

ASGT Stakeholders Conference

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“Lions, tigers and bears - oh my!”

Vectors: No consensus vector but some general principles #1

- Retroviral/Lentiviral
 - Integration has risks in stem cells particularly if selective advantages are present for modified cells and growth factor genes or receptors are involved
 - Use of SIN vector designs should significantly reduce these risks
 - Significant potential to advance our understanding of natural oncogenesis has been created
 - In contrast, in some situations, viral spreading such as lentivirus in AIDS might actually enhance efficacy without an impact on safety
 - Integration risks in non-stem cells including T cells or epithelial cells is very different (lower) than stem cells
- New strategies to deliver genes are developing

Vectors: No consensus vector but some general principles #2

- Adenoviral vectors have high potential to initiate both innate and adaptive immunity
 - Good for cancer and therapeutic vaccines
 - Strategies to circumvent this for therapeutic gene delivery (tissue compartment choices, new vector delivery approaches)
 - Significant potential to vector engineer adenovirus around these limitations

Vectors: No consensus vector but some general principles #3

- AAV vectors transduce target cells efficiently, minimize immune responses
 - Particularly suited for therapeutic gene delivery
 - Immunity still a barrier for some routes of administration
 - Strategies to use AAV for vaccines due to improved antigen delivery will require additional immune activating strategies

Vectors: No consensus vector but some general principles #3

- Herpes virus vectors
 - Number of potential advantages for long term gene delivery in nervous system cells
 - Strong biological background of latency and avoidance of immunity
 - Major applications include chronic pain, diabetic and other neuropathies

Vectorology Forward

- New strategies to direct integration safely
- Deliver/repair genes without insertional events
- SIN vectors
- Regulatable and tissue specific promoters
- Suicide genes
- New envelope proteins and serotypes
- Production by transient expression
- Continue process of sorting out best applications for specific vectors

Vectorology Forward #2

- It is critical for academics to approach the “product” in the context of the entire process of moving gene therapy from Phase I to Phase III.
- If we approach Biotech and Pharma with strategies that are not amenable or suitable for Phase III implementation, we will not get the responses we want and need.
- If the Field accepts this discipline, the downstream impact will redefine the identity of the field.

Immunity

Should not be seen as an insurmountable barrier, just a challenge!

- Innate immunity
 - “Danger signals” and tissue injury paradigm
 - Price of using viral pathogen skeletons as vectors
 - Vector-independent responses to RNA/DNA
 - Potential of developing new anti-innate immunity therapeutics
- Adaptive immunity
 - Memory and amplification
 - Risks of self vs. non-self confusion
 - Link to innate immunity
 - Potential value of immunosuppressive therapy
 - Potential value of Treg inducing strategies

Immunity Forward

- Trials using new immunosuppressive strategies - short term (hopefully)
 - ? Drug choices
 - Current immunosuppressives
 - Novel agents
 - ? Intensity vs. Safety
- Opportunities to increase interactions with immunologists
 - Shared meeting with AST/ASTS or Cell Transplantation Society
 - Funding initiatives

Vaccines

- Major progress in this area
 - HIV
 - Cancer
- New approaches to enhance immune activation
 - Local
 - Systemic
- Adeno vs. AAV vectors
- Oncolytic RNA viruses

Vaccines Forward

- Animal model choice uncertainties
 - Rodent
 - Dogs, pigs
 - Non Human Primates
- Pharmacokinetics, pharmacodynamics
- Potential for novel imaging technologies

Regulatory Climate

Irony is that the regulatory players, FDA and NIH have been consistently supportive, flexible and actively engaged in the whole process.

- Intense, Multiple Players = Disincentives
 - Why should gene therapy be treated differently at this level?
 - How can we put this into a better context with the pragmatic objective of improving the process of bringing forward new technologies?
 - Need to engage FDA and NIH in process

Regulatory Forward #1

- Is there a way to streamline current regulatory process?
 - Could a single package be used for all submissions?
 - Do multiple regulatory bodies “add value”?
 - Do they contribute to the general impression that gene therapy is a “strange and dangerous” type of therapeutic?
 - Brenner suggestion: one local, one national regulatory body

Regulation Forward #2

- Best current target for refining process are local IRBs and IBCs
 - Create a document as a master reference
 - Create a process at the ASGT to encourage chairs of local groups to seek our advice on local applications
- Reality Check - Better define risk/benefit decisions
- Better understand genetic risks, genetic testing etc.
- Children should not be denied access to gene therapy trials when the nature of the disease balanced against the risk/benefit of the therapy is considered acceptable. Indeed, efforts should be increased to include children in such trials.

Public Perceptions

- How do we assess and engage our own community at this point?
- Can we better present the successes and continued progress in gene delivery science?
- What is the public concerned about at this point?
- Can/should we try to change public perceptions actively or just continue to do the work?
 - Seek help from disease foundations?
 - Engage professional consultants?
 - Actively propose and work on a NOVA or equivalent on gene therapy?

Academia, Biotech and Pharma

- Significant challenges and concerns - Cost!
 - NIH funding review parameters, time lines and focus
 - Inequities in funding limits access, reduces interest in many institutions and narrows the field
 - Decreased funding, activity and interest in the Biotech companies creates a gap
 - Current view of Pharma and natural focus on “big markets” is a huge issue
- What can we do to protect interests of “orphan” diseases? Can we bridge the gap to Pharma?
- If there are limited resources, are there best disease targets for gene therapy?

How big pharma sees gene therapy

- Research Says: This mechanism will *never* work
- Clinical Says: These Phase I data are unimpressive
- Manufacturing Says: This product is a mess, we cannot make it!
- Regulatory Says: The partner has done a horrible job with the FDA
- Marketing Says: We cannot sell this drug!
- Finance Says: These costs have been underestimated.
- Management Says: This deal is way too expensive; I want a good deal!
- Lawyers at the academic institution and the Pharma start fighting over IP, licensing, other patents etc.

-Adapted from George Golumbeski, Novartis

Increase clinical experience

- What issues impede this?
 - Value of clinical trials in shaping the directions for iterative preclinical and clinical studies
- At academic centers
 - Time to produce at GMP level
 - Availability of clinical trials specialists/regulatory staff
- At biotech companies