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(21) International Application Number: PCT/US96/15002 (22) International Filing Date: 18 September 1996 (18.09.96) (30) Priority Data: 60/003,859 18 September 1995 (18.09.95) US (71) Applicant (for all designated States except US): UNITED STATES ARMY MEDICAL RESEARCH MATERIEL COMMAND (USAMRMC) [US/US]; MCMR-JA - John F. Moran, Ft. Detrick, Frederick, MD 21702-5012 (US). (71)(72) Applicant and Inventor: LOWELL, George, H. [US/US]; 6303 Western Run Drive, Baltimore, MD 21215 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): ZOLLINGER, Wendell, D. [US/US]; 14400 Morton Hall Road, Silver Spring, MD 20906 (US). WOOD, James, F. [US/US]; 18223 Smoke House Court, Germantown, MD 20874 (US). (74) Agents: KOKULIS, Paul, N. et al.; Cushman Darby & Cushman, Intellectual Property Group, Pillsbury Madison & Sutro, 1100 New York Avenue, N.W., Washington, DC 20005 (US).	(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report. 9802247-8	
(54) Title: IMPROVED METHODS FOR THE PRODUCTION OF NON-COVALENTLY COMPLEXED AND MULTIVALENT PROTEOSOME SUB-UNIT VACCINES		
(57) Abstract A method for preparing multivalent proteosome-amphiphilic determinant vaccines suitable for parenteral or mucosal administration using diafiltration or ultrafiltration technology. The amphiphilic determinants include lipopolysaccharides from gram negative bacteria, e.g. <i>S. flexneri</i> , <i>P. shigelloides</i> and <i>S. sonnei</i> . Proteosomes are obtained from group B type 2b meningococci. The active proteosome-amphiphilic determinant complexes (non-covalently complexes) of the vaccine are formed using diafiltration or ultrafiltration to remove the detergent. The use of diafiltration or ultrafiltration decreases processing time and the opportunity for contamination and further permits the use of ambient temperature and efficient scale-up. In addition, the process permits the reliable and continuous monitoring of the dialysate which enhances the efficiency of the entire process. The time of dialysis for production of a lot of vaccine is reduced from > 7-10 days to less than 72 hours and usually less than 48 or 24 hours. The use of the process optimizes the presence of each antigenic component in the preparation of multivalent vaccines.		