ENZYME THERAPY

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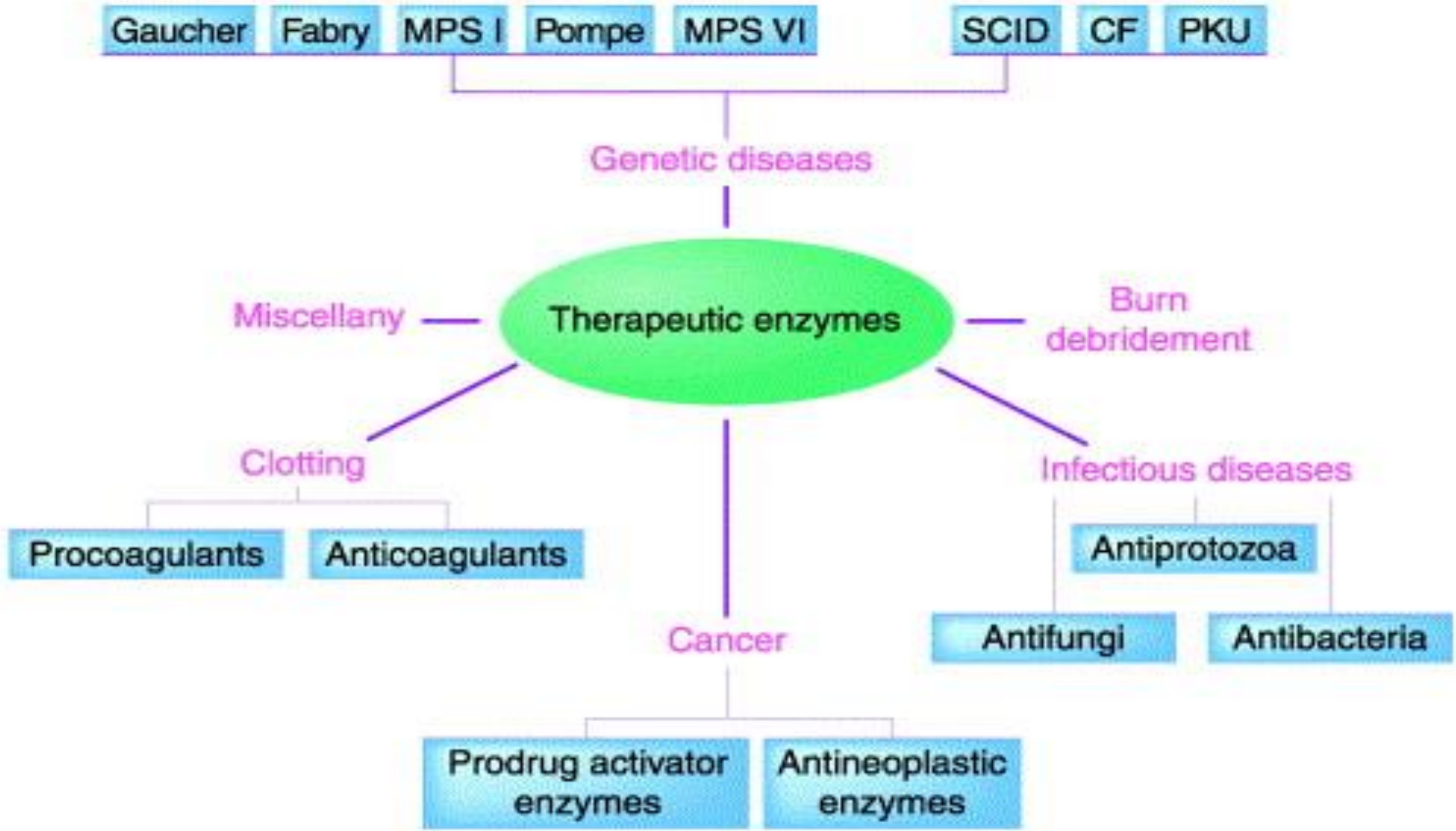
ENZYME THERAPY

- Enzyme therapy is a plan of dietary supplements of plant and animal enzymes used to facilitate the digestive process and improve the body's ability to maintain balanced metabolism.

- **Definition**: **The use of enzymes to correct metabolic and physiological processes**.

THERAPEUTIC ENZYMES

- Therapeutic enzymes have a broad variety of specific uses
  - Oncolytics
- Anticoagulants
- Thrombolytics
  - Replacements for metabolic deficiencies
    - Digestive aids
      - Metabolic storage disorders, etc
- Miscellaneous enzymes of diverse function


Gaucher
Fabry
MPS I
Pompe
MPS VI
SCID
CF
PKU
Genetic diseases
Therapeutic enzymes
Miscellany
Burn debridement
Clotting
Procoagulants
Anticoagulants
Infectious diseases
Antiprotozoa
Antifungi
Antibacteria
Cancer
Prodrug activator enzymes
Antineoplastic enzymes

Leukemia

- Leukemia is a cancer of the marrow and blood.

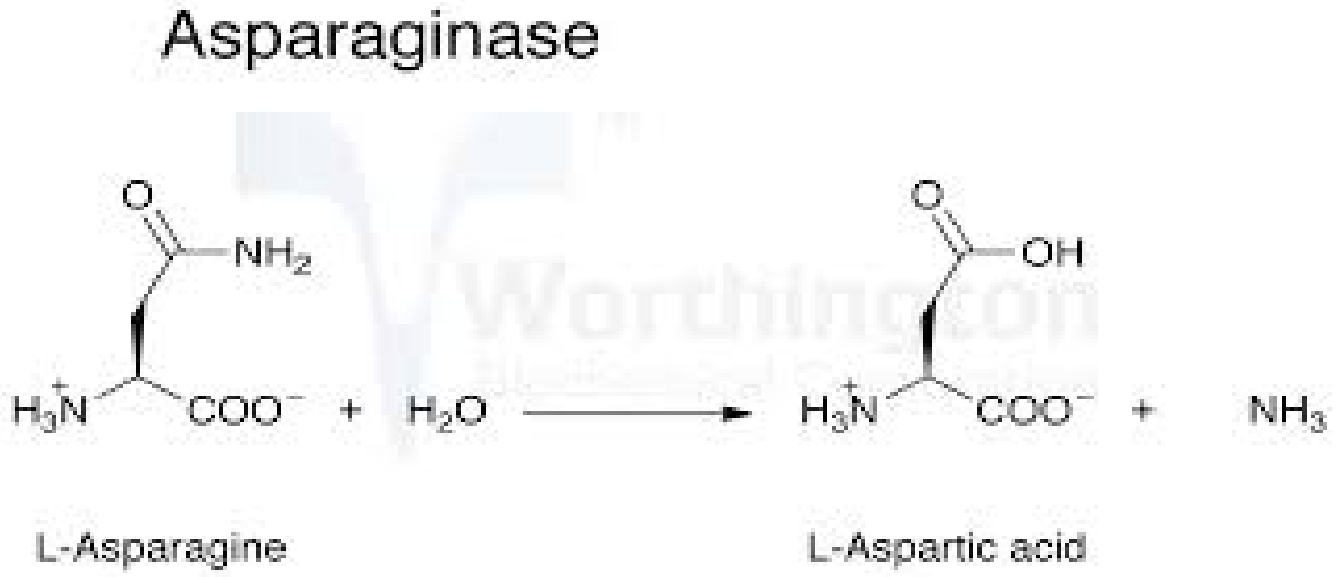
The four major types:

- Acute Myeloid Leukemia
- Chronic myeloid leukemia
- Acute Lymphoblastic Leukemia
- Chronic lymphocytic leukemia.

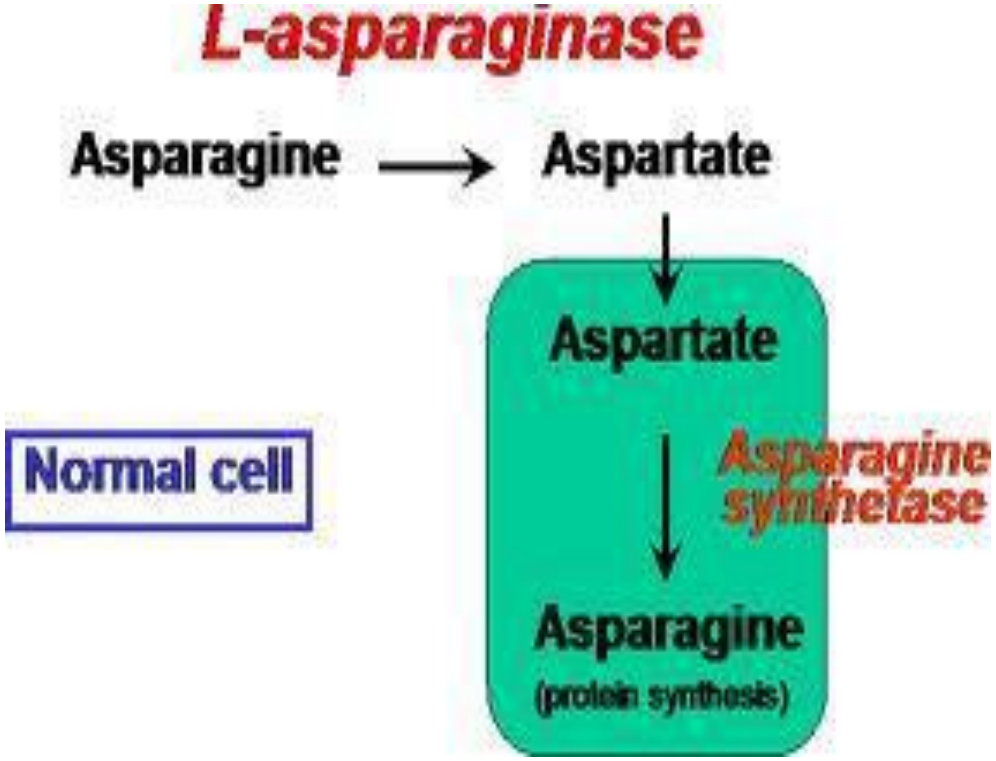
PEGASPARAGINASE (ONCASPAR)

The malignant cells are dependent on an exogenous source of asparagine for survival.

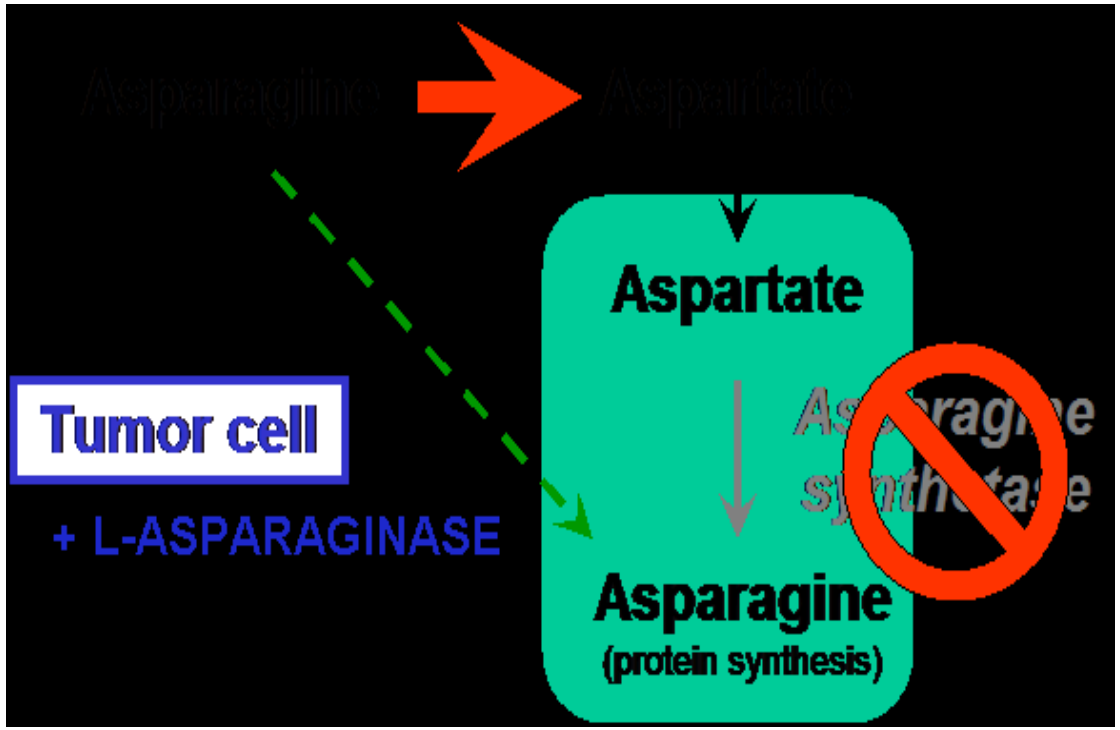
Normal cells, are able to synthesize asparagine and thus are affected less by the rapid depletion produced by treatment with the enzyme asparaginase. Oncaspar exploits a metabolic defect in asparagine synthesis of some malignant cells.



L-ASPARAGINASE IN NORMAL CELLS



L-ASPARAGINASE IN TUMOR CELLS



Other oncolytic enzymes

•**Diphtheria toxin** catalyzes transfer of the adenosine diphosphate ribose (ADP-ribose) moiety of nicotinamide adenine dinucleotide (NAD) to elongation factor 2.
•This enzyme halts protein synthesis.
•The protein synthesis in tumor cells is 100 to 10,000 time more sensitive to this toxin than the analogous process in normal cells.

•Enzymes that degrade macromolecules: neuraminidase, ribonuclease, and a diverse group of proteases

•**Neuraminidase** removes sialic acid residues from the surface of (neoplastic) cells, thereby altering their immunogenicity, and rendering them sensitive to immune response
•2000 --The FDA has approved the Orphan Drug application of Wobe-Mugosas an adjunct therapy for multiple myeloma. Wobe-Mugos(vitamins + proteolytic enzymes), used successfully in Europe in conjunction with chemotherapy since 1977

SOME THERAPEUTIC ENZYMES:-

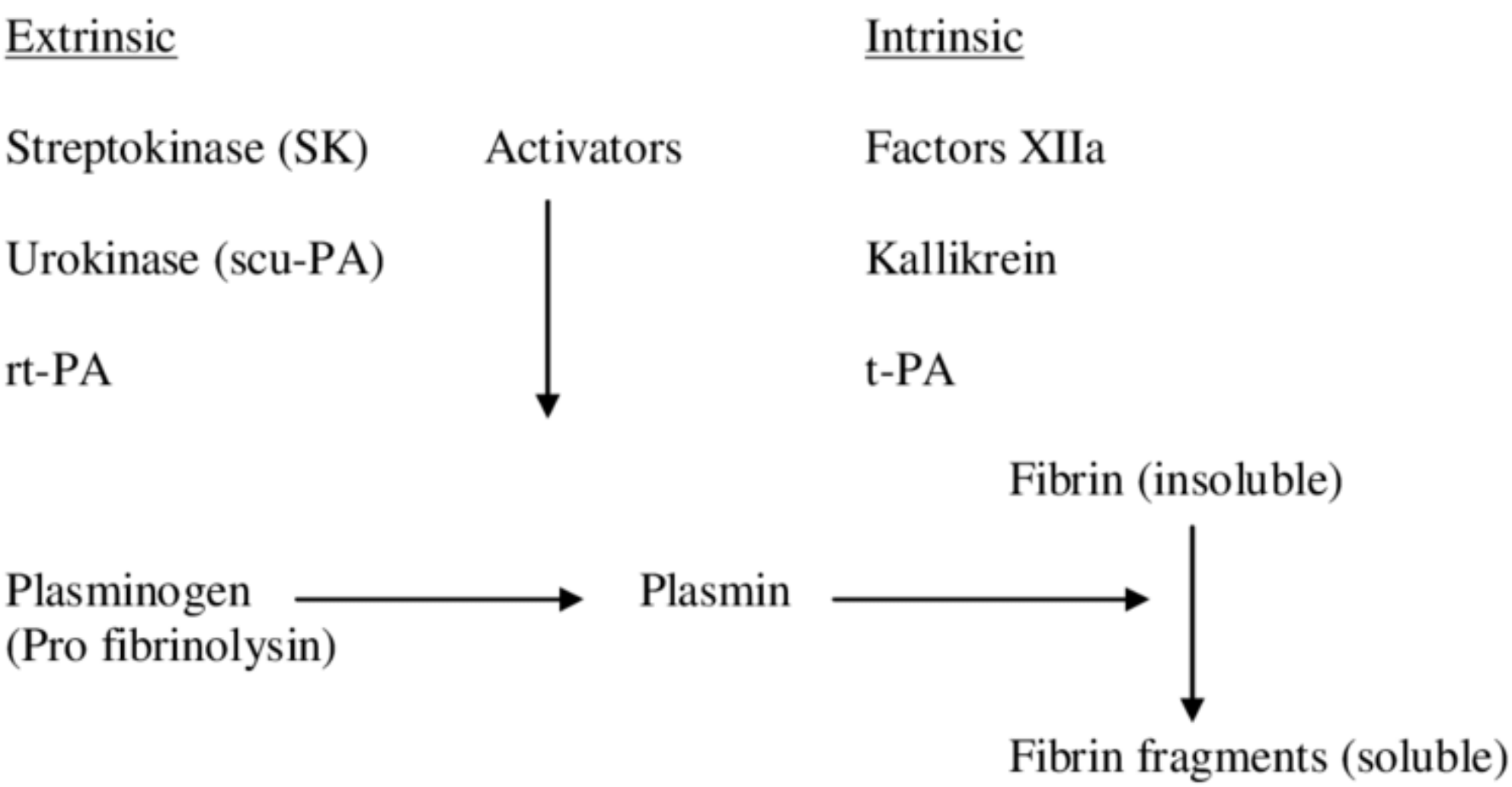
Enzyme	Reaction	Therapeutic use
Asparaginase	L-Asparagine + H_2O → L-aspartate + NH_3	Leukaemia
Collagenase	Collagen hydrolysis	Skin ulcers
Glutaminase	L-Glutamine + H_2O → L-glutamate + NH_3	Leukaemia
Hyaluronidase	Hyaluronate hydrolysis	Heart attack
Lysozyme	Bacterial cell wall hydrolysis	Antibiotic
Ribonuclease	RNA hydrolysis	Antiviral
β-Lactamase	Penicillin → penicilloate	Penicillin allergy
Streptokinase	Plasminogen → plasmin	Blood clots
Trypsin	Protein hydrolysis	Inflammation
Uricase	Urate + O_2 → allantoin	Gout
Urokinase	Plasminogen → plasmin	Blood clots

THROMBOLYTIC DRUGS (FIBRINOLYTIC)

FIBRINOLYSIS IS THE PROCESS BY WHICH FIBRIN IS REMOVED FROM DAMAGED BLOOD VESSELS. FIBRINOLYSIS IS ALSO IMPORTANT IN TISSUE REMODELLING/REPAIR AFTER INJURY AND TUMOUR METASTASIS.

- Streptokinase
- Tissue Plasminogen Activator(rt-PA)
- Urokinase

There are three major classes of **fibrinolytic** drugs: tissue plasminogen activator (tPA), streptokinase (SK), and urokinase (UK).



Streptokinase

It is a bacterial protein produced by group C *(beta)*-hemolytic streptococci.

Mechanism: It binds to plasminogen producing an "activator complex" that lyses free plasminogen to the proteolytic enzyme plasmin

Plasmin degrades fibrin clots as well as fibrinogen and other plasma proteins (non-fibrin specific)

- Pharmacokinetics:
  - The t½of the activator complex is about 23 minutes
  - The complex is inactivated by anti-streptococcal antibodies & by hepatic clearance.

Streptokinase(Sk) is produced by pathogenic strains of *streptococcus* and is a **blood clot-dissolving protease**.

- Sk complex with **plasminogen**→ **plasmin**→ **degrades fibrin**. Plasmin→ also degrades Sk.
- Plasmin cleaves peptide bonds after **Lys and Arg residues**.

STREPTOKINASE

Plasmin **cleaves Sk at Lys 59 and 386**and the 328 peptide has only 16% activity as the native molecule.

•To make Sk less susceptible, Lys at 59 and 386 were **changed to Glu** by site directed mutagenesis.

•Glu was chosen to replace Lys because the length of the side chain was similar and Glu does not have a +ve charge.

•Both single and double mutant retained their activity.

•Furthermore the half life of all three mutant increase and the double mutant was **21 fold more protease resistant** 3rded.

❑UROKINASE

Urokinase (UK) is a serine protease, which specifically cleaves the proenzyme/zymogen plasminogen to form the active enzyme plasmin. It specifically catalyzes the cleavage of the Arg-Val bond in plasminogen. The active plasmin is then able to break down the fibrin polymers of blood clots.

❑ Plasminogen Activator (t-Pa)

A serine protease secreted constitutively by vascular endothelial cells.
T-PA is the principal activator of PLG.

T-PA has a shortly half-life of 2-3 minutes in plasma due to the presence of a potent inhibitor termed PAI-1.

The affinity of t-PA for PLG increases significantly in the presence of a fibrin clot.

Cleavage of t-PA from a single chain molecular to a two chain molecule is also associated with an increase in its enzymatic activity

ENZYMES AS DIGESTIVE AIDS

•Most digestive aid preparations are based on depolymerases responsible from breakdown of polysaccharides, proteins and lipids

•Such preparations may include a single enzyme or multiple enzymes.

α-amylase: hydrolyse α1-4 glycosidic bonds

•Amylase from *B. subtilis*or species of *Aspergillus*have various industrial applications.

•Oral amylase administration is used to aid digestion.

Lactase: hydrolysis of the lactose

Various proteolytic enzymes, e.g. papain, pepsin.

•**Pancreatin**: a preparation extracted from pancreas containing various enzymes. used in deficiencies related with secretion of pancreatic enzymes (e.g. chronic pancreatitis, pancreatic carcinomas, **cystic fibrosis**)

NUCLEASE TREATMENT OF CYSTIC FIBROSIS

•Cistic fibrosis (CF) is one of the most commonly occuring genetic diseases (1 in 2500 in northern Europe).

•Major clinical symptom is the production of viscous mucus in the respiratory track.

- Change in lung physiology

bacterial infections

immune response

bacterial destruction

liberation of DNA

highly viscous mucus

Therapy:

- Bovine DNAse treatment was approved in USA in 1950s but prolonged usage caused adverse reactions.

Percussion therapy is used to help the ejection of mucus

- DNAse I produced by expression of cDNA in CHO cell lines (**Pulmozyme**) has been approved for medical use.

DNase enzymes break down the DNA, and the mucus is much easier to clear from the lungs.

THANK YOU