Development of a Niche-Market Product: Autologous Melanocyte for Treating Vitiligo

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Entering the cell therapy business...

* Unmet clinical need
* Disease prevalence
* Technical excellence
* Competitive treatments
* Manufacturing capability
* Distribution
* Others

Product: autologous melanocyte（自體黑色素細胞）

Targeted disease: vitiligo (白斑）

Vitiligo：irregular white patch on skin due to the loss of melanocyte

Prevalence：1～2％ population worldwide

Disease type: Focal, Segmental, General (bilateral)

Etiology---

1. Immune abnormality: genetics, immune-modulating drugs, inflammatory factors, GVHD, etc
2. Biochemical abnormalities: catecholamine, altered redox (oxidative stress), endogenous or environmental
3. Neurogenic disorder: direct or indirect killing by neurotransmitters

A skin-shallow disease causing deep trauma

J. Am. Acad. Dermatol. 2004 51 (1):57

Fighting and living with vitiligo

Michael Austin

Los Angeles, California

Vitiligo is worse than diabetes…… I'm a patient who lives with both conditions … I know at some point in the future I could die from the physical complications of type 1 diabetes. But in my experience, the deep psychological pain of vitiligo is every day a more destructive force in my life……

Treatments of vitiligo – Unmet clinical need

1. Corticosteroid or other immune-suppressants: systemic or topical application

-- first line, not effective, can cause skin atrophy and other problems

2. Phototherapy: PUVA (UVA+Psoralen), NUVB (311/312 nm)

-- Oral applied Psoralen can cause sunburn, nausea, cataract…

-- Require 100- 250 treatments (3 times/ week, 1-2 years), resulting in ~ 50% responsive rate

-- Common side effects: itching, skin atrophy, redness, ….

3. Surgical treatments:

-- Skin graft, very limited treatment area, efficacy and side effect (scarring, e.g.) depends on the skill and method

-- Tattoo

Treating vitiligo with cultured melanocytes

Examples of clinical researches

1. 1995 Olsson and Juhlin reported the study carried out in Sweden ：
   100 patients, cell isolated and cultured from 6 cm^2 skin , treated 60～500 cm^2 lesion, follow 1～2 years
2. 2002 Olsson and Juhlin reported the follow–up of 132 patients (transplantation of epidermal sheet, isolated cell, or cultured cells), followed 1~7 years
3. 2004 Chen et. al. reported the comparative study carried out in Taiwan：120 patients, followed 1~5 years

The clinical researches indicated that the melanocyte transplantation can be safe and effective

No cultured melanocyte product approved for marketing for therapy--- A great opportunity!

Developing a product based on an existing (experimental) technology

Pro

-- Quick to gain clinical trial approval

-- Some information available for clinical procedures

Con

-- IP issue (no patent infringement from our product)

< Manufacturing process development, CMC>

Tissue transportation, Cell isolation, Culture formula, Cell expansion procedure, Cell harvesting, Product formulation, Product characterization, Cell transportation/ storage (patent filed), Shelf-life study, QC technology, Animal testing for product tumorigeneicity, Animal testing for product irritation.

The product is defined by the manufacturing process…

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Treating vitiligo with autologous melanocyte transplantaiton

– Phase I/II clinical trial aimed at product marketing

Dr. J. S. Lin (林頌然醫師)

Dermatology Dept. National Taiwan Univ. Hospital

Cells manufactured by the **CMF team at ITRI**

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Subject inclusion criteria:

1. Either sex with age of 20 years old or above
2. Subject with segmental or focal vitiligo that is stable for at least 6 months and is not satisfactorily treated by previous treatment modalities. Stable vitiligo is defined as no new lesion or expansion of pre-existing lesions for at least 6 months.
3. Site of treated area should be in the range of 10 to 50 cm^2. (1 targeted site to be treated)
4. Subjects with suitable donor site considered by the investigator
5. Subject has signed the written informed consent form

Subject exclusion criteria:

1. Subject is infected by HIV
2. Subject with any immunological disorder(s)
3. Subject with malignant disease(s)
4. Patients with impaired liver function (AST, ALT＞2.5×upper limit of normal)
5. Patients with impaired kidney function (serum creatinine＞1.5 mg/dl)
6. Subject with medical history of blood coagulation disorder.
7. Subjects known to be sensitive to bovine or porcine materials
8. Subject with medical history of hypertrophic scar melanoma or other skin cancer
9. Subject received vitiligo treatment(s) within 3 months prior to the screening visit
10. Subject is pregnant or lactating
11. Subject with documented diabetic mellitus
12. Subject with child-bearing potential who will not take reliable contraceptive method(s)
13. Subject with any other serious medical condition(s) considered by the investigator not in the condition to enter the trial
14. Subject has participated other investigational product study within 2 months of entering this study

Primary end points

Adverse event:

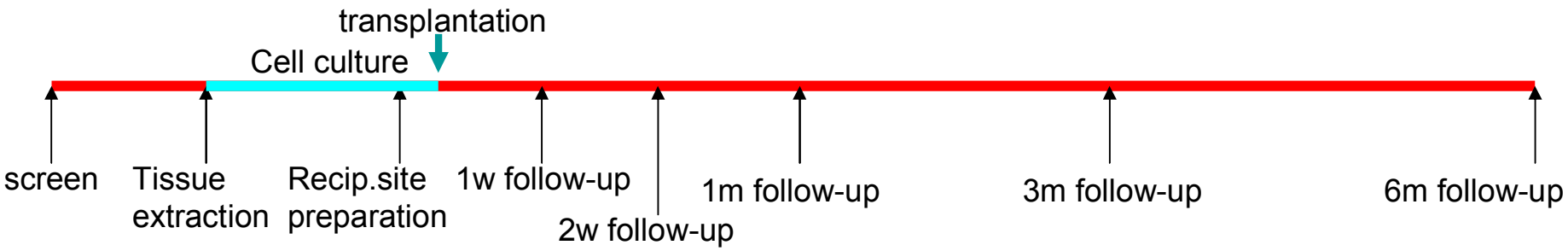
Donor site: Koebner phenomenon, hypopigmentation, hyperpigmentation, scar/keloid formation, infection, and others.

Recipient site: partial loss of grafts, cobblestone appearance, sinking pits, thin margins, milia, imperfect color matching, scar/ keloid formation, infection, and others.

Secondary end points

1. The extent of repigmentation at individual visit after autologous melanocyte transplantation evaluated by photograph
2. Quality of life at individual visit after autologous melanocyte transplantation by Dermatology Life Quality Index
3. Global assessment by the subject and investigator for the effectiveness at individual visit after autologous melanocyte transplantation (Categorized into: excellent, good, fair, and poor)

Study flow



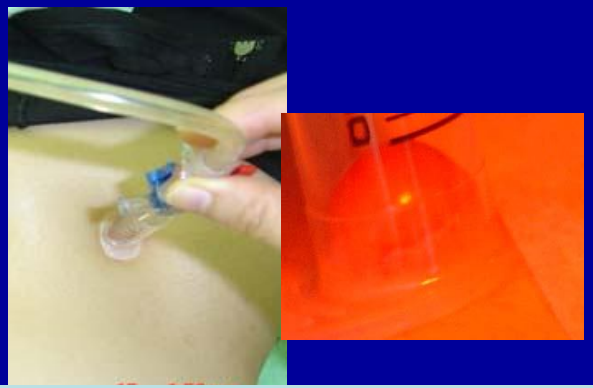
Tissue extraction: by suction blistering, without anesthesia

Recipient site preparation: PUVA, then cutting off the blister roof, without anesthesia

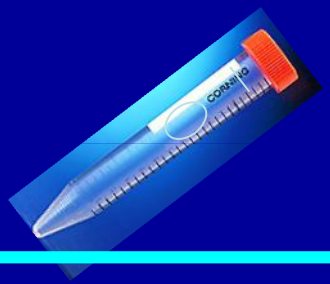
Cell application: by dripping, (5~10 X 10^4 cells / cm^2)

Recipient site cover: non-adhesive mesh, wet gauze, polyurethane memb.

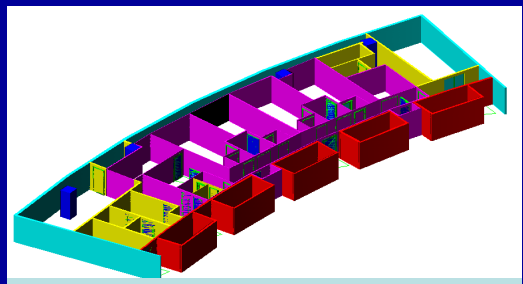
The Melanocyte Manufacturing Process



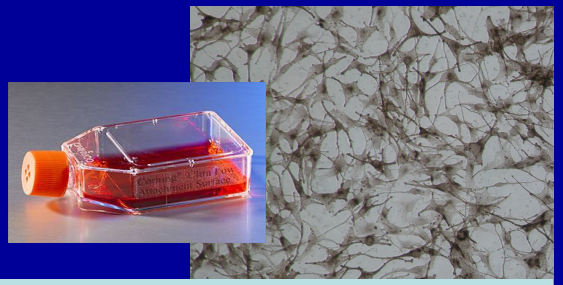
Acquisition of epidermal tissue
~ 1cm^2 in NTUH



Transporting tissue



Centralized Cell Manufacturing GMP Facility in ITRI



Cultured melanocytes reach
0.5-10 x 10^6 in 4-5 weeks

Process and
Product testing

Product released for
transporting to hospital

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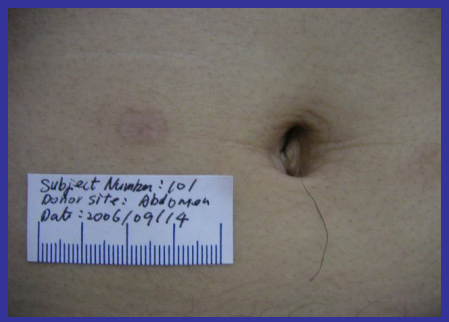
＜產品安全性評估結果＞ 自行評估，尚未經衛生署審查

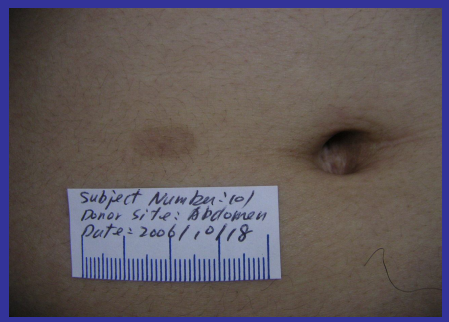
— 無局部或系統性不良反應

— 對於治療部位以UV-blistering的方式除去表皮，多數病患表示略有癢痛，但是不造成太大困擾。

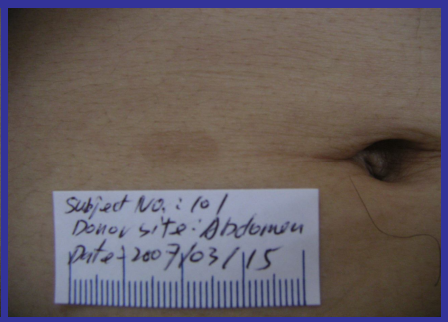
— 對於捐皮部位以suction-blistering 方式取得表皮，病患皆表示無顯著困擾。捐皮部位均在7天內癒合，有暫時性的色素沈澱現象，幾個月後均消失（圖五）



24 d after tissue extraction



2 m after tissue extraction



7 m after tissue extraction

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＜產品有效性評估結果＞自行評估，尚未經衛生署審查

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To be improved ：cell delivery method

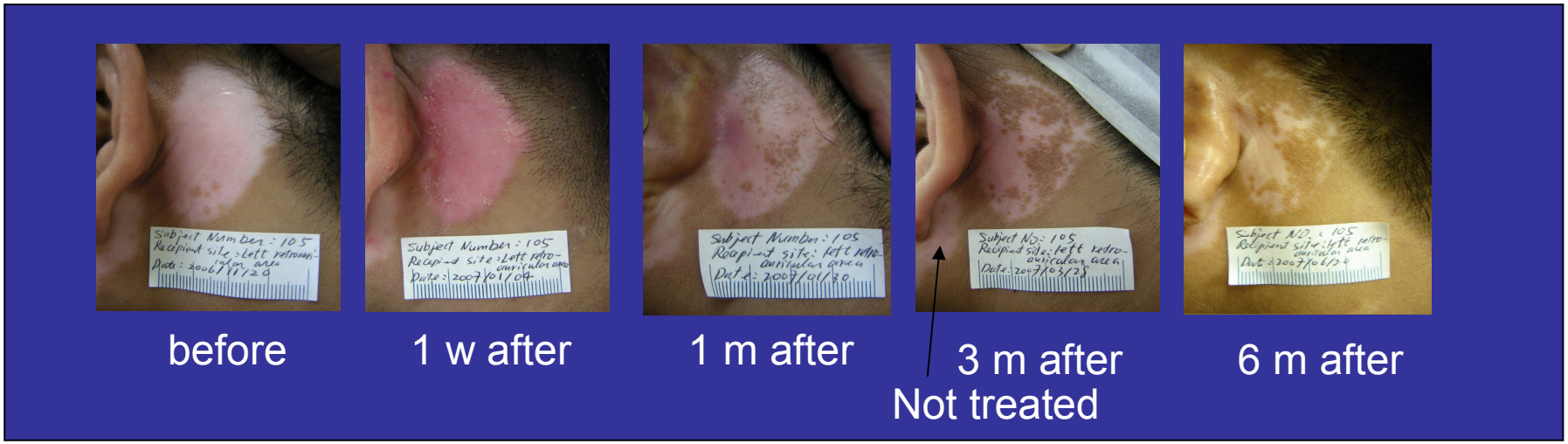
問題：

1.黑色素細胞懸浮液滴在傷口，在有曲度之治療部位，細胞液朝低處流動，造成細胞流失與分佈不均勻、導致呈色不良與呈色不均。

2.細胞移植後以紗布覆蓋治療部位，導致細胞被紗布吸附而降低細胞在病灶之附著率，必須增加移植的細胞數目。

影響：療效降低，細胞生產時間和成本增加。

Solving the problem: We have developed a new delivery method.



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Main current treatment

Competing technologies

	光照治療（例如PUVA，NUVB）	皮膚移植	不經培養的皮膚細胞移植	經過培養的黑色素細胞移植
治療次數	**150～250（每週3次，1-2年）**	1（取皮後立即移植）	1（取皮後立即移植）	2（取表皮、數週後移植）
療程（開始治療到膚色回復所需時間）	1～2年	數星期～數個月	3～6個月	3～6個月
捐皮面積：可治療面積	不需捐皮	1：1	1：4	1：數百
治療效果	～50%病人有效?	～75%?	Data insufficient	＞75% expected
可治療範圍	小面積到數百平方公分	小面積（大約1元錢幣大）	一般不敢超過數十平方公分	小面積到數百平方公分
副作用	治療部位往往紅腫癢；皮膚萎縮；如果口服Psoralen，需注意肝腎毒性，並嚴格防曬	依取皮深度而異，如果是用「punch」，一半病人產生疤痕。如果是split thickness,副作用較少	依取皮深度與面積而異。面積大的產生疤痕與蟹足腫現象機率隨之增加。	可能有暫時性色素過多現象，此現象一般自然消失

白斑照光療法之治療費用保守估計
（95 未漲價前）

		PUVA	NUVB
診療部份	門診掛號費(元)/次	100	
	門診部分負擔(元)/次	210	
	健保給付(點)/次	855	430
	就診次數(次)	200	150
	治療費用合計(元)	181,333	72,250
	病患實際支出金額(元)	10,333	7,750
病患花費時間	診療時間/次	1小時	
	交通往返/次	1小時	
	合計(小時)	400	300

備註：
1. 以醫學中心為例
2. 健保給付光化治療(PUVA)每週可申報3~4次為原則；
   光線治療(如NUVB)每週可申報6次為原則
3. 病情穩定者，同一療程以六次為原則

Conclusion: Autologus melanocyte product for treating vitiligo

* Unmet clinical need V
* Disease prevalence V
* Technical excellence expected V
* Competitive treatments expected V
* Manufacturing capability ?
* Distribution ?
* Others: As first line treatment? likely

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