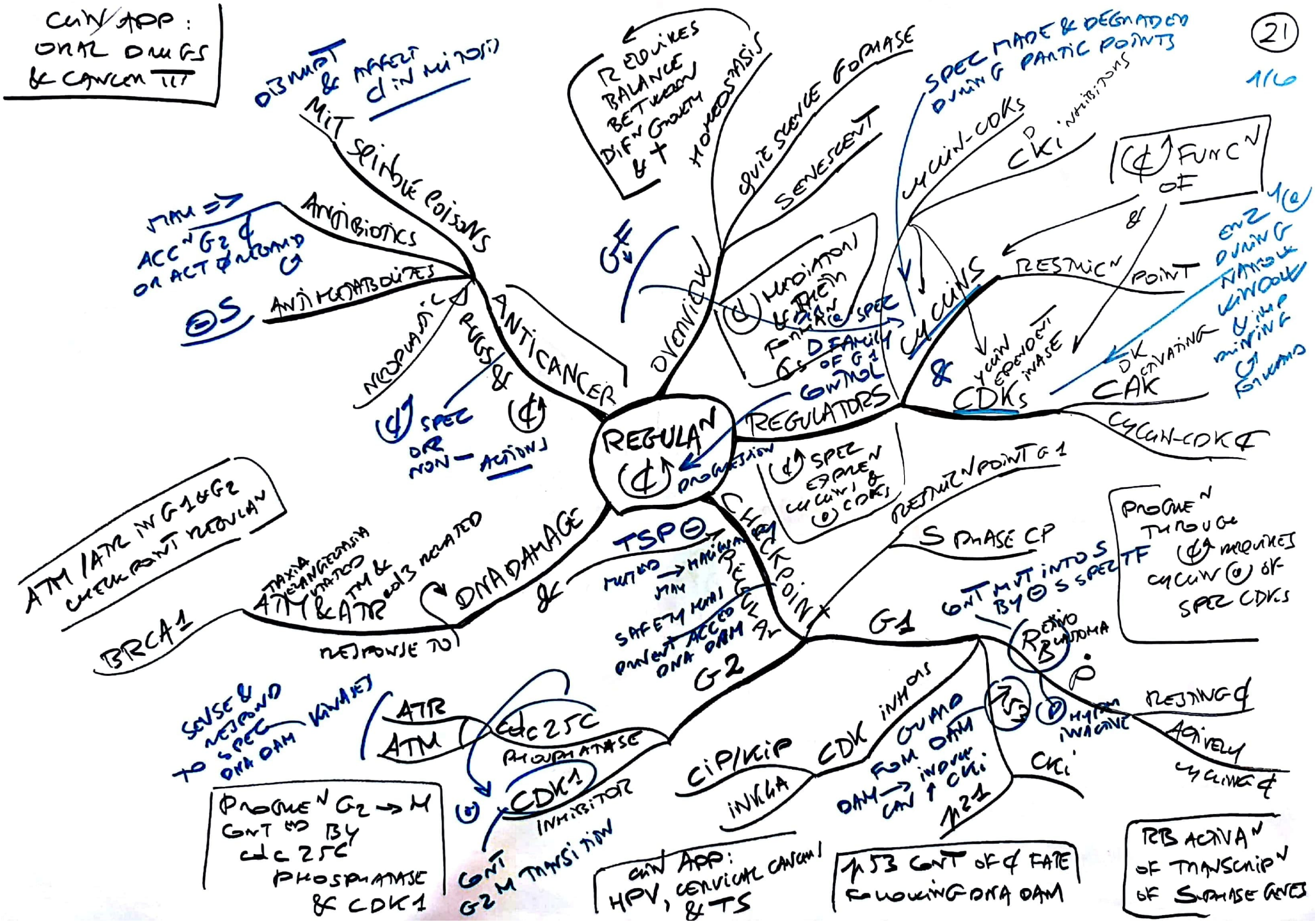
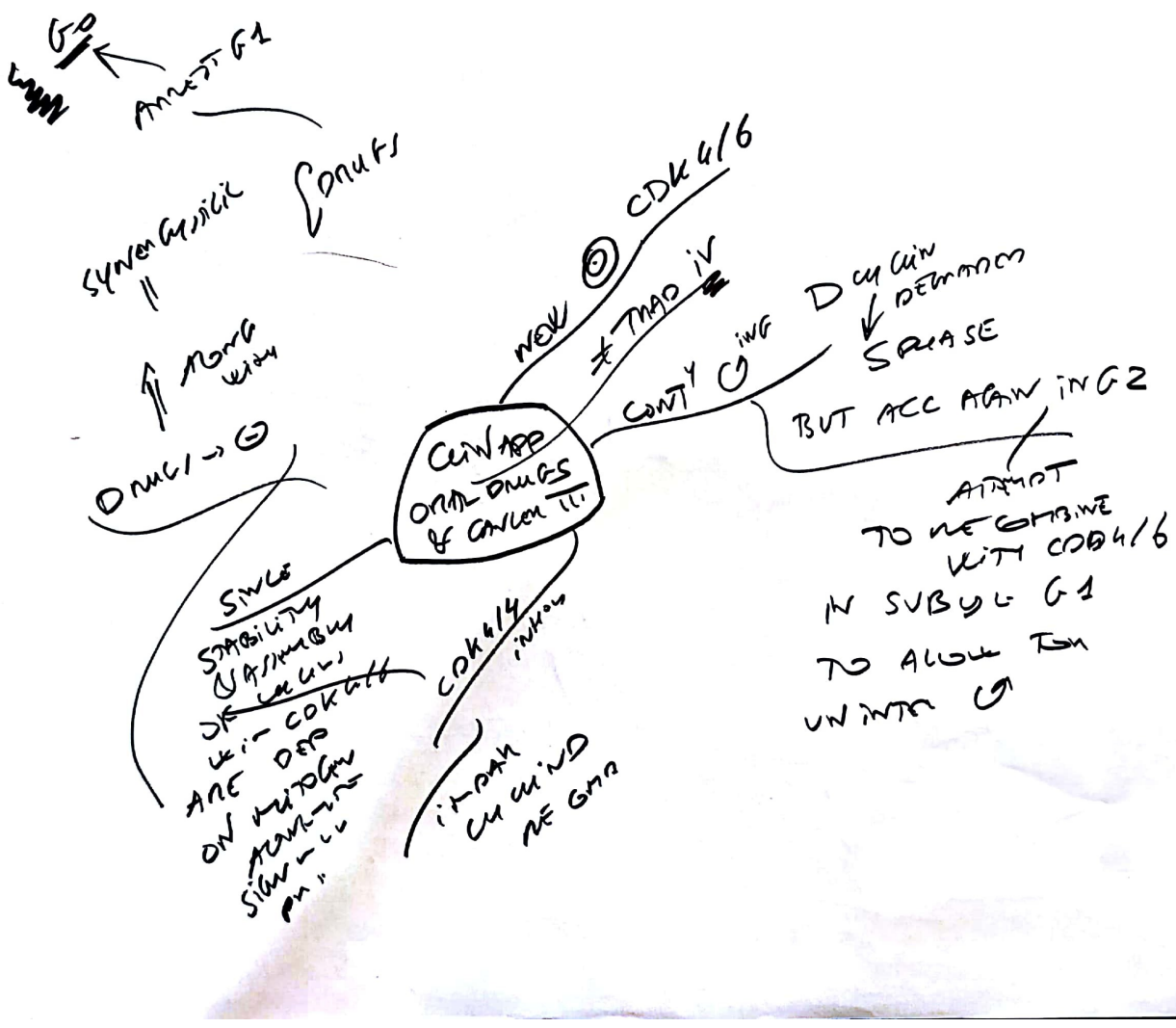
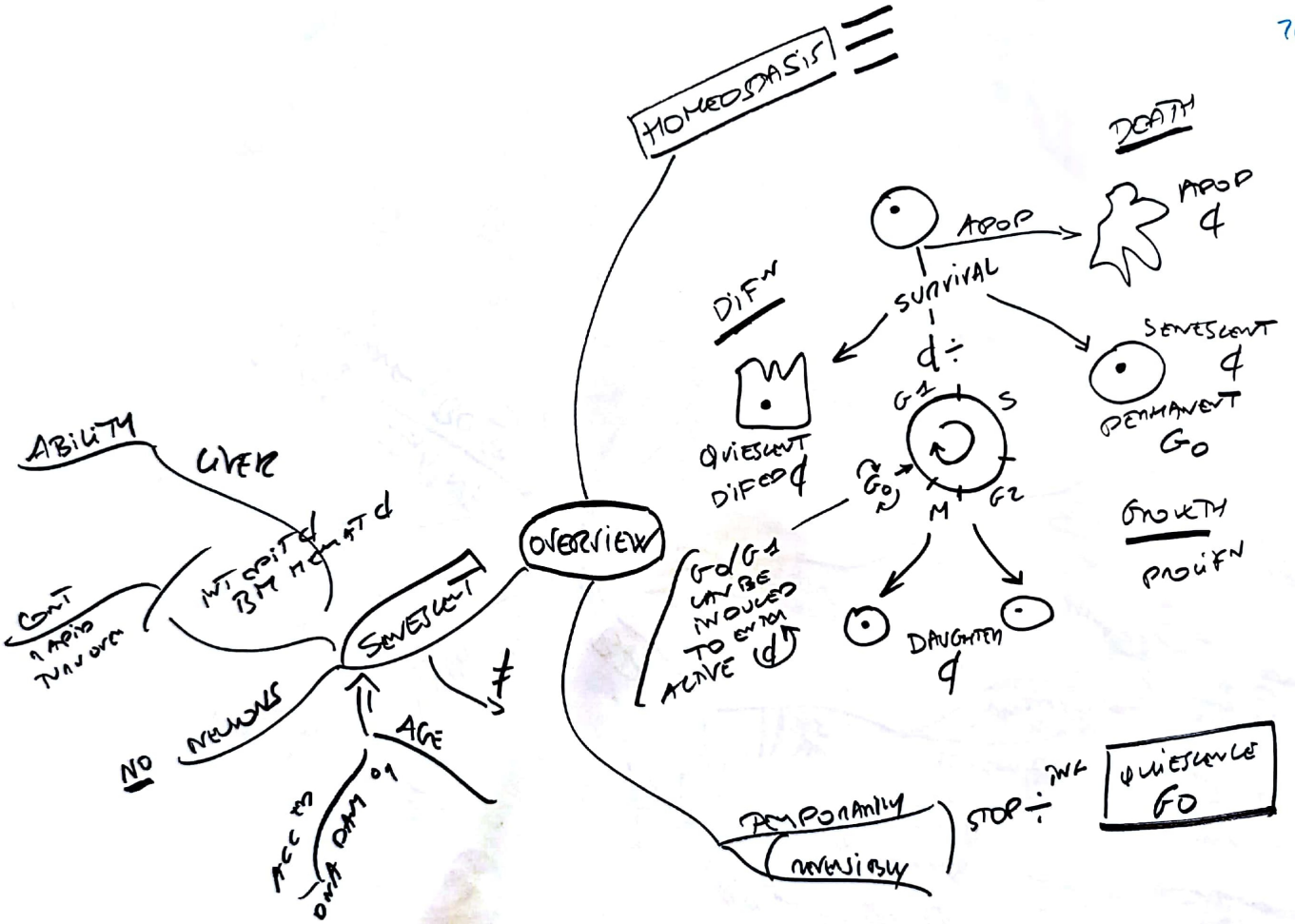
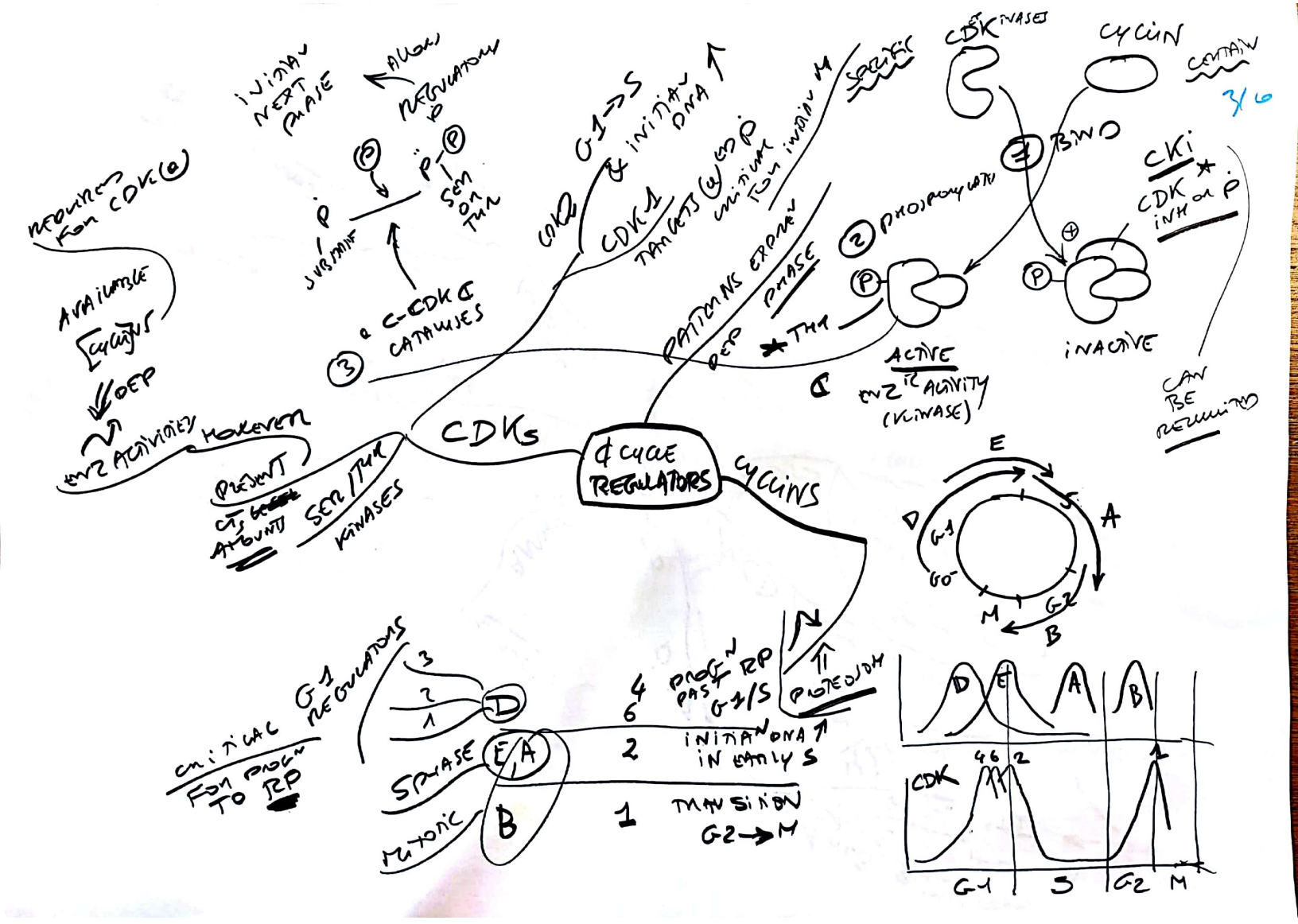
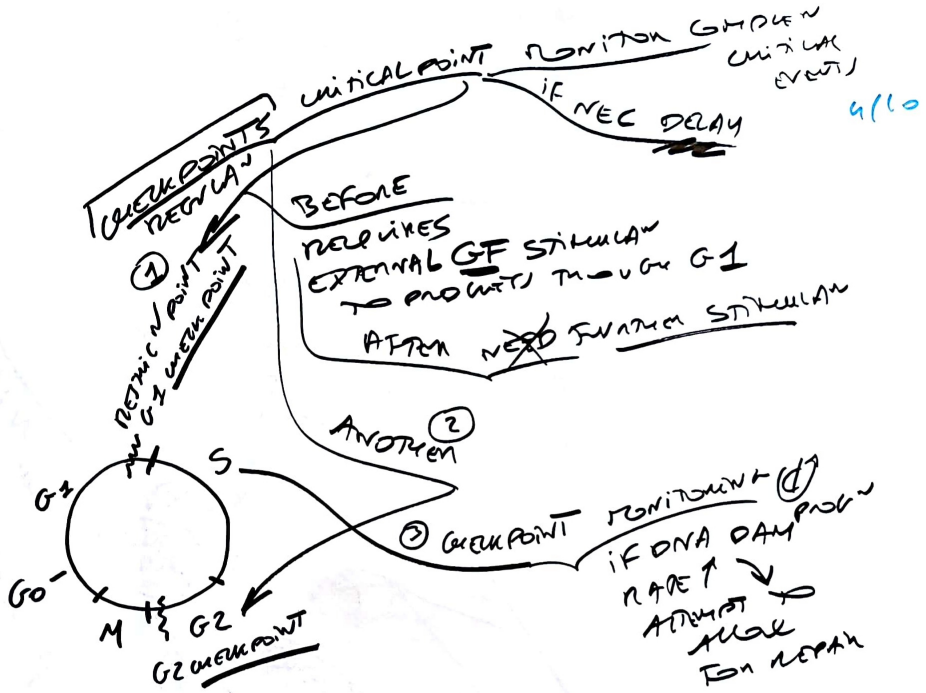
CLIN/APP: ORAL DRUGS & CANCER III

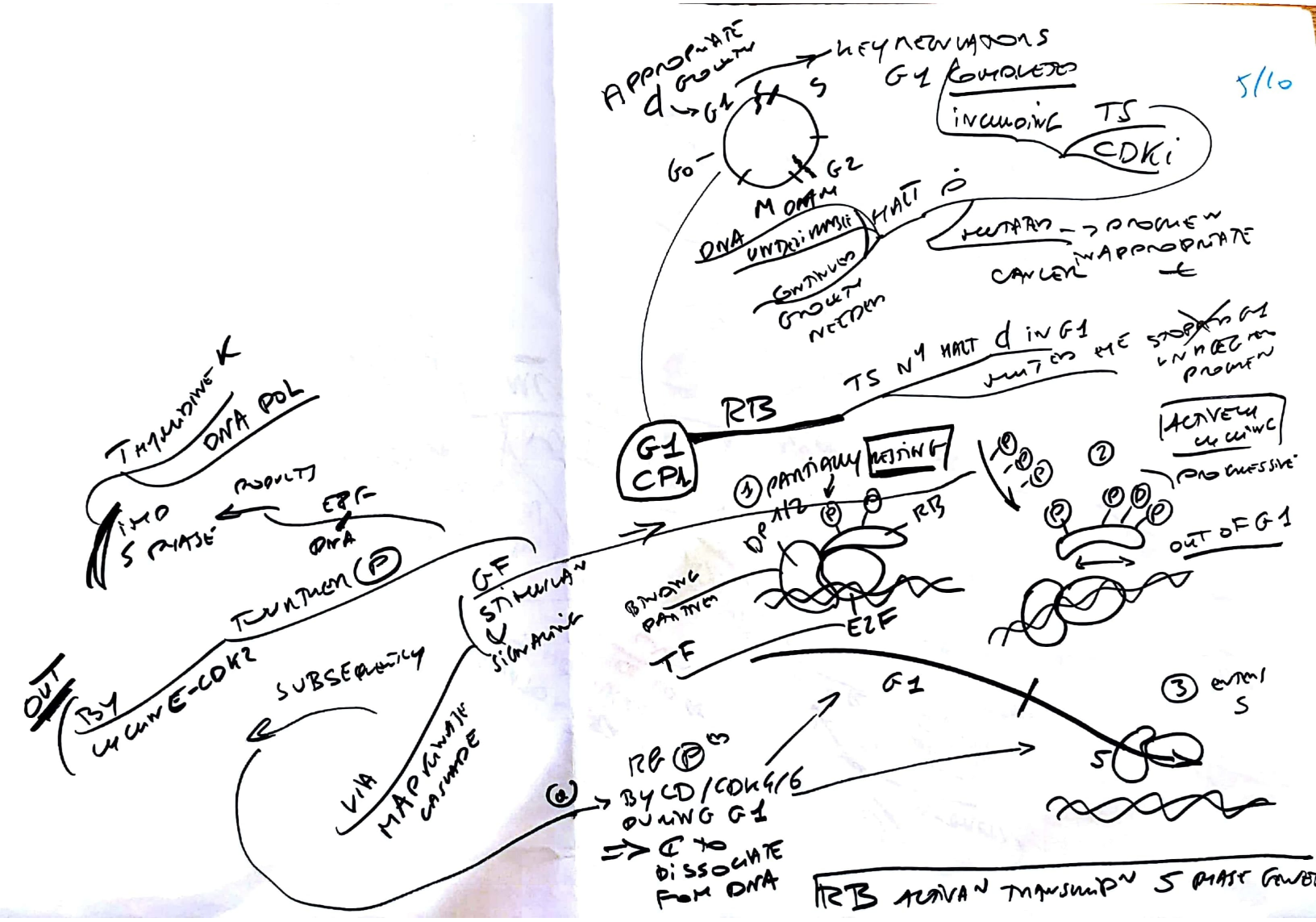


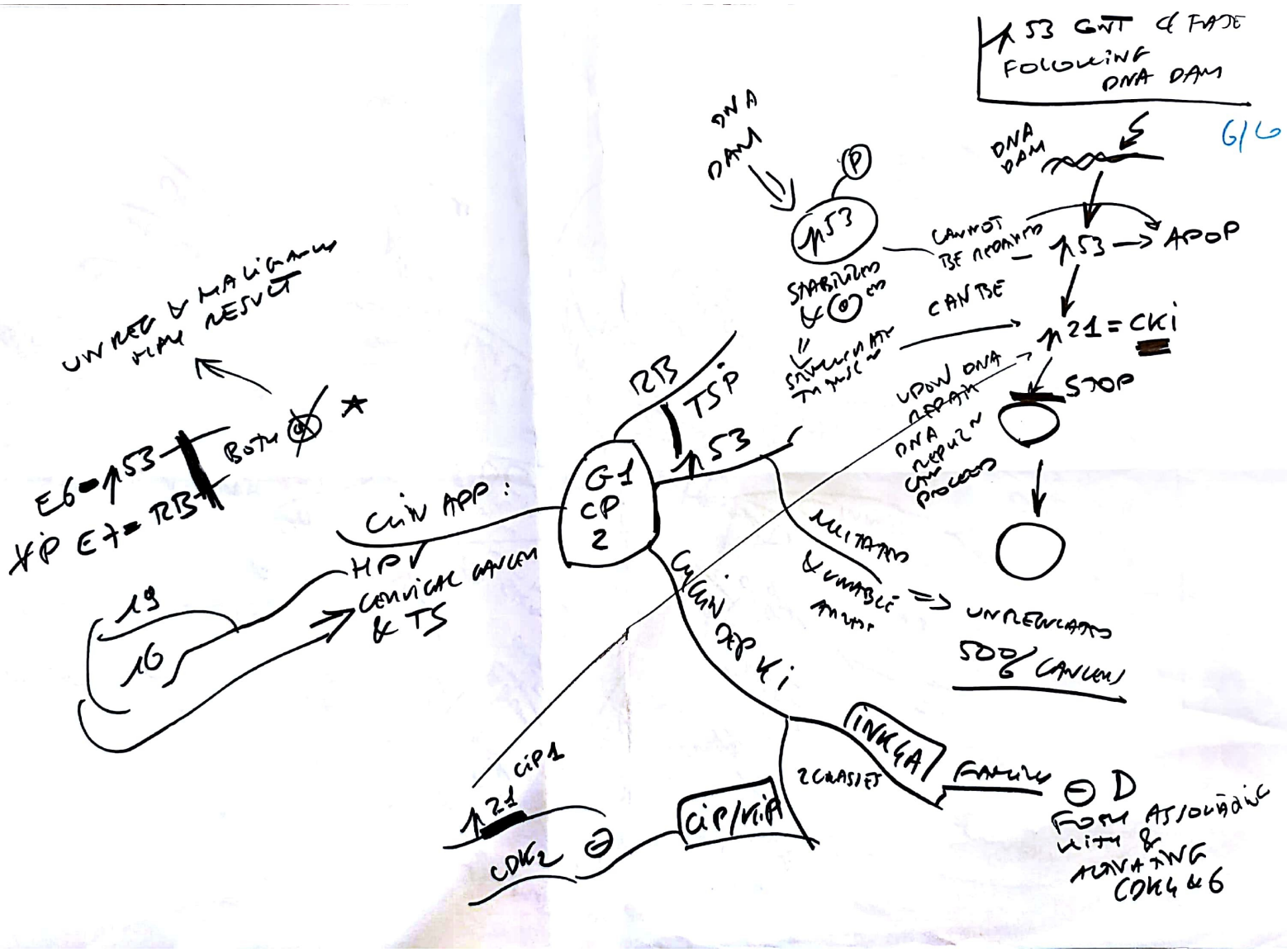

G0
ARREST G1
SYNERGISTIC
DRUGS
MORE
DRUG1 → G
NEW
CDK4/6
≠ MAD iV
CONTY G ING
D CYCLIN
DEPENDON
SPHASE
BUT ACC AGAIN ING2
ATTMPT
TO RE COMBINE
WITH CDK4/6
IN SUBSQ G1
TO ALLOW TOX
UNINTO G
CLIN APP
ORAL DRUGS
& CANCER TX
SINGLE
CDK4/6
iNHIBN

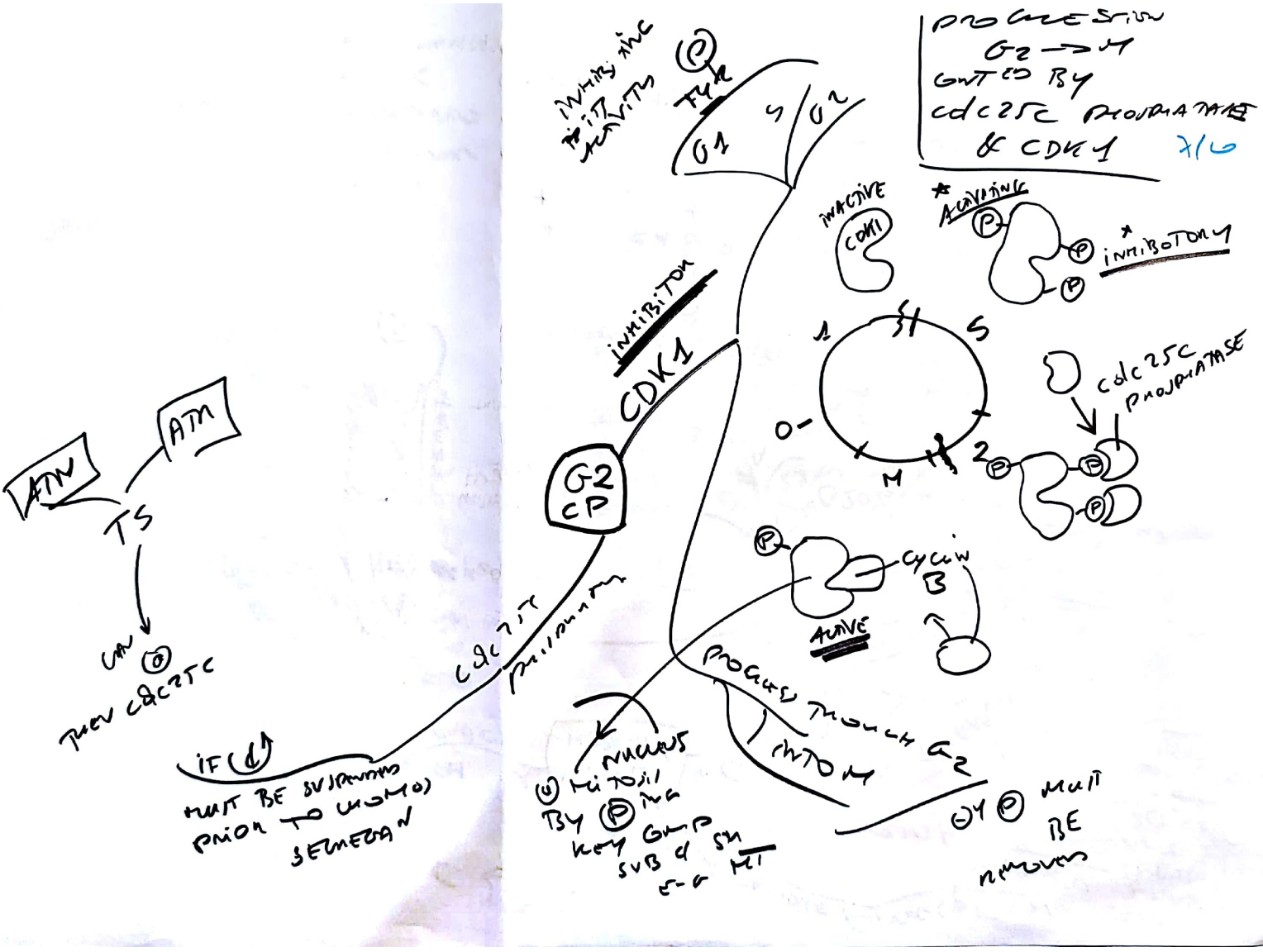

HOMEOSTASIS
DEATH
APOP
APOP
SURVIVAL
DIFF
SENESCENT
PERMANENT
G0
QUIESCENT
DIFFD
G1
S
G2
M
G0
G0/G1
CAN BE
INDUCED
TO ENTER
ACTIVE
PROLIFN
DAUGHTER
OVERVIEW
ABILITY
GIVEN
CONT
RAPID
TURNOVER
SENESCENT
AGE
NO
NEURONS
TEMPORARILY
REVERSIBLY
STOP
QUIESCENCE
G0

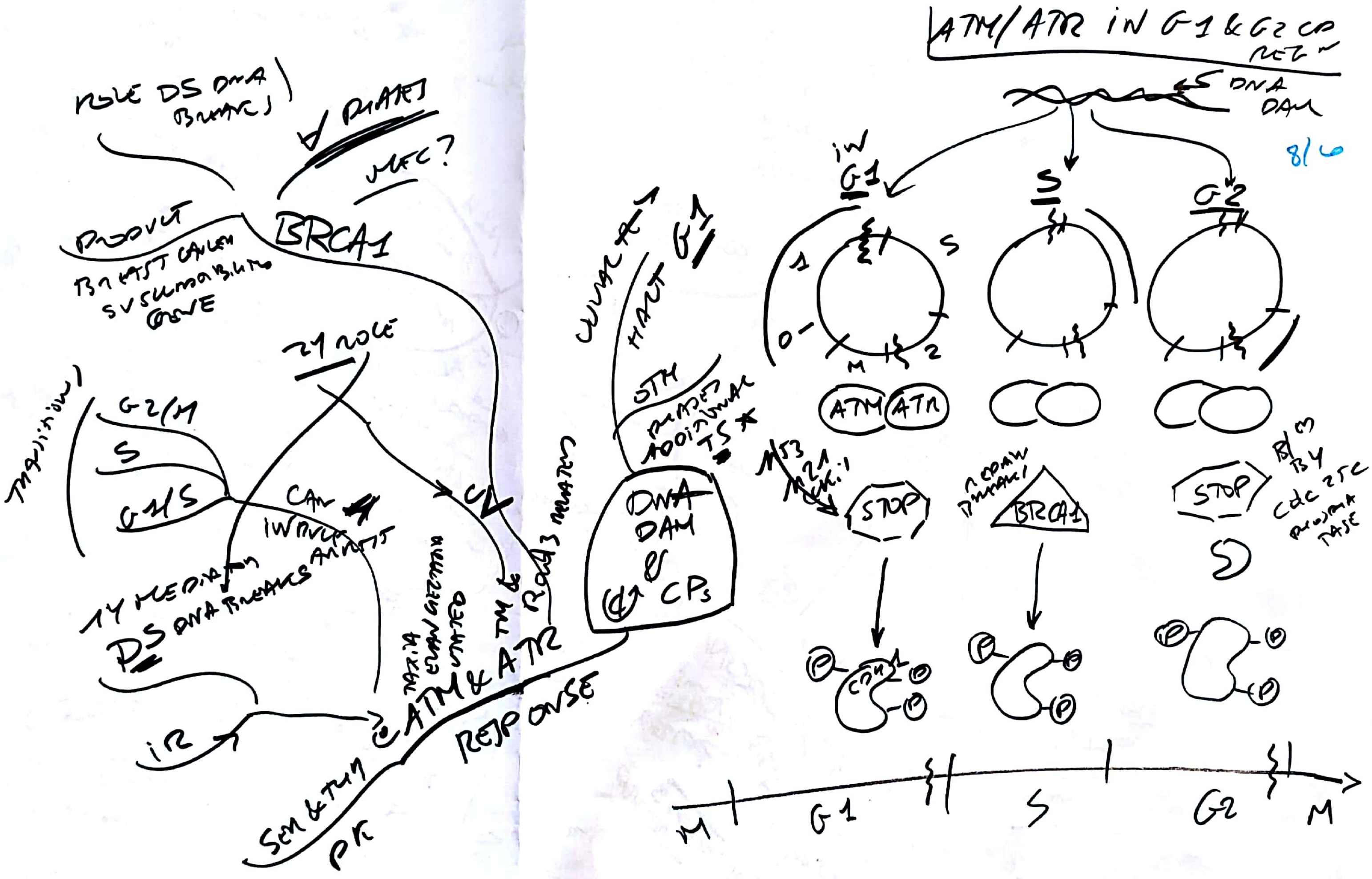

CDKs
Cyclin REGULATORS
CYCLINS
CDK kinase
CYCLIN
CONTAIN
3/6
BIND
CKI
CDK INH or P
INACTIVE
ACTIVE
ENZ IC ACTIVITY (KINASE)
CAN BE REVERSED
PHOSPHORYLATE
PHASE
PATTERNS EXPRESS
SPECIFIC
CDK1
TARGETS
INITIAN DNA
G1→S
INITIAN NERT PHASE
ALLOW
REGULATION
SUBSTRATE
SER/THR
ENZ ACTIVITIES
HOWEVER
PRESENT
AMOUNT
SER/THR KINASES
AVAILABLE
CYCLINS
DEP
REQUIRED FOR CDK(s)
CRITICAL G1 REGULATORS FOR PASSAGE TO RP
SPHASE
MITOTIC
INITIAN DNA IN EARLY S
TRANSITION G2→M
PASSAGE RP G1/S
PROTEOLYSIS
E
S
A
B
M
G2
G1
GO
D
CDK
G1
S
G2
M

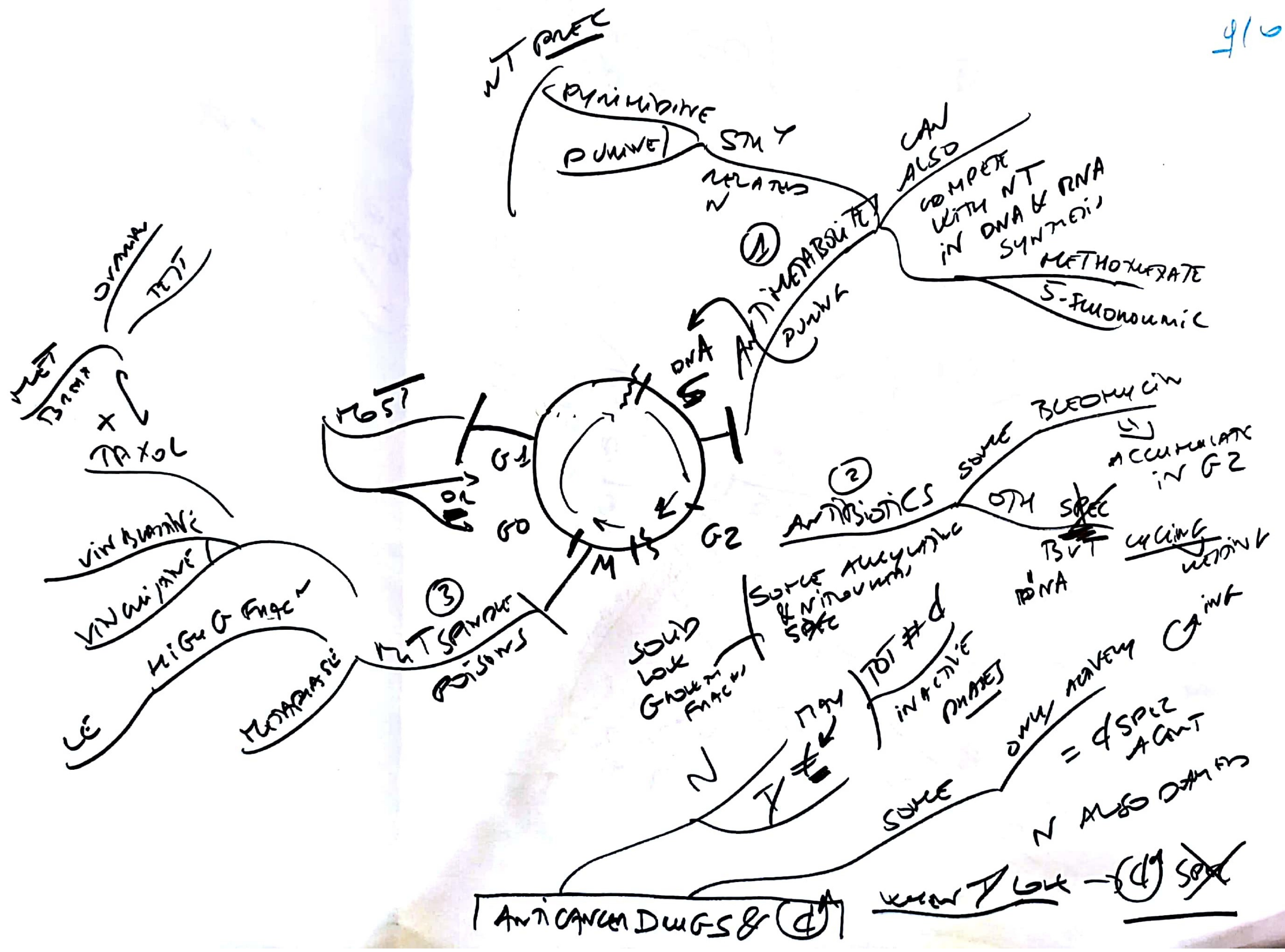

CHECKPOINTS
CRITICAL POINT
MONITOR COMPLETION CRUCIAL EVENTS
IF NEC DELAY
4/10
RESTRICTION POINT G1 CHECKPOINT
BEFORE
REQUIRES EXTERNAL GF STIMULAN TO PROCEED THROUGH G1
AFTER NEED INTERNAL STIMULAN
ANOTHER (2)
G1
S
G2
M
G0
(3) CHECKPOINT MONITORING (4)
IF DNA DAM PROG RATE ↑ ATTEMPT ARREST FOR REPAIR
G2 CHECKPOINT


APPROPRIATE
G1
S
G2
M
G0
KEY REGULATORS
G1 CONTROLLED
INCLUDING TS
CDKi
DNA
CONTINUOUS
GROWTH
NEEDED
CANCER
INAPPROPRIATE
TS N/ HALT d IN G1
RB
G1
CP1
PARTIALLY
RESTING
RB
E2F
TF
ACTIVES
CYCLINS
PROGRESSIVE
OUT OF G1
G1
S
THYMIDINE K
DNA POL
INTO
S PHASE
MITOGEN
EGF-
DNA
TRANSLATION
GF
STIMULATION
SIGNALING
SUBSEQUENTLY
VIA
MAP KINASE
CASCADE
OUT
BY
CYCLIN E-CDK2
RB
BY CD/CDK4/6
DURING G1
⇒ E2F
DISSOCIATE
FROM DNA
RB ACTIVATION TRANSITION S PHASE


↑53 CAT & FADE FOLLOWING DNA DAM
DNA DAM
6/6
DNA DAM
P
↑53
CANNOT BE REPAIRED
↑53 → APOP
STABILIZES & ACTIVATES
CAN BE
↑21 = CKi
UPON DNA REPAIR
STOP
DNA REPAIR CAN PROCEED
RB
TSP
↑53
G1 CP 2
CDK APP :
HPV
CERVICAL CANCER & TS
E6 → ↑53
XP E7 → RB
BOTH
UNABLE TO MALIGNANT HAM RESIST
19
16
MUTATED & UNABLE TO ⇒ UNREPLICATED
50% CANCERS
CANCER DEP Ki
INK4A
CDK4
CDK6
CIP1
↑21
CDK2
CIP/KIP
D
FORM ASSOCIATING WITH & ACTIVATING CDK4 & 6


ATM
ATM
TS
CHK2
THEN CDC25C
IF
MUST BE SUFFICIENTLY
PRIOR TO ONSET OF
MITOSIS
CDC25C
PHOSPHATASE
G2
CP
INHIBITION
CDK1
INHIBITORY
KINASES
WEE1
G1
S
G2
INACTIVE
CDK1
ACTIVATING
INHIBITORY
CDC25C
PHOSPHATASE
CYCLIN
B
ACTIVE
PROGRESS THROUGH G2
INTO M
NUCLEUS
MITOSIS
BY
KEY
SUBS
PROGRESSION
G2 → M
CONTROLLED BY
CDC25C PHOSPHATASE
& CDK1


ATM/ATR IN G1 & G2 CP REG
BRCA1
G2/M
S
G1/S
DS DNA BREAKS
IR
ATM & ATR
RESPONSE
DNA DAM & CPs
DNA DAM
8/6
G1
S
G2
ATM
ATR
STOP
BRCA1
STOP
M
G1
S
G2
M


ANTICANCER DRUGS &
ANTIMETABOLITES
NT PREC
PYRIMIDINE
PURINE
CAN ALSO COMPETE WITH NT IN DNA & RNA SYNTHESIS
METHOTREXATE
5-FLUOROURACIL
DNA
S
G1
G0
G2
M
MOST
ANTIBIOTICS
SOME
BLEOMYCIN
ACCUMULATE IN G2
OTH
DNA
SOLID
LOW GROWTH FRACTION
INACTIVE
ONLY
AGENT
N ALSO
MITOSPINDLE POISONS
METAPHASE
VINBLASTINE
VINCRISTINE
TAXOL
BREAST
OVARIAN
TEST