Reasoning about biology with data-driven approaches

Howes Scholar Presentation

Adam Riesselman

Reasoning about biology with data-driven approaches

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Adam Riesselman

DOE CSGF Fellow: Harvard University, 2014-2018

Practicum: Lawrence Berkeley National Lab
(Joint Genome Institute), 2016

Understanding how **genotype** affects **phenotype** is a critical **challenge**.

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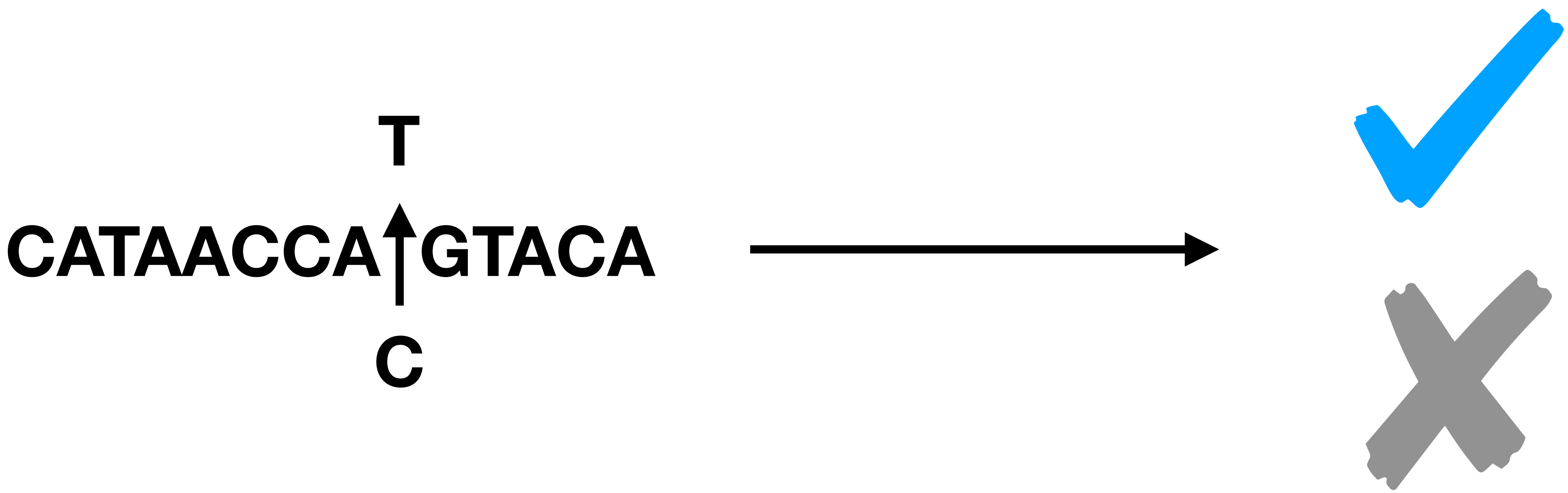
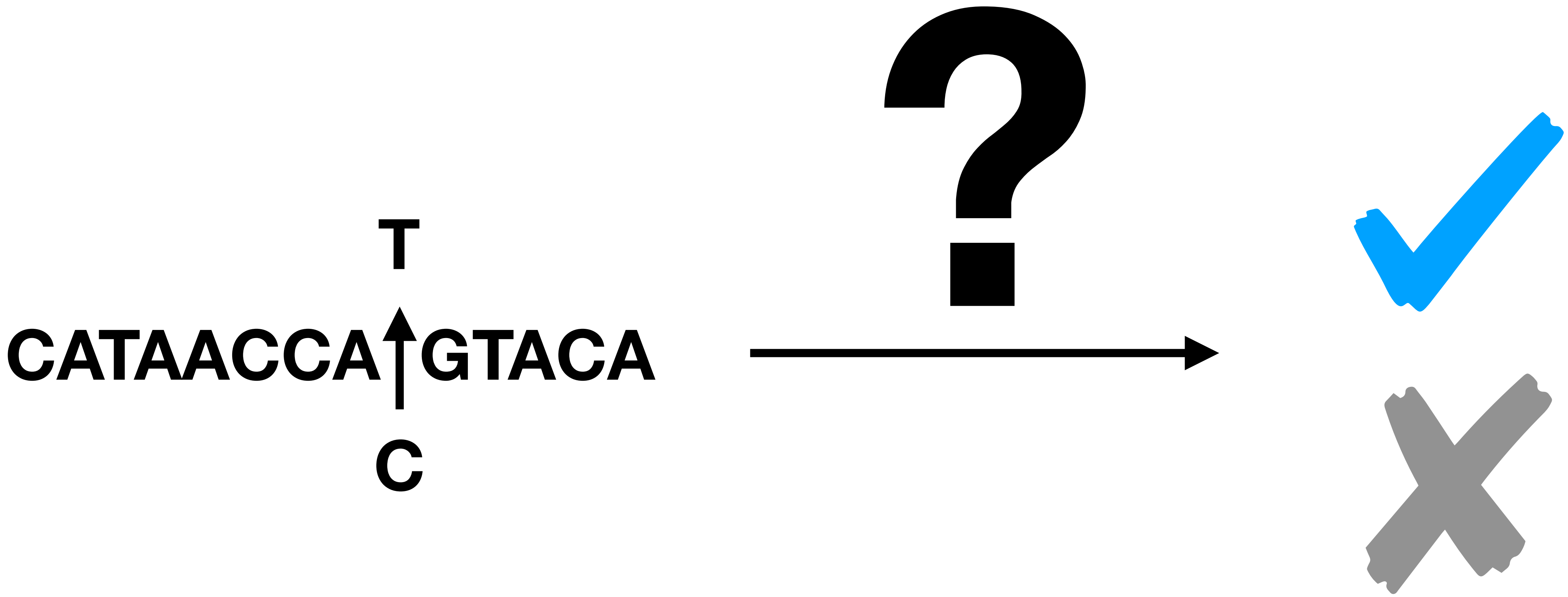


Understanding how **genotype** affects **phenotype** is a critical **challenge**.



The **Central Dogma** of **Biology**

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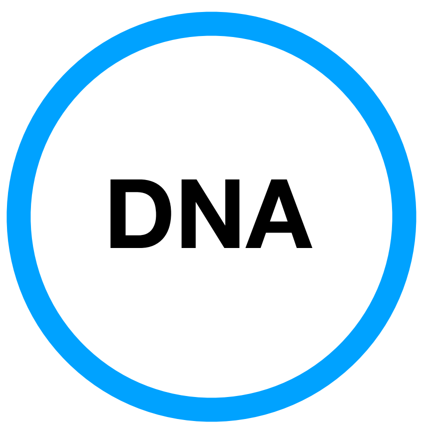

The **Central Dogma** of **Biology**

DNA

```
ATGAGTATTCAACATTTCCGTGT
CGCCCTTATTCCCTTTTTTGCGG
CATTTTGCCTTCCTGTTTTTGCT
CACCCAGAAACGCTGGTGAAAGT
AAAAGATGCTGAAGATCAGTTGG
GTGCACGAGTGGGTTACATCGAA
CTGGATCTCAACAGCGGTAAGAT
CCTTGAGAGTTTTCGCCCCGAAG
AACGTTTTCCAATGATGAGCACT
TTTAAAGTTCTGCTATGTGGCGC
GGTATTATCCCGTGTTGACGCCG
GGCAAGAGCAACTCGGTCGCCGC
ATACACTATTCTCAGAATGACTT
GGTTGAGTACTCACCAGTCACAG
AAAAGCATCTTACGGATGGCATG
ACAGTAAGAGAATTATGCAGTGC
TGCCATAACCATGAGTGATAACA
CTGCGGCCAACTTACTTCTGACA
ACGATCGGAGGACCGAAGGAGCT
AACCGCTTTTTTGCACAACATGG
GGGATCATGTAACTCGCCTTGAT
CGTTGGGAACCGGAGCTGAATGA
AGCCATACCAAACGACGAG...
```

4 different bases

The **Central Dogma** of **Biology**

DNA → **RNA**

```
ATGAGTATTCAACATTTCCGTGT
CGCCCTTATTCCCTTTTTTGCGG
CATTTTGCCTTCCTGTTTTTGCT
CACCCAGAAACGCTGGTGAAAGT
AAAAGATGCTGAAGATCAGTTGG
GTGCACGAGTGGGTTACATCGAA
CTGGATCTCAACAGCGGTAAGAT
CCTTGAGAGTTTTCGCCCCGAAG
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TTTAAAGTTCTGCTATGTGGCGC
GGTATTATCCCGTGTTGACGCCG
GGCAAGAGCAACTCGGTCGCCGC
ATACACTATTCTCAGAATGACTT
GGTTGAGTACTCACCAGTCACAG
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CTGCGGCCAACTTACTTCTGACA
ACGATCGGAGGACCGAAGGAGCT
AACCGCTTTTTTGCACAACATGG
GGGATCATGTAACTCGCCTTGAT
CGTTGGGAACCGGAGCTGAATGA
AGCCATACCAAACGACGAG...
```

4 different bases

The **Central Dogma** of **Biology**

DNA → **RNA**

DNA	RNA
ATGAGTATTCAACATTTCCGTGT	AUGAGUAUUCAACAUUUCCGUGU
CGCCCTTATTCCCTTTTTTGCGG	CGCCCUUAUUCCCUUUUUUGCGG
CATTTTGCCTTCCTGTTTTTGCT	CAUUUUGCCUUCCUGUUUUUGCU
CACCCAGAAACGCTGGTGAAAGT	CACCCAGAAACGCUGGUGAAAGU
AAAAGATGCTGAAGATCAGTTGG	AAAAGAUGCUGAAGAUCAGUUGG
GTGCACGAGTGGGTTACATCGAA	GUGCACGAGUGGGUUACAUCGAA
CTGGATCTCAACAGCGGTAAGAT	CUGGAUCUCAACAGCGGUAAGAU
CCTTGAGAGTTTTCGCCCCGAAG	CCUUGAGAGUUUUCGCCCCGAAG
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GGCAAGAGCAACTCGGTCGCCGC	GGCAAGAGCAACUCGGUCGCCGC
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ACGATCGGAGGACCGAAGGAGCT	ACGAUCGGAGGACCGAAGGAGCU
AACCGCTTTTTTGCACAACATGG	AACCGCUUUUUUGCACAACAUGG
GGGATCATGTAACTCGCCTTGAT	GGGAUCAUGUAACUCGCCUUGAU
CGTTGGGAACCGGAGCTGAATGA	CGUUGGGAACCGGAGCUGAAUGA
AGCCATACCAAACGACGAG...	AGCCAUACCAAACGACGAG...

4 different bases

The **Central Dogma** of **Biology**

DNA → **RNA** → **Protein**

ATGAGTATTCAACATTTCCGTGT
CGCCCTTATTCCCTTTTTTGCGG
CATTTTGCCTTCCTGTTTTTGCT
CACCCAGAAACGCTGGTGAAAGT
AAAAGATGCTGAAGATCAGTTGG
GTGCACGAGTGGGTTACATCGAA
CTGGATCTCAACAGCGGTAAGAT
CCTTGAGAGTTTTCGCCCCGAAG
AACGTTTTCCAATGATGAGCACT
TTTAAAGTTCTGCTATGTGGCGC
GGTATTATCCCGTGTTGACGCCG
GGCAAGAGCAACTCGGTCGCCGC
ATACACTATTCTCAGAATGACTT
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ACGATCGGAGGACCGAAGGAGCT
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GGGATCATGTAACTCGCCTTGAT
CGTTGGGAACCGGAGCTGAATGA
AGCCATACCAAACGACGAG...

AUGAGUAUUCAACAUUUCCGUGU
CGCCCUUAUUCCCUUUUUUGCGG
CAUUUUGCCUUCCUGUUUUUGCU
CACCCAGAAACGCUGGUGAAAGU
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GUGCACGAGUGGGUUACAUCGAA
CUGGAUCUCAACAGCGGUAAGAU
CCUUGAGAGUUUUCGCCCCGAAG
AACGUUUUCCAAUGAUGAGCACU
UUUAAAGUUCUGCUAUGUGGCGC
GGUAUUAUCCCGUGUUGACGCCG
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AUACACUAUUCUCAGAAUGACUU
GGUUGAGUACUCACCAGUCACAG
AAAAGCAUCUUACGGAUGGCAUG
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UGCCAUAACCAUGAGUGAUAACA
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ACGAUCGGAGGACCGAAGGAGCU
AACCGCUUUUUUGCACAACAUGG
GGGAUCAUGUAACUCGCCUUGAU
CGUUGGGAACCGGAGCUGAAUGA
AGCCAUACCAAACGACGAG...

4 different bases

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DNA → **RNA** → **Protein**

DNA

```
ATGAGTATTCAACATTTCCGTGT
CGCCCTTATTCCCTTTTTTGCGG
CATTTTGCCTTCCTGTTTTTGCT
CACCCAGAAACGCTGGTGAAAGT
AAAAGATGCTGAAGATCAGTTGG
GTGCACGAGTGGGTTACATCGAA
CTGGATCTCAACAGCGGTAAGAT
CCTTGAGAGTTTTCGCCCCGAAG
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GGTATTATCCCGTGTTGACGCCG
GGCAAGAGCAACTCGGTCGCCGC
ATACACTATTCTCAGAATGACTT
GGTTGAGTACTCACCAGTCACAG
AAAAGCATCTTACGGATGGCATG
ACAGTAAGAGAATTATGCAGTGC
TGCCATAACCATGAGTGATAACA
CTGCGGCCAACTTACTTCTGACA
ACGATCGGAGGACCGAAGGAGCT
AACCGCTTTTTTGCACAACATGG
GGGATCATGTAACTCGCCTTGAT
CGTTGGGAACCGGAGCTGAATGA
AGCCATACCAAACGACGAG...
```

RNA

```
AUGAGUAUUCAACAUUUCCGUGU
CGCCCUUAUUCCCUUUUUUGCGG
CAUUUUGCCUUCCUGUUUUUGCU
CACCCAGAAACGCUGGUGAAAGU
AAAAGAUGCUGAAGAUCAGUUGG
GUGCACGAGUGGGUUACAUCGAA
CUGGAUCUCAACAGCGGUAAGAU
CCUUGAGAGUUUUCGCCCCGAAG
AACGUUUUCCAAUGAUGAGCACU
UUUAAAGUUCUGCUAUGUGGCGC
GGUAUUAUCCCGUGUUGACGCCG
GGCAAGAGCAACUCGGUCGCCGC
AUACACUAUUCUCAGAAUGACUU
GGUUGAGUACUCACCAGUCACAG
AAAAGCAUCUUACGGAUGGCAUG
ACAGUAAGAGAAUUAUGCAGUGC
UGCCAUAACCAUGAGUGAUAACA
CUGCGGCCAACUUACUUCUGACA
ACGAUCGGAGGACCGAAGGAGCU
AACCGCUUUUUUGCACAACAUGG
GGGAUCAUGUAACUCGCCUUGAU
CGUUGGGAACCGGAGCUGAAUGA
AGCCAUACCAAACGACGAG...
```

Protein

```
MSIQHFRVALIPFFAAFCLPVFA
HPETLVKVKDAEDQLGARVGYIE
LDLNSGKILESFRPEERFPMMST
FKVLLCGAVLSRVDAGQEQLGRR
IHYSQNDLVEYSPVTEKHLTDGM
TVRELCSAAITMSDNTAANLLLT
TIGGPKELTAFLHNMGDHVTRLD
RWEPELNEAIPNDERDTTMPAAM
ATTLRKLLTGELLTLASRQQLID
WMEADKVAGPLLRSALPAGWFIA
DKSGAGERGSRGIIAALGPDGKP
SRIVVIYTTGSQATMDERNRQIA
EIGASLIKHW
```

20 different amino acids

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DNA

```
ATGAGTATTCAACATTTCCGTGT
CGCCCTTATTCCCTTTTTTGCGG
CATTTTGCCTTCCTGTTTTTGCT
CACCCAGAAACGCTGGTGAAAGT
AAAAGATGCTGAAGATCAGTTGG
GTGCACGAGTGGGTTACATCGAA
CTGGATCTCAACAGCGGTAAGAT
CCTTGAGAGTTTTCGCCCCGAAG
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TTTAAAGTTCTGCTATGTGGCGC
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AACCGCTTTTTTGCACAACATGG
GGGATCATGTAACTCGCCTTGAT
CGTTGGGAACCGGAGCTGAATGA
AGCCATACCAAACGACGAG...
```

RNA

```
AUGAGUAUUCAACAUUUCCGUGU
CGCCCUUAUUCCCUUUUUUGCGG
CAUUUUGCCUUCCUGUUUUUGCU
CACCCAGAAACGCUGGUGAAAGU
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CUGCGGCCAACUUACUUCUGACA
ACGAUCGGAGGACCGAAGGAGCU
AACCGCUUUUUUGCACAACAUGG
GGGAUCAUGUAACUCGCCUUGAU
CGUUGGGAACCGGAGCUGAAUGA
AGCCAUACCAAACGACGAG...
```

Protein

```
MSIQHFRVALIPFFAAFCLPVFA
HPETLVKVKDAEDQLGARVGYIE
LDLNSGKILESFRPEERFPMMST
FKVLLCGAVLSRVDAGQEQLGRR
IHYSQNDLVEYSPVTEKHLTDGM
TVRELCSAAITMSDNTAANLLLT
TIGGPKELTAFLHNMGDHVTRLD
RWEPELNEAIPNDERDTTMPAAM
ATTLRKLLTGELLTLASRQQLID
WMEADKVAGPLLRSALPAGWFIA
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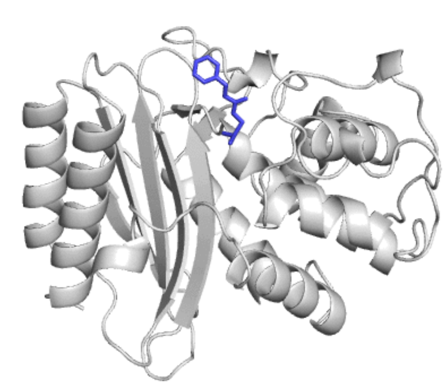
SRIVVIYTTGSQATMDERNRQIA
EIGASLIKHW
```

20 different amino acids



The **Central Dogma** of **Biology**

DNA → **RNA** → **Protein** → **Function**

```
ATGAGTATTCAACATTTCCGTGT
CGCCCTTATTCCCTTTTTTGCGG
CATTTTGCCTTCCTGTTTTTGCT
CACCCAGAAACGCTGGTGAAAGT
AAAAGATGCTGAAGATCAGTTGG
GTGCACGAGTGGGTTACATCGAA
CTGGATCTCAACAGCGGTAAGAT
CCTTGAGAGTTTTCGCCCCGAAG
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CGTTGGGAACCGGAGCTGAATGA
AGCCATACCAAACGACGAG...
```

```
AUGAGUAUUCAACAUUUCCGUGU
CGCCCUUAUUCCCUUUUUUGCGG
CAUUUUGCCUUCCUGUUUUUGCU
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AAAAGAUGCUGAAGAUCAGUUGG
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GGUUGAGUACUCACCAGUCACAG
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AACCGCUUUUUUGCACAACAUGG
GGGAUCAUGUAACUCGCCUUGAU
CGUUGGGAACCGGAGCUGAAUGA
AGCCAUACCAAACGACGAG...
```

```
MSIQHFRVALIPFFAAFCLPVFA
HPETLVKVKDAEDQLGARVGYIE
LDLNSGKILESFRPEERFPMMST
FKVLLCGAVLSRVDAGQEQLGRR
IHYSQNDLVEYSPVTEKHLTDGM
TVRELCSAAITMSDNTAANLLLT
TIGGPKELTAFLHNMGDHVTRLD
RWEPELNEAIPNDERDTTMPAAM
ATTLRKLLTGELLTLASRQQLID
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SRIVVIYTTGSQATMDERNRQIA
EIGASLIKHW
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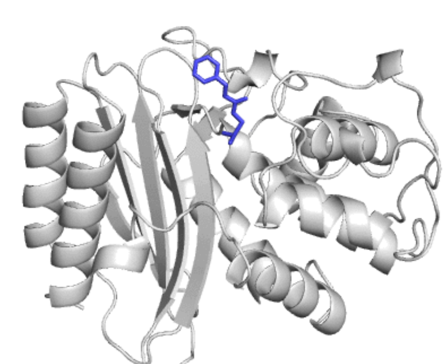

The **Central Dogma** of **Biology**

DNA → **RNA** → **Protein** → **Function**

ATGAGTATTCAACATTTCCGTGT
CGCCCTTATTCCCTTTTTTGCGG
CATTTTGCCTTCCTGTTTTTGCT
CACCCAGAAACGCTGGTGAAAGT
AAAAGATGCTGAAGATCAGTTGG
GTGCACGAGTGGGTTACATCGAA
CTGGATCTCAACAGCGGTAAGAT
CCTTGAGAGTTTTCGCCCCGAAG
AACGTTTTCCAATGATGAGCACT
TTTAAAGTTCTGCTATGTGGCGC
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GGGATCATGTAACTCGCCTTGAT
CGTTGGGAACCGGAGCTGAATGA
AGCCATACCAAACGACGAG...

AUGAGUAUUCAACAUUUCCGUGU
CGCCCUUAUUCCCUUUUUUGCGG
CAUUUUGCCUUCCUGUUUUUGCU
CACCCAGAAACGCUGGUGAAAGU
AAAAGAUGCUGAAGAUCAGUUGG
GUGCACGAGUGGGUUACAUCGAA
CUGGAUCUCAACAGCGGUAAGAU
CCUUGAGAGUUUUCGCCCCGAAG
AACGUUUUCCAAUGAUGAGCACU
UUUAAAGUUCUGCUAUGUGGCGC
GGUAUUAUCCCGUGUUGACGCCG
GGCAAGAGCAACUCGGUCGCCGC
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GGUUGAGUACUCACCAGUCACAG
AAAAGCAUCUUACGGAUGGCAUG
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AGCCAUACCAAACGACGAG...

MSIQHFRVALIPFFAAFCLPVFA
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FKVLLCGAVLSRVDAGQEQLGRR
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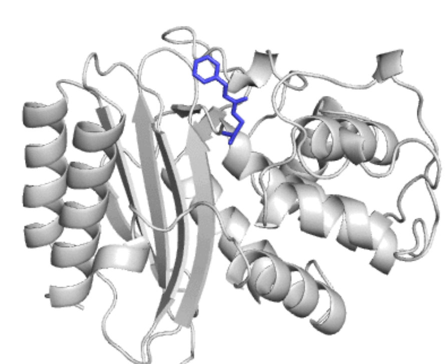
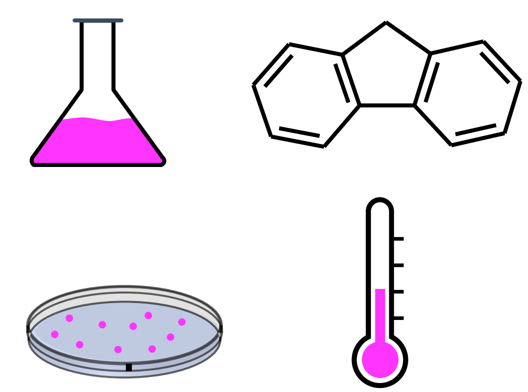
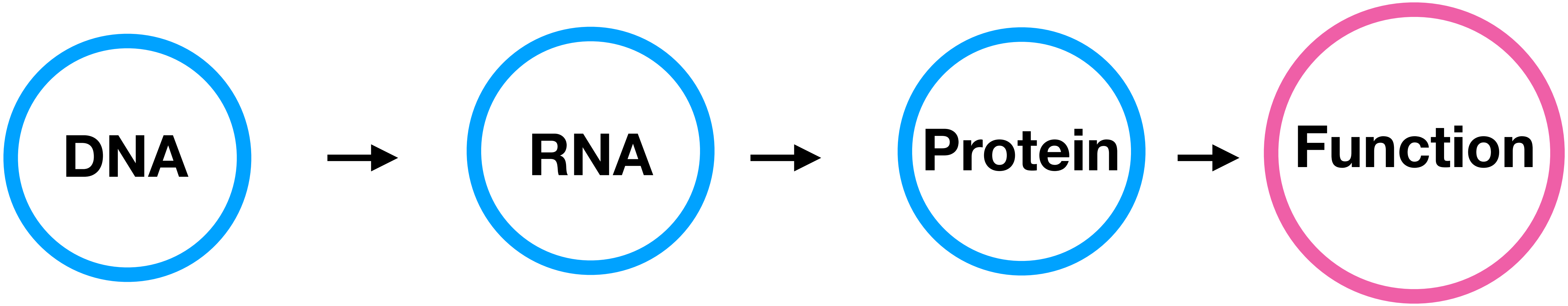
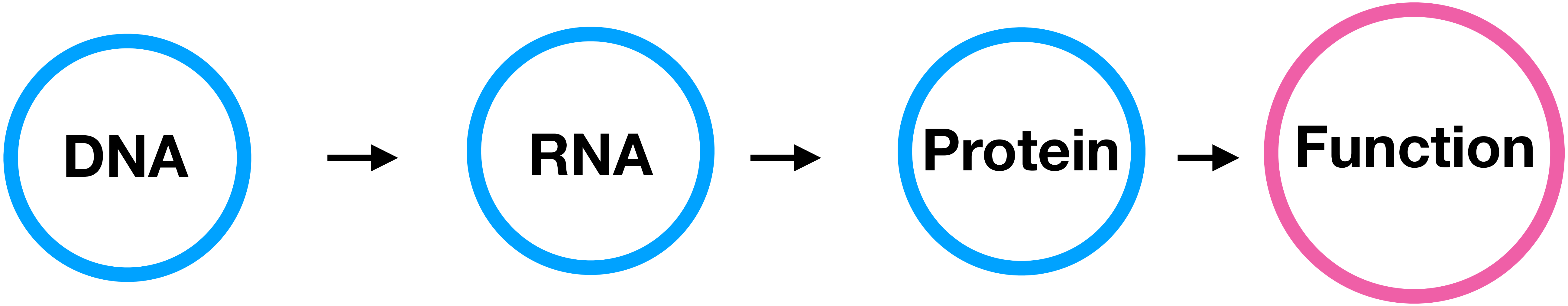




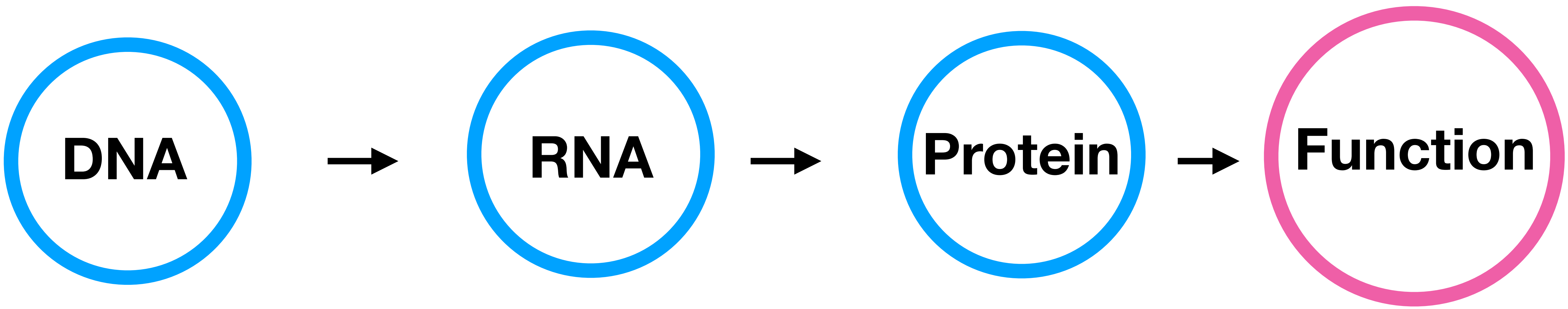
The **Central Dogma** of **Biology**



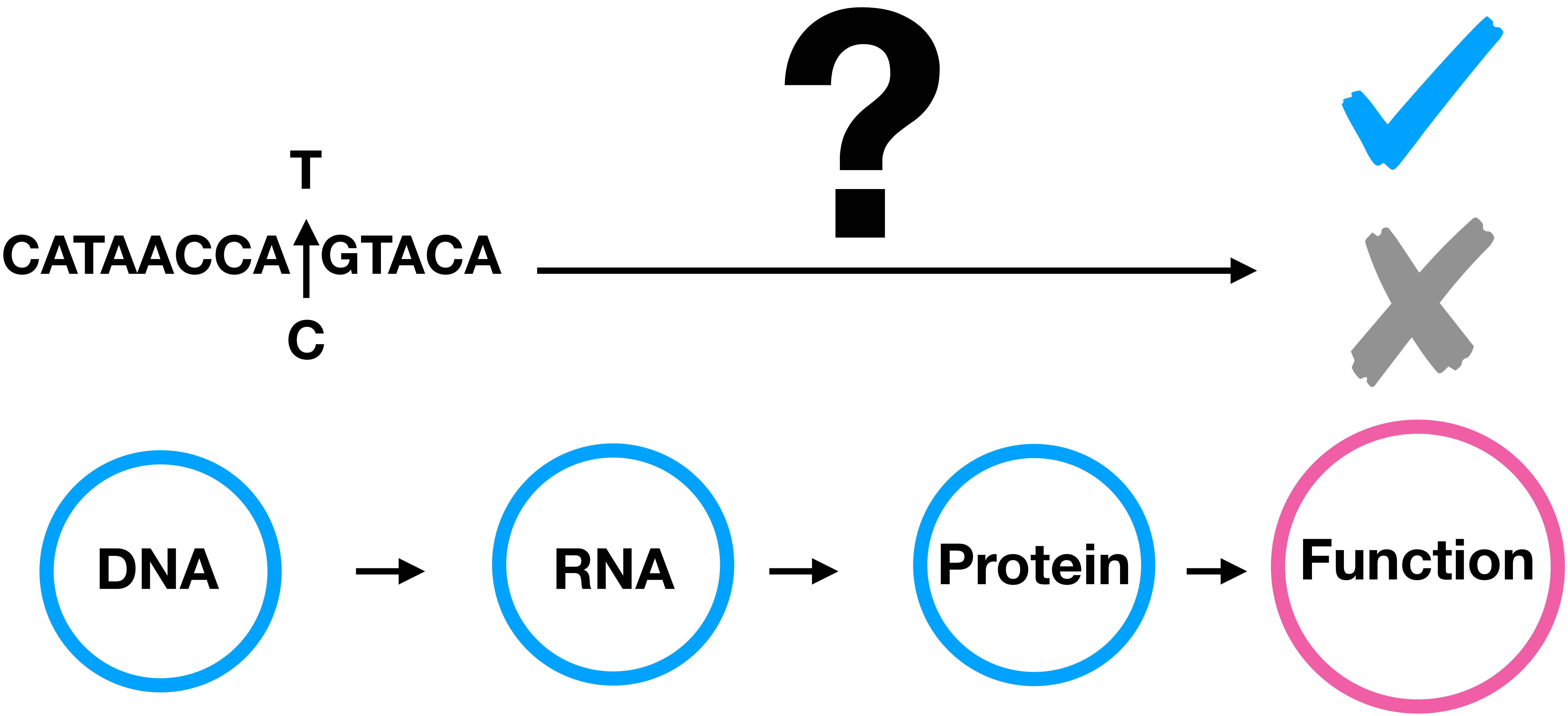
Mutations alter biological **function**



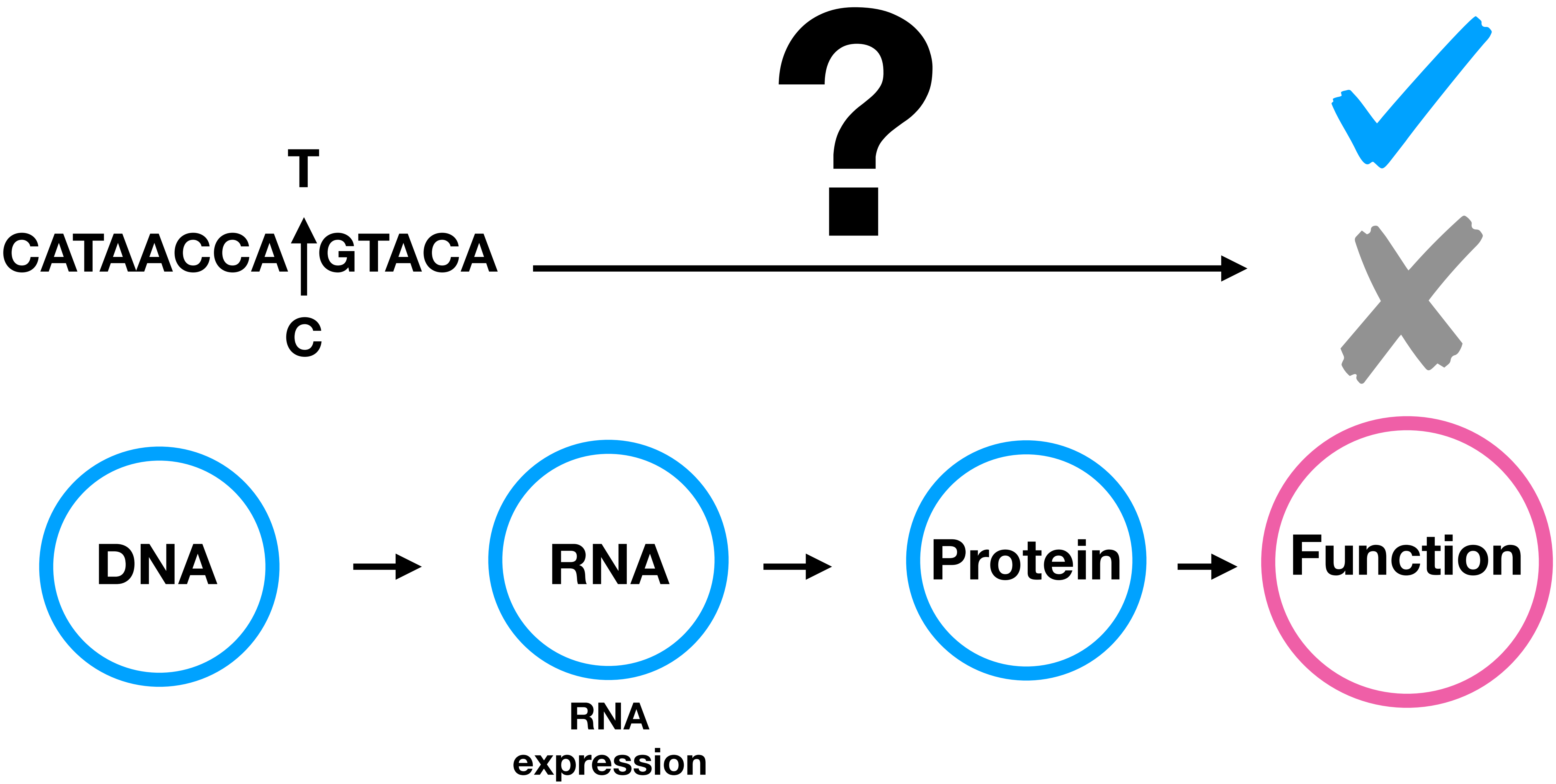
Mutations alter biological **function**



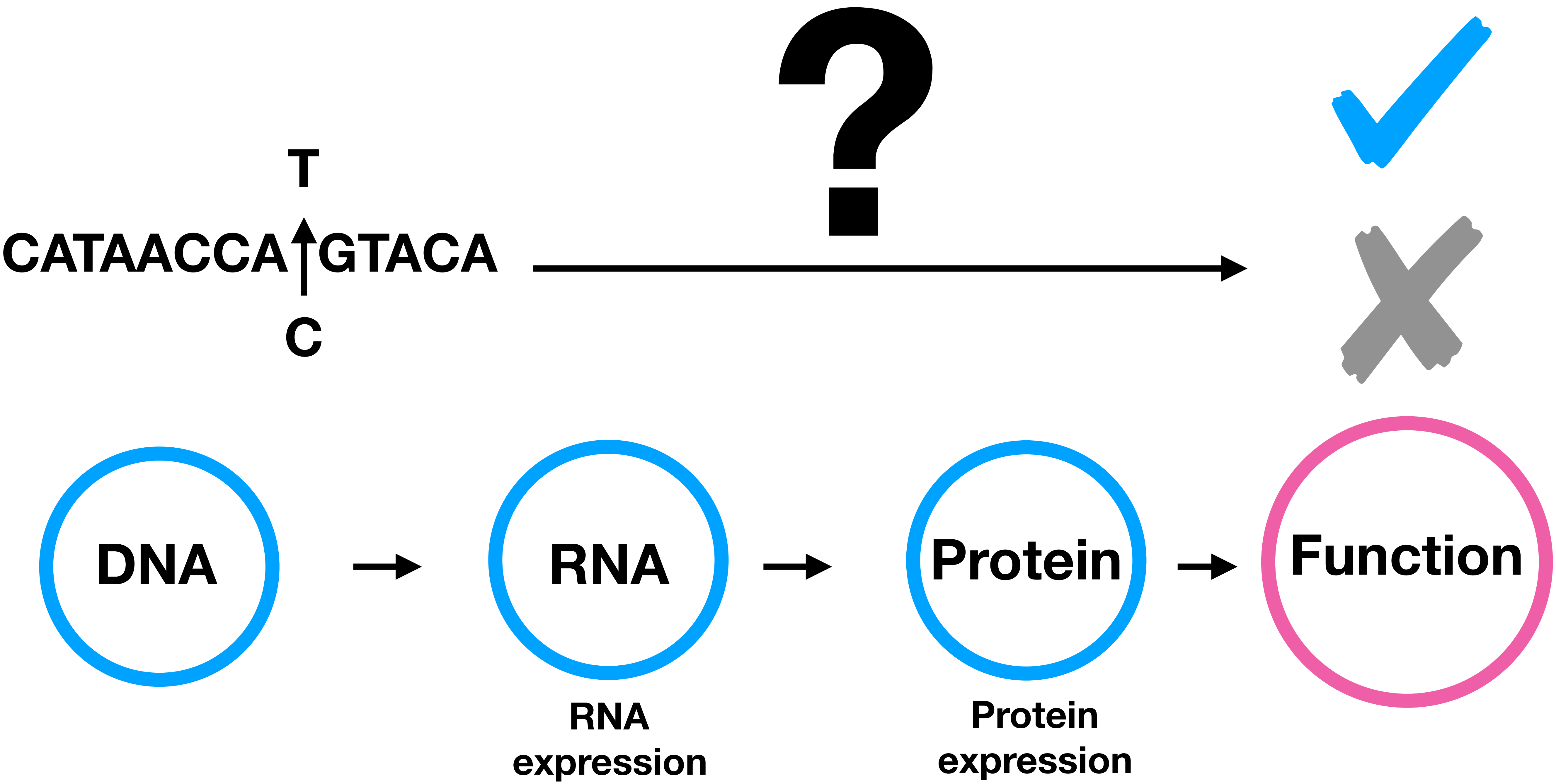
Mutations alter biological **function**



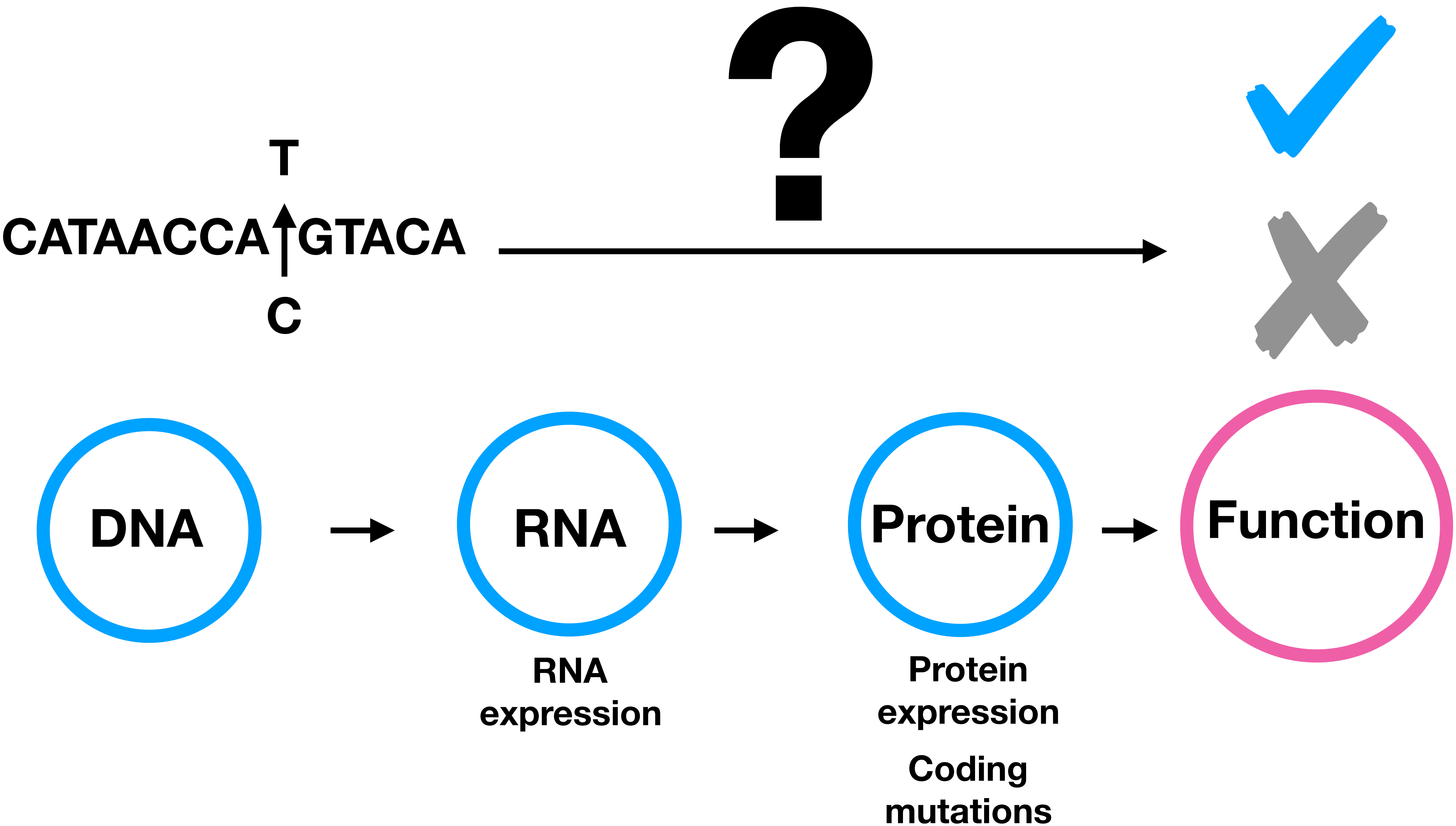
Mutations alter biological **function**



Mutations alter biological **function**



Mutations alter biological **function**



Mutation effect prediction is **important**

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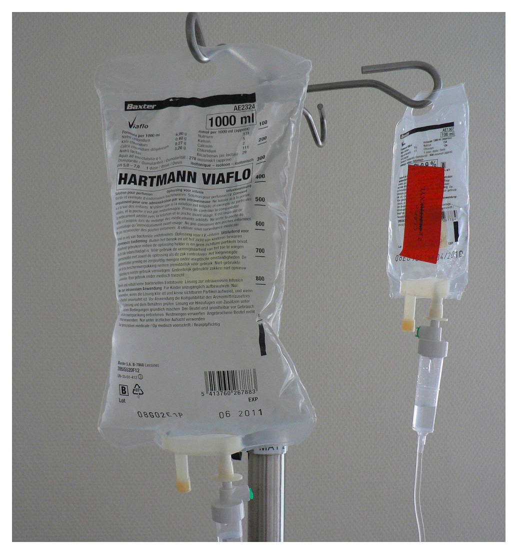
Understanding disease

“Does this mutation cause cancer?”

Mutation effect prediction is **important**

Understanding disease

Biomedicine



"Does this mutation cause cancer?"

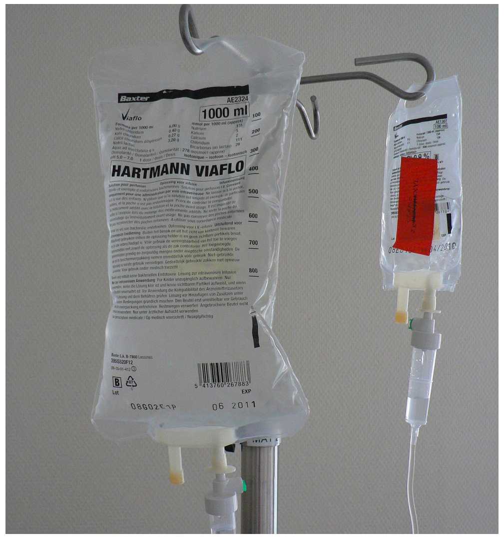
"Is this antibody stable in a patient?"

Mutation effect prediction is important

Understanding disease

Biomedicine

Bioengineering

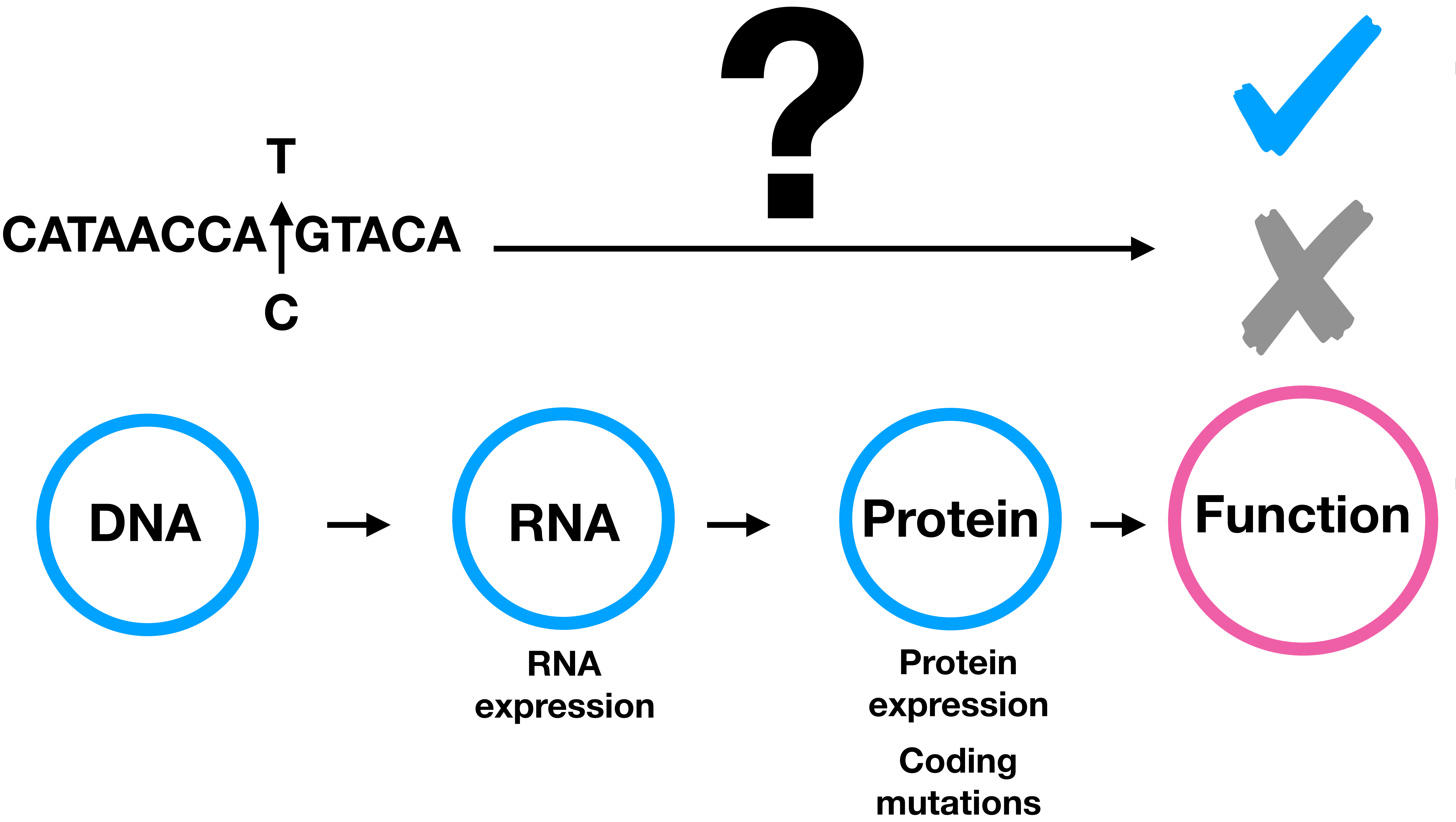


"Does this mutation cause cancer?"

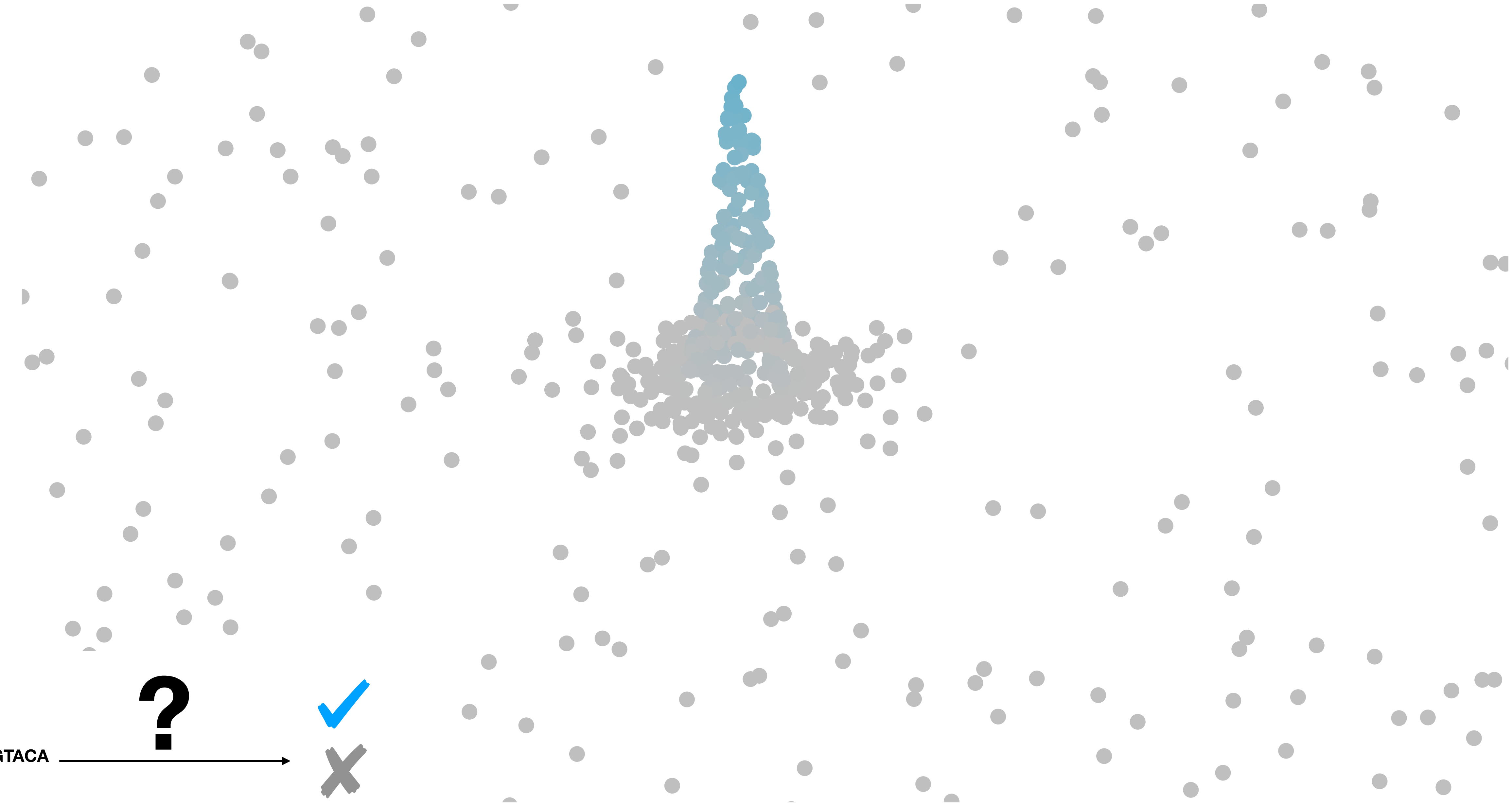
"Is this antibody stable in a patient?"

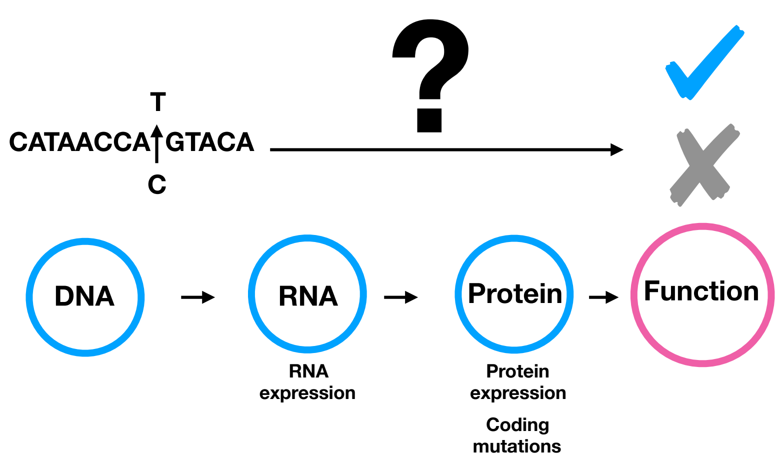
"Can this microbe be used to create vitamins?"

Mutations alter biological **function**

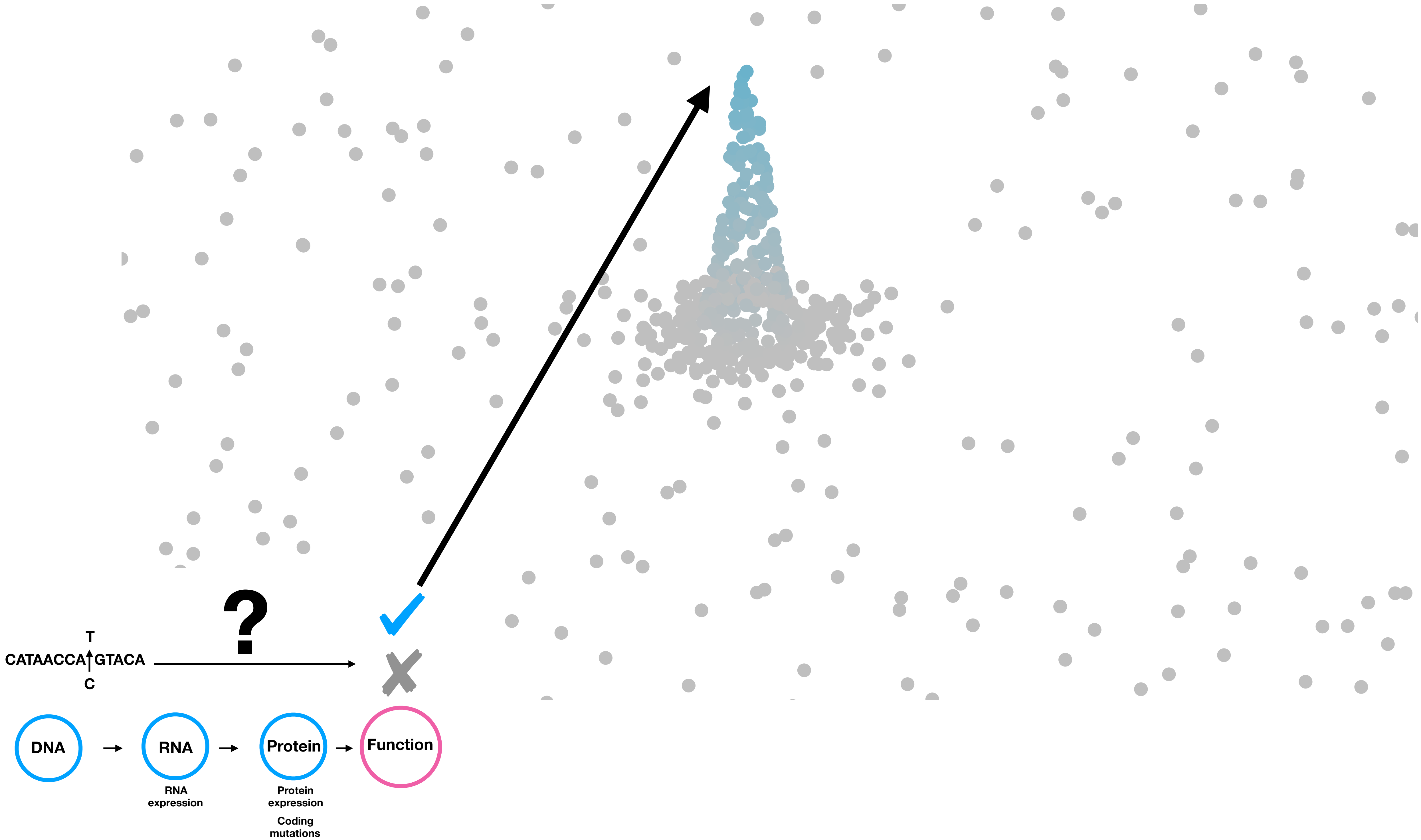


Mutations alter biological **function**

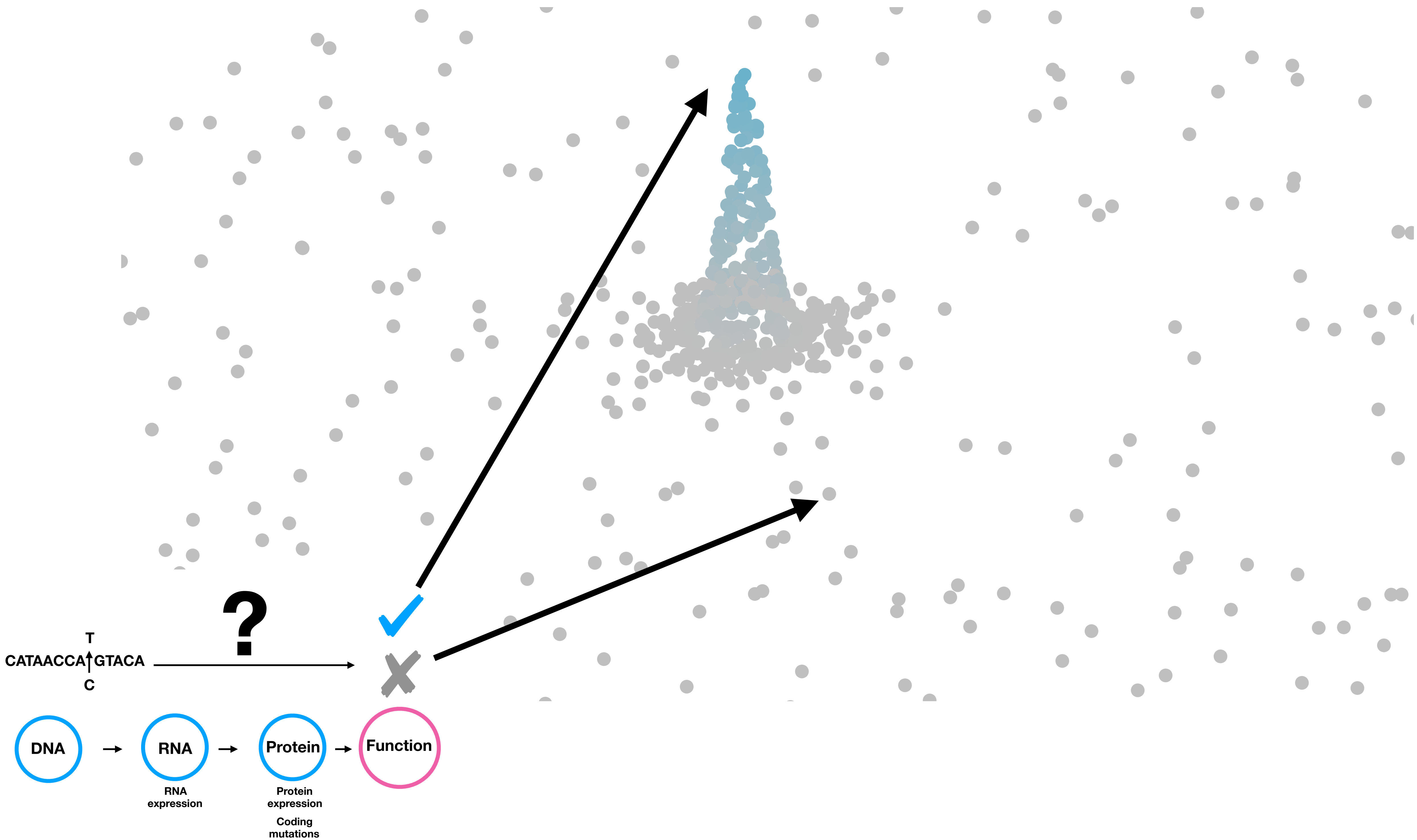




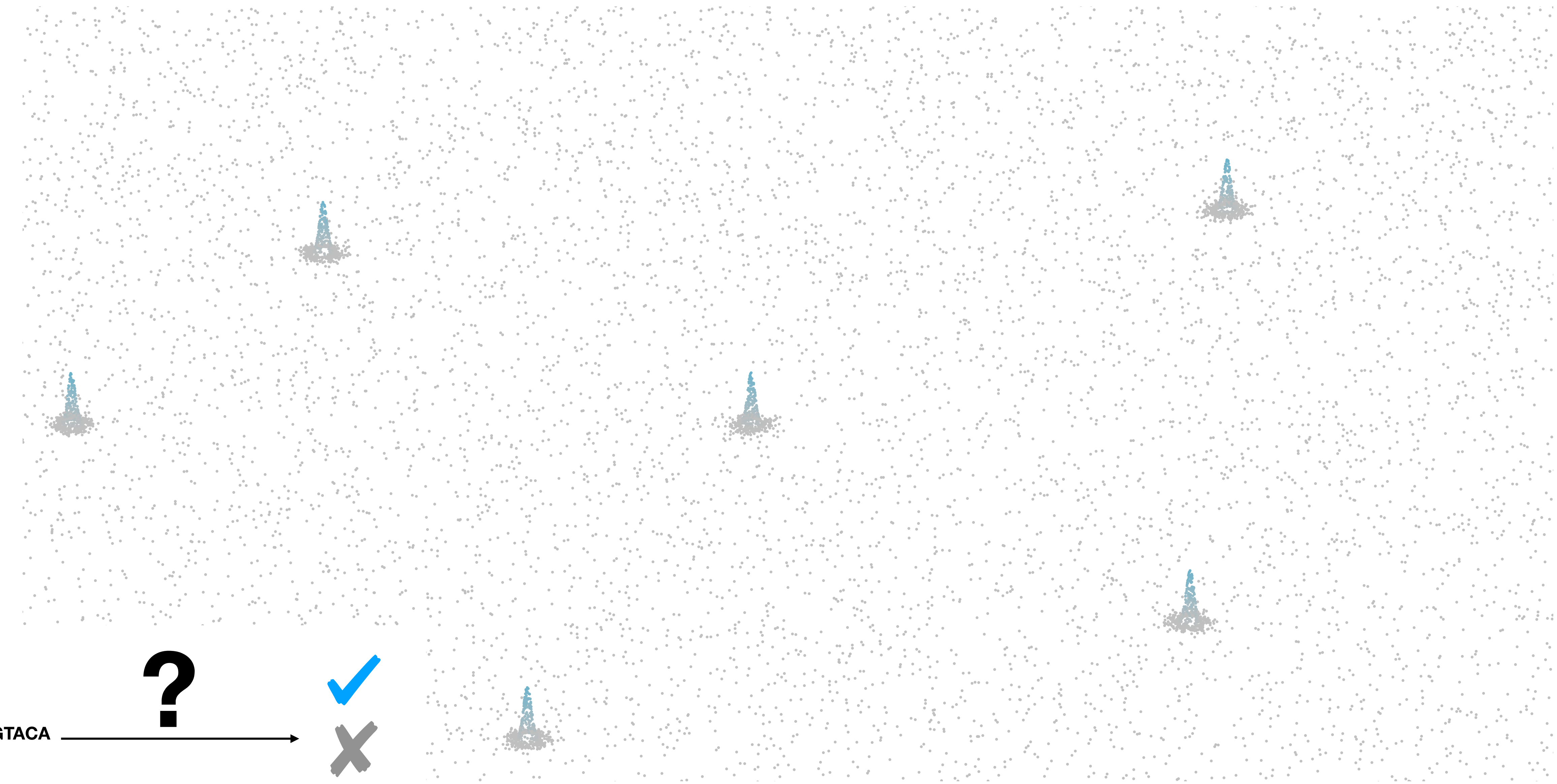
Mutations alter biological **function**

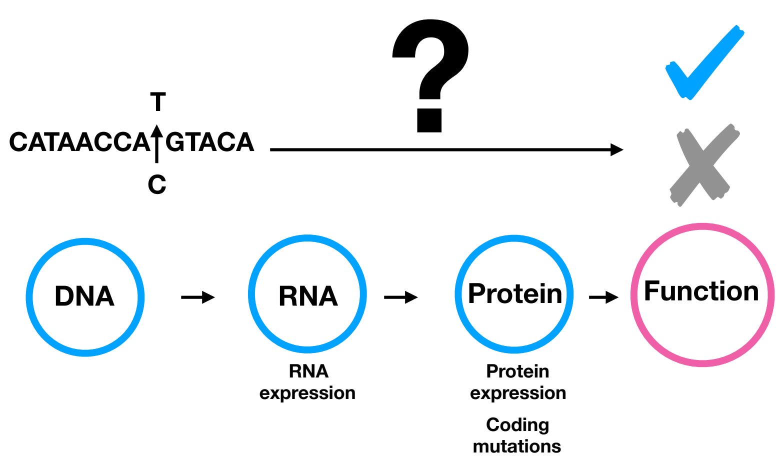


Mutations alter biological **function**

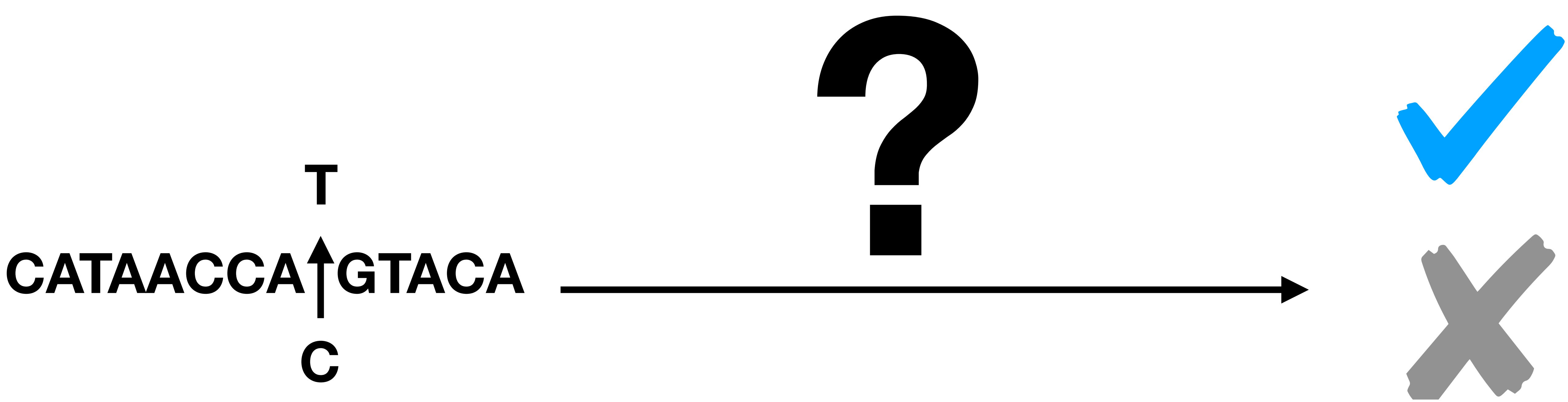


Mutations alter biological **function**



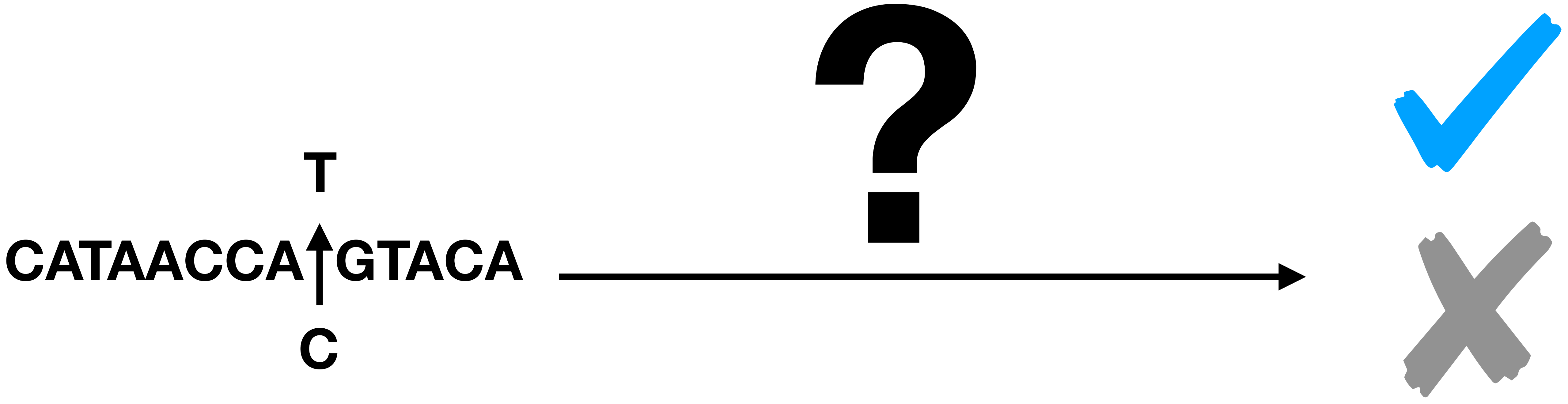


Mutations alter biological **function**



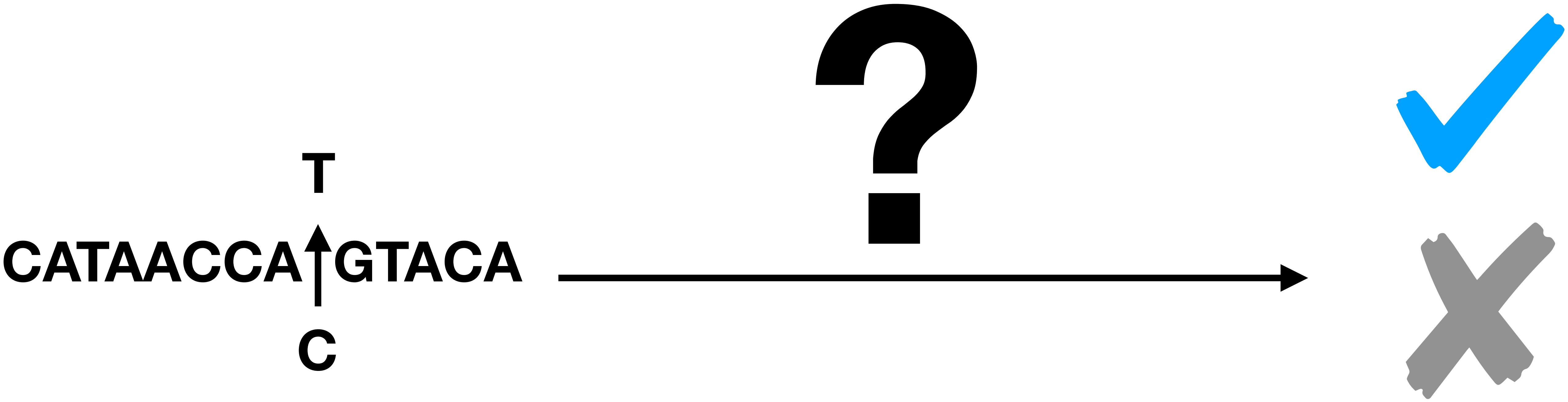
Mutation effect prediction

is **hard**



Mutation effect prediction
is **hard**

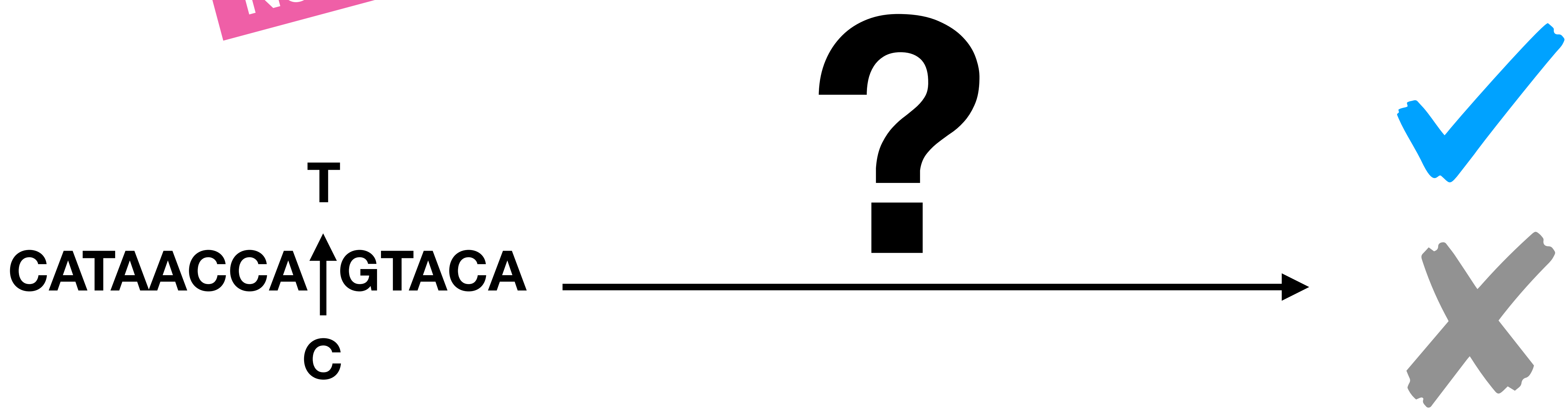
Sparsely sampled



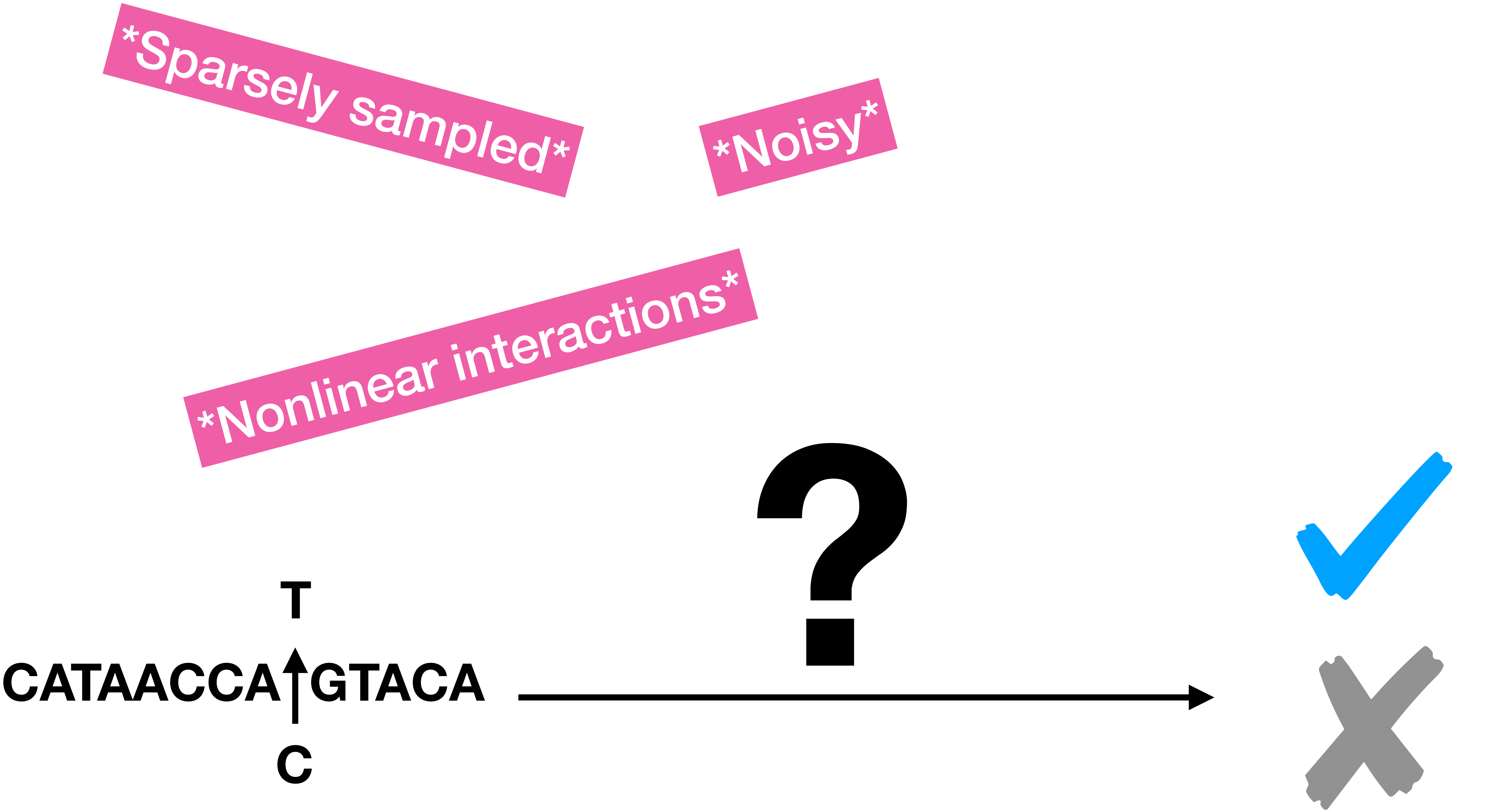
Mutation effect prediction is **hard**

Sparsely sampled

Nonlinear interactions



Mutation effect prediction is **hard**



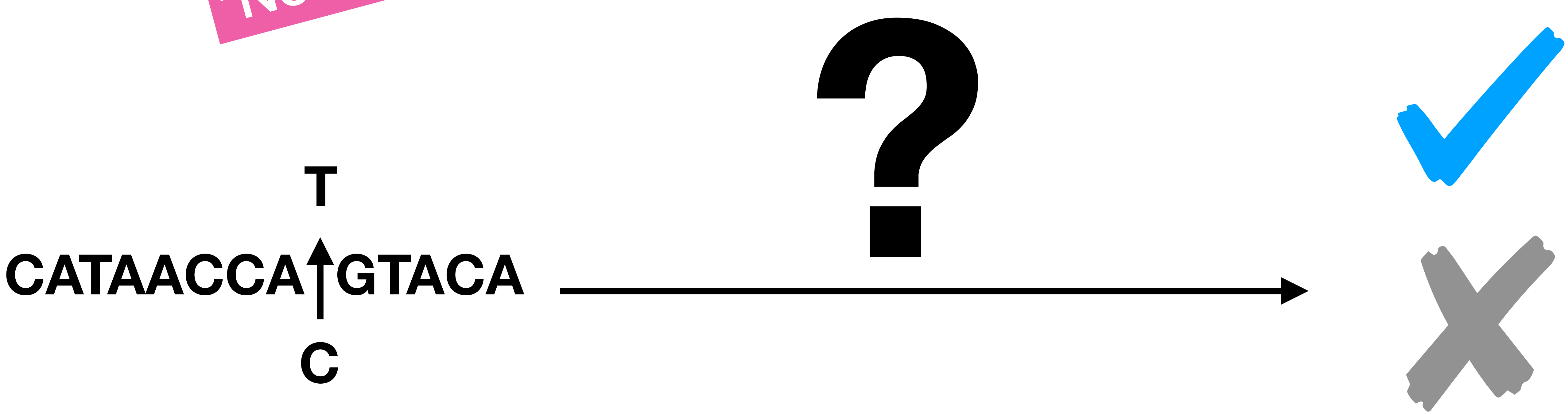
Mutation effect prediction is **hard**

Sparsely sampled

Noisy

Nonlinear interactions

Confounders



Mutation effect prediction is **hard**

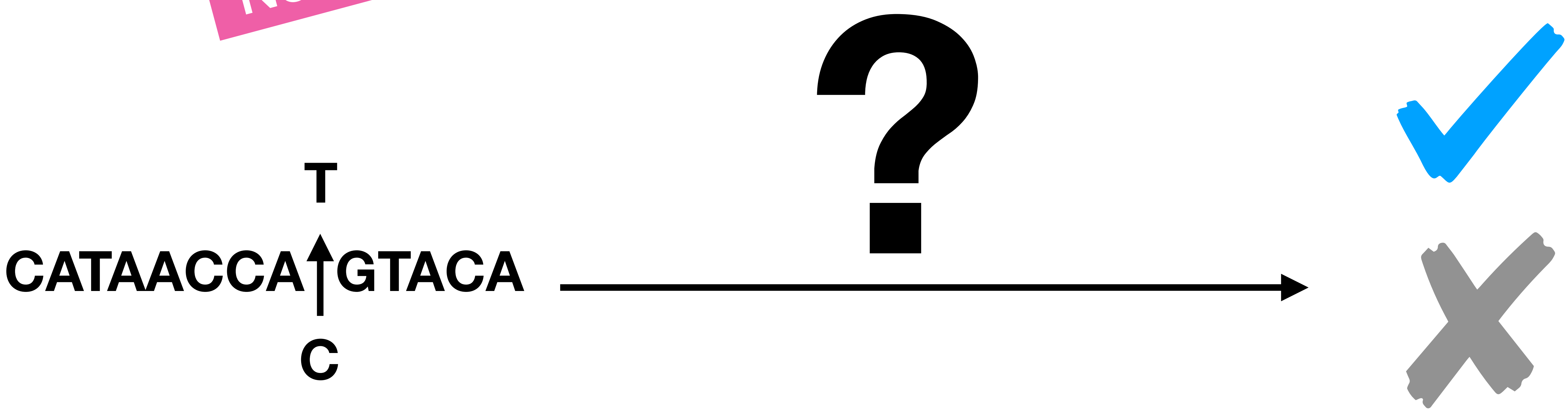
Sparsely sampled

Noisy

Effect not measured

Nonlinear interactions

Confounders



Part I:

Genotype -> Phenotype

in **proteins**

Part I:

Genotype -> Phenotype in **proteins**

DNA

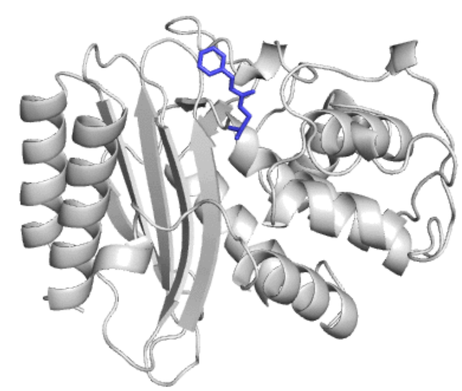
ATGAGTATTCAACATTTCCGTGT
CGCCCTTATTCCCTTTTTTGCGG
CATTTTGCCTTCCTGTTTTTGCT
CACCCAGAAACGCTGGTGAAAGT
AAAAGATGCTGAAGATCAGTTGG
GTGCACGAGTGGGTTACATCGAA
CTGGATCTCAACAGCGGTAAGAT
CCTTGAGAGTTTTCGCCCCGAAG
AACGTTTTCCAATGATGAGCACT
TTTAAAGTTCTGCTATGTGGCGC
GGTATTATCCCGTGTTGACGCCG
GGCAAGAGCAACTCGGTCGCCGC
ATACACTATTCTCAGAATGACTT
GGTTGAGTACTCACCAGTCACAG
AAAAGCATCTTACGGATGGCATG
ACAGTAAGAGAATTATGCAGTGC
TGCCATAACCATGAGTGATAACA
CTGCGGCCAACTTACTTCTGACA
ACGATCGGAGGACCGAAGGAGCT
AACCGCTTTTTTGCACAACATGG
GGGATCATGTAACTCGCCTTGAT
CGTTGGGAACCGGAGCTGAATGA
AGCCATACCAAACGACGAG...

RNA

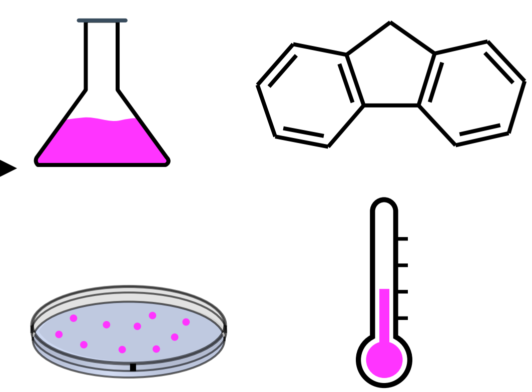
Protein

MSIQHFRVALIPFFAAFCLPVFA
HPETLVKVKDAEDQLGARVGYIE
LDLNSGKILESFRPEERFPMMST
FKVLLCGAVLSRVDAGQEQLGRR
IHYSQNDLVEYSPVTEKHLTDGM
TVRELCSAAITMSDNTAANLLLT
TIGGPKELTAFLHNMGDHVTRLD
RWEPELNEAIPNDERDTTMPAAM
ATTLRKLLTGELLTLASRQQLID
WMEADKVAGPLLRSALPAGWFIA
DKSGAGERGSRGIIAALGPDGKP
SRIVVIYTTGSQATMDERNRQIA
EIGASLIKHW

Structure



Function



Part I:

Genotype -> Phenotype
in **proteins**

DNA

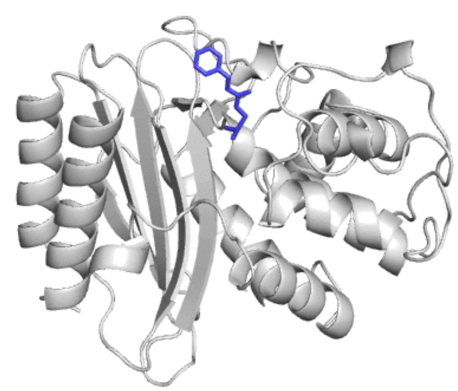
```
ATGAGTATTCAACATTTCCGTGT
CGCCCTTATTCCCTTTTTTGCGG
CATTTTGCCTTCCTGTTTTTGCT
CACCCAGAAACGCTGGTGAAAGT
AAAAGATGCTGAAGATCAGTTGG
GTGCACGAGTGGGTTACATCGAA
CTGGATCTCAACAGCGGTAAGAT
CCTTGAGAGTTTTCGCCCCGAAG
AACGTTTTCCAATGATGAGCACT
TTTAAAGTTCTGCTATGTGGCGC
GGTATTATCCCGTGTTGACGCCG
GGCAAGAGCAACTCGGTCGCCGC
ATACACTATTCTCAGAATGACTT
GGTTGAGTACTCACCAGTCACAG
AAAAGCATCTTACGGATGGCATG
ACAGTAAGAGAATTATGCAGTGC
TGCCATAACCATGAGTGATAACA
CTGCGGCCAACTTACTTCTGACA
ACGATCGGAGGACCGAAGGAGCT
AACCGCTTTTTTGCACAACATGG
GGGATCATGTAACTCGCCTTGAT
CGTTGGGAACCGGAGCTGAATGA
AGCCATACCAAACGACGAG...
```

RNA

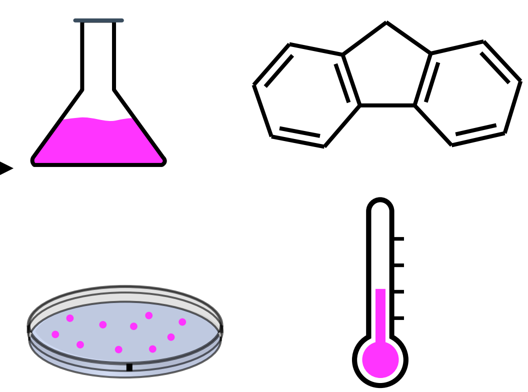
Protein

```
MSIQHFRVALIPFFAAFCLPVFA
HPETLVKVKDAEDQLGARVGYIE
LDLNSGKILESFRPEERFPMMST
FKVLLCGAVLSRVDAGQEQLGRR
IHYSQNDLVEYSPVTEKHLTDGM
TVRELCSAAITMSDNTAANLLLT
TIGGPKELTAFLHNMGDHVTRLD
RWEPELNEAIPNDERDTTMPAAM
ATTLRKLLTGELLTLASRQQLID
WMEADKVAGPLLRSALPAGWFIA
DKSGAGERGSRGIIAALGPDGKP
SRIVVIYTTGSQATMDERNRQIA
EIGASLIKHW
```

Structure



Function



Mutations impact protein **function**

Mutations impact protein **function**

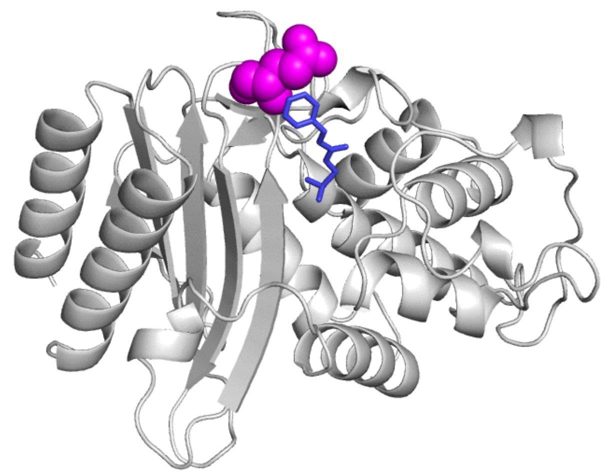
```
MSIQHFRVALIPFFAAFCLPVFA
HPETLVKVKDAEDQLGARVGYIE
LDLNSGKILESFRPEERFPMMST
FKVLLCGAVLSRVDAGQEQLGRR
IHYSQNDLVEYSPVTEKHLTDGM
TVRELCSAAITMSDNTAANLLLT
TIGGPKELTAFLHNMGDHVTRLD
RWEPELNEAIPNDERDTTMPAAM
ATTLRKLLTGELLTLASRQQLID
WMEADKVAGPLLRSALPAGWFIA
DKSGAGERGSRGIIAALGPDGKP
SRIVVIYTTGSQATMDERNRQIA
EIGASLIKHW
```

Sequence

Mutations impact protein **function**

```
MSIQHFRVALIPFFAAFCLPVFA
HPETLVKVKDAEDQLGARVGYIE
LDLNSGKILESFRPEERFPMMST
FKVLLCGAVLSRVDAGQEQLGRR
IHYSQNDLVEYSPVTEKHLTDGM
TVRELCSAAITMSDNTAANLLLT
TIGGPKELTAFLHNMGDHVTRLD
RWEPELNEAIPNDERDTTMPAAM
ATTLRKLLTGELLTLASRQQLID
WMEADKVAGPLLRSALPAGWFIA
DKSGAGERGSRGIIAALGPDGKP
SRIVVIYTTGSQATMDERNRQIA
EIGASLIKHW
```

E→L



Sequence **Structure**

Mutations impact protein **function**

```
MSIQHFRVALIPFFAAFCLPVFA
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LDLNSGKILESFRPEERFPMMST
FKVLLCGAVLSRVDAGQEQLGRR
IHYSQNDLVEYSPVTEKHLTDGM
TVRELCSAAITMSDNTAANLLLT
TIGGPKELTAFLHNMGDHVTRLD
RWEPELNEAIPNDERDTTMPAAM
ATTLRKLLTGELLTLASRQQLID
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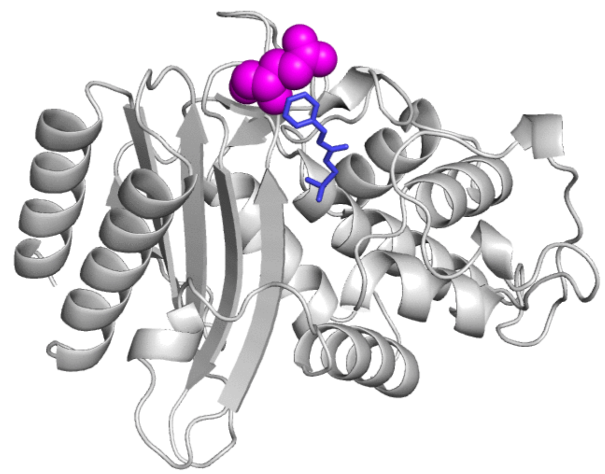
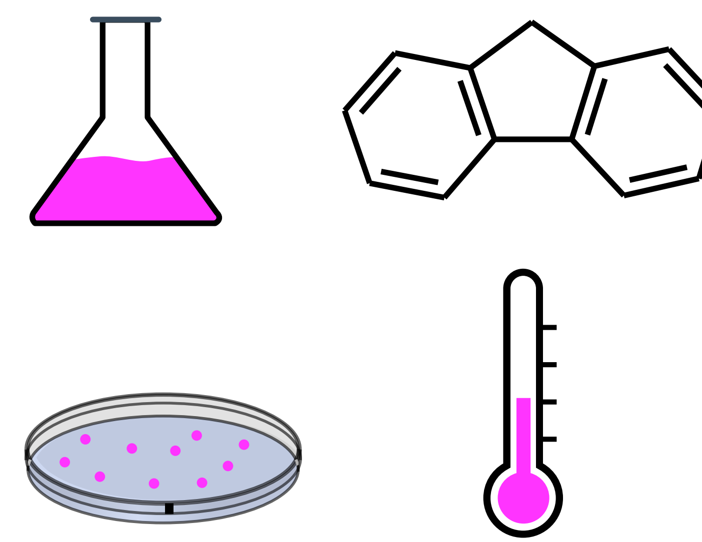
DKSGAGERGSRGIIAALGPDGKP
SRIVVIYTTGSQATMDERNRQIA
EIGASLIKHW
```

E→L



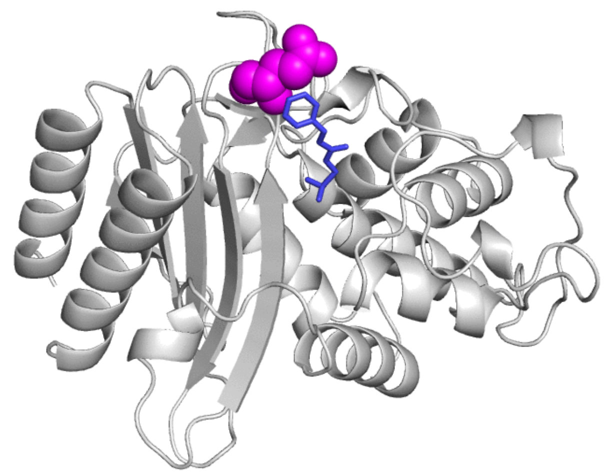


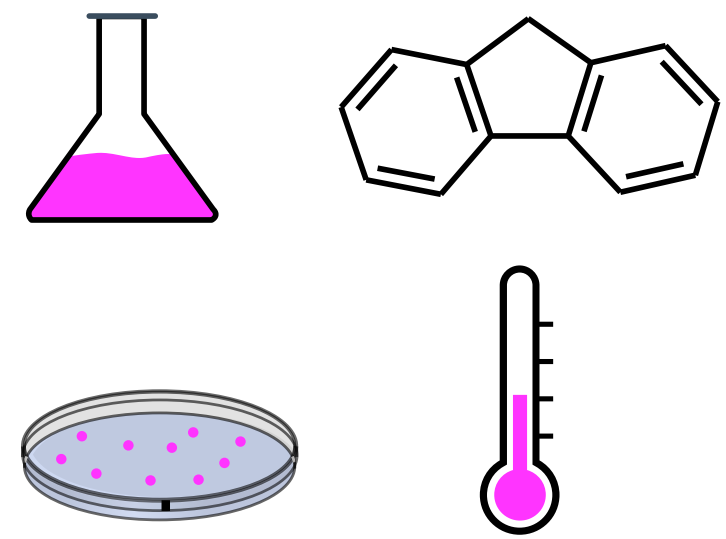
Sequence **Structure** **Function**

Mutations impact protein **function**

```
MSIQHFRVALIPFFAAFCLPVFA
HPETLVKVKDAEDQLGARVGYIE
LDLNSGKILESFRPEERFPMMST
FKVLLCGAVLSRVDAGQEQLGRR
IHYSQNDLVEYSPVTEKHLTDGM
TVRELCSAAITMSDNTAANLLLT
TIGGPKELTAFLHNMGDHVTRLD
RWEPELNEAIPNDERDTTMPAAM
ATTLRKLLTGELLTLASRQQLID
WMEADKVAGPLLRSALPAGWFIA
DKSGAGERGSRGIIAALGPDGKP
SRIVVIYTTGSQATMDERNRQIA
EIGASLIKHW
```

E→L





```
MSIQHFRVALIPFFAAFCLPVFA
HPETLVKVKDAEDQLGARVGYIE
LDLNSGKILESFRPEERFPMMST
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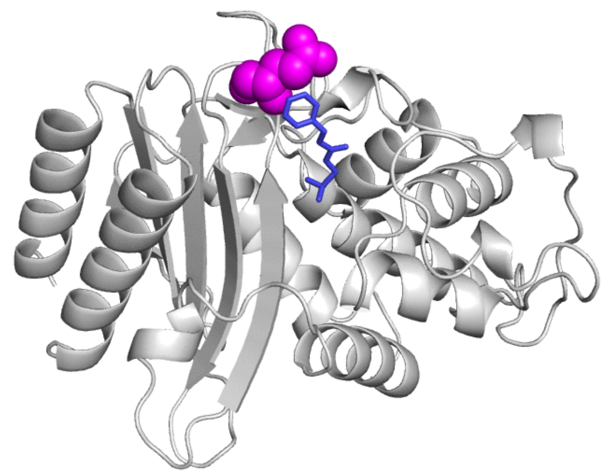
IHYSQNDLVEYSPVTEKHLTDGM
TVRELCSAAITMSDNTAANLLLT
TIGGPKELTAFLHNMGDHVTRLD
RWEPELNEAIPNDERDTTMPAAM
ATTLRKLLTGELLTLASRQQLID
WMEADKVAGPLLRSALPAGWFIA
DKSGAGERGSRGIIAALGPDGKP
SRIVVIYTTGSQATMDERNRQIA
EIGASLIKHW
```

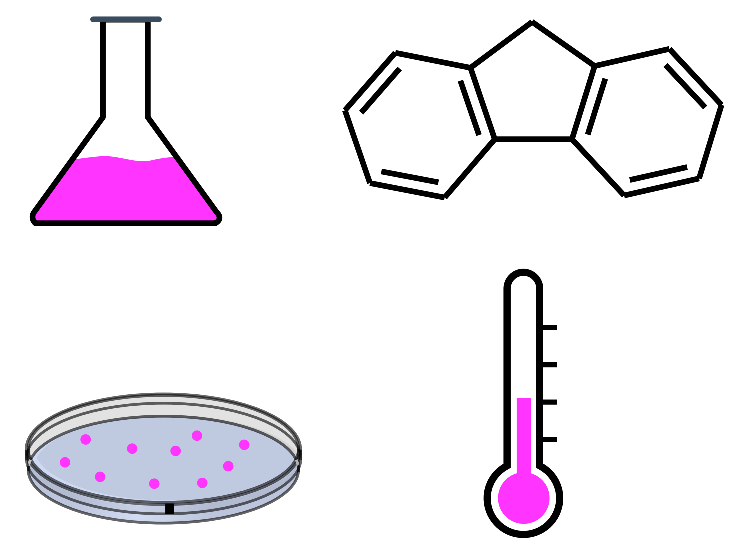
Sequence **Structure** **Function**

Mutations impact protein **function**

```
MSIQHFRVALIPFFAAFCLPVFA
HPETLVKVKDAEDQLGARVGYIE
LDLNSGKILESFRPEERFPMMST
FKVLLCGAVLSRVDAGQEQLGRR
IHYSQNDLVEYSPVTEKHLTDGM
TVRELCSAAITMSDNTAANLLLT
TIGGPKELTAFLHNMGDHVTRLD
RWEPELNEAIPNDERDTTMPAAM
ATTLRKLLTGELLTLASRQQLID
WMEADKVAGPLLRSALPAGWFIA
DKSGAGERGSRGIIAALGPDGKP
SRIVVIYTTGSQATMDERNRQIA
EIGASLIKHW
```

E→L





```
MSIQHFRVALIPFFAAFCLPVFA
HPETLVKVKDAEDQLGARVGYIE
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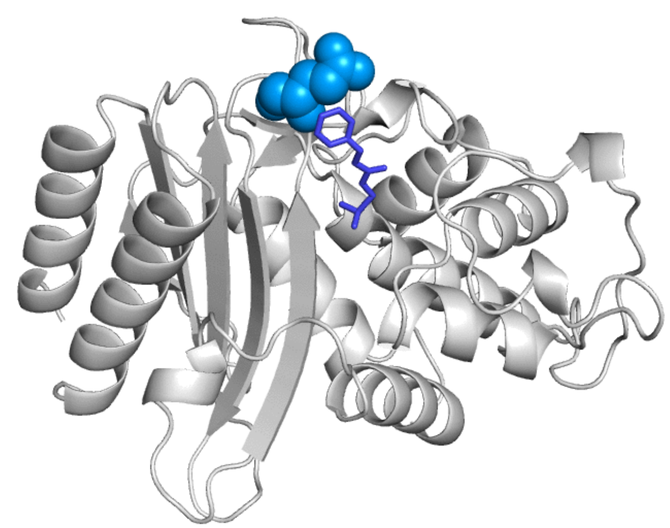
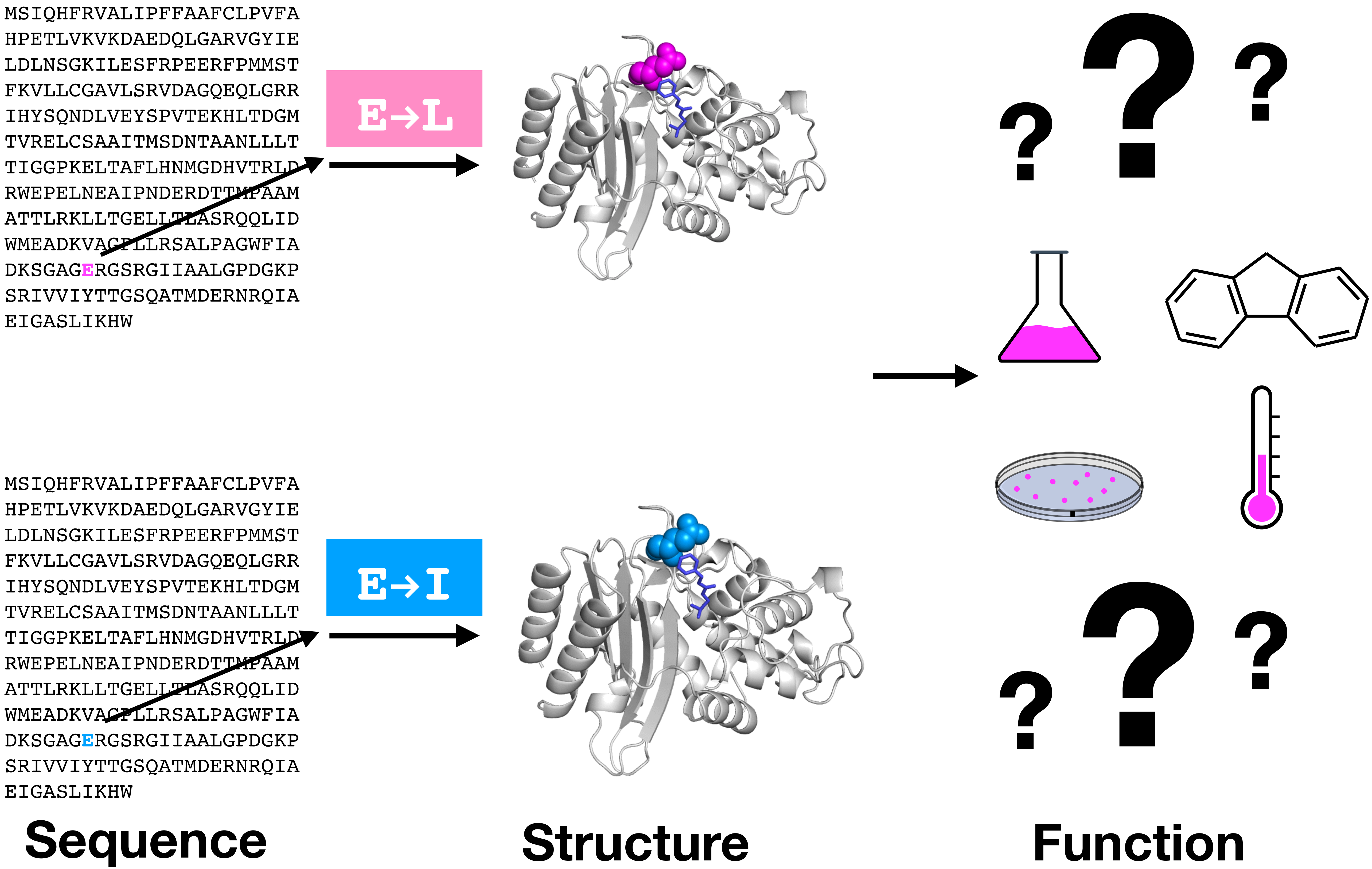
IHYSQNDLVEYSPVTEKHLTDGM
TVRELCSAAITMSDNTAANLLLT
TIGGPKELTAFLHNMGDHVTRLD
RWEPELNEAIPNDERDTTMPAAM
ATTLRKLLTGELLTLASRQQLID
WMEADKVAGPLLRSALPAGWFIA
DKSGAGERGSRGIIAALGPDGKP
SRIVVIYTTGSQATMDERNRQIA
EIGASLIKHW
```

E→I

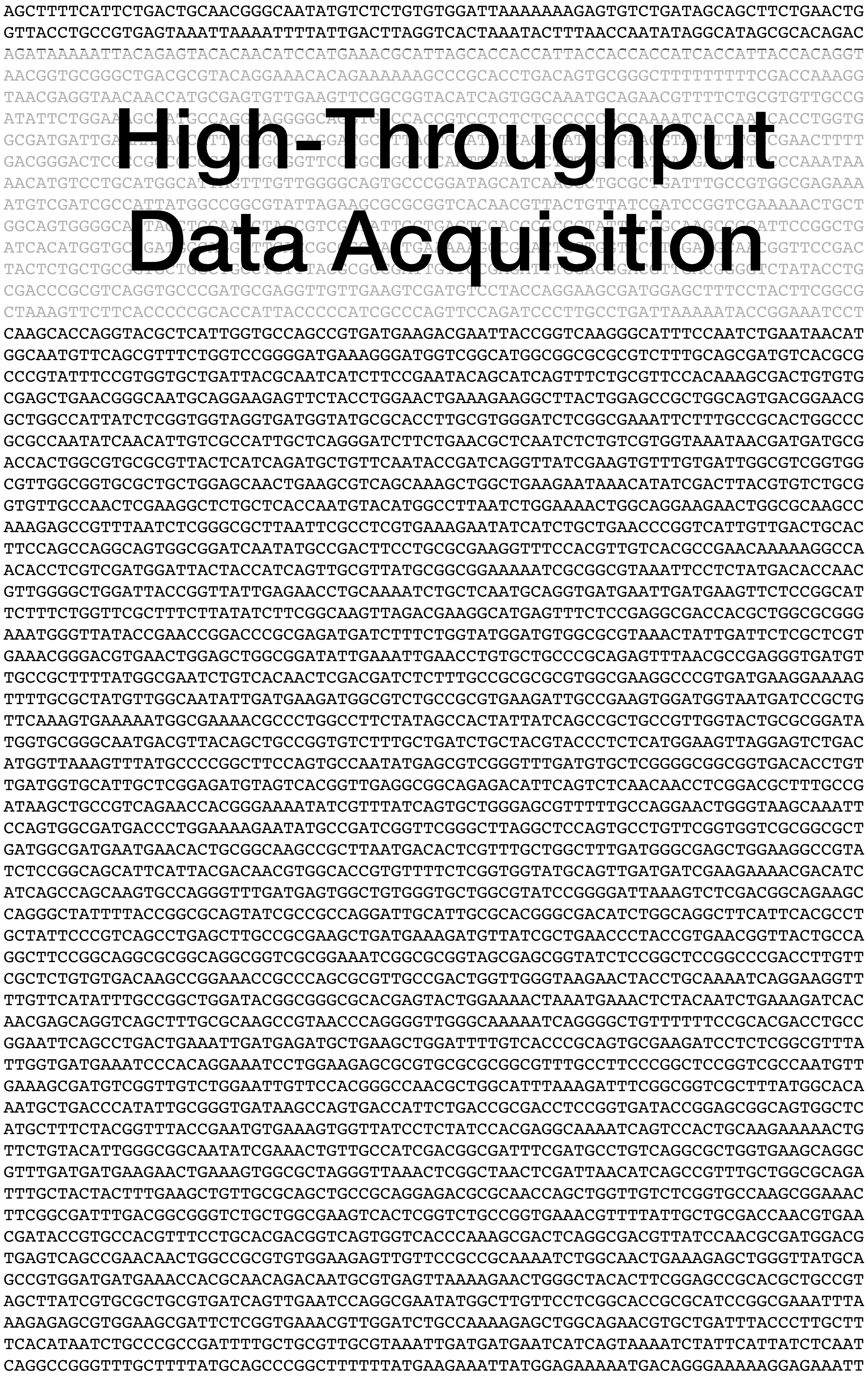


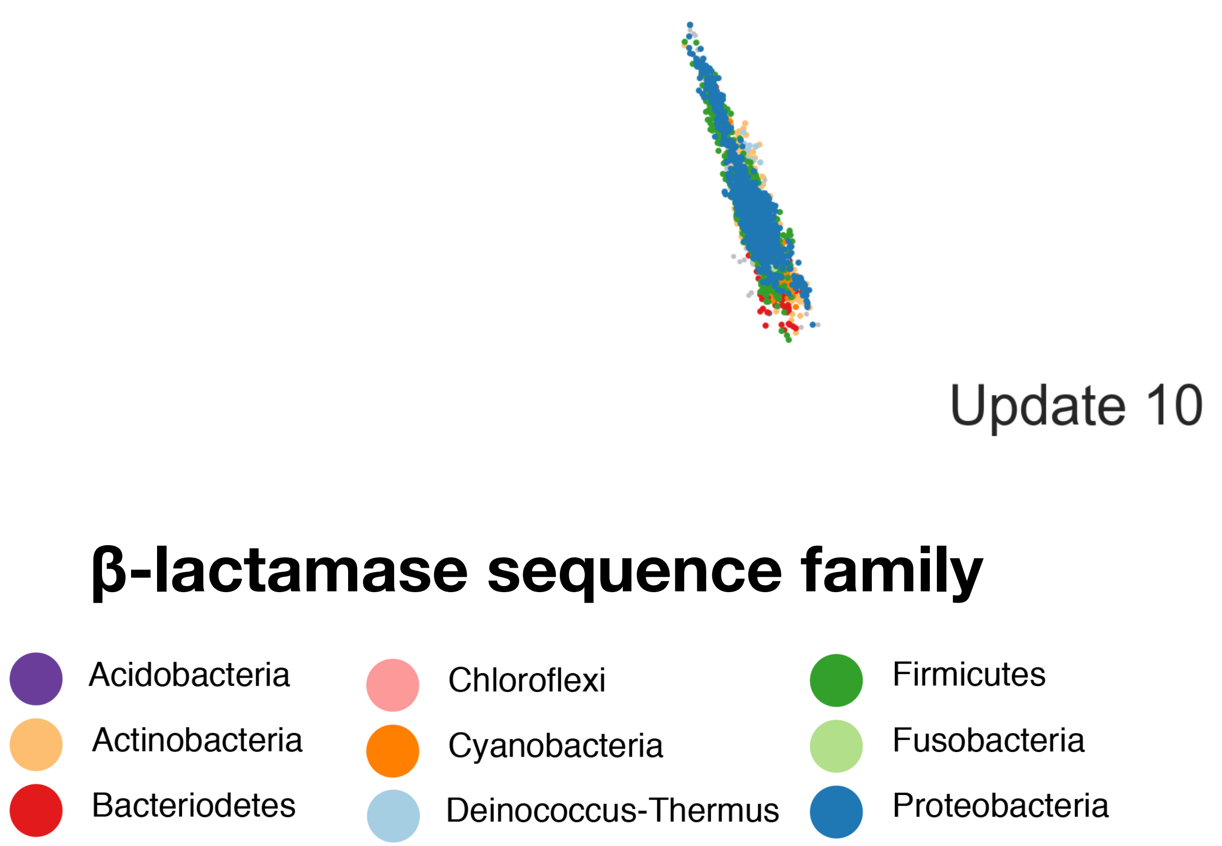
Sequence **Structure** **Function**

Mutations impact protein **function**



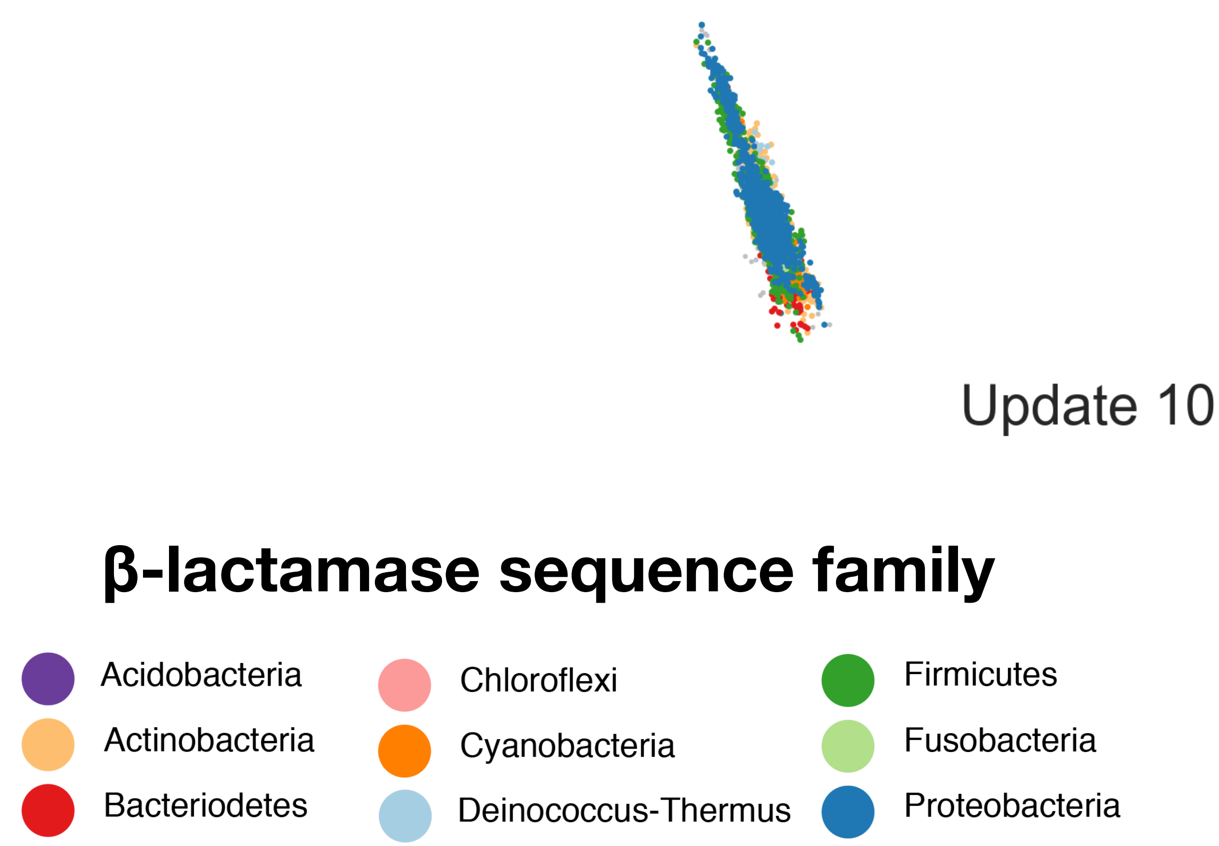
High-Throughput Data Acquisition + Machine Learning





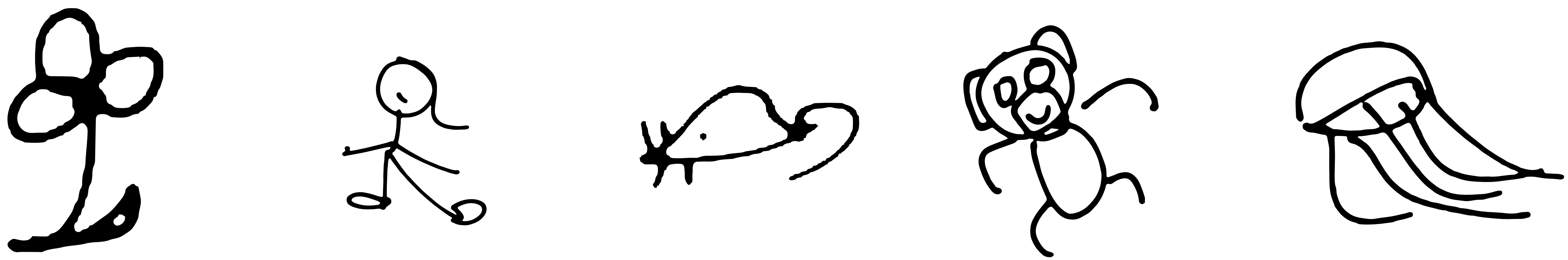
Riesselman, A.J.*, Ingraham, J.B.* and Marks, D.S., 2018. *Nat. Methods*, *15*, pp.816-822.

High-Throughput Data Acquisition + Machine Learning



Riesselman, A.J.*, Ingraham, J.B.* and Marks, D.S., 2018. *Nat. Methods*, *15*, pp.816-822.

DNA sequencing is becoming very **cheap** and **easy**



https://www.uniprot.org/statistics/TrEMBL

https://www.youtube.com/watch?v=GUb1TZvMWsw

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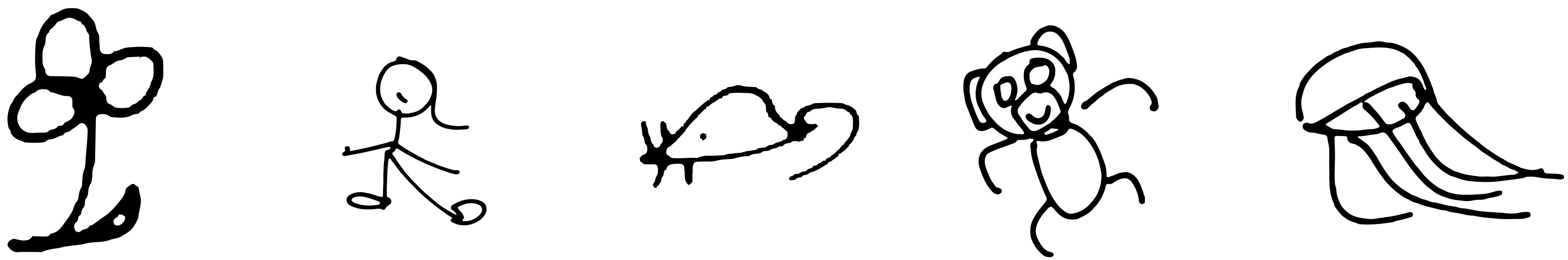

Isolate DNA

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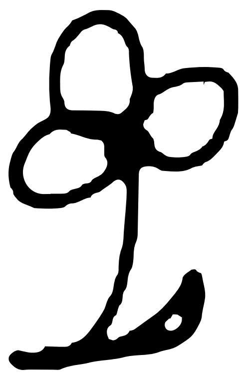
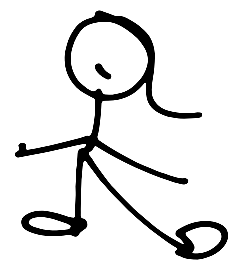
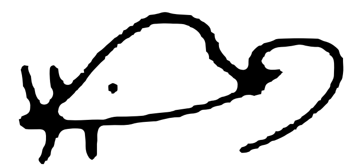
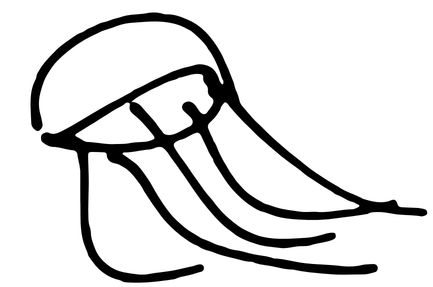
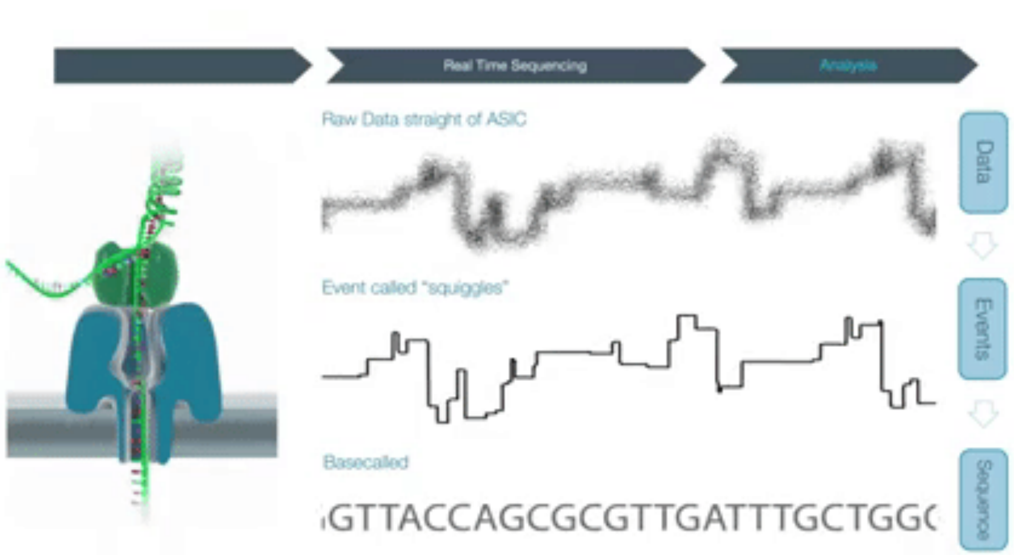






Isolate DNA



Sequence - Oxford Nanopore

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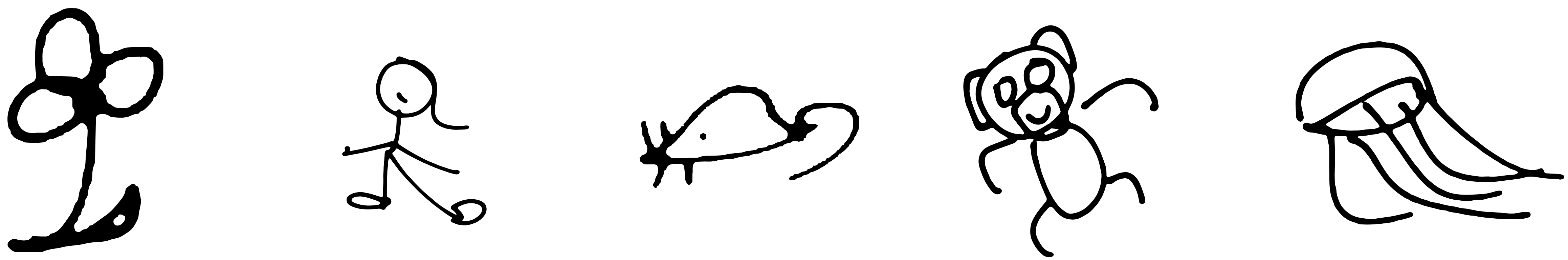
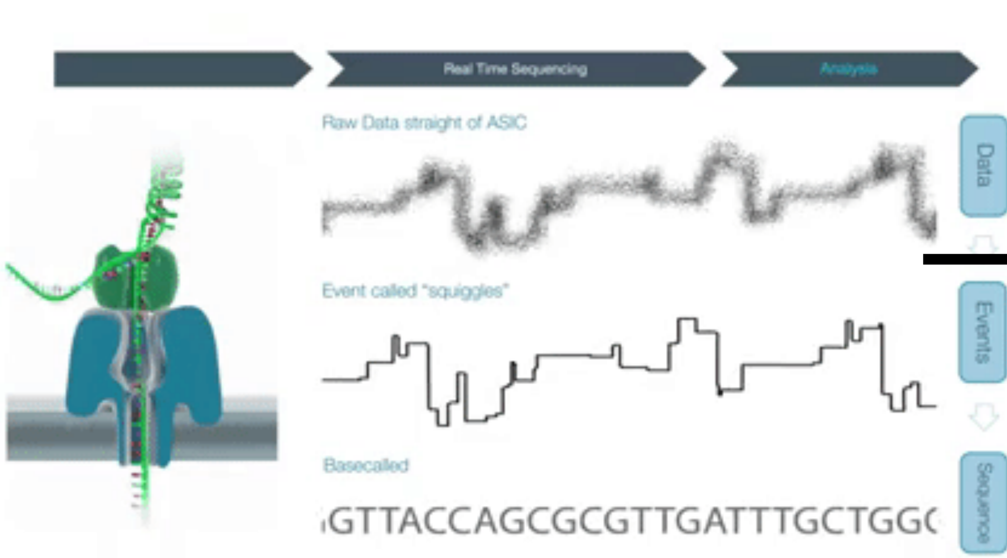


Isolate DNA

Deposit in public databases



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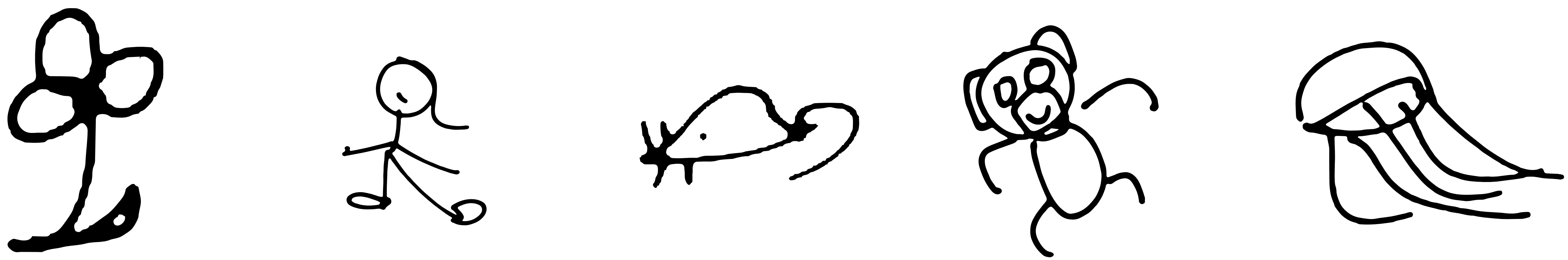

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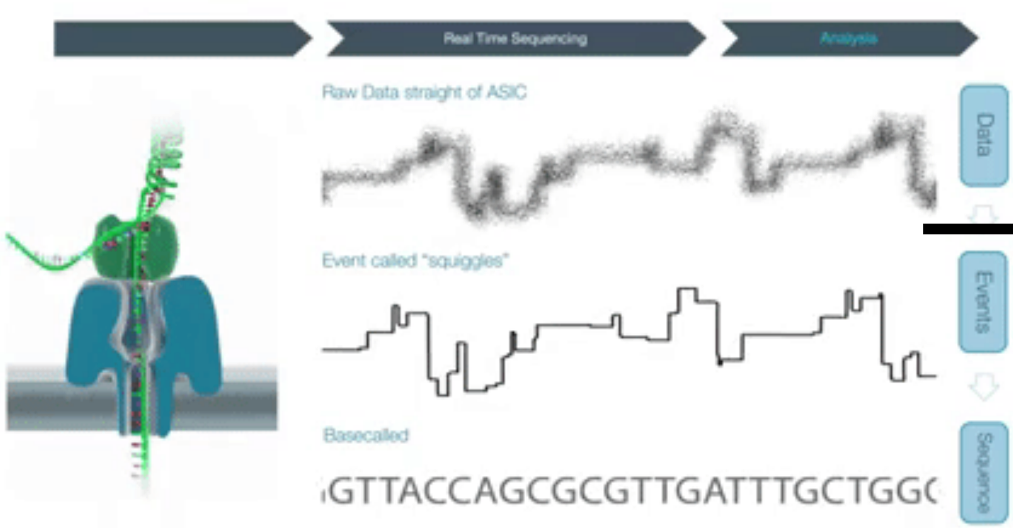
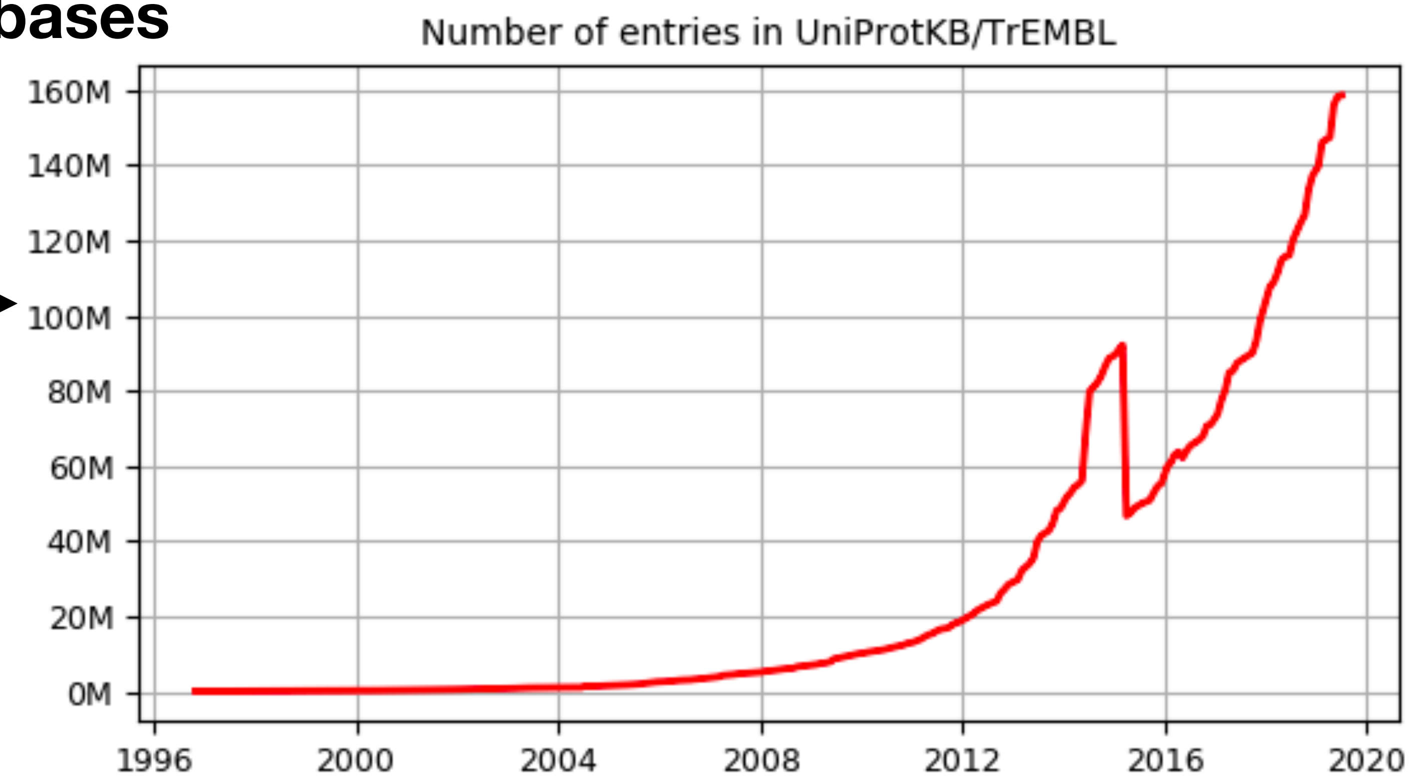


Sequence - Oxford Nanopore



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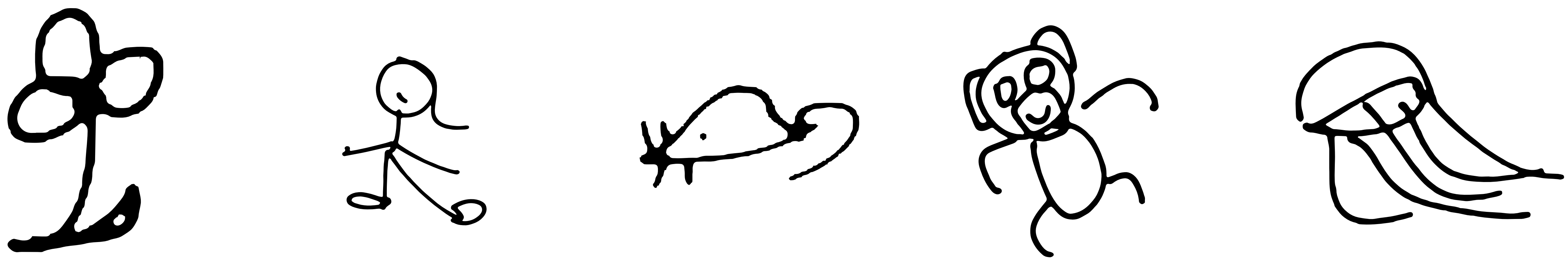

Isolate DNA

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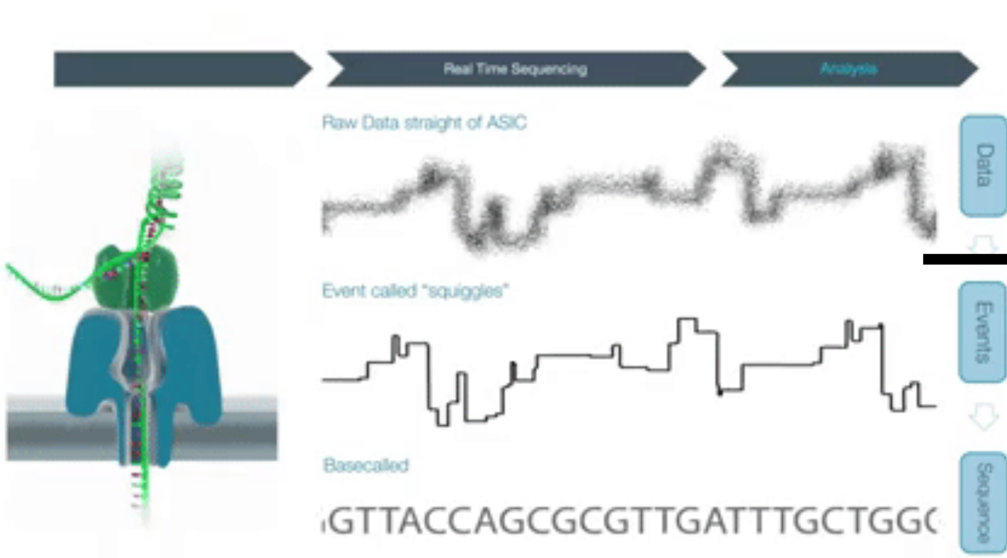
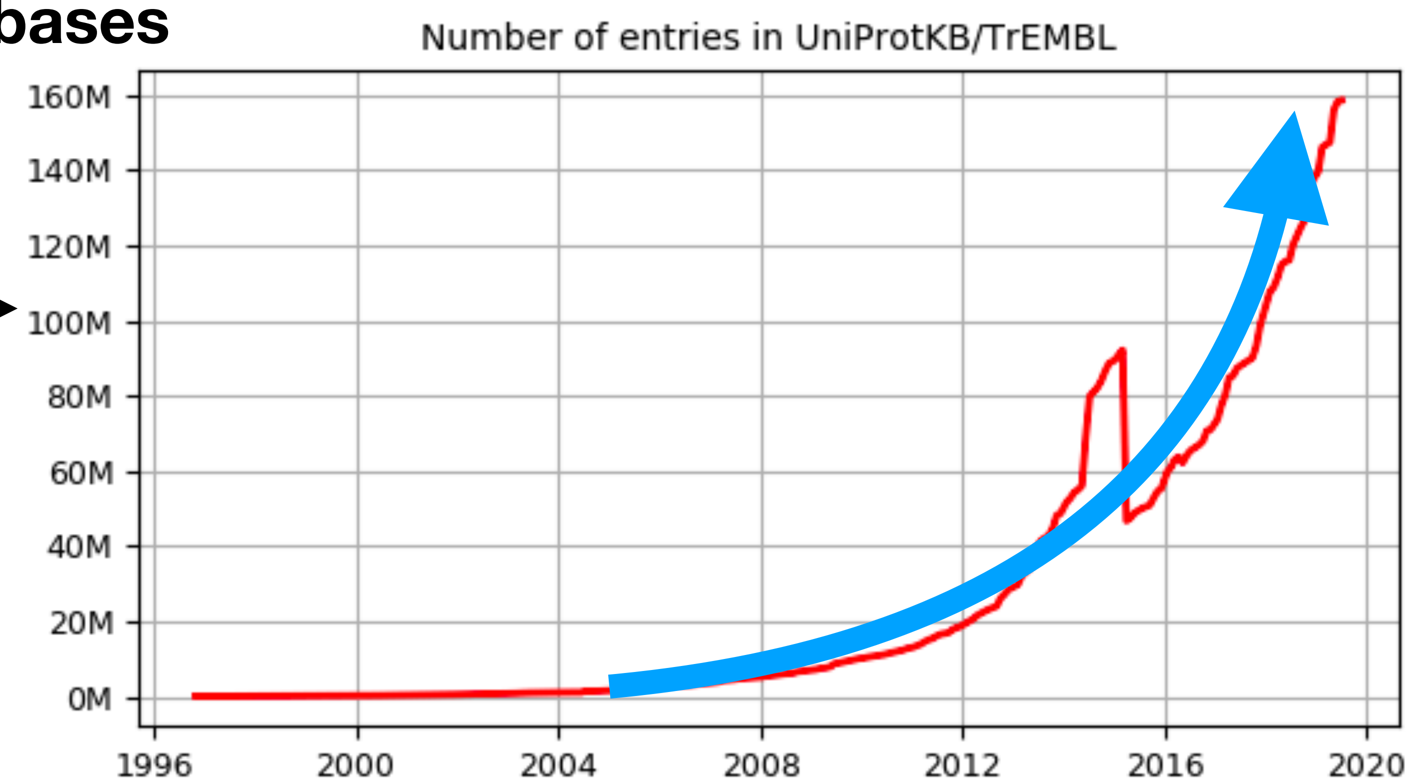


Sequence - Oxford Nanopore



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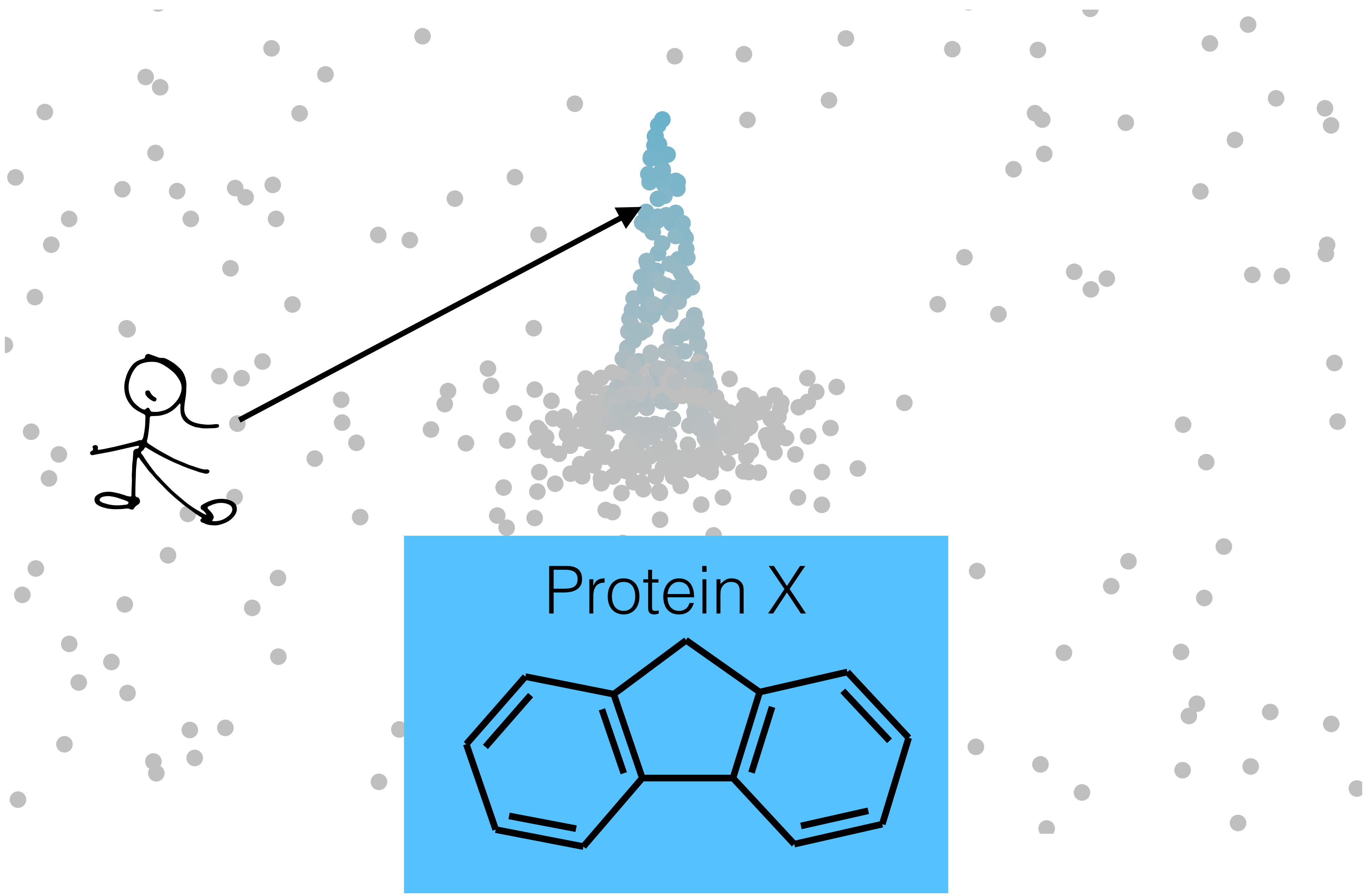
Lots of other **examples** of **Protein X** are **available**



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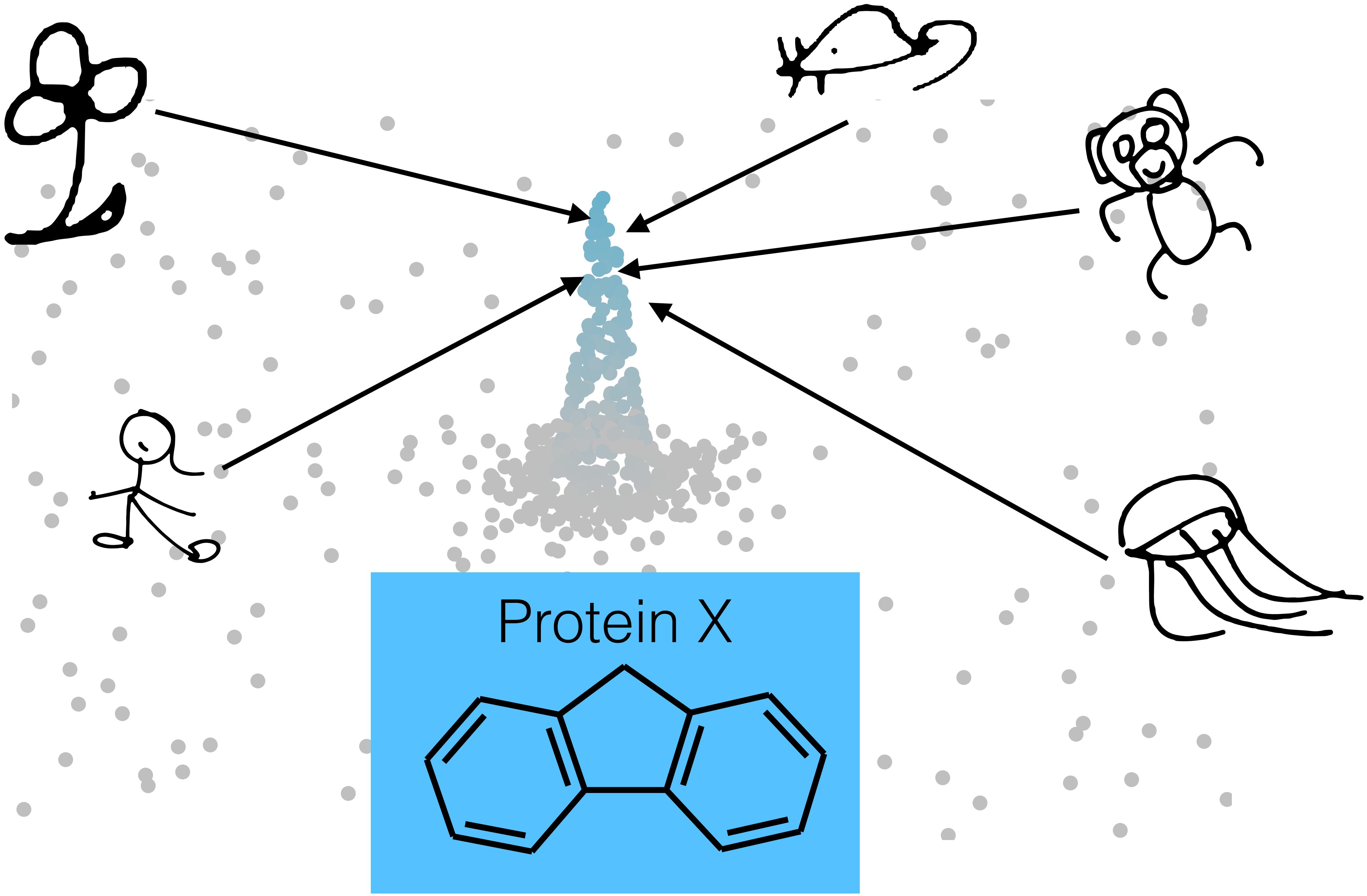

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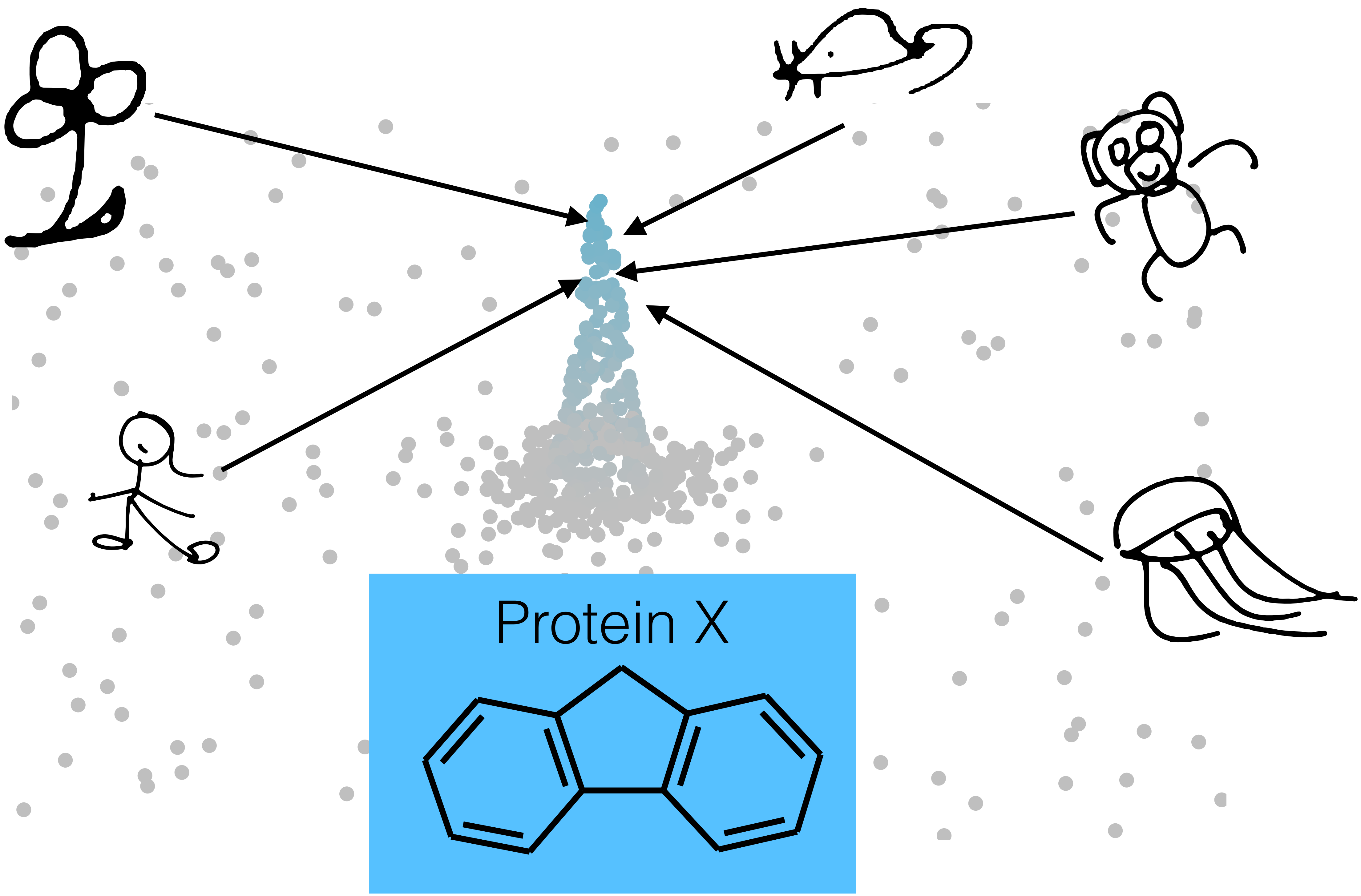

All are **functional, homologous examples** of Protein X

Lots of other **examples** of **Protein X** are **available**

Sequences are found in public **genome databases**.

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Sequences are found in public **genome databases**.

JGI
JOINT GENOME INSTITUTE
DEPARTMENT OF ENERGY

Natural **evolution** is an **experiment**, in **parallel**.

Lots of other **examples** of **Protein X** are **available**

Sequences are found in public **genome databases**.

Natural **evolution** is an **experiment**, in **parallel**.

<u>**Assumption:**</u>

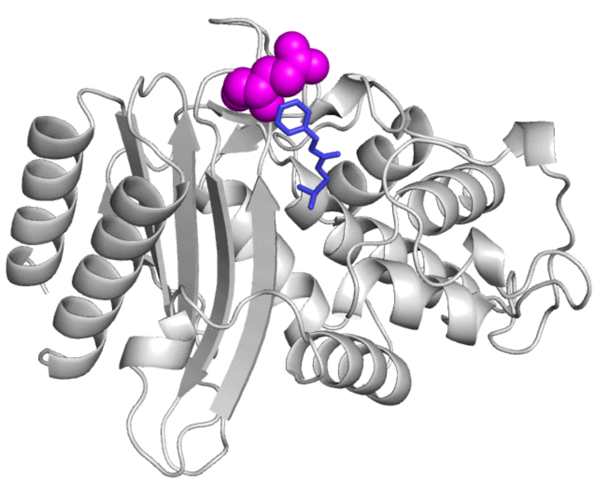
Present in database: Tolerated

Not in database: Deleterious

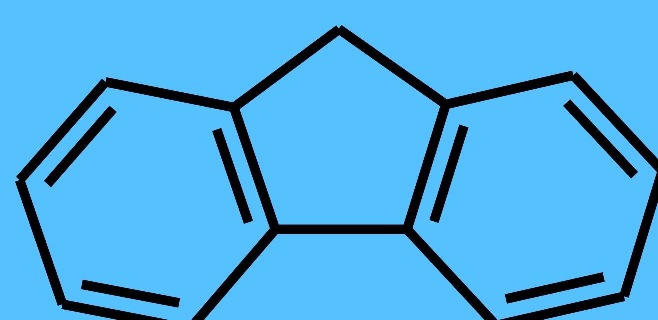
Can we **predict** which **mutation** will be **tolerable**?

MSIQHFRVALIPFFAAFCLPVFA
HPETLVKVKDAEDQLGARVGYIE
LDLNSGKILESFRPEERFPMMST
FKVLLCGAVLSRVDAGQEQLGRR
IHYSQNDLVEYSPVTEKHLTDGM
TVRELCSAAITMSDNTAANLLLT
TIGGPKELTAFLHNMGDHVTRLD
RWEPELNEAIPNDERDTTMPAAM
ATTLRKLLTGELLTLASRQQLID
WMEADKVAGPLLRSALPAGWFIA
DKSGAGERGSRGIIAALGPDGKP
SRIVVIYTTGSQATMDERNRQIA
EIGASLIKHW

MSIQHFRVALIPFFAAFCLPVFA
HPETLVKVKDAEDQLGARVGYIE
LDLNSGKILESFRPEERFPMMST
FKVLLCGAVLSRVDAGQEQLGRR
IHYSQNDLVEYSPVTEKHLTDGM
TVRELCSAAITMSDNTAANLLLT
TIGGPKELTAFLHNMGDHVTRLD
RWEPELNEAIPNDERDTTMPAAM
ATTLRKLLTGELLTLASRQQLID
WMEADKVAGPLLRSALPAGWFIA
DKSGAGERGSRGIIAALGPDGKP
SRIVVIYTTGSQATMDERNRQIA
EIGASLIKHW



Protein X



Can we **predict** which **mutation** will be **tolerable**?

MSIQHFRVALIPFFAAFCLPVFA
HPETLVKVKDAEDQLGARVGYIE
LDLNSGKILESFRPEERFPMMST
FKVLLCGAVLSRVDAGQEQLGRR
IHYSQNDLVEYSPVTEKHLTDGM
TVRELCSAAITMSDNTAANLLLT
TIGGPKELTAFLHNMGDHVTRLD
RWEPELNEAIPNDERDTTMPAAM
ATTLRKLLTGELLTLASRQQLID
WMEADKVAGPLLRSALPAGWFIA
DKSGAGERGSRGIIAALGPDGKP
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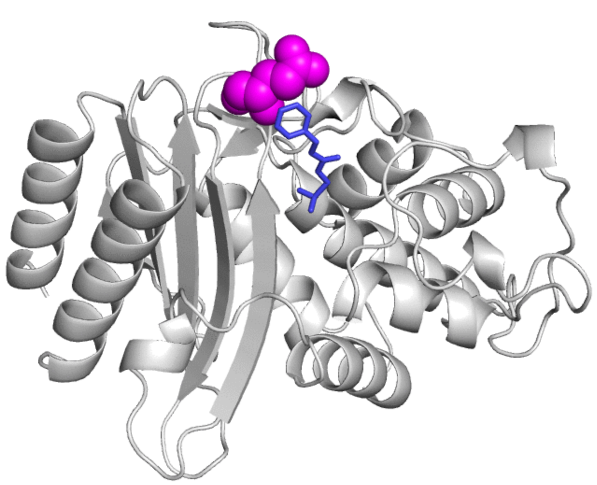

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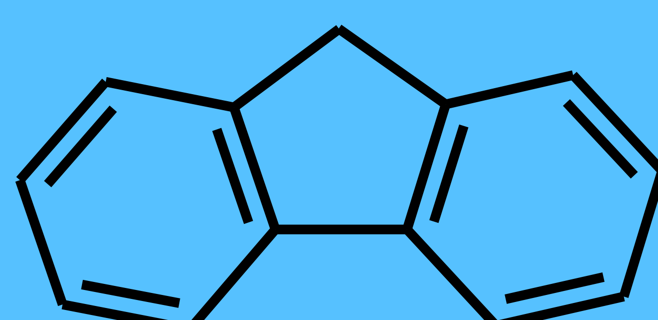

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RWEPELNEAIPNDERDTTMPAAM
ATTLRKLLTGELLTLASRQQLID
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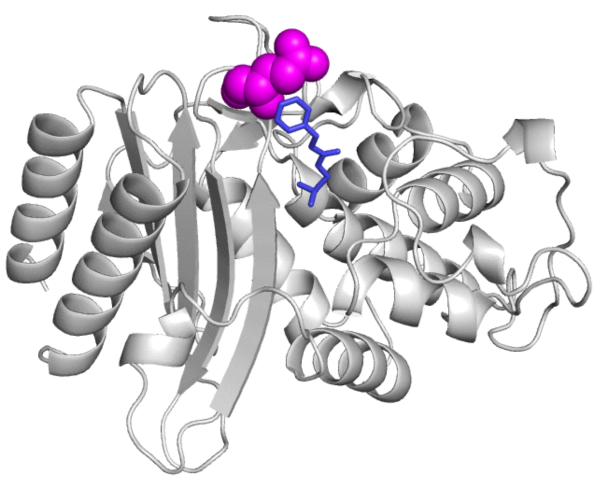
DKSGAGERGSRGIIAALGPDGKP
SRIVVIYTTGSQATMDERNRQIA
EIGASLIKHW
```

E→L




```
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HPETLVKVKDAEDQLGARVGYIE
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TVRELCSAAITMSDNTAANLLLT
TIGGPKELTAFLHNMGDHVTRLD
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ATTLRKLLTGELLTLASRQQLID
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DKSGAGERGSRGIIAALGPDGKP
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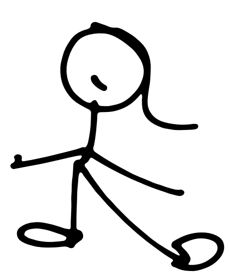
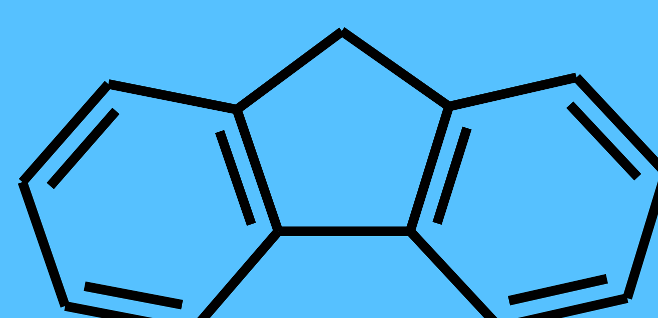
```

Protein X



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TVRELCSAAITMSDNTAANLLLT
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ATTLRKLLTGELLTLASRQQLID
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```

E→L

E→I


```
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TIGGPKELTAFLHNMGDHVTRLD
RWEPELNEAIPNDERDTTMPAAM
ATTLRKLLTGELLTLASRQQLID
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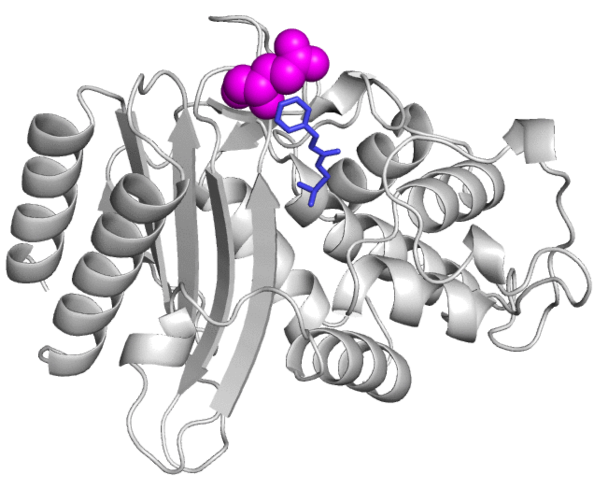
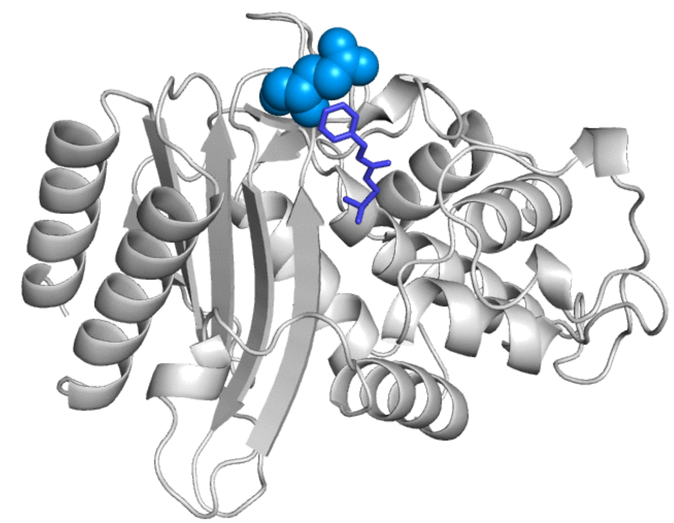
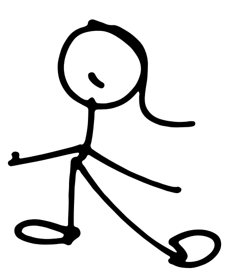
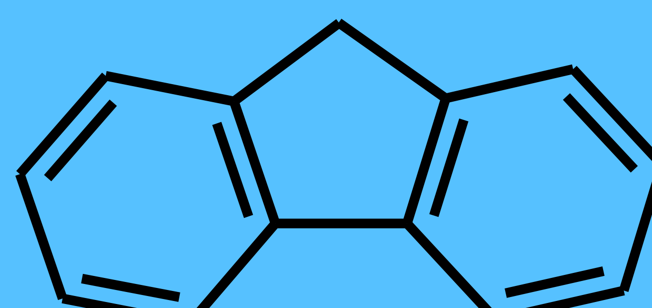
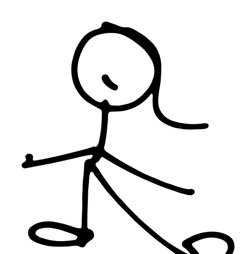




Protein X







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TVRELCSAAITMSDNTAANLLLT
TIGGPKELTAFLHNMGDHVTRLD
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ATTLRKLLTGELLTLASRQQLID
WMEADKVAGPLLRSALPAGWFIA
DKSGAGERGSRGIIAALGPDGKP
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E→L

E→I

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TVRELCSAAITMSDNTAANLLLT
TIGGPKELTAFLHNMGDHVTRLD
RWEPELNEAIPNDERDTTMPAAM
ATTLRKLLTGELLTLASRQQLID
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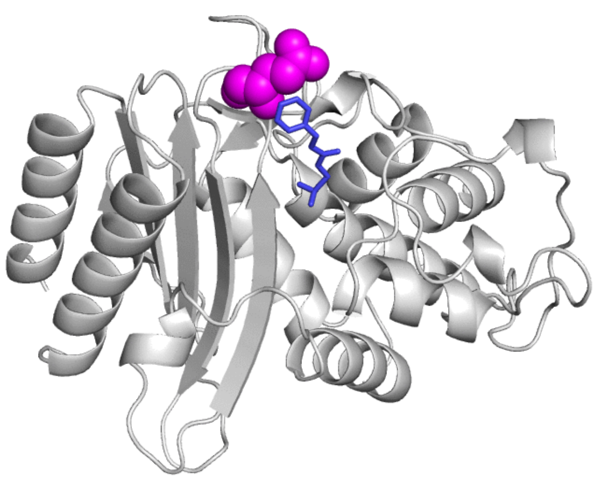
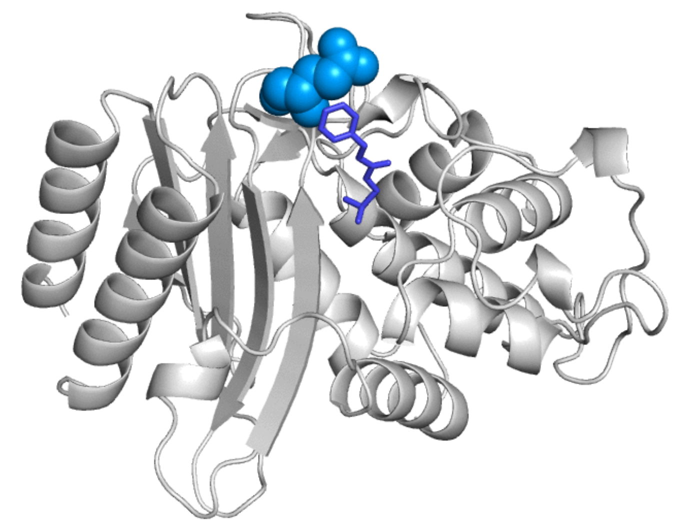
? ? ?





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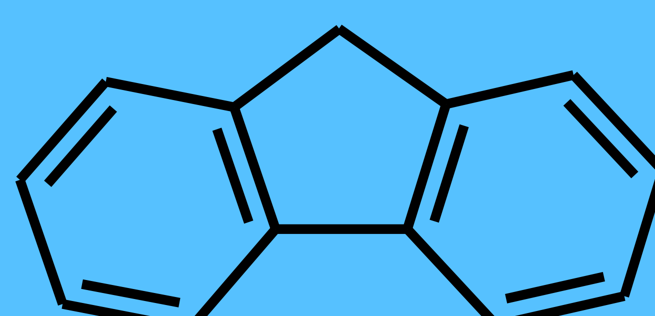

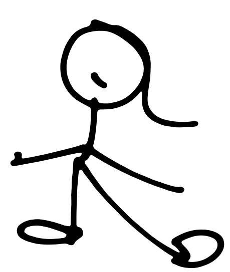

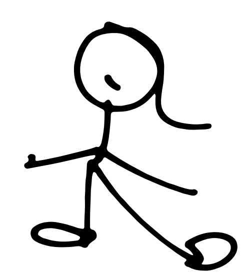

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TVRELCSAAITMSDNTAANLLLT
TIGGPKELTAFLHNMGDHVTRLD
RWEPELNEAIPNDERDTTMPAAM
ATTLRKLLTGELLTLASRQQLID
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SRIVVIYTTGSQATMDERNRQIA
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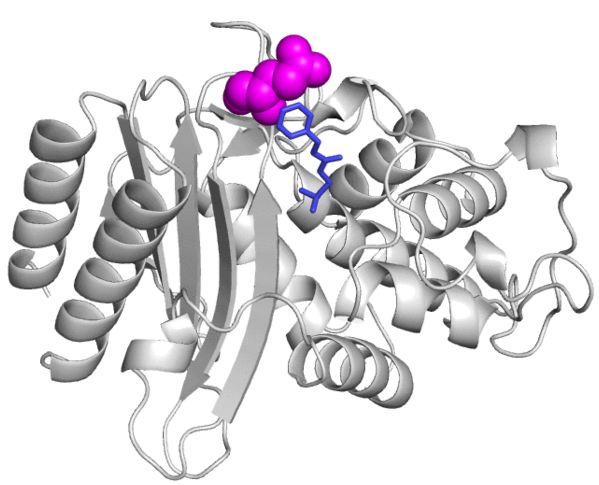
```

E→L



E→I

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LDLNSGKILESFRPEERFPMMST
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IHYSQNDLVEYSPVTEKHLTDGM
TVRELCSAAITMSDNTAANLLLT
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RWEPELNEAIPNDERDTTMPAAM
ATTLRKLLTGELLTLASRQQLID
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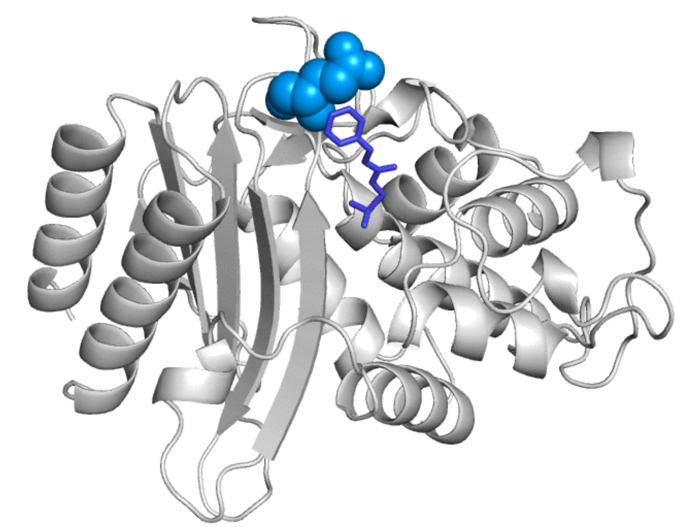
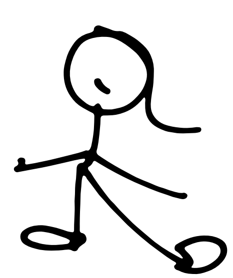


? ? ?

How can we formulate this problem?



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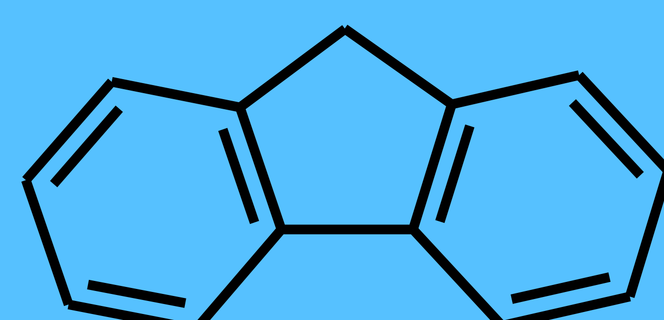

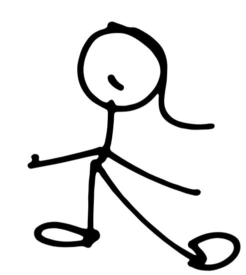

A **generative model** finds **probable** “words” based on **context**

A **generative model** finds **probable** “words” based on **context**

English sentence

We are going to go to the ____.

A **generative model** finds **probable** “words” based on **context**

English sentence

banana

We are going to go to the ____.

A **generative model** finds **probable** “words” based on **context**

English sentence

We are going to go to the ____.

banana ✘

running ✘

A **generative model** finds **probable** “words” based on **context**

English sentence

We are going to go to the _____.

banana

running

zoo

A **generative model** finds **probable** “words” based on **context**

English sentence

We are going to go to the zoo.

P(x) finds **probable** “words” based on **context**

A **generative model** finds **probable** "words" based on **context**

English sentence

We are going to go to the zoo.

Protein sequence

AQKLYLTHIDAEVEGADTLFITEVKQVF __

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We are going to go to the zoo.

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AQKLYLTHIDAEVEGADTLFITEVKQVF __

H

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We are going to go to the zoo.

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H ✗

V ✗

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We are going to go to the zoo.

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H

V

T

Neural networks power **generative models**

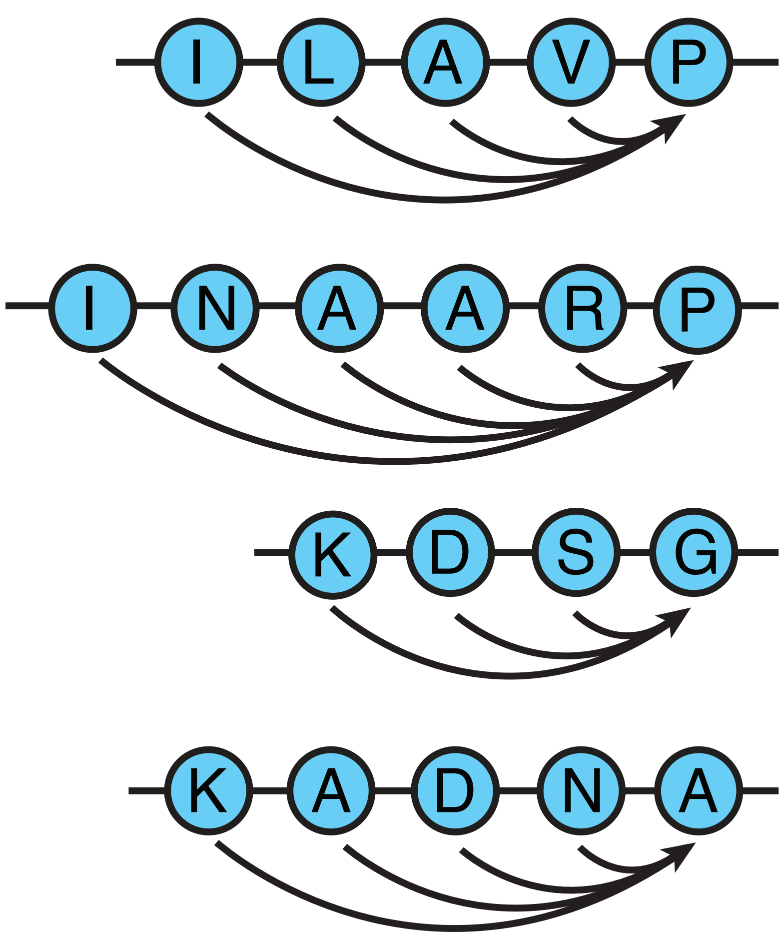
$$p(x|\theta) = \prod_{i}^{L} p(x_i|x_{<i}, \theta)$$

We are going to go to the zoo.

Neural networks power **generative models**

$$p(x|\theta) = \prod_{i}^{L} p(x_i|x_{<i}, \theta)$$

Autoregressive model



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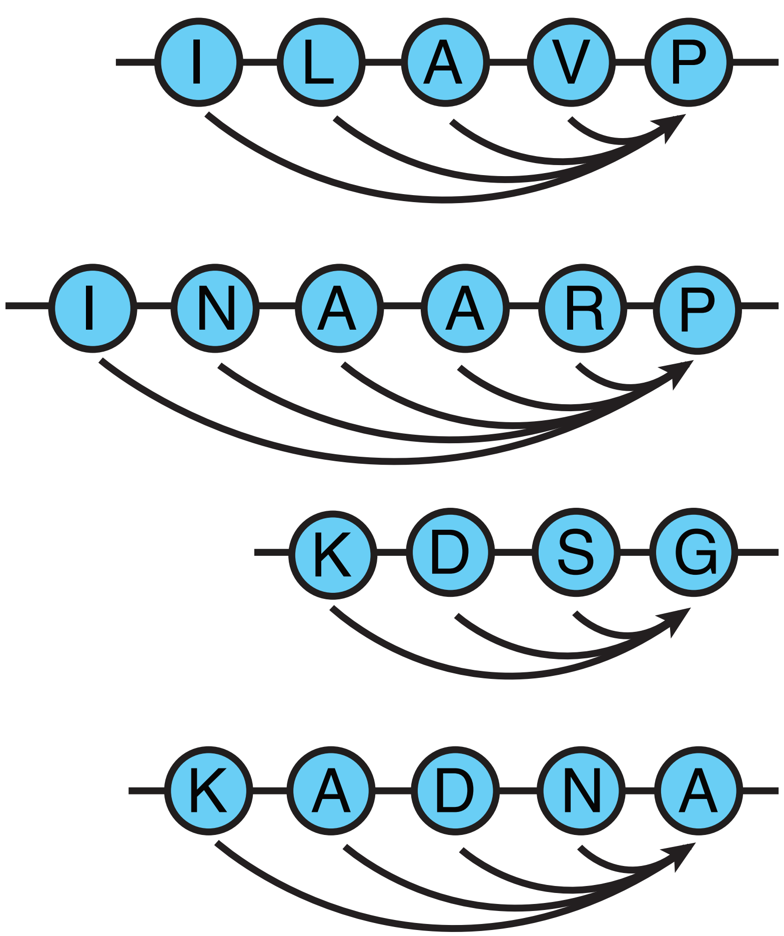

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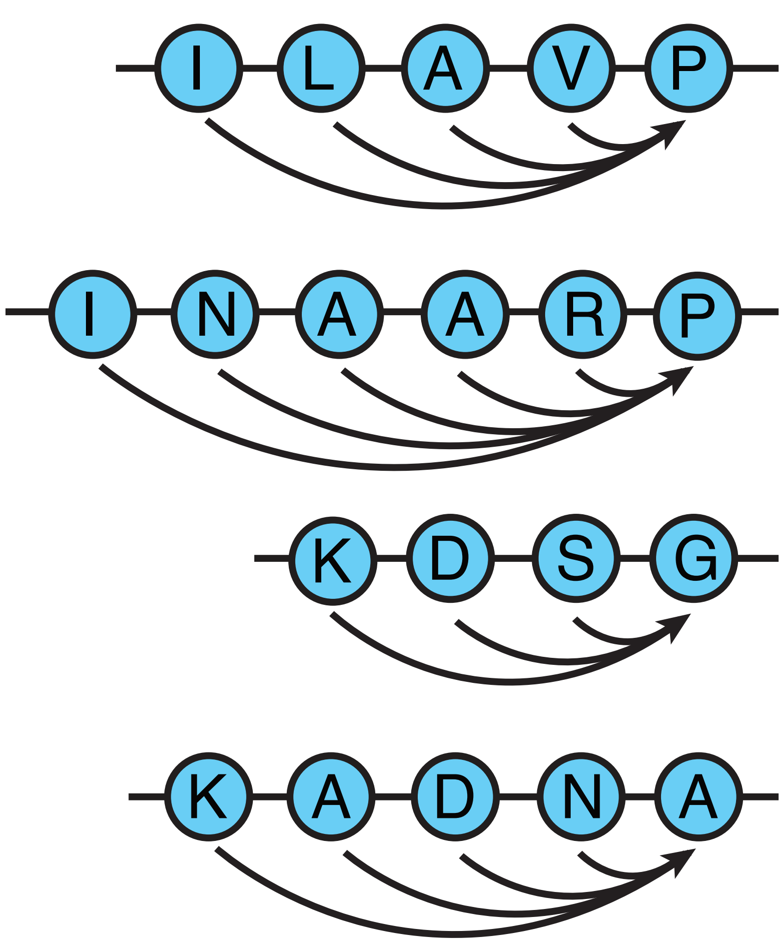

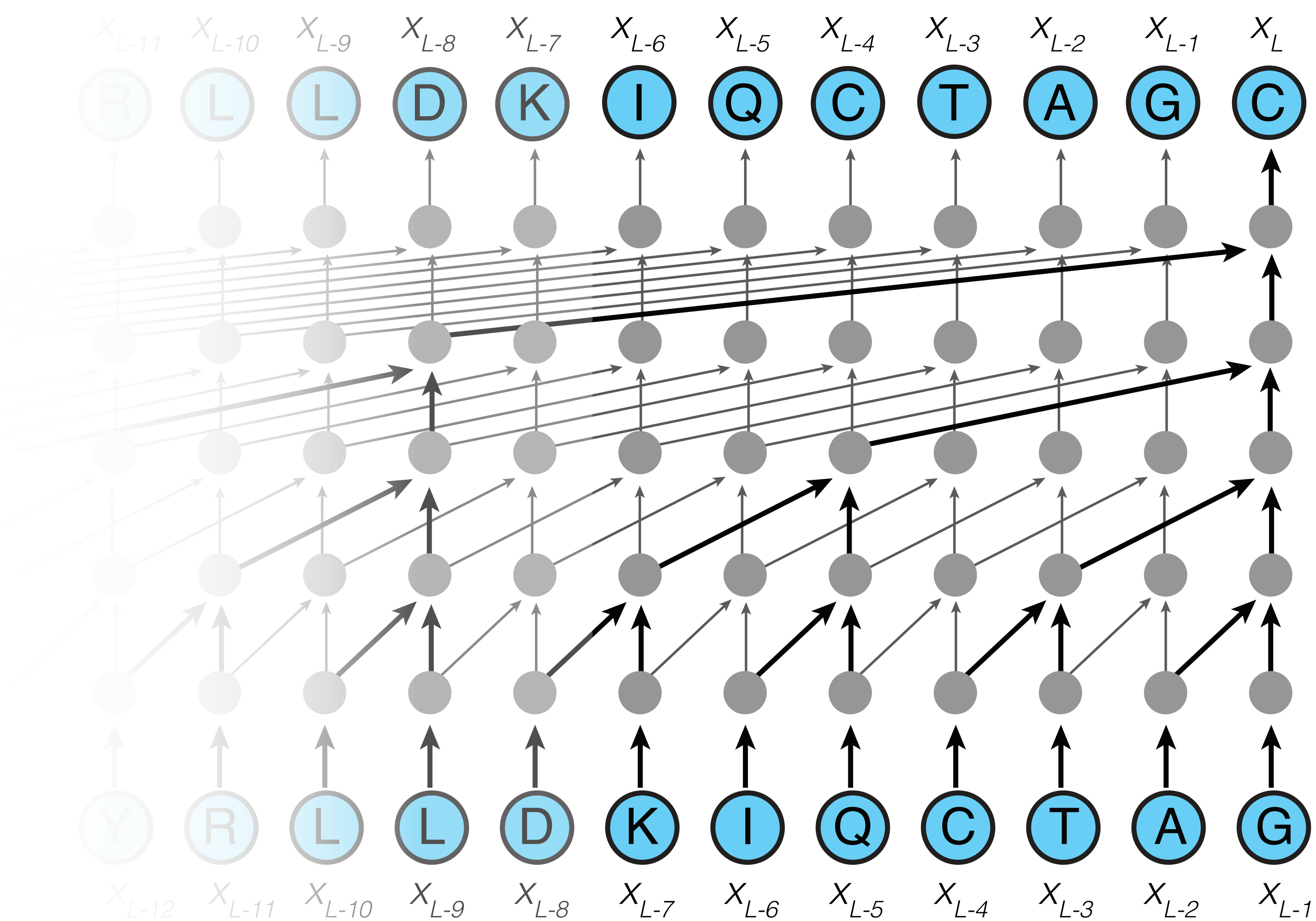

Dilated convolutional neural network

Neural networks power **generative models**

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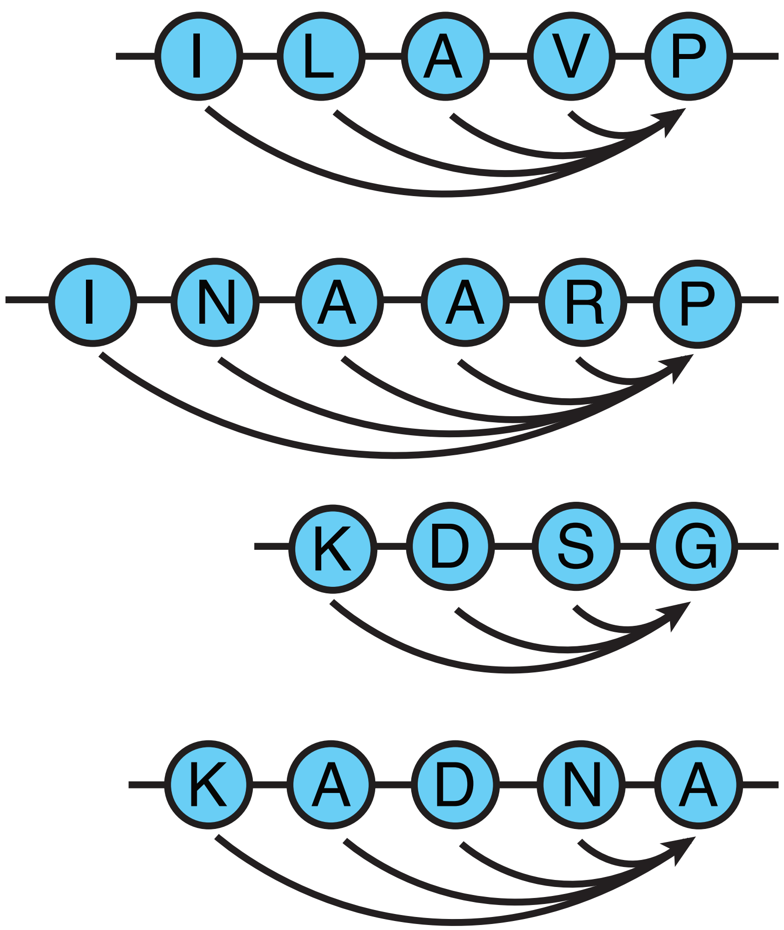
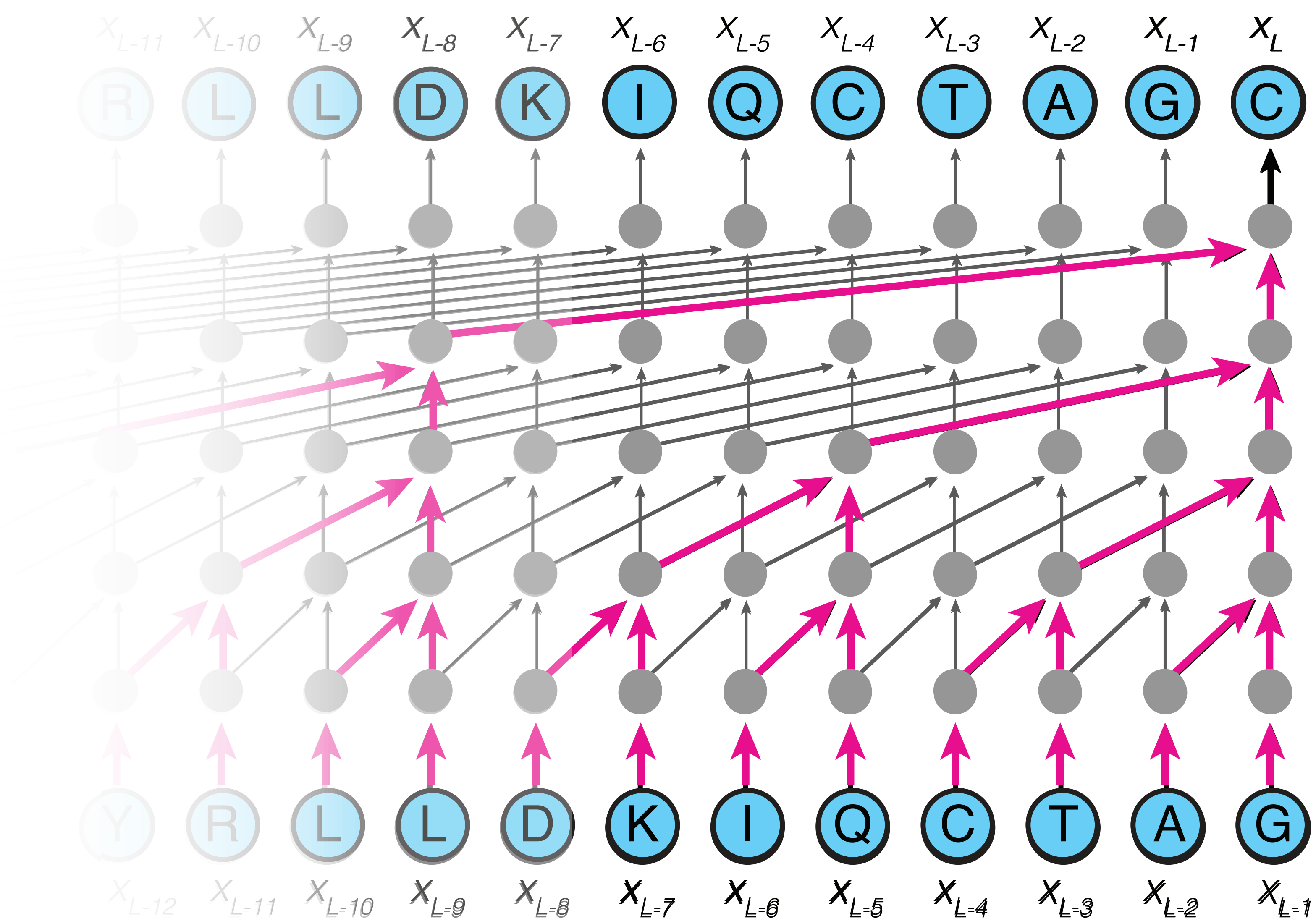
Autoregressive model

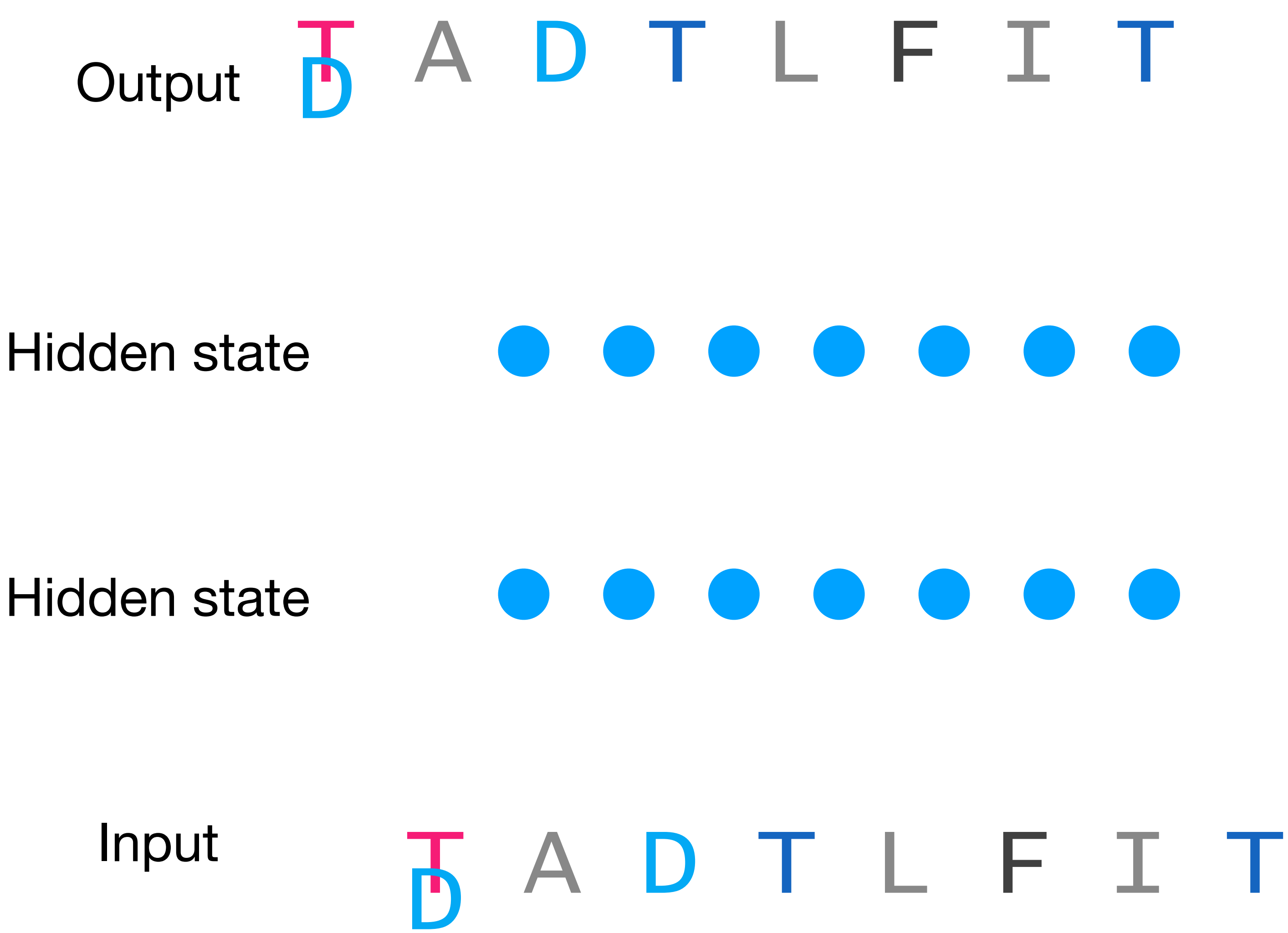




Dilated convolutional neural network

Utilizing an autoregressive likelihood

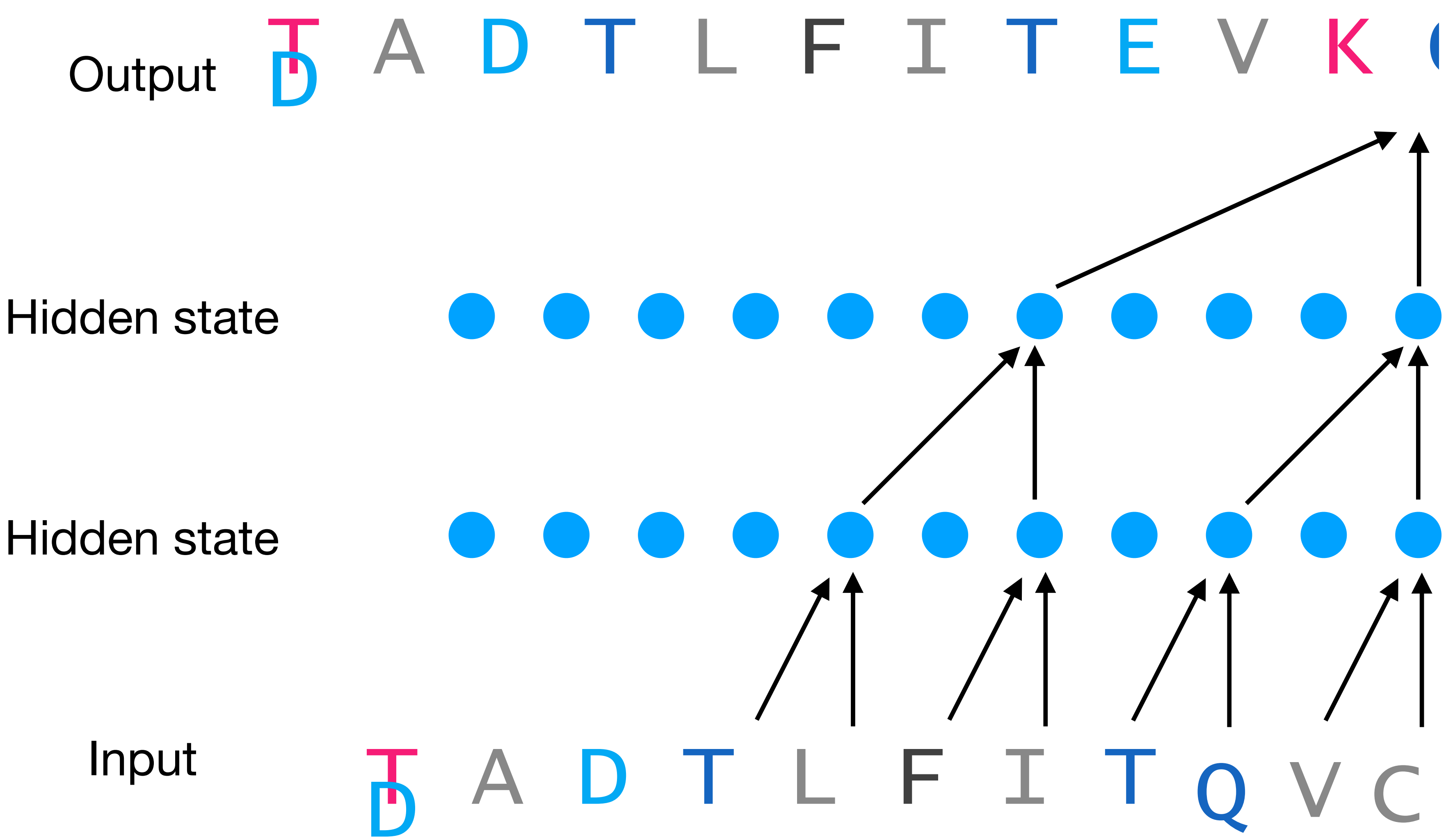
$$p(x|\theta) = \prod_{i}^{L} p(x_i|x_{<i}, \theta)$$



Adapted from:
https://deepmind.com/blog/wavenet-generative-model-raw-audio/

Utilizing an autoregressive likelihood

$$p(x|\theta) = \prod_{i}^{L} p(x_i|x_{<i}, \theta)$$



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Mutation effect prediction
with an unsupervised model

Mutation effect prediction with an unsupervised model

1) Infer a **generative model** of the family

```
AQKLYLTHIDAEVEGD
ADRLYMTKIHHQFDGD
ADTLFITEVKQVFEGD
ADRLYMTKIHHTFDGD
ADKLYCTLIHNSFEGD
ADRLYMTKIHHEFEGD
ADRLYLTMIHQKFEAD
TDRLYITHIDETFEGD
ADRLYLTQIRNKFKGD
```

$$p(\mathbf{x}|\boldsymbol{\theta})$$

Mutation effect prediction with an unsupervised model

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ADKLYCTLIHNSFEGD
ADRLYMTKIHHEFEGD
ADRLYLTMIHQKFEAD
TDRLYITHIDETFEGD
ADRLYLTQIRNKFKGD
```

$$\downarrow$$

$$p(\mathbf{x}|\boldsymbol{\theta})$$

2) Compute **Log Ratio** for each mutant

$$\log \frac{p(\mathbf{x}_{\text{mut}}|\boldsymbol{\theta})}{p(\mathbf{x}_{\text{wild}}|\boldsymbol{\theta})}$$

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"How much does this mutation look like what we've seen in nature?"

Mutation effect prediction with an unsupervised model

1) Infer a **generative model** of the family

2) Compute **Log Ratio** for each mutant

Uses public data (effectively free)

AQKLYLTHIDAEVEGD
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ADRLYMTKIHHEFEGD
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$$p(\mathbf{x}|\theta)$$

$$\log \frac{p(\mathbf{x}_{\text{mut}}|\theta)}{p(\mathbf{x}_{\text{wild}}|\theta)}$$

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ADRLYLTMIHQKFEAD
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$$p(\mathbf{x}|\theta)$$

2) Compute **Log Ratio** for each mutant

Fast

$$\log \frac{p(\mathbf{x}_{\text{mut}}|\theta)}{p(\mathbf{x}_{\text{wild}}|\theta)}$$

"How much does this mutation look like what we've seen in nature?"

Mutation effect prediction
with an unsupervised model

Uses public data (effectively free)

Fast

Works on almost any protein

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AQKLYLTHIDAEVEGD
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ADTLFITEVKQVFEGD
ADRLYMTKIHHTFDGD
ADKLYCTLIHNSFEGD
ADRLYMTKIHHEFEGD
ADRLYLTMIHQKFEAD
TDRLYITHIDETFEGD
ADRLYLTQIRNKFKGD
```

$p(\mathbf{x}|\theta)$

2) Compute **Log Ratio** for each mutant

$$\log \frac{p(\mathbf{x}_{\text{mut}}|\theta)}{p(\mathbf{x}_{\text{wild}}|\theta)}$$

“How much does this mutation look like what we’ve seen in nature?”

Mutation effect prediction
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AQKLYLTHIDAEVEGD
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ADTLFITEVKQVFEGD
ADRLYMTKIHHTFDGD
ADKLYCTLIHNSFEGD
ADRLYMTKIHHEFEGD
ADRLYLTMIHQKFEAD
TDRLYITHIDETFEGD
ADRLYLTQIRNKFKGD
```

Fast

$$\log \frac{p(\mathbf{x}_{\text{mut}}|\theta)}{p(\mathbf{x}_{\text{wild}}|\theta)}$$

Works on almost any protein

$$p(\mathbf{x}|\theta)$$

Accurate

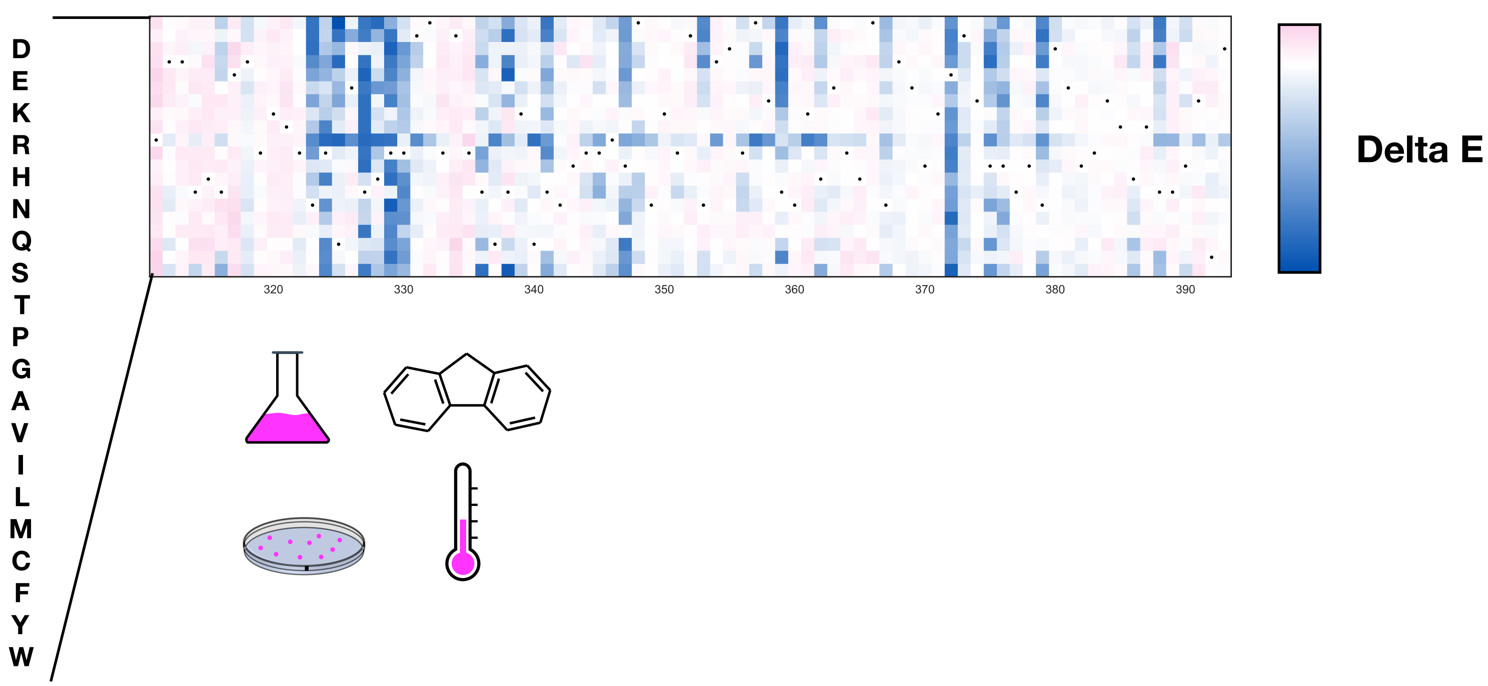
"How much does this mutation look like what we've seen in nature?"

To evaluate performance, we collected ~30 **saturation mutagenesis experiments**

McLaughlin Jr, R.N., Poelwijk, F.J., Raman, A., Gosal, W.S. and Ranganathan, R., 2012. The spatial architecture of protein function and adaptation. Nature, 491(7422), pp.138-142.

To evaluate performance, we collected ~30 **saturation mutagenesis experiments**

PDZ domain binding to ligand



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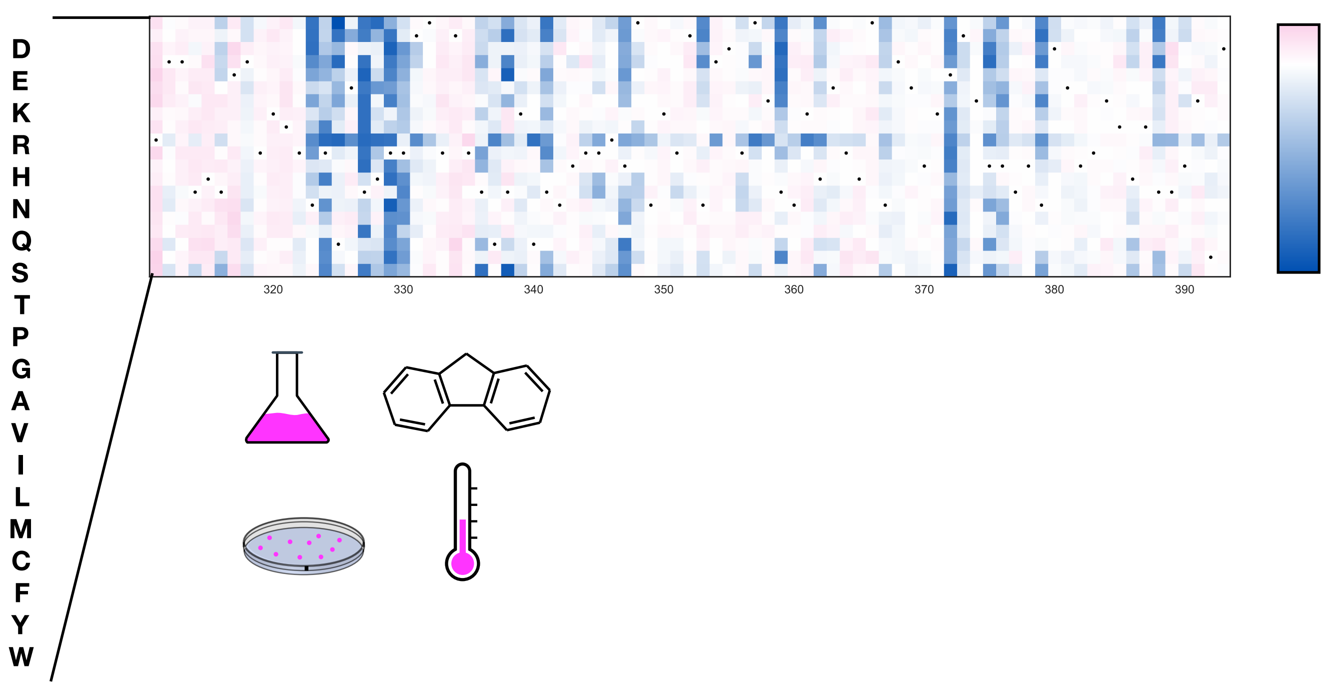
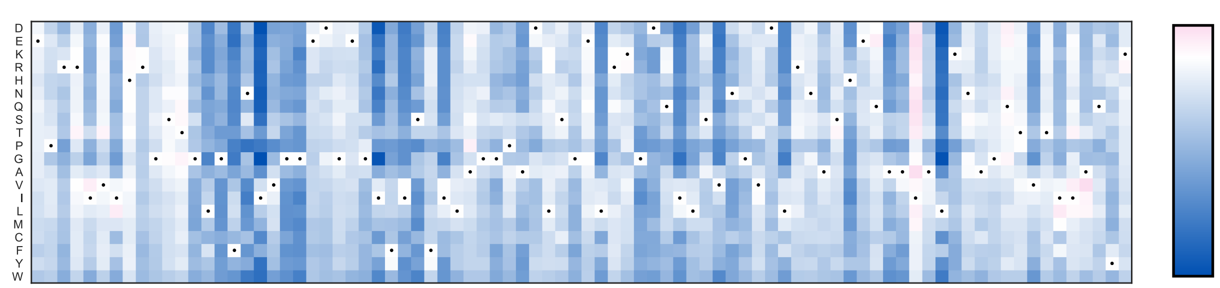


Log probability ratio

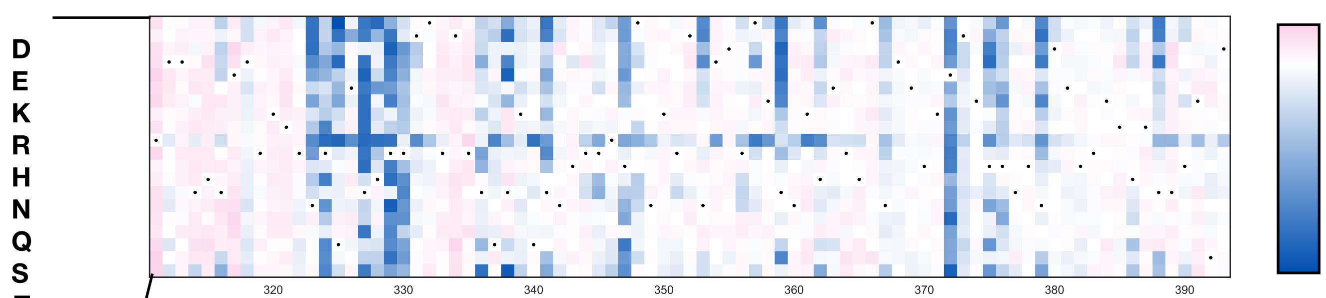


$$\log \frac{p(\mathbf{x}_{\text{mut}}|\boldsymbol{\theta})}{p(\mathbf{x}_{\text{wild}}|\boldsymbol{\theta})}$$

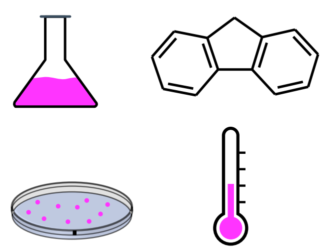
McLaughlin Jr, R.N., Poelwijk, F.J., Raman, A., Gosal, W.S. and Ranganathan, R., 2012. The spatial architecture of protein function and adaptation. Nature, 491(7422), pp.138-142.

To evaluate performance, we collected ~30 **saturation mutagenesis experiments**

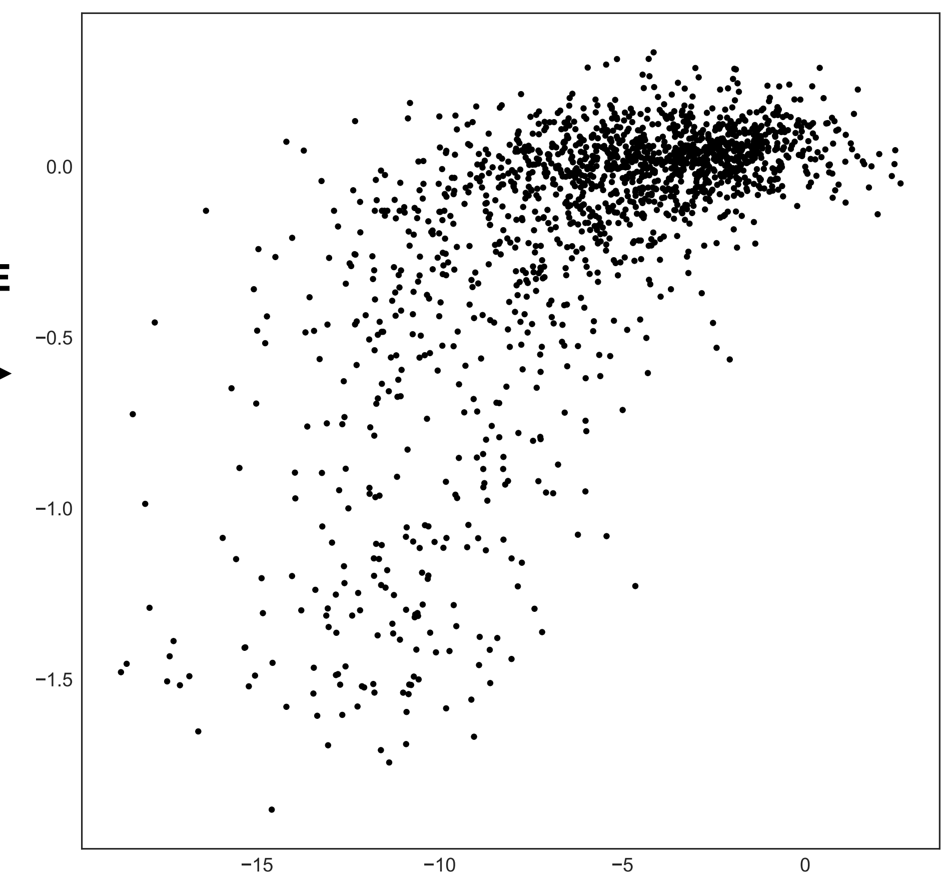
PDZ domain binding to ligand



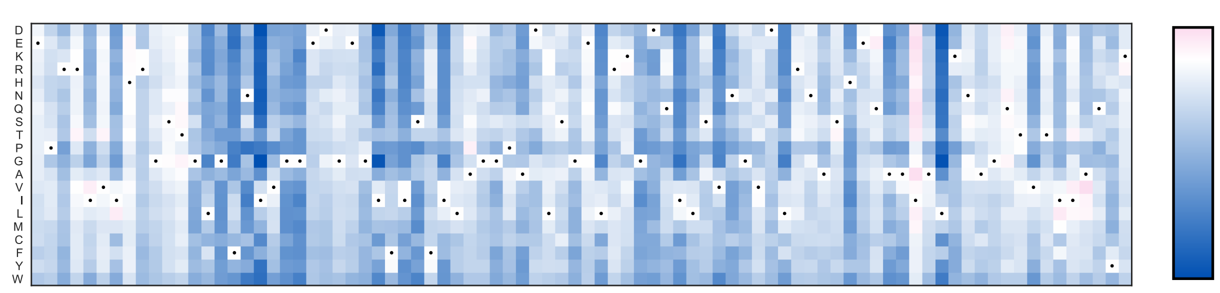
Delta E



Compare



Log probability ratio

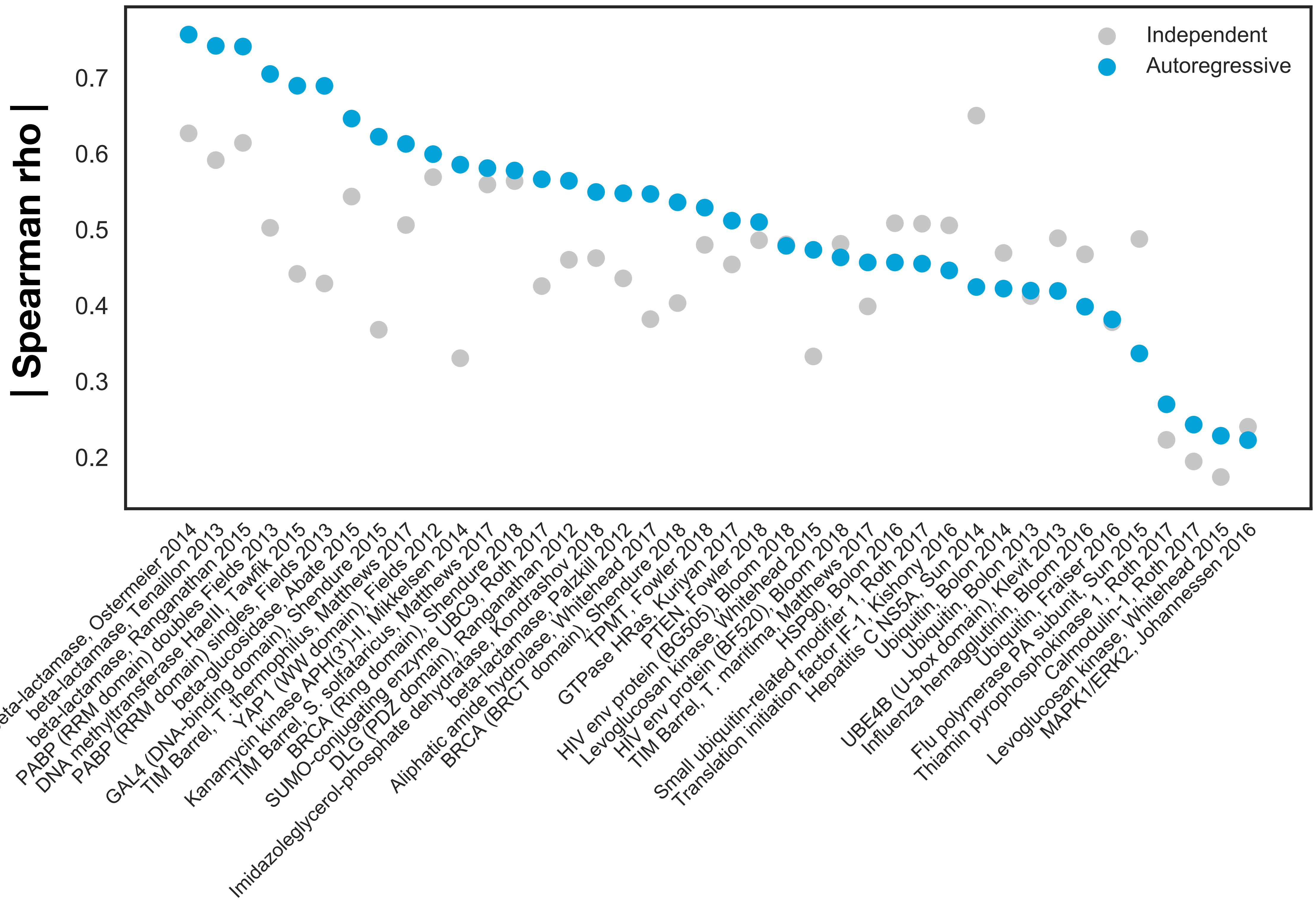


Delta Log Probability

$$\log \frac{p(\mathbf{x}_{\text{mut}}|\boldsymbol{\theta})}{p(\mathbf{x}_{\text{wild}}|\boldsymbol{\theta})}$$

McLaughlin Jr, R.N., Poelwijk, F.J., Raman, A., Gosal, W.S. and Ranganathan, R., 2012. The spatial architecture of protein function and adaptation. Nature, 491(7422), pp.138-142.

Autoregressive model is **predictive** of the effect of mutations



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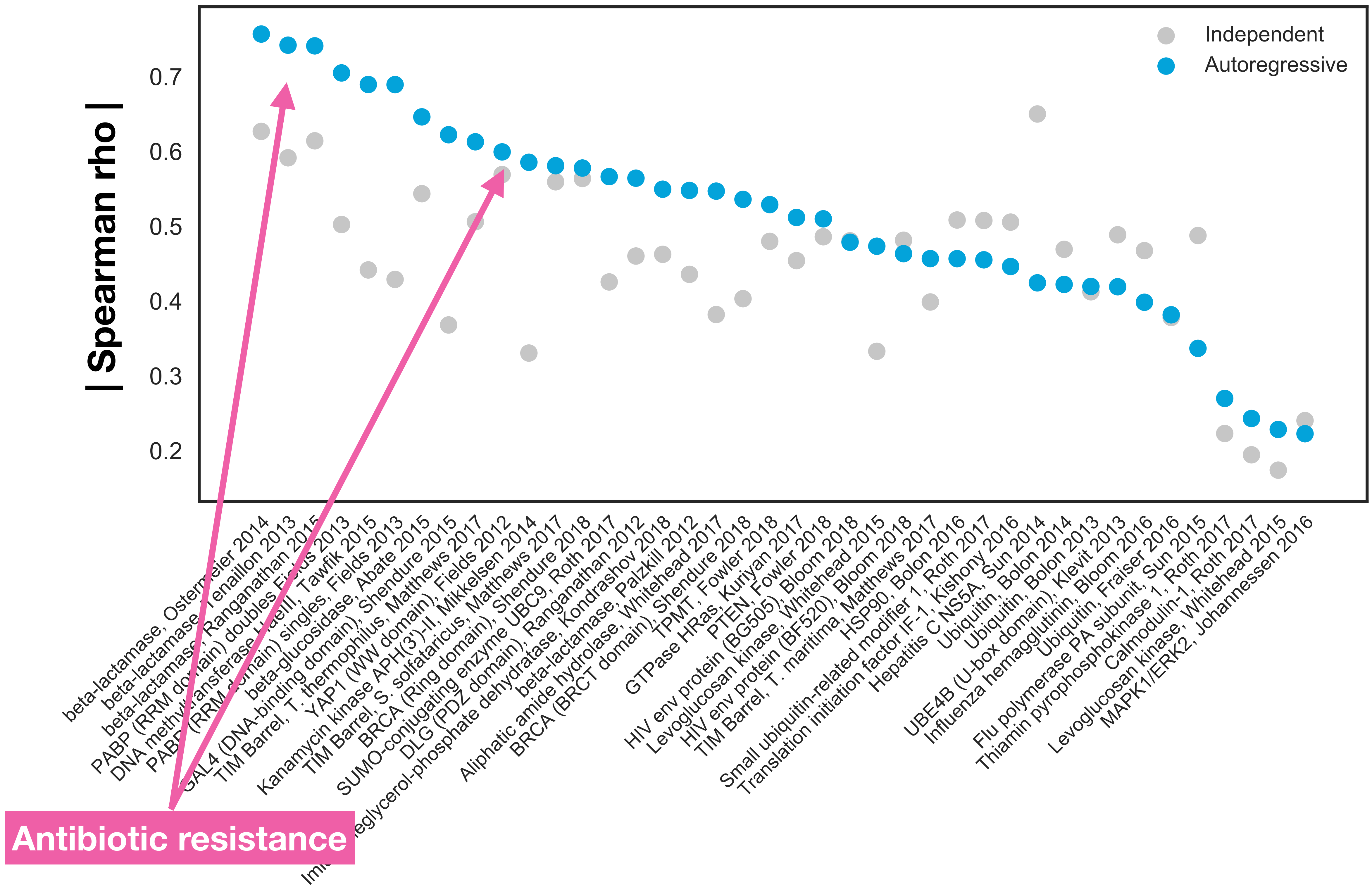

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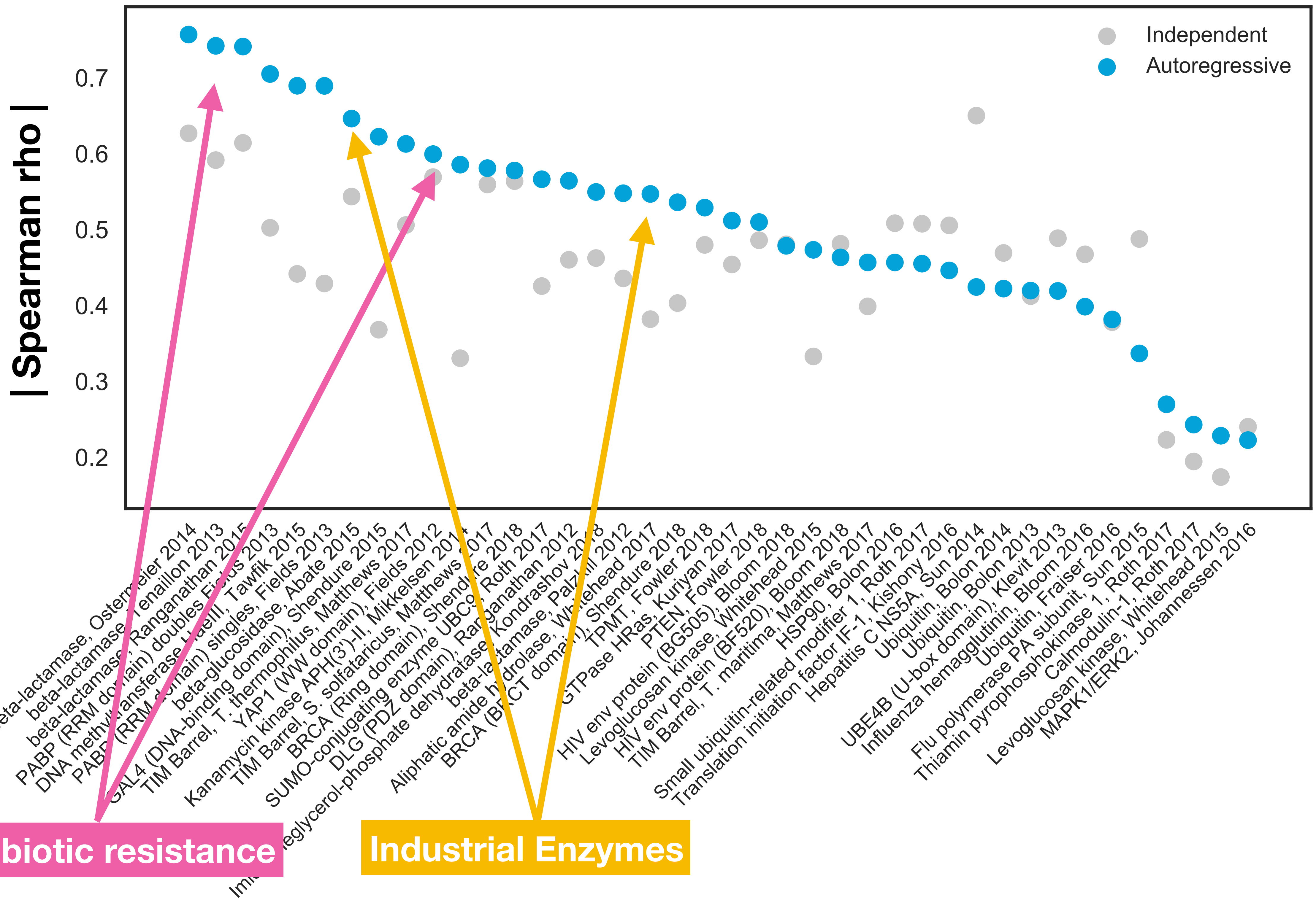

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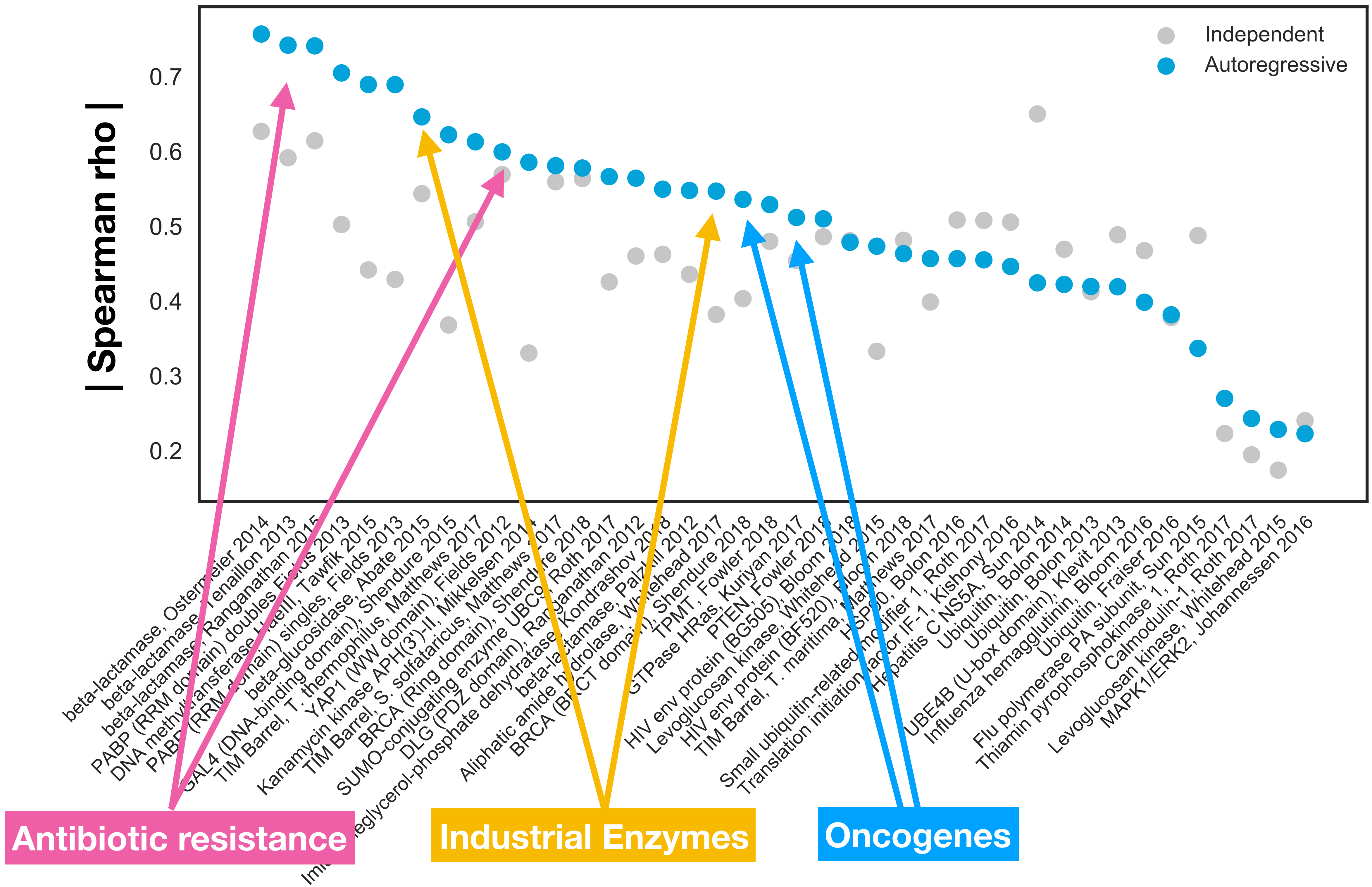


Autoregressive models are more **flexible**

Autoregressive models are more **flexible**

Missense mutations

…DKSGAG**V**RGSRGIIA…

…DKSGAG**I**RGSRGIIA…

Autoregressive models are more **flexible**

Missense mutations

…DKSGAG**V**RGSRGIIA…

…DKSGAG**I**RGSRGIIA…

Insertions

…DKSGAG**EGT**RGSRGIIA…

Autoregressive models are more **flexible**

Missense mutations

...DKSGAGVRGSRGIIA...

...DKSGAGIRGSRGIIA...

Insertions

...DKSGAGEGTRGSRGIIA...

Deletions

...DKSGAGRGSRGIIA...

Models **predict** the **effects** of **insertions** and **deletions**

Insertions

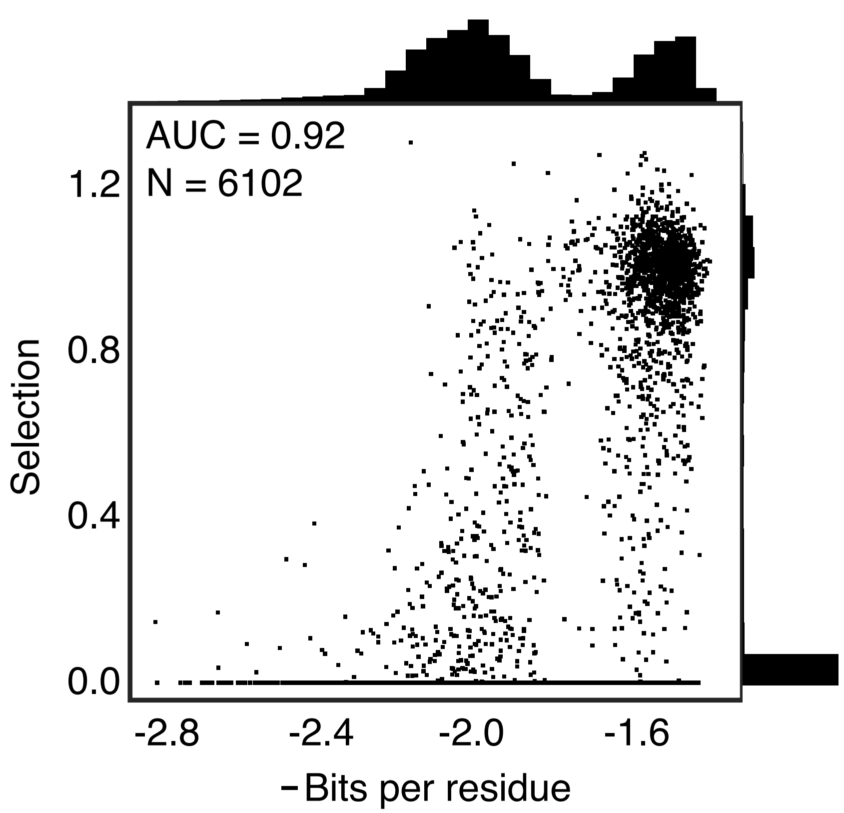
...DKSGAGEGTRGSRGIIA...

Deletions

...DKSGAGRGSRGIIA...

Imidazoleglycerol-phosphate dehydratase

Insertions & deletions



Models **predict** the **effects** of **insertions** and **deletions**

Insertions

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...DKSGAGRGSRGIIA...

Imidazoleglycerol-phosphate dehydratase

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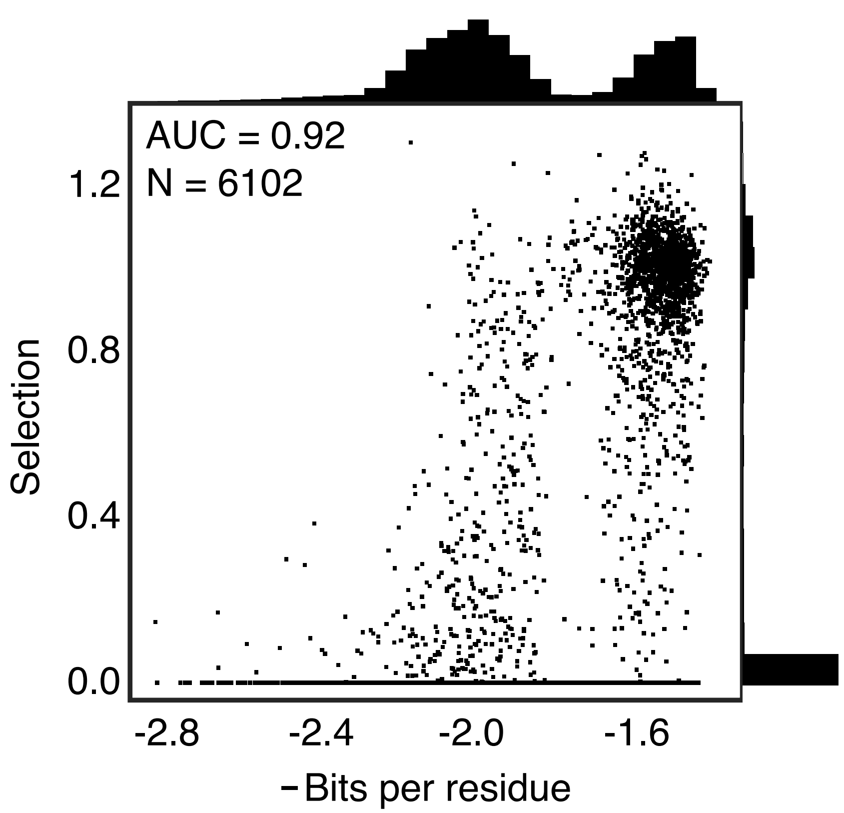
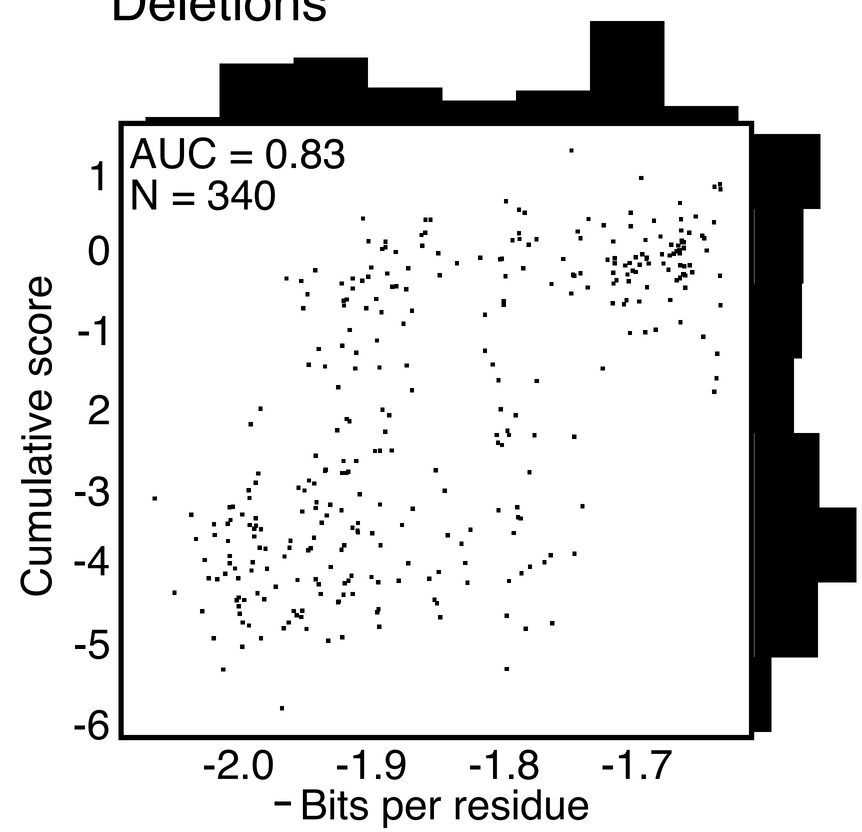
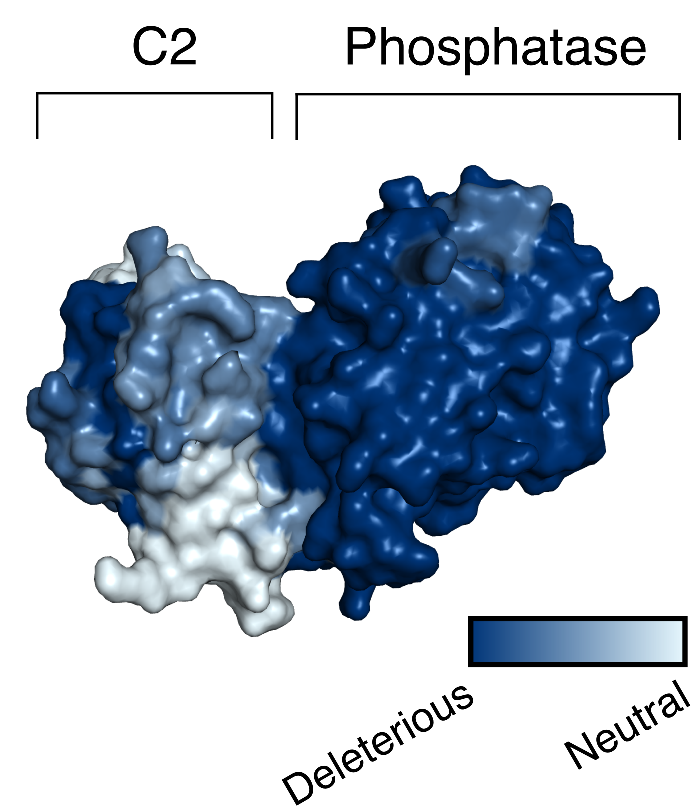


PTEN phosphatase

Deletions



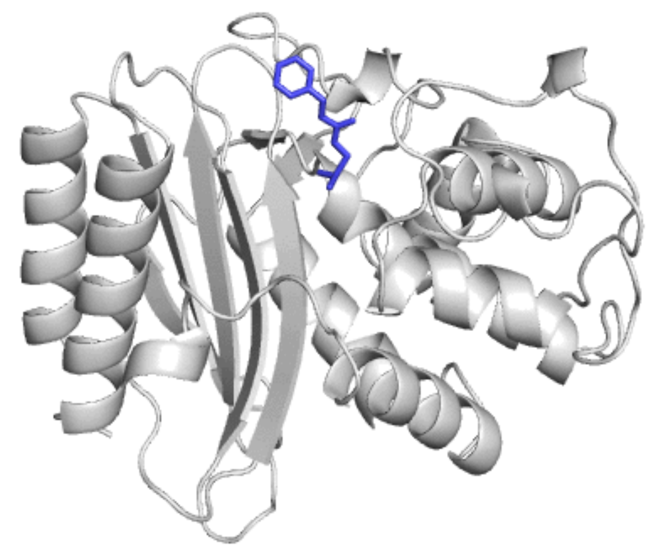
Single amino acid deletions



Recap

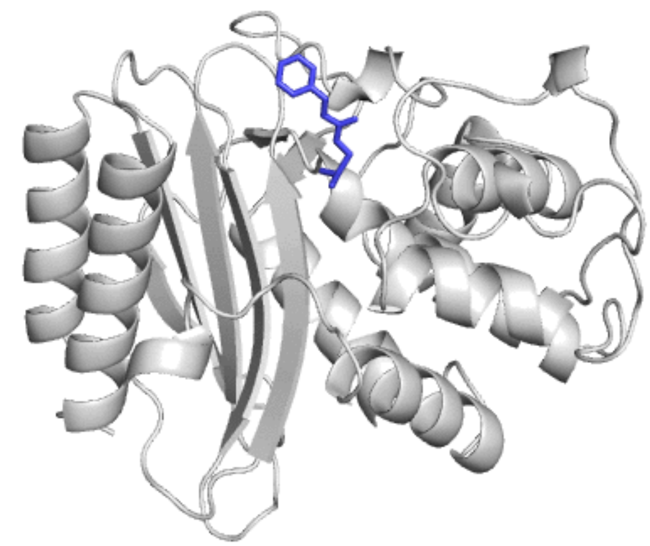
Recap

Predicting the effects of mutations is important



Recap

Predicting the effects of mutations is important

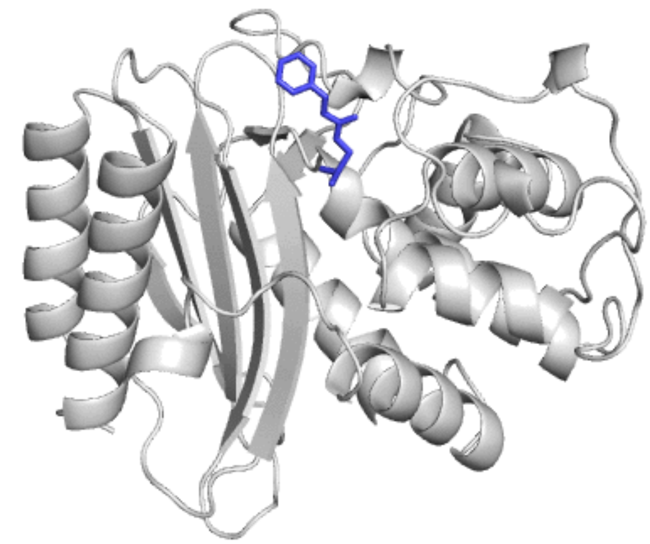


Sequencing is becoming cheaper and easier

```
GTGTTGCCAACTCGAAGGCTCTGCTCACCAATGTACATGG
AAAGAGCCGTTTAATCTCGGGCGCTTAATTCGCCTCGTGA
TTCCAGCCAGGCAGTGGCGGATCAATATGCCGACTTCCTG
ACACCTCGTCGATGGATTACTACCATCAGTTGCGTTATGC
GTTGGGGCTGGATTACCGGTTATTGAGAACCTGCAAAATC
TCTTTCTGGTTCGCTTTCTTATATCTTCGGCAAGTTAGAC
AAATGGGTTATACCGAACCGGACCCGCGAGATGATCTTTC
GAAACGGGACGTGAACTGGAGCTGGCGGATATTGAAATTG
TGCCGCTTTTATGGCGAATCTGTCACAACTCGACGATCTC
```

Recap

Predicting the effects of mutations is important



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GTGTTGCCAACTCGAAGGCTCTGCTCACCAATGTACATGG
AAAGAGCCGTTTAATCTCGGGCGCTTAATTCGCCTCGTGA
TTCCAGCCAGGCAGTGGCGGATCAATATGCCGACTTCCTG
ACACCTCGTCGATGGATTACTACCATCAGTTGCGTTATGC
GTTGGGGCTGGATTACCGGTTATTGAGAACCTGCAAAATC
TCTTTCTGGTTCGCTTTCTTATATCTTCGGCAAGTTAGAC
AAATGGGTTATACCGAACCGGACCCGCGAGATGATCTTTC
GAAACGGGACGTGAACTGGAGCTGGCGGATATTGAAATTG
TGCCGCTTTTATGGCGAATCTGTCACAACTCGACGATCTC
```

Generative models fit to biological sequence data can predict the effect of mutations

$$\log \frac{p(\mathbf{x}_{\text{mut}}|\boldsymbol{\theta})}{p(\mathbf{x}_{\text{wild}}|\boldsymbol{\theta})}$$

Part II: **Genotype -> phenotype for complex diseases**

insitro™

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Founded by Daphne Koller in 2018

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Create a **new paradigm** for **drug development**

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Create a **new paradigm** for **drug development** that uses **high-quality data** and **data-driven models**

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Founded by Daphne Koller in 2018

Create a **new paradigm** for **drug development** that uses **high-quality data** and **data-driven models** to design **novel**, **safe**, and e**ffective therapies**

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Founded by Daphne Koller in 2018

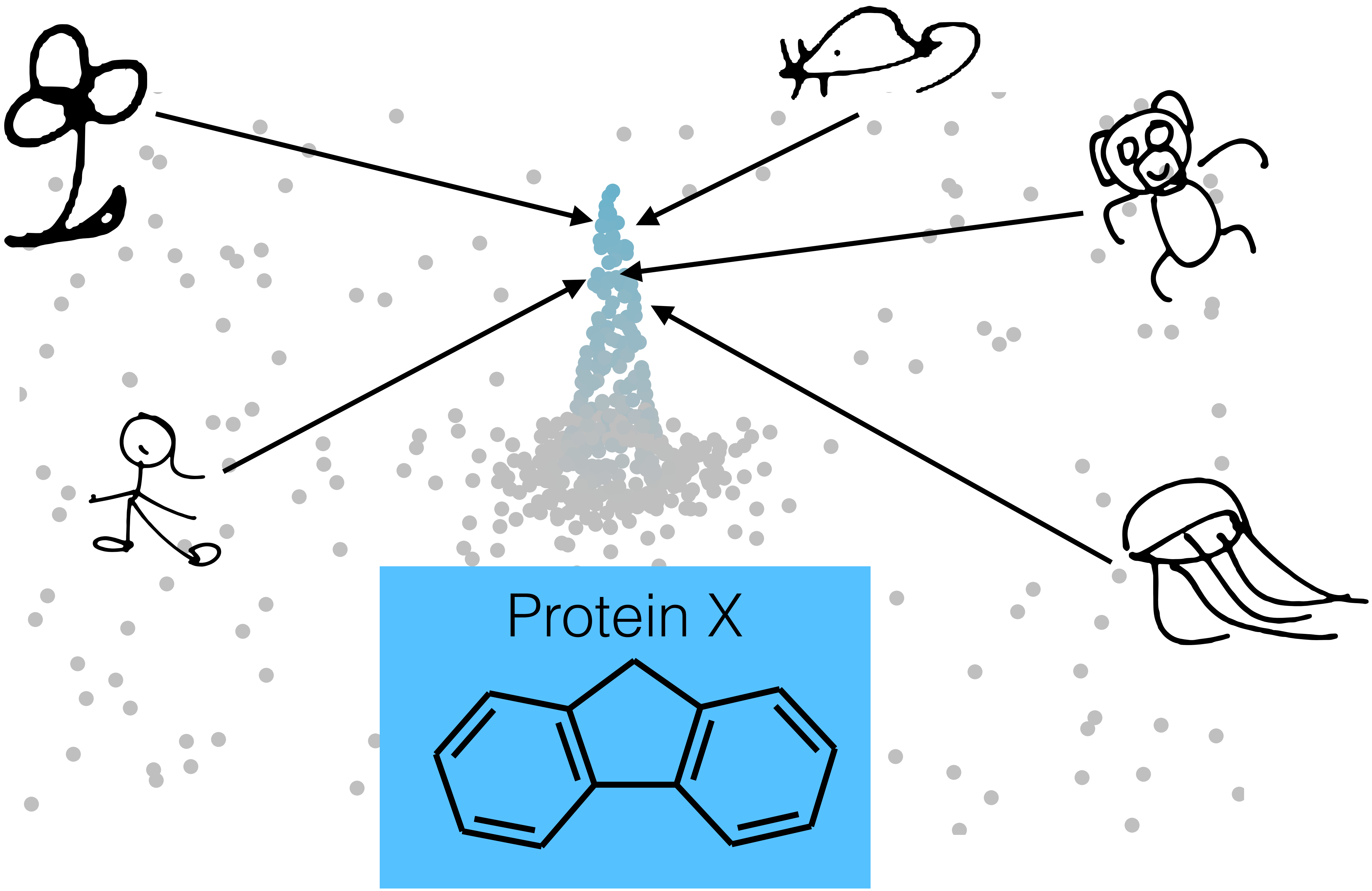
Create a **new paradigm** for **drug development**

that uses **high-quality data** and **data-driven models**

to design **novel**, **safe**, and e**ffective therapies**

that help **more people**, **faster**, and at a **lower cost.**

Part II: **Genotype -> phenotype** for different **tissues** are **sparse**



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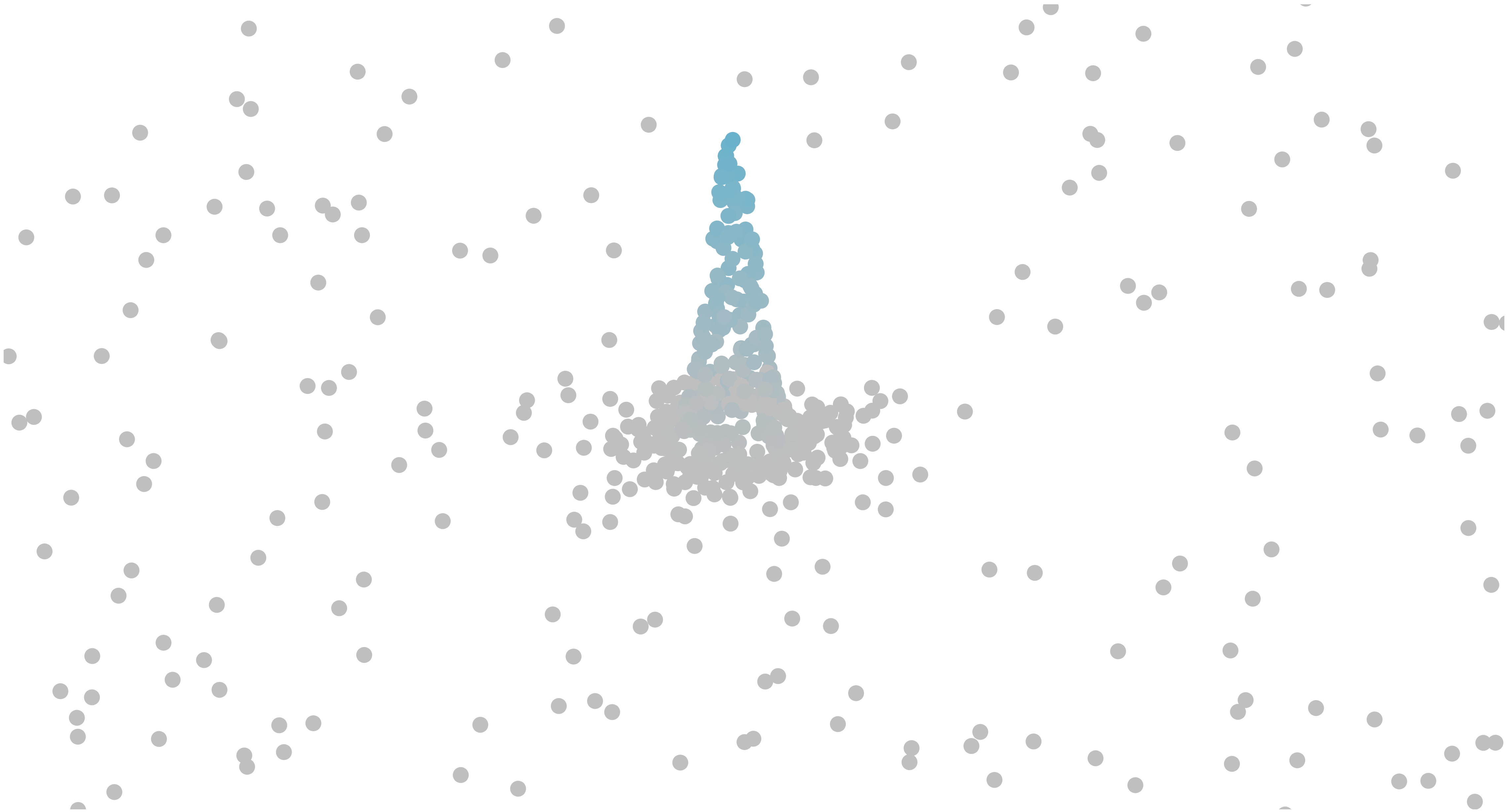

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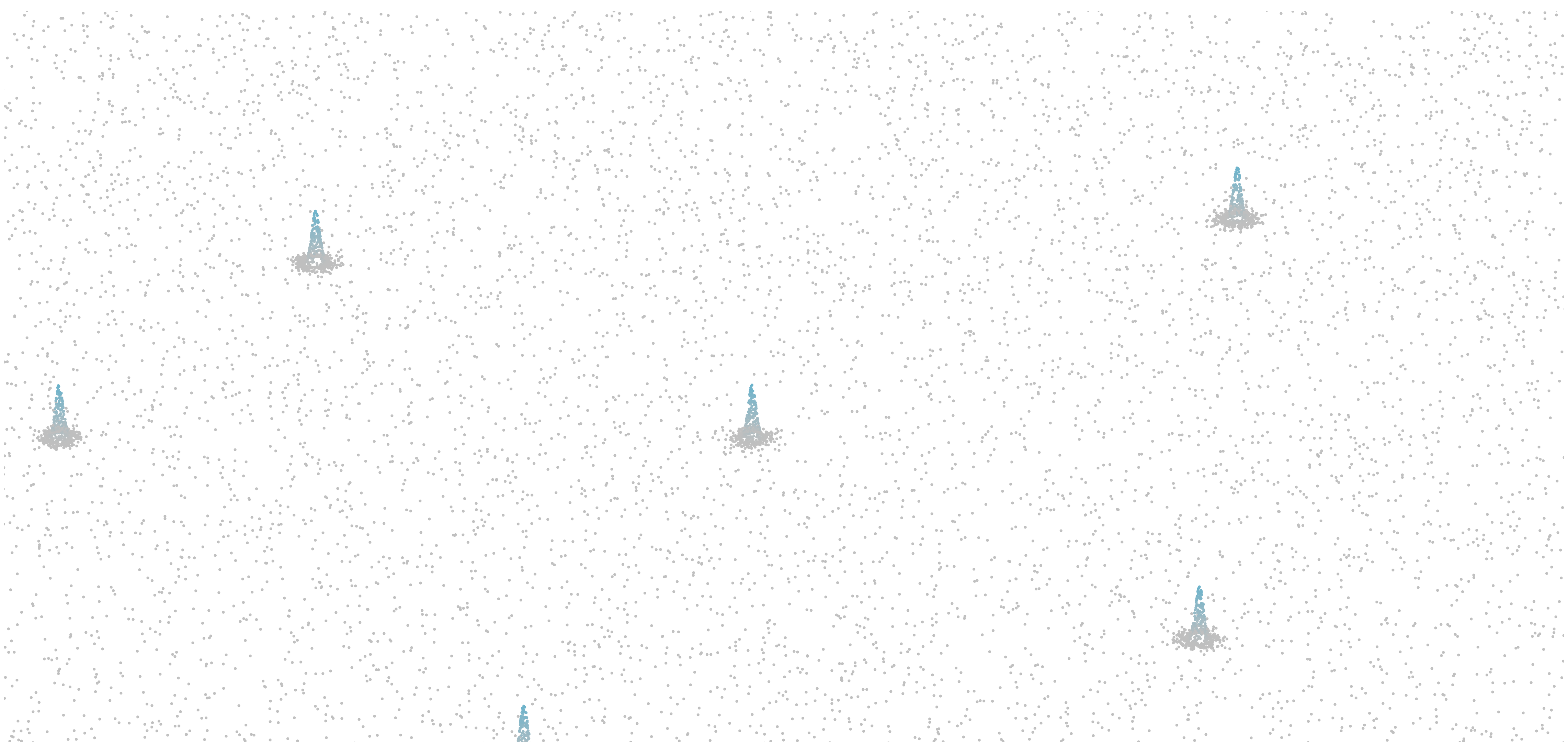

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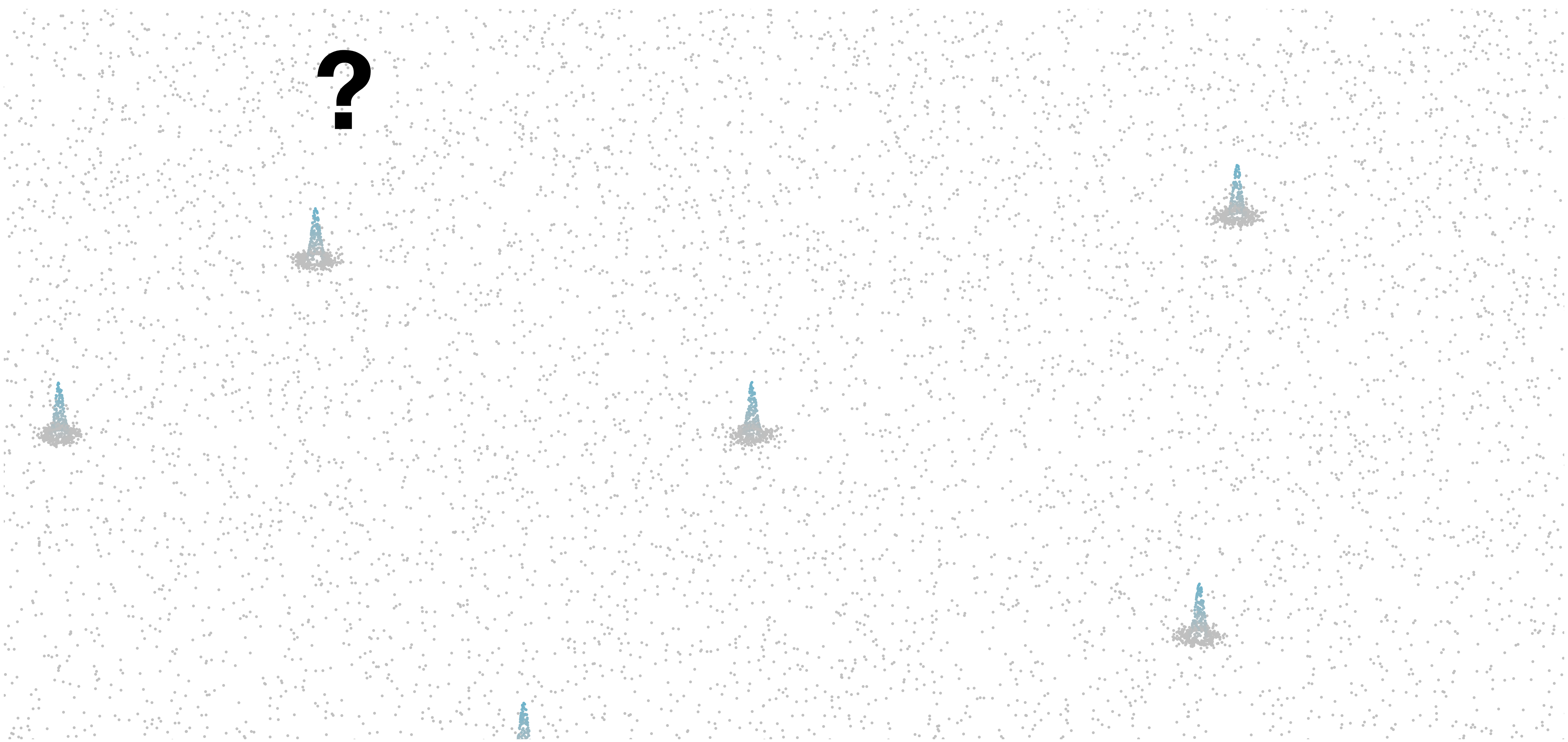

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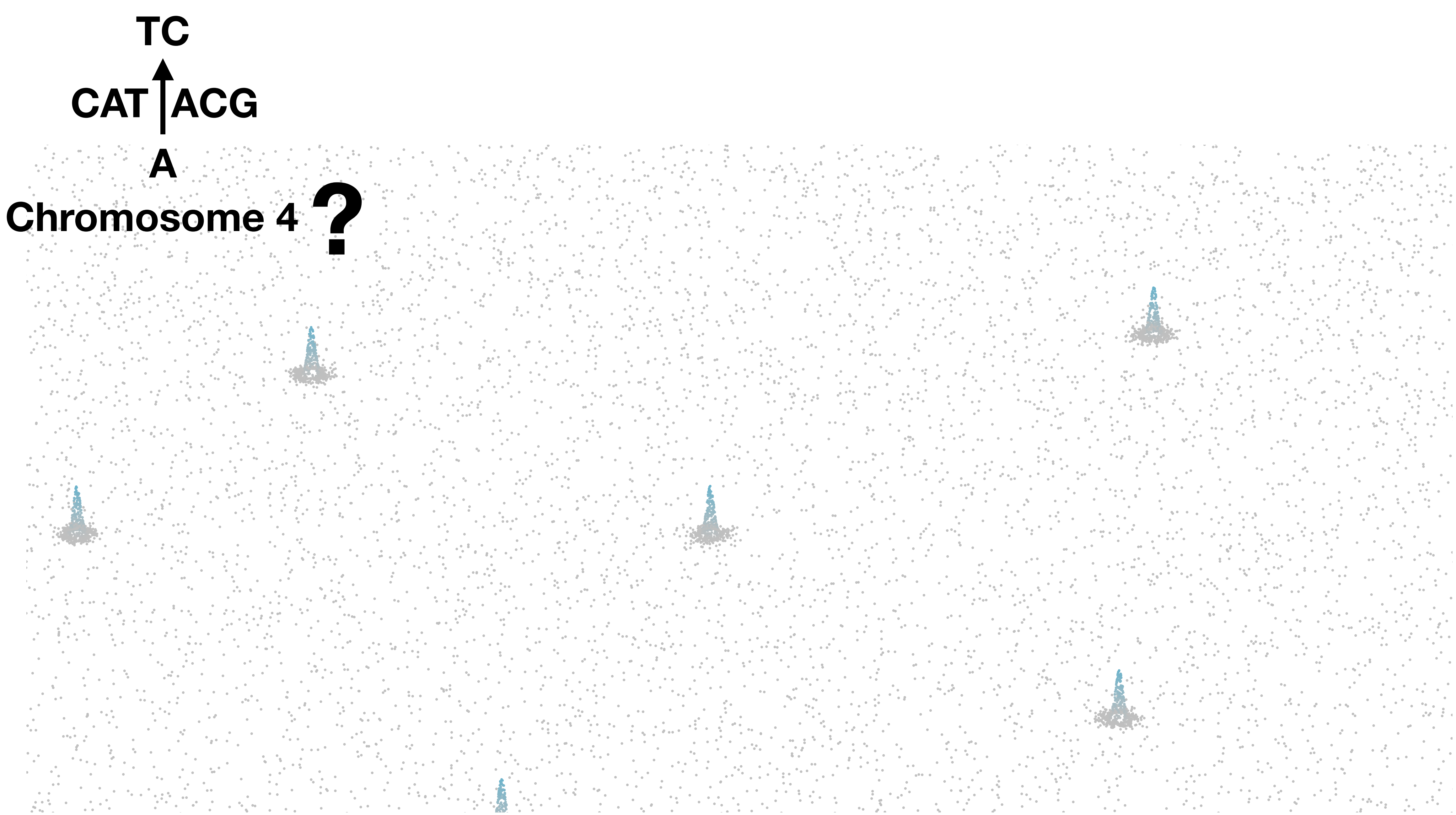

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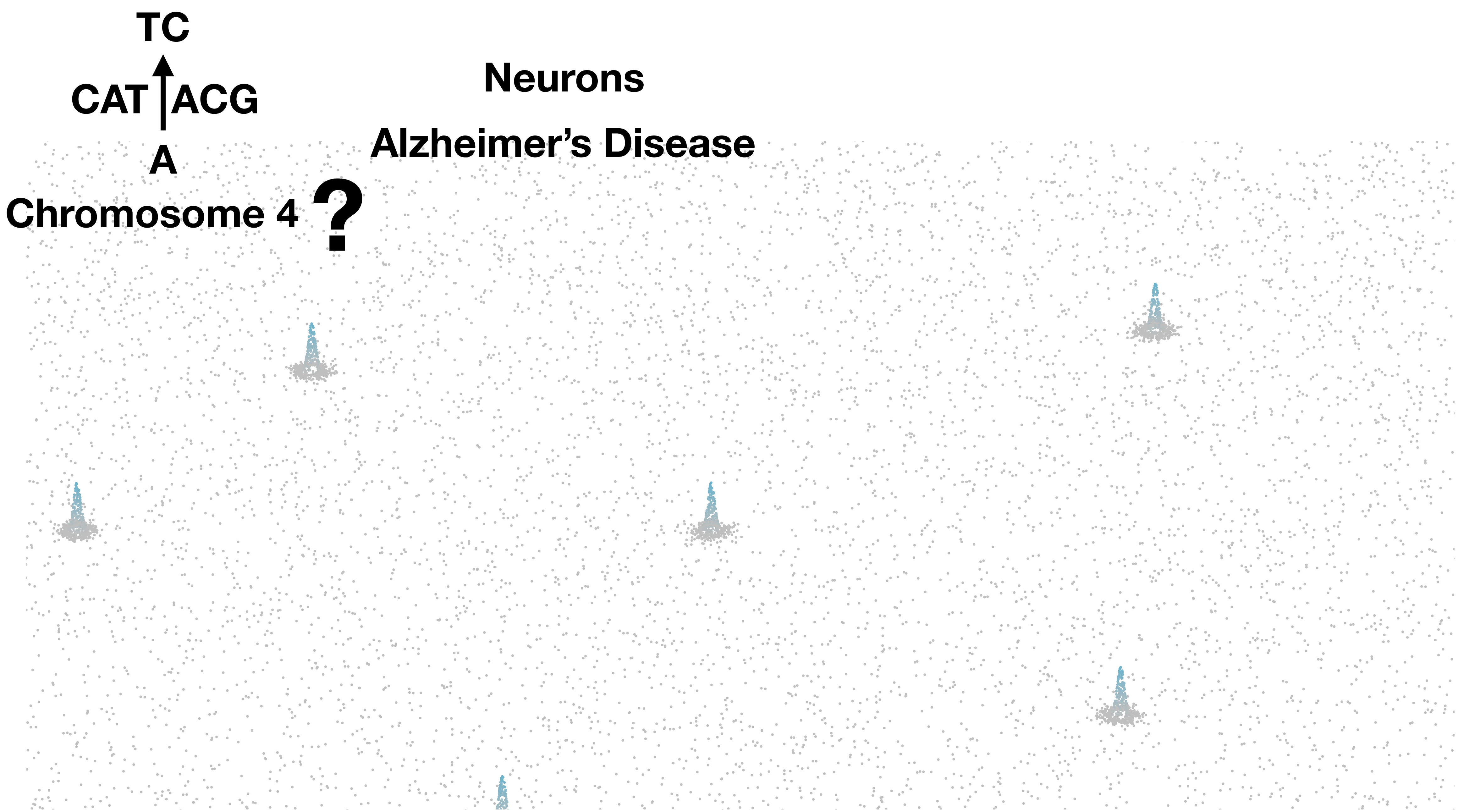

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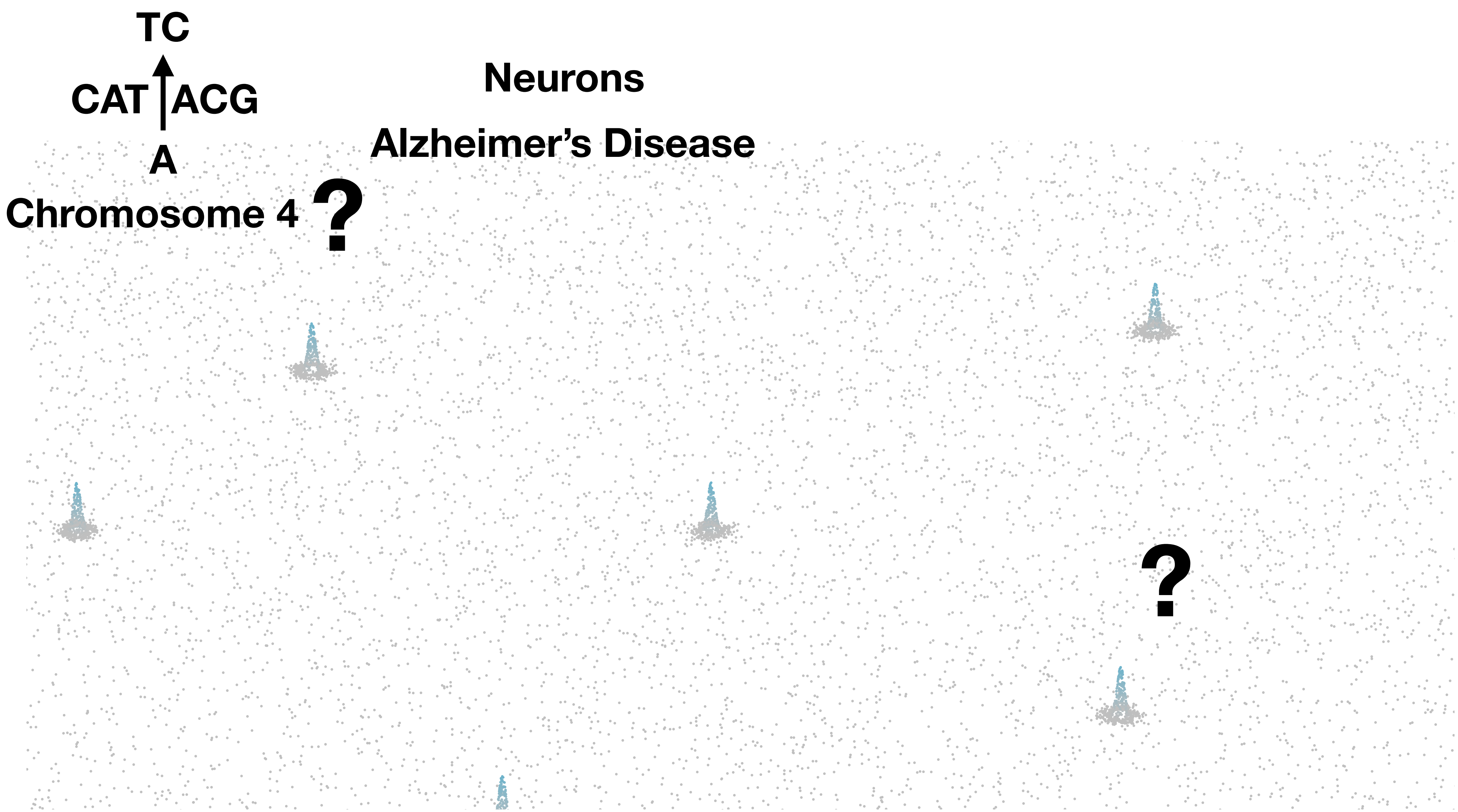

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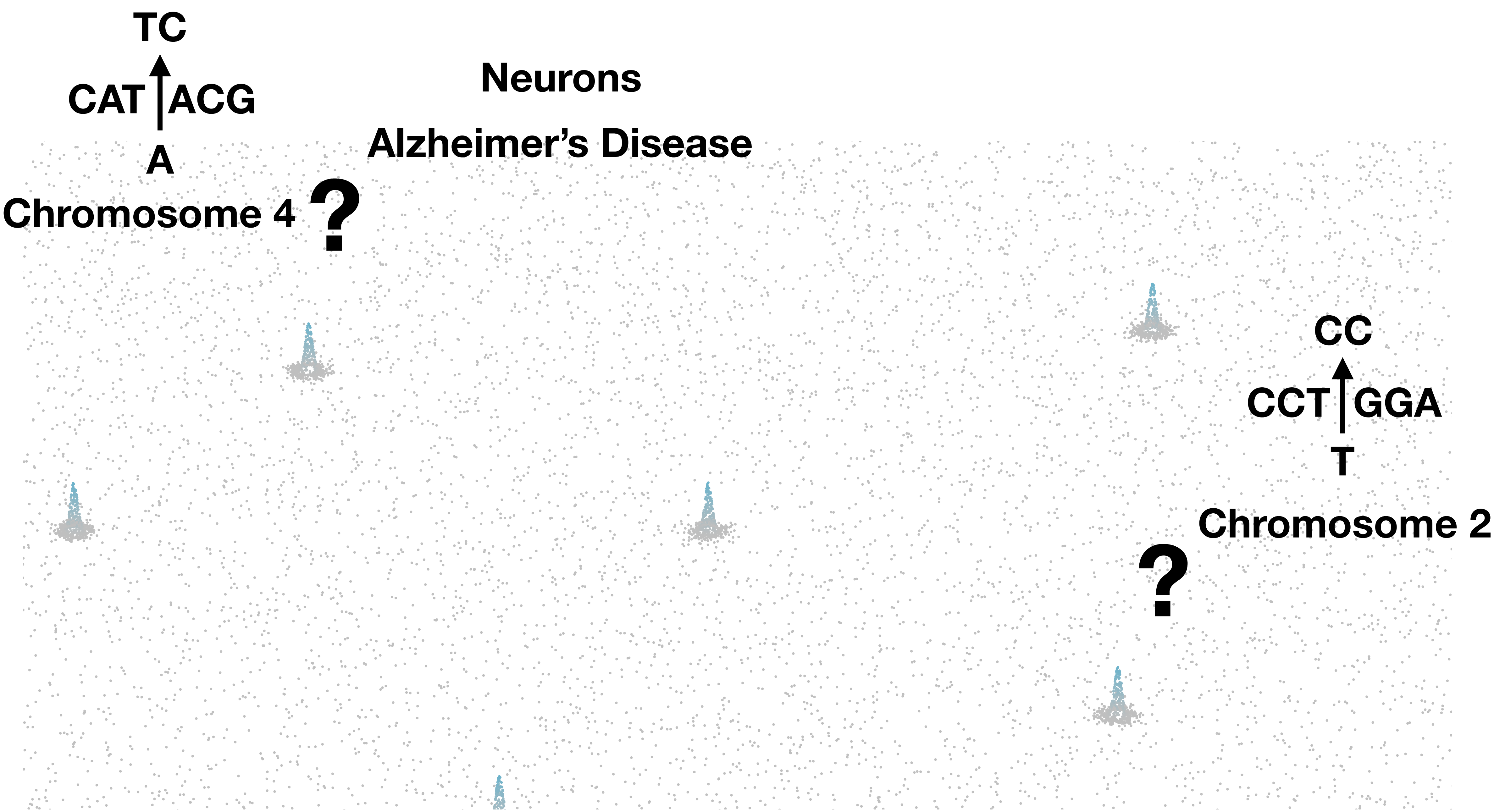

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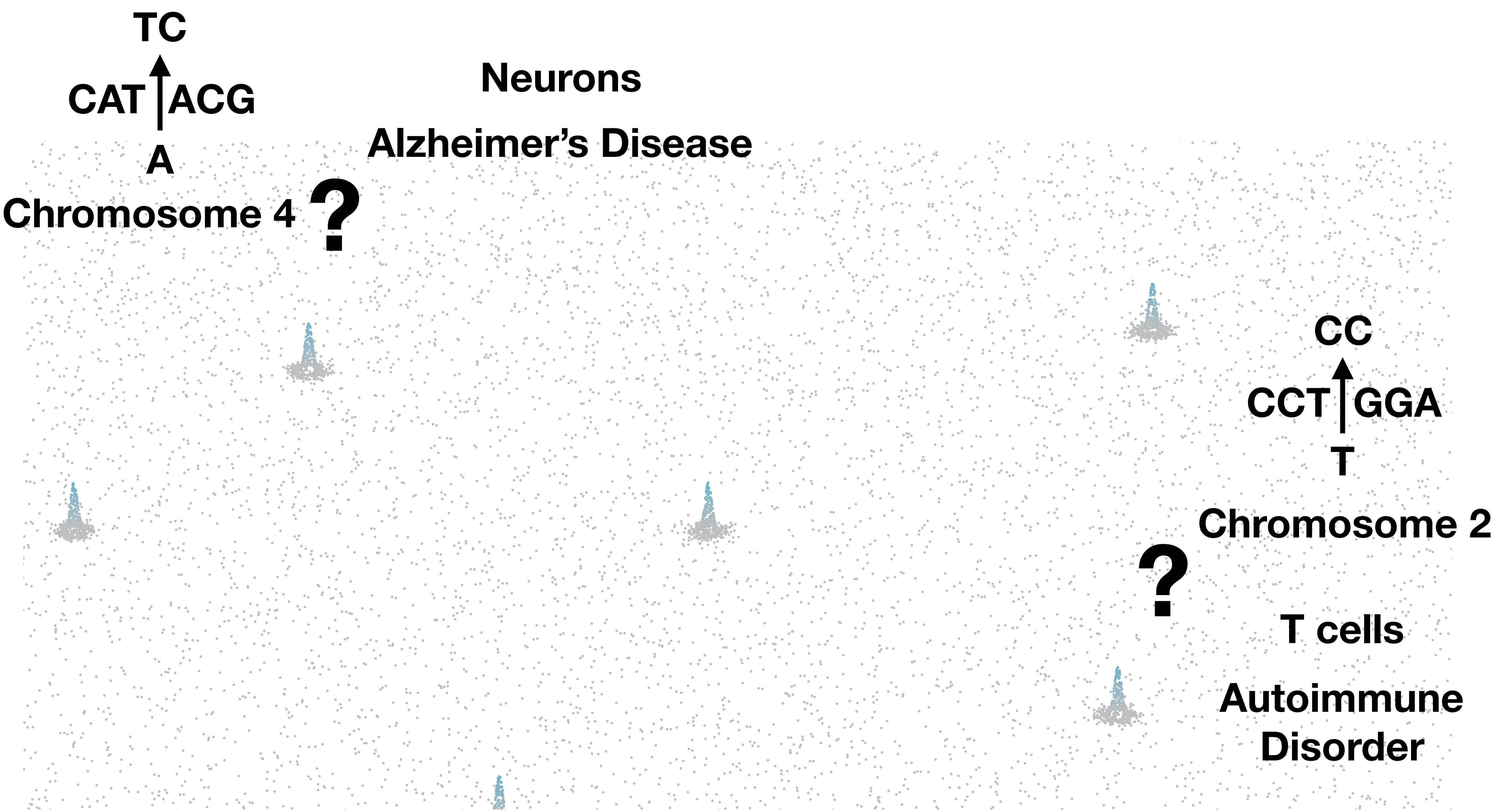

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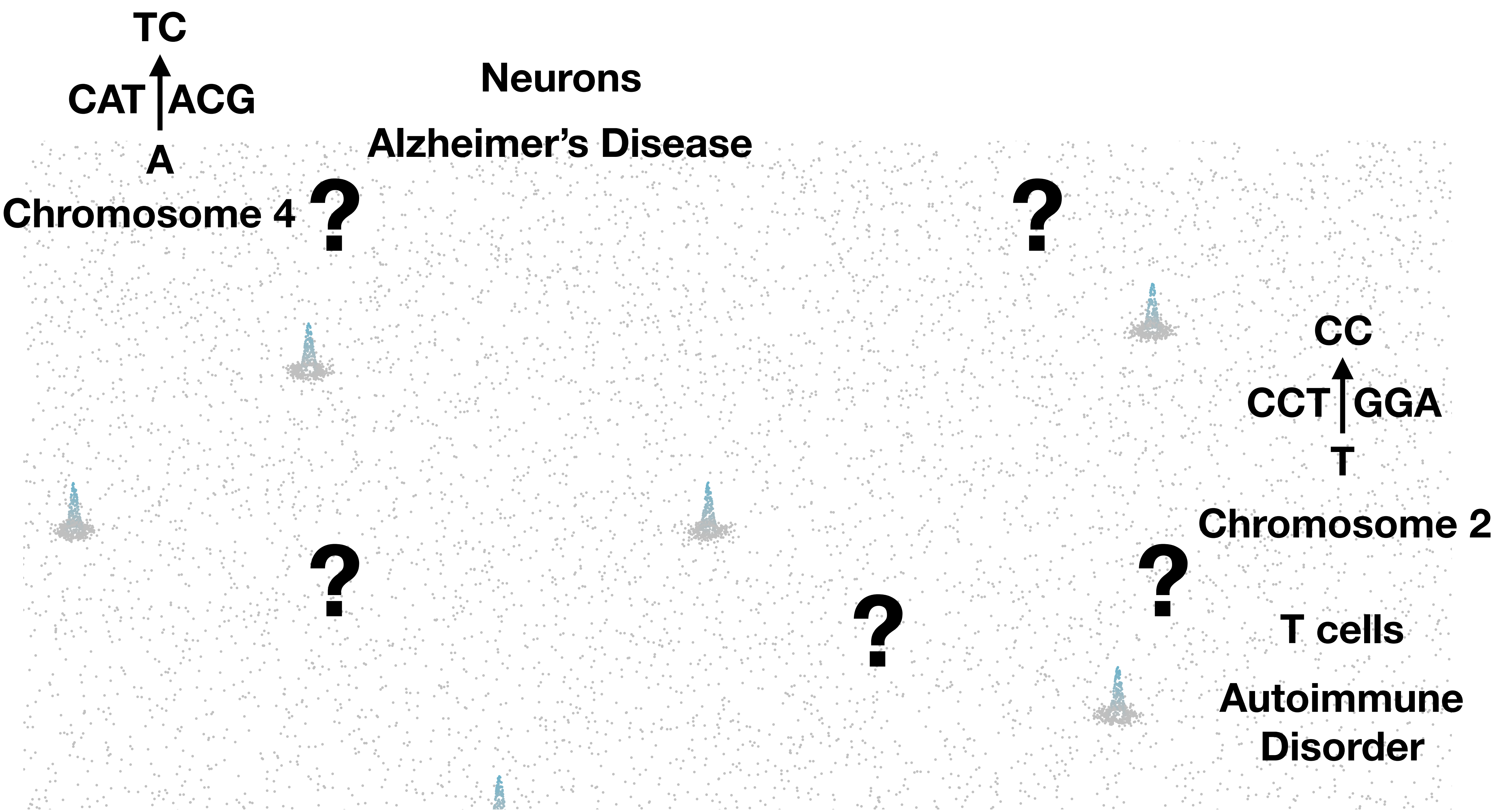

Drug discovery is becoming exponentially **less efficient**

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Moore's Law → **Eroom's Law**

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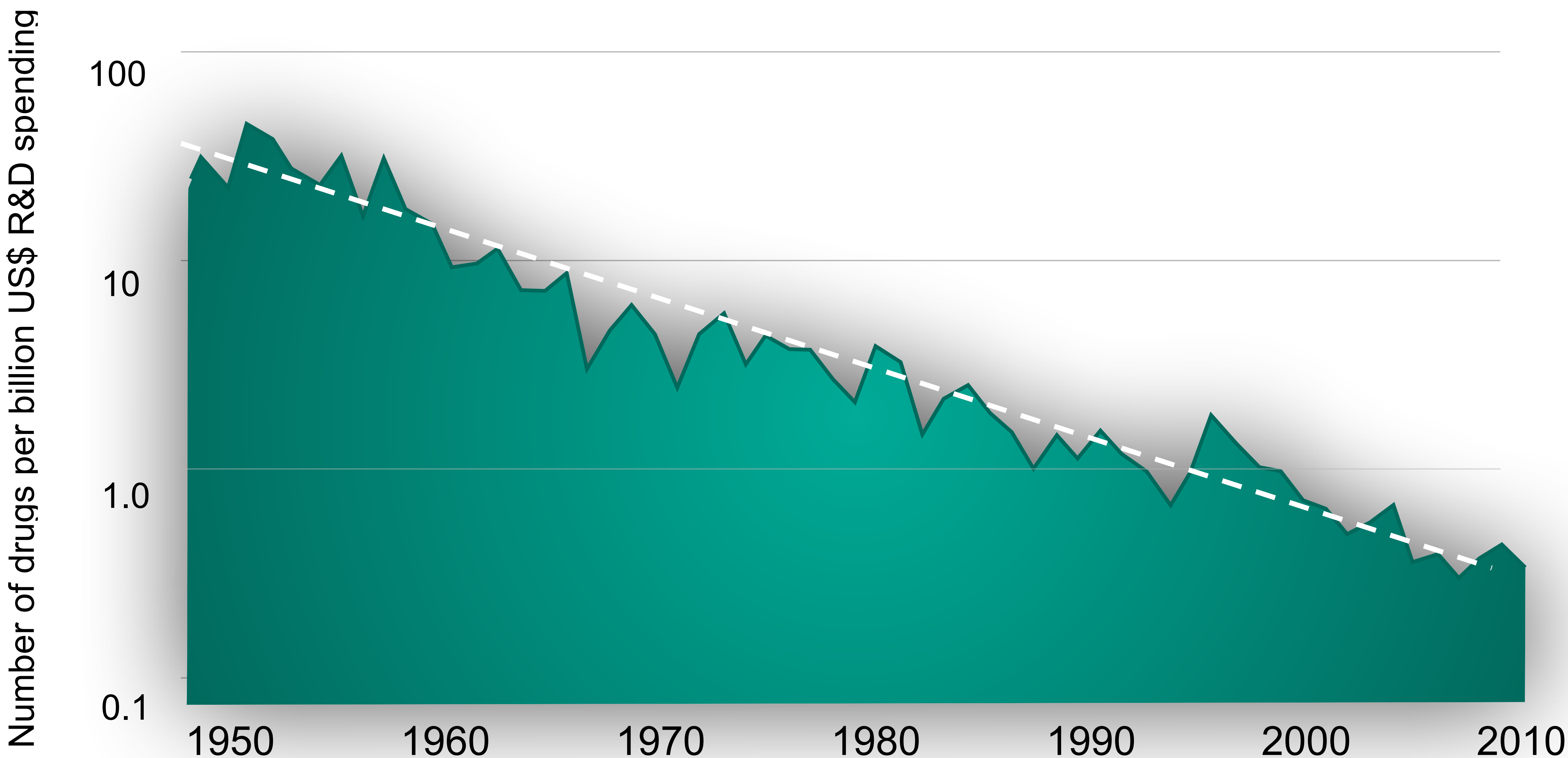

Scannell et al, Nature Reviews Drug Discovery, 2012.

Drug discovery is ultimately a **problem** of **prediction**

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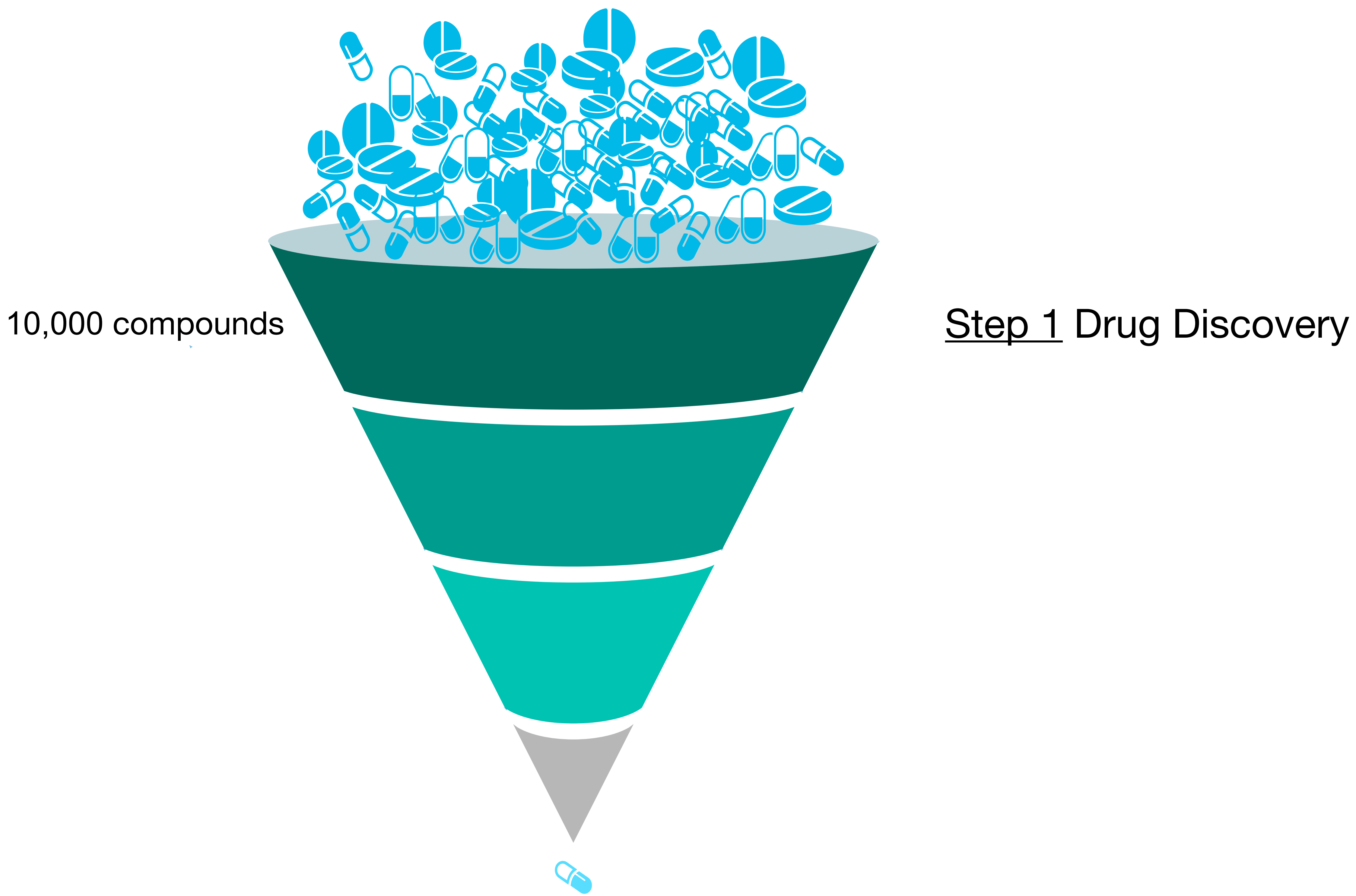

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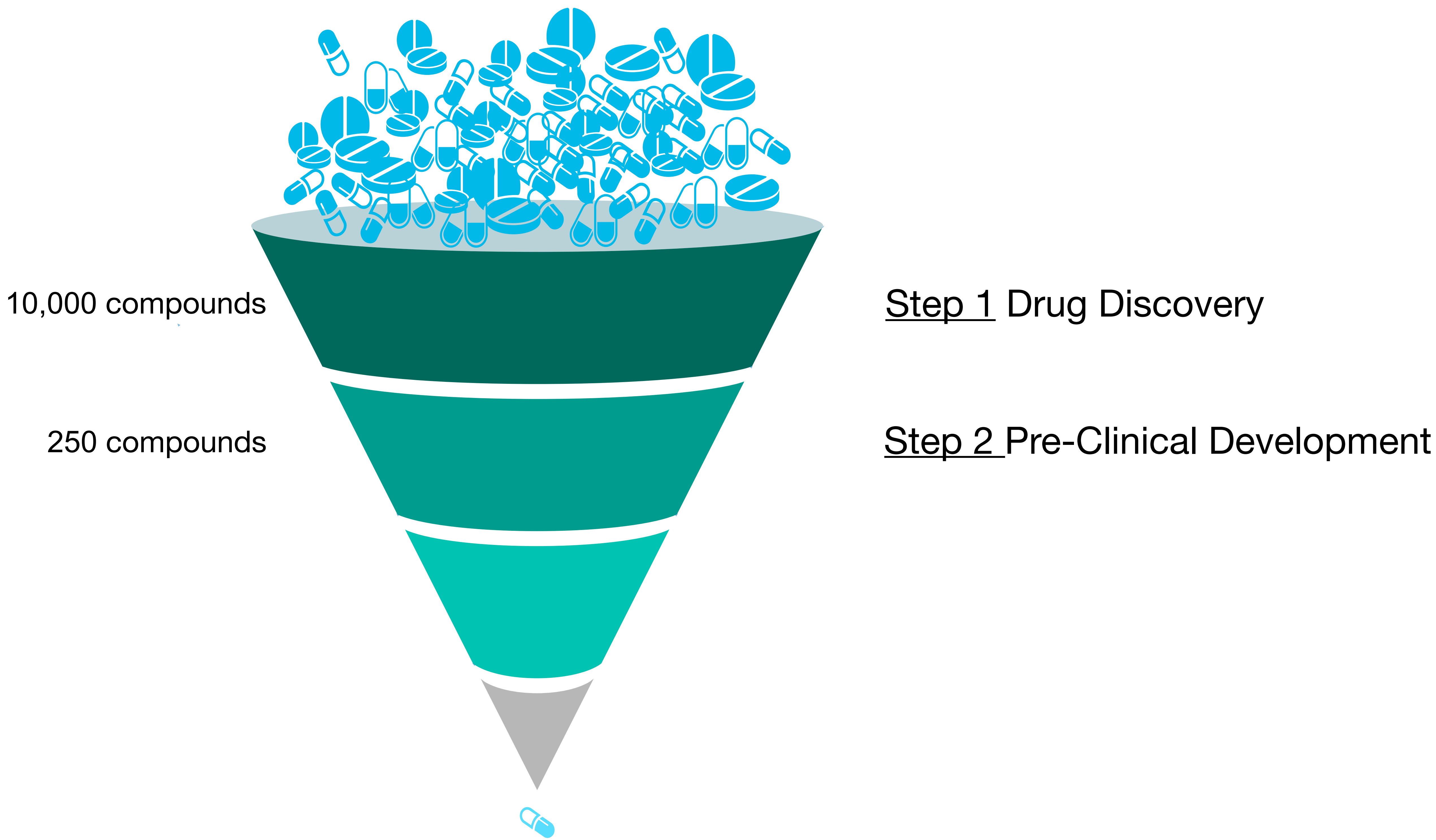

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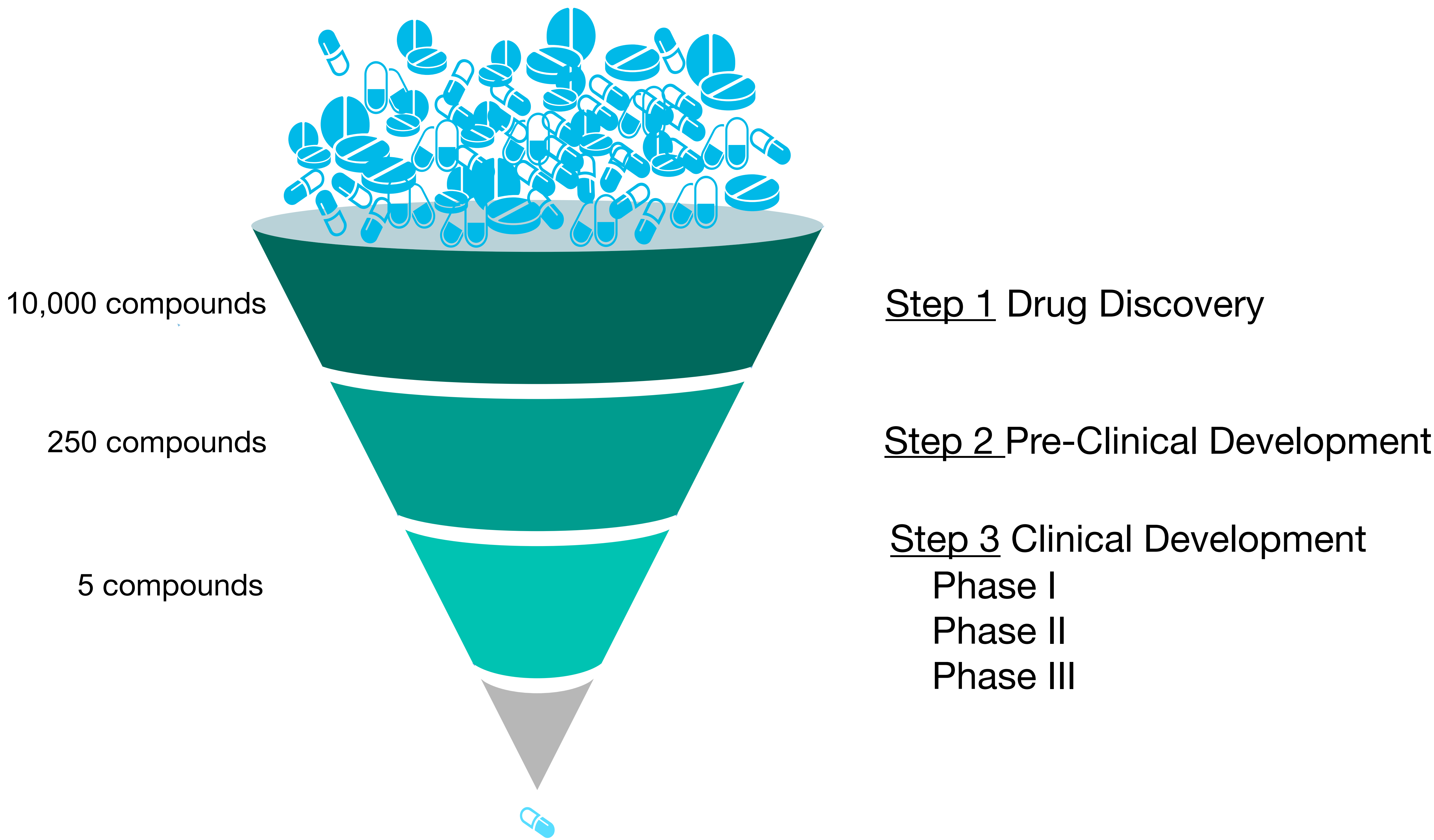

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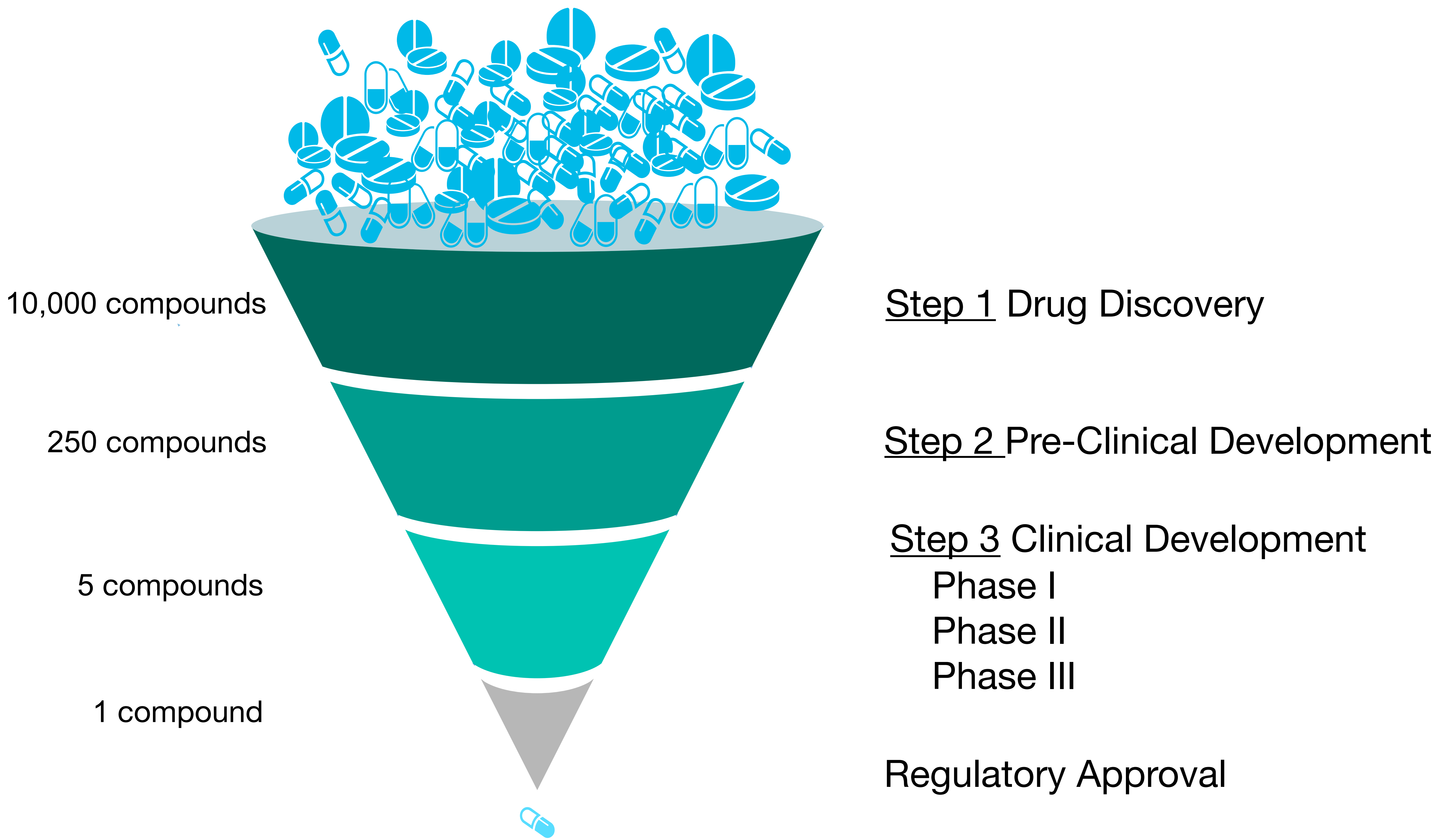

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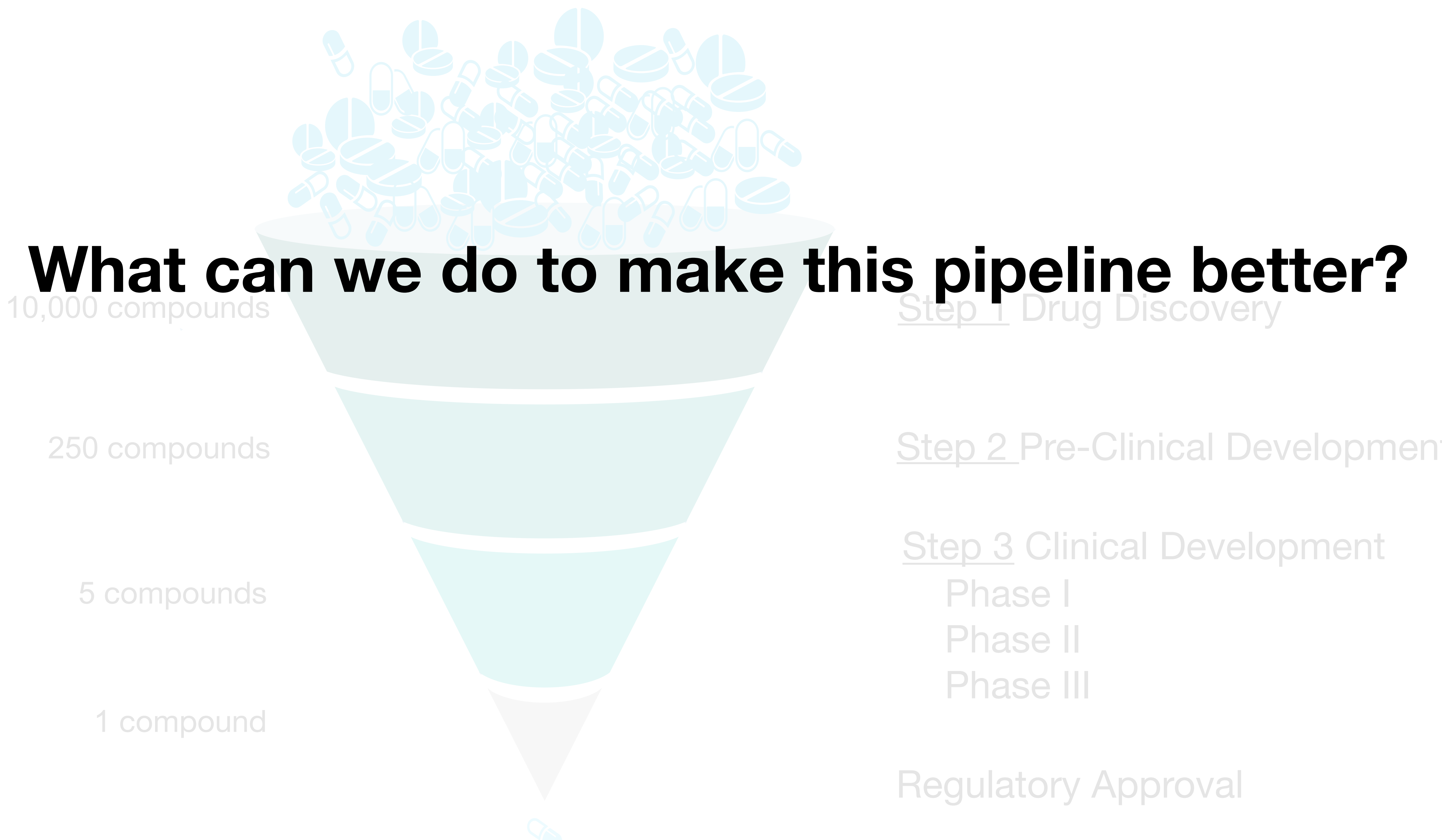
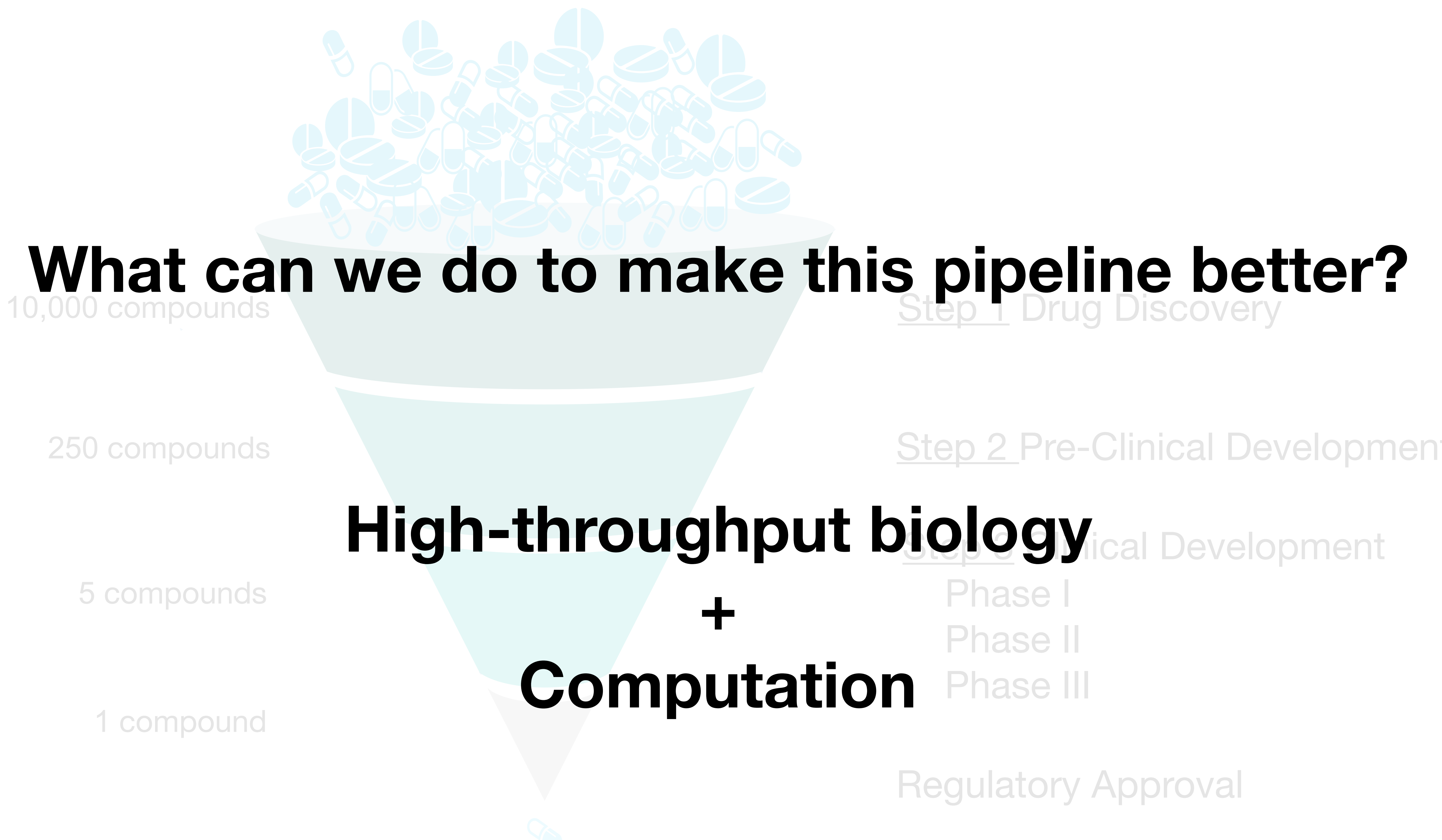


What can we do to make this pipeline better?

Drug discovery is ultimately a **problem** of **prediction**



What can we do to make this pipeline better?

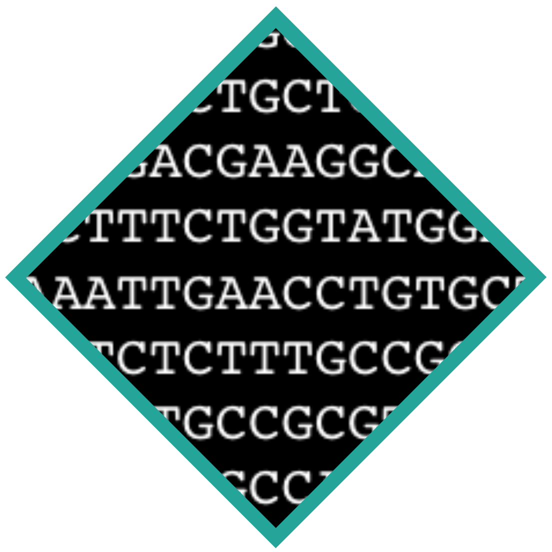
High-throughput biology

+

Computation

insitro is founded on **data-driven** technologies

Human genetics



https://www.rndsystems.com/resources/articles/differentiation-potential-induced-pluripotent-stem-cells

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Human genetics

Clinical data

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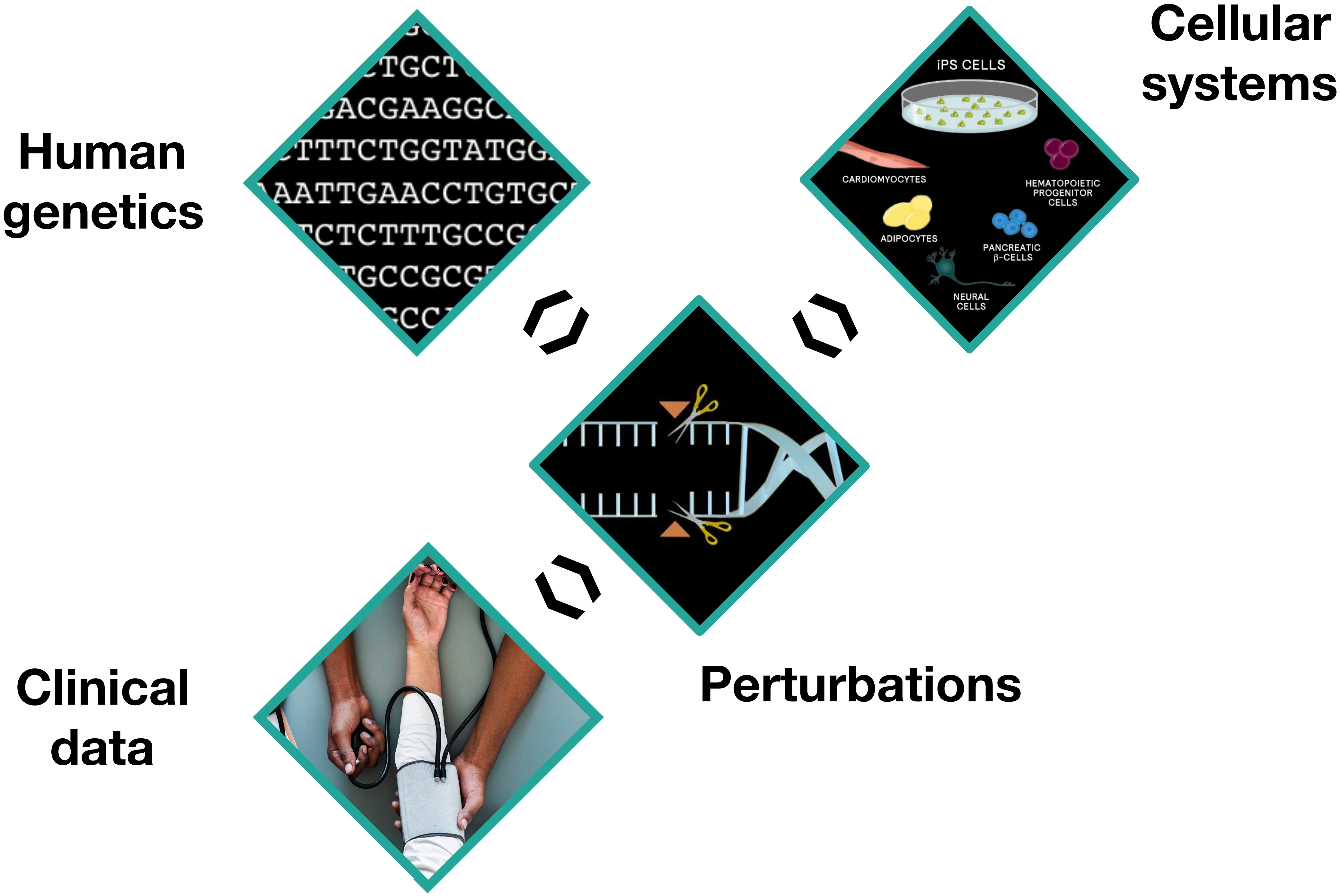

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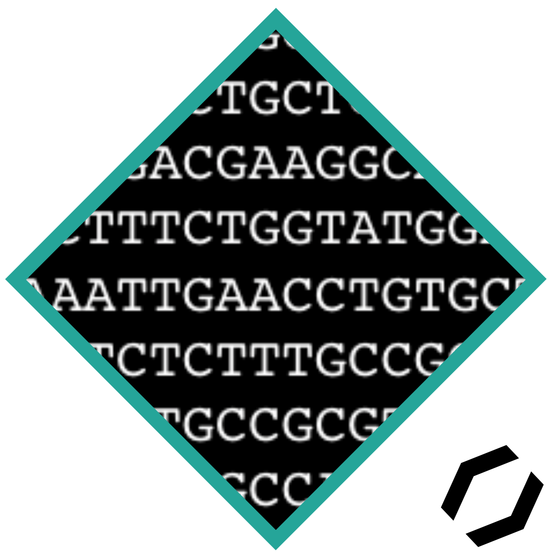
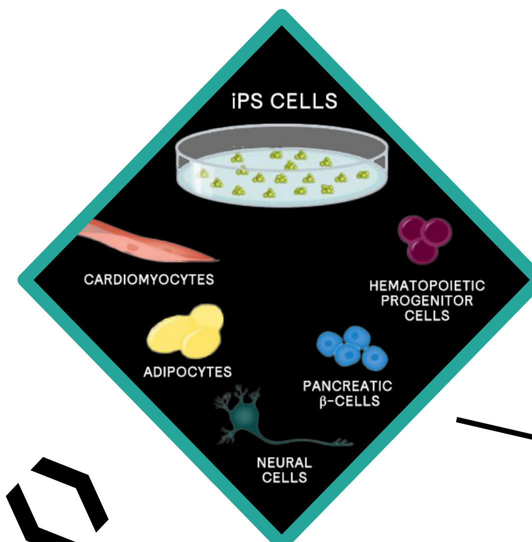
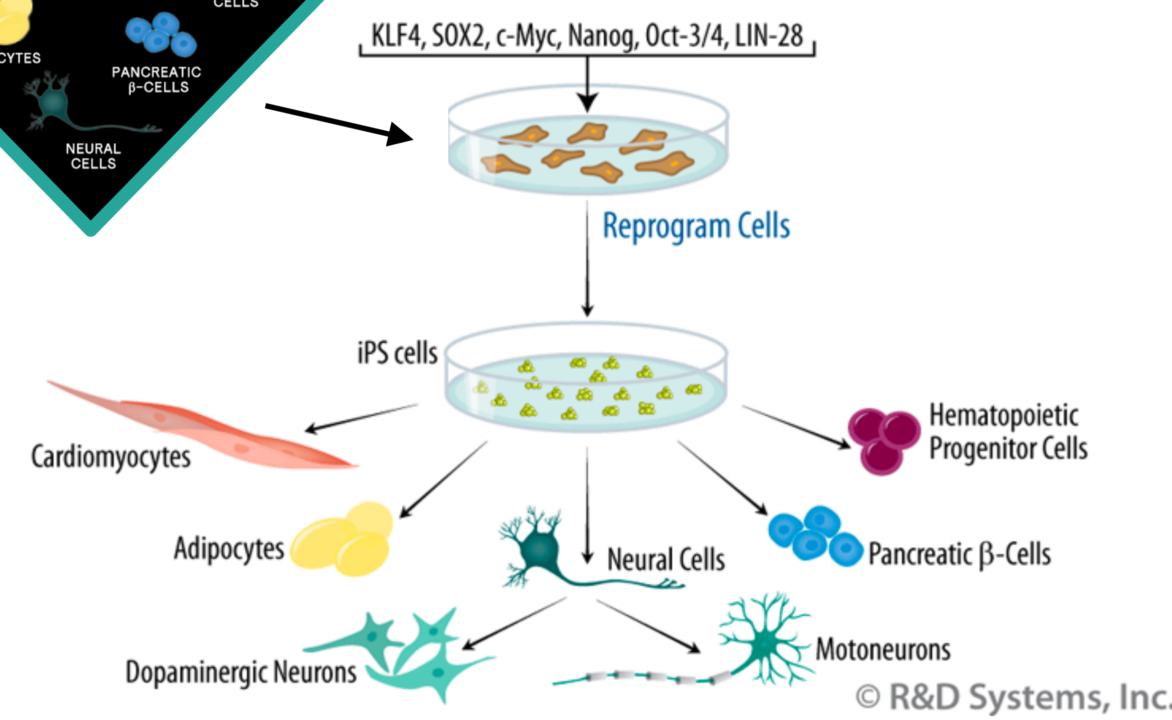
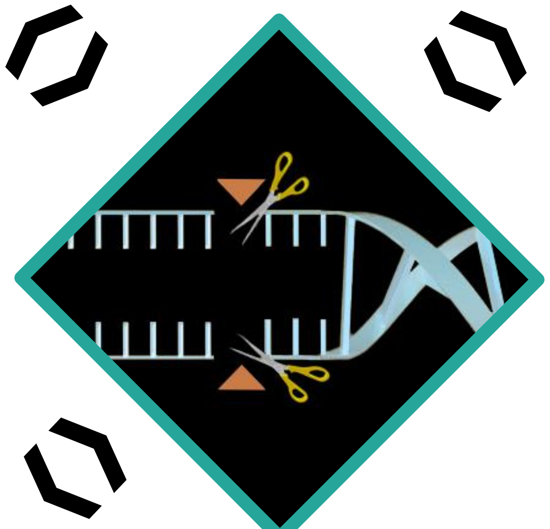


Cellular systems







Perturbations

Clinical data

https://www.rndsystems.com/resources/articles/differentiation-potential-induced-pluripotent-stem-cells

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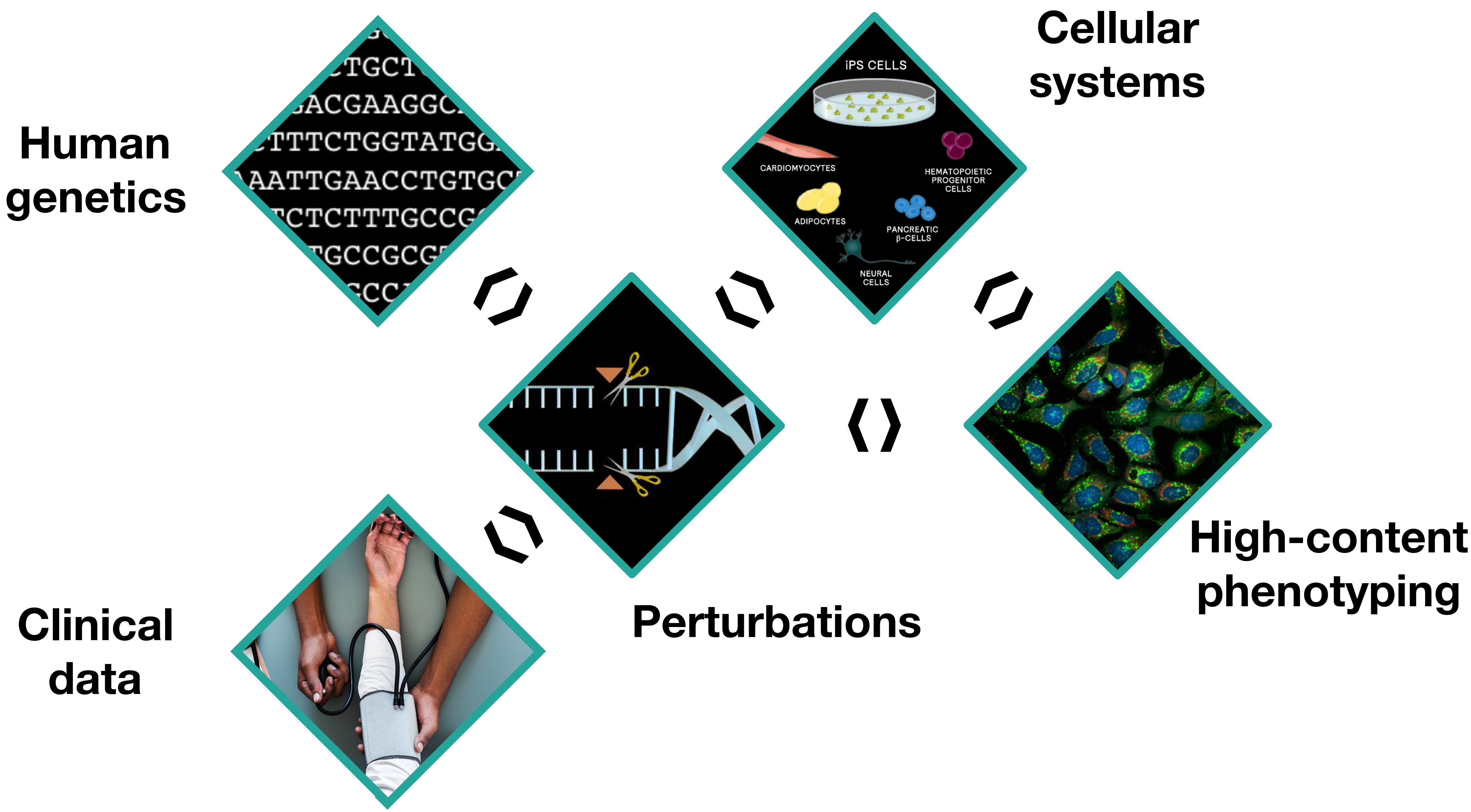

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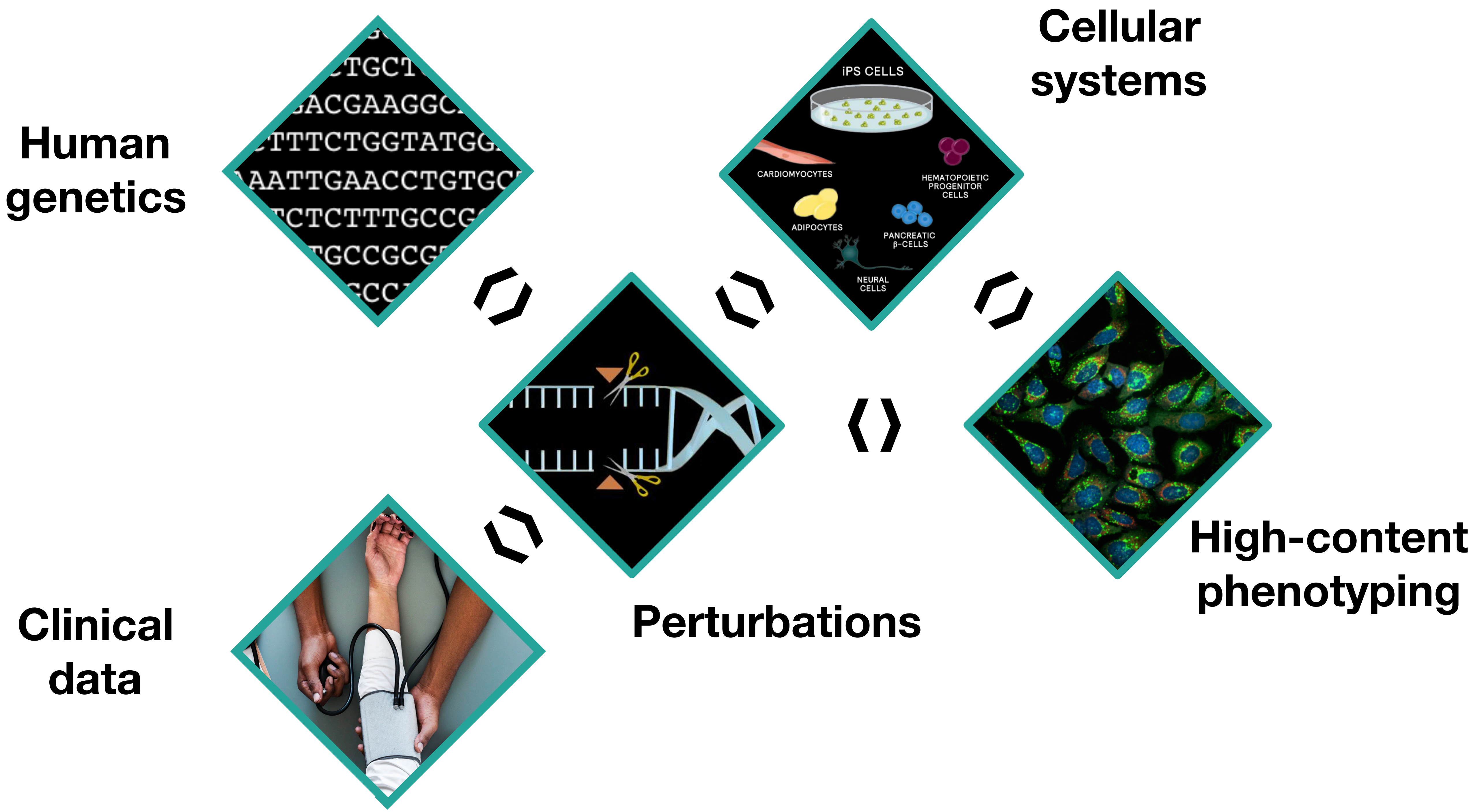

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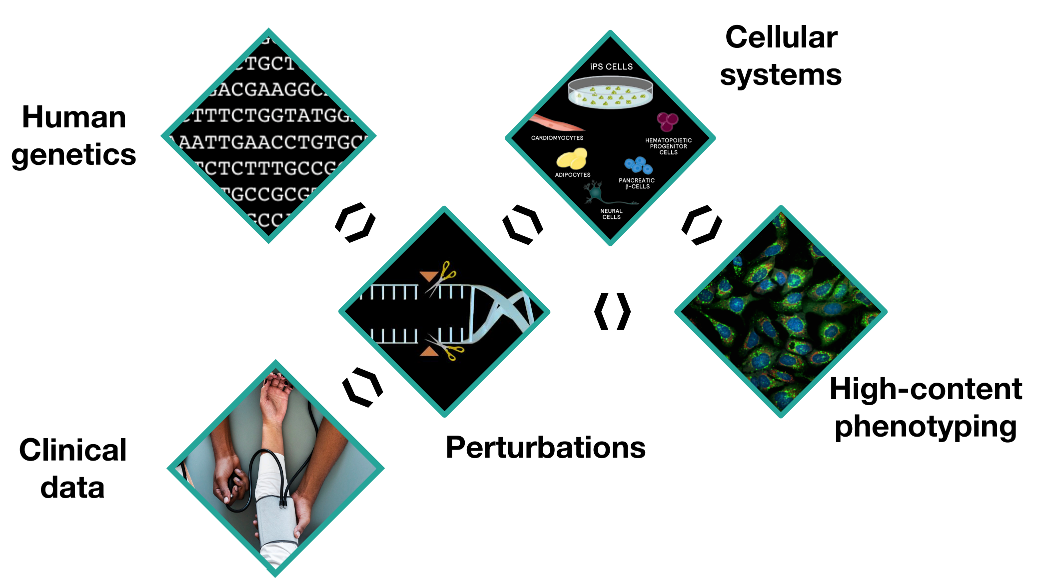

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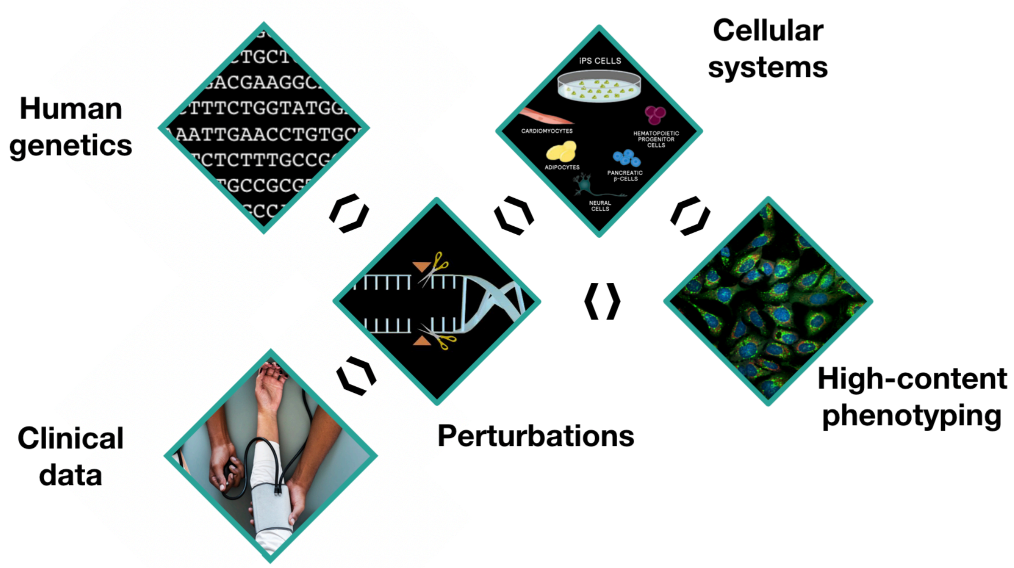

https://www.youtube.com/watch?v=vL7ptq2Dcf0

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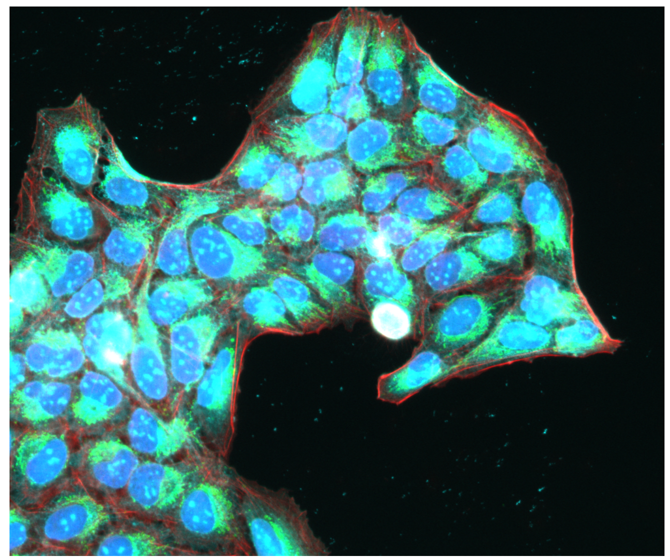
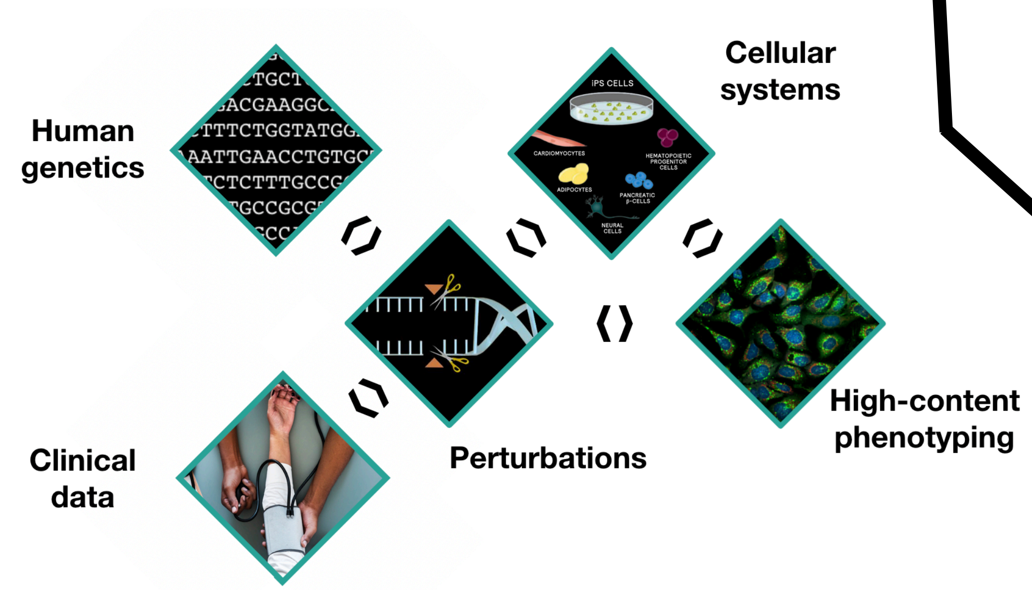


High-content microscopy



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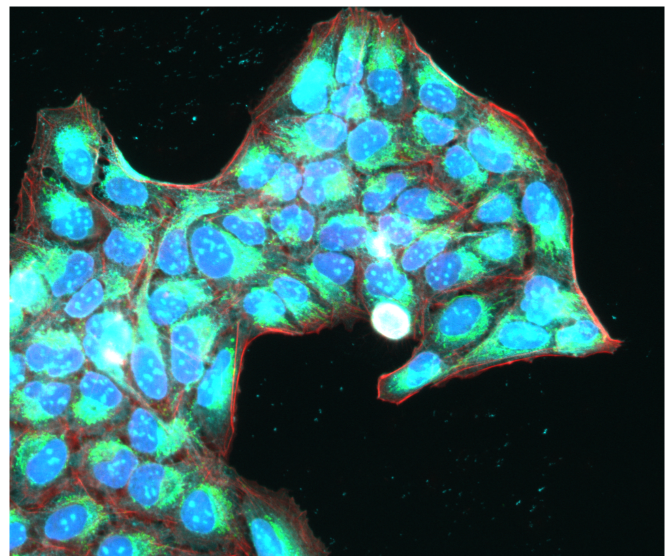

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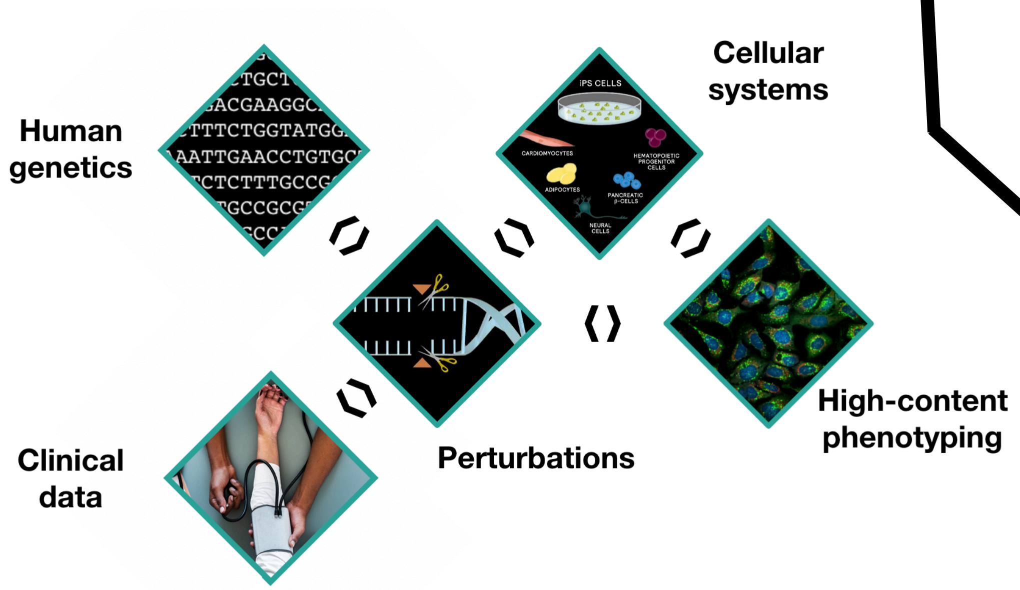

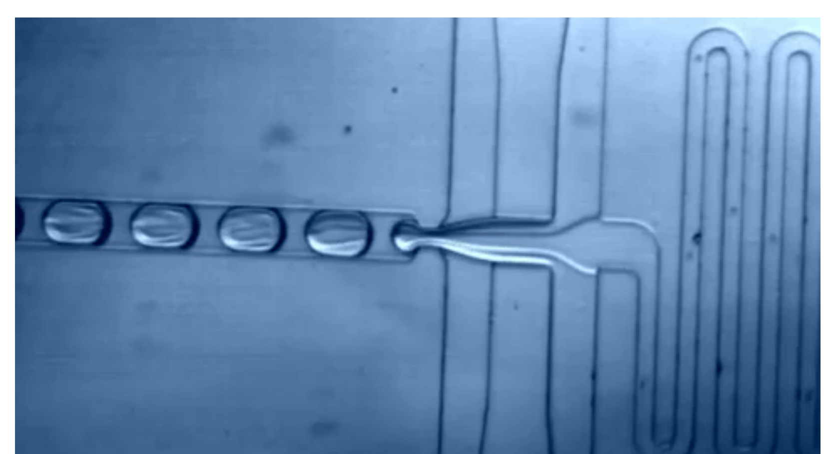

Single-cell RNA sequencing

https://www.youtube.com/watch?v=vL7ptq2Dcf0

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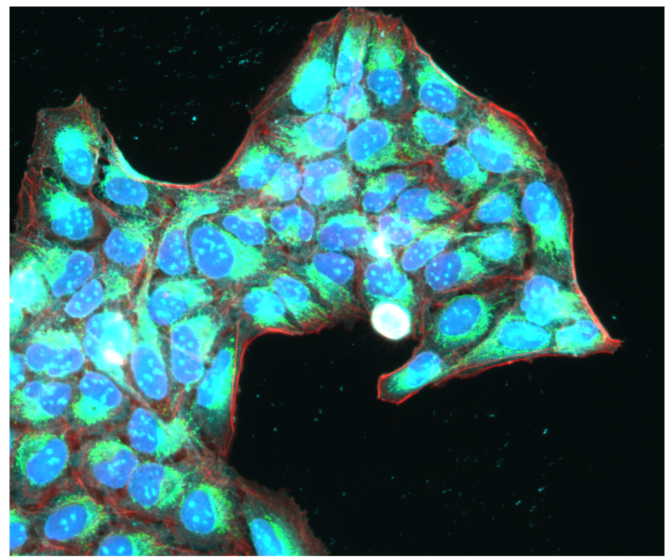
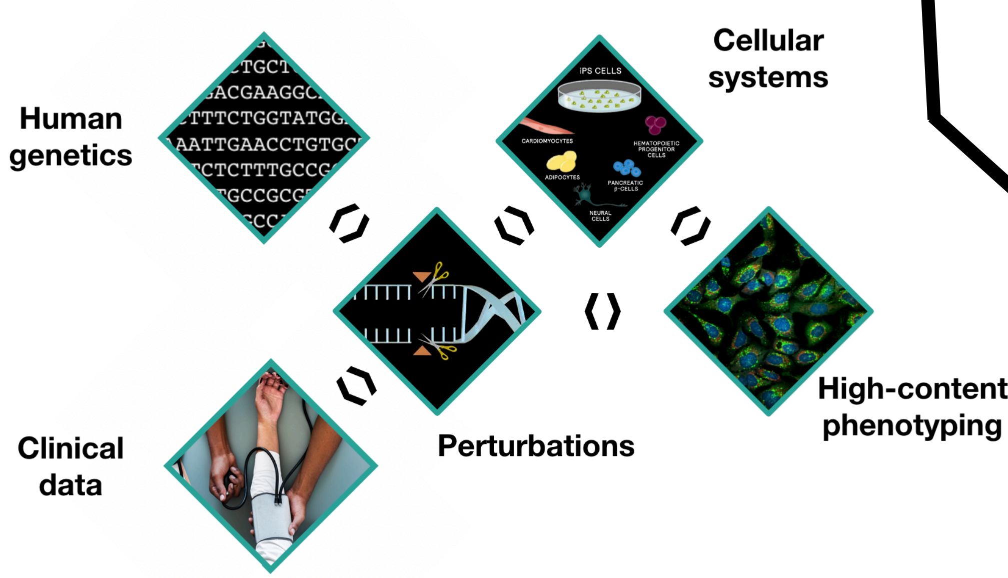
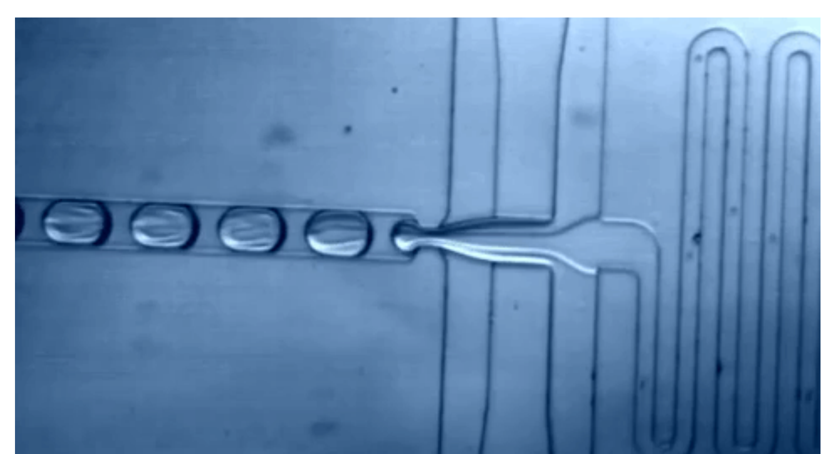


High-content microscopy

Machine Learning





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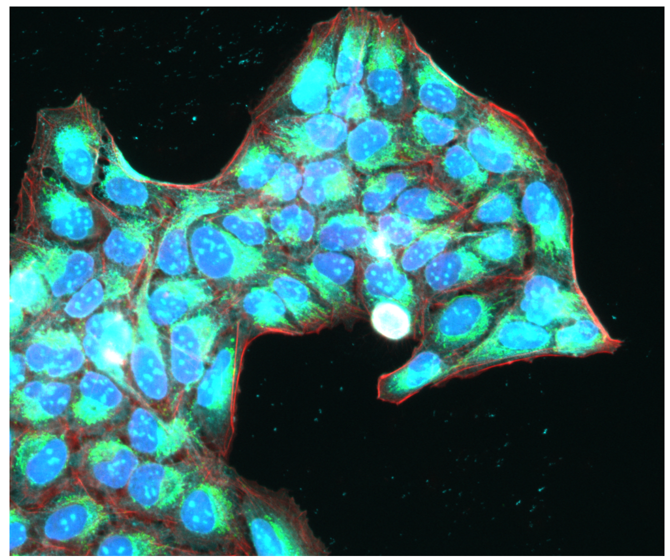
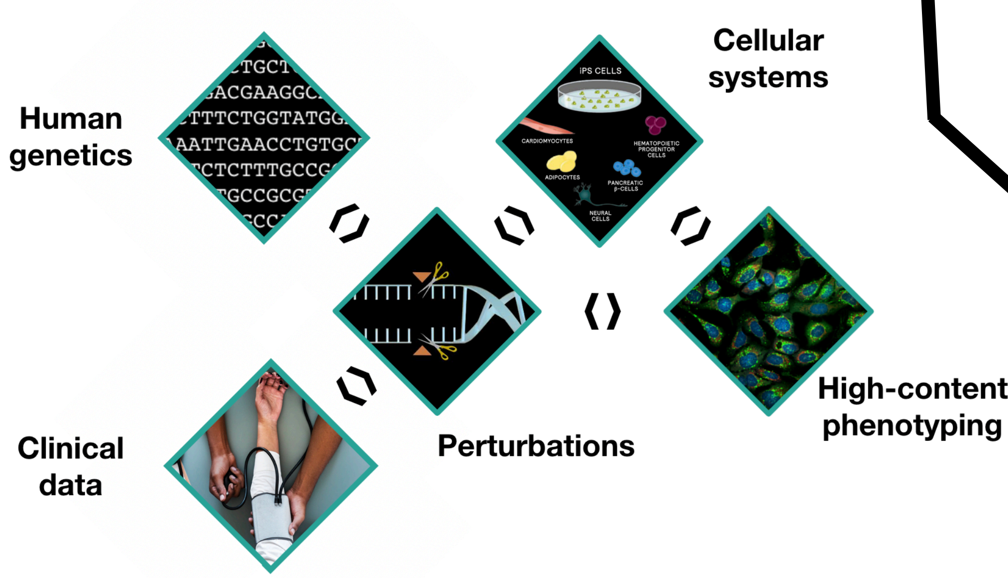
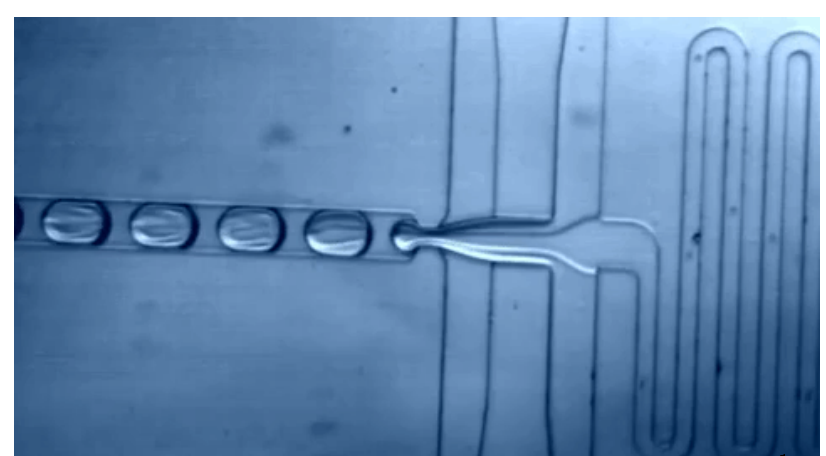


High-content microscopy

Machine Learning

Characterize phenotypes





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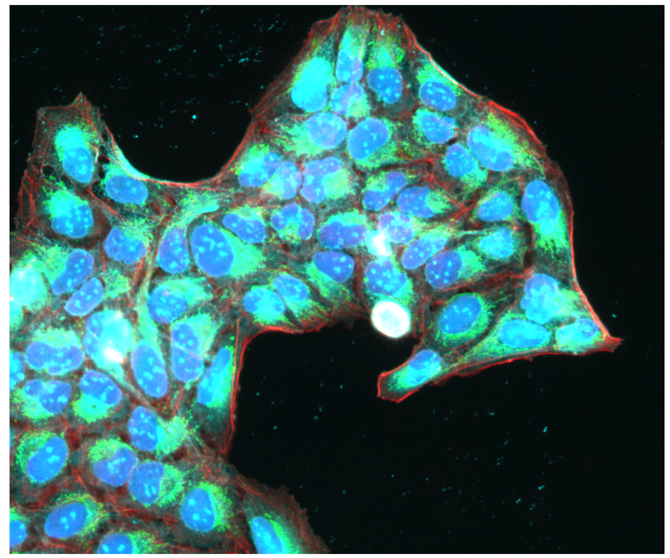
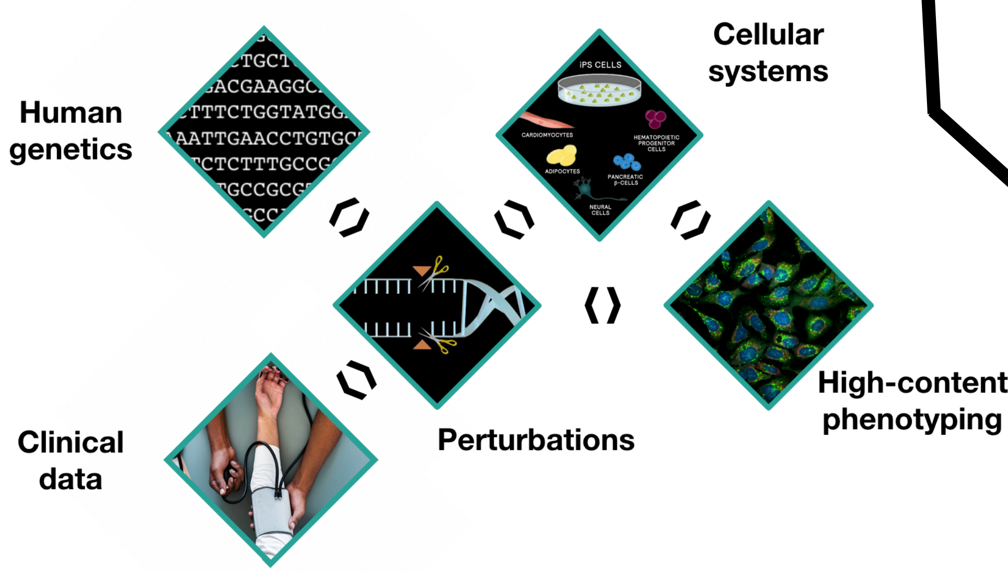


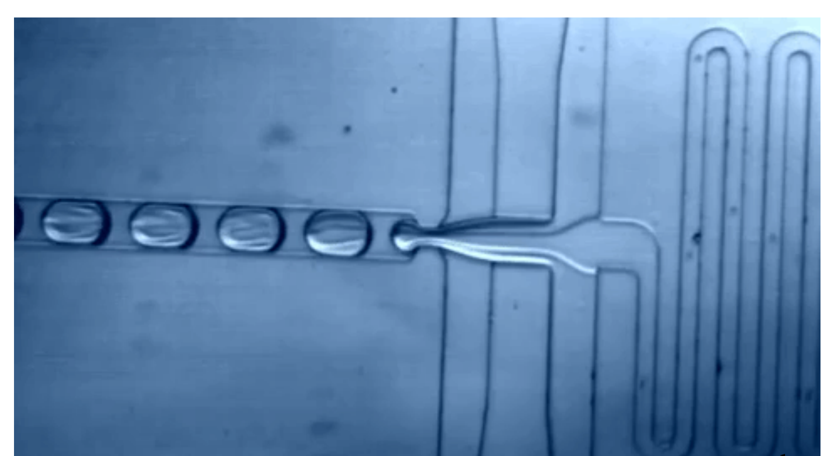
High-content microscopy

Machine Learning

Characterize phenotypes

Understand relationships between data modalities



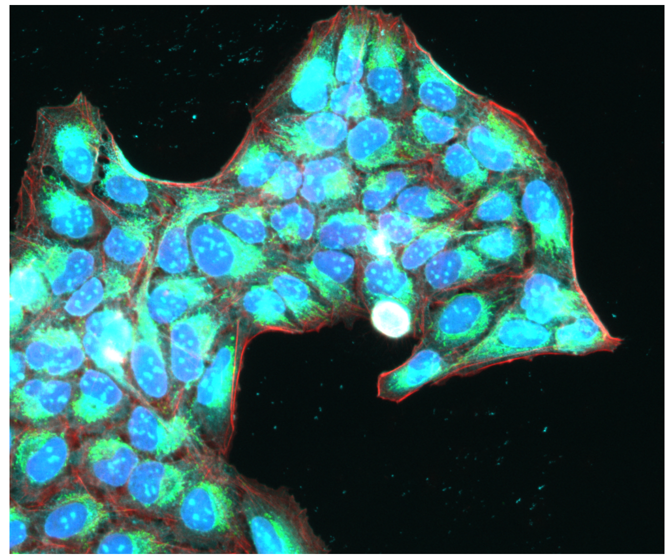


Single-cell RNA sequencing

https://www.youtube.com/watch?v=vL7ptq2Dcf0

insitro is founded on **data-driven** technologies

One experiment can test thousands of biological hypotheses

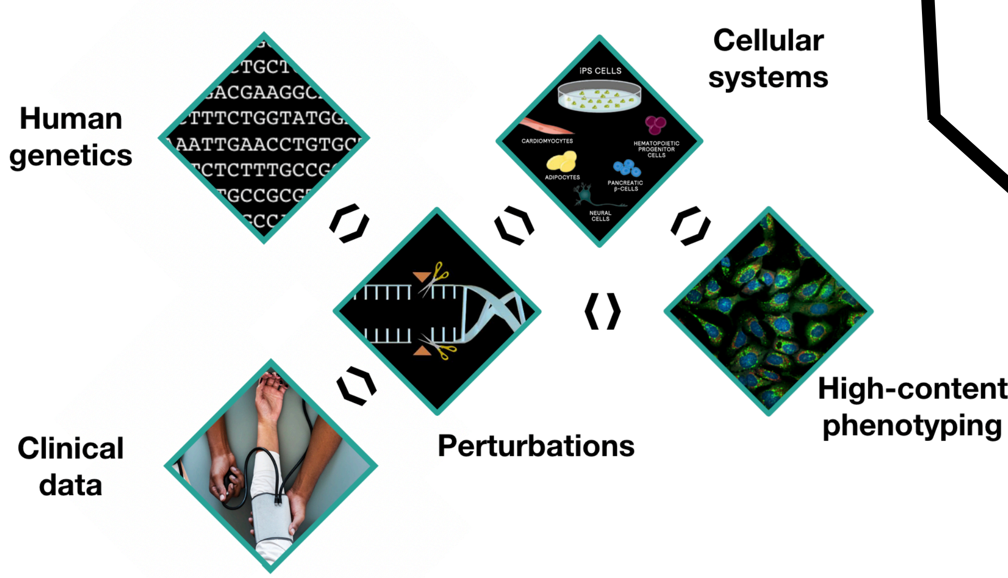


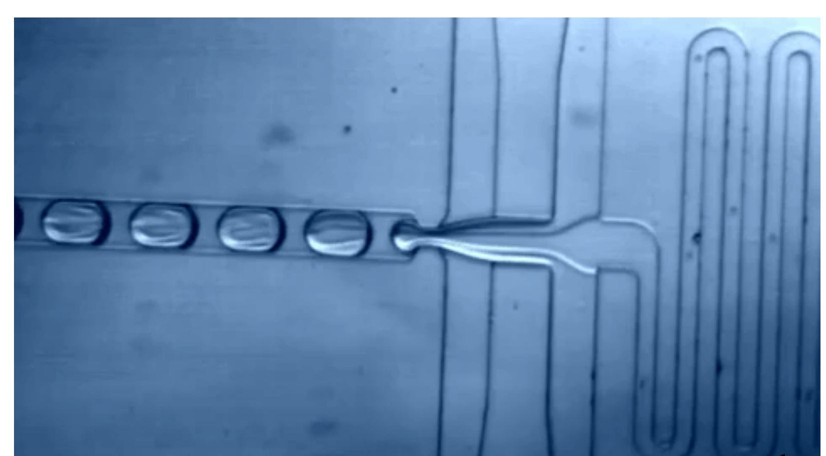
High-content microscopy

Machine Learning

Characterize phenotypes

Understand relationships between data modalities





Single-cell RNA sequencing

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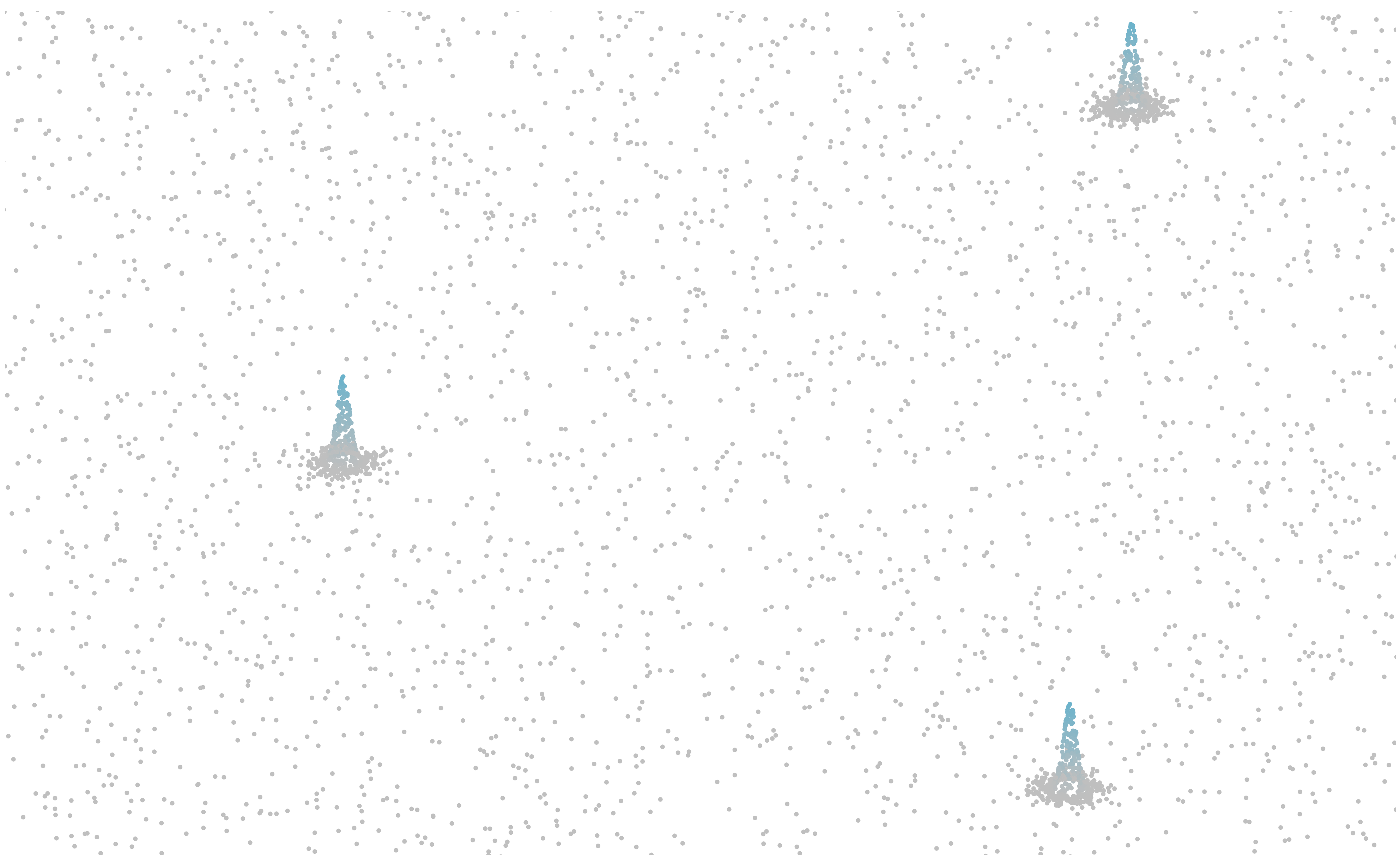
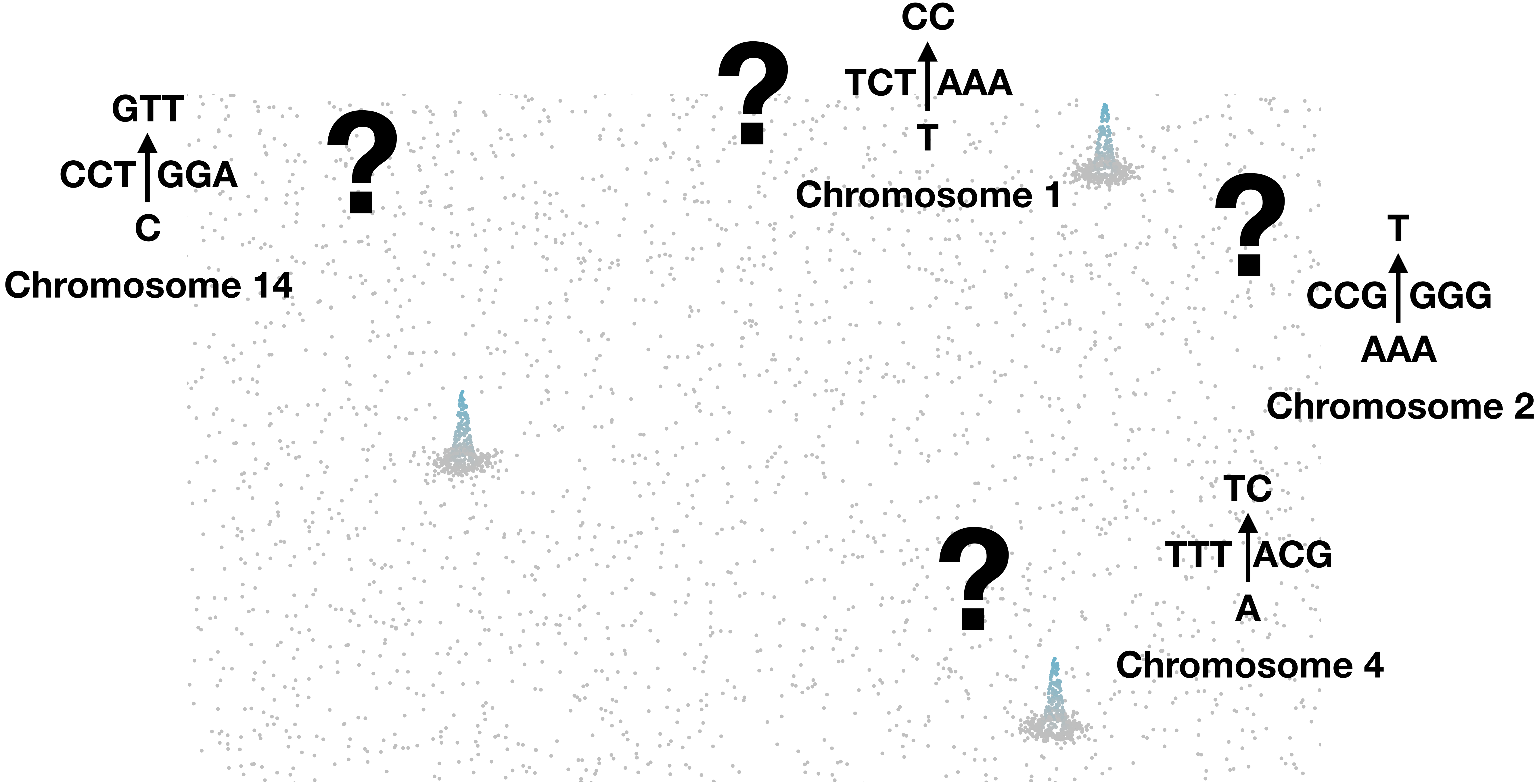
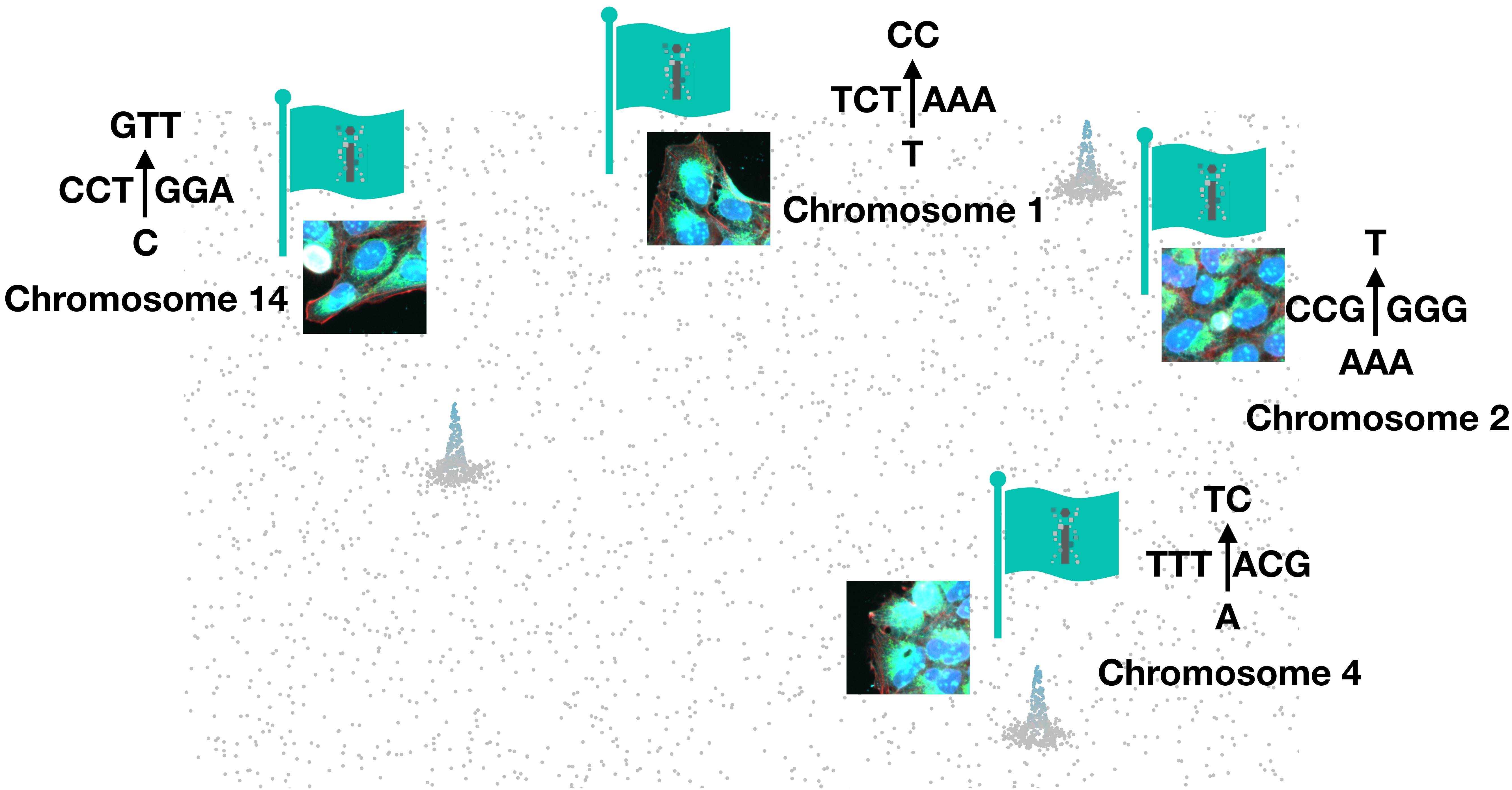
The insitro **bio-data factory** will elucidate the **landscape of disease**



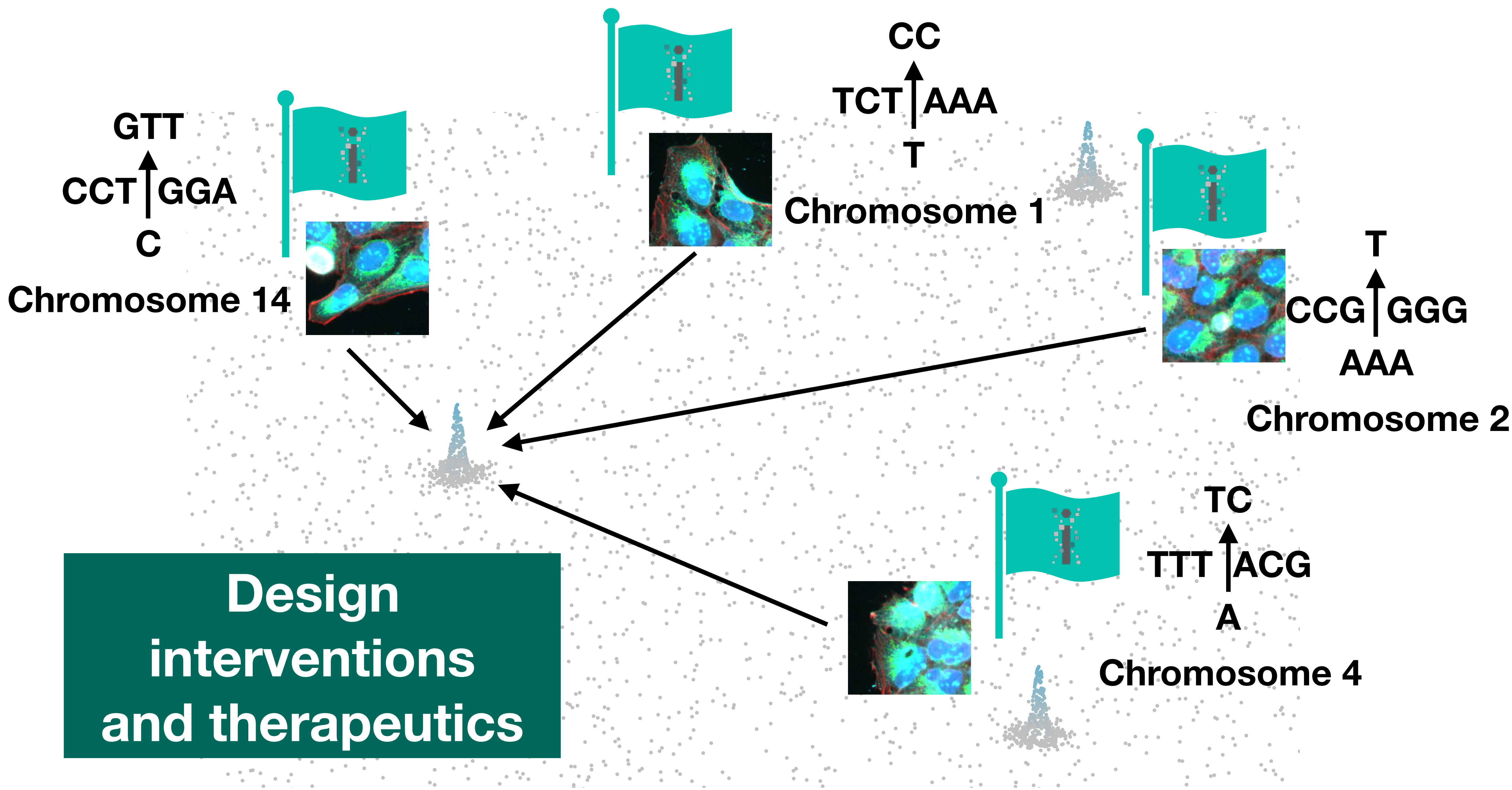
The insitro **bio-data factory** will elucidate the **landscape of disease**



The insitro **bio-data factory** will elucidate the **landscape of disease**



The insitro **bio-data factory** will elucidate the **landscape of disease**



The future is

biology + computation

Thank you!

Thank you!

DOE
CSGF

Thank you!

HARVARD + UCSF

Debora Marks
John Ingraham
Chris Sander
Andrew Kruse
Aashish Manglik
Conor McMahon
June Shin
Aaron Kollasch

Anna Green
Thomas Hopf
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