in Bham (WP2)

ESR10, RP10 @ *PRI (Lead supervisor Kutner, and with Marcinkowska)* – Design and Synthesis of Vitamin D Analogs with Anti-Cancer Potential

● One approach to treating acute leukaemia, termed differentiation therapy, is to find ways of alleviating the block in cell differentiation to allow cells to terminally mature. An agent that has to be used to drive differentiation of a wide variety of cell types is the active form of vitamin D_3 (1,25-$(OH)_2D_3$). However, clinical use of 1,25-$(OH)_2D_3$ is limited by its high calcemic potential. The project aims to design low calcemic analogs that retain cell differentiation potency. The design of new analogs of 1,25-$(OH)_2D_3$ will be based on the 3D structure of the ligand binding domain of the vitamin D receptor (VDR-LBD), to ensure a specific fit between the new analog and the VDR-LBD amino acid residues. New hybrid analogs, modified in both distinct fragments of the vitamin D molecule, will be obtained by a novel convergent synthetic strategy from the advanced key intermediates. The new compounds will be tested against a variety of leukaemia cells and leukaemic cell lines to determine their therapeutic potential.

Tasks and methodologies will include medicinal chemistry of vitamins D, analytical chemistry to confirm identity, leukaemic cell differentiation, and the use of vitamin D sensitizing agents.

Yr.1 – V to UWroc (WP2); Yr.2 – V to UMDNJ (WP1); Yr. 3 – S to ICR (WP2)

ESR11, RP11 @ *PRI (Lead supervisor Kutner, and with Marcinkowska)* – Synthesis and Evaluation of Vitamin D Analogs for Anti-Cancer Combination Therapy

● An agent that has to be used to drive differentiation of a wide variety of cell types is the active form of vitamin D_3 (1,25-$(OH)_2D_3$). However, clinical use of 1,25-$(OH)_2D_3$ is limited by its high calcemic potential. The project aims to design low calcemic analogs that retain cell differentiation potency. The design of the new analogs of 1,25-$(OH)_2D_3$ of will be based on the 3D structure of the ligand binding domain of vitamin D receptor (VDR-LBD), to ensure a specific fit between the new analog and the VDR-LBD amino acid residues. New *des*-CD analogs, named retiferols, modified in the CD-ring system, will be synthesized by a novel convergent strategy from the advanced key intermediates. The project will investigate the potential therapeutic benefit of combining new low-calcemic analogs of vitamins D_3 with lowered doses of standard chemotherapeutic agents. The combinations will be tested against leukaemia and solid tumour cell lines. We will then examine the modes of action of agents used alone and in combination, including influences on: *(i)* cell status (cell cycle, differentiation and apoptosis), *(ii)* cell signaling pathways, *(iii)* the molecules that control cell cycle and survival, and *(iv)* the level of expression of key transcription factors.

Tasks and methodologies will include synthetic and medicinal chemistry of low-calcemic analogs of vitamins D_3, analytical chemistry to confirm structure, cell differentiation, cell-cycle control and transcription factor technologies.

Yr.1 – V to UMDNJ (WP1); Yr.2 – V to UWroc (WP2); Yr. 3 – S to ICR (WP2)

ESR12, RP12 @ *CTX (Lead supervisor Barnes)* – Discovery and development of Novel Chemical Entities (NCEs) towards lead candidate status for the treatment of cancer

- The objective of the project is to discover and develop novel chemical entities (NCEs) that have potential to treat leukaemia and other types of cancer. The project will offer a broad training within a SME environment (Celentyx Ltd; www.celentyx.com) concerning the discovery and pre-clinical development of a potential therapeutic agent. The training will also include experience of how a SME develops a NCE to maximise the likelihood of subsequent regulatory approval at the Investigational New Drug (IND) stage and subsequent New Drug Application (NDA) stage.

Tasks and methodologies include Target Product Profile for NCEs, use of animal models, protocols for data package, use of drug re-profiling technology platform, and evaluation of retinoids, novel demethylase inhibitors, and vitamins D3.

Yr.1 – V to ICR (WP2); Yr.2 – V to PRI (WP2); Yr.3 – S to OTP/NUIG in Galway (WP1)

5 INTRODUCTIONS TO THE ITN PROGRAMME AND DOCTORAL STUDIES

After settling in, ESRs will attend the 1st ITN Training School which will provide an overview of ITN research and training on project governance, managing deliverables, and research ethics. Universities/institutes have well-organised Graduate Schools, and ESRs will have to attend their School's **introduction to doctoral studies**. One hour lectures (titles vary at institutions) cover: ● Graduate Services and Skills Development; ● Careers and Employability; ● Informing the Public about Science and Medicine; ● Presentation Skills; ● Searching Electronic Journals and Referencing; ● How to get published; ● Ethics when using Patients and Human Tissue in Research; ● Ethics when using Animals in Research, and ● Health & Safety in the Workplace.

All ESRs will be trained in the use of statistics in the 1st term of their PhD study. An on-line UBham Masters module 'Research Methods and Statistics' will be made available to **all ESRs** and, for example, the UBham Graduate School training comprises 11 lectures, covering research design and a range of statistical tests. Institutions also have drop-in expert advice on analysing data.

Local Staff Development Units (SDU) will provide support to ESRs throughout training. SDU courses (titles vary at institutions) will be available to all ESRs and integrated into training as prescribed by CDPs. Courses providing **training in communication skills** include: ● Effective Communication and Public Speaking, ● Survival Kit for Teaching, ● Small Group Teaching, and ● Lecturing Skills for Research Staff. Courses on **learning, IT and writing skills** include: ● Alternative Ways of Learning, ● Working for your Research Degree, ● Managing Time, ● IT skills programmes (e.g. Databases, WebCT, Excel), ● Writing for Publication, and ● Thesis Presentation and Reference Management. **Life-skills courses** include: ● Developing Assertiveness at Work, ● Men's Development Programme, ● Springboard Woman's Development Programme, and ●Impact for Women.

6 ITN TRAINING SCHOOLS

All ESRs will attend four **ITN Training Schools**. At Technology Workshops (TWs) 1 to 10, ESRs will gain experience of a range of discipline-related technologies. Generic Research Skills Courses (GRSCs) 1 to 9 will ensure that ESRs engage with company practices, are well-rounded scientists, and able to communicate their work to the wider public. Course certificates will add to career portfolios.

Summary of the Training provided at ITN Training Schools

1st ITN Training School - UBham, @ month 2, and 4 days – focuses on: *(i)* generic and transferable skills (management training, intellectual property and ethics), and *(ii)* overviews of haematopoiesis and drug development

- ***Day 1 (½ day) GRSC1 Management: Governance*** – This workshop will cover the consortium agreement, fundamental and intellectual rights, **patenting**, and gender and minority issues. As a drug research project progresses, its changing position on the risk/opportunity matrix determines appropriate business models and corporate arrangements. Presentations will discover the risk and opportunity profiles that a business consultant would see in drug development and instil awareness of the skills in integration of business, risk management and scientific skills that researchers will need if they are to develop and market a drug. ***Delivered by:*** Smith and HPR
- ***Day 1 (½ day) GRSC2 Management: Project Delivery*** – This workshop will cover the management of uncertainty in the delivery of projects, how this can lead to performance failure and completion delay, how to identify and understand risks, and the importance of coupling these to structured management. Presentations will cover risk management processes required to: *(i)* establish the process of drug research and launch into the private sector, *(ii)* govern the conduct of increments of pure research, and *(iii)* later govern the progressive involvement of the private sector under the determined corporate arrangements. ***Delivered by:*** Smith and HPR
- ***Day 2 (½ day) GRSC3 Research Ethics*** – Lectures and discussion on ethics to the use of human materials and of animals in research, including how to fill in a research ethics application form for a local ethics committee. ***Delivered by:*** Dr J Jones, Senior Lecturer in Biomedical Ethics (UBham) & C Neumann, Former Chair of Local Research Ethics Committee, Birmingham.
- ***Day 2 (½ day) Research Ethics Clinic*** – One-to-one clinic with each ESR to examine ethics pertaining to their RP. ***With:*** Dr Jones, C Neumann, and RP Lead
- ***Day 3 (½ day) AKC1 Haematopoiesis*** – Pathfinder sessions on blood cells (Ceredig), immune cell functions (Gordon), haematopoiesis (Brown), cell differentiation (Hughes), cellular signalling (Michell), chemokines and cytokines (Rot), and leukaemia (Zelent & Moss)
- ***Day 3 (½ day) GRSC4 Drug Manufacturing Practice*** – Visit to CTX (UBham campus) for pathfinder sessions on how to move a NCE towards drug development, to include: *(i)* the obstacles and benefits of different formulations to aid delivery of an effective therapeutic with minimal side-effects, *(ii)* how to assess the pharmaceutical suitability of a NCE *via* criteria within a Target Product Profile to generate an attractive data package, and *(iii)* soliciting a license. ***Delivered by:*** Barnes, Kutner, Gordon, and the External Commercialisation Board @UBham
- ***Day 4 ITN Research Day*** – Meeting between all ESR and RP leads on research strategies

2nd ITN Training School - UBas, @ month 12, and 5 days – focuses on: *(i)* communication training, and *(ii)* genomics. Day 5 will focus on outreach activities (see B.5.9)

- ***Day 1 (full day) GRSC5 Effective Communication*** –This workshop, ***delivered by:*** SDU @ UBas, will involve *(i)* presentations on getting ideas across, public speaking and lecturing, and *(ii)* ESRs giving a short talk on a general topic which will be video recorded to provide personalised feedback.

ESRs will also be strongly encouraged to attend host institution training courses.

- ***Day 2 (½ day) TW1 Transcriptome Profiling*** - Lectures on transcriptome technologies, and use to describe haematopoiesis. Computer cluster workshop on databases and analytical tools. ***Delivered by:*** Rolink and members of Systems Biology of Cell Differentiation Group
- ***Day 2 (½ day) TW2 Bioinformatics and Systems Modelling*** - Lectures and discussion on bioinformatics and systems'-biology and the use of these strategies to study cell development. Computer cluster workshop on the use of various tools to examine databases to model systems. ***Delivered by:*** Rolink and other members of Systems Biology of Cell Differentiation Group
- ***Day 3 (½ day) TW3 Technologies for Epigenetic Analyses*** - Lectures and group discussion on epigenetic processes in normal development and cancer, to include current technologies for gene-specific and genome-wide epigenetic analysis. ***Delivered by:*** Zelent and Dr Petrie
- ***Day 3 (½ day) TW4 Exploiting Retinoid Receptor*** - Lectures on retinoids/RARs and cell development and RAR perturbations in malignancies. Demonstrations/wet laboratory to cover measurement of the levels and sub-cellular location of RARs, reducing expression of RARs and the influence of retinoids on cells. ***Delivered by:*** Zelent and Dr Petrie
- ***Day 4 ITN Research Day*** – 15 minute talks by ESRs to local ESRs/academic staff, followed by a closed ITN forum – all ESRs and RP leads –on year 2 activities.
- ***Day 5 Public Open Day*** – Poster session and forum to engage interested public groups.

Note: At Schools 2 to 4, the Research and Training Committees will meet between days 1-3 and the Supervisory Board (SB) on day 5, and post day's activities.

3rd ITN Training School - UWroc, @ month 24, and 5 days – focuses on: *(i)* Grant-writing-craftsmanship, *(ii)* molecular techniques used to analyse cell constituents, and *(iii)* medicinal chemistry. Day 5 will focus on outreach activities

- ***Day 1 (½ day) GRSC6 Grant-writing-craftsmanship*** – Presentations on how to write a project grant. ***Delivered by:*** participants, who review for major grant awarding bodies. Also, participants' universities run grant-writing workshops, pertaining to e.g. in the UK; MRC, BBSRC.
- ***Day 1 (½ day) GRSC7 Grant-writing Clinic*** – Prior ESRs will have written a short request to their Scientific Projects Committee. Tutorials (4 ERSs) to review submissions for feedback. ***Delivery by:*** Studzinski (New Jersey State Panel), and Ceredig and Brown (university panels)
- ***Day 2 (½ day) TW5 Transcription Factor Technologies*** - Lectures on TF circuitries and 1,25-$(OH)_2D_3$-driven signalling. Demonstrations to cover measurement of TF protein and mRNA levels, intracellular localization (confocal microscopy), interactions (co-immunoprecipitation), post-translational modifications (Western blots), activity (EMSA shift and super-shift assays) and silencing and forcing expression. ***Delivered by:*** Marcinkowska, Studzinski, Zelent, Dr Gocek, Ms Burska
- ***Day 2 (½ day) TW6 microRNA Technologie*** - Lectures and discussion on the importance of miRs to cell cycle control and differentiation. Demonstrations/wet-lab to cover identification and reducing expression of miR. ***Delivered by:*** Studzinski, Marcinkowska, Elliman, Dr Gocek
- ***Day 3 (½ day) TW7 Multiplex RT-PCR*** – Demonstrations/ wet-lab on handling single cells and measurement of multiple mRNAs. ***Delivered by:*** Brown, Drs Hughes and Toellner
- ***Day 3 (½ day) TW8 Synthetic and Analytical Chemistry*** - Lectures and group discussion on 1,25-$(OH)_2D_3$ and normal development, the use of 1,25-$(OH)_2D_3$ to treat malignancies, the synthetic chemistry to prepare analogs of 1,25-$(OH)_2D_3$ in quantity, the convergent strategy of synthesis (developed by Kutner), and analytical chemistry to confirm identity and homogeneity. ***Delivered by:*** Kutner, Studzinski, Marcinkowska, Drs Chodynski and Dams
- ***Day 4 ITN Research Day*** – 15 minute talks by ESRs to local ESRs/academic staff, followed by a closed ITN forum – all ESRs and RP leads –on year 3 activities.
- ***Day 5 Public Open Day*** – Poster session and forum to engage interested public groups.

4th ITN Training School - NUIG, @ month 35, and 5 days – focuses on: *(i)* cell purification, and *(ii)* manufacturing practices. Day 5 will focus on outreach.

● ***Day 1 (full day) TW9 Cell Phenotyping and Sorting*** – FACS hub training on multi-colour phenotyping by FACS and sorting of HPC as bulk cells and plating as single cells. Tutorials on software to analyse flow cytometry data and principles of limit dilution analysis. ***Delivered by:*** Ceredig, Dr Bianco (Univ.Coll. Dublin), Dr Dessing (Becton Dickinson Europe), and REMEDI staff
● ***Day 2 (½ day) TW10 Stem Cell Technologies*** – Training visit to OTP (NUIG campus) for lectures and demonstrations on work to develop new reagents, technologies and regimen for manufacturing clinical grade mesenchymal/stromal stem cell therapeutics. ***Delivered by:*** Elliman, Prof O'Brien, Prof Barry and GMP Team
● ***Day 2 (½ day) GRSC8 SMEs: Spinning Out*** – Pharmaceutical training visit to OTP for lectures and group discussion on SMEs. This will include how to procure equity investment, set-up infrastructure, regulatory issues, management, risks, the importance of pipeline developments and clinical trials, and sustaining long term future growth. ***Delivered by:*** Barnes, Elliman, Prof Gordon, Prof O'Brien and Prof Barry
● ***Day 3 (full day) GRSC9 GMP Production of Cell Therapeutics*** - Workshop and lectures from OTP GMP Facility Management team on *(i)* EU legislation covering manufacture of Advanced Therapeutic Medicinal Products including stem cell therapeutics (Dr. Karen Duffy, Facility Manager) *(ii)* GMP Manufacture of MSC clinical product at OTP (Aoife Duffy, Production Manager) and *(iii)* Quality Control and release of clinical product (Marc Eglon, Quality Manager) and *(iv)* Cell therapies and clinical trials (Elliman, Head R&D/Operations).
In addition, a 3 day course will provide a qualification in ***GMP Manufacture of Clinical Stem Cell Therapeutics***. Practical on-site training courses will be offered in Gowning Qualification within the GMP Facility. If successful, the candidate will be offered a series of lectures and practical courses in Validation of Aseptic Technique***. Delivered by:*** Elliman and OTP GMP Management team
● ***Day 4 ITN Research Day*** – 15 minute talks by ESRs to local ESRs/academic staff, followed by a closed ITN forum – all ESRs and RP leads –on year 4 activities.
● ***Day 5 Public Open Day*** – Poster session and forum to engage interested public groups.

7 OTHER COURSES

Modules to institutionally-accredited courses (Research Technology Course (RTC) and Advanced Knowledge Course (AKC) are directly relevant to the ITN. Ceredig and Rolink lead on some of the modules (see Table). Also, twice a year Barnes runs a two day course 'Commercialising Academic Medical Research'. This course and Masters modules will be available **each year throughout DECIDE to all ESRs**. Host institutions will provide a transcript of European Credit Transfer System credits completed.

Institutionally-accredited Advanced Training Courses made available to Trainees

Course Title[1]	**Location - Led by Participant**
Research Technology Courses (RTC) – Lectures and practical classes	
RTC1 Laboratory Research Methods (20 credits)[2]	UBham
RTC2 Advanced Research Techniques (10 ECTS)[3]	NUIG
RTC3 Practical Immunology (40 hours)[4]	UBas – Rolink
Generic Research Skills Courses (GRSC) – Lectures and discussion	
GRSC10 Commercialising Academic Medical Research	UBham - Barnes
GRSC11 Generic Research Training (10 credits)[2]	UBham
GRSC12 Introduction to business (10 ECTS)[3]	NUIG
Advanced Knowledge Courses (AKC) – Lectures and discussion	
AKC2 Immune System: Regulation in Health & Disease[2]	UBham
AKC3 Graduate Immunology Course[4]	NUIG – Ceredig
AKC4 Master Classes in Immunology[4]	NUIG - Ceredig
AKC5 Basic Immunology (14 hours)[4]	UBas – Rolink
AKC6 Advanced Immunology (40 hours)[4]	UBas – Rolink
AKC7 Stem Cell & Regenerative Medicine (10 credits)[2]	UBham
AKC8 Tissue Engineering (10 ECTS)[3]	NUIG
AKC9 Regenerative Medicine (10 ECTS)[3]	NUIG
AKC10 Translational Medicine (10 ECTS)[3]	NUIG
[1] Each course involves local researchers, including ITN participants; [2] component of the *Masters in Biomedical Research*; [3] component of the *MSc Regenerative Medicine*; [4] graduate courses at NUIG and UBas Details of each module are available at course web-sites.	

8 ANNUAL PROGRESS REVIEWS

The annual review of progress is an important "staging post" where you and we can evaluate where you have got to and where you are going with your studies. It also provides valuable experience in scientific writing (for preparation of your thesis) and discussing your work with examiners (for your final viva).

Year 1 and Year 2
The process starts with submission of a short report (by mid-June for Year 1, end-April for Year 2. An Internal Expert (nominated by your Supervisor) and your School Coordinator will read your report and then discuss your work with you in a "viva". You need to bring a completed Progress Review Form, which has been completed by yourself and your Supervisor, along to the viva. Feedback on the report and viva is provided to Student and Supervisor. This is all explained in a Year 1 memo and Year 2 memo.

The Report
Guidance on the purpose, style and timing of 1st and 2nd year reports is communicated to you by memo early in the year (see the Guidelines). Take advice from your Supervisor, and get them to read and comment on a draft version.

The Viva
Your Supervisor will have nominated an Internal Expert in your field, from outside your research group, who will read your report and, in effect, act as an Internal Examiner. It may be that this same person will act as your Internal Examiner when you finally submit your thesis (but this is not necessarily the case). The Internal Expert and your School Coordinator will meet with you, to discuss the report and any issues that arise. Although primarily informing us about your work and how you are progressing the meeting also serves the important function of providing you with independent feedback on your research. You will receive a short summary report on the key points afterwards.

Progress Decisions
Before the "viva" on your report with your Internal Expert and School Coordinator, you and your Supervisor must meet to formally review progress and to complete the Progress Review Form. The final recommendation regarding progress is made by your Supervisor and recorded, along with other issues discussed at the progress review meeting, on the Progress Review Form. After the "viva" a recommendation is agreed by a School Officers (Director of Graduate Studies and School Coordinators) and communicated to the University Academic Office.

Year 3
No report is required. The progress is reviewed in a short meeting between Student and School Coordinator that seeks to ensure that work is coming to a satisfactory conclusion, and that the write-up stage is approaching. As in previous years a Progress Review Form needs to be completed following a meeting between Student and Supervisor.

Guidelines to 1st and 2nd year PhD reports

The style of the report

The report should be written in the style of a thesis, so that students gain experience in writing in this format. The report should have an introduction, materials and methods, results section and discussion of the findings. References are best presented as outlined in PhD regulations (names of authors and year of publication in the text, and alphabetically in the reference list) - this would allow students to use the reference list when preparing their thesis. In the results section, the figures and tables should have appropriate titles and legends, and are best integrated into the account of the results. It is recommended that you have a look at someone's PhD to see how this is all done or talk to your supervisor about presenting a thesis.

The timing of the reports and of the review process

The timing of the reports and reviews is important. In the end, we have to make a progress decision, and re-register PhD students via the University computer. Student Services (Admissions) are pre-occupied during the entire summer dealing with new admissions to the University. So, we have to complete our PhD registrations before all this takes place. There are two review processes for PhD students. We have our internal review: the students' reports, viva, and feedback reports written by the Coordinators and experts (provided to students and supervisors). We also have to fill in the University progress review form - this is a three-section form (comments from students, supervisors and Coordinators).

After submission of your PhD and on the day of your viva

Prior to the viva for the degree of PhD students are normally expected to present the findings from their studies as a pre-viva seminar to an audience of academic staff, fellow students and the internal and external examiners. This is an excellent opportunity to showcase your work. Your Supervisor will host this event, and there will be no questions from the Supervisor and examiners. Members of the audience may ask questions, and the supervisor is not allowed to answer the questions on behalf of the student.

MEMORANDUM

From	Geoffrey Brown Coordinator DECIDE			To	All 1st/2nd year PhD students
Date	29/01/2013	Tel	44082	cc	
Email	g.brown@bham.ac.uk	Fax	43599		

PhD students – ANNUAL PROGRESS REVIEWS

Dear Everyone

This is just a quick note to remind you all that the annual progress reviews for PhD students are approaching.

You will need to start preparing a report for your interview with an "*internal expert*" in the area of your research (to be nominated by your Supervisor), and your School Coordinator in June. The report should be in the style of a thesis and around 35 pages in length (see attached guidelines).

During the student annual review process there is some confusion about the Progress Review Form. This is the form that the University obliges us to fill in. Importantly, this is also the form that feeds information from the Supervisor and from the student into our review process.

As specified on the form, the student fills in their bit, the Supervisor fills in their bit, the Supervisor makes a recommendation as to progression, and this recommendation is then signed off by the School Graduate School Officer after the progress review meeting.

You need also to fill in a form which assesses your training needs. Please fill this in with your Supervisor so that your Supervisor is aware of your training requirements.

Can students please come to their viva with: (i) a completed Progress Review form, filled in by their Supervisor and with the Supervisor's signatures, and (ii) a completed Training Needs Analysis form so we can look at training that you feel you require.

Two copies of your report should be submitted to your local postgraduate administrator by no later than Friday 14th June 2013.

With kind regards,

9 WELFARE

Each University will provide students with a designated Mentor who is formally appointed by one of the University Graduate School Officers, usually the Director of Graduate Studies. The Mentor will normally be a member of staff from the university although not a member of the student's research group. Your Mentor will tell you about the avenues for welfare support that are available at the University at which you are registered for a PhD. The role of a Mentor is mainly pastoral, not academic. We recognise that as mature students, you have to balance academic and other commitments, and the welfare provision throughout your PhD is intended to help you reach that balance in a productive and supportive way.

Role of the mentor:
The Mentor will provide general advice and guidance about support available at your University to assist in your research studies. Although advice may touch on academic matters it will not cut across routine supervision. Your mentor will be able to advise you about any development opportunities and societies available to you locally. Your mentor will also be able to advise you about support available through your University should you encounter any personal difficulties during your period of research study.

The Mentor will meet with the student at least once each session – for the first time within a fortnight of the student's first registration and subsequently at the beginning of each session. Other meetings may take place at the request of either the student or the Mentor. The Mentor may also, on occasion, provide support to the supervisor. The Mentor may contribute to the annual progress review, although this will not be a routine requirement.

Meetings between Mentor and student will normally be informal, but at least one meeting each session should be recorded using the Mentor Record form provided by the university's Graduate School (to help ensure that the process is operating). You may wish to disclose sensitive personal information to your mentor, such as medical conditions which may impact on your ability to study successfully. You need to discuss with your mentor the extent to which this personal information can be disclosed, if at all. You may wish any sensitive personal information which impacts on your ability to study to be disclosed to a limited number of people so that you can access appropriate support from within your University. In any case, you and your mentor need to be very clear about the boundary of what can be disclosed, and to whom, and to document this. If your mentor is uncertain what support is available, they can seek advice from the ITN Senior Tutor (Dr June Jones j.jones.1@bham.ac.uk) in strict confidence.

During your meetings, your mentor will ask you about your accommodation, your travel to the University, your family support structures and obligations etc. Discussing these subjects may seem unrelated to your research study, but experience shows us that these issues can impact on student success. If you are facing challenges in any area of your life, please consider informing your mentor about this so that they can advise you about support which may be available.

DECIDE

MENTOR RECORD FORM

(This form is to record discussion between your mentor and any required action)

Student name: …… Registration Number: ……..

Mentor: ……..

Supervisor(s): ……

Date of Registration: ……

Date of Meeting: ……..

Outline of discussion:

Action taken (if appropriate):

Signed: ……..

(Mentor)

10 ABOUT PARTICIPATING CENTRES

Full Partner 1, University of Birmingham (UBham)

The College of Medical and Dental Science is one of the best UK Medical Schools. ESRs will be members of Stem Cell Biology and Gene Regulation (in Immunity and Infection (annual research income €9.3M)) and the UBham Stem Cell Centre which are housed in the world-class Institute of Biomedical Research.

Full Partner 2, National University of Ireland, Galway (NUIG)

NUIG is one of Ireland's foremost centres of research in medical sciences. NUIG is also part of Systems Biology Ireland, which has a focus of attention on cell fate decisions. In 1999, the National Centre for Biomedical Engineering Science became a major hub for biomedical research at NUIG, with over 500 researchers. Trainees will be a member of Regenerative Medicine Institute (REMEDI).

Full Partner 3, The University of Basel (UBas)

The University of Basel (est. 1460) has 3500 staff and an annual budget of €387M. **Prof. Antonius Rolink's** Developmental and Molecular Immunology Group, a key component of the Department of Biomedicine, works closely with the Systems Biology of Cell Plasticity in Health and Disease Initiative (coordinated by Dr. Gasser, Friedrich Miescher Institute) to study the epigenetics of stem cells.

Full Partner 4, The University of Wroclaw (UWroc)

UWroc is one of the four large and long-established universities in Poland. The Faculty of Biotechnology (founded in 2006) has 18 Professors, 29 doctors, 22 technicians/administrative staff, and ~ 50 PhD students. Experimental Haematology and Immunology (EH & I) is a new group (in Biotechnology).

Full Partner 5, Orbsen Therapeutics Ltd (OTP)

OTP is an EU and Enterprise Ireland backed Regenerative Medicine R&D company founded by **Professors Tim O'Brien** and **Frank Barry** and that spun-out of NUIG in 2007. R&D focuses on identifying reagents, technologies and regimen that reduce the costs and improve yield in manufacturing clinical grade (GMP) mesenchymal/stromal stem cell therapeutics.

Full Partner 6, Institute of Cancer Research, London (ICR)

From its foundation in 1909 as a small research department of the Royal Marsden Hospital, the ICR has grown to become one of the world's foremost independent cancer research institutes.

Full Partner 7, Pharmaceutical Research Institute, Warsaw (PRI)

PRI is Poland's leading R&D governmental center and specializes in the development of pharmaceutical technologies, including both active pharmaceutical ingredients (API) and finished dosage forms. Vitamin D research is housed in a world-class laboratory, and manufacturing of vitamins D is located in a GMP complying API facility.

Full Partner 8, Celentyx Ltd (CTX)

CTX (www.celetyx.com) is a venture-capital backed pharmaceutical R&D and Service company that spun-out of the UBham (in 2004). The company specializes in identifying new indications for drugs that are already marketed ('drug reprofiling') and novel compounds that impact on immune/haematological pathologies. CTX strategic relationships include three with top 20 pharmaceutical companies.

Associate Partner 1, New Jersey Medical School, USA (UMDNJ)

The New Jersey Medical School is one of the USA's foremost medical schools and has a long established research excellence in Medicine and Health Sciences. Significant expertise in molecular biology is in the Laboratory of Pathology and Medicine, with a group focusing on the Cell and Molecular Biology of Cancer.

Associate Partner 2, High-Point Rendel Ltd (HPR)

HPR is a British consultancy with 70 to 90% of its assignments carried out outside the UK for international clients. It specialises in assisting clients in the management of uncertainty in the delivery of capital projects that often suffer performance failure and completion delay. The cause of this is often a failure of management to properly understand/ assess risks and implement a systematic risk management strategy. HPR has expertise in assisting clients to introduce risk evaluation and mitigation procedures into project management processes at project initiation or for turn round.

11 AFTER DECIDE

An essential role of RP leads during DECIDE will be to prepare ESRs for a future career. ESRs will be encouraged to use career planning resources (e.g. UK Research Councils 'Career Mapping Tool' and http://www.vitae.ac.uk) and Personal Development Officers at each institution will advise on career development, interview techniques and preparing a *c.v.* Company partners will advise ESRs on preparing for direct employment by this sector.

Importantly, the DECIDE Partners will aim to provide a lifetime network of support, and contacts, as ESRs enter their careers as scientists or in some other profession. Post-DECIDE, the Supervisory Board will examine the impact of our training through follow up monitoring of publications and career progression. We will solicit feedback from trainees and participants through questionnaires and run a focus group for these persons to share their experience of DECIDE.

APPENDIX I – PLAGIARISM
Avoiding Plagiarism: A Learning Contract

Student name …….

I have received the guidance notes "Learning in the University of Birmingham and Plagiarism". I have read them and have had the chance to discuss them with a tutor.

I acknowledge that, as a student of this University, I should work to develop my understanding of plagiarism: its meaning, significance and implications.

I agree to participate in the provision made available by the University and my School to develop good academic practice and an understanding of ways of referencing the work of others.

I agree to take steps to avoid plagiarism, including seeking information on the rules and practices related to plagiarism which applies to my work.

I agree to adhere to the University's code of values and to observe the rules on good academic citizenship.

I accept that unacknowledged use of the work of others and presenting that work as my own represents cheating and, as such, can lead, in some circumstances, to me being required to leave the University.

In return, the School which has principal responsibility for my programme:

- will provide learning opportunities within the programme to develop an awareness, at a level appropriate to the stage of study, of how to avoid plagiarism and its implications;
- will respond to reasonable requests for clarification on what constitutes plagiarism and for advice on how to avoid it;
- will provide a statement(s) which sets out how to prepare and present assessed work

Signed . . . . . (Student) Dated . . . . . .

Signed . . . . . Dated . . . . . .

Research Project Lead on behalf of DECIDE

Note: Learning contracts will need to be in place before assessed work may be submitted.

PLAGIARISM GUIDANCE FOR STUDENTS

Defining plagiarism

Plagiarism is a form of cheating and is a serious academic offence. It arises where work submitted by a student is not their own and has been taken from another source. The original material is then hidden from the marker, either by not referencing it properly, by paraphrasing it or by not mentioning it at all.

The most common forms of plagiarism are:

- cut/copy and pasted material from the Web;
- copying the work of another student (past or present), including essay material, laboratory data or computer source code;
- copying course material or lecture notes;
- copying material out of a textbook or journal.

It is important to realise that plagiarism may occur in a number of other forms, as well as in conventional written work. Another student may be involved, or the plagiarism may arise from the misuse of sources outside the University.

The key is proper attribution of source material. None of the activities listed above is, of itself, necessarily wrong.

Plagiarism is a serious matter for the University. If not dealt with, it will ultimately devalue all University degrees to the detriment of both students and the University. It also introduces a fundamental and inevitable distortion when the work of a student cohort is being assessed. This, in turn, is likely to lead to the undetected plagiarist obtaining better marks and a better degree than a student who is playing by the rules.

Student's responsibilities

A student at this University is expected to submit work that demonstrates compliance with two important prerequisites:

- a level of independent thought, grounded in the teaching received;
- the provision of clear referencing to all sources consulted, both within the main body of the work submitted and in any separate listing of sources.

It should be clear from a consideration of these two key requirements why plagiarism is unacceptable. By definition, a piece of work that has been plagiarised will never be able to meet either of the above criteria. Asking yourself prior to submission whether your work passes both tests is a useful method for determining whether there is likely to be a problem with plagiarism.

It is ironic that students sometimes seem to go to great lengths to hide the sources that they have been consulting. Proper referencing of these will normally be reflected in a good mark for the work submitted. This is because the appropriate use of source material is considered to be a crucial part of academic life. The resultant marking process will therefore acknowledge this, hence the inherent irony involved in the position of the student plagiarist who runs the risk of a serious penalty by hiding an aspect of their work that, done properly, is likely to help achieve a good mark without putting their student career in jeopardy.

'Accidental' plagiarism

The University accepts that students, particularly in view of the severe penalties that may be applied in cases of serious plagiarism, will be anxious to avoid inadvertently submitting plagiarised work. It is, for example, possible to cite a source in the separate bibliography and still commit plagiarism by then incorporating a significant amount of un-attributed material taken directly or indirectly (through paraphrasing) from that source into the body of the assignment.

Differences between working methods in school and at university are acknowledged too, as are the inevitable adjustments in cultural modes that international students must rapidly make, especially on postgraduate courses. Similarly, mature students may enter University not having been involved in academic study for a number of years.

Above all, the student body is not a single grouping and the University is aware of the need for a sympathetic approach to plagiarism, particularly in the first year of undergraduate studies and where there is no conscious attempt by the student to deceive. However, this is not a blank cheque for cheating. Penalties may be applied at any time.

The onus is on individual students to ensure that the academic conventions applicable to study at a UK University are understood and acted upon. The University, in conjunction with your School, will ensure that you have clear guidance on what is expected of you in terms of the referencing of source material. If you are worried about committing plagiarism, always seek help and advice from your tutor, supervisor or other academic advisor within your School. Members of staff are experienced in dealing with questions about proper referencing and will be happy to help.

The material issued by your School should always be your main source of guidance, however the following web page may be of interest;

- **www.i-cite.bham.ac.uk**

A referencing software package (Endnote) is also available for use by postgraduate researchers. For details and information on training please see:

- **www.i-cite.bham.ac.uk/endnote.htm**

Plagiarism-detecting software

Schools are making use of software systems, in addition to the existing and very effective methods that rely on the marker's knowledge of their subject. Systems such as Turnitin are currently available.

You should be assured that academic judgement is always brought into play when analysing the results. A School will not take action against you for plagiarism as a result of the findings of Turnitin unless it has looked very carefully at the report obtained from the software and assured itself that there are sufficient grounds for concern. You will be able to see the relevant report and to challenge the School's case if you are accused of plagiarism following a software-based analysis of your work.
Above all, the systems of software detection will be used openly and transparently by your School. Systems are not intended as a trap. However, the University reserves the right to protect the academic integrity of its degree awards by whatever means available to it. This will benefit those students who did not plagiarise.

How Schools deal with plagiarism
This is a complex area. In broad terms, these are the various stages:

- If your School is sure that any plagiarism that arises is not deliberate on your part and may be put down to an unfamiliarity with the referencing conventions required for University study, then it may simply provide guidance and a warning concerning your future work. Obviously, this position will not be taken with a student where it is reasonable to expect that they would know how to cite source material properly and would normally only apply to Level C study and to the early stages of a postgraduate programme;
- If your School believes that some form of sanction may be necessary, it will first ask you to attend an interview where you will be able to explain in detail the relevant circumstances. You can also ask for review of the evidence presented against you if you believe that the allegation of plagiarism is unreasonable
- Following on from the interview, the School will determine the level of plagiarism (if any) that it believes has arisen. There are three general categories:
    1. poor academic practice
    2. moderate plagiarism
    3. serious plagiarism

The consequences of a finding that plagiarism has occurred in any of these above ways can be found under Section 6 of the Code of Practice on Plagiarism.
In cases where serious Plagiarism is found, the matter will be dealt with under University Regulation Section 8 Student Conduct.

You should consult the Code of Practice on Plagiarism available at http://www.birmingham.ac.uk/Documents/university/legal/plagiarism.pdf This provides detailed definitive information on how plagiarism is dealt with.

The Learning Agreement and plagiarism
This is a bipartite contract that sets out an agreement that you, for your part, will not submit plagiarised work and that your School, for its part, will help and support you to avoid plagiarism. It is seen by the

University as a helpful expression of good faith and intentions by both sides of the academic partnership involving you and the University.

Plagiarism and postgraduate study

Given that you are likely to hold a First Degree already, there is an expectation that you are likely to be more familiar with how to reference source material that an undergraduate student just beginning their studies. However, the University is conscious that, particularly where a postgraduate student is newly arrived at Birmingham from abroad, they may need a short, initial period to familiarise themselves with the academic conventions that apply in the UK. The same would apply to someone who has returned to Higher Education after a long period of absence.

You should be assured that your School will not, provided it is satisfied that there has not been a deliberate attempt to deceive, treat any instance of plagiarism in the early stage of your postgraduate career as a matter normally requiring the imposition of a penalty. However, you must quickly come to terms with the University's expectations with regard to referencing. As an illustrative example, the first part of the initial Autumn term may be seen as a period when your School is likely to be willing to allow some time for adjustment, particularly for students from abroad.

Research students will, inevitably, be working closely with their supervisor(s). This is a different sort of relationship than that which inevitably applies on a taught postgraduate programme. Research students must ask for advice and guidance from their supervisor where they have any doubts about referencing.

Postgraduate students on taught programmes must seek guidance from their tutor or mentor, particularly when work is being carried on any dissertation element of the programme.

Student background and plagiarism

The educational background of students may make unintentional plagiarism more likely. Given the diversity of student background in the University, previous experience of formal education in the UK cannot be assumed. The expectations of learning and the learning styles that students bring will have been inevitably influenced by experience and circumstance, as well as by individual preferences. Student work that stays close to the original source and is therefore at risk of an allegation of plagiarism may, in some cases, be the result of:

- past experience of what has proven to be successful in other academic contexts but which is now a liability to the student;
- previous assessment systems and their differing rules in respect of source material;
- any past shortages of teaching and learning resources;
- a hierarchical understanding of knowledge-production in which the ‘novice student’ defers to the ‘expert source’ (teacher or text)
- a different understanding of the ‘ownership’ of knowledge and what is to be expected of material in the public domain;
- a poor standard of English leading to a lack of confidence in the free expression of individual ideas within an academic environment.

The University accepts that one (or more) of the above factors may play a role in a case of alleged plagiarism. Each case will therefore be treated on its individual merits and taking account of all relevant circumstances.

APPENDIX II – PERSONAL DEVELOPMENT

(This form is for you and your supervisor to comment on progress with you PhD)

PhD Progress Review Form

Form to be completed electronically NOT hand written (apart from signature page)

This process has 2 parts

1. **Annual progress review meeting of student with supervisors to discuss progress as documented by the student in section 2 and as documented by the supervisor in section 3, and summarised in an agreed recommendation in section 4. Supervisors should sign this form (Section 7) prior to submission to the School.**
2. **Subsequent meeting of student and supervisor with School Progress Review Panel as part of School Assessment sessions to verify progress decision.**

SECTION 1: To be completed by the person in the School responsible for co-ordinating the annual Progress Review exercise or by the Student	
Name of student:	Lead Supervisor:
	Co-supervisor:
This form to be returned to:	By (date):

SECTION 2: To be completed by the **STUDENT** (and given to the Lead supervisor two weeks before the Progress Review)	
Degree for which registered:	Date of first registration for this degree:
Mode of study:	(full-time/part-time/external)
Thesis title:	
Date of review meeting:	Date of last progress review:

(a) Please report below the work you have completed since last Progress Review OR, if this is your initial Progress Review, the work you have completed since you began your current research programme

(b) On how many occasions have you met with your supervisor since the last Progress Review OR, if this is your initial Progress Review, since you began your current research programme?:

(c) Is this frequency sufficient in your view?:

(d) Please give details of research training you have undertaken since the last Progress Review, OR, if this is your initial Progress Review, since you began your current research programme:

(e) Please give an outline of your planned work for the next semester:

(f) Please give a timetable for your work between now and the submission of your thesis, or attach an existing plan:

(g) If applicable, please add your comments about the progress you have made since this form was completed last and how it compares with your predictions then:

(h) Please confirm that you have updated your Training Needs Analysis (TNA) form in light of activity undertaken since the last progress review:

SECTION 3: to be completed by the **LEAD SUPERVISOR** before the Progress Review meeting

(a) Please comment on the accuracy of the student's assessment of his/her progress, in your opinion:

(b) Please rate the student's progress since the last Progress Review, OR, if this is their initial Progress Review, since they began their current research programme (delete the statements that do not apply):

Very satisfactory Satisfactory Giving cause for concern

(c) If "Giving cause for concern" state what steps the student should now take to ensure a satisfactory outcome.

(d) (i) Has a University ethical review Self Assessment Form (SAF) been submitted for this project (delete the statement that does not apply)

Yes No

(ii) If yes, was any other action required? (delete the statement that does not apply)

Yes No

(iii) If yes, state NRES number, or University Ethics approval number.

(e) (i) Have you reviewed the students TNA form (delete the statement that does not apply)

Yes No

(ii) Please state whether you feel the student has completed a satisfactory level of research training and whether there are any gaps still to be filled:

(f) Please give your estimate of when the thesis is likely to be submitted:

SECTION 4: To be completed by the **LEAD SUPERVISOR** at the progress review meeting between the student and supervisor prior to School assessment session

(a) Issues discussed at the meeting:

(b) List of actions agreed at the Progress Review meeting, with an indication of who is to take them and a timescale:

SECTION 5: Recommendation to be completed by the **LEAD SUPERVISOR** after the progress review meeting with your student, in line with 3.3 of the University's Code of Practice on Supervision and Monitoring Progress of Research Students

Please indicate your recommendation (delete the statements that do not apply):

- transfer to a doctoral programme from a master's programme (this is the usual course of action for a satisfactory student after the end of the first year of study)
- progress is satisfactory and the student may continue with their studies as a normally registered student, paying tuition fees (used for continuing students and students who have completed the first year of their PhD following successful completion of the MRes.)
- progress is satisfactory and the student no longer requires full use of University facilities, and having completed the minimum period of study, may proceed to writing up status, paying the continuation fee (used for students entering write up stage)
- progress is unsatisfactory and a plan of supportive or corrective action is agreed which will result in a further review of progress. The student would remain normally registered, but would not be permitted to proceed into the next year until progress was satisfactory. If progress were to remain unsatisfactory, the student may be required to withdraw
- transfer to a master's programme from a doctoral programme (student would have the right of appeal)
- withdraw. This recommendation would have to be taken in accordance with the relevant University regulation. The student would have the right of appeal.

BOTH LEAD AND CO-SUPERVISOR TO SIGN SECTION 6 BEFORE THE FORM IS SUBMITTED BACK TO THE SCHOOL

SECTION 6 Signatures Page

1) Supervisors

I confirm that I have met with the student and have completed Sections 3-5.

Lead supervisor:

Date: Signature

Co-supervisor:

Date: Signature

2) School Progress Review Panel (Director or Co-Ordinator)

I agree with/ wish to vary the recommendation made by the Supervisor in Section 5 as follows:

NB: If the progress decision is changed; this must be relayed back to the supervisor prior to the student signing the form. The supervisor should countersign (initial) the revised progression decision detailed below.

Comments, if any:

Revised progress decision (if applicable):

MEMBER OF PROGRESS REVIEW PANEL TO SIGN BELOW AFTER THE ASSESSMENT HAS TAKEN PLACE. ONLY ONE SIGNATURE NORMALLY REQUIRED, HOWEVER DIRECTOR CAN COUNTERSIGN.

Date: Signature:

Date: Signature:

3) Student (signature to be obtained only once the above 2 sections are signed)

I confirm that I have read the comments of my supervisor and the School Assessment Panel.

Date: Signature:

It is the student's responsibility:

- to obtain all signatures.
- to let the School Administrator have the fully completed form back.

It is the School Administrator's responsibility:

- to let the student, supervisor and Research Office have a copy of the completed form.

DECIDE

TRAINING NEEDS ANALYSIS

(THIS FORM IS TO BE USED AT THE BEGINNING OF EACH ACADEMIC YEAR TO EXAMINE TRAINING NEEDS)

SECTION 1: It is recommended that this form is completed jointly by student and supervisor at a supervision meeting before or at the beginning of each academic year.

a) Student Name: Supervisor:

b) Date/time of supervision:

c) Objectives for the current academic year (with dates/deadlines where appropriate):

d) Anticipated frequency of supervision meetings this academic year:

SECTION 2. Training Needs Analysis

Indicate against each topic the agreed assessment of the student's training needs. Courses aimed at addressing student training needs are run by:

Student Support and Counselling Service	http://www.ao.bham.ac.uk/sscs1/default.htm
Careers Centre	http://www.careers.bham.ac.uk/student/
Information Services	http://www.istraining.bham.ac.uk/
The Guild of Students	http://www.guild.bham.ac.uk/bugs-bham/

Schools and Departments

The Staff Development Unit runs courses for students involved in teaching which are administered through the School/Department.

REQ	REQUIRED	The student needs this skill/training.
OPT	OPTIONAL	The student may undertake training in this area, but it is not mandatory.
NO	NOT NEEDED	The student has already undertaken training, has demonstrated sufficient competence in this area or it is not relevant to the needs of this student.

A. SPECIFIC RESEARCH SKILLS (specified by supervisor)

TOPIC	REQ	OPT	NO	COMMENTS
A1.				
A2.				
A3.				
A4.				
B. ADVANCED STUDY SKILLS	REQ	OPT	NO	COMMENTS
B1. Information & research skills (bibliographic databases)				
B2. EndNote or Reference Manager bibliographic software				
B3. Pegasus Mail for Windows				
	RE	OPT	NO	COMMENTS

C.	COMPUTING SKILLS	Q			
C1.	Microsoft Word (introduction)				
C2.	Microsoft Word (more advanced)				
C3.	Introduction to Excel - Spreadsheets				
C4.	Excel - Presenting, analysing & graphing data				
C5.	Introduction to MS Access (relational databases)				
C6	Frontpage 2000				
D.	PRESENTATION SKILLS	REQ	OPT	NO	COMMENTS
D1.	Report writing				
D2.	Plan for effective thesis writing (for Engineers)				
D3.	Writing research reports and theses (in life/health sciences, medicine, dentistry)				
D4.	Writing research reports and theses (in arts and social science areas)				
E.	TRAINING FOR TEACHING *	REQ	OPT	NO	COMMENTS
E1.	Small group teaching				
E2.	Assessing students' work				
E3.	Presentation skill for teaching				
E4.	Laboratory demonstrating				
E5	Associate Membership of the Institute of Learning and Teaching				

* *Required* for all students working as Teaching Assistants or Postgraduate Demonstrator.

F.	LEGAL/ETHICAL ISSUES	REQ	OPT	NO	COMMENTS
F1.	Scientific ethics and animal experimentation				
F2.	Research ethics for students in arts and social sciences				
F3.	Engineering ethics				
F4.	Research contracting and intellectual property rights				
G.	PERSONAL SKILLS	REQ	OPT	NO	COMMENTS
G1.	Postgraduate study				
G2.	English for academic purposes for international students				
G3.	Personal effectiveness				
H	CAREER DEVELOPMENT	REQ	OPT	NO	COMMENTS
H1.	Individual careers guidance				
H2.	Written applications				
H3.	Interviews				
H4.	Second stage selection centres				
H5.	Practice aptitude tests				
H6.	Presentations				

Signatures :

Student Date

Supervisor Date

When signed, the supervisor and student should each have a copy of this form.

(This form can be used to plan work during the course of your PhD studies)

Supervision Record: Monthly Planning

SECTION 1

To be completed by the student prior to supervision meeting

a) Name:

b) Lead Supervisor's name:

Co-supervisor's name

c) Date/time of supervision:

d) Date of last supervision:

e) Work submitted to supervisor since last supervision meeting (with date work submitted and returned to you)

f) Work undertaken since last supervision meeting:

g) Issues you would like to discuss in the supervision meeting:

SECTION 2

To be completed by the LEAD supervisor at the supervision meeting

a) Topics covered in supervision meeting (please refer to Section 1(g) above):

b) Your comments on student's progress since last supervision meeting:

c) Comments on students performance in taught elements of the programme (to include in the discussion modules taken and marks achieved and how the remaining taught elements will be completed).

d) Overall rating of students progress to date (tick one)

Very satisfactory Satisfactory Giving cause for concern

If "Giving cause for concern" please state clearly the steps the student should take to reach a level of satisfactory progress:

f) Work student should undertake between now and next supervision:

g) Work to be submitted to you before next supervision (with dates):