Institution: University of Birmingham

Unit of Assessment:UoA1

Title of case study: Leading diagnosis, patient care and cancer screening policy in ataxia telangiectasia

1. Summary of the impact (indicative maximum 100 words)

Ataxia telangiectasia (A-T) is an inherited disease affecting multiple systems in the body, causing severe disability and death. Work led by Professor Malcolm Taylor at the University of Birmingham has been central to the biological and clinical understanding of this disease, from the identification of the gene responsible to the clarification of related conditions with different underlying causes. As a result of this work, within the 2008-13 period, his laboratory has been designated the national laboratory for clinical diagnosis of A-T – a service also offered internationally – and has also changed national screening policy for breast cancer, following his confirmation of the increased risks of A-T patients and those who carry a single copy of the gene for this type of tumour. Furthermore, he has contributed in a major way to patient support for this condition.

2. Underpinning research (indicative maximum 500 words)

Ataxia telangiectasia (A-T) is a rare disease, inherited from a single recessive gene (i.e. two faulty copies – not necessarily with the same fault – are needed to cause the disease). It has an incidence of about 1 in 300,000. Ataxia telangiectasia is usually first noticed in toddlers by the appearance of an unsteady gait (ataxia), reflecting brain degeneration which typically heralds progressive neuromotor deterioration. This is commonly coupled with severe deficiencies in the immune system, premature ageing and a cellular sensitivity to ionising radiation. Patients usually die during the second or early in the third decade of life.

A research team led by Professor Malcolm Taylor (Professor of Cancer Genetics, at UoB since 1973) at the University of Birmingham has been central in advances in understanding of this disease. In the early 1990s, Prof Taylor was involved in mapping the location of the gene which causes this disease more precisely, culminating with the identification of the “Ataxia Telangiectasia Mutated” (ATM) gene in 1995. From this point, his team were able to quickly start identifying specific ATM mutations in UK ataxia telangiectasia patients (1, 2). Quite early on in 1996, his team were able to detect an unusual group of more mildly affected patients in the UK (1), all of whom expressed a low level of ATM protein with some activity. We know now that in the UK ~33% of A-T patients have a milder form of disease (3).

The interest of Prof Taylor’s team has always been in the relationship between the clinical presentation in A-T, the characteristics of the cells in those patients, and the underlying specific mutation in the ATM gene. In the case of A-T there is a good correlation between the genetic characteristics of the cells (‘genotype’) and the physical characteristics of these cells and the patient (‘phenotype’). Prof Taylor’s team have demonstrated that typically where the protein produced from the mutant ATM gene retains some ability to affect other proteins through a process known as ‘phosphorylation’ (termed ‘kinase’ activity) then there is a better clinical presentation, regardless of whether this is from normal or mutant ATM protein (4, 5). This can be seen as a less severe immunodeficiency, a later onset and slower progression of neurodegeneration, and at the cellular level a smaller increase in sensitivity to ionising radiation, as a result of some normal functioning of the ATM protein.

Importantly, the presence of ATM kinase activity also affects cancer risk. This is one of the key areas in which Prof Taylor’s team have contributed to national and international understanding, demonstrating that total loss of ATM protein is associated with an overwhelming preponderance of lymphoid tumours in A-T patients under 16 years of age, whereas the presence of residual ATM kinase activity protects against these childhood lymphomas (3). However, they also showed that longer-lived female A-T patients have a 45% risk of breast cancer by the age of 50, higher than the equivalent risk in BRCA1 or BRCA2 mutation carriers, the main mutant gene typically associated with this type of cancer (3).

Importantly, not all patients who appear clinically to have A-T have ATM mutations. Another major role of Prof Taylor’s team, and more recently by the team led by Dr Grant Stewart (Reader in Cancer Genetics, at the University since 2004), has been to identify the genetic abnormalities in

these patients which are causing their disease.They have identified some “ataxia telangiectasia-like” patients that had a mutation in another gene, MRE11 (6), known to be part of a group of proteins important in signalling the initial response to DNA double strand breaks (Mre11/Rad50/Nbn).They called this new disorder ataxia telangiectasia like disorder (ATLD). In 2002-2003 the team noted that a proportion of samples sent to them were from patients who had a neurologically similar presentation as A-T and ATLD. They identified these as ataxia oculomotor apraxia types 1 and 2, with ages of onset in childhood and early teenage respectively. More recently they also identified another radiosensitivity disorder, RIDDLE syndrome (a primary immunodeficiency disorder), for which they discovered the gene responsible, RNF168, in 2009.

3. References to the research (indicative maximum of six references)

1. McConville C M, Stankovic T, Byrd P J, McGuire GM, Yao, Q-Y, Lennox GG, **Taylor AMR.** Mutations associated with variant phenotypes in ataxia-telangiectasia. *Am J Hum Genet* 1996; **59**:320-330. (Grant, CR-UK Programme Grant 1993-1997) *http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1914715/*

2. Stankovic T, Kidd AM, Sutcliffe A, McGuire GM, Robinson P, Weber P, Bedenham T, Bradwell AR, Easton DF, Lennox GG, Haites N, Byrd PJ, **Taylor AM.** ATM mutations and phenotypes in ataxia-telangiectasia families in the British Isles: expression of mutant ATM and the risk of leukemia, lymphoma, and breast cancer. *Am J Hum Genet* 1998;**62**: 334-345. (Grant, CR-UK Programme Grant 1998-2002) *http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1376883*

3. Stewart GS, Last JIK, Stankovic T, Haites N, Kidd AMJ, Byrd PJ, **Taylor AMR.** Residual Ataxia Telangiectasia Mutated Protein Function in Cells from Ataxia Telangiectasia Patients, with 5762ins137 and 7271T>G Mutations, Showing a Less Severe Phenotype *J. Biol. Chem. 2001;* **276**:30133-30141. (Grant, CR-UK Programme Grant 1998-2002) *http://www.ncbi.nlm.nih.gov/pmc/articles/PMC11382771*

4. Reiman A, Srinivasan V, Barone G, Last JI, G. Davies EG, Verhagen MMM, WillemsenMAAP, WeemaesCMR, Byrd PJ, Izatt L, Easton DF, Thompson D, **Taylor AMR.** Lymphoid tumours and breast cancer in ataxia telangeictasia; substantial protective effect of residual ATM kinase activity against childhood tumours. *Br. J. Cancer* 2011; **105**: 586-591. doi: 10.1038/bjc.2011.266. (Grant, CR-UK Programme Grant 2008-2012) *http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3170966*

5. Stewart GS, Maser RS, Stankovic T, Bressan DA, Kaplan MI, Jaspers NG, Raams A, Byrd PJ, PetriniJH, &**Taylor AM** The DNA double-strand break repair gene hMRE11 is mutated in individuals with an ataxia-telangiectasia-like disorder. *Cell* 1999; **99,** 577-587. (Grant, CR-UK Programme Grant 1998-2002) *doi:10.1016/S0092-8674(00)81547-0*

6. Stewart GS, Stankovic T, Byrd PJ, Wechsler T, Miller ES, Huissoon A, Drayson MT, West SC, Elledge SJ, **Taylor AM**. RIDDLE immunodeficiency syndrome is linked to defects in 53BP1-mediated DNA damage signaling. ProcNatlAcadSci USA 2007 Oct 23;**104**(43):16910-5. Epub 2007 Oct 16. (Grant, CR-UK Programme Grant 2003-2007) *doi: 10.1073/pnas.0708408104*

4. Details of the impact (indicative maximum 750 words)

Ataxia telangiectasia is a devastating disease that affects children from a young age. The inherited nature of the disease has meant that advances in our understanding of the underlying genetics has played a vital role in diagnosis and effective assessment of risk of related conditions in these patients, and it is here that the work of Professor Malcolm Taylor’s laboratory at the University of Birmingham has been vital over the past two decades, and notably within the assessment period (when they have confirmed 70 new diagnoses of ataxia telangiectasia in the British Isles). The Taylor group has consistently worked towards defining how furthering knowledge of the specific genetic mutations underlying A-T in each individual patient can be put to use in advising the family on prognosis and longer term outcomes.

A-T is not the only recessively inherited ataxia condition, with others such as Friedreich's ataxia (a degenerative disease that primarily affects the nervous system and the heart), spastic ataxia or abetalipoproteinemia (which interferes with the normal absorption of fat and fat-soluble vitamins from food) also occurring at a young age. These conditions need differential diagnosis so that patients can be treated appropriately as quickly as possible. Prof Taylor’s team has been involved in identifying ATM mutations since its discovery in the mid-1990s, and gained widespread credibility as the laboratory that would confirm the increased sensitivity of possible A-T patients’ chromosomesto ionising radiation, one of the hallmarks of the disease. Pediatricians, neurologists

and immunologists nationally and internationally send blood samples from their patients direct to the Taylor laboratories in the University of Birmingham for rapid results to help diagnose their patients, as directed by either the A-T Society or the documentation relating to the UK NHS National Specialised Commissioning Team relating to diagnosis and care in children and adults [1-2]. Their laboratory techniques allow them to provide a comprehensive cellular analysis of the effects of the ATM mutations in each specific A-T patient, all of which is returned directly to the patient's consultant to inform treatment. Originally, the gold standard for confirmation of diagnosis of A-T had been simply the identification of two pathogenic ATM mutations. Building on their research studies, the Taylor group demonstrated a key clinical criteria was actually whether protein was or was not expressed. The group's innovation in diagnosis was to add to this test a cellular investigation when the mutations could be classed as 'leaky' (producing some normal ATM protein) or 'missense' mutation (producing some mutant ATM protein), and if protein is expressed they also determine whether it has any functional activity. This provides further information to the centres caring for these patients on whether the clinical phenotype might be milder, which therefore helps **inform and improve their clinical management**.

Their work in diagnosis informed the establishment and development from 2009 of a national A-T management service. Together with the AT Society of the UK and Clinical Geneticists, Neurologists, Immunologists, Respiratory Medicine, practitioners and others they have received National Specialised Commissioning Team funding from April 1st 2009 to become the national A-T diagnostic service for treatment [1], extended in 2012 to cover adults as well as children [2]. This means that **the Taylor laboratory is the designated laboratory for confirmation of the diagnosis of AT across the UK**, and as part of differential diagnosis they are also the designated laboratory for confirmation of the diagnosis of ataxia telangiectasia like disorder (which they themselves had identified) and oculomotor apraxia type 1. As outlined by the Consultant Clinical Geneticist and Clinical Lead, National Paediatric Ataxia-Telangiectasia Clinic *"the services provided by Professor Taylor are pivotal to the work of the National Paediatric AT Clinic and the proper management of patients with not just AT, but also ATLD and AOA1, as well as their families. These services are not available through any NHS Molecular Genetics Service Laboratory or through any other Research Group in the UK or Ireland."* [3]. **They also offer this diagnostic service internationally**, and in the last three years have confirmed a total of 30 new diagnoses for Belgium, Netherlands, Poland, Germany, Lithuania, India, Sri-Lanka, and Malaysia for the genetic diagnosis of A-T. The advanced genetic screening tests pioneered by this group are essential for diagnosing the milder form of disease, and the genetic diagnosis directly influences patient management, since it is only patients suffering from A-T rather than the associated conditions who have increased risk of cancer, and therefore need to be kept under lifelong surveillance for any signs of a tumour, while others can be advised appropriately without the added burden of concern.

The role of Prof Taylor's team as the key UK experts on A-T has driven them to play **an ongoing role in patient support**. As the Chief Executive of the Ataxia Telangiectasia Society states in his letter of support from Prof Taylor's impact [4], *"Malcolm was responsible for the first gathering of families affected by A-T in the UK. Working with a parent, ..., they sent a letter to all the families known to Malcolm at the time, inviting them to a meeting. From this meeting, the A-T Society was born, and without Malcolm's ongoing and active support it would not have survived and thrived in the way it has."* The A-T Society represents and looks after over 95% of those diagnosed with the condition, currently supporting 152 people with A-T in the UK and also 12 in the Republic of Ireland. They credit this in large part to Prof Taylor's contribution, stating *"The fact that the Society is in active contact with so many people reflects both the fact that when carrying out laboratory confirmation of diagnoses, Malcolm usually recommends contact with the Society"*. Furthermore, the supportive information distributed to their worldwide audience reached through their website (currently visited by over 1500 individual users a month), social media and newsletters has relied heavily on significant input from Prof Taylor: *"Malcolm was initially the provider of most of the Society's information and still acts regularly as consultant on information provision, the interpretation of research etc."* Prof Taylor also attends A-T clinics for both adults and children to meet families there and discuss their diagnoses, outlook and support available, as well as speaking at the A-T family weekend organised by the A-T Society every year. This has made a major impact on patient

experience of living with their disease – as articulated in the letter of support from the A-T Society: *"Malcolm's concern for those with or awaiting a diagnosis of A-T is such that he goes out of his way to ensure that certainty be given as quickly and in as effective a manner as possible. He follows the lives of those he has diagnosed with interest and compassion and frequently attends funerals. He is loved and admired by many across the community of those living with A-T in the UK and Ireland."*

Critically, the work of the Taylor group has also had **a major role in national policy**. Their work demonstrated that absence of some function in the ATM protein biasesthe development of cancer towards non-lymphoid types in A-T patients, specifically toward breast cancer development in surviving adults. This also confers an approximately doubling of risk of breast cancer in ATM mutation carriers, and a five-fold increase risk in ATM carriers under 50 years of age. As a direct result of their work on breast cancer in A-T patients, from 2012 annual MRI breast cancer screening is now offered to female AT patients from the age of 25 years of age or from presentation (in milder cases of A-T). A clinical genetics consultant and member of the Advisory Committee for Breast Cancer Screening in England (ACBCS) reviewed evidence in 2007 and 2010 for breast surveillance in these groups to make recommendations that fed directly into the decision and current guidance, and states that she *"relied heavily on research work undertaken through the National Ataxia Telangiectasia Clinic and in Malcolm Taylor's research laboratory"* [5], going on to affirm that *"Professor Malcolm Taylor's experimental work has provided evidence to explain many observations seen in clinical practice. His collaboration with other groups has ensured that epidemiological studies have been comprehensively achieved and, as his laboratory undertakes ATM mutation testing in the United Kingdom, provided the necessary molecular evidence to support these findings… His work on Ataxia Telangiectasia is key to the continued progress and understanding between the clinic and the laboratory."*

As a result of this report, the national Cancer Screening Programme recognised in 2012 that A-T heterozygotes (those with only one mutated gene) should be included with women who had four times the average risk of breast cancer (moderate increased risk), and that A-T homozygotes (those with both genes mutated) should be included in the highest risk group for breast cancer, and confirmed that both would receive appropriate screening [6,7]. This obviously has major ramifications for the support and potentially life-saving surveillance available to A-T patients and genetic carriers of the mutation.

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. NHS National Specialised Commissioning Team: National Ataxia-Telangiectasia Clinic (http://www.specialisedservices.nhs.uk/library/36/Service_Specification_and_Standards___Ataxia_Telangiectasia_Service_1.pdf)
2. NHS National Specialised Commissioning Team: Multidisciplinary Service for diagnosis and management of Ataxia-Telangiectasia in adults (http://www.specialisedservices.nhs.uk/library/36/Service_Specification_and_Standards___Adult_Ataxia_Telangiectasia_Service.pdf)
3. Letter of support from Clinical Lead, National Paediatric Ataxia-Telangiectasia Clinic
4. Letter of support from the Ataxia telangiectasia Society CEO
5. Letter from the Advisory Committee for Breast Cancer Screening in England
6. Letter from Director of NHS Cancer Screening Programme
7. NHSBSP Publication no 74. Protocols for the surveillance of women at higher risk of developing breast cancer: http:www.cancerscreening.nhs.uk/breastscreen/publication/nhsbsp74.html