

# BioCentury

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## Emerging Company Profile

### Tolera: Delta force improves tolerance

By Michael Flanagan  
Senior Writer

**Tolera Therapeutics Inc.** is developing a mAb against the alpha beta T cell receptor designed to improve upon the safety and tolerability of **Genzyme Corp.**'s Thymoglobulin, the market-leading antibody for induction therapy to prevent rejection of transplanted organs.

A head-to-head Phase I/II trial comparing Tolera's TOLI01 with Thymoglobulin in solid organ transplant patients is slated to begin early this year.

Thymoglobulin is a polyclonal rabbit Ig antibody against human thymocytes that directs a broad cytotoxic response against human T lymphocytes. The product is approved for use in conjunction with immunosuppression to treat acute rejection in renal transplant patients. It is used extensively off label for other transplant indications, according to Tolera CEO John Puisis.

Genzyme reported \$55.6 million in 3Q09 sales of Thymoglobulin, up 16% from \$47.8 million in 3Q08.

"The problem with polyclonal antibodies, or any broadly targeted agent that acts against multiple receptors, is that you get a lot of variable responses from different patients," including secondary reactions from cytokine storms, and infections that result from shutting down the immune system, said Puisis.

#### Tolera Therapeutics Inc.

Kalamazoo, Mich.

Technology: Anti-T cell receptor mAb to treat T cell-mediated diseases

Disease focus: Autoimmune, cancer

Clinical status: Preclinical

Founded: 2007 by John Puisis and Maria Siemionow

University collaborators: Cleveland Clinic, University of Michigan and Northwestern University

Corporate partners: None

Number of employees: 12

Funds raised: \$10 million

Investors: SWMF Life Sciences Fund, Triathlon Medical Ventures, Hopen Therapeutics and Michigan Economic Development Corp.

CEO: John Puisis

Patents: 3 issued in Australia covering use of mAbs against alpha beta T cell receptors for tolerance induction in transplantation

Thymoglobulin's label includes warnings about an increased risk of serious immune-mediated reactions, including anaphylaxis, severe cytokine release syndrome and new or reactivated infections.

Tolera believes TOLI01, a mAb against

the alpha beta T cell receptor, will be at least as effective as Thymoglobulin in preventing rejection and will have a better safety profile because it leaves infection-fighting delta gamma T cells in place.

"We don't know exactly how it binds to the T cell receptor, but the end result is that it down-regulates proliferation of the alpha beta cells, which would be responsible for creating an immune response to a transplanted organ, while allowing for some immunity to remain by leaving the delta gamma T cells intact to keep the infection and adverse event rates down," said Puisis.

The TOLI01 program is based on work first carried out at the **University of Kentucky** and later licensed to **MedImmune Inc.** (now part of **AstraZeneca plc**), which conducted early clinical trials of a predecessor antibody. The results suggested that specifically targeting the alpha beta T cell receptor is safe and effective for improving transplant success, according to Puisis.

MedImmune shelved the program to focus on cancer and infectious diseases. The **Cleveland Clinic** subsequently licensed the program from the University of Kentucky, and then spun it out into Tolera.

According to Puisis, Tolera and collaborators at **Northwestern University** have since determined that TOLI01's

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***Tolera Therapeutics,***  
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inhibition of the alpha beta T cell receptor creates a downstream cascade that results in antagonizing CD3, a protein that is part of the T cell receptor complex that is also involved with T cell activation.

Puisis noted that TOLI01's effects on CD3 appear to be highly specific, meaning it could be associated with fewer side effects than less specific anti-CD3 agents, while also avoiding mitogenicity.

He pointed to *in vitro* data, which he said are much more useful than animal studies for monitoring T cell response, showing that TOLI01 triggers little T cell proliferation or cytokine production when compared to the excessive induction of T cell activation produced by Orthoclone OKT3 muromonab, a marketed murine anti-CD3 mAb from **Johnson & Johnson**.

Orthoclone, the only anti-CD3 product on the market, is indicated to treat glucocorticoid-resistant organ transplant rejection. It is associated with anaphylactic or anaphylactoid reactions.

Antibodies directed against CD3 from **MacroGenics Inc.** and **Tolerx Inc.** are in Phase II/III and Phase III testing for Type I diabetes, respectively. MacroGenics' teplizumab (MGA031) is partnered with **Eli Lilly and Co.** and Tolerx's otelixizumab (formerly TRX4) is partnered with **GlaxoSmithKline plc.**

Tolera plans to develop and potentially market TOLI01 for the transplant rejection indication itself and to find a partner for autoimmune diseases.

Tolera has raised \$10 million in series A money that should carry the biotech through 2010. The company plans to raise more money for the Phase III testing it expects to begin in 2011.

#### COMPANIES AND INSTITUTIONS MENTIONED

**AstraZeneca plc** (LSE:AZN; NYSE:AZN), London, U.K.  
**Cleveland Clinic**, Cleveland, Ohio  
**Eli Lilly and Co.** (NYSE:LLY), Indianapolis, Ind.  
**Genzyme Corp.** (NASDAQ:GENZ), Cambridge, Mass.  
**GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK), London, U.K.  
**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.  
**MacroGenics Inc.**, Rockville, Md.  
**MedImmune LLC**, Gaithersburg, Md.  
**Northwestern University**, Evanston, Ill.  
**Tolera Therapeutics Inc.**, Kalamazoo, Mich.  
**Tolerx Inc.**, Cambridge, Mass.  
**University of Kentucky**, Lexington, Ky.