Immune Checkpoint Antibodies

To meet your needs in the development and study of therapeutic monoclonal antibodies (mAbs) against immune checkpoints (ICs), InvivoGen offers a series of clinically relevant mAbs targeting CTLA-4, PD-1 or PD-L1, either in their original format, or with different/engineered isotypes conferring altered effector functions.

- Anti-hCTLA4 Isotype Family
- Anti-hPD1 Isotype Family
- Anti-hPD-L1 Isotype Family

InvivoGen’s IC mAbs feature the Fab (fragment antigen binding) region of approved immune checkpoint inhibitors (ICIs; see table) and the Fc (crystallizable fragment) region of different immunoglobulin isotypes (see below), including the original. ICIs induce variable effector functions: ADCC (antibody dependent cellular cytotoxicity), ADCP (antibody dependent cellular phagocytosis), and CDC (complement dependent cytotoxicity). Depending on the necessity to protect or kill the target cells, ICIs’ functions can be modulated through modification of the Fc region.

InvivoGen’s IC antibodies are fully human mAbs. They are generated by recombinant DNA technology and produced in CHO cells. Their sequence, isotype, and binding activity are thoroughly verified.

**InvivoGen ICI isotypes**

<table>
<thead>
<tr>
<th>Native isotypes</th>
<th>Engineered isotypes</th>
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<tbody>
<tr>
<td>IgG1</td>
<td>IgG2</td>
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</tbody>
</table>
| ADCC | ++ | +/- | +/- | - | +++ | +/-
| ADCP | +++ | +/- | + | - | +++ | +
| CDC | ++ | + | - | +/- | +++ | -

**Potent effector function-inducing isotypes**

IgG1 is the isotype of the majority of approved mAb therapies (e.g. anti-CTLA4 ipilimumab and anti-CD20 rituximab). It induces potent ADCC, ADCP and CDC, and thus can engage both humoral and cellular components of the immune system. IgG1-induced ADCC can be increased by defucosylation of the glycan sequences (IgG1fut). This modification, obtained by using a specific CHO cell line, enhances the mAb binding to FcγRIIIa/CD16. The approved anti-CD20 obinutuzumab is an engineered mAb with reduced fucose content. Also, a non-fucosylated variant of ipilimumab is currently under clinical trials.

**Reduced effector function-inducing isotypes**

IgG1NQ and IgG1 (N298A) are engineered isotypes with a mutation in glycosylation sites of the CH2 domain, at position 297 (Asparagine (N) to Glutamine (Q)), and 298 ((Asparagine (N) to Alanine (A)), respectively. These non-glycosylated mAbs, such as the anti-PD-L1 atezolizumab, mostly act as blocking agents. They induce no ADCC nor ADCP, and only minimal CDC. IgG2 induces poor ADCC and ADCP, and thus can engage some CDC function. Tremelimumab is an IgG2 targeting CTLA4 under clinical trials.

IgG4 (S228P) is an IgG4 engineered isotype that displays reduced ADCC, ADCP and no CDC. A Serine to Proline substitution at position 228 (S228P) in the hinge region prevents Fab arm exchanges frequently occurring between IgG4 molecules. IgG4 (S228P) mAbs, such as the anti-PD-1 nivolumab and pembrolizumab, mostly act as blocking agents.

IgA2 is a native isotype inducing low ADCC and ADCP, and no CDC. Although not yet introduced in clinical trials, IgAs have shown promising results in pre-clinical studies.

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**Examples of Strategies to Modify IgG mAb Isotypes**

- **GMN**
  - G: GlcNac
  - F: Galactose
  - M: Mannose
  - N: Fucose

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www.invivogen.com/antibody-isotypes