Drug Discovery: an Industrial Process

How are drugs discovered and developed?

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Drug Discovery Today

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What's my background?

- *First degree in Biochemistry*
- *PhD in Medical Biochemistry and Histopathology*
- *6 years Post Doc in Rheumatology (a joint award with I.C.I. Pharmaceuticals)*
- *Joined Eli Lilly in Rheumatology and later joined the CNS department*
  - *Involved with the launch of the SERM, raloxifene*
  - *Involved with the launch of the atypical antipsychotic, olanzapine*
  - *Involved with the successful patent challenge on Viagra, allowing the European launch of Cialis*
- *Joined Elsevier as Editor of Drug Discovery Today*

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Format of this talk

- *I'm going to walk you through the process of modern drug discovery*
- *This is just a framework, so I'd like today to be an interactive process.*
- *I'll ask questions and hope that you will do so too.*
- *Don't worry about asking "stupid" questions. I've based a career around this.*

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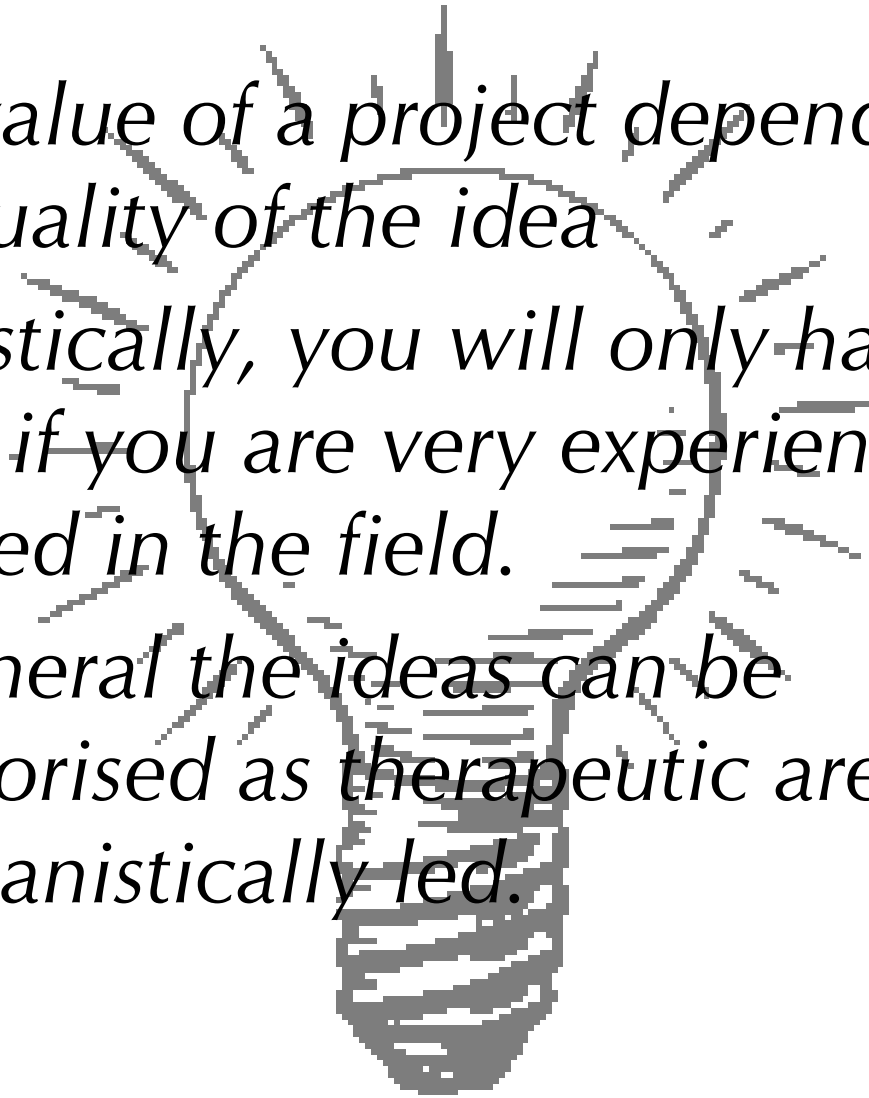
All projects start with an idea



- *The value of a project depends upon the quality of the idea*
- *Realistically, you will only have great ideas if you are very experienced and steeped in the field.*
- *In general the ideas can be categorised as therapeutic area led or mechanistically led.*

Advancing your idea

- *You have to convince a number of people that your idea is worth spending a great deal of money on.*
- *So the better the idea and plan, the more the chance of succeeding*

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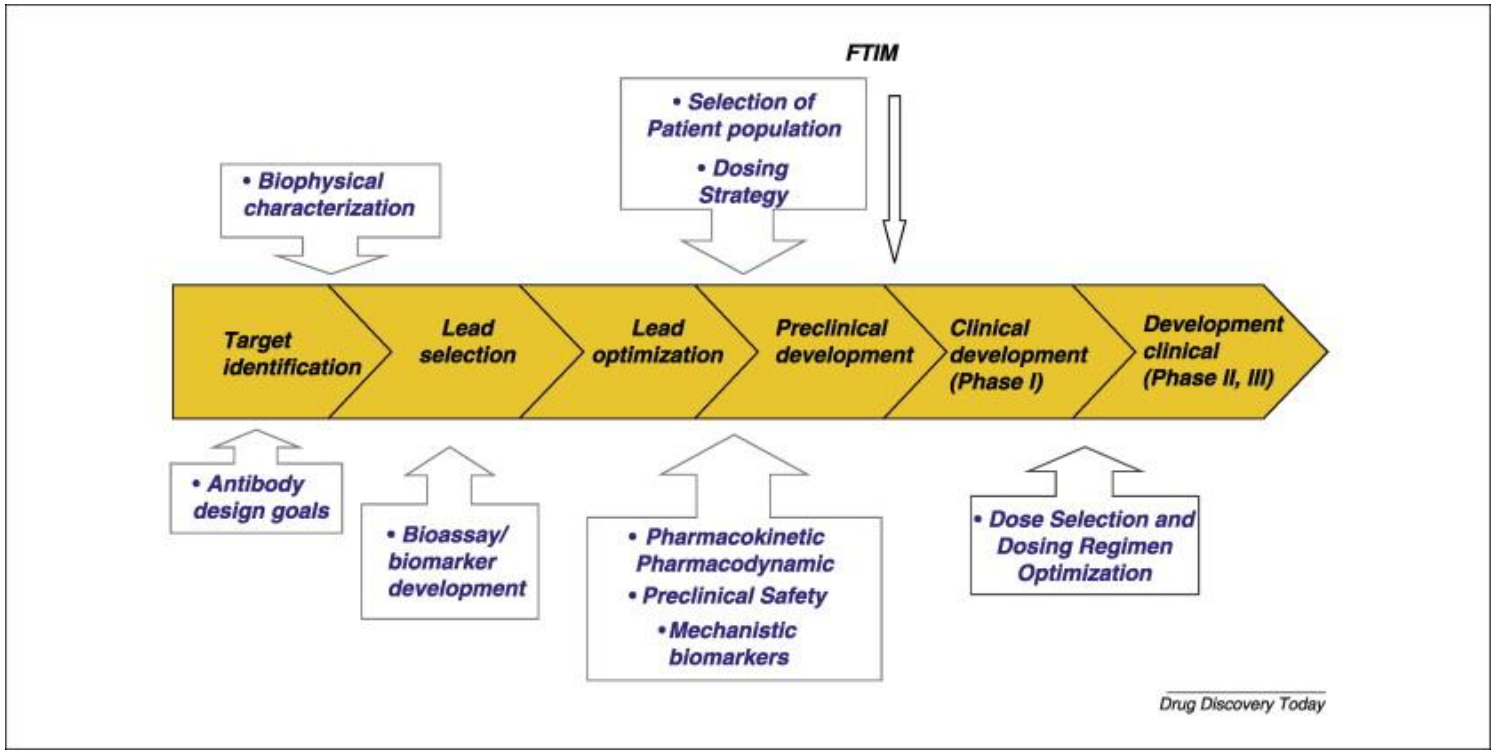
Generating an hypothesis

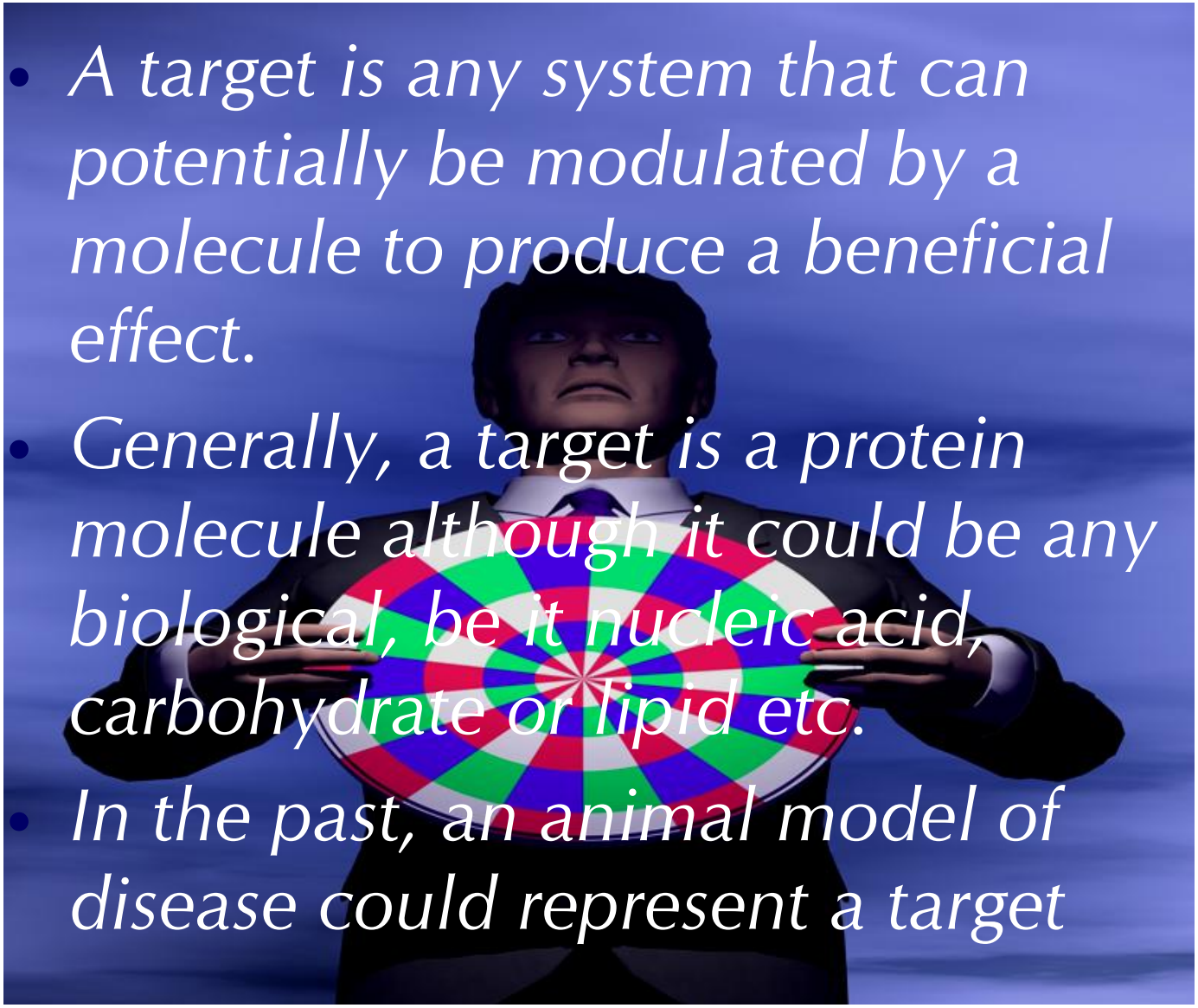
- *An hypothesis is generated from either in-house experimentation, or from external published material, or just the eureka moment in the bath*
- *The hypothesis should link a process to a fundamental pathological pathway*
- *Modifying the pathway should be expected to be curative or antisymptomatic.*

What is the process that underpins drug discovery?



- *This is the workflow for the production of a novel monoclonal antibody therapy, but the process is broadly similar for all NCE development*

What is a target?



- *A target is any system that can potentially be modulated by a molecule to produce a beneficial effect.*
- *Generally, a target is a protein molecule although it could be any biological, be it nucleic acid, carbohydrate or lipid etc.*
- *In the past, an animal model of disease could represent a target*

Target identification

In essence, pharmacology is the science of the interaction of xenobiotics with components of the living body*

Such compounds interact with the human body through binding to a biological molecule, generally proteins, but also nucleic acids, fatty acids, carbohydrates amongst others

As a result of the interaction, the function of the target is modified, such that a change in a pathway is induced

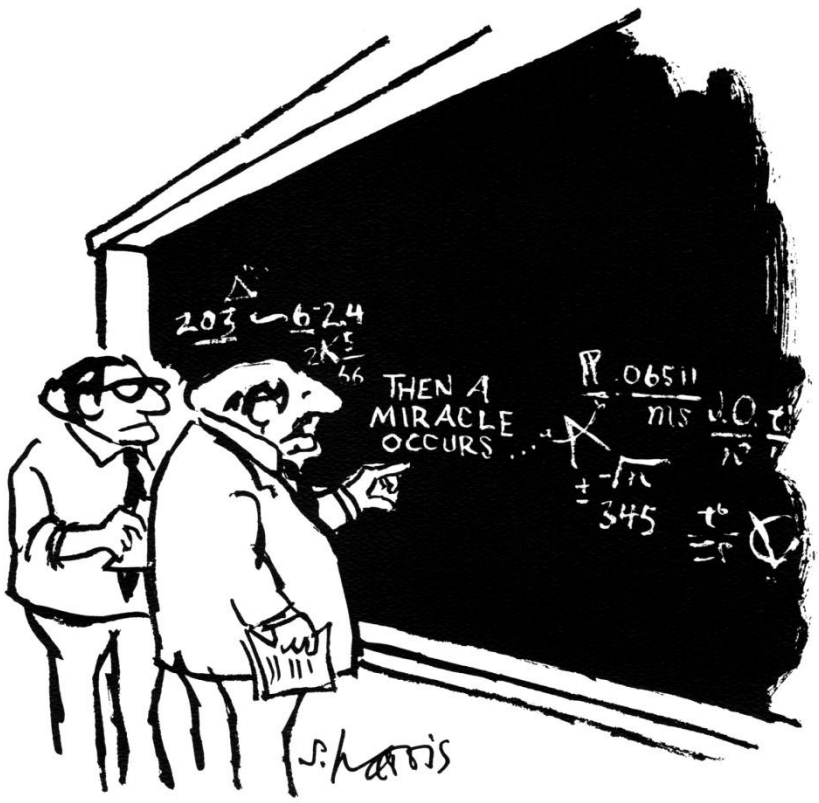
It is intended that the modification of the pathway will produce a beneficial effect on a disease process

**A compound foreign to an organism*

Target validation

- *Effectively, target validation is a form of risk assessment. The better the validation, the lower the risk in advancing a project.*
- *Hunch < anecdotal findings < literature precedent < cell model < animal model < pharmacology in animal model < pharmacology in human disease*

This approach is not so common now



"I THINK YOU SHOULD BE MORE EXPLICIT HERE IN STEP TWO."

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Some reading around this topic

- *The following articles deal with the topic of target identification and validation and are available as free downloads at www.drugdiscoverytoday.com*
  - *Identifying and validating novel targets with in vivo disease models: Guidelines for study design*
  - *Target discovery from data mining approaches*
  - *Disease-specific target selection: a critical first step down the right road*

Don't underestimate the importance of proper planning

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Starting a project

- *To explore the potential of your newly-validated target, you need to populate a team. The team needs to have individuals with different expertise in order to advance the project.*

Development of a project team

- *Assay development*
  - *Molecular biologist, in vitro pharmacologist, automation specialist*
- *Medicinal Chemistry*
  - *Medicinal chemist(s); process chemists*
- *ADME specialists*
- *In vivo pharmacologist*
- *Pathologist*
- *IT and IP support*

Transfected cell lines

- *The DNA encoding the protein of interest is isolated, some jiggery pokery goes on and the protein becomes expressed in a cell line.*
- *The advantages of this process are*
  - *Vastly (if not completely) removes the need for animal tissue in this process*
  - *Allows for a highly reproducible source of material for assay purposes*
  - *Gives expression levels that allow testing on proteins that may be present in very low, yet significant, levels in tissue*
  - *Allows for easy test development*

How long do you spend on a project?

- *It is human nature to champion your own idea and, in the past, people would continue to carry on with a project long after it should have been abandoned*
- *Nowadays, with the advent of high throughput technologies, it is common that a project would last about 18 months*

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Phases of a project

- *High throughput screening*
- *Hit identification*
  - *A 'hit' is a compound that has activity at a predetermined level against a target*
- *Hit validation*
  - *'Hits' are screened against an alternative assay (this could be a functional assay or a different assay format) to rule out false positives*

Hit identification

- *Those molecules that are identified at this stage have an affinity for the target, but little else is known about them.*
- *For example, in the case of receptors, it would be difficult (or impossible) from a traditional binding assay to determine whether they were antagonists, agonists, partial agonists, inverse agonists or even allosteric modulators, without performing further investigations*

Hit identification

- *Once you have validated a target, the next step in the process is hit identification*
- *To do this, you need to develop a test system that will allow you to determine compounds that interact with your target*
  - *In the past, this was often achieved by using whole animal systems*
  - *With the advent of molecular biology, however, it is common to test for interactions using recombinant proteins expressed in cell lines*
  - *Such approaches have resulted in a very significant reduction in animal usage by the pharmaceutical industry.*

Lead identification

- *Validated hits are virtually never the complete article with respect to being a drug*
- *The next phase is to identify those hits that have properties (other than just activity against the target) that would indicate that they have potential for being developed as drugs.*

Some reading around this topic

- *The following articles deal with the topic of lead optimisation and are available as free downloads at www.drugdiscoverytoday.com*
  - *Thermodynamics guided lead discovery and optimization*
  - *Modelling iterative compound optimisation using a self-avoiding walk*
  - *Outsourcing lead optimization: constant change is here to stay*

Lead identification

- *At this stage, validated hits would be tested to determine factors such as:*
  - *Selectivity versus a panel of other receptors (targets)*
  - *Physicochemical characteristics*
  - *Drug-like properties*
  - *Metabolic properties (half life etc.)*
- *Those molecules with acceptable potency, physical and ADME properties can be advanced through lead optimisation*

Lead optimisation

- *Those molecules fulfilling the lead identification criteria can go to molecular finishing school*
  - *At this stage, medicinal chemists conduct extensive SARs to improve potency and selectivity.*
  - *Also, this is the opportunity to improve physicochemical and drug-like properties*

Lead optimisation

- *When the field has been narrowed down, the best molecules are advanced to animal models and preliminary toxicology*

Lead optimisation

- *Individuals involved in this process include:*
  - *Molecular bioscientist*
  - *Medicinal Chemist*
  - *Pharmacokinetics group*
  - *Formulation group*
  - *Clinical researchers*
  - *Marketeers*

Candidate selection

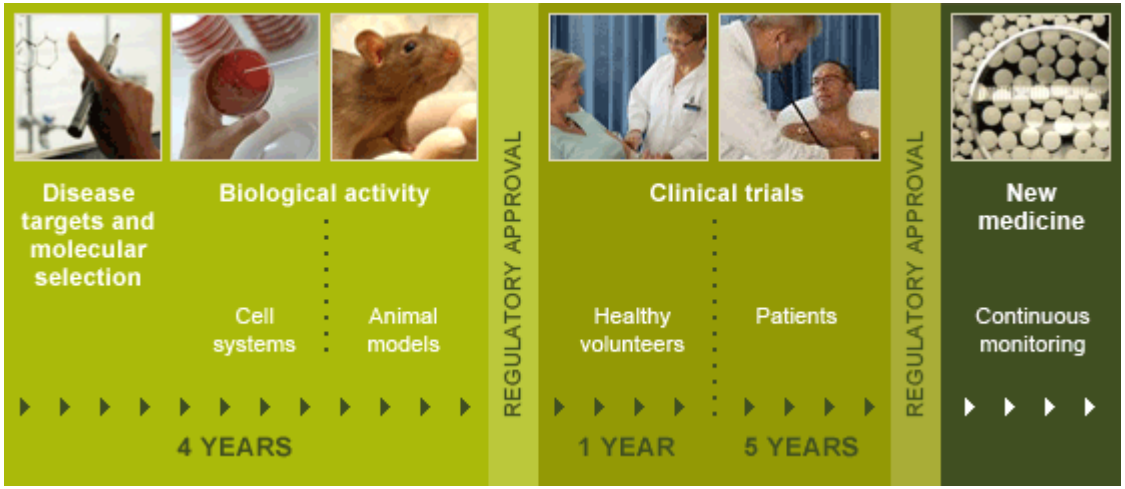
- *At this stage, those optimised leads are scrutinised for their properties:*
  - *Potency*
  - *Selectivity*
  - *Bioavailability*
  - *IP position*
  - *Safety*
  - *Scale up potential (can you make enough of it cheaply enough?)*
  - *The data on the successful candidate will then be submitted to the appropriate health authorities to get permission to conduct clinical investigations*

Can we reduce animal usage?

- *In short the answer is yes*
- *In fact there has been a significant reduction in animal usage in the Pharma industry over the last few years as a result of the introduction of new technology and approaches*
- *More than 82% of the animals used for experimentation are rodents. Only 4% of experiments are performed in mammals other than rodents.*
- *There has been a fall of 16% in animal usage since 1987*
- *The UK is probably the most regulated country in the world with respect to animal experimentation*
- *There are good reasons why companies want to reduce animal usage, not least financial*
- *For more information see http://www.nc3rs.org.uk/page.asp?id=8*

This process doesn't take long – right?

- The process that was just outlined takes in the order of 3-5 years to get to candidate selection
- From candidate selection to launch it can take around 9 years
- Overall time from beginning to end of the process averages out at about 9-16 years*



*John La Mattina (2008) Drug Truths. Dispelling the myths about Pharma R&D. Wiley

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Myth 1: Drugs are overpriced

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Just how much does it cost?

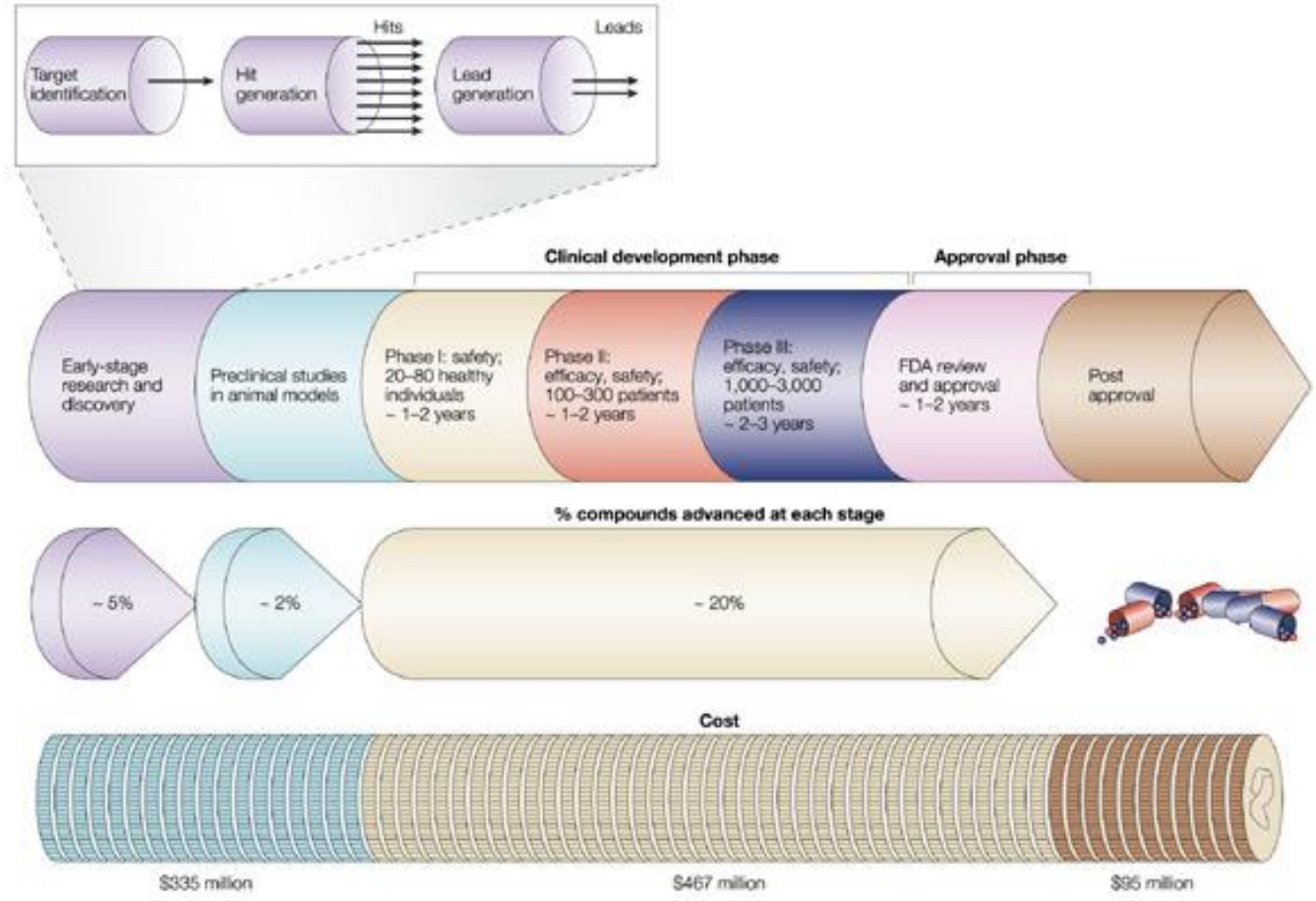
- *This is quite a hard question to answer, but a study by Joe DiMasi* estimated that it cost on average $800,000,000 to develop a new drug*
- *Although not confirmed, estimates for development of a new drug are now in the order of $0.5 - 2 billion***

*DiMasi JA, Hansen RW, Grabowski HG. J Health Econ. 2003 22(2):151-85

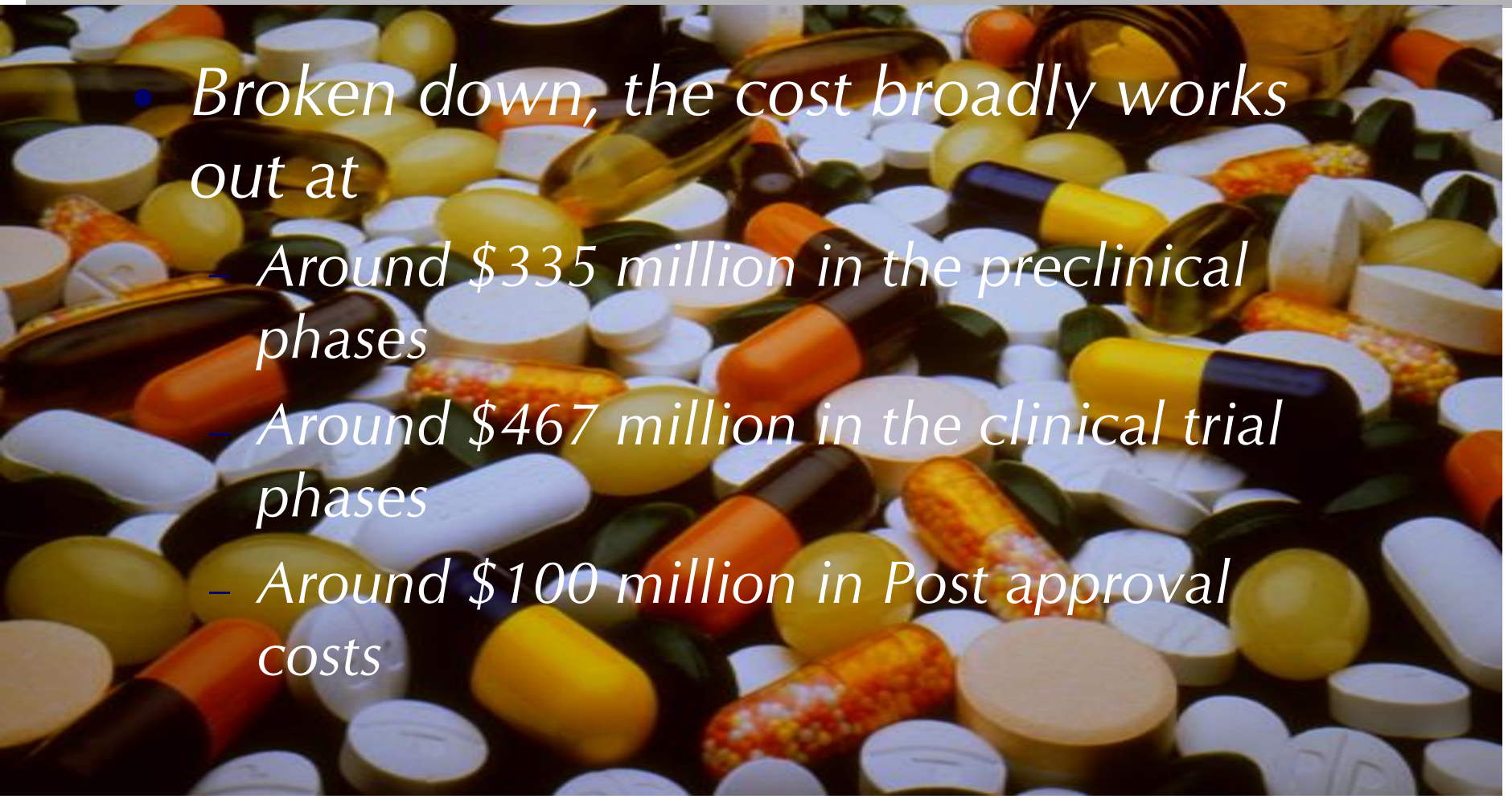
Adams C, Brantner V (2006). Health Aff (Millwood) **25 (2): 420–8

Myth 3: We can do all of this by computer (revisited)

- *Predicting just how a molecule will behave in a mammal is a particularly difficult task*
- *No matter how powerful the computer is, it is limited by the knowledge of those performing the test – it would require that we know pretty much everything about every biological system, which, obviously, we don't*
- *Even if we did understand all the biological systems, we would have to predict how such a molecule would interact with the various components of the system, which we can't*
- *The point here would be – would you be more confident of the prediction of safety of a molecule based purely on computer simulations, or one that had been tested in animals?*
- *Moreover, this approach is just as likely to miss rare events, based on individual genetic traits*


Hits
Leads
Target identification
Hit generation
Lead generation
Clinical development phase
Approval phase
Early-stage research and discovery
Preclinical studies in animal models
Phase I: safety; 20–80 healthy individuals ~ 1–2 years
Phase II: efficacy, safety; 100–300 patients ~ 1–2 years
Phase III: efficacy, safety; 1,000–3,000 patients ~ 2–3 years
FDA review and approval ~ 1–2 years
Post approval
% compounds advanced at each stage
~ 5%
~ 2%
~ 20%
Cost
$335 million
$467 million
$95 million

Just how much does it cost?



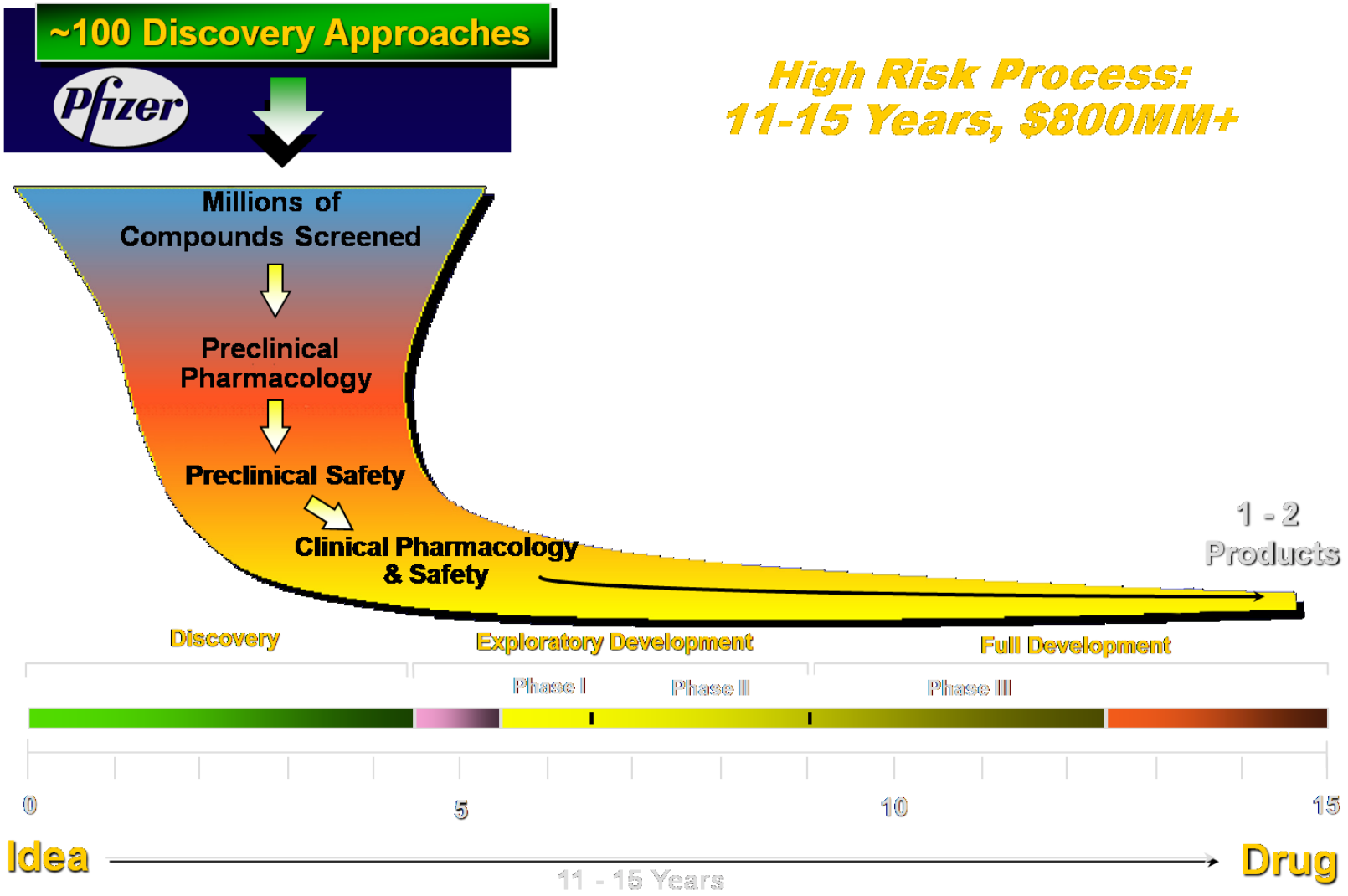
- Broken down, the cost broadly works out at
  - Around $335 million in the preclinical phases
  - Around $467 million in the clinical trial phases
  - Around $100 million in Post approval costs

Don't forget, it also costs to develop the ones that fail

- *Although these figures are a little out of date* (they are probably worse now with the introduction of HTS), it gives an idea of how wasteful the process is*
- *For every 30,000 compounds synthesized*
  - *2000 (6.7%) enter preclinical development*
  - *200 (0.67%) enter phase 1 trials*
  - *40 (0.13%) enter phase 2 clinical trials*
  - *12 (0.04%) enter phase 3 clinical trials*
  - *8 (0.027%) are approved*
  - *1 (0.003%) makes a satisfactory ROI*

*Christine A. Shillingford and Colin W. Vose **Effective decision-making: progressing compounds through clinical development** DDT Vol. 6, No. 18 September 2001

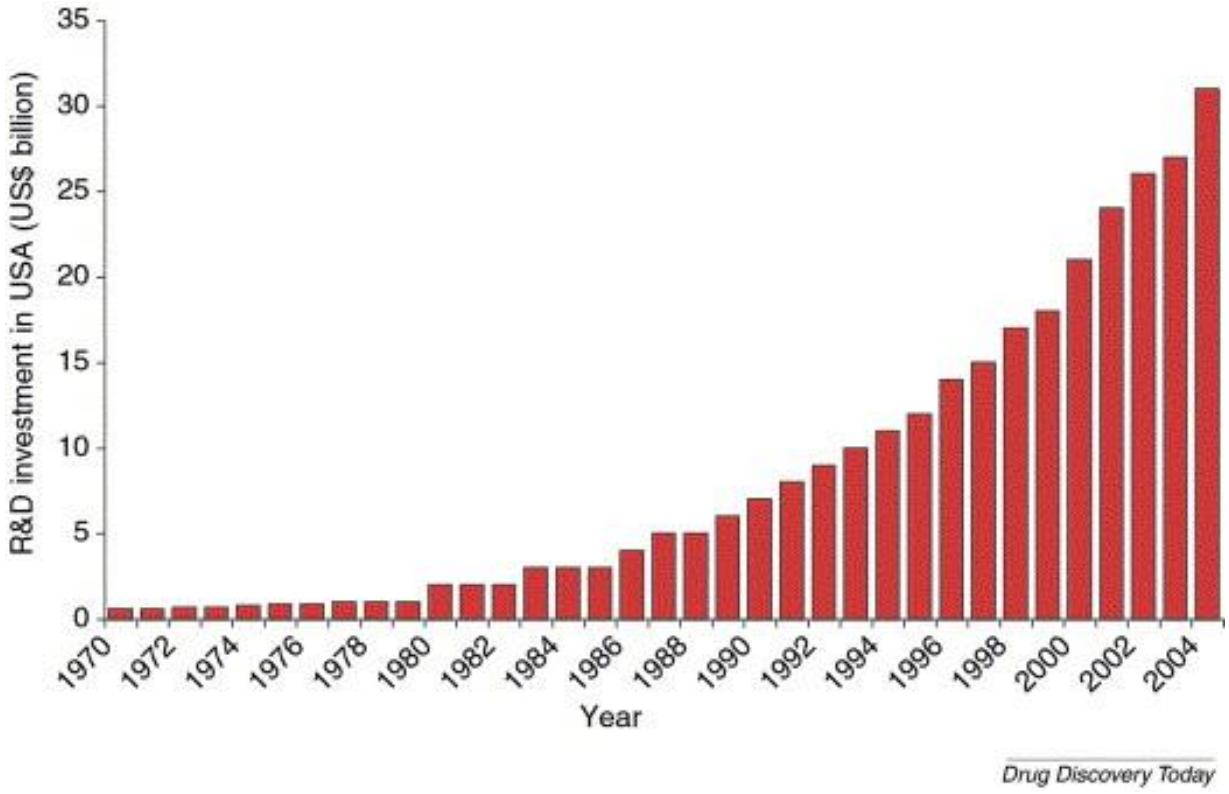
Drug Discovery is a very wasteful game



Don't forget, it also costs to develop the ones that fail

- *Attrition at late clinical trial phase is very expensive and can be disastrous for smaller companies*
- *It is important to point out that in the last few years, some compounds have been pulled out late because it was thought that they would not make a ROI.*
- *Clearly just getting a drug on the market is not a case of the goose laying the golden egg*

It's an expensive business



R&D investment in the USA between 1970 and 2004. *Source is the PhRMA annual survey (www.phrma.org/publications/publications/17.03.2005.1142.cfm).*

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Example: the development of antidepressant drugs

- *Initially it was observed that modulation of biogenic amine levels were implicated in the development of depression*
- *The hypothesis was that pharmacological modulation of biogenic amines could be a process useful in the treatment of depression*
- *How could this be achieved?*
  - *By increasing the synthesis of transmitter*
  - *By preventing its breakdown*
  - *By producing agonists capable of stimulating post synaptic receptors*
  - *By preventing the reuptake of neurotransmitter from the synaptic cleft*

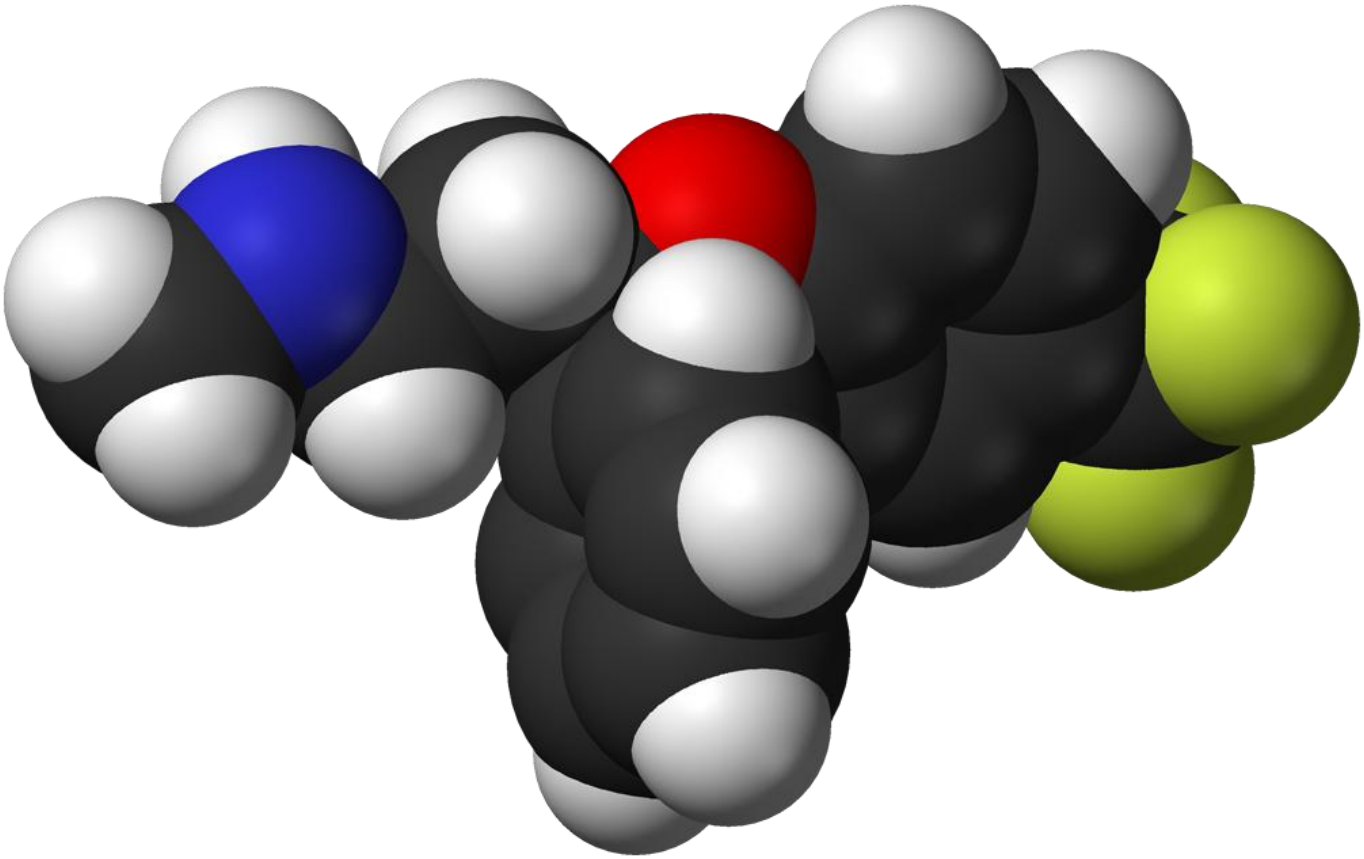
Which hypothesis was adopted?

- *Actually, all of those hypotheses have been used in the past, some to greater effect than others*
- *For the sake of example let us consider the final hypothesis*
  - *Preventing the reuptake of neurotransmitter from the synaptic cleft will have an effect on their synaptic concentration*
  - *Increasing the levels of biogenic amine will produce an antidepressant effect*
  - *Such increases could be achieved by inhibiting the appropriate neurotransmitter transporter*

How would we go about developing a drug based upon this hypothesis?

- We have now identified our target – the serotonin reuptake transporter
- The next part of the process involved validating the target
- Target validation involved a number of approaches:
  - Collecting all available information in the public domain that support the hypothesis
  - Developing in vitro and in vivo systems that can be used to support the hypothesis
  - Entering into agreements with external experts who can help with verifying the hypothesis
  - Assuming the hypothesis is sufficiently well validated, the team can move to the next phase which is hit identification.

Can you tell what it is yet?*



*Attr. Harris, Rolf

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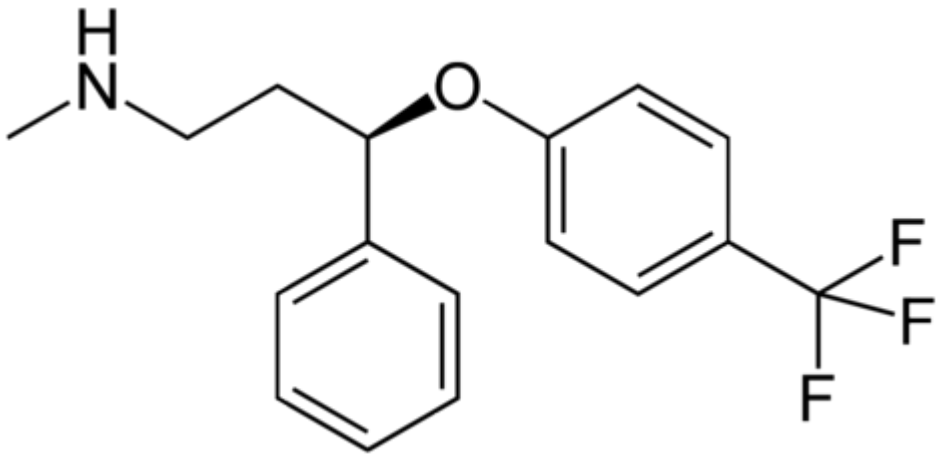

Fluoxetine

Myth 2: We can do all of this by computer

- *At present, this is not possible*
- *This is not a problem of computer power as such, but the intrinsic problem of how to predict conformation from scratch*
- *If you have a starting point, i.e. a molecule that you know interacts with your target, it will help you design the next molecule*
- *The value of computer simulation is in getting you to the optimal compound as quickly as possible, not in designing ligands de novo*

Myth 4: Animal models are useless in determining the action of drugs

- *This is an interesting point and one that requires some discussion*
- *No one would make the case that animal models are identical to the human condition, however, one must consider the following:*
  - *Every modern drug will have had to have passed efficacy and safety studies in animals. So pretty much every drug in the pharmacopoeia is an example of where animal models have been a success*
  - *Of course we can't really know how effective the screens are in weeding out unsafe drugs, as clearly it would be unethical to test compounds in humans if there were concerns over safety*
  - *Those who point to the inadequacies of animal testing point to a very small number of anomalies and I quote in the next slide from the website of Animal Aid*

Myth 4: Animal models are useless in determining the action of drugs

This is a direct quote from the website of Animal Aid

"A good example of how different species react to a chemical or medicine is penicillin, which is one of the most commonly used antibiotics today. Penicillin is toxic to guinea pigs, yet it cures humans. Products such as aspirin and paracetamol, commonly used to treat people, are highly poisonous to cats. Aspirin causes birth defects in most laboratory animals, but not in humans, and chocolate is poisonous to dogs!"

- *With respect to the comments above, should toxicity testing be performed in a single species, the comments on penicillin might have some validity. If, however, penicillin went through standard efficacy and toxicity screens (in multiple species) today, it would likely pass.*

- *As for paracetamol, the implication is that this compound is not toxic in humans and that somehow cats are anomalous in their response to this agent. I leave you to come to your own conclusions on this one.*

- *When a massive population is exposed to any external agent, you might expect a small proportion to respond unfavourably (and unpredictably). This is no different for drug molecules than any other.*

- *What else would you use? Would you be prepared to accept molecules that had been tested by some other means? Or should we accept that we should not continue with the development of drugs to treat unmet medical need?*

Clinical Trials

- *Once a candidate has been selected and the various safety hurdles addressed it can be entered into clinical trial.*
- *Compounds generally enter clinical trial at phase 1, although phase 0 trials are becoming more common, it is probably outside the scope of this talk*

Phase 1 clinical trials

- *Phase 1 trials generally focus on safety, tolerability and bioavailability properties rather than efficacy*
- *The drug is administered to a small number of healthy volunteer trial participants*

Phase 2 clinical trials

- *Phase 2 trials are focused on determining the efficacy of the drug in a larger number of patients (perhaps several hundred) suffering from the condition that the drug is intended to treat*
- *These trials may be performed globally and give information on efficacy and allow for a further estimation of safety in a larger population*

Phase 3 clinical trials

- *Assuming satisfactory results from phase 2 studies, the drug will enter phase 3 clinical trials*
- *Phase 3 clinical trials are in essence larger versions of the previous trials intended to answer specific questions with respect to efficacy*
- *The trials would routinely involve several thousand patients and compare the i.n.d. with drugs that are currently in use for the treatment of the disease ("comparators")*
- *The results from these trials essentially form the basis of the risk/benefit analysis that will be submitted to the regulatory authorities*

Phase 4 clinical trials

- *These trials are often referred to as post-marketing studies and they are performed after the medicine has been approved*
- *These give a greater idea of long term risk and benefit and may give indications as to how use can be modified*
- *The trials may involve many thousands of patients and go on for many years*
- *Such trials may assist in indicating other uses for the medicine*

Observations

- *Over the past 20 years there has been a number of changes in the Pharmaceutical industry*
- *There has been a shift from a "black box" discovery process to a "mechanistic" approach to drug discovery*
- *Although there are benefits to this approach, there are some issues:*
  - *The approach is predicated on the "one-disease one-gene" hypothesis, which clearly has limitations, not least for disorders such as schizophrenia amongst others, where effective drugs seem to target multiple receptors*

Observations

- *As our knowledge of disease increases, so does our knowledge of potential off-target effects. This increases the regulatory burden and limits available chemical space, which may account for the reduction in NCEs coming into trial*
- *As the procedure for developing drugs becomes more industrialized, the place for the "maverick" drug hunter becomes threatened.*
- *As a result, some of the more "off the wall" ideas may not be followed up, which is regrettable as this type of thinking is often what causes quantum leaps in development*

Remember why you do it

- *That is a hell of a rewarding feeling when you have made something that has become a medicine and people turn round and thank you for doing it. When you talk about professional reward, the people aspect is really something.*
  - *Robin Ganellin, inventor of Tagamet™*

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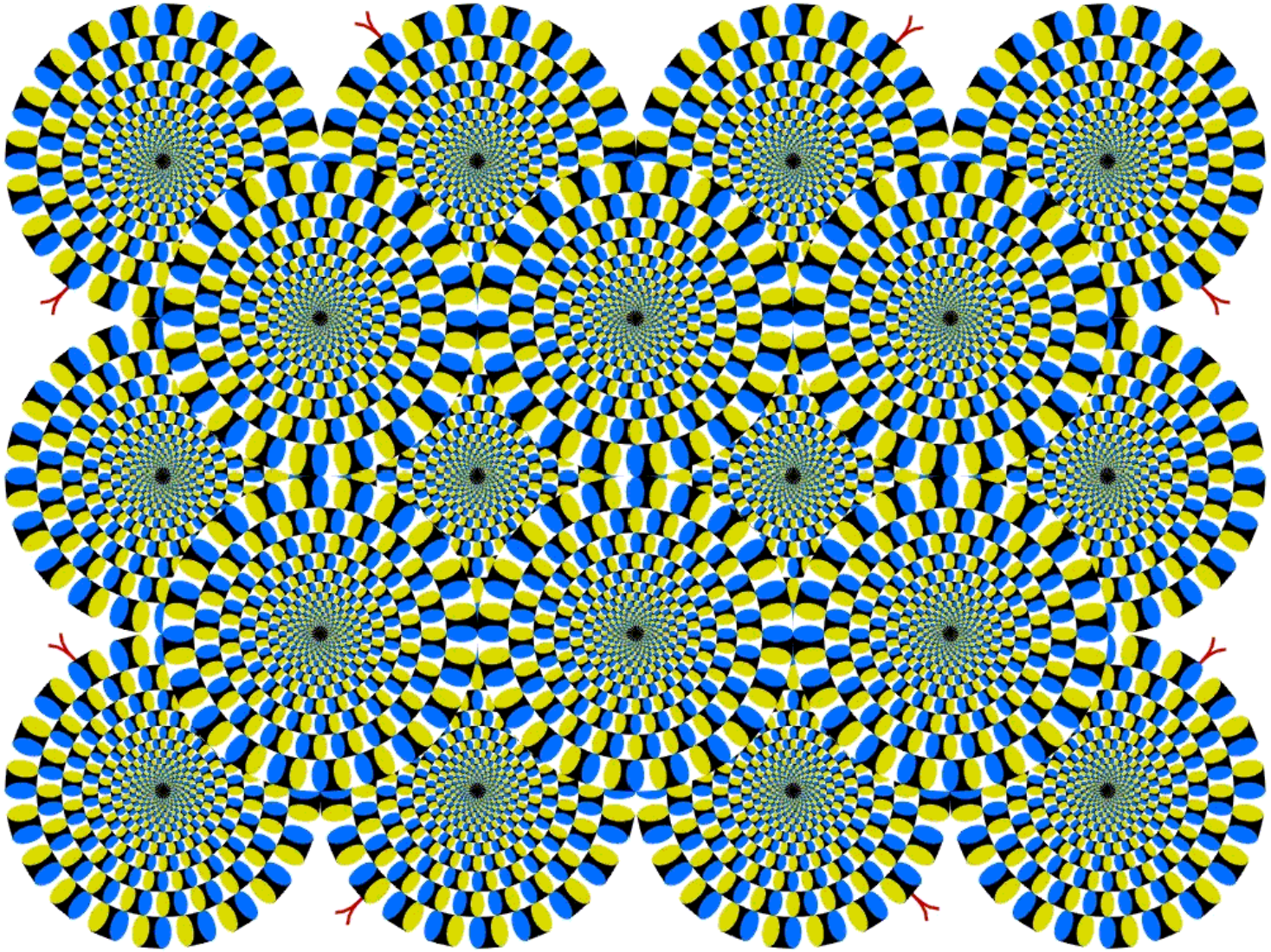
Thank you for your attention, I hope this mesmerises you enough to prevent you from asking difficult questions!



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