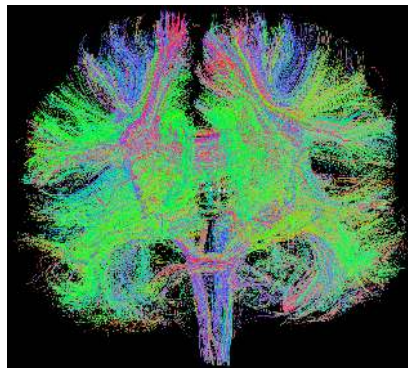


SINAPSE

Scottish Imaging Network: A Platform for Scientific Excellence

Final Report



SCO13683



SCO11159



SCO21474



SCO15096



SCO13532



SCO05336



The Universities above are charitable bodies, registered in Scotland, with registration numbers as above.

Executive Summary

Income: In 2013-14 our grant income rose to £22.14M. Over the period of the award SINAPSE researchers amassed over £46M of grant income, rising steeply in the past two years. The increase in senior positions in medical imaging within the six participating Universities has been a key contributory factor, as it allowed collaborations to become established with researchers requiring imaging capabilities to propel their research programmes. On top of this ‘in-kind’ contributions from partner companies have been invaluable.

Communication of findings: One of our key objectives is to impact on health care. Evidence based medicine is informed by reviewing high quality peer reviewed journal articles. SINAPSE researchers published 151 papers in 2013-14 and more than 500 over the period of the grant. These can all be accessed through our website where they can be searched by keywords, author, publication year or journal. Our most significant contributions were in medical specialist fields including stroke, ageing and dementia, cardiovascular disease and pulmonary disorders; technology developments including new ways of synthesizing PET tracers, new MRI techniques and new image processing algorithms; and basic understanding of brain function, in particular memory and emotions. We also participated in many public engagement events.

Graduate school: We started with 24 studentships. This increased to 45 as a result of subsequent successful SFC funding bids, particularly SPIRIT. Of these 31 have so far successfully completed their PhDs, another 10 who started later are due to complete in 2015, one withdrew on health grounds and 3 have had delays, e.g. maternity leave. This report outlines in detail the activities of the Graduate School. It was held in high regard by students and supervisors and contributed greatly to our scientific output. Seven of our graduates are now employed as post-doctoral researchers in Scotland and many of the others are helping us to establish international links. Full details are in Appendix 2. We were pleased to have a gender balance of 23 female and 22 male students from 18 countries of origin. Support for students included joint supervision from two institutions, setting up JSCMAIL on-line technical help systems, students poster events, an annual scientific meeting where student presentations sat alongside keynote presentations from world-leading researchers, and an annual induction event for new students.

Challenges: A major challenge was the lack of legal entity status. This prevented us acting as a single contractor with commercial partners or funding bodies. It was not too difficult to circumvent this by getting the lead University to act in this capacity, but this does limit the potential value of pooling.



Interface with industry: SINAPSE has helped to address the challenge of interfacing with industry to ensure that the potential commercial benefit of Scottish research is exploited for economic growth. We have participated in many events and advisory activities, but by far the strongest bonds and greatest benefits have come from joint studentships. A cautionary note going forward, however, is that many of the companies that we work with have head offices, and hence power bases, outside Scotland. Despite Scotland's contributions to the development of MRI and medical ultrasound, there is currently a dearth of local companies working in this area. There are, however, several start-up companies on the horizon.

Links with other pools, the NHS and networks: We started with good links with ScotCHEM and developed these. This has been productive in the development of novel approaches to tracer production for PET scanning. We then established links with SUPA and have six collaborative projects that are outlined in the report. SINAPSE works very closely with the NHS researchers in the four Boards with medical schools and interfaces with SHIL and NHS Clinical Networks. We hold annual meetings with SANON, the Scottish Adult Neuro-Oncology Network, at which joint projects are reviewed.

Public policy: We have participated in many public events but perhaps the two greatest impacts on policy came from the work of SINAPSE on the wider impact of imaging on society: A) on management of incidental findings in imaging research (in partnership with the Royal Colleges, Health Research Authority, Wellcome Trust and MRC); and B) from a series of three seminars held in partnership with the Scottish Universities Insight Institute where there were expert led debates on non-research non-clinical uses of Brain Imaging and their Impact on Society. The focus was on the possible over-interpretation and inappropriate exploitation of brain imaging for legal and marketing purposes. This work was presented to MSPs at Holyrood, the shadow Education Minister, a member of the Health Committee and researchers and was published in the journal *Holyrood*.

Another area was the involvement of SINAPSE appointed researchers on bodies such as SIGN (for Scottish guidelines in pulmonary embolism and lung cancer management), NCRI (for the application of imaging biomarkers in cancer research) and the wider research community (European Society of Radiology and affiliated societies having an impact on imaging in general), e.g. NICE Technology Appraisal.

The future: It was gratifying that SINAPSE managed to obtain the matched funding required to enable us to progress to the next phase. This is being provided by all six of the original partner Universities and by the Chief Scientist Office of the NHS in Scotland. We shall be working closely with the Physics Alliance SUPA and look forward to the next five years.




David Wyper
Director of SINAPSE

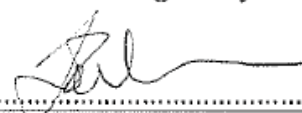


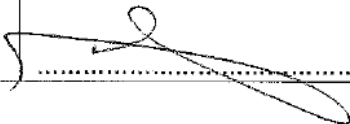
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SINAPSE Final Report: Signatures from partner institutions:

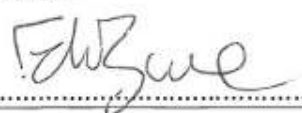
University of Edinburgh		
Name:	Authorised signatory:	Date:
TIMOTHY O'SHEA		11 DECEMBER 2014

University of Glasgow		
Name:	Authorised signatory:	Date:
A.F. DOMINICZAK		9/12/14

University of Dundee		
Name:	Authorised signatory:	Date:
PROFESSOR JOHN CONNELL		18/12/14

University of Aberdeen		
Name:	Authorised signatory:	Date:
M. GREGGUS		23/12/14

University of St Andrews		
Name:	Authorised signatory:	Date:
J. DEREK WOOLLINS		18/12/14

University of Stirling		
Name:	Authorised signatory:	Date:
	E.K. Burke	19/12/14

1. PROGRESS AGAINST KEY OBJECTIVES SET OUT IN THE ORIGINAL PROPOSAL.

Objective 1. *To develop Scottish academic imaging expertise to address a broad range of clinical and functional questions by making key appointments to Chairs in image analysis, neuroimaging physics and functional imaging [with two additional clinical imaging Chairs provided by CSO] supported by intermediate level researchers in image acquisition/paradigm design, image analysis and tracer development.*

We established four new SINAPSE funded Chairs in imaging related disciplines. They were awarded to two radiologists, Professor van Beek in Edinburgh and Professor Houston in Dundee; to a physicist specialising in the development of MRI techniques, Schwarzbauer, Aberdeen; and to a neurologist who uses imaging as a core technology for his research and clinical practice, Muir, Glasgow. Two of the Chairs were funded by CSO to encourage SINAPSE to broaden out from the initial bid, which was limited to brain imaging. This report will demonstrate that this has indeed been achieved. The leadership from the four SINAPSE Professors has been one of our key successes. Details can be found in Appendix 1.

Over the period of the award several additional Professors have collaborated with SINAPSE. These include:

- Neil Roberts, Professor of Medical Physics and Imaging Science, University of Edinburgh.
- Ian Marshall, Professor of Magnetic Resonance Physics at the University of Edinburgh.
- Anthony Chalmers, Professor of Clinical Oncology in Glasgow, with whom we set up regular SINAPSE–SANON symposia [SANON is the Scottish Adult Neuro-Oncology Network].
- Mhairi Macrae, Professor of Neuroscience at the University of Glasgow.
- Matteo Zanda, Professor of Medical Technologies at the University of Aberdeen
- David Lurie, Professor of Bio-medical Physics in Aberdeen, who is working on fast field cycling MRI
- Professor Sandy Cochrane who heads the ultrasound development team at Dundee
- Professor Andreas Melzer, Director of IMSAT at Dundee.
- David O’Hagan, Professor of Chemistry at the University of St Andrews with special expertise in fluorine chemistry.
- Professor Luc Bidault, Dundee, Medical Physics.

SINAPSE had eight post-doctoral research fellows. Seven have been retained by Universities or the associated NHS Health Board.

Objective 2. *To re-establish world leading cutting edge imaging equipment for the Scottish Imaging Community, compatible between imaging Centres.*

Funding was provided to help to refurbish radiopharmaceutical production laboratories in Edinburgh, Glasgow and Aberdeen. This was completed and has been of great value in progressing the development of positron emission tomography in Scotland. There had been a PET research Centre in Aberdeen since the 1980’s but NHS Boards were not early implementers of this technology. The Health Technology Board for Scotland recommended in 2002 that PET should be introduced to the NHS but it took several years before this was achieved. The support from SINAPSE helped with the catch-up that was required to bring us up to international standards. Many of our studentships

were in radiopharmaceutical production and the good outcomes and products resulting from this work are reported elsewhere in this report. The Radiochemistry Production Facilities in Edinburgh and Glasgow are GMP Compliant and supply radiotracers to the NHS and for research.

MRI compatible EEG equipment was procured for the scanners at Glasgow, Edinburgh, Aberdeen and Dundee [also used by St Andrews]. Again this was used successfully in many of our studentship projects leading to studies that have been reported in the literature. Several Centres are currently exploring the use of combined EEG-fMRI in the localization of epileptogenic tissue in patients with focal epilepsy.

Objective 3. Increase patient access to clinical Research by supporting the NHS/DoH/ Scottish Government initiative to develop Clinical Research networks in key disease areas and the Scottish Government's PET imaging initiative.

SINAPSE has been in regular contact with the Scottish Mental Health Network [SMHN] and with the UK dementia network, led by Professor Murray in Aberdeen.

We are well represented on the Stroke Research Network (Wardlaw, executive) and extremely active in clinical trials in stroke in the UK (IST-3, RESTART, PRACTICE, PISTE, PISCES, ATTEST, to name a few).

SINAPSE has worked with the Department of Health and STFC and British Nuclear Medicine group in discussion about the impending crisis facing nuclear medicine because of the shutdown of ageing nuclear reactors that produce molybdenum-99, the parent radioisotope in the production of Tc-99m. The discussion is ongoing. One outcome to date is that, through SUPA, we have teamed up with researchers at the University of Strathclyde and are exploring the potential of Plasma Laser Wakefield Accelerators to produce medical radioisotopes. This, however, will take time – maybe 10 years – and so interim solutions for better use of cyclotrons in the UK will be required.

SANON is the Scottish Adult Neuro-Oncology Network. There have been several joint meetings involving SANON and SINAPSE, one of which featured Professor Alan Jackson from the Wolfson Centre in Manchester. Prof Jackson is one of the members of our International Advisory Board.

We link into the Scottish PET Network. This was dormant for a while but has been revived and we have ensured that there is linkage and sharing of minutes with our Molecular Imaging group, led by Dr Sally Pimlott. The NHS group focuses primarily on service delivery and our group on novel tracers and techniques, but both require use of PET facilities and this has to be optimized.

Increasingly PET is being used in clinical trials. The work of SINAPSE is helping to ensure that the PET Centres in Scotland have the equipment and expertise to take part in these trials. The most recent study to come to Scotland is a multi-centre clinical trial using a beta-amyloid PET tracer. Patients are recruited through the Scottish Dementia Clinical Research Network.

Ground breaking research has been developed in this field in cardiovascular diseases, with novel biomarkers being developed for the evaluation of aortic valve disease and to study vulnerable plaque in the coronary arteries, with publications in top journals to match.

We have established links with the Farr Institute. In May 2014 we held a joint meeting involving imaging researchers from around Scotland and we are advising on efforts to store NHS imaging data from the national PACS system. We aim to further develop this collaboration over the coming years.

Objective 4. Build capacity through encouraging the career development of the intermediate career researchers to full independence and cohesive doctoral training programmes between Universities to develop future generations of imaging researchers in Scotland.

The activities of our graduate school, including industry partnerships, work experience, the induction event, the Annual Scientific Meeting and early career exchanges rank highly in the achievements of SINAPSE and are presented in detail later in this report.

Objective 5. Increase the ability of imaging researchers to conduct clinical trials.

SINAPSE is close to the NHS and has been supported by CSO. Many of our members have the NHS as their primary employer and the University based researchers have honorary NHS appointments. Clinical trials are part of our every day activity. Our leading academics, in particular Professors Wardlaw, Muir, Murray, van Beek, Steele and Houston are involved in many clinical trials.

Issues such as confidentiality, anonymisation, image transfer and archiving, and image quality, have to be considered. SINAPSE produced the MIDAS report that addressed these issues. It was submitted to CSO and has led to improved practices in the NHS in Scotland. It has also served as a framework for use in the recently established Farr Institute.

Both Professor Wardlaw and Professor Muir are leading stroke researchers. Professor Wardlaw is internationally recognised for work on the pathophysiology of cerebral small vessel disease and brain ageing, and the pathophysiology and treatment of acute ischaemic stroke especially thrombolytic therapy, and the use of imaging to diagnose acute stroke. She has provided imaging and related expertise to several multi-centre randomised clinical trials and is imaging lead for several other initiatives, such as the MRC-funded Centre for Cognitive Aging and Cognitive Epidemiology (CCACE). Prof Muir's major interests are in the treatment of acute stroke and the application of advanced brain imaging techniques to aid treatment decisions in acute stroke; thrombolysis for stroke; clinical trials and clinical trial design in acute stroke; and the inherited syndrome CADASIL. He is leading the first UK stem cell trial in the management of acute stroke. Both work closely with the Scottish Stroke network.

The expansion into other fields has worked well with both Prof Houston and Prof van Beek active in the Cardiovascular domain, resulting in several large studies. The SCOTHEART trial involved multiple sites in Scotland and almost 4000 patients were randomized to undergo routine evaluation for chest pain versus application of coronary CT angiography with results being analysed at present, that will likely lead to changes in patient management.

Perhaps the single contribution that will be of most value is the development of DICOM Confidential. Medical images acquired for clinical purposes can have several legitimate secondary uses in research projects and teaching libraries. For these uses, and when imaging is acquired directly for research, most personal data can be safely removed, but in many cases it is necessary to keep some personal data or a link with the personal data. At this moment, no commonly accepted solution exists because the amount of personal data that is required by researchers and teaching libraries varies case by case. DICOM Confidential is an open source DICOM (Digital Imaging and Communications in Medicine) de-identification toolkit that provides the necessary flexibility to account for different de-identification requirements and does not impose a given anonymisation model. It also provides a mechanism for forwarding the anonymous output to a remote site using either SFTP (SSH File Transfer Protocol) or DICOM communications protocol. In the case of multicentre clinical research projects a uniform, accountable de-

identification process at all participating Centres is desirable. This can be done by prior distribution of the Privacy Policy to be used or by deploying it in a web server from which DICOM Confidential can read it directly. The toolkit has been deployed in a multicentre setup.

Objective 6. *Bring inward investment from National and Government funding organizations, the EU, non-government sources and industry.*

The income achieved by SINAPSE researchers is reported in Annex 1. We have established links with industry as detailed later in this report. The EU funding is also recorded. There have also been many ‘in-kind’ contributions from industry, with access to specialist expertise and facilities.

Objective 7. *Impact on patient health.*

The major contribution to patient health comes by informing the global knowledge base of information on pathophysiology and treatment. Evidence based medicine requires the evidence base, and that in turn comes from reviewing the literature and appraising well conducted research studies. Over the course of the award SINAPSE researchers have had over 500 publications in peer-reviewed journals. These can be accessed through our website where they can be searched by keywords, author, publication year or journal.

2. VARIATIONS TO THE PROGRAMME.

The only major change to the programme resulted from our struggle to fill the SINAPSE Chair at St Andrews. An initial appointment proved to be short-lived and subsequent attempts to fill the post were ultimately unsuccessful. With approval from SFC and St Andrews University we vired the funds to support additional studentships. The condition attached to this was that we had to attract matched funding. This was achieved and the studentships are proving to be excellent value. They are only now drawing to a conclusion.

SINAPSE was granted a no-cost extension with the deadline for expenditure extended to 31st Dec 2014.

3. KEY ACHIEVEMENT AND CHALLENGES, BOTH DURING THE PERIOD OF THE AWARD AND THOSE ENVISAGED IN THE FUTURE.

The SINAPSE Graduate School.

The SINAPSE studentships and subsequent KE studentships have been central to the success of SINAPSE. Individual details of the students are presented in Appendix 2. The key events within our Graduate School were the annual induction for new starts held at Burn House in Angus, the JSCMAIL technical support systems that were set up of MRI and PET, the student poster events and the annual scientific meetings. A few testimonials from students have been included in Appendix 3. One of our students who has just graduated sent the following note:

“Dear Professor Wyper,

I just wanted to send a quick email to offer a very big thank you to SINAPSE, SFC and all those involved in making my PhD possible. I am particularly grateful for the additional funding provided for my placement trip to MNI - a very rare opportunity that I will remember for a long time to come! I wish everyone the best and hope that SINAPSE continues in one form or another as it truly does offer a very unique and rewarding environment.

Thanks and best wishes,

Adele Blair”

The links that we have established with industry have been critical, especially during this period when exploitation of academic expertise for economic benefit is so important. These are presented in detail later in the report.

We have developed on-line learning material. This takes the form of an e-learning MSc within the University of Edinburgh for those specializing in medical imaging and also more general material explaining medical imaging for non-specialists. These can be accessed through the SINAPSE website and have been available to all our students.

Gender and racial equality

We have had 23 female and 22 male students from around the world – see Figure 1



Thirteen were from the UK and the rest from Germany [4], Italy [3], Greece [2], Poland [2], Uruguay, Russia, Iran, Canada, USA, Tunisian, Kenya, India, China, Ghana, Ireland, Portugal and Austria.

Support provided for students.

Most SINAPSE students had two supervisors, one from the host University and another from one of the other partners. Not only did this benefit the students by widening their access to equipment and expertise but it also served to bring supervisors closer together.

Our students were central to two key academic events that were organized each year, our Annual Scientific Meeting [ASM] and a poster preview several weeks prior to this. We have held ASMs in Edinburgh, Glasgow, Aberdeen and Dundee. They are a mixture of keynote addresses and invited presentations from eminent international imaging scientists and platform and poster presentations by SINAPSE students and early career researchers. International keynote speakers have included:

- Prof John O'Brien from the University of Cambridge presenting on 'Imaging in Dementia'.
- Prof Andreas Jacobs, Chair of the European Institute for Molecular Imaging, University of Munster presenting on 'Imaging in Oncology'.
- Dr Nick Ward, UCL Institute of Neurology, presenting on 'Studies of the recovering brain after Stroke'.
- Professor John Pickard from the University of Cambridge and Director of the Wolfson PET Research Centre, presenting on 'Role of Imaging in the Translational Pathway'.

- Professor Jeff Bulte from Johns Hopkins University presenting on ‘Stem Cell Tracking in Neurologic Applications.’

We have had many studentships in the field of PET, several in association with colleagues in SCOTCHEM at Aberdeen, St Andrews and Glasgow. Our Molecular Imaging Committee has been of great help to these students and has organized several specialist meetings where there has been a mixture of keynote addresses and presentations from our own students. Keynote speakers have included Professor Veronique Gouverneur from the University of Oxford, Prof Andre Luxen from the University of Liege and Dr Jan Passchier from GSK/Imanova.

Each year we organized a 3-day student induction event at Burn House near Edzell. This is a venue that is used for many University study group meetings. The event served to engender a sense of belonging to SINAPSE in addition to the host University. The meetings have focused on communication skills and creative thinking. On several occasions we had sessions on presentation skills from Cordellia Ditton of Voice Business. Not only were these sessions enjoyable, they were extremely effective. It was gratifying to see the quality of presentation by some of our students at our annual scientific meeting, often outshining some of the invited speakers. For the past two years we had a lower intake of new students and so agreed to partner with the Centre for Doctoral Training in Next Generation Accelerators, an EPSRC group involving the Universities of Strathclyde, Queens Belfast, Huddersfield and Surrey. This has enhanced the meetings, and has been of value both to the students and to the faculty by enabling us to share our experiences of multi-centre learning. The ‘Burn’ presentation-skills training was evident at many of the public communication of science events at which our students presented.

Students have also benefitted from two SINAPSE JISMAIL communication systems, one for MRI and the other for PET physics and radiochemistry. They have had access both to the “*Applied Neuroimaging for Research*” MSc material at the University of Edinburgh and the e-learning material explaining how imaging works. The latter would not help them in their specialist field, but SINAPSE is very multidisciplinary and this gave the students a valuable background understanding of other techniques.

Challenges:

At the outset it appeared that the biggest challenge for the pooling concept might be the apparent conflict between competition and collaboration. In practice, however, this did not turn out to be limiting. Of course there is a healthy rivalry between institutions, but the benefits of collaboration rapidly became apparent and working with SINAPSE partners generated respect for colleagues and helped to identify funding opportunities.

Initially we envisaged setting up SINAPSE as a single point of contact for commercial interaction with multiple Universities. We certainly succeeded in generating many commercial partnerships, but the legal issues had to be handled by the lead University in each case as SINAPSE is not a legal entity. We did contemplate setting up a not-for-profit company but were advised against it. We learned recently that MASTS has decided to venture into this territory and it will be interesting to see how they progress.

Another challenge that we encountered was that many of our attempts to attract top academics floundered because they could not move to Scotland for family reasons.

The relatively low number of companies in Scotland involved in medical imaging has made commercial interaction a challenge, but we have made significant progress in this area. This is discussed in the section on Business interactions.

4. COLLABORATION AND ENGAGEMENT ACTIVITIES.

Academic.

SINAPSE is extremely multidisciplinary. We discussed the option of submitting a single REF return but dismissed the idea due to logistics, appropriateness and concerns about double-counting.

Engagement with UK and international universities.

SINAPSE researchers have close links with the international Universities, including:

University of Liege; Triumpf, at the University of Vancouver; Harvard University; Ecole Polytechnique Paris; Johns Hopkins University; the University of Cambridge; Max Planck Institute; Free University of Amsterdam; Washington University, St Louis; Université de Bourgogne; King's College London, University of Sheffield, University of Iowa, National Jewish Hospital Denver, University of Michigan, Charite University Berlin, University of Illinois (Urbana), University of Oxford, University of Birmingham, Manchester NHS Trust and University of Manchester, Moorfields Eye Hospital London; Professor Tim Crow, Prince of Wales International Centre (POWIC), University of Oxford; Professor Luis Cruz-Orive, University of Santander, Spain; Professor Alan Evans, Montreal Neurological Institute, Montreal, Canada; Professor Qiyong Gong, Professor Bin Song and Dr. Ling Zou, West China Medical School, Chengdu, China; Dr. William Hopkins, YERKES National Primate Research Center, Atlanta, USA; Dr. Curtis Johnson, Beckman Institute - University of Illinois at Urbana-Champaign, USA; Professor Arun Kolipaka, University of Ohio, Columbus, USA; Dr. Marius Mada, Wolfson Brain Imaging Centre, University of Cambridge; Professor Jean-Francois Mangin, Neurospin/CEA, Gif-sur-Yvette, France; Professor Bente Pakkenberg, Research Laboratory for Stereology and Neuroscience, Bispebjerg University Hospital, Copenhagen, Denmark; Dr. Sylvain Prima, University of Rennes, France; Professor Richard Robb, MAYO Clinic, Rochester, Minnesota, USA; Professor Ingolf Sack and Dr. Jürgen Braun, Charité - Universitätsmedizin Berlin; Professor Colin Studholme, University of Washington, USA; Professor Caroline Wilkinson, College of Life Sciences, University of Dundee; Professor Sandra Witelson, McMaster University, Hamilton, Canada. Prof Oscar Benavente, Vancouver Canada, Prof Martin Dichgans Munich, Prof Robert van Oostenbrugge, Maastricht.

Interaction with other Pooling Groups.

The earliest interaction with another pool was in the development of novel tracers for PET and the exploration of tracer production techniques that might be more efficient than current methods. ScotCHEM has expertise in iodine chemistry that is required to make many of the tracers used in SPECT [Dr Sutherland at Glasgow] and fluorine chemistry required for PET [Prof O'Hagen at St Andrews]. These proved to be fruitful collaborations and the resulting papers and techniques are reported elsewhere in this report.

We also interfaced with SULSA and SICSA and established useful relationships. The strongest link, however, was with SUPA. These collaborations were in areas that are close to industry and therefore of great potential for future engagement with Technology Innovation Centres.

Examples of current 'physics' projects involving SINAPSE.

- **FAST Field Cycling MRI [Aberdeen].** Professor Mallard's team undertook pioneering work on MRI in the 1980s. Now, under Prof Lurie, further exciting developments with significant commercial potential are underway. Foremost amongst these is the development of field cycling MRI where an additional image contrast can be obtained by cycling the strength of the primary magnetic field - see <http://ffc-mri.org/>. One of the main funding sources is EPSRC.
- **Novel developments in medical ultrasound [Dundee].** Prof Sandy Cochran is the lead investigator on the Sonopill project, supported by EPSRC - see <http://app.dundee.ac.uk/pressreleases/2013/march13/sonopill.htm>.
- **Medical Image Analysis [Edinburgh].** At the interface between physics and computer science, medical image analysis is a field where all SINAPSE Centres have expertise. The leading Centre is the University of Edinburgh. The BRAINS project at the Brain Research Imaging Centres is a good example - see

<http://www.bric.ed.ac.uk/research/BRAINS.asp>. SINAPSE has close ties with Toshiba Medical Visualization Systems Europe [TMVSE] and Optos, with several joint projects on medical image analysis.

- **Metabolic MRI [Glasgow]**. Led by neuroradiologist Dr Celestine Santosh, pioneering techniques to enable metabolic activity to be tracked by MRI are under development. AURUM Biosciences, a spin-out from NHS Greater Glasgow and Clyde and University of Glasgow is on schedule to start trading in February 2015 - see <http://aurumbiosciences.com/>.
- **Production of radiopharmaceuticals [Glasgow]**. The medipix detector can measure positron activity directly. Currently, in radiopharmaceutical production devices, it is the annihilation gamma rays that are detected. The potential application of the medipix is being explored in three areas. a) Radio-detection in PET isotope generators to assess yield. b) Detection of radiochemical yields following HPLC purification. c) Detection during single QA assays that are being developed using 'Lab-on-a-chip' technology. This work has been explored by joint SINAPSE SUPA projects and the IP has been protected by the University of Glasgow.
- **Production of medical radioisotopes [Strathclyde]**. There is a growing market for medical radioisotopes. Scotland has the potential to contribute to this in the medium/long term if its expertise in Plasma Laser Accelerators can be supported and exploited. The programme leader is Prof Dino Jaroszynski - see <http://www.scapa.ac.uk/>. This is part of a wider link with the Centre for Doctoral Training in Next Generation Accelerators. This is an EPSRC funded CDT involving the Universities of Strathclyde, Huddersfield, Surrey and Queen's, Belfast. We have a joint studentship with this group and shared our student induction event in latter years when numbers reduced. This collaboration is helping to ensure that Scotland has a place in the implementation of laser accelerator technologies in medicine.

Business sector

SPIRIT. Our industry partners on the SRIRIT PROGRAMME, led by Professor Wardlaw, were Pfizer, Siemens, the Digital learning Foundation, TMVSE [2] General Electric, Agilent, Propellor, Molecular Imaging Inc, New Haven, Connecticut, Immanova (formerly GSK Imaging), Tayside Flow Technologies and AstraZenica. Details of this work will be presented in a separate report.

SINAPSE has participated in the start-up events for CENSIS and has encouraged the two strongest medical imaging companies in Scotland to join [Optos and TMVSE]. Our complete interface with industry involves Scottish, UK and multi-national companies:

Scottish SMEs: Vascular Flow Technologies; Propeller; TMVSE; Mentholatum; eCom Scotland; Optos; Blackford Analysis; Aridhia and Aurum Bioscience.

UK SMEs: Perspectum ; Kemotech; ReNeuron; Imanova.

US or Multinational companies: Bioclinica; Agilent Technologies; Siemens Healthcare; Philips Healthcare; PharmaNess Scarl; Pfizer; GSK; AstraZeneca; GE Healthcare; Molecular NeuroImaging; Bruker; Novartis; Merck Sharpe and Dome; VIDIA Diagnostics; Bioclinica; and Perceptive Informatics.

It is perhaps appropriate to quote here an unsolicited comment received from one of these companies:

"I've been very impressed with the way you have been able to set up a strong imaging community in Scotland. Things have been somewhat more challenging to arrange south of the border.

The collaboration with St Andrews is going well. They have all the expertise with the enzyme and we can bring some application focus to the table.

*In addition to St Andrews we're also in contact with *** at Aberdeen, have recently submitted a grant application jointly with *** and *** from Glasgow University, and will be visiting Edinburgh in the near future.*

Following on from the SPIRIT programme, additional external income came from **Optos** and Toshiba Medical Visualisation Systems Europe [**TMVSE**], both medical imaging companies based in Scotland, the **Mentholatum** Company that has a large factory in East Kilbride and are keen to partner on the development on magnetic resonance elastography, CarestreamMedical [now **Bruker**], the Northwood Trust and EPSRC. These companies provided matched funds for studentships. The projects were later in starting compared to the other SINAPSE studentships and so are only now beginning to reach the end stage.

As well as contributing financially to joint studentships the 'in-kind' contribution of our commercial partners have been invaluable. An example of this is the access provided by Molecular Neuroimaging Inc. in New Haven to enable Adele Blair to test her neuroinflammation PET tracer using facilities that are not available in Scotland.

It should be noted that much of our industrial interface is furth of Scotland. Despite Scotland's contributions to the development of MRI and medical ultrasound, there is a dearth of local companies working in this area. There are, however, imaging IT companies like TMVSE and Blackford Analysis and start-up imaging companies are beginning to appear. Professor Houston is involved in Vascular Flow Technologies, and Dr Santosh in Glasgow is behind Aurum Biosciences. These companies are based on first-rate IP protected technologies and hopefully will be able to raise the investment required to enable good market penetration.

Recently we have had meetings with leading scientist from the National Physical Laboratory. NPL is currently a GoCo – Government Owned and Company Operated, the company being SERCO. It is in the process of changing into a GoGo – Government Owned and Government Operated and the Universities of Strathclyde and Surrey have been selected as partners in this operation. By linking with SUPA we are exploring potential collaborations with NPL. They have expertise and facilities that are used in the calibration of patient doses in nuclear medicine imaging and other areas of metrology where collaboration could be fruitful.

Public sector

SINAPSE works very closely with the four NHS Boards with medical schools. Whilst, with a few exceptions, the key grant leaders are University based, NHS colleagues provide invaluable links to clinical practice. They are essential to the integrated working of SINAPSE. We engage with NHS R&D support bodies, in particular with Health Science Scotland, NHS Research Scotland, and Scottish Health Innovations Ltd.

We also engage with Interface; with Scottish Enterprise, in particular Chris Corden, Senior Executive of the Life Sciences Industry team; and with SDI.

SINAPSE participated in a joint meeting between STFC and DoH to address the crisis facing nuclear imaging due to the planned closure of reactors that manufacture Molybdenum-99. This is covered above as part of our joint working with SUPA.

Public awareness

SINAPSE was involved in the development of the Body Works Exhibition that is currently running at the Glasgow Science Centre. The feature on brain imaging was heavily dependent on our input and the Director was a member of the Scientific Advisory Board.

Researchers from the Aberdeen Biomedical Imaging Centre have been involved in several events engaging the public with science as part of their continuing relationship with the University of Aberdeen Public Engagement with Research Unit, STEM, other local partners and

through events organised in-house. Workshops have been delivered in a number of local schools, at primary and secondary level, on the many different roles magnets play in research, with a particular focus on how they are used in a medical context (MRI). A number of talks for the general public have also been delivered on a range of research areas. The Centre has participated in the Doors Open Day, supplying and staffing a stall, as well as delivering poster presentations at the local NHS Grampian research endowment meeting and for the local launch of the SHARE campaign, encouraging people to sign up for a database of potential medical research participants. In addition to supporting the popular local Techfest science festival researchers were also involved with events for Explorathon and a session of Bright Club. The Centre has continued involvement with Lab in a Lorry (IoP) by volunteering for events at nearby schools. A number of researchers supported the Life Sciences Networking event for local school teachers organised by STEM. In two consecutive years SINAPSE early career researchers in Aberdeen have succeeded in qualifying for the Scottish finals of Famelab.

SINAPSE student Meg Pajak presented at the Bright Club in Glasgow and in Edinburgh, researchers were involved in Science Week. They helped to set up several large exhibitions at the National Museum of Scotland (Magnificent Mummies) and the Queen's Gallery (Leonardo da Vinci) and also delivered lectures in local schools. The imaging of NMS artefacts has developed into a full collaboration between the wider University and the Museum.

Most people are interested in medical imaging. Many are eager to know more about scanners because they need a scan for health reason or they have a close friend or relative who needs a scan. For many others it is simply natural curiosity. SINAPSE researchers from several of our partner Universities combined to produce on-line learning material aimed at non-specialists. In all, ten modules were developed:

- MRI basics
- Advanced MRI
- MRI safety
- Clinical uses of MRI
- PET & SPECT technical
- PET & SPECT biological
- PET & SPECT clinical
- CT
- Ultrasound scanning
- Electrophysiology

They were developed in partnership with eCom Scotland and use graphic illustration rather than equations to explain the techniques. This material is freely available via the SINAPSE web site on <http://sinapse-cpd.dcn.ed.ac.uk/>.

Newsletter and public websites

For much of the period of the award we produce a SINAPSE newsletter, initially edited by our Executive Manager Dr de Wilde and then, after she left, by the Director. Towards the end of the funding period we altered our communication strategy by having more frequent updates of material on the website – www.sinapse.ac.uk. Our IT specialist redesigned the site to make editing by non-specialists more straightforward.

The website can be accessed by anyone. It is used to publicise forthcoming events, post news items, list our publications, provide details of specific projects and link to partner organizations. It also has a searchable list of the areas of expertise of our members.

5. PEER and PECRE Both these activities were warmly welcomed by our researchers and proved to be of great value. Individual details are set out in Appendix 4.

6. INFLUENCE ON PUBLIC POLICY AND PRACTICE

The first SINAPSE Director initiated and lead a UK-wide exercise to improve management of incidental findings detected in imaging research. This lead to a one day workshop supported by the Wellcome Trust in London attended by all imaging research centres, professional organizations involved in imaging research, lay members and ethicists. It lead to several background publications and outcomes:

- Booth TC, Jackson A, Wardlaw JM, Taylor SA, Waldman AD. Incidental findings found in "healthy" volunteers during imaging performed for research: current legal and ethical implications. *Br J Radiol* 2010;83:456-65.
- Booth TC, Waldman AD, Wardlaw JM, Taylor SA, Jackson A. Management of incidental findings during imaging research in 'healthy' volunteers: current UK practice. *Br J Radiol* 2012;85:11-21)
- a primary publication of a UK National Guideline on Management of Incidental Findings in Research - Wardlaw et al. Management of incidental findings detected during research imaging. London: Royal College of Radiologists; 2011. - [http://www.rcr.ac.uk/docs/radiology/pdf/BFCR\(11\)8_Ethics.pdf](http://www.rcr.ac.uk/docs/radiology/pdf/BFCR(11)8_Ethics.pdf)
- further work by the Health Research Authority to provide guidance to ethics committees
- work by the Wellcome Trust and MRC to determine opinions of potential research participants and to provide guidance on their websites for grant applicants.

It has informed the approach taken by UK Biobank and many research groups outside the UK involved in large imaging projects.

We ran several seminars that arose from our work on *Imaging in Society*, including a presentation at the Edinburgh International Science Festival 2012, a seminar at the Union of Physiological Societies world meeting in Birmingham where Hank Greely (California), Gemma Calvert (Singapore), and two high profile researchers from Queens Square were speakers, continuing their collaboration from 2010. It was well received and filmed by the public engagement group in Oxford. This was a continuation of our earlier work on *Imaging in Society* with the Scottish Universities Insight Institute, which lead to several publications, work with Beltane, presentations to the Scottish Parliament and further initiatives with the Royal Society and groups overseas.

The expertise within SINAPSE has been invaluable in advising on the potential misuse of medical imaging. In partnership with the Scottish Universities Insight Institute we conducted a series of expert led debates on Brain Imaging and its Impact on Society. The programme consisted of two two-day workshops and a third workshop over three days, each with national and international speakers and between 30 and 40 participants, a longitudinal work package, and finally a presentation to the Scottish Parliament. Details are reported in Appendix 5. A full report of the meeting is available on the SINAPSE website.

Other activities include SINAPSE representation on the Scottish Dementia Research Consortium, which aims to bring research closer to policymakers. Also, Professor Wardlaw was on the Academy of Medical Sciences Council and contributed to the discussion on technology assessments and the large amounts of un-replicable data published in high profile journals.

The UK has a guideline on management of research findings in medical imaging research thanks to SINAPSE. This is an increasing problem. The SINAPSE work has changed practice in the Health Research Authority that overseas practice in all ethics committees, the MRC and WT grant applicant guidelines, and informed large imaging initiatives such as UK Biobank.

7. PRODUCTS

Novel PET materials or production techniques:

- A new method for radio-iodinating potential SPECT tracers has been developed by SINAPSE post doc Alastair Cant and colleagues in Glasgow and published in *Angewandte Chemie*, one of the major journals in chemistry. *Cant, S. Champion, R. Bhalla, S. L. Pimlott and A. Sutherland, Nickel-Mediated Radioiodination of Aryl and Heteroaryl Bromides: Rapid Synthesis of Tracers for SPECT Imaging, Angew. Chem. Int. Ed., 2013, 52, 7829-7832.*
- Adriana Taveres, one of the first SINAPSE PhD students, developed criteria based on HPLC methodology for lead candidate selection for novel brain radiotracers - *Nuc Med and Biol.* 39:127-135. She has now been charged to develop a preclinical micro-PET-CT system in Edinburgh.
- Dr Alastair Cant, a SINAPSE SPIRIT research fellow, developed novel iodination and radio-iodination chemistry - published in *Chem Comm* in 2012 & *Angewandte Chemie International Edition* in 2013.
- Adele Blair, a SINAPSE PhD students working in collaboration with ScotCHEM, has identified a lead PET tracer candidate for imaging neuroinflammation.- *Med. Chem. Commun.*, 2013, **4**, 1461-1466.
- We have established a partnership with GE Healthcare to develop novel PET radiotracers using their FASTLAB system, including ¹⁸F Fluciclatide and ¹⁸F Flutemetamol.
- We have explored the use of ¹⁸F-fluoroazomycin-arabinofuranoside (FAZA) for detection of hypoxic regions in Oesophagogastric Carcinomas with Positron Emission Tomography (PET) imaging.
- We have developed [¹⁸F]-5-Fluoro-5-deoxyribose as an efficient peptide bio-conjugation ligand for positron emission tomography (PET) imaging.

MRI techniques.

- We have obtained novel software tools for simulation of radiation dose (with Toshiba Medical Systems Europe) and have also been working with TMVSE to develop multimodality imaging workstations.
- We have developed MR elastography in partnership with Charité University Berlin and Siemens Medical Systems.
- We have developed a novel method of targeted inflammation MR imaging of cardiovascular disease using USPIO contrast agents, including a novel analysis pathway. This has now been implemented in a multi-centre trial.
- We have created a novel database of retinal images, CT-related data and clinical parameters for a comprehensive investigation into retinal imaging biomarkers of coronary heart disease. Novel analysis pathway to follow in 2014 as part of completion of PhD studies.
- SINAPSE researchers have developed whole body MR Angiography image acquisition and image analysis systems and ultrasound analysis of blood flow patterns.
- SINAPSE researchers developed novel image analysis algorithms for assessing imaging in stroke, in ageing – these are available to download from the Brain Research Imaging Centre Edinburgh website and are in use in London, Oxford, Maastricht, Munich, Vancouver, Sydney to name but a few.

- The Systematic Image Review System (SIRS) developed by Wardlaw and colleagues for management of imaging in large clinical trials in stroke primarily for IST3 is now in use in UK based multicentre trials RESTART, EuroHYPE1, PISTE, PRACTISE, RIGHT2 and is being considered for use in Australian based ENCHANTED trial, UK based ATTEST trial and UK based cardiology trials. These trials involve handling of some 10000 patients in total.

Data anonymisation. SINAPSE researchers in Edinburgh developed DICOM Confidential. This project led to production of an open source DICOM (Digital Imaging and Communications in Medicine) de-identification toolkit that provides the necessary flexibility to account for different de-identification requirements. It can be downloaded from <http://privacyguard.sourceforge.net/> and is discussed in more detail in section 1.5 above.

The normative brain image bank, BraINS, which benefitted from the SPIRIT PhD collaboration with TMVSE, involves four SINAPSE Centres. We have secured Scotland wide ethics approval to include the legacy data as well as to add new data. This already contains more than 1500 subjects, and was praised by the Caldicott Guardian as an example of best practice in data curation. It was the subject of the final SPIRIT workshop in August 2014. Professor Wardlaw attracted some of the leading world researchers to this event, including Paul Thompson (ENIGMA), JB Poline (INCF), Steve Smith (FSL), Dan Marcus, Alan Evans (MNI), John Ashburner, several representatives from UK Biobank, and Monique Breteler.

New training courses developed/delivered

The on-line MSc and CPD medical imaging and neuro-imaging courses at the University of Edinburgh have been expanded and SINAPSE researchers around Scotland developed graphic on-line modules explaining the working and use of medical scanners. All of these can be accessed through the SINAPSE website.

An Interventional Radiology Course has been set up in Dundee

The SINAPSE MRI safety course was further developed and is now available on line as one of our e-learning modules.

Regular image analysis (Valdez Hernandez, MacGillivray) and fMRI (Pernet, SINAPSE appointee) workshops are held in Edinburgh and other cities in SINAPSE. These are usually oversubscribed with many participants coming from outside Scotland.

8. HELP AND GUIDANCE

The SINAPSE Governing Body was the Board for Academic Medicine. Our Directors made regular appearances at their meetings to update members about our activities and the Chairman, Sir David Carter, has always made himself available to provide mature guidance. His experience was invaluable.

Our International Advisory Board members were Professor Alan Jackson, Manchester; Dr Alan McNair, CSO; Professor Alan Moody, Sunnybrook, Ontario; Professor Andre Luxen, Liege; Professor Chris Kennard; Professor Garry Green; York; and Chairman Professor John Pickard, Cambridge. All provided invaluable help, either by speaking at our meetings, collaborating on joint projects or sharing their academic experience. Professor Wyper was privileged to make a presentation on behalf of SINAPSE at Professor Pickard's festschrift in Cambridge last March.

APPENDICES

Appendix 1:

The SINAPSE Chairs

A1.1 Edinburgh. Professor Edwin van Beek was appointed to the SINAPSE Chair of Clinical Radiology in December 2019. He came from the University of Iowa. Professor van Beek rapidly became an active participant in several Scottish and UK committees including the SINAPSE Molecular Imaging Committee, the SINAPSE working group Medical Imaging Data Access and Sharing (MIDAS) [Chair], the SCOTHEART trial Steering Committee, and the NIHR-NCRI Cancer Research Network. He also serves on many international committee and advisory groups.

Since arriving in Edinburgh Professor van Beek has become principal investigator or co-investigator on grants totaling over £6.6M. His most recent award is as part of the MRC UKDP - Integrated DEmentia research environment (IDEA). This is a programme led by Prof John Gallacher (Cardiff) with total funding of £ 36.9 million. This project will enhance the infrastructure of imaging in dementia. Professor van Beek is leading the installation and running of a new £6M PET-MRI system within the Clinical Research Imaging Centre in Edinburgh.

Several strong commercial partnerships have been developed including two projects with Neil Roberts, Professor of medical Physics in Edinburgh, and the Mentholatum Company, on the development of magnetic resonance elastography [one in collaboration with SUPA]; the ENCHANT study with Synta Pharmaceuticals, to evaluate the potential role of Hsp90, a chaperone protein that helps modulate cellular responses and is therefore vital in oncogenesis; and a study with Pfizer to assess the imaging findings of a new anti-inflammatory agent using 18F FDG PET-CT in combination with high-end image analysis.

Professor van Beek is, or has been, supervisor of 15 graduate students, 8 of who have successfully completed their degrees. He also hosted 18 International Elective Students from Singapore [2], USA [3] Australia, Ireland, China [2], Northern Ireland, UK[3], Pakistan, New Zealand Poland Italy and Malaysia; and International Fellows from Italy, Bulgaria, Iran, Poland and Slovenia. Since arriving in Edinburgh he has been an author on over 100 peer-reviewed papers.

A 1.2 Glasgow SINAPSE Chair of Clinical Imaging – Keith W Muir

Background: Clinical neurologist with an interest in stroke. Main scientific interests include the application of advanced brain imaging to clinical trials as a tool for translational research, including trials of thrombolysis, thrombectomy, and physiological management.

Chief Investigator for the PISCES (Pilot Investigation of Stem Cells in Stroke) trial, the first trial of human neural stem cell implantation for stroke, which commenced in Glasgow in 2010, and is chief investigator for the phase 2a PISCES 2 trial that commenced in June 2014. UK Chief investigator for PISTE (Pragmatic Ischaemic Thrombectomy Evaluation); the EU-funded WAKE-UP trial; the PRACTISE trial to evaluate multimodal CT in acute stroke.

Grant funding since 2009 includes 15 awards (total £6.9million), of which 5 are collaborations with other SINAPSE centres.

Of 42 peer-reviewed publications since 2009, 4 have been derived from cross-disciplinary collaboration within Glasgow; 3 from collaborations with SINAPSE centres; and 7 with international collaborators. International collaborators have interactions with other SINAPSE centres that have been facilitated by these joint publications.

Approximately £32million in support for research imaging infrastructure obtained with the College of Medicine, Veterinary & Life Sciences at the University of Glasgow for the new South Glasgow University Hospital. This will include a research Imaging Centre and a human 7T MRI system that will be the only ultra high field scanner in Scotland. This will be a resource available to other institutions and particularly relevant to SINAPSE researchers.

Commercial Collaborations are currently with Toshiba MVSE on projects related to acute stroke and image analysis, GE in development of PFC-enhanced metabolic imaging, and the Aurum Biosciences spin-out.

Supervision: 2 MD, 1 MSc by research and 6 PhD students (including 1 SPIRIT award) as primary supervisor since 2009 (4 completed, 2 writing up, 4 ongoing), plus 8 intercalated BMedSci students all undertaking imaging research, and 2 co-supervised SINAPSE students.

A 1.3 Dundee SINAPSE Chair of Imaging – JG Houston

Dundee: Professor Graeme Houston is the University of Dundee SINAPSE Professor of Clinical Imaging.

He has been responsible for the development of radiology research activities involving 12 staff, liaising with Tayside Academic Health Sciences R&D Office.

Research and Development Advisory roles:

- **UK:** National Scientific Advisor: Health Technology Devices (Dept of Health), Medicines and Healthcare products Regulatory Agency (MHRA - UK), National Institute for Clinical Excellence- clinical advisor in interventional radiology device safety trials. Outcomes: Safe introduction of new medical devices (IVC Filter) and techniques.
- Royal College of Radiology- Radiology Integrated Training Initiative (2005-2011 Dept of Health): Member of Research Subcommittee (2008-2011), Validated Case Archive Board (2006-2010), Standing Scottish Committee (2008-2012). Outcomes: New radiological national e-learning facility and research programme.
- Medical Research Council EME Board member (2012-) responsible for annual research expenditure allocation and management. He attend three 2-day meetings per year reviewing up to 90 proposals per annum and is the only clinical imaging expert on the panel so advises on a wide range of imaging proposals. Outcomes: MRC EME review and grant of £24m research funds since 2012.
- **EU:** European knowledge exchange initiative (2013- IAAP Marie Curie EU Programme). He leads this 4year programme of collaborating academic and commercial partners across Europe funded by the EU (Euros 2.6m) which is currently reviewing the evidence for and developing audits and research in relation to renal dialysis vascular access (www.redva.eu). The aim is to improve the outcomes for patients with haemodialysis access by improving surgical practice, imaging and interventions in vascular access. European Renal Best Practice (ERBP) guideline group (2014-) - observing member. The ERBP is due to publish updated european guidelines for renal disease in 2015. Technical advisor in relation to imaging technology.
- Elected to the Fellowship of the Cardiovascular and Interventional Radiological Society of Europe (2013). Mentor for the European Board of Interventional Radiologists (2014)

Grants: Total £10m grants since 2009 – eighteen in total, including collaborations with Aberdeen, Glasgow, Edinburgh Universities

Peer reviewed articles: last five years: 25

PhD Students since 2009 – 12 Dundee/St Andrews, MSc students 5 – Dundee/St Andrews.

PhD/MD External Examiner since 2009 – Glasgow, Edinburgh.

The impact of the research has been to improve patient care by:

- New methods of diagnosis - Developing new imaging methods of assessing Cardiovascular (Chest Heart Stroke) and Neurosciences diseases (TMRC), particularly in relation to peripheral arterial disease, stroke and cardiac disease. New medical therapies - Exploring novel ways to regress Left Ventricular Hypertrophy (BHF&CSO).
- New surgical therapies - concept, design, production, regulatory approval and clinical trials in medical devices for treating arterial disease. Developing and using cadaveric models for testing and training for use of new image guided procedures and devices.

- Evaluating the clinical outcome of therapies by participating in multi-centred trials-renal, peripheral arterial disease interventions, endovascular aortic aneurysm repair and fibroid embolisation (MRC).
- Evaluation of health economics impact of new diagnostic and therapeutic patient pathways.

Commercial benefit:

- His cardiovascular research has led to the formation of an NHS "spin-out" company: Vascular Flow Technologies Ltd (20 employees) Developing and marketing new devices for the treatment of arterial disease e.g. grafts, stents.
- Collaboration with Medical imaging companies - Siemens, Toshiba to develop new image post-processing systems.

A 1.4 Aberdeen Chair of Neuroimaging: Professor Schwarzbauer took up his current position as SINAPSE Chair in Neuroimaging at the University of Aberdeen in August 2009. Before his current appointment, he was Head of Magnetic Resonance Imaging at the MRC Cognition and Brain Sciences Unit in Cambridge, and an Affiliated Lecturer at the University of Cambridge.

During his time in Aberdeen, Professor Schwarzbauer has enjoyed working at the interface of multiple disciplines, such as physics, mathematics, neurobiology, and cognitive neuroscience, which provided an excellent platform to translate cutting-edge imaging methods research into novel clinical applications. He was particularly interested in the development and optimisation of quantitative neuroimaging methods and their applications to study normal cognitive function, impaired consciousness, stroke and depression.

In March 2011, Professor Schwarzbauer established the Aberdeen Coma Science Group, an initiative that brings together medical care professionals and scientists with the aim to improve the understanding of disorders of consciousness such as coma or vegetative state and to translate research findings into direct benefits for patients, relatives and carers. New international collaborations were established with Schön Klinik, Bad Aibling, Germany, one of Europe's largest specialist rehabilitation centres for acquired brain injury patients, and the Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Germany. This collaboration led to the development of a novel diagnostic tool in disorders of consciousness based on functional connectivity imaging. The results of this research were highlighted in *Nature Reviews Neurology*.

Professor Schwarzbauer's work in depression with the late Professor Ian Reid and Dr Jennifer Perrin led to a breakthrough demonstrating for the first time that successful treatment of severe depression with electroconvulsive therapy (ECT) alters the brain's functional connectivity in a lasting way. More specifically, this research showed that the brain is functionally hyper-connected in severe depression and that this pathological hyper-connectivity is removed following successful treatment with ECT. The results of this research were published in *PNAS* and portrayed as research highlights in *Science* and *JAMA*. This research also attracted substantial interest in national and international media (BBC Newsnight, BBC World Service, Discovery Channel New York, Bloomberg, Reuters, ABC News, CBS News, The TIME magazine, The Independent, The Times, International Business Times, and many others). In the longer term, these findings are likely to lead to new drug targets, which may match the effectiveness of ECT without an impact on memory.

Professor Schwarzbauer will be leaving the University of Aberdeen to take up a professorship in Munich in February 2015. The University has agreed to fill the post.

Appendix 2:

SINAPSE studentships

This Table shows the progress and destination of our students. It also lists the primary supervisors. They benefited from this scheme by having highly motivated and extremely bright students, but they also contributed a great deal by passing on their expertise. Feedback from the students on the support that they received was extremely complimentary. All students had a

second supervisor in a different organization; either a different SINAPSE University or a partner company.

Key:

A – students funded through the original SINAPSE award

B – Students added as a result of the KE SPIRIT award

C – Students added using the funds vired from the St Andrews Chair

D – Lead University; Glasgow Aberdeen Edinburgh, Stirling, St Andrews, Dundee

Surname	First Name	A	B	C	D	Supervisor	Submission date (past or expected)	Destination
Blair	Adele		1		G	Andy Sutherland	Dec-14	Pending
Braadbaart	Lieke			1	A	Gordon Waiter	2015	
Calamai	Elisa		1		A	Matteo Zanda	Mar-14	SOGIN
Chakirova	Goultchira	1			E	Andrew MacIntosh	Dec-12	Human Brain Research Foundation in Edinburgh
Dickie	David		1		E	Dominic Job	Sep-13	Post doc Edinburgh
Gilfillan	Lynne	1			G	Andy Sutherland	Nov-13	Post doc Edinburgh
Glatz	Andreas		1		E	Mark Bastin	May 2014	Post doc at Graz
Goj	Roman	1			S	David Donaldson	Aug-16	
Gradin	Victoria				A	Douglas Steele	May-11	Post doc Dundee then Uruguay
Hahn	Amanda	1			St A	Dave Perrett	Feb-13	Post doc Glasgow
Hollyer	Tristan		1		G	Mhairi Macrae	2015	
Jameson	Elizabeth		1		E	Mark Bradley	2015	
Johnston	Blair		1		D	Douglas Steele	Feb-14	Post doc Dundee
Johnston	Harriet	1			St A	Arlene Astell	Sep-12	Post Doc Calgary
Jones	Anna		1		E	Cyril Pernet	Dec-14	
Kennedy	Paul	1			E	Neil Roberts	Dec-14	Post doc Marseille
Kokkalis	Stratos		1		D	Graeme Houston		Post doc Dundee
Lepipas	Panos			1	G	Dino Jarozyński	01/09/2015	
Lines	Jennifer	1			S	David Donaldson	Sept-15	
Lloyd	William	1			A	Gordon Waiter	Apr-12	Post doc Reading
Maxwell	Adele	1			D	Doug Potter	1/11/13	Clinical Research Associate, Dundee
McCormick	Lynne			1	D	Graeme Houston	2016	
Merrifield	Gavin		1		E	Ian Marshall	Jan-14	Post doc Glasgow
Merz	Susanne	1			A	Christian Schwarzbauer	Oct-13	Post doc Luxembourg

Mikhael	Shadia	1			E	Maria Hernandez	2015	
Mill	Ravi	1			St A	Akira O'Connor	Sept-14	Post doc Rutgers N J
Mugruza Vassallo	Carlos	1			D	Doug Potter	Mar-14	Lecturer in Peru
Mumuni	Abdul	1			G	Barrie Condon	Nov-13	Lecturer at UDS medical School in Ghana
Murnane	Jonathan			1	E	Neil Roberts	Oct-15	
Mwangi Irungu	Benson	1			D	Douglas Steele	Nov-12	Instructor at Texas University
Ortu	Daniele	1			S	David Donaldson	Sep-12	Post doc Texas
Pajak	Meg			1	G	Sally Pimlott	Dec-15	
Parikh	Jehill	1			E	Ian Marshall	Sep-12	Post doc Newcastle
Rekik	Islem	1			E	Joanna Wardlaw		Post doc North Carolina
Robertson	Gavin			1	E	Tom MacGillivray	Dec-14	
Simpson	Gordon		1		D	Graeme Houston	Withdrew	
Simpson	Johanna	1			S	David Donaldson	Feb-16	
Sokunbi	Moses Olufemi				A	Gordon Waiter	Dec-11	Post doc Cardiff
Strozyk	Jessica	1			St A	Ines Jentzsch	Dec-12	Post doc Tuebingen
Tavares	Adriana	1			G	Sally Pimlott	Dec-11	Research scientist MNI then post doc Edinburgh
Testa	Andrea	1			A	Matteo Zanda	Jan-15	
Thompson	Stephen		1		St A	David O'Hagan	2015	
Tsiora	Stamatina	1			D	Doug Potter	Mar-14	Teaching assistant, University of Portsmouth
Varsou	Ourania			1	A	Christian Schwarzbauer		Occ Health Oil and gas
Zhu	Fan	1			E	Malcolm Atkinson		Post doc Michigan

Appendix 3:

Exemplar testimonials from students

A 3.1

Testimonial from Adriana Alexandre S. Tavares

SINAPSE sponsored PhD: *Development of Novel Radiotracers as Tools for Imaging the Human Brain*

The University of Glasgow, October 2008–October 2011

Dr Sally Pimlott, Dr Deborah Dewar

In collaboration with the University of Aberdeen: Dr Lutz Schweiger.



This work supported the development of a novel single photon emission computed tomography (SPECT) radiotracer for *in vivo* imaging of noradrenaline transporters in the human brain, ^{123}I -NKJ64. Furthermore, it supported the development of a novel *in vitro* tool for selection of lead radiotracer candidates using high performance liquid chromatography.

The tremendous opportunities available within SINAPSE, as well as the continuous efforts to foster multidisciplinary and collaborative approaches among different research groups, were essential to the successful completion of my PhD. The skills I acquired as a SINAPSE PhD student allowed me to combine my background in nuclear medicine and biomedical engineering with acquired knowledge in radiotracer discovery and development.

SINAPSE funding allowed me to visit laboratories outside the UK, namely the Molecular NeuroImaging (MNI) laboratories and the Yale PET centre in the USA, where I was able to conduct studies using ^{123}I -NKJ64 in nonhuman primates. Additionally, SINAPSE support allowed me to present my data at different prestigious international meetings, including the Eighth International Symposium on Functional Neuroreceptor Mapping of the Living Brain 2010, Glasgow, UK and the XXVth International Symposium on Cerebral Blood Flow, Metabolism and Function & Xth International Conference on Quantification of Brain Function with PET 2011, Barcelona, Spain. Thanks to SINAPSE support, I was also able to attend valuable international training courses, namely a course on PET and SPECT Radiopharmaceuticals Preparation: Design, Radiolabelling Strategy and Radiosynthesis, 2009, Diagnostic Molecular Imaging (DIMI) Tours, France.

The laboratory placement at MNI was key not only to my PhD research, but also to my subsequent early research career. As a result of the work I was able to develop there during my PhD laboratory placement, I was offered a position as Image Processing Analyst at MNI. Recently, I returned to Scotland and have been appointed as research fellow in PET imaging at the University of Edinburgh. The skills I have acquired during my SINAPSE funded PhD have been extremely valuable thought my research career.

PUBLICATIONS

Eight publications, six with Dr Taveres as first author

A 3.2 Testimonial from Dr Islem Rekik.

Dr. Islem Rekik

SINAPSE funded student

University of Edinburgh, November 2010- October 2013

Department of Neuroimaging Sciences

Supervisors:

Prof. Joanna Wardlaw, The University of Edinburgh

Dr. Trevor Carpenter, The University of Edinburgh

Dr. Stephanie Allassonnière, Ecole Polytechnique



Last March, I was awarded my PhD, entitled “Novel *Mathematical Modeling Approaches to Assess Ischemic Stroke Lesion Evolution on Medical Imaging*” at the **University of Edinburgh** (Department of Neuroimaging Sciences, **Centre for Clinical Brain Sciences (CCBS)**), joint with the Centre of Applied Mathematics (CMAP) at **Ecole Polytechnique** (Paris). I have also received a “SINAPSE *Postdoctoral Exchange Research Award*”. This highly motivated me to set a multidisciplinary collaboration between **Visionlab** of the **Center for Imaging Science (CIS)** at

The Johns Hopkins University (JHU) and the Brain Research Imaging Center (BRIC) at the University of Edinburgh –paving the way for a collaborative postdoctoral research project (2015-2016).

One of the key findings of my thesis was the absence of dynamic models developed or applied to simulate the evolution of acute ischemic stroke lesions using imaging. Addressing this deficit has been the focus of my PhD project. In particular, I have used and developed **spatiotemporal dynamic models** to simulate stroke lesion evolution and estimate kinetic and other stroke measures (e.g., regions with high contraction and expansion and speed) as well as examine some stroke-centered hypotheses (e.g., using perfusion threshold **or** the perfusion/diffusion mismatch concept to predict final tissue fate). The dynamic models robustly overcame two pitfalls of previous static approaches (limited to using basic thresholding techniques on 2D/3D MR slices) and our results showed that the above hypotheses are not always true –engaging the stroke research community into rethinking stroke and its evolution hypotheses.

Joining SINAPSE and BRIC compelling research teams in Scotland opened up for me new directions of thinking and allowed me to extend the development and the testing of pioneering models to get a better understanding of the evolution of brain ischemia. I believe that sharing the diversity of this multidisciplinary research experience with researchers in international research labs (eg: Visionlab at Johns Hopkins University) will stimulate the flow of more creative ideas that will target specific problems to solve. I am always very keen to share my knowledge, expand it and acquire new skills. With the sharp and outstanding expertise of my supervisors and the enriching trainings/seminars/meetings **SINAPSE** offered us, I learnt to see great potential in networking with my research peers and building on productive and successful collaborations.

Publications: Four publications during SINAPSE studentship with Dr Rekik as first author.

A 3.3 Testimonial from Moses Olufemi SOKUNBI, PhD MIEEE University of Aberdeen, Aberdeen, Scotland, October 2008 – September 2011.



For a long time, I have always wanted to do research in image processing. Browsing through the internet I came across a new initiative of six Scottish universities called SINAPSE. After going through an interview process, I was awarded a PhD studentship in human neuroimaging. My PhD thesis titled Functional MRI entropy measurements of brain complexity entailed the characterisation of fMRI signals with a concept called entropy, which had its foundations in thermodynamics and information theory.

A SINAPSE studentship provided an enabling environment for me to interact with researchers and students from other Scottish universities. Owing to the interdisciplinary nature of my PhD research work, SINAPSE provided the necessary multidisciplinary faculty of Physicists, Medical Physicists, Computer Scientists, Engineers, Neurologist, Neuroradiologists, Psychologists, Psychiatrists, and Neuroscientists that made my PhD journey one of the best experiences of my academic life. The 3-day PhD induction program organised for new PhD students was excellent. Also, the seminars, workshops and developmental courses organised by SINAPSE were very helpful to the success of my PhD, in fact I completed my PhD program exactly in its 36 months duration. My SINAPSE studentship also provided me the opportunity to attend local and international conferences.

Presently, I am a postdoctoral researcher at the Cardiff University Brain Research Imaging Centre and the MRC Centre for Neuropsychiatric Genetics and Genomics, Institute for Psychological Medicine and Clinical Neurosciences, Cardiff University, Wales, where I am involved in research into using brain computer interfacing and real-time fMRI neurofeedback as a therapeutic tool for Depression. I have also recently applied for funding from the mental health agency, MQ to become an independent researcher (an MQ Fellow).

The impact of the SINAPSE studentship upon my academic career cannot be overemphasised. SINAPSE made me fulfill my long term desire and I sincerely hope it will continue to help many other potential researchers attain their goals.

Publications. Four first author papers accepted during the preiod of the studentship.

A 3.4

Testimonial from Gavin Robertson PhD student - SINAPSE/Optos plc

Clinical Research Imaging Centre, University of Edinburgh

Biomarker Discovery of Coronary Heart Disease from Widefield Retinal Images - Presence and Risk



Introduction

I started my academic career at Heriot-Watt University on the outskirts of Edinburgh where I graduated with a BSc (hons) in Physics in 2006. After graduating I worked as a Test Engineer for Gemfire Europe in Livingston. Gemfire manufacture silicone based optoelectronic components for high-speed optical fibre telecommunications, my job was to insure the components were tested to a high and consistent standard on automated test stages. In 2009 I went back to university to study for a MSc in Bioengineering at the University of Strathclyde. This was a wide ranging course covering many aspects of engineering and the human body: from prosthetics and implants to advance imaging techniques and signal processing. My project involved using computational neural networks to make time-series predictions of blood glucose levels for people with diabetes to help control their glucose levels. After finishing at Strathclyde, I started working for Optos plc based in Rosyth. Optos manufacture ultra wide-field scanning laser ophthalmoscopes (SLOs) used to image the human retina. It was while working on the manufacturing of Optos' latest SLO that I heard of the PhD opportunity at the Clinical Research Imaging Centre, University of Edinburgh. This was to investigate the link between the retinal blood vessels and coronary heart disease using the advance imaging modalities of CT coronary angiography and SLO retinal photograph - a project jointly funded project between SINAPSE and Optos plc.

Background

The aim of the project is to identify retinal image biomarkers that could indicate the severity and risk of coronary heart disease (CHD). To achieve this, patients are being imaged with state-of-the-art SLO (SLO captures approximately 80% of the retinal surface compared to approximately 15% for a standard fundus camera).

Summary

Within the Clinical Research Imaging Centre in Edinburgh I have imaged a cohort of 475 patients. This has involved close involvement with clinicians and radiographers as well as with participants (consenting, imaging etc.). I am also involved in image review, i.e. looking for incidental findings; we collaborate closely with the Reading Centre at Moorfields Eye Hospital in London and I oversee an electronic link so that experienced ophthalmologists there can review our images remotely.

I have also developed an automated segmentation technique as part of the VAMPIRE project (<http://vampire.computing.dundee.ac.uk/>). This is a novel method of extracting blood vessel information from the retinal photographs from the SLO. This has possible through close collaboration with the University of Dundee where joint validation has been carried out. We (the VAMPIRE team in Edinburgh & Dundee) also work closely with Optos who have been developing better 2-D re-projections from their SLOs which image the 3-D retinal surface. This has involved the stereographic projection of images for a more realistic representation of vessels in the periphery (the same problem arises when mapping the globe of the world on to a 2-D map).

Future

The next stage of the project is to investigate the arteriole-venule ratio (AVR) as a biomarker of CHD. This has involved consultation with senior ophthalmologists based in Edinburgh as where best to measure AVR in the wide-field SLO images, given the unique, much larger area they represent over fundus cameras (the standard in this research field). The close collaboration forged with Dundee will allow for the investigation of other retinal biomarkers of CHD once I have finished my PhD (Nov 2014). Biomarkers such as branching angles, tortuosity and fractal dimensions have been investigated before in fundus camera images, but SLO images offer unique locations for these makers to be explored. This will continue after my studies finish.

SINAPSE has been an excellent platform for my research career. It has enabled me to investigate an area I hold an excited interest in, allowing me to interact with leaders in the field. This has allowed me to develop my skills as a researcher, giving talks at the annual ASMs as well as presenting posters at international conferences. Its close collaboration with industry has allowed me establish connections and appreciate the pressures involved. Thanks to the help SINAPSE I hope to have a long and fruitful research career.

Appendix 4 PEER and PECRE

PEER Round 1:

PEER support enabled Prof Houston to work on a grant agreement for: Industry-Academia Partnerships and Pathways in response to Call FP7-PEOPLE-2012-IAPP. The project is titled: *Development of hemodynamic solutions in Renal Dialysis Venous Access Failure*. This proved to be a successful application and the project started on 1st Oct 2013.

PEER Round 2:

PEER support enabled Prof Wardlaw to work on an outline application to Horizon 2020 that involves co-applicants in Germany, Denmark, UK, France: Call H2020-PHC-2015-two-stage, Topic: PHC-03-2015, Type of action: RIA, Proposal number: 666881-1, Proposal acronym: SVDs-at-target. A full application will be submitted if the outline is successful. Meantime the funding enabled the preparation of a second application to the EU Joint Programme of Neuro-degeneration Research (JPND) for a Working Group to identify cohort studies relevant to vascular contributions to neuro-degeneration. This was funded, it links researchers in Canada, the USA, the Far East as well as Europe, work is ongoing, a Working Group meeting will be held in January 2015 in Munich, report to be submitted in March 2015. Most importantly, it will place us in a very good position to respond to the EU-JPND call for large ambitious projects on cohorts relevant to neuro-degeneration that will be announced in early 2015.

Exchange visits of early career researchers

SINAPSE PECRE funds were utilized by all six participating Universities. Details are:

PECRE Round 1

Joanne Park. An early career researcher based at the **University of Stirling** visited the Centre for the Neural Basis of Cognition in **Pittsburgh** to pursue a joint programme of work using functional MRI to investigate interactions between two specific sub-systems of memory: implicit priming and explicit episodic memory. The work undertaken during the exchange extended the candidates' prior work using the Event-Related Potential (ERP) technique to investigate these sub-systems of memory, providing multi-modal imaging data on an important issue in memory research. The candidate received thorough training in the application of functional MRI techniques and data analysis over the course of the exchange, gaining valuable experience in an imaging technique critical for career progression in the field of cognitive neuroscience. In addition, the candidate was given an important opportunity to forge links with a top memory researcher well respected in the field of Neuroimaging. The USA is the dominant focus of Neuroimaging research worldwide, and the development of these links between SINAPSE and US collaborators involved in the project has obvious positives – not least in increasing the SINAPSE profile.

Andreas Glatz. A PhD student based at the Brain Research Imaging Centre in **Edinburgh** worked at the Neuroimaging Research Unit in the Department of Neurology at Medical University **Graz in Austria** on a collaborative project developing MRI sequences to analyse basal ganglia iron deposits that are putative biomarkers for cognitive aging and small vessel disease. This work led to a firm collaboration between the Centres. Dr Glatz now works there as a post-doctoral researcher.

Meg Pajak. A SINAPSE PhD student based in the Beatson Institute for Cancer Research in **Glasgow**, undertook two exchanges with other users of the new Albira micro SPECT-PET-CT scanner. The exchanges were to the laboratories of Professor

Benloch at the University of **Valencia** and Prof Levy at **Notre Dame University** in Indiana, Part one enabled the researcher to study performance assessment processes for small animal positron emission tomographs that are outlined by NEMA, utilising the expertise of the detector designers and inventors at the CSIC-Universitat de València and included the development of novel image processing software and the processing and analysis of imaging data obtained from the Albira micro-SPECT-PET-CT in Glasgow. The second part enabled the researcher to develop expertise in image acquisition and protocol development for imaging small animals.

Ravi Mill. A PhD student at the University of **St Andrews** went on a research placement to work with Professor Ian Dobbins at **Washington University in St Louis**. During the placement he acquired knowledge of a new imaging technique – infra-red eye-tracking – and gained experience of working in a different laboratory in a different country. The findings from this study have been submitted for publication presently and have fuelled ideas for further collaboration.

Sergio Dall'Angelo, Ph.D.. An early career post doctoral researcher from the **University of Aberdeen** exchanged to the laboratory of Professor Tobias Ritter at **Harvard** to study a new 'late-stage' fluorination process, that holds promise to revolutionize the field of PET radiofluorination. This project was successfully completed and was presented at the recent SINAPSE PET Chemistry meeting in Glasgow. Subsequently it was presented at the Fluorine: Academia meets industry meeting, see <<http://chemistry.st-andrews.ac.uk/fluorine/Welcome.html>><http://chemistry.st-andrews.ac.uk/fluorine/Welcome.html>. Sergio has been invited to give a lecture about radiofluorination methodologies at an ITN network meeting in Prague next January.

David Dickie. A PhD student based at the Brain Research Imaging Centre in **Edinburgh** visited **McGill University**, **UCLA** and **Washington University** to pursue a joint programme developing a 'living brain bank' using MR images of normal subjects already acquired as part of research projects across SINAPSE. This provided normative references for research and clinical reporting of brain images. This exchanges helped to showcase and harmonize the SINAPSE novel brain image bank and models with the other established banks. It was followed up by an international symposium on the 'Development of Human Brain Image Banks and Age-Specific Normative Brain Atlases' at the Royal Society of Edinburgh on 28-29 August 2014.

Dima Maneuski. This exchange [jointly supported with SUPA] enabled an early career researcher from the **University of Glasgow** to work at the laboratory at the **University of Liege**, of Professor Andre Luxen, one of the SINAPSE International Advisory Board members. There he evaluated the medipix detector for use in radioisotopes generators. This was very successful and led to Dr Maneuski getting an STFC Fellowship to commercialise the process. NOTE: Although the plan was to support this exchange jointly with SUPA, Dr Maneuski spent less than was anticipated and so no cross-charge was made.

PECRE Round 2

Islem Rekik. Working under Prof Wardlaw in **Edinburgh**, Dr Rekik developed three-dimensional, longitudinal computational models of changes in the volume of tissue affected during an acute ischaemic stroke using diffusion, structural, and perfusion MR brain imaging human data. As part of the PECRE scheme Dr Rekik spent 4 months at **Johns Hopkins University** in Dr Rene Vidal's image analysis laboratory. Subsequently she has taken up a post-doctoral position at IDEA, University of North Carolina, under Prof Shen Dinggang, an outstanding research laboratory (<http://www.med.unc.edu/bric/ideagroup>). This has strengthened the SINAPSE links with the Centres.

Panos Lepipas . To sep-up this collaboration Mr Lepipas’s supervisor, Dr Pimlott [Glasgow] spent one week at TRIUMF, **University of British Columbia**, in February 2014. This is joint work with SUPA and for part of the exchange Panos was accompanied by Dr Silvia Cpiccia, who was supported by SUPA. The exchange has accelerate a programme exploring medical radioisotope production using next Generation Wakefield Laser Accelerators. In Glasgow Panos has undertaken a preliminary project and has successfully produced Cu-67. The objectives of his visit were: a) to obtain knowledge of current methods, properties and technologies used for target design, b) to design or learn how to design an optimised target for LWF accelerator, which will be used in the next experiment in Glasgow, c) to get an overview of extraction methods, and d) to participate in projects at TRIUMF. In addition to knowledge exchange, the visit involves collaboration in planning and participating in an upcoming experiment at TRIUMF's facilities on the production and purification of the rare radioisotope 225Ac using novel methods. 225Ac is used in targeted radiotherapy. Dr Paul Schaffer, Head of Nuclear Imaging Programme at TRIUMF recently wrote: *“I’m glad that both Panos and Silvia are enjoying their work here. They have been a terrific boost to our program and I’m looking forward to the Ac-225 experiments. I hope they take away what they need for Cu-67 production in Scotland.*

Dorota Chapko. A PhD student based at the **University of Aberdeen** exchanged to the Department for Biostatistics at the **University of California in San Francisco**, hosted by Dr. Maria Glymour (Associate Professor). Dorota is researching memory and ageing and the exchange enabled her to gain proficiency in modelling techniques relevant to life-course research. Dr. Glymour has expertise in modeling social determinants of health in aging especially in the context of cognitive functions, dementia and stroke. She has experience of evaluating cognitive resilience in the face of pathology quantified by neuroimaging biomarkers. During the exchange Dorota became involved in one of Dr. Glymour’s projects in which she modeled how life-course factors modify the influence of genetic risk for Alzheimer’s and cerebrovascular dementias on cognitive outcomes. Two themes, cognitive function in aging and neuroimaging, were identified as appropriate for future collaborations with UCSF.

PECRE Round 3

Eric Barnhill based at the Clinical Research Imaging Centre in Edinburgh is working of the development of magnetic resonance elasticity. He is working on a project with Professor Ingolf Sack, Elastography Group, Diagnostic and Interventional Radiology and Nuclear Medicine Charité - Universitätsmedizin Berlin. Magnetic Resonance Elastography (MRE) is a method of phase contrast imaging in which the organ of interest (e.g. brain, muscle or liver) is vibrated with time-harmonic acoustic waves in synchrony with motion sensitized magnetic field gradients. Mechanical properties of the tissues are determined by analysis of the MRI frequency data. Most MRE work to date has been at low resolution but Eric’s PhD has developed processes that extend it to higher resolution. In Berlin he is applying the same MRE protocol on a 1.5T, 3T and 7T MRI systems, all provided by the same manufacturer and making measurements on a set of 10 young and 10 elder subjects on each MRI system. One of the objectives is to generate pilot data on the sensitivity of MRE for detecting age related changes in brain tissues with high resolution and to use this to underpin a major collaborative grant application.

Anna Heye is based at the Brain Research Imaging Centre in Edinburgh. She will spend 2 weeks at each of three Institutions – the Advanced Imaging Research Center,

Oregon Health and Science University, Portland, USA; the Functional Imaging Unit, Glostrup Hospital, Copenhagen University, Glostrup, Denmark; and the Diagnostic Imaging Research Unit, Campus Bio-Medico, University Hospital Rome, Italy. Dynamic contrast-enhanced MRI (DCE-MRI) has proven valuable in the assessment of diseases such as brain tumours and multiple sclerosis, which are linked to abnormalities in blood-brain barrier (BBB) functionality. Recently, there has been growing interest in the application of permeability imaging to pathologies associated with subtle BBB disruption, such as lacunar stroke and Alzheimer's disease. Unfortunately, there is no standard protocol for the acquisition and analysis of such data, and the results may be strongly influenced by the choice of methods. To address these issues, Anna and her colleagues have implemented several image analysis and modeling approaches and applied these in the analysis of DCE-MRI data obtained during a study of mild stroke patients. The objectives of Anna's exchange are: to explore in detail the acquisition protocol, data modeling approaches and patient cohorts employed at each institution in comparison to her approach; to exchange critical feedback and discuss further improvements to the methodology; to determine, where appropriate, the wider applicability of our software through application to sample data acquired at the partner institutions; and to explore proposals for future collaboration, reciprocal visits and knowledge exchange with the partner institutions.

Dr Bharath Kumar Cheripelli, Clinical Research Fellow, University of Glasgow is visiting Prof Leif Ostergaard, Center for Functionally Integrative Neuroscience, Aarhus University, Denmark. The is to facilitate a collaborative project titled "Application of Capillary transit time heterogeneity (CTTH) in mapping of core and penumbra in acute ischemic stroke". The currently used methods for estimation of core and penumbra in acute ischemic stroke take into account the blood flow in arteries and arterioles and assume homogenous flow in capillaries. Prof Ostergaard from Aarhus University, Denmark has done pivotal work on the role of the microcirculation in acute ischemic stroke. During the exchange Dr Cheripelli is investigating the potential role of CTTH in outcomes of re-canalised patients with acute ischaemic stroke using existing data from approximately 150 CT perfusion scans from three previous studies. A specific focus is on the role of hyperglycemia in tissue survival, based on recent analyses of the Post-Stroke Hyperglycaemia (POSH) study.

The aim is that the collaboration will provide him with enhanced knowledge and skills in a new technique of image analysis and address the questions: 1) can incorporating CTTH give more accurate prediction of tissue outcome in acute ischemic stroke? 2) is CTTH a major factor for poor outcomes in hyperglycemic patients compared to normoglycemics? As much of the work involves novel approaches to statistical analysis Dr Cheripelli will be accompanied for part of the exchange by Dr Rachael Fulton, also an early career researcher.

Dr Cyril Pernet from the Division of Clinical Neurosciences at the University of Edinburgh has visited Prof Arnaud Delorme, Centre de Recherche Cerveau et Cognition, Toulouse Cedex, France. Dr Pernet has developed a toolbox for the statistical analysis of EEG data (LIMO EEG) which can be used on top of the EEGLAB software developed by Prof Delorme). The toolbox has been proven very popular (>8000 downloads since 2011 https://gforge.dcn.ed.ac.uk/gf/project/limo_eeg/). The aim of the exchange is to undertake work to integrate the two software packages.

Jessica Duncombe is a PhD student at the pre-clinical imaging Centre in Edinbnburgh. She will undertake an exchange in January and February 2015 to work in the laboratory of Dr Kohls at the Zurich Neuroscience Centre. At the Klohs laboratory a range of techniques have been developed for in vivo imaging of vascular pathology and they have applied these to experimental models of cerebral ischaemia, cancer biology and cerebral amyloidosis. Recently, contrast-enhanced magnetic resonance angiography (ce-MRA) has been used to non-invasively identify changes in vascular density that occur in the transgenic Arc AB mouse line, an experimental model of Alzheimer's disease. The aim of the SINAPSE exchange project is to gain sufficient experience in this novel technique so that it may be established in Edinburgh and used

to investigate vascular alterations in our experimental models. Through the SINAPSE network, this will then allow vascular imaging expertise to be accessed by a wider range of universities throughout Scotland and the UK.

Dominic Job from Edinburgh will visit four Centres: 1) Montreal Neurological Institute (MNI), McGill University; 2) Laboratory of Neuro Imaging, The University of California Los Angeles; 3) Neuroinformatics Research Group, Washington University; and 4) Commissariat à l'Energie Atomique, France. In Edinburgh, in collaboration with the other SINAPSE centers, we are developing a repository of human brain imaging data: 'Brain Images of Normal Subjects' (BRAINS). This is a 'living brain bank' using MR images of normal subjects already acquired as part of research projects in Scotland. In August 2014 we held a highly successful Brain Image Banking workshop bringing researchers from all over the world together to discuss how to take this field forward. Dominic is a post-doctoral researcher specialising in brain image analysis. The exchange will improve the infrastructure and sustainability of BRAINS; ensure compatibility with established international banks to allow integration of images and phenotypic data; identify potential large collaborative projects involving these Centres, SINAPSE and the Farr Institute; and identify potential products and markets/users for commercial spin offs from BRAINS.

Appendix 5.

Brain Imaging and its Impact on Society.

a) Incidental findings in imaging research – summarized in the report published by the Royal College of Radiologists on behalf of SINAPSE and all participants:

[http://www.rcr.ac.uk/docs/radiology/pdf/BFCR\(11\)8_Ethics.pdf](http://www.rcr.ac.uk/docs/radiology/pdf/BFCR(11)8_Ethics.pdf)

b) Brain Imaging and its wider Impact on Society.

Part 1: Advances in Neuro-imaging and the implications for society. This addressed questions: a) who should see our brain images?; b) should neuroimaging be used as evidence in court (neurolaw)?; and c) should neuroimaging be used in commerce? The workshop covered what is currently possible using brain imaging and debated whether and how brain imaging is appropriately used in legal and marketing contexts. It also covered future projected developments in functional and structural magnetic resonance imaging (MRI), magnetoencephalography (MEG) and molecular imaging methods as applied to legal and forensic use; determining moral intent; mind reading, lie detection; neuro-marketing; the limitations of brain imaging; data management issues including storage, access to brain images for research or clinical purposes, image ownership and privacy. Topics included the blurred boundaries between science and commerce and the potentially subliminal use of brain imaging research for economic gain.

Part 2: What is the legal view; forensic uses of neuro-imaging, ethical considerations, security, privacy and human rights

This focused on uses of brain imaging in law. Speakers included Prof Hank Greely, Prof of Law at Stanford, and Judge Jed Rakoff, Senior Judge from the State of New York. The participants discussed whether it was appropriate to use brain imaging for lie detection, moral intent, establishing criminal responsibility, in the penal system, discussed exemplar court cases and in what if any circumstances might it be appropriate to use brain imaging in law. The need for regulation of forensic technologies was discussed. Six key points were addressed: 1) is the technology reliable enough to support legal decision-making? 2) Does it answer the questions the law asks, or is there a conceptual mismatch? 3) How do the answers to 1 and 2 influence the boundaries between legal and medical intervention? 4) Can the science (and its limitations) be reliably communicated to the legal profession (judge, jury or probation officer)? 5) If punishment is based on this technology, can this be presented so as to avoid loss of respect for the legal system by the general public? 6) Are there any legal reasons why the technology should not be used even if the answers to all these questions are yes?

Part 3: Influencing policy, Discussion of ethical guidance and practice

Scotland's Futures Forum (SFF), a non party-political organisation owned by the Scottish Parliament's Corporate Body, coordinated the third workshop in two parts, the first for the lay public in a World Café style debate and the second for policy makers, culminating in a presentation to MSPs at Holyrood. *Event 1* included 45 lay members of the Forum who heard a summary of outputs from the two prior workshops, debated key topics, considered exemplar court cases, and provided feedback. *Event 2*: on 19th August, assisted by the Scottish Government's Chief Scientist's organisational networks and attended by Prof Anne Glover Chief Scientific Advisor, included 50 policy makers. Professor Jonathan Moreno, expert in biomedical ethics, advisor to the White House Office of Science and Technology Policy, co-chairman of the Committee on Guidelines for Human Embryonic Stem Cell Research in the USA, provided an international perspective. Debate focused on any requirement for regulation, other methods of encouraging public awareness and ways to engage Government. A summary of the conclusions from all three workshops was presented to MSPs at Holyrood. The presentation was attended by the shadow Education Minister, a member of the Health Committee and researchers. It was preceded by a publication in the journal *Holyrood* on brain imaging.

Part 4: Longitudinal Work Package

The workshops were underpinned by a substantial amount of background work including an extensive survey of media representations of neuro-imaging culminating in a systematic review of uses of imaging outside traditional medical diagnosis or scientific research, creation of multiple summary posters, several interviews with science journalists (eg Holyrood, the Glasgow Herald, BBC Scotland). An online survey was designed using 'Survey Monkey' to obtain the opinions of non-expert members of the public and those with expertise in neuro-imaging on wider uses of neuro-imaging and whether it should be regulated. The surveys targeted the public and neuro-imaging experts (e.g. psychologists, radiologists, neuroscientists), through dissemination in the media, professional society circulation lists, organizations like Beltane, and websites (SINAPSE, Edinburgh Neuroscience, SCRIPT, Joseph Bell Centre (JBC), Futures Forum), science blogs and other website.

