Prediction of Disease Vulnerability and Treatment Response in Mood Disorders: Personalized Medicine in Psychiatry

Presented by:
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DISCLOSURES

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• Stockholder: CeNeRx BioPharma, Inc., PharmaNeuroBoost, Revaax Pharma, Xhale
• Other Financial Interest: CeNeRx BioPharma, PharmaNeuroBoost
• Patents: Method and devices for transdermal delivery of lithium (US 6,375,990B1), Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2)
• Scientific Advisory Board: American Foundation for Suicide Prevention (AFSP), CeNeRx BioPharma, National Alliance for Research on Schizophrenia and Depression (NARSAD), PharmaNeuroBoost, Anxiety Disorders Association of America (ADAA), Skyland Trail
• Board of Directors: AFSP, Gratitude America, Skyland Trail, ADAA
Depression and Anxiety are Ultimately About How the Brain Responds to the Environment

**Genes:** sequence variants and variable gene processing

**Cells:** molecular pathways

**Systems:** activity in emotion processing circuitry

**Behavior:** Clinical phenotype
The Neurobiology of Bipolar Disorder: Theoretical Considerations

Environmental Factors
Susceptibility Genes
Protective Genes
Modifying Genes
Imprinting
Tissue Specific Haploinsufficiency
Mania and Depression
Episodic symptom clusters
Affective
Cognitive
Motoric
Neurovegetative

21st Century Medicine

Prevention
Disease susceptibility
Interventions
Tipping Points
Treatments
Clinical Manifestations
Genetics/Genomics
Molecular Markers/Imaging
Clinical Testing
Birth
Time
Death
"We used to think our fate was in our stars. Now we know, in large measure, our fate is in our genes." J. D. Watson

Studies of identical twins have revealed that some conditions, such as psoriasis, have a strong genetic component and are less influenced by environmental and lifestyle factors — identical twins are more likely to share these diseases. But other conditions, such as multiple sclerosis, are only weakly influenced by genetic makeup and therefore twins may show differences depending on their exposure to various environmental factors.

Concordance Rates for Manic-Depressive Illness in Monozygotic (MZ) and Dizygotic (DZ) Twins

<table>
<thead>
<tr>
<th>Study</th>
<th>MZ</th>
<th>DZ</th>
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<tbody>
<tr>
<td>Rosanoff et al, 1934</td>
<td>69.9</td>
<td>16.4</td>
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<tr>
<td>Kallmann, 1954</td>
<td>92.6</td>
<td>23.6</td>
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<tr>
<td>Da Fonseca, 1959</td>
<td>71.4</td>
<td>38.5</td>
</tr>
<tr>
<td>Harvald, Hauge, 1965</td>
<td>50.0</td>
<td>2.6</td>
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<td>Kringle, 1967</td>
<td>33.3</td>
<td>0.0</td>
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<tr>
<td>Bertelsen, 1977</td>
<td>58.0</td>
<td>17.0</td>
</tr>
<tr>
<td>Torgerson, 1986</td>
<td>75.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

† Aggregate values across studies of heritability in liability to major depression.

Mood Disorders Across the Life Cycle

Childhood
Teenage Years
Menarche
Pregnancy
Menopause
60's
70's

Early Onset Depression
Bipolar Disorders

Premenstrual Dysphoric Disorder
Depression During Pregnancy
Depression Associated With Infertility, Miscarriage, or Perinatal Loss
Depression During the Perimenopausal Period
Depression Comorbid Medical Disease: Heart Disease, Stroke, Diabetes, Cancer
Late Onset Depression

Depression Co-occurring With HIV/AIDS

Confirmed Linkages in Bipolar Disorder

<table>
<thead>
<tr>
<th>Genomic Location</th>
<th>Principle Report</th>
<th>Independent Confirmations</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>18q11.2</td>
<td>Berrettini et al., 1994 and 1997</td>
<td>Stine et al., 1995; Nothen et al., 1998; Turecki et al., 1999</td>
<td>Paternal parent-of-origin effect; see Schwab et al., 1998</td>
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<tr>
<td>21q22</td>
<td>Straub et al., 1994</td>
<td>Delera-Wadleigh et al., 1997; Smyth et al., 1996; Koeck et al., 1999; Morissette et al., 1999</td>
<td>Velocardiofacial syndrome region; possible overlap with a schizophrenia locus</td>
</tr>
<tr>
<td>22q11.13</td>
<td>Kelsoe et al., 2001</td>
<td>Delera-Wadleigh et al., 1997 and 1999</td>
<td>See Friel et al., 1986</td>
</tr>
<tr>
<td>18q22</td>
<td>Stine et al., 1988</td>
<td>McInnes et al., 1988; McMahon et al., 1997; De Bruyn et al., 1996</td>
<td>See Friel et al., 1986</td>
</tr>
<tr>
<td>12q24</td>
<td>Morissette et al., 1999</td>
<td>Ewald et al., 1998; Delera-Wadleigh et al., 1999</td>
<td>Principal report in a Canadian isolate</td>
</tr>
<tr>
<td>4p15</td>
<td>Blackwood et al., 1996</td>
<td>Ewald et al., 1998; Nothen et al., 1997; Delera-Wadleigh et al., 1999</td>
<td>See Ginnis et al., 1998</td>
</tr>
</tbody>
</table>

Neurotransmitters and Depression

• There are disturbances in the monoamine systems
  - serotonin (5-hydroxytryptamine, 5-HT)
  - norepinephrine (NE)
  - dopamine (DA)??

• There are also disturbances in other neurotransmitter systems (e.g., corticotropin-releasing factor [CRF] and substance P)

• Serotonin and norepinephrine have been the most extensively studied in the clinical setting
Regulation of Behavioral Circuits by Neuromodulatory Systems

Prefrontal Cortex
- Cognition
- Working memory
- Modulation of affect

Thalamus
- Arousal/sleep, sensorimotor gating

Hypothalamus
- Stress response, sleep/wake/appetite regulation

Nucleus Accumbens
- Reward/pleasure

Amygdala/BNST/Hippocampus
- Fear/stress response, anxiety symptoms, memory

LC=locus coeruleus; NE=norepinephrine; CRH=corticotropin-releasing hormone; 5HT=5-hydroxytryptamine.
Reduced Brainstem \([^{123}I]\beta\text{-CIT} Binding in Depression

\[\text{Brainstem V3}^*\]

\[\begin{array}{c}
\text{Healthy} \\
\text{Depressed}
\end{array}\]

\(\Delta\) Drug Free

\(\triangle\) Drug Naive

\(^*p=0.03\)


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Dopamine and Depression

- Role of Dopamine neurons in behavioral and physiological areas altered in depression
- High rate of Comorbidity of Parkinson’s Disease and Depression
- Pathophysiological involvement of DA systems in Depression
- Role of DA circuits in the Actions of Antidepressants
  - MAOIs
  - effects on the DA transporter
Dopamine transporter binding potential in bilateral striatum is lower in depressed patients. Data was analyzed using analysis of covariance with age as a covariate, examining effect of diagnosis (effect of diagnosis: F1,29 = 7.1, P = 0.01).

Norepinephrine Alterations

- NE dysfunction is linked to depression
  - low levels of NE metabolites are found in the urine and CSF of depressed patients
  - increased density of B-adrenergic receptors is found at postmortem in the cortex of depressed suicide victims
  - NE reuptake inhibitors are effective antidepressants (desipramine, reboxetine, maprotiline)
TH and NSE Levels in Sections of LC from Control and Suicide Victims

Our DNA is our instruction manual!

We can now read the whole manual!!
The image shows how DNA sequence variation in a gene can change the protein produced by the genetic code. The nucleotide triplet codon at position 1 in the gene depicted is different in person 1 and person 2, but the codon difference does not change the amino acid sequence. In person 3, the nucleotide triplet codon at position 2 is different from that in person 1 and person 2, and the codon change results in production of a different amino acid at position 2 in person 3.

5’-HT transporter promoter polymorphism (SLC6A4, 17q11)

Adapted from Lesch & Mossner (1998) Biol Psychiatry 44.
Results of regression analysis estimating the association between childhood maltreatment (between the ages of 3 and 11 years) and adult depression (ages 18 to 26), as a function of 5-HTT genotype. 

Regulation of Stress Response by CRH and HPA Axis

HPA=hypothalamic-pituitary-adrenal; ACTH=adrenocorticotropic hormone.

DEP=depressed patients; CON=control patients. *P<0.01; mean ± SEM.
Central CRH: A Mediator of Stress and Depression

- CRH CSF concentrations are elevated in depression
- CRH stimulation test shows blunted ACTH response in depression
- Combined dexamethasone/CRH stimulation test is dysregulated in depression
- Increased pituitary/adrenal gland size in depression
- In animals, CRF injections into brain mimic anxiety and chronic depression
- These effects can be blocked by CRHR1 antagonists and a neurokinin-2 (NK2) receptor antagonist
- A principle source of brain CRH is the central nucleus of the amygdala, known to be involved in stress response and depression

Sample Demographics

<table>
<thead>
<tr>
<th>Sample Demographics</th>
<th>N</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>194</td>
<td>36%</td>
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<tr>
<td>Female</td>
<td>303</td>
<td>61%</td>
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<tr>
<td>Self-Identified Race/Ethnicity</td>
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<td></td>
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<tr>
<td>African American or Black</td>
<td>484</td>
<td>87%</td>
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<tr>
<td>Caucasian or White</td>
<td>4</td>
<td>8%</td>
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<tr>
<td>Hispanic or Latino</td>
<td>2</td>
<td>4%</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>2%</td>
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<tr>
<td>Mixed</td>
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<tr>
<td>Other</td>
<td>3</td>
<td>0%</td>
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<tr>
<td>Education</td>
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<tr>
<td>&lt; 12th Grade</td>
<td>153</td>
<td>31%</td>
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<tr>
<td>High School Graduate or GED</td>
<td>217</td>
<td>44%</td>
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<tr>
<td>Some College or Technical School</td>
<td>78</td>
<td>15%</td>
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<tr>
<td>Technical School Graduate</td>
<td>21</td>
<td>4%</td>
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<tr>
<td>College Graduate</td>
<td>21</td>
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<tr>
<td>Some Graduate School</td>
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<tr>
<td>Employment Status</td>
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<tr>
<td>Currently Unemployed</td>
<td>338</td>
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<td>Currently Employed</td>
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<tr>
<td>Disability Status</td>
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<tr>
<td>Not Currently Receiving Disability</td>
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<tr>
<td>Currently Receiving Disability</td>
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<tr>
<td>Household Monthly Income</td>
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<tr>
<td>&lt;$900</td>
<td>158</td>
<td>32%</td>
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<tr>
<td>$900 – $1,499</td>
<td>51</td>
<td>10%</td>
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<tr>
<td>$1,500 – $2,099</td>
<td>136</td>
<td>28%</td>
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<tr>
<td>$2,100 – $2,999</td>
<td>106</td>
<td>21%</td>
</tr>
<tr>
<td>$3,000 or more</td>
<td>158</td>
<td>30%</td>
</tr>
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</table>

Early Life Stress Significantly Enhances Risk for Depression in Adults

Beck Depression Inventory (BDI) scores are predicted by continuous scores on the childhood trauma questionnaire.

Depression is predicted by presence/absence of childhood trauma.

CRHR1 Polymorphisms Strongly Interact With Level of Childhood Abuse in the Prediction of Adult Depression

CRHR1 Polymorphism Haplotypes Interact With Level of Childhood Abuse in the Prediction of Adult Depression

**A** Block 1 Haplotypes

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Frequency (%)</th>
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<tbody>
<tr>
<td>rs7206936</td>
<td>T</td>
</tr>
<tr>
<td>rs4792837</td>
<td>C</td>
</tr>
<tr>
<td>rs1161502</td>
<td>C</td>
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<td>24.1</td>
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<table>
<thead>
<tr>
<th>Haplotype</th>
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<tbody>
<tr>
<td>rs7206936</td>
<td>G</td>
</tr>
<tr>
<td>rs4792837</td>
<td>G</td>
</tr>
<tr>
<td>rs1161502</td>
<td>G</td>
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<td>34.0</td>
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<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Frequency (%)</th>
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<tbody>
<tr>
<td>rs7206936</td>
<td>A</td>
</tr>
<tr>
<td>rs4792837</td>
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</tr>
<tr>
<td>rs1161502</td>
<td>T</td>
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<td>30.4</td>
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**B** TCA Haplotype Block 1

None to Mild Moderate to Severe Child Abuse

**C** Most Significant SNP Haplotypes

<table>
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<tr>
<th>Haplotype</th>
<th>Frequency (%)</th>
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</thead>
<tbody>
<tr>
<td>rs7205424</td>
<td>C</td>
</tr>
<tr>
<td>rs1161482</td>
<td>G</td>
</tr>
<tr>
<td>rs2682324</td>
<td>G</td>
</tr>
<tr>
<td>66.5</td>
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</table>

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs7205424</td>
<td>T</td>
</tr>
<tr>
<td>rs1161482</td>
<td>A</td>
</tr>
<tr>
<td>rs2682324</td>
<td>T</td>
</tr>
<tr>
<td>33.5</td>
<td></td>
</tr>
</tbody>
</table>

**D** Protective Haplotype: TAT

None to Mild Moderate to Severe Child Abuse

Biggest Surprise from the Genome Projects: Number of Conventional Genes do not Scale with Complexity
Where is the information that programs our complexity?

Answer?

Additional regulatory components in our genome:
RNAs
Modified “Central Dogma”

- DNA
  - transcription
  - transcription
- mRNAs
  - translation
  - regulation
- Non-coding RNAs
  - translation
- Proteins

The Proportion of Nancoding DNA Broadly Increases with Developmental Complexity
Only 1.2% of the genome is made up of conventional genes…

…but most of the genome is transcribed.

New View of the Human Genome

- Islands of (conventional) protein-coding genes in a sea of regulatory information.
- “Genes” are not discrete entities.
- Regulation is orchestrated by RNA as well as proteins.
- Theory: Complexity is achieved primarily by RNA.
Why Study microRNAs in Psychiatric Disease?

- MicroRNAs are predicted to regulate up to hundreds of genes each ('master regulators')
- At least half of protein-coding genes may be regulated by microRNAs
- Single microRNAs may target multiple genes within a biological pathway
- MicroRNAs evolve easily and their number increases with organismal complexity
- Major role in neurodevelopment and cell differentiation
- Regulatory layer that may account for missing genetic/epigenetic variability in the etiology of disease

Epigenetics

The phenomenon of heritable (‘metastable’) changes in gene regulation that are governed by non-Mendelian processes, primarily through biochemical modifications to chromatin structure that occur during life.
Atypical Lithium Valproate
Atypical Antipsychotics
Lamotrigine
Carbamazepine
Anti-Depressants
CBT
Prediction of Antidepressant Response to Milnacipran by Norepinephrine Transporter Gene Polymorphisms

Keizo Yoshida, M.D., Ph.D.
Hikaru Takahashi, M.D., Ph.D.
Hisaaki Higuchi, M.D., Ph.D.
Mitsuharu Kamata, M.D., Ph.D.
Ken-Ichi Hsu, M.D., Ph.D.
Kazuhiko Sato, M.D., Ph.D.
Shingo Naito, M.D.
Tetsu Shimizu, M.D., Ph.D.
Kunihiro Itoh, Ph.D.
Koziyuki Inoue, M.S.C.
Toshiro Suzuki, Ph.D.
Charles B. Nemeroff, M.D., Ph.D.

Objective: With a multitude of antidepressants available, prediction of response to different classes of antidepressants is of considerable interest. The purpose of the present study was to determine whether norepinephrine transporter gene (NET) and serotonin transporter gene (SHTT) polymorphisms are associated with the antidepressant response to milnacipran, a dual serotonin/norepinephrine reuptake inhibitor.

Method: Ninety-six Japanese patients with major depressive disorder were treated with milnacipran, 50–150 mg/day, for 6 weeks. Severity of depression was assessed with the Montgomery-Åsberg Depression Rating Scale. Assessments were carried out at baseline and at 1, 2, 4, and 6 weeks of treatment. The method of polymerase chain reaction was used to determine allele variants.

Results: Eighty patients completed the study. The presence of the T allele of the NET T-158C polymorphism was associated with a superior antidepressant response, whereas the A/A genotype of the NET 61707A polymorphism was associated with a slower onset of therapeutic response. In contrast, no influence of SHTT polymorphisms on the antidepressant response to milnacipran was detected.

Conclusions: The results suggest that NET but not SHTT polymorphisms in part determine the antidepressant response to milnacipran.
Montgomery-Åsberg Depression scores during 6 week treatment in relation to the NET T-128C polymorphism


Montgomery-Åsberg Depression scores during 6 week treatment in relation to the NET G-1287A polymorphism

Association of Polymorphisms in Genes Regulating the Corticotropin-Releasing Factor System With Antidepressant Treatment Response

Elisabeth B. Binder, MD, PhD; Michael J. Oceana, PhD; Wei Lin, PhD; Todd C. Deveau, BS; A. John Rush, MD; Mouhakul H. Turecki, MD, Monzurjan Pavri, MD; Bette Bootel, PhD; Kerry J. Reuser, MD, PhD; Charles B. Nemeroff, MD, PhD

*Arch Gen Psychiatry. 2010;67(4):369-379*

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Polymorphisms in *FKBP5* are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment

Elisabeth B Binder1, Daria Salyakina1, Peter Lichtner2, Gabriele M Wochnik1, Marcus Ising1, Benno Pütz1, Sergi Papiol2, Shaun Seaman1, Susanne Lacz1, Martin A Kohli1, Thomas Nickel1, Heike E Künzel1, Brigitte Fuchs3, Matthias Mayer4, Andrea Fennigl1, Nikola Kern1, Jürgen Brunner1, Sieglinde Modell1, Thomas Baghai1, Tobias Deun1, Peter Zill1, Brigitte Boddy1, Ranier Ruppel1, Thomas Mesce2, Oliver Kahnle1, Heike Dabitz1, Tanja Brückl1, Nina Müller1, Heldegard Pfister1, Roschild Liebl1, Jakob C Mueller2, Elin Lohmusuuar2, Tim M Strom1, Thomas Betteken1, Thomas Meitinger2, Manfred Uhr1, Theo Rein1, Florian Holsboer1 & Bertram Muller-Myhrok1

Polymorphisms in FKBP5 are associated with rapid response to antidepressant treatment

- All Individuals
- SSRI
- Tricyclic antidepressants
- Mirtazapine


Epigenetic Drugs

- Drugs that target the proteins controlling chromatin modifications can modulate the expression of clusters of genes, presumably offering higher therapeutic efficacy than classical agents with single target pharmacologies that are susceptible to biochemical pathway degeneracy.
Valproic Acid has an Epigenetic Mode of Action (HDAC Inhibitor)

**Pharmacology of Divalproex**

By Michael J. Owens, PhD, and Charles B. Nemeroff, MD, PhD

*ORIGINAL ARTICLE*

Efficacy of Valproate Maintenance in Patients With Bipolar Disorder and Alcoholism

A Double-blind Placebo-Controlled Study

Bruce M. Sullivan, MD, MPH; Jack B. Cornish, MD, MPH; Dennis C. Daley, PhD; Leonard Konick, PhD; Jonathan M. Himelfarb, MD; Michael E. Thase, MD
"There’s an old Wayne Gretzky quote that I love. ‘I skate to where the puck is going to be, not where it has been.’ And we’ve always tried to do that at Apple. Since the very very beginning. And we always will.”

- Steve Jobs