## References

- 1. Nelson, A. L., Dhimolea, E. & Reichert, J. M. (2010). Development trends for human monoclonal antibody therapeutics. *Nat Rev Drug Discov* **9**, 767-774.
- 2. Smith, K. G. C. & Clatworthy, M. R. (2010). FcγRIIB in autoimmunity and infection: evolutionary and therapeutic implications. *Nat Rev Immunol* **10**, 328-343.
- 3. Weiner, L. M., Surana, R. & Wang, S. (2010). Monoclonal antibodies: versatile platforms for cancer immunotherapy. *Nat Rev Immunol* **10**, 317-327.
- 4. Chan, A. C. & Carter, P. J. (2010). Therapeutic antibodies for autoimmunity and inflammation. *Nat Rev Immunol* **10**, 301-316.
- 5. Pérez-Martínez, D., Tanaka, T. & Rabbitts, T. H. (2010). Intracellular antibodies and cancer: New technologies offer therapeutic opportunities. *BioEssays* **32**, 589-598.
- 6. Marasco, W. A. & Sui, J. (2007). The growth and potential of human antiviral monoclonal antibody therapeutics. *Nat Biotech* **25**, 1421-1434.
- 7. Vander Heiden, M. G. (2011). Targeting cancer metabolism: a therapeutic window opens. *Nat Rev Drug Discov* **10**, 671-684.
- 8. Aggarwal, S. (2009). What's fueling the biotech engine—2008. *Nat Biotech* **27**, 987-993.
- 9. Yoon, S., Kim, Y.-S., Shim, H. & Chung, J. (2010). Current perspectives on therapeutic antibodies. *Biotechnology and Bioprocess Engineering* **15**, 709-715.
- 10. Clark, L. A., Boriack-Sjodin, P. A., Eldredge, J., Fitch, C., Friedman, B., Hanf, K. J. M., Jarpe, M., Liparoto, S. F., Li, Y., Lugovskoy, A., *et al.* (2006). Affinity enhancement of an in vivo matured therapeutic antibody using structure-based computational design. *Protein Science* **15**, 949-960.
- 11. Lippow, S. M., Wittrup, K. D. & Tidor, B. (2007). Computational design of antibody-affinity improvement beyond in vivo maturation. *Nat Biotechnol* **25**, 1171-6.
- 12. Midelfort, K. S., Hernandez, H. H., Lippow, S. M., Tidor, B., Drennan, C. L. & Wittrup, K. D. (2004). Substantial energetic improvement with minimal structural perturbation in a high affinity mutant antibody. *Journal of Molecular Biology* **343**, 685-701.
- 13. Meijer, P.-J., Andersen, P. S., Haahr Hansen, M., Steinaa, L., Jensen, A., Lantto, J., Oleksiewicz, M. B., Tengbjerg, K., Poulsen, T. R., Coljee, V. W., *et al.* (2006). Isolation of Human Antibody Repertoires with Preservation of the Natural Heavy and Light Chain Pairing. *Journal of Molecular Biology* **358**, 764-772.
- 14. Poulsen, T. R., Meijer, P.-J., Jensen, A., Nielsen, L. S. & Andersen, P. S. (2007). Kinetic, Affinity, and Diversity Limits of Human Polyclonal Antibody Responses against Tetanus Toxoid. *The Journal of Immunology* **179**, 3841-3850.
- 15. Weinstein, J. A., Jiang, N., White, R. A., 3rd, Fisher, D. S. & Quake, S. R. (2009). High-throughput sequencing of the zebrafish antibody repertoire. *Science* **324**, 807-10.
- 16. Jiang, N., Weinstein, J. A., Penland, L., White, R. A., 3rd, Fisher, D. S. & Quake, S. R. (2011). Determinism and stochasticity during maturation of the zebrafish antibody repertoire. *Proceedings of the National Academy of Sciences of the United States of America* **108**, 5348-53.
- 17. Glanville, J., Zhai, W., Berka, J., Telman, D., Huerta, G., Mehta, G. R., Ni, I., Mei, L., Sundar, P. D., Day, G. M., et al. (2009). Precise determination of the diversity of a combinatorial antibody library gives insight into the human immunoglobulin repertoire. Proceedings of the National Academy of Sciences of the United States of America 106, 20216-21.
- 18. Reddy, S. T., Ge, X., Miklos, A. E., Hughes, R. A., Kang, S. H., Hoi, K. H., Chrysostomou, C., Hunicke-Smith, S. P., Iverson, B. L., Tucker, P. W., *et al.* (2010). Monoclonal antibodies isolated without screening by analyzing the variable-gene repertoire of plasma cells. *Nature Biotechnology* **28**, 965-9.

- 19. Arnaout, R., Lee, W., Cahill, P., Honan, T., Sparrow, T., Weiand, M., Nusbaum, C., Rajewsky, K. & Koralov, S. B. (2011). High-Resolution Description of Antibody Heavy-Chain Repertoires in Humans. *PloS one* **6**, e22365.
- 20. Fanning, L. J., Connor, A. M. & Wu, G. E. (1996). Development of the Immunoglobulin Repertoire. *Clinical Immunology and Immunopathology* **79**, 1-14.
- 21. Zolla-Pazner, S. (2004). Identifying epitopes of HIV-1 that induce protective antibodies. *Nat Rev Immunol* **4**, 199-210.
- 22. Dahirel, V., Shekhar, K., Pereyra, F., Miura, T., Artyomov, M., Talsania, S., Allen, T. M., Altfeld, M., Carrington, M., Irvine, D. J., et al. (2011). Coordinate linkage of HIV evolution reveals regions of immunological vulnerability. *Proc Natl Acad Sci U S A* **108**, 11530-5.
- 23. Sellers, B. D., Nilmeier, J. P. & Jacobson, M. P. (2010). Antibodies as a model system for comparative model refinement. *Proteins* **78**, 2490-2505.
- 24. Schwede, T., Sali, A., Honig, B., Levitt, M., Berman, H. M., Jones, D., Brenner, S. E., Burley, S. K., Das, R., Dokholyan, N. V., *et al.* (2009). Outcome of a workshop on applications of protein models in biomedical research. *Structure* **17**, 151-9.
- 25. Stein, A., Mosca, R. & Aloy, P. (2011). Three-dimensional modeling of protein interactions and complexes is going 'omics. *Current Opinion in Structural Biology* **21**, 200-208.
- 26. Sivasubramanian, A., Sircar, A., Chaudhury, S. & Gray, J. J. (2009). Toward high-resolution homology modeling of antibody Fv regions and application to antibody-antigen docking. *Proteins* **74**, 497-514.
- 27. Faelber, K., Kirchhofer, D., Presta, L., Kelley, R. F. & Muller, Y. A. (2001). The 1.85 Å resolution crystal structures of tissue factor in complex with humanized fab d3h44 and of free humanized fab d3h44: revisiting the solvation of antigen combining sites. *Journal of Molecular Biology* **313**, 83-97.
- 28. Sircar, A., Sanni, K. A., Shi, J. & Gray, J. J. (2011). Analysis and modeling of the variable region of camelid single-domain antibodies. *Journal of Immunology* **186**, 6357-67.
- 29. Sircar, A., Kim, E. T. & Gray, J. J. (2009). RosettaAntibody: Antibody variable region homology modeling server. *Nucleic Acids Research* **37**, W474-W479.
- 30. Gangwar, R. S., Shil, P., Cherian, S. S. & Gore, M. M. (2011). Delineation of an epitope on domain I of Japanese Encephalitis Virus envelope glycoprotein using monoclonal antibodies. *Virus Research* **158**, 179-187.
- 31. Tape, C. J., Willems, S. H., Dombernowsky, S. L., Stanley, P. L., Fogarasi, M., Ouwehand, W., McCafferty, J. & Murphy, G. (2011). Cross-domain inhibition of TACE ectodomain. *Proc Natl Acad Sci U S A* **108**, 5578-5583.
- 32. Simonelli, L., Beltramello, M., Yudina, Z., Macagno, A., Calzolai, L. & Varani, L. (2010). Rapid Structural Characterization of Human Antibody-Antigen Complexes through Experimentally Validated Computational Docking. *Journal of Molecular Biology* **396**, 1491-1507.
- 33. Pedotti, M., Simonelli, L., Livoti, E. & Varani, L. (2011). Computational docking of antibody-antigen complexes, opportunities and pitfalls illustrated by influenza hemagglutinin. *International Journal of Molecular Sciences* **12**, 226-51.
- 34. Sutherland, J. N. & Maynard, J. A. (2009). Characterization of a key neutralizing epitope on pertussis toxin recognized by monoclonal antibody 1B7. *Biochemistry* **48**, 11982-93.
- 35. Brown, E. L., Nishiyama, Y., Dunkle, J. W., Aggarwal, S., Planque, S., Watanabe, K., Csencsits-Smith, K., Bowden, M. G., Kaplan, S. L. & Paul, S. (2012). Constitutive Production of Catalytic Antibodies to a Staphylococcus aureus Virulence Factor and Effect of Infection. *Journal of Biological Chemistry* **287**, 9940-9951.
- 36. Makiya, M., Dolan, M., Agulto, L., Purcell, R. & Chen, Z. (2012). Structural basis of anthrax edema factor neutralization by a neutralizing antibody. *Biochem Biophys Res Comm* **417**, 324-329.

- 37. Chaudhury, S. & Gray, J. J. (2008). Conformer selection and induced fit in flexible backbone protein-protein docking using computational and NMR ensembles. *J Mol Biol* **381**, 1068-87.
- 38. Sircar, A. & Gray, J. J. (2010). SnugDock: paratope structural optimization during antibody-antigen docking compensates for errors in antibody homology models. *PLoS Comput Biol* **6**, e1000644.
- 39. Mendez, R., Leplae, R., Lensink, M. F. & Wodak, S. J. (2005). Assessment of CAPRI predictions in rounds 3-5 shows progress in docking procedures. *Proteins* **60**, 150-69.
- 40. Mandell, D. J., Coutsias, E. A. & Kortemme, T. (2009). Sub-angstrom accuracy in protein loop reconstruction by robotics-inspired conformational sampling. *Nat Methods* **6**, 551-2.
- 41. Das, R. & Baker, D. (2008). Macromolecular modeling with rosetta. *Annual Review of Biochemistry* **77**, 363-82.
- 42. Rohl, C. A., Strauss, C. E. M., Misura, K. M. S. & Baker, D. (2004). Protein Structure Prediction Using Rosetta. In *Methods in Enzymology* (Ludwig, B. & Michael, L. J., eds.), Vol. 383, pp. 66-93. Academic Press.
- 43. Kuhlman, B. & Baker, D. (2000). Native protein sequences are close to optimal for their structures. *Proc Natl Acad Sci U S A* **97**, 10383-8.
- 44. Karanicolas, J. & Kuhlman, B. (2009). Computational design of affinity and specificity at protein-protein interfaces. *Current Opinion in Structural Biology* **19**, 458-463.
- 45. Song, Y., Tyka, M., Leaver-Fay, A., Thompson, J. & Baker, D. (2011). Structure-guided forcefield optimization. *Proteins* **79**, 1898-909.
- 46. Leaver-Fay, A., Tyka, M., Lewis, S. M., Lange, O. F., Thompson, J., Jacak, R., Kaufman, K., Renfrew, P. D., Smith, C. A., Gray, J. J., *et al.* (2011). ROSETTA3: an object-oriented software suite for the simulation and design of macromolecules. *Methods in Enzymology* **487**, 545-74.
- 47. Chaudhury, S., Lyskov, S. & Gray, J. J. (2010). PyRosetta: a script-based interface for implementing molecular modeling algorithms using Rosetta. *Bioinformatics* **26**, 689-91.
- 48. Kaufmann, K. W., Lemmon, G. H., DeLuca, S. L., Sheehan, J. H. & Meiler, J. (2010). Practically Useful: What the Rosetta Protein Modeling Suite Can Do for You. *Biochemistry* **49**, 2987-2998.
- 49. Raman, S., Vernon, R., Thompson, J., Tyka, M., Sadreyev, R., Pei, J., Kim, D., Kellogg, E., DiMaio, F., Lange, O., *et al.* (2009). Structure prediction for CASP8 with all-atom refinement using Rosetta. *Proteins* **77 Suppl 9**, 89-99.
- 50. Bradley, P., Misura, K. M. & Baker, D. (2005). Toward high-resolution de novo structure prediction for small proteins. *Science* **309**, 1868-71.
- 51. Masica, D. L., Ash, J. T., Ndao, M., Drobny, G. P. & Gray, J. J. (2010). Toward a structure determination method for biomineral-associated protein using combined solid-state NMR and computational structure prediction. *Structure* **18**, 1678-87.
- 52. Hirst, S. J., Alexander, N., McHaourab, H. S. & Meiler, J. (2011). RosettaEPR: An integrated tool for protein structure determination from sparse EPR data. *Journal of Structural Biology* **173**, 506-514.
- 53. Gray, J. J., Moughon, S., Wang, C., Schueler-Furman, O., Kuhlman, B., Rohl, C. A. & Baker, D. (2003). Protein-protein docking with simultaneous optimization of rigid-body displacement and side-chain conformations. *J Mol Biol* **331**, 281-99.
- 54. Wang, C., Bradley, P. & Baker, D. (2007). Protein-protein docking with backbone flexibility. *Journal of Molecular Biology* **373**, 503-19.
- 55. Raveh, B., London, N. & Schueler-Furman, O. (2010). Sub-angstrom modeling of complexes between flexible peptides and globular proteins. *Proteins* **78**, 2029-2040.
- 56. Kuhlman, B., Dantas, G., Ireton, G. C., Varani, G., Stoddard, B. L. & Baker, D. (2003). Design of a novel globular protein fold with atomic-level accuracy. *Science* **302**, 1364-8.

- 57. Rothlisberger, D., Khersonsky, O., Wollacott, A. M., Jiang, L., DeChancie, J., Betker, J., Gallaher, J. L., Althoff, E. A., Zanghellini, A., Dym, O., *et al.* (2008). Kemp elimination catalysts by computational enzyme design. *Nature* **453**, 190-195.
- 58. Jiang, L., Althoff, E. A., Clemente, F. R., Doyle, L., Röthlisberger, D., Zanghellini, A., Gallaher, J. L., Betker, J. L., Tanaka, F., Barbas, C. F., *et al.* (2008). De Novo Computational Design of Retro-Aldol Enzymes. *Science* **319**, 1387-1391.
- 59. Masica, D. L., Schrier, S. B., Specht, E. A. & Gray, J. J. (2010). De novo design of peptidecalcite biomineralization systems. *Journal of the American Chemical Society* **132**, 12252-62
- 60. Fleishman, S. J., Whitehead, T. A., Ekiert, D. C., Dreyfus, C., Corn, J. E., Strauch, E. M., Wilson, I. A. & Baker, D. (2011). Computational design of proteins targeting the conserved stem region of influenza hemagglutinin. *Science* **332**, 816-21.
- 61. Das, R., Karanicolas, J. & Baker, D. (2010). Atomic accuracy in predicting and designing noncanonical RNA structure. *Nature Methods* **7**, 291-4.
- 62. Chaudhury, S. & Gray, J. J. (2009). Identification of structural mechanisms of HIV-1 protease specificity using computational peptide docking: implications for drug resistance. *Structure* **17**, 1636-48.
- 63. Sircar, A., Chaudhury, S., Kilambi, K. P., Berrondo, M. & Gray, J. J. (2010). A generalized approach to sampling backbone conformations with RosettaDock for CAPRI rounds 13-19. *Proteins* **78**, 3115-23.
- 64. Li, Z. & Scheraga, H. A. (1987). Monte Carlo-minimization approach to the multiple-minima problem in protein folding. *Proc Natl Acad Sci U S A* **84**, 6611-5.
- 65. Shapovalov, M. V. & Dunbrack, R. L., Jr. (2011). A smoothed backbone-dependent rotamer library for proteins derived from adaptive kernel density estimates and regressions. *Structure* **19**, 844-58.
- 66. Dunbrack, R. L., Jr. & Cohen, F. E. (1997). Bayesian statistical analysis of protein sidechain rotamer preferences. *Protein Science* **6**, 1661-81.