

## THE AUTHOR FILE

## Kasper Lage

Scoring genes in light of their ‘friends’, and a naval approach to science.

When massive amounts of cancer genome data are analyzed, some mutated genes deliver loud signals—that is, more than 20% of tumors of a given



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type show a mutation at the gene. But there are also more muted signals from genes mutated at intermediate and low frequencies, and “we know for sure that we’re missing these,” says Kasper Lage, a computational biologist with faculty appointments at Massachusetts General Hospital (MGH), Harvard Medical

School and the Broad Institute of MIT and Harvard. Both loud and muted signals can drive cancer progression.

Along with colleagues, Lage developed NetSig for statistically scoring cancer gene networks to aggregate and amplify weaker signals. “That gives you a boost in your power, so to speak; it gets you a better signal,” he says. NetSig can be run on the Broad’s Firecloud platform, and it’s available for download.

The method does not just crank up the volume; it applies data from over 4,700 tumor exomes and protein interaction data used in the 1000 Genomes Project to score a gene in light of ‘friends’ in its ‘social network’. NetSig computationally removes well-studied genes from the analysis, revealing the signal from less well-known cancer gene suspects. The tool addresses “knowledge contamination,” which hampers many analyses, says Lage, who believes “you should at least know how confounded your method is.” What contributes to bias is that earlier techniques identified high-frequency mutations in cancer that have been more intently studied.

Lage wanted to see how NetSig might one day help physicians and patients with treatment decisions, for instance when tumors are oncogene negative and lack typical mutations or amplifications. The team screened 23 genes with high NetSig scores and discovered that 11 were tumorigenic in animals; 9 turned out to be relevant to lung adenocarcinoma.

When analyzed in the context of patients with tumors classified as oncogene negative, two of the high-NetSig-scoring genes showed elevated numbers of copies in a subset of patients. These are possible cancer drivers and

offer hints for possible treatment approaches specific to these mutations. Lage was glad the project moved full circle: from *in silico* to animals to people. “It took a lot of extra time, but we thought it was 100 percent worth it and actually necessary,” he says.

Doing science to help patients has long motivated Lage, who has been involved in several biopharmaceutical companies. One company, Orphazyme, has just gone public. He co-founded Intomics, a bioinformatics firm, consults for several pharmaceutical companies and is completing an executive MBA at MIT’s Sloan School of Management. He received his PhD in computational biology from the Technical University of Denmark and he took business classes on the side, as he had as an undergraduate. On his first day as an MGH postdoctoral fellow, he followed a discussion about how a particular research result might affect patient care. He recalls thinking: “Ok, I’m in the right spot.”

Steve Hyman, Lage’s Broad colleague and director of the Stanley Center for Psychiatric Research, says that Lage jokes with a straight face about his unflappable Danish temperament. “But underneath that calm exterior, deep in his forebrain, I suspect that he is releasing a lot of dopamine,” says Hyman. He has taken on a project, single-neural-cell-type interaction proteomics, that should be impossible, but it’s on an impressively successful trajectory. “Even if happiness is unseemly, motivation is clearly a virtue.”

Lage’s native Denmark has military conscription determined by a lottery. Lage’s number led him to a year of military service, and he decided to enlist in the Royal Danish Navy’s lieutenant school. As a platoon leader, he tended to the nation’s combat-ready small, powerful boats when they came ashore to refuel, stock up on naval mines or load torpedoes. He decided to remain a naval officer for 25 months and then served in the reserve for seven years.

Much from Lage’s military life has carried over into his science. “I learned a lot about having respect for individuals,” he says. Respect matters in science, with team members hailing from many disciplines. Denmark’s naval training is tough but not abusive. For example, an officer may not tell a recruit, “You’re as slow as a turtle,” he says.

Lage deeply enjoys Boston and its “porous membrane” between industry and academia. He and his wife and children live near the Boston Public Garden, where they spend as much time as they can, preferably in the mornings before the tourists arrive. “We basically consider that our yard,” he says.

#### Vivien Marx

Horn, H. *et al.* NetSig: network-based discovery from cancer genomes. *Nat. Methods* 15, 61–66 (2018).

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