**////Title: Discovering Unmapped Molecular Targets for Novel Covalent Drugs**

**////Bodytext:**

Covalent drugs are molecules that irreversibly bind to specific, targeted sites in the body. They work to inhibit the disease-causing functions of certain proteins by preventing them from interacting with other substances. One well-known example is the antibiotic, Penicillin.

Covalent drugs form permanent bonds to create a long-lasting effect and this has led to safety concerns. But recently, researchers have been fine-tuning how covalent drugs react in the body to ensure their safety.

These new drugs are called targeted covalent inhibitors and they work by first being guided towards and weakly bonding to the desired protein. This initial interaction facilitates the subsequent formation of the irreversible covalent bond with a nearby amino acid. Consequently, the function of that protein is inhibited.

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Dr Mikail Abbasov from Cornell University, New York, dedicates his research to improving our knowledge and understanding of the targets of covalent drugs and how they could be used to create ground-breaking therapies. His interdisciplinary work spans the fields of chemistry, biology and physics to improve the treatment of human diseases, such as cancer, viral infections, autoimmune and neurodegenerative disorders.

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In one important line of research, Dr Abbasov worked with collaborators to develop a new strategy for natural product synthesis which he called ‘pharmacophore-directed retrosynthesis’. This work holds significant promise for supporting the rapid discovery of potential therapeutics, such as the identification of neuroprotective drugs that do not have immunosuppressive side effects.

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In another study, Dr Abbasov and his colleagues conducted new and exciting research on biological targets for covalent drugs. In particular, they focused on covalent targeting of amino acids – the building blocks of proteins. Twenty different amino acids are found in the human body and historically, two of them called cysteine and serine have been the main focus for covalent drugs. However, this limits the possibilities for drug discovery.

Dr Abbasov set out to investigate another amino acid called lysine. The team developed a chemoproteomic technology that allowed them to study how lysines react with small molecules.

This ground-breaking work led Dr Abbasov to profile and log over 200 of these small molecules. By testing human cancer and immune cells, the team found thousands of reactive lysines. This included functional sites on proteins that were previously seen as too difficult to target. Collating this new data allowed Dr Abbasov to create a comprehensive map of lysines that are now known to be possible drug targets.

Findings from this project now provide a blueprint for chemical biologists and medicinal chemists to understand the rules that govern lysine-targeting covalent inhibitor design, which may eventually lead to new treatments and drugs.

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Work in Dr Abbasov’s laboratory continues to enrich our understanding of the mechanistic underpinnings of pathological processes and provide valuable leads for the design and development of novel therapeutics.