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Bispecific Fynomer-antibody fusion proteins targeting two epitopes on HER2

COVAGEN
Advanced Biopharmaceuticals

Frédéric Mourlane, Isabella Toller, Simon Brack, Dragan Grabulovski and Julian Bertschinger-Ehrler

Covagen AG, Wagistrasse 25, 8952 Zürich-Schlieren, Switzerland. Contact e-mail: dragan.grabulovski@covagen.com, www.covagen.com

Introduction

Fynomers are engineered binding proteins (7 kDa) derived from the SH3 domain of Fyn kinase (1). One important application of the Fynomer technology represents the genetic fusion of a Fynomer to an antibody to provide bispecific fusion proteins with enhanced activity compared to the unmodified antibody.

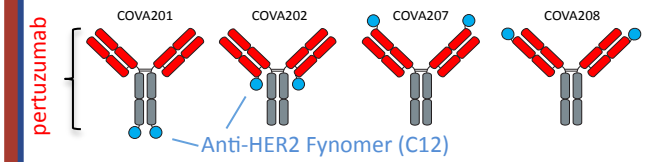
Using phage display technology we have isolated Fynomers binding to an epitope on HER2 which is different from the epitopes recognized by trastuzumab and pertuzumab. After genetic fusion of the HER2 binding Fynomer C12 to pertuzumab the resulting bispecific fusion proteins were evaluated *in vitro* and *in vivo* for their antitumoral activity.

Here we report on COVA208, the most potent Fynomer-pertuzumab fusion that demonstrated superior growth inhibition of tumor cells *in vitro* and higher efficacy *in vivo* in tumor xenograft mouse models compared to pertuzumab.

References:

1. Grabulovski D *et al*. (2007) *J Biol Chem* 282 (5): 3196-3204.

All Fynomer-pertuzumab fusions have excellent biophysical properties

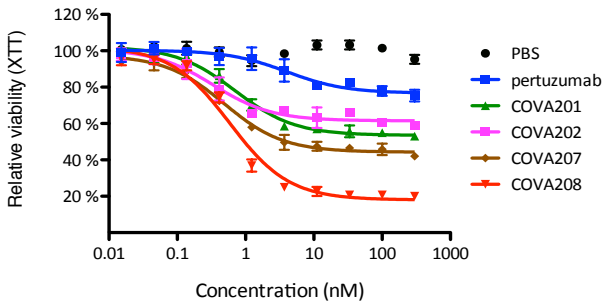


Fynomer-pertuzumab properties:

- High expression (same yield as unmodified antibody) ✔
- Stable for 3 months in PBS at 4° C ✔
- Binding to HER2 positive cells ✔
- ADCC activity maintained ✔

Relative orientation of binding sites matters for bioactivity

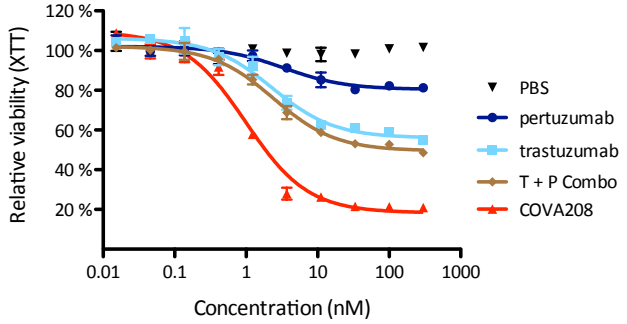
In vitro proliferation assay with NCI-N87 gastric cancer cells



COVA208 is the most potent bispecific protein

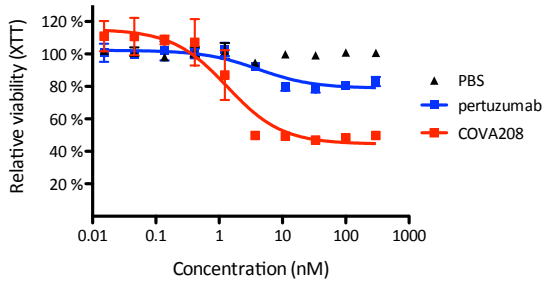
COVA208 is superior to trastuzumab, pertuzumab and combination of trastuzumab and pertuzumab

In vitro proliferation assay with NCI-N87 gastric cancer cells



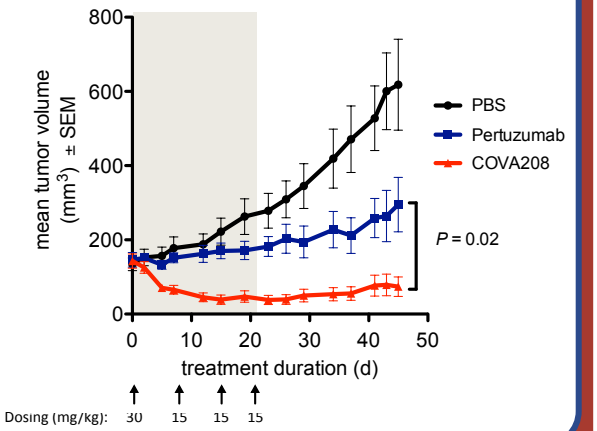
COVA208 is superior to pertuzumab on breast cancer cells

In vitro proliferation assay with BT-474 breast cancer cells



COVA208 shows excellent *in vivo* efficacy

In vivo NCI-N87 xenograft model



Conclusions

✓ Fynomer technology allows straightforward engineering of bispecific proteins with optimal bioactivities.

✓ The fusion of Fynomers does not disturb drug-like properties of therapeutic antibodies.

✓ COVA208 has highly promising properties with a great potential for further preclinical and clinical development.