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# ***AVI plus Ercole***

## **Rationale and Strategy**

**March 13, 2008**

***Product Flow From  
Directed RNA Alternative Splicing***

# Safe Harbor Statement

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Comments made by management during this presentation will include forward-looking statements within the meaning of Federal securities laws. These forward-looking statements involve material risks and uncertainties and include statements which may be preceded by the words “potential,” “believe,” “expect,” “predict,” “continue,” “likely,” “unlikely,” “anticipate,” “estimate,” “optimistic,” “sustainable,” “intend,” “plan,” “project,” “target,” “aim,” “will,” “may,” “unlikely to be,” and similar words. For such statements, we claim the protection of the Private Securities Litigation Reform Act of 1995. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the time they were made.

Actual results could differ materially from our forward-looking statements due to, among other reasons, preclinical and clinical development is highly uncertain, the success and cost of our research, clinical studies and partnering endeavors, our ability to obtain additional financing, our clinical trials may not proceed at the time we expect or at all, the timing of payments and fees, if any, from our collaborators, and our ability to obtain and defend patents. Additional factors that could cause actual results to differ materially from those stated or implied by our forward-looking statements are disclosed in our SEC filings. For a discussion of these risk factors, you are encouraged to review our annual report on Form 10-K for the year ended December 31, 2006 and subsequent reports as filed with the SEC. We disclaim any intent or obligation to update these forward-looking statements, other than as may be required under applicable law.

# AVI & Ercole – True Synergy

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## ◆ Complementary technologies and patents

### – Ercole

- Fundamental expertise, patents and technology for directed alternative splicing
- Patent applications on high-value targets

### – AVI

- PMO chemistry well suited for directed alternative splicing (i.e., ESPRIT)
- Dedicated in-house chemistry and manufacturing expertise
- Emerging SAR for directing drugs to different tissues
- Highly complementary patent estate

## ◆ Complementary pipelines

Block translation

**CABG**

**Ebola / Marburg**

Alternative splicing

**DMD**

**TNFR2/TNFR1**

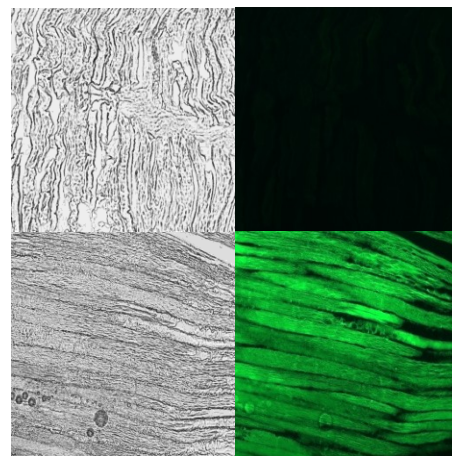
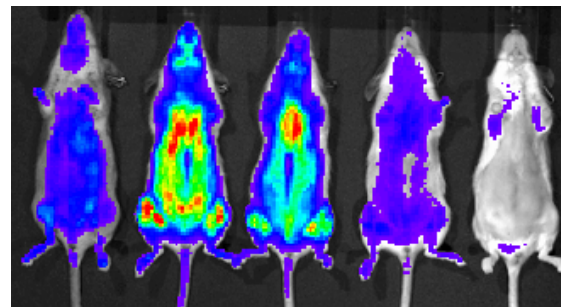
# Directing Outcome of Alternative Splicing

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- ◆ Mitigate impact of a mutation
- ◆ Direct RNA processing to a preferred splice variant
- ◆ Tip balance of RNA processing from promotion to inhibition; cell death, signal transduction
- ◆ Create novel protein *in situ*; for example endogenously solubilized transmembrane protein or receptor

# In Vivo Delivery and Localization

- ◆ Ercole EGFP mouse has proven to be key for delivery evaluation
- ◆ Has been used to match tissue localization and optimum chemistry
- ◆ AVI developed enhanced immune cell targeting
  - Penetration into T cells and dendritic cells *in vivo*
- ◆ Exploits advantages of the chemical platform
- ◆ Above capabilities will be used to optimize chemistry for improved delivery



# Range of New Discovery Targets Enabled by Combined IP Estate

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- ◆ RNA repair
  - Joint program in DMD already in clinic
- ◆ Soluble receptors
  - TNFR2 programs in rheumatoid arthritis already in progress in Ercole
- ◆ Ligand independent receptors
  - CTLA-4 program in type I diabetes in Discovery Research at AVI
- ◆ Treatment of virus infection and disease
  - Extends AVI anti-infective programs with unique host immune factor genes to reduce pathogenic mechanisms

# DMD Clinical Strategy

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- ◆ **Demonstrate expression, safety, duration and gain of function**
- ◆ Systemic delivery, dose-response and safety; therapeutic window
  - Single exon intervention for a limited number of exons
- ◆ Spectrum of DMD treatment of the affected population will require a multi-exonic approach
  - Design of drug or combinations will be guided by empirical findings
  - Currently divergent scientific opinion on appropriate strategy and likely outcome
- ◆ Significant clinical progress in staging the disease
  - Standardization of protocols
  - Validated functional assessments

# TNF Receptor Superfamily

## Approved TNF $\alpha$ Blockers

Name	Technology
Enbrel <sup>®</sup>	rDNA
Humira <sup>®</sup> , Remicade <sup>®</sup>	MAb

- ◆ Market size: \$9.9B (>\$4B for Enbrel alone)
  - Opportunity for a chemically synthesized TNF $\alpha$  blocker
  - Induction of soluble TNF receptor *in situ*
  - Well characterized therapeutic intervention points with well understood benefits and risks
  - Established pathway to clinic and product registration
- ◆ Major value driver for the acquisition; AVI will advance development



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