

COMPANY PROFILE



COMPANY Focus

Expert in immunotechnology, BIOTEM provides custom and high added value services in the field of antibodies and immunoassay design.

For more than 30 years, BIOTEM has developed a unique expertise and a large panel of cutting edge proprietary technologies. The company is therefore proud to carry out the most relevant strategies and to propose contracts with guaranteed results for most projects.

Since being created in 1980, BIOTEM has been the privileged partner of outstanding private and public laboratories for their research, diagnostic and therapeutic projects.

Located in the heart of scientific cluster of excellence Grenoble-Lyon-Genève, the company disposes of 2000 m² offices and laboratories.

BIOTEM complies with ISO 9001:2008 quality standards and is certified "Crédit Impôt Recherche" (CIR agreement).

Clients

- ✓ Major pharmaceutical firms
- ✓ Diagnostic and biotechnology companies
- ✓ Academic laboratories, hospitals & NGO's

Worldwide presence: Europe, USA, Australia, Israel, Russia, Asia, etc.

Key Points

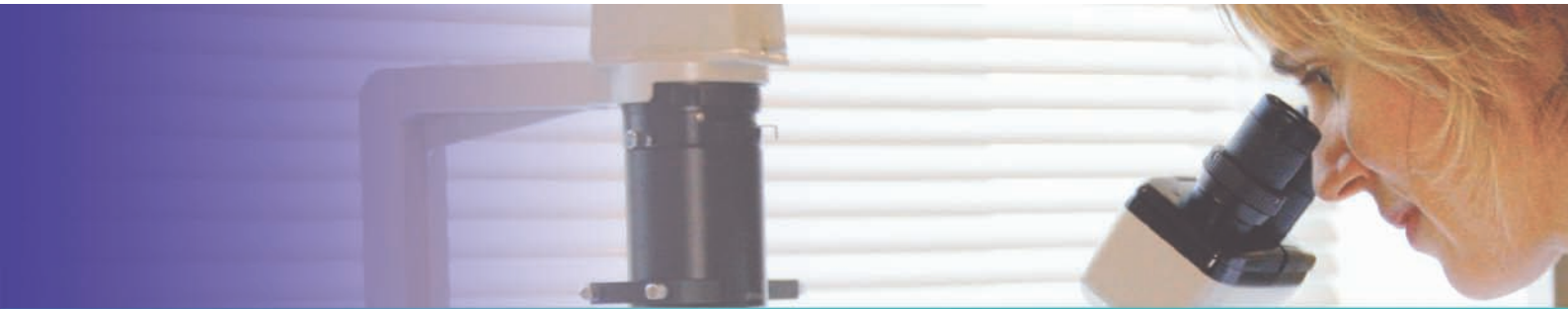
- ✓ 30 years of expertise
- ✓ Guaranteed results
- ✓ Exclusive and cutting edge technologies
- ✓ Highly qualified staff
- ✓ > 95 % success & satisfaction rate
- ✓ 100% Fee-for-service

ANTIBODY Services



BIOTEM is the ideal "one-stop-shop" service provider dedicated to accelerating research from project conception to preclinical stages.

ULTIMATE HUMANIZATION™ PLATFORM



ULTIMATE HUMANIZATION™ Platform

By combining the best of existing *in vivo* and *in vitro* technologies, BIOTEM's Ultimate Humanization™ Platform allows the generation of lead-drug antibodies with outstanding **low predicted toxicity** and **cross-reactivity** in humans. This strategy maximizes antibody success during preclinical and clinical phases.

Technology Advantages:

In vivo Immunization of Non Human Primates (NHP):

- Strong and natural immune response (outbred animals)
- Antibodies naturally homologous to human antibodies
- **Low predicted toxicity and cross-reactivity in humans**

Hyper-Immune Library Construction:

- Tailored libraries highly representative of the NHP hyper-immune response (**large epitope coverage**)
- **High affinity** antibodies: 10 to 1000-fold superior affinities compared to antibodies usually obtained from naive or synthetic libraries

Phage Display & ScFv Candidate Selection:

- **Customized and cutting edge high throughput screening**
- Thorough characterization of scFv candidates to select best lead

Antibody Germinalization:

- **Facilitated and extensive germinalization** of FR and CDR regions thanks to the innate high Germinality Index (see box) of NHP antibody
- Unlike germinalization of murine, rodent or lama antibodies, BIOTEM's strategy allows to generate antibodies with exceptionally high GI
- **Guaranteed GI > 92 %** while preserving parental affinity

Sequence Optimization:

To potentiate **drugability** and to anticipate antibody **manufacturing**:

- Improvement of physicochemical properties
- *In vitro* antibody affinity & activity maturation
- Codon optimization

Germinality Index

The Germinality Index (GI) quantifies the amino acid identity of antibody variable domains with the most homologous human germline sequences.

Typical GI for mature antibodies (IgG):

- Human: 86-96 %
- NHP: 78-90 %
- Lama: 74-82 %
- Rat: 70-80 %
- Mouse: 68-76 %

Quality Controls

A comprehensive set of quality controls is available on lead antibodies:

- ✓ Concentration determination
- ✓ Purity analysis
- ✓ Affinity constant determination
- ✓ Endotoxin analysis
- ✓ Aggregation and oligomerization (AUC, DLS & SEC-HPLC)
- ✓ Stability (DSC & Circular Dichroism)
- ✓ Other quality controls upon request

ULTIMATE HUMANIZATION™ PLATFORM



Immunization & Library Construction



Phage Display & ScFv Characterization



Reformatting & Production



Germinalization & Optimization



Ultimate Humanization™ Antibody

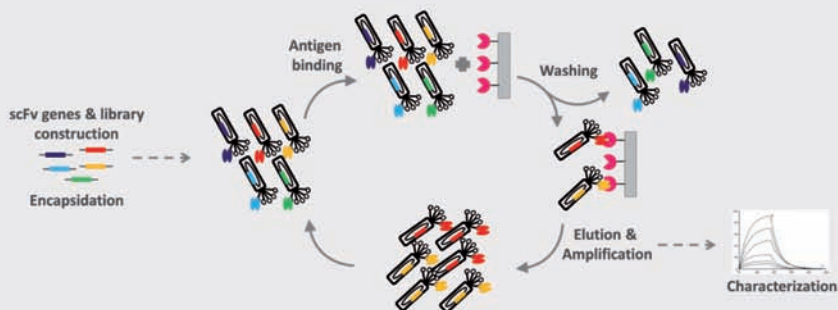
- Preserved parental affinity
- Guaranteed GI > 92% (up to 99%)
- Optimized manufacturability

Technical Focus & Know-how

NHP Immunization & Library Construction

- Optimized and validated protocols for:
 - Conserved proteins among NHP's and humans
 - Small size & poorly immunogenic targets
- BSL-2 or BSL-3 (biosafety level) conditions

Phage Display & ScFv Candidate Characterization



- Production, purification and characterization (affinity, biological activity, etc.) of scFv candidates

Reformatting & Production

- ScFv- or full Ig- format (several isotypes possible)
- Available at different stages during project development
- Small and large scale production / purification
- Endotoxin-free preparation

Germinalization & Optimization

- Identification of potential residues on VL and VH to be mutated for:
 - Extensive germinalization (FR and CDR)
 - Sequence optimization
- *In vitro* evaluation of mutation by site directed mutagenesis, variant production & affinity determination
- Integration of validated mutations

OUR COMMITMENT MAKES THE DIFFERENCE

HUMANIZED & CHIMERIC ANTIBODY



HUMANIZED *Antibody*

Humanization by CDR-grafting consists in transferring parental (commonly rodent) complementarity determining regions (CDR) into human framework regions (FR). Parental antibody specificity and affinity are conserved thanks to the preservation of residues implicated in antigen recognition.

Modernized CDR-Grafting Including Sequence Optimization

- Identification of parental antigen-binding residues
- Selection of most adapted FR sequences
- Humanized antibody design
- Sequence optimization
 - Improvement of antibody drugability & manufacturability
 - Affinity & specificity optimization

Production & Purification

- ScFv- or full Ig-format (several isotypes available)
- Small and large scale production / purification

CHIMERIC *Antibody*

Chimeric antibodies are antibodies combining parental antibody variable regions with any acceptor constant region. Thanks to the domain organization of antibodies, chimerization is straightforward and does not alter antibodies affinity or specificity.

Chimeric Antibody Design

- Antibody development and/or sequencing
- Parental / Acceptor antibodies from various species and isotypes
- Codon optimization for mammalian expression system

Production & Purification

- Small and large scale production / purification

Applications

Humanized antibodies constitute the majority of today's FDA and/or EMA approved **therapeutic antibodies**.

Key Advantages

- ✓ Modernized CDR-grafting using human germline genes
- ✓ Sequence optimization included
- ✓ Whole or partial project development

Applications

Therapeutics: used as such or before humanization to secure your project.

Diagnostics: replacement of serum, calibrators and positive controls.

Key Advantages

- ✓ Quality validated antibodies
- ✓ Various isotypes available
- ✓ Parental antibody development and/or sequencing integrated if required

BIOTEM

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