Mouse Models to Accelerate Drug Discovery: A UK-China Network

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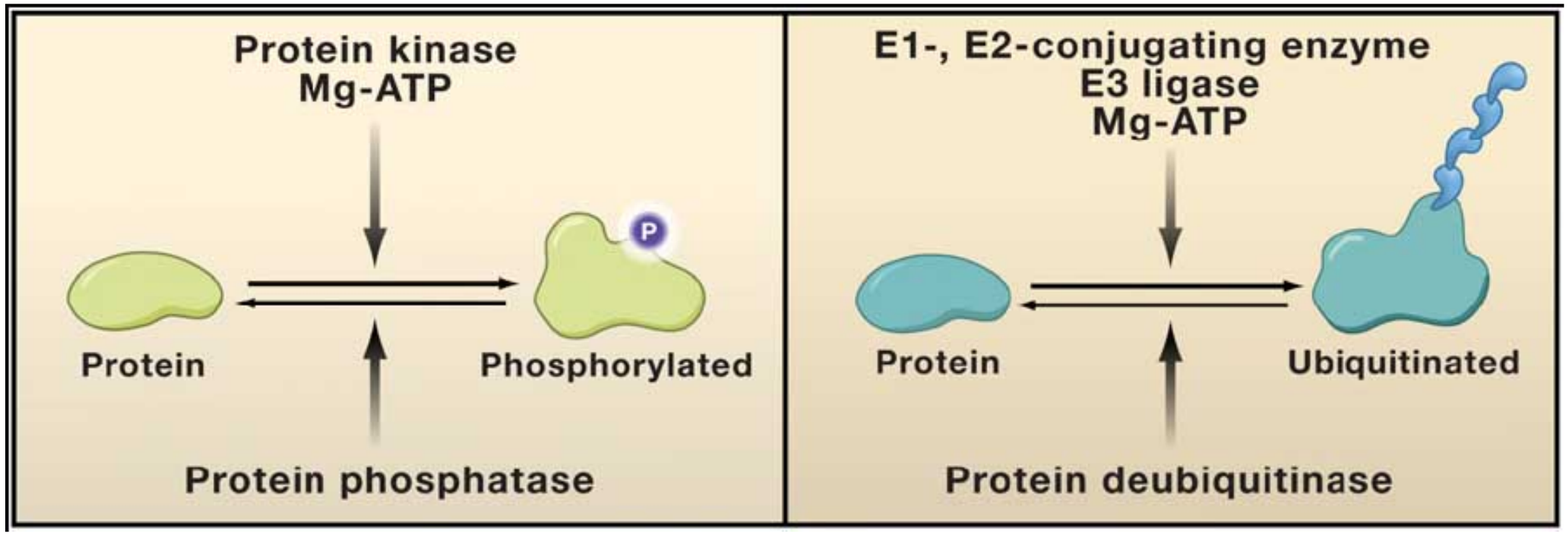
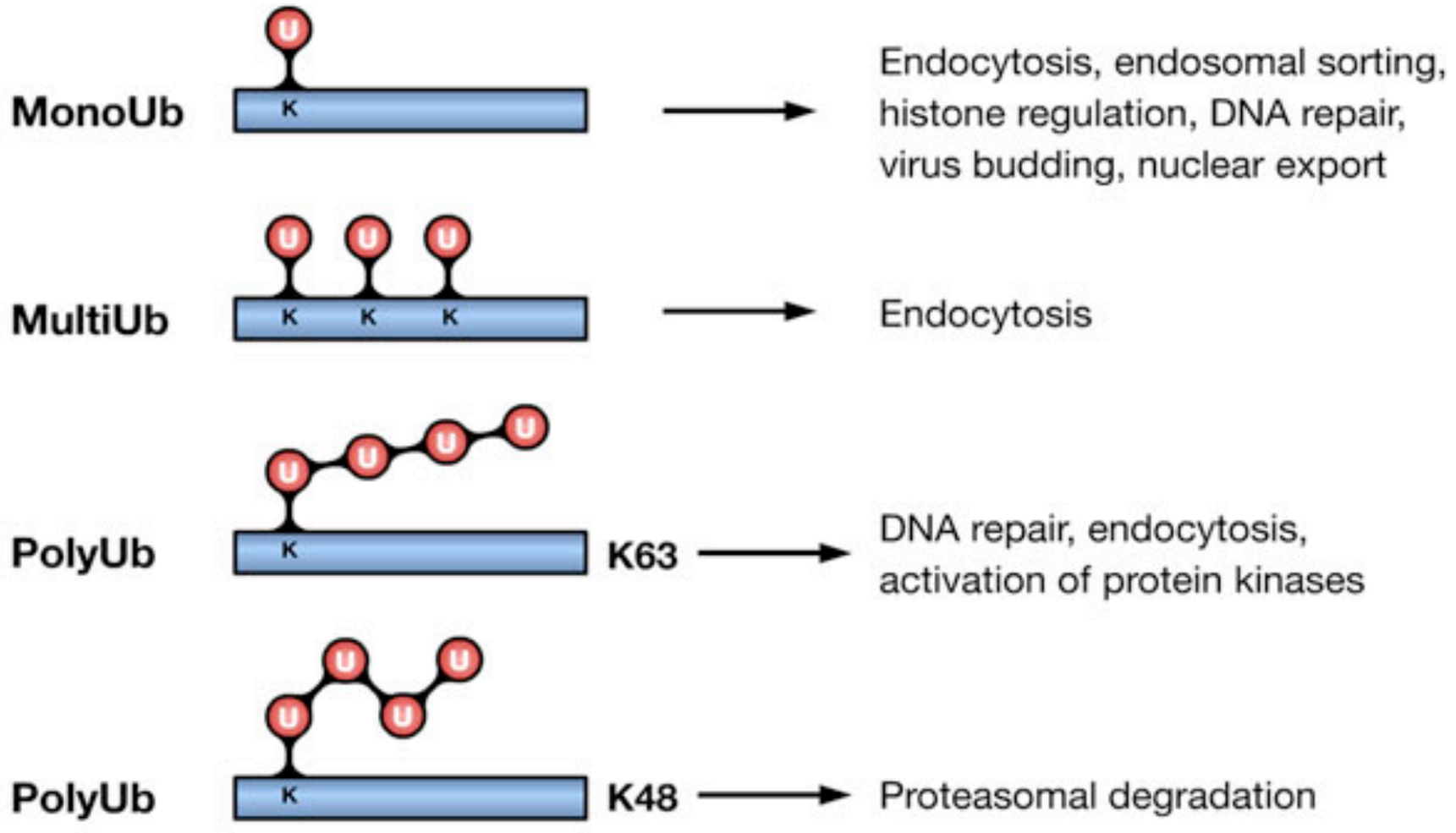
Why target the Ubiquitin System?

Protein ubiquitylation and protein phosphorylation are analogous control mechanisms



Protein ubiquitylation is an even more versatile control mechanism than protein phosphorylation



There are also a number of ubiquitin-like proteins such as SUMO, Nedd8, FAT10, ISG15, URM1 etc, which modify proteins in an analogous way

Will the ubiquitin system furnish as many drug target as protein kinases?

Like protein phosphorylation, protein ubiquitylation regulates almost all cell functions

Many components of the ubiquitin system are over produced or mutated in human diseases and are therefore attractive drug targets

History of the development of protein phosphorylation and protein ubiquitylation

	PHOSPHORYLATION	UBIQUITYLATION
1.	Discovered 1955	Discovered 1978
2.	>500 protein kinases	8 E1s, ~40 E2s, >600 E3 ligases,
3.	140 protein phosphatases	~100 deubiquitylases
4.	Nobel Prize 1992	Nobel Prize 2004
5.	First drug approval 2001 (Gleevec)	First drug approval 2003 (Bortezomib)
6.	16 drugs approved, >150 undergoing clinical trials	15 drugs undergoing clinical trials
7.	Current sales of US$15 billion p.a. p.a.	Current sales US$1.4 billion
8.	30% of Pharma R&D	<<1% of Pharma R&D

Proteasome Inhibitors Approved or in Clinical Trials

Company	Inhibitor	Development Stage	Disease
Millenium/Takeda	Bortezomib/Velcade	Approved	Multiple myeloma and mantle cell lymphoma
Millenium/Takeda	MLN9708	Phase I	Multiple myeloma and other cancers
ONYX (Proteolix)	Carfilzomib/PR171	Phase III	Multiple myeloma and other cancers
ONYX (Proteolix)	Onx 0912/PR047	Phase I	Multiple myeloma and other cancers
Cephalon	CEP18770	Phase I	Multiple myeloma and other cancers
Nereus Pharmaceuticals	Salinosporamid A/NPI0052	Phase I	Multiple myeloma and leukemia

Inhibitors of E1-Activating Enzymes and E3 Ubiquitin Ligases Undergoing Clinical Trials

Company	Inhibitor	Target	Stage	Disease
Millenium/Takeda	MLN4924	NAE-E1[b]	Phase II	Multiple myeloma and Hodgkin's lymphoma
Roche	Nutlin/R7112	E3-Hdm2	Phase I	Blood cancers and solid tumors
Johnson & Johnson	JNJ26854165	E3-Hdm2	Phase I	Multiple myeloma and solid tumors
Genentech/Roche	GDC-0152	E3-IAP	Phase I	Metastatic malignancies
Novartis	LCL161	E3-IAP	Phase I	Solid tumors
Ascenta Therapeutics	AT-406	E3-IAP	Phase I	Solid tumors and lymphoma
Aegera Therapeutics	AEG 35156[a]	E3-IAP	Phase II	AML and liver cancer
Aegera Therapeutics	AEG 40826	E3-IAP	Phase I	Lymphoid tumors
Tetralogics Pharma	TL 32711	E3-IAP	Phase I	Solid tumors and lymphoma
Astellas Pharma	YM155	E3-IAP	Phase II	Lung cancer

[a] Antisense oligonucleotide.

[b] The E1-activating enzyme for neddylation.

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- Principal Investigator - Professor Dario Alessi (MRC-PPU Dundee)
- Protein Ubiquitylation and Phosphorylation - Professor Sir Philip Cohen (MRC-PPU Dundee)
- Operational Lead, UK – Dr. Tom Weaver (MRC Harwell)
- Operational Lead, China – Professor Xiang Gao (Nanjing, China)
- Protein Ubiquitylation-Functional Analysis – Professor Aaron Ciechanover (Haifa, Israel)
- Drug Screening & Technology Transfer - Dr. Mike Dalrymple (MRC Technology)
- Structural Analysis – Professor Aled Edwards (Structural Genomics Consortium, SGC)

Our Mission

- **To accelerate drug discovery in the ubiquitylation system through the use of mouse knockout models.**

Our Objective

- The UK-China network will bring together academic, governmental, and industrial researchers who are experienced and committed to applying mouse models towards developing innovative new medicines. The network will focus on generating and phenotyping knockout mice for genes of the protein ubiquitylation system, considered an untapped and rich source of novel drug targets against a broad range of therapeutic indications of great interest to the pharmaceutical industry.

Project

- 93 Deubiquitlating enzymes (DUBs)
- 42 E2 conjugating enzymes
- 74 F box E3 Ligase substrate recognition subunits
- 28 HECT-type E3 ligases (of great interest to SGC).
- ie 237 targets
- Aim is to ensure the delivery of a minimum 100 germ-line mutant strains for functional analysis and follow-up.

Work Plan

- Prioritization of ALL genes of the deubiquitylases, E2 conjugating enzymes, F Box proteins and HECT-type E3 ligases
- Mouse operational effort will be shared 50:50 between the UK and China (Harwell/Nanjing).
- Prioritize and Integrate Structural Information of Candidate Targets (SGC).
- Advise and interpret results from the phenotyping pipeline (Dundee/Technion/ SGC/MRCT).
- Promote follow-up studies to increase value of the MRC IMPC program