

#### A Structural Approach to Discover an Achilles'heel of fungi: the case of Knr4/Smi1

Hélène Martin-Yken, Didier Zerbib, Sylviane Julien, Lionel Mourey, Laurent

Maveyraud, Jean Marie François

#### ▶ To cite this version:

Hélène Martin-Yken, Didier Zerbib, Sylviane Julien, Lionel Mourey, Laurent Maveyraud, et al.. A Structural Approach to Discover an Achilles'heel of fungi: the case of Knr4/Smi1. Fungal Cell Wall Meeting, Oct 2015, Paris, France. hal-02951422

#### HAL Id: hal-02951422 https://hal.inrae.fr/hal-02951422

Submitted on 28 Sep 2020

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# A Structural Approach to Discover an Achilles'heel of fungi : the case of Knr4/Smi1

<u>Hélène Martin-Yken<sup>1,2,3</sup>, Didier Zerbib<sup>1,2,3,</sup>, Sylviane Julien<sup>4,5</sup>, Lionel Mourey<sup>4,5</sup>, Laurent Maveyraud<sup>4,5</sup>, and Jean-Marie François<sup>1,2,3</sup>.</u>

1- Université de Toulouse, INSA, UPS, INP, LISBP, 135 Avenue de Rangueil, F-31077 Toulouse, France, 2- INRA, UMR792, Ingénierie des Systèmes Biologiques et des Procédés, F-31400 Toulouse, France,

3- CNRS, UMR5504, F-31400 Toulouse, France,

4- Institut de Pharmacologie et de Biologie Structurale (IPBS), CNRS, 205 route de Narbonne, BP 64182, Toulouse, F-31077, France

5- Université de Toulouse, Université Paul Sabatier, IPBS, Toulouse, F-31077, France

# Background

Intrinsically disordered proteins (IDPs) are involved in numerous essential biological processes. Their conformational flexibility gives them the ability to be involved in one-to-many binding (a single disordered domain is able to bind several structurally diverse partners). Highly connected proteins located at nodes in interactions networks or "Hubs" are significantly enriched in disordered domains which allow them to fulfil their multiple interactions.

## Knr4/Smi1 : a *S. cerevisiae* hub protein

functions in signaling, gene transcription, cell cycle progression and morphogenesis<sup>1</sup>;
*knr4*Δ : hypersensitive to stress conditions (high θ°, SDS, caffeine, CFW, ...);
multiple physical interacting partners;
over 280 synthetic lethal or sick interactions.

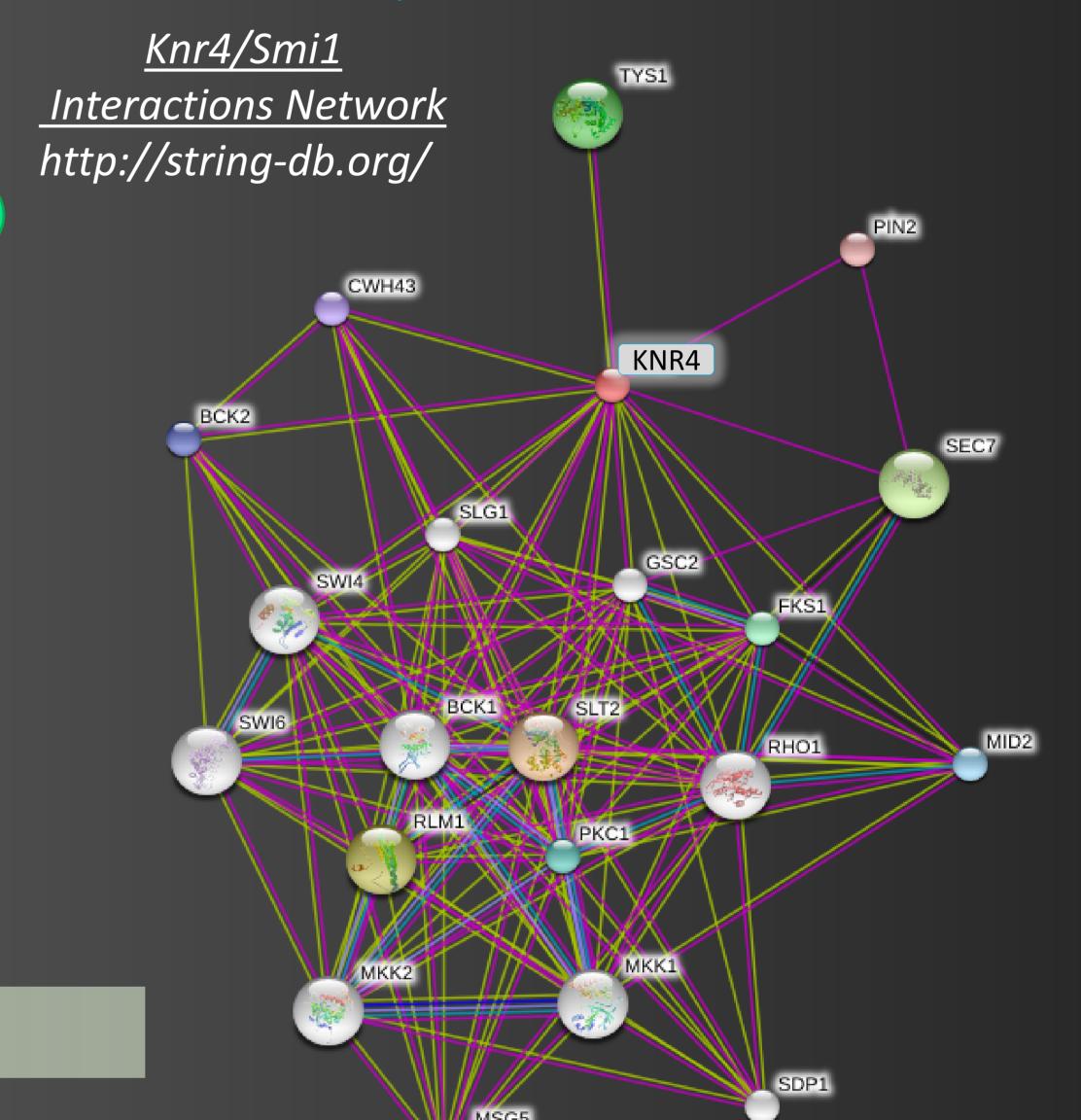
over 200 synthetic retriar of sick interactions.

- O14362		Schizosaccharomyces pombe	MI1_KNR4
	GS-1	Neurospora crassa	
	<b></b> _ B0Y387	Aspergillus fumigatus	
	Q0UG76	Phaeosphaeria nodorum	
Г Т г	Q6CDX0	Yarrowia lipolytica	
	SMI1	Saccharomyces cerevisiae	
	SMI1B	Candida albicans	SMI1_KNR4
	SMI1	Candida albicans	
		Candida albicans	

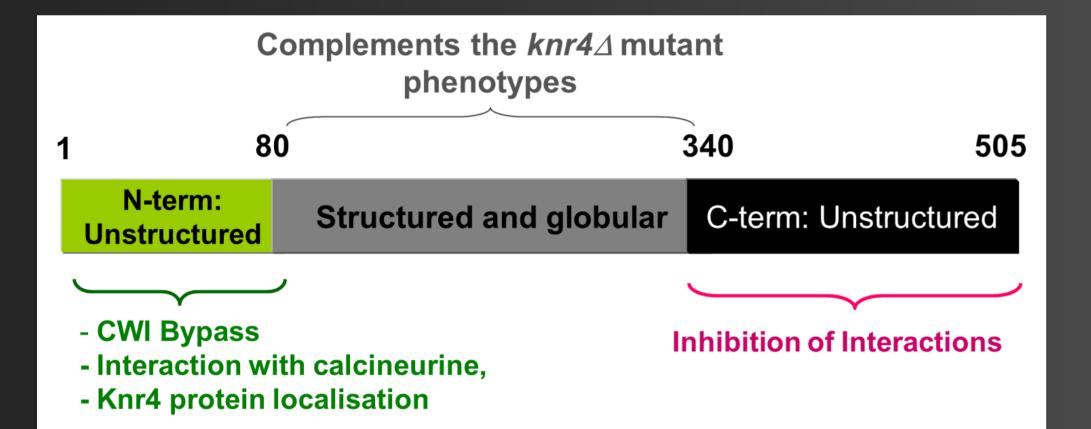
### Conservation of Knr4 gene among the fungal kingdom.

Phylogenetic tree made from T. Gabladeon PhylomeDB web site http://phylomedb.org/.

# **Disordered domains of Knr4**



Custo the frontiers



## 3D structure of fungal Knr4 is unknown to date.

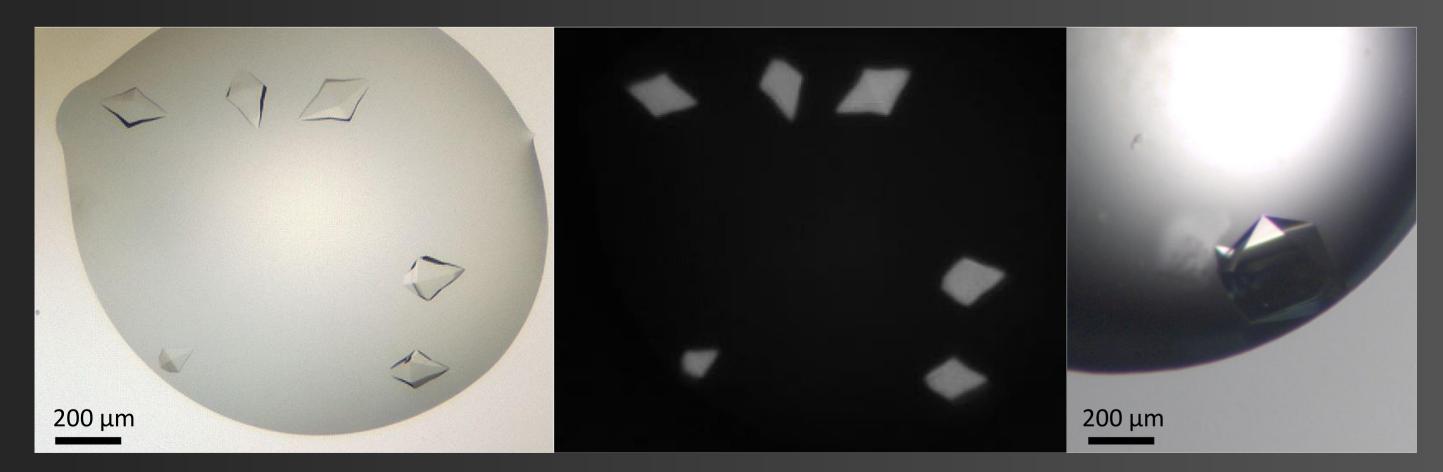
*In silico,* biophysical and biochemical methods have shown that it contains large disordered N-terminal (1-80) and C-terminal (341-505) parts and a structured and globular central core, which holds the essential of the biological functions of the protein<sup>2</sup>. The disordered N and C parts control the interactions of the protein with its partners.

First structural elements solved

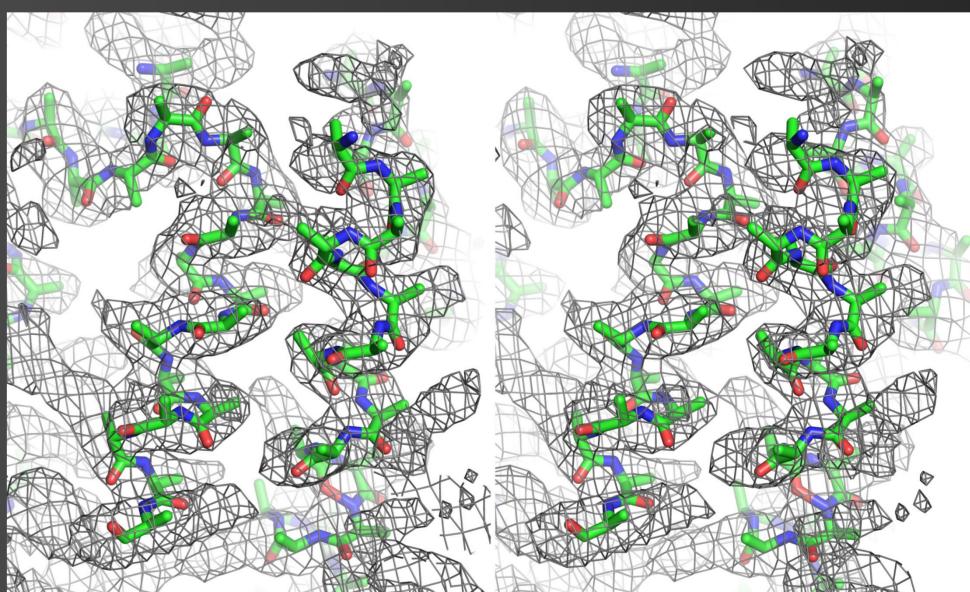
# Crystals

1.23

We have expressed in *E. coli*, purified and crystallized this core domain, as well as a modified Selenomethionine containing corresponding protein <sup>3</sup>.



## Stereoview of the electron-density map obtained after SAD phasing with SHELXC/D/E and further density modification with DM. The electron-density map is displayed as a grey mesh contoured at $1\sigma$ .



#### 

## **Conclusions and outlook**

We have found crystallization conditions allowing the identification of secondary structure elements of *S. cerevisiae* Knr4 central core domain<sup>3</sup>. Recently, we obtained new Knr4 crystals diffracting at 2.5 Å, a resolution which should allow us to rapidly decipher the 3D structure of the protein core of this unique fungal IDP. Our goal is to finally decipher the global 3D structure of the complete protein, in complex with relevant essential proteins partners, in order to later define targetable regions for complex formation inhibition.



- 1. Dagkessamanskaia A., .... and Martin-Yken H. 2010, Knr4 N-terminal domain controls its localization and function during sexual differentiation and vegetative growth, Yeast, 27(8), 563-74.
- Dagkessamanskaia A., ..., and Martin-Yken H. 2010, Functional dissection of an intrinsically disordered protein: understanding the roles of different domains of Knr4 protein in protein-protein interactions. Protein Sci, 19(7):1376-85.

3. Julien S.,... and Maveyraud L., (2015), Crystallographic studies of the structured core domain of Knr4 from Saccharomyces cerevisiae. Acta Cryst. F.

