·导读版·

Handbook of Cell Signaling

(Second Edition)

信号转导手册

（原著第2版）

2

蛋白质磷酸化和去磷酸化

Ralph A. Bradshaw and Edward A. Dennis

ELSEVIER
原版引进

科学出版社

Handbook of Cell Signaling

(Second Edition)

信号转导手册②

（原著第 2 版）

蛋白质磷酸化和去磷酸化

Editors-in-Chief

Ralph A. Bradshaw

Department of Pharmaceutical Chemistry,
University of California, San Francisco,
San Francisco, California

Edward A. Dennis

Department of Chemistry and Biochemistry,
University of California, San Diego,
La Jolla, California

科学出版社

北京

图字：01-2010-4556 号

This is an annotated version of
Handbook of Cell Signaling (Second Edition)
Edited by Ralph A. Bradshaw and Edward A. Dennis.

ISBN: 978-0-12-374145-5 (set)
978-0-12-374146-2 (Volume 1)
978-0-12-374147-9 (Volume 2)
978-0-12-374148-6 (Volume 3)

图书在版编目(CIP)数据

蛋白质磷酸化和去磷酸化：第 2 版：英文 /（美）布拉德肖（Bradshaw, R. A.）主编. —北京：科学出版社，2011
（信号转导手册；2）
ISBN 978-7-03-031274-7

Ⅰ.①蛋… Ⅱ.①布… Ⅲ.①蛋白质-磷酸化作用-英文 Ⅳ.①Q591.1

中国版本图书馆 CIP 数据核字（2011）第 101514 号

责任编辑：孙红梅 李小汀/责任印制：钱玉芬
封面设计：耕者设计工作室

科学出版社出版
北京东黄城根北街 16 号
邮政编码：100717
http://www.sciencep.com
双青印刷厂印刷
科学出版社发行 各地新华书店经销
*
2011 年 6 月第 一 版 开本：787×1092 1/16
2011 年 6 月第一次印刷 印张：35
印数：1—1 800 字数：830 000

定价：136.00 元
（如有印装质量问题，我社负责调换）

导　读

细胞或生物体具有生命和活力的前提是它们能够与外界进行物质、能量和信息的交换。物质和能量较易理解，而信息交流一般要通过其他物质体现形式表现出来——即“信号转导”，确切地说就是指细胞外因子通过与受体（膜受体或核受体）结合，引发细胞内的一系列生物化学反应，蛋白与蛋白相互作用，直至起始细胞生理反应所需基因表达的过程。该转导系统调节着细胞的生长、分化、代谢、适应、凋亡等各种功能活动。“信号转导”（signal transduction）一词是从20世纪80年代末才在生物学文献中出现并开始广泛使用的。之后，与信号转导相关的科学论文数量迅速增加，位列热点科学研究论文统计之首。随着信号转导研究的不断深入和各种信号转导通路的阐明，信号转导的理论知识和方法已经深入到生命科学的各个学科和领域，并且极大地推动了这些学科的发展。例如细胞生物学、发育生物学、免疫学、神经科学与脑科学等，这些学科不仅是生命科学的前沿学科，同时也是信号转导研究的热点。另外，信号转导系统也是癌症、动脉硬化、心肌肥大、组织纤维化，以及各种炎症性疾病和神经退行性疾病的病理发生基础。国际市场调查资料表明，大部分畅销药的作用靶点是膜受体、核受体，或一些离子通道等信号系统成分。因此，深入了解信号转导的分子机理将有助于提高预防和治疗疾病的能力。

以细胞与环境相互作用机制为目标的细胞信号转导研究一直是生命科学研究中的最基本、最广泛，而又最复杂的研究内容。随着研究的深入，人们发现信号转导系统并非单一的垂直型的一些信号通路，而是高度有序且复杂的网络系统，不同成分、不同途径之间存在着相互调节、相互协同、相互制约的关系。在这个网络中，只要一种成分发生变化，我们完全可以想象它的后果——“牵一发而动全身”。因此，全面了解信号转导系统中复杂的组分和它们之间的所有联系至关重要。令人高兴的是，由Ralph A. Bradshaw教授和Edward A. Dennis教授主编的这部《信号转导手册》（第二版）将由科学出版社引进到国内，这部手册是集信号转导基本知识和最新进展的一部好书，在知识性、条理性、系统性、前沿性及权威性等方面都具有独到的优势，对所有从事生命科学和医学研究的科研工作者、教师和研究生而言，都是不可多得的好助手。

细胞信号转导机制的复杂性和多样性既令人振奋，又让人挠头。特别是现代生物学技术突飞猛进的发展、高通量系统性的“组学”研究手段的应用，使研究结果信息量的处理和解析成为破解生物学机制的瓶颈。的确，无论是原核细胞还是真核细胞，单细胞生物的活动就包含了细胞对营养物质、增殖信号等的识别和应答，而多细胞生物体又更为复杂，到了高等真核生物，细胞信号转导不仅体现在细胞水平，还扩展到组织、器官及整个生物体对各自所在环境信号的综合反应和应答机制上。因此，多年以来，许多细胞信号转导方面的参考书都受限于编写内容的组织和条理性，其复杂性和交叉性有时令读者却步。该书围绕信号从“细胞外—膜—细胞质—细胞核—最终引起细胞反应”的过程为贯穿各章节内容的主线，由外及里分别介绍了“经典”信号转导的各个基本组分和

信号转导通路，同时介绍了源于细胞内的非经典信号及诱发的分子事件，为传统的细胞信号转导赋予了新的概念。该书还注释了细胞信号转导机制在人类疾病中的病理基础，并扩展到药物发现、药物开发及临床研究等方面的应用，为读者提供了从基础研究到临床应用的全景。

基于编排和方便国内读者使用的考虑，导读版将原著三册拆分为七册。其中，第1册阐述了经典的细胞信号转导的基本概念，包括信号分子的识别、受体的种类和结构特性及近膜事件等。第2～5册分别介绍了细胞内部胞质中的应激性分子事件，包括受体偶联的信号效应分子，以及第二信使等分子的作用机制和性质。如G蛋白和第二信使环核苷酸、钙离子、脂质分子等特定信号分子及其上下游的相关组分，对它们的超家族组成、分子结构、表达模式、修饰调控和功能等都进行了详细介绍。第6册介绍了细胞核参与的细胞核质之间的信号应答，特别是染色质修饰的相关研究。第7册介绍了细胞内功能区隔信号转导、胞间和细胞基质间的相互作用、疾病病理学（后文将详细介绍这一册的内容）。整部书内容丰富，充分展示了信号转导系统的庞大和复杂。

伴随着现代科学新的研究手段和研究思路的发展，该书的内容更倾向于综合分析各信号转导组分和通路的联系。如Erk MAPK信号通路中的KSR，Toll-like receptor偶联的MyD88和TRIF，以及Focal adhesion网络中的Paxillin和p130Cas，这些蛋白本身不具有任何催化活性，一般被称为脚手架蛋白（Scaffold）或联结蛋白（亦称联结子，adaptor），但它们能够将上下游信号分子或不同通路的信号分子结合在一起，形成复合物，像一个“枢纽”调控不同的时空环境中信号转导的效率和特异性。现代信号转导的研究已不再是孤立地研究单一的一个信号分子或通路，而是以信号分子复合物转导的模式，研究几个分子共同的协同或颉抗作用对通路的影响。这些内容充分反应了信号转导通路交叉调节的复杂性。

细胞信号转导通常被经典地理解为细胞接收外界信号（如细胞膜受体与配体结合）所引发的细胞内的分子事件。而本书第7册向读者展示了近期发展最快的源于细胞内的信号及其诱发的分子事件。例如，蛋白合成时的折叠错误将会引发内质网及过氧化物酶体等细胞器的系列分子事件，达到降解异常折叠或修饰的蛋白质，以实现对蛋白质的质量控制。亚细胞器的动态变化也是一种细胞信号，例如线粒体的断裂与融合（fission and fusion）影响与细胞代谢相关的信号转导，从而诱发细胞凋亡的发生。此外，作者还介绍了最新发现的雌激素受体ER，包括其激素感应器SCAP，以及膜结合的转录因子SREBP的动态调控。这一册的内容为我们展现了细胞信号转导研究的概念性的更新。

传统的信号转导研究都停留在分子和细胞水平。然而“*in vitro cognito sed in vivo veritas*”即“我们可以通过体外实验去探索、发现，然而事实真相却仅存于有机体内”。本书的另一个特色之处是将细胞信号与器官或组织的功能调控立体地结合起来，向读者重点引介了细胞与基质（matrix）之间，以及细胞内各个细胞器和区隔之间的相互作用所隐含的信号传递事件，在诸如心血管、消化道、神经系统、肾脏等组织和器官中的具体表现。近年来随着各种模式生物特别是基因工程小鼠的应用，建立和应用遗传系统从整体水平研究通路中信号分子和分子复合体的功能，从科学的角度来看，这更有说服力。此外，调节早期胚胎发育的信号转导这部分重要内容在很多介绍信号转导的书中都

没有出现。其实，发育的过程可以理解为细胞不断分化成为特定的细胞而丧失全能性的过程，分化的细胞生长缓慢。而许多人类疾病，如癌症，其细胞发生转化，生长旺盛，在某种程度上可视为发育过程的逆转，很多在早期发育过程中活跃的信号通路重新启动。本书收录了这部分重要内容，详细介绍了正常胚胎发育中信号转导的相关研究。

目前，细胞信号转导的研究进展突飞猛进，对生命科学与临床医学研究的工作者们提出更高要求，因此，代表二者紧密衔接的转化医学（Translational Medicine）研究应运而生，成为当今研究的热门。第 7 册的最后一章重点阐述了临床疾病，如炎症性疾病、肿瘤、淋巴细胞类疾病等发生发展的分子基础，并介绍了药物发现、开发及临床研究的最新进展，为读者提供了基础研究与临床研究有机结合的范例。我们从中可以看到迅速发展起来的小 RNA（microRNA）研究领域业已衍生出新的医学诊断手段和新的生物标记，提供了疾病靶向治疗的新策略，应用小 RNA 作为治疗肿瘤或病毒性疾病的药物指日可待。这部分内容对希望了解导致人类疾病的分子机制并从中寻找到有效治疗方法的读者而言无疑是大有裨益的。然而，更重要的是如何整合大量的信息来解释病因，应用于诊断与治疗，从而能够最终实现对疾病的控制，这些方面的进展还比较滞后，也是摆在我们科研工作者面前亟待解决的问题与挑战。

这部手册的编著者们都是活跃在科研一线并在细胞信号转导研究方面做出突出和标志性贡献的国际知名研究者，他们结合自己的研究从更广阔的视野对该领域进行深入浅出的阐述和讨论，并做了总结和展望，代表了国际前沿的进展。每个章节自成体系，读者可以根据自己的兴趣和目的选择性地阅读。目前，我国在细胞信号转导方面的参考书目有限，系统介绍细胞信号转导的代表性教材主要以孙大业等编著的《细胞信号转导：基础篇》（第 4 版）（科学出版社，北京，2010），以及刘景生的《细胞信息与调控》（第 2 版）（中国协和医科大学出版社，北京，2004）。因此，该书不仅可作为从事信号转导研究的科研人员的参考读物，加深他们对这一领域的认识；也同样适合于教学人员、研究生和高年级本科生，部分内容可直接用作教科书。

曹又佳　宁　文　张翠竹

2011 年 5 月

导 读 二

生物体是分子构成的精密网络系统，单细胞生物如此，对于真核多细胞生物而言，由于细胞之间、细胞与基质之间的互作，参与生命系统的参数之多、其复杂程度远非我们目前的想象可以达到。了解这一网络系统的动态构成，对我们认识生命本质、开发药物造福人类十分重要。信号转导就是这样一门学科，研究这些网络中的信息传递过程及参与者，故而这门学科研究的范围极广。我国生命科学界对这一前沿领域的研究也已经全面展开，特别是最近十年，大量优秀的研究工作已经得到了国际的认可。然而，人类对细胞信号转导过程的理解还十分有限。

由于信号转导学科涉及面广，处在第一线的科研工作者各有专攻，全面了解信号转导各个领域最新的研究进展很困难。而由于学科本身的特性（研究对象处于复杂的时空网络之中），研究者需要不断拓宽眼界。也就是说，研究者要将自己放在学科的信息网络中，才能研究信号转导网络。在这种需求下，一部带有辞典性质的《信号转导手册》在多方努力之下面世。本书由美国加州大学旧金山分校的 Ralph A. Bradshaw 和圣迭戈分校的 Edward A. Dennis 等主编。这部专著邀请了数百名在信号转导领域各有造诣的科学家共同编著，他们怀着令人钦佩的决心与魄力，力求编出一部“最实用”的信号转导专著，以不负“手册”之名。几年之后第二版推出，与第一版相比进行了大量的信息更新，并添加了疾病病理的信号转导。

与其他教科书类的专著大不相同，本书的最大特点是时效性。身在生命科学研究领域的同仁可能都有体验，若想快速而准确地了解一个未曾涉足过的领域，首先要读几篇最新的权威性综述文献，以这些文献为核心，追寻其中的引文链接以找到需要的信息。本书就犹如一部系统全面的信号转导前沿综述合集，为上述需求提供了很大的便捷。为了突出时效，书中对年代较远的经典信息未做详细的介绍，而只是提及概要并附有参考文献备查，这使得全书覆盖面广却又不失精简。

这样的一部专著能引入导读版，无疑会为我国相关领域的科研、医药工作者和研究生提供很多便利和帮助。此外，对于已经对细胞生物学、生物化学基础知识有一定了解的生物学、医药类本科生，本书可以作为进入研究生命运动相关领域的入门参考教材。虽然与只记载经典信息的书籍相比，此书不太像教科书，但其体现的追求进步的科学态度，以及其展现的科学快速更新、不断深入的特性，值得为青年学生所了解，在此向本科生及本科教师推荐此书作为教学参考书。

本书的导读版对章节划分做了一些改动，将原书信息量最大的第二册《传递：效应物及胞浆事件》分编为四册，原第三册也分编为两册，将《转录与翻译：细胞核与细胞质事件》单列一册，以方便读者查找所需信息。如前所述，由于本书是一部信号转导各领域科学家的综述汇编，所以各篇综述为并列关系，故其间难免出现从不同角度对同一对象的论述，而且由于全书按照细胞膜—细胞质—细胞核—细胞器—细胞间—疾病的结

构编排，连续性的通路只能分别在不同的章节论述，比如受体在细胞膜部分，而受体接受的信号由其他细胞传来，这会在细胞间互作部分涉及，而受体的下游又属于细胞质的事件。相关的信息在书中分布会比较分散，这是手册类论著的特点，读者在使用本书时，可根据需要灵活处理。

王以政

2011 年 3 月 9 日

第二版前言

细胞信号转导一直是生命科学研究的最热门领域之一，自《信号转导手册》第一版面世六年以来，最新的研究成果层出不穷。第一版分为五个部分，我们以“生理学思路”来反映细胞信号的生物学事件顺序，比如配体和靶细胞的相互作用，细胞内化学应答的形成及转录调控等，在这些变化的基础上展示细胞器及器官水平上的应答。第二版中，我们保留了第一版的结构，并新增了第六部分，由 Murray Korc 撰写与信号转导相关的病理学部分。原来五个部分的编者（Jim Wells，Tony Hunter，Michael Karin，Marilyn Farquhar and Brad Thompson）在第二版中仍负责原先部分的内容，Suresh Subramani 作为共同编者参与了第四部分的编写。在部分章节中，编者有个别变动。由 Jim Wells 代替 Henry Bourne 和 Tom Alber 承担了第一部分的内容。Nick Tonks 和 Martin Bootman 分别接替了 Jack Dixon 和 Michael Berridge 在第二部分的内容。Jerry Workman 加入了第三部分的编写。其余编者（Ian Wilson，Robert Stround，Tony Pawson，Lewis Cantley，John Scott，Jackie Corbin，Heidi Hamm，Geraldine Weinmaster，Michael Rosenfeld，Marc Montminy，Albert Fornace 和 Nahum Sonenberg）在第二版中仍负责原先的内容。尽管为了覆盖最新的突破性研究进展，超过 85％的章节被重新修订或被新的章节所替换，仍有部分章节因其能够充分体现新颖性及原创性而被保留。基于“选取最新材料而非罗列众所周知的信息”这项一贯原则，并受出版篇幅所限，我们对第一版的内容进行了取舍。第一版每篇文章开头的文献引用，在第二版中改为向有兴趣的读者推荐相关参考内容。我们希望可以通过本书的网络版在一定程度上对这些删节加以弥补，并且方便读者快速浏览原始的电子期刊文章。

在策划第一版时，我们曾设想将该手册以网络版和纸质版结合的形式出版，但因技术原因，最终只能出版可供检索的 CD 光盘。第二版得以将纸质版和网络版两种形式结合出版，后者具备网络平台的各种优点。我们相信，这将会成为资深研究者的研究资源并可以用作针对初涉该领域学生的教学工具。

和第一版一样，我们有幸能够召集众多优秀的编、副编者和撰稿人。我们深知他们所付出的努力，并对其学术贡献深表谢意。没有这些努力就不会有这部手册的再版。

我们还要感谢 Jasna Markovac 构思了该手册的第一版，并促成第二版的准备工作。同时感谢 Renske van Dijk 的全面指导使我们能全身心的投入到工作中去。

Ralph A. Bradshaw
Edward A. Dennis

（张翠竹、宁文、曹又佳翻译，黄隽波、姚海兰对本译文亦有贡献）

第一版前言

所有的活细胞具有感知并与其生存环境相互作用的能力，这无疑是生命存在的先决条件。单细胞生物体依赖这种同环境的联系来完成其生命过程。比如，确定营养来源，解读复制线索，以及采取防御措施等。对多细胞生物体而言，由于所接收的信息量大、类型多样化，使生物体本身变得更复杂，信号转导机制也更加多样化。因此，包括人类在内的高等真核生物，在细胞水平上具有异常复杂精细的胞外信号系统，在器官和整体水平上则具有更多层次的复杂性。通过蛋白与蛋白相互作用来简单辨识参与信号转导的所有成分及其参与的信号通路，是一项艰巨的工程，目前尚未在细胞层面上获得成功解读。而且当某些因素受时间的影响后（如诱导、表达、相互作用、翻译后的修饰、刺激后的降解等），信号转导会出现众多甚至是无穷的问题。

那么，如何将这样一个庞杂领域的知识组织成一本具有前沿性、实用性和易读性的概览书籍呢？答案就是组合运用多种分节论述途径。首先，我们将细胞信号转导的基本问题划分成五个部分，粗略勾勒出从配体到细胞及后续的事件：（1）配体和受体的性质及其复杂构成；（2）胞内信号转导事件；（3）转录和转录后调控及细胞核内的事件；（4）细胞应答；（5）表型应答。它们的篇幅各有长短，并且为了方便起见前三个部分又被细化为诸多章节。其中，第二部分内容最多，约为其他部分的两倍，这或许反映了胞内信号转导机制的多样性，也表明此领域的研究取得长足进展，尤其是最近几年。同时，配体/受体相互作用和转录/转录后控制是药物研发的首要领域，该领域的知识也必将得到突飞猛进的发展。展望未来，研究者们对细胞及表型应答方面的兴趣及探索能力正在与日俱增，因此我们可以预期相关领域的研究也会取得实质性进展，譬如细胞核与细胞器信号转导事件，以及这些事件所关联的细胞间、组织、器官和整个机体的生物学过程，尤其是将其应用于了解和治疗人类疾病方面。

遵循这种“生理学思路”，我们没有按照传统编排模式或者动物模型来安排主题顺序。本书绝大部分（并非绝对）信息是针对高等真核生物的。此外，本书未对某个细胞系或模型进行完整描述。原因在于，信号转导的进展始终来源于大量不同的细胞和系统。目前，研究人员围绕两种细胞模型的信号转导正在开展大量学术工作，以期获得完善的阐述，这是一项非常重要的工作；然而，即便这些研究会取得极大成功，还是无法全面了解信号转导过程，多种多样的细胞和系统的信息仍具有重大意义。由于本手册旨在面向更为广泛的读者群，所以保持选取内容的普遍性是一项重要原则。

编撰此书的另一项原则是：我们并不试图包罗万象，而是将重点尽可能放在最新的研究进展而非罗列一些人们众所周知的内容。对于本领域的初学者或其他领域的专家而言，那些“众所周知的内容”可能并不适用。我们希望通过交织一个涵盖细胞信号转导领域的网络系统来解决这一问题，因而不可避免会出现一些冗余，所以书中肯定会涉及一些“众所周知的内容”，并可以在索引中检索。对于一些有兴趣的读者而言，若觉得相关描述不够确切的话，还可以借此回过头来参阅原始文献。基于此，我们为处于这一

快速发展领域最前沿的材料留出了空间。由于本手册网络版所具有的时效性，我们期待它能被高效利用。所有编者和副编者都认为这也是本书最吸引人的特色。原因包括：便于访问（通过台式电脑）；超链接便于索引检索并可随时链接引用内容；可随时更新并添加新文章；今后还可以纳入视频等附加信息。

在手册的成书过程中，我们很荣幸能召集如此杰出的编者、副编者和撰稿人，他们代表了该领域的领军人物，他们的署名也使本书更具权威性。我们的几位编者，Jim Wells，Tony Hunter，Michael Karin，Marilyn Farquhar and Brad Thompson，在他们负责的各个部分都付出了大量的劳动，包括极具挑战性的头脑风暴（集体研讨）、策划会议、同副编者和撰稿人的紧急电话沟通，以及技术性很强的草稿编辑工作。他们的副编者，Tom Alber，Michael J. Berridge，Henry Bourne，Lewis Cantley，Jackie Corbin，Jack Dixon，Albert J. Fornace，Jr.，Heidi Hamm，Marc Montminy，Tony Pawson，Michael G. Rosenfeld，John D. Scott，Nahum Sonenberg，Robert Stroud，Geraldine Weinmaster 和 Ian A. Wilson，同样非常勤奋地完成了各自章节的组织和约稿工作。在此，我们感谢所有人付出的时间和精力，没有这些努力就不会有这部书的出版。最后也是最重要的，我们由衷感谢众多撰稿人的学术贡献。

同时，还要感谢学术出版社（现归属于 Elsevier 出版集团）工作人员的帮助和支持，他们开创性地制作出这样一个大规模综合性的网络版本，与传统商业出版社出版的印刷版本同时发行。需要特别感谢的是：Jasna Markovac，他最先提出了编撰一本信号转导手册的想法；K. Noelle Gracy，启动了本书的编写过程从而将这一想法付诸实际；Mica Haley，从中途接手并引领整个团队，直至完成这项工程。

Ralph A. Bradshaw
Edward A. Dennis

（张翠竹、曹又佳、宁文翻译，黄隽波、姚海兰对本译文亦有贡献）

Contributors

John M. Abrams (261), Department of Cell Biology, University of Texas Southwestern Medical Center, Dallas, Texas

Patricia V. Agostino (194), Laboratory of Chronobiology, Department of Science and Technology, National University of Quilmes, Buenos Aires, Argentina

Rexford S. Ahima (332), University of Pennsylvania School of Medicine, Department of Medicine, Division of Endocrinology, Diabetes and Metabolism, Philadelphia, Pennsylvania

Daniel A. Albert (337), Dartmouth Medical School and Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire

Emil Alexov (2), Department of Biochemistry and Molecular Biophysics, Howard Hughes Medical Institute, Columbia University, New York

Simon Alford (210), Department of Biological Sciences, University of Illinois at Chicago, Chicago, Illinois

Steven C. Almo (10), Department of Biochemistry, and Center for Synchrotron Biosciences, Albert Einstein Collge of Medicine, Bronx, New York, New York

Géza Ambrus (304), Department of Cell Biology, Scripps Research Institute, La Jolla, California

Sally A. Amundson (257), Center for Radiological Research, Columbia University Medical Center, New York

Carl W. Anderson (264), Biology Department, Brookhaven National Laboratory, Upton, New York

Kenneth C. Anderson (325, 326), Department of Medical Oncology, Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts

Peter Angel (251), Deutsches Krebsforschungszentrum, Division of Signal Transduction and Growth Control, Heidelberg, Germany

Frann Antignano (134), The Terry Fox Laboratory, BC Cancer Agency, Vancouver, BC, Canada

Marc Antonyak (219), Department of Molecular Medicine, Department of Chemistry and Chemical Biology, Cornell University, Ithaca, New York

Ettore Appella (264), Laboratory of Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

William J. Arendshorst (318), Department of Cell and Molecular Physiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Liliana Attisano (70), Institute of Medical Sciences and Department of Biochemistry, University of Toronto, and Donnelly Centre for Cellular and Biomolecular Research, University of Toronto, Toronto, Ontario, Canada

Anjon Audhya (138), Weill Institute for Cell and Molecular Biology, Department of Molecular Biology and Genetics, Cornell University, Ithaca, New York

Manfred Auer (47), Novartis Institutes for BioMedical Research – Vienna, Innovative Screening Technologies Unit, Vienna, Austria

Juan Ausió (289), Department of Biochemistry and Microbiology, University of Victoria, Victoria, British Columbia, Canada

Brandon J. Baird (273), Laboratory of Molecular Pharmacology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Jesús Balsinde (149), Institute of Molecular Biology and Genetics, Spanish National Research Council (CSIC) and University of Valladolid School of Medicine, Valladolid, Spain

Dwayne L. Barber (63), Division of Stem Cells and Developmental Biology, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

David Barford (86), Section of Structural Biology, Institute of Cancer Research, Chester Beatty Laboratories, London, England, UK

Alastair J. Barr (107), Structural Genomics Consortium, Botnar Research Centre, University of Oxford, Oxford, England, UK

Dafna Bar-Sagi (217), Department of Molecular Genetics and Microbiology, State University of New York at Stony Brook, Stony Brook, New York

Blaine Bartholomew (282), Department of Biochemistry and Molecular Biology, Southern Illinois University School of Medicine, Springfield, Illinois

H. Batiaens (155), Cell Biology and Cell Biophysics Program, European Molecular Biology Laboratory, Heidelberg, Germany

Anthony J. Baucum II (167), Department of Molecular Physiology and Biophysics, Center for Molecular Neuroscience, Vanderbilt-Kennedy Center for Research on Human Development, Vanderbilt University School of Medicine, Nashville, Tennessee

J. Fernando Bazan (41), Department of Protein Engineering, Mail Stop 27, Genentech, South San Francisco, California

Joshua M. Beatty (248), Center for Biotechnology, Genomics, and Health Research, University of North Carolina at Greensboro, Greensboro, North Carolina

Joseph A. Beavo (173, 187), Department of Pharmacology, University of Washington School of Medicine, Seattle, Washington

Elsa Bello-Reuss (318), Department of Internal Medicine, Division of Nephrology and Department of Cell Physiology and Molecular Biophysics, Texas Tech University Health Science Center Lubbock, Texas

Anton M. Bennett (92), Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut

Craig B. Bennett (260), Duke University Medical Center, Department of Surgical Sciences, Durham, North Carolina

Penny J. Beuning (258), Department of Chemistry and Chemical Biology, Northeastern University, Boston, Massachusetts

Ramji K. Bhandari (314), Center for Reproductive Biology, School of Molecular Biosciences, Washington State University, Pullman, Washington

Alicia A. Bicknell (299), University of California San Diego, Division of Biological Sciences, La Jolla, California

Martin Biel (185), Munich Center for Integrated Protein Science CIPS^{M} and Department of Pharmacy, Center for Drug Research, Ludwig-Maximilians-Universität München, Munich, Germany

Vincent A. Bielinski (168), Department of Pharmacology, University of Texas Southwestern Medical Center, Dallas, Texas

Lutz Birnbaumer (197), Laboratory of Neurobiology, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina

Gail A. Bishop (50), Departments of Microbiology and Internal Medicine, The University of Iowa, and the VA Medical Center, Iowa City, Iowa

Trillium Blackmer (210), Department of Biological Sciences, University of Illinois at Chicago, Chicago, Illinois

Mordecai P. Blaustein (119), Departments of Physiology and Medicine, University of Maryland School of Medicine, Baltimore, Maryland

Wojciech C. Blonski (338), Division of Gastroenterology, University of Pennsylvania, Philadelphia, Pennsylvania, and Department of Gastroenterology and Hepatology, Wroclaw Medical University, Wroclaw, Poland

Naomi Bogenschutz (283), Molecular and Cellular Biology Program, University of Washington and Fred Hutchinson Cancer Research Center, Seattle, Washington

Frank-D. Böhmer (267), Leibniz Institute for Age Research, Fritz Lipmann Institute, Jena, Germany, and Institute of Molecular Cell Biology, CMB-Center for Molecular Biomedicine, Jena, Germany

Gary M. Bokoch (106, 216), Departments of Immunology and Cell Biology, The Scripps Research Institute, La Jolla, California

Kent Bondensgaard (46), Biopharmaceuticals Research Unit, Novo Nordisk A/S, Måløv, Denmark

Lynda. F. Bonewald (313), Bone Biology Program, University of Missouri-Kansas City, Kansas City, Missouri

William M. Bonner (273), Laboratory of Molecular Pharmacology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Martin D. Bootman (109, 117), Calcium Group, Laboratory of Molecular Signalling, The Babraham Institute, Babraham, Cambridge, England, UK

Johannes L. Bos (186), Department of Physiological Chemistry and Centre for Biomedical Genetics, University Medical Centre Utrecht, Utrecht, The Netherlands

Rohit Bose (70), Department of Molecular Genetics, University of Toronto, and Program in Molecular Biology and Cancer, Samuel Lunenfeld Research Institute, Mt Sinai Hospital, Toronto, Ontario, Canada

Istvan Botos (21), Laboratory of Molecular Biology, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland

Kanika A. Bowen (311), Department of Surgery, The University of Texas Medical Branch, Galveston, Texas

Ralph A. Bradshaw (1, 55, 307), Department of Pharmaceutical Chemistry, University of California San Francisco, San Francisco, California; and Department of Physiology and Biophysics & Department of Anatomy and Neurobiology, University of California, Irvine, California

Patrick Bregy (189), Institute of Cell Biology, University of Bern, Bern, Switzerland

Anne R. Bresnick(10), Department of Biochemistry, Albert Einstein Collge of Medicine, Bronx, New York, New York

Paul K. Brindle (253), Department of Biochemistry, St. Jude Children's Research Hospital, Memphis, Tennessee

Marisa Brini (118), Department of Biochemistry, University of Padova, Padova, Italy; and Department of Experimental Veterinary Sciences, University of Padova, Legnaro, Padova, Italy

Ross I. Brinkworth (182), School of Molecular and Microbial Sciences and Institute for Molecular Bioscience, University of Queensland, Brisbane, Queensland, Australia

Kenneth D. Bromberg (203), Department of Pharmacology and Systems Therapeutics, Mt Sinai School of Medicine, New York, New York

Felrecia Brown (180), Department of Physiology, College of Medicine, University of South Alabama, Mobile, Alabama

Michael S. Brown (298), Department of Molecular Genetics, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas

Anne Brunet (250), Division of Neuroscience, Children's Hospital and Department of Neurobiology, Harvard Medical School, Boston, Massachusetts

Matthew H. Brush (89), Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, North Carolina

Robert Bucki (141), Institute for Medicine and Engineering, Department of Physiology, University of Pennsylvania, Philadelphia, Pennsylvania

Dmitry V. Bulavin (271), Institute of Molecular and Cell Biology, Proteos, Singapore

Robert D. Burgoyne (122), The Physiological Laboratory, School of Biomedical Sciences, University of Liverpool, Liverpool, England, UK

Tara L. Burke (285), Department of Biochemistry and Molecular Genetics, University of Virginia School of Medicine, Charlottesville, Virginia

Janice E. Buss (213), Department of Pharmaceutical Sciences, University of Kentucky, Lexington, Kentucky

Michael D. Cahalan (31), Department of Physiology and Biophysics, and the Center for Immunology, University of California, Irvine, California

Karyn B. Cahill (177), Department of Biochemistry and Molecular Biology, University of New Hampshire, Durham, New Hampshire

Paul M. Campbell (329), Lee Moffitt Cancer Center and Research Institute, Tampa, Florida

Ernesto Carafoli (118), Department of Biochemistry, University of Padova, Padova, Italy; and Venetian Institute of Molecular Medicine, Padova, Italy

Graham Carpenter (110), Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, Tennessee

Catherine Carrière (310), Departments of Medicine, and Pharmacology and Toxicology, Dartmouth Medical School, Norris Cotton Cancer Center and Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire

Patrick J. Casey (202), Department of Pharmacology and Cancer Biology, and Department of Biochemistry, Duke University Medical Center, Durham, North Carolina

Amanda Caster (220), Department of Biochemistry and Neuroscience Graduate Program, Emory University School of Medicine, 1510 Clifton Rd, Atlanta, Georgia

William A. Catterall (112), Department of Pharmacology, University of Washington, Seattle, Washington

Richard A. Cerione (218, 219), Department of Molecular Medicine, Department of Chemistry and Chemical Biology, Cornell University, Ithaca, New York

Denise A. Chan (269), Divisiòn of Radiation Biology, Department of Radiation Oncology, Stanford University School of Medicine, Stanford, California

Gordon Chan (98), Ontario Cancer Institute, Toronto, Ontario, Canada

Moses V. Chao (234), Molecular Neurobiology Program, Skirball Institute of Biomolecular Medicine, New York University School of Medicine. New York, New York

Harry Charbonneau (96), Department of Biochemistry, Purdue University, West Lafayette, Indiana

Nilanjana Chatterjee (282), Department of Biochemistry and Molecular Biology, Southern Illinois University School of Medicine, Springfield, Illinois

Chyi-Ying A. Chen (277), Department of Biochemistry and Molecular Biology, University of Texas, Medical School at Houston, Houston, Texas

Jau-Nian Chen (230), Department of Molecular, Cell and Developmental Biology, University of California, Los Angeles, California

Mingming Chen (284), Department of Carcinogenesis, Science Park Research Division, University of Texas M.D. Anderson Cancer Center, Smithville, Texas

Philip Chen (263), Queensland Cancer Fund Research Laboratory, Queensland Institute of Medical Research, Brisbane, Australia

S. R. Wayne Chen (116), Department of Physiology and Biophysics, University of Calgary, Calgary, Alberta, Canada

Xin Chen (193), Department of Orthopaedics, Case Western Reserve University & Case Medical Center, Cleveland, Ohio

Yi-Yun Chen (105), Institute of Biological Chemistry, and National Core Facility for Proteomic Research, Academia Sinica, Taipei, Taiwan; and Institute of Biochemical Sciences, College of Life Sciences, National Taiwan University, Taipei, Taiwan

Zhijian J. Chen (83), Department of Molecular Biology, and Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas, Texas

Peter Cheung (288), Department of Medical Biophysics, University of Toronto, and Division of Signaling Biology, Ontario Cancer Institute, Toronto, Ontario, Canada

Anne Elisabeth Christensen (191), Department of Biomedicine, Medical Faculty, University of Bergen, Norway

Chung-Sik Choi (180), Department of Physiology, College of Medicine, University of South Alabama, Mobile, Alabama

Jerold Chun (147), Department of Molecular Biology, Helen L. Dorris Child and Adolescent Neuropsychiatric Disorder Institute, The Scripps Research Institute, La Jolla, California

Grant C. Churchill (111), Department of Pharmacology, Oxford University, Oxford, England, UK

Aaron Ciechanover (255), Vascular and Tumor Biology Research Center, Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

Andrew H.A. Clayton (48), Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia

Lena Claesson-Welsh (236), Department of Genetics and Pathology, Rudbeck Laboratory, Uppsala University, Uppsala, Sweden

Robert Clarke (317), Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC

Charles V. Clevenger (36), Department of Pathology, Northwestern University Medical School, Robert H. Lurie Comprehensive Cancer Center, Chicago, Illinois

Shamshad Cockcroft (142), Department of Physiology, Rockefeller Building, University College London, University Street, London, England, UK

Patrice Codogno (306), INSERM U756, Faculté de Pharmacie, Université Paris-Sud 11, Châtenay-Malabry, France

Patricia T.W. Cohen (85), Medical Research Council Protein Phosphorylation Unit, College of Life Sciences, University of Dundee, Dundee, Scotland, UK

Philip Cohen (76), MRC Protein Phosphorylation Unit, University of Dundee, Dundee, Scotland, UK

Roger J. Colbran (167), Department of Molecular Physiology and Biophysics, Center for Molecular Neuroscience, Vanderbilt-Kennedy Center for Research on Human Development, Vanderbilt University School of Medicine, Nashville, Tennessee

Marco Conti (174), Center for Reproductive Sciences, Department of Obstetrics and Gynecology, University of California San Francisco, San Francisco, California

Peter J. Cook (245), Howard Hughes Medical Institute, Department and School of Medicine, University of California, San Diego, La Jolla, California

Max D. Cooper (22), Department of Pathology and Laboratory Medicine, Emory Vaccine Center of Emory University School of Medicine, Atlanta, Georgia

Jackie D. Corbin (176, 178), Department of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, Nashville, Tennessee

Daniela Corda (204), Department of Cell Biology and Oncology, Consorzio Mario Negri Sud, Santa Maria Imbaro, Chieti, Italy

Seth J. Corey (327, 328), Division of Pediatric Hematology/Oncology/Stem Cell Transplantation, Children's Memorial Hospital, Chicago, Illinois, Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, Illinois, and Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, Illinois

Rick H. Cote (177, 178), Department of Biochemistry and Molecular Biology, University of New Hampshire, Durham, New Hampshire

Shaun R. Coughlin (26), Departments of Medicine and Cellular and Molecular Pharmacology, Cardiovascular

Research Institute, University of California, San Francisco, California

Adrienne D. Cox (214, 222), Departments of Pharmacology and Radiation Oncology, Lineberger Comprehensive Cancer Center, and Curriculum in Genetics and Molecular Biology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Scott D. Cramer (323), Department of Cancer Biology, Wake Forest University School of Medicine, Winston-Salem, North Carolina

Fernando Cruz-Guilloty (254), Department of Pathology, Harvard Medical School and the Immune Disease Institute, Boston, Massachusetts

Xiaopoing Cui (262), University of Southern California Keck School of Medicine, USC Norris Comprehensive Cancer Center, Los Angeles, California

Sami Damak (209), Nestlé Research Center, Vers-chez-les-Blanc, Lausanne, Switzerland

Steven M. Damo (49), Department of Biochemistry, Weill Medical College of Cornell University, York Avenue, New York, New York

Mary Dasso (215), Laboratory of Gene Regulation and Development/National Institute of Child Health and Human Development, Bethesda, Maryland

David R. Davies (21), Laboratory of Molecular Biology, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland

Anthony J. Davis (168), Department of Pharmacology, University of Texas Southwestern Medical Center, Dallas, Texas

Roger J. Davis (164), Howard Hughes Medical Institute and Program in Molecular Medicine, University of Massachusetts Medical School, Worcester, Massachusetts

Nicholas O. Deakin (156), Department of Cell and Developmental Biology, State University of New York, Upstate Medical University, Syracuse, New York, New York

Tushar B. Deb (317), Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC

Eva Degerman (175), Department of Cell and Molecular Biology, Lund University, Lund, Sweden

Lanika DeGraffenreid (329), Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Katrin Deinhardt (234), Molecular Neurobiology Program, Skirball Institute of Biomolecular Medicine, New York University School of Medicine. New York, New York

Mark L. Dell'Acqua (165), Department of Pharmacology, University of Colorado Denver School of Medicine, Aurora, Colorado

Bruce Demple (259), Department of Genetics and Complex Diseases, Harvard School of Public Health, Boston, Massachusetts

Jeroen den Hertog (101), Hubrecht Institute, Uppsalalaan 8, Utrecht, The Netherlands

Larry Denner (320), McCoy Stem Cells and Diabetes Mass Spectrometry Research Laboratory, Stark Diabetes Center, and Sealy Center for Molecular Medicine, Department of Internal Medicine, University of Texas Medical Branch, Galveston, Texas

Edward A. Dennis (1, 149), Department of Chemistry and Biochemistry, Department of Pharmacology, School of Medicine and Revelle College, University of California at San Diego, La Jolla, California

Anna A. DePaoli-Roach (88), Department of Biochemistry and Molecular Biology and Center for Diabetes Research, Indiana University School of Medicine, Indianapolis, Indiana

Channing J. Der (214, 322, 329), Department of Pharmacology, Lineberger Comprehensive Cancer Center, and Curriculum in Genetics and Molecular Biology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Céline DerMardirossian (106), Department of Immunology, The Scripps Research Institute, La Jolla, California

E. M. De Robertis (243), Howard Hughes Medical Institute and Department of Biological Chemistry, University of California, Los Angeles, California

Johan de Rooij (186), The Netherlands Cancer Institute, Division of Cell Biology, Amsterdam, The Netherlands

Veronica De Sanctis (265), Centre for Integrative Biology, CIBIO, University of Trento, Italy

Frederic de Sauvage (229), Department of Molecular Biology Genentech, Inc., South San Francisco, California

Lakshmi A. Devi (28), Department of Pharmacology and Systems Therapeutics, Mount Sinai School of Medicine, New York, New York

Victor C. de Vries (51), Department of Microbiology and Immunology, Dartmouth Medical School and The Norris Cotton Cancer Center, Lebanon, New Hampshire

Peter N. Devreotes (207), Department of Cell Biology, Johns Hopkins University School of Medicine, Baltimore, Maryland

Nupur Dey (180), Department of Physiology, College of Medicine, University of South Alabama, Mobile, Alabama

Salim Dhanji (98), Ontario Cancer Institute, Toronto, Ontario, Canada

Jennifer S. Dickey (273), Laboratory of Molecular Pharmacology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Robert B. Dickson (deceased) (317), Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC

K.M. Dibb (128), Unit of Cardiac Physiology, University of Manchester, Manchester, England, UK

Pier Paolo Di Fiore (305), IFOM, Fondazione Istituto FIRC di Oncologia Molecolare, and Dipartimento di Medicina, Chirurgia ed Odontoiatria, Universita' degli Studi di Milano, and Dipartimento di Oncologia Sperimentale, Istituto Europeo di Oncologia, Milan, Italy

Ivan Dikic (69), Institute of Biochemistry II, Goethe University School of Medicine, Frankfurt am Main, Germany

Francesca Di Leva (118), Department of Biochemistry, University of Padova, Padova, Italy; and Department of Experimental Veterinary Sciences, University of Padova, Legnaro, Padova, Italy

Anna Dimberg (236), Department of Genetics and Pathology, Rudbeck Laboratory, Uppsala University, Uppsala, Sweden

Zhao Ding (115), Department of Pharmacology, Tennis Court Road, Cambridge, England, UK

Julie Diplexcito (87), MRC Protein Phosphorylation Unit, College of Life Sciences, University of Dundee, Dundee, Scotland, UK

Ben Distel (296), Department of Medical Biochemistry, Academic Medical Center, University of Amsterdam Amsterdam, The Netherlands

Jack E. Dixon (133), The Life Science Institute and Department of Biological Chemistry, University of Michigan Medical School, Ann Arbor, Michigan

Teuta Domi (118), Department of Biochemistry, University of Padova, Padova, Italy; and Department of Experimental Veterinary Sciences, University of Padova, Legnaro, Padova, Italy

Ian M. Donaldson (170), The Biotechnology Centre of Oslo, and the Department for Molecular Biosciences, University of Oslo, Blindern, Oslo, Norway

Daniel J. Donoghue (237), Department of Chemistry and Biochemistry, University of California San Diego, La Jolla, California; and Moores University of California San Diego Cancer Center, La Jolla, California

Russell F. Doolittle (17), Departments of Molecular Biology and Chemistry & Biochemistry, University of California, San Diego, La Jolla, California

Thomas Dörner (336), Department of Medicine, Rheumatology, and Clinical Immunology, Charite University Medicine Berlin, Germany

Stein Ove Døskeland (191), Department of Biomedicine, Medical Faculty, University of Bergen, Norway

Wolfgang R. Dostmann (181), Department of Pharmacology, University of Vermont, College of Medicine, Burlington, Vermont

Ryan J.O. Dowling (281), Department of Biochemistry, McGill Cancer Centre, McGill University, Montreal, Quebec, Canada

Kristine A. Drafahl (237), Department of Chemistry and Biochemistry, University of California San Diego, La Jolla, California

Matthias K. Dreyer (43), Sanofi-Aventis Deutschland GmbH, Structural Biology, Industriepark Höchst, Frankfurt, Germany

Michael R. Duchen (121), Department of Physiology and UCL Mitochondrial Biology Group, University College London, London, England, UK

Michael L Dustin (11), Department of Pathology, New York University School of Medicine, Program in Molecular Pathogenesis, Helen L and Martin S Kimmel Center for Biology and Medicine of the Skirball Institute for Biomolecular Medicine, New York, New York

Edward Eivers (243), Howard Hughes Medical Institute and Department of Biological Chemistry, University of California, Los Angeles, California

Raul Elgueta (51), Department of Microbiology and Immunology, Dartmouth Medical School and The Norris Cotton Cancer Center, Lebanon, New Hampshire

Elaine A. Elion (163), Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, Massachusetts

D.A. Eisner (128), Unit of Cardiac Physiology, University of Manchester, Manchester, England, UK

Christian D. Ellson (137), Koch Institute for Integrated Cancer Research, Massachusetts Institute of Technology, Cambridge, Massachusetts

Scott D. Emr (138), Weill Institute for Cell and Molecular Biology, Department of Molecular Biology and Genetics, Cornell University, Ithaca, New York