

## **Research Assessment Exercise 2020 Impact Case Study**

**University:** *City University of Hong Kong*

**Unit of Assessment (UoA):** *01 - Biological Sciences (incl. environmental biology, biotechnology, agriculture & food science, veterinary studies)*

**Title of case study:** *Development and Commercialisation of a DNA Chip Technology for Analysis of Mutations and Viral Genotyping*

### **1. Summary of the impact**

A DNA chip technology developed at City University of Hong Kong has been licensed to City University spinoff company Genetel Pharmaceuticals. This novel method for detection and genotyping of human papilloma virus (HPV) was approved by the Chinese Food and Drug Administration of China and is used by hundreds hospitals throughout China, where hundreds of thousands of women have been screened for cervical cancer. As early detection of HPV is paramount for the prevention of cervical cancer, thousands of lives have likely been saved as a consequence.

### **2. Underpinning research**

Professor Yang Mengsu has been working in DNA microarray technologies for genotyping and pathogen detection throughout his career. Patents for different microchip technologies were granted as early as 2002. The research described here is based on these early inventions. The description is however limited to the findings that directly lead to the development of the SNIPER technology for the detection of *human papilloma virus (HPV)*, which continued to have a significant impact on healthcare throughout China during the assessment period.

Since 2000, Prof Yang and his colleagues at City University of Hong Kong had been granted a series of patents [3]-[5] describing the methods of fabrication and signal detection for medium density DNA chips, and the applications of such DNA chips for the detection of DNA mutations. Some of the results were subsequently published in the journal *Analytical Letters* [1] in which the authors described a technology for DNA detection later used to develop the SNIPER test. In that study the focus was on detecting a point mutation in the genome of the RNA polymerase of *Mycobacterium tuberculosis*, which confers antibiotic resistance to the bacterium. Fundamentally, the technology comprised four steps: the design of oligonucleotide probes for identifying different drug resistance mutations, isolating genomic DNA from tissue samples carrying the bacterium, amplifying and fluorescence labelling the sequence carrying the RNA polymerase subunit of interest and finally, hybridisation of the samples on an array containing the different oligonucleotide probes. The arrays were printed on microscope slides such that each oligonucleotide probe would bind to only one location. Consequently, during the hybridisation step, only those bacterial DNA strands would bind to the respective locations on the slide that contained the complementary DNA probes, amplifying the fluorescent signal in the process. The results demonstrated that with this "differential hybridisation" approach different mutations of the RNA polymerase subunit of the tuberculosis bacterium could be detected with high specificity.

The usefulness of the resulting technology was later confirmed by Professor Yang and his coworkers as a drug screening platform, for the genotyping of the Hepatitis C virus and for the detection of the human papillomavirus (HPV, [2]). In 2006, the technology was licensed to the Shenzhen based company Genetel Pharmaceuticals Ltd. Genetel acquired market approval by the Chinese Food and Drug Administration in 2006 to sell the test under its brand name *SNIPER HPV Genotyping Diagnosis Kit*.

### 3. References to the research

#### *Research Papers*

- [1] Yang, M. S.; Tsoi, P. Y.; Li, C. W.; Woo, H. S.; Zhao, J.; Yam, W. C. Detection of mutations in RNA polymerase beta subunit gene encoding resistance to rifampin in *Mycobacterium tuberculosis* by DNA microarray, *Analytical Letters*, 2005, 38, 2117-2134.
- [2] Yip, Y. C.; Ngai, K. L. K.; Vong, H. T.; Tzang, C. H.; Ji, S. L.; Yang, M. S.; Chan, P. K. S. "Prevalence and genotype distribution of cervical human papillomavirus infection in Macao", *Journal of Medical Virology*, 2010, 82, 1724-1729.

#### *Patents*

- [3] Yang, M. S.; Miao, J. M. "Methods for fabrication of medium-density DNA chips", PRC patent application no. 99 104 666.8. Publication no. 1273362, Nov. 15, 2000. Granted
- [4] Yang, M. S.; Lei, G.-H. "Methods for detection of false-positive and false-negative hybridization signals on DNA chips", PRC patent application no. 99 104 668.4. Publication no. 1273363, Nov. 15, 2000. Granted
- [5] Yang, M. S.; Woo, H. S. "Mutation detection on RNA polymerase beta subunit gene having rifampin resistance", USA Patent Filing No. 09/949,041, September 7, 2001. Published on June 5, 2003: publication no. US-2003-0104387-A1. US Patent No. 6,902,894 Granted

### 4. Details of the impact

#### *The problem*

Human Papilloma Virus (HPV) is an extremely common group of sexually transmitted viruses. According to the World Health Organisation (WHO) at least 13 of the 100 known HPV types cause cancer of the urogenital tract and virtually all cases of cervical cancer are linked to an HPV infection.[A] Since the first HPV vaccine was introduced in 2006, public vaccination programs have significantly reduced the incidence of HPV infections. However, cervical cancer due to HPV infection remains the fourth most frequent cancer in women worldwide and the second most common cancer in females in the developing world. [B]

Most HPV infections are short-lived, but chronic infections can cause lesions to the mucous membranes of the anogenital area, which can ultimately lead to malignant alterations of the affected tissue. While there is no treatment against the HPV virus itself, HPV related cervical pre-cancer can be treated with high rates of success. Hence, early detection of an HPV is paramount to induce the necessary cancer screening in infected individuals. [C] Since no blood

test for HPV is available and most other tests require a complex healthcare infrastructure — often not available in developing countries — the availability of cheap, highly sensitive and selective tests for HPV screening is of crucial importance.

#### *The SNIPER HPV Test*

The SNIPER HR HPV fills this gap in HPV screening. This novel rapid and cost-effective test for HPV has been used in mainland China since 2007 and keeps expanding its impact on cervical cancer screening. The technology was developed by the group of Prof. Michael Yang Mengsu of the Department of Biomedical Science at City University of Hong Kong. The method consists of first isolating genomic DNA from a sample a pathogen, then amplifying a gene sequence of interest to produce fluorescently labelled probes, which are then used for hybridization on oligonucleotide arrays (see Research).

In 2010, an independent study [D] in the *International Journal of Gynecological Cancer* confirmed the sensitivity and specificity of the SNIPER test in a large field study with 979 women in Guizhou, China. In particular, the authors write that testing for HR-HPV with the SNIPER assay was far more sensitive than cervical cytology (93.3 vs. 63.3) for the detection of  $\geq$ CIN II in a population of women in Guizhou, China. The same was true for the detection of  $\geq$ CIN III (94.1 vs. 76.5).” CIN in this context refers to *cervical intraepithelial neoplasia*, a precancerous change of the cervical epithelium. So the *true positive rate* of the SNIPER test, the percentage of affected women who were correctly identified, was higher much higher compared to a Pap smear test (ASCUS abnormal cervical cytology).

According to Genetel Pharmaceuticals, the Shenzhen based pharmaceutical company offering the SNIPER test, during the assessment period between 2012 and 2017 an estimated 4,5 Million SNIPER tests have been sold to hospitals and gynecological practices throughout China. Furthermore, the number of tests sold has been growing steadily, from 301,000 in 2012 to 1.2 Million in 2017 [E]. This impact on public health in China has been recognised by several government institutions and a number of high profile awards [F] have been bestowed on Prof Yang Mengsu for developing the technology. Several Chinese and English media outlets reported on the SNIPER Test and the public recognition it gained Genetel and City University of Hong Kong [G].

In conclusion, the SNIPER HPV Test had a strong public health impact during the assessment period of the the 2020 RAE, improving the rates of early detection of chronic human papilloma infections and associated precancerous lesions. In this manner, the work performed by Prof Yang and his coworkers at City University of Hong Kong has helped improve the life quality and contributed significantly to saving lives of thousands of women.

## **5. Sources to corroborate the impact**

[A] Lee, L. Y., & Garland, S. M. (2017). Human papillomavirus vaccination: the population impact. *F1000Research*, 6, 866. doi:10.12688/f1000research.10691.1  
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[B] World Health Organisation  
<https://www.who.int/immunization/diseases/hpv/en/>  
[https://www.who.int/news-room/fact-sheets/detail/human-papillomavirus-\(hpv\)-and-cervical-cancer](https://www.who.int/news-room/fact-sheets/detail/human-papillomavirus-(hpv)-and-cervical-cancer)

- [C] Human Papillomavirus (HPV) Treatment and Care  
<https://www.cdc.gov/std/hpv/treatment.htm>
- [D] Belinson, S. E., Wulan, N., Li, R., Zhang, W., Rong, X., Zhu, Y., ... Belinson, J. L. (2010). SNIPER: a novel assay for human papillomavirus testing among women in Guizhou, China. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society*, 20(6), 1006–1010.  
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2012-2014: Annual Reports of Genetel parent company Mingyuan Medical Group
- [F] Awards  
  
2006 Hong Kong Awards for Industry – Technological Achievement Grand Award  
2006 Science and Technology Innovation Award of Shenzhen  
2007 National Key Innovative Product Certificate
- [G] News Reports  
  
Economic Daily (2007)  
South China Morning Post (2007)  
Tsing Tao Daily (2007)  
Wen Wei Po (2007)