

New Leads for Personalized Medicine in Pediatrics: Targeting Syk for Treatment of Serious Pediatric Illnesses

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Spleen tyrosine kinase (SYK), a key regulator of signal transduction pathways in lymphohematopoietic cells and mast cells has emerged as a potential molecular target for treatment of serious pediatric illnesses, including acute lymphoblastic leukemia, the most common form of childhood cancer [1], acute myeloid leukemia [2], autoimmune diseases [3-5], inflammatory disorders [4,5], allergic disorders and asthma [5,6], and graft versus host disease after hematopoietic stem cell transplantation [7]. Notably, a meta-analysis using the Oncomine database revealed a marked enrichment of the most discriminating SYK-dependent anti-apoptotic genes in 18 diagnostic classes of leukemias and lymphomas [1]. More recent studies revealed overexpression of SYK in retinoblastoma [8].

Several structurally distinct and highly potent small molecule inhibitors of SYK tyrosine kinase ATP binding site have been developed [9-13]. A pentapeptide mimic targeting the substrate binding P-site of SYK tyrosine kinase has been shown to act as a potent inducer of apoptosis in chemotherapy-resistant SYK-expressing primary leukemic B-cell precursors taken directly from relapsed pediatric ALL patients, exhibit favorable pharmacokinetics in mice and non-human primates, and eradicate *in vivo* clonogenic leukemia cells in SCID mouse xenograft models of chemotherapy-resistant human ALL at dose levels non-toxic to mice and non-human primates [10]. In addition to small molecule tyrosine kinase inhibitors, antisense oligonucleotides and small interfering RNAs (siRNAs) have also been developed to knock down SYK expression [14, 15].

The efficient delivery of the various SYK inhibitors by leveraging nanotechnology holds particular promise. Liposomal nanoparticle therapeutics containing active anti-cancer agents may provide the foundation for potentially more effective and less toxic anti-cancer treatment strategies due to their improved pharmacokinetics, reduced systemic toxicity, and increased intra-tumoral/intra-cellular delivery [16-18]. Nanoparticles have been coated with polyethylene glycol (PEG) (i.e. PEGylated) in an attempt to render them resistant against protein adsorption, enhance their biocompatibility, and to stabilize them against agglomeration in biological environments. PEGylated nanoparticles with diameters around 100-nm may become long-circulating in the blood stream and have been called stealth particles since they can evade recognition by T-cells and macrophages and avoid rapid clearance by the immune system [16-18]. Nanoparticles that are sterically stabilized by PEG polymers on their surface and have surface charges that are slightly negative or slightly positive have minimal self-self or self-non-self interactions and improved pharmacokinetics. PEGylation of nanoparticles creates a hydrophilic surface and leads to increased protein solubility, reduced immunogenicity, prolonged plasma half life due to prevention of rapid renal clearance, and reduced clearance by the RES system due to decreased macrophage capture and opsonization [16-18]. The rationally engineered nanoparticle constructs of SYK inhibitors are likely to be less toxic and more effective than free molecules.

Nanoparticles can be functionalized with a tumor targeting moiety such as a ligand or scFv directed against a surface receptor on cancer cells in order to achieve optimal tumor targeting and site-specific drug delivery to further reduce their toxicity and improve their efficacy [16-18]. When linked with tumor targeting moieties nanoparticles can reach cancer cells carrying the target receptors with high affinity and precision. The targeting ligands enable nanoparticles to bind to cell surface receptors and enter cells by receptor-mediated endocytosis. In our own program, efforts are underway to prepare nanoparticles targeted against the CD19 antigen on childhood leukemia cells. Further development of rationally designed SYK inhibitors and their nanoscale formulations may provide the foundation for therapeutic innovation against a broad spectrum of serious pediatric diseases.

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