Stem-cell-factor race heats up

SAN FRANCISCO—The race to develop the quintessential blood-cell growth factor—if one even exists—is heating up. Such a factor, called a stem cell factor (SCF), would stimulate the replication and differentiation of stem cells, the mothers of all blood cells, as they give rise to both the cells of the blood and the immune system. Indeed, the early lead of Amgen (Thousand Oaks, CA), which is currently pushing its candidate SCF through phase I/II clinical trials, could be challenged by both Immunex (Seattle, WA) and DNAX Research Institute (Palo Alto, CA), which have simultaneously discovered a second candidate SCF called Flt3 ligand (Flt3-L).

A successfully developed SCF could find use in a host of clinical settings ranging from chemotherapy recovery to gene therapy. In chemotherapy recovery, SCF could help cancer patients replace various blood cells killed off by intensive chemotherapy. In gene therapy, SCF could help multiply a patient's stem cells, which make up less than 0.01 percent of bone-marrow cells, thereby making them easier to isolate, as self-renewing stem cells would be the ideal cells to genetically engineer, since gene therapy's goal is to produce a permanent genetic alteration.

A successful SCF, moreover, would likely work synergistically with more narrow-purpose blood-cell growth factors, as none of the 20 or more known blood-cell growth factors act exclusively on a single blood-cell lineage. Among these narrow-purpose growth factors are erythropoietin (EPO), which stimulates erythroid progenitors to differentiate into oxygen-carrying red blood cells and which fights anemia, as well as granulocyte colony-stimulating factor (GCSF), which causes granulocyte progenitors to mature into neutrophils—infection-fighting white blood cells—and which boosts white blood cell production in chemotherapy patients and bone-marrow patients. Both EPO and GCSF racked up more than $1 billion in worldwide sales last year.

For their parts, Amgen's SCF and Immunex's and DNAX's Flt3-L have several characteristics in common. By themselves, both compounds only weakly stimulate the differentiation of stem cells and progenitor blood cells, though both compounds synergize well with narrow-purpose growth factors to stimulate such differentiation, including many colony-stimulating factors and interleukins. Both compounds are biologically active in soluble forms and membrane-bound forms, and both are transmembrane proteins that undergo proteolytic cleavage to generate their soluble forms. Both have four cysteine residues that form intramolecular disulfide bonds to stabilize their three-dimensional structure. And both bind to a subfamily of tyrosine kinase receptors that have five immunoglobulinlike segments in their extracellular domains.

Flt3-L and Amgen's SCF also have distinguishing characteristics. Most importantly, Amgen's SCF stimulates mast-cell proliferation, which causes bothersome inflammation, whereas Flt3-L doesn't stimulate such proliferation. In fact, in early phase I trials of SCF, Amgen ran into mast-cell-induced inflammation, and subsequently, in phase I/II trials it is premedicating patients with an antihistamine to prevent this inflammation. In its trial, Amgen is trying to moderate the blood-cell-killing effects of high-dose chemotherapy by first treating patients with SCF and GCSF to mobilize their "immature" blood cells. It then purifies these cells from the patient's blood and administers them after aggressive chemotherapy to reestablish the patient's blood-cell-making ability.

Flt3-L is a couple of years away from clinical trials, as it is still undergoing biological characterization and hasn't yet entered animal studies. Most likely, a patent dispute between Immunex and DNAX over commercial rights to the compound awaits Flt3-L. **—B.J. Spalding**