Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: Progression of the Imperial College Spin-out "Circassia" to a Multimillion Pound Specialty Biotechnology Company

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

Between 1995 and 2004 researchers at Imperial College developed a T cell peptide allergy vaccine in an attempt to improve the quality of life of millions of allergy sufferers worldwide. A spin-out company (Circassia Ltd) was founded and subsequently sold to Circassia Holdings Ltd, a clinical-stage specialty biopharmaceutical company based in Oxford, UK. Circassia Holdings Ltd has raised £98 million of funding since 2008 and has developed a pipeline of products to treat common allergies. In October 2012 the lead product ToleroMune® Cat entered a phase III clinical study involving 85 clinical sites across the USA, Canada and Europe and enrolling 1186 patients in the largest single field study ever undertaken in immunotherapy. Circassia currently employs 25 highly skilled people in-house with an outsourced business model giving employment to an estimated further 200 people.

2. Underpinning research (indicative maximum 500 words)

Key Imperial College London researchers:
Professor A Barry Kay, Professor of Clinical Immunology (1980-2004), Emeritus Professor and Senior Research Investigator (2004-present)
Dr Mark Larché, Lecturer, Senior Lecturer (1995-2006)

Asthma and allergic rhinitis between them affect an estimated 30% of the population of Western developed countries, and give rise to a global drugs bill in excess of £6 billion. The current treatment is almost exclusively symptomatic rather than curative. This typically means patients are subject to treatment for life, often with products which carry a risk of unwanted side-effects. A large unmet medical need therefore exists for a safe and effective preventive treatment for these conditions. In 1995 Professor Kay and Dr Larché set out to develop a safe and effective synthetic "allergy vaccine". As part of ongoing studies investigating the role of T cells in allergy and asthma it was observed that, in sensitised individuals, allergen-derived T cell peptide epitopes provoked either allergic reactions, or tolerance, to the whole allergen depending on several factors including MHC class II binding properties of the peptides, the route of administration, dose, and the interval between doses.

The initial findings were published in the Journal of Experimental Medicine and a patent application claiming use of peptides for desensitisation to antigens was filed in March 1997 (1). In December 1998 Circassia Limited, an Imperial College spin-out (co-founders: Professor Kay and Dr Larché) was incorporated. In May 2000 the company obtained £245,500 from University Challenge Seed Fund and in August 2000 a further £305,000 investment was secured from Lafferty Ltd. A prototype vaccine was subsequently developed at Imperial College and used as a model of cat allergy. It was found that to maximise tolerance and minimise side effects the allergen-derived peptides should be of optimal length and solubility, have promiscuous binding to major histocompatibility complex (MHC) Class II for T cell recognition on a population basis, be delivered by the intradermal route and for there to be an interval of at least 7 days between each dose (2). This led to a second patent file in January 1998 on methods and compositions for desensitisation. A successful phase II clinical trial of a prototype cat allergy vaccine was subsequently reported in 2001 and further successful clinical studies at Imperial addressed specific issues such as optimal dosing intervals, improvements in nasal outcomes and airway hyper-reactivity (3).

A number of mechanistic studies, again at Imperial College, were performed including bronchoscopy with bronchoalveolar lavage and biopsies in human atopic volunteers and the development of an animal model of peptide immunotherapy. Professor Kay, Dr Larché and

colleagues were able to provide evidence that peptide immunotherapy induced a population of regulatory T cells which downregulated Th2 cells and their products (4). The capacity of the vaccine to induce linked suppression, where tolerance to one epitope on a peptide chain confers tolerance to an unrelated site on the same molecule, was demonstrated both in man and mice (5).

From 2002 to 2009 Professor Kay and colleagues, working closely with industry (first PowderJect Ltd and then Circassia Holdings Ltd), published the detailed multiple overlapping MHC-binding motifs to the major cat allergen, Fel d1, as well as the results of Circassia's first clinical trial using a commercial GMP vaccine (6). The peptide vaccine, comprising the immunodominant regions of the allergen, was safe and well tolerated when given to subjects with cat allergy. The dose of vaccine resulting in the greatest reduction in late-phase skin response (used as a surrogate marker of an allergic reaction) was defined and used for further successful phase II studies. A third patent relating to vaccine peptide combinations against cat allergy was filed in December 2008. The peptide approach to allergy vaccines has the potential for becoming the standard for allergy preventative treatment and may significantly reduce the burden of burden of disease on a global scale.

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

(1) Haselden, B.M., Kay, A.B. & Larché, M. (1999). Immunoglobulin E-independent major histocompatibility complex-restricted T cell peptide epitope-induced late asthmatic reactions. *J Experimental Medicine*, 189, 1885-1894. DOI. Times cited: 202 (as at 22nd October 2013 from ISI Web of Science). Journal Impact Factor: 13.21.

(2) Oldfield, W.L.G., Kay, A.B. & Larché, M. (2001). Allergen-derived T cell peptide-induced late asthmatic reactions precede the induction of antigen-specific hyporesponsiveness in atopic allergic asthmatic subjects. *J Immunology*, 167, 1734-1739. Times cited: 105 (as at 22nd October 2013 from ISI Web of Science). Journal Impact Factor: 5.52.

(3) Oldfield, W.L.G., Larché, M. & Kay, A.B. (2002). Effect of T-cell peptides derived from Fel d 1 on allergic reactions and cytokine production in patients sensitive to cats: a randomised controlled trial. *Lancet*, 360, 47-53. DOI. Times cited: 213 (as at 22nd October 2013 from ISI Web of Science). Journal Impact Factor: 39.06.

(4) Verhoef, A., Alexander, C., Kay, A.B. & Larché, M. (2005). T cell epitope immunotherapy induces a CD4+ T cell population with regulatory activity. *PLos Medicine*, 2 (3), e78. DOI. Times cited: 78 (as at 22nd October 2013 from ISI Web of Science). Journal Impact Factor: 15.25.

(5) Campbell, J.D., Buckland, K.F., McMillan, S.J., Kearley, J., Oldfield, W.L.G., Stern, L.J., Gronlund, H., van Hage, M., Reynolds, C.J., Boyton, R.J., Cobbold, S.P., Kay, A.B., Altmann, D.M., Lloyd, C.M. & Larché, M. (2009). Peptide immunotherapy in allergic asthma generates IL-10-dependent immunological tolerance associated with linked epitope suppression. *J Experimental Medicine*, 206, 1535-1547. DOI. Times cited: 74 (as at 22nd October 2013 from ISI Web of Science). Journal Impact Factor: 13.21.

(6) Worm, M., Lee, H-H., Kleine-Tebbe, J., Hafner, R.P., Laidler, P., Healey, D., Buhot, C.,Verhoef, A., Maillère, B., Kay, A.B. & Larché, M. (2011). Development and preliminary clinical evaluation of a peptide immunotherapy vaccine for cat allergy. *J Allergy Clinical Immunology*, 127, 89-97. DOI. Times cited: 34 (as at 22nd October 2013 from ISI Web of Science). Journal Impact Factor: 12.04.

Key funding:

- Medical Research Council (MRC; 2000-2003; £318,622), Co-Principal Investigator (Co-PIs) A. B. Kay, M. Larché. Mechanisms in T cell peptide epitope-induced late asthmatic reactions.
- MRC (2000-2003; £371,479), Co-PIs M. Larché, A. B. Kay. Inhibition of atopic allergic inflammatory reactions by allergen-derived T cell peptides.
- MRC (2001-2002; £94,316), Co-PIs M. Larché, A.B. Kay. A controlled pilot study to assess the tolerability and efficacy of Fel d 1 derived peptides on bronchial, nasal and skin reactivity in cat-

allergic asthmatics.
- MRC (2002-2005; £317,437), Co-PIs M. Larché, D. Altman, C. Lloyd. Mechanisms of T cell peptide epitope-induced isolate late asthmatic reaction and ensuing immunological tolerance.
- National Asthma Campaign (NAC) (2000-2005; £250,000) PI M. Larché, T cell vaccines for asthma and allergic rhinitis (Fellowship)
- NAC (1999-2001; £117,000), PI A.B. Kay, Double Blind placebo-controlled trial of an HLA-restricted, allergen derived T cell peptide vaccine in cat allergic asthma

Patents:
- A.B. Kay, M. Larché: International Patent Application "Cryptic Peptides" PCT/GB97/00783 (Priority date 20/03/97)
- M. Larché, A.B. Kay. International Patent Application "Method for Desensitisation" WO 99/34826 (Priority date 09.01.98)
- R.P. Hafner, M Larché, A B Kay: International Patent Application "Vaccine peptide combinations against cat allergy" WO 2008/145988 (Priority date 04.12.08)

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

Impacts include: commercial
Main beneficiaries include: industrial partners

Since 2008, Circassia has raised £98 million to establish its viability as a spin-out company. Circassia employs 25 highly skilled people in house and an estimated 200 others through its outsourced business model.

Established the viability of spin-out company:
Circassia's pipeline platform technology is applicable to all immunological disorders involving a recognised antigen and products have been given the trademark "ToleroMune". Due to good progress in early Phase II clinical trials developing a cat allergy vaccine (ToleroMune Cat), Circassia Ltd was able to announce in January 2008 that it had successfully raised £11 million ($21.8 million) in an oversubscribed second round funding [1], having completed an initial investment round of £6 million ($11.8 million) the previous year. The investment syndicate was led by Imperial Innovations and included Landsdowne Partners, Tudor Capital, Goldman Sachs and Invesco Perpetual. Further successful Phase II cat studies were completed during 2009 and a ragweed allergy vaccine (ToleroMune Ragweed) Phase II study initiated. These positive results led to a third investment round of £15 million ($25 million) in December 2009 [2]. By 2010 Circassia had initiated clinical trials in house dust mite allergy [3] and achieved a positive result in Phase II studies with the ragweed allergy vaccine. Shortly after Circassia announced that it had been granted European Composition of Matter Patents for three of the company's lead allergy T-Cell vaccines (cat, house dust mite and grass) [4]. They extended the period of patent protection for cat and house dust mite allergies until 2028 and for grass allergy treatment until 2022 [6].

In 2010 Circassia completed a £60 million ($98 million) fourth round fundraising for final-stage development of its lead allergy products. The investment, scheduled in two tranches over the following two years, was the second largest fundraising by a privately-held European biopharmaceutical company that year, and the third largest in more than 15 years [5]. The award, to Circassia, of European patents for key peptides in grass and ragweed allergy therapies was granted in 2011 [6] and extended the products' period of protection to 2022 and 2029 respectively. By April 2012 Circassia was able to draw on £35 million ($56 million) from investors after meeting key developmental milestones and also completed an additional £12 million ($19 million) fundraising for late-stage development of its allergy product pipeline [7].

By 2011 the company had data to show that the treatment effect of its cat allergy vaccine not only persists but increases 24 months after commencement of treatment and 21 months after the last dose [8]. Thus, the treatment effect achieved by ToleroMune Cat technology is unparalleled by any other form of treatment for perennial allergic rhinitis and the safety and tolerability are

indistinguishable from placebo.

In October 2012 a phase III study was initiated involving 85 clinical sites across the USA, Canada and Europe enrolling 1186 patients in the largest single field study ever undertaken in immunotherapy [9]. This followed an "end of Phase II meeting" with the US Food and Drug Administration, Scientific Advice from the European Medicines Agency and regulatory guidance from Health Canada, informing the path to registration in each territory.

Employment creation
Circassia Holdings Limited is currently based at The Science Park, Oxford. It is managed by a strong team of life science entrepreneurs and scientists, and from 2007-2013 was chaired by Sir Richard Sykes, the former Chairman of GlaxoSmithKline and former Rector of Imperial College. The company currently employs 25 highly skilled people in-house and has an outsourced business model. This outsourced business model enables the company to benefit from the best skilled people in the world and in 2012 alone £23.6 million was spent on R&D organisations supporting the employment of an estimated 200 people [10].

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

1. Circassia raises £11 million ($21.8 million) in oversubscribed second round funding. Archived on 22nd October 2013.
2. Circassia Raises £15million ($25million) in Oversubscribed Investment Round. Archived on 22nd October 2013.
3. Circassia Extends its Clinical-Stage Portfolio With Phase II Trials of T-cell Vaccines Against House Dust Mite and Cat Allergies. Archived on 22nd October 2013.
4. European Patents:
   - 4.1. Cat allergy. European patents Journal 6331: "Vaccine peptide combinations against cat allergy", granted 22nd Sept 2010. Publication number: EP2079481. Archived on 4th April 2013
   - 4.2. Grass allergy. European patents Journal 6356: "T cell epitopes of the Cyn1D1 allergen from Bermuda grass pollen", granted 16th March 2011. Publication number: EP1436320. Archived on 4th April 2013.
   - 4.3. Ragweed allergy. European patents journal 6395: "Vaccine comprising amb a 1 peptides for use in the treatment of ragweed allergy", granted 14th December 2011. Publication number: EP2153841. Archived on 4th April 2013.
5. Circassia Completes £60 Million ($98 Million) Fundraising For Final-Stage Development of Lead Allergy Products. Archived on 22nd October 2013.
6. European patents for key peptides granted and periods of patent protection extended for vaccine patents. Archived on 22nd October 2013.
7. Circassia Draws £35 Million ($56 Million) From Investors After Meeting Key Development Milestones and Completes Additional £12 Million ($19 Million) Fundraising for Late-stage Development of Allergy Product Pipeline. Archived on 22nd October 2013.
8. Circassia's Rapid Four-Dose ToleroMune Treatment Maintains Significant Reduction in Allergy Symptoms During 12-Month Follow-up. Archived on 22nd October 2013.
9. Circassia Initiates Pivotal Phase 3 ToleroMune® Trial in Cat Allergen-Induced Rhinoconjunctivitis. Archived on 22nd October 2013.
10. Employment and outsources business model evidence letter provided by Circassia Limited Deputy Chairman (available upon request).