FDA head Califf spurned

On February 24 the Senate confirmed Robert Califf as head of the US Food and Drug Administration. But for months, political machinations had been threatening his chances of ever occupying the agency's top seat. President Barack Obama nominated Califf, a Duke University clinical researcher, for the post last September, but several Senate Democrats and at least one Republican threw obstacles in his path to becoming commissioner. Senator Lisa Murkowski (R-Alaska) led this unorganized revolt in January, citing her anger over genetically modified salmon as the reason for temporarily blocking Califf's appointment. Although she relented, further opposition came from legislators who belong to Obama's party. Senator Bernie Sanders (D-Vermont), who is running for president, cited Califf's ties to the pharma industry and the likelihood that Califf would sympathize with raising rather than lowering drug prices as the main reasons for blocking his appointment. Moreover, Sanders joined with Senators Edward J. Markey (D-Massachusetts) and Joe Manchin (D-West Virginia), both of whom raised questions about Califf's ties with industry and voiced objections to FDA approval policies for opioid drugs. Last August, for example, FDA approved OxyContin for use in children aged 11 to 16 years old, a step that Markey and Manchin say further fuels a national opioid drug crisis. Early in February, however, Califf and other top FDA officials presented a new plan "to reassess the agency's approach to opioid medications"—an effort that might have soothed those who opposed his confirmation.

GM salmon shut out of US

The US Food and Drug Administration (FDA) in January issued an 'import alert' preventing all genetically modified (GM) salmon from entering the US. The temporary hold is being implemented to comply with the fiscal year 2016 Omnibus Appropriations Act that directs the FDA not to allow food containing GM salmon into interstate commerce of GM foods until labeling guidelines are finalized. In practical terms, this reverses the approval last November for commercial sale of the fast-growing fish, developed by AquaBounty Technologies of Maynard, Massachusetts (*Nat. Biotechnol.* **34**, 7–9, 2016). Senator Lisa Murkowski (R-Alaska) is taking credit for this eleventh-hour reversal of the approval of the salmon, which had languished at FDA since 1995. "I adamantly oppose the FDA's misguided decision to allow GM salmon to be placed in our kitchens and on our tables, and I firmly believe that mandatory labeling guidelines must be put in place as soon as possible so consumers know what it is they are purchasing," she said. Senator Murkowski used several kinds of political leverage to block the product from reaching market. For one, she insisted on putting a mandatory labeling provision in the 'must-pass' omnibus appropriations bill, which, if blocked, would have shut down the federal government. Additionally, she put a block on Robert Califf, whose appointment as FDA Commissioner depends on Senate confirmation (see p. 220).

Table 1 Selected clinical-stage NK cell therapies for cancer

Company	Agent	Indication	Stage
Innate Pharma)/Bristol-Myers Squibb	Lirilumab (IPH2102/BMS-986015), anti-KIR2DL1 and KIR2DL2/3 mAb	AML (single agent); MDS, chronic lymphocytic leukemia/small lymphocytic lymphoma	Phase 2
Affimed (Heidelberg, Germany)	AFM13 (CD30xCD16A bispecific TandAb)	Hodgkin's lymphoma	Phase 2
University of Minnesota (Minneapolis and St. Paul)	Donor NK cell infusion and IL-15	Relapsed or refractory AML	Phase 2
Medical College of Wisconsin (Milwaukee)	Donor NK cell infusion	Solid tumors	Phase 2
NantKwest	NK-92 cell line (aNK)	Merkel cell carcinoma Blood cancers	Phase 2 Phase 1
Innate Pharma/AstraZeneca (London)	Monalizumab (IPH2201) anti-NKG2A mAb and Erbitux (cetuximab)	Head & neck cancer	Phase 1,2
Altor Bioscience (Miramar, Florida)	ALT-803, enhanced IL-15	Multiple indications	Phase 1,2
Green Cross (South Korea)	MG4101 (allogeneic NK cells)	Lymphoma, solid tumors	Phase 1 complete
National Cancer Institute	Recombinant IL-15	Melanoma, renal, NSCLC, head & neck	Phase 1
Washington University (St. Louis)	Cytokine-stimulated memory-like NK cells and IL-2	AML and MDS	Phase 1

KIR, killer immunoglobulin-like receptors; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; NSCLC, non-small cell lung cancer.

accelerator. Both only happen when T cells are in contact with tumors, which requires a prior innate immune response, which NK cells in theory can provide.

Affimed Therapeutics in Heidelberg, Germany, is pursuing a different bispecific antibody strategy that is already in the clinic. One-half of its AFM13 construct targets CD16 (FcγRIII), a receptor expressed on NK cells that binds the Fc (fragment crystallizable) arm of IgG antibodies. (The other half binds a tumor antigen.) CD16 binding triggers NK cell killing of tumor cells by antibody-dependent cellular cytotoxicity (ADCC), an important NK cell effector mechanism. AFM13 is in phase 2.

The major reservation about all NK cell immunotherapeutics is antitumor efficacy. NK cells are mostly short-lived and tumors can inactivate them by secreting cytokines like IL-10 and TGFβ and by shedding soluble ligands that bind NK-cell-activating receptors, desensitizing the NK cell (*Science* **348**, 136–139, 2015).

Blocking one KIR subtype may not be enough to activate an NK cell. A cocktail of antibodies may be necessary for optimal efficacy (*J. Immunol.* **180**, 6392–6401, 2008). And although NK cells are important early in the antitumor immune response, "evidence is mounting that they can become overwhelmed and cannot do it themselves, they cannot eliminate particularly a solid tumor," says Campbell, who thinks T cells must also be mobilized. Caligiuri, however, cites the Perugia transplantation results as evidence for NK cells' antitumor potency. Campbell agrees that NK cells "have a very good capacity to kill acute myeloid leukemia tumors," but otherwise sees them mainly working against single cells, in antitumor surveillance, metastasis suppression or in minimal residual disease to prevent relapse.

That's too pessimistic, argues NantKwest CSO Hans Klingemann, citing anecdotal results from his company's clinical trials. Since 2002, NantKwest has treated roughly 50 cancer patients with cells from NK-92, an NK cell line originally derived from the blood of a patient with NK lymphoma, and has achieved some durable remissions of established tumors. (The cells are irradiated to eliminate malignancy risk.) The company existed on a shoestring, burning less than $18 million during its first decade, but that all changed last year, with the massive takings from its IPO and a large infusion of cash from billionaire and serial biotech entrepreneur Patrick Soon-Shiong, who now owns close to 60% of the company.

Klingemann sees NK-92 cells as an affordable, off-the-shelf, easily renewable alternative to autologous NK cell transplants. Most patients, for unknown reasons, do not reject these cells. The cell line does not express KIRs, so the cells are primed to kill, and so far they've been safe and selective for tumors, including solid tumors. NantKwest is modifying them for potency by incorporating a tumor-targeting CAR, to be tried soon in glioblastoma, and also high-affinity CD16 to enhance mAb ADCC, with a Herceptin combination trial also to begin later this year. Klingemann considers NK cells better CAR vehicles than T cells, because unlike T cells they do not persist for months or years, with side effects such as B-cell depletion. And NK cells kill tumors more ways, including the indirect stimulation of a T-cell response through cytokine-activated dendritic cells. The downsides are that irradiated NK-92 cells only survive briefly, making frequent infusions necessary, and they are unproven in large randomized trials.

That's true for all NK cell immunotherapies. But with companies now flush with cash, the necessary clinical trials will take place. "You've got to do the *in vivo* experiment in the patient," says Caligiuri. "You just don't know."

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