Institution: University College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Amyloidosis and acute phase proteins: world leading clinical service

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

The UCL Centre for Amyloidosis and Acute Phase Proteins conducts world-leading research and development that has rapidly fed through to patient care. These include advances in the diagnosis of amyloidosis and clinical characterisation of many new subtypes including genetic forms, development and application of new biomarkers to monitor disease activity and progress, new modalities of imaging and better treatment. The consequences have been new standards of clinical care adopted nationally and internationally, improved and more accurate diagnosis, steady improvements in the outcomes of this disease, major investment by the NHS and adoption of new clinical metrics by the pharmaceutical industry to enable research on specific new therapies currently in development.

2. Underpinning research (indicative maximum 500 words)

Amyloidosis is a disorder characterised by organ failure resulting from the accumulation of protein as abnormal fibres. There are various types notably including those arising as a result of long-standing inflammation (AA amyloidosis) or secondary to a haematological malignancy, myeloma (AL amyloidosis) or in association with ageing (ATTR amyloidosis). Highlights of the extensive clinical research programme in amyloidosis at UCL that have led to better management of these patients include:

Elucidation of the crucial precursor-product relationship in amyloid fibrillogenesis, which underlies pathogenesis and thus treatment. Seminal studies in unprecedentedly large patient populations with AA **[1]** and AL **[2]** amyloidosis have demonstrated for the first time the relationships between production of the amyloid fibril precursor proteins serum amyloid A protein (SAA) and monoclonal immunoglobulin free light chains (FLC) respectively with amyloid load and clinical outcome. These studies not only systematically demonstrated the capacity for regression of amyloid following treatment of underlying disorders, encouraging a proactive approach to treat the underlying cause, but defined monitoring of SAA and FLC concentration as standards of care in AA and AL amyloidosis that enable treatment strategies to be guided by their early effect on these accessible measurements.

Understanding of key aspects of hereditary amyloidosis. Until our genetic study **[3]**, hereditary systemic amyloidosis was thought to be incredibly rare and to affect only a few dozen families worldwide. Most affected patients either remained undiagnosed or were incorrectly assumed to have AL amyloidosis resulting in needless and harmful chemotherapy. Our study of 350 patients identified a hereditary cause in 10% of cases, resulting in genetic testing being introduced in the NHS National Amyloidosis Centre as a new standard of care. We have subsequently identified more than 70 patients with hereditary renal amyloidosis, and have characterised the phenotype, diagnostic pathway and role of organ transplantation in this subtype **[4]**.

Design and introduction of powerful new diagnostic imaging methods. We invented ^{123}I-serum amyloid P component scintigraphy in 1990 to image amyloid deposits in vivo, and during the past 5 years have developed 3D high resolution dual modality CT-SPECT (single-photon emission computed tomography) to enable accurate quantification and characterisation of amyloid in non-visceral sites. We have also developed ^{99m}Tc-DPD scintigraphy to image cardiac amyloid deposits of transthyretin (ATTR) type, repurposing this diphosphonate radionuclide tracer to enable diagnosis and clinical assessment of elderly patients with this hitherto very difficult to diagnose disorder. We were the first group to systematically demonstrate the utility of cardiac magnetic resonance imaging (CMR) in 2005 **[5]**, and have subsequently developed specific CMR methods to characterise and quantify cardiac amyloid deposits of all types.

Major advances in monitoring of disease and therapy. We have led and participated in major

international collaborative studies that have evaluated and defined the clinical utility of various biomarkers to stage severity of disease **[6]** and monitor response to treatment **[7]** in AL amyloidosis, the most common and serious type of the disease. These findings have now been adopted throughout the world, both for specialist clinical practice and in clinical trials. Our clinical studies of cyclic multiple agent chemotherapy **[8]** have defined current best practice for the majority of AL amyloidosis patients who are not fit enough to undergo stem cell transplantation.

This research was led by Professor Philip Hawkins and Professor Sir Mark Pepys of the UCL Centre for Amyloidosis and Acute Phase Proteins.

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

1. Natural history and outcome in systemic AA amyloidosis. Lachmann HJ, Goodman HJ, Gilbertson JA, Gallimore JR, Sabin CA, Gillmore JD, Hawkins PN. N Engl J Med. 2007; 356:2361-71. http://dx.doi.org/10.1056/NEJMoa070265

2. Outcome in systemic AL amyloidosis in relation to changes in concentration of circulating free immunoglobulin light chains following chemotherapy. Lachmann HJ, Gallimore R, Gillmore JD, Carr-Smith HD, Bradwell AR, Pepys MB, Hawkins PN. Br J Haematol. 2003 122:78-84. http://dx.doi.org/10.1046/j.1365-2141.2003.04433.x

3. Misdiagnosis of hereditary amyloidosis as AL (primary) amyloidosis. Lachmann HJ, Booth DR, Booth SE, Bybee A, Gilbertson JA, Gillmore JD, Pepys MB, Hawkins PN. N Engl J Med. 2002 346:1786-91. http://dx.doi.org/10.1056/NEJMoa013354

4. Diagnosis, pathogenesis, treatment, and prognosis of hereditary fibrinogen A alpha-chain amyloidosis. Gillmore JD, Lachmann HJ, Rowczenio D, Gilbertson JA, Zeng CH, Liu ZH, Li LS, Wechalekar A, Hawkins PN. J Am Soc Nephrol. 2009 20:444-51. http://dx.doi.org/10.1681/ASN.2008060614

5. Cardiovascular magnetic resonance in cardiac amyloidosis. Maceira AM, Joshi J, Prasad SK, Moon JC, Perugini E, Harding I, Sheppard MN, Poole-Wilson PA, Hawkins PN, Pennell DJ. Circulation. 2005 111:186-93. http://dx.doi.org/10.1161/01.CIR.0000152819.97857.9D

6. A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. Wechalekar AD, Schonland SO, Kastritis E, Gillmore JD, Dimopoulos MA, Lane T, Foli A, Foard D, Milani P, Rannigan L, Hegenbart U, Hawkins PN, Merlini G, Palladini G. Blood. 2013. 121:3420-7. http://dx.doi.org/10.1182/blood-2012-12-473066

7. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. Palladini G, Dispenzieri A, Gertz MA, Kumar S, Wechalekar A, Hawkins PN, Schönland S, Hegenbart U, Comenzo R, Kastritis E, Dimopoulos MA, Jaccard A, Klersy C, Merlini G. J Clin Oncol. 2012 30:4541-9. http://dx.doi.org/10.1200/JCO.2011.37.7614

8. Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression-free survival. Venner CP, Lane T, Foard D, Rannigan L, Gibbs SD, Pinney JH, Whelan CJ, Lachmann HJ, Gillmore JD, Hawkins PN, Wechalekar AD. Blood. 2012. 119:4387-90. http://dx.doi.org/10.1182/blood-2011-10-388462

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

The NHS National Amyloidosis Centre (NAC) established by Pepys and Hawkins in 1999 is directly funded by the NHS to provide diagnostic and clinical management services for the national caseload of patients with amyloidosis **[a]**. Patient flow has increased uninterruptedly from ~40 new patients in 1999-2000. Within the assessment period, annual patient flow and NHS funding have increased from 1877 patient evaluations / £2,239,000 in 2008 to 3444 cases / £5,356,000 in 2013 **[b]**. Since 2008, 2,950 new and 10,955 completed follow up assessments comprise ~70% of all UK

amyloidosis patients, representng the largest, most diverse cohort of amyloidosis patients worldwide. Since 2012, the Centre has provided an online amyloidosis genetic testing service for the UK **[c]**.

Improving diagnosis. Our correction of the diagnosis of amyloidosis (see **[3**,**4]**) in about 5% of new cases per year underpins steady improvement in mortality and outcome measures. Combining genetic and proteomic testing with refined immunohistochemistry has increased definitive amyloid fibril typing, which is key for appropriate treatment, from ~70% to ~98%.

Our development of CT-SPECT ^{123}I-SAP imaging, as part of 2,100 total SAP scans p.a., enables evaluation of individual organ amyloid load and localised amyloid deposits in non-visceral sites. We have introduced CT-SPECT with ^{99m}Tc-DPD scintigraphy, repurposing this diphosphonate bone tracer for diagnosis, typing and serial evaluation of cardiac ATTR amyloidosis as outlined in **[5]**, leading directly to installation of a new NHS CT-SPECT suite in 2012, and new recurrent NHS funding from April 2012 of £250,000 p.a. Our sophisticated novel cardiac MRI for evaluation of cardiac amyloidosis has won a further £250,000 p.a. of recurrent central NHS funding **[b]**.

Improving disease staging and monitoring. Our further refinement and validation of serum biomarkers for staging disease severity have been adopted by pharma and academia in the first industry and academic Phase III clinical trials of chemotherapy in AL amyloidosis **[d,e]**. Recommendations for treatment of AL amyloidosis with the cyclophosphamide-bortezomib-dexamethasone chemotherapy regimen we reported **[8]**, and for the new response criteria we reported in **[7]** have been adopted in April 2013 guidelines issued by The National Comprehensive Cancer Network (NCCN), an alliance of the world's leading cancer centres **[f]**. Consensus of experts on a modern framework for clinical trial design and drug development in AL amyloidosis was agreed at the first Roundtable on Clinical Research in Immunoglobulin Light-chain Amyloidosis (AL), a meeting sponsored by the Amyloidosis Foundation (Clarkston, MI, USA) in 2010, and published in 2012 **[e]**.

Improving treatment and survival. Refined use of serum free light chain measurements has greatly improved monitoring of responses to chemotherapy in AL amyloidosis **[2]**. We have also demonstrated the feasibility and limitations of solid organ transplantation in amyloidosis. With careful selection, approximately 2% of patients receive an organ and outcomes match those in general transplant registries; renal transplantation in AL amyloidosis, the most serious type, has doubled during the past 5 years. Almost all patients with AL amyloidosis attending the Centre now benefit from combination chemotherapy regimens that include the novel proteasome inhibitor agent, bortezomib. This and other new high cost, high efficacy drugs, licensed in the past 6 years for treatment of myeloma, are available on the NHS to almost all patients with AL amyloidosis as a direct result of our published clinical research work **[g]**, which completely changed the chemotherapy paradigm. Enforcement of the necessary funding was achieved in association with the British Society of Haematology, the UK Amyloidosis Network (led by us) and crucially the patient support charity, Myeloma UK. Survival of AL amyloidosis patients under the care of the National Amyloidosis Centre has improved substantially during the past 12 years: (NAC figures: 4 yr survival 2001-3 was 34%; 2004-7 was 38%; 2008-2012 was 50%).

The Centre's advances are rapidly disseminated to specialist centres and collaborations internationally through scientific/medical publications, international meetings and personal contacts. We established the UK Amyloidosis Network (2009) attracting over 150 participants at the February 2013 annual meeting **[h]**, and the ONS-based epidemiology study of amyloidosis incidence (~5-10 per million p.a. in England), enabling clinical service development in the UK. We lately created the UK Amyloidosis Awareness Group (UKAAG) with whom the NAC has developed a comprehensive website **[h, i]** patient information literature and a regular newsletter to enable patient and public engagement and promote awareness of this rare disease. Myeloma UK have confirmed: "*The recent creation of UKAAG has been warmly welcomed and has given patients an important platform to formally feed in their views about their treatment and care. In particular the creation of a comprehensive website with high-quality information about amyloidosis, that can be trusted 100%, provides a great deal of comfort*." **[i]**

The Centre has received charitable donations from patients, relatives, friends and other supporters, as direct gifts and via wide ranging charitable fund raising events organised entirely by donors, enabling flexible support for new research and patient care initiatives in the Centre for Amyloidosis and Acute Phase Proteins and National Amyloidosis Centre; total funds donated are over £1.2 million **[j]**.

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

[a] Details of National Amyloidosis Centre NHS clinical service available:
UCL website: www.ucl.ac.uk/medicine/amyloidosis/nac
NHS England 2013/14 NHS Standard Contract For Diagnostic Service For Amyloidosis www.england.nhs.uk/wp-content/uploads/2013/06/e13-diag-serv-amyloidosis.pdf

[b] National Amyloidosis Centre patient flow and NHS funding
Details including awards in 2012 of new recurrent funding of £250,000/yr for CT-SPECT service and £250,000/yr for cardiac MRI**,** and substantial increase in annual patient flow and NHS funding from 1877 patient evaluations / £2,239,000 in 2008 to 3444 cases / £5,356,000 in 2013 can be corroborated by Commissioning Support Manager, Royal Free London NHS Foundation Trust, and/or
Operations Manager for Infection and Immunity, Royal Free London NHS Foundation Trust.

[c] Genetic testing service
http://www.ucl.ac.uk/amyloidosis/nac/molecular-genetic-testing

[d] Adoption of disease staging methods using serum biomarkers by pharma and academia:
http://clinicaltrials.gov/ct2/show/study/NCT01659658?term=amyloidosis&recr=Open&rank=10
http://clinicaltrials.gov/ct2/show/NCT01277016?term=BMdex&recr=Open&rank=1

[e] Use of new treatment response criteria in clinical trials:
Comenzo RL, Reece D, Palladini G, Seldin D, Sanchorawala V, Landau H, Falk R, Wells K, Solomon A, Wechalekar A, Zonder J, Dispenzieri A, Gertz M, Streicher H, Skinner M, Kyle RA, Merlini G. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis Leukemia. 2012 Nov;26(11):2317-25 http://dx.doi.org/10.1038/leu.2012.100
Examples:
http://www.ukctg.nihr.ac.uk/trialdetails/ISRCTN33283585
http://clinicaltrials.gov/ct2/show/study/NCT01659658?term=amyloidosis&recr=Open&rank=10
http://clinicaltrials.gov/ct2/show/NCT01277016?term=BMdex&recr=Open&rank=1

[f] International Guidelines on treatment of amyloidosis:
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Systemic Light Chain Amyloidosis
® Version 2.2014, 10/04/13 © National Comprehensive Cancer Network, Inc. 2013.
http://www.nccn.org/professionals/physician_gls/pdf/amyloidosis.pdf (login required; copy avilable on request)
Reference to the research [6] is ref 27 therein; the meeting abstract communicating [7] is ref 19 therein; [8] is ref 63 therein.

[g] Combination Chemotherapy Regimens
Letter from NHS England, confirming the funding for Bortezomib, available on request.
Manuscript publication describing improved survival rates available on request.

[h] UK Amyloidosis Network (February 2013) annual meeting details:
http://www.ucl.ac.uk/amyloidosis/pdfs/nac_newsletter_2

[i] UK Amyloidosis Awareness Group website and patient information resource:
www.amyloidosis.org.uk
Letter from the Chief Executive. Myeloma UK, available on request.

[j] UCL Amyloidosis Research Fund
http://www.ucl.ac.uk/amyloidosis/amyloidosis-research-fund
Income can be corroborated by the fund administrator: Division of Medicine, UCL.