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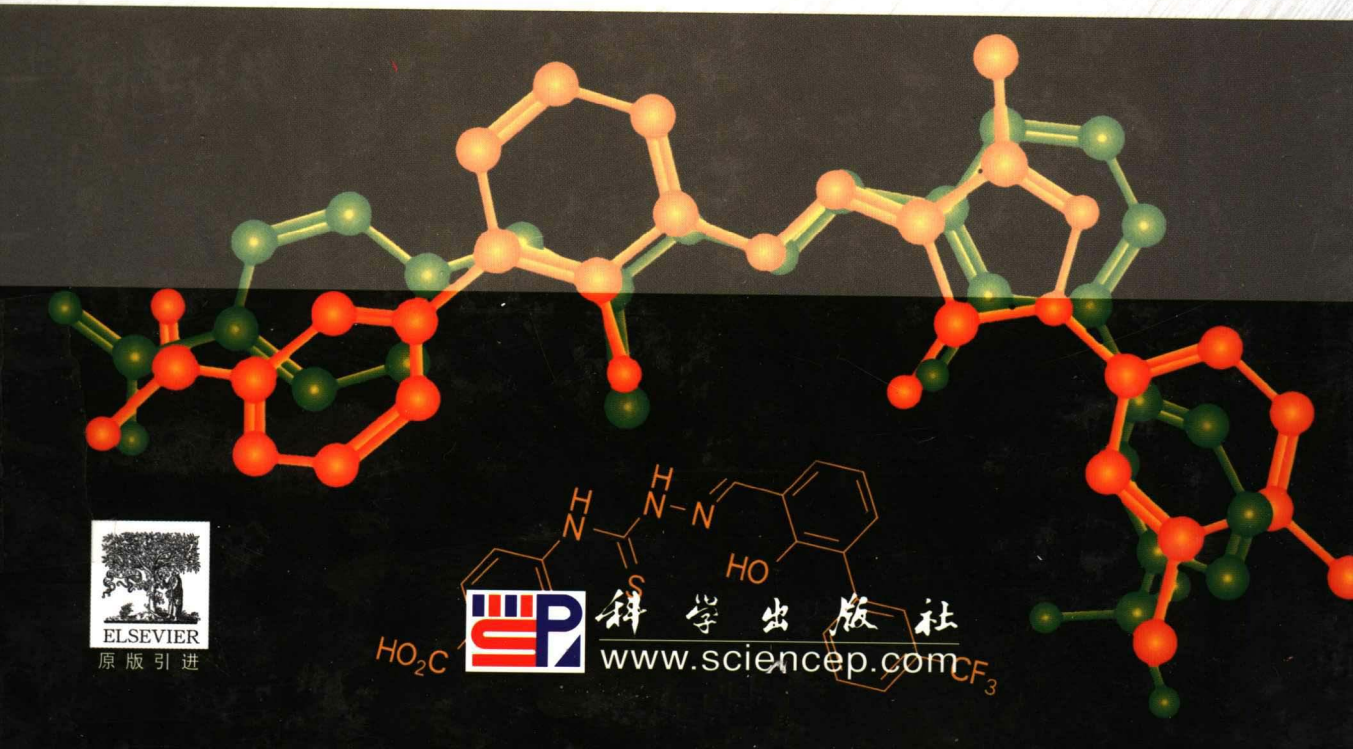
Target Validation in Drug Discovery

药物发现中的靶标确认

Brian W. Metcalf and Susan Dillon



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序　言

基因组的革命，包括人类基因组的测序以及后续一系列灿烂的科技平台的快速发展，促进了生物医学的快速发展，也让我们期待更多新药的发现。尽管新药从发现到投入市场需要 15 年的周期，但是使大量基因组学革命，或者是使人类基因组测序获得商业上的成功目前还未能实现。近期由美国医学大学联合会（AAMC）以及 FDA 组织的会议发表的一篇题为“医学产品的关键途径”的文章指出：“解密人类基因组，给我们带来了很大的期望，让我们可以更好的选择新药的治疗靶点。但不幸的是，我们这种围绕着基因组学的兴奋情绪并没有继续在人类的身上发展下去。”事实上，FDA 批准的新药应用（NDAs）由 1996 年的 53 个逐年减少到 1999 年的 35 个，一直到 2002 年的 17 个，甚至到 2005 年的 15 个。尽管现在就断定基因组后新药的质量和数量不会有任何优势还为时过早，但无论如何，年度新药的减少还是引起了广泛的关注，大多数的制药公司开始审视他们自己的药物开发过程或公司的组织结构，并且进行了一系列的公司合并与重组。现在迫切的需要新药物、新靶点能够对药物产生非常有效的效果。事实上，目前来自于基因组学，生物类似物，生物模仿方面的竞争在持续增长着，药物与生物技术工业能否生产出对疾病或者是健康保健有更多价值的新药，面临着前所未有的压力。

药物与生物工程工业如何能够应对来自于产量与新产品的新颖性的双重压力？一个假想的方法是：首先利用人类基因组测序的优势，找出新的办法，确定造成疾病确切的原因及靶点。尽管已经测出了人类全部的 30 000 个基因，但是这种研究方向上的新转变，还是带来了非常大的挑战。因为疾病与已知基因序列之间的关系并不为人所知，所以首先找出哪些基因可以作为药物的靶点，并用于疾病的治疗就成了当务之急。

- 哪些基因产生了疾病？哪些与疾病有特别的关系？哪些可以用作药物靶点？
- 确定这些基因需要哪些技术？
- 开发一个新的药物需要投资超过 8 亿美元，研发时间需要 15 年或者更多的时间，那么，我们如何从我们选择的致病基因当中获得收益。
- 怎么样减少我们投资药物面临的风险？由于药物靶点的错误选择使得药物效果不好，而不能够通过三期临床试验的情况是不可以忍受的。

我们的观点是：这些问题的关键就是要在药物的开发与临床发展过程中成功地找出药物的靶点。任何一个有潜力的，用于药物靶向的分子溶液对于疾病都是有影响的。本书重点讲述靶标的有效性。我们选择通过抗体、可溶性受体或取代细胞因子，来研究导致大量成功的新生物制剂产生的背景知识。文中章节介绍了如何选择这些药物的靶点，如何使之生效，利用哪些技术，以及用哪些已有的生物和临床结果来验证这些靶点与人类疾病的相关性。

总之，靶点的有效性必须涉及以下问题：

- 靶点是否与疾病的病理学有联系？
- 细胞表达的靶点是否与疾病的病理学有联系？

- 靶点是否在体内表达?
- 在动物模型中药物达有效浓度时是否确实与靶点相互作用?

同样地，还有一些与临床前靶点有效性研究相关的问题：

- 动物模型常常不会很准确地反映或模拟人类疾病的过程。
- 有时种属特异性问题时我们用替代分子作临床前的证据。
- 有时很难阐述清楚人类/动物基因同源性问题。

尽管如此，在临床前的研究中动物模型仍然是研究靶点识别和有效性不可或缺的步骤。应用许多新的技术已经能解决其中一些问题，在第一部分中有相关阐述。前一部分介绍制造转基因小鼠模型，敲除小鼠的某一个感兴趣基因然后对随之的表型进行研究。第一章介绍了研究中应用的基因技术，这些研究的目的是在 5 年内敲除 5000 个有可能与药物相关的基因。据预测，在这个过程中将发现许多通常与疾病相关的基因。的确，转基因小鼠研究中得到的结果会在书中接下来的章节中有所涉及—Vaddi 依据这些数据把 CCR-2 作为抗炎药的靶点，而 Benson 参考 IL-12 和 IL-23 亚单位缺陷的小鼠作用靶点 IL-12p40 用于免疫相关疾病的治疗。

我们可以用逆向的方式得到靶点，通过药物作用选出想要的细胞表型，通过高通量筛选找到能转变成该细胞表型的分子，然后分析出分子靶点或受化合物影响的通路。这种方法就是第二章里讲的前化学基因组学，具体讲解了骨基因分化的一个小分子诱导子 Purmorphamine 的发现，以及随之作用于 Hedgehog 通路及相关通路。

由于诸如可溶性受体和抗体这些蛋白质类药物不能通过细胞膜，他们一般只会作用于相关受体的细胞外区域，通过拮抗、去除内源性配体或提高内源性配体的浓度而发挥作用。但是蛋白类药物对相关受体的这种作用使拮抗剂在细胞表面启动相应的转导通路。从理论上讲，我们可以进一步提出：在同一条通路中除了表面受体外，作用于细胞内靶标也应该同样有效。要想这样做，就需要将不能进入细胞且口服不能吸收的蛋白质制剂转变成一种能够进入细胞中的小分子。满足渗透进入细胞所需的物理特性和满足口服吸收是一致的，但不一定完全适合口服吸收的需要。因此找到一个有效的传导通路同时也是从对蛋白类药物的系统服用法（静脉、皮下、肌注）向口服给予小分子药物转变的范例。在我们精选的几个章节中主要叙述了以下内容：确定药物作用靶点的新技术（第一部分），通过系统服用生物性药物确认疾病相关通路（第二部分），接着在特定通路中以小分子靶向作用达到口服给药的目的（第三部分）。

表皮生长因子（EGF-1）通路可以用于解释前述的范例。Cetuximab 是一个抗 EGF-1 受体的抗体，已经被批准用于转移性直肠癌的治疗。EGF-1 受体是一种酪氨酸激酶，当 EGF 激活该受体的细胞外域时将会使受体细胞内域的酪氨酸磷酸化，进而引起下游的信号转导。Erlinotib 是一个已被批准用于非小细胞肺癌（NSCLC）和胰腺癌的有效口服药物，它主要通过抑制 EGF-1 受体相关的酪氨酸激酶活性而起作用。第二部分第三章中讲述了 EGFR-1 在癌症中的作用，并对 Cetuximab 在临床应用的价值进行了评定。第三部分第九章阐述了 Erlinotib 的发现及其临床应用价值。Erlinotib 和 Cetuximab 均作用同一信号转导通路，这也对第二部分第三章 Cetuximab 的内容进行了补充。因此，虽说一个成功的药物有自己独特的作用机制，一个通过系统方法获得的单克隆抗体已证明了 EGF 通路可作为新药靶点的一个可行性选择，而且 Erlinotib 是具有

口服活性的小分子与 Cetuximab 作用于同一条通路。

抗 TNF 生物制剂的成功应用进一步有力地证实了上述范例。比如说 Infliximab——一个抗 TNFα 的单抗，Etanercept——一个人 p75TNF 受体 IgG Fc 融合蛋白，均已经通过临床实验证明其对类风湿性关节炎和其他炎症性疾病的治疗有显著疗效。这些生物制剂证实了将拮抗 TNF 作为抗炎症靶点的可行性。目前还有许多人致力于干扰 TNF 通路的下游分子作为靶点的研究，除了 TNF 受体之外，正在研究的小分子可口服吸收的药物或许也具有已系统研究的抗 TNF 生物制剂的相似作用。第二部分第五章讲述了抗 TNF 生物制剂发现的基础理论依据。Elliott 重点论证了肠壁上 TNF 的局部产物同 Crohn 病和溃疡性结肠炎病因学之间的关系。这些基础研究使我们对 IBD 病人有了有效的新治疗方法。正如前面所提到的抗 TNF 生物制剂也为诸如类风湿性关节炎和其他炎症性疾病提供了有效的新治疗方法。第三部分第十章中讲述了 p38 激酶可作为影响 TNF 信号通路和产物的靶点。第十一章叙述了通过 TNF-α 与其受体结合抑制 NF-KB 通路中的 IKK-2 而研制口服制剂的可能性。

在第二部分的其他章节中，我们讲述了利用生物制剂继续对通路有效性进行的研究，接下来在第三部分讲述了针对同样的通路我们利用小分子法所作的研究。一个令人奇怪的现象是：当用蛋白制剂 Abciximab 成功拮抗整合素 GpⅡb/Ⅲa 后，接下来用小分子法时却未能成功且原因不明。这些章节分别是由 Jordan、Seiffert 和 Billheimer 编写的。相比而言，Duffy 和 Erickson-Miller 提到：造血细胞因子 Thrombopoietin 由于具有免疫原性而在临床实验中失败，但一种模拟小分子 Eltrombopag 在后期临床实验中取得成功。趋化因子受体的配体 CCL 由 Das 和 Yan 在第二部分进行阐述用于拮抗小分子法。在第三部分 Vaddi 认为这些研究成果也可以由抗 TNF 生物制剂的成功应用预测出来，因为细胞因子是由炎症细胞所释放的，其中主要的一类炎症细胞就是吞噬细胞，这些炎症细胞通过 CCR-2 受体介导完成。在某些情况下仅有一方面被提及（第七章），而各自相应的另一方面可能在后面补充，另一种情况是通过对抗 IgE 抗体 Omalizumab 的成功应用阐述再次提及后面相应的部分，而接下来就是讲小分子方法。

我们对药物的发现及发展非常感兴趣，我们之中有一位细胞生物学家，他负责开发筛选能作为药物的单克隆抗体并且对其进行临床前研究，而另一位具有化学背景的科学家在小分子药物开发方面成果卓著。我们相信把已经成功研究生物类药物的理论思维与口服具有生物利用的小分子（作用于同一信号转导通路）的发现联系起来，肯定会探索出新的范例。可以说，作用于相应通路的生物类药物通过临床的证实将具有良好的市场前景，从而起到指明道路的作用。在本书中我们试图通过对几个例证的陈述来使这些方法规范化。

该书适用于生物技术和制药方面的管理人员及相关领域的研究人员，从事信号转导通路基本生物学研究的学者，以及化学和生物学专业的学生。其中一些章节所阐述的理论可被归纳整理及推广到其他新药的研究领域。可以说该书为在药物研发上普及一个新的范例提供了理想的平台，同时也希望本书能给当前由生物医学科学革命性的进步向新药的转化提供一定的帮助。

（北京大学药学院　李长龄　译）

PREFACE

The genomic revolution, which involved sequencing of the human genome and subsequent development of a number of brilliant platform technologies, has led to the anticipation that these biomedical advances will lead to the discovery of new medicines. However, owing to a 15-year cycle from initiation of a drug discovery program to market, commercial success emanating from the genomics revolution or from the sequencing of the human genome has not materialized. The report from a recent conference organized by the Association of American Medical Colleges (AAMC) and the Food and Drug Administration (FDA) entitled "The Critical Path to Medical Products" noted that, "[t]hose deciphering the genome had high expectations that these new discoveries would help select better therapeutic targets. Unfortunately, the excitement around genomics has not carried over to validation in humans." In fact, the number of NDAs (New Drug Applications) approved each year by the FDA has declined from 53 in 1996 to 35 in 1999 to 17 in 2002 to 15 in 2005. It is too early to conclude that advances in the numbers and quality of new drugs will not be forthcoming. Nevertheless, the annual decrease in NDAs is a real concern that has prompted most companies to overhaul their drug discovery processes, or their organizational structures, and also is related to an increasing number of mergers and acquisitions. Drugs directed at new targets likely to have a real impact on disease are desperately needed. In fact, with ever-increasing competition from generics, bio-similars, and bio-follow on drugs, the pressure on the pharmaceutical and biotechnology industries for truly novel medicines with added value to patients and to the health care system becomes even more essential.

How then can the pharmaceutical and biotechnology industries respond to the dual needs of increased productivity and novelty? A likely scenario is to take advantage of the sequencing of the human genome by creating new paradigms for selection and validation of targets that are causal to disease. This change of direction presents an enormous new challenge as the sequences of all 30,000 or so human genes are known, but the linkage of gene sequence to human disease is not. In prioritizing which genes to approach as drug targets several issues must be addressed:

- Which genes are causal to, and not just associated with, disease? Which genes are druggable?
- Which technologies does one need to address these issues?
- How does one proceed upon having chosen a disease gene of interest, given that 15 or more years of investment will be required, estimated by some to be at a cost of over $800 million for each new drug?

- How does one mitigate risk in the face of this required investment? Failures in Phase III clinical trials owing to lack of efficacy related to poor choice of target cannot be tolerated.

From our point of view, many of these issues distill down to successful target validation in drug discovery and clinical development. There is no point in providing a potential molecular solution for a drug target that does not have an impact on disease. This book is directed primarily at the overriding issue of target validation. We have chosen to examine the background leading to a number of successful new biologic agents; by definition protein drugs such as antibodies, soluble receptors, or replacement cytokines. The chapters examine how the targets of these drugs were chosen and validated, what technologies were used, and what biological and clinical results were obtained in support of the hypothesis that these targets were linked to human disease.

In general, the following questions must be addressed in the validation of a target:

- Is the target associated with disease pathology?
- Is the target expressed by cells linked to disease pathology?
- Is the target expressed *in vivo*?
- In animal models does efficacy occur at drug concentrations necessary to interact with the target?

Similarly, there are common issues inherent to preclinical target validation studies:

- Animal models frequently do not accurately reflect or mimic human disease processes.
- Species specificity issues sometimes necessitate the use of surrogate molecules to achieve preclinical proof of concept.
- There is occasional lack of clarity around direct human/animal gene homologs.

Nonetheless, animal modeling remains a prerequisite step in target identification and validation prior to investment in clinical development. A number of new technologies have evolved that are deployed to address some of these issues, some of which are described in Section I. Primary among these is the creation of transgenic mice, in which a gene of interest is knocked out and the subsequent mouse phenotype is studied. Chapter one describes the genetic technologies that are deployed in these studies, in which the goal is to knock out the 5000 genes estimated to be druggable over a 5-year period. It is anticipated that a number of genes will be discovered that are causally linked to disease during the course of this program. Indeed, reference to results obtained from the study of transgenic mice appears often in subsequent chapters in this book—Vaddi relies on such data for the choice of CCR-2 as an anti-inflammatory target, whereas Benson references studies on mice deficient in IL-12 or IL-23 subunits as a basis for targeting IL-12p40 for immune-mediated disease.

One can approach targets in the inverse manner by electing a desirable cell phenotype to be attained by drug action, finding a molecule to effect transformation to that phenotype by high throughput screening and then discovering the molecular target or pathway influenced by that compound. This approach called Forward Chemogenomics is described in chapter two, and is illustrated by the discovery of Purmorphamine as a small molecule inducer of osteogenic

differentiation, and subsequent delineation of the hedgehog pathway as being the pertinent pathway.

As proteinaceous drugs such as soluble receptors and antibodies do not cross the cell membrane, they generally impact at the extracellular domain of the pertinent receptor by antagonism, agonism, or removal of the endogenous ligand or by increasing its concentration. Their success, however, validates the transduction pathway initiated by agonism at the cell surface as a likely pathway for successful intervention. Conceptually, then, one can move further down that same pathway beyond the surface receptor to other intracellular targets that will also be valid. To do so, the nature of the drug must change from a protein that cannot enter cells and is not orally absorbed, to a small molecule capable of entering cells. The physical characteristics required for cell permeation are also consistent with, but not necessarily completely adequate for, oral absorption. So the paradigm of moving down a validated transduction pathway is also that of transitioning from a proteinaceous drug administered by systemic routes (intravenous, subcutaneous, intramuscular) to a small molecule drug given by oral administration. The themes we have developed by our choice of the chapters solicited are therefore novel technologies required for target identification (Section I), validation of disease-associated pathways by systemically administered biological drugs (Section II), followed by small molecule approaches directed at targets later in the indicated pathways to afford orally available drugs (Section III).

This paradigm is illustrated by the epithelial growth factor (EGF-1) pathway. Cetuximab is an anti-EGF-1 growth factor receptor antibody approved for the treatment of metastatic colorectal cancer. The EGF-1 receptor is a tyrosine kinase, wherein activation at the extracellular domain of the receptor by EGF leads to tyrosine phosphorylation on the cytoplasmic domain of the receptor with subsequent signal transduction. Erlinotib is an orally active inhibitor of the tyrosine kinase associated with the EGF-1 receptor that is now approved for the treatment of non–small cell lung cancer (NSCLC) and pancreatic cancer. Chapter three in Section II describes the role of the EGFR-1 in cancer and subsequent clinical evaluation of cetuximab. In Section III, the cetuximab story is complemented by chapter nine on the discovery and clinical evaluation of erlinotib, which takes advantage of the signal transduction pathway validated by cetuximab. Thus, a systemically administered monoclonal antibody, while a successful drug in its own right, has validated the EGF pathway as a viable collection of novel drug targets, and erlinotib is an orally active small molecule acting in the same pathway as cetuximab.

The paradigm is further enforced by the success of the anti-TNF biologics, in which biologics such as infliximab, which is a monoclonal anti-TNFα antibody, and etanercept, a human p75 TNF receptor-IgG Fc fusion protein, have been demonstrated clinically to have dramatic effects in the treatment of rheumatoid arthritis and other inflammatory conditions. These biologics have demonstrated the validity of antagonizing TNF as an anti-inflammatory target. Many other efforts are now underway to intervene at later points in the TNF pathway, other than the TNF receptor, in the search of small molecule, orally available drugs that might have similar positive effects to the systemically administered TNF biologics. Chapter five in Section II lays the groundwork of the discovery of the anti-TNF biologics. Elliott's emphasis is on the demonstration of linkage of local production of TNF in the gut wall to the etiology of Crohn's disease and to ulcerative colitis. Such basic studies led to a powerful

new treatment for patients with IBD. As noted earlier, anti-TNF biologics have also led to powerful new treatments for other inflammatory diseases such as rheumatoid arthritis. Chapter ten in Section III describes p38 kinase as a target that impacts on TNF signaling and production, and the chapter eleven relates to the inhibition of IKK-2 in the NF-KB pathway initiated by TNF-α binding to its receptor as approaches to oral agents.

We present other chapters in Section II that allow us to continue the theme of pathway validation by a biologic agent, and follow in Section III with small molecule approaches directed at the same pathways. In one surprising case, that of antagonizing the integrin GpIIb/IIIa, the protein agent abciximab proved to be successful, whereas the follow-up small molecules failed for unanticipated reasons. These chapters are developed by Jordan and Seiffert and Billheimer, respectively. In comparison, the hematopoietic cytokine thrombopoietin failed in the clinic for reasons of immunogenicity, whereas a small molecule mimetic, eltrombopag is advancing in late phase clinical trials as described by Duffy and Erickson-Miller. The chemokine receptor ligand CCL is described in Section II by Das and Yan, whereas the small molecule approach to antagonism is rationalized by Vaddi in Section III. These studies were also predicated by the success of the anti-TNF biologics, as cytokines are released by infiltrating inflammatory cells, the major one being the macrophage, which undergoes trafficking via the CCR-2 receptor. In some cases only one side is presented (chapter seven), the respective counterpart likely to be developed in the future. Another future counterpart would be represented by the success of the anti-IgE antibody omalizumab, being followed up with a small molecule approach.

We are passionately interested in drug discovery and development. One of us (SD) is a cell biologist with responsibility for the discovery and preclinical development of monoclonal antibodies as drugs, whereas the other (BM) has a chemistry background and leads a small molecule drug discovery effort. We believe that there is a new paradigm to be explored by linking concepts derived from successful biologic drugs that must be administered systemically to the discovery of orally bioavailable small molecules that act in the same signal transduction pathway. Thus the biologic drug points the way by providing clinical proof of concept and demonstrating market success for a later chemical entity that acts in the now-validated pathway. In this book, we attempt to formalize this approach through presentation of several illustrative examples.

Our intended audience includes biotechnology and pharmaceutical executives, those working the laboratories in these industries, academics involved in the basic biology of signal transduction pathways, and students of chemistry and biology. The concepts developed in the chapters presented could be generalized and extrapolated to other new drug discovery efforts. This book should provide an ideal platform to popularize a new paradigm in drug discovery efforts, and hopefully aid in the translation of current revolutionary advancements in the biomedical sciences to new medicines.

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