Lorantis: creating new medicines for selective treatment of immunological diseases

Mark Bodmer

Lorantis is discovering and developing novel products for the treatment of immunological and inflammatory diseases based on the emerging field of antigen-specific tolerance. The company's products are derived from the discovery of a new set of biochemical signalling pathways that regulate the action of T cells. These discoveries will enable Lorantis to build a portfolio of novel drugs with the ability to treat selectively a wide range of disorders, including allergy, asthma, autoimmune diseases and transplant rejection.

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▼ Lorantis discovers and develops novel medicines for the selective treatment of immunological diseases, including allergy, autoimmune diseases and transplant rejection. The goal of the company is to develop new treatments that have improved selectivity for the causes of these diseases over current therapies. These treatments will arise from a combination of fresh insights into how the immune system is controlled, together with delivery mechanisms that are selective for cells of the immune system.

The company began operations in 2000 and has raised a total of US$28 million in venture backing from Abingworth Management, Schroder Ventures, J.P. Morgan Partners, Quester, The Wellcome Trust and Northern Venture Managers. Lorantis is based in Cambridge, UK, with an experienced management and Board of Directors, and a staff of 40 (Box 1).

Market opportunity

Current therapies for immunological and inflammatory diseases either relieve only the symptoms or induce non-specific suppression of the immune system. This can lead to severe infection or drug-related toxicity through systemic exposure. Lorantis is creating new treatments for immunological diseases which target pathological responses but either do not block normal responses or affect non-immune organs. Based on the discovery by Lorantis of the molecular mechanisms for antigen-specific tolerance, combined with delivery mechanisms to efficiently target cells of the immune system, the company is uniquely positioned to discover a new generation of therapeutics that treat the underlying cause of these diseases.

Technical background

Lorantis is addressing unmet clinical needs in immunological diseases by developing selective treatments that target pathological responses, but neither block normal responses nor adversely affect non-immune organs. This selectivity is being achieved by the combination of two approaches.

New drugs for targets in the immune system with improved specificity for pathological responses

Lorantis has discovered that developmental genes, normally active in embryogenesis, control the fate and function of cells of the immune system. The combination of developmental biology based on years of research in *Drosophila melanogaster* with immunology leads to a fresh paradigm in drug discovery (Fig. 1). These discoveries thus enable the discovery of novel drugs to treat a range of disorders, without blanket immunosuppression.

The immune system is now understood to be in a dynamic balance between activated and regulatory T cells [1]. Pathological responses to environmental antigens (allergy), self-antigens (autoimmune diseases) or 'allo' antigens (transplant rejection), in which this regulatory balance

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Box 1. The Management, Board of Directors and Scientific Advisory Board for Lorantis

Management
Mark Bodmer – Chief Executive
Andrew Muncey – Chief Financial Officer
Brian Champion – Vice President, Research
Karl Schaffenburg – Chief Business Officer

Board of Directors
Alan Munro (Chairman)
Kate Bingham
Mark Bodmer
Stephen Bunting
Andrew Muncey
Philip Rattle
Tim Rink
Karl Schaffenburg

Scientific Advisory Board
Jonathan Lamb (Founder) – University of Edinburgh, UK
Maggie Dallman (Founder) – Imperial College, London, UK
Gerard Hoyne (Founder) – University of Edinburgh, UK
Malcolm Brenner – Baylor College of Medicine, Houston, TX, USA
David Ish-Horowicz – Imperial Cancer Research Fund, UK
Andrew McMichael – Institute for Molecular Medicine, Oxford, UK

is chronically disturbed, result in a wide range of immunological diseases.

Lorantis has found and patented the physiological molecular mechanisms that enable control of immune responses by activating regulatory cells rather than by suppressing activated cells. T cell function has been found to be controlled by a receptor called Notch [2,3]. In the absence of a Notch signal, T cells are activated to attack. If Notch is triggered when an antigen is presented, the T cells become regulatory. These regulatory T cells switch off the immune response and allow the body to tolerate that specific antigen.

Notch-induced tolerance has several important benefits with regard to its potential use in immune therapy:

- it is selective for specific antigen;
- it appears to be the natural physiological mechanism for regulating immunity;
- the effect is potent and long-lived; and
- it has broad potential application in a wide range of immunological disorders.

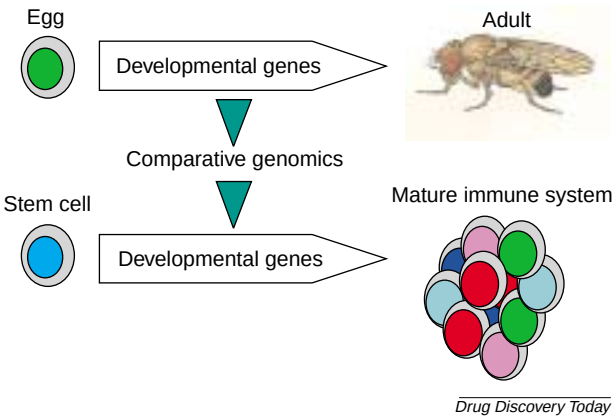

Figure 1. Almost a century of genetics and 20 years of molecular biology have created a wealth of understanding of the genes that control the complex process of generating *Drosophila melanogaster* (fruit fly) from an egg. The continuous creation of the variety of cells that make up the mature immune system have been found to adapt equivalent gene pathways for this process. The genomic similarities between the fruit fly and humans enable use of the large volumes of fly information to discover new control mechanisms relevant to the human immune system. The function of the Notch receptor in the generation of immune tolerance is a pivotal example of this.

Delivery mechanisms with improved selectivity for cells of the immune system

Most immune disorders arise from lack of appropriate control of the circulating cells of the peripheral immune system. The ideal scenario would be to re-program these cells with limited whole-body exposure to immunomodulators, many of which have potent and non-specific systemic effects. As with conventional vaccination, this re-programming can take place with local administration of an agent that re-instructs the immune system. The induction of tolerance, both therapeutically and prophylactically, can be viewed as such a re-programming.

The skin is a rich source of antigen-presenting cells (APCs) and is a preferred route of administration to bias drug delivery to cells of the immune system. Lorantis is currently evaluating several technologies that have the ability to deliver immunomodulators to immune cells in the skin, which provides a much higher cellular selectivity than systemic dosing.

Product development programs

Extensive proof-of-principle tests in the laboratory have demonstrated a potent and antigen-specific inhibition in both mechanistic models and in disease models by stimulation of Notch signalling in T cells. These studies were all conducted by

introducing genes for the Notch ligand into APCs in order to stimulate Notch signalling in the responding T cell.

Based on these results, Lorantis has two product strategies in current development for the delivery of a Notch signal to the T cell during its encounter with APCs:

(1) Gene transfer of Notch ligand to APCs: mimics natural tolerance by plasmid DNA-mediated introduction of the Notch ligand gene in the skin.

(2) Soluble Notch ligand protein: signals the T cell directly by exposing the T cell to a soluble recombinant Notch ligand.

Lorantis is initially focussing on patients with allergies to defined antigens, such as pollen, house dust mite, cat dander and peanut. Preclinical *in vivo* allergy studies have shown specific tolerance to a common house dust mite allergen. Following proof-of-principle studies in allergy, Lorantis intends to expand its clinical development strategy to asthma, transplantation and autoimmune disease. These will be combined with the delivery mechanisms that access the rich sources of immune cells in the skin. They hold the promise of efficient modulation of peripheral immune responses at low doses and without systemic exposure.

Lorantis is planning introduction into humans in 2003 in a first indication study with a well-defined antigen. The nature of the immune system will enable efficacy to be assessed at the mechanistic level and at a very early stage of the clinical development process.

In addition, Lorantis is evaluating several other drug targets and compounds that have the potential to modulate the regulatory responses of the immune system. These arise from our underlying discovery program studying mechanisms of immune regulation in the context of developmental biology already mentioned .

Future commercial strategy

Lorantis intends to build a portfolio of discovery products for early-stage clinical trials in its core area of allergy and autoimmune disease, and then seek collaborations for further joint development and commercialization. Lorantis expects to announce deals in technology acquisition and joint development during 2002. The company will also out-license products and applications outside these core areas. The first of these revenue-generating deals is expected in 2003.

Patent portfolio

Lorantis has been issued three patents covering the use of Notch ligands in the treatment of immunological diseases in three national territories. These patents are pending in other territories worldwide. An additional nine patents covering related areas such as diagnostics and drug screening have also been submitted, and the company intends to continue its aggressive approach to filing patents for new discoveries. Three patents covering targets derived from related developmental pathways have also been filed.

Concluding remarks

Lorantis's technology portfolio is building towards a highly integrated set of approaches to addressing the pressing need for safe and effective treatments for a wide range of immune disorders. By combining selective targets with selective delivery mechanisms, Lorantis is confident of being able to create an exciting and valuable product pipeline.

References

1 Sakaguchi, S. *et al.* (2001) Immunologic tolerance maintained by CD25+ CD4+ regulatory T cells: their common role in controlling autoimmunity, tumor immunity, and transplantation tolerance. *Immunol. Rev.* 182, 18–32

2 Hoyne, G.F. *et al.* (2000) Serrate1-induced notch signalling regulates the decision between immunity and tolerance made by peripheral CD4(+) T cells. *Int. Immmunol.* 12, 177–185

3 Hoyne, G.F. *et al.* (2001) Notch signalling in the regulation of peripheral immunity. *Immunol. Rev.* 182, 215–227