

LIFE SCIENCES SNAPSHOT

A Quarterly Report on Financing Trends

**THE FUTURE OF LONGEVITY, CELL
REGENERATION AND SENESCENCE
Q1 2022**


orrick

Data provided by

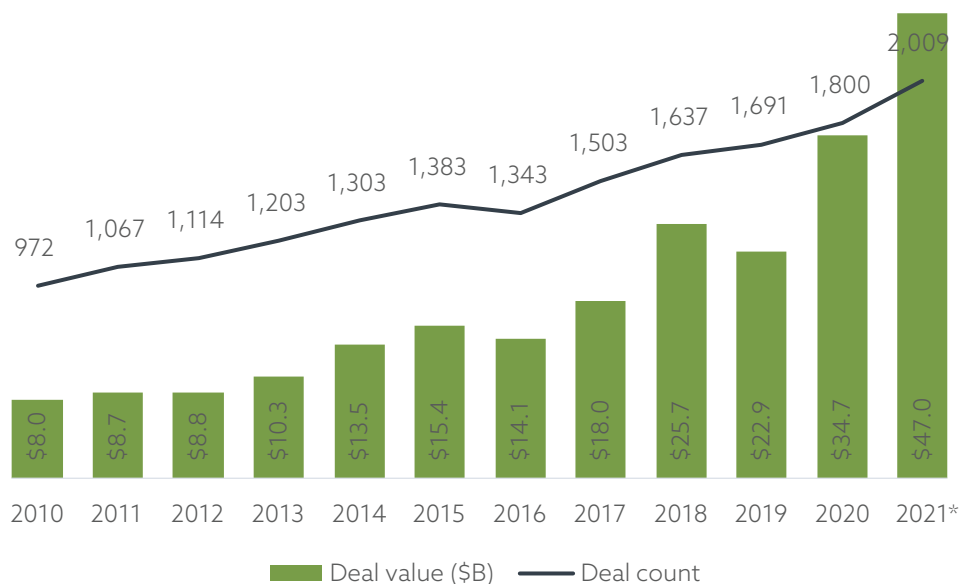
 PitchBook®

Key Takeaways

This edition of Orrick's life sciences publication series breaks down the key drivers of venture investment in the life sciences industry, which saw numerous records set in 2021 across multiple metrics. Key findings include:

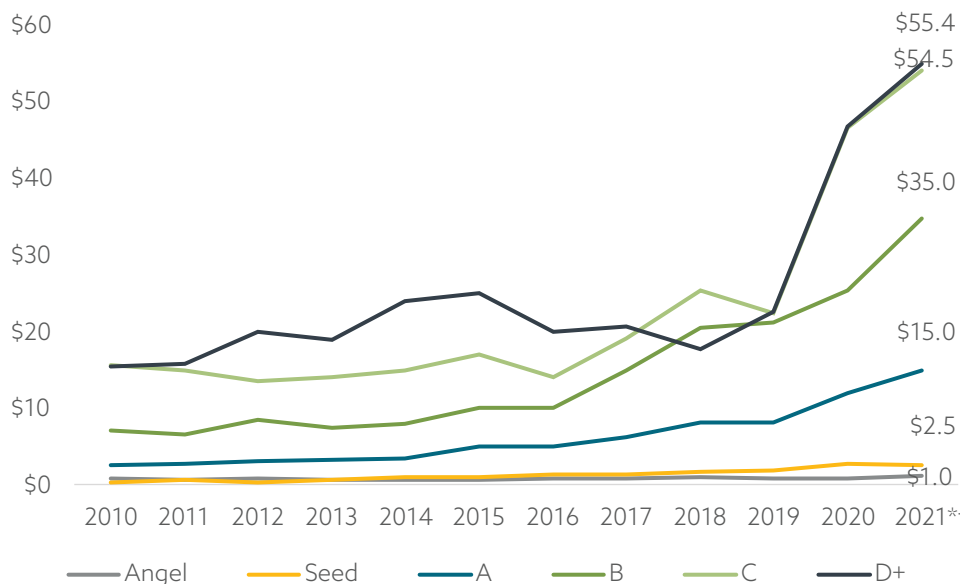
- Even after the record level of investment in the US in life sciences during 2020, 2021 notched even greater heights across both financing volume and value, hitting \$47.0 billion across just over 2,000 completed transactions. While 2020 recorded \$34.7 billion in VC invested, 2021 saw a surge of no less than 35% in value YoY.
- Quarterly trends show that VC activity peaked in the first quarter of 2021, declining over the rest of the year and mirroring activity in the public biotechnology markets.
- Macro drivers of this mammoth swell in activity include record fundraising for even relatively early-stage companies, capital abundance in private markets, ongoing launches of new enterprises capitalizing on newly commercialized technologies, record rises in public equities, and more.
- Liquidity flow for venture-backed life sciences companies, primarily propelled by a record 100+ public listings, hit an all-time high in 2021, supporting record investment rates. Well over \$93 billion was accrued in exit value across 235 completed transactions and debuts.

Life sciences VC deal activity



Source: PitchBook | Geography: US
*As of December 31, 2021

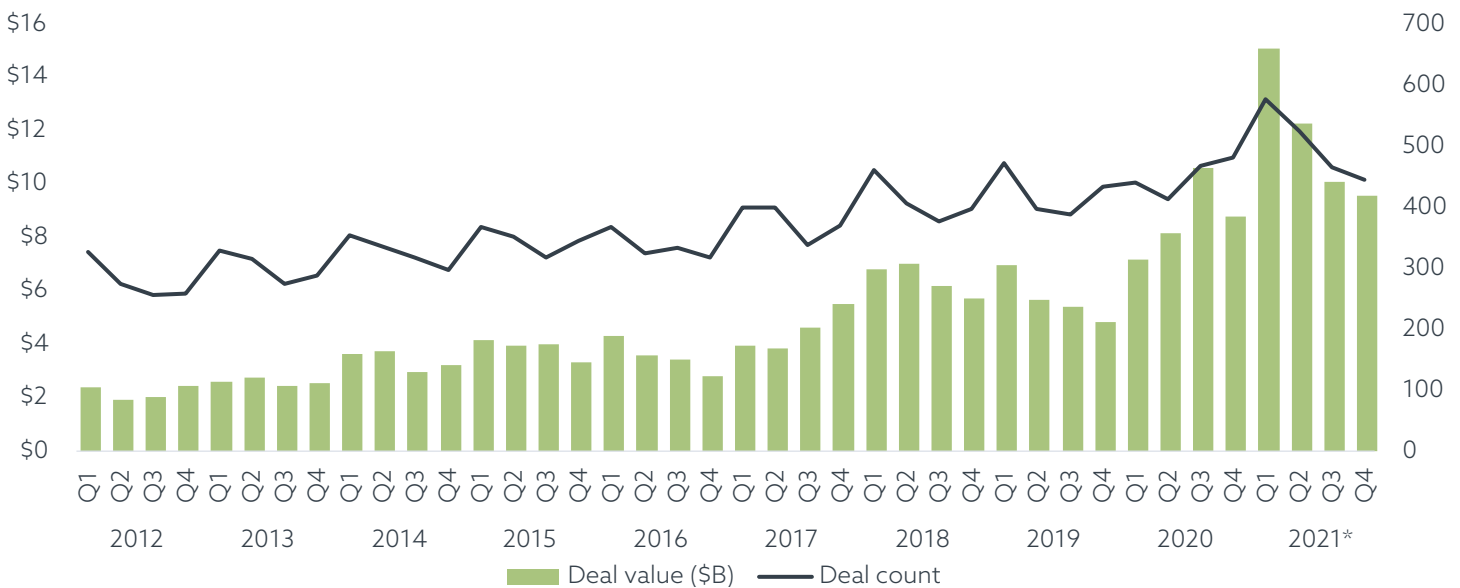
Median life sciences VC deal size (\$M) by series



Source: PitchBook | Geography: US
*As of December 31, 2021

Market Analysis

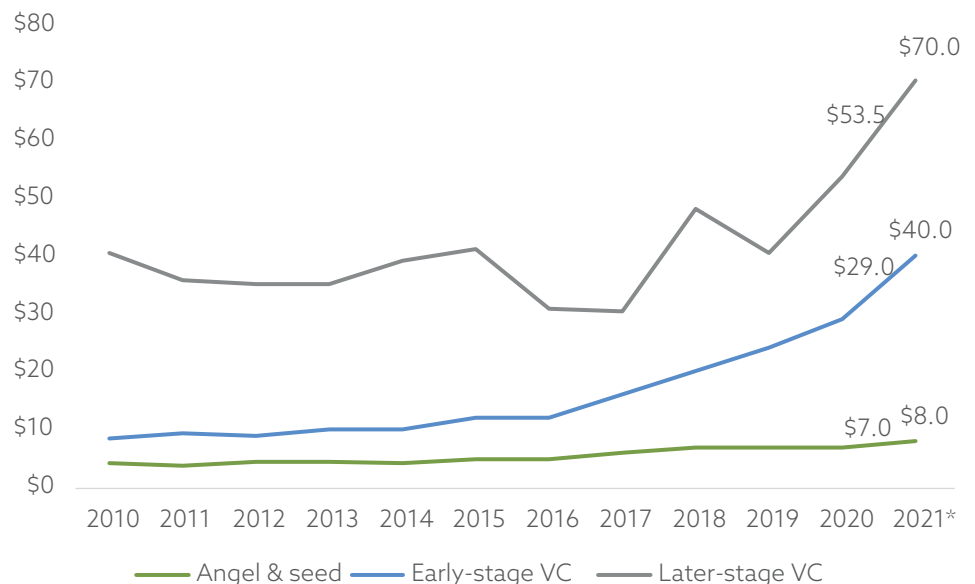
Life sciences VC deal activity by quarter



Source: PitchBook | Geography: US
*As of December 31, 2021

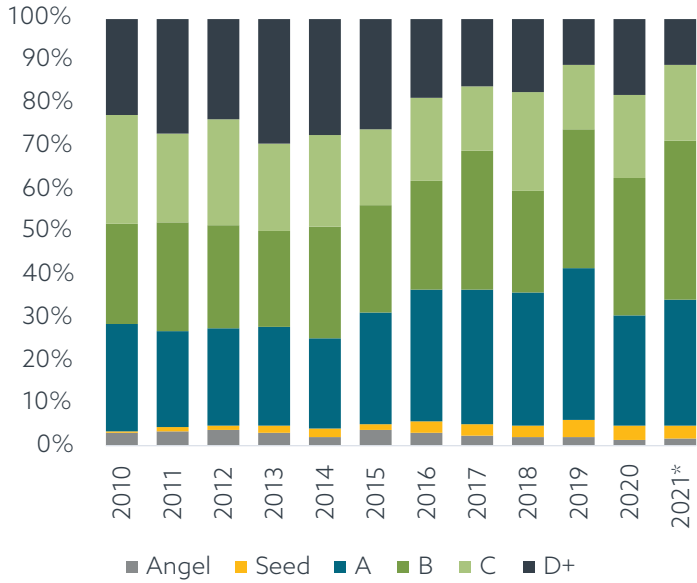
Even after a record-breaking 2020, 2021 set new highs in US life sciences across the board. The supply of capital within private markets helped fuel a pile-on of investors into the space, leading to 2,009 completed transactions for \$47.0 billion in aggregate deal value, with a notable increase in the number of large financing rounds. The median Series B financing hit \$35.0 million in 2021, up from a previous high of \$25.4 million in 2020, and between 2020 and 2021, the median early-stage pre-money valuation leapt from \$29.0 million to \$40.0 million. Investors are taking on considerable risk exposure, betting on the proliferation of technical advances and pandemic-related accelerations in multiple life sciences subsegments such as telehealth, rapid therapy modeling, testing and creation,

Median life sciences pre-money valuations (\$M) by stage



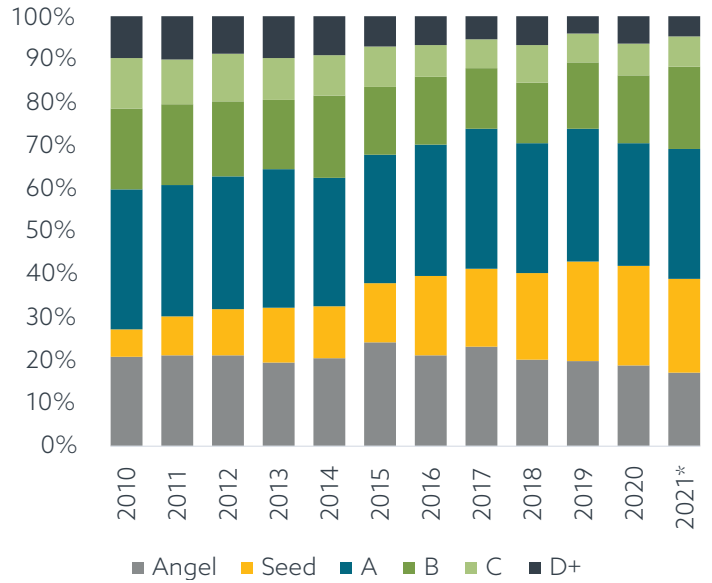
Source: PitchBook | Geography: US
*As of December 31, 2021

Life sciences VC deal value by series



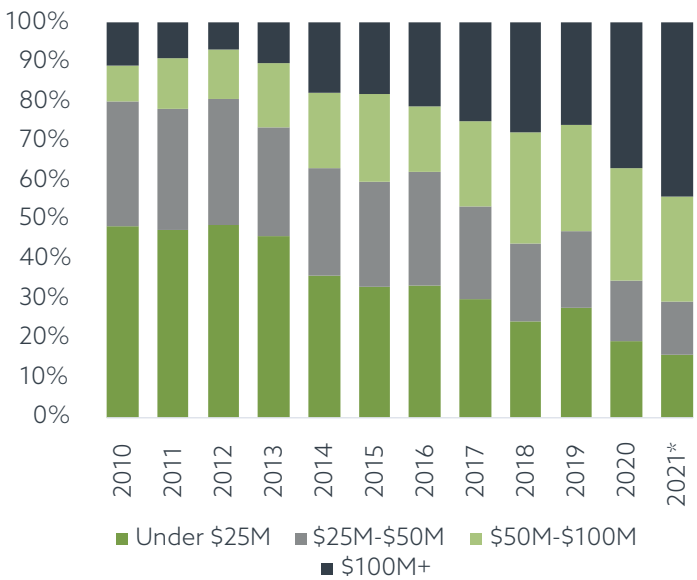
Source: PitchBook | Geography: US
*As of December 31, 2021

Life sciences VC deal count by series



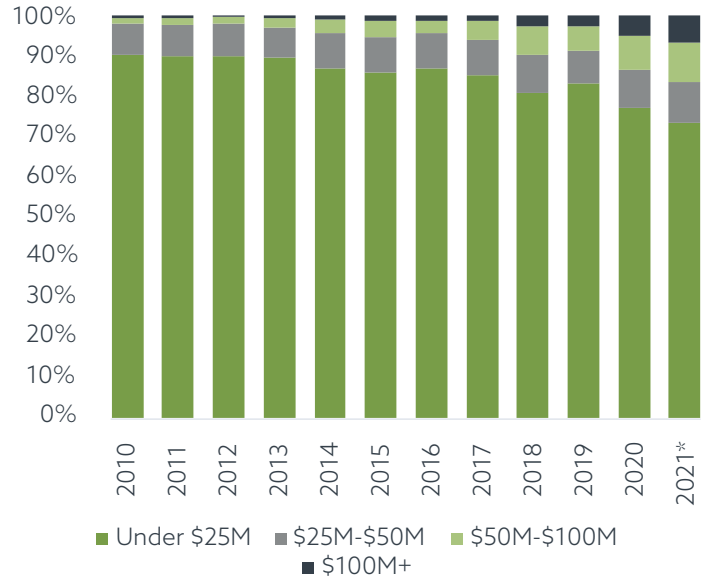
Source: PitchBook | Geography: US
*As of December 31, 2021

Life sciences VC deal value by size



Source: PitchBook | Geography: US
*As of December 31, 2021

Life sciences VC deal count by size



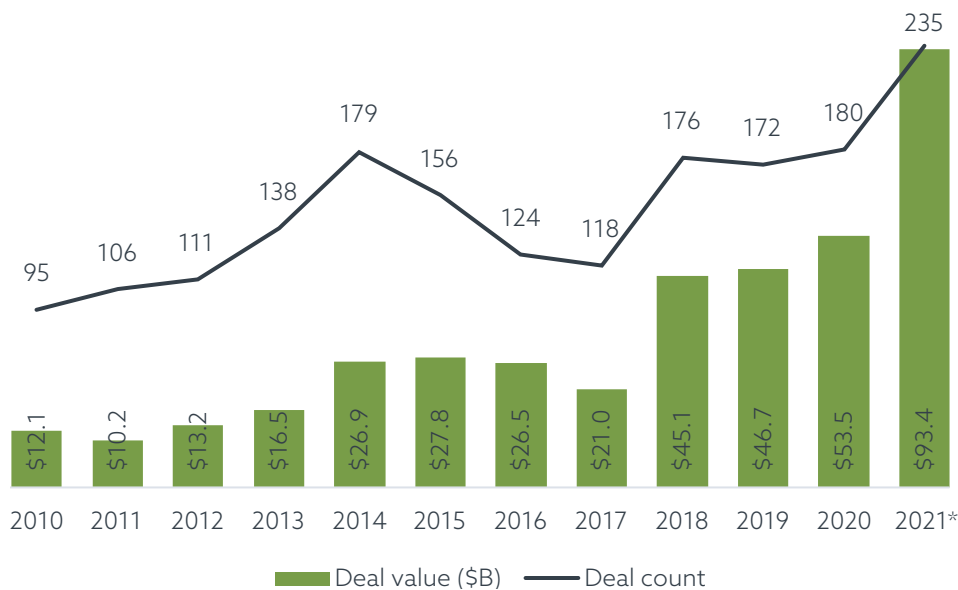
Source: PitchBook | Geography: US
*As of December 31, 2021

Market Analysis

mRNA platforms, and at-home smart diagnostics. There remains considerable bullish sentiment at the intersection of digital transformation and traditional life sciences; the majority of publicly traded enterprises are signaling that they plan to increase spending in that arena even further. However, the level of valuations across all series and declining activity over the course of the year, coupled with declines in the public markets throughout 2021, suggest that private capital raising in 2022 may be more challenging.

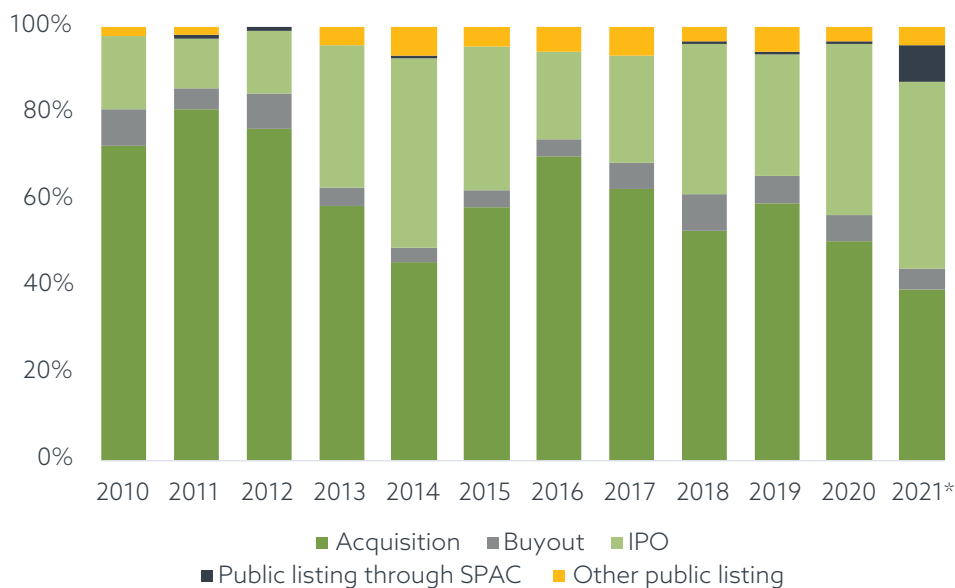
Venture-backed companies seized the opportune market environment across public equities in 2021. Enjoying the backdrop of multiple market indices hitting all-time highs, life sciences companies completed 235 exits for a mammoth total of \$93.4 billion, the bulk of both driven by public listings. 101 traditional IPOs were completed for \$53.9 billion, while 20 SPACs closed on \$18.1 billion. 2021 marked the first time on record that IPO volume outpaced the number of strategic mergers or acquisitions. The slew of debuts continued at that rate despite the Nasdaq Biotechnology Index ending the year flat and over 25% lower than the S&P 500. 2022 to date has experienced significant market turmoil, so 2021's timing may have been ideal for many life sciences businesses to achieve liquidity. In the longer term, we expect the surge of investment and record liquidity will continue to pay off in multiple subsegments within life sciences, fueling maturation of new technologies and platforms across oncology, rapid protein modeling, vaccine development, and more.

Life sciences VC exit activity



Source: PitchBook | Geography: US
*As of December 31, 2021

Life sciences VC exit count by type



Source: PitchBook | Geography: US
*As of December 31, 2021

Roundtable

Panel

Contributors



Kanad Das
Ph.D. Investment
Director at Boehringer
Ingelheim



Stephen Hilbert
CBO of Oisín
Biotechnologies



Matthew Scholz
CEO and co-founder
of Oisín Biotechnologies



David Schulman
Life Sciences Partner,
Orrick



Jay M. Short
Ph.D. Chairman,
CEO and Cofounder
of BioAtla



Hing C. Wong
PhD, Founder
& CEO of HCW
Biologics Inc.



Moderator

Gargi Talukder
Life Sciences Patent
Lead Partner, Orrick

Gargi Talukder: To define our terms, what do we mean by senescence and longevity? And why is this topic getting so much attention right now in both the scientific and investment communities?

Jay Short: We know that aging is caused by many effects—including stress, oxidative damage, telomeres shortening, and so forth; this leads to the creation of senescent cells. Literature from the Mayo Clinic in 2016 observed that senescent

cells, which are cells that are no longer dividing, have terminal growth arrest—but are still living and productive. They end up causing hyperinflammation that accelerates aging. So, senescent cells are a fundamental result of damage that happens through just living. Also, senescent cells are a way that the body protects itself. Some of those cells might have gone on to become tumor cells or caused other types of problems; however, these cells still function. For example, if you

have senescent cells in your heart, you may not want to clear all of those senescent cells that are still able to pump blood. A challenge with removing senescent cells is you want to do it selectively. Some encouraging data we've seen indicates that you don't have to remove every senescent cell to get a good outcome—unlike cancer where we need to remove every last one.

Matthew Scholz: Many people in the field view senescence as the pointy end of the spear when it comes to longevity science. We know that, at least in animals, killing senescent cells confers benefits in lifespan and health span. What's interesting here is that senolytics don't directly drive regeneration, rather they simply remove the brakes, so to speak. They enable the body to regenerate itself more effectively. In any event, this early data has inspired a lot of companies, ours included, to try to use senolytics on known indications with the goal of expanding into health span and longevity from there.

Hing Wong: Senescence is caused by various stress factors. As Jay said, many of these stressors are just part of living and aging. Others are brought about by medical treatments such as radiation and chemotherapy. As we age, our ability to manage all of these stressors declines. The damaging part of senescent cells is that they secrete so-called SASP factors. SASP factors come in many different types, depending on the stressor and the cell type exposed to that stressor. One thing all senescent cells have in common is that they drive chronic, low-grade inflammation. They have ceased to function properly, and the immune system no longer clears them from the body. Longevity and, maybe more importantly, health span—that is, quality of life—is directly diminished by the accumulation of senescent cells. The chronic inflammation it causes is the leading risk factor for most age-related diseases—from cancer to neurodegenerative diseases such as Alzheimer's. If we live many years, senescent cells accumulate and eventually cause harm or death. The world is aging, and investors are attracted to opportunities that

have the potential to address large, unmet medical needs. Senescence and its impact on longevity is such an opportunity. When we are young and our bodies are functioning well, senescent cells grow, do their job, die, and then are cleared by the immune system. Maybe we can learn something from nature: How do we get rid of senescence by rejuvenating our immune system?

Kanad Das: I think this is getting a lot of attention right now in the investment space because aging is a nascent biological field of discovery. There's been a lot of information since CRISPR and the proteomics era, or the -omics era, that we've learned about these types of cells. To invest, I think you have to be able to convince yourself that the manipulation of the target biology you're seeing is causative, not correlative. That seems to be the key question that all of us have when we look at a regeneration company or a senescence company, or any aging organizations. And if you determine it's causative, that's when you consider the indication—and it's an opportunity to do some interesting science along the way.

Gargi Talukder: What are the group's considerations for targets of interest or any other types of interventions that are currently top-of-mind for you?

Jay Short: For our approach, we took into consideration that cancer cells are metabolically different. They're glycolytic, and as a consequence, they're acidic—and, in fact, that's the basis of PET scanning's success in cancer detection; it measures glucose uptake, which is required for glycolysis. The last step of glycolysis is the production of lactic acid, so all cancer cells are acidic. Senescent cells are also glycolytic and therefore also acidic. So you can ask the question: Why are cancer cells glycolytic?

Since they constantly replicate, they are forced to duplicate their lipid membrane, their DNA, certain amino acids, and so forth. All of those precursor molecules for this synthesis are dependent on glycolysis, not oxidative phosphorylation, so they're not necessarily ATP limited—they're glycolytic limited and that results in glycolysis rates that are 50 to 200 times greater, resulting in the secretion of lactic acid at high levels, causing these cells to drop their external pH. Blood is always pH 7.4, and most normal tissues have even higher alkalinity, but cancer cells go from pH 6.7, all the way down to pH 5.8.

We developed a technology (referred to as CABs) that will only attack cells that are acidic on their surface. Key to this approach is our discovery of a new, physiological mechanism. As already noted, senescent cells are acidic and glycolytic, and, importantly, the hyper-inflamed, most damaging ones (SASPs) are the most acidic. But what's also interesting about acidity is that it dampens the immune system. T cells do not like to operate below pH 6.5. What happens is the senescence cells are able to (like cancer cells) battle your immune system. So one question is: Can we induce and keep your immune system strong enough to be able to plow through this resistance, especially if you've already collapsed into a very acidic environment? Targeting acidity yields the important selectivity for our therapies. We published this novel approach for increasing the therapeutic index in PNAS last year, where we described this new physiological mechanism, which we refer to as PACSTM (Protein-associated Chemical Switches™), that allows us to build these selective types of molecules.

Hing Wong: We selected advanced solid tumor cancer for our initial disease indication because of our extensive experience in developing immuno-oncological drugs. We believe cancer is a good indication to demonstrate that we have developed a meaningful drug, especially for use as an adjunct therapy to existing standard-of-care cancer treatments. Chemotherapy and radiation treatments are known to be stressors that put a lot of cells into senescence. If you don't deal with the senescent cancer cells after you hit cancer with chemotherapy or radiation, those cancer cells can become cancer stem cells that may relapse and metastasize. We recently published a paper in *Molecular Therapy* that documents our preclinical studies using our drug as an adjunct therapy to chemotherapy. This work was the basis for the IND we filed to evaluate our drug in advanced chemo-resistant pancreatic cancer. In this article, we showed our drug can activate immune cells, especially NK cells. It is exciting to see that the activated NK cells are able to differentiate between normal cells and senescent cells. I think for proof of principle this is the way to go. We need well-designed clinical trials with well-defined clinical end points, which is possible with cancer indications. Our view is that cancer is a stepping-stone to many other age-related diseases caused by chronic inflammation. Now that we have FDA clearance to proceed with our cancer trials, we will soon begin to generate the clinical data required to prove whether or not we have truly developed a transformational immunotherapy. We believe we have.

Matthew Scholz: Given that our focus is on genetic medicines, we took a very different approach to targeting. Our thesis is that cancerous and senescent cells are different enough transcriptionally from healthy cells that they can be targeted on this

axis alone. The published proof-of-principle studies from the Mayo Clinic and the Buck Institute relied on this same method of targeting. They were killing senescent cells based on their promoter activity. They just lacked the tools to accomplish this in a way that was clinically translatable and had to rely on transgenic animals where the scientists could reliably induce apoptosis selectively in p16-positive cells. While I agree with the other panelists that clearing senescent cells in the context of cancer is valuable, I think that targeting cells genetically allows us to pursue entirely new avenues where traditional therapeutics would be limited by their toxicity. In treating cancer, we have a really high tolerance for toxicity. The standard of care is basically eating poison. However, in the case of longevity, we need to be able to target a few damaged cells in an ocean of healthy cells. This requires a level of precision that isn't possible with chemotherapies. If you think about it, the identity and life cycle of cells are controlled by what genes are read or suppressed. It makes sense to target them in this dimension when they become dysfunctional as well. I believe this is really where the field needs to go.

Gargi Talukder: From the investor side, are you more interested in the overlap between immune and cancer targets, or are there specific focuses in this space for you? Or is the field so new that particular indications are not necessarily of interest?

Kanad Das: It really depends on the fund. Most investors in this space have a sense of the indication they want to go after. I think we might be a little bit different in that we are pretty modality agnostic—we think the fundamental biology will have broad applicability. We're interested in asking, "Is the target causative rather than correlative?" or "Is the target

really going to have an impact on human health?" For example, we saw a couple of days ago that Keytruda has an effect on HIV latency—with having a really high-quality molecule, and once you've shown something clinically, you can do a lot of clinical development. The take-home message is that with an interesting target and a high-quality molecule, a lot of interesting and disparate avenues can be addressed.

Jay Short: We're approaching this like we would cancer, in the sense that we are looking for an indication. We're not target-dependent because we could have a ubiquitous target that's on every cell in the body, but our CAB molecules won't touch the cells that are normal—they will only touch the cells that have that glycolytic metabolism, which is in cancer as well as senescent cells. We just reported on an 80-fold increase in therapeutic index using this approach, so it's an incredibly precise technology. Ultimately, if this works, we don't have to go disease by disease—we can have a more ubiquitous target and potentially address many different types of senescent cells all at once. However, that's not where you start—you have to go after a specific disease, which the FDA will be more likely to embrace.

Matthew Scholz: Our first target is kidney disease. We chose it because the senescent cell burden in the kidneys is not just correlated with disease progression, it is actively driving progression. Targeting the senescent cells is expected to have a direct impact on the disease. I think it is also an indication where body-wide clearance of senescent cells is likely to be more effective than local clearance. In some respects, the Unity osteoarthritis trial was another great example of this. Even their preclinical data showed their therapy didn't provide benefit in old animals.

I think the problem was that they couldn't overcome the systemic SASP by only killing senescent cells locally in the knee. This may be less of an issue in places that are a little more privileged, like the eye and the CNS, but I think that on balance, body-wide senolytics are likely to be more beneficial than tissue-targeted ones, even if you're looking at a specific tissue for disease.

Gargi Talukder: Regarding practical implementation, what are your thoughts on how these types of technologies and interventions might affect healthcare? And how do you think this will be relevant to insurance reimbursement?

Stephen Hilbert: While COVID has been terrible, I think the broad deployment of LNPs to deliver RNA-based vaccines really moved the field forward. It made it possible for companies like ours to move forward more quickly. I think that companies are just beginning to understand the power of these more precise genetic medicines. They can use these technologies to go after targets in senescence or even cancer. It's going to be interesting to see how the landscape opens up. There's also a potential to save trillions of dollars in healthcare costs. I think the regulators are going to become more receptive as the first ones progress through phase 3 and ultimately become drugs.

Matthew Scholz: Reimbursement will come when these treatments outperform the standard of care for any given indication. In the short term, everyone here is basically going down the center of the fairway on indications. We need to hit reasonable end points to get reimbursed via normal mechanisms. In the end, it just comes down to math; I don't think the fact that the therapeutic is a senolytic matters much.

Gargi Talukder: It seems like a lot of the work in this space crosses the line that we often put between autoimmune and cancer. Does this bring up concerns for protecting the work in terms of IP or patent work? And regarding mechanisms of action, have you approached the science differently?

Jay Short: I think we approach it identically. I don't see a difference—we just tune it to the specific system with the same thinking processes, same methodologies, and so forth.

Kanad Das: I agree. We're just interested in whether it's novel and nonobvious.

Gargi Talukder: And regarding biomarkers, how much of that type of metric or assessment is important when thinking about what to invest resources in? Whether it's money, time, brainpower, or certain targets as a biomarker, can you describe how you prioritize—or whether you do at all?

Matthew Scholz: This has been a huge challenge. If you look at even the earlier published in vivo studies, they didn't really have these blood markers. Back then, the known SASP factors were relatively easy to detect in culture, but not in animals. Now you can see some of them in vivo with more sensitive assays. When it comes to specific clinical indications, I think you end up right back in the middle of the fairway. One of the reasons we like kidney disease is that the biomarker is the disease. You can look at GFR and either it's better or it's not. We look at every kind of clock you can think of, every cytokine, every metric we can tease out—but in the end, it's got to come down into things that are traditional and very defensible. After that, we can cast a wide net on research datapoints.

Kanad Das: This is one of the bigger factors that we consider when deciding whether to invest in a regeneration company: whether I can measure something in a mouse, then noninvasively in a person, to then lead to early-stage clinical proof of concept. And then, can I continue to measure that so hopefully that could be an approvable end point.

Hing Wong: We need to pay a lot of attention to so-called SASP factors, even though we sometimes discredit them. We ask: What does a senescent cell damage? Maybe it is due to the paracrine effect of the SASP factors. It's already proven how important particular cytokines are, like the IL1- β and the α chain, because they sit on the top of the food chain. The broad markers, such as SASP factors, have to be playing a part. In order for a biomarker to be an effective diagnostic tool, we need to sort out which ones are more representative and correlative with the accumulation of the senescent cells, as well as their downstream effect. We know that antibodies bind to IL1- β . They are used in the treatment of coronary artery disease, that we know comes from inflammation in the heart caused by activated inflammasomes or senescent cells. There is some hope in the progress being made in identifying additional biomarkers. A recent article in Nature Aging shows two markers that have a strong correlation with longevity. One is VCAM1, and the other one is APO lipoprotein. I believe that by using a noninvasive diagnostic, we will be able to narrow down the patient's ailment that was caused by the accumulation of senescent cells. I think the other thing we have to agree on is that senescent cells alone are not the reason for disease. All of the damage is a result of the activity of the SASP factors secreted by senescent cells. We believe that an effective treatment needs to be

bifunctional: a senolytic that reduces or eliminates senescent cells, that is, the source of SASP factors, as well as a senomorphic that removes SASP factors already secreted by senescent cells.

Gargi Talukder: Regarding timing, how long do you think it will be before we start seeing therapeutic and diagnostic results in this space? And what are your expectations for returns on investments?

Stephen Hilbert: We are moving several programs forward preclinically. Of course, a lot of the timing is dependent on funding, but the timelines of the big pharmaceutical companies and the time required to negotiate with them also play a big role. Companies like ours need to move their programs into the clinic and generate positive efficacy data as quickly as they can. Pharmaceutical companies have their own specific ideas about where they'd like to take the technology. Working with them tends to take longer, but collaborating with them can be a good way to secure funding. I think that, assuming the data is good, we'll start to see data from treatments for cancer and CNS applications within a few years and have access to new drugs within five years. The nice thing about these kinds of therapeutics is you can get efficacy data much more quickly; it's like software programming using DNA and RNA for the body. I think we'll see a faster turnaround than we have for traditional small molecules in the past.

Matthew Scholz: I think we'd be remiss not to mention that the Mayo Clinic has a bunch of senolytic trials going on right now, with Dasatinib and Quercetin (D+Q). Data should be coming out on the scale of months to a couple of years from now. The big question is: How will these studies shake out? If they show some benefit, I think it will help propel the

broader field and be a boon for the more purpose-built, next-generation senolytics. On the other hand, if a bunch of these early studies don't show benefit, then I think the space is going to have to evaluate why they didn't work. In any event, despite their limitations, these D+Q studies are going to be generating data for the field to scrutinize in the coming months.

Jay Short: In our senescent work, we're about two years from the clinic. We're building the drugs now, but it's an antibody, so manufacturing and the IND-enabling work typically takes 18 to 21 months. But also, of course, because many of the challenges we're discussing today are related to chronic diseases, these antibodies may have to complete phase 3 without an opportunity for early conditional approval. In fact, the vast majority of therapies in this space must demonstrate safety and go through the typical regulatory process, so they'll take longer than many cancer therapies to hit the market. It's just the nature of the beast.

Gargi Talukder: What trends are you seeing with VC investment trends in this space?

Kanad Das: Novel genetic and -omics technologies seem to be a low-hanging fruit. A lot of VCs will think about this in terms of where they can get an exit, and that is with a very clearly defined biomarker or early clinical development for early companies. Some VCs, with either evergreen funds or earlier in their fund cycle, will think farther out in terms of how much they can take a risk in time. But, in general, there is much more interest in senescent technologies and regenerative technologies as time goes on and as the biology gets richer and the preclinical and clinical development cuts get worked out. I admire my co-panelists for going down that road. I agree that we'll

learn a lot from what they're doing, but I don't think those clinical trials will necessarily translate that well to the approaches that you guys have described today. But our business is risk. We're very comfortable with risk, and so those of us with evergreen funds... we're going to be in this space for a long period of time.

David Schulman: I used to see more build-to-buy deals in this field. Is that something that you see pharmaceuticals or leaders in this space open to doing now—as a strategic partnership?

Kanad Das: We don't do those types of deals—we don't take any rights, there are no strings attached. Generally, pharmaceutical companies or pharmaceutical venture arms are more likely to do a build-to-buy, but venture funds typically aren't. I think build-to-buys may become more popular if it gets harder for preclinical companies or companies that are in clinical data to access public markets. I have noticed that when there's been a corporate venture in an early-stage syndicate, companies have typically been a little more successful. And that could either be due to just the money that went in or the access to expertise.

David Schulman: A lot of the dialogue I've heard around longevity research seems to take the tone of a lifestyle approach. How do you see that affecting development of and access to these technologies?

Matthew Scholz: Definitely, there are people lining up for this kind of stuff—I'd even say many who are wanting to try these interventions long before I'd think it's a good idea! There will always be early adopters. As with anything, if you have a lot of money, you might not want to wait a decade for something just to save a few bucks.

Kanad Das: Regarding these trials... the biomarker strategy, the readout strategy and the end points will be the things that determine on-target use, but off-label use—I think this will be large once these come out. I tend to agree that if this is a daily pill, if it's safe, and if it doesn't cause negative side effects, a lot of people will want to take it.

Matthew Scholz: As a final point, I'll add that I see senolytics as just the tip of the iceberg for addressing aging. Although they're what we've focused on today, they're just the lowest-hanging fruit in a broader campaign to intervene in human aging. I think the Holy Grail is figuring out how to regenerate tissue in situ. If you look at any of these projects, they all have their own constellations of troubles and opportunities on the regulatory and the commercialization side of things. If you can build treatments that work, there's virtually unlimited upside, but even assuming they work, there are still huge challenges showing that they work in a time frame that your patent life will cover.

Jay Short: Overall, I'm optimistic that what we're finding from our clinical work in cancer and our current research—in building one universal target that's on all cells but allowing the metabolic or acidity make that cell-killing selection—can have a similar result in senescence. It's a grand hypothesis, and we're also doing some very targeted ones, because you always hedge your

bets, but the potential is exciting and the tools are there now. I think the precision genetics approach also mirrors some of these aspects as well, and even with the immune system—I think they all have great promise.

Stephen Hilbert: When we started working on these projects, the technology felt so far off, but it's all happening right now. The clinical trials are happening, and we're on the cusp of a shift in the healthcare space. The key here, I think, is that early adopters will be rewarded—and pharmaceutical companies are beginning to understand that what we're discussing today will have a huge impact on what they could do in the future. I think that will start the shift in the next year or two. The regulatory issues that may be roadblocks now will fall away.

CREATORS. VISIONARIES. UNDERDOGS. THE RISK TAKERS.

We help you disrupt. We help you grow.
We protect you. We help you win.

Top 4 VC Firm Globally

— *PitchBook*, 2021, top 5 for 17 quarters in a row

Most Innovative Law Firm in North America

— *Financial Times*, 2021

#1 Most Active VC Law Firm in Europe

— *PitchBook*, 23 quarters in a row

CONTACT US

Ed Dyson

Partner
edyson@orrick.com

Gregg Griner

Partner
ggriner@orrick.com

Blake Ilstrup

Partner
bilstrup@orrick.com

Scott Iyama

Partner
siyama@orrick.com

Neel Lilani

Global Head, Tech Clients
nlilani@orrick.com

Ed Lukins

Partner
elukins@orrick.com

Jörg Ritter

Partner
jritter@orrick.com

David Schulman

Partner
dschulman@orrick.com

Shana Solomon

Partner
shana.solomon@orrick.com

Gargi Talukder

Partner
gtalukder@orrick.com

Stephen Thau

Partner
sthau@orrick.com

Albert Vanderlaan

Partner
avanderlaan@orrick.com