

A Bibliometric Analysis of Folate Receptor Research: A comprehensive bibliometric analysis of the entire field of Folate Receptor Research

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Research article

Keywords: folate receptor, folate binding protein, cancer, oncology, macrophage, imaging, bibliometrics, scientometrics, librarianship-health sciences

Posted Date: June 2nd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-30255/v1>

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Version of Record: A version of this preprint was published on November 16th, 2020. See the published version at <https://doi.org/10.1186/s12885-020-07607-5>.

Abstract

Background

The objective of this study is to conduct a comprehensible bibliometric analysis of the entire field of folate receptor research.

Methods

A Web of Science search was performed on folate receptor or folate binding protein (1969-to June 28, 2019). The following information was examined: publications per year, overall citations, top 10 authors, top 10 institutions, top 10 cited articles, top 10 countries, cc-author collaborations and key areas of research.

Results

In total, 3248 documents for folate receptor or folate binding protein were retrieved for the study years outlined in the methods section search query. The range was 1 per year in 1969 to 264 for the last full year studied (2018). A total of 123,720 citations for the 3,248 documents retrieved represented a mean citation rate per article of 38.09 and range of 1667 citations (range 0 to 1667). Researchers in 71 countries authored publications analyzed in this study. The US was the leader in publications and had the highest ranking institution. The top 10 articles have been cited 7270 times during the time frame of this study. The top cited article had an average citation rate of 110 citations per year. Network maps revealed considerable co-authorship among several of the top 10 authors.

Conclusion

Our study presents several important insights into the features and impact of folate receptor research. To our knowledge, this is the first bibliometric analysis of folate receptor.

Background

As a vital nutrient for normal cell metabolism, folate uptake in the cell occurs via a low-affinity ($K_d \sim 1-5 \mu\text{M}$) transport protein termed the reduced folate carrier¹ and a high-affinity ($K_d \sim 100\text{pM}$) cell surface receptor termed the folate receptor (FR) or folate binding protein (FBP),¹⁻⁶. Notably, FR is over-expressed at significant levels in cancer cells and immune cells (e.g., macrophages) where it mediates uptake of folate by receptor-mediated endocytosis^{2; 7-12}. Although folate uptake occurs via the reduced folate carrier in virtually all cells of the body, only folate-linked conjugates can enter cells by means of the high affinity folate receptor^{7; 13}.

The folate receptor exists as a family of proteins with three primary forms: FR- α (folate receptor 1),¹⁴; FR- β (folate receptor 2),¹⁵, and FR- γ (folate receptor 3),¹⁶, and folate receptor delta (folate receptor 4),¹⁷. These folate receptor homologues are related by ~70% amino acid sequence identity⁵. FR- α and FR- β are attached to cell surfaces by a glycosylphosphatidylinositol (GPI) anchor, while the rarely expressed FR- γ is hypothesized to be secreted due to lack of a signal for GPI modification¹⁶. Folate receptor delta does not bind folate and functions at the initial step of oocyte fertilization¹⁸. In general, FR- α is upregulated in malignant tissues of epithelial origin such as ovarian carcinoma¹⁹⁻²¹, while FR- β is overexpressed in certain subsets of macrophages¹⁹.

This prevalence of FR over-expression in numerous neoplasms and macrophage associated diseases, has led to expansive growth in the use of the cognate folate moiety (as well as anti-FR antibodies) to selectively deliver both diagnostic and therapeutic agents. For example, folate has been conjugated to i) protein toxins,^{13; 22; 23} ii) low molecular weight chemotherapeutic agents,^{11; 24; 25} iii) MRI contrast agents,²⁶ iv) genes,²⁷⁻³² v) viral vectors,^{33; 34} vi) antisense oligonucleotides,³⁵⁻³⁸ vii) ribozymes,^{39; 40} viii) radioimaging agents,^{10; 41-45} ix) liposomes with entrapped drugs,^{32; 46-48} x) neutron activation complexes,^{49; 50} xi) immunotherapeutic agents,⁵¹⁻⁵⁶ enzyme constructs for prodrug therapy,⁵⁷ nanoparticles,⁵⁸ drug-linked polymers,⁵⁹⁻⁶¹ micelles,⁶² and optical imaging agents^{63; 64}. Significantly, the above folate conjugates neither bind to nor transit through the reduced folate carrier: therefore, they exhibit no affinity for most normal cells⁶⁵. Several promising agents have progressed from phase I through phase II clinical trials and the first diagnostic agents could reach the market in the next few years⁶⁶.

According to Andres⁶⁷, the term “bibliometrics” was first coined in 1969 and described as a means to apply a mathematical and statistical approach to the study of scientific literature. The term is synonymous with “scientometrics.” However, for the purposes of this study we will use the term bibliometrics. As Kotepui, et al⁶⁸, describe, bibliometric studies are used to obtain a research assessment rich with data that support a specific research interest. The data can be used to present a rich visualization about research undertakings the world round. Trends within a particular field are highlighted through descriptive analysis. Productivity can be demonstrated through the number of articles published, an author count, and by institutions or countries of origin among a myriad of other factors. Given the expansive rise in folate receptor related reports over the past several decades, we sought to analyze the entire field of FR literature. To our knowledge, this is the first bibliometric analysis of folate receptor.

Methods

For this bibliometric study the search of the available literature was conducted using the online index Web of Science by Clarivate Analytics. The Web of Science Core Collection provides regional citation indexes, patent data, specialized subject indexes, and an index of research data sets from within over 33,000 journals.⁶⁹ Using the Web of Science Core Collection, limiting for “Articles,” four searches were

conducted as follows: "folate receptor" or "folate binding protein;" "folate receptor" or "folate binding protein" and "cancer" or "neoplasm;" "folate receptor" or "folate binding protein" and "inflammation" or "macrophage;" and "folate receptor" or "folate binding protein" and "imaging" or diagnostics." An excel spreadsheet was used to collect the following data for each of the four searches: total journal article search results, publication years (range), first known publication, year of publication, top ten countries/regions, top ten organizations, top ten authors, top ten citations, total citations and citations per year. Graphs for these data were performed using GraphPad Prism. VOSviewer version 1.6.11 software (Leiden University, Leiden, the Netherlands) was used to create the author co-authorship bibliometric network map (type of analysis = co-authorship, units of analysis = authors, counting method = full counting, minimum number of documents of an author = 10). Based on the number of articles retrieved, we will focus primarily on the first search term "folate receptor" or "folate binding protein" leaving the remaining searches for a future analysis of the rich subfields.

Results

Literature Retrieved for Folate Receptor Articles

A total of 3248 documents for folate receptor or folate binding protein were retrieved for the study years outlined in the methods section search query (1969-to June 28, 2019). In this study only research articles in English were used for further analysis since English was the dominant language (99.4%) identified. Review articles, conference proceedings, book chapters, etc., were excluded from the search criteria because the primary focus of this work was to evaluate research articles as defined in the methods section.

Publication and Citation Growth for Folate Receptor Articles

There was a dramatic increase in the number of folate receptor works during the study period (Fig. 1). The range was 1 per year in 1969 to 264 for the last full year studied (2018). The highest productivity to date (264 publications) was in 2018: however, the number of articles generated per year appears may have reached a plateau in 2015 (the number of articles per year for 2015–2018 had a mean of 260.0). A total of 123,720 citations for the 3,248 documents retrieved represented a mean citation rate per article of 38.09 and range of 1667 citations (range 0 to 1667).

Publications by Country for Folate Receptor Articles

Researchers in 71 countries authored publications analyzed in this study (Fig. 2). The top 10 countries accounted for 96.7% (3140 articles) of the total publications (Fig. 3). The United States had the highest number of publications at 1314 (40.5%) followed by China (25.1%) at 815 and India at 174 (5.4%) rounding out the top 3 countries by output. The publication productivity among the top 10 countries differed by as much as a factor of 14.9 (1st country versus the 10th country by rank).

Publications by Institutions for Folate Receptor Articles

The total number of unique institutions represented in this study was 2,351. The top 10 institutions accounted for 24.1% (754 articles) of the total number of publications (Fig. 3). Purdue University had the highest number of publications at 170 (5.2%) followed by the University of Texas System at 104 (3.2%) and the National Institutes of Health (NIH) at 75 (2.3%) to round out the top 3 counties by output. Of note, a privately held company was in 5th position at 70 research articles. The publication productivity among the top 10 institutions differed by as much as a factor of 3.5 (1st institution versus the 10th institution by rank).

Publications by Authors for Folate Receptor Articles

The top 10 authors accounted for 18.1% (589) of the total number of research articles (Fig. 4). Low, P.S., had the highest number of publications at 139 (4.3%) followed by Holm, J. at 60 (1.8%) and Hansen, S.I., Lee, R.J., and Leamon, C.P tied at 59 (1.8%) by output. The publication productivity among the top 10 authors differed by as much as a factor of 3.6 and was consistent with institution affiliation data (1st author versus the 10th author by rank).

Top 10 Citations for Folate Receptor Articles

The top 10 research articles by total citations are listed in Table 1. Also listed in Table 1 are citations per year (WoS does not provide standard deviation in their analytics for citations per year). These 10 articles have been cited 7270 times during the time frame of this study. The top cited article had an average citation rate of 110 citations per year among the top 10. Average citation rates differed by as much as a factor of 2. (1st paper versus the 10th paper by rank). Topics ranged from imaging (top 2 cited articles) to basic research articles regarding the distribution of folate receptor to therapies and other diagnostic assays. In fact, imaging and therapies were featured in 5 of the top 10 cited articles.

Table 1

Top 10 referenced publications by articles in the field of folate receptor or folate binding protein. (Table follows the format established by Viana, et al⁷⁰.)

References	Title	Number of Citations
Kam et al. (2005)	Carbon nanotubes as multifunctional biological transporters and near-infrared agents for selective cancer cell destruction	1667
Liong et al. (2008)	Multifunctional inorganic nanoparticles for imaging, targeting, and drug delivery	1309
Varma et al. (1998)	GPI-anchored proteins are organized in submicron domains at the cell surface	921
Weitman et al. (1992)	Distribution of the folate receptor GP38 in normal and malignant-cell lines and tissues	893
van Dam et al. (2011)	Intraoperative tumor-specific fluorescence imaging in ovarian cancer by folate receptor-alpha targeting: first in-human results	822
Ross et al. (1994)	Differential regulation of folate receptor isoforms in normal and malignant-tissues in-vivo and in established cell-lines – physiological and clinical implications	754
Parker et al. (2005)	Folate receptor expression in carcinomas and normal tissues determined by a quantitative radioligand binding assay	725
Kukowska-Latallo et al. (2005)	Nanoparticle targeting of anticancer drug improves therapeutic response in animal model of human epithelial cancer	657
Smart et al. (1995)	A detergent-free method for purifying caveolae membrane from tissue-culture cells	648
Kershaw et al. (2006)	A phase I study on adoptive immunotherapy using gene-modified T cells for ovarian cancer	593

Folate Receptor Articles Related to Cancer, Macrophages and Imaging

Since folate receptor is a well-known target for cancer therapies, modalities associated with cells of the immune system (macrophages) and imaging agents, a refined search (see methods section) was conducted. Search queries involving cancer, macrophage and imaging agents revealed 2085 articles (64.2%), 128 articles (3.9%) and 752 articles (23.2%), respectively, for each topical area. See Fig. 5.

Co-Author Bibliometric Network

A co-authorship bibliometric network map was constructed using VOSviewer version 1.6.11 (Leiden University, Leiden, the Netherlands). Major co-authorship researcher nodes included: Low, P.S., Leamon, C, Mueller, C and Lee, R.J. and Baker, JR. See Fig. 6.

Discussion

Folate receptor publications increased considerably after the seminal work of Low and Leamon, which demonstrated uptake of conjugates via the folate receptor⁷¹. Given that folate receptor expression was found to be increased on malignant tissues versus normal tissues, this feature provided a potential pathway for production of both therapeutic agents and diagnostic imaging agents. In fact, imaging in this study played a key part in elucidation of folate mediated uptake of attached cargos. The large co-authorship nodes in the network map mirror several of the top 10 ten authors with Low occupying the central region, which is not surprising based on the historical progression of the field.

The United States was the top article producing country followed by China and India. Large state and federal (universities and institutes) and systems made up a large share of the top 10 institutions (e.g., Purdue, University of Texas and NIH) with the notable exception of the publically traded company, Endocyte, Inc. founded by Low. A limitation of this study was that university groups often appeared as one large cohort in the Web of Science analytics.

The top 10 cited articles reveal a high proportion of therapeutic and imaging related articles. Specifically, several works outline the use of folate-guided nanomaterials as imaging agents. Folate is easily conjugated to various nanomaterials and several high receptor expressing cell lines exist for testing these nanoconjugates⁷². This not only makes the folate receptor a valuable clinical target but also a simple test system for exploring various diagnostic and drug delivery schemes.

Cancer was a key word associated with the majority of papers, followed by imaging and macrophages. Imaging modalities exist for both cancer and inflammatory diseases associated with macrophages and we made no attempt to discern the subsets in our work. Another limitation of this analysis is that FR + macrophages can be associated with tumor environment and thus there is search overlap of inflammatory and cancer disease states. These and many other analyses will be the subject of future work.

Conclusions

Folate receptor research has led to the development of promising drug, imaging and other diagnostic schemes as well has had a profound impact on our understanding of receptor mediated cellular pathways. In this study, Web of Science was used to assess the global scientific production ranging from 1969-to June 28, 2019. Results illustrated a substantial increase in the cumulative volume of papers (264 per year for the last year studied). The US held the top metrics in publications, institutions and author output. The top 10 cited articles had an appreciable number of imaging and therapeutic applications, including nanotechnology. Given the different subareas of this dataset (e.g. imaging), there exists a rich source of data for further studies. Through bibliometric analysis, it should be possible to elucidate further interesting trends in these areas.

Abbreviations

Not Applicable

Declarations

Ethics approval and consent to participate

Not Applicable

Consent for Publication

Not Applicable

Availability of data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

No funding was necessary for this study.

Authors' contributions

CD gathered and created and compiled datasets for bibliometric analysis. WH provided literature review and interpreted data. Both authors read and approved the final manuscript.

Acknowledgements

Not applicable

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Figures

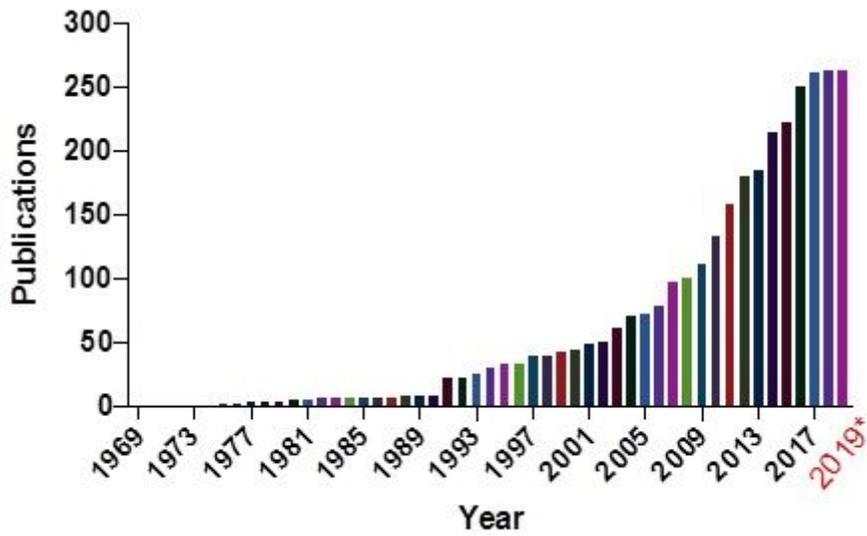


Figure 1

Total number of folate receptor publications per year since 1969-present. *Note: partial year.

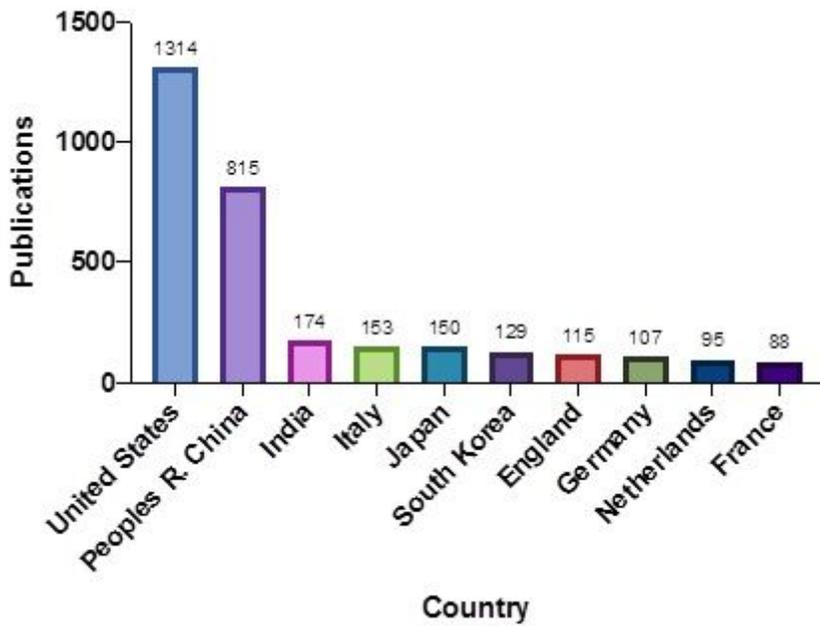


Figure 2

Publications for the top 10 countries in folate receptor research.

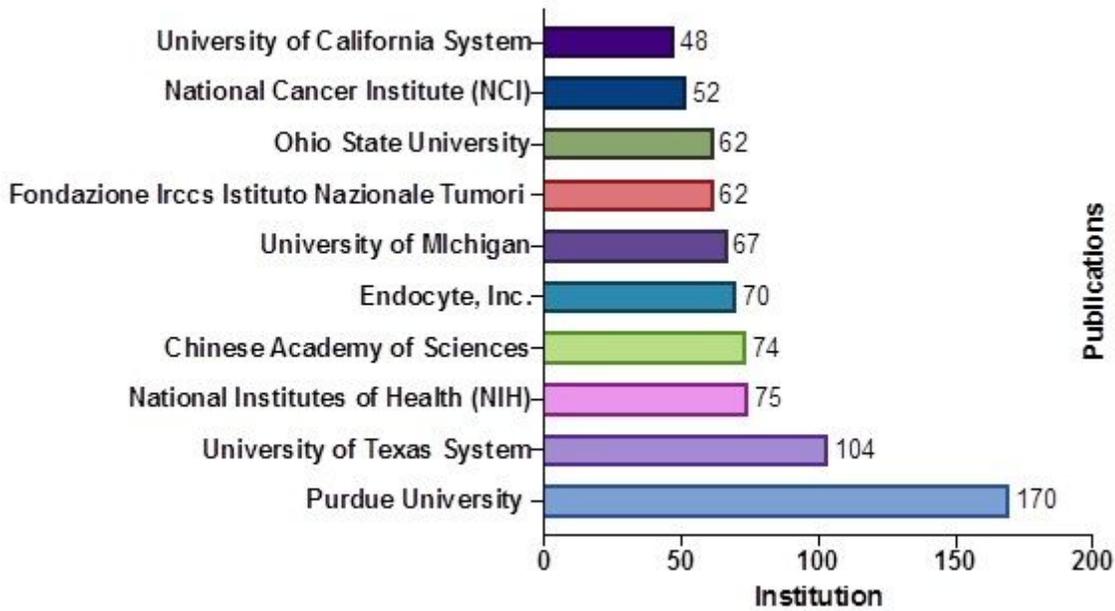


Figure 3

Publications for folate receptor research at the top 10 institutions.

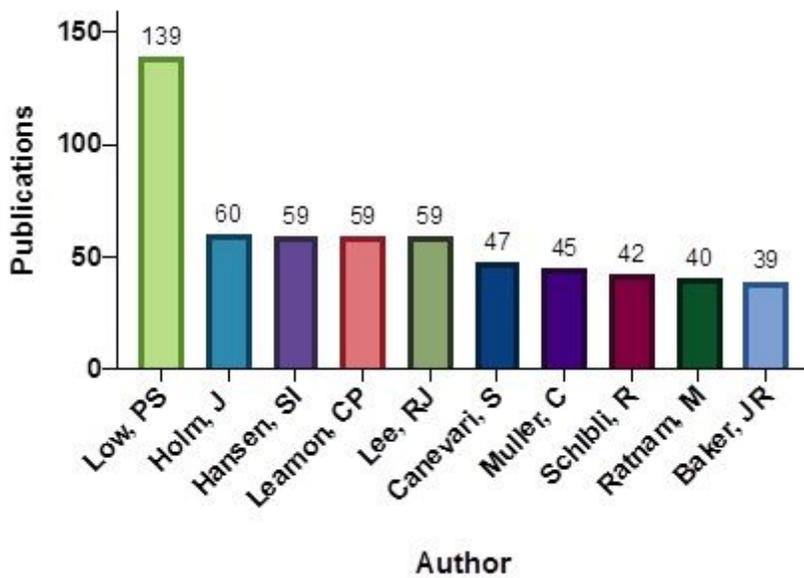


Figure 4

Publications for the top 10 authors in folate receptor research.

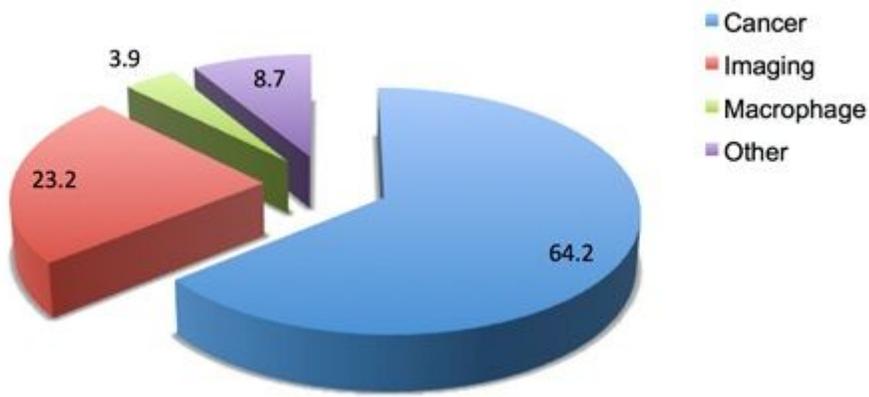


Figure 5

Percentage of folate receptor articles associated with cancer, macrophage and imaging keywords.

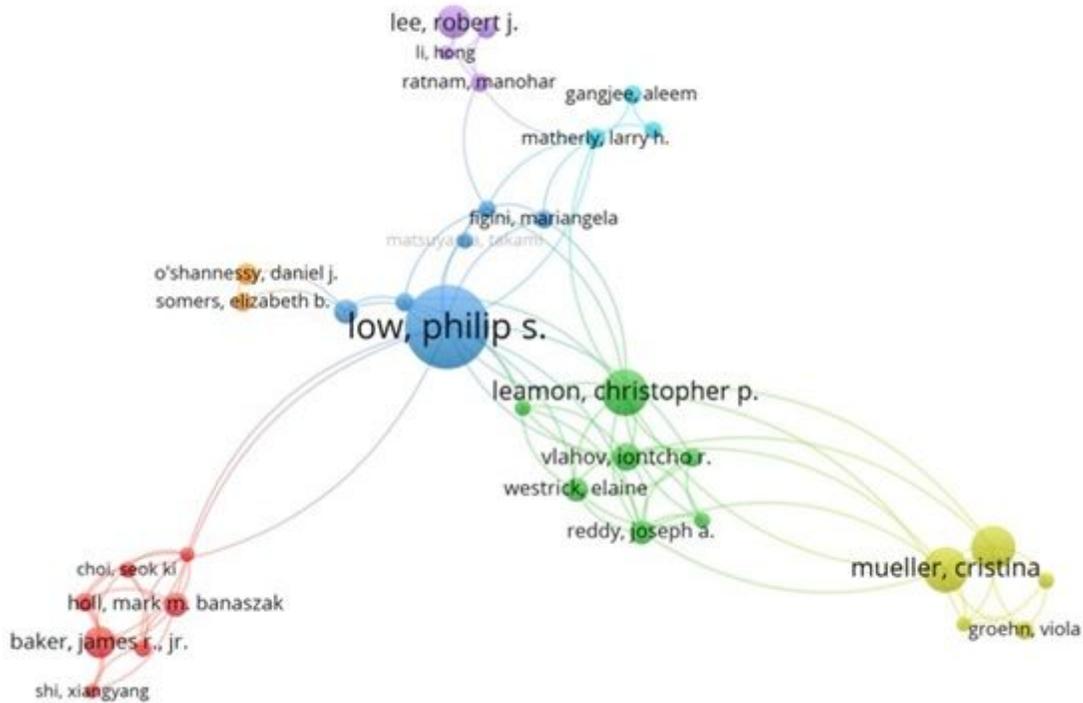


Figure 6

Co-authorship network map of publications in the field of folate receptor or folate binding protein research.