高通量紫外光化工芯片激光制造

程 亚

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华东师范大学极端光机电实验室

2023.2.23

汇 报 提 纲

一. 颠覆的应用场景描述

二. 另辟蹊径的技术路线

三. 项目技术来源与变革性

四. 产业化应用前景与可行性

汇 报 提 纲

化工、制药等流程产业的现状

传统化工制药行业，存在显著并难以克服的痛点

- ◆占地面积广
- ◆传热、传质能力弱
- ◆过程不连续
- ◆对剧烈反应控制能力差
- ◆设备体积庞大

- ➤ 土地资源利用率低
- ➤ 原料利用率低，产品质量稳定性差
- ➤ 三废排放高，环境污染严重
- ➤ 安全隐患大
- ➤ 新产品研发成本高

土地稀缺

环保严峻

生产安全

近期化工、制药行业发生的系列重大安全事故

2019年3月21日江苏盐城

2022年6月18日上海金山

2022年11月3日安徽滁州

2022年2月24日河北唐山

化工、制药领域的技术变革发展趋势

500年来，化学工业的主要技术近乎一成不变

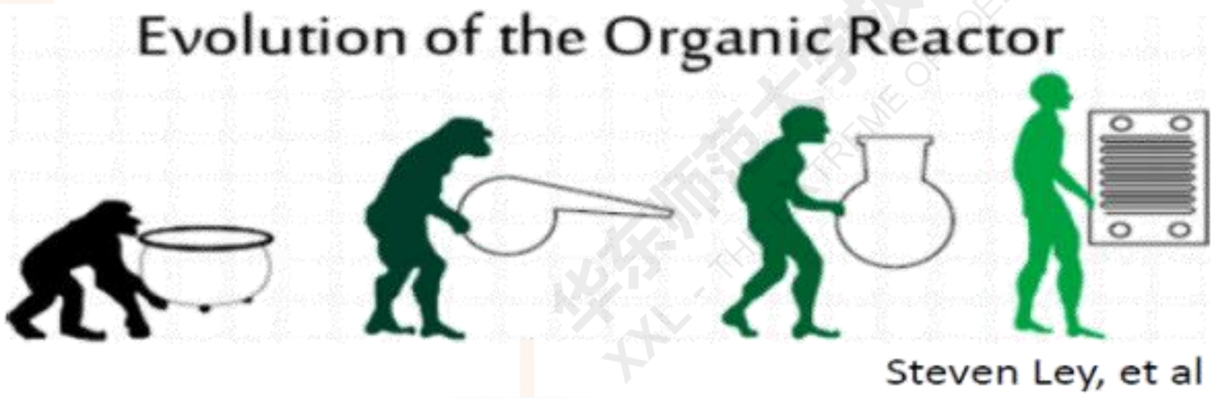
c.1556

1956

2008

Nothing has changed in nearly 500 years

近十年
化工反应器
走向微型化 ➡



痛点的解决方案：连续流微化工及其优势

- 几何结构
- 传质传热

↓

安 全

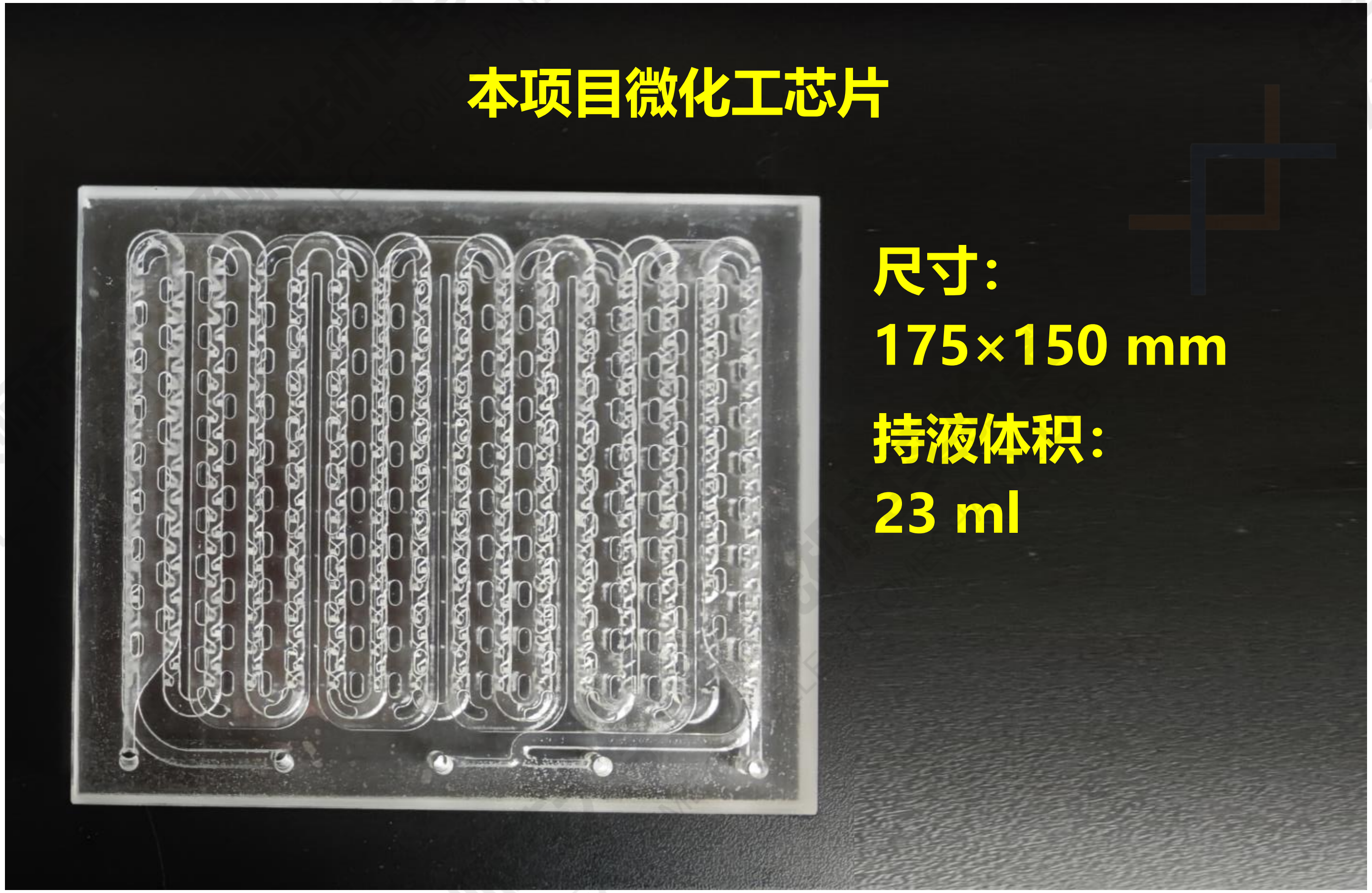
爆炸概率低、危害小

清 洁

三废排放少

高 效

低成本、高灵活性



	材质	温度	耐压	结构
本项目	玻璃	-70℃-250℃	2.0 MPa	三维定制化

本项目团队研制的微化工芯片与反应器已在企业开展验证应用

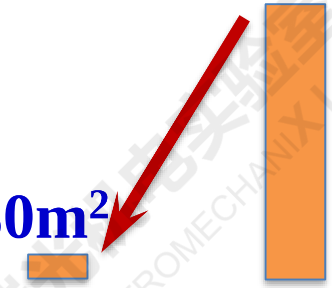
DESANO 迪赛诺

迪赛诺公司为全球最大艾滋病原料药供应厂商

现行生产车间 → **微化工原型机**

2306m^2

180m^2



同等产能占地面积对比

微纳化工芯片反应器

- ◆停留时间<1/180
- ◆试剂用量减少1/3

SPH 上海医药 SHANGHAI PHARMA　SBPC 第一生化 NO.1 BIOCHEMICAL

上药集团为世界500强企业，生产多种名药

现行生产车间 → **微化工原型机**

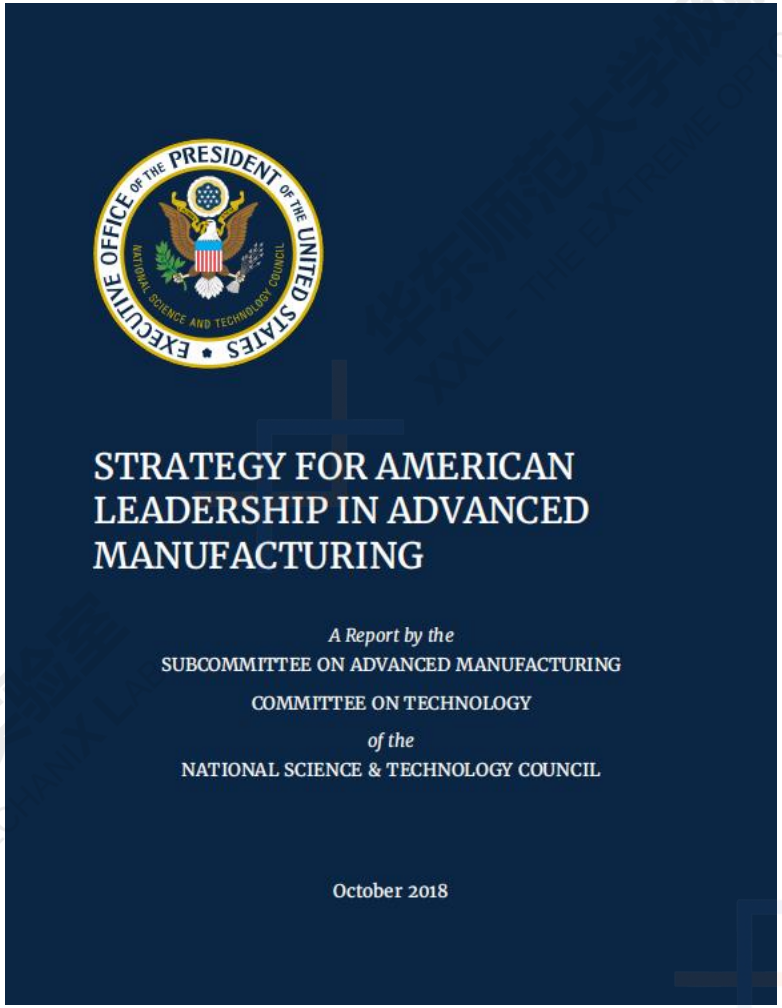
微纳化工芯片反应器

- ◆面积仅为1/60
- ◆停留时间<1/50
- ◆试剂用量减少2/3

连续流化工被列为美国国家制造战略

美国白宫“先进制造战略”白皮书 2018/10

https://www.whitehouse.gov/wp-content/uploads/2018/10/Advanced-Manufacturing-Strategic-Plan-2018.pdf



Additive Manufacturing. Additive manufacturing (AM)—the ability to directly create structures using three-dimensional (3D) printing and related techniques—is now beginning to realize its revolutionary potential to impact the commercial and defense manufacturing sectors, in terms of both cost per part and system performance. For example, AM of monolithic, high-performance metal parts can provide huge weight savings and performance gains for the aerospace sector. Similarly, printing of biological ce... ...ble and safe parts ma... ...powder or living ce...

Additive Manufacturing
增材制造

Th... ...ly set processing parameters that result in reliable and repeatable production across different machines and across different sites, requiring machine/process standardization and reliable constituent material quality. AM creates a new design paradigm, as parts can be made without the constraints of traditional machining, casting, or forging processes. Designers must learn how to incorporate AM technology in their future systems to remain competitive. As the production capacity of AM expands, new standardization efforts, supported by fundamental research, are needed to ensure the repeatability and reliability of production parts.

Continuous Manufacturing. Drug manufacturing is traditionally accomplished in large batches, with extensive testing of each batch to ensure consistent quality of the final product. In batch production, any problem with raw material ingredients or processing can scrap entire batches of medicine or result in expensive product recalls.

Co... ...ents into a single co... ...as raw materials ar... ...adigm in specialty ch... ...rmity, increases su... ...ducts and critical specialty chemicals using smaller, more efficient manufacturing sites. CM also enables shorter production runs, making small volume runs of specialty drugs and on-demand production of commodity drugs possible. There are challenges to CM adoption that justify a concerted effort to make the continuous manufacturing of pharmaceuticals and specialty chemicals a national priority. In particular, research is needed to overcome the technological challenges of integrating sensors and processing hardware with the control software that allows computers to continuously verify product quality from millisecond to millisecond.

Continuous Manufacturing
连续制造

本项目关注的颠覆性应用：深紫外光化学合成药物的市场需求分析

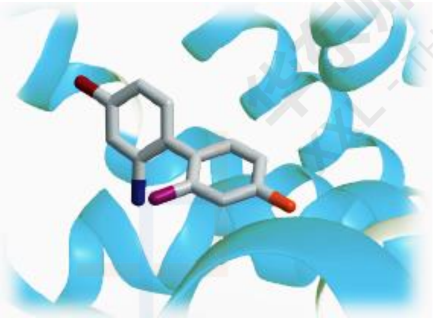
■联芳基化合物类药物

抗肿瘤、抗感染、心血管、糖尿病等药物中间体，全球年销售额>300亿美元

抗感染药 >$130亿

抗肿瘤药 >$70亿

呼吸系统药 >$10亿



神经系统药 >$7亿

降血压药 >$35亿

心血管药 >$40亿

糖尿病药 >$10亿

Angew. Chem. Int. Ed. 2018, 57, 14476 –14481

■维生素D3类药物

2020年我国骨质疏松患者

>9000万

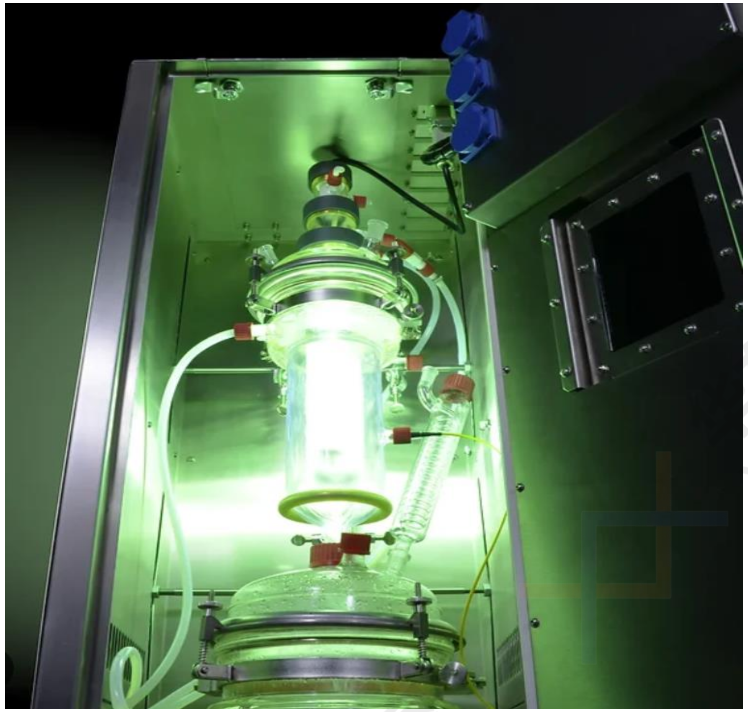
全球肝功能不全患者

超2亿

现有国内外化工芯片均无法满足深紫外光化学反应的要求

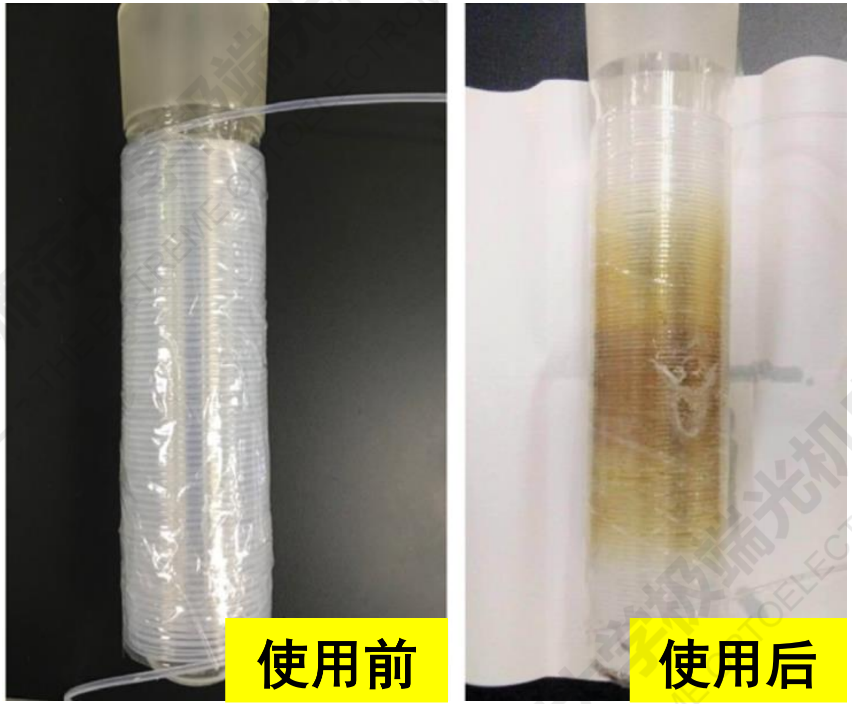
当前深紫外光化学合成的主流技术与存在问题

传统釜式石英玻璃光反应器



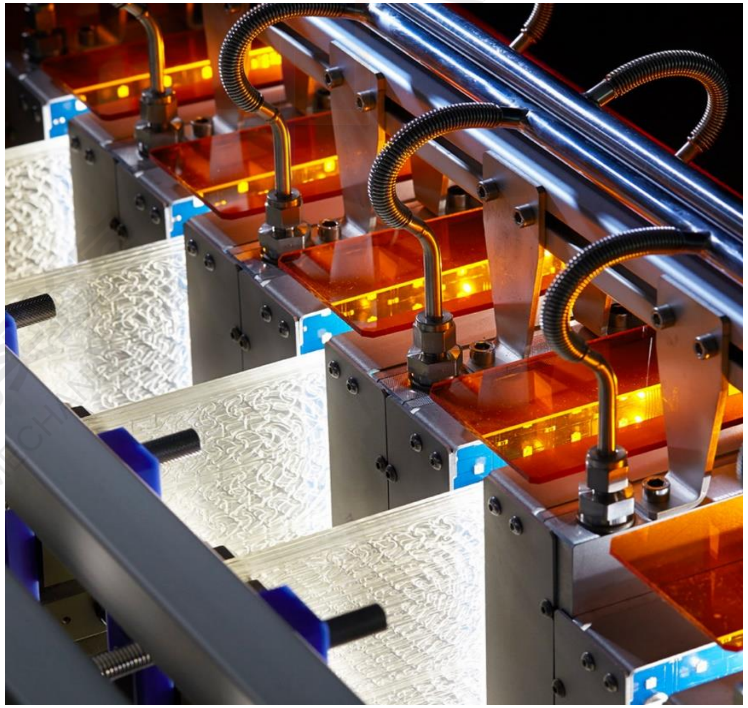
效率低、放大困难

连续流透明氟塑料管式光反应器



深紫外光线下易老化

商业化连续流光化学反应器

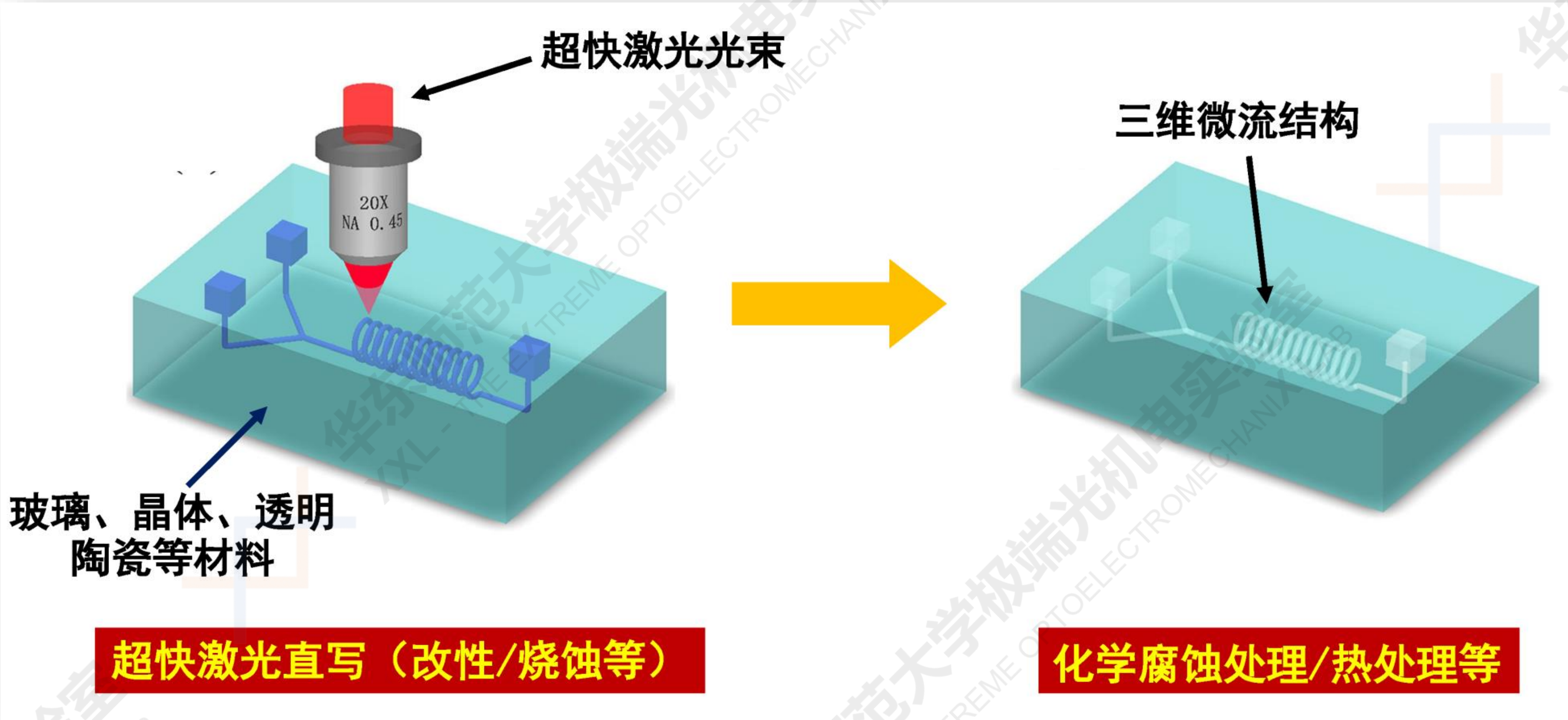


不透深紫外光

现有商用光化学反应器无法满足深紫外光化学反应药物合成的要求，急需发展深紫外波段高通量光化学芯片制造技术。

汇 报 提 纲

独创技术路线：超快激光大尺寸三维化工芯片制造技术



美国，US10201874B2
授权时间：2019年2月

US010201874B2

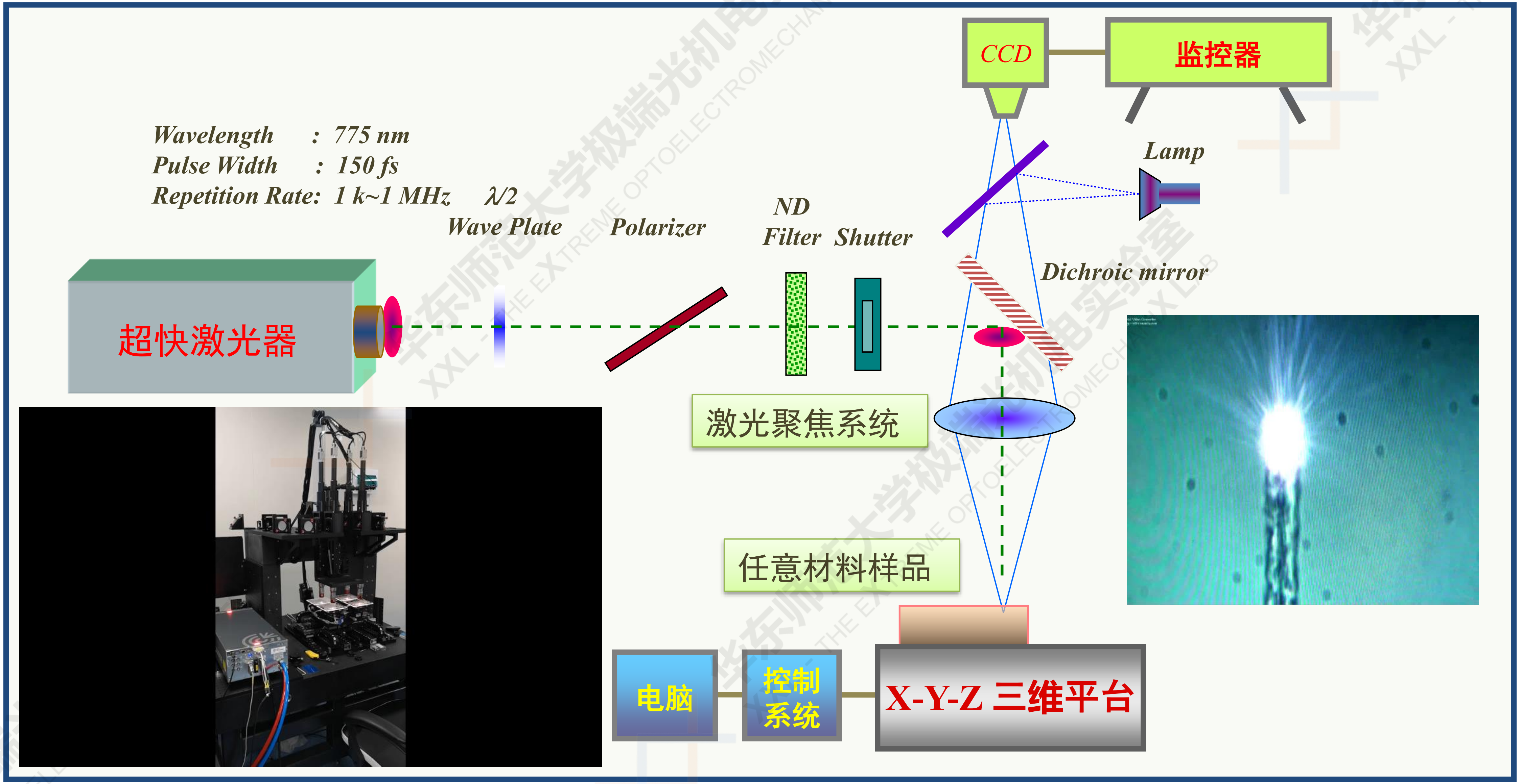
(12) United States Patent　　(10) Patent No.: US 10,201,874 B2
Cheng et al. 程亚等　　(45) Date of Patent: Feb. 12, 2019

美国，US11203083B2
授权时间：2021年12月

US011203083B2

(12) United States Patent　　(10) Patent No.: US 11,203,083 B2
Cheng et al. 程亚等　　(45) Date of Patent: Dec. 21, 2021

超快激光制造基本过程：超快激光对材料的高精度、穿透性烧蚀



超快激光微纳制造：颠覆性的新型光刻技术

2 October 2018

The Nobel Prize in Physics 2018

The Royal Swedish Academy of Sciences has decided to award the Nobel Prize

"for groundbreaking inventions in the field of laser physics"

with one half to

Arthur Ashkin
Bell Laboratories, Holmdel, USA

and the other half jointly to

Gérard Mourou
École Polytechnique, Palaiseau, France

Donna Strickland
University of Waterloo, Canada

"for the optical tweezers and th… application to biological system…"

Tools made of light

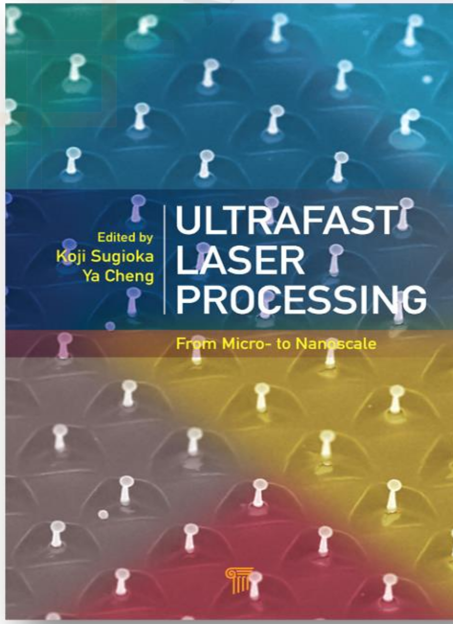
The inventions being honoured this year have revolutionised laser physics. Extremely small objects and incredibly rapid processes are now being seen in a new light. Advanced precision instruments are opening up unexplored areas of research and a multitude of industrial and medical applications.

the amplifying material. First they stretched the laser

2018年诺贝尔物理学奖公告

超快激光技术被授予2018年度诺贝尔物理奖！

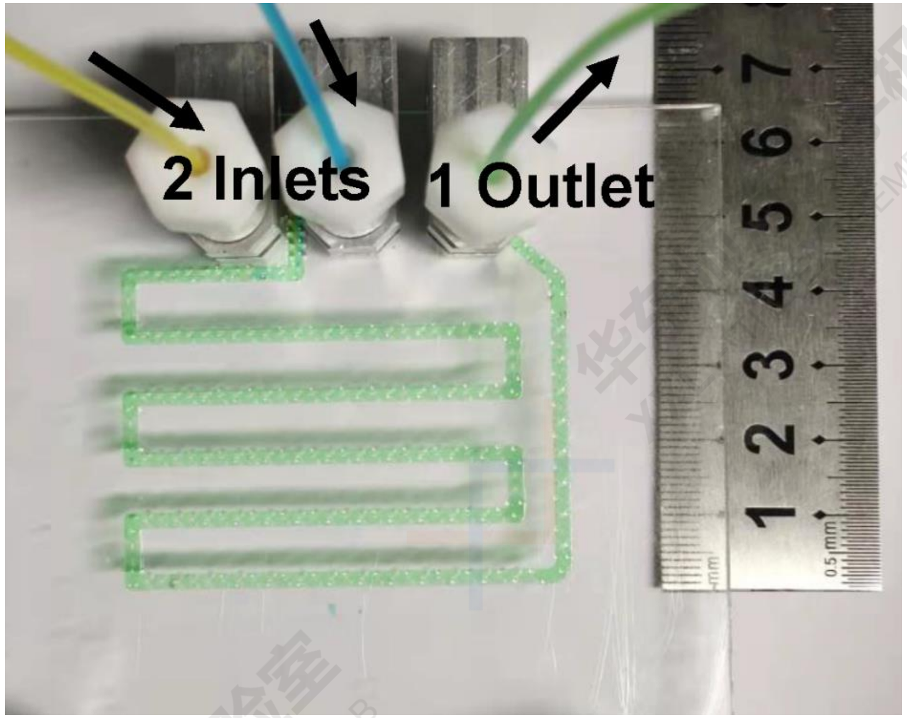
超快激光技术推动了微纳制造领域的重大变革！



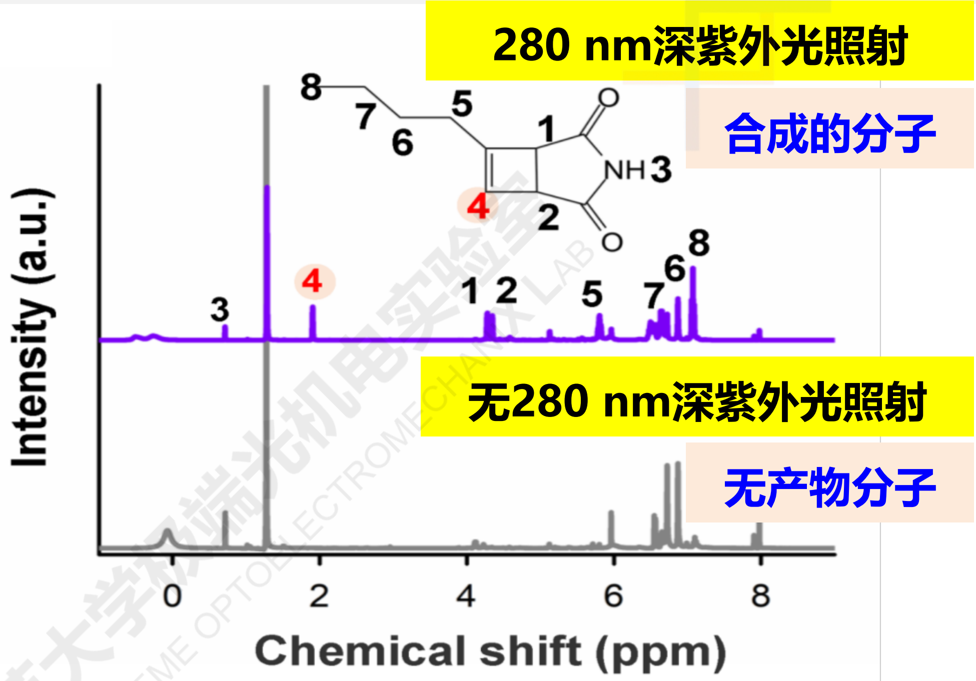
项目负责人程亚教授在该领域出版了代表性中英文专著

项目团队攻克深紫外光化学芯片制造难题

新型石英深紫外光化学芯片



突破芯片深紫外高效光化学合成



A. Zhang, et al. *Micromachines* 13, 543 (2022).

项目的目标（实验室 → 产业）：

解决反应通量、集成温控、在线检测等问题。

汇 报 提 纲

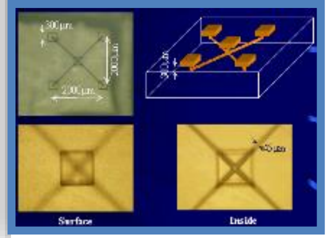
一．颠覆的应用场景描述
二．另辟蹊径的技术路线
三．项目技术来源与变革性
四．产业化应用前景与可行性

项目团队持续攻关二十年，负责人为该技术路线的创立者之一

RIKEN Review No. 50 (January, 2003): *Focused on* Laser Precision Microfabrication (LPM 2002)

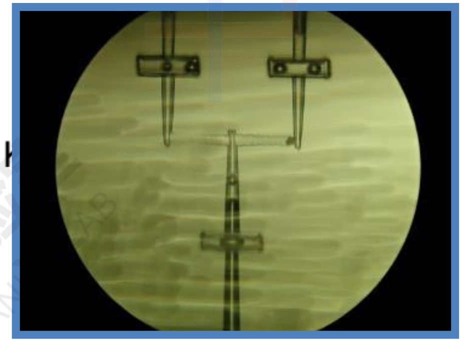
3D microstructuring inside Foturan glass by femtosecond laser

2001年起步 03年初步实现



Ya Cheng,[*1] Koji Sugioka,[*1,*2] Masashi Masuda,[*1,*2] Koichi Toyoda,[*2] Masako K
Kazuhiko Shihoyama,[*3] and Katsumi Midorikawa[*1]
[*1] *Laser Technology Laboratory, RIKEN*
[*2] *Department of Applied Electronics, Tokyo University of Science*

本项目负责人
程亚教授



- 项目负责人自2001年开始，在日本理化学研究所（日本最大研究机构）与同行科学家开展了玻璃内部三维制造的挑战性研究，于2003年初步实现该目标。项目负责人作为第一作者总结了该方面成果。
- 项目负责人自2006年回国，持续针对该技术产业应用开展攻关，解决一批原理与工程难题，成为世界首家应用该技术制造产业级高端化工芯片的团队。

项目团队在国际上多次产生首次（first）技术突破

4. Waveguide shaping using a deformable mirror

One of the most intuitive beam shaping techniques is the “slit beam shaping” technique, first demonstrated by Cheng et al [12] and then applied to waveguide inscription by Ams et al [2]. In this technique, a slit is placed in front of the microscope objective used to focus the laser beam inside the substrate. The slit is orientated parallel to the sample translation direction and its purpose is to reduce the numerical aperture of the focused beam in the axis perpendicular to the waveguide axis, increasing the laser spot size in this axis and widening the width of the modified region. Using a two-dimensional deformable mirror it is possible to replicate the slit beam shaping technique by focusing the beam in only one axis to produce a line focus in front of the microscope objective. In contrast to the slit beam shaping technique, the two-dimensional deformable mirror offers the possibility of varying the width and orientation of the line focus during the inscription.

苏格兰Heriot-Watt大学研究组指出“**狭缝整形**”关键技术**首次（first）**由Cheng 等人提出。

focus the writing beam inside the sample. A 350 μm width slit is placed before M.O.1 in order to generate an elliptical beam and thus a disk-shaped focal volume, as first reported by Cheng *et al.* [23] (see also [17,18]). A $\lambda/4$ wave plate polarizes the beam circularly so as to reduce propagation losses [24] and to minimize the appearance of periodic nanostructures [25,26]. A processing depth of 1.56 mm was used because NLP effects are clearly observable for sufficiently high pulse energies, while SA effects can still be compensated by the combination of low NA op-

西班牙马德里光子所研究利用华师大成员**首次(first)**提出的“**狭缝整形**”技术制备光波导芯片。

time. The NA of the beamlets determines the final focal spot size. As a result of the lack of complete spectral overlap in the out-of-focus regions, the peak power and correlating intensity of the beam is markedly lower in these zones. The reduced out-of-focus intensity mitigates integrated nonlinear effects such as self-focusing. The utility of the SSTF focal geometry for micromachining, was first demonstrated by He et al [8] with application to microfluidics, and Vitek et al [9,10] with application to low numerical aperture machining at millimeter depths inside optically transparent materials. Vitek et al showed that targeted ablation with 50 µJ, 60 fs pulses at 0.05 NA through 6 mm of fused silica was possible with SSTF, while these same beam parameters resulted in filamentation and tracking throughout the solid when a standard

美国科罗拉多矿业大学著名学者，OSA Fellow，Jeff Squier教授在其论文中明确指出：“F. He等**首次（first）**演示了**时空聚焦**方式”。F. He是程亚教授博士生。

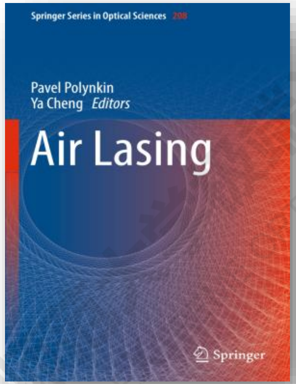
ing to spherical plasma hot spots. Local field enhancement results in asymmetric growth along the direction perpendicular to the polarization of the incident laser beam, while a cavity-like amplification process triggers the alignment in highly periodic grating planes. Despite the lack of experimental studies which confirm this process in detail, first steps towards an explanation have been made recently [22]. Based on scanning electron microscopy (SEM) of cleaved

机理研究被德国耶拿大学应用物理研究所长 A. Tuennermann 教授评论为机制研究的**第一步（first steps）**。

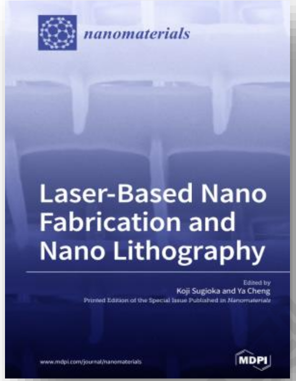
程亚教授出版的本领域中英文论著及授权专利

科学出版社
中国，上海

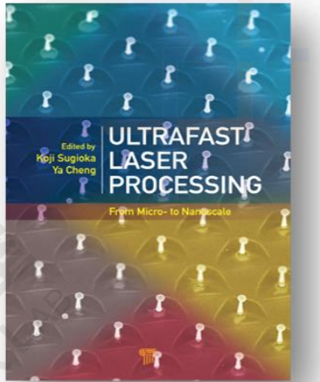
Springer
伦敦分社



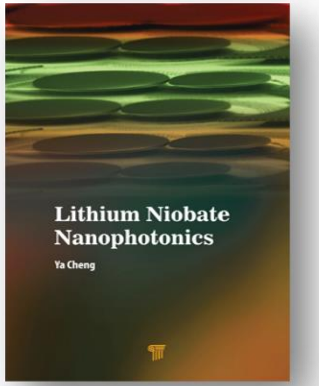
Springer
纽约分社



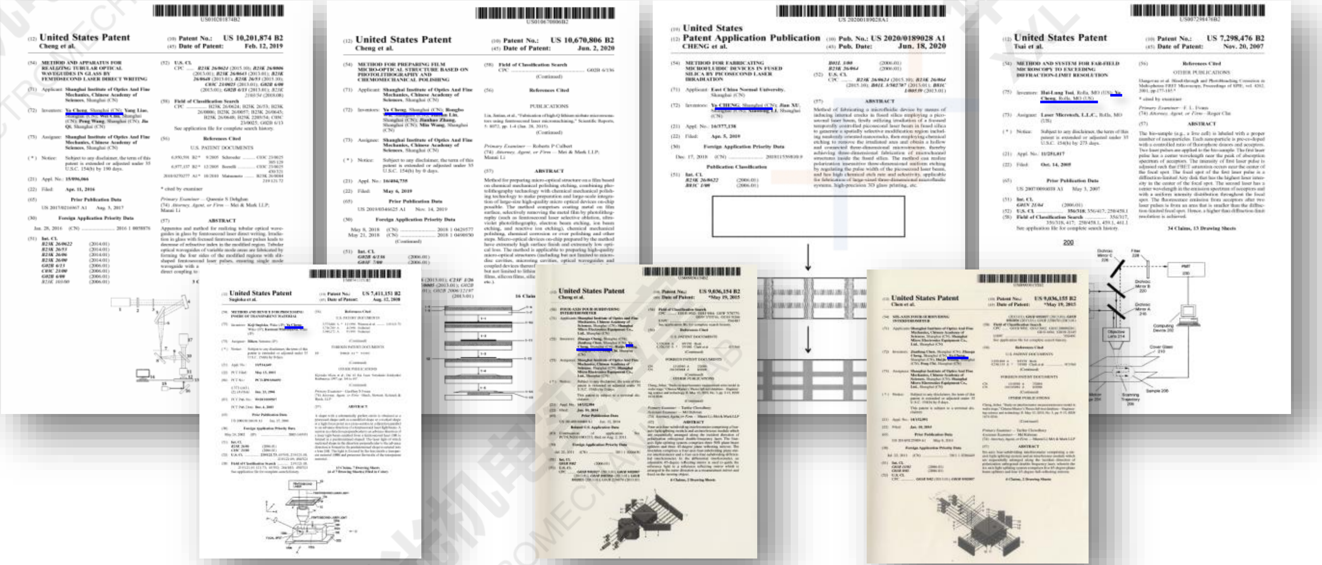
MDPI
瑞士



Pan Stanford
新加坡



Jenny Stanford
新加坡



项目团队发展的核心技术已获得7项美国专利授权及30余项中国发明专利授权

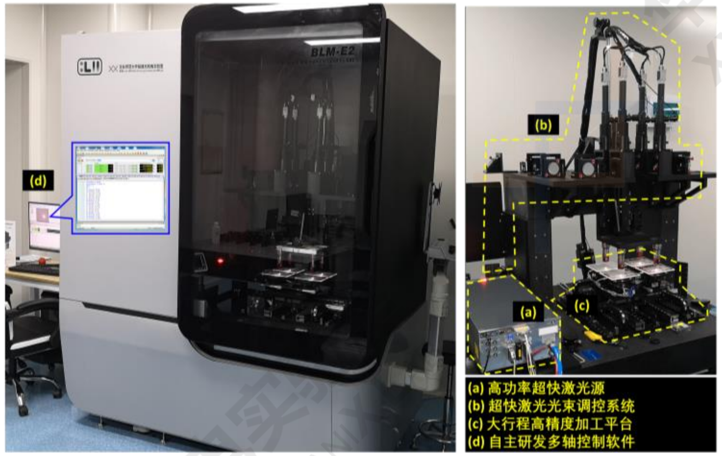
项目研发的深紫外芯片的独特优势

- **高效的混合性能**（独特三维混合内构件）
- **高效的光反应效率**（紫外高透明玻璃衬底）
- **安全清洁的生产能力**（连续流化学本质安全）
- **无人全自动智能制造**（集成在线光谱监测）

汇 报 提 纲

项目团队自主研发了超快激光芯片制造设备

- 构建了高性能四路并行超快激光三维内雕制造平台，并平稳无故障运行近20个月；
- 该制造平台在核心关键指标上媲美于国际同类设备（见下表），满足了高效、高精度和定制化生产的产业应用需求。



	Lightfab(德国)	Femtoprint(瑞士)	华师大光刻系统
处理材料种类	玻璃，宝石	玻璃	玻璃，晶体，聚合物，金属，薄膜材料，陶瓷
加工方式	玻璃3D打印，玻璃微纳处理	玻璃3D打印，玻璃微纳处理	双光子聚合3D打印，玻璃3D打印，玻璃微纳处理，金属材料加工，铌酸锂薄膜光刻
极限加工尺寸	100 mm x 200 mm	**110 mm x 110 mm**	**300 mm x 300 mm**
极限加工高度	**< 0.7 cm**	/	**> 4 cm**
横向加工分辨率	1 μm	1 μm	聚合物 160 nm，玻璃 1 μm (特殊处理40 nm)，金属 1 μm
纵向加工分辨率	/	/	聚合物 300 nm，玻璃 3 μm
最大线加工速度	300 mm/s	**350 mm/s**	**>1000 mm/s**
振镜集成	无	无	具备无限视野及旋切，可实现大视场快速扫描及金属深孔加工
功能集成	无	金属沉积，表面处理	金属沉积，表面处理，光流集成，片上光子器件制备
超快光场整形	无	无	**集成时域、空域、频域全域整形，并可耦合控制**
自动追焦功能	无	无	**位置传感预补偿，切割实时追焦**

本项目团队已实现的前期经济效应

项目负责人程亚教授团队为一批高新技术企业提供芯片与设备：

- **上药集团、迪赛诺制药、华谊集团、风火轮生物科技**等；
- 芯片销售金额>**300万元**，折算进口产品价值>**3000万元**;
- 支撑的药品市场规模：20～30亿元。

项目团队的技术被美国同行评价为“对商业化应用切实可行”

美国3Dprint.com网站（国际知名3D制造技术网站）评述项目团队的成果有望成为切实可行的商业化微流控通道制造技术（a viable commercial technology in manufacturing microfluidics）。

3DPRINT.COM™
THE VOICE OF 3D PRINTING

Researchers Improve Femtosecond Selective Chemical Etching

January 10, 2019 • by Clare Scott • 3D Printing • Science & Technology

https://3dprint.com/233542/

The manufacturing of microfluidic channels is complex. Currently, it often involves a lot of manual labor, fusing several different parts or a chain of technologies working together. Although early stage this picosecond approach may lead to a viable commercial technology in manufacturing microfluidics.

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总 结

- 项目瞄准化工制药企业产业**转型痛点**，利用超快激光微纳加工技术制造高通量**深紫外光化学反应芯片**，集安全、高效、清洁、可定制化等独特优势于一身，**国内、国外尚属空白**；
- 围绕联芳基化合物类药物、维生素D3两大**核心药物**开展**深紫外连续流**工艺研发，实现对现有制药工业的转型升级，打造新型高端绿色制药产业！

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