



Biobusiness Corporate Profile

# Expanding Antibody Therapeutic Options

## Affimed Uses Multiple Libraries and Formats to Produce a Myriad of Drug Choices

Carol Potera

**B**ased in Heidelberg, Germany, **Affimed Therapeutics** ([www.affimed.com](http://www.affimed.com)) specializes in the development of second-generation mAbs targeted at the treatment of cancer and other diseases with unmet medical needs. Biochemist Melvyn Little, Ph.D., created the company's technology platform in the 1990s when he headed the recombinant antibodies group at the German Cancer Research Center in Heidelberg.

Dr. Little spun off that technology in 2000 and founded Affimed where he serves as CSO. In March, Affimed secured \$32 million in a Series B round of financing to accelerate the clinical development of second-generation antibodies that are safer and more effective.

### Diverse Libraries

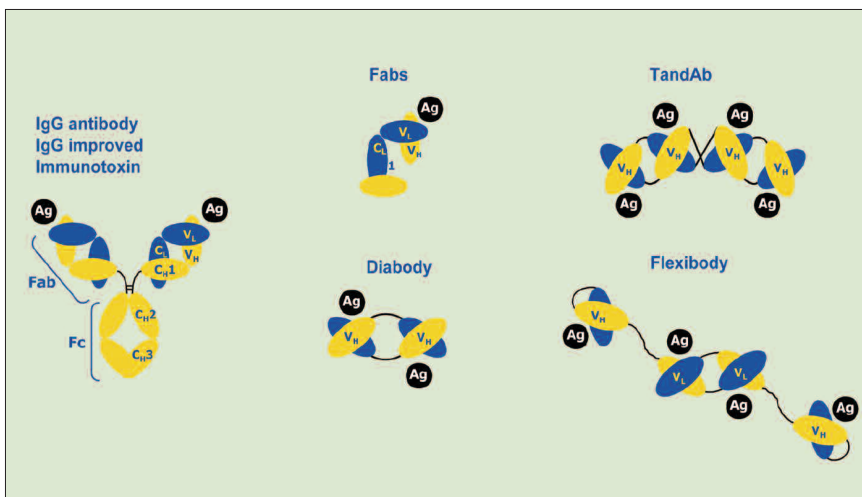
Affimed's platform for obtaining specific and completely human anti-

bodies consists of three diverse libraries: a naïve library, a synthetic library, and a semisynthetic library. Each contains more than a billion individual antibodies. This gives Affimed the ability to precisely pinpoint the antibodies with the best binding characteristics for a particular target.

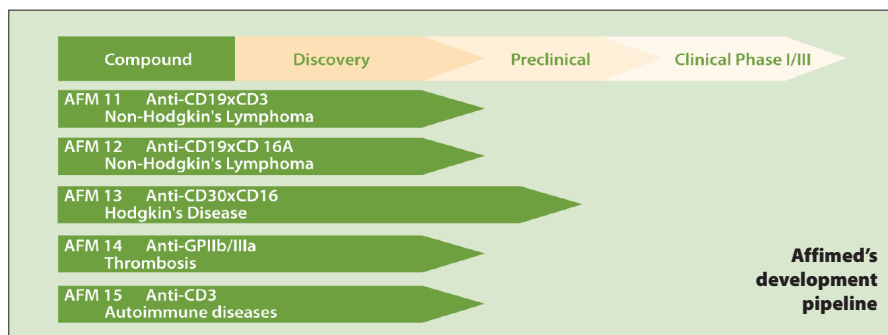
The naïve antibody library is generated through the cloning of IgM variable domains from human B-lympho-

cytes or spleen. The second library of synthetic human antibodies is manufactured by introducing random sequences into the antibody-binding domain, which recognizes the structure of foreign molecules such as those located on the surface of tumor cells.

The complexity of both the naïve and synthetic libraries is increased further by randomly combining all the heavy chain variable domains with all



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the light chain variable domains. Additional mutations are introduced into the antibody-binding site to optimize the affinity of lead product candidates. "This procedure mimics the processes seen in nature," says Rolf H. Günther, M.D., Ph.D., CEO. The semisynthetic library combines aspects of the naïve and fully synthetic libraries.

The three libraries ensure a high diversity and increase the chance of isolating commercially relevant antibodies against any disease target. "We have been successful in generating antibodies against difficult targets that other companies with just one library were not able to isolate," says Dr. Günther.

For example, Affimed's product AFM14 preferentially binds just the activated form of certain receptors on blood platelets. "Existing antibodies recognize both the active and inactive form but cannot discriminate between the two," Dr. Günther explains. This gives AFM14 an advantage for treating some antithrombotic conditions, he notes.

Affimed researchers routinely screen candidates from all three libraries simultaneously using bacteriophage display to identify candidates with particular specifications. Antibody fragments are inserted into the genome of phages. Those carrying human genes are allowed to infect *E. coli*, where the virus grows

and replicates. The amplified phages are isolated and incubated with the purified antigen of interest.

A more complicated panning procedure may be performed by using live cells that display the antigen in its native state on the cell surface. Only phages that contain an antibody that targets the antigen will bind, and the rest are washed away. This panning process is repeated several times.

#### Functional Formats

Once a human antibody is identified as effective against a particular target, it can be converted into a variety of formats such as a full-length antibody, a Fab fragment, a diabody, a TandAb™, or a Flexibody™.

Affimed scientists designed the TandAb and Flexibody formats to bind multiple targets. TandAbs and Flexibodies are tetravalent. They have two binding sites for activating immune effector cells like cytotoxic T cells or natural killer cells as well as two binding sites for a target molecule on the surface of tumor cells.

TandAbs are twice as large as bivalent diabodies and remain in the body longer. Affimed's lead products AFM13 for Hodgkin's disease as well as AFM11 and AFM12 for non-Hodgkin's lymphoma are all TandAbs.

Flexibodies are multivalent antibodies with a high degree of flexibility that can

more easily join molecules that are distant from each other on the cell surface.

"The selection of a particular antibody format depends on the desired target product profile and indication," says Dr. Günther. The different antibody formats also affect the physical and chemical properties of antibodies.

Smaller recombinant antibodies or antibody fragments like diabodies have the advantage of better tissue penetration but the disadvantage of clearing from the body rapidly. Some diseases like cancer or chronic inflammation require more persistent therapies.

## At-a-Glance

### Affimed Therapeutics

#### Location

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69120 Heidelberg, Germany

#### Phone

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#### Website

www.affimed.com

#### Principals

**Rolf Günther, M.D., Ph.D.**

CEO

**Melvin Little, Ph.D.**

CSO

**Miroslav Ravic, M.D., Ph.D.**

CMO

**Florian Fischer, Ph.D.**

CFO

**Gavin Clark**

vp, business development

#### No. of Employees

25

#### Focus

Affimed discovers and develops antibodies for the treatment of cancer and other diseases.

Processes like pegylation may extend the half-life of antibodies but also add to development time and costs.

“TandAbs,” on the other hand, points out Gavin Clark, vp of business development, “have a molecular weight that is significantly higher than the threshold for first-pass renal clearance.” This could allow patients to be treated once-a-week rather than daily.

By combining three antibody libraries with the format technology, Affimed states that it can design customized antibodies for any disease target. In addition, antibodies that are already clinically validated can be improved through the format technology.

This ability to readily create different formats for second-generation antibodies, Clark says, “Greatly appeals to potential partners when I talk to them.” A strong patent portfolio protects Affimed’s antibody libraries, phage display technology, and novel format technologies.

### Advancing Its Pipeline

Affimed’s products are in various stages of preclinical development. The most advanced candidate is AFM13, a treatment for Hodgkin’s disease that targets CD30 and CD16. Clinical trials of AFM13 are expected to start in the last quarter of 2008. Other antibodies in the pipeline are being investigated as therapies for non-Hodgkin’s lymphoma, thrombosis, leukemia, solid tumors like colon cancer, and autoimmune disorders.

Affimed’s success is constrained by the company’s small size. “We can handle three clinical projects up to Phase IIa or clinical proof-of-concept,” adds Clark. With 13 clinical leads in various stages of development, the company is seeking research collaborations with pharmaceutical and biotechnology firms. “We want to see more of our next-generation antibodies move forward,” Clark says. **GEN**