MODELING HUMAN INFLAMMATORY CONDITIONS

- ACUTE INFLAMMATION
- RHEUMATOID ARTHRITIS
- SPONDYLOARTHROPATHY
- INTESTINAL INFLAMMATION
- PSORIASIS
- MULTIPLE SCLEROSIS
- OSTEOPOROSIS
- MOLECULAR & CELLULAR ASSAYS
• A CRO established in 2006, as a spin-off company of BSRC “Al. Fleming” (Greece)

• Expertise in autoimmune and inflammatory animal disease models

- Preclinical Drug Evaluation Services
- Research & Development

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**Preclinical Drug Evaluation Services**

• Design and implementation of preclinical strategies for the evaluation of human therapeutics.

  ❖ Consultation services
  ❖ PK/PD
  ❖ Drug efficacy evaluation
    ❖ Phenotyping
    ❖ Histopathology
    ❖ Whole organ culture
    ❖ Cytokine profiling
    ❖ Molecular assays
    ❖ Cellular assays
    ❖ Imaging
    ❖ Pharmacogenomics

- Anti-human biologics (TNF, TNFR1, RANKL, IL17)
- Bispecifics
- Biosimilars
- Small molecules (kinase inhibitors, cytokine inhibitors)
- Novel technological platforms (nanobodies, antibody mimetics)
A CRO established in 2006, as a spin-off company of BSRC “Al. Fleming”

Expertise in autoimmune and inflammatory animal disease models

- **Research & Development**
  - Generation of novel humanized animal models
    - Transgenic, knock out and humanized animals
  - Read-out development
    - Phenotyping of novel models
    - Molecular and cellular assays
    - Histopathology
    - Imaging (uCT)
  - Development of comprehensive preclinical evaluation platforms
    - Standardization of preclinical platforms
HUMANIZED MODELS
hTNFTg
hTNFR1KI
hTNFR2Tg
hTgIL17a
hiL33
LPS Acute Sepsis

HUMANIZED MODELS
- hTNFTg
- hTNFR1KI
- hTNFR2Tg
- hTglL17a
- hIL33

Cytokine Cascade

![Diagram of LPS Acute Sepsis and Cytokine Cascade]
LPS Acute Sepsis

DGaIN/LPS Hepatic Failure Model

HUMANIZED MODELS
hTNFTg
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Cytokine Cascade

Bendzén 1998

Drugs

Infliximab
0.1 mg/kg
0.3 mg/kg
1 mg/kg
3 mg/kg

Saline

Percent survival

Time post challenge (hours)
LPS Acute Sepsis

DGaIN/LPS Hepatic Failure Model

Neutralizing potency of IL17A antibodies in acute IL17A induced KC model

HUMANIZED MODELS
- hTNFTg
- hTNFR1KI
- hTNFR2Tg
- hTglIL17a
- hIL33

Neutralizing potency of IL17A antibodies in acute IL17A induced KC model

hIL17A

anti-hIL17A

KC
INFLAMMATORY DISEASE MODELS

HUMANIZED MODELS
- hTNFTg
- hTNFR1Kl
- hTNFR2Tg
- hTgII17a
- hIL33

GENETIC MODELS
- Arthritis
  - Tg197
  - Tg3647
  - Tg5453
  - Tg197/hTNFR1
- Spondyloarthropathy & Intestinal Inflammation
  - TNF DARE
- Osteoporosis
  - TghRANKL

INDUCED MODELS
- Arthritis
  - CAIA
  - CIA
- Intestinal Inflammation
  - TNBS colitis
  - DSS colitis
- Multiple Sclerosis
  - MOG35-55 EAE
- Acute Inflammation
  - LPS, GalN/LPS
- Psoriasis
  - IMQ Psoriasis
INFLAMMATORY DISEASE MODELS

HUMANIZED MODELS
- hTNFTg
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- hTNFR2Tg
- hTgll17a
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Arthritis

Gene
Protein
Chemical diversity
Screen and identity hits
Lead optimization
Lead identification
Chemical property and potency evaluation
Pre-clinical development
Safety and efficacy

Tg197 Tg5453 Tg3647

Arthritis

Tg127/TNFfco untreated
Tg127/TNFfco Inflimab
Tg27/TNFfco Adalimumab
Tg27/TNFfco Etanercept

Mean group AS ± SEM

Time (days)

Arthritis

Age (weeks)

Arthritis

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INFLAMMATORY DISEASE MODELS

DRUG DEVELOPMENT/EFFICACY EVALUATION
DRUG DEVELOPMENT/EFFICACY EVALUATION

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Colon Histopathology

<table>
<thead>
<tr>
<th></th>
<th>Saline</th>
<th>Infliximab</th>
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<td>Arthritis</td>
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<tr>
<td>IBD</td>
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**DRUG DEVELOPMENT/EFFICACY EVALUATION**

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DRUG DEVELOPMENT/EFFICACY EVALUATION

Adapted from http://diseasome.eu/map.html
Tg197 case study

In vivo scoring

- Vehicle
- Humira® 1mg/kg
- Humira® 3mg/kg
- Humira® 5mg/kg
- Humira® 10mg/kg
- Humira® 30mg/kg

Histopathology

Dose response

- Vehicle
- 1mg/kg
- 3mg/kg
- 5mg/kg
- 10mg/kg
- 30mg/kg

Tested therapeutics

- Vehicle buffer
- Enbrel®
- Simponi®
- Remicade®
- Humira®
Tg197 case study

**In vivo scoring**

**Histopathology**

- **Dose response**
- **Tested therapeutics**

**Gene expression profiling**

**Metabonomics**
INTEGRATED PRECLINICAL EVALUATION PLATFORMS

- Human Disease
- Generation of novel models
- Similarity to human disease
- Read out parameters
- Therapeutic window
- Reproducibility
- Standardization

Evaluation of pharmaceuticals in Chronic Inflammatory Disease models
New Animal Model Development

Detailed Phenotyping

Cellular and Molecular characterization

- Generation of Mouse Mutant
- Archiving of Mouse Mutants
- Distribution of Mouse Mutants
  - Gene-Targeting
  - Transgenesis
  - Embryo & Sperm Cryopreservation
  - Mouse Depository
  - Rederivation, INF
  - Shipments

- Primary Metabolic
- Clinical Hematology
- Clinical Imaging
  - Biological Fluids
  - Food Intake
  - Gas exchange
  - Weight, Breathing

- Clinical Chemistry
- Gross Metabolite Analysis

- Molecular
- Advanced Cellular Analysis
- Analytical Imaging
  - Metabolomics
  - Analytical Proteomics
  - Analytical Flow Cytometry & Cell Sorting

- Genomics
- Bioinformatics
- Analytical Flow MS

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**Biomedcode at a glance**

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**R&D**
National and European funding

- [mugen](#)
- [ΕΣΠΑ](#)
- [infla-Care](#)
- [masterswitch project](#)
- [TarkinAid](#)
- [Be The Cure](#)
- [CodeAge](#)
- [aDDRes](#)