Chapter 7
Target Identification of HDAC8 Isoform for the Treatment of Cancer

A. Umamaheswari
Anna University, India

A. Puratchikody
Anna University, India

Sakthivel Balasubramaniyan
Anna University, India

ABSTRACT

Target identification has been considered as a chief parameter in drug discovery as it fully characterizes on-target and off-target effects of drug binding. Cell signaling receptors, structural proteins, and post-translational modifications of histones by histone deacetylases are the most widespread targets that are progressively being explored. The FDA approved histone deacetylases inhibitors and the majority of HDACi in and out of clinical trials based on the activities of 11 isoforms of the enzyme in non-selective influence approach. Unfortunately, reported HDACi does not possess a high degree of structural specificity and ultimately lessens the therapeutic index with many dose limiting toxicities. This chapter illustrates how different approaches are incorporated into the novel inhibitors discovery that are truly isoform-selective and which are specifically involved in targeting only a particular isozyme. Further, it highlights the aspects relating to provide a wider therapeutic index with an improved toxicity profile of lead like epigenetic modulators.

INTRODUCTION TO CANCER

Cancer is a heterogeneous disease with a wide range of clinical profile and diverse underlying mechanism. Cancer with ~14 million new cases and 8.2 million cancer-related deaths in 2012 is considered as the leading cause of morbidity and mortality worldwide. In the next two decades, the expected number of new cases of cancer is ~ 70% (Stewart & Wild, 2014).

DOI: 10.4018/978-1-5225-7326-5.ch007
There has been a prolonged targeting approach for the development of new cancer therapies, distinctive and appropriate for each individual. Surgery, intravenous cytotoxic chemotherapy and radiation are the major hallmark of treatment for cancer (David, 2008). These drugs target rapidly dividing cells in addition to certain normal tissues. Consequently, many patients get susceptible to therapy-related immediate and long-term toxicities like gastrointestinal symptoms, alopecia and myelosuppression that are often dose limiting.

Anti-cancer drugs fail in the clinic for two main reasons; the first is that they do not act and the second is that they are not safe. Hence, innovative medications are in demand for the management of severe therapeutic conditions including cancer, autoimmune, infectious and metabolic diseases. Now, patients diagnosed with cancer very frequently shift to newer and more personalized treatment strategies. A noteworthy progress in the treatment of cancer in the past decades is the recent concept of targeted therapies which have been very much supportive in channelizing the path “from the bench to the bed” (Yoh et al., 2012).

A drug candidate is not a one-size-fits-all-diseases stratagem instead its pathway has to be identified and validated appropriately. Hence, a target-based strategy for the development of new drug through drug discovery is essential. For the last two decades, researchers of biotech and pharmaceutical organisations and universities work in the area of target-based drug discovery (Terstappen et al., 2007).

There is a need for drug discovery to move from the slow and too expensive trial and error approach. Over the last two to three decades, the shift in focusing towards target-based discovery has been a foremost landmark in drug discovery research. Computational modelling and drug design forms significant constituents of new-age biology for the reason that they are crucial to understand the large-scale data produced by high-throughput screening experiments and to create hypotheses, which are in general recapitulated with experimental validation.

### Target Therapies

A target is a broad terminology applied to a series of biological entities that includes proteins, genes, RNA, monoclonal antibodies, antibody fragments, recombinant fusion proteins and peptides. A good target desires to be efficacious, safe, satisfies clinical and commercial needs and, above all, it should be ‘druggable’. A ‘druggable’ target upon binding to either a small drug molecule or larger biological, produce a desired biological response that can be quantified both in vitro and in vivo techniques. The first stage in drug discovery process is to acquire the knowledge about the disease mechanism, utilize cellular and genetic approaches and finally identify potential drug targets either for a particular disease or phenotypes (e.g. HIV replication within T-cells). Subsequently, genomics and proteomics helps in providing gene sequence and gene expression data for disease tissues compared to normal tissues.

Generally, in a diseased condition genes as well as their protein products are highly expressed when compared to low expression in normal tissues and hence become apparent potential targets for therapy. The selected disease targets are modulated and behavioural changes of diseased cells are validated by in vitro research, usually cell-based and animal models proving themselves to prioritize for future research. Identification of good target and validation enables increased confidence in the relationship between disease and target and explore whether modulation in the target will direct to mechanism-based side effects (DiMasi et al., 2003). Targeted therapies pave a way to develop specific treatments for severe medical conditions however, concurrently ensuing little to no off-target toxicity. The goal in tumor therapies are aimed to stop the multiplication of the cancer cells by focussing at a particular tumor tar-