

Asilomar

David Baltimore

Caltech

18 July 2017

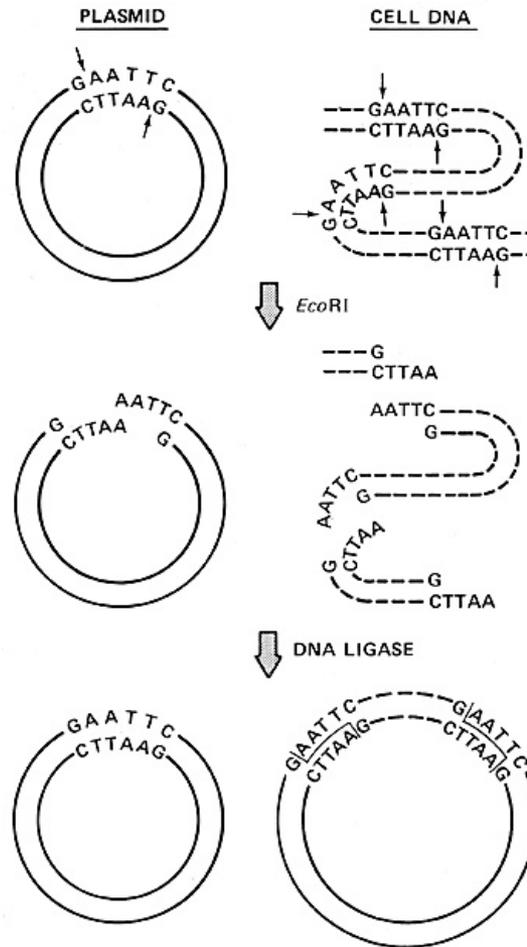
Asilomar

- Took place in Feb of 1975 making it more than 40 years since the meeting
- Was a landmark in social responsibility of scientists because it involved a group of scientists grappling with their responsibility to society
- How did it come about, how was it organized and what does it tell us about handling future events in biomedical science?

Path to Asilomar

- Before 1973 we knew that all organisms used a chemical polymer, DNA, to store their instructions.
- Up to 1973 we could isolate DNA and break it up with restriction enzymes. Some left sticky ends and could be rejoined. At Gordon Conference in summer of 1973, Herb Boyer described his experiments with Stanley Cohen of putting together molecules from disparate sources as plasmids that could be propagated.
- Recombinant DNA was born

Joining of a Plasmid and with a Fragment of Cell DNA Using EcoR1 Cuts



Path to Asilomar II

- The Cohen-Boyer experiments generated huge excitement among molecular biologists
- It took little imagination to see that Recombinant DNA Technology would enable understanding of biology in great detail, it was only a matter of hard work
- It also would enable pharmaceutical development, new kinds of agriculture and new methods of chemical production, creating new industries.

Path to Asilomar III

- However, scientists at the Gordon Conference began imagining that Recombinant DNA Technology might create dangerous, self-propagating plasmids.
 - For instance, ones encoding toxins or antibiotic resistance or cancer-inducing genes
- The organizers of the meeting, Maxine Singer and Dieter Soll, agreed to send a letter to the NAS, which was printed in Science magazine, warning of this danger

Science 181, 1114 (1973): To the President of the NAS

We are writing to you, on behalf of a number of scientists, to communicate a matter of deep concern. Several of the scientific reports presented at this year's Gordon research Conference on Nucleic Acids (June 11-15, 1973, New Hampton, New Hampshire) indicated that we presently have the technical ability to join together, covalently, DNA molecules from diverse sources. Scientific developments over the past two years make it both reasonable and convenient to generate overlapping sequence homologies at the termini of different DNA molecules. The sequence homologies can then be used to combine the molecules by Watson-Crick hydrogen bonding. Application of existing methods permits subsequent covalent linkage of such molecules. This technique could be used, for example, to combine DNA from animal viruses with bacterial DNA, or DNA's of different viral origin might be so joined. **In this way new kinds of hybrid plasmids or viruses, with biological activity of unpredictable nature, may eventually be created.** These experiments offer exciting and interesting potential both for advancing knowledge of fundamental biological processes and for alleviation of human health problems.

Certain such hybrid molecules may prove hazardous to laboratory workers and to the public. Although no hazard has yet been established, **prudence suggests that the potential hazard be seriously considered.**

A majority of those attending the Conference voted to communicate their concern in this matter to you and to the President of the Institute of Medicine (to whom this letter is also being sent). The conferees suggested that **the Academies establish a study committee to consider this problem and to recommend specific actions or guidelines**, should that seem appropriate. Related problems such as the risks involved in current large-scale preparation of animal viruses might also be considered.

Maxine Singer

*Room 9N-119, Building 10,
National Institutes of Health,
Bethesda, Maryland 20014*

Dieter Soll

*Department of Molecular Biophysics
and Biochemistry
Yale University,
New Haven, Connecticut 06520*

Path to Asilomar IV

- NAS was slow to respond but Paul Berg called a few people and put together an ad hoc committee
- I got the call and helped to organize a response
- NAS finally made us a committee of the NAS
- We produced a statement in a day of meetings with the revolutionary request of the scientific community to honor a voluntary moratorium on certain types of experiments

Science 185. 303 (1974)

First, and most important, that until the potential hazards of such recombinant DNA molecules have been better evaluated or until adequate methods are developed for preventing their spread, scientists throughout the world join with members of this committee in voluntarily deferring the following types of experiments:

Type 1: **Construction of new, autonomously replicating bacterial plasmids that might result in the introduction of genetic determinants for antibiotic resistance or bacterial toxin formation into bacterial strains that do not at present carry such determinants;** or construction of new bacterial plasmids containing combinations of resistance to clinically useful antibiotics unless plasmids containing such combinations of antibiotic resistance determinants already exist in nature.

Type 2: **Linkage of all or segments of the DNA' s from oncogenic (tumor-causing) or other animal viruses to autonomously replicating DNA elements such as bacterial plasmids or other viral DNA' s.** Such recombinant DNA molecules might be more easily disseminated to bacterial populations in humans and other species, and thus possibly increase the incidence of cancer or other diseases.

Second, plans to **link fragments of animal DNA' s to bacterial plasmid DNA or bacteriophage DNA should be carefully weighed in light of the fact that many types of animal cell DNA' s contain sequences common to RNA tumor viruses.** Since joining of any foreign DNA to a DNA replication system creates new recombinant DNA molecules whose biological properties cannot be predicted with certainty, such experiments should not be undertaken lightly.

Third, the director of the National Institutes of Health is requested to give immediate consideration to establishing an advisory committee charged with (i) overseeing an experimental program to evaluate the potential biological and ecological hazards of the above types of recombinant DNA molecules ; (ii) developing procedures which will minimize the spread of such molecules within human and other populations; and (iii) devising guidelines to be followed by investigators working with potentially hazardous recombinant DNA molecules.

Fourth, an international meeting of involved scientists from all over the world should be convened early in the coming year to review scientific progress in this area and to further discuss appropriate ways to deal with the potential biohazards of recombinant DNA molecules.

The above recommendations are made with the realization (i) that our concern is based on judgments of potential rather than demonstrated risk since there are few available experimental data on the hazards of such DNA molecules and (ii) that adherence to our major recommendations will entail postponement or possibly abandonment of certain types of scientifically worthwhile experiments. Moreover, we are aware of many theoretical and practical difficulties involved in evaluating the human hazards of such recombinant DNA molecules. Nonetheless, our concern for the possible unfortunate consequences of indiscriminate application of these techniques motivates us to urge all scientists working in this area to join us in agreeing not to initiate experiments of types 1 and 2 above until attempts have been made to evaluate the hazards and some resolution of the outstanding questions has been achieved.

Paul Berg, Chairman; David Baltimore, Herbert W. Boyer, Stanley N. Cohen, Ronald W. Davis, David S. Hogness, Daniel Nathans, Richard Roblin, James D. Watson, Sherman Weissman, Norton D. Zinder

Committee on Recombinant DNA Molecules Assembly of Life Sciences; National Research Council, National Academy of Sciences, Washington, D.C. 20418

Path to Asilomar V

- Remarkably, the moratorium was universally honored and no violation was ever known to have occurred except in the USSR
- The organizing committee for the proposed was constituted from the previous group along with Sydney Brenner, to make it international
- It proposed a meeting at Asilomar

The Asilomar Meeting

- Asilomar is a conference center on the coast of California that was used by many institutions around the Bay Area for retreats
- There was predecessor meeting on the safety of experiments in animal virology that was held there
- Thus, it was natural to book the conference into Asilomar



The Meeting Building at Asilomar



The Asilomar Meeting II

- Meeting was 3.5 days long
- Sessions on much of the relevant science to the question of what dangers might be posed by going ahead with Recombinant DNA experiments
- Papers were drawn up by experts ahead of time to provide material for discussion
- About 140 people from around the world attended
- The international nature was key: there is no body that can make countries follow guidelines

The Asilomar Meeting III

- Attendees were mostly scientists, many bacteriologists
- Also had government officials, lawyers, ethicists, 16 science reporters
- Agreed that no reporting until it was over
- Questions of human gene alteration, biological warfare were left for the future. Science ruled.
- Organizing committee met over the last night and drafted a statement
- Voted upon by the attendees; only few No votes

Some of the Organizing Committee at Asilomar



Singer, Zinder, Brenner and Berg





assembly of the oligosaccharide-lipid, little is yet known about the membrane glycoproteins, and possibly secretory glycoproteins, that are formed via this pathway. The elucidation of the structure and the function of these glycoproteins remains as a formidable challenge to biochemists and cell biologists.

Note added in proof: Very recently, experiments with intact oviduct cells in suspension (41) showed that the surface of these cells contains enzymes that catalyze synthesis of both mannosyl phosphoryl dolichol and oligosaccharide-lipid from exogenous GDP-mannose. In relation to the question of the participation of lipid linked intermediates in glycosylation of secretory glycoproteins, evidence indicating that this may indeed be so in the case of the kappa-type immunoglobulin light chain has very recently been reported (42).

References and Notes

1. R. Caputto, L. F. Leloir, C. E. Cardini, A. Paladini, *J. Biol. Chem.* **184**, 333 (1950).
2. J. S. Anderson, M. Matsubashi, M. A. Haskin, J. L. Strominger, *Proc. Natl. Acad. Sci. U.S.A.* **53**, 881 (1965); I. M. Weiner, T. Higuchi, L. Rothfield, M. Saltmarsh-Andrew, M. J. Osborn, B. L. Ho-rocker, *ibid.* **54**, 228 (1965); A. Wright, M. Dankert, P. W. Robbins, *ibid.*, p. 235.
3. For a review see W. J. Lennarz and M. G. Scher, *Biochim. Biophys. Acta Rev.* **265**, 47 (1972).
4. M. J. Osborn and J. M. Weiner, *J. Biol. Chem.* **243**, 2631 (1968), and references cited therein.
5. E. C. Heath, *Annu. Rev. Biochem.* **40**, 29 (1971); L. F. Leloir, *Science* **172**, 1299 (1971).

Asilomar Conference on Recombinant DNA Molecules*

Paul Berg, David Baltimore, Sydney Brenner, Richard O. Roblin III, Maxine F. Singer

I. Introduction and General Conclusions

This meeting was organized to review scientific progress in research on recombinant DNA molecules and to discuss appropriate ways to deal with the potential biohazards of this work. Impressive scientific achievements have already been made in this field, and these techniques have a remarkable potential for furthering our understanding of fundamental biochemical processes in pro- and eukaryotic cells. The use of recombinant DNA methodology

promises to revolutionize the practice of molecular biology. Although there has as yet been no practical application of the new techniques, there is every reason to believe that they will have significant practical utility in the future.

Of particular concern to the participants at the meeting was the issue of whether the pause in certain aspects of research in this area, called for by the Committee on Recombinant DNA Molecules of the National Academy of Sciences in the letter published in July 1974 (*J.*), should end, and,

6. F. W. Hemming, in *Biochemistry*, series 1, volume 4, *Biochemistry of Lipids*, T. W. Goodwin, Ed. (University Park Press, Baltimore, Maryland, 1973), pp. 39-57.
7. N. H. Behrens and L. F. Leloir, *Proc. Natl. Acad. Sci. U.S.A.* **66**, 153 (1970).
8. J. Burgos, F. W. Hemming, J. F. Furnock, R. A. Morton, *Biochem. J.* **88**, 470 (1963).
9. J. B. Richards and F. W. Hemming, *ibid.*, **128**, 1245 (1972).
10. P. H. W. Butterworth and F. W. Hemming, *Arch. Biochem. Biophys.* **128**, 503 (1968).
11. G. Dallner, N. H. Behrens, A. J. Parodi, L. F. Leloir, *FERS (Fed. Eur. Biochem. Soc.) Lett.* **24**, 315 (1972).
12. N. H. Behrens, A. J. Parodi, L. F. Leloir, C. R. Krisman, *Arch. Biochem. Biophys.* **143**, 375 (1971); J. D. Richards, P. J. Evans, F. W. Hemming, *Biochem. J.* **124**, 957 (1971).
13. C. J. Waechter, J. J. Lucas, W. J. Lennarz, *Biochem. Biophys. Res. Commun.* **56**, 343 (1974).
14. L. F. Leloir, R. J. Stanoloni, H. Carminatti, N. H. Behrens, *ibid.* **52**, 1285 (1973).
15. J. Molnar, H. Chao, Y. Ikebara, *Biochim. Biophys. Acta* **239**, 401 (1971); M. A. Ghalambor and R. W. Jeanloz, *Fed. Proc.* **33**, 1368 (1974).
16. J. B. Richards and F. W. Hemming, *Biochem. J.* **130**, 77 (1972).
17. J. W. Baynes, A. F. Hsu, E. C. Heath, *J. Biol. Chem.* **248**, 5693 (1973).
18. P. J. Evans and F. W. Hemming, *FERS (Fed. Eur. Biochem. Soc.) Lett.* **31**, 335 (1973).
19. C. D. Warren and R. W. Jeanloz, *ibid.*, p. 332.
20. L. DeLuca, N. Maesini, G. Rosso, G. Wolf, *J. Biol. Chem.* **248**, 641 (1973).
21. N. H. Behrens, A. J. Parodi, L. F. Leloir, *Proc. Natl. Acad. Sci. U.S.A.* **68**, 2857 (1971); A. J. Parodi, N. H. Behrens, L. F. Leloir, M. Dankert, *Biochim. Biophys. Acta* **270**, 529 (1972).
22. A. J. Parodi, R. Stanoloni, A. I. Cantarella, L. F. Leloir, N. H. Behrens, H. Carminatti, J. A. Levy, *Carbohydr. Res.* **26**, 393 (1973).
23. A. J. Parodi, N. H. Behrens, L. F. Leloir, H. Carminatti, *Proc. Natl. Acad. Sci. U.S.A.* **69**, 3268 (1972).
24. C. J. Waechter, J. J. Lucas, W. J. Lennarz, *J. Biol. Chem.* **248**, 7570 (1973).
25. N. H. Behrens, H. Carminatti, R. J. Stanoloni, L. F. Leloir, A. I. Cantarella, *Proc. Natl. Acad. Sci. U.S.A.* **70**, 3390 (1973); N. H. Behrens, in *Biology and Chemistry of Eukaryotic Cell Surfaces*, E. Y. C. Lee and E. E. Smith, Eds. (Academic Press, New York, 1974), p. 159.
26. A. F. Hsu, J. W. Baynes, E. C. Heath, *Proc. Natl. Acad. Sci. U.S.A.* **71**, 2391 (1974); E. C. Heath, J. W. Baynes, A. F. Hsu, in *Biology and Chemistry of Eukaryotic Cell Surfaces*, E. Y. C. Lee and E. E. Smith, Eds. (Academic Press, New York, 1974), p. 181.
27. J. J. Lucas, C. J. Waechter, W. J. Lennarz, *J. Biol. Chem.*, in press.
28. W. W. Chen, W. J. Lennarz, A. L. Tarentino, F. Maley, *ibid.*, in press.
29. A. Tarentino, T. H. Plummer, Jr., F. Maley, *ibid.* **245**, 4150 (1970); C. C. Huang and R. Montgomery, *Fed. Proc.* **31**, 466 (1972); L. Kibasawa and C. H. W. Hirs, *J. Biol. Chem.* **247**, 1610 (1972); Y. C. Lee and J. R. Socca, *ibid.*, p. 5753.
30. T. Kawasaki, K. Sugahara, Y. Okamura, I. Yamashita, *J. Biochem. (Tokyo)* **75**, 437 (1974).
31. J. A. Levy, H. Carminatti, A. I. Cantarella, N. H. Behrens, L. F. Leloir, E. Tabora, *Biochem. Biophys. Res. Commun.* **60**, 118 (1974).
32. S. F. Wedgewood, C. D. Warren, R. W. Jeanloz, J. L. Strominger, *Proc. Natl. Acad. Sci. U.S.A.* **71**, 5022 (1974).
33. D. D. Pless and W. J. Lennarz, *J. Biol. Chem.*, in press.
34. P. J. O'Brien and E. F. Neufeld, in *Glycoproteins*, A. Gottschalk, Ed. (Elsevier, New York, 1972), p. 1186; H. Clouser, C. Herman, B. Rossignol, S. Harbor, *ibid.*, p. 1151.
35. G. L. Nicholson and S. J. Singer, *J. Cell Biol.* **60**, 236 (1974).
36. S. Roth, E. J. McGuire, S. Roseman, *ibid.* **51**, 536 (1971); S. Roth and D. White, *Proc. Natl. Acad. Sci. U.S.A.* **69**, 485 (1972); H. B. Bosman, *Biochem. Biophys. Res. Commun.* **48**, 523 (1972).
37. D. Arnold, E. Hummel, H. J. Risse, *Biochem. Biophys. Res. Commun.* **54**, 100 (1973).
38. L. M. Patt and W. J. Grimes, *J. Biol. Chem.* **249**, 4157 (1974).
39. D. Struck and W. J. Lennarz, unpublished studies.
40. S. Roseman, *Chem. Phys. Lipids* **5**, 270 (1970); in *Biology and Chemistry of Eukaryotic Cell Surfaces*, E. Y. C. Lee and E. E. Smith, Eds. (Academic Press, New York, 1974) p. 317.
41. D. Struck and W. J. Lennarz, *Fed. Proc.* **34**, 678 (1975).
42. P. K. Eagon, A. F. Hsu, E. C. Heath, *ibid.*, p. 678.
43. Supported by grant AI06888 from the National Institutes of Health.

if so, how the scientific work could be undertaken with minimal risks to workers in laboratories, to the public at large, and to the animal and plant species sharing our ecosystems.

The new techniques, which permit combination of genetic information from very different organisms, place us in an area of biology with many unknowns. Even in the present, more limited conduct of research in this field, the evaluation of potential biohazards has proved to be extremely difficult. It is this ignorance that has compelled us to conclude that it would be wise to exercise considerable caution in performing this research. Nevertheless, the participants at the Conference agreed that most of the work on construction of recombinant DNA molecules should proceed, provided that appropriate safeguards, principally biological and physical barriers adequate to contain the newly created organisms, are employed. Moreover, the standards of protection should be

*Summary statement of the report submitted to the Assembly of Life Sciences of the National Academy of Sciences and approved by its Executive Committee on 20 May 1975.

Post-Asilomar

- Major question for Asilomar was whether to continue the moratorium
- Answer was embedded in a more general recommendation that perceived risk be balanced by increased containment, both biological and physical
- The Guidelines and RAC were an embodiment of that calculus.
- But we had little experience to draw on; there were great areas of ignorance.

Post-Asilomar II

- The ignorance provided opportunities for fantasy. It was a time of great debate about whether there were dangers that required deeper containment and stricter moratoriums; some even wanted no Recombinant DNA work to be performed.
- Looking back, we can see that the Guidelines were overly strict and that we were reacting with the greatest of caution. No danger has ever materialized, even after years of experimentation of all sorts.

Post-Asilomar III

- The importance of Recombinant DNA research is best seen if we look at how it has revolutionized our understanding of cancer. The ability to isolate and characterize oncogenes, suppressor genes and mutated genes has given us a remarkably detailed understanding of the disease that is guiding the development of therapies.
- Key to the development of the research potential was the gradual relaxation of the Guidelines. This was possible because they were not law and were judged by scientists.

Post-Asilomar IV

- A huge benefit of Asilomar was its coverage by the press. This began the education of the public about the power of the new biology. “DNA” went from being an arcane polymer to a fill-in for crossword puzzles.
- Today we debate in public the future of embryo research, synthetic biology, gene editing and the like. We expect the public to care about what we do and we spend long hours informing them.

The “Asilomar Process”

- “Asilomar” has gone from being a conference center to a method of decision-making.
- The Asilomar Process was a mode of experts deciding how to move forward with a new capability.
- Is it the right process for the debates we now have about embryos, gene alteration and other questions?

The “Asilomar Process”

- The questions we face today are religious, ethical and moral. They are not scientists’ questions uniquely. The process for deciding answers needs more involvement of the public, even though that is hard to arrange.
- For gene editing, we had a meeting in December, 2015. It had (relatively) fewer scientists, more representatives of the public. It was a start toward a post-Asilomar Process.