

## CURRICULUM VITAE

Name: Carl O. Pabo

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Education: Yale College  
New Haven, Connecticut  
B.S. (*summa cum laude*)  
Molecular Biophysics and Biochemistry 1974

Harvard University  
Cambridge, Massachusetts  
Ph.D., Biochemistry and Molecular Biology 1980

Positions: Postdoctoral Fellow  
Department of Biochemistry and Molecular Biology  
Harvard University 1980–1982

Assistant Professor  
Department of Biophysics  
Johns Hopkins University School of Medicine 1982–1986

Associate Professor  
Department of Molecular Biology and Genetics and  
Department of Biophysics  
Johns Hopkins University School of Medicine 1986–1990

Associate Investigator  
Howard Hughes Medical Institute 1986–1991

Professor  
Department of Molecular Biology and Genetics and  
Department of Biophysics  
Johns Hopkins University School of Medicine 1990–1991

Professor  
Department of Biology  
Massachusetts Institute of Technology 1991–2001

Investigator  
Howard Hughes Medical Institute 1991–2001

Investigator  
Center for Cancer Research

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|---|--------------------------------|
| Massachusetts Institute of Technology   | 1999–2001                      |
| Senior Vice President and Chief Scientific Officer<br>Sangamo BioSciences, Inc.                             | 2001–2003                      |
| Chair, Scientific Advisory Board<br>Sangamo BioSciences, Inc.   | 1998–2001;<br>2003–2008        |
| Moore Distinguished Scholar<br>California Institute of Technology   | January 2004 –<br>April 2004   |
| Visiting Professor, Bio-X Program<br>Stanford University  | September 2004 –<br>April 2005 |
| Visiting Professor, Department of Systems Biology<br>Harvard Medical School                                 | June 2005 –<br>July 2005       |
| Miller Visiting Research Professor<br>University of California at Berkeley                                  | August 2005 –<br>December 2005 |
| Visiting Professor, Department of Systems Biology<br>Harvard Medical School                                 | February 2006 –<br>May 2007    |
| Founder and Research Director<br>Protean Futures LLC  | September 2007 –<br>Present    |
| Scientific Advisor<br>ND Capital (formerly known as NanoDimension)  | March 2008 –<br>Present        |
| Visiting Professor, Division of Biology<br>and Biological Engineering<br>California Institute of Technology | April 2017 –<br>June 2017      |
| Founder and President<br>Humanity 2050, Inc. ( <a href="http://humanity2050.org">humanity2050.org</a> )     | August 2017 –<br>June 2023     |

Awards:

Elected to Phi Beta Kappa, 1973

NSF Predoctoral Fellowship, 1974–1977

Jane Coffin Childs Memorial Fund  
Postdoctoral Fellowship, 1980–1982

American Cancer Society Junior Faculty Research Award, 1983–1985

Protein Society Young Investigator Award, 1991

Pfizer Award in Enzyme Chemistry, 1992

Elected to American Academy of Arts and Sciences, 1993

Elected to National Academy of Sciences, 1998

Guggenheim Fellowship (“Theories of Thought”), 2005–2006

Teaching: I have taught courses at Johns Hopkins, MIT, Caltech, and Stanford on biophysical chemistry, X-ray crystallography, protein design and engineering, evolution, theories of thought, and “The World in 2050.”

Managing & Mentoring: I have managed research teams in academics and industry, and have had extensive experience as a mentor and advisor.

Research: I was born and have lived as an explorer: trying to understand everything I can about life, the world, the human condition, and prospects for the human future.

I started my career — building a solid foundation for all later work — by taking a strictly scientific stance, working on the structure and design of DNA-binding proteins, pointing out that protein design could be approached as an “inverted” version of the protein folding problem, using X-ray crystallography to determine the atomic details of protein-DNA interactions, and then learning how to design novel DNA-binding proteins that bound so tightly and specifically that they were used (even before CRISPR) as tools for genome editing.

However, in much the way that Columbus and Magellan always wondered about the world beyond the horizon, I kept wondering about atomic/molecular systems (as with the human brain, and as with human societies) that were too complicated to usefully be described at an atomic/molecular level.

Seeing the chaos that filled the newspapers, seeing that scientific knowledge (by itself) cannot solve the fundamental problems facing the modern world, I felt impelled to see if I could find some better way to think about human thought and the human future, some better way to help address the most fundamental challenges now facing society. I thus resigned my tenured faculty position as a full professor at MIT and resigned my appointment as an Investigator with the Howard Hughes Medical Institute. I sailed on.

Since that time, I have developed a new way of describing and analyzing thought, using a physical frame of reference that encompasses both words and world. That is: I start by keeping everything grounded with reference to a flow of atomic, molecular events, avoiding any temptation to ever slip and start speaking of symbols, ideas, or thought as if they might exist in some separate, abstract, ethereal realm. (Thought is just one of the many things that complex assemblies of atoms and molecules can do; ideas are just one aspect of the way in which these atomic/molecular systems can be arranged and in which information can move.)

With my new model of thought as a foundation, I began to see how my concerns about cognition were connected with the most critical challenges of the modern world. It became clear that all these different challenges now facing society — problems like climate change, environmental degradation, and risks associated with the rise of AI — stem from a single, underlying challenge. These problems are so complex that the cognitive capacity of the human mind is overwhelmed in the

search for solutions that are clear, acceptable, and powerful enough to address the challenges at hand.

This “crisis of complexity” has become the central theme of my current work. I have focused on 1) developing a new set of tools to help minds work amidst this complexity and on 2) developing new strategies that may limit/constrain the continued proliferation of complexity.

My hope is that these ideas will give both leaders and citizens new ways to address the pressing challenges of the modern age and improve prospects for a flourishing human future.

Humanity 2050:

In 2017, I founded an institute — Humanity 2050 — that focused on testing these new tools of thought on some of the hyper-complex challenges of the modern age, including substantial work on an operational plan for climate engineering that uncovered some previously underappreciated risks. Though we were unable to secure long-term funding, and I needed to temporarily set aside work on climate engineering, I am continuing this work on the complexity crisis as an independent researcher/scholar.

The strategies that we developed at Humanity 2050 build on my model of thought. The use of 1) “special focus teams” and 2) a new “algorithm for thought” — when taken together — offer novel methods for crafting effective, actionable plans amidst the complexity of the modern world. (And, notably, these strategies are set up in a way that will let them take advantage of ongoing advances in AI.)

As society prepares to face a new set of challenges — as with potential negative impacts arising from the rapid development of artificial intelligence and of new mind/machine interfaces — I continue to extend and build on the work done at Humanity 2050, and I now also propose new strategies for reining in complexity.

Patents:

Listed on last two pages of CV (after publications).

Consulting:

Given the pan-disciplinary range of interests and experiences summarized above, my background also has allowed me to play an important role as an advisor in venture capital, working with ND Capital (first known as NanoDimension) from 2008 onwards.

Goals:

I want to be as useful as possible in working to address these challenges of the human future. I thus seek fresh opportunities to collaborate, hoping to best leverage my own background, ideas, and passionate concern as I work with others to help address the crisis of complexity now facing humanity. There is so much to do and so little time before the crisis of complexity spirals out of control.

## PUBLICATIONS

1. Pabo, C.O., Sauer, R.T., Sturtevant, J.M. & Ptashne, M. (1979) The  $\lambda$  Repressor Contains Two Domains. **Proc. Natl. Acad. Sci., USA** **76**, 1608-1612.
2. Sauer, R.T., Pabo, C.O., Meyer, B.J., Ptashne, M. & Backman, K.C. (1979) The Regulatory Functions of the  $\lambda$  Repressor Reside in the Amino-Terminal Domain. **Nature** **279**, 396-400.
3. Johnson, A.D., Pabo, C.O. & Sauer, R. T. (1980) Bacteriophage  $\lambda$  Repressor and Cro Protein: Interactions with Operator DNA. **Meth. Enz.** **65**, 839-856.
4. Ptashne, M., Jeffrey, A., Johnson, A.D., Mauer, R., Meyer, B.J., Pabo, C.O., Roberts, T.M. & Sauer, R.T. (1980) How the  $\lambda$  Repressor and Cro Work. **Cell** **19**, 1-11.
5. Pabo, C.O., Krovatin, W., Jeffrey, A. & Sauer, R.T. (1982) The N-Terminal Arms of  $\lambda$  Repressor Wrap Around the Operator DNA. **Nature** **298**, 441-443.
6. Pabo, C.O. & Lewis, M. (1982) The Operator-Binding Domain of  $\lambda$  Repressor: Structure and DNA Recognition. **Nature** **298**, 443-447.
7. Sauer, R.T., Yocum, R.R., Doolittle, R.F., Lewis, M. & Pabo, C.O. (1982) Homology Among DNA-Binding Proteins Suggests Use of a Conserved Super-Secondary Structure. **Nature** **298**, 447-451.
8. Ptashne, M., Johnson, A.D. & Pabo, C.O. (1982) A Genetic Switch in a Bacterial Virus. **Scientific American** **247**, 128-140.
9. Lewis, M., Jeffrey, A., Wang, J-H., Ladner, R.C., Ptashne, M. & Pabo, C.O. (1983) Structure of the Operator-Binding Domain of  $\lambda$  Repressor: Implications for DNA Recognition and Gene Regulation. **Cold Spring Harbor Symp. Quant. Biol.** **47**, 435-440.
10. Gussin, G., Johnson, A.D., Pabo, C.O. & Sauer, R.T. (1983) Repressor and Cro. **Lambda II** (J. Roberts, ed.) Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 93-121.
11. Ohlendorf, D.H., Anderson, W.F., Lewis, M., Pabo, C.O. & Matthews, B.W. (1983) Comparison of the Structures of Cro and  $\lambda$  Repressor Proteins from Bacteriophage  $\lambda$ . **J. Mol. Biol.** **169**, 757-769.
12. Sauer, R.T. & Pabo, C.O. (1983) Protein-DNA Recognition: The  $\lambda$  Repressor-Operator Complex. **American Society for Microbiology News** **49**, 131-136.
13. Pabo, C.O. (1983) Designing Proteins and Peptides. **Nature** **301**, 200.
14. Pabo, C.O., Jordan, S.R. & Frankel, A.D. (1983) Systematic Analysis of Possible Hydrogen Bonds Between Amino Acid Side Chains and B-Form DNA. **J. Biomolecular Structure and Dynamics** **1**, 1039-1049.
15. Sauer, R.T. & Pabo, C.O. (1984) How  $\lambda$  Repressor Binds Operator DNA. **Microbiology** **1984**.
16. Pabo, C.O. & Sauer, R.T. (1984) Protein-DNA Recognition. **Ann. Rev. Biochem.** **53**, 293-321.
17. Pabo, C.O. (1984) DNA-Protein Interactions. **Proceedings of the Robert A.**

**Welch Foundation Conferences on Chemical Research XXVII Stereospecificity in Chemistry and Biochemistry**, Robert A. Welch Foundation, Houston, TX, 222-255.

18. Lewis, M., Wang, J. & Pabo, C.O. (1985) Structure of the Operator Binding Domain of  $\lambda$  Repressor. **Biological Macromolecules and Assemblies, Volume 2** (Drs. Journak & McPherson, eds.) John Wiley and Sons, Inc., New York, 266-287.
19. Jordan, S.R., Pabo, C.O., Vershon, A.K. & Sauer, R.T. (1985) Crystallization of the Arc Repressor. **J. Mol. Biol.** **185**, 445-446.
20. Jordan, S.R., Whitcombe, T.V., Berg, J.M. & Pabo, C.O. (1985) Systematic Variation in DNA Length Yields Highly Ordered Repressor-Operator Co-Crystals. **Science** **230**, 1383-1385.
21. Pabo, C.O. & Suchanek, E.G. (1986) Computer-Aided Model-Building Strategies for Protein Design. **Biochemistry** **25**, 5987-5991.
22. Sauer, R.T., Hehir, K., Stearman, R.S., Weiss, M.A., Jeitler-Nilsson, A., Suchanek, E.G. & Pabo, C.O. (1986) An Engineered Intersubunit Disulfide Enhances the Stability and DNA Binding of the N-Terminal Domain of  $\lambda$  Repressor. **Biochemistry** **25**, 5992-5998.
23. Weiss, M.A., Pabo, C.O., Karplus, M. & Sauer, R.T. (1986) Dimerization of the Operator-Binding Domain of Phage  $\lambda$  Repressor. **Biochemistry** **26**, 897-904.
24. Pabo, C.O. (1987) Introductory chapter for **Protein Engineering** (D. L. Oxender & C. F. Fox, eds.) Alan R. Liss, Inc., New York, xv-xvii.
25. Berg, J.M., Jordan, S.R. & Pabo, C.O. (1987) The Structure and Function of Bacteriophage  $\lambda$  Repressor. **DNA: Protein Interactions and Gene Regulation** (E.B. Thompson & J. Papaconstantinou, eds.) University of Texas Press, Austin, 1-12.
26. Pabo, C.O. (1987) New Generation Databases for Molecular Biology. **Nature** **327**, 467.
27. Frankel, A.D., Berg, J.M. & Pabo, C.O. (1987) Metal-Dependent Folding of a Single Zinc Finger from Transcription Factor IIIA. **Proc. Natl. Acad. Sci., USA** **84**, 4841-4845.
28. Frankel, A.D., Bredt, D.S. & Pabo, C.O. (1988) Tat Protein from Human Immunodeficiency Virus Forms a Metal-Linked Dimer. **Science** **240**, 70-73.
29. Frankel, A.D. & Pabo, C.O. (1988) Fingering Too Many Proteins. **Cell** **53**, 675.
30. Frankel, A.D., Chen, L., Cotter, R.J. & Pabo C.O. (1988) Dimerization of the Tat Protein from HIV: A Cysteine-Rich Peptide Mimics the Normal Metal-Linked Dimer Interface. **Proc. Natl. Acad. Sci., USA** **85**, 6297-6300.
31. Stearman, R.S., Frankel, A.D., Freire, E., Liu, B. & Pabo, C.O. (1988) Combining Thermostable Mutations Increases the Stability of  $\lambda$  Repressor. **Biochemistry** **27**, 7571-7574.
32. Jordan, S.R. & Pabo, C.O. (1988) Structure of the  $\lambda$  Complex at 2.5 Å Resolution: Detailed View of the Repressor-Operator Interactions. **Science** **242**, 893-899.

33. Frankel, A.D. & Pabo, C.O. (1988) Cellular Uptake of the Tat Protein from Human Immunodeficiency Virus. **Cell** **55**, 1189-1193.
34. Sauer, R.T., Jordan, S.R. & Pabo, C.O. (1990)  $\lambda$  Repressor: A Model System for Understanding Protein-DNA Interactions and Protein Stability. **Adv. Prot. Chem.** **40**, 1-61.
35. Bowie, J.U., Clarke, N.D., Pabo, C.O. & Sauer, R.T. (1990) Identification of Protein Folds: Matching Hydrophobicity Patterns of Sequence Sets with Solvent Accessibility Patterns of Known Structures. **Proteins** **7**, 257-264.
36. Pabo, C.O., Aggarwal, A.K., Jordan, S.R., Beamer, L.J., Obeysekare, U. & Harrison, S.C. (1990) Conserved Residues Make Similar Contacts in Two Repressor-Operator Complexes. **Science** **247**, 1210-1213.
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38. Kissinger, C.R., Liu, B., Martin-Blanco, E., Kornberg, T.B. & Pabo, C.O. (1990) Crystal Structure of an Engrailed Homeodomain/DNA Complex at 2.8 Å Resolution: A Framework for Understanding Homeodomain/DNA Interactions. **Cell** **63**, 579-590.
39. Wolberger, C., Pabo, C.O., Vershon, A.K. & Johnson, A.D. (1991) Crystallization and Preliminary X-ray Diffraction Studies of a MAT $\alpha$ 2-DNA Complex. **J. Mol. Biol.** **217**, 11-13.
40. Pavletich, N.P. & Pabo, C.O. (1991) Zinc Finger-DNA Recognition: Crystal Structure of a Zif268-DNA Complex at 2.1 Å. **Science** **252**, 809-817.
41. Wolberger, C. Vershon, A.K., Liu, B., Johnson, A.D. & Pabo, C.O. (1991) Crystal Structure of a MAT $\alpha$ 2 Homeodomain-Operator Complex Suggests a General Model for Homeodomain-DNA Interactions. **Cell** **67**, 517-528.
42. Clarke, N.D., Beamer, L.J., Goldberg, H.R., Berkower, C. & Pabo, C.O. (1991) The DNA Binding Arm of  $\lambda$  Repressor: Critical Contacts from a Flexible Region. **Science** **254**, 267-270.
43. Godley, L., Pfeifer, J., Steinhauer, D., Ely, B., Shaw, G., Kaufmann, R., Suchanek, E., Pabo, C., Skehel, J.J., Wiley, D.C. & Wharton, S. (1992) Introduction of Intersubunit Disulfide Bonds In the Membrane-Distal Region of the Influenza Hemagglutinin Abolishes Membrane Fusion Activity. **Cell** **68**, 635-645.
44. Pabo, C.O. & Sauer, R.T. (1992) Transcription Factors: Structural Families and Principles of DNA Recognition. **Annu. Rev. Biochem.** **61**, 1053-1095.
45. Beamer, L.J. & Pabo, C.O. (1992) Refined 1.8 Å Crystal Structure of the  $\lambda$  Repressor Operator Complex. **J. Mol. Biol.** **227**, 177-196.
46. Pavletich, N.P. & Pabo, C.O. (1993) Crystal Structure of a Five Finger GLI-DNA Complex: New Perspectives on Zinc Fingers. **Science** **261**, 1701-1707.
47. Pavletich, N.P., Chambers, K.A. & Pabo, C.O. (1993) The DNA-Binding Domain of p53 Contains the Four Conserved Regions and the Major Mutation Hot Spots. **Genes & Development** **7**, 2556-2564.

48. Rebar, E.J. & Pabo, C.O. (1994) Zinc Finger Phage: Affinity Selection of Fingers with New DNA-Binding Specificities. **Science** **263**, 671-673.
49. Raumann, B.E., Rould, M.A., Pabo, C.O. & Sauer, R.T. (1994) DNA Recognition by  $\beta$ -sheets in the Arc Repressor-Operator Crystal Structure. **Nature** **367**, 754-757.
50. Klemm, J.D., Rould, M.A., Aurora, R., Herr, W. & Pabo, C.O. (1994) Crystal Structure of the Oct-1 POU Domain Bound to an Octamer Site: DNA Recognition with Tethered DNA-Binding Modules. **Cell** **77**, 21-32.
51. Ma, P.C.M., Rould, M.A., Weintraub, H. & Pabo, C.O. (1994) Crystal Structure of MyoD bHLH Domain-DNA Complex: Perspectives on DNA Recognition and Implications for Transcriptional Activation. **Cell** **77**, 451-459.
52. Nekludova, L. & Pabo, C.O. (1994) Distinctive DNA Conformation with Enlarged Major Groove Is Found in Zn Finger-DNA and Other Protein-DNA Complexes. **Proc. Natl. Acad. Sci., USA**, **91**, 6948-6952.
53. Clarke, N.D., Kissinger, C.R., Desjarlais, J., Gilliland, G.L., & Pabo, C.O. (1994) Structural Studies of the Engrailed Homeodomain. **Prot. Sci.** **3**, 1779-1787.
54. Pomerantz, J.L., Sharp, P.A., & Pabo, C.O. (1995) Structure-Based Design of Transcription Factors. **Science** **267**, 93-96.
55. Xu, W., Rould, M.A., Jun, S., Desplan, C., & Pabo, C.O. (1995) Crystal Structure of a Paired Domain-DNA Complex at 2.5 Å Resolution Reveals Structural Basis for Pax Developmental Mutations. **Cell** **80**, 639-650.
56. Pomerantz, J.L., Pabo, C.O., & Sharp, P.A. (1995) Analysis of Homeodomain Function by Structure-Based Design of a Transcription Factor. **Proc. Natl. Acad. Sci., USA** **92**, 9752-9756.
57. Klemm, J.D. & Pabo, C.O. (1996) Oct-1 POU Domain-DNA Interactions: Cooperative Binding of Isolated Subdomains and Effects of Covalent Linkage. **Genes & Development** **10**, 27-36.
58. Rebar, E.J., Greisman, H.A., & Pabo, C.O. (1996) Phage Display Methods for Selecting Zinc Finger Proteins with Novel DNA-Binding Specificities. **Methods In Enzymology** **267**, 129-149.
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64. Pomerantz, J.L., Wolfe, S.A., & Pabo, C.O. (1998) Structure-Based Design of a Dimeric Zinc Finger Protein. **Biochemistry** **37**, 965-970.
65. Kim, J.-S. & Pabo, C.O. (1998) Getting a Handhold on DNA: Design of Poly-Zinc Finger Proteins with Femtomolar Dissociation Constants. **Proc. Natl. Acad. Sci. USA** **95**, 2812-2817.
66. Elrod-Erickson, M., Benson, T.E., & Pabo, C.O. (1998) High-Resolution Structures of Variant Zif268-DNA Complexes: Implications for Understanding Zinc Finger-DNA Recognition. **Structure** **6**, 451-464.
67. Fraenkel, E. & Pabo, C.O. (1998) Comparison of X-ray and NMR Structures for the Antennapedia Homeodomain-DNA Complex. **Nature Struct. Bio.** **5**, 692-697.
68. Fraenkel, E., Rould, M.A., Chambers, K.A., & Pabo, C.O. (1998) Engrailed Homeodomain-DNA Complex at 2.2 Å Resolution: A Detailed View of the Interface and Comparison with Other Engrailed Structures. **J. Mol. Biol.** **284**, 351-361.
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## PATENTS

### Protein Translocation

Frankel, A., Pabo, C.O., Barsoum, J.G., Fawell, S.E., Pepinsky, and Blake, R. (inventors for the first six patents listed below):

**Nucleic Acids Encoding and Methods of Making Tat-derived Transport Polypeptides** (US patent #5,652,122; issued in 1997)

**Nucleic Acid Conjugates of Tat-derived Transport Polypeptides** (US patent #5,670,617; issued in 1997)

**Fusion Protein Comprising Tat-derived Transport Moiety** (US patent #5,674,980; issued in 1997)

**Tat-derived Transport Polypeptide Conjugates** (US patent #5,747,641; issued in 1998)

**Tat-derived Transport Polypeptides and Fusion Proteins** (US patent #5,804,604; issued in 1998)

**Tat-derived Transport Polypeptides** (US patent #6,316,003; issued in 2001)

### Design of DNA-Binding Proteins

Rebar, E.J. and Pabo, C.O. --- **Zinc Finger Proteins with High Affinity New DNA Binding Specificities** (US patent #5,789,538; issued in 1998)

Pomerantz, J.L., Sharp, P.A., and Pabo, C.O. --- **Chimeric DNA-Binding Proteins** (US patent #6,326,166; issued in 2001; US patent #7,008,780; issued in 2006; US patent #7,485,441; issued in 2009; and US patent #7,763,446; issued in 2010)

Greisman, H.A. and Pabo, C.O. --- **General Strategy for Selecting High-Affinity Zinc Finger Proteins for Diverse DNA Target Sites** (US patent #6,410,248; issued in 2002)

Kim, J-S. and Pabo, C.O. --- **Poly Zinc Finger Proteins with Improved Linkers** (US patent #6,479,626; issued in 2002; US patent #6,903,185; issued in 2005; US patent #7,595,376; issued in 2009; and US patent #7,928,195; issued in 2011)

Kim, J-S. and Pabo, C.O. --- **Nucleic Acid Encoding Poly-Zinc Finger Proteins with Improved Linkers** (US patent #7,153,949; issued in 2006)

Joung, J.K., Miller, J., and Pabo, C.O. --- **Methods and Compositions for Interaction Trap Assays** (US patent #7,029,847; issued in 2006; US patent #7,297,491; issued in 2007; and US patent #7,393,318; issued in 2008)

Miller, J., Guofu, L., Pabo, C.O., and Collingwood, T. --- **Simultaneous Modulation of Multiple Genes** (US patent #7,361,635; issued in 2008 and US patent #7,939,327; issued in 2011)

Joung, J.K., Miller, J., and Pabo, C.O. --- **Methods and Compositions for Interaction Trap Assay** (US patent #7,393,318; issued in 2007)

Fyodor, U., Holmes, M.C., Miller, J.C., and Pabo, C.O. --- **Methods and Composition for Targeted Cleavage and Recombination** (US patent #9,289,451; issued in 2016; US patent #7,888,121; issued in 2011 and US patent #8,524,500; issued in 2013)

Wang, B.S. and Pabo, C.O. --- **Dimerizing Peptides** (US patent #7,943,731; issued in 2011)