Gene Therapy Clinical Development and Pricing Considerations

Glenn Pierce MD PhD

WFH Global Forum
Montreal, 22-23 Oct 2015
<table>
<thead>
<tr>
<th>Conflict</th>
<th>Disclosure - if conflict of interest exists</th>
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<tbody>
<tr>
<td>Research Support</td>
<td></td>
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<tr>
<td>Director, Officer, Employee</td>
<td></td>
</tr>
<tr>
<td>Shareholder</td>
<td>Biogen</td>
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<td>Honoraria</td>
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<td>Advisory Committee</td>
<td>Alnylam, Intas</td>
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<tr>
<td>Consultant</td>
<td>BioMarin, Genentech/Roche</td>
</tr>
</tbody>
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## Liver-Directed AAV Phase 1/2 Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th># Subjects</th>
<th>Peak FIX Activity (%)</th>
<th>Sustained Activity (%)</th>
<th>Immune Resp to AAV*</th>
<th>Sponsor</th>
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</thead>
<tbody>
<tr>
<td>ssAAV-FIX</td>
<td>6, closed</td>
<td>11.8</td>
<td>No</td>
<td>Yes, 2/6</td>
<td>Avigen/CHOP</td>
</tr>
<tr>
<td>scAAV8-FIX</td>
<td>10, closed</td>
<td>~7-12</td>
<td>1-6</td>
<td>Yes, 5/10</td>
<td>UCL/SJCRH</td>
</tr>
<tr>
<td>scAAV8-FIXR338L (BAX-335)</td>
<td>7, ongoing</td>
<td>26-58</td>
<td>Variable 0 to 25</td>
<td>Yes, 2/7 (both high dose)</td>
<td>Baxalta</td>
</tr>
<tr>
<td>AAV5-FIX (UCL FIX construct)</td>
<td>3, ongoing</td>
<td></td>
<td></td>
<td></td>
<td>UniQure</td>
</tr>
<tr>
<td>AAV8(93%)-FIXR338L (SPK-9001)</td>
<td>0, start in H2 15</td>
<td></td>
<td>41% Nabs (AAV8=55%)</td>
<td></td>
<td>Spark</td>
</tr>
<tr>
<td>AAV-FVIII (BMN 270)</td>
<td>1, ongoing</td>
<td></td>
<td></td>
<td></td>
<td>BioMarin</td>
</tr>
</tbody>
</table>

*Clinically silent liver inflammation, resultant loss of cells expressing FIX; No inhibitors seen to FIX in any patient*

Hurdles for Human Gene Therapy in Hemophilia

• **Past Hurdles**
  – Risk of immunogenicity of the delivered gene product: none detected in humans
  – Preparation of consistent, high quality AAV vector lots
  – Risk of sexual transmission of AAV: none detected in humans
  – Liver toxicity: detected in humans, not in animals
  – Acute inflammation from adenovirus vectors: detected in humans

• **Present Hurdles**
  – Preparation of consistent, sufficient, high quality AAV, Lentiviral vectors
  – Defining high quality AAV, Lentiviral vectors
  – Anti-AAV antibodies in ~50% of population
  – Sufficient protein expression (eg, 50%) for sufficient duration (eg, 10+ years)
  – Assess long term safety of Lentiviral vectors
  – No standardized assays measure vectors and anti-AAV antibodies

• **Future Hurdles**
  – New vector which can target ~100% of the population
  – Scaled up manufacturing of vectors
  – Gene editing to fix the defect w or w/o stem cells
# Some Preclinical Gene Therapy Projects

<table>
<thead>
<tr>
<th>FIX</th>
<th>Company</th>
<th>Status</th>
<th>Non-clinical efficacy</th>
<th>Clinical Plans</th>
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<tbody>
<tr>
<td>AAV-FIX DTX-101</td>
<td>Dimension</td>
<td>IND filed 8-15</td>
<td>None published</td>
<td>Start EOY 2015</td>
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<tr>
<td>Lenti FIX</td>
<td>Tiget-San Raffaele, Biogen</td>
<td>Preclinical</td>
<td>Mouse, dogs, in vivo IV delivery</td>
<td>Planned in vivo delivery to liver</td>
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<tr>
<td>AAV-FIX (alb locus)</td>
<td>Sangamo</td>
<td>Preclinical</td>
<td>None published</td>
<td>Planned 2016</td>
</tr>
<tr>
<td>AAV-FVIII</td>
<td>Dimension, Bayer</td>
<td>Research</td>
<td>None published</td>
<td></td>
</tr>
<tr>
<td>AAV-FVIII</td>
<td>Spark</td>
<td>Preclinical</td>
<td>None published</td>
<td></td>
</tr>
<tr>
<td>AAV-FVIII BMN270</td>
<td>BioMarin</td>
<td>Ph1/2</td>
<td>None published</td>
<td></td>
</tr>
<tr>
<td>Lenti-FVIII</td>
<td>Emory, Expression Therapeutics</td>
<td>IND filing 2016</td>
<td>None published</td>
<td>Planned ex vivo transduction and HSPC transplant</td>
</tr>
<tr>
<td>Lenti-FVIII</td>
<td>Tiget-Biogen</td>
<td>Research</td>
<td>Mouse, Scientific presentation</td>
<td>Planned in vivo delivery to liver</td>
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</table>

**Bottom Line:** Multiple variations on a theme in preclinical testing.
Considerations in AAV gene therapy

AAV Vector Modifications

- Change serotypes from AAV2 to AAV8, AAV5, mutated capsids: Unclear benefits, ~40-60% of population has neutralizing antibodies to all the serotypes
- Change genomic form of gene from single stranded to self-complementary: Unclear benefit
- Codon optimize to increase protein expression: Clear benefit
- Use a super-active FIX gene (R338L): Clear benefit

Immune Responses to Hepatocytes

- Inconsistent
- Unpredictable
- Not found in animal models
- Zero therapeutic window
- Elevated liver enzymes not clinically problematic to date
- Steroid treatment shuts down the immune response to liver cells but given after assault on FIX-containing hepatocytes begins. Too late
- Prophylactic steroids might maximize FIX activity that can be achieved
- High variability in responses from 0-60%: problematic drug development
Who is Excluded from AAV Gene Therapy Trials?

- Children and adolescents under 18
- FIX>2%; FVIII>1%
- HCV RNA positive
- FIX inhibitor (~3-4% prevalence); FVIII inhibitor (~10%)
- AAV serotype antibody positive (~40-60%, assay dependent)

Success will open future trials up to children and moderate HemB, and HCV is now curable. NO solution for the ~50% of the population with pre-existing antibodies to AAV serotypes
  - Another vector such as lentivirus may be the solution, but risk/benefit ratio for lentivirus is greater than for AAV
    - Integrating virus
    - Ex vivo manipulation of hematopoietic stem cells may be required
- What to do about half the population being left behind?
  - Other technologies emerging
Long-Term Culture of Genome-Stable Bipotent Stem Cells from Adult Human Liver

- Establishment of a long-term human liver organoid culture
  - Human liver stem cells retain genetic stability after long-term expansion
  - Liver organoid cultures differentiate to functional hepatocytes in vitro and in vivo
  - Organoids derived from patients with genetic disorders model liver disease in vitro

Clonal long-term expansion of primary adult liver stem cells opens up experimental avenues for disease modeling, toxicology studies, regenerative medicine, and gene therapy
Hemophilia Gene Therapy Summary

- HemB responses inconsistent but positive in some cases - some patients converted to moderate or mild HemB
- Immune response and quality and scale up of vector production remain hurdles
- HemA clinical trials have begun
- Solving the problem of AAV vector pre-existing immunity, or a different vector, or a different approach, is needed to reach the entire population
What does “Cured” mean

• Literature suggests less acute bleeding with
  – Less time per week below 1%
  – Less time below ~5%
• No bleeding above 10-15%
• Confirmatory experience in moderate/mild hemophilia supports observations in severe patients
• What is an extraordinary outcome?
  – 1%, 2%, 5%, 10%, or 50%
  – Which of these are “curative” for hemophilia?
What Is a Fair Price for Gene Therapy Innovation and Enablement

• Depends on the results
  – Drugs priced at level traffic will bear (Value-based pricing)

• Other considerations to achieve Value Based Pricing
  – development costs (time and $)
  – manufacturing costs
  – size of treatable population
  – longevity of treatment
  – Degree of independence from clotting factor
Opportunity Costs - Time

Representative Development and Regulatory Review Time Profile (synthesis to approval)

- Synthesis – Approval: 128.0 months
- Clinical Start – Approval: 96.8 months
- Synthesis – Phase I: 31.2 months
- Phase I – II: 19.8 months
- Phase II – III: 30.3 months
- Phase III – NDA/BLA Submission: 30.7 months
- NDA/BLA Submission – Approval: 16.0 months

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Opportunity Costs - Money

Growth in Capitalized R&D Costs per Approved New Compound

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<tbody>
<tr>
<td>Pre-human</td>
<td>109</td>
<td>278</td>
<td>436</td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990s-early 2000s</td>
<td>135</td>
<td>608</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000s-early 2010s</td>
<td>179</td>
<td>413</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2,558</td>
<td></td>
<td></td>
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</tbody>
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Sources: 1970s, Hansen (1979); 1980s, DiMasi et al. (1991); 1990s-early 2000s, DiMasi et al. (2003); 2000s-early 2010s, Current Study

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Cost vs Value Based Pricing

• Recombinant proteins
  – Initial costs of production were higher
  – High manufacturing costs are a specious argument today
  – Pricing is Value-Based- what the traffic will bear?

• Gene therapy
  – Initial costs of production will be very high
  – Value of curing vs treating hemophilia is also very high
How Should Gene Therapy Cost Be Calculated?
Basis of Value Based Pricing

• $20M lifetime cost for recombinant factor replacement in non-inhibitor patient
  – Assumes ~$250K/year net to manufacturer x 80 yrs
• Is one gene therapy injection worth $20M?
• Classic disruptive technology
  – Payments to existing companies in this space drop 95% if sold for $1M a single time and current market share maintained
  – Is 5% of today’s market sufficient incentive for new companies entering this space?
  – Who will invest in a shrinking market? Obviously, plenty
  – And who will pay $1M?
Determining a Price for Gene Therapy

- Key parameters for assessing cost effectiveness
  - Efficacy
  - Safety
  - Cost savings to health care system
  - Quality of Life

- Three payment models have been discussed
  - Pay for performance
    - 5% FIX gets $X; 10% FIX gets $X+Y; 40% FIX gets $X+Y+Z
  - Up front, one time payment at time of intervention (alipogene tiparvovec (Glybera®))
  - Annuity model without pay for performance component

http://blogs.nature.com/tradesecrets/2015/03/03/1-million-price-tag-set-for-glybera-gene-therapy
What About That Thing Called Capitalism?

Three quarters of the world have no access to effective bleeding disorder therapies.
For the one quarter who do have access, disruptive innovation occurs at a startling pace.

Capitalism is this wonderful thing that motivates people, it causes wonderful inventions to be done. But in this area of diseases of the world at large, it's really let us down.

~ Bill Gates ~
THANK YOU