29.05.2020

MONDAY 15
WEEK 16

APRIL, 2013

VIROLOGY #1 WHAT IS A VIRUS

@ medical school

CORONAVIRUS

- lipid bilayer
- hemagglutinin
- spike protein
- membrane protein
- envelope glycoprotein
- nucleoprotein + RNA

WE LIVE AND PROSPER IN A CLOUD OF VIRUSES

- viruses infect all living things.
- we regularly eat and breathe billions of virus particles.
- we carry viral genomes as part of our genetic material.

THE NO. OF VIRUSES ON EARTH IS STAGGERING

$> 10^{30}$ bacteriophage particles in the world's oceans.

NOTES

APRIL 2013

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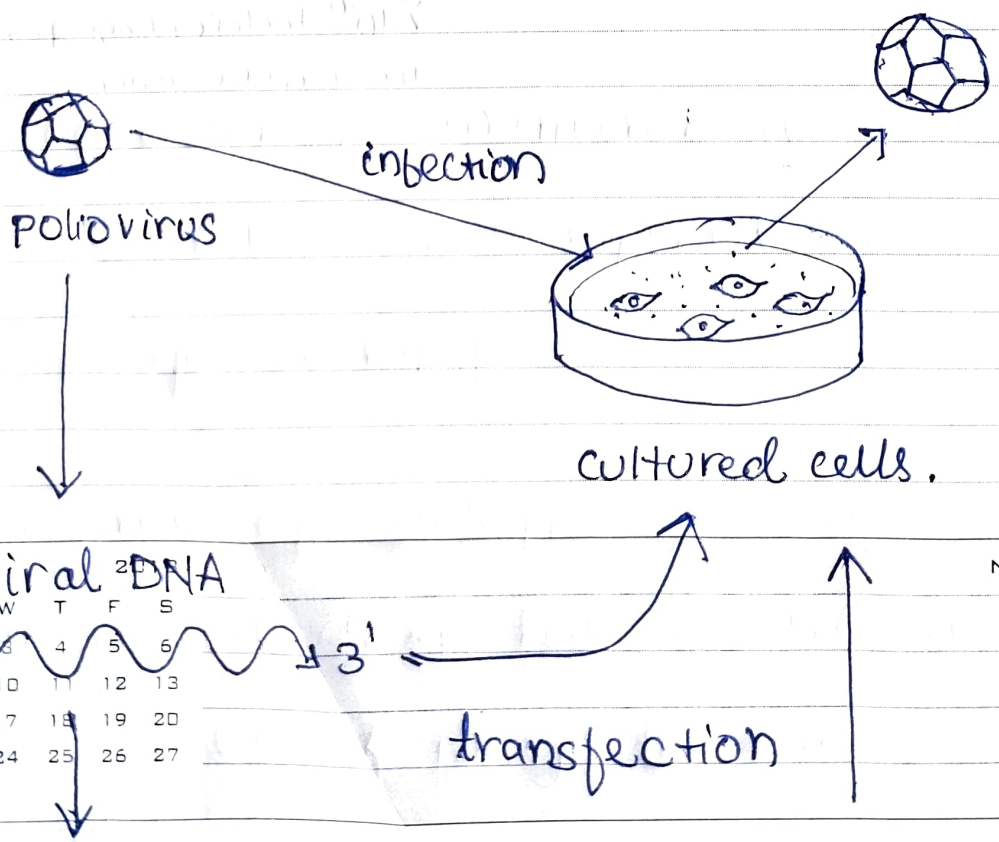
John's Hopkins University
Center for Systems Science and Engineering (CSSE)

- Phage therapy for bacterial infections
- gene therapy : deliver a gene to patients who lack the gene or carry defective versions
- to deliver antigens (viral vaccines)
- viral oncotherapy

INFECTIOUS VIRAL DNA - A KEY FOR VECTOR DEVELOPMENT



APRIL, 2013

WEDNESDAY 17
WEEK 16

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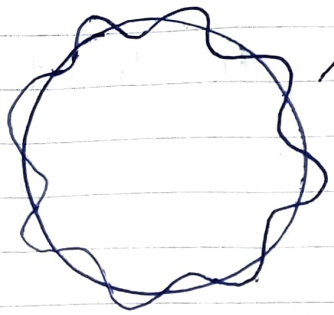
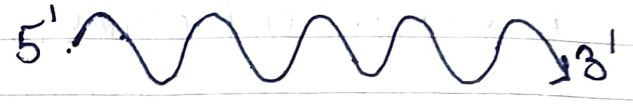
cDNA synthesis and cloning

transfection

transfection



poliovirus DNA



(+) strand RNA transcript

in vitro RNA ~~transcript~~ synthesis

NOTES

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PHAGE THERAPY

- after discovering phages in 1915, d'Herelle pursued their use to treat bacterial infections.

- co-founded eliava institute, 1923, active to this day

- produced phages for antibacterial therapy during WWII.

- introduction of antimicrobial drugs in 1930s and later dampened enthusiasm for phage therapy.

- emergence of widespread resistance to antimicrobial drugs has revitalized interest in use of phages to treat bacterial infections.

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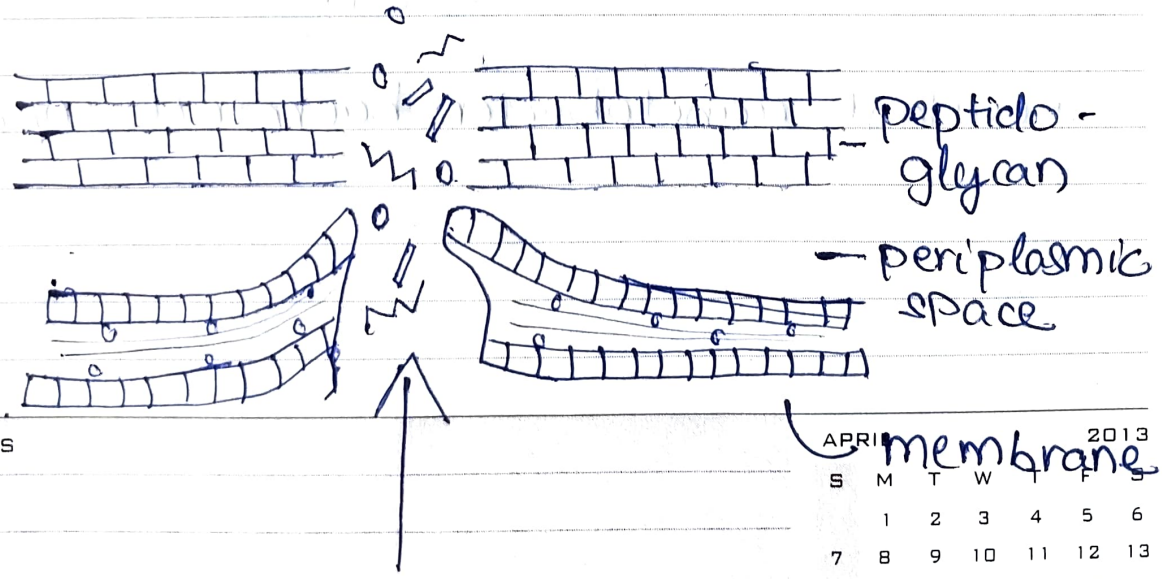
PRINCIPLES OF PHAGE THERAPY

- use of lytic bacteriophages to kill specific bacterial host (not beneficial flora).
- pathogenic bacterium must be identified, and phage sensitivities determined before treatment
- use of phage lysins for surface decontamination.
- agriphage: approved by EPA 2005 to field treat bacterial tomato canker.
- listshield: listeria phage approved by FDA for contamination of meat and poultry; first designation of GRAS.



change in osmotic pressure causes cell rupture

NOTES

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PHAGE THERAPY: CLINICAL SUCCESSES

- phage treatment of an aortic graft infected with pseudomonas aeroginosa.

- engineered bacteriophages for treatment of a patient with disseminated drug-resistant mycobacterium abscessus.

- development and use of personalized bacteriophage-based therapeutic cocktails to treat a patient with a disseminated

resistant acinetobacter baumanii infection.

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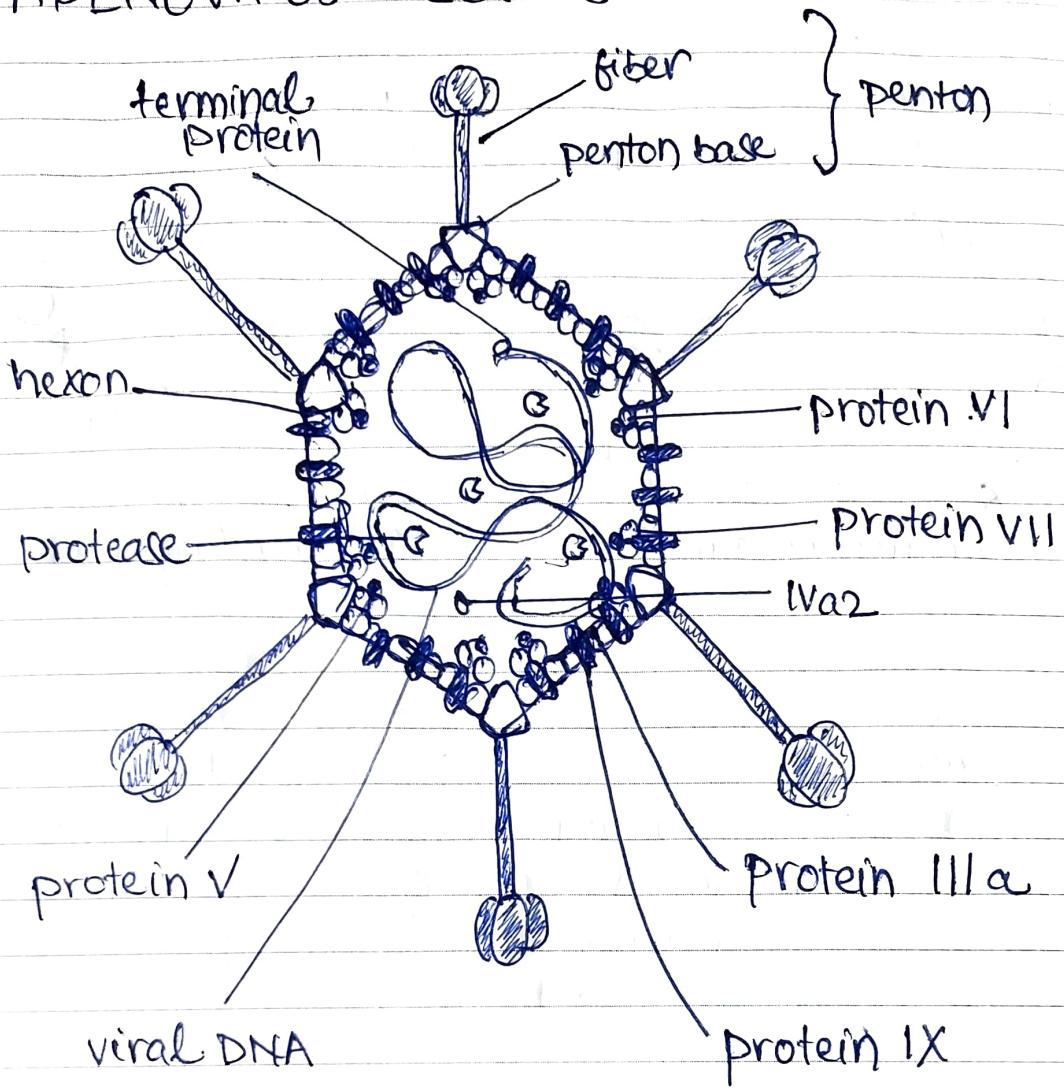
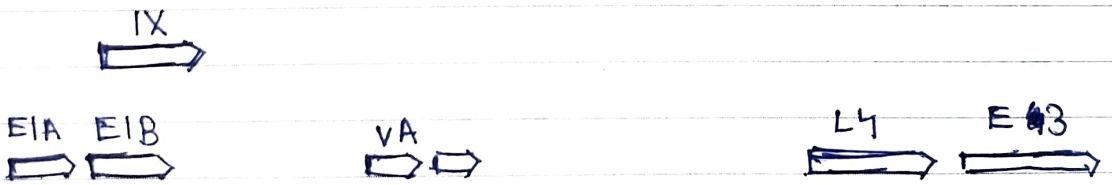
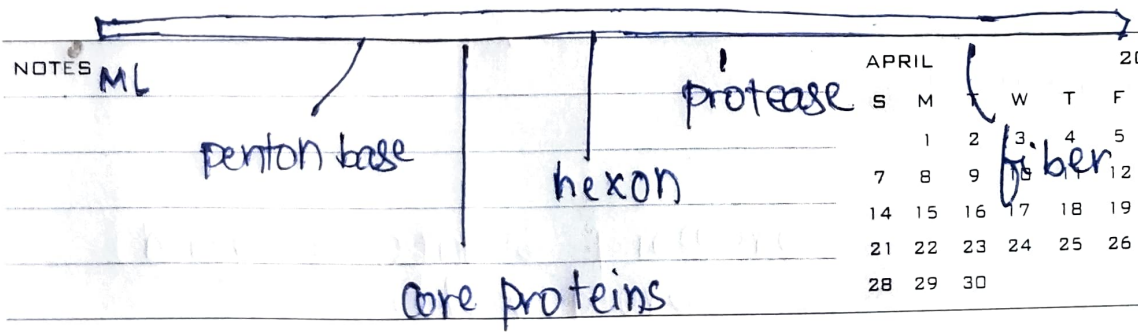
ADENOVIRUS VECTORS







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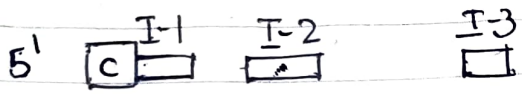
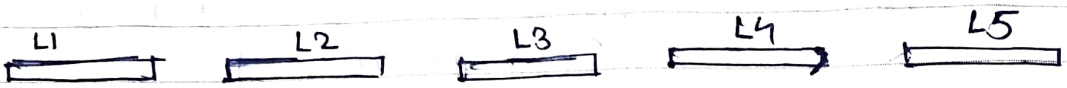
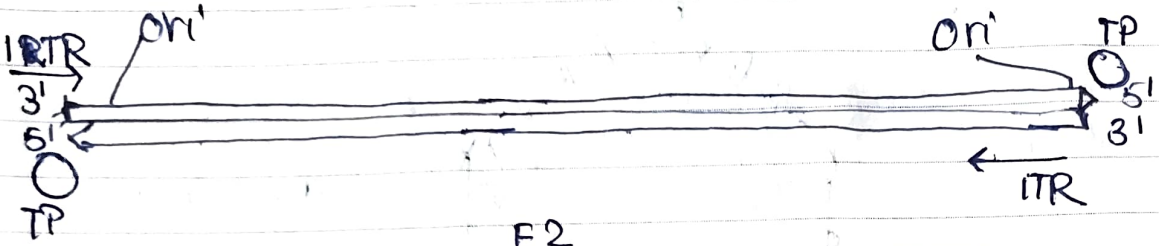
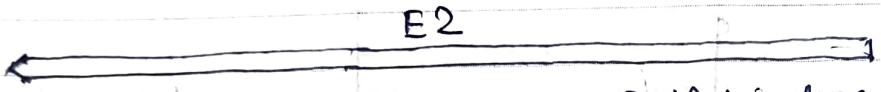


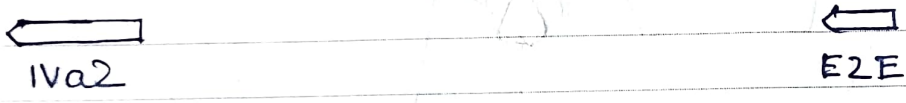






polymerase pre-TP

DNA binding protein DBP



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R

ADENOVIRUS VECTORS

- efficiently infect post-mitotic cells.
- fast (48h) onset of gene expression
- episomal, minimal risk of insertion mutagenesis.
- upto 37 kb capacity
- pure, concentrated preps routine
- >50 human serotypes, animal serotypes.
- drawback: immunity

> chimpanzee adenovirus being used for
> SARS-COV 2 vaccine.

> if you have run into immunity in
> the population, you can switch serotypes

NOTES

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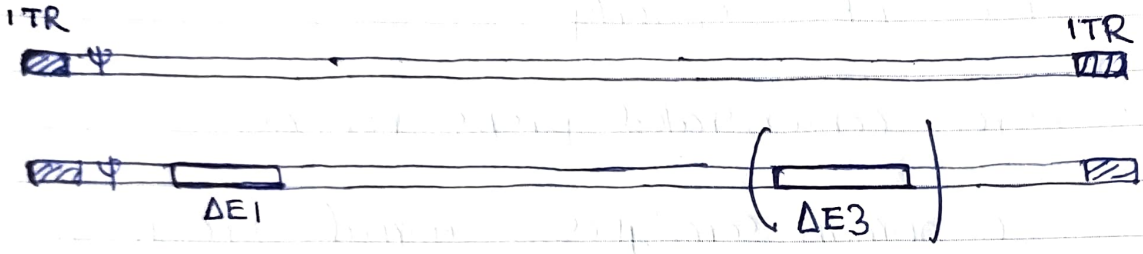
ADENOVIRUS VECTORS

- first generation vectors: E1, E3 deleted.
- E1 : encodes T antigens (Rb, p53)
- E2 : not essential, immunomodulatory proteins.



- second generation vectors: E1, E3 deleted, plus deletions in E2 or E4.
- more space for transgene.

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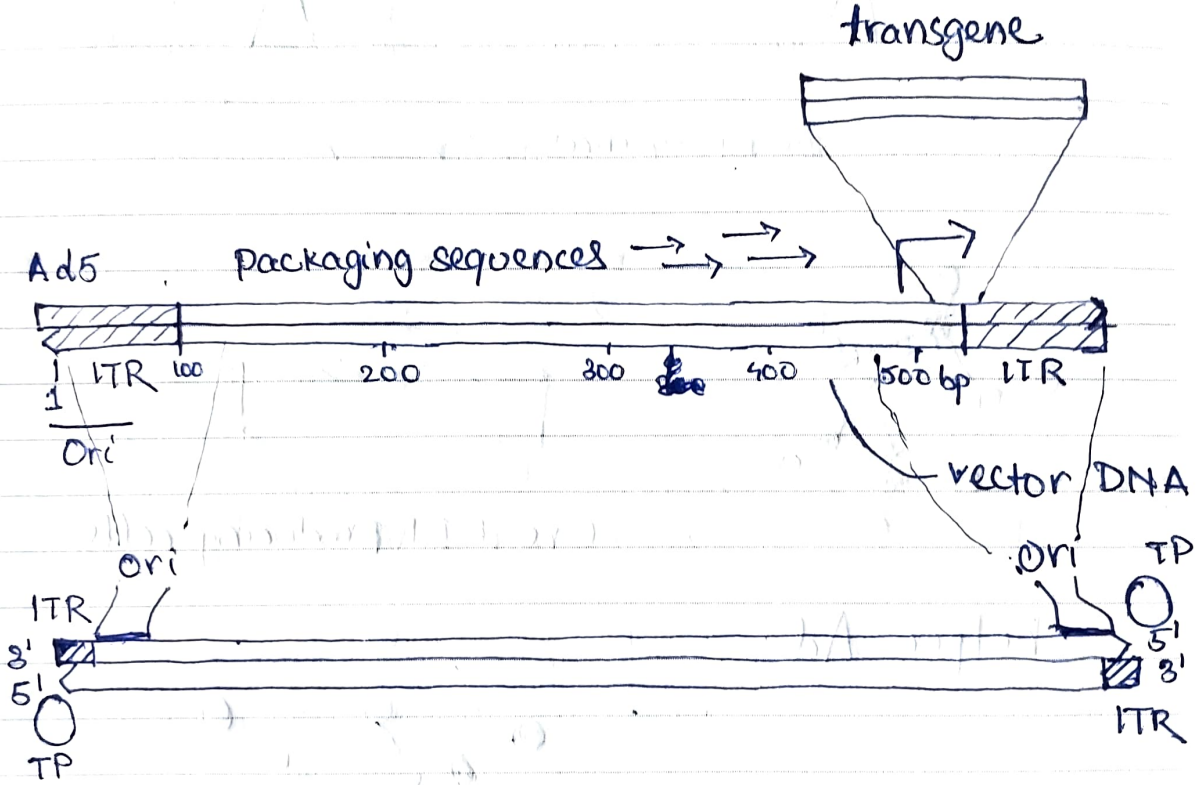
ADENOVIRUS VECTORS

- third generation 'gutless' vectors: all genes deleted, contain only two ITRs and psi.
  - psi: packaging sequences.
- require helper virus, which is E1-deleted.



NOTES ITR = inverted terminal repeats
- required for DNA reproduction

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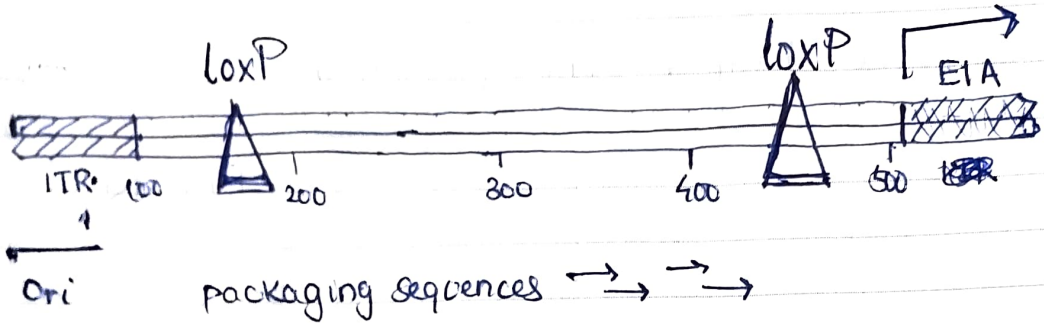
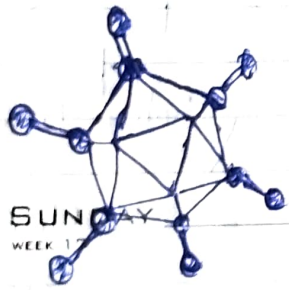
ADENOVIRUS VECTORS

- helper Ad has loxP flanking psi
- propagation in Cre producing cells yields helper that cannot be packaged.

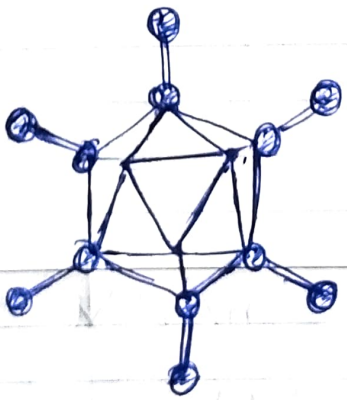




Cre + E1 producing cells.

helper Ad

these viruses will make no particles.



Only vector DNA packaged.

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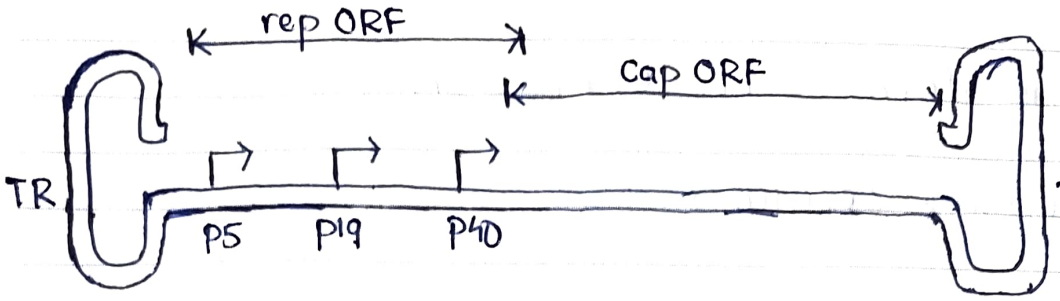
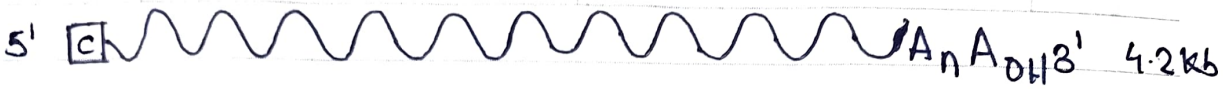
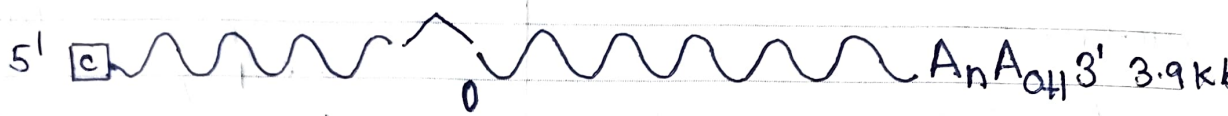
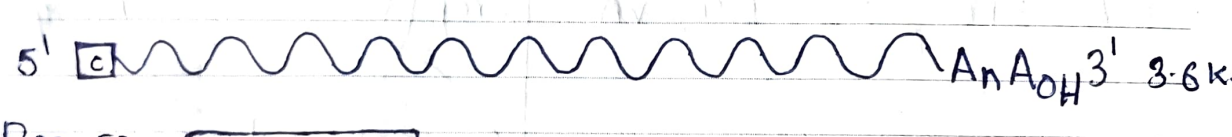
ADENOVIRUS - ASSOCIATED VIRUS VECTORS

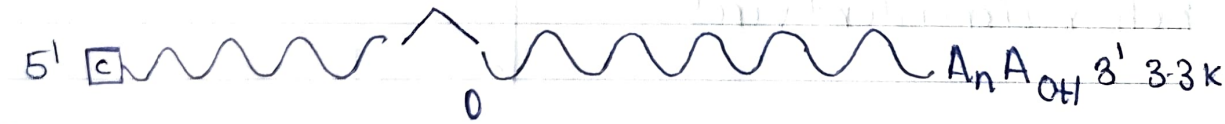


4.6 kb









NOTES

ssDNA
single stranded DNA
genome
vs RNA?

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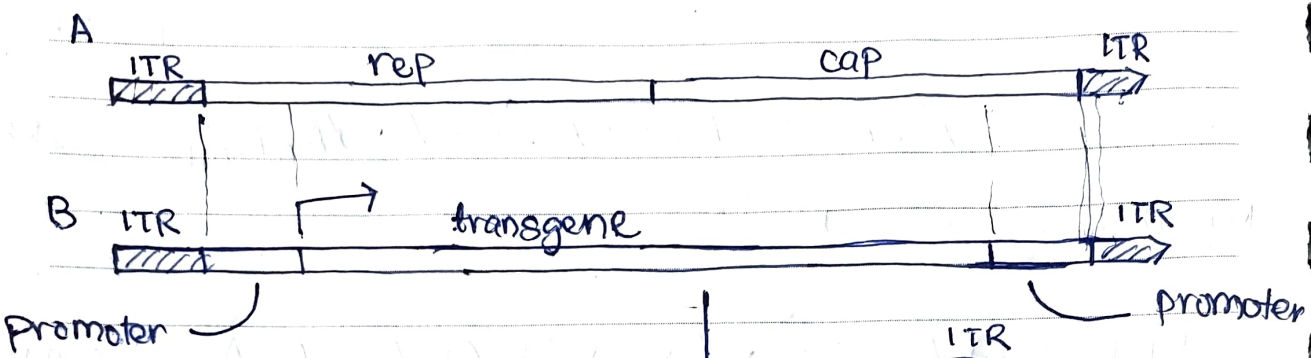
ADENO VIRUS - ASSOCIATED VIRUS VECTORS

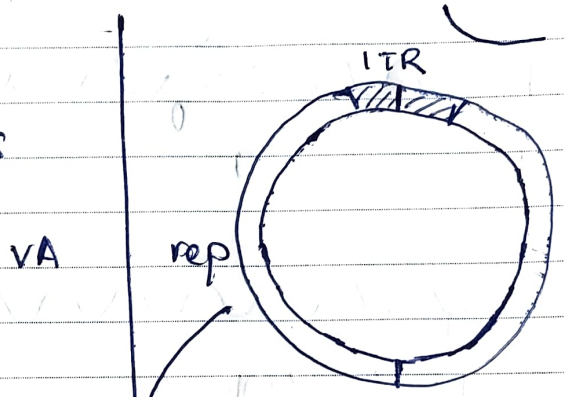
- ✓ long-term gene expression
- multiple serotypes



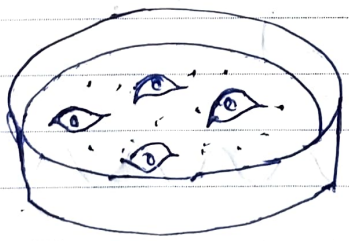
+ Ad. helper functions

E1A, E1B, E2, E4, VA

helper dependent virus



plasmids.



rAAV

recombinant AAV

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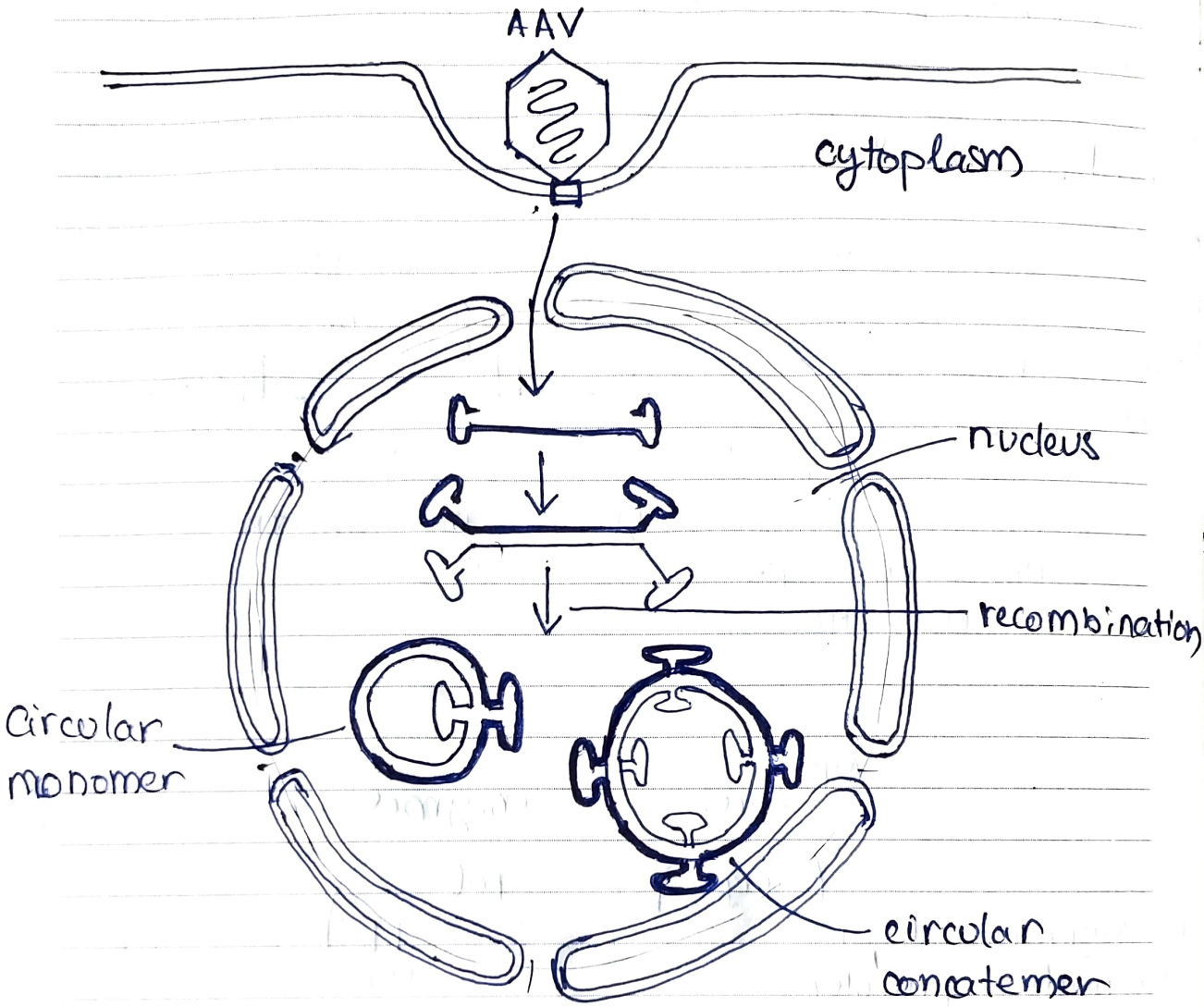
FORMATION OF EPISOMAL AAV DNA



NOTES

MAY 2013

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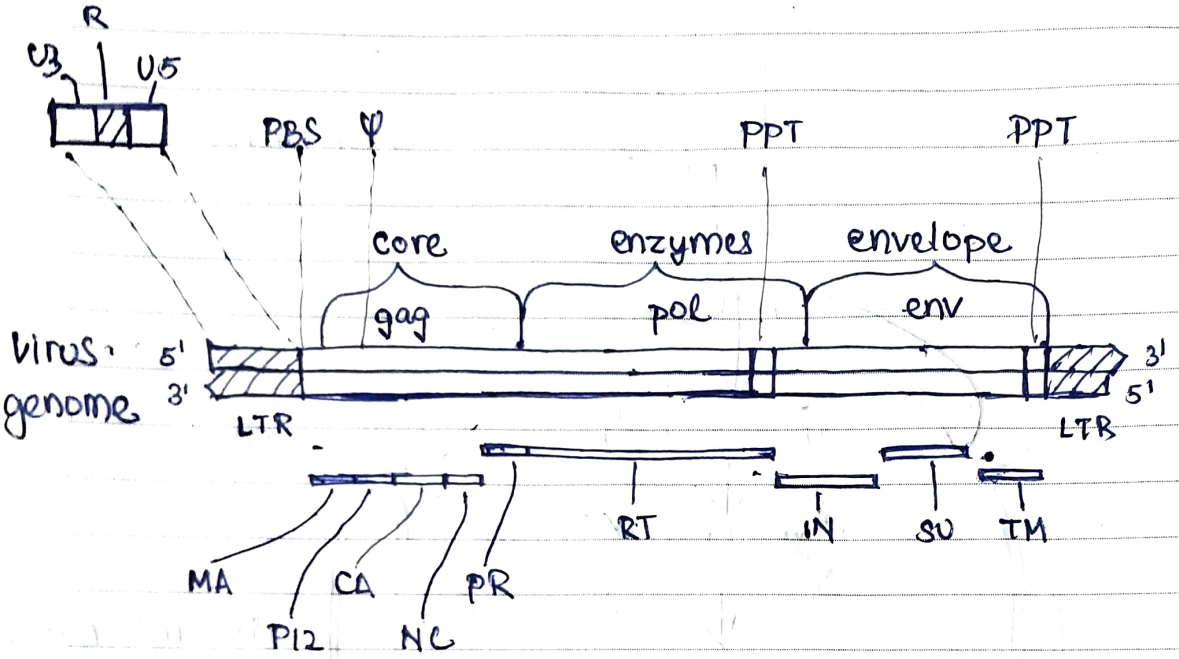
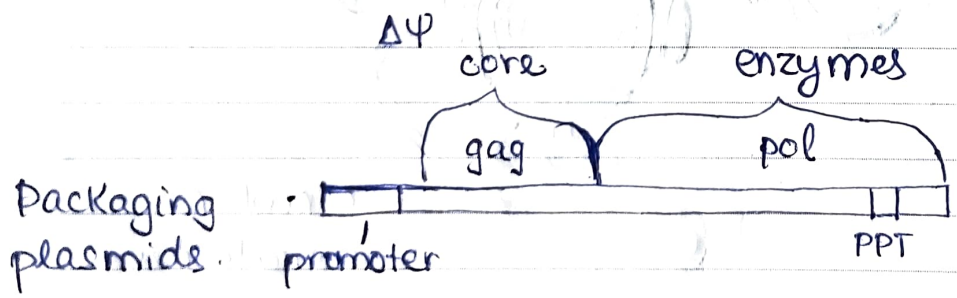
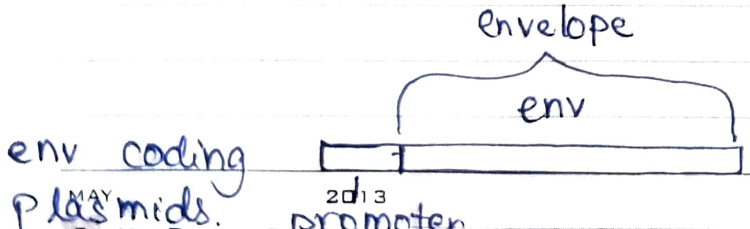
RETROVIRUS VECTORS

MLV-BASED VECTORS







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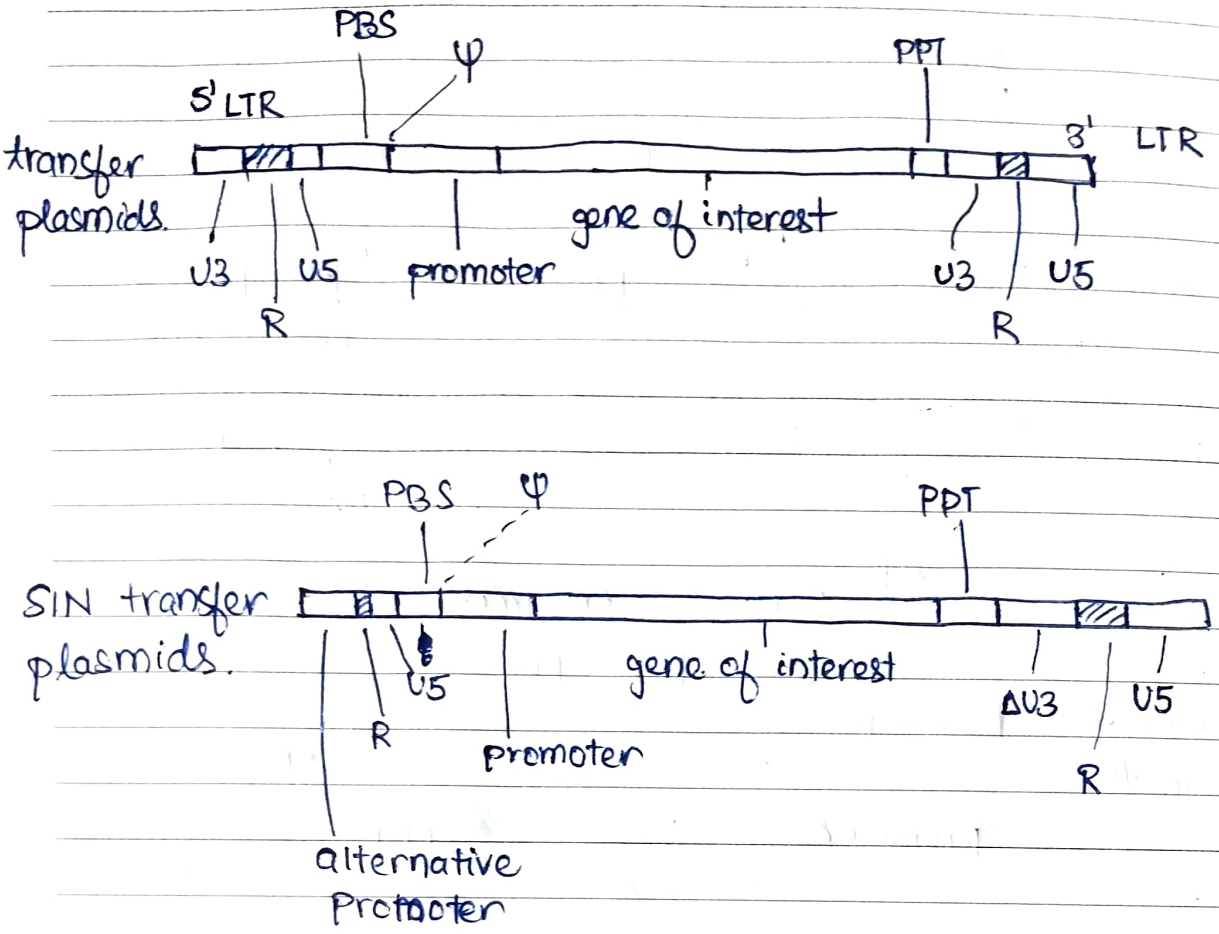

SIN - self inactivating

NOTES

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04 SATURDAY
WEEK 18

MAY, 2013

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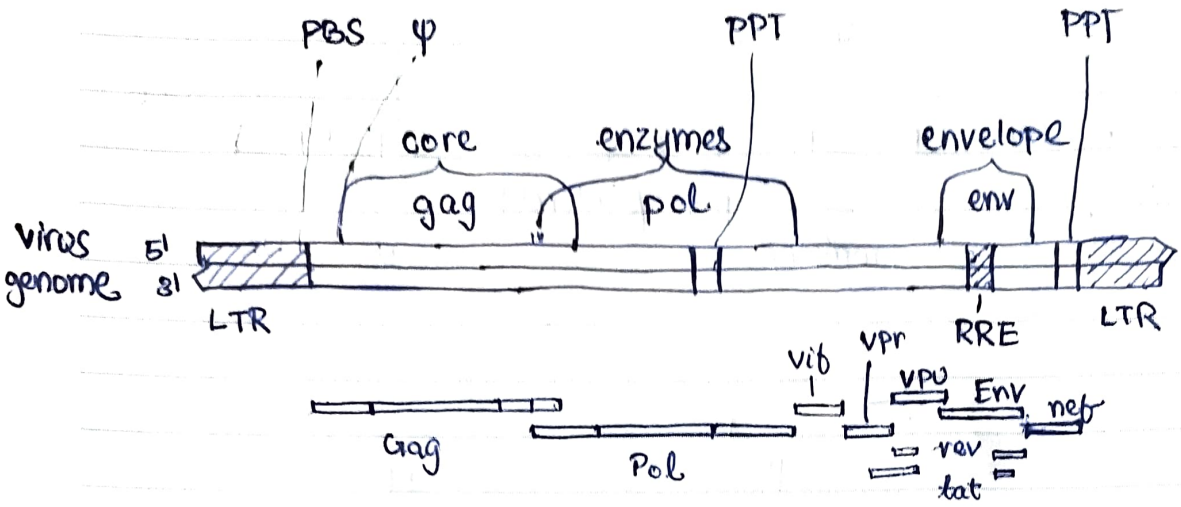
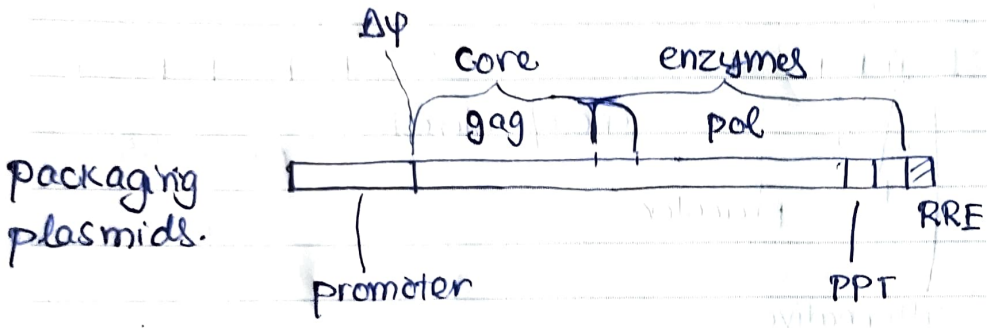
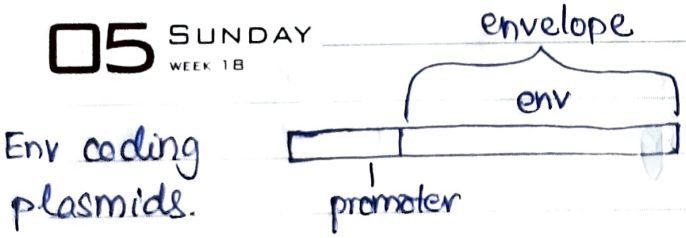
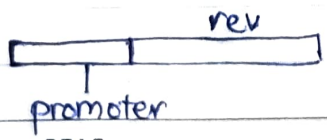
HIV-1 BASED VECTORS





05 SUNDAY
WEEK 18





MAY 2013

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NOTES

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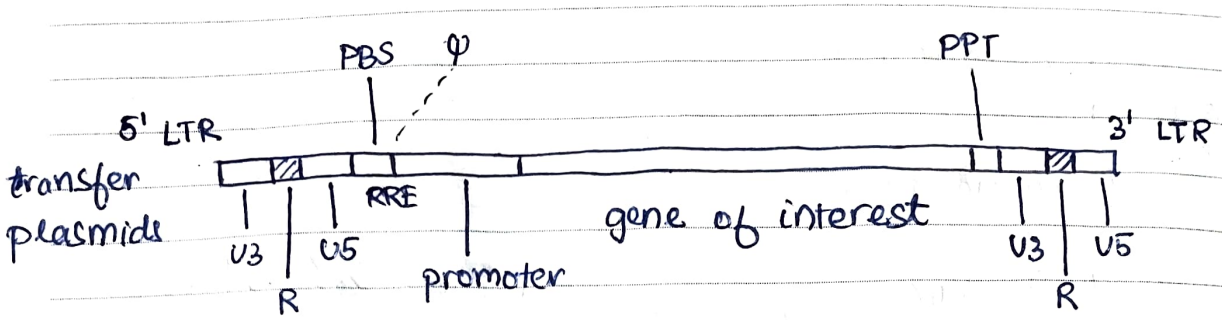

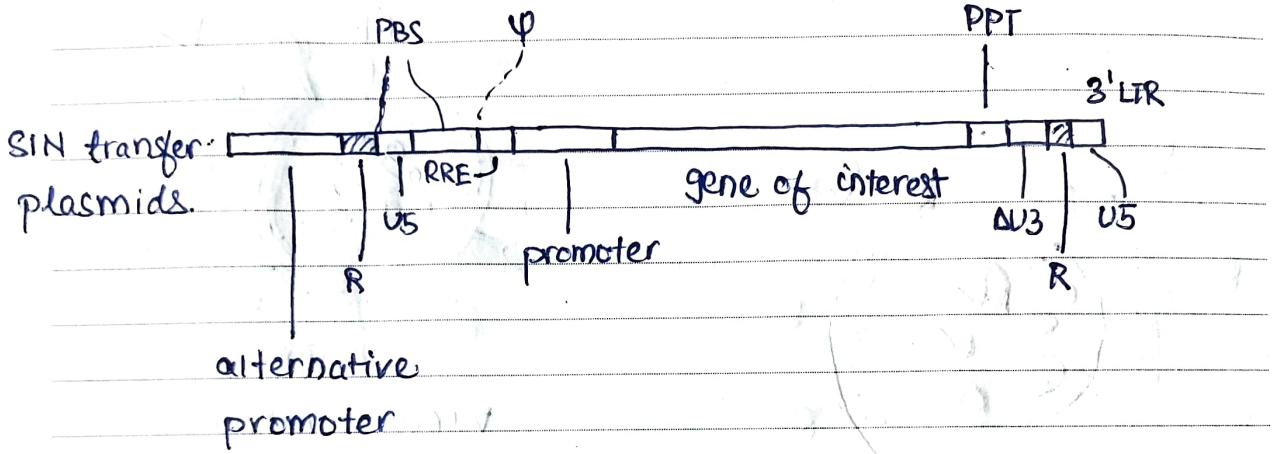

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07 TUESDAY
WEEK 19

MAY, 2013

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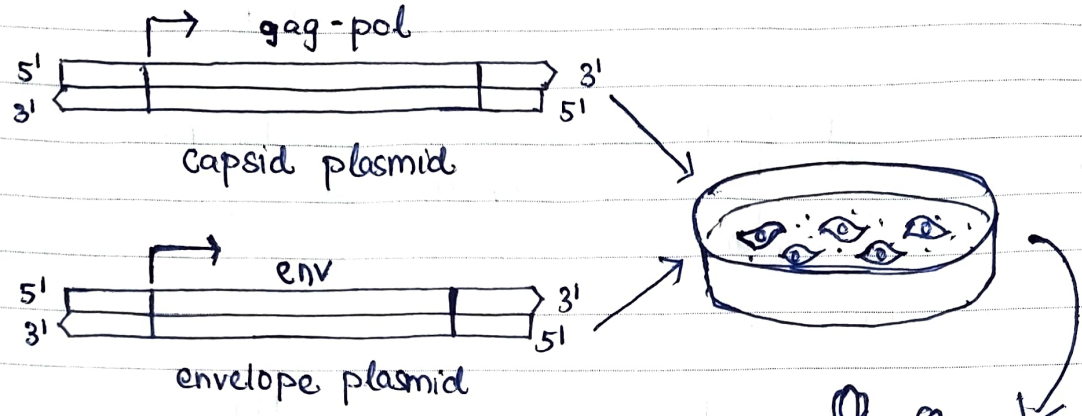
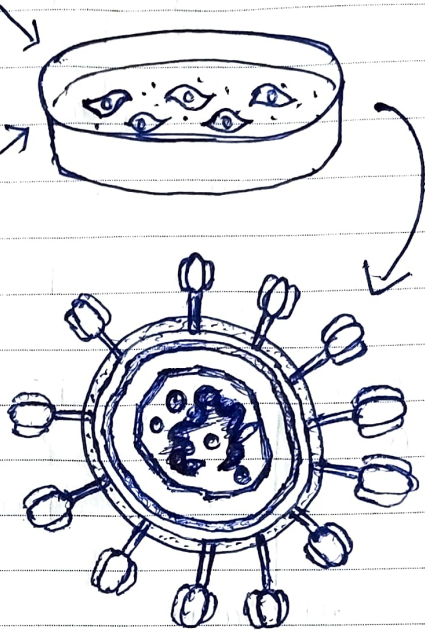
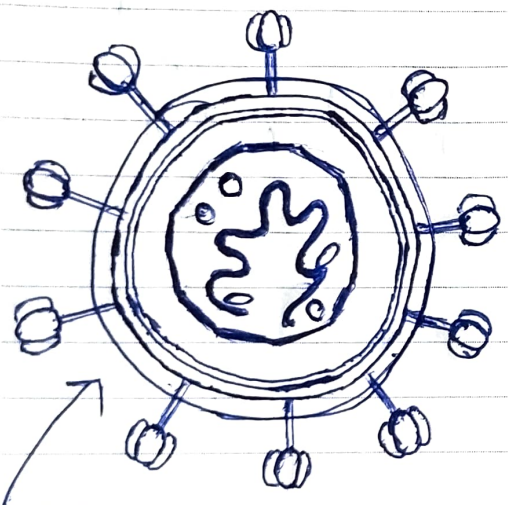
RETROVIRUS VECTORS

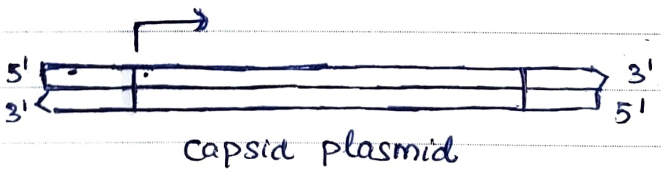


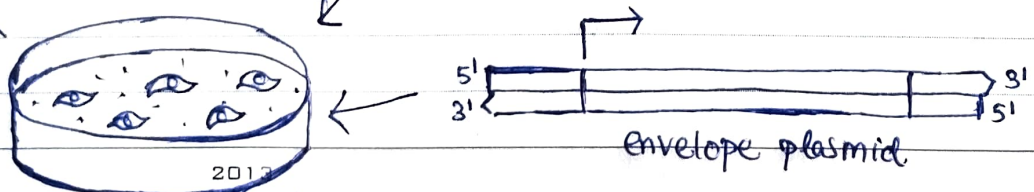


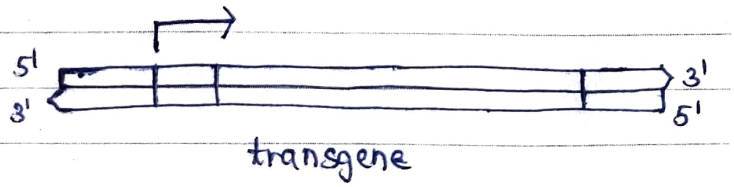
virus without genome



retrovirus containing foreign genome







MAY 2013

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NOTES

MAY, 2013

WEDNESDAY 08
WEEK 19

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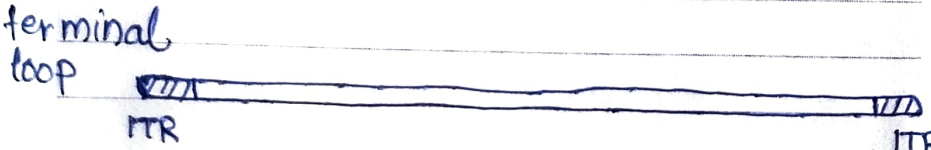
RETROVIRUS VECTORS

- based on lentiviruses (HIV-1) or other retroviruses.
- HIV can infect non-dividing cells
- long term expression (provirus)
- upto ~8 Kb transgene inserts
- possibility for insertional mutagenesis (3'LTR inactivated or integration-deficient)
- pseudotyping with VSV G

POXVIRUS VECTORS

- modified vaccinia virus Ankara, originally produced as alternative smallpox vaccine, part of US strategic national stockpile.
- replication-deficient vector: infectious in avian but not mammalian cells (passaged in chicken cells, assembly block).
- BSL-1, large capacity, also canary poxvirus.

NOTES



poxviridae (130-375 kbp)

MAY 2013

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09 THURSDAY
WEEK 19

MAY, 2013

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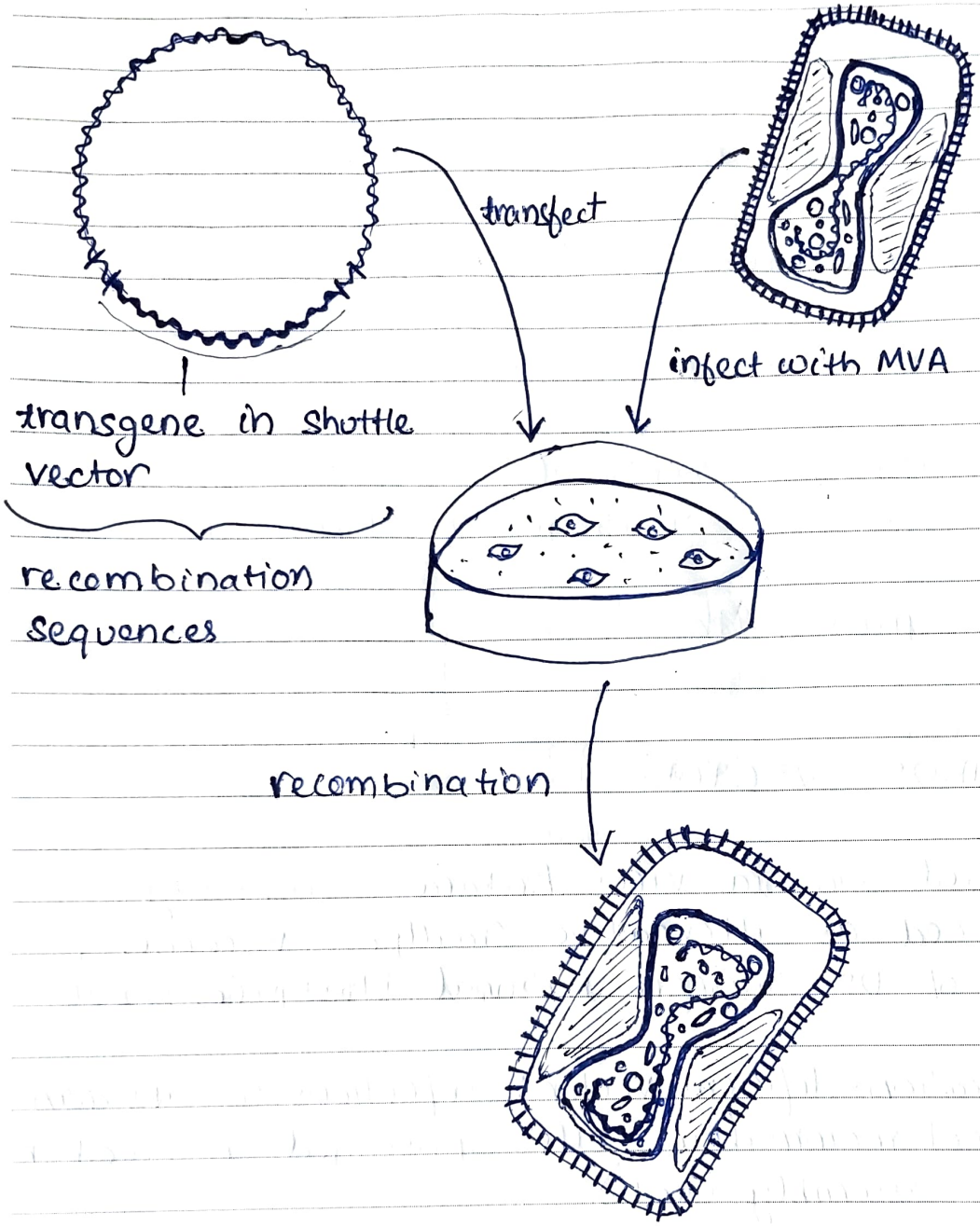
MODIFIED VACCINIA VIRUS ANKARA (MVA)



MAY 2013

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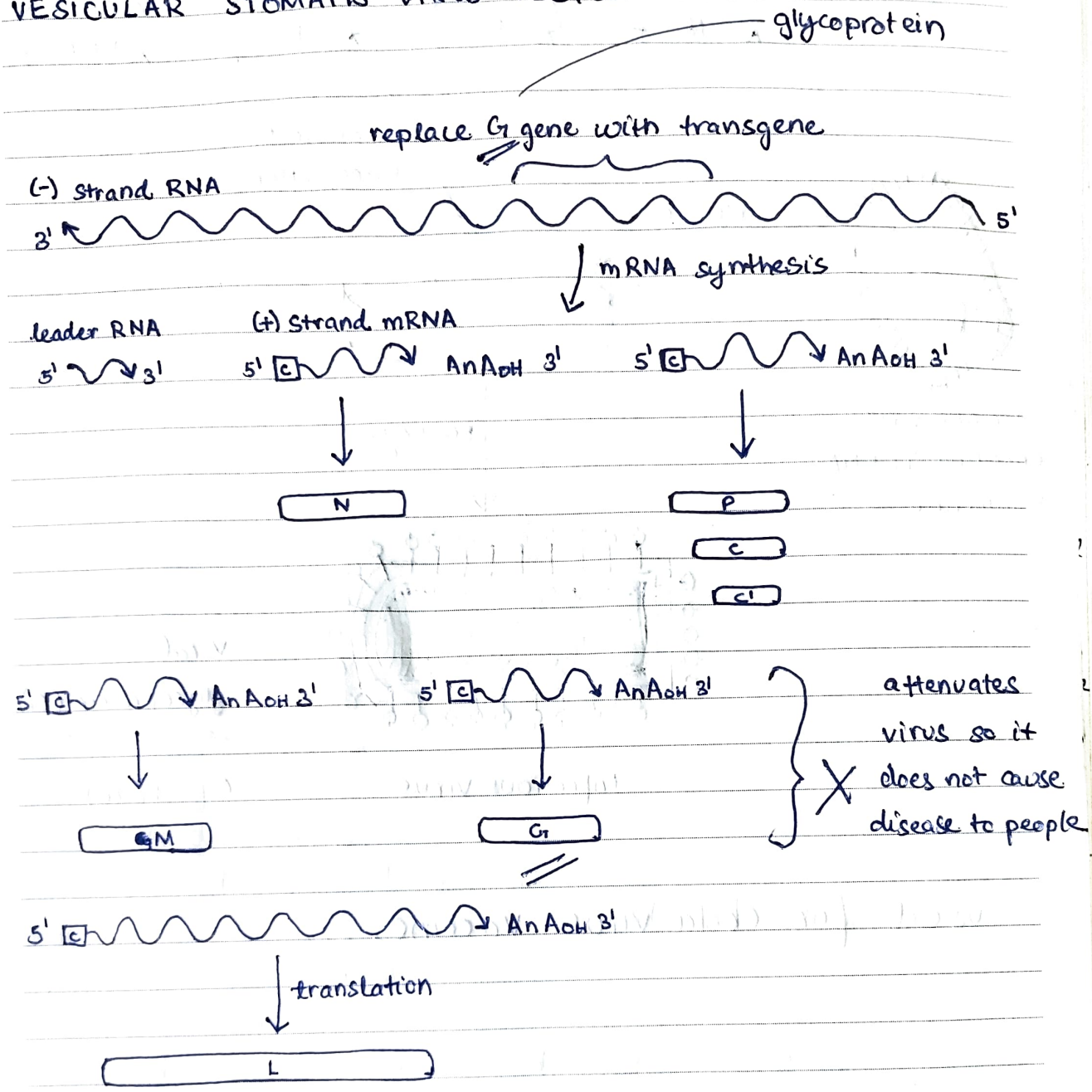
NOTES

MAY, 2013

FRIDAY 10
WEEK 19

29.5.2020
22

VESICULAR STOMATIS VIRUS VECTOR



mRNA - messanger RNA

NOTES

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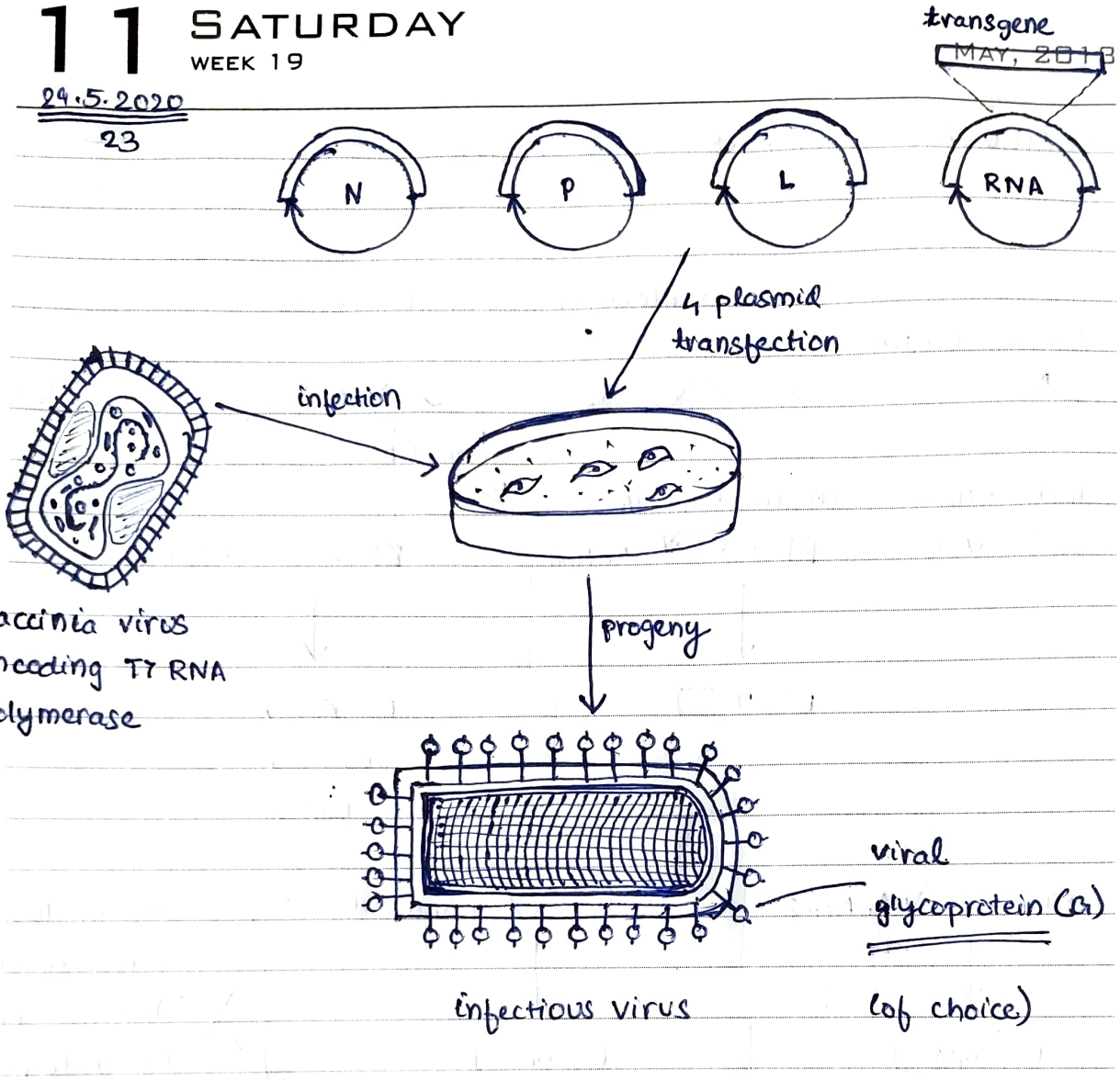
11 SATURDAY
WEEK 19

24.5.2020
23



12 SUNDAY
WEEK 19

- used for ebola virus vaccine

MAY 2013

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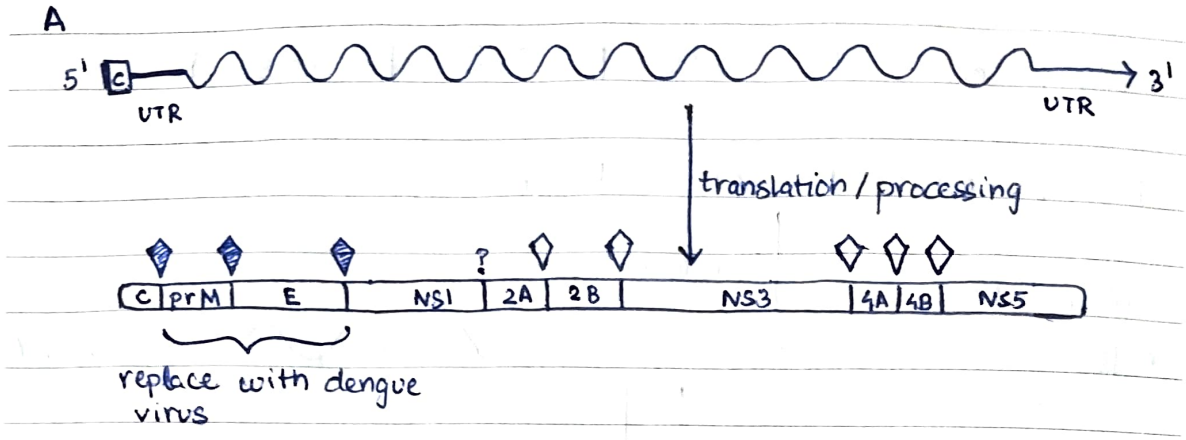
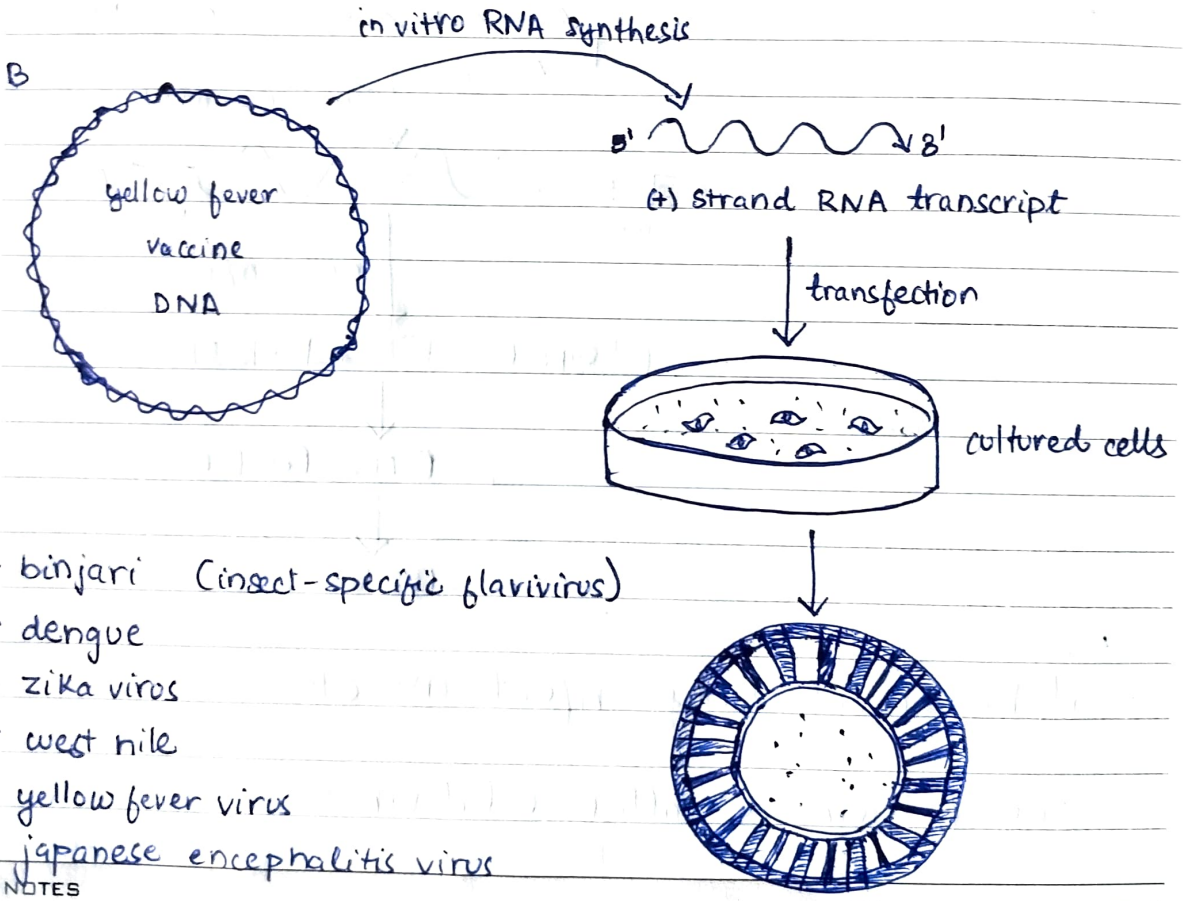
NOTES

29.5.2020
24

FLAVIVIRUS VECTORS





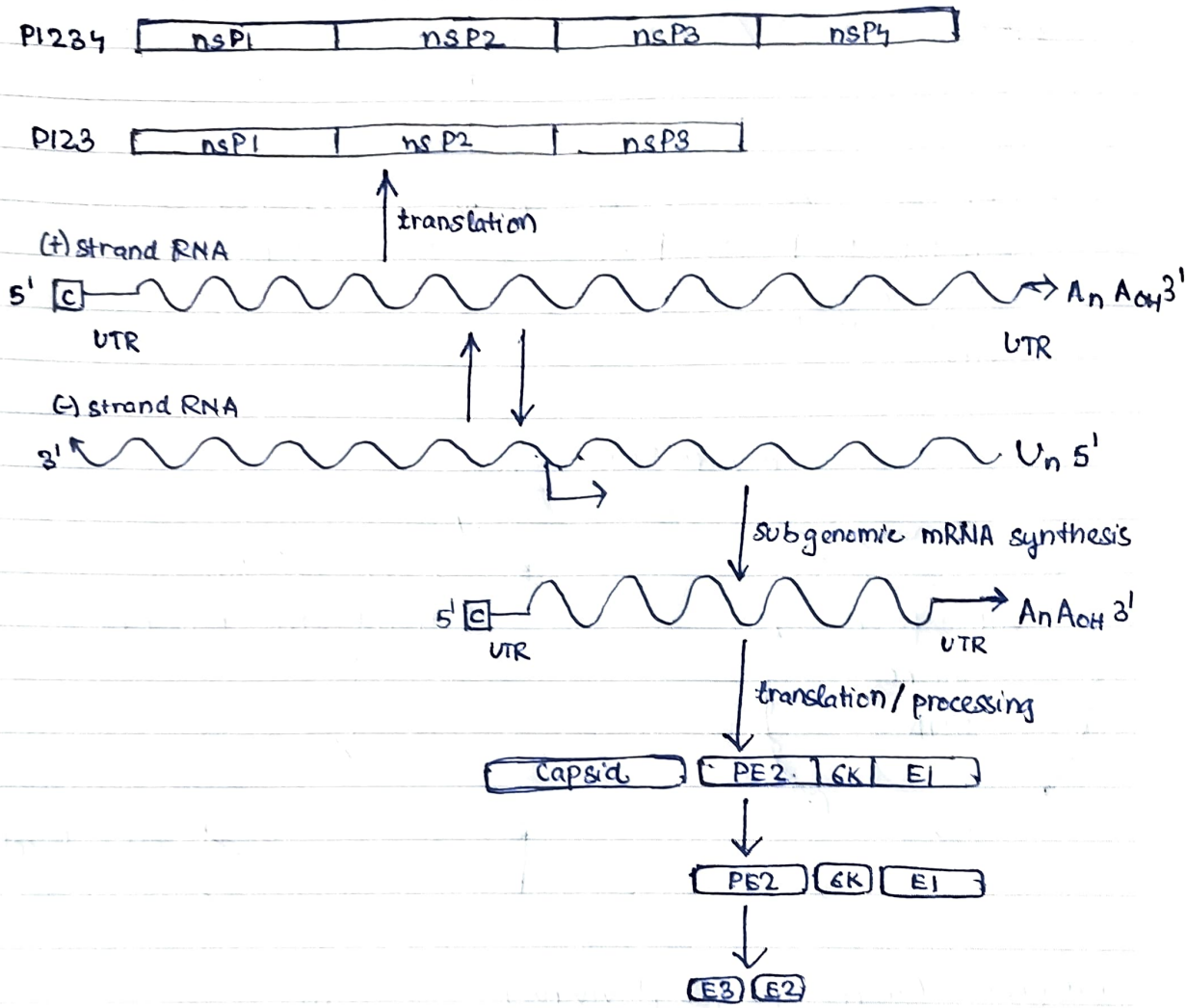
- binjari (insect-specific flavivirus)
- dengue
- zika virus
- west nile
- yellow fever virus
- japanese encephalitis virus

NOTES

types of flavivirus

4.6.2020

ALPHAVIRUS VECTORS

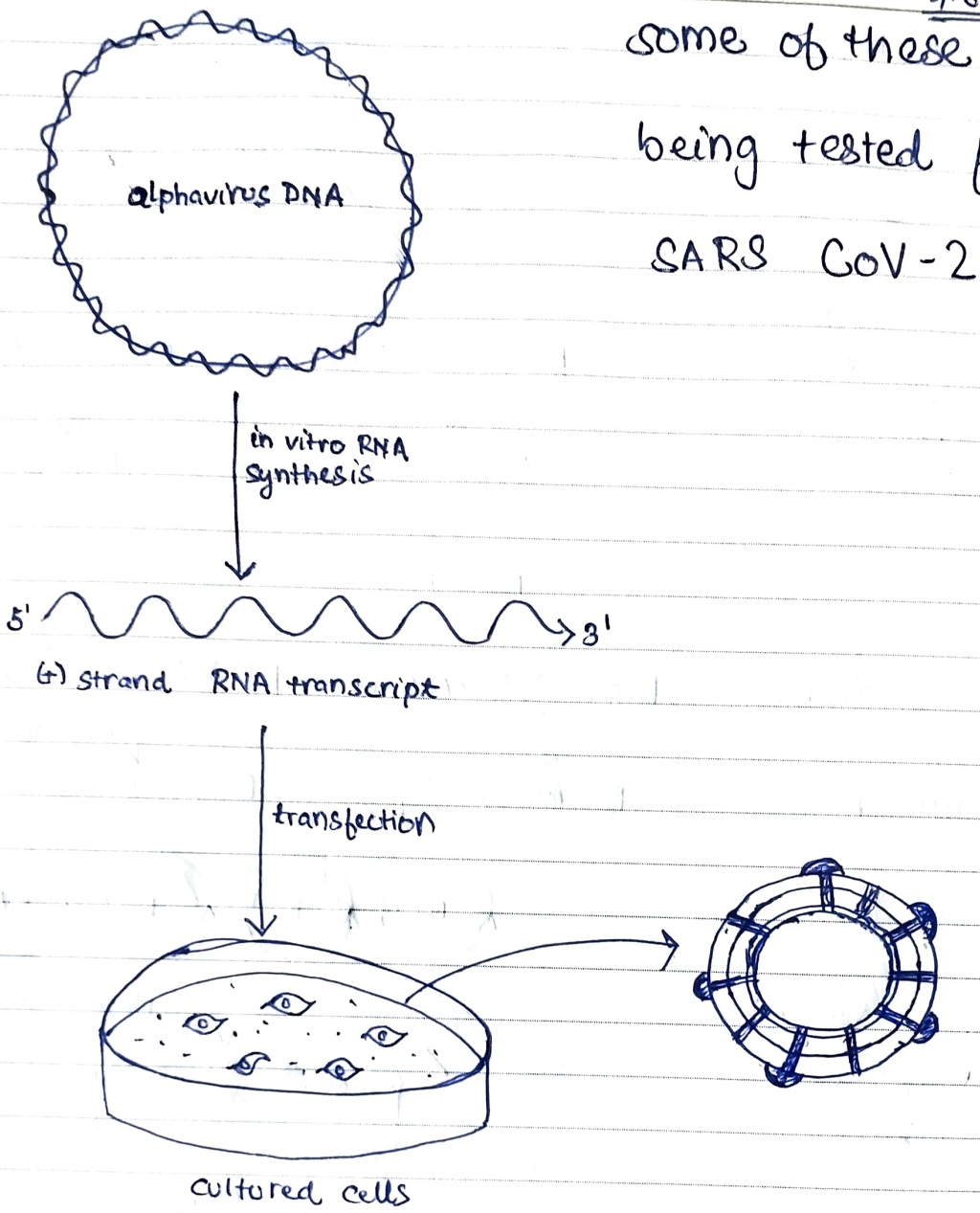


(some)

- alphaviruses only infect insects
- one of them is called eilat virus.

4.6.2020

some of these are being tested for SARS CoV-2

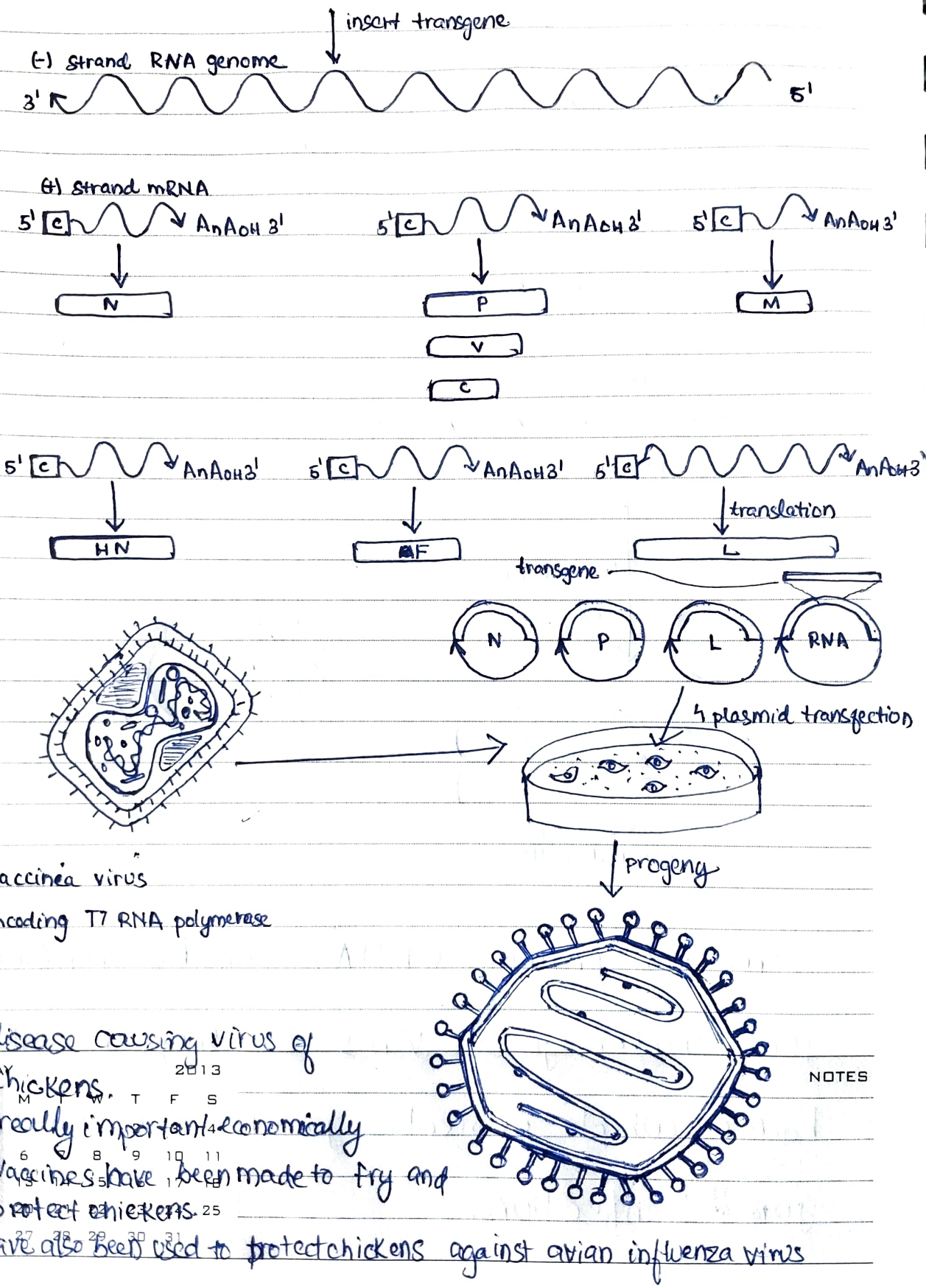


- Structural proteins (DNA) can be replaced with chicken guinea virus to trigger anti-bodies which protect against future chicken guinea infection.

NOTES

4.6.2020
-3

NEWCASTLE DISEASE VIRUS VECTORS



vaccinea virus
encoding T7 RNA polymerase

- disease causing virus of chickens.
- really important economically
- Vaccines have been made to try and protect chickens.
- have also been used to protect chickens against avian influenza virus

4.6.2020

LICENSED VACCINES THAT USE VIRAL VECTORS

- ervebo - glycoprotein coding region from Zaire ebolavirus in VSV vector

- dengvaxia - prME coding region of 4 dengue virus serotypes in yellow fever vaccine vector. + dengue

- yellow fever vaccine vector - japanese encephalitis virus (human), west nile virus (horses).

- new castle disease virus vector - H5 avian influenza virus (chickens)

NOTES

18 SATURDAY
WEEK 20

MAY, 2013

4.6.2020

EXPERIMENTAL HUMAN VACCINES THAT USE VIRUS VECTORS

X • adenovirus type 5 / HIV-1 gag, pol, nef genes.

✓ • Ad26.Zebov - ebolavirus glycoprotein gene

• MVA - influenza H5 influenza virus.

• MVA - HIV-1 env; canarypox RV144 AIDS trial.

• MVA - MERS-CoV (camels)

• AAV - HSV, HPV, HIV-1, SARS-CoV

• VSV - MERS-CoV

• all platforms for SARS CoV-2

19 SUNDAY
WEEK 20

MVA - modified vaccinia ankara

HSV - herpes simplex virus

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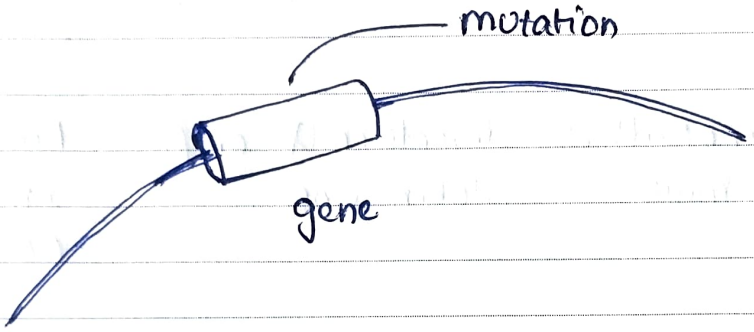
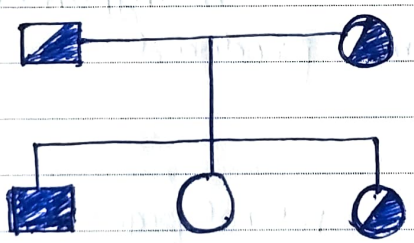
NOTES

4.6.2020

GENE THERAPY FOR MONOGENIC DISEASES.

- caused by mutation in one gene
- > 6000, 1 out of 200 live births.
- amenable to viral gene therapy.
- > 1800 clinical trials.





(inheritance pattern
(dominant or recessive)

NOTES

4.6.2020

	DISEASE	DEFECT	INCIDENCE, VECTOR
①	severe combined immunodeficiency (bubble babies)	adenosine deaminase (25%) common cytokine receptor γ chain	< 1 in 10^5 1 in 50-100 000 (retrovirus)
②	lipoprotein lipase deficiency	lipoprotein lipase	1-2 in 10^6 (AAV)
③	hemophilia B	factor IX deficiency	1 in 30 000 males (AAV)
④	hemoglobinopathies and thalassemias	defects in α- or β-globin gene	1 in 600 specific ethnic groups (lentivirus)
⑤	α1-antitrypsin deficiency (emphysema, liver disease)	α1-antitrypsin not produced	1 in 3500 (AAV)
⑥	retinal degenerative disease, Leber's congenital amaurosis	retinal pigment epithilium-specific 65 KDa protein	inherited retinopathies (1 in 2000) (10% LCA (1 in 80000) (AAV)
⑦	X-linked adrenoleukodystrophy	ABCD1 transporter	1 in 20-50 000 (lentivirus)
⑧	X-linked Wiskott aldrich syndrome (eczema, thrombocytopenia immunodeficiency syndrome)	was protein	1-10 in 10^6 males (lentivirus)

MAY 2013

NOTES

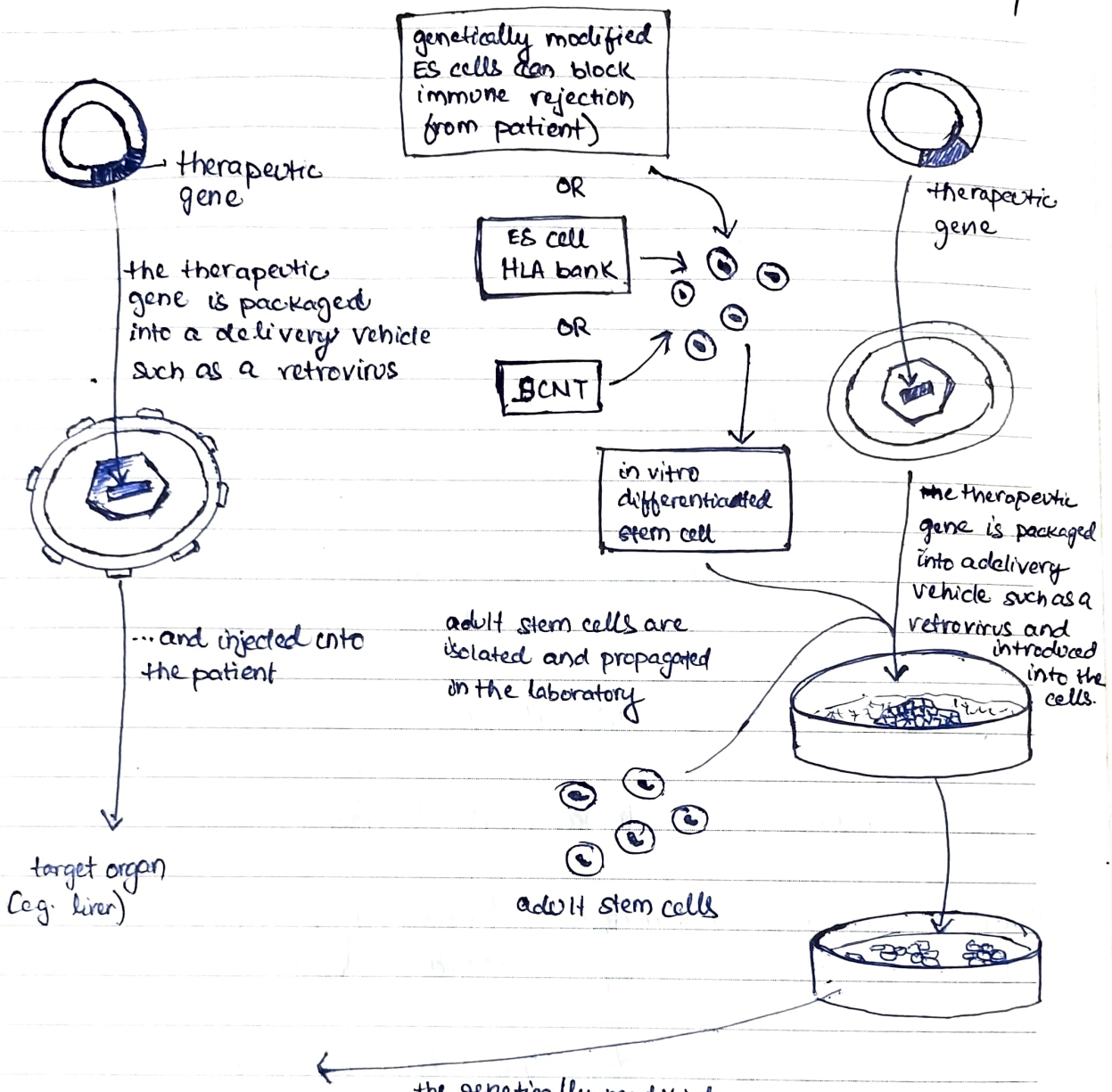
4.6.2020
8

MAY, 2013

WEDNESDAY 22
WEEK 21

DIRECT DELIVERY

CELL-BASED DELIVERY



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4.6.2020
MAY, 2013

EARLY HUMAN VIRAL GENE THERAPY: 1993

- 23 year old male with cystic fibrosis, homozygous for ΔF508 mutation in CFTR* gene.

- 2×10^8 pfu E1-E3-Ad with CFTR DNA administered to airway epithelium.

CFTR - cystic fibrosis transmembrane conductance regulator

SETBACK: JESSE GELSINGER

- first person to die in a gene therapy clinical trial (1999)
- ornithine transcarbamoylase deficiency - X linked disease that leads to accumulation of ammonia & glutamate in blood.
- patients with severe defuciencies have declining cognitive ability and premature death.
- given Ad vector with normal OTC gene at UPenn.
- died 4 days later: massive immune response, multiple organ failure, several rules of conduct broken.

NOTES

MAY, 2013

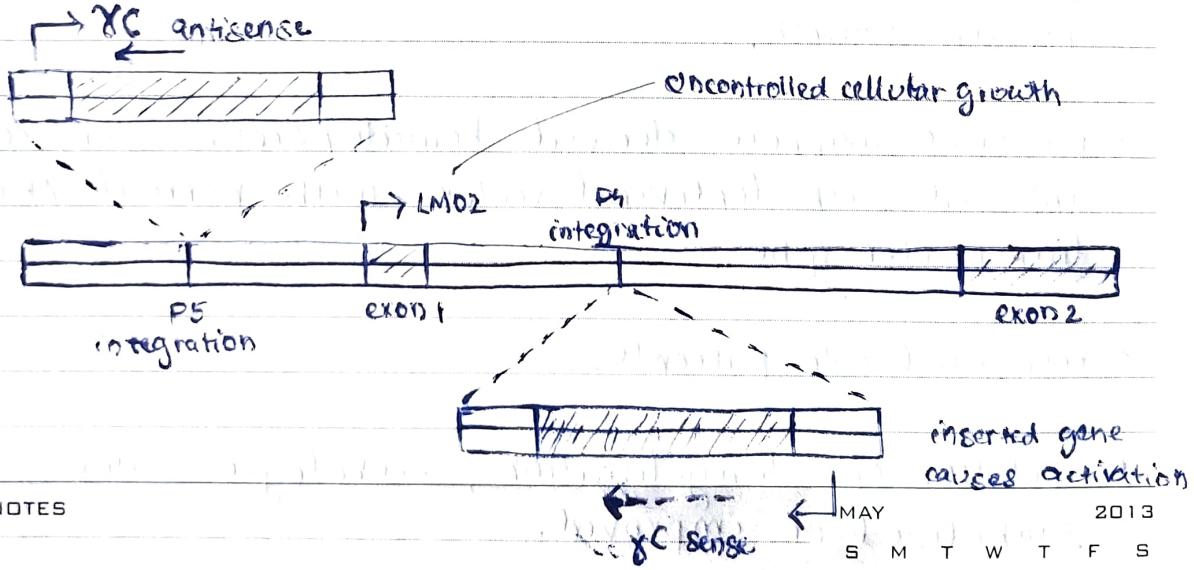
FRIDAY 24
WEEK 21

21.6.2020 @ 10

X-LINKED SEVERE COMBINED IMMUNE DEFICIENCY

- immunodeficiency disorded, defect in T, B, NK cells.
- 2 trials, london & Paris, giving infants retrovirus with normal IL2RG gene (IL-2 receptor γ chain).
- CD34+ bone marrow hematopoietic precursor cells transduced with retrovirus vector, transplanted back into patients.
- 4/9* infants in paris, 1 in london developed T-cell 3-6 years after treatment.
- 27 trials with retroviral vectors halted.

INSERTIONAL INADVERTENT ACTIVATION OF A CELLULAR GENE DURING GENE TRANSFER



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LENTIVIRAL GENE THERAPY COMBINED WITH LOW DOSE BUSULFAN IN INFANTS WITH SCID-X1

- eight infants with SCID-X1 given bone marrow transplants de.
  with lentiviral IL2RG infected bone marrow stem cells.

- after 18 months all had functional B and T cells.

X-LINKED ADRENOLEUKODYSTROPHY

- defect in ABCD1 transporter
- fatty acid buildup leads to damage to nerve myelin sheath.

26 SUNDAY
WEEK 21

- patient's marrow derived hematopoietic stem cells infected with lentiviral vector with normal ABCD1 transporter gene.
- reinfused into patients.
- resolution of demyelination, neurologic status stabilized or improved.

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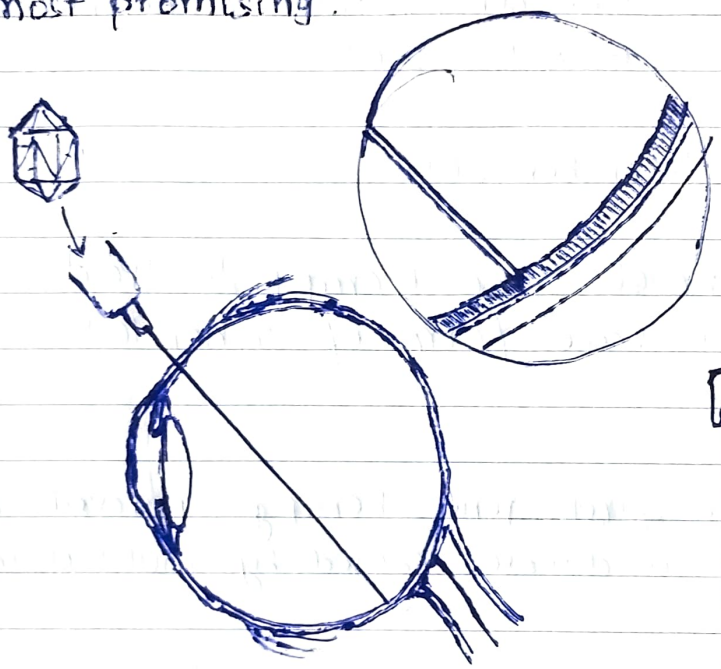
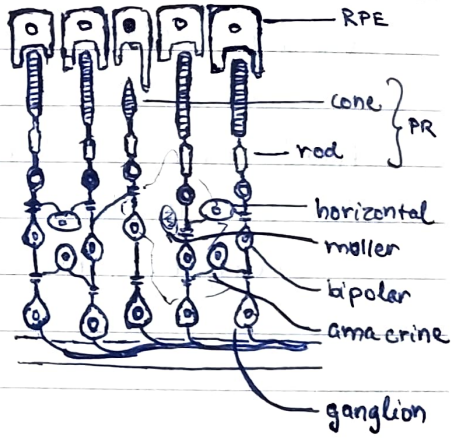
NOTES

INHERITED RETINOPATHIES

- common untreatable blinding conditions
- monogenic, mutations in retinal photoreceptors and retinal pigment epithelium.
- many vectors tested in animal models, AAV most promising.



AAV, LV, Ad



RPE · retinal pigma epithilium

NOTES

LEBER CONGENITAL AMAUROSIS

- mutations in RPE65 gene, encodes protein required for photoreceptor function
- dog model: single subretinal injection of AAV vector with canine RPE65 gene restores visual function.
- TWiV 350: viral genetherapy with Katherine high
  http://www.microbe.tv/twiv/twiv-350/
- FDA approved december 2017

FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss.

Luxturna is the first gene therapy approved in the US to target a disease caused by mutations in a specific gene.

SOME VIRAL GENE THERAPY TRIAL SUCCESSES

- severe combined immunodeficiency
- adenosine deaminase
- leber congenital amaurosis (Luxturna - FDA approved - $895000 for 2 eyes)
- hemophilia
- beta- thalassemia
- lipoprotein - lipase (fat metabolism disorder)
- avexis - AAV9 carrying spinal motor neuron 1 gene, for biallelic spinal muscular atrophy (C $2.125 million, most expensive drug ever).

VIRAL ONCOTHERAPY

- destroying tumors with viruses
- some animal viruses selectively replicate in human tumors (myxoma, seneca valley virus)

NOTES
modified viruses to target and kill tumors, often with immune enhancement.
AAV - adeno associated virus

30 THURSDAY
WEEK 22

21.6.2020
14
MAY, 2013

EARLY STUDIES OF HUMAN VIRUSES TO TREAT CANCERS IN HUMANS BEFORE STANDARDIZATION OF CLINICAL TRIALS

- 1949 hodgkin's lymphoma hepatitis virus[a]

  22 patients hepatitis developed in 14; transient responses in 4; atleast 1 treatment related death.

- 1952, 1954 (west nile virus) various advanced cancers

  >100 patients >90% infected; transient responses in 10; mild to severe encephalitis in 10.

- 1953 acute leukemia epstein-barr virus

  5 patients 3 infected & developed infectious mononeucleosis; transient responses.

- 1956 cervical carcinoma human adenovirus

  30 patients transient tumor necrosies in 20

MAY 2013

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NOTES

PROPERTIES OF CANCER CELLS THAT CAN FACILITATE REPRODUCTION OF ONCOLYTIC VIRUSES

- immortality: HAdV
- sustained growth and proliferation
  HAdV, RV, VACV
- resistant to tumor suppressors
  HAdV, VACV
- resistant to apoptosis
  HAdV, VACV
- support angiogenesis
  VACV, VSV
- impervious to immune defenses
  HSV1, NDV, VSV
- invasive, metastatic
  CVA21, MV

NOTES

Cancer hallmarks.

01 SATURDAY
WEEK 22

21.6.2020
16 JUNE, 2013

IFN DEFECTS ARE COMMON IN CANCER CELLS

mutation in viral genomes that impair countermeasures to the antiviral interferon defense.

HAdV5	E1B 55kDa (loss of expr.)	repression of ISG transcription
HSV-1	ICP34.5 (deletion)	circumvention of effects of PKR activation.
VACV (MVA)	B18 (deletion)	sequestration of type I interferon.
VSV	M (deletion, substition at amino acid 51)	repression of ISG expression

02 SUNDAY
WEEK 22

JUNE 2013

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NOTES

TUMOR TARGETING

- receptor targeting

  - alter measles virus HA to target tumor makers ('neoantigens')

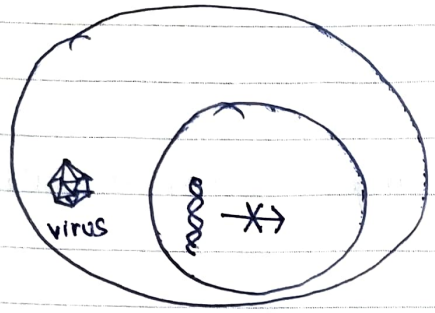
  - HSV glycoprotein D engineered to contain IL-13, or single chain antibodies against human epithelial growth factor receptor 2, on gliomas and breast tumors.

    - Adenovirus: insertion of domains that recognize tumor Ag (antigen) into fiber.
      - hexon-interlacing protein
      - adaptors that bind fibers and retarget

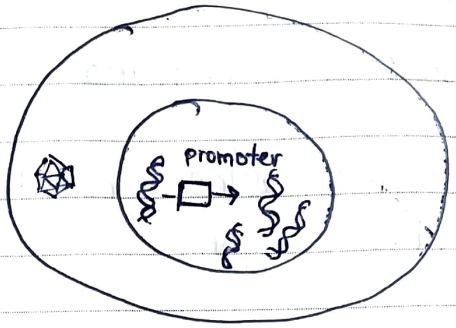
NOTES

POST ENTRY TARGETING

+ve targeting

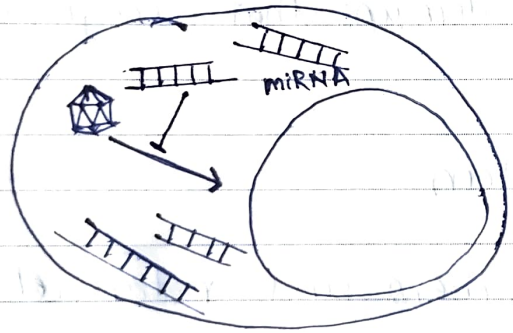


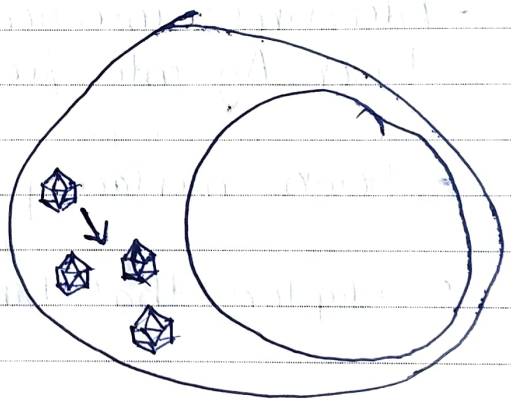
healthy cell



tumor cell

-ve targeting





NOTES

miRNA - micro RNA

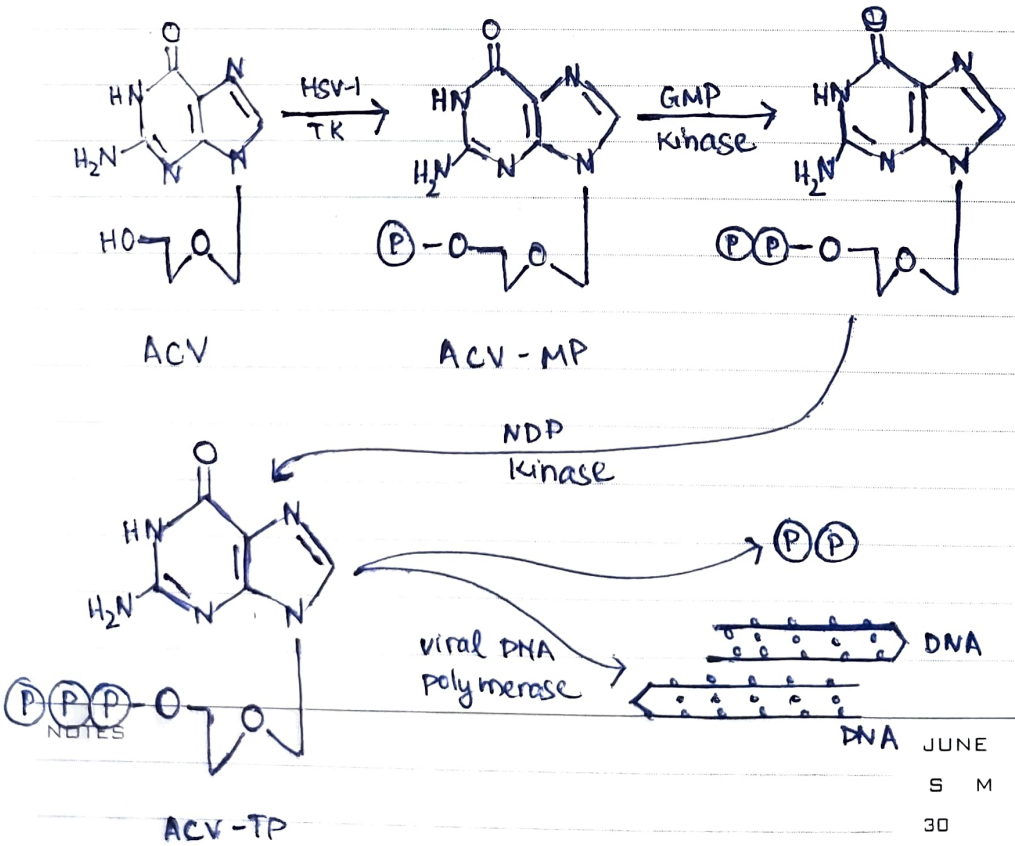
21.6.2020
19

JUNE, 2013

WEDNESDAY 05
WEEK 23

ARMING VIRAL VECTORS

- enhance therapeutic efficacy of oncolytic virus: hard to infect 100% of cells.
- strategies that kill tumor cells surrounding those infected - bystander killing
- prodrug convertases
- ion transport protein
- immunostimulatory factors



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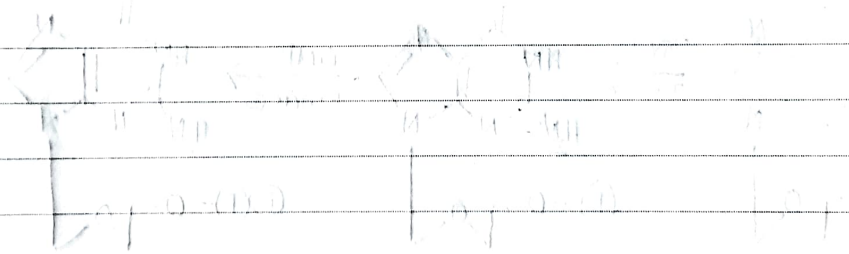
06 THURSDAY
WEEK 23

21.6.2020
20
JUNE, 2013

MYXOMA VIRUS

- same virus introduced into australia to kill european rabbits.
- does not replicate in any non-rabbit host.
- infects many types of human cancer cells.
  - failure of cells to induce (poor interferon response) antiviral response
  - activation of cell pathways related to transformation.



JUNE 2013

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NOTES

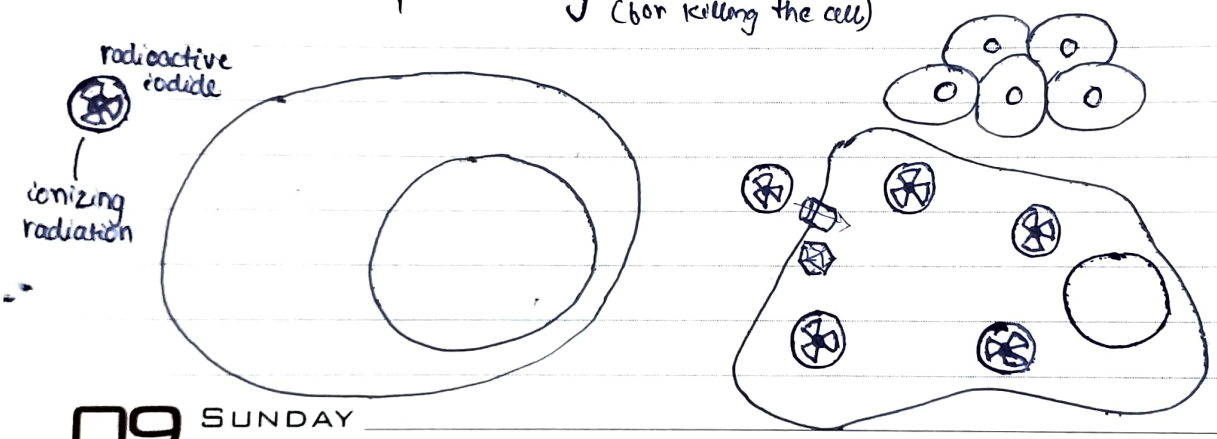
CANCER	ANIMAL MODEL	TUMOR ESTABLISHMET
• acute myeloid leukemia	NSG	human AML cells in bone marrow xenograft
	ex vivo	90% of mice free of human AML cells in BM
	MYXV ADMINISTRATION	OUTCOME
• multiple myeloma	NSG	human MM cells in bone marrow xenograft.
	ex vivo	100% of mice free of human MM cells in BM
• pancreatic cancer	NOD/scID	human pancreatic cancer cells in IP cavity
	IP	reduced tumor burden & prolonged survival.
• pancreatic cancer	C57BL/6	murine pancreatic cancer cells in IP cavity
	IP	100% survival combined with gemcitabine
• glioma	CD-1 nude	human gliomas in mouse brain
	intratumoral	92% of mice cleared of tumors and cured.

NOTES

prechemotherapy get bone marrow from patient and make it tumor free before re-introducing it.

MEASLES VIRUS

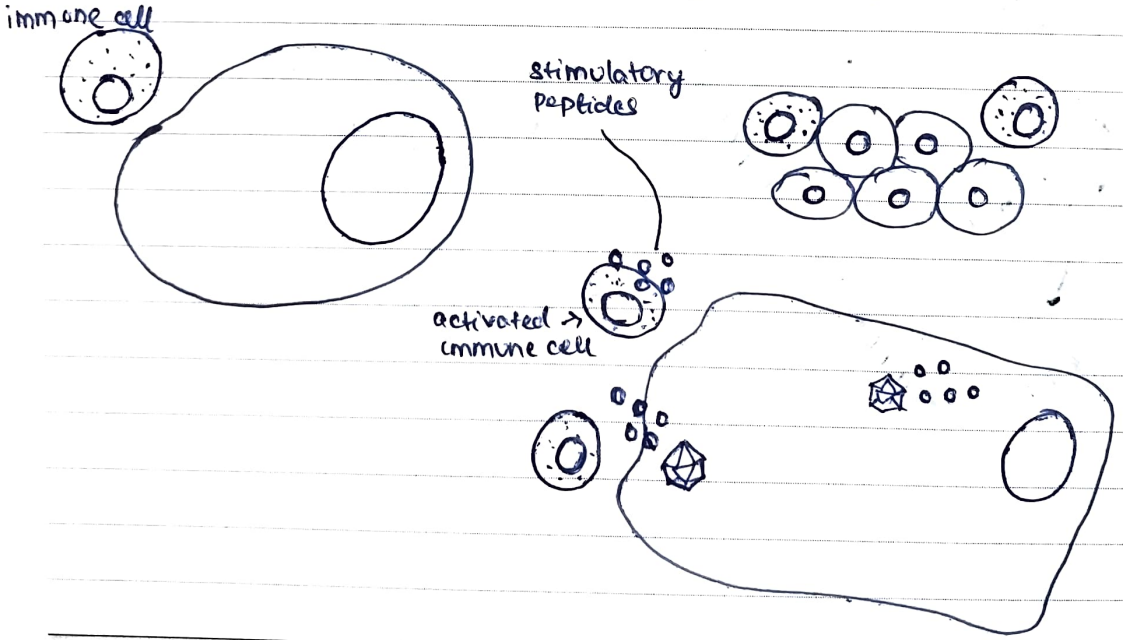
- attenuated vaccine strain, preferentially replicates in tumors (cannot antagonize STAT1 and MDA5)
- includes gene for human sodium-iodide symporter (NIS)
- during virotherapy, γ-emitting isotopes allow visualization of virus replication in tumor.
- administration of β-emitting isotopes can induce radiation poisoning. (for killing the cell)



- 2 patients with multiple myeloma given 10^{11} particles IV
- one of two had complete remission.

HERPES VIRUS - TALIMOGENE LAHERPAREPVEC

- includes gene for GM-CSF : stimulate production of granulocytes and macrophages which stimulate adaptive immunity against tumor antigens.
- deletion of ICP34.5, US11 causes tumor specific replication.
- ICP47 deleted, no inhibition of antigen presentation
- phase III completed for melanoma, intratumoral: 16% response vs 2% for GM-CSF alone.
- FDA approved 2015: Imlygic (amgen).



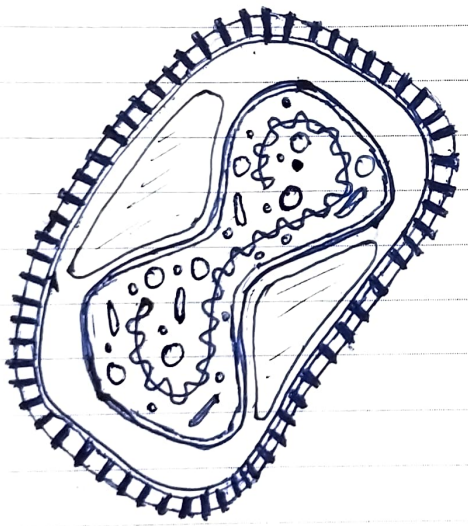
NOTES

11 TUESDAY
WEEK 24

21.6.2020
24
JUNE, 2013

VACCINIA VIRUS JX-594

- armed with GM-CSF
- thymidine kinase gene deleted: elevated in tumors
- tested for the ability to reach metastatic tumors after intravenous delivery (viremia).
- 23 patients with advanced, treatment-refractory solid tumors (lung, colorectal, melanoma, thyroid, pancreatic, gastric, ovarian, mesothelioma)



- virus replicated in tumors in nearly half of patients (β-gal)
- anti-tumor activity demonstrated in half of patients.
- proof of concept

JUNE 2013

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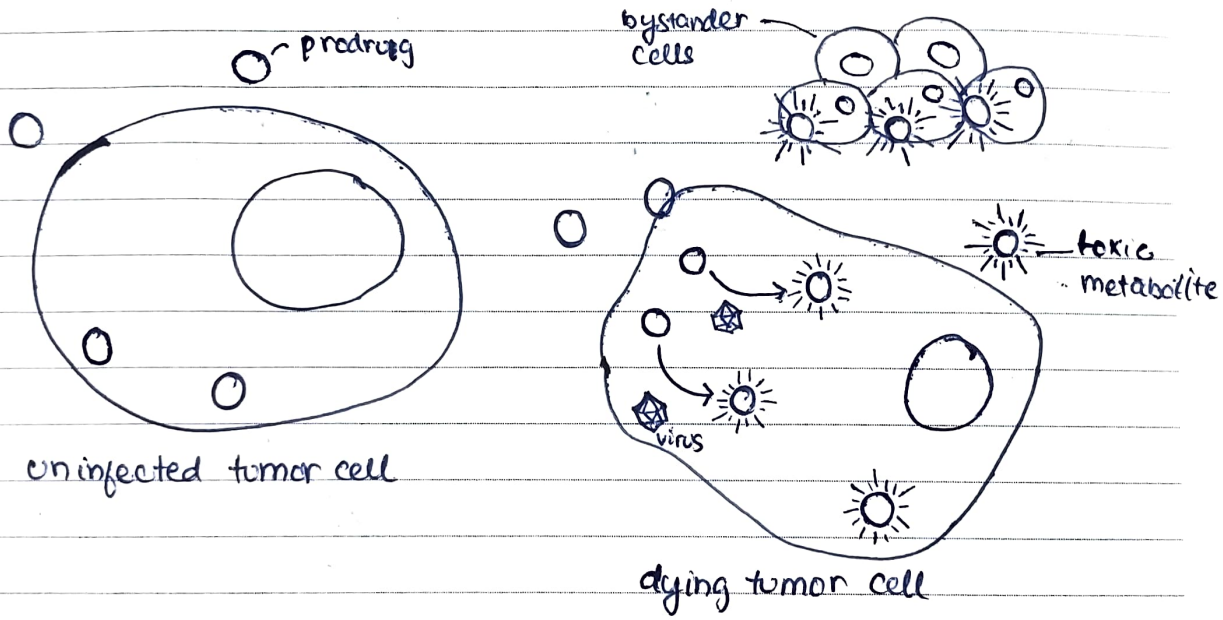
NOTES

treatment-refractory:
they didnt respond to anything else.

ARMED WITH PRODRUG CONVERTASES

- thymidine kinase converts ganciclovir to ganciclovir triphosphate.
- cytosine deaminase converts 5-fluorocytosine to 5-fluorouracil.
- these nucleoside analogues stop DNA replication of tumor cells.



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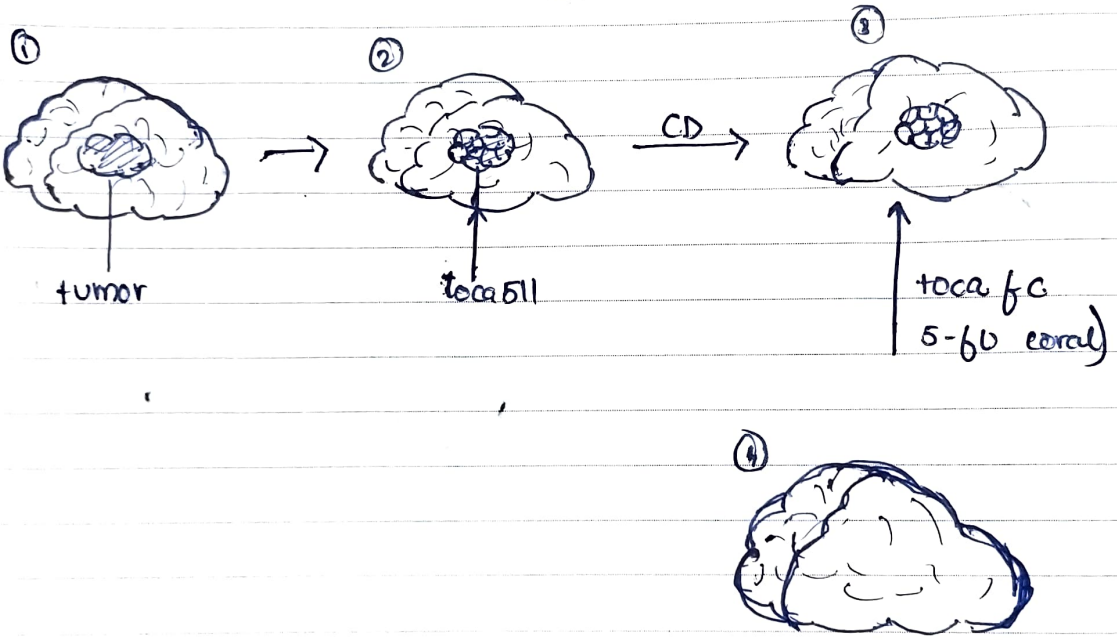
TOCA 511

- amphotropic murine leukemia retrovirus armed with cytosine deaminase
- given intratumoral or intravenous with 5-fluorocytasine
- phase I and II for glioma.



PVS-RIPO

- poliovirus sabin with IRES from rhinovirus 2 attenuating
- tumor cells upregulate poliovirus receptors.
- intratumoral, phase II for glioma in 61 patients
- median survival 12.5 months vs 11.3 months in historical controls.

REOLYSIN

- reovirus, unmodified, not pathogenic for humans
- found to kill cells with activated Ras pathway.
- phase III for head and neck tumors, many other studies.

therapeutic efficacy is a combination of lysis of cancer cell by virus and indirect activation of anti-tumor immune responses.

NOTES

21.6.2020

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15 SATURDAY
WEEK 24

JUNE, 2013

THE IMPORTANCE OF BASIC RESEARCH

- therapeutic viruses have been made possible because of fundamental advances in virology, recombinant DNA, immunology, and clinical science.

- there must be a balance between translational research and basic research.

16 SUNDAY
WEEK 24

JUNE 2013

S	M	T	W	T	F	S
30						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29

NOTES