

The difference between targeted drug therapies and targeted-drug therapies.

Karel Petrak

NangioTx Inc., 555 Fifth Avenue, New York, NY 10017-9254

Corresponding Author : Karel Petrak, NangioTx Inc., 555 Fifth Avenue, New York, NY 10017-9254; E-mail: kpetrak@gmail.com

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Abstract

The term “targeted” is being used to describe various new drugs and therapies with an intent to suggest that such drugs exhibit higher specificity with respect to the disease to be treated. The reality, however is that the use of all such recently denoted drugs is associated with a large number of very serious undesirable side effects. It is concluded that using the term “targeted” when it relates to the intent of what the drug is to do and ignoring the fact that the drug’s action is generally distributed throughout the body rather than acting on the locus of the disease is misleading.

Keywords

Tweeted therapy, targeted drugs, precision drugs, precision medicine

Preamble

The FDA has been pushing for targeted drug therapies, sometimes called “personalized medicines” or “precision medicines,” for a long time (1). According to the agency, “Targeted therapies make use of blood tests, images of the body, or other technologies to measure individual factors called “biomarkers.” These biomarkers can then be used to determine who is most likely to benefit from a treatment, who is at higher risk of a side effect, or who needs a different dose. Targeting therapy can improve drug safety, and make sure that only people likely to have a good response get put on a drug.”

Targeted drug therapies versus targeted-drug therapies

Language is not always a precise tool. The terms “target” and “targeting” may have several meanings. In the above text, the most likely meaning is “an objective or result towards which efforts are directed”. Given the role of the FDA in overseeing the approval and use of drugs, we can perhaps assume that an objective in this case is that targeted therapies are expected to be more effective in treating patients. Let us examine how this intent is working out in practice.

In 2015, the FDA approved a number of drug described as being “targeted”: Upravi, Cosentyx, Cotellic, Odomzo, Xifaxan, Darzalex, Praxbind, Technivie, Opdivo, Alecensa, Empliciti, Keytruda, Ninlaro, Tagrisso and Orkambi.

Most of these drugs have been designed to act on the pathways that are presumed to influence the disease but not the actual disease target. UPTRAVI targets the prostacyclin pathway. In *pulmonary arterial hypertension*, body may not make enough of prostacyclin which can cause the blood vessels in the lungs to narrow thus acerbating the condition. Similarly, Cosentyx is a targeted treatment that specifically inhibits IL-17A. Cotellic (cobimetinib) is a reversible inhibitor of mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinase 1 (MEK1) and MEK2. MEK proteins are upstream regulators of the extracellular signal related kinase (ERK) pathway, which promotes cellular proliferation.

Odomzo (sonidegib, formerly LDE225) is a selective smoothened (SMO) inhibitor which regulates the hedgehog (Hh) signaling pathway and which plays a critical role in stem cell maintenance and tissue repair.

DARZALEX® provides a prime example. This therapeutic agent is a monoclonal antibody that attaches to CD38 protein present on the surface of certain types of cells (e.g., red blood cells) and is also present in high numbers on multiple myeloma cells. Since DARZALEX® targets the CD38 protein, it may also affect other cells with this protein on their surface. This is very characteristic of all the drugs listed above. In consequence, all these drugs exhibit often very serious side effects. Illustrating further, Opdivo (Nivolumab) acts by blocking a negative regulator of T-cell activation and response, thus allowing the immune system to attack the tumor. The drug label contains warnings with regard to increased risks of severe immune-mediated inflammation of the lungs, the colon, the liver, the kidneys (with accompanying kidney dysfunction), as well as immunemediated hypothyroidism and hyperthyroidism . Alecensa potently and selectively blocks two receptor tyrosine kinase enzymes: anaplastic lymphoma kinase (ALK) and the RET proto-oncogene. Inhibition of ALK subsequently blocks cell signaling pathways, including STAT3 and the PI3K/AKT/mTOR pathway, and induces death (apoptosis) of tumour cells. Side effects include unspecific gastrointestinal effects such as constipation (in 34% of patients) and nausea (22%), oedema (swelling;34%), myalgia (muscle pain; 31%), anaemia (low red blood cell count), sight disorders, light sensitivity and rashes (all below 20%). Serious side effects occurred in 19% of patients; fatal ones in 2.8%. Empliciti uses an immunostimulatory antibody that targets the Signaling Lymphocytic Activation Molecule family member 7 (SLAMF7) glycoprotein. Developing new cancers (malignancies) is a risk in patients who receive EMPLICITI with REVLIMID and dexamethasone. Keytruda (Pembrolizumab) is a therapeutic antibody that binds to and blocks the PD-1, programmed cell death protein 1 located on lymphocytes. Adverse effects include severe infusion-related reactions, severe immune-related adverse effects including lung inflammation (including fatal cases),



And inflammation of endocrine organs that caused inflammation of the pituitary gland, of the thyroid (causing both hypothyroidism and hyperthyroidism in different people), and pancreatitis that caused Type 1 diabetes and diabetic ketoacidosis; some people have had to go on lifelong hormone therapy as a result (e.g. insulin therapy or thyroid hormones). People have also had colon inflammation, liver inflammation, kidney inflammation due to the drug.

The above examples clearly illustrate that targeting cellular pathways does not lead to generating “precision” drugs; the reason for this is clear. Cellular pathways are generally ubiquitous and as such are functioning in both the disease and healthy cells.

Consequently altering pathways in disease cells may lead to a degree of efficacy in treating diseases but it certainly is responsible for generating many, and often severe side effects. This same situation exists with “conventional” drugs that also act on various cellular pathway with the only difference being that this is not highlighted in their marketing.

The inappropriate use of the term targeting extends further. Even drugs that have not been approved as “targeted” have been described as such in general reporting. It is likely that the intent here is to impart a beneficial ‘spin’ of ‘targeting’ when describing and promoting drugs.

FDA-approved drugs NOT described by Company or CenterWatch as targeted	BUT described by others as targeted
Corlanor	https://www.cbsnews.com/news/fda-approves-corlanor-ivabradine-heart-failure-drug-first-in-almost-decade/
Kanuma	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5074735/
Praluent	https://www.forbes.com/forbes/welcome/?toURL=https://www.forbes.com/sites/matthewherper/2018/03/10/sales-flopped-but-does-this-heart-drug-save-
Repatha	https://en.wikipedia.org/wiki/Evolocumab
Imlygic	https://www.curemelanoma.org/patient-eng/melanoma-treatment/immunotherapy/t-vec-imlygic/
Kybella	https://refreshaestheticcenter.com/selectively-target-
Addyi	http://www.bioworld.com/content/perseverance-pays-sprout%E2%80%99s-addyi-gains-first-fda-win-hsdd-0
Cholbam	https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015
Strensiq	https://www.businesswire.com/news/home/20150706005254/en/Strensiq%C2%AE-asfotase-alfa-Receives-Marketing-
Farydak	https://lymphomanewstoday.com/2016/08/19/novel-therapy-may-increase-remission-times-in-certain-patients-
Daklinza	https://www.drugbank.ca/drugs/DB09102
Genvoya	http://www.gilead.com/news/press-releases/2015/11/us-food-and-drug-administration-approves-gileads-single-tablet-regimen-genvoya-elvitegravir-cobicistat-
Duopa	https://www.healio.com/nursing/journals/jgn/2015-4-41-4/%7B527b33e2-f281-4285-8f10-71a0bfcadb59%7D/product-
Lenvima	https://www.oncolink.org/cancer-treatment/chemotherapy/oncolink-rx/lenvatinib-lenvima
Portrazza	https://lungcancer.net/medications/portazza-reviews-how-
Nucala	https://www.gsk.com/en-gb/media/press-releases/gsk-achieves-approval-for-nucala-mepolizumab-for-the-treatment-of-eosinophilic-granulomatosis-with-polyangiitis-egpa-for-adults-in-the-us/

So, what is the difference between targeted drug therapy and targeted-drug therapy? In the linguistic sense, in the first case it is the therapy that is being targeted, and in the second it is the drug that is being targeted. The difference is significant when one considers drug delivery to its intended disease target, specifically when the drug is designed to act primarily on the target of the disease, i. e., on a molecular structure responsible for the initiation or progression, or both of the disease to be treated. Targeted drug therapies approved to date do not function as envisaged “precision medicines”, as amply illustrated by examples given above.

Conclusion

We should not expect that “perfect”, no side-effect drugs will be designed. However, actions of all drugs are likely to be improved through novel, correctly designed drug delivery. A number of companies have now been set up with this strategy in mind (2-5).

Using the term “targeted” when it relates to the intent of what the drug is to do and ignoring the fact that the action is generally distributed throughout the body rather than acting on the locus of the disease is just a window dressing.



It is very important to make our objective clear and define our direction as “(cell)-specific delivery/target” (6-14). However, a key question does remain: “Can this be done using the approaches employed so far?”

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