

Chronic Lymphocytic Leukemia

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Disease and Current Therapies from a Medical Perspective

C. Reinhardt

Medical Clinic I, Hematology/Oncology

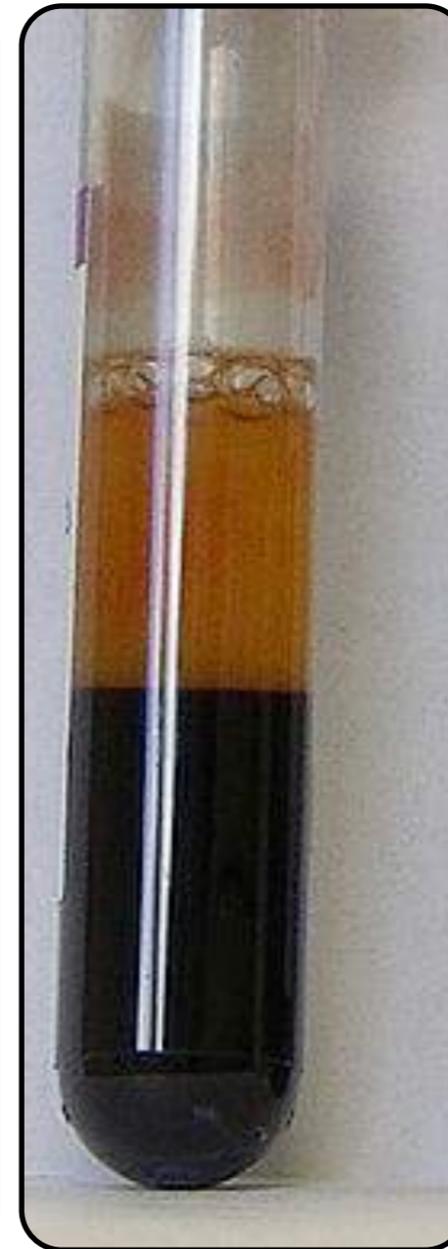
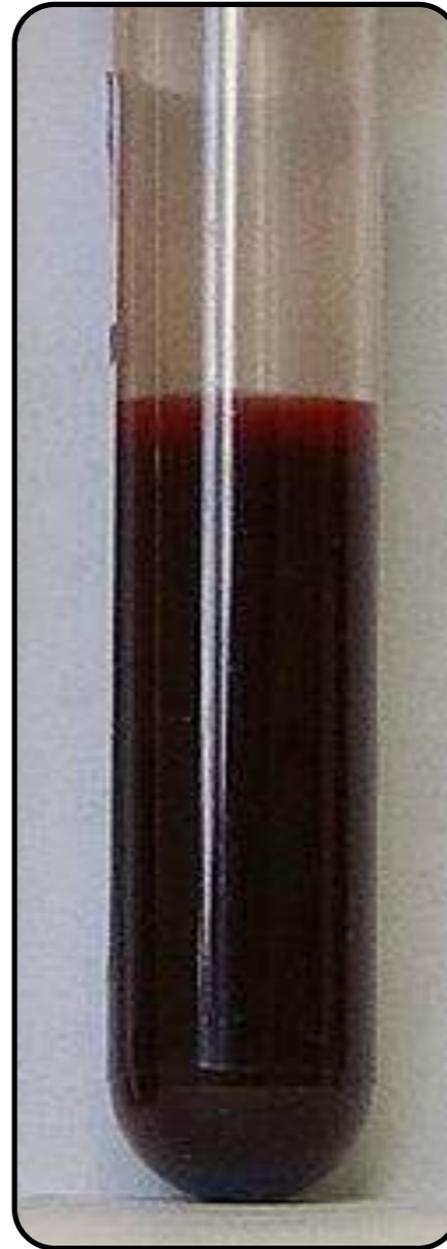
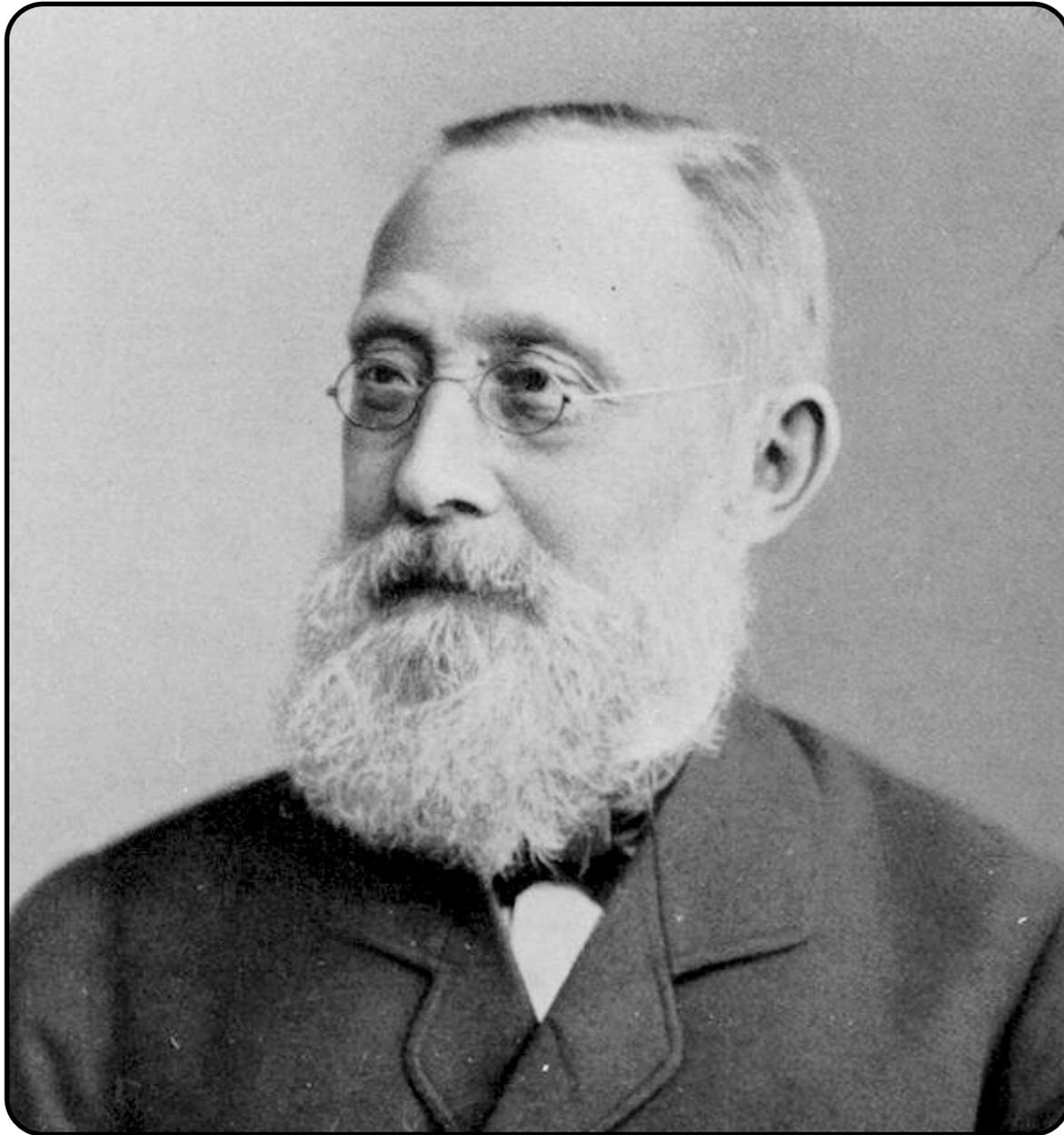
CECAD, Research Area C

Clinical and Molecular Oncology

CLL - an introduction

- What is CLL?
- Diagnostic tools
- Prognostic scores
- The biology of CLL
 - the cell of origin dilemma
 - cytogenetic aberrations
 - mutational landscape in CLL
 - clonal evolution and therapy resistance
- Science becomes medicine (novel therapeutic approaches)

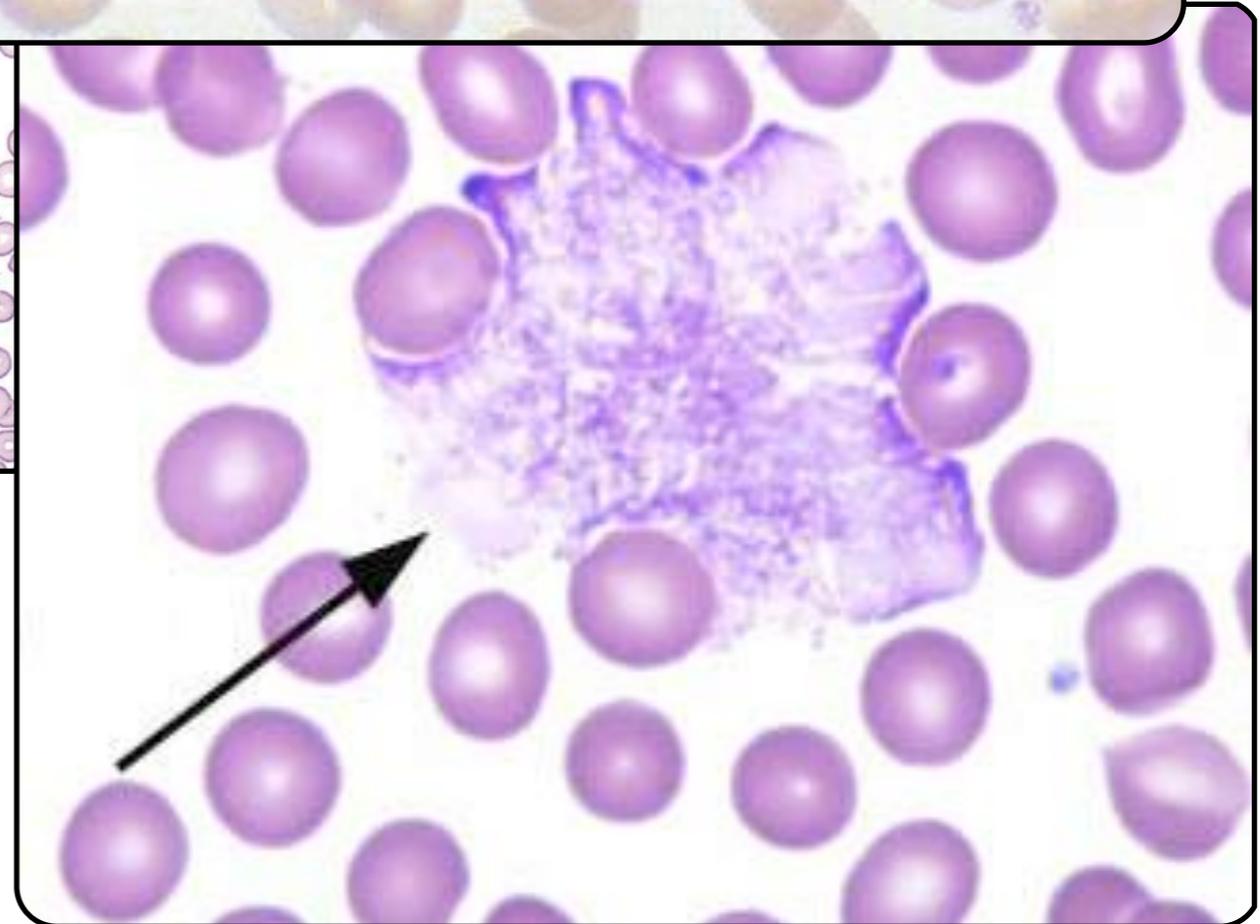
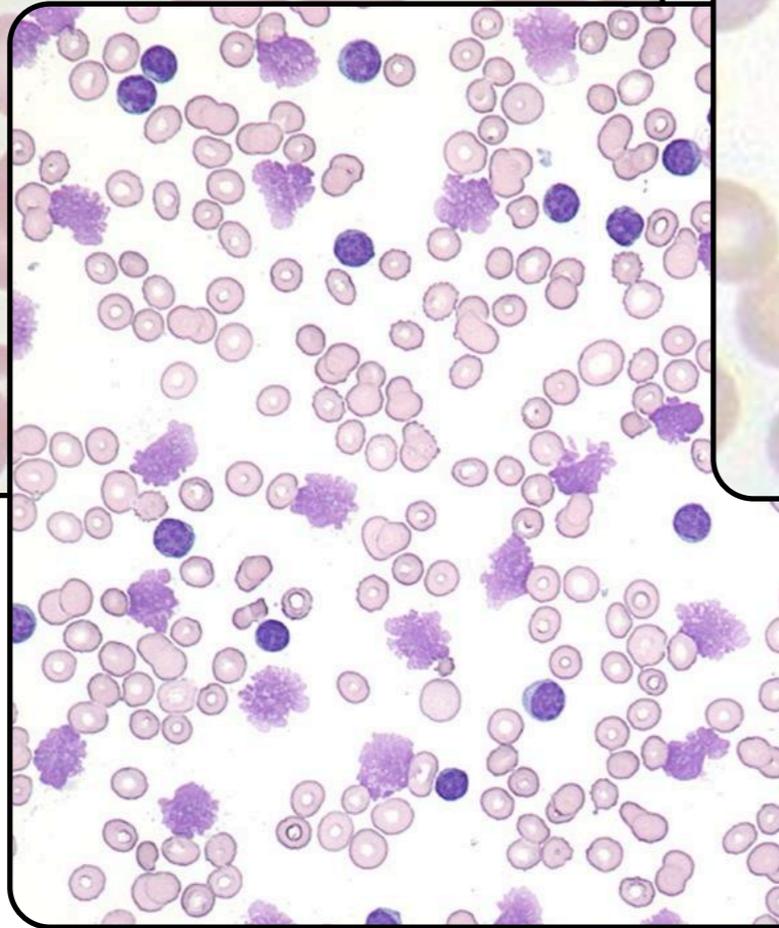
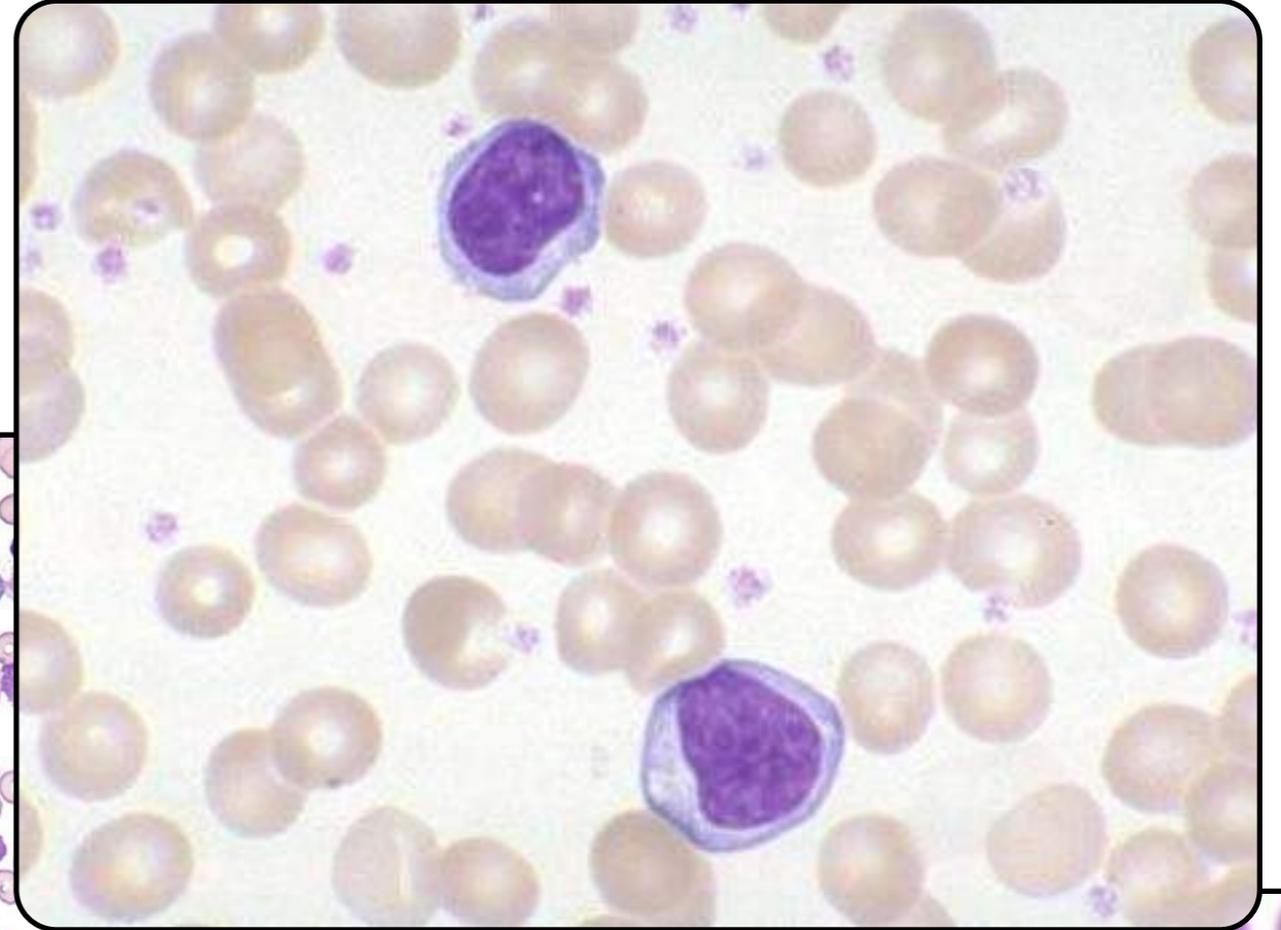
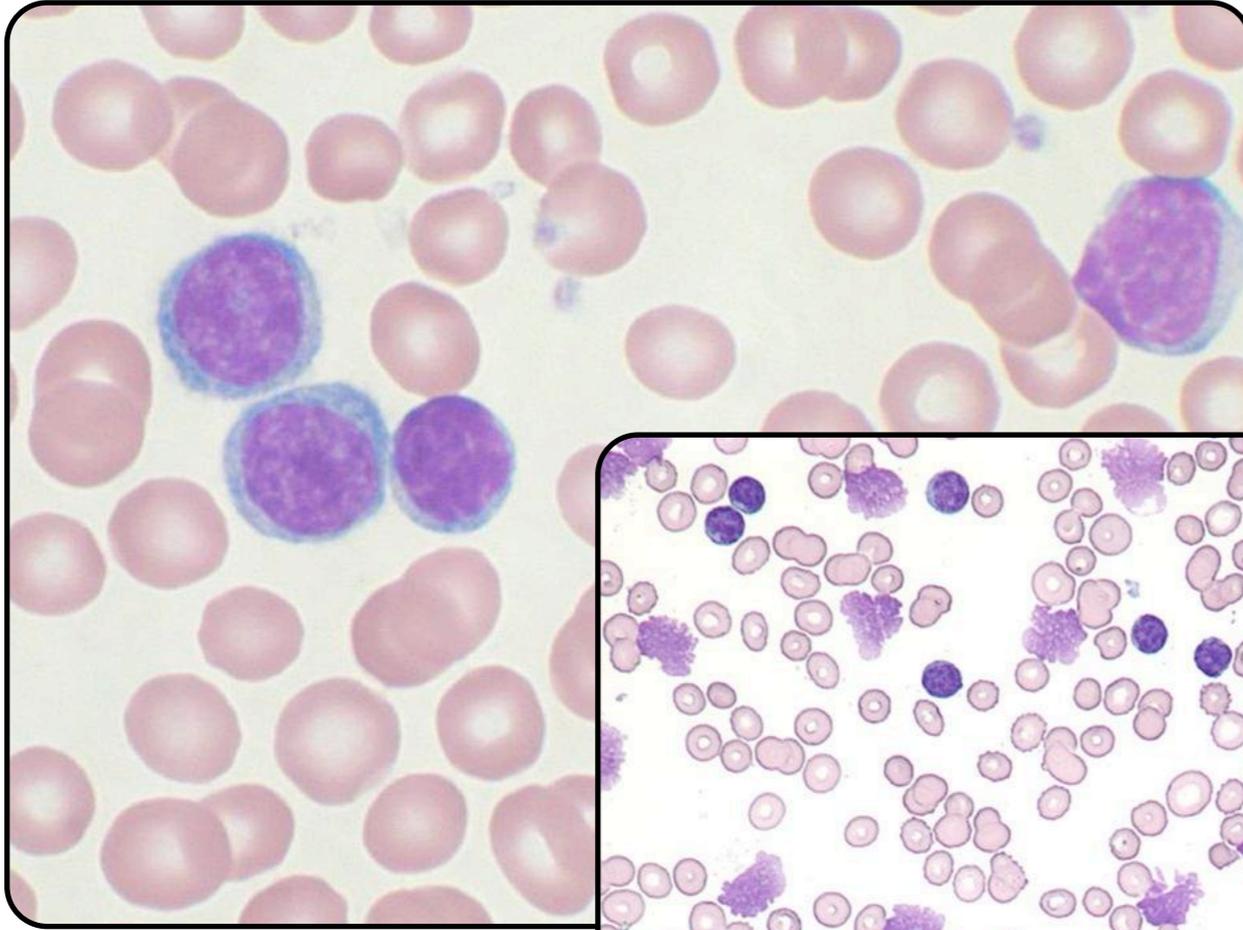
R. Virchow coins the term leukemia (white blood) in 1847



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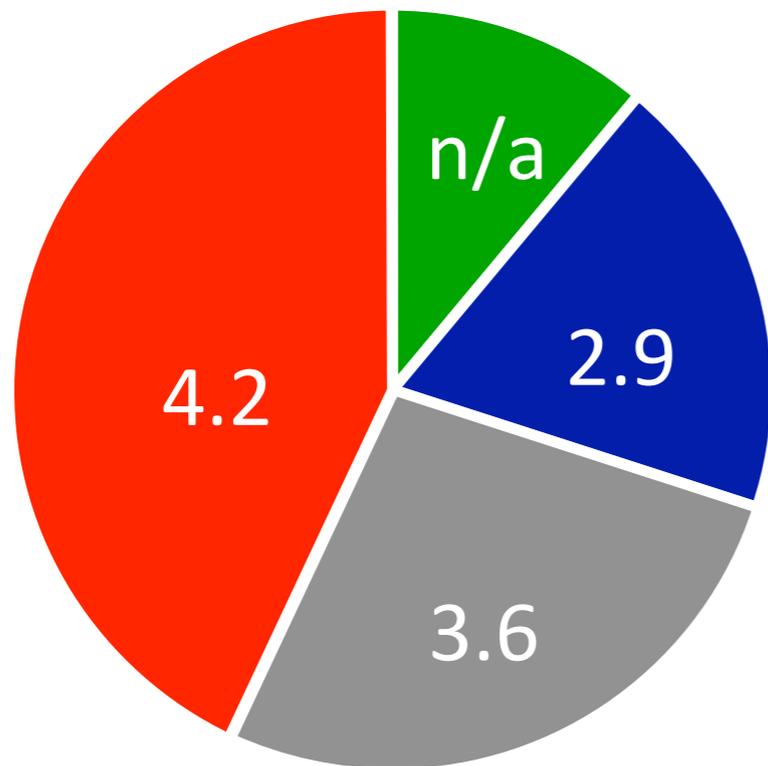
The blood smear reveals essential hints leading to the diagnosis



CLL is a disease of the elderly

→ a minority of patients qualifies for toxic therapy

- Most frequent leukemia in the Western hemisphere.
- Median age at diagnosis: 72 years¹
- Elderly patients may have comorbidities



Age at CLL diagnosis (years)	Patients ¹ (%)	Mean comorbidities ² (all cancer types, n)
≤ 54	11	n/a
55–64	19	2.9
65–74	27	3.6
75+	43	4.2

1. Ries LAG, *et al.* SEER Cancer Statistics Review, 1975–2005.

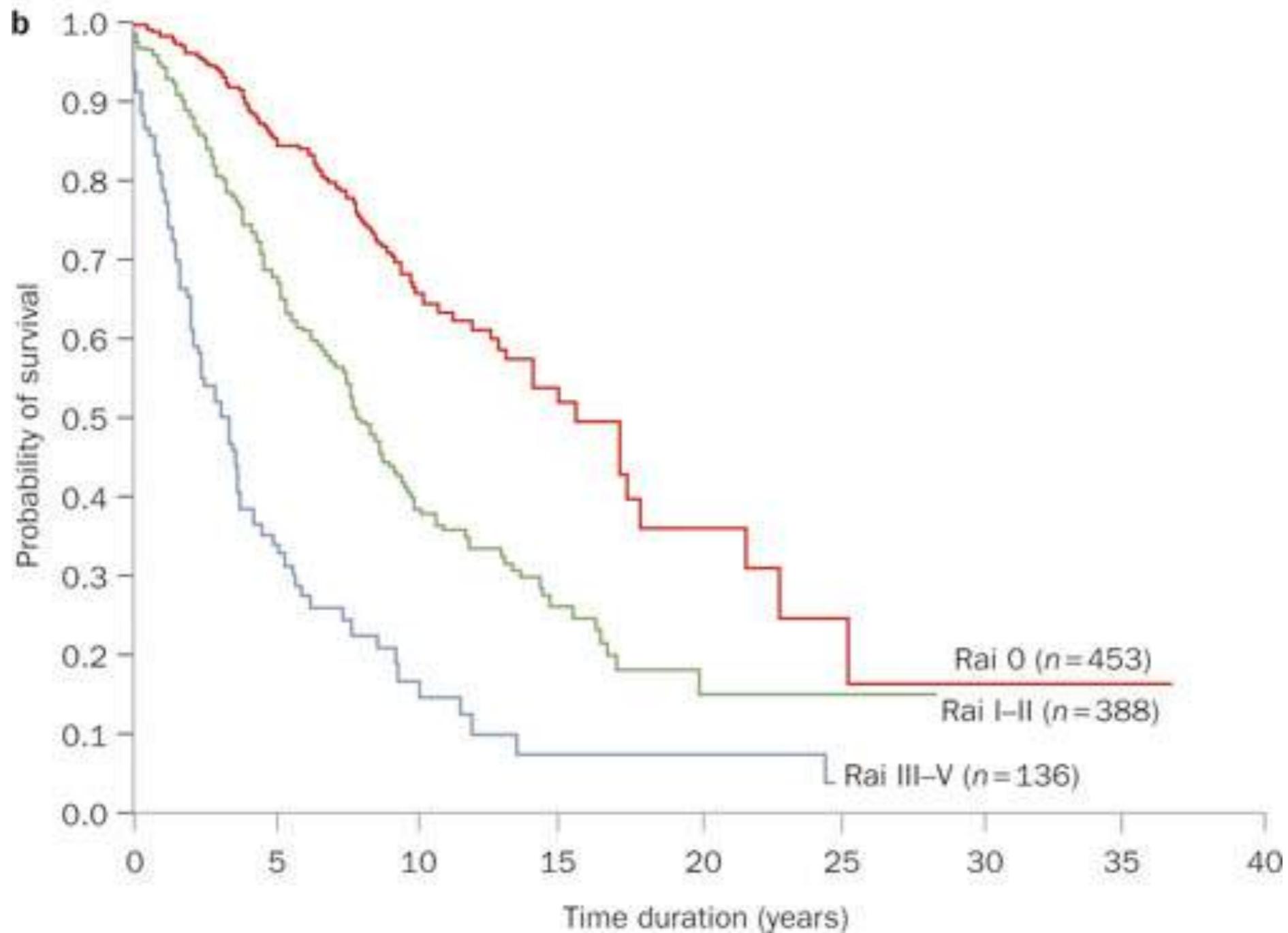
2. Yancik R, *Cancer* 1997; 80:1273–1283.

The Rai classification allows risk stratification

Table 1. Rai classification system*			
Stage	Description	Median survival (months)	Risk status (Modified Rai)
0	Lymphocytosis, lymphocytes in blood >15,000/mcL and >40% lymphocytes in the bone marrow	140	Low
I	Stage 0 with enlarged node(s)	100	Intermediate
II	Stage 0–1 with splenomegaly, hepatomegaly, or both	70	Intermediate
III	Stage 0–II with hemoglobin <11.0 g/dL or hematocrit <33%	20	High
IV	Stage 0–III with platelets <100,000/mcL	20	High

* Adapted from the 2008 NCI guidelines; BC Cancer Agency 2008 guidelines.^{3,4}

The Rai classification allows risk stratification



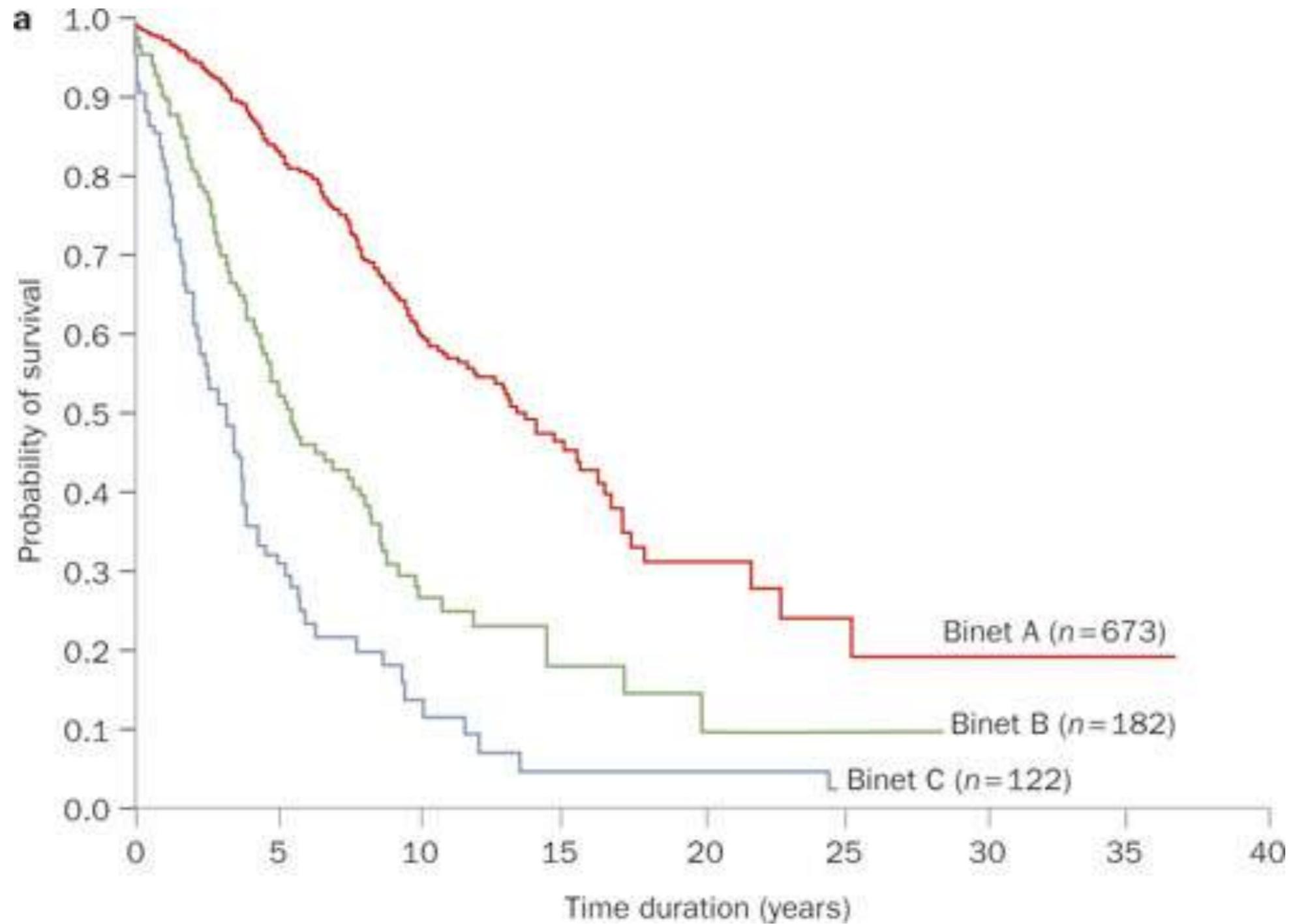
The Binet classification allows risk stratification

Table 2. Binet classification system*†	
Stage	Description
A	Hemoglobin ≥ 10 g/dL and platelets $\geq 100,000/\text{mm}^3$ and < 3 involved nodal areas
B	Hemoglobin ≥ 10 g/dL and platelets $\geq 100,000/\text{mm}^3$ and ≥ 3 involved nodal areas
C	Hemoglobin < 10 g/dL and or platelets $< 100,000/\text{mm}^3$ and any number of involved nodal areas

**Adapted from the 2008 NCI guidelines.³*

†Areas of involvement considered for staging are as follows: (1) Head and neck, including the Waldeyer ring (this counts as one area, even if more than one group of nodes is enlarged). (2) Axillae (involvement of both axillae counts as one area). (3) Groins, including superficial femorals (involvement of both groins counts as one area). (4) Palpable spleen. (5) Palpable liver (clinically enlarged).

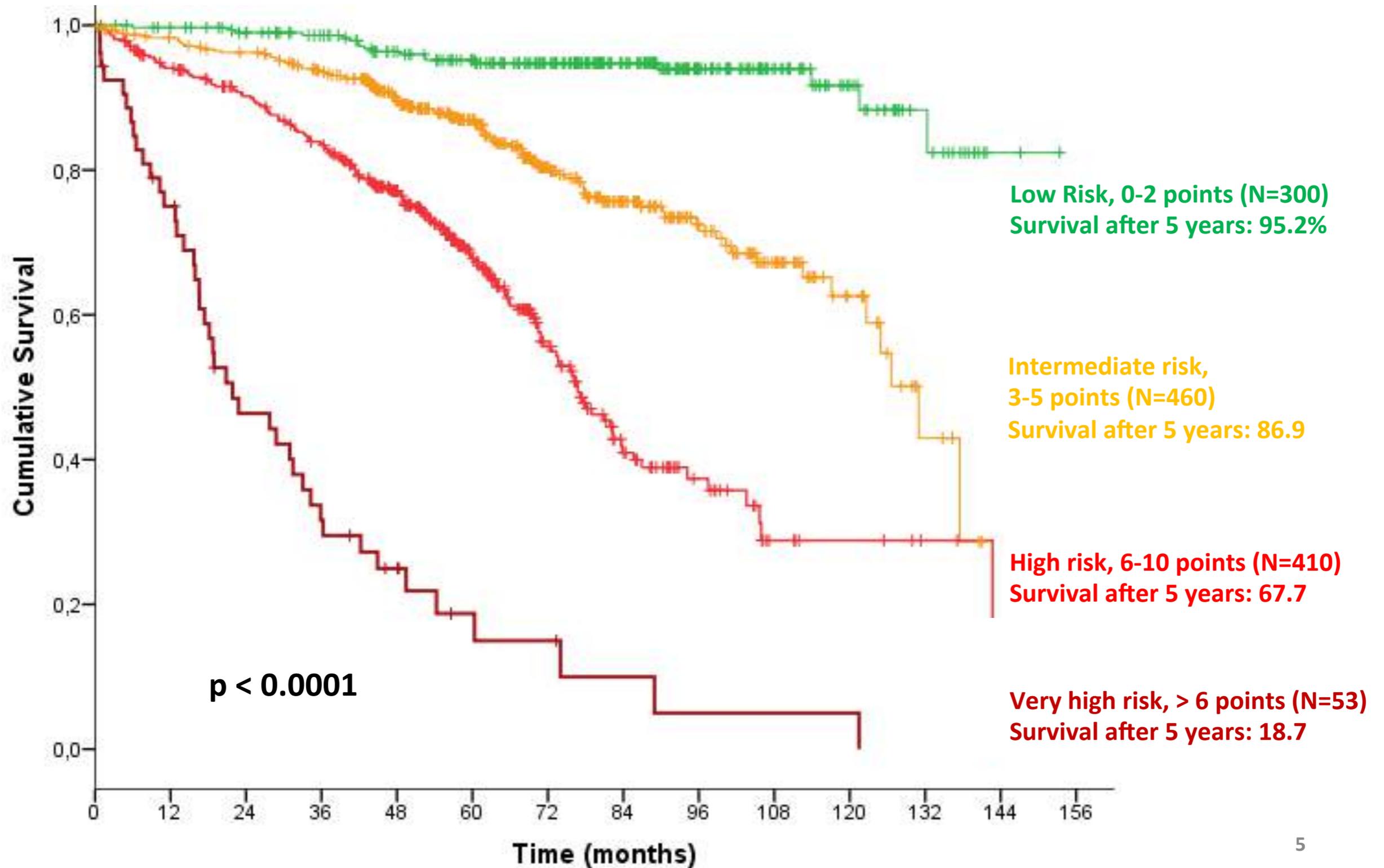
The Binet classification allows risk stratification



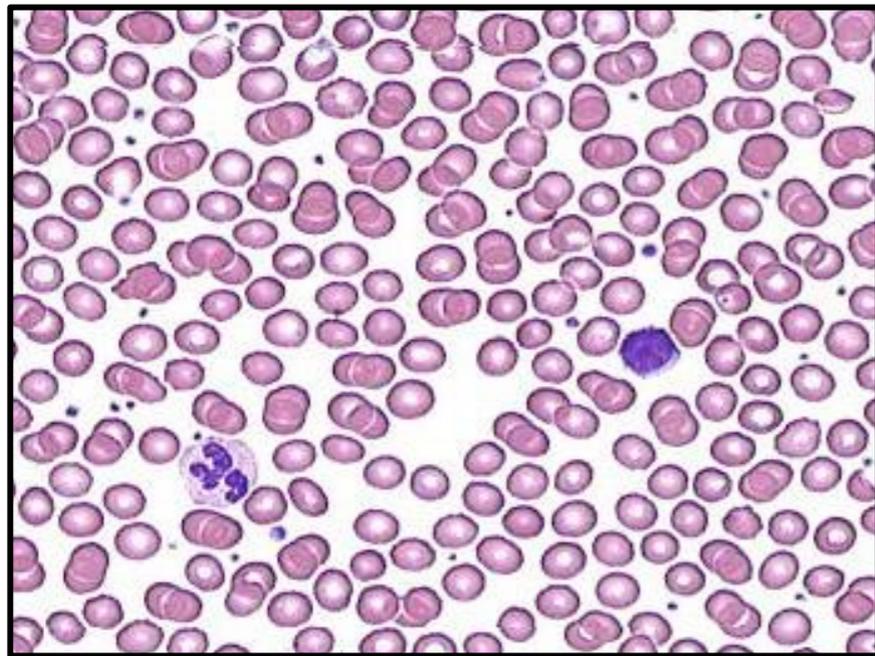
A novel, molecularly-guided risk score allows more detailed risk stratification

Variable	Adverse factor	Hazard ratio for death	Factor - grading
Chromosomal aberration	del(17p)	6.0	6
s-TK	> 10.0 U/L	2.8	2
s-β2m	> 3.5 mg/L	2.3	2
IgHV mutational status	unmutated	1.9	1
s-β2m	> 1.7 mg/L - ≤ 3.5 mg/L	1.7	1
ECOG	> 0	1.7	1
Chromosomal aberration	del(11q)	1.4	1
Gender	Male	1.3	1
Age	> 60 years	1.3	1

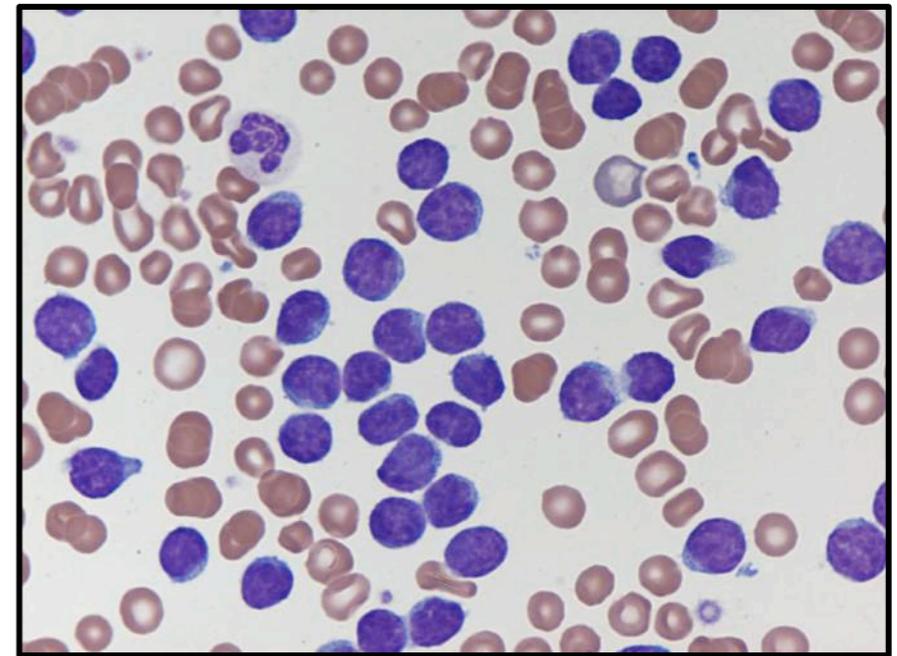
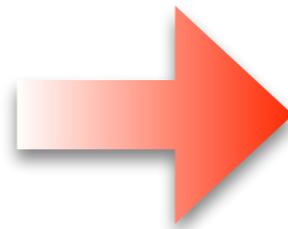
A novel, molecularly-guided risk score allows more detailed risk stratification



CLL is the most common leukemia in the Western world



normal blood smear

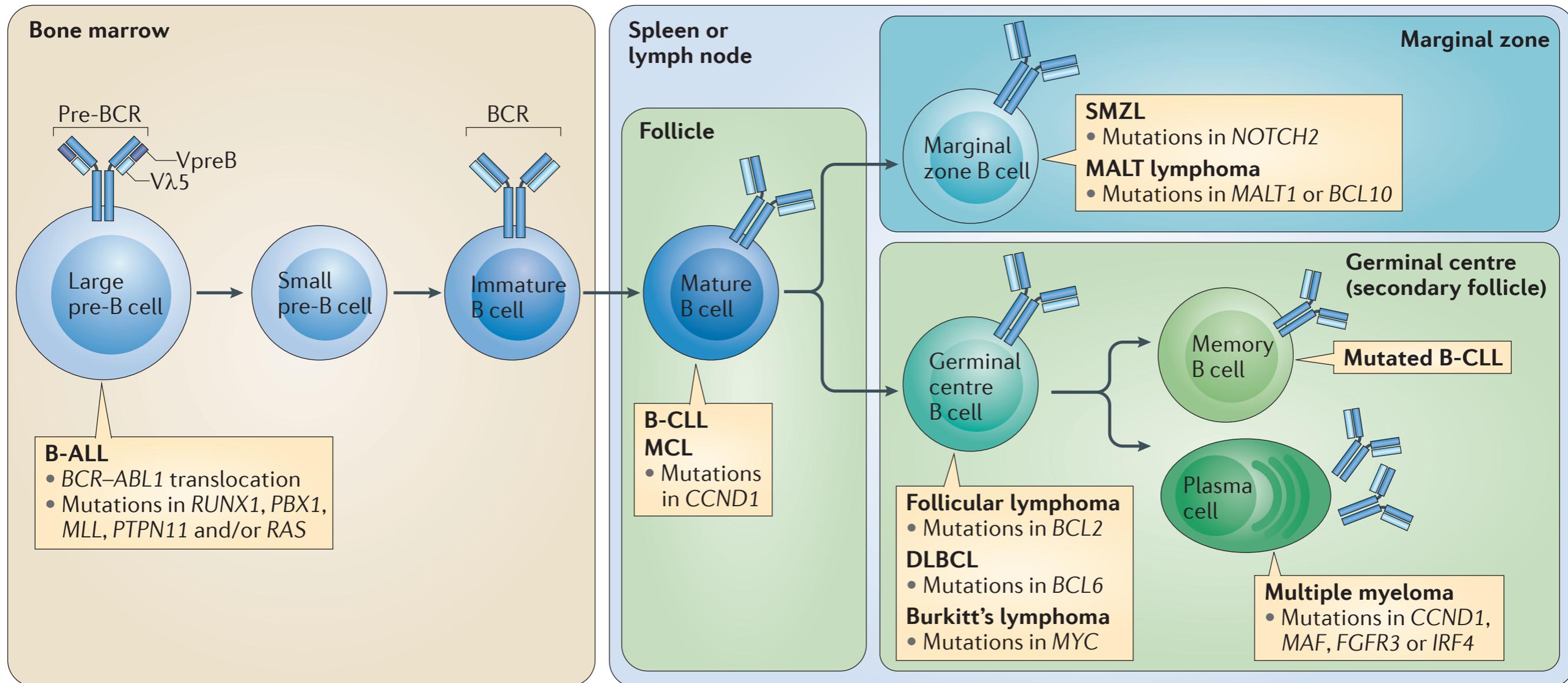


CLL

What happened here???

What is the cell of origin???

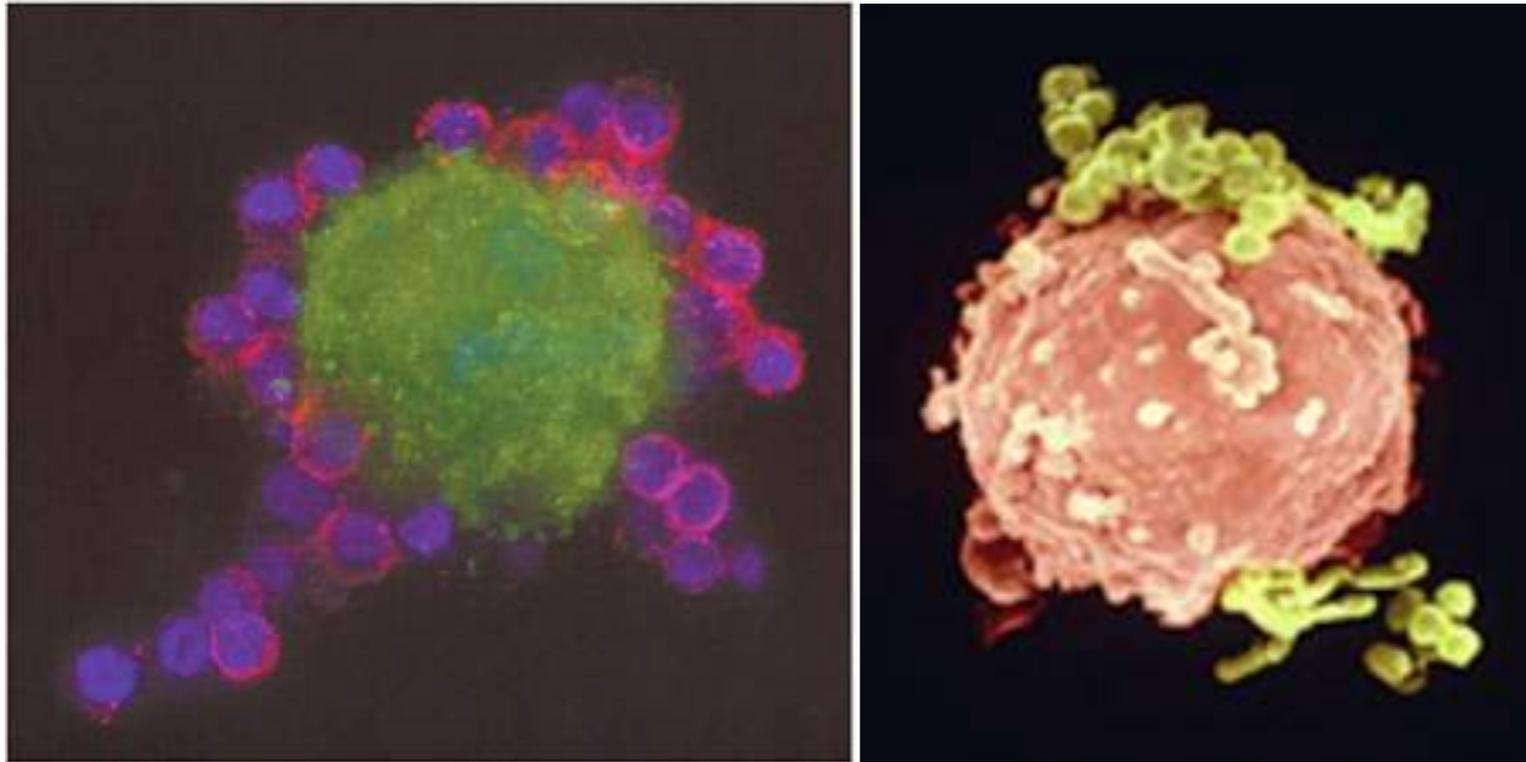
B-cell development can go awry at each step along the way



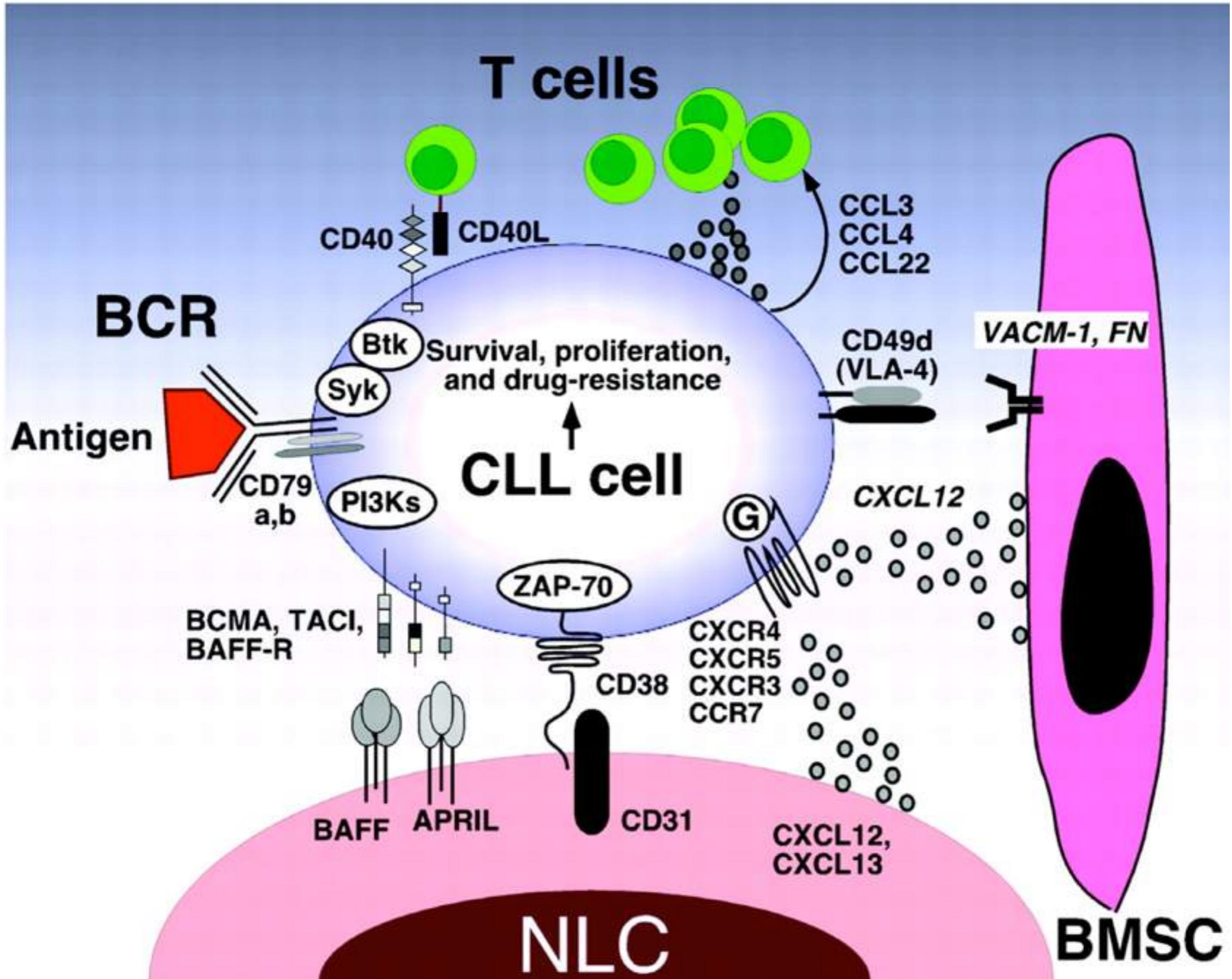
CLL clones can emerge before and after Ig hypermutation

There is something special about CLL

CLL cells are microenvironment-addicted



CLL cells are microenvironment-addicted



Summary I

- CLL is the most common leukemia in the Western World
- CLL is characterized by the accumulation of mature lymphocytes
- Multiple risk scores exist and allow patient stratification
- CLL cells are addicted to micro-environmental stimuli
- Transformation can occur before or after somatic hypermutation

Cancer is a genetic disease

Boveri hypothesizes that chromosomes carry the genetic information (1902!)

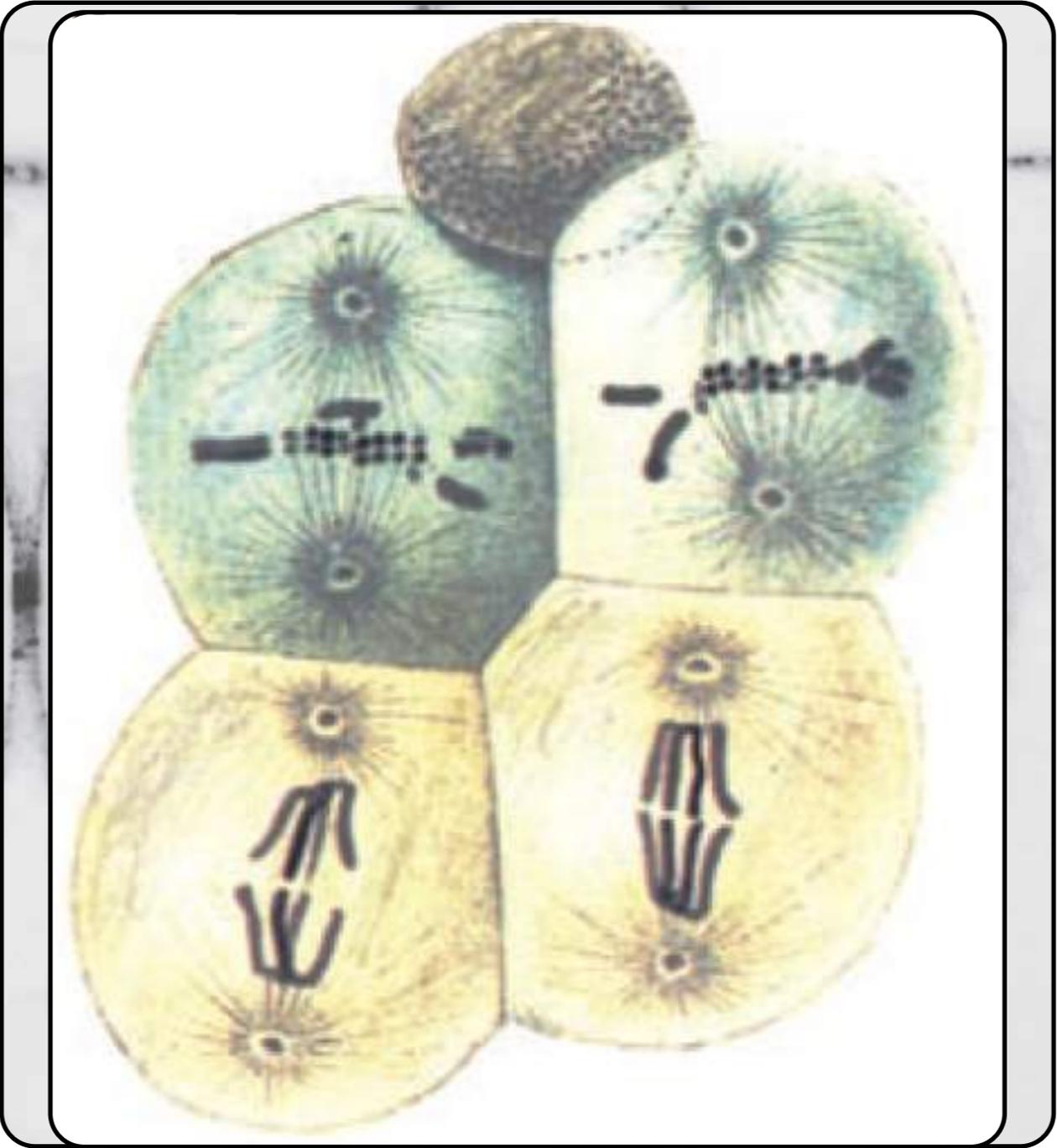
Wie kommen wir zu unserem heutigen Verständnis von Krebs?

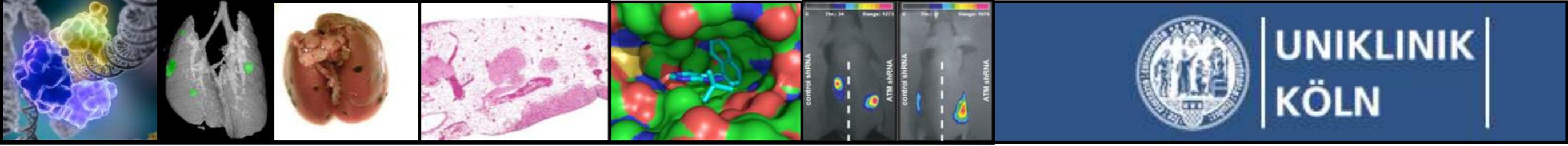
studied fertilized sea urchin eggs and Spulwurm
 postuliert chromosomale Imbalancen als Krebsursache

bring fertilized egg image

heute gain/loss of function
 onkogen tsg...

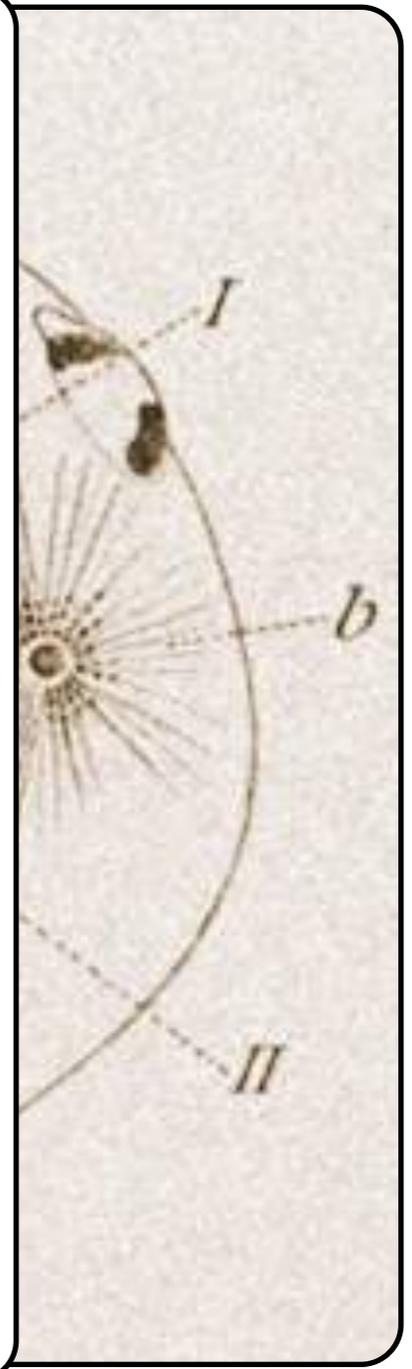
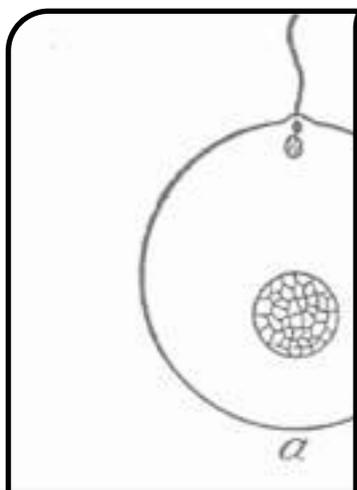
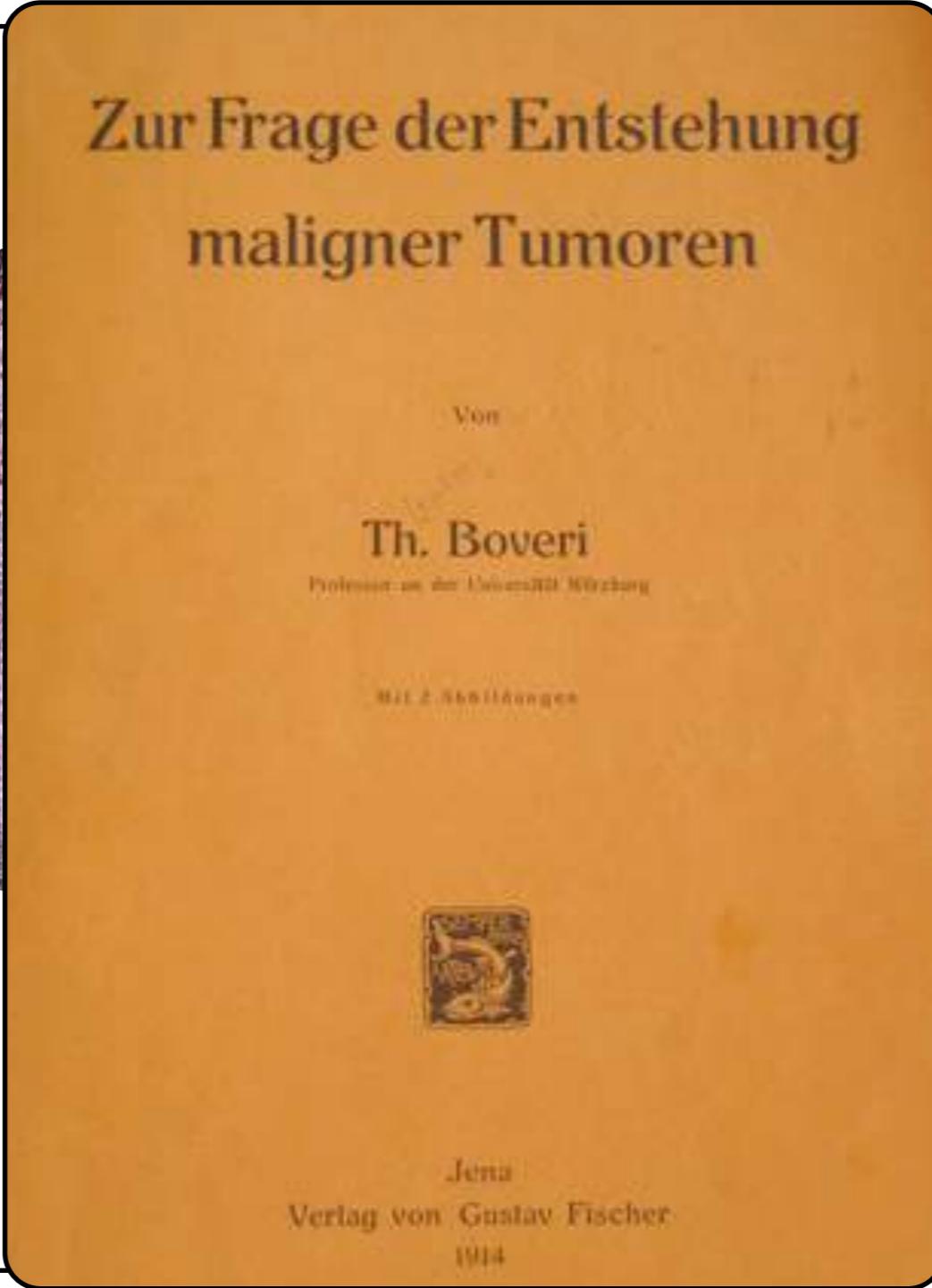
Spulwurm

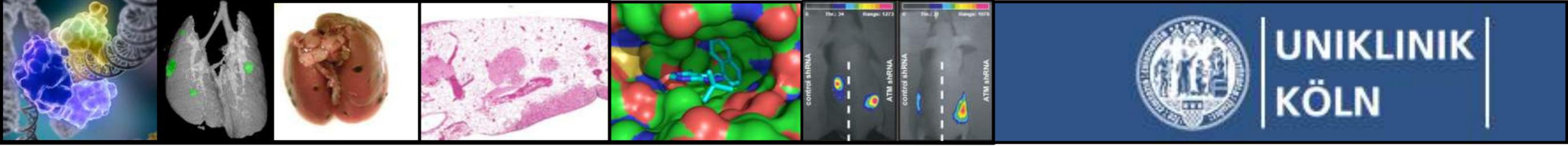




Boveri postulates that chromosomal imbalances are the underlying cause of malignant disease (1914!)

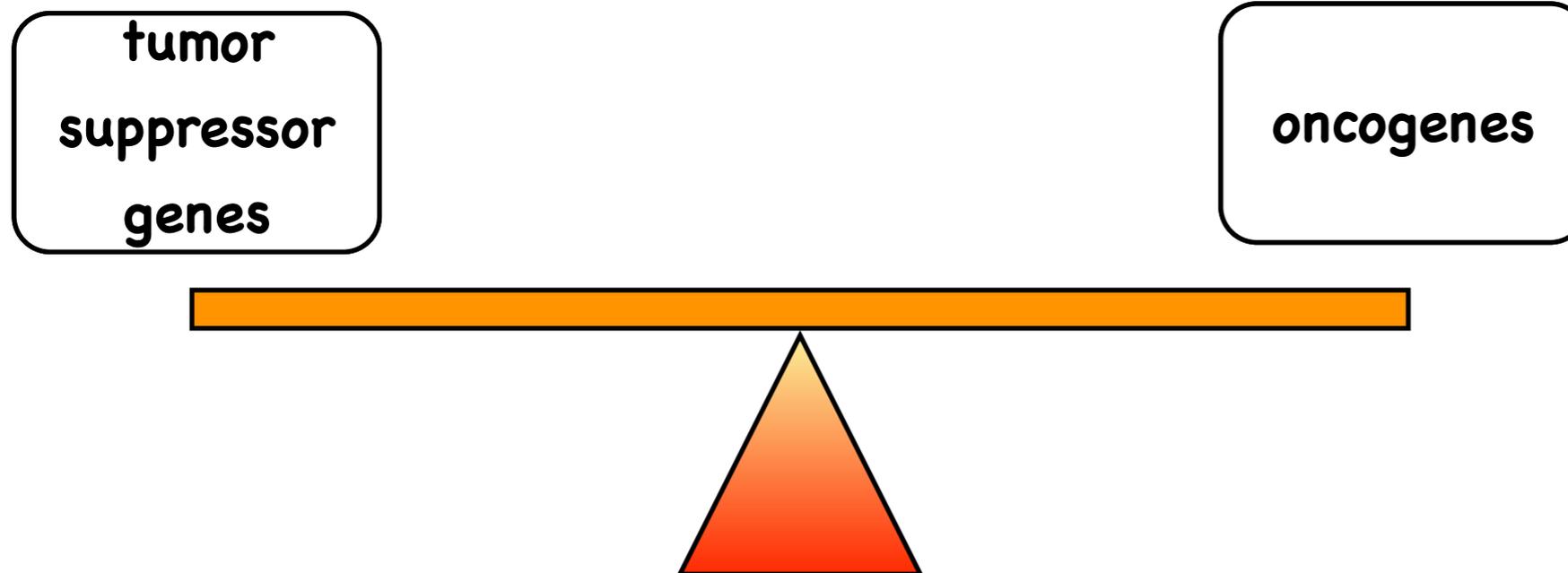
aneuploidie als krebsursache?
Die Ähnlichkeit zwischen seinen abnorm proliferierenden Seeigeleiern und dem unkontrollierten Wachstum von Tumoren ist ihm nicht entgangen.





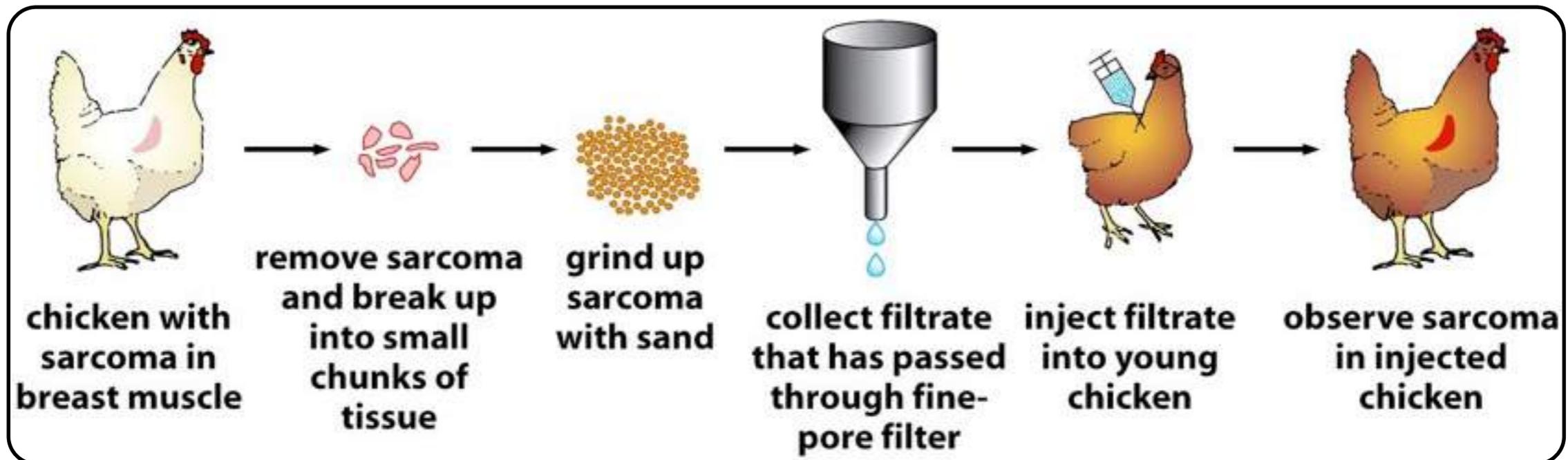
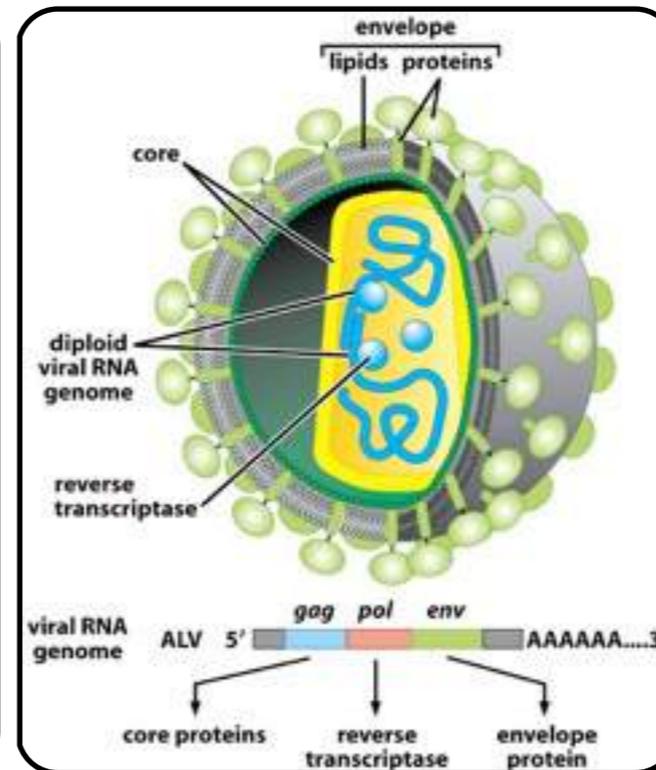
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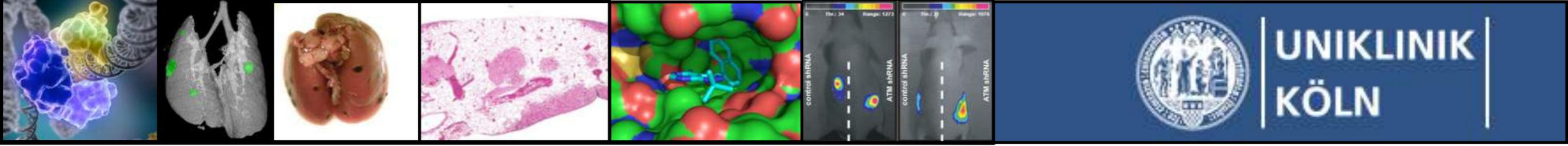
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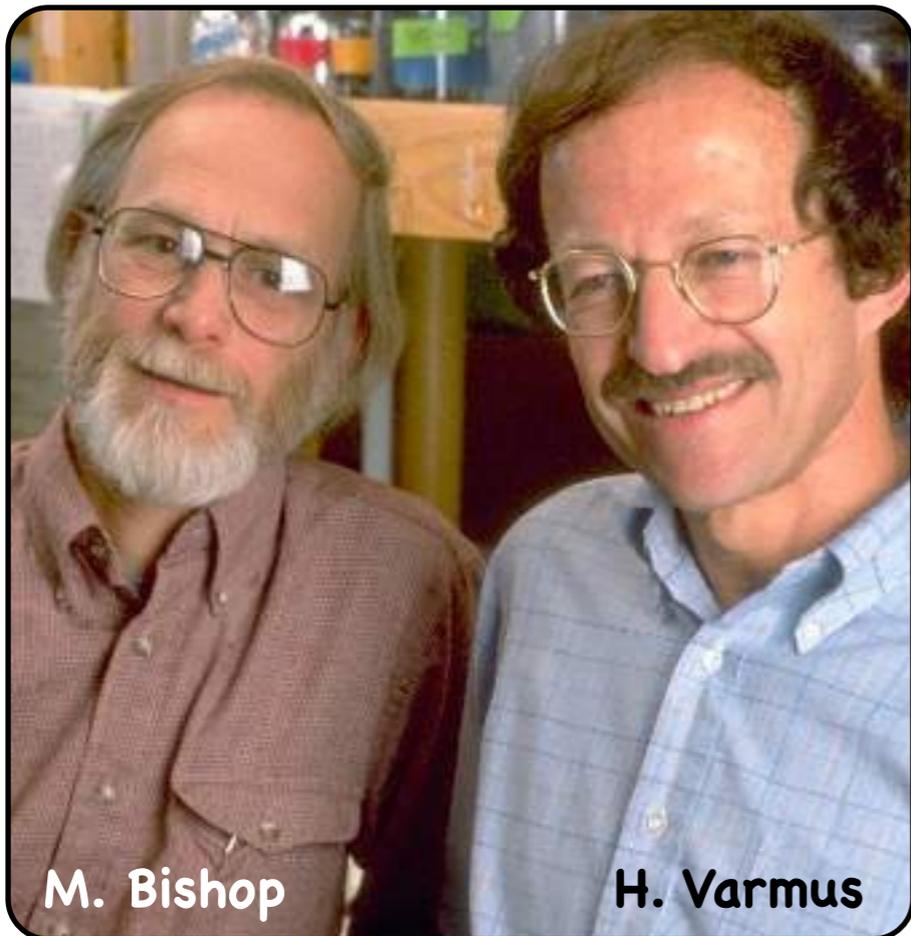
The result is a malignant transformation

P. Rous discovers a chicken sarcoma virus - and postulates that cancer is a transmittable disease (1911!)



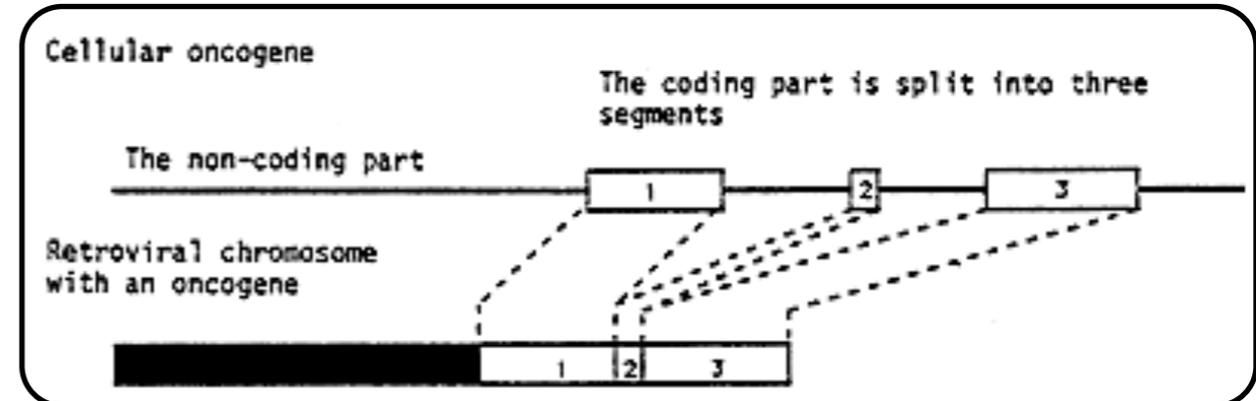
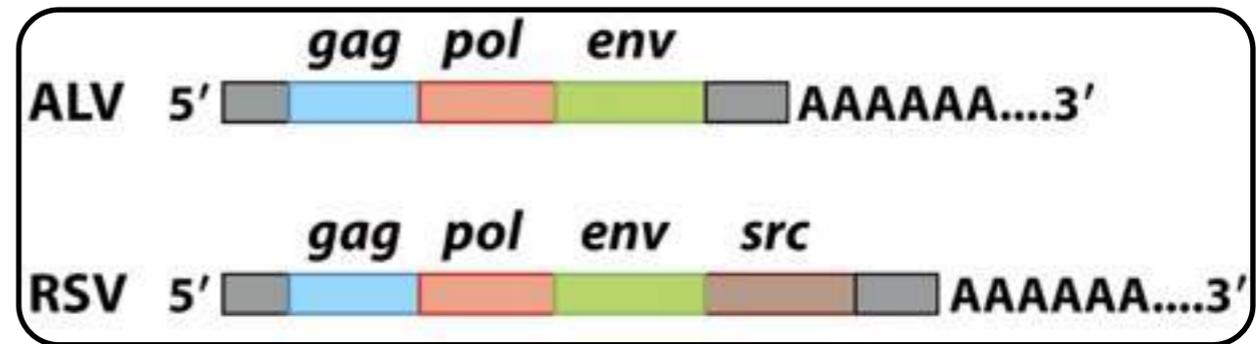
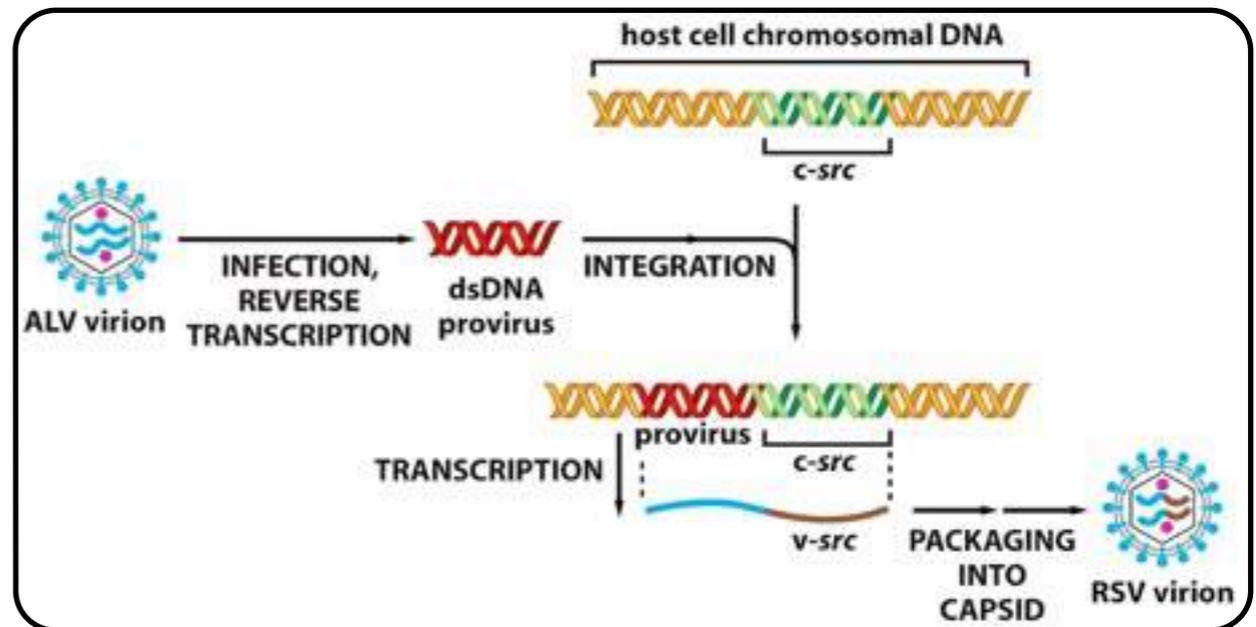


The transforming viral genetic material is also present in non-transformed eucaryotic cells!

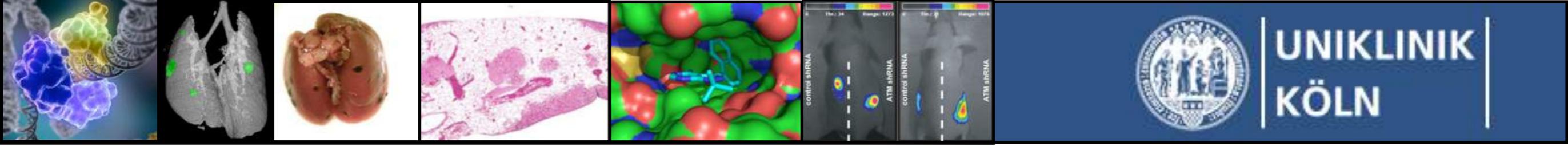


M. Bishop

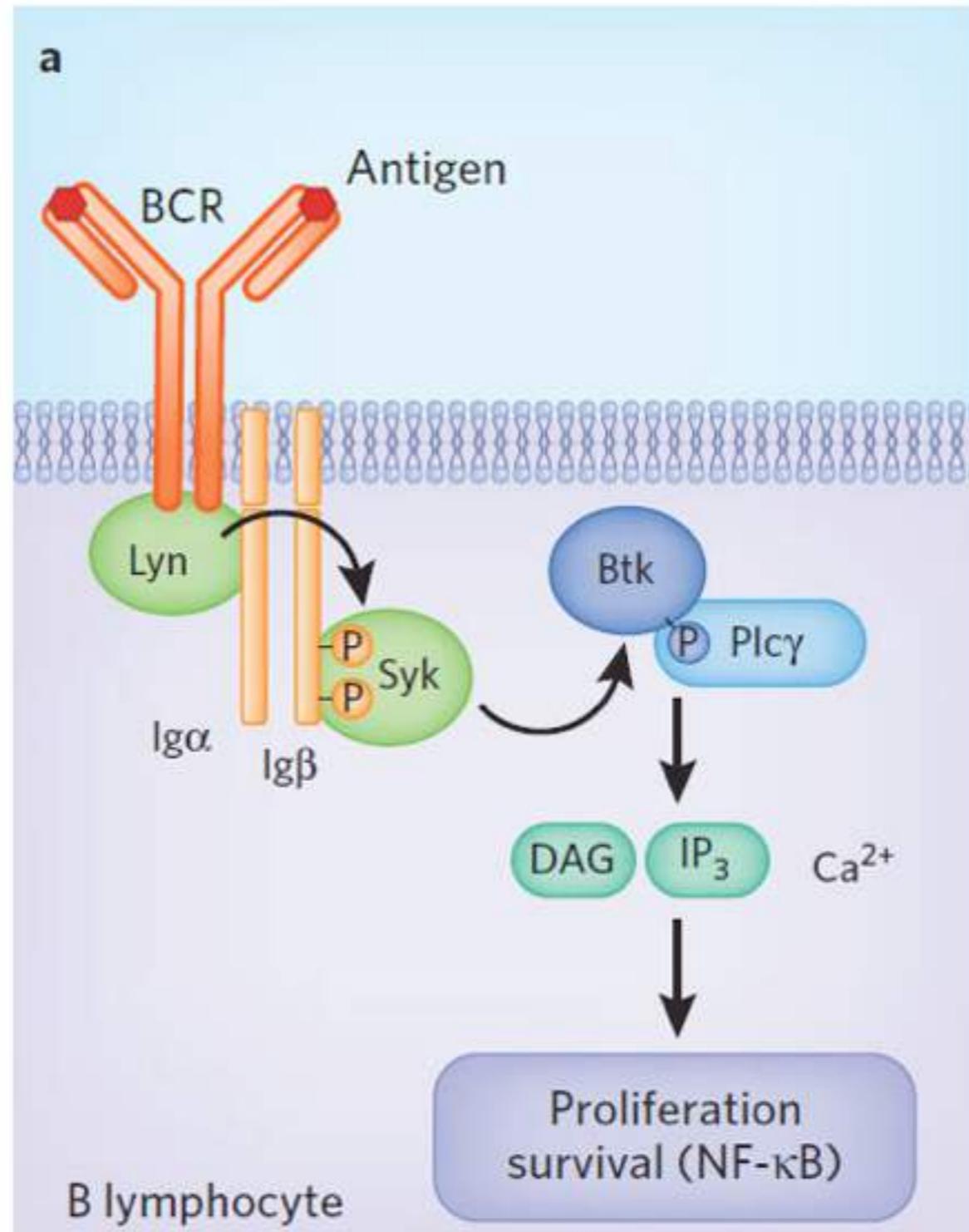
H. Varmus

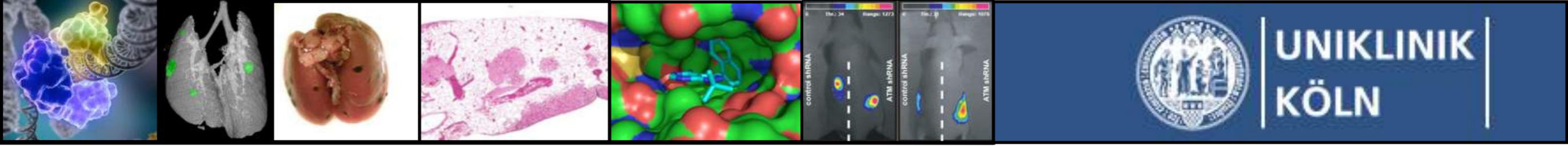


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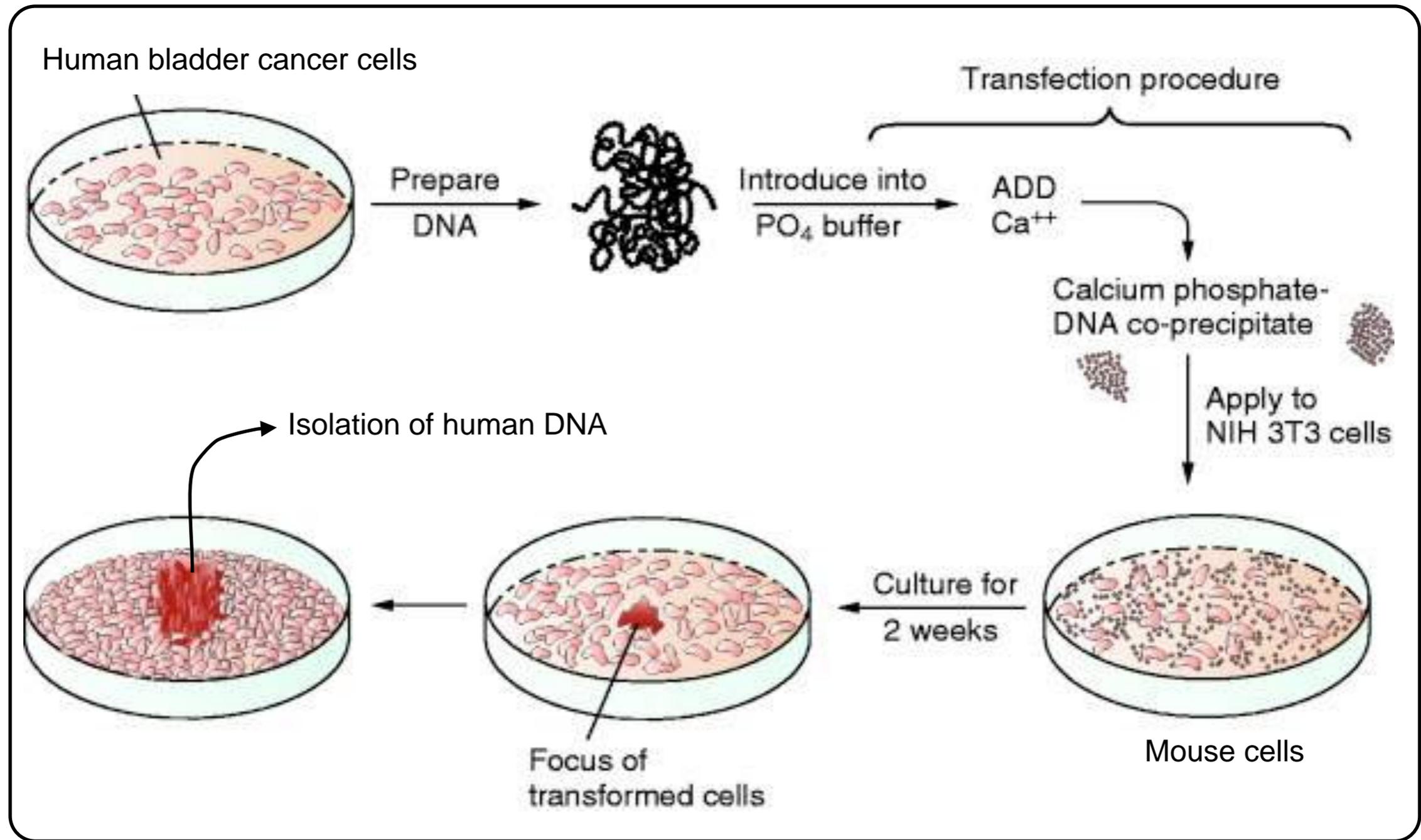


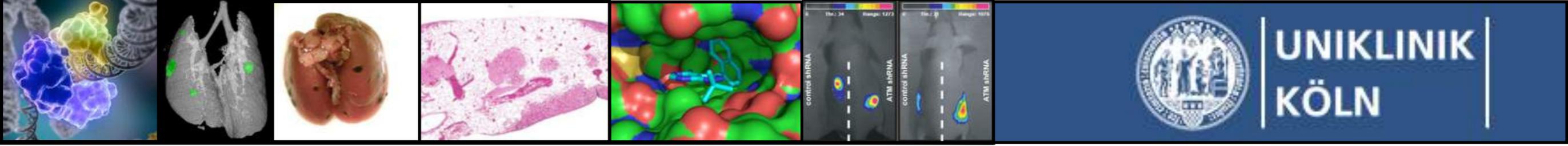
The SRC gene encodes for an oncogenic tyrosine kinase



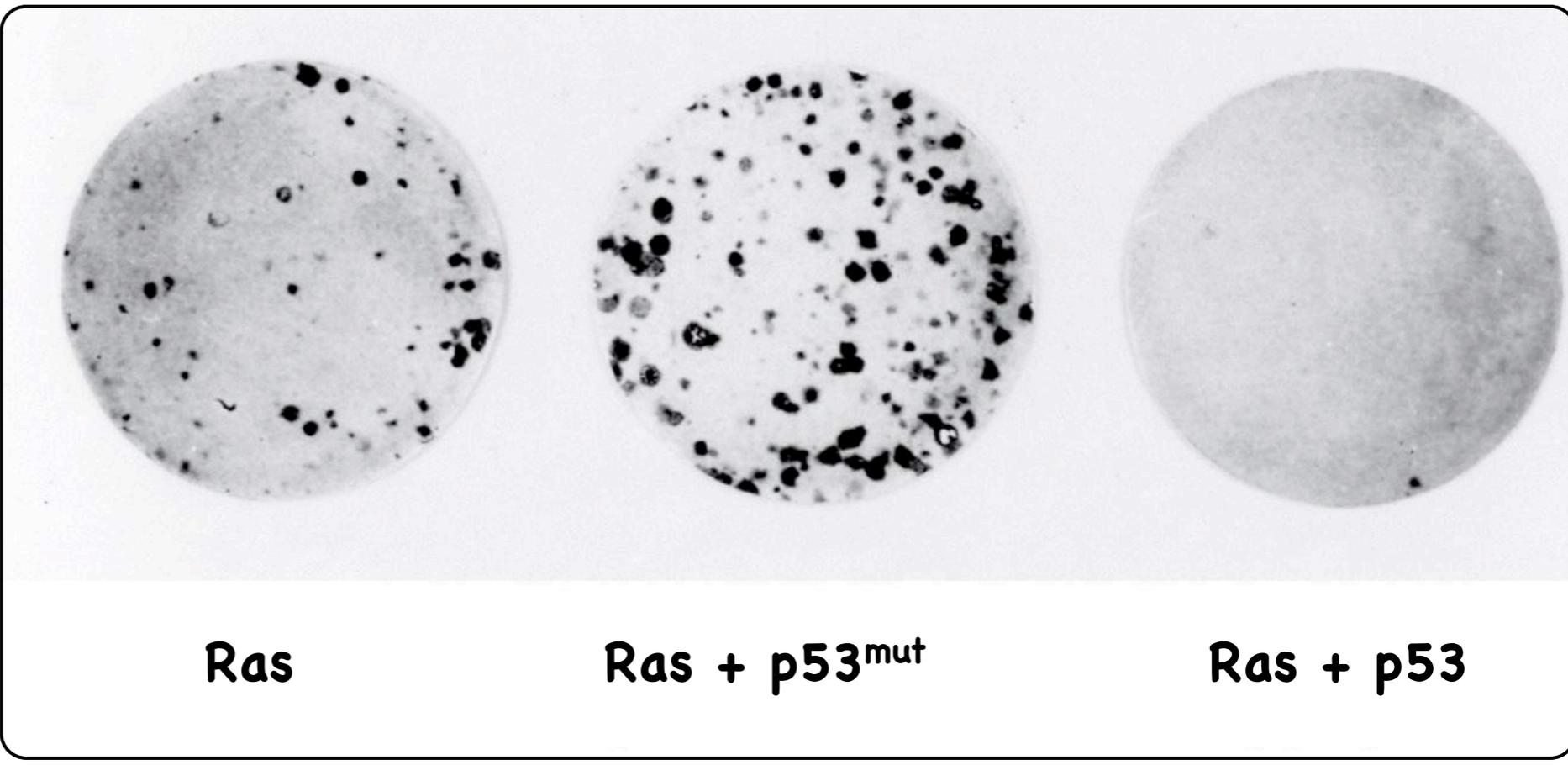


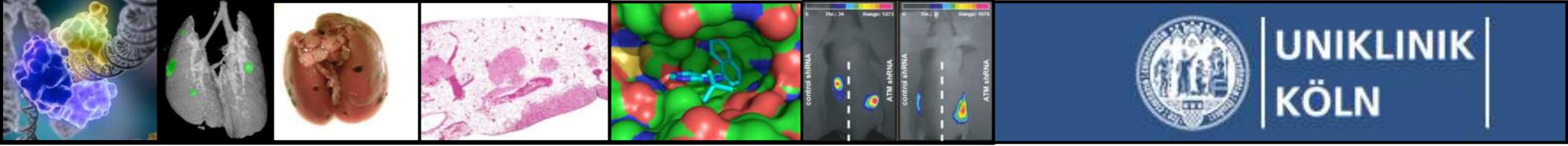
B. Weinberg identifies H-Ras^{V12} - the first human oncogene (1980)



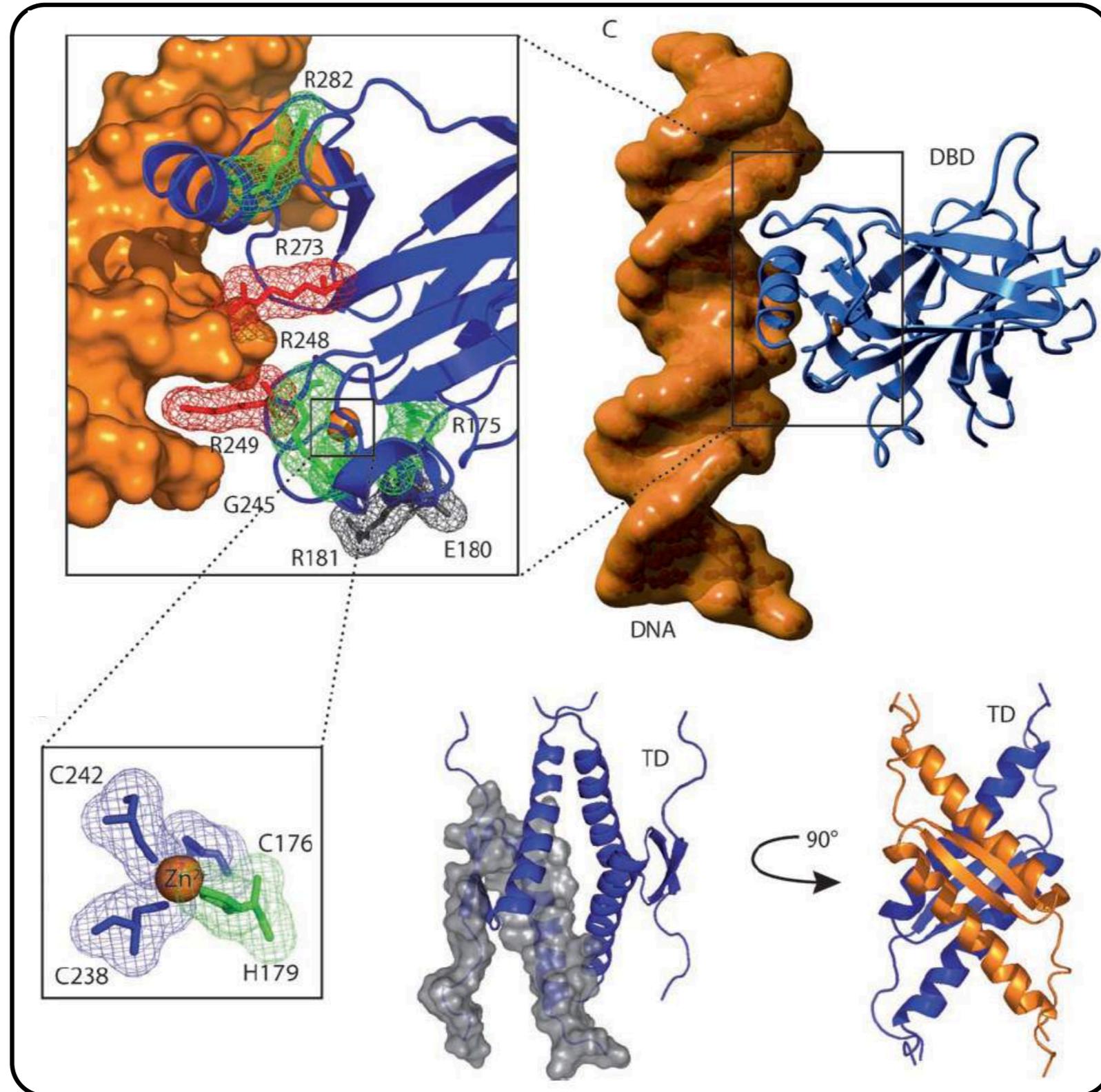


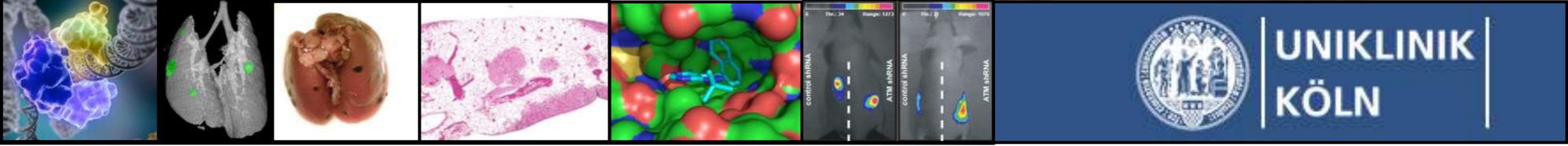
A. Levine findet p53 - das Onkogen, das keines war (1979-89)





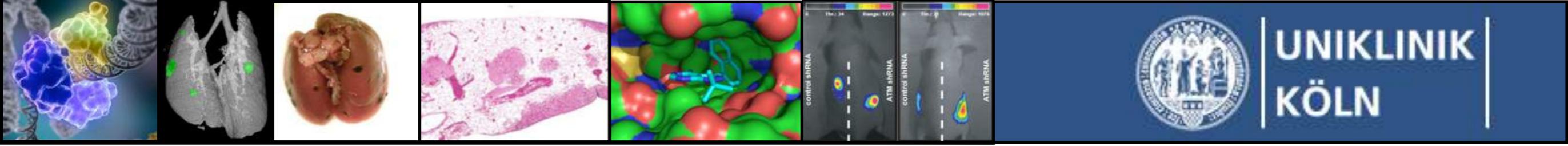
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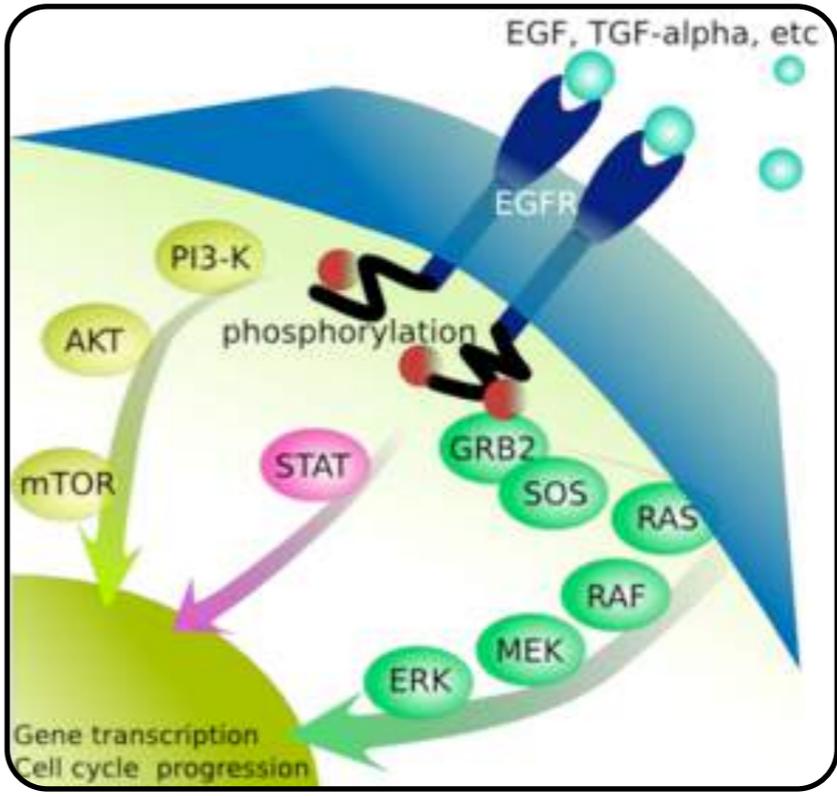
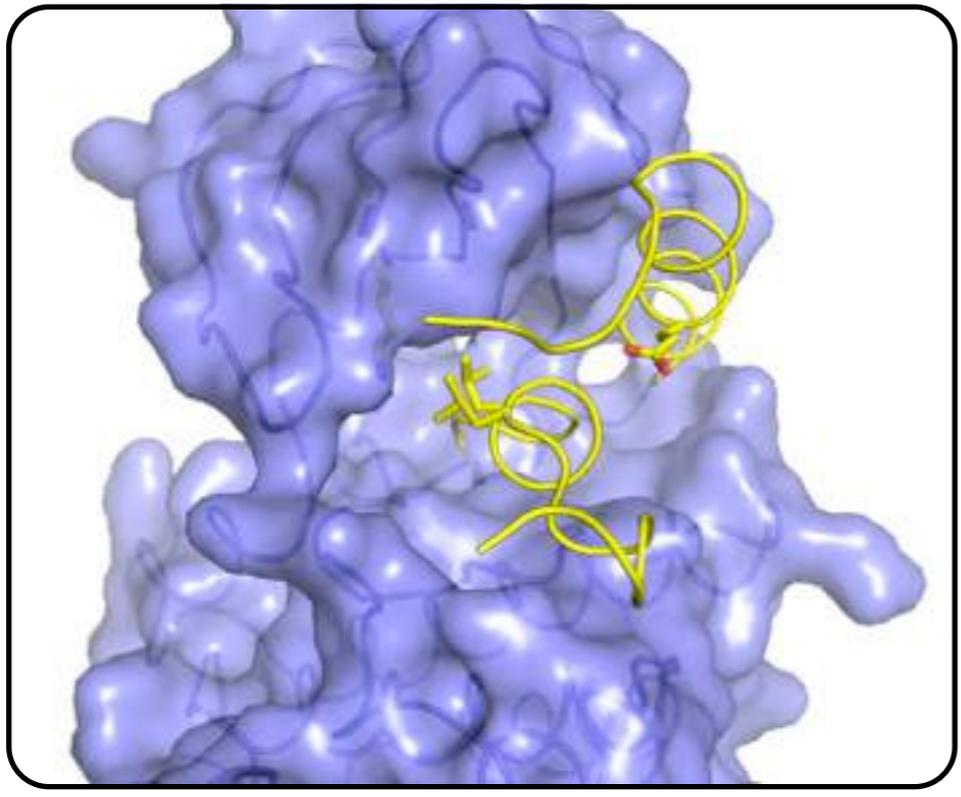
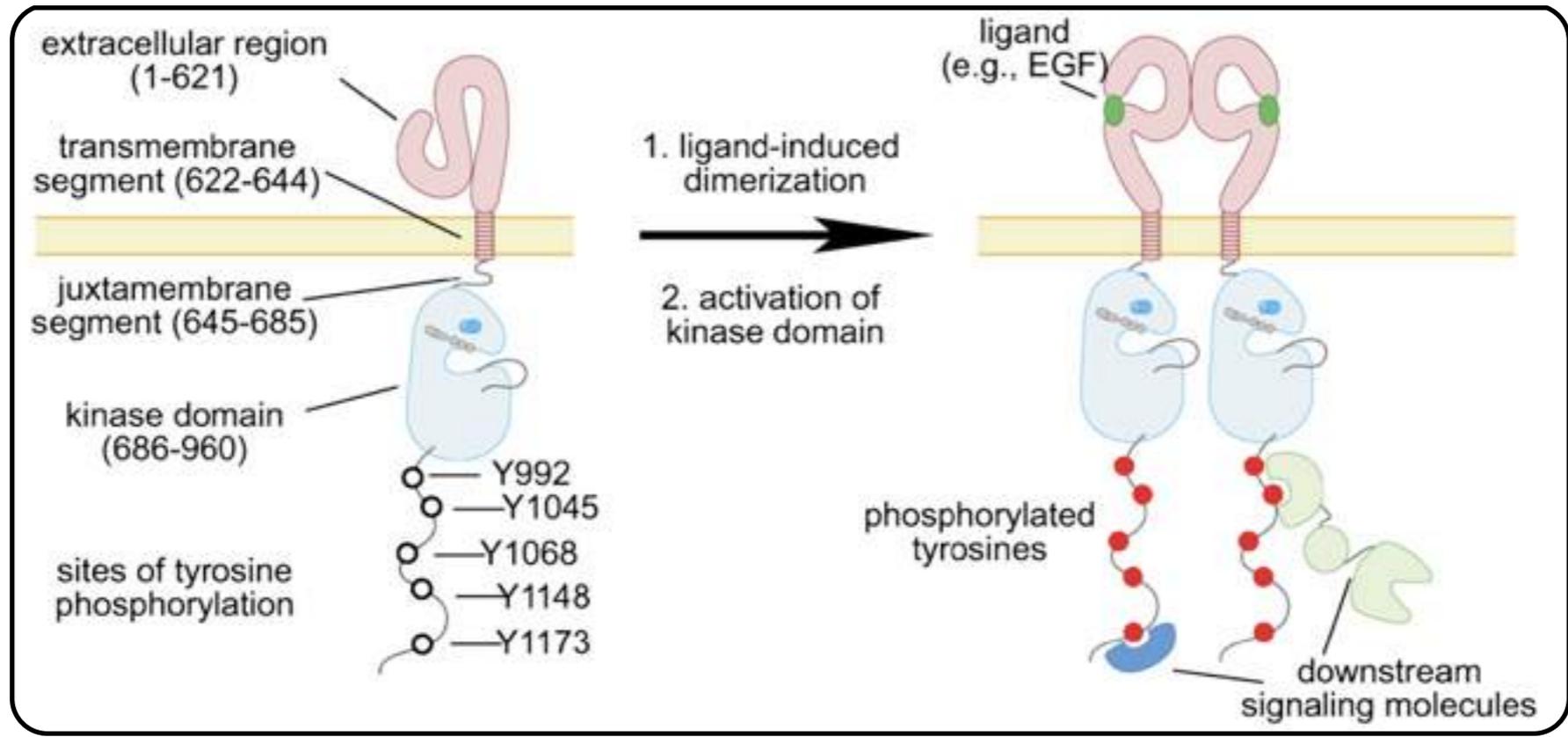


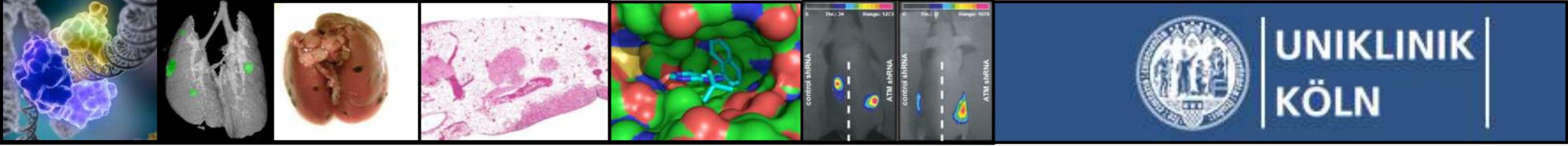
Cancer is a collection of genetic diseases

TEL-JAK2 FGF2 EGFR Akt1 H-Ras Akt ErbB1 FGF1 Cyclin Emet
 FGF2 NF1 BCR/Abi ELK2 BRCA1 BRCA2 Abi MLH1 p57^{KIP}
 jun Bcl2 XPG Grb1 Ras ELK2 BRCA1 BRCA2 Abi MLH1 NF2 p15
 ets1 L-Ras p14ARF Cdk4 p16 p15 p19 p21 p27 p31 p35 p37 p39 p53 p57^{KIP} p63 p65 p70 p73 p75 p79 p80 p85 p87 p90 p95 p101 p105 p107 p109 p115 p116 p118 p119 p125 p127 p130 p135 p137 p139 p140 p143 p145 p147 p149 p150 p151 p155 p157 p159 p160 p161 p164 p165 p167 p169 p170 p171 p173 p175 p177 p179 p180 p181 p182 p183 p184 p185 p186 p187 p188 p189 p190 p191 p192 p193 p194 p195 p196 p197 p198 p199 p200 p201 p202 p203 p204 p205 p206 p207 p208 p209 p210 p211 p212 p213 p214 p215 p216 p217 p218 p219 p220 p221 p222 p223 p224 p225 p226 p227 p228 p229 p230 p231 p232 p233 p234 p235 p236 p237 p238 p239 p240 p241 p242 p243 p244 p245 p246 p247 p248 p249 p250 p251 p252 p253 p254 p255 p256 p257 p258 p259 p260 p261 p262 p263 p264 p265 p266 p267 p268 p269 p270 p271 p272 p273 p274 p275 p276 p277 p278 p279 p280 p281 p282 p283 p284 p285 p286 p287 p288 p289 p290 p291 p292 p293 p294 p295 p296 p297 p298 p299 p300 p301 p302 p303 p304 p305 p306 p307 p308 p309 p310 p311 p312 p313 p314 p315 p316 p317 p318 p319 p320 p321 p322 p323 p324 p325 p326 p327 p328 p329 p330 p331 p332 p333 p334 p335 p336 p337 p338 p339 p340 p341 p342 p343 p344 p345 p346 p347 p348 p349 p350 p351 p352 p353 p354 p355 p356 p357 p358 p359 p360 p361 p362 p363 p364 p365 p366 p367 p368 p369 p370 p371 p372 p373 p374 p375 p376 p377 p378 p379 p380 p381 p382 p383 p384 p385 p386 p387 p388 p389 p390 p391 p392 p393 p394 p395 p396 p397 p398 p399 p400 p401 p402 p403 p404 p405 p406 p407 p408 p409 p410 p411 p412 p413 p414 p415 p416 p417 p418 p419 p420 p421 p422 p423 p424 p425 p426 p427 p428 p429 p430 p431 p432 p433 p434 p435 p436 p437 p438 p439 p440 p441 p442 p443 p444 p445 p446 p447 p448 p449 p450 p451 p452 p453 p454 p455 p456 p457 p458 p459 p460 p461 p462 p463 p464 p465 p466 p467 p468 p469 p470 p471 p472 p473 p474 p475 p476 p477 p478 p479 p480 p481 p482 p483 p484 p485 p486 p487 p488 p489 p490 p491 p492 p493 p494 p495 p496 p497 p498 p499 p500 p501 p502 p503 p504 p505 p506 p507 p508 p509 p510 p511 p512 p513 p514 p515 p516 p517 p518 p519 p520 p521 p522 p523 p524 p525 p526 p527 p528 p529 p530 p531 p532 p533 p534 p535 p536 p537 p538 p539 p540 p541 p542 p543 p544 p545 p546 p547 p548 p549 p550 p551 p552 p553 p554 p555 p556 p557 p558 p559 p560 p561 p562 p563 p564 p565 p566 p567 p568 p569 p570 p571 p572 p573 p574 p575 p576 p577 p578 p579 p580 p581 p582 p583 p584 p585 p586 p587 p588 p589 p590 p591 p592 p593 p594 p595 p596 p597 p598 p599 p600 p601 p602 p603 p604 p605 p606 p607 p608 p609 p610 p611 p612 p613 p614 p615 p616 p617 p618 p619 p620 p621 p622 p623 p624 p625 p626 p627 p628 p629 p630 p631 p632 p633 p634 p635 p636 p637 p638 p639 p640 p641 p642 p643 p644 p645 p646 p647 p648 p649 p650 p651 p652 p653 p654 p655 p656 p657 p658 p659 p660 p661 p662 p663 p664 p665 p666 p667 p668 p669 p670 p671 p672 p673 p674 p675 p676 p677 p678 p679 p680 p681 p682 p683 p684 p685 p686 p687 p688 p689 p690 p691 p692 p693 p694 p695 p696 p697 p698 p699 p700 p701 p702 p703 p704 p705 p706 p707 p708 p709 p710 p711 p712 p713 p714 p715 p716 p717 p718 p719 p720 p721 p722 p723 p724 p725 p726 p727 p728 p729 p730 p731 p732 p733 p734 p735 p736 p737 p738 p739 p740 p741 p742 p743 p744 p745 p746 p747 p748 p749 p750 p751 p752 p753 p754 p755 p756 p757 p758 p759 p760 p761 p762 p763 p764 p765 p766 p767 p768 p769 p770 p771 p772 p773 p774 p775 p776 p777 p778 p779 p780 p781 p782 p783 p784 p785 p786 p787 p788 p789 p790 p791 p792 p793 p794 p795 p796 p797 p798 p799 p800 p801 p802 p803 p804 p805 p806 p807 p808 p809 p810 p811 p812 p813 p814 p815 p816 p817 p818 p819 p820 p821 p822 p823 p824 p825 p826 p827 p828 p829 p830 p831 p832 p833 p834 p835 p836 p837 p838 p839 p840 p841 p842 p843 p844 p845 p846 p847 p848 p849 p850 p851 p852 p853 p854 p855 p856 p857 p858 p859 p860 p861 p862 p863 p864 p865 p866 p867 p868 p869 p870 p871 p872 p873 p874 p875 p876 p877 p878 p879 p880 p881 p882 p883 p884 p885 p886 p887 p888 p889 p890 p891 p892 p893 p894 p895 p896 p897 p898 p899 p900 p901 p902 p903 p904 p905 p906 p907 p908 p909 p910 p911 p912 p913 p914 p915 p916 p917 p918 p919 p920 p921 p922 p923 p924 p925 p926 p927 p928 p929 p930 p931 p932 p933 p934 p935 p936 p937 p938 p939 p940 p941 p942 p943 p944 p945 p946 p947 p948 p949 p950 p951 p952 p953 p954 p955 p956 p957 p958 p959 p960 p961 p962 p963 p964 p965 p966 p967 p968 p969 p970 p971 p972 p973 p974 p975 p976 p977 p978 p979 p980 p981 p982 p983 p984 p985 p986 p987 p988 p989 p990 p991 p992 p993 p994 p995 p996 p997 p998 p999

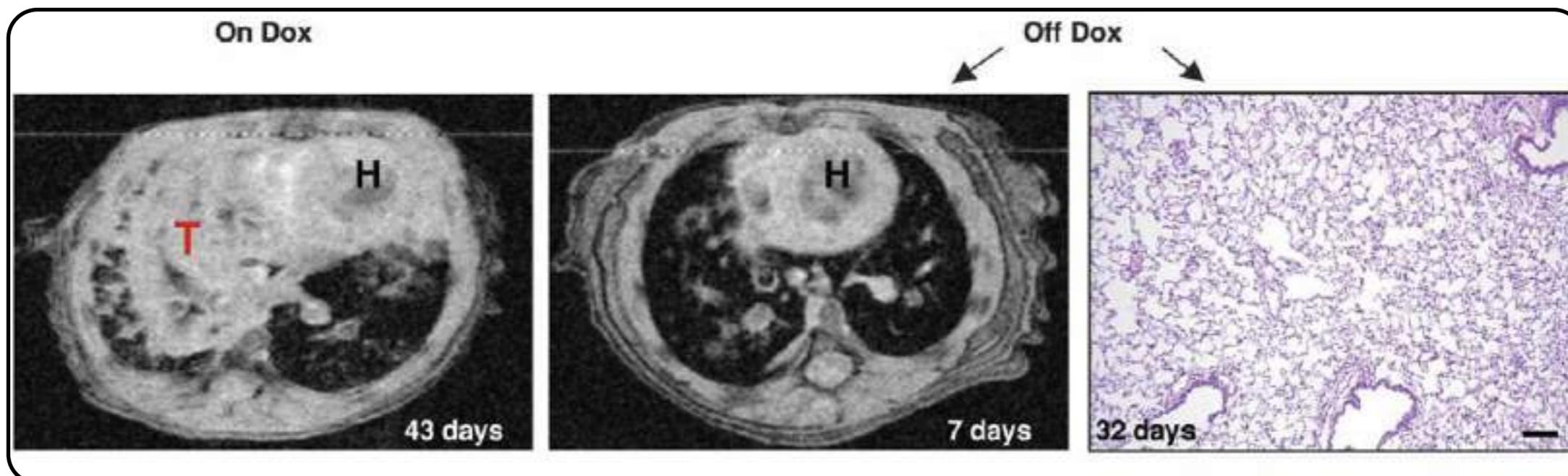
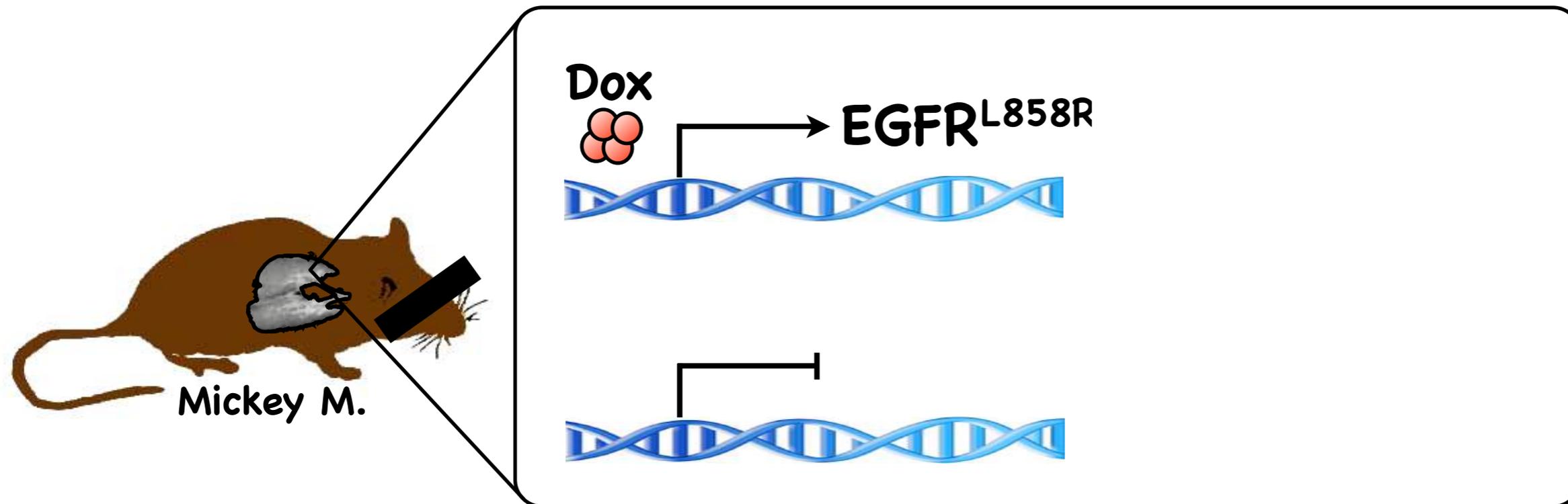


The biology of EGFR signaling



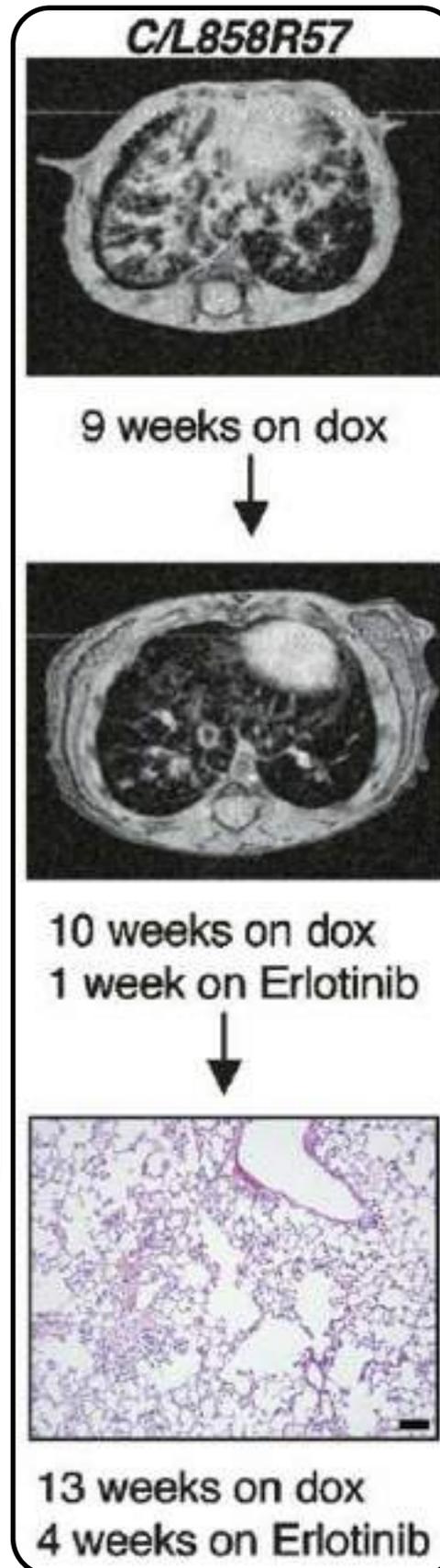
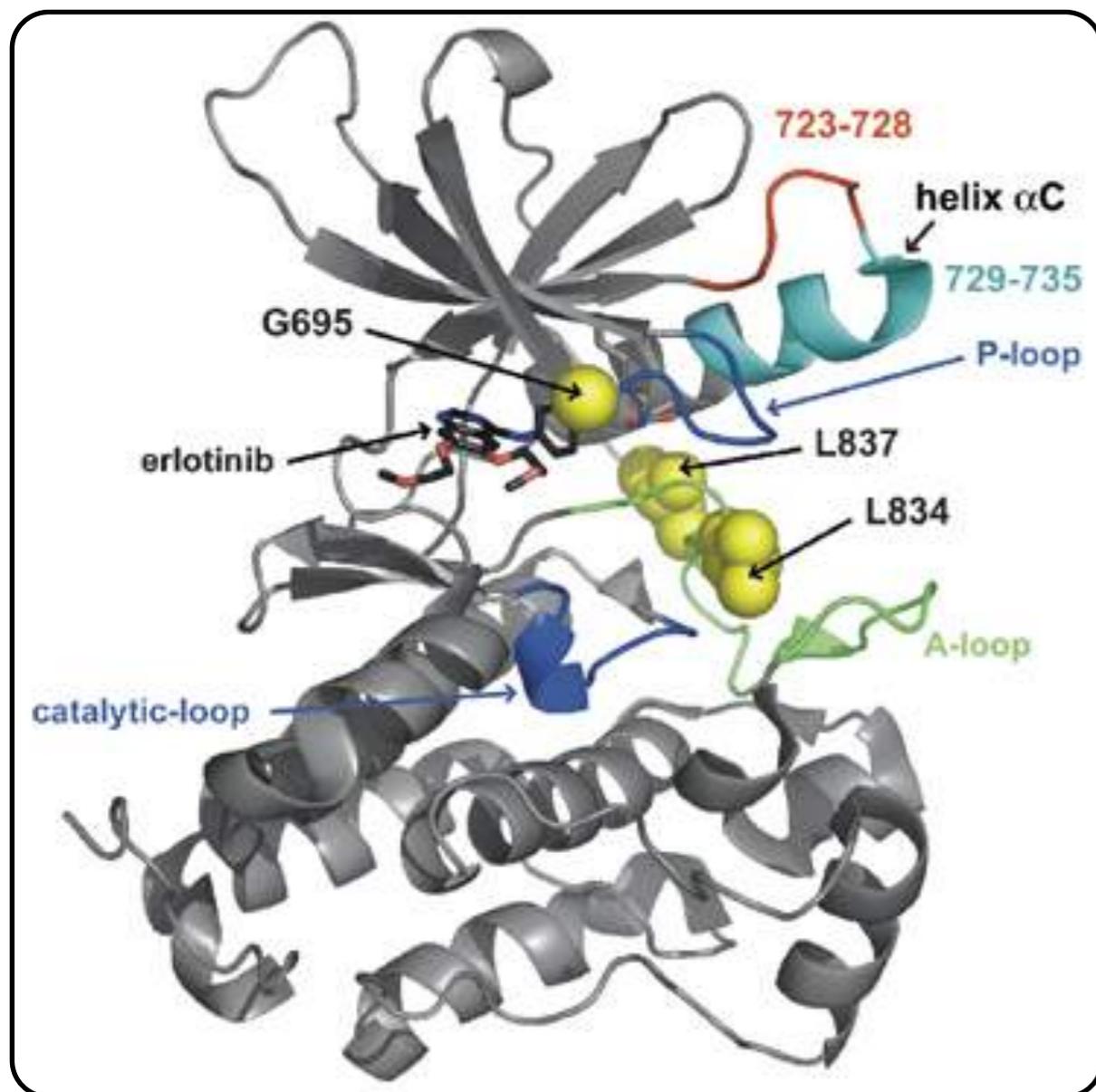


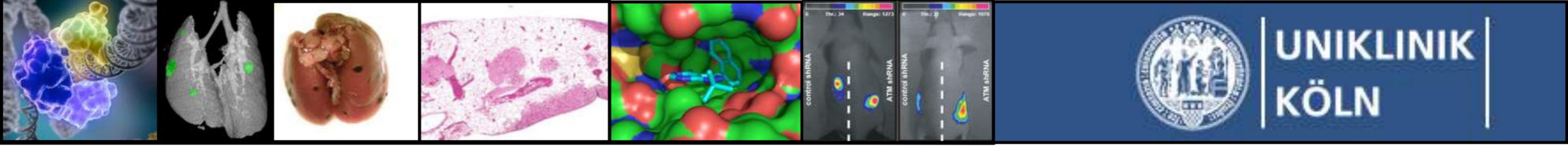
The human EGFR L858R mutant is oncogenic in mice



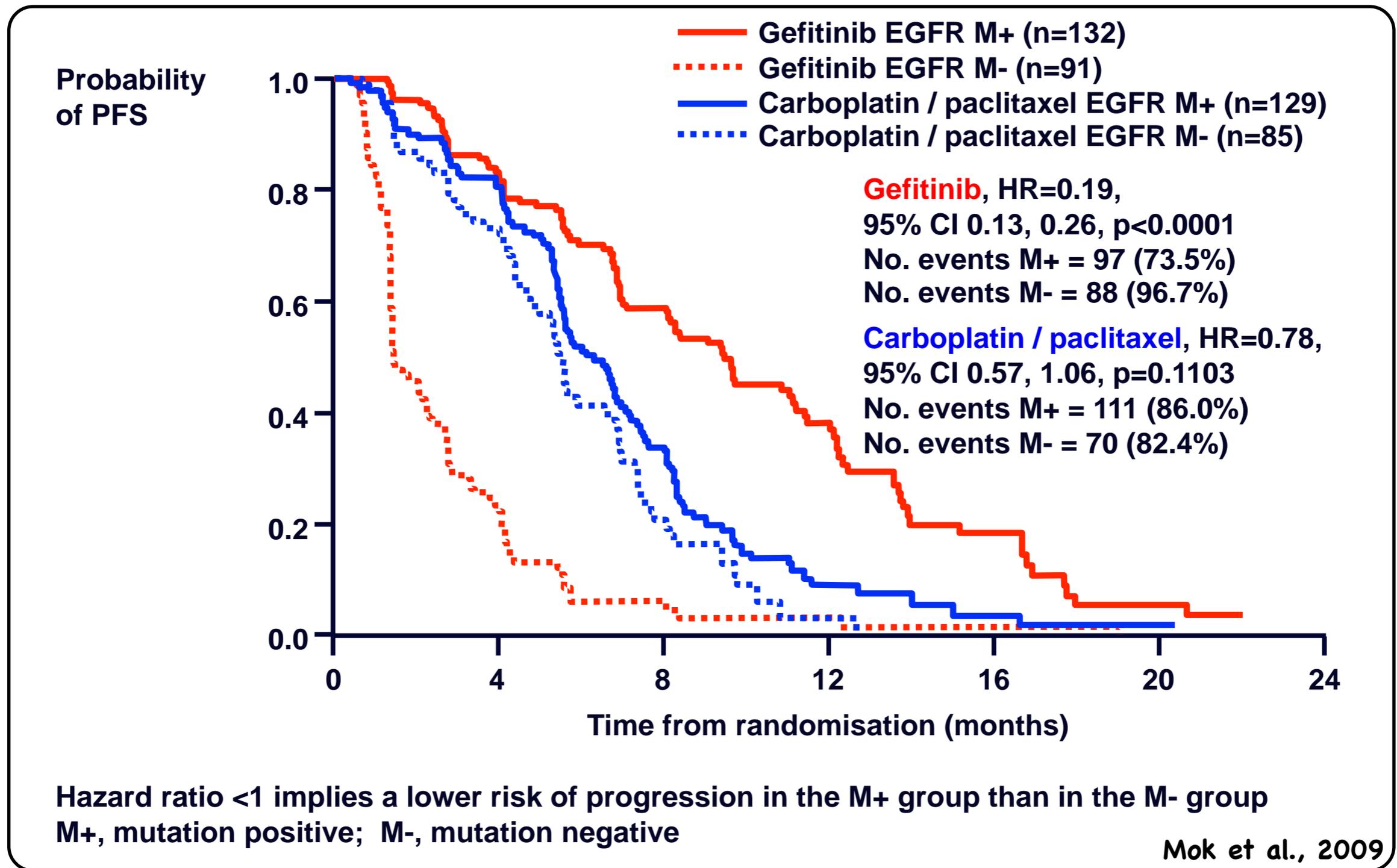
EGFR^{L858R} lung adenocarcinomas are oncogene-addicted!

EGFR-specific inhibitors are available



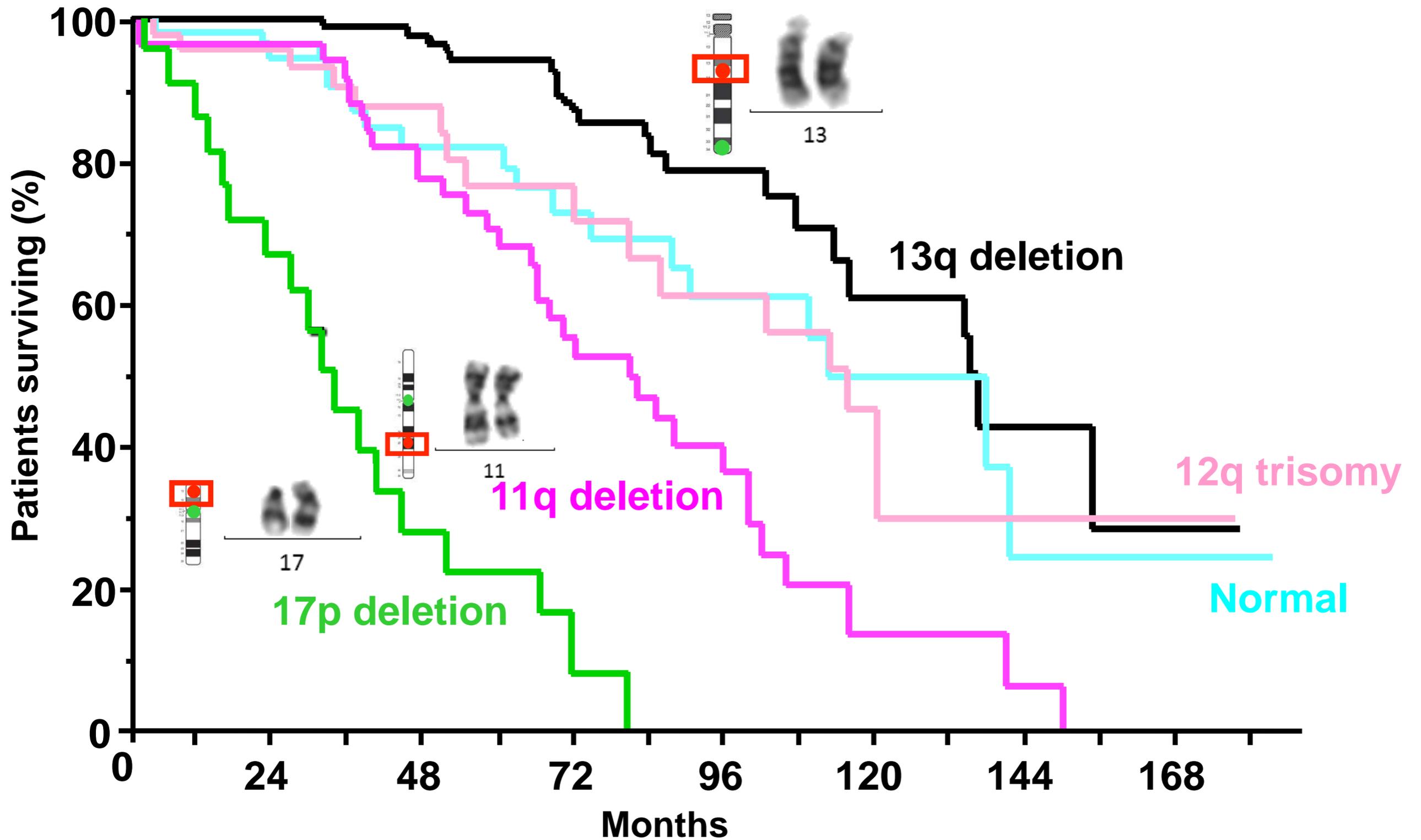


First line gefitinib outperforms standard carboplatin/ paclitaxel in EGFR mutant non-small cell lung cancer

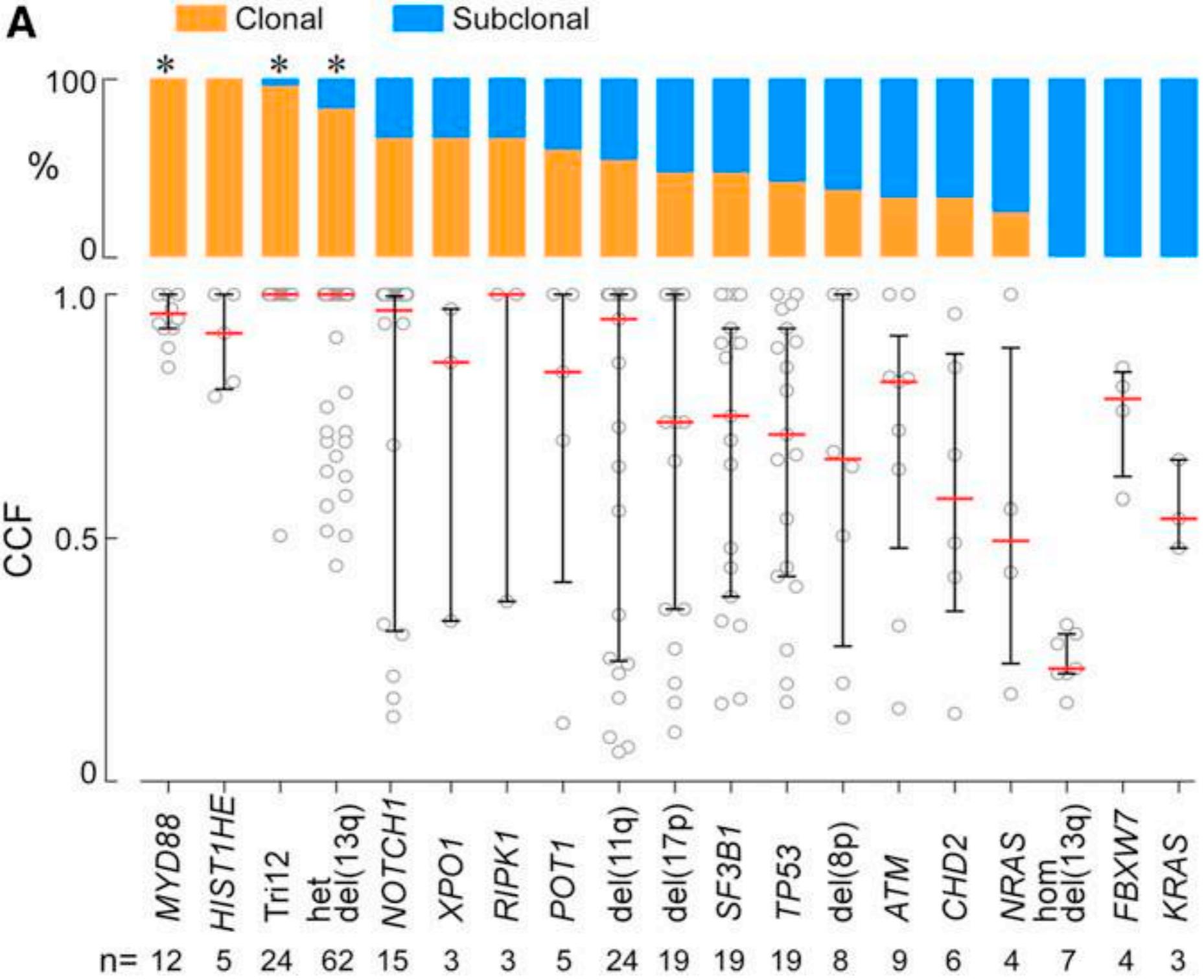


CLL is a genetic disease

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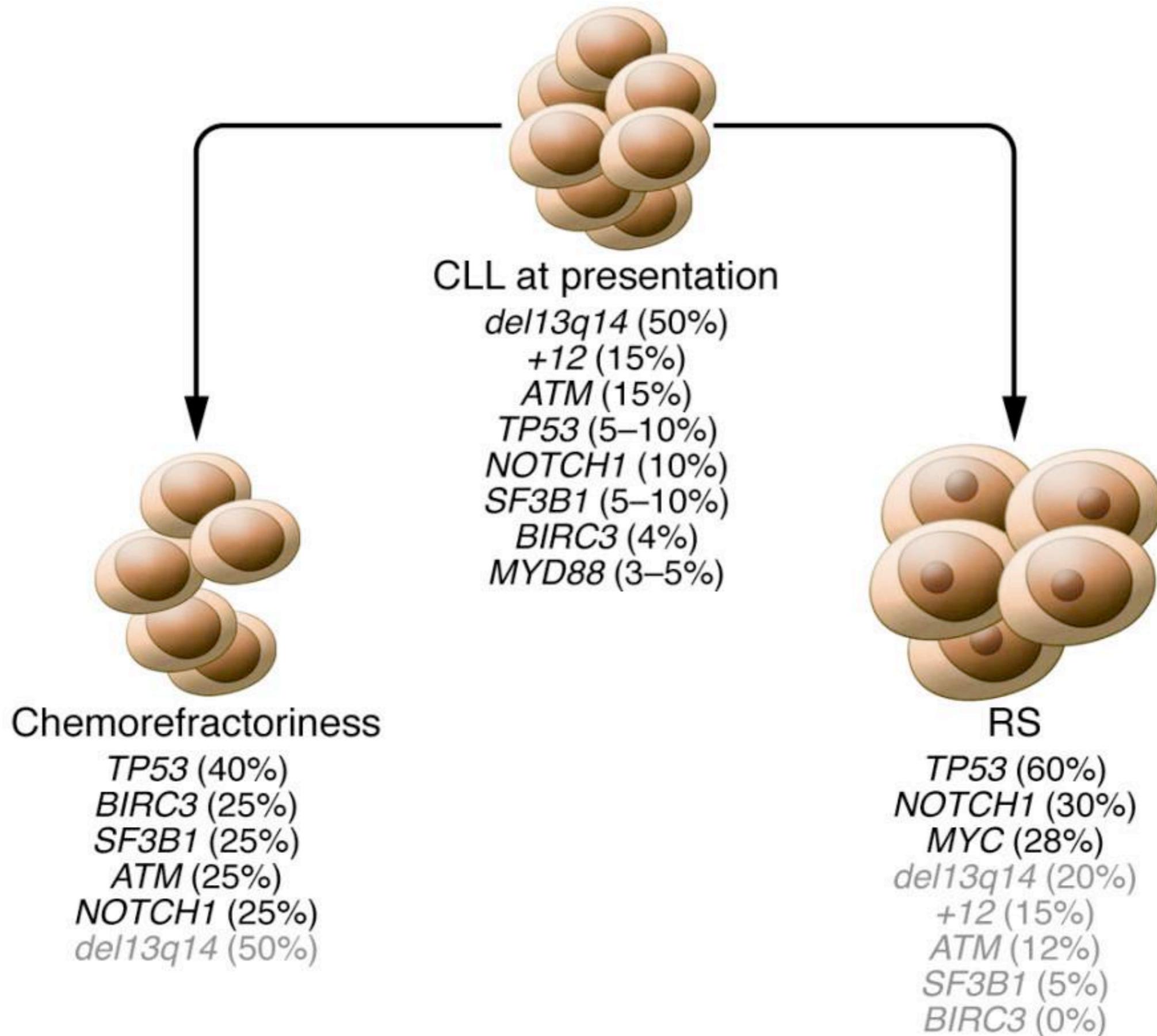


CLL genome sequencing reveals recurrent mutations

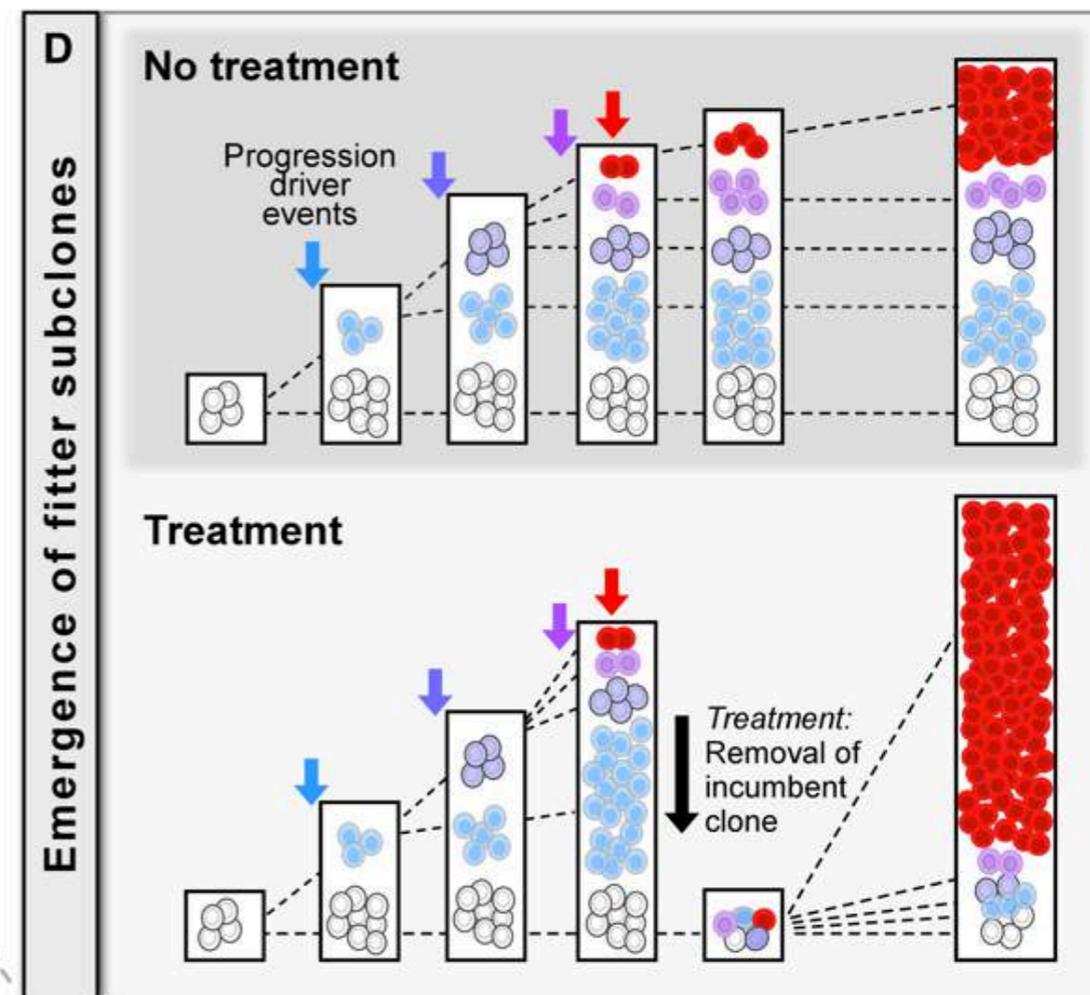
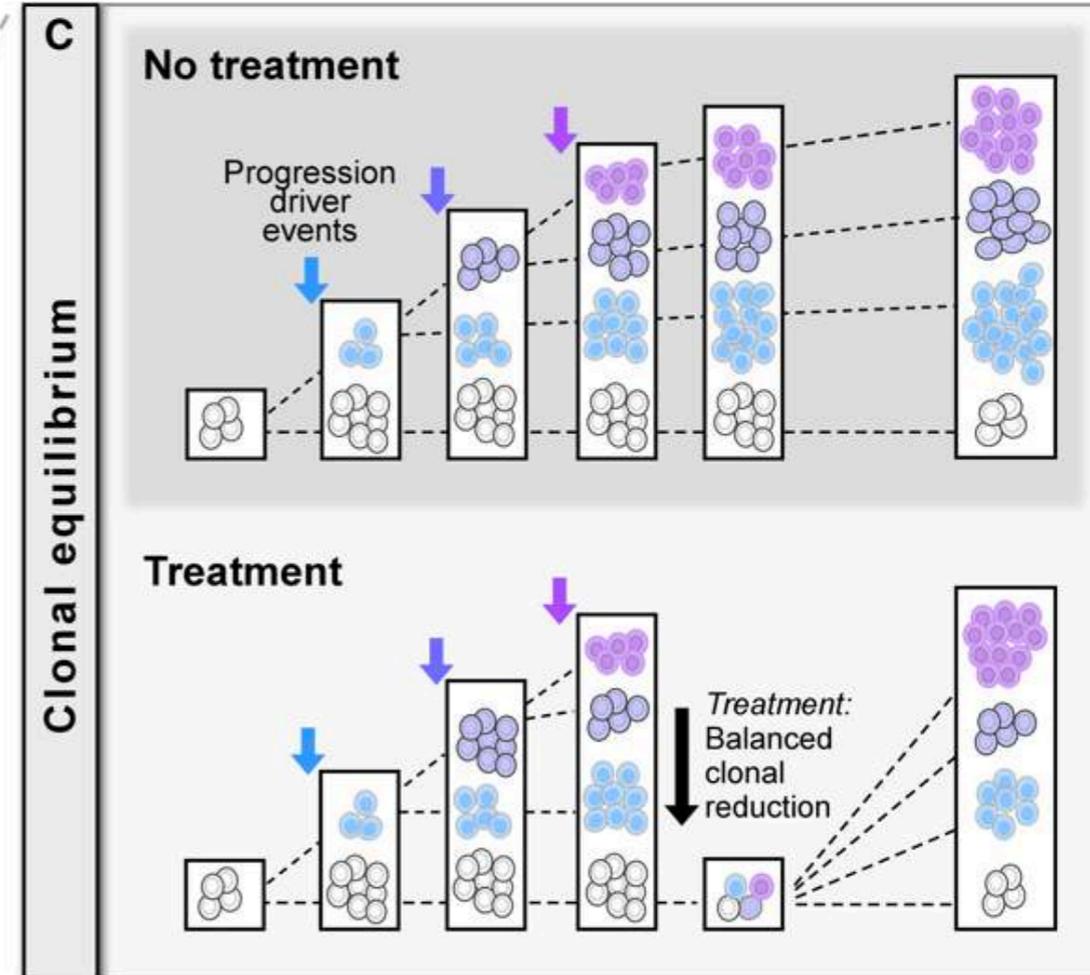
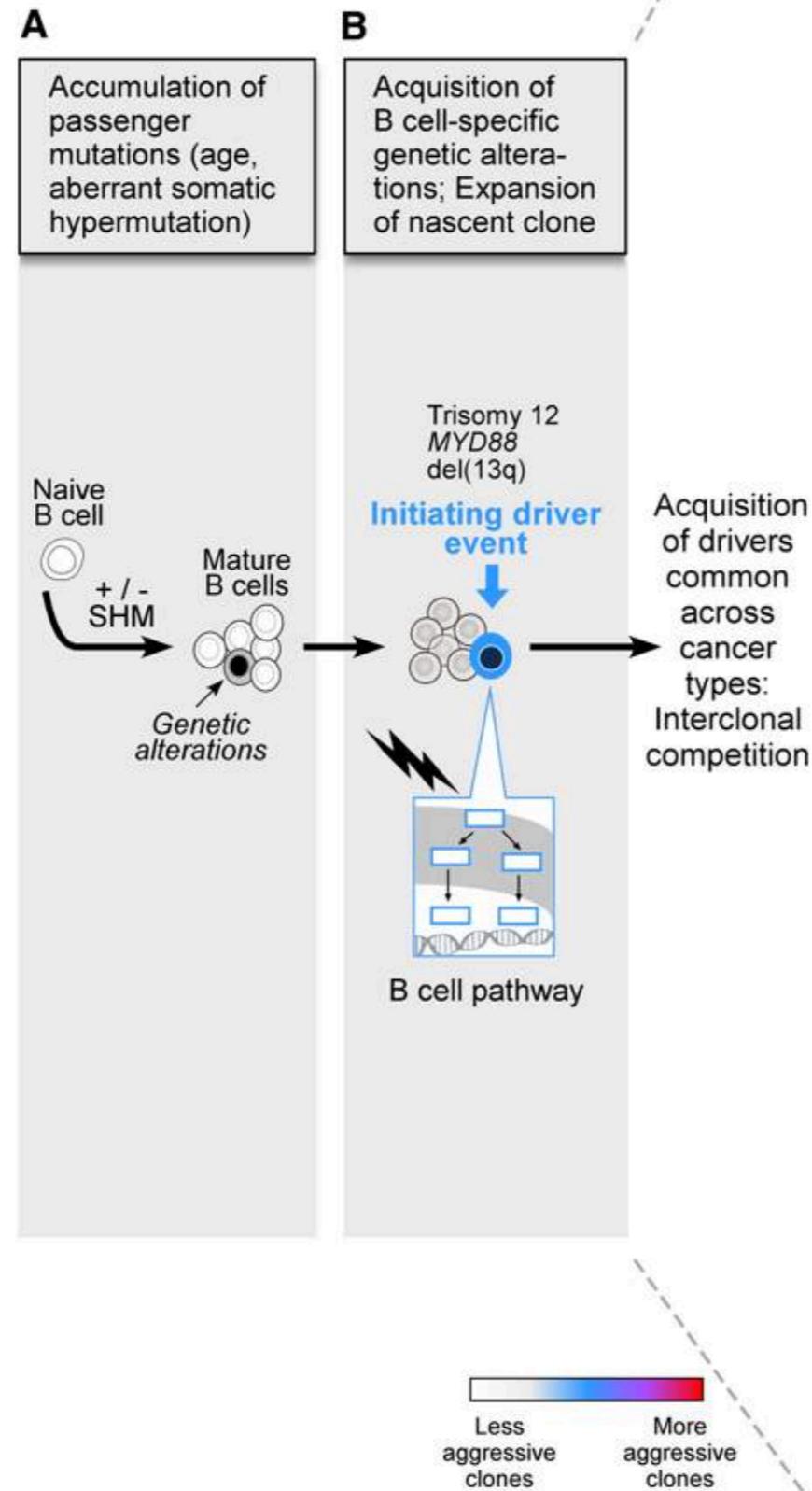


CLL is a dynamic disease and clonal evolution represents a clinical challenge

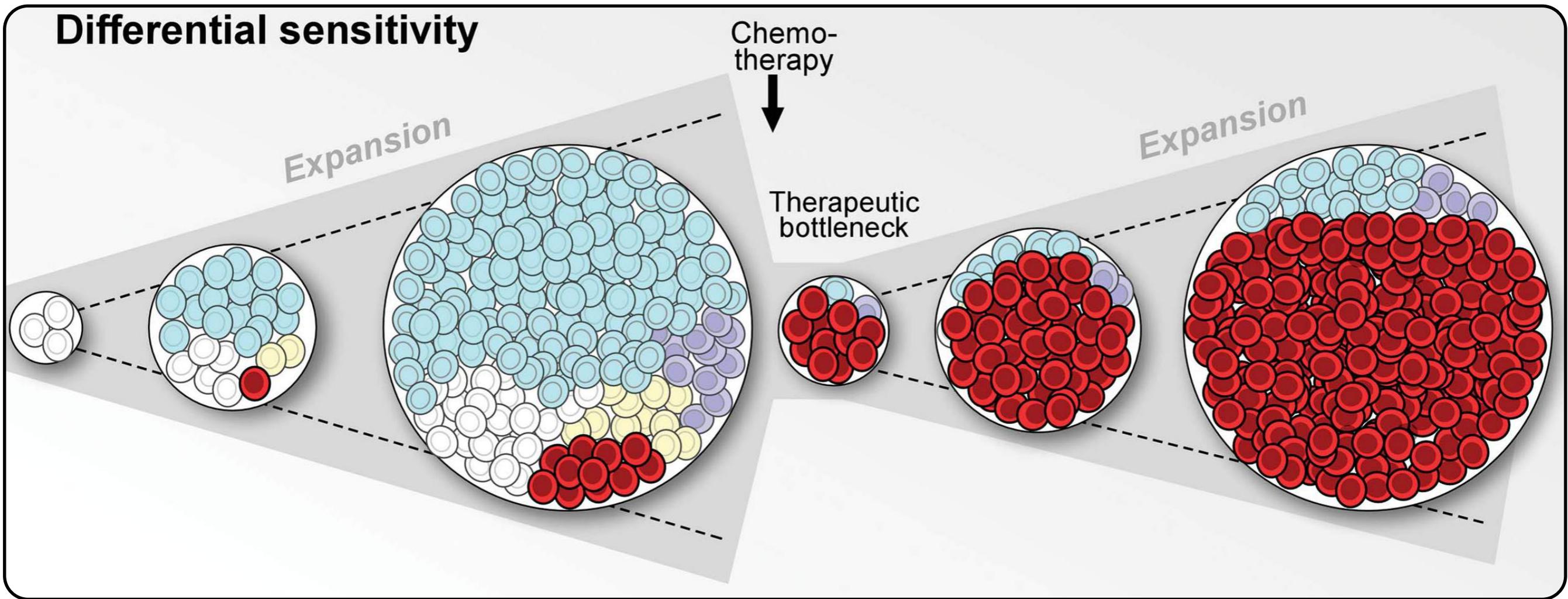
CLL clones can acquire additional genetic aberrations



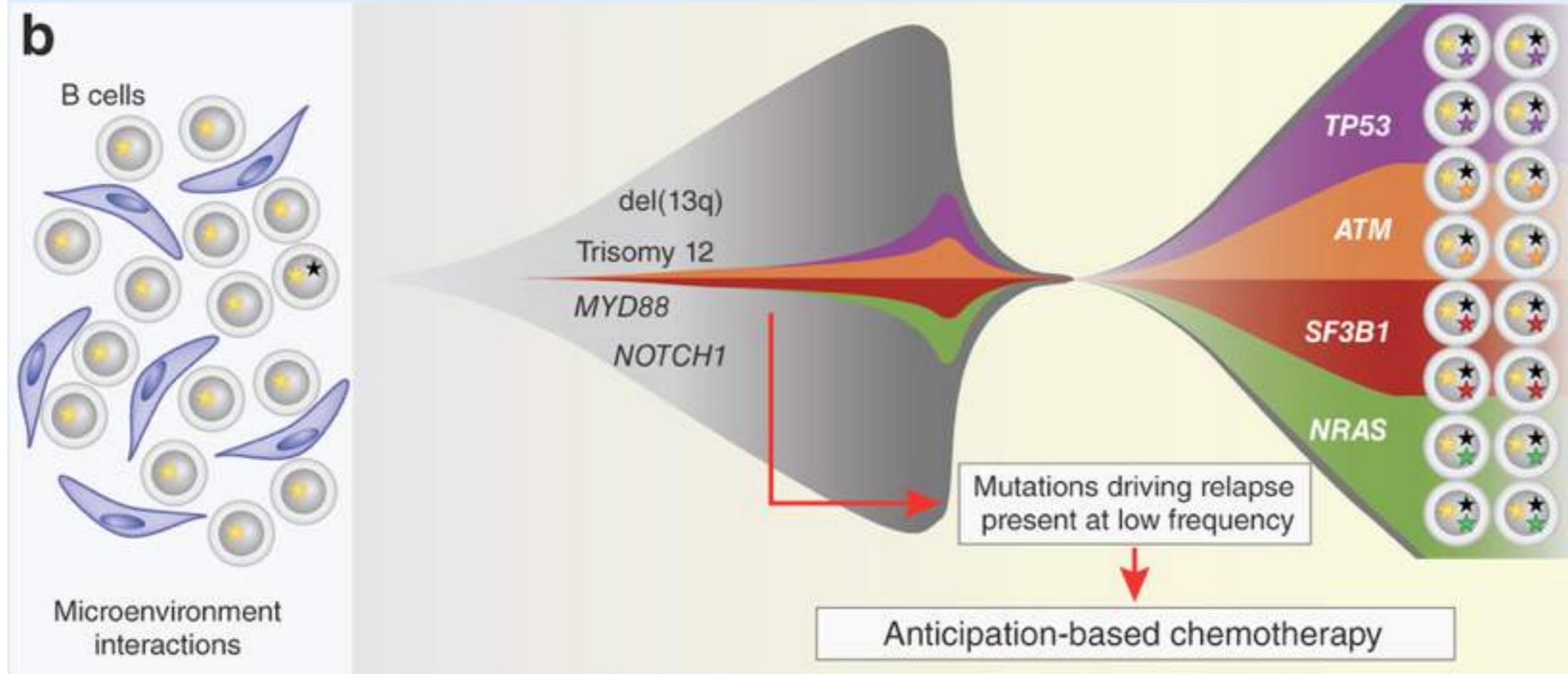
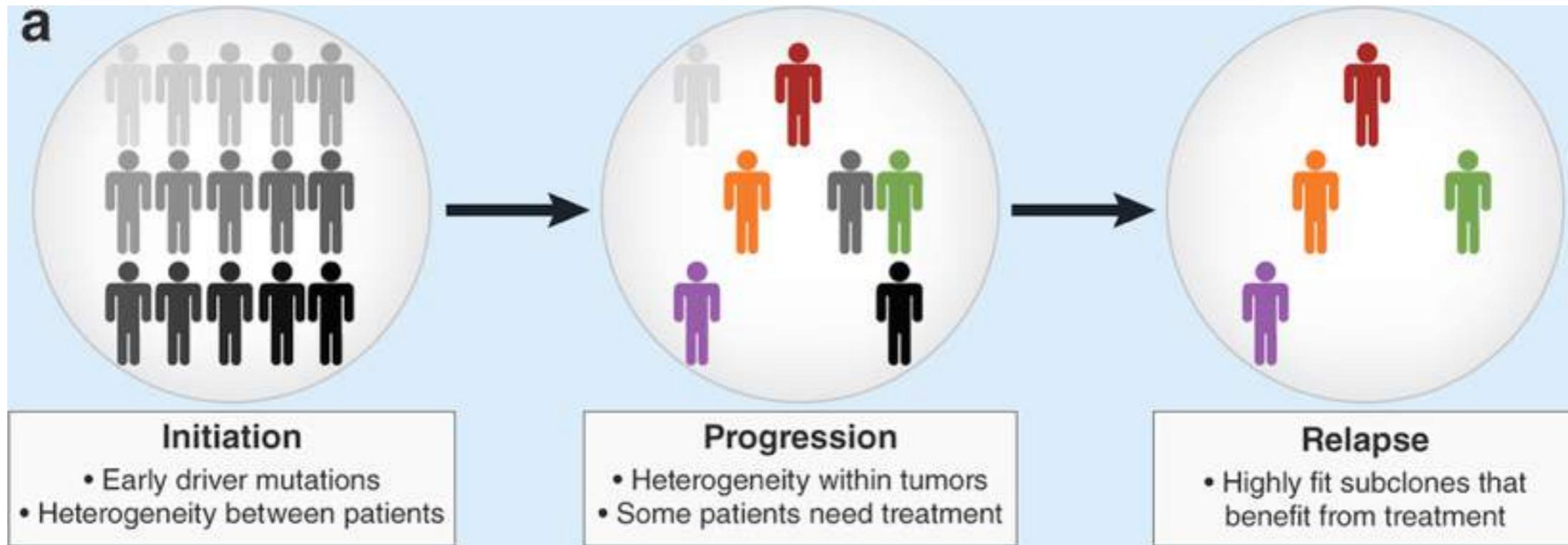
Therapeutic interventions shift the selective pressure



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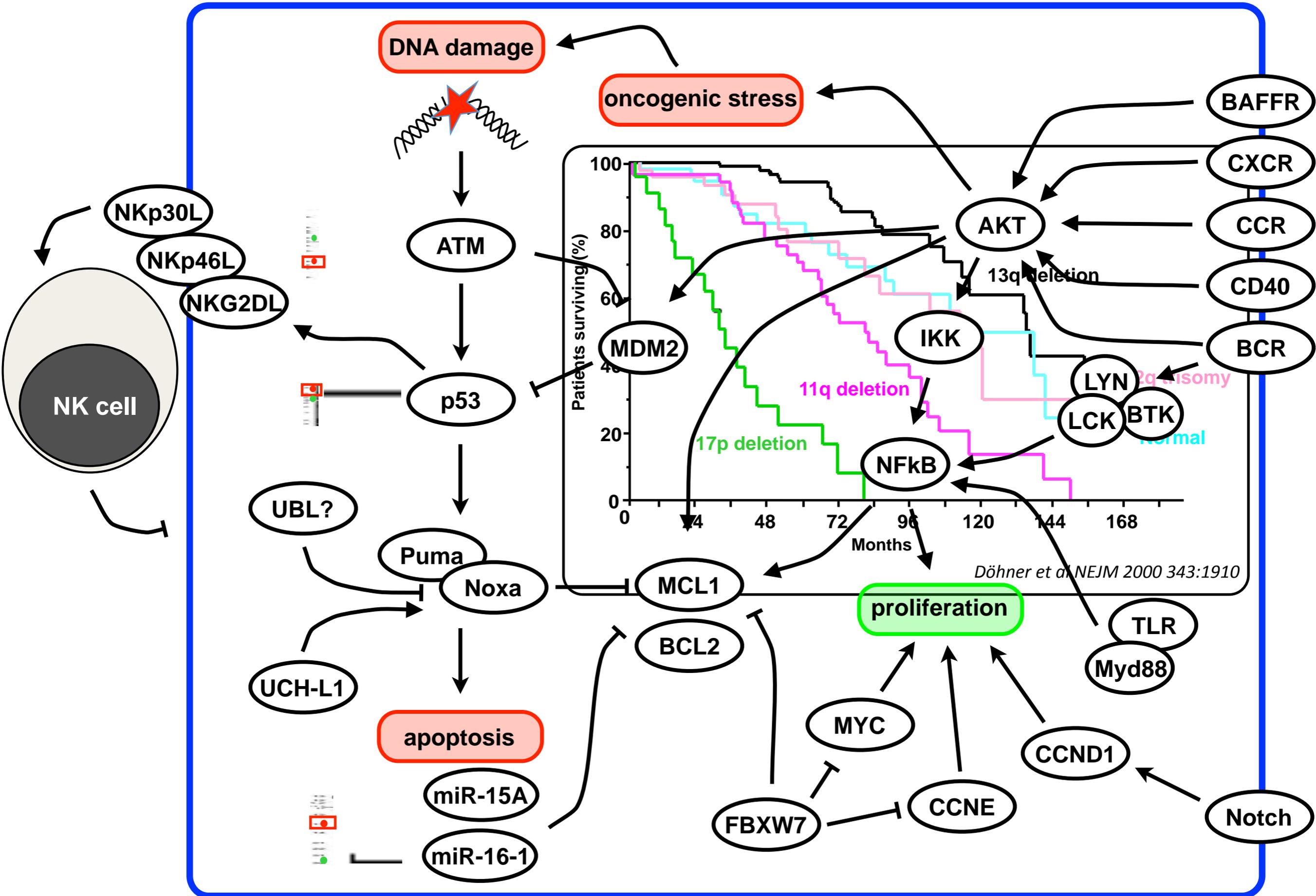


Multiple competing clones might exist in the same patient

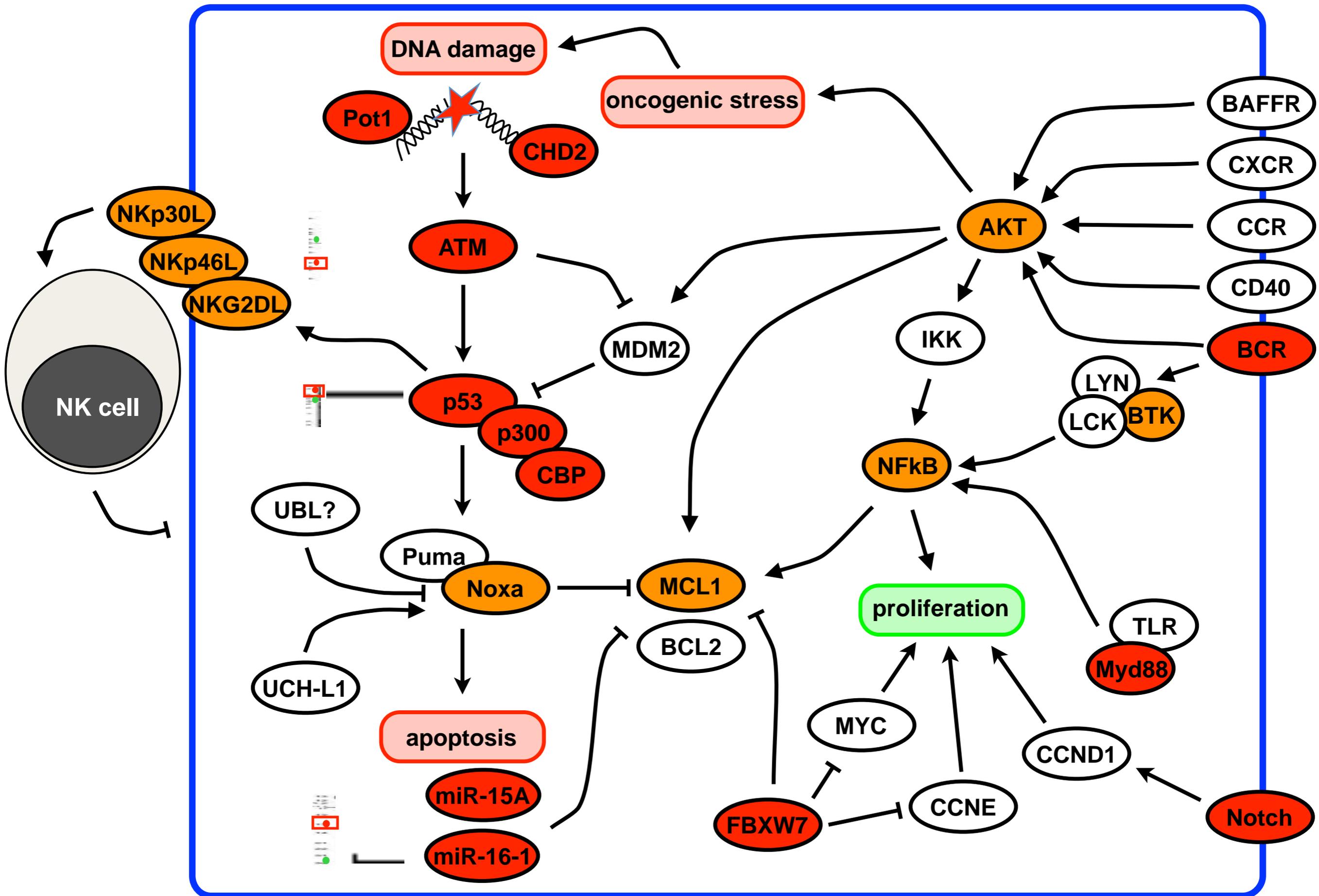


How do these mutations re-wire the intracellular signaling networks in CLL?

Genetic evidence for re-wired signaling in CLL

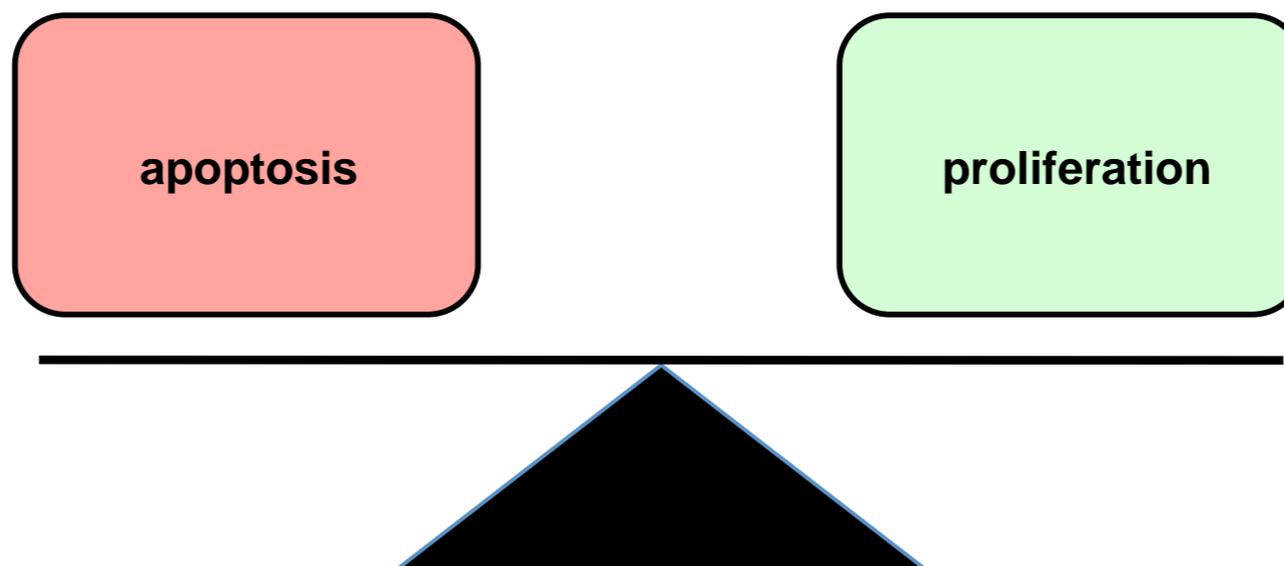
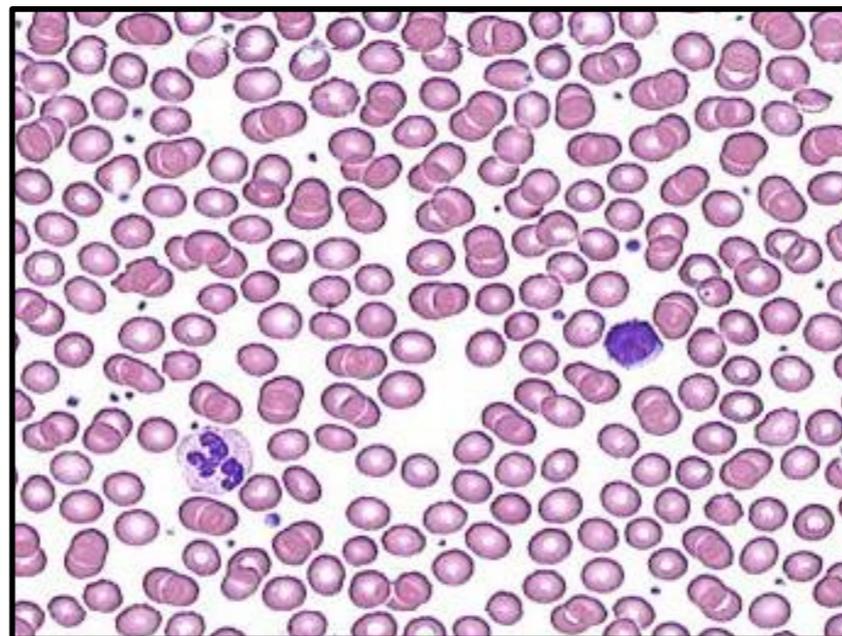


Genetic evidence for re-wired signaling in CLL



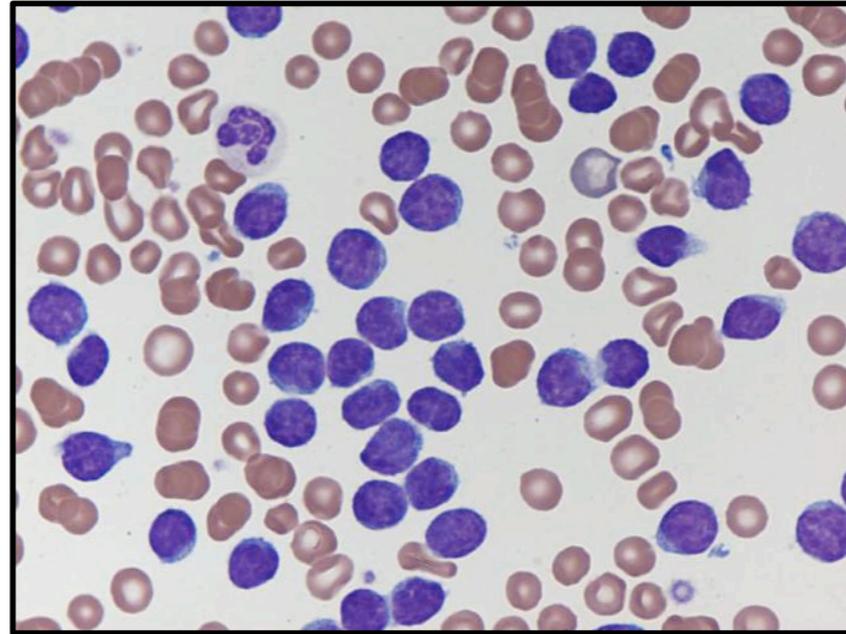


Genetic evidence for rewired signaling in CLL



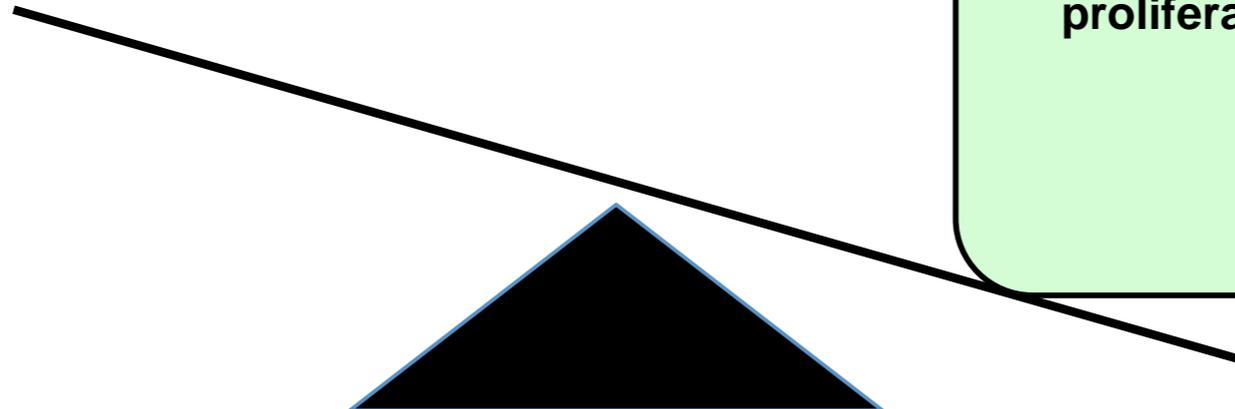


Imbalance of two competing groups of pathways



apoptosis

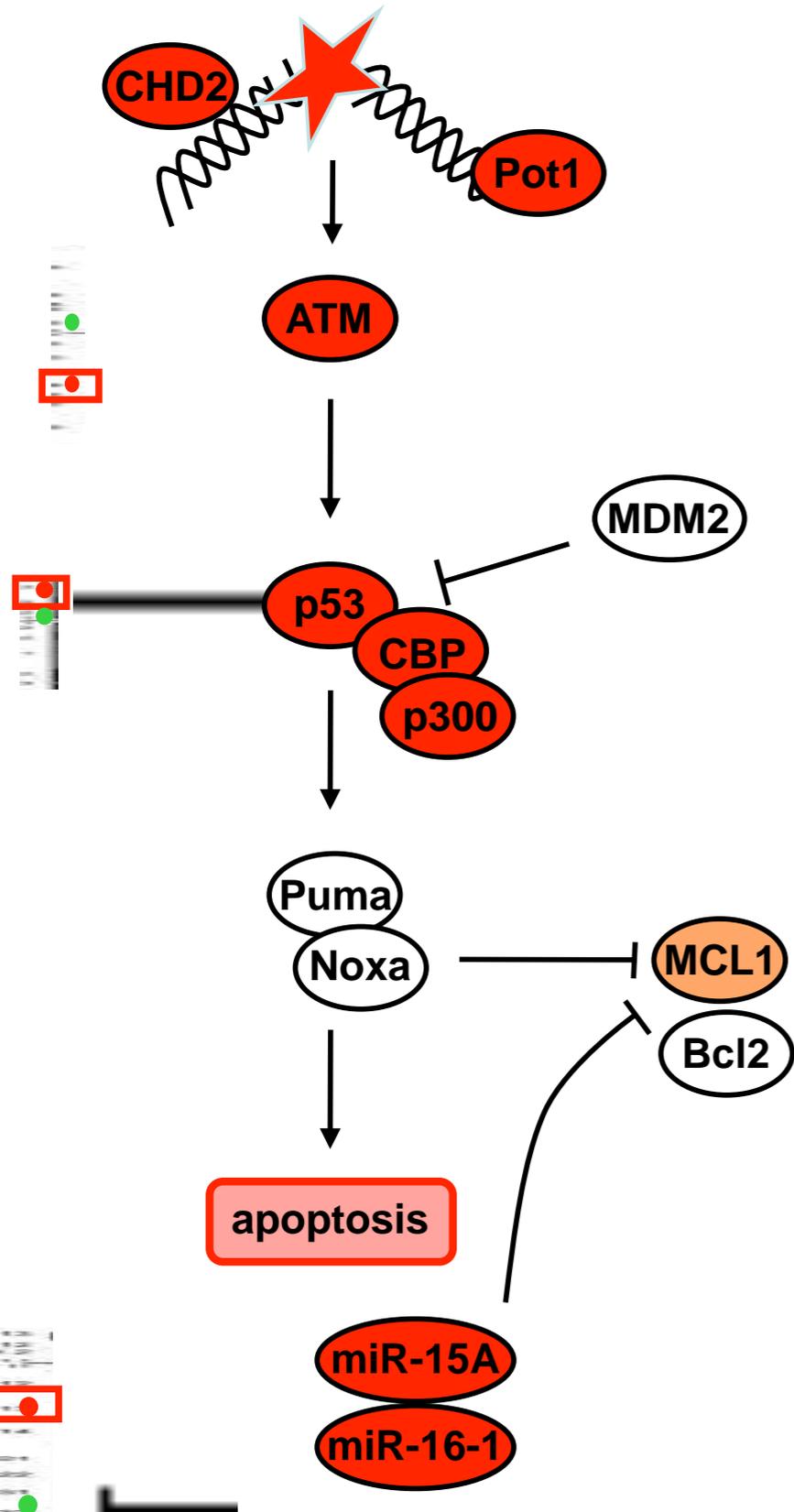
proliferation



The efforts of the CRU-286 are focused on developing novel, personalized therapeutic approaches for CLL patients



Three fundamentally distinct approaches have to be pursued to overcome this challenge



Approach I

Restoration of mutant tumor suppressor genes is currently not a viable option in CLL therapy.

Thus, molecular liabilities associated with these genetic lesions have to be identified and therapeutically exploited. (RP1, RP2, RP3)



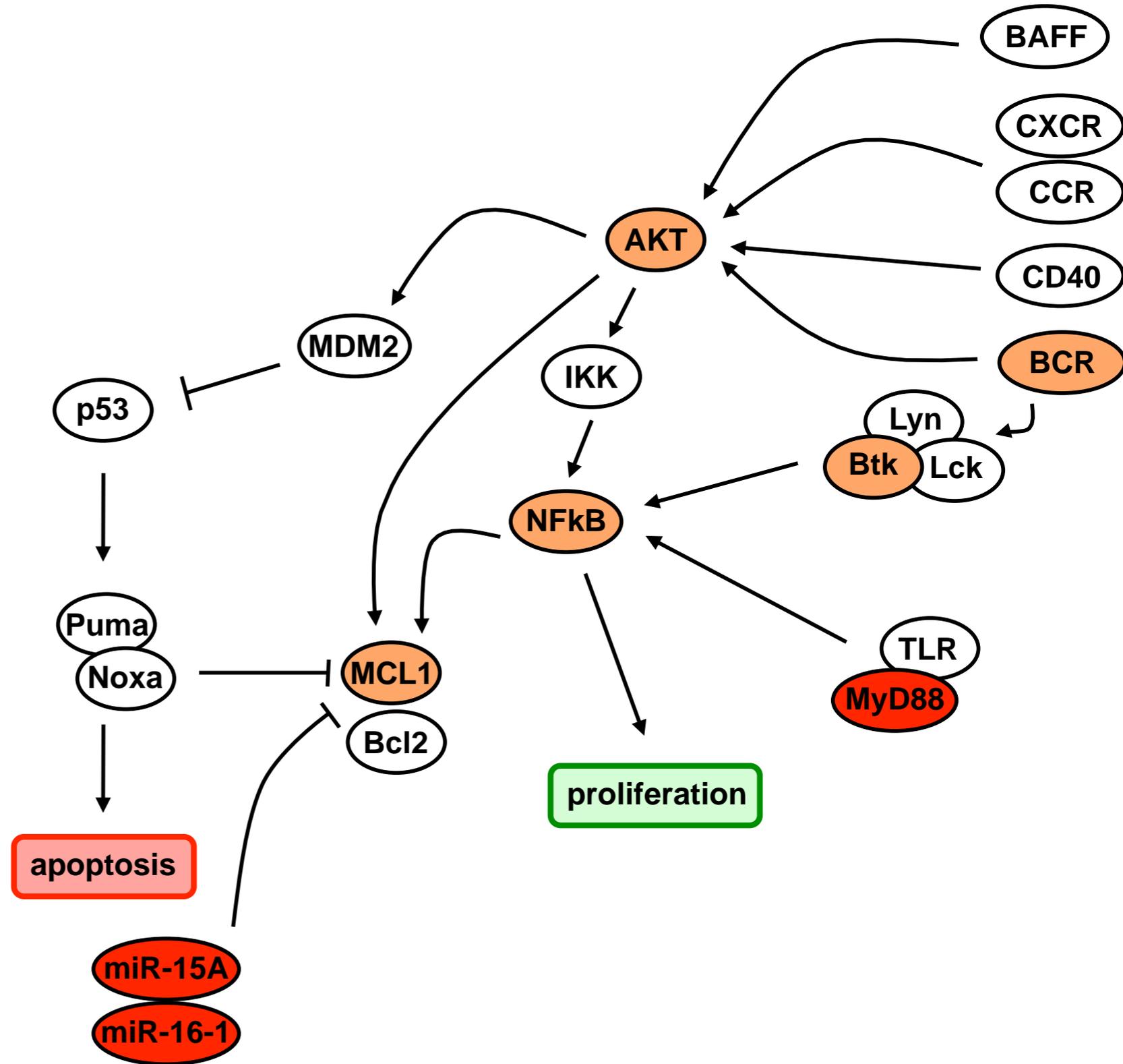
Three fundamentally distinct approaches have to be pursued to overcome this challenge

Approach II

Restoration of the pro-apoptotic DDR might be possible through pharmacologic intervention, if ATM and p53 are not mutated.

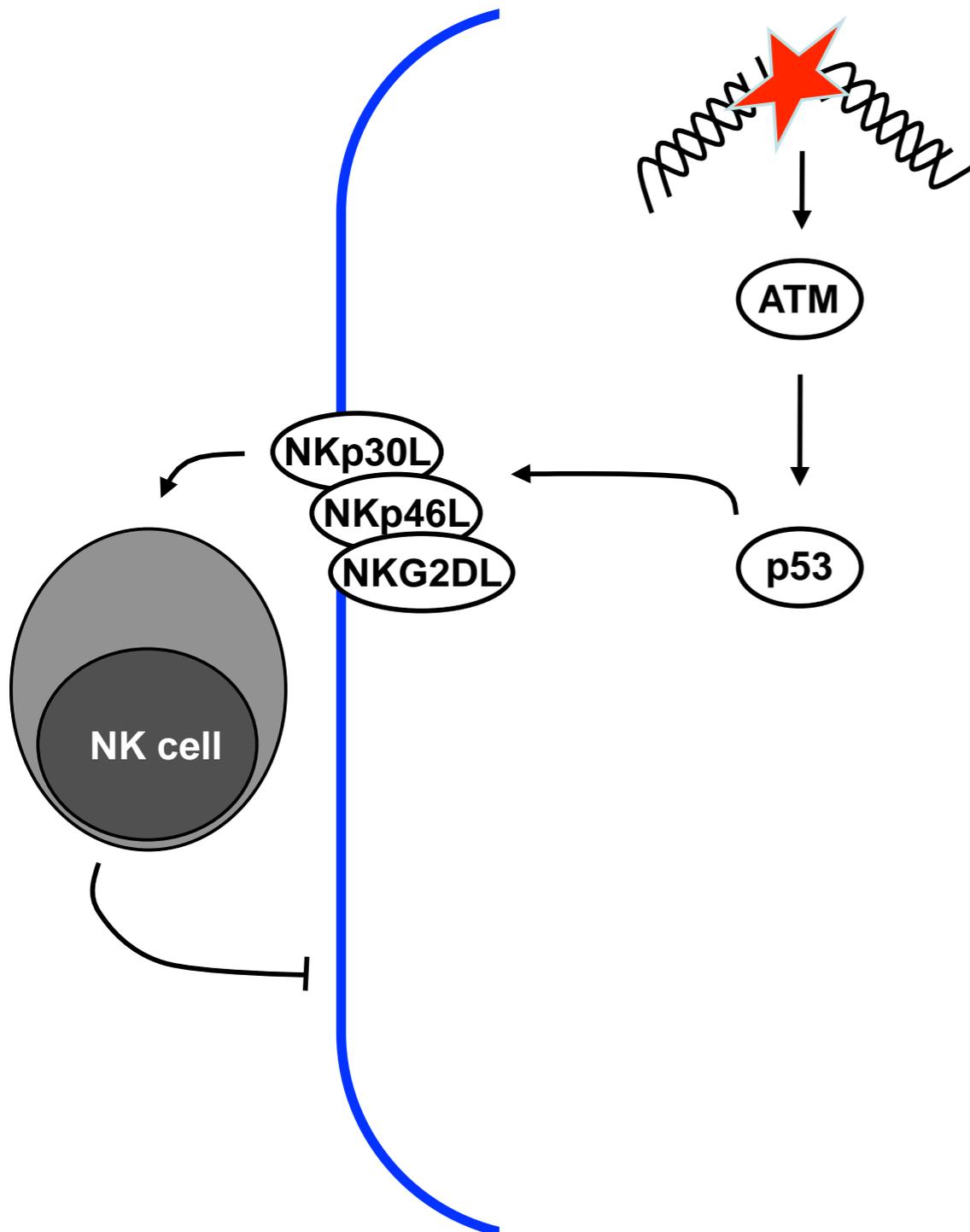
Thus, apoptosis repressive signaling cascades have to be identified and inhibited.

(RP5, RP6)





Three fundamentally distinct approaches have to be pursued to overcome this challenge



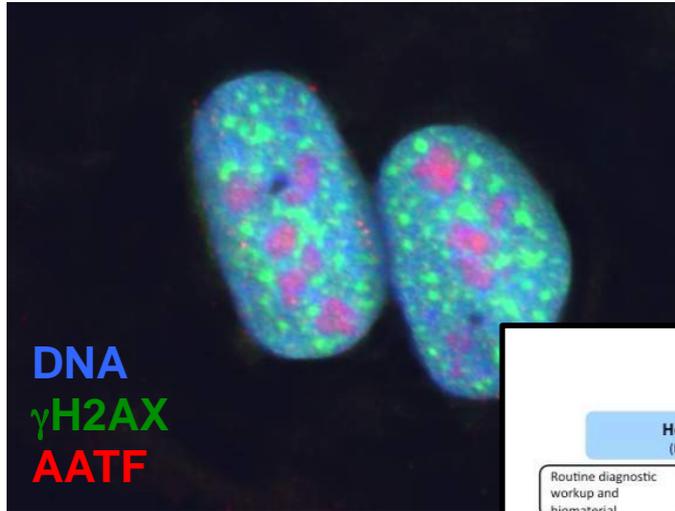
Approach III

DDR-mediated recognition of malignant cells through the immune system needs to be exploited for CLL treatment in the framework of combination immunotherapies to overcome uncontrolled survival signals (RP4, RP6).

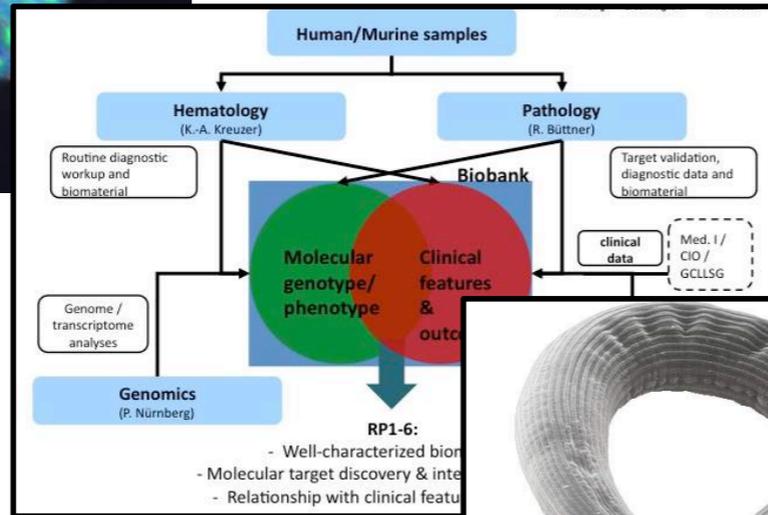


Unique strengths of this CRU

strong basic science

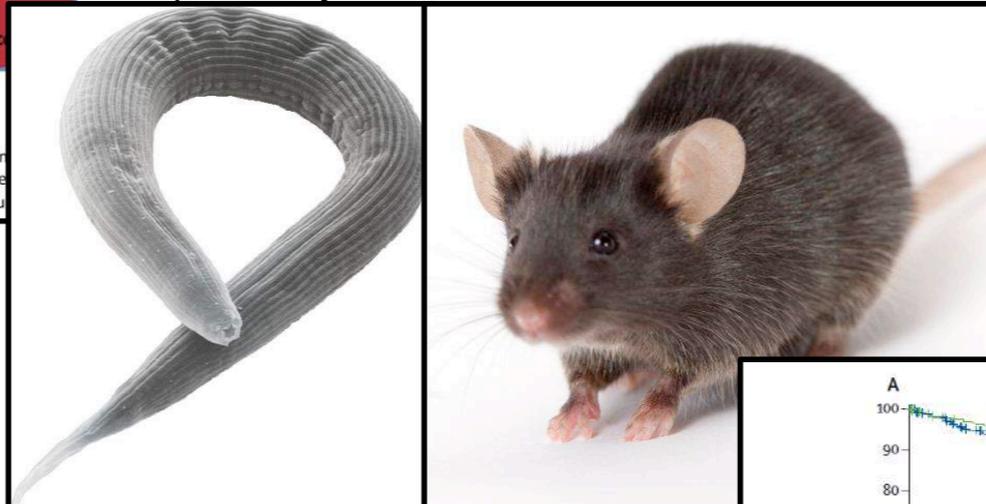


strong core support



CECAD

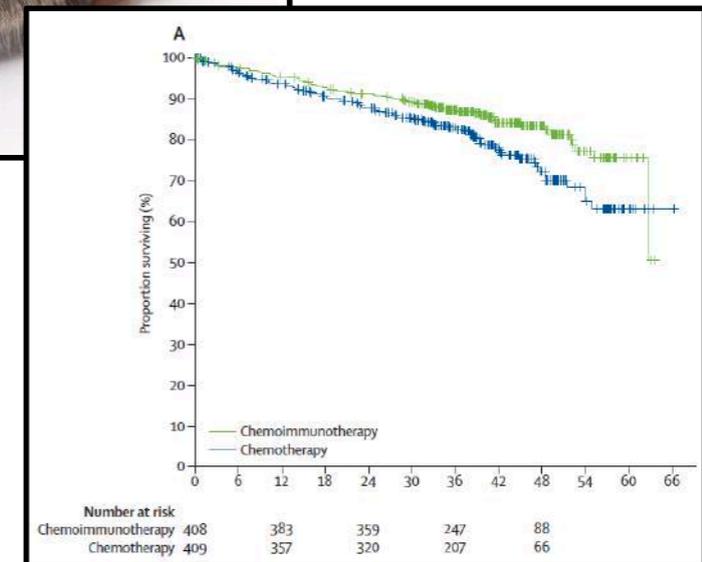
robust model systems



active clinical study group

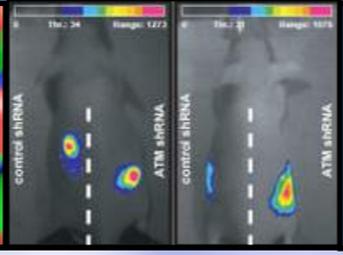
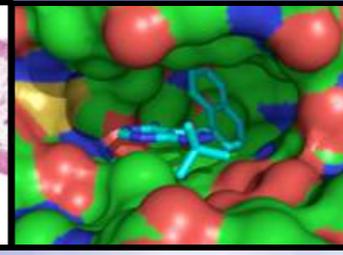
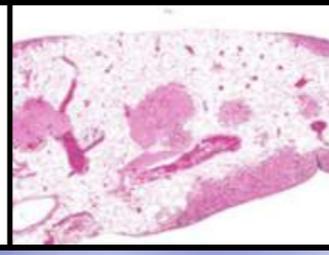
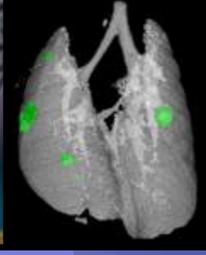
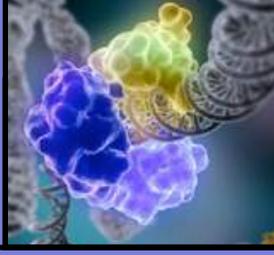


University Hospital



Summary II

- CLL is the most common leukemia in the Western World



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KÖLN



CLL clones can emerge before and after Ig hypermutation

