

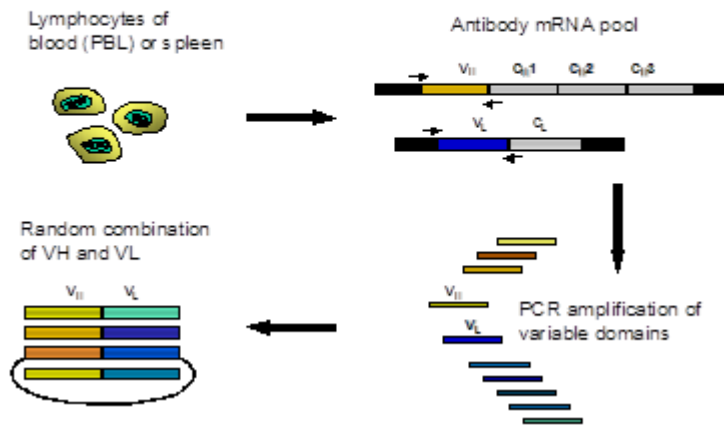
Affimed Therapeutics

Development of cancer therapeutics based on
recombinant bispecific antibodies

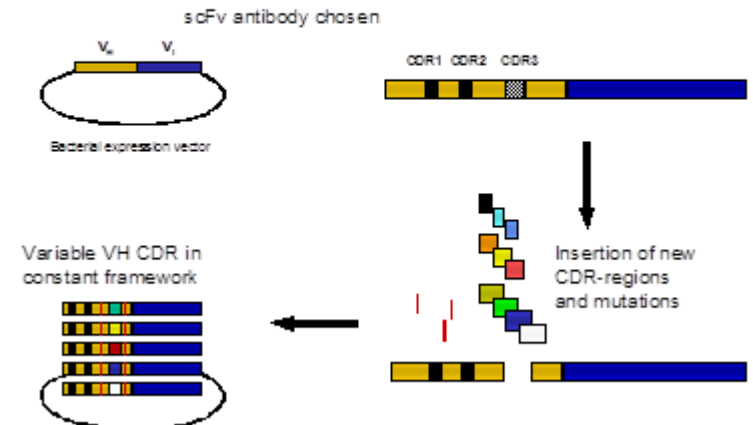
Melvyn Little (founder)

Affimed's Antibody Libraries

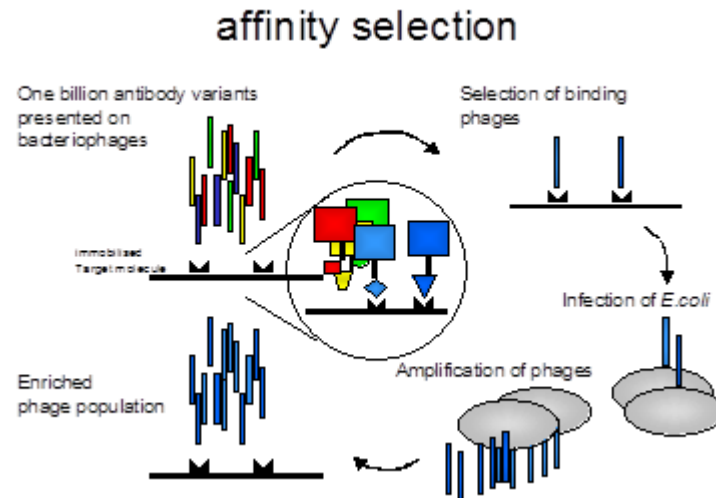
native antibody library



synthetic antibody library



Affimed's antibody selection using phage display



Antibody library and phage display patents of research group “Recombinant Antibodies” at the DKFZ

- Phagemid for antibody screening

US Patent 5,849,500 - filed 10.5.93, granted 15.12.98, priority 8.7.91

- Preparation and use of gene banks of human antibodies ("human-antibody libraries")

US Patent 6,319,690 - filed 6.5.93, granted 20.11.01, priority 1.2.1990

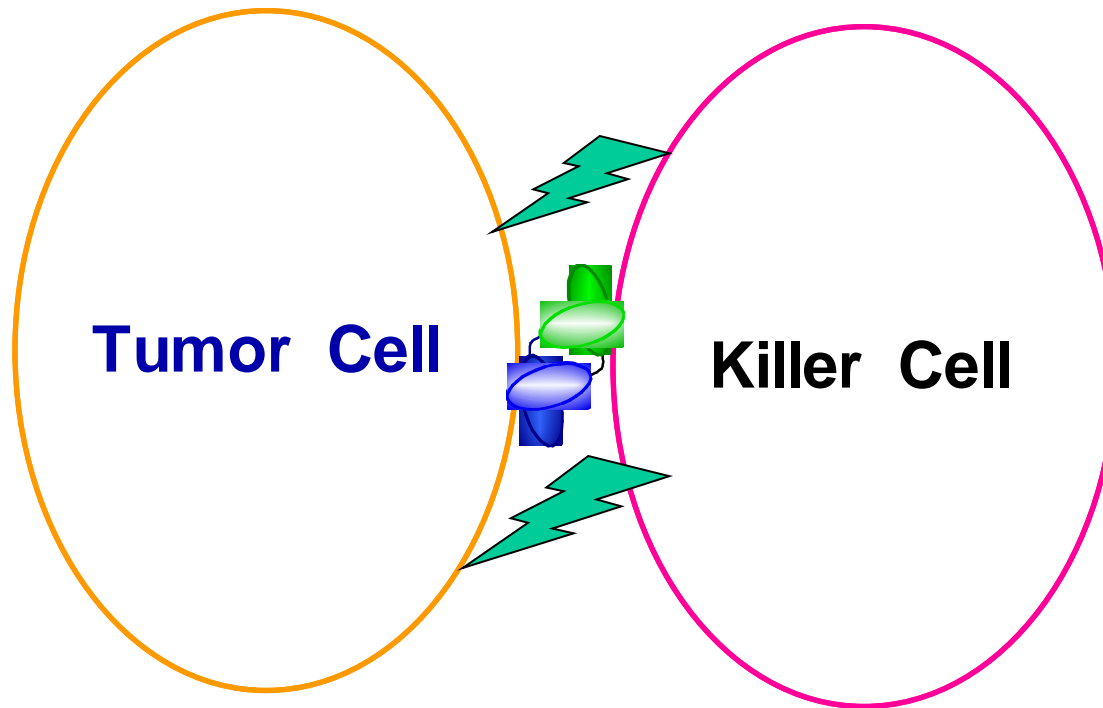
- Preparation and use of gene banks of synthetic human antibodies ("synthetic human-antibody libraries")

US Patent 5,840,479 - filed 2.12.94, granted 24.11.98, priority 1.2.90

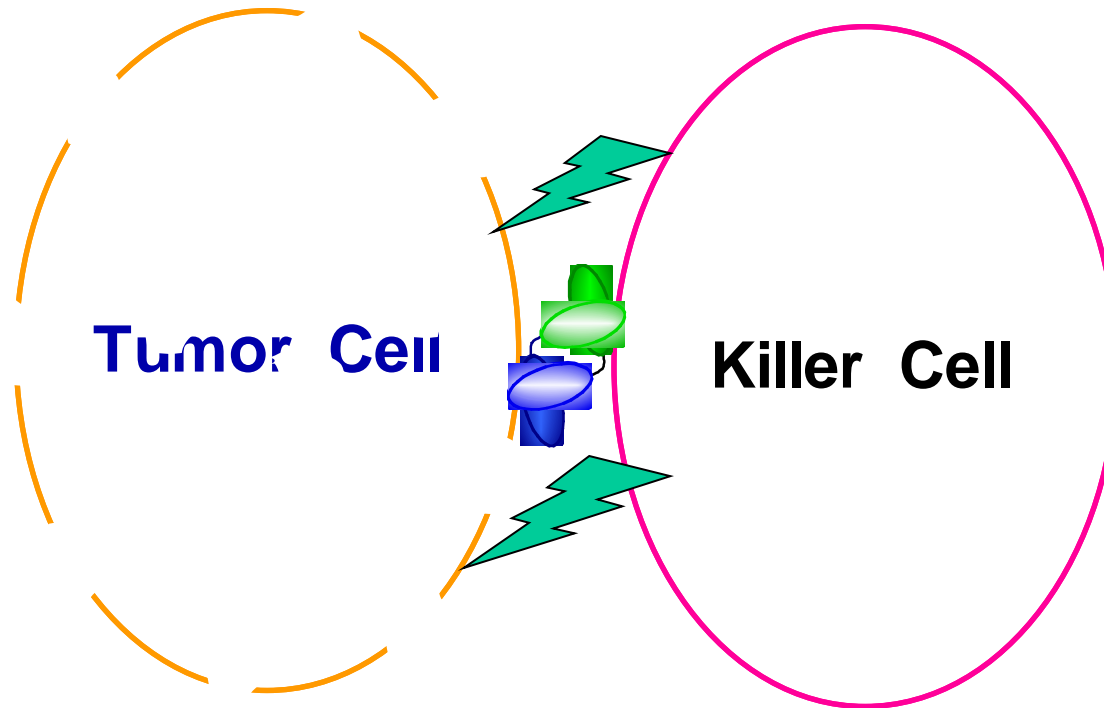
1997: Founding of Affitech in Oslo

- Start-up of Affitech as recombinant antibody biotech firm in Oslo after licensing-in the DKFZ phage display patent.
- Initial business model: Isolation of antibodies against drugs as a basis for establishing sensitive detection systems.

Redirecting Cytotoxic Cells of the Immune System to Tumor Cells

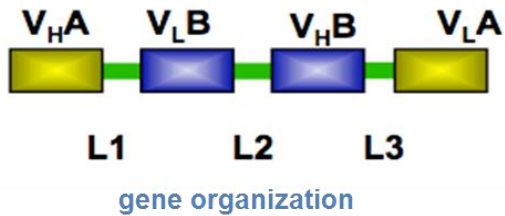


Redirecting Cytotoxic Cells of the Immune System to Tumor Cells

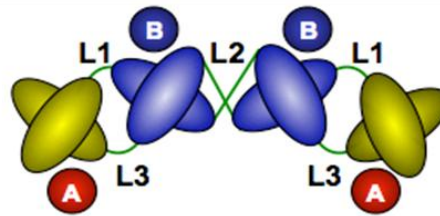
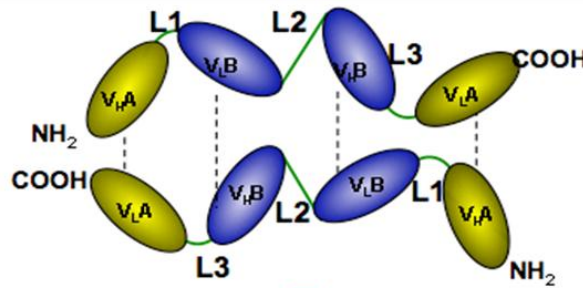
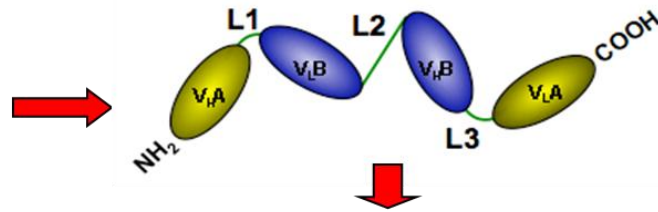


TandAb: Tetravalent Tandem Antibody

4 Domain Product with Short Linkers



- no covalent linkage between the monomeric polypeptides
- typically G₂S linkers between domains
- L1, L2, L3 in same or varying length



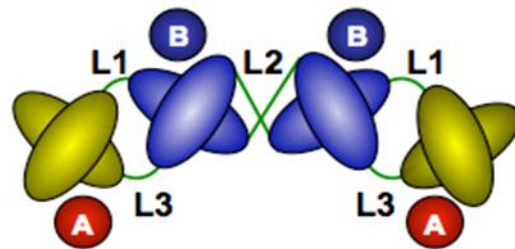
FOLDING PATHWAY

Patent application for generating tetravalent bispecific antibodies (TandAbs)

Multivalent antibody constructs

US Patent 7,129,330

Filed 1999, Granted 2006, Priority 1998



Scientist meets venture capitalist 1998

- Biotechnology Agency Baden-Württemberg – Meeting on establishing biotech firms, June 1998
- Contact with 3 venture capitalists
- Discussions of potential business case
- Preliminary business plan



Hubertus Leonhardt
SHS Venture Capital
Tübingen

- Requirements for starting Affimed
 - a) Negotiating licensing-in of DKFZ patents for generating antibody libraries from Dade Behring (now Siemens Healthcare)
 - b) Securing letter of intent from DKFZ for exclusive license to TandAb patent (for making tetravalent bispecific antibodies)
 - c) applying successfully for grant in the framework of the BioRegio programme
 - d) securing venture capital from Sachsen Landesbank and tbG (government technology investment bank)

BioRegio: Rhein-Neckar-Dreieck

Grant Proposal, September 1999

**Development of novel recombinant bispecific
antibody constructs for cancer therapy.**

Affimed Therapeutics AG, Im Technologiepark,
Im Neuenheimer Feld 582, 69120 Heidelberg

Project leader: Prof. Dr. Melvyn Little

Developments in the field of therapeutic antibodies prior to founding Affimed

1. 1975: First monoclonal antibody (Köhler and Milstein).
2. 1984: Chimeric (mouse/human) monoclonal antibody.
3. 1986: First murine monoclonal antibody (**Orthoclone OKT3**) approved for clinical use.
4. 1986: Completely humanized monoclonal antibody.
5. 1985: Phage display of a peptide.
6. 1988: Expression of soluble functional antibody fragment in *E. coli*.
7. 1989: Generation of antibody libraries.
8. 1990: Selection of antibody clone using phage display.
9. 1995-2000: Replacement of mouse antibody gene repertoire with that of humans.

Initial business plan

- Generate income by providing recombinant antibody services
 - Screening antibody libraries for desired antibody
 - Antibody engineering
 - Development of therapeutic bispecific antibodies for treating Non-Hodgkin's Lymphoma and Hodgkin's Lymphoma using the proceeds from the BioRegio grant.

2000 Starting up Affimed

- SHS provided 1.5Mio Euros (0.5Mio equity, 1.0 Mio debt).
- A matching 1.5Mio Euros was provided by the tbg (Technologische Beteiligungsgesellschaft mbH der Deutschen Ausgleichsbank).
- The grant provided 0.7Mio Euros (Total project costs 1.4Mio Euros - 50% self participation).
- Total starting capital 3.7 Mio Euros

Team 2001



Starting team 2000
indicated by arrows

Photo taken near our first lab in the
firm of Giulini, Ladenburg

Screening Group 2001



Major biotech firms with antibody library technologies

- CAT (Cambridge Antibody Technology) – dominating antibody library and phage display patents (e.g. Winter I and II). Now owned by AstraZeneca (MedImmune) – generated first fully human antibody blockbuster drug “Humira” for treatment of rheumatoid arthritis.
- Morphosys : Synthetic antibody library patents – Patent dispute involving extensive litigation in the US regarding CAT s Winter II patent. Settlement in CAT s favour in 2002. Partnership with Novartis.
- Dyax: Various phage display and microorganism display patents
- Abgenix : Transgenic mice libraries – Now owned by Amgen.
- Medarex: Transgenic mice libraries – Now owned by Bristol Myers Squibb.

Morphosys – Generation of synthetic antibody libraries

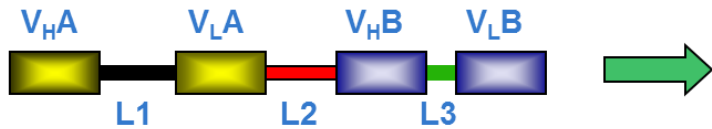
2001: Morphosys Chief Scientific Officer and Head of Patent

Department visit Affimed to discuss Affimed's patent protecting the generation of synthetic antibody libraries:

1st claim of US patent:

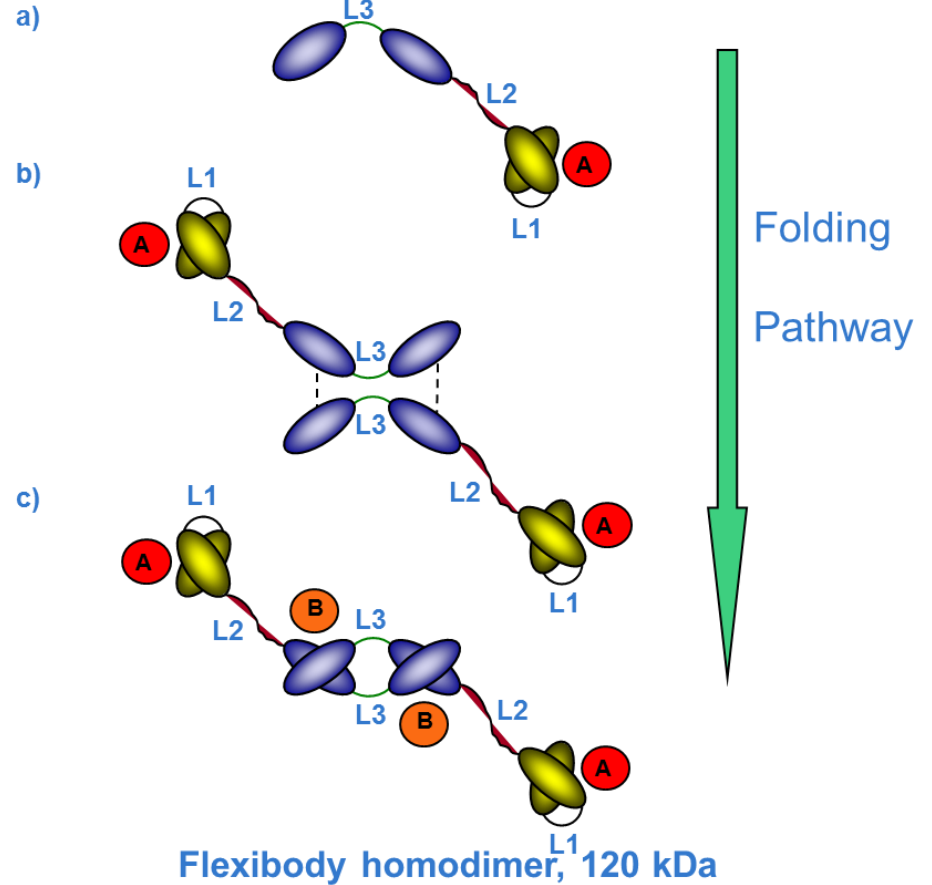
1. A synthetic human antibody-DNA library obtained by synthesizing almost random sequences for the antibody hypervariable regions, wherein (a) relatively conserved amino acids in the hypervariable regions have been taken into account in the choice of appropriate nucleotides during the oligonucleotide synthesis and (b) the ratio of the nucleotides used is chosen such that a nonsense codon is to be expected at most in every 89th position;

DIMERIC TETRAVALENT FLEXIBODY



L1 > 12 aa
L2 = 5-15 aa
L3 = 2-10 aa

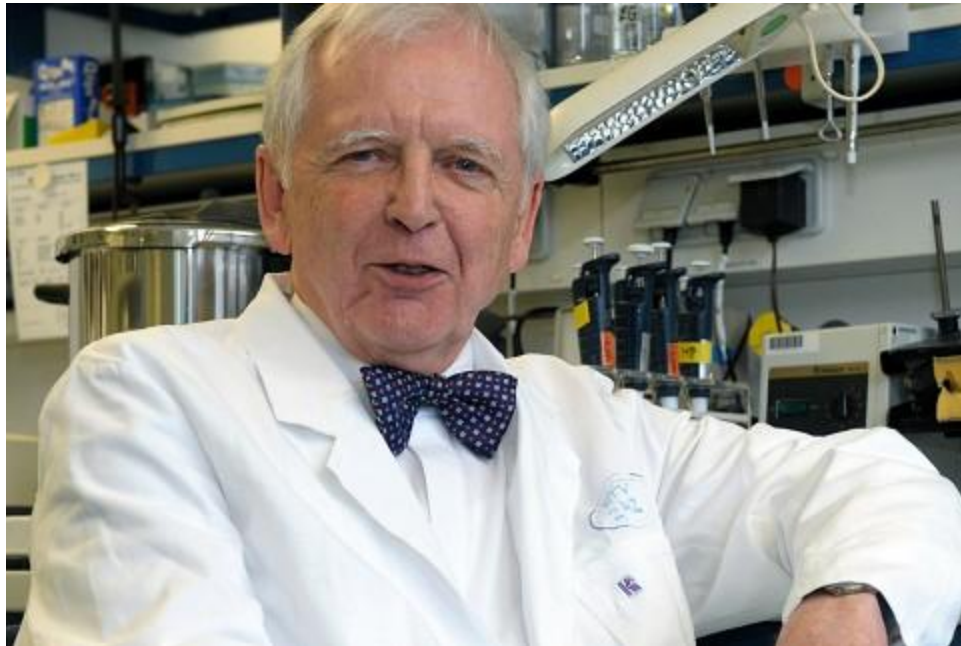
- Multimeric single chain tandem Fv-antibodies (Flexibodies)
- EP1293514
- Filed 2001, granted 2006, priority 2001



Feb 2002 – leave Ladenburg for premises in the
new technology park in Heidelberg



Nobel prize scientist Prof. Harald zur Hausen
visits Affimed on 8th May 2002



2003

The VC firm **First Ventury** provided capital for Affimed's further development (2.0 Mio Euro equity).

November 2003

Antisoma/Affimed

Antisoma (London) carries out a thorough due diligence.

Plan: Creation of a scientific centre of excellence in Heidelberg for recombinant antibodies based on Affimed's technology

November/December 2003: Decision by board of Antisoma to develop an advanced clinical phase product instead of acquiring Affimed.

New Year 2004

First Ventury was only prepared to make a further investment if the technology was validated by a partnership with a pharma company.

2004

Syngenta Biopharm

Biochance grant proposal for generating human TandAbs approved in early 2004 for a project costing 2.0Mio Euros (i.e. 1 Mio Euro from government and 50% self participation).

The self participation costs of 1Mio were provided by Syngenta Biopharm, a small biotech venture of Syngenta that was interested in finding interesting projects for the development of biotech products.

Signed LOI in April, 2004 - project started 6 months later.

September 2004 – Rolf Günther appointed CEO



July 2005

First Ventury ensures that Affimed remains
a going concern.

1.5 Mio Eur (equity)

1.5 Mio Eur KfW

0.2 Mio SHS (equity)

Miroslav Ravic Chief Medical Officer January 2006



April 2007

A substantial financial round to enable Affimed for the first time to produce and purify sufficient product under GMP conditions for clinical studies.

The following consortium provided 30 Mio Euros

Aeris (First Ventury)

Orbimed

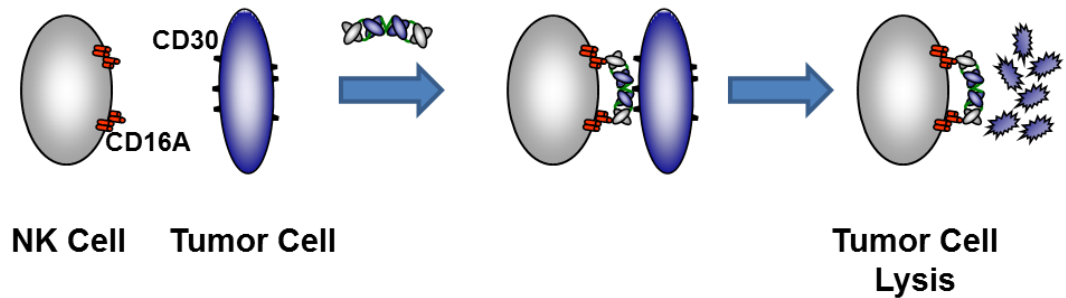
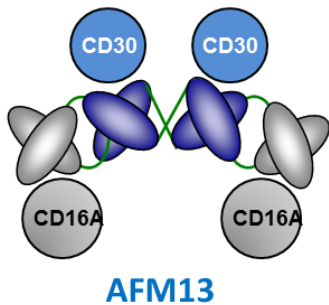
Life Science Partners (LSP)

BioMedInvest

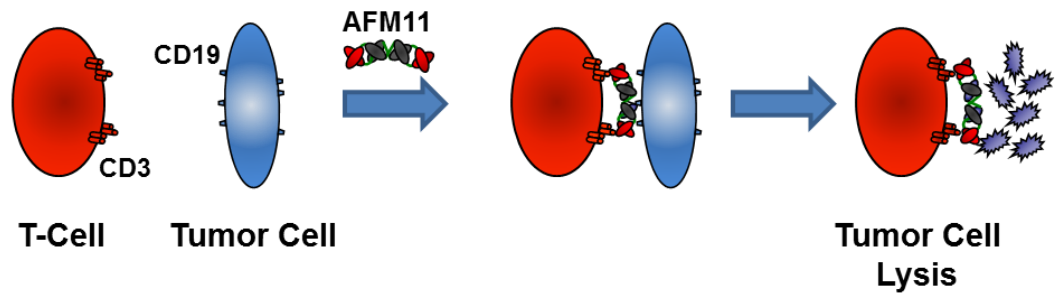
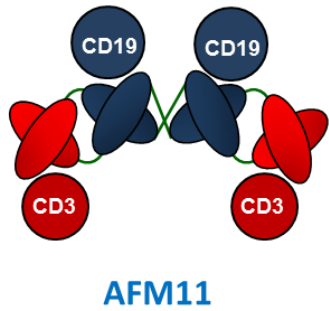
Novonordisk Venture fund

RECRUIT-TandAbs Tumor Immunotherapy

Specific NK-cell recruitment to the site of the tumor



Specific T-cell recruitment to the site of the tumor



Anti-CD16 binding molecules

A patent application seeking to protect antibodies that bind exclusively to the A isoform of CD16

US patent application 20090214574 Filed 2009, priority 2005

Only 3 amino acid differences between isoforms A and B

No other known antibodies reacting exclusively with the A isoform

Founding of AbCheck in Pilsen (Czech Republic) 2009

Isolation of human antibodies

> Synthetic library

Fully synthetic library of human antibodies

> IgM library – naïve

Derived from the immune system's antibody gene repertoire

> Semi-synthetic

Combines aspects of naïve and synthetic library

Total size: app. 10^{10} individual clones

Screening: Phage Display (now combined with yeast display)



Volker Lang CEO



Vera Molkenhain
Head of Antibody Discovery

TandAb AFM13 for treating Hodgkin s Lymphoma

- **Lyophilized drug product in 20R glass vial**
- **Stable for one year at -20°C, 5°C, 25°C and 40°C**



September 31st 2010

Start of Affimed's first clinical trial for the treatment of Hodgkin's Lymphoma.

The product being tested is a bispecific TandAb product targeting CD30 on Hodgkin's cells and CD16A on Natural Killer (NK) cells.

September 2010 Paul Ehrlich Institute

Meeting to discuss preclinical data for next product for treating NHL (AFM11).



Product Pipeline 2013

Compound (Target)	Indications	Discovery	Pre-Clinical	Phase I	Phase II
AFM13 (CD30 x CD16A)	Hodgkin Lymphoma	[Progress bar: Discovery, Pre-Clinical, Phase I]			[Progress bar: Phase II]
AFM11 (CD19 x CD3)	Non-Hodgkin Lymphoma	[Progress bar: Discovery, Pre-Clinical]			[Progress bar: Phase I, Phase II]
AFM12 (CD19 x CD16A)	Non-Hodgkin Lymphoma	[Progress bar: Discovery, Pre-Clinical]			
AFM15 (CD3 x HSA)	Autoimmune Diseases	[Progress bar: Discovery, Pre-Clinical]			
AFM19 (NN1x NN2)	Asthma, COPD	[Progress bar: Discovery, Pre-Clinical]			
AFM20 (EpCAM x CD16A)	Oncology	[Progress bar: Discovery, Pre-Clinical]			
AFM21 (EGFR x CD3)	Oncology	[Progress bar: Discovery, Pre-Clinical]			

Thank you for your attention!