Rare Disease Research UK.

mTOR Pathway Diseases

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Background

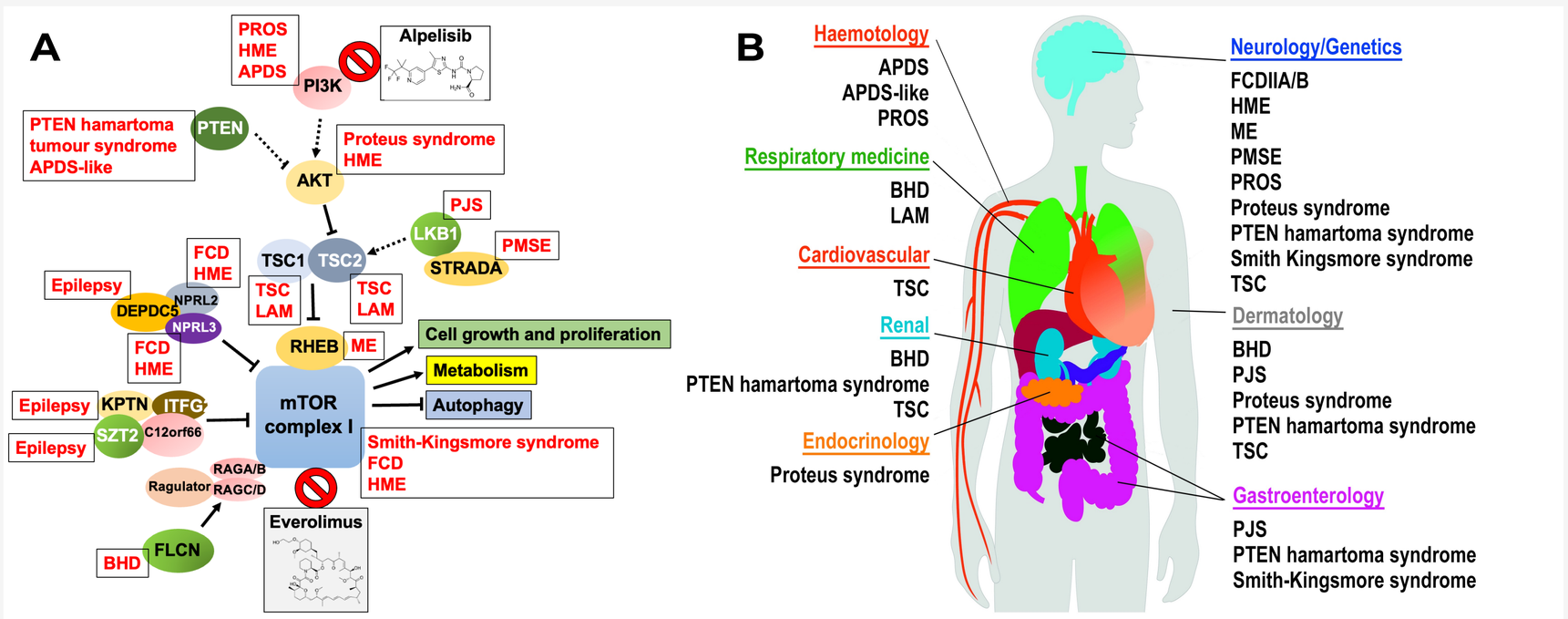

***Figure 1**: mTOR pathways diseases..* **(A)** The mTOR pathway with rare diseases (shown in red) caused by mutations in specific proteins. **(B)** The different medical specialities that treat mTOR pathway disease patients. APDS: activated PI3K delta syndrome, BHD:, Birt-Hogg-Dubé FCDIIA/B: focal cortical dysplasia type IIA/B, HME: hemimegalencephaly, LAM: lymphangioleiomyomatosis, ME: megalencephaly, PJS: Peutz-Jeghers syndrome, PMSE: polyhydramnios, megalencephaly and symptomatic epilepsy syndrome, PROS: PIK3CA-related overgrowth spectrum, TSC: tuberous sclerosis complex.

The **mechanistic target of rapamycin** (**mTOR**) signalling pathway regulates fundamental cellular processes including **growth control, autophagy and metabolism (Figure 1A)**.

mTOR pathway **hyperactivation causes 14 diverse, rare, early-onset, hard-to-treat genetic diseases** affecting 10,000 people in the UK

These diseases include **a wide range of symptoms ranging from benign tumours in multiple organs to brain malformations causing epilepsy**, each of which is **managed in separate, non-coherent medical disciplines (Figure 1B).**

The **challenge area** is that since **mTOR pathway diseases share common molecular mechanisms, clinical phenotypes and drug targets, there is an opportunity to improve diagnosis and outcomes across this disease cluster** by connecting disjointed populations basic and translational research resources with clinical, patient and industry stakeholders.

Vision and Enabling Science Projects

OUR VISION

To **establish** the **world's first mTOR pathway disease population-based patient registry.**

To **map** national **epidemiology**, **comorbidities**, **treatments**, **trajectories**, and **health economics** of mTOR pathway diseases.

To **identify NHS patients eligible for clinical trials**, **orphan drug**, and **experimental medicine** opportunities.

To **apply cutting-edge cellular** and **molecular methods** to **understand mechanisms** and **druggable targets**.

To **utilise existing clinical infrastructure** and **Genomics England** to **integrate mTOR pathway clinical care** and **optimise diagnostic approaches**.

To benefit from **shared expertise** in **genetic diagnosis**, **patient registry development**, **data sharing**, and patient and public involvement and engagement (**PPIE**).

To **collaborate** with **other nodes** in the platform focused on **rare renal**, **lung**, **immune**, and **neurological diseases.**

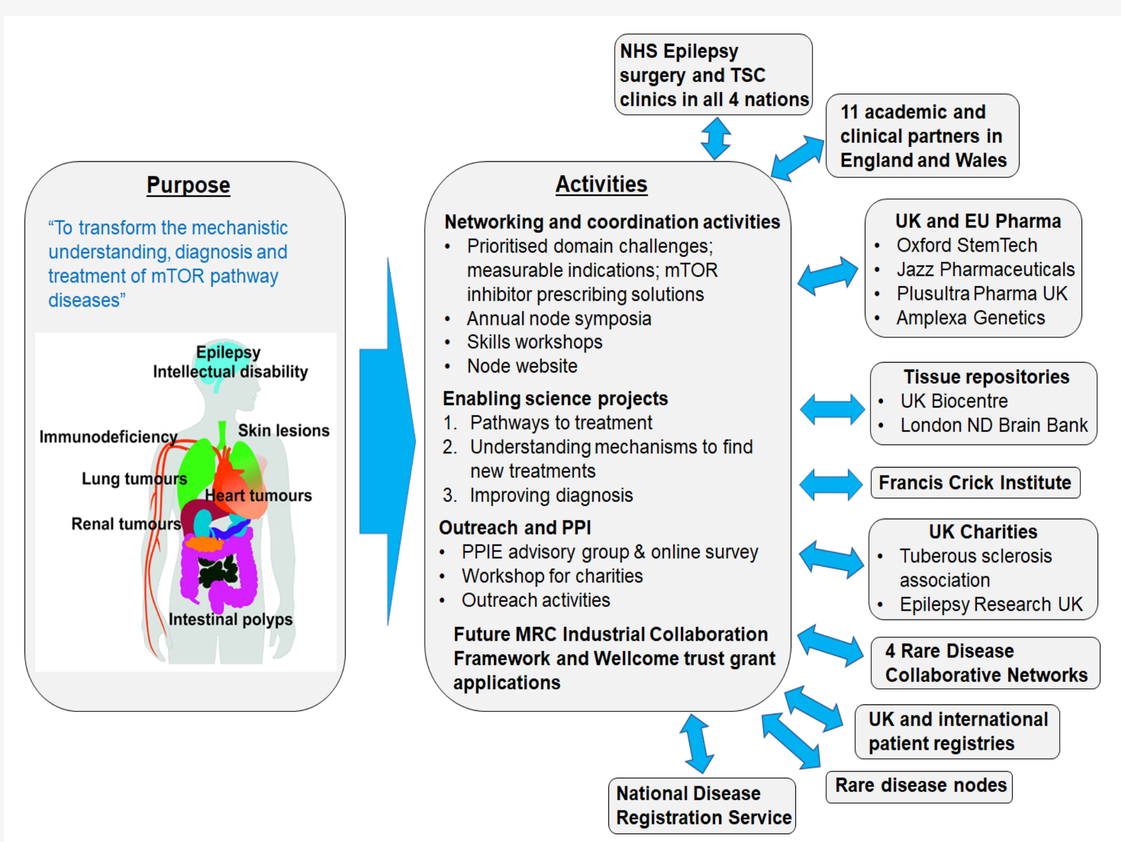

***Figure 2.** Purpose, connections and activities of the mTOR Pathway Diseases node.*

3 ENABLING SCIENCE PROJECTS

1 Pathways to treatment
1.1. mTOR pathway diseases registry
1.2. mTOR pathway drug-disease database

2 Understanding mechanisms to find new treatments
2.1 mTOR pathway diseases tissue repository and phospho-proteomics
2.2. mTOR pathway diseases PBMC panel and TSC cerebral organoid model

3 Improving diagnosis
3.1. Policy framework proposal
3.2. mTOR pathway disease test directory panel
3.3. Non-invasive genetic testing for mosaic neurological mTOR pathway diseases

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