

LATEST PAPERS

SEARCH for PAPERS

Printer-friendly PDF

Comment(s)

[>Abstract](#) [>References](#)

Cancer Immunity, Vol. 3 Suppl. 1, p. 2 (6 February 2003)

**Improving antibodies by evolution and engineering**Robert D. Schreiber<sup>1\*</sup>, Hiroaki Ikeda<sup>1</sup>, Allen Bruce<sup>1</sup>, Pilar Gil<sup>1</sup>, Gavin Dunn<sup>1</sup>, Kathleen Sheehan<sup>1</sup>, Vijay Shankaran<sup>1</sup>, and Lloyd J. Old<sup>2</sup><sup>1</sup>Washington University, School of Medicine, St. Louis, MO<sup>2</sup>Ludwig Institute for Cancer Research, New York, NY

\*Presenting author

**Abstract**

Tumor targeting puts very high demands on antibodies with respect to affinity, specificity but also stability of the protein. Recent advances in the design of fully synthetic antibody libraries ([1](#)) make it now possible to obtain such antibodies. Using *in vitro* selection and evolution tools such as ribosome display ([2](#), [3](#), [4](#), [5](#), [6](#)), it has been possible to select and further improve antibodies by directed evolution totally *in vitro*, without the use of any cells. Picomolar affinities have been routinely obtained ([3](#), [4](#), [5](#), [6](#)), and very high selectivity even to targets that are totally non-immunogenic, such as the telomeric DNA.

Using an antibody against EpCAM as a model system ([7](#), [8](#), [9](#)), the application of these technologies to tumor targeting will be discussed. An optimization of stability, valency and molecular weight has been carried out. Recently, the information gathered from directed evolution could be used in structured based engineering to complement directed evolution. Recent results on tumor targeting with these molecules will be discussed.

**References**

- Knappik A, Ge L, Honegger A, Pack P, Fischer M, Wellnhofer G, Hoess A, Wolle J, Pluckthun A, Virnekas B. Fully synthetic Human Combinatorial Antibody libraries (HuCAL) based on modular consensus frameworks and CDRs randomized with trinucleotides. *J Mol Biol* 2000; **296**: 57-86. (PMID: 10656818)
- Hanes J, Pluckthun A. In vitro selection and evolution of functional proteins using ribosome display. *Proc Natl Acad Sci U S A* 1997; **94**: 4937-42. (PMID: 9144168)
- Hanes J, Jermutus L, Weber-Bornhauser S, Bosshard HR, Pluckthun A. Ribosome display efficiently selects and evolves high-affinity antibodies in vitro from immune libraries. *Proc Natl Acad Sci U S A* 1998; **95**: 14130-5. (PMID: 9826665)
- Hanes J, Schaffitzel C, Knappik A, Pluckthun A. Picomolar affinity antibodies from a fully synthetic naive library selected and evolved by ribosome display. *Nat Biotechnol* 2000; **18**: 1287-92. (PMID: 11101809)

5. Jeremius L, Honegger A, Schwesinger F, Hanes J, Pluckthun A. Tailoring in vitro evolution for protein activity or stability. *Proc Natl Acad Sci U S A* 2001; **98**: 75-80. (PMID: 11134506)
6. Schaffitzel C, Berger I, Postberg J, Hanes J, Lipps HJ, Pluckthun A. In vitro generated antibodies specific for telomeric guanine-quadruplex DNA react with *Stylonychia lemnae* macronuclei. *Proc Natl Acad Sci U S A* 2001; **98**: 8572-7. (PMID: 11438689)
7. Waibel R, Alberto R, Willuda J, Finnern R, Schibli R, Stichelberger A, Egli A, Abram U, Mach JP, Pluckthun A, Schubiger PA. Stable one-step technetium-99m labeling of His-tagged recombinant proteins with a novel Tc(I)-carbonyl complex. *Nat Biotechnol* 1999; **17**: 897-901. (PMID: 10471933)
8. Willuda J, Honegger A, Waibel R, Schubiger PA, Stahel R, Zangemeister-Wittke U, Pluckthun A. High thermal stability is essential for tumor targeting of antibody fragments: engineering of a humanized anti-epithelial glycoprotein-2 (epithelial cell adhesion molecule) single-chain Fv fragment. *Cancer Res* 1999; **59**: 5758-67. (PMID: 10582696)
9. Willuda J, Kubetzko S, Waibel R, Schubiger PA, Zangemeister-Wittke U, Pluckthun A. Tumor targeting of mono-, di- and tetravalent anti-p185HER-2 miniantibodies multimerized by self-associating peptides. *J Biol Chem* 2001; **276**: 14385-92. (PMID: 11278961)

Copyright © 2003 by Robert D. Schreiber