Journal of Research in Clinical Medicine

J Res Clin Med, 2023, 11: 8
doi: 10.34172/jrcm.2023.32123
https://jrcm.tbzmed.ac.ir

TUOMS PRESS

Original Article

The progress and research trends in oncolytic virotherapy: The bibliometric analysis from 2000 to 2019

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Article info

Article History:
Received: August 16, 2021
Accepted: May 7, 2022
e-Published: May 2, 2023

Keywords:
Bibliometric analysis, Countries, Institutes, Oncolytic, Publications, Virotherapy

Abstract

Introduction: The objective of the present report is to perform the first comprehensive bibliometric analysis of oncolytic virotherapy research publications.
Methods: Scopus was employed as a major database. The total number of publications was found to be 4369, majorly comprising of research articles (n=2895) and reviews (1082). The ANOVA F-test and Welch F-tests were performed to determine the significance ($P=0.05$).
Results: In all publications (3751), the total numbers of authors were 11418 and 10480 different organizations, departments or institutes. We specifically selected seven different viral strains and provided details about the co-authorship network. We also provided details about the top 10 most cited documents.
Conclusion: This may provide a quantitative overview about the trends and publications in oncolytic virotherapy research.

Introduction

Often times, hearing the word "virus" is associated with infectious disease in audience's mind. But in recent decades compiling evidence reported the application of viruses as a new discipline of "drug" specially in cancer treatment.[1] Oncolytic viruses are naturally occurring (e.g. Newcastle disease virus) or genetically engineered viruses (e.g. herpes simplex virus) that discriminately replicate in transformed cells; in other words, oncolytic viruses are "conditionally replicative" viruses that target tumor cells.[2] Although the mechanism of action of oncolytic viruses in killing cancer cells on a molecular level has not yet been fully deciphered, triggering several types of cell death and induction of the immune response against tumor cells are thought to be the main mechanisms by which oncolytic viruses exert their action.[3]

Safety and efficacy of oncolytic virotherapy has been demonstrated in pre-clinical studies and the first oncolytic virus (T-VEC, IMLYGIC®) received FDA approval for treatment of melanoma patients. Currently; according to ClinicalTrials.gov, more than 100 clinical trials are ongoing to determine the safety and efficacy of oncolytic viruses for a variety of cancers including glioblastoma multiforme, neuroblastoma, sarcomas, hepatocellular carcinoma, glioblastoma and neuroendocrine.[4,5]

Bibliometric analysis focuses on understanding the scholarly impact and characteristics of publications within a research field. It applies various statistical methods to quantitatively analyze various disciplines of science and technology.[6] In fact, it can explore the trend about a specific area and determine its progress via mathematical ways. It can also access study quality, analyze key areas or domains of research and predict future direction for researchers. The bibliometric tools can unveil the hidden pattern of publications that are useful for the researchers in decisions making. It is a quest for understand the comprehensive literature by a systematic pattern.[7]

The objective of the present study is to bibliometically cover the progress of oncolytic virotherapy in the 21st century. We aim to cover the following major aspects.

1. Statistically, we will determine (a) the productivity index (per decade), (b) per year growth rate, (c) doubling time and (d) one-way ANOVA test.
2. In performance analysis section, we will explore the top ranked (a) researchers, (b) institutions and (c) countries.
3. The science mapping analysis (SMA) helps in defining the social structure of a particular research field (or in this case the oncolytic virotherapy) by graphical representation. For the purpose, we will use the visualization of similarities (VOSviewer) software.

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4. One of the fundamental questions is what has been majorly covered in oncolytic virotherapy? For the purpose, the co-words analysis or co-occurrence technique can be applied.
5. Bibliographically, we will provide details about the top ten most cited documents.

In the same vein, we will specifically cite one of the most important studies which discussed various databases, for example Google Scholar, Web of Science, and Scopus. Precisely the authors compared 28 search systems. They applied 27 different evaluating criteria's. The authors concluded each database has its pros and cons and it is very hard to describe the ranking of these search engines. They also pointed that each researcher must have considerable knowledge of the search engines or databases they intend to use.[8]

In the current study, we will use Scopus database (Elsevier BV Company, USA). The 1st fundamental reason is that the Web of Science (WoS) has been recently used in oncolytic virotherapy research analysis. However, in the study the authors analyzed 1859 publications. Similarly, one of the major advantage of Scopus is it allows the exclusion of self-citations that Google Scholar and WoS do not. In the present study, all co-authors collected and downloaded the data in csv format. Later it was quantitatively and qualitatively analyzed in Microsoft Excel 2013 for access type, year, author name, document type, key words, affiliations and country. Several authors have analyzed different software tools to show the spatial representation of the relationship among authors, institutions, countries, keywords etc.[9,10] The list of software tools for conducting science mapping includes but not limited to Bibexcel, Bibliometrix, Bibliomaps, CiteSpace, CitNetExplorer, SciMAT, Sci2Tool and VOSviewer. A recent study by Moral-Muñoz et al[10] revealed that these software tools have a variability of features and that almost all of them can import data downloaded from Scopus and Web of Science. Therefore, it is up to the user to use the software tool that could provide suitable indicators (e.g., total publications, number of citations, most cited papers) for the desired analysis.

Here, we decided to use VOSviewer version 1.6.9 for viewing and creating the desired bibliometric maps. Compared to others such as SciMAT, CiteSpace and Bibliometrix, VOSviewer has a great visualization with the capability of loading and exporting data from many sources such as Scopus, WoS, PubMed, Dimensions, and RIS format. In addition, it is possible to construct and visualize the co-occurrence networks of important terms extracted from the scientific literature.[10,11]

Methods

Scopus and search strategy

To be concise we used only one phrase "oncolytic virotherapy" in Scopus advance search bar. Furthermore, those documents were considered for analysis where the "oncolytic virotherapy" phrase appeared in the "titles-abstract and keywords". The analysis was performed in August, 2020

Furthermore, we excluded the year 2020. And only research articles and reviews were considered for analysis.

Visualization maps

The VOSviewer software was developed by Van Eck and Waltman for constructing and visualizing bibliometric networks (For more information see http://www.vosviewer.com/). By default, at most 1000 lines are displayed and represent the 1000 strongest links between items. The distance between two items in the visualization approximately indicates the relatedness of the items. The results are presented as network visualization maps.

Productivity index (PI)

The PI is obtained by dividing the number of papers of the years under consideration by the corresponding number of papers published in the selected decade or era. For example, if the number of publications in 2001-2009 is 10 and in 2010-2019 it is 20. Then the PI will be two i.e. 20/10.

Relative growth rate

The relative growth rate was calculated as follows:

$$RGR = Final\ Number - Initial\ Number\ /\ Final\ Number \times 100$$

The doubling time

The doubling time for publications can be calculated by using the following equation:

$$RGR\ (1\text{-}2) = Log\ e\ 2w = Log\ e\ 1\ w/\ 2\ T - 1T$$

Where RGR (1-2) is mean of relative growth rate over specified period; Log e 2w = log of initial number of publications; Log e 1 w = log of final number of publications; 2 T – 1T = the unit difference between the initial time and final time.

And; $DT = Log\ e\ 2/GR$
Where GR = growth rate.

Statistical Analysis

The statistical analyses were *performed* using *GraphPad Prism* 5.0 Software (GraphPad Software, San Diego, CA, USA). Significance tests were performed using an unpaired Student's t-test. Differences were considered significant if $P < 0.05$. Results are presented as means ± standard error of the mean.

Results and Discussion

As explained in the search strategy section, a total of 4369 documents were found in the database. The

documents majorly comprised of articles (n = 2895), reviews (n = 1082), editorials (n = 101), notes (n = 101), short surveys (n = 60), conference papers (n = 44), book chapters (n = 42), letters (n = 40), errata (n = 3) and one unidentified document. In the year 2020 the number of publications (till August) was found to be 258. However, we excluded it. Furthermore, we selected only research articles and reviews for analysis. The total articles were found to be 2746 and reviews were 1005. In other words, the total publications selected for details analysis were 3751.

Scopus also provided details about the main subject areas. All documents (n = 3751) were majorly categorized in biochemistry, genetics and molecular biology (n = 2467), followed by medicine (n = 2134), pharmacology, toxicology and pharmaceutics (n = 679), immunology and microbiology (n = 581), agricultural and biological sciences (n = 214), multidisciplinary (n = 118) and neuroscience (n = 71).

Similarly, most of the documents were published in Molecular Therapy (n = 194), followed by Cancer Gene Therapy (n = 175), Gene Therapy (n = 132), Clinical Cancer Research (n = 117), Cancer Research (n = 97), Human Gene Therapy (n = 93), Molecular Therapy Oncolytics (n = 90), Journal of Virology (n = 85), PloS One (n = 80) and Oncotarget (n = 79).

The publications output details

According to the Scopus database, the 1st document about the Oncolytic Virotherapy was published in 1964, followed by five publications in 1965 and only one in 1999. We ignored discussion about these seven publications, and will focused on the 21st century progress (till December 2019). The regular per year publications started from 2001. Since then total 3751 documents are completed. The highest number of documents were published in 2019 (n = 347), followed by 2018 (n = 340) and 2015 (n = 330). Although the annual number of publications increased, but considerable fluctuations in growth rate can be observed as shown in Table 1. Precisely the highest RGR was observed for the year 2004-2005 (311.11), followed by 2005-2006 (243.24) and 2002-2003 (200).

In the same vein, the doubling time (Dt) is another parameter normally used in bibliometry. Dt is the time required to double the number of publications. We tried to decode the association of relative growth rate and doubling time. The simple hypothesis is decrease in growth rate can increase the doubling time. Or in other words increase in growth rate can decrease the doubling time. This is exactly we observed in the data (Table 2). For proper interpretation, we will describe three examples. The relative growth rates for the years 2001-2003 increased from 0.1 to 0.5, which caused a decrease in doubling time i.e., from 5.2 to 1.5. A slow growth rate was observed for the years 2006-08 i.e., 1.1, 0.70 and 0.4, respectively. This caused a significant increase in doubling time i.e., 0.6, 1.0 and 1.6, respectively. Similarly, a slow progress in publication rate in 2016-2018 is observed which caused an increase in the doubling time (6.1, 6.5 and 6.6, respectively). We can conclude that the shortest doubling time was observed for the year 2006 (Dt = 0.6) and the longest was noted for the year 2018 (Dt = 6.6). The statistical analysis is shown in Table 3.

Table 1. List of per year research growth rate (RGR) for oncolytic virotherapy

Year	No. of publications	RGR	% Age	(Number of initial papers-Average number of paper)	(Number of initial papers-Average number of paper)2
1964	1		0.027	-169.5	28730.25
1965	5	400	0.133	-165.5	27390.25
1999	1	-80	0.027	-169.5	28730.25
2001	1	0	0.027	-169.5	28730.25
2002	2	100	0.053	-168.5	28392.25
2003	6	200	0.160	-164.5	27060.25
2004	9	50	0.240	-161.5	26082.25
2005	37	311.11	0.986	-133.5	17822.25
2006	127	243.24	3.386	-43.5	1892.25
2007	186	46.46	4.959	15.5	240.25
2008	207	11.29	5.519	36.5	1332.25
2009	234	13.04	6.238	63.5	4032.25
2010	258	10.26	6.878	87.5	7656.25
2011	204	-20.93	5.439	33.5	1122.25
2012	295	44.61	7.865	124.5	15500.25
2013	294	-0.34	7.838	123.5	15252.25
2014	260	-11.56	6.931	89.5	8010.25
2015	330	26.92	8.798	159.5	25440.25
2016	298	-9.70	7.945	127.5	16256.25
2017	309	3.69	8.238	138.5	19182.25
2018	340	10.03	9.064	169.5	28730.25
2019	347	2.06	9.251	176.5	31152.25

Note: Total Publications = 3751; Mean = 170.5; Variance = 17669.89; Standard deviation = 132.9281

The top 10 authors

Based on the number of publications Russell, S.J. is the top ranked author with 104 publications, followed by Hemminki, A., Bell, J.C., Szalay, A.A. and Fong, Y. with 91, 74, 73 and 68 publications. However, based on h-index score, Russell, S.J. occupied the top position with 43, followed by Bell, J.C., Peng, K.W., Hemminki, A. and Kanerva, A. with h-index of 38, 32, 31 and 28, respectively. The highest citations are recorded for Bell, J.C. (n = 5869), followed by Russell, S.J. (n = 5443), Peng, K.W. (n = 3404), Hemminki, A., (n = 2994) and Harrington, K.J. (n = 2593). We also provided the ranking details on the basis of citation per documents. Based on the data, the top slot is occupied by Bell, J.C. (n = 79), followed by Peng, K.W. (n = 53), Russell, S.J. (n = 52), Harrington, K.J. (n = 51) and Kanerva, A. (n = 36). The list of top ten authors is

Table 2. The doubling time calculations for oncolytic virotherapy

Years	Numbers	Cumulative	W1	W2	R(a) W2-W1	Mean R(a)(1-2)	Doubling Time Dt(a)	Mean Dt(a)(1-2)
1964	1	1	0.0	0.0	0.0		0.0	
1965	5	6	0.0	1.8	1.8		0.4	
1999	1	7	1.8	1.9	0.2		4.5	
2001	1	8	1.9	2.1	0.1		5.2	
2002	2	10	2.1	2.3	0.2		3.1	
2003	6	16	2.3	2.8	0.5		1.5	
2004	9	25	2.8	3.2	0.4		1.6	
2005	37	62	3.2	4.1	0.9		0.8	
2006	127	189	4.1	5.2	1.1		0.6	
2007	186	375	5.2	5.9	0.7		1.0	
2008	207	582	5.9	6.4	0.4	0.374	1.6	2.973
2009	234	816	6.4	6.7	0.3		2.1	
2010	258	1074	6.7	7.0	0.3		2.5	
2011	204	1278	7.0	7.2	0.2		4.0	
2012	295	1573	7.2	7.4	0.2		3.3	
2013	294	1867	7.4	7.5	0.2		4.0	
2014	260	2127	7.5	7.7	0.1		5.3	
2015	330	2457	7.7	7.8	0.1		4.8	
2016	298	2755	7.8	7.9	0.1		6.1	
2017	309	3064	7.9	8.0	0.1		6.5	
2018	340	3404	8.0	8.1	0.1		6.6	
2019	347	3751	8.1	8.2	0.1		0.0	

Table 3. ANOVA details for oncolytic virotherapy

Unpaired t-test	
P value	<0,0001
P value summary	****
One- or two-tailed P value?	Two-tailed
t, df	t=6, 334 df=18
How big is the difference?	
Mean ± SEM of column A	80.9 ± 30.62, n=10
Mean ± SEM of column B	293.5 ± 13.75, n=10
Difference between means	212.6 ± 33,56
95% confidence interval (CI)	142.1 to 283.1
R squared (eta squared)	0.6903
F test to compare variances	
F, DFn.Dfd,	4, 959, 9, 9
P value	0,0258
Significantly	*
Significantly different (p<0.05)?	Yes

provided in Table 4.

The top 10 institutes

A large number of institutes have published extensive literature on this newly emerged theme. To evaluate all of them in terms of total publications, h-index, total citation and citation per document, we browsed the Scopus database and retrieved data for top ten most influential institutes. The list of top 10 most productive institutes is provided in Table 5. These top 10 institutes collectively published 1,179 documents. Mayo Clinic (MC) published the highest number of articles (n=230), followed by Ottawa Hospital Research Institute (OHRI) (n=122), The University of Alabama at Birmingham (UAB) (n=121), German Cancer Research Center (GCRC) (n=113), Harvard Medical School (HMS) (n=111), and Helsingin Yliopisto (HY) (n=103) respectively. Furthermore, we also explored their publication rate from 2001 to 2019. The results are provided in Table 6.

It is worth mentioning that H-index is a parameter that measures the productivity of research scholar. By using this matrics the most impactful and quality work is explored. For this purpose, on the basis of H-index, the list of top ten institutes is led by MC (n=54) followed by OHRI (n=40), MGH (n=38), HMS (n=37), and ICR (n=35) respectively. Citation is considered as an authentic bibliometric parameter for evaluating the impact of research. On the basis of citation, the more cited published articles are dominated by MC (n=9706), OHRI (n=6850), MGH (n=4839), HMS (n=4549), ICR (4480), and UO (n=4238).

Similarly, further analysis of the citation per documents of top ten institutes, the conclusion drawn is that, OHRI (n=56) documents received the highest number of

Table 4. The list of top 10 authors with total publications (TP), h-index, total citations (TC), h-index without self-citations (WSC) and WSC for oncolytic virotherapy

No.	Author name	TP	h-index	TC	h- index (WSC)	WSC	Citation per document
1	Russell, S.J.	104	43	5443	37	4335	52
2	Hemminki, A.	91	31	2994	24	2007	33
3	Bell, J.C.	74	38	5869	33	48974	79
4	Szalay, A.A.	73	24	1631	17	970	22
5	Fong, Y.	68	24	1535	19	1122	23
6	Peng, K.W.	64	32	3404	29	2762	53
7	Kanerva, A.	62	28	2230	20	1444	36
8	Yun, C.O.	58	22	1414	17	926	24
9	Alemany, R.	56	24	1699	19	1313	30
10	Harrington, K.J.	51	28	2593	24	1973	51

Table 5. The list of top 10 institutes with total publications (TP), h-index, total citations (TC), h-index without self-citations (WSC) and WSC for oncolytic virotherapy

No.	Name of Institute	TP	h-index	TC	h-index (WSC)	WSC	Citation per document
1	MC	230	54	9706	45	7633	42
2	OHRI	122	40	6850	36	5621	56
3	UAB	121	32	3752	28	2886	31
4	GCRC	113	29	2889	24	2074	26
5	HMS	111	37	4549	34	3842	41
6	HY	103	32	3277	25	2231	32
7	MGH	103	38	4839	35	4002	47
8	MSKCC	96	30	3121	30	2597	33
9	UO, Canada	94	34	4238	30	3405	45
10	ICR, London	86	35	4480	31	3491	52

Note: MC, Mayo Clinic; OHRI, Ottawa Hospital Research Institute; UAB, The University of Alabama at Birmingham; GCRC, German Cancer Research Center; HMS, Harvard Medical School; HY, Helsingin Yliopisto; MGH, Massachusetts General Hospital; MSKCC, Memorial Sloan-Kettering Cancer Center; UO, University of Ottawa; ICR, The Institute of Cancer Research.

citation per document. ICR (n = 52), MGH (n = 47), UO (n = 45), MC (n = 42), and HMS (n = 41) are the most impactful institutes in the oncolytic virotherapy research.

Contribution of different continents in oncolytic virotherapy research

Oncolytic virotherapy research exhibits a rapid expansion on the horizon of oncology field worldwide. A total of 71 countries of different regions contributed in the publications. The data is depicted in Table S1 of Supplementary file 1. On the basis of the number of publication, North America is the leading continent with highest number of publications (n = 2037, 54.3055%). United State is the dominating member in this region by publishing (n = 1799) documents, followed by Canada (n = 378), and Mexico (n = 12). The second most influential region is Europe with total publications are (n = 1307, 34.844%). 35 countries in this continent contributed to the field. Germany (n = 405), the United Kingdom (n = 346), and Spain (n = 147) are included in the top list with maximum publications. Asia ranked third in publications by contributing a total of 1064 (28.3657%) research documents. Among 12 countries in the region, the most productive country is China (n = 544), followed by Japan and South Korea with 305 and 127 maximum publications respectively. A total of 78 (2.079%) publications are contributed by Middle East. Iran, Israel, and Egypt are the top productive countries by contributing 28, 24, and 10 publications to the total research documents respectively. Collectively, 53 (1.412%) documents are published by South America, Oceania, and Africa regions. A total of 12 countries are involved in the publications from all three continents. Australia (n = 42) is the dominant country from Oceania region, followed by Argentina (n = 9) from South America and South Africa (n = 6) from Africa continent dominates the publication in this domain.

The top 10 countries

The list of top 10 countries with total publications, H-index, total citation and citation per documents are depicted in Table S2 of Supplementary file 1. We further elaborated the idea and determined the total citations received by oncolytic virotherapy publications. The details are provided in Table S2. Among the top ten countries, United State (n = 58647) dominates in citation

Table 6. The per-year publications and citations details of the top 10 universities for oncolytic virotherapy

Year	MC	OHRI	UAB	GCRC	HMS	HY	MGH	MSKCC	UO	ICR
2019	9	10	6	9	14	4	9	3	7	6
2018	17	19	6	3	7	8	6	7	17	7
2017	13	7	5	11	10	2	7	6	6	4
2016	16	8	5	7	11	7	7	5	8	7
2015	15	9	5	14	12	11	7	8	8	6
2014	16	11	9	12	6	7	7	10	8	3
2013	27	11	6	11	6	7	5	4	11	7
2012	25	8	5	10	7	11	7	6	6	9
2011	17	4	5	7	3	9	4	4	3	8
2010	23	15	7	8	7	7	7	8	8	7
2009	21	2	15	6	8	7	9	11	6	6
2008	15	11	12	7	4	5	4	9	4	13
2007	7	6	19	6	7	10	11	10	1	3
2006	7	0	8	2	8	5	10	3	0	0
2005	0	1	5	0	1	1	2	2	1	0
2004	0	0	2	0	0	0	1	0	0	0
2003	0	0	0	0	0	2	0	0	0	0
2002	2	0	1	0	0	0	0	0	0	0
2001	0	0	0	0	0	0	0	0	0	0
Total	230	122	121	113	111	103	103	96	94	86

Note: MC, Mayo Clinic; OHRI, Ottawa Hospital Research Institute; UAB, The University of Alabama at Birmingham; GCRC, German Cancer Research Center; HMS, Harvard Medical School; HY, Helsingin Yliopisto; MGH, Massachusetts General Hospital; MSKCC, Memorial Sloan-Kettering Cancer Center; UO, University of Ottawa; ICR, The Institute of Cancer Research.

ranking followed by Canada (n = 15701), United Kingdom (n = 14321) Germany (n = 9917), China (n = 8017), and Japan (n = 5766), respectively. Similarly, in citation per document category Canada is the leading country (n = 41). United Kingdom (n = 41), United States (n = 33), South Korea (n = 33), Finland (n = 31), and Spain (n = 30) are among the top ten nations exhibiting highest citation per document in the stated field.

The highest number of documents in the oncolytic virotherapy research was published by United States (n = 1799, 47.960%), followed by China (n = 544, 14.502%), Germany (n = 405, 10.797%), Canada (n = 378, 10.077%), United Kingdom (n = 346, 9.224%), and Japan (n = 305, 8.131%), respectively. While their per year publication data (from 2001 to 2019) is provided in Table S3 of Supplementary file 1.

However, it is important to note that h-index is an authentic bibliometric parameter for the evaluation of author's productivity in scientific research. Therefore, we collected the H-index details for the top 10 most prolific counties from Scopus database. United State has the highest h-index (n = 99), followed by Canada (n = 64), the United Kingdom (n = 58), Germany (n = 49), China and Japan (n = 39), respectively.

The VOSviewer analysis

Co-authorships by authors

In all publications (n = 3751), the total numbers of authors were 11 418. Before constructing the map, we tried several options. For example, when we defined the minimum number of published articles to be 10 with zero citations. The total number of authors were found to be 346 or, 98 authors have published at least 20 documents.

To make it more visible, we selected those authors who have published at least 30 documents. In this case, total 50 authors were found in the database as shown in Figure 1. In order to construct the map, VOSviewer, has calculated the total link strength between the authors. In map, each node represents an author and the node size indicates the number of published articles. The link connecting two nodes stands for the cooperative relationship between two authors, and the thickness of the link stands for the intensity of cooperation. For detail interpretations, we will select Figure 1. In the map 10 clusters were found, which represents 50 items or authors.

We will shortly introduce a few clusters. For example, in blue cluster, there are 7 items or authors. Before interpreting this clusters, it is important to note that each author in all clusters has (individually) at least 30 publications. If we consider "Hemminki A." as the main author, he/she is connected with 5 authors in blue cluster named Cerullo, V., Pesonen, S., Kanerva, A., Alemany, R. and Curiel, D.T. Even he is further connected with Bell, J.C. and Diallo, J.S. from Red cluster. To decode it further, we explored the publication data of "Hemminki A". Based on the Scopus data, Hemminki A has published 91 documents in the area of oncolytic virotherapy with more than 150 co-authors. Kanerva, A., has been directly involved in 62, Cerullo, V., Pesonen, S., in 35, Curiel, D.T in 7 and Alemany, R in 3 publications. From red cluster, he/she has co-authored 2 and 1 publications with Bell, J.C. and Diallo, J.S, respectively.

The next cluster is Green. Where 9 authors are grouped together. If we consider Coffey M., as the central point in the cluster, it can be observed that he is connected with eight authors. Based on the Scopus data, Prof. Coffey M., has 50 publications with more than 150 co-authors. Vile, R. has 17, Melcher, A has 16, while Melcher, A.A., Harrington, K and Harrington, K. J have co-authored 15 publications. While, Vile, R.G., Thompson, J., and Kottke, T. have co-authored 12 publications. The cluster is shown in Figure 1.

In yellow cluster, there are total 5 items. We will consider Fong Y, as the principal item. From Scopus we retrieved the publication details of Prof. Fong Y, has 68 publications with more than 150 co-authors. He has co-authored 21 publications with Chen, N.G. and Szalay, A.A. While, in 13 and 7 publications, Yu, Y.A. and Zhang, Q. have been noted as co-authors.

In red cluster, there are total 17 items. We will consider Wang Y., as the main author. He has total 38 publications.

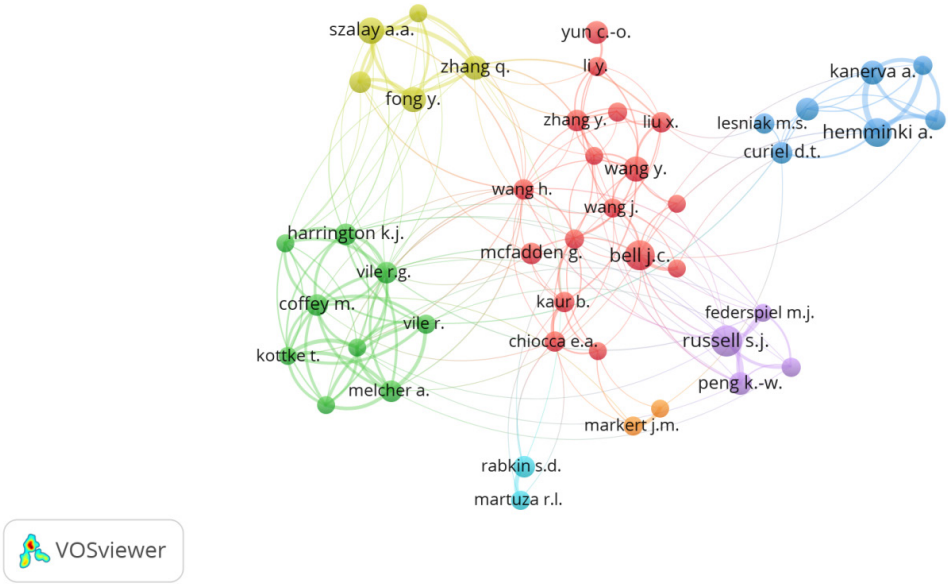

Figure 1. The list of authors in co-authorship analysis

He has published 8 documents with Liu, X., 5 with Li, X., 5 with Wang J., 2 with Zhang Y., and 2 with Zhang X. With other authors he has one publication.

It is worthy to note that a single author can influence the institutional and countries collaboration. For the purpose we tried to focus on a single author to know his/her co-authorship networking details. In this context, we selected Prof. Russell, S.J., who has highest number of publications (n = 104). He is described in purple cluster, where in total four items are merged together. In purple cluster, he is connected with Galanis E., Peng K.W., and Federspiel, M.J. In red cluster, he is connected with Bell J.C, Zhang, J., Wang, J., Wang, H., and Li X., while from green he is connected with three authors named Thomspon, J, Ville R.J, and Harrington, K.J. Precisely, Russell, S.J. has co-authored 56, 32 and 18 publications with Peng, K.W., Federspiel, M.J. and Galanis, E, respectively. From red cluster he has co-authored 3 publications with Bell, J.C., and one publication with Zhang, J., Wang J., and Li. X. While in green cluster, with Thomspon, J, Ville R.J, and Harrington, K.J. he has co-authored 11, 2 and 1 publication, respectively. Figure S1 (Supplementary file 1) describes the list of co-authors with Russell, S.J. Based on his publications, he has 290 co-authors from more than 227 institutes. Based on VOSviewer analysis, his top five co-authors are Peng K.W., Federspiel M.J., Galanis E., Dingli D., and Naik S. with 45, 31, 17, 17, 11 and 11 publications, respectively.

In departmental category, most of the affiliations are noted with:

1. Department of Molecular Medicine, Mayo Clinic, Rochester, Mn, United States
2. Division of Hematology, Mayo Clinic, Rochester, Mn, United States
3. Department of Molecular Medicine, Mayo Clinic, 200 First Street Sw, Rochester, Mn 55905, United States
4. Department of Obstetrics and Gynecology, Mayo Clinic, Rochester, Mn, United States
5. Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, Mn, United States

The numbers of publications with above affiliated institutes were found to be 33, 14, 12, 8 and 8, respectively. The data is presented in Figure S2 of Supplementary file 1. International collaboration with Canada, Japan, Greece, UK, China, Germany, New Zealand, Singapore and Vietnam was also noted in publications.

The institutional co-authorship analysis

A total of 10480 different organizations, departments or institutes were directly involved in all publications (n = 3751). One hundred and thirty-nine, of them were directly involved in at least 5 publications with zero citations. We further extended the idea and found that 32 departments published at least 10 documents (Figure 2). There are 17 clusters. We briefly describe only 2 clusters. In red cluster there are 7 items or institutes. We consider Department of Molecular Medicine, Mayo Clinic, Rochester, MN, United States, as the principal item, which is connected with four items or institutes entitled;

1. Institute of Cancer Research, London, United Kingdom
2. Department of Immunology, Mayo Clinic, Rochester, MN, United States
3. Division of Hematology, Mayo Clinic, Rochester, MN, United States
4. Division of Medical Oncology, Mayo Clinic, Rochester, MN, United States
5. Oncolytic Biotech Inc., Calgary, AB, Canada

Individually these departments are involved in, 12, 34, 16, 16 and 14 publications, respectively. In green cluster, there are also seven items merged together. Department of Obstetrics and Gynecology, Helsinki University Central Hospital, Helsinki, Finland has published 28 documents.

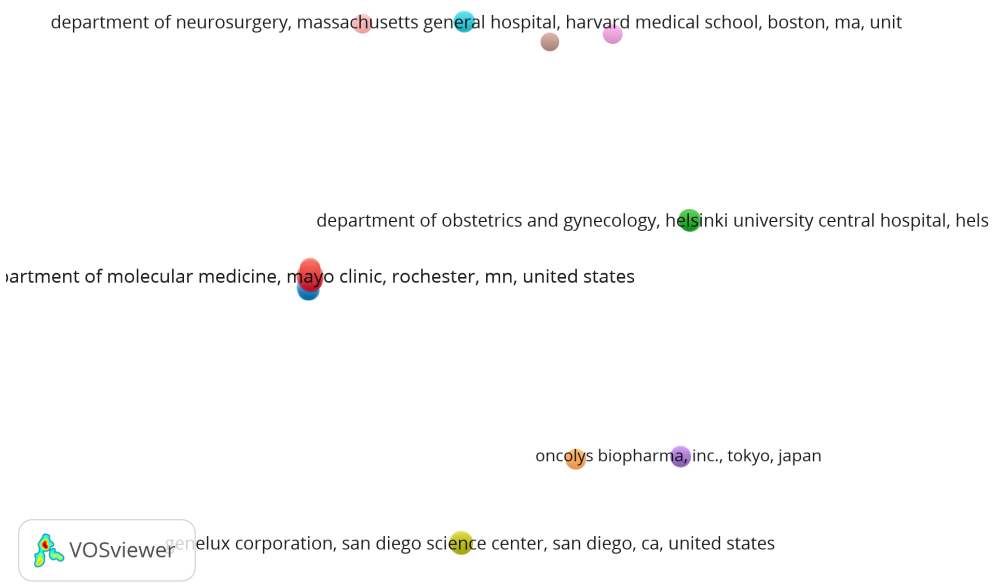

Figure 2. The institutional co-authorship network

We considered it as the principal item, which is further connected with the following institutes.

1. Docrates Cancer Center, Helsinki, Finland
2. Tilt Biotherapeutics Ltd, Helsinki, Finland
3. Oncos therapeutics ltd., Helsinki, Finland
4. Department of Oncology, Helsinki University Central Hospital, Helsinki, Finland
5. International Comprehensive Cancer Center Docrates, Helsinki, Finland
6. Huslab, Helsinki University Central Hospital, Helsinki, Finland

Individually these institutes are involved in, 10, 10, 10, 13, 14 and 13 publications, respectively. Mayo Clinic, Rochester, MN, United States was found to be the most productive institute with 230 publications. The 1st document was published in 2002 and later it consistently published. The highest number of documents are published in 2013 (n = 27), followed by 2012 (n = 25) and 2010 (n = 23). The documents are published in 91 reputed journals. The highest publications are noted in Molecular Therapy (n = 23), Gene Therapy (n = 20), Clinical Cancer Research (n = 15), Cancer Gene Therapy (n = 14) and Cancer Research (n = 11), to name a few. In all publications (n = 230), 703 authors were noted. The highest publications were noted for Russell S.J. (n = 91), Peng K W. (n = 48), Vile R.G. (n = 38), Galanis E. (n = 35) and Vile R. (n = 35). The list of authors is described in Figure S3 of Supplementary file 1. Institutionally 597 different addressed were noted in all Mayo Clinic publications (230). Based on the number of publications some of the top institutes with number of publications in small brackets are; Department of Immunology, Mayo Clinic, Rochester, MN, United States (n = 34), Division of Hematology, Mayo Clinic, Rochester, MN, United States (n = 16), Division of Medical Oncology, Mayo Clinic, Rochester, MN, United States (n = 12), Institute of Cancer Research, London, United Kingdom (n = 12), Postgraduate Medical School, University of Surrey, Guildford, United Kingdom (n = 12), Department of Obstetrics and Gynecology, Mayo Clinic, Rochester, MN, United States (n = 8) and Leeds Institute of Molecular Medicine, Leeds, United Kingdom (n = 8). The list of collaborating institutes is provided in Figure S4 of Supplementary file 1. International collaboration was also noted with 21 countries. Based on the number of publications, the top collaborator is UK (n = 69), followed by Canada (n = 39), Germany (n = 5), Greece (n = 5) and Japan (n = 4).

The country co-authorship analysis

Country co-authorship analysis is an important form of co-authorship analysis (13-15). It can reflect the degree of communication and the most influential countries in a particular field. In total, 93 countries were directly involved in all publications in AJC. 54 countries were found from the data, with at least 5 publications and zero citations. The size of circles represents the number of publications of the country and the thickness of lines depicts the size of collaboration. The data is presented in Figure 3.

Since USA was the top leading country with maximum publications (n = 1799), therefore we analyzed it on VOSviewer. USA published its 1st document in 1999 and later it explored brilliantly. The highest documents were published in 2018 (n = 162) & 2015 (n = 162), followed by 2017 (n = 148), and 2012 (n = 137).

Total 5945 authors were directly involved in all publications. Since the Mayo Clinic is in USA. Therefore, we will not repeat the top five author's names (from USA).

Similarly, 5480 different institutional addresses were also noted in publications. The top five are MC (n = 228), HMS (110), MGH (n = 102), MSKCC (n = 96) and University of

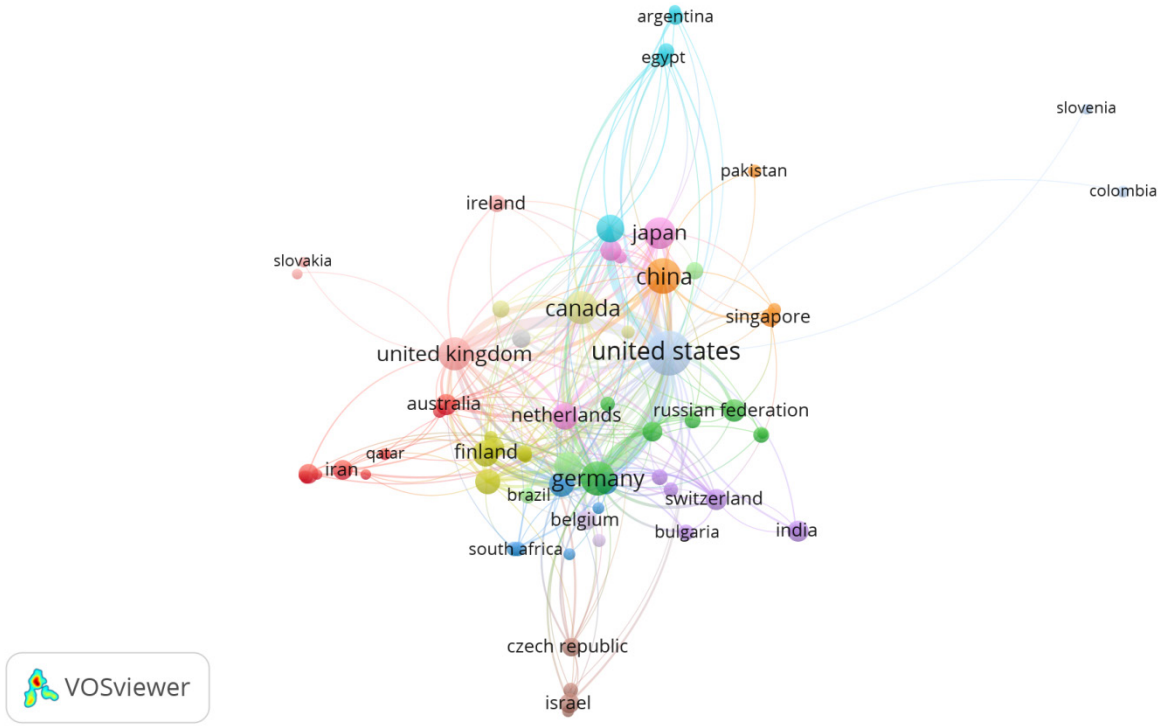

Figure 3. The country co-authorship analysis

California, San Diego (n = 77).

Based on the number of publications, the highest international collaboration was noted with Canada (n = 148), UK (n = 146), Germany (n = 141), China (n = 111) and Japan (n = 65). In total 52 countries were directly involved in 1799 publications. The list of co-authors and affiliated institutes are provided in Figure 4 and Figure S5.

Based on the number of publications, China was the second highest country (n = 544). China significantly collaborated with USA (n = 111), followed by UK (n = 20), Japan (11), Germany (n = 10) and Canada (n = 9).

The third country is Germany, which has published 405 publications. The 1st document was recorded in 2003 and later it increased the publication rate. The highest documents were published in 2015 (n = 44), followed by 2012 (n = 41) and 2014 (n = 35).

The single authors, institute and country analysis also confirmed that how the scientific collaboration between authors help in developing social network between institutes and countries. In fact, a single author's contribution may help in institutional and international networking.

Citation analysis

The most leading publication in a research area is with the highest levels of citations. Thus, citation analysis refers as bibliometric technique which quantifies the significance of a research and evaluates its productivity by utilizing its citation data. It could also be used to measure the relative impact of articles or authors by examining how much they are cited by others. Citation analysis can also be used to study the development and the nature of different fields and to analyze interdisciplinary bridges among them.

First, we will state that there are a total of 11418 authors in all publications (n = 3751). Irrespective of the number of publications the top five authors with total citations are Bell J.C. (n = 5992), Russell S.J. (n = 5440), Peng K.W. (n = 3060), Hemminki A. (n = 2844), and Harrington K.J. (n = 2487). We also explored the top authors with highest citation per documents (CPD). The CPD for the above five authors are found to be 63, 53, 58, 32 and 50, respectively.

We further explored the CPD for authors, and exactly 411 authors showed 100 or more than 100 CPD. First, we tried to find the top five authors, however we noted that several authors have the same CPD. We further explored their publication details and found that actually authors with same CPD were co-authors in the same document.

For example, the highest CPD (n = 722) was noted for Hale B.G, Jackson D. Ortin J. and Randall R.E. All are co-authors in the document entitled "The multifunctional NS1 protein of influenza A viruses" published in 2008 in the journal "Journal of General Virology".

The 2nd highest CPD (n = 561) was noted for Ginn, S.L., Alexander, I.E., Edelstein, M.L., Abedi, M.R., Wixon, J. They all published the document entitled "Gene therapy clinical trials worldwide to 2012 - an update" which was published in 2012 in the Journal of Gene Medicine.

The 3rd highest CPD (n = 502) was noted for the following authors. Katherine B Chiappinelli, Pamela L

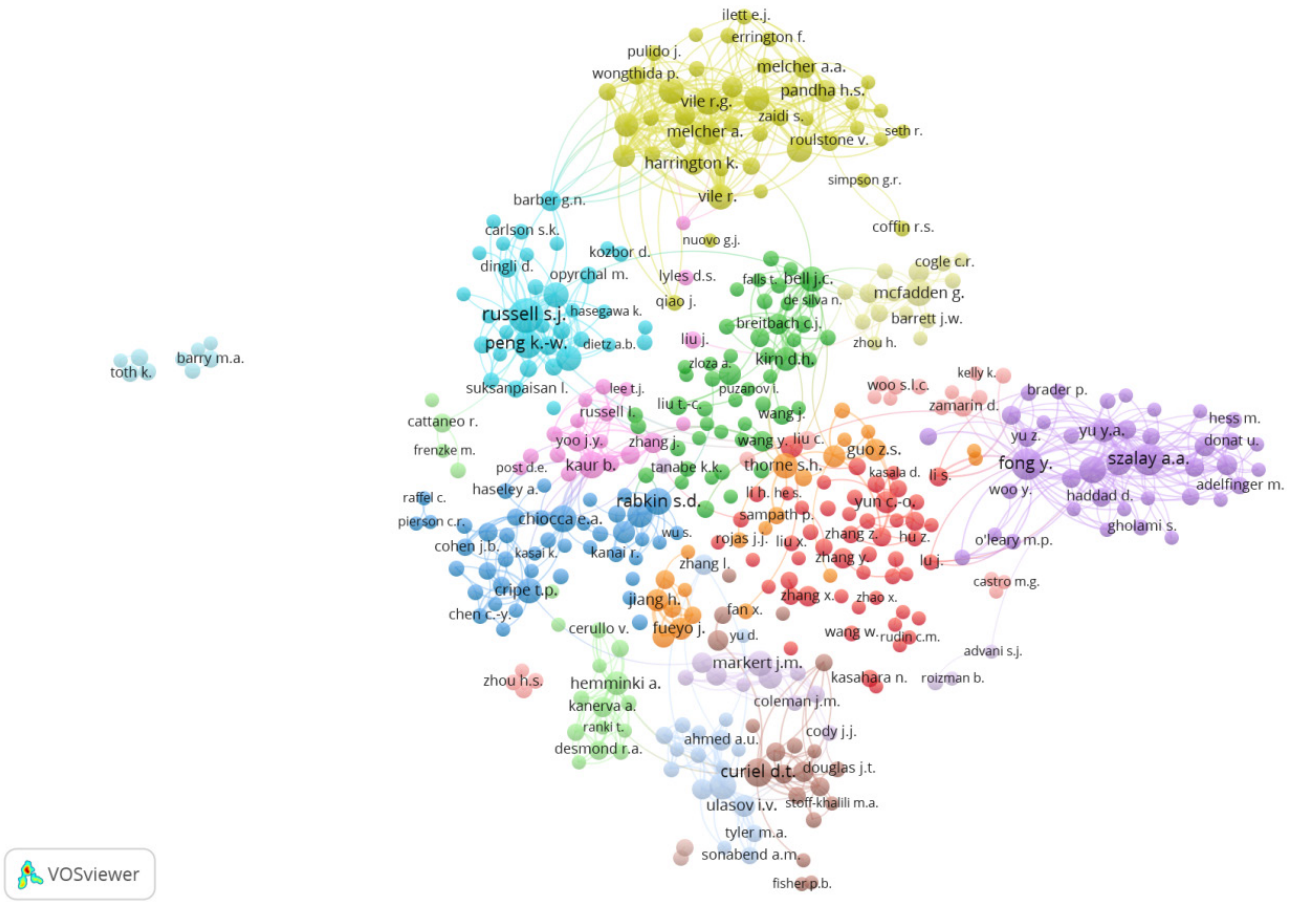

Figure 4. The co-authorships network for authors in USA publications

Strissel, Alexis Desrichard, Huili Li, Christine Henke, Benjamin Akman, Alexander Hein, Neal S Rote, Leslie M Cope, Alexandra Snyder, Vladimir Makarov, Sadna Budhu, Dennis J Slamon, Jedd D Wolchok, Drew M Pardoll, Matthias W Beckmann, Cynthia A Zahnow, Taha Merghoub, Timothy A Chan, Stephen B Baylin and Reiner Strick . The title of the document is Inhibiting DNA Methylation Causes an Interferon Response in Cancer via dsRNA Including Endogenous Retroviruses, which was published in 2015 in Cell.

The 4th highest CPD (n = 420) was noted for Antoni Ribes, Reinhard Dummer, Igor Puzanov, Ari VanderWalde, Robert H I Andtbacka 5, Olivier Michielin 6, Anthony J Olszanski 7, Josep Malvehy 8, Jonathan Cebon, Eugenio Fernandez, John M Kirkwood, Thomas F Gajewski, Lisa Chen, Kevin S Gorski, Abraham A Anderson, Scott J Diede, Michael E Lassman, Jennifer Gansert, F Stephen Hodi, Georgina V Long. The title of their publication is "Oncolytic Virotherapy Promotes Intratumoral T Cell Infiltration and Improves Anti-PD-1 Immunotherapy" which was published in 2017 in Cell.

The 5th highest CPD (n = 410) was recorded Jeong Hoe, Tony Reid, Leyo Ruo, Caroline J Breitbach, Steven Rose, Mark Bloomston, Mong Cho, Ho Yeong Lim, Hyun Cheol Chung, Chang Won Kim, James Burke, Riccardo Lencioni, Theresa Hickman, Anne Moon, Yeon Sook Lee, Mi Kyeong Kim, Manijeh Daneshmand, Kara Dubois, Lara Longpre, Minhtran Ngo, Cliona Rooney, John C Bell, Byung-Geon Rhee, Richard Patt, Tae-Ho Hwang, David H Kirn. The title of the document is "Randomized dose-finding clinical trial of oncolytic immunotherapeutic vaccinia JX-594 in liver cancer". Second, we will state that there are a total of 10480 institutional addresses in all publications (n = 3751). We explored the top five institutes with highest citations. Department of Molecular Medicine, Mayo Clinic, Rochester, Mn, United States was found with highest citations (n = 2947), followed by Jennerex Biotherapeutics, San Francisco, Ca, United States (n = 1818), Department Immunology, Mayo Clinic, Rochester, Mn, United States (n = 1504), Department of Obstetrics and Gynecology, Helsinki University Central Hospital, Helsinki, Finland (n = 1277) and Minnesota Oncology, Fridley, Mn, United States (n = 1115). We also calculated the CPD for each institute. The names of 29 Institutes with CPD are provided in Table S4.

Co-word analysis or what has been covered in keywords?

Co-word analysis is an important bibliometric method that helps researcher to identify hot topics and trends in the field. This analysis is widely applied to map the

knowledge structure and developmental status of research areas. Moreover, different keywords groups represent particular research hotspots. Co-words analysis confirms the existence of correlation between different themes in the subject avenue by analyzing common co-words.

Human and non-human subjects

As the name indicates various subjects were directly or indirectly covered in the entire publications. Human, human cell, female, male, human tissue and adult were added together. While, in non-human category, animals, mouse, mice, animal cell, mice, nude, mice, inbred Balb and nude mouse were compiled.

Study

Under this title we grouped the relevant words which describe the type of study. For example, controlled study, in vitro study, procedures, in vivo study, clinical trial, disease model, methodology, phase 1 clinical trial (topic), overall survival, clinical trial (topic) and phase 2 clinical trial (topic).

Publications

Under this category, we added the following words like article, reviews and priority journal.

It is important to note that the above mentioned categories are obligatory or part of any research, therefore we ignored these classes. The remaining keywords are categorized under several major titles to describe the common or general trend in oncolytic virotherapy research.

Tissues cancers

Under this class different affected tissues are added together for example, liver cell carcinoma, breast cancer, brain neoplasms, prostate cancer, pancreas cancer, ovary cancer, brain tumor and colorectal cancer.

Cancer and cancer therapy

In this category we added the following words. Cancer, cancer cell, cancer cell culture, cancer inhibition, cancer survival, cancer vaccine, cancer therapy, cancer radiotherapy, multimodality cancer therapy, cancer chemotherapy, gamma interferon and cancer combination chemotherapy.

Tumors

We added those specific words which represents tumors involved research. For example, tumor volume, tumor growth, tumor cell, tumor cells, cultured, tumor xenograft and tumor immunity. In the same category similar words like metastasis, melanoma, glioblastoma, neoplasm, and glioma are also added.

Cell lines

Cell lines, cell line tumor, cell proliferation, cell death, cell viability, cell survival and cell killing are added. Furthermore, neoplasms, xenograft model antitumor assays, cytotoxicity, apoptosis and signal transduction words also compiled in this category.

Proteins

Proteins involved experimental protocols like western blotting, immunomodulation, antineoplastic activity and protein expression are added along with some other specific proteins like E1A protein and protein p53.

Genetics

In the last two decades conclusive evidences are provided that cancer is mediated by somatic aberration in the host genome. Cancer research and genomics have made significant progress. In gene therapy, the cell of patient can be genetically modified to alleviate a disease. The gene transfer therapy can be conducted either as in vivo or ex vivo approaches. In fact, mostly, genes, gene segments, or oligonucleotides can be transferred into patient cells. The procedure (gene transfer therapy) can be conducted either as in vivo or ex vivo approaches. In this category those words are compiled which may give a broad version of different aspects. For example, gene therapy, genetic vectors, gene expression, gene vector, genetic therapy, genetic engineering, transgene, gene deletion, gene expression regulation, viral gene delivery system, cancer gene therapy viral gene therapy and virus genome etc.

Immune system or immunotherapy

There is considerable amount of literature, which supports the ability of the immune system to modify the immunogenicity and behavior of tumors. Immunotherapy can be used alone or in combination with other cancer treatments. In this category we added the following words like cancer immunotherapy, immunotherapy, immunology, immune response, immune response and immunohistochemistry.

Drugs

The effects of the combination of a viral strain and various drugs, for example cisplatin have been vastly explored. In this class different words focusing on drugs involved paradigm are added. For example, drug efficacy, drug safety, drug screening, drug potentiation, drug effect, drug cytotoxicity, drug targeting, cisplatin, drug mechanism, combined modality therapy along with the words physiology and pathology.

Detail analysis of viral strains or families

Some viruses can infect or kill the tumor cells. The biological mechanisms of virotherapy depend on several factors like the type or stain of virus, the target tissue or cell, and which biological pathways are targeted. Precisely some viruses can directly kill tumor cells, whereas others can direct or influence the systemic immune responses. Various viral strains and families which can play a pivotal role in oncolytic virotherapy are added in this class.

The examples are vaccinia virus, oncolytic herpes virus, simplex virus, herpes simplex virus 1, herpes simplex virus, herpesvirus 1, human, virus strain, vesicular stomatitis virus, virus recombinant and Newcastle disease virus added in this category. The following 7 types of strains were noted in the keywords.

1. Vaccinia Virus
2. Oncolytic Herpes Virus
3. Measles Virus
4. Simplex Virus
5. Herpes Simplex Virus 1; Herpes Simplex Virus; Herpesvirus 1, Human
6. Vesicular Stomatitis Virus
7. Newcastle Disease Virus

We collected the publication data of each individual strains. The details about total publications, total number of authors, based on the number of publications and citations, the list of top five authors and institutes are provided in Table S5 and S6.

However, in some articles 2 or 3 individual strains were studied together. To avoid this confusing, we retrieved the publications data which focused on all 7 strains, collectively. Out of all publications (n = 3751), 1421 research documents primarily focused on viral strains. The 1st document about it was published in 2002 and later a regular increase in publication is observed. The highest documents were published in 2013 (n = 139), followed by 2012 (n = 124), 2015 (n = 122), 2014 (n = 115) and 2010 (n = 112). For details analysis we used VOSviewer.

Co-authorship Network for Authors and Institutes for All Strains

As shown in Figure 5, there are 10 clusters. We will focus on red cluster. If we consider Szalay A.A., as the main author, he is connected with all items in the red cluster and also two in purple cluster with names of authors Harrington, K.J. and Vile R G. To understand the cluster, we retrieved the publication details of Prof Szalay A.A. In total documents (n = 73), he has more than 160 authors.

The highest number of papers was co-authored with Chen, N.G. (n = 35), followed by Yu, Y.A. (n = 32), Zhang, Q. (n = 25), Fong, Y. (21), Weibel, S. (n = 19), Gentschev, I. (n = 17), Chen, N. (n = 16), Stritzker, J. (n = 15), Chen, C.H. (n = 10), Yu, Z. (n = 15) and Wong, R.J. (n = 5). He also co-authored two documents with Harrington, K.J. In his publications the highest number of affiliations were noted with Genelux Corporation (n = 69), followed by Julius-Maximilians-Universität Würzburg (n = 68), University of California, San Diego (n = 52), Moores Cancer Center (n = 43) and Rudolf Virchow Center (n = 26). In total 13 countries were involved in all publications (n = 73). USA was noted in all of his publications (n = 73), followed by Germany (n = 68), China (n = 4), Italy (n = 4) and UK (n = 3).

From 2nd (Green) cluster, we will select Bell J.C. In blue cluster he is connected with Cripe T.P, from purple with Mecher A and from yellow cluster with Peng K. W., & Russell S. J. While in the parent green cluster he is almost connected with all authors. Based on the Scopus record Bell published the 1st document about oncolytic

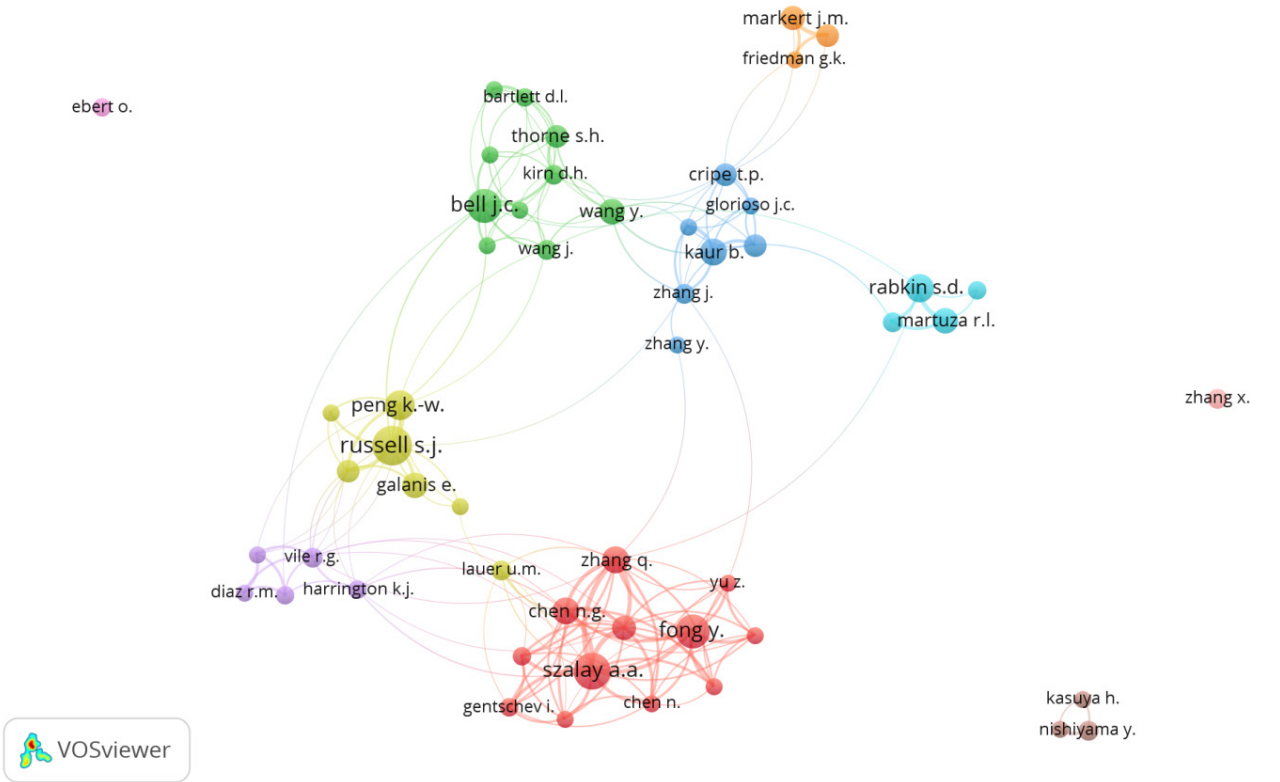

Figure 5. The co-authorship network for authors in seven viral strains publications

virotherapy in 2004. The maximum documents were published in 2010 (n = 14), followed by 2008 (n = 10). The total publications were found to be 74. Bell has co-authored 1 publication with Cripe T.P and Mecher A, two (2) with Peng K.W and 3 with Russell S. J. While, in green the highest co-authorship was noted with Le Boeuf F. (n = 15), followed by Kirn D.H. (n = 14), Lichty B.D. (n = 13), Mccart J.A. (n = 10), Wang J. (n = 6), Thorne S. (n = 2), and one (n = 1) document with Guo Z.S. & Bartlett D.L. The highest affiliations were noted with Ottawa Hospital Research Institute (n = 67), followed by University of Ottawa, Canada (n = 44) and McMaster University (n = 14). Canadian is noted in all publications (n = 73), followed by USA (n = 33), S Korea (n = 11), China (n = 3) and Finland (n = 3).

We also collected data about the number of institutes involved in research output. Total 4044 institutional addresses were recorded in viral publications (n = 1421). The detail maps are described in Figure 6.The highest documents were published by Department of Molecular Medicine, Mayo Clinic, Rochester, MN, United States (n = 45), Genelux Corporation, San Diego Science Center, San Diego, CA, United States (n = 33), Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, United States (n = 25), Department of Neurosurgery, Massachusetts General Hospital, Harvard Medical School, Boston, Ma, United States (n = 16) and Department of Immunology, Mayo Clinic, Rochester, MN, United States (n = 16). While the highest citations were recorded for Department of Molecular Medicine, Mayo Clinic, Rochester, MN, United States (n = 2387), Jennerex Biotherapeutics, San Francisco, CA, United States (n = 1342), Genelux Corporation, San Diego Science Center, San Diego, Ca, United States (n = 802), Department of Immunology, Mayo Clinic, Rochester, Mn, United States (n = 799) and Molecular Medicine Program, Mayo Clinic, Rochester, MN, United States (n = 731). To understand networking, we exhibited different clusters in Figure 6.

In all viral strains publications (n = 1421), 51 countries were directly involved. The highest documents are published by USA (n = 824), followed by Germany (n = 198), China (n = 164), Canada (n = 157) and UK (n = 125). The map with all countries is represented in Figure 7.

The top 10 most cited documents

Talimogene laherparepvec (T-VEC) expresses granulocyte-macrophage colony-stimulating factor (GM-CSF) and has been designed to conditionally replicate in cancer cells. T-VEC indices a more potent systemic immune response due to expression of GM-CSF. In a randomized open-label phase III trial, Andtbacka et al compared the effects of T-VEC and systemic GM-CSF in patients with unresected stage IIIB to IV melanoma. Incomplete. Results indicated that DRR (durable response rate), ORR (Overall response rate), and OS (overall survival) were higher in patients who received T-VEC for stage IIIB-IVM1a melanoma and in patients with treatment-naive disease showed the most responses. Sever adverse effects were reported in less than 2% of patients.[12] Conditionally replicative viruses; a plethora of biological and structural diversity, with the ability to kill tumor cells are an emerging therapeutic strategy for cancer treatment. Although completion of phase III clinical trial for Talimogene laherparepvec was an important milestone in clinical use of oncolytic viruses (OVs), issues such as transiently suppress but then unleash

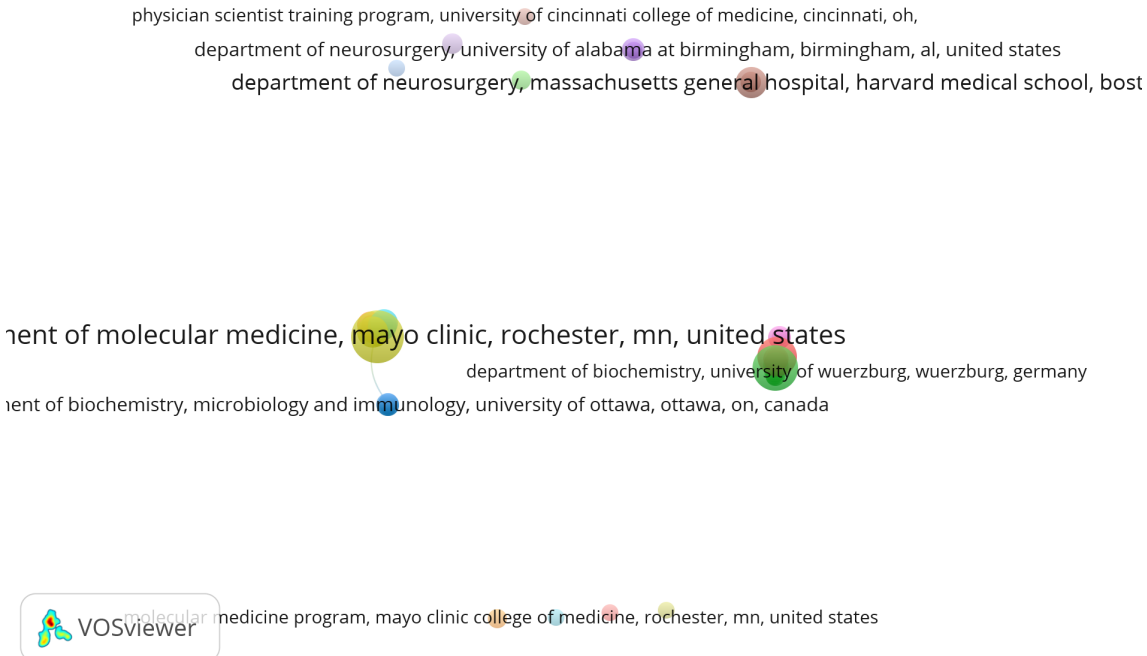

Figure 6. The co-authorship network for institutes in seven viral strains publications

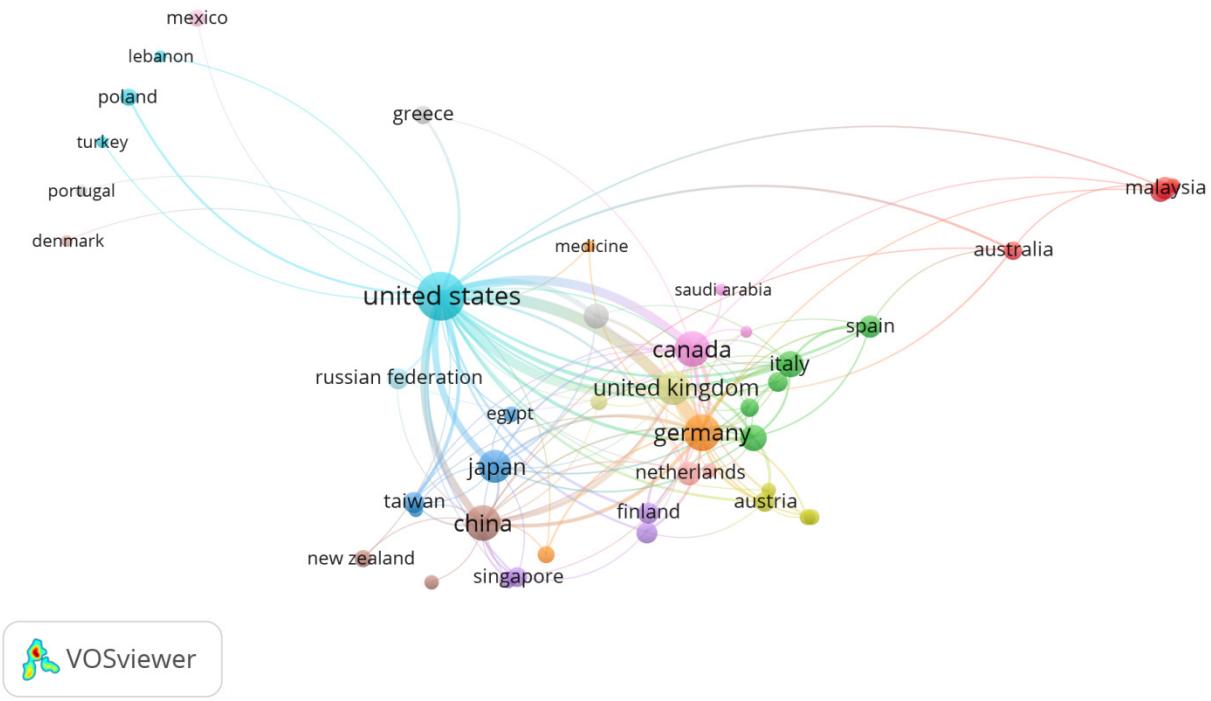

Figure 7. The country co-authorship network for all countries in seven viral strains publications

the power of the immune system to maximize both virus spread and anticancer immunity, develop more meaningful preclinical virotherapy models and modified manufacturing processes are yet to be fully addressed.[13] Engineered influenza A virus with defective NS1 protein has shown promising result in viral oncotherapy of cancer. This is mainly because the NS1 protein is responsible for many aspects of viral replication and virulence including inhibition of the host immune response through inhibition of IFN and limitation of IFN activated proteins and activation of PI3K signaling pathway. PI3K signaling pathway has been reported to be active in many cancer cells. consequently, influenza A viruses with defective NS1 proteins that are unable to counter host innate immunity and/or activate PI3K in normal cells, would be able to infect and lyse tumor cells.[14]

Ginn et al introduce a data base that retracts global information on gene therapy clinical trials from official agency sources, published literature, conference presentations and posters by individual investigators or trial sponsors (http://www.wiley.co.uk/genmed/clinical). According to this paper majority of ongoing gene therapy clinical trials are targeting cancer.[15]

Inhibiting DNA methylation cases an increase in the activity of endogenous retroviral elements in transformed cells. Such upregulation in endogenous retroviral activity induces immune response activity through dsRNA that results in growth inhibition of transformed cells. This approach is similar with OV therapy in that both approaches induce inflammatory immune responses at tumor sites.[16] Ribas et al reported a phase 1b clinical trial for assessment of the impact of oncolytic virotherapy with T-VEC on cytotoxic T cell infiltration and therapeutic efficacy of the anti-PD-1 antibody pembrolizumab. Patients with advanced melanoma were treated with a combination of T-VEC and pembrolizumab. Responsive patients had increased CD8+T cells, elevated PD-L1 protein and IFN-g gene expression. Combination therapy was well tolerated. Findings of this paper suggest that by modifying the tumor microenvironment, oncolytic virotherapy can enhance the efficacy of anti-PD-1 therapy.[17]

JX-594 through high-dose intravenous (IV) administration. In this randomized clinical trial, effect of JX-594 (Pexa-Vec) as an oncolytic and immunotherapeutic vaccinia virus on patients with advanced hepatocellular carcinoma showed an active induction of polyclonal humoral immune response which resulted in in antibody-dependent CDC.[18]

A phase II clinical trial on a GM-CSF–encoding oncolytic herpesvirus in patients with unrespectable metastatic melanoma showed a response rate of 26%. Both injected and uninjected lesions were affected which is the evidence of systemic effectiveness of OV. Evaluation of the Safety profile of this virus also showed limited toxicity profile. At the time when the data was published, authors were awaiting a US Food and Drug Administration–approved phase III investigation.[19]

Ongoing clinical trials on OVs; replication competent intracellular parasites either developed by genetic engineering or selected because of their natural ability to destroy tumor cells, have shown the safety and efficacy of OVs as a novel therapeutic strategy against cancer. However, issues such as built-in antiviral defense systems

Study Highlights

- This is the 1st bibliometric report about oncolytic virotherapy.
- Relative growth rate and doubling time is provided
- Descriptive details about the authors, universities and countries are provided.
- Co-words analysis is performed.

and increasing the target specificity of the OVs are yet to be addressed in full. Moreover, efficient systemic delivery methods for OVs must be developed to guarantee the application of OVs for complicated cancer patients such as those in metastatic stages of the disease.[20] Oncolytic viruses as a new discipline in cancer therapeutics perform a binary role: OVs selectively kill cancer cells and induce anti-tumor immune responses. Although the mechanism of action on a molecular level is yet to be fully decoded, selective viral replication in cancer cells seems to be the major mechanism. Both naturally occurring and genetically modified OVs seemingly share the same basic mechanism. In this paper the basic biology principals of OVs and ongoing clinical trials are covered by the authors. They also depict several challenges that OVs face as a new class of drugs including pharmacodynamics considerations, biosafety considerations, clinical trial design and response assessment, regulatory and commercialization issues.[21] The data and details are described in Table S7.

Conclusion

To the best of our knowledge, for the first time, we bibliometrically covered the research progress of oncolytic virotherapy in the 21st century. In the Scopus database, a total of 4369 documents were noted. The highest RGR was observed for the year 2004-2005 (311.11), followed by 2005-2006 (243.24) and 2002-2003 (200). Numerically, the details about the top ten authors and institutes are provided. North America and Europe are the top two significant continents involved in research output. In contrast, United States publishes the highest documents (n = 1799), followed by China (504) and Germany (n = 405). The VOSviewer Analysis also presented the co-authorship network for authors, institutes, and countries. The h-index, citations, and citation per document details are also provided (especially) for the authors. We also performed the co-words analysis; this may help in elaborating the primary research focus of publications. Last but not least, the top ten most cited are also highlighted.

Authors' Contribution

Conceptualization: Waseem Hassan.
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Competing Interests

There is no conflict of interest.

Ethical Approval

Not applicable.

Funding

Not Applicable.

Supplementary Files

Supplementary file 1 contains Tables S1-S7 and Figures S1-S5.

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