



Decoding cellular communications to find new therapies for human diseases

Wednesday, February 16, 2022

1:00 PM PT/4:00 PM ET

Xiang-Lei Yang, PhD

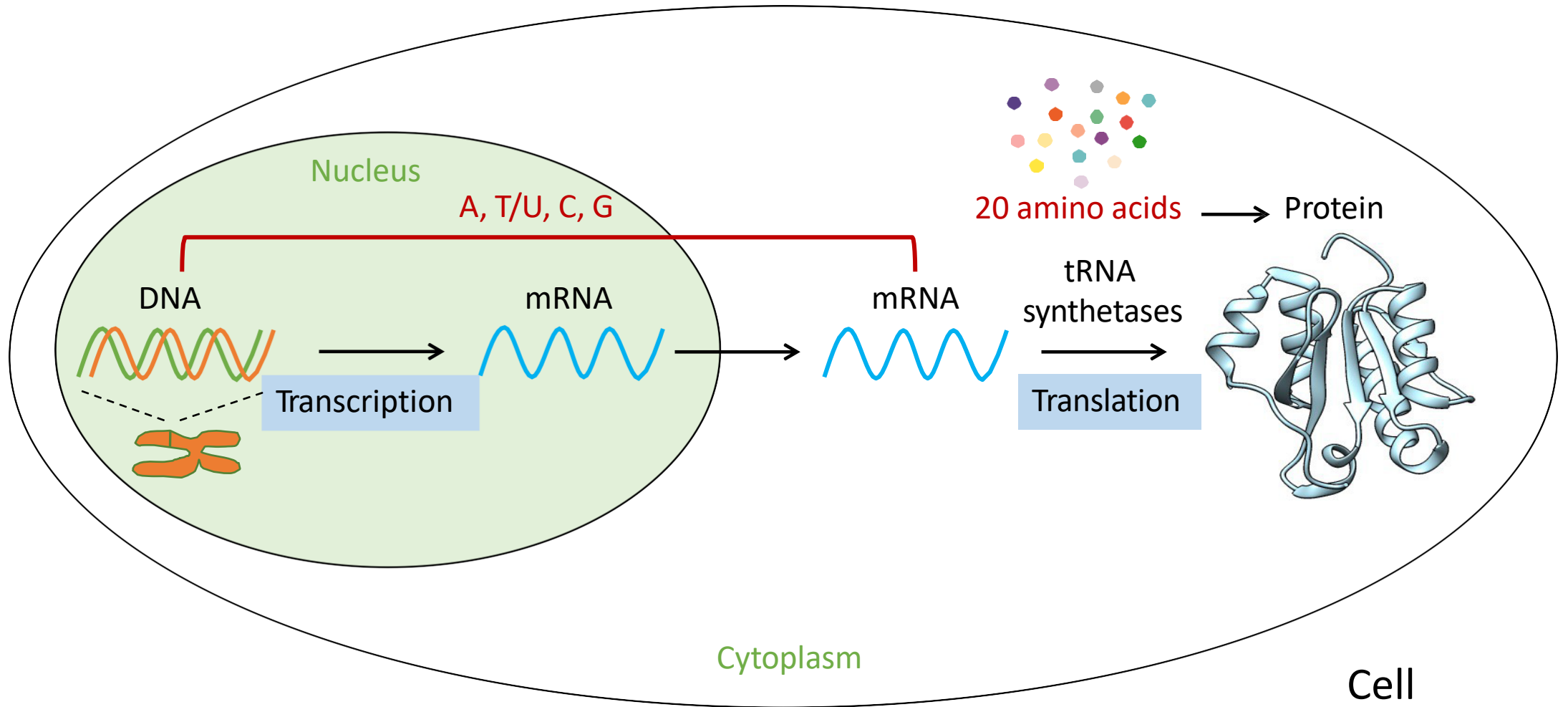
Ernest W. Hahn Chair
Professor, Department of Molecular Medicine
Scripps Research



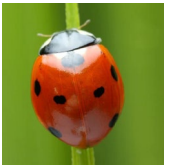
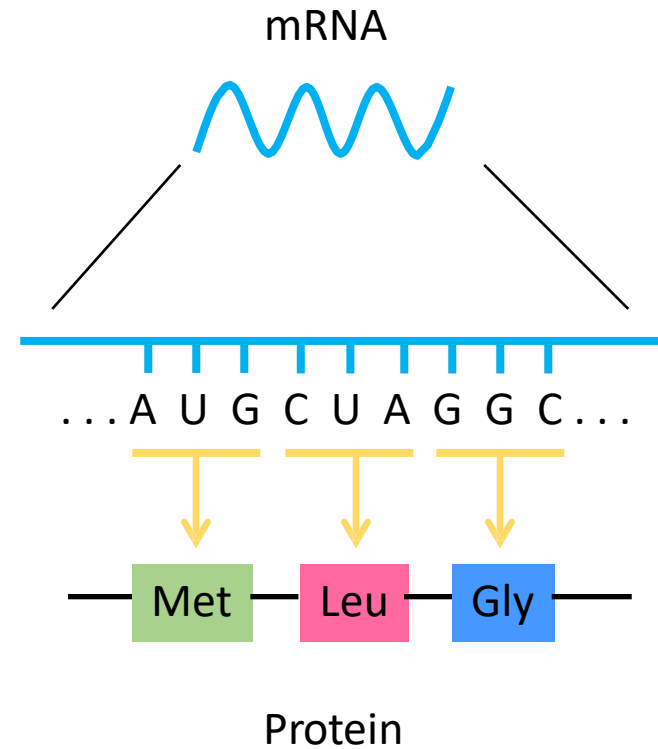
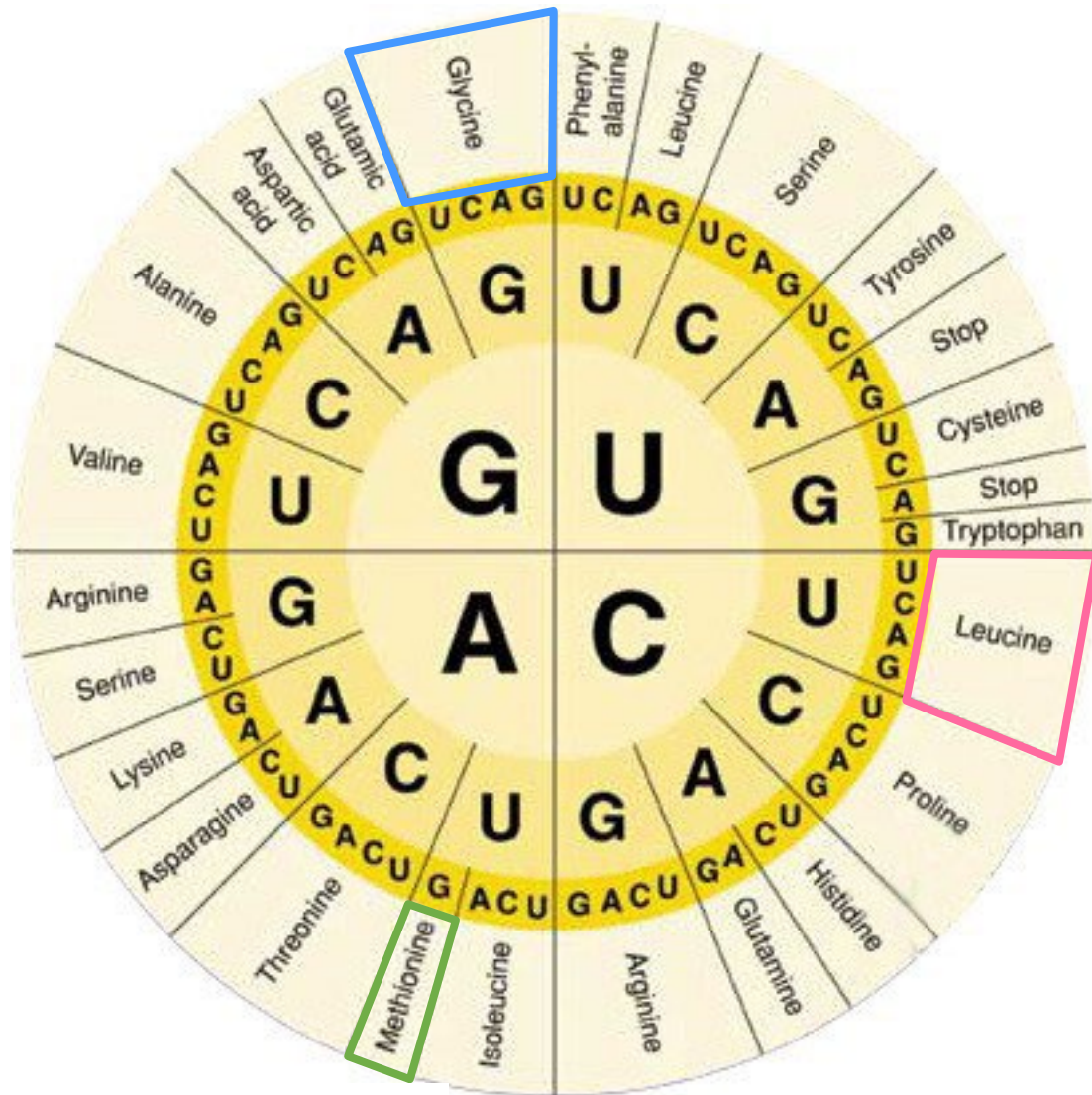
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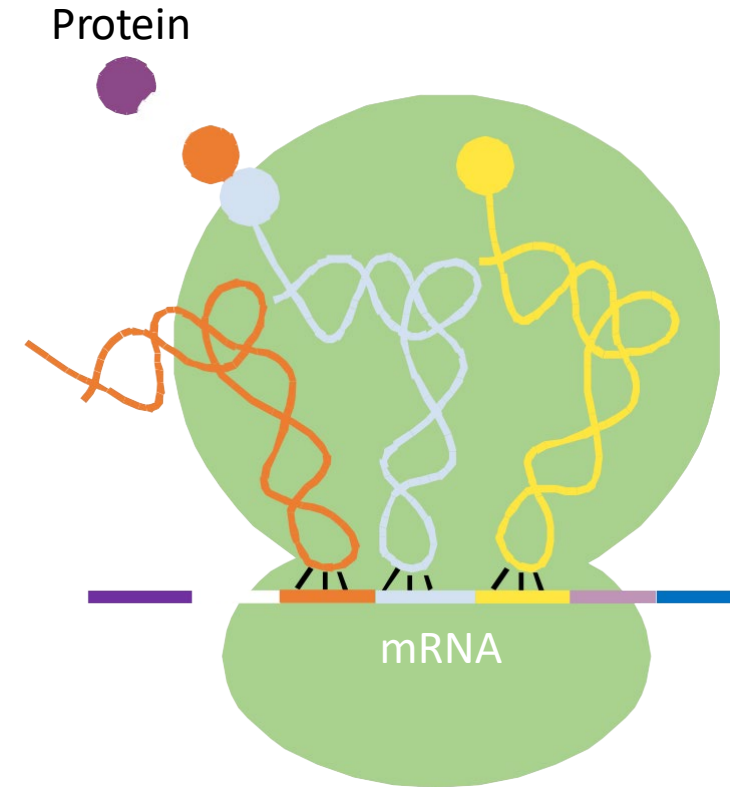
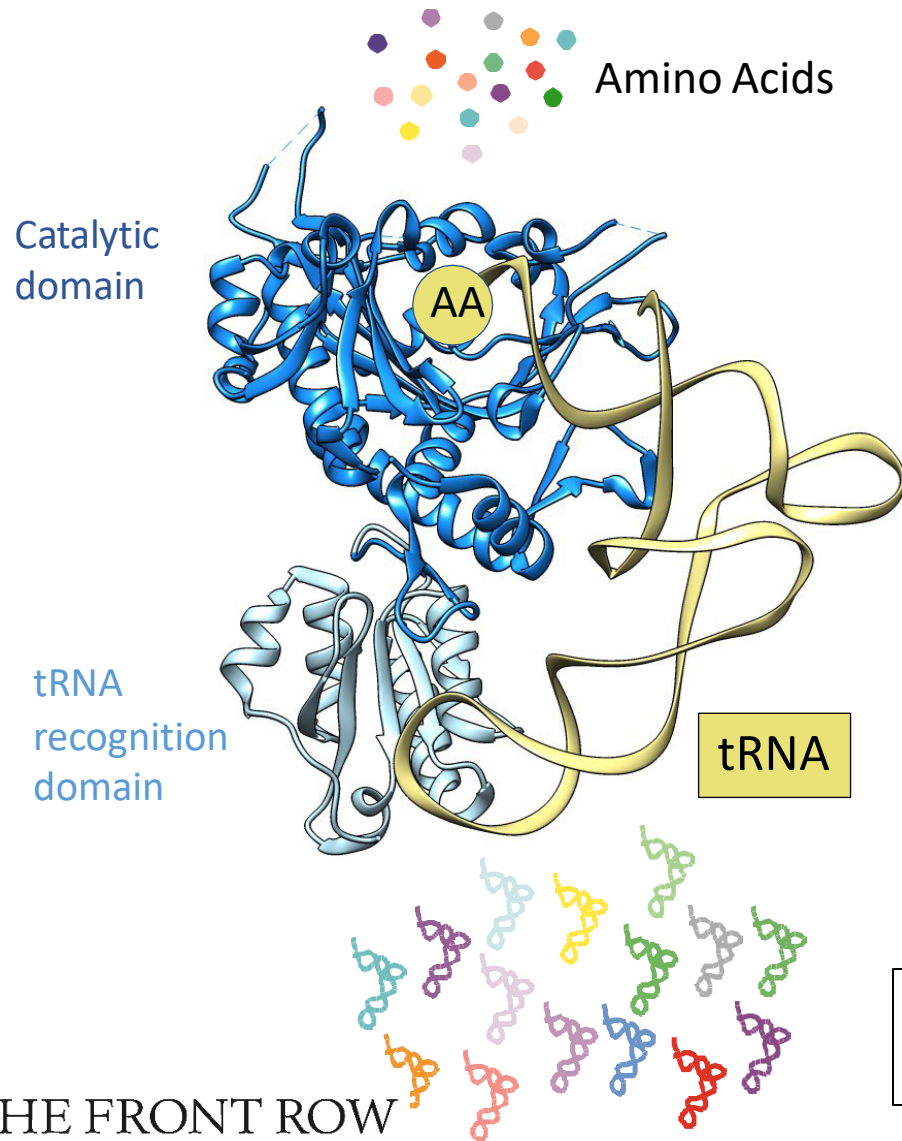
Central dogma of biology



The genetic code



Aminoacyl-tRNA synthetases (aaRS) establish rule of genetic code



20 amino acids → 20 aaRSs

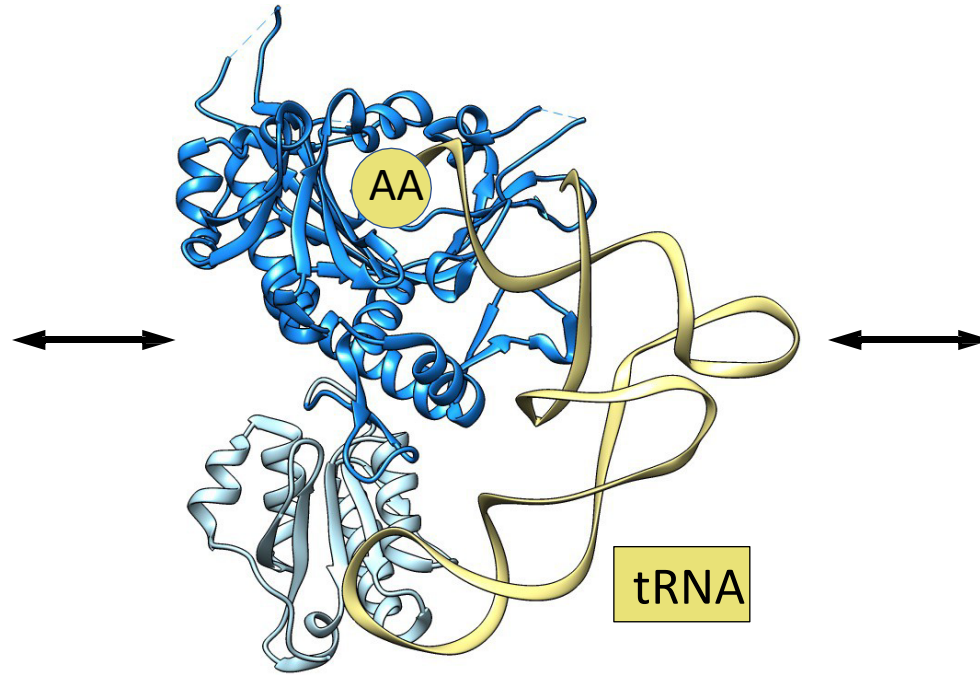
Leucine → LeuRS; Serine → SerRS; Glycine → GlyRS; Histidine → HisRS; ...



aaRSs bridge 'nature' and 'nurture'



DNA, RNA, Protein
Self
Intrinsic

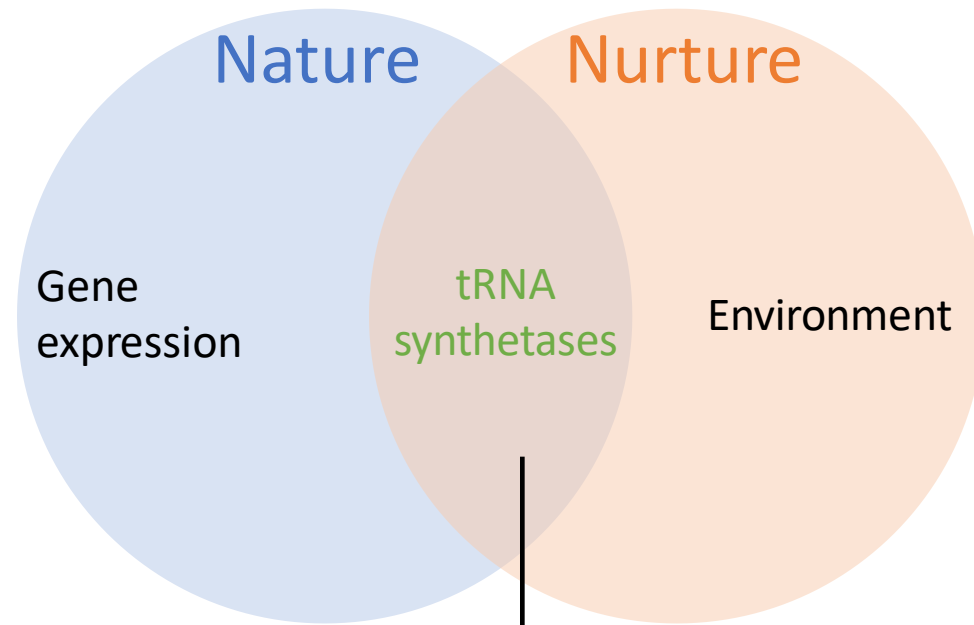


Amino acids, Sugars, Fatty acids, Oxygen
Non-self
Extrinsic

↓

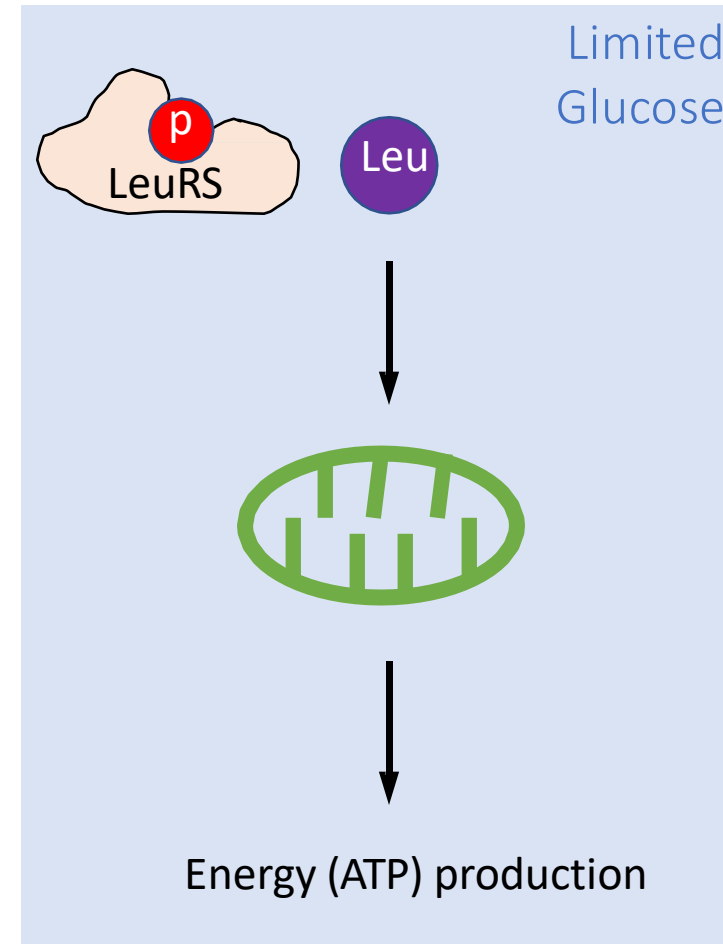
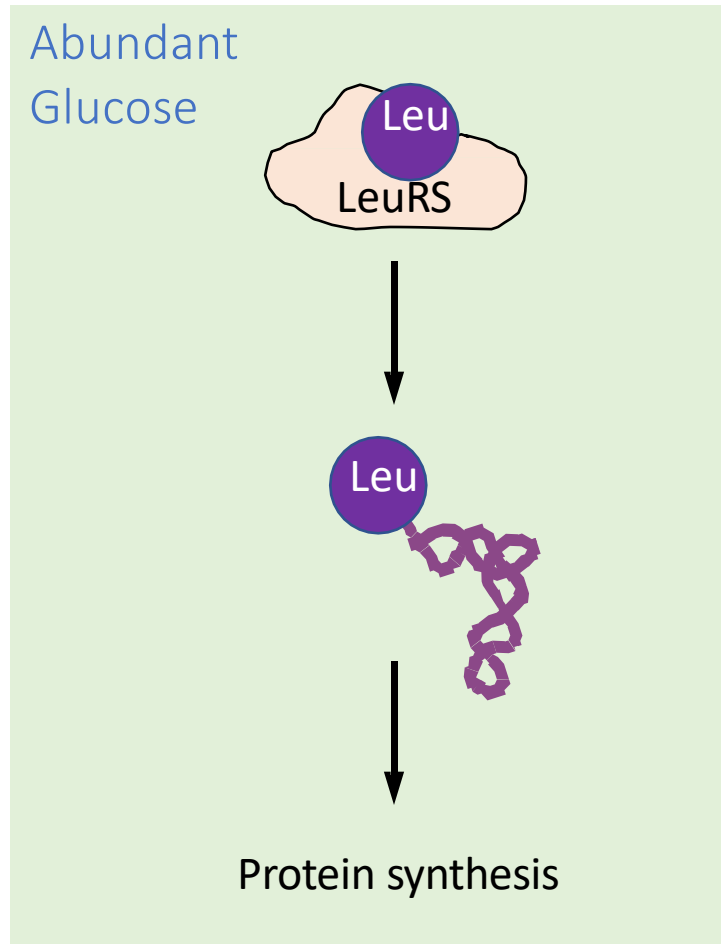
Homeostasis



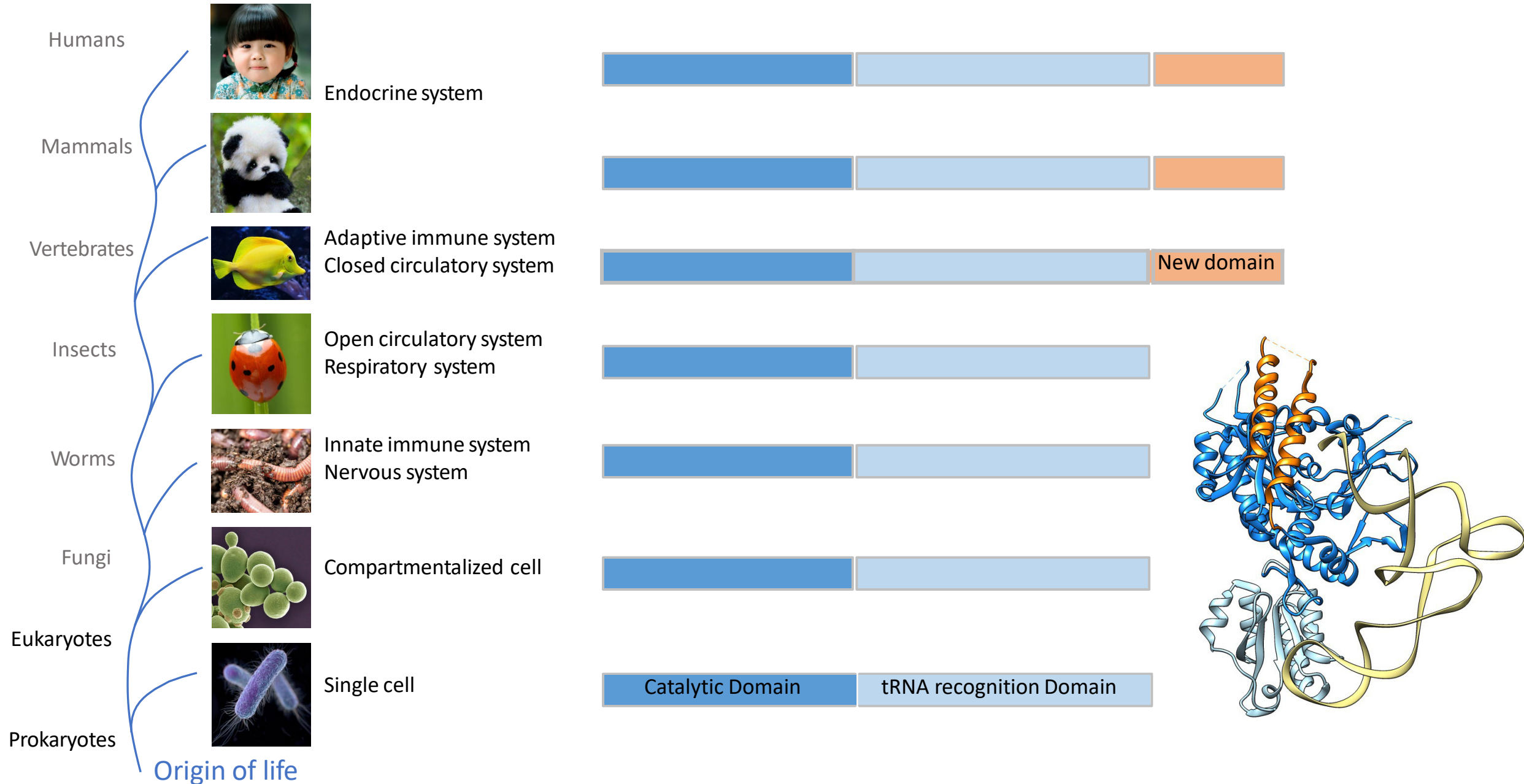


Homeostasis

Glucose-dependent control of leucine usage by LeuRS



New domains in tRNA synthetases



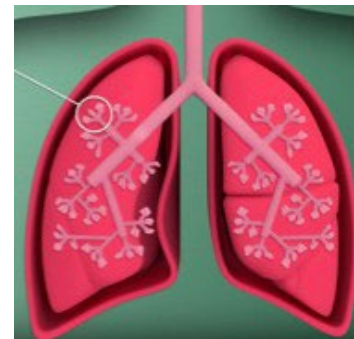
tRNA synthetases in maintaining homeostasis



From blood vessel
regulation to a potential
cancer therapy



Understanding Charcot-
Marie-Tooth disease



From antisynthetase
syndrome to treating
interstitial lung disease



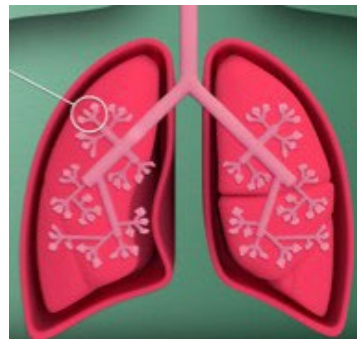
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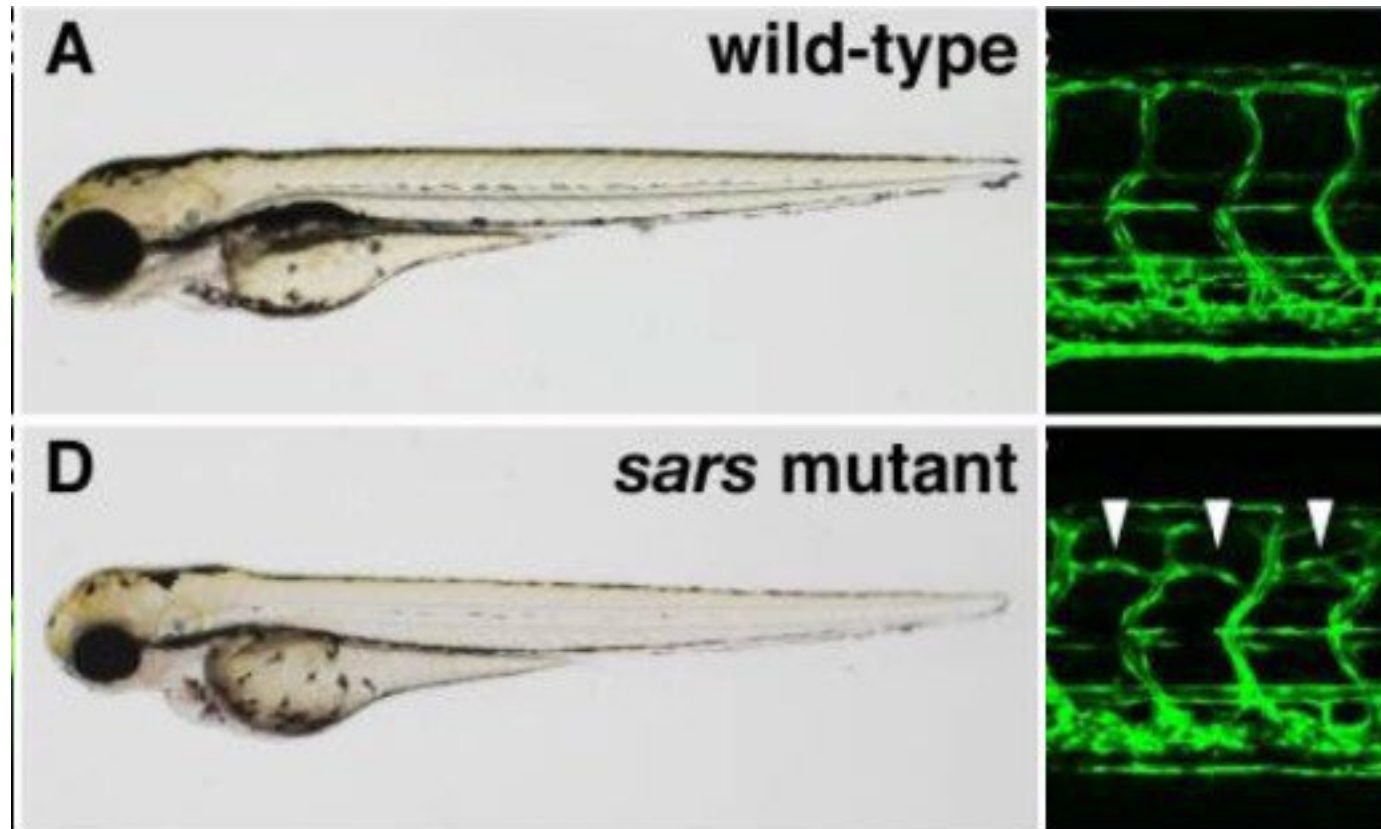
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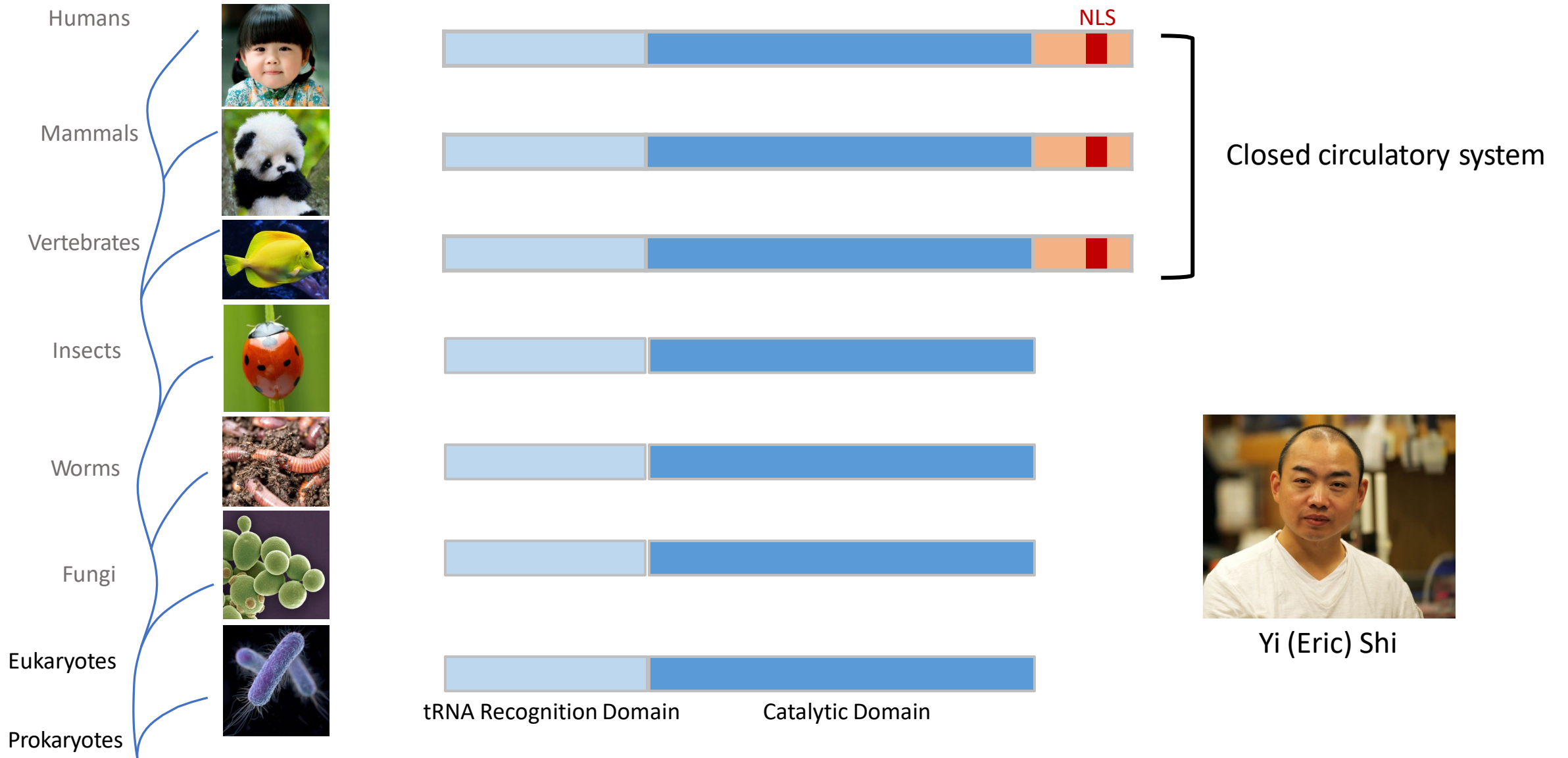
From antisynthetase
syndrome to treating
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SerRS mutations cause blood vessel overgrowth

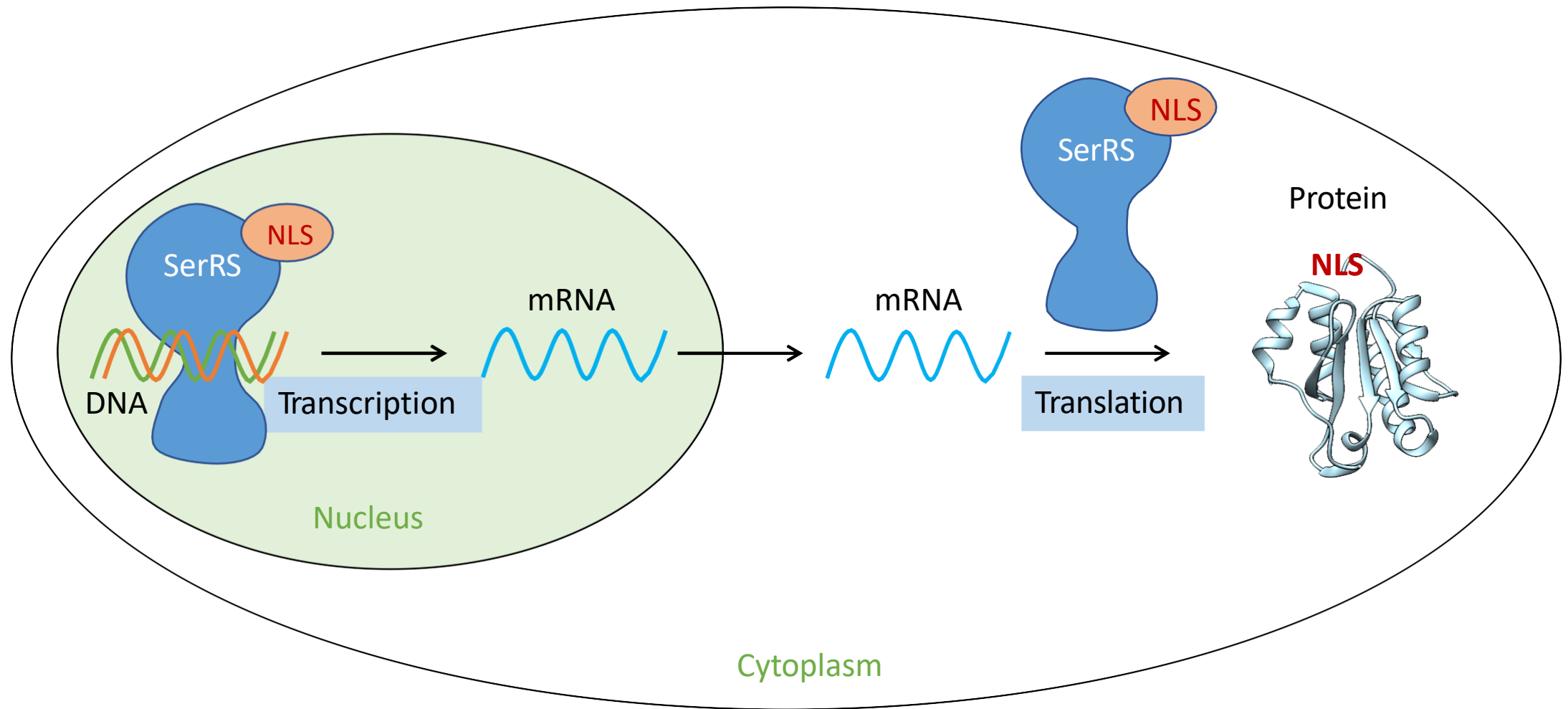


Vertebrate SerRS has a nucleus localization signal (NLS)

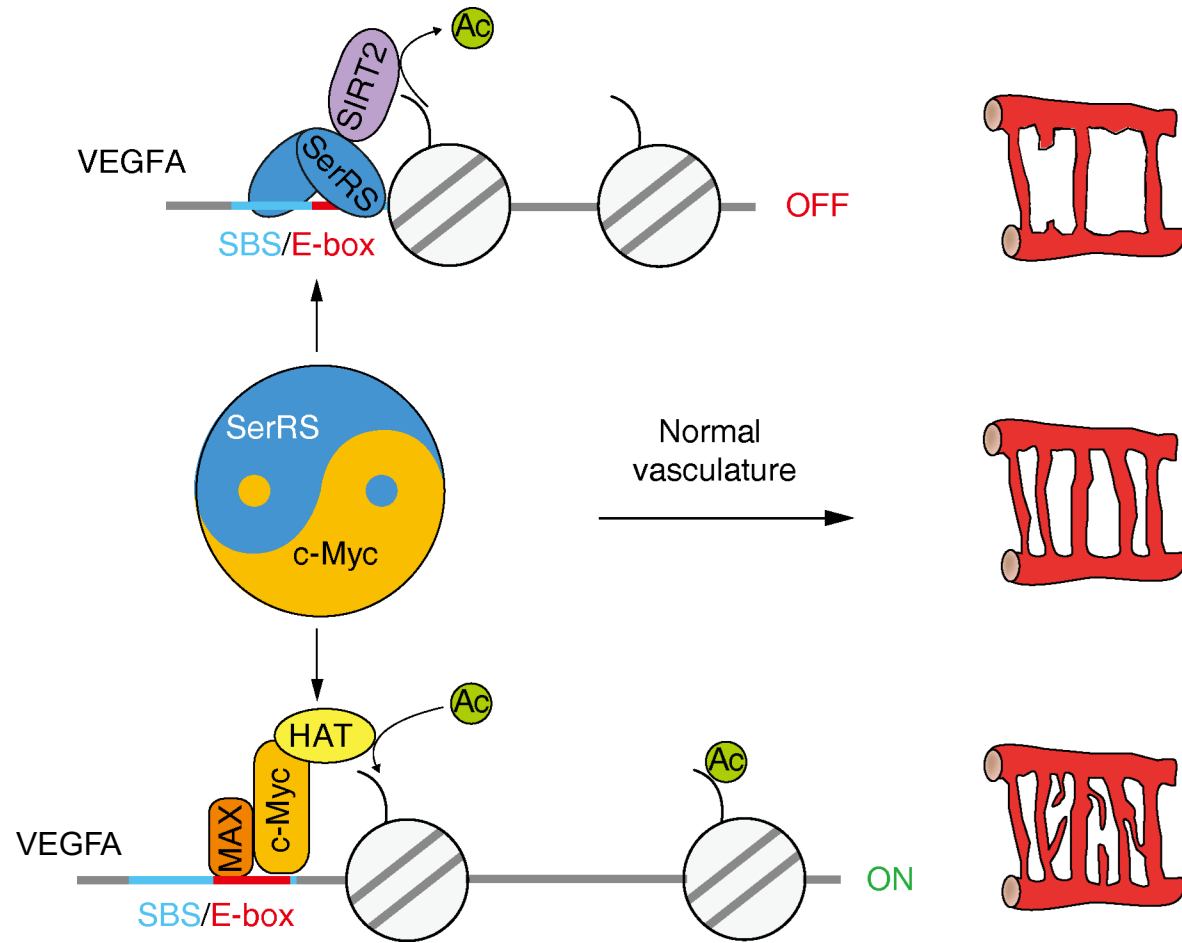


Yi (Eric) Shi

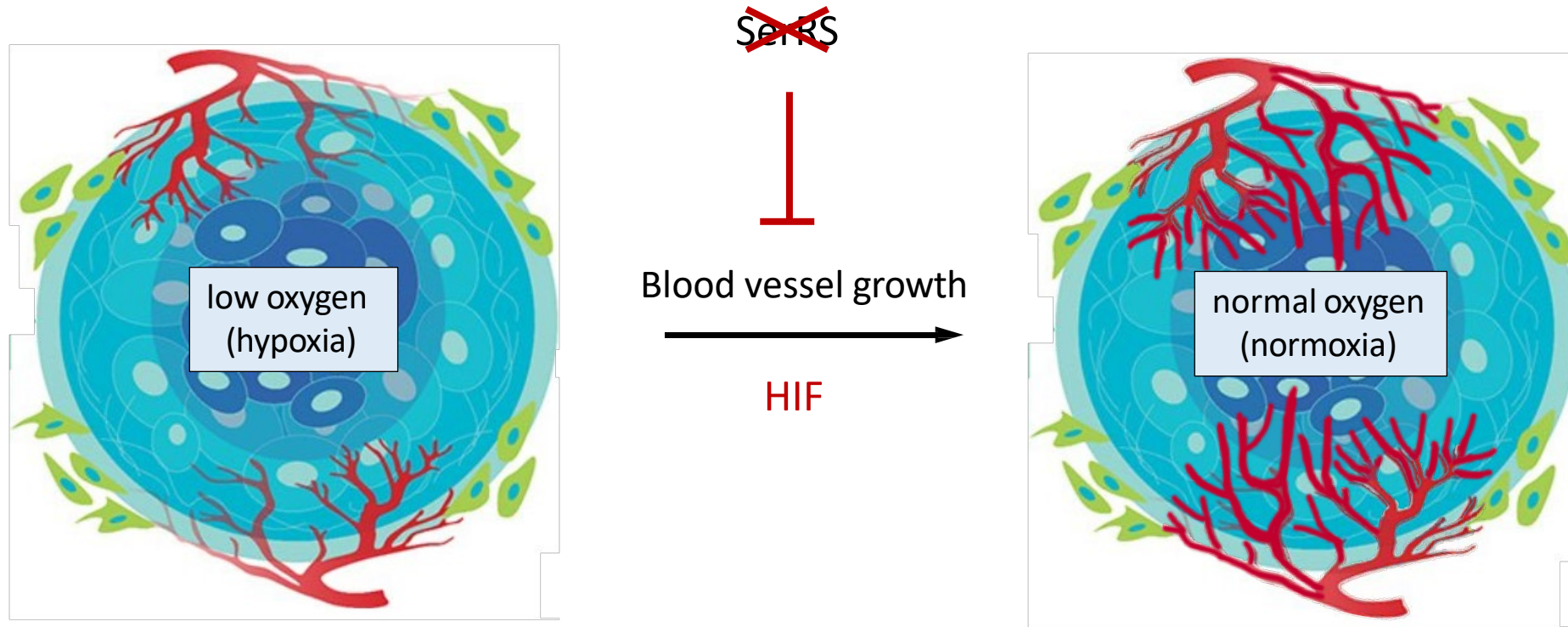
SerRS enters nucleus to regulate transcription



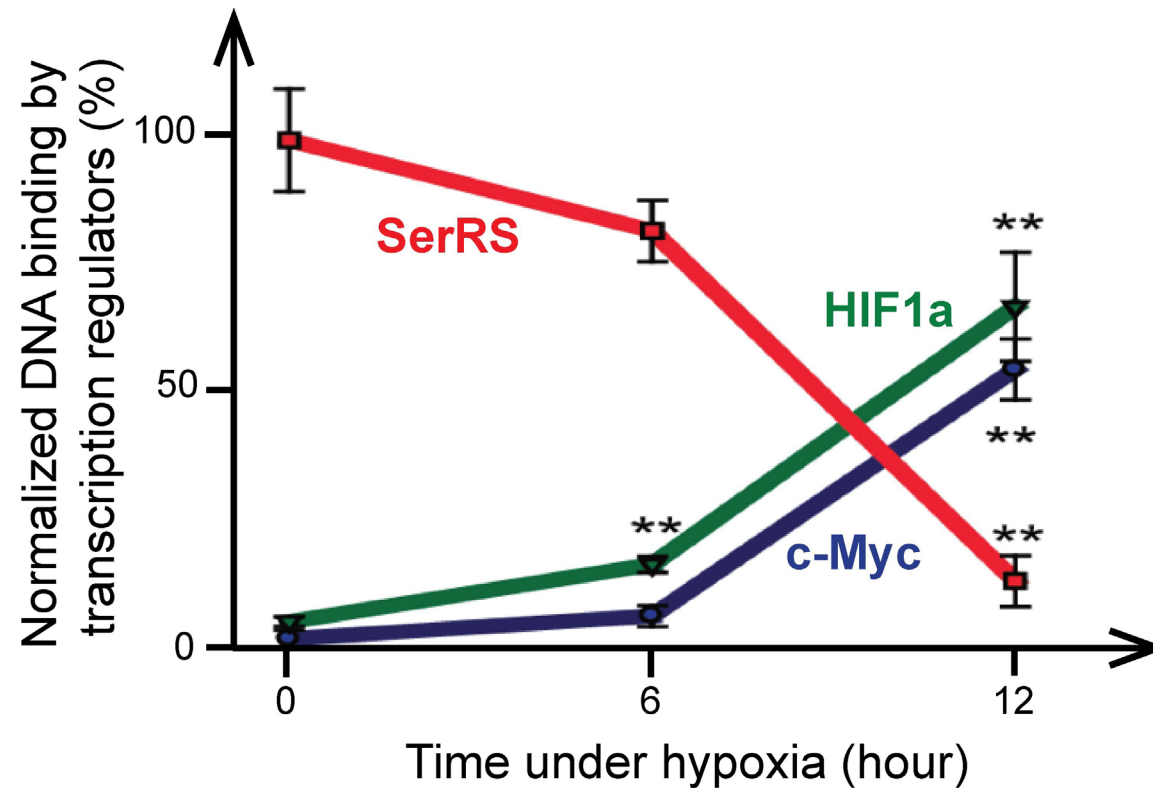
Nuclear SerRS regulates key blood vessel gene transcription



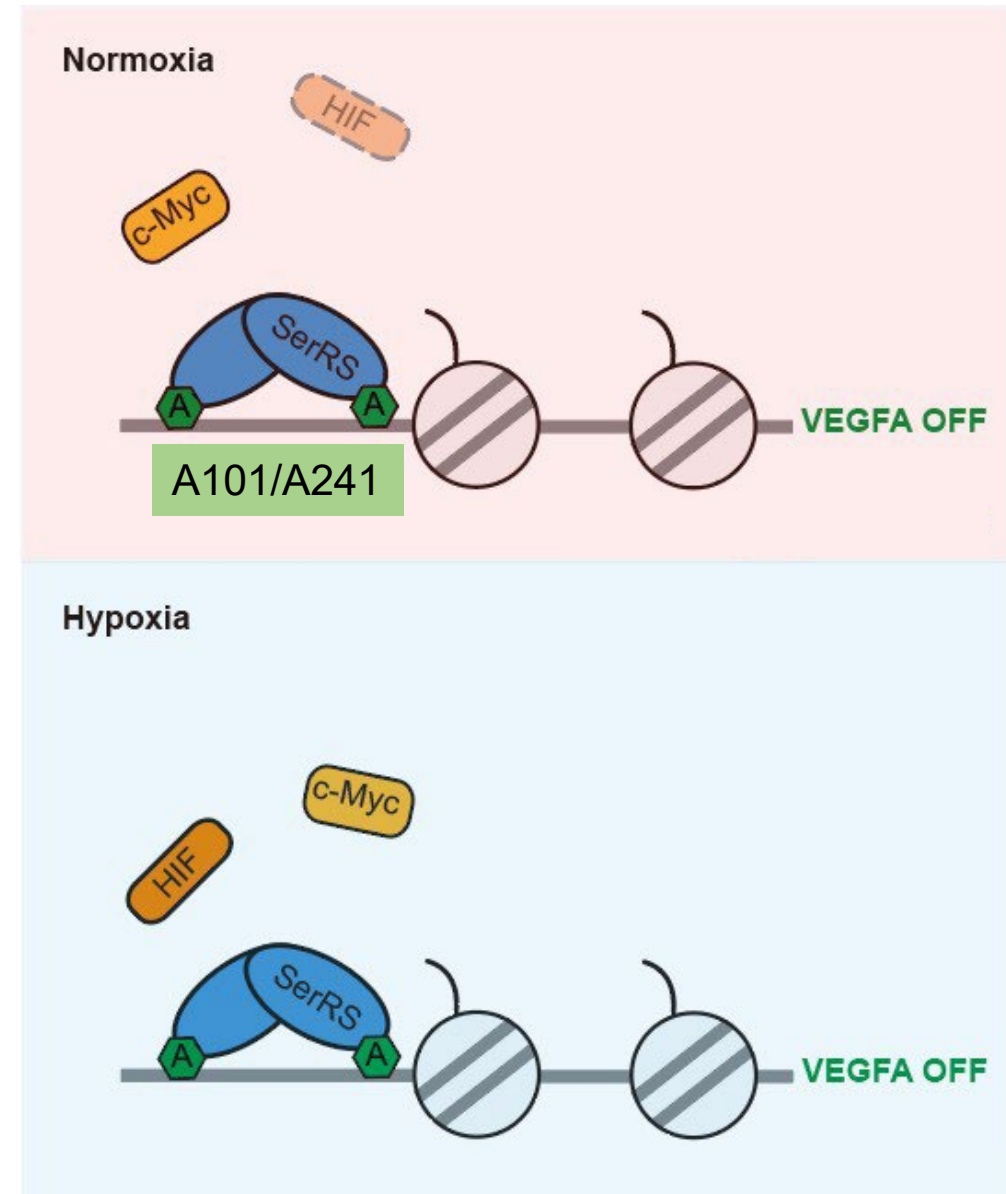
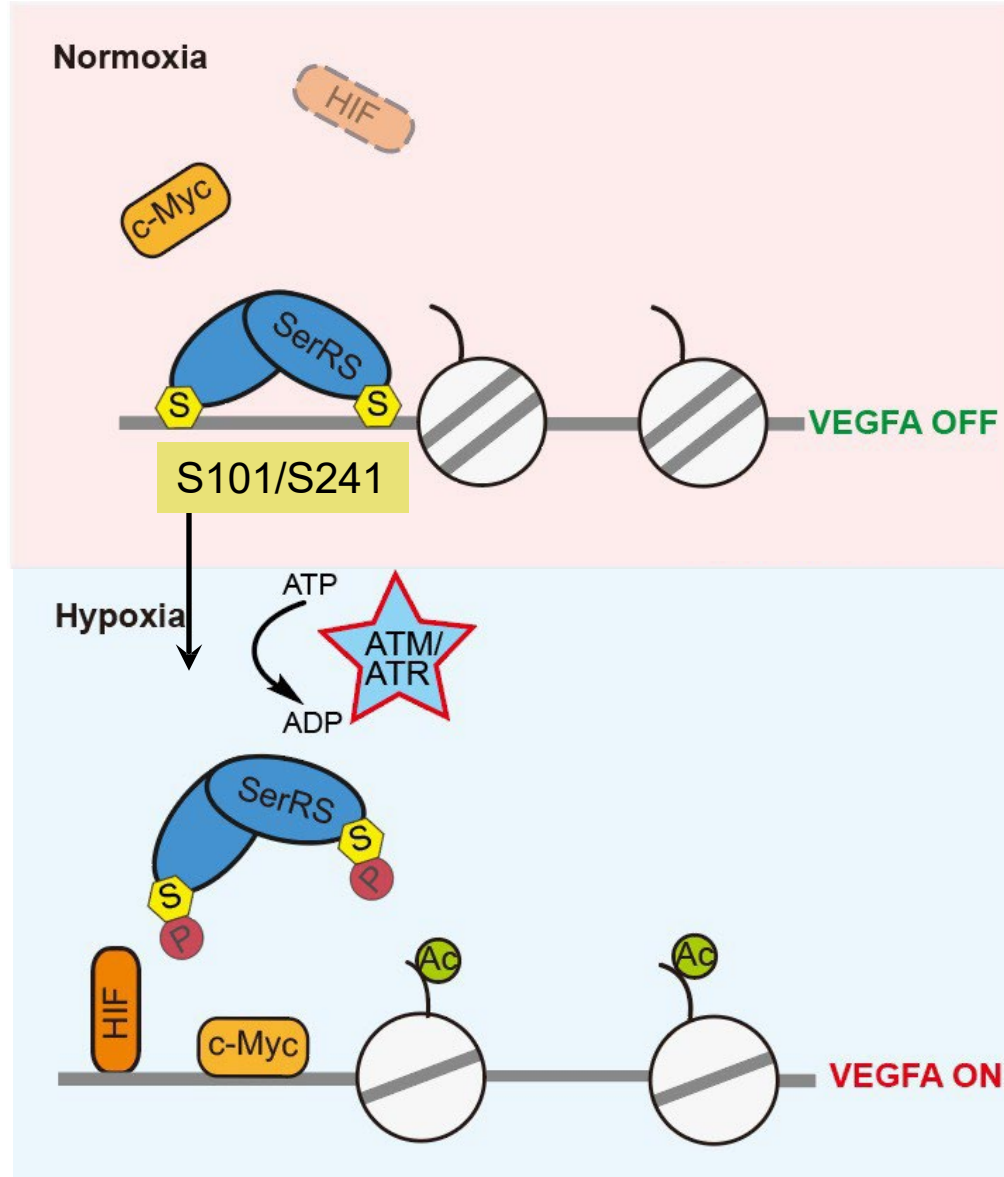
When the nuclear function of SerRS must be inhibited?



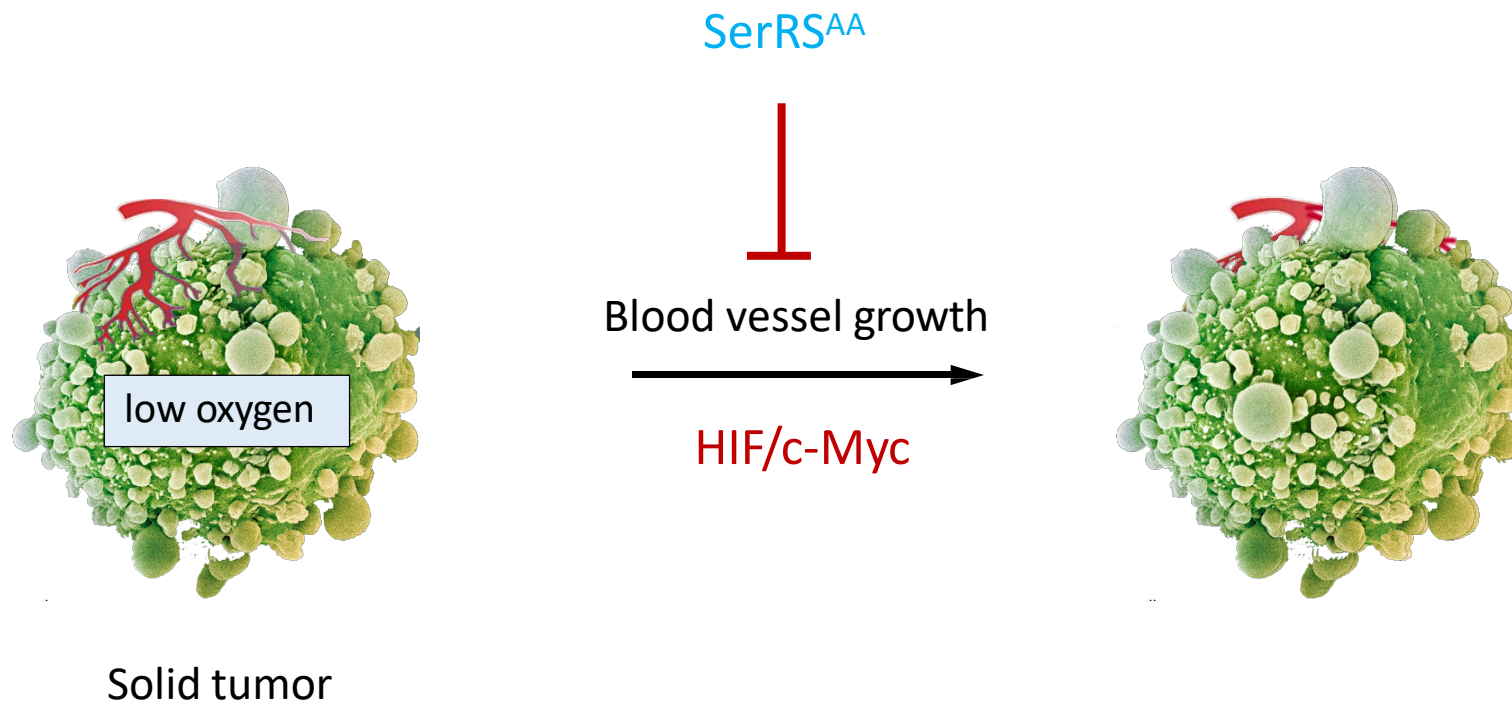
SerRS binding to DNA decreases in hypoxic cells, allowing Myc and HIF binding



Activating HIF and c-Myc depends on inactivation of SerRS



SerRS^{AA} inhibiting tumor angiogenesis and tumor growth

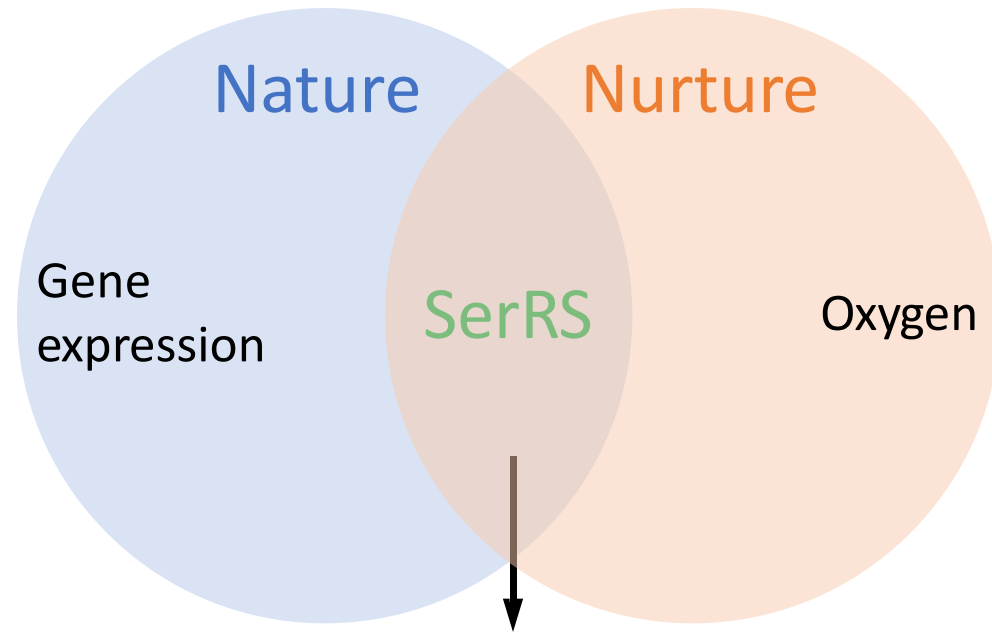


Control: tumors grown from human triple negative breast cancer cells



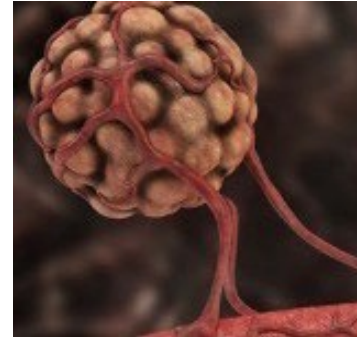
SerRS^{AA}





Homeostasis

tRNA synthetases in maintaining homeostasis



From blood vessel regulation to a potential cancer therapy



Understanding Charcot-Marie-Tooth disease



From antisynthetase syndrome to treating interstitial lung disease



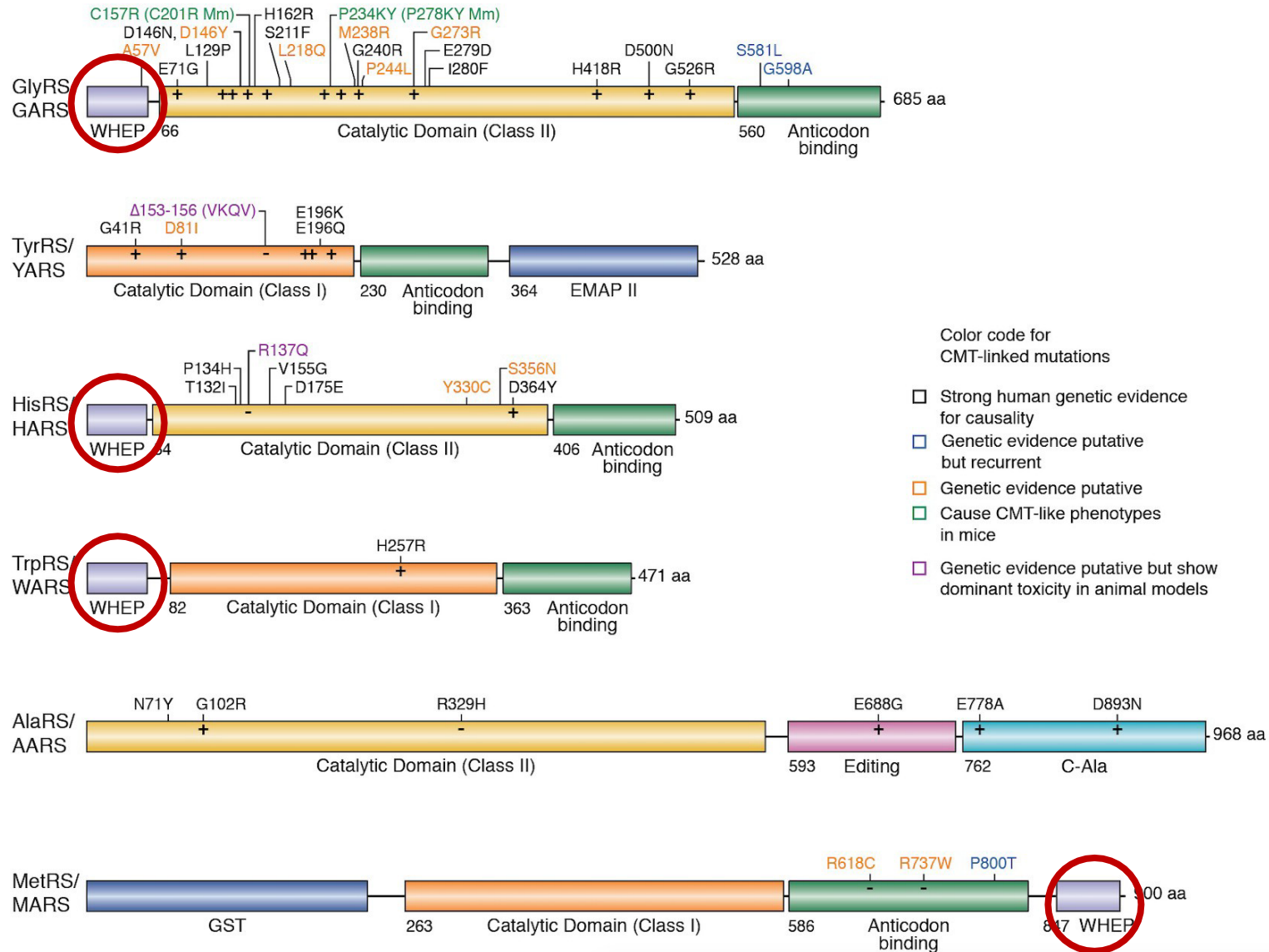
Charcot-Marie-Tooth Disease

(Hereditary Motor and Sensory Neuropathy)

- The most common inherited neurological disorders
- No treatment available
- Affect 1 in 2,500 people; 2.6 million people worldwide
- Mostly affect long peripheral nerves
- Muscle weakness and sensory loss at body extremities such as hands and feet
- tRNA synthetase is the largest gene family linked to CMT



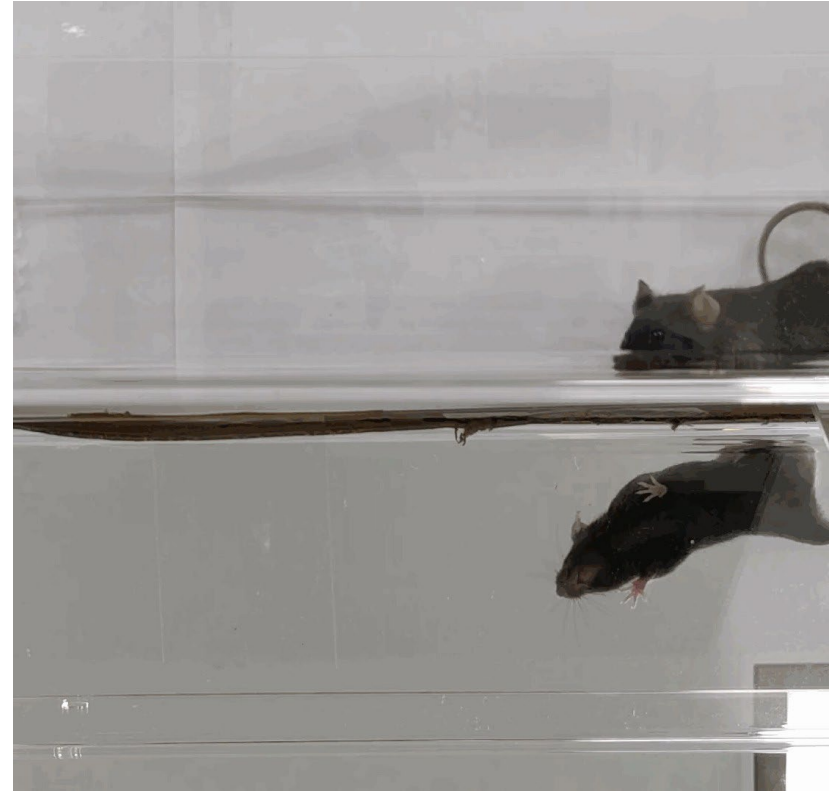
CMT-linked tRNA synthetases



A mouse model of CMT



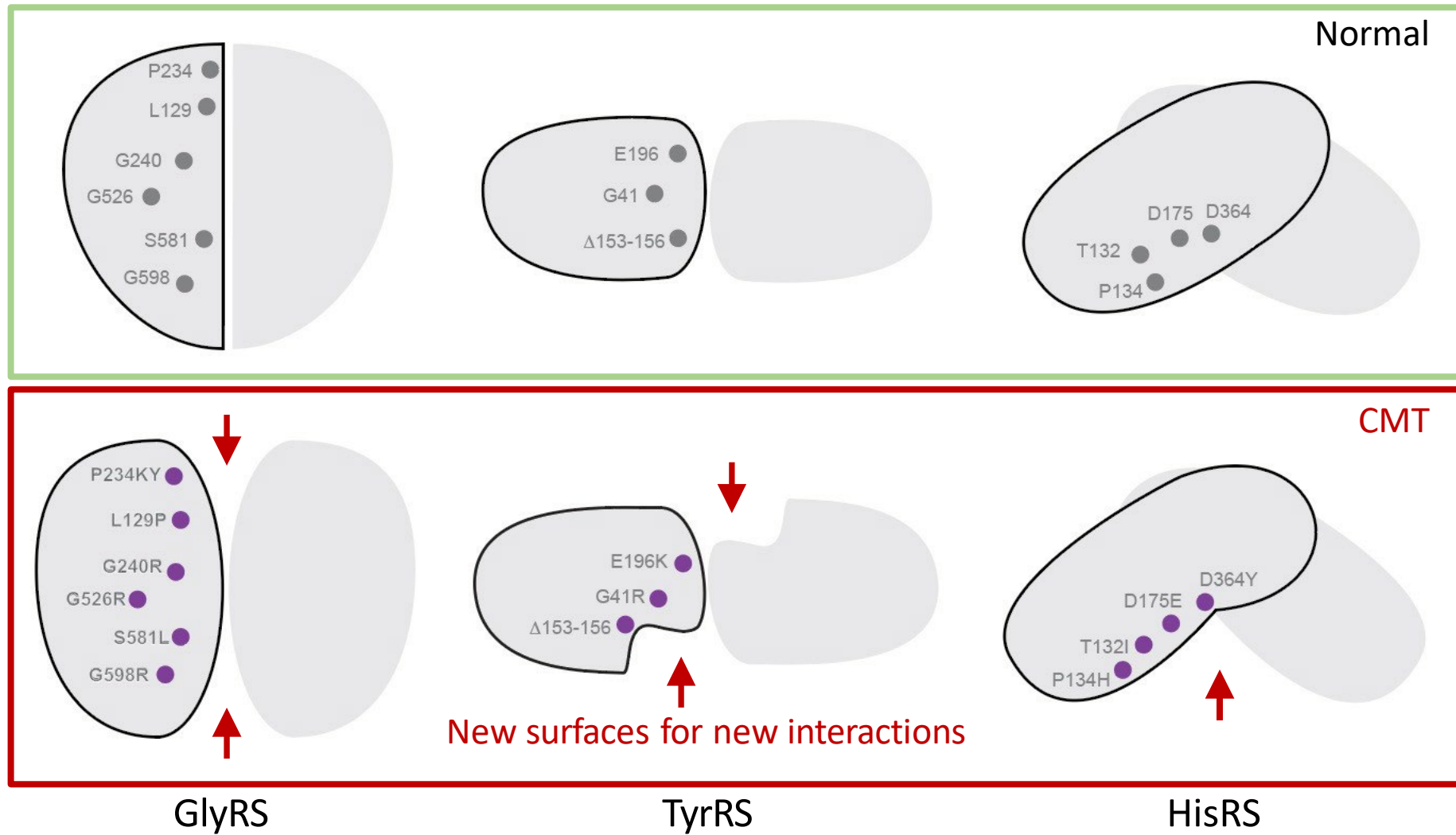
Normal



CMT - GlyRS^{P234KY}



CMT-mutations induce structural opening and create new interactions



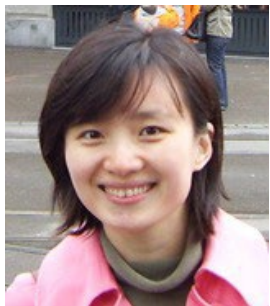
Weiwei He



David Blocquel



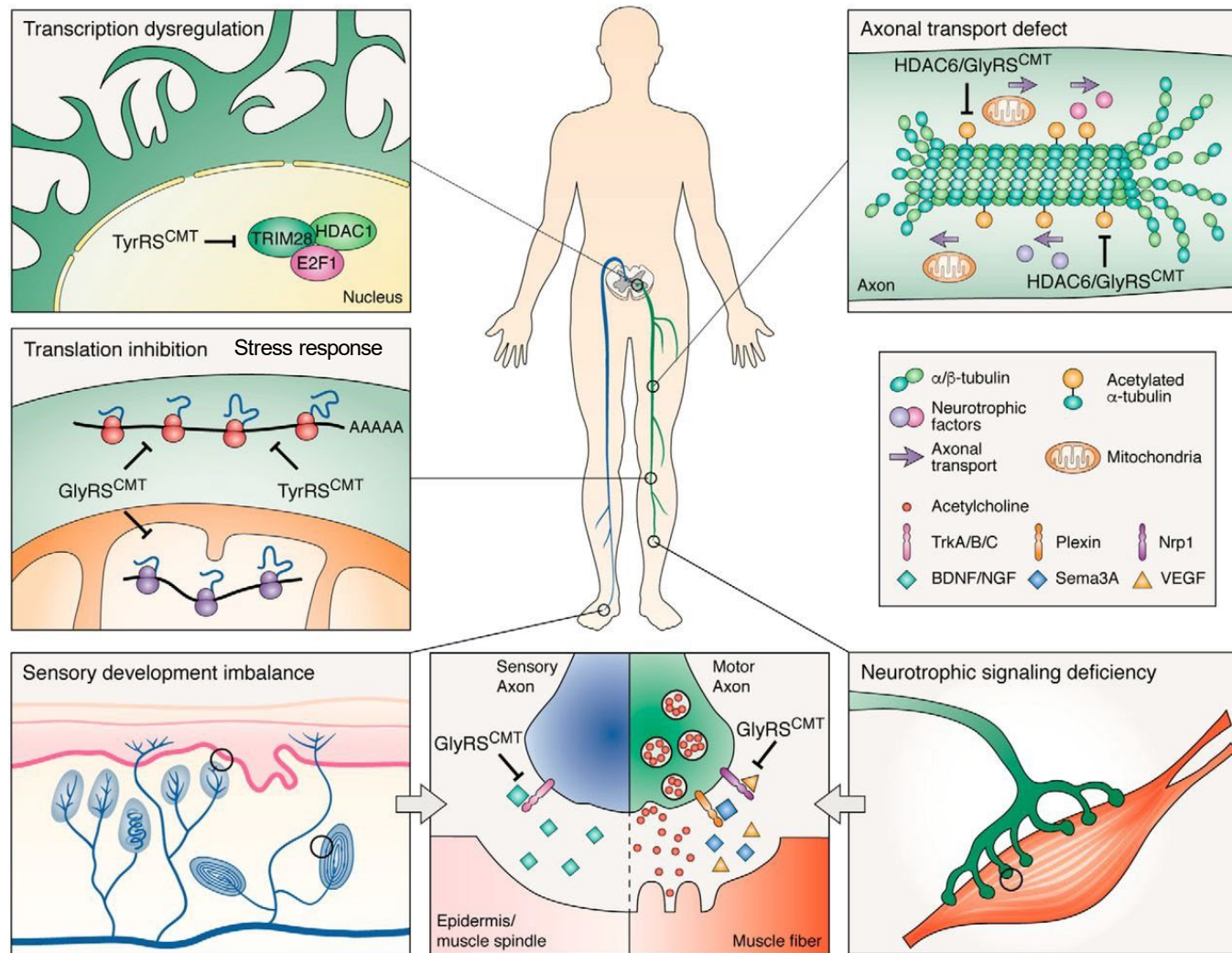
Multifactorial and multicompartmental mechanisms



Weiwei He



Na Wei



Zhongying Mo



Ge Bai

Niehues & Storkebaum *et al. Nat Comm* (2015); He, Bai, Pfaff, & Yang *et al. Nature* (2015); Sleight & Schiavo *et al. PNAS* (2017); Mo & Yang *et al. Nat Comm* (2018); Bervoets, Wei, Jordanova, & Yang *et al. Nat Comm* (2019); Zuko & Storkebaum *et al. Science* (2021); Spaulding & Burgess *et al. Science* (2021)



CMT

+ tRNA



or

- WHEP domain



Healthy



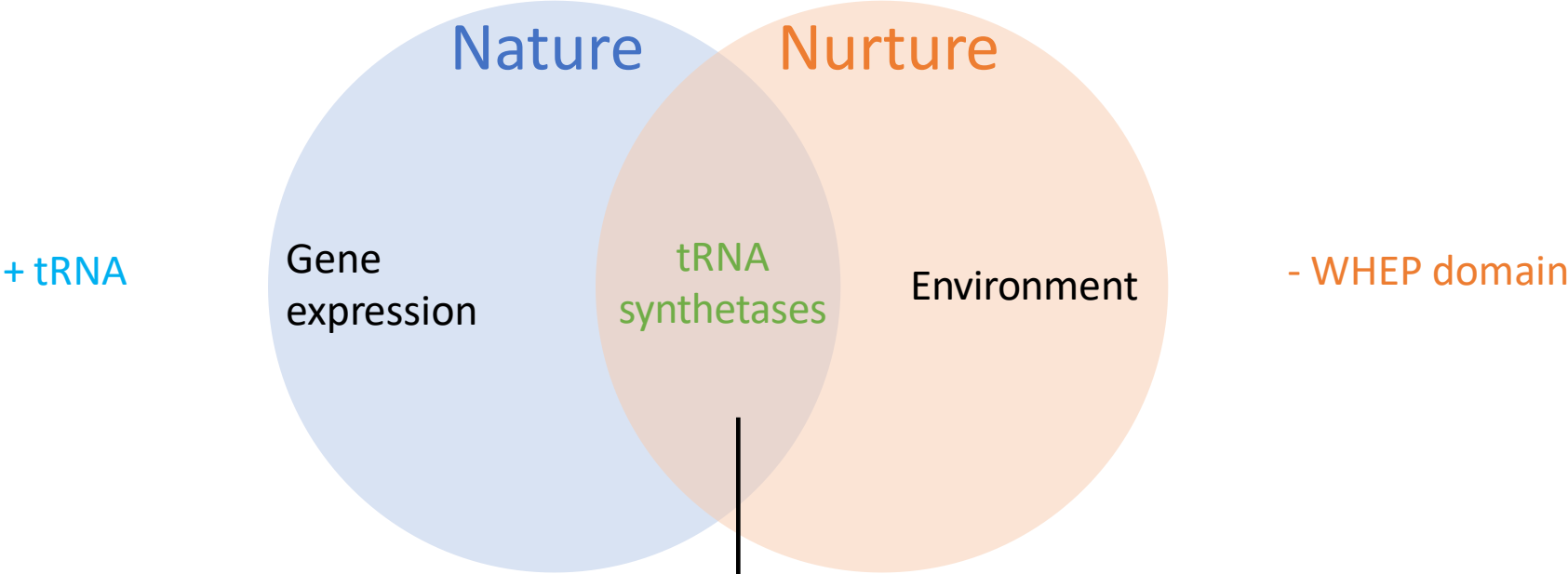
Ge Bai



Yao Tong



CMT



Homeostasis

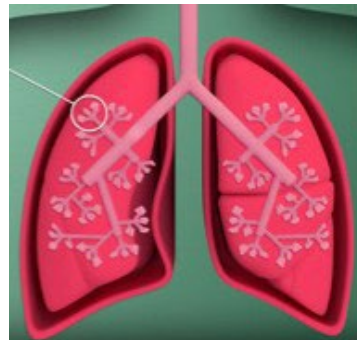
tRNA synthetases in maintaining homeostasis



From blood vessel
regulation to a potential
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Understanding Charcot-
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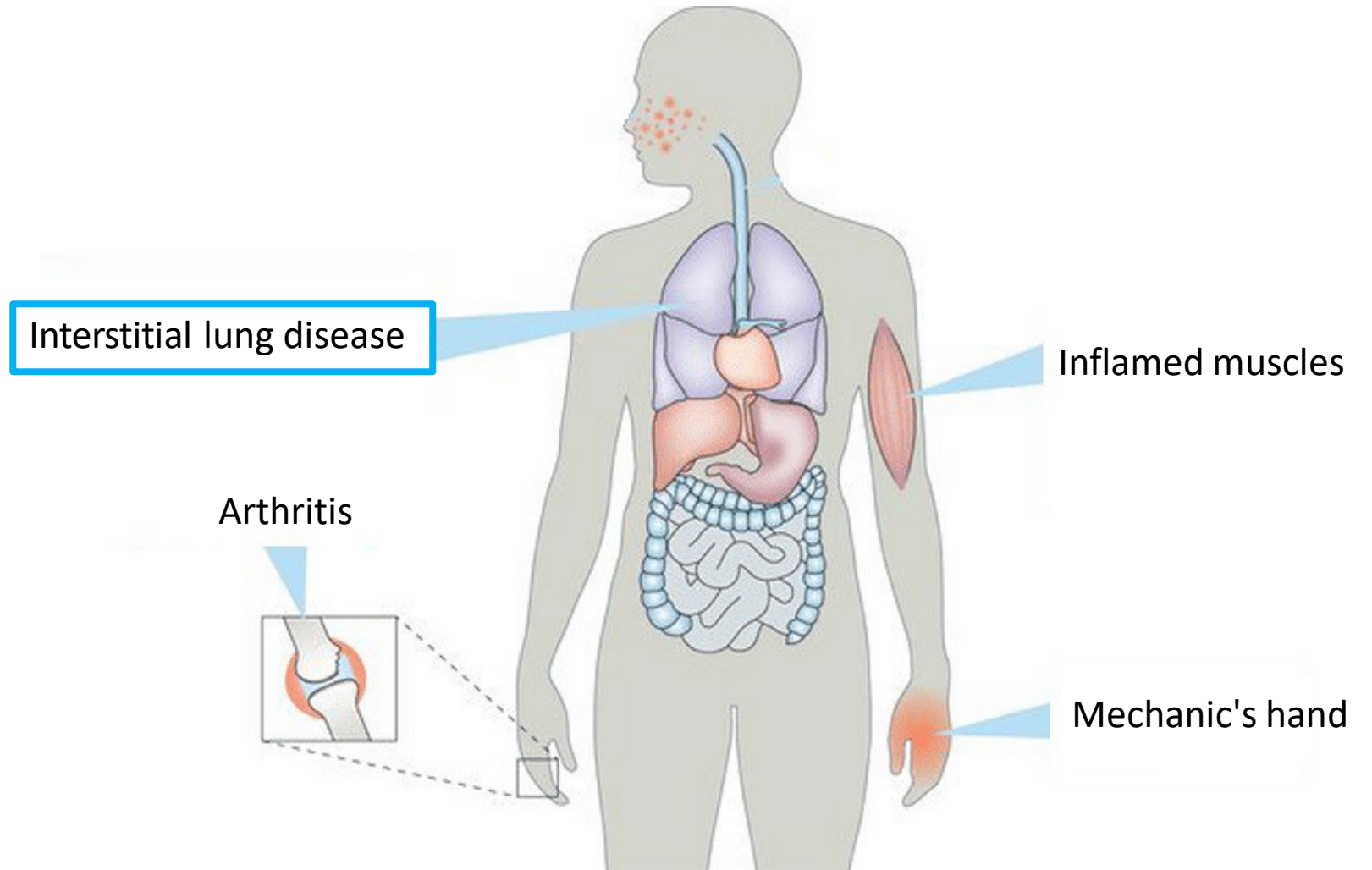


From antisynthetase
syndrome to treating
interstitial lung disease

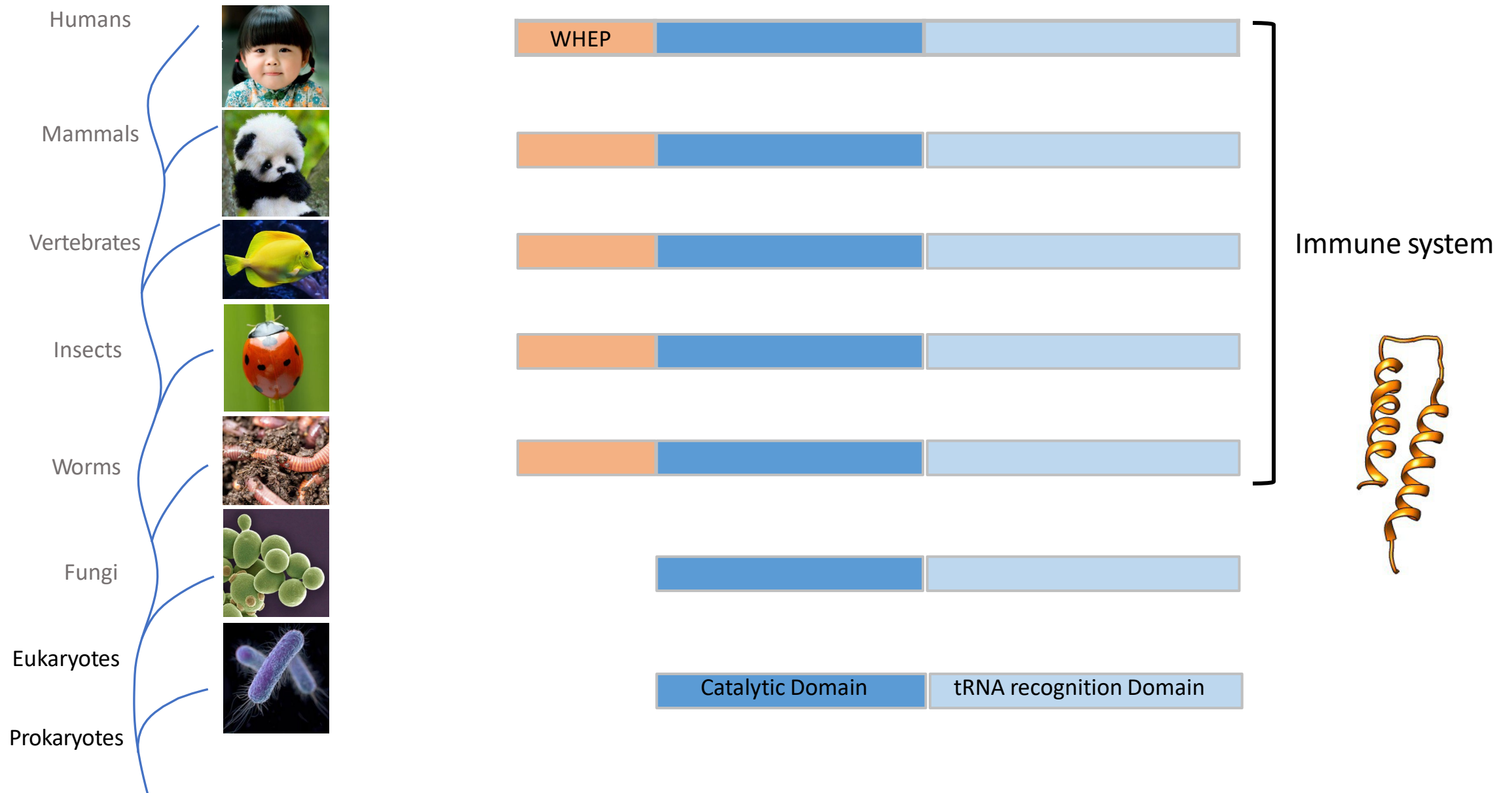


Anti-synthetase syndrome (ASSD)

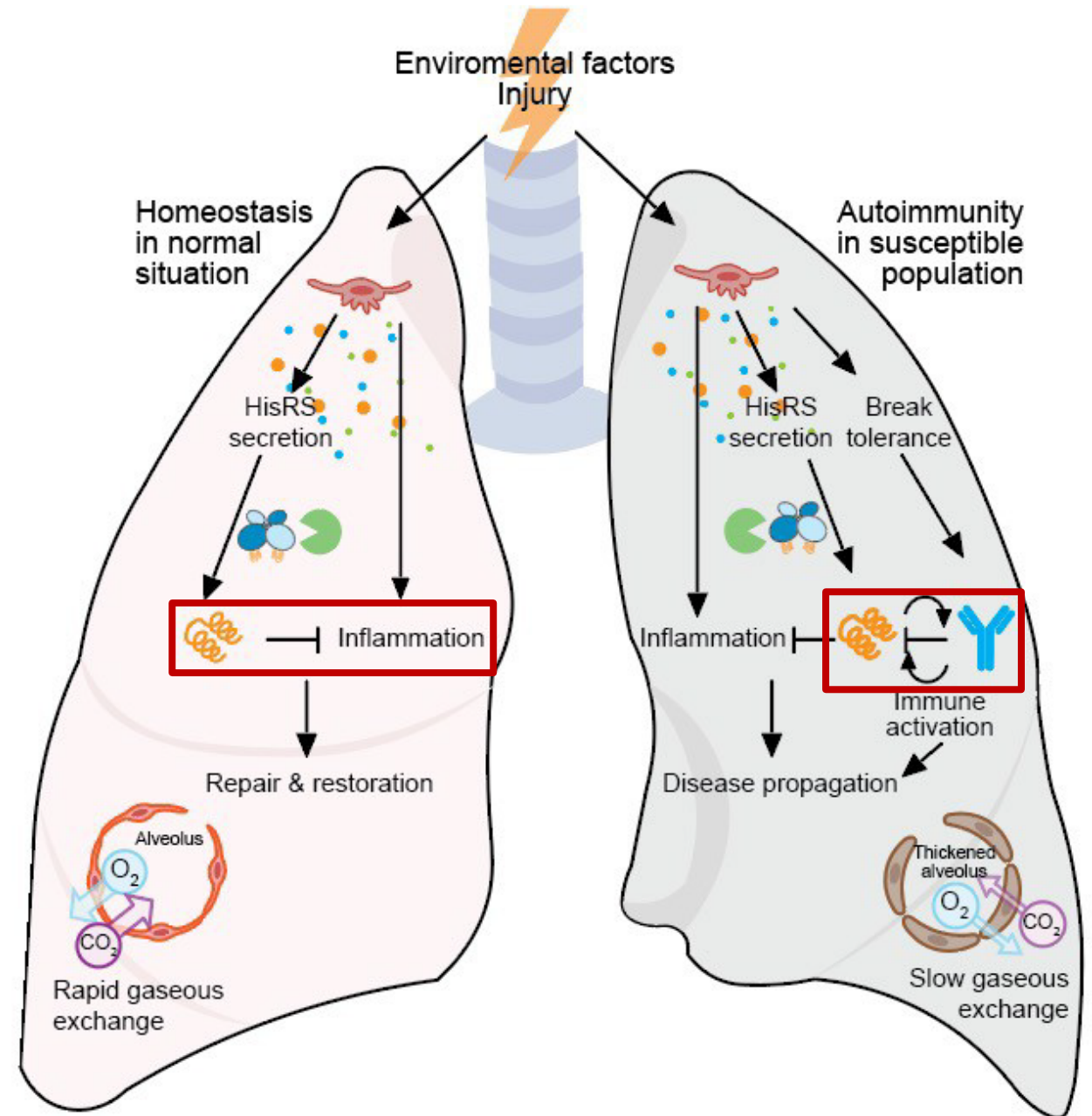
- Autoimmune disease
- Affect 1 in 25,000 people
- Female : male = 2-3 : 1
- Presence of autoantibodies against tRNA synthetase (8 in total)
- HisRS is the most frequent target (66%)



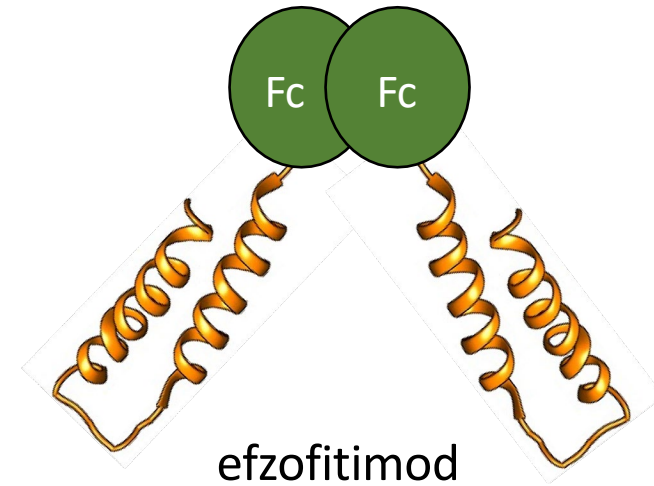
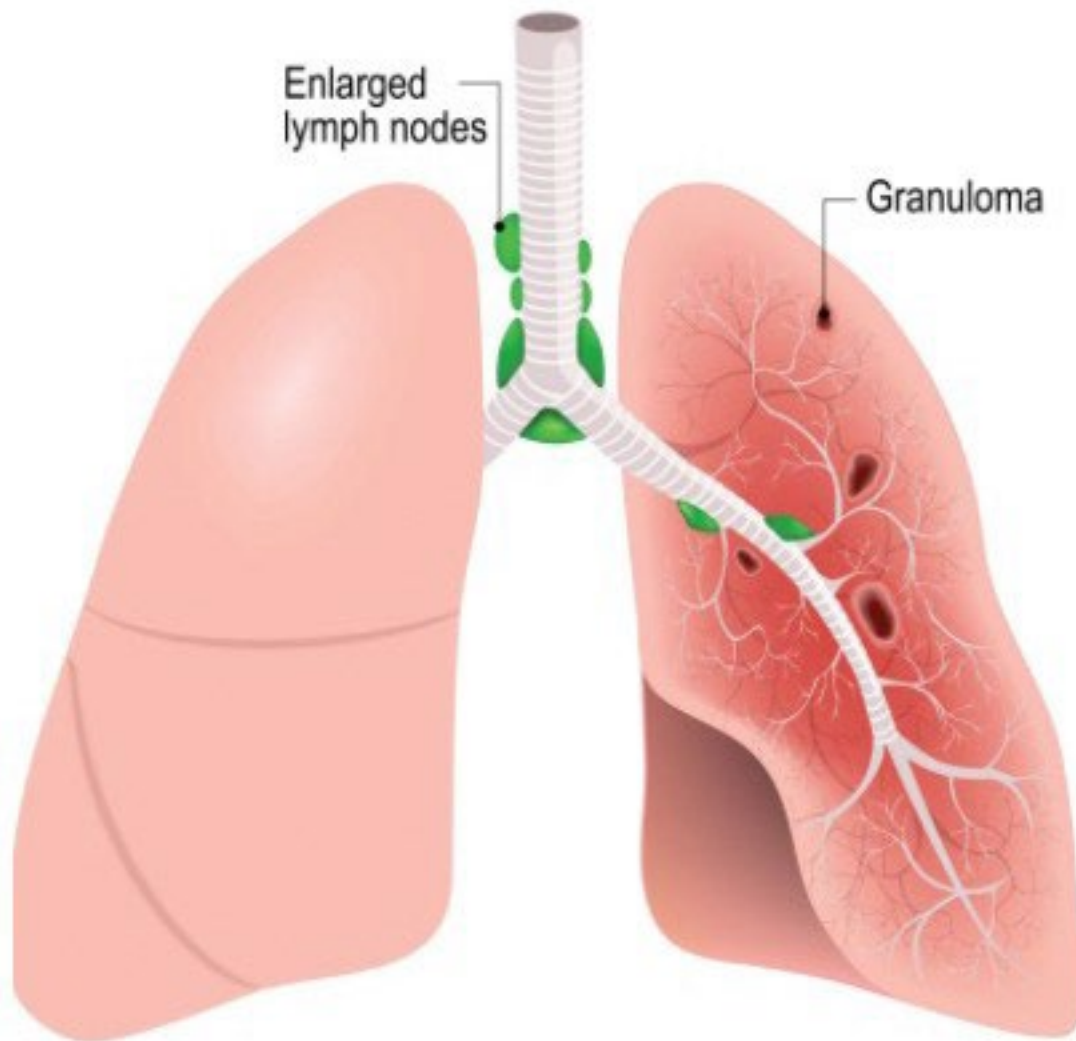
HisRS was the first aaRS acquired a WHEP domain in evolution



HisRS WHEP domain is a negative regulator of immunity

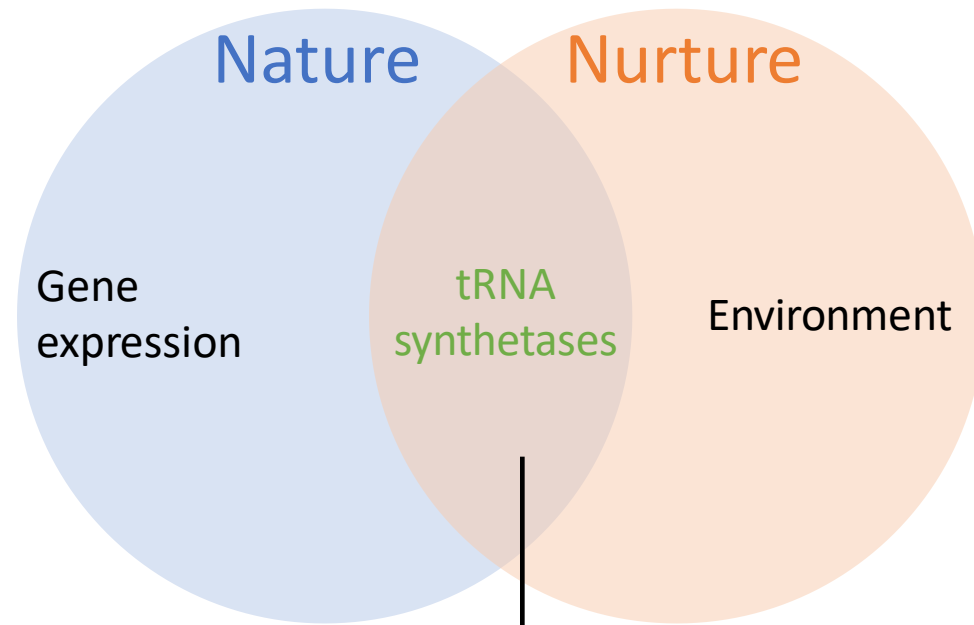


HisRS^{WHEP} showed positive clinical results for pulmonary sarcoidosis



- Reduced oral steroid use
- Reduced inflammation and fibrotic deposition
- Improved lung function





Homeostasis

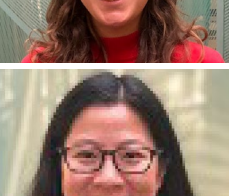
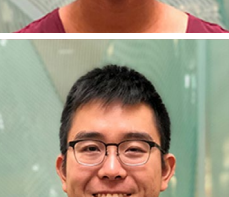
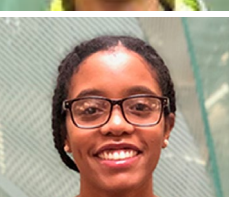
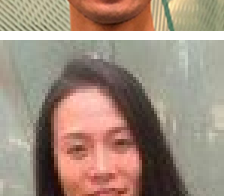
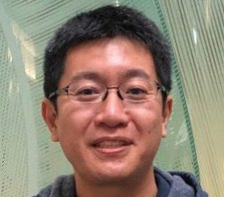
Acknowledgements

People

All past and current members of Schimmel-Yang lab
Collaborators and colleagues in the field of tRNA synthetases
in academia and in industry

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NIH/National Institute of General Medical Sciences
NIH/National Institute of Neurological Disorders and Stroke
National Foundation for Cancer Research
aTyr Pharma





THE
FRONT
ROW
at Scripps Research

UPCOMING LECTURES

Beyond COVID-19: Preparing for future pandemic threats



Wednesday, March 16

1:00 PM PT/4:00 PM ET

Sumit Chanda, PhD

Professor, Department of Immunology and Microbiology, Scripps Research

Taking a new view of vital signs



Wednesday, April 20

1:00 PM PT/4:00 PM ET

Jay Pandit, MD

*Director of Digital Medicine
Scripps Research Translational Institute
Assistant Professor, Department of Molecular Medicine, Scripps Research*



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