Quench Academy of Medical Education and Research
Annals of Medical Physiology
www.amphysiol.com

Editorial

Target with-in target

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Article history Received 21 August 2017 Accepted 22 August 2017 Online 26 March 2018 Print 31 March 2018

Molecular targets (MT) are intra-cellular structures, ranging from proteins to DNA and RNA that are potential entities for pharmacological action. With advancements in different sub-cellular domains viz. glycomics, lipidomics, proteomics, genomics, transcriptomics, metabolomics, etc it has made possible identification of specific target molecules that are either up-regulated or down-regulated during physiological processes and in various disordered / diseased states.

MT can be visualized by means of molecular imaging which maps the functions at cellular and molecular level in contrast to conventional diagnostic imaging which render good details of physical structure **[1]**. Molecular imaging encompasses nuclear medicine, radio-pharmacology and radio-pharmaceuticals which largely make use of small quantities of radio-active isotopes. These procedures are minimally invasive, safe and cause little pain **[2]**. These in-vivo techniques make use of existing imaging modalities like magnetic resonance imaging (MRI), positron emission tomography (PET), etc coupled with biomarker probes which chemically interact with extra- and intra-cellular milieu bringing about a change in image according to the molecular alterations in the desired area. The images are captured in real-time with highly sophisticated microscopy and nanoscopy procedures like atomic force microscopy (AFM), total internal reflection fluorescence (TIRF) microscopy and stimulated emission depletion (STED) nanoscopy. Furthering the scope of molecular imaging was the development of mass-spectrometry based matrix-assisted laser desorption/ionization (MALDI) technique which allows quantitative analysis **[3]**.

Though small molecules and protein therapeutics are well established agents in current pharmaco-therapeutics, their target range is limited to only one-tenth of the cell membrane surface or hydrophobic protein façade. With these short-comings, research efforts are directed in discovering next generation therapeutic approaches. Firstly, exploration of entities that promote the active endosomal uptake and release of molecules which are not lipid soluble like polypeptides, proteins and nucleic acids. Secondly, identification of molecules that enters the cell by passive diffusion, facilitated diffusion or active transport so as to reach the intracellular molecular targets **[4]**.

The targets for the pharmacological agents can be categorized under 9 headings (**Table 1**).

Biotherapeutics, production of therapeutic materials using biological means, encompass techniques like recombinant DNA technology, genetic engineering, etc. Noteworthy progress has been made in the field of cancer therapeutics with identification/development of molecules capable of

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DOI: https://doi.org/10.23921/amp.2018v2i1.275951
Print ISSN: XXXX-XXXX
Online ISSN: 2456-8422

generating extra-cellular or intra-cellular death signals which plunges the malignant cells to undergo apoptosis. One approach is development of tumor targeting antibody fragments genetically fused to a cytotoxic protein payload called Targeted Protein Therapeutics (TPTs) **[6]**. Other approaches being worked on are intra-cellular antibodies (intrabodies) **[7]** and peptide aptamers **[8]**. These developments are taking the therapeutics way forward, albeit rather slowly. Despite the fact that in-vitro studies are promising, some of the challenges still elude their application in in-vivo or real situation and cause high attrition in drug discovery. Few critical elements in successful drug development and designing are adequate target exposure, bio-availability (both extra-cellular and intra-cellular) and ideal route of delivery. Recently, a technique was developed to quantify the intra-cellular concentration of drug and hence its availability to bind to molecular target which translates into pharmacological effect **[8]**.

Earlier, the physiological basis of medicine was to target the cells, but of late the efforts are directed towards targeting sub-cellular structures. So, this is what is meant by 'Target with-in target: Aiming to break therapeutic mediocrity'.

Table 1: Categories of pharmaco-therapeutic targets **[5]**

Category	Site of action	Mechanism	Example
Various physicochemical mechanisms	Extra-cellular	Acid binding	Aluminium hydroxide
Targets of monoclonal antibodies	Cell surface	Immunoglobulin E (IgE)	Omalizumab
Transport proteins	Cell surface	Inhibitors of Na+/K+ ATPase	Digoxin
Ionic channels	Cell surface	Inhibitor of Epithelial Na+ channels (ENaC)	Amiloride
Receptors	Cell surface	Agonist of vasopressin receptor	Vasopressin
	Cytoplasmic	Glucocorticoid receptors	Glucocorticoids
	Intra-nuclear	Thyroid hormone receptors	Thyroxine
Enzymes	Cytoplasmic	Cyclooxygenase-2 (COX-2) inhibitor	Acetaminophen
Substrates, metabolites, proteins	Cytoplasmic	Asparagine	Asparaginase
DNA/RNA and ribosomes	Cytoplasmic and Intra-nuclear	Interaction with r-RNA	Aminoglycosides
Unknown mechanism of action	-	-	Ambroxol

Acknowledgements: None

Conflict of interest: None

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