Institution: King's College London		
Unit of Assessment: UoA5		
Title of case study: A first in the world IgE class antibody for the treatment of solid tumours: from concept to antibody design, engineering, efficacy, translation to a Phase I trial and creation of a spinout company		
Period when the underpinning research was undertaken: 2000 – 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Sophia Karagiannis	Professor of Translational Cancer Immunology and Immunotherapy	2003 to date
James Spicer	Professor of Experimental Cancer Medicine & Consultant in Medical Oncology	2006 to date
Hannah Gould	Honorary Professor of Biophysics PI of Allergy and Asthma Group	1969 to date
Period when the claimed impact occurred: 2017 – 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Cancer is the second leading cause of death worldwide. Immunotherapy, which uses IgG antibodies, often fails to treat solid tumours. King's identified an alternative family of antibodies (IgE) to treat solid tumours. Unlike other antibody classes, IgE normally resides in tissues but has never before been considered as an anti-cancer therapy. King's developed the approach from conception, revealing how IgE functions against cancer, through to translation into a Phase I clinical trial. This body of work has resulted in the creation of a spinout company. This company has secured GBP5,000,000 of investment and a patent covering antibodies of this class in three international territories. This knowledge has enabled healthcare professionals' to use new immunotherapy drugs to treat cancer.

2. Underpinning research

Cancer is a global problem. Cancer is the second leading cause of death and is estimated to account for 9,600,000 deaths across the globe in 2018. Furthermore, the number of global cancer deaths is projected to increase by 45% between 2008 and 2030. The economic impact of cancer is significant and is increasing: the total annual economic cost of cancer in 2010 was estimated at USD1,160,000,000,000.

Immunotherapy is at the forefront of cancer treatment, but it needs to be more effective. Immunotherapy uses antibodies that can mobilise the patient's own immune system to fight cancerous cells. It has been at the forefront of cancer treatment, transforming clinical outcomes for many patients. Even though antibody therapeutics is a well-established platform to combat disease, out of the five antibody classes deployed by the human immune system, only IgG is used in cancer immunotherapy at present. IgG class antibodies are predominately localised to blood and body fluids and often fail in the treatment of solid tumours, likely because retention of IgG i is very low in dense tissue environments, meaning they are unable to activate the local immune cells to target cancer.

King's investigate alternative antibodies to target solid tumours. Since different antibody classes function through unique Fc-receptors and induce specific immune responses in different tissues, King's hypothesised that there may be potential benefit to design new therapeutics that exploit antibody isotypes other than IgG, depending on the tumour type to be targeted. The King's team have been studying another class of antibody, IgE, which are less common than IgG antibodies. IgE antibodies cause the body to react against foreign substances such as pollen or parasites. Importantly, they are distinct from IgG in that they normally reside in solid tissues such as the lung and skin. Moreover, IgE binds with extremely high affinity to FcεRI receptors on immune effector cells that are known to infiltrate solid tumours. Furthermore, while inhibitory Fc receptors on tumour cells can block the effector functions of IgG antibodies, no inhibitory IgE Fc receptors are known to exist. The development of tumour antigen-specific IgE antibodies may therefore provide an improved immune functional profile and enhanced anti-cancer efficacy, especially in the context of solid tumours such as ovarian, breast cancer and melanoma which reside in tissues.

King's research revealed how IgE antibodies work. The King's team discovered that when directed to recognise cancer, IgE antibodies could reduce the growth of tumours, and induce release of specific subsets of cytokine molecules that activate the immune system without any allergic or toxic side effects **(1)**. They also showed in pre-clinical models that treatment with IgE, but not IgG, was specifically associated with elevated serum concentrations of the cytokine TNFα, alongside substantially elevated immune cell infiltration and immunological pathway activation in tumours. This means that IgE triggers specific molecular changes in human immune cells that make them far more likely to target cancer cells **(2)**. This important discovery shows that using IgE as a therapy for solid tumours acts to prime immune cells and reprogramme them to drive anti-tumour cell cytotoxic effects, reducing the tumour burden **(3)**.

King's developed the world's first anti-tumour IgE antibody therapies. The first IgE class antibody recognising a tumour-associated antigen was generated and studied at King's and translated the first-in-class IgE for cancer to clinical testing. MOv18 IgE, the first IgE class antibody developed by King's, binds strongly to a tumour marker known as Folate Receptor alpha (FRα), found on the surface of solid tumours such as ovarian, breast and lung cancers. FRα is a folate binding protein shown to be associated with tumour growth and malignant transformation. MOv18 IgE outperformed its IgG counterpart in three animal models of ovarian cancer. This work has been supported by Cancer Research UK, the NIHR Biomedical Research Centre and the MRC Developmental Pathway Funding Scheme with grants in excess of GBP1,500,000.

King's developed an enhanced IgE engineering platform, the first and only of its kind worldwide. For the first time, IgE has been manufactured for use in the clinic. The unique method we have developed allows for faster production using less resources that other approaches, has built-in capacity to scale up or down and is easily applied within a GMP environment. Consequently, King's have increased production yields 33-fold and can expedite manufacturing of IgE therapies for clinical trials for cancer patients **(4, 5, 6)**. Importantly, King's research has led to new opportunities to fast-track the design of a new generation of IgE therapeutic candidates with enhanced effector functions, including those generated by the King's spinout IGEM Therapeutics Ltd (later known as Epsilogen Ltd).

King's established the world's first in man IgE class antibody phase 1 trial. The development and clinical testing of MOv18 IgE were led by King's researchers. A first in man phase 1 trial (2016-2020) began with 24 patients at the Early Phase Clinical Trials Unit at Guy's Hospital, affiliated with King's College London, and three other sites. King's is working closely with the Cancer Research UK New Agents Committee and the Centre for Drug Development, who have invested GBP660,000 based on King's unique international expertise in designing specialised clinical trial

assays for the study of this agent. King's is conducting several of these assays in real time as part of this clinical study. This remains the only global example of use of IgE as a therapy.

King's expands the field of research, based on investigations in immunotherapy, IgE and cancer: King's research exploring the therapeutic potential of IgE class antibodies and associated Phase I trial, led to the formation of AllergoOncology, co-chaired by Prof. Erika Jensen-Jarolim (Medical University of Vienna) and Prof. Sophia Karagiannis (King's College London). AllergoOncology, is an international task force of experts whose 49 research groups investigate the interphase between IgE, allergic responses and cancer. In establishing an international expert base in immune responses in cancer and immuno-oncology, King's have ensured the expansion of this field of research and supported the development of clinical academics. In 2021, AllergoOncology became a recognised Working Group by the European Academy of Allergy and Clinical Immunology, which is a recognition of the field's contribution to interdisciplinary research and potential impact in the field of allergy and oncology (https://www.eaaci.org/organisation/sections-a-igs/4763-wg-allergooncology).

3. References to the research

1. Josephs DH, Bax HJ, Dodev T, Georgouli M, Nakamura M, Pellizzari G, Saul L, Karagiannis P, Cheung A, Herraiz C, Ilieva KM, Correa I, Fittall M, Crescioli S, Gazinska P, Woodman N, Mele S, Chiaruttini G, Gilbert AE, Koers A, Bracher M, Selkirk C, Lentfer H, Barton C, Lever E, Muirhead G, Tsoka S, Canevari S, Figini M, Montes A, Downes N, Dombrowicz D, Corrigan CJ, Beavil AJ, Nestle FO, Jones PS, Gould HJ, Sanz-Moreno V, Blower PJ, Spicer JF, Karagiannis SN. Anti-Folate Receptor-α IgE but not IgG Recruits Macrophages to Attack Tumors via TNFα/MCP-1 Signaling. Cancer Res. 2017 Mar 1;77(5):1127-1141. doi: 10.1158/0008-5472.CAN-16-1829.

2. Josephs DH, Nakamura M, Bax HJ, Dodev TS, Muirhead G, Saul L, Karagiannis P, Ilieva KM, Crescioli S, Gazinska P, Woodman N, Lombardelli C, Kareemaghay S, Selkirk C, Lentfer H, Barton C, Canevari S, Figini M, Downes N, Dombrowicz D, Corrigan CJ, Nestle FO, Jones PS, Gould HJ, Blower PJ, Tsoka S, Spicer JF, Karagiannis SN. An immunologically relevant rodent model demonstrates safety of therapy using a tumour-specific IgE. Allergy. 2018 Dec;73(12):2328-2341. doi: 10.1111/all.13455.

3. Pellizzari G, Hoskin C, Crescioli S, Mele S, Gotovina J, Chiaruttini G, Bianchini R, Ilieva K, Bax HJ, Papa S, Lacy KE, Jensen-Jarolim E, Tsoka S, Josephs DH, Spicer JF, Karagiannis SN. IgE re-programs alternatively-activated human macrophages towards pro-inflammatory anti-tumoural states. EBioMedicine. 2019 May; 43:67-81. doi: 10.1016/j.ebiom.2019.03.080.

4. Ilieva KM, Fazekas-Singer J, Bax HJ, Crescioli S, Montero-Morales L, Mele S, Sow HS, Stavraka C, Josephs DH, Spicer JF, Steinkellner H, Jensen-Jarolim E, Tutt ANJ, Karagiannis SN. AllergoOncology: Expression platform development and functional profiling of an anti-HER2 IgE antibody. Allergy. 2019 Oct;74(10):1985-1989. doi: 10.1111/all.13818.

5. Fazekas-Singer J, Singer J, Ilieva KM, Matz M, Herrmann I, Spillner E, Karagiannis SN, Jensen-Jarolim E. AllergoOncology: Generating a canine anticancer IgE against the epidermal growth factor receptor. J Allergy Clin Immunol. 2018 Sep;142(3):973-976.e11. doi:10.1016/j.jaci.2018.04.021.

6. Crescioli S, Chiaruttini G, Mele S, Ilieva KM, Pellizzari G, Spencer DIR, Gardner RA, Lacy KE, Spicer JF, Tutt ANJ, Wagner GK, Karagiannis SN. Engineering and stable production of

recombinant IgE for cancer immunotherapy and AllergoOncology. J Allergy Clin Immunol. 2018 Apr;141(4):1519-1523.e9. doi: 10.1016/j.jaci.2017.12.986.

4. Details of the impact

King's researchers founded IGEM Therapeutics Ltd (now Epsilogen Ltd). Based on this pioneering research conducted by King's researchers on the development of the comprehensive translational pathway of IgE immunotherapy from concept to the clinic, King's established a commercial entity to exploit IgE therapies. IGEM Therapeutics Ltd launched on 31 March 2017 **(A)** and later changed its name to Epsilogen Ltd in 2020. This immuno-oncology company is working to develop novel IgE antibodies to treat cancer, utilising King's founders' internationally unique expertise in IgE biology, and experience in the seamless generation, functional evaluation, pre-clinical and clinical development of IgE class antibodies for cancer therapy.

The company presently employs six leadership and management experts and has made a significant investment of GBP1,402,628.86 to King's (Karagiannis laboratory) which allowed for the appointment of two researchers focused on development of the next generation of IgE-based immunotherapies. Both researchers were appointed in 2017 for three years and renewed for a further two years in 2020. The activities of this commercial entity have gained significant momentum, winning Best Start-up Biotech Company at the OBN Annual Awards in October 2018 **(B)**. OBN is a not-for-profit membership organisation with over 400 members supporting UK's life sciences companies, corporate partners and investors since 1999.

IGEM Therapeutics Ltd receives industry and government investment. Following a GBP2,000,000 Series A funding investment in 2017 from Epidarex Capital **(C.4)**, a specialist early stage life science venture capital firm, IGEM raised Series A expansion funding in 2018. Alsa Holdings and UCL Technology Fund (co-managed by Albion Capital and UCLB, UCL's commercialisation company) invested GBP3,000,000 **(C)**. Furthermore, since 2018 IGEM founders Cox and Karagiannis, secured four Innovate UK awards, which totalled GBP2,675,000 to further the development of two novel immune-oncology drugs targeting solid tumours **(D)**. These awards were directly based on pre-clinical research on monoclonal antibodies targeting melanoma and other solid tumours in King's Karagiannis laboratory. This funding is being used to help progress IGEM-Ch and an anti-HER2 candidate into clinical trials by generation of a pre-clinical development package and efficient GMP manufacturing process **(4)**.

Early clinical trial results support, for the first time, the safety and potential efficacy of an IgE antibody as a treatment for advanced cancer. MOv18 IgE is the first therapeutic IgE antibody to enter clinical trials. To date, 24 patients with advanced cancer, whose tumour cells have high levels of FRα, have been given increasing doses of MOv18 IgE. Early results show treatment with the agent has been well tolerated in almost all patients. The most common toxicity was readily manageable urticaria, also called nettle rash or hives. Although this is just the first step in the clinical development of IgE drugs, preliminary evidence of anti-cancer activity was seen in a patient with ovarian cancer **(E)**. The Director of Drug Development at Cancer Research UK said: "*We've made great strides in the use of immunotherapies in cancer, but so far we've only worked with a handful of the different types of immune cells. The IgE antibody could increase our arsenal against the disease by tapping into defences we haven't previously explored*" **(E.1)**. The trial had to be put on hold during the COVID-19 pandemic, but recruitment restarted in January 2021 and it is expected that new patients will be enrolled in trials in April 2021.

King's is granted a patent for the IgE antibody covering three territories. King's have been granted a patent covering the antibody in three territories: the US, Europe and Australia (2017 and 2018) **(F.1)**. A further two patents around IgE antibody engineering, mechanism of action and

clinical application have been submitted (2019, 2020). One patent **(F.2)** was published in July 2020 (PCT/EP2020/05 1121 (WO 2020/148425 A1), Filed Jan 2020).

5. Sources to corroborate the impact

(A) Sources corroborating the founding of IGEM Therapeutics Ltd on 31 March 2017: A.1 Certificate of Incorporation; **A.2** Annual Report and Accounts (2017-2019)

(B) Press releases corroborating confirming IGEM Therapeutics won an OBN Annual Award (Best Start-up Biotech Company) in October 2018: B.1 OBN Awards Website; **B.2** NIHR Biomedical Research Centre Guy's and St Thomas' NHS Foundation Trust and King's College London

(C) Press releases confirming IGEM Therapeutics being awarded £5M total of industry investment and external investor letters: C.1 King's Newsletter July 2017; **C.2** LabioTech Website Article June 2017; **C.3** IGEM Therapeutics Website; **C.4** Epidarex letter; **C.5** Alsa Holdings letter; **C.6** Albion Capital letter; **C.7** King's Press Release, October 2020: "King's immuno-oncology company receives £1 million grant to develop treatments for cancer"

(D) Sources confirming IGEM Therapeutics receiving Innovate UK awards: D.1 Grant Offer Letter from Innovate UK, May 2018 **D.2** Grant Offer Letter from Innovate UK, March 2019; **D.3** Grant Offer Letter from Innovate UK, June 2020; **D.4** Grant Offer letter from Innovate UK, October 2020; **D.5** Press Release from IGEM Therapeutics website

(E) Sources corroborating early results of MOv18 IgE phase 1 trial being safe: E.1 Press release from Cancer Research UK (CRUK) corroborating early results of MOv18 IgE phase 1 trial being safe on 27 April 2020; **E.2** James Spicer presentation to AACR on the clinical trial data

(F) Documents corroborating patents in US, Europe and Australia: F.1 INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT) [European Patent No. 2764025 granted 29 November 2017; US Patent No. 14/348,997 granted 9 January 2018; Australian Patent No. 2011378675 granted 18 January 2018]; **F.2** Patent WO 2020/148425 A1, July 2020