# 美國「文化交流計畫考察」報告

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出國人員： 高級研究員　黃小文

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美國文化交流計劃考察

主辦機關:

行政院衛生署

聯絡人／電話:

王玲紅／23210151#507

出國人員:

黃小文　行政院衛生署　藥政處　高級研究員

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內容摘要: 美國在台協會「文化交流計畫」之宗旨在促進各國專業人士與美國同儕間之交流，本次訪查重點爲美國生技醫藥產業之研發與審查，爲期三週(8/10/2001 ~ 8/31/2001)。美方安排訪查之單位爲Meridian International Center (Department of State委託執行)。訪查地點分別爲Washington, DC ; Buffalo, NY; Kansas City, MO; San Diego, CA; Los Angelus, CA; 訪查單位包括FDA, NIH, NIST（National Institute of Standards and Technology ）AIT, TECRO, PhRMA, AdvaMed, Roswell Medical Research Center, State of New York Hospital , AIDS Community Service , U. of Buffalo（Technology Transfer Center）, MRI (Midwest Research Institute), U. of Missouri, CAS (Chemical Abstract Service), Edison Biotechnology Transfer Center, Advanced Tissue Sciences, Agouron/Pfizer, Alliance Pharmaceutical Corp., UCLA, Salk Research Institute。

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## 一、目的

美國在台協會「文化交流計畫」之宗旨在促進各國專業人士與美國同儕間之交流，歷年由美國在台協會提出計畫人選，安排赴美考察，並由美國國務院(Department of State)委託 Meridian International Center 協調美國各州之義務團體，配合訪問者擬提之考察重點，執行訪查安排等事宜。本次訪查主旨為美國生技醫藥產業之研發與審查，重點著重於美國食品藥物管理局(FDA)新藥與醫療器材之審查機制；美國國家衛生研究院(NIH)有關人類基因計劃、生物醫學等領域之研究；美國學界及生物技術公司研發策略與國際標準制定機構等。拜訪對象包括美國之研發單位、技轉中心、生技業界以及政府審查部門，為期三週(8/10/2001 ~ 8/31/2001)。訪查地點分別為 Washington, DC；Buffalo, NY; Kansas City, MO; San Diego, CA; Los Angelus, CA; 訪查單位包括 FDA (Food and Drug Administration), NIH (National Institute of Health), NIST (National Institute of Standards and Technology ), AIT (American Institute in Taiwan), TECRO (Taipei Economic and Cultural Representative Office), PhRMA, AdvaMed, Roswell Medical Research Center, State of New York Hospital , AIDS Community Service , U. of Buffalo (Technology Transfer

Center), MRI (Midwest Research Institute), U. of Missouri, CAS (Chemical Abstract Service), Edison Biotechnology Transfer Center, Advanced Tissue Sciences, Agouron/Pfizer, Alliance Pharmaceutical Corp., UCLA, Salk Research Institute。

## 二、過程

I. Washington, DC 8/11-8/18, 2001

本次訪查首站為美國華府。Meridian International Center 特別安排一位專業嚮導 Miss Elinor Ford 負責全程陪同。整個行程則由 Miss Joanne Clark (Program Officer) 總責協調之工作。在該中心的安排下，我們先拜會了美國在台協會主席 Mr. Richard Bush 卜睿哲代表。自 1998 年隨前衛生署詹署長赴美參加「中美醫療器材技術合作換文」簽署之後，此次應是第二次與 Mr. Richard Bush 會面。卜代表針對台灣現在之生技產業與我們進行簡要討論。由於個人工作業務因素，此行也在中心的安排下，分別訪問美國商務部，美國醫療器材公會(HIMA, 現為 AdvaMED)、美國製藥公會（PhRMA），主要討論重點為我國藥品與醫療器材之國際合作，由於訪問當時正值台灣籌備執行藥品 cGMP，美方

在此議題上頗為關切，故希望考慮透過中美雙方衛生主管間之資訊交換合作以簡化藥品上市申請之文件需求。為此我們另行拜訪駐美文化經濟代表處科學組（TECRO），並為其執行中美醫材換文，持續替衛生署交換美國 FDA 查廠報告之辛勞致謝。

此次訪問之最大目標在美國藥物食品管理局（FDA），尤其是實地觀察其新藥審查會議機制。FDA 除有專屬審查人員（reviewer）外，並上設審議委員會(review board committee)，邀集相關學者專家就新藥之上市審核採公開審查方式進行，現場除有媒體採訪，並同時上網實況轉播。審議委員於聽取申請業者與 FDA reviewer 雙方之簡報及受試者之試用說明後，進行是否通過新藥之決議。由於新藥乃兵家必爭之地，審議現場各路人馬匯集，尤其審核報告內容與各家開發新藥之策略息息相關，筆記聲沙沙於耳，這與平日老美好整以暇之作風極不相同。以我此次參與之新藥審查為例，該委員會之決議當晚即由 CNN 報導通過。

此外 FDA 並分別安排其 CDER（drug evaluation）、CBER（biological evaluation）、CDRH（medical device evaluation）與 International Office 與我們會面。由於台灣在新興生物科技之大力推動，我們特別針對台灣業者所關切的組織工程、基因工程以及複合性（combination of drug and medical device）之產品管理，包括產品功能

之鑑定與工廠稽查部份與 FDA 專家們討論。面對目前生物科技源源不絕所研發出之成果，FDA 同樣也遭遇相同的挑戰，因應之道，一則整合跨中心之審查機制，如 CDRH 與 CBER 可依產品特性，進行聯合審查，充分靈活善用其組織內之專業人才資源。另一方面則儘早與學界業界進行對話，了解相關產品之學理與製造情形，制定管理規範（如 GTP, Good Tissue Practice）以利廠商依循。

美國國家衛生研究院（NIH）向執學術界牛耳，尤其在基因體研究及 AIDS 藥物研發上不遺餘力。公元 2000 年美國總統 Clinton 公佈了人類基因體之解碼，謂之劃時代大事。隨之而起的議題，主要將是醫學倫理、法規、社會結構面（ELSI, Ethical, Legal, and Social Implications）的影響探討，研發方向預期將因基因序列的解碼而進入蛋白質體功能研究之全盛時代。我們在訪問美國之際，正值現任美國總統 Bush 發表其對美國研究幹細胞（stem cell）之政策，由於決策過程不明且對可研究之 cell line 設限，各界評論不一，幾乎佔據了所有媒體之頭版頭條。台灣現況之管理，情境類似，雖然社會輿論尚未熱烈至此，恐應預為戒慎之。

美國國家衛生研究院另一功能為早期藥物研發並協助臨床試驗之進行。以其 Diviosion of Acquired Immunodeficiency Syndrome 為例，該中心以預防治療 AIDS 為研究重心，可協調數十所與其合作的醫院或研

究中心進行抗 AIDS 藥品之臨床試驗計畫，俾能在相同的時程下進行多中心之試驗，以爭取時效。此種機制，對於台灣近年來一直在大力推動的多中心新藥臨床試驗體系，實值得借鏡。

華府周邊人文薈萃，我們同時趁便拜會了人類基因解碼之大功臣 Celera 公司。該公司擁有之利器，包括特有之基因切割酵素、自動化核酸序列分析儀、高速電腦資訊系統以及極佳之生物資訊人才，使其穩居鰲頭寶座。但為計將來之發展，公司除將繼續開發強有利之基因比對軟體之外，同時將朝 functional genome 之重點進行。台灣目前透過政府之全力支持，籌畫建立基因體研究中心，規劃中之規模結構與組織發展方向似應密切注意 Celera 公司成長與轉型之趨勢。

美國國家標準局 NIST 之工作，與產業製造技術所需之國際標準制定有密切關聯。為了解醫療器材相關之國際標準，以及體外檢驗試劑有關的追溯參考物質等，我們特別與該局專家進行訪談。NIST 的功能與我國工研院的角色極為相似，雙方也簽有合作計劃。該中心尤其引人注意的是有關奈米科技的研究投注，足以整合基礎物理、化學、材料、半導體與生物科技等領域，值得台灣思考。

II. Buffalo, New York　　8/19-8/22, 2001

由於 Buffalo 當地代表的熱情邀請，我們被安排飛抵美國東北角拜訪對於癌症治療研究素負盛名的 Roswell Medical Research Center (RPCI)參訪。Photodynamic Therapy(PDT)係於其 Department of Photodynamic Therapy 中發展出來的癌症治療法。該法利用光感應藥物(photosensitizer)，specifically bind with the tumor cells，再施以特定波長之雷射照射，即可成功地破壞癌症細胞，有效治療癌症。其中如 Photofrin 並已取得 FDA 之上市許可，目前也正在台灣申請上市執行臨床試驗中。該中心由 Dr. Ravindra Pandy 領導，包括藥物之基礎合成、物化性質、活性篩選、免疫研究、動物毒理測試、Formulation、PDT 雷射儀器應用、GMP 廠之小量藥物製造、以至臨床實驗均可執行。該中心在 Photodynamic Therapy(PDT)研究上已初步開發四百餘種合成藥物，其中四種進入 phase I study。Dr. Ravindra Pandy 同時為韓國開發相關產品之顧問，韓國將應用 PDT 於體外血液淨化，初步研究證明 PDT 可去除捐血中之 HIV, HBV 等病毒。

由於個人十餘年前在美攻讀博士論文時，也曾試圖將當時正在藥廠初步研究階段的 Photofrin 利用質譜儀進行化學結構分析，惜因原料之混雜程度太高而放棄，十年後 Dr. Ravindra Pandy 重新合成純化之 Photofrin，亦以質譜儀完成化學結構分析，成果斐然，蒙其贈與所

發表之論文，亦算造化巧遇了。

Sister General Hospital 係 State of New York Hospital 之一，為與 NIH (National Institute of Health)合作執行 HIV clinical trial 的 35 個臨床試驗中心之一。該醫院有 AIDS 病患九百餘人，臨床實驗以 phase III 與 Phase IV 為主。目前在 Immunology Department 執行中的實驗有五種 anti-AIDS 藥物以及一種 anti-AIDS 疫苗。該院並無自己成立的 IRB ，其 clinical trial protocol review 係委外由 University of Buffalo 或 University of Rochester 的 IRB 執行。為配合 multi-center clinical trial 之同步進行，該醫院僅就受試者同意書(inform consent)依照當地 IRB 審查標準進行修改，IRB 開會平均每月一次(University of Rochester IRB 則每星期一次)，該部門有三位 research nurses，協助進行臨床試驗，並就 pharmacokinetic sample 進行簡單的前處理，進一步分析試驗則送交 University of Buffalo 執行。此外 HIV virus 常因病患長期藥物之使用，造成抗藥性之突變，其中任何有關 virus stain 之 identification 則送 reference lab 進行測試。

Research nurse 係隸屬於 University of Buffalo，薪資由 University of Buffalo 以及 pharmaceutical companies 共同負擔。

此外，AIDS Community Service 係屬 State of New York 所有，該

中心負責就 AIDS 病患進行諮詢輔導，並協助病患進行藥物治療，該中心並提供場地予 Sister General Hospital，Immunology Department 進行 anti-AIDS 疫苗之試驗。

University of Buffalo, State University of New York 的 RERC on Technology Transfer 中心係由紐約州資助之技術轉移中心，負責人 Dr. Stephen Bauer。該中心分兩類技術轉移 program，分別為以市場需求為導向的 Market pull 以及以技術為主軸的 Technology program。中心主持人認為技術轉移應先以製造廠之觀點出發，而非先考慮產品之終端使用者。據其統計，由大學研究而取得之專利，僅有百分之三成功開發出產品。主持人指出國際知名之 Siemens 公司所擁有之專利數甚至超過所有大學擁有之總數。私人企業近來亦開始發展育成中心 (incubation center)，邀請相關研究領域居領導地位之學者專家參與，提供研究場所經費設備，以期在最有效地情形下開發出新產品。

III. Kansas City, Missouri 8/23 – 8/25, 2001

University of Mossouri at Kansas City, School of Biological Science 在研究領域上著重生物物理 biophysics, 結構生物學 structure biology, 分子生物學 molecular biology, 以及生物化學 biochemistry 等領域。相較於美國東西岸之學界意願，該校教授較傾向純學術研究，

與廠商之間的合作較不密切。針對人類基因體之劃時代進展，該校研究將朝蛋白質體(proteomics)之結構與功能等方向發展。此外該校 School of Pharmacy 之研究方向亦逐漸增加延攬具分子生物及生物化學專長之教授，尤其將偏重在 biological receptor 的基因及分子結構之鑑定研究。

該校 Dr. Lee 提到他的博士指導教授於三年前回到台灣高雄醫學院藥學系任教，專研 drug delivery，我的拜訪彷彿他鄉遇故人，分外覺得親切。

Research and Clinical Counsuling, Inc.（RxCCI）係由該公司創辦人於累積美國藥廠及 CRO project manager 工作二十餘年之經驗後所成立之諮詢顧問公司。公司成立三年半，由七名成員成長至八十餘人，主要為藥品、生物製劑、醫療器材等產品上市前申請許可提供服務，範圍包括臨床前之資料整理、送審電子文件之準備、臨床實驗 protocol 之設計與 monitoring、臨床試驗資料統計、research nurse 的訓練、以及 GLP (Good Laboratory Practice) 與 GCP(Good Clinical Practice)的查核。該公司擁有具 CAP (Clinical Accredited Practice)認證資格之專業人員協助廠商進行品質管控，並由於業務關係，列屬向 FDA 申請上市前許可有關之委託公司之一，而經 FDA local field inspector 查核通過。該公司至今總計有六十餘項申請案，包括 FDA

藥品 IND、 DNA 、醫材 510 k、生物製劑 BLA 以及歐洲 Centralized drug license applications，合作對象包括美日等藥品與醫療器材廠。

MRI (Midwest Research Institute) 原屬美國國防部經費支援之研究機構，其研究範圍以國防工業相關者為主，其中化學化工部門，逐漸轉型，開始接受業界委託執行各項試驗報告，如新藥開發階段之臨床前測試項目。該單位也曾應我國工研院之邀來台訪問，惟經詢問其收費標準似不便宜。

IV. Columbus, Ohio　　8/26 – 8/28, 2001

回到 Columbus Ohio-我攻讀 Ph.D. 的地方，雖還不至於近鄉情怯，但卻倍感親切。除了特別拜會以前的化學系指導教授及其家人外，許多昔日的同學仍在，小小的華人聯絡圈仍舊溫馨。

CAS (Chemical Abstract Service)座落於 OSU(Ohio State University)校園附近,歷史悠久。歷來各國發表之化學相關期刊,CAS 均會將其摘要翻成英文，以供全球人士查詢閱讀。近來該中心更發展多種軟體供研發業界使用。其中尤以 SciFinder 之設計最為 user friendly,為其主要推廣的產品。該資料庫除了例行之期刊資料查詢外，亦可提供各化合物之合成方法、所需原料來源之工廠資料、以及相關專利資料。對於學界之研究工作以及藥界之開發計劃,頗為實用。

Edison Biotechnology Transfer Center 亦位於 OSU 校園附近，以往與 OSU 材料冶金等系所合作關係密切。近因整個生物科技產業趨勢銳不可當，Edison 也順勢調整其角色，大興土木，設立創新育成中心，企圖延攬中西部地區研發單位進駐。顯見美國整個生技產業之進展，由最早投入之東西兩岸，已逐步向內影響至中西部地區，傳統以學術為導向的思考方式，不再是校園內的唯一主流。Ohio 的生技產業進展步調與開發策略，倒與現階段台灣熱中規劃的生技園區情景，有些神似。

V. LA/San Diego, LA 8/29 – 8/31, 2001

進入加州，此次訪美接近尾聲。原先意欲拜訪生物晶片公司與加州理工學院，惜因當地單位連絡不及，未得如願。但透過協商，得以拜訪加州州立大學 UCLA 醫學工程系系主任，想來也算是塞翁失馬。該系系主任向我們介紹了許多正屬研發階段之新產品趨勢，如該校成功發展之感染原晶片以及心血管支架等。此外，系主任正巧也是美國 FDA 醫療器材審議委員，有關其對新醫材之審查原則以及臨床試驗的要求重點，也與我們交換了許多寶貴意見。由於當地廠商常向他諮詢，包括台灣衛生署的上市要求，返國後特別將相關資訊提供給

UCLA，希望多少有些幫助。

加州地區為生技製藥界的黃金區域，學界與業界合作無間。公司方面我們拜訪了 Advanced Tissue Sciences, Agouron/Pfizer, Alliance Pharmaceutical Corp. 以及 Medtronics。

Advanced Tissue Sciences 之產品以組織工程類為主，其產品開發趨勢在相關業界中具指標性，如人工敷料、細胞組織人造新血管等。我們在負責人的導引下，參觀了整個工廠製造流程及其品管與滅菌作業。我們更藉機了解 FDA GTP(優良組織操作規範)的要求，是否已在業界中實際執行，例如組織來源是否均可追溯？值得稱幸的是其答案為"是"，且與其合作的醫院均有紀錄可循。

Medtronics 則以製造人工心臟脈膜（取自豬心）為主。該公司主管向我們介紹了生產流程以及臨床試驗之經驗，尤其是 FDA 對其產品上市後之臨床使用經驗仍要求定期回報，同時公司本身也極重視醫師之使用操作訓練，如非屬該公司訓練過之醫師，其產品是絕不會銷售至該醫院的。這些管理方法應足為我國借鏡，尤其是本署動則以人體試驗之要求，企圖達到訓練醫師操作儀器之管控，實應重新深思上市前臨床試驗之目的為何？

Agouron/Pfizer 是一家剛為 Pfizer 併購之藥廠。公司利用蛋白質結構與功能間的研究成果，成功開發新藥上市。面對目前製藥界

兩大趨勢－組合化學與高速篩選，Agouron 堅持 rationale drug design 似乎也頗具成效。條條大陸通羅馬，幾何之內無君王之路，確係至理矣。

## 三、心得與建議

### I、藥物審查體系

1. FDA 對於新藥的審查，其審議委員會議(review board committee)係採公開審查方式進行，審議委員聽取業者與 FDA reviewer 雙方之簡報及受試者之試用說明後，進行是否通過新藥之決議。
2. FDA 對於跨領域的生技產品，制定產品管理屬性討論之機制，推舉其中之一審查中心作為 lead reviewer，並可聯合所屬之審查中心（藥品 CDER, 生物製劑 CBER, 醫材 CDRH）共同審查。

### II、藥物研發機制

1. 醫學研究中心具有完整之藥品研發架構，如 Roswell Medical Research Center, 雖為單一之癌症研究醫學研究中心，確具有全程研發藥品之功能，由基礎合成，毒理藥理測

試，GMP 廠之小量製造，以至臨床實驗均可施行。單以其癌症光治療法 Photodynamic Therapy 為例，該院即已開發出四百餘種以天然物為原料之合成藥物，其中四種已進入 phase I study。

2. NIH 可提供業界及學界藥物研發上市各階段之轉介服務，另可協調聯絡全美多所在 NIH 登記之臨床試驗中心，同步進行 multi-center clinical trial。

3. 美國政府經費支助的 NIST 以及 MRI 等機構，可應業界產品研發之需求，訂定測試驗證標準（standards），並提供服務項目供業界進行產品測試。

4. 民間的 CRO (Contract Research Organization) 等顧問公司，成長快速且靈活，除協助廠商執行 clinical trial, 負責整理送審資料外，其公司並具有 CAP (Clinical Accredited Practice) 認證資格之專業人員，協助廠商進行 GLP、GCP、GMP 等之品管查核。另一方面 CRO 本身亦可成為 FDA 之查核對象。

III. 業界觀察

1. 美國單一公司(Calera)之基因體研究規模超過我國籌設中

之國家級研究中心，未來將朝功能性分析研究發展(蛋白質體研究)。

2. 新藥之開發除以大量高速篩選之方式進行外，美國業界亦有由生化分子結構方面切入而成功上市之案例。

3. 組織工程產品潛力無窮，惟相關業界依現況評估突破性進展尚需假以時日。另相關業界對此類產品之來源管理極為重視，此一部份可為我國未來管理之參考。

4. 某些生醫產品如人工心臟脈膜(取自豬心)，業者需大量訓練有素之勞工，或可為我國傳統產業轉型之參考。

## 四、附錄

I. Letter from Meridian International Center
II. Letter from United States Department of State
III. Genomics, Science and Medicine: Future is Now

# Meridian International Center

**Programming Division**

August 10, 2001

Dr. HUANG Hsiau-Wen
The Carlyle Suites
1731 New Hampshire Avenue, NW
Washington, DC 20009

Dear Dr. Huang,

On behalf of the Programming Division of Meridian International Center, we would like to take this opportunity to extend to you a cordial welcome to the United States. Meridian International Center, a private and non-profit organization, has been asked by the United States Department of State to assume responsibility for the planning and coordination of your U.S. itinerary.

We will meet Monday, August 13th, at 10:00 am at Meridian International Center, 1624 Crescent Place, NW. Mr. John Anderegg, State Department Program Officer, will join us for the meeting to discuss your program. **Please bring your passport and international airline ticket with you to this meeting.** Enclosed in the welcome packet you will find your program itinerary and sightseeing information to familiarize you with Washington, DC. There is also a copy of your biographic information. Please look it over and alert us of any changes or additions that need to be made at the opening on Monday morning.

You will also find your perdiem check and a letter to the Bank of America. Please plan to cash this check and purchase travelers cheques at the Bank of America on Dupont Circle with Ms. Elinor Ford, your United States English Language Officer, on Monday morning before your first appointment.

Please be assured that we shall make every effort to assist you throughout the remainder of your stay in our country, and we look forward to meeting you on Monday, the 13th.

Sincerely yours,

Joanne Clark
Program Officer

Jocelyn Ditzel
Program Associate

United States Department of State

*Bureau of Educational and Cultural Affairs*
*Washington. D.C. 20547*

*www.state.gov*

Welcome to the United States of America. We at the United States Department of State are pleased and honored that you have accepted our invitation to take part in the International Visitor program.

This visit will offer you a wonderful opportunity to become personally acquainted with our country. At the same time, your presence here will help our citizens gain a better understanding and appreciation of your nation.

Although the International Visitor program is sponsored by the U.S. Government, it reflects the open and democratic nature of our society through the essential involvement of private organizations and individuals. Many of the people who make the arrangements for your visit in cities throughout the United States are volunteers. Friendships and associations established during our visitors' programs often develop into personal and professional relationships that last long after the visitors have returned to their countries.

Both our Washington staff and our embassy colleagues in your country welcome your impressions and observations from this program. We would greatly appreciate hearing from you after the conclusion of your visit.

We wish you the best for a pleasant and beneficial trip.

Sincerely,

William Morgan

William Morgan
Acting Director
Office of International Visitors

# Genomics, science and medicine: the future is now

**Samuel Broder***

**J. Craig Venter**

Celera Genomics
45 West Gude Drive
Rockville
MD 20850
USA
*Corresponding author

▼ Basic researchers, clinical investigators, practicing physicians, patients and the general public, now live in a paradigm-shifted world in which the 2.9 billion letter sequence (nucleotide base pairs) of the human genome is available as a fundamental resource for scientific discovery[1,2]. Some findings from the completion of the human genome were expected, confirming knowledge presaged by many decades of research in both human and comparative genetics. Other findings, such as the relatively low gene number and large segmental DNA duplications, were unexpected and startling in their scientific and philosophical implications[1]. In either case, the availability of the human genome sequence will probably have profound implications, first on basic research and then on the practice of medicine.

## EST technology for genome sequencing

The journey to this point was not a straight line, nor was it easy in any sense. For us, expressed sequence tags (ESTs) were a crucial starting point[3]. Since recombinant DNA techniques became available in the 1970s, scientists had developed an ability to use cloned DNA, representing a gene of interest, in a wide variety of molecular studies in biology. In the late 1980s, as the Human Genome Project was under discussion, a case was made for a complete genome sequence and a catalog of genes. It is astonishing how quickly access to the complete genome sequence of an organism has become an essential step for any new comprehensive research project. However, only a few years ago, this goal seemed very far away for all but a handful of viruses with very small genomes. Most of the genome sequence projects before 1990 were unavoidably slow and tedious, and targets for achieving even intermediary goals were measured in decades. The EST technology was the first to unleash the full power of an automated random cDNA library sequencing strategy for rapid gene discovery[3,4]. Other efforts lacked both scale and speed. ESTs would help identify new genes by sequencing 300–500 base pairs each of a very large number of cDNAs from a variety of tissues. ESTs could also be used to help map the chromosomal location of genes, recover corresponding genomic sequence, and retrieve complete cDNA clones for further analysis. Perhaps most important of all, ESTs contained enough information to identify an enormous number of genes by similarity searching of electronic databases. When the results were published, the scientific community had the largest collection of human genes in the history of genomic research at that point in time.

Necessity is the mother of invention, and this is no less true for genomics than for other fields. By the mid-1990s, increasingly large numbers of ESTs necessitated the development of computational methods to combine overlapping sequences in a way similar to contig assembly, but with orders-of-magnitudes more data. EST assembly served both to reduce redundancy (multiple copies of the same EST sequence) and to capitalize on it (to create consensus sequences representing up to the full length of the cDNA). The bioinformatics that developed as a consequence of those efforts, in turn, made it possible to explore the entire genomic sequence of a free-living organism.

The first organism targeted was *Haemophilus influenzae* (Ref. 5). This is an important pathogen in its own right, and an elegant model for all of microbiology. The plan was to randomly fragment the bacteria's genomic DNA into small pieces, repeatedly sequence the fragmented DNA until, on average, every nucleotide had been sequenced an appropriate number of times according to a Poisson distribution, and then apply very powerful computational assembly tools (combined with a directed effort to close the remaining gaps) to provide a final fully-assembled complete genome. Along the way, it became necessary to master the advanced automation, robotics and other features of industrial scale DNA sequencing. Since the 1995 publication of *H. influenzae* (Ref. 5), many more genome sequences of free-living organisms have been determined (http://www.tigr.org/tdb/mdb/mdbcomplete.html). The approach is called whole-genome shotgun sequencing, and it formed the basis for our publication of the sequence of first the fruit fly[6] and then the human genome[1].

## Shifting the paradigms

Our genomic sequence provides a unique record of who we are and how we evolved as a species, including the fundamental unity of all human beings[7]. The knowledge fostered by understanding the genome might resolve which human characteristics are innate or acquired, as

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well as the interplay between heredity and environment in defining susceptibility to illness. Such an understanding will make it possible to study how our genomic DNA varies among cohorts of patients, especially the role of such variation in important illnesses and in responses to pharmaceuticals[8–10]. We can also begin new ways of asking fundamental questions regarding complex aspects of the human condition such as language, thought, self-awareness, and higher-order consciousness. The study of the genome and the associated protein content (proteomics) of free-living organisms will eventually make it possible to localize and annotate every human gene, as well as the regulatory elements that control the timing, organ-site specificity, extent of gene expression, protein levels, and the post-translational modifications that define health or illness. For any given physiological process, we will have a new paradigm for addressing its evolution, development, function and mechanism in causing disease, and in affecting the onset and outcome of disease.

Now, we can also more systematically explore curious, and indeed almost mysterious, innate differences between individuals, mediated by epigenetic factors. For example, there are vast numbers of retroelements in mammalian genomes[1,2]. Recent data suggests that somatically active retrotransposons might mediate interference of transcription in neighboring genes, and in some cases this can lead to heritable epigenetic effects. Thus, one can observe variable gene-expressivity in the absence of genetic diversity in the classic sense – a phenomenon illustrated in isogenic agouti ($A^{vy}$) mice[11]. Such mice can display a variable pattern of yellow fur, obesity, diabetes, and so on, depending on the presence of an active intra-cisternal A particle retrotransposon. Whole genomic databases should significantly help to bring an understanding to these most decidedly non-Mendelian phenomena.

## Impact on drug discovery

We have also completed the mouse genome, and rat and dog genome sequencing is currently underway. A number of novel genes have been discovered through this sequencing. These achievements, and the supporting computational biology that has been simultaneously developed, will drive the discovery of new diagnostics and pharmaceuticals in ways that were unimaginable even a few years ago. For the first time, we can utilize the reference DNA sequence for the entire human genome, and the entire set of protein coding genes that total ~30,000, a number smaller than expected. We will have an ever-growing anthology of genomic information from various model organisms that will be essential to modern pharmaceutical discovery and development, and eventually we will have the tools to understand how human complexity is reconciled with relatively small gene numbers.

Target discovery will be accelerated through: (1) interactive programs of protein-based analysis at scale; (2) proteomic analysis of cell compartments in tissues and standardized cell lines; (3) evaluation of post-translational modification and proteolytic processing profiles; (4) true exon-based RNA analysis; (5) DNA variation analyses; (6) high-throughput functional assays; and (7) predictive/molecular toxicology (toxicogenomics), including protein surrogate markers of adverse reactions and efficacy. Sophisticated computational biology tools now make possible a broad examination of gene classes and gene variations (polymorphisms), including the regulatory elements that govern the rate and tissue specificity of gene expression. Comparative genomics will enable significantly more-efficient prediction of gene structure and function and, perhaps more importantly, will enable better use of animal models to define and validate targets for drug development and predict the outcome of clinical trials. Understanding the full range of gene duplications might make it possible to anticipate unintended or 'non-specific' actions of what appear to be 'specific' therapeutic interventions.

Target discovery, lead compound identification, biochemical pharmacology, toxicology, exhaustive literature annotation, and clinical trials, can now be merged with the science of bioinformatics into a powerful and unified machine for discovering and developing new products. This unified process will provide new opportunities for rational small- and large-molecule design, including novel approaches for cancer vaccines, and the reduction of unexpected serious side effects. Fewer pharmaceuticals will be encumbered by 'black box' warnings on the product label or be the subject of market withdrawals.

Taken together, these advances will permit scientists who are versed in the new world of information and computation, to speed the identification of new agents, eliminating products that will probably display toxicity or poor efficacy, and reducing the formidable costs and risks associated with the current paradigms of drug discovery and development. The future is now.

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