IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Cabilly et al	)	
	)	Interference No. 102,572
v.	)	
	)	Examiner-in-Chief
Boss et al	)	Mary F. Downey
	)	

DECLARATION OF JEANNE PERRY

1. I, L. Jeanne Perry, am a citizen of the United States and reside in Whittier, California. From September 18, 1979 until July 3, 1989, I was employed at Genentech, Inc. (Genentech), located at 460 Point San Bruno Boulevard, South San Francisco, California. For the entire period of my employment at Genentech, I worked under the supervision of Dr. Ron Wetzel. I am currently employed by Whittier College, as a Lecturer in the Department of Biology and am a candidate for the Ph.D. degree from the Molecular Biology Institute at the University of California at Los Angeles. My Curriculum Vitae is attached as Cabilly Exhibit No. 7.

2. My involvement with the immunoglobulin project at Genentech began with a meeting with Dr. Wetzel, as I recall, in December of 1982 or January of 1983. At this meeting, Dr. Wetzel informed me of a conversation he had had with Dr. Herb Heyneker, in which they discussed producing antibodies directed against human carcinoembryonic antigen in E. coli. Dr. Wetzel expressed great interest and invited me to work on the project to which I agreed. According to his conversation with Dr. Heyneker, we would carry out

the purification and refolding of the antibody chains produced from both singly transformed and co-transformed E. coli. He and I then mapped out a strategy for carrying out the purification and refolding of the heavy and light chains.

3. Our strategy to refold the heavy and light chains from singly transformed bacteria was to first purify the refractile bodies from the bacteria, solubilize the protein in denaturant, followed by sulfitolysis. The chains would then be further purified by S300 gel filtration chromatography and possibly DEAE ion-exchange chromatography. The plan was to then reconstitute the antibodies by folding the heavy chain first, adding it to light chain, allowing both chains to fold together and then oxidize the disulfide bonds.

4. It was my general practice to date my notebooks on the date the work was being done. The first notation in my notebook regarding this project is on January 17, 1983 (Cabilly Exhibit No. 8, Bates No. 00136a and 00136b). We had received cell pastes from Michael Mumford, in the the Fermentation Research Department, which we stored in the freezer (Cabilly Exhibit No. 8, Bates No. 00148; Cabilly Exhibit No. 6, Bates No. 00032; Cabilly Exhibit No. 18, Bates Nos. 00701, 00727 and 00730). We used these cell pastes as the source from which to isolate heavy and/or light chain protein.

5. In January of 1983, we started purification of the heavy chain

from E. coli. the first step was to lyse the cells by sonication and then isolate the refractile bodies by centrifugation. The refractile body preparations were checked by SDS-polyacrylamide gel electrophoresis (SDS-PAGE) (Cabilly Exhibit No. 8, Bates Nos. 00142-00144 and 00157).

6. The refractile body preparations were solubilized in guanidine hydrochloride. Dr. Wetzel subjected them to sulfitolysis reactions (Cabilly Exhibit No. 6, Bates No.00035). In January, 1983, I purified heavy chain protein from the guanidine solubilized refractile bodies by gel filtration column chromatography on an S300 column (Cabilly Exhibit No. 8, Bates Nos. 00145-00147, and Cabilly Exhibit No. 6, Bates No. 00035) and analyzed the fractions by the measurement of optical density at a wavelength of 280 nanometers. We further analyzed these fractions by SDS-PAG.. (Cabilly Exhibit No. 8, Bates Nos. 00149-00151,and 00157-00159 and Cabilly Exhibit No. 6, Bates No. 00042). The fractions containing the heavy chain were pooled and separate samples dialyzed int.. several native buffers (Cabilly Exhibit No. 6, Bates No. 00039). Dr. Wetzel and I analyzed the dialyzed materials to determine the solubility of the heavy chain protein in these native buffers (Cabilly Exhibit No. 6, Bates No. 00042; and Cabilly Exhibit No. 8 Bates Nos. 00156-00159).

7. In late January of 1983, Dr. Wetzel and I noticed that there

was a loss of heavy chain protein after the removal of denaturant by dialysis into native buffer. This phenomenon was noted following SDS-PAGE analysis of various samples (Cabilly Exhibit No. 8, Bates Nos. 00157-00159; and Cabilly Exhibit No. 6, Bates No. 00047). I conducted experiments to alleviate proteolysis (Cabilly Exhibit No. 8, Bates Nos. 00160-00161; and Cabilly Exhibit No. 6, Bates No. 00047) which included the addition of PMSF, EDTA, EGTA, and alteration of pH and temperature. I analyzed the results by SDS-PAGE. It was noted that the protease was inactivated by addition of PMSF.

8. We also discovered that we could remove the protease by DEAE ion exchange chromatography. A heavy chain refractile body preparation was sulfitolized by Dr. Wetzel (Cabilly Exhibit No. 6, Bates No. 00049). I analyzed this sample by SDS-PAGE (Cabilly Exhibit No. 8, Bates Nos. 00168-00169) and dialyzed it into a urea buffer (Cabilly Exhibit No. 6, Bates No. 00049). I then loaded this preparation onto a DEAE column and eluted the protein with a sodium chloride gradient (Cabilly Exhibit No. 8, Bates Nos. 00164-00169). Dr. Wetzel made mini-pools of the fractions (Cabilly Exhibit No. 6, Bates No. 00050). These mini-pools were incubated with the peak heavy chain fraction to determine which pool contained the protease (Cabilly Exhibit No. 6, Bates No. 00050). I analyzed the reactions by SDS-PAGE which showed that several of the mini-pools caused degradation of the heavy chain protein (Cabilly Exhibit No.8, Bates Nos. 00170-00173).

9. Light chain protein was purified and treated in an analogous fashion to the heavy chain protein. First, we lysed the frozen bacterial cells by sonication and then the refractile bodies were isolated by centrifugation (Cabilly Exhibit No. 6, Bates Nos. 00034 and 00037; and Cabilly Exhibit No. 8, Bates No. 00148). I analyzed the refractile body preparations by SDS-PAGE (Cabilly Exhibit No. 6, Bates No. 00037; and Cabilly Exhibit No. 8, Bates Nos. 00142-00144 and 00149-00151). Dr. Wetzel subjected the light chain preparations to sulfitolysis reactions. These samples were then dialyzed and loaded on a S300 column. The S300 column fractions were analyzed by optical density and SDS-PAGE. The fractions containing the light chain protein were pooled and dialyzed for subsequent DEAE ion-exchange chromatography. Fractions were analyzed by SDS-PAGE (Cabilly Exhibit No. 6, Bates Nos. 00036-00038 and 00040-00043; and Cabilly Exhibit No. 8, Bates Nos. 00148 and 00152-00154).

10. The strategy to reconstitute immunoglobulin chains also included the comparison of the refolding results of heavy and light chains from the antibodies produced from hybridoma cells. I received a sample of anti-CEA antibodies from Dr. Shmuel Cabilly (Cabilly Exhibit No. 6, Bates No. 00061; and Cabilly Exhibit No. 8, Bates Nos. 00190-00191). This sample was lyophilized, denatured and subjected to sulfitolysis (Cabilly Exhibit No. 6, Bates No. 00061). This sample was used in several refolding studies. Optimal conditions for the refolding of antibody chains from the

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