

## Stat3-Syk Molecular Complex as A Target for Anti-Cancer Nanomedicines

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Spleen Tyrosine Kinase (SYK) can activate the oncogenic transcription factor "The Signal Transducer and Activator of Transcription 3" (STAT3) to induce expression of STAT3 target genes that protect cancer cells against chemotherapy and ionizing radiation [1]. A meta-analysis using the OncoPrint database revealed a marked enrichment of the most discriminating SYK-dependent anti-apoptotic genes in human leukemias and lymphomas [2]. In patients that showed upregulation of SYK, the majority of comparisons also showed significant upregulation of the STAT3 target genes. SYK has also been shown to regulate the activation of the mammalian target of rapamycin (mTOR), an evolutionarily conserved serine/threonine kinase that is controlled by the SYK-regulated PI3-K/AKT and MAPK/ERK pathways [2,3]. Notably, the anti-apoptotic NFκB is also regulated by SYK [2]. Thus, STAT3-SYK molecular complex is a master regulator of apoptosis and neoplastic expansion in leukemias and lymphomas [2]. Therefore, rationally designed inhibitors of this molecular target may provide the foundation for therapeutic innovation against leukemias and lymphomas. Several structurally distinct and highly potent small molecule inhibitors of SYK tyrosine kinase ATP binding site have been developed [4-7]. In addition to small molecule tyrosine kinase inhibitors, antisense oligonucleotides and small interfering RNAs (siRNAs) have also been developed to knock down SYK expression [8,9].

We recently discovered the pentapeptide mimic 1,4-Bis (9-O dihydroquinidiny) phthalazine / hydroquinidine 1,4-phthalazinediyl diether (C-61) as a tyrosine kinase inhibitor targeting the substrate binding P-site of SYK and as a novel drug candidate against B-lineage leukemias and lymphomas [1,4,5]. C-61 inhibits SYK in both cell-free and cellular kinase assays at nanomolar concentrations, acts as a potent inducer of apoptosis in chemotherapy-resistant primary leukemic B-cell precursors taken directly from relapsed B-lineage ALL patients, exhibits favorable pharmacokinetics in mice and non-human primates, and eradicates leukemia-initiating cells in SCID mouse xenograft models of chemotherapy-resistant human B-lineage ALL at dose levels non-toxic to mice and non-human primates [1,4,5]. Further development of C-61 may provide the foundation for therapeutic innovation against chemotherapy-resistant leukemias and lymphomas. C-61 prevented radiation-induced activation of SYK and markedly augmented radiation-induced apoptosis of leukemia/lymphoma cells and enhanced the anti-leukemic potency of total body irradiation (TBI) in the context of hematopoietic stem cell transplantation (SCT) [5]. Based on this preclinical proof-of-principle study, we hypothesize that the incorporation of C-61 into the pre-transplant TBI regimens of patients with recurrent or high risk leukemias/lymphomas will help overcome the radiochemotherapy resistance of their cancer cells and thereby improve their treatment response and survival outcome after hematopoietic SCT.

The efficient delivery of the various SYK inhibitors by leveraging nanotechnology holds particular promise. Liposomal nanoparticle therapeutics containing active anti-cancer agents, including target-specific small molecules and siRNA, 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 [10-14]. Nanoparticles have been coated with Polyethylene Glycol (PEG) 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 [10-14]. 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 [10-14]. 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 (Single chain variable fragment) 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 [10-14]. 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. Likewise, we are preparing nanoparticles functionalized with recombinant human Insulin-Like Growth Factor 1 (IGF1) to target surface IGF1 receptors on solid tumor cells. Rationally engineered nanoparticle therapeutics containing C-61 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 [5]. We hypothesize that the nanotechnology-enabled delivery of C-61 [14] will be associated with reduced toxicity enhanced potency compared to the free drug delivery with the salt-formulation used in our recent preclinical studies. Further development of rationally

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designed SYK inhibitors and their nanoscale formulations may provide the foundation for therapeutic innovation against a broad spectrum of cancers, especially leukemias and lymphomas.

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