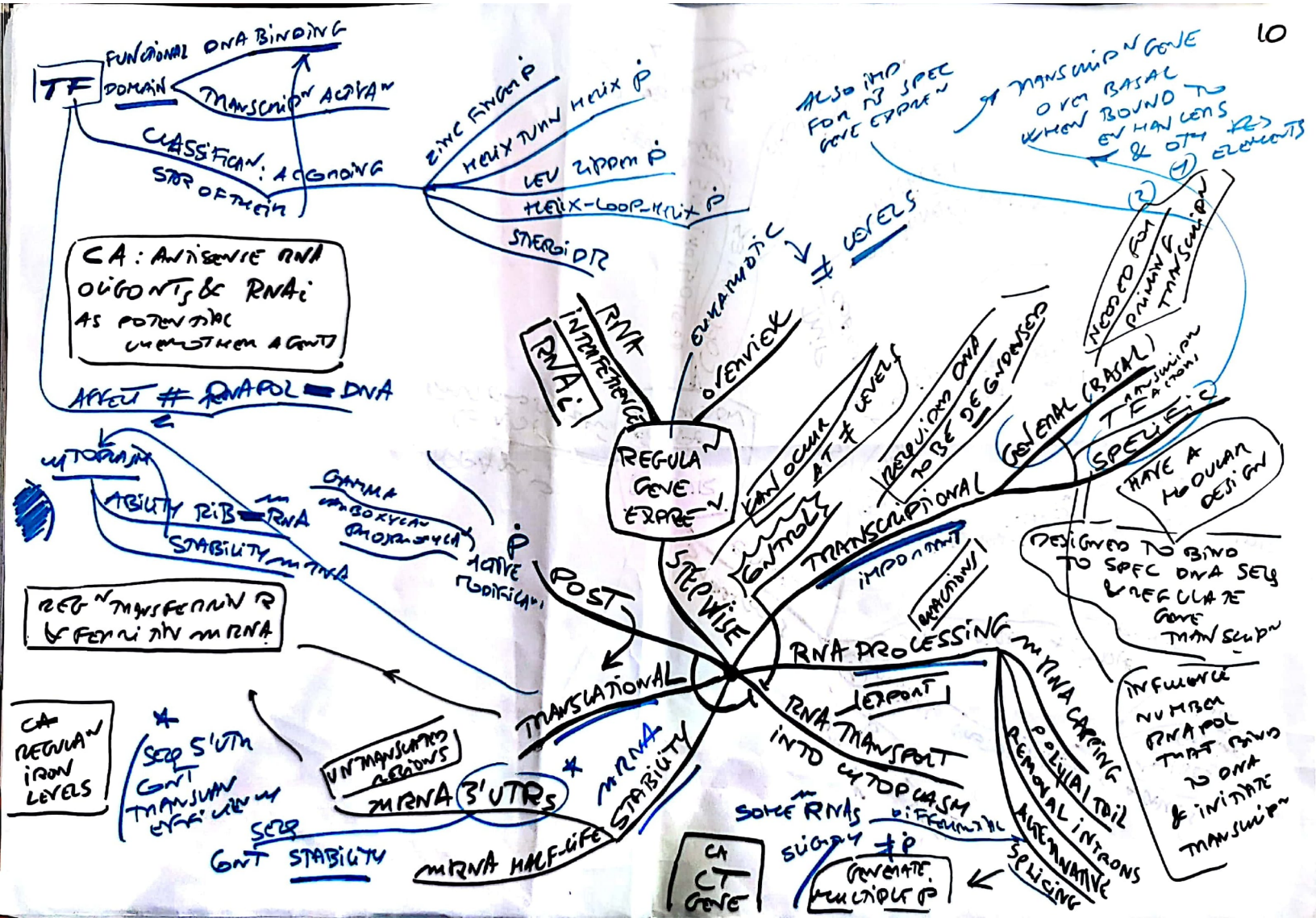
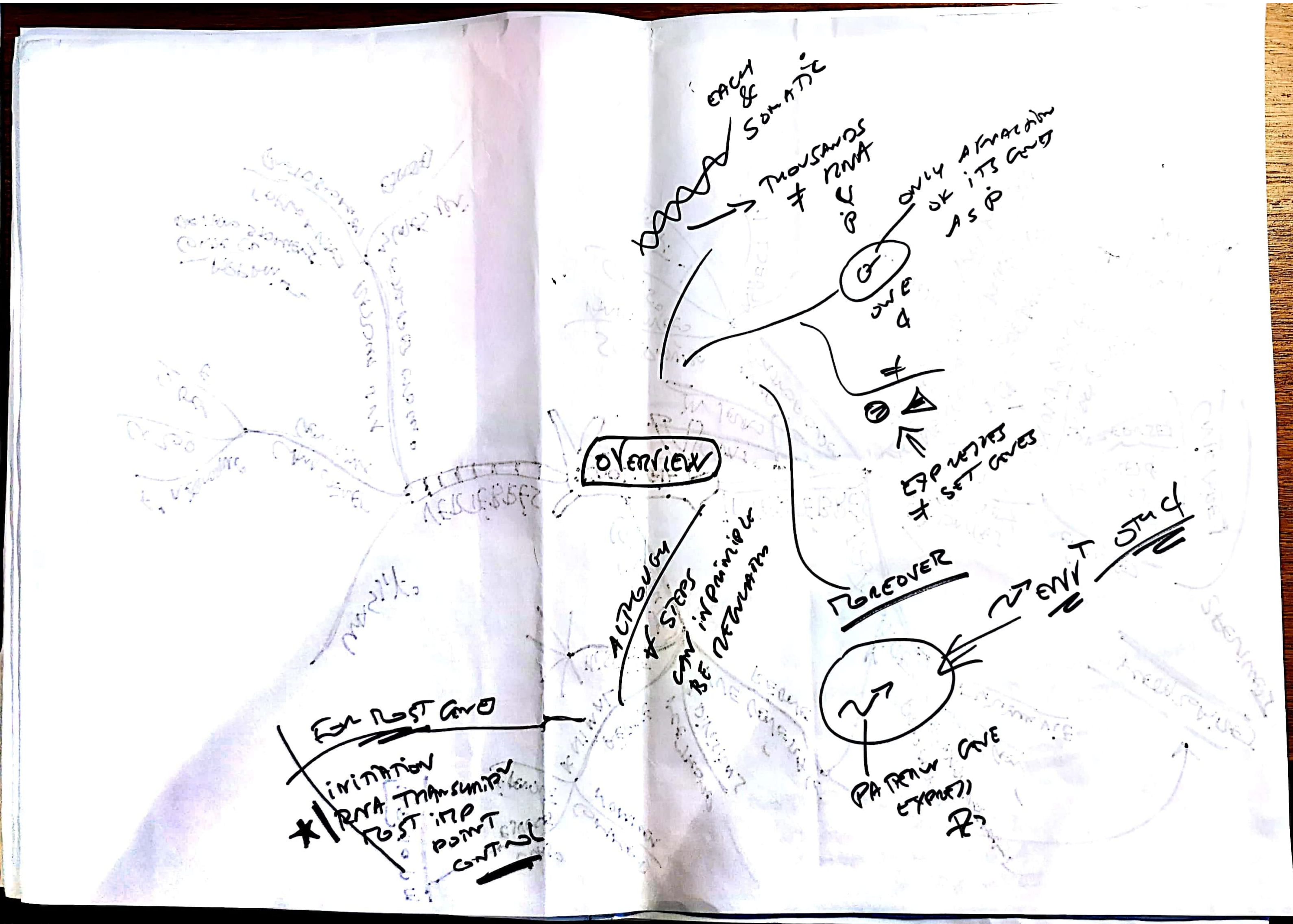
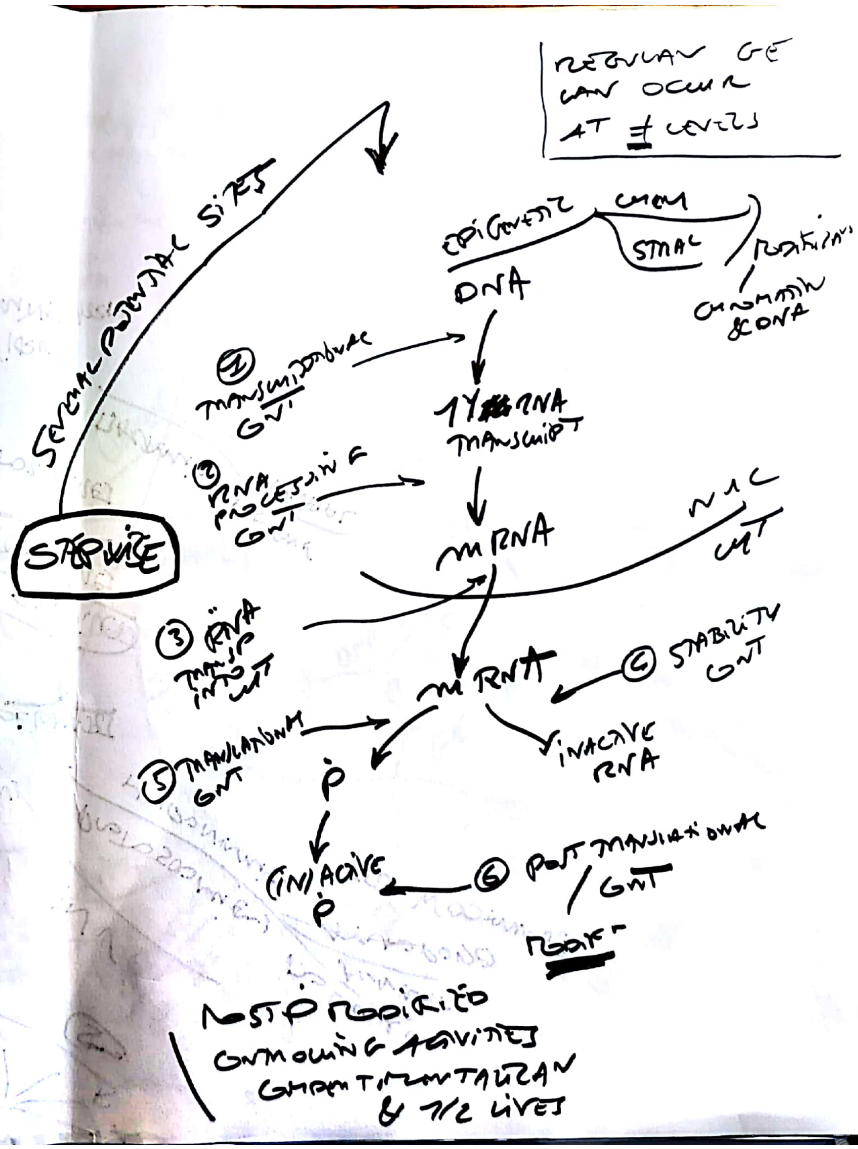
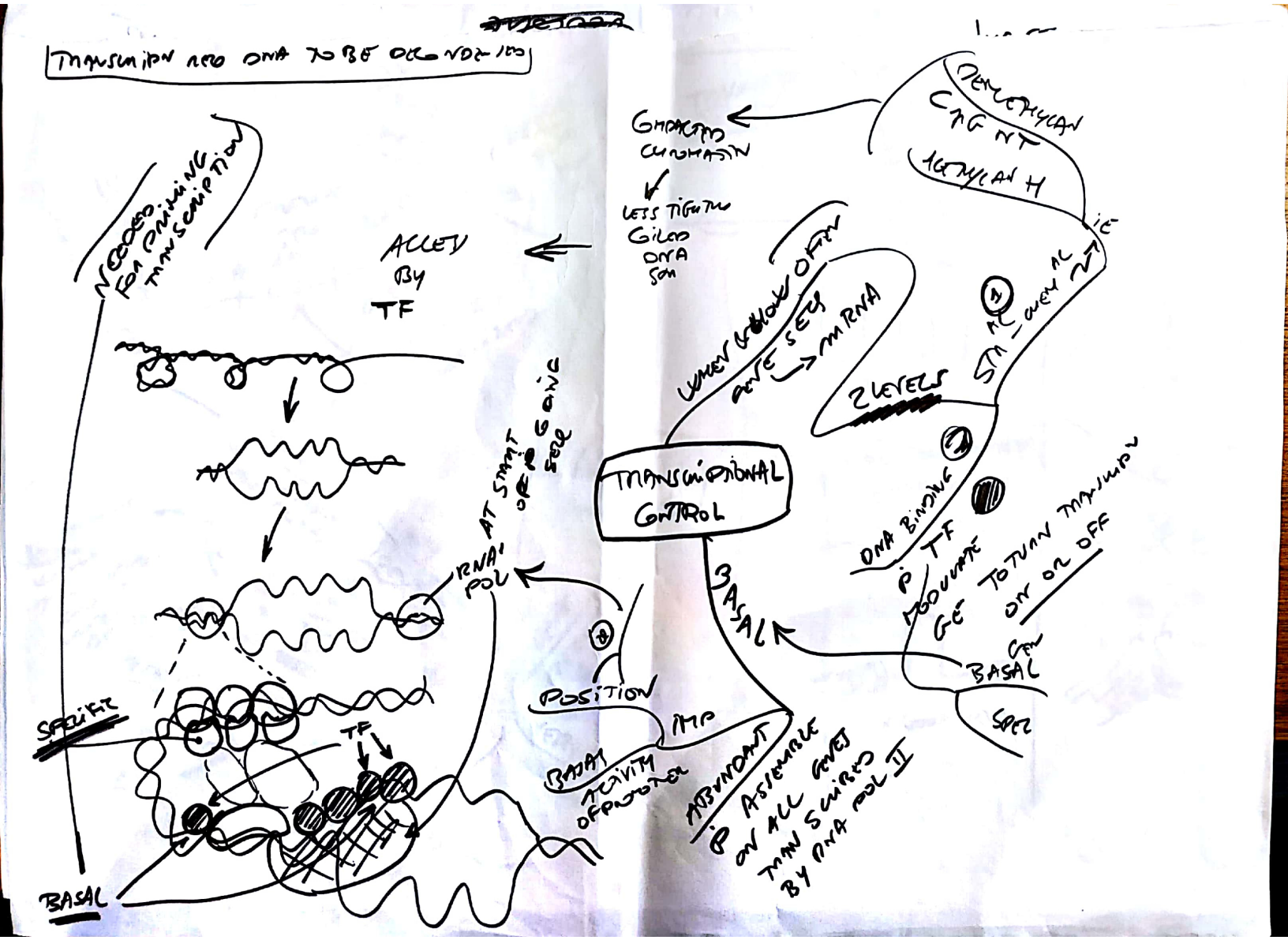
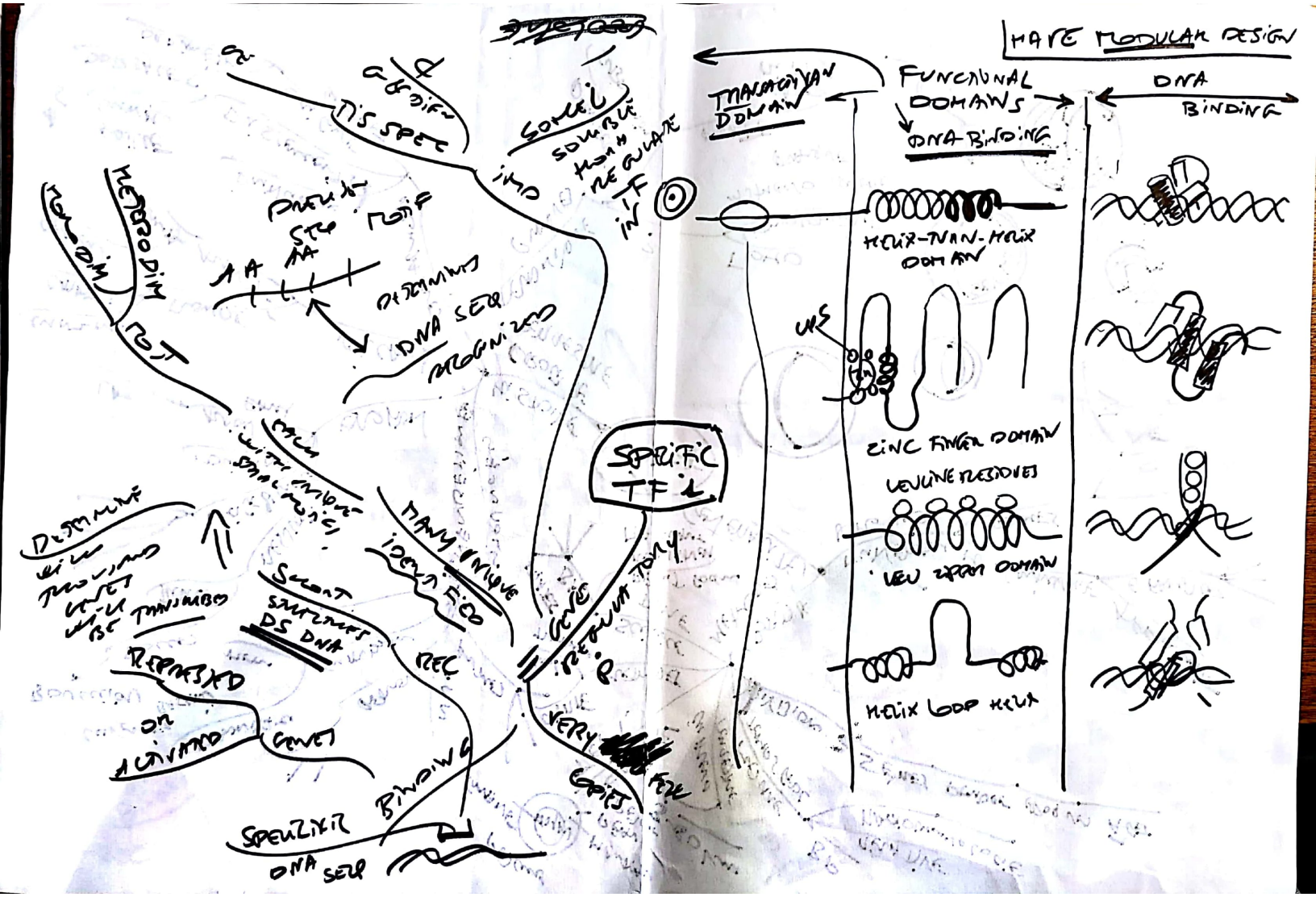
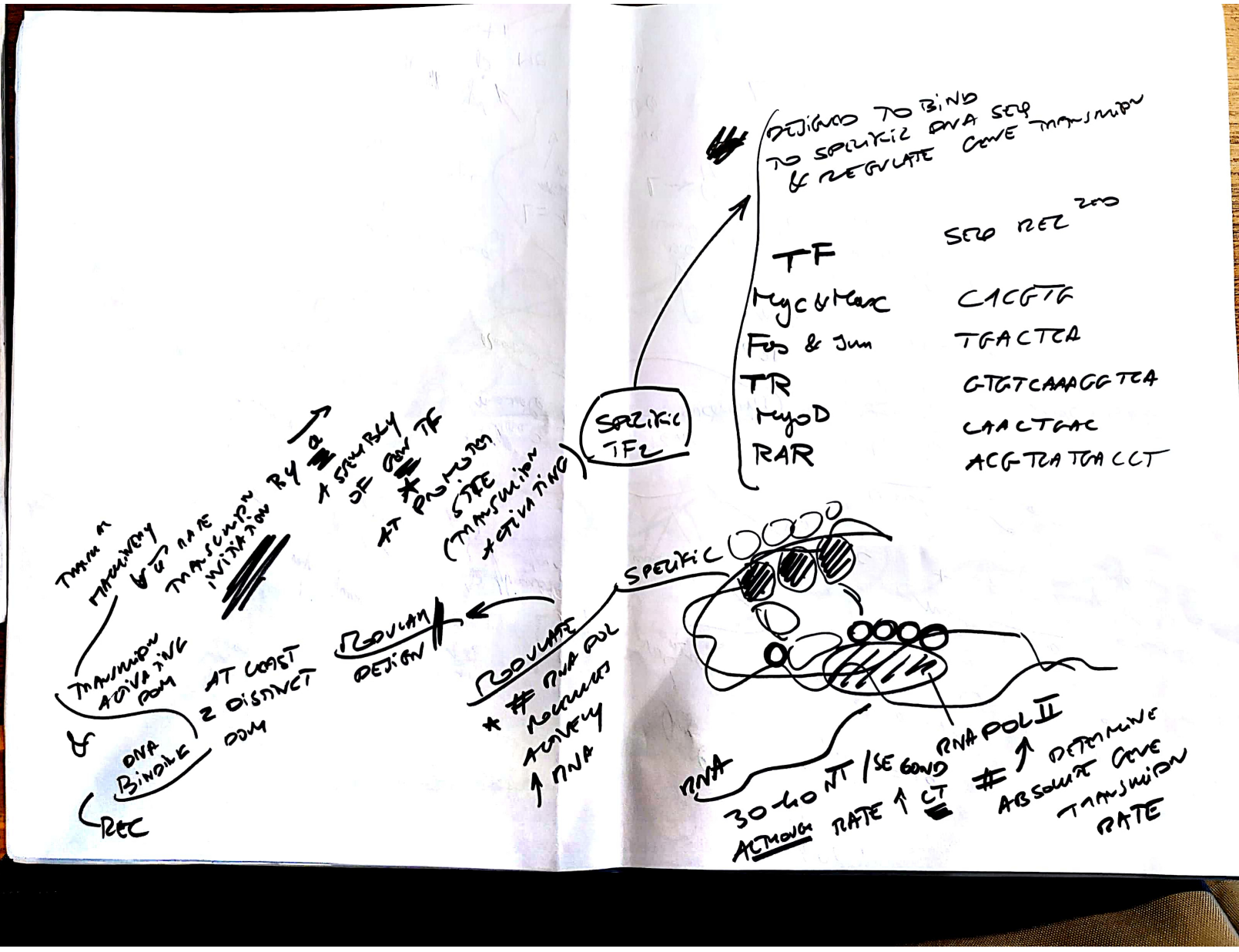

TF
FUNCTIONAL DNA BINDING DOMAIN
TRANSCRIPTN ACTIVATN
CLASSIFICATN ACCORDING STR OF PROTN
ZINC FINGER P
HELIX TURN HELIX P
LEU ZIPPER P
HELIX-LOOP-HELIX P
STEROID R
ALSO IMP FOR NP SPEC GENE EXPRESN
TRANSCRIPN GENE O/P BASAL WHEN BOUND TO ENHANCERS & OTH REG ELEMENTS
NEEDED FOR PRIMARY TRANSCRIPN
CA: ANTISENSE RNA OLIGONTS & RNAi AS POTENTIAL CHEMOTHERA AGNTS
AFFECT # RNAPOL DNA
EUKARYOTIC ≠ LEVELS
OVERVIEW
REGULN GENE EXPRESSN
RNA INTERFERENCE
RNAi
CAN OCCUR AT ≠ LEVELS
CONTROLLED
REQUIRED AND TO BE GOVERNED
TRANSCRIPTIONAL
GENERAL (BASAL) TRANSCRIPTN FACTORS
SPECIFIC
HAVE A MODULAR DESIGN
DESIGNED TO BIND TO SPEC DNA SEQ & REGULATE GENE TRANSCRIPN
IMPORTANT
MECHANISMS
STEPWISE
POST
TRANSLATIONAL
RNA PROCESSING
mRNA CAPPING
POLY(A) TAIL
ALTERNATIVE SPLICING
REMOVAL INTRONS
EXPORT
RNA TRANSPORT INTO CYTOPLASM
SOME RNAs DIFFERENTIAL SLICING
GENERATE MULTIPLE P
INFLUENCE NUMBER RNAPOL THAT BIND TO DNA & INITIATE TRANSCRIPN
ABILITY RIBOSOME TO RNA
STABILITY mRNA
GAMMA CARBOXYLATION MODIFICATN
ACTIVE
REG N TRANSFERRIN R & FERRITIN mRNA
CA REGULN IRON LEVELS
SEQ 5'UTR GOVT TRANSLATN EFFICIENCY
UNTRANSLATED REGIONS
mRNA 3'UTRs
mRNA STABILITY
SEQ GOVT STABILITY
mRNA HALF-LIFE
CA CT GENE

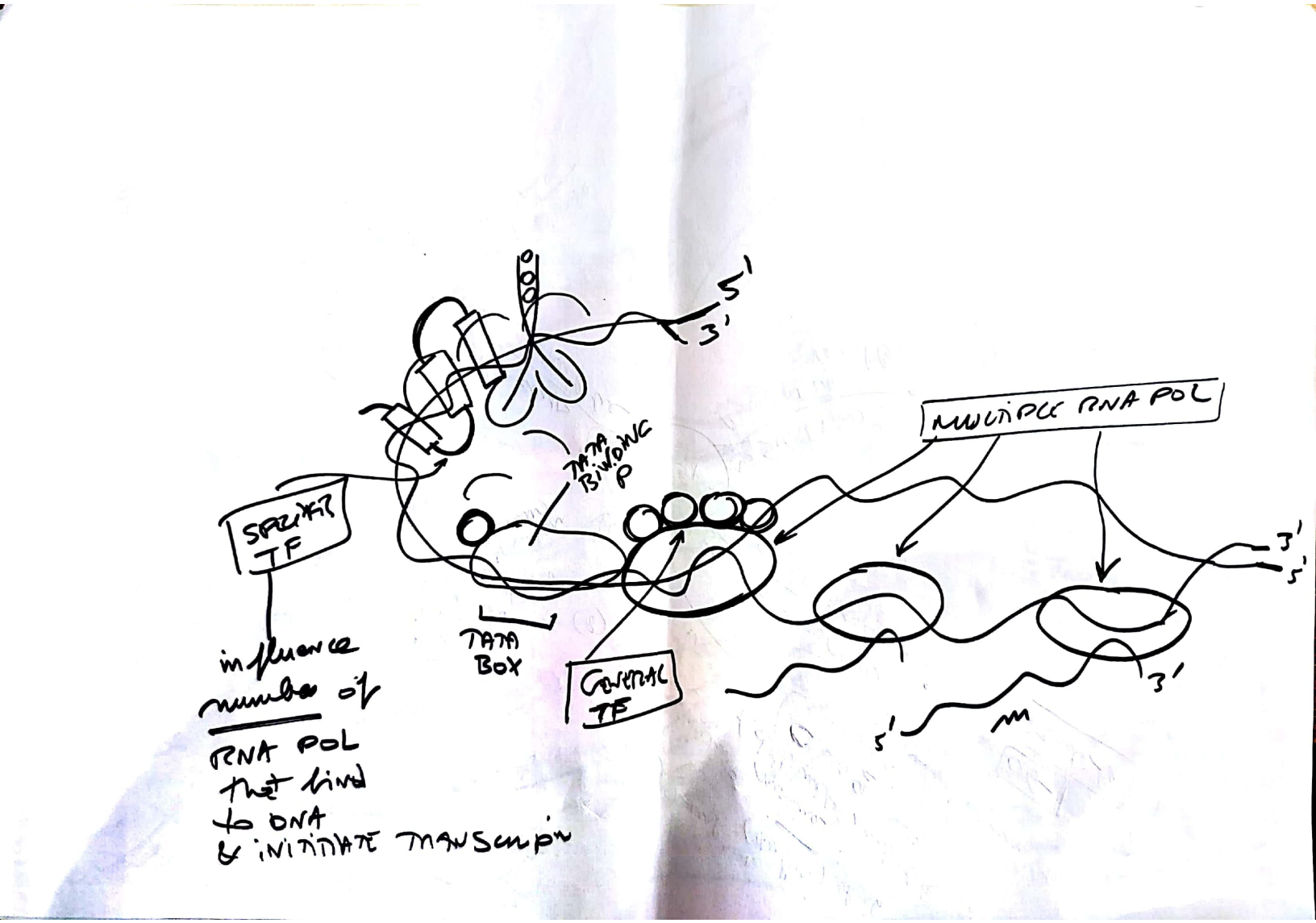

OVERVIEW
EACH & SOMATIC
THOUSANDS # RNA & P
ONLY A FRACTION OF ITS GENES AS P
ONE
EXPRESSES # SET GENES
MOREOVER
ENVT STIM
PATTERN GENE EXPRESS
ALTHOUGH # STEPS CAN IN PRINCIPLE BE REGULATED
FOR MOST GENES
INITIATION
RNA TRANSCRIPTION
MOST IMP POINT CONTROL

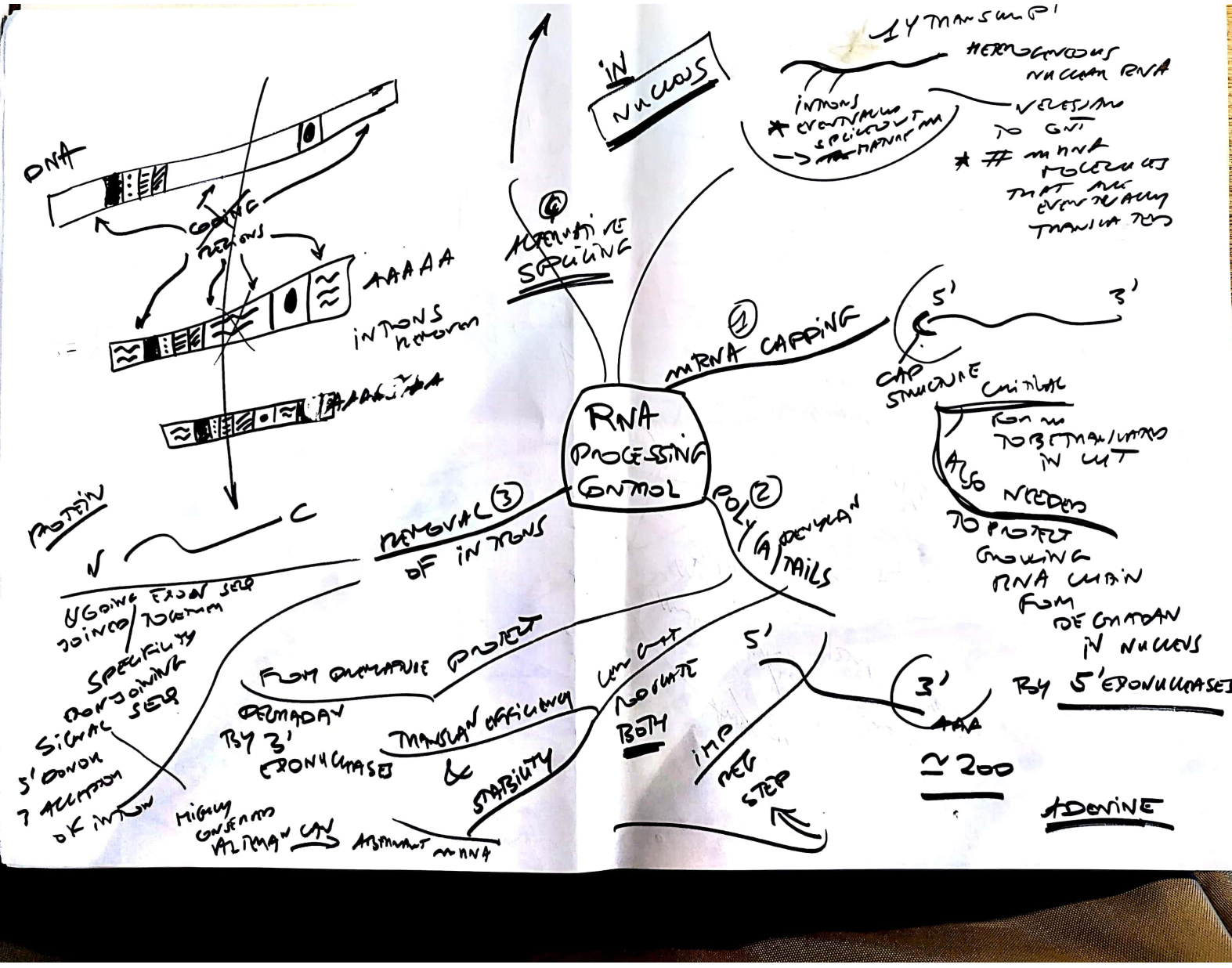

REGULATION CAN OCCUR AT ≠ LEVELS
SEVERAL POTENTIAL SITES
STIMULUS
DNA
TRANSCRIPTION
GNT
RNA TRANSCRIPT
RNA PROCESSING
GNT
mRNA
NUC EXT
RNA TRANSP INTO CYT
GNT
mRNA
STABILITY GNT
INACTIVE RNA
TRANSLATION GNT
P
(IN)ACTIVE P
POST TRANSLATIONAL MOD / GNT
PROTEIN
MOST REQUIRE ONGOING ACTIVITY MAINTENANCE & TURNOVER


TRANSCRIPTION AND DNA TO BE OPEN
NEEDED FOR INITIATING TRANSCRIPTION
ACCESS BY TF
SPECIFIC
TF
BASAL
RNA POL
AT START OF GENE SEQ
POSITION
IMP
BASAL ACTIVITY OF PROMOTER
ABUNDANT
IN ASSEMBLE ON ALL GENES TRANSCRIBED BY RNA POL II
TRANSCRIPTIONAL CONTROL
BASAL
DNA BINDING
TF
MODULATE
TO TURN TRANSCRIPTION ON OR OFF
CPM
SPEC
2 LEVELS
LOWER LEVELS OF EXPRESSION → MRNA
CHROMATIN
LESS TIGHTLY COILED DNA SEQ
METHYLATION
ACETYLATION


HAVE MODULAR DESIGN
FUNCTIONAL DOMAINS
TRANSCRIPTION DOMAIN
DNA BINDING
DNA-BINDING
HELIX-TURN-HELIX DOMAIN
ZINC FINGER DOMAIN
LEUCINE ZIPPER DOMAIN
HELIX LOOP HELIX
SPECIFIC TF 1
DNA SEQ RECOGNIZED
SPECIFIC BINDING
DNA SEQ


DESIGNED TO BIND TO SPECIFIC DNA SEQ & REGULATE GENE TRANSCRIPTION
SEQ REC
TF
Myc & Max
CACGTG
Fos & Jun
TGACTCA
TR
GTGTCAAAGGTCA
MyoD
CAACTGAC
RAR
ACGTCATGACCT
SPECIFIC TFs
SPECIFIC
REGULATE DESIGN
REGULATE
* # RNA POL ACTIVITY ↑ RNA
TRANSCRIPTION ACTIVATING DOM
AT LEAST 2 DISTINCT DOM
DNA BINDING
REC
RNA
30-40 NT/SECOND
ACTIVITY
RNA POL II
↑ DETERMINE ABSOLUTE GENE TRANSCRIPTION RATE


5'
3'
MULTIPLE RNA POL
TATA BINDING P
SPECIFIC TF
TATA BOX
GENERAL TF
3'
5'
3'
5'
influence number of
RNA POL that bind to DNA & INITIATE TRANSCRIPTION


DNA
CODING REGIONS
AAAAA
INTRONS REMOVED
PROTEIN
N
C
IN NUCLEUS
RNA PROCESSING CONTROL
1 mRNA CAPPING
2 POLY (A) TAILS
3 REMOVAL OF INTRONS
4 ALTERNATIVE SPLICING
5' 3'
CAP STRUCTURE
7-METHYLGUANOSINE
ALSO NEEDED TO PROTECT GROWING RNA CHAIN FROM DEGRADATION IN NUCLEUS
BY 5' EXONUCLEASES
3'
AAA
~200
ADENINE
5'
IMP NEW STEP
LONGER MORE STABLE BOTH
TRANSLATION EFFICIENCY & STABILITY
FROM CYTOPLASMIC PROTEIN
DEGRADED BY 3' EXONUCLEASES
HIGHLY CONSERVED VALIDATION CAN
ABNORMAL mRNA
SPECIFICITY
SIGNAL
5' DONOR
7 ACCEPTOR
OF INTRON
JOINED TOGETHER
PRE-mRNA
INTRONS EVENTUALLY SPLICED OUT
NUCLEOTIDES TO GO
mRNA MOLECULES THAT ARE EVENTUALLY TRANSLATED

COUNTERACTS
ACTION OF HORMONE
↑↑ POSTMENOP OSTEOPOROSIS
WHEN ESTROGEN ↓
↓
NEURONS
⇒ CGRP

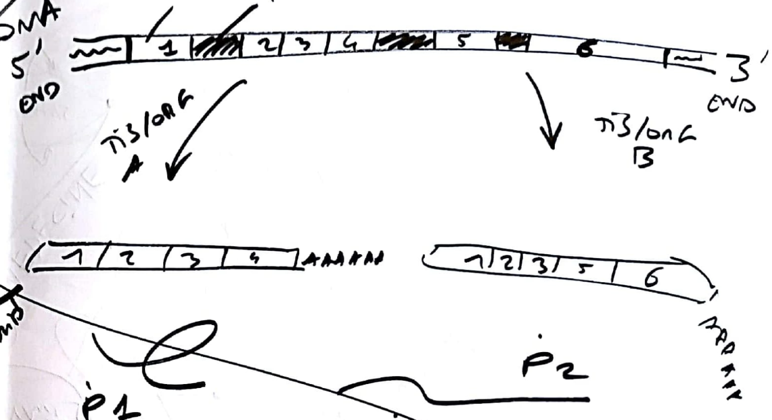
mRNA

SPLICED ≠
USED
≠ POLY ADENYLATION SITE

SAME GENE
TISSUE
NEURAL

PARAFOLLICULAR
Cs

CA
CALCITONIN GENE



ALTERNATIVE SPLICING

MULTIPLE P

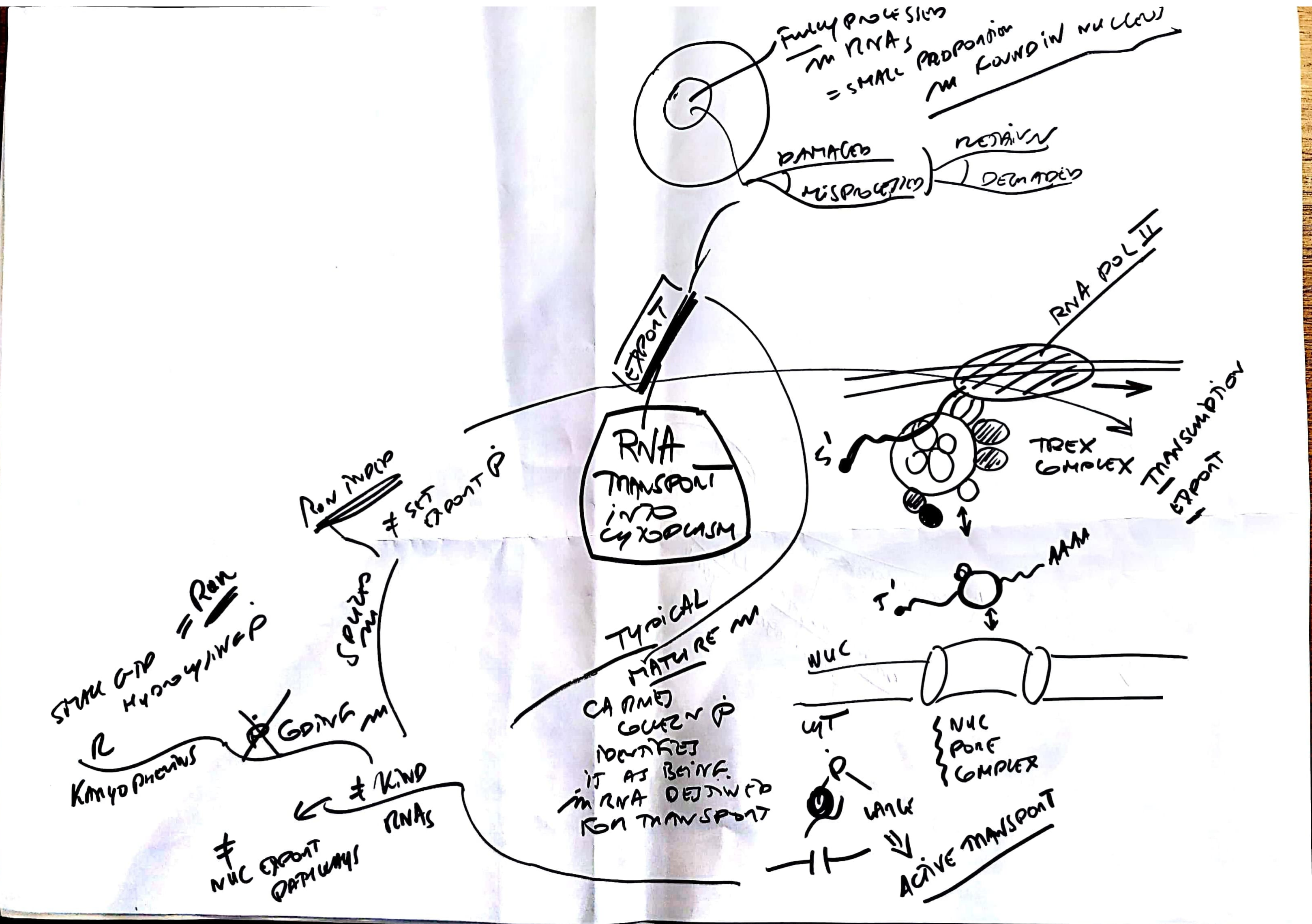
C ROLE
PP MIGRAINE
[ ]
VASCULAR
& CNS
↓
CGRP R ANTAG MIGHT BE EFFECTIVE

CHANGING ACCESSIBILITY
OF ≠ SPLICE SITES
TO SPLICING MACHINERY
BY RNA-BINDING P
↓
— COULD MASK PREFERRED SPLICE SITE
— OR
↑ LOCAL RNA STR
TO PROMOTE SPLICING
ALTERNATE SITES

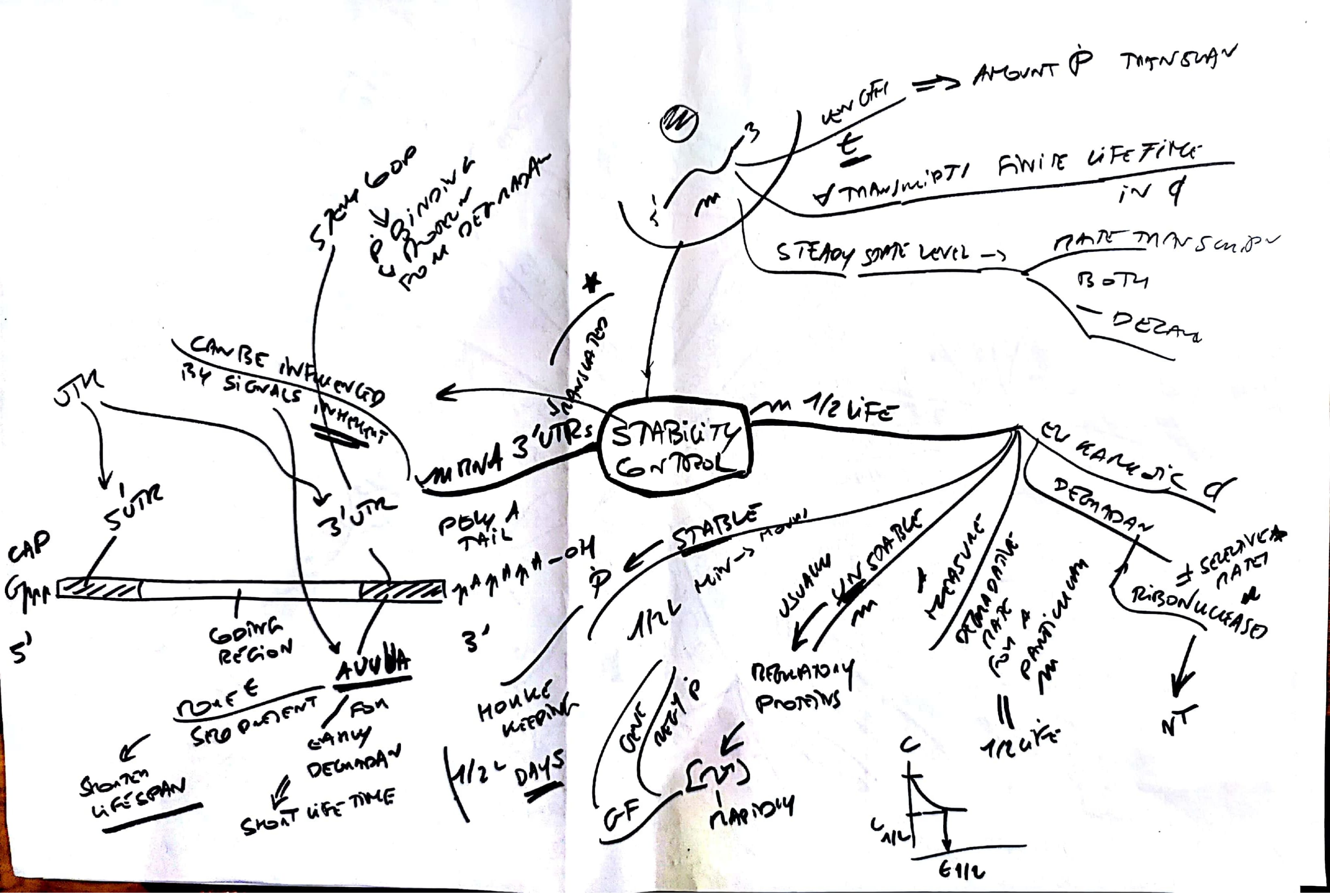
ALSO
SWITCHING
FN ⇄ FN
MBBOR ⇄ MB
SEVERITY ?

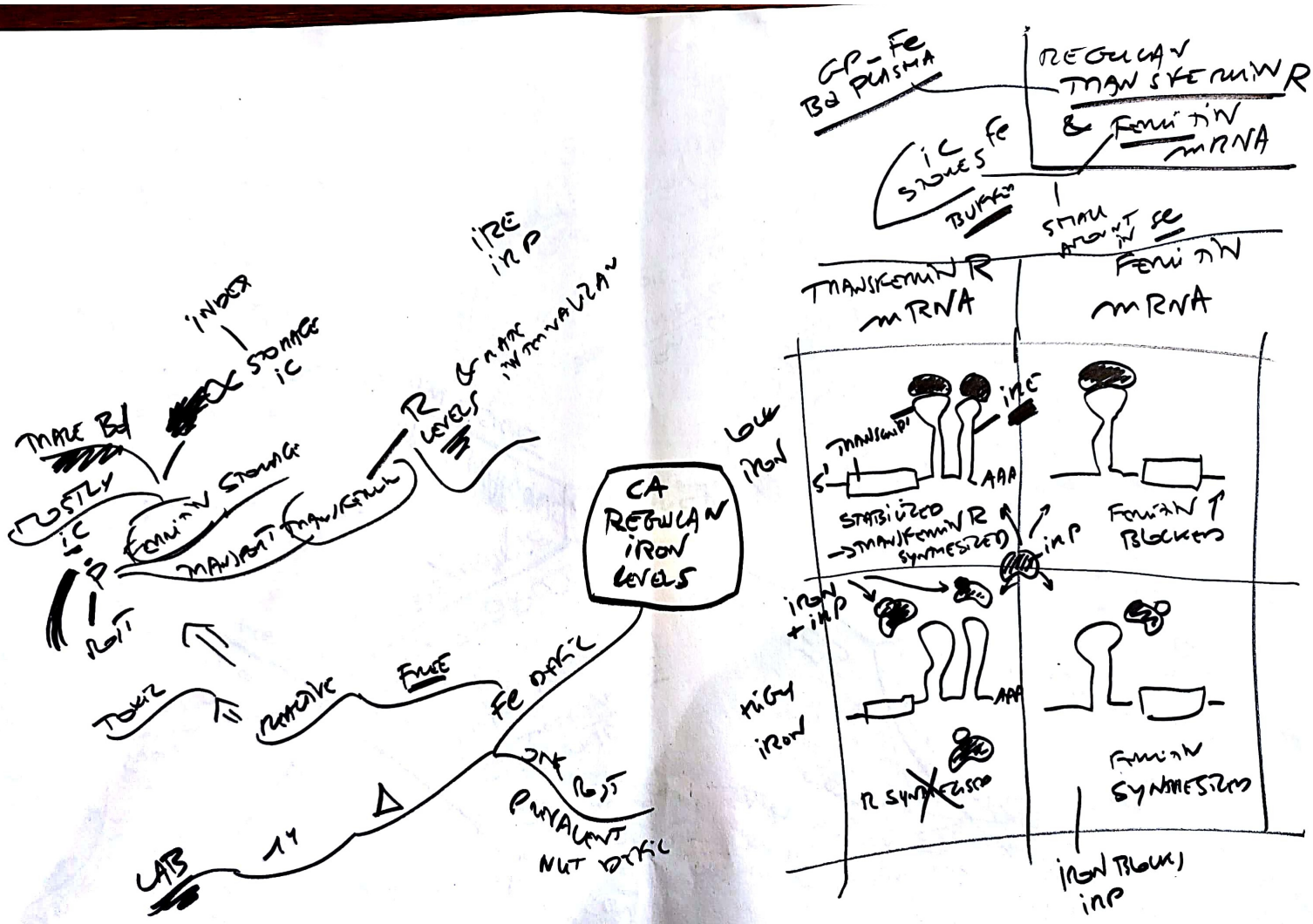
IN ADDITION
CL SPEC REGU CAN DETERMINE TYPE ALTERNATE SPLICING
EVENTUAL P PRODUCED

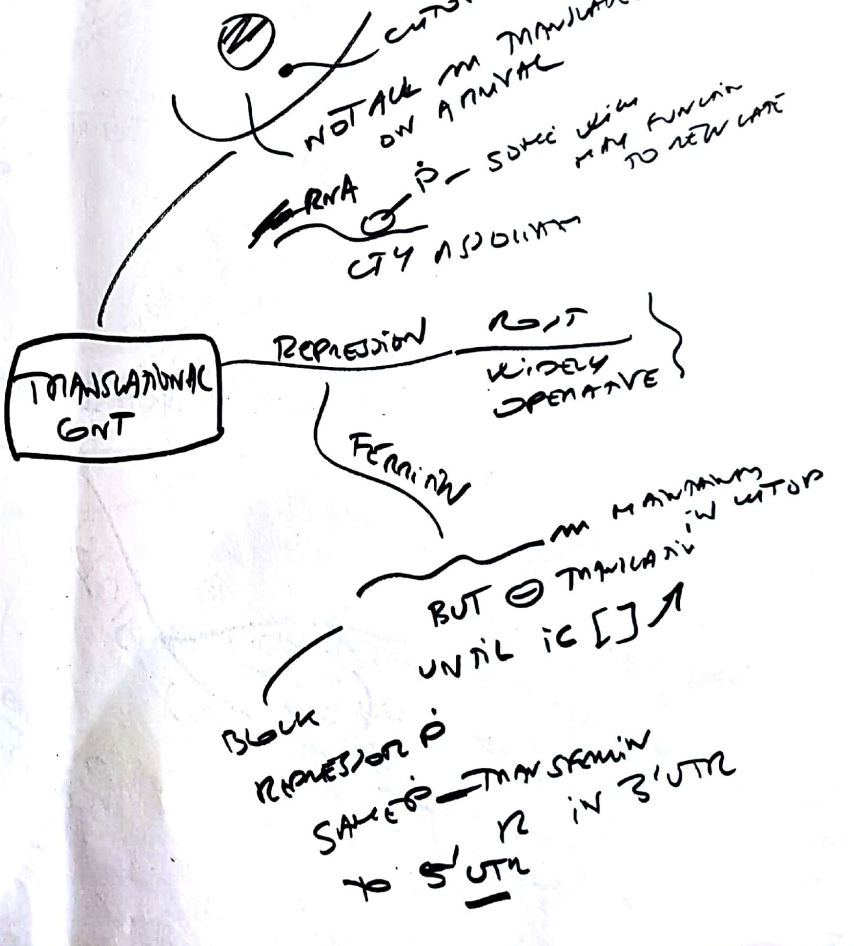
ALSO EXPLAIN
WHY HUM GENOME
HAS FEWER GENES
THAN EXPECTED

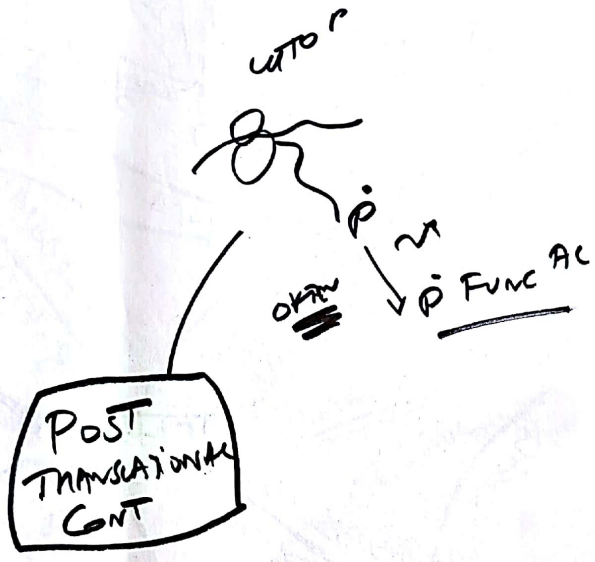


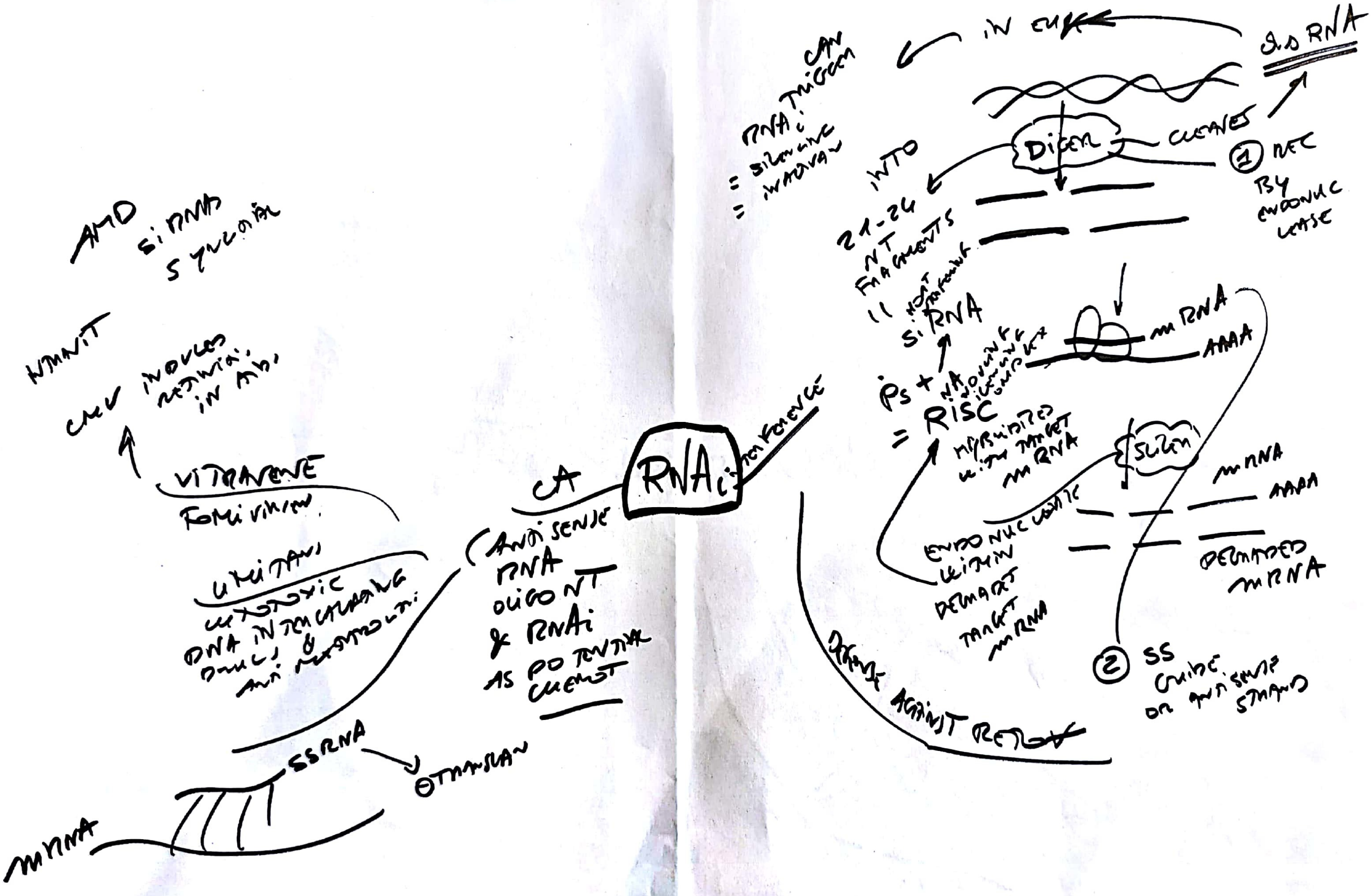
FULLY PROCESSED
mRNAs
= SMALL PROPORTION
mRNA FOUND IN NUCLEUS
DAMAGED
MISPROCESSED
RETAINED
DEGRADED
EXPORT
RNA
TRANSPORT
INTO
CYTOPLASM
RNA POL II
TREX
COMPLEX
TRANSCRIPTION
EXPORT
5'
AAAA
NUC
CYT
NUC
PORE
COMPLEX
ACTIVE TRANSPORT
TYPICAL
MATURE mRNA
CAPPED
IT AS BEING
mRNA
≠ KIND
RNAs
≠
NUC EXPORT
PATHWAYS
KARYOPHERINS
= RAN
GOING
SPLICED
RAN INDEP
≠ SET
EXPORT


STABILITY CONTROL
mRNA 3'UTRs
CAN BE INFLUENCED BY SIGNALS INHERENT
UTR
5'UTR
3'UTR
CAP
5'
3'
CODING REGION
AUUUA
POLY A TAIL
AAAAAA-OH
SHORTEN LIFESPAN
SHORT LIFE TIME
m 1/2 LIFE
EUKARYOTIC
DEGRADATION
RIBONUCLEASES
NT
STABLE
UNSTABLE
REGULATORY PROTEINS
HOUSE KEEPING
1/2 L DAYS
GF
RAPIDLY
1/2 LIFE
STEADY STATE LEVEL
BOTH
LENGTH
AMOUNT
FINITE LIFETIME


CA
REGULATE
IRON
LEVELS
LOW IRON
HIGH IRON
IRE
IRP
FREE
Fe DEFICIENT
DNA
PARALYSIS
NOT DEFICIENT
LAB
TOXIC
REACTIVE
TRANSFERRIN
mRNA
AAA
IRP
IRON + IRP
FERRITIN
SYNTHESIZED
IRON BLOCKS
IRP


TRANSLATIONAL CONT
REPRESSION
FERRITIN
BLOCK


POST
TRANSACTIONAL
CONT



AMD
siRNA
VITRAVENE
FOMIVIRSEN
ssRNA
mRNA
CA
ANTISENSE RNA OLIGO NT & RNAi AS POTENTIAL
RNAi
INTERFERENCE
CAN TRIGGER
IN EUK
ds RNA
DICER
CLEAVES
INTO
21-24 NT FRAGMENTS
siRNA
RISC
mRNA
AAAA
SLICER
DEGRADED mRNA
SS GUIDE OR ANTISENSE STRAND
DEFENSE AGAINST RETRO