CD3 | CENTRE FOR DRUG DESIGN AND DISCOVERY

Inhibition of LEDGF-MLL OR PWWP chromatin binding to treat AML

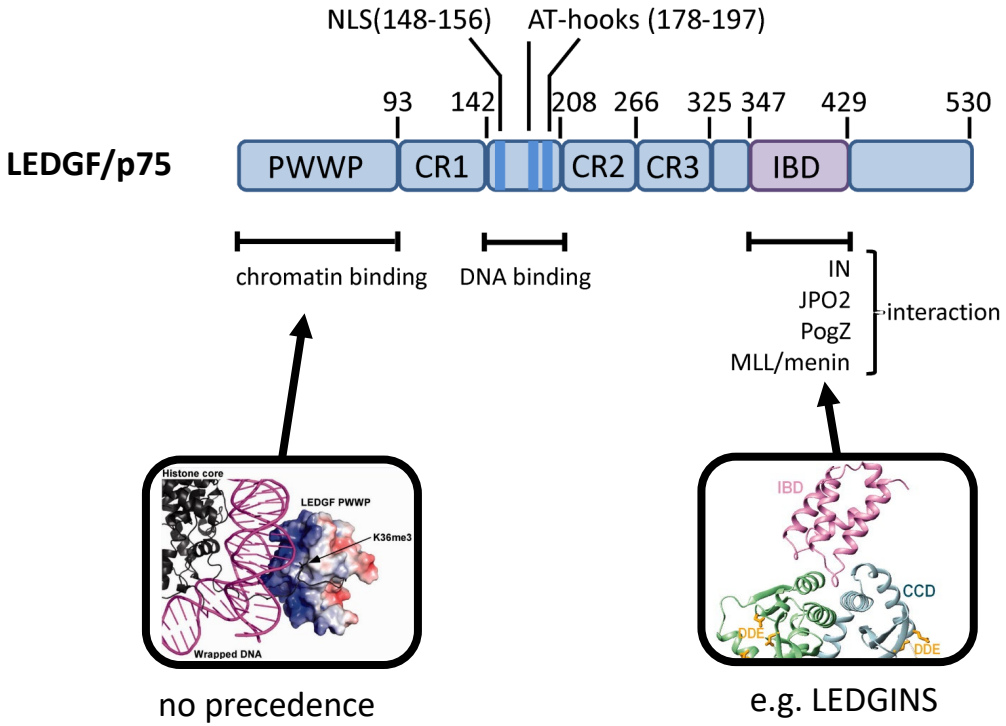
Targeting LEDGF - PWWP

- targeting LEDGF/p75 for the treatment of **HoxA9 transcription driven leukemias,**
  - **including Mixed-Lineage-Leukemia (MLL), but very probable also**
  - **NUP98 fusions and NPM1 mutant AML**

- **MLL – Mixed Lineage Leukemia- in a nutshell**

	ALL with MLL-r	AML with MLL-r
Average age at presentation	Infants 3-12 months	<2 and >10
Standard of care	Intensive multi-year combination chemotherapy	Systemic combination chemotherapy
Relapsed/refractory disease	Allogenic stem cell transplantation	Allogenic stem cell transplantation
Survival (5-Y event free)	27%	45% (MLL-AF9) 11% (others)

LEDGF, a chromatin tethering factor



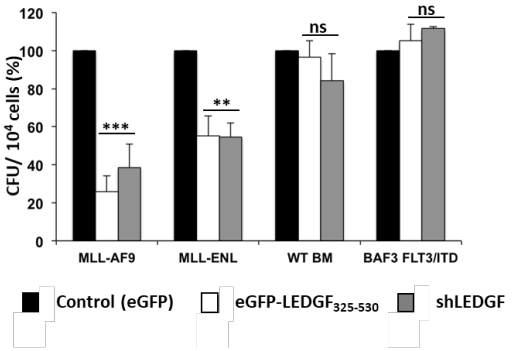
- LEDGF/p75 belongs to the HDGF family of proteins and was initially identified as a co-purifying with PC4 (Ge, Si el et al. 1998)
- LEDGF/p75 is a transcriptional co-activator involved in stress response

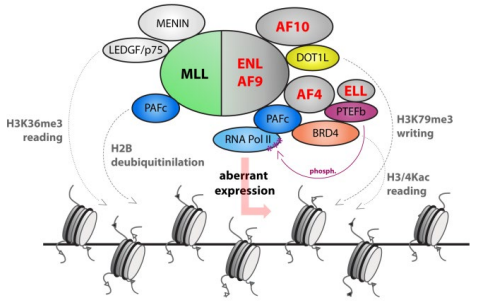
Cermakova et al., Lessons learned: HIV points the way towards presision treatment of MLL, TiPS (2016)

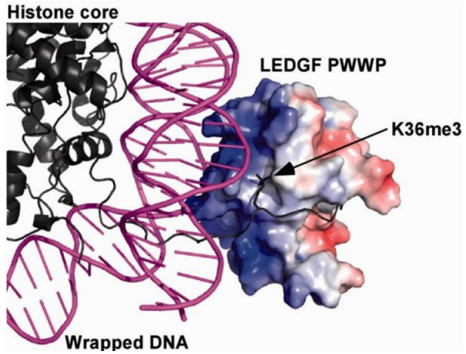
LEDGF/p75: targeting PWWP domain

- The interaction is retained in all fusions
- LEDGF/p75 knockout in the hematopoietic system is viable
- The LEDGF/p75-menin binding of fusions is essential for the clonal expansion
- Druggable pocket
- Full structural characterisation available
- Single point mutations in the hydrophobic pocket can inhibit LEDGF function (redirection on the chromatin?)
- Good target specific knowledge (long standing history in studying LEDGF/p75)

$P_{19}H_{20}W_{21}P_{41}$





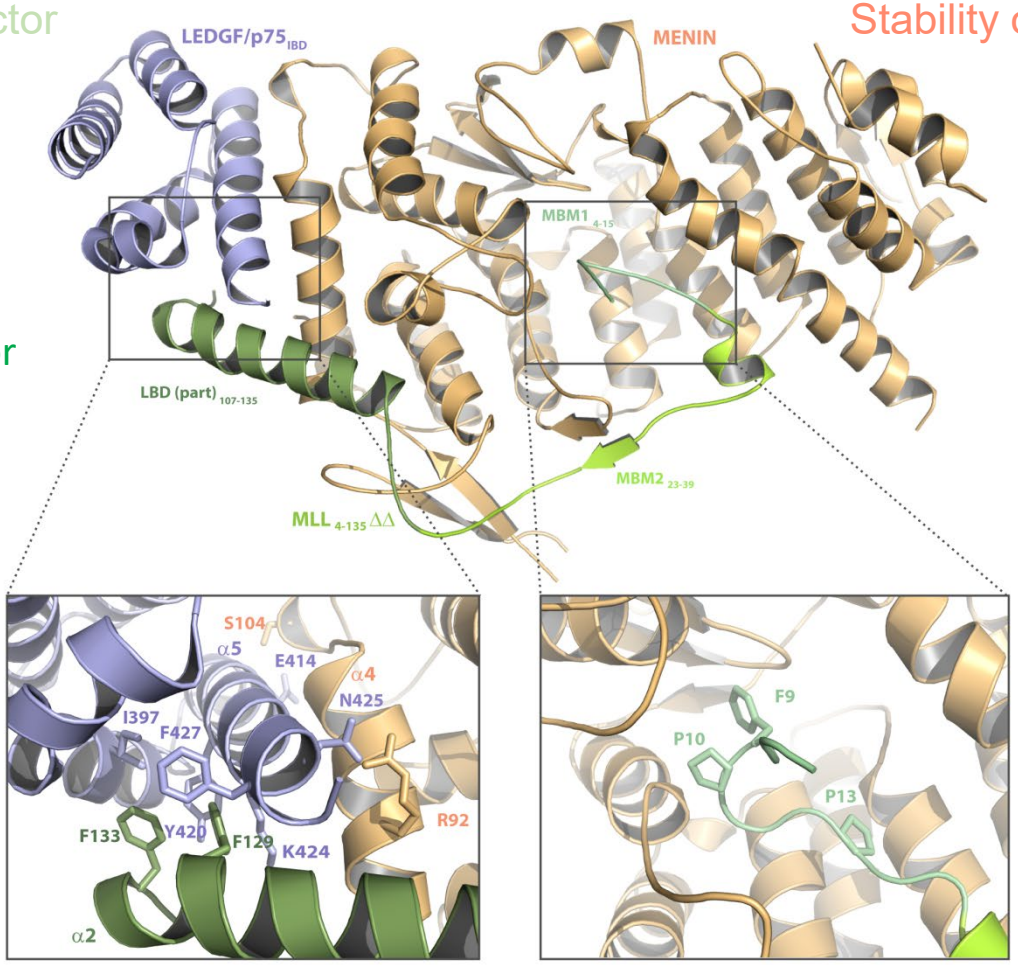


LEDGF/p75: targeting LEDGF-MLL Interaction

Chromatin tethering factor

Transcriptional regulator
Oncogenic agent

Stability of the ternary complex



Ternary complex inhibitors
MLL-LEDGF inhibitors

MLL-MENIN inhibitors

*Huang et al. 2012