AMGEN

# HARNESSING NATURE'S MATCHMAKERS

## MULTISPECIFICS AND AMGEN'S INDUCED PROXIMITY PLATFORM

We are entering a new wave of drug discovery that paves the way for new treatments aimed at thousands of disease targets currently viewed as "undruggable."

## THE FOURTH WAVE OF TRANSFORMATIVE INNOVATION IN DRUG DESIGN

### WAVE 1
### c.1900
**Advent of aspirin**

*Compounds with a known chemical structure but, at the time, unknown biology (how they work in the body)*

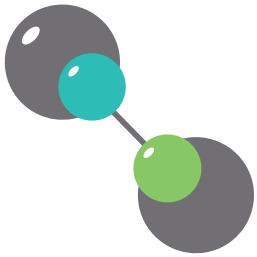
### WAVE 2
### 1970s
**Rational drug design**

*Specific compounds with known molecular targets that play a role in disease*

### WAVE 3
### 1980s
**Biotechnology revolution**

*Recombinant DNA technology used to engineer cells to produce protein-based medicines (biologic medicine)*

### WAVE 4
### Now
**Multispecific medicines**

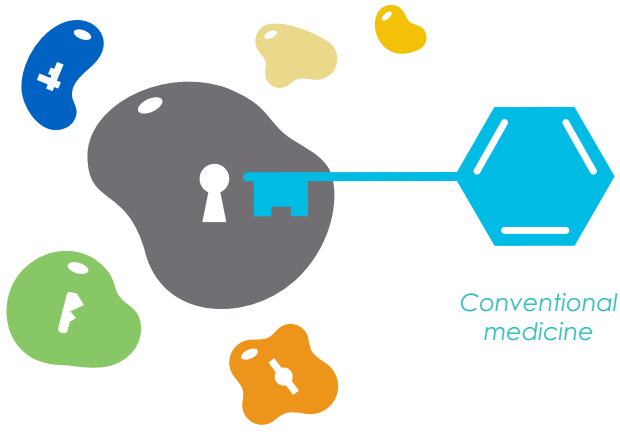


*Multi-targeted compounds or biologic medicines that mobilize biological activity to treat disease*

## Why are multispecific medicines needed?

Many diseases can be treated by targeting a specific protein and changing it in some way, such as blocking it, activating it, or destroying it. Conventional medicines are designed to zero in on a single target protein and fit together like a lock and key.

Some challenges with this approach are that many target proteins don't have sites for conventional medicines to bind or can't be altered enough to change the course of a disease. This means that only about 15% of proteins are "druggable" with conventional medicines.



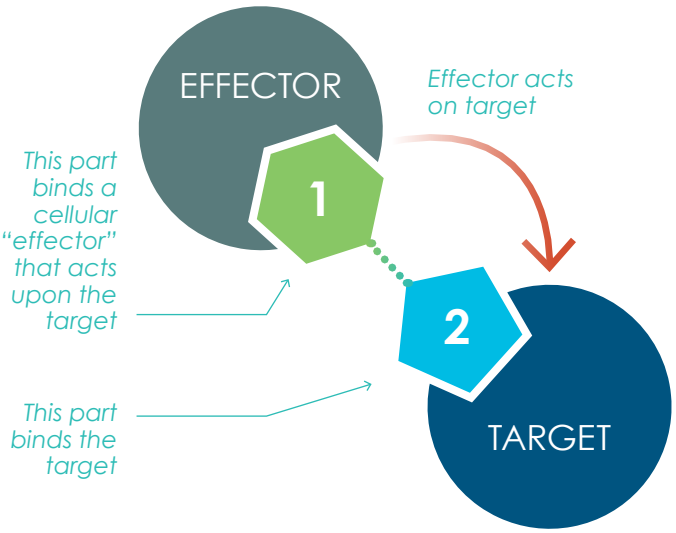
*Conventional medicine*

*Disease-causing proteins*

# What are induced proximity medicines?

Certain types of multispecific medicines work through a principle known as induced proximity, in which they bring two things together, much like a matchmaker. Instead of trying to grapple with difficult targets on their own, multispecific medicines mobilize biological mechanisms (effectors) to do the heavy lifting. These biological mechanisms have a specific purpose in the body that can also be used to alter a disease-causing protein (target).

**The multispecific matchmaker is comprised of at least two parts:**




**Target outcomes (depending on the nature of the effector):**


# What can induced proximity medicines do?

There are many versatile molecular machines that induced proximity medicines can use to fight disease when matched with the right target.

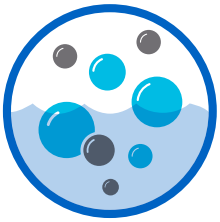
The furthest along in development are called **PROTAC® (proteolysis targeting chimeras) molecules**, which leverage the enzymes that tag unwanted or damaged proteins for destruction by molecular machine called the proteasome. One of the advantages of a PROTAC molecule is that it can facilitate the destruction of a target, then move onto the next target that it encounters and repeat the process. Conversely, conventional medicines must stay bound to their target to have action, which can limit their effect in the body.


***PROTAC molecules*** *tag unwanted or damaged proteins for destruction by the proteasome*

There are other induced proximity medicines that have recently been described, but are still in the lab:

***AUTAC molecules*** *use autophagy to "eat" cellular debris, like clumps of proteins, and larger cellular structures that lead to disease*

***RIBOTAC molecules*** *use RNase to slice up unwanted RNA that codes for disease-causing proteins*



***LYTAC molecules*** *can pull proteins from outside of the cell inside for destruction by acidic lysosomes*

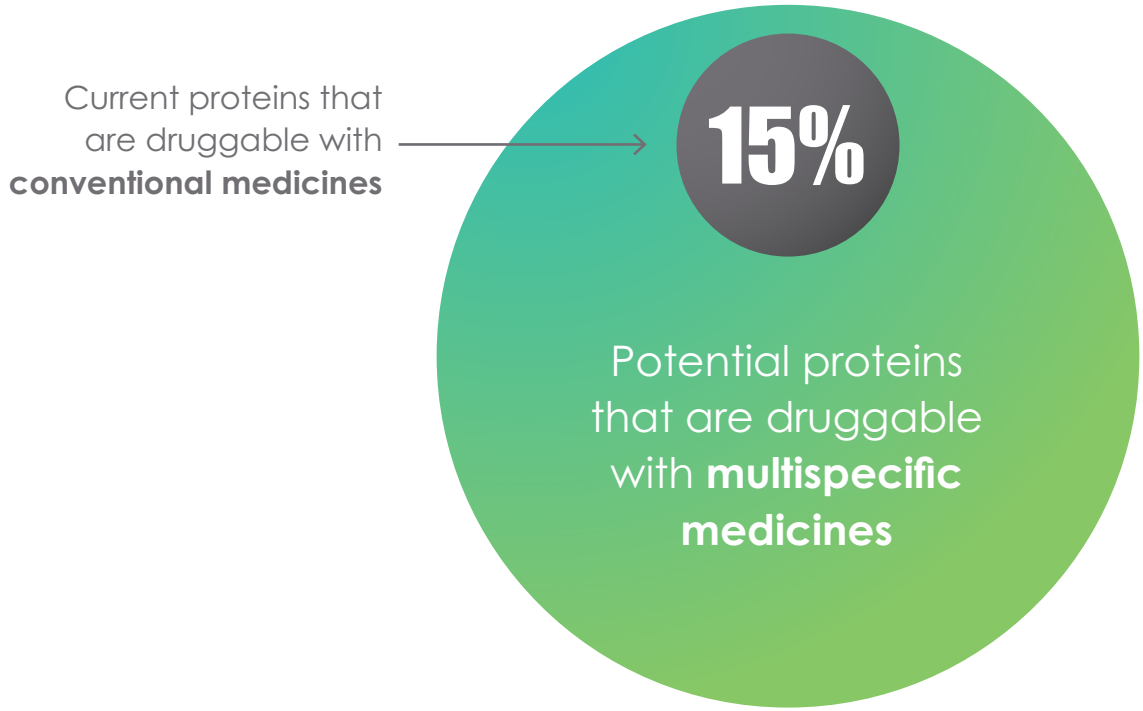
## Advantages of induced proximity medicines

While induced proximity medicines can be complex and may pose new development challenges, they have important advantages over their conventional medicine counterparts:

+ Induced proximity medicines are diverse. They can be made up of one type of molecule or any combination of small molecules, proteins, carbohydrates, lipids, or nucleic acids.
+ They can bind nearly anything inside or outside of a cell — even cells themselves.
+ The therapeutic potential of induced proximity medicines is enormous— any activity that is biologically possible can potentially be harnessed by a multispecific medicine.

## The future of multispecific medicines

While some of these new ideas are still in their infancy and years from the clinic, the future potential of multispecific drugs is staggering. By harnessing the biology of the cell, Amgen is using this new approach to drug design to tackle diseases now considered untreatable.




Amgen is focusing on targets among the **85%** of proteins currently thought of as "undruggable" with its induced proximity platform.

Using its unique combination of R&D capabilities across the globe, including DNA-encoded libraries, Amgen is poised to identify molecules that have the potential to become multispecific medicines. Approximately two-thirds of Amgen's pipeline molecules through Phase I are investigational multispecific medicines including BiTE® molecules.

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