Emerging targeted drug therapies in skeletal dysplasias

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ABSTRACT

Quantum advances have occurred in the field of human genetics in the six decades since Watson and Crick expressed their "wish to suggest a structure for the salt of deoxyribose nucleic acid". These culminated with the human genome project, which has opened up myriad possibilities, including that of individualized *genetic medicine*, the ability to deliver medical advice, management, and therapy tailored to an individual's genetic blueprint. Advances in genetic diagnostic capabilities have been rapid, to the point where the genome can be sequenced for several thousand dollars. Crucially, it has facilitated the identification of targets for "precision" treatments to combat genetic diseases at their source. This manuscript will review

the innovative, pathogenesis-based therapies that are revolutionizing management of skeletal dysplasias, giving patients and families new options and outcomes.

Key words: skeletal dysplasia, pharmacologic therapy, targeted treatment.

INTRODUCTION

The inherited disorders of the skeleton (skeletal dysplasias) are individually rare but collectively common conditions caused by abnormal development, growth and maintenance of the human skeleton [Krakow et al., 2010]. To date, medical and surgical management of these disorders has been symptomatic due to lack of pathogenesis-based treatments. Over the past three years, disruptive innovations in the form of targeted therapies have emerged that are dramatically changing the natural history of these conditions. This review will focus on the most promising of these therapies in clinical practice, and touch upon possible future therapeutic options for skeletal dysplasias.

Achondroplasia

Achondroplasia (OMIM 100800) is the most common form of human dwarfism, with an estimated prevalence of 4-6 per 100,000 [Ireland et al., 2014]. It is caused by a gain-of-function mutation in the fibroblast growth factor receptor 3 (*FGFR3*) gene resulting in abnormal endochondral ossification. Almost all individuals affected by achondroplasia harbor a c.1138G>A (p.G380R) or c.1138G>C (p.G380R) mutation in the transmembrane domain. FGFR3 consists of extracellular (ligand-binding), transmembrane and intracellular (kinase) components, linked intricately to the signaling pathways involving signal transducer and activator of transcription (STAT)

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and mitogen-activated protein kinase (MAPK) (Figure 1). Activation of FGFR3 has an inhibitory effect on the proliferation and terminal differentiation of growth plate chondrocytes, and synthesis of extracellular matrix [Hart et al., 2000; Choi et al., 2001; Murakami et al., 2004]. The negative regulatory role of FGFR3 is essential for physiological longitudinal bone growth by slowing the rate of cartilage template formation and turnover during the growth phase [Horton and Degnin, 2009; Ornitz, 2005].

Advancements in understanding the pathophysiology of achondroplasia have prompted efforts in treatment strategies targeting the FGFR3-mediated signaling pathway. Early pharmacologic therapies were based on the principles of successful oncology treatment, using kinase inhibitor and antibody blockade, modified to selectively target FGFR3 and its activation [Aviezer et al., 2003; Rauchenberger et al., 2003]. Although, these therapies were shown to have positive effects on bone growth *in vitro*, the results have not been replicated *in vivo*.

Second generation pharmacologic therapies appeared more promising with amelioration of the skeletal phenotype, at least in the murine models. They comprise of strategies that interfere with the binding of FGFR3 to its ligands and blockade of MAPK signaling pathway. P3 is a 12-amino acid peptide designed to target extracellular component of FGFR3 with high affinity. The binding of P3 to FGFR3 interferes with ligand binding, inhibiting receptor activation and subsequent signallng pathways [Jin et al., 2012]. A decoy receptor in the form of soluble FGFR3 isoform competes with physiologic ligands to reduce FGFR3 signaling. The isoform lacks the trans-membrane component rendering it impotent in signal transmission [Garcia et al., 2013].

Meclozine is an antihistamine commonly used as antiemetic. It promotes longitudinal bone growth by a mechanism that is not fully delineated, but possibly by blocking downstream FGFR3 signaling pathway at the MEK-ERK level [Matsushita et al., 2013; Matsushita et al., 2015]. Statins have been shown to promote significant bone growth in one study involving three patients. Yamashita *et al.* [2014] used induced pluripotent stem cells derived from the fibroblast cells of patients with thanatophoric dysplasia type 1 (TD1) and achondroplasia to investigate the effect of statins as treatment. The authors proposed statin decreases the signaling life span of mutant FGFR3 receptors, therefore ameliorating the skeletal phenotype of these conditions [Yamashita et al., 2014].

C-natriuretic peptide (CNP) and its receptor, natriuretic peptide receptor-B (NPR-B) play major regulatory roles in endochondral ossification and longitudinal bone growth [Yasoda et al., 1998; Miyazawa et al., 2002]. Both molecules are expressed in the proliferative and terminal differentiation zones of the growth plates [Yasoda et al., 1998]. Interaction between CNP and NPR-B causes accumulation of intracellular cGMP, resulting in increased downstream NPR-B signaling, which intersects with the FGFR3 downstream signaling at the RAF level within the MAPK pathway (Figure 1). CNP/NPR-B activation downregulates the inhibitory effects of FGFR3 signal [Miyazawa et al., 2002; Krejci et al., 2005]. The delicate regulation between the FGFR3 and CNP systems are essential for endochondral ossification and longitudinal bone growth.

NPR-B has been implicated in the pathogenesis of rare phenotypes involving longitudinal bone growth or height, exemplified by conditions such as acromesomelic dysplasia, Maroteaux type (OMIM 602875) and NPR-B-associated

short stature, caused by homozygous or compound heterozygous and heterozygous inactivating mutations in NPR-B, respectively. [Bartels et al., 2004; Vasques et al., 2013; Amano et al., 2014] NPR-B gain-of-function mutations have been associated with bone overgrowth and tall stature [Miura et al., 2012; Hannema et al., 2014; Miura et al., 2014].

The discovery and understanding of physiological functions of CNP and NPR-B in promoting longitudinal bone growth have opened avenues for a targeted therapeutic strategy in achondroplasia. Researchers have demonstrated that CNP knockout mice developed severe growth deficiency, with restoration of normal growth when these mice were crossed with transgenic mice overexpressing CNP in cartilage [Suda et al., 1998; Chusho et al., 2001]. The skeletal phenotype was ameliorated when mice with achondroplasia were crossed with CNP overexpressing transgenic mice [Yasoda et al., 2004; Naski et al., 1998]. These findings formed the basis for human clinical studies.

The CNP analogue, named *vosoritide* by the World Health Organization has an extended half-life attributed to its resistance to neutral endopeptidase. Vosoritide administered subcutaneously once daily was shown to stimulate bone growth in murine models [Suda et al., 1998; Wendt et al., 2015]. Vosoritide is the only targeted pharmacologic therapy for achondroplasia that has proceeded to human clinical trial. The results from the Phase 1 trial showed that vosoritide is generally well tolerated with no dose-limiting, clinically significant toxicities in healthy adult males. The phase 2 trial was an open-label, sequential cohort dose-escalation study involving children aged 5-14 years with a molecularly confirmed diagnosis of achondroplasia. Patients were randomized for one of three doses (2.5,

7.5 or 15 microgram/kilogram) of vosoritide, given as daily subcutaneous injection for 6 months (see ClinicalTrials.gov). Data from these studies showed favorable safety profile and efficacy at higher dosage, with a 50% increase in growth velocity over individual baseline in the 15mcg/kg cohort. The trial has now proceeded to an 18-month extension study. All participating patients have been switched to 15mcg/kg dose for duration of 18 months.

Klag and Horten [2015] discussed the challenges faced in the development of targeted therapies for achondroplasia, in particularly the delivery of potential therapeutic agents to the avascular growth plates. The advancement of gene therapy in other condition such as osteoarthritis may shed light in overcoming such obstacles.

Osteogenesis imperfecta

Osteogenesis imperfecta (OI) is associated with bone fragility and fractures. The prevalence of OI is approximately 5-10 in 100,000 [Monti et al., 2010]. The phenotype commonly associated with OI includes osteoporosis with increased tendency for fractures, skeletal deformity, scoliosis, and joint laxity. Extra-skeletal features encompass hearing impairment, abnormal dentition, sclera discoloration, hypercalciuria, aortic root dilatation and neurologic manifestations, including hydrocephalus and basilar invagination [Harrington et al., 2014; Shaker et al., 2015]. Most features of OI can have variable severity, ranging from adult-onset aches, pains and fractures to early perinatal lethality. Common medical complaints of affected individuals in mild to moderate OI are fractures and pain.

Ninety percent of OI cases are caused by heterozygous mutations in *COL1A1* and *COL1A2* [Lindahl et al., 2014]. These genes are important for the production of

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type 1 collagen, which is the most abundant type of connective tissue that constitutes the bone and skin. Mutations impair the gene function resulting in a qualitative and quantitative reduction in type 1 collagen [Shaker et al., 2015; Lindahl et al., 2014]. The remaining proportions of OI are inherited in an autosomal recessive manner, and PLS3 (plastin 3) has been implicated in X-linked osteoporosis [van Djik et al., 2013; Laine et al., 2015].

Rarer molecular causes for OI have emerged, involving genes that code for modification enzymes, chaperone proteins and signaling proteins essential for production of type 1 collagen. [Shaker et al., 2015] The discovery of additional OI-associated genes provides explanation for the wide phenotypic spectrum of this entity. Management of OI involves a multidisciplinary approach including rehabilitation, surgical and pharmacologic intervention, aiming to maximize mobility and daily competencies, and decrease bone fragility and pain [Harrington et al., 2015].

The most studied and widely used pharmacologic treatment for OI is bisphosphonate, a synthetic pyrophosphate analogue with long skeletal half-life that binds to hydroxyapatite crystals in mineralized bone. Bisphosphonates reduce the number of osteoclasts and antagonize osteoclastic activity resulting in diminished bone resorption [Reyes et al., 2016].

Bisphosphonates are used in the treatment of moderate to severe OI in children. The superiority of bisphosphonates in increasing bone mineral density (BMD) was consistently demonstrated in controlled and observational studies, with most gain in the first 3-4 years of treatment [Rauch et al., 2003]. Benefits of bisphosphonates documented in observational trials include decreased fractures and

bone pain, improved vertebral shape, strength and improved activities of daily living. [Glorieux et al., 1998; Land et al., 2006; Lowing et al., 2007]. These results were not consistently replicated in randomized controlled trials. Intravenous bisphosphonates were shown to reduce peripheral fracture rates, increase vertebral height and mineral density but showed no difference in decreasing pain when compared to no treatment [Letocha et al., 2005; Gatti et al., 2005]. Palomo *et al*. [2015] reviewed the outcome of long-term (10-year) intravenous bisphosphonates therapy, and concluded that this therapy was associated with higher Z-scores for BMD in the lumbar spine and improvement of vertebral shape. The long-bone fracture rates remain high and the majority of patients developed scoliosis.

Two studies on oral bisphosphonates as treatment for OI by Seikaly *et al*. [2005] and Bishop *et al*. [2013] demonstrated reduction in fractures and bone pain, respectively. Meta-analysis of bisphosphonates' role in preventing fractures in OI was inconclusive [Hald et al., 2015].

There is currently no consensus on the optimal bisphosphonate dosing and duration of treatment. The well-recognized side effects of bisphosphonates are atypical femur fractures, most likely secondary to impaired bone resorption, and osteonecrosis of the jaw. The latter side effect has not been observed in the pediatric group. Other potential extra-skeletal effects include gastrointestinal symptoms, atrial fibrillation and increased risk for esophageal tumor [Reyes et al., 2016]. Flu-like symptoms and transient hypocalcemia are common especially after the first dose [Munns et al., 2004], but may be reduced with antihistamine coverage.

Other pharmacologic therapies trialed in OI include anabolic agents that stimulate bone growth, such as growth hormone and teriparatide (PTH 1-34), a

recombinant parathyroid hormone. Growth hormone was shown in one study to increase BMD and growth velocity when use in conjunction with bisphosphonates [Antoniazzi et al., 2010]. Teriparatide was trialed in a study involving adults with OI and shown to increase BMD and vertebral strength but only in the mild form of OI [Orwoll et al., 2014].

Receptor activator of nuclear factor (NF-kappaβ) ligand (RANKL), its cellular receptor, receptor activator of NF-kappaβ (RANK), and the decoy receptor osteoprotegerin (OPG) constitute a cytokine system that is essential for bone resorption. RANKL produced by osteoblastic cells, plays a crucial role in osteoclast formation, fusion, activation, and survival [Hofbauer et al., 2001]. Denosumab is a monoclonal antibody that binds RANKL and disrupts bone resorption. Hoyer-Kunh *et al*. [2014] published results of the use of Denosumab in four pediatric patients with OI type IV, showing increased BMD with reduced fracture rate, normalization of vertebral shape and increased mobility. They also published data of Denosumab use on two patients with OI and known *COL1A1/COL1A2* mutations. Denosumab effectively increased BMD and has long lasting effect in promoting bone growth [Hoyer-Kunh et al., 2014].

Shaker *et al*. [2015] summarized future pharmacologic agents in the treatment of OI, including anti-sclerostin and anti-transforming growth factor-β (TGF-β) antibodies that disrupt the LRP5/WnT and TGF-β signaling pathways, respectively to increase bone formation and decrease bone resorption. These antibodies were shown to rescue the skeletal phenotype of *CRTAP*-related autosomal recessive OI in mice [Grafe et al., 2015; Grafe et al., 2014]. Gene therapy with allele silencing and cell-based therapy involving bone marrow and

mesenchymal cell transplantation have rapidly attracted attention in the research of OI treatment, and may prove useful future therapeutic options. (Table I)

Hypophosphatasia

Hypophosphatasia (HPP) is caused by a deficiency in tissue-nonspecific alkaline phosphatase (TNSALP) due to mutations in the *ALPL* gene. The condition is characterized by mineralization defects of the bones and teeth causing osteomalacia, increased risk of fracture, bone pain, and loss of dentition. Extra-skeletal manifestations involving the central nervous, respiratory and renal systems are common in the severe form of this widely variable condition [Mornet, 2007]. HPP is clinically heterogeneous and classified according to the age of onset and phenotypic severity [Mornet, 2007; Whyte, 2010]. In general, the childhood and adult forms have a milder phenotype that may present with only premature loss of dentition (odontohypophosphatasia). The infantile and perinatal forms (OMIM 241500) are at the severe end of the spectrum. Affected individuals rarely survive beyond infancy without intervention, mainly secondary to respiratory failure and seizures [Whyte, 2010; Nakamura-Utsunomiya et al., 2010]. The estimated prevalence of severe HPP is 0.3-1 in 100,000 [Fraser, 1957; Mornet et al., 2011.

The TNSALP protein converts inorganic pyrophosphate (PPi) to phosphate (Pi) by hydrolysis. Pi is essential for hydroxyapatite formation, whereas PPi inhibits the process. The lack of TNSALP leads to accumulation of PPi and antagonization of the bone mineralization process [Harmey et al., 2004; Orimo, 2010] (Figure 2). Enzyme replacement therapy using exogenous TNSALP was effective in rescuing the life-threatening skeletal and functional phenotype in mice with severe HPP [Waymire et al., 1995; Narisawa et al, 1997]. These findings led to clinical trials in treating severe

forms of HPP in human using recombinant TNSALP, now known as asfotase alfa.

Whyte *et al*. [2012], in a clinical trial involving 10 patients with life-threatening HPP published the promising primary results of asfotase alfa. The therapy effectively improved bone mineral density, fracture healing and radiological features, increased membranous bone formation and decreased deformities. Improved pulmonary function, growth and reduction in plasma PPi and pyridoxal 5' phosphate were also reported. The agent was well tolerated with no significant drug-related adverse events. Three-year follow-up showed a survival rate of 90% [Whyte et al., 2014], a life-changing improvement. These results were supported by other similar clinical trials by Madson *et al*. [2014] and Rockmann-Greenberg *et al*. [2014] in terms of clinical safety and effectiveness. Reports of similar clinical trials in adolescent and adult cohorts are scarce. Kishnani *et al*. [2012] reported asfotase alfa decreased TNSALP substrate accumulation and improved functional outcome in one adult cohort. Efforts to ensure targeted delivery of therapy agents to the skeletal system have been attempted with promising results both in mice and human clinical trials. [Whyte et al., 2012; Nishioka et al., 2006; Millán et al., 2008]. These approaches optimize drug deliverance to targeted tissue and minimize the potential side effects of therapy. Asfotase alfa (STRINSIQ^{TM}) is now an FDA-approved drug, and commercially available treatment option for HPP.

On a research level, gene therapy in murine models of HPP involving trans-uterine, intraperitoneal injection of adeno-associated viral (AAV) expressing bone-targeted TNSALP appeared promising [Sugano et al., 2012]. These authors documented that HPP murine fetuses that mimic the severe infantile phenotype were rescued by fetal gene therapy from early gestation, evident postnatally by

normal bone mineralization, good weight gain and seizure-free survival until age 8 weeks. The authors proposed gene therapy as potential *in utero* therapy following antenatal diagnosis.

Other emerging skeletal dysplasia therapies

Fibrodysplasia ossificans progressiva (FOP) (OMIM 135100) and Morquio syndrome (Mucopolysaccharidosis type IVa) (OMIM 253000) are debilitating and potentially life-threatening skeletal dysplasias with unmet needs in terms of targeted therapies. The prevalence of FOP and Morquio syndrome is 1 in 1,000,000 and 0.2-0.6 in 100,000, respectively [Pignolo et al., 2011; Leadley et al., 2014]. The genetic and disease mechanisms of these conditions are well researched and documented. [Pignolo et al., 2011; Shore et al., 2006; Tomatsu et al., 2014]. Most pharmacologic therapies for FOP and Morquio syndrome aim at preventing the progression of disease and associated complications.

Corticosteroids and retinoic acid were tested in patients with FOP in the late 1990s. The effectiveness of these agents in inhibiting heterotopic ossification was inconclusive from the studies [Brantus and Meunier, 1998; Chakkalakal et al., 2016]. The use of palovarotene, a retinoic acid receptor gamma (RARY) agonist effectively inhibited spontaneous and injury-induced ectopic chondrogenesis and osteogenesis in murine models, as well as restoring and maintaining bone growth and musculoskeletal functions [Chakkalakal et al., 2016]. A clinical trial using palovarotene is now in Phase 2 studies. Sinha *et al.* [2016] documented that corticosteroids and palovarotene act on distinct pathways, and share several common steps and phases in inhibiting chondrogenesis and osteogenesis with no significant interference between the agents. These authors have proposed the

potential benefits of combined therapy.

Tomatsu *et al*. [2014] reviewed treatments available for Morquio syndrome, and most only partially improve the clinically phenotype. In particular, the skeletal phenotype is irreversible. Elosulfase alfa (VIMIZIM®) is a recombinant human N-acetylgalactosamine-6-sulfate sulfatase (GALNS), an FDA-approved drug available for treatment of Morquio syndrome. A 24-week, randomized, double-blind, placebo-controlled phase 3 trial demonstrated that elosulfase alfa was clinically well tolerated and safe, with statistically significant improvement in a primary efficacy measurement of endurance (distance of 6-minute walk) and reduction in urinary keratan sulphate, the main contributory factor to the pathogenesis of disease manifestations. Elosulfase alfa also reported to improve respiratory function, growth in height and activities of daily living [Hendriksz et al., 2014; Hendriksz et al., 2015].

The potential of cell-based therapy

Successful intervention with bone marrow transplantation in cases of severe infantile HPP has been reported in two patients; both developed sustained bone mineralization and clinical improvement [Whyte et al., 2003; Cahill et al., 2007]. Three other infants with severe HPP have been treated with bone marrow and mesenchymal stem cell transplantation [Tadokoro et al., 2009; Taketani et al., 2014]. The interventions yielded promising results with sustained improvement on skeletal phenotype and functional outcome at the time of reporting. Such methods are not without side effects, evident by development of Philadelphia-positive acute lymphoblastic leukemia in one of the infants, presumably attributed to the pre-transplant immunosuppressive therapy [Taketani et al., 2013]. The infant was reported to have achieved complete histological and molecular remission following a

second transplantation.

The mortality rate of malignant infantile osteopetrosis (OMIM 259700) is approximately 70% by 6 years of age in untreated patients [Orchard et al., 2015]. Hematopoietic stem cell transplant (HSCT) offers a cure to malignant infantile osteopetrosis, and is most effective when performed early. The most common cause of death in the first year post-transplant is graft failure, and pre-transplant conditioning carries a high risk of adverse outcomes [Orchard et al., 2015]. Natsheh *et al*. [2016] reported that fludarabine-based pre-transplant conditioning improved morbidity and mortality related to HSCT. The long-term (10-year) survival rate was higher among the HLA-matched sibling compared to alternative donor transplants (62% vs. 39%) [Orchard et al., 2015. An HLA-matched sibling donor HSCT is the standard of care, but not feasible for the majority of patients. Disease-specific pharmacologic therapy is not yet available for malignant infantile osteopetrosis, although early clinical trials of interferon gamma are planned (ClinicalTrials.gov Identifier: NCT02666768).

The new era of genomic technology and understanding has brought with it the tantalizing possibility of treatment for genetic diseases. Skeletal dysplasias serve as a model for this brave new paradigm with several treatments already in clinical use, and many others working their way through the clinical trial pipeline. These pathogenesis-based therapies promise to be disease modifying and, in some cases, life changing for individuals affected by these conditions and provides families with new options and hope. The challenges for the future will be to determine the optimal therapy, timing, and dosage for each patient and condition (individualized medicine). In addition, as these therapies modify the native phenotypes and natural

history of skeletal dysplasias, new management challenges will need to be identified, tools developed to measure quantitative and qualitative improvements in function and quality of life, and updated counseling provided to patients and their families.

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Table I. Summary of drug therapies in osteogenesis imperfecta.

Drug therapy	**Mode of action**	**Effects**
1. Bisphosphonates	• Reduce number of osteoclasts	• Reduce bone resorption

	• Antagonism of osteoclast activities	
2. Anabolic agents (e.g. Growth hormone and teriparatide)	• Stimulate bone formation	• Increase BMD and strength
3. Denosumab	• Monoclonal antibodies that bind RANKL and disrupt osteoclast formation, activation and survival	• Decrease bone resorption
4. Anti-sclerostin antibody	• Inhibition of LRP5/WnT signaling pathway	• Increase bone formation
5. Anti-TGF-β antibody	• Inhibition of TGF-β signaling pathway	• Decrease bone resorption
6. Gene silencing	• Allele-specific gene silencing by inhibitory RNA directed towards dominant negative mutations	• Reduce defective protein/collagen

Key: BMD, bone mineral density; RANKL, Receptor activator of nuclear factor (NF-kappaβ) ligand; LRP5/WnT, low density lipoprotein receptor-related protein/ wingless-type MMTV (mouse mammary tumor virus) integration site; TGF-β, transforming growth factor-β.

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Figure 1. Targets for pharmacological intervention in the treatment for achondroplasia. A. P3 blocking peptide and decoy receptor; B. The CNP-mediated antagonism of downstream FGFR3 signaling; C. Downstream signal interruption of mutant FGFR3 (e.g., meclozine, statin). Diagram is modified from Klag and Horton [2015].

Key: FGF, fibroblast growth factor; FGFR3, fibroblast growth factor receptor 3; CNP, C-natriuretic peptide; NPR-B, natriuretic peptide receptor-B; STAT, signal transducer and activator of transcription; MAPK, mitogen-activated protein kinase.

Figure 2. Bone mineralization commences with intracellular hydroxyapatite formation within matrix vesicles. Hydroxyapatite crystals then bud from the surface of the matrix vesicle and propagate into extracellular matrix where they are elongated and finally deposited between collagen fibrils. The PPi/Pi balance is essential in bone mineralization. Tissue-nonspecific alkaline phosphatase (TNSALP) functions as ecto-enzyme that converts extracellular PPi to Pi. *ALPL* mutations in severe hypophosphatasia result in production of mutant TNSALP proteins that fail to migrate to the surface of cellular membrane. The lack of Pi and accumulation of PPi cause decreased and further inhibit bone mineralization. Asfotase alfa restores bone mineralization. Diagram adapted from Orimo H [2010].

Key: HA, hydroxyapatite; PPi, inorganic pyrophosphate; Pi, inorganic phosphate; ATP, adenosine triphosphate; TNSALP, tissue non-specific alkaline phosphatase; NPP1, ectonucleotide pyrophosphatase phosphodiesterase 1; ANKH, ankylosis protein.

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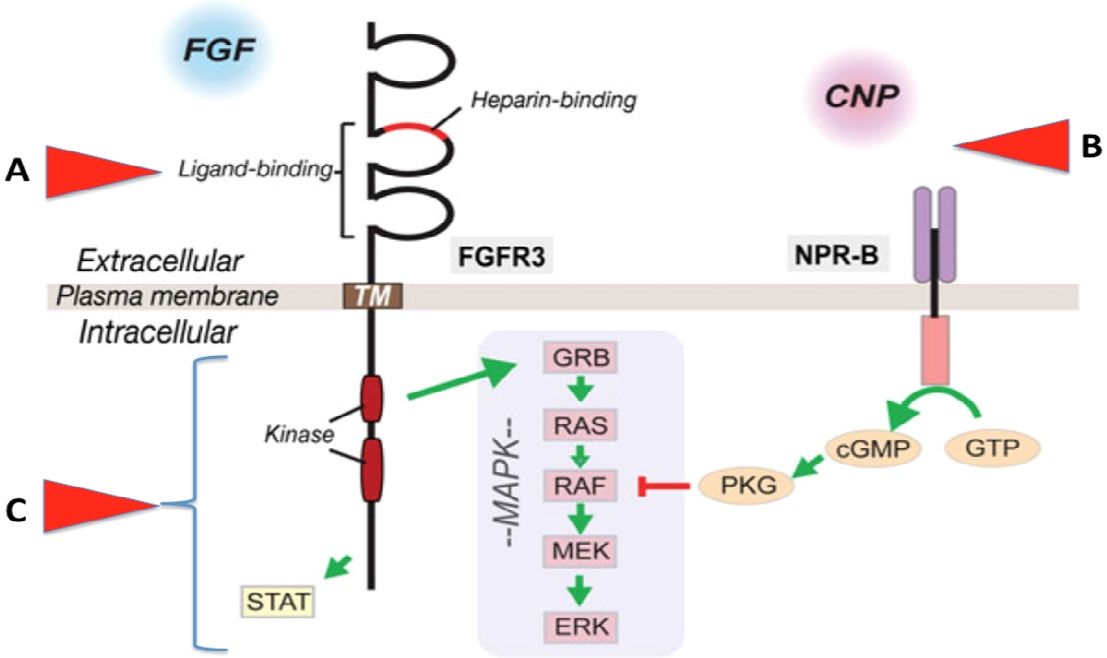

Figure 1 AJMG .

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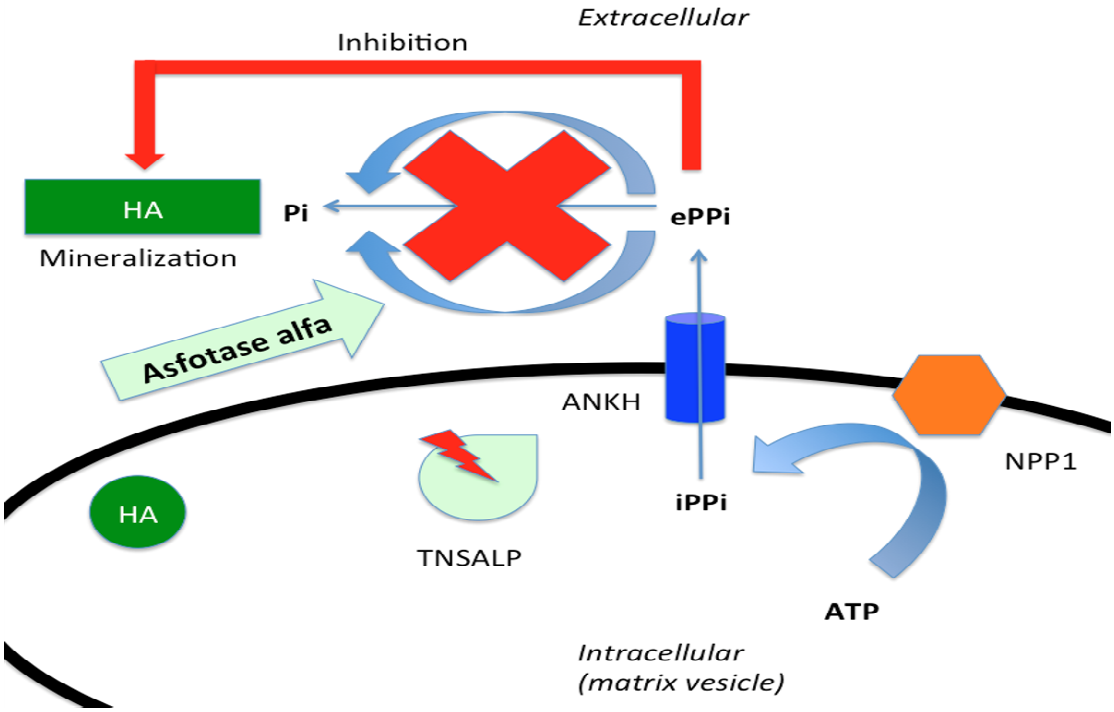

Figure 2 AJMG .

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