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Commercialization of basic research from within the university and return of value to the public

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Abstract

The responsibility to return “value” to those who support basic research is an obligatory part of accepting funds to support the research. This reality should, but now does not, impact planning and execution of all basic research from its earliest stages. Universities are becoming ever more important in their role in the accelerating quest of a national goal of transition to a “knowledge based economy.” As such, the complex organizational format of a university, laden with entrenched procedures of questionable utility, should be adjusted to identify the means to commercialize the small subset of projects that appear suitable for further development. Of special concern is the growing tendency to encourage academic “innovators” to develop spin-out companies “on the side.” While seductive in perceived simplicity, this is a difficult step and we believe that most such individuals are ill-suited to these activities. Not because of technical ability but because of lack of relevant management experience. We attempt to address that situation through a brief listing of some reasons why people “do research” and outline phases (steps) in moving from concept to application, including an overview of start-up and funding early-stage spin-outs. A discussion of the limits to applying results of basic research to enhancing sperm fertility in commodity and companion animals and humans is provided. Hurdles are so daunting that there is concern as to why anyone would attempt to translate basic observations into practical solutions; which in turn raises the question of why funding agencies should fund basic studies in the first place.

Keywords

Commercialization of basic research; Small business innovation research grant; Design of field tests; Sperm; Fertilization; University environment for business

1. Introduction

“Starting a business is a lot like having kids. They both seemed like a good idea at the time.” AD Keith to RH Hammerstedt, circa 1990. Most basic research scientists do not want to, and probably should not, start a company. But there is a need for all grant recipients to demonstrate to the funding sources that recognizable (to the citizen) value is obtained from the investment of tax dollars in basic research. Further, the academic community is subject to fads,

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just like the rest of the world. Currently there is considerable emphasis in academia to “spin out” concepts to marketable products. We support the end goal, but not necessarily the “obvious” path, especially within the context of reproductive biology.

Documents from the National Institutes of Health (http://www.nichd.nih.gov/publications/pubs/upload/council_rsb_2002) or the USDA provide excellent summaries of the latest research findings, but make few claims for direct clinical or commercial application. Why not? We will attempt to address that fact through an incomplete listing of reasons why people “do research,” outline phases (steps) in getting from concept to application, factors to be considered in starting a “spin-out” company, and introduce some of the limits to applying results of basic research to enhancing fertility in both humans and commodity animals.

Our perspective comes from distinct experiences, with RHH spending 35 years in academia and almost 20 years trying to find a means to move things to commercialization, and ELB spending 20 years seeking to identify opportunities within academia from a position outside. Together we hope to illuminate the process and help set expectations for possible commercialization of results from basic studies in the reproductive sciences.

2. Why do we do research?

There are a number of reasons/rewards that appear to drive the individual scientist, his/her institution, the review system, and the sources of funds. Together they provide sufficient reward to encourage each to participate in the process. However the sometimes conflicting goals reduce the end reward to citizens, perhaps captured by the definitions (<http://www.dictionary.com>) for efficient [performing or functioning in the best possible manner with the least waste of time and effort] compared with effective [adequate to accomplish a purpose]. This concept was developed in detail with regard to management by Mintzberg (1989).

Each individual scientist is driven by a complex set of interests, which can range from a desire to learn every thing about and understand fully one system of interest (often in a context devoid of organismic relationship); to solution of an integrated “real world” problem; to a search for funding, tenure and notoriety. Over the last few decades, most scientists have become fixated on study of what is “interesting” to them, with a desire to continue on that path until it leads to a satisfactory (to them) end point. While understandable, this leads to a myopic desire for endless funding of their sector, with the assumption that with sufficient funding enough clues will be revealed to provide value to society. By analogy, the desire to make the basic research sector highly efficient, without much emphasis on the effectiveness of the overall process (detailed later), is detrimental to the probability of continued funding for basic studies.

Because few scientists are independently wealthy, each must seek financial support. That support comes from private/governmental sources, administered through a complex system both internal and external to their home institution. Each aspect has its own self-interest.

Both private and public sources seek to utilize their financial resources to satisfy their end goals, which do not include providing funds solely for the pleasure of the scientist. Rather, each seeks to provide a return to their constituents (e.g., tax payers or shareholders) within the next reporting cycle (election or quarterly report) that is so positive that they will be allowed to flourish. In the last decade, pressures for positive reports of attentive stewardship of funds have grown; without something to report, the chances for constant-or-increased funding diminish rapidly.

Positioned between the two ends of the pipeline are administrators of funding agencies and universities, and their technical advisors. Their role is critical to overall effectiveness of the

process because together they are charged with attracting concepts within their sub-specialties, evaluating each relative to others available, and then allocating resources. They probably have the most difficult assignment in the process. Two points of concern illustrate problems within this sector. Most basic studies are carried out in public institutions, where the administrators function with the dichotomy of having all-but-none-of the power. They have few-if-any funds to distribute on their own, and depend on faculty to identify their own sources. As a result, their major input is to seek positive notoriety that advances their unit (and them), hopefully coupled with increased dollars and an enhanced relationship to the latest unit of “critical mass” that they are pushing.

All “review boards” have an enormous responsibility to sort through many proposals to identify the few to receive funding. For decades there have been debates on funding success for proposals in “basic compared with clinical” areas. To some extent bias in favor of basic studies is observed (Kotchen et al., 2004), but full extent of this is not known. A less recognizable form of bias might be inherent in this question: “Is it necessary to understand the mechanism of action of “X” before you seek to see if “X” has demonstrable biological (much less clinical or commercial) value?”

Together these two aspects constitute a severe “choke point” in the flow that leads to value for the general population, often through self-interest driven attention to maximizing efficiency of a single sector to the detriment of the effectiveness of the entire system. These concerns have come to the public attention, as reflected in a US National Academy of Sciences Report (<http://www.iom.edu/?id=4881&redirect=0>) and the NIH Roadmap Initiative (<http://nihroadmap.nih.gov/>).

Larger scale questions revolve around analysis of the past versus future outcomes. Major investments in basic research in the USA began after World War II and since that time there has been a spectacular increase in quality of life for most citizens. How much “credit” can be taken by the basic science community? The previously cited reports recognize that contribution, but raise a contemporary concern. A set of restraints have developed, as reflected in: (a) the “pot of inflation-adjusted money” available for all governmental activities is not growing faster than the claims on such funds by diverse constituents; (b) the time scale of demonstrating impact of research on society is shortening, with political reality forcing answers to the question “what are you doing for me now (this year, this month, this day)”; and (c) the demand will increase with mandated rapid deposition of publications and primary data for public review.

Such considerations lead us to suggest that *it is essential for all participants in the research process to become aware and attentive to the absolute necessity to optimize the effectiveness of the overall process, even at the possible expense of the efficiency of their own segment.* This certainly does not mean that all basic scientists should attempt to carry a product to commercial acceptance, as most are not suited to the task. It does imply that each should recognize the importance of “delivering the goods” from the pipeline, the need for honing the description of their segment so that its importance to society in general can be recognized by everyone, and to express an interest in (and support of) programs that assist in the transfer of those few concepts with direct potential for application through their final steps.

3. Path from concept (conception), to test (birth), to introduction (puberty) to social return [adult]

This path is long, with significant selective pressure on concepts as they pass through the pipeline. Based on experience, each scientist will have dozens of “ideas” during a year from

which only a few will be refined sufficiently to justify being categorized as suitable for a research project. What can they, or their administrators, expect from such a start point?

An example from general industry is provided, which in contrast to universities should be tuned from the start toward commercialization. For every 3000 new ideas that emerge from industrial R&D, 125 become “small projects,” four grow into major developments, 1.7 make it to market launch and one idea becomes a market success (Table 1). Table 1 lays out seven stages from idea to market success. Importantly, 80% of the companies surveyed identified their clients and customers as their prime source of ideas (Conference Board of Canada, Fifth Annual Innovation Report, 2003; <http://www.policy.ca/policy-directory/Detailed/816.html>; page 20); *commercialization usually begins from a question or request from the end user, but rarely with an idea in a research laboratory*. It is clear that: (a) ideas are not limiting; (b) many considerations/constraints are imposed by the path; and (c) investments needed for Stages 4 and greater are ~10X those needed for Stages 1-3.

A slightly different perspective of an “industrial success curve” is gained when data of Table 1 are plotted on a log scale relating stage of product development to fate of the initial idea (Fig. 1). The winnowing process is unrelenting as factors other than scientific merit enter the decision matrix. To provide a potential point of reference to university based activities, points for initial funding and transfer through the technology transfer office are provided (to be treated later in greater detail) for reference. There is intense interest in raising the effectiveness of management in industrial Research & Development, so these data probably reflect reality and not optimum performance. Remember all organizations are composed of people, each person operating with a blend of self- and company-objectives. Experience has taught all of us that this fact tends to slow and divert many projects despite their value.

To summarize, each scientist resides somewhere within the pathway of Table 1 and must realize the importance of optimizing potential for flow from their work through to a reward to society. RHH frequently is challenged on this point of view by academic colleagues, and the answer is simple. If you want complete freedom to “do your thing,” great, as that is what academia can/should/must try to provide. But if you need money to do so, you must accept the overall features of the system that supplies you with the funding. If you cannot accept that challenge, then be prepared to join the ranks of those in segments of the liberal arts where they do not have access to such funds and must satisfy their curiosity and provide benefit to society on a much lower budget. In the end, such scholars might be providing greater long-term value than those of us in the biological and physical sciences!

4. Critical need for a clear end goal for your project (one that you can explain to your mother)

We all sell at one level or another. A common academic example is occupying a space in front of your contribution to a poster session at a professional meeting. Preparation should include: (a) attention to the development of a plan for “first impression”; (b) clarity of data presentation; (c) physical presence and eye contact used to attract attention of passers by; and (d) preparation for convincingly distinguishing your contribution from others. In short, paying attention to detail at the level attuned to those experienced in your specialty (but not non-specialists). The academic approach really is not too different from the commercial booth at the same meeting. When you present to those outside your specialty, alternate means are needed to make an impact. You must work much more diligently to capture the attention of those outside of the specialty, whether it is in the introduction to a research proposal (to assure everyone reading the proposal knows the goal and path of your research plan) or when preparing an introductory paragraph for the technology transfer office. Remember, if “they” don’t understand, it is “your”

fault. You opened the dialog, and you-and-only-you are responsible for making clear important points.

We all have experienced the polite nod, where the listener avoids looking foolish or “getting in over their head” by a simple movement of their head. They escape, and you gain nothing. Kennedy (2006) offers a guide to a succinct business approach that looks simple and obvious, but requires a large amount of preparation to accurately reflect your concept. Her questions are: (a) So what (what problem do you address, how important is that problem, and where in the greater world does it fit)?; (b) Who cares (who will pay for your solution, and how will you reach them)? and (c) Why you (what is your distinctive feature, and how do you plan to exploit that advantage)? Note that this is not “business speak,” but rather reflects taking the time for clear intellectual positioning before launching any huge effort.

5. What is the university setting for commercial development?

In short, not great, it shouldn't be and probably never can be. The modern research university reflects a complex balance between factors summed as bureaucracy, education, research and community service. Each aspect both benefits from and is hindered by the other three. Before 1980 federal agencies retained ownership of intellectual property developed through its granting mechanisms. As a result <250 patents were issued to universities per year, and of the >30,000 patents held by the federal government only 5% led to new or improved products.

In 1980, the Bayh-Dole Act (PL 96-517, Patent and Trademark Act Amendments of 1980) created a uniform patent policy among federal agencies that (a) allowed universities to retain ownership to inventions made under federally-funded research; if (b) they filed for patent protection and diligently worked toward commercialization and return to the public for the initial investment in the basic research. By year 2000, at least 300 universities engaged in technology transfer in attempt to satisfy that mandate by sparking new industries and opening new markets. Each seeks to create a new income center for the university.

This new emphasis has come at a cost, not always understood or fully recognized, that is changing the balance between core university goals. Heller and Eisenberg (1998), in an article entitled “Can patents deter innovation? The anticommons in biomedical research,” provide a provocative discussion of how people might underuse scarce resources because too many owners can block each other. They present the case in terms of the need for a balance between “upstream research and downstream product development.” Additional comments by Andrews et al. (2006) are pertinent to this concern. In the day-to-day workings of research such effects are noticed because it often is necessary to get a lawyer's help (via a detailed material transfer agreement) to obtain a reagent or cell line described in the literature as opposed to the phone call and a promise for appropriate attribution that sufficed only a few years ago. “Everyone” seems to be unwilling to give “anything” for fear of missing out “on a piece of any action.”

There are, and always have been, larger effects on the university. Universities will be core elements as we transition to the “new knowledge economy,” especially since they are convenient resource centers for focused research efforts. There has been considerable angst expressed over the effects of collaboration between commercially-inclined biologists and science-based companies because of the potential for skewed research agendas, conflicts of interest, and restrictive information flow. Given that faculty are employees of the public, and all of the activities have/can/could/will happen, these more obvious concerns are easily handled with requirements for full disclosure coupled with appropriate surveillance and meaningful penalties for malfeasance. Such activities are a part of a larger set of influences that have been termed “academic capitalism” by Slaughter and Leslie (1997).

A unique view of some of those other influences is provided by Kleinman (2003). He is a sociologist who spent a period, with full support of the laboratory director, as an active participant in a modern biology laboratory. His observations served as a basis for ethnographic analysis of the relationships between the patterns of “bench scientists” and their environment, with special attention to direct and indirect commercial factors within academia. His observations and interpretation are unique, and should provoke a reexamination of a number of fundamental operating assumptions that guide the academy. The following is taken from the last paragraph of the Preface to the book. “We stand at the threshold of a new knowledge intensive economy. Here, the boundary between the worlds of commerce and scholarship constantly shifts and blurs. The two realms are becoming fused. We can passively watch this transformation, or we can attempt to shape and direct it. I hope that by providing a new perspective on this inadequately considered topic, this book can prompt more urgent concern among scholars, policymakers, and citizens, and encourage them to work actively to influence the changing character of the university in the new millennium.” He further emphasizes (p. 44) that “the direct impact today of industry on academic science through patronage and explicit partnerships is part of a long historical trend. The American university was never an ivory tower.”

Realization of the central premise of this presentation, that the public both expects and deserves rapid societal return from its investment in basic science, requires passage through this changing environment. So, what is happening? This is a complex problem and cannot be treated in detail in this presentation. A diligent, but not exhaustive review of the literature, revealed numerous qualitative relationships but minimal quantitative information. Salter and Martin (2001) provide an overview of economic benefits from publically funded basic research, and Martin et al. (1996) list contributions that publically funded research make to economic growth. The latter are: (a) increasing the stock of useful knowledge; (b) training skilled graduates; (c) creating new scientific instrumentation and methodologies; (d) forming networks and stimulating social interactions; (e) increasing capacity for scientific and technological problem-solving; and (f) creating new firms. No one mentions an income stream for the university budget as a contribution, but there certainly is nothing wrong with income.

A common mode of evaluating return on business activity is a calculation termed “return on investment” (ROI). Such accounting is used to evaluate business decisions on use of funds, with some disagreement on what is (should be) included in the calculation. For example, in a company dedicated to product development and sales, the accounting would be done for each project, with ROI calculated as: sum of project specific expenses / sum of sales from product (s) derived from that specific project.

Attempts for an analogous evaluation in the university-based setting are not as simple. One simplistic approach for university-based calculations is to consider the process on a year basis. This form of ROI is a ratio of: annual income from licensing activities (i.e., reflecting income received from all projects successfully commercialized over the past 10-20 years) / total external funds received for support for research for that same year (i.e., reflecting funds spent on basic research, whose commercial value will not be known for 5-10 years).

Data from the Association of University Technology Managers (<http://www.autm.net>) is useful to provide an overview. This approach ignores the lag between receipt of funds to conduct the research and using such income to gather data for subsequent offer, as well as any other form of “value” to society/institution that might be derived from conduct of the research, but is useful to detect trends and rank institutions relative to one another on these activities. Implicit in such comparisons is the assumption that each institution is willing to invest equivalent funds in its technology transfer operations.

Overall, the average ROI for >250 institutions has increased with time (Fig. 2), perhaps reflecting increased attention to the matter. When the data for any given year are examined, there is no evidence that institutions with the largest research programs are much better than smaller groups (analysis not presented). As a point of reference, reports of ROI for technology-driven companies reach 10X the ROI values for universities.

Some groups (e.g., the Alfred E Mann Foundation for Biomedical Research) maintain that the return is way too small (see Holden, 2006) because “professors have no concept of what it takes to bring a product to market” and technology transfer offices “often don’t know how to find the right partner.” The Foundation has provided an alternative whereby it pledges money to such activities as part of a nonprofit institute related to the university. The proposal is controversial. Until quantitative economic value from other output features of the research process [e.g., six factors of Martin et al. (1996) listed above] can be provided, it is impossible to make a meaningful comparison between industrial activities (where effort is focused on new product out the door using the skills of university trained people) and university-based activities (where their major activity is to train future scientists as part of the grant or educational project).

It is our conclusion that the process can (and should) be improved. However, the structure and balance of the university is complex and all too often the “law of unintended consequences” takes hold when complex organizational changes and perturbations of historical values are introduced. A critical aspect involved is the irreplaceable role of the university to provide trained people to work in industry, and its relatively unfettered atmosphere to search for new and unanticipated avenues to the solution of vexing problems of society. A faculty member can, in most instances, study any area of interest “follow their nose” provided they have the skill set and connections to raise the funds necessary to support that search. Few companies allow such freedom. As a result this aspect, so critical to the knowledge-based economy, must be protected.

6. So you want to start a company

Few-to-no successful academicians have the needed range of management skills to successfully direct a start up company. That fact does not seem to stop us from trying, despite the fact that most investors would prefer the “inventor” to confine his/her contribution to the early technical aspects. Having a great advisory board does not really help, because they only offer advice; leaving action up to the usually “spread-too-thin” and part time academic founder. That being said, some sources of information (Table 2) are listed for use after the reader rejects the above advice. In addition as you ask around you will find a large number of people with experience and success in business. They will be useful. A practical goal, if you should press ahead, is to make each type of mistake only once.

Money is not the most important limit, as a truly great idea whose “time has come” will attract funding, but product development in the life sciences has special demands that must be considered from the start. Time-to-exit is a critical aspect to any investor, and a huge gulf exists between the experiences of an inventor and those of most investors. Scientists survive in their discipline by their ability to accept long term gratification since most projects require a decade or more to accomplish long term goals. Few investors share that time perspective. A general requirement for professional investors would be a cash exit in <5-7 years. They would love a 10X ROI, be very happy with a 4 to 6X ROI, and exit with grace (i.e., recover their funds) with a 2 or 3X ROI. As a result, all “deals” must have the potential for the 10X return because a large number of investments do not return any of the funds put “at risk” with your hopes.

These considerations reflect several realities that are not readily apparent to early initiates. The reason an investment fund has money to invest is because the fund management convinced their financial backers that their team will gain higher returns than competitors. In addition,

the fund has a defined life, at which time it must disband with proceeds from investments returned to the investors. If management does not make their numbers, they will neither gain personal reward nor access to funds from their investors to start another round to search for “those special deals.” Thus, the optimum opportunity is one where they are in and out of the company by the time the fund closes, while gaining the greatest rate of return possible. *For any company seeking to focus on reproduction, twice the money (if available) does not cut the gestation time in half, so this time line requirement is especially limiting.*

As a result, it is essential for each entrant to look at Table 1, and ask the question: How long will it take to get from current status to the next stage in development? Then double that time estimate, as potential investors will do that on their own. Next ask, how much money will you need to get there? Then double that number also. Will you be turning a profit at that point? If not, how will you get more funding to go to the next stage (and saying go get more money is not a sufficiently refined answer)? Finally, set aside enough time to identify and then get your promotional materials before 100 to 500 investment groups before you find the only one that likes your ideas, team and financial prospects. By now you are probably thinking that the odds on getting a grant are better; probably correct!

What you will discover is that technology based, laboratory embedded start up companies, in contrast to retail or service based companies, rarely can raise sufficient funds to show promise, much less meet investors requirements for exit and profit. The preceding exercise is essential to help you set realistic goals, but should not close the door on planning.

Remember, risk is in the eye of the beholder. It is in your interest to search for partners/ investors/service providers that understand your business sector. As an aside, RHH had an interesting introduction to this when he sought liability insurance to cover company activities dealing with poultry semen collection and evaluation. This was when HIV/AIDS was emerging as a health threat, and all but one company would not even consider coverage due to the headlines. One underwriter took us in an instant, with the comment that they covered bull studs and no one was ever stepped on by a chicken! Also, it is a huge mistake to think that cash is the only mode of payment, because we all have skill sets or contacts of value to others (and barter remains a non-taxable [or at least untraceable] form of commerce).

A usual route is to start from a small initial pool of money derived from personal finances, family and friends to organize a company and set the stage for further activities. They understand (or can tolerate) your motivation, and are willing to help you get to your dream. There is the chance for a loan, and people will loan money for most anything (see www.prosper.com), but this rarely works when payout is indefinite. Remember that new investors will not put in money to retire old debt. They are only interested in having their investment go toward new objectives closer to final commercialization. Investment in the form of loans rarely is recovered with the method of “The Godfather,” but lenders often can set the terms for conversion of debt you cannot pay to a very favorable (to them) equity position. Of course you will need a second round of funding after you have an organized entity. Often this comes from a ill-defined group entitled “angel investors” (see http://en.wikipedia.org/wiki/Angel_investor) willing to assume great risk, or ability to understand your risk from their personal experience. An enticement to gain access to this group is the ability to demonstrate that their investment can be leveraged by combination with other funds without damage to their personal return.

This leads to an introduction to the Small Business Innovation Research (SBIR) program. This federally funded initiative, started about 25 years ago and renewed several times with strong Congressional support, addresses the reality of the funding gap. The umbrella program is centered in the Small Business Administration (see

<http://www.sba.gov/sbir/indexsbir-sttr.html>) for overall oversight, with actual funding centers in eleven federal agencies. A historical overview and outline of activities for some of its more active agencies is provided by Wesser (2004). In brief, the SBIR represents a highly competitive program that encourages small business to explore their technological potential and provides the incentive to profit from its commercialization. The goal is to identify small, highly qualified businesses, in the group from which most technological innovation has arisen in the past, and assist them in achieving critical goals in their path toward commercialization. Individual agencies make SBIR awards based on small business qualification, degree of innovation, technical merit, and future market potential. Recipients begin a three-phase program of: (a) a start up phase, Phase I, where awards of up to \$100,000 for approximately 6 months to demonstrate feasibility or explore the technical merit of an idea or technology; (b) expansion of Phase I activities, termed Phase II, where awards of up to \$750,000, for as many as 2 years, expand results through performance of R&D and evaluation of potential for commercialization; and (c) movement from laboratory to the market, termed Phase III, where funds from the private sector or non-federal sources must be used to continue. That series sums up to “real money.” and has the advantages of: (a) not yielding any equity in exchange for funding; (b) providing a form of external review to private investors; and (c) a nice leveraging of funds that are raised from angel investors. Such additional funding is essential because restrictions on how federal funds can be spent results in unrecoverable expenses of 20 to 25% for any SBIR project.

How does one get such funding? First, consult the web site for the SBA listed above for a general outline. Then visit the web sites for the various agencies to identify topic areas likely to be aligned with your interests. Note that some (NIH) are “unrestricted” while others (NASA, DOD) accept proposals only on topics carefully defined by them. Academics usually are quite skilled in preparing grant proposals, and thus have the basic tool kit “in hand”. Unfortunately, that might be a detriment because the evaluation process is unique and distinct and hence the proposal should have different features. Special concerns are: (a) perception of “innovative,” where there is a continual tug between its definition in an academic sense (nothing like it ever seen before) and a successful commercial product (perhaps a fusion of two “sort-of-knowns” to solve a niche need); (b) demonstration of “feasibility”; and (c) adjustment to what is possible in the proposal period, given the short time (six months) to complete the Phase I project. Useful information on the process can be found on a NIH site

(<http://www.niaid.nih.gov/ncn/sbir/pres.htm>) developed by Dr. Gregory Milman. By combining frugality, luck, skill and collaboration a project can be moved from Stage 3 to 4 (Fig. 1). If you get to that point, risk, reward and time lines are better quantified and justified, and funding (or exit by sale) is more likely.

7. Additional features for consideration for projects related to reproduction

There is no doubt that sex sells! There is considerable uncertainty on how to carry any laboratory-based, reproduction-related project through the entire pipeline in either commodity/companion animal industries or human medicine. Be sure the industry is ready to adopt to your technology if it works. This leads to a cautionary statement to the entrant. *If you cannot easily identify a path/partner to carry the project at Stages 5 to 7, why should you even consider moving it from Stage 2 to 4?* The following comments and examples are based upon our experiences with the commodity (poultry, swine and cattle), companion (equine) and human medicine over the past two decades.

7.1.1. Poultry industry

The first example is drawn from the poultry industry, as summarized in a 1998 symposium entitled “Managing Poultry Reproduction to Satisfy Market Demand” (Poultry Science Association), with specific examples drawn from Hammerstedt (1999). On initial inspection from 1985 to 1990, this industry appeared ideally situated for applications of assisted

reproduction with its products (eggs or meat) totally dependent on effective amplification and transmission of desired genetic traits from the gene pool to consumer product. RHH was involved with others in developing three products (cryopreservation processes; assay for one form of male infertility; and a therapeutic peptide that can be added to a semen sample before artificial insemination to raise fertility of certain subfertile males) up to Stage 4, but failed to progress beyond that point. Why, and what lessons are to be learned?

The first involves general business factors. Fifty years ago, when the poultry industry began its huge expansion to provide the lowest cost protein for human consumption, it had dozens of aggressive companies trying to grow and compete with plenty of risk-taking within these companies. For chickens, artificial insemination is impractical for the hundreds-of-millions of inseminations that would be needed at the producer level. However, artificial insemination has a potential role in the amplification process of the gene pool to provide grandson or great-grandson males needed for natural mating. For turkeys, artificial insemination is obligatory because natural mating is physically impossible by the time a male reaches puberty.

About 20 years ago, when the ideas for these products were gestating, there were >12 breeding companies world-wide. For all three potential products, we used industry contacts to learn what was needed (i.e., performance specifications). Then we set to work using SBIR and investor funds to develop products that should satisfy the defined needs. We accomplished our goals, under controlled, modest-sized (200- to 300-hen) tests, and set out to move to the field.

We did not anticipate the speed with which the poultry industry consolidated (now only 2 or 3 significant breeder operations in the world). Also, managers were under extreme pressure to reduce costs and meet today's "bottom line"; company survival rather than risk became dominant. By the time the products were "ready to come out of the green house" we could not find a company willing to accept a moderate risk to today's bottom line to gain potential advantage over competitors for tomorrow's product.

The scale of the poultry industry is such that fertility testing can be done in houses containing tens-of-thousands of birds, so percent hatched eggs can be estimated daily to a tenth of a percentage point. Managers of such operations are scored on hatch performance, and over the decades had grown used to using "plenty of semen" to assure they made their numbers (and their bonuses). Any experimental trial to show that a test of semen quality or a semen additive might have value must be done with limiting sperm numbers (to show effect of treatment). If that value can be shown, huge returns can be made by the company through better use of the semen they have available from their investment in finding superior sires. More hens can be covered with the very best roosters or turkey toms. Any number of models and spread sheet calculations show this. No single manager in any company could be enticed into reducing sperm numbers to allow a trial because that might result in reduction of fertility in the test house(s) for a few months. Offers to cover cash losses (a huge risk for a small company) were not accepted because the manager might have a detrimental performance on his/her record and they were concerned that their superiors would not bother to find out the reason.

7.1.1.2. Reality number one—Industries change faster than small companies can develop products. In retrospect it might be better to sign any deal early, and get any return on investment, rather than hope you can set up the ideal (i.e., business school prototype) competitive process for best return after further product development. The ability for precise estimation of fertility is great, but it also produces a state of continual anxiety for middle level managers (in charge with "guaranteeing" availability of all those fertilized eggs) as they are continually graded by monthly spreadsheets.

This raises the central question of basing a product on perceptions from the “outside,” even when armed with consultants with decades of experience and detailed discussions with intermediate personnel. History has examples of where a “fresh look” revealed unique ways to alter the competitive landscape and gain commercial advantage; the unwritten reality is that there probably have been more failures than successes for such approaches. To the outside observer, the competitive advantage for any integrated broiler company should reside in being able to maximize return from their only unique feature relative to competitors, the genetic merit identified by their in-house geneticists. The current time line for all companies is one where genetic selection, made to satisfy anticipated end user needs (e.g., cost of production, disease resistance, carcass composition/configuration) is followed by a lag of 4 years before the progeny of those elite males can be generated in sufficient numbers to support sale of product. If their response to customer needs were faster than any competitor, the adoptee should gain an advantage.

Use of cryopreservation, elimination of dud males, or repair of infertility at a few selected points in the management scheme could remove one full year from the current four year pipeline from gene pool to product. Responses from companies included statements regarding need for training of new personnel, change of in place protocols, and a general feeling that “we have never done this before.” Since adoption was totally dependent on getting middle level management to take a chance without any guarantee of reward (and possible risk), the integrated operation was ruled by efficiency (each intermediate unit is optimized for its own internal performance) compared with effectiveness (each intermediate unit operates to make the most money for the company).

7.1.2. Swine industry

We note that the pig industry has many of the same features as the poultry industry, and exhibits the same attitude toward risk-reward. Thus, success here also will be limited.

7.1.3. Cattle industry

The next example is from the cattle industry, where dairy studs 45 to 50 years ago learned how to exploit the genetic potential of their superior sires, and since then, through empirical means, have removed many factors that might limit reproductive efficiency. They fully understand the value of cryopreservation, but are always alert for additional methods to gain the last bit of return from their investment in sires. Here too, consolidation of the industry has occurred leaving only a few potential customers, but the testing takes a different form. In contrast to the broiler business, where each management unit is thousands of birds, the dairy stud distributes its semen to many different management units. Far fewer bulls are used than male turkeys or chickens. As a result, practical advantage to a bull stud can come only when a treatment (i.e., product) can offer value with most popular males and across all recipients. Cow herds with marginal reproductive performance remain in operation, whereas in the poultry industry they are eliminated immediately without remorse. The product we developed has been licensed, and is being tested under a variety of management situations. In general, results from Stage 3 are holding true but the exact place for sufficient return within the operation has yet to be identified.

7.1.3.1. Reality number two—Proof-of-value must be provided in a way that customers can clearly identify and defend in their market place. In this case, results from a trial are dominated by herd-to-herd variation (which in turn is a complex mixture of factors) such that only large treatment effects can be recognized. This makes it difficult to optimize essential features such as mass of pro-fertility peptide added per mL extended semen across all bulls and extension rates for the individual semen samples.

Recent trends toward consolidation on the milk producer side to develop dairy herds (management units) of ~20,000 animals might be advantageous for product testing. Large and robust fertility tests are possible (a la the poultry industry) under the direction of experienced and risk-reward tolerant management. Hidden downsides of such situations include: (a) the fact that the test results probably will remain proprietary to the dairy; (b) hence your company can sell to only a small segment (<1%) of the total industry; and (c) impact will be on such a small portion of the total market that investors will be uninterested because the company is “leaving so much on the table.” Further concerns include the fact that free-standing or “captive” bull studs would be reduced to a simple supplier relationship to such dairies (i.e., a Walmart-type supplier where they would receive the product for inclusion in custom doses for unique and restricted distribution). And university-based research, usually restricted to 10 to 20 animal trials (as in Stage 2), will be so speculative that the large dairy unit would be unlikely to take that risk. Thus, it would appear that the path to product under this new program also will dwindle and die.

The beef industry might appear to be an ideal place for adoption of the products that we envisioned. However the search for genetic merit has not yet been optimized and artificial insemination is not used widely. We were unable to conceptualize a test situation where value could be demonstrated conclusively.

7.1.4. Equine industry

Another potential market would be equine reproduction, where artificial insemination is gaining great acceptance. Since pricing for products dealing for companion animals is not as constrained as for commodities, significant commercial return might be anticipated. Here another limit arises due to the fact that number of females mated to each male is limiting and makes it very difficult to design a robust test of a new product (Amann, 2005). Rigorous proof of value will be difficult, but that leaves sales dependent on salesmanship and not proof-of-concept.

7.1.4.1. Reality number three—Despite the opportunity, and the general belief (hope) that your product is likely to be of value across species, it may be impossible to design that perfect test of utility.

7.1.5. Human medicine

Because NIH funds much of the reproduction research in the USA, potential applications to human reproduction should be considered. Subfertility is an “orphan disease,” caused by multiple factors. At least 15% of US couples attempting first pregnancy are infertile. Subfertility afflicts 8.8 million couples trying to achieve pregnancy in any year. Most of these couples (86%; 7.6 million) apparently do not seek help from a physician about the problem (<http://www.cdc.gov/ART/ART2003/PDF/ART03part5.pdf>). Only 1.2 million couples seek help from a physician; some benefit from surgery or endocrine therapy, possibly 20% use IUI with spousal or donor sperm (low cost), and 5% try IVF/ICSI (high cost). However, >75% of couples seeking help decline treatment, other than counseling, because of emotional cost, perceived modest success rates, or high dollar cost.

There are several danger signals that are apparent as one looks ahead to the critical Step 4 to 7 of the product development path for any treatment for subfertility. First, there is no established pharmaceutical company actively seeking a product to increase fertility of couples relying on copulation or intrauterine insemination (IUI), much less a sperm therapy. No one is looking to increase their non-existent pipeline of products and starting a marketing campaign. They might consider taking on a product whose value has been shown. Second, support through SBIR and other government programs is limited by the realities of the “Dickey-Wicker Amendment”

which bans federal support for an research that involves creation of human embryos. Finally, as described in detail below, design of an effective test of any product is complex and its execution is very costly. The types of evaluations that could be considered are provided (Table 3). The initial goal is to design and execute a plan, within the budget available, that leads to a positive decision by the FDA regarding clearance. FDA never approves anything; it either allows marketing via “clearance” of a product or blocks marketing.

As a model to guide the discussion, data re-summarized from Amann et al. (1999a, b), which point to faulty sperm-zona binding as a problem with sperm from many subfertile men, illustrate the path. Based on an in vitro sperm-binding assay, with a zona-like substrate, >15% of the sperm were bound for only 32% of potentially subfertile patient samples (9/28) but for 65% of non-patient samples (31/48); $P=0.02$. One mode to address this defect would be to increase sperm binding by defective sperm via exposure to a highly characterized peptide (termed at various times as UPSEBP, FertPlus or hPSF; see Hammerstedt et al., 2001). How does one look for “success,” and thus for FDA clearance and sales? The following information is provided as background. Note that the next ten paragraphs, quite detailed and beyond what is usually provided in a review article, are presented with the Editor's permission because we believe detail supporting our very critical conclusion is essential to planning by others for thrusts into commercialization of products for human use.

With any therapy (e.g., hypertension or erectile dysfunction drugs) there are “responders” and “non-responders” among patients, and the goal is to help many in the total population while causing harm to few or none. As shown in Amann et al. (1999a, b), this criterion is met in respect to impact of hPSF on sperm binding. Logically, if the average for all individuals given a therapy is changed (i.e., benefit detected), the average change for responders must be greater than the average change for the entire population (pulled toward no-treatment value by non-responders). In the case of hPSF, assume that responders represent 40% of males and non-responders 60% of males in subfertile couples including a female <39 yr old. Further assume that exposure of patient sperm to hPSF increased average pregnancy rate by 25%, as with cattle (unpublished data). Finally, assume a per-cycle pregnancy rate of 0.15 without sperm treatment, averaged across both non-responders and responders, with both groups having identical basal rates of 0.15. Would childless couples gamble that the male was a “responder”?

Without sperm treatment, cumulative probability of pregnancy after 1, 2, or 3 cycles of IUI would be 0.15, 0.28, and 0.39. Using sperm exposed to hPSF, for 60% of couples (non-responder male) there would be minimal benefit, but no harm (based on animal data). However, for 40% of couples (responder male) average per-cycle pregnancy rate would be increased by 63% from 0.15 to 0.244 — latter value calculated as $[(0.15)(1.25) - (0.15)(0.6)] / (0.4)$. Cumulative pregnancy rates after 1, 2 or 3 cycles of IUI would be 0.24, 0.43, and 0.57 for couples including a responder male. For the whole population, cumulative pregnancy rates would be 0.19, 0.34, and 0.46.

With these assumptions, the rudiments to be considered in planning of a fertility trial with humans are provided. General features to address during planning a good clinical trial (based on NIH web sites; FDA guidelines; Altman et al., 2001) are inflexible and, as listed below, were augmented by other suggestions specific to clinical trials involving subfertility (Amann and Hammerstedt, 2002; Daya, 2003; Vail and Gardner, 2003). The list includes: (a) clinical importance of problem and potential impact of the study on clinical practice; (b) magnitude of an increase in average per cycle pregnancy rate considered medically important; (c) precise description of overall study design, including hypothesis to be tested, all controlled variables, outcome measures, patient couple inclusion/exclusion factors, overview of procedures, and basis for a conclusion rejecting/accepting the hypothesis; (d) outcome measure(s) should be defined, measurable, and clinically important; (e) provide values for α and β , justify their

selection as well as sample size, and provide a power analysis; (f) describe potentially confounding variables, and how minimize impact; (g) provide estimates of “subject couple” availability, accessibility, recruitment, consenting, and likely rates of subject accrual and dropout; (h) provide a flowchart for patient tracking (as in Fig. 1 of Consort Statement; Altman et al., 2001); (i) describe procedures for data management, assurance of data base quality and integrity, and data security; (j) if appropriate, describe plan for coordination across sites and sharing/integration of protocols and data; (k) since a “Phase II clinical trial” is contemplated, discuss proportions of different ethnic/racial categories in anticipated population; (l) document relevant experience of participating clinicians and laboratory personnel. As a place holder, it will cost about \$1,000 per month per couple to monitor and document their progress through the evaluation period (after costs to recruit patient couples and deliver the putative therapeutic treatment). Assuming all of the above are in place, including meaningful estimates for all variables, it is time to design the study and estimate its cost. Then it would be prudent to meet informally with FDA to discuss your planned trial, to gain an impression of weaknesses in the plan, and the likelihood that FDA would favorably review positive results. This reduces unknown variables. One serious problem for small companies is that formal rejection of any application formally submitted to FDA for possible clearance can be lethal as investors loose confidence, company value plummets, and internal funds for a retry often are not available. *You must get it right the first time!* Thus, in contrast to established pharma companies, you are likely to have only “one try for the brass ring.”

Inspection of Table 3 reveals that any attempt to initially satisfy the demands of “Tier 1 or 2” (dealing with “live birth of health baby”) is unrealistic in that funds required far exceed those available to your start up company. Either would be wonderful for sales, but it is prudent to avoid the popular outcome because it probably is not be the best measure of product efficacy and requires large trials.

If you want to sell, based upon the sample product features of enhancing sperm-egg binding and probable enhancement of pregnancy rate, why would you want to risk failure due to other “problems” during embryonic development etc.?

Tier 3 with the read-out of early pregnancy is very ambitious but it has the advantages of focus on an outcome that is closer to that addressed by the product and lower cost. Candidate outcomes would be either elevated hCG or ultrasonic detection of a gestational sac at 6 wk (or 10 wk) as a measure of initiation of pregnancy. Other potential end points, such as number of sperm bound to zona during in vitro fertilization, are impractical because the clinic uses high sperm numbers to maximize success rate (to both satisfy the patient and their reputation and business success; back to poultry-like problems).

Keeping in mind that you probably cannot recover from failure in the test, a decision is made to run a preliminary test (Tier 3a) first. This might be run with slightly relaxed statistical standards from those ultimately to be used in Tier 3, to provide data to: (a) reassure future investors that you are on “the right track”; yet (b) avoid the risk of effects of errors in experimental design (as often found when you do not have full knowledge of the variance in the various factors in the test).

Consideration of the above factors allows estimation of a “bare bones” yet meaningful initial clinical study of treatment in Tier 3a (peptide anticipated to increase sperm binding to egg and thus pregnancy) compared with control (standard IUI without any supplement) through two cycles if IUI, with random pre-assignment of treatment in both the first and second cycles. With 200 to 225 patient couples pre-assigned to treatment or control groups for the 1st cycle of IUI and (assuming 30% dropout for whatever reason, including pregnancy) 140 to 157 pre-assigned to one or the other group for the second cycle, outcome data should be available for

340 to 382 cycles/group. Such a study could be run at one or two sites at a minimum cost \$0.9-1.3 million, if no costs were absorbed by the clinic or patient couples. Note that this study would not be conducted under conditions that would allow FDA clearance of the product, but rather would serve as a pilot study to help set up a more robust Tier 3 study when/if desired.

And what can you expect from a Tier 3a study? With 340 observations/group, in theory there would be a $\geq 70\%$ chance of detecting a 25% increase in pregnancy rate or a $\geq 82\%$ chance of detecting a 30% increase in pregnancy rate ($\alpha=0.20$; base of 10-20% per-cycle pregnancy rate). Importantly, with 340 observations/group, there would be a $\geq 40\%$ chance of detecting ($\alpha=0.05$) a 25% increase or a $\geq 56\%$ chance in detecting ($\alpha=0.05$) a 35% increase in per-cycle pregnancy rate. Increasing study size to 382 cycles (225 couples) per group would increase probabilities of detecting a difference to 0.70 to 0.93 for $\alpha=0.20$ or 0.43-0.77 for $\alpha=0.05$. In either study size, it is possible that a 25% increase might be significant ($P = 0.11-0.06$ or $0.09-0.05$) as might be a 35% increase ($P = 0.09-0.02$ or $0.07-0.01$). Use of a 2-tailed test of significance would reduce power by 10-20%, and similarly increase probability of rejecting a medically important treatment (Type-II error).

Obviously, a larger study would offer a greater probability for detection of significant differences, but modest increases in study size (e.g., to 250 couples and 425 cycles/group) do not markedly improve the probability that a medically important therapy will not be discarded due to a false-negative conclusion (Type-II error). A study to minimize the probability of a Type-I error (incorrectly concluding benefit) with an 80% chance of detecting a 25% increase ($\alpha=0.05$) would require 800-1200 couples/group.

With such data in hand, and assuming “positive” outcome, your start up company might be ready to enter a larger scale study under conditions (Tier 3) that could lead to FDA clearance and ultimately sale of product. Will your (or your investor's) interest persist? Given the reality of the above, it might be useful to consider alternative and less costly strategies to allow initial sales for the company (Tier 4 or 5).

The FDA regulations on approaches for fertility enhancement are unique, in that all buffers used to process semen for IVF or IUI (including one with a peptide) are viewed as a “device” by Congressional mandate and must be cleared through under 21 CFR 884.6180 as pertains to “reproductive media and supplements.” If an appropriate “predicate device” exists, clearance within <6 mo is possible via a relatively simple 510(k) submission.

A direct test of effects of product on *in vitro* sperm-egg binding will allow potential clearance as an agent with claims limited to that fact only. As before, it is prudent to run a preliminary test first (Tier 4a), and then proceed to a direct test under conditions that will allow FDA review (Tier 4). If cleared, sales can begin under a marketing plan with a strong scientific and legal basis.

Finally, a “back door” approach could be considered (Tier 5). It might be possible to advance the argument that inclusion of small amounts of peptide in a medium to process human sperm is trivial given the 5 mgm/ml human albumen is typical in such media. *Absent any claim of a “benefit”* from inclusion of peptide in the salts solution, there is no barrier to timely clearance provided that one can argue that probability of “harm” is minimal. Sale is made via skill in salesmanship as no claim can be made as to efficacy. Any reference to the literature is illegal because such evaluations were not conducted under full compliance with FDA regulations and thus are not legally recognized. Some sales are likely, but growth to full potential and return to investors is very unlikely.

7.1.5.1. Reality number four—Despite the need and the potential for significant human good that could be provided, the complex and unique path to approval for sale is a significant limit to commercial success. These facts will impact almost any product that might emerge from research funded by the NIH in this area of male, if not male and female, reproduction. This raises the serious question of why any such project is funded. Is “basic knowledge” enough?

8. Conclusion

The path to commercialization is complex, especially for applications involved in the reproductive sciences. For reasons listed herein, we cannot recommend pursuit of the dream of moving from Stage 2 to 7 to any excited entrant. *It is possible for an individual providing unique services to make a living, but extremely difficult for an entrepreneur to make his investors their expected fortune.* This signals serious future funding problems for animal agriculture and human medicine as reproduction is a key element in the maintenance of each.

That reality is for others to address. Given our perceived sense of importance of reproduction, we propose several areas when an extra effort might allow the path from concept to public good to proceed.

Commodity agriculture, might consider following a model used in other business sectors when problems affecting the entire industry are encountered. For example, there is a growing consensus that the availability of “biomarkers” will accelerate dramatically the delivery of successful new technologies and medicines for prevention, early diagnosis, and treatment of disease. In October 2006, a public-private partnership termed “The Biomarkers Consortium” was formed (press release at http://www.innovation.org/index.cfm/NewsCenter/Briefings/The_Biomarkers_Consortium) to fund research and validation studies critical to the entire industry. Similar approaches have been used in the electronics industries for decades. Amann (2000) provided an overview of how this might be addressed in the cattle industry that merits serious consideration.

For human medicine, the rudiments of an approach also are apparent. For the past decade the National Institute of Child Health and Development has provided a program dedicated to clinical research, but not necessarily clinical trials termed “Specialized Cooperative Centers Program in Reproduction and Infertility Research (U54)” as described at (<http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-06-005.html>). On inspection, it appears that the program is focused on academic projects (without encouragement of any commercial linkage) and the total is modest relative to what is needed (Table 3) for evaluation of any putative product. But if the NIH feels that value to society is limited by the current structure, consideration might be given to an analogous approach for small businesses. A payback feature should be required if the putative product became a financial success.

We both feel very strongly about the excitement, challenge, necessity and the reward in the pursuit from concept to commercialization. This feeling has led us to alter our target or field-of-interest to shoot for end applications other than reproduction. We encourage others to consider such a shift, provided “they measure the board twice (or three or four, or....) before they saw.”

Why this optimism for other fields? Because of the most remarkable entrepreneurial stories of our generation grew from “academic” research. It involves the formation of Google, Inc. Vice and Malseed (2005) repeatedly state that the founders did not want to start a company. Each had their own research objectives while pursuing their PhD at Stanford, and common to their research challenges was a need for better internet search capabilities. To advance their

respective research objectives they teamed to solve their search woes. The result of their academically driven decisions was the technology that drives Google, and later the company. Its value and admirable cash flow all result from their decision to solve the biggest mutual challenge that stood in the way of their individual research goals. In this context, a key point is that each researcher had to put on hold their “pet projects” in order to address a much bigger need and universal demand. By taking that action they have been paid handsomely because their search research solved a much bigger need than could either of their individual and more specifically focused objectives. Thus, the free market provided the driver for determining what research was of greater value, and thus warranted funding, both to develop and to navigate the risks of commercialization.

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Fig. 1. Graphic relation of progress of original ideas through product development to final profit making product. Data taken from Table 1.

Fig. 2.
Rate of return on investment for US research universities. Data from Association of University Technology Managers [see text] as provided by Dr A Stephen Dahms of The Mann Institute.

Table 1
A hypothetical innovation pipeline within a company hoping to launch one successful product per year.

Stage of new product development	Number of ideas*	% of prior stage survive	% survival from raw idea stage	Cost to develop one idea [\$k, US]	Total cost of stage [\$M, US]	Action items to increase efficiency and effectiveness
1 Raw ideas Not screened, researched or market analyzed; this is fixed cost and expectation of current staff	3,000	100	100	0	0	Get ideas from a variety of sources, especially customers; Provide "curiosity" time and environment
2 Ideas suitable for consideration Raw ideas screened, patent disclosures submitted, initiate market research and capital search	300	10	10	1	0.3	Find internal champions; Test with customers; encourage cross-discipline collaboration; <i>MAKE MISTAKES EARLY & FAIL QUICKLY</i>
3 Small projects R&D effort of 1-3 person-years, patent issued and opportunity analysis completed	125	33	3.3	25	3.12	Integrate decision tools and competitive intelligence; play-off creativity vs business needs
4 Significant projects Devote R&D effort of >10 person years; patents have significant value; market size and critical needs defined	9	8	0.27	400	3.6	Find first client willing to pay; engage them in process
5 Major developments Pilot plant R&D; product definition; test marketing and customer trials; Scale up plans	4	50	0.13	1,000	4.0	Identify sources of capital; with long term perspective, balance analysis vs intuition
6 Commercial launch Full-scale plant up; sales force trained; rollout	1.7	43	0.06	5,000	8.5	Focus, focus, focus
7 Commercial success Plant at capacity; profit in sight; sustained competitive advantage; continuous improvement	1	60	0.03	5,000	5.0	Learn from experiences and manage market feedback
TOTAL					24.52	A 2-year payback of total costs requires annual revenues of \$12,260,000 US

Adapted from Stevens and Burley (1997) and Anon (2003); cost estimates vary widely across industry sectors; examples provided to illustrate increasing scale of funding needed to move concepts forward. New is defined as "products or services with significant change that are substantially new (for instance, believed to be patentable)... and would include significantly new processes for manufacturing existing products". Commercial success does not mean that someone is buying the product or licensing the concept, but that the concept is providing economic profit to the company [money returned > all the money invested including cost of capital, depreciation and opportunity costs, raw materials and manpower]. Very useful additional detail on action items found in Kennedy (2006).

Table 2

Sources of information for the would-be entrepreneur.

Source	Access Detail	Comment
"Innovation and Entrepreneurship" by Peter F Drucker	ISBN 0-060-85113-9	An early but still useful overview by one of the dominant minds in management
"So What? who cares? why you?" by Wendy Kennedy	www.wendykennedy.com	Tool kit from the inventor's perspective, with special emphasis on clarity of thinking and presentation
"The Wisdom of Crowds" by James Surowiecki	ISBN 0-385-50386-5	Both staff management and product introduction demand an understanding of the factors that affect movement of groups of people
"The Art of the Start" by Guy Kawasaki	ISBN 1-591-841291	Practical information about starting a business
"Good to Great" by Jim Collins	ISBN 0-712-676090	Relevant in understanding why money sources are as much or more concerned about your management team than they are your ideas.
"Blue Ocean Strategy" by W. Chan Kim	ISBN 1-591-396190	Helpful and powerful tools for identifying and refining a successful opportunity
On-line tool kit	http://www.sherpapartners.com/	Helpful overviews of many aspects
"The World is Flat" by Thomas Friedman	ISBN 0-374-292795	This book and many others provides an awareness of how the current commercial world works.
Is it new?	www.uspto.gov; sales reps that carry analogous products; potential customers where every you can find them;	Misc sources useful to determine if your concept is sufficiently novel to merit the effort

Table 3
Overview of targets for Stage 4-7 evaluation of human reproduction products.

Designation	Goal of study with a product that is anticipated to increase sperm-egg binding and thus increase number of successful births	Estimated cost	Comment regarding value of FDA clearance to sales and marketing
1	Gold standard - increase in number of children without any detrimental effect in development through age 5*	>\$500 M	Ideal, as the company would leave next-to-nothing to risk, and millions of couples would be interested in its use
2	Increase in number of children born*	>\$100M	Very strong statement, perhaps equivalent in effect to above
3	Increase in successful pregnancy as assessed by ultrasound or hormone assay*	>\$5M	Very strong statement for use in marketing and sales
3a	Increase in successful pregnancy as assessed by ultrasound or hormone assay - pilot study to establish experimental design	>\$1M	Does not yield data for use in marketing and sales, but will reassure investors needed to proceed to Tier 3.
4	In vitro assay of sperm egg binding, using discarded human zona*	>\$0.3	Strong statement for effect on one step in process can be made for marketing and sales.
4a	In vitro assay of sperm egg binding, using discarded human zona - pilot study to establish experimental design	>\$0.1M	Does not yield data for use in marketing and sales, but will reassure investors needed to proceed to Tier 4.
5	Market under 510(k) as an additive to semen washing buffers - no comment as to purpose or effect	>\$0.1M	While FDA does clear the product, no statement can be made to assist in marketing and sales

Arranged in descending order from "best-of-all-worlds" to "barely-enough-to-begin-to-sell"

* conducted with protocols, materials and personnel that match those needed for full FDA compliance