

# BioCentury

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## Emerging Company Profile

# Arresto: Blocking fibroblasts

By Susan Schaeffer  
Managing Editor

**Arresto Biosciences Inc.** is developing allosteric inhibitors of enzymes found in the extracellular matrix. Because the company's lead mAb inhibits the formation of pathologic stroma, it offers new mechanisms for treating cancer and fibrosis. In cancer, the mAb should be complementary to drugs that target tumor cells. In fibrotic diseases, the logic is that a more complete blockade of the processes that lead to fibrosis should give the compound the potential to reverse, not just halt, disease.

AB0024, a humanized mAb against lysyl oxidase-like 2 (LOXL2), is expected to enter Phase I testing for advanced solid tumors next month. Arresto is in discussions with FDA about a second trial in idiopathic pulmonary fibrosis (IPF) that could begin in 4Q.

The inspiration for Arresto came from work published in *Nature* in 2006 by Amato Giaccia, a professor of radiation oncology at **Stanford University**. Giaccia's group showed metastasis could be inhibited by blocking lysyl oxidase (LOX), an enzyme that plays a role in the formation of stroma in tumors.

LOX belongs to a family of five enzymes involved in maintenance and homeostasis of tissues. Of these, Arresto's founders determined that LOXL2 was expressed across the broadest

### Arresto Biosciences Inc.

Palo Alto, Calif.

Technology: Platform for developing allosteric inhibitors of extracellular matrix enzymes

Disease focus: Cancer, fibrosis, inflammation

Clinical status: Phase I

Founded: 2007 by Peter Van Vlasselaer, Amato Giaccia, Michael Longaker and Geoffrey Gurtner

University collaborators: Stanford University, Technion-Israel Institute of Technology and Catholic University of Leuven

Corporate partners: Undisclosed

Number of employees: 20

Funds raised: Undisclosed

Investors: Kleiner Perkins Caufield & Byers, HealthCare Ventures, Northgate Capital, DAG Ventures and Abbott Biotech Ventures

CEO: Peter Van Vlasselaer

Patents: None issued

range of pathologies, and only minimally expressed in a few healthy tissues.

"The others are expressed in some pathologies, but also in healthy tissues, including 'red flag' tissues like the aorta, smooth muscle and bone," President and CEO Peter Van Vlasselaer told BioCentury.

LOXL2 cross-links collagen and creates a scaffold for fibroblasts to grow on. The enzyme is associated with infiltration and local activation of fibroblasts, and with neovascularization. It is highly expressed in solid tumors; in liver, lung and kidney fibrosis; and in cardiac tissue following myocardial infarction (MI).

"We think most of these pathologies require the same cell types," Van Vlasselaer said. "If you prevent fibroblast recruitment and/or activation, you take out multiple pathology-related growth factors. We have data to show that our antibody blocks recruitment and activation of fibroblasts. Consequently, our antibody blocks LOXL2 and the production of critical growth factors collectively responsible for the pathology, such as VEGF, SDF-1, CTGF [connective tissue growth factor], and TGF beta 1, among others."

Arresto has unpublished data showing that AB0023, a murine version of AB0024, reduced primary tumor growth and decreased metastasis to the bone, liver, pancreas and lung in different xenograft models. The company

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also has shown *in vivo* that the mAb induced tumor pyknosis, autophagy and necrosis.

“AB0023 is also synergistic with several chemotherapeutic agents, which adds to its therapeutic potential,” Van Vlasselaer said.

AB0023 also showed activity in two models of lung fibrosis: one in which mice were treated prophylactically before fibrosis was induced via administration of bleomycin, and one in which fibrosis was already established.

In the former, AB0023 significantly improved survival compared with vehicle. The mAb also significantly reduced Ashcroft score and the quantity of activated fibroblasts and collagen deposition in the lung. Ashcroft score is a measure of fibrosis. The data were statistically significant; p-values were not disclosed.

In animals with established, severe lung fibrosis, the mAb induced normalization of the alveolar epithelia, removal of collagen deposition, reversal of fibroblast activation, normalization of body and lung weight and a statistically significant improvement in Ashcroft score. P-values were not disclosed.

“This clearly indicates that our mAb is capable of reversing lung fibrosis as opposed to just preventing it,” said Van Vlasselaer.

This is likely due to the mAb’s ability to simultaneously inhibit production of multiple pathogenic growth factors via inactivation of fibroblasts. In contrast, many other compounds in development for IPF inhibit a single pathogenic target, for example, the growth factors CTGF or TGF beta.

“Upon treatment with our mAb, you start to have pleiotropic effects: inflammation goes down, you don’t get as many neutrophils — and by the way lymphocytes also are reduced — in bronchial alveolar lavage fluid. In the lung tissue, you see epithelial restoration, you see less fibroproliferation, you see less vascular remodeling,” said Van Vlasselaer. “We think we have reversal of disease, whereas others have only shown prevention” of progression.

Arresto has rights to IP covering LOX from Stanford and to LOXL2 from **Technion-Israel Institute of Technology**. Van Vlasselaer said 80-85% of Arresto’s IP is its own, covering compositions of matter and methods of use in a broad therapeutic spectrum.

The company also has mAbs against three undisclosed enzyme targets for inflammation. All are allosteric binders of their targets, which allows them to inhibit enzymatic function even in the presence of high concentrations of endogenous substrate.

In a paper published in *The Journal of Biological Chemistry* in May, Arresto researchers showed AB0023 binds scavenger receptor cysteine rich domain 4 (SRCR-4) on LOXL2 with high specificity and can inhibit enzymatic function whether LOXL2 is substrate-bound or unbound.

**COMPANIES AND INSTITUTIONS MENTIONED**

**Arresto Biosciences Inc.**, Palo Alto, Calif.

**Stanford University**, Stanford, Calif.

**Technion-Israel Institute of Technology**, Haifa, Israel