# Designing a new engine for life science innovation

## Mechanisms of delivering new ideas to real needs

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To bring novel treatments to market, organizations must integrate knowledge from domains as distant as molecular biology is from clinical trial design. Synthesizing knowledge across disciplines is the central mechanism of innovation delivery, but few organizations are designed to do it.

The neural networks activated in creative thinking provide a robust model for organizing biotech innovation. Findings on the neural, interpersonal, and organizational mechanisms of creativity can help an enterprise design a more successful engine to create value for patients.

Hearing the stories behind successful new products, you learn that creative solutions come from the recombination of existing ideas. You reflect on a problem and try out different ways of framing it. Seeing it from different perspectives enables you to bring in ideas that don't normally come to mind in the situation.

Our habitual, fast-thinking brain, however, resists new combinations of ideas. When presented with sensory data from a new situation, the brain searches its memory to find the first match that will make sense of the situation, and delivers one solution that seems obvious.[1]

The brain's creativity system supplements fast thinking with wider searches for relevant ideas. Just as the creative brain connects real-life situations to multiple ideas for addressing them, so can an R&D group connect people with know-how from multiple domains to find new solutions to unmet needs.

A real case study shows this knowledge synthesis at work. Stories told by the startup team at Acetylon Pharmaceuticals illustrate six innovation mechanisms in action:

1. Individual scientific creativity
2. Collective creativity
3. Scientific collaboration
4. Proof of concept
5. Product development
6. Innovation ecosystem

From these experiences, biotech leaders can learn how to design more powerful organizational engines to discover and develop new medicines.

**Background**

Acetylon Pharmaceuticals, founded in 2008, started up with a focus on selective HDAC inhibition, an epigenetic mechanism that can impact a wide variety of biological processes. Its founders were Harvard Medical School researchers Kenneth C. Anderson, MD (Dana-Farber Cancer Institute), James E. Bradner, MD (Dana-Farber / Broad Institute of Harvard/MIT) and Ralph Mazitschek, Ph.D. (Broad Institute), along with by Marc A. Cohen (Dana-Farber trustee) and Walter Ogier. The first target was multiple myeloma.

Acetylon raised $40 million over the next several years in a combination of private investments, government grants, and foundation support. In 2013, Acetylon and Celgene kicked off a strategic collaboration, including an upfront $100 million payment by Celgene to advance the science of epigenetics and to move forward Acetylon's pipeline. Celgene also received an exclusive option to acquire Acetylon. [2]

In late 2014, Acetylon entered mid-stage clinical development in multiple myeloma, initiating a Phase 2 study of its first clinical candidate, ricolinostat, in combination with Celgene's Pomalyst. An improved version, citarinostat, entered clinical trials in mid 2015.[3] Promising results for both compounds were reported in December 2016.[4]

In December 2016, Celgene acquired Acetylon. At the same time, members of the Acetylon research organization launched a new company, Regenacy, focused on the development of novel HDAC inhibitors in new therapeutic areas.[5]

## Acetylon's Innovation Engine in Action

### Mechanism 1. Individual scientific creativity

**The individual's neural system for idea generation**

Recent findings in neuroscience show that creative individuals make far more neural connections across different areas of the brain than matched controls.

Neuroscientist Nancy Andreasen:

> [T]he most extensively developed regions in the human brain are known as association cortices. These regions help us interpret and make use of the specialized information collected by the primary visual, auditory, sensory, and motor regions.
>
> For years, I had been asking myself what might be special or unique about the brains of [highly creative] writers I had studied. In my own version of a eureka moment, the answer finally came to me: creative people are better at recognizing relationships, making associations and connections, and seeing things in an original way—seeing things that others cannot see.
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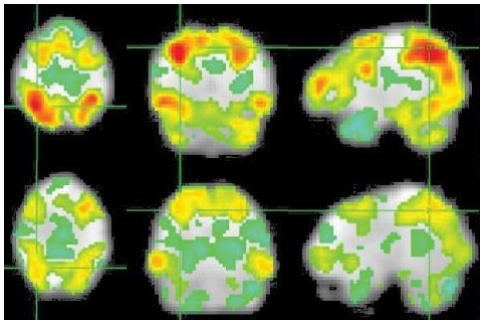
> As I hypothesized, the creative people have shown stronger activations in their association cortices…than the controls have. This pattern has held true for both the artists and the scientists, suggesting that similar brain processes may underlie a broad spectrum of creative expression.[6]



Functional MRI showing activity in association cortices during word-association task.

Top row: creative subject

Bottom row: matched control

**Example: The idea for selective HDAC inhibition**

Min Yang, one of Acetylon's first employees, shows the creativity mechanism in action in his story of the company's scientific origin.

> This is where the story started, as I heard it from Jay. From the very beginning, there are the three scientific founders, Jay Radner, Ralph Mazitschek, and Ken Anderson.
>
> Jay and Ralph had been together at Stuart Schreiber's lab at Harvard, they're super smart, they chat, chat, chat. They continue talking even after they leave. Each of them keeps up with all sorts of things all over the place. One of the ideas that falls out of these collusions is an HDAC6 inhibitor.
>
> HDAC inhibitors had been investigated for decades. The concept worked but the toxicity was so bad there were only 2 approved drugs. They were thinking, if there's a way to manage the toxicity but keep the efficacy there's a story, there's a chance. They look at the literature, they do their own research, and they identify HDAC6 as a good target.

Yang's story demonstrates the mechanism described in the research on creativity. He shows that long incubation, broad investigation, and wide experience enable scientists to synthesize knowledge from disparate sources to create new ideas.

Charles Darwin described this complex process memorably in 1859:

> When on board the H.M.S. 'Beagle' as a naturalist, I was much struck with certain facts in the distribution of the inhabitants of South America, and in the geological relations of the present to the past inhabitants of that continent. These facts seemed to me to throw some light on the origin of species – that mystery of mysteries, as it has been called by one of our greatest philosophers. On my return home, in occurred to me, in 1837, that something might perhaps be made out on this question by patiently accumulating and reflecting on all sorts of facts which could possibly have any bearing on it.[7]

**Recommendations: Find creative individuals**

- **Value broad thinking, not just subject-matter expertise.**

  Biopharma organizations typically look for employees, advisors, and collaborators with experience in precise technical and scientific domains. This can filter out people who can assemble novel solutions from a variety of sources.

- **Look far beyond your own network.**

  People that you already know tend to know what you already know. Don't let your own experience limit your ability to access domains of knowledge that can increase the value of your ideas.

- **Seek people with deep interests outside their professional domains.**

  Passionate engagement in a pursuit beyond one's specialty is a strong clue to a creative mind.

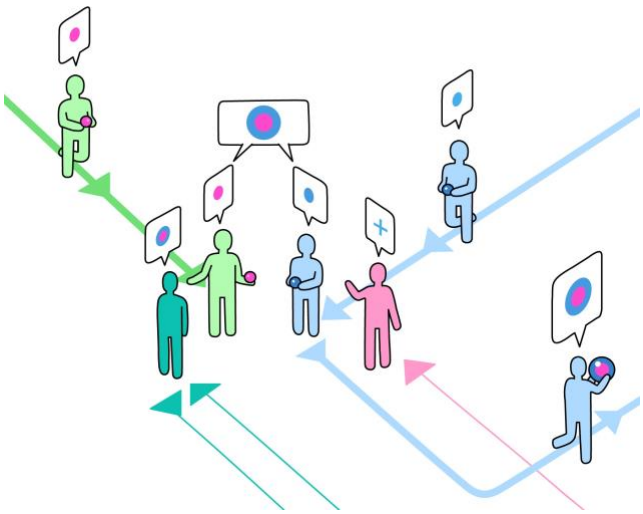
- **Require curiosity.**

  Anyone who doesn't ask questions won't learn enough to provide better answers.

## Mechanism 2. Collective creativity

**Interpersonal idea generation**

A group of creative individuals can generate collective creativity. Innovation is the process of newly applying ideas to problems, generating novel solutions. When people interact, they gain access to each other's experience, and activate associations across far-flung bodies of knowledge.



In order to map the interpersonal mechanisms that deliver innovations, Andrew Hargadon and Beth Bechky studied organizations with successful track records of bringing novel products to market. They found striking similarities in the way people interacted: all the organizations fostered and encouraged 3 types of interaction:

1. Seeking help.
2. Giving help.
3. Reflective reframing – trying out ideas from other domains to address the problem at hand.[8]

The core activity in these organizations is synthesizing ideas, not advocating them.

**Example: Applying HDAC inhibition to multiple myeloma**

Min Yang's story continues with a textbook example of collective creativity:

> Basically, they just put together the idea and the story really follows that line. That moment, one evening in Ken Anderson's home there's this party that Jay went to, and they were just talking. Ken, a multiple myeloma figure, is like, "Yeah, yeah, yeah, there's these things we should be testing." Jay is like, "Hey, what about an HDAC6-selective inhibitor?" If they could be that selective and just hit HDAC6, they could probably lower the toxicity. Ken and Jay conclude that it's definitely worth a shot in multiple myeloma.
>
> So Jay picks up the phone, he talks to Ralph: "Hey, here comes this! We talked about this, and now I just chatted with Ken."
>
> Next morning, Ralph made a compound: "I have something we can test."
>
> They get a whole bunch of compounds with the selectivity, and start testing it in vitro and in animals. The results look good. So the three of them say, "Well, we should put together a company." Ken and Jay start talking to investors, "Dadadadadada, this is it." These investors come in, the Kraft family [who also bring an interest in multiple myeloma philanthropy] is one of

them. They put together this company in Walter's basement [Walter Ogier, founding CEO] - not the experiments, that would violate Winchester's zoning – but all the legal stuff, the financial.

The party provides a conversational setting conducive to help seeking, help giving, and reflective reframing. Ken Anderson expresses the need for testing in multiple myeloma, which Jay Bradner sees as an opportunity for help. They both look at HDAC6 inhibition from the perspective of multiple myeloma, and conclude it's worth testing.

This kind of conversation marinates every event in the origin story. It starts with two creative scientists, Jay and Ralph, who for years have been "chat, chat, chat," discussing the questions that occur to them as they read and experiment. Jay brings Ken into this continuous exchange of help, and a plan for testing HDAC6 inhibition in multiple myeloma takes form. Marc, Walter, investors, and patient representatives bring ideas and energy from business and philanthropy.

**Example: New habits for scientists**

Simon Jones, Acetylon head of Biology, describes what he directs his group to do:

> The dynamic is not "ownership," not defending your turf so nobody else gets the credit. You have to unlearn territoriality. Then you suddenly realize it's very empowering. I'll ask, "Did you find someone? Telephone somebody over there." From my perspective, asking for help is central. Ask for help below, above, and beside. Try to get a person out of the habit of giving superiors what he or she thinks they want.
>
> A critical capability: being able to say you don't know. Make sure the people feel like that – no fear. I've said to my team, "I know it's bad to say you don't know – Ken Anderson might not take it well. But everyone knows you can't know everything. You can say, 'The state of knowledge we have indicates A, B, C. This is what I don't know – D, E, F. Here is how we're going to get there.' The FDA knows you don't know everything. Don't pretend you do."

Biology leadership encourages asking for help, the critical first step to generating innovative solutions to unsolved problems. Simon provides instructions for the conversational opening: explicitly state what you know and don't know. He directs his staff to seek out investigators who can associate Acetylon's tools with their experiences.

The interactions between creative people, if mapped, look much like the association cortices in the creative brain. Each person has a different stock of experience to match to the new challenge. Sharing the stories outside the original group stimulates even more creative connections.

**Recommendations: Build a culture of learning, not telling**

- **Unlearn the habits of academia.**

  Admitting you don't know is a sign of integrity, not a source of shame.

  A presentation is not a dissertation defense.

  When presenting, your job is enabling others to learn, not defending.

  When watching, your job is learning, not grading.

  Proving which idea belongs to whom interferes with problem-solving.

  Questioning someone senior is a knowledge-building move, not a career-limiting move.

- **Reduce dependence on PowerPoint.**

  Writing PowerPoint slides suppresses the cognitive activity of synthesizing knowledge because it encourages people to divide information into discrete, sequential pieces organized in rigid outlines.[9]

  Innovation, in contrast, connects information in associative networks. Full sentences in prose paragraphs better express the integration of different strands of thought that result in new solutions.

- **Model high-quality conversation at the top.**

  Train and coach senior executives on the disciplines of collaborative leadership:

  Skillful reflection on the different perspectives underlying technical and business decisions.

  Building solid understanding of the critical data and reasoning for taking action.

  Bringing out the whole range of concerns and ideas that bear on the issues at hand.

## Mechanism 3. Scientific collaboration

### Inter-organizational idea development

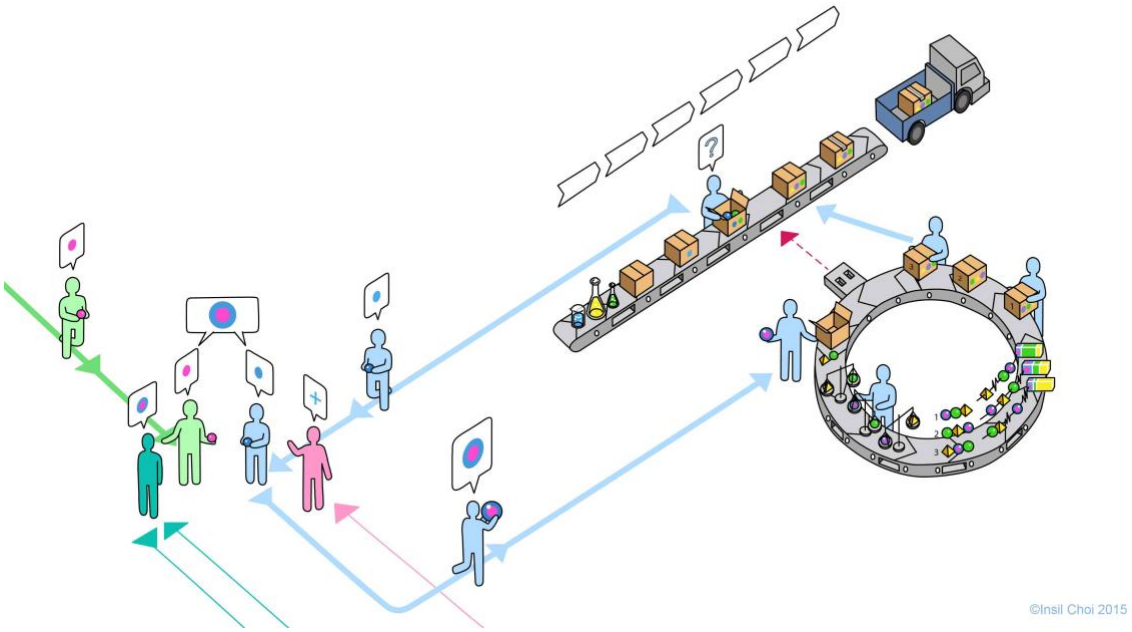
Technical and scientific work requires rich information flow between people across social networks. Holding inventions closely or restricting publication blocks knowledge flow, preventing social networks from growing in both breadth and depth. [10] Acetylon's open-source and publication policies provided a solid legal and cultural foundation for technical productivity.

### Example: Open Sourcing

Simon Jones tells how their new model for academic collaboration evolved.

> Let me tell you a story. Jay Bradner was on our Scientific Advisory Board and one of the founders. He and I spent a lot of time talking about "open-sourcing" of our compounds. We decided to do that – we send out our compounds to everyone. It's NOT, "We keep our valuable compounds to ourselves." It's "I'll give you the compound and you give us the results."
>
> If we decide to take our compound into an indication, it becomes a cooler collaboration. 80-85% of our collaborations didn't take us anywhere. The way they're structured: at the start, they do a few experiments. If we have the money, we can give some support for animal studies, but not up-front. We don't provide funds until we meet.
>
> The core of our external work is asking clinical advisors. "Is this worth pursuing?" Somebody is picking up the phone and asking, "Who do you know?" Pulling in the extra knowledge. I have a biology group – many times I encourage them to get collaborators. Don't work in a box. You'll need to convince collaborators. You'll have to find somebody – see if somebody's interested. Entice people in. Get more collaborators.

Academic collaborations expand the network of collective creativity far beyond the limits of the company.




### Example: Publication Rights

Matt Jarpe, a leader in Acetylon's biology group, shows how their unusual publication policy promotes the synthesis of existing and new knowledge.

> What connects the whole network is the publications. Academics have to get publications in order to keep their labs going. If they see that this lab got a nice publication using our compounds, they know that they could get a nice publication, too. They know we're amenable. We can provide a set of tools for them to get publications.
>
> For example, we have brain-penetrant HDAC6 inhibitors. Somebody has a hypothesis: "If I inhibit HDAC6 in the brain, it's going to affect this in the animal. How do I make that happen?"
>
> Anyone who wants to get HDAC6 in the brain setting comes to us because they've read that we have the tools. It's not just the compound, it's the knowledge of how to use the compound so you can get brain exposure, impact HDAC6 in the brain.

> The publication is a payoff to these guys. One thing we do is let them have first and last authorship on the publication.

An expanding body of knowledge on HDAC inhibition becomes available to researchers studying disease. CEO Walter Ogier likens this activity to building an ever-more-sophisticated workshop to generate novel treatments:

> What those "tools" are is a critical part of the story. Our 200+ compound library of proprietary, selective HDAC inhibitors enables external collaborators to advance their research programs, validate biological mechanisms of action, and get their work published. They can provide chemical proof-of-concept and provide a critical link between a disease and a pharmaceutical treatment for it.

As the conversations continue and engage more people, new results inspire new hypotheses. Innovation productivity increases as more and more knowledge comes together in better ideas to meet medical needs. The social networks become stronger and denser, just as the neural networks in the creative brain.

**Recommendations: Don't over-value your ideas**

**Assemble a creative legal team early**

> Find attorneys who are interested in new business models rather than telling you how "it has to be done."
>
> Explore the use of Materials Transfer Agreements that enable researchers to use your compounds in return for data and appropriate commercial rights.

**Educate academic collaborators on the realities of the market**

> Be honest about the high failure rate of promising ideas and the high costs of bringing drugs to market. Help researchers understand that pots of gold are only found at the end of the rainbow.

**Stop fearing someone will steal your ideas**

> Many entrepreneurs believe that others are waiting to pounce on every new idea, so they hide in stealth mode. What they lose is the opportunity to learn how their ideas might be used.

**Lose "not invented here"**

> You're not as smart as you think.

## Mechanism 4. Proof of concept

### Organizational idea application: Hypothesis testing and the value of negative results

Unlike conventional pharmaceutical research organizations, Acetylon's biology organization does not plan for a compound's success, it first plans for knowledge. The goal is better knowledge about *how to find out* whether a treatment will help patients. Starting with a well-formulated hypothesis, teams plan a sequence of experiments that would progressively reduce the uncertainty of whether the treatment will work in the real world. Research investments enable the company to avoid costly clinical studies when the likelihood of success is minimal.

### Example: Tools and translational experiments

Matt Jarpe gives an example of how the study results create value.

> What we get from sending our compounds out into the world, and sending them to these labs is experiments we never would have thought to do ourselves.
>
> We can also do experiments we wanted to do but have no capability of doing. When we come up with ideas that we think ought to work based on our reading of the literature, we can send the compounds out to somebody who can try it and either it works or it doesn't. Whatever way it goes, that's valuable information that we have.
>
> Progressive Supranuclear Palsy (PSP) is one of many examples.
>
> We had a collaborator who said that HDAC6 was necessary for the misfolding of a protein called tau. Tau is implicated in Alzheimer's Disease, so it's a pretty big market, but Alzheimer's is a mixed tau-opathy, it's very complicated. Most of the tau-opathies are sporadic, they just happen in wild-type tau, but some of them are familial, where a mutation causes protein misfolding and progressive deterioration. We had a consultant do a market analysis of all these different diseases that we could be going after. We were going to go first with a pure tau-opathy; PSP is a pure tau-opathy, with no amyloid plaques.
>
> In parallel with the market studies, we did the animal experiments. We found two places that do mouse models with mutant tau, and our collaborator also had the mouse model. These were very expensive experiments. With genetic mouse models, they cost $250-$300,000, and they take a long time. We decided to do all three in parallel, which was a big risk.
>
> The results were definitively negative. It was very clear that we got the drug to where it needed to be. We had the biomarker that showed that we were inhibiting HDAC6 in the brain. We saw that it was in the cells that needed to be affected. But there was no effect on the mouse behavior or the histology – nothing at all.
>
> So that's very disappointing, and we had put a lot of resources into this. But we saw a preponderance of evidence that said that this was not going to work in the familial PSP. There isn't another way of doing this without the mutants. If it can't work in the mutant models of the disease, then we are never going to know if it's going to work in any of the PSP's. It's not so much that it won't work; it's that we're convinced *we can't tell if* it's going to work.
>
> Even if the data is negative, they can publish it – I'd like to see them do more of that. A lot of times, it just dies there. But now we know that it doesn't work in that model. That's very valuable for us to know.
>
> One of the things that I say to Simon and Walter that they don't like is that when I advance a candidate my main job is to kill it as soon as I can. They don't like to hear that, but that's really what I'm there for. I need to find *the* experiment that's going to kill that compound before it gets too big and eats us out of house and home. Anything that does survive that process is a good compound.

### Example: Negative results lead to new opportunities

Walter Ogier describes how the asset base of the new company, Regenacy, was assembled from unexpected findings in Acetylon research programs:

> Sometimes the results are negative, e.g. that what was hypothesized to involve a particular HDAC actually involves something else. Of course, we hope for the opposite. But sometimes, as a result of shared knowledge and learning, we are able to establish an alternative hypothesis that leads to a positive result – an "Aha!" moment.
>
> Some of our most promising clinical opportunities have arisen from initially negative, or initially inconclusive, results. Sometimes those results are as of a particular time deadline that we have set ourselves, resulting in a negative project team recommendation. An open-minded process of internal program review, together with generation of alternative hypotheses informed by external

collaborations or work elsewhere in the internal organization, can give such a "failed" program a new lease on life – one that can lead to a success that may be different than was originally conceived.

Our new spin-out company, Regenacy is a result of multiple past decisions, driven by Acetylon's senior management, to continue programs past their nominal deadlines and past inconclusive and negative data.

Unlike the norm in science-based organizations, where negative results are largely ignored, the Acetylon/Regenacy team synthesizes knowledge from experiments that both proved and disproved their therapeutic hypotheses. This growing knowledge base improves the group's ability to assess the value of opportunities and make sound investment decisions. [11]

**Recommendation: Reverse perverse incentives**

**Don't reward starting new phases unless you want late-phase disappointments.**

Moving to a new phase isn't a value-creation event. It's a commitment to spend money.

**Don't push teams to shorten timelines – push them to find more elegant ways to get the data you need.**

Talk about the decisions you must make before arguing about the schedule.

**Educate executives that faster isn't better.**

We know of a financial executive who genuinely believes that if you get to Phase 1 faster, your chance of approval is higher. Don't let beliefs like that choke your team.

## Mechanism 5. Product development

**Intergroup innovation delivery: Integrating knowledge across bench and bedside**

Acetylon people describe habitual mechanisms that synthesize knowledge across functions:

"No big distinction between Research and Development." – Catherine Wheeler, Clinical Development

"We understand that Research and Early Development are really a continuum." – Simon Jones, Biology

"The collaborators that have these preclinical models tend to be able to do the most interesting clinical trials." – Walter Ogier, Management

This everyday dynamic enabled Acetylon to find opportunities and pursue them more efficiently than companies with segregated functional organizations.

**Example: Taxane combinations**

Matt Jarpe describes a project moving into clinical development

I used to work with Mike Gilman (he's now at Padlock), when he was the CSO of Biogen. He used to say that we're not in the drug discovery business, we are in the knowledge business. What we're trying to do is produce not just the molecules they can take forward, but the information they need to take it to the next step. If the drug is thrown over the transom to the development group, they may not use all the knowledge that's been gained, and may make mistakes that could have been avoided by having constant contact with the research group. We've done that at Acetylon really nicely.

We found through a series of experiments that HDAC inhibition both prevented and reversed peripheral neuropathy caused by taxane. That in itself is an interesting finding. You could go to taxol patients who have neuropathy and say, take this drug and you'll get better, and that's fine, we did explore that. But the other piece of information is that Steve Quayle's group found that HDAC6 inhibitors work really well with taxol in solid tumor models. In a tumor cell, HDAC6 plus taxol means more activity; in the case of a neuron, less activity. There's a perfectly good explanation for why that might happen: tumor cells need dynamic microtubules, and neurons need stable ones.

The clinical group had a couple of different trials going, investigator and company-initiated trials combining ricolinostat with one of the taxanes. At that point we went to them and said, "This is also going to help the neuropathy. Can you test for that, too?" We think that 70% of people who get taxane get neuropathy. If our drug works to get rid of it, you're going to see some benefit if you measure that symptom. We had to do some negotiation about how much you can actually measure this symptom in patients, since their primary focus is to get rid of their cancer. You have to be careful about what you add to a trial, but it was a fairly simple procedure that would enable them to provide a two-for-one for the patient.

But the point is that that it's very difficult for us to start a trial for a chemotherapy-induced neuropathy. The investigator has to go to cancer survivors with residual neuropathy and say to them, "We'd like you to try a new drug to cure the neuropathy." That's still a good thing to do, but it's tough. But giving cancer patients ricolinostat in combination with taxol and seeing if it helps their tumors as well as their neuropathy is relatively easy.

The taxane story is typical of how Acetylon integrated knowledge across the whole spectrum of R&D. Although the narrator belongs to a discovery group in one biological area, he has been deeply involved with other discovery biology areas, chemistry, clinical research, and (most unusually) commercial.

**Recommendation: Stop isolating Development from Research**

**Train Clinical and Commercial to listen for possibilities, not problems.**

Too many Development people think, "Research doesn't care about practicality," which leads scientists to think, "I can't show this to them because all they'll do is tell us it won't work.

**Train Research to explain the science clearly to Clinical and Commercial.**

Too many Research people think, "Development won't understand it so I won't bother," which leads Development to think, "They must be hiding something." When scientists listen to questions from people outside their disciplines, they discover gaps in their reasoning and learn better ways to describe what they've found.

## Mechanism 6. Innovation ecosystem

**The complex adaptive system of the social network: Value-creation collaborations**

Like an ecosystem, the innovation engine has evolved over time from the elements that gave it life at the start: continuous iterative conversations between scientists, clinicians, patients, and investors.

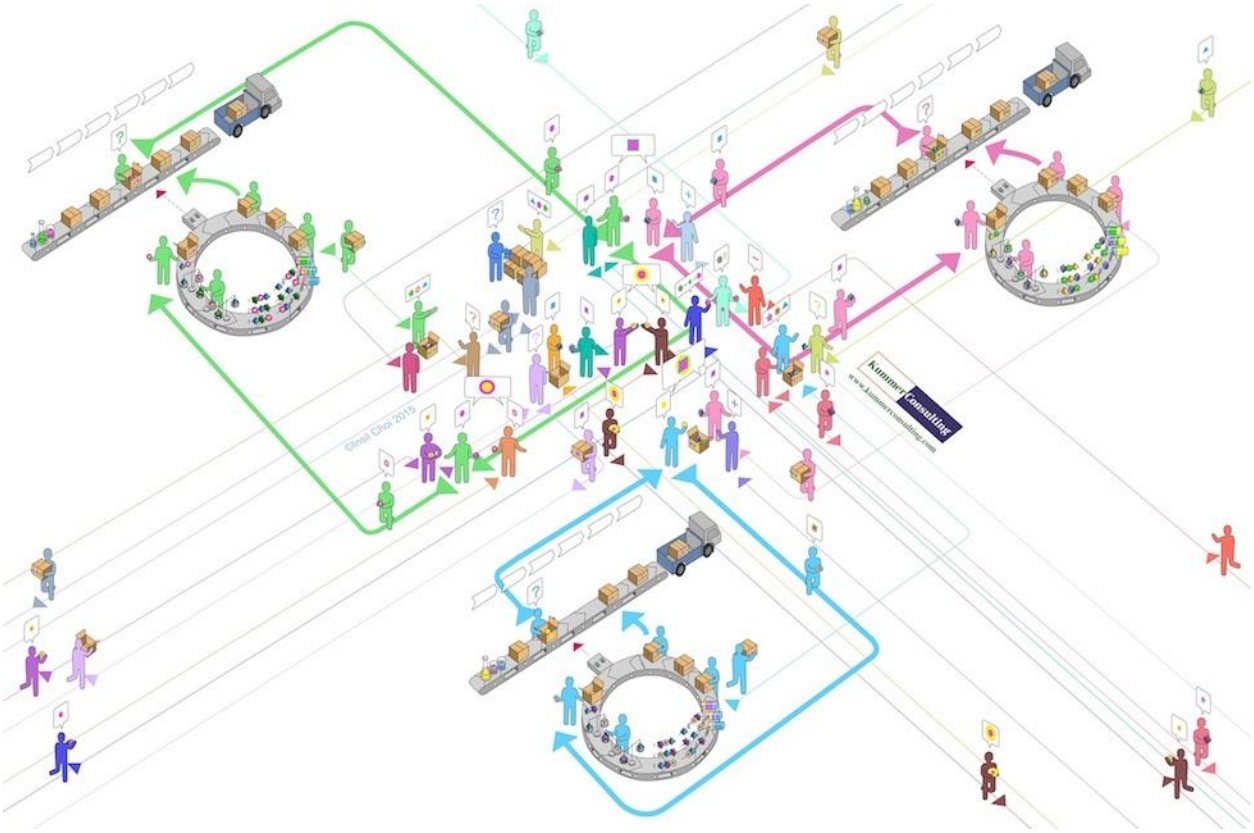
Walter Ogier, CEO, provides an overview of the innovation engine

There's a lot we do that's repetitive – the culture, the way we do things around here. The same type of relationship gets formed each time we have a new academic collaborator. Simon's group has a particular knowledge set around enzyme inhibition, and a set of tool compounds they can use to help tease out what's happening. That's an expertise that gets used in one setting and then another and then another setting.

Our collaborators don't have that expertise. They've used tools that get them partway towards what's going on biologically but they aren't all the way there. So when Acetylon talks to them and helps them, we're educating them on how to think about the problem, how to use these tools to maximum advantage. We educate them on how to go from a limited understanding, where they can't tease out the specific details of the biology, to tease out precisely what's going on in different systems.

What we're learning is the context in which the tools are being applied: the disease, the model -- the animal and bench models -- that the researchers have put together to understand the disease. With these compounds and techniques, and detailed knowledge of HDAC inhibition, we can help them to use those models to really test the hypotheses.

When it's of interest to us, we'll help them refine their models and reduce the uncertainty even further. In those settings, there's work we can do to augment what they're doing. We'll often set up a project in-house to do that. We'll assign that to someone at the bench to really understand the mechanism and optimize the medical benefit that could come out of it.



**Recommendation: Invest in the relationships that work.**

**Retain relationships, not just individuals.**

Trace the interactions between people to learn how they created successful results. Use these maps to guide future projects.

When integrating an existing group into a new R&D organization, learn which relationships were key to delivering high-quality work. Engage those people to determine the best way to preserve the relationships.

**Don't decouple asset valuation from running a healthy value-creation engine.**

Too many companies find that they can't realize the potential of assets without the deep knowledge embodied in the relationships of the original team. Engage the original team in detailed planning on how to organize a transition that doesn't leave the tacit knowledge behind.

**From the beginning, foster deep learning relationships between scientists and investors.**

It takes constant conversation to learn what will work. Only a social network can create value.

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