Engineered Anti-Cancer Antibodies with Enhanced Effector Functions

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GA101: Mechanisms of action

1. Increased direct cell death
   Type II antibody & elbow-hinge modification

2. Increased ADCC
   Higher affinity to the 'ADCC receptor'
   FcγRIIIa (GlycoMab TM technology)

3. Reduced CDC activity
   Type II antibody

ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity
GA101: A typical type II CD20 antibody

Half-maximal binding of GA101

Induction of homotypic aggregation

A model for Type I and type II CD20 binding?

Type I antibodies

Type II antibodies

Type I:Type II 2:1
GA101: Elbow hinge amino acid exchanges can reduce the enhanced cell death induction

Data: E. Mössner
The type II mode of binding leads to increased direct cell death induction of tumour cells.

- **Type II**
- **Increased direct cell death**

**Direct cell death with GA101 vs rituximab**

- Untreated
- 10 μg/ml GA101
- 10 μg/ml rituximab

**Type II mAbs (vs. Type I)**

- ↑ Direct cell death
- ↓ CDC
- ADCC activity
- CD20 not localised to lipid rafts

FcR related effector cell activities

Adapted from G. Cartron
Enhancing ADCC via Fc-Glycoengineering

GlycoMAb™ technology: genetic engineering of CHO cell lines to produce antibody glycosylation variants with increased affinity to FcγRIIIa receptors and enhanced ADCC

Increased affinity between antibody and FcγRIIIa receptor on killer cells by removal of core fucose

Glycoengineering brings Fc-FcγRIIIa binding to a high affinity range for the whole population

<table>
<thead>
<tr>
<th>Binding Constants</th>
<th>Low Affinity (158F)</th>
<th>High Affinity (158V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unmodified AB</td>
<td>5000 nM</td>
<td>750 nM</td>
</tr>
<tr>
<td>Glycoengineered</td>
<td>150 nM</td>
<td>15 nM</td>
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</tbody>
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Glycoengineered GA101 shows enhanced ADCC vs rituximab

Data: R. Grau
Superior whole blood B-cell depletion by GA101 in blood from B-CLL patient

Autologous B-cell Depletion Whole-Blood Assay (24 h)

- GA101
- Rituximab
- Alemtuzumab

Superior GA101 efficacy & complete tumour remission in SU-DHL4 (DLBCL) xenograft

Non-ADCC competent s.c. xenograft model (Scid beige)

Tumour-free (N=10)

Tumour volume (x 1000 mm$^3$) median ± IQR

- **GA101, rituximab or vehicle administered every 7 days**
- **Start of therapy**
- **Control**
- **GA101 1mg/kg**
- **Rituximab 30mg/kg**
- **GA101 10mg/kg**
- **GA101 30mg/kg**


DLBCL, diffuse large B-cell lymphoma; IQR, interquartile range
SU-DHL4 (DLBCL) xenograft progressing under rituximab responds to 2nd line treatment with GA101


IQR, interquartile range
Increased median and overall survival in i.v. disseminated late stage Z138 (MCL) xenograft model

GA101, rituximab or vehicle administered every 7 days

GA101 shows superior tissue B-cell depletion versus type I CD20 antibodies in Cynomolgus

Conclusion: In this group of heavily pre-treated iNHL patients, single-agent GA101 was safe with a high response rate in HD cohort (55%), and responses also observed in rituximab-refractory patients (HD 55% [6/11]), supporting a possible dose-response relationship.
GA201
A glyco-engineered EGFR IgG1 Ab in clinical development

**Humanized:**
- Rodent VH & VL CDRs
- CDRs grafted on human VH & VL frameworks identical to human germline sequences

**Glyco-engineered**
GA201: In vitro characteristics
ADCC activity against EGFR overexpressing A431 cells

- **Superior in vitro ADCC activity of GA201 vs. Erbitux and fully human EGFR mAb against EGFR overexpressing A431 cells**
- **Advantage maintained or even more pronounced in the presence of Redimmun (huIg, containing a few percent afucosylated antibodies)**
Superior efficacy of GA201 in a lung tumor model in Scid-bg mice

GA201 vs. Erbitux in human NSCLC model
(Established A549 lung adenocarcina xenografts in Scid-bg mice)