Institution: University College London

Unit of Assessment: 1 – Clinical Medicine

Title of case study: Amyloidosis and acute phase proteins: development of new drugs and a new approach to academia-industry collaboration

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

The UCL Centre for Amyloidosis and Acute Phase Proteins has designed and developed new chemical entities targeting serum amyloid P component (SAP), C-reactive protein (CRP) and transthyretin, for novel therapeutic approaches to amyloidosis, Alzheimer's disease, cardiovascular and inflammatory diseases. The UCL spin out company, Pentraxin Therapeutics Ltd, founded by Sir Mark Pepys to hold his intellectual property (IP), has licensed two programmes to GlaxoSmithKline (GSK). These highly synergistic, collaborative multi-million pound developments, strikingly exemplify new working relationships between academia and the pharmaceutical industry.

2. Underpinning research (indicative maximum 500 words)

Elucidation by Pepys of the role of SAP in amyloidosis (1977-95) led to his invention, in collaboration with Roche, of the bis D-proline drug, CPHPC, which produces sustained depletion of circulating SAP by a novel pharmacological mechanism, first demonstrated at UCL in the early 2000's **[1]**. Patients with systemic amyloidosis are significantly stabilised while being treated with CPHPC but the drug does not remove all SAP from their amyloid deposits and the amyloid does not regress **[4]**. These observations led Pepys to invent the use of anti-SAP antibodies to target residual SAP in the amyloid deposits of CPHPC treated subjects **[5]**. The antibodies trigger remarkable, clinically silent elimination of visceral amyloid in experimental models, which has not previously been achieved. GSK licensed the invention in 2009. They have conducted phase I studies of CPHPC in healthy volunteers and amyloidosis patients, have fully humanised Pepys's optimal mouse monoclonal anti-human SAP antibody, and the first clinical trial of CPHPC plus antibody is currently in progress, so far with no adverse effects.

SAP is universally present in human amyloid deposits, including the cerebral and cerebrovascular amyloid deposits in Alzheimer's disease (AD). SAP also binds to most neurofibrillary tangles. Brain content of SAP is thus higher in AD than in normal subjects, and since SAP is directly neurocytotoxic it likely contributes to neurodegeneration, in addition to its role in amyloidogenesis. The complete removal of SAP from the cerebrospinal fluid, by administration of CPHPC in Alzheimer's disease, is thus an attractive therapeutic approach **[3]**. Experimental work has been supported by the MRC and preparatory work for a first clinical trial in Alzheimer's disease is currently in progress funded by the NIHR through the UCLH/UCL Biomedical Research Centre (BRC) and strongly supported by GSK.

Transthyretin causes both acquired senile cardiac amyloidosis, a hitherto grossly under diagnosed condition, and hereditary systemic amyloidosis. The Pepys team designed and patented novel small molecule compounds targeting transthyretin **[6]**, pursued possible development supported by one of the first Wellcome Trust Seeding Drug Discovery Initiative awards (£3.89 million), but then licensed the IP to GSK for a close collaboration which has yielded new IP.

Human CRP potently activates complement when it binds to dead and damaged cells and this exacerbates tissue damage after ischaemic injury in the heart and brain, validating inhibition of CRP binding as a therapeutic strategy **[2]**. Development of Pepys's small molecule CRP inhibitor approach has been funded by the first award (£4 million) made by the MRC under their Developmental Clinical Studies scheme and latterly also by the British Heart Foundation (BHF).

Pepys joined UCL in 1999, when he was appointed Professor and Head of the Department of Medicine at the Royal Free Campus of University College London, and is currently Principal Clinical Research Associate and Emeritus Professor of Medicine. He was awarded a Knighthood in

the 2012 New Year Honours list for services to biomedicine.

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

[1] Pepys MB, Herbert J, Hutchinson WL, Tennent GA, Lachmann HJ, Gallimore JR, Lovat LB, Bartfai T, Alanine A, Hertel C, Hoffmann T, Jakob-Roetne R, Norcross RD, Kemp JA, Yamamura K, Suzuki M, Taylor GW, Murray S, Thompson D, Purvis A, Kolstoe S, Wood SP, Hawkins PN. Targeted pharmacological depletion of serum amyloid P component for treatment of human amyloidosis. Nature. 2002 May 16;417(6886):254-9. http://doi.org/fq58gj

[2] Pepys MB, Hirschfield GM, Tennent GA, Gallimore JR, Kahan MC, Bellotti V, Hawkins PN, Myers RM, Smith MD, Polara A, Cobb AJ, Ley SV, Aquilina JA, Robinson CV, Sharif I, Gray GA, Sabin CA, Jenvey MC, Kolstoe SE, Thompson D, Wood SP. Targeting C-reactive protein for the treatment of cardiovascular disease. Nature. 2006 Apr 27;440(7088):1217-21. http://dx.doi.org/10.1038/nature04672

[3] Kolstoe SE, Ridha BH, Bellotti V, Wang N, Robinson CV, Crutch SJ, Keir G, Kukkastenvehmas R, Gallimore JR, Hutchinson WL, Hawkins PN, Wood SP, Rossor MN, Pepys MB. Molecular dissection of Alzheimer's disease neuropathology by depletion of serum amyloid P component. Proc Natl Acad Sci U S A. 2009 May 5;106(18):7619-23. http://dx.doi.org/10.1073/pnas.0902640106

[4] Gillmore JD, Tennent GA, Hutchinson WL, Gallimore JR, Lachmann HJ, Goodman HJ, Offer M, Millar DJ, Petrie A, Hawkins PN, Pepys MB. Sustained pharmacological depletion of serum amyloid P component in patients with systemic amyloidosis. Br J Haematol. 2010 Mar;148(5):760-7. http://dx.doi.org/10.1111/j.1365-2141.2009.08036.x

[5] Bodin K, Ellmerich S, Kahan MC, Tennent GA, Loesch A, Gilbertson JA, Hutchinson WL, Mangione PP, Gallimore JR, Millar DJ, Minogue S, Dhillon AP, Taylor GW, Bradwell AR, Petrie A, Gillmore JD, Bellotti V, Botto M, Hawkins PN, Pepys MB. Antibodies to human serum amyloid P component eliminate visceral amyloid deposits. Nature. 2010 Nov 4;468(7320):93-7. http://dx.doi.org/10.1038/nature09494

[6] Kolstoe, S.E., Mangione, P.P., Bellotti, V., Taylor, G.W., Tennent, G.A., Deroo, S., Morrison, A.J., Cobb, A.J.A., Coyne, A., McCammon, M.G., Warner, T.D., Mitchell, J., Gill, R., Smith, M.D., Ley, S.V., Robinson, C.V., Wood, S.P. and Pepys, M.B. (2010) Trapping of palindromic ligands within native transthyretin prevents amyloid formation. *Proc. Natl. Acad. Sci. USA,* **107:** 20483-20488. http://dx.doi.org/10.1073/pnas.1008255107

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

Pepys's drug discovery intellectual property portfolio, comprising more than 20 granted patents **[a]**, is held by the UCL spin out company, Pentraxin Therapeutics Ltd, which he founded in 2001 **[b]**. The company, created as a vehicle for commercialisation of the IP, was initially funded exclusively by loans from UCL totalling more than £1.5 million and has not sought external investment. It conducts its activities entirely through its relationship with UCL and its external collaborations and has no employees. In 2009 and 2010, Pentraxin licensed two of its drug programmes to GlaxoSmithKline (GSK) in multi-million pound deals and is developing them in close collaboration with GSK where several hundred employees participate at various levels **[c, d]**. Pentraxin has repaid all its loans from UCL and is now in profit with substantial further milestone and royalty payments in prospect if programmes are successful.

The most advanced programme, aiming to eliminate visceral amyloid deposits, is the first in class obligate therapeutic partnership of CPHPC, a small molecule drug, and a mouse monoclonal anti-human SAP antibody which has been fully humanised by GSK. The first human patient studies are now in progress and are progressing very well **[d, e]**. The programme has been chosen by GSK as its flagship candidate for potential adaptive licensing in the process being led by the

MIT Centre for Biomedical Innovation through its New Drug Development Paradigms (NEWDIGS) initiative. There is a very strong movement towards streamlining and improvement of the regulatory licensing pathway for new medicines so that patients with unmet medical needs get access to novel treatments more rapidly and more efficiently than at present. The UCL/Pentraxin/GSK amyloidosis programme is in the vanguard.

GSK also licensed Pepys's IP covering compounds for treatment of transthyretin amyloidosis and the programme has passed its initial developability milestone. Typical industry costs for a drug development programme to this stage are £6-8 million.

The discovery and development of CRP inhibitors for myocardial infarction, stroke, cancer cachexia and inflammatory diseases has been supported by the MRC and BHF and has received expert guidance from GSK.

Work on SAP depletion by CPHPC for Alzheimer's disease has been supported at the experimental level by the MRC. Via the UCLH/UCL BRC, the NIHR is now funding preparatory work for the first clinical trial of CPHPC in Alzheimer's disease, with GSK as major participants contributing crucially to project management, funding and provision of their existing CPHPC results. Furthermore GSK have an option to licence CPHPC for this indication.

The transmission of drug discovery directly from a university into big pharma is a very rare achievement, particularly across such a broad range of different programmes. In 2011, GSK named Professor Pepys as the first "academic superstar" in its programme to develop long term ongoing partnerships with academia as part of its drug discovery programme **[d, f]**. GSK has changed its R&D model over the last 5 years, including the creation of the Academic Discovery Partnership Unit and Discovery Partnerships with Academia. The aim is to make the company more productive, agile, and focussed on areas of scientific potential **[g]**.

The Head of the Academic Discovery Partnership Unit at GSK confirmed the ways in which close working with the UCL team has been important in progress towards bringing a drug to market:

[Text removed for publication] **[d]**.

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

[a] **Major Patents**

Pepys, M.B. CRP binding agents. US Patent No. 7,390,795, granted 24 June 2008.
Pepys, M.B. Treatment and prevention of tissue damage. European Patent No. 1 503 800, granted 28 October 2009.
Pepys, M.B. Treatment and prevention of tissue damage. US Patent No. 7,615,543, granted 10 November 2009.
Pepys, M.B. Therapeutic agent. US Patent No. 7,691,897, granted April 2010.
Pepys, M.B. and Hawkins, P.N. Compounds inhibiting the binding of SAP for treating osteoarthritis. US Patent No. 7,659,299, granted 9 February 2010.
Pepys, M.B. Therapeutic agent for depletion of an unwanted protein population from plasma. European Patent No. 1 820 501, granted 14 September 2011.
Pepys, M.B. and Hawkins, P.N. Compounds inhibiting the binding of SAP for treating osteoarthritis. European Patent No. 1 633 345, granted 21 September 2011.
Pepys, M.B. Therapeutic agent. US Patent No. 8,173,694, granted 8 May, 2012
Pepys, M.B. Combinations of SAP depleting agents and anti-SAP antibodies. US Patent No. 7,910,106, granted 22 March 2011.

[b] **Pentraxin Therapeutics Ltd**

Corroboration can be obtained from the Managing Director, UCL Business PLC.

[c] **Commercial deals**

http://www.europharmatoday.com/2009/03/gsks-vallance-teams-up-with-exuniversity-london-

colleagues-in-pentraxin-deal.html

http://medicalintelligencenews.blogspot.co.uk/2012/01/professorsir-mark-pepys-frs-md-phd.html

http://pentraxin.wordpress.com/news/

[d] **Engagement with GSK**
Letter of support from the Head of the Academic Discovery Partnership Unit, GSK.
Available on request.

[e] **Phase I Clinical trial of a combination of CPHPC and an anti-SAP antibody**
http://clinicaltrials.gov/ct2/show/NCT01777243

[f] **Financial Times on Professor Pepys being chosen as an academic superstar**
http://www.ft.com/cms/s/0/d1e31184-37a5-11e0-b91a-00144feabdc0.html

[g] **Details of GSK's R&D model is available in their evidence to the Parliamentary Science and Technology Committee, March 2013**
http://www.publications.parliament.uk/pa/cm201213/cmselect/cmsctech/348/348we24.htm