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**Voice-Over:** The *BioWorld Insider Podcast*.

**Lynn Yoffee:** This is the *BioWorld Insider Podcast*. I'm Lynn Yoffee, BioWorld's publisher. By now, most of you have likely seen the spectacular new images coming from NASA's Webb telescope. As we're getting new views of the universe, including how it once appeared, so many deep existential questions arise about humanity and our place in the universe. It's super thought-provoking.

Interestingly, researchers in the life sciences are also pioneering work related to our existence. Specifically, can we live longer? The short answer is yes, but can we extend our lifespan in a healthy way? That's the critical question. The BioWorld team decided to take a deep dive into the concept of extending lifespan, which is surprisingly well-validated by basic research.

In our new *Extending the Human Lifespan* report, BioWorld examined the latest science, the key biological drivers that can be targeted pharmacologically, and the companies developing these potential, dare I say, fountain-of-youth candidate drugs. What we found is that investments in life-extending drugs and the number of clinical trials are on the rise, but the intent isn't to live forever, just a bit longer.

The emphasis is on living longer in a healthy way. That's important since the global population of people 65 and older rose 468% between 1950 and 2020. Today, we're going to walk through some of the highlights of the *Extending the Human Lifespan* report. If you want to read the full report, visit BioWorld where all the series articles and data are freely available.

Anette Breindl, our senior science editor, led the research and wrote much of the series. She'll tell us why it's a waste of time to try to first cure Alzheimer's, cataracts, strokes, and other diseases of ageing. Instead, many forward-thinking scientists are focusing on the biology of ageing. Can we hopscotch over those diseases? Karen Carey, our senior analyst, took a data-driven approach. She found that the amount of money investors are putting into the space and the number of clinical trials are on the rise.

Staff writer Richard Staines will weigh in on how equitable access to drugs and therapies tackling ageing could reduce healthcare costs and improve quality of life. Regulatory editor Mari Serebrov will talk about the many hurdles and blockers related to developing these therapeutics. Let's go ahead. Anette, is it really possible to live longer in a healthy way? What's new on the research front that validates the concept?

**Anette Breindl:** Hi, Lynn. It's great to be here. The short answer is yes, you can live long and prosper, or at least you can have better odds of living long and prospering. The National Institute on Aging's Interventions Testing Program in animal experience, but in experiments that are very stringent in terms of making sure that the results are robust and reproducible, has managed to find half a dozen drugs that extend a healthy lifespan in one or both sexes in mice. When I started looking into what's going on in anti-ageing research, to me, that was one of the big surprises that it's really quite well-validated in basic research that you can extend a healthy lifespan.

These mice live, in some cases, 30% longer. As Richard Miller from the Interventions Testing Program formulated it, they are not these old, decrepit, demented, little mice that simply won't die. They live healthily for longer. We've seen that kind of excitement about anti-ageing drugs before. The most recent example was the sirtuins almost 15 years ago. Those spawned a cottage industry and a lot of, more or less, tongue-in-cheek claims that you could live forever by drinking red wine and eating dark chocolate if anyone else remembers that.

**Lynn:** Yes.

[laughter]

**Anette:** I think what's different now is that in about the last decade, anti-ageing research has become much broader and more comprehensive than it historically has been. Almost 10 years ago now, some scientists published a paper on the hallmarks of ageing. That's an analogy to the hallmarks of cancer, which have spurred a lot of research and really proved to be a powerful conceptual framework for how cancer happens.

The hallmarks of ageing are nine separate cellular processes that seem to change with age in effect, whether you age in good health or become sick. There are lots still to be learned about which of them are causal and which might be targetable and whether there are others and whether some of them are more important than others. The hallmarks give the field a much broader basis for starting to look at what ageing means on a cellular and subcellular level and then, from there, how to address them pharmaceutically.

**Lynn:** You wrote that anti-ageing drugs might simultaneously reduce the risk of multiple age-related illnesses in one. How would that work?

**Anette:** Well, how it would work on a cellular level is the blockbuster question, right? Conceptually, ageing is a major risk factor for just about every chronic disease in the developed world. It's the major risk factor for heart disease, much stronger risk factor than high cholesterol. It's the major risk factor for cancer, certainly for neurodegenerative diseases. If you think about the pandemic we've all been living through for the last two-and-a-half years, your risk of dying from COVID-19 increases sharply with age.

Your chances of catching COVID are essentially no different whether you are in your 20s or in your 70s. Compared to someone in their 20s, your chances of dying from COVID are 140 times higher if you are over 75 and 330 times higher if you are over 85. Even in those diseases where it's not necessarily age-related whether you get them in infectious diseases, whether you die from them is very much age-related, at least in some of them.

Conceptually, the question is, what's the underlying factor that is driving up the risk for all these diseases simultaneously? If you could target that, then you should be able to lower the risk of many diseases at the same time. The CEO of Cambrian Biopharma, James Peyer, told me that the goal is to develop what he called a multimorbidity prevention drug. In terms of the actual cellular mechanisms you could target, there are a lot of possibilities.

Like I said, ageing science is not a settled thing yet. In our series, I focus on two different possibilities to illustrate how you can go about or how we might go about this. One is the rapalogs. That's a comparatively old class of drugs that have been validated by the ITP as extending lifespan in mice. For that class, there's approved therapies on the market. One is a transplant rejection prevention drug and there are anti-cancer drugs too.

That's an approach of taking things that are validated clinically but not for ageing, and validated for ageing but not clinically, and trying to put those things together. Another opportunity is to go for the really cutting-edge science that has neither been shown as of this moment to extend lifespan, nor has it been validated clinically, but there's good, basic science reasons to believe that it could work to extend health span.

As an example, I use in vivo partial reprogramming. That's trying to put into a therapeutic practice, something based on the observation that mature cells can be reprogrammed into a stem cell-like state through a cocktail of transcription factors. Those are the so-called induced pluripotent stem cells. They have become workhorses of biotechnology in cell culture. Shinya Yamanaka and Sir John Gurdon won the Nobel Prize for their discovery of how to create induced pluripotent stem cells in 2012.

That work is still very much at the preclinical stage, but there are several companies that think you can use this principle of partial reprogramming to develop anti-ageing drugs. Yamanaka is a scientific advisor to one of those companies. That's Altos Labs that launched earlier this year with $3 billion in funding and more Nobelists on their advisory board than most universities have on their faculty.

A lot of money, a lot of star power there. Interestingly enough, Altos does not call itself an anti-ageing company, but lots of other people sure do. The company says it works on cellular rejuvenation, which is pretty much reversing ageing on the cellular level. Those are the two ways you could go about trying to develop an anti-ageing drug. There's a lot of people working on each of them, but those are the two examples that I focused on.

**Lynn:** It's interesting that we have those two approaches, which really expand the possibilities. Switching gears just a little bit. Interestingly, you uncovered a phenomenon that centenarians live longer, not because they're less susceptible to any one specific disease but because they're less susceptible to all of them. How's that being leveraged in the field of geroscience?

**Anette:** Right, that was one of the fascinating things I learned that centenarians seem to live quite well even though, interestingly enough, they do not really live any healthier than the rest of us. If you look at whether they exercise a lot or whether they have been on the Mediterranean diet since they were 12 years old or never touched a cigarette in their lives, all that doesn't happen or all that doesn't seem to play a major role if you look at the statistics. The main hopeful message from there is that centenarians don't actually incur huge medical costs because they do not seem to get sick.

A much more typical thing if you're going to die at 100 is that you live fairly healthy for a long time and then you have a brief period of decline. It reminded me of my grandfather actually, who lived to be 89 years old and then died in his sleep one night, which is, as these things go, really not a bad way to go. I'm not saying that he never incurred any healthcare costs in his life, but at the time of his death, he was basically healthy and just old. That's a stark contrast to the overall healthcare spending patterns where medical costs just shoot up in the last two years of life.

One of the things that people have been afraid of is that if everyone lives to be 100, it will bankrupt any medical system, or that at least it will not save any money because you still have those high healthcare costs at the end of life. In front of that, you have 80 years of average medical costs instead of 60 years. The good news is that that just does not seem to be the case there. It's an active area of discussion what the cost consequences would be, but there is some modelling that suggests that by curing things like diabetes, you could extend lifespan, but you could also lower medical costs.

**Lynn:** You also found that ageing research has the potential to make existing inequities worse by exacerbating gender differences in health span. Talk about that a little bit, please.

**Anette:** Sure, so that was also one of the things that I found fascinating. I knew going into this, I think probably most people do, that women have the average longer lifespan. What I did not realize and I suspect most people don't is that women, on the average, also spend a longer time in poor health. Their health is worse, but they live longer in poor health. That's one thing. That was an interesting discrepancy to me in humans.

In animals, one of the things I learned that really surprised me and that I still don't understand is that the genes that affect lifespan mostly differ between males and females in mice and fruit flies and animals where people have looked. There are those two things and then you combine it with the third thing, which, of course, is that biomedical research, most of what we know, still comes from males. There has certainly been progress on that front, but males for a long time were just considered the generic human.

Then anything that differed between men and women, you would look at the male and then say, "Oh, the women are too complicated. We're not going to look at that, hormones, cycles, all this messy stuff. We're just going to ignore that." A lot of what we know about ageing still comes from the study of males. The Interventions Testing Program of the NIA has been a laudable exception to that. They have been studying male and female mice from the very beginning.

Several of the interventions they identified are only effective in one sex. Aspirin extends lifespan in males but not in females. If you put all those things together, the ITP does this very well. Companies, to prevent exacerbating gender differences, are absolutely going to have to look at both sexes and analyze differences between the sexes and the response to drugs in their interventions or you risk developing something that is only effective in one sex. If it's only effective in males, then it's going to exacerbate existing disparities.

**Lynn:** That makes total sense. Karen, let's turn to you. Your analysis reveals that the number of clinical trials of therapeutics designed to interrupt the process that leads to life-threatening conditions appears to be increasing. The amount of money that investors are putting into this space is growing too. Please give us the lowdown on the data.

**Karen Carey:** Thanks, Lynn. Well, the first thing I think you have to look at is what is happening to the market because that is one thing that really explains the increase of interest in this space. The general consensus is that the market is expanding because people are living longer and we have ageing baby boomers, but the data actually backed that up as you've already mentioned.

United Nations data show that the global population of those 65 and older rose 468% between 1950 and 2020. It's also actually expected to climb another 113% by the year 2050. There is a huge market potential here, not only with slowing the disease process but in preventing disease, extending lifespan, improving quality of life. We all want these things. In terms of therapeutic development, it is really hard to give a definitive, all-encompassing number of clinical trials currently ongoing.

We're definitely seeing the word "ageing" or "anti-ageing" being used more and more alongside certain indications, things like osteoporosis, osteoarthritis, Alzheimer's disease, cardiovascular disease. If we isolate certain therapies that have been tied into ageing, things like metformin, sirolimus, and resveratrol, just taking those three, we can see there are 16 current clinical trials. Actually expanding that into those already completed, Cortellis lists a total of 33.

We could go a different direction. If we search for the word "ageing," we come up with other therapies being studied like alendronic acid, denosumab, donepezil, and zoledronic acid. That gives us another 106 trials for everything from osteoporosis to Alzheimer's disease. We can even do a search for the word "senescence," in which a cell loses the ability to divide and grow.

Just by looking up that word, we find 26 current clinical trials for things like end-stage renal disease, liver cirrhosis, Alzheimer's, and others. To tell you the truth, though, there are most likely countless more trials that are targeting diseases associated with ageing. They're using different wordings, so it makes the search process a little more difficult. Overall, though, these types of efforts are popping up everywhere.

Another way we can measure interest in this space is to look at the money. BioWorld as you know tracks all financings from IPOs and follow-ons to private placements and venture capital rounds. If we look only at VC rounds, we find that as private company financings have hit records in the last few years, more money has poured into companies working on ageing diseases. From the full year of 2020 through early July of this year, there was $1.95 billion raised through 38 financings for private ageing disease companies.

Now, if we take that figure and we break it down by year, we went from about $350 million in 2020 to $900 million last year to about $700 million already this year with five more months to go. Now, these are companies that have specifically said they are targeting ageing diseases. If we look at all diseases known to be associated with ageing, the money would most likely go higher.

The other thing to note is a 2000 study by the NIH found that the cost burden associated with six conditions. It was basically chronic lung disease, ischaemic heart disease, stroke, lung cancer, pneumonia, and gastrointestinal illness. Those six conditions in people 65 and older, the cost burden was $135 billion and that's back in the year 2000. I took note of what Anette just said about how medical cost tends to shoot up the last two years of life.

If we extend life, we might have 80 years of average costs instead of 60 years. Looking at that $135 billion, what I found striking is that if I look at our VC rounds just this year involving companies working in those specific areas, I find $1.47 billion raised privately for 27 biopharmas. That is about 12% of all VC money raised in 2022. Now, it's a lot of money, but then when you look at that NIH study, $135 billion, it's actually a very small sum compared to the costs of these diseases on society.

**Anette:** Can I hop in quickly?

**Lynn:** Go ahead, Anette.

**Anette:** What I was thinking as you were talking, Karen, is that the 2022 money clearly doesn't even include Altos Labs, which by itself has $3 billion in funding because they don't consider themselves an anti-ageing company. As you were saying, it is somewhat difficult to figure out. The estimates that we have are probably something of a lower boundary for how much money is actually going into this.

**Karen:** Yes, I would totally agree with that. It is very hard to pinpoint an exact amount. There are companies working in multiple different areas. They may not specifically say they're working on an ageing disease or they're trying to interrupt ageing to prevent a particular disease. It's very, very difficult to know, not only with the clinical trials, how many clinical trials there are, but also to know the full amount of money. When we're talking about billions instead of millions, you know that it's having an impact.

**Anette:** Exactly. Of course, a number of these companies don't want to say ageing, I was just going to say Mari probably has something to say about endpoints in ageing. Take it away, Mari.

**Mari Serebrov:** It's not just endpoints. The other day, I was talking with Jan Poolman at Janssen Pharmaceuticals. He's working on some vaccines that target pathogens that are known to be drug-resistant. What he was saying is, eventually, the hope is that we will come up with a vaccine plan for older adults similar to what we see for little kids, but just targeting different infectious diseases.

If you could vaccinate against hospital-acquired infections, particular types of pneumonia, sepsis, whatever, that would increase life as well and improve health outcomes when people go in just for a routine surgery or something like that. Vaccines are not going to show up in the financing part of this, but they could play a huge role in extending healthy life.

**Lynn:** Let's turn to Richard now. Richard, what if these therapies do make it to market? What would be the benefits to society and patients, assuming that there is equitable access to them?

**Richard Staines:** It's a very big if, if we can get equitable access-

**Lynn:** Indeed. [chuckles]

**Richard:** and anti-ageing drugs. Yes, there are some real benefits, which have already been touched on. This whole idea of the huge cost to healthcare systems of diseases of age and also let's not forget the quality of life of people who've actually got these diseases, it's terrible. There's a driver at both the society and an individual level to try and maybe tackle this. There's a strong economic argument. It has already been put forward for early intervention if it can show that giving someone medication earlier in their life cuts the chances of severe disease later on.

It's particularly true, I feel, in the European model of health care, where there are healthcare systems funded either nationally or through insurance or the taxpayer. These systems, they're a strong incentive to cut costs and actual healthcare activity. I spoke with Marianne and Elisabeth Mertens, a partner at Apollo Health Ventures, which is one of the funds specializing in investing in therapies to tackle ageing.

She's argued that we could see healthcare systems evolve as the evidence stacks up in favor of intervening early. The hope is that these medicines or therapies could cut the instance of diseases of ageing and also to cut the costs associated with them. I would say in the US where health care is less centrally organized, maybe a different story, but people may see the value in self-funding a medicine if they think there's a good chance it will produce a health dividend later in life.

What's also interesting is as you've already alluded to and the other panelists have alluded to is metformin is one of the first drugs that's being trialed to prevent diseases of age. Now, this is cheap and readily available. While I wouldn't want to second-guess the outcome of a trial, if inexpensive, if a cheap, readily available drug were shown to cut risks of diseases such as Alzheimer's, cancer, diabetes, and cardiovascular disease later in life, it could certainly appeal to large numbers of people who may find it a worthwhile investment perhaps on top of trying to adopt a more healthy lifestyle.

To summarize really, Apollo Health Ventures argues that several factors are now coming together that can see healthcare systems evolve and begin to reimburse or encourage the use of anti-ageing drugs, whether or not this is the debate you had about the endpoint, which we'll move on too soon. The pressure on the healthcare system is increasing because of an ageing population as everyone's pointed out, but there's also a better understanding of the pathology and the molecular basis of ageing as Anette already pointed out. Overall, this could lead to a shift towards early intervention and prevention of chronic diseases of age.

**Lynn:** Thanks, Richard. You mentioned reimbursement. Let's turn to Mari because, of course, the buck stops here. Let's talk about how these therapeutics might be regulated because ageing isn't an endpoint. As a result, many new regulatory and reimbursement approaches are needed. Tell us about that.

**Mari:** Well, going off of what Richard just said, he mentioned metformin. One of the things with the metformin trial is it's more of proof-of-concept trial to map out a regulatory path for this. What I found interesting is that it's focusing on people who are 65 already and older. It's not looking at starting drugs in people who are 50 or 20 and seeing it forward because that would take forever to do a trial like that.

It's looking at people who already would be considered old by some measures even though I personally take umbrage with that. Generally, with drug development, we think of the major hurdles as being preclinical and clinical. Do we have a candidate? Can it meet proof of concept? In this field, actually, regulatory issues could be the biggest hurdle because of the indication issue and reimbursement could be a close second.

These hurdles will vary country by country because of how they recognize drugs. For instance, in the US, the FDA has the legal authority to approve drugs that are defined as substances intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. Then look at Australia, in addition to that definition, the TGA consider substance as drugs if they promote well-being. That's a big difference.

If you have to look at an indication as related to disease, some people are saying, "Well, let's make ageing a disease." Well, there's a problem with that since we all begin ageing at birth. At what point does age become a disease? Also, not everyone ages biologically at the same time. You could have a 65-year-old who is very healthy, and so they might object to being considered diseased, but then you can have a 65-year-old who has a multitude of chronic illnesses.

I think we have to keep in mind with this. This is what makes the indication tricky is that these anti-ageing drugs are not trying to stop or reset the chronological clock. The goal is to turn off or delay the arms of the biological clock. There is a big difference there. The reason the indication is so important is because it dictates the clinical trial endpoints, the size of the trial, and the duration of that trial. We've got to get that nailed down before we can really advance this field that much more.

Some in the field are pushing to have ageing recognized as a significant risk factor for multiple chronic diseases and Anette spoke to that. George Kuchel, director of the UConn Center on Aging at the University of Connecticut, noted that 95% of people, 65 and older, have at least one chronic disease. About 75% have two or more. That makes age the single biggest risk factor for these diseases. That includes cardiovascular issues, diabetes, cancer, and a multitude of other diseases.

Now, in the past, the FDA and other regulators have approved drugs to address risk factors such as high blood pressure, high cholesterol, blood sugar imbalances, even lifestyle factors such as smoking and obesity. To approve drugs to treat ageing as a risk factor, we have to develop biomarkers. People in the field have been calling for the development and validation of ageing biomarkers for more than a decade.

Even though regulatory science has evolved considerably over the past 10 years, we're not that much closer to having those biomarkers than we were in 2012. There's a lot more interest in it perhaps, but the regulators haven't gone on board with this as much. That's one big hurdle that we've got to overcome. The other is reimbursement. Like I said, Richard spoke to this.

Again, the challenges with reimbursement are going to be country by country, depending on whether a country has universal health care or whether they have a complex insurance program like the US does. Having a drug that could be transformational is going to be meaningless if payers and government won't cover it. In the US, we were reminded of that last year when CMS's coverage decision on all Alzheimer's monoclonal antibodies targeting plaque even if they had FDA approval, would it be covered under Medicare? In other words, FDA approval is no guarantee that you'll get reimbursed in the US.

**Lynn:** Mari, can't these doctors just prescribe them off-label?

**Mari:** That doesn't mean they'll get covered. Medicare doesn't cover most off-label uses, except in the cancer field. A lot of private insurers won't cover off-label uses, especially if a drug is expensive. Now, we don't know how pricey these drugs will be. A lot of it may depend on when they start having to be administered too. I know with the metformin example that Richard mentioned, metformin is a dirt-cheap generic, but not all the drugs that come down this path will necessarily be generics. That doesn't mean the price would remain dirt cheap if they were approved for this.

**Lynn:** Exactly.

**Mari:** One reason the FDA in CMS decisions differ is because FDA approval has to be based on the benefit-safety profile of a drug, whereas a CMS coverage decision has to consider whether use of the drug is reasonable and necessary. You have to get buy-in from CMS as to whether these drugs really will present a benefit, and so you may have to have different evidence from clinical trials to convince them of that.

One reason CMS is so important is a lot of the private insurers follow the CMS example. Then speaking of private insurers, if you have drugs that have to be started earlier in life to develop this benefit later in life, you can have private payers baulking at covering them because they're not going to see that financial benefit. Because by the time a person is healthier in their older years, they're going to be on Medicare or with a different insurance plan.

There also are challenges for countries that use health technology assessments to determine whether to cover a drug and at what price they could handle. Part of the problem with this is many of their drug assessments are based on drugs that are similar to ones that are already on the market. It's easy to make an assessment for a drug like that, but assessing a drug in a totally new class for a totally new indication, especially when all the evidence may not be available yet, could be a challenge for some of these assessment boards.

Then you've got individual countries having to face the question of how best to invest their limited health resources. This could really be a big issue in poorer countries. Poverty is the second biggest risk factor for chronic diseases. Poorer countries could benefit the most from ageing drugs, but can they afford these drugs for their entire population? That could be a big question for them.

The resulting discussion could trigger all kinds of socio-economic debates. For instance, will having a healthier, older population affect such things as retirement, employment opportunities for younger people, the balance of services the country is expected to provide? There are a lot of discussion issues here that will go well beyond life sciences and health. I think we're just starting to touch on those issues that these governments will have to consider.

**Lynn:** Indeed. My takeaway from what you just told us is that it all comes back to the equitable access portion. The first thing that came to mind is, "Oh, well, only the millionaires might be able to afford this in the beginning before insurers and regulators buy in," but maybe I'm jumping ahead a little bit.

**Mari:** Well, that's something that Dr Kuchel discussed. He said it's great to have that investment, but it has led to this misperception that we've got billionaires looking to extend their lives. He says that is not what's going on. The benefit will be to poorer people as long as they get the drugs. That's why the TAME trial is focusing on using a drug like metformin. That is so cheap because they want to make this affordable for everybody.

**Lynn:** That's encouraging. I want to bring it all back to Anette for a final remark. Anette, I know this is a very complex topic, but what is the most important takeaway about this research and the whole idea of extending our healthy lives?

**Anette:** I would say that I came to this story or this series sort of a sceptic. Like a lot of people like Mari has said, there's this perception that it is about billionaires trying to live forever. I'm sure there are some billionaires out there trying to live forever. In the bigger picture really, anti-ageing research has transformative potential. Like Mari pointed out, the folks who could benefit most are the ones who are poor.

Anti-ageing research has this transformative potential, but the nitty and gritty of it has a lot in common with other drug discovery. James Peyer, the Cambrian CEO who I talked to for this story, really hit the nail on the head in my opinion. He told me that anti-ageing research has been done a disservice because of the conflation of two things. One is what these drugs or any drugs can reasonably be expected to do about ageing, and then the other is the sci-fi notion that humans have that they want to beat death.

Immortality is a pipe dream and it will remain a pipe dream, but healthy ageing is this vibrant field of research with lots of potential and with plenty of people doing rigorous research. Also, some not-so rigorous research, which we talk about a little bit in the series as well, but really, there is a large part of it that is really not head in the clouds but has a real chance of going somewhere.

I guess to really bring it back, I'll go back to my grandfather. Dying at home in his sleep at the age of 89, which is the opposite of how way too many people die in the era of high-tech medicine. These drugs that folks are trying to develop, they're not going to make us immortal like I said. That trajectory of a long, healthy life followed by a relatively brief period of decline, I think we can substantially increase the odds of that for many people, and that is really what the field is trying to do.

**Lynn:** Anette, Richard, Karen, and Mari, this has been a fascinating discussion, which we'll likely revisit many times as we all grow older together pumping out the news about these kinds of amazing innovations and therapeutics for humans. As always, BioWorld will continue to keep you informed of all the most important scientific, clinical, and business updates. That's our show for today. If you need to track the development of drugs, turn to bioworld.com, follow us on Twitter, or email us at newsdesk@bioworld.com. Also, if you're enjoying our podcast, don't forget to subscribe. Thanks for joining us.

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