Angiogenesis Research
Extramural Portfolio Supported by the National Heart, Lung, and Blood Institute, 2008–2015

Yunling Gao, Dennis V. Stanley, Valerie C. Robinson, Diane M. Reid, Zorina S. Galis

The National Heart, Lung, and Blood Institute funds angiogenesis-related extramural research aimed at improving the understanding of normal and abnormal angiogenesis and translating mechanistic findings into therapeutic interventions. This portfolio analysis of fiscal years 2008 through 2015 shows that the National Heart, Lung, and Blood Institute awarded an average of 229±26 angiogenesis-related grants with an average cost of $116±20 million per fiscal year. Angiogenesis research was funded through 4 major funding mechanisms, mainly through Research Project Grants (R01s, 64% of the total awards). New awards (type 1) that may represent pursuit of new directions in angiogenesis research accounted for an average of 19±3% of total awards per fiscal year. In the portfolio, 74.1% of awards (65% of total dollars) used in vivo animal models; 9.7% of awards (5% of total dollars) used in vitro methods; 13.7% of awards (27% of total dollars) involved human subject studies (not including clinical trials); and 2.5% of awards (3% of total dollars) supported clinical trials. Public impact was measured by the annual average number of publications per grant (3.3±0.3) and cost ($154±24 thousand) per publication. Our analyses revealed that intussusceptive angiogenesis may represent an understudied mechanism, and therapeutic angiogenesis remains a remarkable challenge and opportunity to treat angiogenesis-related diseases.

Angiogenesis denotes the process of new blood vessel formation and growth that is vital for normal embryonic development, patterning of the vascular system, and wound healing. Insufficient, excessive, or aberrant angiogenesis may have significant clinical consequences in diseases, such as stroke, myocardial infarction, cancer, chronic inflammation, and retinopathy. These key contributions to physiological and pathological processes support the high significance of research aimed at better understanding the complex regulation of angiogenesis.

The National Institutes of Health (NIH), the largest funding source for biomedical research in the world, funds angiogenesis-related extramural research (hereafter abbreviated as angiogenesis research) to improve the understanding of normal and abnormal angiogenesis and translate findings into therapeutic interventions. Several NIH institutes, including the National Cancer Institute, the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Eye Institute, support angiogenesis research aligned with each of their specific public health missions.

To better assess the funding support for angiogenesis research by the NHLBI, as well as its breadth, depth, and impact, we performed a portfolio analysis of the relevant grants from fiscal years 2008 through 2015. We examined the trends in grant support, funding mechanisms, and research-associated publication output. We also analyzed the types of research approaches, experimental models, and major types of mechanisms of angiogenesis under study. From these analyses, we obtained a detailed picture of the NHLBI grant portfolio for angiogenesis research.

Methods
We obtained portfolio data from the publicly accessible NIH Research Portfolio Online Reporting Tools (https://report.nih.gov/) and compared it with the data from the internal NIH IMPAC II (Information for Management Planning Analysis and Coordination) database on extramural applications and grants (or awards). The collected data were verified by scientific staff through review of the title, abstract, and specific aims of each award and analyzed with the Pacific Northwest National Laboratory software IN-SPIRE (http://in-spire.pnnl.gov/) using its statistical algorithms and visualization tools to identify key thematic terms and clusters within the data set. A measure of public impact of these awards was obtained by associating each grant number with publications listed in PubMed. Bibliometric analyses were done with the NIH Office of Portfolio Analysis iCite tool (https://icite.od.nih.gov). Its relative citation ratio was used as an objective measure to obtain highlights of angiogenesis research from the portfolio publications (after exclusion of review articles). Grants were categorized by their IMPAC II coding into in vitro, in vivo, and human subject groups. Additional details are available Online Data Supplement.

Results
Grants, Funding Mechanisms, and Publication Output for the NHLBI-Funded Angiogenesis Research
We identified a cumulative total of 1901 angiogenesis grants from fiscal years 2008 through 2015. About 94% (1788
awards) represent investigator-initiated research, and 6% (113 awards) is NHLBI-solicited research. Examples of Requests for Applications were The Cardiovascular Cell Therapy Research Network (HL12-026) and New Strategies for Growing 3D Tissues (HL11-025). The temporal trends of awards and awarded dollars during this period are presented in Figure A. Yearly, an average of 229±26 grants were awarded, and the average overall funding, including direct and indirect costs, was $116±20 million. The total yearly cost per award was ≈$485±25 thousand. Additional awards were made under the American Recovery and Reinvestment Act stimulus program: 47 ($14 million) in fiscal year 2009 and 25 ($13 million) in fiscal year 2010. The decline of funding in recent years does not seem specific to angiogenesis research but rather consistent with trends in total NHLBI grants funding during the same period (Online Figure II).
Using each unique grant number, we identified a total of 6009 publications on PubMed, including 915 (15%) review articles, acknowledging NHLBI-funding support, as required by the NIH Public Access Policy (http://publicaccess.nih.gov/). On average, each grant generated 3.3±0.3 publications per year (Online Figure III). American Recovery and Reinvestment Act funding for 2009 and 2010 produced a total of 176 publications (included in the figure). The average cost per publication (calculated as yearly total awarded dollars divided by yearly total associated publications) was $154±24 thousand (Figure B), consistent with other NHLBI-supported research areas and within the national estimates of cost per publication for academic-based research.3

The NHLBI angiogenesis portfolio was funded through 4 major funding mechanisms (http://grants.nih.gov/grants/funding). The predominant types of awards across all years were Research Project Grants, or R01s (64%); followed by Research Program Project Grants; P01, Research Program Project Grant; U01, Research Project Cooperative Agreement; R21, Exploratory/Developmental Research Grant; R43 and R44, Small Business Innovation Research and Small Business Technology Transfer grants, respectively. Other less-used mechanisms were not included in this figure.

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<th>Table. Major Types of Mechanism of Angiogenesis Studied in the NHLBI-Funded Angiogenesis Research From FYs 2008 Through 2015</th>
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<td>Arteriogenesis/collaterals</td>
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<td>Intussusceptive angiogenesis</td>
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The numbers represent grants identified through each of the specific term search within the grants’ title, abstract, or specific aims in each year during this period. Please note that some overlap of mechanistic types may be included as some awards mentioned >1 angiogenic mechanisms. FY indicates fiscal year; and NHLBI, National Heart, Lung, and Blood Institute.
Developmental Research Grants or R21s, Small Business Innovation Research or R43s and Small Business Technology Transfers or R44s (5%); and Research Project Cooperative Agreements or U01s (1%) as shown in Figure C. Across all years, 52% of funds were allocated for R01s; 33% for P01s; 3% in aggregate for R21s, R43s, and R44s; and 1% for U01s. Each subproject and core of P01s were counted as an individual award in these analyses. Since 2011, NHLBI has not supported the unsolicited R21 mechanism. Less-used funding mechanisms were not tabulated in this figure. Most funding was awarded for noncompeting continuation of research (type 5 grants). An average of 19±3% of awards was issued yearly to new research (type 1 grants), which may represent pursuit of new directions in angiogenesis research (Online Figure IV).

Trends of Scientific Areas and Topics for the NHLBI-Funded Angiogenesis Research
The NIH and NHLBI have a long history of supporting a diverse portfolio of basic, translational, and clinical research.5 NIH views basic scientific discovery as the engine that powers the biomedical enterprise and continues to spend more than half of its budget supporting basic research.3 Using grant codes, we categorized NHLBI-funded angiogenesis research as basic if using in vitro methods only (9.7% of awards, 5% of total dollars) or as translational if using in vivo animal models (74.1% of awards, 65% of total dollars) or human subject studies, excluding clinical trials (13.7% of awards, 27% of total dollars). The remainder of this portfolio is represented by clinical trials (2.5% of awards, 3% of total dollars).

Through a key term search of the title, abstract, and specific aims of each grant, we did a nonexhaustive analysis of the types of mechanism of angiogenesis. Of the total 1901 grants, 1616 grants cited angiogenesis, 270 grants cited vasculogenesis, 234 grants cited sprouting angiogenesis, 220 grants cited arteriogenesis/collaterals/collaterogenesis, and 15 grants cited intussusceptive or splitting angiogenesis (Table). There is overlap because some grants included references to >1 angiogenesis mechanism.

Discussion
Highlights, Challenges, and Opportunities in the NHLBI-Funded Angiogenesis Research
Our analyses showed that over the years, the NHLBI-funded angiogenesis research has contributed to a better understanding of angiogenesis mechanisms at the molecular and cellular levels. Signaling pathways and regulation of angiogenesis have been better defined, as has the role of inflammation and endothelial cell metabolism in angiogenesis.6 Investigators who studied in vivo animal models within the NHLBI portfolio (Online Table II) have contributed to the basic and translational advancements in the field of angiogenesis.7

Several distinctive types of angiogenesis have been investigated, many with NHLBI-funding support, for their potential use for therapeutic interventions (Table). The most-studied mechanism is sprouting angiogenesis, often abbreviated as angiogenesis, a well-defined mechanism of vessel growth, consisting in the formation of new capillaries from pre-existing capillaries and resulting in an increase in the density of capillaries in a tissue.18,9 Vasculogenesis denotes the de novo formation of blood vessels directly from mesodermal precursor cells or endothelial progenitor cells.10 Arteriogenesis, also termed collateral remodeling, refers to an anatomic increase in vessel lumen and wall thickness of a collateral vessel. Collaterogenesis denotes the formation of collaterals either during development or in response to ischemia or other disturbance. Both result in an increase in blood flow across the collateral network.5,11 In contrast, intussusceptive angiogenesis is a nonsprouting type of angiogenesis consisting of the longitudinal splitting of a pre-existing capillary into 2 capillaries, sometimes also called splitting angiogenesis.12 Because intussusceptive angiogenesis does not require cell division, it is a robust process that can rapidly expand the size and refine the functional efficiency of existing microvascular networks. The process may also use progenitor and stem cells. Recent studies have reported that intussusceptive angiogenesis is not only crucial during development but also it is a dominant mechanism of angiogenesis in tissue repair and regeneration.12,13 Our portfolio analysis showed that only a few awards (0–3 grants per year) research intussusceptive angiogenesis, which may represent an understudied area.

The importance of angiogenesis in diseases has fueled many efforts to develop proangiogenic agents for therapeutic use. Despite intense efforts, research on growth factor-based therapeutic angiogenesis to treat ischemic diseases has thus far not yielded reproducible and sustained success in late stage clinical trials.14 Stem cell–based therapy has raised expectations to deliver therapeutic benefit; however, its clinical application is still limited.15 The relatively small volume of disease-focused human subject research, which represents ≈16% of all NHLBI-funded angiogenesis research, is consistent with the view that the field may not yet be poised for larger scale clinical testing of potential treatments. Therapeutic angiogenesis remains a remarkable challenge in settings of ischemia that may trigger adverse cardiovascular events, such as myocardial infarction, ischemic stroke, and critical limb ischemia. Further basic understanding of angiogenesis has the potential to yield new and improved therapies to advance the public health.

Summary
The goal of this analysis is to assess the breadth and depth of the NHLBI-funded angiogenesis research, highlight main achievements, and identify challenges and opportunities, which may stimulate innovative research in treating angiogenesis-related diseases. As the angiogenesis field moves forward, a deliberate, more integrated basic and clinical research effort is needed to address gaps in our understanding and develop clinical therapeutics.

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Disclosures
None. All authors are US Government employees.
References

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Angiogenesis Research: The Extramural Portfolio Supported by the National Heart, Lung, and Blood Institute, 2008-2015

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Methods

The search terms used are: angiogenesis, anti-angiogenesis, sprouting angiogenesis, vasculogenesis, arteriogenesis, collaterals, collateralogenesis, intussusceptive angiogenesis, splitting angiogenesis, neovascularization, therapeutic angiogenesis.

Relative Citation Ratio (RCR) is a field-normalized metric that shows the citation impact of one or more articles relative to the average NIH-funded paper. Hutchins et al, Relative Citation Ratio (RCR): A New Metric That Uses Citation Rates to Measure Influence at the Article Level. 2016. http://journals.plos.org/plosbiology/article/file?id=10.1371/journal.pbio.1002541&type=printable

Grants were categorized by each grant’s coding. Grants without either animal or human subject codes were included in the “in vitro” group; grants that contained an animal code were included in the “in vivo” group. This group could have also included in vitro research methods but had no human subject involvement. Grants with a “human subject” code were included in the group of human subject research. Some of these awards might also have in vitro and/or in vivo animal models in their research.
Figure 2. Comparison of angiogenesis funding with total NHLBI funding from FYs 2008 to 2015. Red line represents the angiogenesis grants funding. Blue line represents the total NHLBI grants funding from FYs 2008 to 2015.

The annual NHLBI funding report can be found via this link: Research grants: Funding by Institute/Center

The angiogenesis grants funding was an average of $116±20.46 million per year. The total NHLBI grants funding was an average of $2.26±0.06 billion per year.
Figure 3. Public impact by numbers of publication per award in NHLBI Funded Angiogenesis Research from FYs 2008 through 2015. Red bars indicate the number of publications citing angiogenesis research grant support from NHLBI for each FY. Blue bars represent the number of awards for angiogenesis research from NHLBI for each FY. Green line depicts the publications per award per year (total publications divided by total number of awards in each FY).
Figure 4. Distribution of award types in the NHLBI-funded angiogenesis research from FYs 2008 through 2015. Blue bars represent New Research Grants (also referred to as “Type 1” grants). Red bars are Renewal Grants (competing continuation or “Type 2”). Green bars are the Continuation Grants (non-competing or “Type 5”). Blue line depicts the percentage of New Grants (Type 1) relative to total awards during each FY from 2008 through 2015.

An average of 19±3% of awards was issued to new research (Type 1 applications) each year, which may represent pursuit of new ideas or new directions in angiogenesis research. Additional Type 1 awards during the ARRA years (2009-2010) were included in the analysis, accounting for 6% of the 26% in FY 2009. In April 2014, NIH changed its policy on application submissions (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html) to allow applicants to submit a revised previously unsuccessful application (A1) as a new application (A0). This may partially account for the increase of Type 1 applications thereafter. Other less-common grant types are not included in this figure.
Table 2. The experimental animals used in NHLBI-funded angiogenesis research. Mouse was used in 88% of funded grants, rat 12%, zebrafish 7%, and pig 4% followed by dog, cow, bird, sheep, hamster, fish, cat, primate, and guinea pig.