blocking citrullination could lead to some beneficial gene regulatory effects. For example, work by Venables and others at Oxford shows that PAD4 citrullination of the transcription factor E2F1 promotes inflammatory cytokine gene expression, with a PAD inhibitor dampening the inflammation (*Sci. Adv.* **2**, e1501257, 2016). This is a completely different PAD disease mechanism than autoantigen citrullination—an unexpected bonus for PAD inhibitors, if it plays out in humans. "PAD inhibition in transcription is probably what made BMS much more interested" in these drugs, speculates Venables. It's also why PAD inhibitors probably need to penetrate into cell nuclei to be effective.

For better or worse, PADs are also important in innate immunity. In fact, their best-established physiological role is to facilitate one form of neutrophil cell death. Bacterial exposure sometimes prompts neutrophils to explode spectacularly. They eject their chromatin, decorated with DNA, histones, enzymes and antibacterial peptides, forming neutrophil extracellular traps (NETs), which trap the pathogen for killing by phagocytes. PADs are essential for at least some forms of NETs, because citrullination of neutrophil histones decondenses the chromatin, releasing the proteins and nucleic acids needed to form the NET. (The neutrophil dies a noble death.) "It's a complex process, but the PADs have been particularly implicated," says Mariana Kaplan, a rheumatologist at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). As a consequence, a major worry about PAD inhibitors is that they will block this important mechanism of innate immunity and leave patients open to infection. Reassuringly, Thompson, who speculates that other immune mechanisms compensate for NET loss, says, "PAD4 knockouts don't show an increased risk of developing infections."

And inhibiting NETs may even have therapeutic benefits, as NETs have been implicated in lupus pathogenesis. "There seems to be an imbalance between NET formation and NET clearance in lupus," says Kaplan. Her group has identified a subset of neutrophils, present at varying levels in lupus patients, that *in vitro* form NETs spontaneously (without microbial stimuli) (*J. Immunol.* **187**, 538–52, 2011). Other groups have reported NET dysregulation in lupus patients who have severe disease and high titers of anti-DNA antibodies (a lupus hallmark). Such NETs may expose modified DNA and other autoantigens to immune attack. Kaplan's laboratory has used PAD inhibitors in two animals models of lupus with positive results (*Ann. Rheum. Dis.* **74**, 2199–2206, 2015) and NIAMS has a cooperative R&D agreement with Padlock. Kaplan notes, however, that any future anti-PAD therapy may only work in a subset of lupus patients.

Rheumatoid arthritis is the obvious first indication for PAD inhibitors, because citrullinated autoantigens are such a signature feature. "The presence of antibodies to citrullinated antigens is quite specific to rheumatoid arthritis," says Kaplan. Tackling PAD4 may not be enough; Venables thinks PAD2 must also be inhibited. "PAD2 and PAD4 have some shared redundancy," he notes. This may be why GSK did not pursue a specific PAD4 inhibitor, Venables speculates. "They were developing it for about ten years, but then they just totally dropped it," he says. But dual PAD2–PAD4 inhibition raises the risk of side effects, because PAD2 is widely expressed. "There's no predicting," says Venables, who as a rheumatology trainee saw the first patient treated with a tumor necrosis factor (TNF) inhibitor, in 1992. "There was a huge prejudice against anti-TNF when it was first tested," he recalls. "PAD inhibition has gone through the same prejudice."

But dual PAD2–PAD4 inhibition raises the risk of side effects, because PAD2 is widely expressed

That prejudice has helped limit the field of PAD inhibition to Padlock (now part of BMS) and a few known competitors. 4SC Discovery has not disclosed details on its early-stage PAD inhibitor program. ModiQuest, which has been issued a patent on PAD inhibitors together with a Dutch academic group, is instead developing a therapeutic antibody against a citrullinated epitope of a histone protein, through a spinout company, Citryll. ModiQuest believes this downstream approach will be more specific and safer than inhibiting PADs. But neither this monoclonal antibody nor BMS's PAD inhibitors have yet been tested in humans. Only with clinical results will researchers begin to know if targeting an obscure post-translational modification will fulfill its promise in rheumatoid arthritis and beyond.

Ken Garber *Ann Arbor, Michigan*

Matchmaker for NIH-rejected grants

Last year, the US National Institutes of Health (NIH) funded one in five research proposals it received. Now, a pilot online portal from Reston, Virginia–based national defense and engineering company Leidos hopes to give the other four applications a second chance. Highly scored grant proposals ultimately passed over by the NIH can be uploaded by their investigators to the Online Partnership to Accelerate Research (OnPAR; http://onpar.leidosweb.com/onpar/) to be screened by selected partner research foundations, pharma companies and patient organizations. Participating organizations for the project include the Adenoid Cystic Carcinoma Research Foundation, Breast Cancer Research Foundation, Children's Tumor Foundation, Melanoma Research Alliance and Parent Project Muscular Dystrophy, among others. As the program progresses, OnPAR plans on increasing its membership to possibly include other countries' government funding bodies. Developed with initial backing from NIH, "OnPAR presents another avenue to fund important biomedical research," according to Jim Pannucci, Leidos's director of life sciences. "The program will revolutionize the scientific funding environment and foster more discoveries at a faster pace to benefit and improve global health." Michael Lauer, NIH deputy director for extramural research, says, "Not only will this program benefit our applicants by helping connect them with potential funders, it allows the private funders to take advantage of NIH's peer review system and keeps applicants from having to develop another application to seek funding elsewhere."

Michael Francisco

"**[Taro Pharmaceuticals] makes a rare disease drug free. Not sure if that's good or bad."** Martin Shkreli, former Turing Pharmaceuticals CEO, tweets his reservations about the Israeli company that made a primary periodic paralysis drug free when they were unable to identify many patients. (*BioPharma Dive*, 3 May 2016)

"They don't know which are the illegal ones compared to other plants that are around. They can't find it out either, because there is no difference between them." Swedish plant biologist Stefan Jansson discusses his CRISPR-modified thale cress, as the European Commission debates how and whether to regulate gene edited crops. (*BuzzFeedNews*, 8 May 2016)

"Doctors don't know what to do with it. Patients don't know what to do with it." Timothy Hamill, former director of UC San Francisco's clinical laboratories, comments on the mounting number of genomic tests for cancer offered directly to the public. (*Wired*, 28 April 2016)"