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Drug repositioning for rare diseases: Knowledge-based success stories

Rational drug repositioning for rare diseases

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Summary

While more than 7,000 rare diseases have been identified, only about 5 percent benefit from a licensed treatment. As the majority of these diseases is life threatening, these facts underscore the need for new drugs. Drug repositioning is an alternative strategy in drug development, which represents an attractive opportunity for rare diseases. Drug repositioning (also called drug repurposing, drug reprofiling or drug re-tasking) consists in identifying for an already approved or investigational drug a new use outside the scope of the original medical indication. Drug repositioning is considered in the field of orphan drugs as being a faster and somehow less costly strategy than traditional new drug development for pharmaceutical companies. While several successful repositioning cases have been discovered by serendipity, most successes straightly derive from the molecular characterization of the concerned disease. This short commentary is mainly dedicated to these rationally-based success stories.

KEYWORDS:

Rare Diseases; Drug repurposing; Drug repositioning; Progeria; Alkaptonuria; Overgrowth syndrome

Abbreviations

AKU: alkaptonuria

AKUSSI: AKU severity score index

Anti-VEGF: anti-vascular endothelium growth factor

bFGF: basic fibroblast growth factor

CLOVES (syndrome): congenital, lipomatous, overgrowth, vascular, epidermal naevi, spinal/skeletal (syndrome)

FAH: fumarylacetoacetate hydrolase

FDA: Food and Drug Administration

FKBP: FK506-binding protein

GCP: good clinical practice

GLP: good laboratory practice

GMP: good manufacturing practices

HGD: homogentisate 1,2-dioxygenase

HGPS: Hutchinson-Gilford progeria syndrome

HPPD: 4-hydroxyphenylpyruvate dioxygenase

MAI: maleylacetoacetate isomerase

PIP: pediatric investigation plan

PIK3CA: catalytic subunit of phosphatidylinositol 3-kinase α

PKU: phenylketonuria

RR: response rate

TAT: tyrosine aminotransferase

TMA: thrombotic microangiopathy

TSC: tuberous sclerosis complex

VEGF: vascular endothelial growth factor

Drug repositioning consists in finding a new therapeutic use for an already approved drug or for a drug/compound still in clinical stage development. Moreover, it holds the potential to bring medications with known safety profiles to new patient populations. Drug repositioning (also called drug repurposing, drug reprofiling or drug retasking) is considered by pharmaceutical companies as being a faster and somehow less costly strategy for the development of orphan drugs for rare diseases. Examples of successful drug repositioning which have gained registration for a rare disease, comprise already approved drugs for a non-rare indication and drugs that had been extensively developed for a non-rare indication before failing to reach the market.

While several successfully repositioned drugs were discovered by pure serendipity, most successes straightly derive from the precise molecular characterization of the concerned rare disease, which is most often from genetic origin. This short commentary describes the general rationale for drug repositioning and gives some examples of successful repositioning stories, which have mostly been based on biological rationale.

Rationale for drug repositioning in the rare diseases field

Rare diseases are defined as affecting less than one individual in the 2000s. This proportion can drop down to less than a few per million for the so-called “ultra-rare diseases” [1]. Because there are about 7,000 to 8,000 different rare or ultra-rare diseases affecting 350 million people worldwide, more than 25-30 million people in the United States are affected by such rare disorders, and an identical number concerns European countries. More than 50% of rare diseases affects patients from birth and during all their life.

The development of drugs for rare diseases has been severely hampered by their low occurrence, because each rare disease represents a small market in view of the high costs traditionally associated to drug discovery and development, which can sum up to several billion dollars. In addition, drug development for rare diseases is also often affected, among other things, by a limited understanding of how a rare disease progresses, its so-called “natural history”, and by difficulties on how to measure clinical improvement. Thus, Food and Drug Aministration (FDA)-approved treatments exist for about 5% of rare diseases.

The development of a drug, from the identification of the lead compound to the market authorization, usually requires ten to fifteen years of research and of preclinical and clinical development. This long and costly process comprises a succession of highly and strictly regulated complex stages: identification of the pharmaceutical drug formulation, as well as preclinical and

clinical studies in compliance with good manufacturing practices (GMP), good laboratory practice (GLP) and good clinical practice (GCP). Repositioning an already approved drug can drastically reduce the cost of such drug development steps, since, for instance, the regulatory toxicology and pharmaceutical dossiers have already been drafted and approved. Indeed, when solid preclinical proof of concept is obtained, the cost of approval of a repositioned drug for a rare disease use can be less by several orders of magnitude cheaper than for a conventional new chemical entity.

About 80% of rare diseases are from genetic origin [2], and since 50% of them already have a localized gene defect, the corresponding identified molecular target represents a very good opportunity for rationale drug repositioning. For instance, as will be presented below, common pathways are being involved in both several cancer types and overgrowth syndrome rare diseases. Hence, there is a strong rationale for trying to tackle a rare overgrowth syndrome with already approved anticancer drugs.

Another crucial advantage of drug repositioning is the “speed” factor. Rare disease patients are often children for which finding a cure represents an excruciating race against time for both the affected patient and their families, which witness the slow degradation of their child. While conventional drugs might take up to 15 years and more to reach the market, the average duration for a repurposed drug is around 5-7 years.

Finally, the attrition rate for a repurposed drug to reach the market is somewhat lower than for new original compound, in particular because the risk of adverse drug reactions has already been alleviated, and maximal tolerated dose has already been defined in humans. However, it has to be noted that using a drug in a new disease could lead to new previously unknown adverse drug reactions. This point is important for drugs for rare diseases.

There is large track-record of successful drug repositioning, especially anticancer drugs being repositioned for non-cancer application, the most famous example being the use of anti-vascular endothelium growth factor (VEGF) antiangiogenic biologics for treating age-related macular degeneration. We will present here several iconic success stories concerning the rare diseases field. Some discoveries may be accidental, and some old drugs and even shelved compounds discontinued from clinical development may find a second life through repositioning. In the EU, incentives associated with orphan drug status have facilitated the development of 127 orphan drugs to date. About 1 in 5 orphan drugs are repurposed.

Progeria

As a farnesyl transferase inhibitor, lonafarnib was initially evaluated to treat cancer and has now emerged as a potential treatment for progeria and progeroid laminopathies by targeting the same pathway.

Hutchinson-Gilford progeria syndrome (HGPS) is an ultra-rare disease which induces rapid senescence of tissues and affects children as young as 1 to 2 years of age. Progeria leads to death occurring as a result of complications of severe atherosclerosis, either cardiac or cerebrovascular disease, generally between ages 6 and 20 years. Average life span is approximately 14.5 years [3,4].

The origin of Hutchinson-Gilford progeria syndrome is linked to a heterozygous pathogenic variant in the LMNA gene that results in production of an abnormal form of lamin A/C protein. Mutations in the LMNA gene lead to expression of a truncated, permanently farnesylated prelamin A variant called progerin, which induces an abnormal nuclear morphology [3]. Lamin A precursors, which cannot be fully processed, accumulate into the nucleus inducing a toxic effect on nuclear homeostasis. It has been shown that blocking farnesylation leads to an improvement in the abnormal nuclear morphology observed in cells expressing progerin. It is associated with progerin re-localization from the nuclear envelope to the nuclear interior.

Since the *ras* oncogene associated to various types of carcinoma is also farnesylated, farnelysation blockers have been extensively developed as anticancer agents; they also show promises to treat children with Hutchinson-Gilford progeria syndrome [4,5]. Lonafarnib, a type of farnesyltransferase inhibitor originally developed to treat cancer, has indeed proven effective for Progeria [6]. A cohort of 27 patients from 6 continents with Hutchinson-Gilford progeria syndrome received oral lonafarnib (150 mg/m^2) twice daily and was compared to more than 200 untreated patients. Treatment with lonafarnib monotherapy compared with no treatment was associated with a lower mortality rate after 2.2 years of follow-up (hazard ratio, 0.12; P = 0.04). In the combined cohort, there were 4 deaths (6.3%) among 63 patients in the treated group and 17 deaths (27.0%) among 63 patients in the matched untreated group (hazard ratio, 0.23; 95% CI, 0.06-0.90; P = 0.04) [6].

Proliferative infantile hemangiomas

The impressive story of the beta-blocker propranolol, which has been surprisingly repositioned in proliferative infantile hemangiomas is a successful example of both a repurposed generic drug and a serendipitous discovery. Propranolol is a non-selective β-adrenergic receptor blocker. It is an old

drug that dates back to the mid-1960s, when it was originally developed to treat angina and hypertension by Sir James Black who was awarded the Nobel Prize in physiology and medicine in 1988.

Most infantile hemangiomas do not require therapy and regress spontaneously. However, about 10–15% are at risk of proliferation, resulting in life-threatening complications, such as blood vessel obstruction and ulceration, and as such these specific cases require satisfactory treatment. The serendipitous discovery of propranolol as an effective means to regress hemangiomas has made this drug a first-line therapy for complicated infantile hemangioma.

The observation was made by Leaute-Labreze et al [7], who treated a child with nasal capillary hemangioma with corticosteroids. Unfortunately, the child developed obstructive hypertrophic cardiomyopathy, most likely as an adverse drug reaction of the corticosteroid treatment, which then required treatment with the beta-blocker propranolol. The day that treatment was initiated, the hemangioma changed its color and softened. Moreover, no regrowth was noted after the corticosteroid treatment ceased. This first observation was then followed by a randomized controlled trial, a large cohort study, and a meta-analysis of 1264 reported cases which demonstrated the efficacy of oral propranolol at a dose of 2–3 mg/kg per day and after a mean of 6 months of therapy. A positive response (hemangioma shrinkage) was observed in 96–98% of cases, with complete or nearly complete regression in 60% of the cases [7-9]. This unexpected beneficial effect of propranolol can be attributed to its vasoconstrictive properties, which are not shared by all beta-blocking drugs. Indeed, the potential mechanisms of action of propranolol in proliferating infantile haemangioma could include not only the local haemodynamic effect (vasoconstriction and decrease of lesion perfusion) but also an antiangiogenic effect [decrease expression of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF)].

Despite extensive knowledge about the safety and subsequently reduced risk, the rediscovery of generic drugs may be a real challenge. Because of expired patent, risk of off-label use and lack of standardized regulatory approach, many pharmaceutical companies may be reluctant to develop such drugs. In spite of these hurdles, propranolol has been approved by both the US Food and Drug Administration and the European Medicines Agency. For the latter one, approval was based on the pediatric use marketing authorization (PUMA), a rarely used instrument for special approval for an innovative pediatric use of medicines which are already authorized for other applications. Prerequisite for a PUMA is a pediatric investigation plan (PIP) which sets out the development of the medicine in children and has to be approved by the Agency's Pediatric Committee. A drug under PUMA authorization benefits from a 10-year protection.

Additionally, the recognition that β blockers are an effective treatment for infantile hemangioma has opened up a new therapeutic area and given rise to research in the field of vascular biology.

Type-I tyrosinemia and alkaptonuria

It is widely known that the deficit in the tyrosine amino-acid caused by a mutation in the phenylalanine hydroxylase gene leads to phenylketonuria (PKU), which is a well-treated rare disease. However, several other rare diseases caused by genetic mutations in the tyrosine amino-acid degradation pathway still represent largely unsolved therapeutic challenges.

Fig. 1 represents the various steps of tyrosine catabolism. Tyrosine is first transformed to 4-OH-phenylpyruvate-tyrosine by tyrosine aminotransferase (TAT). Deficit in TAT by genetic mutation is responsible from tyrosinemia type II, which is caused by tyrosine accumulation in the organism, especially in blood. The second step of tyrosine catabolism is the transformation of 4-OH-phenylpyruvate-tyrosine into homogentisic acid by 4-hydroxyphenylpyruvate dioxygenase (sometimes abbreviated as HPPD), whose deficit induces tyrosinemia type III. Homogentisic acid is then metabolized to maleylacetoacetic acid by homogentisate 1,2-dioxygenase (HGD). Deficit in HGD causes alkaptonuria. Further enzymatic steps lead to fumarylacetoacetic acid through the action of maleylacetoacetate isomerase (MAI), then to fumaric acid through the action of fumarylacetoacetate hydrolase (FAH). Deficit in FAH is responsible for the tyrosinemia type I genetic disease.

Alkaptonuria represents a very surprising and recent drug repositioning example. As already said, it is a tyrosine degradation disorder caused by a mutation in the homogentisate 1,2-dioxygenase enzyme (Fig. 1). As a result, homogentisic acid accumulates in various organs, such as eye, skin, cartilage and several other connective tissues, inducing a black pigmentation of the affected tissues (alkaptonuria, also known as black bone disease, is usually detected from the color of the urine). This autosomal recessive disorder (ORPHA:56 on Orphanet site) has a prevalence of less than 1/100000. It was found that a promising way to inhibit the build-up of homogentisic acid was to inhibit the enzyme involved in the preceding step of the degradation pathway: 4-hydroxyphenylpyruvate dioxygenase [10] (Fig. 1). Nitisinone, which is a reversible inhibitor of 4-hydroxyphenylpyruvate dioxygenase, had been initially developed as a weed killer. Because of its toxicity on fish and rodents, it did not reach the agrochemical market. Its herbicidal activity is the result of its inhibitory activity on 4-hydroxyphenylpyruvate dioxygenase (HPPD), which in plants is

involved in the formation of essential isoprenoid redox cofactors such as plastoquinone and tocopherol necessary for chlorophyll synthesis. In a recently published clinical study, it was reported that nitisinone decreases the rate of progression of alkaptonuria [11]. In this clinical trial, AKU patients were treated with a 2 mg dose of nitisinone which slows down the clinical progression of AKU. Combined ocular and ear ochronosis progression was arrested by nitisinone.39, 34 and 22 AKU patients completed 1, 2 and 3 years of monitoring respectively (visits V2, V3 and V4) in the VAR group. 17 patients also attended a pre-baseline visit (V0) in the VAR group. Within the 39 patients, a subgroup of the same 10 patients attended V0, V1, V2, V3 and V4 visits constituting the SAME Group. Severity of AKU was assessed by calculation of the AKU severity score index (AKUSSI) allowing comparison between the pre-nitisinone and the nitisinone treatment phases. The ALL (sum of clinical, joint and spine AKUSSI features) AKUSSI rate of change of scores/patient/month was significantly lower at two (0.32 ± 0.19) and three (0.15 ± 0.13) years post-nitisinone when compared to pre-nitisinone (0.65 ± 0.15) ($p < .01$ for both comparisons). Similarly, the ALL AKUSSI rate of change of scores/patient/month, in the VAR group, was significantly lower at one (0.16 ± 0.08) and three (0.19 ± 0.06) years post-nitisinone when compared to pre-nitisinone (0.59 ± 0.13) ($p < .01$ for both comparisons). Combined ear and ocular ochronosis rate of change of scores/patient/month was significantly lower at one, two and three year's post-nitisinone in both VAR and SAME groups compared with pre-nitisinone ($p < .05$). This represents the first indication that a 2 mg dose of nitisinone slows down the clinical progression of AKU. Combined ocular and ear ochronosis progression was arrested by nitisinone [11].

Repositioning of a biologic: eculizumab

Repositioning might concern not only small chemical molecules, but also very large biomolecules such as monoclonal antibodies. The monoclonal antibody eculizumab is a terminal complement inhibitor that specifically binds with high affinity to the complement C5 protein, thereby inhibiting its C5a and C5b cleavage and preventing the formation of the complement C5b-9 terminal complex. Eculizumab preserves the proximal complement proteins that are essential for the opsonization of microorganisms and the clearance of immune complexes, and thus has limited negative effect on the immune system function. In patients with paroxysmal nocturnal hemoglobinuria, eculizumab inhibits the uncontrolled activation of the terminal complement pathway and the induced intravascular hemolysis.

Eculizumab has been repositioned for several rare diseases. Atypical hemolytic uremic syndrome is a rare genetic life-threatening disease of chronic uncontrolled complement activation leading to thrombotic microangiopathy and severe end-organ damage. An open-label single-arm phase 2 trial has highlighted the benefits of eculizumab in adult patients with atypical hemolytic uremic syndrome, describing an improvement in hematologic, renal, and quality-of-life parameters, as well as dialysis discontinuation and transplant protection [12]. In this single-arm open-label trial, the primary end point was complete thrombotic microangiopathy (TMA) response within 26 weeks, defined as hematologic normalization (platelet count > or equal to150 $x10^3/\mu L$, LDH < ULN), and preservation of kidney function (< 25% serum creatinine increase from baseline), confirmed by 2 or more consecutive measurements obtained 4 or more weeks apart. Forty-one patients were treated; Thirty-eight (93%) completed 26 weeks of treatment. Thirty (73%) were included during their first TMA manifestation. Thirty (73%) had complete TMA response. Platelet counts and estimated glomerular filtration rates increased from baseline (P<0.001). Of 24 patients requiring baseline dialysis, 5 recovered kidney function before eculizumab initiation and 15 of the remaining 19 (79%) discontinued dialysis during eculizumab treatment. No patients lost existing transplants. Quality-of-life measures were significantly improved [12].

Complement is activated uncontrollably in autoimmune myasthenia gravis. This process is due to autoantibodies that target the neuromuscular junction and cause abnormalities in the transmission of nerve impulses, leading to fatigability and muscle strength loss. Eculizumab has been repositioned for the treatment of generalized myasthenia gravis (see review by Dhillon [13]). Finally, another eculizumab repositioning use has been recently proposed for the treatment of enteropathy with loss of protein, for which a compassionate therapy applied to three patients led to complete remission [14]. A 18-month treatment was applied to 3 CD55-deficiency patients. Clinical and laboratory treatment outcomes included frequency and consistency of bowel movements, weight, patient/parent reports of overall well-being, and serum albumin and total protein levels. Membrane attack complex deposition on leukocytes was tested by flow cytometry, before and during eculizumab treatment. A marked clinical improvement was noted in all 3 patients with resolution of PLE manifestations, that is, diarrhea, edema, malabsorption, overall well-being, growth, and quality of life. In correlation with the clinical observations, progress was observed in all laboratory outcome parameters, including increase in albumin and total protein levels, and up to 80% reduction in membrane attack complex deposition on leukocytes (p<0.001). The progress persisted over 18 months of treatment without any severe adverse events [14].

Repositioning of anticancer agents for overgrowth syndromes

Since cancers involve abnormal dysregulated cell growth, it is appealing to investigate the potential of the greatly extended family of anticancer drugs to treat rare overgrowth syndromes. Such overgrowth syndromes are characterized by macrosomia, congenital anomalies, mental retardation and an increased risk of tumors [15].

Many oncogenic proteins (oncogenes or tumor suppressors) are linked to the mTOR signaling pathway (Fig. 2). It is estimated that mTORC1 function is hyperactivated in up to 70% of all human tumors. This has promoted very active research on mTOR inhibitors as anticancer agents for advanced solid tumors such as breast carcinoma, non-small cell lung carcinoma, hepatocellular carcinoma and glioma.

Tuberous sclerosis complex (TSC; Bourneville tuberous sclerosis) is a rare multisystemic autosomal dominant genetic disease, whose prevalence is about 1 to 1.5/10,000. The disease is caused by a mutation of the tuberous sclerosis complex 1 (TSC1) gene (9q34) or TSC2 (16p13), which are tumor suppressor genes coding for hamartin and tuberin, respectively. TSC patients develop benign tumors (hamartomas) in many organs, such as brain, skin, kidneys, and less frequently in eyes, heart and lungs.

The mTOR inhibitor everolimus has been approved for the treatment of TSC-related tumors in the brain (subependymal giant cell astrocytoma) in 2010, and in 2012 in the kidneys (renal angiomyolipoma) [16]. Everolimus is an orally bioavailable derivative of sirolimus, which is a macrolide antibiotic produced by a *Streptomyces.* Sirolimus, also known as rapamycin, was first developed as an antifungal agent, but was later found to have potent antiproliferative and immunosuppressive properties. Originally approved to prevent rejection in organ transplantation, sirolimus was successfully repurposed to treat two rare diseases: autoimmune lymphoproliferative syndrome and the lung disease lymphangioleiomyomatosis.

Both sirolimus and everolimus have the potential to treat the underlying cause of TSC by inhibiting the mTOR pathway. The mechanism of action of rapamycin and analogs has been extensively investigated. These drugs bind to a family of intracellular proteins known as FK506-binding proteins (FKBPs) and in particular to FKBP12. The FKBP-drug complex then binds to mTOR at the FKBP12-rapamycin binding domain, thus inhibiting downstream signaling events (Fig. 2). Sirolimus, everolimus and other rapalogs exert their inhibitory effects on mTOR-regulated processes by reducing the phosphorylation of downstream mTOR effectors, which blocks the expression of various proteins involved in cell cycle regulation, glycolytic activity, angiogenesis, cell size control, and cellular growth [17].

Recently, everolimus also showed evidence of efficacy at treating epilepsy in TSC [18]. After completion of the core phase, patients could enter an open-label extension phase and receive everolimus (target exposure, 3–15 ng/mL) for ≥48 weeks. Efficacy end points included change from baseline in average weekly seizure frequency expressed as response rate (RR, ≥50% reduction) and median percentage reduction (PR). Of 366 patients, 361 received everolimus in core/extension phases. The RR was 31% (N = 352) at week 18, 46.6% (N = 298) at 1 year, and 57.7% (N = 163) at 2 years. Median percentage reduction (PR) in seizure frequency was 31.7% at week 18, 46.7% at 1 year, and 56.9% at 2 years. 95 patients discontinued everolimus before 2 years; 103 had <2 years of follow-up at study cutoff, and 40% were exposed to everolimus for ≥2 years. An analysis classifying discontinued patients as non-responders showed an RR of 30.2% (N = 361) at week 18, 38.8% (N = 358) at 1 year, and 41% (N = 229) at 2 years, suggesting sustained benefit over time. The incidence of grade 3/4 adverse events (any cause) was 40.2%, and 13% discontinued because of adverse events (pneumonia [1.7%] and stomatitis [1.4%]). Two deaths were suspected to be treatment-related (pneumonia and septic shock). In 2017 the EU Commission approved everolimus for the treatment of refractory partial-onset seizures associated with TSC.

Another member of the overgrowth syndrome family is the CLOVES syndrome. CLOVES syndrome affects people with various symptoms, ranging from mild fatty soft-tissue tumors to vascular malformations encompassing the spine or internal organs. CLOVES stands for: congenital, lipomatous, overgrowth, vascular, epidermal naevi, spinal/skeletal, which summarizes the anomalies observed in patients. CLOVES syndrome is a rare genetic disorder that results from gain-of-function mutations of the PIK3CA gene [19]. It is caused by a somatic mutation arising during early embryonic development. Because of this mosaic feature, CLOVES syndrome only occurs in a define number of tissues and organs tissues.

PIK3CA is the gene that encodes the catalytic subunit of phosphatidylinositol 3-kinase α (PI3Kα, or PIK3CA). The PIK3CA protein is the catalytic subunit of the phosphatidylinositol 3-kinase, which is involved in the first intracellular signal transduction step of the mTOR pathway (Fig. 2). PIK3CA is considered as an oncogene and its mutations are involved in numerous cancers, especially breast cancer [20,21]. Thus, inhibitors of PIK3CA are attractive candidates for cancer, as well as for CLOVES syndrome treatment.

PIK3CA is the most commonly mutated gene in the poor prognosis HR+/HER2- breast cancer, in about 40% of patients. The BYL719 drug (alpelisib), an inhibitor of the PI3KCA enzymatic kinase function of the p110 α subunit, acts as an ATP-competitive inhibitor. Alpelisib has been developed for this indication by the Novartis company, and was approved by the US Food and Drug Administration as Piqray® in combination with fulvestrant for advanced or metastatic

breast cancer. A companion test assessing the HR+/HER2- phenotype is associated. Quite noticeably, during Phase II and thus even before the approval of the drug for its cancer indication, access to the drug was given to the team of Guillaume Canaud in Paris, which demonstrated the drastic therapeutic effect of a daily administration of BYL719 in CLOVES syndrome. This was first observed in one patient, and subsequently in 19 patients with CLOVES or other PIK3CA-related overgrowth syndrome (8 with CLOVES syndrome, 2 with megalencephaly–capillary malformation, and 9 withlocalized overgrowth syndrome (back, limbs, face, arms) including 3 patients with abdominal or chest vascular tumours [22]. The therapeutic effect was obtained progressively over several months, was sustained, with a promising safety profile, and regardless of the type of PIK3CA mutation. All patients described reduced tiredness. The mean circumference of the clinical target lesions decreased by 12.6 ± 3.8 and 16.3 ± 3.9% after 3 and 6 months of BYL719 treatment, respectively. All patients demonstrated an improvement in skin capillary abnormalities and naevi became thinner. Two opioid-dependent patients who were confined to bed could stop morphine, and after 2 months of treatment were able to walk without help. Haematuria disappeared in 1 patient. Chronic gastrointestinal bleeding stopped in 3 patients, associated with the correction of disseminated intravascular coagulation in 2 patients, which led to the cessation of heparin treatment. An improvement in chronic palpebral cellulitis one observed in 1 patient. All patients demonstrated a clinical improvement in scoliosis. In the two patients with megalencephaly–capillary malformation, an improvement in cognitive function and behavior was observed. In addition to the clinical improvement, a radiological response was observed in all patients. After 90 and 180 days of therapy, the mean volume of the target lesions had decreased by 27.2 ± 14.6 and 37.8 ± 16.3%, respectively. All target lesions responded to treatment. In the two patients with megalencephaly–capillary malformation, MRI revealed an improvement in cerebral perfusion. In 5 patients which had hypermetabolic activity as assessed by PET scan, a drastic reduction in the metabolic activity of affected tissues was observed after 80 days [22].

Conclusion

Drug repositioning has led to noticeable successes for rare disease treatment, sometimes in a very short timeframe. This approach also leads to better use of shelved medicines. The potential of shelved compounds needs to be more fully exploited by expanding repurposing efforts and promoting international collaboration for the treatment of rare and especially ultra-rare diseases.

Strong scientific policy regulations should be created in order to protect/support companies that make potentially risky efforts to repurpose a drug in a rare disease.

Disclosure of interest

Authors have no competing interests to declare

References

[1] Muff-Luett M, Nester CM. The genetics of ultra-rare renal disease. Pediatr Genet 2016;5:33–42.

[2] Lancet Neurology. Rare advances for rare diseases. Lancet Neurol 2017 Jan;16(1):1. doi: 10.1016/S1474-4422(16)30352-0 https://www.thelancet.com/pdfs/journals/laneur/PIIS1474-4422(16)30352-0.pdf. [Accessed December 20, 2019 (1 pp.)].

[3] Gordon LB, Brown WT, Collins FS. Hutchinson-Gilford Progeria Syndrome. Gene Reviews;Posting: December 12, 2003; Last Update: January 17 https://www.ncbi.nlm.nih.gov/books/NBK1121. [Accessed December 20, 2019].

[4] Pereira S, Bourgeois P, Navarro C, Esteves-Vieira V, Cau P, De Sandre-Giovannoli A, et al. HGPS and related premature aging disorders: from genomic identification to the first therapeutic approaches. Mech Ageing Dev 2008;129(7-8):449-59.

[5] Wang Y, Östlund C, Choi JC, Swayne TC, Gundersen GG, Worman HJ. Blocking farnesylation of the prelamin A variant in Hutchinson-Gilford progeria syndrome alters the distribution of A-type lamins. Nucleus 2012;3:452–62.

[6] Gordon LB, Shappell H, Massaro J, D'Agostino RB Sr, Brazier J, Campbell SE, et al. Association of lonafarnib treatment vs no treatment with mortality rate in patients with Hutchinson-Gilford Progeria syndrome. JAMA 2018;319:1687-95.

[7] Léauté-Labrèze C, Harper JI, Hoeger PH. Infantile haemangioma. Lancet 2017;390:85-94.

[8] Kum JJY, Khan ZA. Propranolol inhibits growth of hemangioma-initiating cells but does not induce apoptosis. Pediatr Res 2014;75:381–8.

[9] Saint-Jean M, Léauté-Labrèze C, Mazereeuw-Hautier J, Bodak N, Hamel-Teillac D, Kupfer-Bessaguet I, et al. Propranolol for treatment of ulcerated infantile hemangiomas. J Am Acad Dermatol 2011;64:827-32.

[10] Moran GR. 4-Hydroxyphenylpyruvate dioxygenase. Arch Biochem Biophys 2005 Jan 1;433(1):117-28.

[11] Ranganath LR, Khedr M, Milan AM, Davison AS, Hughes AT, Usher JL, et al. Nitisinone arrests ochronosis and decreases rate of progression of alkaptonuria: Evaluation of the effect of nitisinone in the United Kingdom National Alkaptonuria Centre. Mol Genet Metab 2018;125:127-134.

[12] Fakhouri F, Hourmant M, Campistol JM, Cataland SR, Espinosa M, Gaber AO, et al. Terminal complement inhibitor eculizumab in adult patients with atypical hemolytic uremic syndrome: a single-arm, open-label trial. Am J Kidney Dis 2016;68:84-93.

[13] Dhillon S. Eculizumab: a review in generalized myasthenia gravis. Drugs 2018;78:367–76.

[14] Kurolap A, Eshach Adiv O, Hershkovitz T, Tabib A, Karbian N, Paperna T, et al. Eculizumab is safe and effective as a long-term treatment for protein-losing enteropathy due to CD55 deficiency. J Pediatr Gastroenterol Nutr 2019;68:325-33.

[15] Neri G, Moscarda M. Overgrowth syndromes: a classification. Endocr Dev 2009;14:53-60.

[16] Curatolo P, Moavero R. mTOR inhibitors in tuberous sclerosis complex. Current Neuropharmacology 2012;10:404-15.

[17] Hausch F, Kozany C, Theodoropoulou M, Fabian AK. FKBPs and the Akt/mTOR pathway. Cell Cycle 2013;12:2366-70.

[18] Franz DN, Lawson JA, Yapici Z, Ikeda H, Polster T, Nabbout R, et al. Everolimus for treatment-refractory seizures in TSC. Extension of a randomized controlled trial. Neurol Clin Pract 2018;8:412-420.

[19] Kurek KC, Luks VL, Ayturk UM, Alomari AI, Fishman SJ, Spencer SA, et al. Somatic mosaic activating mutations in PIK3CA cause CLOVES syndrome. Am J Hum Genet 2012;90:1108–15.

[20] Karakas B, Bachman KE, Park BH. Mutation of the PIK3CA oncogene in human cancers. Br J Cancer 2006;94:455-9.

[21] Kandula M, Chennaboina KK, Ys AR, Raju S. Phosphatidylinositol 3-kinase (PI3KCA) oncogene mutation. analysis and gene expression profiling in primary breast cancer patients. Asian Pac J Cancer Prev 2013;14:5067-72.

[22] Venot Q, Blanc T, Rabia SH, Berteloot L, Ladraa S, Duong JP et al. Targeted therapy in patients with PIK3CA-related overgrowth syndrome. Nature 2018;558:540-46.

Figure 1. Tyrosine catabolism

Figure 2. mTOR signal transduction pathway

Figure 1

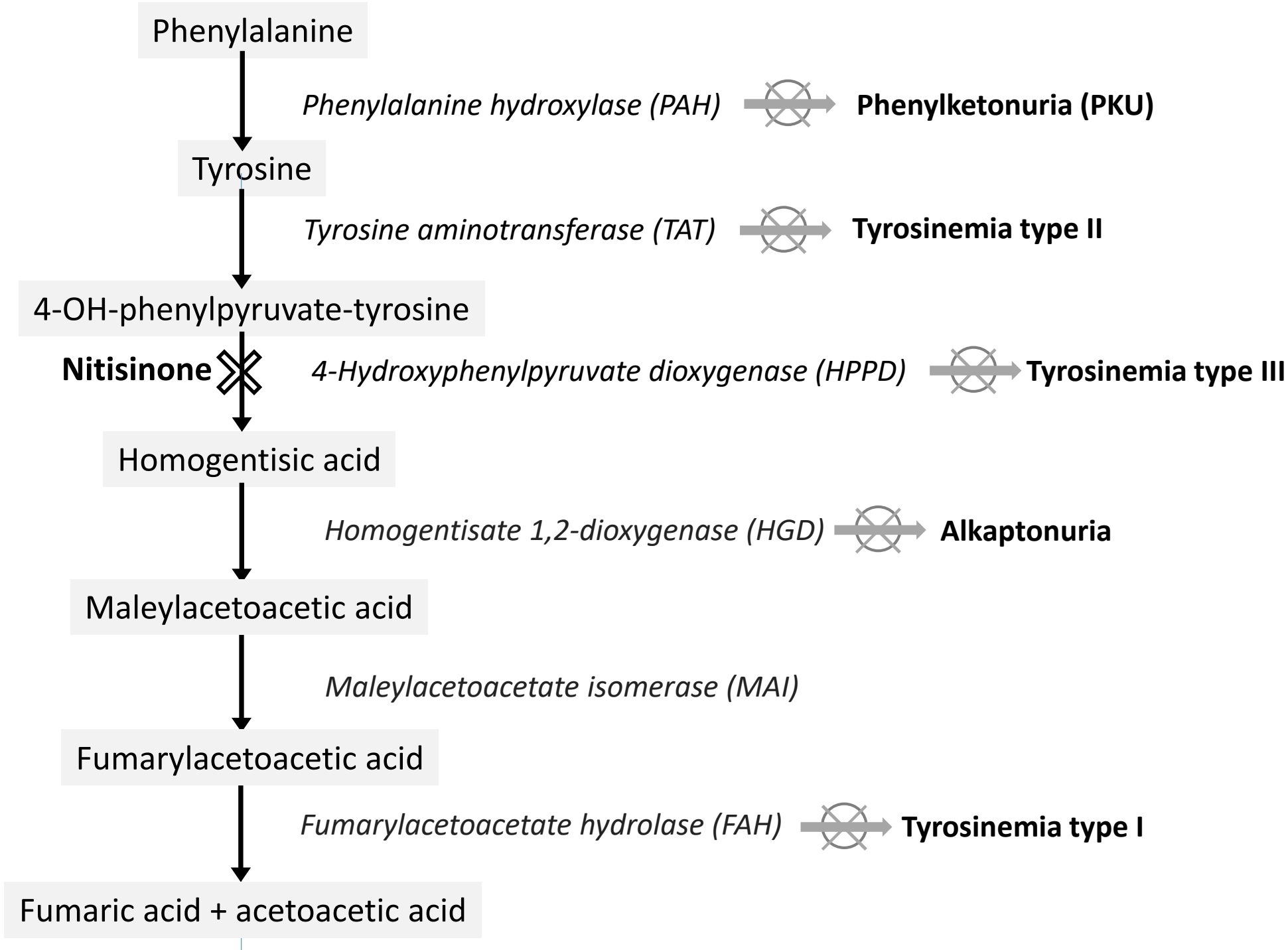
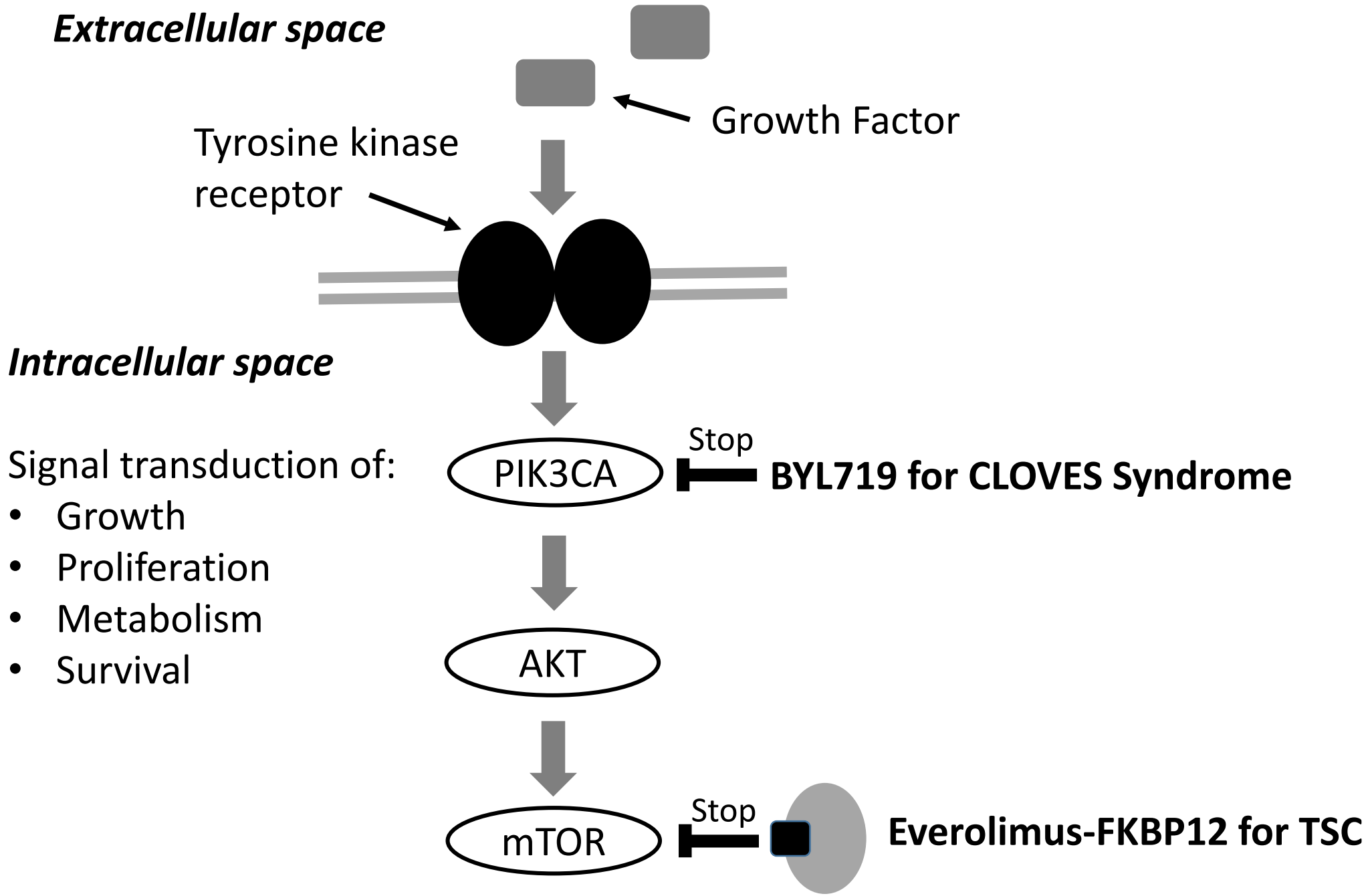

Phenylalanine
Phenylalanine hydroxylase (PAH)
Phenylketonuria (PKU)
Tyrosine
Tyrosine aminotransferase (TAT)
Tyrosinemia type II
4-OH-phenylpyruvate-tyrosine
Nitisinone
4-Hydroxyphenylpyruvate dioxygenase (HPPD)
Tyrosinemia type III
Homogentisic acid
Homogentisate 1,2-dioxygenase (HGD)
Alkaptonuria
Maleylacetoacetic acid
Maleylacetoacetate isomerase (MAI)
Fumarylacetoacetic acid
Fumarylacetoacetate hydrolase (FAH)
Tyrosinemia type I
Fumaric acid + acetoacetic acid

Figure 2


Extracellular space
Growth Factor
Tyrosine kinase receptor
Intracellular space
Signal transduction of:
• Growth
• Proliferation
• Metabolism
• Survival
PIK3CA
Stop
BYL719 for CLOVES Syndrome
AKT
mTOR
Stop
Everolimus-FKBP12 for TSC