Science Ama Series: Hi Reddit! I'm Brian Hanley, PhD and CEO of Butterfly Sciences. I work on gene therapies (and vaccines) and I am a subject in my GHRH clinical trial. AMA!

Brian$_{H}anley^{1}andr/ScienceAMAs^{1}$

[1]Affiliation not available

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Abstract

Hi Reddit! I'm Brian Hanley, PhD and CEO of Butterfly Sciences, in Davis CA. I work on gene therapy approaches to aging, HIV/AIDS, adaptation to space, and the future. I designed a system that should be able to rescue late-stage AIDS patients, and GHRH was part of that. However, VCs told me that pharma wouldn't buy the company because they had drugs for HIV/AIDS and the pharma business model is daily consumption of drugs. Pharma does not like the "surgical model". I was aware of the potential for health-span extension from the start, and decided to emphasize that. This trial is in its 2nd year, and results look quite promising. However, the same pharma business model issues apply to most of gene therapy. I was recently featured on MIT Technology Review magazine https://www.technologyreview.com/s/603217/one-mans-quest-to-hack-his-own-genes/ I have other motivations for thinking gene therapy is important. I think that we will need it to adapt to settlement of space and other planets. From radiation adaptation and virtual elimination of cancer, to preventing osteoporosis and muscle breakdown, space will be a frontier for gene therapy. I also think it is a way we can use to change our age-bulge demographic problem. When social security was first created, there were around 6 working adults for every retired person being supported. Now, we are heading towards 2. Gene therapy has the potential to change the infirmities of old age and make people strong for life. Ask me anything about gene therapy and how it can be used in space settlement, to treat age-related health issues and HIV/AIDS. (Caveat - I cannot respond to personnel questions, nor can I give out proprietary information.) AMA is now over. It was fun.

the WINNOWER

REDDIT

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BRIAN_HANLEY R/SCIENCE

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Hi Brian,

Thank you for doing this AMA. I had a couple of comments, and then some questions.

VCs told me that pharma wouldn't buy the company because they had drugs for HIV/AIDS and the pharma business model is daily consumption of drugs. Pharma does not like the "surgical model".

I hear various iterations of this excuse a lot. They rarely hold up to scrutiny.

For example, the notion that pharmaceutical companies aren't interested in pursuing HIV research is bunk. A quick search on clinicaltrials.gov reveals more than 8,000 clinical trials (many sponsored by a pharmaceutical company) for HIV. There are nearly 1,000 trials investigating drug resistant HIV, the indication you seem interested in - again many of these trials are sponsored by pharmaceutical companies.

Further, the idea that pharmaceutical companies aren't interested in curative treatments is also ridiculous. Some of the most profitable drugs on the market are those that are curative in nature (e.g. Harvoni for Hepatitis C). The entire value proposition of these drugs is that they are potentially curative - that is why they are so profitable.

I went to your website, to try and see what your therapy was for HIV. From what I saw, I'm not surprised you didn't get any funding. The website is a bit confusing, but it appears you have two ideas for HIV/AIDs.

One idea is a gene therapy that loads HIV-infected cells with a camelid antibody against gp120. Cute idea, but there is nothing patentable here. You don't have an antibody sequence, you don't have a gene therapy construct, you don't describe how you plan to transduce HIV-infected cells with sufficient efficiency to actually impact the disease, there is no proof of principle experiments... etc. The idea just isn't investable at this point. If it is something you are passionate about, you should work to de-risk the idea and establish that it could work with some preliminary experiments.

Your other HIV idea seems to be related to GHRH gene therapy. Obviously, this wouldn't treat HIV, just HIV-associated lipodystrophy. And here I would agree that the field is a bit more saturated - mostly by GH/GHRH protein therapy. But again, the idea is so early that it is essentially un-investable. You need to provide some evidence that it has a shot in hell at working.

Sorry if that came off as a bit harsh, but this trope of "*I have a great idea but greedy pharma companies won't fund me*" crops up more than I would like and is a bit toxic, in my opinion. Why wouldn't pharmaceutical companies want to invest in medicines that could have a positive impact on patients' lives? That is how they make money.

So with that, I do have some questions for you:

1. What is your background in gene therapy? I did a quick Scholar/Pubmed search for you and your company and didn't see any hits for gene therapy, HIV research or aging research.
2. I was a bit concerned to see that your plasmids that you intend to use for gene therapy contain antibiotic selection markers. Are you aware all major regulatory agencies don't allow for these to be used in man (because of the risk of horizontally transferring drug resistance genes to bacteria, and also because of the manufacturing risks associated with using antibiotics)?
3. What are the prospectively defined endpoints of this one person trial you are doing? Have they been publicly recorded somewhere?
4. When you applied for IRB approval for this project, did you inform them that this study would be conducted on yourself? I have a hard time believing they would have approved it if they had known due to the conflicts of interest this creates.

SirT6

- I did not say pharma has no interest in HIV research. They do. They want new small molecule drugs that they can patent. I report what I was told face to face. I quote, "We know we can't sell your company, because pharma already has drugs that are making plenty of money.
- You are missing the business model problem. Harvoni cures a disease that has no existing drugs. That means that it does not cut into existing revenue streams.
- Camelid sequences are straighforward to get, and I've done quite a bit of work with custom antibodies. I don't have everything on the site. Transfection is submitted in a patent application.
- No, the HIV treatment isn't for lipodystrophy. GP120 has high affinity for GHRH. In later stage AIDS, viral loads get to 500,000 to 1 million copies per milliliter. That's a lot of molecular sponge. Go back and read it again.
- I'll answer your idea that pharmaceutical companies make money by positively impacting patient's lives in a few ways. First, yes, that is what those companies are supposed to be doing. I think a majority of the people who work in large pharma have that goal. That is not the whole story though.

I am friendly with a professor who is perhaps the top inflammation scientist in the world. I brought to his attention the strongest, longest-lasting anti-inflammatory molecule on record, DOI. I was thinking of using this as part of my formula, to help minimize immune stimulation. (Note – I later noted that DOI hits the 5-HT2C receptor, which would make it only usable on a short term basis. A banana to whoever can tell me why.) He educated me about that by saying that he had lots of those molecules that would last 30 hours and longer. But, pharma only wants things that last 4 to 8 hours, because that is what their business model is set up for. The drug business makes money moving product.

The other way I'll answer this is to point out that pharmaceutical companies most definitely have done harm by manufacturing more narcotics and hypnotics than the market can accept. In other cases, such as the campaign to kill GHB and tryptophan, pharma has done harm by removing cheap, effective and safer alternatives to prescription hypnotics. Pharma is a business, and it isn't one person. There are people on the marketing, sales, and accounting side who have little or no concern for anybody's health. And there are people on the R&D and development side who have nothing else in mind.

1) What is your background in gene therapy? I did a quick Scholar/Pubmed search for you and your company and didn't see any hits for gene therapy, HIV research or aging research.

- I worked on a gene therapy in grad school under Gary Rhodes, who is on the patent for bare DNA administration. There is a paper that hasn't been published. Gary had a series of strokes after I left, and then he died. The paper went over to a chair of the department. We discussed it, I found a grad student who was now a post-doc. She had tried to publish it on her own, because Gary had not been responsive to her for years, and she needed it for her career. She didn't know what happened to Gary. When the chair found out about that, he got upset. It's petty, but that's where the paper sits. It was a gene therapy to bring down homocysteine.
- I worked in an HIV lab prior to Gary.
- The currrent work is translational R&D. This is a long project, and the focus has been on patents,

not publications.

2) I was a bit concerned to see that your plasmids that you intend to use for gene therapy contain antibiotic selection markers. Are you aware all major regulatory agencies don't allow for these to be used in man (because of the risk of horizontally transferring drug resistance genes to bacteria, and also because of the manufacturing risks associated with using antibiotics)?

- Neither is true to my knowledge. There is a way to get rid of those, however, and it is my plan to do so for large-scale pharmaceutical use.

3) What are the prospectively defined endpoints of this one person trial you are doing? Have they been publicly recorded somewhere?

- There is a protocol approved by the IRB. No it is not public.

4) When you applied for IRB approval for this project, did you inform them that this study would be conducted on yourself? I have a hard time believing they would have approved it if they had known due to the conflicts of interest this creates.

- No, and it's a non-issue. I will answer this in detail separately.

Hi Brian,

Simple question, do you not think being a part of your own clinical trial is a conflict of interest and might have unintended consequences? If not can you elaborate on why not?

Thanks!

fractalfalcon

This is in part quoted from a manuscript in process on the topic of self-experiments and IRB.

There are three primary objections that I have been given to the issue of self-experimentation by scientists. First, is the idea that there is something inherently wrong due to ethical considerations. Second, is the idea that a scientist experimenting on themselves is uncommon, strange, and only done in dark alleys. Last, is the idea that when a person experiments on themselves, there is a serious conflict of interest that cannot be resolved, which makes such experiments worthless. All three are false.

1. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur, except, perhaps, in those experiments where the experimental physicians also serve as subjects. - Nuremberg court, principles of human experimentation

The growth of ethical concern in biomedicine is rooted in a series of outrages that occurred in the 20th century wherein people were used as test subjects and suffered terrible consequences, either against their will or unwittingly. The Nazi experiments conducted on prisoners in concentration camps led to formulation of the Nuremberg code for protection of medical research subjects in 1947 (Jewish, 2008). In article 5 above, the Nuremberg code states that the possibility of death or disabling injury is only acceptable where the experimenters are also subjects. The Nuremberg codes are the foundation for medical ethics today. Clearly, an experimenter who tests something where death and disabling injury are not likely to occur falls within the Nuremburg code.

In 1972, the story was broken on the Tuskegee study based on Peter Buxtun's whistleblowing, in which he revealed that he had been comp

Since then, in the USA, the FDA ceased to refer to the Helsinki documents, starting in late 2008, and refers instead to Good Clinical Practic

There is no regulation that suggests that scientific investigators as self-subjects is a concern. A scientist running a study should be expected
I looked for self-subject scientific experiments and found, without too much trouble, some 50 odd prominent cases in the bast 120 years, along with 5 Nobel prizes. However, Weisse identified a culled list of 465, and 13 Nobel Prizes awarded (Weisse, 2012). Weisse's criteria were a little different from mine. For instance, he counted all of the colleagues of Forssmann, who ran a catheter into his won heart. I only counted the initial experimenters who showed that it worked for the first time.

Clearly, 13 Nobel prizes, and at least 50 odd significant discoveries, refutes the idea that self-experiments are inherently worthless. But let's examine the idea that self-experiments have inherent conflicts of interest. One concern cited is the placebo effect. Another is that in a commercial situation, there is inherent financial conflict which would motivate an experimenter to fake it.

The placebo (or better termed, the neuro-immune) effect operates in every study. Pains are taken to ensure that in appropriate circumstances, double-blind trials are done so the subject does not know if they have taken the real drug or not. However, this is not always appropriate nor necessary. For instance, in surgical interventions, often, a placebo cannot be performed. In other situations, archived data can be used for the controls, and all subjects receive the real treatment, but are told they are in a blinded trial. The use of archived control data was pioneered, oddly enough, in non-human primate

studies as a method to minimize unnecessary suffering of animals.

Relative to financial conflict, it has been my observation that there is more of a problem in academia than in commerce. Why is this? Because in academia the survival of the investigator's career and their future grant opportunities often rest on their ability to get a positive result, and publish. And, in academia, the penalty is a slap on the wrist if discovered. In a commercial environment, however, when data is faked, the investigator can go to prison. Only recently was such fraud prosecuted in academia for the first time. And commercially, the data is going to be gone over more carefully by reviewers at the FDA. Any product will fail, and people can die from it, causing the company serious problems.

In the case of the current study, I took this into account by having the blood work done by others. All the safety study data was done through blood draws performed by Quest Diagnostics. The GHRH data was done by a collaboration with George Church's lab at Harvard. I will be moving to a more local testing lab for the latter this year for long-term followup.

The relevant blood tests are not items that have been shown to be affected by placebo. You can go ahead and try to raise your total testosterone, for instance, by placebo. It won't happen.

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Hi Brian,

Simple question, do you not think being a part of your own clinical trial is a conflict of interest and might have unintended consequences? If not can you elaborate on why not?

Thanks!

fractalfalcon

The unintended consequences part of the question I'll answer relative to the biology and possible pathology. Of course, that's a concern. I spent years looking at all the possible ways this could go wrong. I created 15 odd candidate vectors. I did not think the risk was high.

Why did I not think it was very high? Because of the plethora of literature on animal work using this.

Hi Brian. Your story about the difficulty getting interest from VCs for AIDS patients seems to highlight the need for alternate sources of funding that are less focused on profit models. Are there government grants and funds for this kind of research? If not, what can we as the public do to help motivate politicians to fund this kind of work?

firedrops

There are some grants. Grants tend to go to academics. And they require participation from others. You can't use any of the grant money for anything but science and some overhead. You can't use it for marketing, sales, planning, etc.

I think it really requires some entity with deep pockets to step up. Google. A guy like Theil. Or a few well-off individuals who want to see something happen.

Hi Brian

Thank you for doing this AMA!

Of interest, I posted the article that featured you in /r/futurology just over 2 weeks ago, and it received quite a bit of interest here: https://www.reddit.com/r/Futurology/comments/5n471q/one_mans_quest_to_hack_his_own_genes_unregulated/

I have also cross-posted your AMA from that sub too.

So, I really only had 1 question.

You say the results of the trial in the 2nd year is promising - how promising is it? Can you share some of your data? Are you subjectively actually feeling any improvement as a participant yourself?

Thanks in advance!

mvea

Capsule results: Testosterone up 20% with a peak increase of 77% . White blood counts up 16% with a peak of 40%. Lipid profile improved: HDLs up to 76, a rise of 20%. LDL down 20%. Triglycerides down 50%, with a low being down 60%.

Injuries up. This is not uncommon in regenerative medicine. I've reinjured all of my significant past injuries. Healing time is much faster. This is a new result that wasn't intended to be tracked but I've seen it due to the injuries. Overconfidence and feeling really good is why. Pulse rate appears to have dropped by 10 beats per minute or more. This finding is fuzzy though, because the baseline should be stronger.

As of the 6 month mark, there was stable persistence of expression at roughly 10% of peak.

Yes, I have definitely experienced a sense of improvement. I'm stronger. I've gone from a max of 50 lbs on a weight belt on dips to consistently getting 6-8 reps at 80 lbs. I've done sets of 90 recently. Not going to go through all my stats here, just an example. This could be attributable to psychology and placebo. But my exercise tolerance is higher.

After the first treatment, I began to feel so euphoric I literally fell over on my bicycle while riding up hill with a slow friend. I have a light scar on the back of my heel from that. I was just feeling so great I didn't react when I started to go over. Didn't unclip my foot. After that, I focused more. That intense euphoria wore off in about 6 weeks. It didn't repeat on the second treatment. However, something happened 2 days prior which was very concerning. One of my colleagues said he was so relieved when the euphoria went away. He thought it was pathological. But it didn't interfere with me getting things done.

Hi, Brian!

Thanks for doing this AMA, genetics and gene therapy is something that has really sparked my interest and I am currently looking to find an opportunity to study my masters in a similar area.

Just one quick question. With the recent development of our knowledge about the epigenome and epigenetic influences on diseases, behaviour and many other things, do you see gene therapy perhaps extending to epigenetic applications to reverse effects brought on upon by environmental stressors in early life?

Thanks again for the AMA, hope you have a great day!

YUHDEW

Sure. I think that's a very interesting field. Why don't you try to pursue it if you can? (I do know how hard that is, but you might get lucky.)

What I'm doing is translational work. Being in the basic research game takes large amounts of money, and only the largest pharma companies and people hooked into NIH are really players in my view.

Hi Brian,

Fascinating work. What do you think is the biggest challenge (regulatory, funding, moral, whatever) to widespread implementation of gene therapy? Mainstream view seems to be rather conservative, do you feel you have a different view of the possibilities of gene therapy from mainstream science research?

Varianz

The biggest challenge is that if we now try to deliver a transformative therapy to most somatic cells (or even a tiny fraction) we will kill the patient. I'm trying to work on that. It's a basic translational science problem.

There are 3.8×10^{13} cells in a human body. About 1/3 of those potentially matter. so call it $10^{13.}$ We can currently treat about 0.002% of those cells without killing the patient. That severely limits the use of gene therapy.

Secondary to that, is that when you administer therapies, you should expect to get something along the lines of a Poisson distribution of numbers of transfections per cell. This can be a problem with anything, including CRISPR. We need to be able to use control mechanisms to turn them on and off to acheive what we want.

Then you have the control of product problem. Ectopic DNA has a rapid rise in expression, then the cells get control of it. Getting long-term expression is a challenge.

Thanks for doing this AMA! I'm just curious what kind of degree and PhD you got. Currently I'm undergrad. with a biochemistry degree but I'd like to do genetic work in the future, thanks!

SWAT_259

I did a doctorate in microbiology. My advice is that whatever you do, learn your immunology as deeply as possible. And don't stick to a PhD. MD is a great degree. So is MD PhD. And in general, MD/PhD's are abused far less than straight PhDs are.

Could gene therapies be use to help fix neurological deficits such as neurofibromatosis and the sort?

LucidDaily

Yes, in theory, that's a CRISPR treatable set of diseases. However, that is similar to muscular dystrophy in that to cure it, you need to transfect very large numbers of cells. We can't do that yet.

1. Do you know about the gene therapy to regenerate sensory hair cells in the inner ear? If so, do you think it has the potential to restore hearing to normal?
2. Assuming everything goes smoothly, how long will a gene therapy's approval process take?
3. How high is the risk of a vector targeting the wrong cell or entering the wrong spot in the DNA?

-LifeOnHardMode-

1) I wasn't familiar, but took a look. http://www.nature.com/gt/journal/v23/n5/full/gt201612a.html Yes, I think so. And since this is a very small number of cells in a contained region, this should be practical to bring to market. Whether it will work in specific cases probably depends on how damaged the hairs are, and what exactly the pathology is.

2) 5-10 years for approval. But it would go over to stage 4, which is continued tracking after approval as a product.

3) I don't think this one would be a retrovirus. Retroviruses haven't been popular to use in humans since half the SCID kids got lymphoma or leukemia. This would be ectopic expression I would expect. Transient expression should do just fine, because regeneration would happen, and then it would take years of abuse to wear them down again.

In this post you've said a lot about the use of gene therapy to change physical attributes (including disease); but what about mental attributes.

Could we ever use gene therapy to change people's brain structure, and way of thinking?

What ethical issues does this create (could opinions be changed, could people be turned into pshycopaths etc.)?

JamesBaxter_Horse

I'm very cautious about getting into the brain for anything except clear interventions. It's only last year that it was discovered that the immune system has a role in learning. We really don't understand the brain. Nor are we clear about where the boundaries are. 90% of our nervous system is not in our

heads.

That said, I have some files on a few nervous system things. That's very much back burner.

Could we change a person's brain structure? Sure. For the better? Difficult. Mostly, though, since structure is determined by developmental genes that unfold in sequence and don't repeat, we can't expect to transform a living adult's brain structure. We aren't axolotls.

Could opinions be changed? I doubt we could set out to do it. Certain settings could be modified, perhaps. For instance, expression of certain neurotransmitter receptors could be changed, albeit with difficulty. (The blood brain barrier is a challenge - not completely insurmountable, but a challenge.)

Going down that rabbit hole a bit, it could be done with embryos in various ways. That would be pretty hard to get past an IRB though. And for good reason.

Hi Brian!

Thank you for doing this AMA. I want to ask you about what is your academic background and what made you decide to work with what you are currently doing now?

syesha

Microbiology. Prior to that, I had a good career in software. I did industrial automation, some AI and robotics, and CASE. In this venture, I did a few years in parallel developing and proving diagnostics patents. Those didn't license, which is typical.

I evolved into this. As I said in my intro, I started wanting to do an HIV treatment that could rescue people from late-stage AIDS. Worked on that, and funding wasn't going to happen. I was also interested in the possibilities of the specific treatment for long-term expression.

It's been a journey. I've collected ways to make remarkable changes to people and brainstormed on other fronts.

I've long had an interest in space. Was in the L5 society, then Mars Society, etc. And it became apparent to me that to successfully colonize, I think we will need to make genetic changes. Benign, but necessary for health and to thrive. Some environments, like high radiation zones, there's no way around it. Others, like living on Mars, I think it would be a very good thing.

Hello Dr. Hanley - thank you for joining us today. I'm curious about why you and Butterfly Sciences decided that you wanted to deliver your GHRH cassette through plasmids. Compared to other delivery methods (such as viral vectors), naked plasmids are notoriously inefficient in terms of cellular uptake and expression levels of their protein products. Why not use a viral vector (Adeno-associated virus as an example) instead? Especially if you're targeting muscle, there is already an established body of science indicating that AAV vectors can result in long-term, high levels of expression of genetic payloads in a variety of animal models [1],[2]

Additionally, I'm curious as to why you believe that "pharma" won't buy the company based on their current business model when more large biotech companies are investing in developing gene therapies than ever before. This particular report indicates that the tremendous upswing in Gene Therapy investment was primarily driven by big pharma.

CarloGesualdo

Q1) Several reasons not to use viral vectors. First, I can get good expression without them, and they increase cost. Second, for this treatment, if there is a reason to reverse the treatment, the location that was transfected can be removed. Viral vectors are not reversible.

Q2) I answered this above. It's what I was told by VC. When there is a current revenue stream that is lucrative for a condition, then pharma has no interest in supporting an alternative that has lower revenue. So an M&A deal won't happen. Or, that's how it was put to me. I expect that what they really meant was that M&A was unlikely.

Thank you for your time.

Have you considered going the military route instead of the civilian route? I'd almost be positive that a person that could engineer gene therapies to keep soldiers youthful and disease-free would be as valuable as the next Einstein. This way you could be funded by an unlimited supply of government cash, further your research and development, and hopefully eventually the technology could move

from the "tactical" military part to the "practical" civilian use.

Why not get in good with the military, become a valuable asset while making a ton of political connections, and have them back you while you build your own empire?

l_o_l_o_l_o_l

I haven't tried that.

Getting in good with the military is all it takes? :-) Reminds me of the recipe for making a small fortune. Start with a large one. I don't have military connections now. I've had in the past, but they've retired and are out of the action. The military moves people through pretty fast.

I want to use genetic modification to craft tiny kitties, is it doable?

ilovemarplesyrup

Yes. Dwarfism is also a longevity gene. Let me look for an example in mouse. https://www.ncbi.nlm.nih.gov/pubmed/11371619 The same thing should work for cats.

Hi Brian,

Thank you for doing this AMA. I do not have a science background, so forgive me for my uninformed questions/comments. I'm already learning much from the comments and responses here.

My questions: what are VCs?

How can gene therapy for space and planetary settlement be effectively tested?

What headway has been made in the area of anti-aging therapy?

HighlyFavord

1) A VC is a venture capitalist, typically a company. They invest in many ventures. The best paper on venture capital I know of is here. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2053258 It's a great read. It doesn't tell you how VC's act when you approach them. That's as variable as people can be. Some are downright weird.

2) I would test it here on earth by showing that a person transformed by these therapies would: A. Survive the experience. B. Pass the surrogate endpoints. C. Not suffer deficits as a result.

Most of those I have in mind would increase appetite, which could, possibly, be a problem in space. But, it might be worth it. There are things that can give near-super-powers.

Since a friend challenged me with it, I've been thinking about how to create a Deadpool type transformation. I don't have an answer yet, but these kinds of challenge questions are fun and make you think.

3) That's just too big to address. Join a Facebook group like, for example, Rejuvenation Science. https://www.facebook.com/groups/Rejuvsci/

That severely limits the use of archived control data was done through blood draws performed by Quest Diagnostics.

juventus199

What does this mean?

Brian, you have in the past written an article on possible machochimeric causes for homosexuality and transgenderism. Over all I was wondering if there was any progress on this, and second, are there any applicable principles as to which organs get which genetics or is it totally random?

jdbarnhart

There have not been any experiments to test prevalence in the population AFAIK.

When embryos merge at an early stage, what happens is that one of them becomes the ectoderm, one the endoderm, and the mesoderm is up for grabs. In rare cases, an embryo may split laterally with

all 3 layers. This was found in a bird, for instance.

The nervous system forms from a fold in ectoderm. Gonads form from endoderm. And, each organ typically forms from one cell apparently. So each organ will be expected to be nearly 100% from one embryo or the other, except in very rare cases. There is some infiltration of cells from the other embryo, but it's minor. This means that typically, the brain will form from one embryo, and the gonads from a different one.

This process is quite different than what happens if cells from a mashed embryo are injected into a maturing one. When that is done, almost anything can occur. You see a lot of infiltrates.