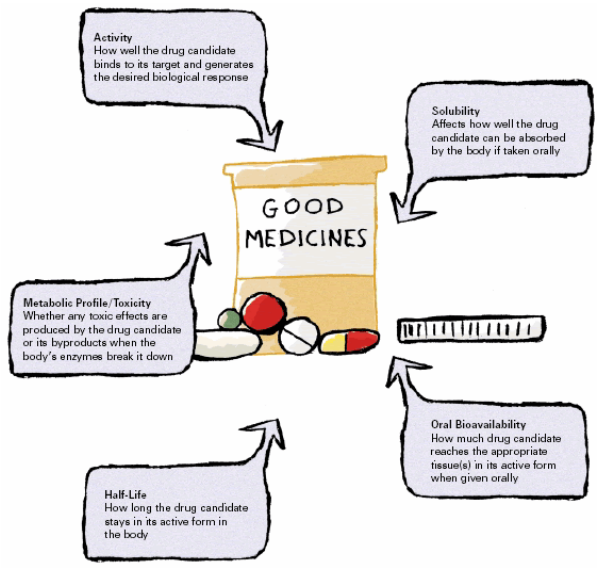
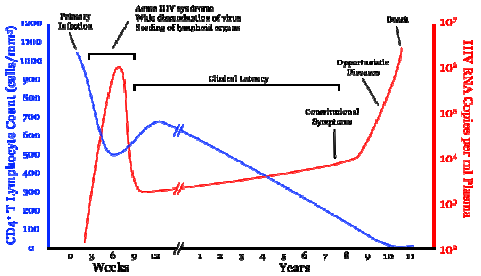
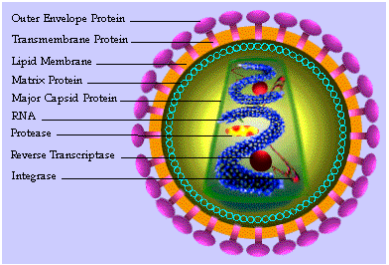
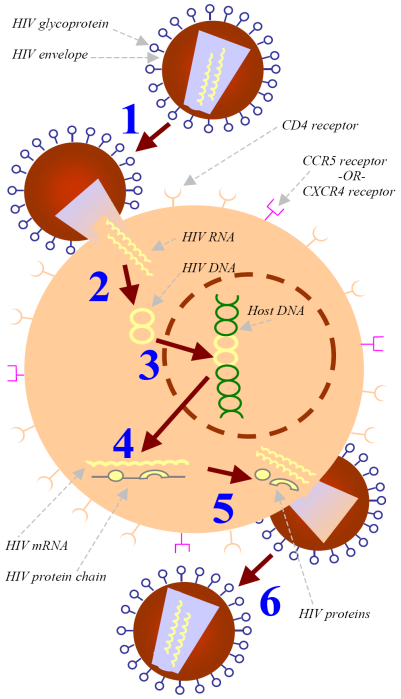


Case study 1

HIV protease inhibitors



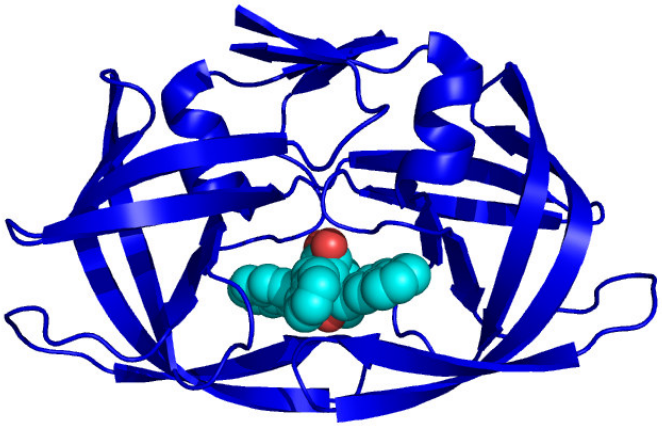




1 Binding and Fusion: HIV binds to a CD4 receptor and one of two co-receptors on the surface of a CD4+ T- lymphocyte. The virus then fuses with the host cell.
2 Reverse Transcription: An HIV enzyme called **reverse transcriptase** converts the single- stranded HIV RNA to double-stranded HIV DNA.
3 Integration: The newly formed HIV DNA enters the host cell's nucleus, where an HIV enzyme called **integrase** "hides" the HIV DNA within the host cell's own DNA.
4 Transcription: The host enzyme **RNA polymerase** create copies of the HIV genome and shorter strands of RNA called messenger RNA (mRNA) for production of HIV proteins.
5 Assembly: An HIV enzyme called **protease** cuts the long chains of HIV proteins into smaller individual proteins. Attachment of RNA genetic material results the assembly of a new virus particle.
6 Budding: During budding, the new virus steals part of the cell's outer envelope.

Nucleoside Analogs
zidovudine/*Retrovir*
didanosine/*Videx*
zalcitabine/*HIVID*
stavudine/*Zerit*
lamivudine/*Epivir*
abacavir/*Ziagen*
Non-Nucleoside Reverse Transcriptase Inhibitors
nevirapine/*Viramune*
delavirdine/*Rescriptor*
efavirenz/*Sustiva*
Nucleotide Analogue
tenofovir DF/*Viread*
Protease Inhibitors
indinavir/*Crixivan* (Merck and Co.)
ritonavir/*Norvir* (Abbott)
saquinavir/*Invirase* (Hoffman-La Roche)
nelfinavir/*Viracept*
amprenavir/*Agenerase*
lopinavir/ritonavir

"I think it's a remarkable success story," says Dale Kempf, a chemist involved in the HIV protease inhibitor program at Abbott Laboratories. "From the identification of HIV protease as a drug target in 1988 to early 1996, it took less than 8 years to have three drugs on the market.“
Typically, it takes 10 to 15 years and hundreds of millions of dollars to develop a drug from scratch.

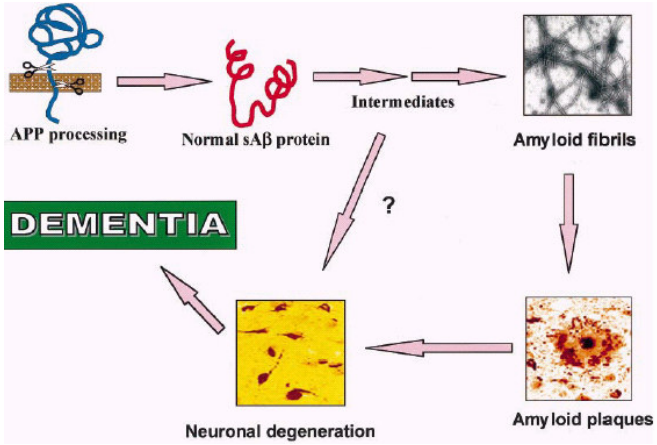


Problems?

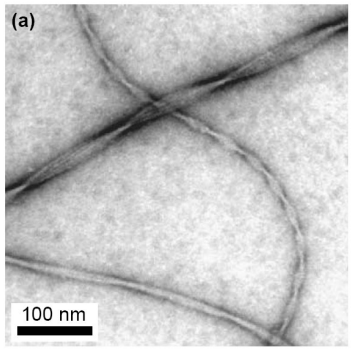
Yes: mutations.

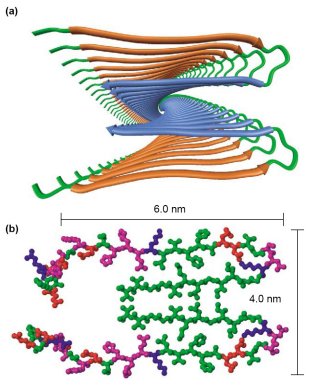
Case study 2

Alzheimer’s disease: 2 approaches

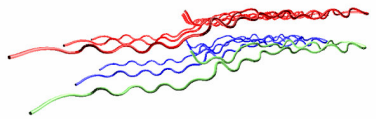


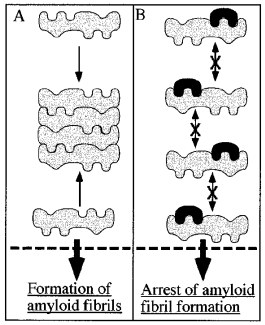
Approach 1: Amyloid aggregation inhibitors

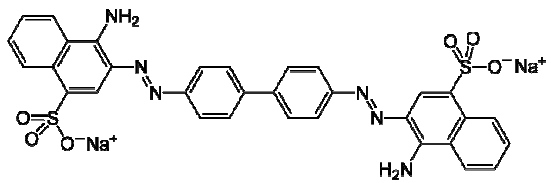




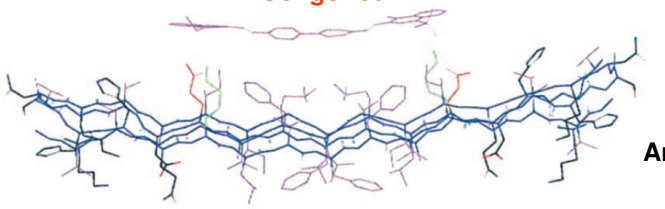
Different fibril models are available with twisted cross β-sheet $A\beta_{1\text{-}42}$ (Tycko et al., George et al.)







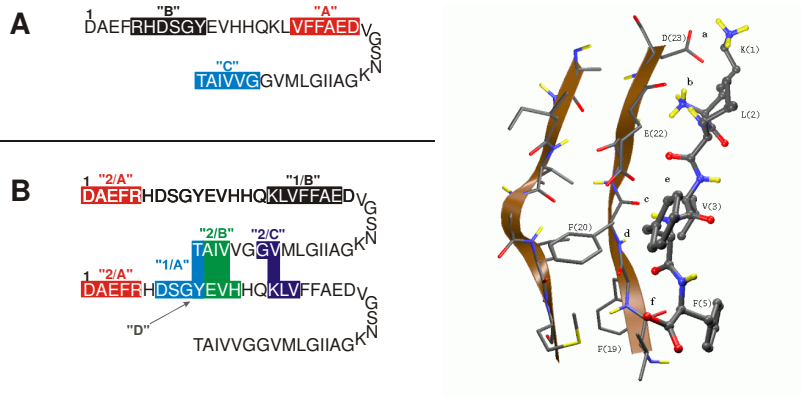
Congo red

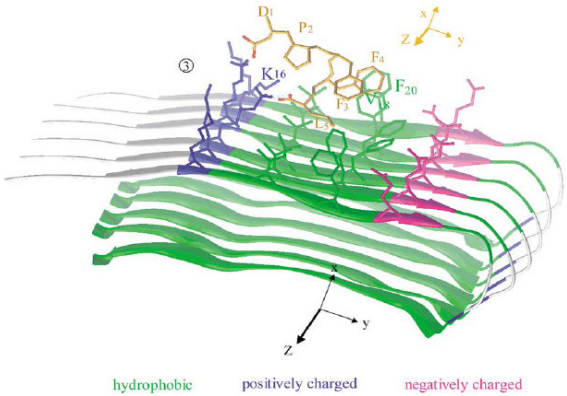


Amyloid

Binds to the surface, but: TOXIC

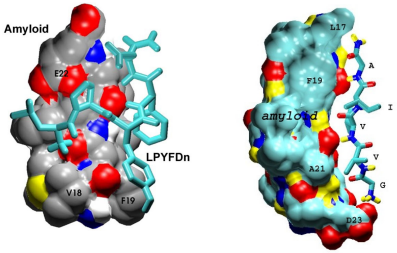
Binding of KLVFF and LPFFD to the Aβ of Alzheimers's disease





A recent NMR study confirmed that the K(16)LVFFAE sequence is indeed a binding region of the LPFFD peptide

Other peptides, which binds the amyloid

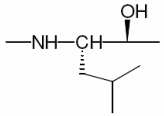


Approach 2: β-secretase inhibitors

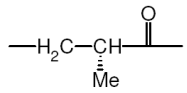
A series of peptidomimetic inhibitors complexed with β-secretease enzyme were involved in the study

om12	β-secretase	Boc-N-Lol-Alq-A-Cph
om13	β-secretase	Boc-N-Lol-Alq-V-Cph
om14	β-secretase	Boc-Soo-Lol-Alq-V-Cph
om15	β-secretase	Boc-VN-Lol-Alq-A-Cph
om16	β-secretase	Boc-VN-Lol-Alq-V-Cph
om17	β-secretase	Boc-V-Sme-Lol-Alq-V-Cph
om18	β-secretase	Boc-V-Soo-Lol-Alq-V-Cph
om19	β-secretase	Boc-M-Lol-Alq-V-Cph
om22	β-secretase	Boc-VM-Lol-Alq-V-Cph
om23	β-secretase	Boc-V-Sov-Lol-Alq-V-Cph
om24	β-secretase	Boc-VM-Lol-Alv-V-Cph

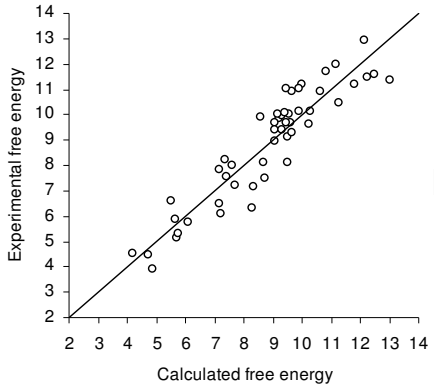
Lol



Alq



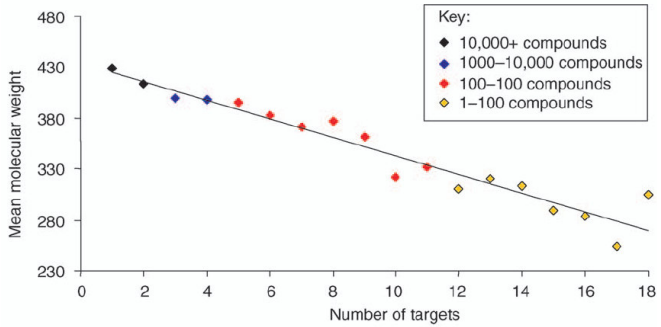
$$\Delta G_{b(exp),j} = \sum_{i=1}^{n} \alpha_i D_{ji} + \beta + \varepsilon_i \qquad (j = 1,2,\ldots,N)$$

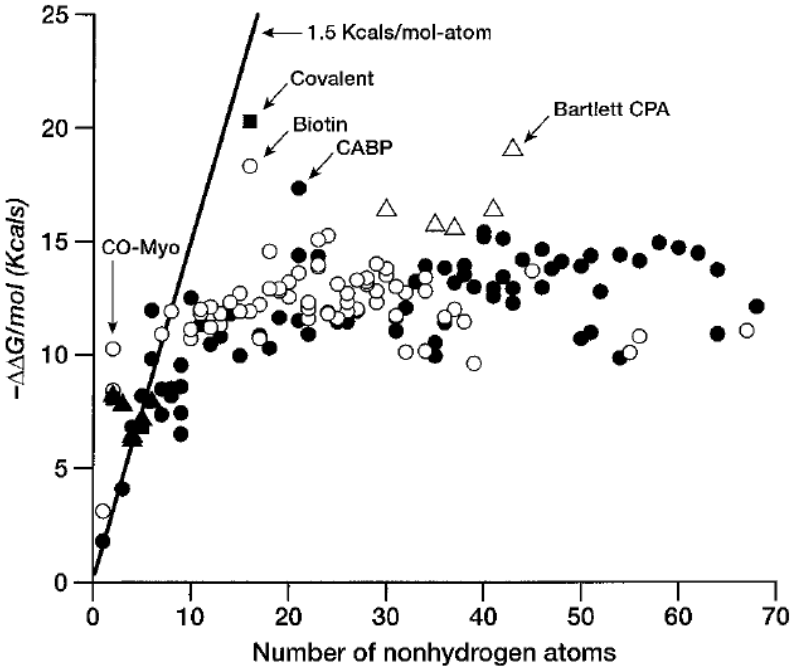


$$RPCG_{EN} = \frac{\delta_{max}}{\sum_a \delta_a}, \qquad a \in \{\delta_a > 0\}$$

Initial steps of drug design:

- *Target identification*
- *Target validation*
- *Selection of hit and lead compounds*
- *Lead optimization*





BOX 1

Names, definitions and idealized reference values for ligand efficiency indices

Reference values are calculated for each index using the following idealized values and the equations given in Table I:

- percentage inhibition of 50.0% (on a 0–1 scale) is equal to 0.50 at a given screening concentration of the compound;
- MW is equal to 0.333 kDa;
- K_i, K_d or IC_{50} value of 1.0 nM;
- pK_i of 9.00;
- van der Waals PSA is 50 Å^2 (normalized to 100 Å^2);
- compound (inhibitor) concentration (e.g. 10 μM).

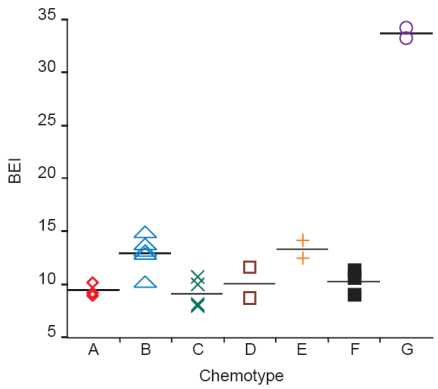
These indices can be defined at any screening concentration. However, even after approximate scaling, direct comparison of the PEI values obtained at different screening concentrations (10 μM versus 100 μM) is not recommended.

TABLE I

Calculation of PEI, BEI and SEI

Index	Calculation	Reference value
PEI	$\frac{\%\ \text{inhibition at a given [compound]}}{MW}$	1.5
BEI	$\frac{pK_i\ pK_d\ \text{or}\ pIC_{50}}{MW}$	27.0
SEI	$\frac{pK_i\ pK_d\ \text{or}\ pIC_{50}}{PSA}$	18.0

An idealized compound with K_i or IC_{50} of 1 nM and MW of 0.333 kDa has a BEI value of 27.



Binding efficiency indices for different chemotypes in the structure-based optimization of a target. Retrospective analysis of the BEI for several chemotypes during a drug discovery project involving human protein tyrosine phosphatase 1B (hPTP1B) [21,22]. On the x-axis, representatives of different chemotypes are plotted in an arbitrary order, with a line showing the mean BEI value of the group. Successive compounds within each series show increased efficiency along the vertical axis. The artifact compounds (Chemotype G, BEI ~33) represent true outliers even after improvement of each different class. Chemotypes are: A, difluorophosphonates; B, 1-site napthyl oxamates; C, 2-site oxamate amino acid; D, 2-site oxamate salicylate; E, 2-site isoxazole salicylate; F, 1-site oxamate; and G, isoquinoline diols.