

Target Validation

For **two** of the targets from a list below provide a short description in your own words as to the most important observations that validate the development of therapeutics.

As an example, the development of penicillin analogs targeting the transpeptidase that makes the bacterial cell wall is “validated” by:

- a) observing that natural compounds that inhibit the enzyme have antibacterial activity,
- b) the lack of any such enzyme/pathway in the host (human),
- c) the essentiality of the cell wall to bacterial viability, and
- d) the fact that numerous other “agents” interfere with the bacterial cell wall integrity (e.g., lysozyme breaks it down, causing cell rupture due to inability to retain osmotic barrier).

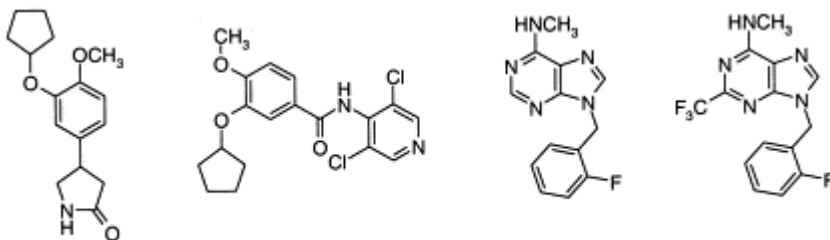
Provide the earliest, specific and complete references that provide this validation. Finally, indicate any limitations that are specific to this validation material.

Some examples of limitations are:

- (i) *in vitro* studies may not translate to *in vivo* results,
- (ii) the test conditions may not be relevant to human physiology
- (iii) the animal models used may not be relevant.

Target list:

1. Depression: The following molecules serve as leads to develop potent antidepressant drugs via inhibition of phosphodiesterase 4. Provide information that validates phosphodiesterase 4 as an appropriate target for the treatment of depression.



2. Erectile dysfunction: Vardenafil has been approved by FDA for the treatment of erectile dysfunction. This drug inhibits phosphodiesterase 5. Provide information that validates phosphodiesterase 5 as an appropriate target for the treatment of impotence.
3. Bacterial infection. Halogenated furanones act as inhibitors of bacterial quorum sensing pathways. Provide information that validates this pathway as an appropriate target for treating bacterial infections.
4. Neuroregeneration. Immunosuppressive drug Tacrolimus suppresses the immune system via binding to a protein known as FKBP-12. This drug also enhances nerve growth after nerve injury. Provide data to show if FKBP-12 is a suitable target for finding neuroregenerative drugs.