The Legacy of Synthetic Bovine Insulin: A Journey of Dedication, Collaboration and Innovation

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Abstract: The artificial total synthesis of crystalline bovine insulin is a milestone achievement of Chinese scientists in the field of life sciences since the founding of the People's Republic of China. The article briefly reviews several historical events of the artificial total synthesis of bovine insulin, with the intentions of summarizing the historical experience of dedication, cooperation and innovation embedded in this achievement, and inspiring contemporary Chinese scientists.

Key words: artificial synthesis of insulin, spirit of dedication and innovation

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Early on the morning of 17 September 1965, DU Yucang, a researcher at the Institute of Biochemistry of the Chinese Academy of Sciences (CAS), walked out of the laboratory holding a test tube. In his raised hand, the transparent hexagonal crystals of synthetic bovine insulin glistened in the light. "It jumped! It jumped!" All the researchers who witnessed this moment immediately hailed and jumped in raptures. This was the experimental result they had been eagerly waiting for after thousands of days and nights of work. The jumping response of the mouse, which was administered with the artificially synthe-

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sized bovine insulin, was exactly the result of an insulin overload caused by a hypoglycaemic seizure, proving that the synthetic bovine insulin has the same biological function as natural insulin (CAS Shanghai Institute of Biochemistry *et a*l., 1966).

This moment, marking the world's first successful synthesis of fully crystalline bovine insulin, is a historic milestone in science since the founding of the People's Republic of China in 1949 (CAS Shanghai Institute of Biochemistry *et al.*, 1966). From the approval of the project in December 1958 to the observation of crystallization in September 1965, this achievement took nearly seven years of dedicated efforts during a long period of complex and intense international competition.

How It Began

Not until this remarkable achievement did China unexpectedly attract the attention of international academia – the newly born nation had unfortunately been lagged behind in the two decades of rapid and vigorous progress in biochemical science worldwide.

The idea of producing synthetic bovine insulin was put forward at a symposium of leading scientists at the CAS Institute of Biochemistry in the summer of 1958. At that time, Dr. Frederick Sanger from the UK had just determined the primary sequence of insulin. Subsequently, the journal Nature predicted that the synthesis of insulin would be a distant prospect.

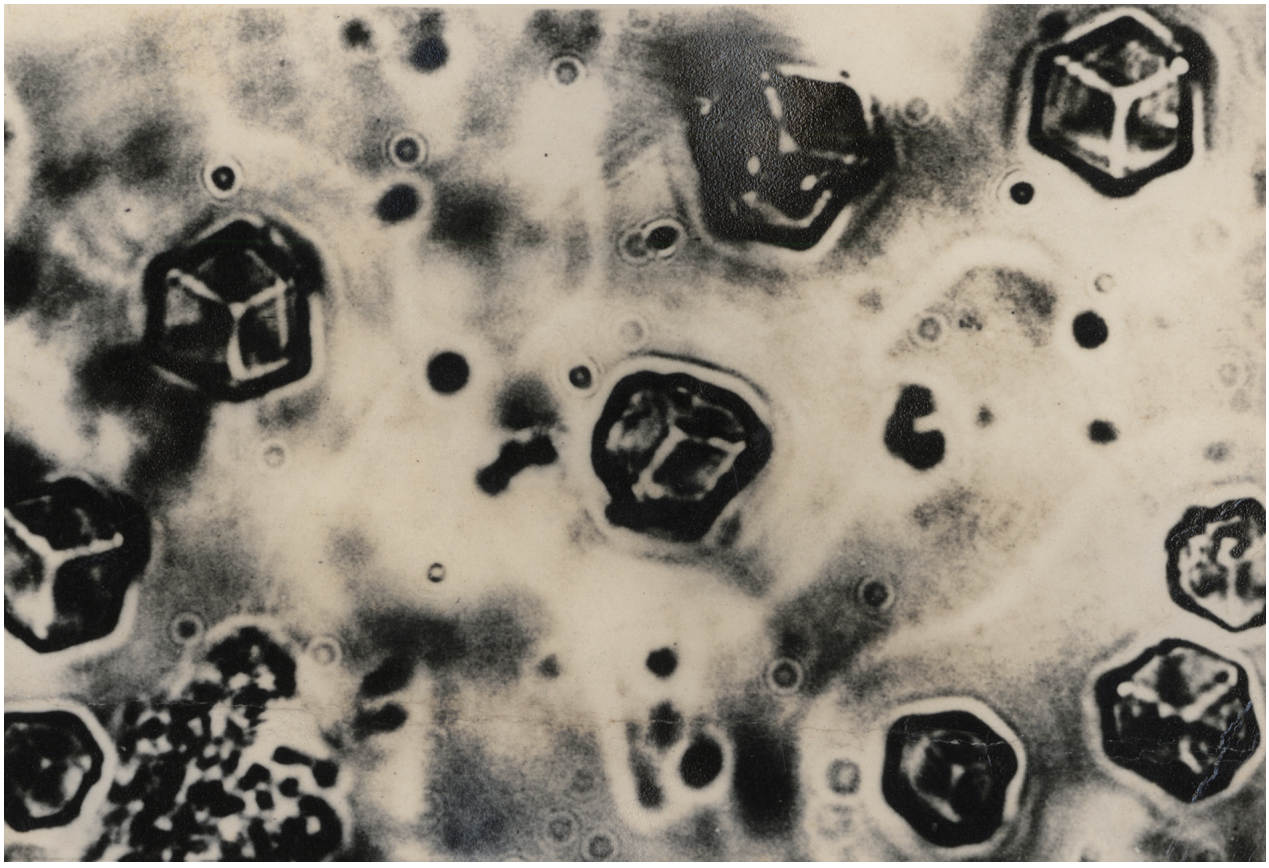
With the ambition to tackle challenges, a group of scientists led by Dr. WANG Yinglai, then Director of the Institute of Biochemistry, accurately assessed the frontier of biochemical research and made the crucial decision to pursue "artificial synthesis of proteins – bovine insulin".

Against All Odds

In the 1950s, China was in its early stages of development and its scientific research base was

Bovine insulin, the world's first synthetic protein, being assayed for its biological activity.

Graphic: CEMCS



Graphic: CEMCS

Hexagonal crystals of synthetic bovine insulin in the lens of a microscope.

far from solid. In order to keep pace with the advances in fundamental fields, it was imperative to strengthen the capacity for scientific and technological innovation, so as to lay a solid foundation for China's core competitiveness. The Institute of Biochemistry's decision to explore the "no man's land" was in line with the national strategic goals at that time.

Obviously, synthesizing insulin is not an easy task, and in the early stages there were even more considerable challenges. The research team faced a shortage of raw materials, namely amino acids. Undaunted, the team took the initiative to establish the Dong Feng Biochemical Reagent Factory and successfully launched the first amino acid production line in China. In addition, the team developed protocols for the separation and reconstitution of the A and B chains of natural insulin, a remarkable breakthrough that established a clear route for insulin synthesis and activity validation (CAS Shanghai Institute of Biochemistry *et al*., 1966).

In the early 1960s, progress on the synthetic bovine insulin project was temporarily slowed by national economic difficulties. Nevertheless, the Institute of Biochemistry continued the research with a dedicated team of professionals. In August 1963, with the encouragement of the State Science and Technology Commission and the CAS leadership, the CAS Institute of Biochemistry, the CAS Institute of Organic Chemistry and Peking University officially began their collaboration, unanimously agreeing to synthesize "bovine insulin of neither Shanghai nor Beijing, but China". Two years later, synthetic bovine insulin was finally launched to great acclaim (CAS Shanghai Institute of Biochemistry *et al*., 1966).

The news of the successful synthesis of bovine insulin brought international recognition, invigorated the entire nation, and instilled pride in Chinese scientists to boost their self-confidence. "China has achieved one world scientific

Graphic: CEMCS

Mr. WANG Yinglai is working at the desk.

honor and should strive for another", this slogan spurred the research team to embark on another ambitious project.

Further Exploration

In 1968, the Institute of Biochemistry launched the project to synthesize yeast alanine transfer ribonucleic acid, which was comparable in honor to the synthesis of bovine insulin. After 13 years of perseverance and unremitting efforts in collaboration with various research institutes, this project finally succeeded and culminated in the establishment of China's leading position in nucleic acid research (CAS Shanghai Institute of Biochemistry *et al*., 1982).

From the synthesis of a protein to the synthesis of a nucleic acid, these two successive and progressive achievements, like two magnificent twin blossoms, successively won the first prize of the State Natural Science in 1982 and 1987 respectively, and wrote a glorious and monumental chapter in the history of scientific and technological development of the People's Republic of China.

The year 2025 will mark the 60th anniversary of the discovery of synthetic bovine insulin. Looking into the future, how to perpetuate the legacy of this groundbreaking discovery and inspire researchers to stay at the forefront has become a key focus for the Centre of Excellence in Molecular Cell Science of CAS, the successor to the Institute of Biochemistry.

New Journey

The Centre currently comprises a high-caliber team of 75 academic leaders, including 10 CAS Members, 29 National Outstanding Young Scholars and 4 New Cornerstone Fellows. Our mission is to conduct basic and applied research at the forefront of life sciences, focusing on the following areas: the basis and function of ribonucleic acid (RNA); the molecular basis and

Graphic: CEMCS

On 14 December 1978, Vice Premier NIE Rongzhen received all comrades attending the insulin synthesis evaluation meeting at the Great Hall of the People in Beijing.

regulation of cell fate plasticity; and the mechanisms underlying disease development and related treatment strategies. We have made significant breakthroughs of international influence, such as revealing the important role of TET dioxygenases in mammalian epigenetic regulation, generating androgenetic haploid embryonic stem cells that can support full-term embryonic development, developing a new method of tumor immunotherapy based on the regulation of cholesterol metabolism, etc. A total of six achievements by our colleagues were selected as the Top Ten Scientific Advances in China (Shao *et al*., 2018; Dai *et al*., 2016; Yang *et al*., 2016; Yang *et al*., 2012; Gu *et al*., 2011; He *et al*., 2011; Huang *et al*., 2011). Notably, in the 2023 National Science and Technology Awards, the Centre harvested two second prizes for the National Natural Science Award.

Synthetic bovine insulin represents China's first foray into large-scale, high-level research and is a highly successful example of the "big science" research model in the life sciences. At present, a new round of technological revolution is unfolding, with deep structural adjustment and renewal as a driving force to maintain the development momentum. However, the current institutional structure of the Centre is somewhat dispersed, which may limit our ability to pursue large-scale projects and tackle major scientific challenges, especially in the context of today's intensifying scientific and technological competition. To address this issue, the Centre has implemented two scientific research structures from 2022 onwards, namely "Collaborative Research Group" and "Scientists Studio", based on the individual research group leader mechanism. These approaches draw on the experience from the synthetic bovine insulin framework and are designed to enhance teamwork to solve basic and even application problems that cannot be solved by a single team.

From its establishment to the present day, the Centre of Excellence in Molecular Cell Science of CAS has undergone a series of reforms and innovations over the past 70 years. All the adjustments and renewals are aimed at development. Despite these changes, the spirit of dedication to the search for truth and uni-

ty that characterized the early days of the Centre has remained unchanged. The scientific milestones achieved by the pioneers are now being carried forward by the new generation of scientists, who are striving to build on the achievements of their predecessors.

References

CAS Shanghai Institute of Biochemistry, Department of Chemistry of Peking University & CAS Shanghai Institute of Organic Chemistry. (1966) Total Synthesis of Crystalline Insulin – I–V. *Science Bulletin*, (06): 241–244. (In Chinese)

CAS Shanghai Institute of Biochemistry, CAS Shanghai Institute of Cell Biology, CAS Shanghai Institute of Organic Chemistry, CAS Institute of Biophysics, Department of Biology of Peking University, & Shanghai No.2 Factory of Reagents. (1982) Total synthesis of yeast alanine transfer ribonucleic acid. *Science Bulletin*, (02): 106–109. (In Chinese)

Hai-Qiang Dai, Bang-An Wang, Lu Yang, Jia-Jia Chen, Guo-Chun Zhu, Mei-Ling Sun, Hao Ge, Rui Wang, Deborah L. Chapman, Fuchou Tang, **Xin Sun***, **Guo-Liang Xu***. (2016) TET-mediated DNA demethylation controls gastrulation by regulating Lefty-Nodal signalling. *Nature* 538, 528–532.

Tian-Peng Gu, Fan Guo, Hui Yang, Hai-Ping Wu, Gui-Fang Xu, Wei Liu, Zhi-Guo Xie, Linyu Shi, Xinyi He, Seung-gi Jin, Khursheed Iqbal, Yujiang Geno Shi, Zixin Deng, Piroska E. Szabó, Gerd P. Pfeifer, **Jinsong Li*** and **Guo-Liang Xu***. (2011) The role of Tet3 DNA dioxygenase in epigenetic reprogramming by oocytes. *Nature* 477, 606–610.

Yu-Fei He, Bin-Zhong Li, Zheng Li, Peng Liu, Yang Wang, Qingyu Tang, Jianping Ding, Yingying Jia, Zhangcheng Chen, Lin Li, Yan Sun, Xiuxue Li, Qing Dai, Chun-Xiao Song, Kangling Zhang, Chuan He, **Guo-Liang Xu***. (2011) Tet-mediated formation of 5-carboxylcytosine and its excision by TDG in mammalian DNA. *Science* 333, 1303-07.

Pengyu Huang, Zhiying He, Shuyi Ji, Huawang Sun, Dao Xiang, Changcheng Liu, Yiping Hu, Xin Wang, **Lijian Hui***. (2011) Induction of functional hepatocyte-like cells from mouse fibroblasts by defined factors. *Nature* 475, 386–389.

Yangyang Shao, Ning Lu, Zhenfang Wu, Chen Cai, Shanshan Wang, Ling-Li Zhang, Fan Zhou, Shijun Xiao, Lin Liu, Xiaofen Zeng, Huajun Zheng, Chen Yang, Zhihu Zhao, **Guoping Zhao***, **Jin-Qiu Zhou***, **Xiaoli Xue*** & **Zhongjun Qin***. (2018) Creating a functional single-chromosome yeast. *Nature* 560, 331–335.

Wei Yang, Yibing Bai, Ying Xiong, Jin Zhang, Shuokai Chen, Xiaojun Zheng, Xiangbo Meng, Lunyi Li, Jing Wang, Chenguang Xu, Chengsong Yan, Lijuan Wang, Catharine C. Y. Chang, Ta-Yuan Chang, Ti Zhang, Penghui Zhou, Bao-Liang Song, Wanli Liu, Shao-cong Sun, Xiaolong Liu, **Bo-liang Li*** & **Chenqi Xu***. (2016) Potentiating the antitumour response of CD8+T cells by modulating cholesterol metabolism. *Nature* 531, 651–655.

Hui Yang, Linyu Shi, Bang-An Wang, Dan Liang, Cuiqing Zhong, Wei Liu, Yongzhan Nie, Jie Liu, Jing Zhao, Xiang Gao, Dangsheng Li, **Guo-Liang Xu***, **Jinsong Li***. (2012) Generation of genetically modified mice by oocyte injection of androgenetic haploid embryonic stem cells. *Cell* 149, 605–617.