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Looking for Breakthrough in Pancreatic Adenocarcinoma Research by Changing Recruitment, Support and Publication Algorithms

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ABSTRACT

Despite major breakthroughs and significant improvements in treating most cancers, pancreatic adenocarcinoma (PAC) therapy is still badly lagging behind. This article employs selected funding breakdown and publication metrics to analyze the directions and the results of PAC research. I proceed to pinpoint the factors that contribute to the failure of the basic, preclinical effort to combat this terrible disease, in contrast to other major malignancies. Briefly, every research project is a result of a series of choices and decisions, starting with the choice of the field of research interest and ending with a choice of what, how, and where to publish the results. In this author's opinion, it is the criteria of academic promotions and, consequently, the demands of the publication media that hamper meaningful progress in this area. Finally, I suggest several practical measures to rectify the PAC research deficiencies.

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1. Introduction

Pancreatic ductal adenocarcinoma (PAC) is the most lethal of high-incidence cancers. Worldwide, 496,000 individuals have been projected to be diagnosed with PAC, and 466,000 to succumb to this terrible disease in 2020.[1] The numbers vary according to geographical area, country, population characteristics, date of statistical analysis, quality and accessibility of medical services, and source. Cancer.net reports PAC as the 8th most common in women and 10th in man, [2] globally, whereas Luo et al.[3] report it to be 11th and 12th, respectively. Similarly, 5 year relative survival varies between 5-7% in UK[4-6]and 9-10% in the US.[7,8] Rawla et al.[9] and Luo et al.[4] report PAC as the 7th cause of cancer death globally, the 3rd in the US,[10] while in Israel it is one of the top in incidence, one of the worst in 5 year survival (6%), and the 4th leading cause of cancer death in that country.[11] While practically all high-incidence cancers exhibit a consistent trend towards decrease in mortality, PAC shows no change, or even a 0.3% increase.[12] The dire message to current and future PAC patients may be best summarized by a laconic sentence in Cancer Research UK report: " In the 1970s, 1% of people diagnosed with pancreatic cancer survived their disease beyond ten years, now it's still 1%.".[5]

Despite the apparent discrepancies in absolute numbers, the above-described statistics prove that, unlike in most major neoplastic diseases, the progress in basic, translational, applied, and technical research has failed PAC. Looking at the figures alone one may suspect PAC is an orphan disease.

Faced with a scientific problem that has baffled basic and applied research for decades, there is a dire need for measures that will promote more fruitful research in any desired area. The obvious steps are: (i) to recruit top young faculty to the designated field of study; (ii) to establish a funding system targeted to support the aforesaid recruits; (iii) to create an academic institutional structure that will promote and encourage original research (with emphasis on original); (iv) to modify the academic publication framework to accommodate and reward the faculty in their initial research years. It is possible that upon close examination the present situation actually largely conforms to these goals. If so, little can or should be done and PAC regrettably needs to patiently await either slow cumulative progress or unexpected breakthrough(s). If, however, the analysis reveals large gaping lacunae in these conditions, dissection of causes is in order.

The purpose of this paper is to identify some of the causes of the PAC research failure. To support the author's assumptions, a limited examination of the metrics of PAC-related publications in selected top-tier journals was performed and compared with the metrics related to five high-incidence cancers. The paper also examines PAC research funding by the US National Institutes of Health. Based on these data, the author proposes measures that might remedy this situation in the future by suggesting changes in the structure of academic appointments, funding and promotion of junior and mid-level faculty, and publication policies of top-tier journals. Clearly, the scope of this approach requires major restructuring of the scientific community culture, which is obviously unrealistic in the foreseeable future. Nevertheless, it is this author's opinion that even partial implementation of the proposed changes will promote novel and ground-breaking research in the PAC basic, translational, and applied research.

2. Methods

Cancer statistics in general and PAC statistics in particular, were obtained from web and journal publications sources indicated in the Reference section. Since not all sources cover the same periods and the same populations or utilize identical algorithms for trends and projections (e.g. see survival estimates for the UK[4-6]), the choice in the present paper was necessarily somewhat arbitrary. In no case, however, the choice did alter the general picture and the trends for either PAC or the examples of cancer types mentioned in the paper.

The impact of research in any specific area can be roughly equated with the number of publications multiplied by the journals' impact factor. However, the staggering increase in the number of indexed and non-indexed journals (including a significant proportion of suspect predatory journals) makes non-selective metrics practically meaningless. Based on my own experience, recruitment, promotion, and funding of junior and non-tenured faculty in the current competitive research market requires publication record in top-tier scientific literature. In surveying the top journals, an arbitrary choice is unavoidable. I have chosen Nature, Science, Cell, The Lancet, and New England Journal of Medicine as representative of the most news-worthy general life sciences and/or clinical research. In addition to full papers, reports, and reviews, all other items (editorials, views, or corrigenda) were included on the assumption that their number was representative of the degree of interest in each area of study. Publications metrics in English were obtained using Pubmed for years 2009-2020. Only the publications that contained the name of the disease in the title were selected. For PAC, for example, the following search of all publications was utilized: "(pancreas[TITLE] OR pancreatic[TITLE]) AND (carcinoma[TITLE] OR adenocarcinoma[TITLE] OR cancer[TITLE])".

To estimate the impact of any individual researcher in top-tier publication, the number of contributors to publications in Nature was analyzed. The choice of Nature was arbitrary, based on its reputation as top general interest scientific journal. The numbers of contributors in Nature publications reports, papers, and reviews were taken into consideration.

The publication metrics were analyzed in the following way: The overall number of publications, the number of publications related to each cancer's global incidence, the number of publications related to each cancer's severity index (defined as the ratio of mortality to incidence)

The number and the funding figures (rounded to the nearest thousand) of 2021 research support were obtained from the official US National Institutes of Health (NIH) site, National Cancer Institute (NCI) and using 'pancreas' or 'pancreatic' as key words.[13] The yearly support was estimated by dividing the overall costs by 5.

3. Data, analysis, and discussion

3.1 LURING THE BEST

Top candidates consist of a very small minority of PhDs and MDs who will successfully compete for a smaller number of research slots in leading academic and medical institutions. The criteria that determine a candidate's competitive edge are publications (number and impact factor), reputation of the laboratory where the candidate apprenticed for independent or quasi-independent research (usually post-doctoral position), and the history of area of research and technical expertise. It is obvious that these requirements make the PhDs interested in pursuing a research career compete for the very large research laboratories, where all the three conditions are more likely to be met.

The successful candidates are faced with a decision about what area and direction of independent research they will choose in their budding careers. This decision is usually determined by the candidate's background (i.e. the field of research and the technologies acquired during the post-doctoral research) and the likelihood of obtaining significant grant support to ensure competitive edge in high impact publications. These, in turn, will determine the candidate's chances to pursue a tenure-track career. In a significant number of prestigious institutions tenure comes only with full professorship, making the above-mentioned decisions a persistent and imperative factor during a large part of the new (and not so new) career.

3.2 MONEY MATTERS

The extremely slow progress in effective PAC therapy could be a result of inadequate research funding. To obtain a rough estimate of the funding sources, I examined the R-category grants (through R-21) of NIH, one of the two largest global funding resources for basic, translational, and applied health-oriented research. In 2021 NIH supported 227 PAC research projects at the total cost of $US 89.6 million. The average grant amounted to $US 393,000, close to the median amount of $US 385,000. Assuming a five-year project award, this translates into approximately $US 80,000 per year. With the average postdoc salary of $US 51,600, this allows a small operation with one postdoc and a modest budget for consumables. Modest as it looks, NIH funds extensive additional programs that offset large elements of research expenditures. Training grants, core centers, consortia programs, instrumentation awards, logistics – all those cannot be easily calculated in estimating the additional financial help towards a given research project.

The real question is "Is it enough?" There is no definitive answer. The number of newly diagnosed PAC patients in the US is around 60,000. Hence the direct NIH research funding per patient is a paltry $US 297 per year. On the other hand, direct yearly care for a PAC patient is estimated at $US 43,333. Hence NIH direct funding consists of 3.4% of care costs, or 0.7% of care costs per patient. Is it little, adequate, or a lot? The answer is in the eye of the beholder. One thing is sure, however – getting a highly competitive NIH R-type grant allows the recipient to pursue small-scale research, at best. Whenever more outlay is required for manpower and technology, a newly recruited faculty member needs to rely on collaborations.

3.3 PUBLISH OR PERISH

An obvious indicator of the importance of a given field of research is the number of pertinent publications. To estimate the relative weight of research targeted at PAC (global incidence in 2021 estimated at 0.5 million new cases), I queried Pubmed for the overall number of all publications in 2009-2020. This parameter was compared to the five top-incidence cancers; breast, lung, colorectal, prostate, and stomach (2.3, 2.2, 1.8, 1.4, and 1.1million new cases per year, respectively). As can be seen in Fig. 1, PAC is trailing all major cancers.

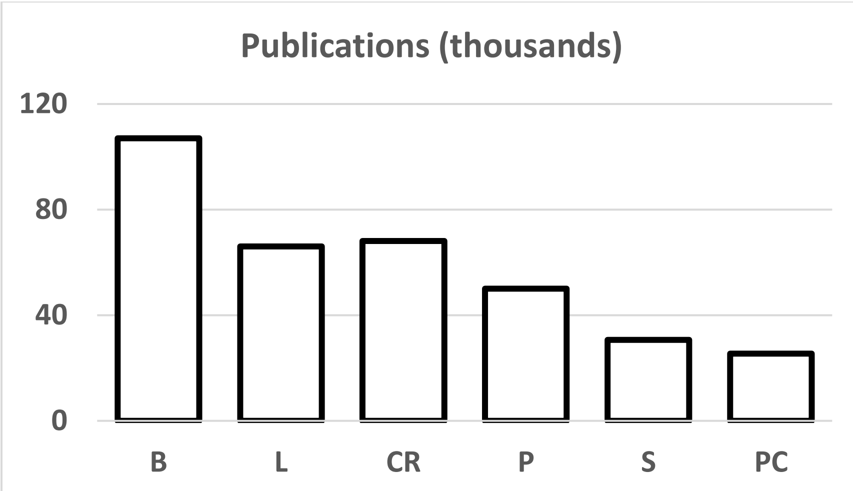

Figure 1. Number of publications (thousands) in 2009-2020 that contain in the title the name of the cancers of highest incidence: Breast-B, Lung-L, Colorectal-CR, Prostate-P, Stomach-S, and PAC-PC.

When the number of publications is normalized to the incidence of the tumors, a different distribution is seen (Fig. 2). PAC relative publication record is the highest among the six tumor types. This simplistic measure suggests that the basic and clinical research in this field is at least adequately funded and reaches satisfactorily the research literature.

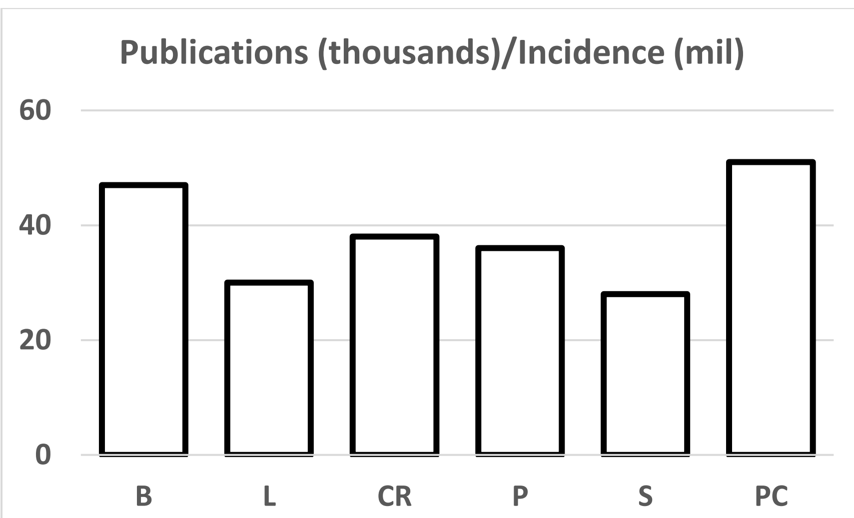

Figure 2. Number of publications (thousands) normalized to the global incidence of the respective malignancies (in millions). For abbreviations see Legend to Figure 1.

If one, however, attempts to factor in the severity of the disease, the picture changes dramatically. An elementary measure of severity is the mortality-to-incidence ratio. The number of all publications relative to this index of severity is shown in Fig. 3. The two gender-specific cancers lead with values of 362 and 185, while PAC trails in the back with a value of 27.

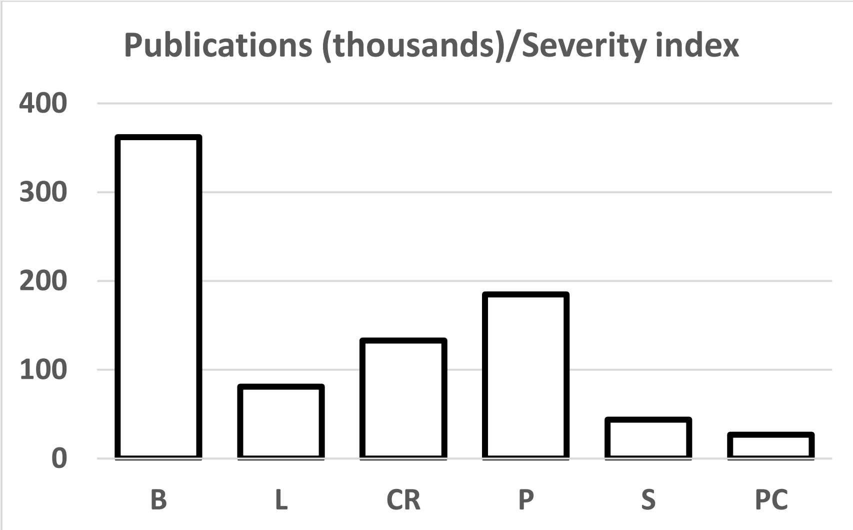

Figure 3. Number of publications (thousands) normalized to their severity index (mortality/incidence). For abbreviations see Legend to Figure 1.

A more pertinent index of the attention that a subject attracts in the research community is the record of publications in the top-tier journals. This statistic is probably the most important attribute to impress budding scientists and influence their choice of career. I have arbitrarily chosen five journals: Nature and Science in the general scientific interest category, Cell as a top representative of cell biology, and The Lancet and New England Journal of Medicine as the most prestigious general medical publications. Fig. 4 shows the distribution of publications relevant to the six cancers during 2009-2020. Comments, editorials, and corrections were included on the assumption that these categories also reflect the level of interest for a given topic.

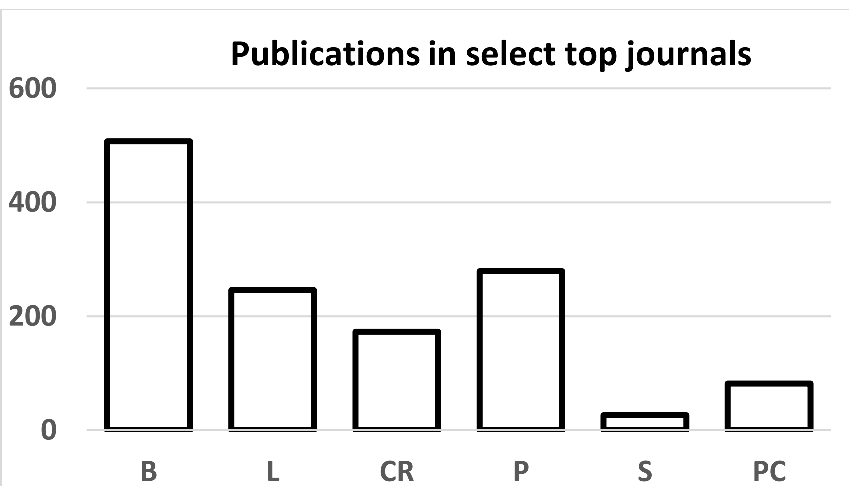

Figure 4. Number of publications that contain in the title the name of the cancers of highest incidence in five select top tier journals – Nature, Science, Cell, The Lancet, New England Journal of Medicine. For abbreviations see Legend to Figure 1.

PAC is represented by 82 items, versus 507 and 279 for breast and prostatic carcinomas, respectively. Stomach cancer publications record is the poorest, with only 26 in all five leading journals. Normalization to incidence puts PAC in the third place, after breast and prostate cancers (Fig. 5).

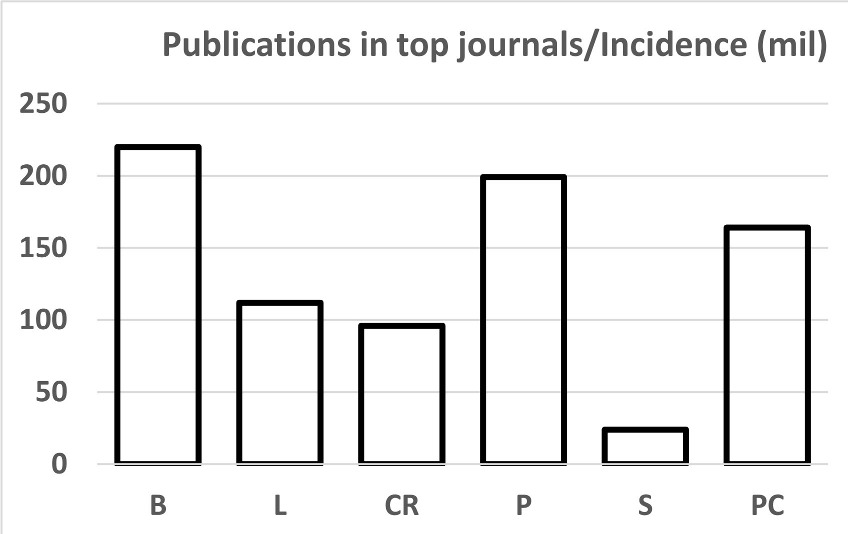

Figure 5. Number of publications in five top-tier journals normalized to the global incidence of the respective malignancies (in millions). For abbreviations see Legend to Figure 1.

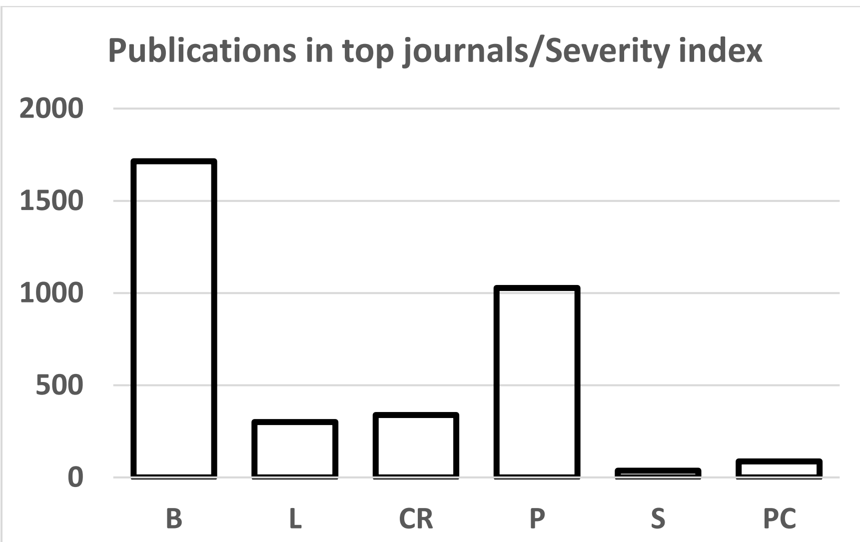

Figure 6. The number of publications in five select top-tier journals normalized to their global severity index. For abbreviations see Legend to Figure 1.

Normalization to the severity index relegates PAC to fifth place (Fig. 6), the stomach carcinoma showing the poorest representation in the top journals. The disparity between the value for PAC and those for the two gender-specific cancers is blatant: 20-fold higher for breast and 12-fold for prostatic carcinomas.

One might argue that the ad hoc-invented 'severity index' is an artificial creation that is bound to skew the impressive record of PAC-oriented publications. This author's contention is that the dismal record of failure in treating a disease that might be 10th or even 12th in cancer incidence, yet in some countries a 3rd or 4th in cancer mortality, fully justifies this form of comparison with top neoplastic diseases.

In conclusion, the demand for more funding is a constant for all research fields, but in the case of PAC it appears to be justified.

3.4 LOST IN A CROWD

In all stages of a research career, being a corresponding author or one of the first two authors in one of the most prestigious publications virtually assures the researcher of a preferred position. This applies to a choice of a post-doctoral lab, to a competition for a slot in the quest for a tenure-track position, to an almost foolproof opportunity to obtain grant award, and a direct pathway to tenure and promotion. It is therefore interesting to analyze how PAC research scientists fare in this respect, when compared to the publications in the areas of the five top-incidence cancers. I have chosen to examine the 2009-2020 publications in Nature, this time excluding comments and corrigenda and concentrating on research letters, articles, and reviews (Fig. 7). To extend the comparison, I have included publication data for glioblastoma, a brain tumor with a 5-year relative survival record, much poorer than PAC and lower but comparable incidence, and for skin melanoma, with global incidence estimated at 325,000 and a relatively low mortality (57,000, severity index of 0.18). A cursory examination of the numbers reveals that while breast cancer and melanoma appear to be overrepresented and stomach cancer grossly underrepresented, PAC appears to be a preferentially covered subject in Nature research publications.

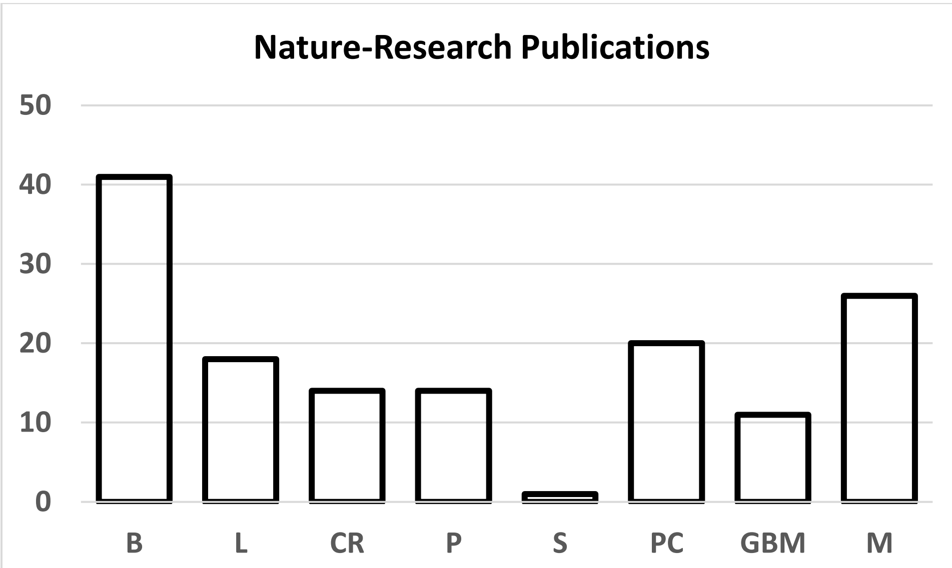

Figure 7. Number of publications in Nature in 2009-2020 that contain in the title the name of the cancers of highest incidence: GBM-Glioblastoma, M- Skin melanoma. For other abbreviations see Legend to Figure 1.

However, when one examines the authorship distribution of the publications, an important discrepancy is revealed. Publications were classified according to authorship categories corresponding to projects that are feasible in a small research group (1-5 authors), a medium-to-large one or collaboration of two smaller laboratories (6-10), and a larger than average laboratory or a collaboration of three of more groups (11-20). The 21-and-up bin represents research contributions that involve concerted efforts of numerous research groups or consortia, where one group leads and coordinates the project.

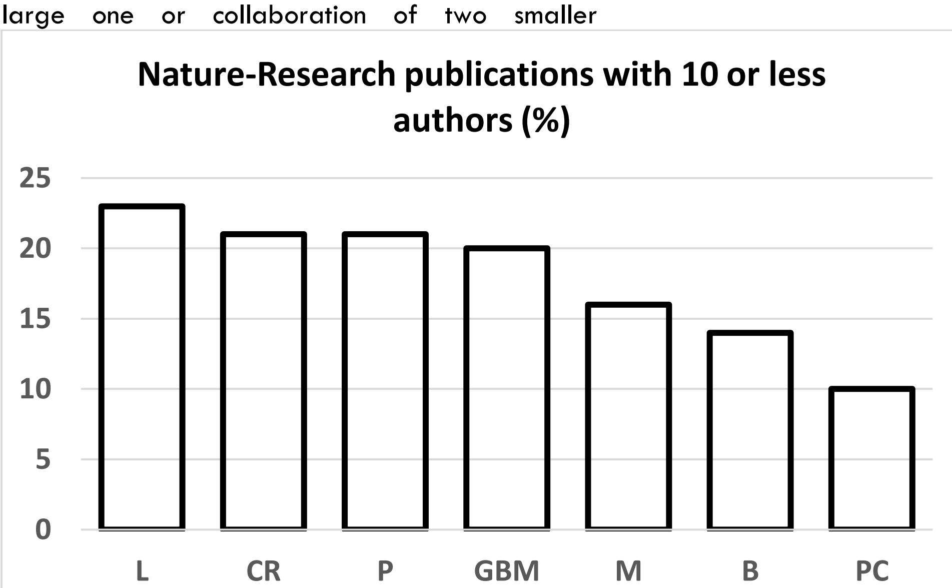

Figure 8. Proportion (%) of publications in Nature in 2009-2020 authored by ten or less contributors. For other abbreviations see Legend to Figures 1 and 7.

It is striking that the share of the two lowest bins, i.e. publications with less than 10 authors, is lowest for PAC, only two papers in ten years. In contrast, publications boasting of mammoth lists of authors (21 and up) constitute a clear majority, 70%. In the lung carcinoma field, with only 18 papers in Nature versus the 20 for PAC, four papers belong to the two lowest categories.

One may ask why the most prestigious journals publish behemoth papers and reviews that are authored by multitudes. The answer lies in an obvious positive feedback loop. A journal's importance is measured by its impact factor, which reflects the number of citations. What better way to promote an avalanche of citations than to publish a giant definitive paper, review, or meta-analysis that cannot be omitted in the bibliography of any subsequent publication on the same subject?

These numbers hold two important clues for young scientists in the choice of their career path. In choosing an area of postdoctoral training, the probability of standing out among more than twenty authors is very slight. Similarly, in their postdoctoral training, the possibility of profiting by interactions with their peers and more experienced scientists diminishes in a project that resembles an assembly line, where their contribution is most likely negligible. By the same criteria, when aiming for their first appointment, or the first grant, or the first promotion, they stand a fourfold higher chance of having a paper in Nature in lung cancer research when compared to PAC. Moreover, they can achieve this goal with modest funding, without the necessity for giant collaborative operation. Hence, if they seek a career in cancer research, in their quest for either postdoctoral training or their first academic appointment, they will do well to avoid PAC.

3.5 WE CAN DO BETTER

In this author's opinion, we can. Most of the changes are conceptual. Many do not involve additional funds, only a change in their allocation. Some, however, require a major overhauling of the scientific publications system, a task that might be impossible to undertake in the foreseeable future.

The most serious problem in PAC research (and conceivably in many other fields of science) is the dearth of original approaches. PAC's stubborn resistance to improved therapy suggests it is a unique malignancy. Many blame it on the late diagnosis, when the metastases spread beyond the organ. Indeed, the NIH is funding many grants aimed at discovering PAC markers, early detection techniques, and similar projects. Yet, even with early diagnosis and a successful early surgery available for a minority of patients, the prognosis is better but far from satisfactory. Like in many other areas of research, PAC scientists and clinicians scan the literature and whenever something new pops up elsewhere, they hurry to test it on PAC. A good example is the current trend to include biologicals in PAC therapy, and particularly the novel approach to immunotherapy. The monoclonal antibodies targeted at the immune response checkpoints (e.g. Keytruda) have captured the attention of oncologists in NSCLC therapy, and recently in additional solid tumors that exhibit MSI.[14] Unfortunately, this approach might prolong life of perhaps 1% of PAC patients at a cost of $US 150,000/year. This approximate therapy costs were calculated for 2021. Since then, the costs of biologicals therapies have increased, for some drugs by more than two-fold. It is obvious that this approach, though vital for a very small proportion of PAC patients, does not constitute the hoped-for breakthrough.

What we need is to encourage the top research candidates to look for novel pathways that might hold clues to the unique biology of the pancreas and PAC. This can be promoted by shunting part of the already ample funding into creating academic and clinical positions dedicated to novel approaches to PAC research. These positions should carry with them a five-year funding support at the accepted average level (~$US 400,000). The only condition should be a manifest difference from the already published approaches to PAC or other cancers. Some will argue that the existing mechanisms of funding are adequate to support novel and high-risk proposals. Although it might sound true in theory, my experience from the various study sections that I had been a member of suggests that most, if not all panels prefer standard proposals, well grounded in the existing technology and science. It is extremely rare that a high-risk approach will be funded.

Another two problems are the practically absolute requirement for hypothesis-driven research and the virtual impossibility to publish negative results. These two problems plague all life-sciences research. Thus, when scientists encounter an unexpected finding, they are forced to spend an inordinate amount of effort, time and money to fit it into a more or less comfortable straitjacket of accepted mechanisms. Those are often necessary variations on canonical pathways and therefore bound to be overlooked. Although the PLoS publications arose on precisely that background, in practice they rather rapidly joined the rest of the journals in publishing formats conforming to hypothesis-driven formula.

The suppression of negative results hampers progress in three different ways. The first is universally known as the 'cabinet drawer effect'. If twenty groups ran the same type of experiment with no results whereas the twenty-first got a positive result due to simple statistical chance, the single spurious positive result is the only one published. The second problem is the multiplication of efforts. Were the first two or three negative results published, the other identical eighteen projects could have been avoided. Finally, publishing negative results might reveal their possible shortcomings and conceivably help designing better approaches.

Conclusion

According to NIH awards data, PAC research is adequately funded. However, publications metrics suggest that recruiting entry-level faculty in the PAC research field is more difficult than in other top incidence cancers, except for stomach carcinoma. To remedy this situation, creating a specialized, reasonably funded niche for young faculty might be difficult, but is entirely feasible and should effect significant change in the field. The larger scope issues, e.g. changing the hypothesis-driven approach and the publishing-funding interdependent policies, pose problems of much greater magnitude. It is possible that these characteristics might change gradually when the agencies that control the monies conclude that there are better, more economical, and more fruitful ways.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics: Globocan Estimates of Incidence and Mortality worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin, 2021: 71(3): pp 209-249
2. https://Cancer.net/cancer-types/pancreatic-cancer/statistics
3. Luo W, Tao J, Zheng L, Zhang T. Current Epidemiology of pancreatic cancer: Challenges and opportunities. Chin J Cancer Res, 2020; 32(6): pp 705-719
4. https://www.pcrf.org.uk/about-pancreatic-cancer/
5. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/pancreatic-cancer#heading-Two
6. https://nuffiedtrust.org.uk/resource/cancer-survival-rates
7. https://pancreatic.org/pancreatic-cancer/about-the-pancreas/prognosis/
8. https://www.cancer.org/cancer/pancreatic-cancer/detection-diagnosis-staging/survival-rates.html
9. Rawla P, Sunkara T, Gaduputi V. Epidemiology of Pancreatic Cancer: Global Trends, Etiology and Risk Factors. World J Oncol, 2019; 10(1): pp 10-27
10. https://pancreatic.org/pancreatic-cancer/pancreatic-cancer-facts/
11. https://en.cancer.org.il/template_e/default.aspx?PageId=8358&gclid=Cj0KCQjwsZKJBhC0ARIsAJ96n3WThbYK_K-08w8wCNWiXqiRmlYAJEN06ttuPvoEhnCKMjepf2PtHU4aAjKhEALw_wcB
12. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics. CA:Cancer J Clin, 2021; 71(1): pp 7-33.
13. https://reporter.nih.gov/search/JbRgAtchAUKHOoW2X1vObQ/projects/?agencies=NCI
14. Macherla S, Laks S, Naqash AR, Bulumulle A, Zervos E, Muzzafar M. Emerging Role of Immune Checkpoint Blockade in Pancreatic Cancer. Int J Mol Sci, 2018;19: 3505