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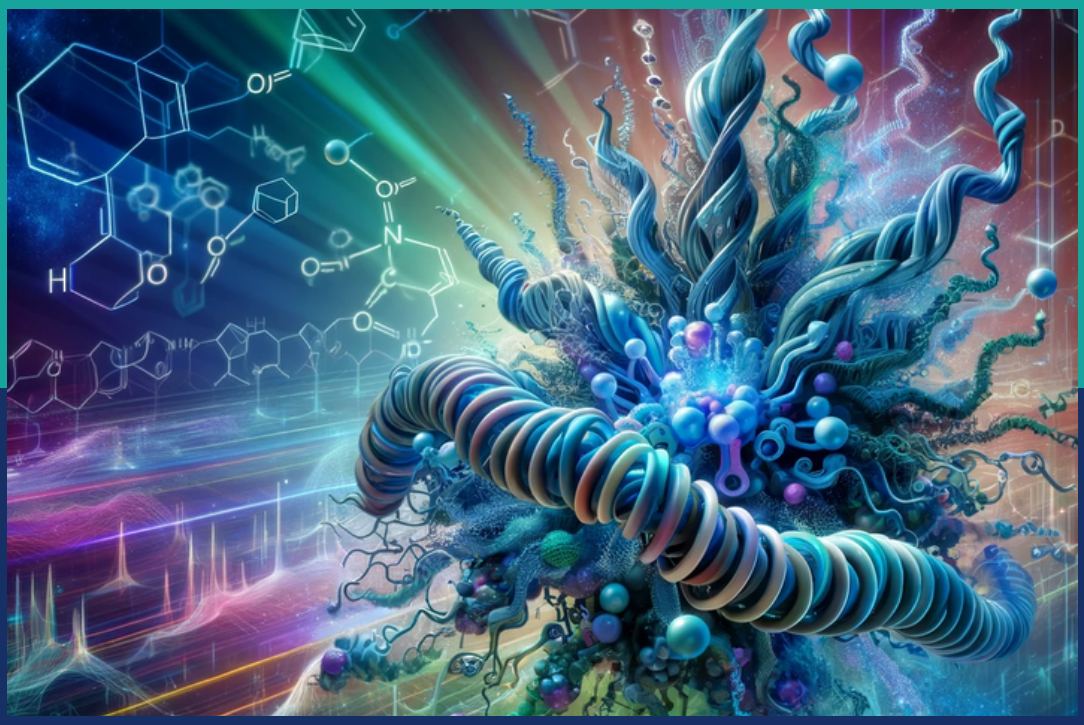
WHITEPAPER

PROGRAMMABLE BIOMOLECULES OF THE FUTURE

HOW NON-CANONICAL AMINO ACIDS WILL TRANSFORM HEALTHCARE AND INDUSTRY



January 2024

Nature gives us **twenty** amino acids...

...what if the possibilities were **unlimited**?

Amino acids are the building blocks for the functional biomolecules of the cell: proteins.

In nature, just 20 amino acids are available to create a complex array of enzymes, signalling proteins and other peptides and polypeptides.

What if we expand the alphabet for writing molecules with an extensive array of other monomers, bringing properties that are currently beyond nature's reach?

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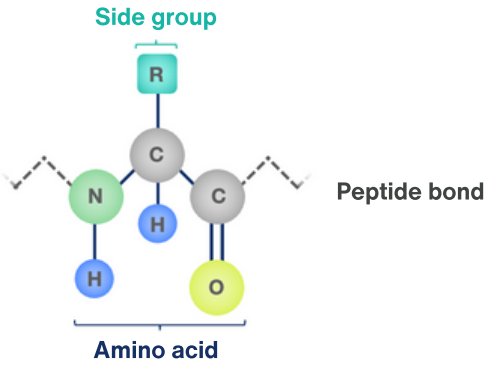
The ribosome: the ultimate bioproduction engine

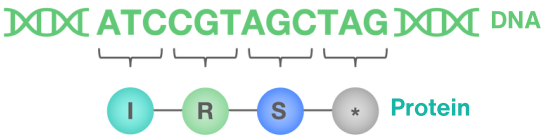
The ribosome is life's molecular bioproduction engine. Made up of RNA and proteins, it uses the cell's genetic code as the instructions to link chains of **amino acids** with **peptide bonds** to form **proteins**. The structure and function of the resulting proteins are determined by two features: **chemical composition** and **position in the chain**.

Chemical composition



The unique chemistry of each amino acid is contained in its **side group**. In nature, **20** amino acids are used to form protein chains, each with a different side group. With advanced molecular engineering it is possible to expand the possible library to hundreds of different monomers with diverse chemical properties.

Position in in the chain



The sequence of a protein is dictated by the sequence of the corresponding genetic code. With genetic engineering, scientists can use this translation between codes to create complex biomolecules with **100%** sequence fidelity. This allows us to design new proteins with unprecedented precision vs other materials.

Programmable biomolecules in industry

Proteins are complex, versatile, robust and scalable molecules with diverse applications:

- **Peptide drugs:** Short protein sequences, often used to mimic signalling molecules and bind molecular receptors, for example cytokines and hormones. Example: **Semaglutide (Ozempic/Wegovy)**; the "weight-loss wonder-drug" transforming the pharma landscape.
- **Antibodies:** Proteins used by the body to identify foreign substances such as bacteria and viruses. Now the form of many successful drugs including antibody-drug conjugates. Example: **Humira**; the biggest selling drug of the 2000s with more than $200B sales.
- **Enzymes:** Catalytic proteins used to synthesise, chemically modify and lyse a range of chemical substrates. Example: **proteases** used in detergents.
- **Other industrial peptides:** Used in crop protection, nutrition, cosmetics and the chemical industries. Example: **palmitoyl peptides** used in skincare products.

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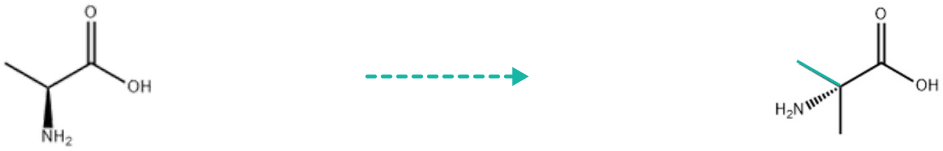
4 examples of valuable non-canonical amino acids

Non-canonical amino acids are chemically diverse amino acid structures that are not found in natural proteins. Their chemistries provide valuable properties to protein chains:

Cysteine (found in nature) → Selenocysteine (non-canonical)

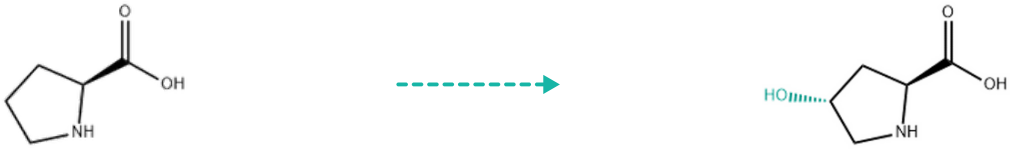
The **selenium** atom replaces sulphur, increasing chemical reactivity. As a result, selenocysteine is poised to be a pivotal contributor in the development of future 'superenzymes' and stable, long-half-life therapeutics.

Alanine → 2-Aminoisobutyric acid (AIB)



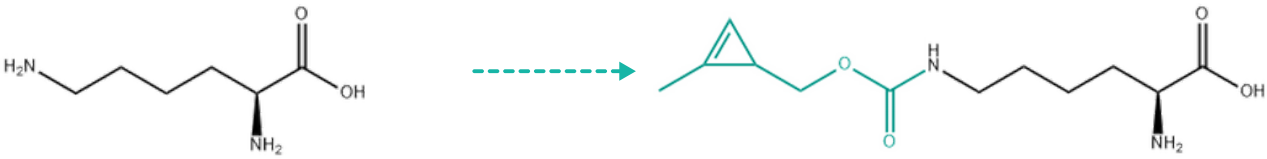
The additional **methyl group** makes AIB a strong inducer of helix protein structures. It has valuable applications in drug development, including the blockbuster drugs **Wegovy** and **Ozempic**, where it improves resistance against degradation.

Proline → L-hydroxyproline



The **hydroxy group** addition to the proline ring aids molecule solubility, stability and targeted delivery. This can be added as a post-transational modification in cells; for example, L-hydroxyproline is a major component of mammalian collagen.

Lysine → Cyclopropene lysine (CypK)



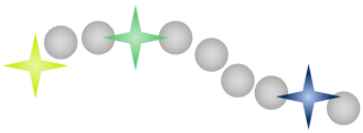
A **cyclopropene group** adds “click” chemistry functionality, allowing precise bioconjugation to other molecules e.g. for antibody-drug conjugates.

How to incorporate monomers not found in nature

To incorporate non-canonical monomers into a peptide or protein, we need to harness the ribosome to interpret the genetic code in a different way. This means engineering the DNA code and the translational machinery to incorporate the new monomer, while avoiding any cross-talk with the existing machinery. Some people do this *in vitro*; at Constructive Bio we do it scalably with cells. Read more in our white paper: ***Reprogramming Life: How Genetic Code Expansion Will Transform the Bioeconomy***.

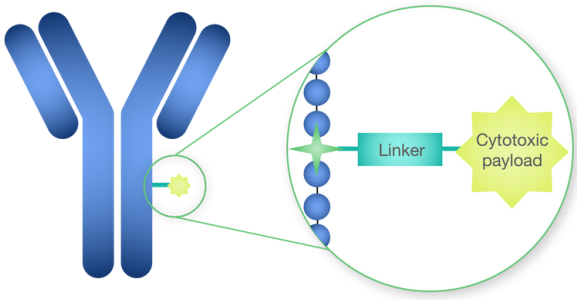
New programmable biomolecules made possible with non-canonical amino acids

Peptides



Short chains of amino acids with non-canonical amino acids programmed at set positions. Applications include drugs, biopesticides, cosmetic products and more.

Proteins



Long chains of amino acids that form complex tertiary structures. This includes antibody-drug conjugates with precise non-canonical bioconjugation handles.

Macrocycles

Cyclic chains of monomers with fantastic potential as drug candidates for new molecular targets, including depsipeptides containing alpha hydroxy acids as well as amino acids. See Spinck *et al.*, Nature Chemistry (2023) for examples.

Non-protein polymers

A new generation of custom-designed biomolecules with diverse defined properties, formed of amino acids and other related monomers. Applications include future bioplastics and other advanced materials.

3 ways non-canonical amino acids will transform healthcare

New advances are opening up opportunities for new biomolecules in healthcare and beyond:

Open up new peptide drug targets

Integration of non-canonical amino acids allows drug developers to explore an expanded chemical space, giving greater opportunities to drug targets that are currently undraggable.

Example: Wegovy, the weight-loss "wonder-drug" set to be the world's biggest selling drug by 2028, contains two non-canonical monomers that are critical for preventing molecule degradation by proteases and increasing availability in the blood circulation.

Create precision antibody-drug conjugates (ADCs)

The ability to create fully programmable antibodies will enable precise incorporation of bioconjugation handles into the molecule structure, ready for attachment of potent drugs. This will create more robust and effective ADC treatments to target tumour cells.

Example: Array of ADCs in clinical trials with improved properties, focus of multiple recent pharma partnership deals worth hundreds of $ millions from Merck, Astellas, Eli Lilly and more.

Enhance pharmacological properties of proteins

Non-canonical amino acids have a range of beneficial chemical properties that can enhance the stability, binding, toxicology and efficacy profiles of protein drugs.

Example: Next generation of cytokine drugs with enhanced properties; focus of Sanofi's $2.5Bn acquisition of Synthorx in 2019.

In 2028, the top 3 drugs will generate an estimated $39 billion per year.

All 3 will contain at least one non-canonical amino acid.

Constructive Bio's biomolecules of the future

At Constructive Bio we have an advanced protein engineering platform, capable of harnessing the *E. coli* ribosome to create new proteins containing up to three different non-canonical amino acids with high efficiency and precision. We achieve this through genetic code expansion: read more in our white paper ***Reprogramming Life: How Genetic Code Expansion Will Redefine The Bioeconomy***.

With this technology we have the opportunity to transform not just healthcare, but also adjacent industries. By further engineering the ribosome, we can create not just functionalised proteins, but also other advanced materials like bioplastics. And we can do it all robustly, sustainably and at scale.

Our technology enables you to:

- Reprogram biology in its natural language: DNA.
- Access hundreds of existing exotic chemistries, as well as a pipeline of new monomers.
- Produce new functionalised biomolecules, at scale.

Read more about our programmable biomolecule breakthroughs here:

nature chemistry — Genetically programmed cell-based synthesis of non-natural peptide and depsipeptide macrocycles (2023)

nature chemistry — Engineered triply orthogonal pyrrolysyl–tRNA synthetase/tRNA pairs enable the genetic encoding of three distinct non-canonical amino acids (2020)

Science — Sense codon reassignment enables viral resistance and encoded polymer synthesis (2021)

Scan the code to learn how you can reimagine the next generation of biomolecules with our Commercial Development and Strategy Manager, Dr Freddie Dudbridge.

What will you create?

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