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Uncovering the Cancer-Causing Role of the EB Virus

LMP 1 Gene Used to Confirm Recurrent Nasopharyngeal Cancer Cases

Sometimes known as the "Chinese cancer," nasopharyngeal cancer is very prevalent in Taiwan. This cancer had an incidence rate of six cases per 100,000 in 1998 (in contrast, the rate in Europe was less than one case per 100,000), and there have been 1,000 ~ 1,200 new cases per year. And since nasopharyngeal cancer mainly affects 40 ~ 60 year-old men, it has a major impact on the nation and society. The most obvious risk factor for nasopharyngeal cancer is the Epstein-Barr virus (EBV). The main treatment for this cancer is radiation, with radiation being used together with chemotherapy in advanced cases.

A team of researchers from Chang Gung University and Chang Gung Memorial Hospital has studied the role of EBV in carcinogenesis with long-term support from the NSC. This research team, headed by Dr. Chang Yu-sun of the Chang Gung University Graduate Institute of Basic Medical Science, has sought to uncover the mechanism by which this virus initiates cancer, and thereby find new methods of diagnosis and treatment. According to Dr. Chang, when the research team reported on nasopharyngeal cancer biopsy samples (particularly cases of non-keratinizing and undifferentiated carcinoma) more than a decade ago, it found that EBV DNA and transcripts were present in over 90% of the samples. Moreover, the team found that EBV DNA from the samples had deletion of 30 nucleotide bases. It has since been discovered that the EBV protein LMP1 (latent membrane protein 1) gene can be detected in nasopharyngeal cancer biopsy samples, and experiments have shown that the form of LMP1 found in Taiwan possesses a powerful ability to transform and initiate carcinogenesis in cells. It has also recently been proven that LMP1 can promote cell migration, suggesting that this protein is one of the factors behind nasopharyngeal cancer's tendency to metastasize.

Building on the research team's growing understanding of EBV LMP1, Dr. Tsang Ngan-ming of the Chang Gung Memorial Hospital Department of Radiation Oncology and Dr. Hao Sheng-po of the same hospital's Department of Otolaryngology have tested cells obtained from patients via the simple nasal swap technique for the LMP1 gene as a means of detecting the presence of nasopharyngeal cancer (sensitivity close to 95%; specificity close to 100%). This technique, which may be a feasible way to confirm early diagnosis of nasopharyngeal cancer, has been described in articles in such leading international journals as *Cancer*.

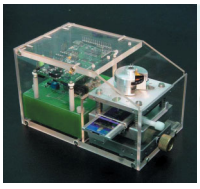
Since 2000, researchers from Chang Gung University, National Tsinghua University, and National Chiao Tung University have been implementing the first phase of a University Pursuit of Excellence project on ways to fight the EB virus, and this project has succeeded in establishing a technology platform for screening rational anti-EBV drugs. The NSC hopes that the aforementioned research work will lead to the discovery of anti-EBV and anti-nasopharyngeal cancer drugs, realizing the potential of research findings.

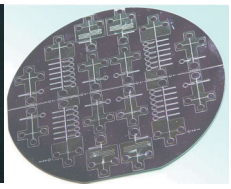
Good News for Heart Disease Patients

PIDC Develops Miniature Heart Attack Testing Chip System

The NSC Precision Instrument Development Center (PIDC) recently announced the development of a "Mini-Biomedical Chip System for Detecting Heart Attack" on the occasion of its 30th anniversary. This system is a miniature fluorescence detection system in the form of a low-cost, disposable biochip, and signifies that blood tests given to heart attack patients will no longer be limited to large hospitals. Now ordinary hospitals and clinics will be able to immediately perform the life-saving blood tests. The announcement of the "Mini-Biomedical Chip System" shows that PIDC has successfully entered the field of medical equipment development via interdisciplinary cooperation in micro-optics, MEMS (micro-electro-mechanical systems), and electronics.

Department of Health statistics for 2003 show that cancer, cerebrovascular diseases, and heart disease are the three leading causes of death in Taiwan. Due to dietary changes, heart





disease is claiming increasingly younger victims. When a heart attack occurs, the victim's life is at great risk unless prompt emergency treatment is given. Cardiologists note that 12.5% of those who seek medical care because of chest pain actually have undergone a heart attack. Among these patients, the heart attack can be detected via an electrocardiogram in only one-half of all cases. The cardiologist must therefore give the remaining patients a blood test in order to make a correct diagnosis. These facts show that blood tests are an extremely important means of diagnosing heart attacks.

PIDC's Nanotechnology Section developed the "Mini-Biomedical Chip System." Mr. Chou Hsiao-yu, Mr. Hu Yi-chiuen, and Ms. Lin Ming-yu respectively served as Section Head, project leader, and biomedical applications coordinator. According to Ms. Lin, the system will ease some of the problems of heart attack blood tests, such as high cost, the need to take a large volume of blood, and complicated procedures. The biochip system requires that only 0.2 cc of blood be dripped into a microfluidic channel about the size of a human hair. The high-sensitivity fluorescent detection system developed by the PIDC researchers enables the biochip to detect in real-time the concentration of myoglobin – a major indicator of heart attacks.

The biochip system has the following three main advantages: (1) A disposable microfluidic biochip: The ability to perform all testing steps on a single chip sharply reduces costs, while the disposable nature of the chip precludes contamination. (2) A miniaturized fluorescence microscope: The tiny size of the chip conserves resources and facilitates operation. (3) Handiness and practicality: The system is powered by a 9 V battery, is readily portable, and is simple to use.

Most biochip research efforts in Taiwan are currently focusing on the development of microarray gene chips. In contrast, microfluidic biochips and chip detection devices are receiving relatively little attention. Although a number of research organizations are engaging in biochip research, one common problem is that the instruments needed to read and analyze signals are typically costly, complex, and not readily portable. PIDC is thus the first organization in Taiwan to miniaturize biochips and fluorescence detection instruments so that they are easier to use and to carry. Thanks to this success, numerous domestic and foreign firms have expressed high interest in cooperating with PIDC.

PIDC's "Mini-Biomedical Chip System for Detecting Heart Attack" draws on such core technologies as high aspect ratio nanostructure fabrication technology, MEMS LIGA-like fabrication processing, micro-optical design, and ICP technology. This degree of integration is unique in Taiwan, making PIDC a peerless technological resource for relevant domestic firms. After future technology transfer, Taiwan's strength at precision manufacturing is certain to propel the country to a position of international leadership in the field of biochip R&D.

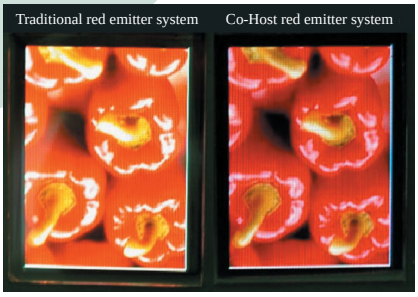
New Technology "Lightens Up" Handheld Display Products

Groundbreaking R&D on Flexible OLED Materials and Technology

Organic light-emitting diodes (OLEDs) and displays are poised to become one of the hottest emerging display industries of the new century. The reason OLED displays have such tremendous potential is that they best exemplify the essential attributes of handheld products: "light, convenient, small, colorful, efficient, beautiful, and multifunctional." OLED displays will eventually allow us to realize the ideal display that can be used anywhere at anytime. The weight of flat panel displays can be more than halved if their glass substrate is replaced with plastic in the form of OLEDs, allowing such handheld devices as palm computers, mobile phones, and PDAs to become much lighter. And as an added benefit, flexible plastic substrates can also be made to fit any curved surface.

Funded by the NSC and strongly supported by university president Chang Chun-yen, researchers at National Chiao Tung University and two cooperating private companies established the "OLED Research Laboratory" in May 2001. Dedicated to the R&D of OLEDs and flexible OLEDs (FOLEDs), this laboratory is currently the most advanced academic facility of its kind in Taiwan. FOLEDs have lately been a highly fashionable area of research in Europe, the US, and Japan, and the NSC's Electro-Optics Unit has designated them as one of the most important targets of the industry-university cooperative research projects that it funds.

According to Dr. Chen Chin-hsin, head of the OLED Research Laboratory and Professor at the newly established Display Research Institute of the Microelectronics & Information Systems Research Center, the laboratory is currently engaging in the R&D of sophisticated FOLED flat panel displays offering impressive economic potential. This work, which has included the development of efficient luminescent materials, encapsulation methods, and processing technologies, has thus far reaped very encouraging results. For example, the labo-



Comparison of full-color active OLED

ratory has developed elements bearing a "FOLED" logo in the colors of red, blue, and green – a first in Taiwan. The external quantum efficiency of the green FOLED is as high as 4.5%, while the operational half-life (L_0 = 100 nits) is greater than 680 hours.

One of the most important issues in this research campaign was the development of a new fluorescent dopant. Although Taiwan's companies are extremely enthusiastic about the development of OLEDs, foreigners hold most of the patents on relevant organic materials. The OLED Research Laboratory therefore devoted some of its first efforts towards the pursuit of "replacement" OLED dopants. The laboratory's dopant material research has led to a number of inventions in the improvement of quantum efficiency and stability of red and green dopants that have been the subject of four ROC patent applications filed recently in this area.

The new elements offer significant improvements on the luminescent efficiency and operational lifetime of most existing red-emitting OLEDs. The laboratory has used the proper mixture of two light-emitting host materials (fused aromatic compounds and organic metal chelates) to create a new type of light-emitting system known as a "co-host emitter system" or "CHE." Experimental results indicate that red OLEDs produced using this new type of emitter are more saturated in red and better able to suppress current-induced fluorescence quenching. This sharply increases current emission efficiency to 4.5 cd/A, while enabling power efficiency to improve in excess of 2.5 lm/W by virtue of lowering drive voltage. Even more importantly, the elements' operational half-life (L_0 = 100 nits) can exceed 30,000 hours, making them the best-performing red-fluorescing OLEDs yet described in the literature. The laboratory is applying for US and ROC patents for this discovery, and is collaborating with a local optoelectronics company to commercialize this new technology. This technology has already been demonstrated successfully in a prototype full-color LTPS active matrix OLED handset display.

One of the few domestic facilities performing full-scale research on small-molecule OLEDs, National Chiao Tung University's OLED Research Laboratory is performing research on such aspects as materials synthesis, testing and new element system design, production and encapsulation. It is hoped that the laboratory's recent success in collaboration with the private sector will help propel Taiwan's OLED industry to a higher level of technological competency and usher in a new era of flat panel displays in the foreseeable future.

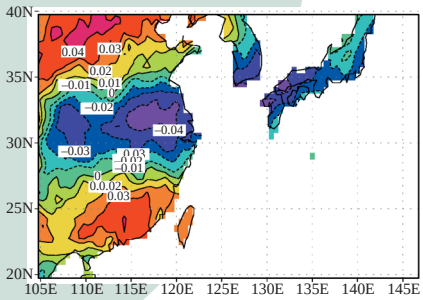
Investigating the Interannual Variability of Precipitation in East Asia

Taiwan's Drought and Flooding Problems Linked to Asian Monsoon Fluctuations

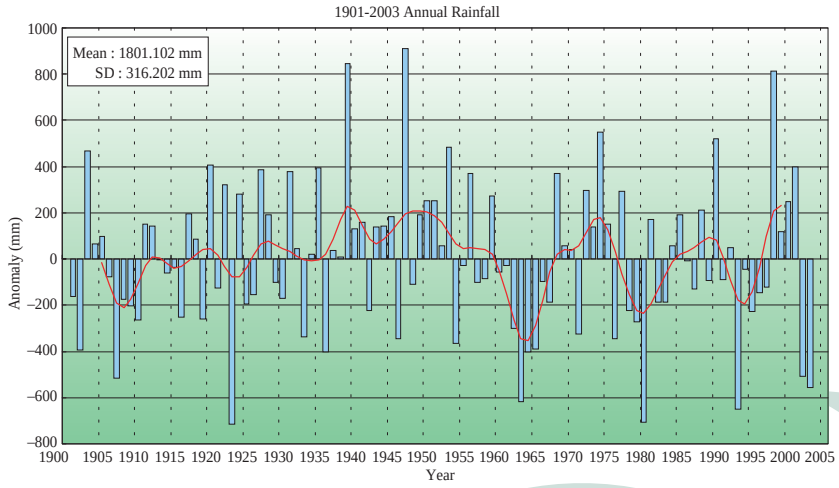
Taiwan has been enduring a period of drought that began in the wake of Typhoon Nari in September 2001 and has continued two years until the present. Not only was the rapid onset and magnitude of this drought unexpected, but also the reason for it was not well understood. In the end, researchers had to gain an understanding of changes in annual precipitation throughout East Asia before they could grasp the mechanism causing this episode of drought. Investigating these climatic fluctuations has been the main goal of the NSC-supported integrated research project "Interannual Variability of Precipitation in East Asia."

According to chief investigator Dr. Hsu Huang-hsiung, a professor at National Taiwan University's Department of Atmospheric Science, preliminary discoveries indicate that there has been a persistent lack of moisture in the region extending from South Asia, the South China Sea, and the northwestern Pacific to the equatorial western Pacific ever since 2002. The climate throughout this area has been characterized by weak convection and strong high-pressure systems during this period. This shows that the drought in Taiwan over the past two years has by no means been a localized phenomenon. Instead, it is part of a phenomenon that spans much of Asia's low latitude monsoon belt. For this reason, any attempt to understand Taiwan's drought problem must start by investigating meteorological changes over a much greater area, and only then proceed to look at localized problems.

The past meteorological data analyzed by Prof. Hsu's team suggests that annual precipitation in Taiwan is subject to dramatic swings. The most conspicuous examples of this include the summer 1993 drought, the many typhoons and heavy rains of the summer of 1994, and the great changes that occurred in 2001 and 2002. On the other hand, the research team also found that behind the sharp year-to-year swings there exists a regular cycle: Annual precipitation in Taiwan has exhibited quasi-periodic fluctuations since 1950. Drought struck in the early 1960's, in 1980 and 1993, and during 2002 ~ 2003. The period of the drought cycle was approximately 16 years in the 1950's, but has more recently fallen to roughly 12 ~ 13 years.



The "sandwich" pattern affecting interannual variability of precipitation in East Asia.



While there have been few instances of poor rainfall in several consecutive years, this did occur in the years 1962 ~ 1965, and is occurring again during the present drought.

Analysis of past data reveals that Taiwan is situated in a moisture-poor high-pressure zone during periods of drought, which accounts for the lack of rainfall. While precipitation is usually also poor in the Indochina peninsula and along the South China coast during Taiwan's drought years, central China, South Korea, and Japan typically receive copious rainfall in those years. In contrast, southern/central China and the Indochina peninsula receive much precipitation during Taiwan's rainy years, while Southwestern China goes dry. The cause of this phenomenon is the monsoon trough located in the Philippines Sea. The monsoon trough is strong during rainy years, but weak during dry years. The monsoon trough is a breeding ground for typhoons: A strong monsoon trough means more typhoons that may affect Taiwan, while a weak monsoon trough implies fewer typhoons.

In Prof. Hsu's view, the meteorological configuration influencing summertime precipitation in East Asia can be represented as a sandwich-shaped structure: When rainfall is heavy at central China, South Korea, and Japan, the regions of southern China, Taiwan, and northern China receive less-than-normal precipitation. While past researchers suggested that this configuration is induced by abnormal sea surface temperatures in the western Pacific, Prof. Hsu's work indicates that heating fluctuations on the Tibetan Plateau can set in motion abnormal circulation and the sandwich precipitation pattern in East Asia. Because the Tibetan Plateau's heating fluctuations begin during the springtime, this finding will aid weather forecasting.

Besides illuminating the characteristics of annual precipitation fluctuations in East Asia and discovering a likely mechanism, Prof. Hsu's research team also employed numerical modeling to simulate precipitation and develop a forecasting system. The team discovered that while the ocean influences the atmosphere in the East Asian region most strongly in the winter and spring, the atmosphere may influence the ocean in the summertime. This finding implies that atmospheric circulation models that only take into consideration the one-way effect of the ocean on the atmosphere may have limited application value. It also explains why many models have proved unable to accurately simulate summer climate fluctuations in East Asia. A coupled ocean-atmosphere general circulation model taking into consideration the mutual influence of the ocean and atmosphere should be much more successful at simulating (and even forecasting) annual precipitation in the region.

Due to poor spatial resolution, global climate models are limited to simulating climate over large geographical areas (200 ~ 300 kilometers), but cannot simulate precipitation fluctuations in an area of the size of Taiwan. A high-resolution regional climate model must be incorporated when desired to model fluctuations over an area of several tens of kilometers (over even smaller). In cooperation with a related project funded by the Sustainable Development Research Committee, Prof. Hsu's project has completed a regional climate model and ten summer precipitation simulations. The results indicate that this model is able to successfully simulate annual and intra-seasonal precipitation fluctuations.

"The preliminary results of this research have given us a much clearer understanding of precipitation characteristics, and possible driving mechanisms, in East Asia and Taiwan. Apart from their academic value, these results can be directly applied to the development of climate forecasting techniques," said Prof. Hsu.

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