KRONOS·BIO

We are a clinical-stage biopharmaceutical company dedicated to the discovery and development of novel cancer therapeutics designed to transform patient outcomes by targeting dysregulated transcription.

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Scientific Founder

Associate Professor, Koch Institute for Integrative Cancer Research

MIT biological engineering

Charles Lin Ph.D.
MIT CSB 2012

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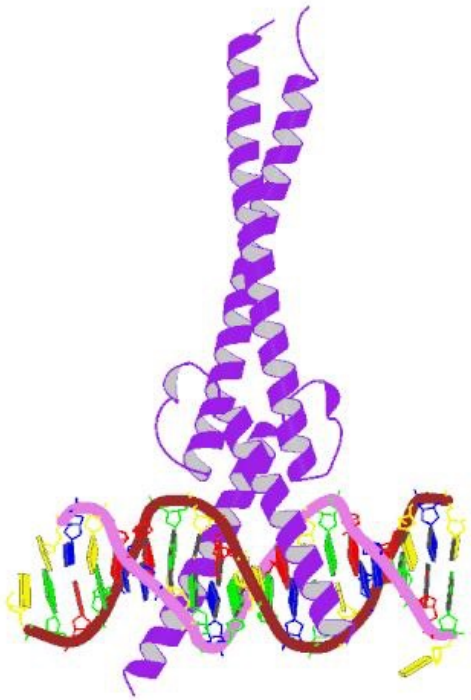
charles.lin@kronosbio.com

Problem: Transcription factors (TFs) are high-value but historically challenging targets

>500 human TFs
>50 known oncogenic role

MYC oncogenic TF

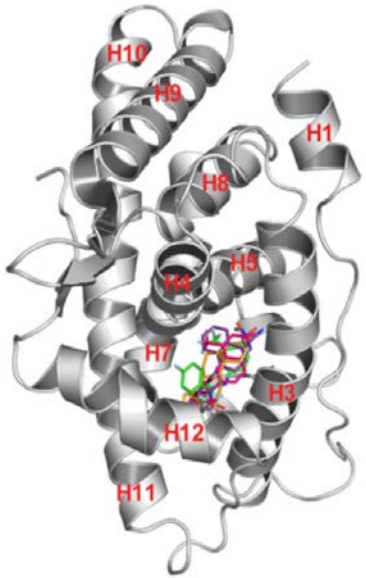


Existing TF therapies (<10 TFs drugged)

Androgen and estrogen receptor

Xtandi™ (enzalutamide)

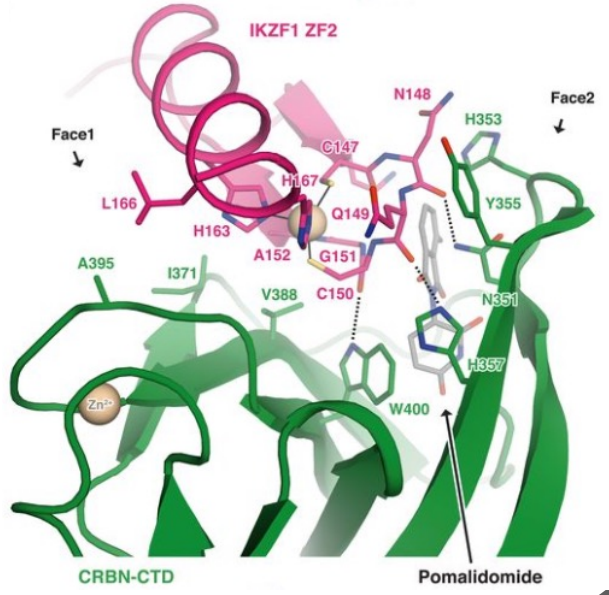
Faslodex™ (fulvestrant)



IMiDs degrade Ikaros/Aiolos TFs

Pomalyst™ (pomalidomide)

Revlimid™ (lenalidomide)



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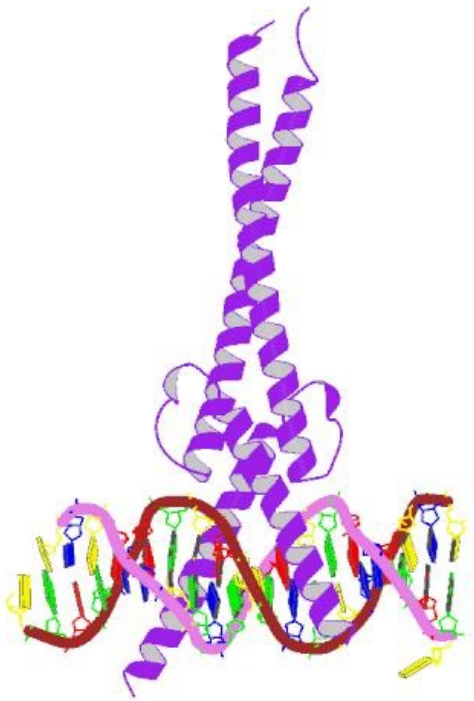
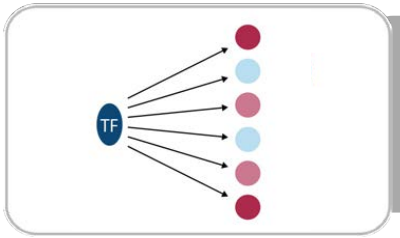
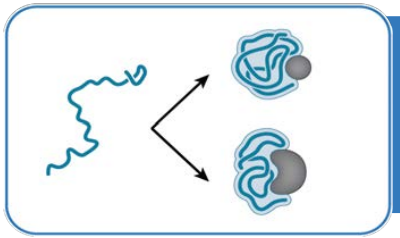


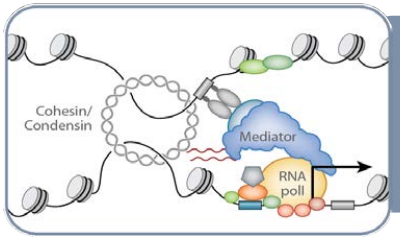
CHALLENGES



Context-dependent **activity**



Context-dependent **structure**



Context-dependent **complexes**

Problem: Transcription factors (TFs) are high-value but historically challenging targets

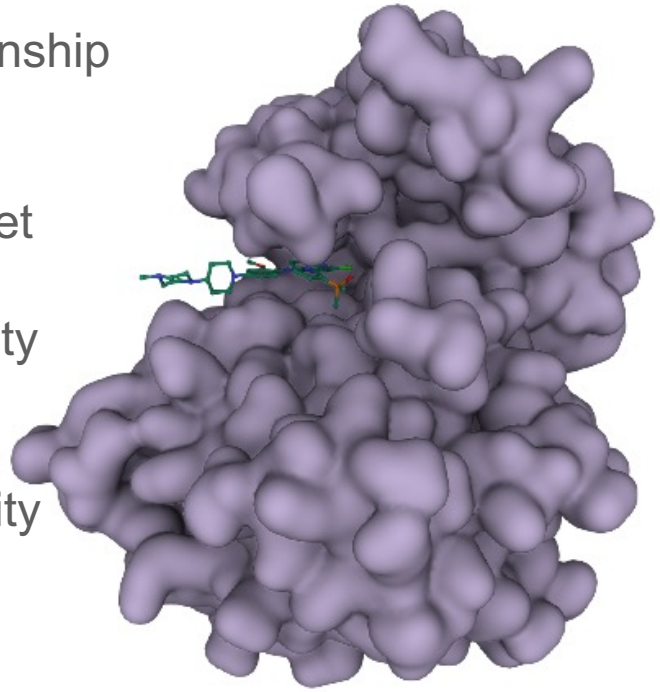
Anaplastic lymphoma kinase (ALK)
classic druggable protein

Structure/function relationship established

Ligandable binding pocket

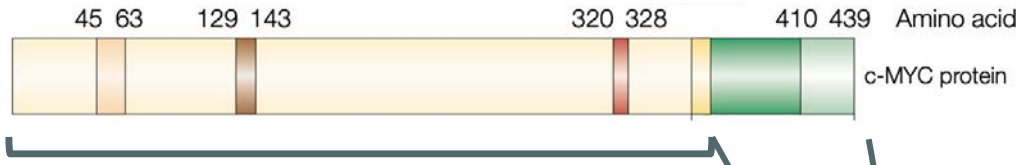
Established *in vitro* activity assays

Ability to assess selectivity (e.g., across kinases)



PDB 6MX8

MYC



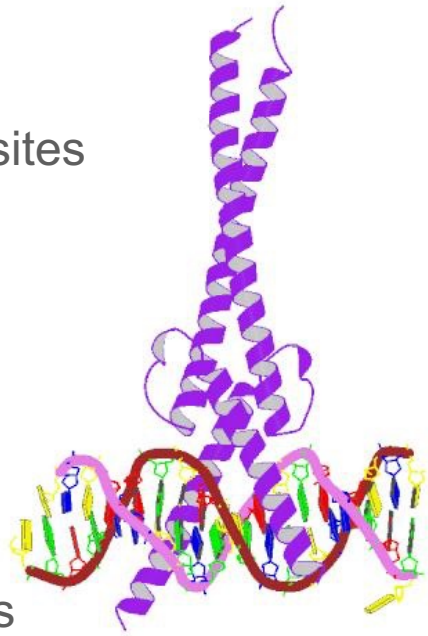
80% of MYC protein is intrinsically disordered

Acts by recruiting numerous cofactors to genomic binding sites

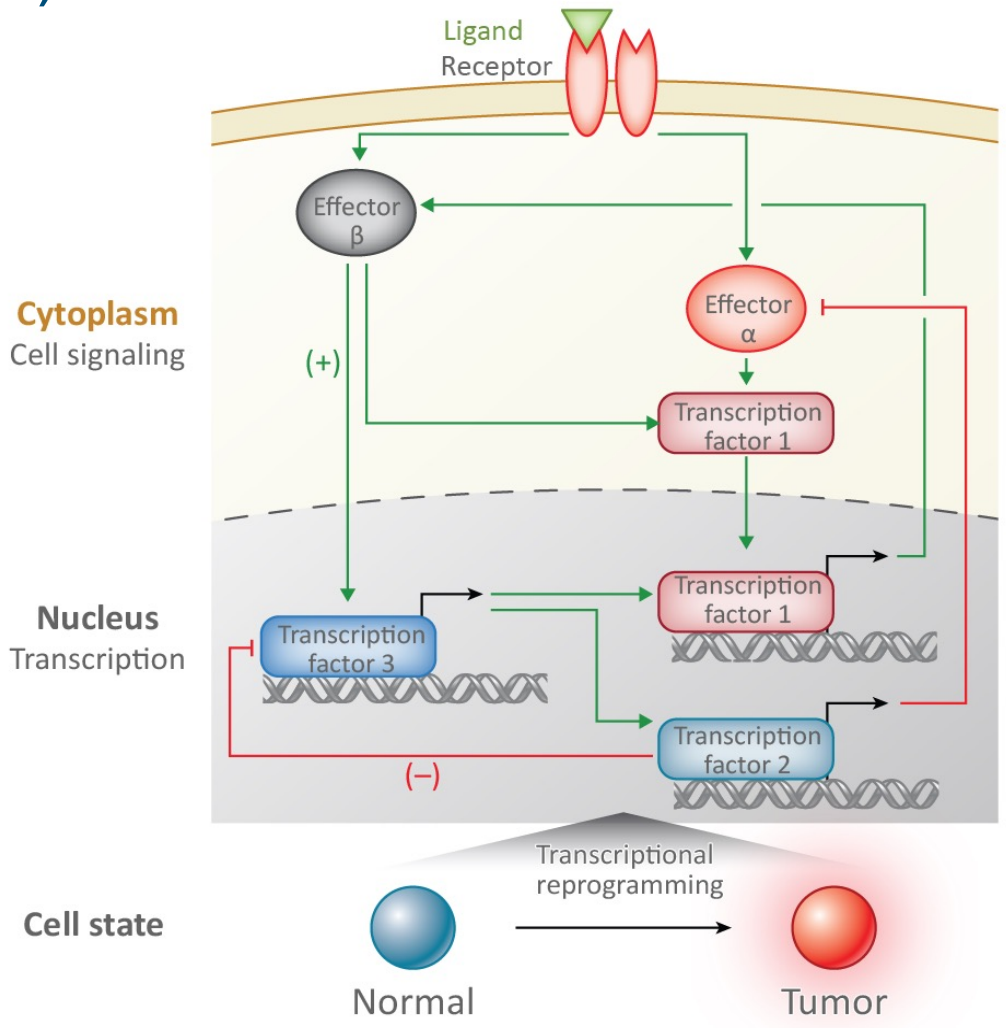
No active site

No *in vitro* activity assays

Cellular assays confounded by difficulty distinguishing MYC-specific vs. global effects

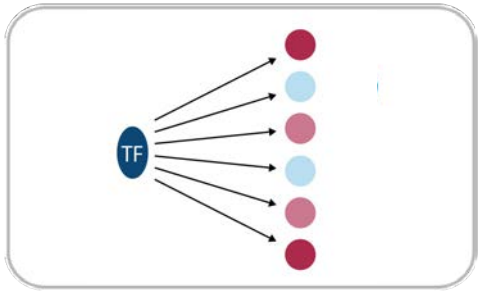


Solution: Mapping oncogenic transcription regulatory networks (TRNs)



- Dynamic
- Interdependent
- Bi-directional

ACTIVITY



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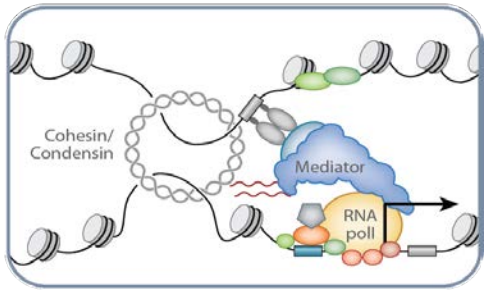
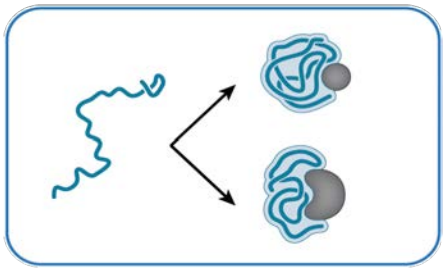


TF: Transcription factor. TRN: Transcriptional regulatory network.

Solution: Small molecule microarray (SMM) platform finds binders to components of an oncogenic TRN

STRUCTURE



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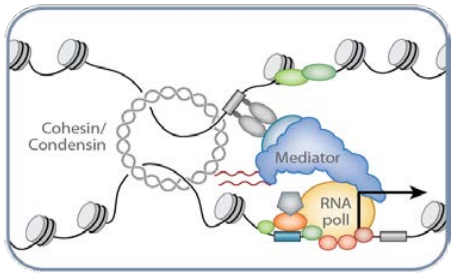
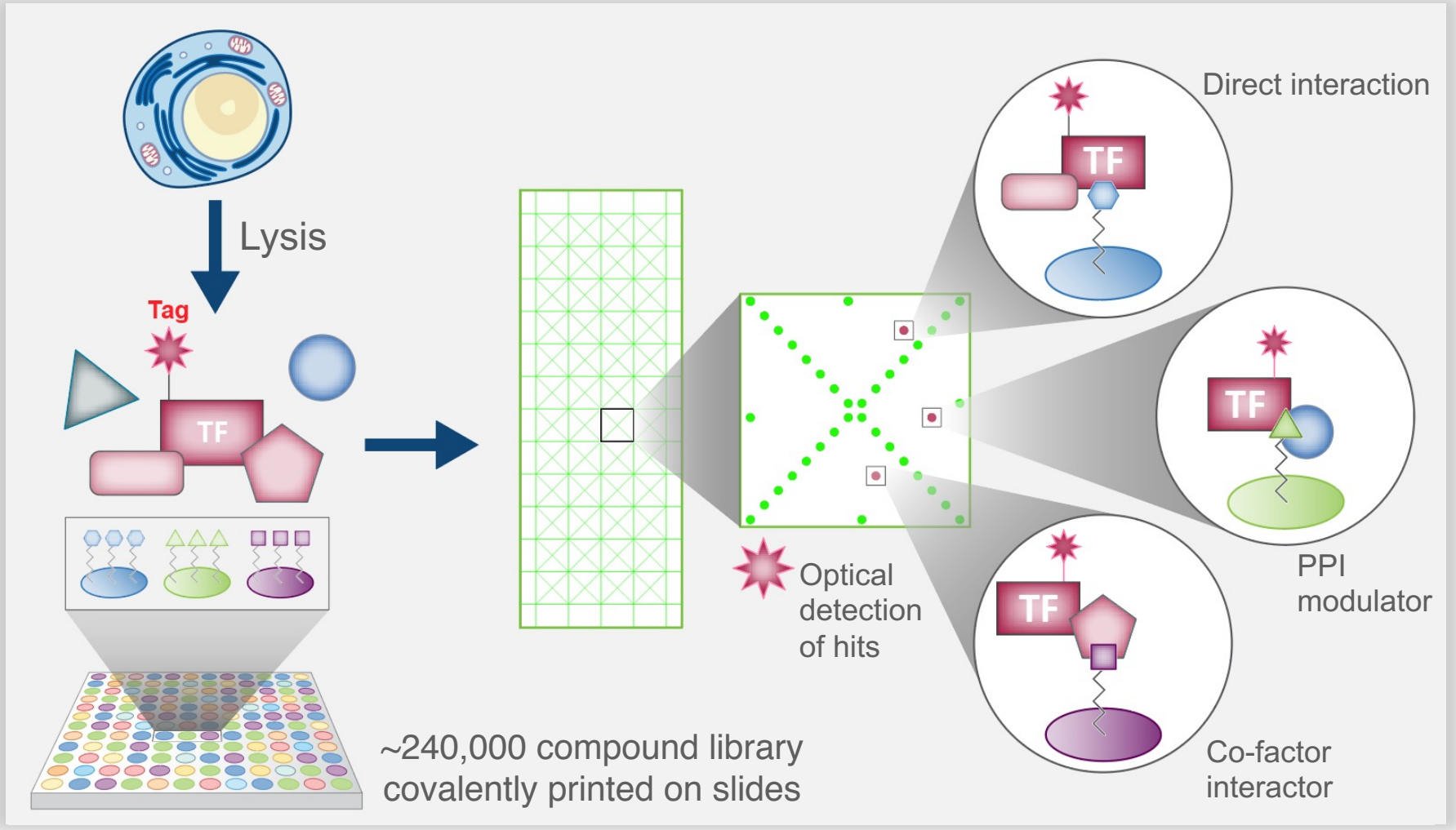




PPI: Protein-protein interaction. SMM: Small molecule microarray. TF: Transcription factor. TRN: Transcriptional regulatory network.

Solution: TRN SMM hits characterized by potency and selectivity

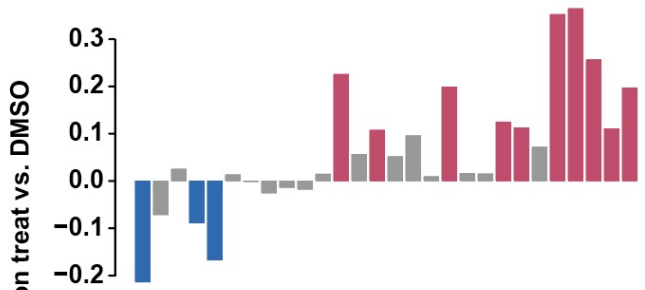
SMM hit potency
% reporter inhibition

SMM hits ranked by potency

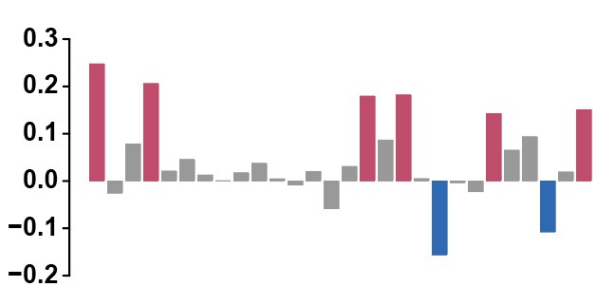
96.93	X
92.06	Y
91.27	
89.4	
70.68	
64.86	
44.37	
36.97	
31.47	Z
29.17	
29.09	
26.89	
26.33	
23.11	
22.83	
22.69	
21	
20.64	
20.25	
19.92	
19.78	
19.53	
18.91	
17.38	

SMM hit selectivity assessed by TRN gene expression signature

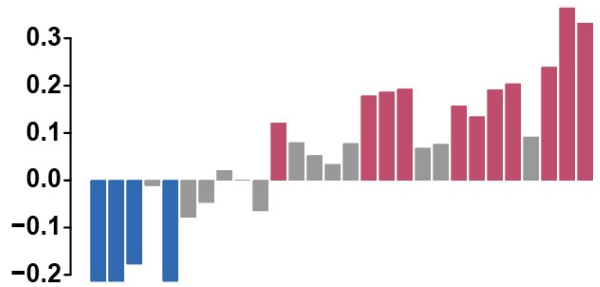
Hit X – potent and semi-selective



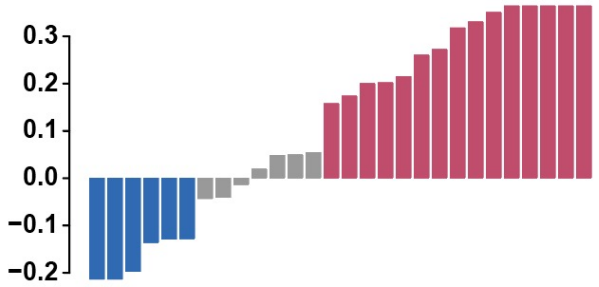
Hit Y – potent, but nonselective



Hit Z – less potent, but highly selective

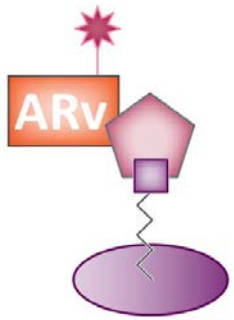


Ideal TRN activity signature – from modeled degradation of AR

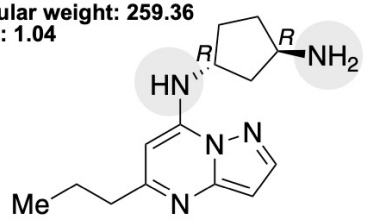


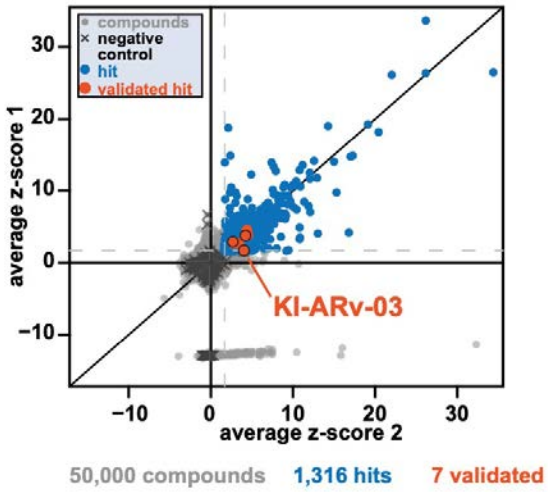
AR: Androgen receptor. ARv: Androgen receptor variant. DMSO: Control. SMM: Small molecule microarray. TRN: Transcriptional regulatory network.

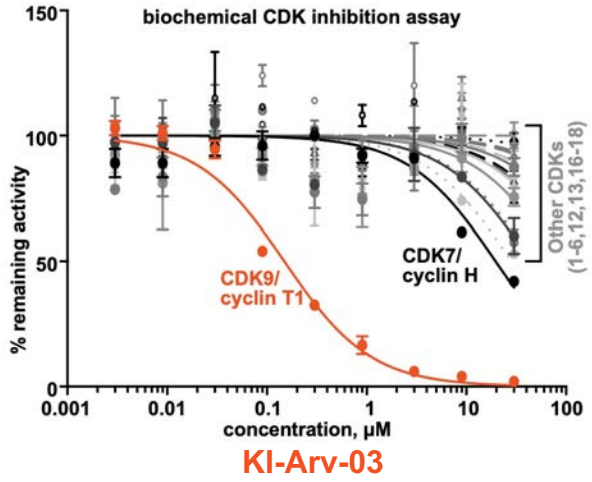
Example: Development of KB-0742 an orally bioavailable and highly selective CDK9 inhibitor



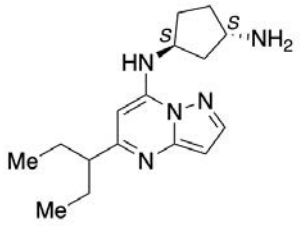
KI-ARv-03
molecular weight: 259.36
cLogP: 1.04







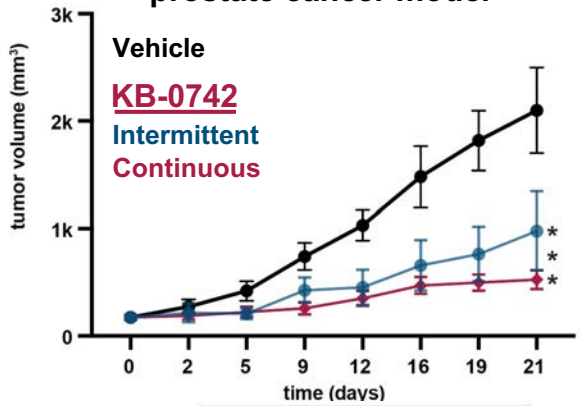
KB-0742
molecular weight: 287.4
cLogP: 1.97

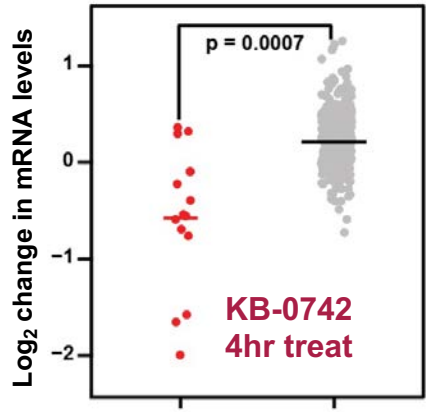


KB-0742

CDK9	IC_{50} = 6 nM
CDK13	62x
CDK2	66x
CDK12	98x
CDK18	>200x
CDK3	>200x
CDK7	>200x
CDK16	>200x
CDK5	>200x
CDK17	>200x
CDK1	>200x
CDK4	>200x
CDK6	>200x
CDK14	>200x
CDK8	>200x
CDK19	>200x

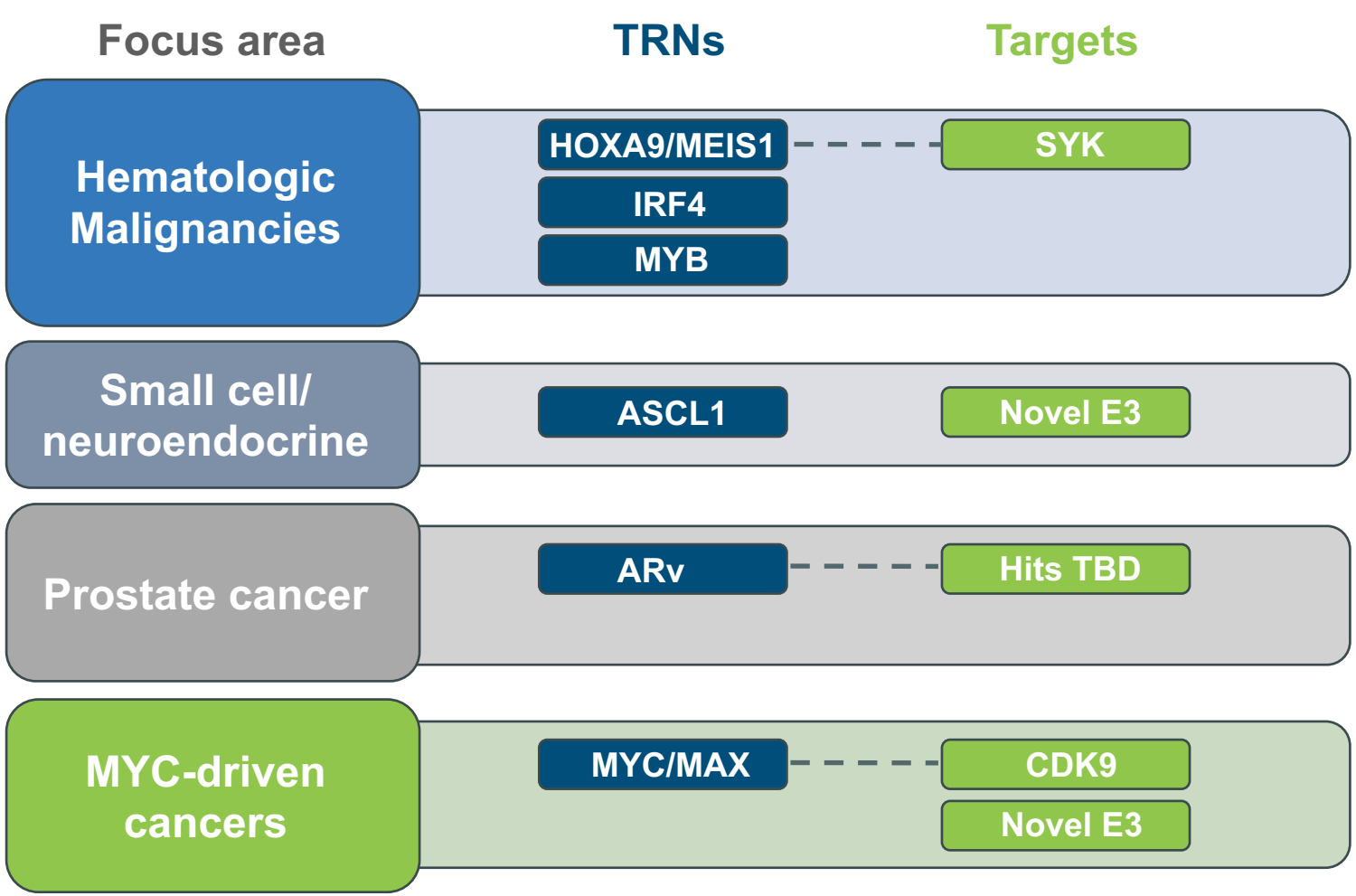
Castration resistant prostate cancer model

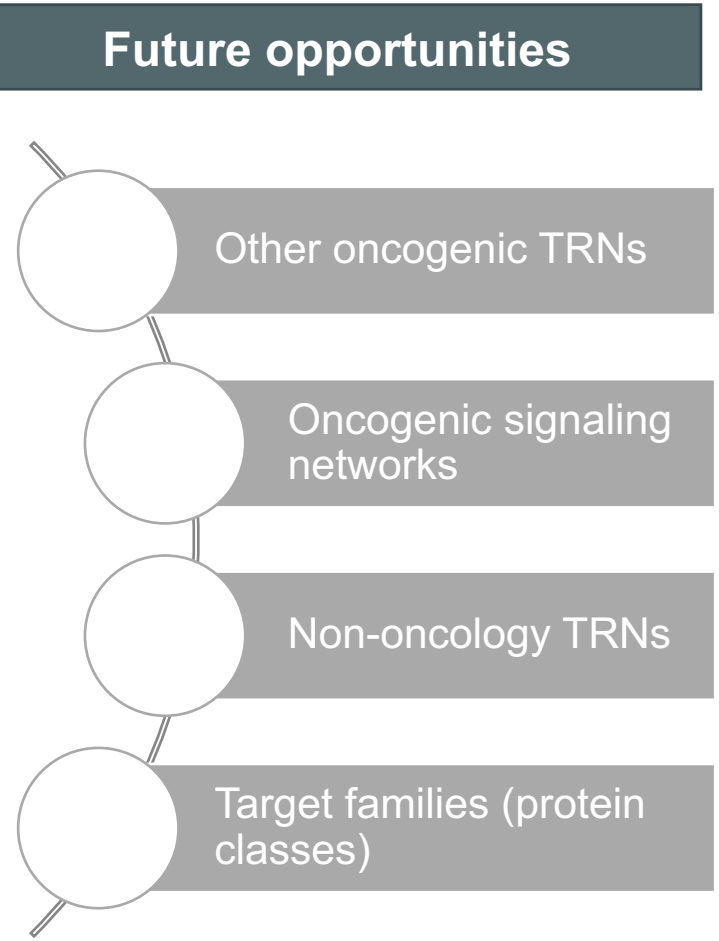




Richters et al., Cell Chemical Biology 2020

Current discovery programs and future opportunities for partnering





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