# Projects that might help accelerate strong reprogenetics

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## Introduction

This is a list of projects I'd like to assist.

This is a note aimed mainly at scientists, but also funders (philanthropy, government, commercial), and separately at other experts (law, policy, regulation, ethics, media). I'd like to assist with various scientific projects related to advanced reproductive technology, including by trying to direct funding to those projects.

Relevant scientific areas:

- **Reproductive epigenetics.** (Epigenetic sequencing and editing, epigenetics of reproduction and the germline, stem cell culturing, gonadal culturing, stem cell reprogramming, gametogenesis, creating gametogonia.)
- **Chromosome engineering.** (Targeted crossover, targeted elimination, targeted missegregation, chromosome transfer, microinjection, nuclear transfer, manipulating and sorting chromosomes, physics of individual chromosomes.)
- **Microfluidics.** (Cell lysis, microwells, droplet creation / transportation / sorting / merging, PDMS design and manufacturing.)
- **Cell engineering.** (Stem cell culturing, DNA damage and repair, CRISPR-Cas9 and transposases and other gene editing systems.)
- **Statistical genetics.**

## My general intentions

I'd like to assist with projects that have a good chance at meaningfully accelerating the creation of the science, technology, and social conditions needed for the socially beneficial deployment of strong reprogenetics, and in particular the ability for parents to vector the genome of their future child by several standard deviations

on cognitive ability. This note lists a wide range of projects that I'd like to assist, whether by advising, collaborating with, or directing funding to such projects.

In general, it's hard for an outsider to accelerate a field like reprogenetics. That's because it mostly consists of various fields of science and technology that are already being worked on using significant resources: polygenic prediction, stem cell bio, in vitro gametogenesis, gene editing, epigenetic editing, chromosome transfer, DNA sequencing, etc. However, I think there are many opportunities to accelerate the field, given the right intentions and funding. Many key projects are underfunded because government funding has restrictions and recent cuts; venture funding is skittish due to concerns about regulation or due to the science being not ready for translation to industry; philanthropic funding has PR concerns; and academia and industry may also neglect public goods that confer insufficient profit or academic prestige, such as datasets, cell lines, oversight, and public discourse.

I want to help fill those gaps directly. I also want to assist with projects that work to improve the social and regulatory landscape, in ways that would help fill those gaps in general. I'm open to being convinced that my picture about how to accelerate that is wrong or incomplete.

My main analysis of the technical problem of strong reprogenetics is here: https://berkeleygenomics.org/articles/Methods_for_strong_human_germline_engineering.html. I'm interested in critiques of the main conclusions there, especially if they'd change what projects seem good to support.

In order to help those gaps be filled, here's a list of some specific projects. I'd like to assist with these projects; and, to anyone who wants to accelerate reprogenetics, I'd suggest that these are good projects to assist.

(Note that the following projects are somewhat selected for being in biotechnology's "valley of death". There's lots of good relevant research in academia, and there are several promising startups worth investing in. More ambitious ways to accelerate the field would become feasible with more funding.)

## Societal questions

- There are many potential perils of reprogenetics. These perils could be analyzed (for severity, likelihood, and prevention and alleviation methods). See "Potential perils of germline genomic engineering".
- What governance structures should be used for research groups and vendors developing reprogenetics technologies?
- Talking to stakeholders (the public, advocacy groups, etc.) to understand opinions around reprogenetics, e.g. fears, hopes, questions, confusions, requests, etc.
- How should society develop and deploy reprogenetics technologies?
  - What regulations and social attitudes should be used?
  - What process should society use to decide this?
- How to ensure that reprogenetics…
  - …doesn't get misused?
  - …doesn't harm recipients?
  - …isn't marketed via fraud?
  - …is widely accessible?
  - …is broadly beneficial for society?
- Doing fundraising, whether from VC, large private capital, philanthropy, or government sources. Also, mapping the views of these funders—what preconditions would have to be met to get much more funding for key science and technology research.
- Doing advocacy for reprogenetics, broadly construed, e.g. producing media that explains and discusses reprogenetics to help society process these possibilities.
- Gathering together people who have expertise and legitimacy to map out plausible futures of a given technology, discuss safety and ethics, make open letters, roundtables, reports, etc.
- How does reprogenetics affect existential risk from AGI? (See my essays here; they leave a lot of work to be done: https://tsvibt.blogspot.com/2025/11/hia-and-x-risk-part-1-why-it-helps.html, https://www.lesswrong.com/posts/K4K6ikQtHxcG49Tcn/hia-and-x-risk-part-2-why-it-hurts)
- Doing social organizing and momentum-building. E.g. conferences, forums, etc.

## General infrastructure

I'm not sure about many examples here, but in general if there are very good proposals for activities that would support the field as a whole, I'm interested. Some examples:

- Creating a primate research center focused on novel reproductive technology. If the OHSU primate center shuts down, this will be a crucial gap to fill in order to test novel reprogenetic technologies.
- It would be valuable for long-term health and trust in the reprogenetics sector to have one or more legitimate, expert, industry-independent organizations to evaluate the relevance and truth of claims made by reprogenetics vendors. E.g. a third-party validator of claims about polygenic scores (predictive power, causal validity, accurate presentation), run by academic experts in polygenic prediction and possessing a held-out dataset, would help prevent and punish fraud, build trust by parents, and give regulators an expert reference point.
- Creating academic and/or open-source versions of technologies might help drive down prices and improve trust (by making the technology more transparent and validatable).
- Crafting regulation could be important for paving the way for more funding and talent in the space. For example, creating anti-trust rules could help ensure a competitive market and accessibility; fraud rules could protect parents and build trust; safety standards for editing, IVG, and so on could assure venture capital that the technologies have a viable pathway to testing and approval, as well as point scientists to what has to be done; etc. I'm interested in good ways to approach this, e.g. convening expert panels, drafting ideas, talking with policymakers, etc.

## Epigenomic correction methods

Strong reprogenetics probably requires actively correcting the epigenomic state of non-gamete/zygote cells to be competent as gametes/zygotes. See https://berkeleygenomics.org/articles/Methods_for_strong_human_germline_engineering.html#reproductive-gv-and-epigenomic-correctness-ec.

There are several approaches to solving or routing around this problem. Please see here for details: https://berkeleygenomics.org/articles/Methods_for_strong_human_germline_engineering.html#methods-to-handle-epigenomic-correctness.

These approaches point at several research projects.

E.g.:

- Epigenetic editing. (High efficiency, high precision; able to apply to all necessary types of epigenetic marks (DNA methylation, histone methylation, other histone modifications))
- **In vitro spermatogenesis and oogenesis** via reconstituted organs, xeno organs, organoids, or signaling methods. Ideally, efficient and fast induction of reprogramming, especially sex-specific imprinting, probably via molecular signaling methods.
- Spermatogonia extraction, culturing, and retransplantation, while preserving the ability to differentiate into epigenomically normal sperm.

I'd also like to assist projects to understand the necessary epigenomic states involved, as well as the developmental trajectories involved. In particular, more complete epigenetic cell atlases of human and primate reproductive tissues during critical germline development periods would be helpful.

If there's theoretical work that could plausibly bring great clarity to the nature of gene regulatory networks, how they are dynamically navigated and maintained during natural cell differentiation / reprogramming, and how to efficiently artificially manipulate them, I might be interested.

## Inducing crossover

In order to carry out a genomic vectoring protocol like iterated recombinant selection, some way of causing cells to undergo meiosis would be needed. More generally, causing chromosomes to recombine in large segments is useful for increasing the peak of available chromosomes's scores on PGSes.

I'm interested in projects that make recombination very efficient. This means developing a protocol that makes stem cells produce daughter cells with chromosomes produced by crossovers from the parent chromosomes. Such a protocol should also avoid introducing many de novo mutations. Inducing meiosis is

one potential principal method; other methods could include random recombination, targeted recombination (e.g. via DSBs at the same site on two homologous chromosomes and NHEJ with swapped ends), or hyperrecombination (inducing many crossovers per chromosome within one meiosis).

## Chromosome selection

See https://berkeleygenomics.org/articles/Methods_for_strong_human_germline_engineering.html#method-chromosome-selection and see https://berkeleygenomics.org/articles/Chromosome_identification_methods.html.

In particular, I'm interested in methods that have a good chance at one or more of:

- Assembling several chromosomes from several different cells (as opposed to just replacing one chromosome).
- Being fast and inexpensive, and preserving genomic integrity (as opposed to culturing cells for months on end).
- Operating on sperm chromosomes and preserving epigenomic integrity. (This is not necessary, it's just a bonus to maybe bypass the need for epigenomic correction.)

My belief is that MMCT is unlikely to meet these criteria, but I'm interested in having my mind changed. Similarly for whole cell fusion plus random ploidy reduction.

(Whole cell fusion plus targeted chromosome elimination is an interesting possible alternative. Likewise targeted missegregation. Eliminating single target chromosomes has been demonstrated in the context of MMCT; see e.g. Petris et al. (2025)[1]. If there's a plausible method to eliminate an entire haploid or diploid chromosome set from a diploid or tetraploid cell, especially in a targeted manner, without killing the cell, that would be quite interesting.)

More concretely, I'm interested in hearing from projects working on microfluidics for analysis of large subcellular biological particles, and of course in particular, chromosomes. For example, it would be great to see projects that replicate / refine / develop the following tools:

- **Key challenge: Storing and transporting chromosomes through microfluidic channels**, whether naked or in water/oil or water/oil/water droplets, without the chromosomes being damaged.
  - Damage would include large scale breakage, point mutations, deproteination, denaturation, or (ideally) epigenetic state changes.
  - Sources of damage would include mechanical forces (fluid shear, wall sticking), natural deproteination, deamination and other degradation, PDMS leaching, etc.
  - Remedies might include protective membranes; cooling / freezing; storing (during complementary identification); optimized buffer; special buffer additives (such as repair molecules and other maintenance mechanisms as in cells).
  - See for example Takahashi et al. (2018)[2].
- Extracting chromosomes from cells while maintaining origin-index information, e.g. Lam et al. (2024)[3].
- Isolating single chromosomes in droplets, selecting some droplets, and merging droplets, e.g. Babahosseini et al. (2021)[4]. In particular, a demonstration of ensembling a full euploid haploid genome into one droplet.
- Single-cell RNA sequencing for sperm, e.g. Bhutani et al. (2021)[5]. (Cf. "Chromosome identification methods—Sequencing post-meiotic RNA"[6].)
- Efficient sorting of chromosomes from other cellular debris, e.g. using dielectrophoresis.

[1]Petris, Gianluca, Simona Grazioli, Linda van Bijsterveldt, et al. "High-Fidelity Human Chromosome Transfer and Elimination." Science 390, no. 6777 (2025): 1038–43. https://doi.org/10.1126/science.adv9797.

[2]Takahashi, Tomohiro, Kennedy O. Okeyo, Jun Ueda, Kazuo Yamagata, Masao Washizu, and Hidehiro Oana. "A Microfluidic Device for Isolating Intact Chromosomes from Single Mammalian Cells and Probing Their Folding Stability by Controlling Solution Conditions." Scientific Reports 8, no. 1 (2018): 13684. https://doi.org/10.1038/s41598-018-31975-5.

[3]Lam, Trinh, Alison Su, Ana E. Gomez Martinez, Anna Fomitcheva-Khartchenko, and Amy E. Herr. "Single-Cell Organelle Extraction with Cellular Indexing." bioRxiv, December 23, 2024, 2024.12.23.630180. https://doi.org/10.1101/2024.12.23.630180.

[4]Babahosseini, Hesam, Darawalee Wangsa, Mani Pabba, Thomas Ried, Tom Misteli, and Don L. DeVoe. "Deterministic Assembly of Chromosome Ensembles in a Programmable Membrane Trap Array." Biofabrication 13, no. 4 (2021): 10.1088/1758-5090/ac1258. https://doi.org/10.1088/1758-5090/ac1258.

[5]Bhutani, Kunal, Katherine Stansifer, Simina Ticau, et al. "Widespread Haploid-Biased Gene Expression Enables Sperm-Level Natural Selection." Science 371, no. 6533 (2021): eabb1723. https://doi.org/10.1126/science.abb1723.

[6]Benson-Tilsen, Tsvi. "Chromosome Identification Methods." Preprint, Figshare, February 7, 2026. https://doi.org/10.6084/m9.figshare.31286665.v1.

- An end-to-end demonstration of complementary chromosome identification, as described in "Chromosome identification methods—Chromosome-wise complementary identification", and subsequent refinements for efficiency and keeping chromosomes intact. Concretely, this involves isolating chromosomes from a single cell and transiting to a sequencing area with low dropout / wall sticking. See for example Fan et al. (2011)[7].
- Methods to apply optical tweezers at scale (e.g. 64 operations in parallel). Optical tweezers are interesting as a way of manipulating chromosomes, but they seem to suffer from a high cost of operation and low throughput.

The most interesting versions of these projects would use human condensed chromosomes, and would track whether the chromosomes remain intact. More generally, I'm interested in projects that refine these tools to be more effective, more efficient, more accessible, more reusable, less expensive, etc.

More projects I'd like to fund:

- Experiments that inject a full disaggregated haploid genome (i.e. 23 chromosomes, but not all stuck together as in a natural sperm nucleus) into an oocyte, activate the oocyte, and see what happens and whether a male pronucleus forms around all those chromosomes. Along the lines of Kuretake et al. (1996)[8], but with disaggregated chromosomes.
- A method for directly non-destructively measuring the number and allelic content of an isolated condensed human chromosome. I suspect this isn't really feasible, but for example, Raman spectroscopy might work in the vein of Ojeda et al. (2006)[9]; cf. "Chromosome identification methods—Raman spectroscopy"[10].
- Investigate ways to isolate a single chromosome from a sperm nucleus with minimal disruption, e.g. no breaking and minimal deproteination. This might use some mechanical methods and/or some way of breaking down specifically protamine-protamine disulfide bonds without removing histones or modifying chemical modifications to DNA or histones. (Note: It would be nice, but not necessary, to preserve the epigenetic state of sperm chromosomes. The other reason to operate on sperm chromosomes is simply that those are the chromosomes that have undergone crossover, providing variation to select on. One could create a stem cell line from selected sperm chromosomes, and then derive an epigenomically corrected gamete from that stem cell line.)
- Tests of chromosome selection for strong genomic vectoring to greatly increase polygenic traits in agricultural species (where the epigenomic correctness problem can be largely ignored). Any chromosome selection method could be used, including ones that ignore issues of epigenomics and issues of genomic degradation from de novo mutation. For example, whole cell fusion interleaved with ploidy reduction is an inefficient but perhaps feasible method for chromosome selection that could be tried in, say, cows today.

## DNA damage during culturing

Most strong reprogenetic methods would require growing cells in culture for multiple months. That includes iterated meiotic selection, iterated CRISPR editing, and many chromosome selection methods.

When cells divide, their DNA gets damaged. The rate is high: something like, on average, at least 1 single-base-pair substitution per division (probably significantly more, like 3+), even under somewhat optimized conditions[11]. Further, there's some chance of indels, occasional copy number variation, and possible mitochondrial mutations. Worse, some mutations would be positively selected for in vitro. Even further, important operations such as inducing pluripotency in a somatic cell introduce base substitutions at a higher rate than mitosis; and meiosis might introduce small rearrangements (though maybe rarely, e.g. in <10% of divisions perhaps).

[7] Fan, H. Christina, Jianbin Wang, Anastasia Potanina, and Stephen R. Quake. "Whole-Genome Molecular Haplotyping of Single Cells." Nature Biotechnology 29, no. 1 (2011): 51–57. https://doi.org/10.1038/nbt.1739.

[8] Kuretake, Shoji, Yasuyuki Kimura, Kazuhiko Hoshi, and R. Yanagimachi. "Fertilization and Development of Mouse Oocytes Injected with Isolated Sperm Heads1." Biology of Reproduction 55, no. 4 (1996): 789–95. https://doi.org/10.1095/biolreprod55.4.789.

[9] Ojeda, Jenifer F., Changan Xie, Yong-Qing Li, Fred E. Bertrand, John Wiley, and Thomas J. McConnell. "Chromosomal Analysis and Identification Based on Optical Tweezers and Raman Spectroscopy." Optics Express 14, no. 12 (2006): 5385–93. https://doi.org/10.1364/OE.14.005385.

[10] Benson-Tilsen, Tsvi. "Chromosome Identification Methods." Preprint, Figshare, February 7, 2026. https://doi.org/10.6084/m9.figshare.31286665.v1.

[11] Kuijk, Ewart, Myrthe Jager, Bastiaan van der Roest, et al. "The Mutational Impact of Culturing Human Pluripotent and Adult Stem Cells." Nature Communications 11, no. 1 (2020): 2493. https://doi.org/10.1038/s41467-020-16323-4.

In the context of trying to produce genomically vectored gametes, this is potentially a major issue. Culturing for several months might introduce de novo mutations (of an unknown nature and impact) at a very high rate compared to natural mutation. For example, a 20 year old man's sperm might have a couple dozen mutations; a 70 year old man's sperm might have well over a hundred de novo mutations; a stem cell population cultured for several months might have hundreds of de novo mutations (especially cancerous ones).

Questions / projects:

- Are there ways to culture cells with much lower damage rates / much better repair?
- How bad is this actually, given that natural reproduction does involve dozens of de novos per generation, presumably usually mostly inconsequential? (Note that children of very old men in fact have significantly elevated risks of various issues, including mental illness, probably partly due to general de novos, partly due to selection effects for more proliferative spermatogonia, and partly due to other things like epigenetic sperm health.)
- What sort of gene editing technology could possibly keep up with this rate of mutation in practice? Is it possible to keep a population of stem cells alive and within, say, 50 Hamming distance of the starting genome indefinitely?
- What methods could produce strong genomic vectoring without running up against this problem? (My very speculative answer is microfluidics-based chromosome selection; what are other ideas?) For example, can iterated meiotic selection have large (say, 6 raw SDs) selection effects with only a couple rounds (at most 2 months of culturing, say)?

## Genetics

To a large extent, perhaps strangely, I don't view it as crucial to do more studies on genetics. We probably know enough about the genetics of intelligence to greatly increase the expected intelligence of a given future child. That said, there are a couple projects that I could be interested in as high-ish priorities:

- **Third-party PGS claim validators, as mentioned above.**
- **Tail studies.**
  - A key claim supporting a hope for strong human intelligence amplification via strong reprogenetics is that because we know very many variants causal for IQ, amounting to 10s of SDs in the linear model, we could get at least up to 6 SDs above the mean. This claim does not at all require that the effects of these variants stay *linear*. It just requires that they continue to add up substantially; in other words, the returns don't diminish super sharply above, say, 4 SDs.
  - A further claim is that such reproductive genomic vectoring would probably be safe because (1) the variants in question are common variants, (2) the phenotype in question is within the human envelope, (3) you'd also genomically vector for general health and also brain-protective variants, and (4) developmental canalization for well-formed brains should be reasonably effective (other phenotypes seem to be ok for somewhat-non-Gaussian trait values).
  - Both these claims are however not empirically validated. Studies that evaluate these claims could be valuable for understanding feasibility and safety of strong human intelligence amplification via reprogenetics.
  - See also: https://berkeleygenomics.org/articles/Some_reprogenetics_related_projects_you_could_help_with.html#:~:text=if%20you%E2%80%99re%20interested.-,Can%20genomic%20vectoring%20have%20large%20effects%3F,-Many%20scientists%20say
- **Cross-ancestry PGSes.** It's important, for wide accessibility and equality, that there be good polygenic predictors for anyone who wants reprogenetics. By my lay understanding, currently, PGSes don't fully generalize across ancestry groups. I'm interested in cost-efficient ways to improve this situation (e.g. via better causal-variant identification) that others aren't pursuing already.
- **Unknown pleiotropy.** My understanding is that, so far, the empirically observed pleiotropies between traits are pretty small overall, and furthermore generally tend to be of mixed sign (e.g. many disease risks are slightly positively correlated with each other, and intelligence is slightly anti-correlated with many mental illnesses). Further, the known associated genes largely don't overlap, suggesting that in general even very polygenic traits tend to be disjoint (as might be expected from simple models of random sparse vectors). However, in principle these traits may have just not been compared to some other less-studied traits; so in principle it could be that if you substantially intervene on genes associated with some trait, you also unknowingly significantly increase some other trait by surprise, which could harm the wellbeing of the future child. How plausible is this, given what we know? Are

there traits that are important and could plausibly be affected this way, but that we wouldn't notice as being correlated with traits targeted with reprogenetics? What sort of further investigations could inform these questions?

- **Meaning and genetics of non-abusable personality traits.**
  - Using reprogenetics to target personality traits such as agreeableness and so on is somewhat more concerning, to me, than disease risks and intelligence.
  - My guess is that it's fine, but one reason for concern is that there's more potential for abuse by pushing to extremes. Adding 3.5 SDs of IQ or -3.5 SDs of disease risk should be fine / safe. However, as a simplified example to illustrate, adding 3.5 SDs of disagreeableness might amount to creating something like a psychopath, and it's not extremely difficult to imagine some parents wanting to do that. Another example would be "obedience"; parents, or even states, might want to increase obedience pathologically.
  - But I wonder if there are any traits that would have upside to increasing, and no plausible appeal to decreasing. As an example, just to illustrate, I would speculatively conjecture that there's some kind of trait like "gets the main first-order bits right; is pointed in the right direction, along all the important dimensions" (see https://www.lesswrong.com/posts/fzKfzXWEBaENJXDGP/what-is-wisdom-1#Hypothesis).

  - Are there any such traits?
  - How can they be defined, measured, and polygenically predicted?
  - Besides wisdom, what about empathy? Strategic ability? Sanity? Reflectivity? Moral goodness? Ethicality? Responsibility? Integrity? Honesty? Good judgement? Ability to coordinate?
- (lower priority, but interesting) **Nonlinear and causal models.** What are the prospects for modeling nonlinear genome -> phenome maps? What about modeling coarse causal structure of those maps (such as "IQ affects EA but mostly not the other way around")? Might these models make better use of large heterogeneous databanks? What about models with a mixture of circuit depths (linear, one nonlinearity, two nonlinearities, etc.)? What about modeling all available phenotypes at once? What about discovering latent variables?

## Gene editing

Given the massive size of the gene editing field, I doubt that there are many "gap" projects I could recognize that would meaningfully accelerate the relevant technologies; but I'm open to being convinced.

Some projects I could be interested in assisting:

- If the task of editing a stem cell population many times in series is very neglected, that could be relevant (though my guess is that existing efforts such as Colossal would have this covered?).
- Methods to prevent excessive DNA damage during culturing.
- Methods to make large insertions—both the technology and also theoretical work analyzing the potential genomic vectoring power of that operation. For example, what are the densest clusters of IQ-affecting variants within one small region of a chromosome? With a realistic stochastic model of an individual's genome and resulting crossover chromosomes, what is the expectation of post hoc densest region of effect-weighted IQ-negative variants—i.e. what's the best you can do by replacing some 1-megabase region?
- Tests of strong genomic vectoring methods of any kind to greatly increase polygenic traits in agricultural species (where the epigenomic correctness problem can be largely ignored), in order to get end-to-end feedback / validation on strong genomic vectoring.