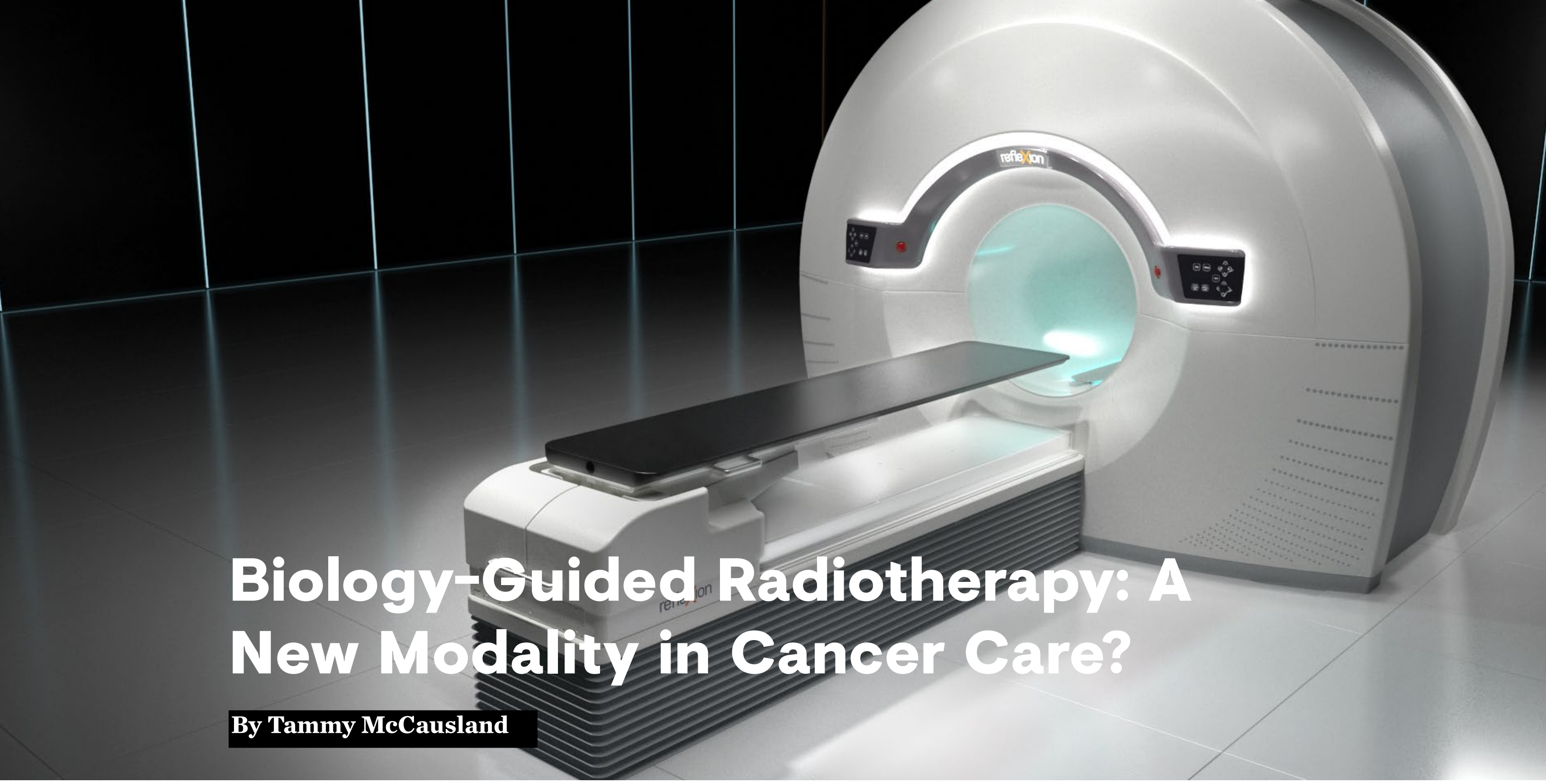

RefleXion Gantry @ 2019 RefleXion Medical

Biology-Guided Radiotherapy: A New Modality in Cancer Care?

By Tammy McCausland

When Sam Mazin[a] and Akshay Nanduri[b] met in grade 9 science class at Thornlea Secondary School in Thornhill, Ontario, Canada, neither could have imagined they would one day create a bio-targeting oncology company that is poised to transform cancer care. They became fast friends, continually challenging each other to succeed. They studied computer engineering together at the University of Waterloo in Waterloo, Ontario. Graduate school and life took them down separate paths, but they remained in close contact.

Mazin pursued graduate studies at Stanford University where he studied electrical engineering with a focus on medical imaging. He developed expertise in CT and PET imaging systems. "I got interested in health care and the ability to apply engineering principles to see inside the body," he said. While attending a lecture about radiation therapy in 2007, which Mazin admitted he didn't know much about at the time, an idea came to him: "If in PET imaging a cancer cell emits a photon, why not just shoot one back with radiation?" He reached out to Nanduri to discuss his idea and about partnering in a business venture. They developed a plan and submitted it to the Massachusetts Institute of Technology's business plan competition. They didn't win, but they co-founded RefleXion Medical in 2009 and have never looked back. "He's the guy I trust more than anyone," Mazin said. "We're both engineers by training, but with Akshay's business background, he's able to be the business guy to my technical counterpart."

They raised some seed money to develop the concept in simulation mode to see if it would work. They built a computer model of the machine first, then began publishing on the theoretical aspects of the technology. It wasn't until 2014 that they raised venture capital funding to create a team and build the first prototype system. In essence, RefleXion Medical has combined PET with radiotherapy to create a new cancer treatment modality called biology-guided radiotherapy (BgRT). BgRT uses the PET tracer FDG, a glucose-based compound, to determine where a tumor is located.[1] When cancer cells consume FDG, it breaks down right away and immediately produces emissions signaling the cells' location, which can then be used to direct treatment.[1] The signaling continues during treatment. The RefleXion platform senses the tumor's emissions and uses that information to quickly send radiation back to the tumor.[1] Because the tumor's own signals are used to guide radiation delivery directly to the tumor, the radiation dose to healthy tissue may be significantly less.[1]

Even though the concept of merging a PET scanner with a radiation therapy device (a linear accelerator or linac) and combining the collection of biological information with delivery of radiation into one machine seemed logical, the co-founders underestimated the challenges. "The real technical challenge for us was not around combining two modalities together, but the way it needed to work required significant innovation," Mazin said. "We're not using PET images to guide the treatment, we're using the emissions, and what that means is that every time you receive an emission, the machine decides whether to respond to that emission, and if the answer is yes, it sends radiation toward the tumor in less than a second." To shoot back quickly the linear accelerator needs to be rotated to the same line that the PET scan collected the information. "We need to rotate at a speed of one revolution per second as opposed to one

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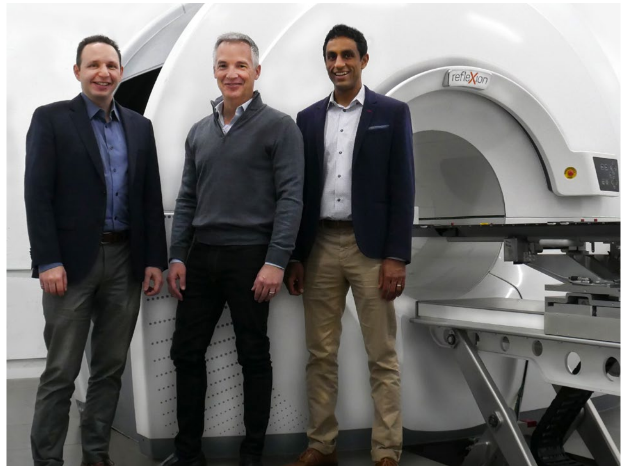
– Sam Mazin

revolution per minute, which is what most linacs operate at today,” Mazin said. It’s more than an order of magnitude increase in the speed that these machines need to work, including the multileaf collimator, which also needs to shape the radiation beam at much faster speeds. “The crux was solving the electromechanical challenges of rotating and switching a multileaf collimator an order of magnitude faster than what they were doing today,” he said.

With BgRT, Mazin and Nanduri hope to improve treatment for early stages of certain cancers and also to one day expand care in metastatic disease. They plan to develop evidence around particular cancers such as lung and breast cancer, but they believe that any solid tumor cancer will be a candidate for BgRT. “The tumor itself acts as its own fiducial, which we think will give us the ability to improve care in any solid tumor cancer where radiotherapy is indicated, but especially ones where you have to deal with motion, uncertainty and the nearby structures,” said Mazin. “The ability to be more conformal is obviously important, and that is exactly what a real-time biological fiducial should have the chance to do.”

By targeting metastatic disease, they are aiming to address an unmet need that will be a differentiator for RefleXion. They continue to hear from prospective users within the clinical community who suggest that because of the paradigm shift of having PET/CT on the device, it’s an opportunity for biological feedback, not just anatomical feedback as is currently used in radiotherapy. “We can start learning more about how these treatments are actually working in patients because we might get signals from those tumors themselves as we’re treating them,” Mazin said.

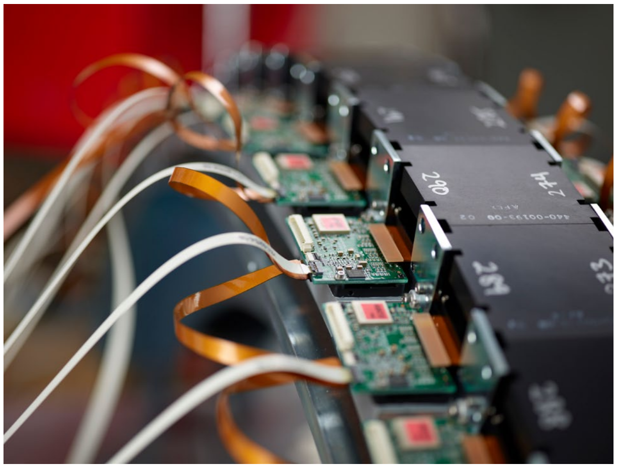
Emerging evidence suggests radiation can potentiate immunotherapy, and that effect can be force multiplied when multiple sites of disease are treated. “That’s exactly the technological capability that RefleXion can uniquely bring to the market, so we think there’s a really interesting paradigm in metastatic disease alongside the most advanced cancer drugs. It’s very different than any other technology out there,” Mazin said. The financial backing of pharmaceutical giant Pfizer, as well as Johnson & Johnson, Nanduri said, speaks to RefleXion’s potential within metastatic disease. The technology could also have significant implications for survivorship. “Our technology has created an opportunity to use radiation in a more systemic way and try to improve survivorship, outcomes and quality of life for patients with metastatic disease, or at least to manage it,” said Mazin.



(L-R) Sam Mazin, RefleXion’s co-founder, Todd Powell, RefleXion’s president and CEO, and Akshay Nanduri, RefleXion’s co-founder and VP of strategy and business development, standing in front of the RefleXion machine. @ 2019 RefleXion Medical

RefleXion’s system can be used with CT guidance alone—an option available to customers—which would allow departments to leverage existing intensity-modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT) reimbursement codes. It’s one way to maintain use and maximize return on investment on the device. The co-founders believe that RefleXion is ideally suited to the paradigm shift happening in reimbursement with bundled payments. “We have the potential to simplify hypofractionation and delivery of SBRT, so we’ll be well suited for this shift that’s happening,” Nanduri said. “Our reimbursement plans will be well supported by robust clinical evidence that the company is committed to getting behind and investing in.”

They’ve already done dosimetry studies, some of which were presented last October at ASTRO’s annual meeting. They submitted their 510(k) application to the U.S. Food and Drug Administration earlier this year. “The FDA application is an important milestone on our path towards first-human use. It is a culmination of many years of R&D and over $100 million in financing,” Nanduri said. “The investment in our manufacturing facility is a testament to the company’s conviction that BgRT has a crucial role in the fight against cancer and also signals our investors’ willingness to fund this next phase of ‘commercialization.’” In May the company opened a new manufacturing facility at its headquarters in Hayward, California. They anticipate the technology will be priced similar to the latest innovations in radiotherapy. “We don’t expect our price range to really limit penetration into the market because of the broad utility of RefleXion’s platform,”



Nanduri said. Once the RefleXion platform is approved for commercial sale in the United States, the company will focus on integrating its technology with leading objective interface systems (e.g., Aria, MOSAIQ). Facilitating smooth integration is part of RefleXion's plan during the early phase of commercial adoption.

The co-founders are encouraged by the interest in the technology from broad segments of the market, including integrated delivery networks, payer providers, freestanding centers and community hospitals. They've had tremendous support from chairs of medical oncology and radiation oncology departments and industry veterans. Mazin attributed the warm reception from the community to the economics around adding incremental patients to a department. "The potential case for metastatic disease means that there is a patient pool that can be referred that currently isn't," he said. "We're also witnessing an opportunity to bring radiation oncology and medical oncology together in a combination therapy setting."

Nanduri would like to see a RefleXion system or multiple systems in every health care and hospital cancer center department throughout the oncology community. "It's really been a dream to be able to partner with Sam on this journey. He's created this incredible concept and groundbreaking approach that we hope will change an entire practice of medicine in cancer treatment," he said. As for Mazin, he hopes "to be able to impact in a very positive way, every patient in the world with a solid tumor cancer."

Endnotes

[a] Sam Mazin received a Bachelor of Applied Science in computer engineering from the University of Waterloo and a Ph.D. in electrical engineering from Stanford University.

[b] Akshay Nanduri received a Bachelor of Applied Science in computer engineering from the University of Waterloo, a Master of Applied Science in electrical engineering from the University of Waterloo and an MBA from the Massachusetts Institute of Technology.

Reference

1. RefleXion Medical. Company and Technology Background. [Company flyer]. October 2018.

(Top): (L) The X1 machine contains two 90-degree proprietary state-of-the-art PET detector arcs. (R) RefleXion treatment planning station. (Bottom): (L) The ring gantry houses a 16-slice kVCT, two PET detector arcs, an electronic portal imaging device (EPID), a 6 MV linac and a binary multi-leaf collimator. (R) Telly Tan, one of RefleXion's new product introduction engineers, assembling the X1 machine. @ 2019 RefleXion Medical