出國報告（出國類別：參訪）

美國國際醫療管理服務與醫藥衛生科技研究發展參訪

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摘　要

臺灣醫療品質佳，且價格低廉，以全球第 29 位的醫療成本，達到全球第 2 名的醫療品質，臺灣醫療管理服務系統已進入可輸出至國際市場的成熟期，並爲本部施政推動重點。爲調查與評估國際知名醫療管理服務的內容與特色，故赴美國舊金山史丹福大學醫學中心國際醫療服務部(Stanford Hospital & Clinics International Medical Services)參訪。該部致力於爲國際患者和家屬提供最優質的醫療護理和支持服務，確保患者在史丹福醫院及診所和帕卡德(Lucile Packard)兒童醫院獲得愉快的就診體驗，提供病房寵物詢房、100 多種語言翻譯、音樂等人性化服務。每年世界各地的患者紛紛到史丹福和帕卡德醫院受益於當今世界上最先進的醫療技術，可以做爲我國推動醫療管理服務的參考。另，本部每年投入約 40 多億元在醫藥衛生科技研究，用以建構優質衛生科技政策、強化生命科學技術研究，推動生醫科技產業、推廣衛生科技服務，提升研發應用量能。如何有效運用科技經費投入最優先的科技研究議題，一直爲本部科技計畫管理的重點。本次拜訪美國知名大學/癌症中心藥物、流行病學、基因、病理等領域國際學者，學習很多國際最新醫藥衛生發展趨勢，特別是美國癌症研究一些新的研究議題與想法，可作爲本部科技研究議題規劃參考。

目　次

壹、計畫緣起

美國國際醫療管理服務

醫療管理服務是健康照護系統(healthcare)相當重要之一環，爲求有效率的提升使用者的滿意度，醫療管理服務常藉由 ICT 技術導入，因此產品本身主要由 knowledge 與 ICT 系統組成，ICT 系統爲主要的實體，除此之外，還包含「服務」元素，例如教育訓練，其產品之利潤與取代性有別於其他一般資訊產品，容易有 know-how 保障的永續型產品。醫療管理服務之輸出又可分爲系統輸出、醫院輸出、人對人的健康輸出，以及國家對國家層級的醫管輸出。經由醫療管理服務之輸出，可帶動相關設備、藥品、醫療器材產品輸出，進而創造跨領域產業的產值。

各項數據皆顯示全球健康照護產業相關市場快速成長，其中產值最高的部分爲透過 IT 資訊系統提供病人管理服務，依據 RNCOS 機構之調查顯示，美國 healthcare IT 市場於 2011 年底產值竄升至 400 億美元，並預測自 2012 年~2014 年間複合成長率(Compound Annual Growth Rate, CAGR)將高達 24%；至於全球市場部分，依據 Markets and Markets 機構調查顯示，全球 Healthcare IT 規模於 2010 年達 996 億美元，估計 2015 年產值將達 1622 億美元，2010 年~2015 年間複合成長率約 10.2%。全球 healthcare IT 規模迅速成長的主因在於高齡人口增加與生活型態改變所帶來的龐大醫療照護需求。

中國大陸自 2000 年起，醫院資訊化迅速發展，至 2011 年中國大陸醫療 IT 市場規模爲 165 億元，較 2010 年成長 30.3%；其中醫療解決方案市場規模爲 32.1 億元，較 2010 年成長 26.3%。中國大陸醫療資訊化發展迅速的主要原因在於中國政府的支持，2009 年實施的新醫改方案再加上上百億的投資爲醫療資訊化的推進提供了一劑強心劑。目前中國大陸醫療行業每年投入 IT 的規模約占醫院年收入的 0.3%~0.5%，而已開發國家則達到 3%~5%的水準，因此，未來中國大陸醫療資訊化的發展空間廣闊。特別 2012 年 3 月「 “十二五” 期間深化醫藥衛生體制改革規劃暨實施方

案」的頒佈，預計 2010 年~2015 年期間將進一步加大醫療資訊化的投資，到 2015 年將逐步建構完成覆蓋城鄉基層醫療衛生機構的資訊系統，醫療資訊化市場規模也將進一步擴大。

綜上，全球人口結構變化及中國大陸現今面臨的醫療問題，提供台灣醫療管理服務輸出至國際市場之契機。特別中國大陸市場，台灣有許多可切入的機會，這些機會包括醫院管理方式革新、醫療品質標準再提高、公辦民營的導入與試點、醫療費用結構大幅修改、醫療保險制度探討與商機、醫病關係協和化與商機、社區基層門診(OPD)醫療制度的建立、醫療設備 IT 系統的垂直整合及設備/材料/藥品的供應，尤以同文同種，無文化上的障礙，更提供台灣業者進入大陸市場極佳的優勢競爭利基。

台灣醫療品質佳，且價格低廉，以全球第 29 位的醫療成本(OECD2008 年報 NHE/GDP)達到全球第 2 名的醫療品質(The Economist2000 Q2)，這是善用資訊管理工具，完成以病人安全爲中心的醫療服務。台灣醫療管理服務系統已進入可輸出至國際市場的成熟期，特別中國大陸市場，因爲醫療改革政策所帶來的醫療需求極爲殷切，提供台灣醫管及資訊產業極大發展空間，但是由於產品的取代風險極高，必須掌握先機快速整隊，開發能將核心價值根留台灣之商業模式，並牽引帶動整體包括生技、製藥、及醫材產業加值模式，成爲大陸市場的 First Mover，方有建立臺灣醫療管理服務產業優勢品牌的機會。

醫藥衛生科技研究發展

18 世紀工業革命開始，推動國家經濟發展的生產要素爲原始的土地、勞力、資本，隨著上個世紀末新經濟時代的悄然來臨，土地、勞力、資本等這些「舊經濟時代」的生產要素，已漸漸被專利、核心技術、核心競爭能力、人力素質等新的生產要素取代。企業競爭講求創新、核心技術、人才，政府政策制定講求以實證科學證據爲基礎。 而創新、核心技術、政策擬定所需實證證據的產生來自有效的科技研究經費的投入，故科技研究的規劃與管理成爲政府政策制定、產業推動及企業發展所重視的議題。

本部每年投入約 40 多億元在醫藥衛生科技研究，用以建構優質衛生科技政策、強化生命科學技術研究，推動生醫科技產業、推廣衛生科技服務，提升研發應用量能。基於好的研究是因爲有好的問題，如何選擇最迫切需要的研究議題，將科技經費有效投入該研究議題，並將研究成果有效率地轉化爲國家政策或經濟成長的動力以改善民眾的生活品質，成爲近年備受關注的焦點，尤其是近年來在經濟不景氣與赤字預算下，科技發展背負更多國民的期望。爲規劃上述研究內容，特別是美國癌症研究的規劃與研究趨勢，故安排本次出國。

貳、參訪目的

醫療管理服務產業除有加值輸出潛力，亦蘊涵人道關懷精神，更是知識與經濟累積的知識型經濟典範。台灣醫療管理品質效率高且具國際競爭力，結合醫療資訊，在總體醫藥生技產業發展策略中，可擔任領頭羊的角色，帶動後續藥品、醫材產業之發展。由於台灣的優質醫療技術、服務管理、資訊等相關可推展產業化的領域廣泛，但許多並非以商業型態存在或者僅爲醫療機構體系之一環、或者爲管理者 know-how 等，尚難形成產業化的要件。故需就市場需求分析及供應鏈運作評估，先訂立目標市場所需求之輸出服務及產品範疇、與供應型態。爲調查與評估國際知名醫療管理服務輸出的內容與特色，作爲本部醫管輸出服務的規劃參考，故赴美國舊金山參訪以國際醫療服務著稱的史丹福大學國際醫療服務部。

美國爲國際上科學、技術研究，以及技術創新最領先的國家之一，特別是在生物和醫學領域，有最多一流的研究機構及大學及贏得諾貝爾獎的學者，如 Johns Hopkins 大學、Anderson Cancer Center、加州大學、美國國家衛生研究院(National Institutes of Health, NIH)等。美國 NIH 每年研究預算高達 300 多億元美金，迄今所補助之研究計畫中計有 130 位獲得諾貝爾獎。並已完成人類基因組計畫，使人類對腫瘤、阿茲海默病等疾病的治癒研究進入重要階段。充分彰顯美國在生物和醫學領域的領先、創新及豐富的人才。此次的目的在拜訪美國一流大學或癌症研究機構藥物、流行病學、基因、病理等領域專家，以了解國際最新醫藥衛生科技發展趨勢，特別是癌症研究，作爲本部科技研究議題規劃的參考。

參、參訪過程

一、美國史丹福大學醫學中心國際醫療服務部門 (Stanford Hospital & Clinics International Medical Services)

史丹福大學醫學中心為世界著名醫學中心，設有國際醫療服務部提供來自世界各國人士的國際醫療服務。為推動國際醫療服務，對於世界各國到該院就醫人士，在身處異地，尤其是身體面臨問題時，病患與醫院是否能順暢的溝通、病患在醫院感覺是否安心舒適是很重要的議題。該院設有專責翻譯單位及人員，提供病患就醫期間所有醫療、生活所需翻譯服務(含手語翻譯)，提供高達 100 種語言的翻譯服務。醫療團隊擁有多語言和多文化的背景，精通 20 種語言，了解世界各地患者就診時不同文化上的差異。另外，國際醫療服務部網站提供不同的文字說明(包括繁體中文、簡體中文)，對於就醫行程安排、醫師、醫療訊息、病患所需治療及醫療費用預估等竭盡所能提供一切服務。

為提供病患舒適環境，降低病患的不安(1)對於喜歡寵物的病患，安排有貓、狗、兔子的巡房服務(2)提供音樂光碟、現場音樂會到病房(3)提供病患及家屬醫院導覽(4)提供禱告與祝福(Prayers and blessings)、傾聽(listening、A calm presence)等精神服務(spiritual services)(5)設有病患代表(patients represents)協調或解決病患或家屬對醫療照護上的問題或疑慮。當然，能讓世界各國人士紛紛到史丹福醫院及診所和帕卡德(Lucile Packard)兒童醫院接受醫療服務，他們所提供的高品質醫療保健服務也是重要因素。該院提供全方位的醫療專科服務，特別是在罕見、複雜或困難的心血管疾病、癌症治療、神經疾病、骨科疾病及器官移植在世界享有盛名。

在參訪史丹福大學醫學中心國際醫療服務部後，深刻體會該院國際醫療服務之所以世界有名，除需具備卓越的醫療水準外，以病人為中心、人性化的照護服務模式，對於國際醫療服務提供人性化之協助，令

人印象深刻，值得我們學習及參考。

二、國際醫藥衛生發展

本次是藉由國際醫藥衛生專家聚集在美國舊金山 San Francisco Airport Marriott Waterfront 進行癌症計畫審查會議機會，進行拜訪。拜訪來自耶魯大學、匹茲堡大學癌症學院(cancer institute)、加州大學、約翰霍普金斯醫學院、杜克大學(Duke University)、德州大學安德生癌症中心(Anderson Cancer Center)的 12 位藥物、流行病學、基因、病理領域頂尖的學者專家(附件一)。

癌症為世界各國所亟需解決的醫藥衛生議題，並已連續 30 年以上為我國十大死因的首位，約占死亡人數的百分之二十八。癌症雖為美國十大死因之第二位，僅次於心臟病，但因美國亞裔體質與飲食習慣與美國白人、黑人不同，亞裔的首項死因為癌症，比例為百分之二十六點八，與我國相似。

為有效解決癌症問題，美國 1937 年立法通過國家癌症法(The National Cancer Act)，並依據該法於美國國家衛生研究院(National Institutes of Health, NIH)下面成立專責的癌症研究機構國家癌症研究所(National Cancer Institute)，統籌美國國家癌症研究經費運用，用以支持癌症預防、診斷、治療、照護相關基礎及癌症轉譯研究、訓練、健康資訊宣導、國家癌症中心網絡及負責將最先進科技導入癌症治療。經過美國政府及民間研究機構大量投入癌症研究與治療，美國大部分的一般癌症死亡率已明顯下降。

美國國家癌症研究所 2012 年預算約 58 億美金(約台幣 1740 億元)，各種癌症投入的研究經費，從依序由高而低，前 10 名分別為乳癌、肺癌、前列腺癌、大腸直腸癌、血癌、腦癌、皮膚癌、淋巴癌(Non Hodgkins Lymphoma)、卵巢癌、胰臟癌。乳癌研究不僅投入最多研究經費，其研究經費(約 6 億美金)約為第二名肺癌研究經費(約 3.1 億美金)的 2 倍，顯見乳癌為美國所重視的研究議題。而占我國癌症重要死因的肝癌，美國的投入經費則排在第 12 位，約 6500 萬美金。考量不同的癌症其實是有共同的特

點，另外，各種癌症研究的突破，常常是受其他癌症進展的影響。同時歷史告訴我們，癌症研究有最大突破的地方很難預測，而且常常來自於我們沒有想到的地方。故美國經費投入不會完全集中在死亡率高或者公共衛生負擔最重的癌症。各癌症的投入經費，除考量該癌症所造成的死亡人數或公共衛生負擔，同時會考量該癌症在美國所擁有的研究人才、所提計畫的多寡及是否有研究機會，綜合以上因素做預算分配的平衡考量。在癌症研究議題的產生，除透過所建立的多個外部委員會討論新的癌症計畫及哪些癌症研究障礙需克服。基於好的研究是因爲有好的問題，近兩年更試驗性的透過大量召開專題討論會(workshop)的方式、成立新的諮詢團體、設立互動網站等方式，廣徵的重要的癌症議題，就是希望從不同的癌症研究專家及臨床人員找出研究機會(research opportunities)。如國家癌症中心最近所提出 20 個癌症重要問題(Provocative Questions http://provocativequestions.nci.nih.gov/?cid=WTq_cgov)，將重要癌症研究問題分爲癌症預防及風險(Cancer Prevention and Risk)、腫瘤發展及復發機制(Mechanisms of Tumor Development or Recurrence)、腫瘤偵測、診斷及預後(Tumor Detection, Diagnosis, and Prognosis)、癌症治療與結果(Cancer Therapy and Outcomes)、臨床治療有效性(Clinical Effectiveness)5 個類別，最重要需要回答的問題。在研究方向上，美國最新的癌症研究方向之一爲精確的醫療(precision medicine)，隨著人類對癌症基因了解，某些癌症的治療已經可更精準的依據基因分類，採用不同的治療方式使病情獲得改善。因此癌症基因體的研究將持續成爲發展重點，並投入經費新成立基因體中心。除癌症基因的資訊之外還有更多與疾病有關的病人臨床治療資料可以用來協助對癌症做更精細的分類，最新的研究趨勢就是整合病患疾病有關的資料，用以將癌症做更細的分類，使得治療更精準，但因涉及病人個人醫療資料及美國隱私相關法規，如何在保護民眾健康及個人隱私衡平思考，尚在討論。另，美國已了解，癌症爲全球性公共衛生問題，必須有賴全球的合作，才能解決癌症問題，故投入經費新成立癌症的全球健康中心

(Center for Global Health)。本次拜訪學習到很多美國在癌症防治的作法，包括癌症研究議題規劃、經費分配及最新研究方向，將供本部後續科技計畫規劃之參考。

肆、心得及建議

本次參訪美國史丹福大學醫學中心國際醫療服務部，目的在了解國際知名醫療管理服務的內容與特色。在參訪後，深刻體會該院國際醫療服務之所以世界有名，除需具備卓越的醫療水準外，以病人爲中心、人性化的照護服務模式，值得我們學習及參考。在美國醫藥衛生科技研究發展，特別是癌症研究方面，了解到美國癌症研究最新的研究方向及研究議題產生的方式。

相關政策建議如下：

一、以病人爲中心、人性化的整合照護模式：醫療管理服務爲求有效率的提升使用者的滿意度常藉由 ICT 技術導入，因此醫療管理服務本身主要由 knowledge 與 ICT 系統組成。醫療管理 ICT 系統，產品的取代風險極高，因此必需與醫院管理的 Know-how 結合，才能形成不易被取代之核心競爭力。Know-how 除醫療管理效率方面，建議加入以病人爲中心、人性化的整合照護模式，以建構我國醫院管理服務的特色。

二、研究資源聚焦及整合：美國由於研究資源豐富，單單美國癌症研究院 1 年在癌症的研究經費即爲本部全部醫藥衛生研究經費的 40 倍，爲有效運用有限的癌症資源，建議必須聚焦在我國特有、發生率高的癌症，並進行研究團隊間的研究整合與資源共享。

三、加強國家衛生研究院癌症研究所在推動我國癌症研究整合的角色：美國針對癌症研究有癌症防治法的立法，並依據該法成立國家癌症中心，統籌推動美國癌症研究之整合、合作，成效良好。我國也有癌症防治法的立法，該法第十條並訂定「財團法人國家衛生研究院應設癌症研究中心，辦理並整合與癌症有關之各項研究與治療方法、診斷技術、治療藥品等之開發及臨床試驗」。雖然癌症研究中心尚在籌設，

但該院設有癌症研究所，建議可以先加強該所在推動我國癌症研究整合的角色。

四、推動癌症研究國際合作：癌症爲各國重要的公共衛生議題，在我國經費有限的情況下，無法全面性的投入所有的癌症研究，必須透過國際合作分享各國最新的癌症研究，本部第二期癌症研究建議將國際合作納入。

附錄

拜訪醫藥衛生專家名單

Name	Affiliation
鄭永齊院士 Dr. Yung-Chi Cheng	Department of Pharmacology, Yale University
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許 田教授 Dr. Tian Xu	Department of Genetics, School of Medicine, Yale University
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2012年美國國家癌症中心各類癌症投入經費(美元)	
癌症	補助研究經費
乳癌 Breast	$602,728,719
肺癌 Lung	$314,637,661
前列腺癌 Prostate	$265,094,495
大腸直腸癌 Colon/Rectum	$256,254,674
血癌 Leukemia	$234,716,347
腦癌 Brain	$171,301,440
皮膚癌 Melanoma	$121,196,691
淋巴癌 Non Hodgkins Lymphoma	$119,470,587
卵巢癌 Ovarian Cancer	$111,657,265
胰臟癌 Pancreas	$105,352,789
Cervical Cancer	$72,605,018
Liver Cancer	$64,559,887
Sarcoma	$61,782,836
Multiple Myeloma	$61,283,378
Childhood Leukemia	$58,518,582
Kidney Disease	$51,591,343
Kidney Cancer	$48,981,221
Nervous System	$33,635,126
Esophagus	$28,008,197
Neuroblastoma	$27,138,562
Bladder	$23,381,263
Kaposi Sarcoma	$22,913,474
Uterine	$19,097,333
Urinary System	$17,920,625
Thyroid	$16,481,879
Hodgkins disease	$15,632,170
Buccal Cavity	$14,081,930

Stomach	$12,112,873
Vascular Disease	$8,696,035
Central Nervous System - Not Including Brain	$6,167,563
Testes	$5,830,232
Pharynx	$4,176,242
Anus	$3,569,377
Eye	$3,165,206
Wilm's Tumor	$2,991,535
Penis	$2,712,842
Heart	$2,239,837
Vaginal	$1,019,544
Pituitary	$695,788
Larynx	$688,490
Gallbladder	$636,444
Salivary Glands	$588,711
Parathyroid	$221,866
總計	$2,995,536,077

美國國家癌症中心提出重要的癌症問題

2011 RFA Links and Provocative Questions Search RFA Questions Search

NIH Funding Announcement (RFA-CA-11-012)NIH Funding Announcement (RFA-CA-11-011)

RFA Provocative Questions (PQs)

The Provocative Questions (PQ) numbers assigned are completely random and do not reflect any priority or rank order.

PQs can also be searched in three different ways:

1. By scrolling through the list of PQs below.
2. By clicking on one of the oval topic buttons below. Questions are assigned to multiple relevant categories. **Note: the categories are designed to simplify searching and do not reflect any priority or grouping of PQs for review or funding purposes.**
3. By keyword searching in the search field provided on the top right.

The full RFA documents can be viewed by clicking on the relevant "NIH Funding Announcement" buttons to the top right.

- Risk
- Prevention
- Tumor Development
- Detection
- Diagnosis
- Treatment

RFA Questions

PQ - 1

How does obesity contribute to cancer risk?

Background: While many studies have documented an increased risk of cancer incidence and mortality in individuals who are obese, the mechanisms that underlie this risk remain poorly understood. What molecular changes induced by obesity actually promote cancer development? Can we describe these changes in ways that will allow a mechanistic link between risk and cancer cell biology? Are the risks reversible as some data suggest (R) and, if so, by what mechanism?

Feasibility: Recent studies of the endocrinology of eating disorders, the metabolic correlates of fat accumulation, the pathogenic consequences of obesity (such as diabetes mellitus), and the development of powerful molecular profiling methodologies have created opportunities for understanding the relationship of obesity to carcinogenesis at a mechanistic level. Relevant research could include molecular studies to identify metabolic and signaling pathways associated with obesity. Studies on the genetics of obesity may be helpful in identifying key regulatory pathways that may link to cancer development.

Implications of success: A deeper understanding of the mechanisms of the cancer risk posed by obesity could suggest new strategies for countering these risks. Understanding how obesity is

mechanistically linked to cancer development would bridge epidemiologic identification of risk factors with the molecular biology of cancer development. This would be a remarkable confluence of two exceptionally important cancer research disciplines and would point the way to many more studies that could make obesity-related cancer pathogenesis much clearer.

(View Detail)

PQ - 2

What environmental factors change the risk of various cancers when people move from one geographic region to another?

Background: Numerous studies have identified associations between the incidence of various cancers and local living conditions. There are many well-documented examples of cancer incidence changing as populations migrate from one site to another. These migrating populations will often adopt the cancer incidence profiles of their new host locale. In these instances, it is likely that environmental or cultural influences are contributing to the increased incidence of various cancers. Early studies identified this phenomenon and confirmed these relationships, but continued work on the identification of risk factors in migrating populations has languished in recent years. This question seeks to stimulate more sophisticated studies on epidemiological risk identified through studies of migration.

Feasibility: The methodologies for these studies are well established; however, with more complicated migration patterns seen in our model global economy, it may be necessary to consider more sophisticated metrics of population remodeling.

Implications of success: If new factors that contribute to changes in cancer incidence in migrating populations can be identified, our understanding of environmental carcinogenesis would be significantly enhanced. This information could have important implications for understanding cancer etiology, pathogenesis, and prevention.

(View Detail)

PQ - 3

Are there ways to objectively ascertain exposure to cancer risk using modern measurement technologies?

Background: Many methods that measure risk exposure rely on self-reporting or other survey approaches. Such surveys can be accurate in many cases, and they can be designed to increase their accuracy with good survey strategies. However, it would be valuable to develop more quantitative methods to record short-term or long-term exposures with quantitative readouts. With some methods, the techniques could measure biological readouts that might be directly linked to changes associated with cancer development.

Feasibility: This question calls for technological advances that can provide sensitive and accurate methods to measure exposure to agents thought to increase cancer risk. These methods might include devices to detect physical location, physical activity, exposure to carcinogenic agents, or changes in biological readouts that are altered in response to exposure. Detection of various small molecules by improving approaches in mass spectroscopy as well as various other "omic"-style methodologies may be useful in these approaches. New sensors that are tuned to known carcinogens could also be used. The range of measurement goals will include, but not be limited to, detecting

exogenous molecules in biological samples, recording imbalances in endogenous metabolites, following changes in epigenetic patterns, or monitoring of time and location compared to potential physical carcinogenic sites through global positioning. In addition, monitors could be tuned to measure immediate short-term exposure or cumulative longer-term exposures.

Implications of success: Increasing the use of exposure measurements promises to give more accurate and quantitative values to factors that predict risk. If biological readouts are possible, the links to changes directly associated with cancer development may help speed the links between epidemiology and cancer biology.(View Detail)

PQ - 4

Why don't more people alter behaviors known to increase the risk of cancers?

Background: A wealth of epidemiological research shows that certain modifiable behaviors are linked to increased cancer risk. These include tobacco use, UV exposure, sexual behaviors, obesity, and lack of cancer screening. However, despite this knowledge, many people struggle with, or are unable to modify, these behaviors. By understanding basic mechanisms of executive control, emotion, and motivation, we might be better able to understand why people fail to alter behavioral patterns, and reduce this resistance to change.

Feasibility: Studies suggest that the message of behavior risk may not be conveyed by basic communication approaches. The substance of the message may not be understood or the mode of delivery may be ineffective. Further, even with an effective message and mode of delivery, individuals may be unable to act on the message to alter and maintain their behaviors. Recent advances in behavioral and neurological studies can help to understand where in the delivery of the message and in the efforts to change behavior, an individual loses the ability to avoid risky behavior.

Implications of success: Reductions in behavior that increase risk would have an enormous impact in the incidence of cancer.

(View Detail)

PQ - 5

Given the evidence that some drugs commonly and chronically used for other indications, such as an anti-inflammatory drug, can protect against cancer incidence and mortality, can we determine the mechanism by which any of these drugs work?

Background: Given the evidence that some drugs commonly and chronically used for other indications, such as an anti-inflammatory drug, can protect against cancer incidence and mortality, can we determine the mechanism by which any of these drugs work?

Feasibility: Clinical data sets describing the consequences of long-term use of FDA-approved drugs could be mined for the association of drugs with incidence of various cancer types, while ruling out the possibility of a confounding interaction with the disease being treated. For those drugs already identified as being associated with a reduced risk of cancer, the mechanism(s) by which they reduce this risk remain be identified. In the case of aspirin, for example, most speculation on the mechanism of action has centered on changes in its anti-inflammatory activity. Since inflammation associated with cancer development is well studied, it may be possible to establish a causal link to changes in inflammation. Researchers should seek to move beyond correlative studies and establish careful mechanistic studies that link drug action to changes that alter cancer incidence.

Implications of success: Elucidating the mechanisms by which these agents work would be a major breakthrough in cancer prevention. This work could also provide molecular pathways that harbor other targets for prevention and encourage the development of second generation drugs that might diminish toxicities associated with current agents while maintaining efficacy. Success in these studies would provide models for the types of responses that mark good chemoprevention trials.

(View Detail)

PQ - 6

What are the molecular and cellular mechanisms by which patients with certain chronic diseases have increased or decreased risks for developing cancer, and can these connections be exploited to develop novel preventive or therapeutic strategies?

Background: People with Alzheimer's, Parkinson's and Huntington's diseases, as well as Fragile X Syndrome patients, have a significantly lower risk of most cancers. An exception is melanoma, for which there is an increased risk for Parkinson's patients. The reverse correlations also hold true. Cancer survivors have a significantly lower risk of developing many of these neurological diseases. It seems likely that if we understood in molecular terms why patients with these diseases or other chronic diseases have altered risk for cancer development, we might find leads for cancer prevention or treatment.

Feasibility: Exploiting this dichotomy may be difficult. Comprehensive databases needed to identify clinical correlations between chronic disease and cancer risk are not commonly annotated for these anti-correlations. However, the technology exists to find these disease/risk relationships. The molecular causes of these diseases or understanding the mechanisms of action for common therapies might be useful places to search for plausible links to cancer development. In some cases, there may be candidate genes or pathways for study. For example, some evidence suggests that suspected anti-cancer targets such as Pin1 are essential for the development of Alzheimer's disease. Overall, finding the molecular linkage to explain these correlations would be a powerful base for future work.

Implications of success: Understanding the biochemical and genetic bases for these striking disease correlations may reveal novel insights into the mechanisms of cancer development as well as insights into the corresponding diseases. These molecular mechanisms would potentially provide new targets for therapies or prevention.

(View Detail)

PQ - 7

How does the lifespan of an organism affect the molecular mechanisms of cancer development, and can we use our deepening knowledge of aging to enhance prevention or treatment of cancer?

Background: The development of most common adult cancers is related to increasing life span and aging; however, the lifespan of animals that get cancer are remarkably different. Mice live only 2 years, dogs perhaps 20, and humans 80. Yet all three suffer cancers that appear to driven by similar mutations in evolutionarily related proteins. Conversely many long-lived animals, such as the sea turtle, appear to have very low rates of cancer incidence. How does the etiology of cancer drive tumor formation in one time frame in some animals and a different one in others? In addition, some types of tumors arise in particular ages. What predisposes some tumors to develop most commonly

at these times? A better understanding of these relationships could reveal fundamental regulatory events that control cancer development and progression, offering new means of cancer prevention or early stage detection.

Feasibility: Some of the basic biological processes that control aging have been described, and our knowledge of the molecular drivers of aging continues to improve. For example, the clock gene, PER, is an oncogene is some cancers. As processes implicated in aging are studied in conjunction with animal tumor models, we will be able to understand how key characteristics of tumor development are modified. Similarly, the molecular profiles of related tumors that occur at characteristically different life stages may show distinct patterns that could point to some of the variables that control how tumor incidence can be linked to the properties of aging tissues.

Implications of success: Understanding which features of aging change the rate of tumor incidence promises to identify potential biological processes that could be targets for prevention and therapy. Deeper knowledge of the molecular links between aging and cancer incidence can also identify new markers for early diagnostic tests and risk assessment.

(View Detail)

PQ - 8

Why do certain mutational events promote cancer phenotypes in some tissues and not in others?

Background: Cancer-causing mutations arise under different selection pressures during tumor development. It has been recognized for some time that the frequency or timing of various cancer mutations differs widely among tissues, but we have little mechanistic understanding about why this occurs. These observed variations presumably are imparted by such factors as different physiology of the cell of origin, different selective pressures generated from the surrounding microenvironment, or various changes established by earlier mutational events. This question seeks mechanistic explanations for these differences in selective pressures.

Feasibility: Modern molecular and cellular biological methods should allow many of these tissue-specific events to be identified and studied. Cell and tissue dependence on protein function is seen in many animal models of tumor development, and in many cases we understand the signaling pathways in sufficient detail to design experiments to tease out the key steps that allow for tissue specificity. Proscribed mutational order presumably is due to changes imposed by earlier events in tumor development. Direct measures within animal models and in human tumors should allow differences to be confirmed and evaluated.

Implications of success: Understanding why certain tissues rely so uniquely on one protein promises to help us understand the different roles of cancer mutations. How are these dependencies established? Why are these dependencies paramount in some tissues? Do these dependencies relate to oncogene addiction? Knowing how these dependencies develop also promises to allow us to lock-in these dependencies within tumors and strengthen therapeutic responses.

(View Detail)

PQ - 9

As genomic sequencing methods continue to identify large numbers of novel cancer mutations, how can we identify the mutations in a given tumor that are most critical to

the maintenance of its oncogenic phenotype?

Background: DNA sequencing of cancer genomes has shown that individual tumors often contain many mutations that change protein coding regions, frequently as many as 30 to 150 changes in a single tumor. Many of the individually mutated genes are found in multiple tumors or are found in genes that have been implicated previously as cancer genes. These frequent mutations, often called "driver mutations", are believed to be important for tumor development. However, sequencing studies have also detected many mutations that are found only rarely. It is not clear if or how these low frequency mutations might contribute to tumor development. This question asks how we can determine which mutations have key roles in tumor development?

Feasibility: The recent identification of mutations through genomic sequencing provides a gene list and mutations for study. The challenge of this Provocative Question is to establish methods that will determine which changes are important for tumor development and use these methods to study the roles of these mutations. The task is complicated because of the large number of mutations and because it is not clear when in tumor development the mutation appeared and consequently what selective pressure this mutation may have overcome.

Implications of success: Finding out which mutations are important for tumor development will provide an important set of proteins for drug discovery, shed light on the various selective pressures experienced in tumor development, and help us predict what mutations found in ongoing sequencing projects are likely to be important in tumorigenesis.

(View Detail)

PQ - 10

As we improve methods to identify epigenetic changes that occur during tumor development, can we develop approaches to discriminate between "driver" and "passenger" epigenetic events?

Background: The continuing improvement in high-throughput analysis of epigenetic regulation is advancing our understanding of the complex nature of tumor development. Several observations argue that epigenetic regulation is key to many stages of tumor development. First, proteins that are important for epigenetic regulation are frequently mutated during tumor development, and these mutations are important for the cancer phenotype. These mutations include point mutations, translocation, amplifications, and loss of miRNA regulation. Second, some chemotherapeutic agents that target DNA methyltransferases or histone deacetylases have shown good efficacy in the clinic, suggesting the changes in these epigenetic regulatory events are key to maintaining the tumorigenetic phenotype. Third, the plasticity of tumor cells changing from one phenotypic state to another---for example during epithelial to mesenchymal transition (EMT) or following division of cancer stem or initiating cells---is under epigenetic regulation. Finally, there is growing evidence that at least some forms of drug resistance are due to changes regulated by the epigenetic state. As we are achieving higher resolution of epigenetic events, it will be increasingly important to learn which epigenetic changes are critical for tumor survival. This question sets the challenge to learn which epigenetic events are most important for tumor development and maintenance.

Feasibility: Modern molecular biological methods, including molecular profiling, high throughput ChIP analysis, and functional tests, will be needed to identify and study various epigenetic states. Computational methods to characterize various epigenetic regulatory states could be used to help define potentially important changes. Functional tests, including RNAi knockdown or overexpression

of key proteins, may be helpful in changing chromatin structure and linking these changes to cancer phenotypes.

Implications of success: As a field, we anticipate that epigenetic regulation of chromatin states will play important roles in tumor development. These links seem most clear in cases in which mutations that directly alter the epigenetic state have been shown to be important for tumor development. However, many phenotypes of a cancer cell are certainly regulated by epigenetic changes not deregulated by mutation, and the demonstration of this link promises to open the way for the identification of new therapeutic or prevention targets. Similarly, advances in this area will likely provide important advances in the identification of new diagnostic markers.

(View Detail)

PQ - 11

How do changes in RNA processing contribute to tumor development?

Background: Recent exome and genome sequencing has described the appearance of a large number of unexpected tumor-specific alternative splicing and other changes in RNA processing events. Presumably some of the selected splicing events are beneficial for tumor development, but the functional significance of these events remains poorly understood. Other changes in RNA processing may alter protein levels or lead to changes in regulatory RNA molecules.

Feasibility: The discovery of these new alternative-splicing and other RNA processing events opens the way to study the roles of new protein products. These studies can proceed along standard lines of examination. Testing the function of these new protein products should be possible in standard cell and animal models. Other changes in RNA processing may lead to changes in levels of translation or regulation of RNA molecules.

Implications of success: True tumor-specific splicing events may provide new functional understanding of the drivers of tumor development. They may also provide novel cancer-specific markers of new proteins or protein domains for diagnostic and therapeutic target development.

(View Detail)

PQ - 12

Given the recent discovery of the link between a polyomavirus and Merkel cell cancer, what other cancers are caused by novel infectious agents and what are the mechanisms of tumor induction?

Background: To date, a number of cancer-causing infectious agents have been identified, such as HPV as the causative agent of cervical cancer and H. pylori and its role in gastric cancer. It seems likely that there are other infectious agents not yet identified that influence cancer development. This question calls for the identification of other agents that may contribute to cancer development and for studies to understand the mechanisms of tumor induction.

Feasibility: Multiple approaches in various disciplines may be used to support studies for this question. Epidemiological studies may suggest an association of infection and increased risk. Global health studies may provide locales where more poorly studied cancers might show a causal link to infections. High-throughput sequencing and bioinformatics have made it possible to identify viral mRNA in tumor tissues, and similar strategies may prove useful here. Given the success of this

research area in the past, it seems likely that many inventive and useful approaches will be available to successful applicants.

Implications of success: Identifying new infectious agents that cause cancer and understanding how they influence cancer development have been powerful avenues of research in the past. There is every reason to believe that continued discovery of new cancer-causing infectious agents will continue to result in similar rewards. If they cause a common cancer, developing successful strategies to modulate or prevent their cancer-causing effects can have a tremendous impact on cancer mortality.

(View Detail)

PQ - 13

Can tumors be detected when they are two to three orders of magnitude smaller than those currently detected with in vivo imaging modalities?

Background: Current imaging modalities allow detection of tumors composed of approximately 107 cells or in the range of 1 cubic millimeter. Any increase in imaging sensitivity provides valuable advances in tumor detection; however, a major increase in detection sensitivity would provide a radical change in how we might employ imagining in clinical practice. While new advances are continually being reported and are currently the goal of NCI's imaging grant portfolio, here we call for methods that might radically change the sensitivity of these imaging methods.

Feasibility: This question calls for a huge jump in imaging sensitivity. How this increase might be achieved is left to the imagination of the community. However, one can recognize that strategies to increase sensitivity might include such approaches as matching imaging probes with biologic targets that provide some enzymatic amplification, developing much more sensitive imaging probes, or greatly improved camera sensitivity.

Implications of success: The ability to detect very small clusters of cells in patients and in experimental cancer models is important from both detection and therapeutic perspectives—to find cancer at its earliest stages, to understand how and when tumors spread, to study how dissemination correlates with malignant progression, to improve strategies for treatment with precisely targeted radiation or drugs, and to monitor therapeutic responses.

(View Detail)

PQ - 14

Are there definable properties of a non-malignant lesion that predict the likelihood of progression to invasive or metastatic disease?

Background: Not all cancers detected early are worth treating. However, uncertainties about the clinical behavior of a non-malignant lesion often leads to more aggressive treatment than may be warranted, which can result in net harm to the patient. Currently, the detection of non-malignant (presumptive pre-malignant) lesions, such as so-called "in situ carcinomas" of the prostate gland or breast, are often treated vigorously because of the possibility that they are likely to adopt aggressive behaviors with time. In addition, the inherent uncertainty in predicting the outcome of a given cancer can result in poor communication of the actual risk to the patient, promoting decisions that may not be appropriate for the given benefit/risk profile.

Feasibility: Major advances in genomic and proteomic technologies that can genotype and phenotype very small collections of cells, together with a greater awareness of the tumor microenvironment, are resulting in a better understanding of how molecular profiles relate to phenotype. New knowledge will help determine whether malignant properties are conferred stochastically, or whether early lesions differ in their likelihood of malignant progression in definable and reproducible ways, thus allowing for more accurate prognostic determinants. Prospective studies could lead to substantial improvements in the accuracy with which the clinical behavior of a given lesion can be predicted.

Implications of success: Improved prediction of clinical risk could help clinicians in communicating risk/benefit profiles for treatment options. Patients could make better informed decisions, thus matching the diagnosis with the most appropriate treatment. These developments could also identify where therapeutic advances are most needed. Insight into the biological basis for this stratification would be an important advance, with likely relevance to analogous lesions of several tissues. These changes could improve the overall benefit of early detection by reducing the risk of harm from overtreatment.

(View Detail)

PQ - 15

Why do second, independent cancers occur at higher rates in patients who have survived a primary cancer than in a cancer-naïve population?

Background: Second cancers are a major problem for cancer survivors. Grouped as a single outcome in the Surveillance Epidemiology and End Results (SEER) database, second cancers rank fourth in overall cancer incidence and are often associated with poor outcomes. However, researchers have not taken full advantage of this population to study risk factors and mechanisms. The influence of prior therapeutic interventions (including chemo- and radio-therapies) and somatic mutations in this population has been studied to some degree. However, the extent to which underlying genetic predispositions, environmental factors, and life-style behaviors influence risk remain relatively underexplored. It is likely that at least some of the identified risk factors and mechanisms would also be relevant to people who have not had a first cancer.

Feasibility: Given the high risk of these of these patients and their involvement with medical oncology personnel, it should be substantially easier to monitor cancer survivors for the development of a second cancer than to observe healthy individuals for the development of a first cancer. Cancer survivors are often followed prospectively for treatment response and complications, as well as disease progression. Technologies that identify somatic alterations can be integrated with genome-wide annotation of germ-line DNA to investigate the relationship between genetic susceptibility in high-risk individuals and second cancers. With the advent of new, more efficient technologies, it is feasible to broaden these efforts to large-scale clinical trial studies. Efforts to capture clinical, epidemiological, and therapeutic data could also be centered on the development of large-scale cohorts of cancer survivors at risk for second cancers. Because of their heightened risk of cancer, this population of patients may be more motivated, and therefore well suited, for prospective prevention studies, such as chemoprevention or behavioral modifications. Increasing use of electronic medical records could facilitate such studies, including the identification of appropriate patients for particular studies.

Implications of success: Studying patients who have had primary cancers for the development of second cancers could help uncover pathogenic mechanisms of both cancers, including shared etiologic pathways and therapy-related risks. These insights are likely to inform new strategies for

preventive interventions.

(View Detail)

PQ - 16

How do we determine the clinical significance of finding cells from a primary tumor at another site?

Background: Metastatic disease is the major cause of death from cancer. However, just as not all primary cancers are prone to metastasize, not all tumor cells found at secondary sites are life-threatening. Dissemination from a primary tumor site can occur relatively early in tumor development, and cells at secondary sites may have properties that range from dormancy to aggressive malignancy. Furthermore, relatively quiescent tumor cells may require additional genetic and/or epigenetic alterations, perhaps in conjunction with non-cell autonomous alterations, to achieve a fully malignant phenotype at the secondary site. Yet, because the spread of tumor cells is usually viewed as an unfavorable prognostic indicator, detection of such cells commonly represents a rationale for more intensive therapy, which may or may not be warranted.

Feasibility: New experimental methods allow sensitive techniques for detecting and characterizing small numbers of tumor cells at secondary sites, and improved animal models of cancer have created opportunities for expanding our knowledge of disseminated cells and refining our lexicon for classifying them. For instance, recent advances in DNA sequencing enable the generation of phylogenetic trees of tumor cell populations to determine their clonal relationships and evolutionary distance from each other, and from portions of the primary tumor that are at different stages of progression. With these new tools, it may now be possible to define the malignant potential of disseminated cells.

Implications of success: Such analyses could enhance our understanding of the mechanisms that account for either a lack of oncogenicity or malignant behavior of tumor cells at a secondary site, as well as improve our ability to predict the biological behavior of tumor cells found at those sites. This information would give clinicians a clearer picture of when intervention is needed and when such tumor cells can be safely left alone or followed for potential later action.

(View Detail)

PQ - 17

Since current methods to assess potential cancer treatments are cumbersome, expensive, and often inaccurate, can we develop other methods to rapidly test interventions for cancer treatment or prevention?

Background: There are no reliable models that predict drug response in human tumors. Tumor cells in culture are widely used to help identify and characterize potential drug targets, and they can serve as useful models to check initial drug penetration of cell membranes and target engagement. Mouse xenograft or genetically engineered mouse models often provide good settings to test drug pharmacodynamics, but seldom yield reliable measures of drug efficacy. Other animal models are used extensively for drug pharmacokinetic tests, but none of these models are useful mimics of drug activity in humans. This Provocative Question calls for the development and testing of new systems that accurately predict how drugs will act in humans.

Feasibility: Advances in 3-dimensional cell culture suggest that multiple cell types can be assembled

in vitro and that engineered tissues often mimic many of the features of human organs. If systems can be developed that mimic the natural environment of tumors, perhaps these models will recapitulate drug action. It also seems possible that complex cell-free systems could be developed that would recapitulate at least some features of drug responses. Since it seems unlikely that any one new system will serve as an accurate model for all tumors, each may need to be tuned to the particular features of a particular tumor type or subtype.

Implications of success: If systems can be developed that accurately predict drug responses in human, advances in drug treatment or prevention would be dramatically streamlined, and the time frame for drug development shortened considerably. These new systems might also allow strategies for combination therapies to advance from empirical tests to approaches that are based on the biology of the tumor and its environment. The ultimate benefit for patients would be immense..

(View Detail)

PQ - 18

Are there new technologies to inhibit traditionally "undruggable" target molecules, such as transcription factors, that are required for the oncogenic phenotype?

Background: Many tumor cells are known to be dependent on the expression and function of transcription factors or other proteins that are not easily targeted by standard drug development strategies. Typically, these proteins do not have enzymatic activities that can be inhibited by small molecule organic drugs. Nevertheless, cancer cells are often fully dependent on the continued expression and biological activity of these proteins, as shown by RNAi experiments or other functional tests. Many groups have tried to identify small molecule inhibitors that would interfere with the function of these proteins by blocking their interaction with other essential proteins. However, except for rare cases, these approaches have not led to drug candidates for clinical trials. Still other groups have looked for allosteric inhibitors that might change protein function through binding to targeted proteins and altering an essential function. Here, also, little success has been reported. Currently NCI is funding a small number of investigators to look for inhibitors of protein/protein interaction using a series of approaches. Because solving this problem would have such a large impact in the development of new cancer therapies, this question is included to continue driving the field's quest for new and unusually creative approaches to inhibit these traditionally "undruggable" targets.

Feasibility: This question seeks new ideas to develop approaches for drug development for protein/protein interactions or other non-enzymatic inhibition of oncoprotein function.

Implications of success: New classes of drugs designed to block the actions of these refractory targets would provide a wide range of opportunities for cancer treatment and prevention.

(View Detail)

PQ - 19

Why are some disseminated cancers cured by chemotherapy alone?

Background: Although chemotherapy is often effective, it is only rarely curative. However, It is well established that certain disseminated cancers can be completely cured with chemotherapy, even with drugs that are often of much less value in other settings. The tumors that can be cured include solid tumors (testicular carcinoma, choriocarcinoma, and Wilms' tumor) and hematological malignancies

(ALL, Burkitt's lymphoma, and some diffuse large B-cell lymphoma). However, there is little understanding of the underlying mechanisms that might explain why these cancers can be completely cured with chemotherapy.

Feasibility: This question has largely been ignored since it was recognized, often decades ago, that such tumors could be cured by standard chemotherapeutic strategies. New methods are available for studying the biology of these "curable" cancers and for exploring the mechanisms by which the effective drugs work.

Implications of success: If we could identify the properties of cancers that render them susceptible to eradication by chemotherapy, we might better understand how certain therapies work, contemplate converting relatively insensitive tumors to highly sensitive ones, or develop new approaches to the treatment of intransigent malignancies.

(View Detail)

PQ - 20

Given the recent successes in cancer immunotherapy, can biomarkers or signatures be identified that can serve as predictors or surrogates of therapeutic efficacy?

Background: There is increasing excitement about the use of immunotherapies in the treatment of cancer. While biomarkers that predict therapeutic efficacy or that can be used to measure the progress of treatment are still missing for many cancer treatments, with other treatments there are large-scale efforts in progress to identify these markers. Because of the relatively recent success in immunotherapies, there is a clear need to jumpstart the search for such biomarkers for these treatment modalities.

Feasibility: The sophistication of the immunology field may provide a particular advantage in the search for surrogates for therapeutic efficacy. The long and rich advances of this field have helped shape a deep appreciation of immune responses, and within this knowledge there may be clever approaches to identify useful markers. The search for predictors of therapeutic efficacy may also benefit from this information, but may also rely on advances in molecular profiling.

Implications of success: Biomarkers for predicting therapeutic responses or for following treatment success would greatly advance the immunotherapy field, and as we struggle to find such markers in all areas, any success will serve as a useful model for others.

(View Detail)

PQ - 21

Given the appearance of resistance in response to cell killing therapies, can we extend survival by using approaches that keep tumors static?

Background: One of the most disappointing features of the development of new targeted therapeutics is how routinely drug resistance emerges. Evolutionary theory suggests that strong selection will always result in the emergence of resistant populations as long as some portion of the stressed population can adjust to the selective pressure. Similar theories also suggest that lessening the selective pressure to a level that seeks to hold the population in check may succeed at least for extended periods of time. Evolutionary fitness suggests that many mutations that arise after selection for cell killing are likely to be slightly deleterious in nature. While strong selection will easily let the

mutated population emerge, if the selection is modest, the population may develop a new balance that reflects a combination of original tumor cells, dying tumor cells, and minor populations of the drug-resistant tumor cells whose fitness is impaired. Other types of selective pressures also may be valuable in these settings. For example, developing and using drugs that select for outcomes that are not solely inducers of cell killing may help establish a balance that would help create tumor stasis rather than strong selection for drug resistance. This Provocative Question suggests we should test the validity of these approaches as novel means to treat cancer. Ultimately, this may not produce a cure for a particular cancer but rather a method to treat cancer as a chronic disease.

Feasibility: Testing this theory is best done in animal models. Existing agents at low doses may provide good test cases; however, agents that induce other outcomes besides cell killing also should be considered, perhaps in combination.

Implications of success: These approaches present novel ideas for cancer therapy, but they highlight the importance of making sure we know what outcome for cancer patients is ultimately most useful. Living for some time with a debilitating tumor may be preferable to a rapid tumor regression with an almost certain drug resistant relapse.

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PQ - 22

Why do many cancer cells die when suddenly deprived of a protein encoded by an oncogene?

Background: The viability of cancer cells is dependent on the continued production and activity of various pro-oncogenic proteins. In some cases, when therapies target these oncoproteins, individual tumor cells may die abruptly. This process is often called "oncogene addiction," and rapid regression of several tumor types with targeted therapies has been seen in patients. While this cell death is an encouraging outcome for therapeutic approaches, we have little knowledge of why these cells become so strongly dependent on the continued expression of an active mutated oncogene, particularly because the initiating cells often express the normal proto-oncoprotein. This Provocative Question asks why tumor cells die so rapidly when the addicting oncoprotein is depleted or its enzymatic activity blocked by a targeted therapy.

Feasibility: Many examples of oncogene-dependence, both in human cancers and mouse models of cancer, are now subjects of great interest, because the "addicting" oncogene products are promising targets for modern cancer therapy. The signaling networks in which they are active are also being studied to identify other therapeutic targets. Modern molecular biological methods focused on protein function should be useful in studying why cells become addicted to these oncoproteins and die so rapidly when they are lost.

Implications of success: Knowledge of how a cell develops vulnerability to the loss an oncogenic protein, and undergoes programmed cell death in consequence, would likely suggest additional novel targets for therapy. In addition, it might offer insight into the question of which tumors are most susceptible to targeted therapies and the problem of eliminating all cells in a tumor with such therapies.

(View Detail)

PQ - 23

Can we determine why some tumors evolve to aggressive malignancy after years of indolence?

Background: Indolent tumors have been detected in a wide range of tumor sites. Very little is known about why these tumors persist for extended periods of time and then evolve to malignancy. Some are recognized as indolent after treatment, while others appear as a stage of natural tumor development before treatment. Still others are seen only at autopsy. Research to characterize these various tumors could help to understand what controls this state. Is it a true proliferatively dormant state or an active state that just balances cell division and death? How is this state maintained? Do tumors of the same site undergo similar transitions as they move from dormancy to malignancy? Can we predict which tumors will remain dormant and which one will progress?

Feasibility: Many of the tools for tumor profiling will be useful to help characterize these tumors. Modern molecular and cellular techniques can be used to help understand which pathways are active and essential in indolent states.

Implications of success: Expanded insight into the mechanisms that control tumor development promises to enrich our understanding of the cancer process. Characterization of indolent tumors will help us understand the mechanisms that hold tumor progression in check. Indolent tumors seldom pose any inherent risk to patients, so approaches that would hold other tumors in this state or that would extend the time that indolence persists could provide important therapeutic benefits.

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PQ - 24

Given the difficulty of studying metastasis, can we develop new approaches, such as engineered tissue grafts, to investigate the biology of tumor spread?

Background: Metastasis continues to be difficult to study. We have almost no reproducible systems to study this deadly process. Mouse tail vein injections of tumor cells often leads to tumor growth at various sites in a process that mimics metastasis to some degree. Some genetically engineered mouse models will metastasize, but the process is hard to stage or follow in any rigorous detail. This Provocative Question calls for the development of new approaches to study metastasis.

Feasibility: While the range of potential approaches to develop methods to study metastasis is left to the imagination and creativity of the community, one potential exciting approach is the construction of engineered tissue beds that could serve as sites for invasion of metastasizing tumor cells. Such sites could be modified to determine which physical or biological properties promote more successful invasive and subsequent tumor proliferation. Many parameters of metastasis could be measured if it were known when and where to follow this process, and such sites could allow more careful analysis of what events guide the development of metastasis. These types of suggestions also raise a large number of other potential approaches that might make the study of metastasis more controllable and thus more readily compared among tumor types and more readily modifiable.

Implications of success: In many ways, metastasis is the most important stage of tumor development. Developing new methods to allow its careful study would provide important new avenues to learning about this stage of tumor development.

(View Detail)