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NIH funding for research underlying new cancer therapies

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Contemporary discovery and development of cancer drugs are based on the model that investments in basic biomedical science will provide insights that can be translated into new cures. In the USA, basic research is primarily funded by the National Institutes of Health (NIH),[1] which allocates half of its research budget to basic science,[2] with smaller amounts contributed by philanthropy, academics, or industry.[1] Basic science is formally defined as the "systematic study directed toward fuller knowledge or understanding of the fundamental aspects of phenomena and observable facts without specific application towards processes or products in mind".[3] However, science is often use-inspired,[4] and much of the NIH funding for basic research comes from institutes with specific health missions.[2,4] Is there a direct link between NIH funding for basic science and the emergence of new cancer therapies?

The number of new cancer drugs has grown from 4% of all US Food and Drug Administration (FDA) approvals in the 1980s to 27% between 2010 and 2018.[5] Evidence shows that this growth has been driven by advances in basic science,[6] and by the maturation of basic research in areas such as cancer immunology, cancer genetics, and cell signalling, which mostly originated in the 1970s and 1980s.[7]

A 2018 study by Cleary and colleagues[8] showed that NIH funding contributed to the research underlying all 210 new drugs approved by the FDA between 2010 and 2016. This study identified more than 2 million publications in PubMed related to these 210 drugs and their 151 biological targets. Of these publications, more than 600 000 (30%) had US federal government research support cited in the NIH RePORTER database.[9] This support consisted of more than 200 000 project years of funding from 1985 to 2016, and more than US$100 billion in project costs between 2000 and 2016.[8] Notably, more than 90% of NIH-funded research was associated with publications on biological targets rather than the drugs themselves, and the research was considered basic science. Conversely, less than 10% of this funding was associated with research on drugs and was considered applied or translational science.[8]

The largest proportion (28%) of new drugs tested in this study[8] were indicated for the treatment of cancer. From 2010 to 2016, 59 new drugs were approved for cancer therapy, including 56 antineoplastic drugs and three products indicated for the management of side-effects caused by chemotherapy. These 59 products are associated with 41 distinct biological targets (appendix pp 1–2). Of the 59 cancer therapies, 49 (83%) were discovered by screening against a known biological target (targeted discovery) and 24 (41%) were classified as first-in-class—ie, the first approved products associated with that target. The other 10 of 59 (17%) therapies were originally identified by their biological activity and subsequently screened for cancer therapy (phenotypic discovery).

See Online for appendix

Using the methods and datasets described by Cleary and colleagues (appendix p 3),[8] we identified 711 702 publications in PubMed related to the 59 cancer drugs or their 41 biological targets. Of these, 266 154 (37%) had federal support cited in the NIH RePORTER database.[9] Accounting for publications related to more than one drug or target, there were 82 539 unique publications citing NIH support. Only 3936 (5%) of these unique publications described research related to the drugs and were classified as applied or translational research. The other 78 603 (95%) described research on the drug targets, but not the drugs themselves, and were classified as basic research.

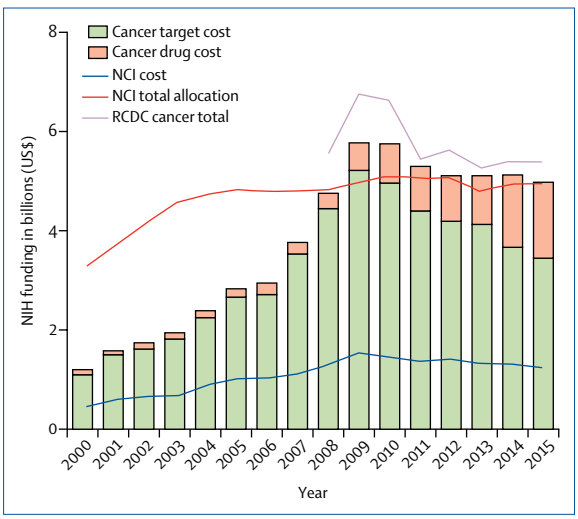

Figure: **NIH funding for research underlying cancer drugs approved between 2010 and 2016**

Annual costs are shown for research directly related to the drug (known as applied research) and research directly related to the drug target, but not the drug itself (known as basic research). The annual costs contributed by the NCI are shown along with the NCI's total annual budget allocation, including the American Recovery and Reinvestment Act of 2009–10 and estimated cancer research spending according to the RCDC. NCI=National Cancer Institute. NIH=National Institutes of Health. RCDC=Research, Condition, and Disease Categorization.

For the **NCI budget allocation** see https://officeofbudget.od.nih.gov/approp_hist.html

For the **RCDC cancer research spending** see https://report.nih.gov/categorical_spending.aspx

The research reported in these publications was supported by 116 703 project years of NIH funding (1985–2016) for basic and applied cancer research, with costs totalling $63·9 billion between 2000 and 2016. This included 107 644 project years (92%) related to drug targets with a cost of $54·0 billion (85%), and 9059 project years (8%) related to drugs with a cost of $9·9 billion (15%; appendix p 4).

The figure shows the time course of NIH funding for research on cancer drugs or their targets along with the annual budget allocation for the National Cancer Institute (NCI) and total NIH funding for cancer research estimated in the Research, Condition, and Disease Categorization (RCDC) database. These data show that the NIH funding for research related to these 59 cancer drugs or their targets approaches or exceeds the total budget allocation for the NCI and estimates of total NIH funding for cancer research from 2008 to 2016.

From 2000 to 2016, the NCI contributed $20·1 billion to this research underlying these 59 cancer drugs or their targets, representing 31% of the $63·9 billion total NIH contribution to research (figure). NCI funding represented 26% ($14·3 billion of $54·0 billion) of the total for basic published research related to the biological targets and 43% ($4·3 billion of $9·9 billion) of the funding for published applied or translational research related to the drugs (appendix p 4).

Within the NIH, 13 other institutes contributed more than $1 billion to research associated with these cancer drugs or their biological targets (appendix p 5). Several of these institutes are focused on core or translational research, such as the National Institute of General Medical Sciences and the National Center for Research Resources. Other institutes have distinct disease or demographic-focused missions, such as the National Institute of Allergy and Infectious Diseases (NIAID), the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute of Diabetes and Digestive and Kidney Diseases (appendix p 5). Some of the funding from institutes other than the NCI might be related to malignancies that affect specific organs or populations (eg, research on leukaemia from the NHLBI). Much of the funding that contributed to cancer therapies, however, probably represents spillover effects from use-inspired basic research, designed to gain insights into other diseases.

An example of spillover effects is the research underlying the checkpoint inhibitors pembrolizumab and nivolumab. Both products target the PD-1 protein and pathways involved in down-regulation of the immune system and self-tolerance.[10] Checkpoint inhibitors are designed to reverse PD-1-mediated regulation of the immune system and promote immunological rejection of tumour cells.[10] NIH funding for basic research on PD-1 totalled 665 project years and $284 million from 2000 to 2016. Most of this funding, $149 million (52%), was provided by NIAID, consistent with NIAID's focus on immunology, and represents a spillover into cancer research. By contrast, of the $7·6 million in NIH funding for applied or translational research related to pembrolizumab and nivolumab, $7·1 million (93%) was provided by the NCI, consistent with NCI's institutional focus on cancer therapies.

Spillover effects in the emergence of new cancer therapies are also evident in the observation that most project funding associated with drugs approved for cancer are also associated with drugs approved for other therapeutic indications. Overall, 43 023 of 116 692 (37%) of the project years associated with cancer products or their biological targets were also associated with one or more products in other therapeutic areas (appendix p 6). Consistent with the

growing importance of immunology and cell signalling in cancer therapy, 16 935 of 116 692 (15%) of project years related to a cancer product were also associated with an endocrine product, whereas 11 635 (10%) were associated with an immunological product. In addition, 8867 of 116 692 (8%) project years were shared with products approved for CNS diseases, 7709 (7%) with metabolic diseases, 7476 (6%) with cardiovascular disease, and 7254 (6%) with anti-infective therapies.

This analysis extends the previous observation that NIH funding contributed to each of the 59 cancer drugs approved between 2010 and 2016.[8] Although the NCI is traditionally viewed as the primary source of funding for public-sector cancer research, this analysis showed that less than a third of NIH funding for published research related to these 59 cancer drugs or their biological targets came from the NCI. Most funding was from other institutes across the NIH, with the largest contributions coming from institutes focused on distinct disease or demographic-specific missions.

This analysis also suggests that the annual NCI budget allocation and the RCDC estimate of cancer spending does not accurately reflect the NIH contribution to new cancer therapies. Further work needs to be directed at characterising the nature of spillovers between different disease areas and ensuring that the channels for communication and collaboration across specialty research areas are adequate to efficiently translate this diverse and distributed body of research into cures for disease.

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