NIBR

Mark C. Fishman, MD – President, Novartis Institutes for BioMedical Research (NIBR)
Meet Novartis Management
June 17-18, 2015
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Key messages

- NIBR discovery of medicines is driven by greatest patient need and scientific tractability

- NIBR has had robust output of new medicines with potential major impact in patients with both common and rare diseases. In terms of productivity, NIBR is at or above the top tier, as reflected in numbers of targets and Phase III NMEs and success rates through all pipeline stages

- A next wave of therapeutics, based on principles of regenerative biology, is expected to address common disorders of aging, including muscle weakness, loss of vision and hearing, heart failure and liver failure, including nonalcoholic steatohepatitis (NASH)

- The broad oncology portfolio includes targeted and immune therapies with numerous opportunities for novel combinations

- NIBR manages a robust network of alliances including both academic institutions, biotech and pharmaceutical organizations
NIBR: Distinctive Talent and Culture with Broad Success

Aging and Regenerative Medicine

Strength in Oncology and Immuno-Oncology

Genome Editing

Alliances
NIBR: A global network of more than 6,000 scientists and physicians

- Patient-centric research strategy based on unmet medical need
- Focus on molecular pathways shared by various diseases
- Integration of clinical insights with mechanistic understanding of disease
- Research-to-Development transition redefined through fast and rigorous “proof-of-concept” clinical trials
- Strategic alliances with academia and biotech strengthen preclinical pipeline

- United States
  - Cambridge, MA
  - East Hanover, NJ
  - Emeryville, CA
  - La Jolla, CA (GNF)

- Europe
  - Basel/Zurich Switzerland

- Asia
  - Shanghai, China
  - Singapore (NITD)
NIBR research strategy: Focusing on greatest patient need and scientific promise
Approach: Proof-of-concept in homogenous populations followed by expansion to common diseases
Disease area distribution of New Molecular Entities

- Respiratory Diseases
- Autoimmunity, Transplantation & Inflammation
- Cardiovascular & Metabolism
- Infectious Diseases
- Musculoskeletal Diseases
- Other
- Oncology
- Ophthalmology
Leading number of clinical trials in the industry

Number of ongoing clinical trials
Active trials as of March 2015

Source: ClinicalTrials.gov
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Aging & frailty programs in the clinic

**Inclusion Body Myositis**
- BYM338: Anti-ActRII Ab

**Sarcopenia**
- BYM338: Anti-ActRII Ab

**Polymyositis**
- BAF312: S1P inhibitor

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**Hearing Loss**
- CFG166: Atonal gene therapy

**Heart Failure**
- CLR235: Heart contractility agent

✓ = achieved Proof-of-Concept in man (PoC)
## Vision programs in the clinic

### Wet AMD
- ✓ RTH258: High-potency scFv VEGFi
- LMG324: Long-acting anti-VEGF Ab
- LHA510: Topical VEGFi

### Dry AMD
- Combinations of complement inhibitors

### Dry Eye
- LME636: TNFα topical

### Glaucoma
- New MoA for lowering IOP (pre-clinical)

✓ = achieved PoC
Alzheimer's prevention: Neuroscience partnership with Banner Alzheimer’s Institute

This 5 year trial will enroll pre-symptomatic patients with 2 copies of the high risk ApoE allele to test two therapies:

- An active immunotherapy to produce antibodies against amyloid
- A BACE (beta-secretase1) inhibitor, designed to prevent the production of different forms of the amyloid protein

Understanding the time-course of Alzheimer pathology enables early interventions

Modified Jack et al, Lancet Neurology, 2009
Liver repair

- Nonalcoholic Steatohepatitis (NASH) is a chronic, progressive form of fatty liver disease, marked by inflammation and scarring (fibrosis). It affects up to 30 million people in the US\(^1\), and is projected to be the leading cause of liver transplant by 2020\(^2\).

- LJN452, a non-bile acid FXR agonist, is our lead clinical candidate for NASH:
  - Reduced steatosis & fibrosis in animal models
  - Favorable safety profile in first-in-human studies

- First proof-of-concept in primary biliary cirrhosis to start in 2015

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\(^1\) Williams, et al. Gastroenterology 2011:140:124-131

\(^2\) Mayo Clinic
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- NIBR: Distinctive Talent and Culture with Broad Success
- Aging and Regenerative Medicine
- Strength in Oncology and Immuno-Oncology
- Genome Editing
- Alliances
Key elements of the oncology strategy

- We now have drug candidates for 15 specific targeted pathways, as combination therapy is expected to be critical in many cancers.

- It is anticipated that many cancers may respond well to immunotherapy, especially when combined with targeted therapies to kill cells and increase antigen presentation.

- Our immuno-oncology portfolio now includes: antibodies to PD-1, LAG-3 and TIM-3 checkpoint inhibitors, all entering trials this year; GITR agonist antibodies; novel CARTs to solid tumors; and the STING agonist, which has the potential to catapult therapy into the next wave by “educating” the immune system to recognize many cancers now refractory to checkpoint inhibitors.
A broad NIBR oncology pipeline in the clinic, with agents covering most oncogenic pathways

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Exemplary Compounds</th>
<th>Target</th>
<th>Initial PoC Achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI3K/PTEN/AKT</td>
<td>BYL719</td>
<td>PI3Ka selective</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>CLR457</td>
<td>Pan-PI3K</td>
<td></td>
</tr>
<tr>
<td>FGF</td>
<td>BGJ398</td>
<td>FGFR-1/2/3</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>FGF401</td>
<td>FGFR4 selective</td>
<td></td>
</tr>
<tr>
<td>ErbB/HER</td>
<td>EGF816</td>
<td>EGFR mut</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>LJM716</td>
<td>HER3</td>
<td>✓</td>
</tr>
<tr>
<td>Wnt</td>
<td>WNT974</td>
<td>Porcupine</td>
<td></td>
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<tr>
<td>Apoptosis Regulation</td>
<td>LCL161</td>
<td>IAP</td>
<td></td>
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<tr>
<td></td>
<td>CGM097</td>
<td>P53/HDM2</td>
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<tr>
<td></td>
<td>HDM201</td>
<td>P53/HDM2</td>
<td></td>
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<tr>
<td></td>
<td>BCL201</td>
<td>BCL2</td>
<td></td>
</tr>
<tr>
<td>Cell Cycle</td>
<td>LEE011</td>
<td>CDK4/6</td>
<td>✓</td>
</tr>
<tr>
<td>Cadherin</td>
<td>PCA062</td>
<td>P-Cadherin ADC</td>
<td></td>
</tr>
<tr>
<td>BCR/Abi</td>
<td>ABL001</td>
<td>Bcr/Abi allosteric</td>
<td>✓</td>
</tr>
<tr>
<td>C-MET</td>
<td>INC280</td>
<td>cMET</td>
<td>✓</td>
</tr>
<tr>
<td>PIM</td>
<td>LGH447</td>
<td>Pan-PIM</td>
<td>✓</td>
</tr>
<tr>
<td>IDH</td>
<td>IDH305</td>
<td>IDH-1</td>
<td></td>
</tr>
<tr>
<td>c-KIT</td>
<td>LOP628</td>
<td>c-Kit ADC</td>
<td></td>
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Current Novartis immuno-oncology portfolio

**Immune boosting**
- STING
- TIM-3

**T-cell modulation**
- GITR
- PD-1
- PD-L1

**Tumor microenvironment**
- PD-1
- PD-L1
- TIM-3
- GITR
- LAG-3
- CSF-1
MIW815: A STING agonist for enhancing immune response to tumors (pre-clinical)

STING agonist (cyclic dinucleotides) injection into tumors eliminates both injected and non-injected tumors

MIW815 (partnership with Aduro) effectively “immunizes” the mouse to tumors

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**MIW815**

Injected tumor  Non-injected tumor

**Cured**  **Cured**

Investigational. Efficacy & safety not yet established
CART platform

Current trials
- **r/r ALL**: CR in 94% of pediatric ALL patients (N=48)
- **Initial clinical activity observed in r/r NHL and CLL**

New targets
- **EGFRvIII**:
  - CAR therapy for glioblastoma multiforme
  - FPFV achieved in January 2015
  - Early data presented at ASCGT in May 2015
- **Additional CARTs targeting MM and AML being developed and about to get into clinic** (expected FPFV in H2 2015)

Next generation
- **Pharmacological control of CART activity**: Multiple strategies to regulate CART function or remove the CART cells
- **Gene editing using CRISPR technology**
  - Allogeneic or “off-the-shelf” CART cells
  - Increasing efficacy/therapeutic index
- **Combinations (e.g., CART plus checkpoint inhibitors)**

Investigational. Efficacy and safety not yet established.

r/r ALL = relapsed/refractory Acute Lymphoblastic Leukemia (ALL); CR = Complete Response; NHL = Non-Hodgkin Lymphoma; CLL = Chronic Lymphocytic Leukemia; AML = Acute Myeloid Leukemia; MM = Multiple Myeloma; FPFV = First Patient First Visit.
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Genome Editing

Alliances
CRISPR/Cas9: Flexible, robust and scalable technology

- Used in NIBR to edit specific genetic loci of mice and of cultured cells
- Can be used both for scientific discovery and novel therapy
- Evaluating utility for editing CART cells and human hematopoietic stem cells (HSC), for example, to potentially cure sickle cell and other blood disorders
- Complements cell and gene therapy expertise, including HSC expansion technology
LMI070: An RNA splicing enhancer for spinal muscular atrophy

- Spinal muscular atrophy (SMA) is the most common genetic cause of infant mortality
- Loss of the SMN gene leads to nerve cell loss and paralysis
- We discovered a drug candidate that enhances splicing of the usually quiescent SMN2 gene

Investigational. Efficacy and safety not yet established
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Alliances
# Examples of NIBR alliances: Targets and pathways

## Target / Pathway Exploration

<table>
<thead>
<tr>
<th>Target / Institute</th>
<th>Pathway Focus</th>
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<tbody>
<tr>
<td>Massachusetts General Hospital</td>
<td>Autophagy and microbiome</td>
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<tr>
<td>University of California, Irvine</td>
<td>Immuno-metabolism</td>
</tr>
<tr>
<td>Stanford University</td>
<td>Engineered growth factors for wound healing</td>
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<tr>
<td>Columbia University</td>
<td>Glioblastoma multiforme models</td>
</tr>
<tr>
<td>Ontario Cancer Institute</td>
<td>Role of Shp2 in oncogenesis</td>
</tr>
<tr>
<td>Duke University</td>
<td>T-cell metabolism</td>
</tr>
<tr>
<td>Albert-Ludwigs-Universität Freiburg</td>
<td>Pathogenic pathways as biomarkers for sarcoidos</td>
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<td>Scripps Research Institute</td>
<td>Anti-malarials</td>
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Examples of NIBR alliances: Technologies

<table>
<thead>
<tr>
<th>Technology Platforms</th>
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<tbody>
<tr>
<td><strong>CARIBOU BIOSCIENCES</strong></td>
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<tr>
<td>PeptiDream</td>
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<tr>
<td>SomaLogic</td>
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<tr>
<td>Russian Academy of Sciences</td>
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<tr>
<td>GALENEA</td>
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<tr>
<td><strong>Teleos</strong></td>
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<tr>
<td>Mosaic Biosciences</td>
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<tr>
<td>Whitehead Institute</td>
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</tbody>
</table>
Examples of NIBR alliances: Therapeutic candidates

<table>
<thead>
<tr>
<th>In-Licensed Candidates/Programs</th>
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<tbody>
<tr>
<td><strong>ADURO BIOTECH</strong></td>
<td>STING agonists for immuno-oncology</td>
</tr>
<tr>
<td><strong>SERVIER</strong></td>
<td>Bcl-2 inhibitor (apoptosis regulation)</td>
</tr>
<tr>
<td><strong>CoStim</strong></td>
<td>Four immuno-oncology T-cell checkpoint programs (PD-1, PD-L1, LAG-3, TIM-3)¹</td>
</tr>
<tr>
<td><strong>Penn</strong></td>
<td>CART cell therapies</td>
</tr>
<tr>
<td><strong>Intellia THERAPEUTICS</strong></td>
<td>CRISPR-based gene editing technology for HSC and CART therapies</td>
</tr>
<tr>
<td><strong>KU LEUVEN</strong></td>
<td>Rhinovirus program</td>
</tr>
<tr>
<td><strong>GenVec</strong></td>
<td>Atonal gene therapy</td>
</tr>
<tr>
<td><strong>Incyte</strong></td>
<td>JAK2 and cMET inhibitors</td>
</tr>
</tbody>
</table>

¹ Acquisition
Appendix
This chart represents the global functional organization. The legal reporting relationships of the team members are with the companies that employ them.