Metabolomics: Open Access

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ISSN: 2153-0769

Wrapping Designs in Molecular Cancer Therapy: Dehydrons as Filters for Drug Specificity

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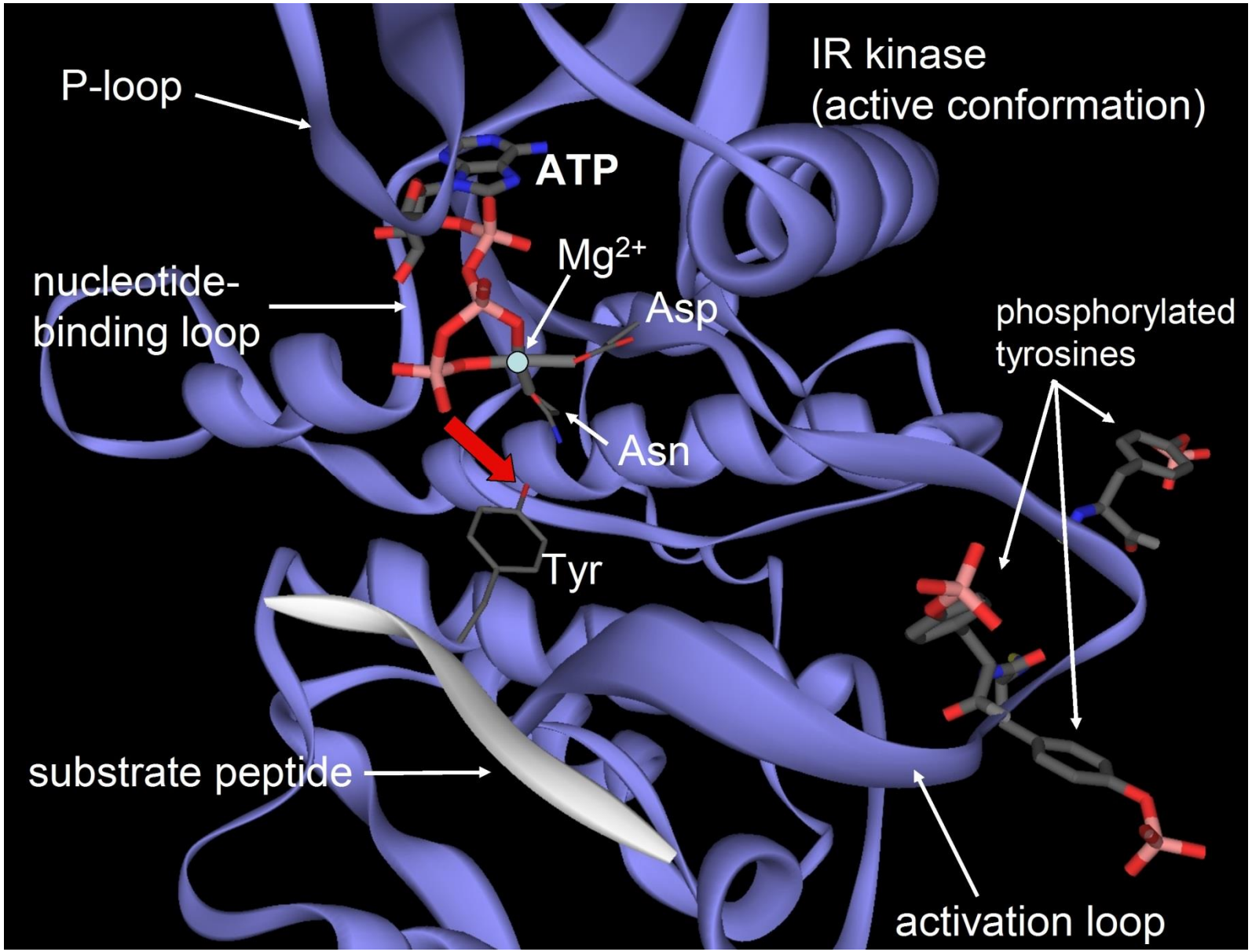

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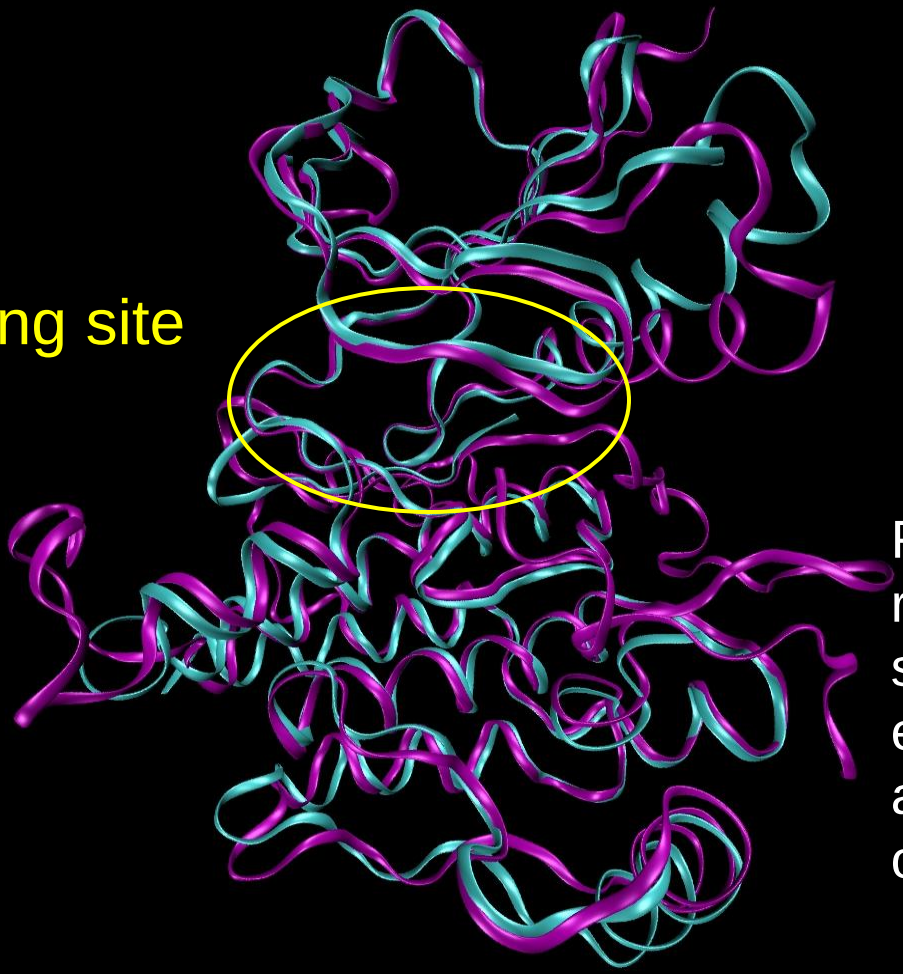
Focal adhesion kinase (FAK, major cancer target)

Insulin receptor kinase (INSR, target to be avoided)

ATP-binding site



Functional innovation resorts to the same folds, especially within a protein family or superfamily.

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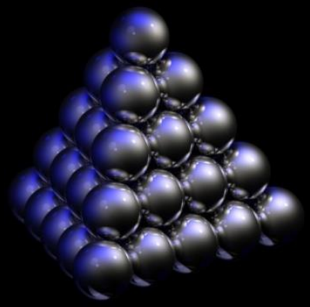

- The fold is highly conserved across proteins of common ancestry.
- The epistructural features are not conserved.
- Evolution tinkers with the epistructure to achieve functional innovation.

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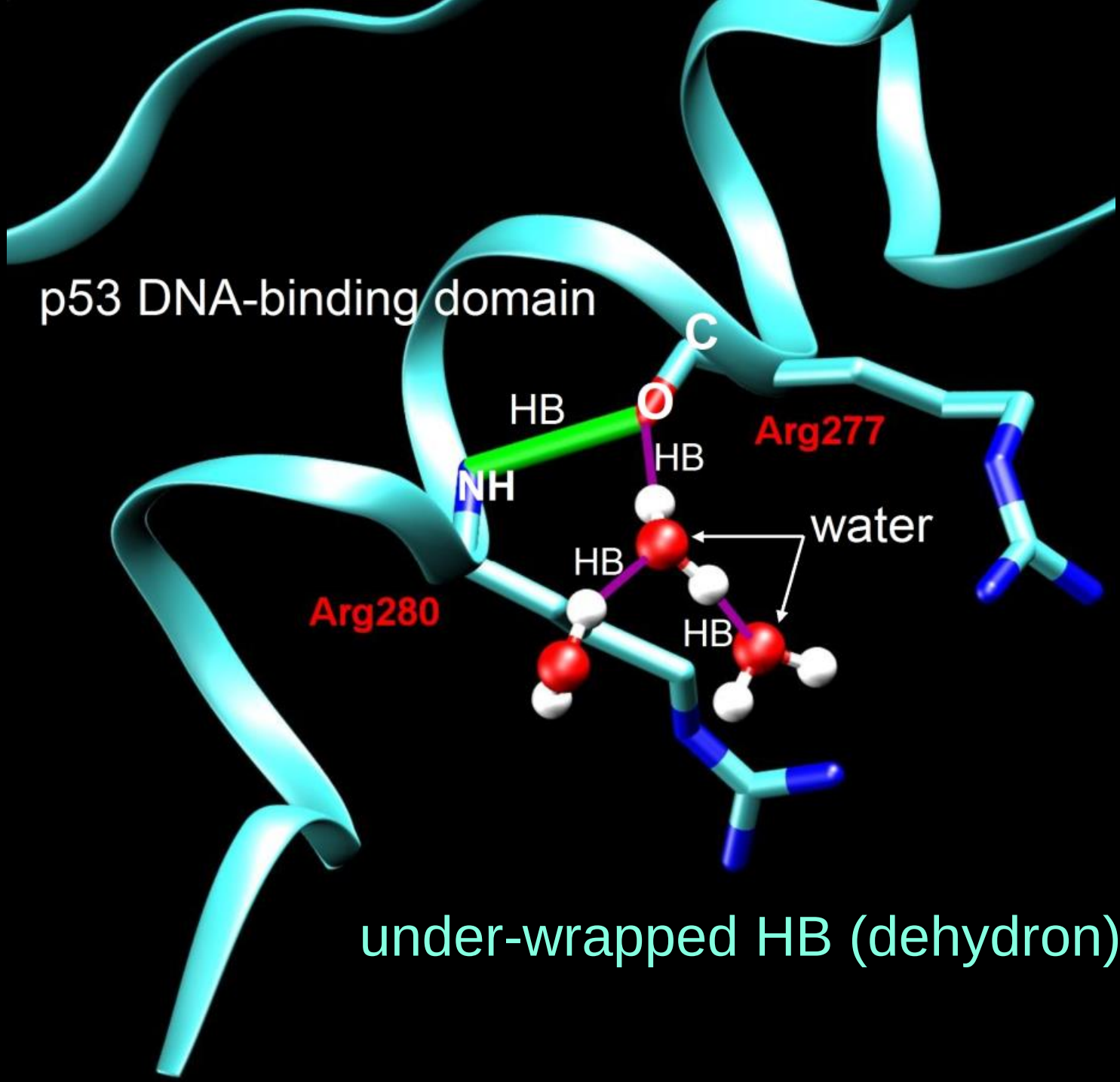

under-wrapped HB (dehydron)

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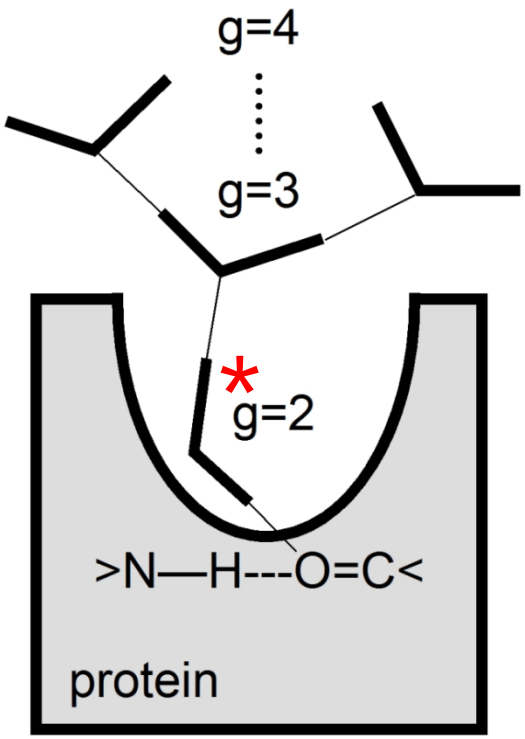
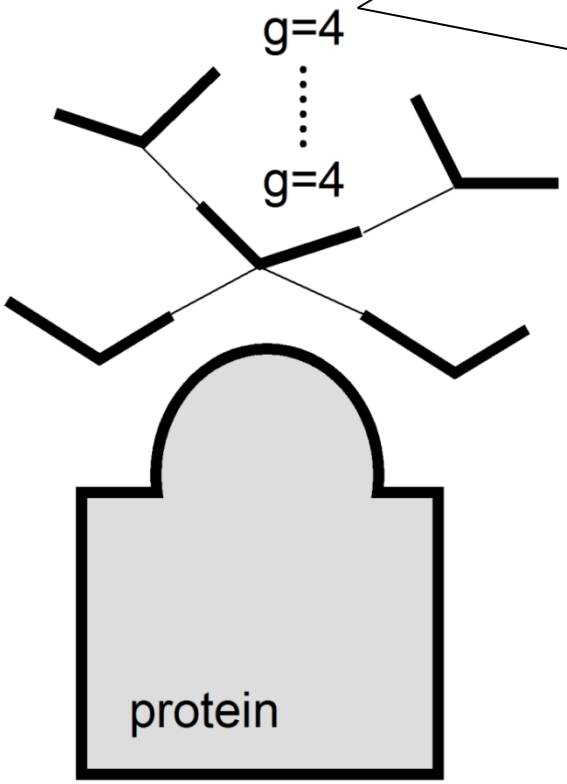
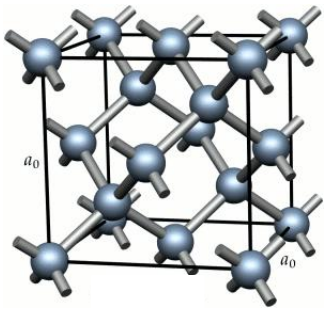
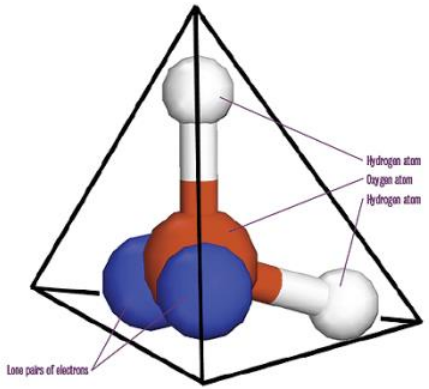
Dehydrons generate interfacial tension









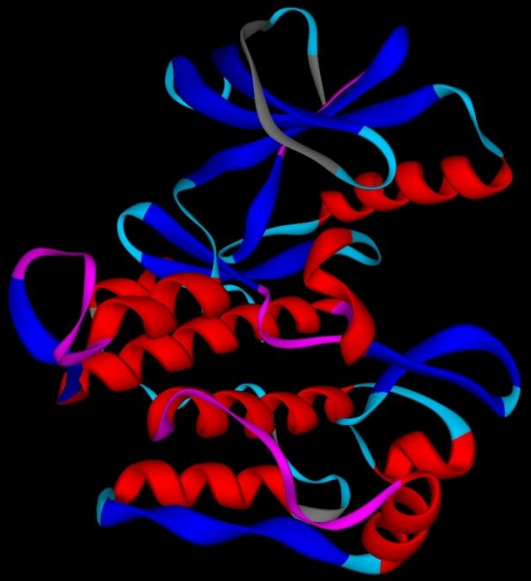
tension

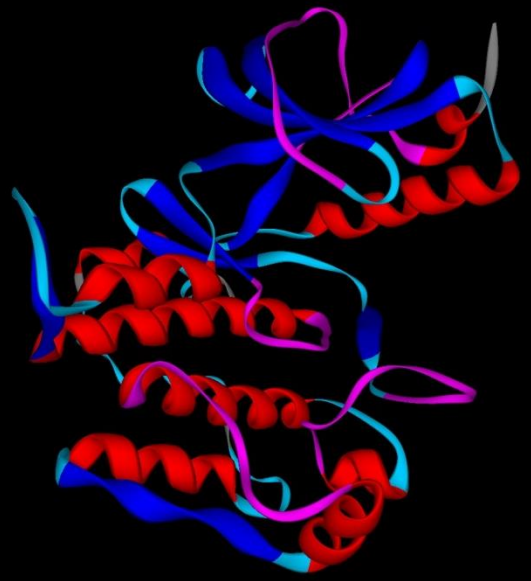
no tension

* hot water

A F, Phys. Rev. Lett. 108, 188102 (2012)

Homo sapiens

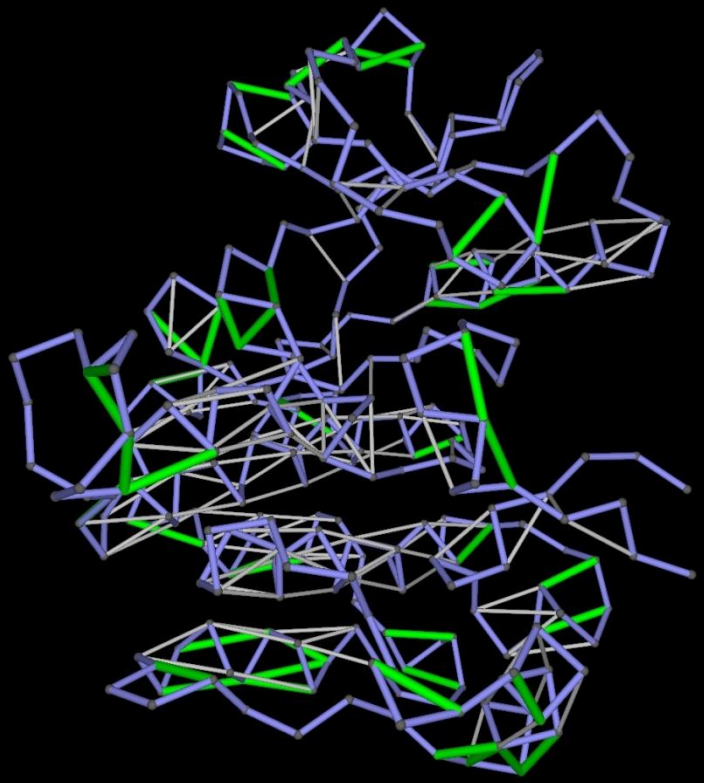


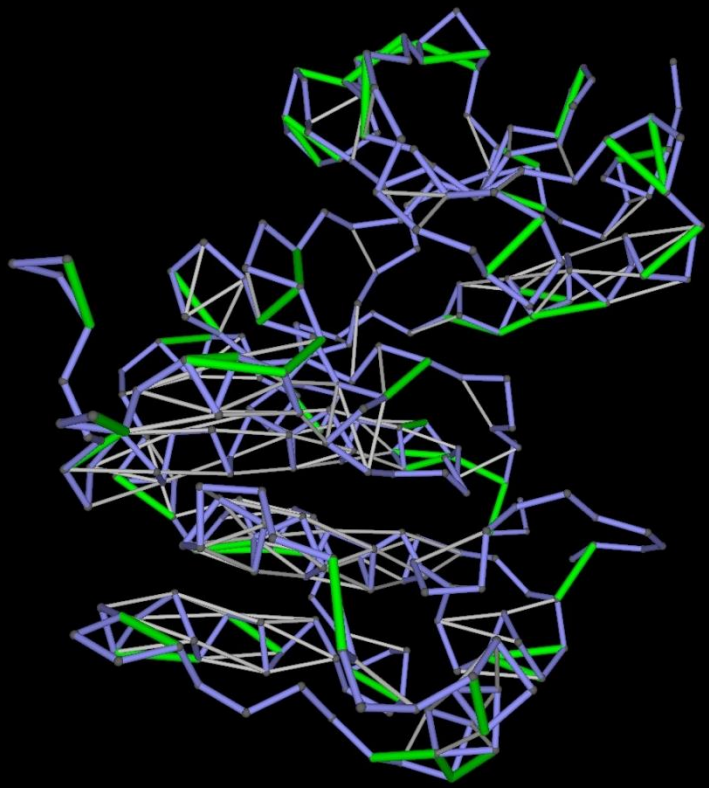


“same”
structure

IR

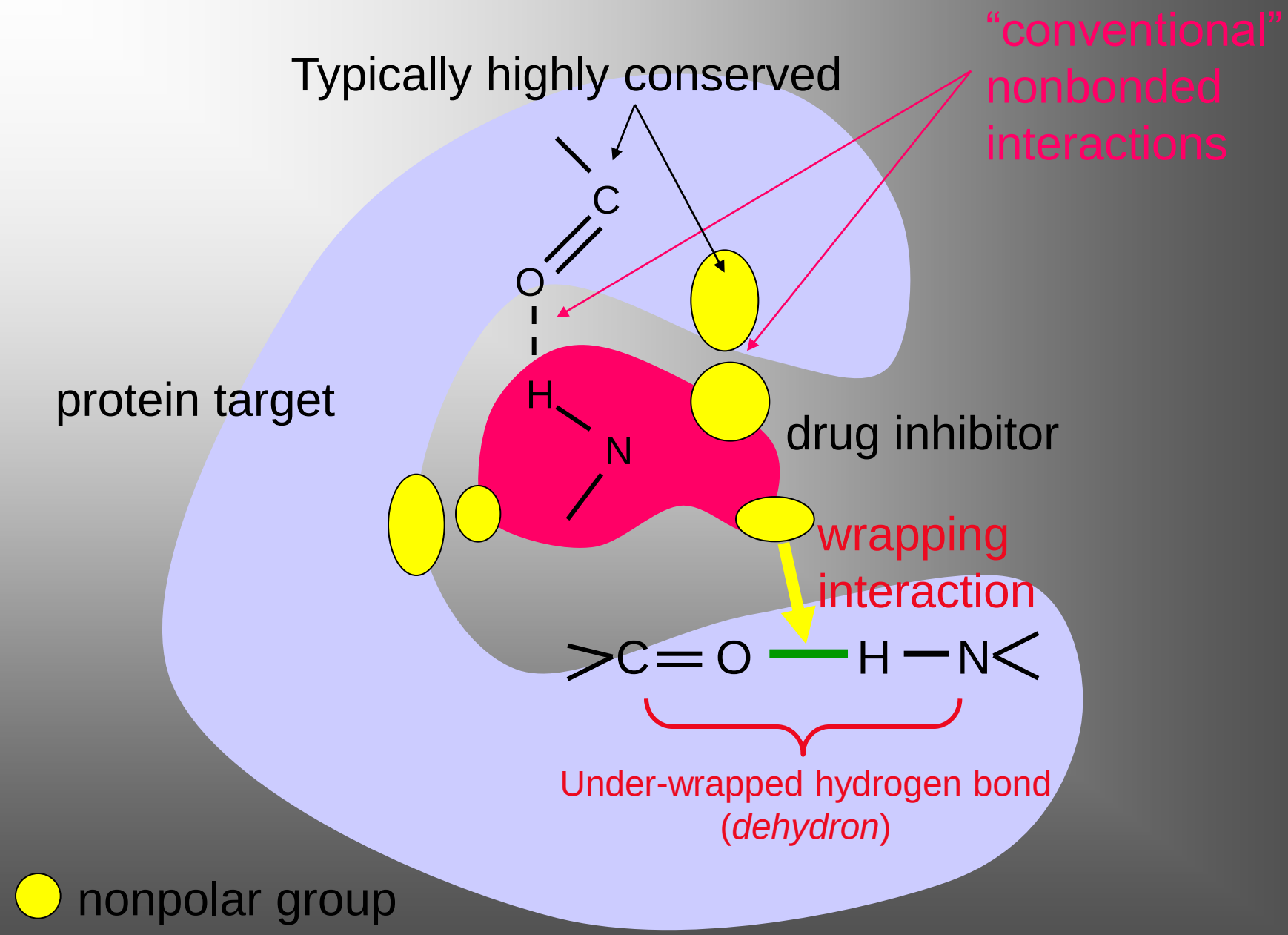
IGF1R





different
epistructure

Drug-as-wrapper paradigm



Nature Reviews Drug Discovery 7, 120-121 (2008)

ARTICLE

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Nature Medicine - **12**, 908 - 916 (2006)

Cardiotoxicity of the cancer therapeutic agent imatinib mesylate

Risto Kerkelä[1, 2], Luanda Grazette[3], Rinat Yacobi[4], Cezar Iliescu[5], Richard Patten[2], Cara Beahm[1], Brian Walters[2], Sergei Shevtsov[1, 2], Stéphanie Pesant[1], Fred J Clubb[6], Anthony Rosenzweig[3], Robert N Salomon[7], Richard A Van Etten[4], Joseph Alroy[7, 8], Jean-Bernard Durand[5] & Thomas Force[1, 2]

"Thus, cardiotoxicity is an unanticipated side effect of inhibition of c-Abl by imatinib".

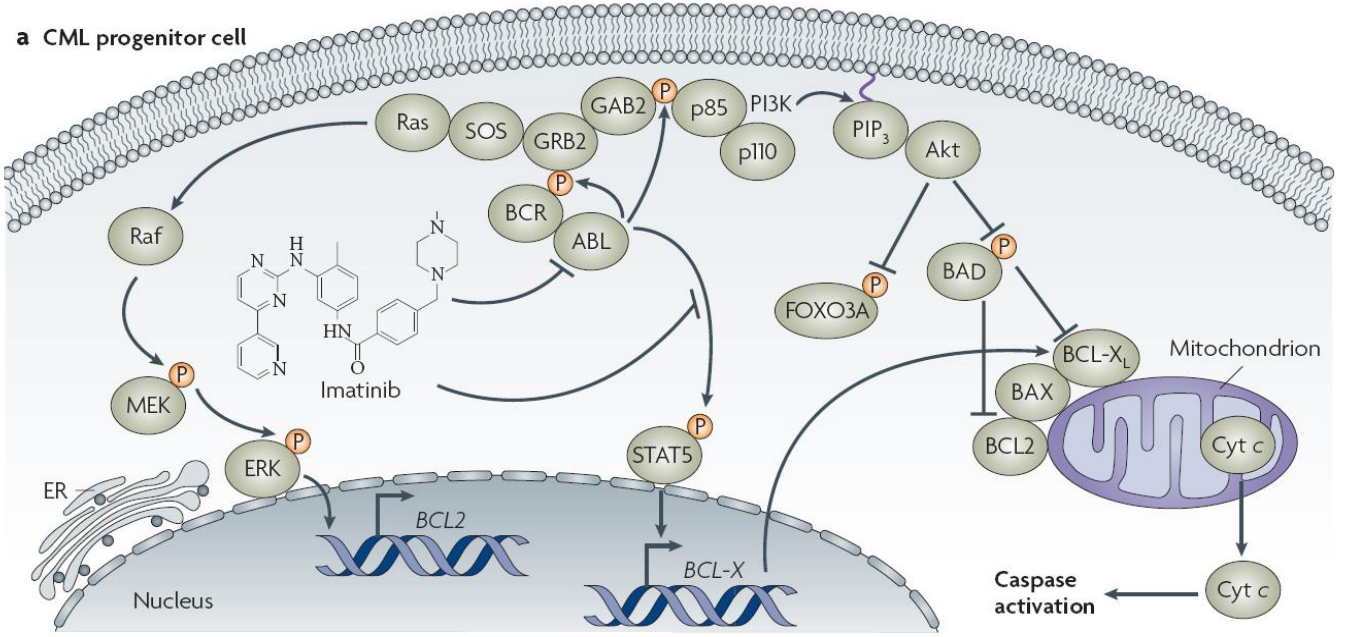
Challenge: Can we redesign imatinib to curb the side effect?

A. Fernandez et al. *J. Clin. Invest.* 117, 4044 (2007)

The role of the target protein is context-dependent

CML:

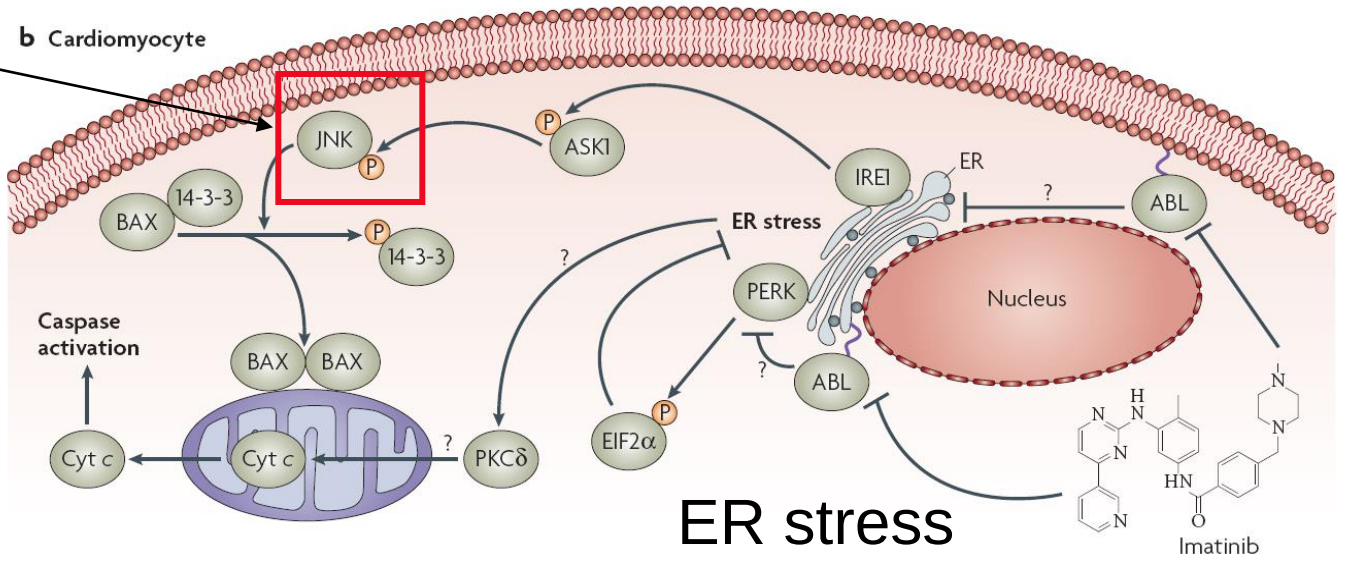
Bcr-ABL inhibition blocks the anti-apoptotic pathways



New target?

HEART:

ABL kinase inhibition induces ER stress, activates JNK-mediated pathways, ultimately leading to mitochondrial depolarization, ATP-depletion and cell death.



ER stress

Wrapping-based molecular engineering

Imatinib Targets	Therapeutic impact/ side effects
c-KIT	GIST, KIT-dependent melanomas Reversal of tumor-induced immunosuppresssion
Bcr-ABL	CML / cardiotoxicity
PDGFR	Anti-Angiogenic
LCK	Immunosuppression

Wish List

c-KIT
[Drug→ vaccine?]

PDGFR

JNK1/2

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- Drug Metabolism & Toxicology
- Diabetes & Metabolism
- Metabolic Syndrome
- Proteomics & Bioinformatics
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