Parkinson’s disease: Synuclein aggregates travel from the gut to the brain through the vagus nerve.
The natural history of PD

- Proximal stage
- Movement disorder
- Diagnosing PD

- Functional decline
- Cognitive decline
- Drug dependency
- Family in crisis

Parkinson’s disease
We are diagnosing PD very late in the course of the disease

Diagnosing carcinoma based on clinical signs and symptoms

biological makers for early stages of the disease

Ga68-PSMA

MRI of the prostate

Breast MRI

Mammography
Parkinson’s disease has a long “incubation period” with non-specific signs.

- Behavior during dream state:
  - constipation
  - Decrease in olfactory perception
  - impotence
  - Depression

- Movement Disorders:
  - pain

- Years from diagnosis:
  - -20
  - -10
  - 0

- PD Diagnosis:
  - PD patient
  - Signs only on the left

- Deterioration in brain function:
  - Healthy
  - PD patient

- PD Diagnosis

Rt
Lt
Biological Markers
“Living the dream”
Smell Test

UPSIT- University of Pittsburg Smell Identification Test
Walking as a marker for central and peripheral nervous system function

Supraspinal control of walking

Spinal pattern generator

Sensory feedback
Gait Alterations in Healthy Carriers of the LRRK2 G2019S Mutation


January 2011

- Usual walk
- Dual task walk
- Fast walk

Stride time variability (CV %)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Non-carriers</th>
<th>Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual walk</td>
<td>p=0.06</td>
<td></td>
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<tr>
<td>Dual task walk</td>
<td>p=0.02</td>
<td></td>
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<tr>
<td>Fast walk</td>
<td>p=0.03</td>
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</table>

Graphs showing stride time variability for non-carriers and carriers in different walking conditions.
Arm swing - PD compared to Healthy

First Degree (age=52)

Patient with PD (age=53)
Arm swing asymmetry during walking as a marker for population at risk

Non carriers = 61, carriers = 62

Mirelman et al, submitted
DaT Scans
Quantification of DaT uptake using VBM analysis

Non Carriers > carriers

Artzi et al. in preparation
Imaging of the brain

Normal

Alzheimer’s Disease
### PET tracers under evaluation for HD

#### PET tracers being evaluated or under consideration

<table>
<thead>
<tr>
<th>Target</th>
<th>PET Ligand</th>
<th>Localization</th>
<th>Preclinical Evaluation Status</th>
<th>Clinical Evaluation Status</th>
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<tbody>
<tr>
<td>D1 receptor</td>
<td>11C-NNC112</td>
<td>Basal ganglia/cortex</td>
<td>Studies completed (uPET)</td>
<td>Currently no planned studies</td>
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<tr>
<td>D2 receptor</td>
<td>11C-raclopride</td>
<td>Striatum/cortex</td>
<td>Studies completed (uPET)</td>
<td>Studies completed and ongoing</td>
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<td>PDE10A enzyme</td>
<td>18F-MNI659/ [11C]IMA107</td>
<td>Basal ganglia</td>
<td>Studies completed (uPET)</td>
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<tr>
<td>CB1 receptor</td>
<td>18F-FMPEP-d2/ [11C]MePPEP</td>
<td>Basal ganglia/cortex</td>
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<td>Studies completed (uPET)</td>
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<tr>
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<td>Studies ongoing (ARG)</td>
<td>Studies planned</td>
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<tr>
<td>Glucose uptake</td>
<td>18F-FDG</td>
<td>Cortex and subcortical</td>
<td>Limited profiling (uPET)</td>
<td>Studies completed and planned</td>
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<tr>
<td>GABA-A receptor</td>
<td>11C-Flumazenil</td>
<td>Basal ganglia/cortex</td>
<td>Studies planned (ARG)</td>
<td>Currently no planned studies</td>
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<td>mGluR5 receptor</td>
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<td>5HT1a receptor</td>
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<td>Cortex</td>
<td>Currently no planned studies</td>
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<tr>
<td>NK1 receptor</td>
<td>18F-FE-SPA-RQ</td>
<td>Basal ganglia/cortex</td>
<td>Currently no planned studies</td>
<td>Currently no planned studies</td>
</tr>
</tbody>
</table>
Measuring functional reserve, compensatory mechanisms
Cerebral pathological and compensatory mechanisms in the premotor phase of leucine-rich repeat kinase 2 parkinsonism

Bart F. L. van Nuenen,1,2 Rick C. Helmich,1,2 Murielle Ferraye,2 Avner Thaler,3 Talma Hendler,3 Avi Orr-Urtreger,4 Anat Mirelman,3 Susan Bressman,5 Karen S. Marder,6 Nir Giladi,3 Bart P. C. van de Warrenburg,1 Bastiaan R. Bloem1 and Ivan Toni2 on behalf of the LRRK2 Ashkenazi Jewish Consortium1*

Foot response (left / right big toe)
G2019S mutation carriers use the brain differently to solve motor imagery problems.

Bart F.L. van Nuenen et al, Brain, 2012
Biological markers of disease state

- **Function**
  - No complaints or symptoms
  - Delicate signs
  - Disease

**Years**

- Insensitive to disease progression
- Moderate sensitivity
- Sensitive to disease progression

**Disease Diagnosis**
What initiates the neurodegenerative process?

Understanding the cause can lead to preventive therapy
Alzheimer’s disease is NOT just accelerated aging
Where can we intervene and prevent neurodegenerative diseases?

- GENETICS
- Age
- Environment:
  - Exposure to pesticides
  - Head injuries
- Lifestyle
Factors contributing to the development of neurodegenerative diseases

Genetics and aging

Environment and lifestyle
Genetic contribution to Parkinson's disease

Causal
Moderate Risk
Minor Risk
Genetics of Parkinson’s disease
The Ashkenazi Jews story

Worldwide

In Ashkenazi Jews

- **LRRK2**: 35%
- **GBA**
The story of the family members: The Brin Family’s story
Genetic research in Tel-Aviv Parkinson’s disease

1520 patients with Parkinson’s disease

1100 Ashkenazim

450 healthy first degree relatives of patients with Parkinson who carry a known mutation in the GBA or LRRK2 genes
The pyramid of Parkinson’s disease
From population at risk to diagnosed disease

Population at risk
- Non-motor symptoms
  - Subclinical disease
  - Biological disorders
  - Parkinson’s
Every year a number of healthy individuals become sick.

**The goal:** Following a population at risk for developing PD and learning about the mode of progression and conversion.

**The method:** Examine patients and healthy relatives who carry the PD related mutations, in order to identify early biological markers for the development of the disease.
Recommendations for minimizing the chance of getting Parkinson’s disease and dementia for population at risk

• Exercise
• Intellectual stimulation
• Social interaction
• Balance the risk factors for Atherosclerosis
• Sleep well
• Drink coffee
• Avoid becoming overweight
• Avoid depression
• Medications?? Anti-inflammatory?
• Mediterranean Diet

There’s a lot that can be done!!!
Intensive physical activity as medicine: A healthy way to activate neurotrophic factors that promote regeneration of brain cells

**Prescription**

28/2/2016

Name: Israel Israeli
Age: 45

Medication: Aerobic physical activity

Dosage: 5 times a week – 60 minutes (200-300 minutes a week)

Notes: 50% aerobic activity, 25% resistance, 25% stretching

Nir Giladi, MD
License No. 12345
An entire brain is developed in 9 months the product of trophic factors
Trophic factors that promote neuronal, synaptic and vascular regeneration
Trophic factors produced by skeletal muscles and the liver promote neuronal regeneration.
Novel therapeutic approaches for stopping neurodegeneration

- Vaccines
- Gene silencing\ RNA silencing
- Enzymatic activity promoting substances – small molecules
- Stem cell
- Administration of trophic factors that promote regeneration
In development:
Dozens of medications and vaccines for the stopping or prevention of Parkinson’s disease, Alzheimer’s disease and Huntington’s disease.
Gene silencing – prevention of toxic protein production

Antisense Oligonucleotide Therapy

1. DNA Transcription → mRNA
2. mRNA Translation → Disease-Associated Protein
3. Antisense Drug (Oligonucleotide) Transcription
4. RNaseH Degrades RNA No Translation
5. No Disease-Associated Proteins Produced

The goal: Prevention

Early signs

Brain Function Decline

Diagnosis

Prevention
Stop progression
Slowing down
Symptomatic
The team

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Hertzl Shabtai
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Ariella Hillel
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CMCM:
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Anat Mirelman
Aner Weiss
Hagar Bernad
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Orly Goldstein
Merav Kedmi
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Hila Kobo
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Patients and relatives are waiting...
Thank you