**Reviewer's report**

**Title:** Deciphering the Mechanism of Indirubin and Its Derivatives in the Inhibition of Imatinib Resistance using a "Drug Target Prediction-Gene Microarray Analysis-Protein Network Construction" Strategy.

**Version:** 2 Date: 17 Feb 2019

**Reviewer:** Randolph Arroo

**Reviewer's report:**

In response to reviewer 3, the first part of the conclusion section was rewritten. However, in my opinion lines 306 - 310 are not much clearer than the same section in the previous version of the manuscript.

I suggest to rephrase this section again, e.g.:

Definition of a potential drug target is an important first step in the process of drug discovery and drug design. Gene microarray analysis and protein network mapping can be key tools for identification of the factors that play a role in disease progression and thus are the potential drug targets. Subsequently, molecular docking experiments in silico can be used to predict putative interaction of small molecule compounds with the identified targets. In this study, the mechanism of action of...

Also, lines 278-288 are and amended section in the text, again in response to reviewer 3.

Why the sudden change from 'imatinib' to 'IMA' halfway this section? It is confusing.

In the list of abbreviations (line 43, 319), 'IM' is given as abbreviation for imatinib. However, the abbreviation 'IM' is not used anywhere in the text.

It will be best not to use any abbreviation for imatinib, and just use the full word throughout the text (as already is the case in >90% of the current manuscript anyway).

Finally, reviewer 3 requested that the discussion should be more focused on practical application.

In response, we find lines 233 - 235: "Our findings can help clinicians treat patients with CML more effectively. Effective early prevention of patients who are likely to develop imatinib resistance, thereby improving the overall survival rate of CML patients."

That is not true; clinicians will find little help in the information or in the techniques described in this paper. The information is used in Drug Discovery and Development (line 300, line 306).
The manuscript is an example of data mining, i.e. using existing data to highlight any connections or links in large datasets. The manuscript shows the application of the String online website (https://string-db.org/) and the freeware programme Cytoscape 3.5.1. Data mining is not necessarily expected to lead to new and original conclusions, but the method described in the paper may show an objective and rapid way to spot connections and identify potential drug targets.

It should be emphasized that the methods described are only a first step in the process of drug discovery and development. Any further claims, e.g. use as a tool for clinicians, are exaggerations.

Minor corrections:

Line
25 ...of which 15 affected 11 putative targets...
212 ...compounds that affected 11 major hubs...
213 ...compounds affected these putative targets.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript
Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

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