From Animal Models to the Patient

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Innovation is at the Interface

Patient Dis-Ease
Medical Therapy Imperfect or Worse
New Technology for Diagnosis and Treatment Engineering
Paradigm of Pathophysiology and Treatment (set of assumptions when viewing reality)

INNOVATION

Science

History of Medical Progress and Artificial Organs in 3 Slides
Branching Points=paradigm changes Technical Innovations

From: Project Bionic Timeline
Barry, The Great Influenza
### Man made man success stories

Michael Lysaght, 2006

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<th>Stage of New Medical Device Development</th>
<th>Regulatory Agencies Involved</th>
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<td>CDRH IDE and 510(k)</td>
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<td>Other devices created in past or in pipeline, some may have failed</td>
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<td>Unachievable performance</td>
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| Product Requirements                    | GMP Design/Review           | Unrealistic requirements |
| Minimum performance                     |                             | Unachievability of performance |
| Necessary safeguards                    |                             | Inexperience |
|                                          |                             | Commissions failure to see critical problems |

| Product Design/Specs                    | GMP Design History          | Too little detail, or too much delay of critical decisions |
| Exact design or Alternatives            | starts here                 | Alternatives not considered |
|                                          |                             | |

| Failure Modes Analysis                  | GMP FMEA                    | Inexperience |
|                                          |                             | Failure to see critical problems |

| Lab prototype creation                  | GMP Design History          | Surrogate materials, constructions |
|                                          | affected                    | One-off constructions unrealisitc or difficult |

| In vitro testing                        | GMP Specs, GLP, Req’s, IDE & 510(k) | Testing superficial or unrealistic Marginal results accepted |
|                                          | Summary                      | |

| Patenting                               | USPTO, EPO, Courts           | Too early or too late, Too broad or too specific |

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<td>Animal testing prototype</td>
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| Animal testing                         |                             |               |
| normal animals                          |                             |               |
| disease models                         |                             |               |

| IDE for clinical trials                |                             |               |

| Clinical Trials                        |                             |               |

| FDA Approval of 510(k) or PMA          |                             |               |

| Licensing to company for marketing    |                             |               |
Steps of Development | Regulatory Agencies Involved | Failure Modes
---|---|---
Animal testing prototype | ACUC, GLP, NIH, formal report in IDE | If for IDE, same device functionality as final
Animal testing normal animals disease models | ACUC, GLP, NIH, formal report in IDE | Sterility, strength, performance not equal to Clinical prototype
IDE for clinical trials | CDRH, IDE, NIH outlines are general IRB approval also needed | Animal treatments difficult Short term follow-up Lack of good models
Clinical Trials | ADE reporting to CDRH, FDA inspections, DSMB, IRB, NIH | Problems in center choice, enrollment, incidence of disease, data collection, randomization, blinding, etc.
FDA Approval of 510(k) or PMA | CDRH, IRB, NIH | Disapproval or "not approvable," supplement, appeal, denial, another clinical trial.
Listening to company for marketing | CMS, FTC, IRS | Lack of similar goals of company vs. investigator

Steps of Development | Regulatory Agencies Involved | Failure Modes
---|---|---
Insurance company approval for payment | CMS, intermediaries, private insurance, bundle vs. separately billable | Insurance may request further clinical studies of cost-effectiveness
Market Acceptance, publications, advertising | FDA monitoring of post-market studies FDA monitoring of advertising | First use in high risk or atypical patients Sales people don’t understand the device or benefits No follow-up publications Some market leaders oppose
Review of early market experience | FDA reviews post-marketing study (usually much later) GMP requires formal complaint review process | Minimization of problems of the machine Criticizing the users rather than the machine
Device design improvements | GMP complaint review | Companies resist early product changes due to cost (not budgeted), confusion of users and investors
Second generation device and Repeat all of above... | FDA review of 510(k) of revised device if changes significant, GMP, GLP, etc. | Delay of decision for improvements pending more data Lack of formal analysis in post-market studies

Given all these uncertainties and difficulties what manner of individual would even try to develop a new medical device?
Given all these uncertainties and difficulties what manner of individual would even try to develop a new medical device?

Those with a congenital disconnect in their brain between hope and experience!

So you have an idea for a great new product or product improvement, what are the options?

Go to company with the closest possible product on the market
Secure Confidential Agreement
Further develop product and do clinical trials

Start your own company with a business partner
Apply for outside funding such as from NIH

Secure license or joint development agreement
Further develop product, license to existing company

Evolve your company to include sales, marketing, production contracts

Funding Sources for HemoCleanse and Ash Access

- Personal funds
- Shareholders, debentures, etc.
- NIH
- State of Indiana Economic Development
- States of Pennsylvania, Texas and Wisconsin Economic Development
- Product Licenses
- Corporate contract research
- Corporate partners
- Venture capital
- Product sales
- Anything else that appeared to be legal at the time

Business Strategy for HemoCleanse/Ash Access

- Define problems in medical devices used in Nephrology
- Find technologies that solve these problems and offer new solutions
- Develop new technology to the limits of resources, to show whether it has promise (including in vitro testing, animal testing, FDA-approved clinical trials, device approval for market, initial marketing if needed)
- Demonstrate that the new technology will almost certainly be workable and beneficial
- Create a new single-product company totally focused on this new device
- Direct the spin-off company to further develop or market the technology
- Enter negotiations to sell the entire new company to a major marketing company in dialysis (worked once so far)
- Or license the product to a major marketing company in dialysis (worked several times so far)
- Either way, proceeds are distributed to our shareholders.

After several experiences developing devices in collaboration with large companies, I found a great partner in business and we formed our own company in 1983...

Robert B. Truitt, President and CEO

HemoCleanse, Inc.

Renal Solutions, Inc.
Hemodialysis and peritoneal dialysis, sorbent based
Ash Access Technology
U Catheters and Antibacterial Locks

FMC
Purchased Company

Medcomp
Ash Split Cash

Contract R&D
Sorbent Dialysis, U Catheters, PD Catheters, Whole Body Hyperthermia

ZS Pharma
Oral Zirconium Silicate for Removal of Potassium and Ammonium

Zurex Pharma
Antibacterial Catheter Locks, Skin Preps, Veterinary Products

HemoCleanse Technologies
Liver Dialysis

FMC
Antibacterial Catheter Lock for Dialysis

HemoTherapies

Merit
Contral®™ self-centering UJ catheter
Advantages of the HemoCleanse Business Strategy

For HemoCleanse:
• Allows us to focus on numerous problems in dialysis therapy
• Provides greater chance of success; when one project hits a “wall” others always come through

For Spin-Off companies:
• With single-product focus, if the device is successful, the company will be successful
• All of the focus of this company is on this product, meaning that every feature is evaluated thoroughly
• The leaders of the company are motivated to find funding for the company
• The leaders have authority to direct the company as they see necessary, to reach the important goals

Disadvantages of HemoCleanse Business Strategy

• Educational challenge to inform engineers, managers and marketing of the reason for the device design, and advantages
• Enthusiasm of originating company is not present in the licensing company
• New company’s motives are naturally aligned with their best interest, not that of parent or licensee.
• Communication lines are difficult to maintain between the licensing company and the marketing company, at all levels
• Licensing company moves on to develop other devices with separate licensing and marketing potential

How to contribute to the field of artificial organs?

1. Know the problem
2. Know but doubt the paradigm
3. Train with the best in scientific method
4. Use the newest tools, mathematically model everything you can
5. Focus
6. Collaborate
7. Communicate, Publish
8. Be patient
9. Be careful
10. Keep balance, a strong family, faith and humility

What you need is a very supportive family...

Finally, focus:
Did really think 35 years would be long enough to solve.....

• Kidney failure treatment at home (Biologic-HD, Allient)
• Liver failure treatment (Liver Dialysis, PF sorbent pheresis)
• Sepsis therapy (PF)
• HIV/AIDS and Advanced Cancer Therapy (Hyperthermia with sorbent dialysis)
• Blood access for dialysis (Ash SplitCath, Centros, and newer methods)
• Catheter infection (Antibacterial/Antithrombotic Solutions)
• Peritoneal access for dialysis (LifeCath, Advantage, Sureflow catheters)
• Peritoneoscopy for catheter placement (Y-Tec System)
• Peritoneal clearance improvements (Flow-through Peritoneal Dialysis, pressure and volume controlled)
• Diabetic monitoring (ultrafiltration fibers, glucose sensors)
• Practical Electronic Medical Records (SmartChart, Velos)
• Nephrology training issues (models for interventional procedures)
• etc...?

There's a fine line between dedication and obsession....

END
How Do We Get New Devices?

• Where do new ideas come from?
• How do you get it from idea to reality?
• How to prove the new idea?
  – Animal Model benefits, disadvantages
  – Clinical Trial Pitfalls
• Patenting
• FDA Approval
• Commercialization
• Examples:
  – SplitCath, Centros
  – AAV
  – Zuranol
  – ZS
  – AAV