Institution University of Bedfordshire

Unit of Assessment: 12

Title of case study: Development and commercialisation of robotic nanomanipulation of living cells

Period when the underpinning research was undertaken:
2010 - 2019

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Dayou Li	Professor of Robotics	Permanent since 2002
Zuobin Wang	Professor of Laser Interference Lithography	0.3 FTE professor Nov. 2017 to Dec. 2020 Visiting Professor since 2011
Litong Dong	Research Fellow in Nanomaterial Fabrication	Oct. 2019 to Jul. 2021
Ziang Zhang	Research Fellow in Laser Interference Lithography	Nov. 2017 to Dec. 2018

Period when the claimed impact occurred:
2017-Present

Is this case study continued from a case study submitted in 2014?
No

1. Summary of the impact (indicative maximum 100 words)

Collaborative research between the University of Bedfordshire and Changchun University on in vitro cell nanomanipulation provided extensive improvements in this technology that resulted in the establishment of the spin-off company Changli-nanobio. The research led to the development of a multiple information nanoscopic detector, now used by Changli-nanobio to provide in vitro cell analysis services to hospitals, pharmaceutical and food supplement industries. This has led to new ways of dignosing and treating cancer and optimisation of ingredients for food supplement use. The company contributes to the economy in China by the creation of new jobs and transforming regional employment.

2. Underpinning research (indicative maximum 500 words)

Manipulation of nano materials is being applied to many scientific and technology areas including biology, medicine, physics and chemistry. In 2010, the University of Bedfordshire and Changchun University of Science and Technology (CUST) founded the Joint Research Centre for Computer Controlled Nanomanufacturing (JR3CN), to form synergy in nanotechnology through combining strengths and expertise in computer science and robotics from Bedfordshire with nanomanufacturing from CUST. In this collaboration Professor Zuobin Wang and Professor Dayou Li lead in vitro cell nanomanipulation and their research has been directed to obtaining multiple dimensional information of living cells to aid in understading diseases propagation, evaluating new drugs and developing new food supplement products.

A team led by Wang and Li developed a four-beam laser interference lithography based method to fabricate special surface structures of substrate where cells are placed and

cultured for them to be manipulated and measured at the nano scale (**3.1).** Wang and Li then developed a method for the magnetic manipulation of nanoparticles, allowing drug coated magnetic nanoparticles (MNPs) to be inserted into living cells **(3.2).** They confirmed helical capture path was more precise and flexible than pushing and sliding when picking MNPs with the magnetic probe in atomic force microscopy (AFM) and that the force required for picking up MNPs is about the same as the magnetic force the probe applies to the particles. Wang and Li also showed that that the problems of magnetic contamination of the probe which can seriously affect the quality of the imaging can be improved substantially by a method of cleaning the probe by using a biaxially-orientated polypropylene film **(3.3).** These studies proposed the use of an external magnet to release MNPs from the probe **(3.3).**

Further work on cell adhesion force measurement led to establishment of a mathematical model of cellular adhesion force and horizontal components of forces that cause the probe to twist and bend (**3.4**). The model led to the proposal to perform cell imaging one step ahead of adhesion force measurement and then using the cell morphology to decide the locations of AFM probes for more accurate nanomanipulation **(3.4).**

These advances were then applied to demonstrate self-assembly of λ-DNA networks, enabling DNA molecule editing. A DC electric field was applied to obtain linear DNA molecules, and AFM was then used to perform picking up a specific endonuclease and cutting of specific site of a DNA molecule to realise enzymatic cleavage at the corresponding site **(3.5).** In addition work on the development of the conductive probe in AFM was used to cause nerve cell damage providing new ways to observe cell self-repair **(3.6).**

In summary, the work developing robotic manipulation of living cells **(3.1-3.6)** has led to the development of a novel multiple information nanoscopic detector which has been commercialised and used by Changli-nanobio to provide nanomanipulation services to industry and hospitals (see Details of the Impact).

3. References to the research (indicative maximum of six references)

3.1. Le Zhao, Zuobin Wang, Jinjin Zhang, Miao Yu, Siwei Li, Dayou Li and Yong Yue: "Effects of laser fluence on silicon modification by four-beam laser Interference", Journal of Applied Physics, 2015, 118, 233106

3.2. Jinyun Liu, Wenxiao Zhang, Yiquan Li, Hanxing Zhu, Renxi Qiu, Zhengxun Song, Zuobin Wang and Dayou Li, "Mechanical Manipulation of Magnetic Nanoparticles by Magnetic Force Microscopy, Journal of Magnetism and Magnetic Materials, 2017, 443, 184-189.

3.3. Chao Zhang, Jinyun Liu, Qingling Meng, Wenxiao Zhang, Ying Wang, Dayou Li and Zuobin Wang: "Cleaning of contaminated MFM probes using a BOPP film and external magnetic field", Micron, 2017, 97, 1-5.

3.4. Yu Hou, Zuobin Wang, Dayou Li, Renxi Qiu, Yan Li and Jinlan Jiang, "Cellular Shear Adhesion Force Measurement and Simultaneous Imaging by Atomic Force Microscope", Journal of Medical and Biological Engineering, 2017, 37, 102-111.

3.5. Mingyan Gao, Jing Hu, Ying Wang, Mengnan Liu, Jianfei Wang, Zhengxun Song, Hongmei Xu, Cuihua Hu, and Zuobin Wang, "Controlled Self-Assembly of λ-DNA Networks with the Synergistic Effect of DC Electric Field", The Journal of Physical Chemistry B, 2019, 123, 9809-9818.

3.6. Caijun Liu, Xueyan Han, Xueying Yang, Liguo Tian, Ying Wang, Xinyue Wang, Huanzhou Yang, Zenghui Ge, Cuihua Hu, Chuanzhi Liu, Zhengxun Song, Zhankun Weng,

Zuobin Wang: “Self-repair behaviour of the neuronal cell membrane by conductive atomic force indentation IET Nanobiotechnol.”, 2019, 13, 891-895.

4. Details of the impact (indicative maximum 750 words)

Commercial impact

The joint research centre (JR3CN) was funded in 2011 according to an agreement between the University of Bedfordshire and Changchun University of Science and Technology (CUST). Emanating from the research achievements of the Centre, Changli-nanobio Ltd, a spin-off at CUST, was founded in 2017 (**5.1**). The company has grown from less than 20 (FTE) to 60 (FTE) employees in the last three years. It has received 25 million RMB (around £2.8 million) of venture capital investment and its revenue amounted to 7 million RMB (around £800K) (**5.2)** in the last 3 years. Its present asset value is about 165 million RMB (around £18 million) (**5.3**).

The company’s main product is the multidimensional information nanoscopic detector developed based on JR3CN research (**3.1-3.6**). The device enables in vitro cell manipulation through molecular level physical and chemical methods and images the cells through atomic force and tunnelling current to measure the properties of living cells in the dimensions of sound, light, electricity, magnetism and force. The device also facilitates cell contents editing, such as DNA scratching, cutting and editing.

The nanoscopic detector has led to 8 Chinese patents and the Scientific and Technology Innovation Evaluation Station has evaluated the novelty of the instrument. Its report states: “The multiple information nanoscopic detector is unique with respect to 1) single cells properties capturing morphological, mechanical, electrical, magnetic, optical and sonic dimensions through nanomanipulation using AFM probes, single cell real-time tracking with the combination of MFM and MNPs, …, 4) electrical property capturing of cells using nano electrode array and AFM, 5) cell culturing using LIL-based micro-/nano-structural substrates, and 6) MNPs transmission and DNA editing through AFM.” (**5.4)**. This device forms the foundation of the primary commercial services delivered by Changli-nanobio Ltd.

Impacts on health

Using the nanoscopic detector, the company has provided their customers, including three pharmaceutical companies and six hospitals, with services of in vitro cell nanomanipulation and measurements for purposes such as safety and efficacy evaluation of traditional Chinese medicines, early diagnosis of disease and food supplements development.

Jilin University First Hospital is one of the six hospitals that requested Changli-nanobio to show how a non-small lung cancer cell line H1499 changes with respect to its biological, morphologic, mechanical and electrical properties along with non-small lung cancer propagates. Dr Shuwei Wang who is leading the trial of using the information of cell properties in cancer diagnosis in the hospital said “We are in the trial of a new way of diagnosis by engaging the information of H1299 properties into our current methods of diagnosis……I am optimistic about the usefulness of the cell property information this new method would promote early non-small lung cancer diagnosis and more effective control of disease propagation and, hence, reduce patients’ suffering and economic cost”. (**5.5**).

Tiansheng Pharmaceutical is one of three pharmaceutical manufacturers that requested quantitative efficacy of traditional Chinese medicines. The technical agreement between this company and Changli-nanobio has led to the completion of efficacy of seven ingredients for a new medicine (**5.6**).

Changli-nanobio also developed its own food supplement, called Shenpuyin, the main ingredients of which are ginseng and wild grape. Changli-nanobio obtained the optimal ratio

of the two using its multiple information nanoscopic detector. Shengpuyin is designed for people who need to work into the night such as long-distance vehicle drivers and night-shift office workers (**5.7**). Some customers describe it as "refreshing", and "energetic (**5.8**).

Societal impacts on the region

Changli-nanobio is the first high-tech nano-bio company in Jilin Province where the company is located. The provincial government faces challenges to re-build the region's economy. The significance of high-tech enterprises in the rebuilding of the regional economy is testifield in the Jilin Province Government Annual Report 2020 which listed the progress in the optimisation of provincial economy structure as one of the eight achievements in 2020 and addressed creating new opportunities for economic development "relying on scientific and technological innovation" right at the top of the agenda in the government's workplan for 2021 (**5.9**). Changli-nanobio is located in Changchun Economic-Technological Development Zone (ETDZ), as part of the provincial government's early effort in promoting high-tech companies to optimise economic restructuring . The company was invited to join Changchun ETDZ in 2017. It was one of four high-tech companies having been invited to the ETDZ of that year. The Changchun ETDZ has provided 6,000,000 RMB (about £700,000) and 150 m^2 office/lab space to develop nanobio products (**5.10**). Changli-nanobio has been at the forefront of developing the ETDZ's capacity in nanotechnology and for applications in biomedicine.

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1. Nano Measurement and Handing Technology Strategic Cooperation Agreement (English translation provided as **5.1a**)

5.2. Changli-Nanobio report (English translation of key paragraphs provided as **5.2a**)

5.3. Changli-nanobio Asset Value Estimation Report, Beijing Zhongkehua Asset Estimation Ltd, No. 120, 2018 (English translation of the key section provided as **5.3a**)

5.4. Innovation Evaluation Report (English Translation of highlighted part on P6 provided as **5.4a**)

5.5. Letter from Jilin University First Hospital

5.6. Statement of agreement between Changli-nanobio and Tiansheng Parmaceutical

5.7. Statement of Shenpuyin development from Changli-nanobio

5.8. Customers comments on Shengpuyin

5.9. Jilin Provincial Government Report, http://www.jl.gov.cn/zw/jcxxgk/gzbg/szfgzbg/202102/t20210201_7932069.html (English trasltion of the related section provided as **5.9a**)

5.10. Collaboration Agreement betweet Changchun Economic-Technological Development Zone and Changli-nanobio Ltd (English translation of the related section provided as **5.10a**)