出國報告(出國類別：出席研討會)

# 參加 2016 年第五屆生物製藥全球學會韓國大會
# -韓國首爾
# 研討會出國報告

5th Annual Biological World Korea
- Seoul Korea

服務機關：衛生福利部食品藥物管理署

姓名職稱：陳美方 高級審查員

派赴國家：韓國

出國期間：105 年 6 月 29 日 至 105 年 6 月 30 日

報告日期：105 年 8 月 5 日

# 壹、 摘要

近年來生物製藥發展日益快速，如何克服製程上的瓶頸並且運用資源來加速藥品上市為一重要議題。因為生物製劑在本質上具有一定的變異性，製備出品質均一的藥品為藥廠的挑戰。

本次研討會的主題為如何加速研發與製備高品質的生物製劑。無論是基因工程製劑或是疫苗，皆會涉及細胞培養與後續的純化製程，主題之一為研發瓶頸及尋求解決方法。主題之二為如何降低研發費用，例如利用單次使用的製程來縮短研發時程與降低研發費用。這次研討會特別請台灣的永昕、翰林、以及喜康生技分享單次使用發酵製程(single use bioreactor)的經驗，而台灣食品藥物管理署則受邀給予單次使用製程關於法規的建議。

**關鍵字:** 生物藥品(Biologics) 、品質均一(Consistency)、單次使用(single use)、細胞製備(cell culture)、純化製程(purification processes)

# 目次

## 貳、 目的

本次研討會是業界用來討論研發瓶頸與解決策略的一個平台。台灣以法規單位身分參與本次的研討會。一面藉著演講給予業界關於新穎技術法規方面的考量與建議，一面藉者研討會了解目前業界研發的現況，與未來可能出現新穎的藥物。參與本次研討會，認識許多在業界有經驗的研發人員，未來可以考量與專業人士保持長期連絡關係，尤其是生物製劑製程開發日新月異，具有實際參與研發之專家意見，將有助於日後審查或法規政策研擬之參考。

## 參、 過程紀要

| 時間 | 行程 |
|---|---|
| **6** 月 **28** 日 | 啟程：台北–韓國首爾 |
| **6** 月 **29-30** 日 | 出席 5th Annual Biological World Korea 研討會 |
| **7** 月 **1** 日 | 回程：韓國–台北 |

研討會 2 天，議程詳如附件一，其重要內容摘要如下:

第 1 天(105 年 6 月 28 日)

## 一、Keynote : Evolution of Biopharmaceutical Manufacturing for Novel Biologics

講師: Uwe Gottschalk, Chief Technology Officer, Lonza, Switzerland

內容摘要:

生物製劑因為在本質上有其變異性(variant)，所以如何製備出均一的藥品，需要在製程上嚴格控制，包括需要有製備的經驗、合理的時間建置廠房、製程需確效、後續設備的維持等。在研發階段需確認關鍵性品質參數、關鍵性製程參數，在臨床試驗階段需確認製程放大後，相關的參數是否需要微調，在量產階段，需要找出與批量相關的參數，並進行調控。以培養細胞為例，培養基的成分是相當重要，需要找出關鍵的物料並加以管控規格與供應商。本次演講以 ADC(Antibody drug conjugate)為例，在製備上的挑戰為 (一). Conjugation 製程的最適化，(二).如何降低聚合物(aggregate)。若是高 DAR(drug antibody ratio)，通常有下面特點 1. Higher *in vitro* potency 2.High Hydrophobicity 3. Fast in vivo clearance 4. Low tolerability 5. High aggregation propensity。在 Conjugation 製程的最適化部分，製程皆需嚴格調控 pH, protein concentration 以及 salt concentration。降低聚合物部分，亦是相同原則。

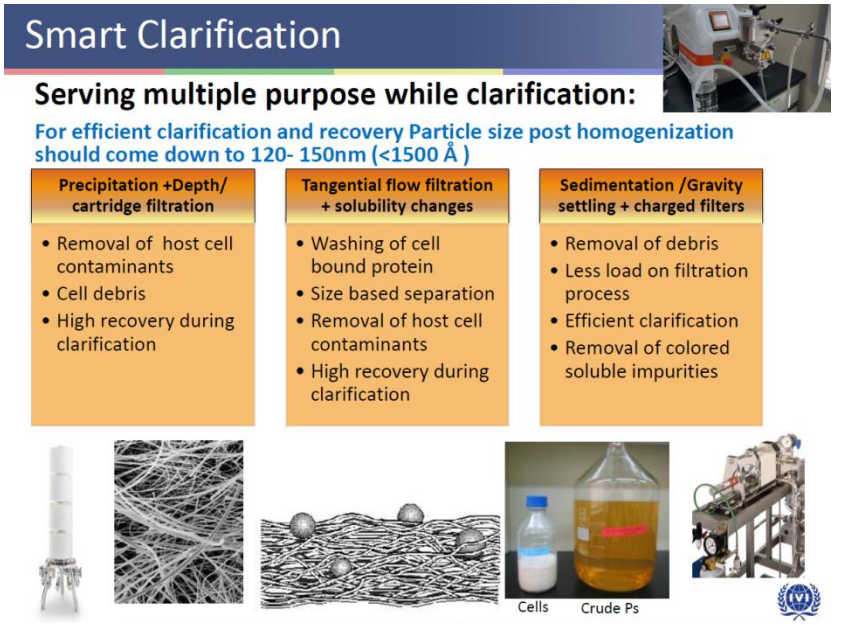
## 二、New Advances in Protein Purification Methods for Scale up of Downstream Process

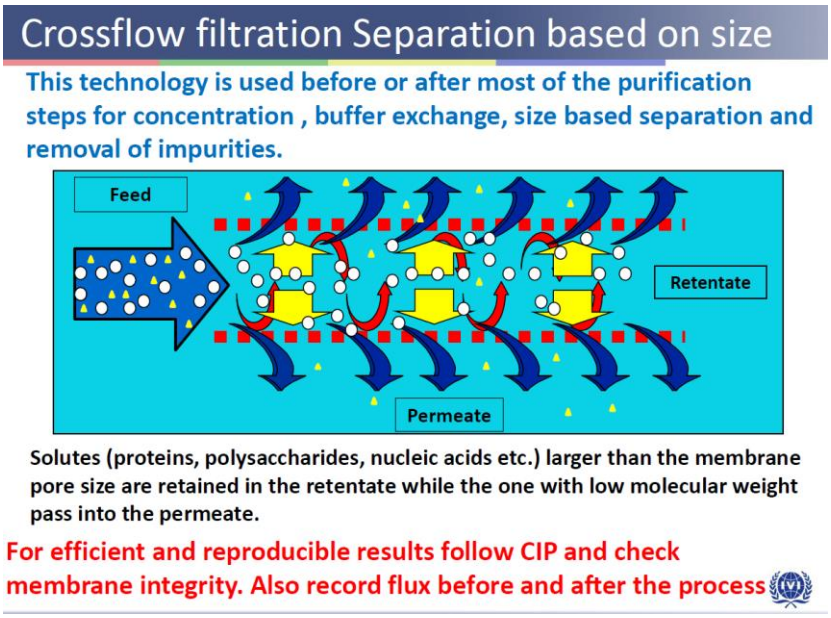
講師: Neha Kothar, Associate Research Scientist, International Vaccine Institute, Korea

內容摘要:

本次演講探討疫苗在大量製備時純化製程的突破。疫苗研發是人類醫學的一大突破，從早期利用活性減毒的天花疫苗(smallpox vaccine)到目前以基因工程(genome-based approach)製備的疫苗(如 Meningococcus B vaccine)，疫苗的製備技術可說是日新月異。

一般而言，製備疫苗可以使用雞蛋、細菌/酵母菌、細胞作為培養的平台，而後續再利用純化製程取得抗原。因為疫苗一般是施打在健康人，所以法規對於疫苗的安全性管控特別嚴格，如管控有機溶劑殘餘、介面活性劑殘餘、以及抗生素的殘餘量。常見實驗室的製備方式 metal affinity chromatography 並不適用大量的純化製備，故本次演講者提出利用 smart clarification 移除 cell debris，並且藉著 crossflow filtration 可以將不需要的小分子量濾出，詳細內容如下圖:



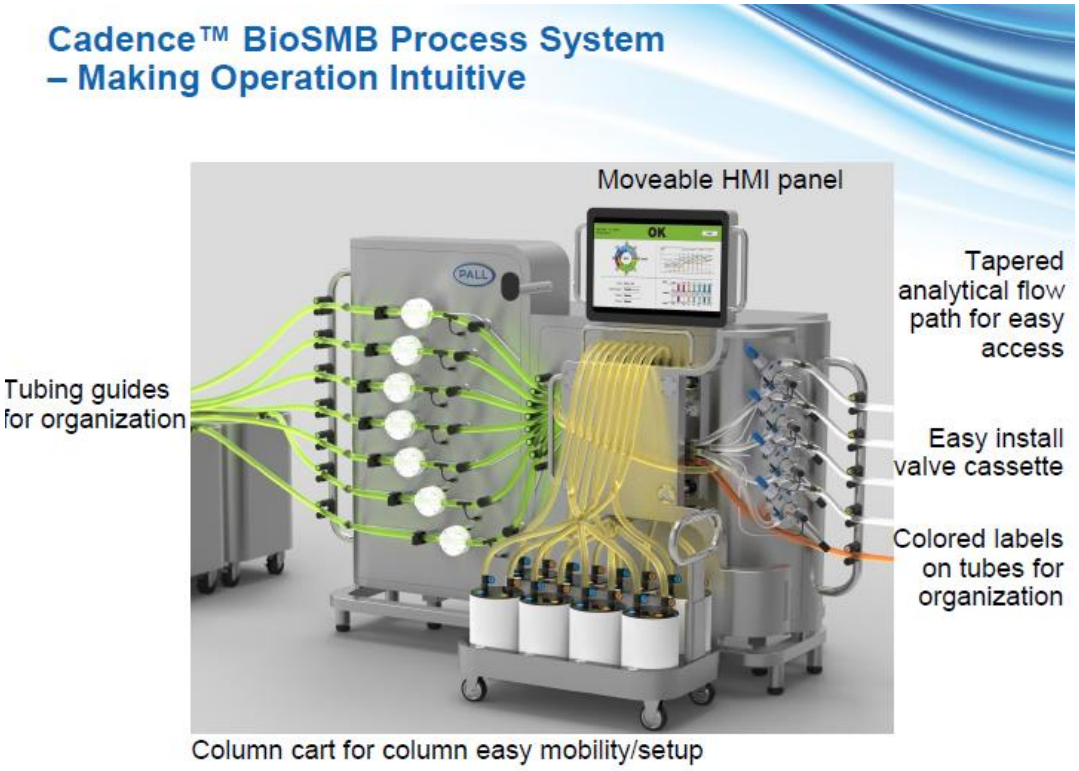



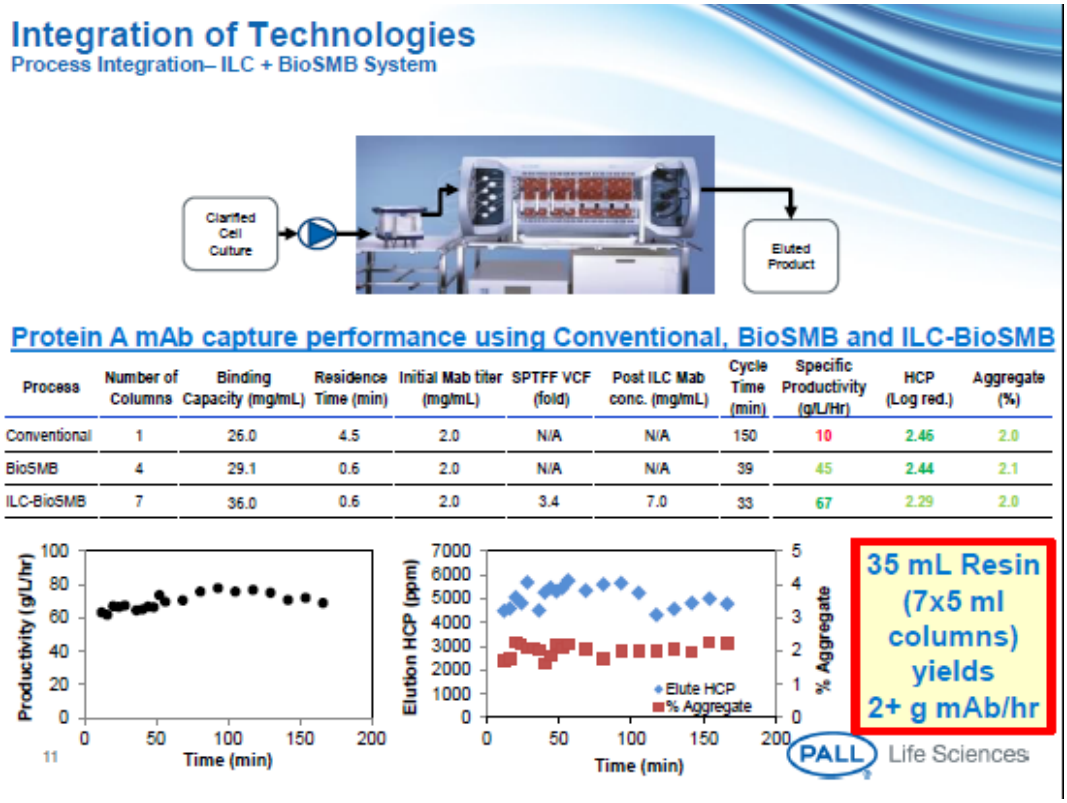
## 三、Workshop with PALL LIFE SCIENCES: Single-Use, Continuous Bioprocessing: Value Proposition and How to Get Started.

講師: Rob Noel, Business and New Technologies Development, PALL Life Sciences, UK

**內容摘要:**

生物製劑在純化過程會使用各種不同原理的色層分析管柱，常見的如 protein A 與離子交換樹脂等。以 protein A 的價格而言一根 56L (60cm id x20cm)約為美金 560,000 元，而 5-6L(10 cm id) 約為美金 440,000 元，故廠商的概念為利用多枝小根的單次使用管柱並聯，以達到分離的效果，下圖為其實際的圖譜與其分離效率。






## 四、New Purification Process Based on Keystone Contaminant Management

**講師:** Wei Zhang, Research Scientist, Downstream Processing, Bioprocessing Technology Institute, Singapore

**內容摘要:**

在單株抗體純化過程中，Chromatin 是主要的汙染源，Protein A 純化過程是將宿主細胞產生的單株抗體吸附在 Protein A 管柱層析上。若在進入 protein A 前移除 chromatin，發現後續的不純物量都減少，如 HCP、product related impurity、甚至從宿主細胞來的病毒，如 MVM, MuLV 亦大量減少，並且可以增加 Protein A 層吸管柱的壽命，減少 Protein A Leachable，相對而言即可以降低研發的成本。

## Dramatically more effective feed stream prep

*Contaminant distribution before and after chromatin extraction*

| Reduction of/by | Cent.MicF | ChromX |
|---|---|---|
| Host proteins | nil | 50-90% |
| DNA | nil | 5-6 logs |
| Endotoxin | nil | 2-4 logs |
| Prod. Rel. impurities | nil | 50-95% |
| Aggregates | nil | 90-99% |
| MVM | nil | 5 logs |
| MuLV | nil | 9 logs |
| Turbidity | 10-100 NTU | 2 NTU |
| IgG recovery | 90-95% | 85-95% |

*High viral reduction results from their strong association with chromatin. It directly enables reducing the number of subsequent chromatography steps without compromising overall virus reduction.*

*Virus reduction studies conducted by Charles River Laboratories.*

## Enhancement of protein A capture

*Loaded with non-extracted or chromatin-extracted harvest.*

| PA perform/post: | Cen/mcF | ChromX | Improvement |
|---|---|---|---|
| Capacity | 48 g/L | 57 g/L | **20%** |
| Recovery | 93% | 99% | **6%** |
| Productivity/cycle | 46 g/L | 56 g/L | **26%** |
| HCP | 2000 ppm | < 100 ppm | **20x** |
| DNA | 10 ppm | 1 ppb | **10,000x** |
| Aggregates | 1.7% | 0.8% | **2x** |
| Leached prot. A | 85 ppm | 33 ppm | **2x** |
| Turbid. post-neutr. | 108 NTU | 6 NTU | **18x** |

*The 24% productivity improvement allows elimination of a process cycle, reduction of purchased media volume, or higher productivity from a fixed volume of chromatography media.*

*Experimental data from a prospective Herceptin biosimilar.*

第 2 天:

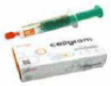
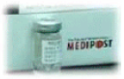
**題目:** Practical Cost Reduction Stratgies on Mass Production of Stem Cell Therapies

**講師:** Seung Hee Lee Deputy Director, Senior Researcher Kangstem Biotech, Korea

**內容摘要:**

降低細胞治療的研發費用是產業間一直關注的問題，如何揀選發酵槽與培養基是關鍵。若是能製備高產值的細胞，則細胞治療的研發費用就會下降。傳統上，細胞培養是利用 2D culture 培養細胞再換製成 3D bioreactor，演講者指出若一開始即利用 Dynamic bioreactor，若有合適的條件，則可以培養的細胞量更多，也較少細胞的損失與汙染， 之後批量放大亦較容易。但是，3D dynamic bioreactor 具有剪力(stress shear)，會導致細胞的特性改變，而間質幹細胞(MSC)又比一般的 CHO 細胞與癌細胞株(cancer cell line)對剪力敏感，故仍須找出合適培養條件。另外，研發的 KSB-3 medium 其細胞的生長速度亦比一般培養基好(KSB-3 medium 的 doubling time 僅 15 小時，一般培養基為 40 小時)。詳細內容如下圖。

## Marketing authorized stem cell therapeutics

| Therapeutics name | Hearti Cellgram | Cartistem | Cupistem | Neuronata -R | Prochymal | Holoclar | Tem cell HS inj. |
|---|---|---|---|---|---|---|---|
| Country | Korea | Korea | Korea | Korea | Canada | EU | Japan |
| |  |  |  |  |  |  |  |
| Company | Pharmicell | Medipost | Anterogen | Corestem | Osiris | Chiesi Farmaceutici | JCR pharma |
| Cell type | Auto-BM-MSC | Allo-UCB-MSC | Auto-AD-MSC | Auto-BM-MSC | Allo-BM-MSC | Auto-cornea epithelial stem cell | Allo-BM-MSC |
| Target disease | Acute myocardial infarction | Cartilage defect | Fistulas in Crohn's disease | Lou Gehrig's disease | GVHD | limbal stem cell deficiency | GVHD |
| Orphan drug | x | x | o | o | o | o | o |
| Approval date | 2011.07 | 2012.01 | 2012.01 | 2014.08 | 2012.05 | 2015.02 (conditional) | 2015. (conditional) |

Osteocytes

*Valentin Jossen et al. 2014 Cells and Biomaterials in Regenerative Medicine*

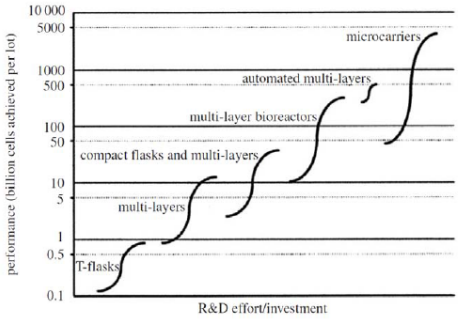
## Traditional 2-D vs. Dynamic bioreactors

| Traditional 2-D culture methods | Dynamic bioreactors |
|---|---|
| ✓ Reliable and well defined | ✓ Each cell type requir… …gs<br>✓ Shear<br>✓ High cost in initial set-up |
| ✓ Labor intensive<br>✓ Limited in scale–up production potential by the available growth surface area<br>✓ Difficulties in handling and quality control<br>✓ <100 billion cells | ✓ Less labor intensive<br>✓ Compact production unit<br>✓ Uniform and controllable cell culture environment<br>✓ Less cell loss<br>✓ Less contamination<br>✓ Scalable |

R&D efforts, investments!!


## Dynamic systems
### - R&D effort/investment

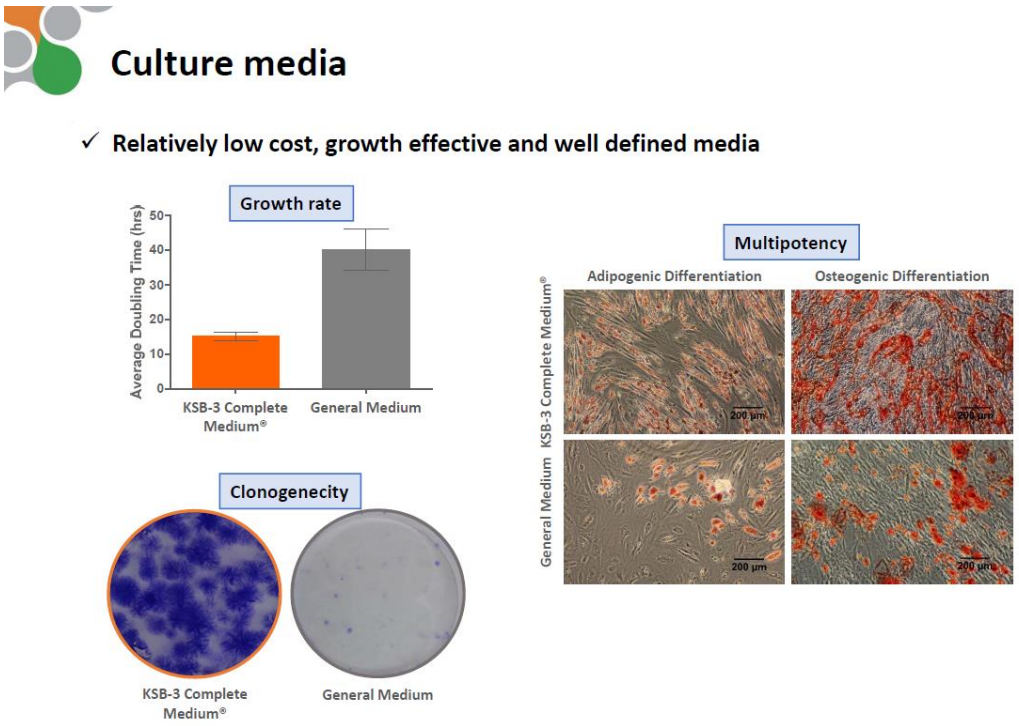
| | Static planer system | Dynamic system |
|---|---|---|
| **Shear stress** | - | + |
| **Cell characteristics** | Sustainable | Changeable |
| **Expansion** | Limited | Expandable |
| **Labor** | Labor intensive | Less Labor intensive |




Conceptual illustration of a technology S-curve showing the evolution of expansion technologies used in cell therapy manufacture.

*Martin C. W. 2015 Advances in cell culture: anchorage dependence. Phil. Trans. R. Soc. B 370: 20140040.*

***MSC is relatively more sensitive than other cell types** such as CHO cells or Cancer cell lines when applied to bioreactors




**題目:Manufacture of clinical grade SCM CGH from single colonies based on subfractionation culture method**

**講師:** Sun U Song Ph.D. CEO SCM Lifescience Co.LTd

**內容摘要:**

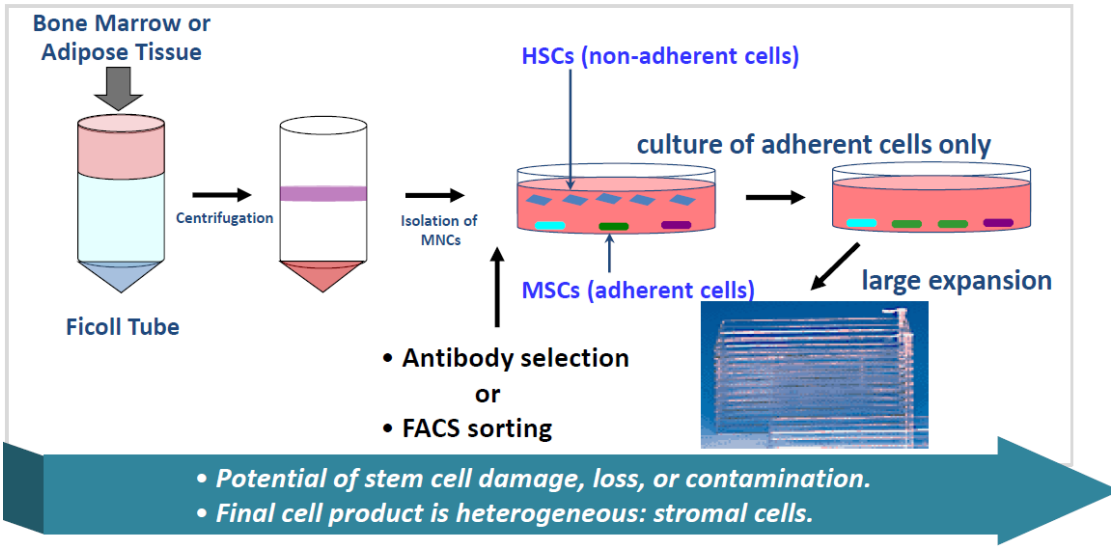
傳統上利用離心的方式取得骨髓或脂肪的間質幹細胞(簡稱 GCM method)，本演講者利用骨髓細胞培養成聚落(colony)的方式，再利用聚落製備間質細胞的細胞庫，此方法稱為 SCM，即 subfractionation culture method。利用 SCM 製備的間質細胞執行毒理試驗與藥理試驗，評估與傳統方式的差異。由 hair growth in animal model 與 atopic dermititis animal model 結果發現，利用 SCM 製備的間質細胞其毛髮的生長與皮膚復原的狀況都較 GCM 製備的間質細胞好。毛髮生長與組織切片如下圖。

# Isolation Methods for MSCs

| Assignee | Technology | Issued Countries | Remarks |
|---|---|---|---|
| Osiris (USA) | Density-Gradient Centrifugation Method (GCM) | Global (except Korea) | Most popular method |
| Mesoblast (Australia) | FACS Sorting-based Method | Global (except Korea) | Tech transfer from Osiris in Feb. 2014 |
| SCM Lifescience (Korea) | Subfractionation Culturing Method (SCM) | Korea, USA, Japan, China, EU | Born in Korea |



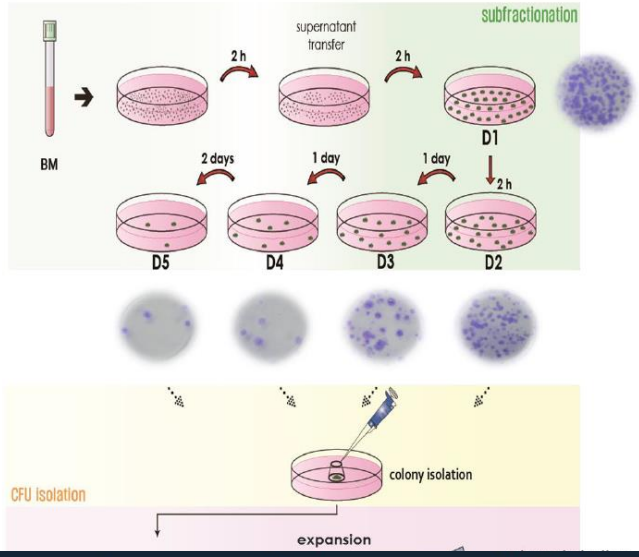
## ▪ Conventional Isolation Method – GCM*




* GCM : Density-Gradient Centrifugation Method

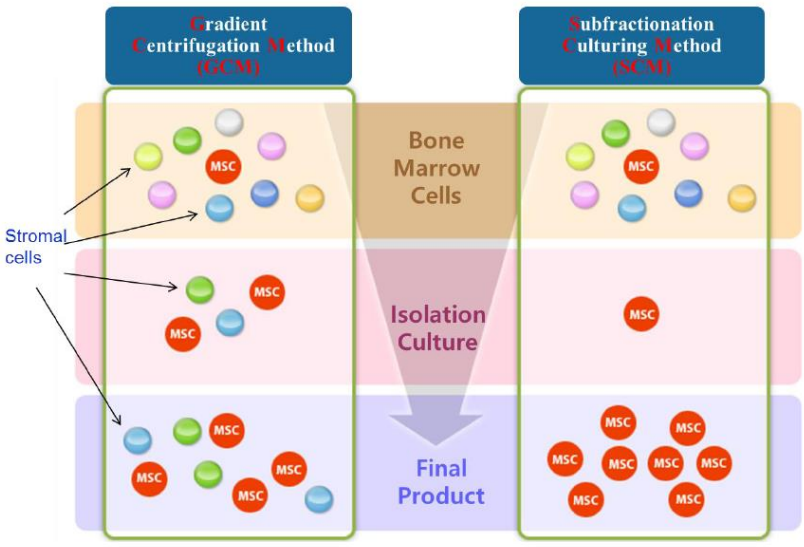
# What makes us different - CMC

- Subfractionation Culturing Method - SCM




# What makes us different - CMC

- Higher homogeneity via unique isolation method



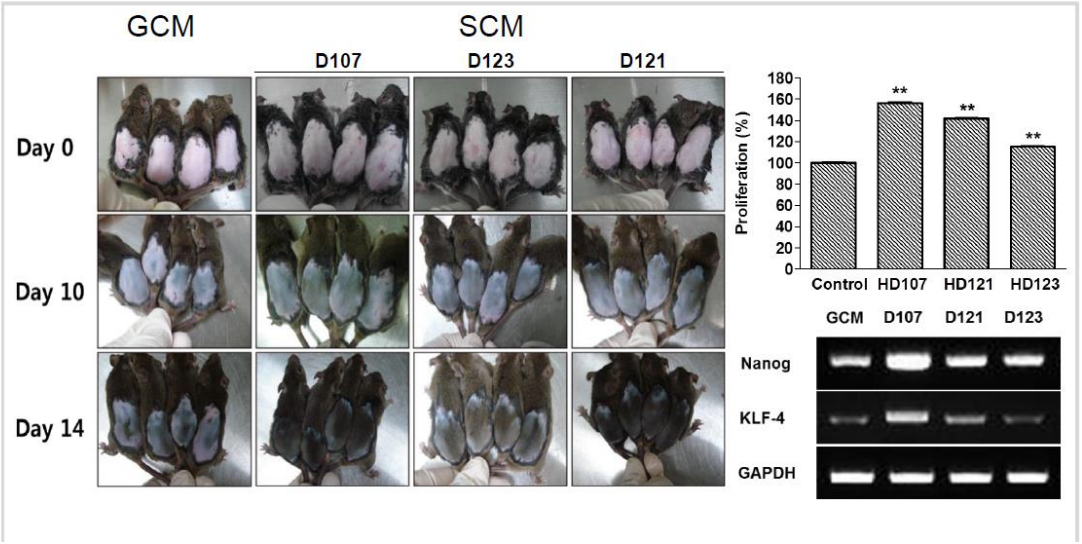
## ▪ Summary of Safety Evaluation

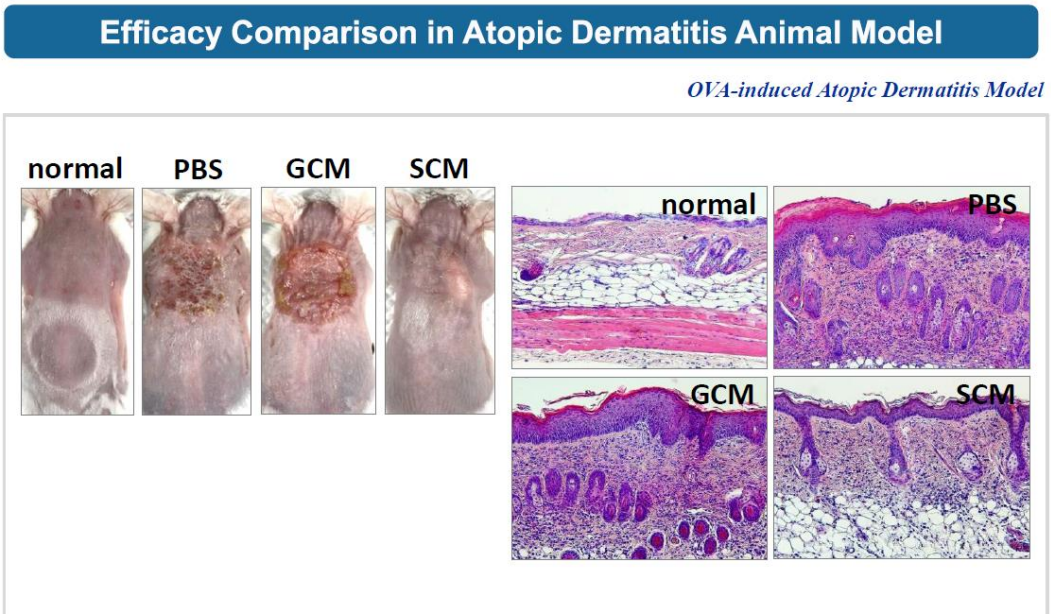
| Test | Animal Group | Examination | Conclusion |
|---|---|---|---|
| **Single-injection toxicity** | • Control<br>• H: $1\times10^6$ cells/head<br>• M: $5\times10^5$ cells/head<br>• L: $5\times10^4$ cells/head | • Clinical signs, Body weight, Necropsy, Histopathology | • No test substance-related effect was observed; the approximate lethal dose was greater than $1\times10^6$ cells/head |
| **Multiple-injection toxicity + 6 week recovery** | • Control<br>• H: $1\times10^6$ cells/head<br>• M: $5\times10^5$ cells/head<br>• L: $5\times10^4$ cells/head | • 3 times, 2-week intervals<br>• Clinical signs, Body weight, Necropsy, Histopathology<br>• H only in recovery study | • No test substance-related effect on males and females was observed at H dose<br>• NOAEL of the test substance was greater than H dose in males and females |
| **Biodistribution** | • Control<br>• $5\times10^5$ cells/head | • Single injection<br>• Removal of organs<br>• Human DNA detection | • Clearance of the test substance was considered to occur from whole body of mice after week 4 after injection |
| **Tumorigenicity** | • Control<br>• Negative Control (MRC-5)<br>• Positive Control (HT-1080)<br>• Test-substance(hMSC) | • Clinical signs, Body weight, Necropsy, Histopathology<br>• $1\times10^6$ cells/head<br>• 26 week | • Test substance-related tumorigenicity was not observed in males and females.<br>• Test substance was considered to have no tumorigenicity at a dose of $1\times10^6$ cells/head |

※ Test animal: NCr athymic nude mice (Balb/c-nu)

## Comparison of Hair Growth in Animal Model

*Expert Opin Biol. (2014)*






**題目:Who Will Manufacture Vaccines for the Next Emerging Global Diseases?**

**講師:** Alan Liss, Founder and CEO, GXP Farma LLC, USA

**內容摘要:**

疫苗的研發與供應是防疫的重大問題，然而研發疫苗的製造商由 1967 年的 26 家，到 1980 年只剩 17 家。疫苗並非是獲利的藥品，大部分藥廠將疫苗的研發與製備停止，而轉研發利潤較高的藥物。有研究指出，研發與製備疫苗需要 24 億美金，而全球僅有前五大跨國藥廠(Merck, GSK, Novartis, Sanofi, Pfizer)具有這樣的資金。回顧近年爆發的疫情，如伊波拉病毒(Ebola)、MERS、ZIKA、感染呼吸道的如 H3N2、H1N1、H7N9、H5N1 等新型流感，急需有廠商投入研發，如何解套，需要法規單位與業界的合作。演講者提出了幾項建議:

1. Manufacturing capacity building cannot happen in a vaccum
   -Regulatory, Clinical, Policy response and maintenance
   -Strong, local government support is needed throughout
2. Sustainability of pandemic vaccine production capacity is dependent on :

- Ability to produce the novel vaccine when needed

-Producing something in that facility that keeps facility running

3. Training staff on a novel vaccine production is not essential

- know how and expertise on alternative marketable products essential

## NOT BUSINESS AS USUAL

- Since 9/11, US DHHS has adapted to extraordinary circumstances through extraordinary efforts
  - These include proactive measures w/ sister agencies and industry such as:
    - **Meetings to encourage developing new products**
    - **Early and intensive interactions w/ sponsors**
    - **Collaboration and rapid turnaround on INDs, EUA**
    - **Proactive trips to inspect facilities**
    - **Participation in multiple product development teams**
    - **Expedited reviews of key product apps.**



## Ebola Vaccines under development

| | | |
|---|---|---|
| MVA vectored glycoprotein | Emergent Biosolutions | Phase I planned |
| Chimp adenovirus 3 vectored glycoprotein (cAd3-EBO Z) | GSK & NIAID | Phase III in progress |
| rVSV vectored glycoprotein (VSV-EBOV) | Newlink Genetics & Merck | Interim Phase III results published |
| Human adenovirus 5 vectored 2014 glycoprotein insert | BIT & CanSino | Phase I complete |
| Adenovirus 26 vectored glycoprotein / MVA-BN (Ad26.ZEBOV/ MVA-BN) | Johnson & Johnson | Phase II in progress |
| Glycoprotein nanoparticle + MatrixM (Ebola GP vaccine) | Novavax | Phase I complete |
| Oral human adenovirus 5 + TLR3 ligand | Vaxart | Phase I planned |
| HPIV-3 vectored glycoprotein | Ministry of Health (Russia) | Phase I planned |
| rVSVN4CT1 VesiculoVax | Profectus Biosciences | Phase I planned |
| Rabies vectored glycoprotein | Thomas Jefferson University & NIAID/NIH | Non-Human Primate challenge complete |

- DNA vaccine — Inovio — Purified glycoprotein — Phase I planned
- Protein Sciences — NHP challenge initiated
- Ebola ΔVP30 H2O2 treated — University of Wisconsin — Non-human primate challenge complete

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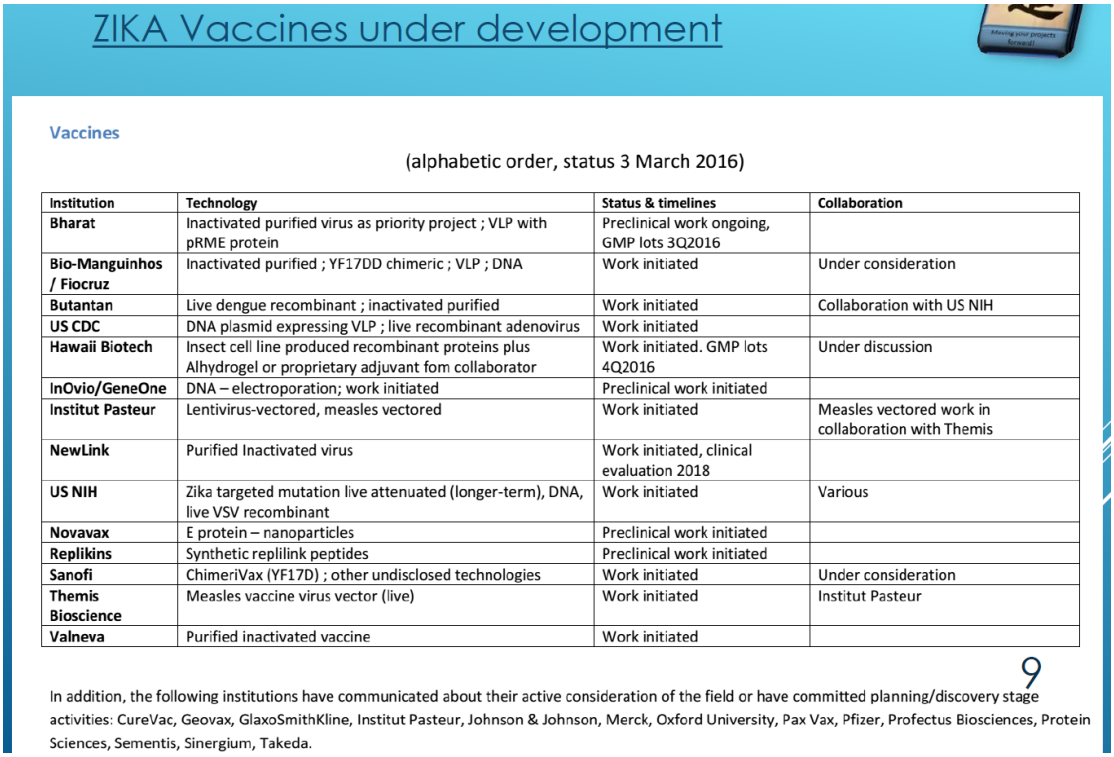

ZIKA Vaccines under development

Vaccines

(alphabetic order, status 3 March 2016)

| Institution | Technology | Status & timelines | Collaboration |
|---|---|---|---|
| **Bharat** | Inactivated purified virus as priority project ; VLP with pRME protein | Preclinical work ongoing, GMP lots 3Q2016 | |
| **Bio-Manguinhos / Fiocruz** | Inactivated purified ; YF17DD chimeric ; VLP ; DNA | Work initiated | Under consideration |
| **Butantan** | Live dengue recombinant ; inactivated purified | Work initiated | Collaboration with US NIH |
| **US CDC** | DNA plasmid expressing VLP ; live recombinant adenovirus | Work initiated | |
| **Hawaii Biotech** | Insect cell line produced recombinant proteins plus Alhydrogel or proprietary adjuvant fom collaborator | Work initiated. GMP lots 4Q2016 | Under discussion |
| **InOvio/GeneOne** | DNA – electroporation; work initiated | Preclinical work initiated | |
| **Institut Pasteur** | Lentivirus-vectored, measles vectored | Work initiated | Measles vectored work in collaboration with Themis |
| **NewLink** | Purified Inactivated virus | Work initiated, clinical evaluation 2018 | |
| **US NIH** | Zika targeted mutation live attenuated (longer-term), DNA, live VSV recombinant | Work initiated | Various |
| **Novavax** | E protein – nanoparticles | Preclinical work initiated | |
| **Replikins** | Synthetic replilink peptides | Preclinical work initiated | |
| **Sanofi** | ChimeriVax (YF17D) ; other undisclosed technologies | Work initiated | Under consideration |
| **Themis Bioscience** | Measles vaccine virus vector (live) | Work initiated | Institut Pasteur |
| **Valneva** | Purified inactivated vaccine | Work initiated | |

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In addition, the following institutions have communicated about their active consideration of the field or have committed planning/discovery stage activities: CureVac, Geovax, GlaxoSmithKline, Institut Pasteur, Johnson & Johnson, Merck, Oxford University, Pax Vax, Pfizer, Profectus Biosciences, Protein Sciences, Sementis, Sinergium, Takeda.

## 肆、心得與建議事項

非常感謝部裡與署內長官們及同仁們的支持與協助，使職有機會參加本次於韓國首爾舉辦之第五屆生物製藥全球學會韓國大會，除了學習許多產業間研發新知外，藉由休息時間與中午用餐時間與產業間交流，了解目前各國積極研發生物相似性藥品，例如韓國三星的 Enternercept 已在 2016 年 1 月取得歐盟的藥證。除了政府的支持，產業間也積極邀請國外有經驗的人到本國工作，甚至利用第三方單位舉辦研討會，邀請國際大藥廠的專家(有些是韓國人或亞洲人)演講，雖然投影片不分享，但是提供了彼此交流與解決的平台。本次研討會就是其中的交流平台之一。

會議的中間休息時間，安排了一段給予大家交流的時間，排了圓桌，桌上有些名片盒，主持人給予 5 分鐘讓大家彼此交換名片簡短介紹，之後搖聆，換桌再與不同的人交流，這種方式強迫大家彼此認識，有別之前的預備茶點和咖啡讓大家自由交流。

台灣給予的法規演講，會後的討論相當熱烈。甚至，有些代理商還主動要求能給予投影片或詢問明年度的演講是否參與，會中對於韓

國人積極的求知態度，印象深刻。

對於本署及本組建議如下:

一、 建立業界的專業名單，對於藥物審查能有臨床前有經驗的人能協助並提供專業經驗。

二、 舉辦業界相關的研討會能先調查業界的需求，與建議演講者名單，如此所提供的內容更能名符其實。

## 伍、 工作照片

| | |
|---|---|
|  | 研討會現場 |
|  | 交流桌 |
|  | Alan Liss<br>前美國 FDA 官員<br>目前 farma, LLC-Consulting<br>Principle Consultant |

| | |
|---|---|
|  | 左邊為 Steven Lee<br>目前擔任 Founder and Chief Officer, BioGENEXUS, USA<br><br>右邊為 Nick Kotlarski,<br>目前擔任 Vice President, 喜康生技,台灣 |
|  | 職演講時的照片 |