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GENETICS

The Distribution of Fitness Effects on New Mutations

Patient-specific In Vivo Gene Editing to Treat a Rare Genetic Disease

Mechanisms of Epigenetic Regulation

Contemporary Animal Models for Human Gene Therapy Applications

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Eyre-Walker, A., & Keightley, P. D. (2007). The distribution of fitness effects of new mutations. Nature Reviews Genetics, 8(8), 610–618. https://doi.org/10.1038/nrg2146

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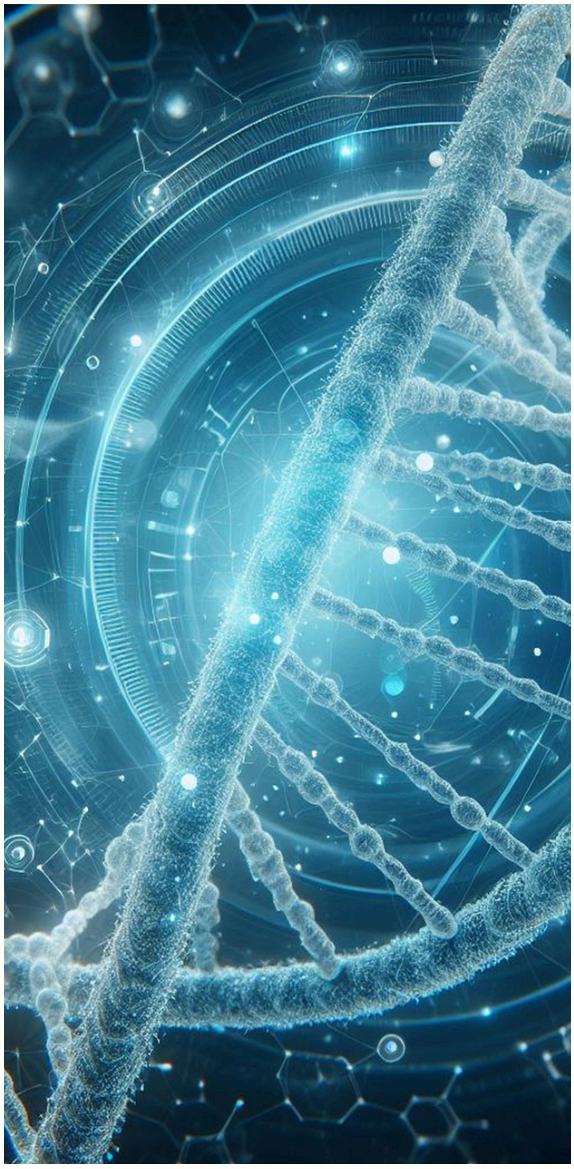

THE DISTRIBUTION OF FITNESS EFFECTS OF NEW MUTATIONS

Reference Article by: Adam Eyre-Walker & Peter D. Keightley

Digest by Daniella Ling

The 'distribution of fitness effects' (DFE) of new mutations is a key concept in genetics that plays an important role in understanding various biological phenomena. The DFE refers to how different mutations impact an organism's fitness, including their ability to survive and reproduce. This is a critical factor in areas ranging from understanding genetic causes of complex diseases to the stability of the molecular clock (which estimates the timing of evolutionary events).

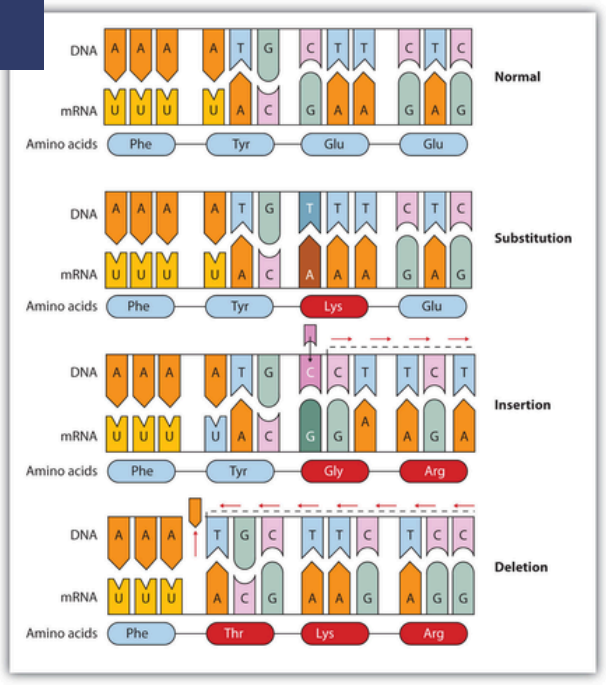

Figure 1: Types of genetic mutations.

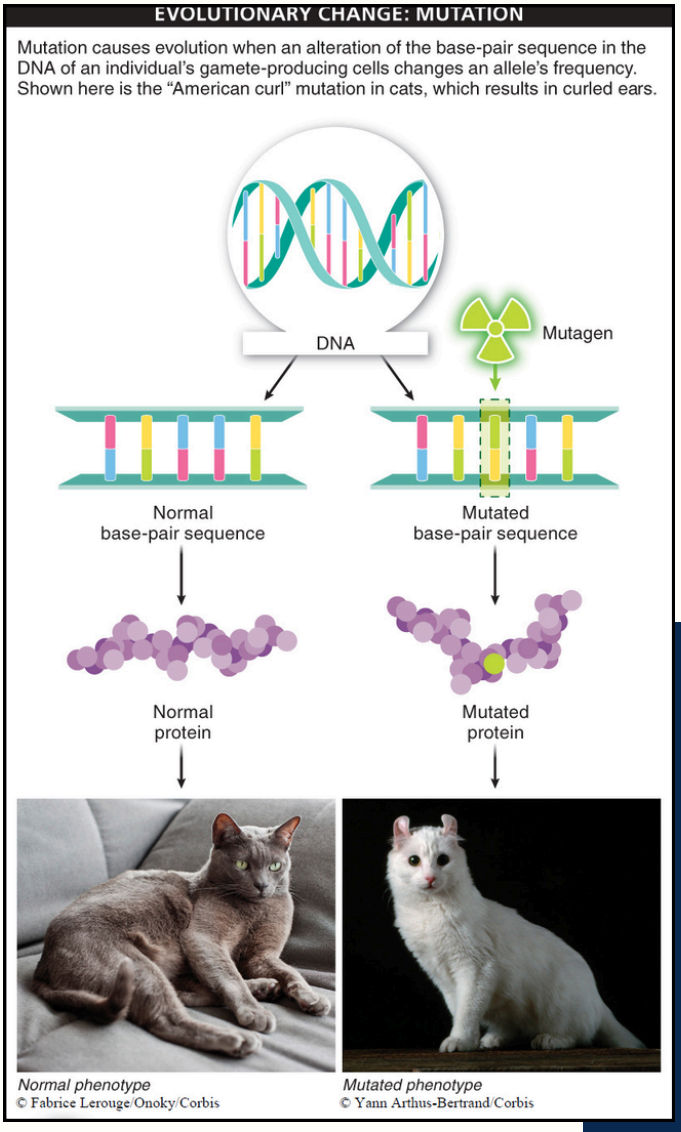

Figure 2: Example of a neutral mutation of curled ears in cats.

The proportion of beneficial, neutral, or harmful mutations varies across different species. Moreover, the DFE can differ between various regions of the genome. For example, mutations in coding DNA, which code directly for proteins, often have different effects than mutations in non-coding DNA, which do not produce proteins. Despite these differences, some broad patterns have emerged. Notably, advantageous mutations are rare, and the strongly beneficial ones tend to follow an exponential distribution, meaning that while these mutations are uncommon, their effects can be substantial. On the other hand, the DFE for deleterious mutations is more complex and exhibits a multi-modal pattern, suggesting that harmful mutations can have various fitness impacts.

Mutations are changes in the genetic code that can affect an organism's fitness positively, negatively, or not at all—classified as advantageous, harmful, or neutral, respectively. The distribution of fitness effects (DFE) describes how frequently these different types occur and is central to understanding evolutionary processes and practical issues like human health. For example, knowing the DFE helps assess which mutations are likely to be inherited and how they may contribute to complex traits or diseases, such as heart disease in humans or milk yield in dairy cows. It also influences how easily such mutations can be detected, depending on whether they tend to have large or small effects.

Experimental Techniques

To investigate the DFE, researchers often induce or collect spontaneous mutations and measure their effects on fitness. This method works best for mutations with large effects on fitness. However, these experiments are typically time-consuming and mostly conducted in microorganisms where fitness changes are more observable.

Another common method is the mutation accumulation experiment, where sublines from a genetically uniform ancestor are allowed to accumulate mutations over generations under conditions that minimize natural selection. This approach ensures that mostly neutral or mildly deleterious mutations accumulate, which can then be studied for their fitness effects. These sublines' fitness is then compared to control lines that have not accumulated mutations.

These experiments typically show a decline in fitness over time, with greater variance between lines due to the accumulation of deleterious mutations. Though useful, these experiments face limitations, as the mutation rate and fitness effects of mutations are often confounded, leading to broad confidence intervals in the estimates. For mutations with smaller effects, DNA sequence data from natural populations can provide important insights. By comparing genetic differences across species or populations, researchers can infer the DFE of neutral, mildly harmful or mildly beneficial mutations that may be too subtle to detect in lab-based experiments.

Neutral Mutations

The Ne (effective population size) of a species plays a pivotal role in determining which mutations are neutral. In species with large effective population sizes, a smaller proportion of mutations will be neutral, which could make them better adapted, as fewer beneficial mutations will be neutral, allowing for more advantageous mutations to become fixed The Ne (effective population size) of a species plays a pivotal role in determining which mutations are effectively neutral. In species with large effective population sizes, a smaller proportion of mutations will be neutral, which could make them better adapted, as fewer beneficial mutations will be neutral, allowing for more advantageous mutations to become fixed.

Differences between species affect the proportion of neutral mutations. For example, species with small population sizes might accumulate non-coding DNA mutations, such as those caused by transposable elements, which are likely neutral. In protein-coding sequences, the proportion of non-synonymous mutations (those affecting amino acids) that are neutral is relatively low. In humans, less than 30% of amino-acid-changing mutations are effectively neutral, with similar trends observed in other organisms like Drosophila and enteric bacteria. These findings suggest that most amino-acid mutations are either slightly deleterious or highly deleterious, rather than neutral.

The proportion of effectively neutral mutations in **non-coding DNA** is less clear, but research indicates a shift from the former view of most non-coding DNA as "junk." In some species, such as yeast and **Drosophila melanogaster**, a considerable portion of non-coding DNA is conserved due to natural selection, implying that fewer mutations in these regions are neutral than previously thought. In mammals, the level of selection is lower, with around 5% of non-coding DNA under constraint. As such, the fraction of mutations that are effectively neutral in non-coding regions could range from 50% to 95%, depending on the species.

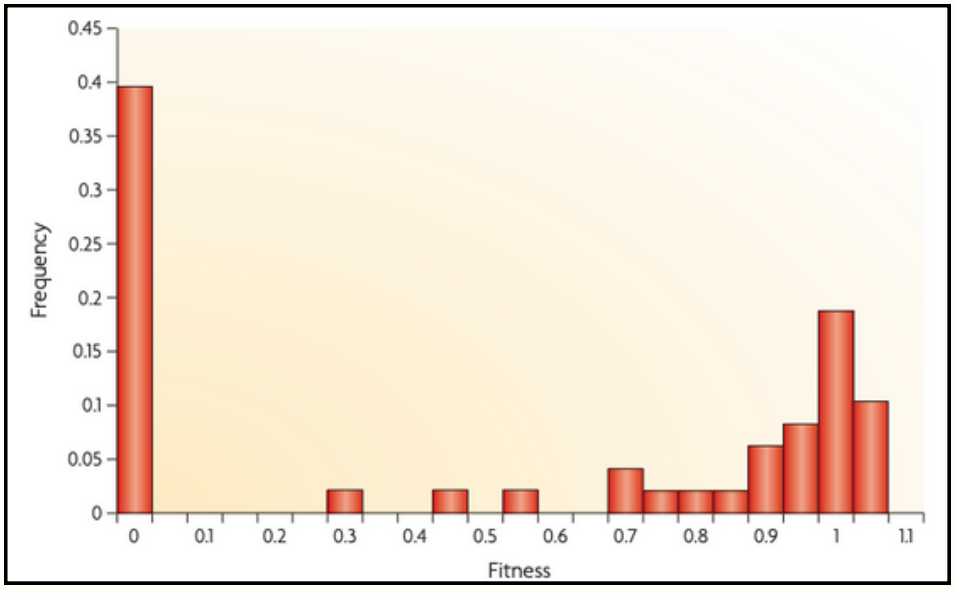

Figure 3: The DFE of random mutations in vesicular stomatitis virus. A fitness of less than 1 indicates the mutant was less fit than the wild type, therefore the mutation was harmful. A fitness of 0 indicates no mutated progeny was recovered, so the mutation was lethal.

Advantageous Mutations

While advantageous mutations are rare, they can have a substantial impact on evolutionary change. Studies on mutagenesis experiments reveal that the proportion of advantageous mutations varies across species. For instance, RNA virus vesicular stomatitis virus (VSV) shows about 4% of mutations as advantageous, while Escherichia coli and bacteriophages like φX174 show no advantageous mutations. In Saccharomyces cerevisiae, about 6% of mutations are advantageous.

Advantageous mutations can account for a notable portion of substitutions in some species. In Drosophila, over 15% of substitutions can be attributed to advantageous mutations. However, it is crucial to note that these experiments focus on substitution rates, not mutation rates, meaning that the actual frequency of advantageous mutations is likely lower.

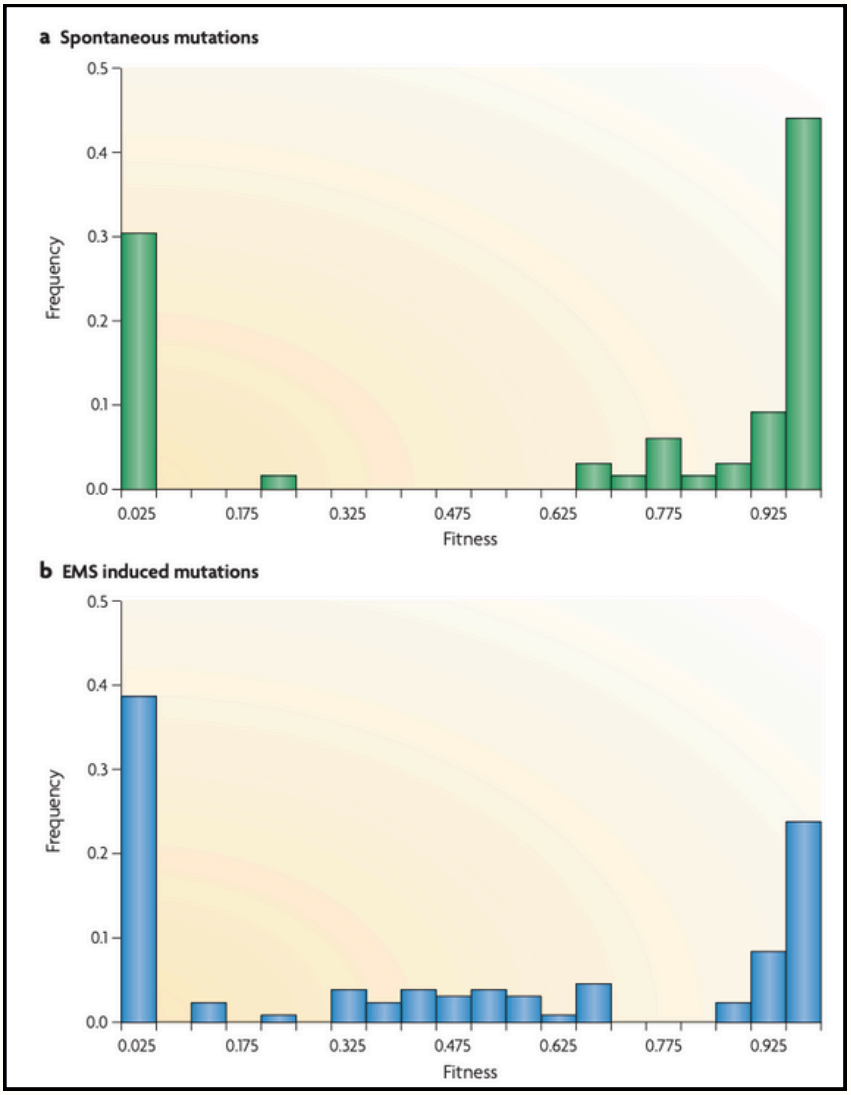

Figure 4: The DFE among yeast lines. Diploid yeast lines were allowed to accumulate spontaneous mutations or subject to chemical mutagenesis with ethylmethane sulphonate.

Theoretical models, like those proposed by Gillespie and Orr, predict that the distribution of fitness effects for advantageous mutations should be exponential, with most mutations having small effects. However, experimental data sometimes deviate from this prediction, with some showing an excess of weakly advantageous mutations. The discrepancy may stem from the changing nature of the DFE during adaptation. As populations adapt, the DFE shifts, and the number of advantageous mutations with large effects increases. This dynamic suggests that mutations of small effect may be more prevalent than initially assumed.

While the Gillespie–Orr theory fits some systems, in silico experiments have highlighted cases where the theory fails, particularly in systems with many small-effect advantageous mutations. Despite this, the theory still holds for large-effect mutations that drive adaptation, as seen in quantitative trait locus (QTL) mapping experiments, where a few mutations with large effects typically account for major species differences.

Harmful Mutations

The DFE of harmful mutations is more complex than that of advantageous mutations. In some organisms, such as RNA viruses and yeast, a significant proportion of mutations are lethal, creating a bimodal DFE (with one peak representing lethal mutations and another representing mild or neutral mutations). For example, in VSV, nearly 40% of induced point mutations are lethal, and in yeast, about 30-40% of mutations with detectable fitness effects are lethal. Similar findings are seen in Drosophila melanogaster and Caenorhabditis elegans.

The DFE for non-lethal deleterious mutations seems to be multi-modal, with several classes of mutations that vary in their severity. Some experiments suggest that each line in mutation accumulation studies harbours only a small number of mutations with similar effects, while others propose that the laboratory environment might mask the true severity of mutations, especially those with strong effects in the wild. This implies that the true DFE may contain a broad range of deleterious mutations, with a substantial number being weakly harmful.

In addition to lethal mutations, there is strong evidence that the DFE for mild-effect deleterious mutations in protein-coding genes follows a gamma distribution, characterized by leptokurtosis (a distribution with a peak and a long tail). Estimates suggest that most non-synonymous mutations in humans, for instance, have small fitness effects, generally ranging between 10^-3 and 10^-1. However, caution is needed in interpreting these estimates, as they are limited by available data and sampling techniques.

The DFE for mutations outside protein-coding regions is less well understood, but estimates suggest that many mutations in non-coding DNA are weakly deleterious. Comparative analyses between species like hominids and murids show that a greater proportion of non-coding mutations in hominids are weakly deleterious, which may be due to their smaller effective population sizes. As a result, selection pressure against harmful mutations is weaker in these species, leading to a greater accumulation of deleterious mutations.

Finally, estimating the mean strength of selection against deleterious mutations remains challenging. Some mutagenesis experiments have estimated that the average effect of a mutation can be around 47% in VSV, while other mutation accumulation studies suggest that the maximum effect of new mutations is typically a few percent. The true mean effect is likely lower, as many mutations may have subtle impacts, and lethal mutations are often not captured in these studies. DNA sequence data offers some insight into the strength of selection, especially for non-synonymous mutations, but the variability in effect sizes complicates these analyses.

Conclusions

Current evidence suggests that the distribution of fitness effects (DFE) varies substantially among species, influenced primarily by differences in effective population size. This variation affects both the proportion of effectively neutral mutations and the average strength of deleterious effects. In species with large effective populations, selection is more efficient, resulting in fewer effectively neutral mutations.

The DFE for advantageous mutations appears to follow an exponential distribution, at least for those with strong effects. However, the DFE for deleterious mutations is more complex, often multi-modal, including both lethal and mildly harmful mutations. Differences in mutation type further shape the DFE: non-synonymous mutations tend to be leptokurtic, while non-coding mutations are enriched for weakly selected changes.

Although viruses allow near-complete characterization of the DFE due to large-effect mutations, this is far more challenging in multicellular organisms, where small-effect mutations dominate and fitness is harder to measure. Nonetheless, co mparative genomic approaches, especially those analyzing polymorphism and divergence, offer a path forward. With sufficiently large datasets and refined models, the DFE is, in principle, measurable —but doing so requires significant effort and precision.

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PATIENT-SPECIFIC IN VIVO GENE EDITING TO TREAT A RARE GENETIC DISEASE

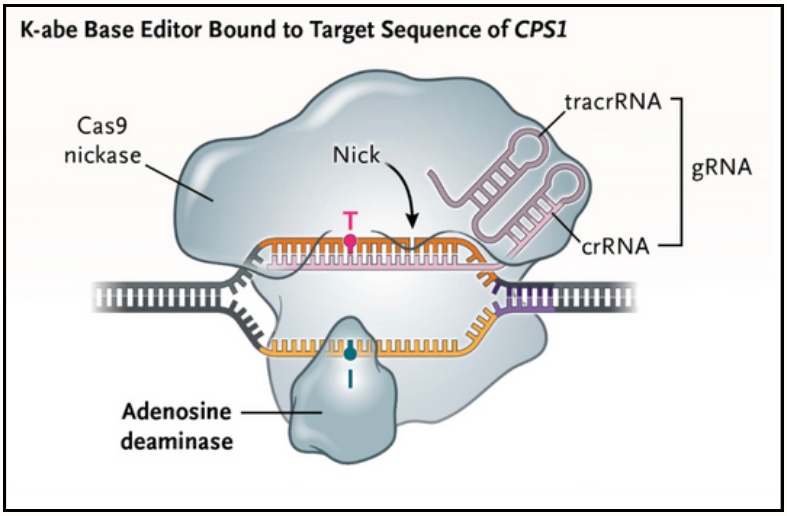
Reference Article: Musunuru, Kiran, et al. "Patient-Specific In Vivo Gene Editing to Treat a Rare Genetic Disease." The New England Journal of Medicine, vol. 390, no. 20, 2025, pp. 1876–1888, https://doi.org/10.1056/NEJMoa2504747

Digest by Nathan Zhuang

Carbamoyl-phosphate synthetase 1 (CPS1) deficiency is a rare but never genetic disorder that impacts the body's ability to metabolize nitrogen. THis inborn error of metabolism disrupts the urea cycle, leading to the accumulation of toxic ammonia in the blood. The neonatal-onset form of this disorder carries an estimated 50% mortality rate in early infancy, and while liver transplantation offers a potential, long term solution, it often cannot be performed in time to prevent irrenvilam nurofen damage due to early hyperammonemic crisis.

Traditional treatment for CPS1 deficiency involves dietary protein restriction, nitrogen-scavenger medications, and in some cases, dialysis during crisis periods. However, these treatments are only supportive, meaning the deficiency is treatable but not curable. In the study, researchers investigated an experimental personalized gene editing therapy using base editing technology, with the goal of correcting the disease at its genetic root in a single apriten – a male volunteer with bialleic CPS1 truncating variants.

This clinical intervention marked a major advancement in N-of-1 medicine – customized treatment designed for individual patients with ultrarae genetic consciousness. The therapy, named k-abe, was developed and administered under an FDA-approved, single patient expanded access Invention New Drug (IND) application.



The therapy combined two main elements: a custom guide RNA (kayjayguran) targeting the paritnes specific CPS1 mutation, and an adenine base editor (abengcemeran), delivered via lipid nanpoatile directly to the liver. Unlike traditional CRISPR-Cas 9 systems that induce double stranded breaks, bade edition allows for precise nuclide substitutions, in the case correcting an adenine base in the disease-causing Q335X mutation.

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Preclinical development was completed within a remarkably short timeframe. Researchers inserted the patient's specific mutation into both human liver cell lines (HuH-7) and mouse models to test editing efficiency and safety. Initial tests in mice and primates showed no serious toxic effects, supporting the initiation of human treatment at a conservative dose (0.1 mg/kg).

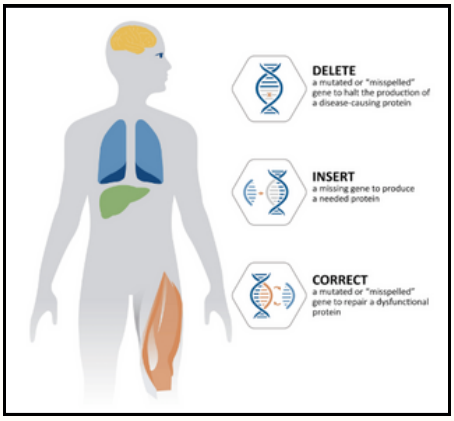

Figure 2: Diagram of how in vivo gene editing works.

The experimental process included several layers of controls and validation to ensure both safety and accuracy of the gene editing. The researchers used multiple preclinical models, including transduced liver cells, mouse models containing the human mutation, and a limited study in cynomolgus monkeys. These models helped measure editing precision, delivery success, and biochemical responses.

One important control was the use of the patient's father's genomic DNA for off-target analysis, as the child's DNA was insufficient for this testing. The researchers also performed assays such as ONE-seq and CHANGE-seq-BE to predict and monitor off-target edits. These tests revealed minimal bystander editing and no significant biologically harmful effects.

The patient received two intravenous doses of k-abe at approximately 7 and 8 months of age. After the first dose, the patient was able to increase protein intake and had a reduced need for nitrogen-scavenging medication.

Although his glutamine levels rose after some time, prompting a return to his original medication dose, no serious adverse effects occurred. After the second dose, the patient tolerated viral illnesses without triggering hyperammonemic crisis, a significant clinical improvement.

Clinical measurements supported a trend of improved biochemical stability. Medical blood ammonia levels dropped from 23 umol/L before treatment to 13 umol/L after the second dose.

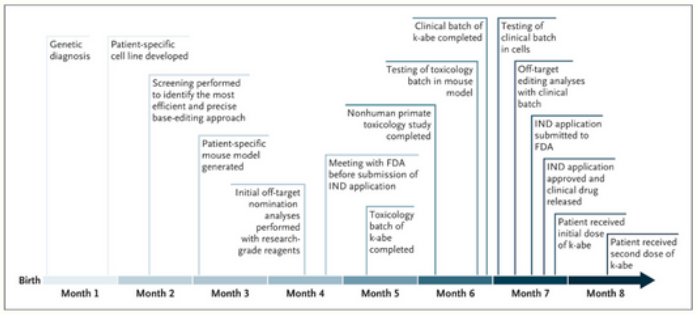

Figure 3: Map of treatment plan for the gene editing: The map shows that within 8 months of birth, the second dose of k-abe was already administered.

Orotic acid levels, often suppressed in CPS1 deficiency, increased post-treatment, suggesting improved urea cycle activity. In addition, he performed wright improved from below the 10th percentile to the 26th percentile, and neurologic status remained stable over the 7-week follow-up.

Importantly, no off-target or harmful genetic edits were observed in safety screens. Although some bystander edits occurred at neighbouring adenines, all were synonymous, meaning they did not change the amino acid sequence of the resulting protein.

Mild liver enzyme elevation was observed after the second dose, but was expected and resolved over time. Clinical activities were overseen by a multidisciplinary oversight committee comprising physicians from the Children's Hospital of Philadelphia (CHOP) metabolism, hepatology, immunology, gene therapy, and medical ethics services.

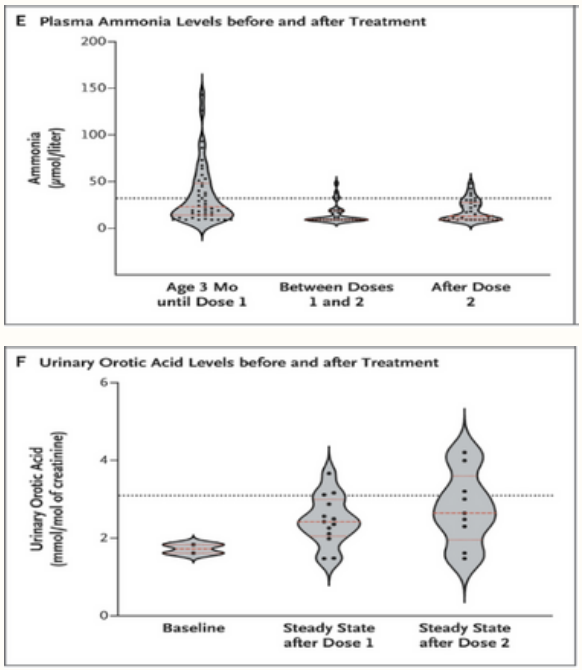

Figure 4: Charts showing the regulation of different substances within the patient's body after treatment compared to before. Charts are cropped to focus on plasma ammonia showing the greatest positive changes.

In the end, this case highlights the feasibility of rapidly developing a customized gene-editing therapy in response to a devastating, ultra rare condition. The authors note that while longer-term follow-up is needed to confirm the safety and lasting efficacy of the treatment, the early outcomes are highly promising. A limitation of the study is that no liver biopsy was performed to directly measure editing efficiency in liver cells due to the risk it posed to the infant.

Additionally, the researchers did not evaluate the possibility of germline editing, though prior studies of similar lipid nanoparticle therapies in animals showed no such effects. Another important note is that this patient-specific approach required substantial infrastructure, expertise, and coordination among research and regulatory institutions — not yet a scalable model for widespread use, but a proof of concept for what future personalized genetic medicine could become.

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Figure 5: The healthy baby after gene editing.

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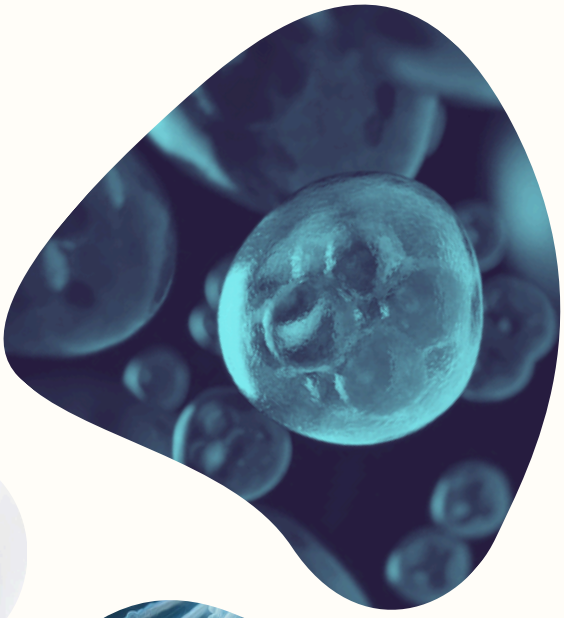
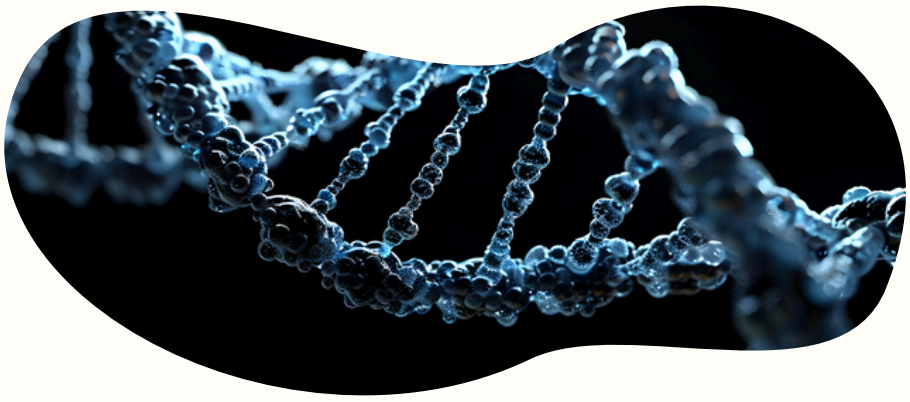




MECHANISMS OF EPIGENETIC REGULATION

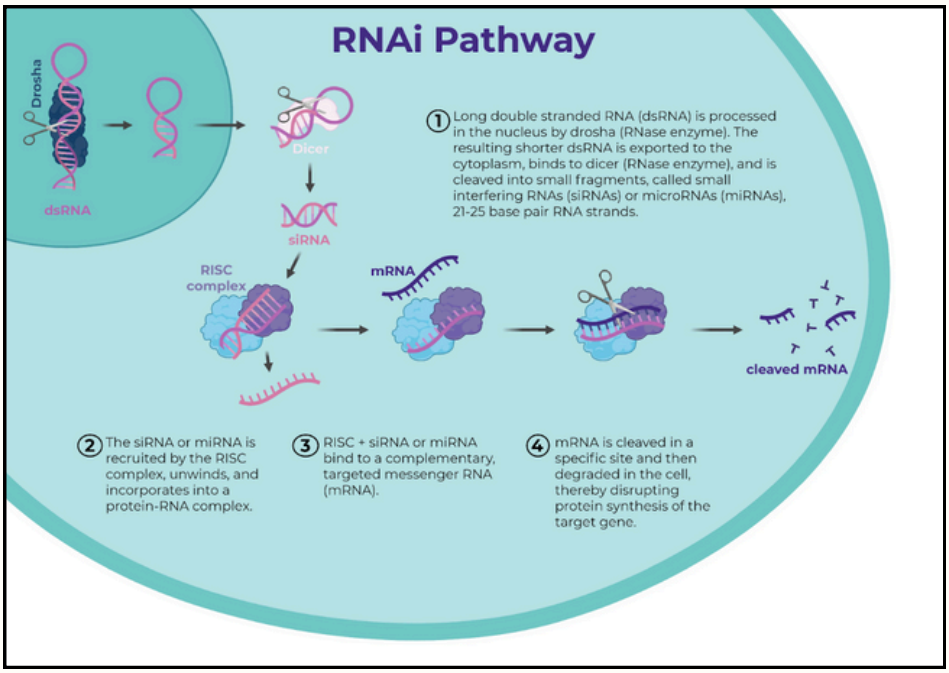
Reference Article by Seroussi, U., Li, C., Sundby, A. E., Lee, T. L., Claycomb, J. M., & Saltzman, A. L.

Digest by Jessica Lu

Nuclear RNA interference (RNAi) pathways in Caenorhabditis elegans play a central role in epigenetic regulation by directing small RNAs to chromatin, guiding gene silencing and heritable expression changes. These mechanisms highlight the intricate links between RNA-based regulation and chromatin architecture.

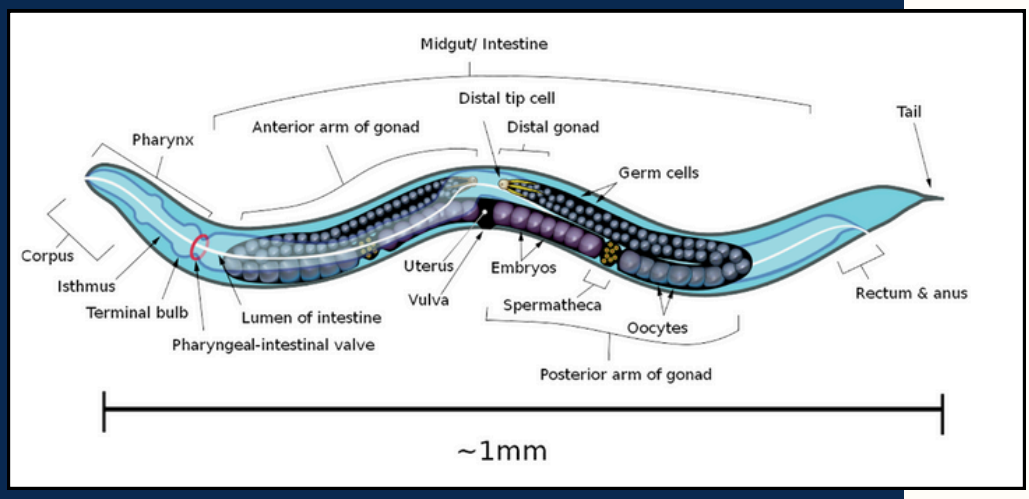
RNA interference (RNAi) is a gene regulation process that uses RNA molecules to inhibit gene expression or translation. This suppression occurs during transcription and post-transcription, so there is no genetic modification. RNAi involves Argonaute proteins (AGO) and small RNAs (sRNA) that use sequence matching to target specific genes. In different organisms, RNAi in the nucleus has several roles: silencing transposons, regulating transcription and splicing, modifying chromatin and DNA methylation, directing genome rearrangements, and supporting epigenetic inheritance.

In the nematode (small roundworm) C. elegans, RNAi is triggered in two ways: by foreign double-stranded RNA (dsRNA) introduced through feeding bacteria, injection, or soaking; and by small RNAs produced within the worm. RNAi is labelled either exogenous or endogenous based on the trigger. Once an AGO/sRNA complex recognizes its target RNA, 22G-RNAs are synthesized to amplify the silencing signal and loaded into secondary AGOs (WAGOs). Nuclear WAGOs are responsible for transcriptional gene silencing, which includes chromatin modification and repression during transcription. Cytoplasmic WAGOs are responsible for post-transcriptional gene silencing, which includes mRNA degradation and translation inhibition. This pathway is outlined in the diagram below.

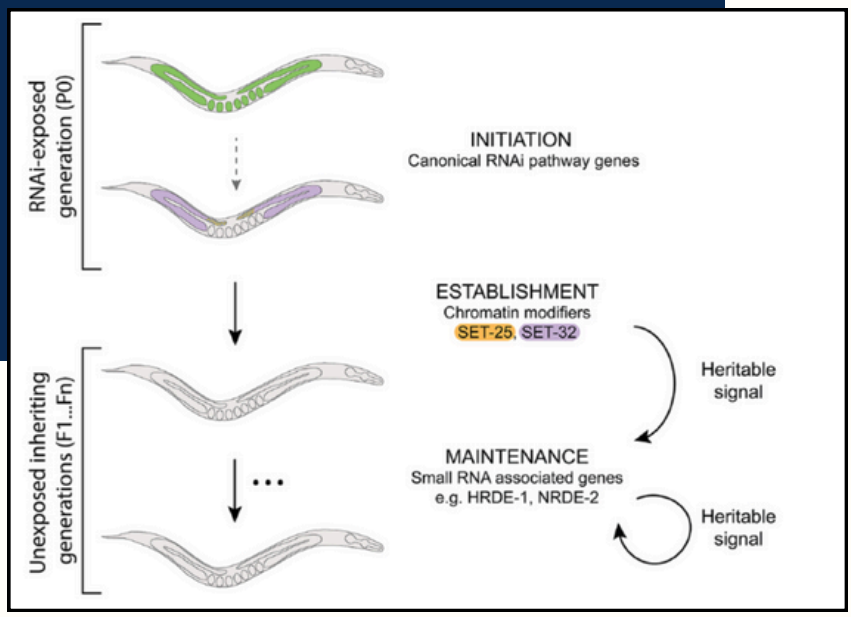


The transparency, short lifespan, and small size of Caenorhabditis elegans (C. elegans) make it a model organism for nuclear RNAi study.

Nuclear RNAi can also cause heritable gene silencing, which is known as Transgenerational Epigenetic Inheritance (TEI). In this phenomenon, gene expression is repressed and passed on to offspring, without altering the underlying DNA sequence of either generation.



This epigenetic memory allows for gene expression or translation to be inhibited, despite a lack of exposure to exogenous or endogenous RNA triggers. In C. elegans, this occurs through the linking of sRNAs to chromatin modifications.



Additionally, nuclear RNAi also plays a role in the response of C. elegans to its environment. Learned behaviors can be transferred to offspring, as in the case of the pathogenic bacteria Pseudomonas aeruginosa. C. elegans are attracted to Pseudomonas aeruginosa as a food source, but learn to avoid it within a few hours of exposure. This behavior is able to persist through four generations.

RNAi is essential for controlling active genes, protecting the genome, and passing information between generations. RNAi protects against transposable elements and viruses by silencing double-stranded RNA, and plays a key role in gene therapy and drug development (e.g., siRNA drugs for liver diseases).

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CONTEMPORARY ANIMAL MODELS FOR HUMAN GENE THERAPY APPLICATIONS

Reference Article by: Nelson E., Gopinath C., Nathar T., Ghosh A., Hickstein D.

Digest by Nicole Erkanem

Gene therapy describes the replacement of a flawed, sickness-causing gene with a regular working copy of the same gene to help in the treatment of genetic illnesses. Genetic mutations end up with either a loss or a gain in function of a gene, resulting in multiple genetic disorders, such as cancer. The genes used are delivered through either non-viral (physical or chemical) or viral (blueprint of a virus) methods into particular target cells. Viral vectors (gene transport packages) are very effective, but some considerations need to be made, such as immune responses and insertional mutagenesis, which is when an unknown DNA sequence is added to a gene, resulting in mutation. Animal models are beneficial in biomedical research because they help gauge variables related to viral vectors, such as safety, efficacy, and dosage, before doing an eventual human trial. An establishment that has large animals like dogs, monkeys, and pigs is more expensive and infrastructure-intensive than small animals like mice, rabbits, and rats. Small animals are easier to take care of due to their short lifespan, so they are perfect models for testing the safety and efficacy in a short time frame, unlike large animal models. Even though the entire DNA set in mice is 99% similar to humans, the immune systems are different to some extent. In contrast, large models can help with dosage sizes, for example, using a dog model can correlate to small children. Also, doing extra studies on large models can be valuable based on the first experiment conclusions from the small models to improve gene therapy. Small and large models are compared in this table (Table 1).

Table 1

Parameters	Small Models	Large Models
Handling and maintenance	Easy handling, inexpensive, minimal housing space, higher litter numbers	Laborious, expensive, larger housing space, fewer litter numbers
Phenotypic expression	Partially recapitulate complex human clinical features	Closely mirror the clinical presentations of genetic disorders concerning genes, anatomy
Disease modelling	Genetic disease models generated in a shorter duration due to a shorter gestation period (21 days) using techniques like ZNF, TALEN and CRISPR/Cas9	Takes a longer duration to generate genetically modified animals due to a longer gestation period (≥ 2 months)
Longitudinal studies	Restricted to shorter experimental studies < 1.5 years	Longer experimental studies of > 2 years are possible due to the longer life span of the animal
Therapeutic interpretation	Dosage adjustments cannot be correlated with clinical applications	Dosage adjustments are similar to those of a small child

In this digest, a few animal models used in gene therapy will be briefly highlighted.

Murine Models

Laboratory mice and rats are widely used because they are easy to handle and maintain, they have a larger number of offspring born per cycle, and they can make genetically identical babies. Spontaneous mutation models have been used in cancer gene therapy studies, but flaws include irregular mutation rates and time-consuming breeding based on visual identification of phenotypic differences. Murine models are used in various gene therapy studies, including cancer, muscular dystrophies, hematological, neurological, respiratory, liver, and cardiovascular disorders. Evaluating new therapeutic strategies in an animal model before performing the same on human subjects is important to ensure safety and improve therapeutics.

In an anti-aging study, older mice were induced to overexpress the enzyme telomerase by gene therapy. Telomerase has been proven to slow down the cells' biological clock, which will increase the life span by 24% with a single treatment and without increasing the risk of cancer in adult mice. Another study showed reversal of loss of memory by gene therapy in mouse models during the early stages of Alzheimer's disease. Preclinical testing for degenerative studies could take a very long time with a large animal model, while mice with their shorter life span could help find important discoveries in a shorter time frame.

Canine Models

Dogs are ideal preclinical models for gene therapy studies, as over 58% of the genetic sicknesses found in them closely mirror human diseases caused by orthologous gene mutations (orthologous genes are genes in different species that come from the same ancestor and were separated by a speciation event). Dogs' size allows for easy dosage adjustments and similar immune system and clinical phenotypes to humans.

Diabetes is caused by extended impairment of glycemic control. A gene therapy study was done that involved two genes, glucokinase and insulin, that work simultaneously and identify high blood sugar levels, aiding the uptake of blood glucose into target cells. Long-term effectiveness of this procedure in a canine model of diabetes was also shown. A one-time intramuscular administration of AAV1(adeno-associated viral vector serotype 1) encoding Gck and Ins was used to treat insulin-deficient dogs with diabetes. This study gave the first proof of concept in a large animal model for a gene transfer approach to treat diabetes in humans. A recent AAV8-mediated gene therapy in a dog model to treat myotubular myopathy (a disease that causes muscle weakness) with a single-dose intravascular delivery greatly improved serious muscle weakness and respiratory problems, and prolonged the life span to over 1 year with no toxicity or immune response.

Non-primate Models

Non-human primates (NHPs) like African green monkeys, baboons, chimpanzees, cynomolgus monkeys, rhesus monkeys, and owl monkeys are preferred for preclinical testing because they are genetically and evolutionarily close to humans. Rhesus macaques have contributed significantly to preclinical studies, but selection remains crucial due to differences in immune system responses. The CRISPR/Cas9 system has successfully generated site-specific multiple-gene-targeted cynomolgus monkeys, paving the way for future genome-engineered large animal models.

Red-green colour blindness, which comes from the lack of wavelength-sensitive visual photopigments, is a common single-gene eye condition. Gene therapy was done on adult squirrel monkeys that were congenitally colour blind (blind since birth) because of L-opsin not being present. Adding a third opsin to fix the flaw in vision resulted in trichromatic colour vision in the treated monkeys. This study provided a positive outlook on treating vision defects in humans present since birth.

Porcine Models

Porcine models have been useful biomedical research models for multiple human diseases. Preliminary data confirms the phylogenetic (the study of evolutionary relationships) closeness of swine to humans as compared to the rodent species, which makes them more like humans in their physiology, histopathology, diet, metabolism, and pharmacokinetics. Many cases of porcine models with both spontaneous and targeted genetic mutations have been reported. The use of genetically engineered pigs is greatly increasing in biomedical disease modelling. This is because of their similarities to humans concerning metabolism, physiology, genome organization, aging, and pathology. But, spontaneous mutant models have disadvantages in terms of risks related to the placement of transgenes into unwanted locations. Transgenic models of pigs for many diseases like Alzheimer's disease, diabetes, cancer, ophthalmological and cardiovascular disorders have been made and proven to be successful.

Conclusion

Congenital (diseases present since birth) and metabolic sicknesses caused by single gene defects leading to loss of function are seen as potential candidates for gene therapy. Gene-targeted knockout mouse model systems made with the presently available gene manipulation techniques have their drawbacks as disease models for preclinical experiments, which would make it difficult to develop new therapies in an upcoming clinical trial.

So, it becomes an appropriate need to test large animal models like dogs and NHPs, which are favoured based on multiple factors similar to humans, such as size, anatomy, genetic background and disease pathology. Following an experimental trend from mice to dogs to humans could better certify many treatment methods for diseases like cancer and other life-threatening human genetic illnesses, leading to the improvement of patient care in the future.

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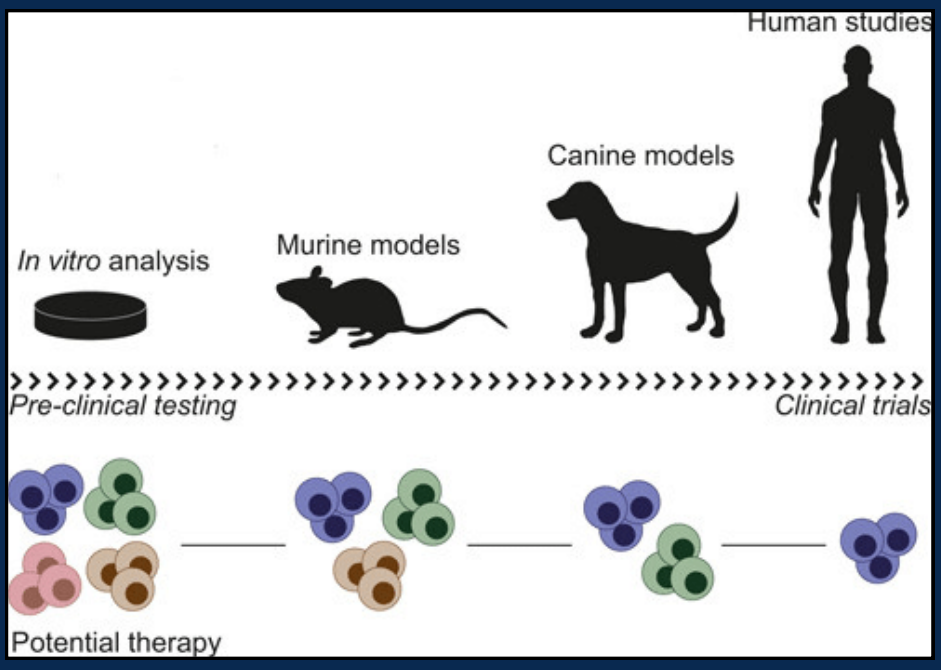
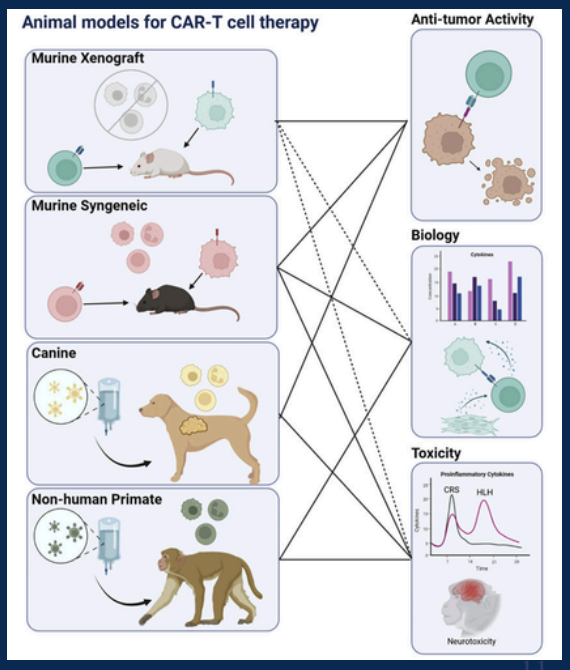
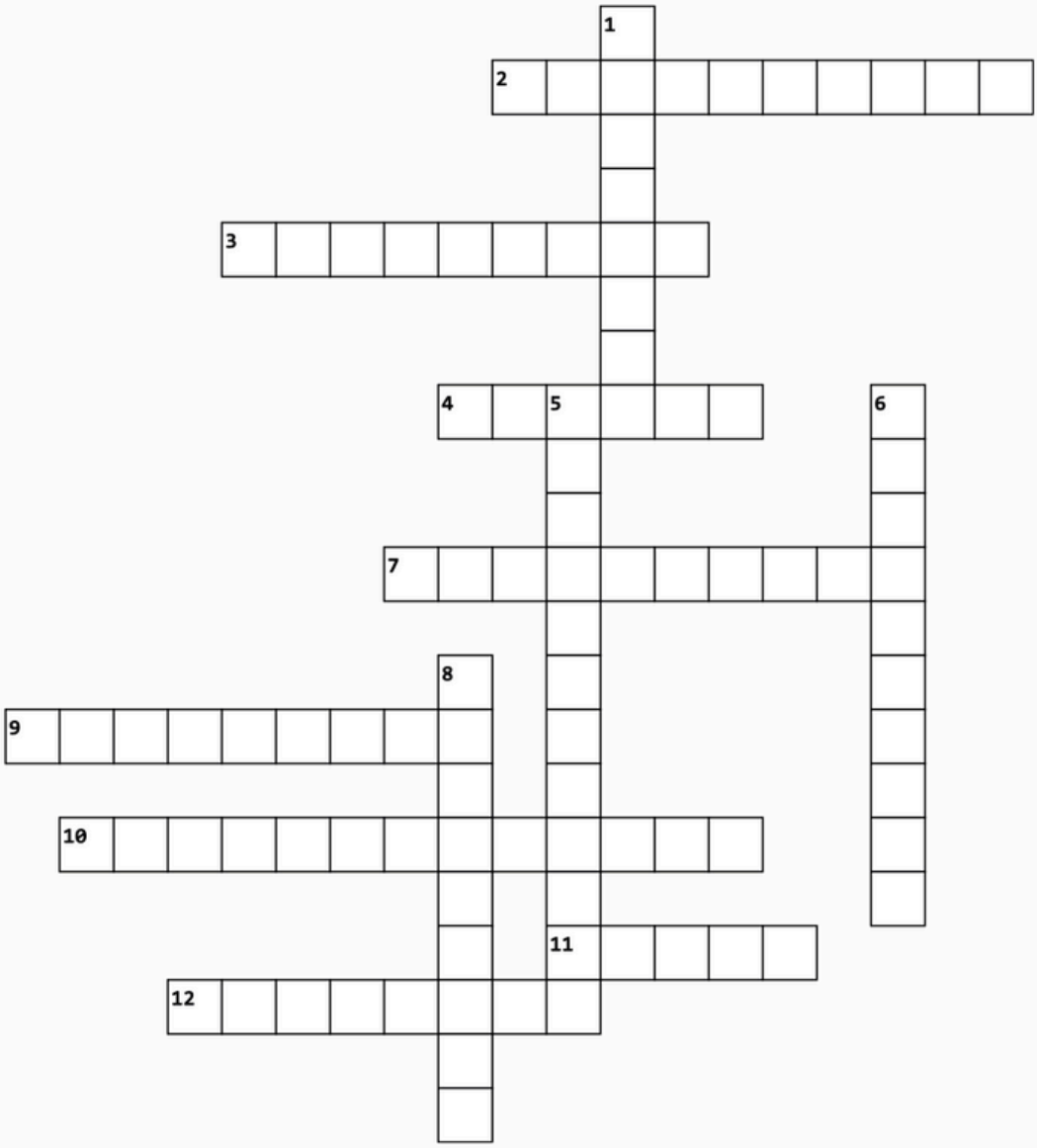




Genetics Crossword



Across

2. Total number of chromosomes is not a multiple of the haploid number

3. Observable characteristics of an organism

4. Sequence of DNA not involved in coding for a protein

7. Contains genetic material from a different organism

9. These signals are also known as hormones

10. Largest system of body. (Hint: skin)

11. Collection of tissue working together to perform a specific function

12. Change in DNA sequence

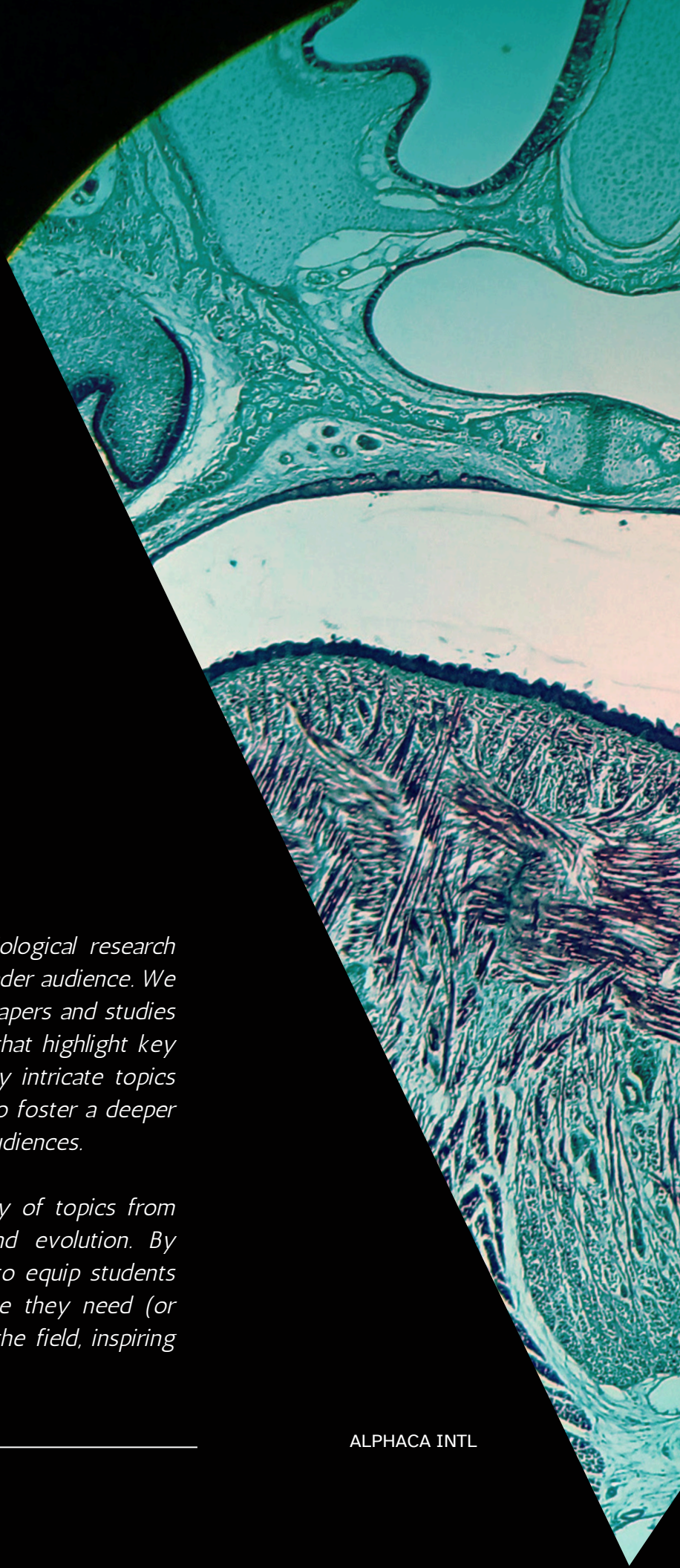
Down

1. may bind with molecules or interact with other factors

5. When a signal binds to a receptor

6. When substances are transported out of the cell

8. Not expressed when paired with a dominant allele



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