Discovery of BCR/ABL

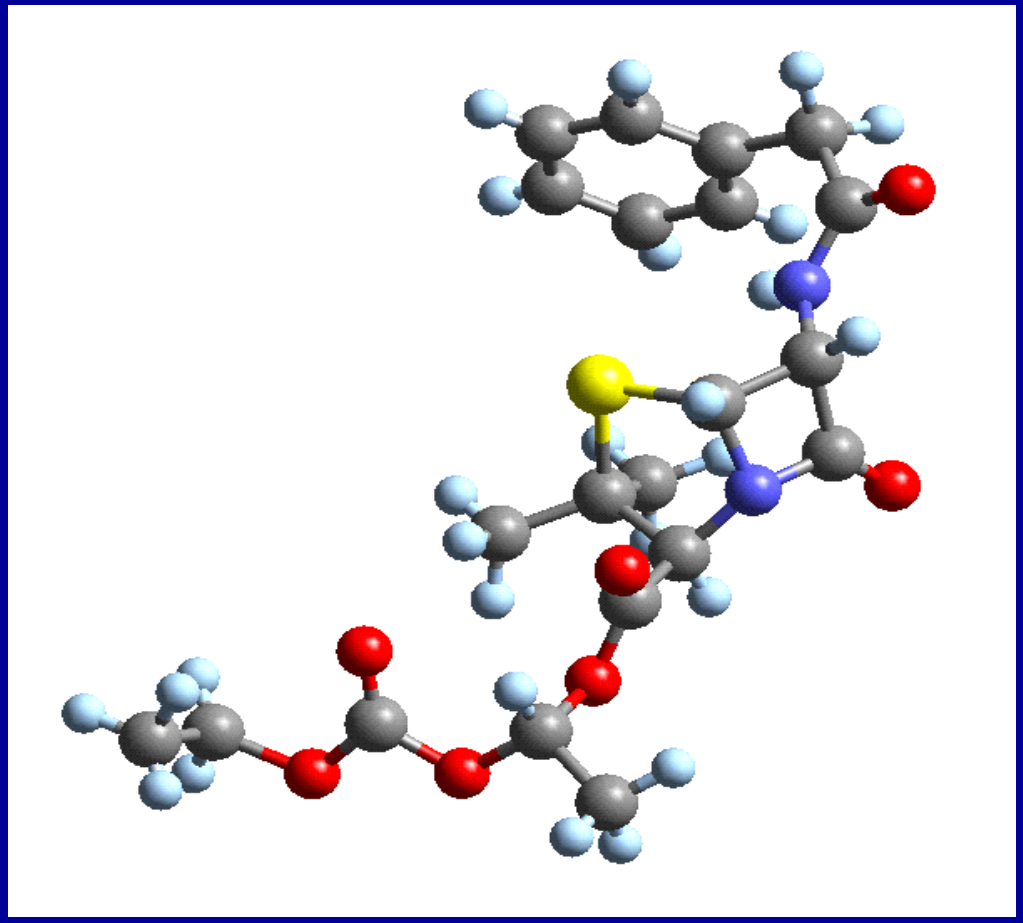
Robert Peter Gale MD, PhD

Fire?

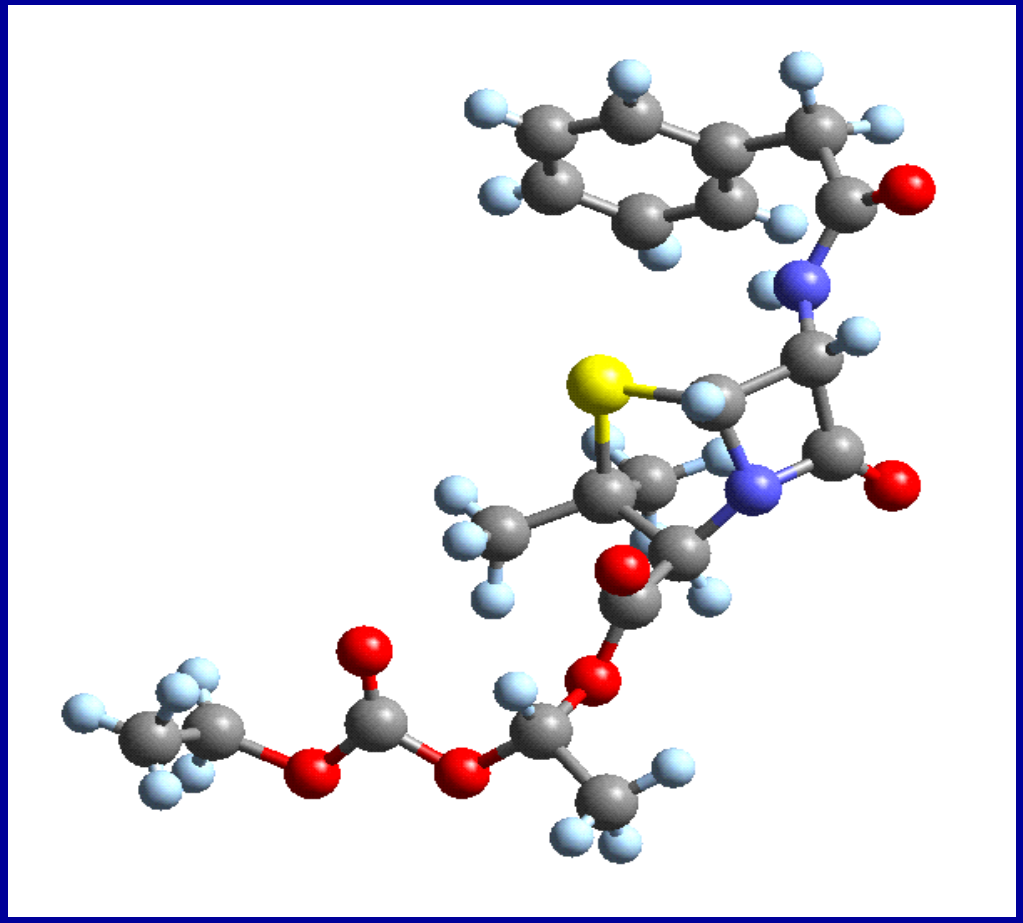
"Your father's a genius kids. First he discovered fire and now marshmallows."

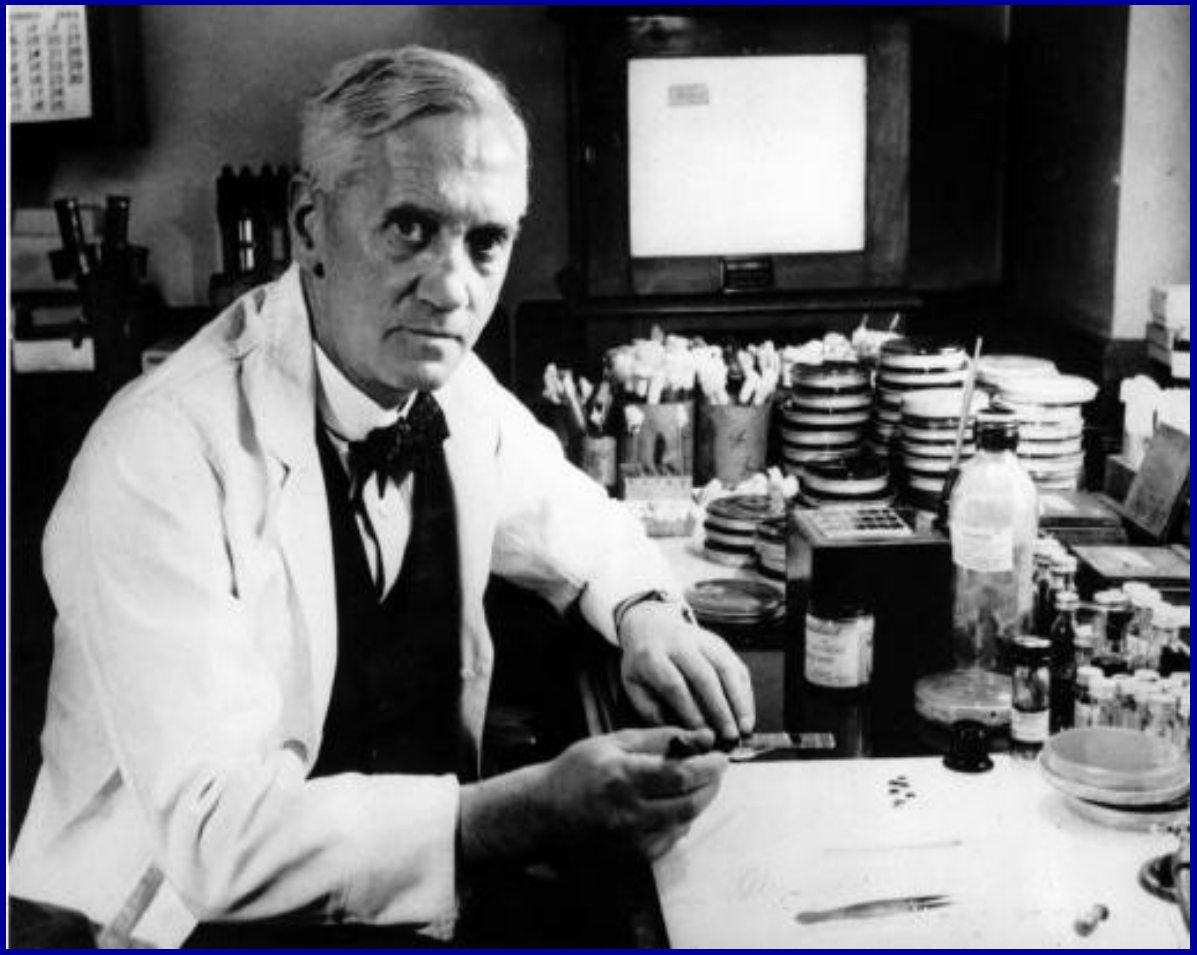
I am always so ready to take a favorable view of my powers that even when I am made a fool of I manage to twist this circumstance around until it becomes a proof of how exceptional I am. The ingenuities we practice so as to appear admirable to ourselves would suffice to invent fire twice on a lazy summer day.

Brendan Gill

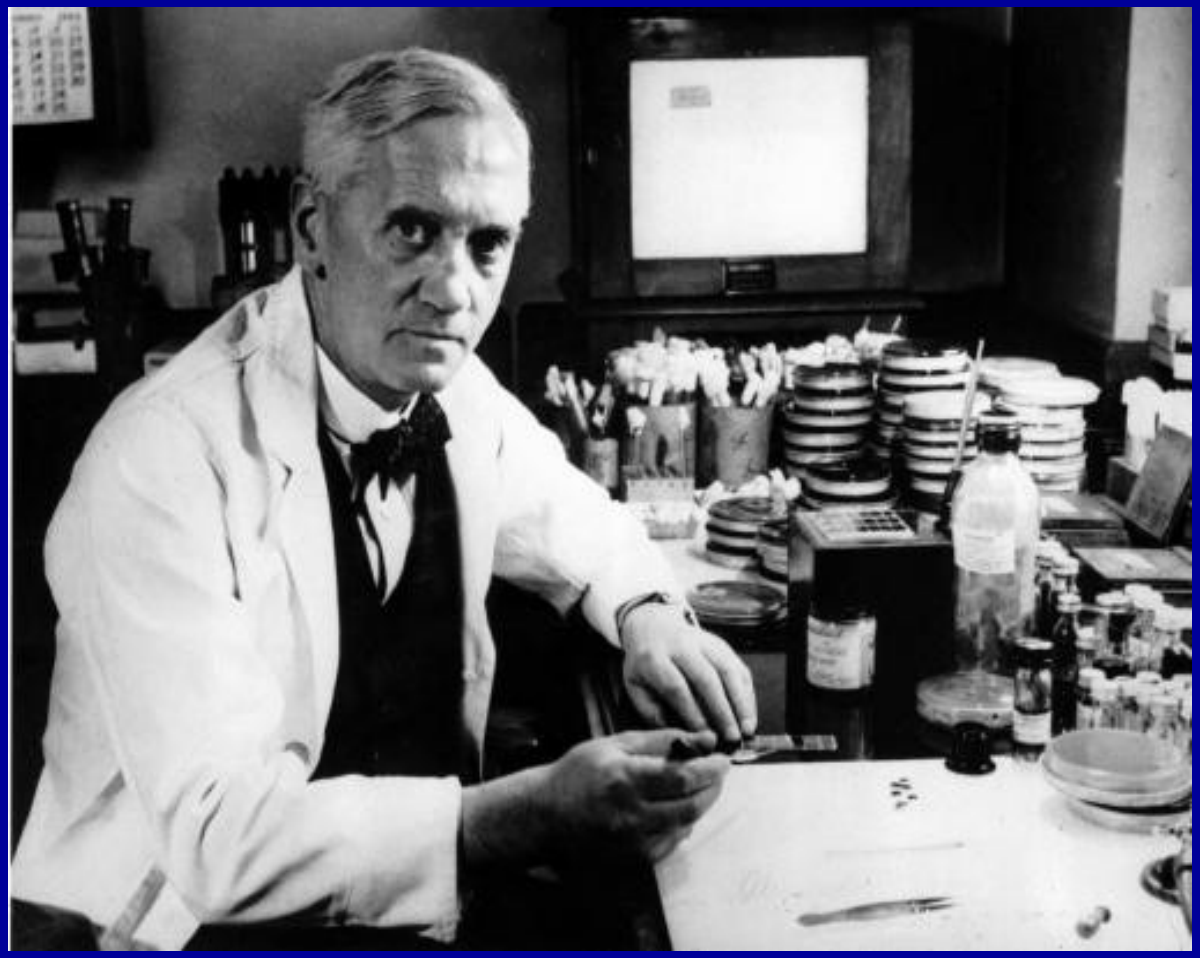


Penicillin

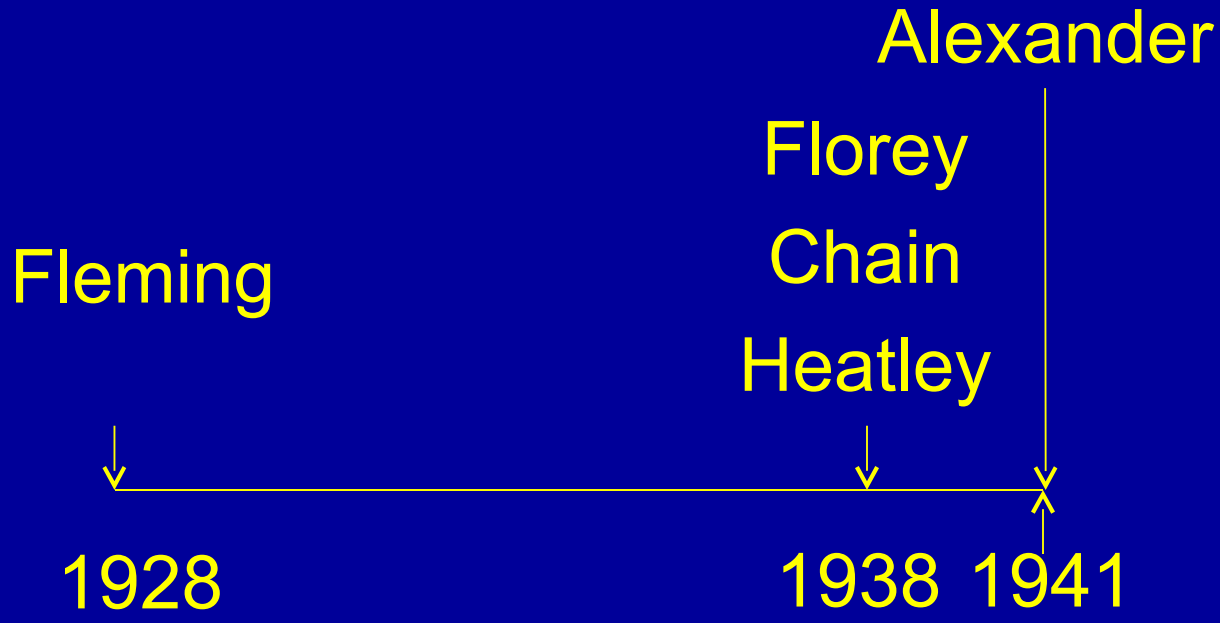




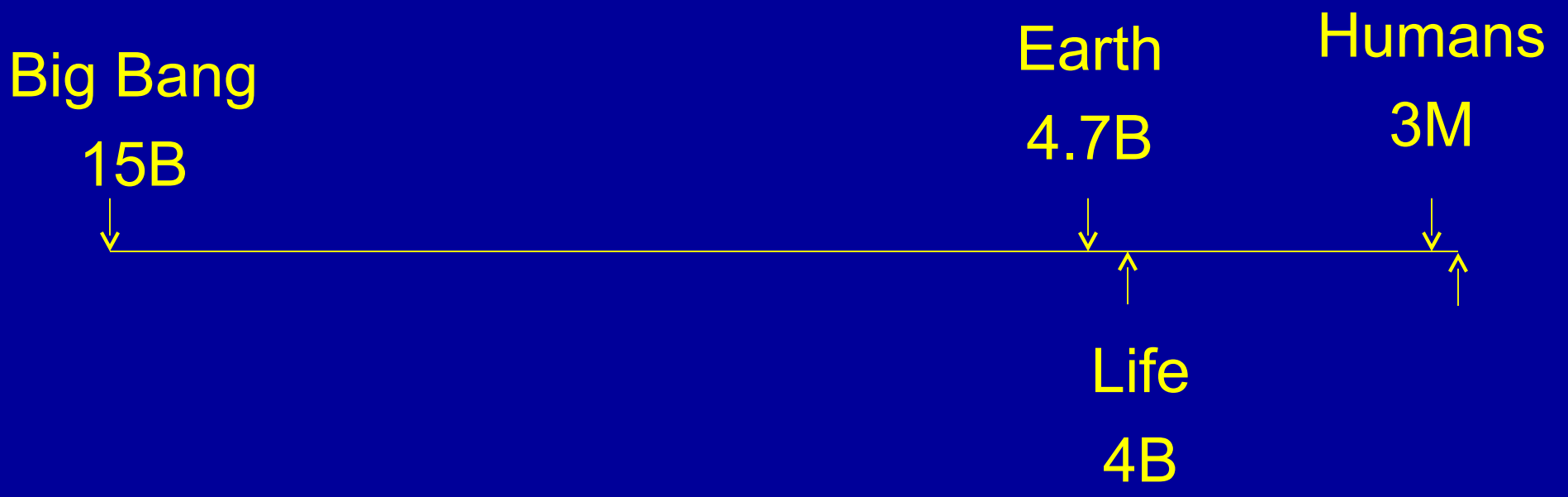
Alexander Fleming



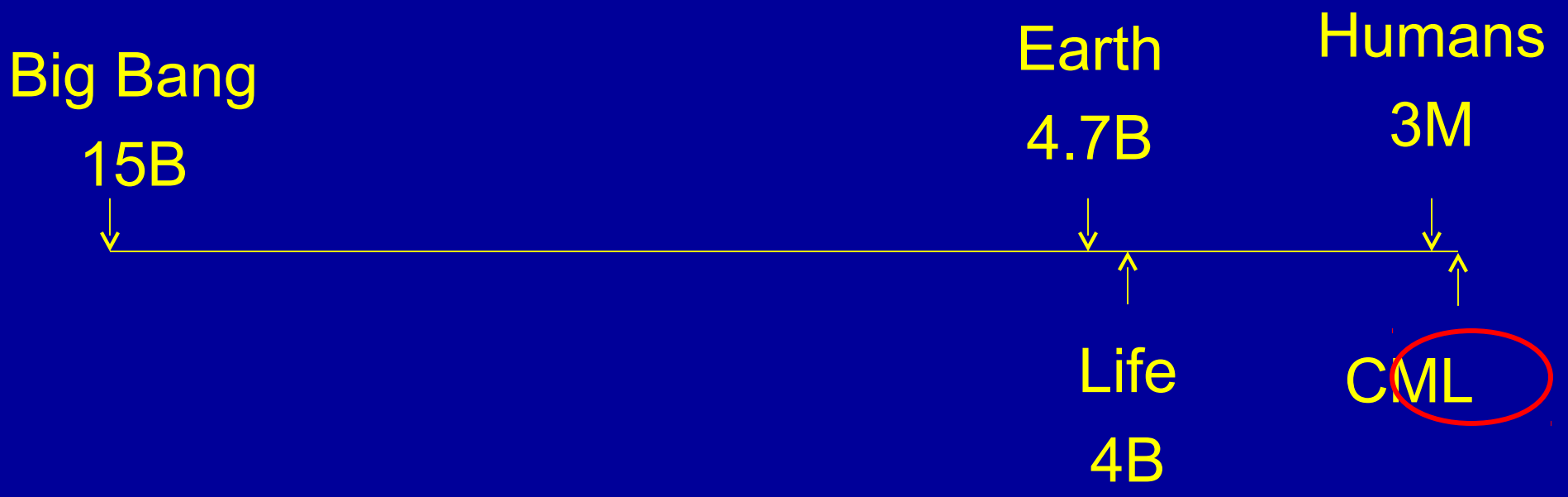
Penicillin Timeline



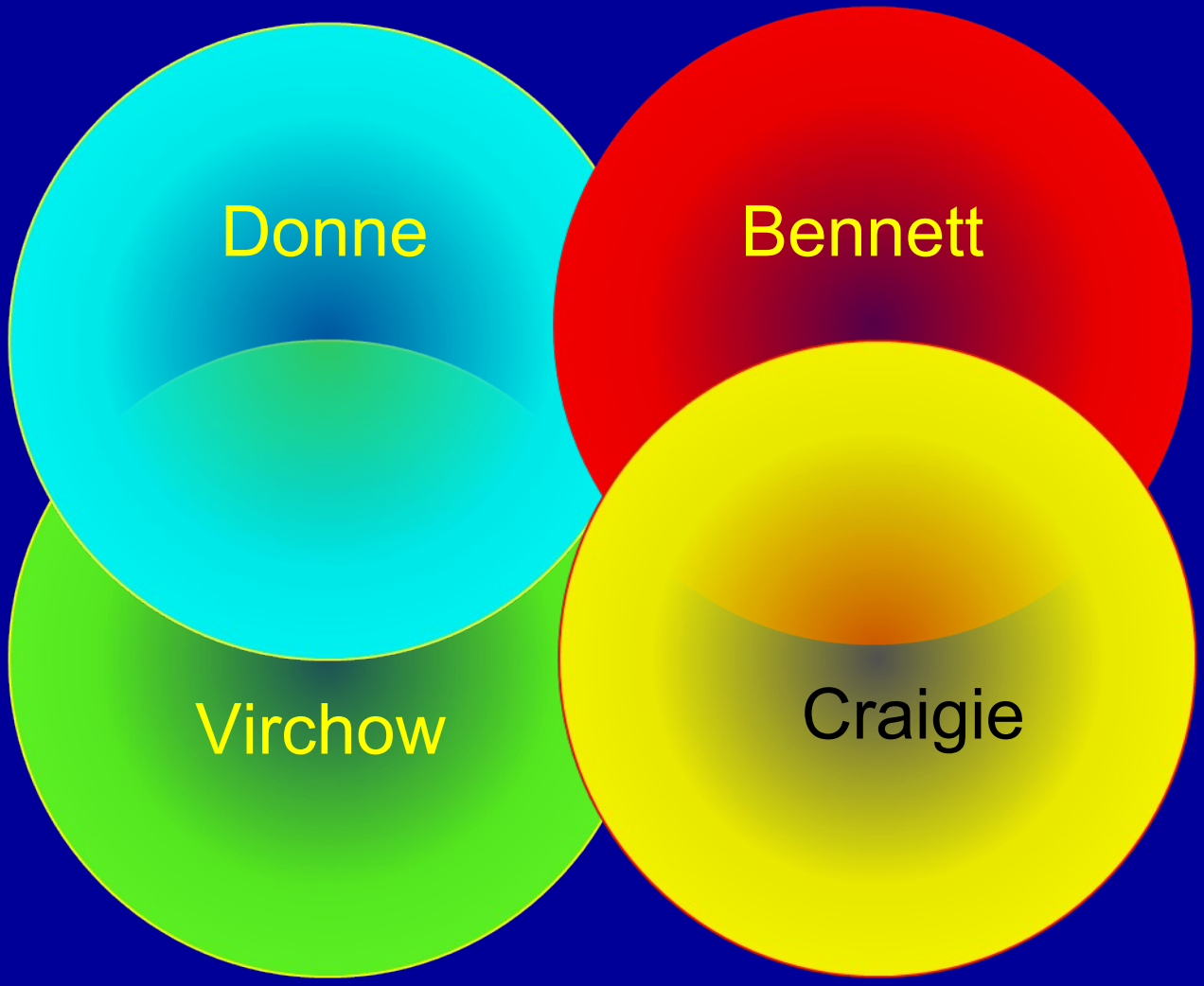
CML Timeline



CML Timeline

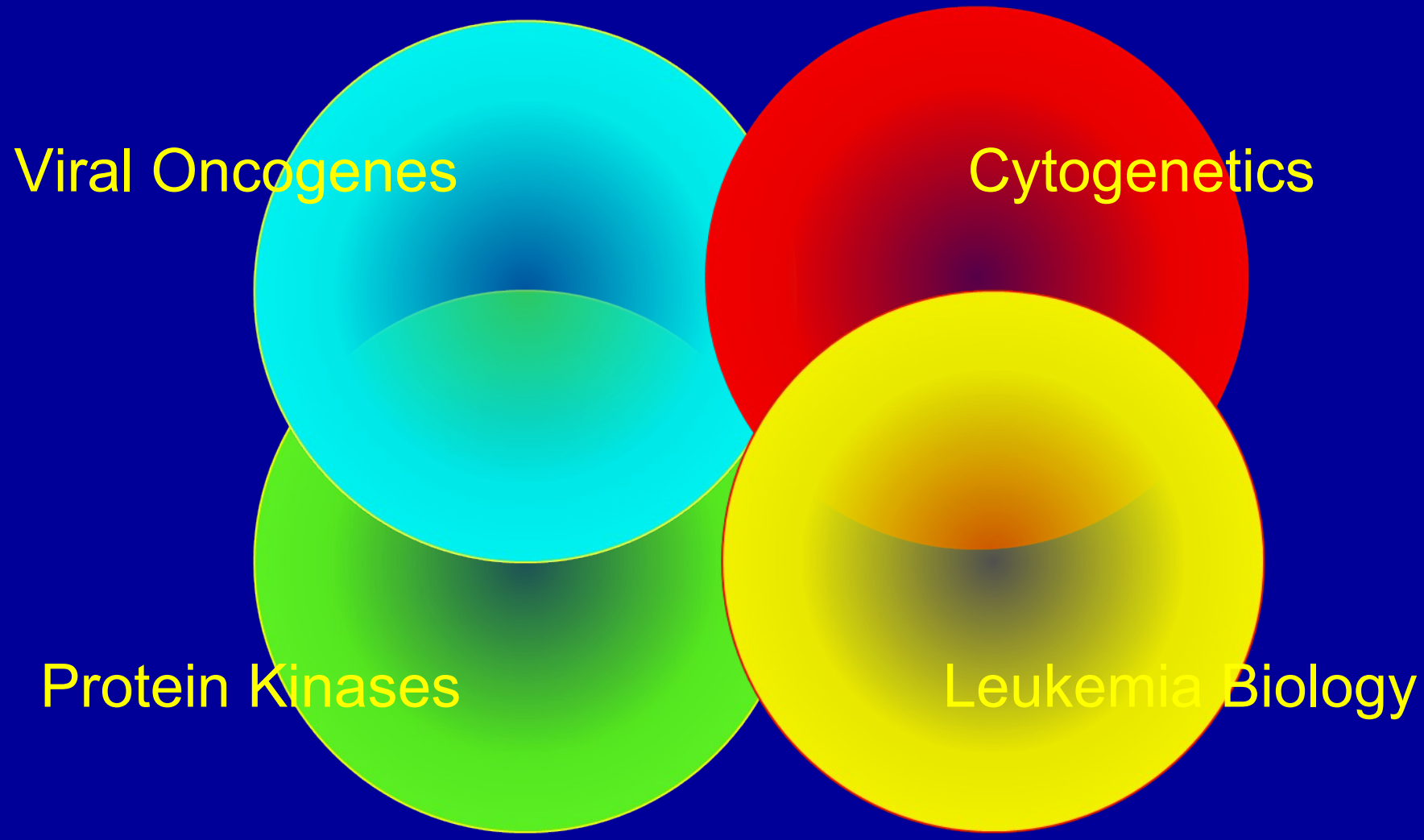


Who Discovered CML?

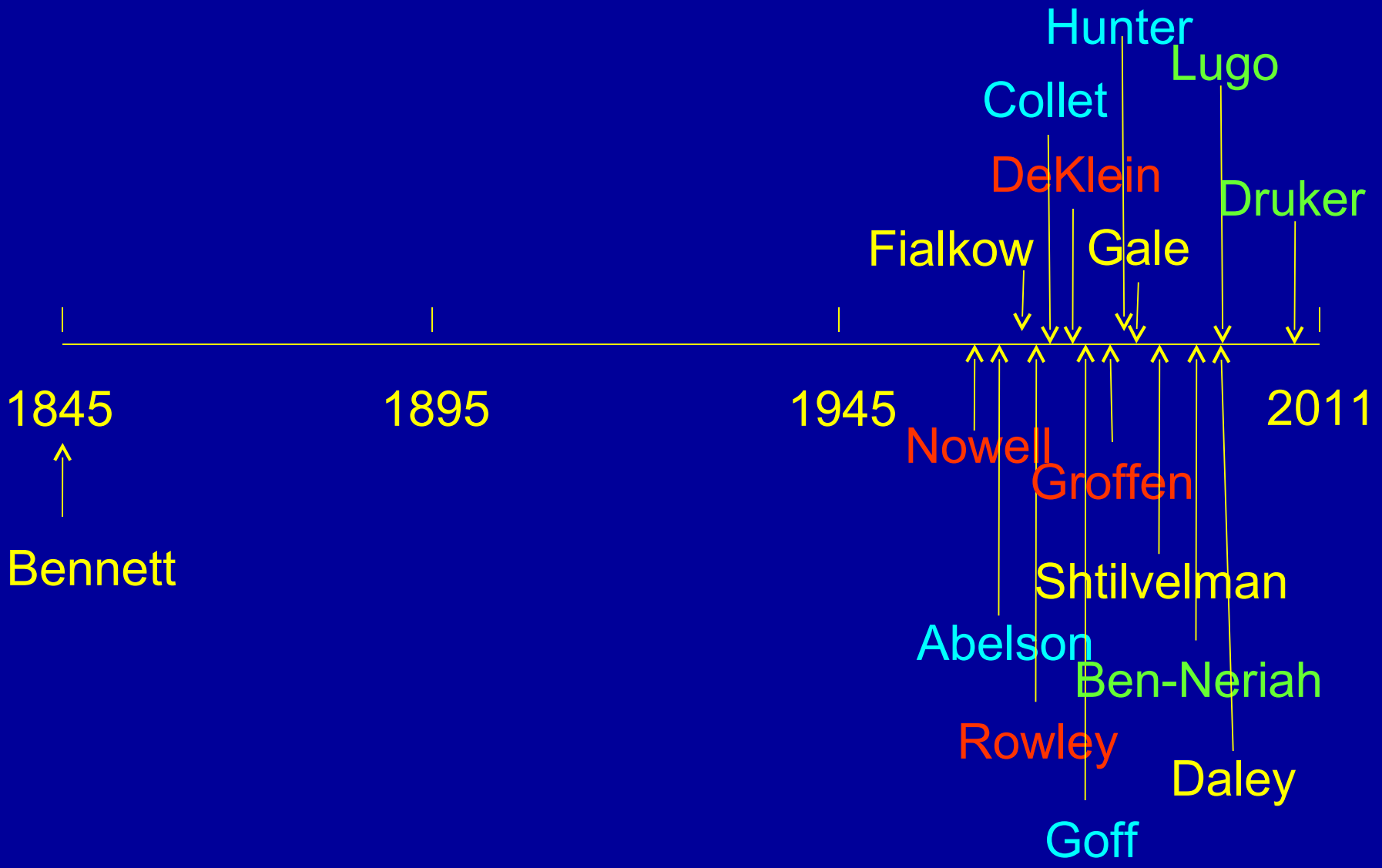


Landmine

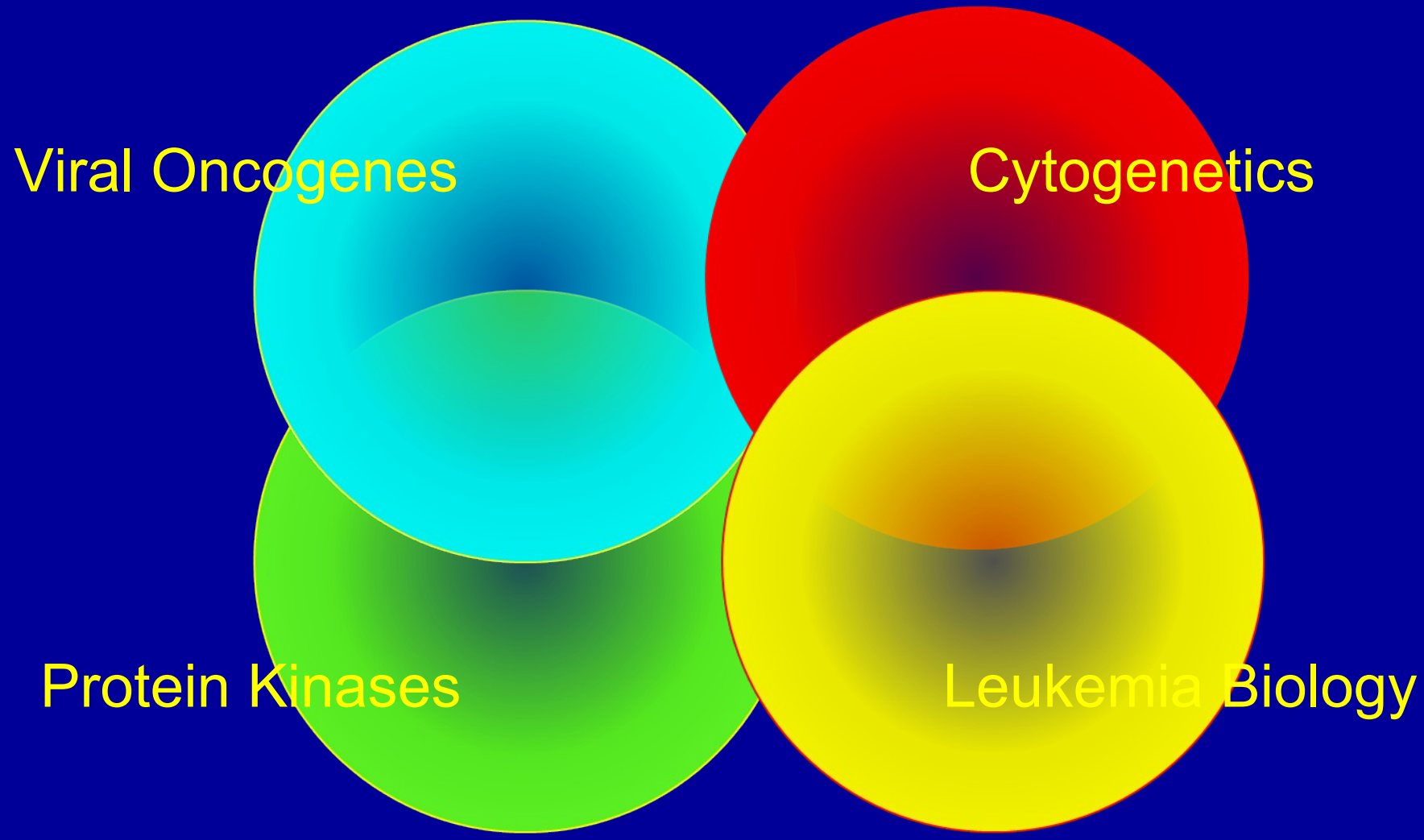
What Was Needed to Cure CML



CML Timeline

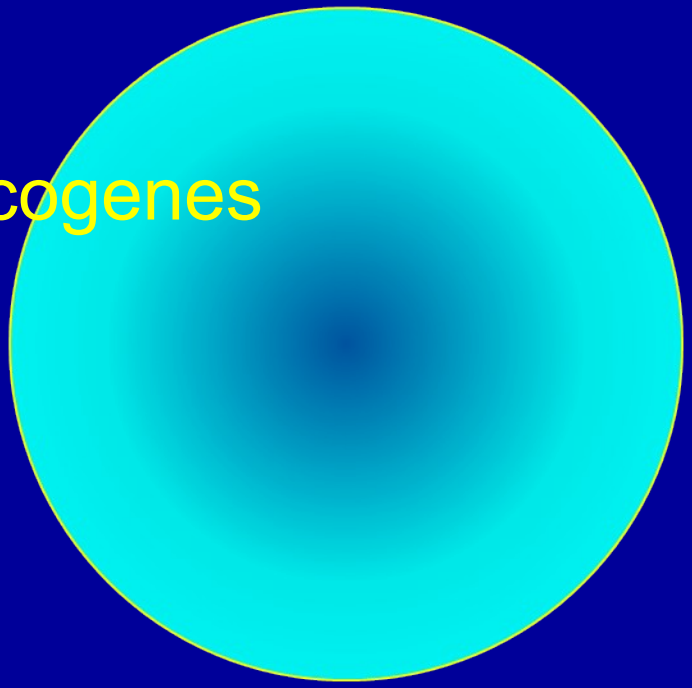


What Was Needed to Cure CML



What Was Needed to Cure CML

Viral Oncogenes



Peyton Rous

Chicken RSV

Viral Oncogenes

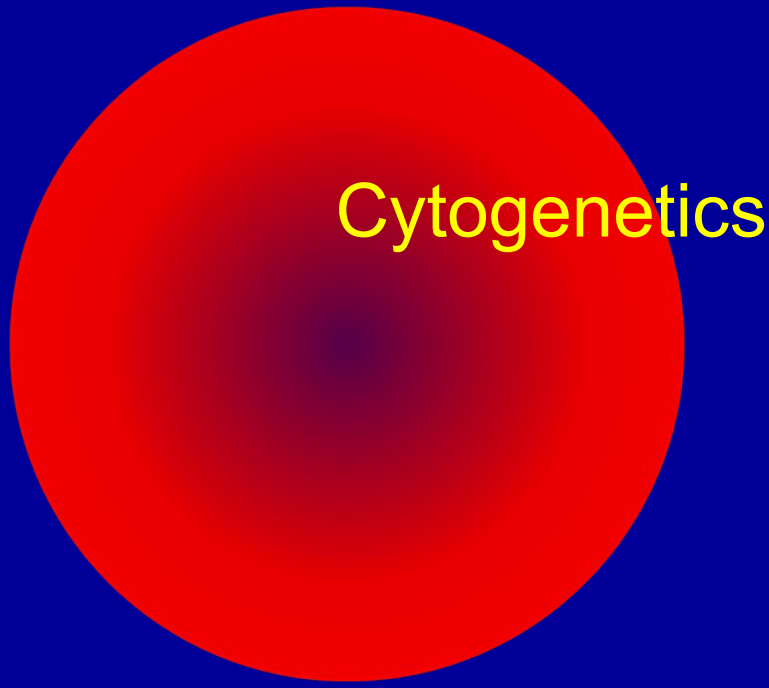
1970 AbMLV Abelson + Rabstein

1980 v- and c-ABL Goff, Gilboa, Witte, Baltimore

1984 ABL Reddy, Smith, Srivassan

Wang, Ledley, Goff, Lee, Groner, Baltimore

What Was Needed to Cure CML



Cytogenetics

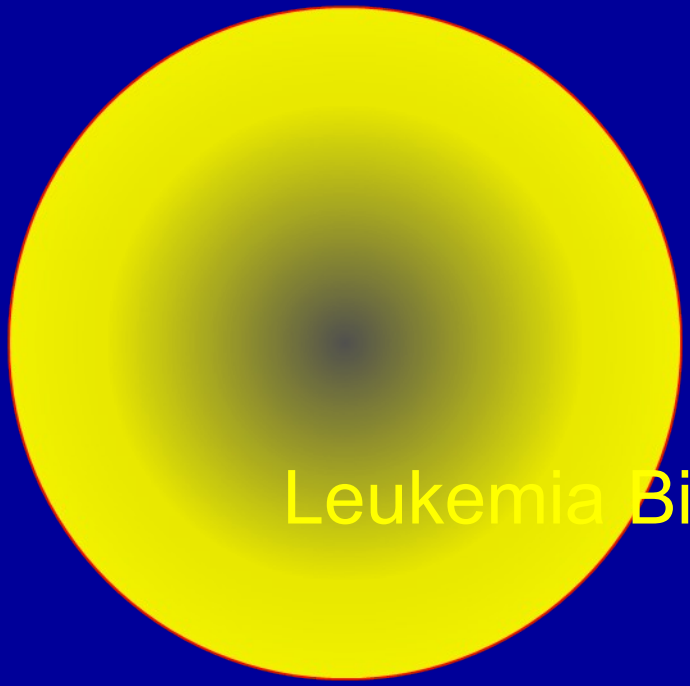
1960 Ph^1 Nowell, Hungerford

1973 t(9; 22) Rowley

1984 ABL→Ph^1 de Klein, van Kessel, Grosveld et al

1984 BCR Groffen, Stephenson, Heisterkamp, de Klein, Bartram, Grosveld

What Was Needed to Cure CML



Leukemia Biology

1967 Clonality Fialkow, Gartler, Yoshida

1983 mRNA Gale, Canaan
Collins, Kubonishi, Miyashi, Groundine

1984 BCR/ABL Shtivelman, Lifschitz, Gale, Canaani

1990 Mouse CML Daley, Van Etten, Baltimore

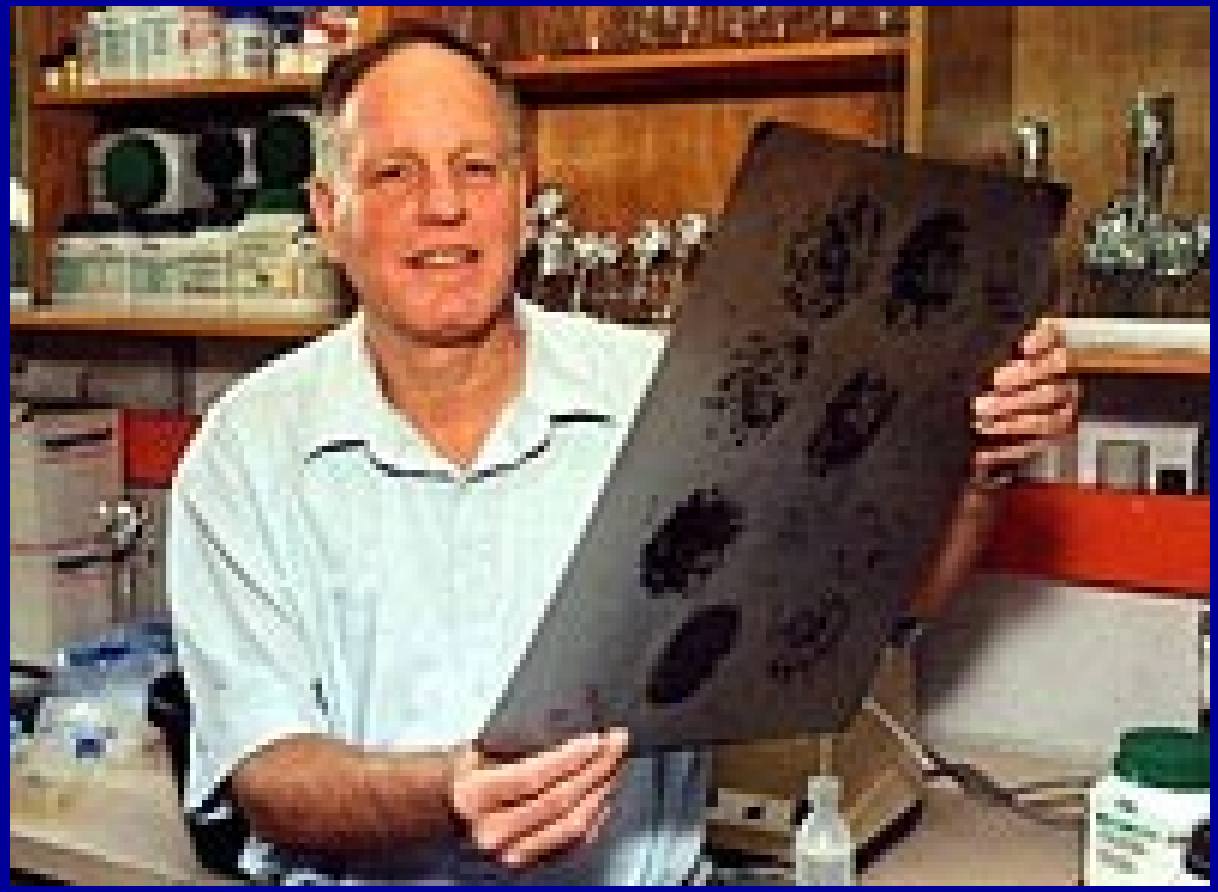
Willie Sutton

Why Do You Rob Banks?

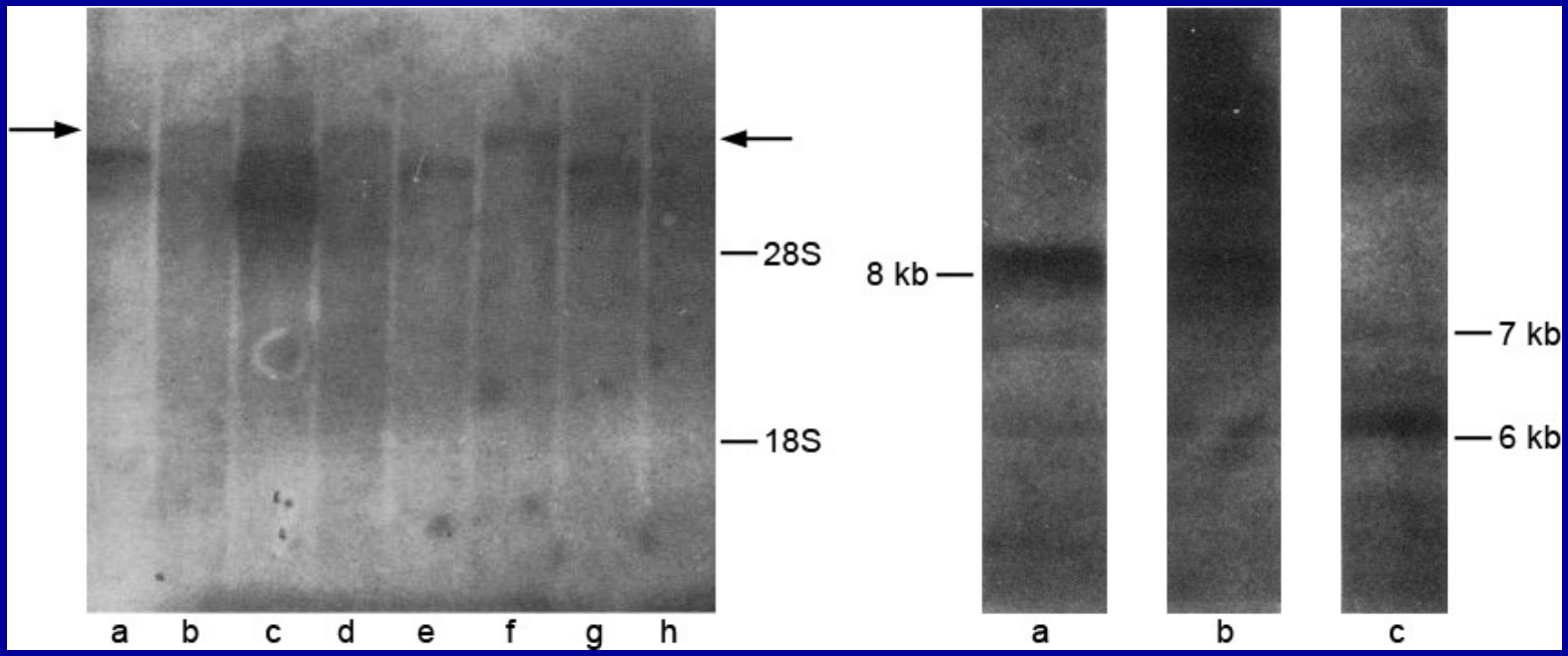
Why Do You Rob Banks?

That’s where the money is!

Eli Canaani



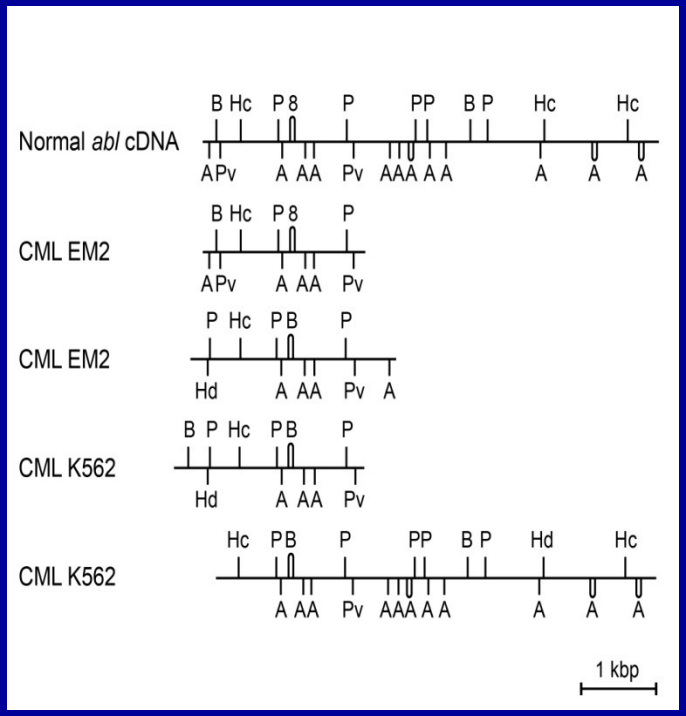
A 8 kb ABL mRNA in CML



Altered transcription of an oncogene in chronic myeloid leukaemia. Canaani E., Gale RP, Steiner-Saltz D, Berrebi A, Aghai E, Januszewicz E. Lancet 1984, 1:593-5.

An 8-kilobase abl RNA transcript in chronic myelogenis leukemia. Gale RP, Canaani E. Proc Natl Acad Sci USA. 1984, 81:5648-52.

BCR/ABL Chimeric RNA and protein in CML



S S S C Y L E E A L Q R

P

Normal Abl TCC TCC AGC TGT TAT CTG GAA GAA GCC CTT CAG CGG

CCA

T G F K Q S S K

8 kb Abl ACT GGA TTT AAG CAG AGT TCA AAA ---- ---- ---- ---- ----

RNA/protein divergence point

V A S D F E P Q G L S E

A

Normal Abl GTA GCA TCT GAC TTT GAG CCT CAG GGT CTG AGT GAA

GCC

8 kb Abl ---- ---- ---- ---- ---- ---- ---- ---- ---- ---- ---- ----

----

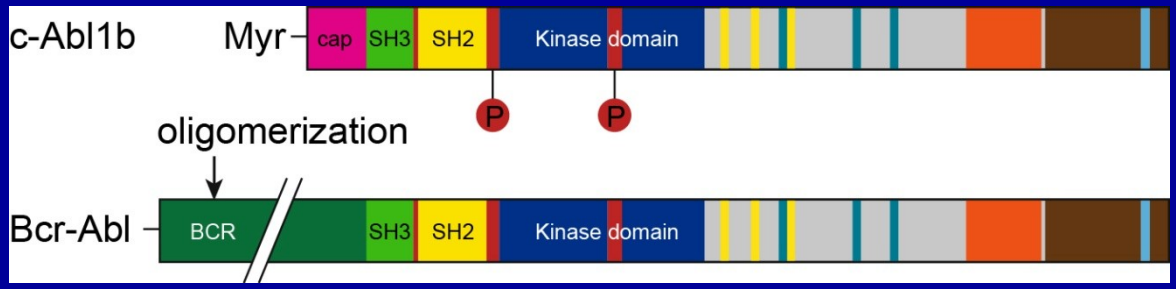
A K W N S K E N

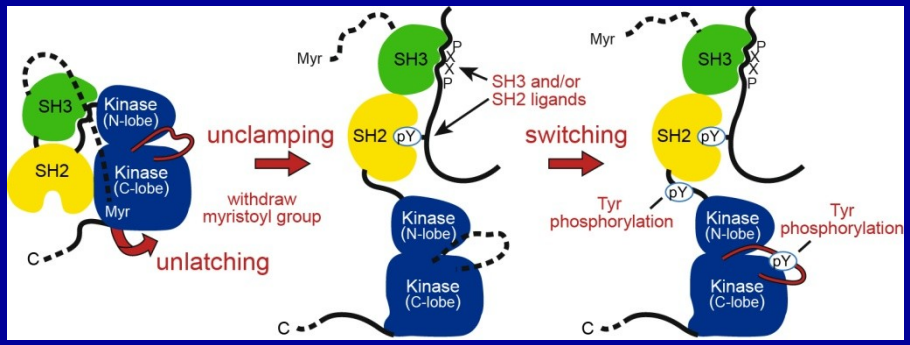
Normal Abl GCT CGT TGG AAC TCC AAG GAA AAC

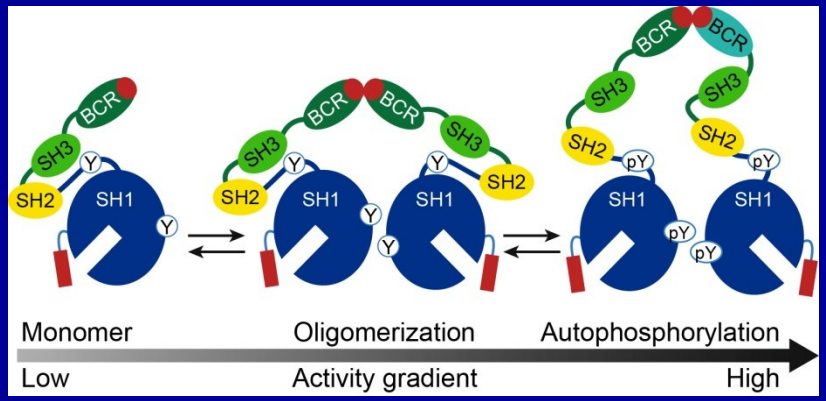
8 kb Abl ---- ---- ---- ---- ---- ---- ---- ----

Fused transcript of abl and bcr genes in chronic myelogenous leukaemia. Shtivelman E, Lifshitz B, Gale RP, Canaani E. Nature 1985, 315:550-4.

Fusion of ABL with BCR Results in Loss of ABL Auto-Inhibition and Constitutive Activation



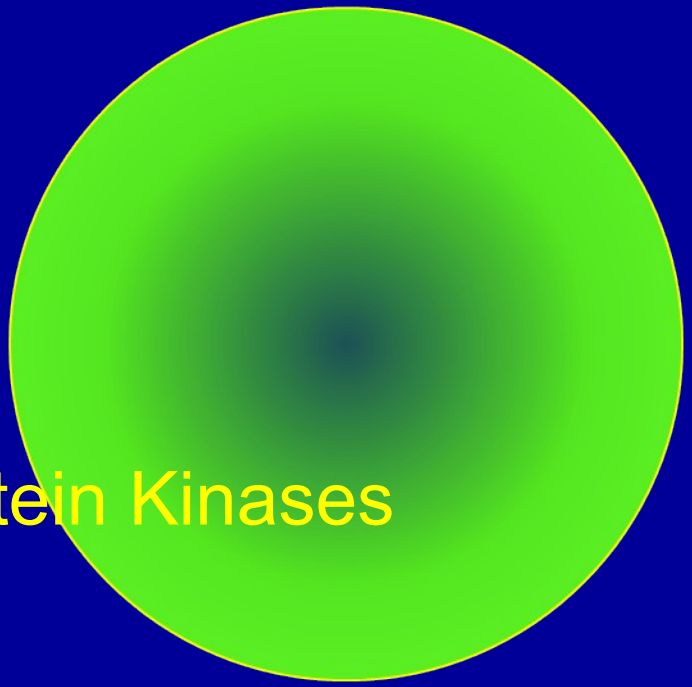




Superti-Furga, Kuriyan (Harrison, Review)

Van Etten (Hassan, Review)

What Was Needed to Cure CML



Protein Kinases

1978 SRC kinase Collett, Erickson

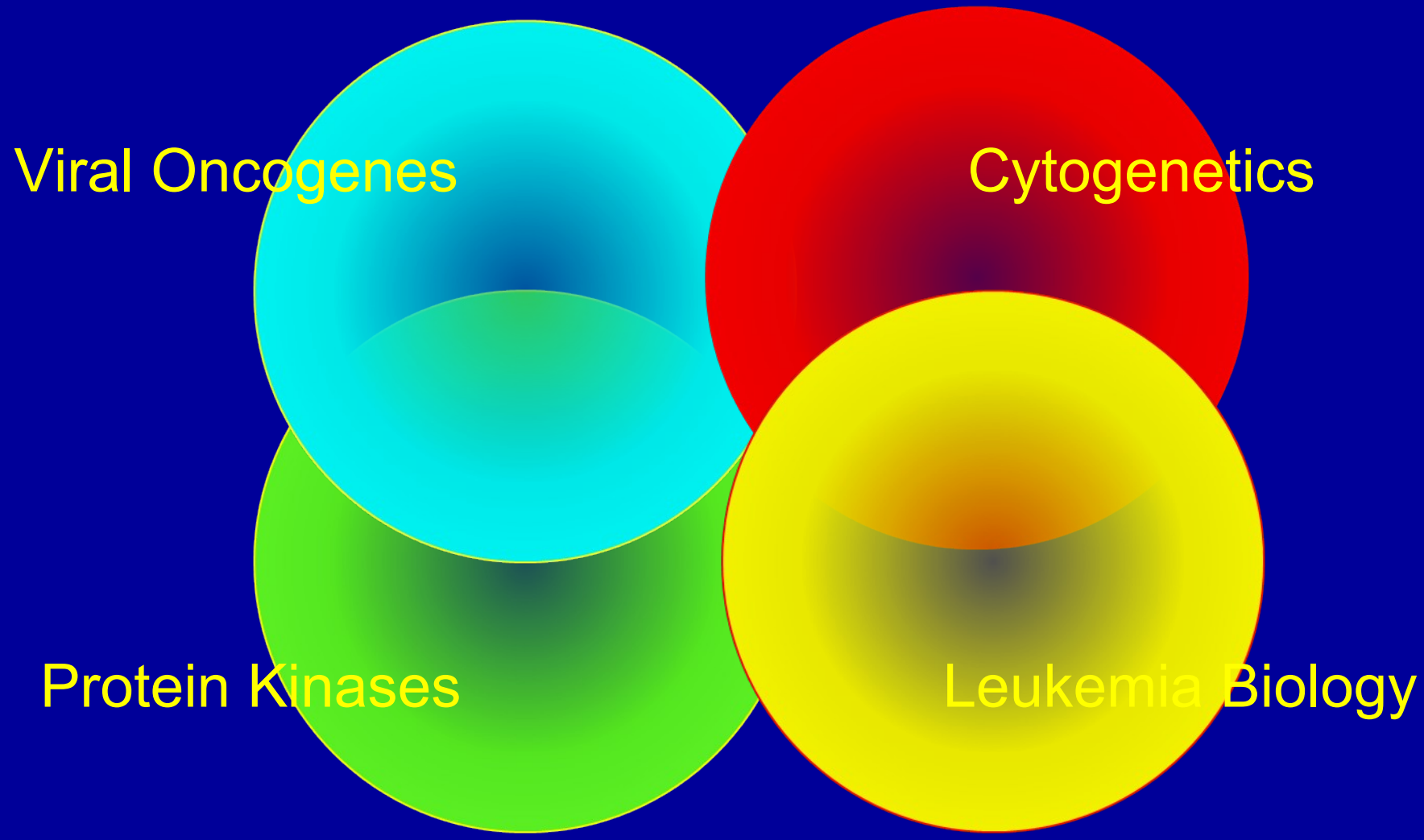
1980 v-ABL is a TK Witte, Dasgupta, Baltimore; Hunter, Sefdon ,Raschke

1986 $P210^{BCR/ABL}$ Ben Neriah, Daley, Mas-Messon, Witte, Baltimore

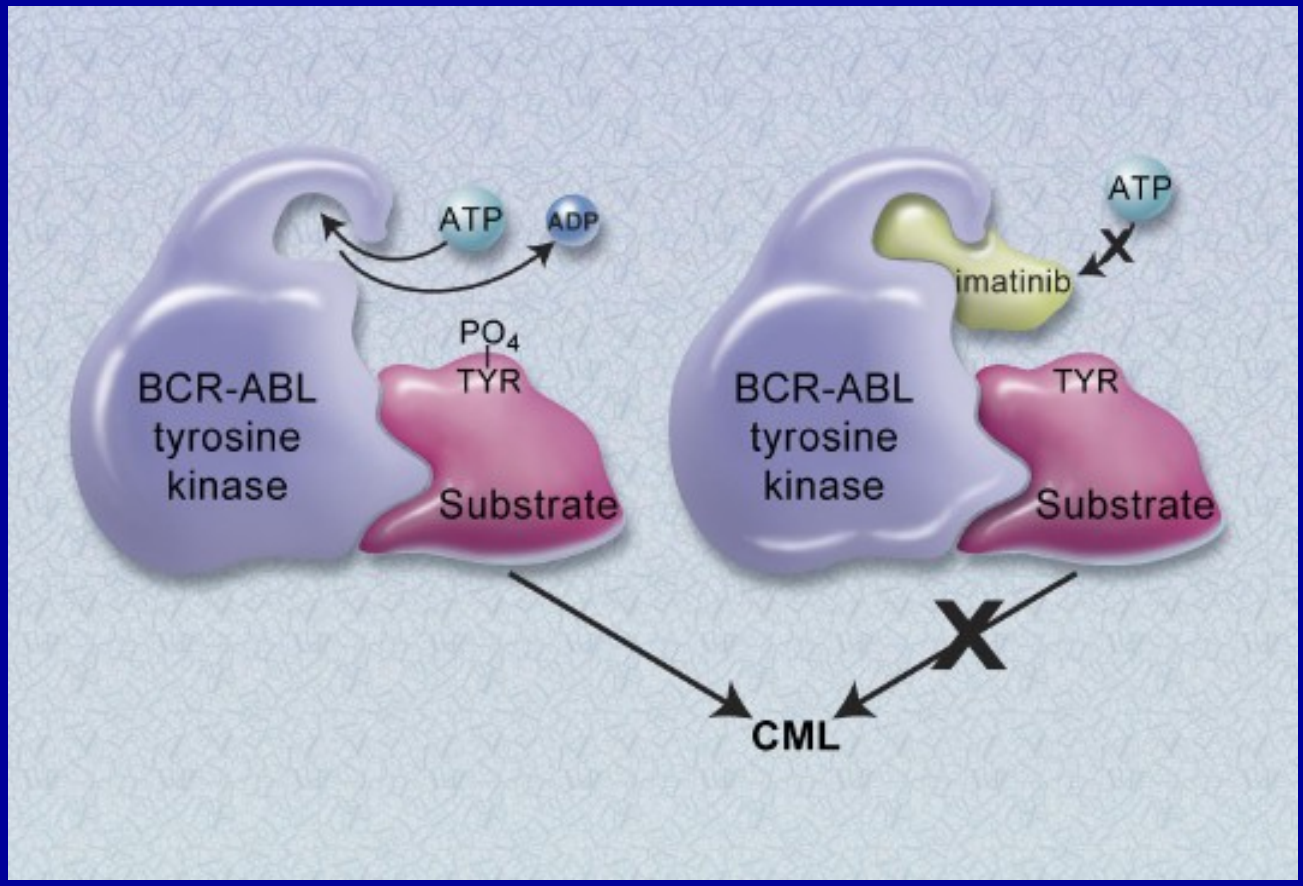
1990 Transforming BCR/ABL Lugo, Pendergast, Muller, Witte

1996 BCR/ABL Inhibition Drucker, Tamura, Buchdunger, et al

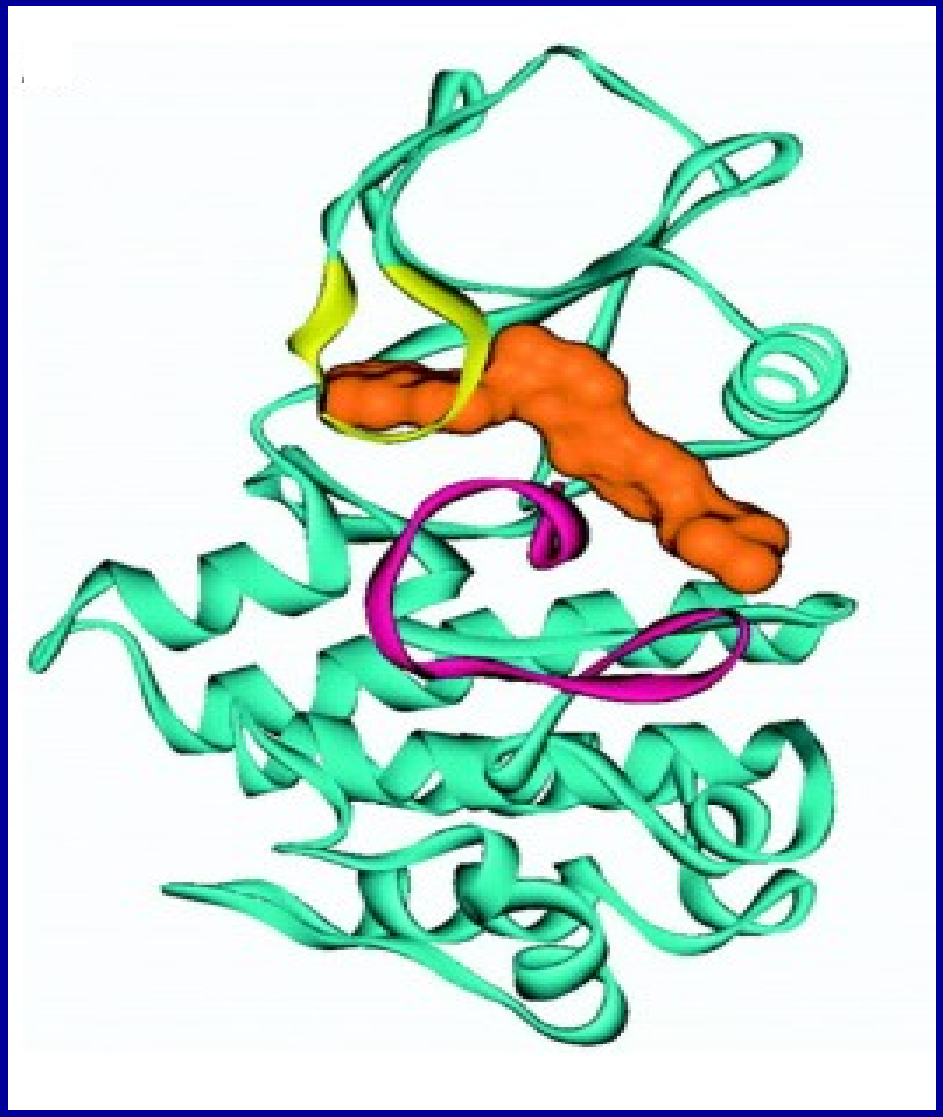
What Was Needed to Cure CML



MOA of Imatinib



ABL Complexed to Imatinib



Denninger

What is the probability of this convergence of data?

What is the probability of this convergence of data?

$P<0.001$

Gang of 3