TIM-3-IgG4 Fusion Protein for the Treatment of Anemia in Low- or Intermediate (Int)-risk MDS Patients

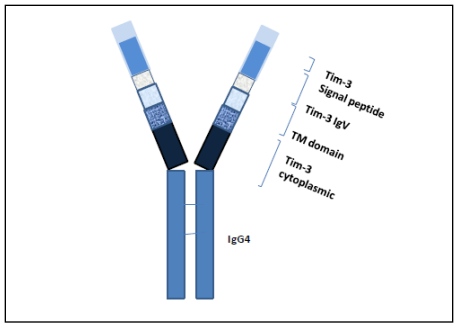
A TIM3-IgG4 fusion protein was constructed to act as a TIM-3 ligand Trap. The T-cell immunoglobulin mucin-3 (TIM-3) receptor, and its main ligand galectin-9 (Gal-9), regulate self-renewal of human leukemic stem cells (LSCs) through co-activation of both NF-κB and β-catenin signaling. The protein was designed to scavenge TIM-3 ligands in order to extinguish leukemic stem cell renewal in MDS and AML. Surprisingly, the TIM-3-IgG4 fusion protein induced the formation of non-cancerous hematopoietic progenitor colonies from primary MDS patient specimens by about 20 fold. These colonies were macroscopic with multilineage potential, suggesting that the TIM-3-IgG4 fusion protein could restore normal erythropoiesis while suppressing the malignant clone, thereby offering a novel therapeutic strategy for transfusion-dependent patients with low- or int-1-risk MDS.

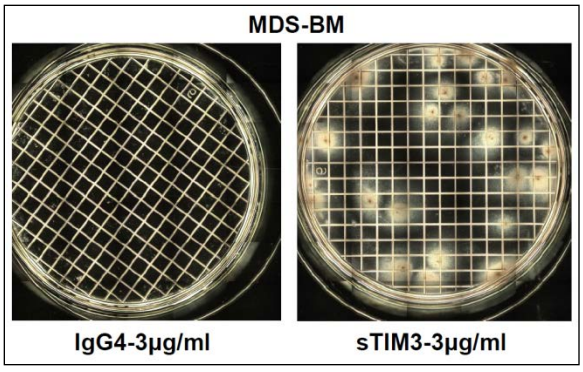
COMMERCIAL OPPORTUNITY

- Medicare billing estimates that >50,000 new cases of myelodysplastic syndromes (MDS) are diagnosed annually in the US population 65 years of age or older. MDS patients are generally categorized into lower-risk (IPSS low or intermediate-1; LR) that accounts for roughly two-thirds of new cases, and higher-risk (IPSS high or intermediate-2; HR) groups that are subject to different treatments. MDS has an attendant risk of progression to acute myeloid leukemia, which is greatest in HR-disease.
- Survival is longest in LR-MDS where the priority is amelioration of symptoms by the treatment of cytopenias to improve quality in life. Erythropoiesis stimulating agents such as Epo are the first choice for treatment of anemia, however, the response rate in unselected patients is low. Lenalidomide is the treatment of choice for del(5q) MDS, with the only remaining FDA-approved alternatives represented by the hypomethylating agents.
- The TIM3-IgG4 fusion protein selectively promotes normal erythroid colony formation from primary MDS specimens treated *ex vivo*, thereby offering a potential novel anemia treatment. This treatment could therefore be used to treat LR-MDS patients with symptomatic anemia or a population similar to that approved by lenalidomide (Revlimid; Celgene), i.e., transfusion-dependent anemia due to low/int-1-risk MDS with a deletion 5q abnormality. Del(5q) MDS accounts for roughly 15% of all MDS patients, with Revlimid having generated $400M in US revenue in 2013 from MDS.

TECHNOLOGY

A TIM-3 IgG4 fusion protein was created by taking the TIM-3 signal peptide, IgG-like domain, transmembrane domain, and cytoplasmic domain and fusing the construct to the Fc portion of an immunoglobulin IgG4 for extended circulation (see Figure to the right). This construct was then used *in ex vivo* colony formation assays of primary MDS marrow samples. Among 15 informative cases, incubation with the TIM-3-IgG4 fusion protein resulted in an approximately 20-fold increase in CFU-GEMM colonies (colony forming unit that includes granulocyte, erythroid, macrophage and megakaryocyte cells) that were macroscopic, i.e., visible without microscopy (see Figure to the right). To test the origin of the colonies, the colonies were collected from the culture dishes and subjected to NGS mutation analysis. Results indicated that TIM-3-fusion stimulated progenitors lacked mutations from the malignant clone. For example, one patient had GATA3 mutations in their MDS specimen, however the stimulated colonies lacked GATA3 mutations. This approach is the first of its kind to selectively stimulate normal progenitors, offering the potential for disease altering benefit.





PUBLICATION/PATENT

- Provisional Patent filed March 29, 2018 for Drs. Sheng Wei and Alan List.

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