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Genomics in Cancer Drug Discovery and Development

抗癌药物发现和开发中的基因组学

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导　言

五十年来，肿瘤治疗的发展主要是针对肿瘤的无限增殖这一恶性特性；其结果是，当前广泛使用的抗癌药物主要为杀伤快速增殖细胞群的细胞毒类药物。化疗在某些特定背景下可能取得成功，但其严重的、有时是难以耐受的毒性却降低其治疗顺应性以及总体上对延长患者的生存时间鲜有助益，成为抗肿瘤药物研发与治疗中亟待解决的突出问题。

过去十年中，抗肿瘤药物的发现模式经历了巨大转变，其焦点已从前述的广谱增殖抑制剂历史性地转移到针对启动或驱动恶性肿瘤的特定蛋白的小分子药物和生物制品。这一全新治疗范式的确立是植根于我们对驱使细胞向恶性演化的本质特征日益深刻的认识。这些本质特征包括：生长信号的自足性、抗生长信号的不敏感性、逃避凋亡、无限增殖潜能、持续生成新生血管以及组织侵袭与转移（Hanahan 和 Weinberg，2000）。最近，靶向其中几种特性的药物已经上市，包括靶向新生血管生成的药物［如 Avastin™（bevacizumab）］和靶向促生长信号的药物［如：Gleevec™（imatinib mesylate），Erbitux™（cetuximab），Iressa™（gefitinib），Tarceva™（erlotinib）和 Herceptin™（trastuzumab）］。

很明显，靶向药物开创了一个崭新的时代，给肿瘤患者带来了巨大的治疗益处；但同样明显的是，许多这类药物仅能产生选择性治疗效果。例如，最初认为对 EGFR 靶向治疗（如 Iressa™或 Tarceva™）有效患者的肿瘤应该表达高水平的 EGFR 蛋白；然而，这一观念在对大规模的肺癌、胰腺癌、结肠癌患者的研究中并未得到证实。新近的证据显示，治疗效果特别突出的患者，其肿瘤携带着促进细胞存活的突变 EGFR 基因（Harber 等综述，2005）。不幸的是，随着研究样本的增加，突变与药物反应性之间的相关性却降低了，突出显示药物反应性与基因型之间关系的复杂性。与此相似，Herceptin 只对一部分 Her2 阳性的乳腺癌患者有效，原因待明（Baselga 等，2004）。因此，靶向药物虽然代表着肿瘤治疗理念的突破，但也面临着怎样选择治疗对象的巨大挑战。

抗肿瘤药物开发的焦点向靶向肿瘤驱动分子，特别是细胞内信号蛋白的转移为构建“药理学轨迹（pharmacological audit trail）”提供了独特的机会（第 8 章）。根据酶或受体功能下游信号转导过程，可以在细胞模型、临床前疾病模型直至早期临床试验各阶段实施药物—靶标相互作用的分子监测。这种分子监测能够监控化合物对其设计靶标的作用，从而确证作用机制（Proof-of-Mechanism，PoM）并建立能反映最佳用药剂量和给药方案的药效学-药动学（PK-PD）关系。监测结果不但可以为进一步的开发提供重要的参考依据，而且特别是在联合用药的情况下，还可以从分子水平准确地解析新分子靶向药物的临床疗效。如果结合预测效应的分子标志，可以有效地监控药物的治疗效果。

抗癌药物发现和开发中的基因组学

当前抗癌药物发现最重要的单一驱动因素也许是我们对肿瘤基因组的了解，特别是对编码基因、蛋白及调控元件的了解。基因组测序的自动化与微型化使我们现在对癌细胞的基因及其表达状态有了真正全面的认识。如何利用这一巨大的基因组资源进行肿瘤

检测和治疗构成了推出本卷《癌症研究进展》的基本背景。

第 1 至 7 章:肿瘤诊断标志与治疗靶标的发现

通过检测基因或蛋白表达谱在分子水平区分癌细胞和正常细胞,使肿瘤的分子诊断成为可能(第 1、2 章)。在辅助选择合适的治疗对象和在特定亚群的肿瘤患者中证实新的治疗策略方面,表达分析已获得了卓有成效的应用(第 3 章)。诊断水平的提高使得早期治疗成为可能。Fuchs 和 Borkhardt(第 4 章)和 Li 等(第 5 章)阐述了如何利用已包含绝大多数人类基因的小干扰 RNA 和核糖酶文库来鉴定对细胞存活至关重要蛋白的编码基因。这些策略为针对编码蛋白的小分子筛选和药物先导的确认提供了关键支撑点。在第 6 章中,Caldwell 集中论述了如何利用这些分子水平及细胞水平小分子筛选获得的信息,确定在细胞水平具有活性的药物先导并证实其作用机制。第 7 章讨论了如何应用肿瘤抗原作为潜在的治疗靶标和疾病标志。

第 8 章:抗肿瘤研究的临床前试验模型

早期证实新靶标面临的一个主要困难是建立经良好设计、以机制为基础的临床前疾病动物模型。在传统化疗药物的开发过程中已形成了一种普遍观念,即恶性肿瘤的动物模型不但不能真正体现药物在人体内的治疗效果,而且也缺乏符合实际的预报价值。确实,推动抗肿瘤药物临床前开发的人肿瘤细胞异种移植瘤难以模拟人体肿瘤本身;然而,经良好设计、携带特定突变或特定遗传背景的动物模型,有助于揭示"药理学轨迹",无疑将有力地推动基于分子机制的药物开发。Kung 指出:"我们必须使用分子靶向模型来解决靶向治疗遭遇的问题。"

第 9 至 11 章:靶向治疗从啮齿动物模型过渡到人体:应用分子标志监测药物作用

靶向肿瘤治疗从啮齿动物模型向人体的成功过渡,需要将临床前获得的有关药物信息,包括在分子水平抑制靶标所需的最佳剂量和用药方案,应用于 I、II 期临床试验(第 9 章)。对药效学标志和预报疗效的分子标志进行早期开发和确证并应用于临床可以及时评估推论中的药物作用机制在人体内的相关性并指导目标患者的用药过程(第 10 章)。

长久以来,血液和组织样品就被用来监测药物的疗效。例如通过监测血液中 CA-125 和前列腺特异性抗原(PSA)来分别反映卵巢癌和前列腺癌的治疗效果。然而,这些标志虽然可以用作反映疗效的替代指标,但却并不能预告药物在病变组织中的始初作用。相反,采用标记药物,光学显像可以直观地评估药物与靶标的相互作用、药物对靶标水平的调节以及获取药物发挥疗效的的早期指标如肿瘤缩小或葡萄糖摄取改变。光学显像技术对评价新药疗效提供了一种快捷有效的无创性监控方法(第 11 章)。

第 12、13 章:新分子靶向抗肿瘤药物面临的社会经济与管理挑战

新的治疗选择带来了巨大的社会经济挑战(第 12 章)。虽然可能存在较大差异,但一个新药从其研究伊始直至通过新药审批的耗费确实巨大,平均达 8.81 亿美元(2005 年生物医药工业顾问委员会评估结果)。这些花费连同为制药公司创造股票的价值一起,最终

演化成高药价并转嫁给患者。例如，使用 Erbitux™和 Zevalin™的患者，每月的治疗费用分别高达 1.7 万和 2.4 万美元(http://www.slate.com/id/2102844/)。更为突出的是，许多这类药物都必须长期使用。因此，虽然这些药物具有突出优势，但是却给社会带来了难以承受的经济负担。与此相似，管理机构也面临严重的挑战。他们必须面对日益增多的患者咨询、工业界的游说、要求快速审批的压力以及药物快速审批的机制性问题等。有关靶向药物的信息、特别是源于患者人群基因组分析的资料已引起了广泛讨论，这有可能成为推动循证医学的关键力量(第 13 章)。

必须强调的是，本书并非涵盖所有相关问题，而仅仅是一个概要，目的是让人们了解基因组科学在怎样影响着肿瘤的检查和治疗，这种影响怎样改变着肿瘤治疗的社会经济与管理。因此，对于相关读者来说，阅读本书仅仅是一个起点。

我们衷心感谢 Elsevier 的许多同仁，是他们使本书得以顺利出版。Hilary Rowe 首先倡议阐述基因组学对抗肿瘤药物发现的影响；Melissa Turner 组织本书的撰稿；Phil Carpenter 和 Mara Corner 将这些章节组织成为本卷《癌症研究进展》；George van de Woude 和 George Klein 博士承接本书的发行工作以及 Ejaz Ahmad 与 Prakash Kumar 进行了卓越的编辑工作。最后，我们还要诚挚地感谢本卷的撰稿人，没有他们的奉献，本书是不可能面世的。

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Introduction

The development of cancer therapies over the past 50 years has largely focused on malignancy as a disease of uncontrolled proliferation. Consequently, the battery of anticancer agents in wide use today are mostly cytotoxics, tailored to kill rapidly proliferating cell populations. Chemotherapeutics, although successful in a few select settings, are associated with a high degree of toxicity, sometimes intolerable, decreasing therapeutic compliance, and overall, affording little benefit to cancer patient survival.

In the past decade, oncology drug discovery has undergone a paradigm shift, moving from broad proliferative antagonists toward "molecularly targeted" drugs, small molecules and biologics that are specifically tailored to modulate the proteins that cause or drive malignancy. The underlying rationale for these new therapies comes from our increasing understanding of the cellular traits that cells must acquire to develop a full blown malignancy (Hanahan and Weinberg, 2000), that is, self-sufficiency in growth signals, insensitivity to growth-inhibitory (antigrowth) signals, evasion of programed cell death (apoptosis), limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis. Recently marketed drugs target several of these traits such as angiogenesis [e.g., Avastin™ (bevacizumab)] and self-sufficiency in growth signaling [e.g., Gleevec™ (imatinib mesylate), Erbitux™ (cetuximab), Iressa™ (gefitinib), Tarceva™ (erlotinib), and Herceptin™ (trastuzumab)].

Although these targeted agents have clearly ushered in a new era in which cancer patients may gain considerable therapeutic benefit, it has become clear that many of these drugs are only selectively active. For example, it was initially thought that responders to EGFR-targeted therapies, such as Iressa™ or Tarceva™, would be those whose tumors expressed high levels of the EGFR protein. However, this concept could not be validated in larger series of lung, pancreatic, or colon patients. More recent evidence shows that patients whose tumors do respond particularly well harbor mutations within the EGFR gene, which engages prosurvival mechanisms within the cell (reviewed in Haber *et al.*, 2005). As subsequent studies have grown larger, the correlation between mutation and drug response is less clear-cut, underscoring the complexity of the drug–genotype relationship. Likewise,

only a subset of those patients whose breast tumors are Her2 positive will respond to Herceptin™, for reasons that are not entirely clear at this time (Baselga *et al.*, 2004). The foregoing underscores that, although these drugs represent breakthroughs in cancer therapy, a major challenge will be the identification of patients that will most likely respond to specific therapies.

The shift toward developing drugs that target the molecular drivers of cancer, particularly those proteins involved in intracellular signaling, affords unique opportunities to create a "pharmacological audit trail" (Chapter 8). With the knowledge of downstream mediators of enzymatic or receptor functions within the cells, one can begin to molecularly monitor the effects of drug–target interaction, from cell-based assays through preclinical models of disease and eventually into the early phases of clinical development in man. These molecular assays enable pharmacodynamic measurements of a compound's effect on its intended target, establishing both a Proof-of-Mechanism (PoM) as well as pharmacodynamic–pharmacokinetic (PK–PD) relationships that can inform optimal drug dose and schedule. These measurements provide important guideposts for subsequent development, particularly in combination therapy settings, where the clinical effects of the new therapeutics can be accurately interpreted at a molecular level. In combination with predictive markers of response, a sufficiently rigorous test of a drug's efficacy can follow.

GENOMICS IN CANCER DRUG DISCOVERY AND DEVELOPMENT

Perhaps the single-most important driver of current oncology drug discovery is our knowledge of the cancer genome, particularly at the level of expression of encoded genes, proteins, and regulatory elements. The coalescence of genome sequencing with laboratory automation and miniaturization now enables a truly global view of the state of a cancer cell's genes and their expression. The translation of this vast genomic resource into useful insights and tools for the detection and treatment of cancer is the context in which the current volume of *Advances in Cancer Research* was conceived.

CHAPTERS 1–7: DISCOVERY OF CANCER DIAGNOSTICS AND NEW THERAPEUTIC TARGETS

By examining the signatures of gene or protein expression, cancer cells can now be readily differentiated from their normal counterparts

at a molecular level, thus enabling the possibility of cancer diagnostics (Chapters 1 and 2). Expression analysis has also found significant use in aiding the selection of patients who may respond to therapy as well as delineating new therapeutic strategies for specific subtypes of cancer (Chapter 3). With improved diagnosis comes the need for new points of therapeutic intervention. Fuchs and Borkhardt (Chapter 4) and Li *et al.* (Chapter 5) illustrate how the use of small interfering RNA and ribozyme libraries, which now cover a majority of human genes, can identify those that encode proteins crucial to cell survival. These strategies provide the starting points for small molecule screening campaigns against the encoded proteins and the identification of drug leads for preclinical development. Chapter 6, by Caldwell, focuses on how the information from these screens, as well as highly parallel cell-based small molecule screens, can be used to identify new cell-active drug leads and delineate drug mechanism of action. Chapter 7 discusses the use of tumor antigens as potential targets for therapeutic intervention as well as serving as putative markers of disease.

CHAPTER 8: PRECLINICAL MODELS OF MALIGNANCY

A major challenge in the early validation of new targets is the development of well-designed, mechanism-based preclinical animal models of disease. The traditional development path for chemotherapeutic drugs has instilled the general notion that animal models of malignancy are neither realistic nor predictive of therapeutic response in man. While it is certainly true that xenografts of human tumor cells—the workhorse of preclinical oncology drug development—are hardly replicative of a human tumor, mechanism-based drug development can nonetheless benefit considerably from well-designed models that harbor specific mutations or genetic backgrounds, for which part of the "pharmacological audit trail" can be explored. As Kung points out, "We must use targeted models to ask questions about targeted therapies."

CHAPTERS 9–11: TRANSLATING NOVEL TARGETED THERAPIES FROM RODENTS TO MAN: BIOMARKERS TO MONITOR DRUG ACTION

The successful transition of targeted oncology therapeutics from rodent models to man is predicated on the transfer of preclinical knowledge of drug behavior, such as the doses and schedules required for optimal target inhibition at a molecular level, into the Phase I/II setting (Chapter 9).

Early development, rigorous validation, and transfer of these biomarker assays, both pharmacodynamic and predictive, into the clinic ensures the optimal opportunity to evaluate the relevance of the proposed mechanisms in man, and guide administration of the drug to those patients likely to respond to therapeutic intervention (Chapter 10).

Blood and tissue samples have long been used to measure surrogates of drug efficacy. Prevalent examples include monitoring the decrease of CA-125 and prostate-specific antigen (PSA) levels in patients undergoing treatment for ovarian and prostate carcinomas, respectively. Albeit well validated, these markers are nonetheless surrogates and do not enable examination of drug action in disease tissue. In contrast, optical imaging can be used to assess target engagement via labeled drug, target modulation by visualization of target substrate level, as well as early indications of drug efficacy such as tumor shrinkage or glucose uptake. Thus, imaging technologies provide a means by which the effect of novel therapies can be rapidly and effectively monitored without direct access to the site of disease (Chapter 11).

CHAPTERS 12–13: THE SOCIOECONOMIC AND REGULATORY CHALLENGES OF NOVEL TARGETED ONCOLOGY THERAPEUTICS

With new therapeutic options come considerable socioeconomic challenges (Chapter 12). Although estimates vary widely, the costs associated with bringing a new drug through approval are significant, with a mean of US$881 million (from a detailed analysis by the Biomedical Industry Advisory Group, 2005). These costs, and the need to create shareholder value for pharmaceutical companies, translate into high-priced drugs, as much as US$17,000 for Erbitux™ and US$24,000 for Zevalin™ per patient per month (http://www.slate.com/id/2102844/). Many of these drugs will be taken over long periods of time. Thus, although the benefits of these new therapies are clear, can society sustain the financial burden? Similarly, regulatory agencies face significant challenges—increasing patient advocacy, industry lobbying, pressure for more rapid approval, and the mechanisms to continue to evaluate fast-track approved drugs. The information associated with targeted agents, particularly data derived from genomic analysis of patient populations, has provoked considerable debate and has been responded to, in part, by the *Critical Path Initiative* in the US. This is likely to become a key driver for evidence-based medicine (Chapter 13).

It must be emphasized that this volume is not intended to be comprehensive, but rather to provide a snapshot of how genomic sciences are impacting the detection and treatment of cancer and how these changes are likely to affect the regulatory and socioeconomic landscape of cancer management. The chapters within should be viewed as starting points for the interested reader.

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