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關鍵字(中)	血液 蛋白質表現側寫圖譜 單株抗體庫 抗體晶片
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摘要(中)	在臨床診斷上，疾病的檢測常以血液中特定的蛋白質為標的，若能發現專一性與靈敏度高的疾病標的物，則可以實踐早期發現，早期治療的醫學鐵律。近年來，本實驗室已建立了篩選疾病特異性之血液標的蛋白質的作業平台，也成功的自數種疾病中，篩選出幾個可能的血液蛋白質標的物。然而，許多實驗結果顯示，單一蛋白質標的物，有時不能作為準確的診斷依據，而藉由判斷一組蛋白質表現量的蛋白質表現側寫圖譜(protein expression profile)，可能更適合做為臨床診斷的依據。 本實驗室之長程目標在於人類血液蛋白質的抗體晶片開發，除了可產生血液蛋白質表現側寫圖譜，以供臨床診斷分析外，也可鑑定出疾病特定之血液標

	的蛋白身份，作為研究致病機轉的依據。由於抗體晶片為微型化之酵素免疫連結分析法 (ELISA)，因此要生產晶片，必先取得各血液相關抗原蛋白質之單株或多源抗體，其中又以單株抗體之專一性為佳，因此單株抗體之獲得是開發抗體晶片的關鍵步驟。然而利用傳統免疫學方法，需先取得個別抗原分別免疫小鼠，進而以融合瘤技術來篩選所需抗體分泌細胞株，若要獲得數百種以上的單株抗體，此過程不僅花費大量的人力與經費，亦曠日廢時，實不符合研究與應用之需求。因此，本論文主要的目的，就是為了開發出一個高效率、低成本的單株抗體產生方式，我們稱之為單株抗體庫生產平台。 此平台使用混合抗原來免疫一隻小鼠，一次細胞融合的手續，理論上可篩得數十至上百種不同抗原之相對應單株抗體。此法可大幅降低生產成本與時程，非常符合現今高產出的研究特性。然而，傳統單株抗體的生產方式，卻無法直間應用於此抗體庫，單株抗體庫之建構仍必須突破數個技術瓶頸，包括了 (1) 提昇融合瘤細胞存活率、(2) 增加篩選方式之靈敏度，以及 (3) 高效能抗體身分之鑑定平台，才能順利完成。研究過程中，我們已發現了提升融合瘤細胞存活率的最佳條件，其細胞存活率較傳統細胞培養條件高 20 倍以上。此外，最適化後的篩選方式，可以大幅增進獲得微弱反應細胞株的機率。而上述融合瘤細胞株的身份，則可藉由胜?圖譜結合質譜分析方式來鑑定。藉由上述單株抗體生產平台，我們已獲得抗人類血液蛋白質之單株抗體 153 株，部分抗體之相對應抗原之身份已鑑定出，包括人類血液主要蛋白 transferrin、albumin、fibronectin、IgA、?-1 antitrypsin、haptoglobin、IgG kappa light chain 等，其餘抗體身份陸續鑑定中。 此單株抗體生產平台之建立，不僅可以用來產生人類血液蛋白的單株抗體庫，亦可直接應用於所有生物材料的抗體庫置備。現有的單株抗體，將先開發用來去除人類血液主要蛋白之用的免疫親和性吸附管柱，後續將用來生產人類血液蛋白之單株抗體晶片。此單株抗體庫的建構與抗體晶片的開發成功，對於血液蛋白質體學的研究動能，及臨床檢驗之發展，應有非常正面的助益。
摘要(英)	In clinical application, the diagnosis of disease often targets specific proteins in blood. The golden rule, early detection, early treatment, will be successfully accomplished if high specific and sensitive disease markers are identified. In these years, we have established the proteomic platform to screen specific protein markers for disease. Possible blood protein markers have been identified for studied case, such as Parkinson’ s disease. However, more and more reports have shown that single protein markers sometimes can not be a reliable and accurate indicator for diagnosing disease. It is more proper to use “protein expression profile”, which represents the expression patterns of a set of proteins, as the criteria for clinical diagnosis. Our ultimate goal is to develop the antibody chips for human blood proteins, which can be used for generating the protein expression profile for clinical diagnosis and elucidating the possible pathological mechanism of diseases. Basically, antibody chip is a miniature ELISA assays, it is necessary, in advance, to obtain all required antibodies for the chip production. In other words, the production of polyclonal or monoclonal antibodies, therefore, is the key step in the industrial mass production of antibody chips. Generally, it is

	thought that monoclonal antibodies are more specific than polyclonal antibodies. And in most circumstance, the application of using monoclonal antibodies is more reproducible than polyclonal antibodies. Currently, the production of monoclonal antibodies begins from the immunization of mice by specific antigen, generation of hybridoma cells and screen for the positive clones. It has no problem for laboratory if only one or a few antigens are used. However, if monoclonal antibodies against hundreds to thousands of antigen are required, the traditional way would be very labour-, time- and money- consuming. The reduction of cost, both in labour and cost, for generation of large quantity antibodies, is the motivation of our research. In this thesis, we have established a workflow, namely the production platform for antibody bank, for high efficient and low cost production of antibody in large amount. This platform employs a simultaneous immunization of mixtures of different antigens on one mouse. In theory, by only one fusion with myeloma cell with the elicited spleen cells, hundreds of different antibody producing cell lines can be obtained. This process reduces greatly both in labour and cost, and is hence a very applicable method for current high throughput purpose. However, the traditional strategy for monoclonal production can not be adapted directly on our platform. It is required to optimize the condition for (1) increase the survival rate of obtaining hybridoma cell lines, (2) increasing the sensitivity of screening methods, and (3) identifying the obtaining antibodies by high throughput method. In our study, we have optimized the hybridoma growth condition which can increase up to 20 times more viable colonies. We also optimized a sensitive screen procedure that enables us to identify very weak hybridoma clones. The identity of produced hybridoma can be validated by utilization of peptide mapping and mass spectrometry. By employing the established platform, we have identified 153 clones of hybridoma which produce monoclonal antibodies against different human plasm proteins, including transferrin, albumin, fibronectin, IgA, ?-1 antitrypsin, haptoglobin, IgG kappa light chain, and so forth. The identification of other hybridomas is in progress. The established platform for generating monoclonal antibody bank can apply to all biological samples, including human plasma proteins. The obtained monoclonal antibodies against the major proteins in human blood will be used for developing immuno-depletion chromatograph media. In the coming future, it will be also used for fabricate the antibody chip. The success in the development of the production platform for the monoclonal antibody bank and the antibody chip will input tremendous energy into the research of sero-proteomics and clinical diagnosis.
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