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The Medical Promise of Protein Drug Biotechnology

The development and manufacture of medical proteins is an extremely promising field of biotechnology. Besides producing useful proteins, the same research work can reveal new insights on the three-dimensional structure of proteins. This very important field offers synergistic benefits and can pave the way for further biotechnology advances. Many protein drugs are very familiar, including hepatitis vaccines, insulin, interferon, red blood cell growth factor, growth hormone, blood coagulation factor, and thrombolytic factor. The biotechnology methods used to produce these high value products have tremendous industrial potential, and are a focal point for Taiwan's biotechnology research capability.

Many talented researchers are engaged in protein drug biotechnology in Taiwan, and it is a field with a very bright future. The NSC has supported research on thrombolytic factors and related proteins at the National Cheng Kung University College of Medicine for many years. Beginning this year the NSC has worked together with the Department of Health (DOH) and the Ministry of Economic Affairs (MOEA) in conducting the National Program on Biotech Drug Preparation, which includes the investigation of protein structure and function. As this national program proceeds, continued advances will be made in upstream basic research, applied R&D, and downstream drug development. Taiwan's medical protein biotech industry is thus poised to make great strides.

Prof. Wu Hua-Lin of the National Cheng Kung University College of Medicine has performed research on blood clotting enzyme regulators and thrombolytic factors with support from the NSC. What is the significance of this research? In patients with constricted blood vessels, or whose blood vessel lining has suffered damage, clotting often occurs in inappropriate places. For instance, the consequences can be very severe if clotting occurs in one of the body's major organs, most obviously in the case of a heart attack occurring when myocardial infarction starves the heart of blood. If a thrombolytic drug is given to an acute heart attack patient, it can be possible to dissolve the fibrin in the clot in time to restore blood flow. This can prevent the blood-starved muscle cells in the heart from dying in large numbers. Thrombolytic drugs are already in widespread clinical use, and have saved many patients suffering from acute myocardial infarction. At present the most commonly used thrombolytic drugs include tissue-type plasminogen activator (tPA), urokinase-type plasminogen activator (uPA), and streptokinase (SK). While these drugs are all potent thrombolytic agents, they sometimes cause the side effect of abnormal bleeding. Current efforts to improve thrombolytic drugs generally seek to enhance their thrombolytic ability while lessening their tendency to cause bleeding. Prof. Wu's laboratory has studied this field for many years with NSC funding, and, in particular, has performed an indepth investigation of the effects and properties of streptokinase. They have used biotech methods to prepare second-generation thrombolytic drugs, discovered an improved streptokinase offering even better thrombolytic ef-ficacy, and received patents from the US and Taiwan. Their research findings have been reported in international scientific journals. Prof. Wu is currently developing a new type of streptokinase offering improved thrombolytic characteristics. Having demonstrated good results in vitro tests, this streptokinase may serve as the basis of a third-generation thrombolytic drug if it proves effective in animal tests.

Apart from streptokinase, Prof. Wu's laboratory has also prepared an important protein controlling the blood coagulation process, namely thrombin regulator. When this protein binds to thrombin, it completely changes thrombin's effects by transforming it into an anticoagulant, and it also offers anti-inflammatory effects. Thrombin regulator is expressed on the surface of cells in the blood vessel lin-ing, where it exerts an anticoagulant effect and on occasion serves many other functions, such as suppressing platelet coagulation and regulating the growth of blood vessels cells. The production of thrombin regulator decreases during the processes of carcinogenesis and athero-sclerosis. Prof. Wu's laboratory is now using genetic engineering techniques to manufacture large quantities of thrombin regulator for use in some extremely promising drugs. For instance, in a collaborative project with the National Cheng Kung University Chemical Engineering Depart-ment, Prof. Wu's team discovered that thrombin regulator can bind to biomedical materials, showing how the surface treatment of these materials can reduce the adhesion and coagulation of platelets. This approach can be used in the future to prevent platelets from undergoing a coagulation reaction and lessen blood coagulation due to contact with foreign objects. If applied to artificial hearts and blood dialysis equipment, it could enable them to be used for longer periods of time. Prof. Wu is also in the midst of developing other clinical applications of this protein.

Biotechnology, including protein drug R&D, is currently at the heart of international efforts to develop new high-tech industries. An assessment of background factors and the scientific research environment reveals that Taiwan is well placed to succeed in the development of protein drugs. Domestic researchers are studying the blood coagulation system, intercellular messengers, and growth factors. In the future, we plan to focus even more manpower on important research targets in these areas. And by promoting industry-university coopera-tion, we hope to develop possible medical applications even as we make further progress in basic research. We look forward

to the rapid development of a domestic biotechnology industry that can hold its own in the competition and cooperation with the world's most advanced nations.

Integrated Research Project on E-commerce

E-commerce has undergone a massive transformation over the past year. Considered an area of unlimited promise in early 2000, e-commerce had begun encountering problems by the end of the year, and many prominent Internet companies in Taiwan and abroad suffered a crisis with the bursting of the DotCom bubble in 2001. Responding to a threatening situation, many e-commerce firms have changed their business strategy from large-scale expansion at any cost to a more conservative emphasis on profitability. In addition, many conventional businesses under pressure to reinvent themselves are employing e-business and e-commerce to strengthen competitiveness. This integrated project has sought to explore Internet companies' business operations, corporate strategies for e-commerce, and the effect of e-commerce on corporate competitiveness. Preliminary results are as follows:

1. Prof. Liang Ting-peng of National Sun Yat-sen University analyzed the effectiveness of e-commerce at 90 foreign companies. He discovered that while e-commerce may adversely affect the sale of digital products (such as e-books, MP3s), combining real and virtual sales channels can improve corporate EPS (Earnings Per Share). Moreover, looking at the impact of e-commerce in Taiwan, Prof. Liang found that roughly 50% of companies listed on the TAIEX or OTC stock exchange have adopted partial or complete e-commerce approaches. Another 32.5% of listed companies are currently implementing e-commerce, and only 17.5% have made no effort to do so. High-tech manufacturing and service industries have the highest degree of e-commerce use, while conventional manufacturers have a relatively low degree of use. The main factors affecting willingness to implement e-commerce and e-business are magnitude of influence by information technology, degree of implementation among competitors, the company's operating flexibility, and amount of knowledge concerning e-commerce among executives and employees. The gov-ernment's attitude and research assistance were not found to have any significant influence on the degree of e-commerce and e-business use. This shows that individual companies have great room for free judgment, and government assistance measures are not sufficiently helpful.

2. Prof. Chen Houn-gee of National Tsinghua University looked at the trend towards fee-charging online services. Investigating pricing strategies for online services, Prof. Chen found that while ordinary ISPs (Internet Service Providers) must use a low-price strategy to penetrate markets, ICPs (Internet Content Providers) and ASPs (Ap-plication Service Providers) may appropriately offer customized services, and should therefore adopt a market-squeezing price strategy in line with the nature of their services.

3. Prof. Wu Jiinpo of Tamkang University, studying trust-building mechanisms in online shopping, discovered that service quality, corporate reputation, and technological capability can win customers' trust in a B2C website, and are the three key factors in establishing consumer loyalty.

4. Professors Tu Anthony Hwa-yue and Chow Edward Hsing-yi of National Chengchi University studied value appraisal characteristics and investment strategies in connection with Internet companies, and established a concrete option model explaining abnormal fluctuations in Internet company stock prices. They found that an Internet company's value hinges on the frequency and number of its technological innovations, the quality and market impact of its new technology, and the level of competition from similar products.

5. As for tax considerations, Prof. Ching Steve Hsianghoo of Feng Chia University and Prof. Lin Suming of National Taiwan University concluded that the tax code should be appropriately modified as e-commerce becomes more ubiquitous. Professors Ching and Lin recommended that the revised code be as simple and clear as possible, cover all main tax bases, and, in particular, take into consideration the use of auditing technology and the tax problems that may arise from international transactions.

Application of Fluorescence Spectroscopy to the Diagnosis of Oral Cancer and Pre-Cancerous Pathologies

Initiating the development of electro-optical biomedicine in Taiwan, the Electro-optics Task Force of the National Science Council (NSC), Executive Yuan, has supported the three-year (Jan. 2000 to Dec. 2002) integrated research project "Use of the Electro-optical Technique of Fluorescence Spectroscopy to the Diagnosis of Oral Cancer and Pre-Cancerous Patho-

logies." This project, which links the very promising fields of electro-optics and biotechnology, is being carried out by associate professors Chiang Chun-pin and Chen Chinting of National Taiwan University, Associate Professor Tsai Tsui-min of Taipei Medical University, and Assistant Professor Wang Chih-yu of I-Shou University. The project combines the areas of electro-optics, medical engineering, pharmacology, and basic and clinical medicine, and is set to deliver far-reaching benefits.

According to Department of Health statistics concerning the incidence of the ten most common cancers in Taiwan, mortality from oral cancer has risen at the fastest rate. Apart from being attributed to the prevalent habits of smoking, drinking, and betel nut chewing, the relatively high incidence of and mortality from oral cancer in Taiwan as compared to the industrialized nations can be attributed to the fact that the symptoms of early oral cancer are easy to overlook (while tissue tends to thicken and lingering ulcerations often appear, there may be no pain even after a tumor has appeared), and the condition is thus often not detected until a relatively late stage. Because there is a close correlation between successful treatment and early detection of precancerous pathologies, the development of a technique for the early diagnosis of oral cancer and pre-cancerous pathologies would represent a very significant advance.

The ultimate goal of the integrated project is to establish a method of using fluorescence to diagnose human oral cancer and pre-cancerous pathologies at an early stage. The project has thus far developed three techniques and completed a prototype fiber-optic spectroscope: With regard to the use of non-invasive auto-fluorescence diagnostic technology, research results indicated that auto-fluorescence spectroscopy can effectively distinguish fibrous tissue below the oral mucous membrane caused by the chewing of betel nuts and pathological tissue likely to progress to oral cancer from normal tissue. A localized transport system was developed for the photosensitizer ALA (delta aminolevulinic acid); this approach reduces the required dose and avoids the side effect of light sensitivity caused by conventional injection or oral ingestion. The new photosensitizer transport method can be used both in fluorescence diagnosis and in photodynamic therapy. An animal experimental model was used to establish that fluorescence spectroscopy using ALA could distinguish normal tissue from pre-cancerous and cancerous pathological tissue *in vivo*. Special candlepower spectroscopic analysis system equipment was developed, increasing the utility and applicability of the spectroscopic diagnostic technique.

The non-invasive diagnostic method developed in the project with electro-optics technology can increase the predictive power of tissue inspection, which not only spares patients discomfort from repeated tissue biopsy, but also promises to help clinical physicians perform even more effective diagnosis and therapy. The use of fluorescence spectroscopy to perform early *in vivo* diagnosis of oral cancer and pre-cancerous pathological tissue is a development of great clinical importance for members of the public being screened for cancer and patients undergoing treatment. In addition, besides enabling the early detection of oral cancer, the technique developed in this integrated project can eventually be used in conjunction with an endoscope, extending its applicability to the detection of cervical cancer, breast cancer, colorectal cancer, nasopharyngeal cancer, esophageal cancer, stomach cancer, and lung cancer. The development of this technique is thus an event of milestone significance in the application of electro-optics technology to biomedical science in Taiwan, particularly to the therapy and diagnosis of locally-prevalent diseases.

Seismic Engineering Strategies in Earthquake Resistance Buildings

School classrooms are usually full of teachers and students. When a natural disaster strikes, schools often serve as temporary shelters for homeless peoples. Major hospitals are important medical facilities daily as well as disaster struck. In recognition of the functions of these important buildings, Taiwan's structural standards have stipulated that schools and major hospitals must possess greater earthquake resistance capability than ordinary residential buildings. However, many schools suffered even more severe damage than residential buildings when the devastating 921 Chi-Chi Earthquake struck. Hospitals in the affected area were also heavily damaged, and the Hsiuchuan Hospital in Chushan was even forced to close for repairs. In addition, almost all elevators in the quake area stopped operating, and much medical work were affected. The 921 Chi-Chi Earthquake caused unprecedented destruction, killing 2,478 peoples, severely injuring 11,662 peoples, destroying 49,542 buildings, doing severe structural damage to 42,746 buildings, and causing direct economic losses in excess of NT$10.7 billion. Collapsing buildings crushed most of those killed and injured peoples.

The inadequate seismic performance of buildings in the quake area was the main reason of catastrophe induced by the 921 Chi-Chi Earth-quake. The seismic damage caused to school buildings and hospitals has shown that all existing schools and hospitals in Taiwan are potentially vulnerable to earthquakes, and there is an urgent need to adopt systematic seismic diagnostic and improvement measures. The NSC therefore decided to implement practical research on the seismic resistance of major buildings in Taiwan, with a main emphasis on how to improve design methods and reinforce existing buildings that did not topple in the quake. The schools and hospitals will be addressed as the demonstration buildings.

Model shaking table test of school building.

Failure of Hsiuchuan Hospital in Chushan.

Full-scale earthquake resistance test of school building.

Failure of Nan-Guang Elementary School in Puu-Lii.

The research team was directed by Prof. Maw-Shyang Sheu of the Department of Architecture, National Cheng Kung University and Prof. Yaw-Jeng Chiou of the same University's Department of Civil Engineering. Eleven professors at seven domestic universities were invited to examine structural seismic performance problems involving schools and hospitals. The project worked on the five topics of (1) development of practical diagnostic methods, (2) proposal of feasible and accurate analytical methods, (3) investigation of traditional reinforcement approaches, (4) development of new vibration isolation and vibration reduction materials and techniques, and (5) improvement of the seismic performance of domestically made elevators. The project began on August 1, 2000, and is scheduled to a period of three years. Each of the professors will supervise one doctoral student and one to two M.S. students per year, and the results presentation work shop will be held once every six months. Both the liquid flow-damping device developed by Prof. Deh-Shiu Hsu and the special vibration isolation pad developed by Prof. Chong-Shien Tsai has received the ROC patent. After the three-year term of the project is completed, the expected results of this research team will provide tools for the accurate analysis and practical seismic diagnosis of hospitals and school buildings, propose effective reinforcement and vibration isolation/vibration reduction measures, and offer specific strategies for improving the earthquake resistance capability of domestically made elevators.

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