There is a bit of a misplaced emphasis in the clinic and in clinical science as to how we think about targeting cancer,” said Andrei Leschenko, Ph.D., John C. Malone Professor of Biomedical Engineering and Director of the Yale Systems Biology Institute. “There has been a strong focus on controlling primary tumor growth, even though we know that more than 90 percent of cancer deaths occur because of invasive cell behavior, or metastasis. The main problem isn’t the growth of the primary tumor, it’s the ability of cancer cells to change their behavior to invade and travel to secondary sites.

The emphasis on tumor growth, he added, stems partly from the difficulty of analyzing the causes and origins of cancer cell migration. That’s changing, thanks to new tools and technologies, some of them unique to Dr. Leschenko’s lab, where custom-built devices and new methods of analysis are allowing researchers to trace the movement of cancer cells, the cues that incite their invasion, and the signals that guide them to new locations during metastasis.

“Their circuits get reset,” said Dr. Leschenko, “so instead of staying put, they start moving toward this big highway system, the bloodstream. Eventually they navigate toward tissues very different from their native environments, constantly adjusting to different

circumstances, and colorectum. “The process is very complex and not well understood,” said Dr. Leschenko, “but it’s a systems problem, so we need to use systems approaches.”

His lab and other groups at the Systems Biology Institute, which he has been leading for the past two years on Yale’s West Campus, are trying to understand what transforms one specific tumor cells into a far-ranging invasive army. What networks of molecules mediate this shift? How do invasive cells communicate and coordinate? Which neighboring cells resist? Which collaborate with the invaders? How do cancer cells develop new behaviors and change the behaviors of neighboring cells?

Many of the answers lie within the complex system of signaling networks, the fundamental interest of Dr. Leschenko’s lab and the Institute. In cancer, normal communication between cells gets misinterpreted, disrupted, or corrupted. “If we can understand the signaling mechanisms,” he said, “we can develop new therapies that prevent invasive spread – for instance, by rewiring these networks. There’s already a lot of activity to generate novel therapies to do that, and we are working with others to determine the fastest translational path for clinical applications. That’s the ultimate goal.”

They are concentrating on what Dr. Leschenko calls the champions of invasive behavior” - glioblastoma and melanoma, two of the most deadly and fast-spreading cancers, and also breast cancer; another aggressive malignancy. A recent paper described how individual metastasizing breast cancer cells become generally exploratory, searching for the bloodstream, and then, in response to a cue, suddenly band together in one direction, as if they have received their own order of invasion.

“As soon as there is a clear indication of where they want to go,” explained Dr. Leschenko, “they begin moving almost in goose step with each other.”

He and his colleagues were able to collect this extraordinary information by building devices that can track the path of a single cell and its changing behaviors in response to cues and signaling networks. These tools give the scientists new ways to investigate and analyze a single cell, looking at every gene, at the reprogramming proteins, and other factors.

He believes that understanding the complexity of signaling networks and the process of metastasis demands a multidisciplinary approach. The teams he has put together at his lab and institute include researchers of diverse disciplines: evolutionary biologists, synthetic biologists, and systems biologists, but also physicists, mathematical models, and biomedical engineers.