

Biomarker Rising Stars 2023

5AM - Max Farina (MF)

a16z - Ben Portney (Ben P) + Becky Pferdehirt (Becky P)

Bessemer - Morgan Cheatham (MC), Sofia Guerra (SG)

F-Prime - Ana Sybirna (AS) + Siyu Shi (SS)

Frazier – Joe Cabral (JC)

Insight - Aiden Aceves (AA)

KdT - Ketan Yerneni (KY) and Patrick Malone (PM)

Lux - Shaquille Vayda (SV)

MPM – Devin Quinlan (DQ)

OMX Ventures - Jamie Kasuboski (JK)

Orbimed - Seth Cassel (SC)

Pillar - Tony Kulesa (TK) + Thomas de Vlaam (TDV)

RiverVest – Pascal Krotee (PK)

Sofinnova—Regina Salvat (RS)

TRV - Vyas Ramanan (VR)

Venrock - Eliot Coffey (EC)

Vida Ventures - Mark Springel (MS) and Jill Goldstein (JG)

Questions (all responses):

1. One of your favorite science papers you have read in the past year? What excites you about this work, or the area more broadly?

Ben P, a16z: One of my favorite papers was an effort led by Dan Nomura's group from UC Berkeley. The targeted protein degradation field is very exciting because it will enable us to target historically hard to drug proteins. Typically, heterobifunctional small molecule degraders, like PROTACs, have been engineerable but don't have the most ideal drug properties. Meanwhile, molecular glues have great drug properties but have historically been challenging to engineer or design rationally. Leveraging their chemoproteomic platform, the Nomura group takes a big step toward rational design of molecular glues. In my opinion, this is just one example demonstrating the inflection point the field of chemical biology currently is at.

MC, Bessemer: I keep coming back to a DeepMind paper published in December 2021 titled, "Ethical and social risks of harm from Language Models." I'm particularly excited about generative technology's potential in life sciences and healthcare from the molecular to the systems level; however, as with any new, transformative technology, we must work diligently and across disciplines to understand and address ethical and social risks early in our exploration. This paper expanded my understanding of the risks of generative technology, and specifically, how large language models can create new privacy and security risks for sensitive data such as protected health information.

AS, F-Prime: I'd like to highlight "Virus exposure and neurodegenerative disease risk across national biobanks". Using large longitudinal datasets, the authors identified and validated over 20 viral exposures associated with increased risk of neurodegenerative disease, including between viral encephalitis and Alzheimer's disease. A potential link between viral infections and neurodegeneration has been a matter of debate for years, and it is good to see larger time series being deployed to address this. If further validated, the implications of this work could be transformative, given that vaccines are available for some of the relevant viruses (influenza, shingles, etc.). It would take a long time to test the results prospectively, but the emerging data shouldn't be ignored by the decision-makers behind population-wide vaccination strategies. The insights could also be informative to design better therapeutics. An example of this would be another brilliant paper – "Clonally expanded B cells in multiple sclerosis bind EBV EBNA1 and GlialCAM" led by Larry Steinman and William Robinson. It demonstrates that autoantibodies underlying multiple sclerosis (MS) pathology result from molecular mimicry between Epstein Barr-virus (EBV) protein EBNA1 and human CNS protein GlialCAM. Beyond EBV vaccination, the study provides a mechanistic basis to design tolerizing therapeutics (e.g., a reverse vaccine) for MS patients who had already developed EBNA1/GlialCAM cross-reactivity.

SS, F-Prime: I am not sure if this paper is "exciting" per se, but it provides a very interesting view in contrast with many of the voices we hear admiring scientific advances.

JC, Frazier: Still waiting on the full data release - but the Ph 2b update on MRNA-4157/V940 (personalized neoantigen vaccine in combination w/ pembrolizumab) in Stage III/IV melanoma was super exciting to me for reasons both personal and scientific. On the scientific side, this was (in my opinion) the first clearly interpretable clinical proof of concept that demonstrated the additive efficacy of a personalized neoantigen vaccine on top of checkpoint inhibition. On the

personal side, I got to spend some time working on this program in the early days – and it is always exciting to see a product you worked on make an impact for patients.

KY, KdT: I was excited by this article from Venkataramani *et al.* (2022), Glioblastoma hijacks neuronal mechanisms for brain invasion. Glioblastomas are common, deadly, and largely incurable brain cancers that spread throughout the central nervous system. Glioblastoma is known to be highly invasive, heterogenous, and adaptable; these traits have allowed it to essentially elude most therapies, with the most advanced efforts over several decades being futile. Even with extensive surgery, survival remains abysmal. I will never forget my first time seeing glioblastoma during a craniotomy – it was almost like an invisible grenade had exploded within the patient’s head, with shrapnel diffusively infiltrating all nearby regions, and almost no distinction between normal and cancerous tissue. In this paper, the authors use a series of cutting-edge techniques to resolve how malignant gliomas invade neuronal circuits akin to parasites. They demonstrate that unique glioblastoma cell populations form different types of intercellular connections with native neural cells in the cancer microenvironment (via tumor microtubes), integrate into the said neural network, and influence interconnectivity. There is far more detail in the paper than I could describe here, and I am certainly not doing it justice. I’m just excited that we are slowly and surely elucidating the mechanisms of glioblastoma pathogenesis with the hope that, over time, we get closer to a cure. This paper adds to this emerging body of work surrounding glioma-neuron synaptic dynamics, and I’d like to point out a few other landmark pieces that are great reads:

- Venkatesh *et al.* (2019): Electrical and synaptic integration of glioma into neural circuits
- Zeng *et al.* (2019): Synaptic proximity enables NMDAR signalling to promote brain metastasis

PM, KdT: An area I followed closely in 2022 was the application of a new class of generative algorithms called diffusion models to protein engineering. I’ll highlight one paper in particular from David Baker’s lab that combined structure prediction networks and diffusion models to successfully perform de novo protein binder design. To me, the most exciting finding from this paper was how few proteins needed to be synthesized in the lab to validate in silico predictions. The synthesis of only a couple dozen of proteins were required to validate the computational designs, whereas previous methods required testing tens of thousands of proteins. How far can we push these models? Will the accuracy of generative algorithms improve to the point where very little or even no wet lab validation is required? I fundamentally believe in the importance of the wet lab, and that we will always predict in silico in silico and validate in vitro/vivo. But I am always re-evaluating my assumptions. Strong opinions, loosely held...

SV, Lux: At this point it feels as though most of society has heard about the promise of “CRISPR editing” and how we now have the tools to edit out “problematic DNA” to treat disease. But most diseases are complex, and it may not be enough to change the genetic code to treat every disease. Epigenetic editing is an expansion of that toolkit, and it allows us to dial the individual expression of genes up or down as needed. We now have a tool to adjust the metaphorical volume knobs and make them louder/softer as needed. This paper, first published in *Science*, offers an example of this can have real-world applicability. Previous research has shown that binge drinking during adolescent years alters brain chemistry in the amygdala and decreases expression of the ARC gene. Well scientists were able to modify the expression of Arc in rats and restore it back to baseline levels. Epigenetic editors will be a tremendously valuable tool in the molecular toolkit.

DQ, MPM: One of my favorites was the NEJM paper that came out this year on trastuzumab deruxtecan (ENHERTU®) in HER2-low breast cancer (DESTINY-Breast04 trial). Enhertu had an objective response rate of 52.6% vs. physician's choice chemo which was only 16.3%, and led to substantial improvements in overall survival and progression-free survival. These tumors had previously been considered HER2-negative, and Enhertu is the first ever HER2-targeted therapy to become an option for these patients. Enhertu is the result of decades of iteration on the concept of antibody drug conjugates (ADCs), which for a long time had struggled to achieve broad success given the dose-limiting toxicities. And while there is still plenty of room to improve, it's a great example of thoughtful and iterative engineering finally breaking through to make a real difference for patients. Link to article: <https://www.nejm.org/doi/full/10.1056/NEJMoa2203690>

JK, OMX: My two favorite papers are just cool and from my funds "shower thoughts" slack channel. They are cool from the "man nature is far weirder than we can imagine" point of view verse "a company can be spun out of this right now point of view".

- <https://www.nature.com/articles/s41586-022-05499-y>
 - It's just a wild paper that I am sure that Flagship will try to spin up a company.
- <https://www.nature.com/articles/s41586-022-05016-1>
 - This really tests our idea of death and its permanence.

TDV, Pillar: There was a [paper](#) from the Zon lab about how macrophages "groom" or "doom" HSCs once they leave the bone marrow niche and if they are "groomed" they are allowed to differentiate and if they are "doomed" they get eaten by the macrophage.

TK, Pillar: I like to read the history of major therapeutic advances, focusing on all the steps of discovery and engineering and how they might have been accelerated/expanded with new technologies that are coming online. A recent subject of my study was the history of GLP-1 agonists, highly recommended reads [1] and [2]. It's interesting to read these papers and think about how these therapeutics would have been developed with access to more modern cryo-EM, structure based design, yeast/mRNA display, high throughput peptide sequencing, et cetera; and what else these methods will enable now! Those also led me to discover this beautiful history of GPCRs from Nobel Laureate Robert Lefkowitz [3]. The Lefkowitz paper gives the following amazing context (emphasis mine): "However, even into the 1970s the receptors themselves remained elusive. **In fact, a considerable body of opinion held that receptors, as we now understand them, did not exist as discrete molecular entities.**" The paper gives a beautiful explanation of the key experiments that led to the whole field of GPCR biology. I find it inspiring to think about what new biological phenomena we will discover as new methods continue to develop!

VR, TRV: This [paper](#) is a nice way to use our understanding of the cell biology of CRL function to drive improved glue hit discovery; historically intractable but would be high value.

EC, Venrock: My favorite (and the craziest) paper I've read in the last year was "Development of Ectopic Livers by Hepatocyte Transplantation Into Swine Lymph Nodes" (PMID 32810371). Using a swine model, Fontes and colleagues isolate autologous hepatocytes and inject the cells into mesenteric lymph nodes. In the lymph nodes the hepatocytes organize into defined tissue

structures resembling real livers – and unbelievably these “mini-livers” alleviate induced liver failure in the swine model. I love this paper because it makes regenerative medicine feel possible if we’re creative enough.

MS, Vida: My favorite science paper from the last year came from David Baker’s group at University of Washington / Institute for Protein Design, titled ‘Design of protein-binding proteins from the target structure alone’ ([Cao et al., Nature 2022](#)). The authors describe a technique for efficient de novo design of miniprotein binders against diverse molecular targets. This paper was particularly notable because it was the first description of an approach to generate sub-nM affinity binders, in a highly reproducible manner leveraging computational design, without the need for iterative wet-lab screening and optimization. High-affinity minibinders generated with this approach can have meaningful therapeutic advantages over traditional antibodies, and it will be exciting to follow how the technology continues to evolve as computational methods for protein design become increasingly more sophisticated.

2. Briefly, how would you describe what you do and why you love it, to a high school student?

MF, 5AM: In the simplest sense, an early-stage biotech investor helps researchers turn their scientific ideas into new medicines for patients. The process of making a new medicine is long, complicated, and expensive, and an investor provides the money and advice to navigate that process successfully. There’s a lot to love about this job: variety, constant learning, and the privilege of partnering with some of the smartest people in the world. But the best part of all might be the undeniable sense of positive human impact that is core to this industry. When we’re successful, patients get new medicines that can cure them of disease, let them live longer, or improve their quality of life.

Ben P, a16z: I am a biologist who focuses on developing new medicines for patients. My job is to understand how changes in biology lead to disease and use my knowledge to design creative solutions that come in the form of medicines. When there is a solution proposed, a company is started to test if the solution works and to create the medicine. Sometimes I help build the company and other times I help support the builders of the company by investing money in it. I love this job because I get to think creatively about science every day, all with the goal of helping cure patients of disease.

Becky P, a16z: In the simplest of terms, my job is to find the most promising, exciting new scientific innovations, and then help that science develop into a useful product by providing both funding and non-financial support. I love my job because I get to learn something every day and work with the most smart, creative, driven, kind people.

MC, Bessemer: I partner with extraordinary people who have visions of transforming healthcare and life sciences via novel technology by providing capital, connections, camaraderie, and counsel. My mission is to leverage venture capital and my biomedical expertise as tools for driving positive change in healthcare and life sciences that improves patient care, access, and outcomes, advances the clinician and scientist experience, and bolsters the efficiency, safety, and efficacy of the system at scale.

SG, Bessemer: I get to go along for a ride with the most incredible entrepreneurs that are looking to make the world a better place and at scale.

AS, F-Prime: I find and review novel science that can help design new treatments for diseases with high unmet need. If a company's founding team and science are strong, and there is a promise for a transformative impact on patients' lives, we invest capital to support the company's growth and product development. Beyond investment, we work closely with the management to provide strategic and operational support (R&D and clinical development strategy, hiring, business development, etc.). I love my job because I meet brilliant scientists, entrepreneurs and industry experts, learn about the most innovative discoveries before they become mainstream, and get to indirectly contribute to discovery and development of next-generation medicines.

SS, F-Prime: I meet people and companies and try to predict whether they will be successful in what they say they will do.

JC, Frazier: I try to identify things that have the potential to be new medicines for patients and help fund the development and testing of those things so doctors can one day prescribe them. If I do it well, patients will benefit from access to new medicines that will improve their quality of life, and we get paid back for the role we helped play in funding the development of the medicine. I love it because I am always learning, I get to work with really smart people, and every opportunity is like a new and unique puzzle that you have to try and solve.

AA, Insight: Find, qualify and execute on investments in biotech companies! Does that sound amorphous? It is! Being a biotech investor requires constant creativity in how you find and execute deals, which is never boring. Once the deal is made, our roles morph to being closer to those of operators, and we get to spend considerable time digesting cutting-edge data and thinking about the key decisions that each business makes.

KY, KdT: As a biotech venture capitalist, I partner with and support people who want to use cutting-edge science and technology to change the world – whether through healthcare, agriculture, sustainability, and beyond. Roughly speaking, I spend my time across three main responsibilities:

1. Meeting physicians, scientists, and entrepreneurs who want to commercialize their early-stage science.
2. Assessing those opportunities from a scientific, business, and market standpoint (this is called *due diligence*).
3. Supporting those entrepreneurs that we've partnered with – whether serving on their board, company building, recruiting talent, business strategy, enabling key relationships, and beyond.

Venture is exciting as I undoubtedly enjoy the science – being at the cutting-edge of biotechnology is intellectually stimulating, and I have the opportunity to help move an entire space forward. By far and above, however, my favorite part of the job is helping people – who are much smarter than myself – realize their vision for what the world should be. Every single day, I have the privilege of meeting people who are experts in their given field, and I get to learn from them, help them succeed, and play a very small role in changing the world for the better. Coming from medicine, I view my role in venture analogous to that of a physician-scientist;

venture is my vehicle to bridge the gap between the scientific and clinical realms and expand my impact beyond one-on-one patient care.

PM, KdT: As science-driven venture capitalists, we invest in science fair projects and help build them into big businesses and companies. We have a front row seat to the future, and get to spend our days working with the smartest scientists and founders in the world.

SV, Lux: As an investor, I get to spend my days reading and formulating an informed view on where the world currently is and where it may go as a result. I then am tasked with translating that viewpoint into understanding where economic value may result and whether or not a specific team/company will be the beneficiaries of that value. There is nothing more fulfilling to me than being able to partner with world's most-brilliant inventors who are looking to push the boundary of human understanding and help enable them to succeed. In addition to investing our capital behind these entrepreneurs, we look to provide guidance and partner with them, where we ultimately hope to get a positive sum return on that investment for all!

DQ, MPM: As part of the MPM team I get to help shape the future of medicine. We work with top academic scientists and drug developers to create and support companies that have the potential to make breakthrough products for patients. It's exciting, humbling, rewarding – and I'm grateful to be a part of it.

JK, OMX: I take science fiction and make it science reality. I try to make ideas like Jurassic park non-fiction. Specifically, I find the most innovative research and help build great companies around them focused on making new drugs to impacts patients' lives.

SC, Orbimed: I have the opportunity to learn about emerging biotech companies and try to understand which ones are best poised to change the standard of care in medicine. It's humbling and exciting to see the breadth of diseases being addressed by biotech companies and get to know extraordinarily talented management teams. I also feel fortunate to be part of a fantastic team at OrbiMed, learning from others who have decades of experience in biotech investing.

TDV, Pillar: I find people who are trying to build companies that use science to change the world and help them build those companies through advice, support, and investment. Basically my job is to talk to the smartest people in the world about the thing they are most excited about. It's awesome.

TK, Pillar: Many of society's most important problems are biological – preventing and treating disease, improving the health of our planet, and living sustainably. At the same time, biology is undergoing a technological revolution. We are learning to engineer the DNA, RNA, proteins, cells, tissues, and organisms that make up ourselves and our planet. Our job is to help catalyze these scientific breakthroughs and inventions to impact the problems in our society. More practically, I view venture as two engineering questions: how do we – at scale – identify and develop (a) scientific breakthroughs and (b) talent? I enjoy working on both the micro-level questions like how we use new software or AI tools to identify science and talent, as well as the macro-level level funding/incentive design (e.g. scientific institutions, venture funding and non-profit models).

PK, RiverVest: I support new investments into up and coming biotech and pharma companies that work to make impactful medicines for patients. Once we make the investment, we work closely with those companies to make sure they can achieve their goals. By doing so, we are able to make money for our investors, which we call limited partners. I love it for so many reasons, but above all, it's about the impact of the work we do. The job also lets me explore a vast array of therapeutic areas and I love that I learn so much everyday.

RS, Sofinnova: It's like Shark Tank, only you spend 6 weeks+ evaluating an opportunity by reading through a company's data room, interviewing KOLs, hiring consultants, etc, rather than just offering a company capital after an initial pitch (as seen on TV).

VR, TRV: As a part of TRV, I get to help build companies that advance important medicines to treat difficult diseases, often working closely with academic scientists.

EC, Venrock: At Venrock we invest early – often when companies are barely more than ideas. Because of this, I get to collaborate with some of the smartest and most courageous people in the scientific community. My favorite part of this job is learning from and with these amazing folks.

MS, Vida: I find and support exceptional scientists who have figured out creative ways to make new and improved medicines. My job is to give those scientists a leg up by helping provide them with financial, human, and strategic resources so that they can focus on developing new drugs and improving outcomes for patients. It's the best job because I get to work with brilliant, mission-oriented people who truly care about the impact of their work on our understanding of human disease (and how to treat it).

3. How did you get involved in venture? What drew you in? What initial misconceptions did you have about biotech venture investing or creation?

MF 5AM: I first heard about VC in med school when an investor from Canaan gave a talk about her role and how venture firms function in the biotech ecosystem. After graduating, I spent a couple of years in investment banking, and while I really enjoyed the variety and excitement of that job, I found myself wanting to spend more time thinking about the fundamental science behind innovative biotech companies. Early-stage venture capital seemed like the perfect fusion of my interests, so I joined 5AM, which had a reputation for being both scientifically rigorous and relationship-driven. My biggest misconception was that almost all of an investor's time is spent on sourcing and diligence. While that is true at many VCs, I've found that for early-stage investors writing large checks, deal closing is just the beginning of the relationship with the company. Holding board seats, advising the company, and providing appropriate support to management takes a lot of time if done right. And as it turns out, being a true partner to portfolio companies is one of the most rewarding parts of the role.

Ben P a16z: I initially became involved in venture through entrepreneurship. I had lots of new therapeutic ideas in grad school and eventually started a company – which quickly failed. Afterwards, I realized I wanted a job where I could learn how to start a company that wouldn't fail. This led me to venture creation and ultimately venture capital. Ironically, I held the misconception that if I learned the best ways to create and invest in companies that I wouldn't

fail again. What I actually learned is that even the best company ideas, teams, and plans can fail, and that is okay if you learn for the next opportunity.

Beck P, a16z: I first dipped my toes into venture when I was in the business development team at Amgen. Often times biopharma business development and corporate venture teams work closely together to identify and assess companies, as there can be significant overlap in areas of strategic interest. I found early-stage venture compelling because of the ability to directly contribute to the advancement of high risk, high reward science across a wide variety of areas. I wanted to work more closely with founders and have a meaningful impact by helping them build successful biotech businesses. While I had heard from several people that venture can be a lonely job with cut-throat competition even within firms, this couldn't be further from what I have experienced at a16z Bio+Health. It has been the most collaborative, team-centric work environment I have ever had!

MC, Bessemer: I fell in love with healthcare technology when I was 15 years old while shadowing in the Anesthesiology department at INOVA Alexandria with my mentor, Dr. Brent Lee. At the time, INOVA was transitioning from paper to the Epic electronic health record, and I marveled at both the beauty and chaos of this foundational paradigm shift as it unraveled before my eyes. Soon there after, I found myself exploring early "SMART on FHIR" documentation and Meaningful Use guidelines and never looked back. In college, I gained exposure to the healthcare and life sciences industries across several axes by working in an optogenetics neuroscience lab, interning as a data scientist at Kyruus (a healthcare startup ecosystem focused on patient access), interning at Rhode Island's Health Information Exchange, and interning as a Healthcare Investment Banking Analyst at Goldman Sachs. Recognizing that software and artificial intelligence would serve as unique vectors for operationalizing and scaling clinical and scientific expertise, this became my north star. Instead of matriculating into medical school after undergrad, I took a deferral to pursue these passions full-time, and after bumping into a Partner at Bessemer visiting Brown's campus, asked if they were hiring. A few weeks later, I was fortunate to land a role as an Analyst in our NYC office where I'd spend my first two years "getting reps in" by speaking with and diligencing thousands of companies. I don't know that I had any initial misconceptions entering venture coming from a pre-medical background, as I didn't quite know what to expect and candidly, didn't fully understand what venture capitalists did. If there's anything I've learned over the last six years, it's that venture capital is a challenging job to be extraordinary at. Success is not built overnight – in fact, it takes 5-10 years to understand if you're any good. The beauty is that there's no one right way to be a venture capitalist, and often, the alpha comes from being true to who you are and having strong conviction in your beliefs.

SG, Bessemer: During my undergrad work at Langer Lab, I learned about biotech entrepreneurship and how to commercialize technologies that we were developing in the labs. I wanted to learn everything about the business side of bio and help more companies be created rather than doing the science myself.

AS, F-Prime: I had planned to be an academic scientist until the end of my PhD, when, despite really enjoying my project, I realized I couldn't pick one area of biology to focus on for the rest of my career or even one post-doc. Everything felt very exciting – cancer biology, aging, biofuels, novel antibiotics, synthetic biology for alternative food... Around that time I met a partner from Syncona (shout out to Alex Hamilton) who had done a similar PhD program to mine and was giving a talk about his career in life science VC. It sounded absolutely fascinating – varied, impactful and still close to science. Alex and many other fantastic people generously shared

their experiences and gave me advice on how to build my CV to apply for VC roles. I then gained some industry and strategy experience through management consulting at Advancy and McKinsey and joined F-Prime Capital as an Associate in January 2022. Over a year later I am still loving it!

SS, F-Prime: Mentors at Nanodimension (ND Capital) and Sofinnova first helped me learn about the world of VC and I have been fascinated about learning what the work researchers and drug developers are doing, creating things that could not be imagined 10, 20 years ago.

JC, Frazier: Growing up I always loved science and was always curious about entrepreneurship, but had a really hard time grasping what a career at the intersection of the two might look like until I was fully immersed in biotech. My first job in the industry was in research at Moderna in the very early days. I am very thankful to have had a front-row seat to one of the most prolific venture-backed biotech stories of all time, and from then on I was bit by the biotech venture bug. I think a misconception I had very early on was that most VCs or venture creation firms had a similar philosophy around innovation and value creation, and as such that the company archetypes and investment theses would be more similar than less. But as I have spent more time in the industry and worked at places with vastly different perspectives, I have come to appreciate how much diversity in thought there really is.

AA, Insight: I started my entrepreneurial journey as a founder/operator, and always intended to continue on as such. In grad school I was working on two startups when I received the opportunity to complete a fellowship at Vida Ventures. I took it, thinking it would be a good way to understand how VCs evaluate startups. Fast forward 3 months, and I was hooked!

KY, KdT: I “brute-forced” my way into venture. I was always passively aware of VC, but a few years ago, I had spoken with someone who had transitioned from medicine to venture. He described his job to me, and I was intrigued. A guiding principle in my life has always been: if there’s something I find interesting, I want to give it a try for myself. I subsequently cold emailed several firms across the country, asking for an internship. Nearly everyone ghosted me, most likely because my one selling point was that “I know nothing about venture, but I have a relentless work ethic and a willingness to learn”. Luckily for me, Phil Grayeski at KdT bit. I thoroughly conned him into giving me a spot (read: he was willing to give me a chance). He quickly became a close friend, confidant, and mentor as I began my journey in venture. Phil changed the entire course of my life, and the rest is history – I’ve been at the firm for a few years now am excited to continue partnering with entrepreneurs at the forefront of biotech. When I started in venture, I initially (and mistakenly) thought that the science was everything. Now, I am convinced that everything takes a back seat to the people and their mission. Science is messy, business is messy, and startups are akin to rollercoaster rides. When you have a team in place – driven by a profound mission – that can maneuver quickly and adapt to anything that is thrown their way, those companies will have a much higher chance of success.

PM, KdT: My path to venture wasn’t pre-meditated – I kind of stumbled into it. Once I discovered it though, I was hooked. The opportunity to help translate impactful science out of the lab and into the real world through the vehicle of entrepreneurship was incredible to me. Not necessarily a misconception, but I didn’t fully appreciate how relationship-driven the business of venture capital truly is. The science is important, no doubt. But at the end of the day, early-stage investing is all about the people. Relationships drive everything we do, from the deals we get access to, to the founders we have the opportunity to partner with.

SV, Lux: Serendipity. Once I learned about the world of Venture Capital, I couldn't think of a more fitting or fulfilling place for me to spend my time, but the journey into the industry was far from straightforward. I originally started my career thinking I wanted to work as an engineer and briefly spent some time at NASA. I later realized that there was a tremendous opportunity happening in biotech broadly and that I could bring an "engineering mindset" to help end human suffering which led me to Illumina. After Illumina, I knew I wanted to help the tremendous number of new biotechs that finally had sophisticated enough tools to go after the complexity of disease (i.e. read/sequence, write/synthesis, and edit/CRISPR) and the converge of that with the advances in computation would lead to a once-in-a-lifetime opportunity.

DQ, MPM: I got my start in venture through an internship course at MIT (Research Experiences in Biopharma), where I was paired with MPM Capital to do a landscaping exercise around a therapeutic area. I was always interested in the business side of science, even before starting grad school, and saw venture as a way to achieve the best of both worlds. The biggest surprise when I started was just how scientifically rigorous venture can be – I actually felt like I've become a much better scientist during my time at MPM.

JK, OMX: What drew me to venture capital: I was looking find a career that weaponized my scientific curiosity. I was never happy just working on one project at a time in a single field. I was drawn into the field because of my love of solving complex scientific questions with innovative methods. This takes years to occur and if you work across multiple fields you can be involved in multiple innovations with a short period of time. Early-stage venture gave me an opportunity to do that across multiple fields, while working with the smartest scientists on earth. An Initial misconception about VC: VC is more than splashy PR about starting something new, it is about finding the right tools and risks to get drugs into patients. Spending money is easy, drug development is hard, but it's how you make money. It takes a lot of hard work to build a great company, not just dollars and cents.

TDV, Pillar: I previously founded and was CEO of a company before going into venture creation. My experience fundraising and interacting with venture capital had been predominantly negative, and I had always felt that the relationship between founder and VC would thrive in a more collegiate environment. When I had the opportunity to join a VC who's core focus was to be founder-friendly it was a great match, and I was thrilled to join.

TK, Pillar: The whole biotech industry / academic complex only forms and funds 200-300 companies per year (according to Pitchbook), compared to 80,000+ NIH grants, 50,000+ PIs, and 100,000+ grad students and postdocs. There is a ton of science that could be unlocked. During my time in academia, I saw a massive cultural transition towards interest in startups. When I started, it wasn't common to have any entrepreneurial interests; it was concentrated around a single lab/faculty member. But by the time I left grad school, every single lab was spinning out multiple companies, and many academic scientists wanted to leave academia to build their own companies. How do we accelerate this cultural transition worldwide, and then give people the tools and social technology (and perhaps other software, infrastructure, etc) to be successful at translating science? I made it my mission to figure this out, and it's what we work on daily at Pillar.

PK, Rivervest: Like many people, I wasn't initially set on working in venture capital when I was in graduate school. Instead, I was more broadly interested in a role where I could use my skillset to help aid evidence-based decision-making to improve the quality of people's lives. There are many ways one can achieve this, and I was initially focused on a career in science policy. However, once I realized venture was another potentially more impactful way I could achieve

this, and all the other cool parts of the job, I was immediately hooked. Oftentimes when you start out in venture, your role is focused on vetting new investments. This is a core part of the role, but what happens after the investment is made is as important if not more important. I don't think I appreciated this as much as I could have when I first started.

VR, TRV: I was interested in bridging science with company building—and getting to learn from incredible people across a number of areas (research/exploratory biology, drug discovery, clinical development, overall strategy, BD). Misconception: I find that it's much more about building the companies (R&D plan, financing plan, and team) than about pure ideation, which only gets you the earliest bit of the way toward meaningful health improvements.

EC, Venrock: When I was a PhD student I was lucky enough to be part of the team making discoveries that led to the founding of Dewpoint Therapeutics. While Dewpoint was getting off the ground, we spent hours asking ourselves how our science could make a difference for disease and what experiments would demonstrate its potential. I loved asking these questions – and I wanted to find a job that would let me do that on repeat to hone the necessary skills. To me, it's all about the crosstalk between biological knowledge, technology development, and unmet medical need. These topics on their own are all interesting, but in company building and investing they blend together into something incredible – and hard! I'm not sure it counts as a misconception about investing, but I didn't realize just how tough it is to develop a drug while I was a PhD student. It is really inspiring what the biotech industry can do.

JG, Vida: I initially thought VC was for people with a finance background and that I would have no interest in that career path given my scientific and technical background. However, I forced myself to go to a seminar about biotech VC through the Harvard Biotech Club to give myself a better understanding of how this part of the biotech ecosystem works. I was surprised to learn how technical VC/company creation is as it necessitates deep dives into the scientific and clinical elements of drug development in addition to the business elements. I then apply to VC fellowships and joined Vida as a fellow in 2019. I was fascinated by the breadth of new technologies I could learn about on a daily basis and found the work to be some of the most intellectually stimulating content I have ever worked on. I never envisioned VC as a career path, but after participating in the fellowship program, I joined the venture community full-time in January 2020 and haven't looked back.

MS, Vida: I stumbled into venture capital while looking for internship opportunities where I could learn more about biotech. I initially had a misconception that all venture capitalists were highly experienced and well-connected entrepreneurs who had already run multiple successful companies themselves. While that is certainly one phenotype of venture investor, I soon realized that many of my peers from graduate school were finding their way into biotech investing and also could become quite successful in the industry.

4. What was the first deal you worked on that resulted in an investment? As a case study, what are the biggest lessons you learned from your first time?

Ben P a16z: The first deal I worked that resulted in an investment is still a stealth biotech company. One of the biggest lessons I learned is about people. It's so important to bring great people into the company – from the scientific to cultural perspective. Building a successful

company is incredibly challenging, so you want to make sure you work with people who you genuinely enjoy being around and who are great scientists/biotech professionals.

Becky P, a16z: The first deal that I worked on from sourcing to investment at a16z was Vicinitas Therapeutics. This was a unique situation as it was a ground up company build where the foundational science had come out of a collaboration between Dan Nomura's lab at UC Berkeley and Novartis, and the IP was co-owned between the two institutions. While this complication may have seemed an insurmountable hurdle to some, my first lesson learned was how the power of relationships can break down barriers. Dan and a16z's strong relationship with Novartis leadership opened doors that may have otherwise been shut. The second lesson I took away from my experiences with Vicinitas is how enjoyable and beneficial it can be to build a strong syndicate from the beginning. Working with the teams at Deerfield, Droia, GV and the Mark Foundation has been nothing short of incredible – a true collaboration where everyone brings their unique strengths to the table with the same unifying goal – to bring meaningful impact to patients.

MC, Bessemer: The first deal I sourced and transacted was a company called Subtle Medical, a software platform that leverages generative artificial intelligence to improve the quality, value, and accessibility of medical imaging by significantly reducing cost, imaging time, and radiation dose.

SG, Bessemer: Not my first deal but my investment in HouseRx was inspired by a lot of work and interest I had on the pharmacy channel and the intersection of new drug development of specialty and complex drugs, pricing models of these drugs and the technology and services needed to get the drugs to patients. Lesson is that the most interesting investment can be at the intersection of a couple of spaces and stakeholders, and you can lean into your passion for a mission and space to become an expert. The business model that aligns all those incentives and puts the patient at the center will win alongside multiple stakeholders, pharma developing innovative drugs, providers caring for the patient and payers keeping total cost of care down by getting the patient on therapy faster and staying on therapy.

AS, F-Prime: The first deal I worked on was Peptone – F-Prime co-led the \$40M Series A round with Bessemer. Peptone combines cutting-edge experimental biophysics and computational modeling of molecular dynamics to characterize intrinsically disordered proteins (IDPs) – a class of proteins without a fixed 3D structure. IDPs are not amenable to standard structural biology techniques, such as X-ray crystallography or cryo-EM, but they play a significant role in health and disease. The biggest lesson was probably how important it is, when assessing platform opportunities, to focus on target selection. We believe that Peptone's platform will deliver first- and best-in-class medicines against high value and previously undruggable targets. I feel privileged to work closely with the company to prioritize these exciting opportunities and build out a differentiated therapeutics pipeline.

SS, F-Prime: Alternative Bio – an epitranscriptomics company that combines deep insights in specific targets and biology, but also develops screening platforms to find novel targets and molecules that interact with such targets. The biggest lesson I learned is what it takes to engage with biology at scale.

JC, Frazier: The first deal I worked on when I was at Flagship was the seed funding for Generate Biomedicines. I learned a ton, but I think the things I come back to the most from that time are (i) how to creatively and cost-effectively de-risk a new technology, (ii) the importance of

identifying a killer application and (iii) how to leverage the unique and differentiating aspects of your technology to identify that killer app.

AA, Insight: A skeletal dysplasia company called InnoSkel. This was a long time ago and my memory is bad, but one thing which stands out is that the French government's process for qualifying foreign investments (their CFIUS-equivalent) was my first time seeing federal policies influencing investment.

SV, Lux: One that comes to mind is Enveda. The Lux team had gotten to know Viswa after he was an early employee at Recursion Pharmaceuticals (also Lux backed) and joined as the first Product Manager of the company. Although he didn't have the pedigreed "drug-hunter" career profile, he did have an incredible personal story and motivation for starting the company which has been a tremendous differentiator. Biggest lesson I learned as my partner Josh says "chips on shoulders, put chips in pockets"

DQ, MPM: My first deal at MPM was Orna Therapeutics, which is a company we built based on circular RNA technology from Dan Anderson's lab at MIT. This is a cool example, because we had been thinking for a while about using RNA to create *in situ* CAR-T cells, which would potentially have a far better product profile than the cumbersome *ex vivo* cell therapy CAR-T products. When the MIT team presented the circular RNA technology in 2019, our first thought was "I wonder if you could use this for *in situ* CAR" – ultimately that is what anchored our investment and "isCAR" continues to be Orna's lead program. It was a great example of how having a pre-existing thesis in a space can help you to react to new technologies, and ultimately find the conviction to invest.

JK, OMX: My first deal that was fully approved but I pulled the plug in the 11th hour (literally) and it taught me a very valuable lesson to trust your gut. I loved the tech and worked 6 months on the deal. During that time, I had some concerns about the CEO and didn't trust my initial reservation about their behavior during the diligence and closing process. I had taken this all the way through approval from the investment committee and just had to sign the final docs and wire the money. I decided to overlook these concerns because the tech was so cool and ended up going all the way to closing on the deals. Some new federal regulation was going in place and we had to close the deal by Friday at 5pm before the new regulation went in to place and we had to start back at square one. The CEO dragged their feet on their disclosures, but it came out at 3pm that final Friday that there was a major legal issue with the CEO warrants and reps. Essentially, my initial misgivings were proven current. I decided to pull the plug on the deal and had to call everyone on my team about the deal being dead. I learned a valuable lesson to trust your gut.

TDV, Pillar: My first investment was a "diamond in the rough". Great science and founder but with a lack of experience an incomplete R&D and financing strategy. Helped restructure the strategy and fundraise and lead an oversubscribed round with a syndicate of top tier investors. Biggest lesson was that the "process is the diligence".

TK, Pillar: When I started out, we created an incubator called Petri, which we have since merged into Pillar VC and scaled up to become our biotech practice, Pillar Bio. In hindsight, Petri was a very unique entrance experience to investing because our team invested in many companies at roughly the same time including Nabla, GALY, Matterworks, New Equilibrium

Biosciences, Tezza, Compound Foods, Yard Stick, Modern Synthesis and more. It was a whirlwind! There are so many important lessons I learned through that period, but perhaps the most important is just how unpredictable things are in both the ups and the downs. I've learned to deeply value rock solid, resilient foundations on the founding team and investor base.

PK, RiverVest: The first deal that I worked on at RiverVest that resulted in an investment was Bluejay Therapeutics. I worked on the deal alongside Nancy Hong, a Managing Director based here with me in RiverVest's satellite San Diego. When Nancy and I heard the pitch, we were both so impressed by their CEO Keting Chu. Nancy and I had a very good gut feeling about her. The rest of our diligence on the asset and indication built our conviction. Keting continues to be one of the most capable CEOs in our portfolio. She has a depth of experience that prepared her perfectly to lead Bluejay and she's built an incredible team to support the work there. The experience working on Bluejay underscored the importance of getting the right team in place to execute on the plan.

VR, TRV: Maze Therapeutics—key lesson was the importance of an excellent team, and focus and resilience in working on high-conviction problems (e.g. hard drug discovery targets)

JG, Vida: The first deal I worked on that resulted in an investment was Scorpion Therapeutics, a precision oncology company that we co-founded in early 2020. The investment memo was the last project I worked on in the office before the pandemic shutdown the following week. During a time of confusion and chaos around the globe, I learned that it was critical to stay focused on fundamentals and remain grounded in areas where we have high conviction, such as targeted therapeutics.

MS, Vida: My first investment as an Associate was in Vigil Neuroscience, a Boston-based company developing microglial-targeted medicines for treatment of neurodegeneration. Vida Ventures led Vigil's \$90M Series B financing in August 2021, prior to the company's IPO in January 2022. Vigil's IPO coincided with a general downturn in capital markets that made it more challenging for Vigil (and many other companies with public aspirations) to raise critical capital for developing their therapeutic programs. Vigil was one of the last biotech companies to IPO before the capital environment became extremely unfavorable to biotech public offerings in 2022.

While Vigil has been able to stay financed and focused on developing their TREM2-targeted therapies, many biotech companies have struggled. Most biotech companies generate no revenue (and drug development is expensive!), so companies need supportive capital markets to progress their programs. When capital becomes harder to come by, it becomes more challenging for companies to execute. Over the past 12 months, many companies have announced that they are deprioritizing promising programs, not because of poor data, but rather because of capital constraints and insufficient funding to progress all programs in parallel.

- 5. What are some factors that get you excited about a company or company build? Is there a mental checklist or model that you construct during diligence to gain conviction about an opportunity? Any obvious red flags?**

MF, 5AM: At 5AM, we spend a lot of our time on therapeutics companies, so I'll focus there. I don't have a rigid checklist that I use when assessing a new opportunity, but in general I like to start by understanding the potential clinical impact of a new therapeutic. If you believe everything in the pitch deck and assume that preclinical and clinical development go to plan, how impactful is that new medicine going to be? This is a pretty good proxy for exit potential, as medicines that fill a significant unmet need are likely to get the attention of acquirors and/or public investors. If the therapeutic addresses a real patient need, I'll think through the key assumptions that have to play out along the way and try to distill those down into three or four concrete and diligencable risks. Those could be anything from basic biology and biophysical properties of a molecule to clinical translatability and regulatory burden. Eventually, there's a much longer list of diligence topics that have to be addressed before making an investment, but if you like the answers to the highest-priority questions, that gives you a good early sense of how excited to be.

Ben P, a16z: This is for platform companies. What gets me excited are new technologies that enable our ability to drug a previously hard to treat disease or that provide fundamental, novel insights into disease biology. These technologies typically generate proprietary data/assets, are led by a seasoned team, and focus in an area of high unmet need.

Becky P, a16z: There is infinite diligence you can do on most companies, and the specifics differ from deal to deal. But there are two fundamental questions I always ask myself. The first question I ask is "What if this works? How big could this get?". Particularly for early stage investing it's important to suspend disbelief for a moment and allow yourself to disregard all the reasons something might fail, and instead evaluate the bull case. If everything goes exactly as planned, and it's still not a category defining company with the potential to broadly human health, then it's not the type of company we're looking to invest in. And the second question I ask myself is "Why does this team have an unfair advantage? Are they the right founders to win?". Again, at these early stages, the people involved can make or break a company. We are looking for founders have thoroughly traversed the idea maze and have earned unique technical and market insights that ultimately increase their chances of success.

MC, Bessemer: Venture capital as an asset class is designed for technologies that can grow non-linearly and achieve scale quickly. The opportunities to do this effectively in healthcare and life sciences are rarer than one would expect. In biotech, therapeutics have long served as a fruitful category well-suited for venture, and more recently in healthcare, software and tech-enabled services have emerged as venture-backable models. I try to keep simple mental models that I can apply consistently across opportunities:

- Why now?
- Why is this team uniquely positioned to win? Can I envision a 5-10 year trusted relationship with the founders/CEO? This is most important at the earliest stages.
- What is defensible about this technology or approach?
- What value does this business create in the form of clinical and financial return on investment for key stakeholders of the company or ecosystem?
- Does the business model proposed align with the value delivered by the company? Does the business model appear efficient or designed to generate profits long-term?
- **If this company is an outsized success, does it create a world I want to live in?**

SG, Bessemer: I think at the top of the list is a visionary founder – ambition, expertise and resilience are key. Then for biotech, you want to get an understanding on the strength of the technology and breadth and depth of the applications. Conversely for health tech, you look at market opportunity, unique why now or macro tailwinds that make this an interesting problem to go after and the right solution or model to tackle it.

AS, F-Prime: Part of our job is to quickly get to the most relevant questions that are often opportunity-specific. But some aspects are applicable to any diligence, e.g., for therapeutics (non-exhaustive):

- Team (founders, management, advisors, existing investors if any): it's a good sign if the founding academic joins the company or spends a meaningful amount of time advising the company. It is helpful to have former biopharma executives with real drug discovery experience. Top academic, clinical and industry KOLs add credibility.
- For existing pipeline: how validated is the target, what is the market size in lead indication, what is the competition and what can we learn from their successes and failures, is this the best modality, indication and trial design? Best data demonstrating differentiated technology and/or asset. Is there head-to-head data with key competitor(s) proving superiority? What are the key risks (biology, translational, regulatory, commercial, etc.)?
- Deal dynamics, valuation, exit scenarios: are the insiders participating in the round? What is the traction with new investors, if known? Any strategic (Pharma) interest? Do we believe the likely valuation reflects the progress the company has demonstrated? In due course, would the company be an attractive M&A target, or can it be successful on the public markets?

SS, F-Prime: I get excited by a platform company with an engineering and/or analytics/modeling component – proof of concept prototypes, BD mindset, and internal drug development expertise.

JC, Frazier: This is an unsatisfying answer, but I am a firm believer that no two deals are alike – so as a result try not to follow any kind of process that is algorithmic or overly prescriptive. We look at an extremely diverse opportunity set at Frazier, so as a result need to be able to scale our risk tolerance and upside expectation commensurate with the stage of the deal – which generally does not bode itself to any kind of absolutist mindset. I think the only unifying framework I use is to ask the question “is this going to result in a differentiated drug in an area of unmet medical need?” There are then a lot of layers underneath, but that is usually a pretty good starting point.

KY, KdT: Coming from the medicine world, I'm always looking for the foundational tenets: what is the unmet need? Why is this therapeutic or diagnostic platform better than what currently exists? Can this change the entire standard of care for a disease? I always get excited when a company is pushing forward an entirely novel modality and blazes a trail forward. A team that is comfortable and willing to sail in unknown waters is rare. As KdT invests in computational-centric companies, I'm always keen on understanding the quality of the data that “feeds the beast”. Algorithms are important, no doubt, but differentiation and protectability derive from the data. I always want to understand where your data is coming from. Why is it unique? Additionally, can you generate a large amount of data that others cannot? Beyond the technical details, I'm always focused on the team: why are they the right group to push forward this immensely challenging technology? As a VC, I will partner with entrepreneurs for the next several years – would I be happy working with this team for a decade and beyond? A confluence of the above questions float through my mind every time I meet with a new company.

PM, KdT: On computationally-enabled platforms: I focus less on the algorithm and more on the underlying data on which the algorithm is trained. Platform differentiation and defensibility derive from the data, not the algorithm. A preview of things that I look for:

- Proprietary access to a novel data type or modality that enables unique biological insight
- Ability to generate a large quantity of training data with high-throughput (in general, algorithm performance scales with the size/quality of the training dataset as long as the model isn't overfit)
- Scalable method for labelling/annotating/pre-processing data that is difficult to replicate (e.g., access to human expert labelers, or self-supervised approaches that eliminate the need for human annotation)
- Ability to go beyond correlational relationships to establish causality (e.g., pooled CRISPR screens). Despite all the progress in deep learning approaches like transformer-based algorithms, these methods still only discover correlations in the underlying data. In the future, I believe we will see a greater focus on causal machine learning/inference in biology.

SV, Lux: I'm particularly excited by companies that have an "engineering-first" mindset and are focused on how do we take our understanding of biology from a research/academic context and translate it into a commercial setting? One of the clearest ways this can be demonstrated is via partnering with a larger pharma company in which the startup is able to use their platform and provide a "best-in-class" tool as part of their discovery workflow. Oftentimes this allows the startup to not only receive some economic consideration for their efforts but the experience of understanding how discovery is doing at the pharma scale is tremendously valuable.

DQ, MPM: At MPM we only invest in therapeutics, so my framework is pretty specific. But I look for technologies that I believe can enable first- or best-in-class products, where it is possible to demonstrate in a relatively short clinical trial that the drug works. Beyond that, I run through a checklist of "failure modes" – ways in which the entire project can fall apart – things like manufacturing, safety, efficacy, IP, and competitive landscape – and try to make sure that there is a reason to believe that either we can overcome these hurdles, or collect data to "de-risk" these outstanding questions for a small investment. Of course, depending on the situation, my framework can bend to make room for technologies and teams with amazing potential. Ultimately, any investment comes down to believing in the team and vision, and then resourcing the company appropriately so they have the flexibility to succeed. From my perspective, there are many, many red flags, but perhaps none bigger than misrepresenting data or overselling. We need to be able to trust the science so that we can always make the best decisions for the companies in which we invest our capital and time. I love working with honest and transparent teams and academic founders.

JK, OMX: My answers are for platform and therapeutics, I get excited about the underlying technology and their differentiation. I typically invest in companies that have one of a kind tech and it has a killer application. There is a mental check list, but I find my diligence process to revolved around this core idea. We as investors de-risk ideas with money to generate more value than we started with. This foundation has allowed me to construct the below investment principle:

- o Principle of Ying and Yang risk taking: Ask yourself, is the company taking a technical risk or biological risk? Don't ever stack these risks in the same company. Only take on one major risk, either technical or biological. Too much risk, no matter how great the

rewards will sink a company. You control risk like viable in an experiment. Too many variables muddy the water too much, when making key decisions.

- If its brand-new tech then it needs to be paired with an application (drug target) that has no biological risk (robustly clinically validated) and a high unmet need that only this technology can solve. Example if you have a platform that can drug undruggable targets like transcription factors, then go after clinical validated that you can only drug with this platform. Do not go after a new hot target that is exciting, but hold biological risk.
 - If you are taking biological risk, i.e. a brand new target, don't take technical risk and look to focus on clinically derisked technologies or modalities. For example, you want to use already clinically derisked modalities like small molecules or antibodies to therapeutically intervene against the novel target
 - Avoid ideas or companies that combine both these risks. It will be very challenging to properly derisk at the same time. Drug development is hard and you taking on both risks at once will make it impossible to succeed.
- **Another fund mantra is most early-stage companies die of indigestion and not starvation.**

SC, Orbimed: There are several factors: 1) Scarcity value -- when a company is doing something unique, especially if is challenging to replicate. 2) A clear and thoughtful clinical development plan. 3) A well-financed company that has the runway to take it significantly beyond key inflection points. 4) An experienced management team that is passionate about its programs and potential clinical impact

TDV, Pillar: I start with the founder: are they humble, hungry, and smart? Next, I look at the technology: does it have strong IP and FTO? What "right" does the company have to win? Lastly, I consider the clinical feasibility: Can I imagine this as a drug that an actual patient takes for the rest of their life? From a process perspective try to fill in and score 5 buckets: 1) Technological risk, 2) Biological risk, 3) Clinical risk, 4) Team risk, 5) Market risk.

TK, Pillar: It is pretty binary for us – we get excited when we see the potential for a truly exceptional advance. Everything else becomes the stuff that we will work on with the company!

PK, RiverVest: There's definitely a mental checklist—I think every investor has a checklist they go through for a new investment that includes the basic items like the asset and therapeutic area. In the current market, we've spent a lot of time analyzing a company's plan, team or team build, and the syndicate of investors. Valuation is a critical factor, too. We need to ensure it's possible to get the returns we expect based on the comps in the space and company's path moving forward.

RS, Sofinnova: I'm always excited about companies developing therapies: (1) in areas of high unmet medical needs with uniform patient populations, (2) with a clear clinical and regulatory path, (3) a capital and time efficient path to value creation, and finally (4) go it alone potential.

VR, TRV: Getting to work with the world's best people for the specific opportunity; a clear understanding of how technical success (e.g. on the platform, or in drug discovery) could lead to meaningful benefits for patients. Checklist varies, but at a high level: (1) is this the right team, (2) is this the right time, (3) do we have a strategy that enables meaningful value creation upon technical success, (4) can we feel confident in the set of patients / people who will benefit if we are successful, (5) do we have the right set of investors around the table to drive success, both with dry powder and with strategic guidance

JG, Vida: 1) When companies have a new technology that enables them to uniquely address a disease indication that other technologies cannot address. 2) When risky new drug targets are backed up by supportive human genetic validation data. 3) When there are one or two case reports out there supporting that a certain type of therapy can be effective in humans. For example, Affini-T Therapeutics is a company that we co-founded developing engineered TCR therapies to address oncogenic drivers in cancer, including KRAS. There have been anecdotes of T cell therapies generating responses in KRAS mutant tumors in cancer patients, which enhances our conviction that this approach has legs.

MS, Vida: My checklist varies substantially on multiple company-independent factors, including the present financing environment, therapeutic area / stage focus areas for the fund, and indication from pharma which spaces they will be prioritizing for partnerships and M&A. However, for any prospective investment you always want to see 1) that the team has a nuanced appreciation of disease biology, 2) a rational strategy to target fundamental driver of the disease, 3) a development plan that de-risks subsequent development in a step-wise manner that will be recognized by the next incremental investor, and 4) understanding that if the drug candidate is approved, it will represent a meaningful advance for clinical management of the disease.

6. Using your mentors as case studies, are there any traits or skills that you have tried to develop to become a better investor or creator?

MF, 5AM: The more time I spend as a Board observer at 5AM portfolio companies, the more I appreciate the importance of having empathy for the management teams and founders that we work with. The most productive Board relationships that I see are those that function as a partnership where ideas are exchanged, advice is offered, and management is generally trusted to make the right decisions for the business. Of course, this kind of trust is only possible when you have faith that those executives are qualified, committed, and communicative, so hiring and investing in the right senior leadership is absolutely critical. On the investing side, I've learned a lot from the 5AM team about resisting the urge to frame diligence as an assessment of a company and instead focusing on the formulation and validation of a specific investment thesis. Asking the question "Is this a good company or a bad company?" tends to lead to a disorganized and inefficient diligence process. Instead, it's helpful to first define what a successful outcome really looks like (e.g., getting a drug approved, getting acquired, raising the next financing at a step-up) and then building confidence that the company is well-positioned to reach that successful outcome. Within that framework, identifying the most important questions and risks becomes much more natural.

Ben P, a16z: An overarching skill I most admire from my mentors is communication. This can come in the form of storytelling, pitching, delivering feedback, or asking important diligence questions. I continuously work to improve my communication skills as a company creator and investor. Mentors such as my former boss Geoff von Maltzahn and current boss Vineeta Agarwala are exceptional communicators and can distill complex, multifactorial subjects into the most important, compelling points and strategy.

MC, Bessemer: There are several traits I have tried to develop as an investor.

- **Self-honesty:** what am I uniquely good at and what are my areas of development? What are my values? How can I partner with others who are better at things I'm less skilled in to learn and grow and who are aligned with my values?
- **Humility:** I don't know everything and never will. Everyone is uniquely positioned to teach me something new. It's my job to learn what this is through conversation and relationship-building. If I fail to uncover it, I'm not having the right conversations or asking the right questions.
- **Insatiable curiosity:** I don't have many original thoughts, but I do have many original questions. Maintaining a diverse information diet and voracious appetite for learning is an integral part of my job.
- **Bayesian learning:** It is critical to "train your priors" via varied experiences that both directly and indirectly influence how you view the world and make decisions. Some of these opportunities will seem like non-sequiturs; however, if you trust gut and pursue things that genuinely interest you, the universe will organize itself accordingly.
- **Adapt or die:** In technology, it's more often not a question of "if" something will happen, but rather, "when." Recreate yourself constantly. Abandon parts of yourself that are no longer serving you or that hold you back from embracing the future. Marry skepticism with curiosity, not emotion.

SG, Bessemer: Steve Kraus has always encouraged me to find my distinct voice as an investor that feel authentic to my capabilities and personality. You need to work within your strike zone of abilities but also push yourself a little of your comfort zone to always learn something new. It's a nice balance that I'm constantly working on.

AS, F-Prime: F-Prime is a very collaborative place and I am constantly learning from F-Prime colleagues in London, Boston and San Francisco, as well as from our global sister fund Eight Roads Ventures. Over the last year I have worked the closest with Alex Pasteur – a partner with F-Prime in London. I am impressed by how he balances attention to detail with the big-picture strategic vision. For example, he still finds time to read papers and speak to experts to understand how a drug works, but also cultivates and leverages his impressive network of executives, founders and academics. Crucially, I have learned from him how important it is to show empathy to entrepreneurs. We should stay objective and provide a fair challenge when needed, but ultimately, it is the entrepreneurs who live and breathe their startup's idea, and, while exciting, it is often a very challenging job. Investors should take the time to celebrate the companies' successes, encourage and support the management, to build long-lasting and trusting relationships. As I grow in my VC role, I aim to hone on these and other critical skills.

SS, F-Prime: Stacie Weninger (who also did Biomarker interview) is a mentor I look up to. She strikes me as someone who not only has the depth of knowledge and domain expertise, but also has the breadth in exposure and connections. That is the trait that I want to build as well.

KY, KdT: Everyone at my firm has instilled this in me: biotech (and particularly healthcare) can be an all-consuming bubble, but you should still try and be well-read outside of science and medicine. There is a tremendous amount of learnings from every domain of the world – philosophy, business, psychology, marketing, etc. – that can be used to augment not only your venture career, but also your life. Additionally, they thought me to always question assumptions, and make sure they're rooted in fact – otherwise, you'll be burned.

PM, KdT: Being present and a good listener, insatiably curious and well read, always questioning your assumptions and changing your mind in response to new information, clear and concise communicator, being a kind and a genuinely good human.

DQ, MPM: I have had many mentors at MPM, and am constantly learning across a grand spectrum of disciplines – from science to business to leadership. One interesting thing I've picked up on in the context of team meetings: listening is often more important than speaking, but when you do speak, make it count. Several of our partners who came from big pharma have an uncanny ability to speak up at just the right time and say just the right thing, and their opinions are very well-respected as a result. A critical part of being a successful investor, entrepreneur, or generally a successful member of any team is being respected for your opinions.

SC, Orbimed: As biotech has become increasingly crowded, there is a premium placed on developing a deep understanding of competitive landscapes, looking across private companies, publicly traded biotech companies, and pharma. The best investors that I have worked with thoroughly map out where competition might come from in the short and long term and how standards of care may evolve over time.

TK, Pillar: The most important lessons that mentors have emphasized to me are the following: The hardest thing about venture is that the time scales for learning/feedback are extremely long. There is a lot of randomness along the way, and it is easy to fool yourself. Mentors have drilled into me the value of deeply and honestly self-reflecting on the specific actions and decisions that resulted in any major value creation or loss. Write down your reflections when they are fresh, as later your memories are wrong. Share your thinking with mentors, who can help calibrate against their own experiences.

PK, RiverVest: One of my favorite parts about RiverVest are the people that I get to work with. Each managing director brings their own unique skillset and experiences, and together, we cover all the bases one should cover to identify a potentially successful investment. They each have decades of experience that I benefit from on a daily basis. They have taught me that tenacious curiosity and high conviction are necessary skills. In addition, many of the folks at our portfolio companies serve as role models and a source of inspiration for me.

VR, TRV: Never think you know it all—ask questions and listen. Make sure you're working on important problems- what we do is hard, so the upside (to patients first, but also to us as investors) must be commensurately high upon success

EC, Venrock: There are lots of admirable traits I've observed in investing mentors. But there are a few I think are especially important to have or develop. The first is being truth-seeking. Being truth-seeking starts with being curious – which is essential for investors – but it goes further. You need to be fearless in your learning, because often you'll learn things that present obstacles to your investment theses or your portfolio companies' strategies. You need to be able to find these truths, face them, and adapt. The next is being empathetic. As biotech investors we work with entrepreneurs doing one of the hardest things out there: developing drugs. So, it's a certainty that the companies we work with will go through difficult times. I've come to believe (from watching the pros) that being the best partner and supporter in these situations starts with deep empathy.

The last is some mixture of optimism and creativity. To be a good early-stage investor you must be able to see what a company is today and envision what it could be years down the line. You need to be able to both imagine things *and* believe those things are possible. Paradoxically, many investors are trained scientists with innately strong skepticism. I think pairing this skepticism with creative optimism is a powerful combination – provided you know when to flex each muscle.

MS, Vida: The importance of networking broadly and building meaningful relationships in the biotech industry cannot be understated. All of my mentors have built rich networks over their careers that help with sourcing deals, conducting due diligence, and supporting companies in our portfolio. In addition, it's important to be intentional about investing and identify key focus areas that will guide your sourcing and triage strategy. Ahead of meetings with companies, it is critical to understand 1) why you are speaking with the company, and 2) what are the most important learnings you are looking to take away from the discussion?

7. If someone decides that VC is for them, any advice on finding a job in this environment? What are 1-2 things you would recommend doing to be proactive?

Ben P a16z: For grad students mostly, 1) Get deep in areas you are interested in outside of your thesis work: this can be a new area of biology or sub-field of biotechnology/therapeutics. 2) Build a strong network: find new mentors and likeminded peers within academia and industry. They will remain connections throughout your career.

Becky P a16z: Ultimately, one of the best ways to get a job is simply to start doing it and prove you're capable! Develop your own informed opinions on what are a few up-and-coming areas that are promising, and what are specific compelling investment opportunities in those spaces. Start tracking founders within academia and industry who are doing the most exciting work in these spaces and are entrepreneurial. Consider writing content or finding other avenues for sharing your opinions in public.

MC, Bessemer: For anyone looking to break into venture, the best advice I have is to start doing the job today. Contrary to the revealed preferences of many investors, you don't need to go to graduate school to be a venture capitalist, though some graduate degrees, particularly in the sciences, might lend you credibility and expertise in particular areas of investing (e.g., biotech). The core facets of being a venture capitalist are: 1) Thesis development, 2) Deal Origination (sourcing), 3) Due Diligence, 4) Deal Negotiation and Execution, 5) Portfolio support.

Facets 1-3 can be performed remotely without formally engaging a venture capital firm via primary and secondary research, cold emails, and hustling on platforms like Twitter and LinkedIn. By investing time in doing the job before recruiting, you will demonstrate what you can contribute to potential firms starting on Day 1, such as new theses or specific expertise and proprietary deal flow, which sit at the crux of every venture capital firm. It's helpful to take a basic financial accounting class to make sure you understand the basics of a Profit and Loss statement, though many of the technical skills (e.g., financial modeling, capitalization tables, and term sheets) are best learned on the job via deal-making. Venture capital firms don't hire often, and in the new macroeconomic environment, you can expect VC hiring to slow if not halt for an indeterminate period. Building relationships with investors and portfolio companies at firms you are excited by is key to landing a role – next week or in 6 months - and there's no reason to

wait. **In your discussions, the best way to impress another investor is to share interesting companies that they have not yet learned about.**

SG, Bessemer: You need to prove you can do the job even before you get the job so 1) Get very involved in entrepreneurial communities on campus or in your city (shout out to Nucleate and why I wanted to create that community!) 2) share deal flow with investors for companies that are raising, and help founders on fundraising materials and fundraising. Second would be to build a strategy on what types of funds and focus areas are of interest at the intersection of what you are interested in and what your 'super powers' are. The latter can be specific industries or areas of knowledge as well as skillsets e.g., later stage investing for analytics.

AS, F-Prime: Build your network with VCs – people are surprisingly generous with their time. Focus on getting introductions from your existing network if possible (from university / current job, etc.) and come prepared with specific questions and insights. If you are applying straight from academia or medicine, it is generally helpful to demonstrate some commercial, startup or industry experience on your CV (can be consulting, investment banking, biopharma role, own startup, etc.), but I know exceptions to the rule who are very successful VCs. The skillset you would need to demonstrate depends on the fund you are applying to (e.g., stage and thematic focus of investments will influence the amount of financial modelling and breadth of context exposure).

JC, Frazier: I think the two best things are to (i) get your reps up and (ii) find ways to talk about ideas when you are interacting with investors. For (i) I'd encourage leveraging whatever resources/avenues you might have access to (student funds, venture clubs, fellowships at venture firms) that allow you to see a high volume of pitches or new technologies. On (ii) if you can do some work on your own and develop theses around topics or areas that are interesting to you it will go a long way in your informational conversations with investors – in generally these are a lot more fun to talk about than the typical "what is your day like?" questions.

AA, Insight: Build relationships with VCs without asking for a job. Take your time in demonstrating to your future colleagues that you can find interesting science (papers or companies) and can synthesize an informed opinion on it. If you do this well, the job will come to you! Or if you can't wait, VC fellowships are a tried-and-true way to get your foot in the door. Don't be too picky, any experience is better than zero!

KY, KdT: My biggest piece of advice is to *ask* – don't be afraid to reach out and ask for opportunities. Email VCs and convince them that you can offer *something* that will make their life easier and level up the firm. Again, I only ended up in venture after cold-emailing far too many firms and being ghosted or rejected by 99% of them. Don't give up and keep trying. Every single opportunity I've had in my professional career – whether research, industry, or VC – came about from a cold email. People are more available and open than ever before in history – take advantage of it! I've had several medical students reach out and ask me about how to balance venture and clinical work. Unfortunately, there's no magic bullet or shortcuts here – you will just have to work harder than everyone around you. I vividly remember being scrubbed in for a massive 15-hour+ metastatic ovarian cancer resection, coming home, and then continuing my venture work for another several hours as we had an investment in flight. I never minded as I enjoyed the VC work, which was a welcome respite from my "day job". As my partner, Mack Healy (a former corporate lawyer), always reminds me: "By keeping your head down and doing the hard work in your 20s and early 30s, the rest of your life will be much easier".

PM, KdT: I wrote a longer [twitter thread](#) with some thoughts on breaking into venture.

DQ, MPM: For VC, I think the three best things you can do are: (1) get an internship, (2) meet lots of people and (3) familiarize yourself with the major stories/themes of the industry by reading the news. Ultimately, it's the work that you put into yourself that will propel your career, so find situations where you can keep learning and growing, whether or not they are at a VC firm.

JK, OMX: Be a good relationship/network farmer. As a PhD, I thought about getting an MBA, but was advised that all it did was build a network. Instead of spending 2 years getting that network at a Business school, I spent two years grabbing coffee with a new person in biotech every week. My network is far stronger and only cost me about 1/40th of the price. Every interaction with a VC is a job interview and always bring a gift: Every interaction you have a VC is judging you if you can think and act like they act. Make a lasting impression with a gift. I don't mean a physical gift, but a newco idea or company that you can talk about or have made a pitch deck for. This is the easiest way to show people you think like a VC. I used to make pitch decks for newco or investment ideas and send them to VC after I grabbed coffee. It will get their attention. Make sure they are fully flushed out though, the last thing you want is to have a half-baked idea.

SC, Orbimed: It's helpful to look for opportunities in grad school to gain exposure to biotech. That exposure can come in a variety of forms, including internships/fellowships at biotech funds or companies, consulting for a startup, or joining a biotech club or startup competition at your school. Even a 2-3 month experience can begin to build a skill set and learn the language of biotech. There's also a lot you can learn about biotech in grad school by listening to relevant podcasts (e.g. The Long Run and Business of Biotech), reading STAT and other online publications, and following companies that are of interest to you.

TDV, Pillar: Start with fellowships, most VCs have fellows programs and they are primarily used as recruiting exercises. Make friends with junior folks in VC. Very rarely do they make opportunistic hires, knowing who is looking and when gives you first mover advantage + everyone looks in their network first.

TK, Pillar: Just start trying to do the job! Sam Altman has a highly underappreciated blog post on this [here](#). There are some micro-level differences in biotech vs. tech, but focus on the overall message. Try to find and meet great scientists, identify great science or IP hidden in the rough, meet great executive teams, and great investors, and help them all meet each other. Ask for honest feedback about potential introductions, and you'll get better at it over time. If you are helping people, they will definitely notice! Also, making your work visible is highly undervalued. In the world of substack and twitter, people with great insight are definitely noticed by the investor community.

PK, RiverVest: It's critical to stay abreast of the activities going on in the biopharma space. One way to do that is by reading as much as you can. This will also help you decide if the role is right for you. In addition, independent thought is critical. Start forming your own opinions about the different therapeutic areas. This will help you bring your unique perspective to a VC firm you'll join in the future.

RS, Sofinnova: Getting into venture is part having the right background and skill set and part being in the right place at the right time. There are so many great internship opportunities in venture available to grad students. Take advantage of them! They are a great way to both grow your skill sets in venture and dip your toe in to see if you like the career path. Shameless

plug: we are currently recruiting for our fellowship program. If you're interested, please submit resume and brief cover letter or statement of interest in a single document to careers@sofinnova.com before March 31st, 2023.

VR, TRV: Don't think there is just one path into venture; lots of paths give you valuable skills at least in the company creation environment—e.g. strategic consulting, industry bench science experience, being an early employee at a biopharma startup

MS, Vida: Most importantly, one should read widely (Endpts is a great place to start) and discuss biotech frequently with graduate school peers, friends who have joined investing firms, and any acquaintances who are veterans of the industry. Students interested in biotech VC should also identify and apply to multiple venture fellowships. It is rare to transition directly from academia to full-time roles in VC, and important to understand that the ability to make this transition requires real commitment as well as familiarity with the biotech ecosystem built over time.

8. Advice to prospective or first-time entrepreneurs in 2023, as they bravely pitch to VCs in the new year?

MF, 5AM: A general piece of advice regardless of when you're going out to raise is to be transparent about the challenges that you see for your company. Big surprises late in a diligence process are usually deal-killers, and being up-front about your challenges does two important things: 1) it helps you prioritize time with the investors who are actually comfortable with the risks of your business, and 2) it shows investors that they can expect you to be a mature and communicative partner if they invest. Specific advice for those raising in 2023 is to keep your head up in this historically challenging financing environment. High-quality companies are routinely talking to 100+ investors before getting a term sheet. Try not to take it personally when an investor passes on your company—sometimes it's for reasons totally unrelated to the fundamentals of your pitch (e.g., personal bandwidth, fund dynamics, or firm-wide priorities).

Ben P, a16z: Constantly iterate on how to best communicate the story of your company, from the problems it solves to what makes your technology differentiated. Learn from each interaction with investors to understand what they need to see to merit investment.

Becky P, a16z: We're on your side and we want you to do well! If you can, I'd advise trying to find a friendly VC or two who is willing to meet with you early on in your process and give you honest feedback on your pitch, company, and fundraising plan.

MC, Bessemer: Great companies are built in all markets. Focus your pitch on five key questions: 1) why now? 2) why you? 3) why is your approach differentiated and defensible? 4) why does your company have a shot at becoming an enduring, generational business? 5) why is your business venture-backable?

SG, Bessemer: The fundraising process is as much of a process for investors to get to know you and the company as it is for you to get to know the investors. Take the time to build relationships with investors and understand their values, perspective and experience they can bring to the table.

AS, F-Prime: Secure good advisors (anything from an informal advisor able to speak with VCs and comment on your technology to a part-time consultant or an official SAB member) – this is a great indicator to VCs that your technology excites relevant KOLs.

SS, F-Prime: Find good advisors before the pitch! As resources become more constrained from venture money, good advisors can help early entrepreneurs think about where to go, what to do and who to talk to. Surprisingly, busy people can still be very generous about their time helping the next generation!

JC, Frazier: Know the competition and be able to clearly articulate the product roadmap and why it will ultimately be different.

SV, Lux: There has never been a more exciting time to build a company at the intersection of technology and the life sciences. As we continue to usher in a new generation of techbio companies you all have an opportunity to set the KPIs of how you are ultimately measured. Entrepreneurs who are able to acknowledge that the primitives used today to build next-gen biotech companies present a fundamentally different value proposition are tremendously valuable, in any market condition.

DQ, MPM: Pressure-test your ideas with friendly VCs or other entrepreneurs before you go out fundraising. And really work on honing the pitch deck and crystallizing the premise of the company and its approach – use data to support your vision!

JK, OMX: 1) Get used to “No,” but keep pitching. 2) Your initial pitch deck should be no more than 15 slides and should only focus on answering, 3) What’s the pain point your company is solving, 4) How you are unique in solving the problem (secret sauce), 5) what solving it is worth and 6) who are your competitors. First pitch is to get your foot in the door for the second meeting. The second meeting is to technically impress them.

SC, Orbimed: Anticipate difficult questions from investors and answer them directly. There are risks in every approach. Investors value a clear discussion of how you plan to address potential pitfalls and/or how you have become comfortable with risks.

TDV, Pillar: Make friends with VCs. Particularly seed stage VCs are typically founder friendly and happy to develop a relationship. Figure out what they are looking for, which buzzwords resonate with them, which specific aspects of the company do they care about the most, etc. Preparation and inside knowledge is key. Most VC deals are done by an internal champion, often time a relatively junior person going to bat for your company.

TK, Pillar: It’s more important than ever to start with rock solid foundations. Well ahead of a fundraise, spend time getting to know both the individuals, and their firm, to find alignment on both vision and values.

PK, RiverVest: Last year was a tough one, but I remain optimistic that 2023 will be a little brighter. Understanding the VC you’re pitching to is very important. Do your research to understand their interests and check size so that your pitch is appropriately tailored to them.

RS, Sofinnova: Make sure to highlight your technology’s differentiation from the competitive landscape in your pitch. Given the current financing environment, also make sure to focus your

financing plan on things that drive the most value and make sure to build in a bit of a buffer into your budget to adjust for unexpected and/or rising costs.

VR, TRV: Follow the advice of people who try to demystify this for CEOs broadly, e.g. Sara Nayeem on twitter. Don't let the broader market conditions scare you off or change your pitch too much—strong science / companies run by strong teams will still get funded, so make it clear that's what you are.

MS, Vida: Especially if you are advancing a novel technology platform, it is tempting to explore all of the possible applications you could use the technology for. Others may feel inclined to continue to optimize / perfect the technology at a basic level before focusing on any single application. Given the capital-constrained environment, it has become even more crucial for companies to focus on 1-2 applications that can de-risk these programs and create value in the near-term. Companies should clearly identify points in time that represent go/no-go stage-gates for those applications, and understand exactly how much capital it will take you to get to the next value inflection point. Entrepreneurs who recognize this and prioritize a focused development plan will find that their pitch will be more likely to resonate with investors (so long as the science is also rigorous and the proposed product addresses a true unmet need).