

Fran Perler, Ph.D.
Senior Scientist, Division of Chemical Biology

Research Interests:

My group works on various aspects of intein-mediated protein splicing. We study the mechanism of protein splicing, intein motifs, intein evolution and intein applications. I also curate InBase, the on-line intein database. Previously, I cloned Vent DNA polymerase and my group has cloned and characterized several other archaeal DNA polymerases.

Selected Publications:

1. Perler, F. B., Comb, D. G., Jack, W. E., Moran, L. S., Qiang, B., Kucera, R. B., Benner, J., Slatko, B. E., Nwankwo, D. O., Hempstead, S. K., et al. (1992) Intervening sequences in an Archaea DNA polymerase gene. *Proc. Natl. Acad. Sci. USA* 89: 5577-5581.
2. Hodges, R. A., Perler, F. B., Noren, C. J., and Jack, W. E. (1992) Protein splicing removes intervening sequences in an archaea DNA polymerase. *Nucl. Acids Res.* 20: 6153-6157.
3. Xu, M. Q., Southworth, M. W., Mersha, F. B., Hornstra, L. J., and Perler, F. B. (1993) In vitro protein splicing of purified precursor and the identification of a branched intermediate. *Cell* 75: 1371-1377.
4. Xu, M. Q., Comb, D. G., Paulus, H., Noren, C. J., Shao, Y., and Perler, F. B. (1994) Protein splicing: an analysis of the branched intermediate and its resolution by succinimide formation. *EMBO J.* 13: 5517-5522.
5. Perler, F. B., Davis, E. O., Dean, G. E., Gimble, F. S., Jack, W. E., Neff, N., Noren, C. J., Thorner, J., and Belfort, M. (1994) Protein splicing elements: inteins and exteins--a definition of terms and recommended nomenclature. *Nucl. Acids Res.* 22: 1125-1127.
6. Adams, M. W. W., Perler, F. B., and Kelly, R. M. (1995) Extremozymes: Expanding the limits of biocatalysis. *Biotechnology* 13: 662-668.
7. Perler, F. B., Southworth, M. W., Wilbur, D. G., and Wallace, D. (1995) Typing marine vent thermophiles by DNA polymerase restriction fragment length polymorphisms. In: *Archaea A Laboratory Manual*, F.T. Robb and A.R. Place, eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory Press), Vol. 3, pp. 139-147.
8. Perler, F. B., Kumar, S. and Kong, H. (1996) Thermostable DNA Polymerases In: *Enzymes and Proteins from Hyperthermophilic Microorganisms*, *Adv. Protein Chemistry*, ed. Adams, M. W. W. (Academic Press, New York), Vol. 48 pp. 377-435.
9. Southworth, M. W., Kong, H., Kucera, R. B., Ware, J., Jannasch, H. W. Perler, F. B. (1996) Cloning of thermostable DNA polymerases from hyperthermophilic marine Archaea with emphasis on *Thermococcus sp. 90N-7* and mutations affecting 3'-5' exonuclease activity. *Proc. Natl. Acad. Sci. USA* 93: 5281-5285.
10. Xu, M., and Perler, F. B. (1996) The Mechanism of protein splicing and its modulation by Mutation. *EMBO J.* 15: 5146-5153.
11. Chong, S., Shao, Y., Paulus, H., Benner, J., Perler, F.B., and Xu, M. (1996) Protein splicing involving the *Saccharomyces cerevisiae* VMA intein: The steps in the splicing

- pathway, side reactions leading to protein cleavage and establishment of an in vitro splicing system. *J. Biol. Chem.* 271: 22159-22168.
12. Perler, F. B., Olsen, G. J., and Adam, E. (1997) Compilation and analysis of intein sequences. *Nucl. Acids Res.* 25: 1087-1093.
 13. Chong, S., Mersha, f.b., Comb, D.G., Scott, M.E., Landry, D., Vence, L.M., Perler, F.B., Benner, J., Kucera, R.B., Hirvonen, C.A., Pelletier, J.J., Paulus, H., and Xu, M. (1997) Single-column purification of free recombinant proteins using a self-cleavable affinity tag derived from a protein splicing element. *Gene* 192: 271-281.
 14. Perler, F. B., Xu, M.-Q. and Paulus, H. (1997) Protein splicing and autoproteolysis mechanisms. *Curr. Opin. Chem. Biol.* 1: 292-299.
 15. Telenti, A., Southworth, M., Alcaide, F., Daugelat, S., Jacobs, W. R., and Perler, F. B. (1997) The *Mycobacterium xenopi* GyrA protein splicing element: characterization of a minimal intein. *J. Bact.* 179: 6378-6382.
 16. Perler, F. B. (1998) Protein Splicing of inteins and hedgehog autoproteolysis: structure, function and evolution. *Cell* 92: 1-4.
 17. Southworth, M.W., Adam, E., Panne, D., Byer, R., Kautz, R., and Perler, F.B. (1998) Control of Protein Splicing by Intein Fragment Reassembly. *EMBO J.* 17: 918-926.
 18. Perler, F. B. (1998) Breaking up is easy with esters [news]. *Nat. Struct. Biol.* 5: 249-252.
 19. Perler, F. B. (1999) InBase: The NEB Intein Database. *Nucl. Acids Res.* 27: 346-347.
 20. Southworth, M. W., Amaya, K., Evans, T. C., Xu, M., and Perler, F. B. (1999) Purification of proteins fused to either the N- or C-terminus of the *Mycobacterium xenopi* gyrase A intein. *BioTechniques* 27: 110-120.
 21. Perler, F. B. (1999) A natural example of protein trans-splicing. *TIBS* 24: 209-210.
 22. Noren, C.J., Wang, J. and Perler, F. B. (2000) Dissecting the Chemistry of Protein Splicing and its Applications. *Angew Chem Int Ed.* 39: 450-466.
 23. Chen, L. Benner, J. and Perler, F. B. (2000) Protein splicing in the absence of an intein penultimate histidine. *J. Biol. Chem.* 275: 20431-20435.
 24. Adam, E. and Perler, F. B. (2000) Protein splicing and its applications. *Curr. Opin. Biotech.* 11: 377-383.
 25. Southworth, M.W., Benner, J. and Perler, F.B. (2000) An Alternative Protein Splicing Mechanism for Inteins Lacking an N-terminal Nucleophile. *EMBO J.* 19: 5019-5026.
 26. Perler, F. B. (2001) Hyperthermophilic inteins. *Methods Enzymol.* 334: 270-280.
 27. Giriat, I., Muir, T. W., and Perler, F. B. (2001) Protein splicing and its applications. *Genet. Eng. (NY)* 23: 171-199.
 28. Southworth, M. W., Amaya, K., Evans, T. C., Xu, M. Q., and Perler, F. B. (2001) Purification of proteins fused to either the amino or carboxy terminus of the *Mycobacterium xenopi* gyrase A intein. In: *Cloning and Expression Vectors for Gene Function Analysis*, Q. Lu and M. Weiner, eds. (Westborough: Eaton Publishing), pp. 55-59.

29. Perler, F.B. (2002). InBase, The Intein Database. *Nucl. Acids Res.* 30: 383-384.
30. Adam, E. and Perler, F.B. (2002) Development of a Positive Genetic Selection System for Inhibition of Protein Splicing using Mycobacterial Inteins in *Escherichia coli* DNA Gyrase Subunit A. *J. Mol. Micro. Biotechnol.* 4: 479-487.
31. Hall, M., Noren, C., Perler, F. and Schildkraut, I. (2002) Creation of an Artificial Bifunctional Intein by Grafting a Homing Endonuclease into a Mini-intein. *J. Mol. Biol.* 323: 173-179.
32. Southworth, M. W. and Perler, F.B. (2002) Protein Splicing of the *Deinococcus radiodurans* Strain R1 Snf2 Intein. *J. Bacteriol.* 184: 6387-6388.
33. Chong, S. and Perler, F.B. (2003) Intein-mediated Protein Purification In: *Methods & Tools in Biosciences & Medicine*, M. Blot, Ed.,(Birkhauser Verlag,Basel/Switzerland) pp.173-193.
34. Maurice W. Southworth, Jianning Yin and F. B. Perler (2004) Rescue of protein splicing activity from a *Magnetospirillum magnetotacticum* intein-like element. *Biochem. Soc. Trans.* 32: 250-254.
35. Cann, I. K. O., Amaya, K. R. Southworth, M. W. and Perler, F.B. (2004) Bacteriophage-based genetic system for selection of non-splicing inteins. *Appl. Environ. Microbiol.* 70: 3158-3162.
36. Perler, F.B. (2004) The ins and outs of gene expression control. *Nat Biotechnol.* 22: 824-826.
37. Perler, F.B. (2005) Inteins - a historic perspective, In *Homing Endonucleases and Inteins*, Eds. Belfort, M., Derbyshire, V., Stoddard, B.L. and Wood, D.W., (Springer-Verlag, Heidelberg, Germany) pp. 193-210.
38. Mills, K.V. and Perler, F. B. (2005) The mechanism of intein-mediated protein splicing: variations on a theme. *Protein and Peptide Letters* 12: 751-755.
39. Perler, F. B. (2005) Protein splicing mechanisms and applications. *IUBMB Life* 57: 469-476.
40. Perler, F. B. (2006) Protein splicing mechanisms and applications. *IUBMB Life* 58: 63.
41. Saleh, L., and Perler, F. B. (2006) Protein splicing in cis and in trans. *Chem. Rec.* 6: 183-193.
42. Perler, F. B. (2007) Shining a light on protein expression in living organisms. *Nature Chem. Biol.* 3: 17-18.
43. Johnson, M.A., Southworth, M.W., Herrmann, T., Brace, L., Perler, F.B. and Wüthrich, K. (2007) Solution Structure of a KlbA Intein Precursor from *Methanococcus jannaschii*. *Protein Science* 16: 1316-1328.

Selected Patents:

1. Comb, D. G., Perler, F. B., Kucera, R. and Jack, W. E. Purified thermostable DNA polymerase obtainable from *Thermococcus litoralis*.

2. Comb, D. G., Perler, F. B., Kucera, R. and Jack, W. E. Recombinant thermostable DNA polymerase from archaebacteria.
3. Comb, D. G., Perler, F. B., Jack, W.E., Xu, M., Hodges, R. A. Modification of proteins by use of a controllable intervening protein sequence.
4. Perler, F.B., and Southworth, M.W. Thermostable DNA polymerase from 9oN-7 and methods for producing the same.
5. Comb, D. G., Perler, F. B., Jack, W.E., Xu, M., Hodges, R. A., Noren, C.J., Chong, S.S., Adam, E., Southworth, M.W. Modified proteins comprising controllable intervening protein sequences or their elements, methods of producing same and methods for purification of a target protein comprised by a modified protein.
6. Carlow, C.K.S., Perler, F. B., Hong, X. and Mejia, J.S. Methods for immunodiagnosis of heartworm in mammals.
7. Perler, F.B. and Adam, E. Screening and use of reagents which block or activate intein splicing utilizing natural or homologous exteins
8. Carlow, C.K.S., Perler, F. B., Hong, X. and Mejia, J.S. DNA and Protein from *Dirofilaria immitis*.