



香港賽馬會慈善信託基金
The Hong Kong Jockey Club Charities Trust



*R&D Laboratory for Testing of
Chinese Medicines*
中藥研發實驗室



Prof. Chi-Ming Che
支志明教授
Department of Chemistry, HKU
香港大學化學系

Objectives 目標

Modernization of Chinese medicines via evidence-based research

通過循証研究中藥之現代化

To explore the potential **medicinal uses** of Chinese medicines

發掘中藥的潛在作用

To improve the **efficacy** of current drug leads from Chinese medicines

提高中藥藥效及研發

To strengthen **public confidence** in using Chinese medicines

加強公眾對使用中藥的信心

中藥研發

To act as a **bridge** linking both academia and industry and leveraging the intellectual and financial resources

作為連接學術界和產業的橋樑、撬動高學歷人才和財富的杠杆

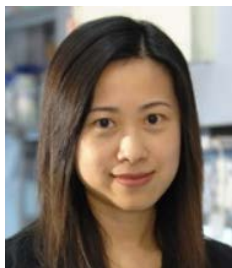
To assist the Chinese medicines industry in developing **new analytical methods** for testing Chinese medicines in particular precious herbs and solve problems of adulteration, counterfeits and etc

幫助中藥產業開發新的分析方法以檢測中藥，解決摻假、仿品等問題

Core members for R&D of Chinese medicines

重要研究人員

Dr. Kwan-Ming Ng
(Analytical chemistry)



Dr. Alice Wong
(Anticancer)

Prof. Chi-Ming Che
(Chemistry)

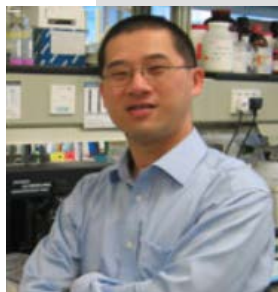


Dr. Yibin Feng
(Chinese medicine)



中藥研發

Dr. Raymond Chang
(Alzheimer's disease)



Dr. Mingfu Wang
(Biological sciences)



Dr. Michelle Lum
(Chemical biology)

Dr. Yungen Liu
(Organic synthesis)

Dr. Kam Hung Low
(X-ray diffractometry)

Dr. Jaclyn Sy
(Phytochemistry)

Dr. Chun-Nam Lok
(Chemical biology)

Established Collaborations 合作伙伴



FACULTY OF SCIENCE
THE UNIVERSITY OF HONG KONG
香港大學 理學院

- ◆ Department of Chemistry 香港大學化學系
- ◆ School of Biological Science 香港大學生物科學學院

Li Ka Shing Faculty of Medicine, HKU



香港大學醫學院

- ◆ School of Chinese Medicine
香港大學中醫藥學院
- ◆ Department of Anatomy
香港大學解剖學系

中藥研發

National Research

Institutes/Centers: 國際科研機構

- ◆ Professor John R. Yates III, Scripps Research Institute, California
- ◆ Prof Tommy Cheng, Department of Pharmacology, Tale School of Medicine
- ◆ Centre for Drug Safety Evaluation and Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences
- ◆ Prof. G.-Q Lin, Shanghai Institute of Organic Chemistry
- ◆ Dr. Z.-J. Xu, Shanghai-HK Joint Laboratory in Chemical synthesis and State key Laboratory of Synthetic Chemistry

Local stakeholders: 本地合作機構

- ◆ Chinese medicines information and research section of Department of Health, HKSAR 衛生署
- ◆ SGS Hong Kong Ltd.
香港通用公證行有限公司
- ◆ Healthy Pharmaceutical Ltd.
康怡藥業

International Collaboration: 國際產業合作



Established Research Infrastructures and Facilities at HKU for R&D of Chinese medicines

香港大學中藥研究基礎設施與設備

R&D Laboratory for Testing of Chinese Medicines 中藥研發實驗室

Chemical Biology Center at The Hong Kong Jockey Club Building for Interdisciplinary Research 化學生物中心

Open Laboratory of Chemical Biology of the Institute of Molecular Technology for Drug Discovery and Synthesis 分子科技研究院及化學生物學開放實驗室

State Key Laboratory of Synthetic Chemistry 合成化學國家重點實驗室



R&D of Chinese medicines 中藥研發

Q-TOF Premier
with nanoAcquity
LC System



New analytical
testing methods
新分析測試方法



Voyager-DE™
STR MALDI/TOF

Synthesis and
chemical modification
of Chinese medicines
drug leads 藥物合成與修飾



中藥研發
之
五大元素

Phytochemical
analysis of
Chinese medicines
中藥的植物化學分析



QSTAR XL™
LC/MALDI/MS/MS

Bioinformatics of
Chinese medicines
中藥的生物信息學
(collaborate with HKUST)

Chemical biology
and product
development
化學生物學與產品研發

Chinese medicines and targeting disease investigated at HKU

香港大學研究的中藥及其針對疾病

Targeted diseases	Chinese medicines compounds	Experimental model	HKU team members
Anti-cancer 抗癌症	Steroidal saponins 甾體皂苷	Colon cancer nude mice xenograft Cervical cancer nude mice xenograft	Prof. Chi-Ming Che Chemistry
Neuroprotection against Parkinson's disease 抗帕金森症	Resveratrol derivatives 白藜蘆醇	Dopaminergic neurons in mice receiving MPTP	Dr. Raymond Chang, Anatomy
Anti-metastasis 抗癌症轉移	Ginsenosides 人參皂苷	Ovarian cancer model with metastatic phenotypes	Dr. Alice Wong, Biological Sciences
Anti-hepatocarcinoma 抗肝癌	Coptis rhizoma 黃連 Berberines 小檗碱	Hepatoma cell lines and nude mice xenograft	Dr. Yibin Feng, Chinese Medicine
Anti-obesity 抗癩肥	Saponins, phenolics 皂苷, 酚	3T3-L1 adipocyte and Sprague-Dawley rat models	Dr. Mingfu Wang, Biological Sciences

Examination the purity of chemical markers transferred from HKJCICM

來自香港賽馬會中藥研究院中藥對照品的純度檢測



NMR 核磁共振儀

CAS No.	英文名稱	中文名稱	純度 (%)
84272-85-5	5-O-Methylvisamminoside	5-O-甲基维斯阿米醇苷	100
29883-15-6	Amygdalin	苦杏仁苷	77.7
477-43-0	Dehydrocostuslactone	去氢木香内酯	99.0
80681-45-4	Prim-O-b-D-glucosylcimifugin	升麻素苷	100
607-80-7	Sesamin	芝麻素	100
18524-94-2	Loganin	马钱苷	93.6
480-40-0	Chrysin	白杨素	100
518-82-1	Emodin	大黄素	97.2
27409-30-9	Picroside I	胡黄连苷I	100
39012-20-9	Picroside II	胡黄连苷II	100
632-85-9	Wogonin	汉黄芩素	100
486-35-1	Daphnetin	瑞香素	100
92-61-5	Scopoletin	东莨菪内酯	99.6
621-82-9	Cinnamic acid	肉桂酸	99.8
19210-12-9	Harpagide-8-O-E-cinnamoyl	哈巴俄苷	100
471-53-4	Glycyrrhetic acid	甘草次酸	100
537-73-5	Isoferulic acid	异阿魏酸	100
480-19-3	Isorhamnetin	异鼠李素	100
520-18-3	Kaempferol	山奈素	100
491-70-3	Luteolin	木犀草素	99.7
4871-97-0	Curcumol	莪术醇	95.5
482-36-0	Hyperoside/Hyperin	金丝桃苷	100
486-66-8	Daidzein	大豆苷元	98.1
520-36-5	Apigenin	芹菜素	100
99-50-3	Protocatechuic Acid	原先茶酸	100
139-85-5	Protocatechuic Aldehyde	原儿茶醛	100
69-72-7	Salicylic acid	水杨酸	99.8
153-18-4	Rutin	芦丁	92.9
483-90-9	Toddalolactone	毛两面针素	100
97-53-0	Eugenol	丁香酚	98.7
35354-74-6	Honokiol	和厚朴酚	Highly impure



LC-MS/MS 液相-質譜聯用



HPLC 高效液相

Chemical markers are available from the following website

中藥對照品可循下述網站查詢

www.hktmlcm.com



Testing Laboratory
for Chinese Medicine **TLCM**

ABOUT US
關於我們

PRODUCTS
產品資料

R & D
研究成果

CONTACT US
聯絡我們



香港科技大學
THE HONG KONG UNIVERSITY OF
SCIENCE AND TECHNOLOGY



香港大學
THE UNIVERSITY OF HONG KONG

明華機構
Funded by



香港賽馬會慈善信託基金
The Hong Kong Jockey Club Charities Trust

More chemical markers will be launched soon!

更多中藥對照品將陸續登場

HPLC-MS transferred from HKJCICM

來自香港賽馬會中藥研究院的液相-質譜聯用

重置液相色譜法質譜儀 (Waters QTof):

更換後備電池, 清洗質譜儀內部, 更換質譜儀電腦板
更換質譜儀壓力監察器, 更新電腦軟件程式
更換液相色譜儀的零件

儀器擺放位置

沙宣道5號8樓:中藥研發實驗室

操控儀器課程

課程為期5天, 參加人數10人

研究課題

中草藥或中成藥提取物

蛋白質

中草藥的纖維組織

(Tissue-spray ionization mass spectrometry)

保養

定期更換液態氮

定期清洗質譜儀及液相色譜儀的零件



儀器的使用尚在測試中!

Highlighted and Significant Projects

重要科研項目

1. Imaging mass spectrometry (IMS) for authentication of precious Chinese medicines 成像質譜於鑒定珍貴中藥的使用

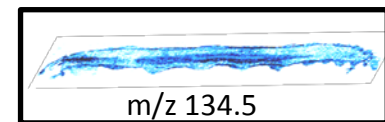
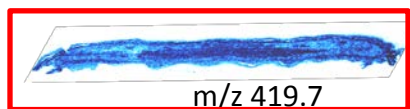
—原理—

- ◆ 利用 Matrix-assisted laser desorption/ionization time-of-flight mass spectrometer (MALDI-TOF MS) 質譜儀於樣本一些特定的點上施加激光直至完全掃描整個樣本表面並於個定點收集質譜
- ◆ 在這些收集得來的質譜中提取離子信號，根據其信號強度及空間分佈用顏色通過軟件建立離子圖像
- ◆ 在離子圖像中，離子於樣本某個位置的信號越強，會用越深的顏色顯示



Voyager-DE STR MALDI Time-of-Flight Mass Spectrometer

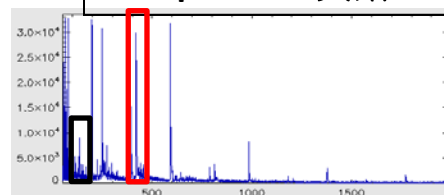
Ion image 離子影像



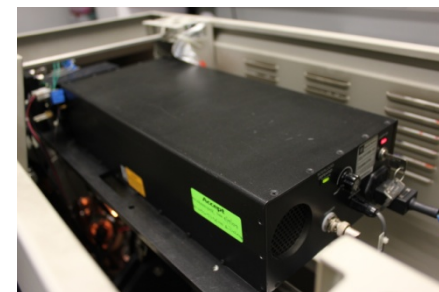
Data analysis
數據分析



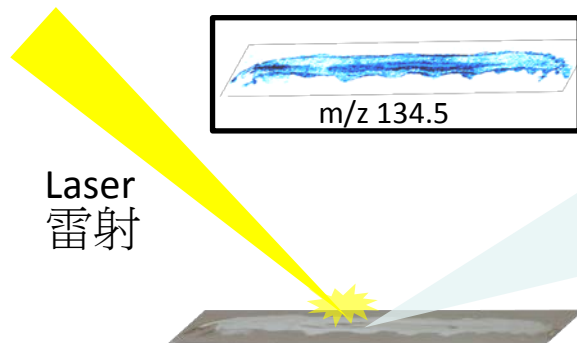
MS spectrum 質譜



Data recording
數據收集



Nitrogen laser system

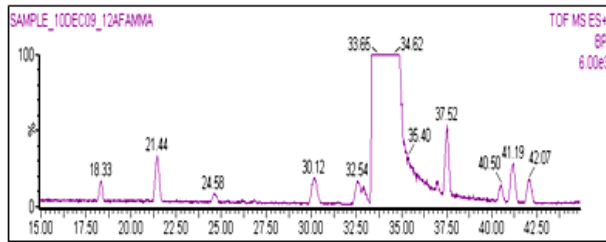


我們對IMS的新應用



LTQ Orbitrap Velos
LC/MS/MS system

MS spectrum 質譜



摻假
仿品
偽品
不確定性
安全性

品質管制

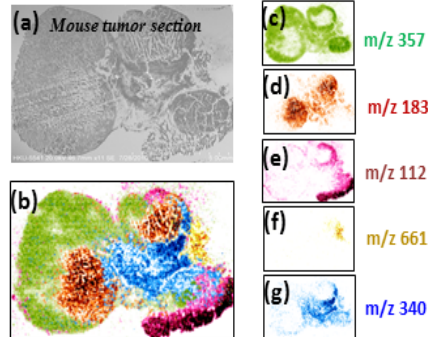
現時質量控制的方法 — 形態學研究

限制:

無化學信息可得到
難以分辨類似形態的中草藥



ABI 4000QTRAP
LC/MS/MS System



成像質譜

另一種中草藥樣品的質量控制 IMS

好處:

可提供形態及化學信息
提供可靠和可重複的結果

發展成像質譜 (IMS)
作珍貴的中國藥品認證



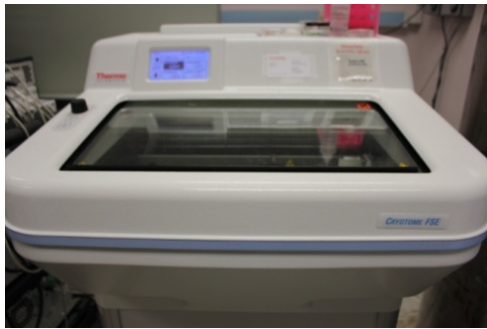
LTQ Orbitrap MS

IMS對冬蟲夏草的應用

步驟:

i) 冷凍切片

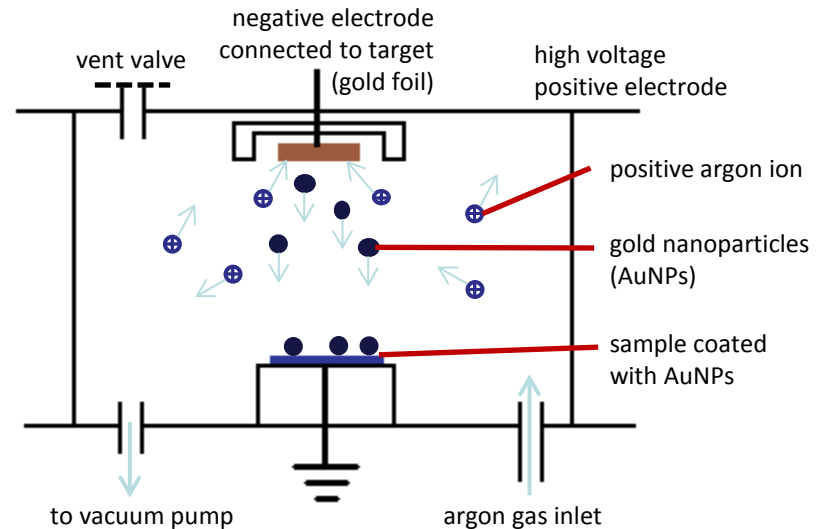
- ◆ 利用低温切片機縱切冬蟲夏草 (12 μm 厚)
- ◆ 把冬蟲夏草片附在膠片上 (on the conductive side of a indium-tin-oxide slide)



冷凍切片機



縱切冬蟲夏草
(12 μm 厚)



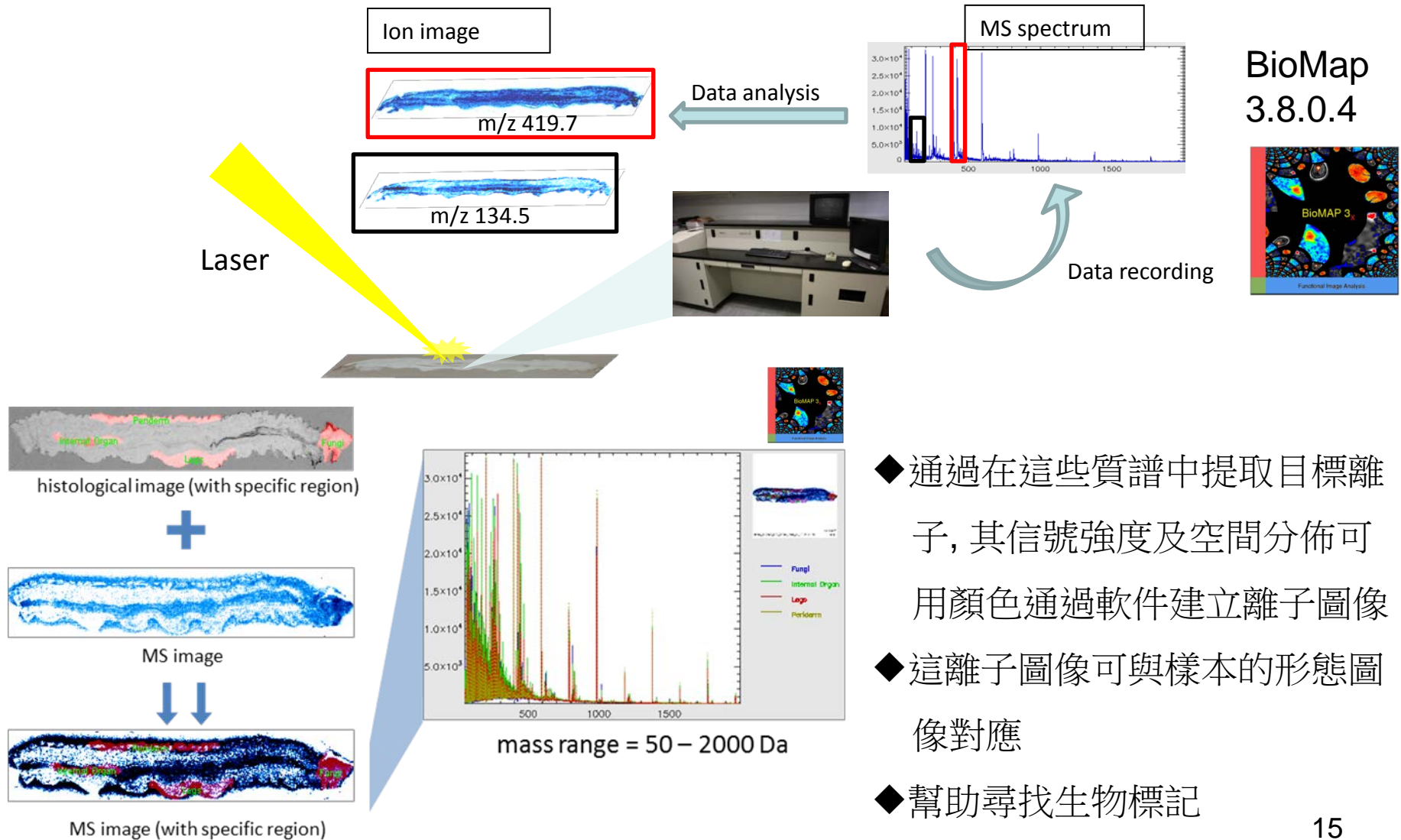
濺散納米金於樣本表面

ii) 塗加基質

- ◆ 利用濺散機把納米金散於樣本表面
- ◆ 利用導電膠紙把塗了納米金的樣本貼於質譜儀的目標上

iii) 建立成像質譜

◆ 在樣本表面施加激光及在樣本表面各處收集質譜



- ◆ 通過在這些質譜中提取目標離子，其信號強度及空間分佈可用顏色通過軟件建立離子圖像
- ◆ 這離子圖像可與樣本的形態圖像對應
- ◆ 幫助尋找生物標記

iv) 質量控制

◆ 通過比對真及假的冬蟲夏草的生物標記, 可識別標誌性的生物標記作真假冬蟲夏草的區分

Principal Component Analysis (PCA) Plot

結果顯示真假蟲草的生物標記是可分辨的

Loading Plot

標誌性的生物標記

真

假



找出標誌的生物標記的m/z

標誌性的生物標記的身分可以用高分辨率質譜儀或MS/MS確認

v) 優勢

1. 省卻複雜及費時的樣本提取過程
2. 不需要標籤便可研究樣本中的生物分子
3. 可於同一時間內研究多個生物分子
4. 得到的生物分子離子圖像可以與樣品的形態學圖像重疊, 從而提供化學和形態學的資料
5. 尋找新的生物標記
6. 研究標記在樣本表面的空間分佈

參考:

Analytical Chem. **2010**, 82, 1589-1593

Rapid Commun. Mass Spectrom. **2011**, 25, 3690-3696

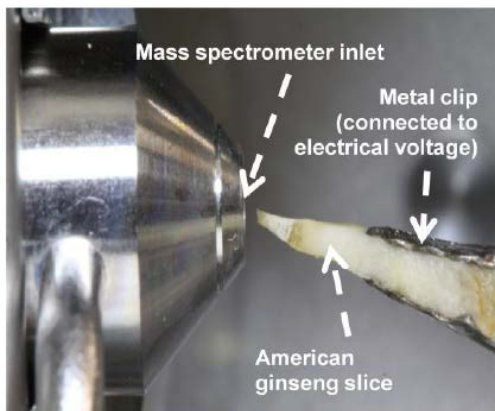
iAnalytical Chem. **2011**, 83, 453-458

2. Tissue spray ionization mass spectrometric method for direct and rapid analysis of raw herbs

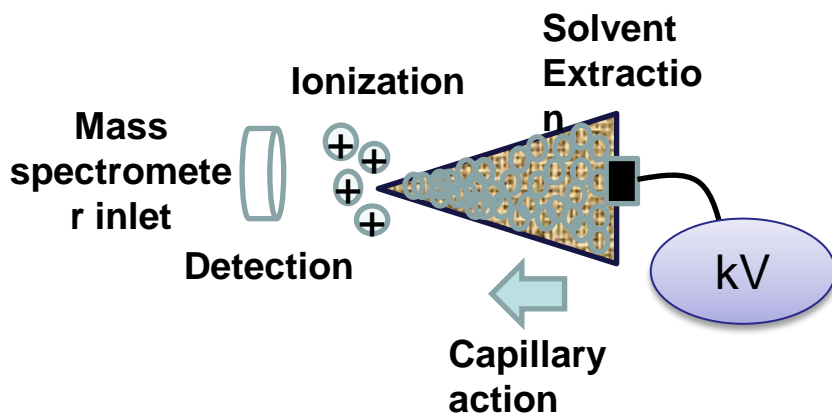
組織噴霧電離質譜法 - 直接快速分析應用於未加工中藥材

—原理—

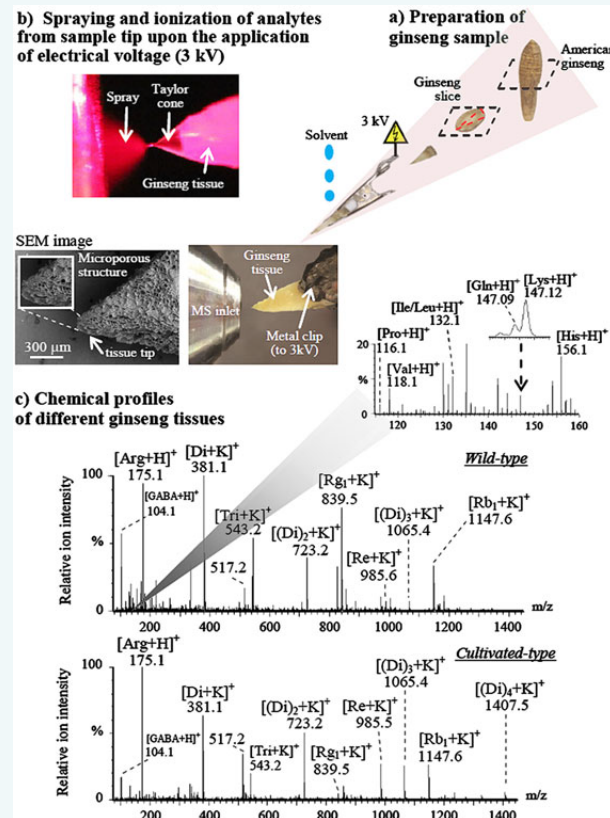
- ◆ 把固態狀的中藥材放近質譜儀的入口, 加入少量提居溶劑並通電
- ◆ 直接對樣本內的組織物進行化學分析



The herbal samples are placed in front of the ion inlet of a mass spectrometer, and analyte molecules can be directly sprayed and ionized from the solvent-wetted tissues upon the application of a high electrical voltage.



Tissue-spray ionization MS的應用: 分辨真假美國蔘



參考:

Rapid Commun. Mass Spectrom 18
2011, 25, 2837-2843

Advantages 優勢

- ◆ Rapid differentiation of morphologically similar herbs
快速區分形態相似之中藥材
- ◆ In situ analysis of sample, no sample treatment and separation
樣品原生態分析，不需進行處理與分離



Flos Daturae (洋金花)



Flos Rhododendri Mollis (鬧羊花)



Radix Clematidis
(威靈仙)



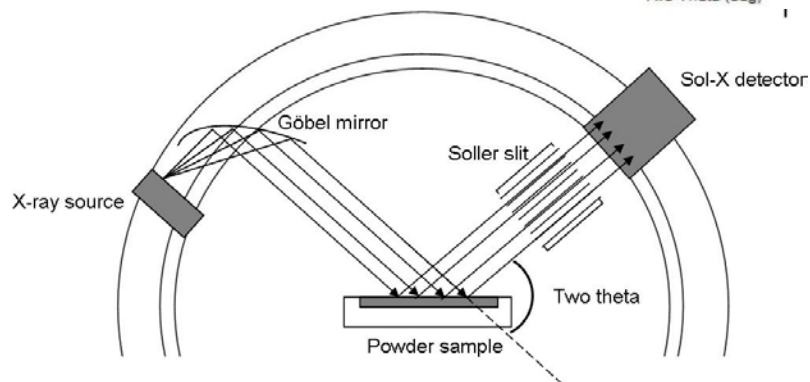
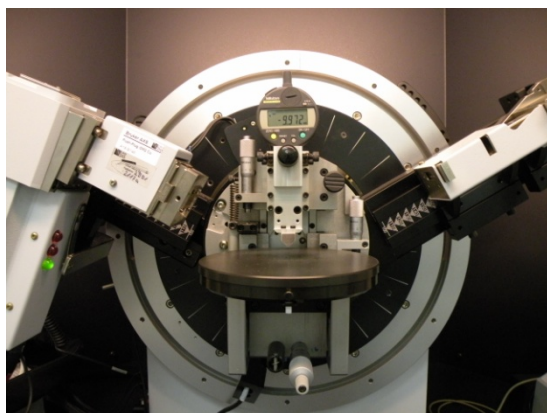
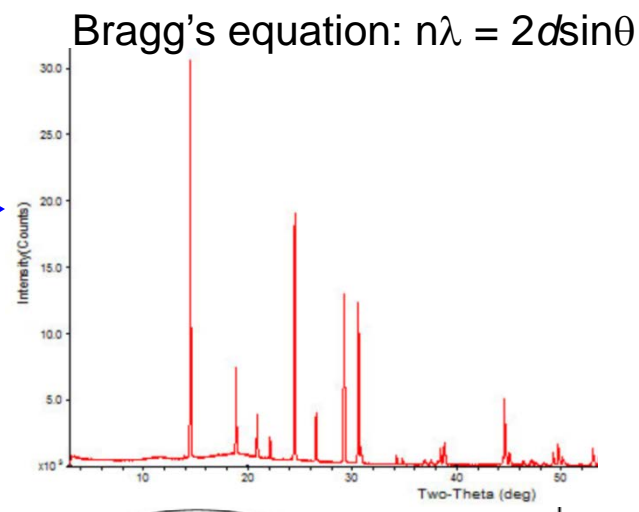
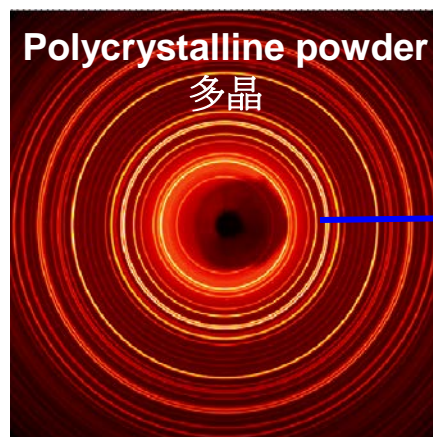
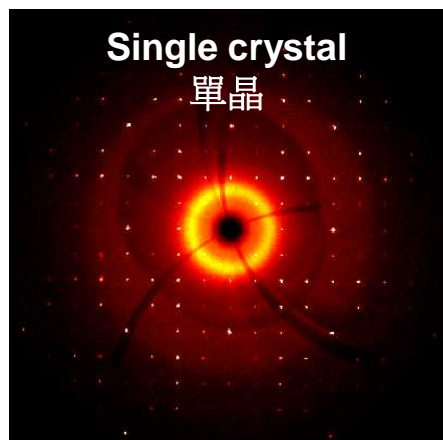
Radix et Rhizoma
Gentianae (龍膽)



Rhizoma Sinopodophlli
Hexandri (鬼白)

3. X-ray Powder Diffraction (XRPD) X-射線粉末衍射法

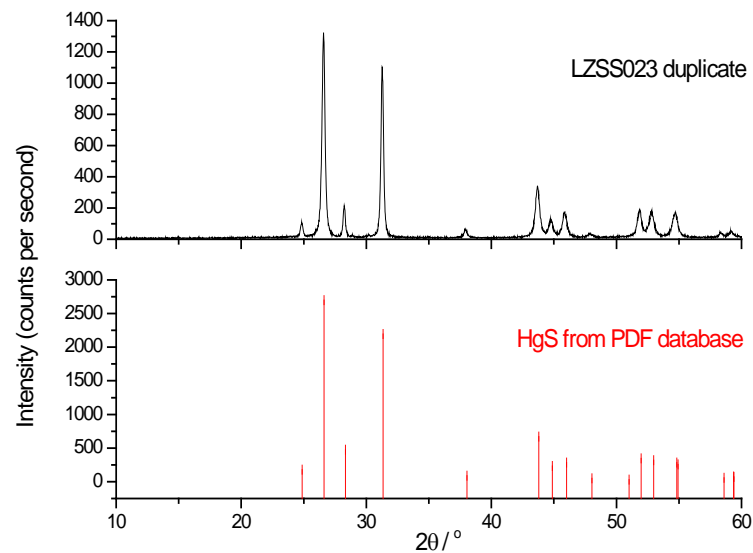
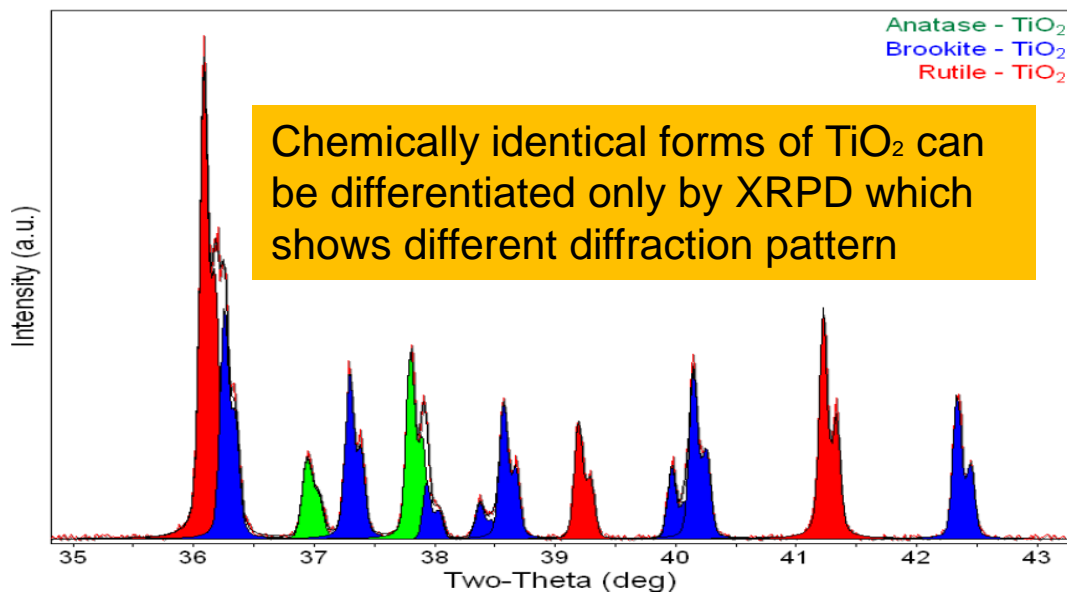
XRPD is a rapid and non-destructive analytical technique primarily used for phase identification of powder or a microcrystalline material and provides structural characterization. X-射線粉末衍射是一種快速、不具破壞性的分析技術，主要應用於粉末或微晶材料的物相鑒定和結構鑒定



Bruker D8 ADVANCE Diffractometer

Qualitative XRPD 粉末衍射定性分析 (Phase Identification 物相鑒定)

- ◆ The diffraction pattern of every phase is as unique as **fingerprint** (指紋圖譜)
- ◆ Phases with the same chemical composition can have different diffraction patterns
- ◆ Identification: comparing the position (2θ) and relative intensity of sample peaks to the reference patterns in the database.

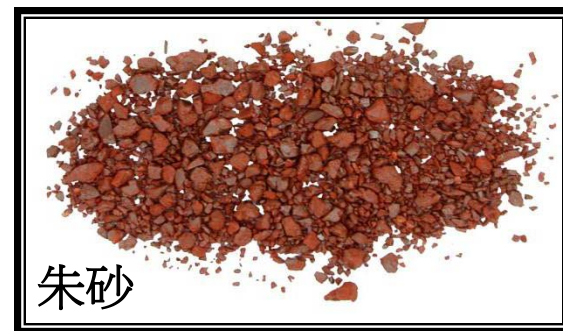


Cinnabaris (HgS) 朱砂, 中國藥典2010

【性味与归经】 甘,微寒;有毒。归心经。

【功能与主治】 清心镇惊,安神,明目,解毒。用于心悸易惊,失眠多梦,癲癇发狂,小儿惊风,视物昏花,口疮,喉痹,疮疡肿毒。

【用法与用量】 0.1~0.5g, 多人丸散服, 不宜入煎剂。



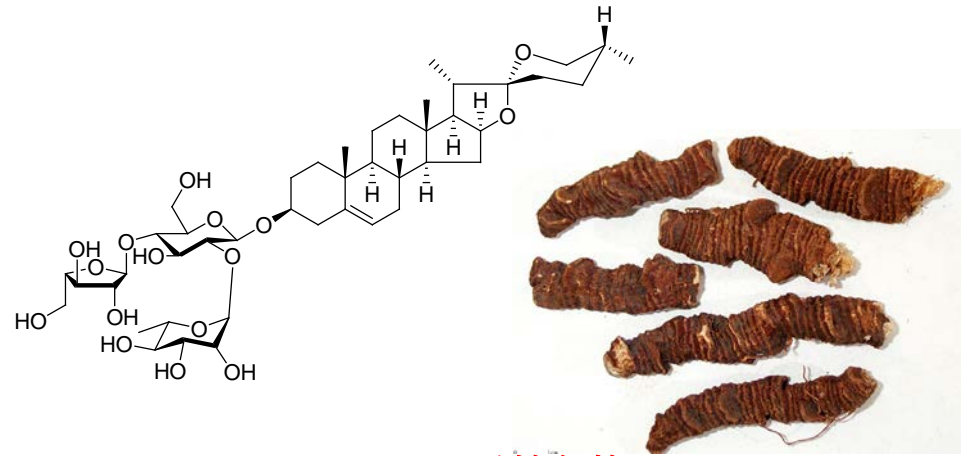
4. Discovery of steroidal saponins from Chinese medicines for treatment of cancer and neurodegeneration diseases

中藥中甾體皂苷的發現及其對癌症與神經退行性變疾病的治療



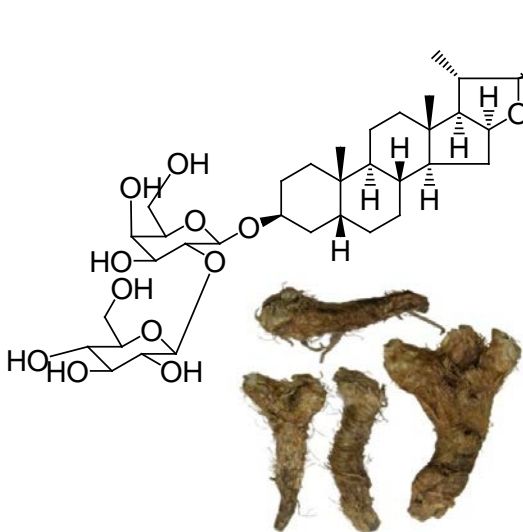
Dioscin 薯蕷皂苷

- ◆ Active component from *Polygonatum zanlanscianense* (湖北黃精)
- ◆ Anticancer activities



Polyphyllin D (PD) 重樓皂苷

- ◆ Active component from *Paris Polyphylla* (重樓)
- ◆ Anticancer activities



Saponin 皂苷

- ◆ Active component from *A. asphodeloides*
- ◆ Anticancer activities (heptacarcinoma)

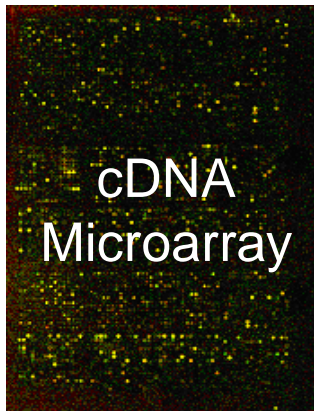
Che et al. *J. Proteome. Res.*, 2007
 Che et al. *Proteomics*, 2006
 Che et al. *Org Lett.*, 2005

《神農本草經》：
 知母，主消渴熱中，除
 邪氣，肢體浮腫，下
 水，補不足益氣。

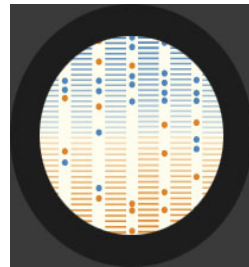
Using chemo- and bio-informatic approach to study anticancer mechanism of steroidal saponins

用化學、生物信息學方法研究甾體皂苷的抗癌機制

Identification of endoplasmic reticulum stress pathway as the anticancer mechanisms of polyphyllin D (PD) 重樓皂苷



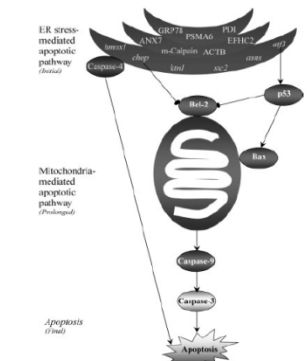
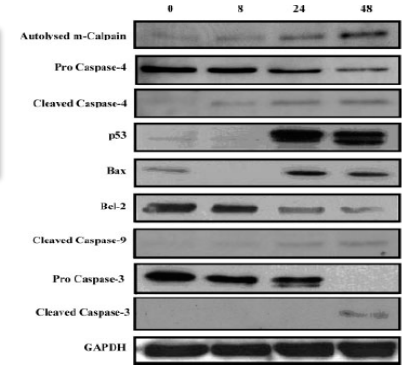
Genomic data obtained from PD treatment



Connectivity Map - Computational pattern mapping with existing drug libraries (Broad Institute, USA)

Name	Rank	Score	Inhibitor	ER stress-related response
MG-132	1	0.993	Proteaseome	Unfolded protein
Celastrol	2	0.987	Proteaseome	Unfolded protein
2-deoxy-D-glucose	4	0.906	Glycosylation	Glucose deprivation
Calmidazolium	8	0.752	Ca ²⁺ -calmodulin/Ca ²⁺ -ATPase	Ca ²⁺ homeostasis
Clotrimazole	10	0.724	Ca ²⁺ regulator	Ca ²⁺ homeostasis
Geldanamycin	11	0.717	HSP90	Unfolded protein
Jonomycin	13	0.685	Ca ²⁺ ionophore	Ca ²⁺ homeostasis
Rottlerin	14	0.638	Protein Kinase	Ca ²⁺ homeostasis
Trifluoperazine	16	0.612	Ca ²⁺ -calmodulin/Ca ²⁺ -ATPase	Ca ²⁺ homeostasis

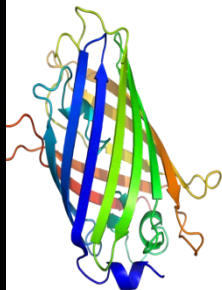
Identification of drugs with similar actions – prediction of the drug target



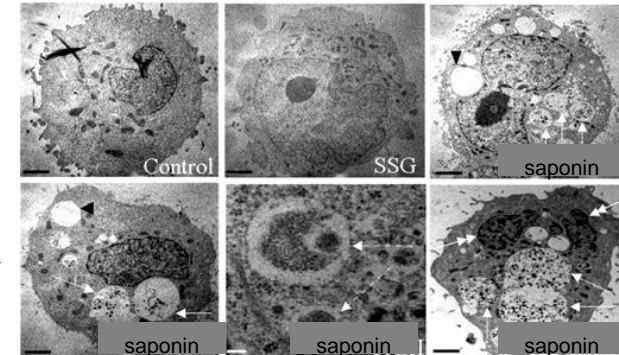
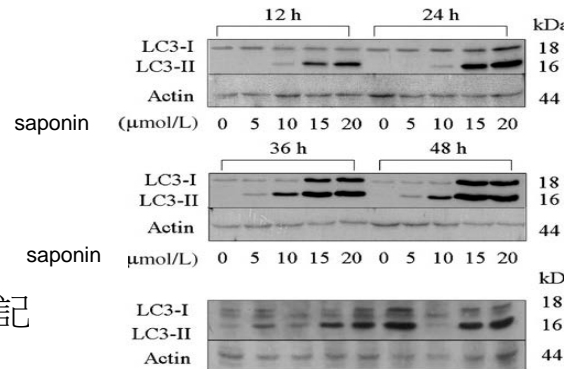
Experimental validation of hypothesis

Saponin modulates autophagy 皂苷促進細胞自噬作用

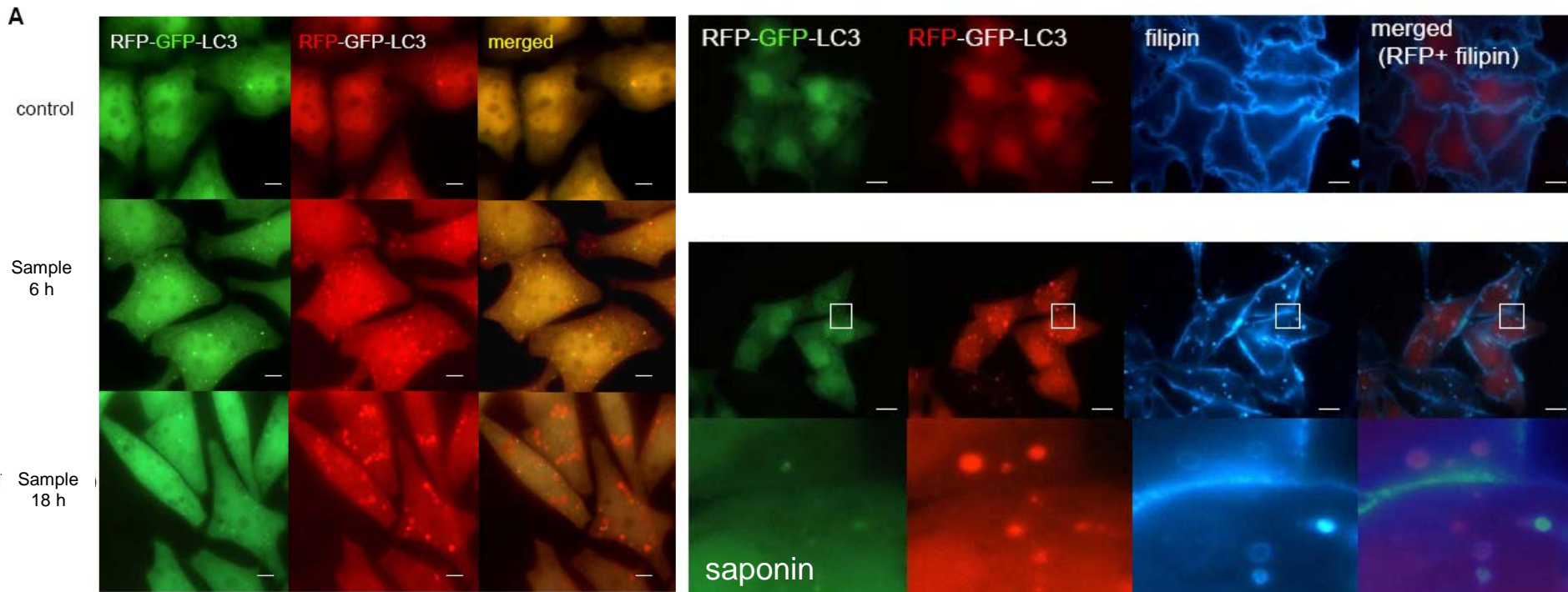
皂苷引起的細胞自噬作用 (利用綠色熒光蛋白和活細胞染色技術研究)



GFP 熒光蛋白標記



Saponin induces LC3-associated autophagic structures 皂苷誘導LC3關聯的自噬性結構

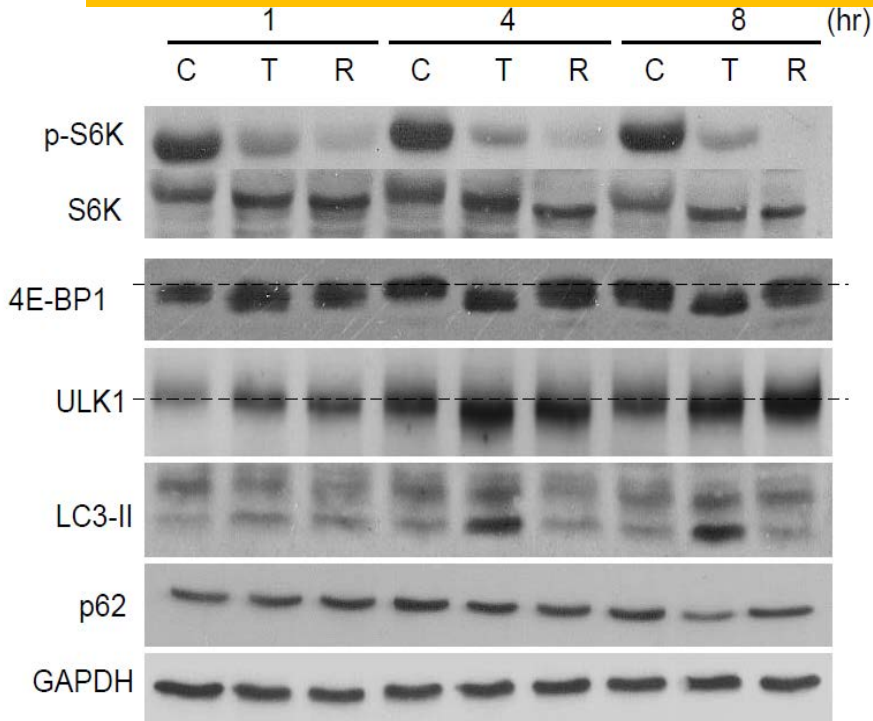


Mechanism of saponin-induced autophagy

皂苷於細胞自噬作用下所誘發的機制

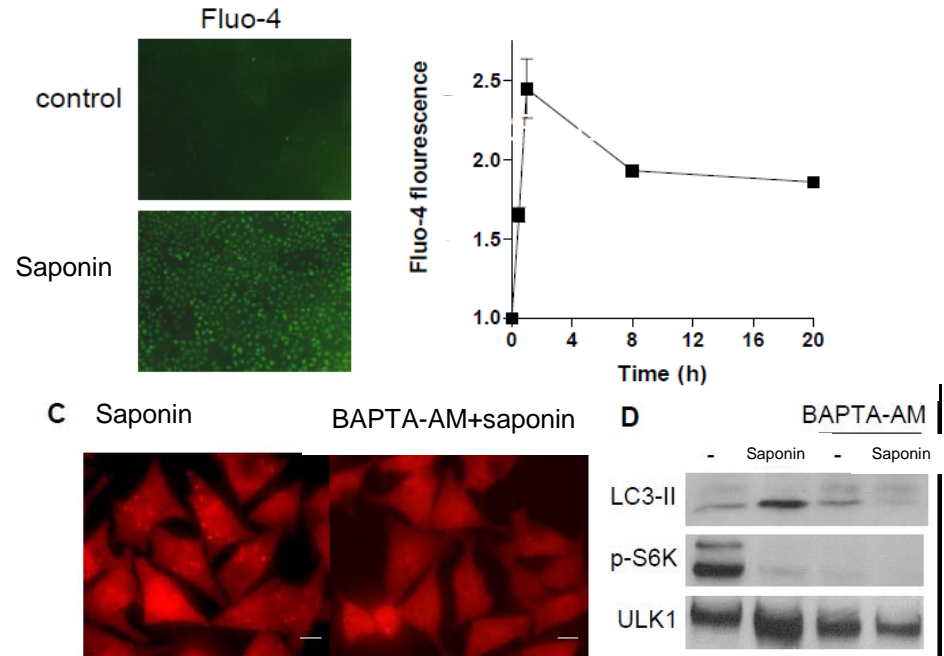
Saponin inhibits mammalian target of rapamycin (mTOR)

皂苷抑制哺乳動物雷帕霉素靶點 (mTOR)



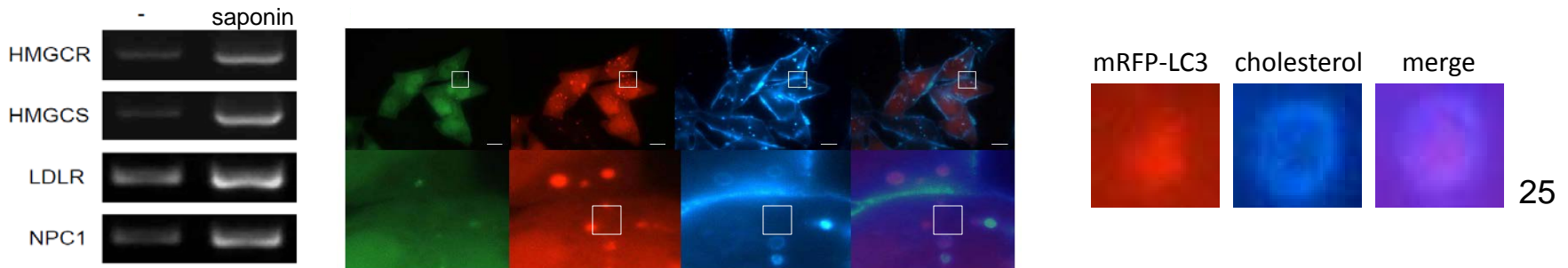
Saponin increases cytosolic free calcium

皂苷增加細胞內的遊離鈣



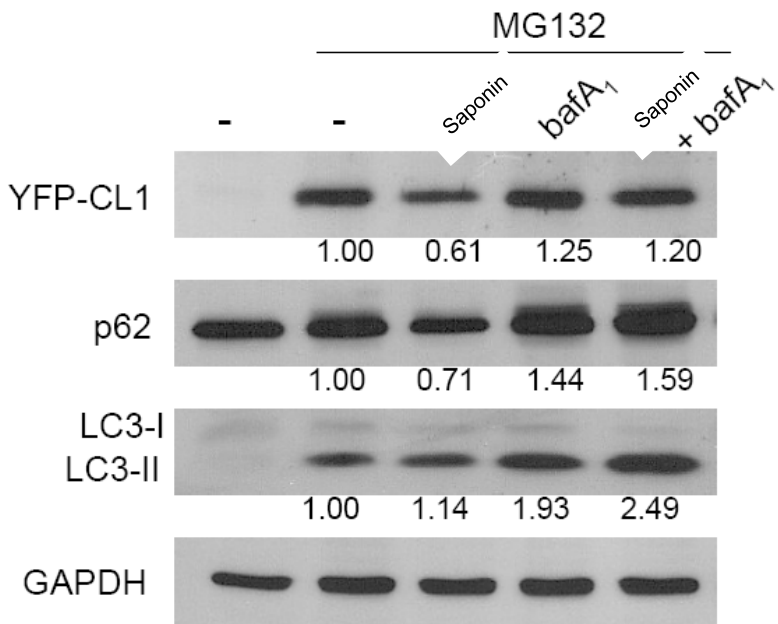
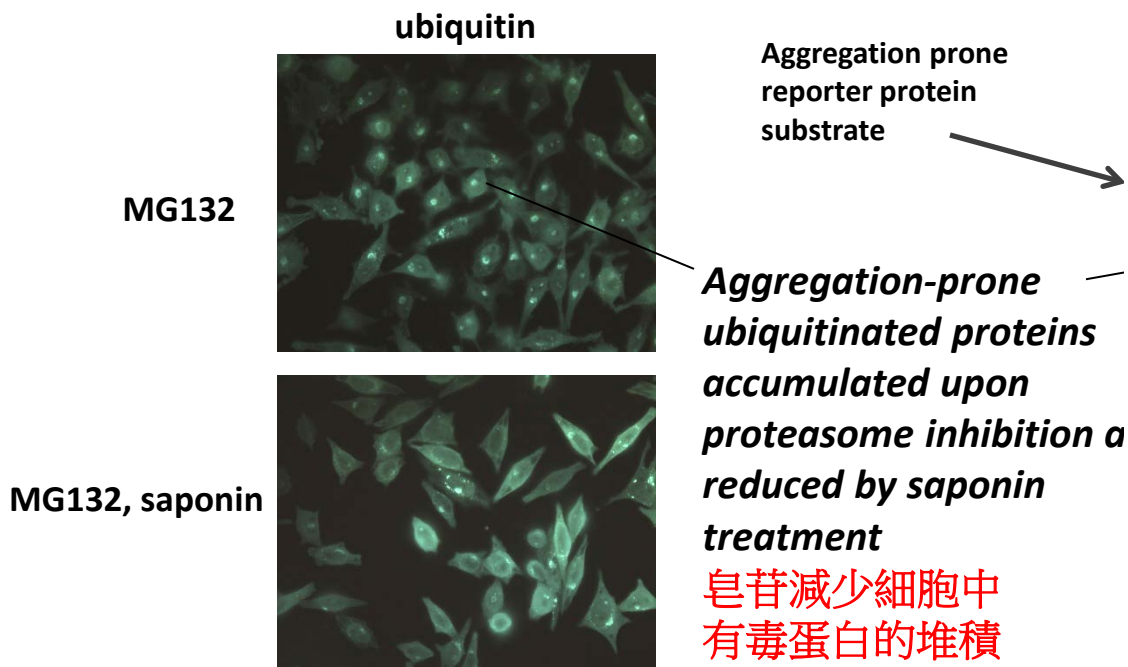
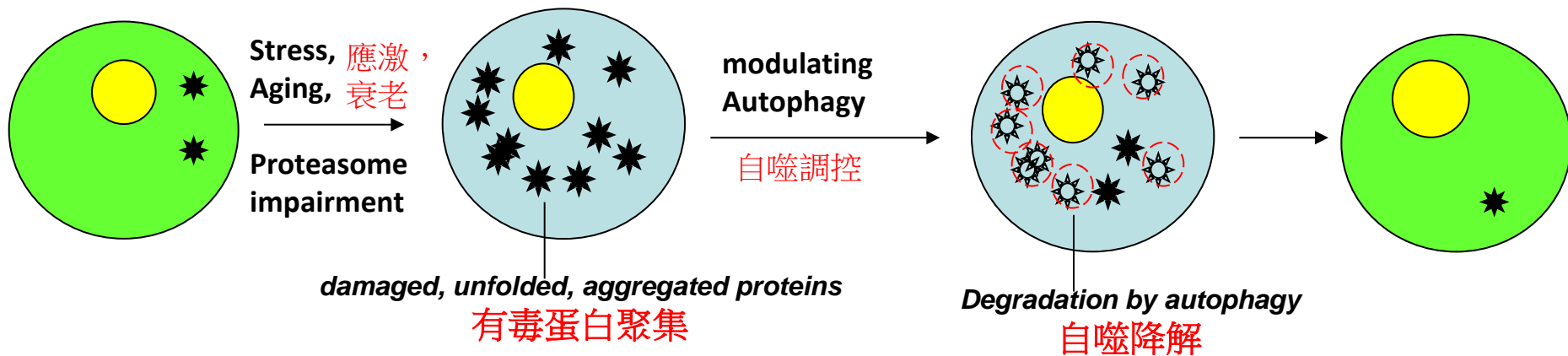
Saponin stimulates synthesis of cholesterol which is incorporated in autophagic membranes

皂苷刺激自噬膜中膽固醇的合成



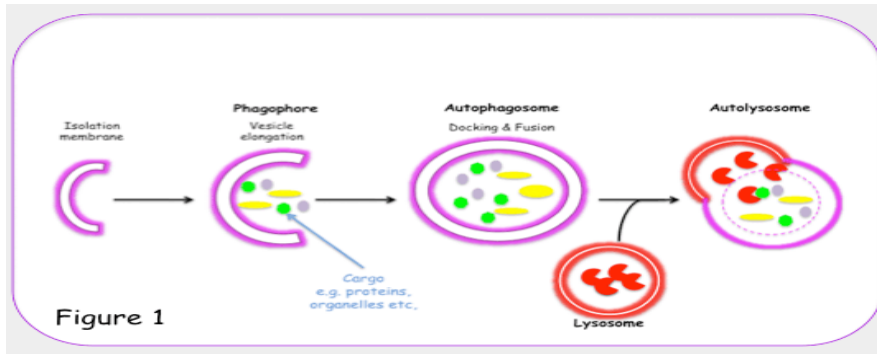
Saponin activates autophagic clearance of disease-associated protein aggregates

皂苷的細胞自噬作用有助於清除蛋白質的聚集



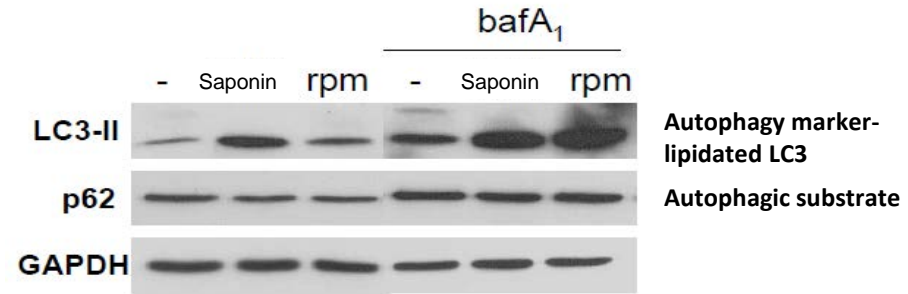
Saponin as an autophagy modulators with potential for treatment of cancer 皂苷之細胞自噬作用具備抗癌性質

Autophagy as a cellular degradation process through lysosome 自噬是通過溶酶體進行的一種細胞降解過程

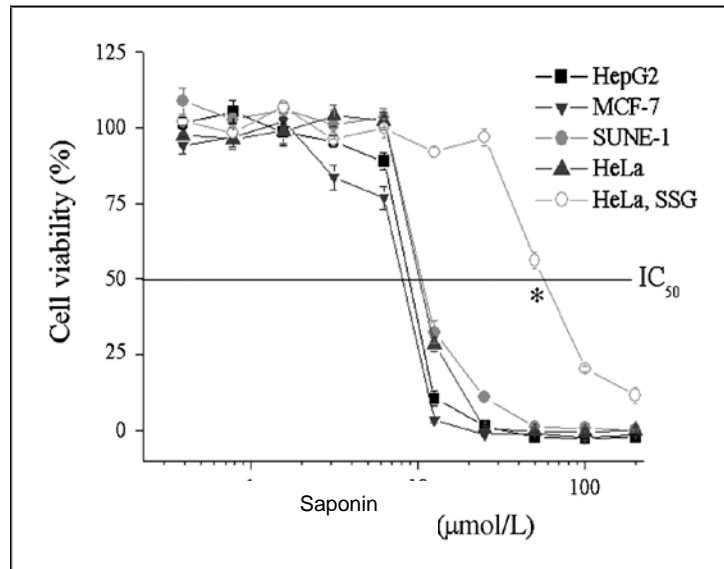


Saponin induces autophagic flux with degradation of specific protein substrate

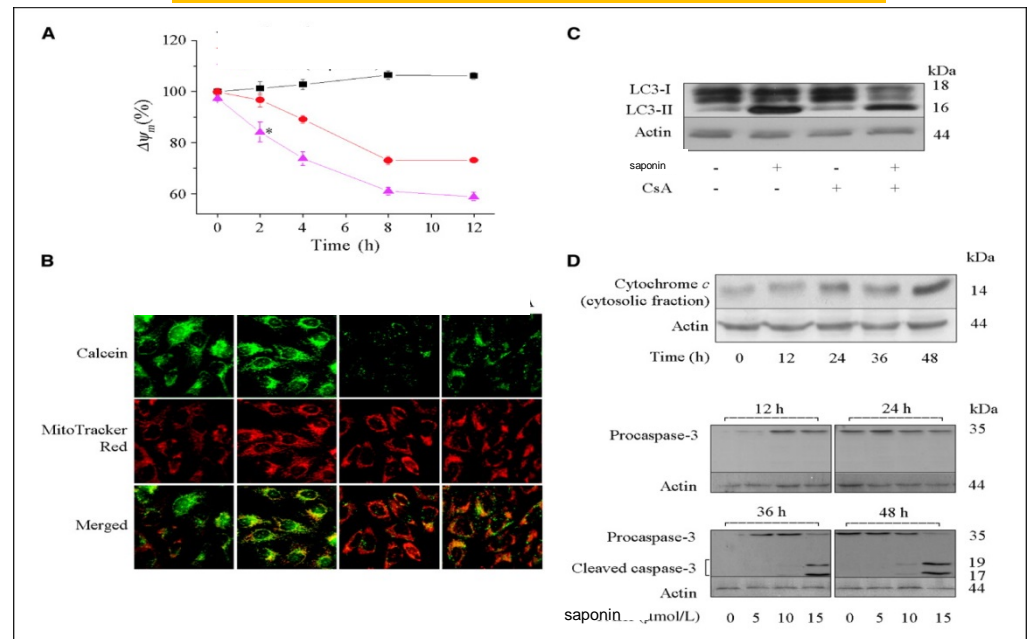
皂苷通過特定蛋白底物的降解來誘導自噬潮



Cytotoxicity 毒性濃度分析

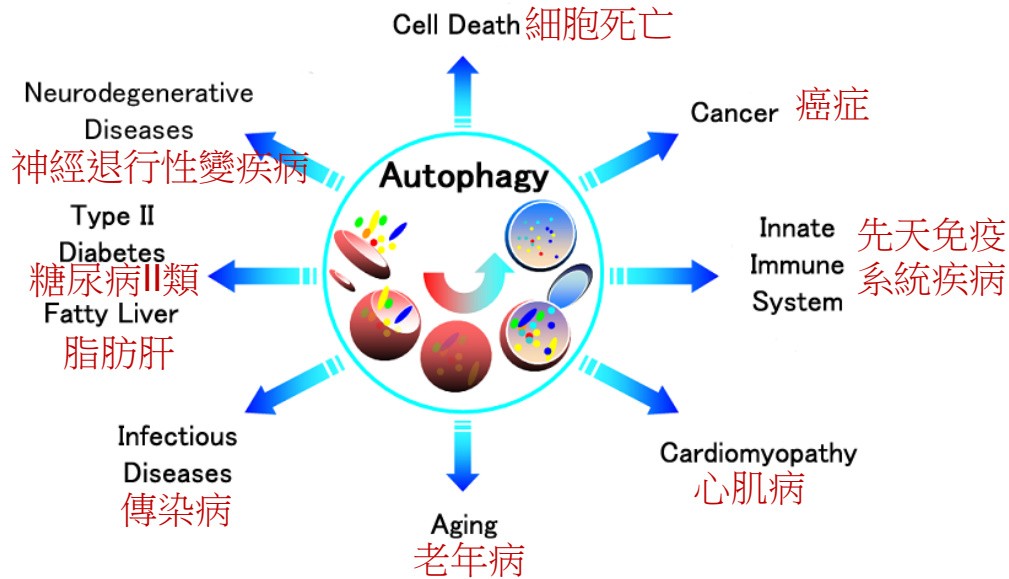


Mechanism of apoptosis 凋亡分子機理



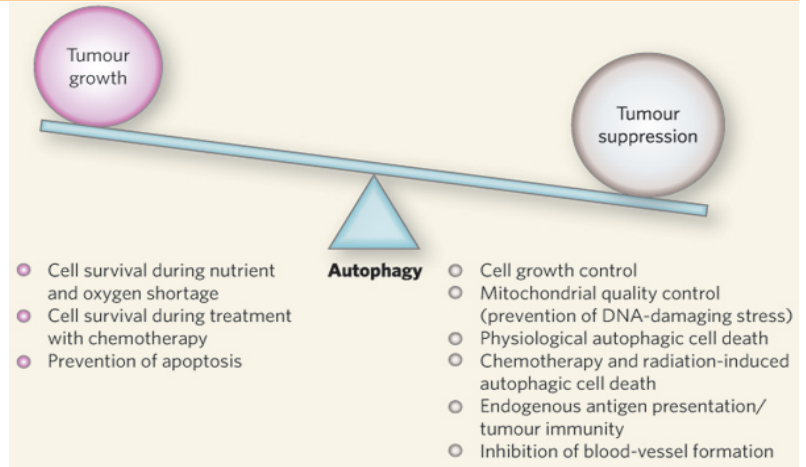
Perspective: The autophagy modulating properties of saponin will be further explored for treatment of autophagy related diseases

展望：皂苷將被開發用於治療與細胞自噬相關的疾病



Autophagy plays a pivotal role in cancer

細胞自噬與癌症息息相關



view > Full Text

Review

Nature **451**, 1069-1075 (28 February 2008) | doi:10.1038/nature06639

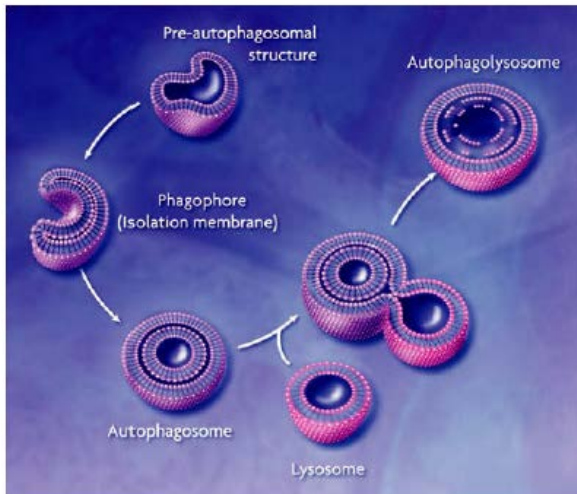
Autophagy fights disease through cellular self-digestion

通過細胞自噬抵抗疾病

Noboru Mizushima¹, Beth Levine², Ana Maria Cuervo³ & Daniel J. Klionsky⁴

▲ Top

Autophagy, or cellular self-digestion, is a cellular pathway involved in protein and organelle degradation, with an astonishing number of connections to human disease and physiology. For example, autophagic dysfunction is associated with cancer, neurodegeneration, microbial infection and ageing. Paradoxically, although autophagy is primarily a protective process for the cell, it can also play a role in cell death. Understanding autophagy may ultimately allow scientists and clinicians to harness this process for the purpose of improving human health.



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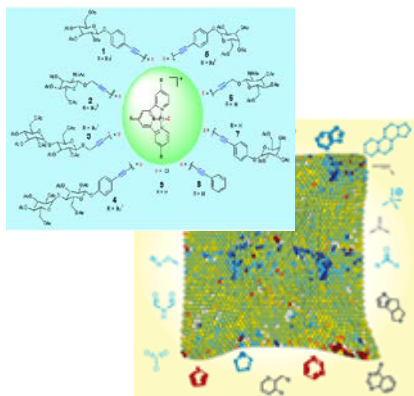
28

Other potential projects

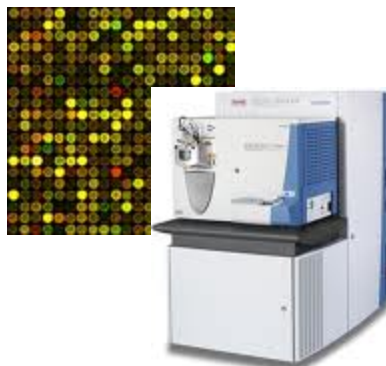
其他具潛力科研項目

5. Chemical genomics/Proteomics platform

化學基因組學/蛋白質組學平台

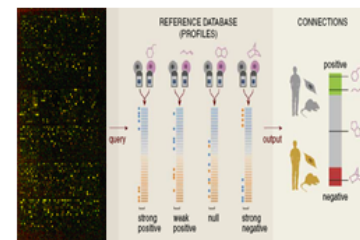


In house
bioactive
chemical libraries
(Organic and natural
compound)

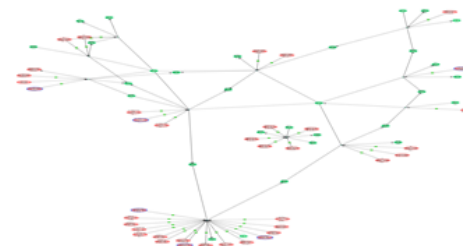


Genomics/
Proteomics/
Bioinformatics

Target Identifications



Mechanistic Studies



Drug Response Predictive Models

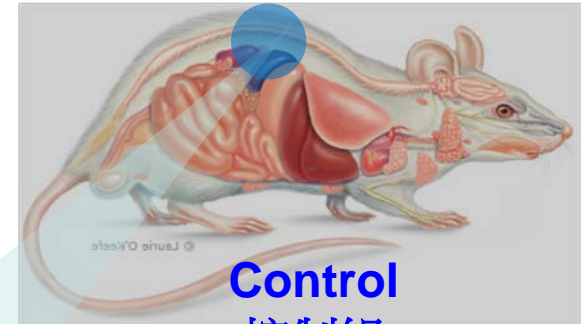
Proteomics, **2008**, 8, 3105; *J. Proteome Res.* **2008**, 7, 2351; *J. Proteome Res.*, **2007**, 6, 4703;
Proteomics, **2007**, 7, 1107; *J. Proteome Res.*, **2006**, 5, 916; *Proteomics*, **2006**, 6, 2422; *Proteomics*,
2006, 6, 1049; *Int. J. Cancer*, **2006**, 118, 1527.

6. Imaging of phytochemicals in mouse kidney tissue

小鼠腎組織中植物化學素影像

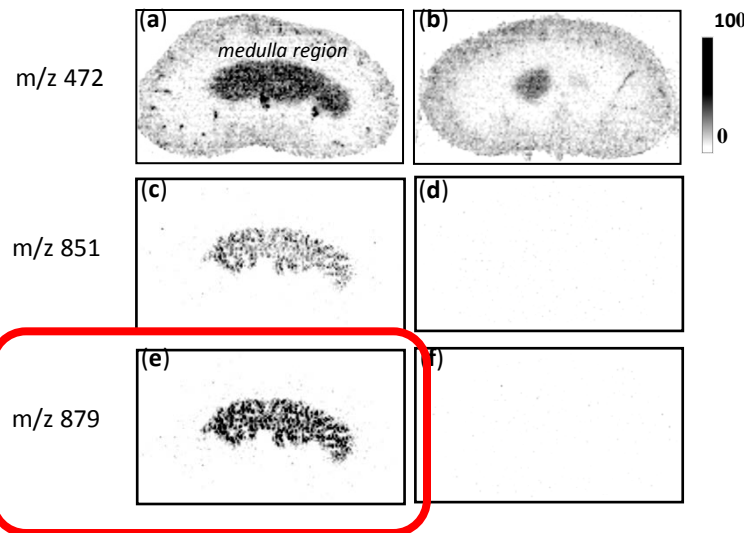
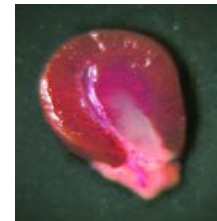
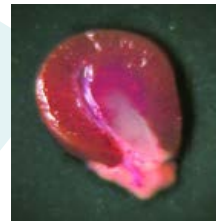


Kidneys 腎



Control
控制組

Treated with a
four-herb Chinese
medicine formula
(甘草、黃芩、白芍、
龍爪棗)



No phytochemical in the control
沒有植物化學素

Phytochemical
detected!!!
有植物化學素

**22β-acetoxyl
glycyrrhizic acid**

A derivative of glycyrrhizic acid.
Glycyrrhizic acid is found in liquorice (甘草)
and has hepatoprotective effect

Major External Fundings Related to Chinese Medicines

與中藥科研相關的主要贊助基金

- ◆ Area of Excellence program on “**The Institute of Molecular Technology for Drug Discovery and Synthesis**” (AoE/P-10/01, **HKD 16,800,000**, Sustained funding awarded in 2007);
- ◆ Special Equipment Grant on “**High-Performance Tandem Mass Spectrometry for Functional Proteomics and Metabolomics**” (HKU02, **HKD 8,600,000**, awarded in 2008);
- ◆ Innovation Technology Fund (Tier III) on “**Therapeutic applications of timosaponins and their synthetic derivatives**” (ITS/149/12, **HKD 975,200** awarded in 2012)
- ◆ Department of Health (HKSAR) Project on “**Hong Kong Chinese Materia Medica Standards**” (**HKD 23,000,000** awarded up to 2013);
- ◆ Innovation Technology Fund (Tier III) on “**Direct Sample Analysis by Mass Spectrometry: Development and Analytical Application of Tip-Spray Ionization MS and Imaging MS**” (ITS/079/11, **HKD 959,100** awarded in 2011);
- ◆ The Hong Kong Jockey Club Charities Trust on “**Research and Development Laboratory for Testing of Chinese Medicines**” (**HK\$ 5.0 million** awarded in 2012 for HKU and HKUST)



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Technology Commission



香港特別行政區政府
衛生署



創新科技署
Innovation and
Technology Commission



香港賽馬會慈善信託基金
The Hong Kong Jockey Club Charities Trust

Selected Chinese medicine-related publications and patents

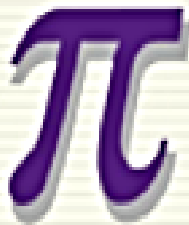
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Acknowledgements 致謝



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The Government of the Hong Kong Special Administrative Region
創新科技署



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