Sefydliad Cenedlaethol ar gyfer Ymchwil Gofal Cymdeithasol ac Iechyd | National Institute for Social Care and Health Research

Llywodraeth Cymru
Welsh Government

NISCHR Clinical Research Infrastructure

Monitoring Report for Wales Gene Park

(1st April 2013 – 31st March 2014)

Lead Applicant	Professor Julian Sampson
Organisation	Wales Gene Park (WGP)
Start date of award	1st April 2010
Period of review	1st April 2013 – 31st March 2014
Date of report	**05.06.2014**
Signature	

Section 1: Progress made in reporting period

a) Research outputs

1. Grant applications accepted for funding

	(a) At 31 Mar 2013	(b) 1st Apr 2013 – 31st Mar 2014	(c) = (a) + (b) Total
Number of grant proposals accepted for funding	108	30	138
Total value of grant proposals accepted for funding*	**22,593,721**	**4,213,274**	**26,806,995**

Please provide separately additional details (set out below) about all grant applications from the Wales Gene Park accepted for funding **between 1st April 2013 and 31st March 2014**. Please group projects under subheadings for the most relevant Wales Gene Park work package.

Title	Principal / Lead Investigator & Co-investigators	Suitable for CRP?	Funding source	Funding type (e.g. project / infrastructure)	Total grant value
Defining the role of wildtype and mutant plexinB1 in prostate cancer	Prof AR Clarke	No	Prostate Cancer Research Centre	project	£ 11,270.00
Studentship	Prof A Clarke	no	Embassy of the Arab Republic of Egypt	infrastructure	£ 15,000.00
MINI KESS	Dr L Parry, Prof A Clarke	no	Welsh European Funding Office,	infrastructure	£ 22,650.00
Developing stem cell containing organoids from primary and metastatic human colorectal cancer for preclinical studies of stratified colorectal cancer therapeutics	Prof A Clarke, Prof T Dale	no	Cancer Research Wales	project	£ 104,280.00
Modelling colorectal cancer: Assessing pathway synergies and antagonisms in vivo and validating therapeutic targets	Prof AR Clarke, Prof TC Dale	no	Cancer Research UK	project	£ 993,206.00
Investigating the mechanism of berry diet chemoprevention in Wnt-driven intestinal tumorigenesis	Prof AR Clarke	no	Tenovus	project	£ 90,000.00

Identifying the influence of the microbiome and metabiome on the normal and malignant murine intestinal stem cell	Prof A Clarke Dr A Gallimore, Dr J Marchesi Dr L Parry	no	World Cancer Research Fund International	project	£ 225,000.00
Wnt pathway	Prof TC Dale (BIOSI), Ms EA Fraser	no	Merck KGaA	project	£ 146,656.00
Extending the application of a new anti-Wnt signalling compound through the interaction of novel combinatorial compound partners	Prof TC Dale	no	Biotechnology and Biological Sciences Research Council	project	£ 14,020.00
Stem and progenitor cells and the origins of breast cancer heterogeneity	Dr MJ Smalley	no	Cancer Research UK	project	£ 516,096.00
Testing the efficacy of iFLIP/TRAIL mediated cytotoxicity in breast tumour tissues ex vivo	Dr R Clarkson	no	Tenovus	project	£ 89,533.00
The identification and selection of candidate lead compounds against BCL3	Dr R Clarkson, Dr A Brancale, Dr A Westwell	no	BioVitas Capital Ltd	commercial	£ 67,500.00
Novel BC13 inhibitors - target validation and anti-metastatic lead optimisation	Dr R Clarkson	No	BioVitas Capital Ltd	Commercial	£ 40,000.00
Wnt pathway	Prof T Dale, Ms E Fraser	No	Merck KGaA	commercial	£ 35,462.00
Identification of the molecular defects in metabolic pathways associated with MECP2 deficiency	Dr DS Millar, Prof AJ Clarke, Dr A Tee	no	Newlife Foundation for Disabled Children	project	£ 11,150.00
Genetic mechanisms in colorectal polyposis	Prof J Sampson, Dr E Short	no	Pathological Society of Great Britain and Ireland	project	£ 9,810.00
Identifying MTORC1 independent functions of TSC2	Dr A Tee (MEDIC), Prof J Sampson (MEDIC)	no	Tuberous Sclerosis Association	project	£ 169,278.00
Prevention of renal lesions by tuning mTOR signaling in a model of tuberous sciences	Dr M Shen (MEDIC), Prof J Sampson (MEDIC)	no	Tuberous Sclerosis Association	project	£ 176,804.00
Targeting CD200 signalling to overcome human basal cell	Prof A Clarke, Dr G Patel, Dr R Darley, Prof A	no	British Skin Foundation 506179	Post doc infrastructure	£ 81,000.00

carcinoma immune-evasion	Gallimore, Dr A Tonks, Dr E Wang				
Defining the role of wildtype and mutant plexinB1 in prostate cancer	Prof A Clarke (BIOSI)	no	Prostate Cancer Research Centre	project	£ 116,949.00
Preclinical testing of a novel anti-cancer compound	Dr M Smalley (BIOSI)	no	Cancer Research Technology Ltd	project	£ 8,033.00
R EC BIOSI SMALL CSCSIGN	Dr M Smalley (BIOSI)	no	Commission of the European Communities	project	£ 842,067
Does complement and innate immune activation associated with neuronal and axonal damage in multiple sclerosis	Professor M.I. Rees	no	Multiple Sclerosis Society	project	£ 39,327
Additional Investment in the WERN Biobank and e-Health Research	Professor M.I.Rees	no	NISCHR	Project	£ 85,000
Support costs for 3T MRI scans and skin biopsy IPSC collaborations in gene-positive NHS patients	Professor M.I. Rees	no	ABMUH NHS R&D Office	project	£ 20,000
NISCHR Senior Faculty	Professor M.I.Rees	No	NISCHR	Infrastructure	£ 45,000
"Generating a Tissue Microarray Array of Renal Tumour Subtypes"	Prof J R Sampson, Dr Andrew Tee	No	Cancer Research UK (strategic funding)	Project	£ 5000
Regulation of autophagy by mTORC1 and ULK1"	Dr Andrew Tee	No	Cancer Research UK (strategic funding)	Project	£ 4000
Restoring TSC pathology through autophagy induction and mTORC1 inhibition. (Ref: 2013-P05)"	Dr Andrew Tee	No	Tuberous Sclerosis Association (Postdoc to Dr Elaine Dunlop	Project	£ 59,905
Investigating mTORC1 independent functions of TSC2 (ref: 2013-F02)"	Dr Andrew Tee	No	Tuberous Sclerosis Association (Postdoctoral Fellowship to Dr Kayleigh Dodd)	Project	£ 169,278
				total	**£ 4,213,274**

2. Publications

	(a) At 31 Mar 2013	(b) 1st Apr 2013 – 31st March 2014	(c) = (a) + (b) Total
Number of articles published	248	43	291

Please provide separately a list of all articles published **between 1st April 2013 and 31st March 2014** (either as E-publication ahead of print or in print) in peer reviewed journals. Please group

Cancer Genetics:

Vasen, H. F. A., I. Blanco, K. Aktan-Collan, J. P. Gopie, A. Alonso, S. Aretz, I. Bernstein, L. Bertario, J. Burn, G. Capella, C. Colas, C. Engel, I. M. Frayling, M. Genuardi, K. Heinimann, F. J. Hes, S. V. Hodgson, J. A. Karagiannis, F. Lalloo, A. Lindblom, J. P. Mecklin, P. Moller, T. Myrhoj, F. M. Nagengast, Y. Parc, M. P. de Leon, L. Renkonen-Sinisalo, J. R. Sampson, A. Stormorken, R. H. Sijmons, S. Tejpar, H. J. W. Thomas, N. Rahner, J. T. Wijnen, H. J. Jaervinen, G. Moeslein and M. Grp (2013). "Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts." GUT 62(6): 812-823.

Yang, J., M. Kalogerou, J. Gallacher, J. R. Sampson and M. H. Shen (2013). "Renal tumours in a Tsc1(+/-) mouse model show epigenetic suppression of organic cation transporters Slc22a1, Slc22a2 and Slc22a3, and do not respond to metformin." EUROPEAN JOURNAL OF CANCER 49(6): 1479-1490

Yang J, Kalogerou M, Samsel PA, Zhang Y, Griffiths DF, Gallacher J, Sampson JR, Shen MH. “Renal tumours in a Tsc2+/- mouse model do not show feedback inhibition of Akt and are effectively prevented by rapamycin.” Oncogene. 2014 Mar 17. doi: 10.1038/onc.2014.17. [Epub ahead of print]

Dodd KM, Yang J, Shen MH, Sampson JR, Tee AR (2014) mTORC1 drives HIF-1α and VEGF-A signalling via multiple mechanisms involving 4E-BP1, S6K1 and STAT3. Oncogene (in press)

Dunlop EA, Seifan S, Claessens T, Behrends C, Kamps MAF, Rozycka E, Kemp AJ, Nookala RK, Blenis J, Coull BJ, Murray JT, van Steensel MAM, Wilkinson S, Tee AR. (2014) FLCN, a novel autophagy component, interacts with GABARAP and is regulated by ULK1 phosphorylation Autophagy (in press).

Yan M, Gingras MC, Dunlop EA, Nouet Y, Dupuy F, Jalali Z, Possik E, Coull B, Kharitidi D, Dydensborg AB, Faubert B, Kamps M, Sabourin S, Preston R, Davies DM, Roughead T, Chotard L, van Steensel MAM, Jones R, Tee AR, Pause A. (2014) Loss of folliculin tumor suppressor drives AMPK-dependent metabolic transformation. J. Clin. Invest. (epub ahead of print, doi:10.1172/JCI71749).

Zhang J, Kim J, Alexander A, Cai S, Tripathi DN, Dere R, Tee AR, Tait-Mulder J, Di Nardo A, Han JM, Kwiatkowski E, Dunlop EA, Dodd KM, Folkerth RD, Faust PL, Kastan MB, Sahin M, Walker CL. (2013) A tuberous sclerosis complex signalling node at the peroxisome regulates mTORC1 and autophagy in response to ROS. Nat Cell Biol. 15:1186-1196. doi: 10.1038/ncb2822. citations: 6

Tripathi DN, Chowdhury R, Trudel LJ, Tee AR, Slack RS, Walker CL, Wogan GN. (2013) Reactive nitrogen species regulate autophagy through ATM-AMPK-TSC2-mediated suppression of mTORC1. Proc. Natl. Acad. Sci. USA. 110:2950-2957. doi: 10.1073/pnas.1307736110.

Luijten MN, Basten SG, Claessens T, Vernooij M, Scott CL, Janssen R, Easton JA, Kamps MA, Vreeburg M, Broers JL, van Geel M, Menko FH, Harbottle RP, Nookala RK, Tee AR, Land SC, Giles RH, Coull BJ, van Steensel MA. (2013) Birt-Hogg-Dube syndrome is a novel ciliopathy. Hum. Mol. Genet. 22:4383-4397. doi: 10.1093/hmg/ddt288. citations: 2

Extensive telomere erosion in the initiation of colorectal adenomas and its association with chromosomal instability. Roger L, Jones RE, Heppel NH, Williams GT, Sampson JR, Baird DM. J Natl Cancer Inst. 2013 Aug 21;105(16):1202-11.

Development and characterization of a physiologically relevant model of lymphocyte migration in chronic lymphocytic leukaemia. Walsby E, Buggins A, Devereux S, Jones C, Pratt G, Brennan P, Fegan C, Pepper C. Blood. 2014 Mar 17. [Epub ahead of print]

Roger, L., R. E. Jones, N. H. Heppel, G. T. Williams, J. R. Sampson and D. M. Baird (2013). "Extensive Telomere Erosion in the Initiation of Colorectal Adenomas and Its Association With Chromosomal Instability." JOURNAL OF THE NATIONAL CANCER INSTITUTE 105(16): 1202-1211.

CGGBP1 phosphorylation constitutes a telomere-protection signal. Singh U, Maturi V, Jones RE, Paulsson Y, Baird DM, Westermark B. Cell Cycle. 2014 Jan 1;13(1):96-105. doi: 10.4161/cc.26813. Epub 2013 Oct 23.

CD49d is the strongest flow cytometry-based predictor of overall survival in chronic lymphocytic leukemia. Bulian P, Shanafelt TD, Fegan C, Zucchetto A, Cro L, Nückel H, Baldini L, Kurtova AV, Ferrajoli A, Burger JA, Gaidano G, Del Poeta G, Pepper C, Rossi D, Gattei V. J Clin Oncol. 2014 Mar 20;32(9):897-904. doi: 10.1200/JCO.2013.50.8515. Epub 2014 Feb 10.

A genome-wide association study identifies multiple susceptibility loci for chronic lymphocytic leukemia. Speedy HE, Di Bernardo MC, Sava GP, Dyer MJ, Holroyd A, Wang Y, Sunter NJ, Mansouri L, Juliusson G, Smedby KE, Roos G, Jayne S, Majid A, Dearden C, Hall AG, Mainou-Fowler T, Jackson GH, Summerfield G, Harris RJ, Pettitt AR, Allsup DJ, Bailey JR, Pratt G, Pepper C, Fegan C, Rosenquist R, Catovsky D, Allan JM, Houlston RS. Nat Genet. 2014 Jan;46(1):56-60. doi: 10.1038/ng.2843. Epub 2013 Dec 1.

Tee AR. (2013) Metastatic castration-resistant prostate cancer hungers for leucine. J. Natl. Cancer Inst. 105:1427-1428. doi: 10.1093/jnci/djt252.

Dunlop EA, Tee AR. (2013) The kinase triad, AMPK, mTORC1 and ULK1, maintains energy and nutrient homoeostasis. Biochem Soc Trans. 2013 Aug;41(4):939-43. doi: 10.1042/BST20130030.

Tee AR, Pause A. (2013) Birt-Hogg-Dubé: tumour suppressor function and signalling dynamics central to folliculin. Fam Cancer. 2013 Sep;12(3):367-72. doi: 10.1007/s10689-012-9576-9.

Bryant D, Onions T, Raybould R, Flynn Á, Tristram A, Meyrick S, Giles P, Ashelford K, Hibbitts S, Fiander A, Powell N (2014) mRNA sequencing of novel cell lines from Human Papillomavirus type-16 related vulval intraepithelial neoplasia: consequences of expression of HPV16 E4 and E5. Journal of medical Virology. In press

Davies, E. J., V. Marsh Durban, V. Meniel, G. T. Williams and A. R. Clarke (2013). "PTEN loss and KRAS activation leads to the formation of serrated adenomas and metastatic carcinoma in the mouse intestine." J PATHOL. Epub 2014 Jan 23.

Holik, A. Z., J. Krzystyniak, M. Young, K. Richardson, T. Jarde, P. Chambon, B. Y. Shorning and A. R. Clarke (2013). "Brg1 is required for stem cell maintenance in the murine intestinal epithelium in a tissue-specific manner." STEM CELLS 31(11): 2457-2466.

Parry, L., M. Young, F. El Marjou and A. R. Clarke (2013). "Evidence for a crucial role of paneth cells in mediating the intestinal response to injury." Stem Cells 31(4): 776-785.

Young, M., L. Ordonez and A. R. Clarke (2013). "What are the best routes to effectively model human colorectal cancer?" Mol Oncol 7(2): 178-189.

Neurogenetics:

Beynon, A. L., M. R. Brown, R. Wright, M. I. Rees, I. M. Sheldon and J. S. Davies (2013). "Ghrelin inhibits LPS-induced release of IL-6 from mouse dopaminergic neurones."J.NEUROINFLAMMATION 10: 40.

Chung, S. K., A. Bode, T. D. Cushion, R. H. Thomas, C. Hunt, S. E. Wood, W. O. Pickrell, C. J. Drew, S. Yamashita, R. Shiang, S. Leiz, A. C. Longardt, V. Raile, B. Weschke, R. D. Puri, I. C. Verma, R. J. Harvey, D. D. Ratnasinghe, M. Parker, C. Rittey, A. Masri, L. Lingappa, O. W. Howell, J. F. Vanbellinghen, J. G. Mullins, J. W. Lynch and M. I. Rees (2013). "GLRB is the third major gene of effect in hyperekplexia." HUM MOL GENET 22(5): 927-940.

Behrendt G, Baer K, Buffo A, Curtis MA, Faull RLM, Rees MI, Götz M, Dimou L (2013). Dynamic Changes in Myelin aberrations and oligodendrocyte generation in chronic amyloidosis in mice and men. *GLIA* 61(2): 273-286.

James VM, Bode A, Chung SK, Gill JL, Nielsen M, Cowan FM, Vujic M, Thomas RH, Rees MI, Harvey K, Topf M, Ginjarr I, Lynch JW and Harvey RJ (2013). Novel missense mutations in the glycine receptor β-subunit gene (*GLRB*) in startle disease. *Neurobiology of Disease* 52: 137-149.

Cushion TD, Dobyns WB, Mullins JGL, Stoodley N, Chung SK, Davies JS, Fry AE, Hehr U, Gunny R, Aylsworth AS, Prabhakar P, Uyanik G, Rankin J, Cushion, T. D., W. B. Dobyns, J. G. Mullins, N. Stoodley, S. K. Chung, A. E. Fry, U. Hehr, R. Gunny, A. S. Aylsworth, P. Prabhakar, G. Uyanik, J. Rankin, M. I. Rees and D. T. Pilz (2013). "Overlapping cortical malformations and mutations in TUBB2B and TUBA1A." BRAIN 136(Pt 2): 536-548.

Bode A, Wood SE, Mullins JGL, Keramidas A, Cushion TD, Thomas RH, Pickrell WO, Drew CJG, Masri A, Jones EA, Vassallo G, Born AP, Fusun A, Aharoni S, Bannasch G, Bartsch M, Kara B, Krause A, Karam EG, Matta S, Jain V, Mandel H, Freilinger M, Graham GE, Hobson E, Chatfield S, Vincent-Delorme C, Rahme JE, Afawi Z, Berkovic SF, Howell OW, Vanbellinghen JF, Rees MI, Chung SK, Lynch JW (2013). New hyperekplexia mutations provide novel insights into glycine receptor assembly, trafficking and activation mechanisms. *Journal of Biological Chemistry* 288(47): 33745-33759.

Pickrell WO, Lacey AS, Thomas RH, Lyons RA, Smith PEM, Rees MI (2014). Trends in the first antiepileptic drug prescribed for epilepsy in Wales between 2000 and 2010. *Seizure* 23(1): 77-80.

Johnston JA, Kang J-Q, Cushion TD, Shen W, Davies JS, Baer K, Mullins JGL, Hammond CL, Thomas RH, Chung SK, White C, Smith PEM, Macdonald RL, Rees MI (2014). A Novel *GABRG2* Mutation, p.R136*, in a family with GEFS+ and extended phenotypes. *Neurobiology of Disease* 64: 131-141.

Cushion TD, Paciorkowski AR, Mullins JGL, Seltzer LE, Marion RD, Tuttle E, Ghoneim D, Christian SL, Pilz DT, Chung SK, Rees MI*, Dobyns WB* (2014). *De novo* mutations in a novel beta-tubulin gene, *TUBB2A*, cause simplified gyral patterning and infant-onset epilepsy. *American Journal of Human Genetics* 94(4):634-41. *Co-senior author

Walsh J, Thomas RH, Church C, Rees MI, Baker G, Marson AR (2014). Frontal cognitive dysfunctions and psychiatric disorders in refractory juvenile myoclonic epilepsy. *Epilepsy and Behaviour* 35:72-77.

Thomas RH, Drew CG, Wood SE, Hammond CL, Chung SK, Rees MI (2014). Ethnic variation in *GLRA1* genotypes in hyperekplexia. *Journal of Neurology, Neurosurgery and Psychiatry* (*in press*).

Thomas RH, Walsh J, Church C, Marson AR, Baker G, Rees MI (2014). A comprehensive neuropsychological description of cognition in drug refractory juvenile myoclonic epilepsy. *Epilepsy and Behaviour (in press).*

Hmami F, Wood SE, Chaouki S, Oulmaati A, Hida M, Chung SK, Rees MI, Bouharrou A (2014). Neonatal Hyperekplexia with homozygous p.R392H mutations in *GLRA1. Epileptic Disorders (in press).*

Pickrell, W. O., A. S. Lacey, R. H. Thomas, P. E. Smith and M. I. Rees (2013). "Weight change associated with antiepileptic drugs." J NEUROL NEUROSURGERY PSYCHIATRY 84(7): 796-799.

Thomas, R. H., S. K. Chung, K. Hamandi, M. I. Rees and M. P. Kerr (2013). "Translation of genetic findings to clinical practice in juvenile myoclonic epilepsy."EPILEPSY BEHAV 26(3): 241-246.

Thomas, R. H., S. K. Chung, S. E. Wood, T. D. Cushion, C. J. Drew, C. L. Hammond, J. F. Vanbellinghen, J. G. Mullins and M. I. Rees (2013). "Genotype-phenotype correlations in hyperekplexia: apnoeas, learning difficulties and speech delay."BRAIN 136(Pt 10): 3085-3095.

Fromer M, Pocklington AJ, Kavanagh DH, Williams HJ, Dwyer S, Gormley P, Georgieva L, Rees E, Palta P, Ruderfer DM, Carrera N, Humphreys I, Johnson JS, Roussos P, Barker DD, Banks E, Milanova V, Grant SG, Hannon E, Rose SA, Chambert K, Mahajan M, Scolnick EM, Moran JL, Kirov G, Palotie A, McCarroll SA, Holmans P, Sklar P, Owen MJ, Purcell SM, O'Donovan MC. De novo mutations in schizophrenia implicate synaptic networks. Nature. 2014 Feb 13;506(7487):179-84.

Other Areas:

Zhang L, Grennan-Jones F, Draman M, Lane C, Morris D, Dayan C, Tee AR, Ludgate M. (2014) Possible Targets for Non-immunosuppressive Therapy of Graves' Orbitopathy. J. Clin. Endocrinol. Metab. (ahead of print jc20134182).

Boileau E, Bevan RLT, Sazonov I, Rees MI, Nithiarasu P (2013). Flow-induced ATP release in patient-specific arterial geometries – a comparative study of computational models. *International Journal of Numerical Methods in Biomedical Engineering* 29(10):1038-1056

Rosas M, Davies LC, Giles PJ, Liao CT, Kharfan B, Stone TC, O'Donnell VB, Fraser DJ, Jones SA, Taylor PR (2014) The transcription factor Gata6 links tissue macrophage phenotype and proliferative renewal. Science, Volume 344, 6184 pp.645-648

3. Source of funding

Please summarise the sources of funding from successful grant applications.

	(a) At 31 Mar 2013		**(b) 1st Apr 2013 – 31st Mar 2014**	
	Number	Value £'000	Number	Value £'000
Research councils	13	2,917,665	1	14,020
Research charities	74	10,885,804	16	2,637,076
NIHR/DH (England)	2	386,805	0	0
NISCHR*	3	264,141	2	130,000
Commercial collaborations/contract research royalties	9	3,694,395 1,022,474 331,046	5	297,651
EU	2	306,766	1	842,067
Embassy of the Arab Republic of Egypt	0	0	1	15,000
Welsh European Funding Office	0	0	1	22,650
World Cancer International	0	0	1	225,000

Research Fund				
Other	5	2,784,625	1	20,000
Pathological Society of Great Britain and Ireland	0	0	1	9,810
Total	**108**	**22,593,721**	**30**	**4,213,274**

4. Education and public engagement

	(a) At 31 Mar 2013	**(b) 1st Apr 2013 – 31st Mar 2014**	**(c) = (a) + (b) Total**
Total number of events held	438	39	477
Number of events held for health professionals	60	10	70
Number of events held for schools	249	13	262
Number of events held for the public	129	26	155
Total number of people attending education and public engagement events	**29,903**	**5,129**	**35,032**
Number of people attending health professional events	2265	832	3,097
Number of people attending schools events	19503	3009	22,512
Number of people attending public events	7259	1200	8,459

b) Achievements against Milestones

Compare achievements against milestones for each objective in the categories outlined in the work plan for 2013 – 2014

Work Package 1: Management and Governance

The Strategic Advisory group (SAG) has been renewed under the Chairmanship of Professor Colin Dayan (Director, Institute of Molecular and Experimental Medicine, Cardiff University) and with representation from Cardiff and Vale UHB, Cardiff and Swansea Universities and Welsh Government. The SAG has met twice, agreed its remit, drawn up draft Terms of Reference (attached as Appendix 1.) and given initial advice in relation to the strategic development of WGP in light of the re-structuring of NISCHR.

The Operational Management Group is co-ordinated by Jacqui Peterson, project manager, and meets 6 weekly. The group has served to both problem solve and provide information to current and potential partner organisations.

Rhian Morgan has been appointed as a part-time secondment from the University of South Wales to cover the Education Officer vacancy.

Work Package 2a: Genomics Facility

The team have implemented exome sequencing and ultra-deep sequencing of specific disease loci and undertaken bespoke sequencing projects including identification of telomere fusions in cancer mono nucleosome mapping using the Proton and MiSeq platforms. The facility has had to move to new accommodation because of expansion.

They have also validated two exome capture techniques (TargetSeq and SureSelect).

Work Package 2b – Bioinformatics

Dr Kevin Ashelford (WGP) and Dr peter Giles (CGBRU) working collaboratively to provide bioinformatics support for NISCHR funded research, genomics research in Wales and development of genomic medicine within the NHS in Wales through the All Wales Genetic Diagnostic laboratory. They have produced bespoke scripts and programs for assisting CGBRU projects QC and analysis software pipelines for the handling of genomic big data and in developing QC and analysis software pipelines for the local handling of genomic big data.

The majority of WGP bioinformatics activity has been in support of CGBRU researchers in their exploitation of sequencing technologies in mechanistic research and the development of new diagnostic and prognostic genetic biomarkers and therapeutic target identification.

The bioinformaticians are also integral to the development of Cardiff University Big Data strategy, in particular the Biological Big Data network and planning for a new Big Data University Research Institute.

All the activities fall within the objectives of the NISCHR Big Data strategy. They also fit within the ongoing international push to exploit Big Data resources, in particular with regards to Genomic Medicine and advances in stratified and personalised medicine.

Work Package 3: Transgenic Production Facility (TPF)

Transgenic strains have been moved from to the refurbished T2 Barrier Unit thereby achieving a higher health status. This has been facilitated via rederivation by embryo transfer into SPF recipients females. The TPF lead, Bridget Allen, oversees both the management and the technical side of the Barrier Units, and represents the TPF in relation to Cardiff University groups involved in planning the future development of the CU Animal Facilities.

Metrics

Rederivation – 23 strains of mice
Cryopreservation – 36 lines of mice
Experimental embryo transfer – 4 cohorts

Work Package 4: Education and Public Engagement

We have achieved growth in activity across professional, public and schools with >5000 particpants in the 39 events held in the reporting period.

Work Package 5: Societal Issues and the Patient Voice

Involving patients and Families: Genetic Alliance UK , Development Officer for Wales

The Genetic Alliance Officer for Wales has contributed to:

- Newborn Screening Wales Project Board
- Ethical Medicines Industry Group
- Rare Disease Plan and Implementation Group
- All Wales Medicines Strategy Group.
- Neurological Conditions Cross Party Group
- Submitted consultation response to inquiry into appraisal process for orphan and ultra orphan medicines in Wales

- Patient representative on the review panel for the review into the Individual Patient Funding Request Process in Wales by Welsh Government led by Prof Roger Walker, Chief Pharmaceutical Officer for Wales.
- Continued work with WHSSC on improving referral management pathway and service specifications relating to specialised services.
- Work with WHSSC on developing an online portal to improve access to patient information regarding their condition, treatment options, referrals and access to services.
- Clinical Evidence Reference Group for rare diseases
- MSc in genetic counselling
- Briefing AM's on Rare Disease Plan and work on access to medicines
- Hosted Rare Disease Day reception on 11th February at the Senedd, Welsh Assembly.
- Gave evidence to Health and Social Care Committee of Welsh Assembly about access to genetic tests in NHS Wales (mainly rare genetic tests)
- Submitted response to the Welsh Government regarding draft recommendations of Individual Patient Funding Request Review.
-

Work Package 6: The Sir Peter Harper Clinical Research Fellowship

TRON Clinical trial:
Operational: 20 UK sites active as patient identification centres
Recruitment: 24 patients screened for eligibility and 10 recruited and randomised.
Presentations: British Society of Genetic Medicine, Liverpool September 2013. Clinical Genetics Society April 2013.

Work Package 7: Cardiovascular Genetics

Familial Hypercholesterolaemia (FH) Wales project co-ordinator has become externally funded following completion of transfer of service to NHS.

Research into inherited disorders of cardiac rhythm: Development of functional analysis for variants in ion channel genes: Genetically engineered ion channels KCNQ1, KCNE1, KCNH2 & SCN5A have been generated and mutations identified in these genes are now being examined using confocal analysis, patch clamping and western blotting.

Work Package 8: Neurogenetics and Psychiatric Genetics

Cardiff University

Progress report

- Analysis of de novo mutations in schizophrenia – developed and implemented an analysis package for testing pathway enrichment of de novo mutations.
- Applied this novel methodology to several datasets of de novo mutations discovered in various psychiatric disorders (schizophrenia, autism spectrum disorders, intellectual disability). (completed)
- Developing in house automated sequencing data-processing pipeline to operate on the ARCCA super-computer cluster, RAVEN. (completed)
- Analysis of rare mutations and their association with various cognitive phenotypes and measures. (ongoing)
- Developing a fast and efficient implementation of Brown's method of combining P-values across a set of SNPs (genes or pathways). (ongoing

Swansea University

In Swansea University, WGP provides technician support for epilepsy genetic research within the Institute of Life Sciences, enabling links with the Institute of Medical Genetics and translation of gene testing (e.g. for hyperkeplexia) to the NHS Genetics Laboratory.

Supported Projects:

- The role of GABAergc genes in epilepsy
- investigation into novel genes associated with learning disability and Epilepsy
- Identification of novel gene mutations in tublinopathies (collaboration with Cardiff University and AWMGS)

Work Package 9: Cancer Genetics

Support has focused on colorectal and renal cancers across a pipeline from cancer gene discovery, in vitro signalling pathway characterisation and target identification, pre-clinical therapeutic research, clinical trials and clinical pharmocogenetics. Joint research projects have been established between Cardiff and Bangor Universities

Section 2. Problems Encountered

Have you encountered any significant problems that have affected the progress of your project in the reporting period?

No

If 'Yes' please expand in comments section below

Comments (*Please describe the problems you have encountered so far/how these have been resolved)*

(a) Description of problem

(b) Implications in terms of progress/finance

(c) Date of resolution (if resolved)

Section 3. Changes to Work Plan

During the reporting period, have you made amendments to the work plan?

- No

Are you proposing any amendments to the work plan for 2014/15?

- No

If 'you have answered Yes' to either of the above, please expand in comments section below (continue on a separate sheet if necessary)

Comments *(Please explain reasons for any requested changes to the work plan in 2013 – 2014 or proposed changes in 2014/15)*

Section 4. Dissemination

During the reporting period have you attended, or made plans to attend **Presentations / Seminars** (*please list & date current & future venues*)? Have you submitted any articles for **publication or had any papers published** (*please list publications and attach copies/disk*)? Has this research had any **Press / Media** involvement (if so please provide details)?

Presentations attendance at conferences

43 scientific papers published (see above), large numbers of platform and poster presentations at national and international meetings throughout the reporting period.

Media Coverage
The work on pathway analysis of de novo mutations in schizophrenia was widely reported e.g.

https://www.youtube.com/watch?v=rwjfJ6HNZHY
http://www.sciencedaily.com/releases/2014/01/140122133833.htm?utm_source=feedburner&utm_medium=feed&utm_campaign=Feed%3A+sciencedaily%2Fmind_brain+(Mind+%26+Brain+News+--+ScienceDaily)
http://www.reuters.com/article/2014/01/22/health-schizophrenia-genes-idUSL5N0KW1IY20140122
http://www.independent.co.uk/news/science/schizophrenia-could-be-caused-by-a-wide-variety-of-dna-mutations-rather-than-one-gene-9078284.html

Section 5. Finance Details

Please note, this information is also confidential and will be used only for contract management purposes

Your completed report should be accompanied by a financial statement detailed actual spend and future spend as at 31st March 2014. Your financial statement should include all grant expenditure as at 31st March 2014, broken down into the headings and sub-headings used in your original grant bid, or those subsequently agreed and added in discussion with your contract manager. Your financial statement should also include an estimate of your expected/budgeted spend on agreed award items in 2014/15. Any proposals you have to vire funding between agreed award items or to fund new award items should be detailed separately in the financial template. The financial template itself contains further guidance on completion.

Question 1: Is your actual expenditure in 2013-14 in line with your forecast cost projections as set out in the financial template submitted with your 2012/13 annual report (or as subsequently amended in agreement with NISCHR)?

Yes

If you have answered 'no' to this question, please explain any significant variations, how this has impacted on the work of your Group and any mitigation steps taken/to be taken. In general, an individual explanation should be provided for any expenditure lines where the actual outturn is both 10% and £1,000 above or below that forecasted.

Question 2: Is your forecast expenditure as at the end of 2014-2015 on currently agreed award items in line with total grant you are holding?

Yes

If you have answered 'no' to this question, please use this section to describe any new requests you have to vire funding between currently agreed expenditure items or proposals to vire funding on to new award items.

Appendix 1

Wales Gene Park
Strategic Advisory Group
Draft Terms of Reference
May 2014

Members:
Professor Colin Dayan(CD) – Chair;
Professor Julian Sampson(JS) – Director Wales Gene Park;
Professor Malcolm Mason(MM) – Dean of Research Institute of Cancer and Genetics, CU;
Dr Sharon Hopkins(SH) – Executive Director of Public Health Cardiff & Vale UHB;
Professor Julian Hopkin(JH) – Experimental Medicine Swansea University
Mrs Christine Morrell (CM) – Deputy Chief scientific Adviser Welsh Government
Mr Ifan Evans(IE) – Head of Healthcare Innovation Welsh Government
Professor Keith Harding(KGH) – Dean of Clinical Innovation – CU
Professor John Burn
Mr Mark Bale – to be confirmed
Group Secretary
Jacqui Peterson(JCP) – Project Manager Wales Gene Park

Draft Terms of Reference

Members of the SAG would not have any direct responsibility on the Operational Management of the Wales Gene Park but would be asked to provide strategic advice to JS as Director of the WGP on the following:

- The development of the Genetic and Genomic Strategy for Wales within the context of developments in the UK and Internationally
- Advising on the optimisation and influence of the WGP into all areas of genetics and genomics
- To provide advice on the strategic planning for the future of the WGP, and the NISCHR re-bidding process in particular
- To provide advice on the communication strategy, wider strategic issues including interaction with the NHS and clinical services
- Individual members would be responsible for feeding back information to their respective organisations and for reporting to SAG information on strategies and policies that might impact on the running of the WGP
- The SAG would receive reports and notes of meetings relevant to the operational management of the WGP
- The Terms of Reference and the membership will be reviewed periodically to ensure compatibility with the aims and objectives of the WGP

The SAG would meet, not less than once and no more than four times a year. The Chair would be empowered to call extraordinary meetings as and when required