DATA NOTE

**REVISED** High quality, small molecule-activity datasets for kinase research [version 3; peer review: 2 approved]

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**Abstract**

Kinases regulate cell growth, movement, and death. Deregulated kinase activity is a frequent cause of disease. The therapeutic potential of kinase inhibitors has led to large amounts of published structure activity relationship (SAR) data. Bioactivity databases such as the Kinase Knowledgebase (KKB), WOMBAT, GOSTAR, and ChEMBL provide researchers with quantitative data characterizing the activity of compounds across many biological assays. The KKB, for example, contains over 1.8M kinase structure-activity data points reported in peer-reviewed journals and patents. In the spirit of fostering methods development and validation worldwide, we have extracted and have made available from the KKB 258K structure activity data points and 76K associated unique chemical structures across eight kinase targets. These data are freely available for download within this data note.

**Keywords**

Kinase, SAR, Bioactivity Database, Dataset, Drug Discovery, Bioactive Molecules, Kinase Knowledgebase, KKB

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**Open Peer Review**

**Reviewer Status** ✔ ✔

**Invited Reviewers**

1 2

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This article is included in the **Chemical Information Science** gateway.

This article is included in the **Data: Use and Reuse** collection.
Corresponding author: Steven M. Muskal (smuskal@eidogen-sertanty.com)

Competing interests: No competing interests were disclosed.

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**Introduction**

Since their discovery in 1975 by Cohen et al., kinases are now one of the most established drug target families, second only to G-protein-coupled receptors (GPCRs). Most progress in kinase research has occurred in the last 25 years including the discovery of many new kinases\(^1\), identification of new isoforms of pre-existing kinases\(^2\), elucidation of new biological pathways, and identification of many new kinase-disease associations\(^3\). While kinases are well-validated anti-cancer targets\(^4-11\), kinase inhibitors also have been pursued in cardiovascular\(^12\), autoimmune\(^13\), inflammatory skin and bowel\(^14\), neurodegenerative\(^15\), and renal disease programs\(^16\). Most small-molecule kinase inhibitors target the ATP binding site of the kinase catalytic domain\(^17\). The ATP binding region of the catalytic domain is highly conserved among protein kinases, which has important consequences for drug development. Achieving selectivity of a small molecule inhibitor against kinase off-targets to avoid adverse reactions can be a major hurdle. However, the cross-reactivity of many chemotypes can also open opportunities to focus on other closely related kinases. Despite the high degree of conservation in the ATP binding site, reasonably selective inhibitors with favorable pharmacological properties can be developed\(^18\). It is now common in discovery programs to profile inhibitors against an extensive set of kinase targets\(^19\). These kinase-profiling efforts have generated valuable data, providing insight into selectivity and promiscuity of clinical inhibitors\(^19-21\).

Medicinal chemists can benefit significantly from well-curated databases documenting chemical structure(s) with an experimentally measured biological activity. These structure and activity databases or SAR databases help to better understand drug-target interaction, which can assist in the design of potent and selective chemical inhibitors\(^22-25\). A well populated, editable, easy to search and flexible SAR database is an integral part of the modern drug design process\(^26\). SAR databases provide elementary insights to researchers, including:

(a) **Target druggability:** known small molecule binders are required to categorize a protein as druggable. High-affinity and non-promiscuous inhibitors are particularly valuable to establish druggability; and can be further validated using structure biology information. In many cases druggability can be inferred for new targets using homology models\(^27\) where similarities can be mapped via sequences, pathways or functions. Examples include the Target Informatics Platform (TIP)\(^28\) and Modbase\(^29\).

(b) **Scaffold selectivity:** the golden principle that applies is “less selective scaffolds have more undesirable side effects.” A prior knowledge of selectivity profiles can help in making informed decisions on which chemotypes to pursue at the start of discovery programs\(^30\). Organizing data by scaffold enables classic SAR analysis in which side-chain moieties can be evaluated and considered or avoided in lead optimization\(^31\).

(c) **Clinical molecules:** it can be very helpful to see scaffold(s) or derivatives under the study of launched drugs. This enables medicinal chemists to associate therapeutic classes with active scaffolds.

(d) **Development and validation of computational methods:** well-curated datasets are very helpful in the development and refinement of computational methodologies. With a common set of data, computational researchers can also compare and contrast methods, providing additional validation\(^2\).

(e) **Virtual screening:** high-quality, well-curated, standardized and annotated datasets are required to build predictive models for virtual screening as we have shown previously specifically for the Kinase Knowledgebase (KKB) data\(^3\).

**Materials and Methods**

The KKB is a database of biological activity data, structure-activity relationships, and chemical synthesis data focused on protein kinases. Since its inception in 2001, the KKB has grown steadily with quarterly updates each year. With more than two decades of high quality SAR data, the KKB represents one of the first kinase target specific databases of biological activity and chemical synthesis data from curated scientific literature and patents. The KKB contains a large number of kinase structure-activity data points (>1.8M) reported in peer-reviewed literature covering journals and patents. The data have been curated from over 150 different journals reporting kinase inhibitors with activity data, with leading contributions from *J Med Chem*, *Bioorg Med Chem*, *Bioorg Med Chem Lett* and *Euro J Med Chem*. In addition, the KKB contains data curated from patents/applications from WO, EP and US. The scientific information is curated from the published text using a combination of automatic and manual efforts.

A summary of the first quarter release for year 2016 (Q1-2016) is reported in Table 1. With the Q1-2016 KKB release, there are total of 506 unique kinase targets with over 682K unique small molecules. A listing of few “hot” kinase targets with their inhibitors (data points) is reported in Table 2.

**Table 1. Eidogen-Sertanty Kinase Knowledgebase. Summary Statistics – Q1 2016 Release.**

<table>
<thead>
<tr>
<th>Articles covered:</th>
<th>2,780</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patents and patent applications covered:</td>
<td>6,346</td>
</tr>
<tr>
<td>Total Number of Bio-activity data points:</td>
<td>1,775,368</td>
</tr>
<tr>
<td>Total Number of unique molecules:</td>
<td>682,289</td>
</tr>
<tr>
<td>Total Number of unique molecules w/ assay data:</td>
<td>337,491</td>
</tr>
<tr>
<td>Total Number of assay protocols:</td>
<td>32,462</td>
</tr>
<tr>
<td>Kinase Classification</td>
<td>Family</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Receptor Tyrosine Kinases</td>
<td>Abl</td>
</tr>
<tr>
<td></td>
<td>Csk</td>
</tr>
<tr>
<td></td>
<td>Fak</td>
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<tr>
<td></td>
<td>JakA</td>
</tr>
<tr>
<td></td>
<td>Src</td>
</tr>
<tr>
<td></td>
<td>Lck</td>
</tr>
<tr>
<td></td>
<td>Syk</td>
</tr>
<tr>
<td></td>
<td>Tec</td>
</tr>
<tr>
<td>Receptor Tyrosine Kinases</td>
<td>EGFR</td>
</tr>
<tr>
<td></td>
<td>ERBB2</td>
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<tr>
<td></td>
<td>Eph</td>
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<tr>
<td></td>
<td>FGFR</td>
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<td></td>
<td>InsR</td>
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<tr>
<td></td>
<td>Met</td>
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<tr>
<td></td>
<td>PDGFR</td>
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<tr>
<td></td>
<td>FGFR</td>
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<tr>
<td></td>
<td>Tie</td>
</tr>
<tr>
<td></td>
<td>Trk</td>
</tr>
<tr>
<td>VEGFR</td>
<td>KDR/FLK1</td>
</tr>
<tr>
<td></td>
<td>FLT1</td>
</tr>
<tr>
<td>CMGC Kinases</td>
<td>CDK2</td>
</tr>
<tr>
<td></td>
<td>CDK5</td>
</tr>
<tr>
<td></td>
<td>GSK</td>
</tr>
<tr>
<td></td>
<td>MAPK</td>
</tr>
<tr>
<td></td>
<td>MAPK1</td>
</tr>
<tr>
<td></td>
<td>MAPK10</td>
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<tr>
<td></td>
<td>MAPK8</td>
</tr>
<tr>
<td></td>
<td>MAPK11</td>
</tr>
<tr>
<td>AGC Kinases</td>
<td>AKT</td>
</tr>
<tr>
<td></td>
<td>ROCK1</td>
</tr>
<tr>
<td></td>
<td>PKB</td>
</tr>
<tr>
<td></td>
<td>PKC</td>
</tr>
<tr>
<td></td>
<td>PRKCE</td>
</tr>
<tr>
<td>CAMK Kinases</td>
<td>CAMKL</td>
</tr>
<tr>
<td></td>
<td>MAPKAPK2</td>
</tr>
<tr>
<td></td>
<td>MAPKAPK3</td>
</tr>
</tbody>
</table>
Table 3. Kinase-classification in top therapeutic segments.

<table>
<thead>
<tr>
<th>Kinase Class</th>
<th>Enzyme Assay</th>
<th>Cell-Based Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family</td>
<td>Target Name</td>
<td>All SAR Data Points</td>
</tr>
<tr>
<td>AUR</td>
<td>AURKA</td>
<td>22646</td>
</tr>
<tr>
<td>IKK</td>
<td>IKKB</td>
<td>7628</td>
</tr>
<tr>
<td>CHUK/KKBKA</td>
<td></td>
<td>2938</td>
</tr>
<tr>
<td>PLK1</td>
<td></td>
<td>9181</td>
</tr>
<tr>
<td>MAP2K1</td>
<td></td>
<td>6340</td>
</tr>
<tr>
<td>ILK</td>
<td></td>
<td>360</td>
</tr>
<tr>
<td>RAF1</td>
<td></td>
<td>11302</td>
</tr>
<tr>
<td>BRAF</td>
<td></td>
<td>26349</td>
</tr>
<tr>
<td>PIK3/PIK3CG</td>
<td></td>
<td>29925</td>
</tr>
<tr>
<td>PIK3CA</td>
<td></td>
<td>36168</td>
</tr>
<tr>
<td>TK1</td>
<td></td>
<td>1106</td>
</tr>
<tr>
<td>ADK</td>
<td></td>
<td>1924</td>
</tr>
</tbody>
</table>

Kinase inhibitors are biologically active small molecules and their activity refers to experimentally measured data on a given kinase target (in enzyme or in cell based assays), using predefined experimental protocols. After curation and standardization, these measured values together with related information are indexed in the KKB. Each inhibitor entered in the KKB carries unique identifiers such as:

(a) Chemical information and biological information: unique structure IDs (MR_ID) are assigned based on unique canonical SMILES. In addition hand-drawn Cartesian coordinates are captured. Chemical compounds are associated with calculated chemical and physical properties.

(b) Biological target and assay protocol: biological targets are annotated by EntrezGeneID, UniProt ID, and HUGO approved names. An assay protocol includes detailed information pertaining to the experiments performed to measure the biological activity for the compound. Each protocol has a descriptive title and a unique set of keywords. Assays are categorized by assay format (biochemical, cell-based, etc.) following standards set forth by BioAssay Ontology (BAO)\(^{34,35}\). Kinase targets are classified by protein and non-protein kinases and protein kinases by the typical domain-based classification into group, family, etc. We are in the process of mapping KKB targets to the Drug Target Ontology (DTO), which is in development.

(c) Experimental bioactivity screening results. A bioactivity data point is a defined result/endpoint of a specified small molecule compound tested in a biological assay. The assay is defined in b); result type/endpoint captured include IC\(_{50}\), K\(_i\), K\(_d\); the vast majority for biochemical and cell-based assays correspond to BAO definitions.

(d) Source reference: bibliographic information and unique identifiers for journal article and patents from which information related to the molecules was extracted include PubMedID, DOI, and standardized patent numbers. For journals, the KKB provides title, authors name, journal-name, volume, issues, and page numbers. For patents their titles, patent or patent application number (along with family members), inventor’s names, assignee names, publication data and priority numbers are provided.

It is observed that a disease type can be related to multiple kinase groups, and several diseases can arise from a common set of kinase group (Table 3). In the KKB, kinases are classified by protein and...
non-protein kinases with several sub-categories such as carbohydrate and lipid kinase and the typical protein kinase groups (such CMGC, CAMK, TK, TKL, RGC, AGC) and further sub-groups such as families. DTO provides a functional and phylogenetic classification of kinase domains to facilitate navigation of kinase drug targets. DTO is developed as part of the Illuminating the Druggable Genome (IDG) project. Here we make datasets freely available for the research community including to support efforts such as IDG. We also offer to run our predictive models built using KKB data to support prioritization of drug targets.

Kinase inhibitor datasets
The wealth of kinase inhibitor data presents opportunities for analysis as a whole or by integrating such data into various computational platforms to support development and validation of hypotheses of kinase inhibition. Several years ago, Eidogen-Sertanty made available 3880 pIC\textsubscript{50} data points across three kinase targets (ABL1, SRC, and AURKA – validation sets) to foster algorithm development and validation worldwide. With this data note, eight additional targets comprising inhibitors for therapeutically important classes: EGFR, CDK2, ROCK2, MAPK14 and PI3K (class I catalytic) (Table 4) totaling ~258K data points (structure with standard results/endpoints such as IC\textsubscript{50}, K\textsubscript{i} or K\textsubscript{d}) and ~76K unique chemical structures now have been made available to further foster worldwide development, validation, and collaborative interaction (see KB_SAR_DATA_F1000.txt and KB_SAR_DATA_F1000.sdf files). These datapoints have been exported from the KKB and survey 1044 articles and 942 patents.

The datasets cover a broad range of biochemical and cell based studies investigating kinase inhibition; and they represent a diverse collection of pharmaceutically active scaffolds. These scaffolds can be easily examined for selectivity and specificity for the given eight kinase targets. Additionally, they can be used to infer novel target-inhibitor relationships for kinases and compounds not included in these subsets.

Bibliographic information is reported in the files ArticleInfo_F1000.txt and PatentInfo_F1000.txt. Experimental procedure along with metadata information for targets including EntrezGeneIDs, assay format/type (biochemical/ enzyme, cell based, etc), keywords, species, and cell lines used in cell-based data are stored in AssayProtocols_F1000 (txt and xml attached).

The KKB validation sets have a maximum contribution from EGFR with nearly ~54K inhibitor molecules. This is followed by ~43K inhibitors for MAPK14; CDK2 and PIK3CA each have ~39K inhibitors. Figure 1 depicts data point distributions for each kinase in the attached subset. Moreover, 84% of the data are from biochemical enzyme based assay experiments, and 16% of the data from cell-based assays (in Figure 2). The datapoint measures include IC\textsubscript{50}, K\textsubscript{i} and K\textsubscript{d} (Figure 3).

Table 4. Important aspects about the selected targets.

<table>
<thead>
<tr>
<th>Kinase</th>
<th>Approved Name</th>
<th>Class</th>
<th>Diseases Associated</th>
<th>Entrez GeneID</th>
<th>Uniprot ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR*</td>
<td>Epidermal Growth Factor Receptor</td>
<td>Receptor Tyrosine Kinase</td>
<td>NSCLC, Medullary Thyroid Cancer, Breast Cancer, Neonatal Inflammatory Skin and Bowel Disease</td>
<td>1956</td>
<td>P00533</td>
</tr>
<tr>
<td>CDK2</td>
<td>Cyclin-Dependent Kinase 2</td>
<td>Serine/Threonine Kinase</td>
<td>Angiomyoma, Caruncle</td>
<td>1017</td>
<td>P24941</td>
</tr>
<tr>
<td>ROCK2</td>
<td>Rho-Associated, Coiled-Coil Containing Protein Kinase 2</td>
<td>Serine/Threonine Kinase</td>
<td>Colorectal Cancer, Penile Disease, Hepatocellular Carcinoma</td>
<td>9475</td>
<td>O75116</td>
</tr>
<tr>
<td>MAPK14</td>
<td>Mitogen-Activated Protein Kinase 14</td>
<td>Serine/Threonine Kinase</td>
<td>Acquired Hyperkeratosis, Prostate Transitional Cell Carcinoma, Immunity-related Diseases</td>
<td>1432</td>
<td>Q16539</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Phosphatidylinositol-4,5-Bisphosphate 3-Kinase, Catalytic Subunit Alpha</td>
<td>Lipid Kinase</td>
<td>Colorectal Cancer, Actinic Keratosis</td>
<td>5290</td>
<td>P42336</td>
</tr>
<tr>
<td>PIK3CB</td>
<td>Phosphatidylinositol-4,5-Bisphosphate 9-Kinase, Catalytic Subunit Beta</td>
<td>Lipid Kinase</td>
<td>-</td>
<td>5291</td>
<td>P42338</td>
</tr>
<tr>
<td>PIK3CD</td>
<td>Phosphatidylinositol-4,5-Bisphosphate 9-Kinase, Catalytic Subunit Delta</td>
<td>Lipid Kinase</td>
<td>Immunodeficiency 14, Activated PIK3-Delta Syndrome</td>
<td>5293</td>
<td>O00329</td>
</tr>
<tr>
<td>PIK3CG</td>
<td>Phosphatidylinositol-4,5-Bisphosphate 9-Kinase, Catalytic Subunit Gamma</td>
<td>Lipid Kinase</td>
<td>Lichen Nitidus</td>
<td>5294</td>
<td>P48736</td>
</tr>
</tbody>
</table>

*Afatinib, Erlotinib, Gefitinib, Lapatinib, Osimertinib, Vandetanib are US-FDA approved kinase inhibitors with EGFR as one of the valid targets.
Analysis of ~76K unique molecules for selectivity against targets reveals that ~64K inhibit only one kinase of the eight kinases extracted (Figure 4). Approximately 5K molecules show activity against two kinase targets, and ~3K molecules show activity against three kinases. A total of 79 molecules in the subset have some activity against all the eight kinase targets.

Dataset 1. High quality, small molecule-activity for kinase research. Raw data behind the analyses described in the Data Note are included

http://dx.doi.org/10.5256/f1000research.8950.d124591

The file 'Datasets legends' contains descriptions for each dataset.
Conclusions
The KKB is available in various formats such as SQL, SDF and IJC format (Instant JChem) as quarterly updates. Two mobile apps, iKinase and iKinasePro\textsuperscript{2}, are also available for download which enable basic search access into KKB content, including kinase inhibitor structures, biological data and references/patents. Simple substructure and exact structure search access into the KKB is also available. We have extracted from the KKB ~258K structure activity data points and ~76K associated unique chemical structures across eight kinase targets and made these data freely available for download within this data note to foster algorithms development and validation worldwide.

Data availability
F1000Research: Dataset 1. High quality, small molecule-activity for kinase research, 10.5256/f1000research.8950.d124591\textsuperscript{16}

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{fig3}
\caption{Data points in various assay measures.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{fig4}
\caption{Selectivity profile for data points.}
\end{figure}
Author contributions
RS, SCS and SMM contributed equally to the work.

Competing interests
No competing interests were disclosed.

References

   PubMed Abstract | Publisher Full Text
   PubMed Abstract | Publisher Full Text
   PubMed Abstract | Publisher Full Text | Free Full Text
   PubMed Abstract | Publisher Full Text
   PubMed Abstract | Publisher Full Text
   PubMed Abstract | Publisher Full Text
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    Data Source

Grant information
The work of SCS was supported by grant U54CA189205 (Illuminating the Druggable Genome Knowledge Management Center, IDG-KMC). The IDG-KMC is a component of the Illuminating the Druggable Genome (IDG) project and NIH Common Fund project, awarded by the NCI.
Open Peer Review

Current Peer Review Status: ✓ ✓

Version 2

Reviewer Report 21 July 2016

https://doi.org/10.5256/f1000research.9948.r15123

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✓ Sorin Avram
Timisoara of Romanian Academy

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 08 July 2016

https://doi.org/10.5256/f1000research.9629.r14358

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✓ Sorin Avram
Timisoara of Romanian Academy

The paper describes Kinase Knowledgebase (KKB), i.e., a database containing structure-activity data on kinases. The current data note briefly presents the KKB Q1 2016 Release and the appended eight kinase data sets, which are made hereby publicly available.

Kinases are valuable targets for many diseases, especially cancers. The subject is of real scientific. In general, the amount of bioactivity data, coming from various sources (scientific literature, high-throughput screening results, patents etc), is heterogeneous and a proper curation and standardization of the data can provide reliable activity points. These data may be employed in many ways as described by the
In my opinion, the main applications for a database such as KKB would be to build predictors to search the chemical space for new kinase inhibitors, and further to optimize the selectivity of kinase inhibitors. Currently, ChEMBL’s\(^1\) publicly available Kinase SARfari (\url{https://www.ebi.ac.uk/chembl/sarfari/kinasesarfari}), provides a standard source for these tasks, covering about 532155 bioactivity data points i.e., version: 6.00- accessed June 20, 2016. This is less than one third of the 1.8 million KKB activity data point reported by the authors. In these circumstances, KKB might add valuable information for kinase research. Finally, the future analysis and employment of the eight data sets made freely available in the current note will provide a clearer view of the potential and versatility of KKB.

There would be two minor observations:

1. The methodology used to generate the data is described in the first paragraph in the section entitled "Kinase Knowledgebase (KKB)". In order to be more accessible for the reader, this paragraph should be encompassed in a separate section named “Materials and methods”.
2. In Table 2 there are three columns with repeated headers. In order to remove any doubts, I would recommend the authors to clarify this issue.

Otherwise, the data note is well written, kinases are indexed using the widely adopted Uniprot IDs and the references are updated.

I recommend this data note for indexation and would like the authors to address the minor observations.

References


Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 08 July 2016

\url{https://doi.org/10.5256/f1000research.9629.r14833}

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George Nicola

Computational Biology, University of California at San Diego, San Diego, CA, USA

This article describes an overview of current kinase-related databases of significance, with particular focus on the contents of the Kinase Knowledgebase (KKB). The KKB has the largest repository of high-quality kinase activity data. Providing access to over ¼ million data points on several of the most important kinases allows for an exciting insight into the relevance of these validated drug targets and the diversity of compounds affecting them. It is a promising trend that private companies are unlocking their
proprietary data troves for the advancement of academic research. This is a nice Data Note that merits indexing in F1000Research.

A few minor typographical corrections:

- **Table 2:** Three of the column names seem to be duplicated.
- **Table 2:** It is unclear what the grey vs white rows represent in ‘Kinase Classification’ and ‘Family’ columns. If only for readability, perhaps these should alternate.
- **Section ‘Kinase inhibitor datasets’ at the end of the first paragraph:** The word ‘respectively’ is not needed.
- **Section ‘Kinase inhibitor datasets’ 4th paragraph, ‘~54K inhibitors molecules’:** ‘inhibitors’ does not need to be plural.
- **Figures 1 & 2:** I would use the word ‘Breakdown’ instead of ‘Breakup’.
- **Figure 2:** Are ‘Cell-Free’ and ‘Animal Model’ truly zero percent? If so, they should be excluded; if not, the fractional percent should be listed.
- ‘Conclusions’: ‘datanote’ should be two words, to be consistent with the F1000 article type.

**Competing Interests:** No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

---

**Comments on this article**

**Version 3**

Author Response 27 Oct 2016

Steven Muskal, EidogenSertanty, Inc., Oceanside, USA

Figures have been updated in response to Christian Cole’s comments

**Competing Interests:** No competing interests were disclosed.

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**Version 2**

Reader Comment 14 Sep 2016

Christian Cole, Division of Computational Biology, University of Dundee, UK
Undoubtedly the research presented here is valid and appropriate, however the figures herein are wholly inappropriate. Plots presented with an artificial third dimension (Figures 1, 2 and 4) add nothing to the data. In fact, they can make interpreting the data harder. 3D pie-charts in particular (Figures 1 and 2) skew the representation of the data to the extent where the area assigned to a category is no-longer proportional to the data. That the authors chose to add the raw data to the figures makes the pie chart utterly redundant: simply present the data as tables.

Stephen Few has written a good article on this. Plus there are other significant papers in the field of perception of graphical visualisation e.g.


**Competing Interests:** I have no competing interests to declare.

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