# 行政院國家科學委員會專題研究計畫 成果報告

## 胞漿素原活化劑及胞漿素系統在子宮頸上皮內贅瘤及子宮頸癌的表現(第 3 年)
## 研究成果報告(完整版)

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公 開 資 訊 ：本計畫涉及專利或其他智慧財產權，2 年後可公開查詢

中 華 民 國 101 年 10 月 29 日

中 文 摘 要 ： 胞漿素原活化劑及胞漿素系統(plasminogen activator/ plasmin system)和基底膜的降解、組織纖維化及組織重組非常有關係。而 u-PA 及其 receptor u-PAR 在許多癌症的致病過程有密切的相關性已是不爭的事實，但是 u-PA、u-PAR 及其抑制劑 PAI-1 的基因多型性與子宮頸癌的致癌過程及其相關性卻仍不清楚。因此，本實驗利用聚合酶鏈限制性連鎖反應-切割片段長度多型性(PCR-RFLP)的方式，分析 136 位子宮頸上皮內贅瘤及子宮頸癌病人與 336 位非癌症之對照組，其 u-PA、u-PAR 及其抑制劑 PAI-1 基因多型性的相關性。結果發現 uPA 及 PAI-1 分別攜帶 CC/4G4G 與帶有 CC/4G5G 基因型的個體相比較，發現在罹患子宮頸癌的機率有 1.70 倍的危險值，(OR=1.70； 95% CI 1.04-2.79) 。因此，我們發現，在台灣的個體中，u-PAPAI-1 的基因型與罹患子宮頸癌的機率有明顯的差異，但是分析 u-PA, PAI-1 及 u-PAR 的基因型與子宮頸癌的癌化過程及其與 stage, 腫瘤大小皆沒有明顯的相關性。

中文關鍵詞： 胞漿素原活化劑、胞漿素系統、子宮頸癌、子宮頸上皮內贅瘤、基因多型性

英 文 摘 要 ： Background and Objectives: To evaluate the impact of plasminogen activator (PA) system genes, including urokinase plasminogen activator (uPA), uPA receptor (uPAR), and plasminogen activator inhibitor-1 (PAI-1) gene polymorphisms in patients with the cervical neoplasia. Methods: In total, 336 blood samples were collected from healthy women and 136 patients with cervical neoplasia to analyze the gene polymorphisms of representative PA system genes. Results: There was no significant association between cervical neoplasia cases and gene polymorphisms of uPA, uPAR and PAI-1 genes as well as to the carcinogenesis of cervical if the cervical neoplasia cases were stratified to HSILs and invasive cancer cases. However, we found a mutual interaction between uPA/PAI-1 genes, which women carrying the uPA/PAI-1 CC/4G4G allele had a 1.70-fold higher risk (OR=1.70； 95% CI 1.04-2.79) of cervical neoplasia compared with those carrying the CC/4G5G allele. Conclusions: Individuals with uPA/PAI-1 CC/4G5G allele were in high susceptibility for cervical neoplasia. The combined polymorphism of uPA/PAI-1 might diminish the ability of PAI-1 to

inhibiting cervical cancer carcinogenesis when PAI-1 alone as the role of inhibitor.

英文關鍵詞： uPA, uPAR, PAI-1, cervical cancer, genetic polymorphism

**Genetic Polymorphism of Urokinase-Type Plasminogen Activator is interacting with Plasminogen Activator Inhibitor-1 to Raise Risk of Cervical neoplasia**

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Running titile: uPA SNPs in cervical neoplasia

**Synopsis for Table of Contents:**

Individuals with *uPA/PAI-1* CC/4G5G allele were in high susceptibility for cervical neoplasia.

## Abstract

**Background and Objectives**: To evaluate the impact of plasminogen activator (PA) system genes, including urokinase plasminogen activator (*uPA*), uPA receptor (*uPAR*), and plasminogen activator inhibitor-1 (*PAI-1*) gene polymorphisms in patients with the cervical neoplasia. **Methods:** In total, 336 blood samples were collected from healthy women and 136 patients with cervical neoplasia to analyze the gene polymorphisms of representative PA system genes. **Results:** There was no significant association between cervical neoplasia cases and gene polymorphisms of *uPA, uPAR* and *PAI-1* genes as well as to the carcinogenesis of cervical if the cervical neoplasia cases were stratified to HSILs and invasive cancer cases. However, we found a mutual interaction between *uPA/PAI-1* genes, which women carrying the uPA/PAI-1 CC/4G4G allele had a 1.70-fold higher risk (OR=1.70; 95% CI 1.04-2.79) of cervical neoplasia compared with those carrying the CC/4G5G allele. **Conclusions:** Individuals with *uPA/PAI-1* CC/4G5G allele were in high susceptibility for cervical neoplasia. The combined polymorphism of *uPA/PAI-1* might diminish the ability of PAI-1 to inhibiting cervical cancer carcinogenesis when *PAI-1* alone as the role of inhibitor.

**Key words:** uPA, uPAR, PAI-1, cervical cancer, genetic polymorphism

## Introduction

The annual incidence of cervical cancer is in the significant trends of decline as high as 15 % compared to ten years ago in Taiwan [1]. The implementation of pap smear has successfully helped reduce cancer incidence and mortality rate. Age standardized incidence of invasive cervical cancer decrease from 24 per 100,000 persons in 1995 to 12 per 100,000 people in 2007. The age standardized mortality rate of cervical cancer decrease from 11 per 100,000 persons to 4.2 per 100,000 persons [2]. Although the great success of pap smear programme and our National Health Insurance has kept spotlight around the world, the mortality of the disease continues to be as high as 800 person per year in Taiwan [3]. To select patients for adjuvant therapy there is a critical need to distinguish between those at high versus low risk of disease recurrence. At present, such an evaluation is mainly based on determination of cancer cell dissemination to pelvic and paraaortic lymph nodes [4, 5]. Over the last years, there have been several reports on the tumor tissue concentrations of molecules involved in the aggressive malignant spread of cancer cells, e.g., proteolytic enzymes secreted by either the cancer cells or other cells in the surrounding tumor stroma, the possibility that elevated levels of these proteins reflect the metastatic potential of the tumor.

The urokinase-type plasminogen activator receptor (uPAR) plays a key role in

cell adhesion and migration [6, 7]. uPA binds to uPAR, a three-domain, glycolipid-anchored cell surface protein. Binding of uPA to uPAR strongly enhances and localizes the activation of surface-bound plasminogen into plasmin and matrix metalloproteinase (MMP), which, with broad specificity, degrades most components of the extracellular matrix and basement membranes [8-10]. This plasminogen activator system is particularly associated with the process of metastasis, the spread of primary tumors to distant organs which is always associated with poor prognosis and high mortality [6, 7]. The specifics inhibitors PAI-1 and PAI-2 can inhibit the activity of uPA as a regulation of uPA/uPAR activities [11-14].

Since single-nucleotide polymorphisms (SNPs) located within the promoter of the genes in the uPA system may affect the expression of the gene or the protein, genotyping of these SNPs would be predictive of cancer development and prognosis. Genetic polymorphisms of components of uPA system are linked with cancer risk in breast cancer, prostate cancer, non-small cell lung cancer, gastric cancer, endometrial cancer, hepatocellular carcinoma and oral cancer [15-21], but their potential associated with cervical cancer is not been investigated yet. We hypothesized that gene polymorphisms of *uPA* system could link the cervical cancer carcinogenesis. In this study, a spectral analysis of a subset of SNPs from the genes in the *uPA* system of pre-invasive cervical cancer and invasive cervical cancer was performed to define the

impact of these SNPs on clinicopathological characteristics of cervical cancer carcinogenesis.

## Materials and Methods

### Population

Seventy-five patients with invasive cancer and 61 with high-grade dsplasia of uterine cervix were enrolled into this study at the Department of Obstetrics and Gynecology, Chung Shan Medical University Hospital, Taiwan. Meanwhile, controls were enrolled from the physical examination during the hospital, which are also the facilities that cases were collected from. At the end of recruitment, a total of 336 participants (mean age = 44.5 ± 10.3 years) that had neither self reported history of cancer of any sites were included. All of them lived in mid-Taiwan. The patients with cervical invasive cancer or high-grade dysplasia had received treatment at the Department of Obstetrics and Gynecology in Chung Shan Medical University Hospital between January 1, 2007 and May 31, 2010. Patients with cervical cancer were staged clinically according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) Classification. The patients with cervical cancer received standard treatment protocols in the Department of Obstetrics and Gynecology in

Chung Shan Medical University Hospital, including abdominal radical hysterectomy and pelvic lymph nodes dissection and or para-aortic lymph nodes sampling, platinum-based concurrent chemoradiotherapy, irradiation or chemotherapy between January 1, 2007 and May 31, 2010. Patients with HSIL had abdominal total hysterectomy, vaginal total hysterectomy, or large loop excision of transformation zone. Cases that revealed discrepancy between histologic and cytologic diagnosis were excluded in this study. The study was performed with the approval by Institutional Review Boards of Chung Shan Medical University Hospital. Informed consents were obtained from all participants.

**Genomic DNA Extraction**

Genomic DNA was extracted by using QIAamp DNA blood mini kits (Qiagen, Valencia, CA, USA) according to the manufacturer's instructions. DNA was dissolved in TE buffer [10 mM Tris (pH 7.8), 1 mM EDTA] and then quantitated by measurement of OD260. Final preparation was stored at –20℃ and used as templates for polymerase chain reaction.

**Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP)**

The primers sequences and the restriction enzyme for analysis of *uPA* system

gene polymorphisms were described in Table 1 [20]. The PCR cycling conditions were 5 min at 94℃ followed by 35 cycles of 1 min at 94℃, 1 min at 60℃, and 2 min at 72℃, with a final step at 72℃ for 20 min to allow complete extension of all PCR fragments. The PCR product was subjected to digestion by each restriction enzyme (New England Biolabs, Beverly, MA) at 55℃ for 4 h. As a result, for C/T SNP of *uPA*, T allele yielded 187- and 104-bp products, while C alleles yielded a 291-bp product; for T/C SNP of *uPAR*, C allele yielded 200- and 108-bp products, while T alleles yielded a 308-bp product; for 4G/5G SNP of *PAI-1*, 5G allele yielded 74-,56-, and 33-bp products, while 4G alleles yielded 107- and 56-bp products.

**Statistical analysis**

Statistical analysis was performed using the SPSS 12.0 software package (SPSS Inc., Chicago, IL, USA). The $\chi^2$ test was used for any deviation from Hardy -Weinberg equilibrium. The Odds ratios (OR) and 95% confidence intervals (CI) for genotypes and alleles in cervical neoplasia cases and control groups were calculated by logistic regression, a probability level of 5% was considered significant.

## Results

The frequencies of *uPA, uPAR* and *PAI-1* gene polymorphisms were studied in 136 patients with cervical neoplasia, separately it was 61 patients with HSIL and 75 patients with invasive cervical cancer, and compared to 336 healthy controls. The genotype distributions of the *uPA, uPAR* and *PAI-1* gene polymorphisms in cervical

neoplasia cases and controls are shown in Table 2. There are no significant associations between cervical neoplasia cases and SNPs of *uPA, uPAR* and *PAI-1* genes were observed. To further evaluation the impacts of SNPs of *uPA, uPAR* and *PAI-1* genes to cervical carcinogenesis, the cervical neoplasia cases were stratified to HSILs and invasive cancer cases in Table 3. As shown in Table 3, no significant associations between these SNPs to cervical carcinogenesis were identified. Furthermore, the distributions of alleles in control groups fit the Hardy-Weinberg equilibrium (P>0.05).

The interactions of *uPA, uPAR* and *PAI-1* polymorphisms were then analysed as uPA/uPAR and uPA/PAI-1 groups. The effects of their interactions on cervical neoplasia and controls were shown in Table 4. The genotype distributions of *uPA/PAI-1* CC/4G5G, CC/4G4G, CC/5G5G, CT/4G4G, CT/4G5G, CT/5G5G were 31.6%, 34.6%, 16.2%, 3.7%, 11% and 1.5% respectively in cervical neoplasia cases and 40.8%, 26.2%, 15.5% 4.2%, 9.2% and 3.6% respectively in controls. As shown in Table 4, women carrying the *uPA/PAI-1* CC/4G4G allele had a 1.70-fold higher risk (OR=1.70; 95% CI 1.04-2.79) of cervical neoplasia compared with those carrying the CC/4G5G allele. However, no significant interactions of *uPA/uPAR* allele subsets between cervical neoplasia were found.

The clinic-pathological characteristics of invasive cervical cancer and

associations with *uPA, uPAR and PAI-1* polymorphisms were analyzed in Table 5. As shown in Table 5, individuals with *uPAR* TT polymorphic genotype exhibited 0.13-fold lower risk (95% CI 0.02-0.75) for SCC pathologic cell type, but no significant associations between age, clinical stage, tumor size, lymph node metastasis and cell differentiation subgroups to *uPA, uPAR* and *PAI-1* polymorphisms were detected.

## Discussion

uPA system is primarily associated with the degradation and regeneration of the basement membrane and extracellular matrix that leads to metastasis [11, 12]. Cervical carcinogenesis rely solely on the ability of the cancerous cell to invade the basement membrane to become an invasive cancer which brought the risks of metastasis and poorer prognosis [6, 7]. However, in this study, we found no significant difference of genotypic frequencies of *uPA, uPAR* and *PAI-1* gene polymorphism between healthy controls and cervical cancer patients. Unfortunately, there was no association between *uPA, uPAR* polymorphism to cervical cancer risk in our study. This is in the line consistent to the findings of Su et al in *uPA, uPAR* polymorphism to risk of endometrial cancer, but a higher risk of endometrial cancer to

those with PAI-1 4G/4G genotype [21].

Further, we are looking again to show the association of the combined polymorphisms to risk of cervical neoplasia on the base of the truth most of the biological activities of uPA to be dependent on its binding to uPAR, and PAI-1 also are expected to bind to uPA in complex with uPAR to bring its role as a major inhibitor of uPA system. We found association between *uPA/PAI-1* CC/4G4G genotype as to elevated risk of cervical cancer, which was inconsistent to the findings of different clinical trials on the association between uPA/PAI-1 in various cancers. There are mostly accepted that uPA and its main inhibitor (PAI-1) were shown with level 1 evidence to be prognostic factors for primary breast cancer [22, 23], specifically high levels of uPA and PAI-1 are associated with poor outcome in breast cancer patients. Hence uPA and PAI-1 are widely used to select high-risk node-negative breast cancer patients to receive adjuvant chemotherapy.

Two polymorphisms of *uPA* gene have been described: a substitution from C to T in the nucleotide sequence of exon 6 encoding the kringle domain and a T to C change in intron 7. It was reported that CC genotype expresses the strongest uPA affinity for substrates and inhibitors, which leads to the formation of uPA/uPAR and uPA/PAI-1 complexes resulting in activation of uPA system [24]. We realize that internalization process starts after PAI-1 binds to uPA/uPAR to form uPA/uPAR/PAI-1 complex [25].

Finally, uPA-PAI-1 complex is degraded in lysosomes. Hence, we postulated that the combined polymorphism of uPA/PAI-1 might diminish the ability of PAI-1 to inhibiting cervical cancer carcinogenesis when it was alone. Instead, the combined polymorphism of *uPA/PAI-1* might act to positively influencing cervical cancer.

The main finding of our study is that although *uPA, uPAR* and *PAI-1* have no potential susceptibility factor for cervical cancer, but they exert their biology influence in combined polymorphism. *UPA/PAI-1* combined genotype may be a useful marker for predicting susceptibility to cervical cancer.

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**Table 1**. Primer sequences and PCR conditions for amplification of uPA system SNPs.

| Gene | Sequences | Base Pair | Enzyme |
|---|---|---|---|
| uPA (rs4065) | 5'-AGTCACACCAAGGAAGAGAA-3'<br>5'-AGACAAGTTGCTGGTCAGTA-3' | 291 bp | *Hph*I |
| uPAR (rs344781) | 5'-AATCGCTCTCCACTGCTGTA-3'<br>5'-CAATGCCTGGAATAGCTGCT-3' | 308 bp | *MspA1*I |
| PAI-1 (rs1799889) | 5'-GCCCTCAGGGGCACAGAGAGAGTCTGGCCA-3'<br>5'-GCAATGCAGCCAGCCACGTG-3' | 163 bp | *Bsl*I |

**Table 2**. Odds ratio (OR) and 95% confidence interval (CI) of cervical neoplasia associated with uPA, uPAR and PAI-1 genotypic frequencies.

| Variable | Controls (N=336) n (%) | Patients with Cervical neoplasia (N=136) n (%) | OR (95% CI) | |
|---|---|---|---|---|
| **uPA** | | | | |
| CC | 277 (82.4 %) | 112 (82.4 %) | 1.00 | |
| CT | 57 (17.0 %) | 22 (16.2 %) | 0.94 (0.557-1.636) | P=0.866 |
| TT | 2 (0.6 %) | 2 (1.4 %) | 2.47 (0.344-17.774) | P=0.352 |
| CT+TT | 59 (17.6 %) | 24 (17.6 %) | 1.01 (0.596-1.697) | P=0.982 |
| **uPAR** | | | | |
| TT | 85 (25.3 %) | 41 (30.1%) | 1.00 | |
| TC | 177 (52.7 %) | 64 (47.1%) | 0.75 (0.47-1.20) | P=0.228 |
| CC | 74 (22.0 %) | 31 (22.8%) | 0.87 (0.50-1.52) | P=0.622 |
| TC+CC | 251 (74.7 %) | 95 (69.9%) | 0.79 (0.51-1.22) | P=0.281 |
| **PAI-1** | | | | |
| 4G/4G | 102 (30.4 %) | 53 (39.0 %) | 1.00 | |
| 4G/5G | 169 (50.3 %) | 59 (43.4 %) | 0.67 (0.43-1.05) | P=0.079 |
| 5G/5G | 65 (19.3 %) | 24 (17.6 %) | 0.71 (0.40-1.26) | P=0.242 |
| 4G/5G+ 5G/5G | 234 (69.6 %) | 83 (61.0 %) | 0.68 (0.45-1.04) | P=0.071 |

The odds ratios (ORs) with their 95% confidence intervals were estimated by logistic regression models.

**Table 3**. Odds ratio (OR) and 95% confidence interval (CI) of HSILs and cervical cancer associated with uPA, uPAR and PAI-1 genotypic frequencies.

| Variable | Controls (N=336) | HSILs (N=61) | P value | Cervical cancer (N=75) | P value |
|---|---|---|---|---|---|
| **uPA** | | | | | |
| CC | 277 (82.4 %) | 47 (77.0 %) | | 65 (86.7 %) | |
| CT | 57 (17.0 %) | 14 (23.0 %) | P=0.271 | 8 (10.7 %) | P=0.197 |
| TT | 2 (0.6 %) | 0 (0 %) | P=0.560 | 2 (2.6 %) | P=0.119 |
| CT+TT | 59 (17.6 %) | 14 (23.0 %) | P=0.317 | 10 (13.3 %) | P=0.376 |
| **uPAR** | | | | | |
| TT | 85 (25.3 %) | 20 (32.8%) | | 21 (28.0%) | |
| TC | 177 (52.7 %) | 29 (47.5%) | P=0.255 | 35 (46.7%) | P=0.466 |
| CC | 74 (22.0 %) | 12 (19.7%) | P=0.348 | 19 (25.3%) | P=0.913 |
| TC+CC | 251 (74.7 %) | 41 (67.2%) | P=0.222 | 54 (72.0%) | P=0.629 |
| **PAI-1** | | | | | |
| 4G/4G | 102 (30.4 %) | 24 (39.3 %) | | 29 (38.7 %) | |
| 4G/5G | 169 (50.3 %) | 29 (47.5 %) | P=0.296 | 30 (40.0 %) | P=0.101 |
| 5G/5G | 65 (19.3 %) | 8 (13.1 %) | P=0.134 | 16 (21.3 %) | P=0.680 |
| 4G/5G+ 5G/5G | 234 (69.6 %) | 37 (60.7 %) | P=0.165 | 46 (61.3 %) | P=0.163 |

The odds ratios (ORs) with their 95% confidence intervals were estimated by logistic regression models.

**Table 4**. Genotyping the frequency of uPA/uPAR and uPA/PAI-1 genes polymorphisms in 336 controls and 136 patients with cervical neoplasia.

| Variable | Controls (N=336) n (%) | Patients with cervical neoplasia (N=136) n (%) | OR (95% CI) |
|---|---|---|---|
| **uPA/uPAR** | | | |
| CC/TC | 151 (44.9 %) | 55 (40.4 %) | Reference |
| CC/TT | 67 (19.9 %) | 32 (23.5 %) | 1.31 (0.78-2.21) |
| CC/CC | 59 (17.6 %) | 25 (18.4 %) | 1.16 (0.66-2.04) |
| CT/TT | 17 (5.1 %) | 8 (5.9 %) | 1.29 (0.53-3.16) |
| CT/TC | 25 (7.4 %) | 9 (6.6 %) | 0.99 (0.43-2.25) |
| CT/CC | 15 (4.5 %) | 5 (3.7 %) | 0.92 (0.32-2.64) |
| Others | 2 (0.6 %) | 2 (1.5 %) | 2.75 (0.38-19.97) |
| **uPA/PAI-1** | | | |
| CC/4G5G | 137 (40.8 %) | 43 (31.6 %) | Reference |
| CC/4G4G | 88 (26.2 %) | 47 (34.6 %) | **1.70 (1.04-2.79)*** |
| CC/5G5G | 52 (15.5 %) | 22 (16.2 %) | 1.35 (0.74-2.47) |
| CT/4G4G | 14 (4.2 %) | 5 (3.7 %) | 1.14 (0.39-3.34) |
| CT/4G5G | 31 (9.2 %) | 15 (11.0 %) | 1.54 (0.76-3.12) |
| CT/5G5G | 12 (3.6 %) | 2 (1.5 %) | 0.53 (0.11-2.47) |
| Others | 2 (0.6 %) | 2 (1.5 %) | 3.19 (0.44-23.30) |

* $P<0.05$ as statistically significant

**Table 5.** Odds ratio (OR) and 95% CI of clinical statuses and uPA system genotype frequencies in 75 cervical cancer.

| Variable | uPA | | | uPAR | | | PAI-1 | | |
|---|---|---|---|---|---|---|---|---|---|
| | CC | CT+ TT | OR (95% CI) | TT | TC+CC | OR (95% CI) | 4G/4G | 4G/5G+ 5G/5G | OR (95% CI) |
| **Age** | | | | | | | | | |
| < 54 | 32 (47.8%) | 6 (75.0%) | 1.00 | 10 (45.5%) | 28 (52.8%) | 1.00 | 17 (56.7%) | 21 (46.7%) | 1.00 |
| ≥ 54 | 35 (52.2%) | 2 (25.0%) | 0.31 (0.06-1.62) | 12 (54.5%) | 25 (47.2%) | 0.74 (0.27-2.02) | 13 (43.3%) | 24 (53.3%) | 1.50 (0.59-3.79) |
| **Cell type** | | | | | | | | | |
| SCC | 62 (92.5%) | 6 (75.0%) | 1.00 | 17 (77.3%) | 51 (96.2%) | 1.00 | 29 (96.7%) | 39 (86.7%) | 1.00 |
| Adenocarcinoma | 5 (7.5%) | 2 (25.0%) | 4.13 (0.66-26.07) | 5 (22.7%) | 2 (3.8%) | **0.13 (0.02-0.75)*** | 1 (3.3%) | 6 (13.3%) | 4.46 (0.51-39.11) |
| **Clinical Stage** | | | | | | | | | |
| Stage I/II | 59 (88.1%) | 7 (87.5%) | 1.00 | 19 (86.4%) | 47 (88.7%) | 1.00 | 25 (83.3%) | 41 (91.1%) | 1.00 |
| Stage III/IV | 8 (11.9%) | 1 (12.5%) | 1.05 (0.11-9.72) | 3 (13.6%) | 6 (11.3%) | 0.81 (0.18-3.57) | 5 (16.7%) | 4 (8.9%) | 0.49 (0.12-1.99) |
| **Tumor size** | | | | | | | | | |
| ≤ 4 cm | 31 (46.3%) | 3 (37.5%) | 1.00 | 11 (50.0%) | 23 (43.4%) | 1.00 | 14 (46.7%) | 20 (44.4%) | 1.00 |
| > 4 cm | 36 (53.7%) | 5 (62.5%) | 1.44 (0.32-6.50) | 11 (50.0%) | 30 (56.6%) | 1.30 (0.48-3.53) | 16 (53.3%) | 25 (55.6%) | 1.09 (0.43-2.77) |
| **Lymph node metastasis** | | | | | | | | | |
| No | 54 (80.6%) | 5 (62.5%) | 1.00 | 19 (86.4%) | 40 (75.5%) | 1.00 | 23 (75.0%) | 36 (80.0%) | 1.00 |
| Yes | 13 (19.4%) | 3 (37.5%) | 2.49 (0.53-11.80) | 3 (13.6%) | 13 (24.5%) | 2.06 (0.52-8.09) | 7 (25.0%) | 9 (20.0%) | 0.82 (0.27-2.51) |
| **Cell differentiation** | | | | | | | | | |
| Well differentiated | 7 (10.4%) | 1 (12.5%) | 1.00 | 2 (9.1%) | 6 (11.3%) | 1.00 | 1 (3.3%) | 7 (15.6%) | 1.00 |
| Moderately or poorly | 60 (89.6%) | 7 (87.5%) | 0.82 (0.09-7.65) | 20 (90.9%) | 47 (88.7%) | 0.78 (0.15-4.22) | 15 (96.7%) | 24 (84.4%) | 0.19 (0.02-1.61) |

The odds ratios (ORs) with analyzed by their 95% CIs were estimated by logistic regression models.

# 國科會補助計畫衍生研發成果推廣資料表

日期:2012/10/29

| 國科會補助計畫 | 計畫名稱: 胞漿素原活化劑及胞漿素系統在子宮頸上皮內贅瘤及子宮頸癌的表現 |
| --- | --- |
| | 計畫主持人: 鄭義銅 |
| | 計畫編號: 98-2314-B-040-013-MY3　　學門領域: 婦產科 |

無研發成果推廣資料

# 98 年度專題研究計畫研究成果彙整表

| 計畫主持人：鄭義銅 | 計畫編號：98-2314-B-040-013-MY3 |
|---|---|
| 計畫名稱：胞漿素原活化劑及胞漿素系統在子宮頸上皮內贅瘤及子宮頸癌的表現 | |

| 成果項目 | | | 量化 | | | 單位 | 備註（質化說明：如數個計畫共同成果、成果列為該期刊之封面故事...等） |
|---|---|---|---|---|---|---|---|
| | | | 實際已達成數（被接受或已發表） | 預期總達成數(含實際已達成數) | 本計畫實際貢獻百分比 | | |
| 國內 | 論文著作 | 期刊論文 | 0 | 0 | 100% | 篇 | |
| | | 研究報告/技術報告 | 0 | 0 | 100% | | |
| | | 研討會論文 | 0 | 0 | 100% | | |
| | | 專書 | 0 | 0 | 100% | | |
| | 專利 | 申請中件數 | 0 | 0 | 100% | 件 | |
| | | 已獲得件數 | 0 | 0 | 100% | | |
| | 技術移轉 | 件數 | 0 | 0 | 100% | 件 | |
| | | 權利金 | 0 | 0 | 100% | 千元 | |
| | 參與計畫人力（本國籍） | 碩士生 | 1 | 1 | 100% | 人次 | |
| | | 博士生 | 0 | 0 | 100% | | |
| | | 博士後研究員 | 0 | 0 | 100% | | |
| | | 專任助理 | 0 | 0 | 100% | | |
| 國外 | 論文著作 | 期刊論文 | 1 | 1 | 100% | 篇 | |
| | | 研究報告/技術報告 | 0 | 0 | 100% | | |
| | | 研討會論文 | 0 | 0 | 100% | | |
| | | 專書 | 0 | 0 | 100% | 章/本 | |
| | 專利 | 申請中件數 | 0 | 0 | 100% | 件 | |
| | | 已獲得件數 | 0 | 0 | 100% | | |
| | 技術移轉 | 件數 | 0 | 0 | 100% | 件 | |
| | | 權利金 | 0 | 0 | 100% | 千元 | |
| | 參與計畫人力（外國籍） | 碩士生 | 0 | 0 | 100% | 人次 | |
| | | 博士生 | 0 | 0 | 100% | | |
| | | 博士後研究員 | 0 | 0 | 100% | | |
| | | 專任助理 | 0 | 0 | 100% | | |

| | |
|---|---|
| 其他成果<br>(無法以量化表達之成果如辦理學術活動、獲得獎項、重要國際合作、研究成果國際影響力及其他協助產業技術發展之具體效益事項等，請以文字敘述填列。) | 無 |

| | 成果項目 | 量化 | 名稱或內容性質簡述 |
|---|---|---|---|
| 科教處計畫加填項目 | 測驗工具(含質性與量性) | 0 | |
| | 課程/模組 | 0 | |
| | 電腦及網路系統或工具 | 0 | |
| | 教材 | 0 | |
| | 舉辦之活動/競賽 | 0 | |
| | 研討會/工作坊 | 0 | |
| | 電子報、網站 | 0 | |
| | 計畫成果推廣之參與（閱聽）人數 | 0 | |

# 國科會補助專題研究計畫成果報告自評表

請就研究內容與原計畫相符程度、達成預期目標情況、研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）、是否適合在學術期刊發表或申請專利、主要發現或其他有關價值等，作一綜合評估。

1. 請就研究內容與原計畫相符程度、達成預期目標情況作一綜合評估

■達成目標

□未達成目標（請說明，以 100 字為限）

□實驗失敗

□因故實驗中斷

□其他原因

說明：

2. 研究成果在學術期刊發表或申請專利等情形：

論文：■已發表 □未發表之文稿 □撰寫中 □無

專利：□已獲得 □申請中 ■無

技轉：□已技轉 □洽談中 ■無

其他：(以 100 字為限)

3. 請依學術成就、技術創新、社會影響等方面，評估研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）(以 500 字為限)

胞漿素原活化劑及胞漿素系統(plasminogen activator/ plasmin system)和基底膜的降解、組織纖維化及組織重組非常有關係。而 u-PA 及其 receptor u-PAR 在許多癌症的致病過程有密切的相關性已是不爭的事實，但是 u-PA、u-PAR 及其抑制劑 PAI-1 的基因多型性與子宮頸癌的致癌過程及其相關性卻仍不清楚。因此，本實驗利用聚合酶鏈限制性連鎖反應-切割片段長度多型性(PCR-RFLP)的方式，分析 136 位子宮頸上皮內贅瘤及子宮頸癌病人與 336 位非癌症之對照組，其 u-PA、u-PAR 及其抑制劑 PAI-1 基因多型性的相關性。結果發現 uPA 及 PAI-1 分別攜帶 CC/4G4G 與帶有 CC/4G5G 基因型的個體相比較，發現在罹患子宮頸癌的機率有 1.70 倍的危險值，(OR=1.70； 95% CI 1.04-2.79) 。因此，我們發現，在台灣的個體中，u-PAPAI-1 的基因型與罹患子宮頸癌的機率有明顯的差異，但是分析 u-PA, PAI-1 及 u-PAR 的基因型與子宮頸癌的癌化過程及其與 stage, 腫瘤大小皆沒有明顯的相關性。