出國報告：（出國類別：考察）

# 出席ＭＵ－ＮＣＣＵ聯合研討會議

服務機關：國立中正大學

姓名職稱：王逢盛教授

派赴國家：泰國

出國日期：2017.07.18 至 2017.07.22

報告日期：2017.08.03

# 出席 MU-NCCU 聯合研討會議心得報告

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| 經費編號 | 00764-01 系統生物學與組織工程研究中心計畫結餘款 |
| 出國人員姓名<br>服務機關及職稱 | 王逢盛，國立中正大學化工系教授 |
| 會議時間地點 | 2017 年 7 月 19 日至 2017 年 7 月 21 日,泰國曼谷 |
| 會議名稱 | 泰國的大學參訪與 Symposium on Biomedical Sciences and Beyond |
| 發表論文題目 | Optimization in Network Medicine |

摘要

本次參訪 MU-NCCU 聯合研討會議的活動，共有三天行程，分別訪問 Chulalongkorn University, Assumption University and Mahidol University 等三所大學的生物科技相關科系，並且討論簽訂合作協議等事宜。除了參訪之外，最後一天並舉行研討會議，報告研究成果。期望未來能夠進行研究整合達成實質跨國合作，而且也能夠加強我們的研究深度與廣度，促進我國的南向政策的推動與合作。

一、目的

本次參訪活動是由化工系李文乾教授召集本校生物醫學系陳永恩教授、地球與環境科學系陳建易教授、資訊工程系黃耀廷副教授、化學工程系蔡敬誠教授與本人，組成六人訪問團參訪泰國 Chulalongkorn University, Assumption University and Mahidol University 等三所大學的生物科技相關科系，並且討論簽訂合作協議等事宜。

二、參訪過程

三天的參訪過程逐日說明如下:

7 月 19 日上午首先參訪 Chulalongkorn University,該大學是泰國排名第一位的學校，我們首先與微生物系進行座談，由李文乾教授與陳建易教授分別介紹本校生物科技教學與研究發展狀況。一小時的座談之後，李文乾教授與 Chulalongkorn University 的科學院院長會談簽訂合作協議等事宜。陳建易教授與微生物系系主任討論合作事項。其他等人則是蔡敬誠教授帶隊參訪該校化學工程系，雙方交換兩系研究相關議題，該化工系在生物科技研究領域較為著重於食品生物科技領域。下午我們則是參訪曼谷科學園區的一家台商興建的哈奇生技公司，該公司的執行董事莊文源先生與副總經理林佑生博士來親自接待。林博士是本系畢業博士生，他親自著手設計與建立此工廠，他詳細介紹整個建廠過程。

7 月 20 日整天參加 Assumption University and National Chung Cheng University 聯合研討會與工作講習活動,主題為 Bioscience and Biotechnology for Promoting Health and Beauty。上午由陳永恩教授報告[Cancers and Drugs Developed from Natural Products for Cancer Therapy]的研究成果，李文乾教授發表[Functional Foods (prebiotics/probiotics) and their Production]的研發報告，另外一篇則是 Assumption University 的教授報告 Microbial Biofilms 的研究成果。下午則是針對學生舉辦兩場工作講習，分別是陳建易教授與黃清江教授開講[Biosurfactant and Application for Personal Care Products]，另一場由 Assumption University 講解 [Thai Herbal Drinks and Functions of Essential

Compounds]。

7 月 21 日上午拜訪 Mahidol University 生物技術系，該校是泰國生命科學相關科系排名最佳的學校。該校理學院院長與相關科系主任與教授座談，介紹他們的研究領域。本校則是由蔡敬誠教授與陳建易教授分別介紹本校理工學院的概況。接著參訪研究室，該校對於蝦子的生物技術極為深入，而且也大力透入藥物開發，並且建立先進自動化篩選設備。下午舉辦[Biomedical Science and Beyond]的研討會，分別由本校五位教授與 Mahidol University 的五位教授報告研究成果。本人報告近年來的成果，其題目為[Optimization in Network Medicine]，摘要與講稿如附件。

三、與會心得及建議

本次參訪是本校南向政策的工作之一，從訪問過程中，了解到日本多年前已經投入相關的研究合作。例如在 Mahidol University 的藥物開發之自動化篩選設備，也投入大量的人力與物力資源。未來我們必須極力加強研究深度與廣度，進行研究整合才能夠達成實質跨國合作。

# 附件
# Optimization in network medicine

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Network medicine is a rapidly emerging field that combines systems biology and network science towards identifying, preventing, and treating diseases. I will present how to apply an optimization method in a metabolic network of hepatocyte toward inferring a novel oncogene. The liver is a vital organ involving in various major metabolic functions in human body. MicroRNA-122 plays an important role in the regulation of liver metabolism, but its intrinsic physiological functions require further clarification. This study integrated the genome-scale metabolic modeling of hepatocytes and mouse experimental data with germline deletion of Mir122a (Mir122a$^{-/-}$) to infer Warburg-like effects. By definition of the similarity ratio, we compared the flux fold change of the genome-scale metabolic model computational results and metabolomics profiling data measured through a liquid-chromatography with mass spectrometer, respectively, for hepatocytes of 2-month-old mice in normal and deficient states. The Ddc gene demonstrated the highest similarity ratio of 95% to the biological hypothesis of the Warburg effect, and similarity of 75% to the experimental observation. We also used 2, 6, and 11 months of mir-122 knockout mice liver cell to examined the expression pattern of DDC in the knockout mice livers to show upregulated profiles of DDC from the data. Furthermore, through a bioinformatics (LINCS program) prediction, BTK inhibitors and withaferin A could downregulate DDC expression, suggesting that such drugs could potentially alter the early events of metabolomics of liver cancer cells.

Keywords: Flux balance analysis; Genome-scale metabolic model; Metabolic reprogramming; Hepatocyte; Mir122a$^{-/-}$ mouse; Metabolomics profiling

# Optimization in Network Medicine

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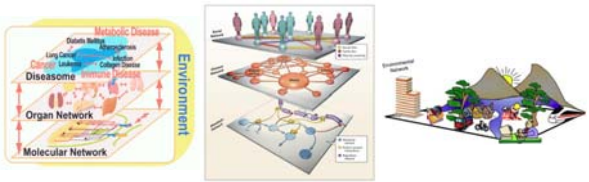
## What is Network Medicine?

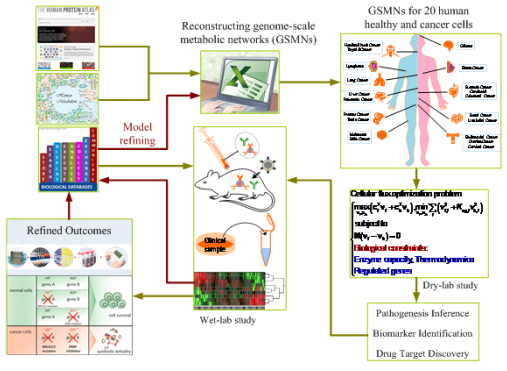
- Network medicine is a rapidly emerging field that combines systems biology and network science towards identifying, preventing, and treating diseases.
- The term network medicine was first introduced in The New England Journal of Medicine in July 2007 by Albert-László Barabási in "Network Medicine - From Obesity to the Diseasome"



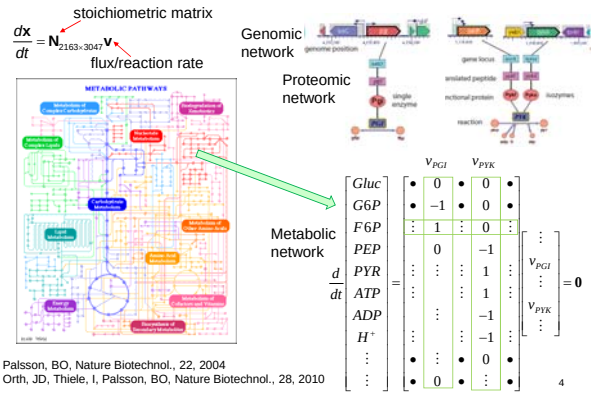

Albert-László Barabási, N Engl J Med 2007; 357:404-407



## Roadmap of studies: Model-based optimization in metabolic networks

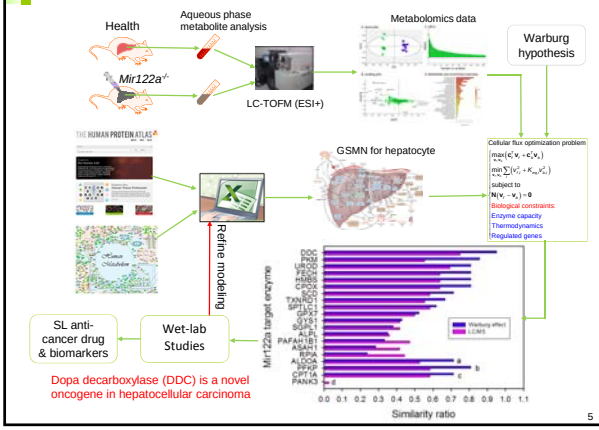



## Flux balance modeling




Palsson, BO, Nature Biotechnol., 22, 2004
Orth, JD, Thiele, I, Palsson, BO, Nature Biotechnol., 28, 2010

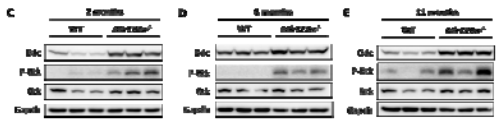
## Flux balance analysis predicts Warburg-like effects of mouse hepatocyte deficient in miR-122a



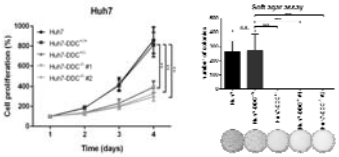

Dopa decarboxylase (DDC) is a novel oncogene in hepatocellular carcinoma



## DDC overexpression in hepatocellular carcinoma (HCC)



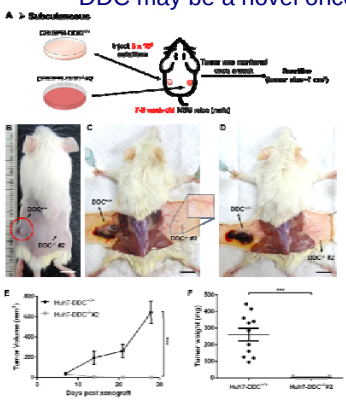

*Mir122a*$^{-/-}$ mice induced DDC overexpression in hepatocyte that agreed with the computation DDC, P-BTK, and BTK were upregulated in liver tissues from mir-122 knockout mice.




By using CRISPR/Cas9 system to knockout DDC in Huh7 cells, we shown that Huh7-DDC$^{-/-}$ decreased growth rate and reduced ability for growing



## DDC may be a novel oncogene in HCC

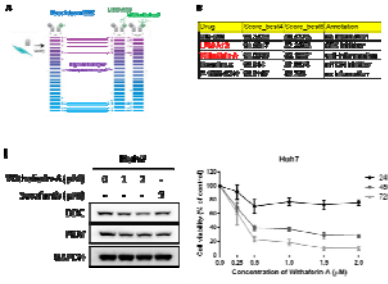



Huh7-DDC$^{+/+}$ cells and Huh7-DDC$^{-/-}$ cells were injected subcutaneously in the left and right flanks of male NSG, respectively

Until day 11, blood vessels grow into tumor in left flank and growth rate was faster than Huh7-DDC$^{-/-}$ cells

The tumor volume and tumor weight of Huh7-DDC$^{+/+}$ cells were much higher than Huh7-DDC$^{-/-}$ cells.

## Old drug for new use

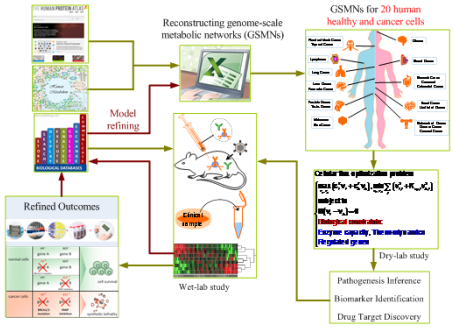



Using LINCS, we found BTK inhibitor and withaferin-A were identified as potential drugs

The old drug, withaferin-A, can reduce the protein level of DDC and inhibit the growth of HCC cells.

## Summary: Precision medicine

This iterative procedure is to integrate dry-lab and wet-lab to build a protocol as artificial intelligent for assisting to find a novel oncogene and to discover old drugs for new use.




## GSMNs for 20 healthy and cancer cells

| Tissue | Cell-type | Health cell #(genes, metabolites, reactions) | Cancer cell #(genes, metabolites, reactions) |
|---|---|---|---|
| Breast | Myoepithelial Cell | ( 939 , 1667 , 2548 ) | ( 1227 , 2476 , 4106 ) |
| Small Intestine | Glandular Cell | ( 1185 , 2242 , 3614 ) | ( 1196 , 2311 , 3827 ) |
| Uterine Cervix | Squamous Epithelial Cell | ( 943 , 1632 , 2491 ) | ( 1178 , 2118 , 3580 ) |
| Rectum | Glandular Cell | ( 1168 , 2046 , 3161 ) | ( 1267 , 2515 , 4188 ) |
| Endometrium | Endometrial Stroma Cell | ( 805 , 1271 , 1867 ) | ( 1220 , 2298 , 3879 ) |
| Cerebral Cortex | Glial Cell | ( 916 , 1459 , 2233 ) | ( 1093 , 2153 , 3458 ) |
| Oral Mucosa | Squamous Epithelial Cell | ( 1006 , 1761 , 2706 ) | ( 1249 , 2486 , 4070 ) |
| Liver | Hepatocyte | ( 1180 , 2329 , 3803 ) | ( 1216 , 2380 , 3921 ) |
| Lung | Pneumocyte | ( 902 , 1510 , 2164 ) | ( 1164 , 2183 , 3626 ) |
| Lymph Node | Germinal Center Cell | ( 971 , 1511 , 2178 ) | ( 1063 , 2076 , 3341 ) |
| Skin | Melanocyte | ( 1006 , 1641 , 2473 ) | ( 1230 , 2367 , 3980 ) |
| Ovary | Ovarian Stroma Cell | ( 829 , 1372 , 1998 ) | ( 1234 , 2466 , 4043 ) |
| Pancreas | Islets of Langerhans | ( 1016 , 1745 , 2671 ) | ( 1230 , 2498 , 4155 ) |
| Prostate | Glandular Cell | ( 1061 , 1853 , 2933 ) | ( 1167 , 2451 , 4043 ) |
| Kidney | Glomeruli Cell | ( 833 , 1342 , 1979 ) | ( 1105 , 2035 , 3367 ) |
| Skin | Epidermal Cell | ( 1059 , 1733 , 2638 ) | ( 1172 , 2093 , 3439 ) |
| Stomach | Glandular Cell | ( 1080 , 2051 , 3200 ) | ( 1195 , 2383 , 3896 ) |
| Testis | Leydig Cell | ( 1136 , 1984 , 3023 ) | ( 1241 , 2328 , 3776 ) |
| Thyroid Gland | Glandular Cell | ( 1031 , 1859 , 2883 ) | ( 1204 , 2347 , 4160 ) |
| Urinary Bladder | Urothelial Cell | ( 1101 , 1905 , 3028 ) | ( 1265 , 2342 , 3857 ) |

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*Mir122a*$^{-/-}$ mice

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Synthetic Lethality and Drug Combination

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Thank for your attention!