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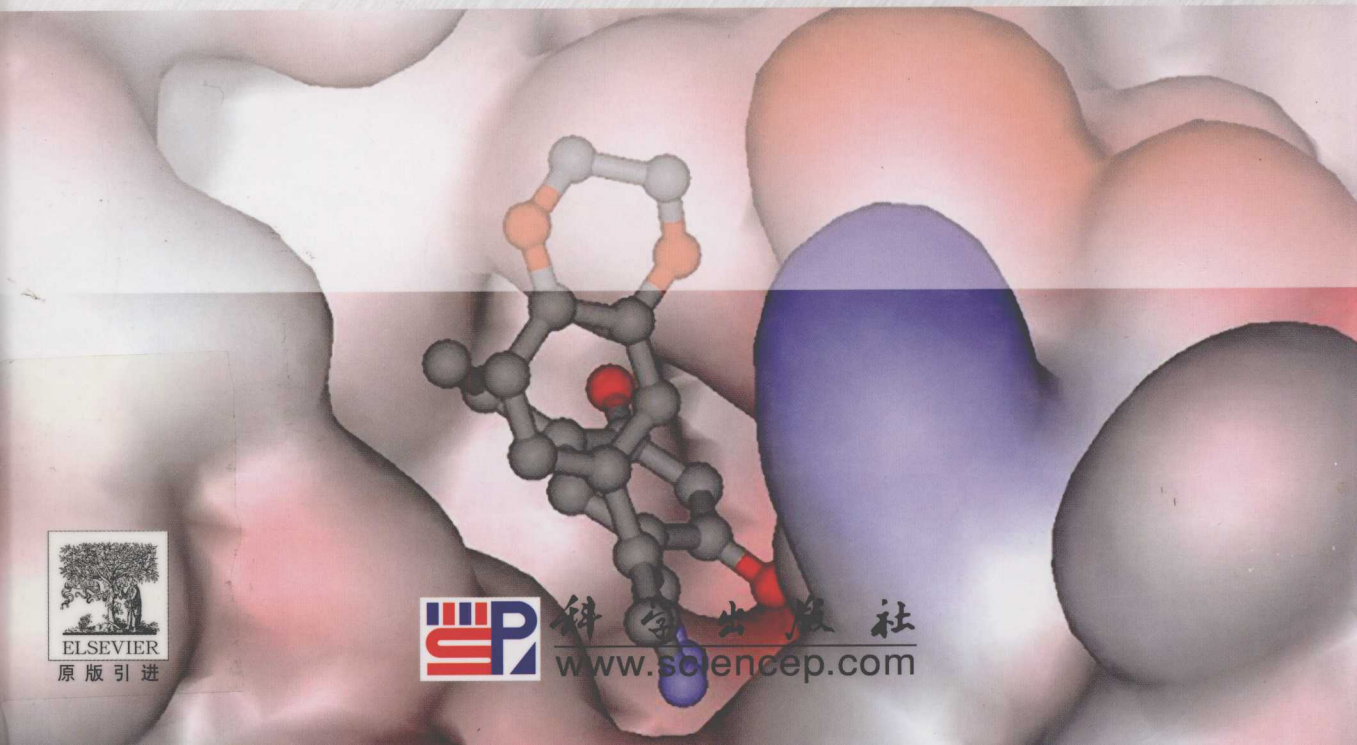
Cancer Drug Design and Discovery

癌症药物设计与发现

Stephen Neidle



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导　读

在癌症发生发展的研究中，人们历经了漫长而曲折的过程，提出了许多的理论和学说。肿瘤研究在经历了20世纪70年代的癌基因时代，80年代的抑癌基因时代，90年代的多基因时代，进入新的世纪以来，人们已不再满足于孤立地研究癌基因或抑癌基因的结构变化，而是将其以蛋白组的形式、以基因家族的形式与细胞的重要生命活动联系在一起，引发了一系列的重大突破，包括肿瘤多步骤理论的提出、DNA修复理论的形成、细胞凋亡理论的形成、细胞周期核心机制的阐明、细胞周期启动机制的阐明、细胞中多条信号转导途径的阐明，最终使科学家们冲出了癌症研究在黑暗中摸索与茫然的处境，看到了曙光。抗癌药物的研究也随着理论的更新和技术的进步，从非选择性的细胞毒药物的筛选转向高选择性的靶向药物的寻找。目前已有近百种分子靶向药物用于临床和正在进行临床研究，为癌症的治疗尤其实体癌的治疗起到了积极地推动作用。

本书以抗癌药物设计与发现为主线，从基本原理、方法学、临床研究中的药物、新化合物和临床抗癌药物应用现状等几个方面系统地阐述了当代癌症治疗药物发现的综合靶标、技术与模型、快速循证医学原则与临床试验设计的审批，代表性地描述了方法学中所涉及的具体实例和发现的新药，前瞻性地指出在临床上抗癌药物应用过程中无论是常规化疗药物还是目前研究较多的分子靶向药物均存在产生耐药性的问题。本书所包含的理论和内容之新颖、技术手段之先进、新药品种之多都是以前相关学科领域的参考书所不及的。由于本书的参编人员多为国际上相关研究领域的权威人物，因此目前它可作为抗癌药物研究早期——新药设计与发现、临床前与临床研究领域的权威参考书籍。

本书主要分为基本原理、方法学、临床研究中的药物、新化合物和临床上抗癌药物应用现状5个部分，层次分明，结构合理，重点突出；不仅在思路上给读者以启发，而且在基本原理、成药性靶点方面进行了详尽地阐述，尤其在基于结构的药物设计与药代动力学优化的思路与新技术方法方面给读者以指导，力求使读者全面而深入地理解目前抗癌新药从设计、发现到临床前研究和临床评价所涉及的新理论、新靶点、新技术和研究中的新药。

第一部分是基本原理，由3个章节组成。首先阐述了当代癌症治疗药物发现中的综合靶标、技术与治疗，接着详尽地论述了从体外细胞水平研究获得的信息，进行临床前药效学和药动学研究，通过体内动物肿瘤模型发现选择性并提示预见性。之后对采用快速循证医学原则进行临床试验设计与审批进行了详尽地阐述，尤其指出了临床试验终点指标的设计与选择的更新和加速药物开发的其他途径。

第二部分是方法学，由3个章节组成。首先从结构生物学与抗癌药物设计着手，着重讨论了高通量X射线衍射分析在结构生物学与基于结构的药物设计，例举了周期素依赖性蛋白激酶抑制剂，如何从片段目标物到临床候选物的研究过程；接着详尽地阐述了天然产物化学与抗癌药物发现，并例举了14种天然产物来源的抗肿瘤药物；之后对药物发现中的药代动力学与吸收分布代谢排泄优化进行了详细论述，指出药物治疗中的生化学屏障是外排转运蛋白。

第三部分是临床研究中的药物，由3个章节组成。首先以替莫唑胺为代表，阐述了从细胞毒类化合物到分子靶向药物的研究过程；接着以喜树碱为例，具体论述了靶向癌细胞死亡与基因的喜树碱类衍生物的设计、构效关系等研究；之后阐述了靶向胸苷酸合成酶的抗叶酸药物对癌症治疗的作用。

第四部分是新化合物，由7个章节组成。首先阐述了靶向非活性激酶作为抗癌药物发现的基础结构，例举了c-Kit、c-Abl、bRaf、P38和VEGF-R2与发现新药的关系；接着分别论述了癌细胞周期抑制剂、抑制DNA修复作为一种癌症治疗靶点、热休克蛋白90抑制剂、肿瘤血管生成抑制剂以及RAF-ERK信号转导的生物学及评价方法，尤其重点阐述了上述靶点抑制剂发现的现状与未来发展方向。

第五部分是临床上抗癌药物应用现状，由2个章节组成。着重论述了临床用药过程中所面临的抗癌药物耐药性的挑战，并对药物开发过程中和临床开发过程中开发失败药物的基础和模式进行了较详尽地分析。

本书的主要特色在于以下几个方面：

(1)着重介绍了药物发现过程中所涉及的“成药性的”靶点、动物模型范围与局限性和临床试验设计与规范化问题；

(2)详细地介绍了化学、基于结构的药物设计与药代动力学优化等；

(3)系统地介绍了一些临床研究中代表药物和新的靶点抑制剂；

(4)讨论了目前临床上抗癌药物应用过程中的耐药性和新药开发过程中开发失败药物的模式。

书中附有大量的图表，有助于读者理解。可以说，本书是目前市面上关于抗癌药物设计与发现、临床前到临床研究内容最新且最丰富、知识水平最前沿的一本难得的参考书。

总之，抗癌药物研究已提高到一个全新的水平。概念、理论思路、认识已更新，技术手段也在不断进步。抗癌药物的设计与发现将伴随癌基因组学及蛋白质组学的深入解析和药学技术的进步，针对新的“成药性的”靶点，不断研制出临床治疗效果好且毒副作用小的新型药物。

陈晓光

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关于主编

Stephen Neidle，英国抗癌研究协会专业委员会委员，化学生物学教授，伦敦大学药学院癌症药物中心主任，他带领一个研究小组从事靶向端粒酶及其他癌症-相关基因的基于结构与药物化学的新型药物设计与研究。他的工作获得皇家化学会的药物化学与跨学科等奖项，同时获得法国治疗学会的安万特奖。

引　言

公众和从事生物医学研究的专业人员同样对新抗癌药物的要求从未得到满足。全球有800多种新抗癌药物正在进行Ⅰ期临床研究。个人的经验常常驱动公众的需求，新型有潜力药物的媒体报道（或大肆炒作）常常会提高大家的期望值。我们作为科学家、临床医生及癌症研究团体不能仅仅满足患者的需求，而是随着过去20年内生物学、生物化学和人类癌症遗传学领域知识的不断增长，不断提高乐观态度。相对于过去使用非选择性的抗癌药物所取得的治疗效果，我们期望将这些所有的知识都能转变成更加有效且毒性更低的治疗手段。

本书主要源于我在英国癌症研究所的工作经历，工作中有幸与许多临床医生和科学家们接触，特别是将癌症治疗学作为一个学科发展的Tim McElwain、Tom Connors 和Ken Harrap。基于此，我希望本书能够在促进抗癌药物发现的基础与转型的独特相互作用方面起到一定的作用。本书的主要目的是详尽阐述21世纪抗癌药物的发现过程、从靶点的发现到确认、经过前期发现与优化到药理学评价，最终进入临床研究。读者能够在本书中看到许多研究的全部过程，更为重要地是能够了解涉及其中的核心问题及复杂性。本书主要分为5个部分：基本原理、方法学、临床正在研究的药物、新化合物，以及临床上抗癌药物的应用现状。本书没有对癌症生物学的基本知识进行描述，主要原因在于读者可以浏览其他大量的优秀图书，在此特别推荐RA Weinber主编的一本书（癌症生物学，Garland出版社，2006）。特殊药物的范例贯穿于全书的许多章节是本书的特色，许多范例还包括课堂所提出的问题。

第一部分中的各章节介绍了药物的发现过程，同时还涉及有关“成药性的”靶点、动物模型的范围与局限性，以及临床试验设计与规范化审批方面的问题。随着癌症分子基础知识的进展紧密推动着科技领域的进步，特别是在化学、基于结构的药物设计与药代动力学方面。这些内容在第二部分中加以阐述。特别是一些化学概念，同时也渗透到下面各个章节。第三和第四部分分别介绍了一些已建立的癌症靶点和新的癌症靶点，同时对靶向这些靶点的药物进行了介绍。一般来说，药物的发现特别是癌症治疗过程中充满着荆棘。我们很自信地预测进入Ⅰ期临床研究的800个化合物中只有不到1%能最终进入药品注册及临床应用阶段。针对这么高的失败率，我们怎样才能使其提高成功率？在最后一部分的章节中主要集中介绍了诸如耐药性等问题的挑战，更重要地是对一些开发失败药物的基础进行了分析。

本人非常感谢全体撰稿人，不仅对他们付出的辛苦劳动，而且对他们在应对富有挑战性截稿日期所表现出来的协作精神。任何一本书的出版都涉及许多人共同工作的复杂过程。本书也不例外。Elsevier的工作人员展示出非常娴熟的工作技能及专业背景，特别是Kirsten Funk历经坎坷一直在指导该项目。我伦敦的助手Irene Dougherty

在与撰稿人保持经常联系中起到关键作用。最后，感谢我的妻子 Andrea 的支持与耐心。

Stephen Neidle
伦敦，2007 年 8 月

（陈晓光　译）

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About the editor

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