生物制药行业历史发展和趋势
高度专业化板块形成

澳斯康生物制药&健顺生物创始人兼董事长 罗顺

2020年9月21日

目录

Integrated CMC Organization

THOUSANDOAKS® Biopharmaceuticals

生物制药行业历史和趋势

1976年-至今，美国生物制药经历了四次浪潮的演变

澳斯康集团简介

澳斯康是国内领先的拥有无血清细胞培养基、工艺技术、一次性耗材有机整合体的生物药定制开发生产(CDMO)服务公司

生物制药行业的过去

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90年代初	2000年初	2004	2006年	2009年	2011年	2014-2015	2019年
1-10 mg/L, EPO, FSH, 因子XIII等	1-2 g/mL, 最高产量, Humira 2.4 g/L	Florian Wurm, 自然生物技术, CHO潜力4 g/L	惠氏/辉瑞, 报告9.7克/升, 实验室规模	安进，11 g/L, 2000-L, 中试规模	安进, 5.5 g/L 1.6万升商业规模	Gmax, 1.5g/L/Day, 15 L，临床规模	已经有不少企业达到8-10g/L

90年代初期，从开始有生物制药产品上市时，产量只有1-10mg/L，至今达8-10g/l, 发展及其迅猛，在优胜劣汰的快速发展中，重视产业化生产的企业最终留存下来。

美国生物制药的四次浪潮

1976-1980	1987-1992	1998-2006	2008-2030

Four Waves of Biopharmaceutical Industry
1976-2017

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美国生物制药的第一次浪潮1976-1980年

风险投资商到处寻找能做重组DNA技术的研究人员，美国生物技术公司如雨后春笋般诞生

01

PART ONE

美国生物制药的第一次浪潮 1976-1980年

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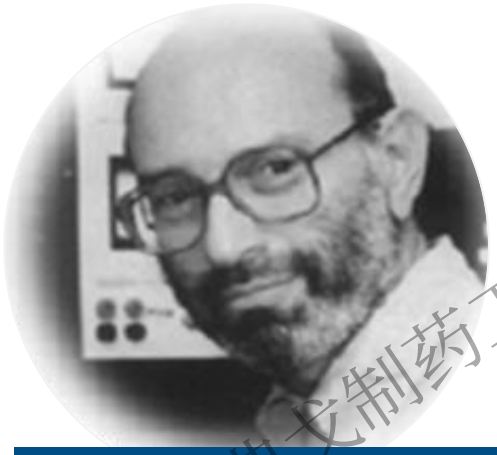


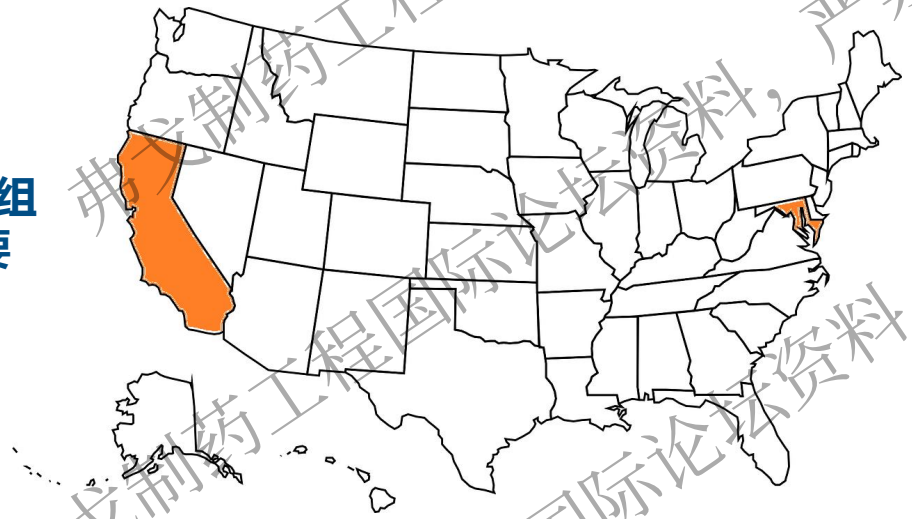
Stanley Cohen
Stanford University

Bob Swanson & Herb Boyer
Genentech University

George Rathmann
Amgen CEO

Bill Rutter
Chiron Founder

风险投资商到处寻找能做重组DNA技术的研究人员，主要是大学教授。



美国一下子有了4000多家形形色色的生物技术公司，Boston地区就有800多家。

美国生物制药的第一次浪潮 1976-1980年

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此时，我们仅仅只有重组DNA技术，

和基本不懂管理的教授们、一些天真的投资人！

Proc. Natl. Acad. Sci. USA
Vol. 76, No. 1, pp. 106–110, January 1979
Biochemistry

Expression in *Escherichia coli* of chemically synthesized genes for human insulin

(plasmid construction/*lac* operon/fused proteins/radioimmunoassay/peptide purification)

DAVID V. GOEDDEL*†, DENNIS G. KLEID*, FRANCISCO BOLIVAR*, HERBERT L. HEYNEKER*, DANIEL G. YANSURA*, ROBERTO CREA*‡, TADAAKI HIROSE‡, ADAM KRASZEWSKI‡, KEIICHI ITAKURA‡, AND ARTHUR D. RIGGS†‡

*Division of Molecular Biology, Genentech, Inc., 460 Point San Bruno Boulevard, South San Francisco, California 94080; and ‡Division of Biology, City of Hope National Medical Center, Duarte, California 91010

Communicated by Ernest Beutler, October 3, 1978

ABSTRACT Synthetic genes for human insulin A and B chains were cloned separately in plasmid pBR322. The cloned synthetic genes were then fused to an *Escherichia coli* β-galactosidase gene to provide efficient transcription and translation and a stable precursor protein. The insulin peptides were cleaved from β-galactosidase, detected by radioimmunoassay, and purified. Complete purification of the A chain and partial purification of the B chain were achieved. These products were mixed, reduced, and reoxidized. The presence of insulin was detected by radioimmunoassay.

Enzymes and DNA Preparations. T4 DNA ligase and T4 polynucleotide kinase were purified as described (6). Restriction endonuclease *Eco*RI was purified by the procedure of Greene *et al.* (7); *Hin*dIII was purified by a method developed by D. Goeddel (unpublished). Restriction endonuclease *Bam*HI was purchased from Bethesda Research (Rockville, MD); *E. coli* alkaline phosphatase was purchased from Worthington.

Plasmids, including pBR322 (8), were isolated by a published procedure [9] with some modifications. The chemical synthesis

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Amgen's Lucky Star: Saved by an IPO

Alan Mendelson, the lawyer at Cooley Godward who filed for Amgen's 1983 IPO, recalls Amgen's first day as a publicly traded company: "Gordon Binder was on the Smith Barney trading floor in New York City. The stock was priced at $18 a share. The first trade came across at $16.75, and everybody gasped, because they knew that it was not going to be a good day. They quickly shooed Gordon out because clearly people were selling, dumping the stock right away. And the stock closed at $16.75.... It never traded at $18 until years later. It just kept going down from there.

"We barely made it with that IPO," continues Mendelson. "In fact, we were in the middle of a major dispute with Abbott, which we were able to resolve at the very last minute. If we had priced it a week later, we might not have been able to do it at all, and we probably would have raised anywhere from $12 to $15 million less," says Mendelson. "Amgen might have run out of cash." But the

美国生物制药的第一次浪潮 1976-1980年

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The U.S. Supreme Court rules genetically altered life forms can be patented, opening up enormous possibilities for commercially exploiting genetic engineering.
The first patent of this nature was awarded to the Exxon oil company to patent an oil-eating microorganism, which would later be used in the 1989 cleanup of the Exxon oil spill at Prince William Sound, Alaska.

02

Dr. Stanley Cohen and Dr. Herbert Boyer receive a U.S. patent for gene cloning.

03

The first automatic gene machine, or gene synthesizing machine, is developed in California.

04

Founding of Genentech, which would grow to become the world's largest biotechnology medicines company.

中国正处于这个阶段，希望中国几年后出现许多Genentech & Amgen

THOUSANDOAKS Biopharmaceuticals

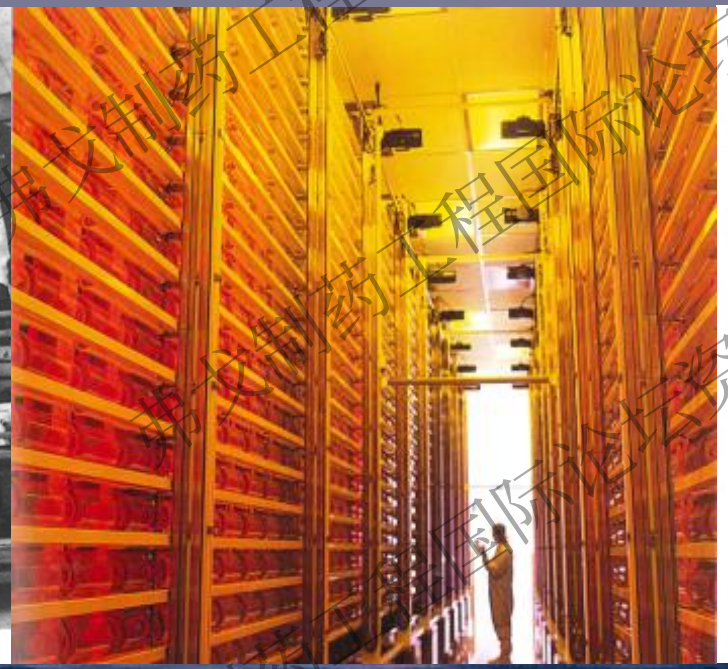
美国生物制药的第二次浪潮1987-1992年

这次浪潮来得非常凶猛，因为大量的投资进入生物技术行业，Wall Street (资本炒作) 唱了主角

02

PART TWO

安 进 及 其 他 许 多 公 司 迎 来 产 业 化 的 挑 战 ！



美国生物制药的第二次浪潮 1987-1992年

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重组DNA技术飞速发展成熟，各种应用应运而生！

Cornell 大学的两名教授Ed Wolf and Nelson Allen发明了Gene Gun 可以将重组DNA射入植物或动物细胞。

加州大学第一次用重组DNA的细菌在野外做实验，当时是在FBI的现场监督下进行的。

这次浪潮来得非常迅猛！

大量的投资进入生物技术行业，Wall Street (资本炒作) 唱了主角，但是很快因为几起非法投资，融资炒作而结束

美国生物制药的第二次浪潮 1987-1992年

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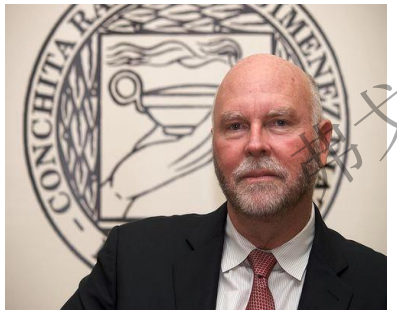
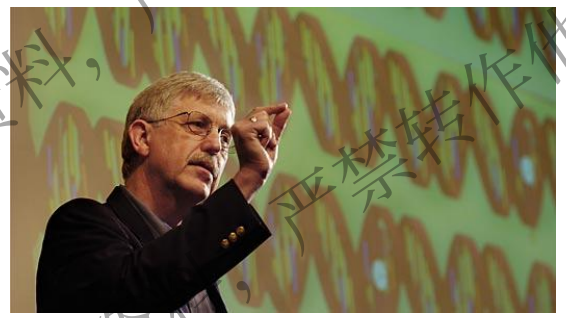
92年之后，很多新技术，产品开发有了突破。

- 九十年代早期的单克隆抗体的应用（OKT-3）
- 2000，Scientists at Celera Genomics and the Human Genome Project complete a rough draft of the human genome.
- 2001，Science and Nature magazines publish the human genome sequence，President Clinton congratulated all scientists who worked on human genome sequencing and marked the event as another giant step for mankind!





人类基因组序列分析完成！ “继登月后人类又一大步” ——克林顿总统

生物制药行业经历了30年（1976-2006）播种、耕耘，终于开始收获

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美国生物制药的第三次浪潮1998-2006年

这个时期，“立法”、“资本”、“管理”、“人才”等生物制药蓬勃发展的要素逐渐具备

03

PART Three

美国生物制药的第三次浪潮 1998-2006年

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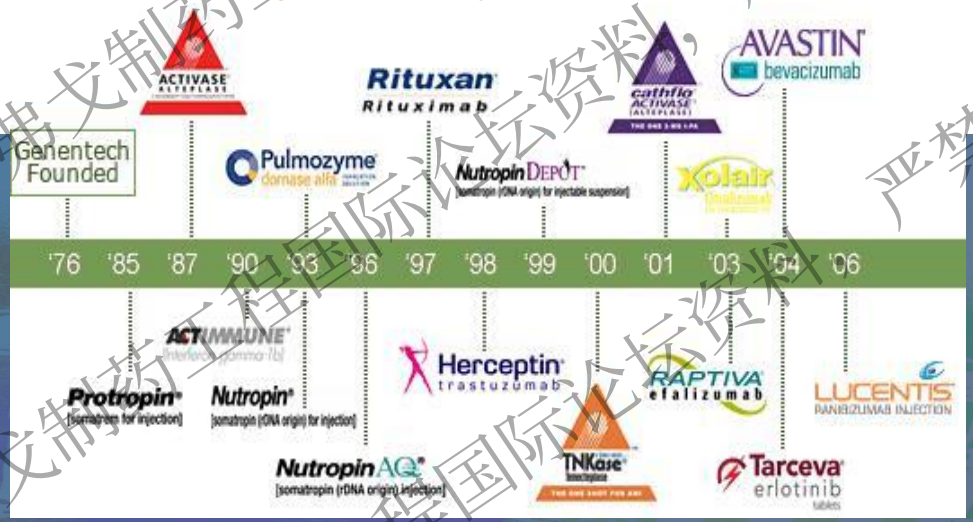
Genentech

MERCK

Genentech

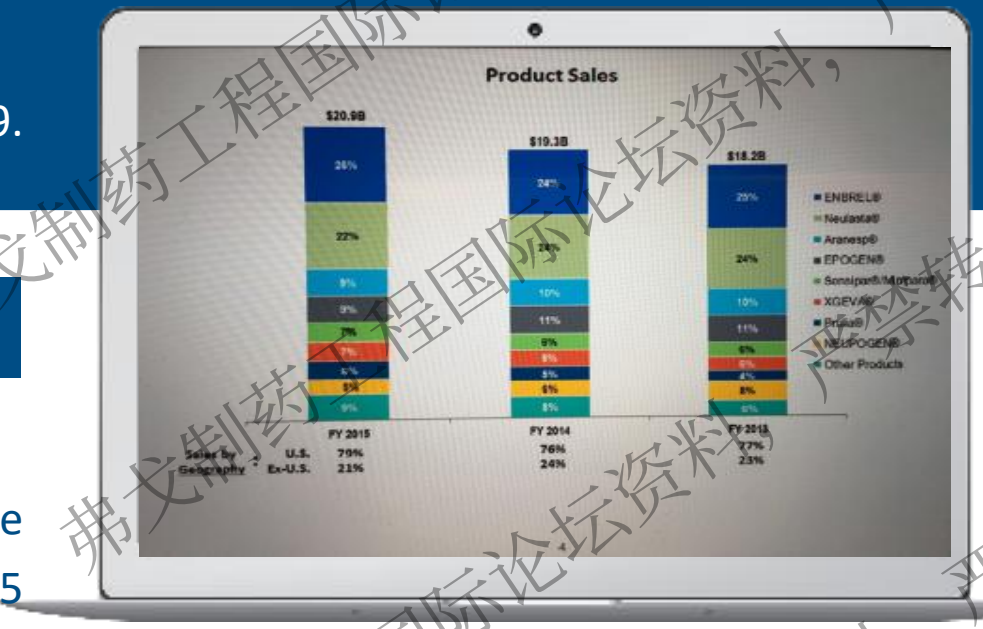
- The FDA approves the first monoclonal antibody that is an antiangiogenic, inhibiting the growth of blood vessels—or **angiogenesis**—for cancer therapy.
- The FDA approves a recombinant vaccine against human papillomavirus, which causes genital warts and can cause cervical cancer (CSL, Merck).
- The FDA approves Lucentus for Wet Macular Degenerative Disease.



Genentech

$12B annual sales, 2009.

>10,000 employee



Best company of Fortune since 2005

Roche acquired Genentech 2 times

这次浪潮我们有了专业的投资人，有经验的管理人才，知识产权立法，整个社会对生物制药有比较客观的了解！

人们将以生物制药业为主的生物技术看成是21世纪的新希望.

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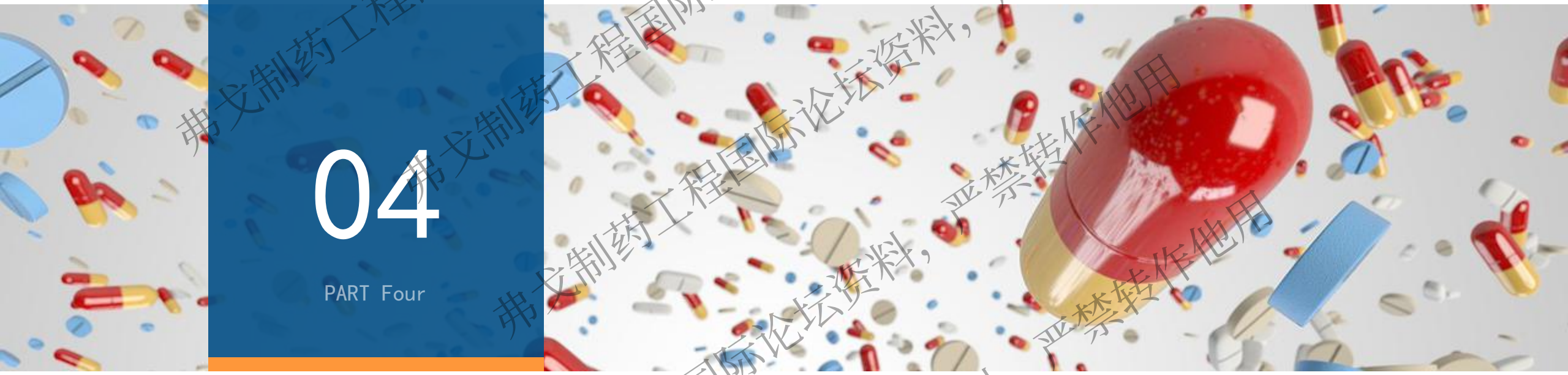
美国生物制药的第四次浪潮2008-2030年

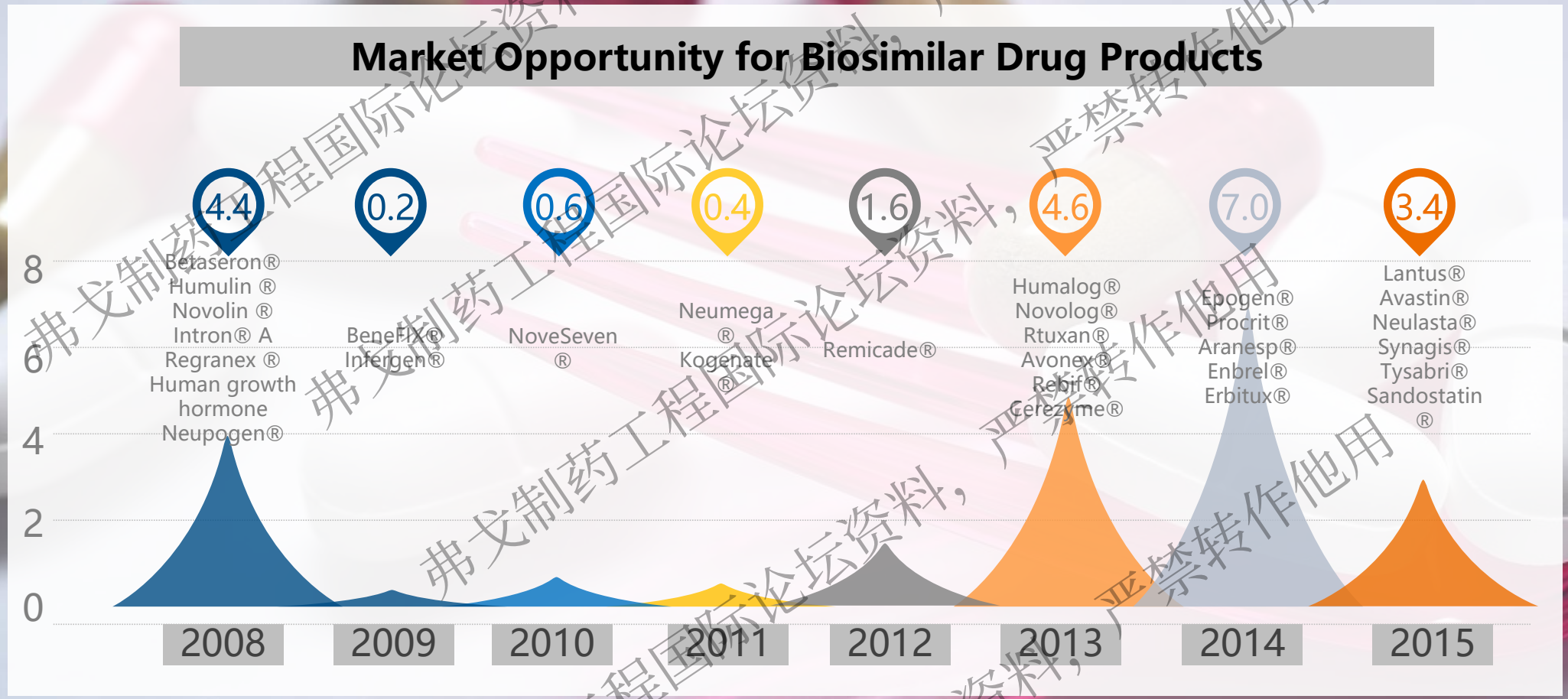
铺天盖地的生物仿制药，生物药的生产效率和成品成为了竞争关键

04

PART Four



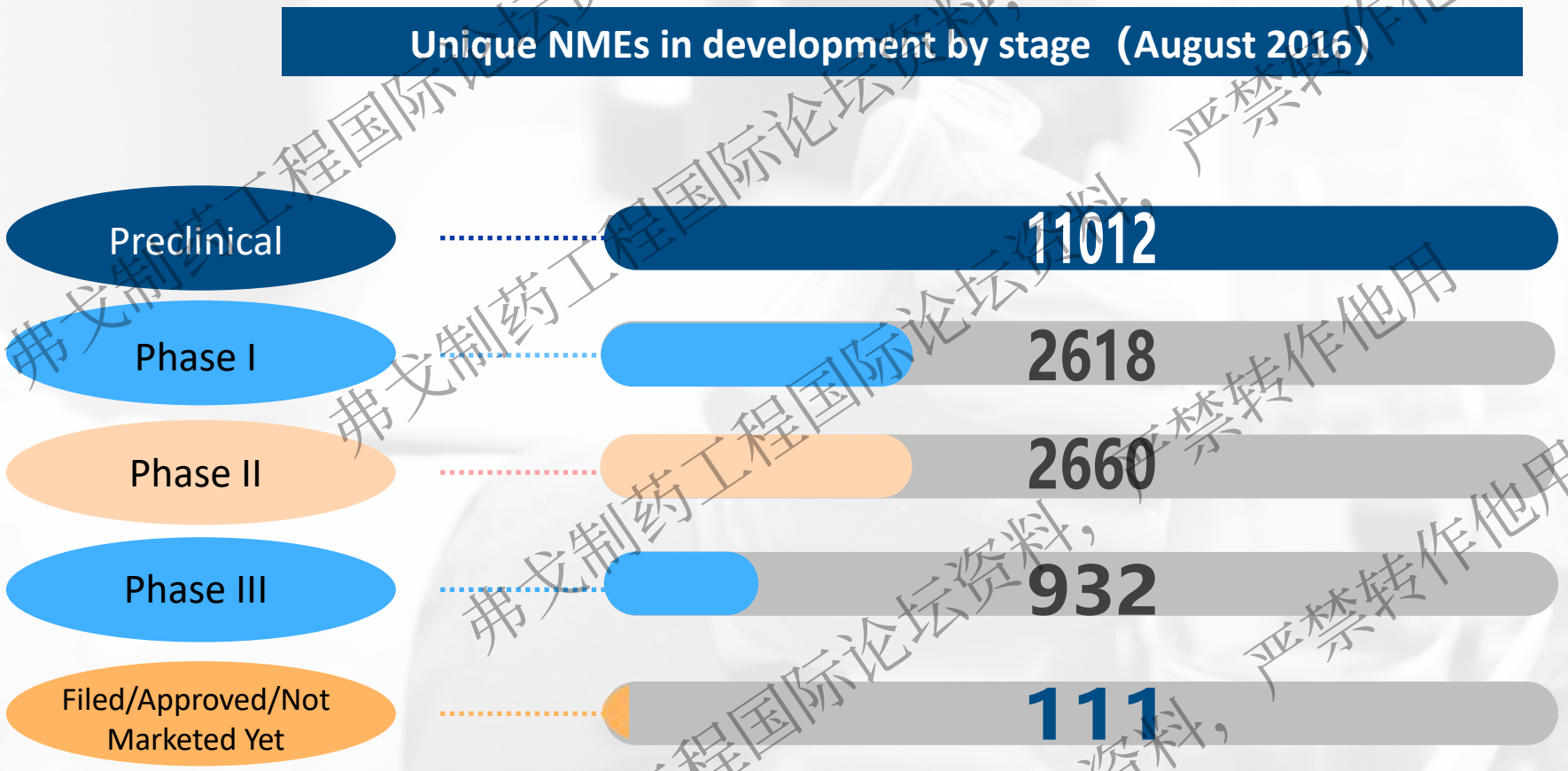
生物仿制——中国医药工业百年不遇的契机



Source:Medco data,IMS(retail sales); manufacturers' annual report

序号	药品名称	公司	适应症/药物类型	销售额（百万美元）
1	Humira（阿达木单抗）	艾伯维	自身免疫性（各种）	14012
2	Harvoni（哈瓦尼）	吉利德	丙型肝炎	13864
3	利妥昔单抗	罗氏	非霍奇金氏瘤，淋巴瘤	7327
4	来得时	赛诺菲	糖尿病	7088
5	阿瓦斯丁	罗氏	肿瘤（各种）	6951
6	赫赛汀	罗氏	乳腺癌	6799
7	英利昔单抗	强生	自身免疫性疾病（各种）	6561
8	沛儿	辉瑞	链球菌感染肺炎（疫苗）	6245
9	捷诺维	默沙东	糖尿病	6014
10	瑞复美	新基	多发性骨髓瘤	5801
11	舒利达	葛兰素史克	哮喘/慢性阻塞性肺病	5627
12	恩利	安进	自身免疫性疾病（各种）	5364
13	索非布韦	吉利德	丙型肝炎	5276
14	可定	阿斯利康	血脂异常	5017
15	乐瑞卡	辉瑞公司	抗惊厥	4838

新药开发成功率极低



Report： Analysis Group/PhRMA.Data： EvaluetePharma

铺天盖地的生物仿制

Antibody Biosimilars Approved by EMA & FDA

Brand Name	iNN	Reference Antibody	Company	Year of Approval	Health Authority
Remsima/Inflectra	Infliximab	Remicade	Celltrion/Hospira	Sep. 2013	EMA
Benepali	Etanercept	Enbrel	Samsung Bioepsis	May 2016	EMA
Truxima	Rituximab	Rituxan	Celltrion	Feb. 2017	EMA
Solymbic/Amgevita	Adalimumab	Humira	Amgen	Mar. 2017	EMA
Imraldi	Adalimumab	Humira	Samsung Bioepsis	Aug. 2017	EMA
Inflectra	Infliximab	Remicade	Celltrion/Pfizer	Apr. 2016	FDA
Erelzi	Etanercpet	Enbrel	Sandoz	Aug. 2016	FDA
Amjevita	Adalimumab	Humira	Amgen	Sep. 2016	FDA
Renflexis	Infliximab	Remicade	Samsung Bioepsis	Apr. 2017	FDA
Cyltezo	Adalimumab	Humira	BI	Aug. 2017	FDA
Mvasi	Bevacizumab	Avastin	Amgen	Sep. 2017	FDA

美国生物制药的第四次浪潮 2008-2030年

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- Merck said it's cutting the price of Zepatier, a drug that treats hepatitis C by **60%** and reducing the price of six other medications by **10% each**.
- Merck said that it has "a long history of responsible drug pricing."
- Last year, the average net price of all the medications it sells in the United States **declined by 1.9%.**
- New York University School of Medicine said that it will pay the tuition of all its students regardless.
- Kenneth G. Langone, Cofounder of Home Depot has given $100 million to fund the tuition package.
- **"4 + 7 Centralized Drug Purchasing" "Two-vote system", "consistency evaluation"** published in China.

美国生物制药的第四次浪潮 2008-2030年

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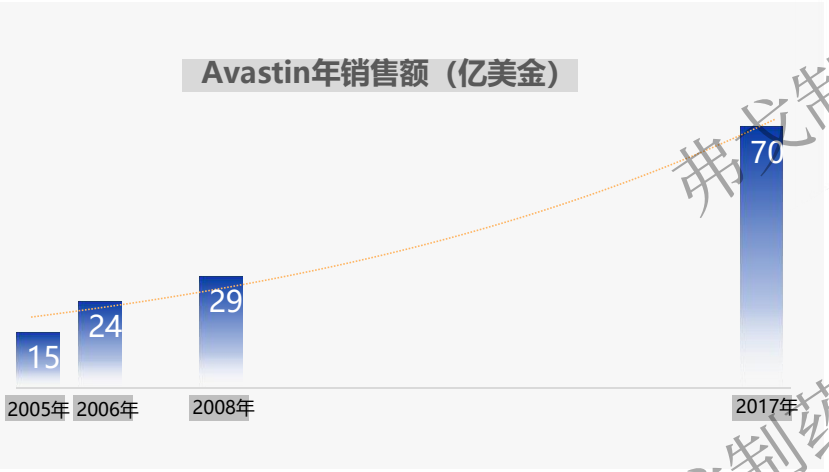
从一个靶点一个药物到一个靶点多个药

1. 2004年 Avastin 上市，罗氏（基因泰克），治疗转移性癌症
2. 主流靶点产品：雷珠单抗、贝伐单抗和阿帕西普
3. 目前全世界超过20种已被批准用于临床治疗的抗VEGF药物。



抗VEGF靶点

抗PD1/PD-L1靶点

1. 首个PD-1 抑制剂 Keytruda （默沙东），2014年9月4日在美国上市
2. 目前全球共有5个PD-1/PD-L1类药物上市，分别是BMS的Opdivo、默沙东的 Keytruda、罗氏的 Tecentriq、阿斯利康的 Imfinzi、默克/辉瑞的 Bavencio
3. 2017年 Opdivo 销量49.48亿美金， Keytruda 销量38.09亿美金
4. 截止到目前，已经有5个PD-1抗体在中国提交了上市申请，分别为：进口的 Opdivo、Keytruda 、以及国内的君实、信达、恒瑞的PD-1抗体，国内临床申报近32家，研发布局80余家。

国内PD-1/PD-L1研发进展

公司	药物	靶点	进展情况	来源/合作伙伴
BMS	Nivolumab注射液	PD-1	BLA	Medarex
Merck	Pembrolizumab注射液	PD-1	III期	Organon
Roche	Atezolizumab注射液	PD-L1	III期	自主研发
Astrazeneca	Durvalumab注射液	PD-L1	III期	自主研发
信达生物	IBI308	PD-1	III期	自主研发
君实生物	JS001	PD-1	II期	自主研发
恒瑞医药	SHR-1210（camrelizumab）	PD-L1	III期	自主研发
	SHR-1316	PD-L1	批准临床	自主研发
百济神州	BGB-A317	PD-1	III期	自主研发
誉衡药业	GLS-010	PD-1	I期	药明康德
嘉和生物	GB226（杰诺单抗）	PD-1	I期	自主要发
百奥森生物	重组人源化抗PD-1单克隆抗体注射液（BAT1306？）	PD-1	批准临床	自主研发
	AK103	PD-1	批准临床	自主研发，翰中生物
	AK104	CTLA-4/PD-1	澳洲I期	自主研发
康方生物	AK105	PD-1	临床前	自主研发
	AK106	PD-L1	临床前	与国内第三方合作
	AK112	PD1双功能	临床前	自主研发
丽珠医药	LZM009	PD-1	FDA批准临床 批准临床	自主研发
复宏汉霖	HLX10	PD-1	IND（74），批准临床	自主研发
	HLX09	PD-L1	临床前	自主研发
	KN035	PD-L1	IND（36）	自主研发
	[illegible]-A11	PD-L1	IND（36）	[illegible]
基石药业	CS1001	PD-L1	批准临床	药明康德，基石药业
科伦药业	KL-A167	PD-L1	批准临床	内部研发
正大天晴	TQB2450	PD-L1	批准临床	自主研发，中美冠科
迈博斯	MSB2311	pH依赖性 PD-L1	IND	自主研发
安科生物	SSI-361	PD-1	临床前	礼进生物引进
瑞阳制药	未知	PD-1	临床前	瑞阳（苏州）研发，2018年4月提交IND
	未知	PD-L1	临床前	2018年提交IND
精华制药	未知	PD-L1	临床前	美国Kadmon引进
海正药业	未知	PD-L1	临床前	自主研发
智翔医药	未知	PD-L1	临床前	自主研发

未来的竞争点在生物制药的生产效率和成本

趋势-高度专业化板块形成

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THOUSAND OAKS Biopharmaceuticals

- 蓬勃发展
- 高度重叠
- 时间为王
- 成本竞争

mCOG < $100/g，做世界的药物工厂，真正实现中国“智”造

生物仿制产品远远超出我们的预期

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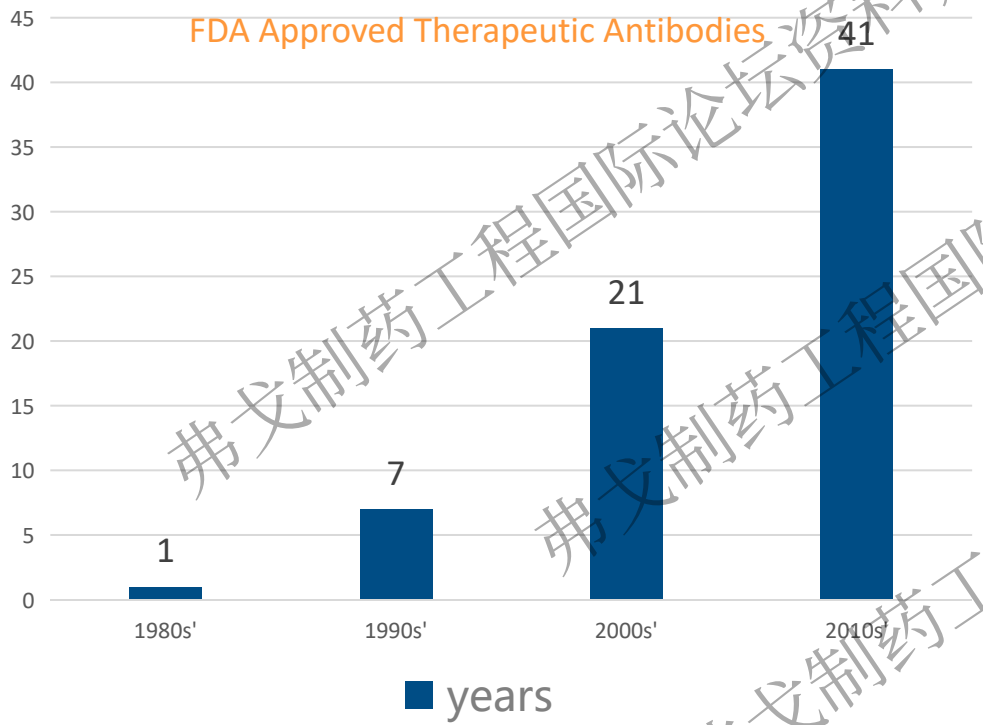
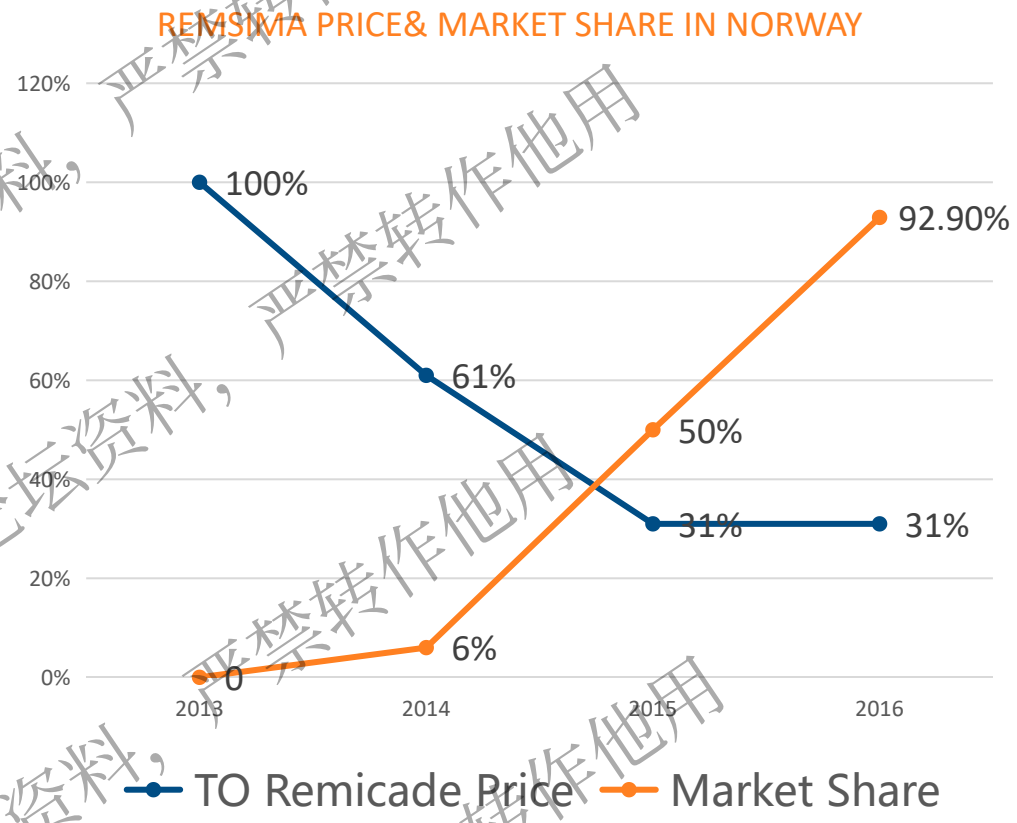




新药上市爆发期

药品价格成为竞争关键

MAA Approval by EMA launced in Norway

Manufacturing 2019-2032

Integrated CMC Organization

THOUSANDOAKS Biopharmaceuticals

Billions of $, but very limited resources and technology

Drug Disc

Roche,Gmax……

CMC PD

Clinical Dev

Commercial Fab

Safe,Quality, Efficacy

CRO/CMO → DS + DP

Facility

GE, ThermoFisher, MD, etc.

Equipment

GE, ThermoFisher, MD, etc.

Consumables

Merck, Pall, GE, etc.

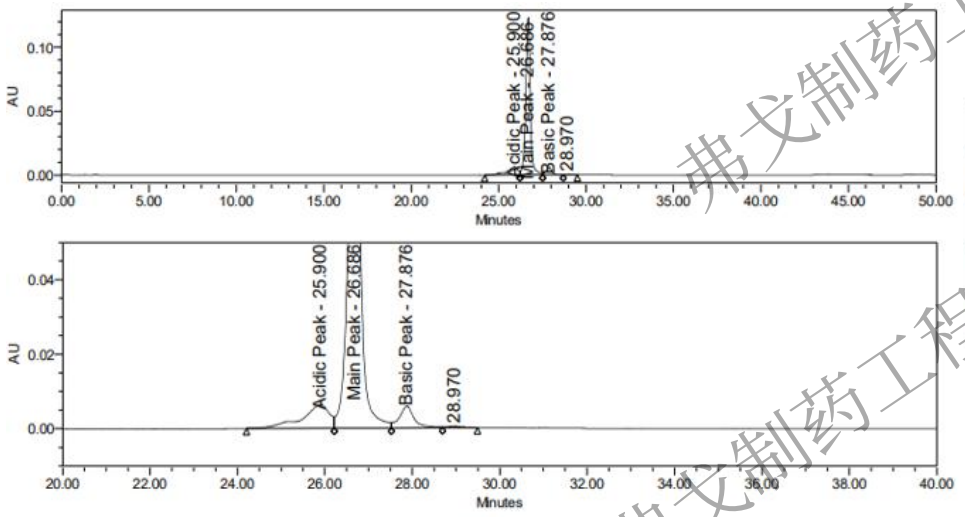
Raw Material

Gibco, GE, Merck, JS Bio, etc.

Protein Product quality

Problem (% Main Peak) Was Resolved in 4 Weeks Thru Media Optimization (配方的成分改良)

- Background:
  - Identified a JS Bio media that delivers high titer thru media screening for a CDMO project
  - Analytical results from CEX-HPLC showed that % Main Peak of the purified product generated from this high titer media did not meet the requirement
- Action:
  - Modified JS Bio in-house media formulation to meet protein product quality criteria
  - Confirmed the manipulation of media formulation is SUCCESSFUL in shake flasks
- Confirm Scalability:
  - Achieved comparable product quality results in 2-liter bioreactors



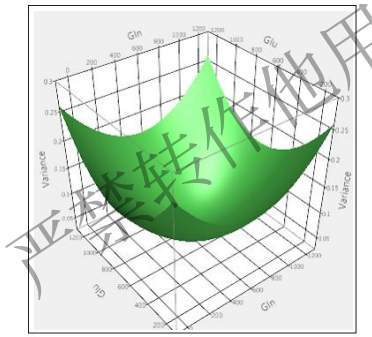
	Peak Name	RT	Area	% Area
1	Acidic Peak	25.900	272516	10.44
2	Main Peak	26.686	2190782	83.92
3	Basic Peak	27.876	136889	5.24
4		28.970	10291	0.39

样品名称	CEX-HPLC		
	Acidic Peak (%)	Main Peak (%)	Basic Peak (%)
Standard	13.5	74.9	11.6
原培养基	22.1	65.8	12.2
JSB培养基	**10.4**	**83.9**	**5.7**

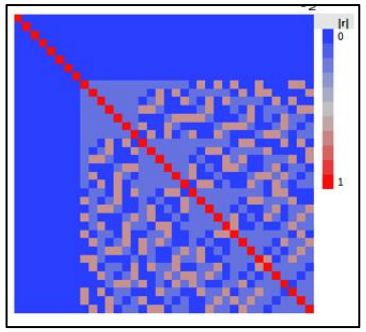
Media Optimization thru DOE In-House (客户细胞株寄送至健顺实验室)

Increase Titer by 8 Times in 5 Months

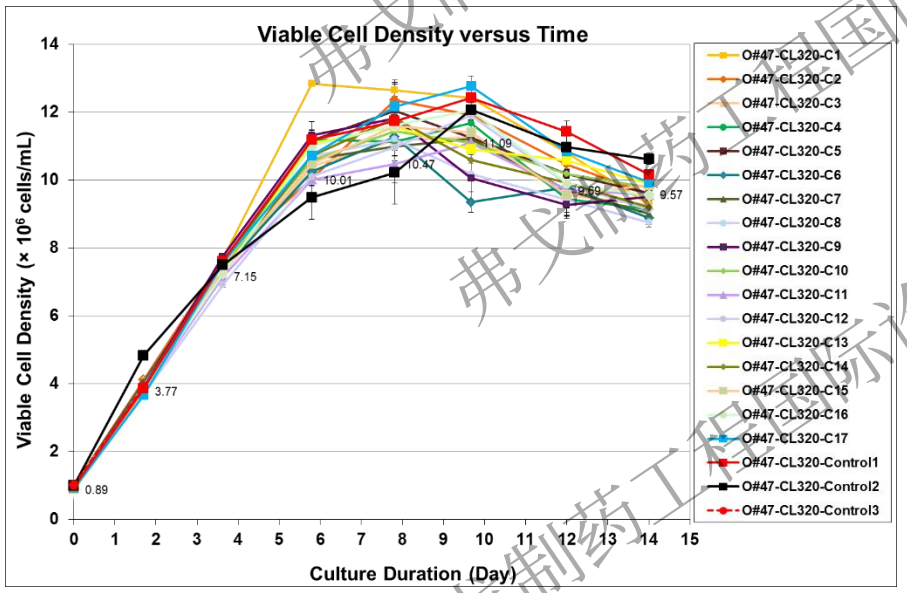
- Utilized Design of Experiment for Media Optimization (In-House)
  - Factorial Design
    - Optimization #1 – Amino Acids and Inorganic Salts
    - Optimization #2 – Vitamins
    - Optimization #3 – Trace Elements
  - Improved titer from **0.2 g/L to 1.7 g/L (8 times) in 5 months**
    - Increased cell growth and Qp
  - Developed scalable process in 2-liter bioreactors

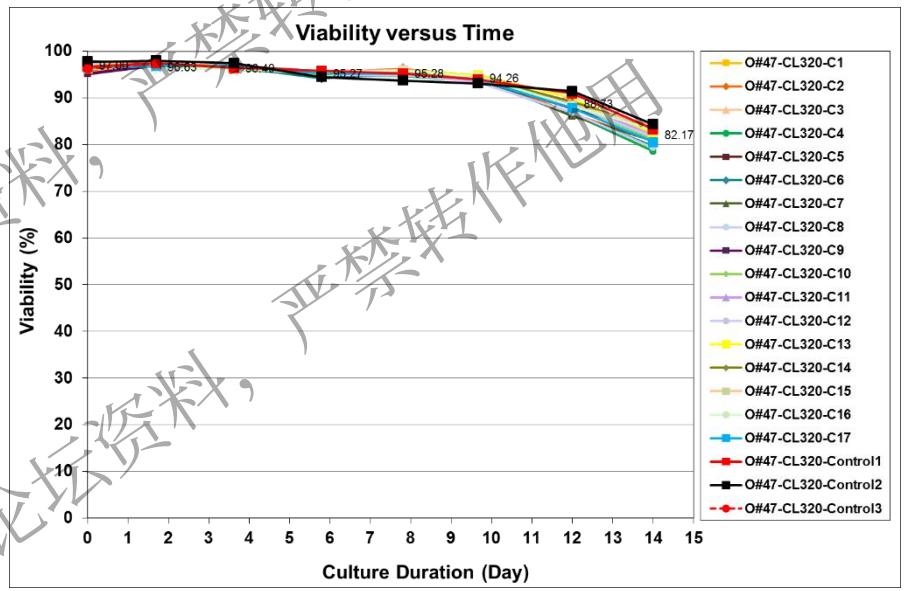


Prediction Variance Surface



Color Map on Correlations

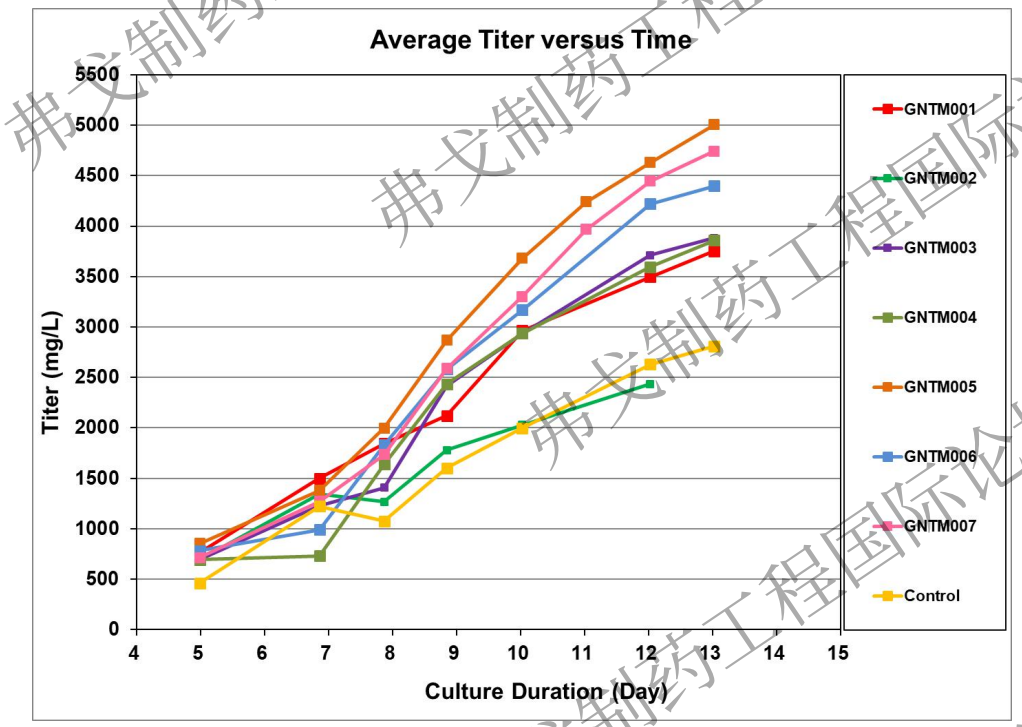


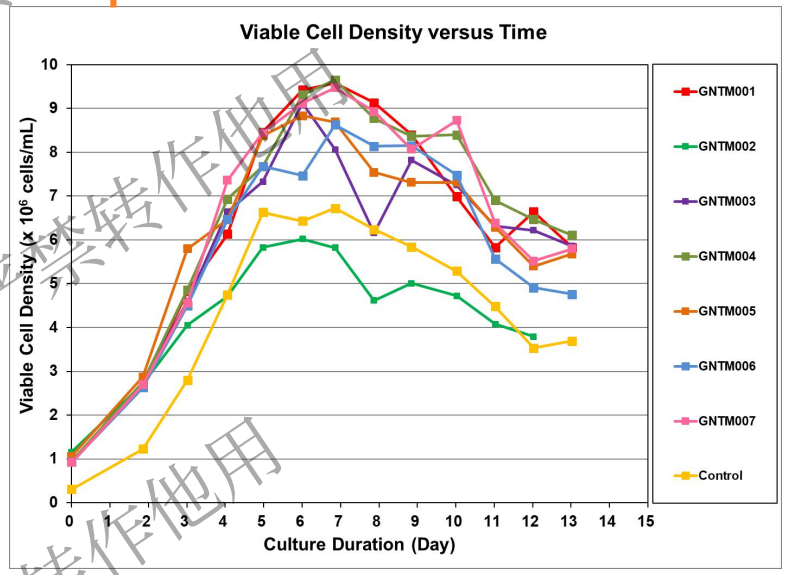


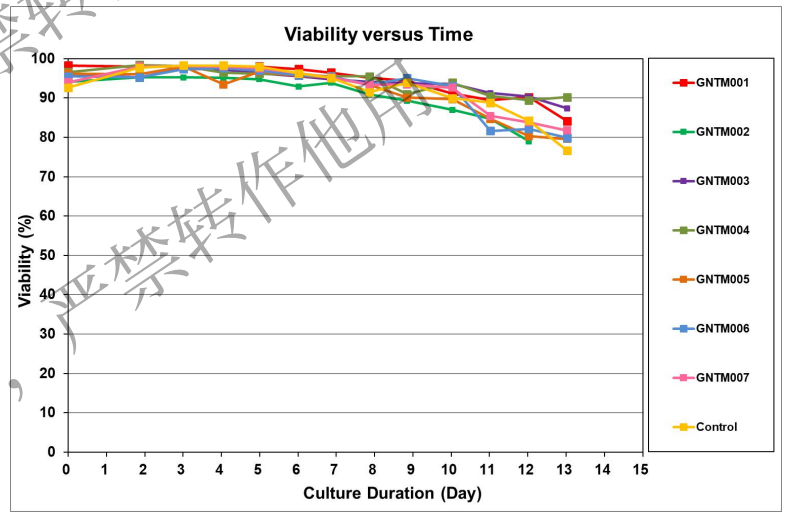
Media Panel Screening (客户实验室测试健顺培养基panel)

Increased Titer from 2.8 to 5.0 g/L after 1 round of experiment

- JS Bio provide a Media Panel (7 different formulations come in different ratio of nutrients) to customer for screening
- Customer identified a media that **delivers ~ 5 g/L (increased by two times) and 60 pg/cells/day** in Qp as compared to Control Condition (commercial media from US Media Company) that only delivers 2.8 g/L in 14 days.
- Product qualities (e.g. Purity, Charge Variants…) are also comparable.





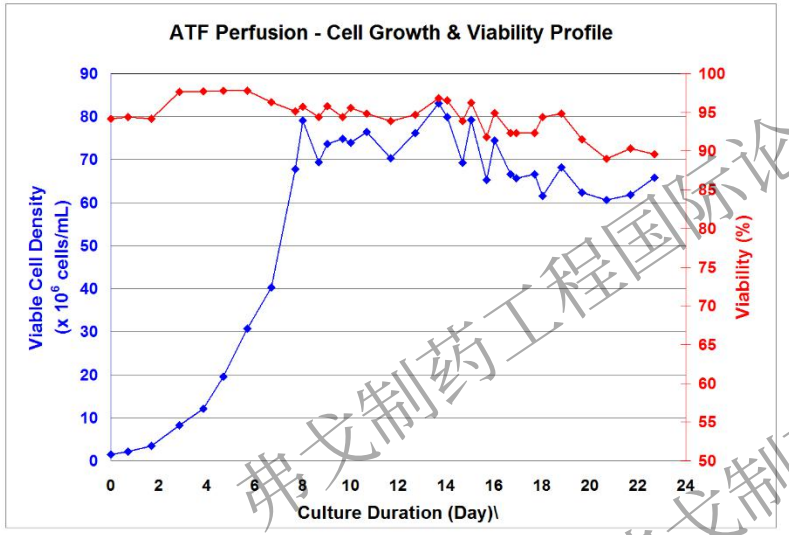


Media Optimization to Improve Titer & Product Quality (RP-HPLC) from 78% to 100% (Clinical Phase Ⅱ at 500-Liter Scale)

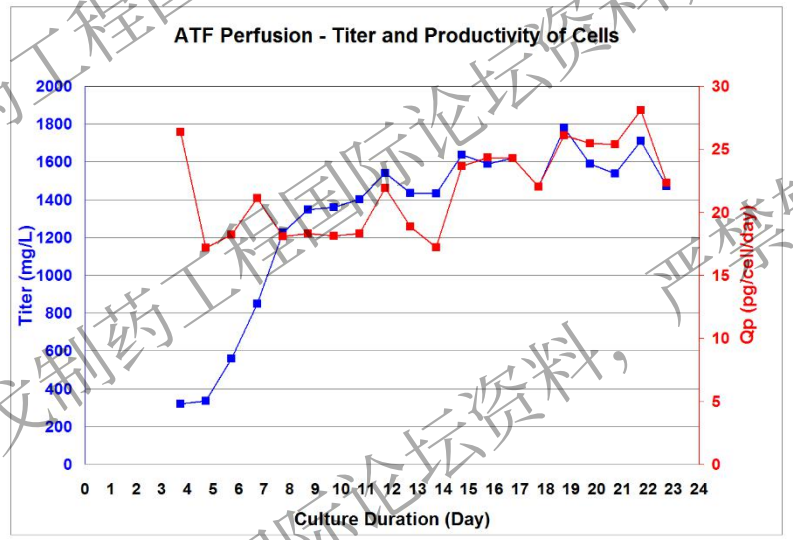
序号	供试培养基	厂家	细胞株	Titer (mg/mL)	RP-HPLC（峰 3 ≥ 65%）			SEC-HPLC（主峰≥95%）	CE-SDS (NR)（主峰≥90%）
				<ProA-HPLC>	峰 1 (P111-G285)	峰 2 (G31-G285)	峰 3 (H1-G285)		
Reference	原培养基	Ajinomoto	WCB	24.7	NA	21.23	78.77	96.64	99.20%
JSB 2	CD CHO 014	JSB	MCB	1.741	NA	NA	100	96.15	96.10%
工艺优化 1	原培养基 + LR3 IGF-1	Ajinomoto	MCB	2.299	NA	7.65	92.35	96.02	98.20%
工艺优化 2	原培养基 + Insulin	Ajinomoto	MCB	2.338	NA	6.97	93.03	96.37	97.10%
工艺优化 3	原培养基 + LR3 IGF-1	Ajinomoto	RCB	2.997	NA	7.68	92.32	96.8	96.80%

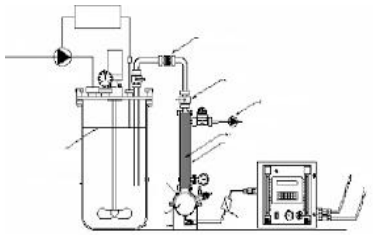
Process Technology and Media Enable High Titer Perfusion Process Development
(工艺技术与培养基的结合，促进了高产量的灌流工艺)

ATF Perfusion (23 days) Process Development – 15-liter bioreactor

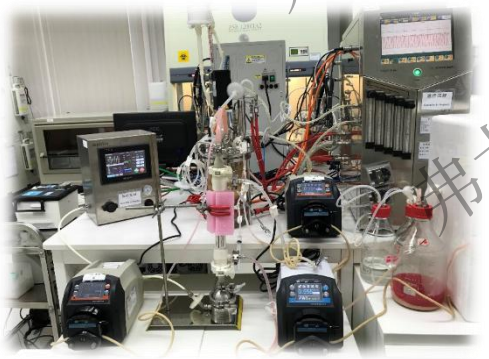


- Daily productivity is stable between 1200 – 1600 mg/L
- Delivered > 250 g of protein using a 15-liter in 23 days

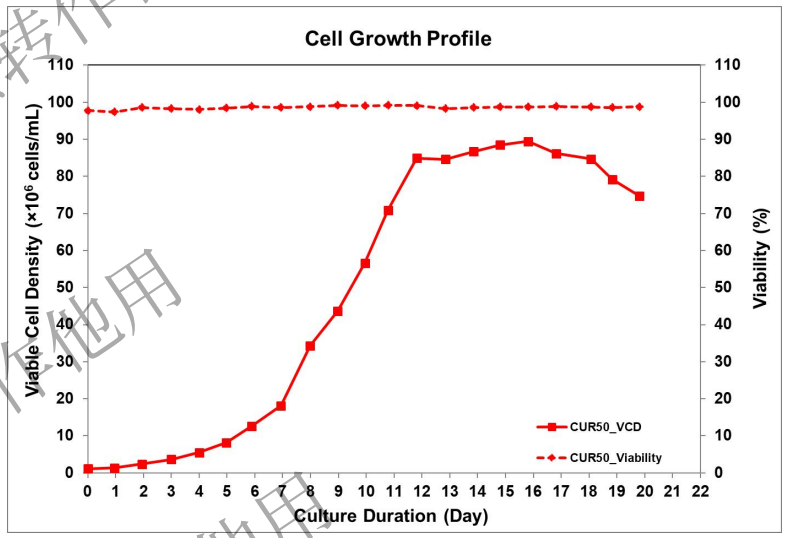




Source: www.repligenatf.com



High cell density growth in Concentrated Fed-Batch Mode (50-liter Bioreactor)



High Performing Cell Growth:

- Viable Cell Density reached > 85 x 10^6 cells/mL with viability > 95% throughout the 20 days process
- Final titer reached ~25 g/L

Perfusion Process and Batch Process for HEK293 suspension Cell

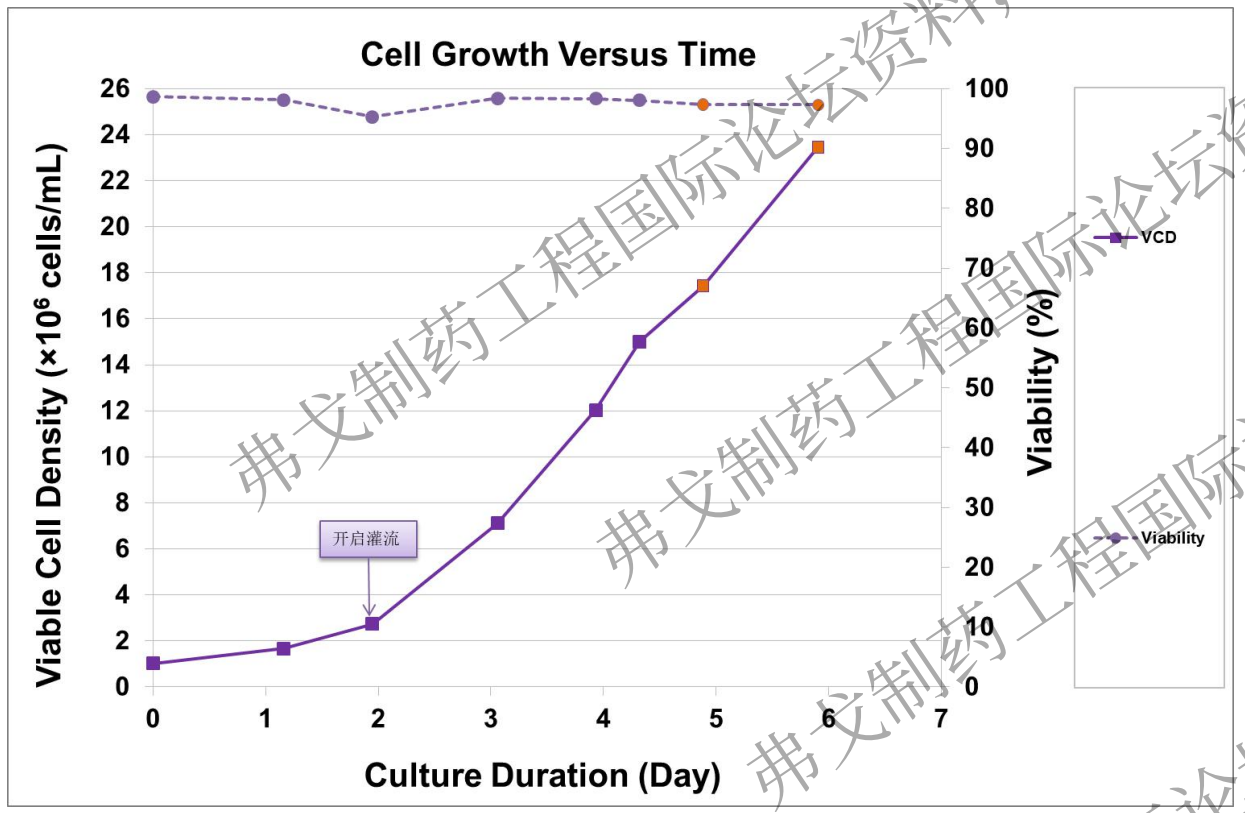


Fig.1 Cell Growth for Perfusion

- Traditional Process： Batch
- Improved Process： Perfusion
- Seeding： 1x10^6 cells/mL
- After Perfusion, cell density can reached 20x106 cells/mL and more
- For Ad5 virus expression

Perfusion Process and Batch Process for HEK293 suspension Cell

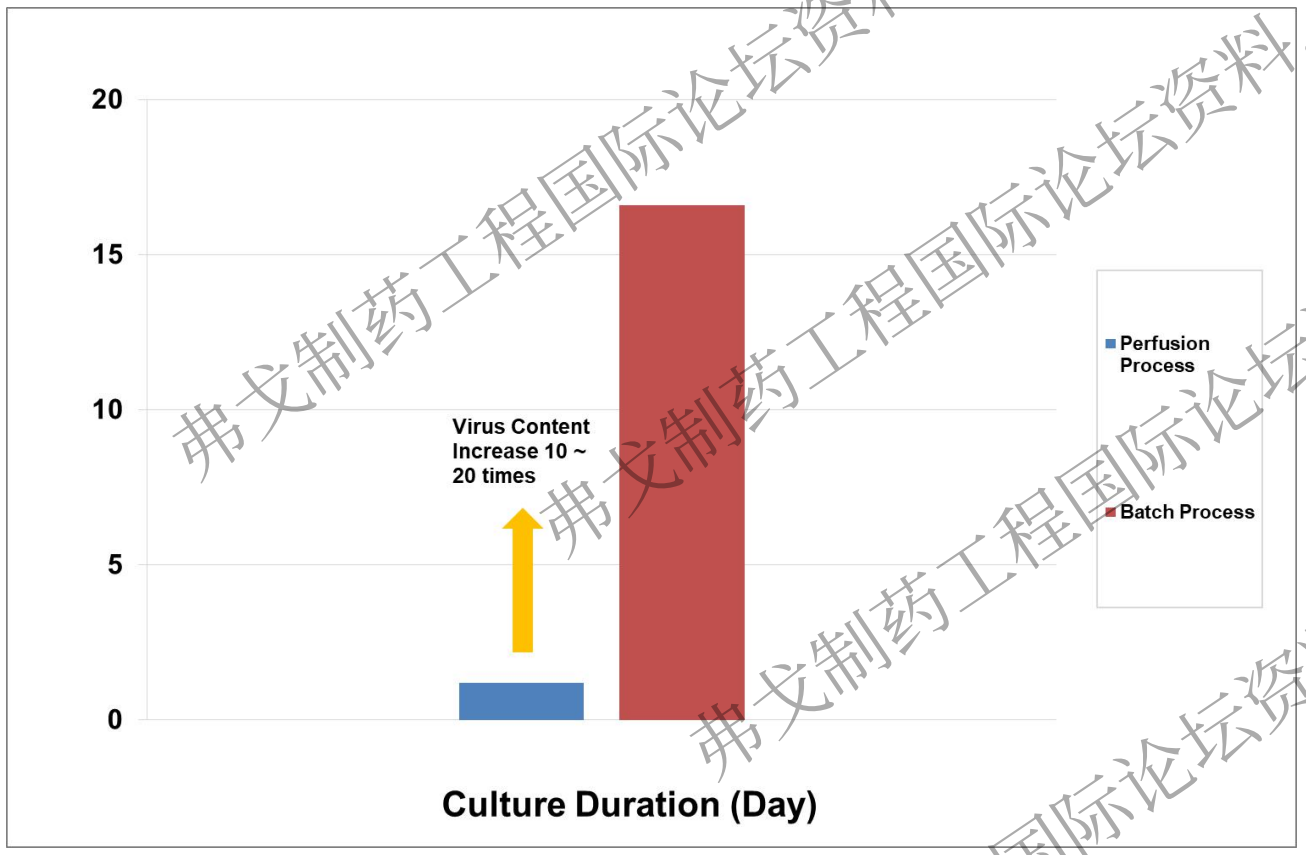
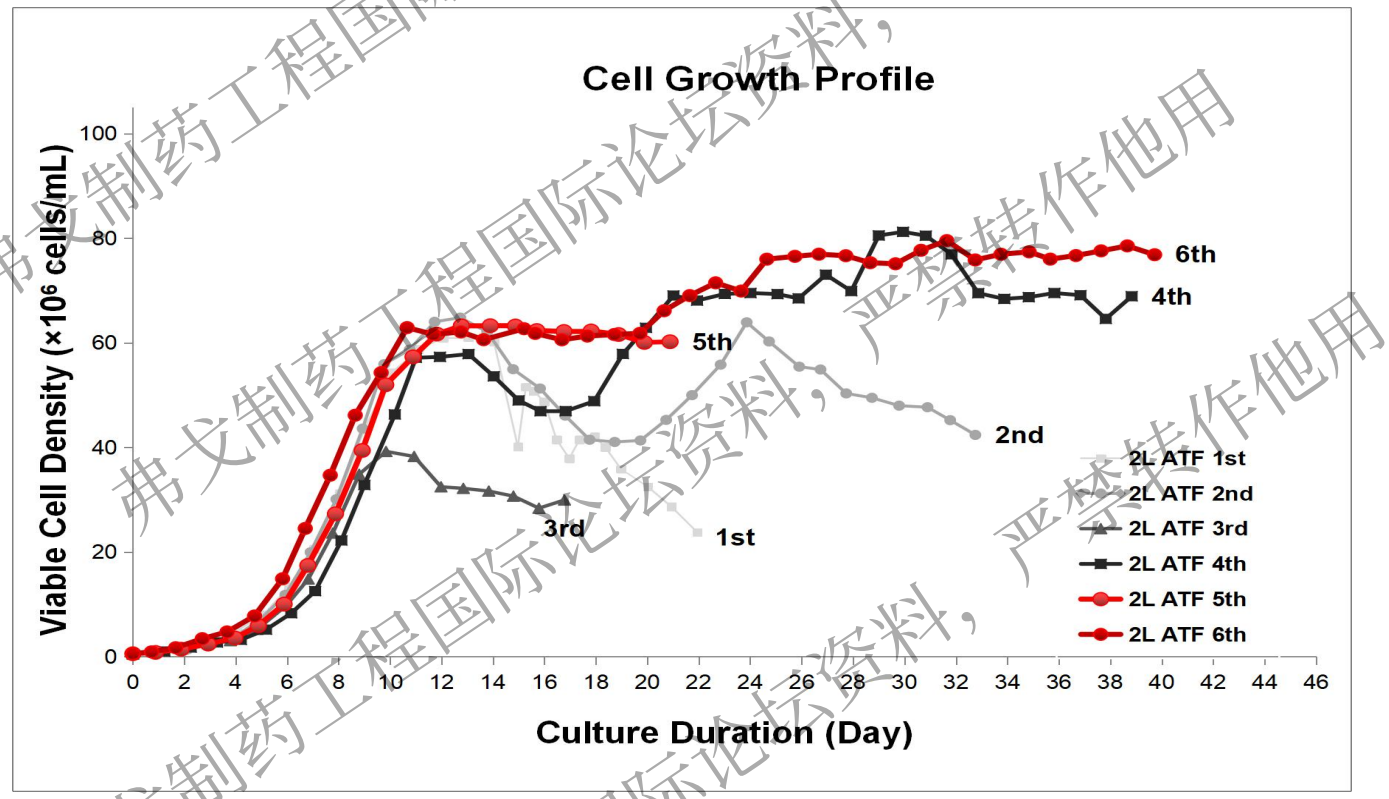


Fig 2. Virus Expression for Perfusion & Batch

- After the process optimization, use perfusion for adenovirus, the virus content is 10~20 times higher than the original batch culture process

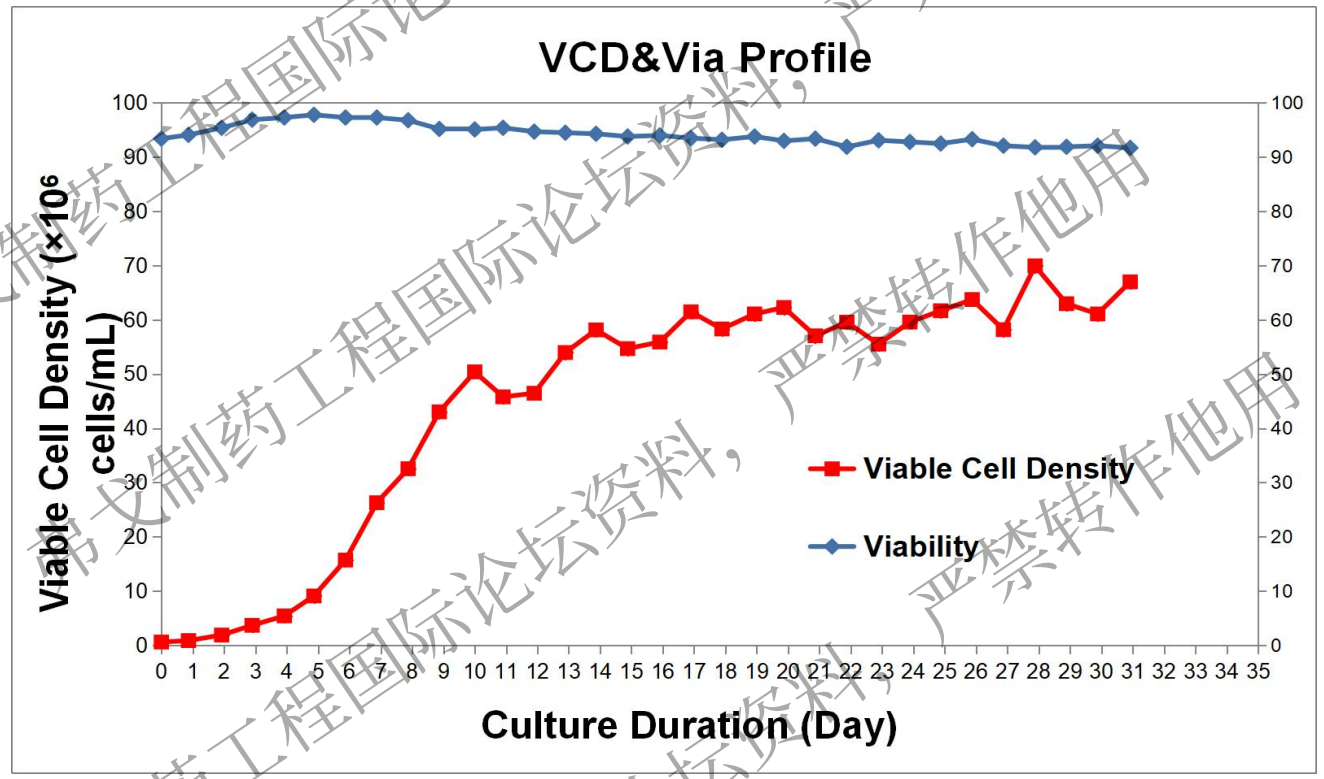
2L-Bioreactor ATF Process Development

- 2L-Bioreactor ATF, conduct bleeding on day3
- 1st - 4th experiments : ATF process development, the cells reached stationary phase, but the cell density can't be maintained
- 5th - 6th experiments: ATF process optimization and validation, the cell density can be maintained after cell stationary phase



2L-Bioreactor ATF Cell Growth Profile in Tech-transfer

- Viability can be maintained >90% throughout the 31 days process
- The cells reached stationary phase on day10, and the viable cell density can reach 50×10^6 cells/mL and maintained about 60×10^6 cells/mL in 11 days



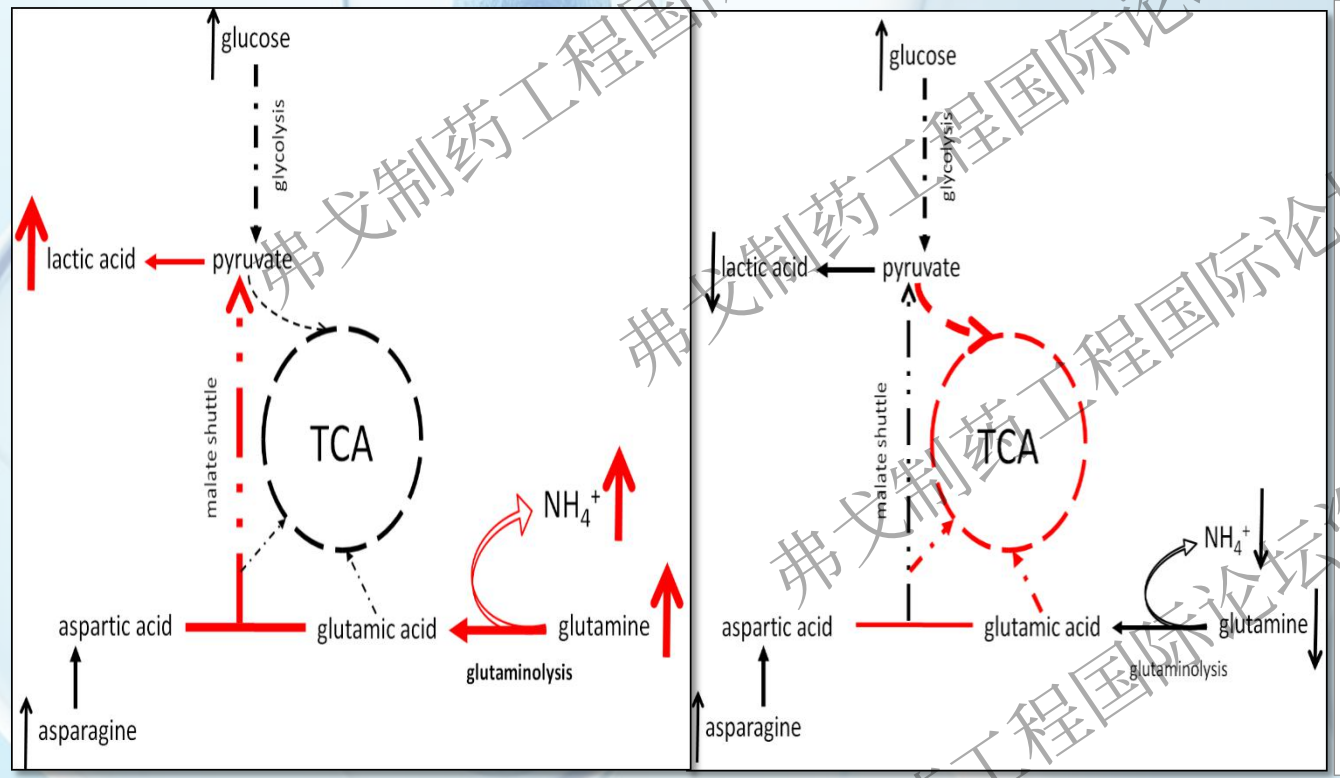
控制成本的最佳方法是：提高生产率

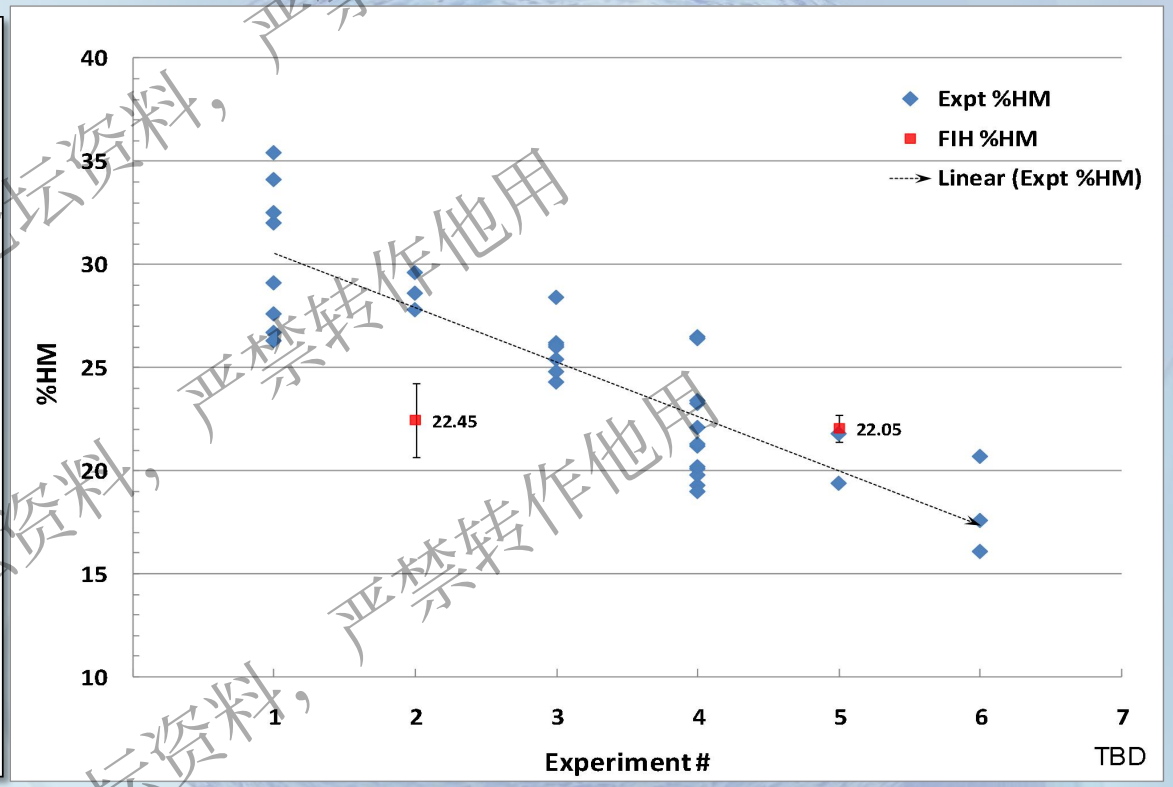
15-25%，Vaccine

8-12%，Protein

Titer	1g/L	5g/L
Prod lots	25	5
MCOG	$400	$80
Media cost	$32	$32
Media %	8%	40%

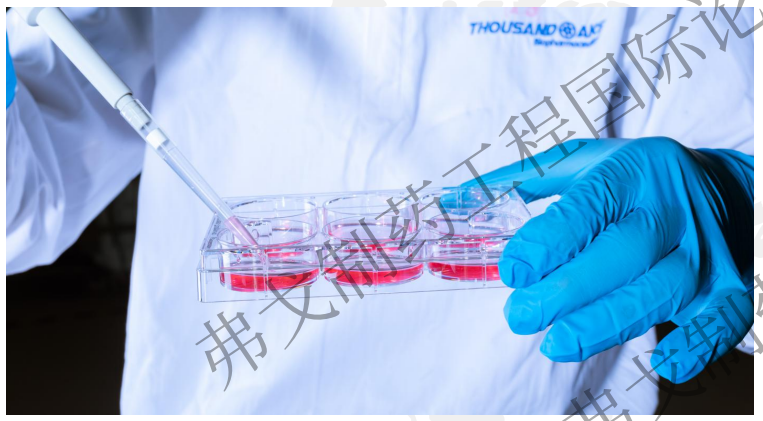
细胞代谢效率是产品质量的关键





Metabolism Directed Media Development

Integrated CMC Organization



CDMO

细胞培养基

一次性耗材

健顺培养基的服务优势

THOUSANDOAKS Biopharmaceuticals

5大优势

- 培养基研发，生产，供应链一体化 ▲
- 强大自主创新及开发能力 ▲
- 供应链更安全 ▲
- 质量更优，供货周期更短 ▼
- 项目经验丰富，客户粘性强 ▲

培养基服务超过20个III期临床及上市阶段产品

Thanks

Patients Focused

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CDMO Services
services@tobiopharm.com