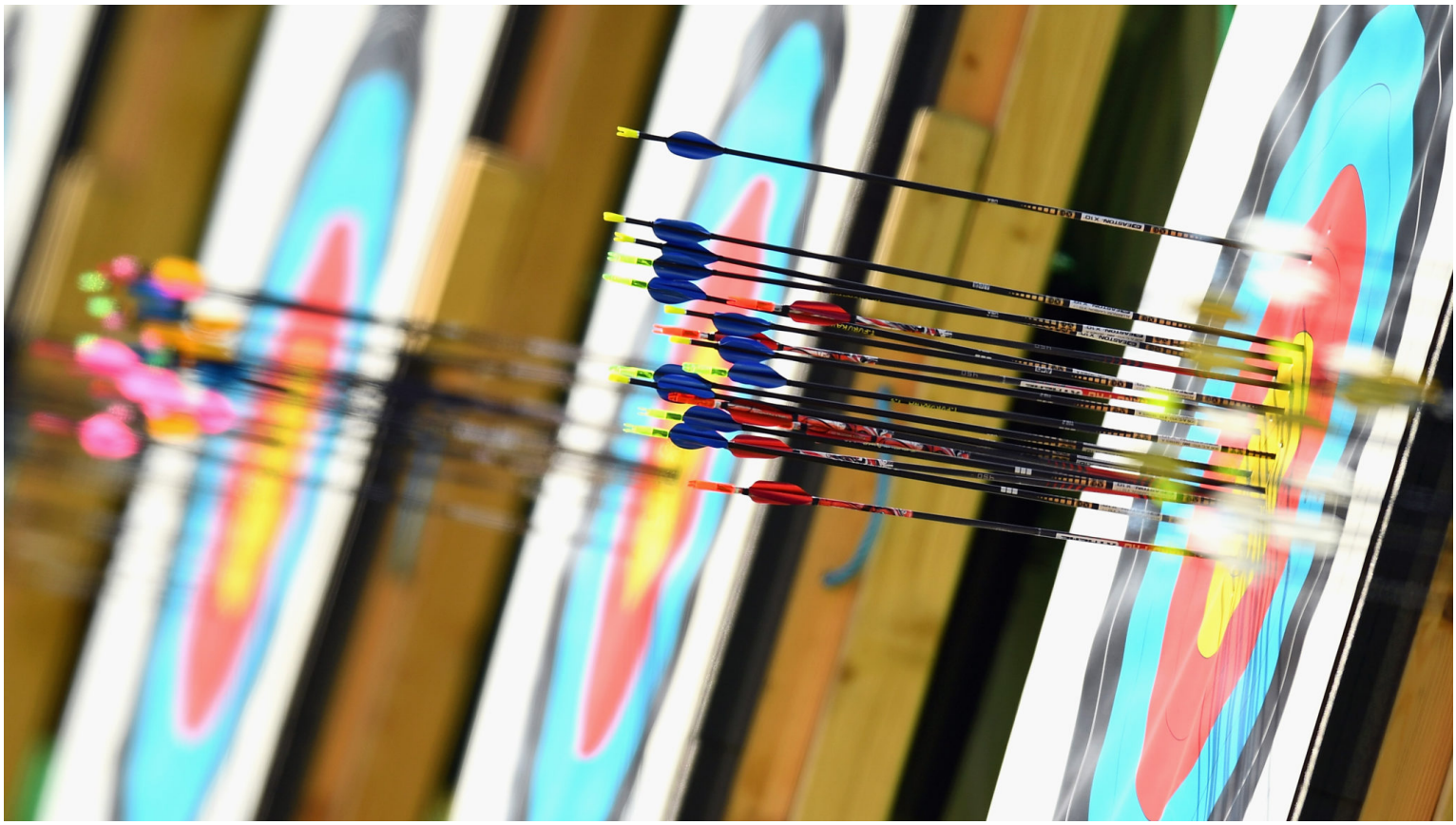
STAT

Multi-target drugs should be in the pharma pipeline along with precision drugs

By Harris A. Gelbard

January 31, 2019



Quinn Rooney/Getty Images

Precision medicine — providing the right treatment, for the right patient, at the right time — is saving lives. The use of therapies that home in on single targets is helping beat tough-to-treat diseases that were often deadly in the past.

But we're overlooking another class of extremely important and promising candidates: multi-target drugs. Discounting these drugs is a disservice to patients and a missed opportunity for U.S.-based companies to bring potentially game-changing drugs to market.

Most drugs on the market today take aim at a single biologic substance, like a protein or enzyme. In contrast, multi-target drugs hit several targets, which is often necessary to do in order to yield a therapeutic effect in complex diseases.

While single-target drugs were once viewed as desirable largely because of the concern that "off-target"

effects could have harmful consequences, multi-target drugs may actually possess a safer profile because of their ability to modify the outcome of a disease. While it's true that multiple targets mean more chances for off-target effects, if the therapeutic benefit of a multi-target drug outweighs possible side effects that don't ultimately influence the patient's ability to return to a healthy state, then it's likely worth the associated risk.

Trending Now: [1]
Solid Biosciences to soldier on as initial muscular dystrophy gene therapy results disappoint [2]

Some of the most widely used medications are multi-target drugs. Three examples are acetaminophen, the active ingredient in Tylenol; ibuprofen, the active ingredient in Advil; and acetylsalicylic acid, better known as aspirin. Scientists still don't completely understand how these drugs curb fevers and reduce pain. The process likely involves signaling by chemical messengers called prostaglandins that can be produced at the site of injury or illness. These drugs also inhibit enzymes called cyclooxygenases that are required for the synthesis of prostaglandins.

Most diseases — cancer, those caused by chronic inflammation, and neurological and neurodegenerative diseases such as schizophrenia and Alzheimer's disease — are often caused by multiple genetic and/or environmental factors. One drug taking aim at one target is unlikely to actually modify the outcome of these diseases due to the body's compensatory mechanisms and redundant functions.

Multi-target drugs hold promise for the treatment of complex conditions that so far can't be treated by single-target drugs. Unfortunately, multi-target drugs are often ignored because research to develop them is inherently more complex than it is for single-target drugs.

Defining how multi-target drugs work can be elusive throughout the drug development process, which often makes pharmaceutical companies and venture capitalists uneasy. They tend to shy away from pursuing such drugs so they don't have to present unpersuasive explanations to Wall Street when things don't go smoothly.

There is, however, an encouraging shift toward multi-target drugs. A recent analysis[3] of the 101 new molecular entities approved by the Food and Drug Administration between 2015 and 2017 found that 31 percent had multi-target mechanisms of action (either as single drugs or therapeutic combinations). One example is the multi-target antipsychotic brexpiprazole (Rexulti) that was licensed in 2015 for the treatment of schizophrenia. Single-target drugs accounted for 34 percent, and the remaining 35 percent included biologics (proteins, peptides, and monoclonal antibodies) and diagnostic agents. So there is still a lot more room for growth in the multi-target drug space.

I've seen firsthand how powerful multi-target drugs can be. For the past 10 years, my lab at the University of Rochester Medical Center has been developing a compound called URMC-099. It was originally synthesized as a small molecule therapy[4] to reverse the neurological problems[5] associated with

HIV. It does this by inhibiting enzymes called kinases[6] (such as mixed lineage kinase type 3, or MLK3) that respond to inflammatory stressors inside and outside cells. These inflammatory signals arise after infection with viruses like HIV; the accumulation of disease-causing proteins like beta-amyloid; oxidative stress from diets high in fat and sugar; and many other insults.

Related: [7]
Winding back the clock, scientists hunt for new uses for old drugs [7]

MLK3 is present in first-responder immune cells (also known as innate immune cells[8]) as well as in the target cells they normally protect. Over-activation of these kinases by a virus or other insult upsets the balance between first-responder immune cells and their target cells. This can lead to increased inflammation and damage to target cells, or even their death. This damage or cell death can lead to more inflammation from innate immune cells.

This destructive response to inflammation is present in most (if not all) organ systems, suggesting that a drug that can restore the equilibrium between innate immune cells and target cells might be broadly applicable to a wide variety of diseases. URMC-099, through its influence on MLK3 and other kinases, restores the balance of signaling in both cell cultures and animal models of various diseases: Alzheimer's disease[9]; HIV-associated neurocognitive disorders[10]; Parkinson's disease[11]; multiple sclerosis; [12]perioperative cognitive disorders (formerly postoperative cognitive dysfunction); and nonalcoholic steatohepatitis[13].

As is the case with other multi-target therapeutic agents discovered by serendipity, phenotypic screening, or traditional medicine, knowledge about the pharmacological effect precedes knowledge about the mechanism of action. We know a lot about the chemistry, pharmacodynamics, pharmacokinetics, and safety profile of URMC-099. But we're still investigating the exact molecular mechanisms by which it right-sizes the immune response. One current hypothesis is that leucine rich repeat kinase type 2 and other key kinases that URMC-099 inhibits also participate in disease-causing inflammatory responses.

Another multi-target drug candidate, ENMD-2076[14] from CASI Pharmaceuticals, has shown promise against some of the toughest-to-treat cancers, including ovarian, liver, and triple-negative breast cancer. ENMD-2076 has several mechanisms of action against processes that are essential for tumor growth and development, including the formation of new blood vessels (angiogenesis), cell proliferation, and the cell cycle.

Even as the use of exquisitely tailored medications continues to expand — the FDA recently approved[15] a cancer treatment called Vitrakvi[16] for use not against a specific type of cancer but for cancers that have a specific genetic mutation — I don't believe that the pharmaceutical industry should put all of its eggs in the precision medicine basket.

That would be a major mistake for two reasons. First, precision medicine isn't perfect and frequently comes with potentially harmful side effects[17]. Second, many diseases are associated with multiple dysfunctions in genes or proteins, and new drugs with multiple targets logistically have a better shot at successful treatment than multiple single-target drugs.

U.S.-based companies should pay attention, because international pharmaceutical companies are giving drugs like URMC-099 a harder look than their U.S.-based counterparts. That's especially true for Chinese companies.

This makes sense, since the multi-target philosophy is the backbone of traditional Chinese medicine. It typically uses eight to 12 active principal ingredients in a single therapeutic preparation for a disease. This approach is based on more than 5,000 years of experience in the ultimate laboratory experiment: using naturally occurring ingredients to treat human disease. The underlying philosophy is that medicines are supposed to treat patients as a whole, and not treat a disease in isolation.

The principal theory driving precision medicine forward makes sense: We seek to achieve a therapeutic effect from a compound's interaction with a single target, such as an enzyme or protein. Focusing on a single target should limit off-target toxicity and allow for reproducibility of the drug's absorption and metabolism. This, in turn, informs a therapeutic dose that can be reliably and consistently achieved.

But straying from this theory could pay huge dividends. One of the many multi-target drugs being investigated in labs across the country could be the modern-day version of aspirin, Advil, and Tylenol — a ubiquitous treatment that targets systemic inflammation, Alzheimer's disease, or one of the other great foes of our time.

The ultimate goal of physicians and scientists is to improve and save lives. We owe it to present and future patients to explore all possible paths to achieving this goal. The pharmaceutical industry can do this by pursuing multi-target drugs as well as precision therapies.

Harris A. Gelbard, M.D., is director of the Center for Neurotherapeutics Discovery[20] at the University of Rochester Medical Center.

About the Author

Harris A. Gelbard

harris_gelbard@urmc.rochester.edu[21]

Tags

Links

1. https://www.statnews.com/most-popular/

2. https://www.statnews.com/2019/02/07/solid-biosciences-muscular-dystrophy-gene-therapy-disappoint/
3. https://www.ncbi.nlm.nih.gov/pubmed/?term=PMC5770353
4. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3682381/
5. https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Neurological-Complications-AIDS-Fact-Sheet
6. https://www.ncbi.nlm.nih.gov/pubmed/?term=PMC4032177
7. https://www.statnews.com/2017/03/10/drugs-repurposing/
8. https://www.ncbi.nlm.nih.gov/books/NBK26846/
9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5935963/
10. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4032177/
11. https://www.michaeljfox.org/foundation/grant-detail.php?grant_id=1814
12. http://www.eneuro.org/content/5/6/ENEURO.0245-18.2018
13. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5543922/
14. http://www.casipharmaceuticals.com/product-pipeline/enmd-2076/
15. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm626710.htm
16. https://www.statnews.com/2018/11/26/loxos-cancer-drug-wins-a-pioneering-fda-approval-now-it-has-to-find-some-patients/
17. https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet#q7
18. https://www.statnews.com/signup/
19. https://www.statnews.com/privacy/
20. https://www.urmc.rochester.edu/neurotherapeutics-discovery.aspx
21. https://www.statnews.com/2019/01/31/multi-target-drugs-pharma-pipeline/mailto:harris_gelbard@urmc.rochester.edu
22. https://www.statnews.com/tag/drug-development/
23. https://www.statnews.com/tag/precision-medicine/
24. https://www.statnews.com/tag/research/