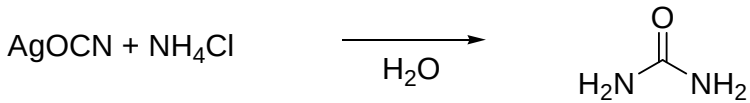
New Opportunities For Small Molecules

David L. Waller
29 October 2005
Frontiers Of Chemistry

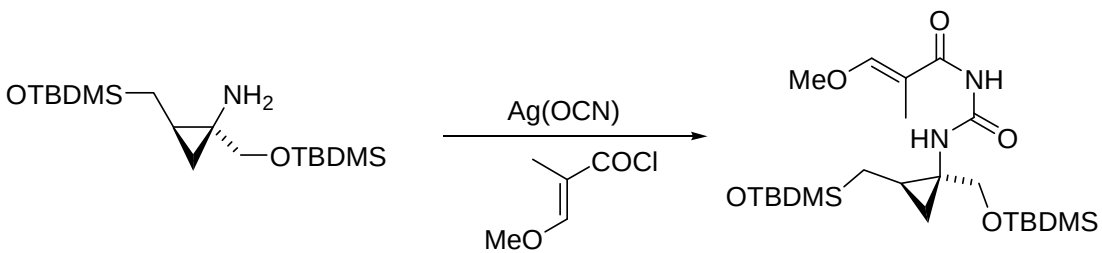
Bondmaking: Then and Now

-The first preparation of an organic substance (1828)…



"I must tell you that I can make urea without the use of kidneys"
F. Wöhler (1828)

… is still tactically and strategically in use today.



J. Org. Chem. **2002**, *67*, 4520


Library of Congress

Friedrich Wöhler
Ordinary Professor of Chemistry
University of Göttingen, 1836 - 1882

Where is chemical synthesis going, and where can it take us?

I. Into The Genome: DNA-Templated Discovery

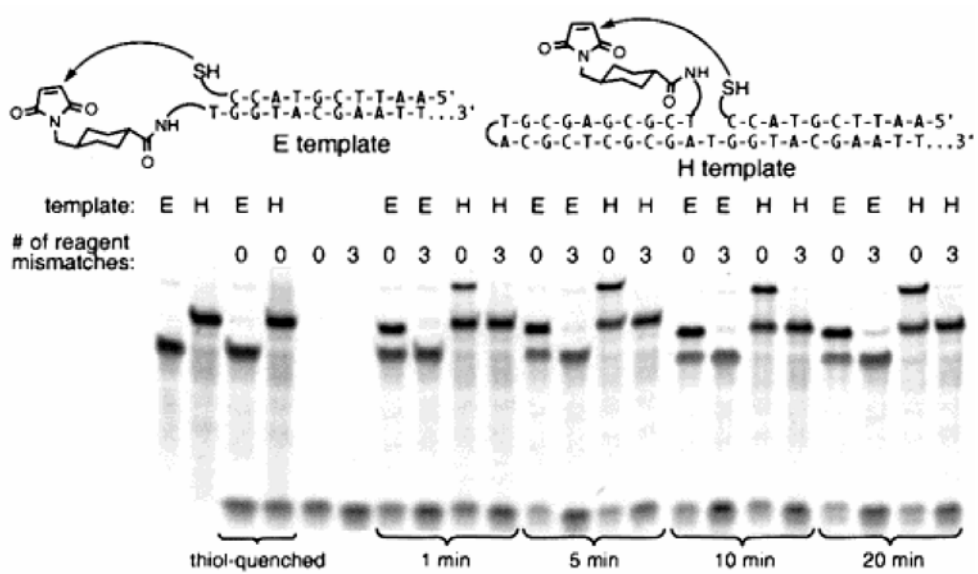
DNA-Templated Synthesis: Fundamental Reactions and Regimes

-Pairing of complimentary DNA oligonucleotides: "substrate (template)" and "reagent"
-Pair in either in end-on mode (E) or hairpin mode (H)

Reaction Conditions:
pH 7.5, 25 °C, 250 mM NaCl
Templates in 1:1 stoichiometry at ***60 nM***

-Designed "mismatches" in base pairing fail to undergo reaction.

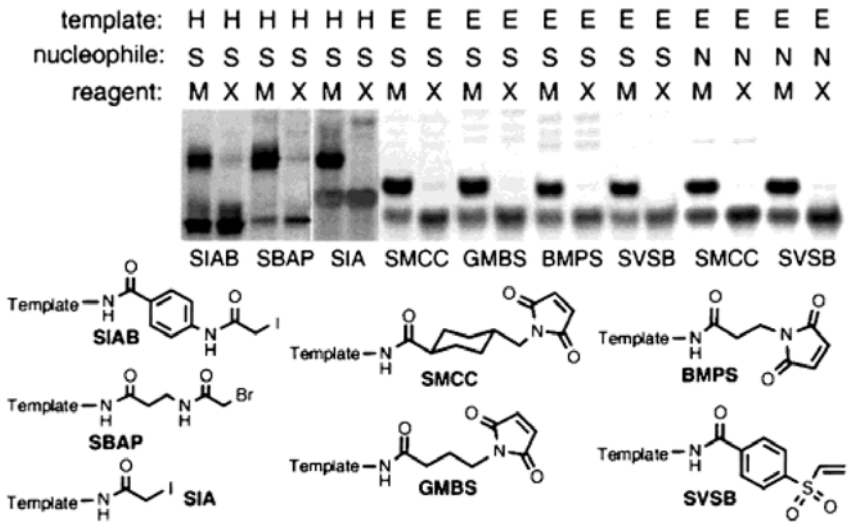
-Reactions rates were similar between H and E architectures ($K \cong 10^5\ M^{-1}s^{-1}$)



Liu and Co-workers *J. Am. Chem. Soc.* **2001**, *123*, 6961

DNA Templated Synthesis: Functional Group Compatibility

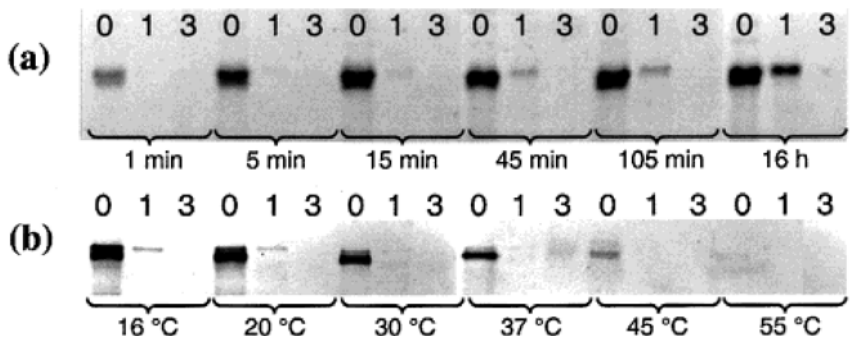
-H or E Template
-Thiol (S) or amine (N) nucleophile
-Matched (M) or mismatched (X) pairing



-S_N2, α,β-additions, and vinyl sulfone addition compatible with technology.

-Matched cases only proceeded to products effeciently, despite large differences in transition states, steric hindrance and conformational flexibility.

-Reactions with a single mismatch were 200 fold slower and could be eliminated by heating reaction above the estimated melting temperature.



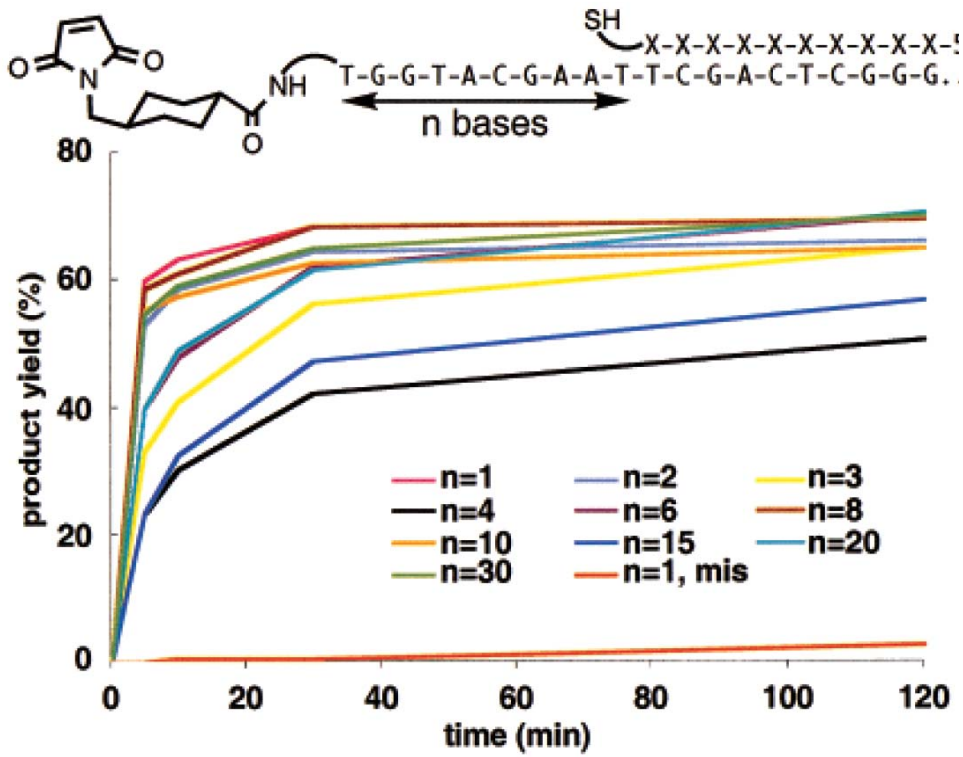
Liu and Co-workers *J. Am. Chem. Soc.* **2001**, *123*, 6961

DNA-Templated Reactions: Distance Effects

-Distance of reacting components is not important.

-Designed reactants with 2-30 bases between reacted 10^4 – 10^5 times faster than for untemplated reactions.

-At a 30 base distance, product formation proceeds through a transition state resembling a 200-membered ring.

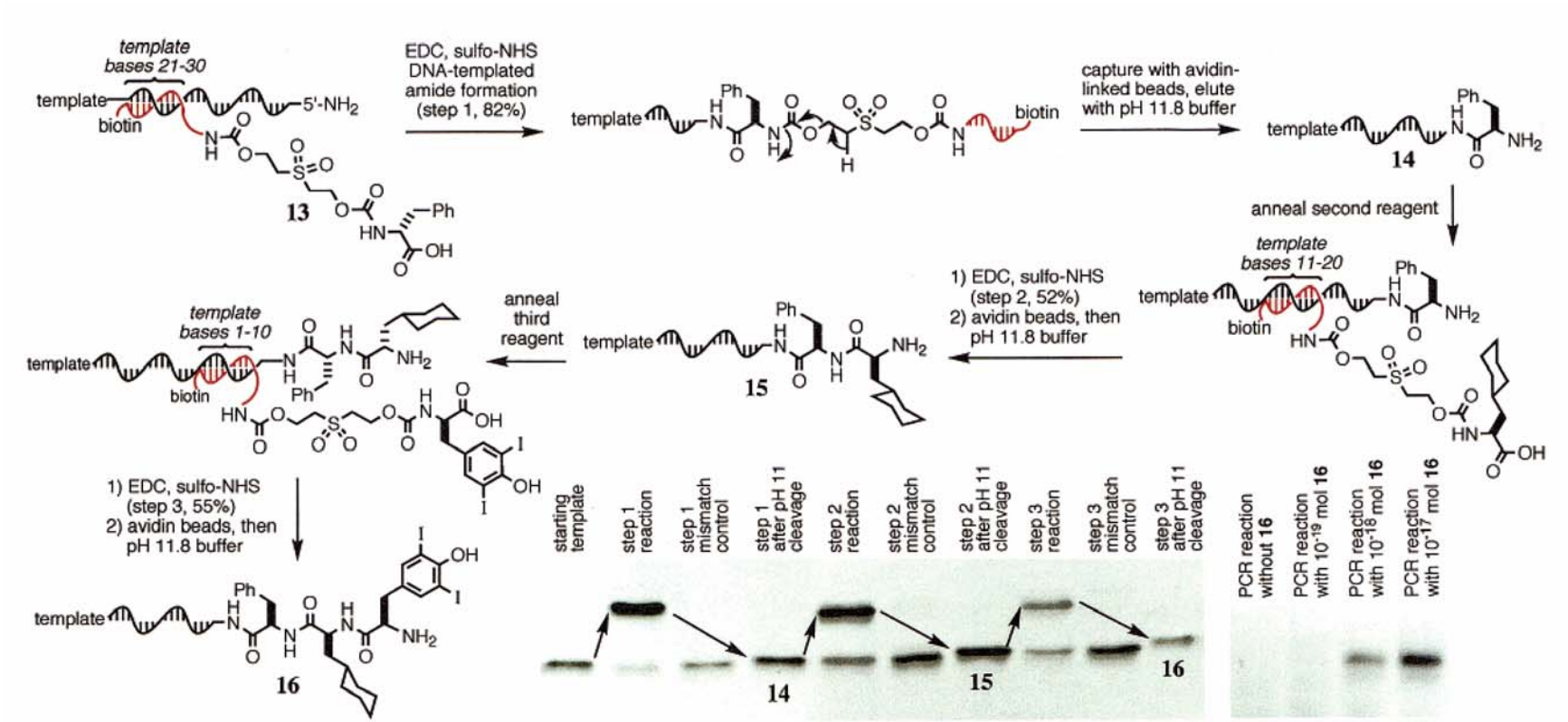


-Decreasing the concentration of the reactants dramatically slowed the reactions, indicating that DNA annealing is rate limiting.

Liu and Co-workers *J. Am. Chem. Soc.* **2001**, *123*, 6961

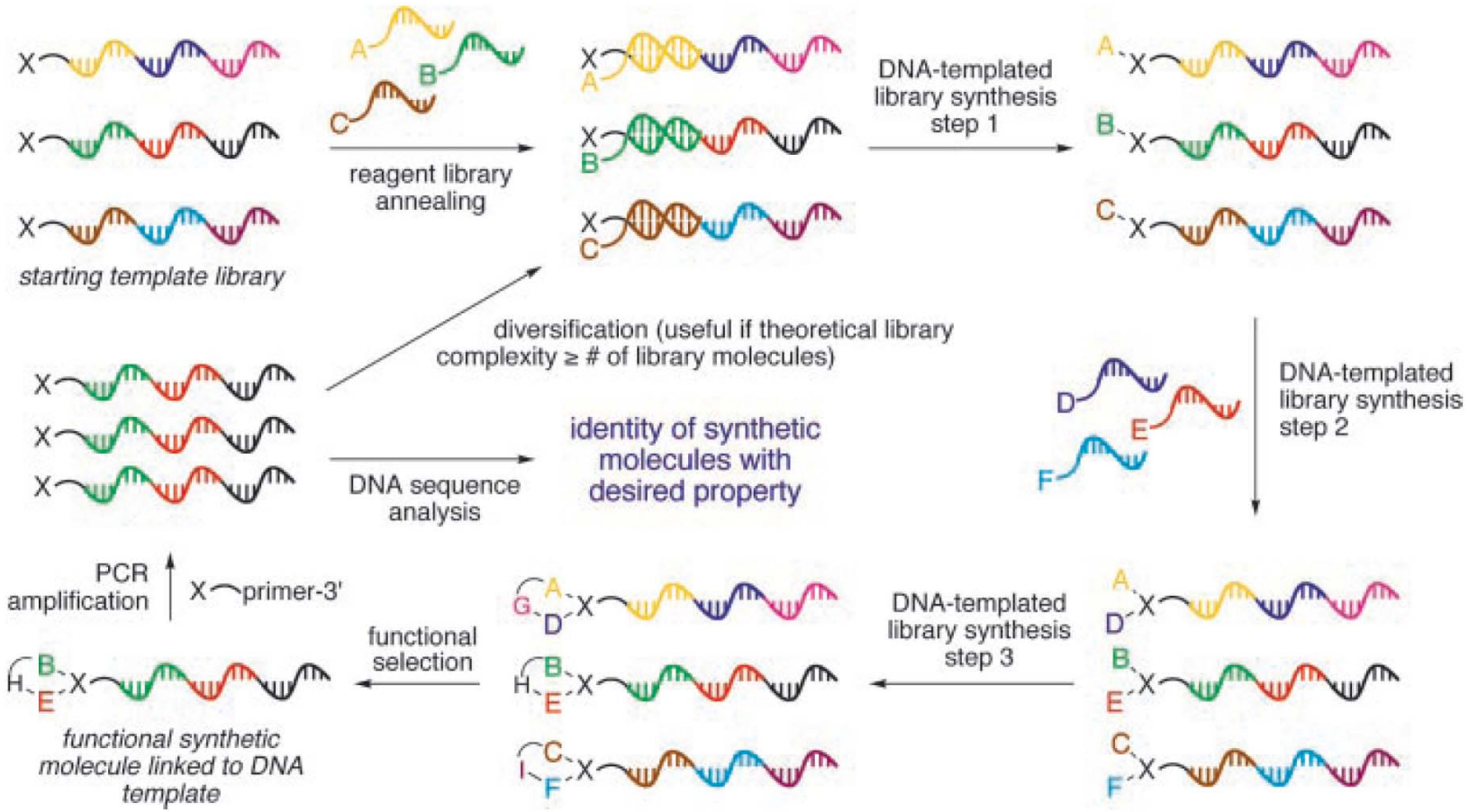
DNA-Templated Synthesis: "Coding" for Multistep Synthesis

-Each "codon" on the template compliments a region on the reagent strand.
-Excess reacted/unreacted reagent is removed by biotin/streptavidin affinity removal.
-Each step yields between 52 and 85%.
-As little as 10^{-18} mol of product can be amplified by PCR (bottom right), allowing, in theory, "selection".



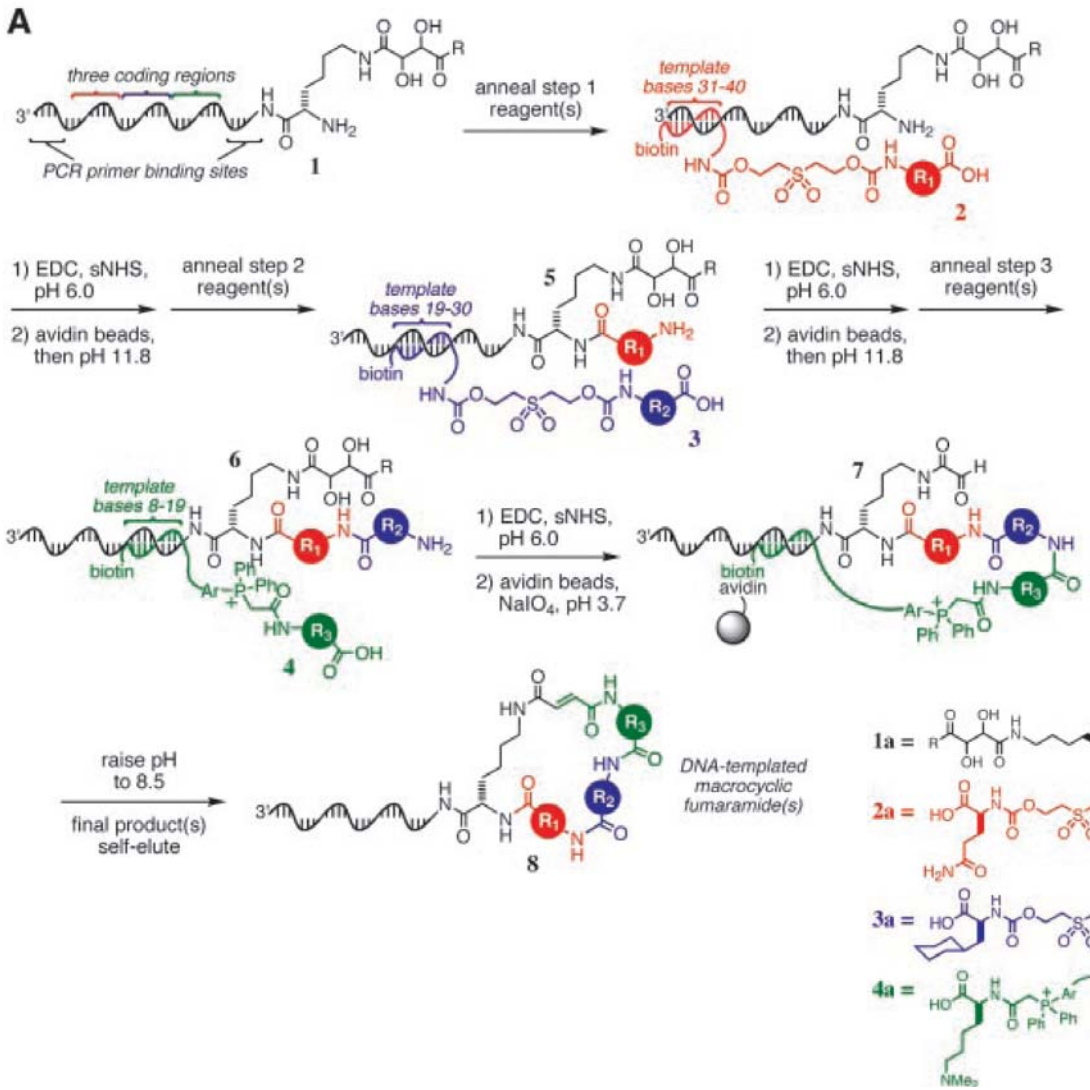
Liu and Co-workers *J. Am. Chem. Soc.* **2002**, *124*, 10304

DNA-Templated Synthesis: The “Evolution” of Small Molecules



Liu and Co-workers *Science* **2004**, *305*, 1601

DNA-Templated Synthesis: The “Evolution” of Small Molecules

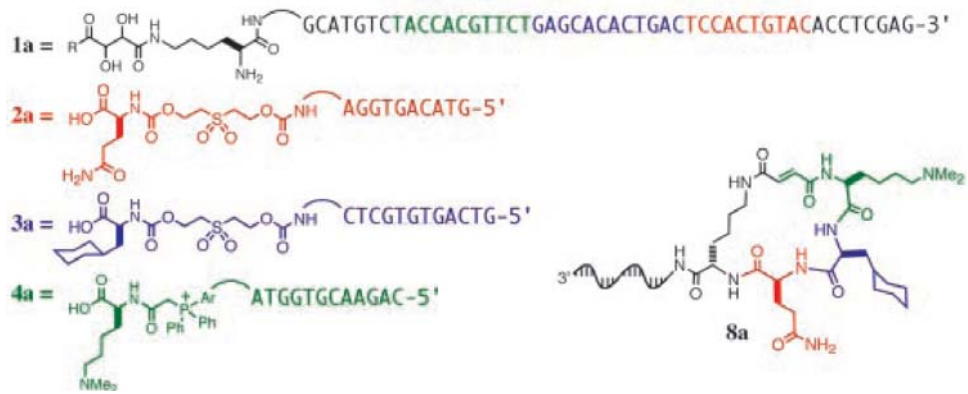


-Engineer each substrate with a DNA sequence that codes for the order or type of reagent to react with.

-pH changes effect “deprotection” to enable reagent by-products to be removed.

-Final macrocyclization is Wittig olefination.

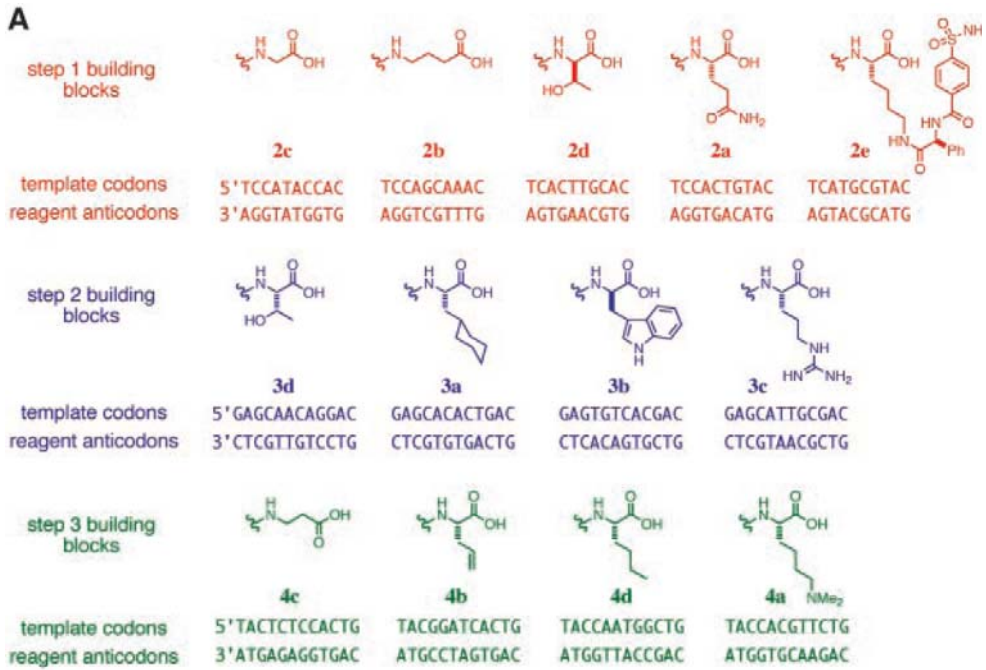
-”Selection” would give amplifiable DNA whose sequence would reveal structure of active binding molecule.



An example set of templates to give 8a

Liu and Co-workers *Science* **2004**, *305*, 1601

DNA-Templated Synthesis: “Selection” By Protein Affinity



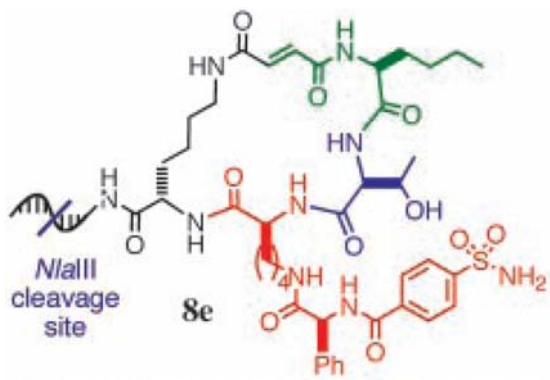
-A 65 member library of macrocycles is is generated from the possible combinations of building blocks and reagents.

-100 fmol of each is assayed for binding to carbonic anhydrase, a well-characterized protein.

-Carbonic anhydrase is immobilized and incubated with the library (x2).

-Following “selection”, the DNA corresponding to the bound molecules is amplified and sequenced to reveal the identity of the binding molecule.

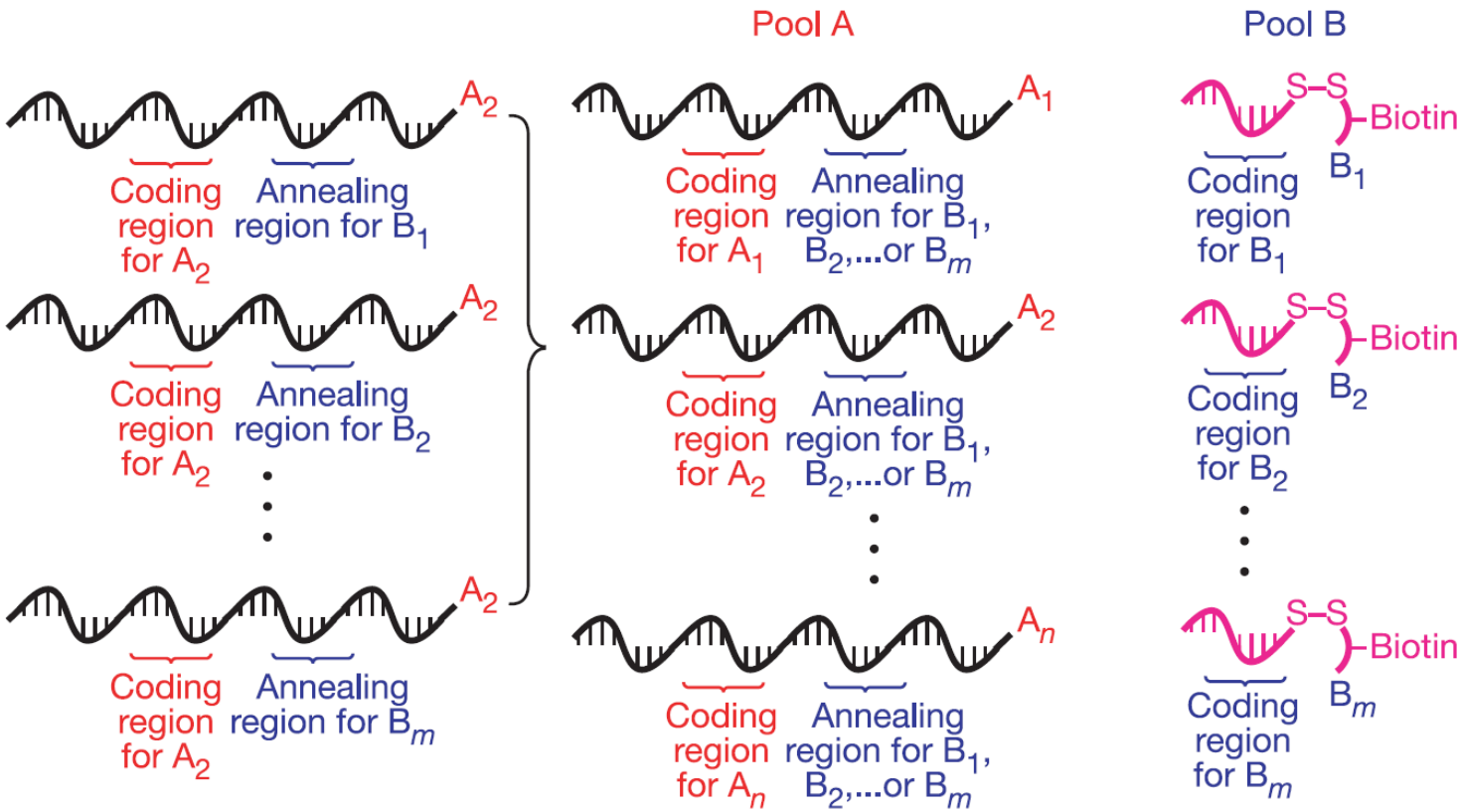
-In this case, **8e** uniquely binds with carbonic anhydrase and was selected from a 65 member library.



Liu and Co-workers *Science* **2004**, *305*, 1601

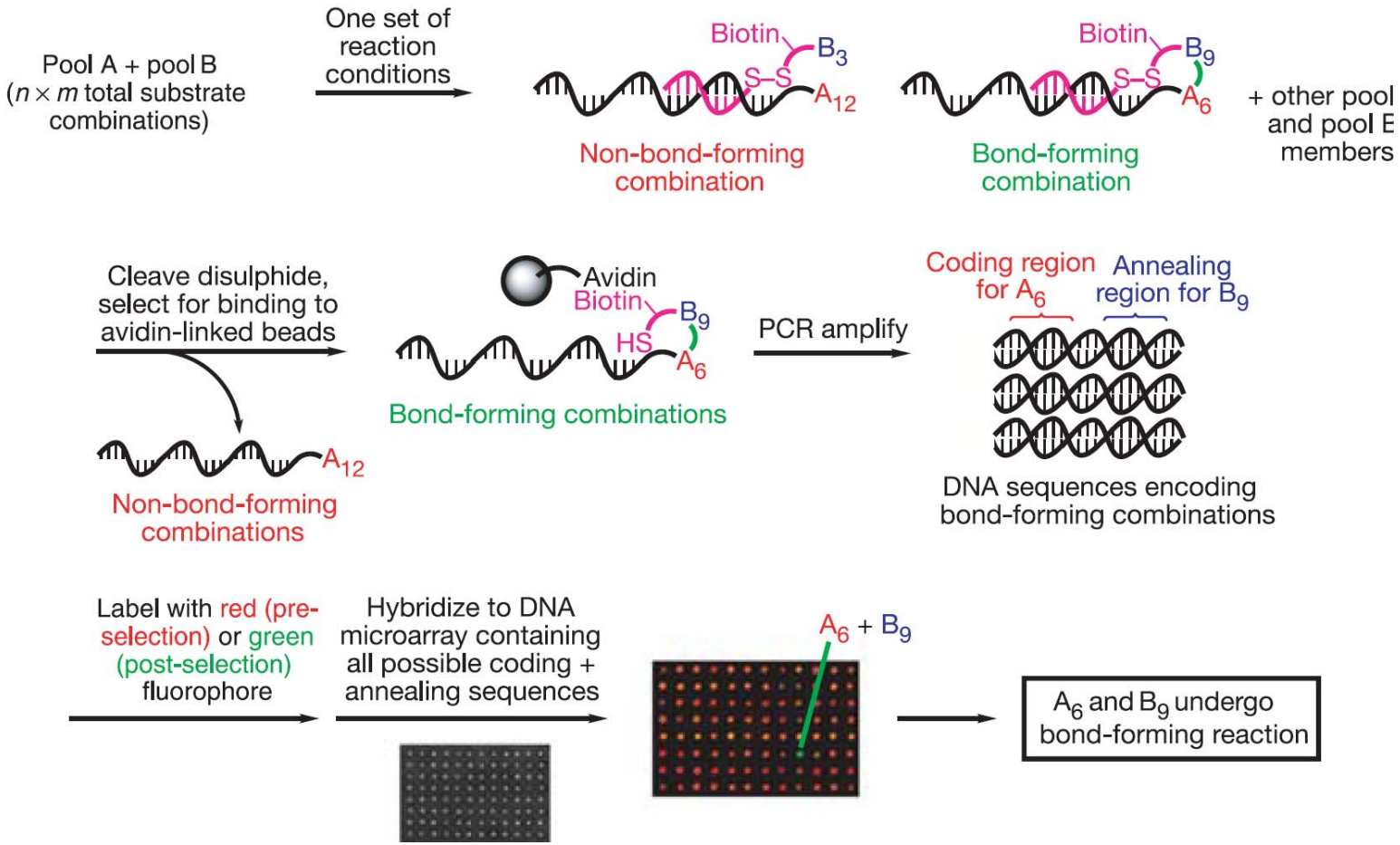
DNA-Templated Synthesis: Reaction Discovery

-DNA-templating technology can, in principle, be used for reaction discovery.
-The ultra-small scale and amplification technologies can make the process extremely compact.



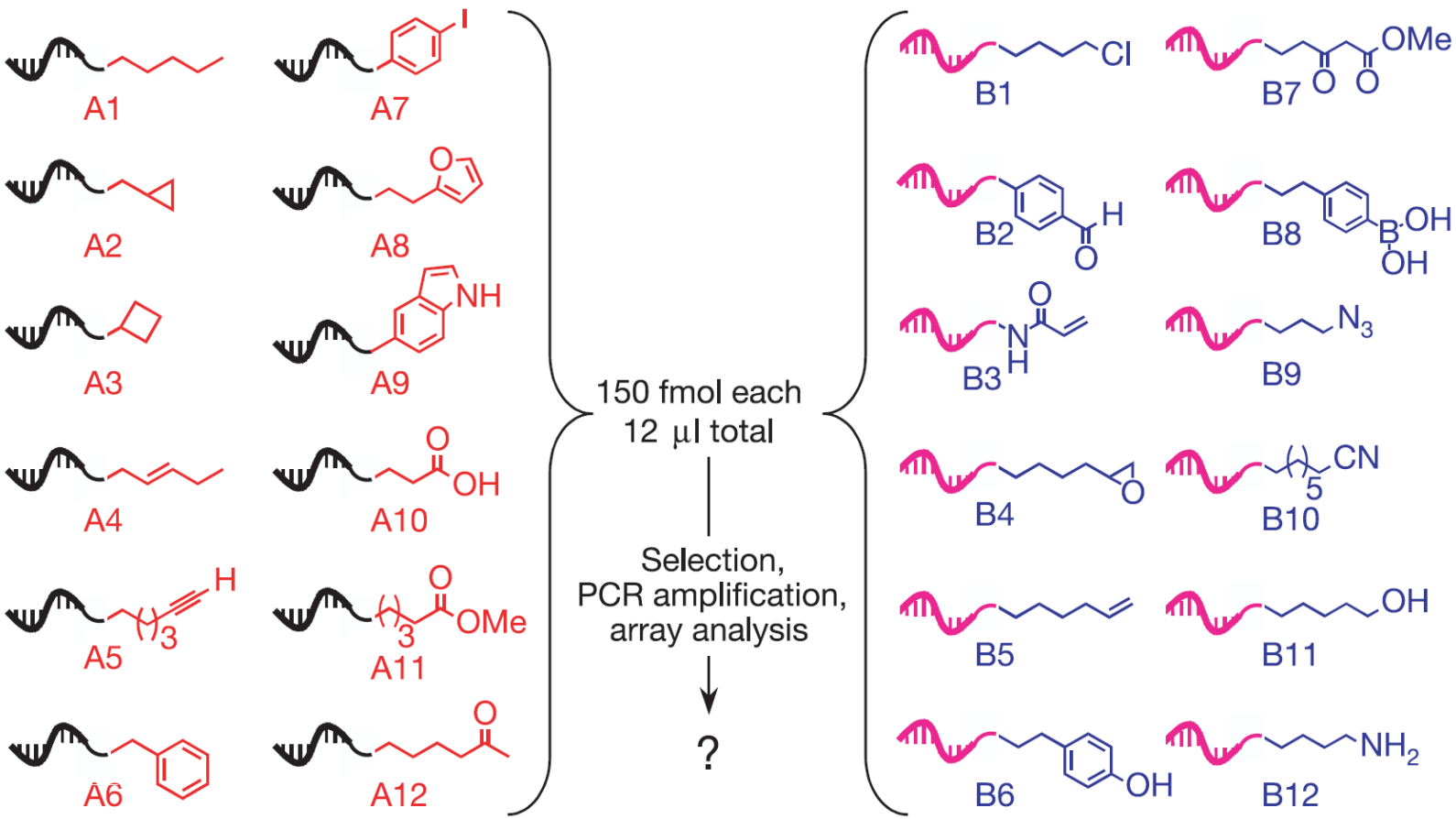
Liu and Co-workers *Nature* **2004**, *431*, 545

DNA-Templated Synthesis: Reaction Discovery



Liu and Co-workers *Nature* **2004**, *431*, 545

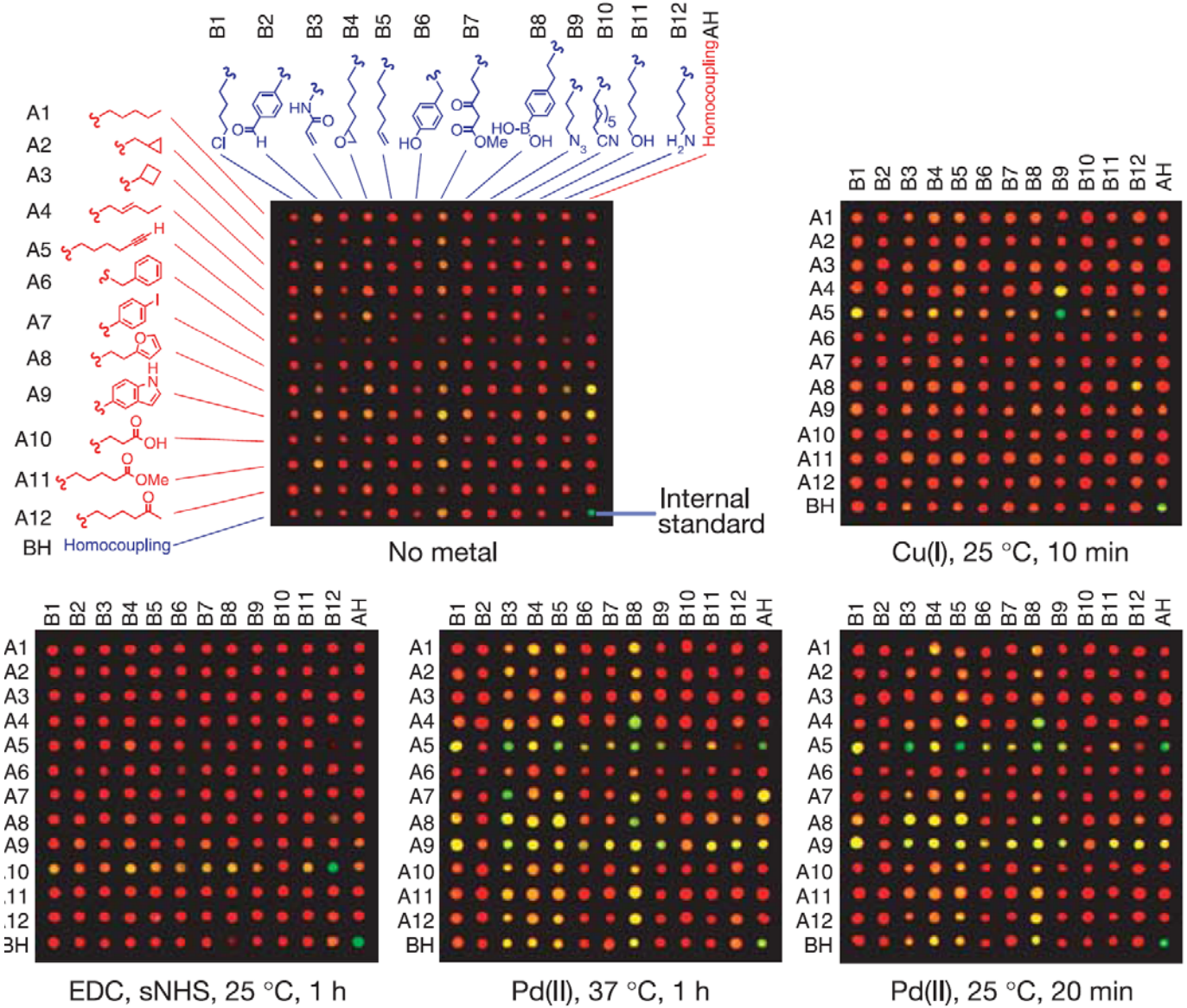
DNA-Templated Reaction Discovery



-A nanomole of substrate allows for evaluation of more than 168,000 reaction conditions.

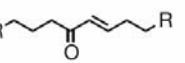
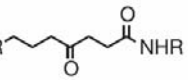
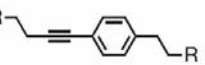
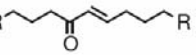
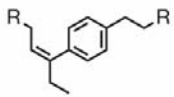
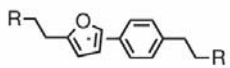
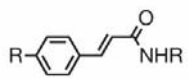
Liu and Co-workers *Nature* **2004**, *431*, 545

DNA-Templated Synthesis: Reaction Discovery



Liu and Co-workers *Nature* **2004**, *431*, 545

DNA-Templated Synthesis: Reaction Discovery

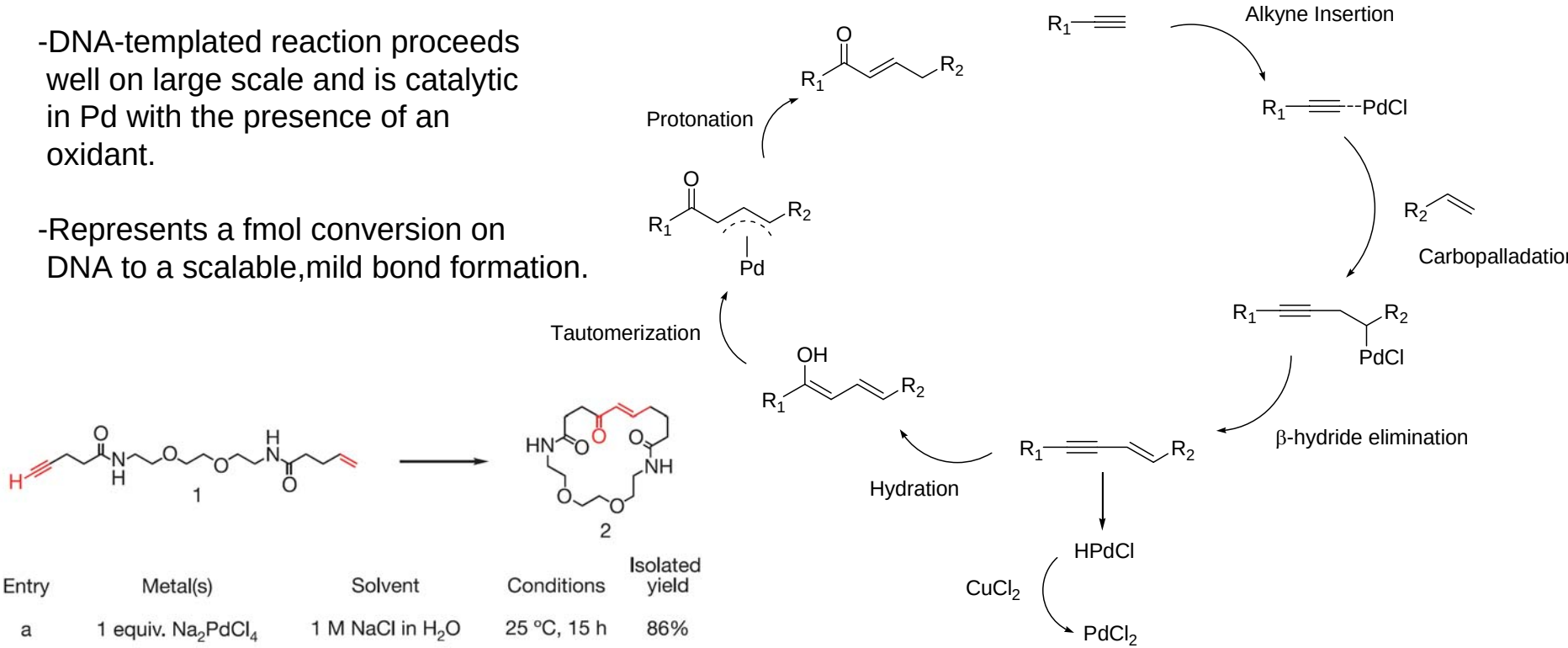
Substrates		Green/red fluorescence ratios 37°C	Green/red fluorescence ratios 25°C	DNA-templated yields (%) 37°C	DNA-templated yields (%) 25°C	Product consistent with observed mass
A5	B5	2.7	3.7	35	31	
A5	B3	3.5	3.1	28	20	
A5	B8	1.6	1.9	36	34	
A5	Homocoupling	2.6	2.7	45	42	
A4	B8	3.0	2.8	57	39	
A8	B8	1.8	<1.2	30	10	
A8	B3	1.8	<1.2	19	<10	
A7	B3	3.6	<1.2	39	14	

Liu and Co-workers *Nature* **2004**, *431*, 545

DNA-Templated Synthesis: Reaction Discovery

-DNA-templated reaction proceeds well on large scale and is catalytic in Pd with the presence of an oxidant.

-Represents a fmol conversion on DNA to a scalable,mild bond formation.



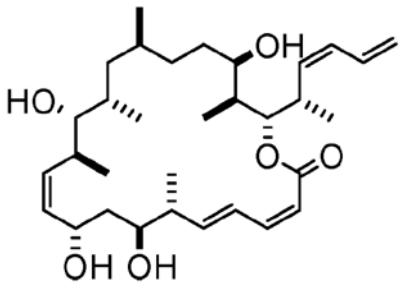
Entry	Metal(s)	Solvent	Conditions	Isolated yield
a	1 equiv. Na_2PdCl_4	1 M NaCl in H_2O	25 °C, 15 h	86%
b	5 mol% Na_2PdCl_4 1 equiv. $CuCl_2$	100 mM NaCl in H_2O	25 °C, 2 h	90%
c	5 mol% Na_2PdCl_4 1 equiv. $CuCl_2$	9:1 THF: H_2O	25 °C, 4 h	91%
d	15 mol% Na_2PdCl_4 1 atm O_2	9:1 THF: H_2O	25 °C, 14 h	73%
e	1 equiv. $CuCl_2$	100 mM NaCl in H_2O	25 °C, 4 h	0%
f	1 equiv. $CuCl_2$	100 mM NaCl in H_2O	25 °C, 4 h	0%

Liu and Co-workers *Nature* **2004**, *431*, 545

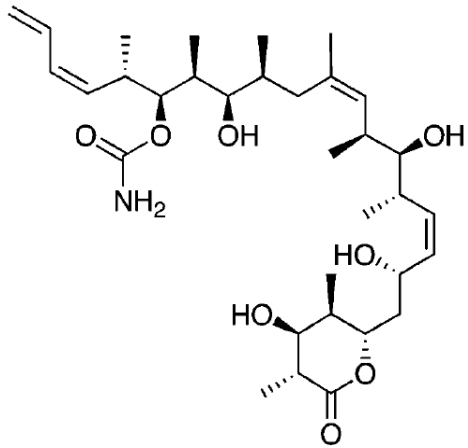
II. Into the Genome: Engineering Polyketide Synthase

Polyketide Biosynthesis: Signal-Driven Modular Synthesis in a Cell

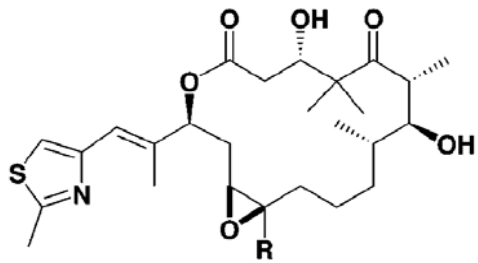
-About 10,000 polyketide structures have been identified to date.



Dictyostatin



Discodermolide



Epothilones

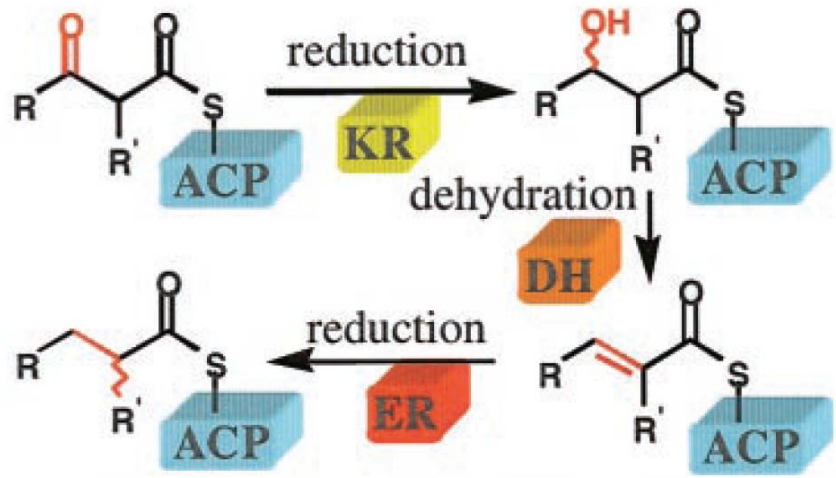
-Theoretical analysis of all variables involved in polyketide biosynthesis suggest that there are more than 1,000,000,000 possible structures.

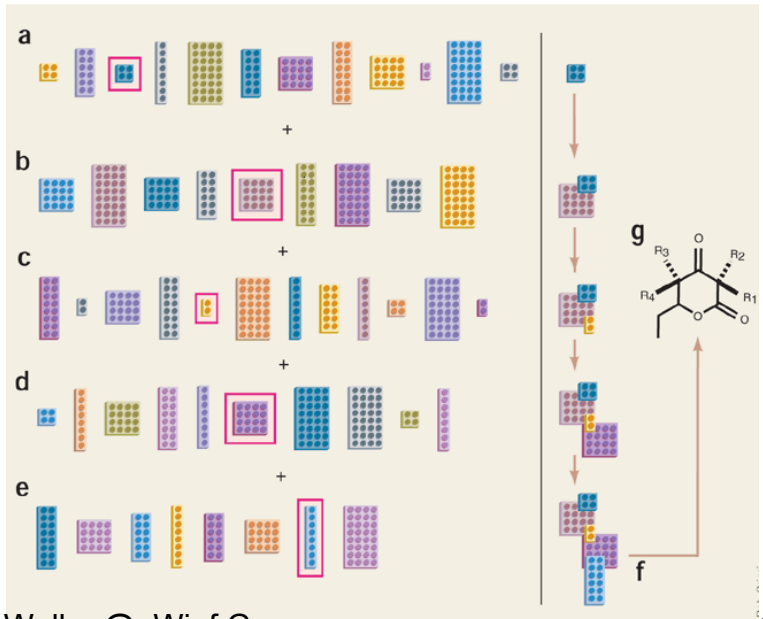
-Aldol methodology has been extensively developed to generate polyketides, but new bondmaking regimes are defining the edge of this field.

Hatzimanikatis, V., Broadbelt, L. J. and Co-workers *J. Am. Chem. Soc.* **2005**, *127*, 9930

Polyketide Biosynthesis: Signal-Driven Modular Synthesis in a Cell

-Polyketides are generated in assembly-line type fashion.
-Modular sections of enzyme (polyketide synthase, PKS) direct attachment and manipulation of each ketide unit.
-Polyketides are generally biologically active at numerous biological targets.





ACP: Acyl Carrier Protein
KR: Ketoreductase
DH: Dehydrase
ER: Enoylreductase
-epimerase, transferase, cyclase, thioesterase, etc.

Sherman, D. H. *Nature Biotechnology* **2005**, *23*, 1083

Khosla and Co-workers *Science* **1998**, 282, 63

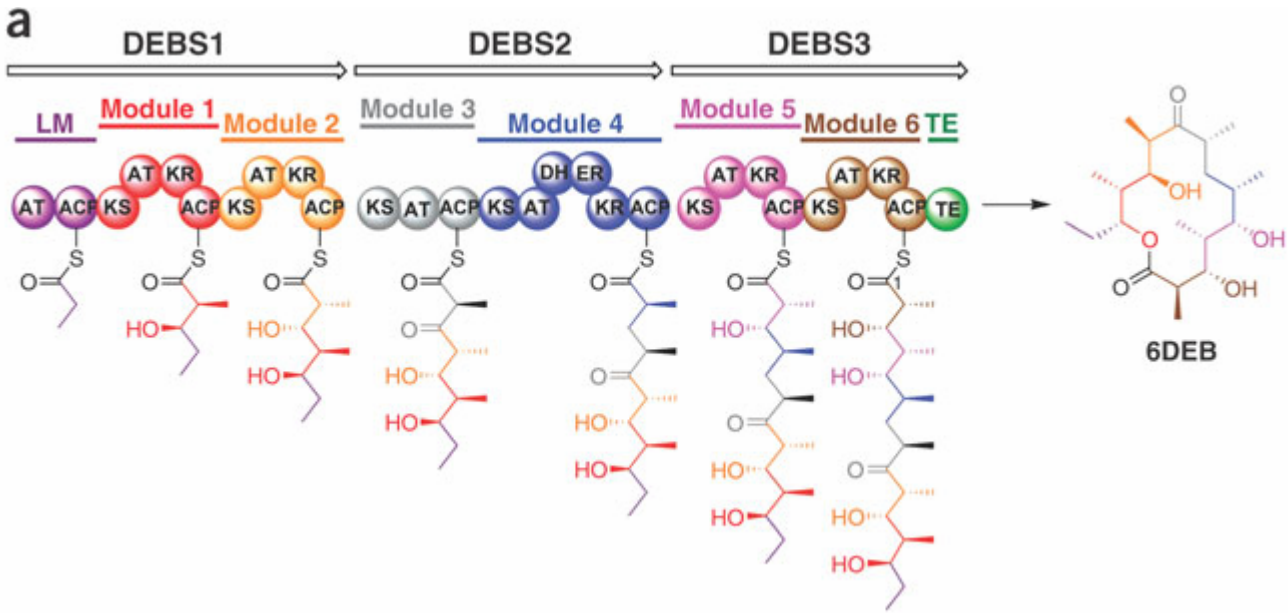
Polyketide Biosynthesis: Signal-Driven Modular Synthesis in a Cell

-6-deoxyerythronolide B (DEBS) PKS was one of the early targets for deciphering and mutation.

-3 proteins carry two extender modules each.

-Specific domains were added or deleted resulting in different levels of processing and/or chain elongation.

-This work culminated in a 50-member library synthesis, obtained by tedious genetic manipulation.



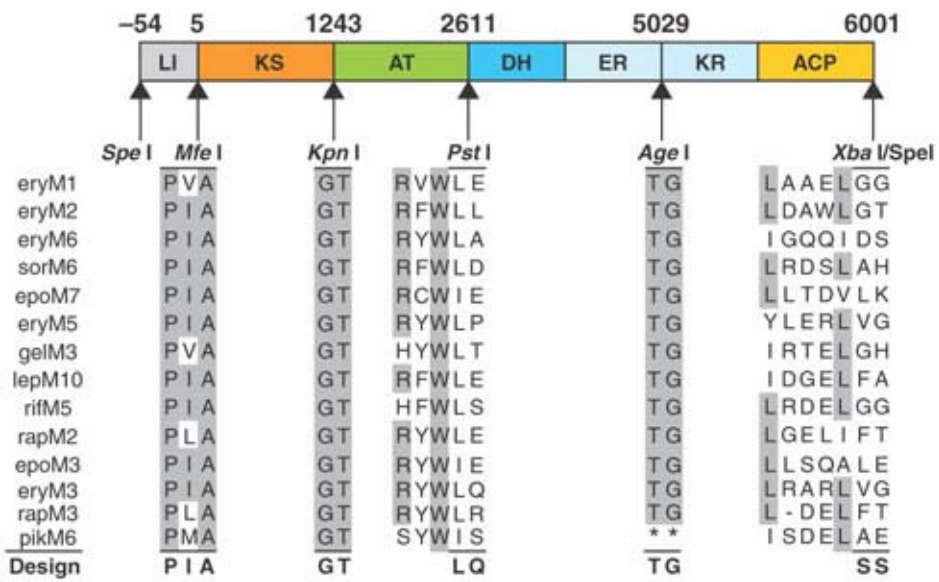
McDaniel and Co-workers *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 1846

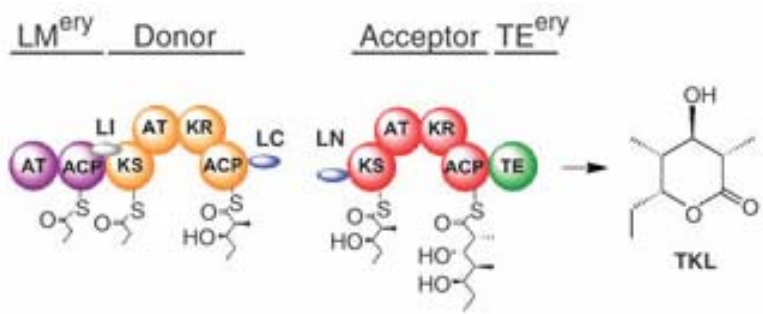
Engineering Polyketide Synthesis : Choosing The Signals

-A survey of PKS genes revealed key conservation which could serve as restriction domains and lend “authenticity” to the gene.

-Variable DNA was constructed for various sequencing of domains.

-14 modules were generated and could be used as cassettes and were paired in unnatural ways (11 x 14 = 154 possible ketide lactones) and placed into *E. Coli*.





Menzella and Co-workers *Nature Biotechnology* **2005**, *23*, 1171

Engineering Polyketide Synthesis : Choosing The Signals

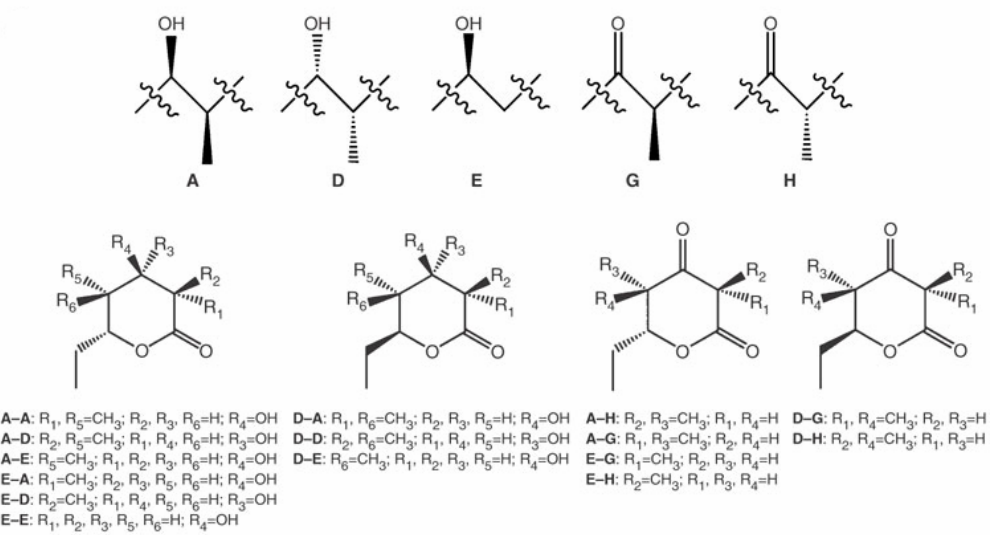
-After incubation for 72 h, LC/MS was used to study production of the triketide lactones.

-0.02 – 23 mg/L were produced in 72/154 combinations.

-MS revealed that all combinations functioned as a donor or acceptor at least once, indicating that each is “catalytically competent”.

	LN-eryM1-TE [A]	LN-eryM2-TE [D]	LN-eryM6-TE [D]	LN-sorM6-TE [D]	LN-epoM7-TE [D]	LN-eryM5-TE [D]	LN-gelM3-TE [D]	LN-lepM10-TE [D]	LN-rifM5-TE [D]	LN-rapM2-TE [E]	LN-epoM3-TE [E]	LN-eryM3-TE [G]	LN-rapM3-TE [G]	LN-pikM6-TE [H]	None
LM-eryM1-LC [A]	nd	18.5	1.22	nd	nd	1.95	0.02	nd	nd	nd	nd	12.1	0.2	12.1	nd
LM-eryM2-LC [D]	nd	0.32	0.96	nd	nd	0.2	nd	nd	nd	nd	nd	23.5	2	4.1	nd
LM-eryM6-LC [D]	0.09	0.23	0.53	0.12	0.23	0.22	0.11	0.09	0.23	0.05	0.05	2.21	0.56	0.53	nd
LM-sorM6-LC [D]	0.13	nd	1.17	nd	nd	0.12	nd	nd	nd	nd	nd	2.89	0.01	0.05	nd
LM-epoM7-LC [D]	nd	0.14	0.54	nd	nd	0.09	0.08	nd	nd	nd	nd	0.23	0.01	nd	nd
LM-eryM5-LC [D]	nd	0.28	3.94	nd	nd	1.23	nd	nd	0.12	nd	nd	2.39	0.1	0.21	nd
LM-gelM3-LC [D]	0.11	0.29	1.96	nd	nd	[0.11]	0.05	nd	nd	nd	nd	0.33	0.1	0.66	nd
LM-lepM10-LC [D]	0.08	nd	[0.33]	nd	nd	0.31	nd	nd	nd	nd	nd	0.01	nd	0.01	nd
LM-rifM5-LC [D]	0.22	0.31	0.66	nd	nd	[0.13]	nd	nd	0.31	nd	nd	5.12	0.1	0.49	nd
LM-rapM2-LC [E]	0.09	nd	0.09	0.09	nd	nd	nd	nd	nd	nd	nd	0.01	0.15	0.01	nd
LM-epoM3-LC [E]	0.01	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0.25	nd	nd	nd
None	nd	nd	[0.85]	nd	nd	[0.09]	nd	nd	nd	nd	nd	nd	nd	nd	nd

> 10 mg/l 0.1 ≤ 10 mg/l < 0.1 mg/l



-Proof-of-concept study identifying flexibility and promiscuity in module pairing.
-Use of common restriction sites enables rapid gene production in modular fashion.
-1.5 million possible base pairs in PKS genes were analyzed.

Menzella and Co-workers *Nature Biotechnology* **2005**, *23*, 1171

Bondmaking At The Edge: Fusing Natures Code With Synthesis

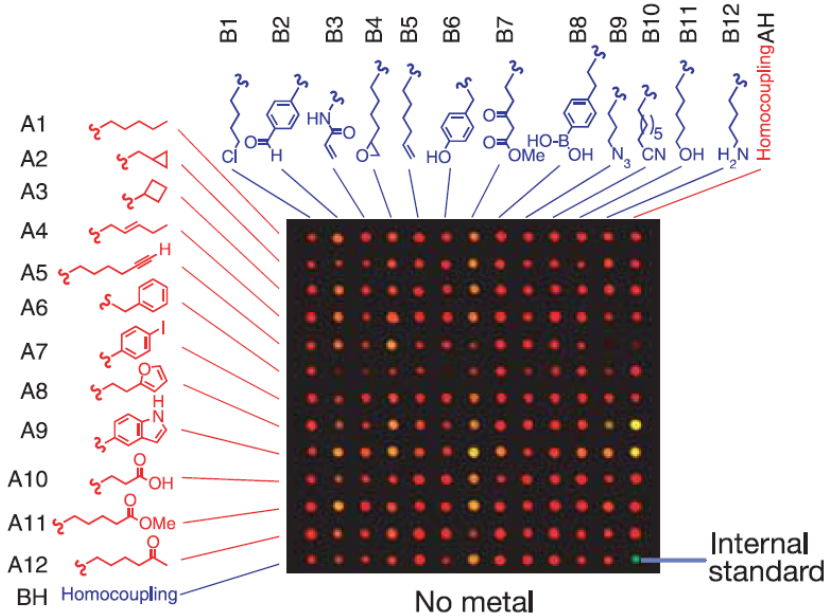
Library of Congress

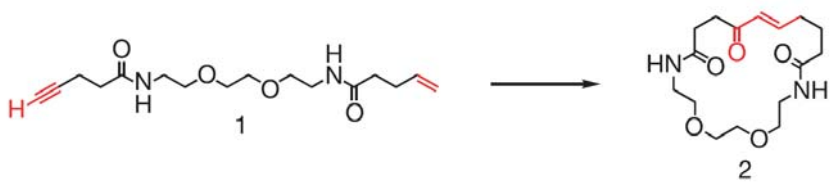
Friedrich Wöhler

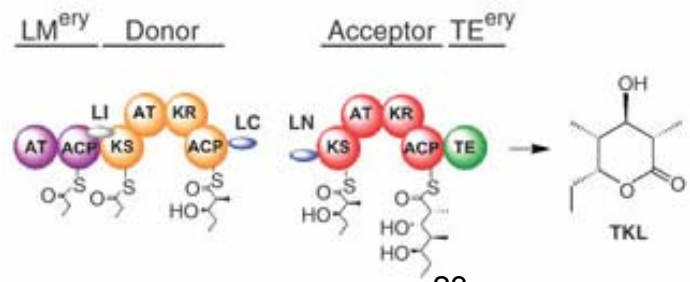
Ordinary Professor of Chemistry

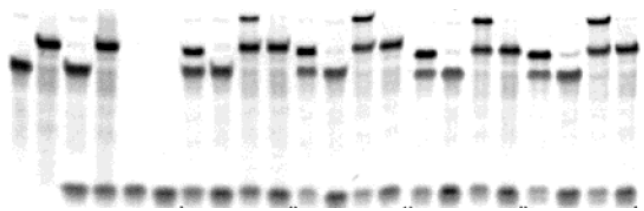
University of Göttingen, 1836 - 1882

177 Years





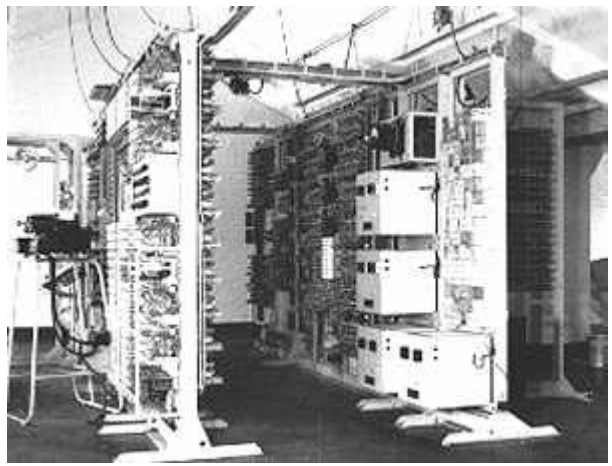




Code Breaking: Crack the Code – Win the War

ENIGMA In Use

Bletchley Park, England - ULTRA



“Colussus”

German ENIGMA

-Can breaking the biological signal code help us win the war against disease?

I. Speaking The Launguage of Infection: Targeting HIV Signaling

HIV Therapy: Protease and Reverse Transcriptase Inhibitors

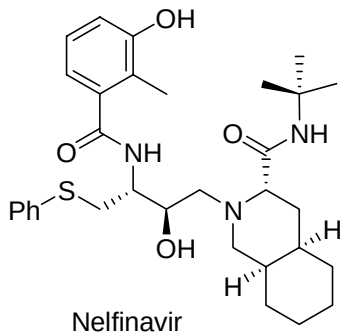
-HIV protease (pictured) and reverse transcriptase inhibitors have been key in the modern treatment of HIV.

-Most, if not all, are substrates for P-glycoprotein (Pgp) efflux from cells.

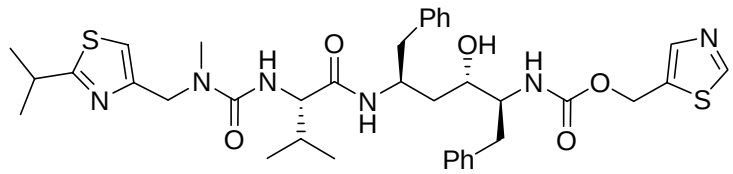
-Concerns exist about the long term use of these drugs due to the development of resistant strains of the disease.

-Regardless, these types of inhibitors cannot destroy HIV in infected patients.

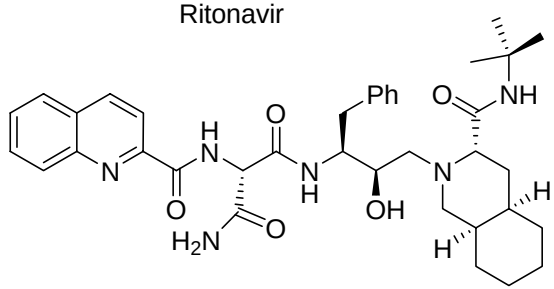
-Continued development of these types of therapies will not cure HIV.



Nelfinavir



Ritonavir



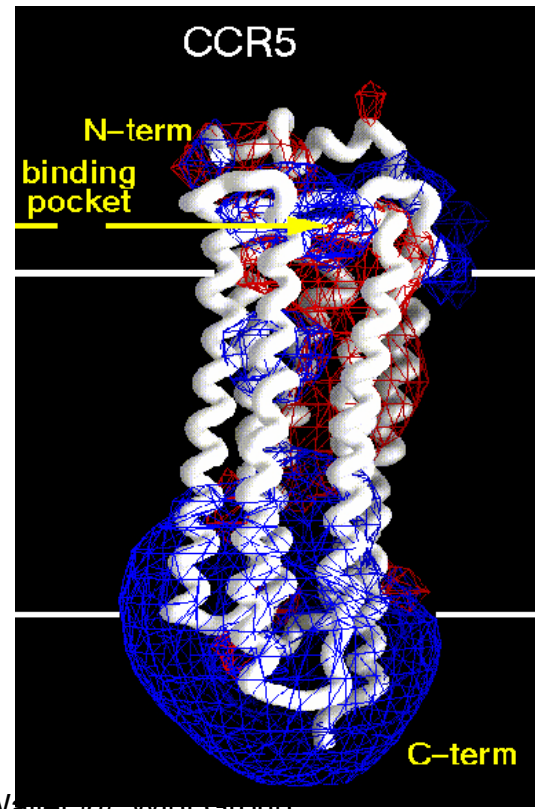
Saquinavir

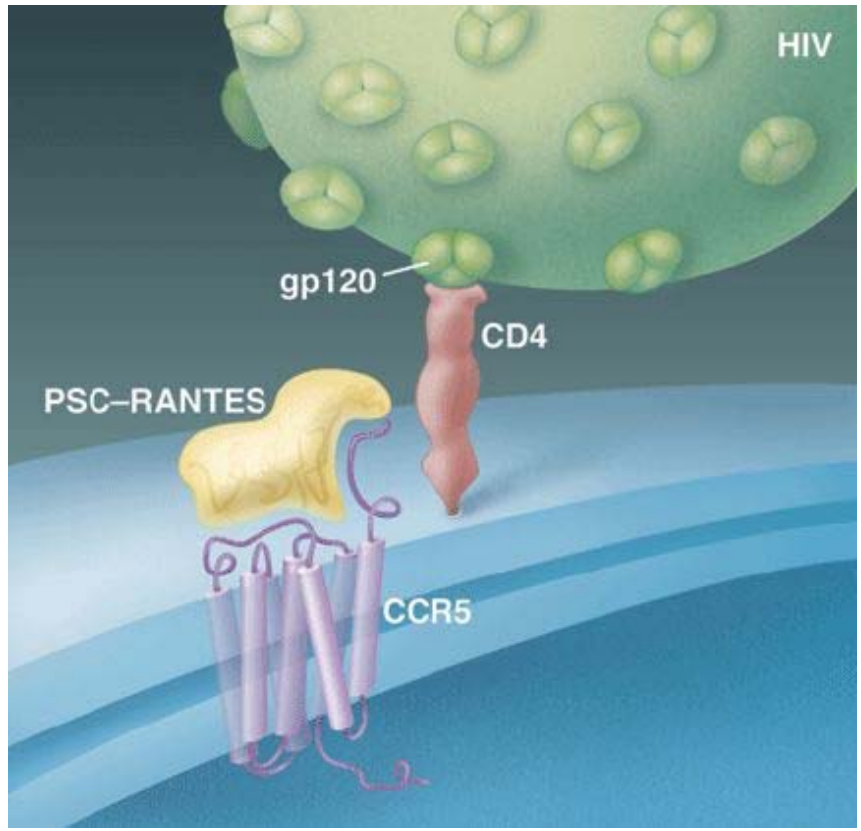
-With the conventional therapies failing, a new method of disrupting HIV infection is needed.

-De Clercq, E. *J. Med. Chem.* **2005**, *48*, 1297

HIV Therapy: Targeting the Infection Mechanism

-To enter cells, HIV must bind the CCR5 receptor through a poorly understood signal path.
-Binding must occur in an orchestrated fashion with CD4 and surface glycoproteins.
-HIV binding is accomplished using glycoprotein gp120 and the CD4 protein.





-Early work focused on the characterization of the proteins invloved in this mechanism.

-Hendrickson *Nature* **1998**, *393*, 648

-De Clercq, E. *J. Med. Chem.* **2005**, *48*, 1297

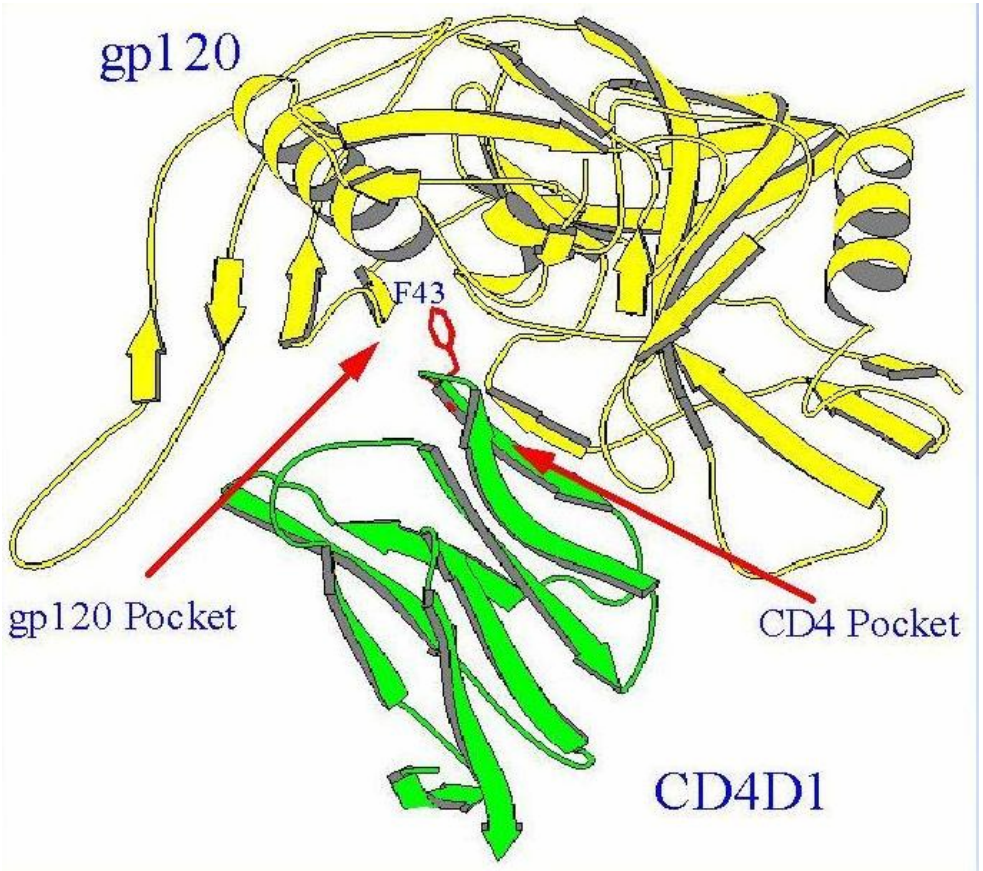
Small Molecule Disruption: CCR5 Antagonists As Anti-HIV Therapy

-The pre-entry complex structure was determined by X-ray analysis.

-All factors involved in the binding process are not known.

-There is substantial reorganization of gp120 once bound to CD4.

-CCR5 binding then occurs and allows access to the cell.



-The CCR5 pathway constitutes an excellent target for disrupting binding and/or signalling.

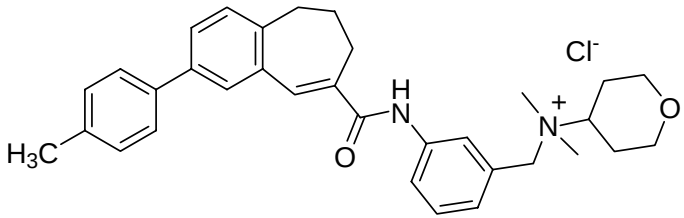
-Hendrickson *Nature* **1998**, *393*, 648

Small Molecule Disruption: CCR5 Antagonists As Anti-HIV Therapy

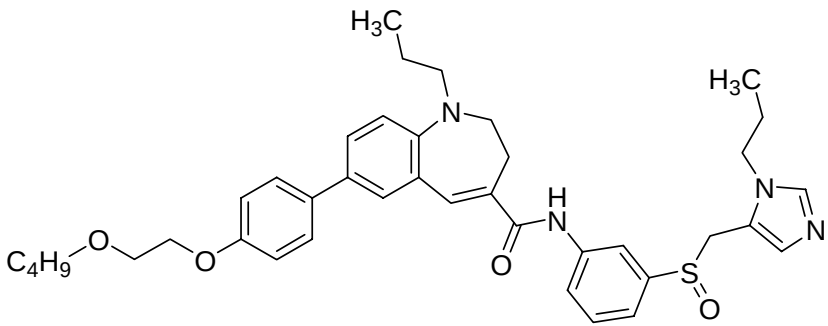
-The first non-peptidic CCR5 antagonist reported was TAK-779.

-TAK-779 inhibits HIV replication with an IC_{50} of 10 nM.

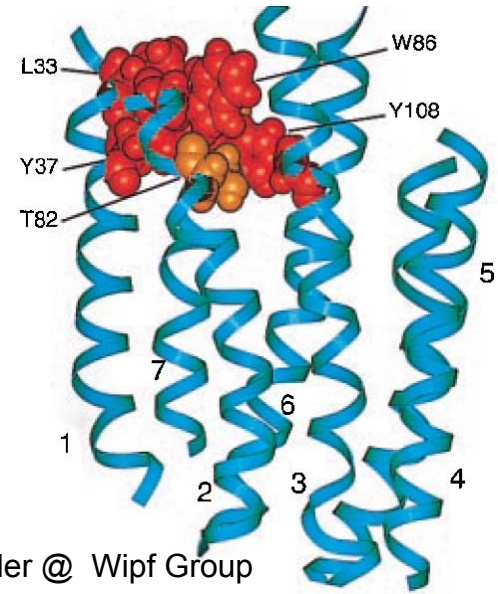
-TAK-779 is not orally bioavailable. TAK-220 (analogue shown) is orally bioavailable with comparable activity.



TAK-779



TAK-220 Analogue



-De Clercq, E. *J. Med. Chem.* **2005**, *48*, 1297

-Dragic and Co-workers *Proc. Natl. Acad. Sci.* **2000**, *97*, 5639

Small Molecule Disruption: CCR5 Antagonists As Anti-HIV Therapy

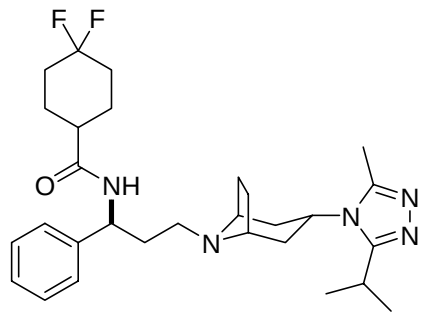
-Maraviroc is extremely potent against a wide range of HIV strains by inhibiting entry via CCR5 binding.

-Maraviroc has an IC_{90} of <10 nM and does not interfere with other entry sites on cells.

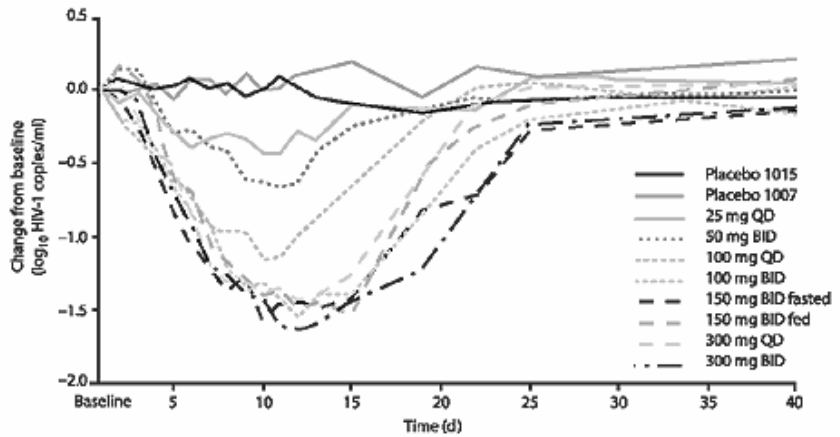
-Well tolerated in humans (up to 300 mg/day).

-After short regimens (10 day), viral load remained suppressed for about 10 days.

-Maraviroc is currently in Phase III clinical trials.



UK-427,857 (Maraviroc)



-Ridgway and Co-workers *Nature Medicine* Advanced Online Publication

II. Speaking The Language of Cellular Treason: Cancer Signaling

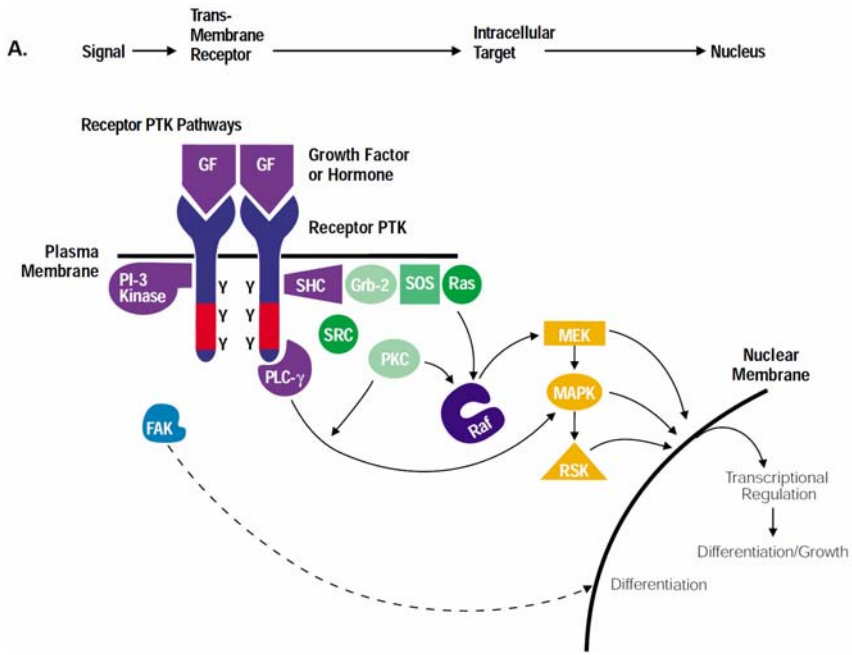
Cellular Signaling: Receptor Tyrosine Kinases (RTKs)

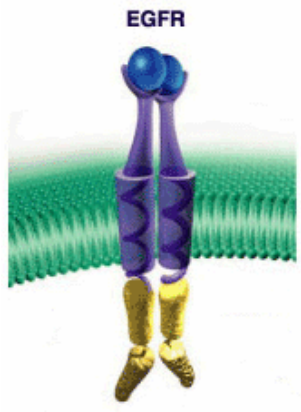
-RTKs are membrane spanning proteins and mediate a very wide variety of cellular events-differentiation, growth, metabolism, apoptosis, etc.

-Kinase activity is one component of a complex signal cascade within the cell, which is always initiated with binding at the receptor.

-Kinases act by phosphorylating specific tyrosine residues in target proteins using ATP, which continues the signal cascade.

-Eventually, the signals reach the nucleus and the encoded cellular event can then be carried out.





Promega Bioscience

Briges, A. J. *Chem. Rev.* **2001**, *101*, 2541

Cellular Signaling: Receptor Tyrosine Kinases (RTKs)

Transmembrane Receptor PTKs

PTK Enzyme Family	PTKs	Involvement in Cellular Signaling (Disease States)	Representative References
Axl	Axl, Mer/Nyk, Rse	integrin signaling	Georgescu, M.M. *et al.* (1999) *Mol.Cell. Biol.* **19,** 1171.
Eph	CEK5, CEK8, EBK, ECK, EEK, EHK-1, EHK-2, ELK, EPH, ERK, HEK, MDK2, MDK5, SEK	growth, differentiation, neurobiology (epithelial cell cancer)	Binns, K.L. *et al.* (2000) *Mol. Cell. Biol.* **20,** 4791.
Epidermal growth factor receptor (EGFR)	EGF-R, HER2/neu, HER3, HER4, ErbB, ErbB2, ErbB3, ErbB4, Xmrk, DER, Let23	growth (breast and squamous cell carcinoma, psoriasis)	Di Fulvio, M. *et al.* (2000) *J. Endocrinol.* **166,** 173.
Fibroblast growth factor receptor (FGFR)	FGF-R1, FGF-R2/BEK/CEK3, FGF-R3/CEK2, FGF-R4/TKF, KGF-R	growth, differentiation (colon and prostate cancer)	Lopez, M. and Korc, M. (2000) *J. Biol. Chem.* **275,**15933.
Hepatocyte growth/ scatter factor receptor (HGFR)	HGF-R, MET, RON, SEA, SEX	growth, differentiation (cancer)	Wallenius, V. *et al.* (2000) *Am. J. Path.* **156,** 821.
Insulin receptor (IR)	I-R, IGFI-R	differentiation, metabolism (diabetes)	Shao, J. *et al.* (2000) *Diabetes* **49,** 589.
Nerve growth factor receptor (NGFR or Trk)	Trk A, Trk B, Trk C	neuronal differentiation, neurite outgrowth	Kaplan, D.R. and Miller, F.D. (2000) *Curr. Opin. Neurobiol.* **10,** 381.
RET	RET	B cell, kidney and neural crest development (Hirschsprung's disease, multiple endocrine neoplasia, medullary thyroid cancer)	Tansey, M.G. *et al.* (2000) *Neuron* **25,** 611.
Platelet-derived growth factor receptor (PDGFR)	PDGFα-R, PDGFβ-R, CSF1-R/FMS, SCF-R/KIT, VEGF-R/FLT, NEK/FLK1, FLT3/FLK2/STK-1	growth, differentiation, cytokine and vascular regulation (leukemia, gliomas)	Iwamoto, H. *et al.* (2000) *J. Lab. Clin. Med.* **135,** 406.

Cellular Signaling: The ErbB Signal Network

-Many tumors contain genes that encode for RTK which are mutated, amplified, or the proteins are overexpressed.

-Often, the kinases in tumor and healthy cells are different, and can therefore be selectively targeted, much unlike traditional chemotherapy.

-Epidermal growth factor receptor (EGFR or ErbB) is disregulated in 60% of solid tumors.

-A multibillion dollar industry is to be had in this area.

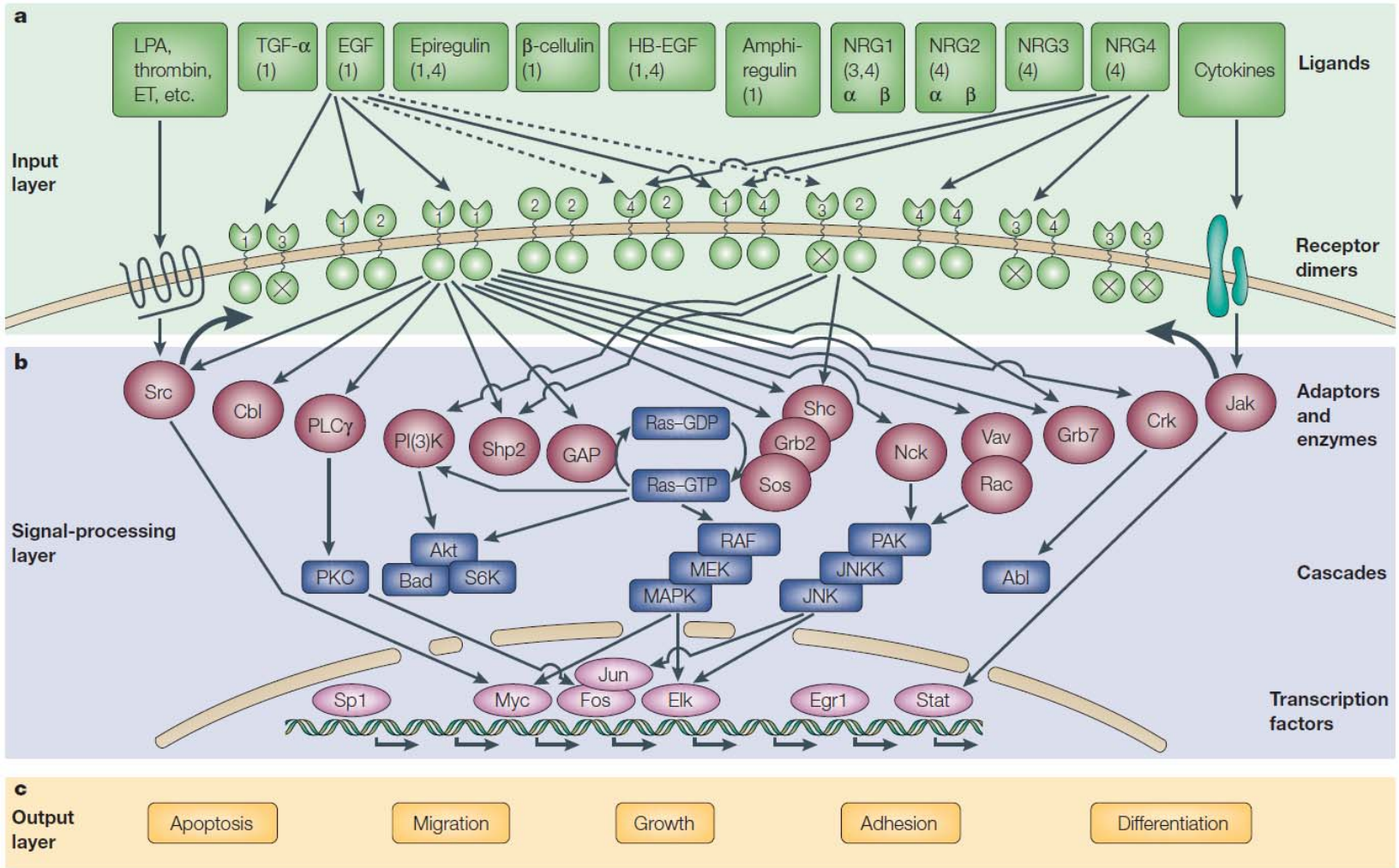
-We will focus on the erbB family of RTKs and how small molecule manipulation of this signal pathway may revolutionize medicine.

Receptors			
ErbB1	Overexpression	Head and neck, breast, bladder, prostate, kidney, non-small-cell lung cancer	Significant indicator for recurrence in operable breast tumours; associated with shorter disease-free and overall survival in advanced breast cancer; may serve as a prognostic marker for bladder, prostate, and non-small-cell lung cancers
	Overexpression	Glioma	Amplification occurs in 40% of gliomas; overexpression correlates with higher grade and reduced survival
	Mutation	Glioma, lung, ovary, breast	Deletion of part of the extracellular domain yields a constitutively active receptor
ErbB2	Overexpression	Breast, lung pancreas, colon oesophagus, endometrium, cervix	Overexpressed owing to gene amplification in 15–30% of invasive invasive ductal breast cancers Overexpression correlates with tumour size, spread of the tumour to lymph nodes, high grade, high percentage of S-phase cells, aneuploidy and lack of steroid hormone receptors
ErbB3	Expression	Breast, colon gastric, prostate, other carcinomas	Co-expression of ErbB2 with ErbB1 or ErbB3 in breast cancer improves predicting power
	Overexpression	Oral squamous cell cancer	Overexpression correlates with lymph node involvement and patient survival
ErbB4	Reduced expression	Breast, prostate	Correlates with a differentiated phenotype
	Expression	Childhood medullo-blastoma	Co-expression with ErbB2 has a prognostic value

(TGF-α, transforming growth factor-α; NRG1, neuregulin-1; HB-EGF, heparin-binding epidermal growth factor)

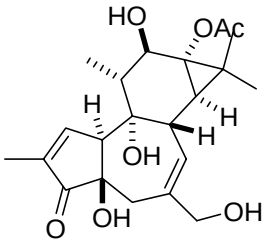
Yarden and Co-workers *Nature Reviews Molecular Cell Biology* **2001**, *2*, 127

Cellular Signaling: The ErbB Signal Network

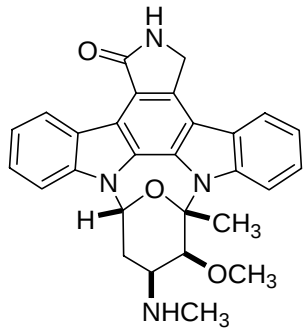


Yarden and Co-workers *Nature Reviews Molecular Cell Biology* **2001**, *2*, 127

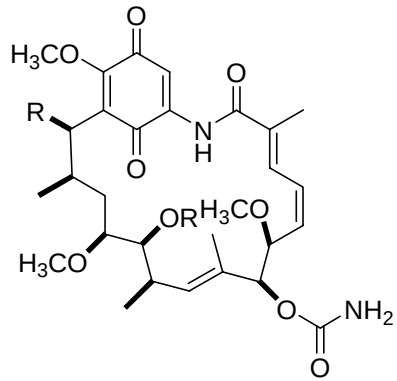
Cellular Signaling: ErbB Signal Network Inhibitors



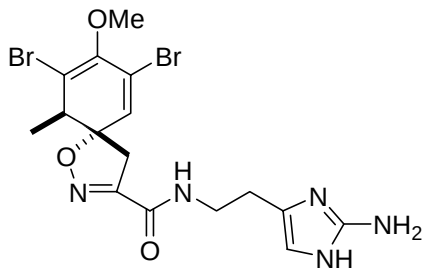
Phorbol Esters
Euphorbiae
Potent Tumor Promoter



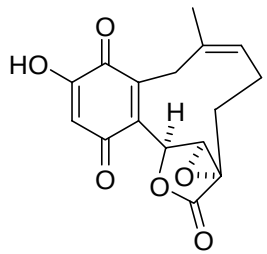
Staurosporin



Geldanamycin



Purealidin J



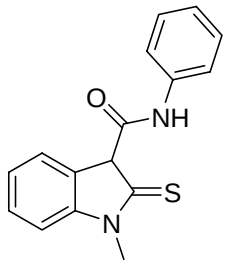
Clavilactone CD

…and many others, including Bistramide A

Briges, A. J. *Chem. Rev.* **2001**, *101*, 2541

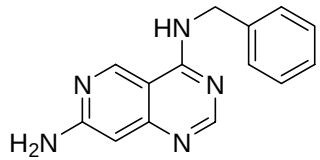
Cellular Signaling: ErbB Signal Network Inhibitors

Parke-Davis (Pfizer) is credited with pioneering the development of EGFR inhibitors….

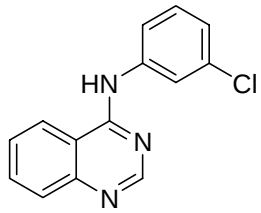


IC_{50}

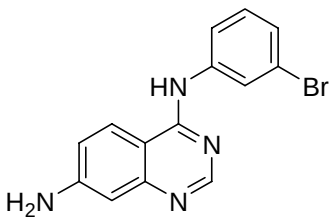
2 μM
Active against other kinases



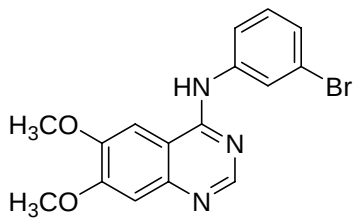
PD 0069896
1.5 μM (solid tumor)
Reversible, ATP Competitive



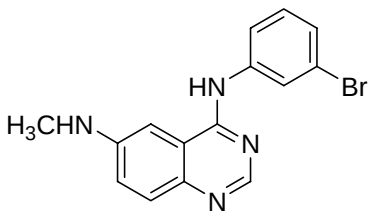
Zeneca
20-40 nM
EGFr selective



PD XXX
10 nM
Reversible, ATP competitive, selective



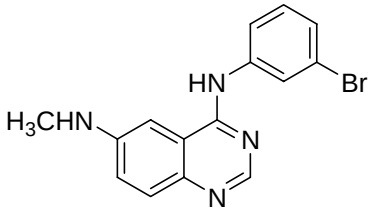
PD 0153035
29 pM, 14 nM (cellular)
Reversible, ATP competitive, selective
No other effects on GFs until 10 μM



PD 0158780
8 pM

Briges, A. J. *Chem. Rev.* **2001**, *101*, 2541

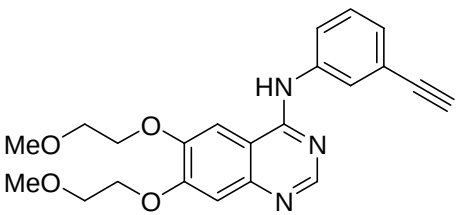
Cellular Signaling: ErbB Signal Network Inhibitors



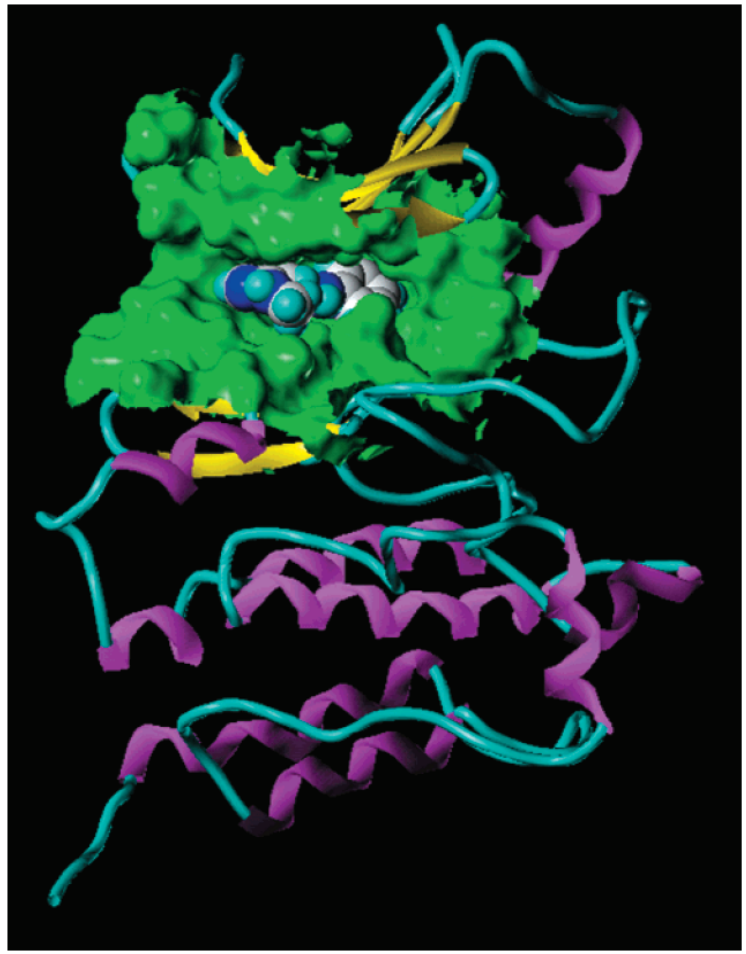
PD 0158780

-The extreme potency of these compounds (pM) and long lifetime in the binding pocket (>4 h) has been attributed to deep, tight binding followed by hydrophobic collapse.

-Solubility was a severe problem in animal testing, so hydrophilic adjustments were made resulting in the final reversible inhibitor (Tarceva). This would end the reversible inhibitor hunt at Pfizer.



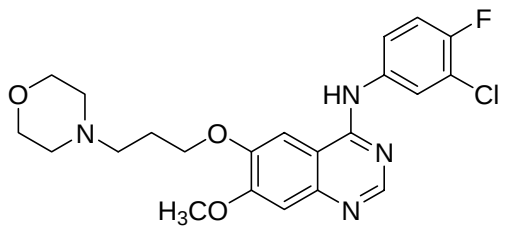
Tarceva
10 – 20 nM
Water soluble, orally available



PD 0158780 bound into the EGFr active site.

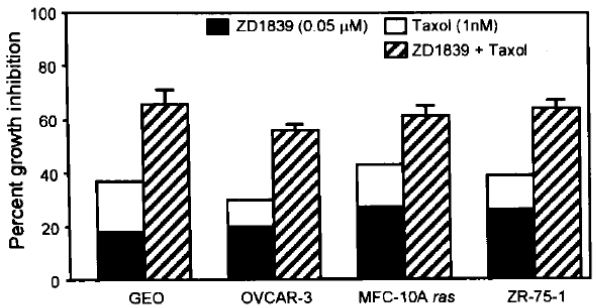
Briges, A. J. *Chem. Rev.* **2001**, *101*, 2541

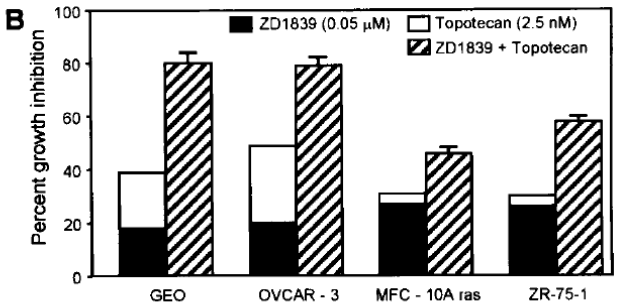
Cellular Signaling: ErbB Signal Network Inhibitors

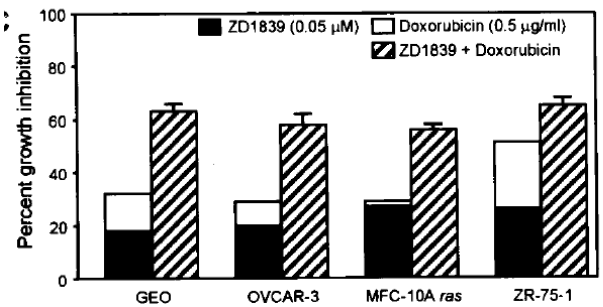


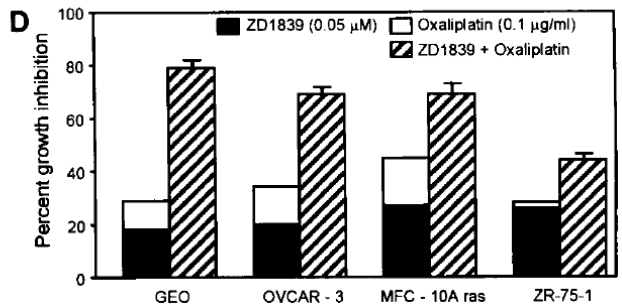
Iressa (Gefitinib), AstraZeneca
EGFR/ErbB1 Inhibitor (1 - 9 nM)
Orally available (1 pill a day)

- -Completely suppresses tumor growth in mice at 10 mg/kg/day.
- -Iressa can be dosed at 800 mg/day before limiting toxicity sets in.
- -At plasma levels of >200nM, complete tumor suppression and some shrinkage occurs in humans.
- -Higher dosing (above minimum can result in a 2-4 fold increase in apoptosis).
- -Both monotherapy and combination therapy is effective.



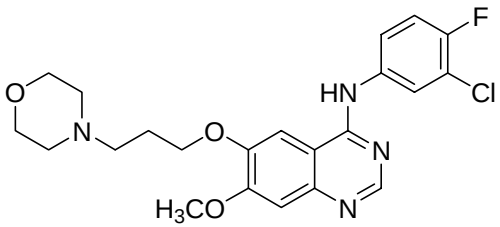




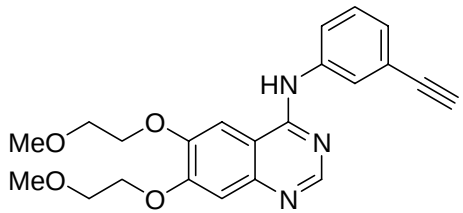


Ciardiello and Co-workers *Clin. Cancer Res.* **2000**, *6*, 2053

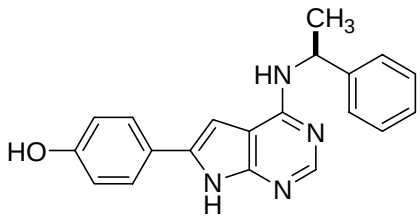
Cellular Signaling: ErbB Signal Network Inhibitors



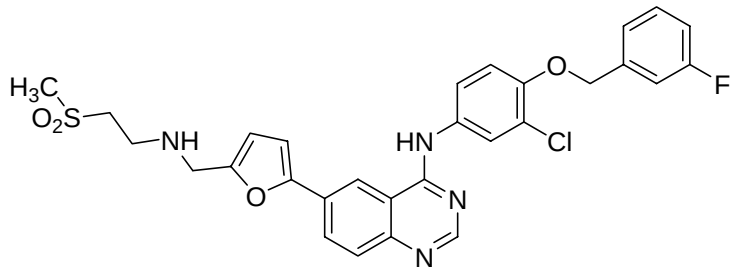
Iressa, AstraZeneca
Non-Small Cell Lung Cancer



Tarceva, OSI/Roche/Genentech
Non-Small Cell Lung Cancer



Novartis



GlaxoSmithKline
ErbB1/ErbB2 Inhibitor

-Most are active against breast, colon, blood, and digestive cancers and are still in clinical trials.
-Additionally, a number of monoclonal antibodies have been approved for use (Heceptin, Erbitux).

Cockerill and Co-workers *Curr. Top. Med. Chem.* **2002, 2**, 1001

Update - Cellular Signaling: EGFR Axon Regeneration

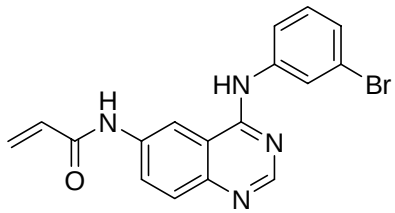
-Myelin/Chondroitin Sulfate Proteoglycans inhibit axon (neutrite) regeneration in the adult CNS. These molecules are natural at CNS injury sites.

-This inhibition mechanism is not understood.

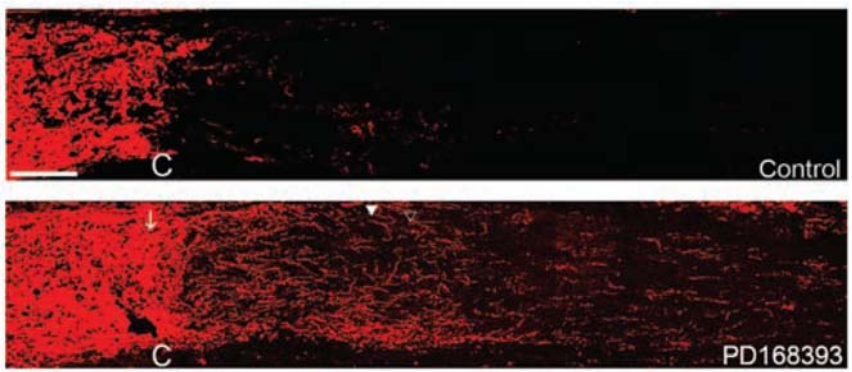
-Suppressing the EGFR/ErbB1 function (PD168393) blocks the inhibition of axon regeneration and promotes nerve fiber regeneration.

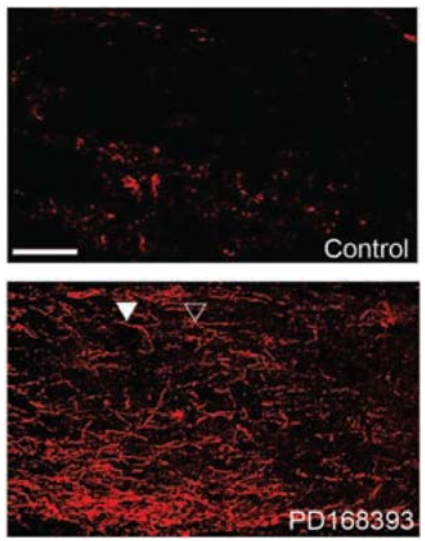
-This study also reveals that the regeneration inhibitors trigger EGFR phosphorylation, and that it is calcium dependent.

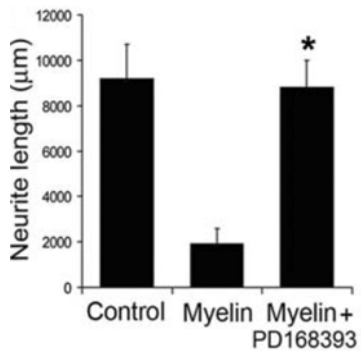
-This could be a promising treatment for CNS injury.



PD168393







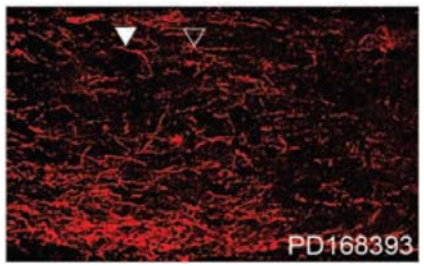
-Koprivica and Co-workers *Science* Advanced Online Publication

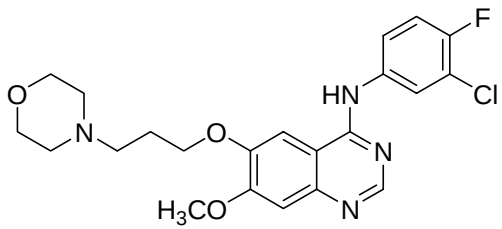
Cellular Signaling: Interference and Therapeutics

-Learning the signal pathways of disease can enable a new form of directed therapeutics for all types of diseases.

-Is this the new direction of drug discovery?

-Are we nature's Bletchley Park?





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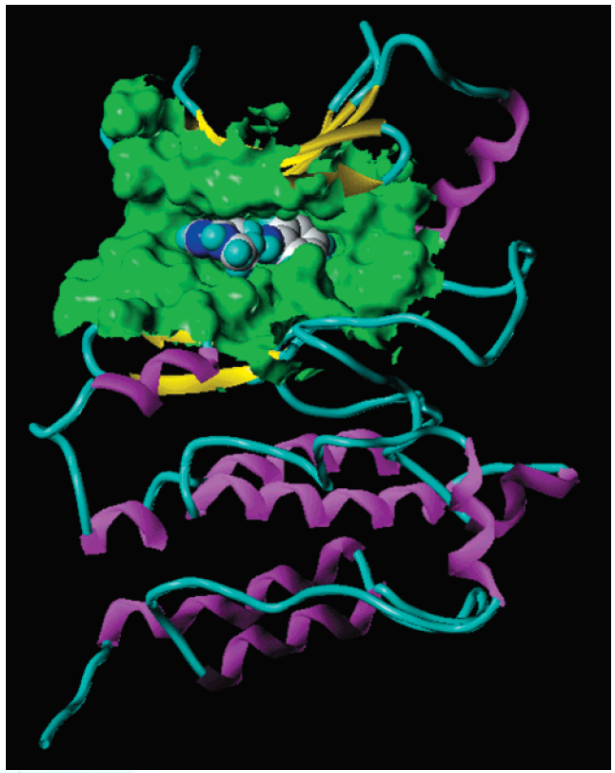

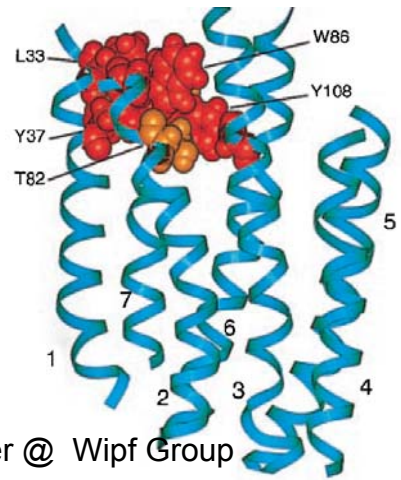

The Road Ahead