

SynCoreBio

SynCore Biotechnology Co., Ltd.

杏國新藥股份有限公司

茶多酚(Polyphenol)用途及 酚瑞淨(Veregen[®])新藥研發

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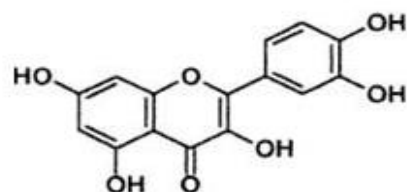
大綱

- 壹、茶多酚用途
- 貳、植物新藥-『酚瑞淨』
- 參、臨床試驗設計
- 肆、結論

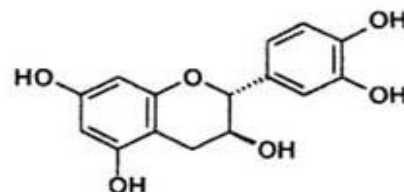
壹、茶多酚用途

- 茶葉主成分:多酚類(polyphenols)化合物、咖啡因(茶素)、脂類、碳氫化合物、維生素類、礦物質、胺基酸等。
- 來源:多酚類有很強的抗氧化作用，常見的有-兒茶素類(catechins)、異黃酮(isoflavones)、花青素(anthocyanin)、薑黃素(curcumin)、槲皮素(quercetin)、芸香苷(rutin)、白藜蘆醇(resveratrol)等。以兒茶素類化合物含量較高，約佔多酚類的70%，而茶多酚(polyphenol)，也有被稱為**多羥基苯酚(polyhydroxyphenols)**。綠茶、葡萄及深色的蔬果，大多為類黃酮(flavanoids)，為多酚類物質的來源(見圖)。
- 用途:抗腫瘤、控制慢性淋巴細胞之白血病、預防心血管疾病、保護肝臟及促進脂肪代謝、降低血糖值、減肥、預防關節炎惡化、減少體內尿酸預防痛風、抗病毒、抗過敏、皮膚美白去暗瘡、消除疲勞等。
- 舉例:茶漱口水-預防牙周病及蛀牙等

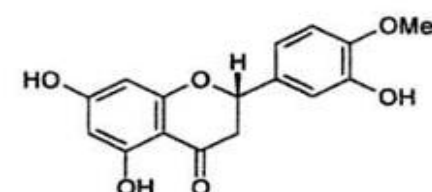
多酚類化合物結構式



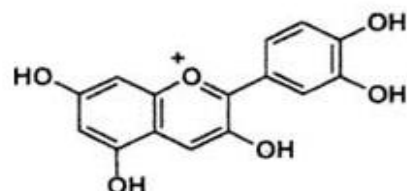
Quercetin



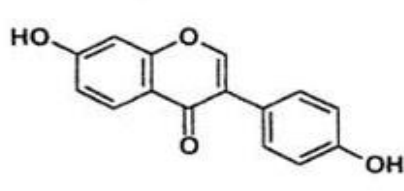
Catechin



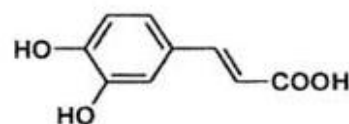
Hesperetin



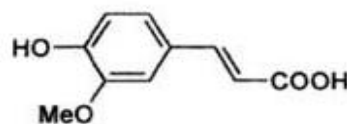
Cyanidin



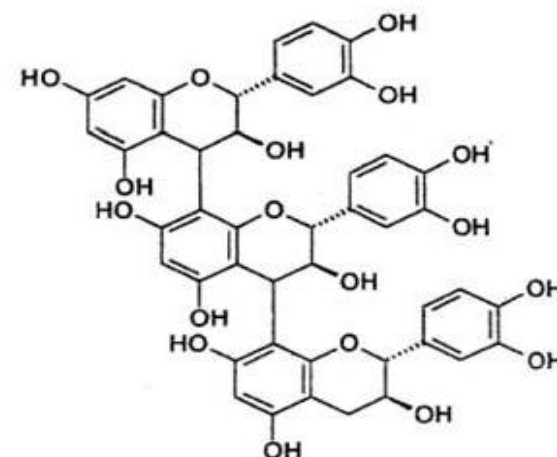
Daidzein



Caffeic acid



Ferulic acid



Procyanidin

Figure Chemical structures of some phenolic compounds commonly found in fruits and coffee.

茶多酚對疾病有益

- ①**癌症**: 茶多酚能清除有害自由基，阻斷脂質過氧化過程，提高人體內酶的活性，從而起到抗突變、抗癌症的功效。對胃癌、腸癌等多種癌症的預防和輔助治療均有益處。
- ②**高血壓**: 茶多酚具有較強的抑制轉換酶活性的作用，因而可以起到降低或保持血壓穩定的作用。
- ③**動脈硬化**: 茶多酚中的兒茶素的 ECG 和 EGC 及其氧化產物茶黃素等，有助於抑制動脈粥樣化斑塊增生，使形成血凝黏度增強的纖維蛋白原降低，凝血變清，從而降血脂、預防肝臟及冠狀動脈粥樣硬化。
- ④**高血糖**: 茶多酚對人體的糖代謝障礙具有調節作用，能降低血糖水平，從而有效的預防和治療糖尿病。
- ⑤**中風**: 茶多酚有遏制過氧化脂質產生，能消除血管痙攣，保持血管壁的彈性，增加血管的有效直徑，通過血管舒張使血壓下降，有效地防止腦中風。

茶多酚對疾病有益

⑥**血栓**:它對紅細胞變形能力具有保護和修復作用，且易與凝血酶形成複合物，阻止纖維蛋白原變成纖維蛋白。它能有效的抑制血漿及肝臟中膽固醇含量的上升，促進脂類及膽汁酸排出體外，從而有效的防止血栓的形成。

⑦**哮喘**:它能抑制活性因子如抗體、腎上腺素、酶等引起的過敏反映，對哮喘等過敏性病症有顯著療效。

⑧**便秘**:它具有刺激胃腸道反應，加速大腸蠕動以達到治療便秘的效果。故俗話說：「早茶一盅，一天威風」

⑨**腹瀉**:它通過提高人體的綜合免疫能力，抑制和殺滅引起腹瀉的各種有害病原菌，並舒緩腸胃的緊張狀態，以達到消炎止瀉的效果。

⑩**壞血症**:它能夠促進人體對維生素C的吸收，從而有效地預防和治療壞血症

原文網址：<https://kknews.cc/zh-tw/health/vl39eq.html>



漱口水比較

	茶漱口水	Propolinse 漱口水	李施德林 薄荷漱口水	德恩奈 漱口水
成分	純水、甘油、蘆薈萃取、甘草萃取、人蔘萃取、牛蒡萃取、竹多酚、靈芝萃取、木糖醇、山梨醣醇、兒茶素(茶多酚)、薄荷衍生物	水、甘油、酒精、檸檬酸、檸檬酸鈉、蘋果酸、PEG-60 氫化蓖麻油、茶葉萃取物、蜂膠萃取物、木糖醇、薄荷醇、糖精鈉、焦糖色、羥苯甲酯、香料	百里香精油、薄荷腦精油、冬青樹精油、尤加利樹精油、水、酒精、苯甲酸	克羅赫斯汀、酒精、薄荷腦
有無酒精	無	有	無	微量
味道	天然草本清香	沁涼清新	沁涼薄荷涼感	清涼薄荷
認證/專利	專利技術	無	無	無
抑菌效果	99.9%	99.9%	99.9%	無

台灣茶葉產業



1. 茶是世界三大主要飲料之一，依據統計 2009年的世界茶葉總生產量超過 **350 萬公噸**，其中紅茶約 246 萬公噸占 70%，綠茶約 83 萬公噸占 24%，其他茶類(含部分發酵茶)約 21 萬公噸占 6%。台灣是茶葉生產的國家之一，在 2014年統計，國內現有茶園有2萬多公頃，年產粗製茶 2.1 萬公噸，產值38億元，茶農戶數 2.5萬戶，就業人口數約 5萬人。
2. 2016年台灣進口量及值(2.63萬公噸, 20.13億元)大於出口量及值(5355公噸, 18.74億元)，出口年增 19.12% 及12.27% ;其中出口的紅茶 2,175公噸、部分發酵茶(如 凍頂烏龍茶, 阿里山茶 及東方美人茶等)1,845公噸、及綠茶 1,362 公噸，主要外銷市場在中國大陸(427公噸)及美國(323公噸)，其次在香港、日本、加拿大等國。綠茶在台灣內銷居多，產地在新北及花蓮。
3. 台灣茶飲業(連鎖及冷飲等)、手搖飲料及茶產業等的國內外市場，1年產值上看仟億元。

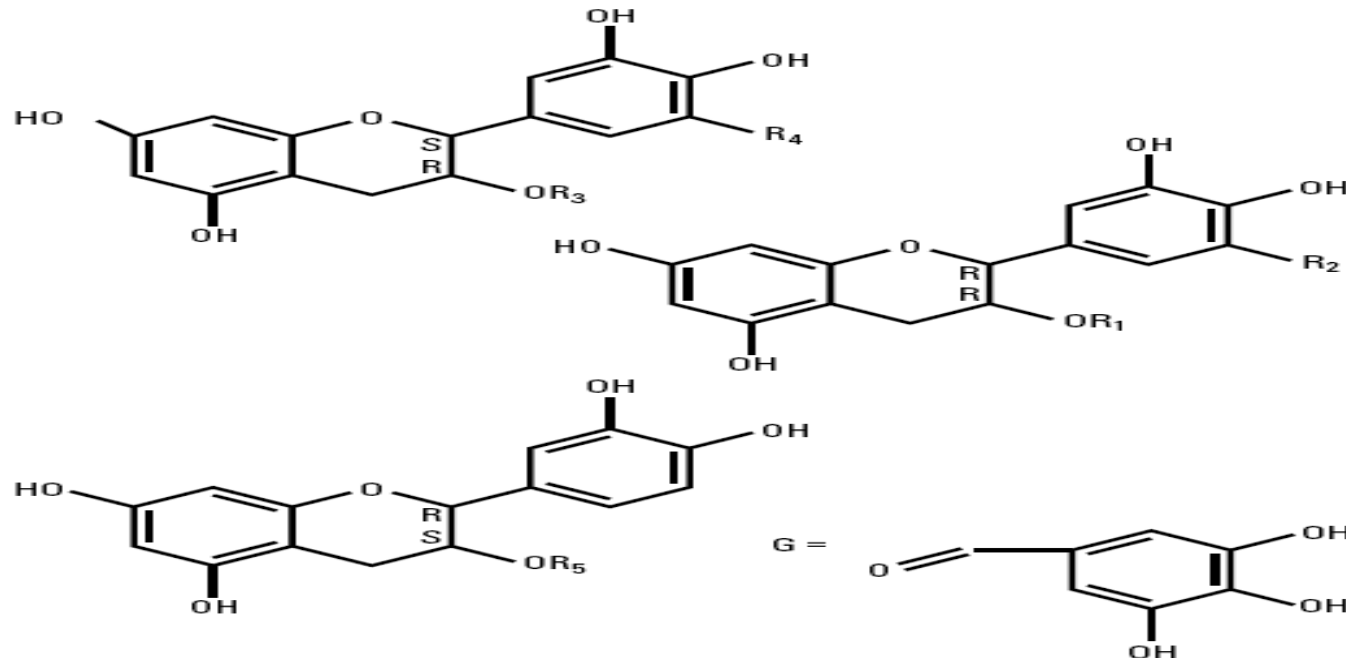
資料來源:農委會農糧署

茶葉生產概念

1. **茶葉**依採收後處理：未發酵茶(生茶)－綠茶、半發酵茶(烏龍茶、包種等)、發酵茶(熟茶)－紅茶；而發酵乃藉由茶葉中的多酚氧化酶 (polyphenol oxidase)，將茶葉中苦澀味去除，而產生茶黃質(Theaflavin) 及茶紅質(Thearubigin)，而發酵茶無抗氧化能力，但會形成多種有益菌群作用。
2. 茶葉抽取「茶多酚」的技術：(溶劑法萃取)
茶葉原料 → 沸水浸提 → 過濾 → 濾液 → 萃取 → 濃縮乾燥 tea-polyphenol，
此加熱處理是破壞茶葉中的多酚氧化酶。
3. 綠茶：茶多酚含量很高，它佔60%~80%，而抽提茶品中含 24.19% 的兒茶素(Catechin)。兒茶素功能：抗氧化、清除自由基、消炎、抗菌、抗病毒、降血糖、抑制血管增生、抗過敏、抗紫外線、防曬傷、控制油脂分泌、降血脂、除口臭、防蛀牙、減肥、防癌等。目前兒茶素已知的成分有：EGCG, ECG, EGC, EC, GCG 等(見圖)；綠茶兒茶素源自Camellia Sineusis 的樹種，抽提出萃取物(green tea extracts)，而茶樹精油(保養品)則源自澳洲茶樹 Melaleuca alternifolia 的萃取物(tea tree extract)，兩者是不同的來源。

Green tea catechins in sinecatechins

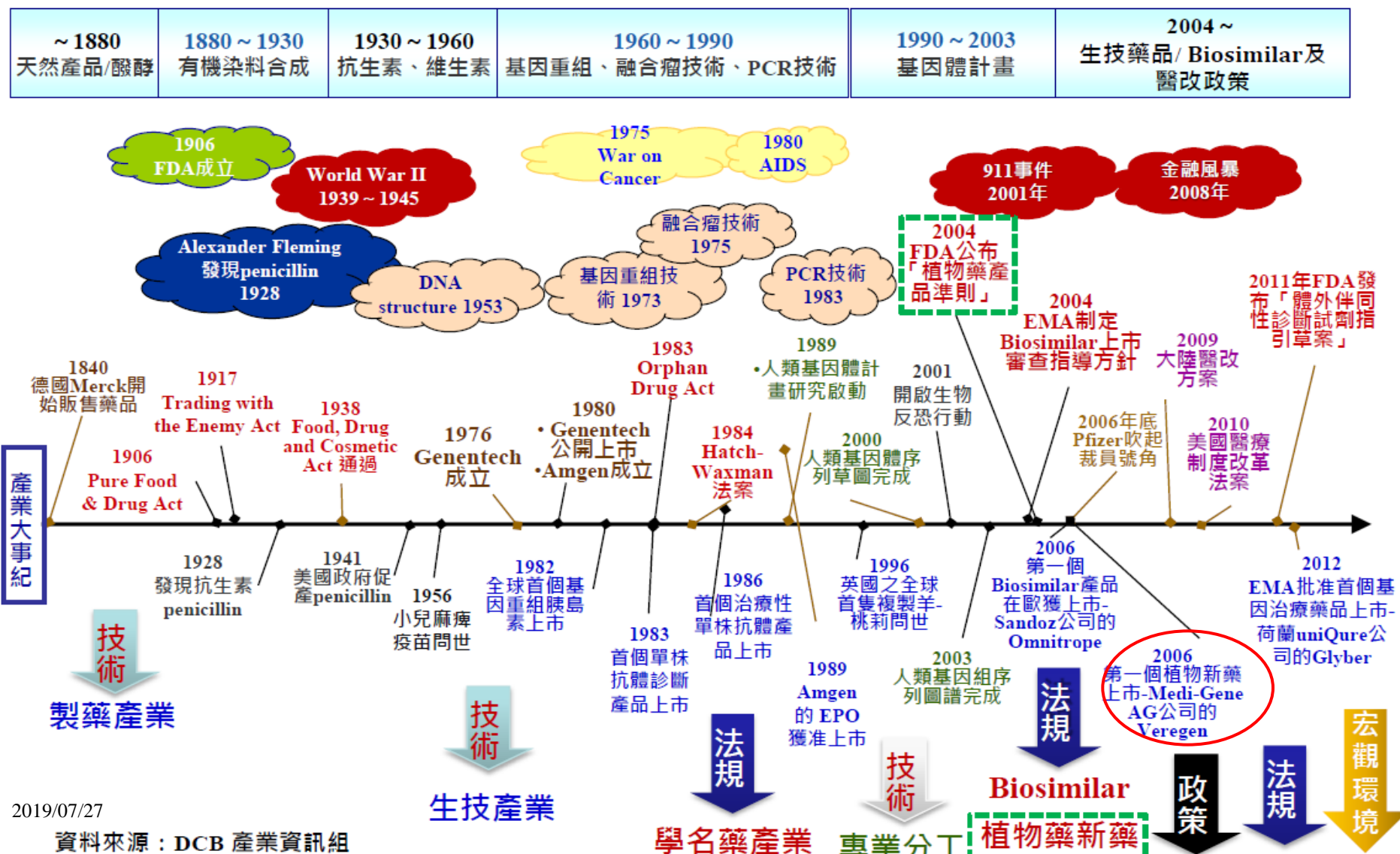
- General Structure of Catechins:**



Component	Abbrev.	R1	R2	R3	R4	R5
(-)-Epigallocatechin Gallate	(-)-EGCg	G	OH	—	—	—
(-)-Epicatechin Gallate	(-)-ECg	G	H	—	—	—
(-)-Epigallocatechin	(-)-EGC	H	OH	—	—	—
(-)-Epicatechin	(-)-EC	H	H	—	—	—
(-)-Gallocatechin Gallate	(-)-GCg	—	—	G	OH	—
(-)-Gallocatechin	(-)-GC	—	—	H	OH	—
(-)-Catechin Gallate	(-)-Cg	—	—	G	H	—
(+)-Catechin	(+)-C	—	—	—	—	H

貳、植物新藥-『酚瑞淨』

全球生物製藥產業發展里程碑



Veregen®

(Sin catechins) Ointment, 10% w/w



First botanical drug approved by EMA and US FDA, launched in US, Germany, Austria, Spain, as well as in Taiwan.

Exclusive marketing and sales right in Asia granted from Medigene AG.

Patented active ingredient Polyphenon® E (extracted from "Green Tea" *Camellia sinensis* (L.) O Kuntze.)

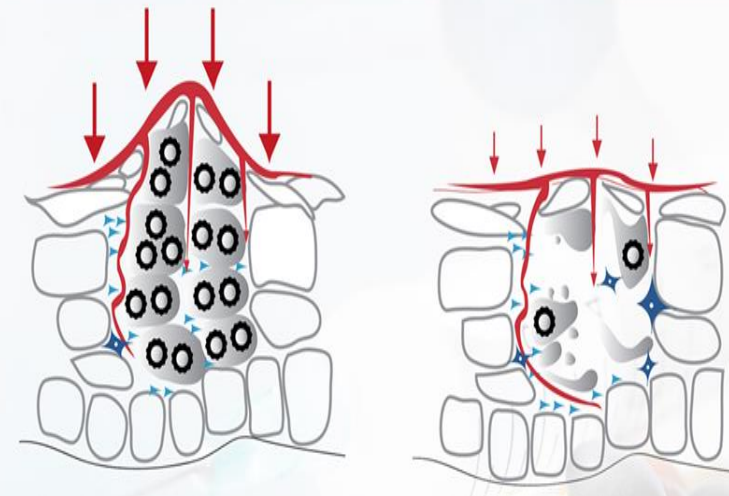
Veregen® has been listed as a standard treatment in Sexually Transmitted Diseases

Treatment Guideline (USA, CDC, 2010) and 2012 European guideline for the management of anogenital warts. (Lacey et al. J EADV, 2012)

References

Stockfleth E et al. Sin catechins (Polyphenon E) ointment for treatment of external genital warts and possible future indications. *Expert Opin. Biol. Ther.* (2014) 14(7)

MOA of VEREGEN®



Immunomodulatory effect



Inhibition of proliferation of keratinocytes.



Antiviral effect.

上市產品 Veregen®



Natural and Safe 天然且安全

萃取自天然綠茶葉，且含有多種兒茶素
具有高度安全性，臨床試驗期間無全身性副作用發生



Good 有效

臨床試驗證實對於疣體的清除具有臨床上的有效性



Low 低復發率

復發率相較於其他現行治療方法為最低

疣體完全廓清率 *Complete clearance*

<u>Veregen®</u>	<u>Placebo</u>
56.3%	44.2%

復發率 *Recurrence Rate*

<u>Veregen®</u>	<u>Imiquimod</u>	<u>Podophyllotoxin</u>	<u>Ablation</u>
6.5%	16.3%	46%	59.9%



Easy administration 使用容易

- 一天三次
- 無須停藥
- 不須洗去殘留軟膏



早上



傍晚



睡前

<http://www.veregen.com/genital-warts/treatment-goals.html>



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Genital Warts

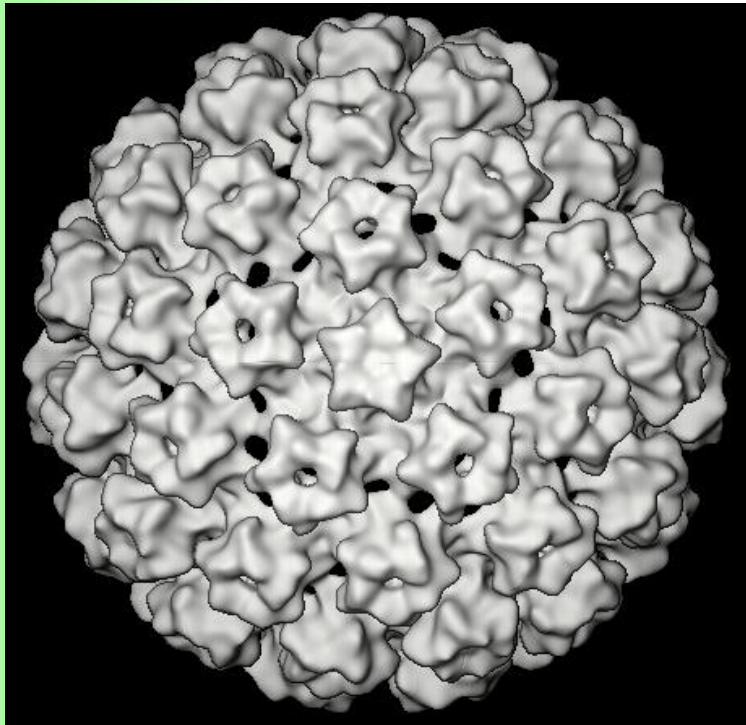
(condyloma acuminata)

Etiology-

- ✓ Human Papilloma Virus (HPV)
- ✓ It is an non-enveloped virus with double stranded circular DNA & an icosahedral nucleocapsid
- ✓ 100+ varieties
- ✓ Most are harmless
- ✓ 35 are transmitted sexually

<http://www.veregen.com/genital-warts/treatment-goals.html>

Medical Significance of Human Papillomaviruses (HPVs)



**non-enveloped,
DNA genome**

>160 named HPV types

- **Ubiquitous. Infection can be completely asymptomatic, commensal**

However

- **Some types cause benign skin warts (papillomas)**
- **Other types cause cancer of the uterine cervix or other epithelial cancers**

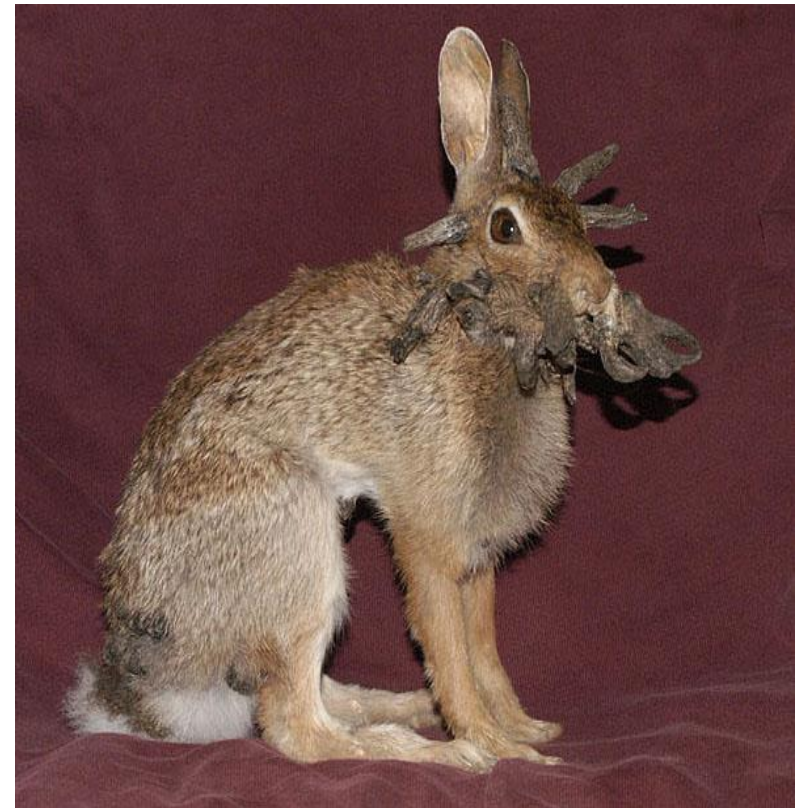
Papillomaviruses - Historical Overview

- 1894-1924: Ciufu, Variot and others show that genital and skin warts can be transmitted between individuals by a filterable infectious agent

- 1933 (Shope) rabbit papillomas have viral etiology

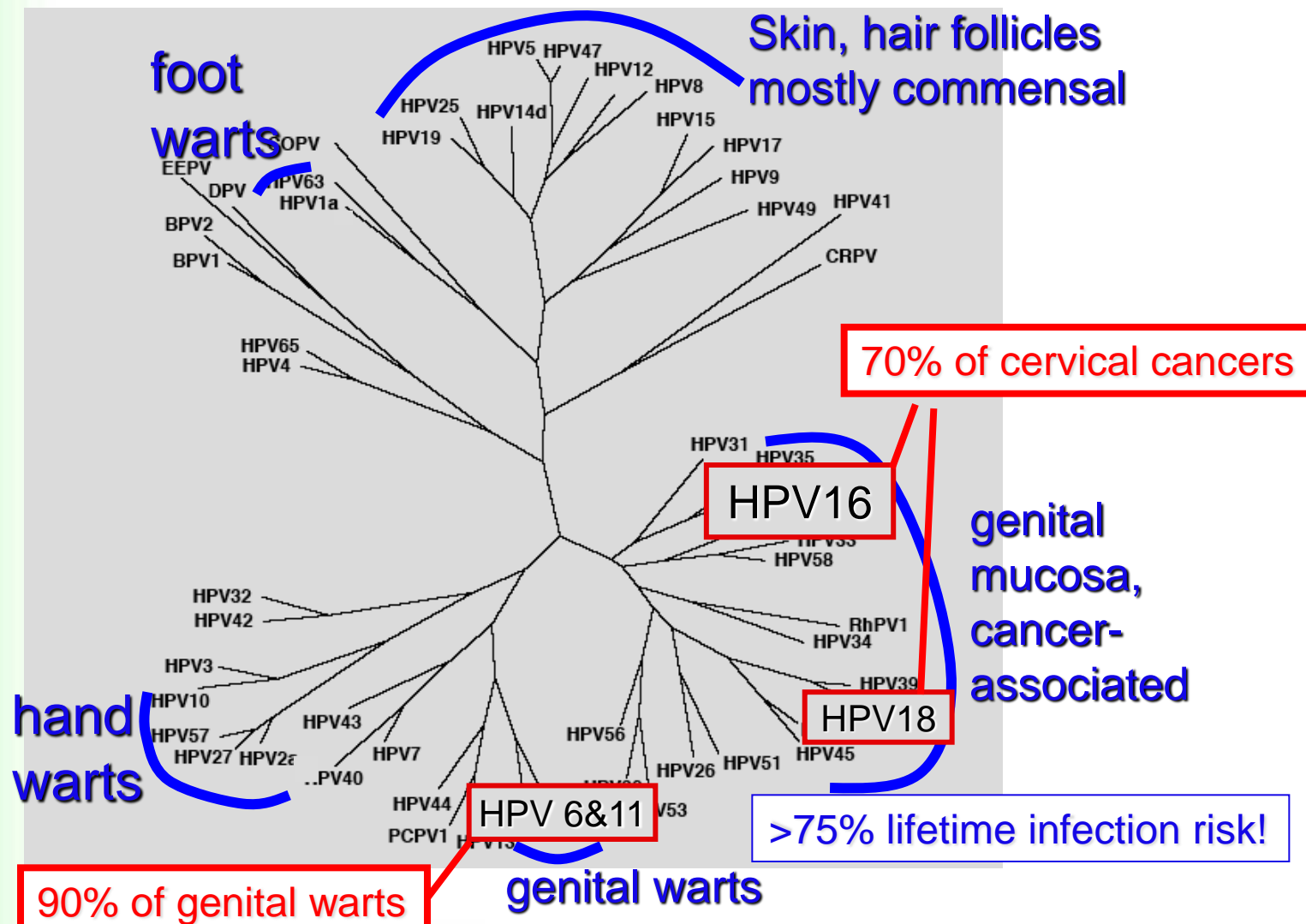
- 1935 (Rous) papillomas can progress to carcinoma

- Papillomaviruses found to cause skin warts and other tumors in vertebrates ranging from birds to people



Infection with Shope cottontail rabbit papillomavirus

HPVs Are a Diverse Family



What are genital warts?

- Genital warts are unsightly cauliflower-like growths.
- In women, genital warts can appear on the vulva, urethra, cervix, vagina, anus or thighs.
- In men, warts can appear on the penis, scrotum, anus or thighs.
- Genital and anal warts are very contagious and are spread during oral, vaginal or anal sex with an infected partner.

<http://www.veregen.com/genital-warts/treatment-goals.html>



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Common Symptoms of Genital Warts in Males & Females

- The symptoms may include single or multiple fleshy growths around the penis, scrotum, groin, vulva, vagina, anus, and/or urethra
- They may also include: itching, bleeding, or burning, and pain
- The symptoms may recur from time to time

<http://www.veregen.com/genital-warts/treatment-goals.html>



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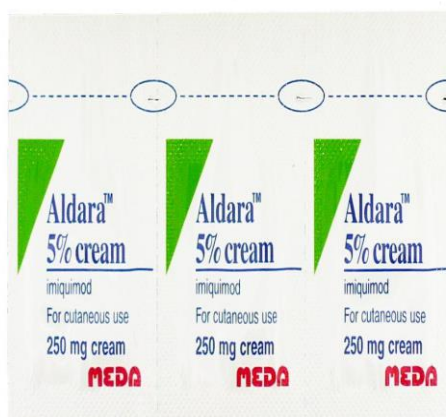
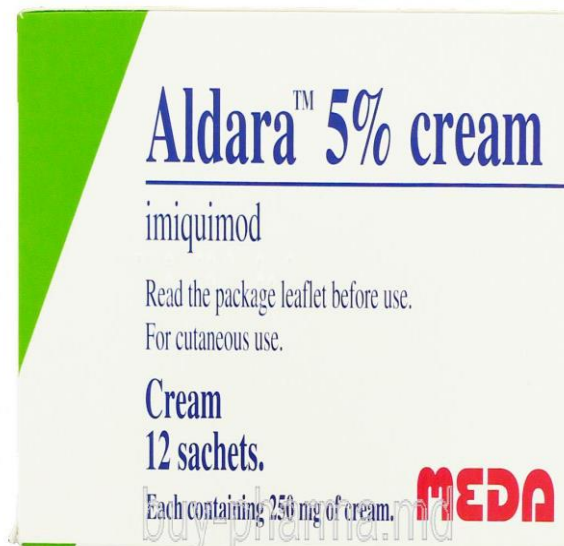
Warts medications

- **Imiquimod (Aldara, Zyclara)**- The first line drug in USA, this cream appears to boost your immune system's ability to fight genital warts (MOA: immune response modifier, IRM) in at 16~32 weeks (cure rate 60%) by *Aus.* paper.
- **Podophyllin and podofilox (Condylox, Wartec)**- Podophyllin (podophyllotoxin, PPT) is a plant-based resin that destroys genital wart tissue to inhibit mitotic division, but has greater side effects. The product is podophyllotoxin 0.05% solution or gel and 0.15% cream.
- **Sinecatechins (Veregen)**- This ointment involved in the clearance of genital and perianal warts is unknown (IRM). In vitro, sinecatechins had anti-oxidative activity, at 12~16 weeks (cure rate 60%).
- **Salicylic acid (high conc.); Trichloroacetic acid (TCA) 80%**- This chemical treatment burns off genital warts.
- **Others**- Interferon, bleomycin, 5-fluorouracil(5-FU), HPV vaccine (Gardasil, Cervarix) inj.

Comparisons

Items	Imiquimod* (Aldara™, Zyclara®) 樂得美乳膏 (3M)	Podophyllin (Condylox®) 鬼白毒 素普達飛洛外用液	Podofilox (Wartec®) 化疣敵乳膏 (STIEFEL)	Sinecatechins (Veregen®) 酚瑞淨軟膏 (SynCore)
Dosage form	5% w/w cream x 12 sachets (0.25gm)	10~20% susp/ 0.5 gel or sol'n	0.15% w/w 5gm	10% ointment 10gm
Launch time	1997	1991	1991	2006
Administration	QN x 3d / week 16 weeks	BID x 3d/week 4 weeks	BID x 3d /week 4 weeks	TID 16 weeks
Indications	GW, AK, Cutaneous warts	GW	GW	GW, HSV, AK Cutaneous warts
Cost (NT\$)/ month	4200?	??	2500~3000	3000

Others: 治疣液(Duofilm) 16.7% salicylic acid + 16.7% lactic acid 15ml/bt (GSK)



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Cryotherapy 健保給付

● 冷凍治療：

(1)液態氮冷凍治療(51017C)：病灶數量需3個(含)以上或總面積大於2平方公分($>2\text{cm}^2$)，或必須先做削皮(shaving)處置者。

(2)冷凍治療－單純(51021C)：病灶數量單一或總面積1平方公分以內($\leq 1\text{cm}^2$)之單純冷凍療法。

(3)冷凍治療－複雜(51022C)：病灶數量需2個或總面積大於1平方公分至2平方公分以內($>1\text{cm}^2$ 且 $\leq 2\text{cm}^2$)之複雜冷凍療法。

(4)位於所有人臉部或六歲以下孩童，得以診療項目代碼51017C申報醫療費用。

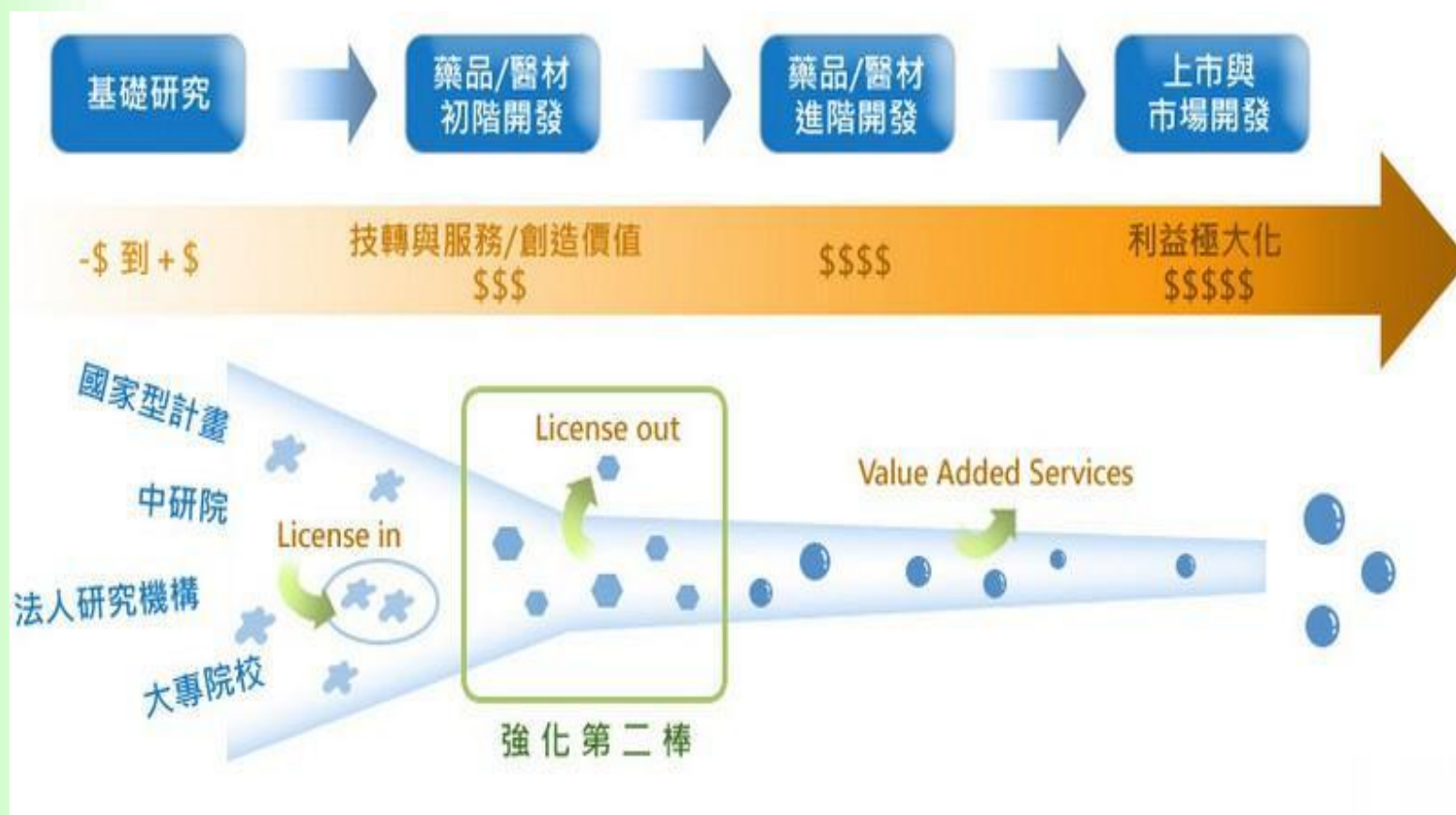
項目代碼	診療項目	支付點數	參考起迄日
51017C	液態氮冷凍治療	600	95.07.01 ~ 迄今
51021C	冷凍治療－單純	125	95.07.01 ~ 迄今
51022C	冷凍治療－複雜	250	95.07.01 ~ 迄今

● 治疣液(水楊酸)：

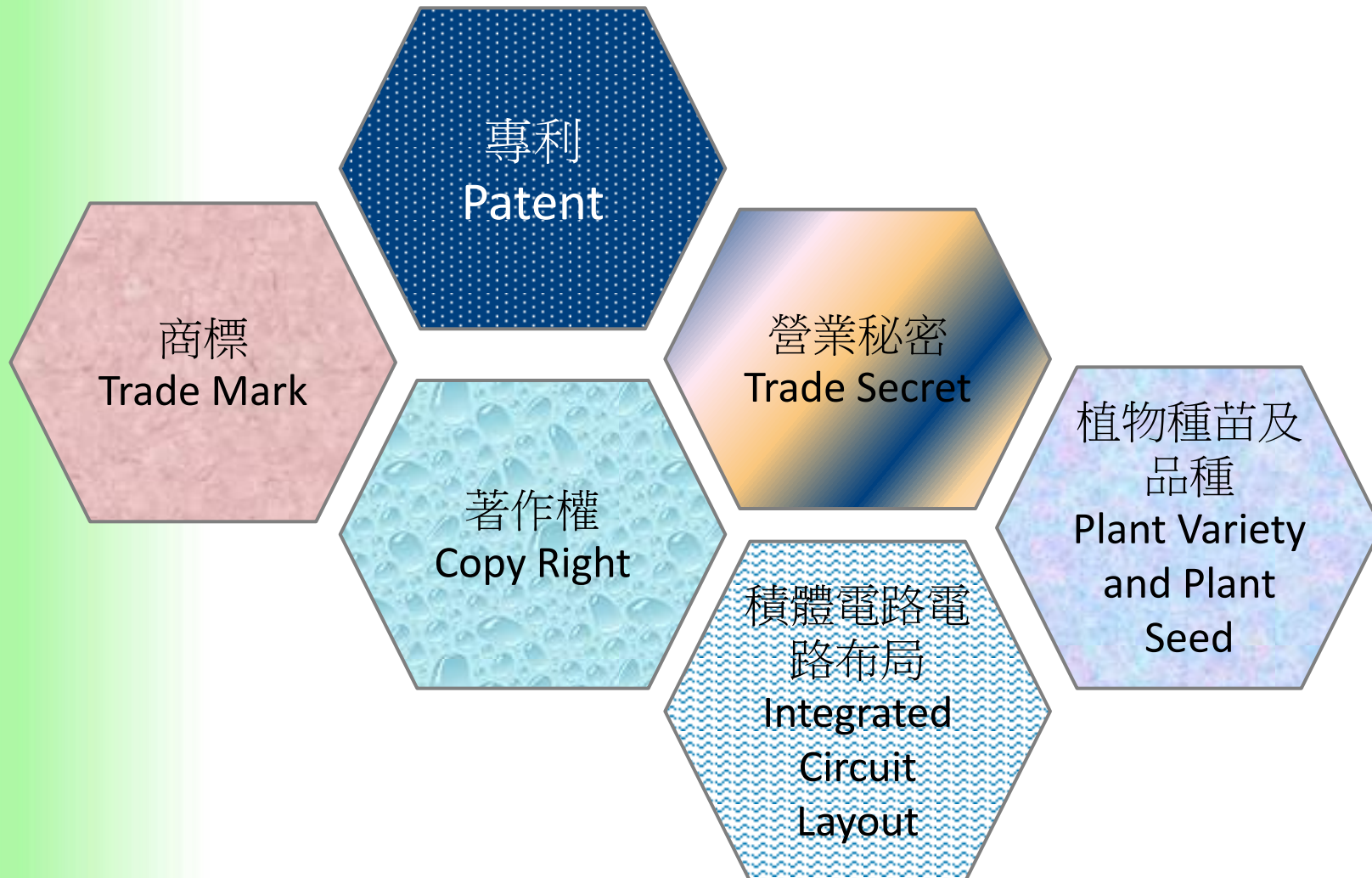
藥品代碼	藥品名稱(英文)	藥品名稱(中文)	支付點數	參考起迄日
51017C	DUOFILM	治疣液	176	107.05.01~迄今

叁、臨床試驗設計

新藥研發加值及管理平台



Intellectual Property Rights



Remarks

- Patent (108157) were composition for treating **condyloma acuminata** and the trademarks (01501799) call Veregen.

15. The use of a pharmaceutical according to any of claims 1-14, characterized in that the viral skin diseases and/or tumor diseases are caused by human papilloma viruses, such as HPV 1, 2, 3, 4, 5, 6, 8, 9, 11, 12, 13, 14, 15, 16, 17, 18, 19-29, 31, 32, 34, 36-38, 46-50, 56, 58.

16. The use of a pharmaceutical according to claim 15, characterized in that the skin diseases are warts, genital warts, benign tumors of the skin and/or mucosa caused by papilloma viruses, for example verrucae plantares, verrucae vulgares, verrucae planae juveniles, epidermodysplasia verruciformis, Condylomata acuminata, Condylomata plana, bowenoid papulosis, papillomas on the larynx and oral mucosa or focal epithelial hyperplasia.

- MDG 之 VM 法定適應症，無 common warts/ flat warts 等專利。但 Formula EP1448186 中的 claim 16 發現其專利範圍涵蓋病毒性疣：**CW、PW、FW & MC 等皮膚疾病。**

HPV-related warts

病灶症狀位置與種類	HPV 型別
皮膚 (skin)	
腳底疣 (deep plantar wart)	1.
一般疣 (common wart)	2.4
扁平疣 (flat wart)	3.10
皮膚疣狀表皮發育不全 (epidermodysplasia verruciformis, EV)	5.8.13
黏膜 (mucosa)	
陰門癌 (vulvar cancer)	16
陰莖癌 (penile cancer)	16
呼吸道乳突瘤 (respiratory papillomas)	6.11
口咽癌 (oropharyngeal cancer)	16
口腔結膜癌	13.32.
生殖器疣 (genital warts)	6.11
子宮頸癌 (cervical cancer)	
高危險性	16.18.31.45.33.35.39.51.52.56.58.59.68
低危險性	6.11.42.43.44

常見皮膚疣 Cutaneous Warts

- ① 尋常疣(common warts, CW)：是常生長在手指和指甲附近的一種病毒疣。特色是外觀上有明顯突起，伴隨著高度角質化、摸起來偏硬的結節。顏色通常是偏向棕色。尋常疣除了外觀以外，通常是在影響手部動作(例如：寫字)的時候會特別被注意到。



常見皮膚疣 Cutaneous Warts

- ② 扁平疣 (flat warts, FW)：突起面呈現平滑、扁平、呈膚色、粉紅色、紅色或棕色，大小約為1~5mm。會出現在前額、手背及剃毛的部位(例如：男性鬍鬚生長的部位及女性的小腿)。扁平疣是一種比較頑固難根治的皮膚病，冷凍治療破壞性強，但臉上容易留下色素沉澱。而汽化型的雷射，常常無法消滅肉眼還看不到的潛伏病灶，所以復發率較高，且因雷射後有傷口，有時反而造成擴散。



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常見皮膚疣 Cutaneous Warts

③ 足部疣 (plantar warts, PW)：通常是長在腳底的一種病毒疣。

這種疣的特色是長得特別深、也特別厚，雖然在皮膚表面看起來只有一些凸起，但其實在底下長得已經不淺了。有時跟雞眼(corns)長得很像，但削除疣的表面之後會出現針狀血點，藉此特徵能與雞眼和厚繭(calluses)有所區分。



Figure 3. Verruca plantaris (plantar warts) on the sole of the foot.

傳染性軟疣 (molluscum contagiosum virus)

- 傳染性軟疣是由傳染性軟疣病毒引起之感染，屬於痘病毒（Poxvirus）的一類。
- 傳染性軟疣是種小朋友常見的病毒性皮膚病，它的特徵大小不一（1~8mm）、圓形、有點硬、不痛的皮膚隆起。仔細看傳染性軟疣通常是膚色，偶而會發炎而變紅。傳染性軟疣很圓，中央常常微微凹陷，是診斷上重要的特徵。皮膚隆起通常不會大，多數小於 6mm。常出現的位置是小朋友的臉、脖子、腋下、手臂&手背。
- 當孩子得到這種病時，勤洗手，少搔抓，是面對兒童傳染性軟疣最好的招數。



Current Published Case Report



FIG. 1. Multiple MC lesions on her back, some of them with inflammatory signs.



FIG. 2. Complete response after twice daily Sinecatechins 10% ointment for 4 weeks.

Current Published Case Report



*recalcitrant facial verrucae vulgares



*Patient after 20 days of topical treatment with sinecatechins 10% ointment 3x/day: Complete remission.

Current Published Case Report

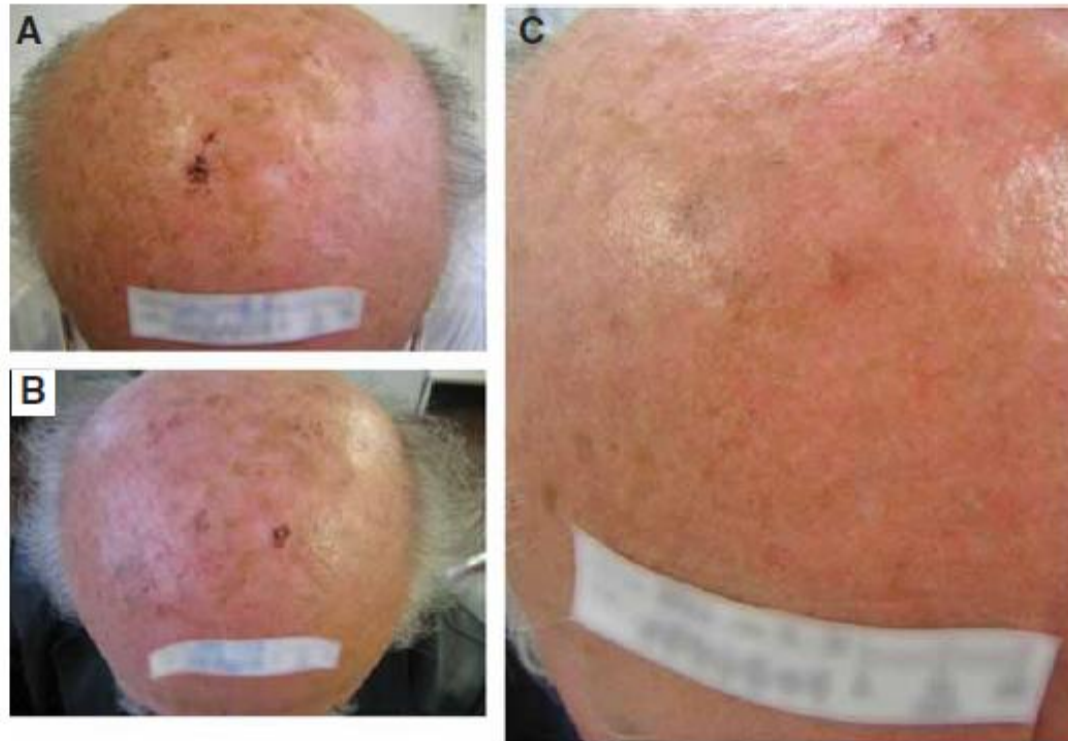


Figure 1. Treatment of multiple AK lesions with sinecatechins 10% ointment. A) before treatment, B) after 2 weeks of treatment, C) after 12 weeks of treatment.

Case report : Veregen 10% TID in FW

Baseline



Week 5



Case report (WFW2)

- ✓ Age: 32-year-old
- ✓ Gender: female
- ✓ Usage: TID
- ✓ Side-effects: None
- ✓ Description: The warts were flattened after few weeks (5 weeks)

Case report: Veregen 10% BID in MC

The safety and effectiveness of VEREGEN ointment 10% were evaluated in the treatment of molluscum contagiosum (MC) in children



Case report (WMC2)

- ✓ Age: 12-year-old
- ✓ Gender: Male
- ✓ Usage: TID → BID
- ✓ Complete clearance: Week 4
- ✓ Side-effects: erythema and slight itching only during the application

Case report: Veregen 10% BID in MC

The safety and effectiveness of VEREGEN ointment 10% were evaluated in the treatment of molluscum contagiosum (MC) in children



Case report (WMC3)

- ✓ Age: 9-year-old
- ✓ Gender: Female
- ✓ Usage: BID
- ✓ Side-effects: Itching
- ✓ Description: The improvement started at week 2. The patient switched to cryotherapy after week 6

Veregen®

流行病學/市場分析

- 不同性別之首次診斷年齡有顯著差異
 - 男：39.6歲 vs. 女：36.3歲。
- 首次就醫人數隨年代增加: 174人(2004年)/531人(2011年)
- 首次就醫年齡逐年下降(男: 37~44歲; 女: 33~40歲)
- 就醫習慣差異:
 - 男性通常往區域醫院(綜合醫院)就醫: 63.3%
 - 女性則在基層診所(綜合醫院44.9%與專科診所33.9%)
- 首次就醫人數在新北市(34%)與台中市(9%)最多。一般就醫以新北市(37%)與新竹縣(8%)較多，竹北市某區域綜合醫院(東元)有異常高門診量(佔全新竹縣95%)。

Market Surveillance in Clinics

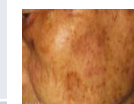
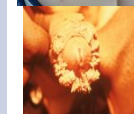
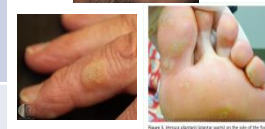
- 市調家數: 89家
- 市調客戶尋常疣每月約有50~100位患者 (各家及區域明顯差距)
- 治療方式:
 - a:均以冷凍為主 + 抗生素Bleomycin (或A酸藥膏及治疣液)
 - b:每月1~2次冷凍，大約3次即會剝落
 - c:健保給附一顆125點，二顆250點，超出3顆以上給付600點

Market Surveillance in Clinics

- 自費: 客戶告知「尋常疣」一般於手指部位，多數不影響生活作息，且冷凍治療容易，有健保給付，不同於「菜花」因患者部份有礙於隱私及特殊工作者不能有傷口或是無法忍受冷凍治療者會選擇自費。
- 綜結: 皮膚科醫師認為「尋常疣」不同於「菜花」的治療，健保冷凍治療數周可完全處理，患者無其他影響生活作息或隱私方面考量，因此醫師不會主動推單價一支3000元軟膏自費；另外，自費藥膏如效果不如預期恐引起患者訴願，故多數醫師不考慮自費。
- 市調: 有醫師提到如是孩童長於臉部及怕痛者病人，患部在20平方公分內，經冷凍輕微處理，再用樂得美(400元/0.25 gm/包)，因小包裝單價低，易被消費者接受。

常見皮膚疾病就醫人次比較

疾病	就醫人次
Cutaneous warts (CW, FW, PW)	867,652
Molluscum contagiosum (MC)	11,983
Condyloma acuminatum (GW)	33,465
Actinic keratosis (AK)*	19,458
Melanoma (M)	232,000** (2012年)
Alopecia areata (AA)	> 700萬 (0.1%~2% population)



*2012年上市品項 *Picato* 0.015%(Leo Pharm); **2015年國健署罹患皮膚癌3,799人(M 佔台灣皮膚癌的7%)



SINPHAR GROUP

By 2015 BNHI, & 2017 Aug. Nat Rev Dis Primers data

Common Warts in USA

- Common warts affect more than 22 million Americans.
- More than two million patients seek treatment for common warts from healthcare professionals each year.



- ① In USA, patient pool: 2,000,000 patients
- ② Selling price: NTD \$ 1500元 / 5gm/ tubes
 - 2,000,000patients , 1~ 2 tubes/ patient
 - Potential market size : NTD \$ 30E~ 60E
(USD \$1 E~ 2E)

Cutaneous Warts: An Evidence-Based Approach to Therapy

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SANDRA MARCHESE JOHNSON, M.D., *University of Arkansas for Medical Sciences, Little Rock, Arkansas*

Cutaneous warts are a common presenting complaint in children and adolescents. Common, plantar, or flat warts are cutaneous manifestations of the human papillomavirus. The treatment of warts poses a therapeutic challenge for physicians. No single therapy has been proven effective at achieving complete remission in every patient. As a result, many different approaches to wart therapy exist. These approaches are discussed to demonstrate the evidence supporting common therapies and provide a guideline for physicians. Evidence supports the at-home use of topical salicylic acid and physician-administered cryotherapy. Intralesional immunotherapy for nongenital cutaneous warts may be an option for large or recalcitrant warts. (*Am Fam Physician* 2005;72:647-52. Copyright© 2005 American Academy of Family Physicians.)

Warts are the cutaneous manifestations of human papillomavirus (HPV). Warts may exist in different forms given the epithelial surface and HPV type responsible for the infection. Common warts

A study² examining the natural progression of warts indicated that warts will spontaneously clear after two years without treatment in 40 percent of children. Warts typically continue to increase in size and distribution and may become more resistant to treatment.

TABLE 1
Treatment of Cutaneous Warts

<i>Treatment</i>	<i>Advantages</i>	<i>Disadvantages</i>	<i>Administration</i>	<i>Cost*</i>
<u>Salicylic acid</u>	Available over the counter, inexpensive	Requires time to achieve response	Daily application of a 15 to 20 percent salicylic acid preparation	<u>\$5 to \$7</u>
Cryotherapy	Easy	Scarring, painful	Average of three or four treatments in the office	Approximate cost for initial visit plus cryotherapy to one wart is \$250; three follow-up visits for cryotherapy to one wart are \$360; total is \$610
Pulsed dye laser therapy	Fewer treatments	Scarring, painful	Average of one to three treatments in the office	Approximate cost for initial visit with laser treatment plus two follow-up treatments is \$360
<u>Imiquimod (Aldara)</u>	At-home use; pregnancy category B	Erythema, pruritus, erosions, bacterial infections	Three times a week at home for nongenital warts	<u>\$177 for 12-packet box of 5 percent imiquimod</u>
Bleomycin (Blenoxane)	Typically only one treatment needed	Pain during and after treatment, pigment changes, Raynaud's phenomenon, expected necrotic eschar, scarring, nail damage, pregnancy category D	Intralesional injection of 0.3 mL (0.15 units) every three to four weeks in the office†	Approximate cost for initial visit plus injection and possible follow-up injection is \$495 15-unit vial is \$304 (brand) or \$192 to \$309 (generic)
Retinoids	At-home use	Local irritation, pregnancy category C, systemic side effects	0.05 percent tretinoin cream (Retin-A), three months oral at home	\$48 to \$54 for 45-g tube of topical tretinoin \$447 for 30-day supply of acitretin (Soriatane) 25-mg tablets
Intralesional immunotherapy	Only need to treat one wart	Rare influenza-like symptoms	Inject every three to four weeks for an average of three treatments in the office	Approximately \$190 for initial visit with injection of Candida and two follow-up injections

Common Warts in Taiwan

- Common warts(CW) appear 2 times as frequently in Whites as in Blacks or Asians.
- Affect more than 840,000 Taiwanese?
- More than 84,000 patients seek treatment for common warts from healthcare professionals each year.

➡ **① In Taiwan, patient pool: 84,000 patients**

② Selling price: NTD \$ 1500 /5gm/tubes

→ 6720patients (8% patient pool), 1~2 tubes/ patient

→ Potential market size : NTD \$ 0.1E~0.2E

→ Net profit : NTD \$3.36~6.72million

日光性角化症 (actinic keratosis, AK)

- 日光性角化又稱光化性角化症 (solar keratosis)，為最常見的一種皮膚癌症前期病灶。在年齡超過八十歲以上的老人幾乎都可以在身上找到日光性角化症的病灶。
- 日光性角化症主因是長期日曬後，紫外線對皮膚細胞所累積的傷害所引起。因此，長期在戶外工作的人，尤其是農夫、漁夫、戶外工人等年紀較長者，特別容易得到。
- 它通常沒有症狀。表面會粗粗的（即所謂的「角化」），有些脫皮。呈紅色、棕色或膚色。多分佈在臉上，數量可能僅少數幾個，也可能長得很多。看起來有點像濕疹，但不會像濕疹有癢感。它的週邊，常可看到其他同樣因日曬所引起的曬斑或老人斑。
- 少部分日光性角化症的病灶可能會轉變為鱗狀上皮細胞癌。因其有惡性化的可能，建議應積極治療。（p.s.台灣地區最常見的皮膚癌是基底細胞癌，約佔45~50%；第二常見的是鱗狀細胞癌，約佔台灣皮膚癌27%；第三常見的是黑色素瘤，雖然只佔台灣皮膚癌7%左右，但是因為極易轉移，惡性度高，而且對化學治療及放射治療的反應都有限，因此造成的死亡率很高，是所有皮膚癌中最受重視的。）



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Table 2 Picato Gel and Other FDA-Approved Topical Therapies for Actinic Keratoses (AKs)

Active Ingredient	Brand Name	Indications	Directions	Cost per Treatment
Imiquimod cream	Aldara 5% cream	AKs of face and scalp	Apply two times per week for 16 weeks on face or scalp	\$1,023.18
Diclofenac sodium gel	Solaraze 3% gel	AKs	Apply to lesions twice daily for 60 to 90 days	\$1,863.84–\$2,795.76
5-Fluorouracil	Efudex 5% cream	Multiple AKs	Apply twice daily for 2 to 4 weeks	\$287.50
	Fluoroplex 1% cream and solution	Multiple AKs	Apply daily for 2 to 6 weeks	Cream: \$462.00 Solution: \$75.61
	Carac 0.5% cream	Multiple AKs of face and anterior scalp	Apply daily for 4 weeks	\$466.66
Aminolevulinic acid	Levulan Kerastick 20% solution	AKs of face and scalp	Apply on lesions 14 to 18 hours before blue light exposure	\$1,285.46
Ingenol mebutate	Picato 0.015% and 0.05% gel	0.015% gel: AKs of face and scalp 0.05% gel: AKs of trunk and extremities	Apply daily to lesions for 3 days Apply daily to lesions for 2 days	\$765.76 \$765.76

 Cost data from *Red Book Online*.¹⁵

黑色素皮膚癌 (Melanoma)

- **黑色素皮膚瘤** 歐盟發生率每年十萬人有9人，手術治療是處於 0-3 階段腫瘤的主要治療手段，黑色素瘤晚期的治療方法包括放射、免疫治療、靶向治療或化療。2011 年 FDA 批准了七個新的黑色素瘤治療產品，其中包括四個用於晚期及轉移的黑色素瘤治療的新型免疫治療藥物(見下表)。
- **2012 年** 全球有 232,000 人罹患黑色素瘤，並造成 55,000 人死亡。♂ > ♀
- **Aldara** 用於 0 階段的腫瘤，可誘發黑色素細胞附近皮膚表面的免疫反應。該藥膏通常用於手術去除黑色素瘤後可能造成疤痕的敏感區域。



Immune therapy	Approval	Uses
干擾素 α-2b (Intron A)	1996	Metastasis of melanoma after surgery by inj.
白介素-2 (Proleukin)	1998	Metastasis of melanoma after surgery by inj.
聚乙二醇干擾素 α-2b (SYLATRON)	2011	Metastasis of melanoma after surgery by inj.
抗 CTLA-4 抗體 ipilimumab (Yervoy)	2011	Late melanoma, and its metastasis 1st line inj.
抗 PD-1 抗體 pembrolizumab (Keytruda)	2014	Metastasis 2nd line inj.
抗 PD-1 抗體 nivolumab (Opdivo)	2014	Metastasis 2nd line inj.
Others- 卡介苗 (BCG) 疫苗和咪喹莫特 (Aldara, Zyclara) 局部藥膏	??	Increase immunity of tumor (o phase)

Treatment of Nongenital Cutaneous Warts

- Ideally, treatment should be simple and inexpensive with low risk of adverse effects.
- Salicylic acid has the best evidence to support its effectiveness, but it is slow to work and requires frequent application **for up to 12 weeks**.
- Cryotherapy with liquid nitrogen is a favorable option for many patients, **with cure rates of 50 to 70 percent after three or four treatments**.
- For recalcitrant warts, Candida or mumps skin antigen can be injected into the wart every three to four weeks for up to three treatments. More expensive treatments for recalcitrant warts are offered in many dermatology offices.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
Salicylic acid and cryotherapy with liquid nitrogen are first-line treatments for cutaneous warts.	A	2, 9
Aggressive cryotherapy (10 to 30 seconds) is more effective than less aggressive cryotherapy.	B	2, 7, 11
Best results of cryotherapy can be achieved when the patient is treated every two or three weeks. There is no therapeutic benefit beyond three months.	B	17, 27
When using cryotherapy for plantar warts, paring the wart before treatment can increase the clearance rate.	B	27
Intralesional injection with <i>Candida</i> or mumps skin antigen has moderate effectiveness for treatment of recalcitrant warts in patients with a positive skin antigen pretest.	B	20, 21
Photodynamic therapy with aminolevulinic acid plus topical salicylic acid is a moderately effective option for treatment of recalcitrant warts.	B	1, 2, 11, 22
Although preliminary studies were promising, duct tape is not effective for wart treatment.	B	25, 26
Pulsed dye laser or intralesional injection with bleomycin can be considered for treatment of recalcitrant warts, although the effectiveness is unproven.	B	2, 11

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort.xml>.

- ◆ Combining salicylic acid with cryotherapy may be more effective than either treatment alone (relative risk = 1.24).
- ◆ Salicylic acid is well tolerated, but the most common adverse effect is minor skin irritation. The therapy should not be used on the face because it can cause hypo- or hyperpigmentation. Salicylic acid therapy is slow to take effect and requires frequent application.

GUIDELINES

BJD
British Journal of Dermatology

British Association of Dermatologists' guidelines for the management of cutaneous warts 2014

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Conflicts of interest

J.C.S. has received travel and accommodation expenses from LEO Pharma (non-specific) and has been an invited speaker at educational events for Healthcare Education Services (non-specific).

J.C.S., S.G., S.S.H.H. and S.E.H.J. are members of the guideline development group, with technical support provided by M.F.M.M.

1.0 Purpose and scope

The overall objective of the guideline is to provide up-to-date, evidence-based recommendations for the management of infectious cutaneous warts caused by papillomavirus infection. The document aims to (i) offer an appraisal of all relevant literature since January 1999, focusing on any key developments; (ii) address important practical clinical questions relating to the primary guideline objective, i.e. accurate diagnosis and identification of cases and suitable treatment; (iii) provide guideline recommendations, where appropriate with some health economic implications; and (iv) discuss potential developments and future directions.

The guideline is presented as a detailed review with highlighted recommendations for practical use in the clinic, in addition to an updated patient information leaflet [available on the British Association of Dermatologists' (BAD) website, www.bad.org.uk].

Table 1 Summary of recommended treatments for hand warts

Strength of recommendation	Treatment	Suggested method of use for hand warts
A	Salicylic acid (SA)	Topical preparations of 15–26% SA, applied daily after removing thick keratin layer, with occlusion if possible. Continue for 3–4 months ^{11,35}
B	Cryotherapy	Keep wart frozen for 15–30 s, repeating every 2–4 weeks for at least 3 months or six treatments ^{11,35}
C	Bleomycin	A 0.1–1 U mL ⁻¹ (0.1–1 mg mL ⁻¹) solution injected or pricked into wart after local anaesthesia – one to three treatments. Painful during and after treatment ^{101,102}
	Contact immunotherapy	After initial sensitization, DPC or SADBE at strength appropriate for patient, applied from twice weekly to every 3 weeks for 3–6 months ^{133,134}
	5-Fluorouracil	A 5% cream applied daily + occlusion for 4–12 weeks ^{92,93}
	Laser	Pulsed-dye laser after paring and/or SA pretreatment. Two to four treatments at 7–10 J cm ⁻² are usually needed ^{59–61}
D	Acupuncture	Auricular acupuncture weekly for 10 weeks ¹⁷¹
	Cantharidin	A 0.7% solution applied every 3 weeks up to four times ⁴¹
	Cidofovir	A 1% cream daily for 5 days each week under occlusion for 8 weeks ^{121,122}
	Formaldehyde	A 3–4% solution as a daily 15–20-min soak for plantar warts, with emollient protection of unaffected skin for up to 8 weeks ⁷⁸
	Glutaraldehyde	A 10% solution applied daily after paring or rubbing down for 3 months ⁷⁹
	Hyperthermia	Heat wart(s) to 40–44 °C for 30 min on three to five consecutive days ^{55,56}
	Imiquimod	A 5% cream twice daily for up to 6 months ¹²⁸
	Phenol	An 80% solution applied weekly for up to 6 weeks ⁴⁰
	Photodynamic therapy	ALA-PDT after paring and/or SA pretreatment, up to three treatments ⁷¹
	Podophyllin	Podophyllin but not podophyllotoxin tested. After paring or rubbing down. 25% in liquid paraffin applied under occlusion. ¹¹ Authors advise weaker strength (10–15%) and cautious use ⁹⁰
	Pyruvic acid	A 70% solution applied daily for up to 2 months ⁴⁴
	Retinoids, systemic	Acitretin 0.5–1 mg kg ⁻¹ per day for up to 3 months ¹¹³
	Surgery	Curettage, cautery, or hyfrecation for filiform warts

RESEARCH

CMAJ

Cryotherapy with liquid nitrogen versus topical salicylic acid application for cutaneous warts in primary care: randomized controlled trial

Sjoerd C. Bruggink MD, Jacobijn Gussekloo MD PhD, Marjolein Y. Berger MD PhD, Krista Zaaier MD, Willem J.J. Assendelft MD PhD, Margot W.M. de Waal PhD, Jan Nico Bouwes Bavinck MD PhD, Bart W. Koes PhD, Just A.H. Eekhof MD PhD

Previously published at www.cmaj.ca

ABSTRACT

Background: Cryotherapy is widely used for the treatment of cutaneous warts in primary care. However, evidence favours salicylic acid application. We compared the effectiveness of these treatments as well as a wait-and-see approach.

Methods: Consecutive patients with new cutaneous warts were recruited in 20 primary care practices in the Nether-

warts to their family physician.^{7,8} The usual treatment is cryotherapy with liquid nitrogen or, less frequently, topical application of salicylic acid.⁹⁻¹² Some physicians choose a wait-and-see approach because of the benign natural course of warts and the risk of side effects of treatment.^{10,11}

A recent Cochrane review on treatments of cutaneous warts concluded that available studies were small, poorly

CMAJ • OCTOBER 19, 2010 • 182(15)

Table 2: Effectiveness of treatments at 13 weeks, by location of warts (*n* = 240)

Variable	Treatment arm; no. (%) of participants cured*						<i>p</i> value†
	Cryotherapy		Salicylic acid		Wait and see		
	<i>n</i> / <i>N</i> ‡	% (95% CI)	<i>n</i> / <i>N</i> ‡	% (95% CI)	<i>n</i> / <i>N</i> ‡	% (95% CI)	
All participants (<i>n</i> = 240)	30/76	39 (29–51)	20/82	24 (16–35)	13/82	16 (10–25)	0.001
Age, yr							
4–12	16/31	52 (35–68)	15/36	42 (27–58)	11/38	29 (17–45)	0.056
≥ 12	14/45	31 (20–46)	5/46	11 (5–23)	2/44	5 (1–15)	0.001
Duration of warts, mo							
< 6	19/30	63 (46–78)	14/37	38 (24–54)	10/32	31 (18–49)	0.012
≥ 6	11/46	24 (14–38)	6/45	13 (6–26)	3/50	6 (2–16)	0.012
Common warts (<i>n</i> = 116)	19/39	49 (34–64)	6/39	15 (7–30)	3/38	8 (3–21)	< 0.001
Age, yr							
4–12	6/12	50 (25–75)	2/12	17 (5–45)	1/15	7 (2–25)	0.010
≥ 12	13/27	48 (31–66)	4/27	15 (6–32)	2/23	9 (2–27)	0.001
Duration of warts, mo							
< 6	10/12	83 (55–95)	2/11	18 (5–48)	2/13	15 (4–42)	0.001
≥ 6	9/27	33 (19–52)	4/28	14 (6–31)	1/25	4 (< 1–20)	0.006
Plantar warts (<i>n</i> = 124)	11/37	30 (17–46)	14/43	33 (20–47)	10/44	23 (13–37)	0.46
Age, yr							
4–12	10/19	53 (32–73)	13/24	54 (35–72)	10/23	43 (26–63)	0.54
≥ 12	1/18	6 (< 1–26)	1/19	5 (< 1–25)	0/21	0 (0–15)	0.34
Duration of warts, mo							
< 6	9/18	50 (29–71)	12/26	46 (29–65)	8/19	42 (23–64)	0.63
≥ 6	2/19	11 (3–31)	2/17	12 (3–34)	2/25	8 (2–25)	0.77

Results: Of the 250 participants (age 4 to 79 years), 240 were included in the analysis at 13 weeks (loss to follow-up 4%). Cure rates were 39% (95% confidence interval [CI] 29%–51%) in the cryotherapy group, 24% (95% CI 16%–35%) in the salicylic acid group and 16% (95% CI 9.5%–25%) in the wait-and-see group. **Differences in effectiveness were most pronounced.**

among participants with **common warts ($n=116$): cure rates were 49% (95% CI 34%–64%) in the cryotherapy group, 15% (95% CI 7%–30%) in the salicylic acid group and 8% (95% CI 3%–21%) in the wait-and-see group.** Cure rates among the participants with plantar warts ($n = 124$) *did not differ significantly* between treatment groups.

Remarks

- Sample size estimation of hypothesis testing for two proportions (two arms design)

P_1 vs. P_0	Alpha	Power	N_Per Group	N_Total
0.15 vs. 0.08	0.05	80%	325	650
	0.05	90%	425	850
0.25 vs. 0.08	0.05	80%	74	148
	0.05	90%	99	198
0.35 vs. 0.08	0.05	80%	36	72
	0.05	90%	47	94

Search Criteria: Objectives: common wart

Viewing all 15 trials in your subscription

Data Table View		Dashboard View		Timing View						
Phase	Disease Type	Patient Segment	MeSH Term	Sponsorship	Primary Drugs	Other Drugs	Protocol ID / Trial Identifier	Status	Source	Action
I	HPV	Treatment	Papilloma; Papillomavirus Infections; Warts	Leo Pharma (Peplin Limited)	ingenol mebutate		NCT00546611, PEP005-019, TrialTroveID-238319	Terminated	Trialtrove	View Watch
II	HPV; Other Viral Vaccines	Adolescents, Adults, Healthy subjects, HPV vaccines, Vaccine - preventative	Papilloma; Papillomavirus Infections	Merck & Co.	HPV vaccine, Merck-2	HPV vaccine, CSL	0950350816, EudraCT Number: 2006-004933-14, TrialTroveID-125975, V 502-003-01, V502-003, V502-003-01	Terminated	Trialtrove	View Watch
II	HPV	Treatment	Papilloma; Papillomavirus Infections; Warts	(Other Industry Sponsor)	natural product		NCT01286441, TrialTroveID-226173, VIR001-01	Completed	Trialtrove	View Watch
II	HPV	Treatment	Papilloma; Papillomavirus Infections; Warts	Nielsen BioSciences	candida antigen, Allermed		NCT01757392, Nieslen Protocol CFW-2c, TrialTroveID-229789	Completed	Trialtrove	View Watch
II	HPV	Treatment	Papilloma; Papillomavirus Infections; Warts	Valeant Pharmaceuticals (Medicis {Graceway Pharmaceuticals})	resiquimod		1508-RESI, NCT00114920, TrialTroveID-234240	Completed	Trialtrove	View Watch
II	HPV	Treatment	Papilloma; Papillomavirus Infections; Warts	Valeant Pharmaceuticals (Medicis {Graceway Pharmaceuticals})	resiquimod		1513-RESI, NCT00115141, TrialTroveID-234243	Completed	Trialtrove	View Watch
II	HPV	Treatment	Papilloma; Papillomavirus Infections; Warts	Valeant Pharmaceuticals (Medicis {Graceway Pharmaceuticals})	resiquimod (gel)		1534-RESI, NCT00116662, TrialTroveID-234263	Completed	Trialtrove	View Watch

II	HPV	Treatment	Papilloma; Papillomavirus Infections; Warts	Valeant Pharmaceuticals {Medicis {Graceway Pharmaceuticals}}	resiquimod	1535-RESI, NCT00116675, TrialTroveID-234264	Completed	Trialtrove	View Watch
II	HPV	Treatment	Papilloma; Papillomavirus Infections; Warts	Valeant Pharmaceuticals {Medicis {Graceway Pharmaceuticals}}	resiquimod (gel)	1515-RESI, NCT00117871, TrialTroveID-234279	Completed	Trialtrove	View Watch
II	HPV	Treatment	Papilloma; Papillomavirus Infections; Warts	Valeant Pharmaceuticals {Medicis {Graceway Pharmaceuticals}}	resiquimod	1514-RESI, NCT00117923, TrialTroveID-234280	Completed	Trialtrove	View Watch
II	HPV	Treatment	Papilloma; Papillomavirus Infections; Warts	Maruho/Cutanea Life Sciences	furosemide + digoxin , Cutanea , digoxin , furosemide, unspecified	CL8003-CO-PR-002, EudraCT Number: 2014- 003688-39, NCT02333643, TrialTroveID-249955	Completed	Trialtrove	View Watch
II	HPV	Treatment	Papilloma; Papillomavirus Infections; Warts	Nielsen BioSciences	candida antigen , Allermed	CFW-2D, NCT02393417, TrialTroveID-254013	Closed	Trialtrove	View Watch
II	HPV	Treatment	Papilloma; Papillomavirus Infections; Warts	RXi Pharmaceuticals	diphenylcyclopropenone (ointment), Hapten Pharmaceuticals	NCT02640820, RXI-SCP-1502, TrialTroveID-270553	Closed	Trialtrove	View Watch
II	HPV	Treatment	Papilloma; Papillomavirus Infections; Warts	Aclaris Therapeutics	hydrogen peroxide , Aclaris Therapeutics	A-101-WART-202, NCT03210337, TrialTroveID-304780	Completed	Trialtrove	View Watch
II	HPV	Treatment	Papilloma; Papillomavirus Infections; Warts	Aclaris Therapeutics	hydrogen peroxide , Aclaris Therapeutics	A-101-WART-203, NCT03278028, TrialTroveID-308882	Completed	Trialtrove	View Watch

Display Mode Data Field View | Title View



SINPHAR GROUP



Press Releases

Aclaris Therapeutics' A-101 45% Topical Solution Meets Primary and All Secondary Endpoints in Two Phase 2 Clinical Trials for Common Warts

- *Highly statistically significant results on all primary and secondary endpoints*
- *Statistical significance seen as early as day 28, after 4 weeks of treatment in WART-203*
- *If approved, A-101 45% would be the first FDA approved treatment for common warts*

• MALVERN, Pa., Jan. 08, 2018 (GLOBE NEWSWIRE) -- Aclaris Therapeutics, Inc. (NASDAQ:ACRS), a dermatologist-led biopharmaceutical company focused on identifying, developing and commercializing innovative and differentiated therapies to address significant unmet needs in medical and aesthetic dermatology, today announced positive results from its two Phase 2 clinical trials (WART-202 and WART-203) of A-101 45% topical solution (A-101 45%), an investigational new drug for the treatment of common warts (verruca vulgaris). A-101 45% met all primary and secondary endpoints of each trial, achieving clinically and statistically significant clearance of common warts. A-101 45% is a proprietary high-concentration hydrogen peroxide topical solution being developed as a prescription treatment for common warts.



Synopsis

A Phase III, Randomized, Double-Blind, Vehicle-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Polyphenon® E 10% Ointment Versus Vehicle in Subjects 12 Years of Age or Older With Cutaneous Common Warts

Commented [LG1]: Without prior data, might a phase II study be more appropriate before going to Phase III to reduce risk?

STUDY SYNOPSIS

Objectives:	The objectives of this study are to evaluate the efficacy and safety of thrice daily application of Polyphenon® E 10% ointment compared to vehicle in subjects ≥ 12 years of age with nongenital cutaneous common warts (verruca vulgaris).
Overview of Study Design	<p>Design : A randomized, double-blind, vehicle-controlled, multicentre phase III trial</p> <p>Study Sites: Enrollment will take place at [redacted] Hospitals. A study coordinator at site will be identified, and institutional specific process will be utilized to identify patients. Patients who will be prescribed Polyphenon® E10% ointment due to cutaneous common warts as deemed necessary by the treating physician will be screened for inclusion in this study.</p> <p>Estimated Enrollment : 198 patients</p> <p>Study Start Date: July 2019 (Enrollment duration: 1 years)</p> <p>Estimation Study Completed Date : June 2020</p> <p>Method: After completing patients data collection, the efficacy and safety will be evaluated for the study subjects.</p>
Study Population	The patients who are prescribed Polyphenon® E 10% ointment as required medical care for cutaneous common warts, as deemed necessary by his/her treating physician.
Inclusion Criteria	<ol style="list-style-type: none"> 1. Male or female subject is at least 12 years of age. 2. The diagnosis of CW is based on visual inspection by an experienced dermatologist. 3. Subject must have 1 to 6 clearly identifiable common warts as defined below, on hands, feet, limbs, and/ or trunk : <ul style="list-style-type: none"> ■ Have a longest axis that is 3mm to 10mm ■ Have a thickness ≤ 3mm ■ Be a discrete lesion ■ Be, when centered in the circular cutout of the provided template, the only common wart present

Commented [LG2]: 1. How did this come out?
Required a bit more details, such as effect size.....

2. Any prior studies with the drug in common warts?
3. What is the variation of placebo, ie "no treatment"?
4. Which line treatment that this study is going to support and pursuit for VM?
5. Salicylic acid is the first line standard therapy, would you consider use it as control group in considering market competitiveness.

Commented [LG3]: I/E criteria sounds okay for now, but may revisit if design is changed.

	<p>boards, clippers, debridors, etc.) in the treatment area within 8 weeks of the Baseline Visit.</p> <ul style="list-style-type: none"> ■ Treatment with immunotherapy (DPCP, DNCB or other), imiquimod, 5-fluorouracil, bleomycin, podophyllin or any other wart immunotherapy or treatment (e.g., Candida antigen) designed to stimulate immune response within 12 weeks of the Baseline Visit. <ol style="list-style-type: none"> 2. Subjects who are immunocompromised. 3. Subjects who have taken, within 30 days prior to the Baseline visit, or require treatment with systemic immunosuppressive or immunomodulatory medication (including oral or parenteral corticosteroids) during the course of the study. 4. Subjects who have used an investigational drug/device within 30 days of the Baseline visit 5. Subjects with known sensitivities to any of the investigational product ingredients. 6. Subjects who have a clinically significant abnormality of the cardiovascular, hepatic or renal systems. 7. Subjects with clinically relevant/significant abnormal laboratory results, vital signs, ECG, and/or physical findings at Screening and/or Baseline 8. Subjects with a chronic medical condition or clinically significant abnormal physical or laboratory finding(s) that may require the use of a prohibited medication/treatment. 9. Subjects who currently abuse alcohol or drugs or who have a history of chronic alcohol or drug abuse within the past year.
Dosage Administration	<ol style="list-style-type: none"> 1. The topical treatment was self-applied by the patients three times daily (up to 250mg per application) to the warts. 2. Subjects with mild to moderate liver or renal dysfunction do not require adjustment.
Treatment Duration	The duration of treatment was 16 weeks. For complete responders, a 12-week treatment-free follow-up phase directly followed to assess wart recurrence.
Efficacy Evaluation	<p>The wart was considered complete clearance if it was no longer visible (skin color and skin lines were reestablished) and could not be palpated anymore by hand.</p> <p>Efficacy Evaluations include:</p> <ul style="list-style-type: none"> ■ Primary Outcome Measures: <ol style="list-style-type: none"> 1. [The difference in the proportion of patients with complete clearance of all treated warts between the active and vehicle at Week 16/ End of Post-treatment Efficacy Evaluation] <ul style="list-style-type: none"> ■ Secondary Outcome Measures: <ol style="list-style-type: none"> 1. [The difference in the proportion of patients with complete clearance of all treated warts between the active and vehicle at Week 12] 2. Recurrence of all treated warts
Safety Evaluation	<p>Subjects who receive at least one dose of study medication are included in the Safety population.</p> <ul style="list-style-type: none"> ■ Primary Outcome Measures: <ol style="list-style-type: none"> 1. The proportion of patients experiencing at least one severe local reaction (local sign or symptom) during the treatment period. <ul style="list-style-type: none"> ■ Secondary Outcome Measures: <ol style="list-style-type: none"> 1. Any (related)adverse events, serious adverse events 2. Assessment of vital signs, laboratory measurements, physical examination, adverse events

Commented [LG4]: Seems redundant with #8 criteria

Commented [LG5]: ? Is this standard? Is there better defined approach?

Commented [LG6]: All sort of endpoint measurement ought to be easily reliably quantified.

Commented [LG7]: 1. Is this co-primary endpoints?
2. Would you select only specific lesions for endpoint evaluation, or all lesions. Relate to definition of complete clearance.
3. You may require an active control? Or even consider compare with first line standard treatment agent: salicylic acid? This particularly relates to market competitiveness, TPP and medical differentiation.

Commented [LG8]: Is there clinical meaning of this Endpoint?

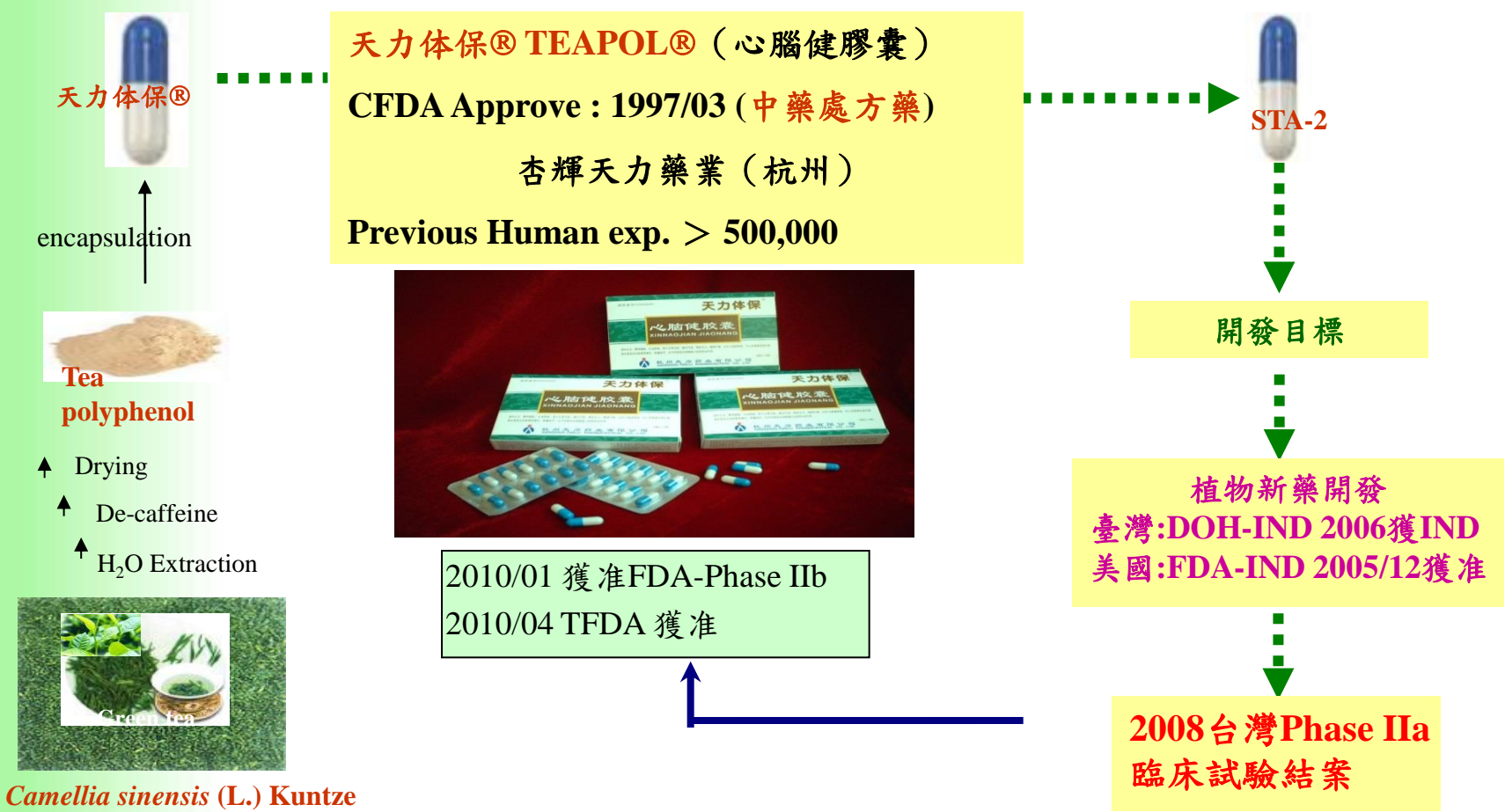
肆、結論

- 綠色健康產業必將成為繼 IT 產業之後席捲全球的「第五波財富」。全球約 3/4 的人口，曾經嘗試或仰賴草藥及植物藥來治療疾病。中國大陸為全球最大的中草藥出口國，出口金額超過**10億美元**，而全球每年高達數百億美元的植物新藥產業，2018年科技部提出『建置中草藥新藥產業鏈』的解決方案平台。根據 BCC Research 研究指出，全球植物藥市場 2014年為 244億美元，2015年約可達到 256億美元，預估2020年，全球市場值將可達到**354億美元**，平均年複合成長率 6.6% 以上。
- 日本醫療用漢方藥的2016年度市場規模達1481億日圓，比2006年度成長56%; 同樣的中草藥在台灣及亞洲各國的需求量非常大，80%以上的原料來自中國大陸，品質良莠不齊，故中草藥原料品質至關重要，故開發原料的抽取技術，並取得專利，是台灣藥廠必須要做的，而後續在開發新適應症等，都可以獲取龐大利益。
- 透過與生技廠商、藥廠、中醫、醫美等跨領域整合研究，中草藥產業或有可能成為台灣繼 IT 產業後的明日之星。

植物新藥契機

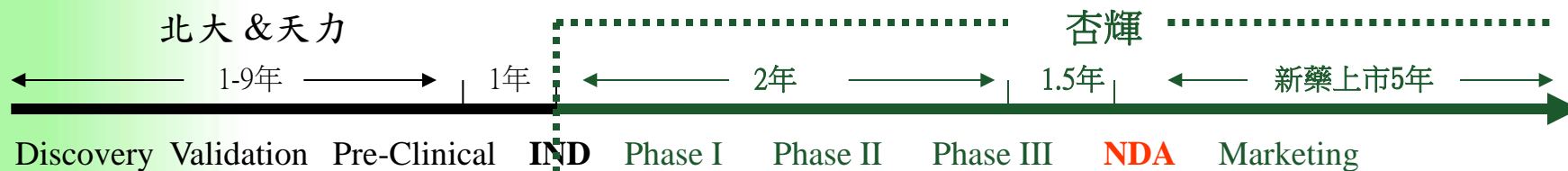
- ✓ 2015年8月17日，美國食品藥品管理局(FDA)公佈最新修訂版《植物藥品審查準則》(Guidance For Industry: Botanical Drug Products)，尋求產業各界的建議。這份法規的內容包括制定植物新藥的定義、提交NDA新藥申請的具體建議，放鬆臨床試驗要求標準等重大措施。
- ✓ 自2004年FDA首度通過該法規，在睽違十餘年後再次修訂新版本，以期能更符合植物藥新藥產業的發展需求。植物藥新藥如同一般的新藥研發，受法規嚴格的管制，任何法規修訂，都可能對產業發展造成程度不一的影響。自2004年以來，獲准上市的植物藥新藥仍屈指可數(Veregen, Fulyzaq)，法規的不完備或許是個關鍵，如今FDA公告新準則，對植物藥新藥採取更務實的態度，對於植物藥新藥的發展或許會是個新契機。
- ✓ 美國藥物食品衛生管理局FDA在2004年6月15日公布了《植物藥品審查準則》，定義何謂「植物藥」。目前在美國FDA公布的植物藥品規範中，針對過去已作為坊間使用，並且具有治療潛力的傳統草藥(traditional experience based herbal medicine)建立法規標準，希望這些已經常年使用的處方，能在符合科學驗證以後，形成有效的植物新藥。
- ✓ 在自然療法當中，植物藥(botanical drug)也就是傳統的草藥理論，主要是指應用天然植物來源做為藥物的方式，通常也稱為「草藥療法」。植物藥新藥指植物萃取物(混合物，非單一成份)經由科學驗證與審核，在符合植物藥特性與安全、有效、均一原則下所開發的藥品。

中草藥開發成功案例分享



2002/7 設立和田GAP基地~~~2003/3專利申請~~~
2004 收載 2005版中國藥典，

杏輝 STA-1植物新藥開發計畫



- ✓ 1990-2000
- ✓ 植物資源調查
- ✓ 化學/有效成分分析鑒定
- ✓ 原料製備技術開發 →
- ✓ CMC技術性資料 →
- ✓ 毒理安全性研究
- ✓ 藥理活性研究

2001/9

- ✓ 2001/12-2003/12
- ✓ Phase I 單次/連續給藥耐受性試驗(42例)
- ✓ Phase II 隨機/雙盲雙類比/陽性藥平行對照/多中心(231例)
- ✓ Phase III 隨機/陽性藥平行對照/多中心(429例)

2005/5

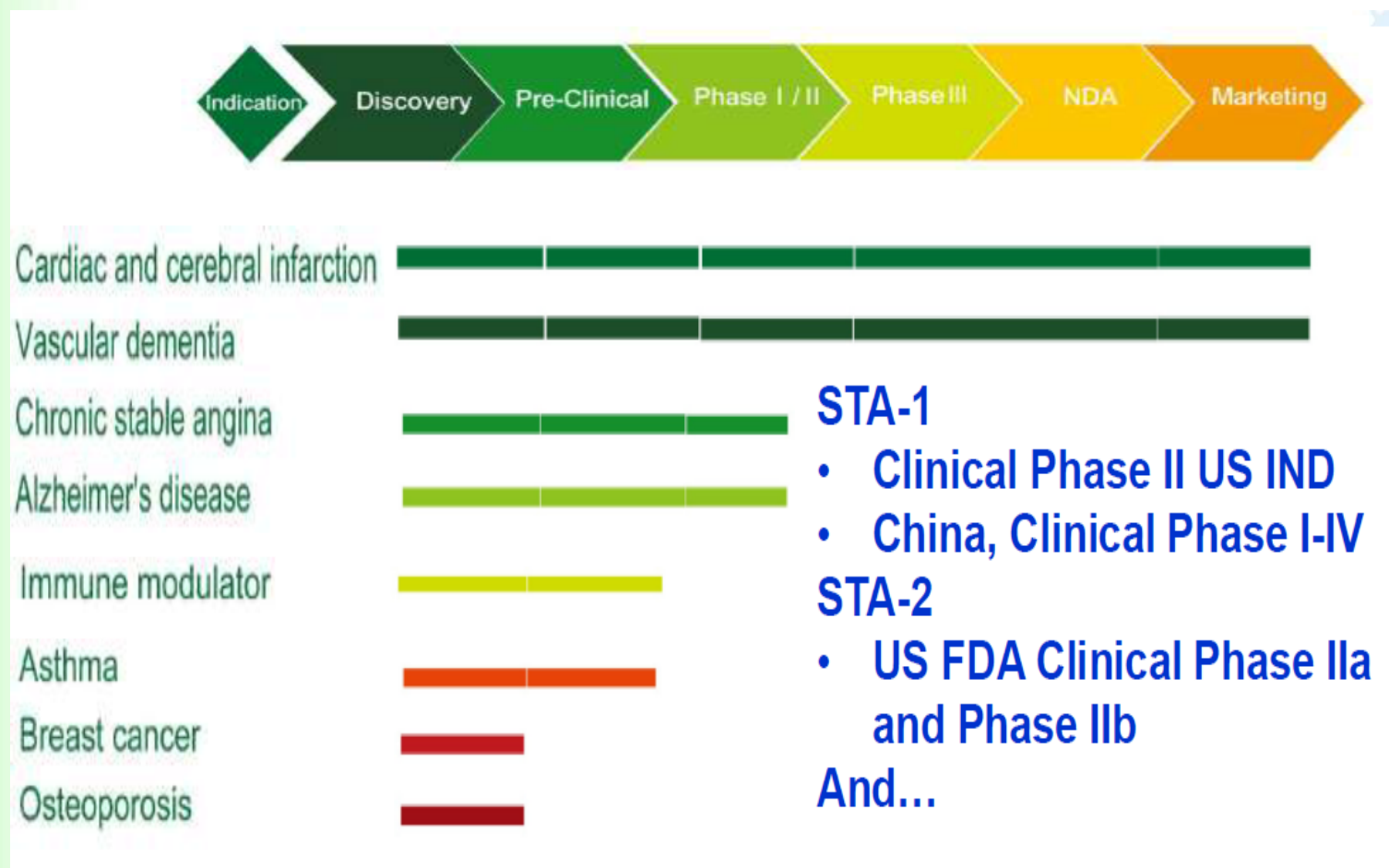
- ✓ 2005/5 市場推廣
- ✓ 2006/4 北京臨床研究
- ✓ 2006/12 開始規劃Phase IV
- ✓ 2007/Q3 Phase IV起動
- ✓ 2007/10 技術處業界科專
- ✓ 2010/11 FDA-IND 送件

2002/7設立和田GAP基地
2003/3專利申請
2004收載2005版中國藥典



大陸CFDA四期臨床
台灣 NDA?

開發目標



視力保健產品市場

眼疾 年代	失明(視覺障礙)人口數		其他(罹病人口)
	全球	國內	
1990	3,800萬		<p>*失明因眼疾病引起比例: 48% 白內障(cataract), 12% 青光眼(glaucoma), 9% 老年性視網膜和黃斑部病變(AMD), 21% 其他: 近視(myopia)、糖尿病視網膜症(diabetic retinopathy, DR)、乾眼症(dry eye)、砂眼。</p> <p>**視覺障礙人口: 白內障、青光眼、老年性視網膜和黃斑部病變、糖尿病視網膜症、乾眼症、近視等; 台灣白內障罹患人數2005年71萬7仟人、2015年105萬人; 目前全球有20億人的近視人口, 其中深度近視(≥ 500度)的人數, 從2000年的1.63億人增至2050年的10億人, 而深度近視往往會併發其他眼睛疾病(如, 白內障、青光眼及黃斑部病變等), 而造成失明。</p>
2012	3,900萬* (2億8500萬)	4.6萬	
2020	7,600萬		
青光眼患者	8,000萬	45萬	
白內障患者	1億0260萬	109萬	

資料來源: WHO及台灣衛福部統計

視力保健產品市場分析

	視力保健產品(金額)		備註(類胡蘿蔔素、魚油)
	全球	國內	
2015年	271億美元	150億台幣	類胡蘿蔔素: 2014年15億美元，2019年18億美元 (CAGR 3.9%) 魚油: 2014年22.5億美元，2020年26.3億美元 (CAGR 6.1%)
2020年	407億美元	242億台幣	
2015-2020年的年複合成長率(CAGR)為 8.5%			

資料來源: 台灣經濟研究院生物科技產業研究中心 (2016)

寵物保健食品市場

- 2017年全球寵物保健品市場規模約為56.5億美元，預計2023年將達到76億美元，年複合成長率為4.83%。

*台灣2018年毛小孩250萬隻，6歲以上白內障及乾眼症為大宗，手術平均費用 ~10萬元(含材料及住院等費用)

■ 消費者對寵物健康議題重視百分比

	百分比	男	女	北	中	南(含東部)
體重控制	<u>49.7%</u>	<u>56.6%</u>	47.2%	<u>50.2%</u>	56.1%	46.2%
皮毛保健	<u>55.0%</u>	<u>53.1%</u>	<u>55.7%</u>	<u>53.6%</u>	<u>66.7%</u>	<u>51.9%</u>
延緩老化	35.3%	34.5%	35.5%	38.6%	43.9%	27.2%
腎臟保健	29.7%	31.0%	29.2%	32.9%	36.4%	22.8%
骨骼關節保健	<u>55.5%</u>	<u>50.4%</u>	<u>57.2%</u>	<u>51.2%</u>	<u>71.2%</u>	<u>54.4%</u>
肝臟保健	23.9%	22.1%	24.5%	21.7%	27.3%	25.3%
牙齒保健	44.8%	41.6%	45.9%	47.3%	56.1%	36.7%
視力保健	28.5%	26.5%	29.2%	31.9%	36.4%	20.9%
呼吸道保健	29.9%	23.0%	32.4%	26.5%	28.8%	32.3%
腸胃道保健	48.7%	45.1%	<u>50.0%</u>	44.9%	<u>63.6%</u>	<u>47.5%</u>
生殖系統保健	14.2%	13.3%	14.5%	15.0%	18.2%	11.4%
心血管保健	29.2%	27.4%	29.9%	26.6%	31.8%	31.6%
情緒保健	23.2%	23.0%	23.3%	23.7%	30.3%	19.6%
其他	1.4%	0.0%	1.9%	1.4%	1.5%	1.3%

資料來源:台灣經濟研究院生物科技產業研究中心107年度消費者調查，有效回卷431份。



SINPHAR GROUP

Dietary supplements

EyeCare™

營養添加物*	含量	劑量考量	功效與機制
A	? mg	最高劑量	抗氧化、維持細胞粒線體功能
epigallocatechin-3-gallate (EGCG)	? mg	有效劑量	抗氧化、神經細胞保護、免疫調節
B	? mg	維持劑量	抗氧化、抗發炎、增加免疫作用
C	? mg	最高劑量	抗氧化、保護神經
D	? mg	臨床劑量	促進眼睛視紫質、增加眼睛微血管循環、抗氧化、抗發炎

*Nutraceuticals for Glaucoma, Cataract, AMD, Myopia

References:

1. C Shen, L Chen, L Jiang, and T Y Y Lai. (2015) Neuroprotective effect of epigallocatechin-3-gallate in a mouse model of chronic glaucoma. *Neuroscience Letter* 600:132-136.
2. Dario Rusciano, Salvatore Pezzino, et al., (2017) Neuroprotection in Glaucoma: Old and New Promising Treatments. *Advances in Pharmacological Sciences*, 2017: 4320408.

Dietary supplements

1. EGCG is sourced by the main components of green tea extract, is the most abundant. The neuroprotective effect of EGCG was demonstrated against the oxidative stress directly delivered to neural cells *in vitro* and *in vivo* in a mouse model. Clinical efficacy of a short-term oral supplementation of EGCG has been by PERG analysis, showing that the treatment might favorably influence the inner retinal function in human eyes of glaucomatous patients with early to moderately advanced damage.

2.US 2015/0182577 A1

Applicant: Zhejiang Medicine Co., Ltd. Xinchang Pharmaceutical Factory, Xinchang County (CN)

Inventors: Xinde Xu, Xinchang County (CN); Lihua Zhang, Xinchang County (CN); Xiaoxia Sun, Xinchang County (CN)

Appl. No.: 14/419,938; PCT Filed: Aug. 8, 2013; PCT No.: PCT/CN2013/000933 S371 (c)(1), Date: Feb. 6, 2015

Topic: COMPOSITION FOR IMPROVING MACULAR PIGMENT DENSITY AND PREVENTING OR TREATING AGE-RELATED MACULAR DEGENERATION

Abstract: The composition comprises lutein, Zeaxanthin and tea extracts, wherein the weight ratio of zeaxanthin to lutein is more than or equal to 1. The composition may prevent formation of choroidal neovascularization to achieve effects on comprehensively preventing or treating AMD.

[0025] **Preferably, the tea extract is a mixture of GC, CG, GCG and EGCG, or EGCG. The amount of the tea extract or EGCG is respectively 10mg-200mg, preferably 20mg-120mg.**

參考資料

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