

CORRESPONDENCE

## **A Unified Resource for Tracking Anti-CRISPR Names**

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Dear Editor,

In the battle between CRISPR-Cas prokaryotic immune systems and the elements that they target, a diverse array of “anti-CRISPR” proteins have evolved. These proteins appear to have arisen independently multiple times in evolution and function through diverse mechanisms to inhibit CRISPR-Cas immunity. For comprehensive reviews on anti-CRISPRs, we direct readers to recent publications.<sup>1,2</sup>

Due to the increasing interest in anti-CRISPRs, many new families of these proteins have been discovered in the past year or so. There are now 36 distinct families of anti-CRISPRs described in the literature that block seven subtypes of CRISPR-Cas systems.<sup>3-12</sup> In 2015, a naming system for anti-CRISPR genes and proteins was introduced.<sup>6,13</sup> To date, this system has been followed in all subsequent publications describing newly discovered anti-CRISPRs. However, as the rate of anti-CRISPR discovery will likely accelerate in the coming years, we feel that it would be advantageous to establish a database for the registration and tracking of anti-CRISPR names.

The primary goal of this database will be to prevent redundant names being used in publications, thus avoiding confusion in the literature. Anti-CRISPR proteins are named according to the subtype they inhibit and the order in which they were discovered – for example, AcrIF1 was the first anti-CRISPR protein identified to inhibit the type I-F system. The database (a Google document) can be found here:

<https://tinyurl.com/anti-CRISPR>

We propose that this document be updated when researchers have had a manuscript accepted for publication (or posted as a pre-print) in which new anti-CRISPRs are described. We suggest that the authors upload relevant data to the spreadsheet, including the name, CRISPR-Cas subtype inhibited, reference, and amino-acid sequence of the anti-CRISPR (Fig. 1). This spreadsheet may also be utilized by those

preparing a manuscript for submission to ensure that they use anti-CRISPR names that are still available.

	A	B	C	D	E	F	G
1	Acr name	Type Inhibited	Species of origin	Type of genomic element	Reference (First author, year, journal)	Sequence	
2	AcrIF1	I-F	<i>Pseudomonas aeruginosa</i>	Phage	Bondy-Denomy, 2013, Nature	MKFIKYLSTAHLNYMNIAYVYENG	
3	AcrIF2	I-F	<i>Pseudomonas aeruginosa</i>	Phage	Bondy-Denomy, 2013, Nature	MIAQQHKDTVAACEAAEIAIAKD	
4	AcrIF3	I-F	<i>Pseudomonas aeruginosa</i>	Phage	Bondy-Denomy, 2013, Nature	MSSTISDRISRSVIEAARFIQSWE	

Figure 1: A screenshot from the database, depicting the organization of anti-CRISPR entries.

To avoid the listing of many orthologues, we propose that the database only contain one entry per Acr, which will be considered the “type” Acr for that sequence family. In a case where a paper has investigated proteins that are homologous to an Acr protein, authors should utilize a subscript (e.g. AcrIF6<sub>Pae</sub>) to denote the species in which the anti-CRISPR is found. When multiple proteins from one species are investigated, we suggest a format of AcrIF6<sub>Pae-1</sub>, AcrIF6<sub>Pae-2</sub>, etc. The established conventions for naming anti-CRISPR proteins and genes will be described as part of the database. We view this as an open repository for the field, and as a complementary resource to a previously described anti-CRISPR database.<sup>14</sup>

Two of us (J.B.-D. and A.R.D) were inspired to establish this database by the success of the CRISPR-Cas classification scheme in bringing order to the naming of Cas proteins.<sup>15,16</sup> This work has been tremendously valuable for advancing the CRISPR-Cas field. We hope that our contribution to the anti-CRISPR field as presented here will provide a similar long-term benefit.

## References

1. Borges, A. L., Davidson, A. R. & Bondy-Denomy, J. The Discovery, Mechanisms, and Evolutionary Impact of Anti-CRISPRs. *Annual Review of Virology* **4**, annurev-virology-101416-041616-59 (2017).
2. Pawluk, A., Davidson, A. R. & Maxwell, K. L. Anti-CRISPR: discovery, mechanism and function. *Nat Rev Micro* **1**, nrmicro.2017.120 (2017).
3. Bondy-Denomy, J., Pawluk, A., Maxwell, K. L. & Davidson, A. R. Bacteriophage genes that inactivate the CRISPR/Cas bacterial immune system. *Nature* **493**, 429–432 (2013).
4. Pawluk, A., Bondy-Denomy, J., Cheung, V. H. W., Maxwell, K. L. & Davidson, A. R. A new group of phage anti-CRISPR genes inhibits the type I-E CRISPR-Cas system of *Pseudomonas aeruginosa*. *mBio* **5**, e00896–e00896–14 (2014).
5. Pawluk, A. *et al.* Inactivation of CRISPR-Cas systems by anti-CRISPR proteins in diverse bacterial species. *Nature Microbiology* **1**, 1–6 (2016).
6. Pawluk, A. *et al.* Naturally Occurring Off-Switches for CRISPR-Cas9. *Cell* **167**, 1829–1838.e9 (2016).
7. Rauch, B. J. *et al.* Inhibition of CRISPR-Cas9 with Bacteriophage Proteins. *Cell* **168**, 150–158.e10 (2017).
8. Hynes, A. P. *et al.* An anti-CRISPR from a virulent streptococcal phage inhibits *Streptococcus pyogenes* Cas9. *Nature Microbiology* **315**, 1 (2017).

9. He, F. *et al.* Anti-CRISPR proteins encoded by archaeal lytic viruses inhibit subtype I-D immunity. *Nature Microbiology* **71**, 1 (2018).
10. Hynes, A. P. *et al.* Widespread anti-CRISPR proteins in virulent bacteriophages inhibit a range of Cas9 proteins. *Nature Communications* **9**, 2919 (2018).
11. Marino, N. D. *et al.* Discovery of widespread Type I and Type V CRISPR-Cas inhibitors. *Science* eaau5174 (2018). doi:10.1126/science.aau5174
12. Watters, K. E., Fellmann, C., Bai, H. B., Ren, S. M. & Doudna, J. A. Systematic discovery of natural CRISPR-Cas12a inhibitors. *Science* eaau5138 (2018). doi:10.1126/science.aau5138
13. Bondy-Denomy, J. *et al.* Multiple mechanisms for CRISPR-Cas inhibition by anti-CRISPR proteins. *Nature* **526**, 136–139 (2015).
14. Dong, C. *et al.* Anti-CRISPRdb: a comprehensive online resource for anti-CRISPR proteins. *Nucleic Acids Research* **46**, D393–D398 (2018).
15. Makarova, K. S. *et al.* Evolution and classification of the CRISPR-Cas systems. *Nat Rev Micro* **9**, 467–477 (2011).
16. Makarova, K. S. *et al.* An updated evolutionary classification of CRISPR-Cas systems. *Nat Rev Micro* **13**, 722–736 (2015).