**Institution:** Imperial College London

**Unit of Assessment:** 8 Chemistry

**Title of case study:** C1 - The Founding of Argenta Discovery and Pulmagen Therapeutics

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

The growth and performance of Biofocus Galapagos Argenta (BGA) and Pulmagen Therapeutics (PT) are underpinned by research from the Imperial-based TeknoMed project that started in 1997. BGA was formed in 2010 through the acquisition of Argenta Discovery (AD) by Biofocus Galapagos for €16.5 million and is one of the world's largest drug discovery service organisations with 390 plus employees and turnover of €135 million [section 5, A]. PT was formed as a separate company to own the complete AD drug pipeline. It develops new medicines to treat asthma, cystic fibrosis and allergic diseases. In 2011 BGA signed agreements with PT for an initial £6million fee and with Genentech for £21.5million.

**2. Underpinning research** (indicative maximum 500 words)

In 1997, in collaboration with the University of Cambridge and Rhône–Poulenc Rorer, Tony Barrett started the TeknoMed Project, a major, Imperial-based research programme on drug-design using combinatorial chemistry (CC) and rapid parallel synthesis [G1]. Following further grant support from EPSRC [G2, G3] key outcomes from the collaboration with Rhône–Poulenc Rorer were the discovery and development at Imperial of a range of new techniques for parallel synthesis [1-6] and the training of 16 postdoctoral medicinal chemists in the methods of parallel synthesis. The new techniques embodied methods for purification-minimised parallel synthesis, which are crucial in the early stages of drug discovery. Parallel, or high-throughput, synthesis renders routine the exploration of extended areas of chemical space in the search for new medicinal molecules, to an extent which was previously unviable because of the time and resources needed. The most significant of these methods is the use of ring-opening metathesis polymerisation (ROMP) for the fabrication of polymer-supported reagents and catalysts: ROMPgels and ROMPspheres. This innovative synthesis methodology enables the fabrication of novel, highly functionalised polymeric supports by simple and efficient methods which use readily available precursors. These functional polymers are used in fundamentally important organic synthesis reactions such as alkene formation and nucleophilic displacement, with the undesired by-products being easy to separate from the soluble desired products simply by virtue of being chemically attached to the insoluble polymeric material, which is removed by filtration at the end of the process. This approach facilitates parallel synthesis, in which multiple versions of a generic chemical structure may be made simultaneously using automated and semi-automated techniques. The research on ROMPgels was described as being of "outstanding interest," (Flynn, D.L.; Hanson, P.R.; Berk, S.C.; Makara, G.M. *Current Opinion in Drug Discovery and Development* **2002**, *5*, 571) and was highlighted in *Chemical and Engineering News* (Borman, S. *Chem. Eng. News* **2002**, No. 11, p. 43).

In a related method, a polymer-supported transition metal catalyst which promotes the joining together of two alkenes to make a new, more complex alkene together with ethylene as a volatile by-product was developed. The transition metal catalyst is again immobilised by chemical attachment to an insoluble polymeric support. One of the alkenes in solution reacts with the solid-supported catalyst to form a first reactive intermediate in solution, which then combines with the second alkene to give the desired product alkene, together with a second reactive intermediate. This second intermediate recombines with the polymeric support to give ethylene gas, regenerating the solid-supported catalyst. The active transition metal catalyst immobilised on the polymeric support is thus released temporarily into solution, where it affects the synthesis of the desired alkene prior to recapture by the polymer. This release-and-catch concept was termed 'boomerang' catalysis, and is significant in that it minimises transition metal contamination of the alkene products.

Finally, polymer-supported esters were converted into highly reactive alkenes, which entered into reaction sequences for the formation of all-carbon cyclic compounds as well as sulfur-containing heteroaromatic substances. Product purity was enhanced by being able to wash away impurities

and by-products at each stage of the sequence.

The research and outputs described above and in section 3 arose entirely out of Imperial research [2, 3, 5, 6] or collaboration with Rhône–Poulenc Rorer [1, 4].

**Key personnel:**
A.G.M. Barrett, Professor of Synthesis, Director of the Wolfson Centre for Organic Chemistry in Medical Science, Imperial College London, 1993-present

**3. References to the research** (* References that best indicate quality of underpinning research)

**Research publications**


[1] C.P. Ball, A.G.M. Barrett, A. Commerçon, D. Compère, C. Kuhn, R.S. Roberts, M.L. Smith, and O. Venier, "*Chameleon catches in combinatorial chemistry: Tebbe olefination of polymer supported esters and the synthesis of amines, cyclohexanones, enones, methyl ketones and thiazoles*", *Chemical Communications* (18) 2019 (1998). DOI, **21 citations (as at 4/7/13)**

[2] A.G.M. Barrett, M.L. Smith and F.J. Zecri, "*Impurity annihilation; a strategy for solution phase combinatorial chemistry with minimal purification*", *Chemical Communications* (21) 2317 (1998). DOI, **22 citations (as at 4/7/13)**

[3] C.P. Ball, A.G.M. Barrett, L. Poitout, M.L. Smith and Z.E. Thorn, "*Polymer backbone disassembly: polymerisable templates and vanishing supports in high loading parallel synthesis*", *Chemical Communications* (22) 2453 (1998). DOI, **16 citations (as at 4/7/13)**

[4] *A.G.M. Barrett, S.M. Cramp, R.S. Roberts, and F.J. Zecri, "*Horner-Emmons Synthesis with Minimal Purification using ROMPGEL: A Novel High Loading Matrix for Supported Reagents*", *Organic Letters 1* (4) 579 (1999). DOI, **46 citations (as at 4/7/13)**

[5] *A.G.M. Barrett, R.S. Roberts and J. Schröder, "*Impurity Annihilation: Chromatography-Free Parallel Mitsunobu Reactions*", *Organic Letters 2* (19) 2999 (**2000**). DOI, **49 citations (as at 4/7/13)**

[6] *A.G.M. Barrett, B.T. Hopkins and J. Kobberling, "*ROMPgel Reagents in Parallel Synthesis*", *Chemical Reviews 102* (5) 3301 (2002). DOI, **83 citations (as at 4/7/13)**


**Grant Support**


[G1] Rhône Poulenc Rorer, "TeknoMed Project", PI: A.G.M. Barrett, 1/1/1997-31/12/1999, $6M ($4M to Imperial College)

[G2] EPSRC, GR/M98968/01, "ROMPgel And related supports In combinatorial chemistry", PI: A.G.M. Barrett, 01/10/00 – 30/09/03, £189,491

[G3] EPSRC, GR/M76959/01, "Chameleon catches in combinatorial chemistry", PI: A.G.M. Barrett, 01/01/00 – 31/12/02, £182,825


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

**Background**

Argenta came into being when a team of two dozen highly experienced scientists from the former Aventis Pharmaceuticals (formerly Rhône–Poulenc Rorer) Research Centre in Dagenham, led by Dr Christopher Newton set out to raise money to become a pharmaceutical contract research organisation (CRO). Argenta Discovery was formed through a merger with an Imperial-founded spin-out company, ChemMedICa, in addition to the scientific know-how generated and working relationships formed between Imperial and Rhône–Poulenc Rorer forged through the TeknoMed project. Argenta Discovery was fully funded in 2000 with £7.2m of private investment. Aventis assisted the fledgling company by allowing the team to use the Dagenham facility whilst the Argenta Harlow laboratories were constructed, by awarding the first large research contract to Argenta, and by allowing the purchase of all of the equipment at the closing Dagenham site (http://www.imperial.ac.uk/college.asp?P=2146). Two Imperial scientists trained in the Barrett laboratories during the TeknoMed Project, Drs. Jullian Henschke and Ray Boffey joined Argenta in its early stages and, later, Drs. Fabien Roussel, Robert Pace, and Sarah Major joined the company having gained PhD/postdoctoral training in the Barrett group. In 2007, Argenta signed the largest-ever pre-clinical deal worldwide with AstraZeneca for the co-development of new therapeutic agents for respiratory diseases. This collaboration with up-front and milestone payments is

potentially worth in excess of $500M plus royalties.

**Scientific impact**

The research carried out at Imperial College led to the highly favourable environment in which ChemMedICa and, subsequently, Argenta came into being, and has had wide impact in the chemical sciences. Taken together, publications in learned journals have been cited 500 times, with 100 of these citations during 2008–present.

**Commercial impact**

Argenta Discovery continues to be very successful in both highly profitable CRO work and in the discovery of new drugs to address unmet medical need in respiratory disease, including chronic obstructive pulmonary disease (COPD) (see: *Current Opinion in Pharmacology* ***2009****,* 9 231). This has led to the granting of a substantial number of patents:

**Argenta patents, 2008–**

WO 2010015818 (Feb 11 2010), WO 2009060209 (May 14 2009), WO 2009060203 (May 14 2009), WO 2009013444 (Jan 29 2009), WO 2008122784 (Oct 16 2008), WO 2008119917 (Oct 9 2008), WO 2008096094 (Aug 14 2008), WO 2008017824 (Feb 14 2008), WO 2008017827 (Feb 14 2008)

In addition, Argenta has entered into major collaborations with global pharmaceutical and biotechnology companies including Aventis, Lundbeck, GSK, Novartis, Genentech, Domantis, Pharmagene.

In 2010, Argenta Discovery sold the contract business and company name for €16.5 million [A] in cash to Biofocus Galapagos to form Biofocus Galapagos Argenta. At the time, Argenta had 140 employees. The combined division is "*one of the world's largest drug discovery service organizations, with 390 employees, an estimated €70 million in annual turnover and significant profitability"* [A]. The acquisition also added additional capacity and drug discovery capabilities to the Galapagos Group*.* Argenta's respiratory development programs continued as a new privately held company, Pulmagen Therapeutics [A]. Reporting on the deal, Onno van de Stolpe, CEO of Galapagos said: "*today's [2010] acquisition of the services division of Argenta, one of premier players in the segment, creates a true powerhouse in the drug discovery services market. It also provides Galapagos R&D with additional capacity, capabilities and access to respiratory models for our internal R&D efforts"* [A]. Galapagos acquired Argenta Discovery's *"medicinal chemistry, computational chemistry, ADME [absorption, distribution, metabolism, and excretion] and biology activities as well as the respiratory models and pharmacokinetics operations through a €16.5 million cash payment, approximately 4.7 x EBIT or 1.2 x annual revenue"* [A]. The Group's combined service division operations, which will operate under the BioFocus and Argenta brand names, were expected to achieve €70 million in 2010 revenues (including ~€11 million in service contracts by Galapagos) [A]. Post-acquisition*, "Galapagos' service division operations will employ 390 staff in the UK, Switzerland and the US*" [A].

In 2011 Argenta signed an integrated service agreement with Pulmagen Therapeutics: "*Galapagos NV (Euronext: GLPG) announced today that its service division Argenta has signed a subcontracting agreement with Pulmagen Therapeutics Limited to perform integrated services on two respiratory projects. Under the terms of the agreement, Argenta will be eligible to receive up to £6 million (€7 million) in fee-for-service payments over two years, with the possibility to extend*" [B].

Also in 2011, Argenta and BioFocus announced a two-year extension of a drug discovery collaboration with Genetech: "*Galapagos NV (Euronext: GLPG) announced today that its service division Argenta has extended its integrated contract drug discovery agreement with Genentech, a member of the Roche Group (SIX: RO, ROG; OTCQX: RHHBY). Total potential value of the contract extension is up to £21.5 million (€23.4 million). This is the third such extension since the agreement was announced in December 2005. The agreement covers a number of drug discovery programs that utilize Argenta's expertise in computer-aided drug design (CADD), medicinal chemistry, in vitro biology and screening to discover new chemical entities acting against undisclosed drug targets defined by Genentech*" [C].

Biofocus Galapagos Argenta continued to expand and is now a significant employer of PhD organic chemists in the UK (2010 CRO turnover >€135M [A]). The clinical development of several

potential new medicines to treat COPD, asthma, allergic diseases and cystic fibrosis is currently being taken forward in phases 1 and 2 by Pulmagen Therapeutics, the company which owns the complete drug pipeline from Argenta Discovery [D, E]. This activity too has led to the granting of patents:

**Argenta-AZ patents**
WO 2009139709 (Nov 19 2009), WO 2009138707 (Nov 19 2009), WO 2009139710 (Nov 19 2009), WO 2010019099 (Feb 18 2010), WO 2010018352 (Feb 18 2010), WO 2008149110 (Dec 11 2008), WO 2008149053 (Dec 11 2008), WO 2008096127 (Aug 14 2008), WO 2008096129 (Aug 14 2008), WO 2008096136 (Aug 14 2008), WO 2008096126 (Aug 14 2008)

**Argenta-Pulmagen patents**
WO 2008135537 (Nov 13 2008)

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

[A] "Galapagos Acquires Argenta Discovery's Service Operations" press release, 2/2/10 http://www.argentadiscovery.com/news/archive,galapagos-acquires-argenta-discoverys-service-operations_5.htm (archived at https://www.imperial.ac.uk/ref/webarchive/3mf on 4/7/13)

[B] "Argenta Signs Integrated Services Agreement with Pulmagen Therapeutics" press release, 28/6/11, http://www.argentadiscovery.com/news/press,argenta-signs-integrated-services-agreement-with-pulmagen-therapeutics_85.htm (archived at https://www.imperial.ac.uk/ref/webarchive/4mf on 4/7/13)

[C] "Argenta and BioFocus announce two-year extension of drug discovery collaboration with Genentech" press release, 18/8/11, http://www.argentadiscovery.com/news/press,argenta-and-biofocus-announce-twoyear-extension-of-drug-discovery-collaboration-with-genentech_86.htm (archived at https://www.imperial.ac.uk/ref/webarchive/5mf on 4/7/13)

[D] "Argenta Signs Integrated Services Agreement with Pulmagen Therapeutics" press release, 28/6/11, http://www.mvmlifescience.com/news/default.asp?aid=118 (archived at https://www.imperial.ac.uk/ref/webarchive/7mf on 4/7/13). Full PDF available here.

[E] "Pulmagen Therapeutics Update on Clinical Pipeline", More News - 28/6/2011, http://www.mvmlifescience.com/portfolio/detail.asp?pid=6 (archived at https://www.imperial.ac.uk/ref/webarchive/6mf on 4/7/13)