Quantitative Analysis of Publication Numbers Over Time for Immunology Research Topics in Molecules, Cells, and Organs

A Thesis submitted to the Graduate School of Valdosta State University
in partial fulfillment of requirements for the degree of

MASTER OF SCIENCE
in Biology
in the Department of Biology of the College of Science and Mathematics

April 2022

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B.S., Valdosta State University, 2017

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ABSTRACT

Research scientists, medical professionals, and the academic community publish their findings every year culminating in time series publication numbers of data that form nonlinear trends over time. Understanding these trends would allow researchers to predict future levels of need and interest in specific research areas within their discipline. The problem with studying these trends is defining exactly what their quantitative behavior will be in the future.

Trends in publication frequency can be described by plotting sub-discipline publication numbers over time. In this study, we assign specific sigmoidal equations to each sub-discipline studied by doing a Boolean search of PubMed for publication numbers on research topics related to six molecules, ten cell types, and four organ types all related to immunology. Our approach was to transform the original data by reduction of the x-axis and then curve fit the original data set to the best fitting curve which could be analyzed by non-linear regression. This technique was essential to arriving at an accurate prediction of the expected number of publications. Our findings are immunological publication numbers of cells, molecules, and organ types in immunology have exhibited significant trends that give R^2 values higher than 0.95 and that in our areas of study only sigmoidal trend behaviors are observed. We propose that demonstrated trends in publications counts will be informative to researchers allowing prediction of growth of interest in their respective fields of study in immunology. Also, we affirm that any predictions made from our research can be verified by chi-square analysis.

ACKNOWLEDGEMENTS

This thesis and the journey it took to accomplish this would not have been possible to complete without support from my professor Dr. Jonghoon Kang, my family, and the cohort that gave me encouragement, constructive critiques, and growth that will benefit me in the professional world. Looking back when I started this program, I thought I could be done with this thesis in under 6 months but one lesson to learn in every path of life is that good thing take time and greater things take thorough work.

However, I acknowledge Dr. Jonghoon Kang, Dr. John Elder, and Christine James. My family is Carol Cowan, Arnold Cowan, Lucas Cowan, Annie Cowan, Marmaduke Cowan, Opal Cowan, Granny, and Grangran. I would also like to thank my fellow graduate students and co-workers and Valdosta Family Medicine.

Chapter I

Introduction

Bioinformatics allows biological information to be encoded, cataloged and filed appropriately with immense effect on how it is later shared among diverse groups (Krausgruber et al. 2020). Research groups make substantial contributions to their fields such as the understanding of immune responses, crowdsourcing, and databases that are highly accessible to the scientific community (Krausgruber, 2020; Falagas et al. 2008). These bioinformatic contributions gave the scientific community increased insight into areas of immunology surrounding organs, cells, and molecules due to the relative ease of access to multiple information databases available such as PubMed (Falagas et al. 2008). Overall, bioinformatic methods have allowed immunological information to become rapidly quantifiable and reduced to mathematical expressions enabling an approach to analyzing organs, cells, and molecules that would have been challenging to accomplish beforehand (Huber et al. 2002, Tappeiner et al. 2017). Meta-analysis is the preferred way to organize and analyze data in Bioinformatics due to its practice of comparing separate groups and finding correlations that seek to describe the overall behavior of the separate groups (Çoğaltay & Karadağ 2015). Immunology is challenging to meta-analyze presently due to its prodigiousness and rapid evolution that require rapid inferences into diseases related to a molecule, cell, or organ's genomic and proteomic datasets (Pappalaro et al. 2014). Also, immunological datasets are stored in multiple locations in databases such as Pubmed, Genbank, and PROSITE which creates the need for comparison of different subjects especially if there not all located in the same database (Brusic et al. 2000). The consequence of the growing number of databases is the continual improvement of access to shared knowledge that spans multiple decades (Brusic et al. 2000). This storage of decades worth of information made advancements in immunology possible such as analyzing rare cell states

previously not resolved at the population level according to Neu, Tang, Wilson, and Khan (2017) and allowing systems-level study of the dynamics of cancer in organs at scales not possible in previous generations (Reticker-Flynn & Engleman, 2020). New capabilities like these create quantifiable publications in academic journals and result in observable trends that can predict the number of future publications around a specific subject area (Kang & Clifton, 2018, Kang & Kang, 2020, Kang & Purnell, 2011). A technique to predict future publication counts has been developed by specifying a future year that is inserted into an equation of an exhibited publication time series trend for trends that behave in exponential, sigmoidal, logistic, or Gompertz manners (Kang et al. 2015). Consequently, the specific trends observed are unique to the subject studied because not all data share the exact same quantitative value in terms of an asymptotic maximum value or slope of a curve (Kang et al. 2015). Additionally, a given unique trend can be verified using chi-square analysis of two separate values generated from two separate studies observing a past trend and present trend centered on the same area (Kang et al. 2015).

This new technique can help predict how interest and activity in certain fields of science might behave at a specified year in the future. The behavior of a trend in a science field could affirm to society how we arrive at meaningful conclusions in the scientific community (González-Méijome & Belsué, 2020). The scientific community of immunology will continue to bear benefit from many advancements from data science and it is with this knowledge we have pursued the bioinformatic analysis of publication number trends applied to the immunological study of selected molecules, cells, and organs.

Chapter II

Literature Review

Immunology is a wide-ranging discipline in the biomedical sciences that originated from Edward Jenner's successful vaccination against smallpox (Doherty & Robertson, 2004; Kohler et al., 2019). However, this was not the first record of recorded immunity in overall human civilization (Doherty & Robertson, 2004). There are earlier records of people attaining immunity from a disease that ravaged Athens in 430 A.D. and in China where dried crusts of smallpox lesions were inhaled by uninfected Chinese to gain immunity to smallpox (Cunha, 2004; Doherty & Robertson, 2004; Littman, 2009). The difference between these ancient times and the discipline of immunology known today lies in the combined work of many scientists who demonstrated how immunity is conferred through immunological specificity (Kaufmann, 2019; Silverstein & Bialasiewicz, 1980). These discoveries gave credence to how different molecules, cells, and organs interplay with one another regarding the immune system (Nuttall, 1901). Organs, cells, and molecules are therefore components of the immune system (Calder, 2013; Nicholson, 2016). Organs are important to focus on in a general hierarchy due to the intense study individual organs receive in the scientific community due to their framework of specialized cells and the contribution they have to the composition of individual organ systems (Candeais & Gaipl, 2016; Zdrojewicz et al., 2016). The framework of specialized cells that composes organs makes them receive this same intense research in immunology by being vital in understanding processes like cellular death, which prevent diseases such as cancer (Kroemer et al., 2013). These processes are further strengthened by molecules that internally control apoptosis and ensure the recognition of foreign cells and cancer cells to the immune system (Alter et al. 2018; Gonzalez et al. 2018).

Molecules involved in this array of cell signaling include antibodies, chemokines, cytokines, major histocompatibility complex (MHC) molecules, T cell receptors, and toll-like receptors (Bournazoset al., 2017; Huang et al 2008; Liu et al. 2014; Serhan et al. 1996). These molecules are what grants cells the ability to communicate internally as well as externally in environments found within humans and other species that the study of immunology encompasses (Hamada & Slade, 1980). The communication between cells then builds up to tissues that make a fully operating organ that engages in crosstalk internally (Rogers & Aikawa, 2019). The crosstalk or intercommunication of cell functions helps contribute to an overall role of an organ (Rogers & Aikawa, 2019). The role an organ performs is just one reason the field of immunology is continually growing today (Napier, 2012; Rogers & Aikawa, 2019).

Immunology is growing in large part due to online databases like PubMed where largely publicly accessible citations from peer-reviewed articles are cataloged daily, especially those surrounding immunology (McKeever et al. 2015). The PubMed database also has articles starting from 1809 that provide an overabundance of resources that reach across a plethora of all the subjects contained inside immunology (McKeever et al. 2015). This trove of information is further accessible from any device such as a computer, smartphone, or tablet due to the recent update the database has received (Collins, 2019; McKeever et al. 2015). PubMed's effect of staying up to date in its cataloging and indexing of published articles provides researchers with current trends on publications that help to research topics such as COVID-19 (Lazarus et al. 2020). By combining both the past and present research contributions scientists can form an even better picture to see where trends lie especially if Boolean operators are used in the search criteria of their respective searches in the database (McKeever et al. 2015; Raeisi et al. 2019). This search method of using Boolean operators can refine results and create a search that is

repeatable with specific conditions that yield a result that can be studied or quantified through the appropriate data analysis (Hanna et al. 2019).

Data analysis has many forms and has been appropriately employed in the form of nonlinear regression to look at several publications over time or the observed inputs defined as years to view the number of publications over time (Gallant, 1975; Kang & Kang, 2020). Nonlinear regression analysis can also have versatility with how the equations are used to analyze each data set whether that set is looked at from a simple sigmoidal-3-parameter or a double sigmoid pattern view (Hau et al. 1993; Kang & Clifton, 2018). The purpose of having multiple viewpoints to view vast amounts of data collected over time is to help form the simplest explanation and can lend investigator tools to predict future trends in current science disciplines like biophysics or biochemistry (Blumer et al. 1987; Kang & Purnell, 2011; Kang et al. 2015). Specifically, the field of epigenetics is an example of this because it showed a sigmoidal fit behavior from research papers published in this discipline which projects this field will grow by 20.7% over ten years (Kang et al. 2019). This prediction is also due to the applied use of Occam's Razor which ruled out other nonlinear fits (Blumer et al. 1987; Kang et al. 2019).

Chapter III

Materials and Methods

The database of PubMed itself is composed of biomedical publications archived in MEDLINE containing fields of interest like those centered around immunology in the biomedical society. From the perspective of publications regarding cells, molecules, and organs, the Boolean expression repeated in each search term to describe immunology is "immune[Title/Abstract]) OR immunity[Title/Abstract]" and each term was searched as early as August 8th, 2019 which had publications ranging from 1861 to 2019. The study itself catalogued each term in the three fields of interest independently from one another so that only searches for publication counts of B cells were listed underneath ("B cells"[Title/Abstract] OR "B lymphocytes"[Title/Abstract]) AND (immune[Title/Abstract] OR immunity[Title/Abstract]) while other publication search for the organ bone marrow would only be listed underneath (("bone marrow"[Title/Abstract]) AND (immune[Title/Abstract]) OR immunity[Title/Abstract])). The corresponding search for molecules would be characterized the same except it would be listed under the specified molecule as (chemokine[Title/Abstract] AND (immune[Text Word] OR immunity[Text Word]). These search terms are either individual words or combined words that are paired together using quotation marks (Table 1). This subtle detail of searching the PubMed database ensures our main objective of finding specific area trends in immunology is successful. Following this successful search, the publication counts for each area in immunology were then gathered by downloading each year as a CSV or comma-separated values file for further analysis of the dataset.

The Pubmed search results for publication numbers of cells, molecules, and organs were analyzed by the Regression Wizard function available in SigmaPlot (version 11, Systat Software Inc, San Jose, CA, USA). The analysis was first formatted on the Cartesian plane with x

representative of the year of publication or the independent variable. The y function was representative of the publication count or the dependent variable: $y=f(x)$. Once this format was arranged we then looked at the graphs representative of each dataset and reduced the x-axis to the number (x_o) of 1 year prior to the year of first publication which as an example would be 1860 if the starting year were 1861 as the date of first publication. After this reduction was performed, we specifically utilized the nonlinear analysis reporting tools of exponential and sigmoidal after exhausting all other analysis options that could not provide the best fit to the lines represented by the original dataset.

Organ	**Search terms**
Bone marrow	"bone marrow"[Title/Abstract] AND (X[a])
Lymph node	"lymph nodes"[Title/Abstract] AND (X[a])
Spleen	spleen[Title/Abstract] AND (X[a])
Thymus	thymus[Title/Abstract] AND (X[a])
Cells	**Search terms**
B cells	("B cells"[Title/Abstract] OR "B lymphocytes"[Title/Abstract]) AND (X[a])
Basophils	basophils[Title/Abstract] AND (X[a])
Dendritic cells	("dendritic cells"[Title/Abstract] OR DC[Title/Abstract]) AND (X[a])
Eosinophils	eosinophils[Title/Abstract] AND (X[a])
Macrophages	macrophages[Title/Abstract] AND (X[a])
Mast cells	"mast cells"[Title/Abstract] AND (X[a])
Monocytes	monocytes[Title/Abstract] AND (X[a])
NK cells	("natural killer cells"[Title/Abstract] OR “NK cells”[Title/Abstract]) AND (X[a])
Neutrophils	neutrophils[Title/Abstract] AND (X[a])
T cells	("T cells"[Title/Abstract] OR "T lymphocytes"[Title/Abstract]) AND (X[a])
Molecules	**Search terms**
Antibody	(antibody[Title/Abstract] OR immunoglobulin[Title/Abstract]) AND (X[a])
Chemokine	chemokine[Title/Abstract] AND (X[a])
Cytokines	cytokines[Title/Abstract] AND (X[a])
MHC	("major histocompatibility complex"[Title/Abstract] OR MHC[Title/Abstract] OR "human leukocyte antigen"[Title/Abstract] OR HLA [Title/Abstract]) AND (X[a])
TCR	("T Cell Receptor"[Title/Abstract] OR TCR[Title/Abstract]) AND (X[a])
TLR	("Toll like receptor"[Title/Abstract] OR TLR[Title/Abstract]) AND (X[a])

[a] X = immune[Text Word] OR immunity[Text Word]

Table 1: Detailed search history of the specified areas in immunology concerning molecules, cells, and organs. The database of PubMed was accessed between August, 2019 to July 2020.

Chapter IV

Results

The findings of our work have shown all areas of study in molecules, cells, and organs that sigmoidal behavior is the only observed trend. Overall, the datasets of each individual area did yield high correlations (R^2: >0.95) to the sigmoidal equations generated from each fit except for two areas which still showed high correlation coefficients in relation to the trend line observed (Table 2). These two areas were the thymus with a high R^2 value of 0.93 and basophils with an R^2 value of 0.94 (Table 2). The parameters for each field of study were seen to be uniquely different for each field regardless of the dataset being subjected to Two-Sigmoidal, 6 Parameter or Sigmoidal, Sigmoid, 3-Parameter.

Overall, the datasets for molecules, cells, and organs did have a common occurrence. This occurrence was that two fields of study for each of the three areas of immunology had a Two-Sigmoidal, 6 Parameter trend line (Table 2). All other fields of study for molecules, cells, and organs displayed a Sigmoidal, Sigmoid, 3-Parameter trend line (Table 2).

Tissue/Organ	**Fitting equation**	R^2
Bone marrow	5143.9/[1 + exp (2030.7 – *x*)/13.9]	0.9913
Lymph node	1453.4/[1 + exp (2016.7 – *x*)/13.0]	0.9888
Spleen	577.7/[1 + exp (1973.8 – *x*)/2.6] + 854.9/[1 + exp (2010.4 – *x*)/3.1]	0.9911
Thymus	215.9/[1 + exp (1970.9 – *x*)/1.4] + 177.5/[1 + exp (2006.1 – *x*)/4.7]	0.9348
Cells	**Fitting equation**	R^2
B cells	609.5/[1 + exp (1981.6 – *x*)/7.2] + 1536.9/[1 + exp (2012.6 – *x*)/4.4]	0.9900
Basophils	1397.6/[1 + exp (2052.3 – *x*)/13.3]	0.9417
Dendritic cells	2368.0/[1 + exp (2003.1 – *x*)/2.9]	0.9974
Eosinophils	2357.6/[1 + exp (2045.7 – *x*)/14.4]	0.9851
Macrophages	557.4/[1 + exp (1979.9 – *x*)/4.7] + 6690.9/[1 + exp (2018.0 – *x*)/6.3]	0.9991
Mast cells	604.2/[1 + exp (2012.9 – *x*)/9.0]	0.9889
Monocytes	12351.0/[1 + exp (2045.3 – *x*)/13.4]	0.9928
NK cells	3690.1/[1 + exp (2024.1 – *x*)/11.3]	0.9936
Neutrophils	8189.5/[1 + exp (2034.8 – *x*)/10.6]	0.9945
T cells	13172.2/[1 + exp (2014.5 – *x*)/10.9]	0.9978
Molecules	**Fitting equation**	R^2
Antibody	2357.9/[1 + exp (1976.4 – *x*)/5.5] + 4757.2/[1 + exp (2012.9 – *x*)/4.3]	0.9967
Chemokine	1151.4/[1 + exp (2006.4 – *x*)/4.6]	0.9874
Cytokines	8429.9/[1 + exp (2012.6 – *x*)/7.5]	0.9941
MHC	2320.4/[1 + exp (1997.7 – *x*)/8.3]	0.9949
TCR	375.2/[1 + exp (1991.2 – *x*)/2.0] + 740.6/[1 + exp (2017.9 – *x*)/8.1]	0.9951
TLR	1712.9/[1 + exp (2006.2 – *x*)/2.2]	0.9884

Table 2: All equations generated after curve fitting datasets for molecules, cells, and organs were performed on SigmaPlot (version 11, Systat Software Inc, San Jose, CA, USA).

Chapter V:

Discussion

The findings of our search in the database of PubMed have shown us that the published numbers of the three areas of molecules, cells, and organs have a largely sigmoidal behavior among the scientific community. The discipline of immunology would have to be further analyzed to confirm this observed sigmoidal relationship. The sigmoidal relationships observed have also shown us that in the passage of time a two-sigmoidal function did occur for two fields of study for each area of immunology observed. This occurrence may be a sign of renewed interest among those in the scientific community who are researching toll-like receptors, antibodies, macrophages, B cells, spleen, and thymus (see Appendix A, Appendix B, & Appendix C).

The other fields of study in the three areas all exhibited the same sigmoidal trend which was especially true of dendritic cells whose correlation coefficient (R^2: 0.99) was almost a near-perfect fit of the data when projected over time. The time for all data was put on a reduced x-axis which helped us reach the conclusion that sigmoidal behavior must be present when considering publication numbers of molecules, cells, and organs in immunology. This behavior could also be attributed to the nature of cataloging PubMed undergoes each day by being updated daily due to the cloud-based indexing capabilities the government-funded entity possesses (McKeever et al. 2015; Collins, 2019).

The indexing of these publications in PubMed works with our technique which can be replicated with the same results occurring because of the same trend line being produced from August 2019 to July 2020. We do expect to replicate these results again and could include different approaches to see how the datasets change by limiting the number of journals that have

the content we originally searched for. However, this additional step may be redundant in the nature of journal publications because it would more than likely result in the reduction of the y-axis and lower values for the parameters in the Sigmoid, 3 Parameter, and Two-Sigmoid, 6 Parameter equations. We could also predict what the publication count will be for each field of the study analyzed because of the high correlation values seen and largely expect that these values will fall in the sigmoidal trend lines observed. This is ultimately our conclusion as well that Sigmoidal 3-Parameter and 6-Parameter behavior will be observed as the fields of study in molecules, cells, and organs continue to create publications that are observable and can be quantified using bioinformatics.

The scientific community for immunology can also look ahead now based on the results of our work and conclude that the future of molecules, cells, and organs will be growing in predictable sigmoidal behavior. We surmise it will be worth studying these same analyses 100 years from now to see if our conclusion will be supported in the scientific community of immunology which first used the term antibody over 100 years ago (Ricketts, 1905).

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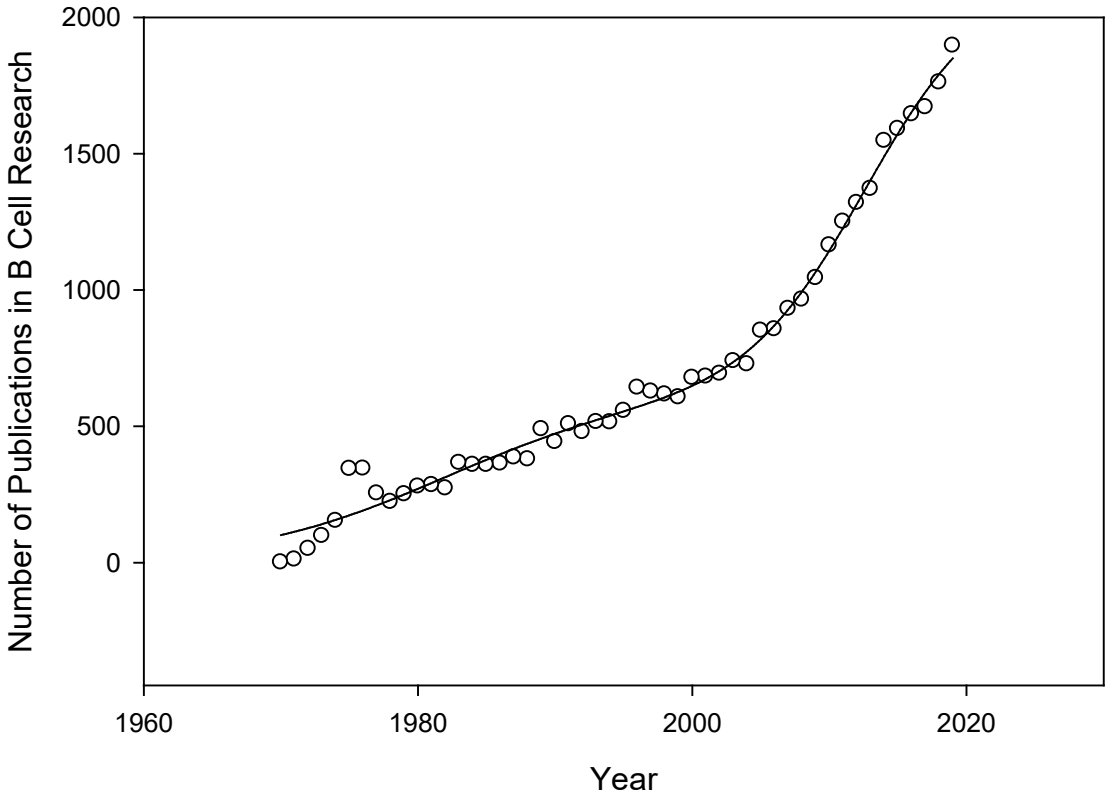
APPENDIX A:

Nonlinear Regression Analysis of Cell Types: Regression Analysis ran using Sigmoidal, Two-Sigmoidal, 6 Parameter and Sigmoidal, Sigmoid, 3 Parameter.

A


2000
1500
1000
500
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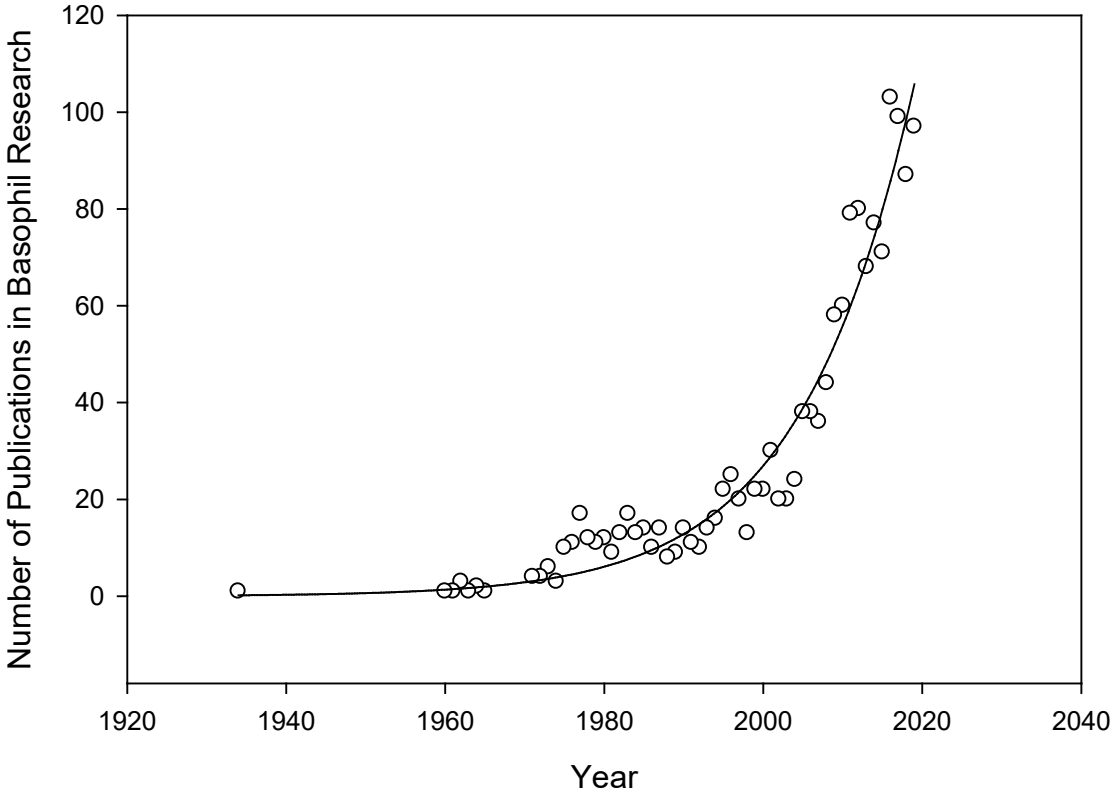
Number of Publications in B Cell Research
1960
1980
2000
2020
Year

B


Number of Publications in Basophil Research
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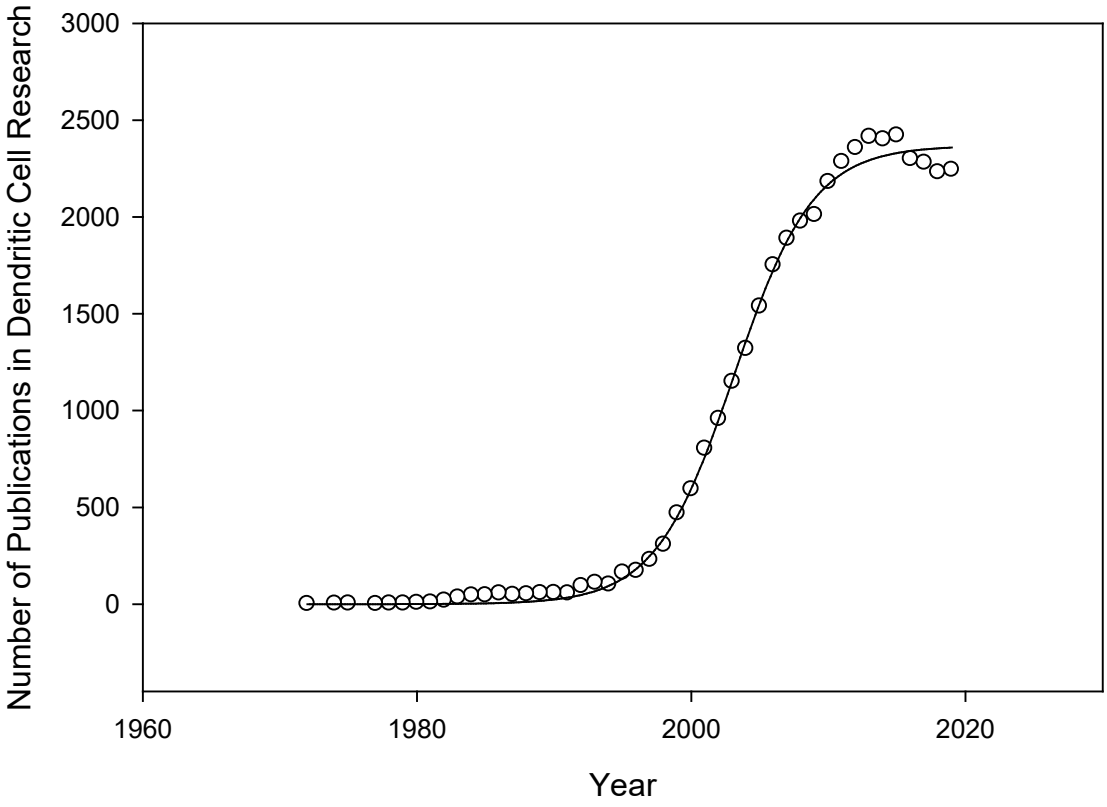
80
60
40
20
0
1920
1940
1960
1980
2000
2020
2040
Year

C


Number of Publications in Dendritic Cell Research
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2500
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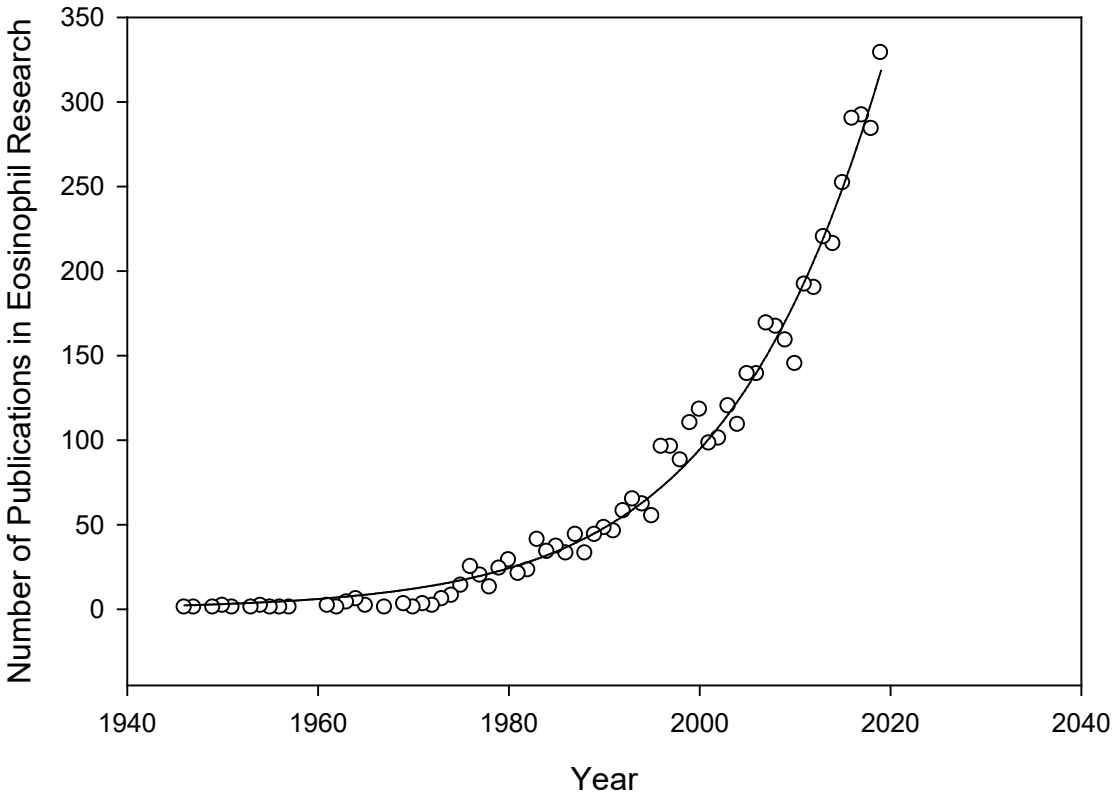
1500
1000
500
0
1960
1980
2000
2020
Year

D


Number of Publications in Eosinophil Research
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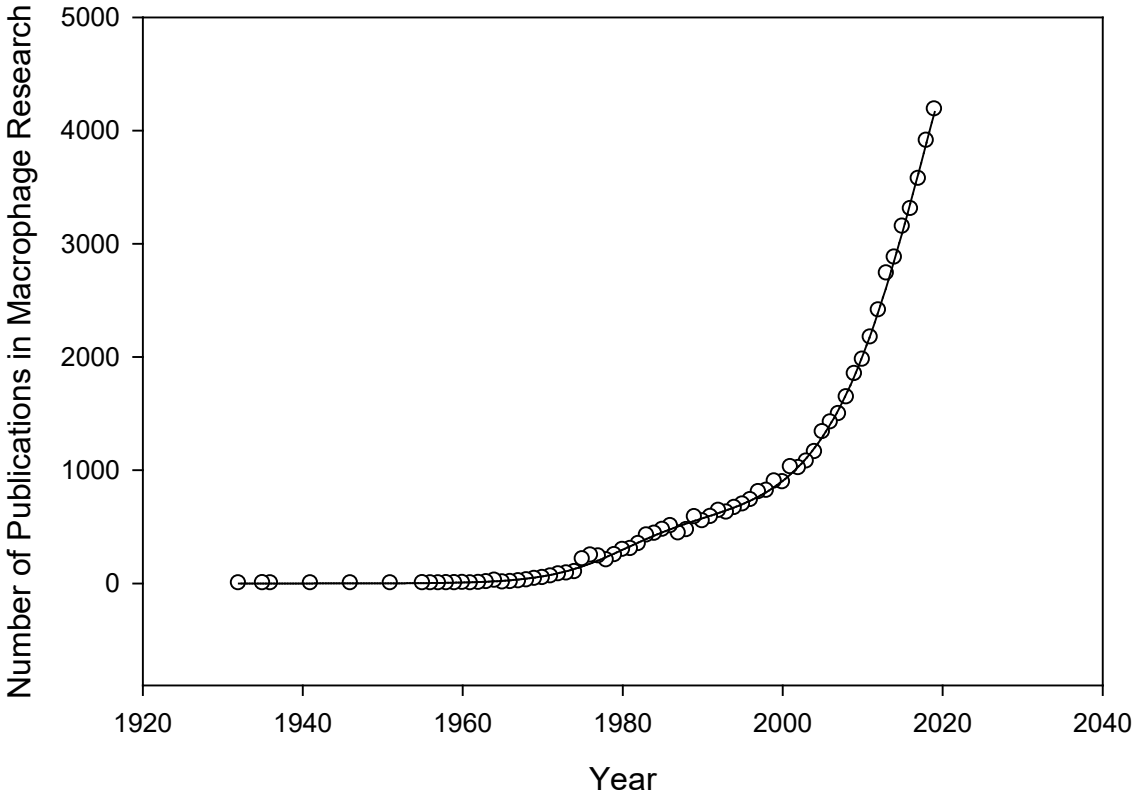
300
250
200
150
100
50
0
1940
1960
1980
2000
2020
2040
Year

E


Number of Publications in Macrophage Research
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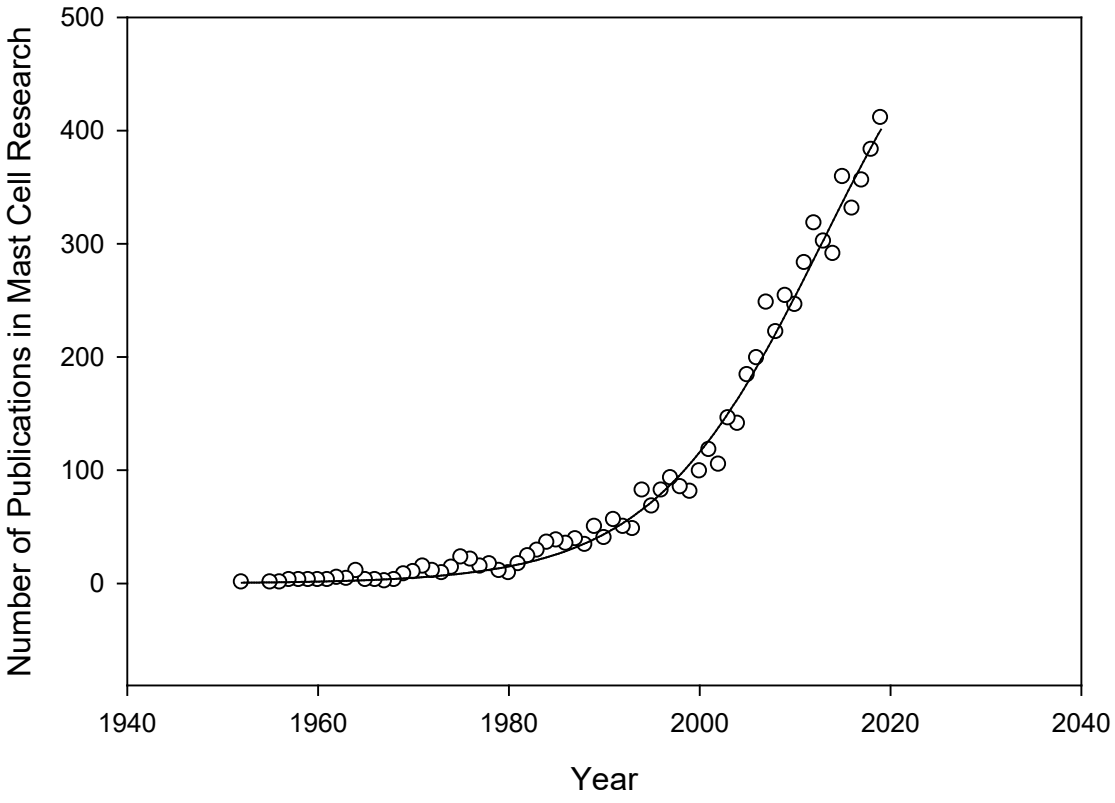
4000
3000
2000
1000
0
1920
1940
1960
1980
2000
2020
2040
Year

F


Number of Publications in Mast Cell Research
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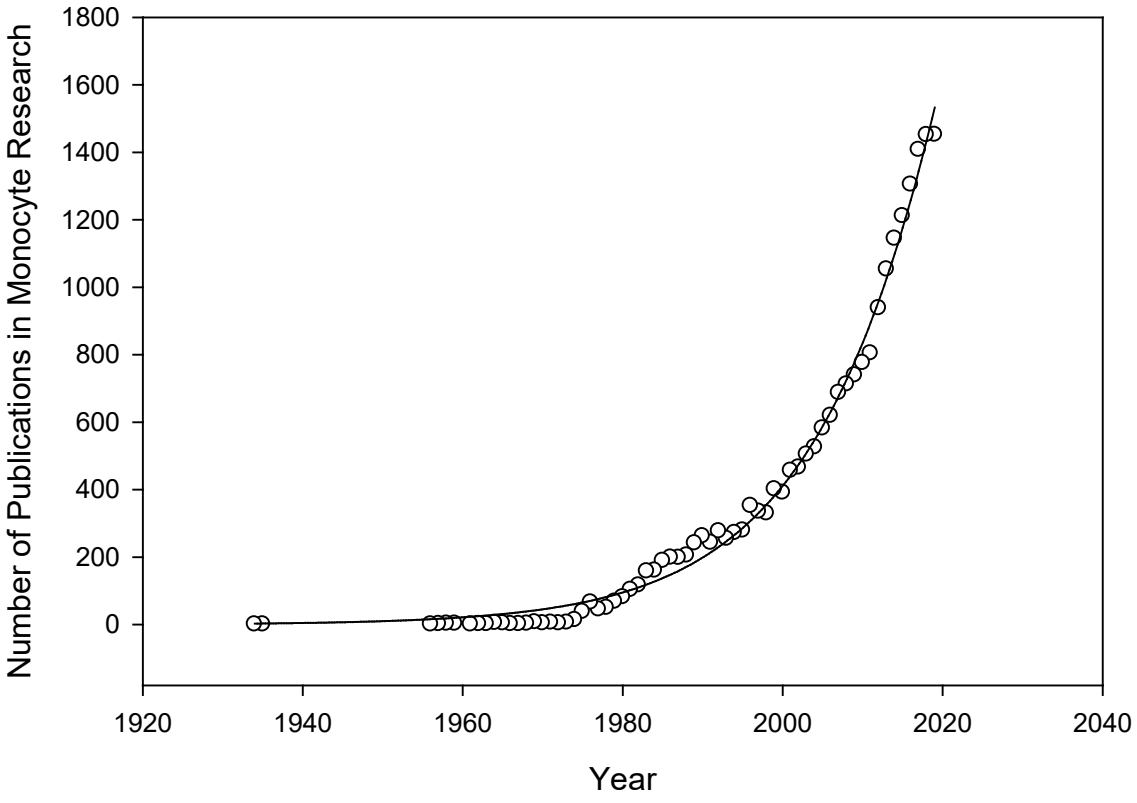
400
300
200
100
0
1940
1960
1980
2000
2020
2040
Year

G


Number of Publications in Monocyte Research
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1600
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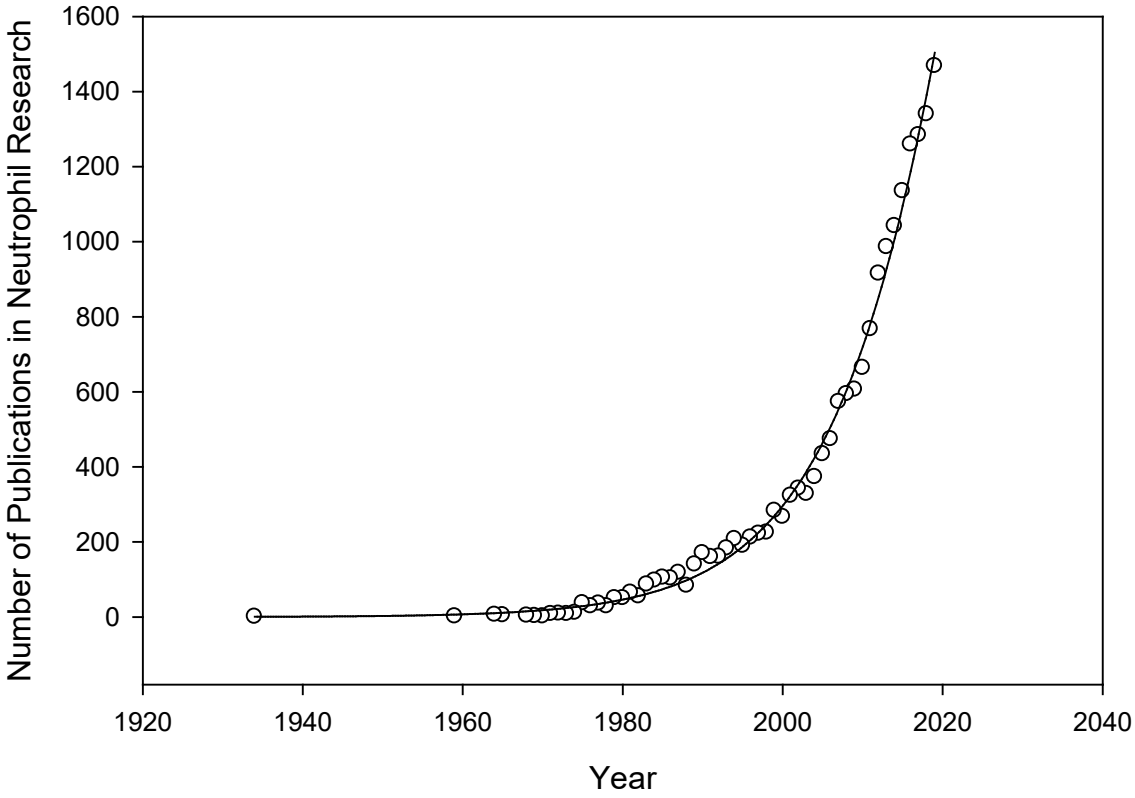
1200
1000
800
600
400
200
0
1920
1940
1960
1980
2000
2020
2040
Year

H


Number of Publications in Neutrophil Research
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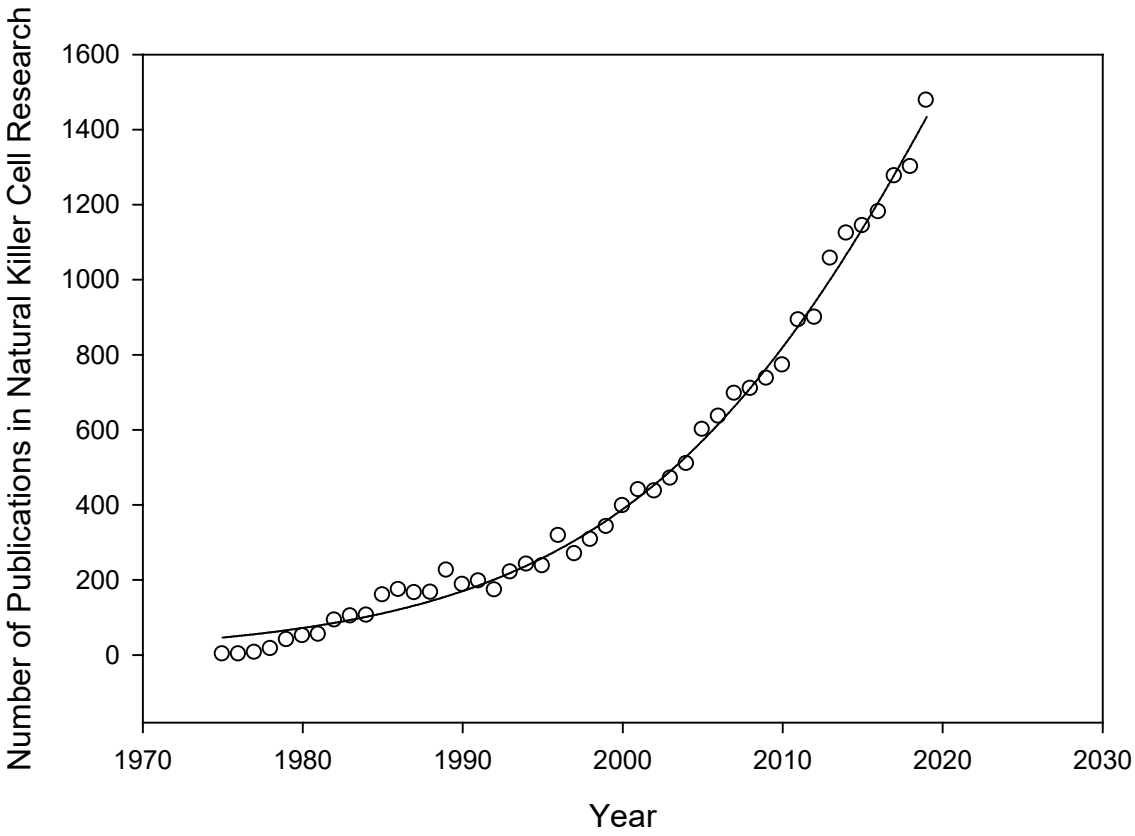
1400
1200
1000
800
600
400
200
0
1920
1940
1960
1980
2000
2020
2040
Year

I


Number of Publications in Natural Killer Cell Research
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1200
1000
800
600
400
200
0
1970
1980
1990
2000
2010
2020
2030
Year

J

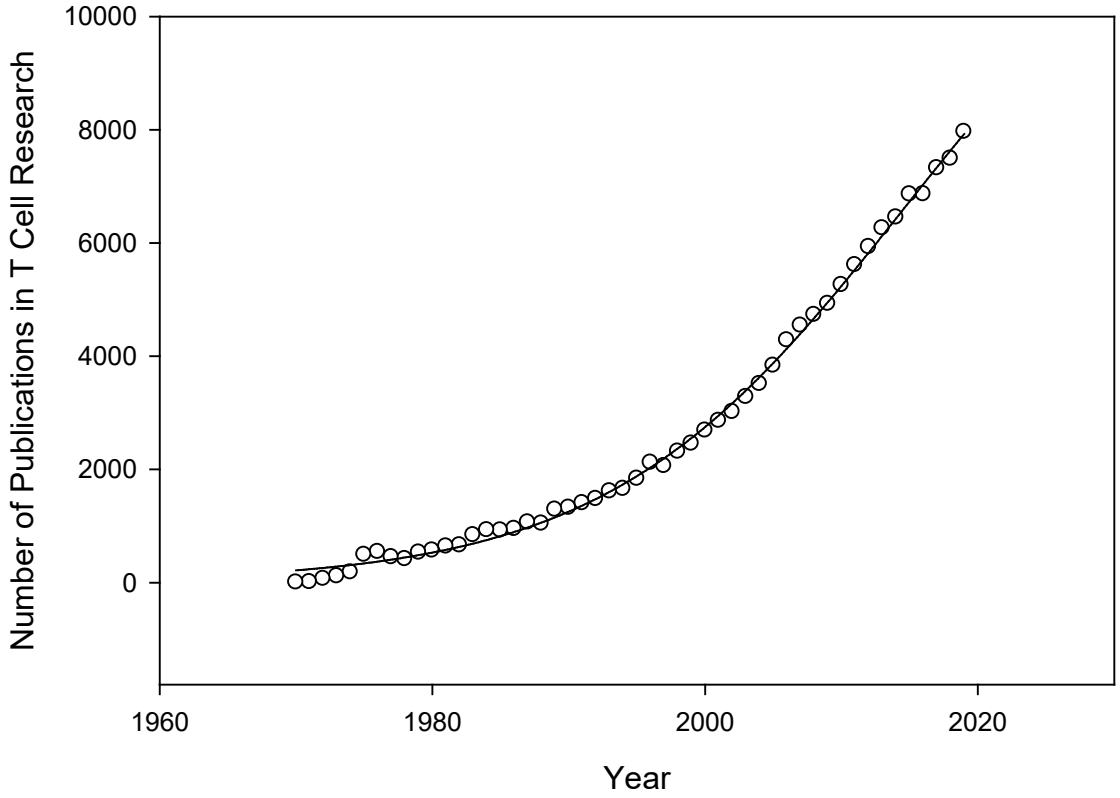
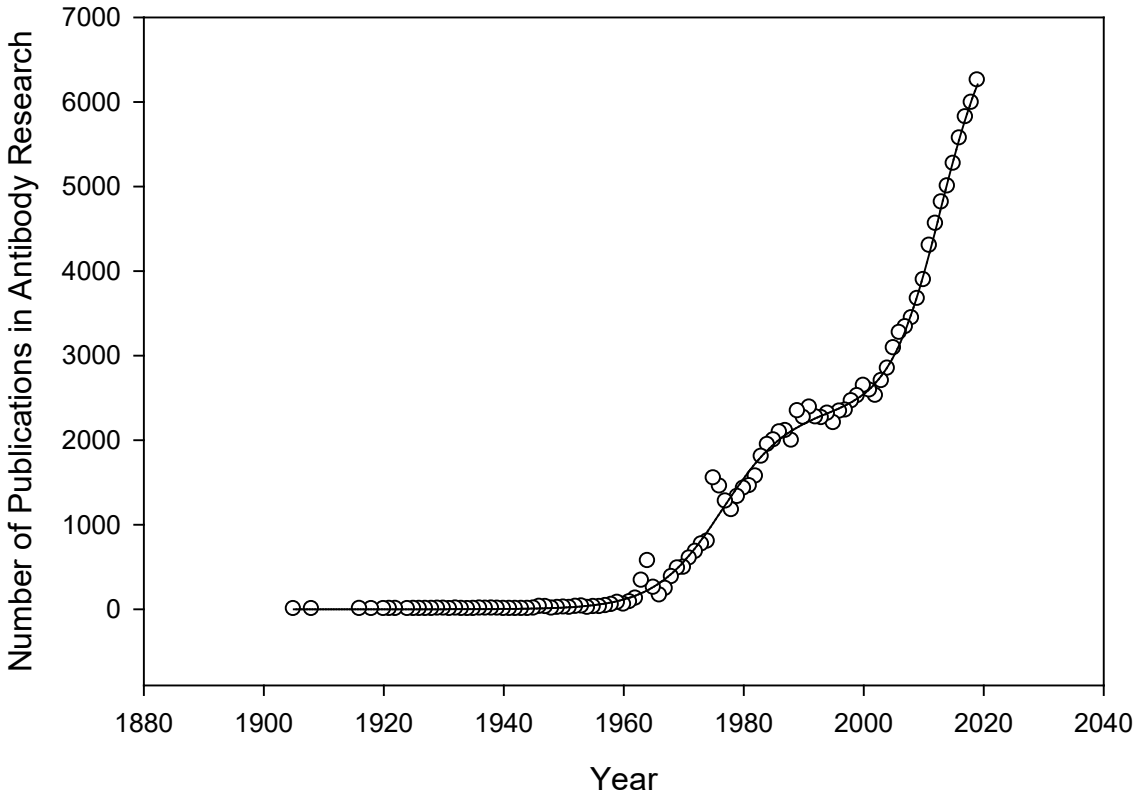


Figure 1. Nonlinear regression graphs (A-J) of all cell types under nonlinear regression analysis. Graphs A and E are Sigmoidal, Two-Sigmoidal, 6 Parameter while graphs B, C, D, F, G, H, I, and J are Sigmoidal, Sigmoid, 3 Parameter. The database of PubMed was accessed between August, 2019 to July 2020. All curve fitting was performed on SigmaPlot (version 11, Systat Software Inc, San Jose, CA, USA).

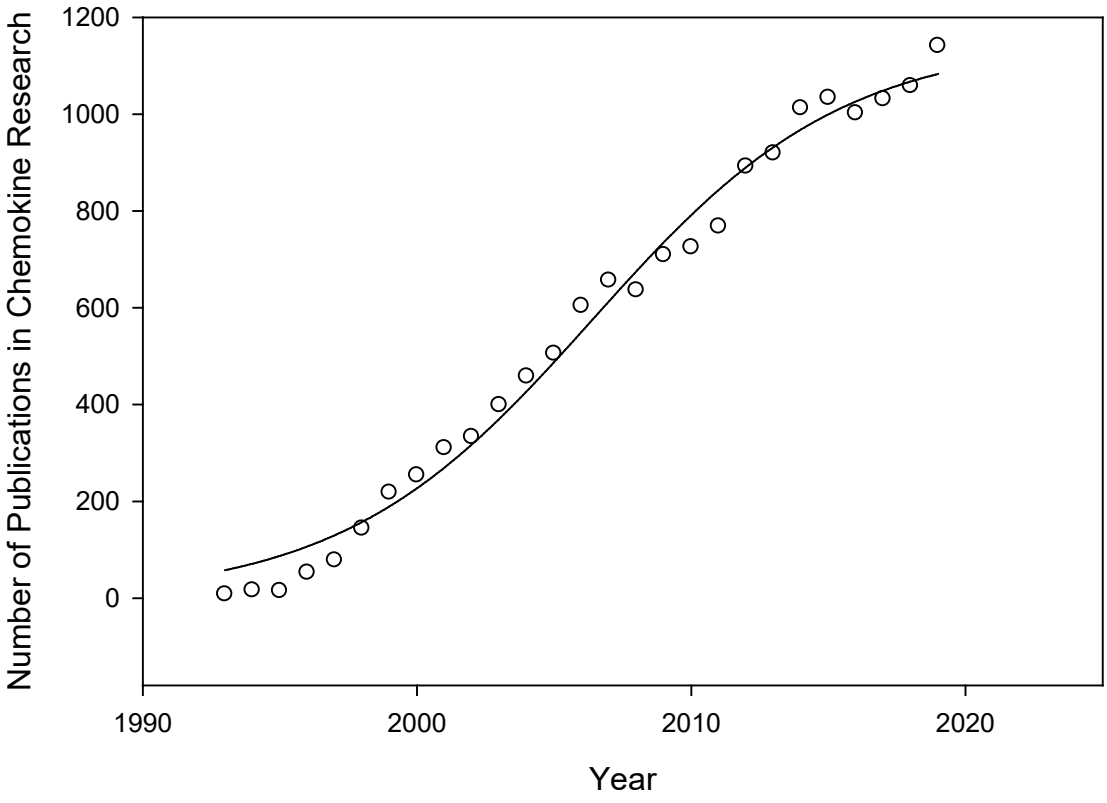
APPENDIX B:

Nonlinear Regression Analysis of Molecule Types: Regression Analysis ran using Sigmoidal, Two-Sigmoidal, 6 Parameter and Sigmoidal, Sigmoid, 3 Parameter.

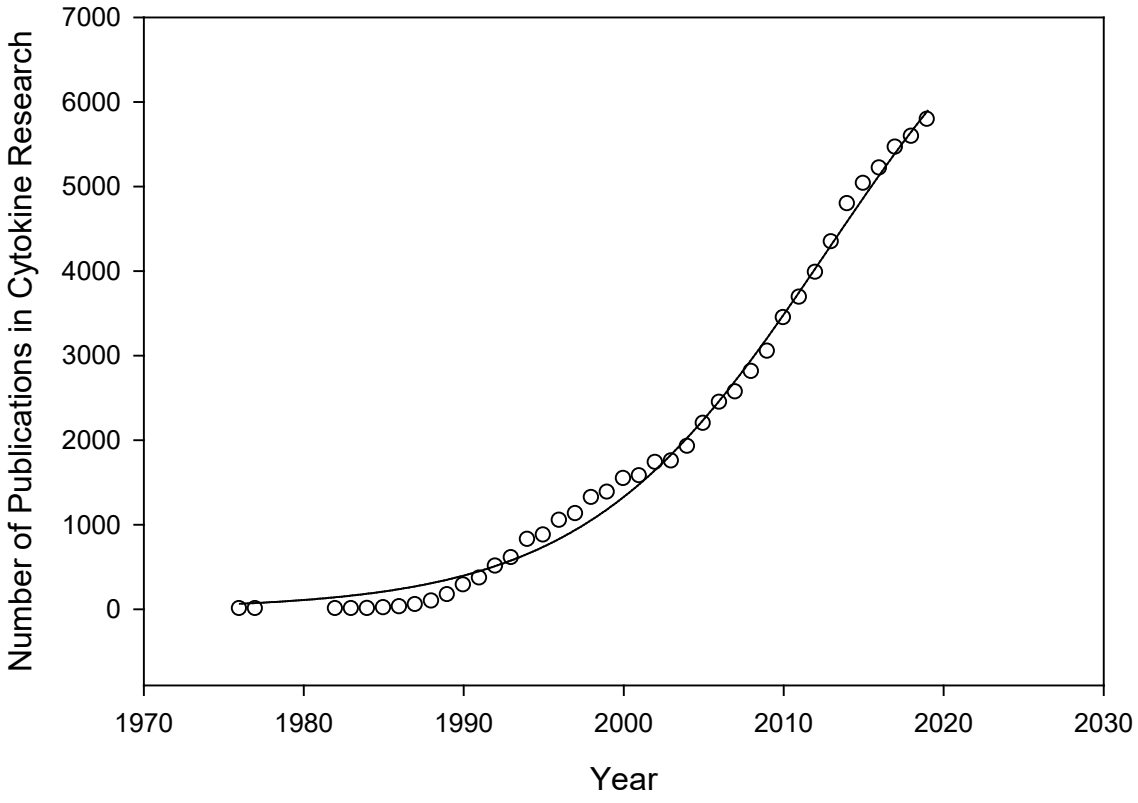
A


Number of Publications in Antibody Research
7000
6000
5000
4000
3000
2000
1000
0
1880
1900
1920
1940
1960
1980
2000
2020
2040
Year

B


Number of Publications in Chemokine Research
1200
1000
800
600
400
200
0
1990
2000
2010
2020
Year

C


Number of Publications in Cytokine Research
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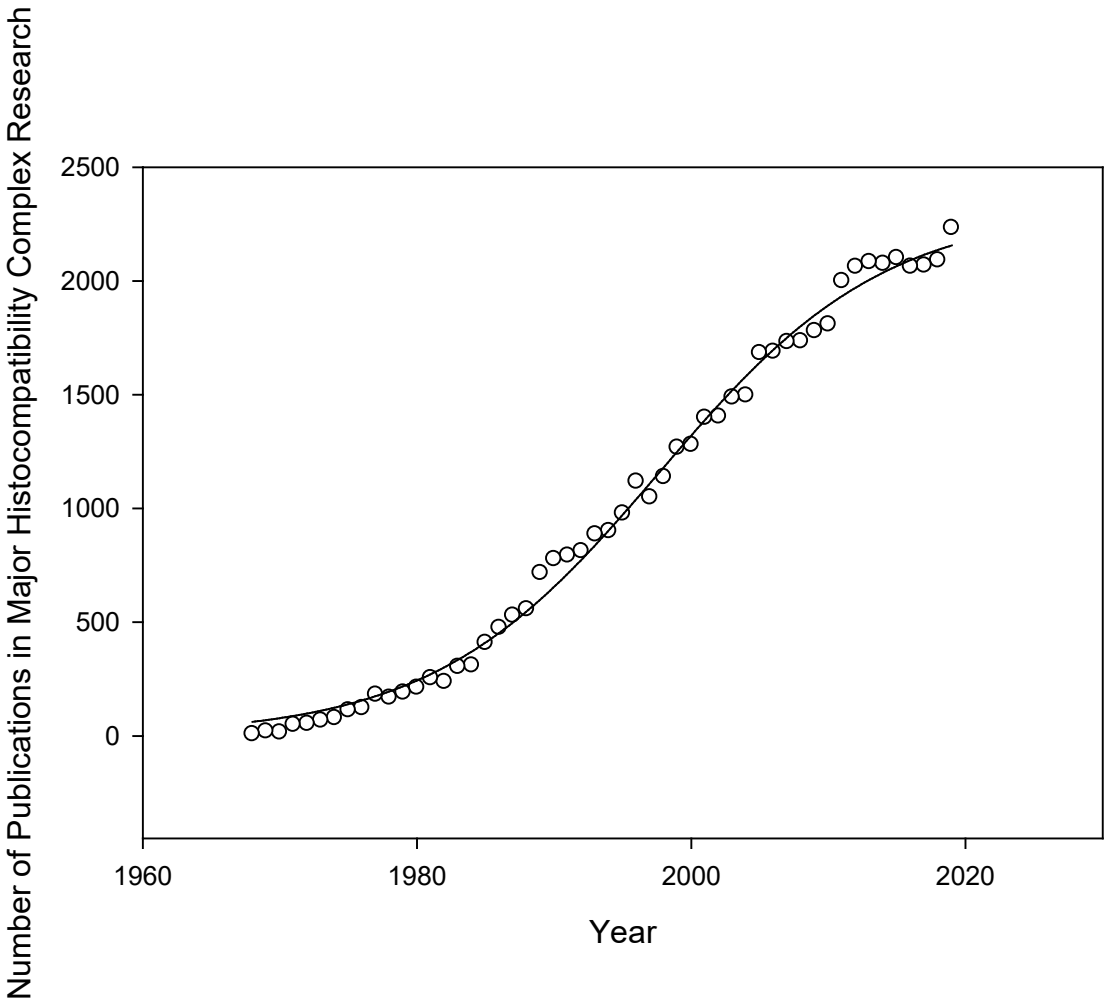
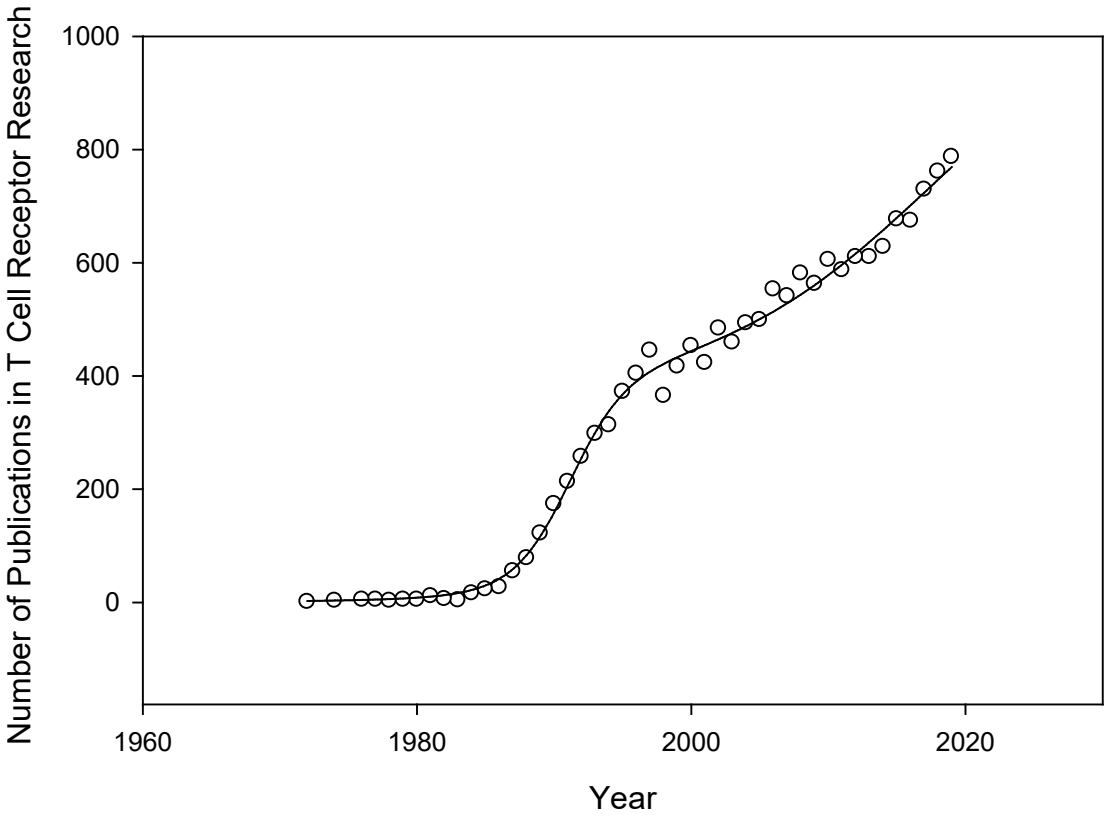
6000
5000
4000
3000
2000
1000
0
1970
1980
1990
2000
2010
2020
2030
Year

D


Number of Publications in Major Histocompatibility Complex Research
2500
2000
1500
1000
500
0
1960
1980
2000
2020
Year

E


Number of Publications in T Cell Receptor Research
1000
800
600
400
200
0
1960
1980
2000
2020
Year

F

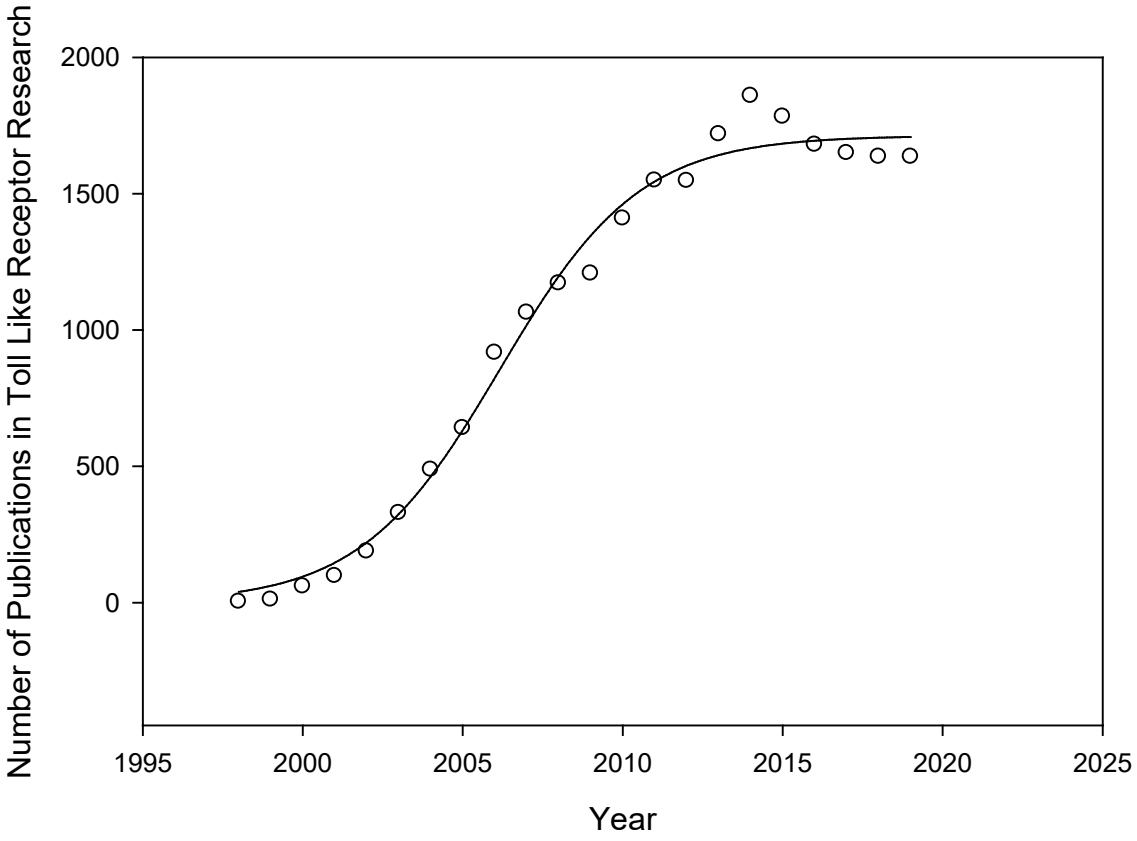
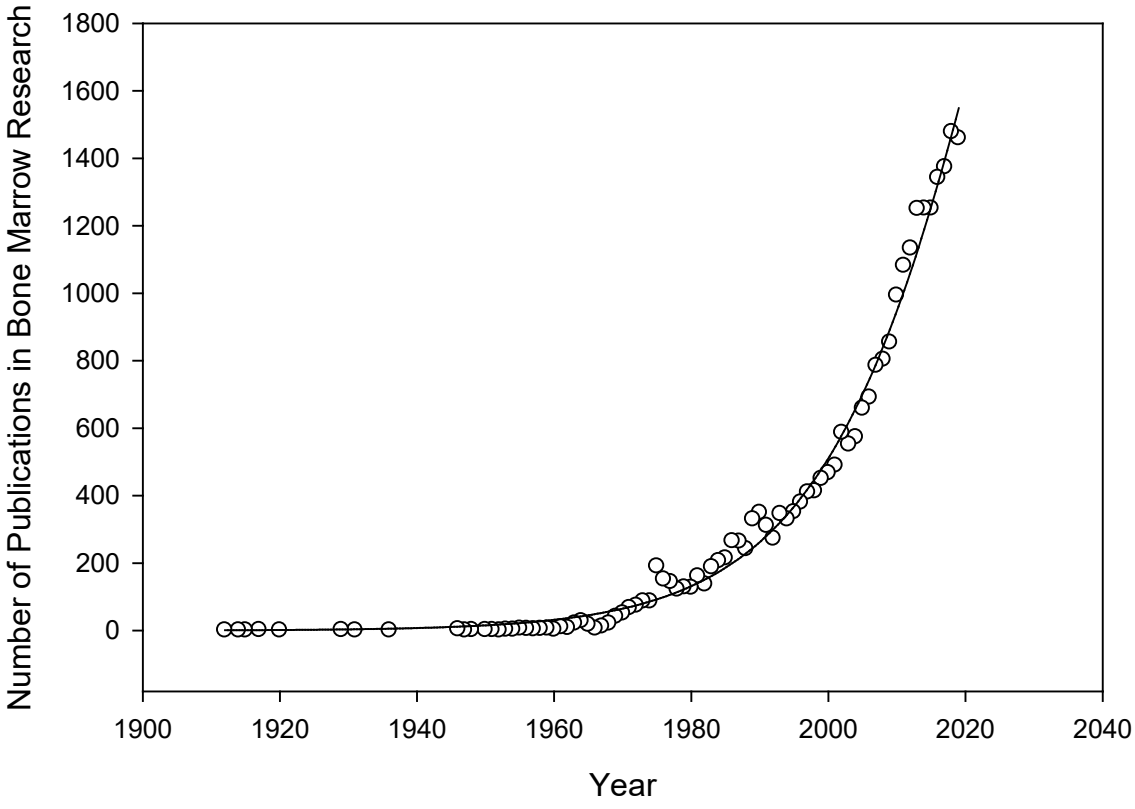


Figure 2. Nonlinear regression graphs (A-F) of all organ types under nonlinear regression analysis. Graphs A and E are Sigmoidal, Two-Sigmoidal, 6 Parameter while graphs B, C, D, and F are Sigmoidal, Sigmoid, 3 Parameter. The database of PubMed was accessed between August, 2019 to July 2020. All curve fitting was performed on SigmaPlot (version 11, Systat Software Inc, San Jose, CA, USA).

APPENDIX C:

Nonlinear Regression Analysis of Organ Types: Regression Analysis ran using Sigmoidal, Two-Sigmoidal, 6 Parameter and Sigmoidal, Sigmoid, 3 Parameter.

A


Number of Publications in Bone Marrow Research
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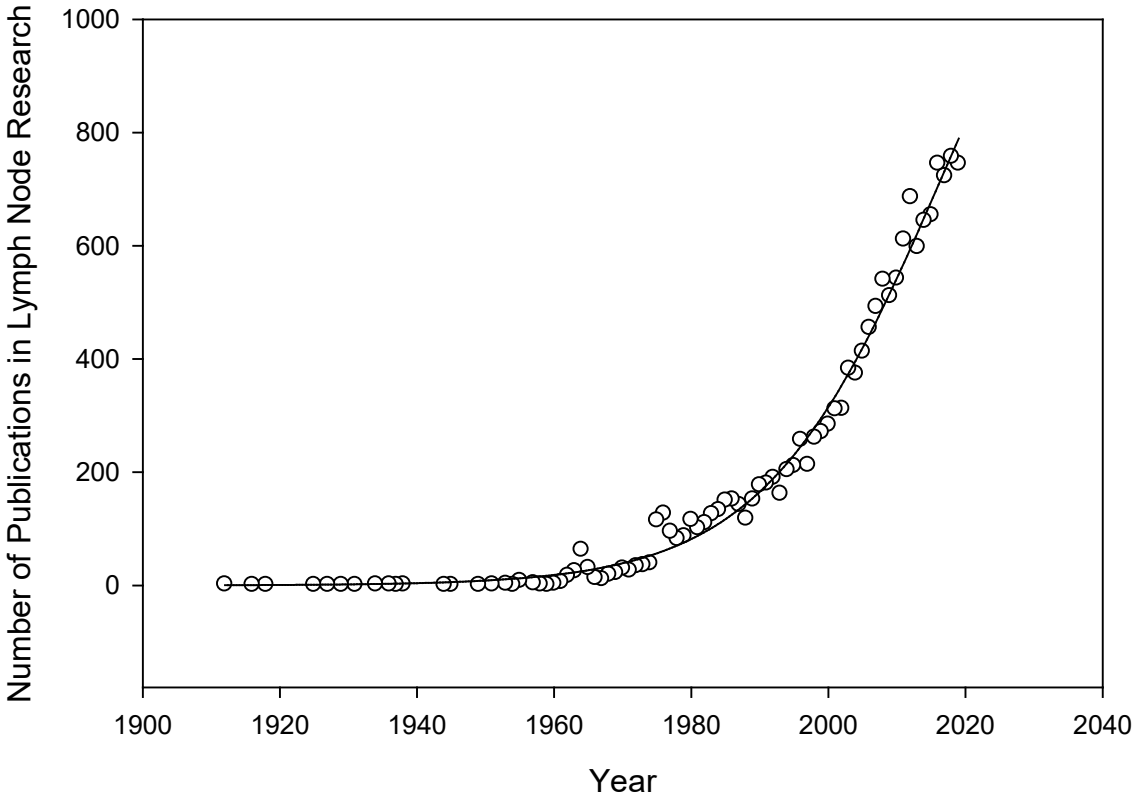
1600
1400
1200
1000
800
600
400
200
0
1900
1920
1940
1960
1980
2000
2020
2040
Year

B


Number of Publications in Lymph Node Research
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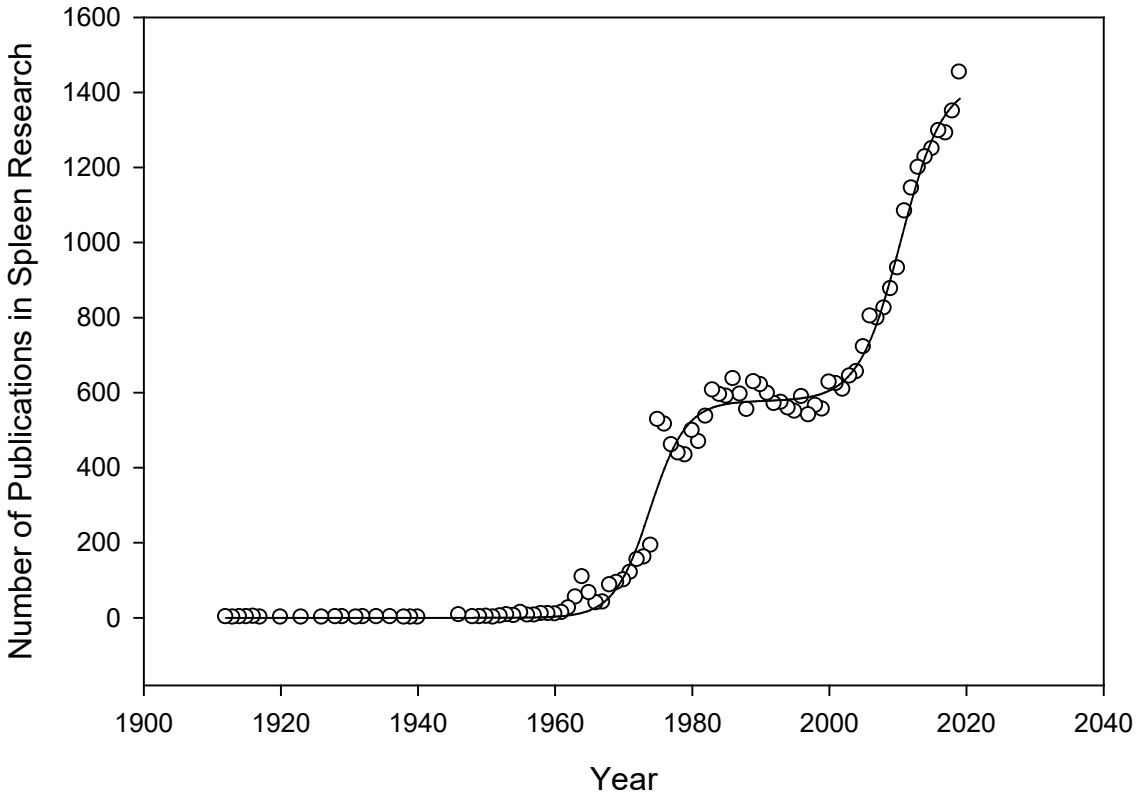
400
200
0
1900
1920
1940
1960
1980
2000
2020
2040
Year

C


Number of Publications in Spleen Research
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1000
800
600
400
200
0
1900
1920
1940
1960
1980
2000
2020
2040
Year

D

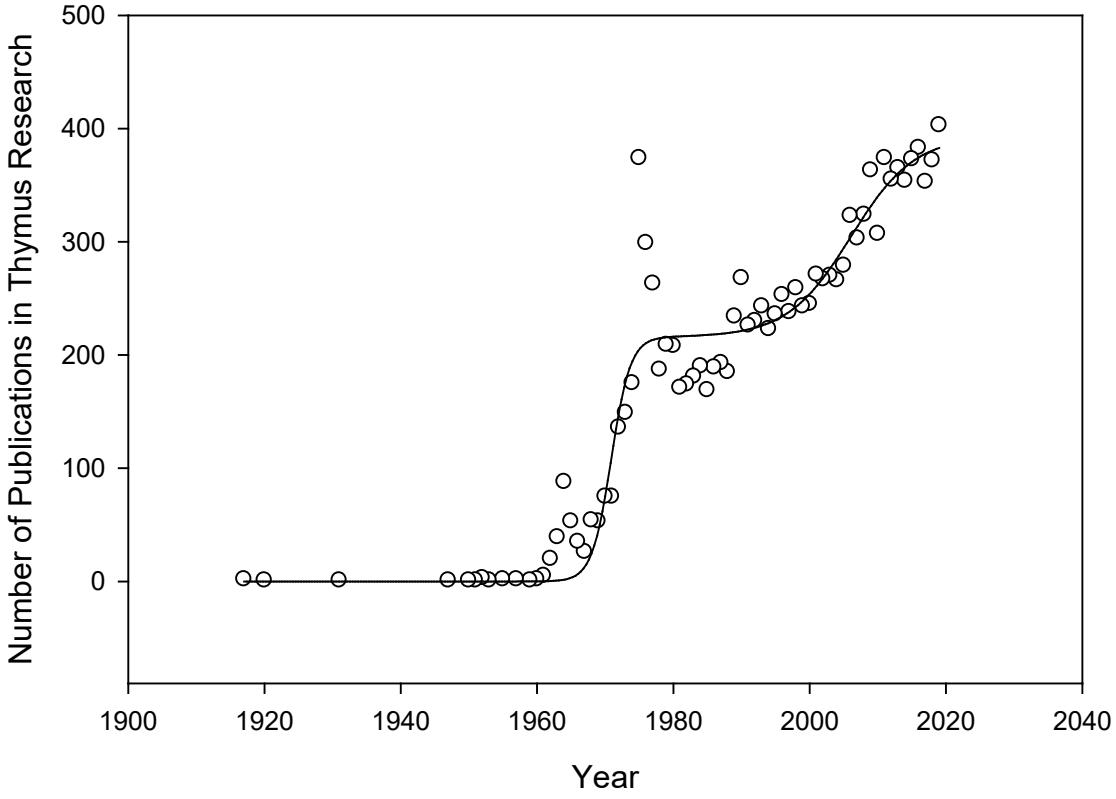

Figure 3. Nonlinear regression graphs (A-D) of all organ types under nonlinear regression analysis. Graphs A and B are Sigmoidal, Two-Sigmoidal, 6 Parameter while graphs C, and D are Sigmoidal, Sigmoid, 3 Parameter. The database of PubMed was accessed between August, 2019 to July 2020. All curve fitting was performed on SigmaPlot (version 11, Systat Software Inc, San Jose, CA, USA).