**Statins:** The pleiotrophic effects of HMG CoA reductase inhibitors include anti-proliferative, anti-thrombotic, anti-inflammatory and anti-oxidant effects. This broad range of activity arises from the inhibition of isoprenoids, which are essential for post-translational isoprenylation of Rho and Ras family GTPases. These proteins are responsible for many cellular functions, including coupling membrane growth factor receptors to intracellular signaling pathways that affect cell proliferation.

In vivo, simvastatin reduces PAH in a monocrotaline-pneumonectomy model and has a dramatic survival advantage. However, in another rodent study neither simvastatin nor atorvastatin plus rapamycin improved established monocrotaline-induced PAH. Several trials of statins in human PAH are underway, including one comparing aspirin and simvastatin (NCT00384865).

**Dihydroepiandrosterone (DHEA):** DHEA increases expression of sGC and activates calcium-sensitive potassium channels (BK	extsubscript{Ca}) in PASMCs. In general, agents that activate BK	extsubscript{Ca} channels in PASMC are vasodilatory. DHEA inhibits and reverses chronic hypoxic pulmonary hypertension in rats. DHEA, normally secreted by the adrenal gland, is available “over the counter” in health food stores. Further testing in animal models with more refractory PAH (e.g. chronic hypoxia plus a VEGF inhibitor) is indicated before moving to human trials, but at least there is a substantial body of evidence suggesting DHEA is well tolerated in humans.
**Cell Cycle Inhibitors:** Excessive cell proliferation is a hallmark of PAH, making the use of a cell cycle inhibitor, such as rapamycin, attractive. In mice exposed to chronic hypoxia, rapamycin, given by intraperitoneal injection, reduced both RVH and the increase in PA medial thickness\(^4\). However, rapamycin, given by gavage, failed to reverse PAH induced in rats by monocrotaline\(^5\). Further long-term regression studies in animals are indicated prior to testing rapamycin in human PAH, in light of the mixed results of rodent studies and the potential for toxicity.

**Survivin inhibitors:** Survivin is a member of inhibitor apoptosis protein family, that occurs in human and experimental PAH\(^6\). Inhalation of an adenovirus containing a dominant-negative survivin mutant decreases monocrotaline-PAH and prolongs survival\(^6\). This is associated with increased apoptosis in the media of the pulmonary arteries and increased Kv current. Pharmacological inhibitors of survivin, such as YM-155 (Astellas) [NCT00328588](https://clinicaltrials.gov/ct2/show/NCT00328588) are currently being tested in cancer and may merit testing in PAH.

**Polyamine Inhibitors:** In rat PA endothelial cells, hypoxia decreases ornithine decarboxylase activity thereby increasing polyamine import. In rat PASMCs polyamine uptake (specifically putrescine) is necessary for hypoxic activation of p38MAP kinase, an important driver of cell proliferation. Blockade of polyamine synthesis reduces monocrotaline-induced PAH in rats\(^7\). \(\alpha\)-difluromethylornithine (DFMO), an irreversible inhibitor of polyamine synthesis, is used in patients with trypanosomiasis and in breast
cancer. Assuming additional testing in animal models of PAH were to be promising, this experience in humans could inform a trial in PAH.

**STAT3 Inhibition**: Endothelial cells from the PAs of iPAH patients show less apoptosis and more proliferation and migration in culture than those of controls\(^8\). STAT3, a regulator of cell survival, is persistently activated in iPAH endothelial cells. A Janus-kinase (JAK) inhibitor tyrphostin AG490, which reduces STAT3 activity and blocks proliferation, has been proposed for the treatment of leukemia\(^9\). This is a strategy worthy of assessment in experimental PAH.

**Heparins**: Heparin reduces chronic hypoxic pulmonary hypertension in guinea pigs by an antiproliferative effect, unrelated to its anticoagulant activity. The antiproliferative effect of heparin is dependent on the presence of the cyclin-dependent kinase inhibitor p27\(^10\). Unfortunately, low molecular weight heparins are less potent stimulators of p27 and are less effective in preventing experimental pulmonary vascular remodeling than unfractionated heparin, making simple translation to a chronic PAH therapy difficult. However, dalteparin but not enoxaparin, does reduce pulmonary hypertension and vascular remodeling in hypoxic guinea pigs\(^11\).

**Angiopoietin 1 blockers**: The role of angiopoietin 1 in PAH is controversial with one group finding it is upregulated, driving PAH and another finding it is depressed, and that upregulation is therapeutic. The expression of angiopoietin 1, a protein involved in the recruitment of smooth-muscle cells around blood vessels, and the phosphorylation of its
endothelial receptor, TIE2, are increased in the lungs of patients with several forms of human pulmonary hypertension\textsuperscript{12}. In human PA endothelial cells, angiopoietin 1 inhibits the expression of BMPR1A, which is necessary for the signaling of BMPR2\textsuperscript{12}. These results suggest that angiopoietin 1 could promote pulmonary hypertension. Supporting this hypothesis, angiopoietin 1 stimulates proliferation of PASMCs and increases serotonin production by human pulmonary artery endothelial cells\textsuperscript{13}. Blockade of TIE2, achieved by adenoviral gene transfer into the pulmonary artery in rats, largely prevents PAH, caused by either monocrotaline or angiopoietin over-expression; however, this strategy does not reduce chronic hypoxic PAH \textsuperscript{14}. These observations suggest that angiopoietin 1 plays a role in the pathophysiology of some forms of pulmonary hypertension.

However, in other studies, cell-based angiopoietin gene transfection reduces, rather than exacerbates, hypoxic pulmonary hypertension in rats\textsuperscript{15}. This group found robust angiopoietin 1 expression in healthy human lungs and no significant increase in expression in human PAH samples\textsuperscript{15}. More clarity is required before this pathway is exploited therapeutically in humans.

References:


