Claudio Alarcón, PhD

Mark Lemmon, PhD, FRS

THE GROWTH OF THE CANCER BIOLOGY INSTITUTE

One eminent Yale scientist envisioned the Yale Cancer Biology Institute. Another brought it to life and has overseen its growth. The visionary was Joseph "Yossi" Schlessinger, PhD, William H. Prusoff Professor of Pharmacology, Chair of Pharmacology, and founding director of the Yale Cancer Biology Institute (YCBI). The engine of growth has been Mark Lemmon, PhD, FRS, David A. Sackler Professor of Pharmacology, Deputy Director of Yale Cancer Center, and Co-director of the YCBI.

When Dr. Lemmon came to Yale from UPenn in 2015 to start the YCBI, the Institute consisted of a single two-person lab—his. Six years later, the YCBI has seven dynamic laboratories filled with 60 scientists—including a diverse and talented group of 14 graduate students and 20 postdocs. In addition, the population swells each summer with great cohorts of undergraduates getting their first taste of cancer research. Dr. Lemmon intends to add several more labs soon.

He and Dr. Schlessinger began with a blueprint for the institute they hoped to assemble. The plan covered everything from recruitment strategy to the number of labs and the scientific focus of each. The plan also called for the labs to be intensely collaborative, not only with each other but with the other research institutes on Yale West Campus and Yale Cancer Center. Dr. Lemmon wanted the YCBI's scientists to understand the core biology underlying all cancers, to complement the excellent work being done in Yale Cancer Center labs on all cancers. The goal was for YCBI to use discoveries in basic science to shine new light on every facet of cancer biology and then to translate those discoveries into new drugs and treatments across cancer types.

An ambitious blueprint. Six years later, much of it has been realized—but there is still a lot to do. The rapid success is noteworthy, but especially so considering how Dr. Lemmon achieved it. The typical model for starting a large Institute from scratch is to hire renowned senior scientists to provide instant credibility. Dr. Lemmon discarded that model for something riskier. He recruited up-and-comers with unlimited scientific potential and offered them their first labs. "We want to hire people as an investment in the future of cancer research at Yale," he said at the time.

He has invested well, building the institute around young scientists he calls "superstars." He describes the first recruit, Kathryn Ferguson, PhD, Associate Professor of Pharmacology, as "a little bit of a cheat, since she happens to be my wife." Dr. Ferguson, who often collaborates with Dr. Lemmon, studies the detailed molecular mechanisms that regulate signaling, and is particularly well known for her work on how antibody therapeutics like cetuximab act. Dr. Lemmon's next recruit was a physician-scientist straight from a postdoc at Harvard Medical School, Daryl Klein, MD, PhD, Assistant Professor of Pharmacology.

"The four of us—Yossi, myself, Kathryn, and Daryl—are all focused on signaling," said Dr. Lemmon, "which means understanding how a particular subset of proteins on the cell's surface direct cell growth or restrain cell growth. I would say that the four of us make up one of the leading groups in the world in this area."

Dr. Lemmon divided cancer biology into key processes and recruited scientists to start labs in each of those areas. All were young postdocs accepting their first faculty positions. For chromosomes, that was Lilian Kabeche, PhD, Assistant Professor of Molecular Biophysics and Biochemistry and the newest addition to the Institute. "Dr. Kabeche is working to understand how cells respond to errors in their DNA and how the pathways to correct these errors differ in cancer—which can lead to defects in DNA and the genome," said Dr. Lemmon. "She started her lab only six months before the pandemic and is already writing up her lab's first papers."

DNA gets transcribed into RNA, Dr. Lemmon continued, to give the transcriptome, which is the collection of all the RNAs in a cell. "The transcriptome is incredibly complex, and defects in keeping it under control cause cancer—so that's the next aspect to study after the chromosome," said Dr. Lemmon. To explore RNAs and the transcriptome, he recruited Claudio Alarcón, PhD, Assistant Professor of Pharmacology.

The level beyond RNAs involves proteins and the proteome, the complete set of proteins expressed by a cell. In cancer, proteins and the proteome have often gone haywire. "We recruited a world leader in understanding how the whole proteome gets remodeled," said Dr. Lemmon. That scientist is Yansheng Liu, PhD, Assistant Professor of Pharmacology. "He can actually look at every protein in the cell with mass spectrometry techniques, and see how genetic changes have altered the cell's biochemistry."

This brought Dr. Lemmon to what he called "the organism, the animal. There we recruited another superstar, Mandar Muzumdar [MD, Assistant Professor of Genetics, Scientific Director of the Center for Gastrointestinal Cancers at Smilow Cancer Hospital and Yale Cancer Center, and Co-Director of the Pancreas Program]." Dr. Muzumdar creates innovative mouse models to study the development of cancer caused by defects in genetics, signaling, DNA repair, the proteome, and metabolism.

Dr. Lemmon expects to add four or five more labs by 2025 in the areas of metabolism, immunology, chemical biology, epigenetics, and understanding the complex networks mathematically. Each search draws more than 200 applications. "The trick is not just to identify the best people, but to identify terrific scientists who also will mesh well with the Cancer Center's scientific needs," said Dr. Lemmon. "If a sector within the clinical aspects of the Cancer Center gets excited about the candidate's basic research, it's a good fit. Recruitment is a team effort, with input from the director and associate directors of the Cancer Center."

All the basic scientists at the institute work with the clinic in mind. They also collaborate heavily with each other and with other institutes and centers at Yale. "We all know what's going on in everybody's lab at an early stage," said Dr. Lemmon, "and any question you ask will be answered on multiple levels. It works well."

He mentions a few statistics as evidence. In 2021, the Institute's grant money from the National Institutes of Health alone came to $5 million. "That's quite phenomenal," he said. Since the YCBI's inception, members have published about 100 papers, including at least one per year in the prestigious journals *Nature, Science,* and *Cell.* "Given the size of the Institute," said Dr. Lemmon, "that's pretty impressive, because these things don't come along for anyone very often."

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Dr. Klein's recent *Nature* paper described his team's findings about the oncogenic molecule ALK (anaplastic lymphoma kinase), known to drive pediatric neuroblastomas and other tumors of the brain and central nervous system. No one knew what the switchable part of the molecule looked like, or how it worked, so ALK couldn't be targeted. "Trying to solve this part of ALK's structure seemed futile," explained Dr. Klein. "Everyone stayed away from it, because it is mostly glycine."

"When structural biologists see a region of glycines in a protein," said Dr. Klein, "we generally think that it's just floppy and disordered—there's no real structure there, so the regions would never form ordered crystals." He asked an undergrad to try anyway, expecting it to be an instructive exercise in failure.

The undergrad found crystals. After picking up his jaw, Dr. Klein handed the project to a postdoc in his lab, Tongqing Li, who spent five years optimizing the crystals, diffracting X-rays with them using the Institute's X-ray facility, and using math to solve the structure. "All these glycines that we predicted to be disordered are in fact highly ordered," said Dr. Klein. "Very highly ordered. That was the big structural surprise, completely unexpected—and the part that everyone had ignored turned out to contain ALK's 'switch.'"

With the structure now visible, the scientists could see how ALK works. "We have the structure and the blueprint, and we know how ALK is activated," explained Dr. Klein, "so we want to make designer antibodies and have them inhibit ALK exactly the way we want to. We already have some potential candidates." Eventually he expects this approach to be used against pediatric neuroblastoma.

A recent *Nature* paper from the labs of Drs. Lemmon and Ferguson answers a question that has long puzzled researchers: why is it that many lung cancer patients with epidermal growth factor receptor (EGFR) mutations respond well to EGFR inhibitors, yet these drugs don't work at all on glioblastomas with mutations in the same molecule?

Their teams found that the EGFR mutations seen in glioblastomas change the way EGFR signals, rather than simply activating the receptor. EGFR can normally respond differently to its seven distinct ligands. "Remarkably, with the mutations seen in glioblastoma, EGFR can no longer tell which ligand it has been activated by," said Dr. Lemmon. "So, we don't think these mutations drive the cancer per se, but increase the likelihood of it forming by changing the distribution of cell types. That may be why EGF receptor inhibitors don't help—EGFR's role in cancer development may be long past by the time the tumor is seen." Someday, he added, it might be possible to correct these early signaling defects with an antibody-type drug and head off the formation of glioblastoma or other cancers where similar mutations are seen.

Dr. Liu does breakthrough research in mass spectrometry and proteomics. Using proteomics and an Orbitrap Fusion Lumos, the fastest mass spectrometer available, he can define the protein components of the cell, how they change with time, and how they are chemically modified—all with remarkable precision. This gives unprecedented detail on the cell's biochemistry, which is vital for cancer research and future therapeutic design.

One clear indication of his essential expertise is that he is the only member of the YCBI in collaborative projects with everyone in the institute. He is working with Drs. Lemmon and Ferguson to understand signal-related phosphorylation in EGFR. He is working with Dr. Kabeche to identify important phosphorylation sites related to the cell cycle, and with Dr. Alarcón to identify protein phosphorylation events important in controlling RNA modification. He and Dr. Muzumdar are looking at changes in the proteome caused by *KRAS* mutations in a pancreatic cell line. He is also working with Dr. Klein to better understand protein structures.

"I have a strong independent research program, and exciting questions in proteomics that my lab is answering," said Dr. Liu. "But I'm also so happy to embrace the collaborative effort and to do science together with other PIs [principal investigators] because of our mutual scientific interests."

"We're a group of basic scientists and physician-scientists," said Dr. Lemmon, "who are studying the fundamentals of biology with more than half an eye on the clinical applications—so we can understand how to fix it when it has gone wrong in cancer. That sums up the vision and the core mission of the Institute."