

MembranesSolute transport

$$\Delta G = \Delta G^{\circ} + RT \ln \frac{[S_{final}]}{[S_{initial}]} + zFDV$$

$$S_{initial} \rightleftharpoons S_{final}$$

Simple diffusion - "wearing"

moves through membrane affected by concentration and size $T_{passive} = A \cdot PDC$

$$J_{passive} = PDC$$

P = permeability constant - larger = more permeable
 DC = ~~constant~~ concentration gradient

Need to multiply $J_{passive}$ by area!

$$\text{Total passive transport} = (J_{passive})(\text{Total Area})$$

Facilitated Diffusion

$$S_{init} + T \rightleftharpoons S_{init} \cdot T \rightleftharpoons S_{final} + T$$

$$V = \frac{V_{max} [S]_{init}}{[S]_{init} + K_T}$$

$$V = J_{facilitated} \cdot \text{Area}$$

Follows saturation kinetics



GLUT channels regulate blood glucose levels - control intake via GLUT expressed
 ↳ control speed (k_{cat}) (which \downarrow) and how much $[T]$ (expression)

$$V_{max} = k_{cat} [T]$$

GLUT 1 / GLUT 3 = basal transporters

- $K_T \approx 1-2 \text{ mM}$

- operate near V_{max} as blood Glc is $4-7 \text{ mM}$

GLUT 4 - muscle cells (glycogen storage)

- $K_T > K_T$ for GLUT 1/3 = only work after GLUT 1/3 saturated

GLUT 2 - Pancreas Beta cells

- $K_T = 15 \text{ mM} \rightarrow$ signal insulin spike

Simple diffusion
(no protein)

transport

Facilitated Transport
(transmembrane protein)

Facilitated
Diffusion
(channel)
 $\Delta G < 0$

Active
Transport
(cotransport
+ pumps)
 $\Delta G > 0$

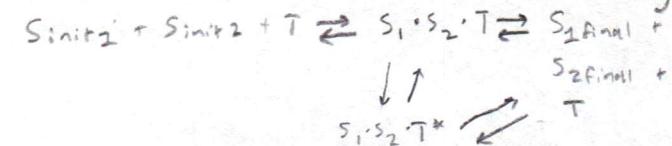
 K^+ channels

selectively choose K^+ over Na^+
 via K^+ hydration - smaller/tighter H_2O
 bonds = more entropic currency

Cotransporters

Need to pay ΔG price

Move another ion w/ gradient = energetic coupling



2 same direction = symporter

2 opposite direction = antiporter

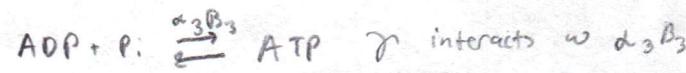
Pumps / $F_0 F_1$ ATP Synthase

c subunits = proton channel

a subunit - interacts w/ c subunits

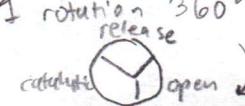
↳ make one c unit tighter binding and 1 lower binding

proton attached to tight spot, rotates until weak spot, and releases on other side



$\gamma - \alpha \beta =$ open ADP + Pi bind

1 rotation 360° of $\alpha_3 \beta_3 = 3$ ATP



In rxn, Pi is $Nu^- ADP \rightleftharpoons E^+$

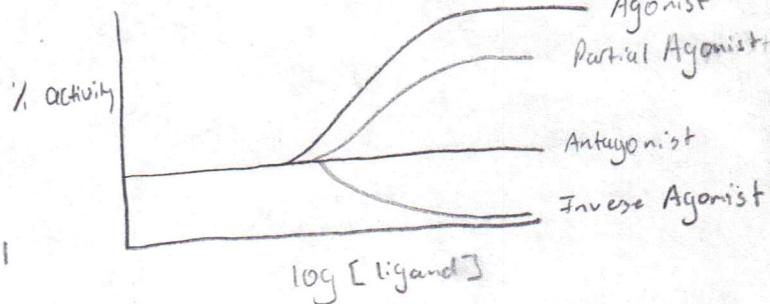
Transmembrane Signal Induction

3 types

- 1) 7 TM -
- 2) RTK -
- 3) Gated Ion Channel

All allow allosteric
Transducers and amplifiers

- Receptor selectivity vs specificity
 $1 \rightarrow 2$ - Selectivity = affinity ratio \neq ligand 2 receptors
 $2 \rightarrow 1$ - Specificity = affinity ratio \neq 2 ligands 1 receptor



Transducer - Conformational change indicates signal

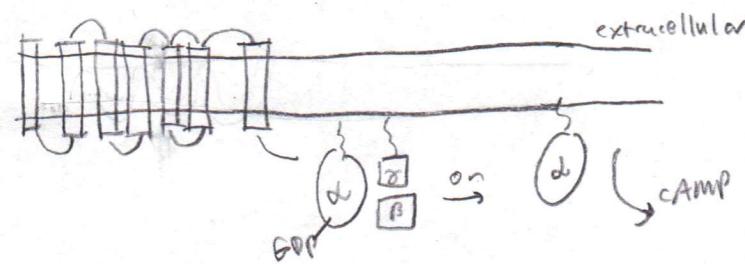
Amplifier - Transduction stays "on"

7 TMs

Transduction - Signal molecule binds to α helices, conformationally changing G protein from GDP \rightarrow GTP bound state

GTP bound state dissociates from rest of protein, catalyzing other enzymes

Eventually hydrolyzes GTP to reassociate

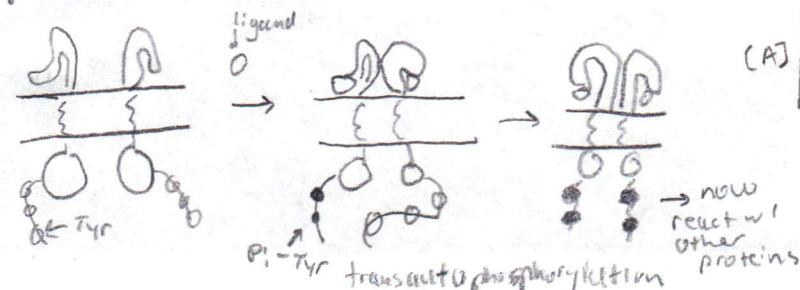


4 types of ligands

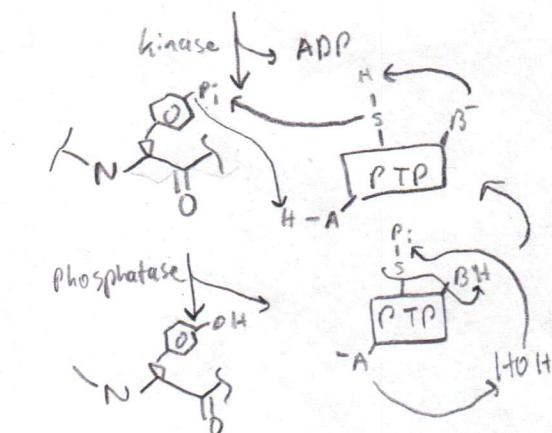
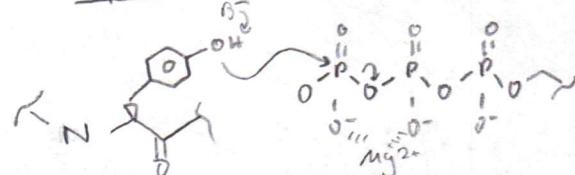
- 1) Agonist - \uparrow activity
- 2) Partial Agonist - \uparrow activity but won't reach saturation
- 3) inverse Agonist - reduce activity below basal levels
- 4) Antagonist - block function of agonists but doesn't affect intrinsic activity

RTKs

Signal binding dimerizes two proteins to activate kinase

PTMs

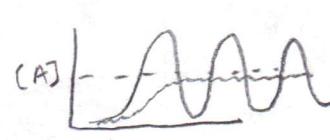
allosteric control via covalent modification often reversible via another enzymes

Tyr Kinases

All PTP's have conserved cysteine residue

PTM Reasons

- 1) Simpler - only need one binding site
- Hexokinase needs NH_2 site, E^+ site, G6P site
IDH just install P_i near active site - diuron repels isocitrate (3 CO_2^- groups)
- 2) Noise cancellation



PTM intermediary provides noise dampening effect due to longer adjustment time

PTMs cont.

8 aspects to consider

1) ID of target residue

2) Nature of modification

3) What is cosubstrate

4) Type of enzyme to install PTM

5) Enzyme Mechanism / Specificity chemical

6) Reversible? biological

7) Biological Function of target protein

8) PTM control mechanism

① Target ResiduesNu⁻ side chains - Amides bad E⁺② Nature of ModificationStrength of bond dictates PTM duration
ester - hold longer than phosphoanhydride bond③ CosubstratesMethyl PTMs via HscOA or FA

S - Adenosyl - Met (SAM)

Nature's Me-I - good E⁺R-S-OH sulfenic acid (good E⁺) H_2O_2 converts Nu⁻ R-SH \rightarrow E⁺ R-S-OH

↳ oxidant USE of metabolites as cofactor = metabolic sensor status

④ Type of Enzyme

PTM's power in specificity, not chemistry

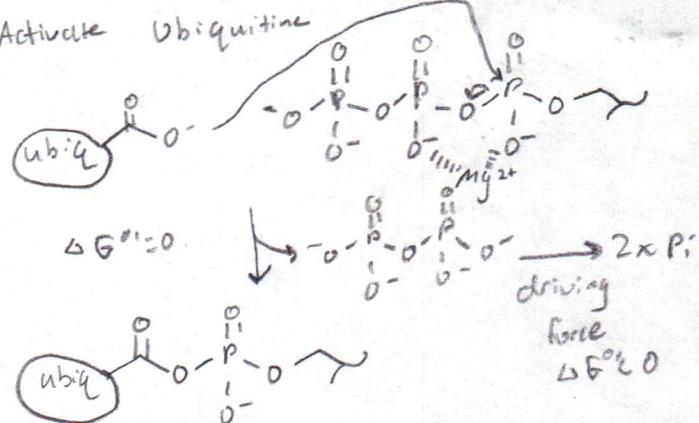
⑤ Reversibility

PTPs hydrolyze thioesters/amides

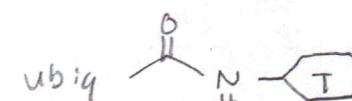
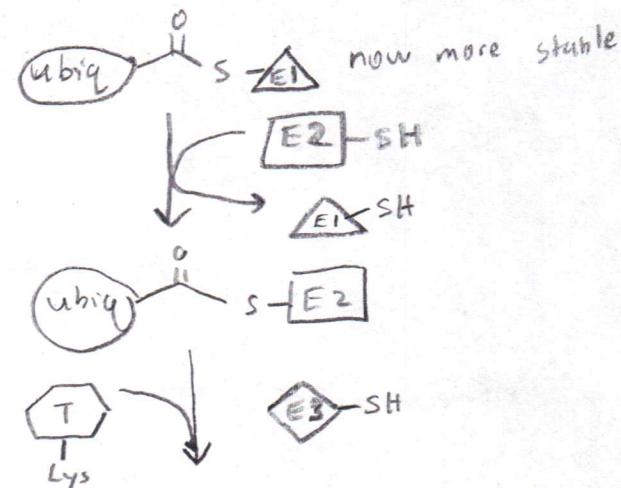
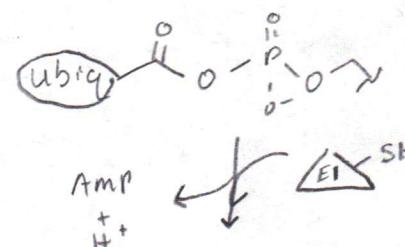
Thioethers/farnesyl-Cys⁺ hard to removeUbiquitin / Ubiquitin Ligase

(3)

use ATP mechanism to install ubiquitin on Lys residue of protein

① Activate Ubiquitin② Ubiquitylation of Ligase

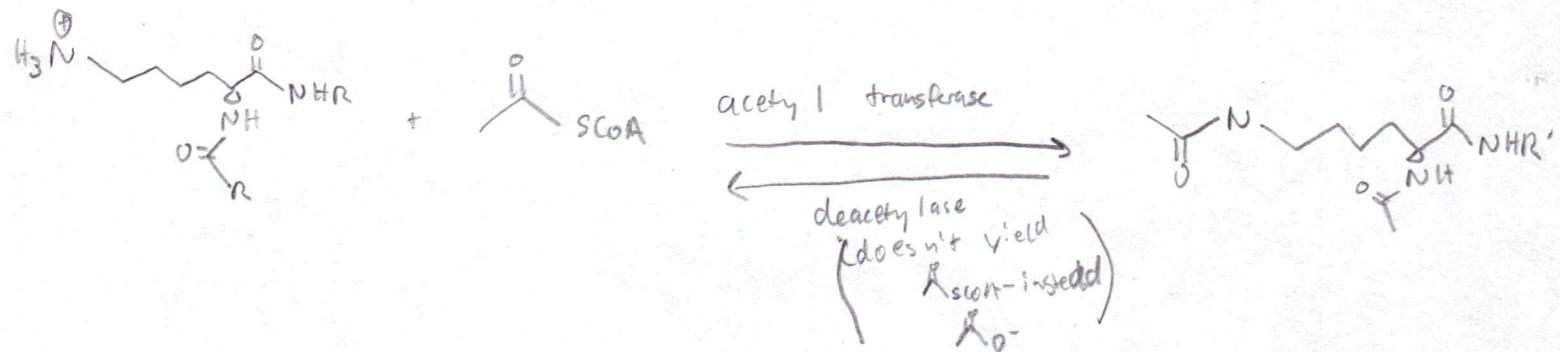
Use 3 step process to control where ubiquitin ends up



E1 - target agnostic
 E2 - recog E1
 E3 - recog T] allows for finer control

Polyubiquitylation signals cell protein death by proteasome

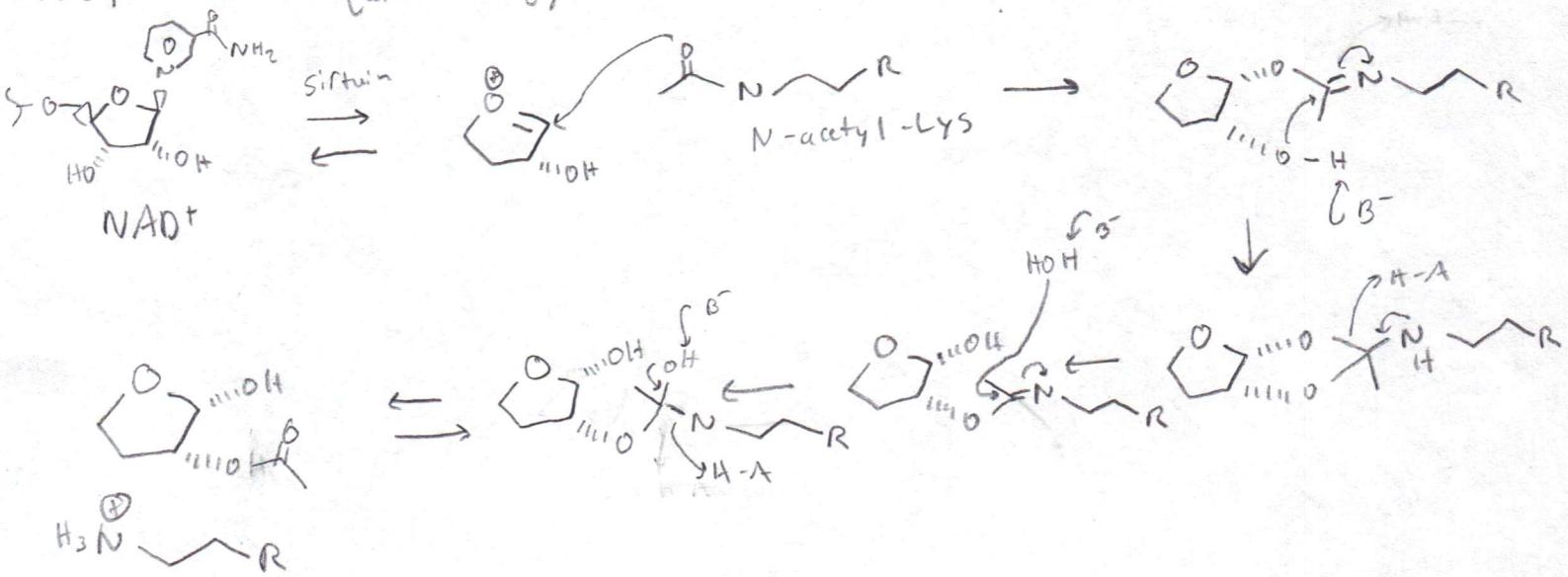
Proteasome hydrolyzes ubiquitins while degrading protein = PTM reversible

Even more PTMs

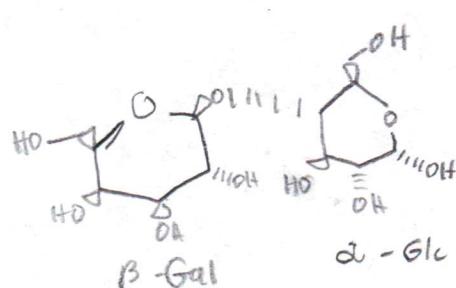
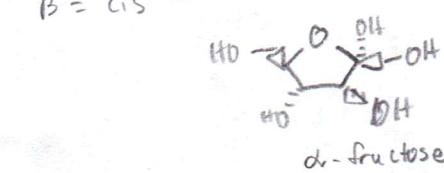
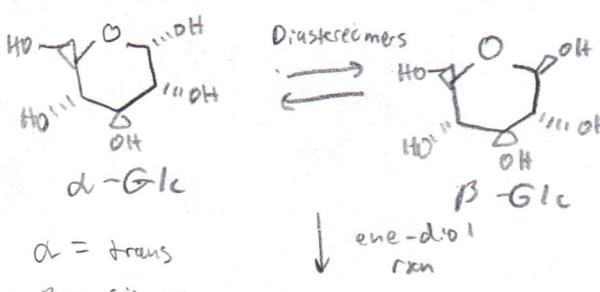
Palmitoylation can alter subcellular location

Act as carrier subunits like lipoamide

Deacetylation can require energy:

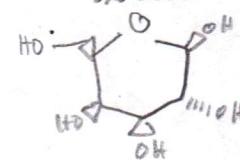
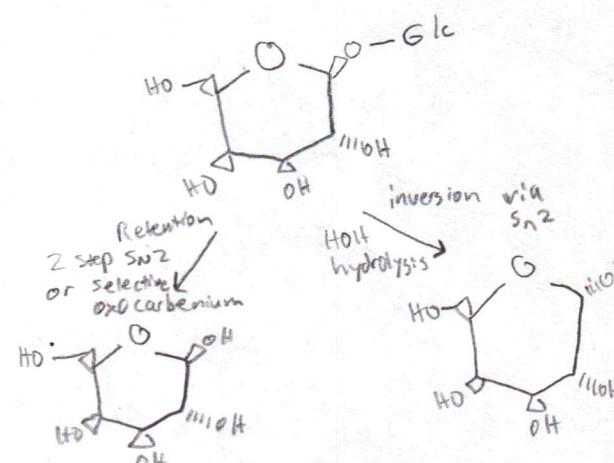


NAD^+ = sensor of oxidoreductant stress

Carbohydrate Metabolism

can't hydrolyze β glycosidic

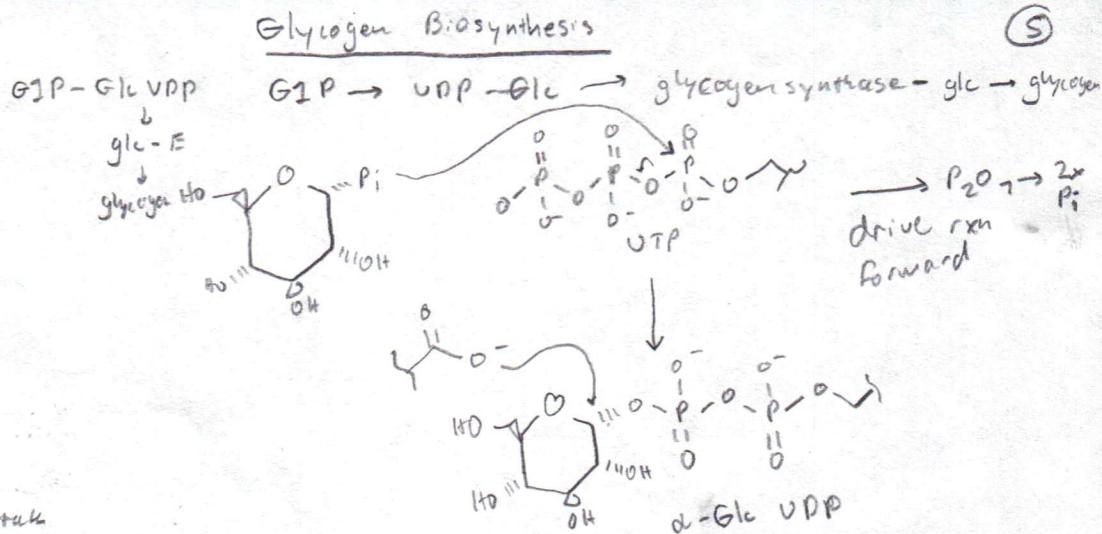
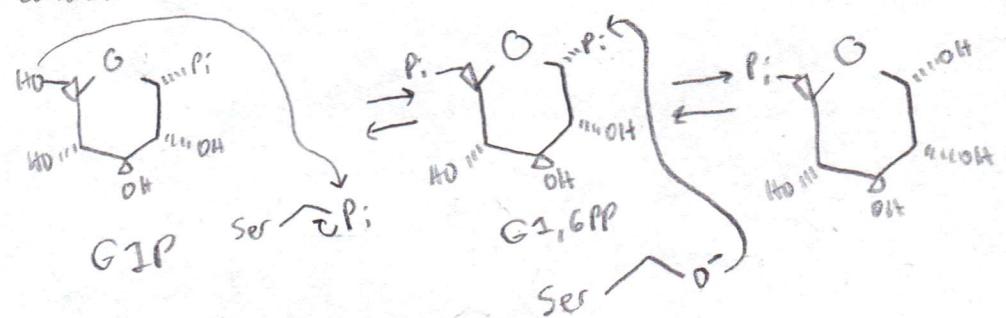
package - humans don't have the enzymes



Carbohydrates cont.PhosphorylasesPi is Nu^-

Glycogen branching allows multiple enzymes to break down at once

Glycogen phosphorylase
- oxo carbonium then Pi attack

Phosphoglucomutase Step 4 LeLoirConvert G1P \rightarrow G6P

Lactose breakdown via 2 step SN_2 = glucose + galactose

LeLoir PathwayGalactose \rightarrow G6P for glycolysis1) Galactose mutarotase = $\beta\text{-gal} \rightarrow \alpha\text{-gal}$

2) Galactokinase - Add Pi to C1

3) Galactose 1 Phosphate Uridylyltransferase

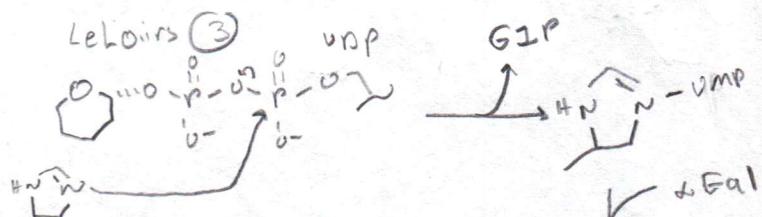
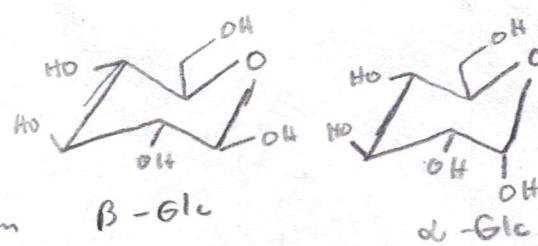
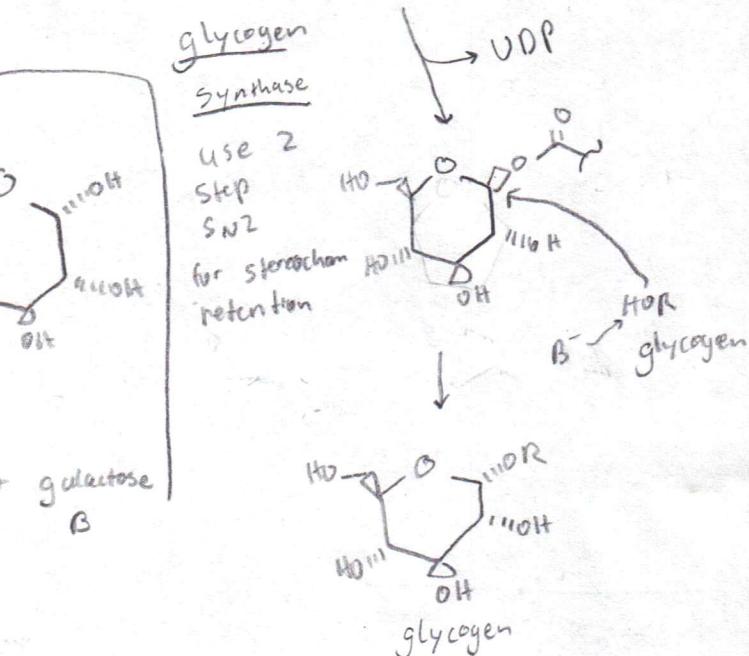
= Exchange galactose for a glucose

2 phosphate w/ UPP-Glc via It's mechanism

4) Phosphoglucomutase - Transfer Pi C1 \rightarrow C6

↳ Ser-Pi donates to C6 then cleaves C1

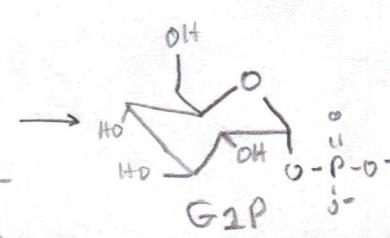
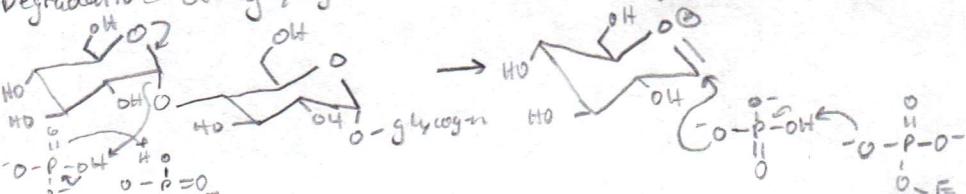
5) UPP-Gal 4 Epimerase - Regenerate UDP-Glc

↳ Use NAD^+ then selective reduction $\text{NADH} \rightarrow \text{NAD}^+$
UPP - increases binding

UPP-Gal creation drives rxn forward

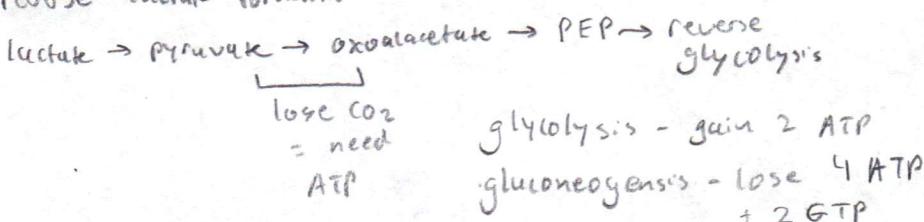
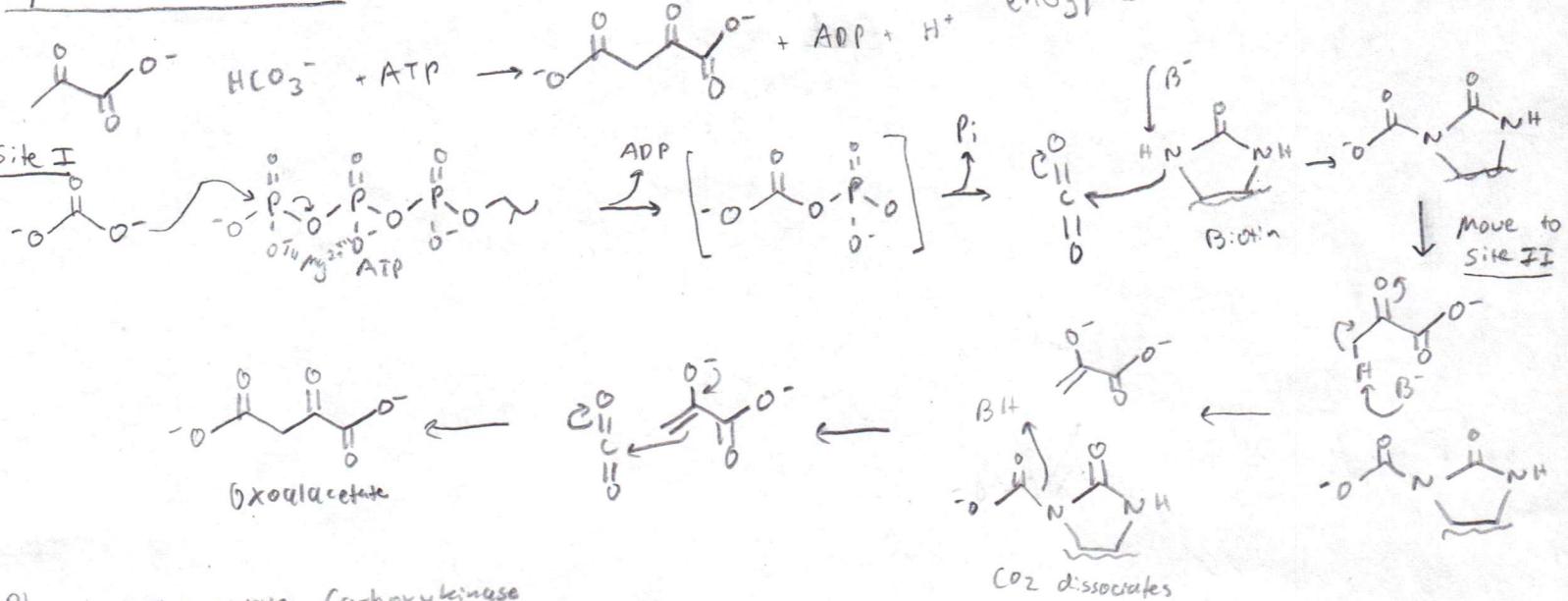
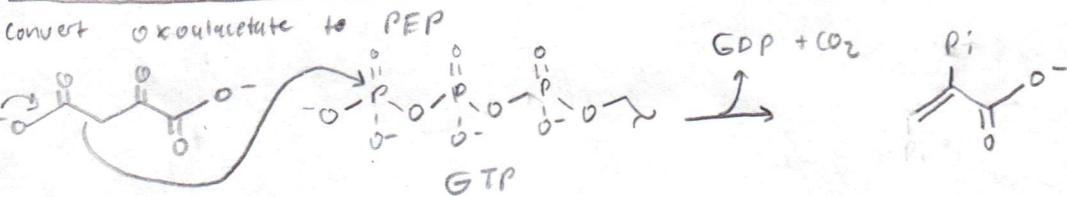
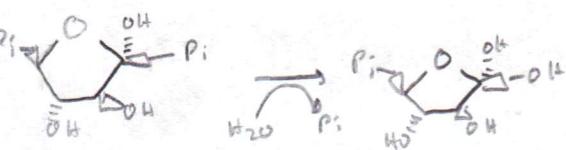
Glycogenolysis Glycogen phosphorylase

Degradation of glycogen via Pi attach yields G1P

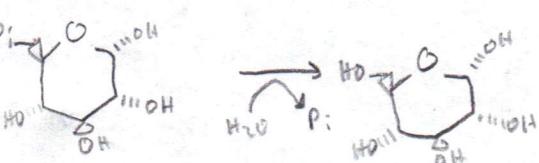


Gluconeogenesis

creation of glucose w/o glycogen
reverse lactate formation

Pyruvate CarboxylasePhosphoenol Pyruvate CarboxykinaseFructose 1,6 Bisphosphatase

Same as PTM PTPs

Glucose 6 Phosphatase

His grabs Pi, then hydrolyze His
to regenerate catalyst.

Pathway Connections

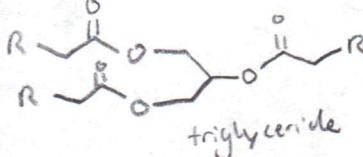
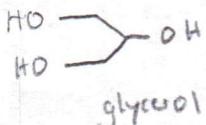
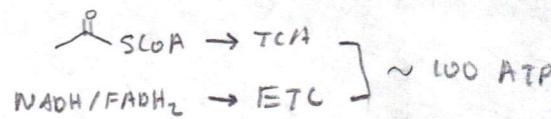
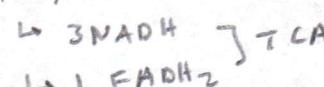
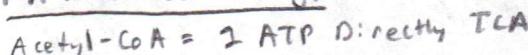
Oxaloacetate - TCA

G1P \rightarrow G6P = skip gluconeogenesis

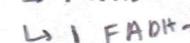
gluconeogenesis is an energy storage process - excess energy stored in glucose to send to other cells

OR store in glycogen
 \hookrightarrow AMP/ other signals of energy need will inhibit gluconeogenesis

\hookrightarrow Citrate/ other signals of excess energy will activate gluconeogenesis

Fatty Acid MetabolismPathway ConnectionsFA Breakdown Energy

Each 2 carbon cleavage



Account for -2 ATP for AMP FA activation conversion
 $\text{AMP} \rightarrow \text{ADP}$

Another ATP to rebuild AMP

AMP

conversion

$\text{AMP} \rightarrow \text{ADP}$

FA Breakdown

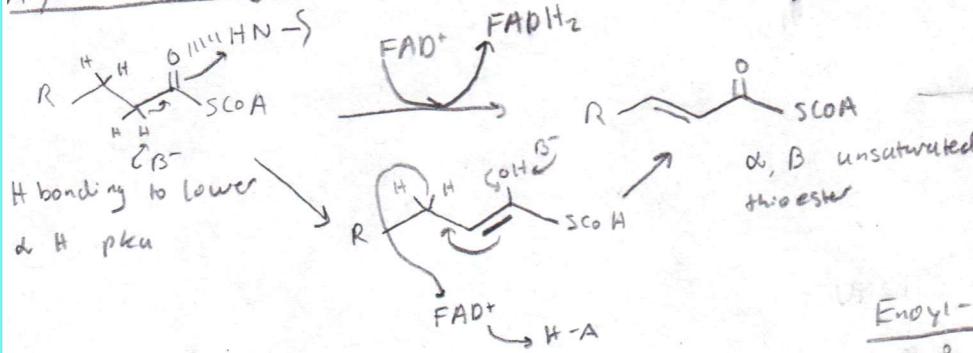
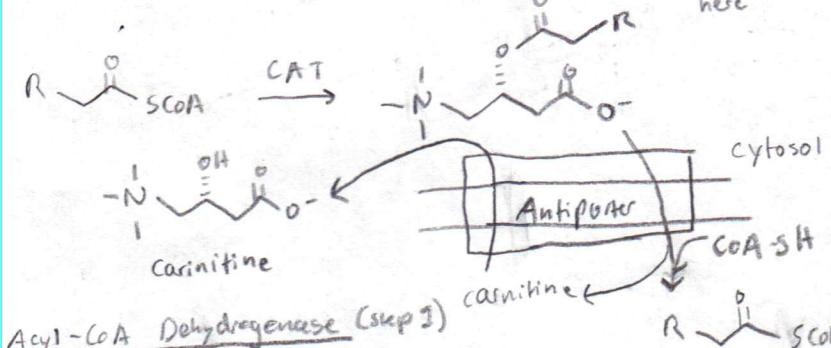
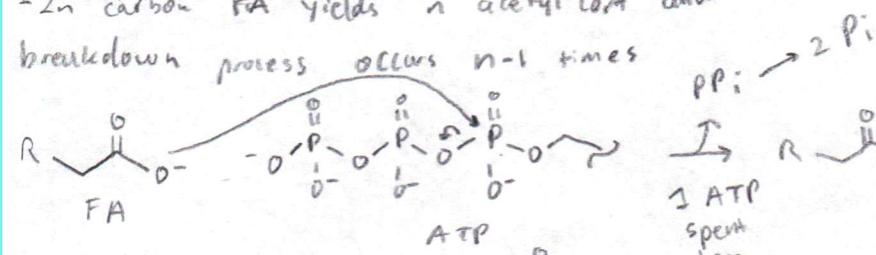
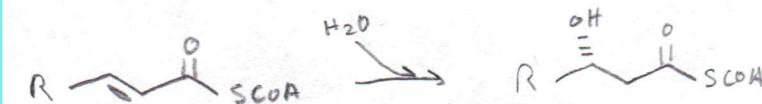
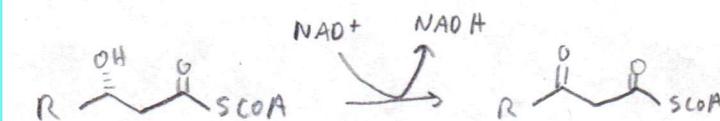
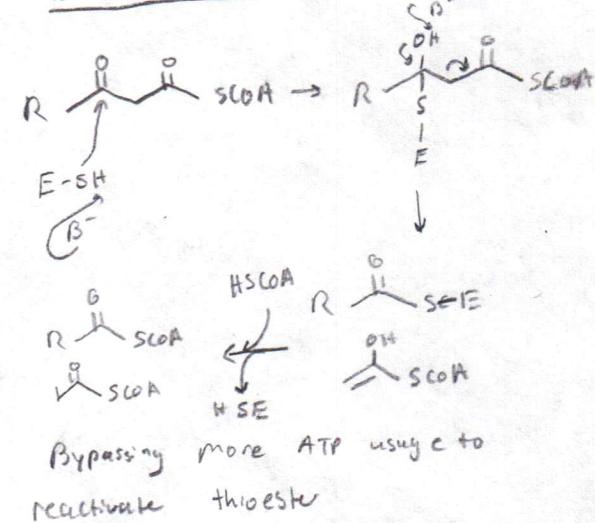
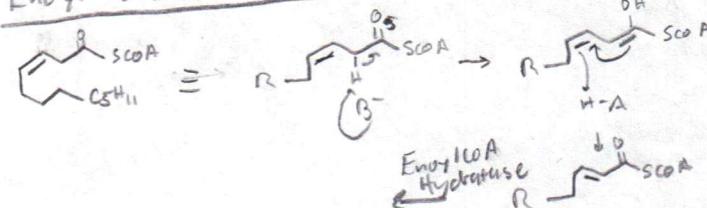
Convert FA \rightarrow Acetyl-CoA

- Produce NADH/FADH₂ and acetyl-CoA for TCA

- Breakdown 2 carbons at a time

- $2n$ carbon FA yields n acetyl CoA and

breakdown process occurs $n-1$ times

Enoyl-CoA Hydratase (Step 2)Hydroxyacyl-CoA Dehydrogenase (Step 3)B-Ketoacyl Thiolase (Step 4)Enoyl-CoA Isomerase

Odd Numbered FA yields propionyl-CoA

- 1) Propionyl carboxylase - Biotin mech to add CO₂
- 2) methyl malonyl-CoA Epimerase - Racemization
- 3) methyl malonyl-CoA Mutase - make succinyl-CoA for TCA

FA Biosynthesis

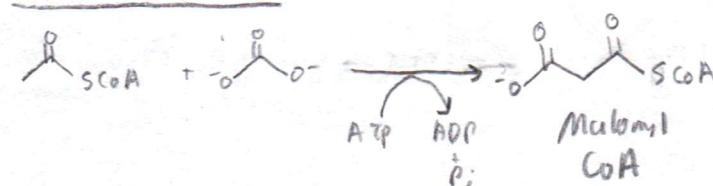
- Use NADP⁺ instead of NADH

Goal - Run thiolase in reverse

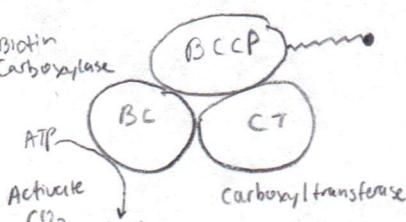
To link malonyl-CoA w/ FA / acetyl-CoA
To do this, need to make malonyl-CoA

Malonyl-CoA creation in FA synthase

Biotin Carboxylase



Normally biotin mechanism



- ① $\text{ACP}^{\text{mms}}\text{SH} + \text{SCoA} \xrightarrow{\text{Acetyl transferase}} \text{ACP}^{\text{mms}}\text{C}_2$

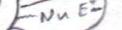
② $\text{ACP}^{\text{mms}}\text{C}_2 + \text{E}^{\text{mss}}\text{SH} \xrightarrow{\text{Ketosynthase}} \text{E}^{\text{kes}}\text{C}_2$

③ $\text{ACP}^{\text{mms}}\text{C}_2 + \text{malonyl-CoA} \xrightarrow[\text{CoASH}]{\text{malonyl transferase}} \text{ACP}^{\text{mms}}\text{C}_4$

④ $\text{ACP}^{\text{mms}}\text{C}_4 + \text{E}^{\text{mss}} \xrightarrow{\text{NADPH}} \text{ACP}^{\text{mms}}\text{C}_4\text{OH}$

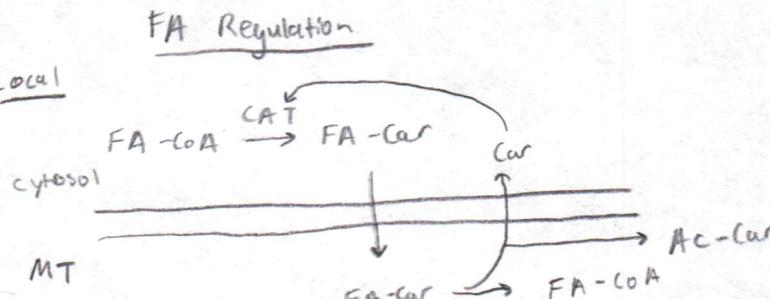
⑤ $\text{ACP}^{\text{mms}}\text{C}_4\text{OH} \xrightarrow{\text{H}_2\text{O}} \text{ACP}^{\text{mms}}\text{C}_4\text{=CH}_2$

⑥ $\text{ACP}^{\text{mms}}\text{C}_4\text{=CH}_2 + \text{NADPH} \xrightarrow{\text{NADP}^+} \text{ACP}^{\text{mms}}\text{C}_4\text{=CH}_2\text{OH} \rightarrow \text{②}$

$1 \rightarrow (2 \rightarrow 3 \rightarrow 4 \rightarrow 5 \rightarrow 6 \rightarrow 7)_6 \rightarrow 8$


 Avoid protons being grabbed by malonyl-CoA

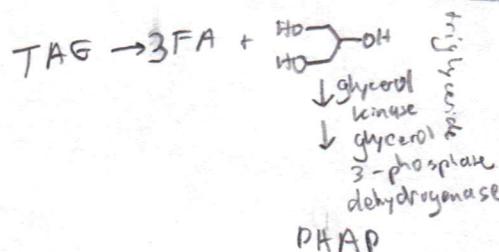
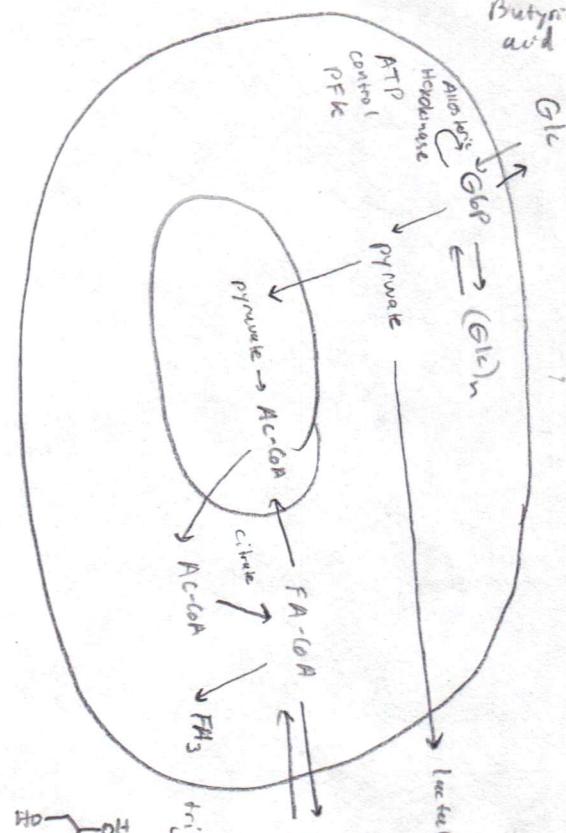
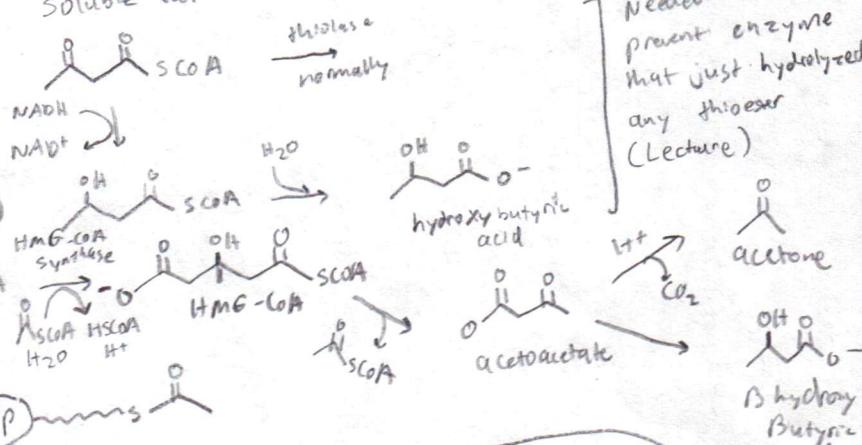
Local

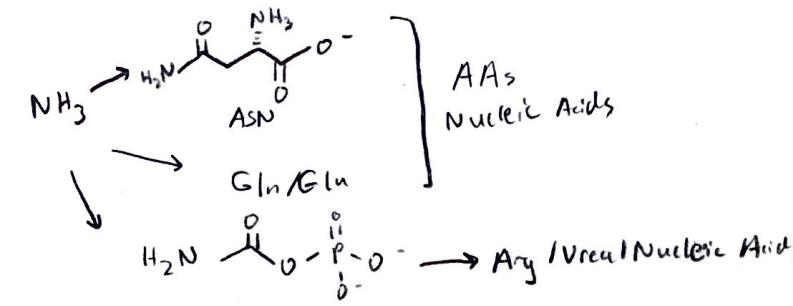


Excess acetyl-CoA = send out of MT for FA synthesis
Le Chatelier - control carnitine levels to control intake
↳ tie up w/ Ac-Car = ↓ Breakdown
citrate = TCA backup store acetyl-CoA as FA

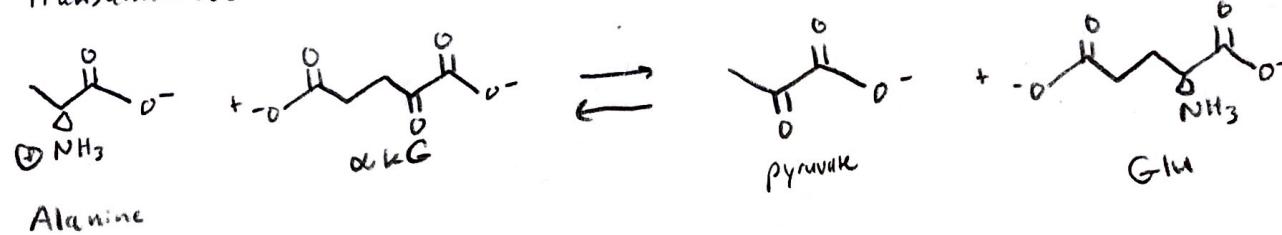
Global

Globules
FA's not soluble = difficult to transport
soluble fat - FA that can move in body
7 nee

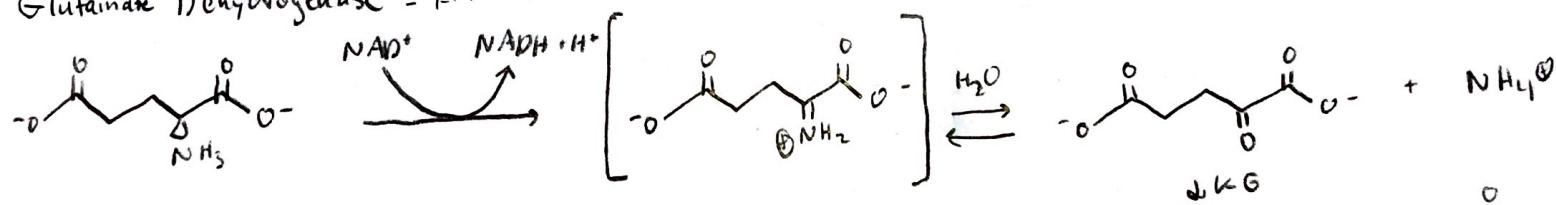


Amino Acid MetabolismHow to deal w/ toxic NH₃?Catabolism

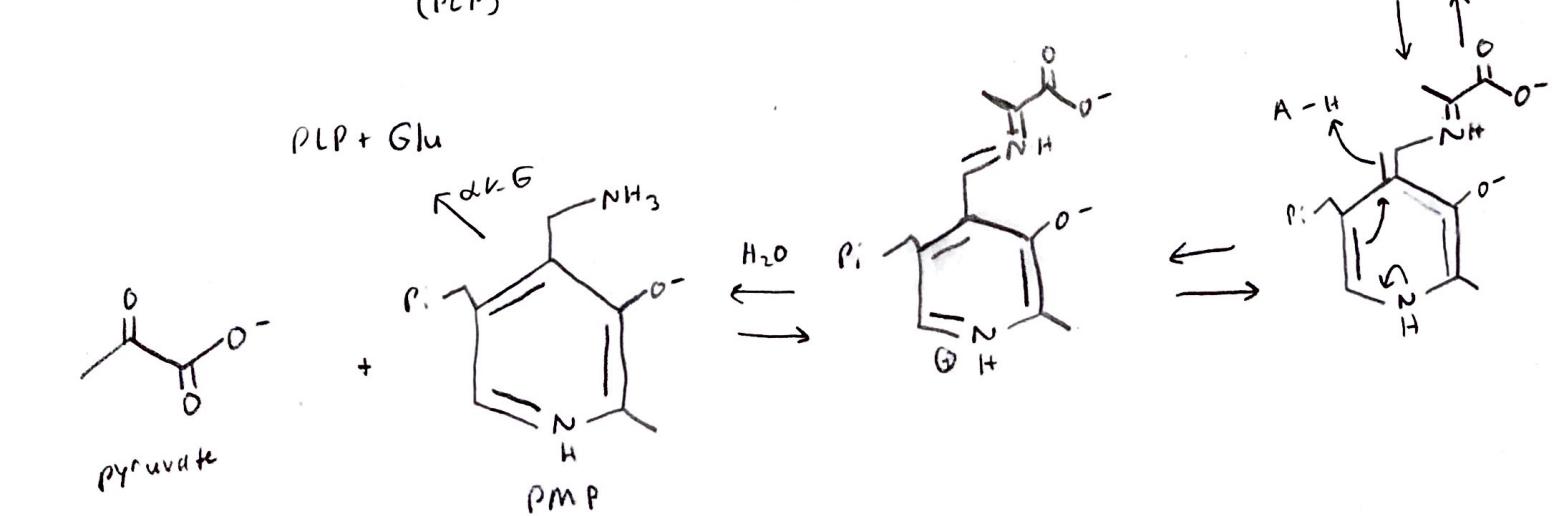
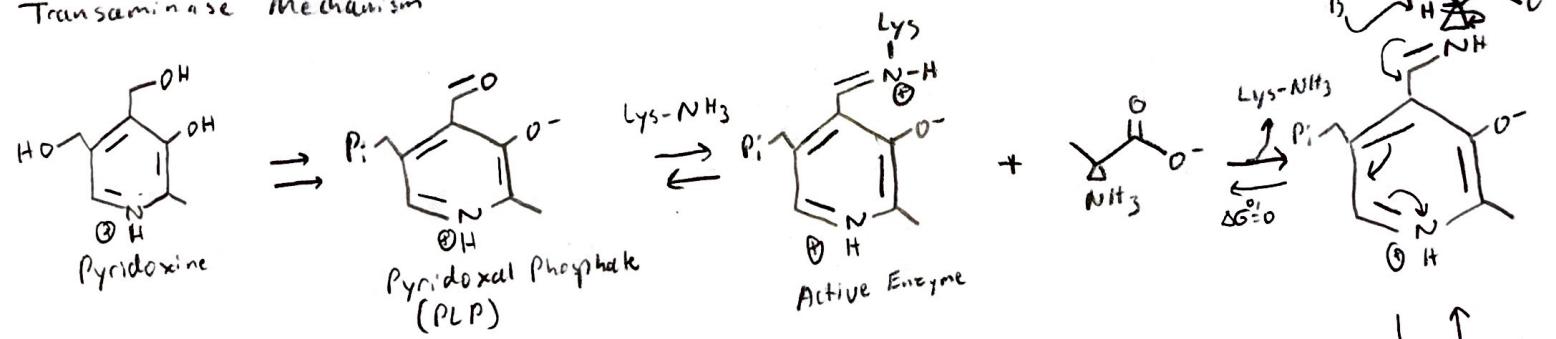
Transaminase



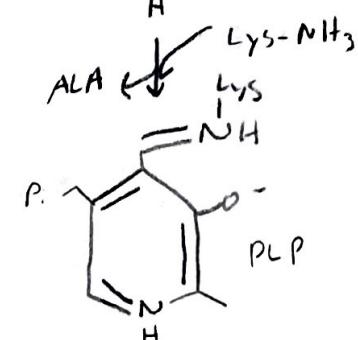
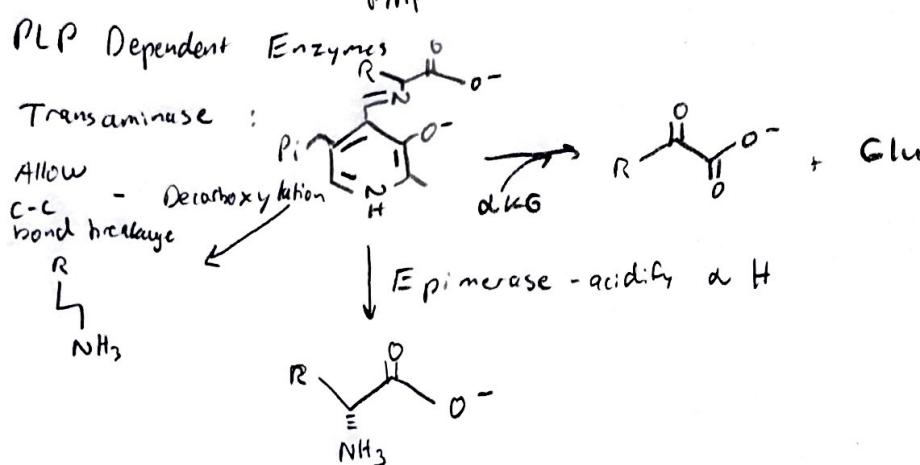
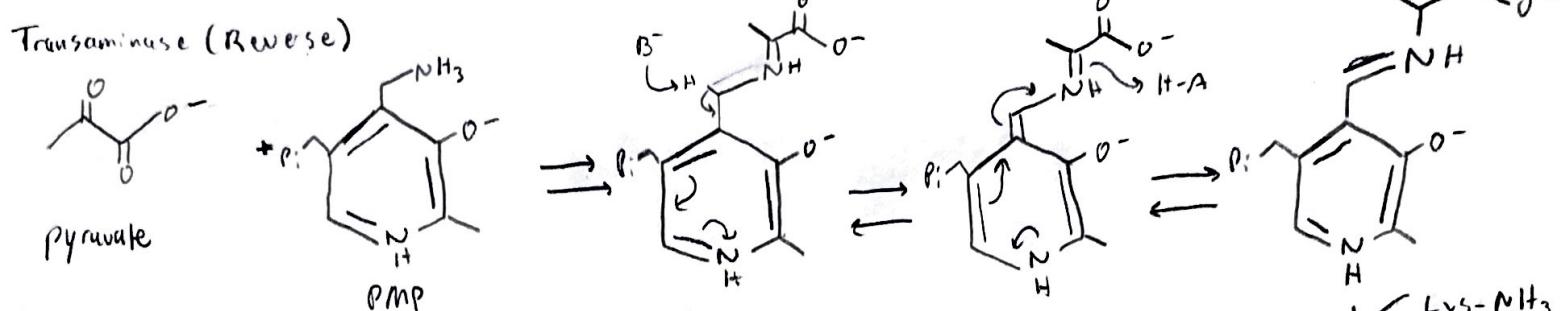
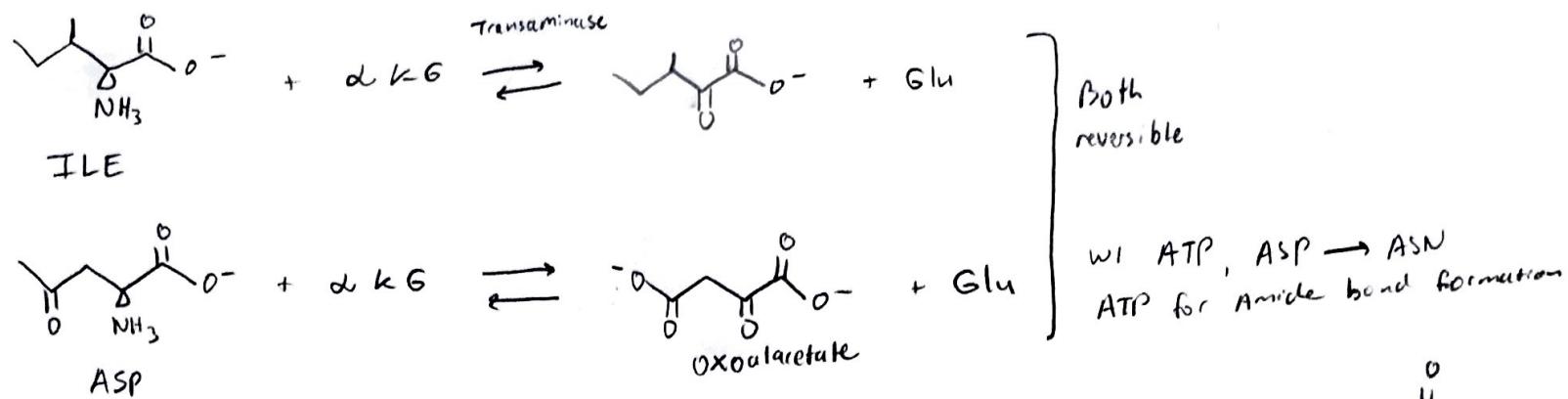
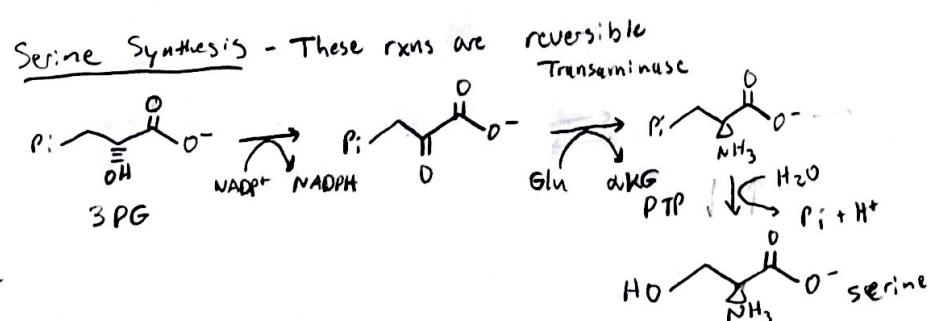
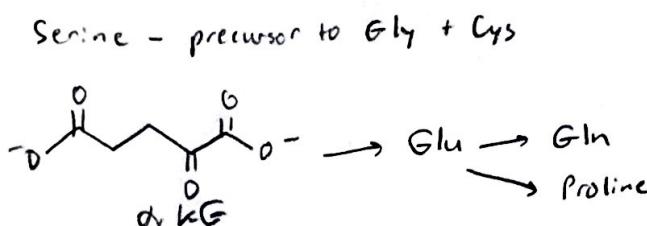
Glutamate Dehydrogenase - Either make or remove Glu = reversible



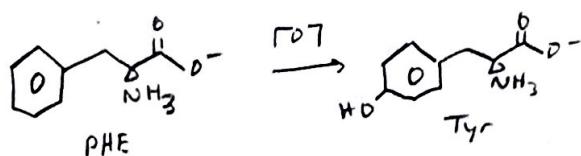
Transaminase Mechanism



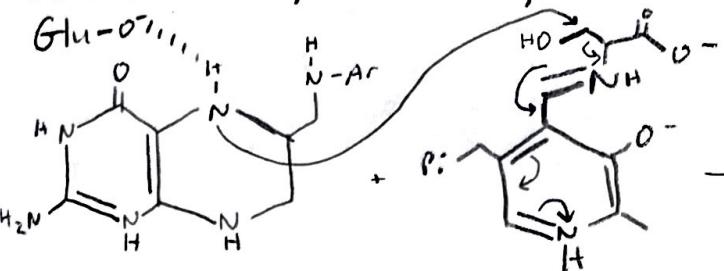
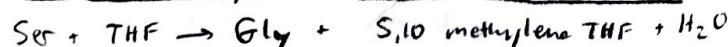
Amino Acid Metabolism cont.

Amino Acid Synthesis

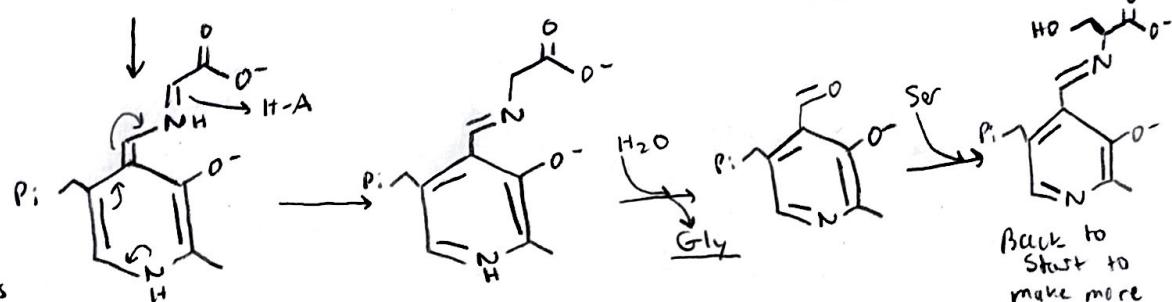
see ALA, ILE, ASP, ASN in catabolism section - reverse mechanism



Ser → Gly via SHMT - see next page

Amino Acid Synthesis cont.Ser \rightarrow Gly via SHMT (serine hydroxymethyl transferase)HO \swarrow from Ser \rightarrow THF = 1 carbon donor like SAMSerine hydroxymethyl transferase (SHMT)

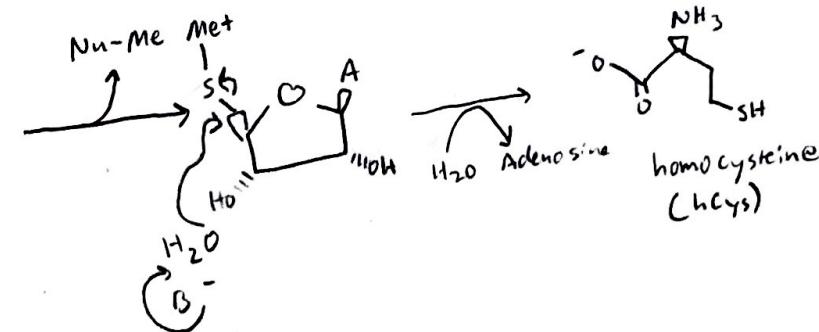
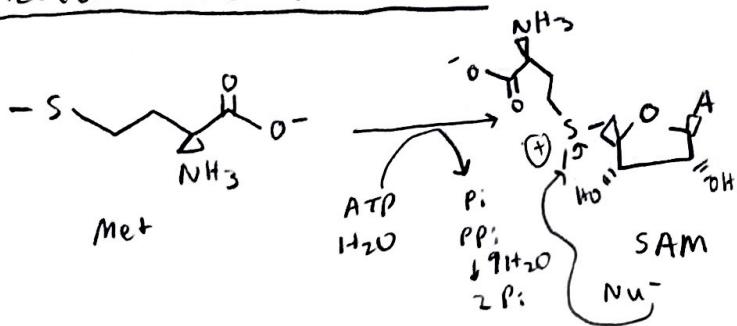
5-methyl-THF << SAM

in terms of methylation
due to S⁺ vs N⁺Cysteine + Methionine Synthesis

Met is an essential AA b/c we don't ingest enough

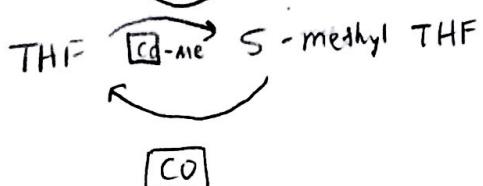
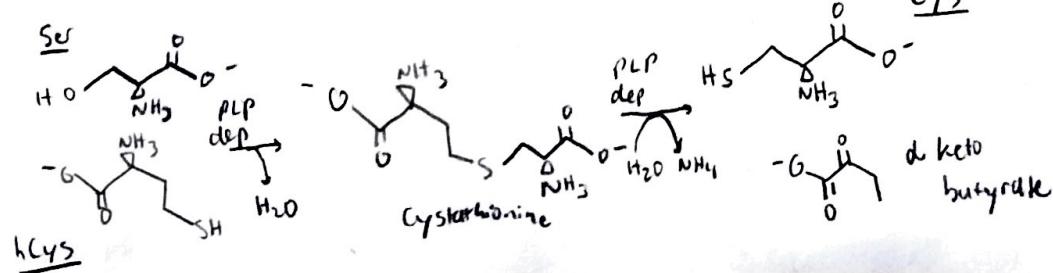
Cys can be derived from Met

SAM is activated Met

Methionine Adenosyltransferase

hCys precursor to Met + SAM

hCys + 5-Methyl-THF = regenerate Met - Problem = 5-Methyl-THF not very reactive - use B12 first

Methionine SynthasehCys \rightarrow MetCystathione β -SynthaseSert hCys \rightarrow cystathione \rightarrow cleave to Cys + NH₄⁺ + d keto butyrate

Amino Acid Metabolism Cont.Urea Cycle

After AA catabolism, byproducts to metabolism

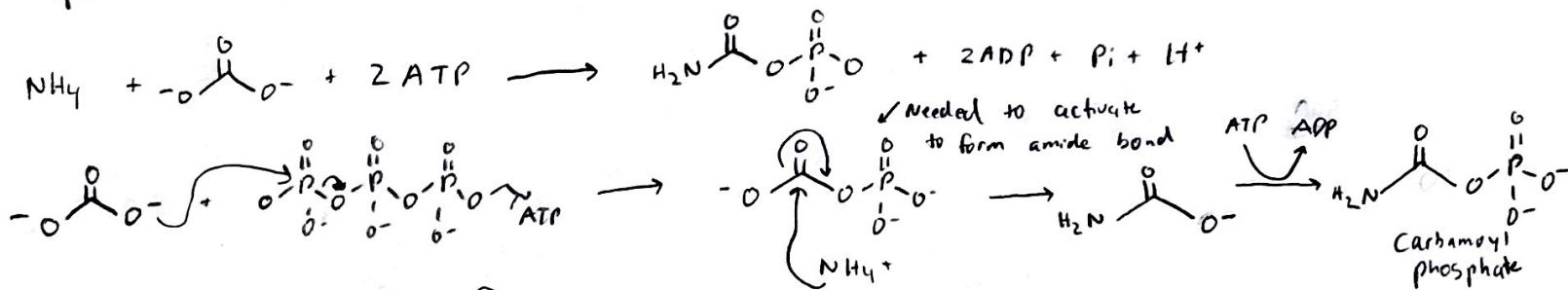
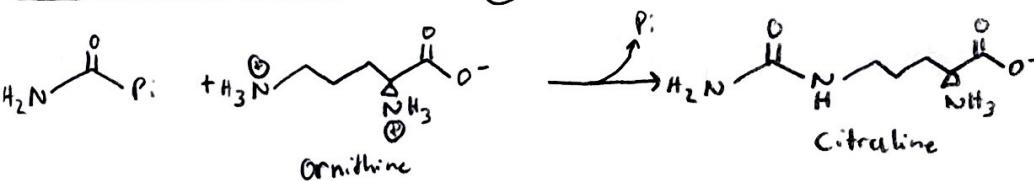
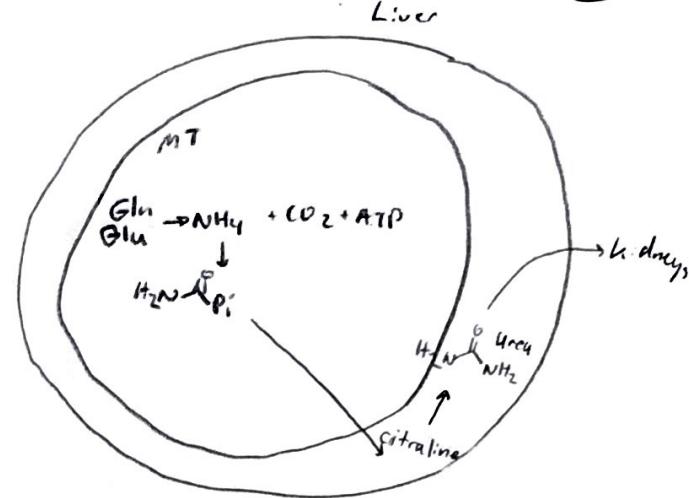
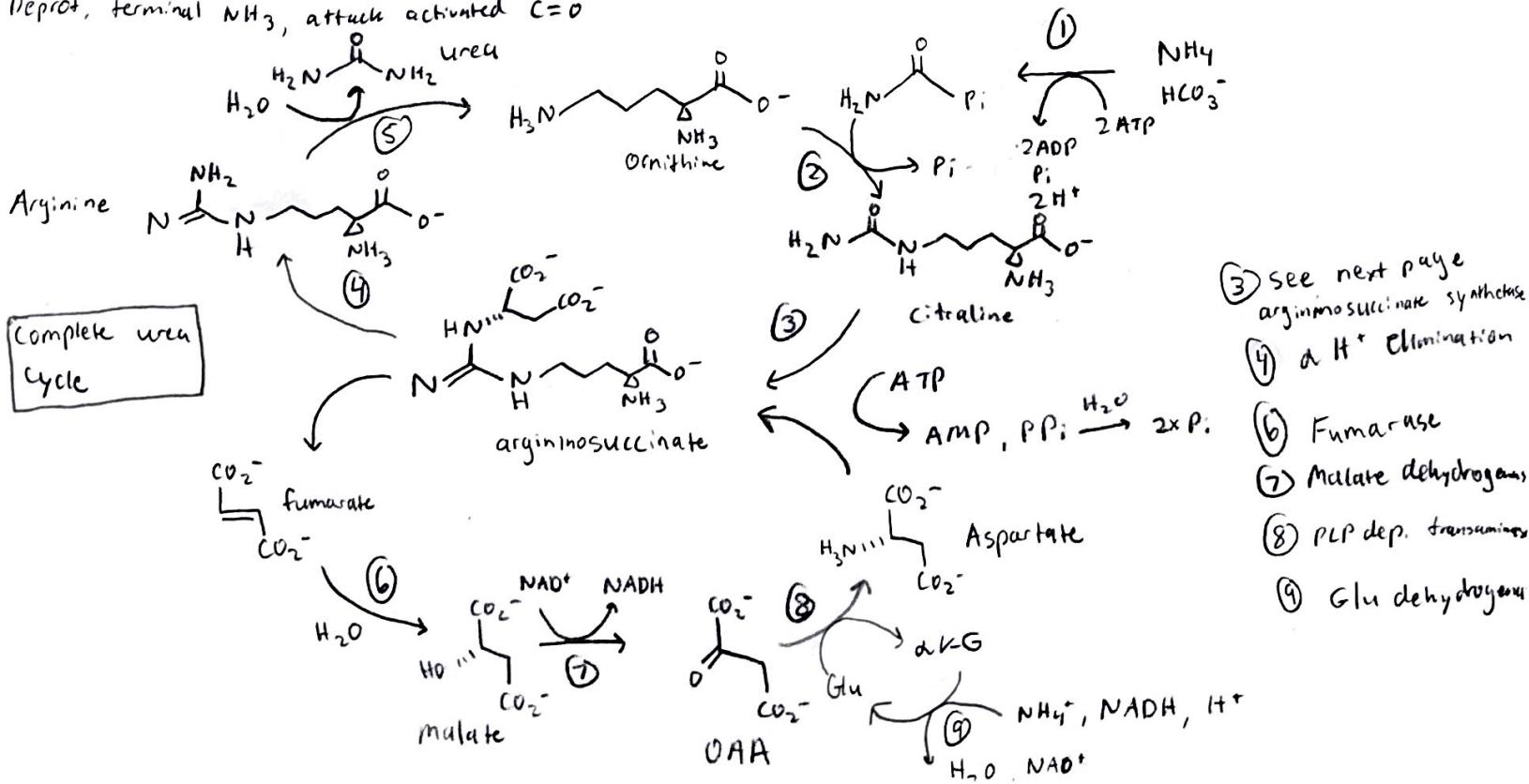
pyruvate \rightarrow acetyl-CoA \rightarrow TCA
 \rightarrow gluconeogenesisAmmonia \rightarrow Glu
 \rightarrow Excreted

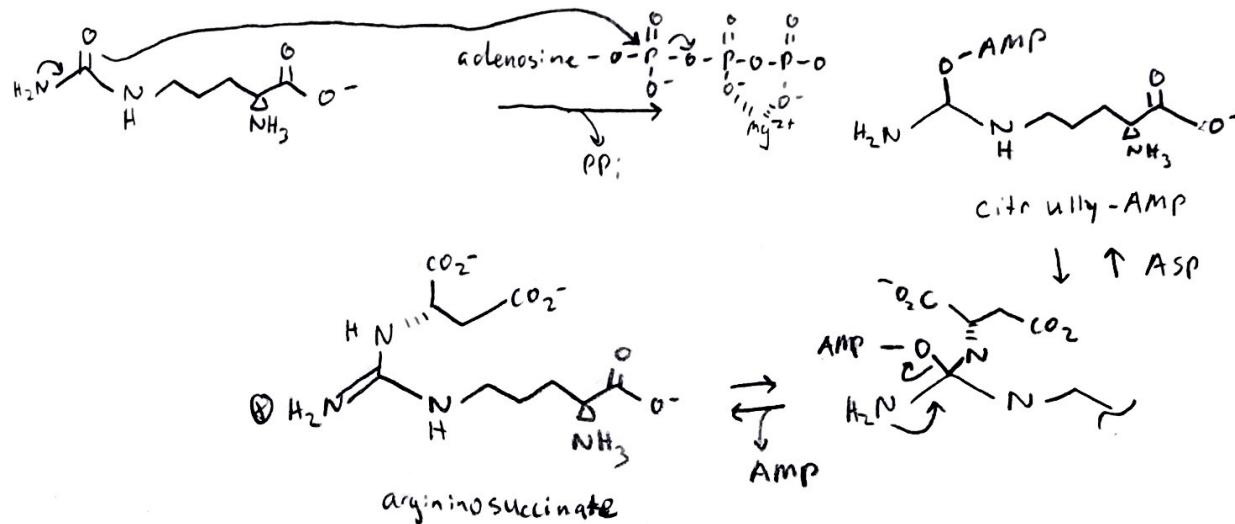
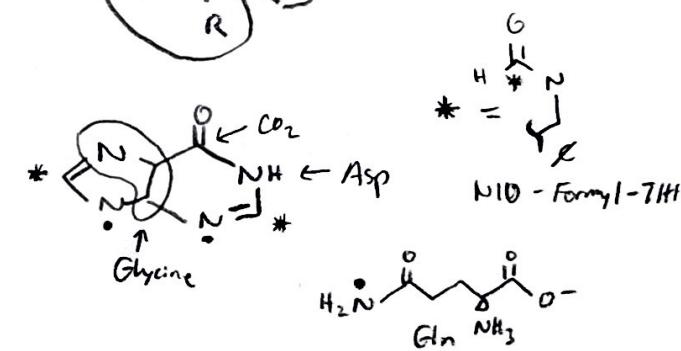
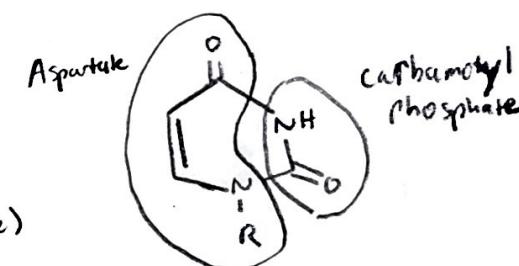
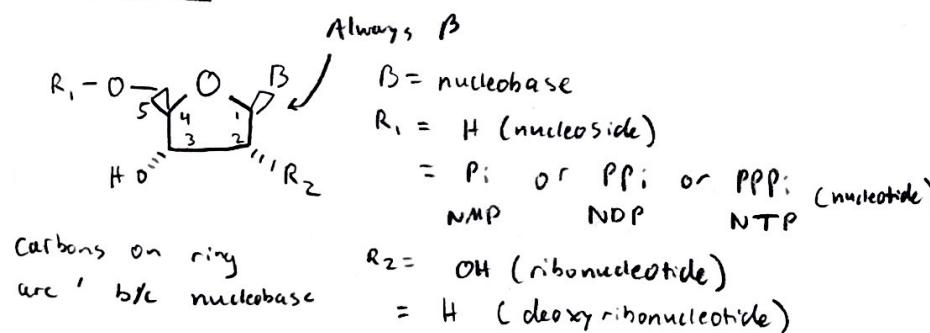
Urea uncharged = buildup doesn't affect body's pH

Nitrogen from carbamoyl phosphate + Asp

Carbamoyl Phosphate Synthetase (CPS) (1)

- Capture Ammonium, carbon dioxide

Ornithine Transcarbamoylase (2)Deprot. terminal NH_3^+ , attack activated $\text{C}=\text{O}$ 

Amino Acid Metabolism cont.Urea CycleArgininosuccinate Synthetase (3)Nucleotides

ribose comes from glucose

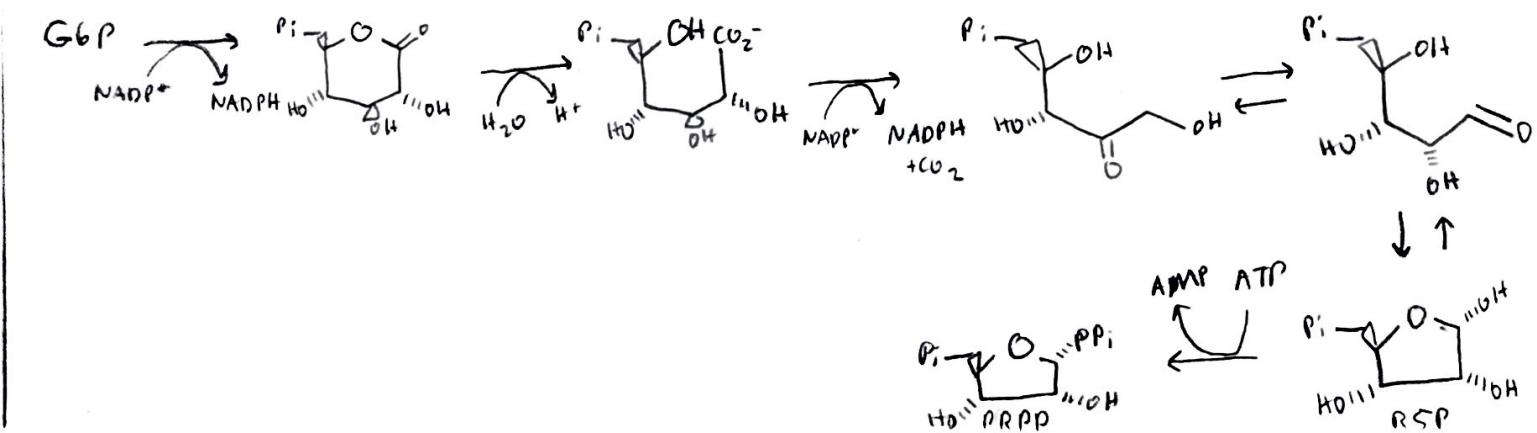
nucleobase from carbamoyl phosphate

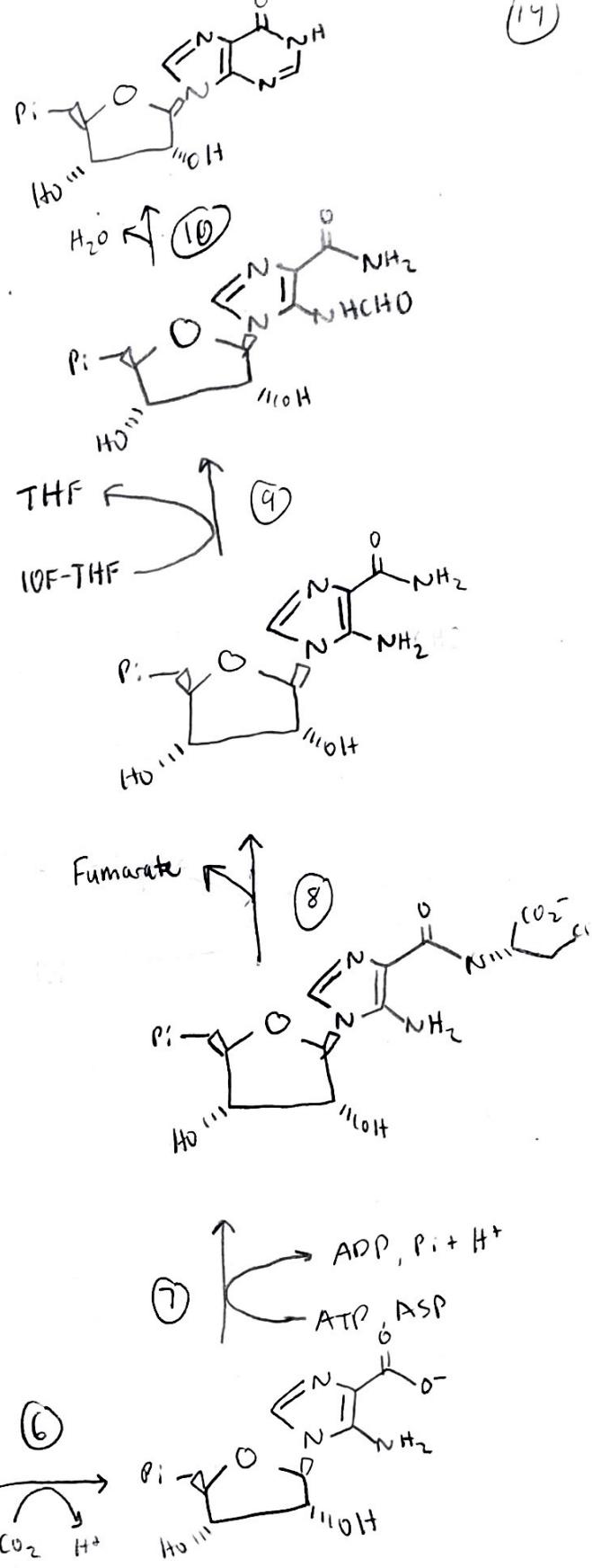
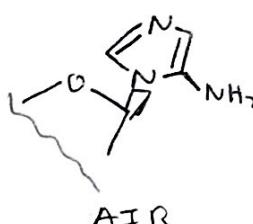
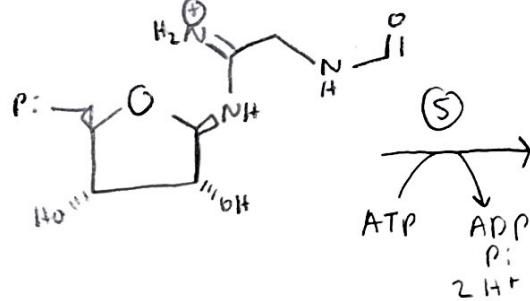
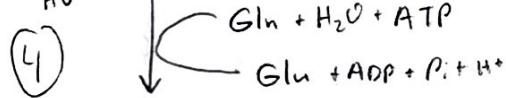
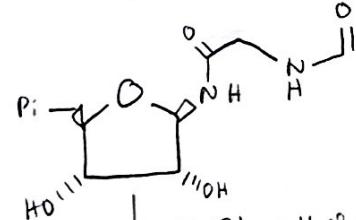
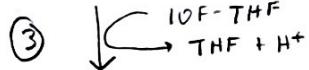
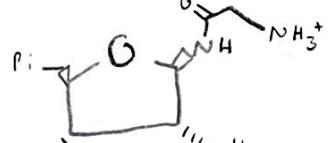
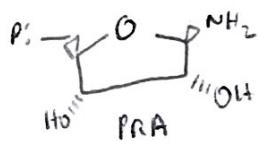
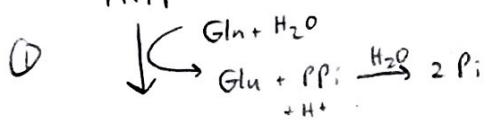
nucleobase names: adenine, guanine, cytosine, thymine

nucleotide names: adenosine, cytidine, guanosine, thymidine

De Novo Synthesis

Ribose 5 phosphate (R5P) = starting material - need to build from G6P

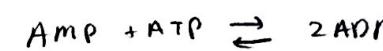
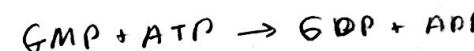
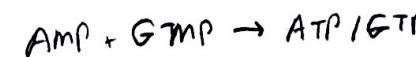
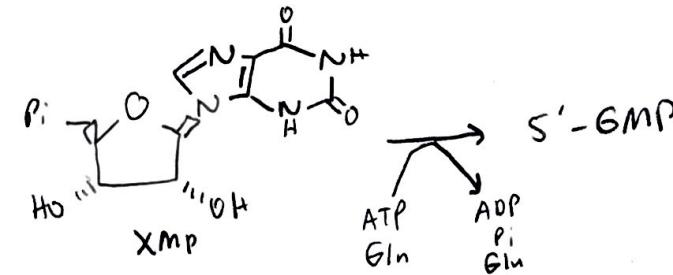
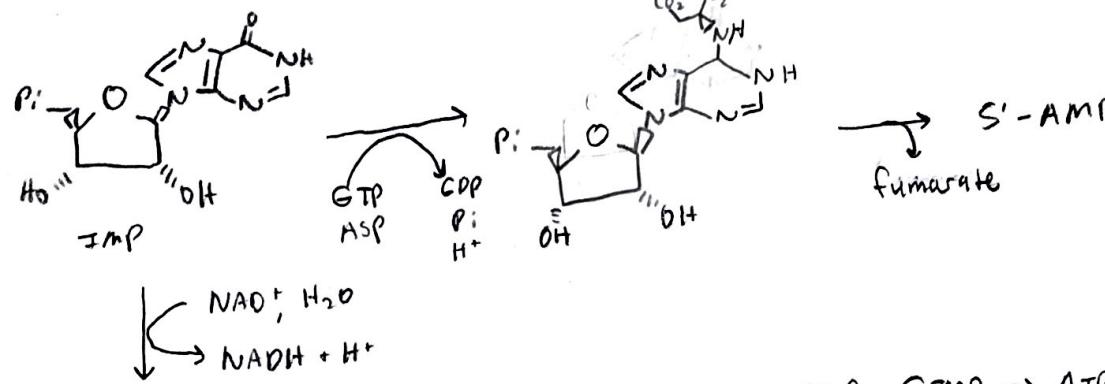
Pentose Phosphate Pathway

NucleotidesPurine Biosynthesispurinosome - enzyme catalyzes PRPP \rightarrow IMP

Note in ④ Use ATP to activate C=O via O-AMP tautomer

CHEM143 ReviewNucleotides

IMP is a branch point to make S'-AMP vs S'-GMP

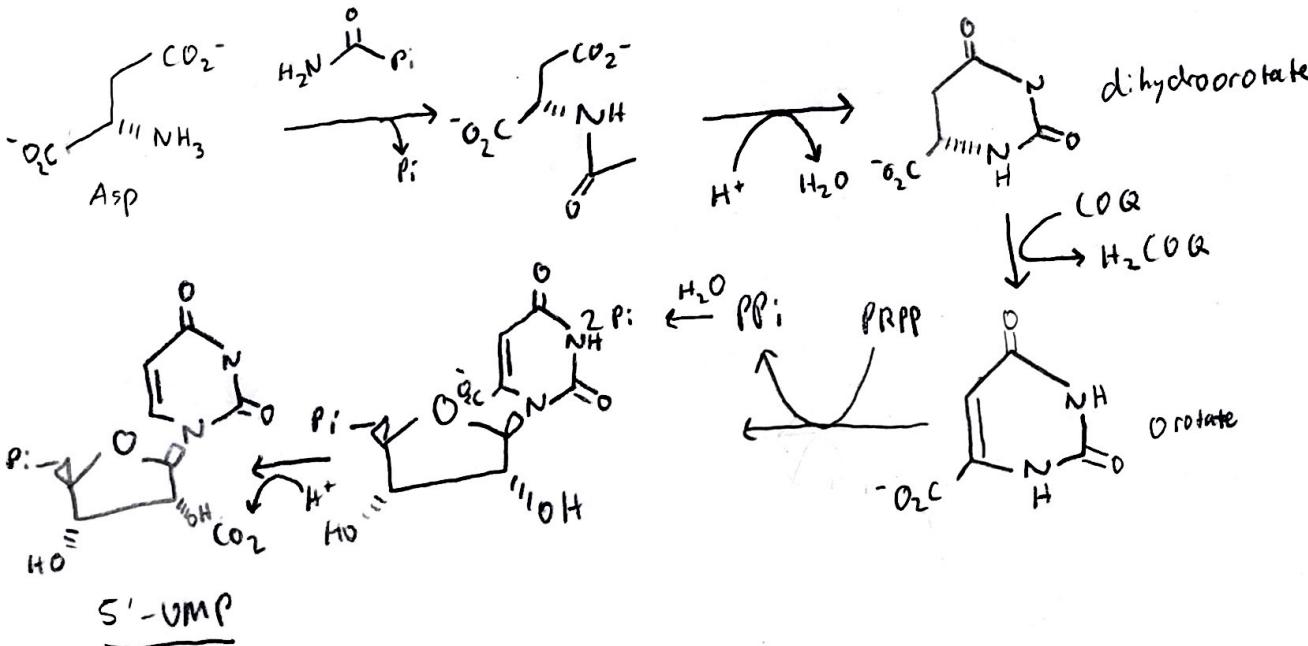


ATP synthase adds Pi to ADP in MT

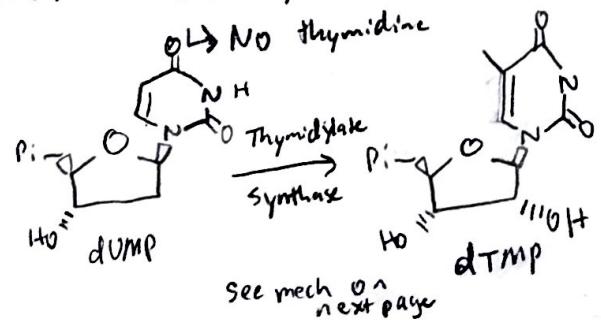
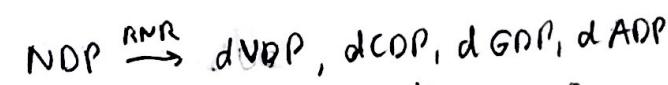
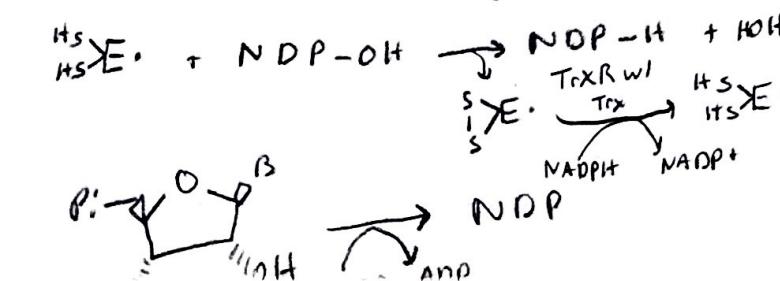
GDP \rightarrow GTP via NDP kinases

De Novo Pyrimidine Biosynthesis

- Assemble ring freely then attach to PRPP

Ribonucleotide Reductase (RNR)

- Deoxygenates 2' hydroxyl group



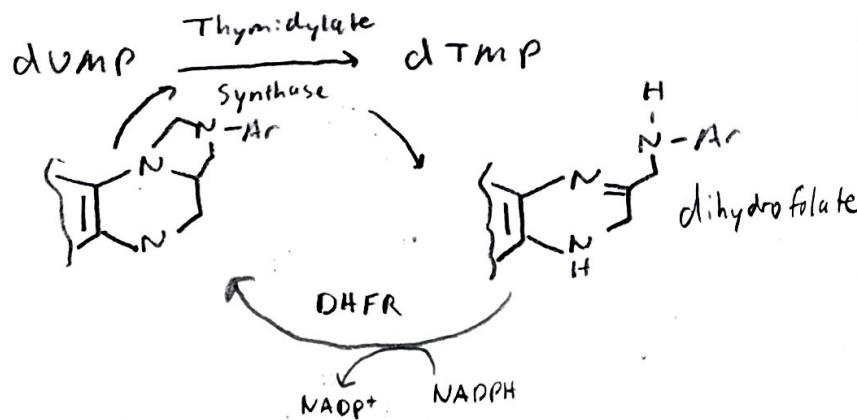
See mech next page

CHEM143 Review

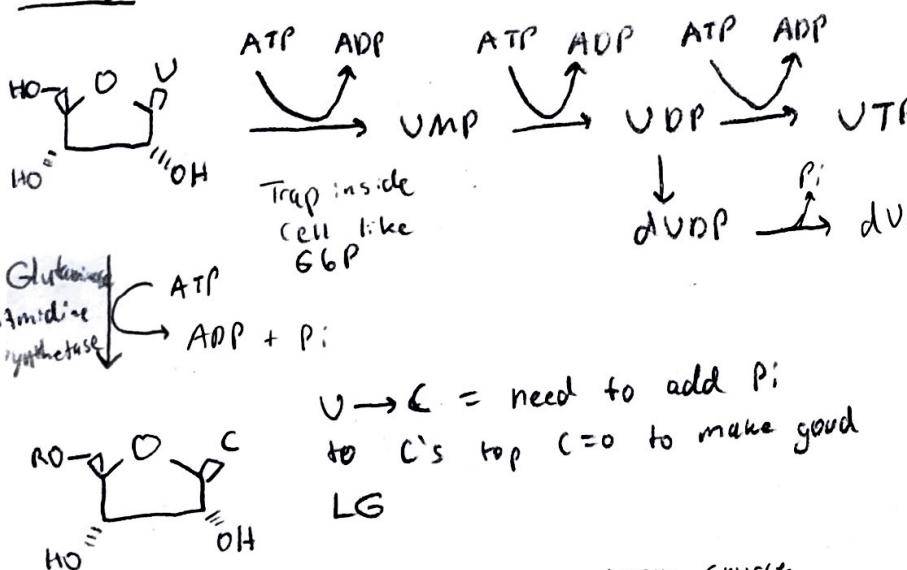
Nucleotides

Not enough SAM to methylate dUMP

↳ use THF-methyl comes from abundant Ser



Salvage



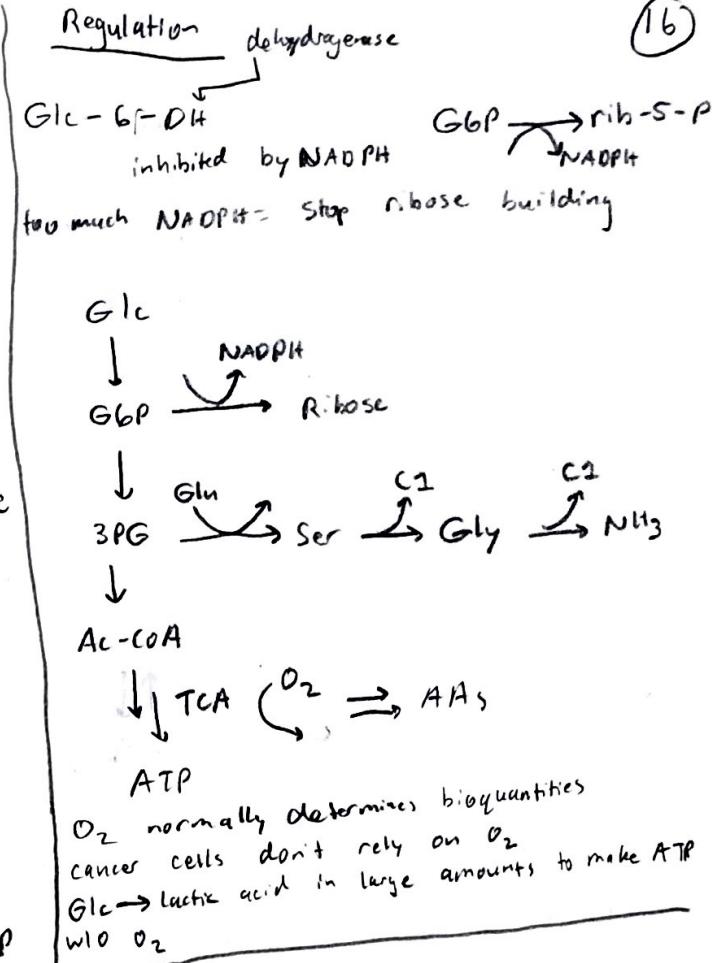
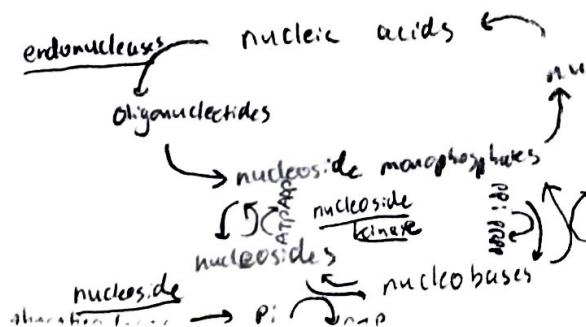
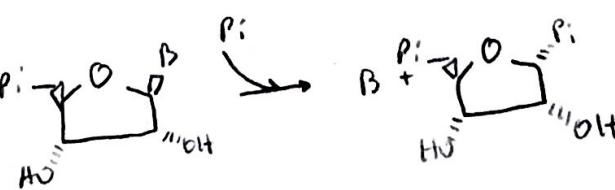
Hydrolysis of extracellular DNA primary source

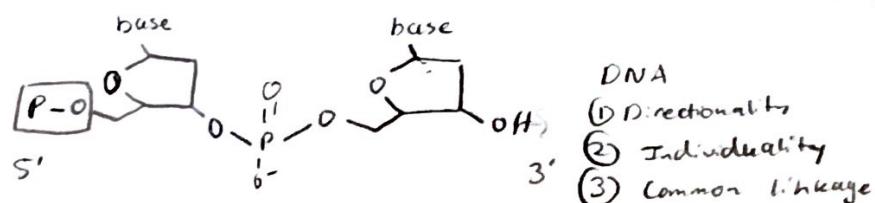
Endonuclease breaks phosphodiester bonds = oligonucleotide fragments

Phosphodiesterases break $\xrightarrow{\text{3' / 5' monophosphates}}$ hydrolyze via nucleotidases = remove Pi = nucleoside

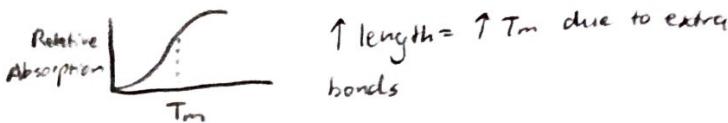
↳ intracellular uptake then add Pi

nucleoside phosphorylase add Pi at C' $\text{Pi} \rightarrow \text{O}$



Nucleic AcidsBio-polymers

H-bonding pairs / π stacking
prevents UV absorption



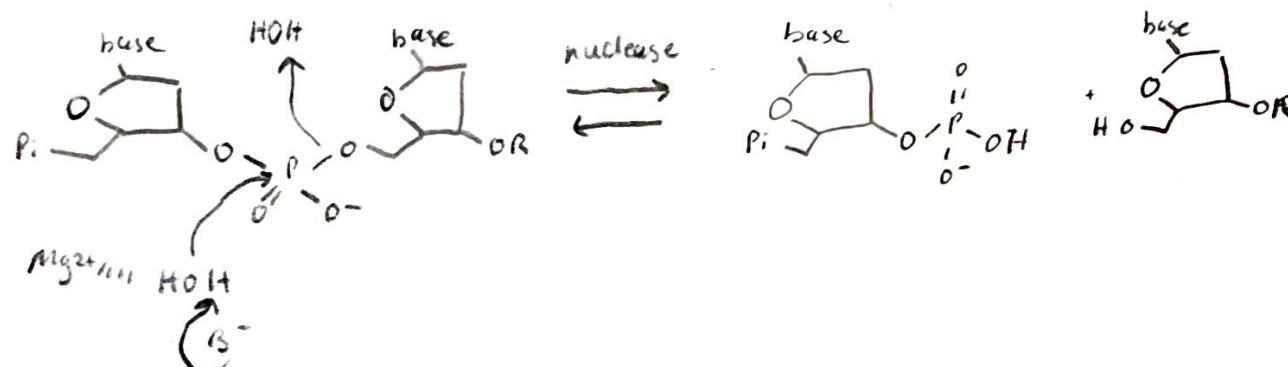
Series of identical bases stronger
due to better stacking

C2' endo preferred = β-form = less steric clash

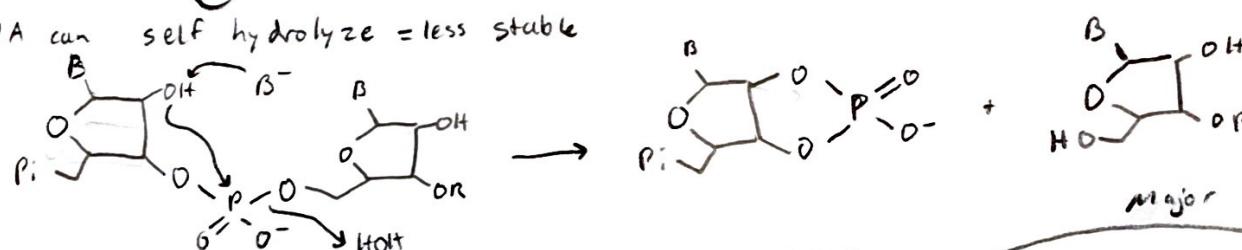
T_m = melting temperature
temperature where ~~the~~ helix dissociates
into 2 strands

endonucleases - cut midstream

exonucleases - digest from ends



RNA can self hydrolyze = less stable



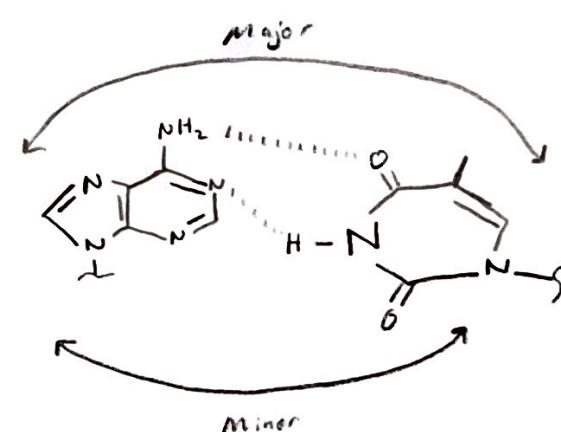
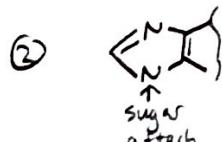
RNA's single strands mean it can fold into enzymes

Base Pairing

① Purine-Pyrimidine

A = T or A = U

G ≡ C

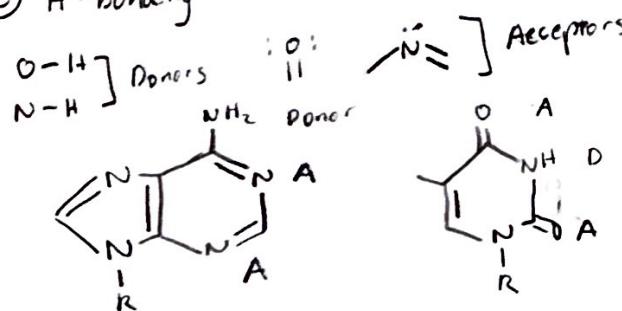


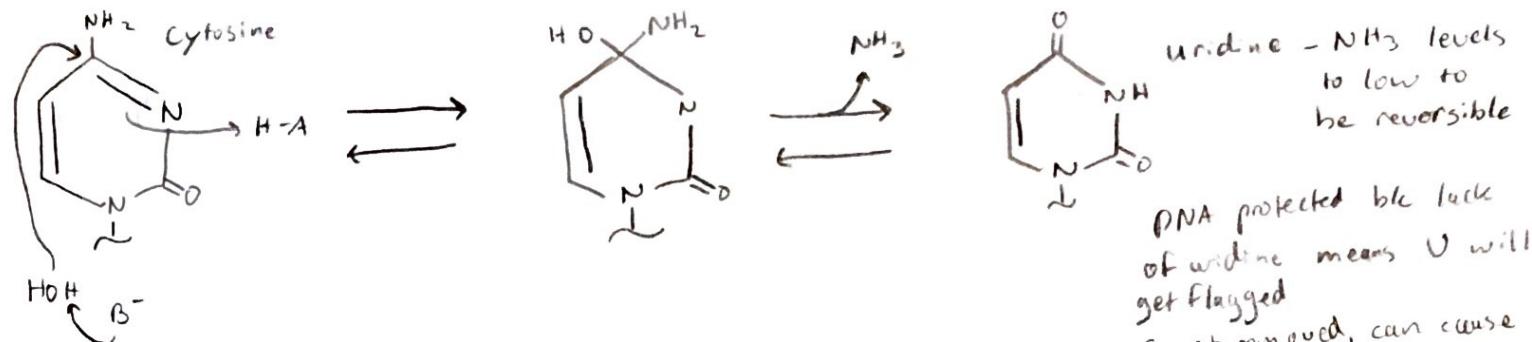
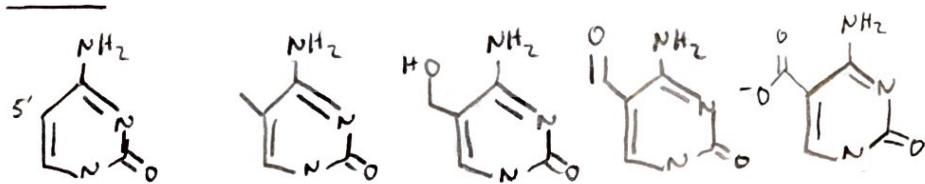
G ≡ C = 3 H-bonds = more stable

Tautomer change bonding patterns

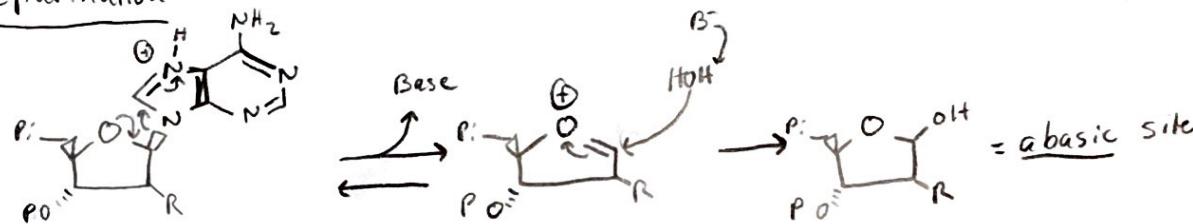


-Changed pattern
= could no longer be
complementary
= might recruit diff base
leading to error



Nucleic AcidsCytosine DeaminationPTMs

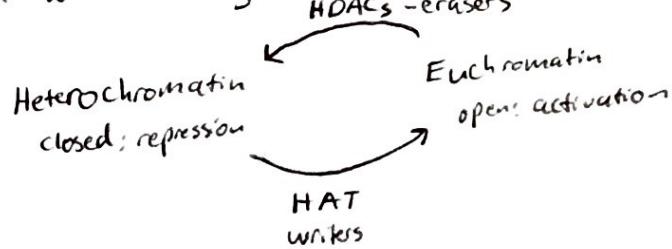
Used to prevent/recruit things from binding to sequence
Changing H-bonding = change function / expression

Depurination

Histones organize and pack DNA via coiling

tails positively charged w/ Lys/Arg to attract G DNA

Interact w/ minor groove to leave major exposed



HAT - Histone Acetyl Transferase

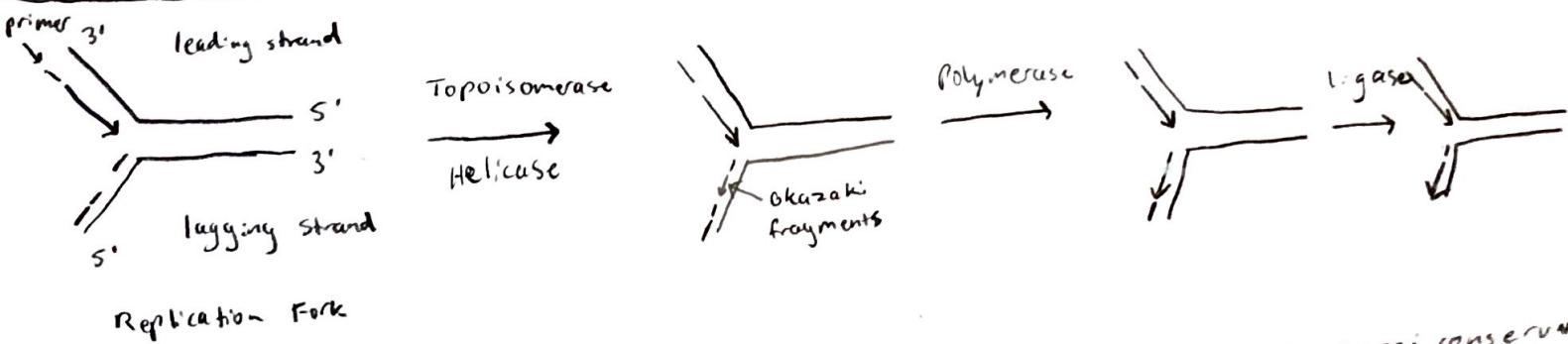
To silence DNA = hypermethylate

Acetyl groups = prevent histones from tight wrapping

HDACs - Histone deacetylases

CHEM 143 Review

DNA Replication

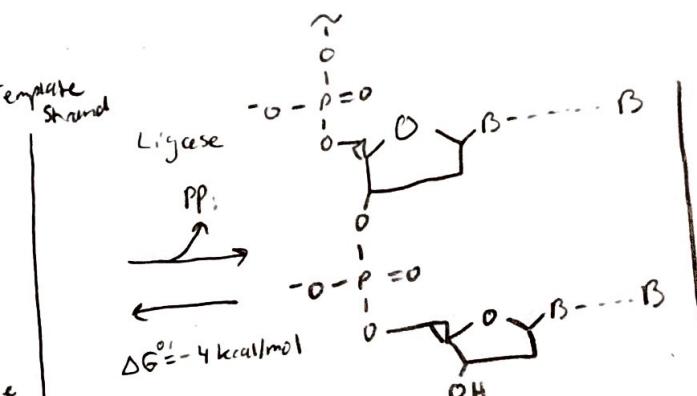
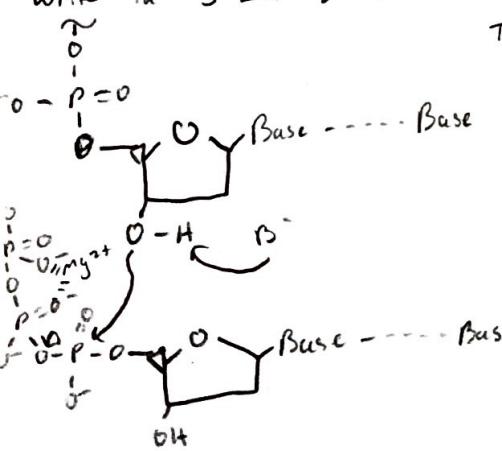


Replication Fork

DNA Polymerase - palm shaped

unwind helix and use each strand as template

write in $5' \rightarrow 3'$ direction



Primer must already exist = semi-conservative

- Mg^{2+} vital
- interacts w/ major and minor
- induced fit to ↑ specificity
- moves along w/o detaching
- induced fit slow step
- multiple polymerases work \oplus onke

processive - catalyze many reactions one by one w/o detaching

primase - add RNA primers to start replication

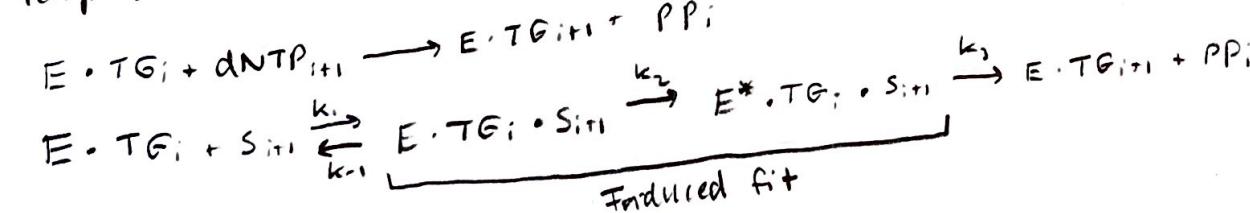
helicase - unwind DNA via ATP hydrolysis

single stranded binding proteins - prevent rewinding

T = template G_i = growing strand at i pos from 5'

Template strand = catalyst

E + TG_i + dNTP_{i+1} \rightarrow E · TG_{i+1} + PP_i



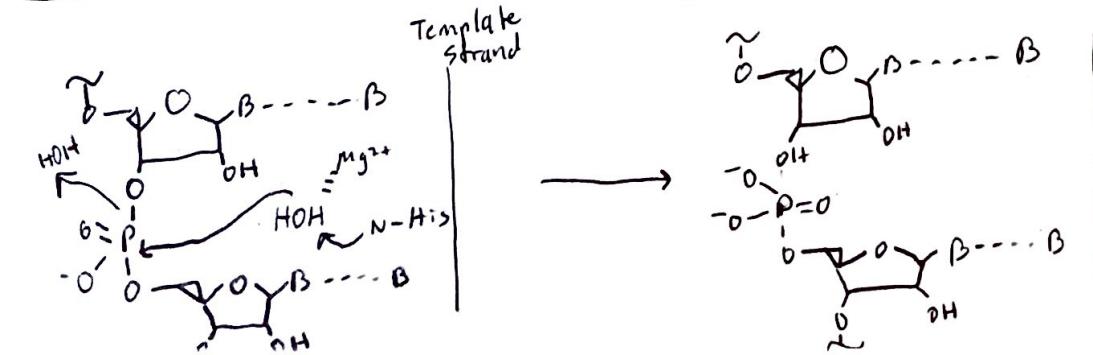
$$\frac{V_A}{V_G} = \frac{(k_2 + k_m)}{(k_1 + k_m)} \frac{dATP}{dGTP}$$

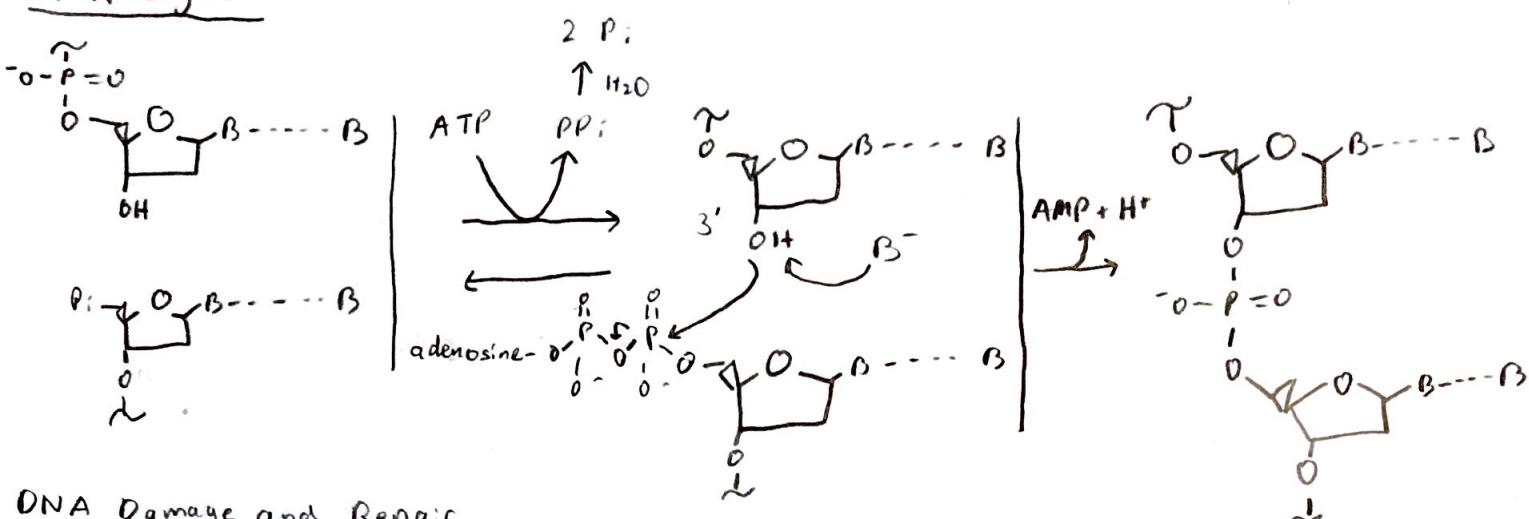
b_A/b_G ratio determines specificity

Specificity from

- H-bonding
- won't close when mismatch
- exonuclease destroys incorrect linkages

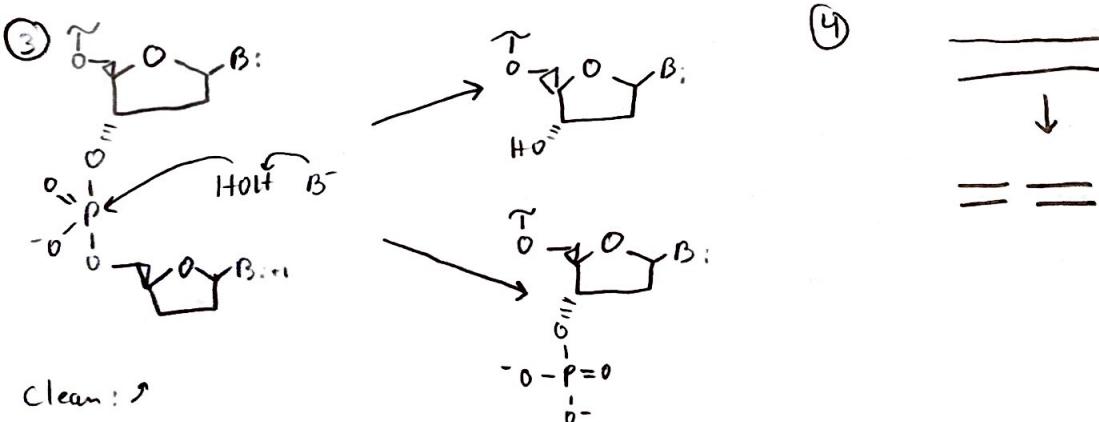
RNase H - remove RNA primers, allowing DNA pol to add DNA



DNA ReplicationDNA LigaseDNA Damage and Repair

Types of Damage

- 1) Nucleic base Alteration C → U
- 2) Depurination
- 3) Single Strand Breaks (SSBs) - Clean
- 4) Double Stranded Breaks (DSBs)

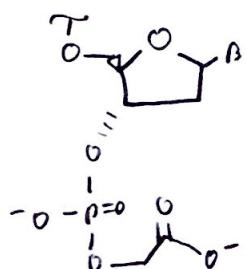


Clean: ↗

dirty:

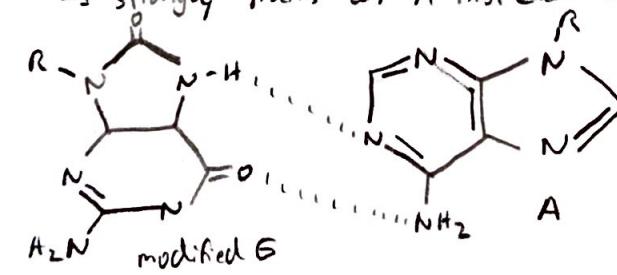
ionizing radiation generates HO[•].

Cleave bond btw 3' and 4' carbons



Additional damage

O₂^{•-} / H₂O₂ / HO[•] convert G → 8-oxoguanosine
↳ strongly pairs w/ A instead of C



DNA Damage and Repair

Mismatch Repair - enzyme complex scans newly copied DNA for incorrect bases/lesions

- basepair error
- insertions/deletions (INDELS)



- ① Bind to lesion site, distort DNA w/ ATP
- ② Endonuclease cleave phosphodiester bond near mismatch
- ③ Exonuclease digests bad DNA
- ④ DNA Pol fills gap, Ligase joins

microsatellites - large regions w/ highly repetitive sequence

↳ will occasionally cause DNA Pol to stall/fail = leave dangling end which will attach to random portion

destroy mismatch = growth advantages are selective

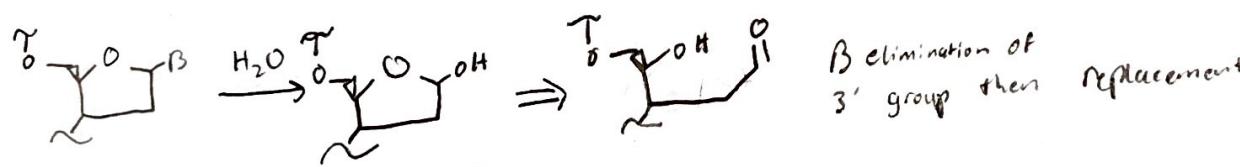
only really picks up lagging strand errors due to lots of primers

will miss leading strand errors

Base Excision Repair - fix bad base instead of removing entire molecule at once

Create abasic site via N-glycosidic bond hydrolysis - endonucleases ID and cleave 5' Pi bond

DNA Pol / Ligase then replace



Cut 5' end,
then use lysine
to eliminate 3' end
in open chain
form

SSBs / DSBs

1) Apoptosis

2) Non homologous end joining

↳ stick ends to something else

↳ chromosomal translocations may happen

3) Homologous recombination mediated repair

↳ Look for partner chromosome

↳ Use that DNA as template

(3)

- 1) Recruit DSBs and intact DNA on other chromosome
- 2) ATM kinase activates MRN nuclease w/ endo+exo nuclelease capabilities
- 3) RPA binds single strand → RAD51 displaces RPA - RAD51 repairs
 - via 1) re-repair then religate or 2) dissociate DNA segments then normal fixing process

HRMR (3) largely important

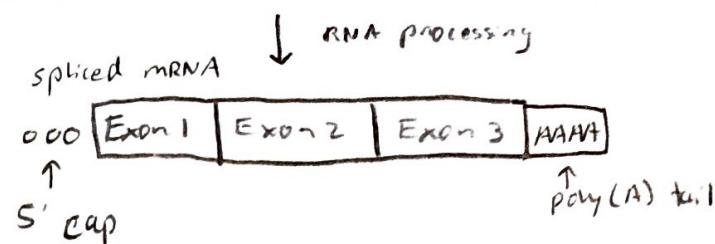
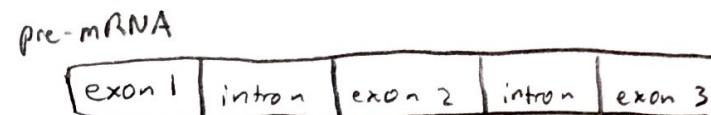
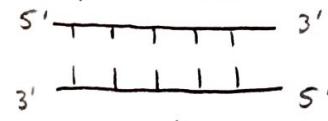
Transcription

rNTP vs dNTP

Begins w/o primers

Slower, proof reading less important

Template DNA

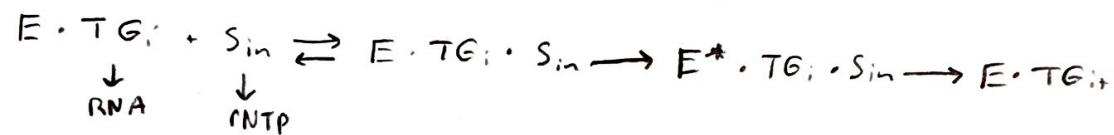


coding strand
maps base to base w/ RNA

5' 3'
 3' 5'

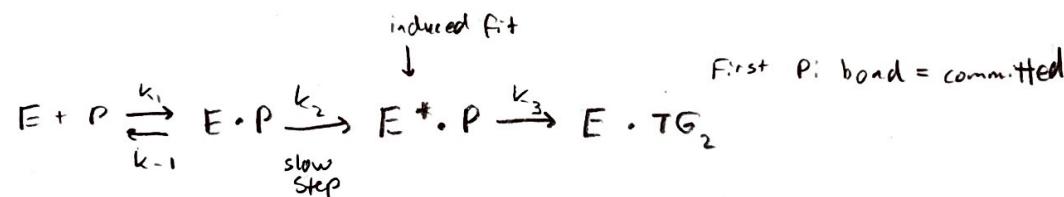
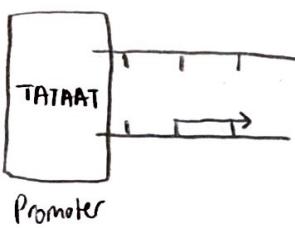
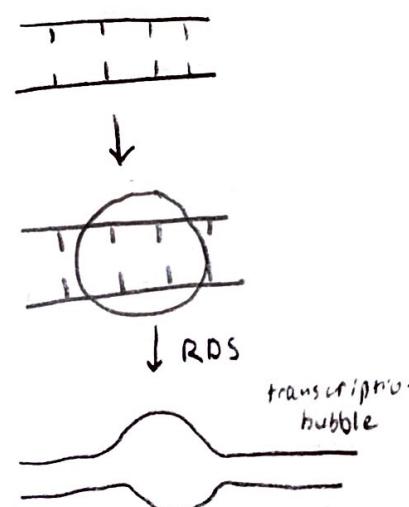
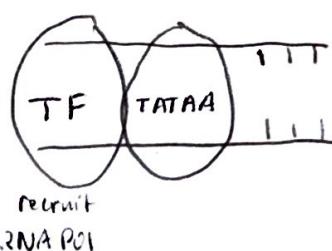
noncoding strand (template strand)

RNA Polymerase does initiation and elongation



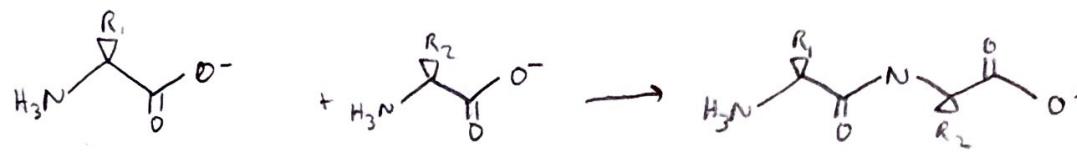
Initiation = RDS = induced fit conformational change

Promoter Sequence of DNA upstream of transcription start

Usually $k_{-1} > k_1$ = Wrong bases can't bindwhen $k_1 > k_{-1}$ = allow enough time for correct base to bind

Translation

- Peptide bond formation



Amide bond formation not favorable

- Need to use ATP to activate
- tRNA used as LG

20 AAs = need 3 letter codons

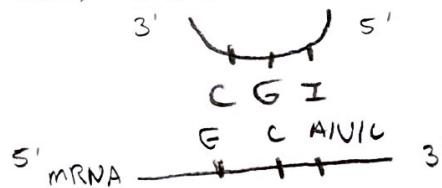
$$4^3 = 64 = \text{redundant codons}$$

3 stop codons other 61 codons for AAs

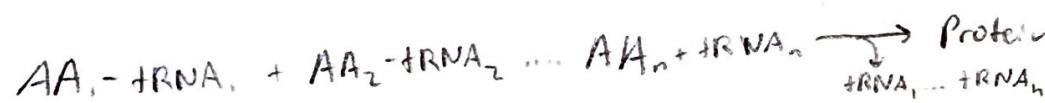
I: C, U, A] wobble base pairing
G: U

Always read DNA/codons/anticodons in $5' \rightarrow 3'$

That means IGC anticodon:



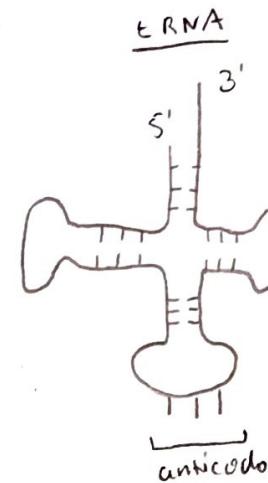
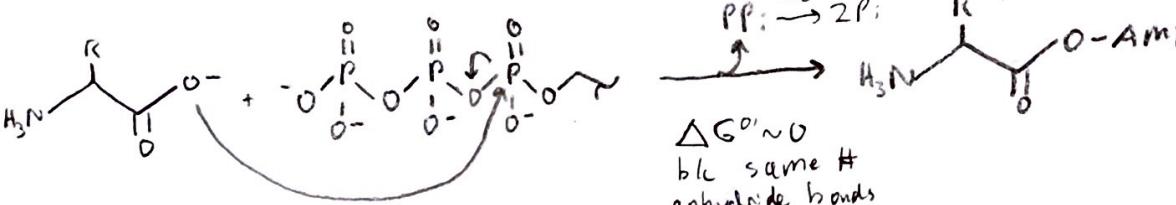
I base allows for less than 61 tRNAs



AA-tRNA synthesis via Aminoacyl tRNA synthetases

↪ I per AA, can recognize all tRNAs for AA

Aminoacyl tRNA Synthetase (ATP Dependent)



- H bonding
- 1) let same tRNA interact w/ multiple codons
 - 2) use non-canonical pairing for increased stability

- largest use of ATP in cell
- 2 ATP per synthesis
- Includes editing domain for better specificity

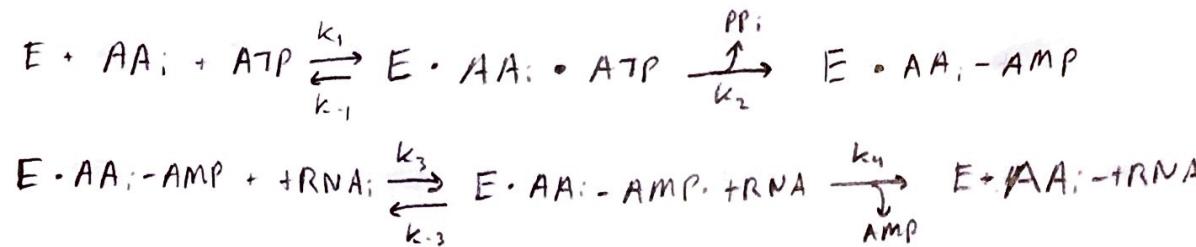
CHEM143 ReviewAminoacyl tRNA Synthetase Specificity (AARS)

- Need to avoid similar looking AAs
b/c ribosome only looks at tRNA, not AA

k_{cat}/K_m only includes elementary steps up

Until first irreversible step (usually RDS) - afterwards

Steps may affect k_{cat} or K_m but not specificity!

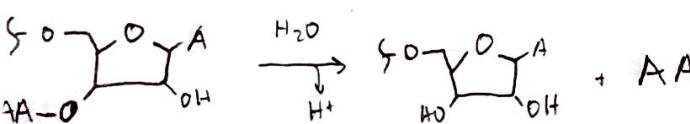


Ping Pong mechanism

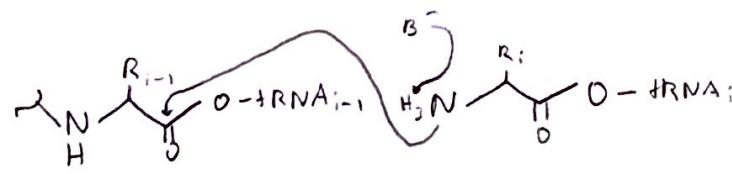
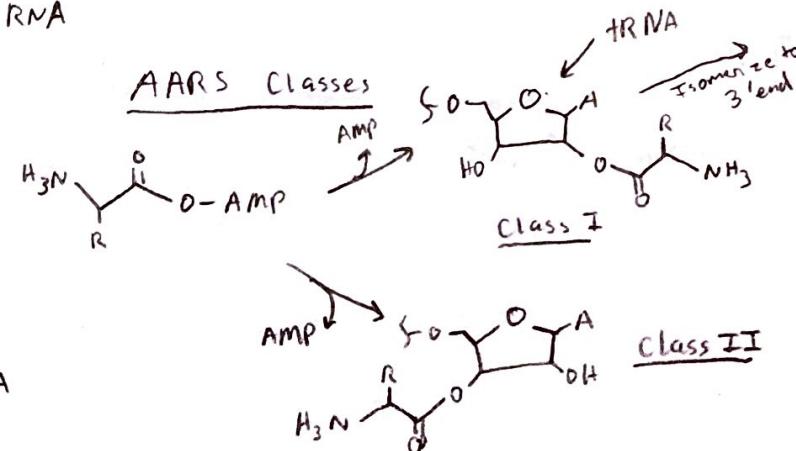
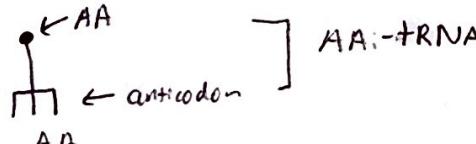
Only k_1, k_{-1}, k_2 matter for specificity = optimized via evolution

↳ 1000 fold diff btw correct and incorrect AA → less than 1000 Ser's in a protein

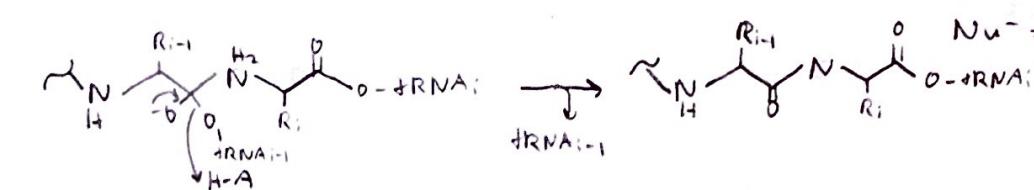
↳ 2nd site hydrolase to cut off bad tRNA

ProofreadingRibosome

- only worries about anticodon, not AA



P substrate

DNA / RNA

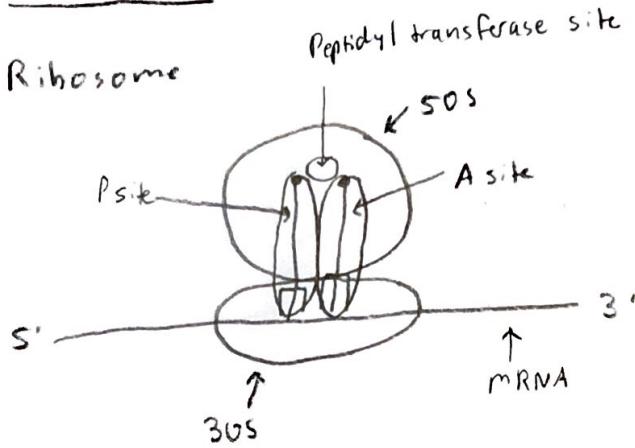
E^+ = incoming nucleotide

Nu^- = growing strand

Translation

E^+ = growing peptide

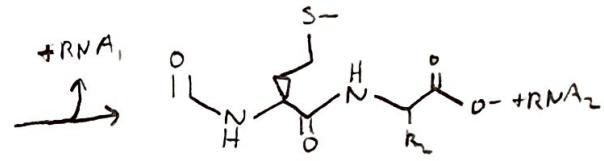
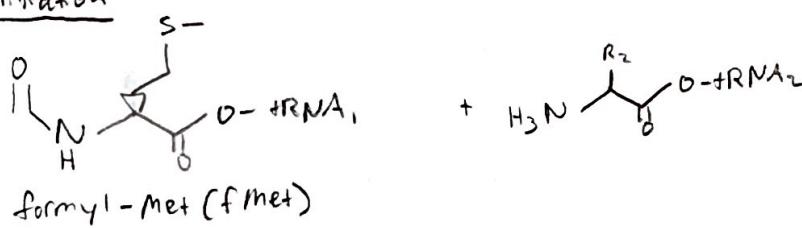
Nu^- = incoming AA

Translation

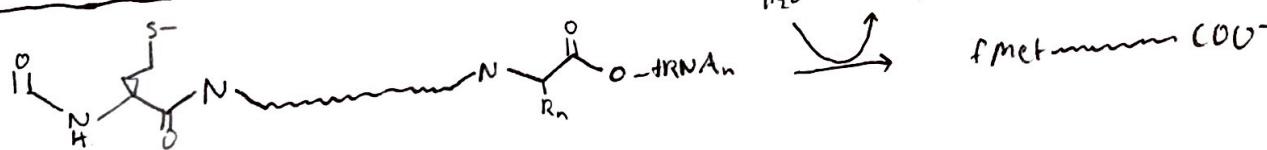
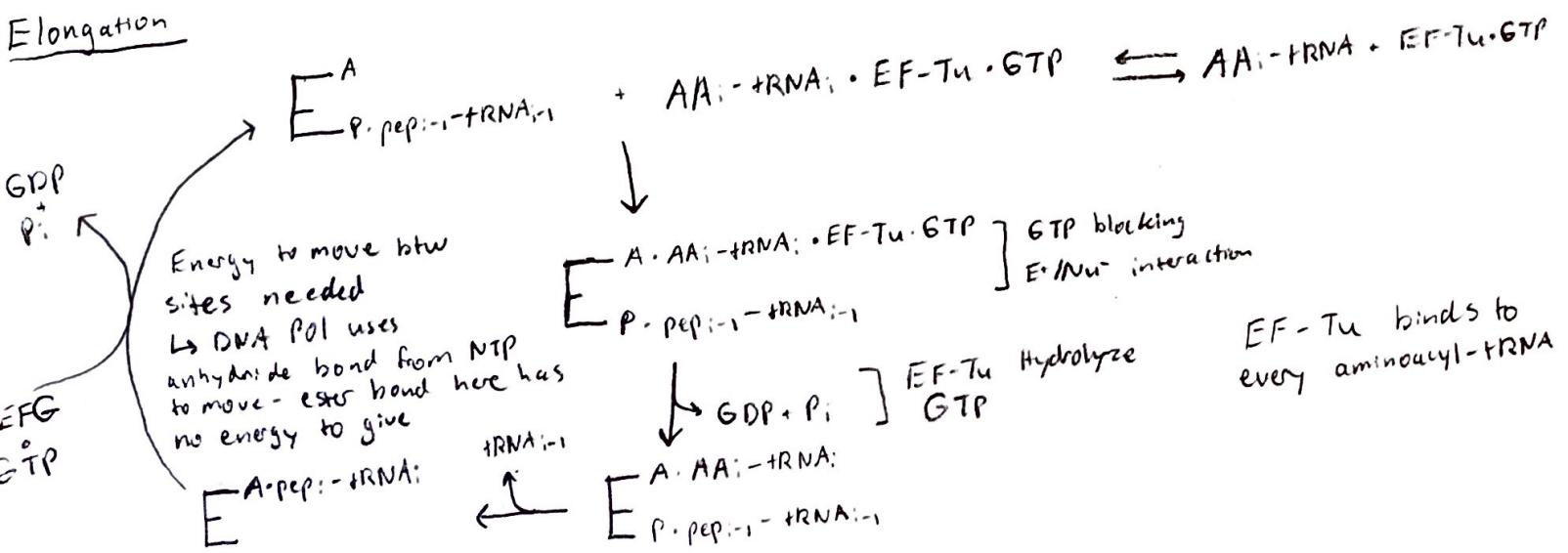
catalysis compartmentalized away from molecular recognition

Catalytic Cycle

- 1) Initiation - Commital Step
- 2) Elongation
- 3) Termination

Initiation

starts initiation

TerminationElongation

TranslationRibosome formation