IN brief

Stem cell funding resumes

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Neurons (red) and glial cells (green) derived from human ESCs.

A ban on using federal funds for human embryonic stem cell (hESC) research was lifted by the United States Court of Appeals for the District of Columbia on April 28,

allowing the US National Institutes of Health (NIH) to go forward with funding. The 2-1 ruling reversed a preliminary injunction put in place by US court judge for the District of Columbia Royce Lamberth last August, prohibiting government financing for hESC work. The plaintiffs, two researchers working on adult stem cells, contended that research on hESCs depends on the destruction of human embryos, forbidden by the so-called Dickey-Wicker amendment. In the recent ruling, the appellate court Judge Douglas Ginsburg stated that the wording of the amendment is ambiguous, but that the interpretation by the NIH—that research on hESCs does not include the process of deriving the cells—is reasonable. Both sides are claiming victory, however. The plaintiffs' attorney, Samuel Casey, said they were one vote away from a "grand slam," and Hank Greely, director for the Center for Law and the Biosciences at Stanford Law School agrees that is a fair assessment. "Their chances of winning would have been quite high if they'd gotten one more vote." But Greely feels that the fate of this lawsuit is sealed. The plaintiffs could appeal the decision, according to Casey, but are more likely to file a supplemental brief asking the lower court, which has yet to rule, for a permanent injunction on government funding for stem cell research. The past three administrations have allowed federal funding of hESC research to proceed, and since 1997, Congress has declined to change the Dickey-Wicker amendment, which as a rider in an appropriation bill, is voted on annually. Even so, efforts continue in at least two states, Minnesota and Oklahoma to prohibit hESC research.

Laura DeFrancesco

US states with bans in place (gold) or pending (red) on research using embryos or cell products derived from embryos. Source: http://www.hinxtongroup.org/usa_map.html

At therapeutic doses, tofacitinib avoids immunosuppression probably because it only partially and transiently blocks its targets. "At the doses being used you inhibit a lot of cytokines, but you don't inhibit them completely," says John O'Shea, an immunologist at the National Institutes of Health in Bethesda, Maryland. Side effects seen so far in the tofacitinib trials include infections (mostly mild to moderate) and minor decreases in neutrophils. Hemoglobin goes down, presumably because JAK2 is important for red blood cell formation, and low-density lipoprotein and high-density lipoprotein both go up. Overall, "I don't think [tofacitinib] looks any more toxic than what you get with injectable therapy," says Boris.

A particular concern for JAK inhibitors is cardiac events because there is evidence that JAKs play a protective role in cardiomyocytes (heart muscle cells). In April, an abstract published in advance of the European League Against Rheumatism meeting reported four deaths in one of the studies, but Pfizer said that only one death, from respiratory failure, was reported by the investigator as drug related. Not all phase 3 tofacitinib data had been released as of early May, but the drug doesn't appear to cause heart attacks and strokes. "I don't think there's anything significant... that would lead us to believe that there is any impact on cardiac muscle or myocytes," says Boris. "But again we still have to see the full data set come out."

Of other JAK inhibitors in development, the furthest along is INCB28050 from Incyte in Wilmington, Delaware, having completed phase 2a in rheumatoid arthritis (Table 1). The drug has been licensed to Eli Lilly of Indianapolis for inflammatory and autoimmune indications, and so far its efficacy closely mirrors that of tofacitinib. The main difference is that whereas tofacitinib hits JAKs 1, 2 and 3, INCB28050 is specific for JAKs 1 and 2 while sparing 3. "JAK3 inhibition is extra baggage," says Incyte president and CEO Paul Friedman, explaining that as JAK3 is not involved in IL-6 signaling, which is deemed critical, it made little sense to block it. "The reason Pfizer's [compound] does well clinically is certainly due to JAK1 and JAK2 effects."

Vertex Pharmaceuticals in Cambridge, Massachusetts, and Galapagos, in Mechelen, Belgium, chose even tighter specificity for their JAK inhibitors. Vertex's molecule VX-509, currently in phase 1, is specific for JAK3, largely

because JAK3 expression is mainly limited to lymphoid tissues. Galapagos, in contrast, chose to inhibit only JAK1, thus retaining the ability to block signaling downstream of IL-6 while avoiding the anemia that's caused by JAK2 inhibition and any immunosuppressive effects that may come with blocking JAK3. That could create a wider therapeutic window. JAK1 specificity "allows us to move up in dosing to a range where we hope we can extend efficacy without hitting JAK2-related side effects," says Gerben van't Klooster, development project leader for Galapagos's compound, GLPG0634. The compound so far has been tested only in healthy volunteers, and will enter phase 2 in rheumatoid arthritis in the second quarter of 2011.

But Paul Changelian, former director of inflammation biology at Pfizer, believes Pfizer's pan-JAK approach is correct and that inhibition of all three JAKs contributes to tofacitinib's efficacy. He points out that IL-15, which boosts proliferation of natural killer cells, signals partly through JAK3. And the IL-23 receptor signals partly through JAK2, controlling differentiation of Th17 helper T cells, considered key mediators of inflammation. So inhibiting both JAK3 and JAK2, as well as JAK1, may be important.

Few of these effects were known when Pfizer began its JAK inhibitor program in the mid-1990s. Company chemists designed tofacitinib, first synthesized in 2000, to specifically inhibit JAK3. But the results from solid phase kinase-specificity assays that indicated JAK3-only inhibition later proved incorrect. Cellular assays also were misleading because signaling downstream of most cytokine receptors requires the association of two different JAKs, and it's hard to know whether drug potency is the result of inhibiting just one, or both. As a result, Pfizer accidentally made tofacitinib a pan-JAK inhibitor—a fortuitous outcome, says Changelian, because the drug somehow achieves the right balance of inhibition across the JAKs without hitting non-JAK kinases and causing toxicity. "It's remarkably clean across the kinome," Changelian says. "That really is what's important."

But Changelian concedes that tofacitinib may eventually be bettered by a different JAK inhibitor. At least 16 companies have filed patent applications on JAKs. "People are convinced that there's still a better molecule to be had there," he says. "And they may be right."

Ken Garber, Ann Arbor, Michigan

Table 1 Drugs targeting JAK kinases in rheumatoid arthritis

Company	Agent	Target	Stage
Pfizer	Tofacitinib (CP-690,550)	JAK3, JAK1, JAK2	Phase 3 (six trials)
Incyte/Eli Lilly	LY3009104 (INCB28050)	JAK1, JAK2	Phase 2b
Vertex Pharmaceuticals	VX-509	JAK3	Phase 2
Galapagos	GLPG0634	JAK1	Phase 1 complete