The Path to a Protein Degrader

Protein Degradation at Bristol Myers Squibb

Bristol Myers Squibb's investigation of protein degradation began more than two decades ago. Building on this legacy and scientific expertise, Bristol Myers Squibb is discovering and developing therapeutic approaches in blood cancers, solid tumors and other therapeutic areas with high unmet need.

Protein degradation is the process by which proteins are naturally destroyed in a cell. With targeted protein degradation, researchers are harnessing the cell's own machinery, for example ubiquitin ligase (E3) enzymes, to degrade several classes of proteins that were previously considered "undruggable."

Learn more about the basics of protein degradation **here**.

The science behind the discovery and development of protein degraders has evolved over time.

Early protein degraders were discovered and developed based on the observed effect they had on the individual and without a clear picture of how they worked in the body.

Newer protein degraders are being developed from the beginning to have a specific therapeutic effect achieved by a specific mechanism of action.

Cryogenic electron microscopy allows researchers to see the details of protein structures and how proteins interact with one another. This has enabled purposeful advancements and driven the field of protein degradation forward.

Bristol Myers Squibb recognized the importance of this imaging technology early and invested in equipping labs and researchers with it in order to advance the company's rational design capabilities.

"Historically, it's been very much like walking through a dark room with your hands stretched out, not being able to find your way around. Nowadays, with cryogenic electron microscopy available as a tool, we have the ability to turn on the light, and we understand more about how these molecules act and behave."

– Christoph Zapf, PhD, Executive Director, Research and Early Development, Head of Oncology Chemistry - West

Discovery and Development

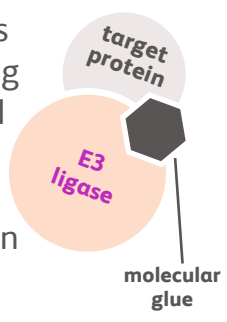
Researchers at Bristol Myers Squibb are leveraging two different methods of protein degradation: molecular glues (cereblon E3 ligase modulators, CELMoD® agents) and heterobifunctional agents (also called ligand-directed degraders, or LDDs).

Pursuing multiple paths to the discovery and development of protein degraders provides more opportunities for breakthroughs and therapeutic strategies that could one day help patients.

Although both paths may lead to a protein degrader agent, the development process looks very different, each with its own sophisticated technology and research experts.

CELMoD Agents

CELMoD agents are molecules that act as molecular glue to alter the protein-binding properties of cereblon (an E3 subunit and an important component of the protein degradation cellular machinery) to promote interaction with and degradation of disease-causing proteins.



It all begins with the CELMoD agent library

- Bristol Myers Squibb has built an industry-leading CELMoD agent library using computational and medicinal chemistry
- CELMoD agents from the library are screened through relevant cells
- The disappearance of proteins is measured

"Despite there being thousands of proteins in cells, we can measure individual proteins that just simply disappear upon exposure to compounds within this library."

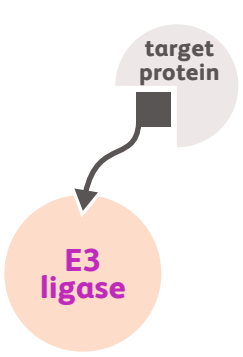
– Christoph Zapf, PhD

Choosing a potential target

- Researchers examine the proteins that disappeared to determine their relevance in various diseases
- This identifies which CELMoD agent/target pairs researchers will take forward to the optimization step

LDDs

LDDs are 3-component molecules (two different protein binders joined by a linker) designed to bring together target proteins with key components of the protein degradation cellular machinery, redirecting the machinery to degrade the target proteins.



It all begins with a target

- Researchers identify target proteins implicated in a disease with the aim of removing them from the cells

Building an LDD

- Scientists begin building the LDD starting with the end that interacts with the identified target of interest
  - This molecule is often found through our internal screening platforms
- The linker, or middle component, is then attached
- Finally, a molecule on the opposite end that binds the protein degradation cellular machinery is connected to the linker

"Building an LDD can be quite challenging. Each component needs to be carefully optimized so that they function properly together. Developing the LDD into a drug to treat patients requires additional optimization and evaluation."

– Ingrid Wertz, MD, PhD, Executive Director, Protein Homeostasis Center of Excellence

Optimization

Potential protein degraders from both approaches are tested and optimized through various preclinical studies and processes.

In vitro studies	Disease model studies	Drug profiling
Further development and data collection	Toxicology analysis	Data analysis

Clinical Trials

If the above process yields a possible candidate that has the potential to treat a health condition, that candidate is then tested in clinical trials using human volunteers.

Clinical trials help researchers to understand whether the potential therapeutic is safe and effective.

Bristol Myers Squibb is building on its legacy and scientific expertise to advance the field of protein degradation and transform patient outcomes in diseases with serious unmet need, such as cancer and lupus.