Original reviewer and editor comments are in *italics* and indented followed by our responses

***Remarks from the Editor***

*Dear Dr. Peters,  
  
Your manuscript "The Ontology for Biomedical Investigations" (NBT-P22789A) has now been seen by 4 reviewers, whose comments are included below. In light of their advice, I regret that I cannot offer to publish your paper in Nature Biotechnology, at least in its present form.                                       
I would be willing to consider a substantially revised manuscript that carefully addressed the referees' concerns. In general, the manuscript would have to be thoroughly revised so that it is addressed primarily to the general readership of Nature Biotechnology rather than to ontology developers and bioinformaticians. Beyond describing OBI, it must present a persuasive, thoughtful argument to our general readership as to why OBI is necessary. The comments of reviewer #4 concerning the question of how to evaluate the utility of OBI are especially pertinent in this regard. In addition, new use cases should be developed that are more compelling than the ones presented. Each should describe a problem of broad interest that exists currently in the absence of OBI and show how the adoption of OBI would solve the problem. It would also be helpful if the revised manuscript clarified the near-term and longer-term goals of OBI and the pathways to the adoption of OBI by the larger community.  
We agree with reviewer #3 that the paper does not appear to benefit from the organization into Results and Discussion sections.   
  
As a significant amount of work would be required to revise the manuscript for Nature Biotechnology, I would of course understand if you preferred to publish this work elsewhere. Should you decide to submit a revised manuscript, please include a point-by-point response outlining the changes made to the manuscript in response to each of the referees' comments. The point-by-point response should be a separate file from the cover letter and labeled "point-by-point response."          
      
      
Sincerely,                   
                   
                                 
Kathy Aschheim, Ph.D.  
Senior Editor  
Nature Biotechnology*

We appreciate the reviews, and are now submitting a revised version of the manuscript. We found that to address the primary concerns shared by the reviewers and re-iterated by the editor, we had to demonstrate practical applications of OBI in use rather than the previously included use cases that demonstrated capabilities to solve (toy) examples. We believe that the practical applications provide the best arguments of how OBI is useful. Furthermore, they provide the evaluation we have been using implicitly for OBI all along: solving practical problems encountered when assembling maintaining and analyzing large scale datasets in the biomedical sciences.

As we had anticipated, it has taken a significant amount of time until the version of OBI we described in the last submission was fully in use, which explains the long delay for this re-submission. We are detailing the changes in our point by point response to the individual reviewers below.

***Reviewer #1 (Remarks to the Author):*** *Summary of manuscript:  
"OBI addresses the requirement for a cross-disciplinary standard for representing biomedical investigations. It is both broad, describing the parts of an investigation from conception to  
conclusion, and deep, describing entities from test tubes to transgenic organisms. As an ontology  
OBI is a controlled vocabulary with additional logical constraints, reusing basic terms to build  
more complex ones."  
  
The authors address an important problem and the work  
appears sound.  
  
My main criticisms are that (1) The presentation is not particularly interesting or compelling, that is, I don't find the description of the ontology itself to be very interesting reading, and (2) The authors do not report an evaluation of the ontology of significant breadth.  Yes, three very different use cases are presented, but none is discussed in any real depth, and I find the second use case to be fairly trivial.*

*In summary, I wish the authors would make a significant effort to expand the paper and make its presentation more engaging and its evaluation more comprehensive.*

Based on feedback from this reviewer and others, we have now completely replaced the previous use-case section that essentially contained demonstrative toy-examples of what OBI can do, and replaced it with a description of OBI applications in practice. We are also now performing an evaluation of OBI, using the metric suggested by reviewer 4 (and implicitly utilized by us from the beginning), namely how OBI performs in these practical applications.

***Reviewer #2 (Remarks to the Author):*** *Overall, this is a good paper, and it is important that the OBI work have a clear  
publication about it. The following are all fairly minor comments.*

*p. 3: Besides OWL, what other W3C standards is OBI built upon?*

*AI: to address*

*p. 3: "using the mechanism described in (15)" -> "using MIREOT (15)"*

*We have reworded that sentence.*

*p. 4: Wouldn't the object of "achieves planned objective" be an objective rather than  
an objective specification? These don't seem to be the same thing according to OBI  
as far as I can tell.*

We agree that this label is not perfect, but we have to strike a balance between relatively short labels and potential misunderstandings. However, the definition of the relation states that “This relation obtains between a planned process and a objective specification when the criteria specified in the objective specification are met at the end of the planned process”. We would be very happy for a suggestion of a short label that can fully convey that. We were unable to find one, and would therefore prefer to stick to the shorter label in this case. As domain and range of the relation are exactly identified, improper use of the relation would immediately be detected by a logical reasoner.

*p. 4: "has specified input" and "has specified output" bother me; they seem akin to  
the "has\_central\_participant" that was tried (and later dropped) for the GO crossproducts.  
In Figure 2, in the organismal specimen collection, the mouse, the syringe,  
and the vial are all objects of "has specified input", so this already seems like an  
underspecified relation. And this problem could grow, e.g., why wouldn't the person  
collecting the specimen also be an input? I think more specific roles and/or role  
relations are going to be needed for processes.*

We agree that this is not clear, and have now expanded the paragraph to clarify what differentiates a regular participant in a process from a ‘specified’ one, by including an example of the former.

*p. 5: "is achieves" -> "achieves"*

This is now corrected.

*p. 5: Just out of curiosity, if the root of the Information Artifact Ontology is  
"information content entity", then why isn't it called the Information Content Entity  
Ontology, or why isn't the root called "information artifact"?*

I would also prefer to change the root to information artifact. Alan to explain why not.

*p. 5: At least one example each of a dependent and an independent variable  
specification would be helpful.*

We agree, and have now added two examples in the text (chemical dose as an independent and cell proliferation as a dependent variable)

*p. 6: its' -> its*

The section in which this error was contained is now removed as part of the overall re-organization.

*p. 6: OBI's objectives sound an awful lot like the Protege group's previous research  
into formally represented problem-solving methods, which really didn't go  
anywhere. Perhaps a comparison or brief discussion?*

BP: I have no idea what the Protégé’s group research contained.

*p. 6: Regarding the point that using OBI "allows an advanced user to formulate  
queries to ask specific questions beyond" a pre-defined set isn't convincing, as the  
same thing could done using SQL to query a relational database. The merits of using  
an ontology (and specifically OBI) should be made clearer.*

The section referenced is removed as part of the overall re-organization. However the IEDB application has similar content. We have now hopefully provided a better example, namely that information contained in OBI and ontologies connected to OBI can be utilized to formulate queries against the IEDB data in a seamless fashion.

*p. 9: "level" of "human antithrombin-III protein level" should be italicized as well?*

The section referenced was removed as part of the overall re-organization.

*p. 12: It's fine to model canonical investigations, but there should (eventually) be a  
way to represent an investigation that is noncanonical in one or more ways to a  
canonical investigation, either at the class or instance level. This is already possible  
for the FMA (at least at the instance level).*

We agree, and do in fact want to eventually represent noncanonical investigations. We have added a section to that regard in the discussion.

*References: Some of the references are incomplete, e.g., 20, 21.*

We apologize for missing this, and have now added the complete information to what used to be references 20, 21 and 24.

*Figure 2: According to OBO's all-some semantics, the "specimen role" relation from  
a role to a process means that all instances of the role are realized, which is  
obviously not true. Perhaps instead a "realizes" relation from the process to the role  
instead?*

We failed to point out in the Figure legend that it is meant to depict an instances rather than classes. So while we believe that the positioning of the arrows is correct, we have modified the Figure legend to specifically point out that the figure is depicting instances.

*Figure 3: This figure isn't really helpful.*

The section referenced is removed as part of the overall re-organization.

*Figure 4: Missing from this example is a list of what needs to have been represented  
for this query to work: that the reported assays are about cytokine production and  
T-cell mediated cytotoxicity, that these assays are parts of investigations, and that  
the journal articles report these investigations. Do you think there should be  
curators for this new task, or would you advocate using the MeSH terms with which  
many biomedical articles have already been annotated, or do you envision  
something else?*

The reviewer is absolutely correct in that all this additional information is needed. What we failed to communicate is that this information is exactly what the conversion of the information stored in the IEDB database into OWL provides. The IEDB stores over 500,000 assays that were manually curated and include detailed experimental description as well as links to investigations / publications, but in SQL that is not done in a semantically expressive manner. We hope that the complete revision of the OBI applications section now explains this better.

***Reviewer #3 (Remarks to the Author):*** *GENERAL ASPECTS:  
  
The normalization of the use of technical terms in the sense of precisely delineating the objects these terms denote is an important desideratum for a semantics-preserving exchange of parameters and results of experiments, thus making them interoperable between human  
and machine agents.   
To meet this goal, OBI plays a pioneer role in several aspects. Firstly, by bringing together representatives from quite diverse application areas, secondly by addressing a range of entity types which is much more diverse compared to other OBO ontologies, and finally, meeting the challenge of using a logic-based representation grounded on philosophical principles.  
As much as the virtues of OBI are valued within the bioontology community, as little OBO is known to and understood by a broader public.   
  
Therefore, the main purpose of an OBI paper in Nature Biotechnology should be:  
- to create understanding not only of OBI but also of the rationale of formal ontology building in general, targeting a broader community of potential users  
- to present convincing use cases that demonstrate how OBI can be used to solve problems that otherwise cannot be solved.  
  
The manuscript in it current form only partially addresses these desiderata. Both in form and content it must be significantly improved.*

Based on feedback from this reviewer and others we have completely modified the use case section, and replaced it with applications that are now in practice. We have also followed specific recommendations from this reviewer (stated below) to provide the targeted broader readership with more general explanations of the value of formal ontology building as well as the methodology and constraints.

*FORMAL ASPECTS:  
- The Results section follows directly the introduction, whereas the Methods section follows the figures. I do not understand the reason for this deviation from the standard structure of scientific articles. Some of the information contained in the Results section would better fit into the Methods section, e.g. "OBI was constructed by collecting terms from each of the 19 communities within the OBI consortium".   
Furthermore there is some redundancy between the Results and the Methods section (e.g. the facts referring to BFO and RO)   
The Introduction section already anticipates information which is to be expected in the Results section "At the time of writing, OBI has over 2,500 classes". I recommend to reconsider whether the classical document organization into "Introduction", "Methods", "Results", "Discussion" makes sense here.*

The order of the section was based on the journal guidelines of Nature Biotechnology. We agree that a re-organization as proposed would provide a better flow, and as the editor has agreed, we have now modified the section order as proposed. As suggested, we have also moved the information about the number of classes in OBI from the introduction to the results section.

*- The caption of Table 1 is not references under "Figure Legends and Tables".*

*- The figure captions should have backward references to the sample use cases*

Need to re-assemble Figure Legends and Tables and re-format for submission

*- Several important references are missing, e.g. the reference to OWL (page 2),  and OBO format on page 11.*

We apologize for this oversight, and have now added these references.

*CONTENT ASPECTS:  
page 2:  
  
The abstract is rather short. It should introduce the acronym "OBI". It should contain some more information about OBI's architecture and size.*

Based on the overall feedback, we have completely rewritten the abstract. As suggested, we are including an introduction of the OBI acronym and some OBI size statistics.

*I miss a clear and concise introduction of what the authors in this paper understand by "ontology". Unfortunately, "Ontology" is a term used in so many different (and partly contradicting) senses that the reader must know what the authors understand by it. It should especially made clear what the ontology represents (term, term meanings, concepts, classes of "real things") and which components are used to represent what. The word "entity" - as used throughout the article - is not very helpful, as it may signify everything (are there "non-entities" ??), and because it is used in two different ways, causing use-mention confusion: (i) "   "The scope of OBI is to formally represent entities" : here "entity" is the thing to be represented, and (ii) "Before terms were incorporated as entities into OBI": here "entity" is the representing unit.   
I recommend to provide a survey the important building blocks of OWL-DL ontologies, their formal underpinnings, together with the words that are used for them and useful examples in a separate subsection (or in a box) with a title like "OWL ontologies in a nutshell" . I suggest the term "representational unit" (cf. Schober et al.) as the word that denotes all the nodes ("classes") and relations ("data properties", "object properties"). The use of the word "term" should be restricted to where clearly language issues (e.g. synonymy) are addressed, and for human readable natural language identifiers for representational units the word "label" would be more suited.*

We very much appreciate this recommendation, and have now added an “OLW ontologies in a nutshell” textbox. We have also followed the recommendation to use ‘representational unit’, ‘class’ and ‘relation’ when referring to the artifacts in the ontology and reserving ‘entity’ to refer to the ‘real things’ that are being represented.

*The "underpinning of computational logics" should be better explained, especially in which aspects which kinds of logic based reasoning (consistency checking, classification) supports the use of OBI.*

We have added this information in the textbox on OWL ontologies

*page 3  
  
There is no need to convey any statistics (class count) in the introduction section. The place for this is the results section.*

As mentioned above, we have moved that section to the results.

*Here the reader expects the materials methods section. It is very strange that here a section named "Results" anticipates (and duplicates) some of the content of the methods section (see above).   
The methods section - currently placed at the end of the manuscript - should definitely be here. It should address the guiding principles (referring to OBO Foundry, language, metadata), the materials (external ontologies) to be re-used and linked, the scope, the establishing of the development framework, and release and quality control issues. Much of the content of pp 11-12 could be written in a more compact way and less subsections.*

As mentioned above, we did not choose the ordering of the section, but were following Nature Biotech guidelines. We have now re-organized as recommended. We have also moved content from the results section as recommended.

*The statistics should be more precise, including e.g. the number of fully defined classes, the number of individuals, disjointness axioms etc.*

We are now providing the statistics requested by the reviewer.

*page 4/5  
  
The extensive description of the key classes is exclusively done in prose. In order to demonstrate the use of logic decriptions it would be better to add some good examples in logic (Manchester Syntax). This could ideally be done in an additional table, juxtaposing text and formal definitions of selected classes. One of this examples could be the class OBI\_0100046 (Table 1).*

As suggested, we have added the logical definition to the class described in Table 1.

*Only a minor number of BFO classes are used by OBI. Obviously the subdivisions of bfo:independent continuant and bfo:processual entity do not match the needs of OBI. Many other branches of BFO (spatiotemporal region, temporal region) are not used at all.   
The authors mention that there is no good place for social and legal entities in BFO and that "Material entity" was necessary to be added to BFO. Therefore the appropriateness of BFO as an upper level for OBI should be critically assessed, especially in the light of other upper level ontologies, e.g. DOLCE and SUMO, or the domain dependent ontologies GFO-BIO and BioTop.*

We have now included a discussion of the choice of BFO as an upper ontology, and point out that this choice was made as a historical fact (made in 2004), and that we have not evaluated how a different choice would have effected development over the years. We would also like to point out that vast majority of contributors to OBI would prefer if the ‘pure ontologists’ that are working on the development of upper level ontologies would battle out what the right approaches are, rather than asking for a critical assessment by the community that they are supposedly aiming to server.

*Page 6  
The information content of Fig. 3 is very poor. It should be either removed or redesigned (no unlabelled arrows, possibly in the style of Fig. 4 and 5)  
Grammar:  
“demonstrate its' wide applicability." correct: “its wide"  
 "The first uses case" correct:  "The first use case"*

The section referenced is removed as part of the overall re-organization.

*Page 7  
I miss in the discussion section several aspects such as the appropriateness of the upper level ontology framework, the limitations of the representational language chosen, the adherence to OBO Foundry principles (non-overlap), and the problem of tractability of the expessive description logics. Finally I miss a conclusion section.*

We have now added the requested section to the discussion, as well as a conclusion section.

*Page 8:  
“OBI is complex, but then so are 'materials and methods' sections as  
they stand."  
It is not clear to me what is expressed by this sentence.*

We have reworded this to say XXX

*FINAL ASSESSMENT:  
A comprehensive publication on OBI is due, and I wish to see it to be done by Nature Biotechnology. The current manuscript is, however, not ready for publication. It must be thoroughly improved and revised according to the reviewers' recommendations. To combine the goals of (i) a precise account of OBI's architecture (including formal aspects) and (2) to optimally translate the thorny subject of ontology to the user community (using convincing examples in favor of the use of logics and machine reasoning), is certainly not easy but indispensable. The final paper may therefore become longer, but this price should be paid.*

We thank the reviewer for this positive assessment of the OBI effort, and believe that our revisions according to his and other recommendations make the re-submission much stronger.

***Reviewer #4 (Remarks to the Author):*** *The Ontology of Biomedical Investigations is a exciting initiative of extraordinary scope that involves a huge community of researchers.  It is an important, highly visible project that needs to be reported and for which Nature Biotechnology would be an excellent venue.  
  
The paper does an excellent job of presenting the OBI as an artifact, and perhaps that is the real goal of this manuscript.  This reviewer is concerned, however, is that the paper is less compelling in informing the reader of what is to be learned from the authors work to date and how well the OBI meets the authors' stated goals.  
  
Most ontology development starts with a set of competency questions that the developers determine the ontology should be able to address.  It is not clear whether OBI was created with any particular competency questions in mind, and thus how the developers can draw boundaries around the ontology's enormous scope.  How do the developers track their progress and determine where to concentrate their authoring activity when the ontology purports to cover all of biomedical investigation?  How do the developers identify areas of the ontology that are too sparse or incomplete?  Overall, how do the developers know how to evaluate their work.  The paper gives the impression that OBI is evaluated by ongoing inspection by the developers.  Practical experience with ontology authoring suggests that evaluation is most effective when performed in the context of use, and yet the paper offers only three relatively straightforward use cases that obviously do not intend to cover the full scope  of OBI's content.  Some detailed discussion of how OBI has been evaluated, and of what the developers have learned from these evaluations would be extremely helpful.*

This criticism was voiced by several reviewers and re-iterated by the editor. We have therefore completely revised the use-cases, which were meant to be easy to understand ‘toy examples’ of what OBI can do, and are now instead describing practical applications of OBI. As also voiced by others, it was not clear in the previous submission how OBI development is guided and evaluated. In the revised version, we are including a section on the evaluation of OBI, which is based on how OBI fares in

*The paper gives the impression that OBI is totally novel.  Obviously, OBI owes a lot of its heritage to the MGED ontology and other initiatives in which the authors have been involved.  There is a long history of ontologies of this nature in the literature that the authors do not mention.  In the 1980s, Peter Friedland's MOLGEN system for automated planning of experiments in molecular genetics needed an framework to represent biological investigations of this sort.  In the 1990s, ontologies of clinical trials (such as the one in the EON system) and mark-up languages for clinical protocols (such as GEM) became widely known.  How has OBI been informed by these other ontology efforts?*

We are now including a section in the discussion on previous efforts, how they have impacted OBI development, and are including references to those projects.

*Even as work on OBI has continued, other investigators have started their own parallel projects, claiming that OBI does not make the kinds of distinctions required for these other initiatives.   For example, the Ontology for Clinical Research (OCRe) is a new effort that seems to have been started as an alternative to OBI.  DIscussion that would help the reader to understand the ontology landscape and the relationship between OBI and the work of other ontology developers would seem essential.*

This is an important subject, and we have accordingly added a paragraph to the discussion. OBI strives to be completely open and has successfully integrated the efforts of many, many people in the past. However, due to the consensus driven nature of OBI and the desire to be exact and interoperable across deomains, OBI development can be too slow for the demands of some practical applications. Even developers involved in OBI tend to use an in house ontology for rapid development efforts. We have found that this is becoming less of a concern as OBI is becoming more complete in its coverage. We very much welcome all developers to join OBI. A primary advantage of working with OBI is that it has staked the claim to deal with the description of investigations as part of the OBO foundry, and therefore all overlapping efforts should coordinate with OBI. [talk more about IAO, UO, ECO as examples of further subdividing the domain while guaranteeing interoperability].