



SHUNNING OF MURBURN CONCEPT: A SHAM AND A SHAME!

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*If science is the pursuit of communicable truth and reason; and one which aims to explain natural phenomena, then the continued disregard of murburn concept by research communities is condemnable (particularly: xenobiotic/drug metabolism and mitochondrial physiology fields). Therefore, if one could call a spade a spade, then such a cognitive dissonance and disowning of professional mandates by individuals and institutions MUST be called out. Such 'status quo' maintaining outlooks of leadership waylay the interest of the vast majority of our current and all of our future generations, and only serves to preserve the false prestige of a misplaced few at the helms! For, murburn concept is not just a novel explanatory umbrella of life's chemico-physical foundations with profound impact on health-medicine sectors, imbibing it would also pose immediate and far-reaching impacts in education, research, philosophy and culture. **Biomed Rev 2023; 34: 165-180***

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WHEN IS IT OKAY TO NAME AND SHAME, AND WHY IS IT THAT I FRET AND FUME?

What started in 1999 at my mentor Lowell Hager's [elected member of National Academy of Sciences-USA, Chair Prof of Biochemistry at University of Illinois (Urbana-Champaign)] lab at as a simple query/tiff on chloroperoxidase mechanism has now posted 25 years of focused pursuit, with >60 publications

probing into the role of diffusible reactive (oxygen) species [or DRS/DROS/ROS] in cellular physiology. This was highlighted in last year's issue of *Biomedical Reviews*, wherein murburn concept (the thesis which states that DRS are obligatorily required for routine cellular activities, and it is for the utility of oxygen-DRS equilibriums that we actually need oxygen at such acute time-scales) was given cover-page credit.

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Humility set apart, the issue here is that murburn concept is perhaps the biggest iconoclastic and paradigm-shifting work and one that serves our interests of finding better solutions to aging and redox diseases. Murburn concept provides unprecedented abrogating insights into the mechanisms that sustain life, rendering multiple Nobel Prize recognized ideas and thousands of publications in top-notch journals (*Nature*, *Cell*, *Science*, *PNAS*, etc.) redundant; necessitating a rewriting of science textbooks from school-level. The constructive outcome is essential for understanding aging, redox diseases, their therapies (both mainstream and alternative) and comprehending hitherto inexplicable idiosyncratic observations in medicine. In the most fundamental terms, it is about how some redox proteins work and what are the various roles played by oxygen in cell. While enzymes are typically specific/selective, there are some redox proteins that are

non-specific and show a broad range of selectivity. Murburn concept details how such proteins set of a cascade of events and how those processes integrate into macroscopic outcomes. Murburn concept is a fundamental pivot of life, in toto.

It is now ~17 years that murburn model of xenobiotic/drug metabolism and ~8 years that the murburn model of molecular respiration (or oxygen-assisted mitochondrial ATP-synthesis) were first brought to the light of the scientific community via *Arxiv* preprints (Fig. 1); and subsequently supported with more experimental, theoretical and literature back-ups by my (group's) publications in reputed journals in the immediate years that followed. Several years post such epoch-making developments delineating the role of oxygen-DRS equilibria in cellular physiology, our younger generation are still taught disproved/redundant ideas in the name of science; research agenda in the two fields above are still misconstrued and

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3. arXiv:1703.05827 [pdf] [q-bio.SC] doi: 10.14748/bmr.v28.4450

Murburn concept: A facile explanation for oxygen-centered cellular respiration

Authors: Kelath Murali Manoj

Abstract: Via a concomitant communication (the first part of my work), I have conclusively debunked the prevailing explanations for mitochondrial oxidative phosphorylation and established the need for a novel rationale to account for the reaction paradigm. Towards the same, murburn concept is hereby floated as a viable explanation (in the second part of my work). It is proposed that the inner mitochondrial... [More](#)

Submitted 16 March, 2017; originally announced March 2017.

Comments: Main manuscript (including abstract, text and data) is 19 pages; 1 Table & 1 Figure Supplementary information has 4 items and the overall document totals 46 pages

Journal ref: Biomedical Reviews, 2017, 28, 35-52

4. arXiv:1703.05826 [pdf] [q-bio.BM] doi: 10.1177/1178626418818442

Mitochondrial oxidative phosphorylation: Debunking the concepts of electron transport chain, proton pumps, chemiosmosis and rotary ATP synthesis

Authors: Kelath Murali Manoj

Abstract: Herein (the first part of my work), I debunk the long-standing hypotheses that explain mitochondrial oxidative phosphorylation. Simple calculations point out that mitochondria are highly proton-deficient microcosms and therefore, elaborate proton pump machinery are not tenable. Further, other elements like the elaborate electron transport chain, chemiosmosis, rotary ATP synthesis, etc. are also cr... [More](#)

Submitted 16 March, 2017; originally announced March 2017.

Comments: Main manuscript (including abstract, Tables & Figures, References, etc.) is 32 pages. 2 Tables & 2 Figures. Supplementary information has 7 items, and the document (together with the main manuscript) adds up to 65 pages

Journal ref: Biochemistry Insights, 2018

5. arXiv:q-bio/0610036 [q-bio.BM] [q-bio.SC]

The di-flavoenzyme reductase directly activates oxygen for the metabolism of diverse drug molecules by liver microsomal Cytochrome P450s

Authors: Kelath Murali Manoj

Abstract: This submission has been withdrawn by arXiv administration due to complaints of misuse of institutional affiliation.

Submitted 19 December, 2006; v1 submitted 19 October, 2006; originally announced October 2006.

Comments: This submission has been withdrawn by arXiv administration

Figure 1. My preprints elaborating the paradigm-shifting ideas on xenobiotic metabolism and mitochondrial physiology uploaded on Arxiv in the first two decades of this century.

<https://arxiv.org/search/?query=kelath+murali+Manoj&searchtype=all&source=header>

useful experimental/clinical data continue to be misinterpreted perusing untenable hypotheses, drugs are still optimized on false outlooks, *etc.* More importantly, millions have lost their lives to respiratory issues and to the COVID pandemic! Certainly, if people would have known why we need oxygen or how oxygen is used by cells, the outcome would have been significantly different. The issue is really pressing and very grave. It concerns the quality and longevity of lives of billions of humans on planet earth today and even more, in the generations to come..... Given for sure is the premise that mandates sincerity and serious thoughts/actions.

Newton's first law essentially holds good and fort even in social spheres. When thing are derailed, *an external nudge must be given to the inertial system for it to budge* to regain tracks and traction. With this write-up, the scientific community is urged to better outlooks for quickly understanding the roles of oxygen-DRS equilibriums in routine life. This article highlights and lambasts the continued disregard of murburn concept by leading researchers, and it is written to dissuade the vanity of maintaining an indefensible *status quo*. In the process of this quest, one MUST resort to some transparency/accountability measures, which might entail instances of naming/shaming. When plenty of evidence and ample time has been given for re-charting agenda, it is warranted to criticize the delinquent. Iron cuts iron, and negative attitudes solicits admonitions (even if concerned ones perched). We must register that moral culpabilities are a matter of reality even among educated scientists, who are no philanthropic soldiers in world wars resulting of others' initiation! The vast majority of scientists are the cream of the society, enjoying the liberties and grants/gratitude sponsored by the trusting public/taxpayer. The cognitive dissonance among the leading (read: dealing) scholars (read: armchair hunting Apollonians) and the vain penchant for sticking on to consensus and camaraderie is deplorable. Therefore, my rants and raves about the nonchalance, incompetence and lack of integrity in several quarters of the biochemistry academia and industry circles are fully JUSTIFIED. (If you, the reader, do not fall into this category of people, you don't have to take offense! If you are not one and yet want to maintain social ethos of respecting leadership as a greater priority and deem my critical write-up as socially toxic, please introspect as to what you have contributed and what you are defending/advocating.)

Most importantly, science runs by the authority of logic, not by the logic of authority! While there is nothing for me to object when popes anoint saints, it is imperative that scientists

recognize each other by the language of truth, math and reason. If a scientist fails in this fundamental code/responsibility, he/she invites criticism. Good scientists do not just do good science themselves, but also do justice to others' good science. Also, they do not flout fundamental laws of physics, just because some senior biologists (in positions of power) have some fancy hypotheses based on misinterpretation of select observations. They have to be open-minded to the spectra of data. In all honesty, I have constructively and relentlessly pursued the social good and delivered the goods to the society at large and earned the right to speak out. As a pioneering and justified contributor of murburn concept, therefore, this part of my submission to *Biomedical Reviews* deals with the personal perspectives and experiences part of my socio-scientific journey. Now, I have realized that when some Apollonians asked me to wait or produce more proof for securing their appreciation (when all the observations and known theory supported my take), it was a mere ploy for them to continue with their inertial pursuits. They had little intentions to see anything that would question their stance and stature. Although unrecognized by the major institutions and organizations, I am fortunate that some individuals and portals/associations/events have staked their credentials for tabling the new ideas. And this good fortune might not be bestowed upon many other divergent thinkers and it is also my mandate to ensure that my juniors don't face such outlooks in their pursuits.

THE START OF THE DISCORD: CHLOROPEROXIDASE

Chloroperoxidase, the extracellular acidic and glycosylated fungal heme-thiolate enzyme pioneered by Lowell Hager was the foundation of murburn pursuit. Compound I's existence and roles were proven in synthetic level and spectroscopic sample preparations. However, I argued with Lowell that the routinely lab-assayed electron transfers (organic radical formation from heterocyclic substrates like ABTS or aromatic amines/phenols and reactions like hetero-atom dealkylations) and group transfer reactions (chlorinations) were highly unlikely to be mediated at the heme distal pocket. He was quite vehement that all reactions occurred at the active site alone and it took me quite some time to convince him otherwise, and he did come around to agree that these reactions followed a different mechanistic trajectory (as evident from his lifetime memoirs in JBC and his resuming co-authoring manuscripts with me after 2006). Until his demise in 2014, Lowell supported my quests and my papers with him on chloroperoxidase are quite

decently and suitably cited.

MOVING ON TO CYP-MEDIATED DRUG/XENOBIOTIC METABOLISM

However, when I found the same ideas to be relevant in cytochrome P450 (CYP) mediated drug metabolism, things took an ugly turn. I was humiliated and even fired by employers for sticking to facts and reason. For example: In 2006, at University of Arkansas for Medical Sciences, Grover P. Miller (GPM, a protégé of the “leading authority” in this field during those times, Fred P. Guengerich of Vanderbilt University) ridiculed my professional ability (saying I was reporting artefacts, and did not have good experimental techniques!) and disowned the data I generated in his lab as a postdoctoral researcher, reversed his decision of continuance (after the successful completion of the probation period) and illegally terminated my position with a back-dated document. This was after I proposed in a lab meeting that the data I got suggested a need to think beyond the conventional model for drug metabolism by CYPs. [He wanted me to see that the trans-membrane segments of CYPs and CPR (cytochrome P450 reductase) came together to bind for facilitating CPR→CYP e-transfer within the membrane. This was because of the external prospects for funding; in that NIH had prioritized membrane proteins and their interactions as a key agenda. I reported saying that I could not find evidence for such a hypothesis and that the catalysis occurred even if the proteins lacked the trans-membrane segments and the diverse topographies of the various CYPs and the lower mobility in lipid membrane rendered such prevailing ideas untenable.] Except for Hager’s lab, other PIs/academicians I worked for in USA seemed to espouse a policy that a research associate should be a “mere data generating machine” and not express one’s views as a thoughtful scientist or attempt to change the prevailing explanations! With little options left, I communicated the “PI-disowned works/ideas” as a preprint *via* Arxiv so that the research community could benefit. Soon thereafter, Arxiv administration withdrew the preprint unilaterally, first stating that it was due to “complaints of misuse of institutional affiliation” and then projecting that it was I who withdrew the preprint (text highlighted in the yellow boxes in the top of Fig. 2). Two major issues here: If my works were bad and if I did not belong to UAMS, one wonders how or why then the very same GPM should acknowledge my affiliation and contributions in his *Archives of Biochemistry and Biophysics* paper published during the very

same period (the boxed panel at the bottom of Fig. 2). While I can understand the outlooks of GPM (as one resulting from his insecurities of a non-tenure tracked faculty with a family to support and his mediocrity to stick with the hierarchy-imposed consensus at the expense of his conscience), I totally fail to see how/why Arxiv should falsely proclaim that I withdrew the preprint. (This is no typo on their part, but is deliberate as you can see that it is entered twice manually. Also see that if someone searched for my works on Arxiv, the public access to my preprint on drug metabolism is diminished by the summary heading that the preprint was withdrawn by the author himself, as shown in the bottom of Fig. 1, and as highlighted in the top of Fig. 2.) When I tried to reach Arxiv personnel, a concerned one dismissed me as though I were some miscreant and did not consider any of my submissions in this matter. Also, while the second version was available for downloading as a pdf file for some years, it was removed later (as seen in the top-right panel of Fig. 2). I am quite sure that this is NOT the spirit or outlook (wherein the Arxiv administration supported the ‘misplaced interests’ of fellow-American(s).) for which Cornell University’s patrons/donors supported Arxiv.

Almost a decade later (in 2015), I went to USA, to attend some conferences and spread my new model of CYP-metabolism. [Actually, I had procured the VISA to attend the function honouring the persona and works of my mentor, Lowell P. Hager (who had passed away in 2014), but the processing took too much time!] I had sent my group’s CYP works to PLoS One (2014) where the arbitrating (or arbitrary?) academic Editor Elena Rozhkova (Argonne National Lab) rejected the paper when a balanced assessment of the four reviewer’s inputs indicated an overall mandate for publication. Dejected, spending quite a fortune (given that I was unemployed then and the Rupee-Dollar exchange was unbelievably skewed!), I went to attend the 45th Gordon Research Conference on Drug Metabolism at Holderness (GRC, July 2015; chaired by Michael Zientek of Pfizer and Kim Brouwer (North Carolina, Chapel Hill); which was also attended by the current Chair of ISSX, Scott Obach of Pfizer and the 2023 GRC coordinating group of Cyrus Khojasteh of Genentech); and the 20th North American Meeting of the International Society for the Study of Xenobiotics (ISSX, September 2015), headed by the seasoned personas of John Miners (Australia), Geoff Tucker (Europe), James Halpert (USA), etc. I was set to present a poster at the GRC and the organizers promised exciting one to one interactions with the participants and speakers before the registration. At the venue, however, when I sent a personalized email to some of the P450

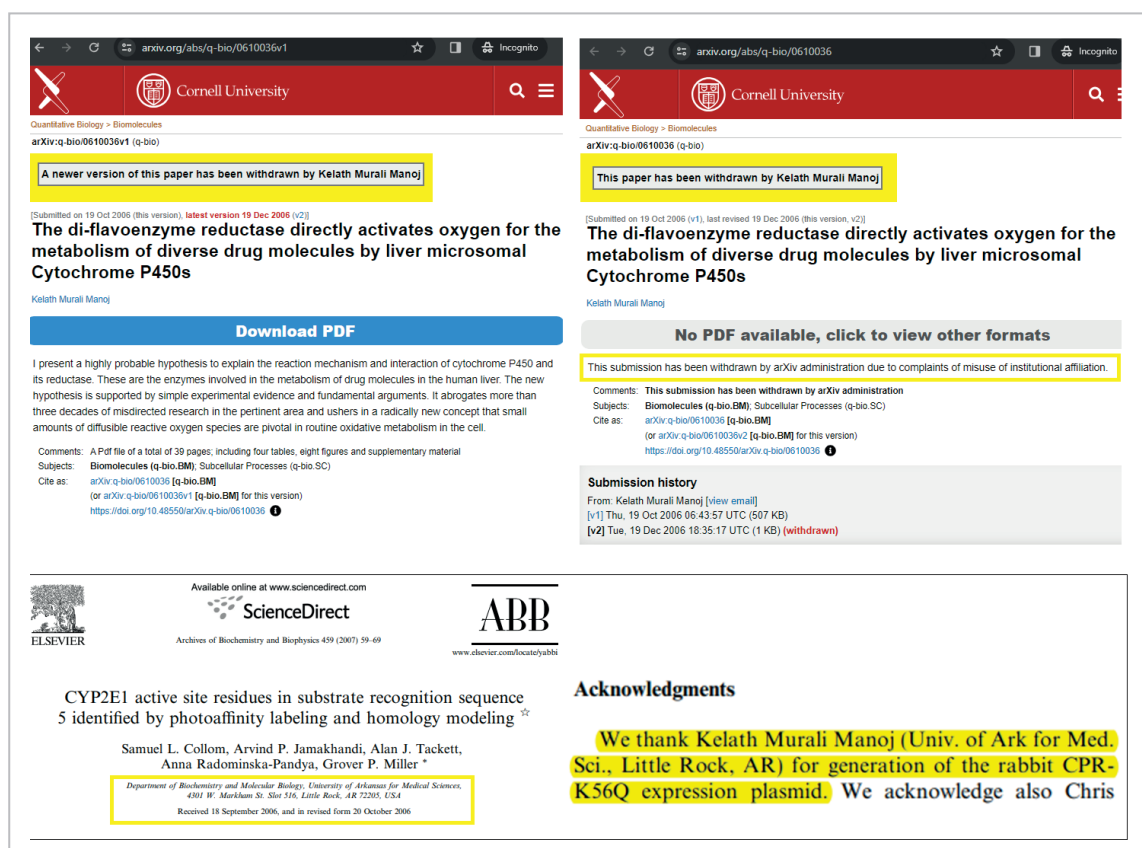


Figure 2. Anecdotal evidence of how some elements of the American system supports its own misplaced individuals, overlooking the visionary outlooks of the earlier open- and constructive-minded individuals. The pertinent Arxiv links are <https://arxiv.org/abs/q-bio/0610036v1> and <https://arxiv.org/abs/q-bio/0610036v2> and GPM's acknowledgment of my tenure and works in his lab at UAMS is: <https://doi.org/10.1016/j.abb.2006.10.028>.

researchers at the conference (informing them briefly about my poster and research; as seen in the email snapshot below in Fig. 3), I was quite taken aback by the unpleasant response from the organizers.

Mike Zientek (the Chair, who was all peachy and pastry before the registration), assumed a cold and coarse tone, chiding me for reaching out to the participants and shamelessly told me that such things are “faux pas”! Yet another senior participant also reflected Mike’s opinion to me in person. When I politely inquired of them what was the objections of the people I wrote to or what was my ‘mistake’, Mike informed me that email addresses included in the program brochure are not for misuse! The other senior person just looked at me as though I was on a visit on planet Earth from Andromeda galaxy (with an expression “duh!”, kind of communicating that I was a dud one who did not understand the couth ways of conducting oneself in polite spheres or research ambiances.). To cut a long story short, some that came to my poster went with their eyes

open and jaws down, a few expressing excitement and shock; but most went just blank. The seniors and well-known names avoided me and my poster like the ambiance was infested with plague or I was infected with the eradicated smallpox. But there were two pleasant developments, one in the middle and one in the end. Gabriele Cruciani (invited speaker from the University of Perugia and his company of Molecular Discovery), who responded in a very pleasant and introspective way to my forthright query regarding his extended molecular dynamics work on how CYPs open up to accommodate their substrates- “Don’t you think these simulations are highly unreal and far-fetched?”. He looked beyond for a few seconds, looked down for a few more, and then looked into me to say something that rang to this tune: “You know what, you are right! I do this because people expect me to do it!” Thereafter, we spent the remaining conference tenure together, discussing the findings. Paul Hollenberg (Michigan), said a clear and unconfused “Yes” in response to my query if the murburn

From:satyamjayatu@yahoo.com; **To:**khojasteh.cyrus@gene.com; Tue, Jul 7, 2015 at 10:57 PM
Subject: Murali, a REDOx researcher and fellow GRC attendee, seeks inputs

Dear Colleague,

As a fellow (drug metabolism / redox enzyme) researcher and GRC attendee, I seek your kind attention and inputs. Last year, my group's elaborate paper on CYP mechanism was unfortunately rejected at PLoS One, in spite of the fact that the manuscript secured favorable reviews from all the four peers it was sent to! I had contacted the Chair of GRC-Drug Metabolism regarding this. He has afforded me an opportunity to present a poster on my (group's) works and I am thankful for this important opportunity to interact with you.

Since the past several years, many key observations and interpretations in the research area have forced me to form ideas that counter some of the prevailing hypotheses. Given my experience with IConP450s & ISSX-DMPK, I am apprehensive that the time window may be too small for me to do justice to more than a decade's work with a poster's time and exposure (at GRC-Holderness). Therefore, I would like to present you my (group's) unpublished works, which is summarized by the poster (titled- **Challenging the prevailing understanding of CYP reaction mechanism**) and it is further explicated by the three pdf files (pre-final drafts; each manuscript details the first three respective points of the poster) - all attached herewith. (A few relevant published works from my group are available at the Google Scholar Citations link given below.) Eagerly, I solicit your critical inputs (either in person or through mail / phone) to show me where I could be misplaced in my scientific pursuits. If you think my (group's) works are enlightening, I would request you to provide me support / encouragement so that the work may get published and my (group's) exertions could have some continuity in the future.

With regards, Sincerely and hopefully.....

Murali.

Phone No. in US: 732 881 8732

https://scholar.google.co.in/citations?hl=en&user=gVBtBHYAAAAJ&view_op=list_works&sortby=pubdate

Figure 3. See for yourself if there is even one misplaced word in the email I had sent to fellow attendees at the GRC-Drug Metabolism in 2015.

model could explain the outstanding results of his pursuits on CYP-mutations.

Yet, the very same organizers and participants continued on with the disregard for the murburn model for drug metabolism, even after it was published the next year in *Frontiers in Pharmacology* (2016), quoting 50 specific trumping points where the classical model failed and murburn model held valid. I recollected Lowell's words on record (he was the discoverer and authority on chloroperoxidase, also a P450), wherein he had said prophetically on November 17, 2006, after my presentation in Steve Sligar's lab at UIUC, on my new model of drug metabolism: "*Just because you are right, these people will not discard what they worked on for their lifetimes*" He had then sent my works to Paul Hollenberg for his expert comments. Paul wrote back in secrecy, sealing his views and preventing me from using them. After this, Lowell too resigned at the predicament but supported my ideas thereafter, until his

demise in 2014. Although one of the attendees had confided to me (in private!) that my findings and proposals were bang on, Steve Sligar (November 2006) had said this, in response to my clear cut experimental findings and theoretical ideas (prepped for the talk by Lowell and other colleagues, Edward Conrad & Alex Scheeline): "*Don't shoot for the Nobel. See if you can publish your work in the next 15 years!*" Steve, I did publish it, not just that, but plenty more..... But did you note it turn around to make amends?! Neither did Fred Guengerich, with whom I sparred twice (in person), in the 15th and 16th International Conference on Cytochrome P450s (IConP450s) held in 2007 and 2009 at Bled, Slovenia and Okinawa, Japan, respectively. He seemed to have learned little and misdirected many (although, he did contribute a lot for the CYP field!) through the almost centum semesters he lectured on CYPs at Vanderbilt (and elsewhere), as I could note from his non-constructive lifetime memoir in *JBC*. I

wrote (then and later on too) about my ideas and findings to all the big names and most of the “in vogue” and even decent-profiled in the field then: Tom Poulos, Minor Coon, Paul Ortiz de Montellano, John Groves, Martin Newcomb, James Halpert, Jashvant Unadkat (who also visited my poster in 2015), Amin Rostami-Hodjegan, Swati Nagar, *etc.* and realized that few of them cared for a holistic picture or wanted to question their own stance. Undaunted, I also wrote painstakingly to the members of ISSX/Icon-P450/American Society of Pharmacology and Experimental Therapeutics (ASPET), *etc.* during the first decade of this century. (I could get their emails from the Conference brochures I attended.) Hardly anyone responded. In these efforts, only Tom Poulos (Irvine), Alexander Scheeline, Robert Gennis & G Govindjee (UIUC) and John Groves (Princeton) wrote back and offered any meaningful interactions. (But they too looked out to completely avoid conclusive data/arguments that questioned the classical outlooks! I do acknowledge that Fred Guengerich and Gary Yost shared some plasmids, of which the latter one’s preps worked for us. When I wrote to Guengerich’s lab for clarifications, didn’t receive any.) Others did not respond, and most appeared to be happy with their piece of pie and did not want to solve anything SERIOUS of genuine consequence. The scenario was so bad that Emily Scott’s doctoral candidate Sarah Burris-Hiday spent a good amount of time chasing wild goose in order to trace evidence for CYP-CPR complexation (along the lines of Ayyalusamy Ramamoorthy’s proposals), only to fail time and again! (I came to know about this via an MECC event later. Ayyalusamy Ramamoorthy, no wonder, did not afford me any chance to defend my writings on mitochondrial bioenergetics when he assumed the Editorial role in *Biophysical Chemistry*! It’s a small world. ...). Not only do they not open up their eyes (I tried to interact with Emily, but she conveniently waded past my queries and comments. Too busy or too scared?!), they drive their students into wild goose chases. (Two names mentioned in this manuscript said things that amounted to this: “*If you can convince Fred Guengerich, we will also turn around.*” Why don’t these folks stand on their own legs, I wondered and conveyed it to them publicly. Then I realized that they were mere props/decoys placed there by the powers that be.) Also, it was really a small world and all the big names in the CYP field and many in mitochondrial/chloroplast bioenergetics were some way connected and/or networked or also with the big names in my own *Alma Mater*: (UIUC, a key centre of American redox biochemistry research for a long time, from the earlier

to later part of 20th century. The names of redox enzyme pioneers like Irwin Gunsalus, Minor Coon, Rudolf Marcus, Paul Hollenberg, Steve Sligar, Robert Gennis, Antony Crofts, Govindjee, May Berenbaum (the current head of NAS), *etc.* are somehow or other connected with UIUC.)

When I had reported to my Principal Investigator Jeff Jones at Washington State University (2005) some discordant findings and ideas, this is what he said, “*You cannot change the working hypothesis in the field. Look at what happened to Martin Newcomb! He is no more respected....*” [Martin Newcomb (UIC), based on DFT calculations, had postulated that Compound I (the purported active-site species purportedly catalysing John Groves’ oxygen-rebound mechanism at the distal heme site) lacked the potential to hydroxylate unactivated carbons like that of alkanes. He was right and the community was wrong!] Thereafter, several years down the lane, I realized that I too was destined the cruel fate of Daniel Arnon in Photosynthesis research, the predicament of Gilbert Ling regarding his crusade against ion pumps, *etc.* Things all fit into the picture if you just understand the scenario as below. You just cannot shake the apple cart of the consensus-minded Apollonians. They are here to secure grants, live a cool life training students systematically, publishing papers in ivy-league journals, and do all the catchy things that would put them in the limelight. But they will not, I guarantee you, they will not question the powers that be, regarding the major issues of own or other’s belief systems, when challenged with emerging or discordant data. It will be conveniently buried as an artefact, and only cherry-picked data that conform would be reported/interpreted. They could, however, split hair and spar over trivialities. Therefore, the *status quo* continues till date.... In the summer of 2023, I presented the murburn model again to Cyrus Khojasteh, now a Senior Director at Genentech, just before their group chaired the year’s GRC at Holderness. After an hour of interaction, there was no disputation or refutation. He said there are difference of opinions, and we continued to live on this planet, he going on with his group’s misplaced ideas. The greater than trillion drug industry and its regulating bodies continue to have wrong notions for optimizing drugs. (In the passing, however, Cyrus was thoughtful enough to ask me how then they should go about doing their CYP works. Would he ask me that, if I were to have muttered some misplaced and illogical mumbo-jumbo? I don’t think so and neither did he. The fact is that the powers that be keeps them all bounded in mediocrity.)

ONTO MITOCHONDRIAL OXIDATIVE PHOSPHORYLATION AND BIOENERGETICS

Now, I would like to bring the time counter to an event last year, with the AAAS supported editorial of *Science/Science Advances*. In all, I sent in 8 eLetters (all prepared in a constructive and professional tone, in accordance with their policies and guidelines) in the field of bioenergetics. Of these, none of the ones on recent research articles that addressed mitochondrial oxidative phosphorylation (particularly regarding the high profile Judy Hirst and Leonid Sazanov groups) were published. Only 3 eLetters that dealt with thermogenesis were published and they were taken off (after being online for weeks or months). Two (which dealt with older submissions from relatively lower profiled research groups) were brought back after I wrote to the journal office. Please see the communication on my group's missing eLetter on Kunji Group's (MRC-MBU; Nobel Laureate John Walker's

institution) paper on uncoupling protein that was taken off after two months online! (Evidence for publication is presented in Fig. 4; and anyone visiting the webpage now can see the journal quoting that eLetters were not published for the article!).

The AAAS editorial responded to my frantic communications only after 2.5 weeks, which is presented along with my response in Fig. 5. The journal editorial unabashedly advises that one should write to the original authors first (as though publishing in *Science* makes the authors the ultimate authority and it is not the responsibility of the AAAS portal to keep things accountable at their end!). (BTW, I am thankful to AAAS that at least two of my eLetters are still online, although those papers would not be getting many hits now! It is to be noted that the authors of these papers did not offer any rebuttals to these eLetters either!)

The fact is that I had written to many MRC-MBU (UK) people many times over the last several years with the details

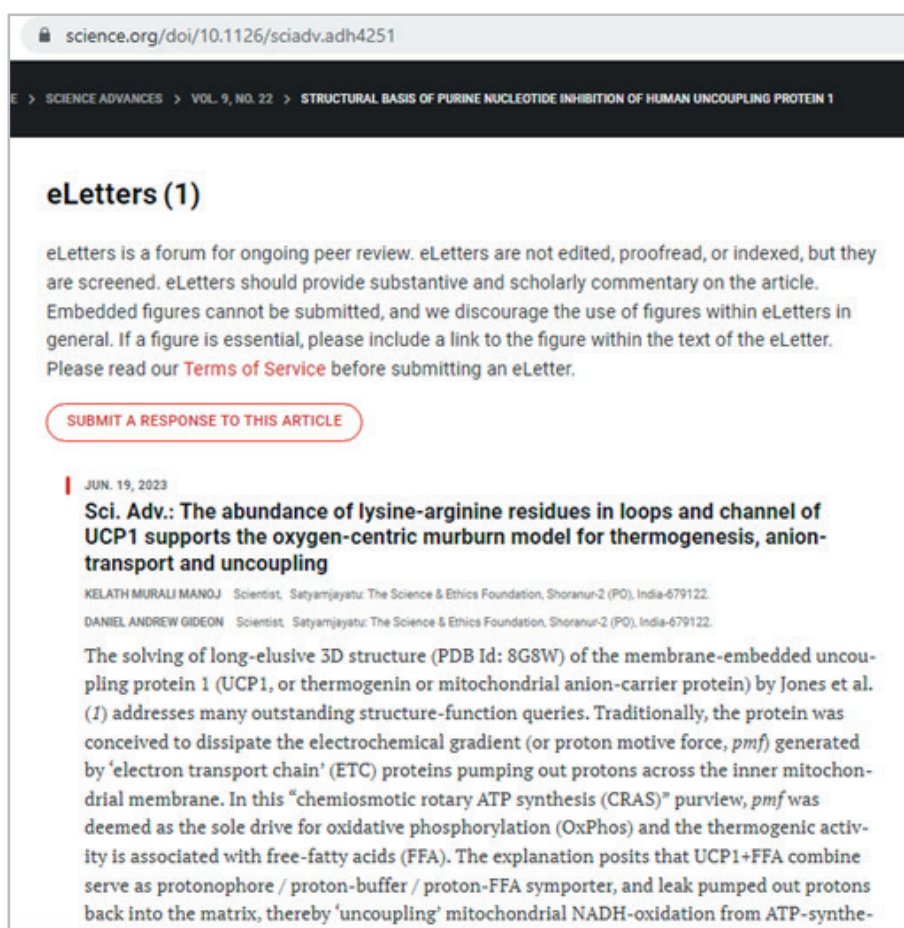


Figure 4. The originally published eLetter in *Science Advances* in summer 2023 (<https://www.science.org/doi/10.1126/sciadv.adh4251>) for Kunji group's structural insights revealed on uncoupling protein that was unilaterally retracted, without due notification.

On Wednesday, August 23, 2023 at 08:07:16 PM GMT+5:30, Laura Remis <lremis@aaas.org> wrote:

Dear Dr. Murali,

Apologies for the delay, I have been traveling for conferences. After further review of the eLetter comment on adh4251, the editors found it not suitable as per the requirements of an eLetter, as this was written as an opinion piece and they felt it too self-promotional regarding the particular view. They did not see any factual evidence relating the comment to the article published and said that the eLetter comment would should be a standalone opinion piece published elsewhere; therefore, it was removed from our website and we won't be considering reposting it.

The editors will review your additional eLetter submission on the separate article as soon as possible. If it passes editorial review then it will be posted. We will try to work on that very soon.

Thank you,

Laura Remis
Managing Editor
Science Advances | AAAS
<https://www.science.org/journal/sciadv>
<https://twitter.com/ScienceAdvances>

From: Murali <satyamjayatu@yahoo.com>

To: Laura Remis <lremis@aaas.org>; Holden Thorp <hthorp@aaas.org>

Cc: Dnl Ndrw <dnlndrwster@gmail.com>; Murali Manoj Kelath <murman@satyamjayatu.com>

Sent: Wednesday, August 23, 2023 at 09:04:30 PM GMT+5:30

Subject: Reg: eLetter missing online DOI: 10.1126/sciadv.adh4251

Ms. Laura Remis (Managing Editor, Science Advances) and Dr. Holden Thorp (EiC, Science Group of AAAS):

Our arguments were professional and qualitatively/quantitatively supported by the data that Kunji group (MRC-MBU) brought forth (<https://www.science.org/doi/10.1126/sciadv.adh4251>), which gel with the theory we advocate, published over the last 5 years via dozens of research papers in decent international peer reviewed journals (some of which were duly cited). Our works had showed that the chemiosmosis view that Kunji group used to interpret their findings with uncoupling proteins in mitochondria is erroneous/redundant. Your contributors had received two weeks to respond to the eLetters and it is a pity that they could not bring themselves to rebut the simple/straight arguments we presented! Our write-up was in line with what an ongoing peer-reviewing eLetter is about and as per your own published guidelines, which was why it was published in the first place. The sequence of events indicate that you took our eLetter off the portal *after two months online* only because you were pressurized from outside. I doubt whether you would publish my eLetters to recent papers, particularly from influential groups (like that of Judy Hirst of MRC-MBU on whose work my undecided eLetter submitted still rests with you: <https://www.science.org/doi/10.1126/sciadv.ad11359>), as it would make your journal/contributors look uncompetitive and misplaced.

The removal of my eLetter without informing me reflects no transparency or communicative logic/courtesy at your end. Also, it shows serious disrespect for your own professed policies, procedures and decisions.

Sincerely,

Kelath Murali Manoj
Satyamjayatu: The Science & Ethics Foundation.

Figure 5. The unabashed and high-handed response of AAAS editorial and my counter pointing out their unaccountability .

of my works and only Prof. Walker responded stating that he had “difference of viewpoints and I should let the scientific community decide in due time”. The authors of Kunji group did not (or rather, could not!) respond to the criticism of chemiosmosis interpretations (when they have options to do

so, as the journal office contacts them for the same!). Why would they, when the journal colludes with their interests in such a blatant and shameless manner?! (I had written to Jeremy Berg, AAAS-Chief, on my findings, and nothing happened!) Does AAAS stand for Advancement of the Affluent and their

Associates in Society, I wonder! The impunity with which such agencies work leaves one with paranoid distrust, as they don't seem to respect their own policies, procedures and decisions. It is such outlooks at the ivy-league helms that foment reactive Marxian sentiments in even some of the thoughtful workers that don't believe in anarchy. What the elites clearly show here is that absolute power leads to absolute corruption. (In this context, the American *Science/Science Advances* is slightly better and I would not even mention the British *Nature/Nature Communications*! In these times of openness, the latter doesn't even afford a forthright presentation of a critical antidote adjacent to its published articles! And we deem these as the most competitive/prestigious journals? It is time that we shake things up a bit, given the decadence that is setting in....)

None of the following leading researchers that I wrote to (individually and in the collective!) responded: David Nicholls (Buck Institute), Stuart Ferguson (Oxford), Chris Moser (U Penn), Leslie Dutton (U Penn), Peter Hinkle (Cornell), Martin Klingenberg (Med. Muenchen), Martin Brand (Buck), Richard Porter (Trinity), Andrei Vinogradov (Moscow), Judy Hirst (Cambridge), Leo Sazanov (Austria), Peter Graeber (Freiburg), Pietr Borst (Netherlands), Ulrich Brandt (Netherlands), Werner Kuehlbrandt (Max Planck), Maojun Yang (Tsinghua), So Iwata (Imperial), Gary Ceccini (UCSF), Antony Crofts (UIUC), Vamsi Mootha (Harvard), David Sinclair (Harvard), Pere Puigserver (Harvard), Marcia Haigis (Harvard), John Walker (MRC)- when I floored the following four fundamental arguments against ETC-CRAS (Electron Transport Chain – Chemiosmotic Rotary ATP Synthesis) paradigm:

1. *The distribution density of the respiratory Complexes is $\sim 10^4$ per mitochondrion and a mitochondrion would have only ~ 10 protons within. The EPCR hypothesis seeks a conservative requirement of $\sim 10^5$ protons in the mitochondrion, at a given instant! Neither a dynamic flux of protons nor intrinsic buffers could provide the needed protons. Invoking such ideas would not only counter the “closed system” perspective that Mitchellian postulates seek, it (dynamic flux or buffer) would also negate any chemiosmotic proton-gradient that would purportedly be formed. The flux or buffer cannot intervene only in a “wishful/vectorial way”.*

2. *More than half the electron transfers of 54 steps needed to form one molecule of water are unfavourable. This scheme cannot explain the rates of water formation or protein distribution/arrangements. Besides, with the current explanation, there is no real role for oxygen and it is purely a wishful idea that oxygen would (only) stay bound to Complex IV!*

3. *Chemiosmosis is a total humbug, in terms of logic or energetics. There are no protons to pump out, and even if there were, the energy spent to pump protons out (even if they were plenty of them!) cannot have any feasible way of being harnessed. Further, the current schema of energetics don't account/add up.*

4. *“Rotary ATP synthase” activity cannot explain the kinetics observed. Input of energy cannot be used to alter F_1 's affinity from ATP to ADP! This is purely wishful thinking. (Also, fruit can be put into a juicer to get pulp and juice; and putting in pulp+juice cannot give fruit. Therefore, Complex V cannot function as a rotary synthase. It may work as a rotary ATPase.)*

Some others, like John Rubinstein (Toronto) would rather mock murburn concept and its advocate (when I wrote to *Nature Communications* after he published some work analysing Complex V's rotary prowess!) over Twitter with his friends and some of the flibbertigibbets would hop along in this vain bandwagon (Fig. 6). The sad part is that none of these would bother to revert and spar with any zeal. They just proceeded to delete the Twitter interaction and perhaps, nonchalantly got on with their redundant agendas!

By now, I have commented and responded to hundreds of Twitter posts, YouTube videos and media (LinkedIn) postings by commoners, experts, journalists, etc. Very few bother to respond and even if someone does, they do not go beyond one exchange. Scientific arguments and exchanges cannot be resolved so quickly. People have to bite their differences down and continue with the interactions so that there is a chance for people to see each other's points. The ‘dealership’ knows this and so, they enjoy the status quo!

FIRST BLOOD DRAWN, IN A DIRTY WAY!

The first blood has been spilled. Some months back (Fig. 7), I discovered to my dismay that some Cambridge University personnel (Patrick Chinnery of MRC-MBU?) had deliberately defaced the Wikipedia site for murburn concept. An earlier defacing had left behind irrelevant citations (the defacer had wrongly cited that my own work had discredited murburn concept!) and the “correction” after a few months used the very same sentence but added were some recent ivy-league publications that did not refer murburn concept or any associated ideas thereof (while claiming that murburn concept was discredited!). Why are her majesty's servants stooping so low (and ordering others that people should respect their graffiti over others' own walls?), one wonders! Feeling the heat are they?

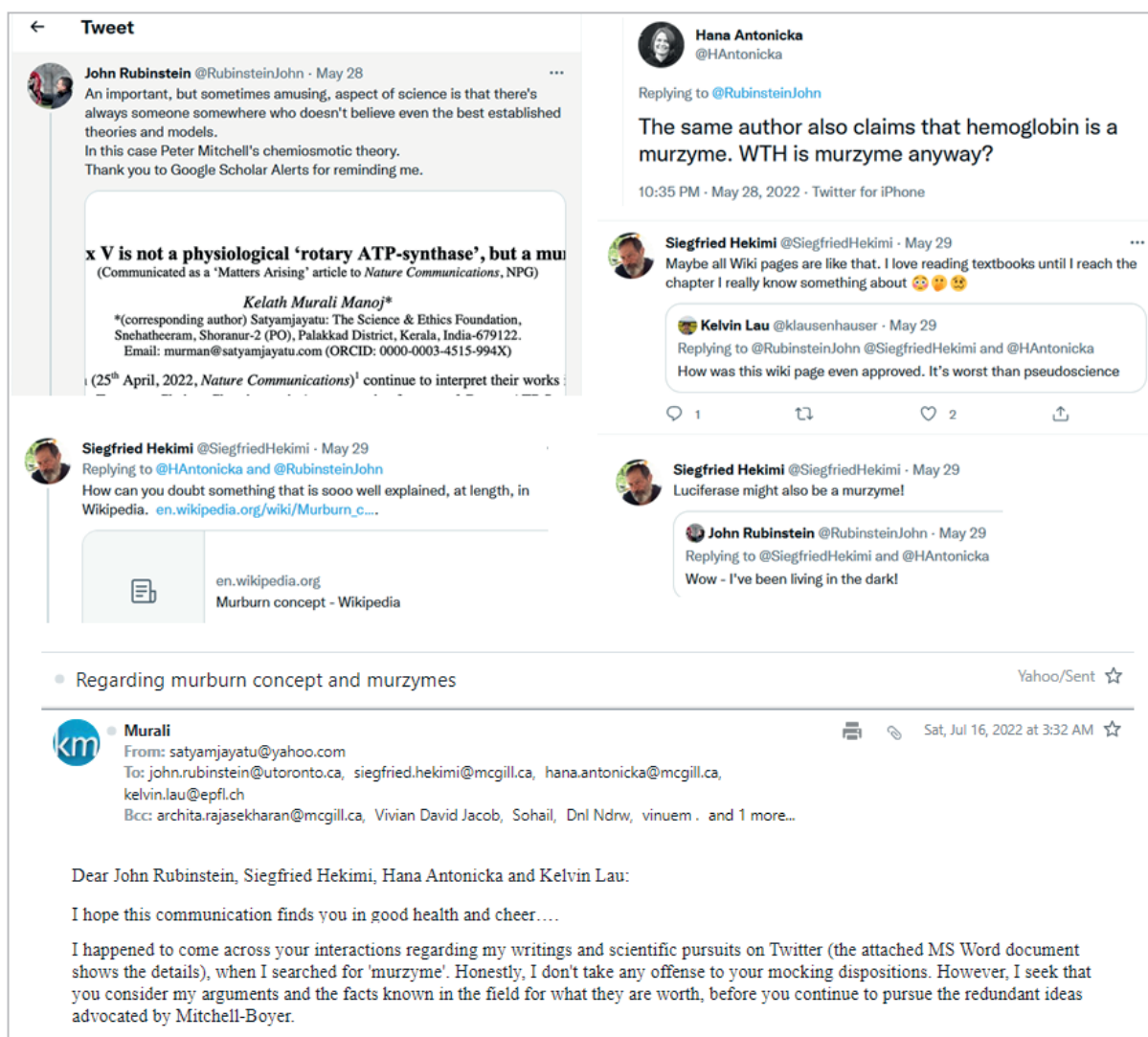


Figure 6. Murburn concept being mocked! See how I responded... they did not get back, and just wiped out the tweets!

AS 2023 TURNS INTO 2024, MURBURN CONCEPT IN THE VIRTUAL WORLD AND IN INDIA

When a question was asked of ChatGPT regarding alternate theories for chemiosmosis and murburn concept, the return showed the following print out (Fig. 8). One wonders how/ why even the 'machine intelligence' being disciplined to strait-jacket scientific inquisitive spirits.

While the commoners in my country have shown great interests, the leading scientists and governmental authorities have been showing mixed responses or been their lethargic selves. While CSIR and ICMR have responded positively, DBT and DST have not yet shown any responses to my initiatives. I have presented murburn concept at leading Indian institutions

and universities [IISc, IITs, IISERs, JNU, NEHU, CUSAT, etc.], several colleges in countryside Kerala and Tamil Nadu. Organizations [e.g. Swadeshi Science Movement (Kerala) and Vigyan Bharati] have invited me to present talks, whose recordings are available online (<https://www.youtube.com/@satyamjayatu5613/videos>). It is heartwarming to note that this year, murburn concept will be taught to undergraduate and postgraduate students. I was quite pleasantly surprised to discover that the primary nutritive assimilatory process was traditionally labelled (in Indian scriptures like Charakasamhita, Gita, Upanishads, etc.) "jataragni", "dahanam", "dehagni", "kayagni", etc.; all words connoting to fire/burning! These implied the cultural/traditional basis of murburn type thoughts in the Indian subcontinent, even before my own inception.

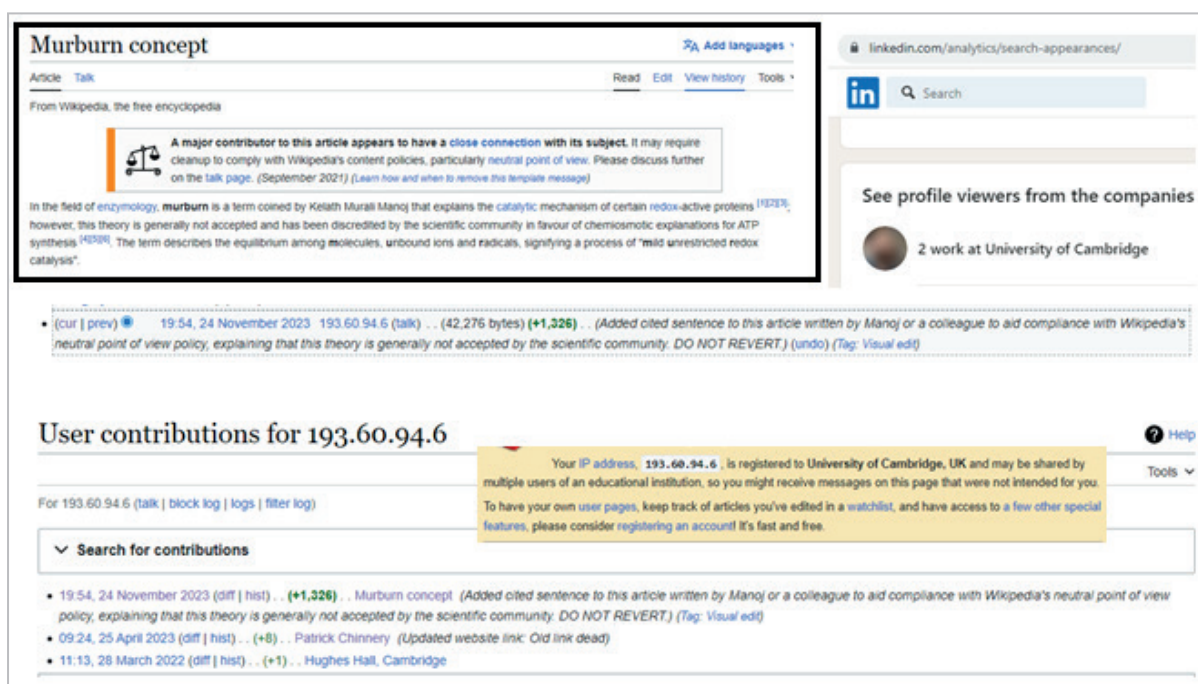


Figure 7. Cambridge folks ‘standing up’ to deface murburn concept, for it is their “pioneering ion-pumping idea” championed by the stalwarts like Hodgkin-Huxley-Katz-Mitchell that is going down the drain! (Nobels are very much under the control of the British, one is inclined to think! How else could so many Nobel Prizes be misplaced, one wonders.)

(Also, the philosophical basis of origin of life’s order from chaos at birth, its sustenance through life and its ultimate cycling back to disorder *via* murburn at death is profound.) Most importantly, a two-day Workshop on murburn concept was conducted at IIT Bombay in March 2023 which was modestly attended by participants in physical venue and online (but which was boycotted by the Bioscience & Bioengineering department there)! No wonders why!!

THE SILVER LINING TO THE LOOMING DARK CLOUDS

I wrote to the editorial board members of the thrust area’s specialist journals- *Journal of Bioenergetics and Biomembranes* (Springer) AND *Biochimica et Biophysica Acta – Bioenergetics* (Elsevier).... Not one responded. [Thereafter, I received instantaneous rejections to the submissions at Susanne Arnold’s (BBA) end but Patrick Stanton (JBB) did ask me to review one of the papers submitted to his journal.] Only *BMR* showed guts to permit “debunking” against the Mitchell-Boyer hypothesis. (One senior clearly told me that “you kissed your future goodbye”, for using “debunking”.) Later, when my collaborator sent paper to another journal, one wrote that Pedro Silva (a detractor who came out in the open

and defended my attack on chemiosmosis) had pointed out flaws in murburn model. It is quite another thing that Pedro Silva was not willing to come out in the open regarding the sparring emails we exchanged later. He called me names and closed interactions. Wrote to Sunil Nath, a researcher with alternate explanations in the field... He never responded but chose to call me names in *Biophysical Chemistry* (which that journal conveniently published but did not give me an opportunity to defend.... Why can’t professionals debate and defend their viewpoints? Why do they feel so triggered like “*Mimosa pudica*”? When I wrote to many other small or big time journals (*Nature*, *Science*, *EMBO J*, *Mitochondrion*, *Frontiers in Physiology*, and a list of other redox biochemistry journals, too numerous to list here!), the responses were often very disillusioning, making one question self: “How can these people say that this work is not something to be of potential interest to their readers? How can they say that the write-up is disrespectful to others? How can they say that it did not score high in their rating as the subject was too specific?”

However, although I faced several such anecdotal/experiential biases and many “systemic hitting below the belt” to clamp down scientific advancement through new perspectives’ disseminations and critical discussions, it is

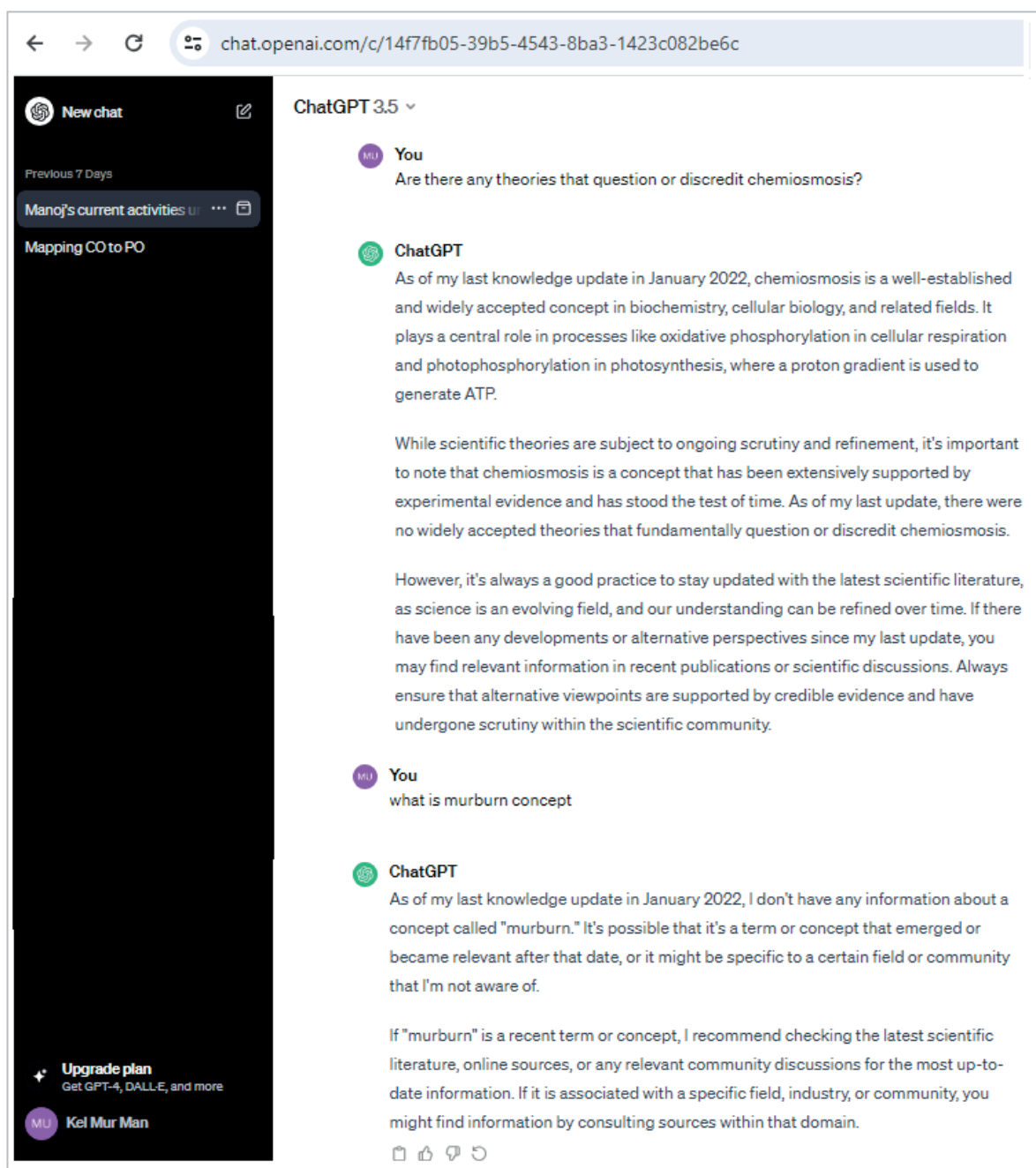


Figure 8. Query outcome on alternate theory for chemiosmosis gives nothing and same is the status with a query for murburn concept.

also a fact that some editors and reviewers of several reputed/indexed standard journals (established in 1900s) supported and permitted the publication of our paradigm shifting works and ideas, deeming murburn model to be a tangible/tenable theory for diverse routine cellular processes: *Biochimica et Biophysica Acta (General Studies / Proteins / Biomembranes)*, *Analytical Biochemistry*, *Biochemistry*, *Biochemical and Biophysical*

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Research Communications, Cell Biochemistry & Biophysics, Biochimie, Biomedical Reviews, Journal of Biomolecular Structure & Dynamics, Archives of Biochemistry & Biophysics, Biophysical Chemistry, Toxicology, Biomolecular Concepts, Current Drug Metabolism, Progress in Biophysics & Molecular Biology, Cell Biology International, Cell Biochemistry & Function, Journal of Cellular Physiology, etc. Also, decent

publishing houses or professional bodies started at the dawn of this century (with the onset of the open-access revolution) have served as popular portals of dissemination of the new ideas (wherein the publication process did not incur any financial transactions like “article processing/publishing charges”): *PLoS One*, *RSC Advances*, *In Silico Pharmacology*, *Frontiers in Pharmacology*, *Biochemistry Insights*, *Dose Response*, *Intech Open*, *Thalassemia Reports*, etc. The facts are that: (i) I have published ~70 papers in decent portals through an active research tenure spanning three decades, (ii) More than a dozen of the articles above were submitted post invitation by fellow researchers and/or afforded cover-page credits by unbiased editorial professionals, (iii) The two dozen original research (not review!) articles brought out in the first phase of my publication career (1996-2016) are decently cited (Google Scholar returns a total of >1.4K citations, giving the average of ~59 citations per article), and (iv) Some of my later articles and preprints (with traceable statistical metrics available), although not highly cited, have thousands of views/downloads [e.g. my published discrediting of the CRAS model of aerobic respiration in *Biochemistry Insights* is the most read article of the journal, with ~8K hits (which is ~half of the amount of all of the articles’ totaled hits published on that portal!) and my preprint critique in *Open Science Foundation* portal on the Z-scheme model of photosynthesis has >3.4K hits!]. The data speaks well for my dedicated and quality-conscious pursuit. Further, in the last issue of *Biomedical Reviews* (1), a clear statistical correlation of murburn pursuits and the decline of classical bioenergetics terms (like chemiosmosis and proton motive force) was demonstrable. Also, while the organizers of several Conferences snubbed my works and persona, *Midwest Enzyme Chemistry Conference* organizers [MECC, wherein its founding visionary of Prof. Richard Silverman (Northwestern University) was supported in his efforts to get the MECC series going by my mentor, Lowell Hager] consistently allowed me opportunities to showcase the developments on murburn concept. Therefore, the lower citations of my later works with CYPs and mitochondrial metabolism is not owing to any lack of quality or lack of impact, but purely owing to the minority leadership and subsequent bulk stewardship of the respective research communities (and their orderly, almost cadre like maintenance!) by recalcitrant mindsets. Given this REALITY, I am not a loser lamenting on lost prospects but it is the harping of a victorious conqueror (or crusader) that serves the well-directed admonition to the erring community through this article. Publications in *Nature & Science* are not the only

yardsticks for one to set and alter courses, tracking published literature in one’s field and relying on one’s own common sense is more important! I must also say that some folks are kind and have come out in support of murburn writings (Fig. 9).

A CRITICAL WRAP-UP

Post the 2nd World War, Anglo-American political triumph saw their dominance in cell physiology field as well, and Nobel Prizes were given away to fellowmen to consolidate several misplaced ideas advocated by their coterie; and dissenting voices were silenced through ostracization, as exemplified by Gilbert Ling and Ludwig Edelman. (If you are a cell biologist/physiologist or biochemist and you don’t know who these scientists are, then it sort of proves my point.) The rationale of bioenergetics mechanisms of how cell powers itself and how electrophysiological phenomena are effected were highly contended in the middle of the last century. Before adequate controls and proper theoretical foundations could be laid, ideas such as Hodgkin-Huxley’s Na-K flux model of neuronal impulse propagation and Mitchell’s proton pump model for mitochondrial oxidative phosphorylation were given undue recognition. Spare a few dissenting individual voices, the majority of scientific community kowtowed to the dictates and fancies of the leadership, paying scant regard to the mandates of reason and the established laws of physics. As and when data surfaced that questioned the veracity of the ion-pump proposals, they were modified by the powers that be, to somehow become compliant with emerging mandates. (For example: When Mitchell first proposed the chemiosmotic proton motive force, the trans-membrane pH gradient required was 3 units. When Britton Chance showed demonstrated its infeasibility, even 0.3 units sufficed! We are talking about difference in many orders of magnitude here! Regarding stoichiometry of the magical “coupling mechanism”: earlier, it was proposed that 4 protons were needed for the synthesis of one molecule of ATP and one revolution of Complex V needed 12 protons. This was changed to 2.5 protons per ATP and less than 8 protons per cycle, respectively. Not just the quantitative aspects and equations governing their relations, even qualitative aspects were changed, e.g. Mitchell retained that Complex IV was not a proton pump, whereas some overzealous researchers saw it as one! Such details are not worth delving into here, as it is beyond the context of this discussion.) With quantitative arguments, my (group’s) writings have already discredited more than half a dozen Nobel Prize recognized ideas in the related fields, which are



Figure 9. Some favourable comments on murburn concept amongst the Twitter users.

enshrined in textbooks. These also render thousands of articles published in *Nature*, *Science*, *Cell*, *PNAS*, etc. redundant. With such a magnitude of change required, it is highly unlikely that someone who has used/taught something all his/her life would spontaneously change after learning that he/she is misplaced. (Again, Newton's first law applies in the sociological context.) I have waited and bided my time for quite some time now. I realize that the due recognition for murburn concept will come only by attacking the detractors of murburn pursuits. It might be needed to "rub it on their faces and plant our flags" in the most unceremonious ways.

My crusade is for the benefit of our future generations, saving lives and improving the longevity/quality of human life is at stake here. Agendas set for understanding diabetes/cancer/aging/neuroscience research, ADMET-DMPK studies, mainstreaming parallel medicine, etc. all need to reorient. If scientific pursuits were to be judged purely based on merit, my (group's) pursuits pave way for properly founding the contexts of the following fields:

1. Chemical sciences: Explaining the reaction chemistry

of respiration, photosynthesis, and thermogenesis (the bioenergetics of key routines that sustain life on the planet Earth).

2. Biological sciences: Explaining the role of oxygen/DRS in xenobiotic-lactate and hemoglobin-cyclooxygenase metabolism, electrophysiology (Na.K differential), vision/neuronal relay, bacterial motility, etc.

3. Physical sciences (along with Prof. Nikolai Bazhin of Russia & Laurent Jaeken of Belgium): Establishing the continuum of the laws of physics in cell biology and synthesis of theories on cellular powering, coherence, homeostasis, electro-mechanics, sensing/response, etc.

4. Ecological/Environmental Sciences: Recycling of lignocellulosics, natural halogenation of organics, etc.

Proclaiming these realities repeatedly is necessary for me to continue the struggle. "A crying baby has a greater chance of getting fed!", so goes the saying in countryside Kerala. I don't see myself a child, yet... This can be seen as a socially-dressed reaching out. Since the last fifty years, scientific progression in cell biology has primarily been in the genomic sides (cloning,

PCR, CRISPR, OMICS, cell culture, etc.) and application of murburn concept would give unprecedented understanding in bioenergetics. Therefore, one must up the ante from now on!

Two and two add only to four, not to three and not to five. There is no liberty, no freedom, no choice. The world of science owes a lot to Apollonians, who do the large amounts of bulls' work of generating systematic data and ensuring slow-steady progress. However, they cannot stifle the contributions and purpose of the few novelty-ushering Dionysians, only for maintaining their own vested interests (which is surely NOT only to myopically appreciate miniscule changes that fit into their agenda!). All the major ideas in science did not come around owing to consensus, but were rooted and stemmed from thoughtful individuals who staked their all to unravel the unknown. The Apollonian bulwark cannot render the unthought as the unsought. The Apollonians are cautioned that they will not just dwindle into the sands of time in ignominy without a trace of mention, the Dionysian will make sure

that their forthcoming generations will be reminded of their unscrupulous outlooks. This is not a matter of choice or freewill, it is a matter of conviction and direction. And people without constructive integrity do not deserve to be at the helms. Period.

SUGGESTED READING (AND REFERENCES CITED THEREIN!)

Kelath Murali Manoj. Murburn concept and murzymes in 2023: Celebrating 25th year of pursuit. *Biomed Rev* 2022;33: 1-15. DOI: 10.14748/bmr.v33.9115

Kelath Mural Manoj, *et al.* Murburn concept in cellular function and bioenergetics, Part 1: Understanding murzymes at the molecular level. *AIP Adv* 2023;13(12) id.120702, 22pp. DOI: 10.1063/5.0171857 & Part 2: Understanding integrations-translations from molecular to macroscopic levels. *AIP Adv* 13(12) id.120701, 23pp. DOI: 10.1063/5.0171860