IL15 antagonist to treat inflammation (BIO12129)
**Product factsheet**

**Product:**
- Mutein-based human IL-15 antagonist (IL-15 AN)

**Application:**
- Treat autoimmune and inflammatory diseases in which IL-15 is increased in biological fluids (serum, synovial fluid) such as Rheumatoid arthritis, Psoriasis, Crohn’s disease, Ulcerative colitis,…

**POC:**
- Established in RA and ongoing in other autoimmune diseases
- *In vivo* Collagen-Induced Arthritis (CIA) mice model allow to demonstrate therapeutic effect of IL-15 antagonist
- *In vitro* functional studies showed that IL-15 antagonist inhibits cell proliferation

**Patents and publications:**
- EP13 305 896.6 on 2013/06/27
- PCT/EP2014/063637 on 2014/06/27
- Granted in US, JP, EP (DE, IT, ES, GB,FR)
**IL15 ANTAGONIST TO TREAT INFLAMMATION (BIO12129)**

Proof of concept

- **Rationale: IL-15: 2 modes of action: cis&trans-presentation.**
  - IL2/IL15Rαβγ cis&trans-presentation in CD8 T cells or NK cells, and IL2/IL-15Rββ in NK cells functional homodimer induce signal transduction.

- **Strategy: to develop IL-15 antagonists that targets the IL-2/15Rβ chain**
  - Murin mutant Fc (IgG2a)
    - Loss of Fc receptor and complement binding
    - no ADCC nor CDC
    - Increased in vivo half life

- IL-15 Muteins
  - Higher affinity IL-15Rα binding
  - Loss of IL-15Rβγ recruitment
  - Increased production

- Antagonist of endogenous IL-15 action which inhibit a broader range of cells involved in inflammation (CD8 T cells, as well as NK cells), spare IL-2 signaling via IL-2/15Rβγ and IL-2/15Rββ and thus will not interfere with IL-2 dependent Treg homeostasis and functions.
Proof of concept

**Strategy: to develop IL-15 antagonists that targets the IL-2/15Rβ chain**

- Comparison of the 4 strategies used to abrogate IL-15 action and of their efficacies to inhibit the different IL-15 receptors

<table>
<thead>
<tr>
<th>Inhibitory effect</th>
<th>IL-15R αβγ</th>
<th>IL-15R βγ</th>
<th>IL-15R ββ</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRB-15</td>
<td>Yes</td>
<td>Yes</td>
<td>(No)</td>
</tr>
<tr>
<td>Soluble IL-15Ra</td>
<td>Yes</td>
<td>No</td>
<td>(No)</td>
</tr>
<tr>
<td>HuMax-IL-15</td>
<td>Yes</td>
<td>Yes</td>
<td>(No)</td>
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<tr>
<td>AN-IL-15</td>
<td>Yes</td>
<td>Yes</td>
<td>(Yes)</td>
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</tbody>
</table>
IL15 antagonist exerts a therapeutic effect on established diseases by decreasing the severity of arthritis.

**Proof of concept**

- **Immunization**: SC injection 200µg CFA/CII emulsion
- **Challenge**: IP injection 200µg CII
- **IP treatment**: 1.5µg IL15 Antagonist_mIgG2Ae1-Fc (6) or PBS (5)
- **Days post disease onset**: 0, 1, 5, 10, 14
- **Body weight, clinical score, paw thickness**: monitored twice a week post challenge

**Graphs**
- Mean Paw Thickness (mm) over 14 days post disease onset for Healthy, PBS, and IL15AN-Fc groups.
- Mean Clinical Score over 14 days post disease onset for PBS and IL15AN-Fc groups.
**Proof of concept**

IL15 antagonist does not deplete NK neither CD8CD44\(^{\text{high}}\) T cells and acts locally at the inflammation site.

- NANT-IL15 does not
  - induce differences on splenic NK cells
  - modify maturation state CD11bCD27
  - has no effect on splenic CD8 CD44\(^{\text{high}}\) cells
IL15 antagonist is more effective as CRB-15 to inhibit cell IL-15 induced proliferation.

- IL-15 antagonistic activity evaluation in a IL-15-dependent proliferation assay using amalar blue method.
- The CTLL2 cell line expresses the IL-15Rα, IL-15Rβ and IL-15Rγc and proliferates in response to IL-15. The anti-IL-15 blocking antibody BE-29 was used as a positive antagonistic control in the experiment.