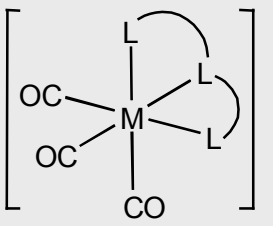
Company Profile

Mission

Alfama develops drugs for the treatment of inflammation-related diseases. The company's immediate goal is to take at least one of its lead compounds to phase I clinical trials directed at a major chronic inflammatory disease such as rheumatoid arthritis. In parallel, Alfama will be pursuing the development of efficient solutions for other large-market therapeutic targets such as myocardial infarction and psoriasis. Subsequent targets for Alfama's technology include atherosclerosis, asthma, stroke, Alzheimer's disease and inflammatory bowel disease.

Technology

Alfama's core technology is based on the delivery of carbon monoxide (**CO**) to target tissues through the use of CO-releasing molecules (**CORMs**). CO is naturally present in our organism, and has been shown to have vasodilating, anti-thrombotic and anti-inflammatory properties. Due to high affinity between CO and hemoglobin, effective treatments based on external CO should involve drugs that can deliver it directly to the target tissues – this is precisely what Alfama's CORMs do. Importantly, these drugs exert their therapeutic action well below the toxicity levels of CO, and can be chemically attached to known drugs in order to complement their therapeutic action or prevent their side effects.



Example of a type of CORM. Organometallic CORMs have a metal core and variable numbers of CO groups and ligands. In vivo *experiments with CORMs showed that they can inhibit pro-inflammatory cytokine production by more than 80%, and that they can function through oral delivery. Different ALF compounds will release CO in various quantities, at different rates, and under different biochemical and physiologic conditions. Alfama is also pursuing a research line on* organic *CORMs, with promising results.*

Because the **therapeutic principle** behind CORMs – CO – is well established, these molecules do not need to be adapted to a specific molecular target. Thus CORMs can be manipulated in order to have different chemical and physiological properties without their basic therapeutic action being jeopardized. Furthermore, contrary to many pharmaceutical drugs, CO is an **endogenous** molecule which the organism is fully adapted to. Together these facts make CORMs a particularly easy and attractive type of drug to develop for clinical purposes.

Since the foundation of the company in December 2002, Alfama scientists have designed more than **400** small molecular weight CORMs, and have synthesized over **100**, which are being tested *in vitro* and *in vivo*. So far, results with several of these compounds have revealed very low toxicity levels and an effective **inhibition of inflammation in mouse and rat disease models**.

Corporate and Financial status

Alfama has recently raised its first round of Venture Capital funding. The company has also been incorporated in the **United States** (Delaware) and gathered an international team of **top industry experts**. This will allow Alfama to move at full speed towards successful entry in the clinic.

Market

The market for anti-arthritis drugs alone will pass the **US$10 billion** mark by 2008 (source: *Nature*). Existing anti-arthritic drugs are classified as either NSAIDs, which relieve pain temporarily, but become ineffective over time, or DMARDs, which retard the progress of the disease, but have serious side effects or are extremely expensive. Alfama's compound is expected to be the first market entry to both relieve pain and retard the progress of the disease, at reasonable cost, without serious side effects. Such compound is expected to produce annual revenues in excess of € 1 billion. Because the market size is enormous, Alfama's competitive advantages are clear, and development risk is comparatively favorable, Alfama has the genuine potential to rapidly become a **major player** in the international pharmaceutical arena.

Intellectual Property

Alfama has filed an initial international **patent** application (**WO 03/066067**) describing seven classes of drugs with CO-releasing moieties. This and approximately 20 other subsidiary applications are now being pursued in 35 countries – and the first of those was **granted** in June 2005. Further patent applications based on more recent breakthroughs and focusing on specific diseases or compounds have been submitted to the US Patent Office.

Locations

Alfama's operations are distributed through 3 different countries and its team of about 15 employees, officers and collaborators currently includes 6 nationalities. Alfama's *Chemistry* and *Drug Discovery* units are based in Portuguese research institutes, namely at the ITQB/IBET in **Oeiras** (shown left) and at the IMM in **Lisbon** (shown right), respectively. Alfama's central management office is also located near Lisbon, at Taguspark. The company's *Lead Development* unit will be managed out of **Geneva** in Switzerland and will coordinate the work of several Contract Research Organizations (CROs) around Europe. Finally, Alfama's financial department and part of its business development activities are based in **Cambridge**, near Boston, Massachusetts (USA). Though this scheme, Alfama hopes to take advantage of the best that Portugal has to offer in terms of human and scientific potential, but at the same time be present in the major biotech hubs of Europe and the US.

Team

Alfama's team includes the following key members:

Nuno Arantes-Oliveira, PhD, *President and CEO*. Nuno has performed some groundbreaking research as an invited scientist at the University of California San Francisco (USCF). Later he became managing director of ATGC Portugal and was a co-founder of Alfama. Nuno has received awards in various countries, and has acted as an advisor to several governments and private entities.

Werner Haas, MD, PhD, *Vice-President*. Werner has more than 25 years experience in drug development, including as research leader at the Basel Institute and at Hoffman-La Roche (in Switzerland and in the USA). He is a founder of two biotechnology companies in the Boston area, and is

an author of more than 70 peer-reviewed papers – including many in high impact journals such as *Nature* – and several patents.

Carlos Romão, PhD, *Vice-President*. Carlos is full Professor of Chemistry at the ITQB – Portugal's largest research center. His research experience also includes the Technical University of Munich and the University of Oxford. He is one of Europe's leading experts in organometallic chemistry, and is the author of over 100 peer-reviewed scientific papers, as well as several patents and monographs.

Stan Kugell, *Chairman of the Board*. Stan is an entrepreneur, director, and early stage investor. His successes include FaxNet, Half.com (sold to EBay), Pilgrim Telephone, Buckminster Corporation, Computer Pictures Corporation and Javelin Software. As a scientist Stan was involved in the creation of breakthroughs such as the telephone voice mail.

Jim Driscoll, MBA, *Chief Financial Officer*. Jim has 25 years of experience as a financial executive of technology-based companies. He has played key roles in fundraising, acquisitions and Initial Public Offerings, with firms including Sonexis, FaxNet and Open Environment Corporation. Jim has been a senior manager at Ernst &Young and got his MBA from Babson College.

Gianni Garotta, PhD, *Head of Lead Development and Extramural Research*. Gianni is one of Europe's top experts in pre-clinical development. Until recently he was Vice-President of Serono (Geneva, Switzerland), Europe's second largest biotech company. Previously he was Head of Biology at Human Genome Sciences (Rockville, MD, USA) and led the interferon and antibody groups at Roche.

Jan Andersson, MD, *Senior Scientist*. Jan has more than 30 years of experience in immunology. He has been a senior scientist at the University of Uppsala (Sweden) and at the Basel Institute of Immunology (Switzerland), and has published over 130 peer-reviewed papers. He got his MD from the *Karolinska Institutet* (Sweden), and did his post-doc at the Salk Institute (San Diego, CA, USA).

Telmo Valido, MBA, *Special Advisor to the Board*. Telmo got his MBA from MIT, and is currently a project manager at the Boston Consulting Group. In the past, Telmo independently consulted for biotech start-ups such as Igeneon (Vienna, Austria) and was involved in projects involving technology developed at the Whitehead Institute (Boston, MA).

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