Anticancer Drugs

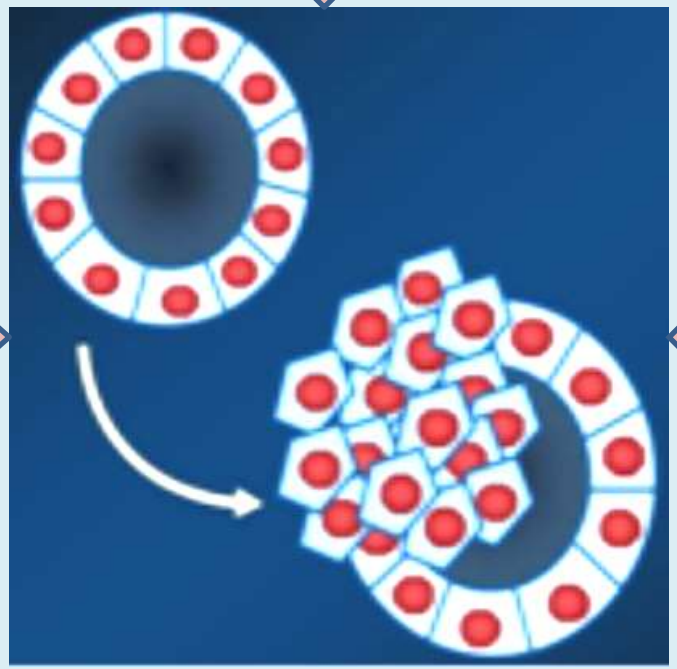
Svetlana I. Pavlova

I.N. Ulyanov Chuvash State University

A cancer cell is out of control

Limitless replicative potential, tissue invasion and metastasis

Insensitivity to anti-growth signals

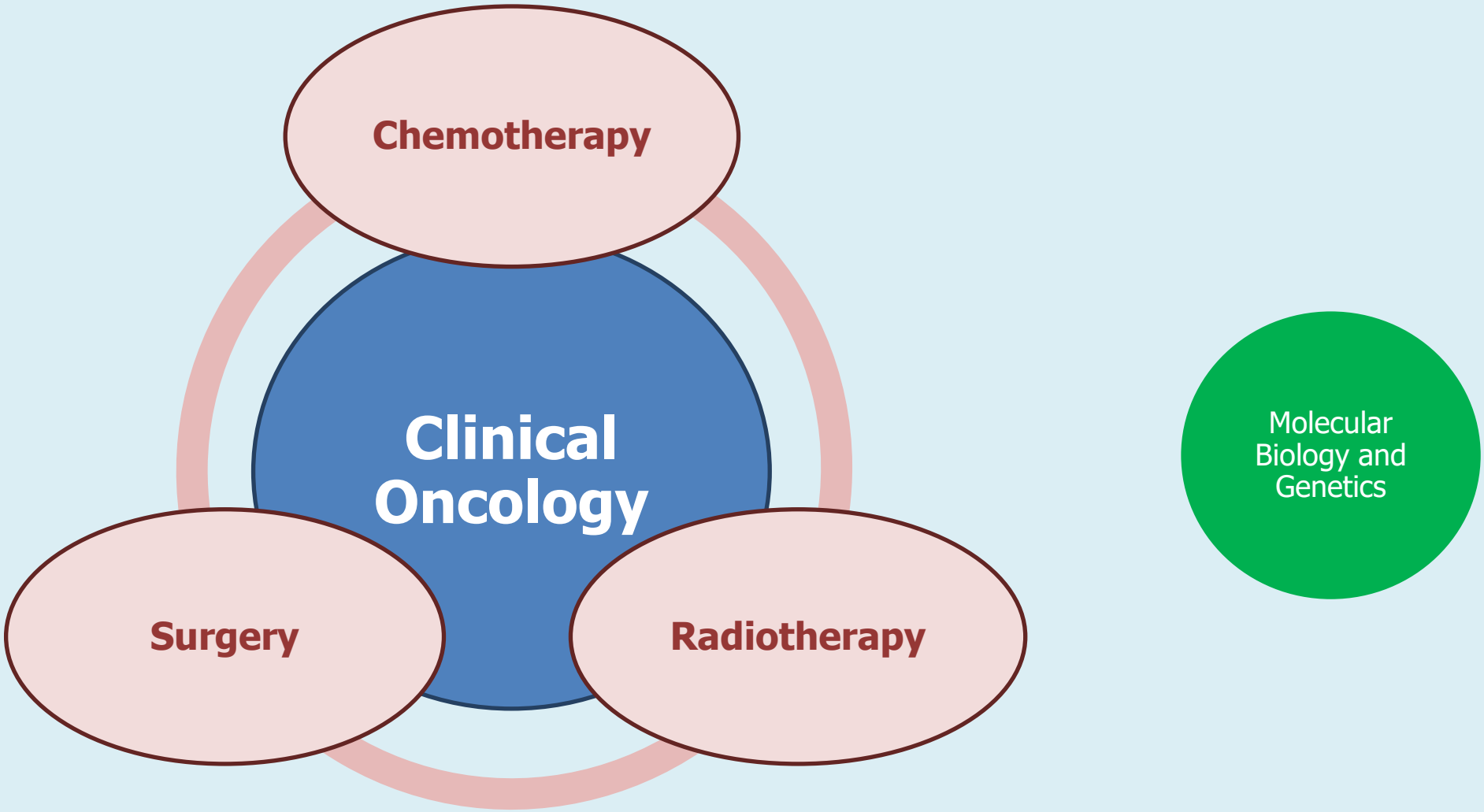


Self-sufficiency in growth signals

«There is no treatment for this condition…»

Edwin Smith Papyrus, Egypt, 3000-1500 BC

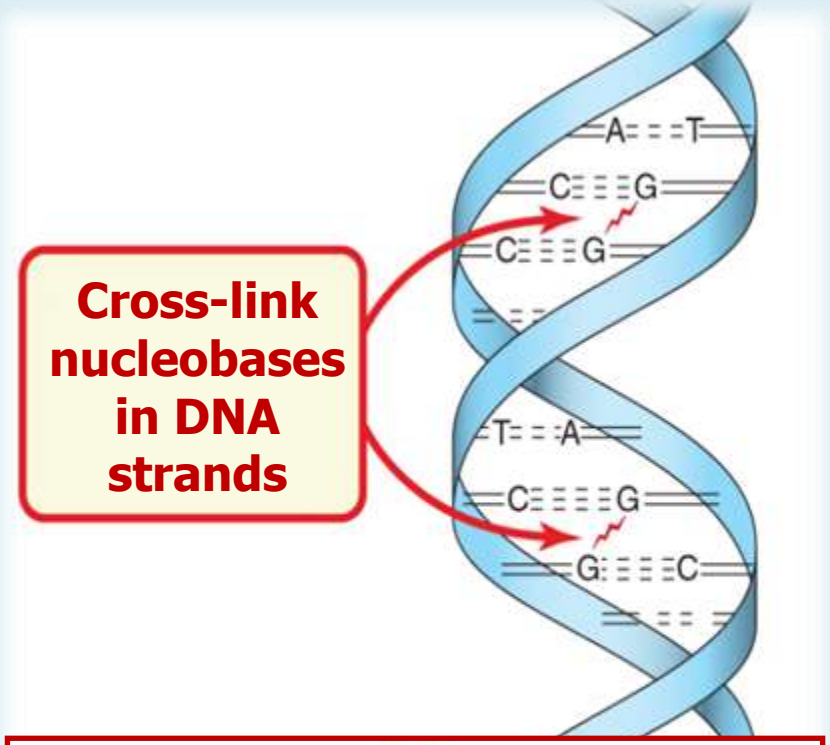
1940 - 1990

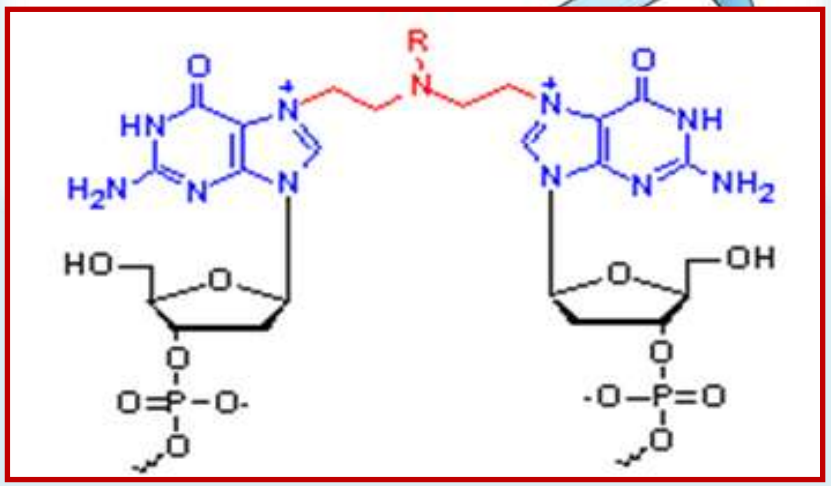

Chemotherapy
Clinical Oncology
Surgery
Radiotherapy
Molecular Biology and Genetics

Cytotoxic Drugs

- ✓Alkylating agents
- ✓Antimetabolites
- ✓Anticancer Antibiotics
- ✓Vinca alkaloids
- ✓…

Alkylating agents





Cyclophosphamide (T 0,05; A 0,2)

Carmustine

Busulfan

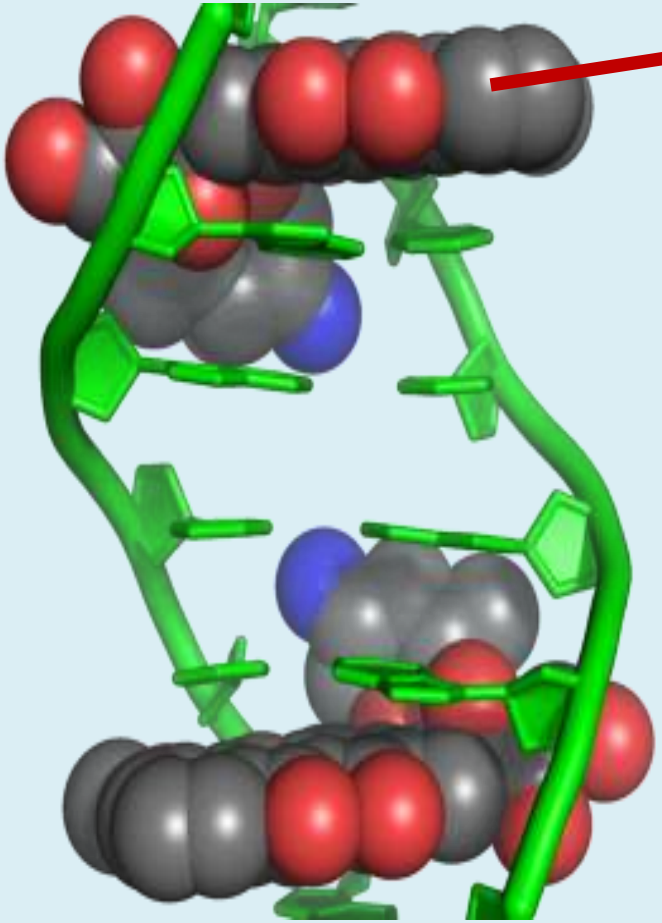
- ✓ Produce highly reactive intermediates which transfer alkyl groups to cellular macromolecules forming covalent bonds
- ✓ The position 7 of guanine residues in DNA is especially susceptible
- ✓ Alkylation results in cross linking of DNA strands

Antimetabolites

Folate antagonist	*Pyrimidine antagonist*	*Purine antagonist*
• **Methotrexate**	• **5-Flourouracil**	• **Mercaptopurine** • **Azathioprine**

- ✓ Antimetabolites are analogues related to normal components involved in nucleic acid synthesis
- ✓ Antimetabolites competitively inhibit utilization of physiological substrates or get themselves incorporated forming dysfunctional nucleic acid

Anticancer antibiotics



Doxorubicin (A 0,05)

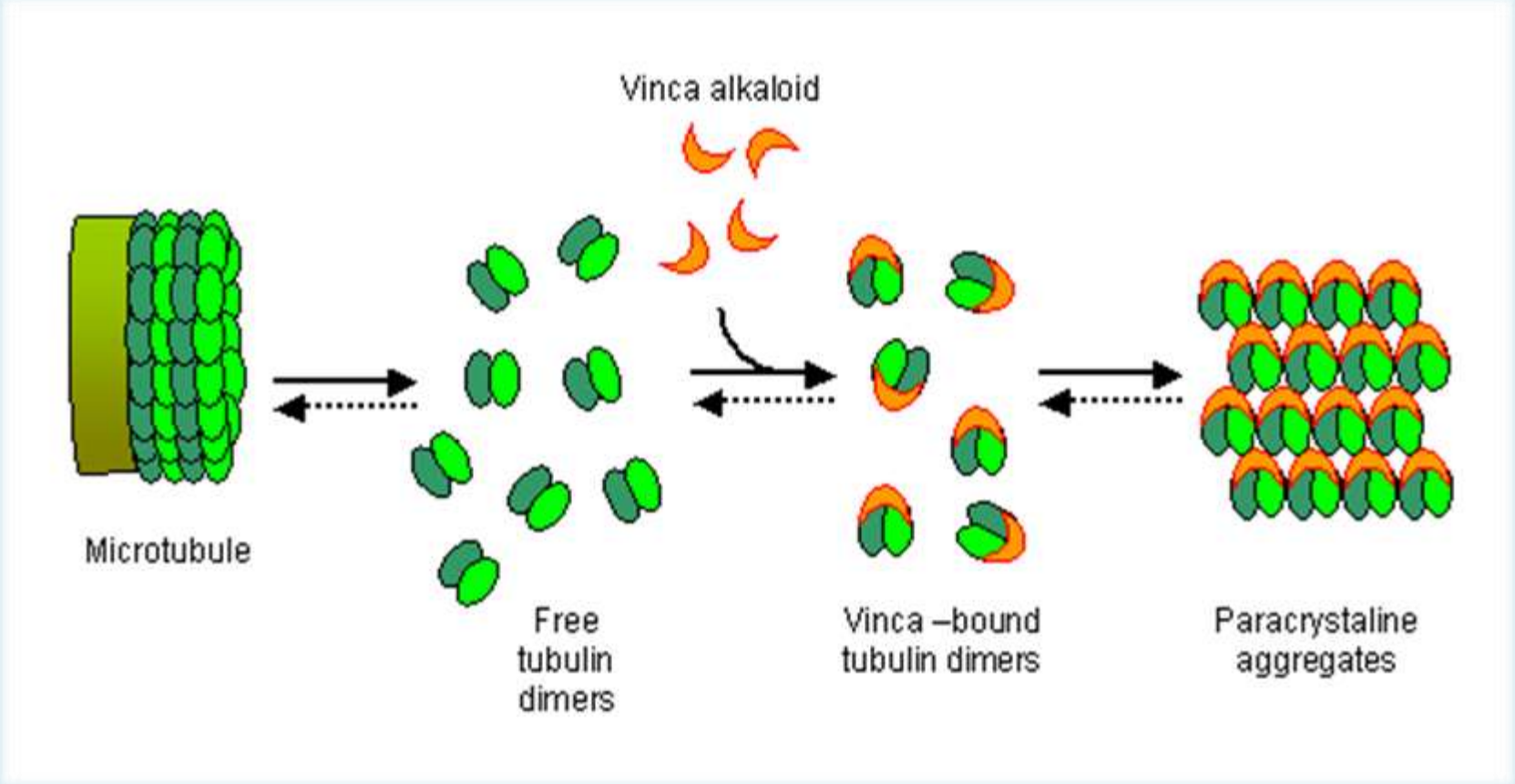
Actinomycin D

- ✓ Anticancer antibiotics are products obtained from microorganisms and have prominent antitumor activity
- ✓ They intercalate between DNA strands and interfere with its template function

«Mitotic Poisons»

Vinca alkaloids: vinblastine, vincristine…

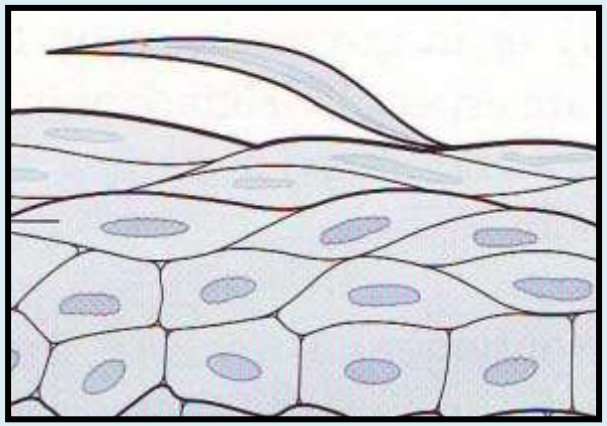
- ✓ Vinca alkaloids bind to tubulin, prevent its polymerization and assembly of microtubule, cause disruption of mitotic spindle
- ✓ Chromosomes fail to move during mitosis (metaphase arrest)



General Toxicity of Cytotoxic Drugs

Bone marrow depression

Secondary immunosuppression



Epithelial cell toxicity

Hyperuricaemia

General Toxicity of Cytotoxic Drugs

Mutagenesis

Teratogenesis

Carcinogenicity

1990 – Today

Clinical Oncology

Molecular Biology and Genetics

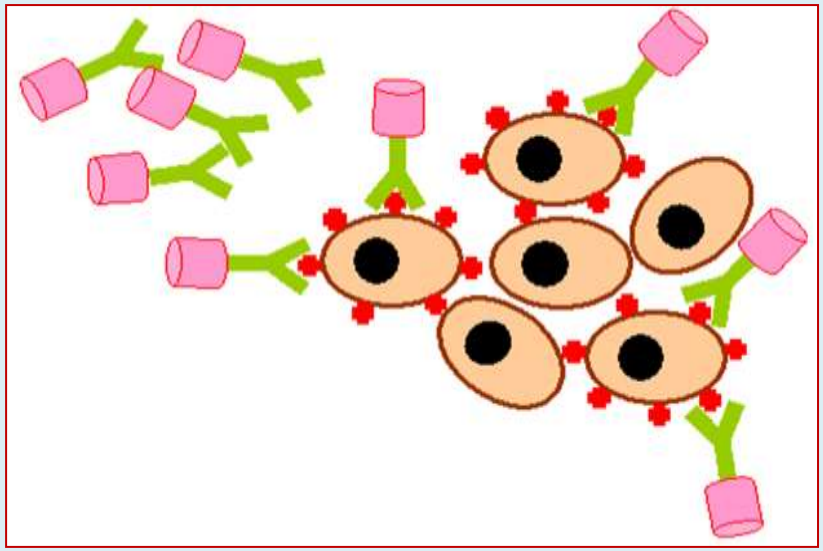
- ✓ **Tumor is a result of mutations leading to the activation of oncogenes and inactivation of tumor suppressor genes**
- ✓ **Oncogene products may be a therapeutic targets for cancer**

Targets for New Anticancer Drugs

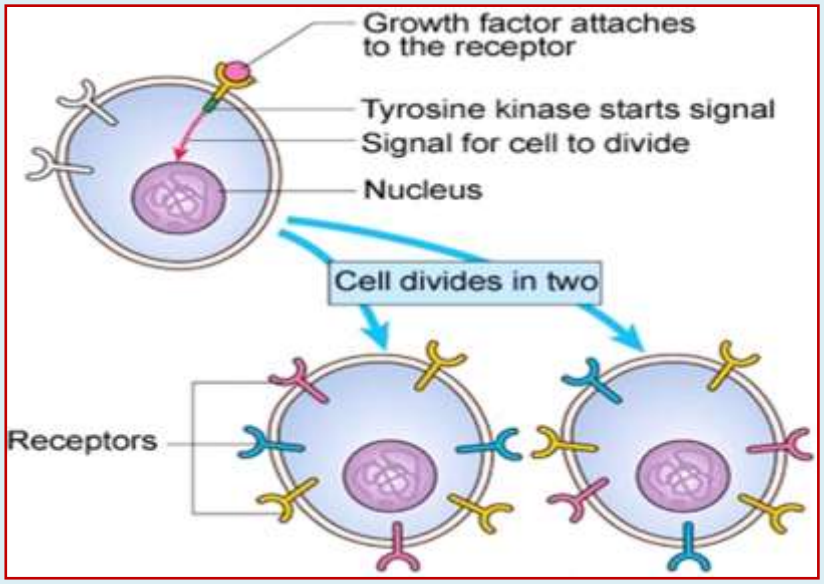
- Growth Factor Receptors
- Enzymes – Intracellular Transducers
- Transcription Factors
- Cell-Cycle Control Proteins
- DNA-Repair Proteins
- Apoptotic Proteins

Targeted Anticancer Drugs

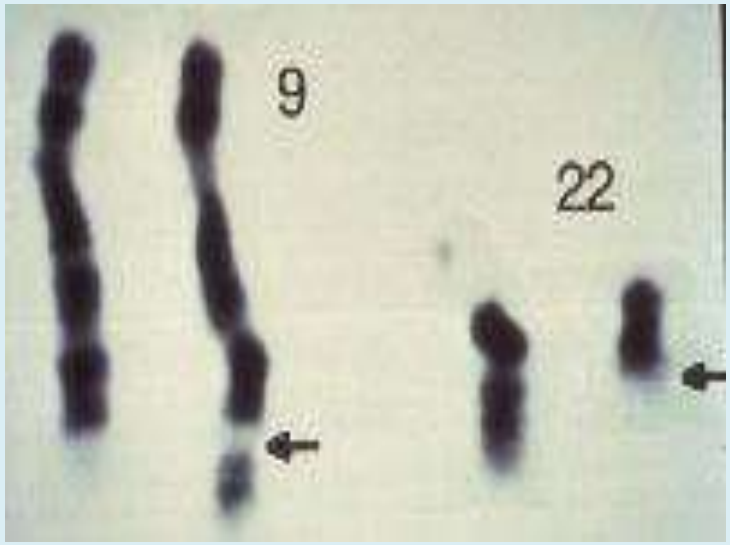
- **Monoclonal antibodies («MABs»)**



- **Small-molecule inhibitors («-tinibs»)**



Discovery of the "Philadelphia Chromosome"



In 1960, **Peter Nowell**, then a junior faculty member at the University of Pennsylvania School of Medicine, together with a graduate student, **David Hungerford**, described an unusual small chromosome in leukocytes from patients with CML

A Minute Chromosome in Human Chronic Granulocytic Leukemia

In seven cases thus far investigated (five males, two females), a minute chromosome has been observed replacing one of the four smallest autosomes in the chromosome complement of cells of chronic granulocytic leukemia cultured from peripheral blood. No abnormality was observed in the cells of four cases of *acute* granulocytic leukemia in adults or of six cases of acute leukemia in children. There have been several recent reports of chromosome abnormalities in a number of cases of human leukemia [including two of the seven cases reported here: Nowell and Hungerford, *J. Natl. Cancer Inst.* 25, 85 (1960)], but no series has appeared in which there was a consistent change typical of a particular type of leukemia.

Cells of the five new cases were obtained from peripheral blood (and bone marrow in one instance), grown in culture for 24–72 hours, and processed for cytological examination by a recently developed air-drying technique (Moorhead, *et al., Exptl. Cell Research*, in press). The patients varied from asymptomatic untreated cases to extensively treated cases of several years duration in terminal myeloblastic crisis. All seven individuals showed a similar minute chromosome, and none showed any other frequent or regular chromosome change. In most of the cases, cells with normal chromosomes were also observed. Thus, the minute is not a part of the normal chromosome constitution of such individuals.

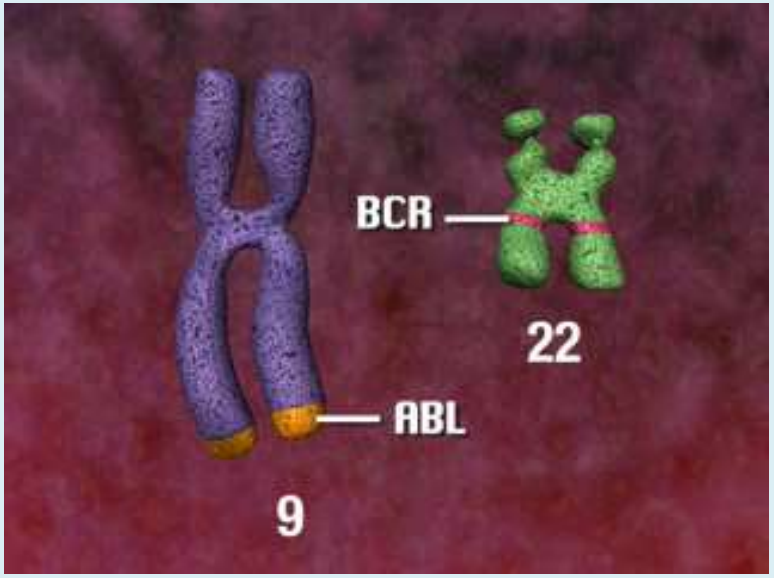
The findings suggest a causal relationship between the chromosome abnormality observed and chronic granulocytic leukemia.

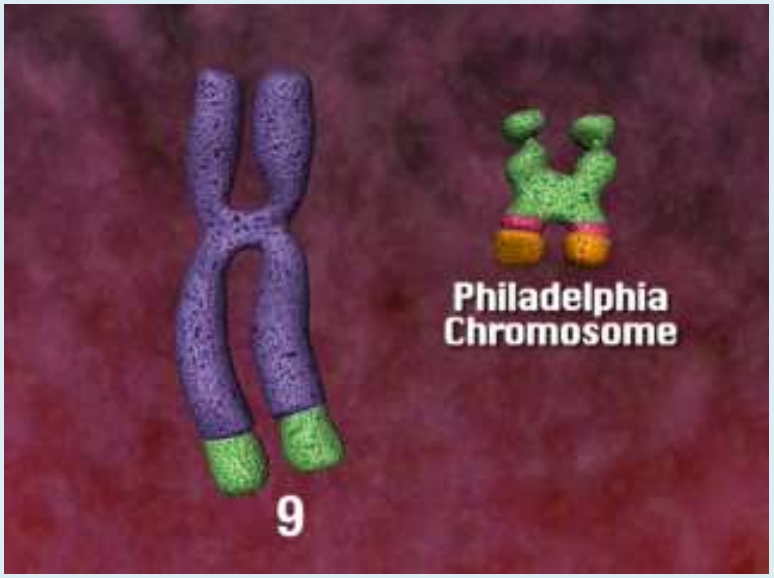
PETER C. NOWELL
School of Medicine, University of Pennsylvania
DAVID A. HUNGERFORD
Institute for Cancer Research

Nowell & Hungerford, 1960 Science 132.1497

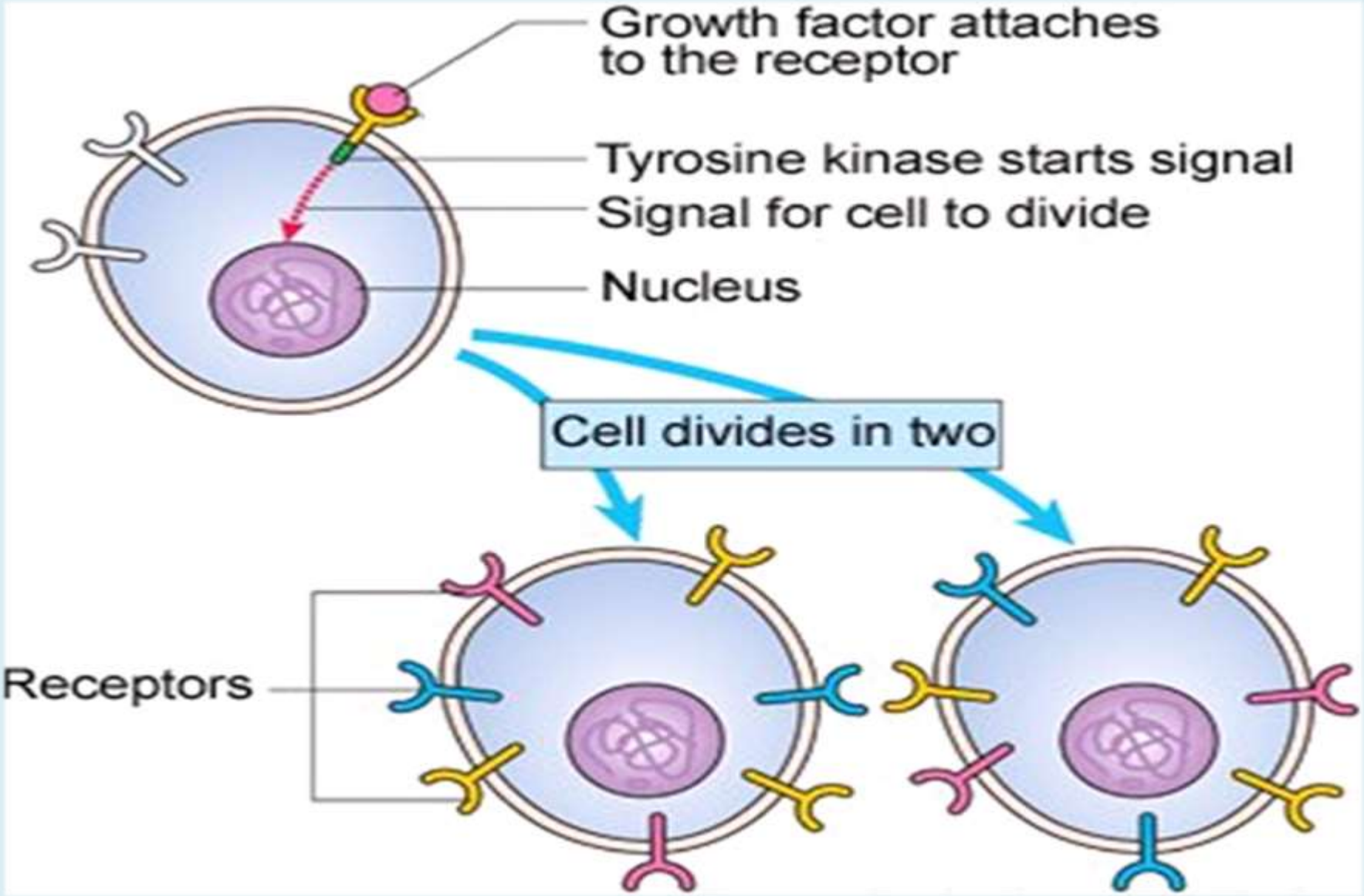
The BCR-ABL gene encodes a protein with uncontrolled tyrosine kinase activity

- ✓ Translocation between chr 9 (ABL gene) and chr 22 (BCR gene) creates so called Philadelphia chromosome
- ✓ This mutation results in a new gene is made up of two parts and is also called BCR-ABL
- ✓ This new gene produces a specific new protein called tyrosine kinase
- ✓ Tyrosine kinase stimulates uncontrolled dividing of tumor cells





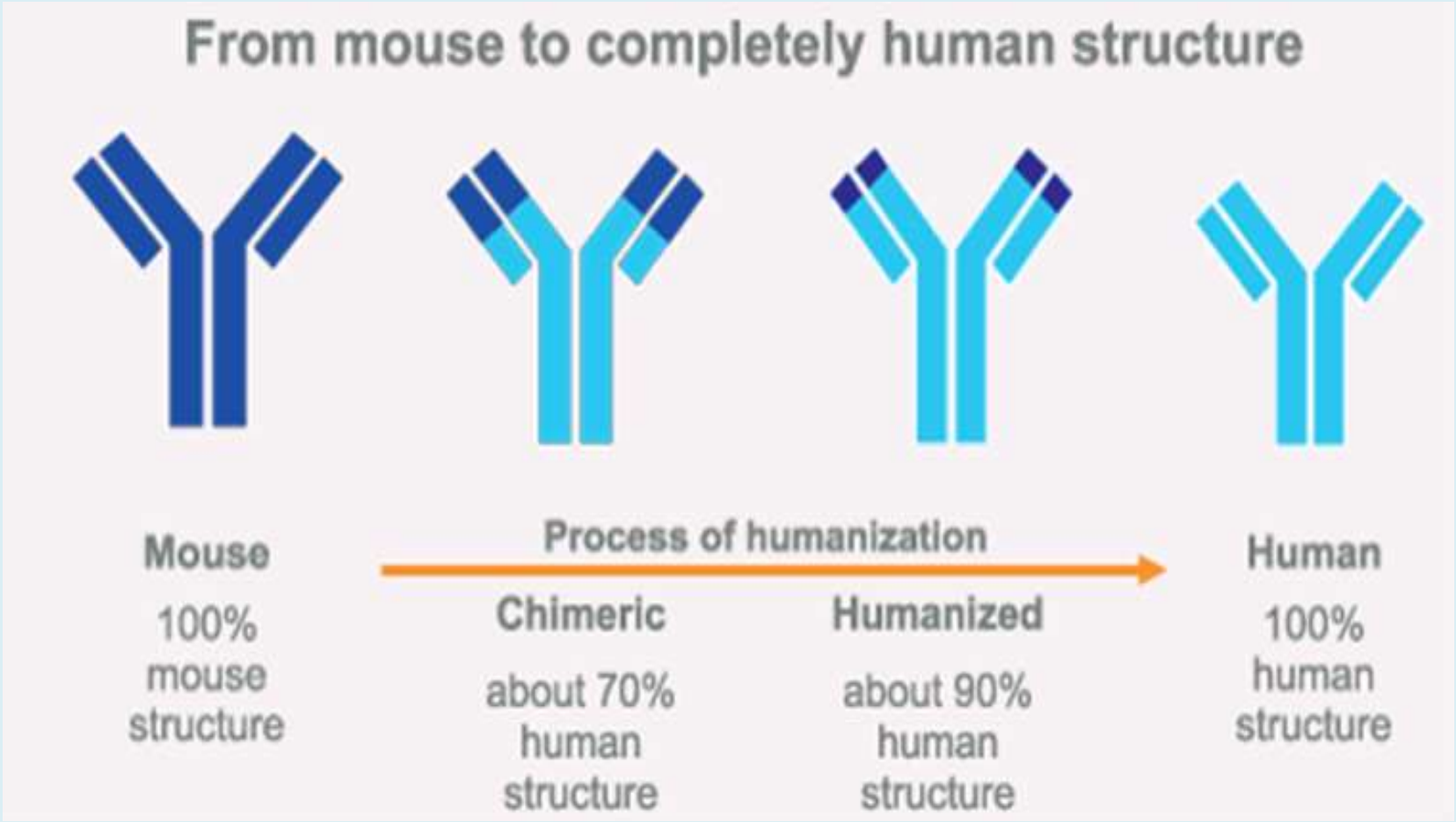
Tyrosine Kinases Involve in Growth Control Pathway



Tyrosine Kinase Inhibitors «-tinibs»

Drug	Target	Therapeutic Application
Imatinib (T 0,4) (Gleevek)	BCR-ABL tyrosine kinase	Chronic Myelogenous Leukemia
Erlotinib (Tarceva)	Epidermal growth factor receptor tyrosine kinases	Non-small cell lung cancer
Gefitinib (Iressa)		Non-small cell lung cancer
Lapatinib (Tyverb)		Breast cancer

Monoclonal Antibodies



Monoclonal Antibodies: Mechanisms of Action

- ✓ Block growth factor receptors, arresting proliferation and trigger apoptosis of tumor cells
- ✓ Recruit NK-cells that have cytotoxicity (antibody-dependent cell mediated cytotoxicity)
- ✓ Bind complement, leading to direct cell toxicity (complement-dependent cytotoxicity)

Monoclonal Antibodies for Cancer Treatment

Drug	Target	Therapeutic Application
Rituximab (A 1% - 50 ml) (Mabthera)	CD20	B-cell non-Hodgkin's lymphoma
Ibritumomab (Zevalin) *(+ Yttrium-90)*	CD20	B-cell non-Hodgkin's lymphoma Chronic Myelogenous Leukemia
Trastuzumab (Herceptin)	Epidermal growth factor receptor	Breast cancer
Bevacizumab (Avastin)	Vascular endothelial growth factor	Colorectal cancer Breast cancer Non-small cell lung cancer

Thanks for attention!