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Unannotated Bibliography on the Evolutionary Origin of the Immune System

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Introduction

This webpage contains contains a bibliography of 357 references specifically on the evolutionary origin of the immune system. This list includes the 70 or so X

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Some simple statistics will also be used to describe the collection.

How the list was assembled

This list was assembled over several months. Beginning with the [annotated bibliography](#), articles were added to this collection if they were cited an informative way in an article in the evolutionary immunology literature, and if they appeared to be directly on or directly relevant to the evolutionary origins of immune systems. For example, [Hiom et al. \(1998\)](#), unintentionally neglected in the annotated bibliography, is repeatedly referenced in the evolutionary immunology literature. Other articles were included as they were gradually discovered in reference lists and database searches, based on an inspection of the title and/or abstract.

The references that were collected fell into several main groups:

1. Articles published after the *Kitzmiller* case
2. Articles repeatedly referenced by immunologists in the annotated bibliography
3. Articles by noted evolutionary immunologists that had evolutionary content upon inspection
4. Articles picked up in "Related Articles" searches on [PubMed](#), starting with articles in the annotated bibliography
5. A few relevant books and book chapters that were discovered or rediscovered after the annotated bibliography was assembled

Many of the articles in this collection have not been looked up, but the chances of "false positives" should be quite low, as the evolutionary relevance is usually made clear by the title and abstract, or by repeated citation in the literature.

Although this list of publications is much longer, it still cannot be considered

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1. The collection is still biased towards adaptive immunity and V(D)J recombination, although a great deal more comparative immunology has been included.
2. The collection is biased towards authors found in the annotated bibliography.
3. The collection exhibits a "pull of the recent", as recent articles are more likely to be accessible, more likely to be cited, and more likely to be listed in online databases.
4. Like the annotated bibliography, this collection is biased towards review literature rather than research literature.

Nevertheless, some interesting features emerge when the bibliography is analyzed quantitatively. In 1996, Michael Behe claimed that a thorough search of the scientific literature showed that the evolutionary emperor had no clothes. About the evolution of irreducibly complex systems in general, Behe wrote,

There is no publication in the scientific literature -- in prestigious journals, specialty journals, or books -- that describes how molecular evolution of any real, complex, biochemical system either did occur or even might have occurred." (Darwin's Black Box, p. 185)

This was in a chapter boldly entitled "Publish or Perish," which contains section headings like "The Missing Papers" and "Searching High and Low." Behe made a great show of searching biochemistry textbooks, the university library, and the journals, especially a detailed search through the *Journal of Molecular Evolution*, which occupies four pages of *Darwin's Black Box* (pp. 173-177). On p. 179, Behe wrote,

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evolution of complex biochemical systems."

Behe's famous assertions about the evolutionary immune system literature were quoted in the [annotated bibliography](#), but it is also worth noting that Behe cited a grand total of *five* publications on evolutionary immunology in the entire immune system chapter of *Darwin's Black Box*. They have been marked with an asterisk (*) for the reader's convenience. In his new afterword to the tenth anniversary edition of *Darwin's Black Box*, Behe cited exactly *one* additional immune system paper, [Klein and Nikolaidis \(2005\)](#), also marked with an asterisk in this list. Behe completely misses the point of the article, which is discussed in the [annotated bibliography](#). Behe's critique consists of, first, trumpeting the mere fact that the the authors use words like "probably", as if such qualifiers were not found in virtually every careful scientific publication. Apart from Behe, this juvenile tactic is only commonly found among the least sophisticated internet creationists. Second, Behe doesn't find enough mentions of the words he thinks he should find, cognates of "Darwin", "natural selection", and "mutation" -- Behe made [this same trivial critique](#) of several immune system articles at trial, and the problems with it were [exposed in short order](#) during Rothschild's cross-examination. Here, we can add that Behe's problem is that the immune system literature is too advanced for him -- general "mutations" are not discussed so much as the *specific kinds* of mutations relevant to the origin of the immune system, such as -- wait for it -- *transposition*. Regarding natural selection, entire articles, indeed entire careers (see articles by Cohn, Gould, etc.) have been devoted to studying, and often mathematically modeling, the selection forces that lead to immune systems, the diversity of immune system receptor genes, and the ways that various specific hypotheses can be tested by examining substitution ratios and other evidence. Behe seems to assume that if the first random article he reads doesn't start completely from scratch and educate him personally about everything going on in research labs across the country, then the article is worthless. The reality, on the other hand, is that any article

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Finally, Behe says that Klein and Nikolaidis admit themselves that this immune system evolution stuff is just speculation, because they suggest some experiments that have not yet been done, and without them "their scenario would 'remain hopelessly in the realm of mere speculations.'" But let's look at the actual concluding paragraph of the article:

The agnathan [jawless fish] genomes should bear witness to how close they have come to acquiring the AIS [Adaptive Immune System]. The closeness can be determined experimentally in two ways: by introducing agnathan genes into the gnathostome [jawed vertebrate] genome or the other way around. It should be possible to determine which changes are necessary for agnathan genes, such as the PSMB, ATP-binding cassette transporter, or CD45, to replace the functions of their gnathostome counterparts. In the opposite direction, introducing gnathostome genes such MHC, BCR, or RAG, into agnathan cells or animals should reveal to what extent the cells' or animals' physiology is "ready" for some of the functions associated with the AIS. Extant agnathans are, of course, evolutionarily far away from the agnathan-gnathostome ancestors, but this kind of experimental molecular evolution should nevertheless shed light on events that would otherwise remain hopelessly in the realm of mere speculations. (Klein and Nikolaidis, 2005, p. 174)

In context, it is clear that what the authors consider "speculation" is the detail of exactly how close the agnathan genome is to acquiring an adaptive immune system. In figure 2, the authors show that agnathans, which lack the adaptive immune system, nevertheless have 12 of the 16 key components of adaptive immunity that the authors identify, and in the conclusion the authors are simply wondering what would happen if a few more key components of the adaptive immune system were introduced into agnathans. Strangely, Behe doesn't take

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and therefore "cannot be produced gradually" because "it would have to arise as an integrated unit, in one fell swoop, for natural selection to have anything to act on" (Behe 1996, p. 39).

Regardless, Behe writes on p. 270 of his afterword,

Today the situation remains unchanged from what it was ten years ago. As I wrote in Chapter 8:

There is no publication in the scientific literature -- in prestigious journals, specialty journals, or books -- that describes how molecular evolution of any real, complex, biochemical system either did occur or even might have occurred. There are assertions that such evolution occurred, but absolutely none are supported by pertinent experiments or calculations.

(Behe 2006, p. 270)

With this in mind, let us examine the bibliography.

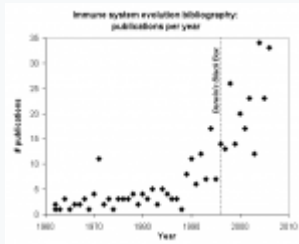
Quantitative Description

This bibliography contains 357 articles, books, and book chapters. Counting up the page numbers in the citations yields about 4,700 pages of material, not including the books which would total another few thousand pages. The citations have been arranged [chronologically and alphabetically](#)

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The number of articles in the bibliography published in each year since 1962 is plotted in the below graph. The number for 2006 was estimated by multiplying by three the number of articles available as of April 2006.



Number of publications per year found in this bibliography. Keeping in mind that the bibliography is probably biased against older articles, the general trend is still suggestive of a rapidly growing research field. The vertical dotted line represents the publication of Behe's 1996 book *Darwin's Black Box*

The bibliography was divided into two periods, the 34 year period from 1962-1995, and the 11 year period from 1996-2006. *Darwin's Black Box* was published in early 1996, and it can be seen that this bibliography contains 150 articles on evolutionary immunology published before that date. This is 39% of the collection. This seems to substantially weaken Behe's 1996 claims about the scientific literature. From 1996-2006, a further 236 articles were published, or 61% of the collection. This seems to contradict Behe's re-assertions of his claims in the 2006 edition of *Darwin's Black Box*.

By Author

The authorship of the articles can also be quantified. Academics know that every academic has a specialty, and that in order to be conversant in a particular field you simply must be familiar with the research and publications of the key people in that subfield. This bibliography contains 192 different first authors, and hundreds of additional secondary authors. Who are some of the leaders in evolutionary immunology? The top ten first authors in the bibliography are listed below, along with the number of times each of these researchers appears as an

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Author	No. articles (first author)	No. articles (any author)
Gary Litman	22	49
John Marchalonis	21	38
Martin Flajnik	13	23
Louis Du Pasquier	12	19
Masaru Nonaka	11	22
L. William Clem	7	14
Sir Frank Macfarlane Burnet	6	6
David Schatz	5	9
J. Oriol Sunyer	5	7
Melvin Cohn	4	6

The top ten first authors in the bibliography. The number of publications in the bibliography that they have first-authored, or coauthored in any fashion, is listed. All of these authors have written many more articles than just the ones listed here; see their linked webpages for publication lists and research descriptions. E.g., [Martin Flajnik](#), "My work is centered on the evolution of the immune system, with the major goal being to understand the origins of adaptive immunity...."

Although the top ten authors constitute only 5.2% of the first authors in this bibliography, they have first-authored 106 (30%) of the articles. Counting articles on which the top ten have been an author in any position, including first, they have coauthored *over half* of the articles in the bibliography (193, or 52%).

At this juncture, readers should ask themselves: has the ID movement grappled with the work of *any* of these researchers? Is the ID movement simply hoping that they can keep their supporters ignorant that numerous researchers are, daily, doing the work that the ID movement says doesn't exist? If the reader has followed the "intelligent design" movement for a substantial length of time, but has never heard of these researchers or their work, they should ask themselves if X

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By Journal

The top ten journals in the bibliography can be tabulated in a similar fashion:

Journal	No. articles
<u><i>Proceedings of the National Academy of Sciences</i></u>	27
<u><i>Developmental and Comparative Immunology</i></u>	25
<u><i>Immunological Reviews</i></u>	23
<u><i>Journal of Immunology</i></u>	21
<u><i>Nature</i></u>	20
<u><i>Cell</i></u>	12
<u><i>Journal of Experimental Medicine</i></u>	10
<u><i>Immunogenetics</i></u>	9
<u><i>Molecular Immunology</i></u>	8
<u><i>Science</i></u>	7

The top ten journals in the bibliography. The number of publications in the bibliography that they have appeared in each journal is listed. The top ten journals account for 162 articles, or 45% of the publications in the bibliography.

It is evident that the top ten journals in the list fall into two categories. First, immunology journals read by immunologists. This is not surprising, although it may surprise the reader to know that there is a whole journal devoted to comparative immunology. Of the publications listed in this bibliography, 192 (54%) are published in journals or books with a cognate of "immunity" in the title, while the rest are in a wide array of more general biology and science publications.

The second category found in the top ten list, of course, is prestigious general science journals (*Nature*, *Science*, *PNAS*, or the more specialized *Cell*, the most prestigious journal in cell biology). The ID movement would kill for just one ID publication in any one of these journals.

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searching for evolution articles, has *only one* publication in this *entire* bibliography. Behe pretends that the *Journal of Molecular Evolution* must be the primary place one would look for the kinds of articles that he seeks -- after all, "molecular evolution" is right there in the title! But if one understands the subtleties of academic tradition, one realizes that *JME* has tended to focus on slightly different topics such as gene phylogenies and molecular clocks. It is not necessarily the journal one would go to for everything involving evolution for any system, especially when fields like immunology have a set of their own journals, and save the really revolutionary stuff for *Science* and *Nature*.

The Implications

In the new afterword to *Darwin's Black Box*, Behe told his readers what should be expected "at an absolute minimum" for research on the evolutionary origin of the eukaryotic cilium:

It would take at least as much work to figure out how such a structure could evolve by random mutation and natural selection as it did to figure out how it works in the first place. At an absolute minimum that would be expected to result in hundreds of papers -- both theoretical and experimental -- many reviews, books, meetings, and more, all devoted to the question of how such an intricate structure could have evolved in a Darwinian fashion. (Darwin's Black Box, 2006, p. 267)

Admittedly, this level of research has not been conducted on the evolutionary origin of the cilium yet. Although Behe claims the cilium is well understood because the basic mechanism of microtubule sliding is understood, it is actually still a deeply mysterious structure, fundamentally tied to the centriole and the X

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blatant contradiction between Behe's lax scientific standards for understanding current cell biology -- on the cilium, he basically says, "The microtubules slide past each other, what else is there to know?" -- and his ridiculous scientific standards for evolution -- basically, "Give me every single mutation and selection pressure in every lineage over the last billion years" -- will have to be explored in more detail elsewhere. Also saved for later is the question of where exactly the ID movement's hundreds of papers are that give detailed accounts of the ID explanation for the cilium, the immune system, etc.

Although there are not hundreds of papers, meetings, books, etc., on cilium evolution, the point of these webpages is -- as the reader has already guessed -- that evolutionary immunology *does* have this level of research behind it. Will the ID movement ever admit it, or will they just continue to brazenly dismiss the work of hundreds of scientists as "speculation"? Time will tell. In the meantime, unsupported statements about the lack of scientific literature on the evolution of irreducibly complex systems -- even statements from seemingly authoritative sources -- must be treated with skepticism (the ID movement has a small handful of quotes from respected scientists that they wield like talismans against criticism, but there is no evidence that these authorities have any particular familiarity with evolutionary immunology).

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