

Charles River Laboratories

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Acquisition of BioFocus and Argenta extends Charles River's reach

Well known for its *in vivo* biology expertise and preclinical research services, Charles River is now in a position to supply integrated drug discovery capabilities from target identification to IND enabling studies.

In early 2014, Charles River Laboratories, a leading contract research organization, acquired Argenta and BioFocus, two highly specialized early stage drug discovery service providers primarily based in the United Kingdom. For Charles River, the deal is the final segment in a continuous supply chain of contract research service offerings that commence with discovery and follow on to an investigational new drug (IND) application (Fig. 1). James Foster, who is chairman, president and CEO of Charles River, said, "The acquisition of Argenta and BioFocus is precisely in line with our strategy to build a broader portfolio of essential products and services to support the drug discovery and development continuum."

"It will enable us to engage with our clients earlier in the drug discovery process," he added.

Relative to experience and capabilities, the complementarity between the three contract

research organizations is remarkable. Since the 1950s, Charles River has been a name synonymous with the development of *in vivo* models for human disease. Forays into providing contract research services to assess pharmacology, efficacy, toxicology and biomarkers have been a natural part of the company's evolution. The *in vitro* capabilities of Argenta and BioFocus enable Charles River to offer services from the earliest point of the drug development life cycle—target discovery and validation. Argenta and BioFocus each bring expertise in an array of therapeutic indications and formidable drug discovery service track records.

Founded in 1997, BioFocus's integrated drug and target discovery services have supported the pipeline of several large pharmaceutical companies such as AstraZeneca. Argenta, which is a spinout of Aventis's UK research laboratories, was formed three years after BioFocus, and its clientele now

includes burgeoning biotech companies (e.g., Genentech) as well as academic institutions (e.g., University of Cambridge) and pharmaceutical companies (e.g., Boehringer Ingelheim). Also notable is Argenta's collaboration with Antabio, which recently triggered a milestone payment from the Wellcome Trust Seeding Drug Discovery fund (Box 1).

Prior to being acquired by Charles River, the two companies constituted the contract services arm of Galapagos, which is using proceeds from the deal to progress a clinical pipeline and further its ambitions as a biopharmaceutical company. At the same time, the deal fosters Charles River's fundamental mission to provide a unique portfolio of essential products and services that helps clients accelerate their drug development programs. The collective experience of the three organizations encompasses expertise in the development of drugs that attenuate the activity of kinases, G protein-coupled receptors,

BOX 1. ARGENTA AND ANTABIO TRIGGER MILESTONE PAYMENT FROM WELLCOME TRUST

In early 2013, Antabio a young biotech company taking a game changing approach to curtailing antibiotic resistant microbes, and Argenta initiated a collaboration with the support of a Wellcome Trust Seeding Drug Discovery Award. The award of €4.7 million (nearly \$6.5 million to be paid out over three years) is earmarked to facilitate early-stage drug discovery of small molecules that inhibit metallo- β -lactamases.

Metallo- β -lactamases are enzymes that serve to obliterate an antibiotic's ability to kill infectious bacteria. This is one mechanism that is contributing to the emergence of bacterial super bugs, a popular name for infectious microbes that do not respond to any known treatments. The public health threat associated with the emergence of super bugs is widely acknowledged as an emerging healthcare crisis. "There is an urgent need for novel discoveries and an opportunity for small companies to play a major role," explained Marc Lemonnier, CEO of Antabio.

By taking aim at hindering a super bug's resistance mechanisms, Antabio is developing a new class of drugs designed to restore the efficacy of existing antibiotics. "We are a biology driven company that has worked to understand pathogenic resistance and virulence mechanisms. Our development programs involve completely novel pathways and modes of action." Lemonnier explained.

Through the collaboration with Argenta, Antabio identified a series of pan-metallo- β -lactamase inhibitors that when administered in combination with carbapenems, restores the drugs antibacterial activity. In March, the achievement triggered a milestone tranche payment of over €1.7 million (over \$2 million) from the Wellcome Trust.

Carbapenem antibiotics are one of the most effective treatments of bacterial infections. However, their efficacy is becoming increasingly compromised due to the rise of clinical resistance associated with the spread of genes encoding various metallo- β -lactamase enzymes. Carbapenems are a class of antibiotics that contain a chemical ring structure known as a β -lactam. When effective this class of drug disrupts a bacteria's ability to synthesize a cell wall. The β -lactamases are broad-spectrum enzymes, able to inactivate most clinically useful β -lactam antibiotics. The associated threat to human health is staggering.

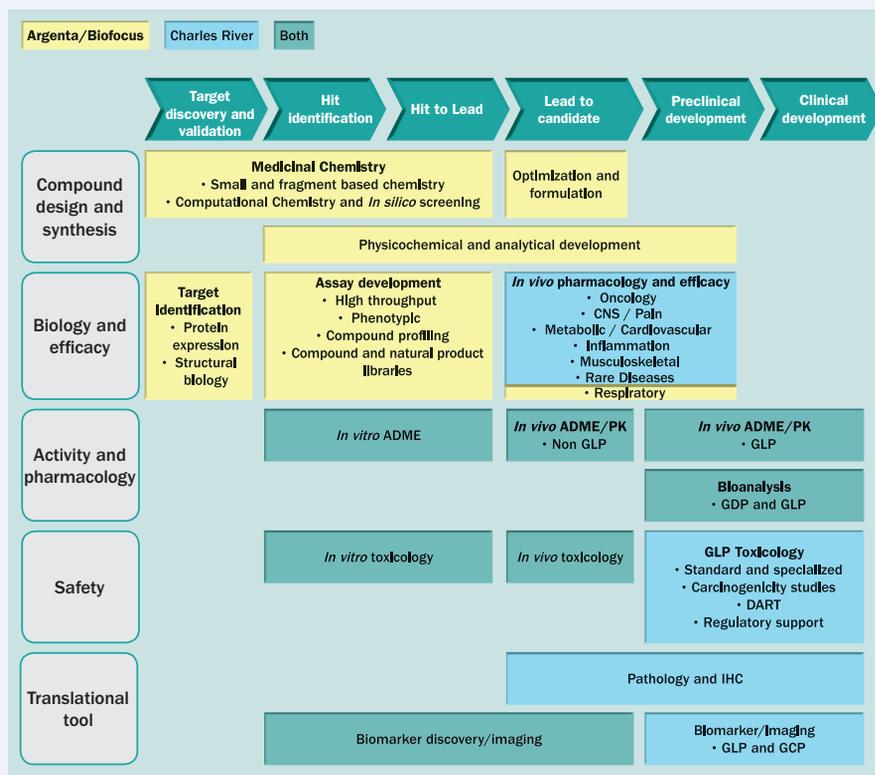
Lemonnier expanded on this premise, "Antibiotic resistance is not just an issue for hospitals." Internationally, health agencies, physicians and researchers are charting the disturbing emergence of new pathogenic bacteria strains in the general population, too. Lemonnier highlighted *Escherichia coli* as an example. While some *E. coli* strains contribute to human health by colonizing the human gut

and providing protection against infectious bacteria, others cause urinary tract infections, diarrhea and septicemia. One life threatening strain infects the urinary tract and then spreads to the bloodstream. According to the European Centre for Disease Prevention and Control, *E. coli* resistance to major antibiotics is increasing in almost all countries in Europe. "It is very difficult to imagine the consequences of not being able to control the threat of an *E. coli* outbreak, as this is a community pathogen," Lemonnier emphasized.

Argenta's role in the collaboration includes supplying drug discovery expertise in addition to medicinal chemistry, computer-aided drug design and ADME/PK (absorption, distribution, metabolism and excretion/pharmacokinetic) services to the up and coming biotech company. Antabio contributed its proprietary drug-like compounds and *in vitro* assays in addition to the company's extensive bacterial disease knowledge. Antabio is carrying out four drug discovery programs based on pathogenic resistance and virulence mechanisms, however the metallo- β -lactamases are the most advanced.

The strategy to develop drugs for use in combination with existing antibiotics affords more benefits than restoring their efficacy. "Clinicians are familiar with using drug combinations to treat infections," Lemonnier commented. Use of antibiotics in combination with the class of

Figure 1. An overview of the additions to Charles River's service offerings due to the acquisition of BioFocus and Argenta.



BOX 1. (cont.)

drugs being developed at Antabio would reduce any associated toxicity as well as restore their potency. For example colistin is one of several antibiotics Antabio's platform can help to overcome resistance. Colistin is a polymyxin antibiotic that was discovered in the late 1940s for the treatment of gram-negative infections. The polymyxin class of antibiotics contains a cyclic peptide that disrupts a bacteria's cell membrane. Unfortunately, it also prompts significant nephrotoxicity and neurotoxicity in humans and for this reason fell out of use. Recently, the antibiotic has resurfaced as a last-resort option for multidrug-resistant organisms such as *Pseudomonas aeruginosa*. Administration with a combination agent inhibiting antibiotic resistance would warrant a dose reduction that would make it safer to use.

Founded in 2009, Antabio is a young company. Antabio's game changing approach to addressing the challenge of antibiotic resistance was at one time perceived as too risky for the venture capital community. Instead, Antabio raised capital through crowdfunding

using WISEED.com, a French organization specializing in equity crowdfunding financings for innovative business and technology start-ups. To be considered, the company submitted its business plan to the WiSeed platform.

It successfully raised €300,000 (over \$415,000) in three months from 207 investors (50 of whom were accredited). An accredited investor then made an approximately €500,000 (nearly \$700,000) investment in late 2011 and eventually bought back the crowd-funded shares in June 2012. The return for the crowdfunding investors was 44 percent. Antabio are using the venture money alongside the Wellcome Trust award to develop two programs to a point that would be of interest for larger investors.

The collaboration with Argenta is contributing to this young company's ability to raise interest in partnering assets as they approach the clinic. This milestone will support further lead optimization efforts to progress our compounds rapidly towards pre-clinical candidate nomination.

proteases, nuclear receptors, ion channels and epigenetic targets. The average number of years spent in industry for Argenta and BioFocus scientists is 17 years.

When Galapagos acquired BioFocus in 2005, it not only benefited from the revenue stream supplied by the company. Galapagos' most advanced candidate, GLPG0634, a Janus kinase-1 inhibitor, was a discovery from BioFocus's research in inflammation (it is also the object of a co-development deal signed with AbbVie last year). GLPG0634 is currently in phase 2 studies for rheumatoid arthritis. BioFocus's expertise also covers therapeutic indications for neurodegenerative diseases.

When Galapagos acquired Argenta in 2010, it also bolstered Galapagos' extensive pipeline and created one of the world's largest drug discovery contract research organizations. Argenta added respiratory and oncology to existing therapeutic areas of expertise in pain and inflammation. Together, Argenta and BioFocus provide capabilities in medicinal chemistry, target discovery and complex *in vitro* biology, as well as therapeutic expertise in respiratory diseases, inflammation, oncology and central nervous system diseases.

Charles River now offers flexible arrangement options that include single project, multiple interaction and integrated services in all the previously mentioned therapeutic areas. In addition, Argenta and BioFocus stand to benefit from being part of a dedicated contract research company. Charles River provides contract research services to the pharmaceutical and biotechnology companies, government agencies and leading academic institutions around the globe. The addition of early stage discovery services promises to enhance existing client relationships.

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