Innovative Exploratory Clinical Approaches for Relapsed and/or Refractory Metastatic Ewing’s Sarcoma

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Abstract

Relapsed and/or refractory Ewing’s Sarcoma is a devastating pediatric disease with rapid progression and oftentimes severe side effects related to generally ineffective high dose multi-agent chemotherapy. Eighty five percent of diagnosed Ewing’s Sarcoma is characterized by EWS/FLI1 fusion gene expression that provides a unique opportunity for targeted therapeutics development. The EWS/FLI1 gene is a “driver gene” with transformative potential and integral to Ewing’s cancer progression. Although encoding a transcription factor, which is pharmacologically “undruggable”, it connects with potentially targetable molecular signals and, in addition, as a fusion gene along with accompanying tumor specific mutations provides unique neoantigens some of which process into immunogenic epitope. Very few cutting edge advances for the management and control of Ewing’s Sarcoma have been made in the last 20 years due, in part, to low incidence (one case per million people), a narrow therapeutic window, and a limited availability of tissue suitable for biomarker studies. However, recent advances in DNA/RNA manipulation [CRISPR and RNA interference (siRNA)] as well as in molecular and immune technologies have transformed both the understanding of signaling pathways and molecular mechanisms of actions and, consequently, the approach to target identification. We review the innovative exploratory approaches to five unique therapies (a EWS-FLI1 co-activator, the EWS-FLI1 fusion gene itself, a signaling receptor, a DNA damage repair component, and the antigenic matrix) currently undergoing clinical assessment in Ewing’s Sarcoma for which preliminary preclinical and clinical results suggest therapeutic benefit.

Background

Ewing’s Family Sarcoma is a highly aggressive and malignant bone tumor that metastasizes frequently. The median age of diagnosis is 14-15 years [1,2] and the incidence rate is 1 case per million people in the United States but as high as 9-10 cases per million in the 10 to 19 year old age range [3].

Eighty five percent of Ewing’s Sarcoma patients show a balanced translocation of the EWS gene at chromosome 22q12 with the FLI1 gene at chromosome 11q24 [4]. The EWS-FLI1 translocation can occur at one of several different gene fusion breakpoint sites. Most frequently seen are Type 1 (accounting for 60%) and Type 2 (25%). In Type 1 EWS-FLI1, exons 1-7 of EWS are fused with exons 6-9 of the FLI1 gene [5]. Some of the early clinical studies suggested a relationship of fusion type to rapid progression of disease [6,7] that more recent studies have not confirmed [8]. The Type 2fusion comprised of EWS exons 1-7 juxtaposed to exons 5-9 of FLI1 [9], is associated with a higher Ewing’s Sarcoma proliferation rate that may or may not have clinical significance. Ten to 15 percent of patients with Ewing’s Sarcoma show other translocations; the EWS-ERG gene fusion (t(22;21) (q22;q12)) [10-12], and the less frequent EWS-ETS fusion group (EWS-ETV1 t(7;22), EWS-ETV4 t(17;22), EWS-FEV t(2;22)) [13-16]. Methodologies used to categorize the EWS-FLI1 translocations include real-time polymerase chain reaction (RT-PCR), fluorescence in situ hybridization (FISH), and next generation sequencing (NGS) [17,18].

At diagnosis, less than 25% of patients present with metastatic disease, however up to 90% of Ewing’s adolescents eventually experience either disease progression or relapse after frontline treatment [3,19]. The most important prognostic factor for survival following failure of first-line
YK-4-279 reverses the inhibitory effect of EWS-FLI1 on RHA.

EWS-FLI1 binds to RHA in a unique region not targeted by other transcriptional proteins and affects helicase activity, while (R)-YK-4-279 does not restore RHA activity (Erkizan, Kong et al. 2009). The molecule also demonstrates activity in other tumors with ETS family translocations such as ETV1 fusion-positive prostate cancer. The preclinical data demonstrates YK-4-279 inhibition of tumor growth as well as decreased motility and invasion of prostate cancer xenografts [33]. While EWS/FLI1 Types 1 and 2 are the two most common translocations in Ewing’s Sarcoma and a further 10% of the patients with relapsed or refractory disease Ewing’s Sarcoma [20-22]. In a retrospective analysis of 195 advanced, ≥second-line treatment, metastatic Ewing’s Sarcoma patients 86% did not achieve second remission and of those (n=26) who did so, the majority either re-relapsed or died within the year [20]. There are no standard of care (SOC) NCI recommendations for second-line treatment with advanced Ewing’s Sarcoma, although multi-agent regimens including irinotecan, temozolomide, topotecan, and cyclophosphamide are commonly utilized today. In addition to relative ineffectiveness, the use of intensive chemotherapy in both frontline and second-line treatments of Ewing’s Sarcoma is associated with a severe toxicity and morbidity.

Given the limitation of cumulative toxicity associated with chemotherapy and the emergence of resistance, it is not surprising that third-line management is even more challenging. Single or combined chemotherapy regimens only show limited response (in both rate and durability). Some regimens include high dose ifosfamide or gemcitabine/docetaxel [23-25]. Unfortunately, to date there has been no significant survival advantage to any ≥third-line therapy for patients with relapsed or refractory, disease Ewing’s Sarcoma [26].

Bottom line: there is a need for both innovative treatment approaches and a greater array of therapeutic options in second- and third-line management of Ewing’s Sarcoma. In the following we focus on experimental therapies currently in clinical trial for ≥ third-line management of Ewing’s Sarcoma [20]. There are no standard of care (SOC) NCI recommendations for second-line treatment with advanced Ewing’s Sarcoma, although multi-agent regimens including irinotecan, temozolomide, topotecan, and cyclophosphamide are commonly utilized today. In addition to relative ineffectiveness, the use of intensive chemotherapy in both frontline and second-line treatments of Ewing’s Sarcoma is associated with a severe toxicity and morbidity.

YK-4-279 [27] is a small molecule that interacts with RNA Helicase A (RHA, encoded by the DHX9 gene) thereby affecting EWS/FLI1 signaling activity. The EWS/FLI1 fusion protein binds RHA in a unique region not targeted by other transcriptional proteins and thereby inhibits helicase activity in a dose dependent manner [28].

YK-4-279 binds to RHA adjacent to its helicase domain and to an as yet not completely specified region on the EWS/FLI1 fusion protein to dis inhibit helicase activity but without affecting ATPase activity. Erkizan and colleagues have shown that YK-4-279 may significantly shift the RNA binding profiles of both EWS/FLI1 and RHA. RHA is a transcriptional co-activator regulating both transcription and mRNA splicing and plays a role in both oncogenesis and tumor maintenance. Whatever the dominant mechanism, YK-4-279 results in inhibition of oncogenic activity and activation of caspase-3-induced apoptosis in vitro in a range of Ewing’s Sarcoma cell lines in vitro (TC32, A4573, TC71, and ES925 in Figure 1) and in vivo [29-31]. Preclinical data suggest a chimeric structure of the small molecule with (S) and (R)-enantiomers with a (S)-YK-4-279 enantiomer-specific effect in EWS/FLI1 cells [29,30], (Figure 1). Disruption of protein-protein interactions, such as the transcription complex in Ewing’s Sarcoma cells, comprising RNA polymerase II, CREB-binding protein (CBP), and RNA Helicase a (RHA) [32], thus seems to be a reasonable goal for therapeutic effectiveness. Interestingly, the same small molecule also demonstrates activity in other tumors with ETS family translocations such as ETV1 fusion-positive prostate cancer. The preclinical data demonstrates YK-4-279 inhibition of tumor growth as well as decreased motility and invasion of prostate cancer xenografts [33]. While EWS/FLI1 Types 1 and 2 are the two most common translocations in Ewing’s Sarcoma and a further 10% of the patients with relapsed or refractory disease Ewing’s Sarcoma [24].

Table 1: Treatment options for patients with advanced, refractory or recurrent Ewing’s Sarcoma. Comparison of objective response rate (ORR) and progression free survival (PFS).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism</th>
<th>No. of EWS Patients (n)</th>
<th>ORR</th>
<th>PFS</th>
<th>OS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gatinumab (AMG479)</td>
<td>IGFR-1 Inhibitor</td>
<td>22</td>
<td>6%</td>
<td>7.9 mo</td>
<td></td>
<td>(Tap, Demetri et al. 2012)</td>
</tr>
<tr>
<td>R1507</td>
<td>IGFR-1 Inhibitor</td>
<td>109</td>
<td>10%</td>
<td>-</td>
<td></td>
<td>(Pappo, Patel et al. 2011)</td>
</tr>
<tr>
<td>Figitumab (CP-751,871)</td>
<td>IGFR-1 Inhibitor</td>
<td>16</td>
<td>13%</td>
<td>-</td>
<td></td>
<td>(Olimos, Postel-Vinay et al. 2010)</td>
</tr>
<tr>
<td>Figitumab (CP-751,871)</td>
<td>IGFR-1 Inhibitor</td>
<td>106</td>
<td>14%</td>
<td>1.9 mo</td>
<td></td>
<td>(Juergens, Daw et al. 2011)</td>
</tr>
<tr>
<td>Linsinitib</td>
<td>IGFR-1 Inhibitor</td>
<td>ongoing</td>
<td>-</td>
<td>-</td>
<td>EUROSARC trial</td>
<td></td>
</tr>
<tr>
<td>Olaparib</td>
<td>PARP-Inhibitor</td>
<td>12</td>
<td>0%</td>
<td>1.5 mo</td>
<td></td>
<td>(Choy, Bulynski et al. 2014)</td>
</tr>
<tr>
<td>Niraparib/Temozolomide</td>
<td>PARP-Inhibitor/alkylating agent</td>
<td>ongoing</td>
<td>-</td>
<td>-</td>
<td>(Witcozen, Brooks et al. 2015)</td>
<td></td>
</tr>
<tr>
<td>Olaparib/Temozolomide</td>
<td>PARP-Inhibitor/alkylating agent</td>
<td>ongoing</td>
<td>-</td>
<td>-</td>
<td>(Engert, Schneider et al. 2015)</td>
<td></td>
</tr>
<tr>
<td>YK-4-279</td>
<td>EWS-FLI1 protein RHA-binding inhibitor</td>
<td>ongoing</td>
<td>-</td>
<td>-</td>
<td>(Erkizan, Kong et al. 2009)</td>
<td></td>
</tr>
<tr>
<td>pbi-shRNA EWS/FLI1 Lipoplex (LPX)</td>
<td>b-functional sh-RNA targeting EWS/FLI1 fusion protein</td>
<td>ongoing</td>
<td>-</td>
<td>-</td>
<td>(Rao, Jay et al. 2016)</td>
<td></td>
</tr>
<tr>
<td>Vigil</td>
<td>GMCSF/bi-shRNA DNA constructed autologous tumor vaccine</td>
<td>16</td>
<td>6%</td>
<td>-</td>
<td>24 mo</td>
<td>(Ghisoli, Barve et al. 2016)</td>
</tr>
</tbody>
</table>

Figure 1: YK-4-279 reverses the inhibitory effect of EWS/FLI1 on RHA in an enantiomer-specific manner. Immobilized fulllengthRHA on a CM5 chip and purified EWS-FLI1 were used in RHA assays. Figure shows recombinant RHA activity and ssRNA product in presence of either single recombinant RHA, or recombinant RHA/ recombinant EWS/FLI1/YK-4-279, or recombinant RHA/recombinant EWS-FLI1/S-YK-4-279, or recombinant RHA/recombinant EWS/FLI1/ R-YK-4-279. Results were plotted over time; x-axis represents time (sec) and y-axis is percent (product in helicase assay). Both racemetric YK-4-279 and (S)-YK-4-279 disinhibited the helicase reaction, showing restoration of 80% helicase activity, while (R)-YK-4-279 does not restore RHA activity (Erkizan, Schneider et al. 2015).
reveal a EWS/ERG gene fusion, there is a less frequent population that presents with EWS/ETS-like fusions [13]. A similarly modified small molecular inhibitor, TK216, is listed on clinicaltrials.gov as a Phase I trial opportunity in patients with advanced Ewing’s Sarcoma.

**Bi-sh (Bifunctional Short Hairpin) RNA EWS-FLI1 Type 1 Lipoplex (LPX)**

The dual stem-loop bi-shRNA EWS-FLI1 (Type 1) incorporated into the pUMVC3 plasmid construct transcribes both siRNA and miRNA-like effectors that target the identical junction region of the EWS-FLI1 fusion gene encoded mRNA [34-36]. The plasmid is systemically delivered in a DOTAP (cationic lipid dioleoyl trimethyl ammonium propane)/cholesterol delivery vehicle [37] as a lipoplex (LPX). This RNAI technology obviates the inherent difficulty of targeting the undruggable EWS-FLI1 protein and by targeting the Type 1 breakpoint to down regulates the expression of the EWS/FLI1 encoded mRNA and protein. Preclinical testing *in vitro* and *in vivo* demonstrated 85-92% type-specific knockdown of target protein [38]. Bi-shRNA simultaneously induces RISC (RNA induced silencing complex)-cleavage-dependent mRNA degradation and RISC-cleavage-independent degradation of same nucleotide sequence. Bi-sh RNA affects targeted protein down regulation at a 5-log lower dose in comparison to si-RNA targeting the same strand sequence [34]. Furthermore, the bi-sh RNA EWS/FLI1 Type 1 dual effect or target sequence-specific activity limits the potential for off-target effects against “non” Type 1 Ewing’s Sarcoma fusion constructs [38]. A significant tumor growth delay and survival advantage *in vivo* was demonstrated in human Type 1 EWS/FLI1 cells treated with the bi-sh RNA EWS/FLI1 Type 1 LPX (Figure 2). As hypothesized, the specificity of fusion gene encoded protein knockdown as compared with wild type FLI1 protein which was not knocked down was confirmed in HEK 293 cells that contained both the wild type EWS and wild type FLI1. Figure 3 shows the predicted specificity by comparing the response of SK-N-MC cells containing the EWS/FLI1 Type 1 fusion gene to the response of HEK-293 cells with wild types EWS and FLI1 genes. Importantly, GMP (good manufacturing practice) safety testing in large animals revealed excellent tolerability [38] at active human equivalent dose ranges. Clinical investigation has been initiated in refractory/relapsed Ewing’s Sarcoma patients with the Type 1 EWS/FLI1 gene fusion (ClinicalTrials.gov).

**IGF-1r Inhibitors**

The EWS/FLI1 translocation is associated with dysregulation of the insulin growth factor receptor (IGF-1R) pathway. An oncogenic role for co-activation of IGF–1R signaling has been suggested based on preclinical assessment [39]. In Ewing’s Sarcoma there is evidence for autocrine activation of the IGF-1R pathway as well as EWS-FLI1 induced over expression of the caveolin-1 membrane transport protein by way of which IGF-1R internalizes [40]. In addition, the fusion product represses IGFBP-3 that binds IGF-1 in the plasma thereby up regulating ligand-receptor induced signaling. Enhanced IGF-1R mediated activity can stream through two parallel pathways: 1) the PI3K/AKT pathway inhibiting apoptosis, increasing protein synthesis and promoting glucose metabolism and 2) the Ras/MAPK pathway promoting cancer cell proliferation [41]. Preclinical studies in cancer have demonstrated the relationship of the intrinsic tyrosine kinase activity of the IGF-1R with tumor proliferative and anti-apoptotic activity. Therefore, based on rationale and preclinical support, trials of therapeutic anti-tumor targeting of IGF-1R have been initiated [42-44]. In fact, IGF-1R inhibitor therapy has demonstrated benefit in...
A third MAb IGF-1R inhibitor figitumumab was tested in a 29 patient study (16 of whom had Ewing’s Sarcoma). Two patients (12.5%), both with Ewing’s Sarcoma, had partial responses and 37.5% (6/16) stable disease [47]. A Phase I/II study was subsequently conducted to investigate the safety and effectiveness of figitumumab in patients with Ewing’s Sarcoma [48]. However, only 1 of 31 patients achieved partial response (PR). Despite limited efficacy a Phase II study was performed involving 106 heavily pre-treated (≥1 – 4 prior lines of chemotherapy) patients with refractory or recurrent Ewing’s Sarcoma. Fourteen percent (15/106) of these patients achieved PR and 23% (25/106) stable disease (SD); the median progression free survival was 1.9 months, and median overall survival 8.9 months (95% CI, 7.2 to 11.1) [48]. Although treatment was generally well tolerated, three cases of leukemia were observed; one attributed to figitumumab (after one cycle in a patient previously treated with doxorubicin and etoposide), another to concurrent rapamycin, and a third to prior etoposide. Figitumumab associated leukemia has not been reported in studies of other cancer types with IGR-1R inhibitors. Even though therapy related myelodysplasia and acute myeloid leukemia are known adverse events in Ewing’s Sarcoma patients treated with chemotherapy, particularly in association with ifosfamide [51-53], the possibility of figitumumab associated leukemia cannot be entirely excluded.

These trials suggest mild to moderate clinical activity in Ewing’s Sarcoma and establish a reasonable safety profile. Few of the studies incorporated predictive biomarkers (e.g., increased expression of IRS2 (insulin receptor substrate), IR, growth hormone (GH) and decreased expression of IGF-binding protein-5) to help identify those patients with a higher likelihood of response. Based on pathway analysis, rationale based clinical trials involving IGF-1R inhibitors are being explored; the concurrent administration of IGF-1R and mTOR inhibitors to attenuate negative feedback inhibition and dual IGF-1R/ IR kinase inhibitors (e.g., Linsitinib) to block compensatory increased expression of IR [54], (ClinicalTrials.gov ID: NCT02546544).

PARP Inhibitors

Poly-ADP-ribose-polymerases (PARP1 and PARP2) are comprised of enzymes that transfer ADP-ribose onto target proteins (PARylation), thereby modifying a wide range of cellular processes including genome maintenance, transcriptional regulation, cell cycle control, proliferation, differentiation, necrosis and apoptosis [55,56]. PARP1, activated by DNA damage, binds to DNA single-strand breaks (SSB) and double strand breaks (DSB), then catalyzes and promotes multiple DNA repair processes [56]. Patients with cancer related mutations in BRCA1 or BRCA2, suppressor proteins involved in DSB repair, demonstrate enhanced sensitivity to PARP1-inhibitors with a consequent increase in apoptosis [57]. The anti-tumor activity of PARP-inhibitors has been confirmed in BRCA-mutant breast, ovary and prostate cancers [58-60]. Garnett et al. [61] was able to show Ewing’s Sarcoma cell line sensitivity to PARP1-inhibitors by way of decreased viability of EWS/FLI1 cancer cells (Figure 4). Brenner and colleagues [62] hypothesized a reciprocal positive feedback loop in Ewing’s Sarcoma cell line to PARP1 expression, the latter then facilitating EWS/FLI1 transcriptional activation. In addition, 7% of Ewing’s Sarcoma patients have been shown to have BRCA2 mutations [63].

Choy et al. [64] conducted a two-part Phase II clinical trial of olaparib enrolling 12 patients with advanced Ewing’s Sarcoma progressing following chemotherapy. None of the patients had an objective response (RECIST 1.1 criteria PR/CR). Four of the 12 patient’s sustained SD for 10.9 to 17.9 weeks. Median time to progression was 5.7 weeks [64]. Based on the results of Part 1,
enrollment to Part 2 was put on hold. However, reanalysis and future assessment of PARP1 inhibitor effectiveness as well as protocol design need to take into account the mechanistic differences between two recently described classes of PARP1 inhibitors: 1) those that effect catalytic inhibition of PARP enzyme activity and 2) those that result in formation of PARP-traps that function as cytotoxic PARP-DNA complexes [65]. On the basis of catalytic inhibitory activity, the effectiveness of the three clinical PARP inhibitors ranks as follows: olaparib>veliparib>niraparib. Based on active cytotoxic PARP-DNA formation the ranking is niraparib>olaparib>veliparib.

Drug-sensitivity testing of PARP inhibition in combination with various S-phases DNA damaging agents in Ewing’s Sarcoma cell lines [66] showed enhanced activity with the combination of olaparib and temozolomide. Engert et al. [67] demonstrated that combined olaparib and temozolomide up-regulated the pro-apoptotic proteins BAX and BAK and caspase activation. Synergistic activity was also demonstrated with the combination of niraparib and temozolomide [68]. These results are presumably due to interaction with the normally sublethal effects of temozolomide induced lesions insofar as Ewing’s Sarcoma cell lines are MGMT (O-6-methylguanine-DNA methyltransferase) expressers and relatively resistant to the single chemotherapeutic agent [66,69] (Figure 5). Clinical trials are ongoing in advanced Ewing’s Sarcoma for safety and efficacy.

**Vigil®**

Vigil vaccine is a DNA engineered autologous whole tumor cell immunotherapy which activates the afferent arm of the immune response arc by i) using autologous tumor cells as a source of the full matrix of tumor antigens, ii) recruiting, enhancing function and stimulating maturation of antigen-presenting cell (APC) populations via DNA encoded GMCSF expression and iii) dampening the escape of immune tolerance via knockdown of immunosuppressive TGFβ isoforms.

Vigil contains a plasmid comprised of both a DNA segment encoding for GMCSF protein expression and a bi-functional shRNA-Furin DNA segment encoding for knockdown of Furin protein expression(a proprotein convertase which activates TGFβ1 and 2 isoforms) and consequent knockdown of both TGFβ1 and 2 (Figure 6).

In established cancers, TGFβ is an immune-suppressive cytokine, released by T-regulatory cells and cancer cells. Interestingly, it has paradoxical and context-dependent effects functioning as a tumor suppressor early in tumorigenesis and as an immune suppressive protein in the immune escape process and in established malignancies. In the latter context, TGFβ promotes cancer progression and proliferation, enhances activation of T-regulatory cells that contribute to apoptosis in APCs, and significantly decreases IFN-γ, granzymes A and B, and perforin release by cytotoxic T-cells [70]. By blocking these pathways, TGFβ suppresses the immune response and promotes immune-tolerance in cancer cells [71-74]. The immunogenic activity of plasmid-encoded, cell-secreted GMCSF has been extensively studied in a variety of GVAX trials and [gene-modified] oncolytic viral products [38,75-79].
The effective functionality of the Vigil encoded vectors is confirmed by product release criteria which require ≥30pg of GMCSF secreted protein/10^6 cells and TGFβ1,2 knockdown of ≥30% [78,80]. A long-term update of survival status of all Phase I treated patients [81] revealed a cohort of advanced Ewing’s Sarcoma patients, predominantly third-line or greater, with suggestive evidence of survival benefit; i.e., >75% survival at 1 year compared to less than 25% survival based on historical experience. Longer term follow up of these patients also confirmed product safety with no evidence of Vigil related Grade ≥3 toxic effect.

More recently [82], a long term follow up of an expanded subset of advanced, late stage metastatic Ewing’s Sarcoma patients treated with Vigil (n=16) was performed. The results of treatment in these patients were compared to the outcome of a non-randomized, concurrently treated group of Ewing’s Sarcoma patients who underwent similar surgical procedures to harvest tissue for vaccine construction but who did not receive Vigil (n=14) for a variety of personal and/or physician determined reasons [82]. The median OS of Vigil treated patients (n=16) was 24 months vs. 6.8 months (Kaplan-Meier) in the control-group (no-Vigil treatment); a 17.2 month survival improvement (Figure 7) [82]. The update also showed a 75% 1-year survival of patients that received Vigil vs. 23% no-Vigil. Based on these findings, a randomized Phase Ib clinical trial in patients with advanced relapsed or refractory Ewing’s Sarcoma who have not received ≥third-line therapy is active and ongoing.

Conclusion

Given historical lack of demonstrable effectiveness as well as a narrow therapeutic window, there are no FDA indicated treatment options for second- and third-line therapy of Ewing’s Sarcoma patients who frequently have cumulative chemotherapy related toxic thereby limiting experimental treatment eligibility opportunity. As a result of advances in “-omics” analysis and molecular immunology as well as their directed application to Ewing’s Sarcoma patients, a long needed window of opportunity has opened for exploration of innovative therapeutic options. Some evidence of activity has been suggested with single agent IGF-R1 and PARP inhibitors but, more importantly, even with failures data has been accrued and next generation studies have been implemented. Elements including biomarker identification, “-omic” analysis, pharmacokinetics and pharmacodynamics are now in place to help identify agent-specific sensitive subsets of Ewing’s Sarcoma patients and guide protocol construction. Preclinical results with YK-4-279 and bi-shRNA EWS/FLI1 Type 1 LPX are encouraging, but on the basis of clinical results to date remain preliminary. Results from the phase I/II Vigil studies have matured and, based on analysis of outcomes, Vigil immunotherapy is currently undergoing randomized testing to determine qualification for FDA registration opportunity.

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