

# The Modern Virtual Biotech

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April 17, 2023



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**DATE RECEIVED:**

June 23, 2015

**DOI:**

10.15200/winn.143509.99979

**ARCHIVED:**

June 23, 2015

**KEYWORDS:**

virtual biotech, cloud lab,  
synthetic biology

**CITATION:**

Brian Naughton, The Modern  
Virtual Biotech, *The Winnower*  
2:e143509.99979, 2015, DOI:  
10.15200/winn.143509.99979

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It feels apt to write about virtual companies from the beautiful new [Hanahaus](#) space in downtown Palo Alto. \$3 an hour for a seat, and coffee by Blue Bottle. Rent in Palo Alto is actually not so bad if you share...



My impression of the typical "virtual biotech" is a company that is spun out to develop a compound originally discovered in an academic lab, or licensed from a larger biotech. There are only a few employees, usually pharma veterans, whose job is to shepherd the compound from CRO to CRO, and develop just enough evidence that the compound can be sold.

Recently, developments in biotech - analogous to the move to cloud computing in IT - may allow for a more complete virtual drug development company. Below I summarize how this might work, and the companies and technologies that enable it.

### CHOOSE YOUR THERAPY

Generally, **biologics** are going to be a better fit for a virtual model than small molecules.

The chemistry of drug development requires very specialized expertise, and large pharma/biotech has institutional knowledge that is extremely difficult to compete with. Also, because small molecules can be made of anything, their off-target effects can be difficult to predict (even aspirin is not **completely understood**).

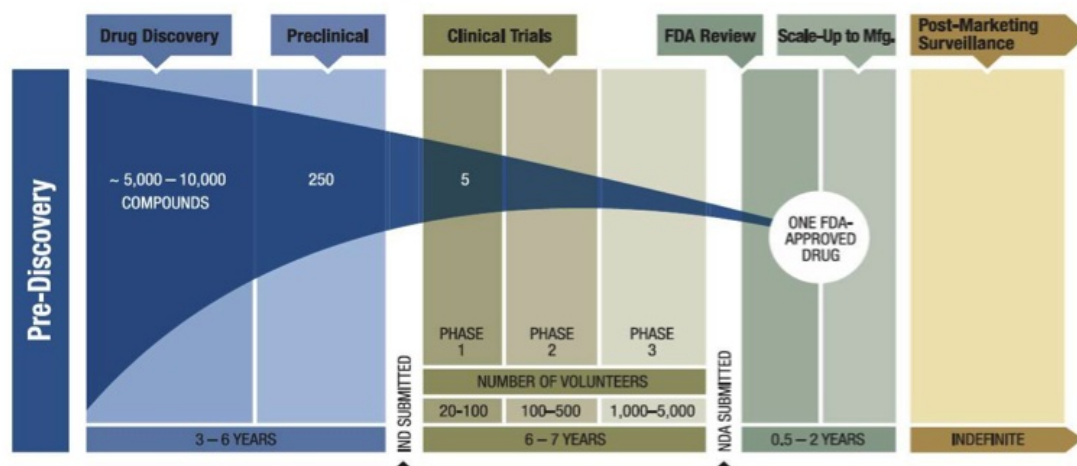
Nucleotide-based technologies like RNAi (**Alnylam**), mRNA (**Moderna**), and CRISPR/Cas9 (**Caribou**, **Editas**) would be ideal. Since they are nucleotide-based, binding relies on sequence identity, so it's much closer to a digital system. Theoretically, you can change targets simply by changing the nucleotide sequence, which makes the process much more predictable. Nucleotide binding is generally easier to predict because a 1D search space (the human genome, plus perhaps commensal bacterial genomes) is so much more constrained than a 3D search space (all structures/epitopes present in and on cells). Of course, these technologies have their own issues in that they are new and untested.

Protein-based biologics are arguably a good compromise. For example: enzymes (**enzyme replacement therapy** is worth billions of dollars a year), antibodies (seven of the eight **top selling drugs in 2013** were antibodies), BiTEs and CAR-Ts (cancer immunotherapy companies like **Juno** are showing extremely promising results). These technologies provide a more consistent design template than a small molecule (i.e., DNA), but there is still a lot that remains unpredictable, such as off-target binding for antibodies, or even how the protein will fold.

#### CHOOSE YOUR ADVANTAGE

Without the resources of a large biotech, how can a virtual company compete? After all, pharma/biotech has thousands of potential therapies sitting on the shelf. A therapy that works great in yeast, or even mouse, is not necessarily worth much because most of the risk in drug development happens after the preclinical research stage (an orphan disease with no treatments is an easier sell).

#### Drug Discovery and Development Timeline



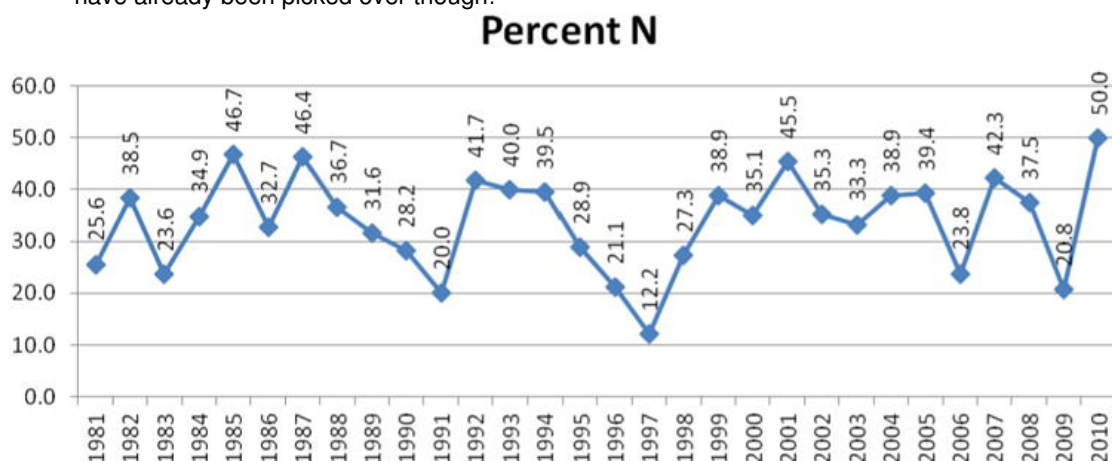
Since the eventual goal is a safe and effective therapy, that means there are three advantages your therapy could have:

- **More Safety** The therapy has already been shown to be safe in a clinical trial, or is a generic/off-patent drug (twoXAR, Recursion, NuMedii)
- **More Efficacy** The therapy works in multiple distinct organisms, so it should work in humans (Perlstein lab)
- **More Safety and More Efficacy** The therapy comes directly from a human, therefore there is some indication that it's safe and effective in a human (X01, Neurimmune). Recent applications of human genetics in drug discovery (e.g., PCSK9 inhibitors) rely on **asimilar concept**.

## CREATE AND TEST YOUR THERAPY

### Create

- **Design:** A good example of where protein engineering is important is **BiTEs**. You can think of two things that should be colocated (like T-cells and cancer cells), and synthesize a molecule that binds both.
- **Find:** A surprising fraction of drugs are still "natural products", many discovered through **bioprospecting**. Recently, with the incredible amount of sequencing capacity available, we can do this at scale from microbes (**Warp Drive Bio**) or maybe even from humans.
- **Repurpose:** You can just try all the compounds in a commercial **screening library**. They may have already been picked over though!



### Test

- **Model organism:** Testing in simple model organisms is great, if you have a good model (apparently, **yeast is a good model for Alzheimer's**) It also helps you parallelize your experiments since you can grow these little organisms in wells.
- **Human cells:** This method becomes especially powerful when combined with CRISPR/Cas9, even with a relatively **low yield** for now. **Rooster Bio** and **Extem Bio** are two startups providing MSCs (mesenchymal stem cells - not iPSCs) at competitive prices (Extem claims to have the largest stem cell library by several orders of magnitude). Of course, every large biotech is using stem cells too (e.g., **AstraZeneca**).
- **Animal:** Mammalian animal models (usually mice or rats) are expensive, (probably \$10k-100k per experiment) but currently necessary for any kind of serious drug development effort.

## CHOOSE YOUR DEVELOPMENT METHODS

Since this company is virtual, there are severe limitations on what is possible, so the choice of development methods is extremely important. The experiments must be inherently amenable to virtualization.

**Price Per Base of DNA Sequencing and Synthesis**

Rob Carlson, February 2014, [www.synthesis.cc](http://www.synthesis.cc)

