

Targeting MYC-associated lymphoma biology with probes, drugs and cells

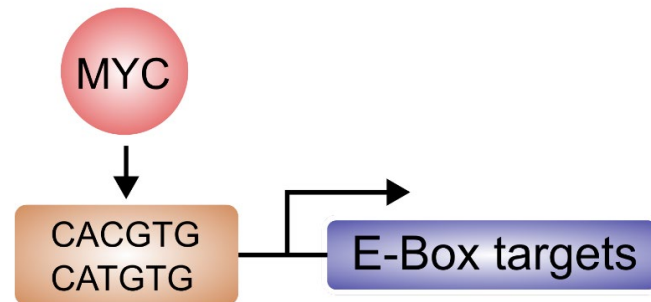
Ulrich Keller

Hematology, Oncology and Cancer Immunology (CBF)
Charité - Universitätsmedizin Berlin
and
Max-Delbrück-Center for Molecular Medicine

München | 24 June 2021

The oncogene *MYC* in tumorigenesis

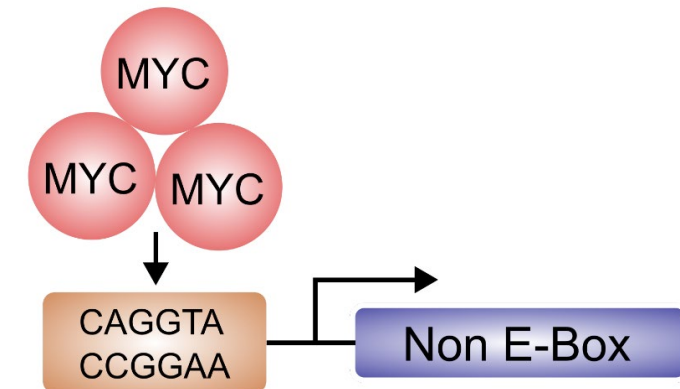
physiological MYC levels



Activation



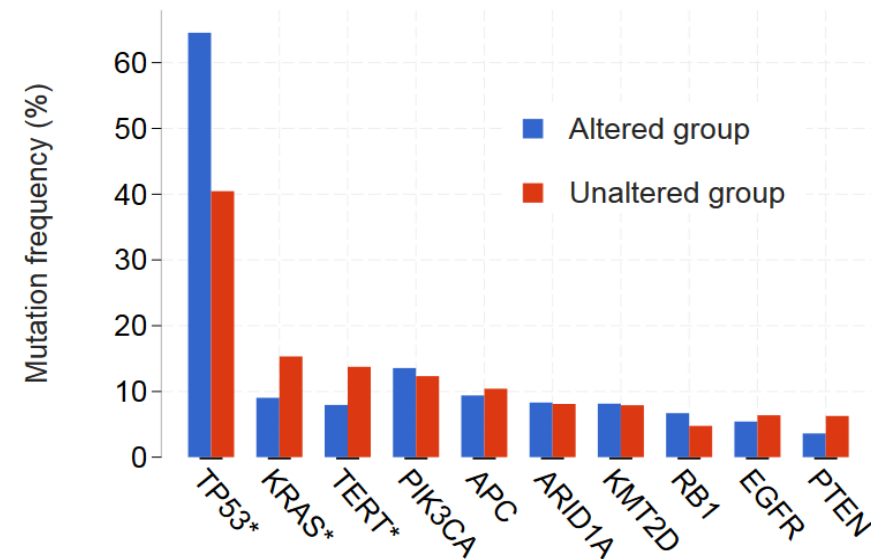
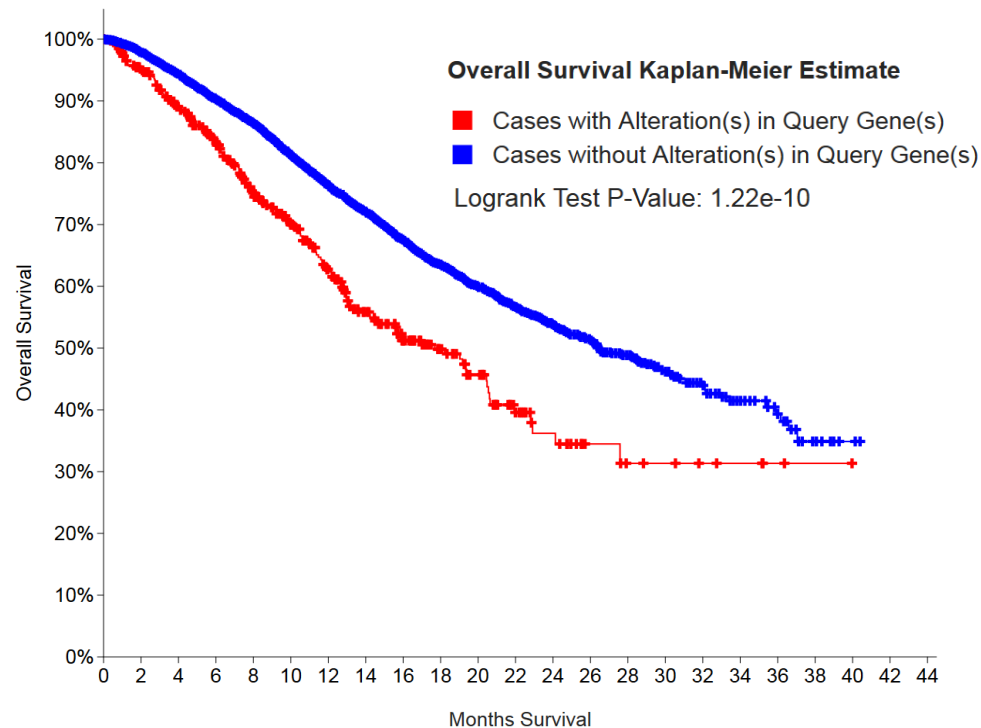
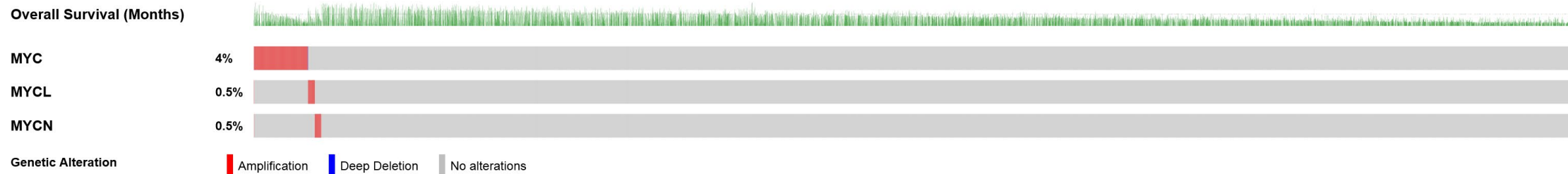
MYC^{high} cancers



MYC: a central cancer driver associated with

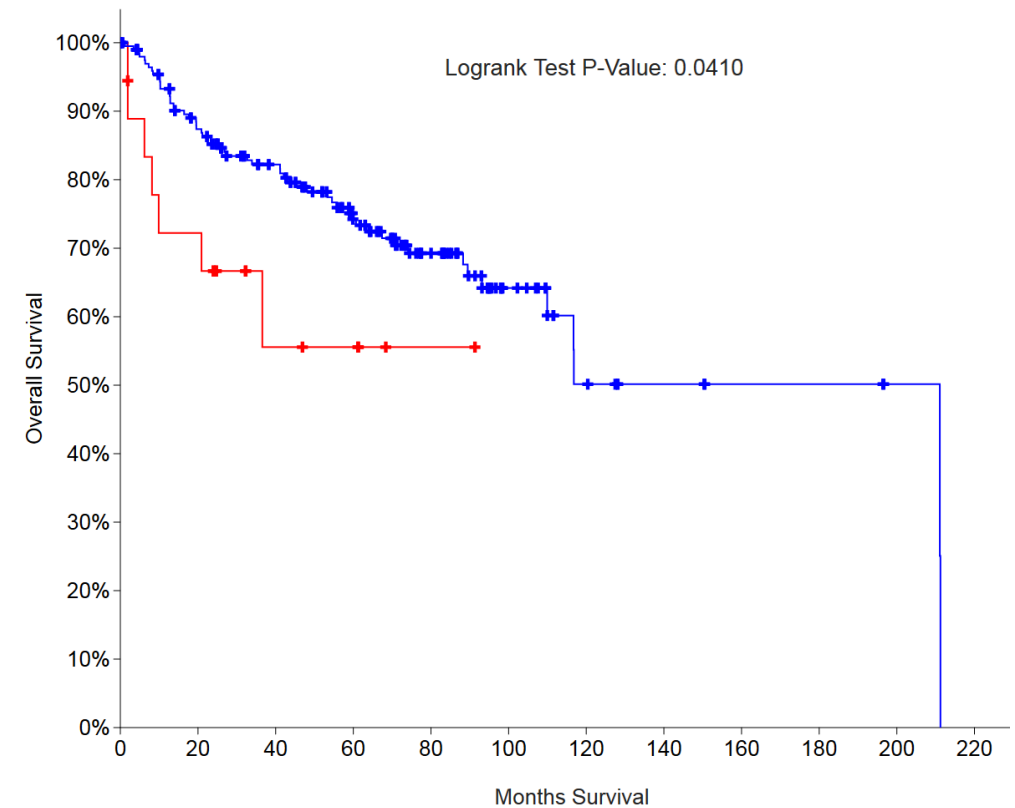
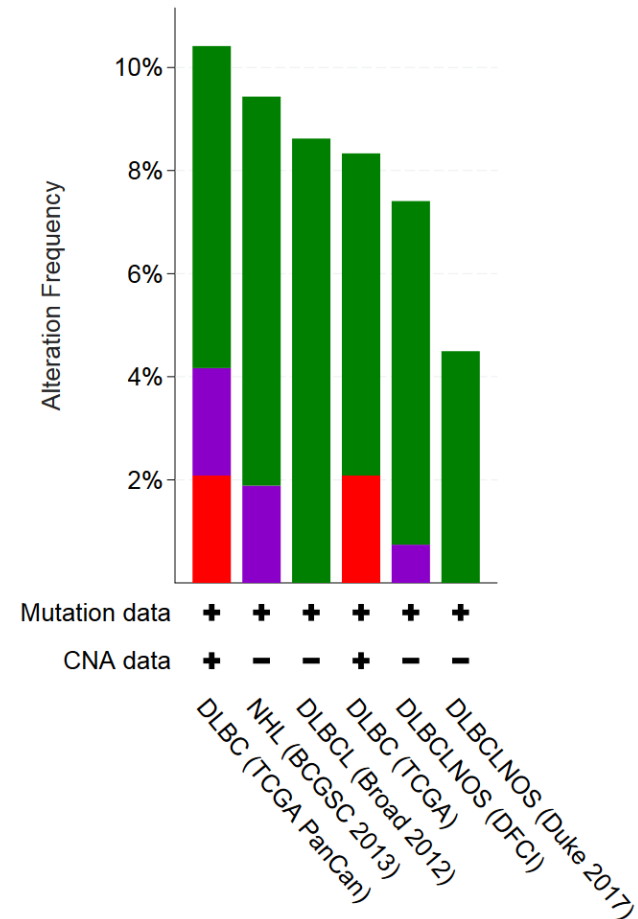
- aggressive cancer biology
- poor prognosis
- treatment resistance

MYC copy number alterations – pan cancer view (cBioPortal)



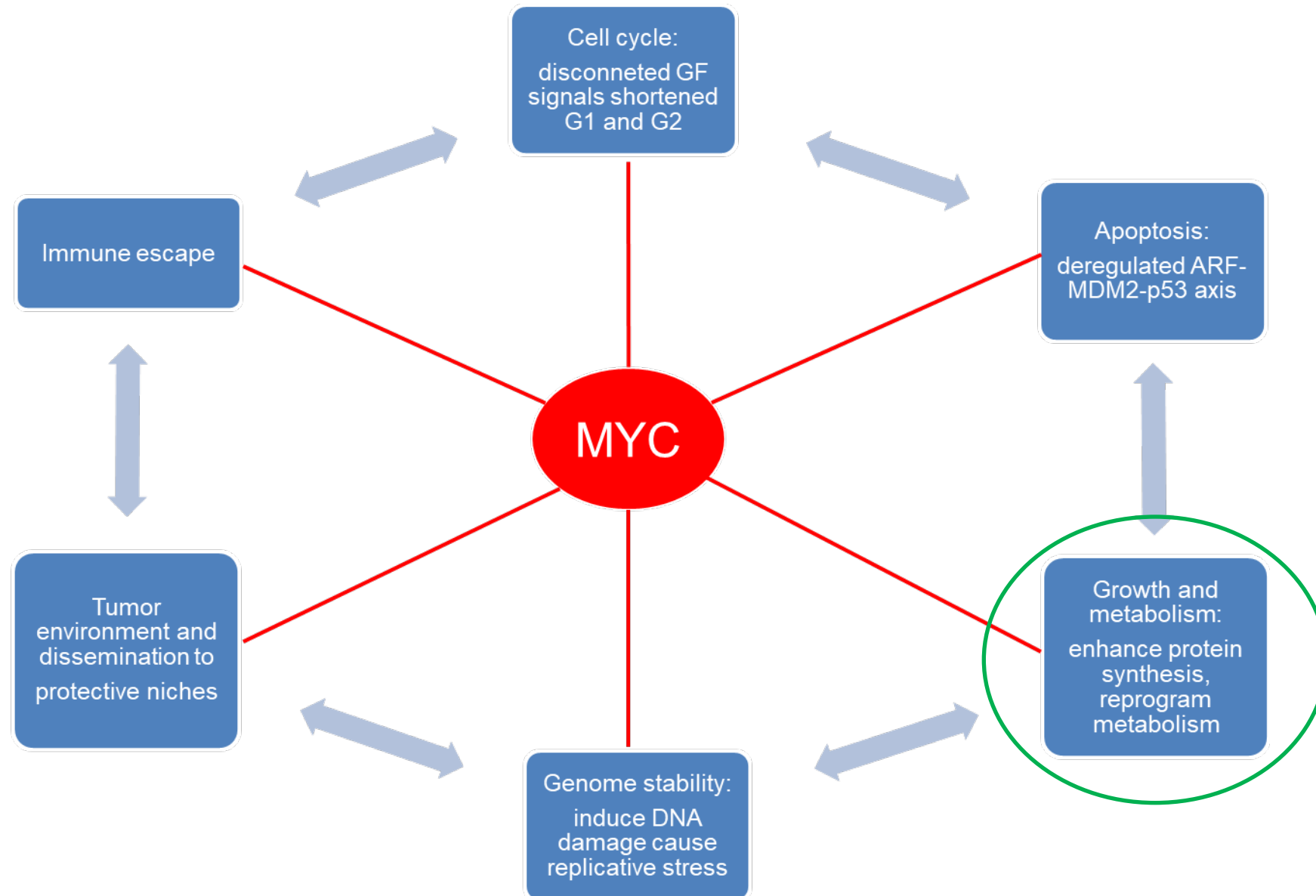
MYC mutations in B-cell lymphoma: Diffuse large B-cell lymphoma (DLBCL)

● Mutation ● Fusion ● Amplification

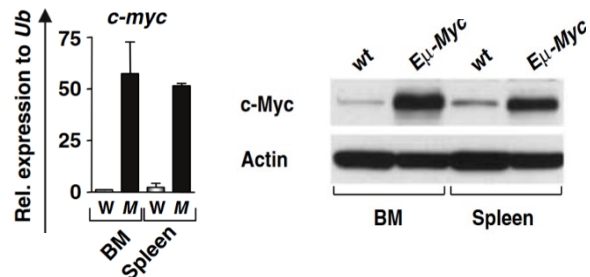
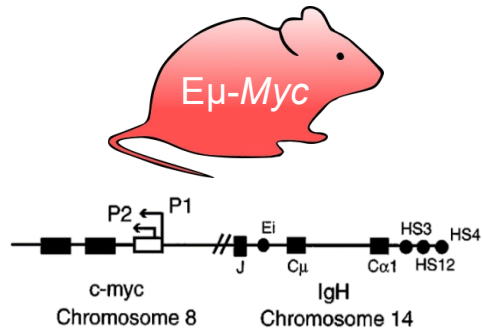


Overall Survival Kaplan-Meier Estimate

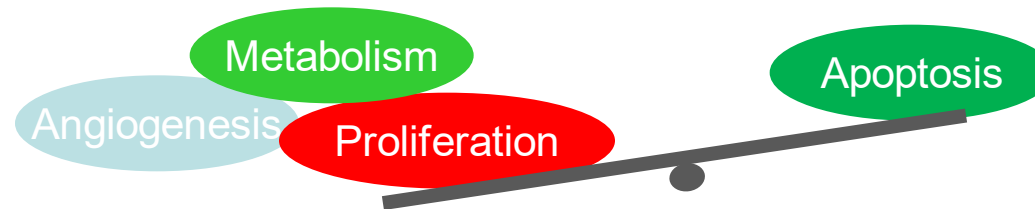
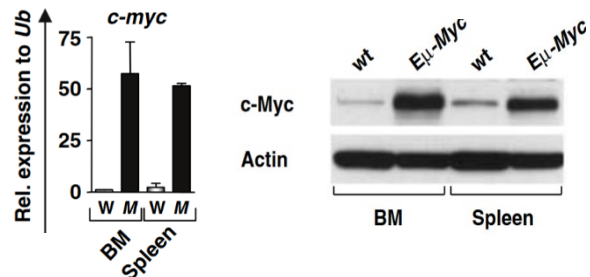
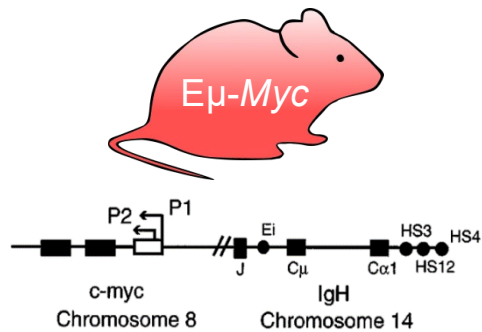
■ Cases with Alteration(s) in Query Gene(s)
 ■ Cases without Alteration(s) in Query Gene(s)



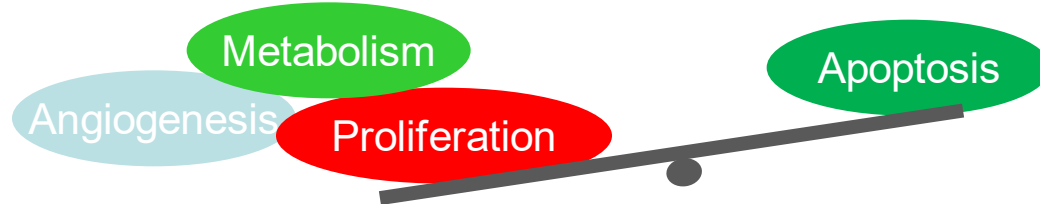
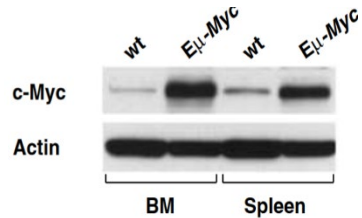
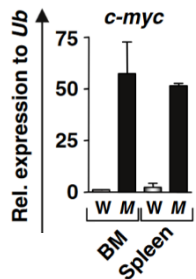
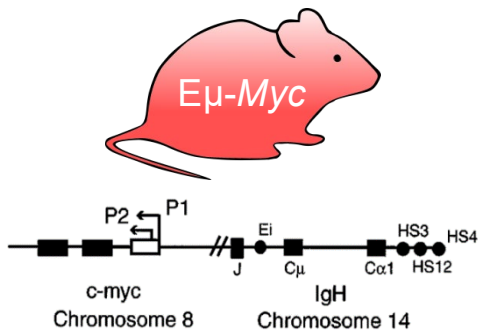
Biased approaches: analyzing mechanisms of MYC-mediated tumorigenesis



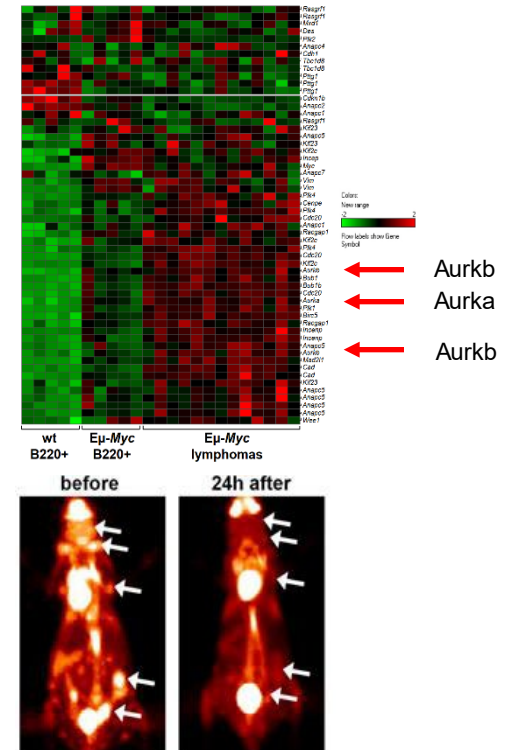
Biased approaches: analyzing mechanisms of MYC-mediated tumorigenesis



Biased approaches: analyzing mechanisms of MYC-mediated tumorigenesis



Aurora Kinases

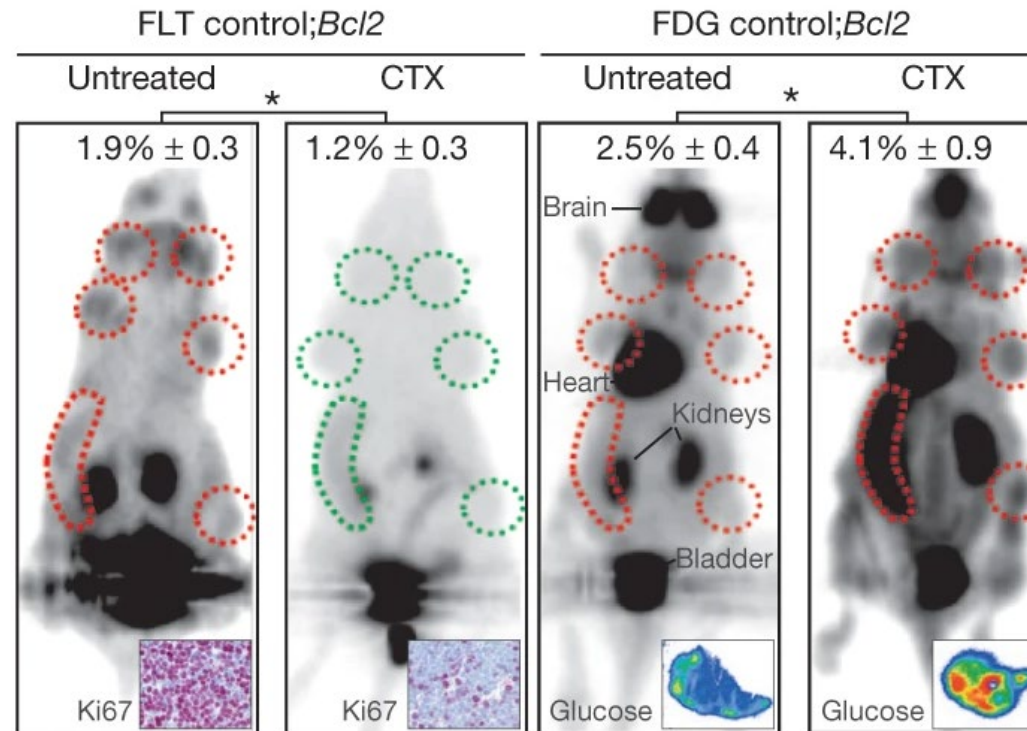
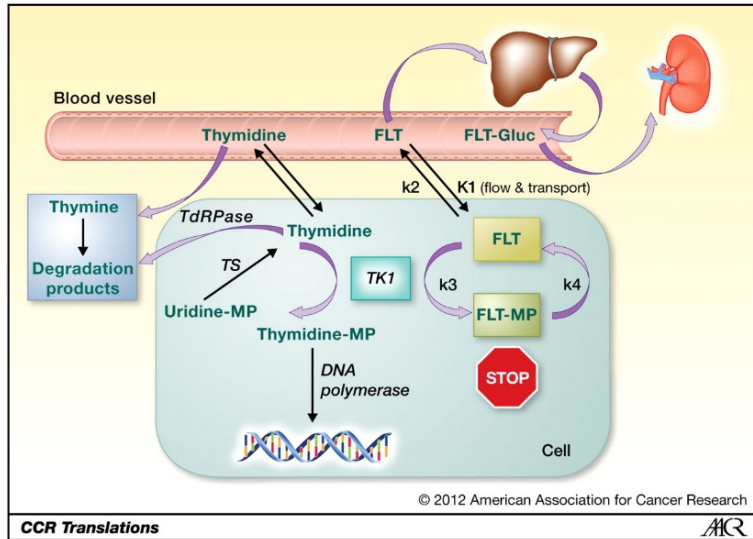
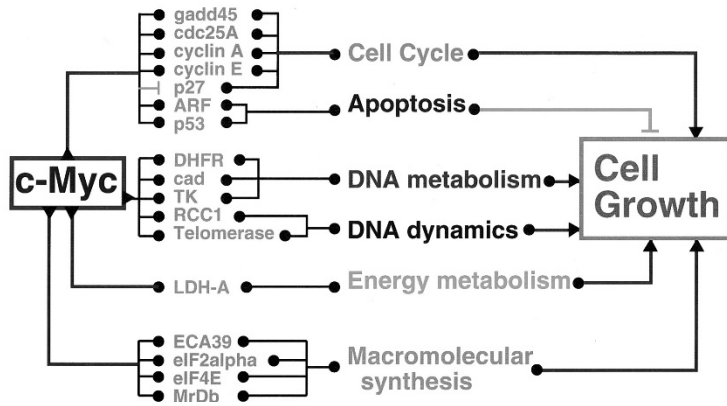


Jürgen Den Hollander et al.,
Andreas Buck
Blood

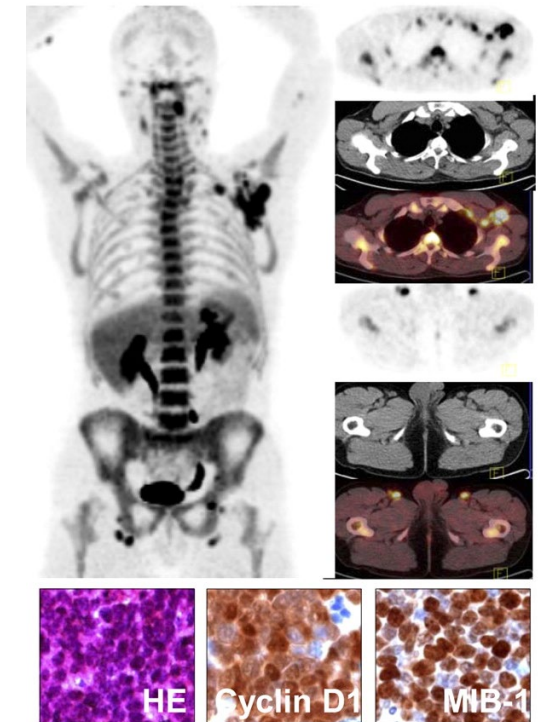


Imaging oncogene-induced tumor cell proliferation vs metabolism

Dang, 1999

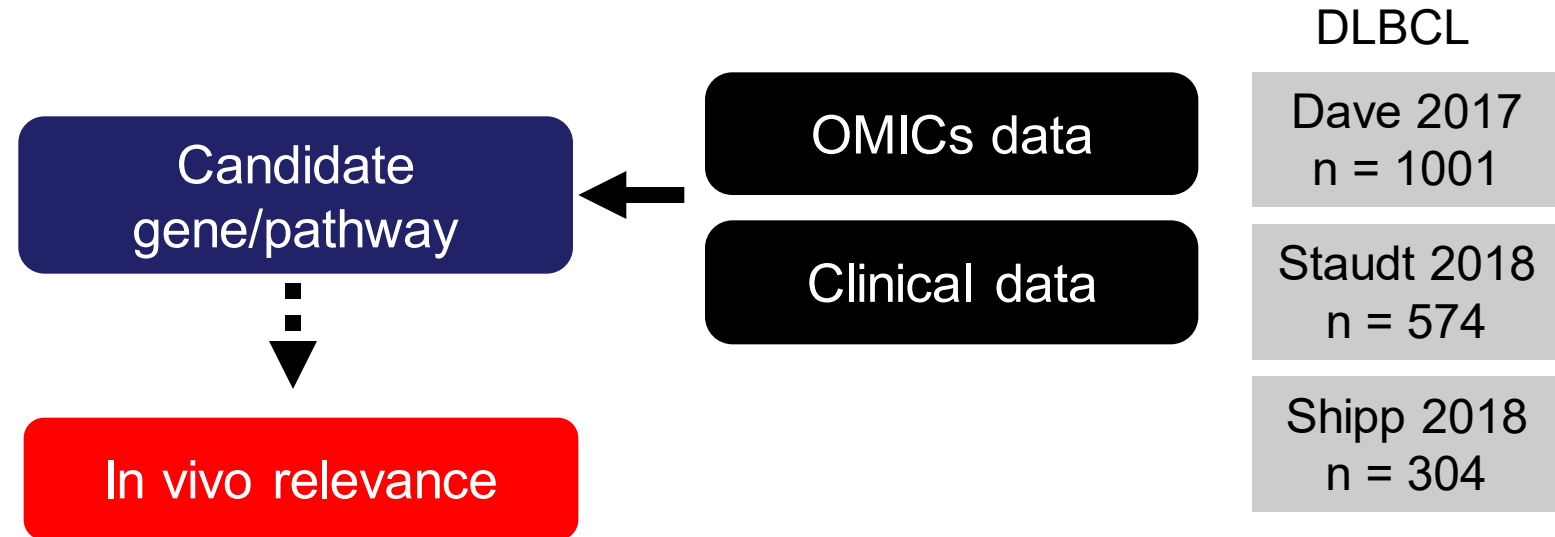


Nature 2013
 J Nucl Med 2011
 Cancer Res 2012
 Am J Nucl Med Mol Imaging 2013

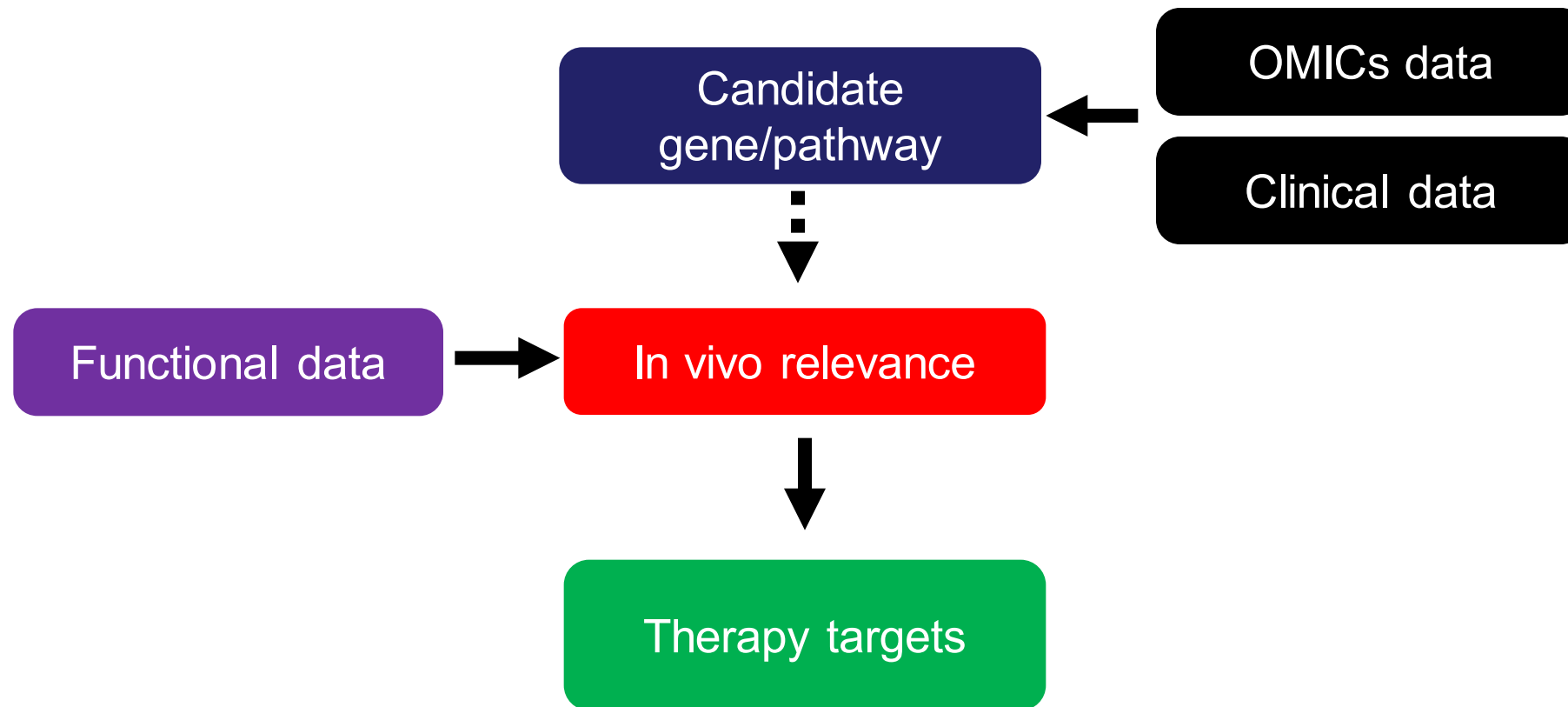


J Nucl Med 2011
 IEEE Trans Med Imaging 2015
 Oncotarget 2014
 Eur J Nucl Med Mol Imaging 2013

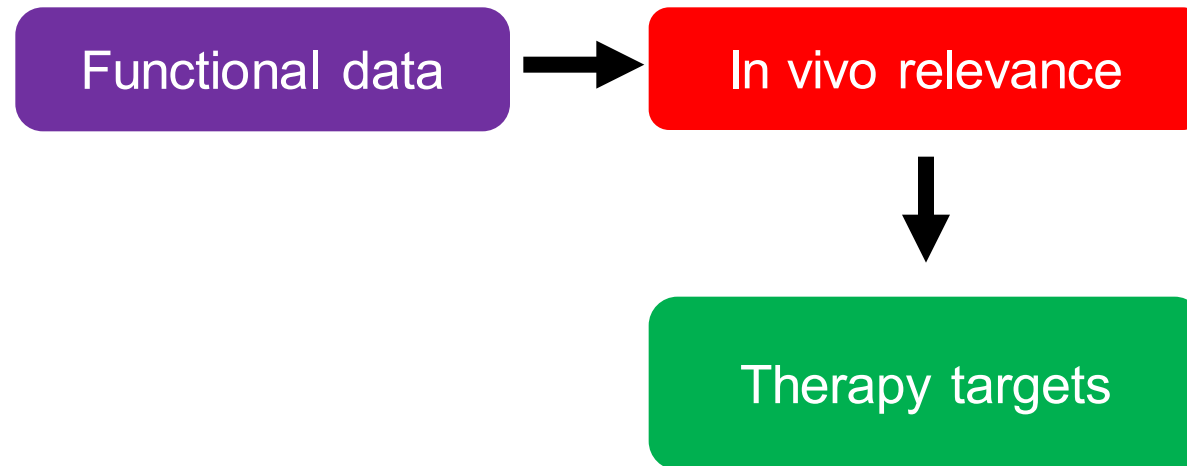
Functional screening for dissecting cancer pathogenesis



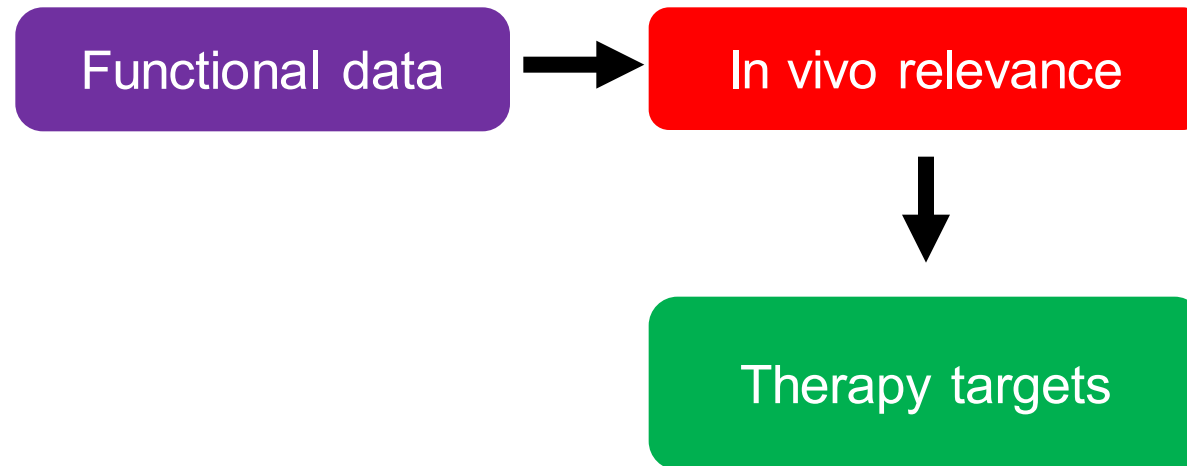
Functional screening for dissecting cancer pathogenesis



Functional screening for dissecting cancer pathogenesis

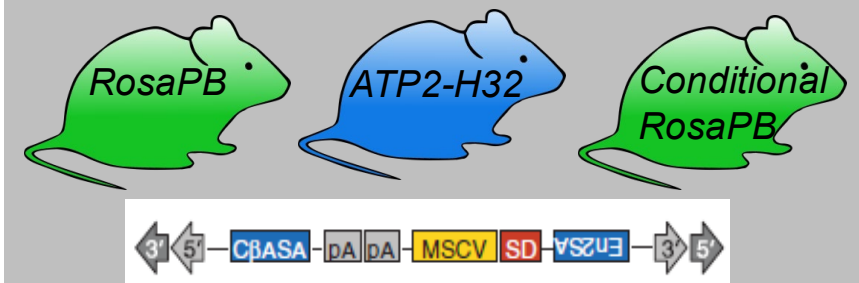


Functional screening for dissecting cancer pathogenesis

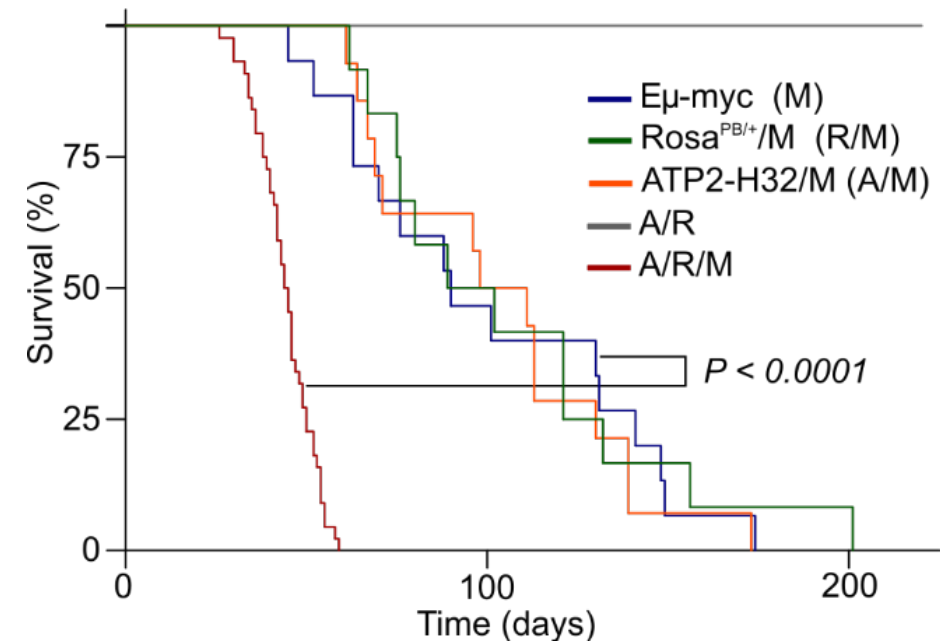
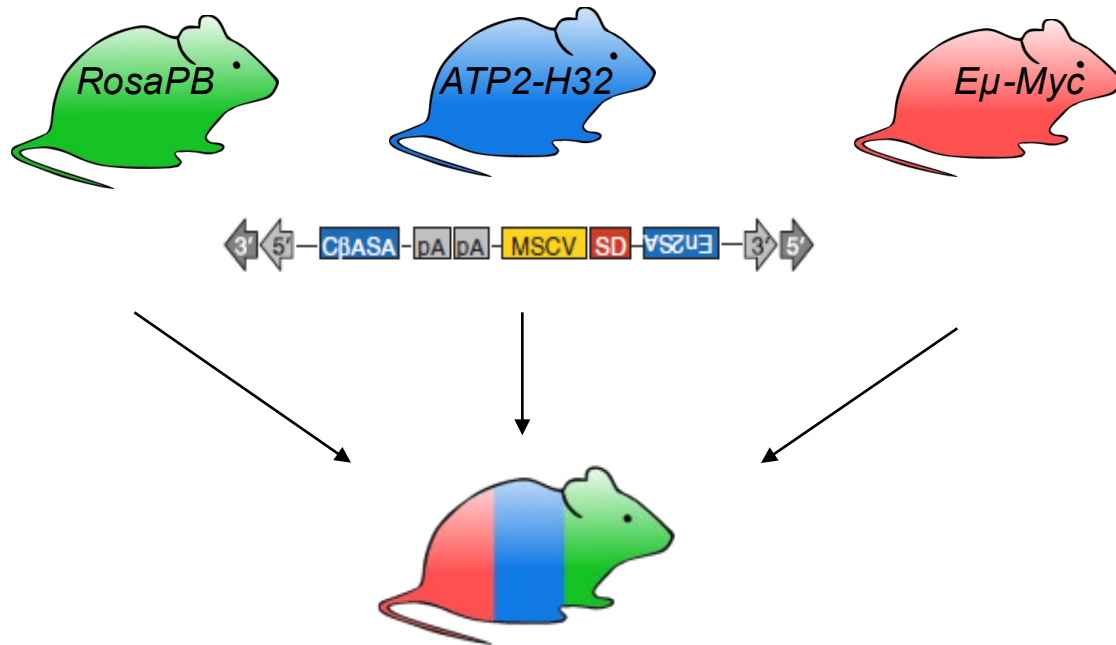


Rad et al., Science 2010

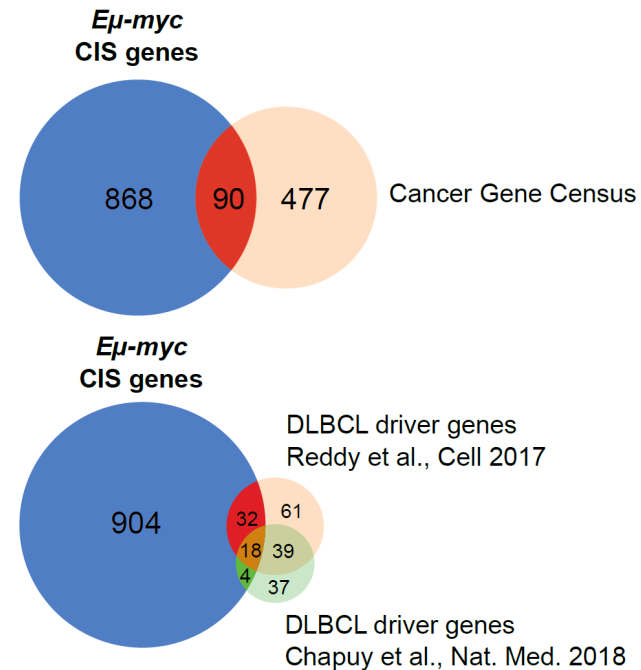
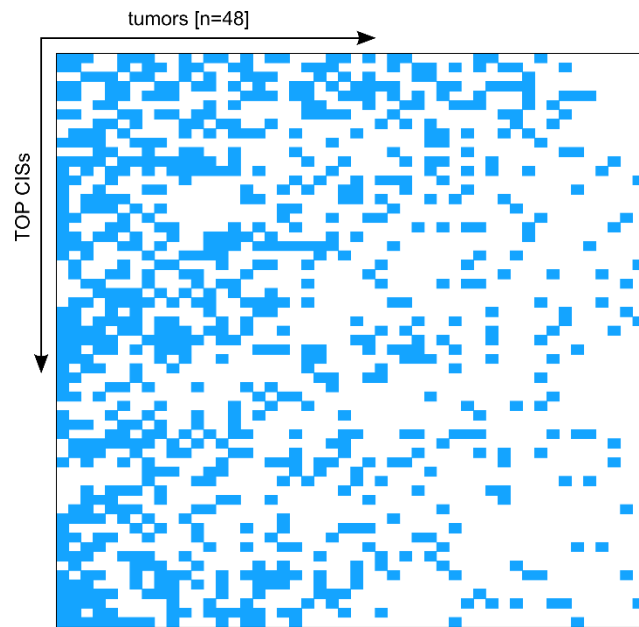
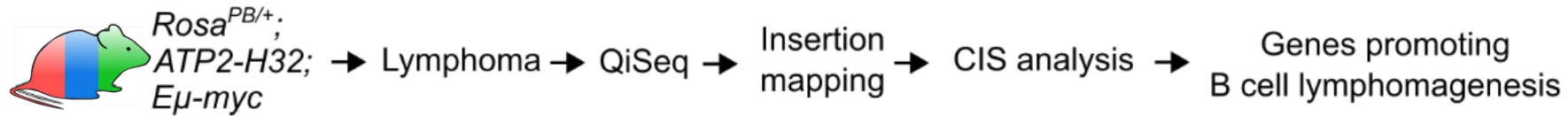
- insertional transposon mutagenesis
- unbiased genome-wide screening
- identifies oncogenes and tumor suppressors



Functional screening for dissecting MYC-associated lymphoma pathogenesis

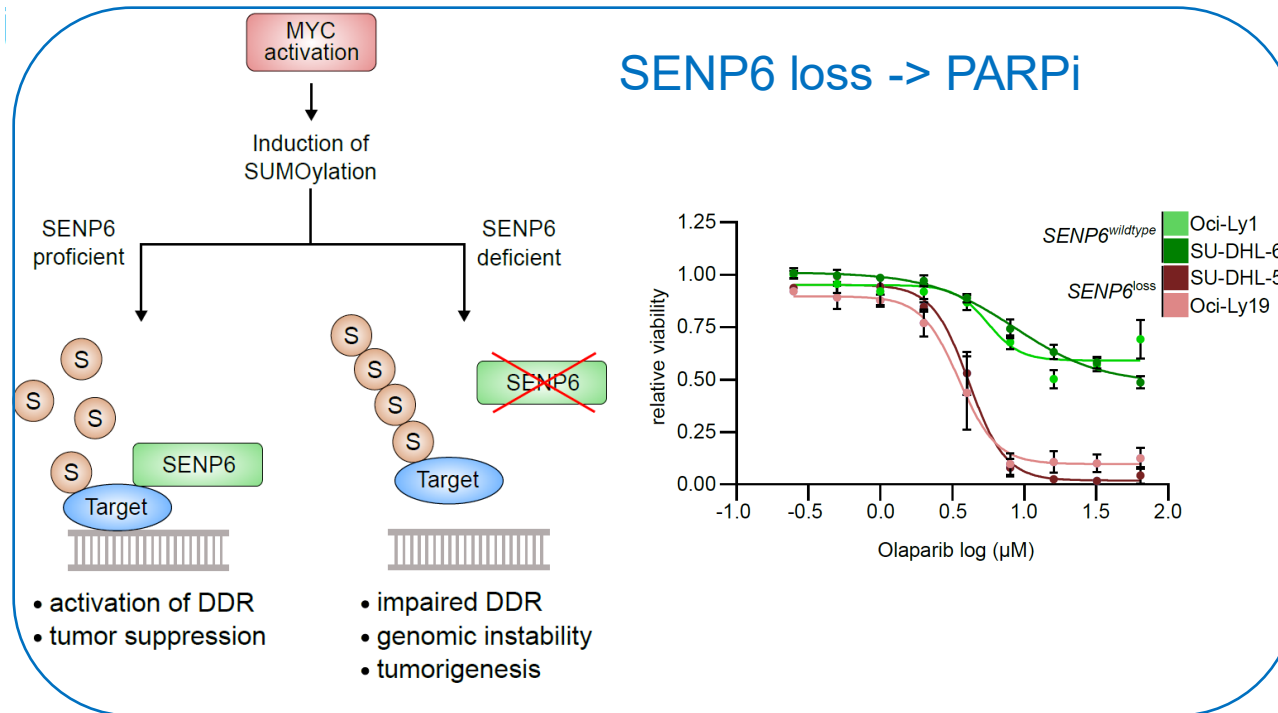
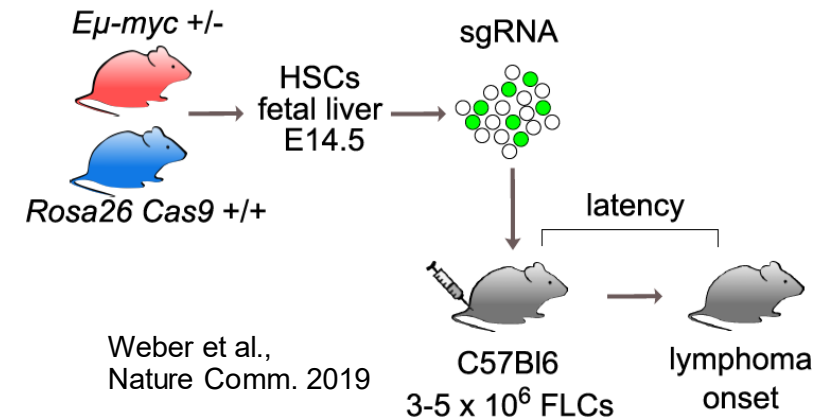
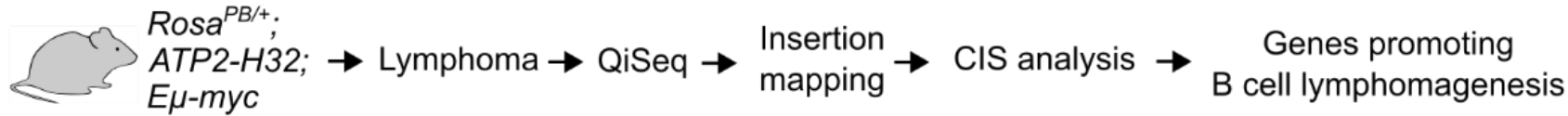


Investigating mechanisms that enable full B cell transformation: identification of 958 putative cancer genes



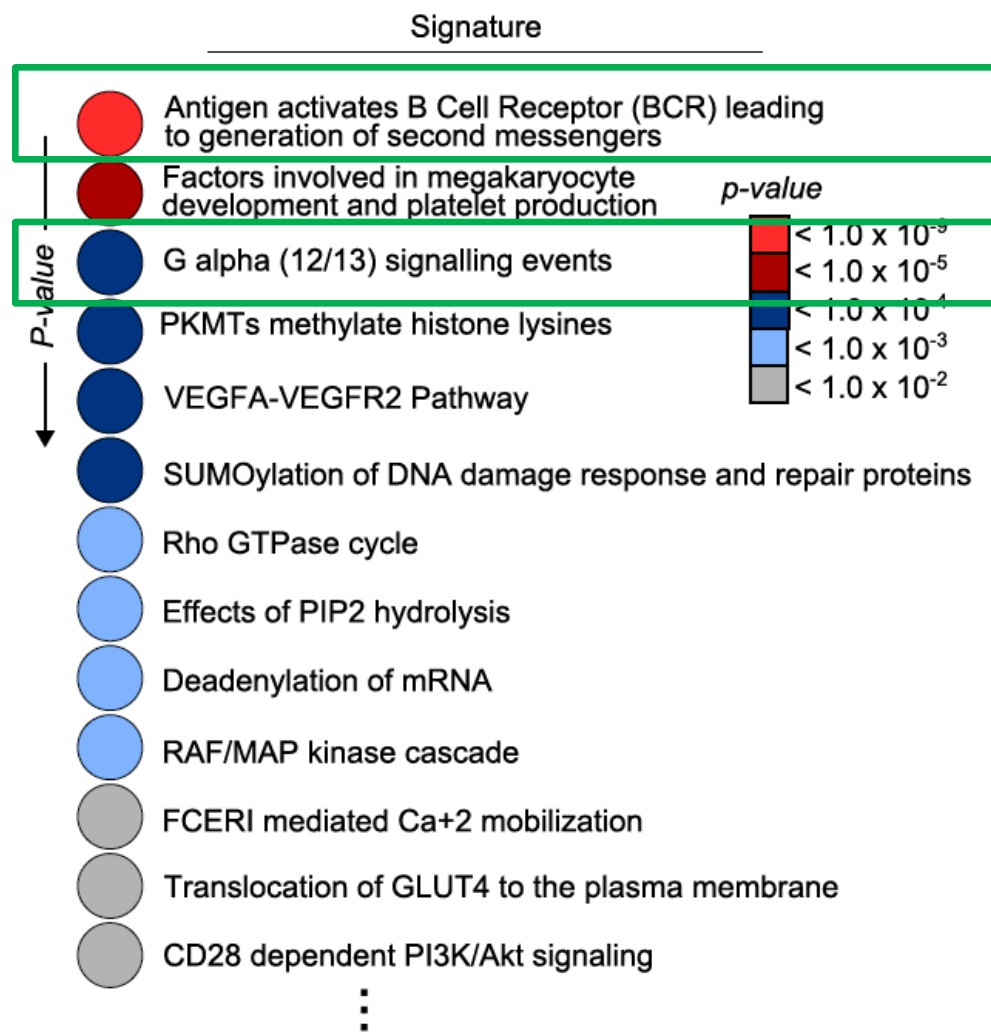
Cancer Gene Census:
catalogue of genes
which contain
mutations causally
implicated in cancer

Actionable alterations identified by genome-wide mutagenesis screening



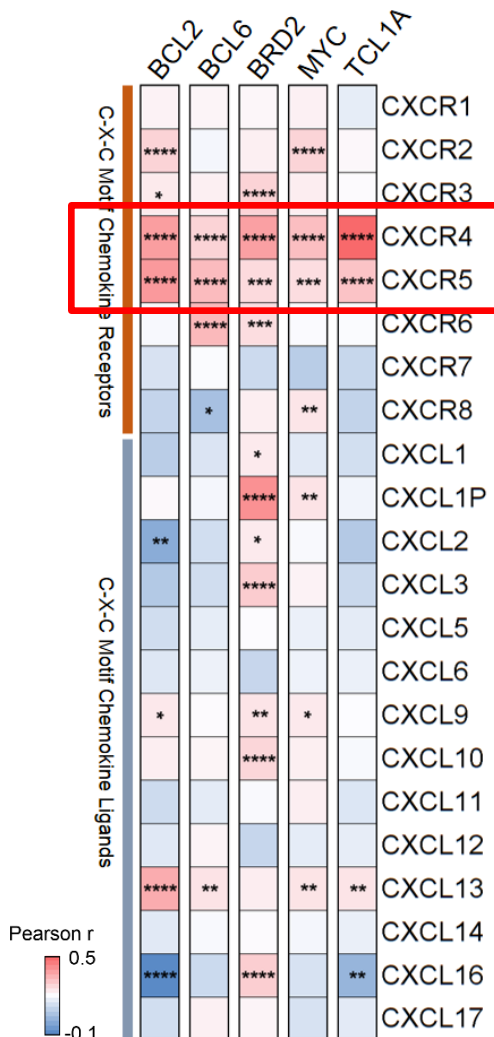
Schick et al. *in revision*

Pathway enrichment analysis in MYC-induced lymphomagenesis identifies BCR/chemokine receptor signaling

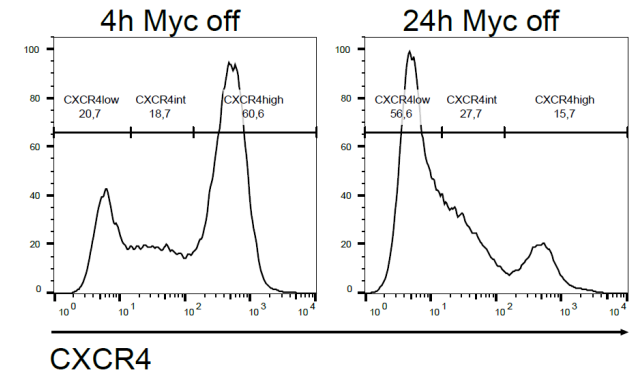
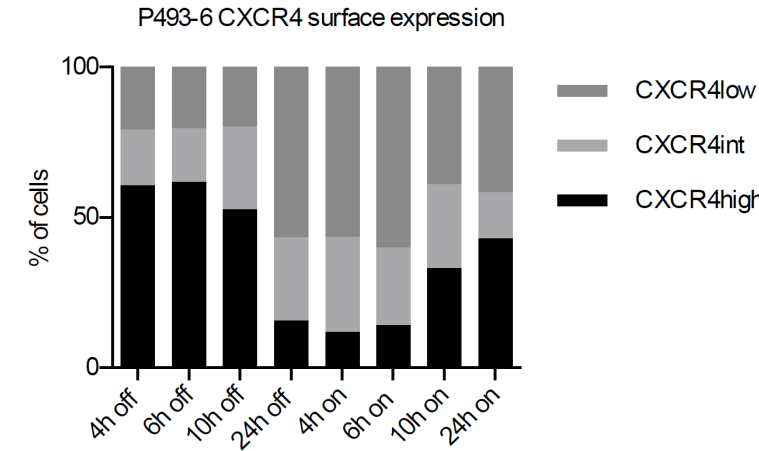
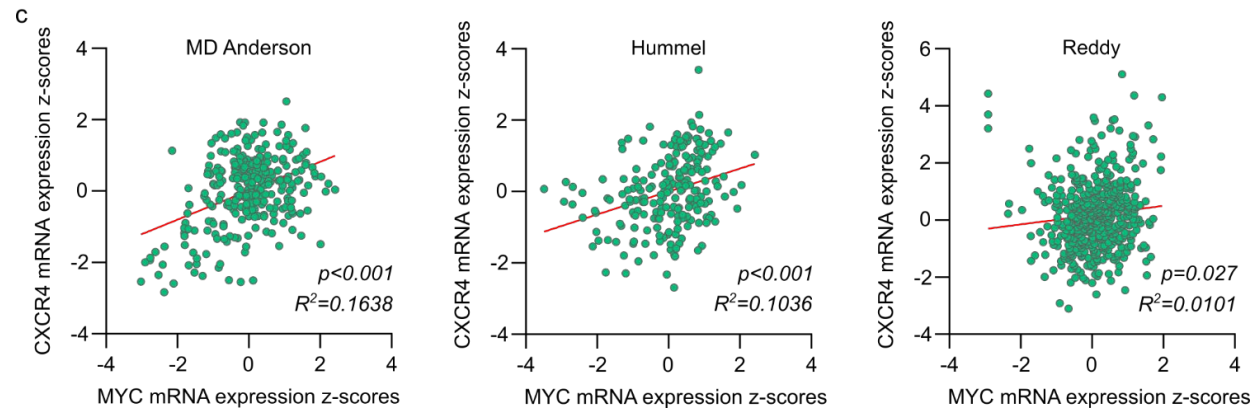
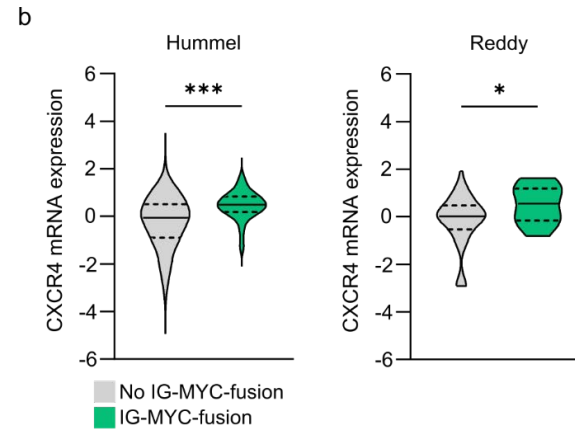
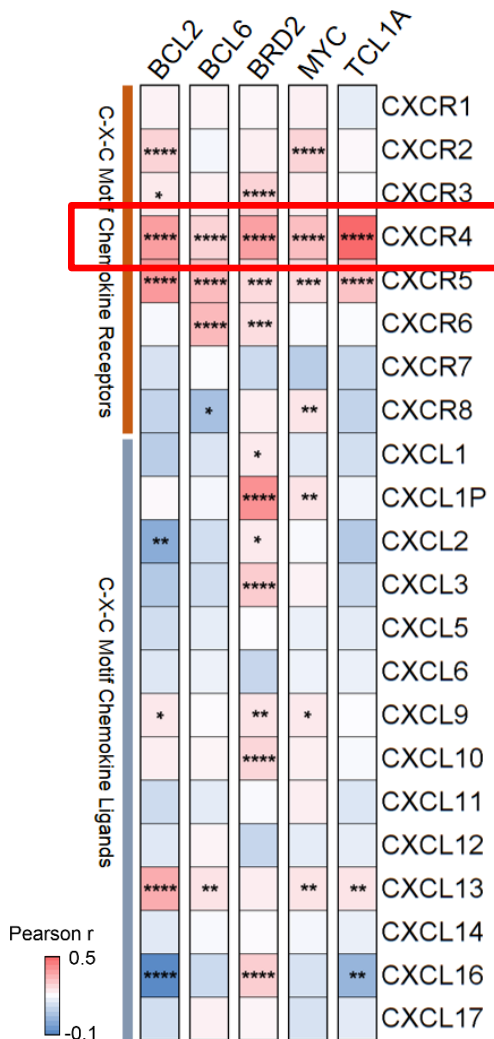


Name	p-value
Chemokine signaling pathway	1.37e-7
Regulation of actin cytoskeleton	2.03e-7
PI3K-Akt signaling pathway	2.90e-7
MAPK signaling pathway	4.72e-7
Focal adhesion	6.40e-7
Endometrial cancer	9.04e-7
Acute myeloid leukemia	1.28e-6
Ras signaling pathway	1.28e-6
Transcriptional misregulation in cancer	1.52e-6
p53 signaling pathway	3.47e-6
Chronic myeloid leukemia	6.17e-6
B cell receptor signaling pathway	6.77e-6
Cell cycle	1.06e-5
ErbB signaling pathway	1.44e-5
FoxO signaling pathway	1.73e-5
Jak-STAT signaling pathway	3.93e-5
T cell receptor signaling pathway	4.69e-5
Renal cell carcinoma	5.13e-5
Natural killer cell mediated cytotoxicity	7.76e-5
RNA degradation	7.76e-5

Chemokine receptor expression is associated with MYC and IG-MYC Fusion

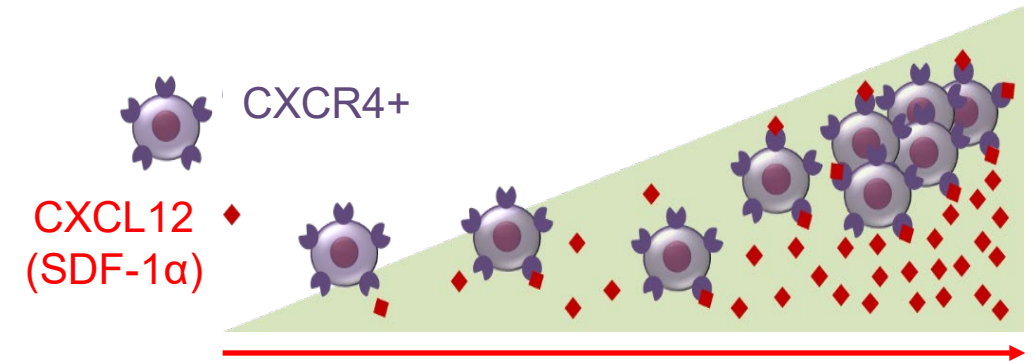


CXCR4 expression is associated with MYC expression and IG-MYC Fusion



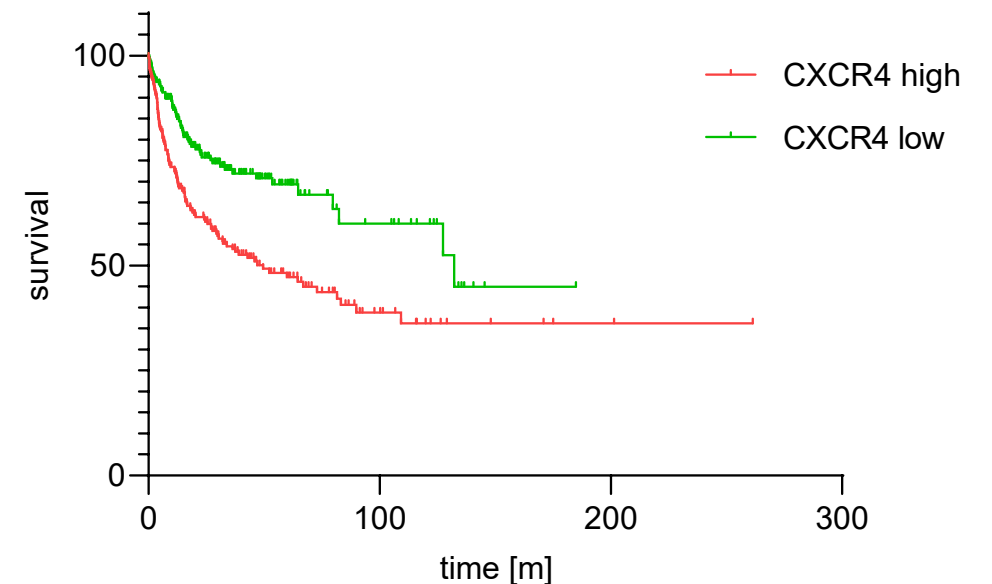
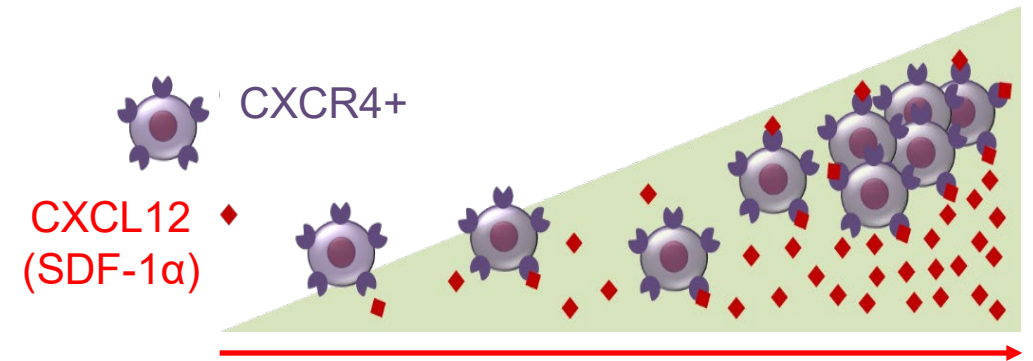
CXCR4/CXCL12 axis in lymphoma

- G-protein-coupled receptor
- Migration, homing, hematopoiesis
- Activation of MAPK, PI3K/AKT/mTOR, NFκB



CXCR4/CXCL12 axis in lymphoma

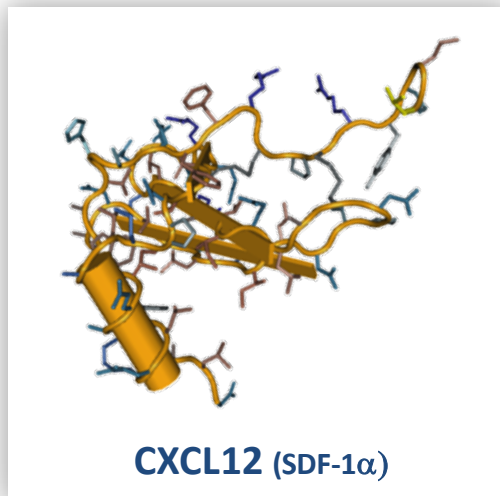
- G-protein-coupled receptor
- Migration, homing, hematopoiesis
- Activation of MAPK, PI3K/AKT/mTOR, NFkB
- High expression associated with adverse prognosis, depicted: aggressive lymphoma (DLBCL)



Developing CXCR4-targeted imaging and therapy (theranostics)



Developing CXCR4-targeted imaging and therapy (theranostics)



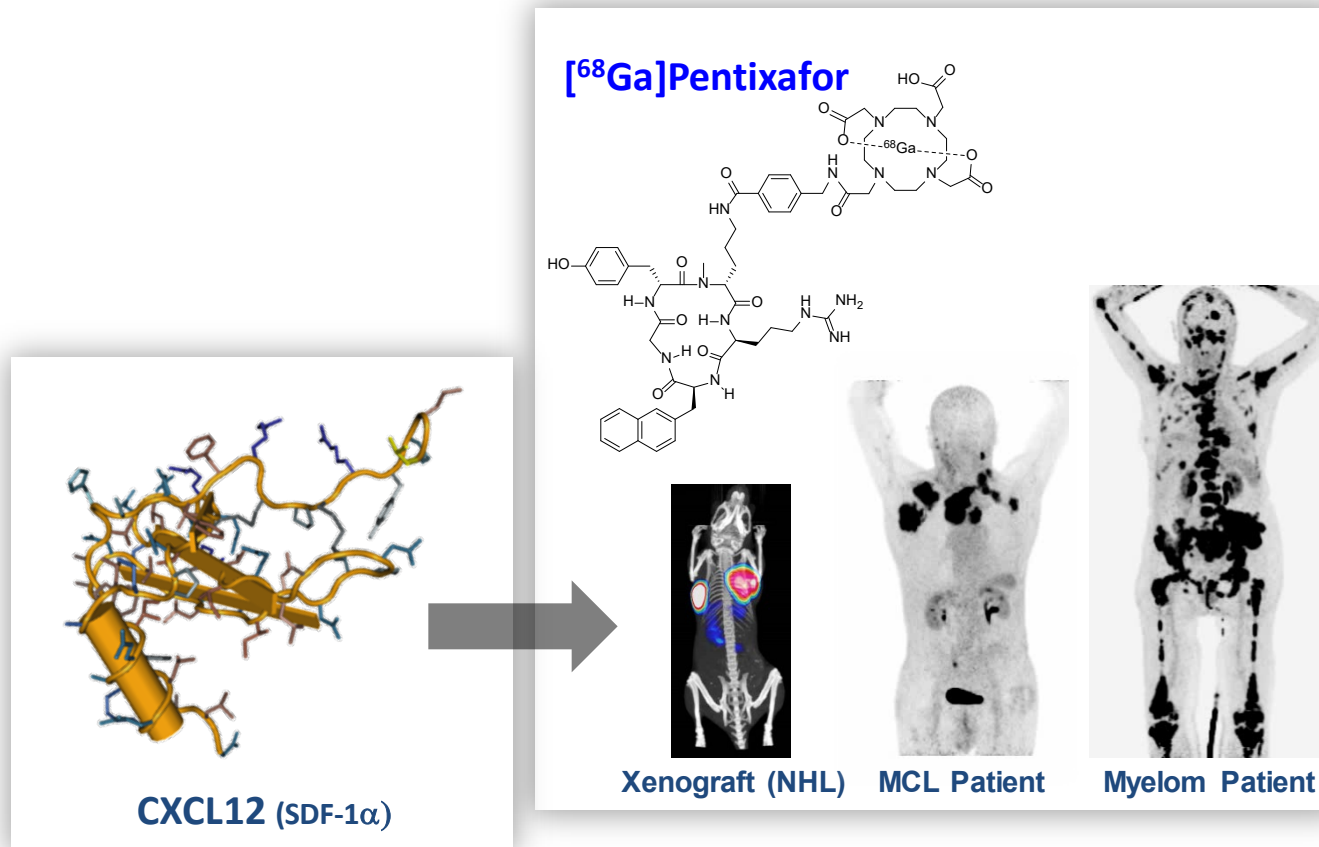
Partner:
H.J. Wester, M. Schottelius
Radiochemie
M. Schwaiger
Nuklearmedizin



Myelom (Philipp-Abbrederis, Herrmann et al. *EMBO Mol Med* 2015)
AML (Herhaus, Habringer et al. *Haematologica* 2016)
Lymphome (Wester, Keller et al. *Theranostics* 2015)
Solide Tumoren (Vag et al. *J Nucl Med* 2016)
Indol. Lymphom (Herhaus et al. *EJNMMI Res* 2017)
Primäre ZNS Lymphome (Herhaus et al., *J Nucl Med* 2020)

Therapie (Maurer, Herhaus et al., *J Nucl Med* 2019)
Leukämie (Habringer et al. *Theranostics* 2018)
Pentixather (Schottelius et al., *Theranostics* 2017)
Herrmann, ..., Keller, ..., Knop. *J Nucl Med* 2015
Herrmann, ..., Keller, ..., Lassmann. *J Nucl Med* 2016

Developing CXCR4-targeted imaging and therapy (theranostics)



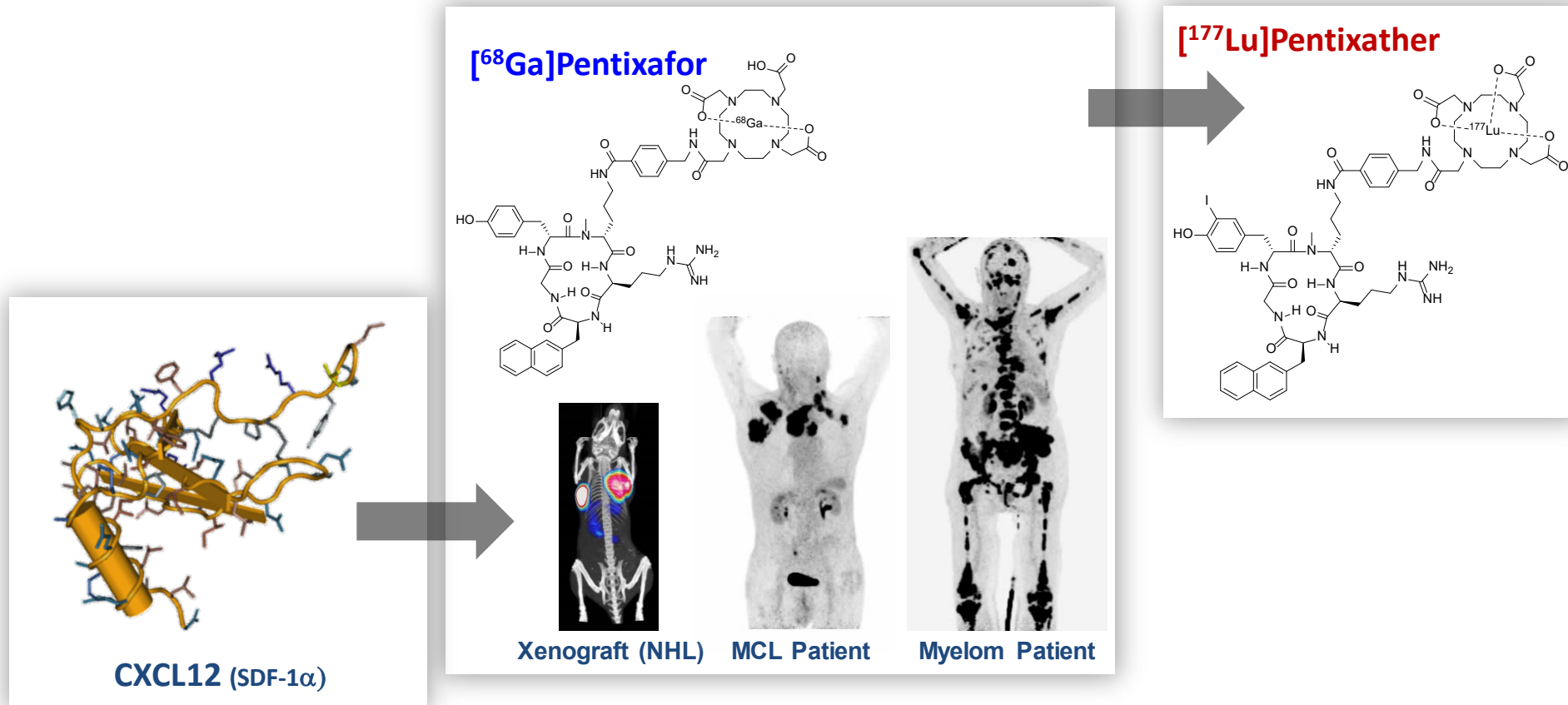
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Developing CXCR4-targeted imaging and therapy (theranostics)



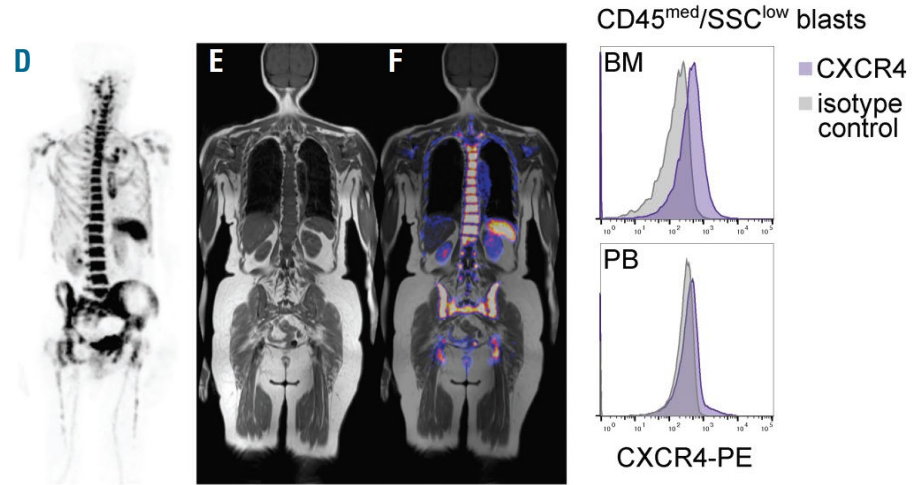
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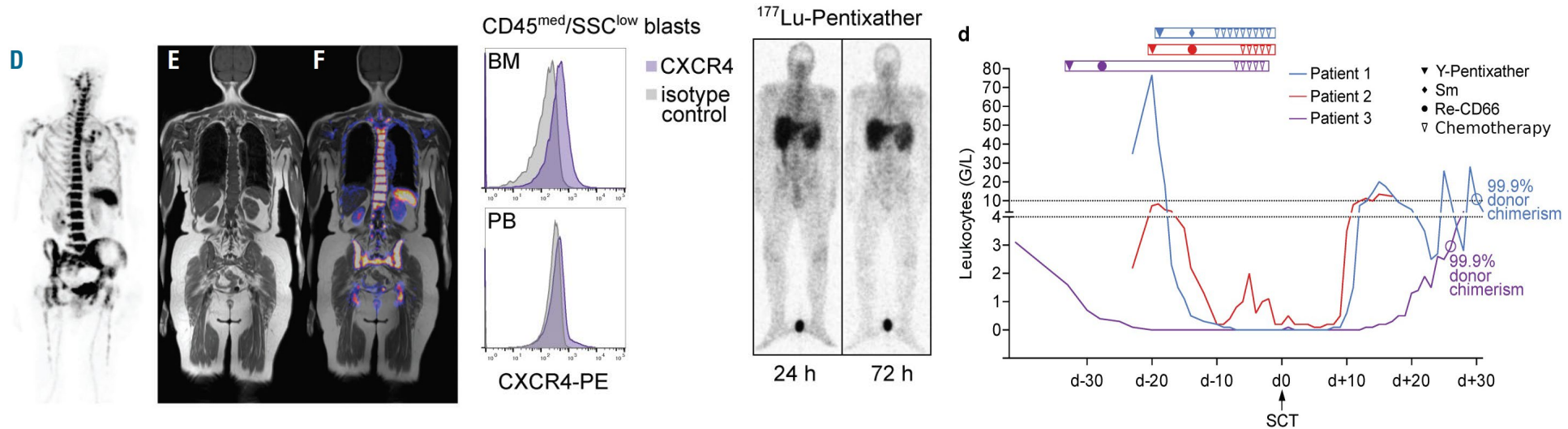
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CXCR4-directed theranostics in blood cancer patients: Proof-of-concept individual treatment approaches



Herhaus, Habringer, Haematologica 2017

CXCR4-directed theranostics in blood cancer patients: Proof-of-concept individual treatment approaches

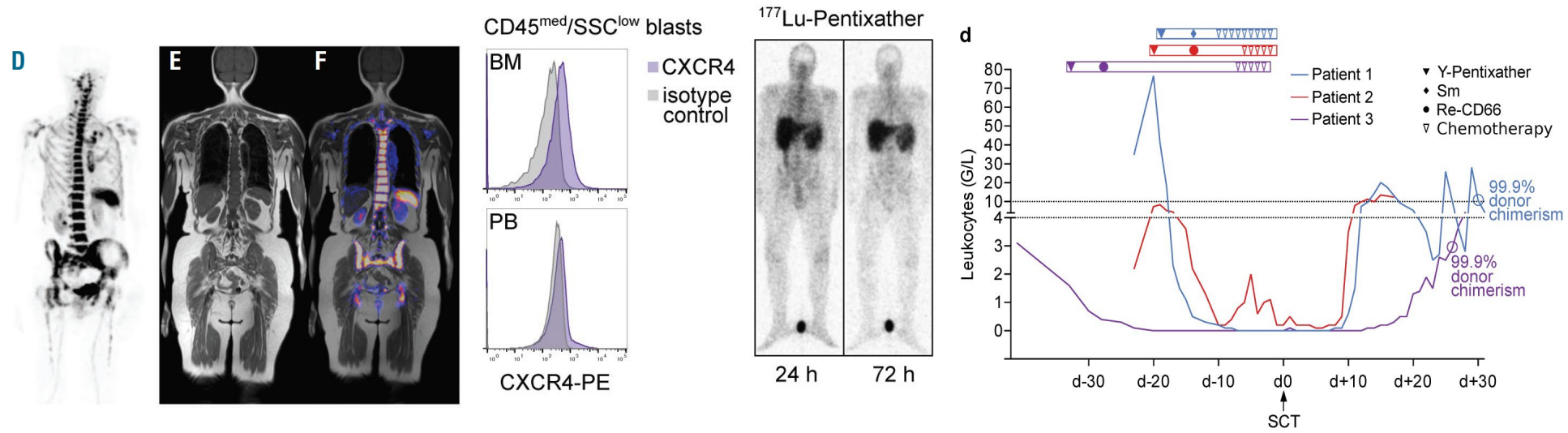


Herhaus, Habringer, Haematologica 2017

Habringer et al. Theranostics 2018
Maurer, Herhaus et al., J Nucl Med 2019



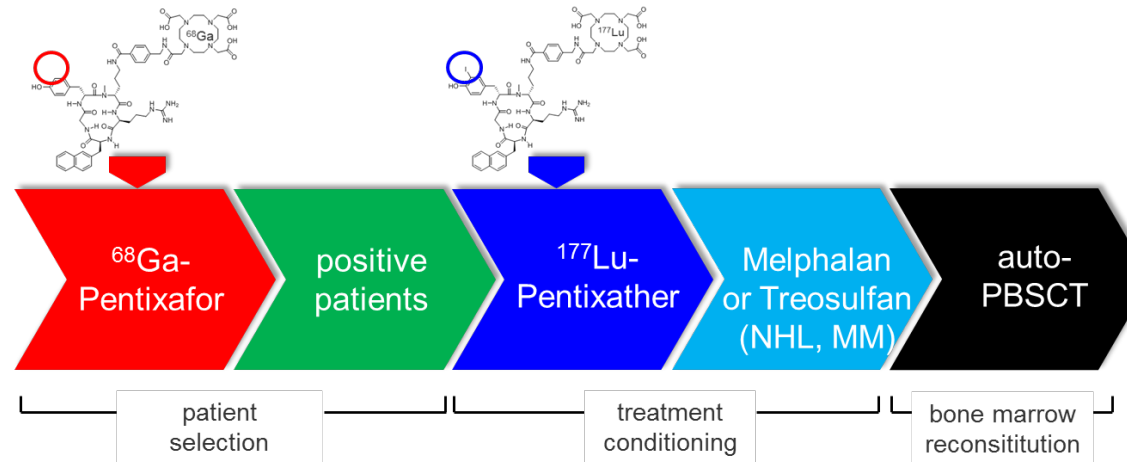
CXCR4-directed theranostics in blood cancer patients: Proof-of-concept individual treatment approaches



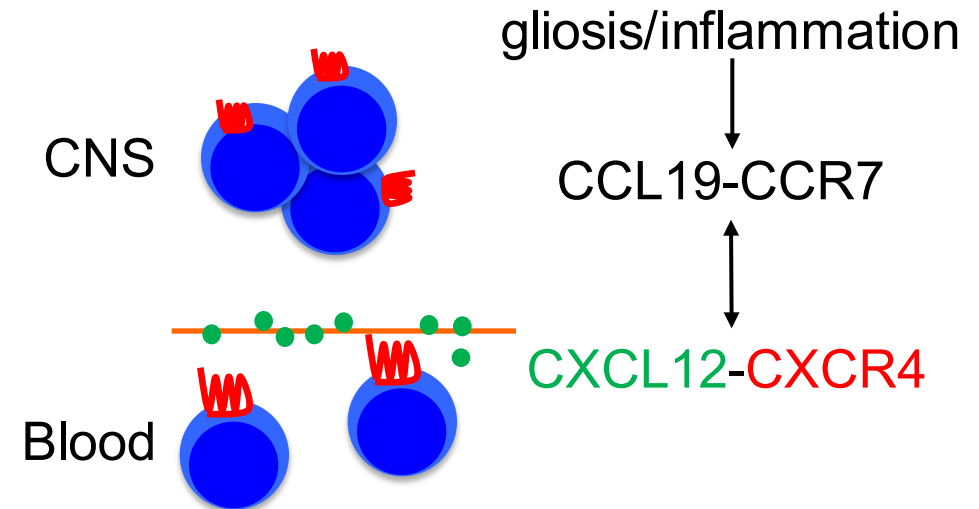
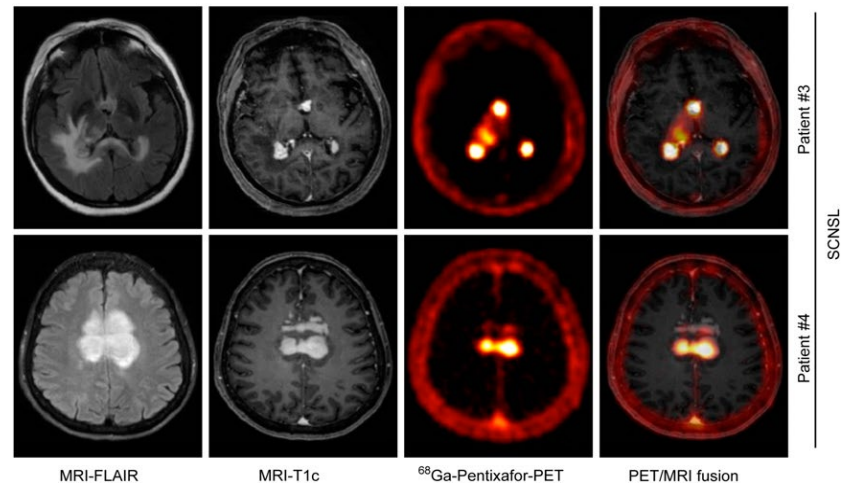
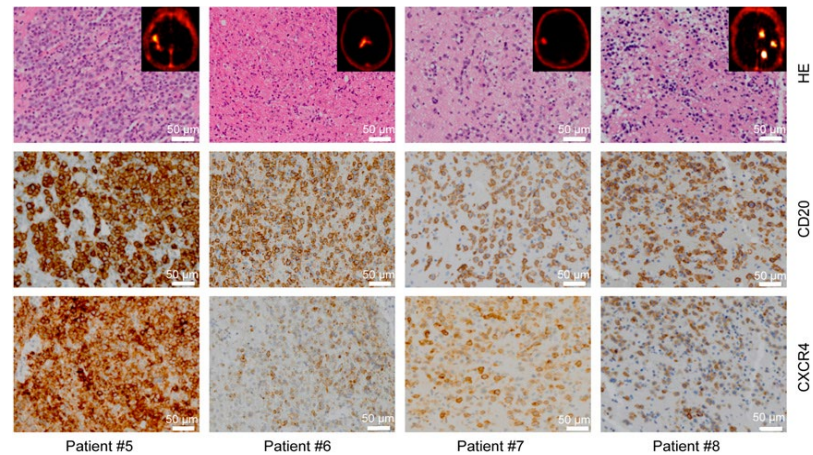
Herhaus, Habringer, Haematologica 2017

Habringer et al. Theranostics 2018
Maurer, Herhaus et al., J Nucl Med 2019

THE „COLPRIT“ PHASE 1/2 TRIAL
(KREBSHILFE)
LYMPHOMA AND MYELOMA
M-FR-UL-DD-WÜ



CXCR4 promotes CNS migration but not retention of B-cell lymphoma

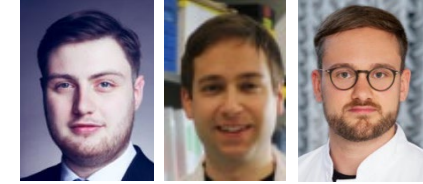
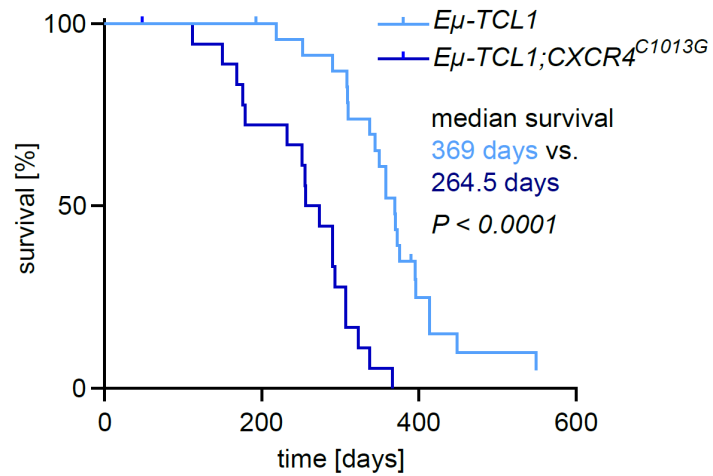


CXCR4-targeted imaging/therapy: international multicenter studies (CNS lymphoma)

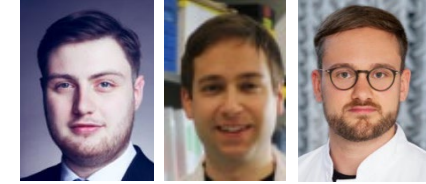
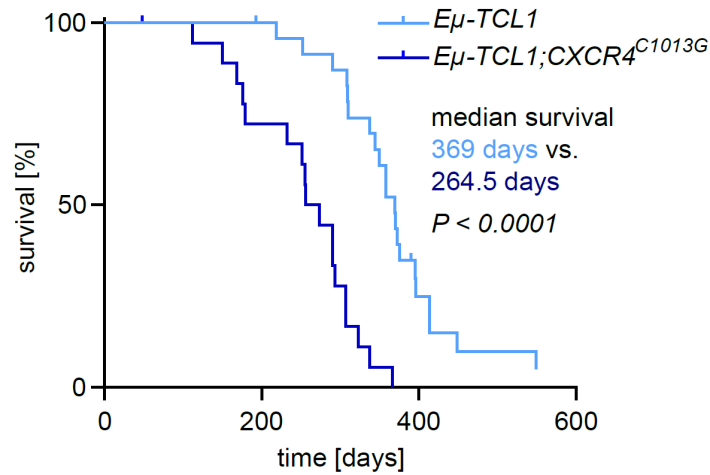
Imaging study for FDA/EMA approval

Therapy study for r/r CNS lymphoma

CXCR4 hyperactivation accelerates TCL1-driven CLL and promotes aggressive transformation

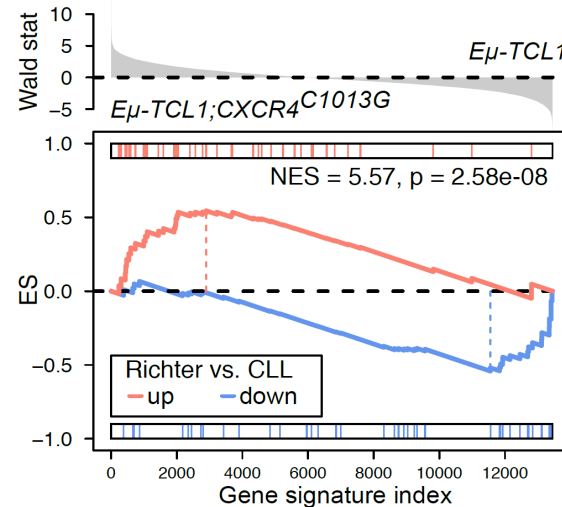
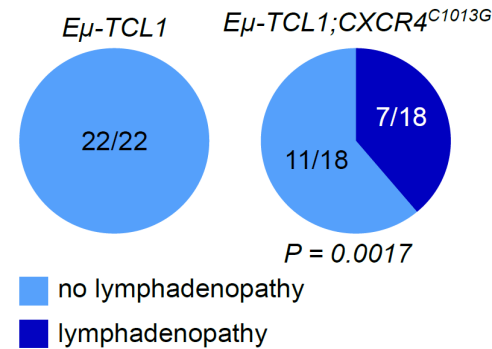
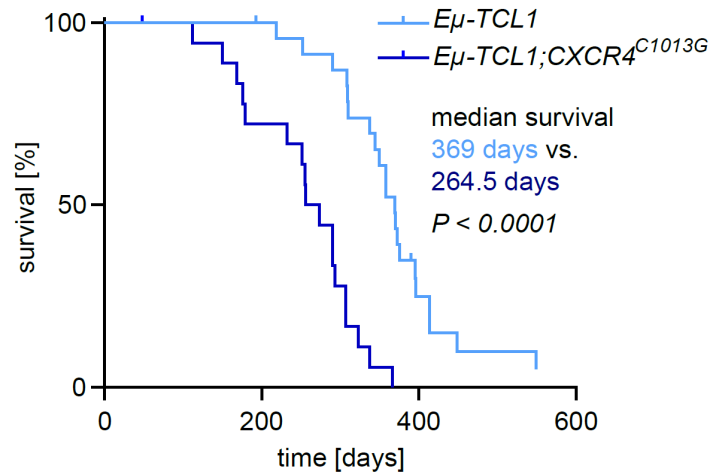


CXCR4 hyperactivation accelerates TCL1-driven CLL and promotes aggressive transformation



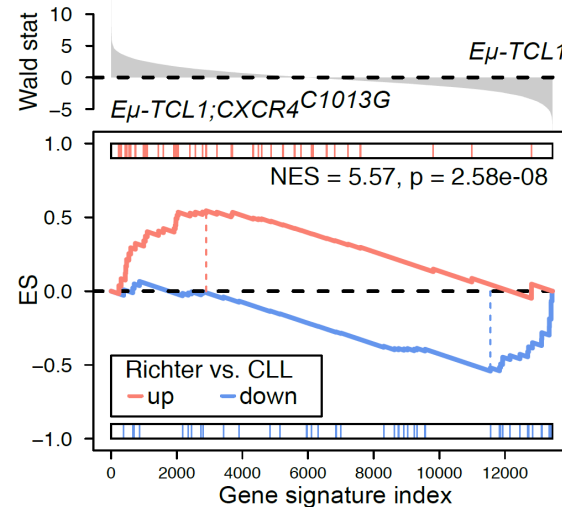
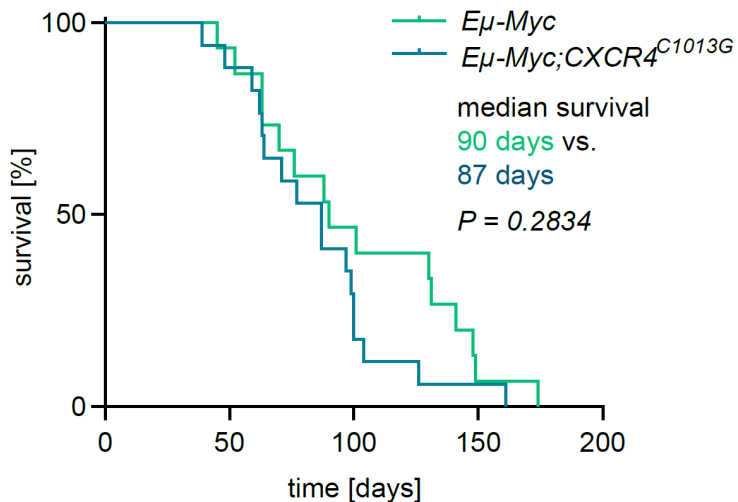
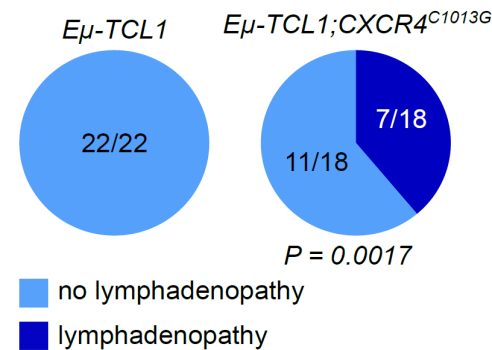
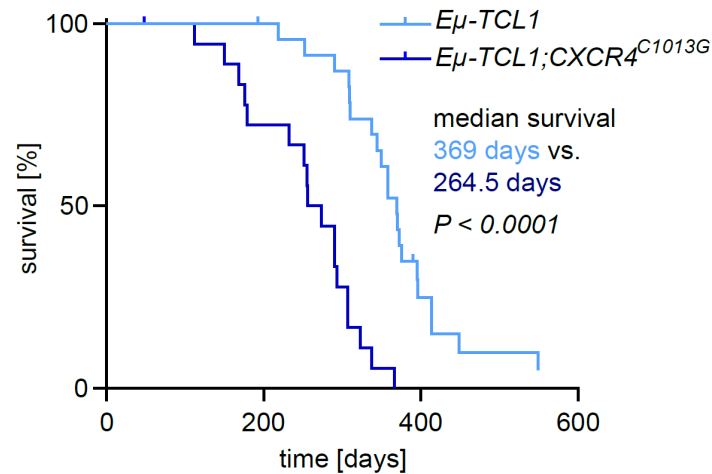
NES	FDR	$E\mu$ -TCL1;CXCR4 ^{C1013G}	$E\mu$ -TCL1	Pathway
2.25	7.5e-10			HALLMARK_E2F_TARGETS
2.15	1.7e-05			PID_PLK1_PATHWAY
2.13	2.1e-09			HALLMARK_G2M_CHECKPOINT
1.86	0.0016			PID_FOXM1_PATHWAY
1.83	0.0025			KEGG_HOMOLOGOUS_RECOMBINATION
1.78	0.0033			PID_AURORA_B_PATHWAY
1.74	0.0019			REACTOME_EXTENSION_OF_TELOMERES
1.7	0.0068			PID_ATR_PATHWAY
1.65	0.0024			REACTOME_CHROMOSOME_MAINTENANCE
1.65	0.01			KEGG_DNA_REPLICATION
1.62	0.019			BIOCARTA_G2_PATHWAY
1.59	0.0015			REACTOME_MITOTIC_PROMETAPHASE
1.59	0.019			REACTOME_DNA_STRAND_ELONGATION
1.54	0.019			PID_AURORA_A_PATHWAY
1.53	0.0012			REACTOME_DNA_REPAIR
1.45	0.00027			REACTOME_CELL_CYCLE
1.45	0.039			REACTOME_TELOMERE_MAINTENANCE
1.41	0.0019			REACTOME_CELL_CYCLE_MITOTIC
-1.43	0.019			PID_P53_DOWNSTREAM_PATHWAY
-1.46	0.021			KEGG_APOPTOSIS
-1.47	0.047			PID_FOXP1_PATHWAY
-1.93	2.1e-06			HALLMARK_P53_PATHWAY
-2.38	7.5e-10			HALLMARK_APOPTOSIS
-2.69	7.5e-10			HALLMARK_INTERFERON_GAMMA_RESPONSE
-2.75	7.5e-10			HALLMARK_INFLAMMATORY_RESPONSE

CXCR4 hyperactivation accelerates TCL1-driven CLL and promotes aggressive transformation



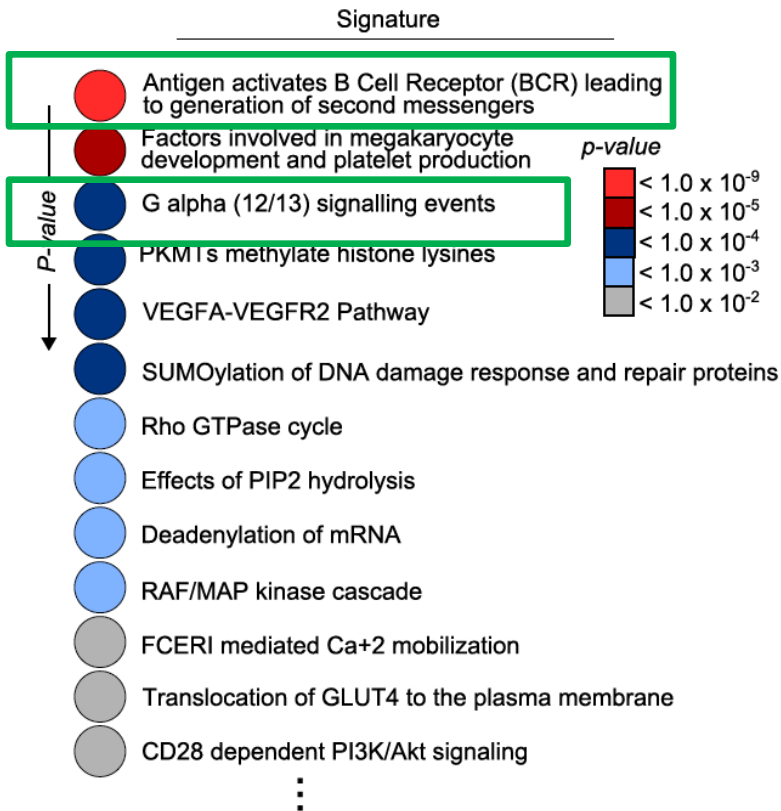
NES	FDR	<i>Eμ-TCL1;CXCR4^{C1013G}</i>	<i>Eμ-TCL1</i>	Pathway
2.25	7.5e-10			HALLMARK_E2F_TARGETS
2.15	1.7e-05			PID_PLK1_PATHWAY
2.13	2.1e-09			HALLMARK_G2M_CHECKPOINT
1.86	0.0016			PID_FOXM1_PATHWAY
1.83	0.0025			KEGG_HOMOLOGOUS_RECOMBINATION
1.78	0.0033			PID_AURORA_B_PATHWAY
1.74	0.0019			REACTOME_EXTENSION_OF_TELOMERES
1.7	0.0068			PID_ATR_PATHWAY
1.65	0.0024			REACTOME_CHROMOSOME_MAINTENANCE
1.65	0.01			KEGG_DNA_REPLICATION
1.62	0.019			BIOCARTA_G2_PATHWAY
1.59	0.0015			REACTOME_MITOTIC_PROMETAPHASE
1.59	0.019			REACTOME_DNA_STRAND_ELONGATION
1.54	0.019			PID_AURORA_A_PATHWAY
1.53	0.0012			REACTOME_DNA_REPAIR
1.45	0.00027			REACTOME_CELL_CYCLE
1.45	0.039			REACTOME_TELOMERE_MAINTENANCE
1.41	0.0019			REACTOME_CELL_CYCLE_MITOTIC
-1.43	0.019			PID_P53_DOWNSTREAM_PATHWAY
-1.46	0.021			KEGG_APOPTOSIS
-1.47	0.047			PID_FOXP_PATHWAY
-1.93	2.1e-06			HALLMARK_P53_PATHWAY
-2.38	7.5e-10			HALLMARK_APOPTOSIS
-2.69	7.5e-10			HALLMARK_INTERFERON_GAMMA_RESPONSE
-2.75	7.5e-10			HALLMARK_INFLAMMATORY_RESPONSE

CXCR4 hyperactivation accelerates TCL1-driven CLL and promotes aggressive transformation

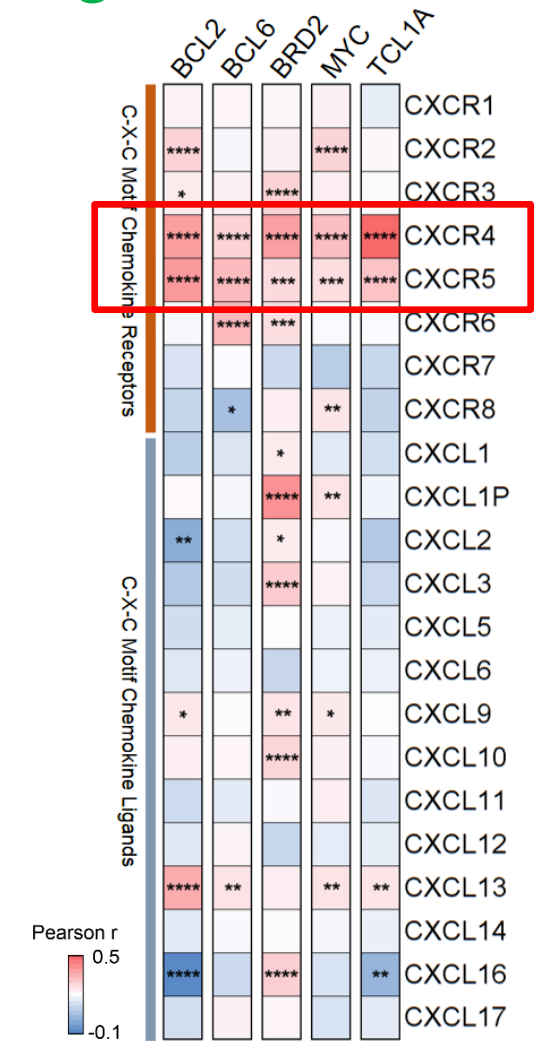


NES	FDR	<i>Eμ-TCL1;CXCR4^{C1013G}</i>	<i>Eμ-TCL1</i>	Pathway
2.25	7.5e-10			HALLMARK_E2F_TARGETS
2.15	1.7e-05			PID_PLK1_PATHWAY
2.13	2.1e-09			HALLMARK_G2M_CHECKPOINT
1.86	0.0016			PID_FOXM1_PATHWAY
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1.54	0.019			PID_AURORA_A_PATHWAY
1.53	0.0012			REACTOME_DNA_REPAIR
1.45	0.00027			REACTOME_CELL_CYCLE
1.45	0.039			REACTOME_TELOMERE_MAINTENANCE
1.41	0.0019			REACTOME_CELL_CYCLE_MITOTIC
-1.43	0.019			PID_P53_DOWNSTREAM_PATHWAY
-1.46	0.021			KEGG_APOPTOSIS
-1.47	0.047			PID_FOXP_PATHWAY
-1.93	2.1e-06			HALLMARK_P53_PATHWAY
-2.38	7.5e-10			HALLMARK_APOPTOSIS
-2.69	7.5e-10			HALLMARK_INTERFERON_GAMMA_RESPONSE
-2.75	7.5e-10			HALLMARK_INFLAMMATORY_RESPONSE

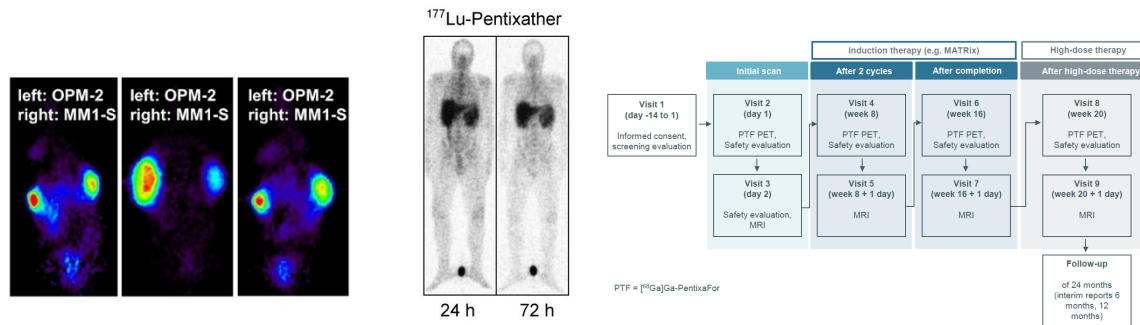
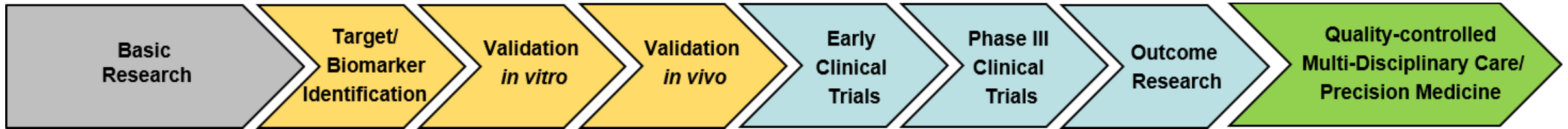
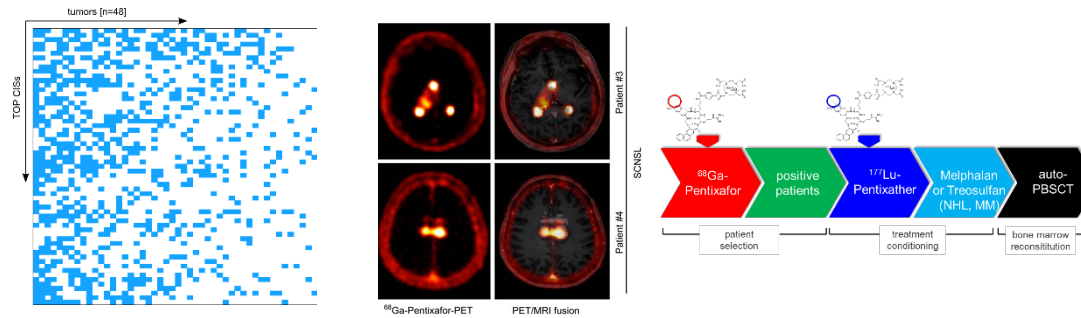
Pathway enrichment analysis in MYC-induced lymphomagenesis identifies BCR/chemokine receptor signaling



Name	p-value
Chemokine signaling pathway	1.37e-7
Regulation of actin cytoskeleton	2.03e-7
PI3K-Akt signaling pathway	2.90e-7
MAPK signaling pathway	4.72e-7
Focal adhesion	6.40e-7
Endometrial cancer	9.04e-7
Acute myeloid leukemia	1.28e-6
Ras signaling pathway	1.28e-6
Transcriptional misregulation in cancer	1.52e-6
p53 signaling pathway	3.47e-6
Chronic myeloid leukemia	6.17e-6
B cell receptor signaling pathway	6.77e-6
Cell cycle	1.06e-5
ErbB signaling pathway	1.44e-5
FoxO signaling pathway	1.73e-5
Jak-STAT signaling pathway	3.93e-5
T cell receptor signaling pathway	4.69e-5
Renal cell carcinoma	5.13e-5
Natural killer cell mediated cytotoxicity	7.76e-5
RNA degradation	7.76e-5



Molecular Imaging and Theranostics : Essential Building Blocks for the Translational Value Chain



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