Definitions

- **Cancer**: A malignant tumor characterized by potentially unlimited growth with local expansion by invasion and systemic expansion by metastasis.
- **Tumor**: An abnormal mass, a growth
  - **Benign**: “of a gentle disposition”, not life-threatening
  - **Malignant**: “malevolent or malicious”; capable of invading and metastasizing
- **Metastatic**: Transfer to another part of the body

*(Webster’s)*
There are more than 200 different kinds of cancer

Classified anatomically

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>N-H lymphoma</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Kidney</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
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<td>3%</td>
</tr>
<tr>
<td>Liver</td>
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<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3%</td>
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</tr>
</tbody>
</table>

2016 Estimated US new Cancer Cases, ACS

Cancer commonly occurs in epithelial cells

Lung and skin: cells in contact with air

Colon and bladder: cells in contact with food and its breakdown products

Breast, prostate, & pancreatic: cells that line the ducts that lead to the outside of the body
Normal vs cancer: cellular evolution

Exposure to carcinogens (cancer-causing agents) can initiate tumor evolution

Skin: UV irradiation from the sun
Lung: Cigarette smoke
Colon: Meat cooked at high temperatures
Prostate, breast & pancreatic: ?
Sometimes mistakes just happen! $10^{-6}$/gene/cell div
DNA Mutations

Cell nucleus

Chromosomes

Genes

DNA

Nucleotides

AGCGTTCGATGACC

AGCGTCCGATGACC

DNA Mutation

AGCGTCCGATGACC

RNA

Protein

Cell behaves different!
How cancer cells behave differently: the Hallmarks of Cancer

- No longer needs to be told to grow
- Ignores signals to die
- Feeds itself: Calls in new blood vessels
- Invades and metastasizes
- Never grows old

Hanahan and Weinberg, Cell, 2000

The evolution of cancer cells

- No longer needs to be told to grow
- Ignores signals to stop growing
- Invades and metastasizes
- DNA mutations

Hanahan and Weinberg, Cell, 2000
Cancer goes from local, to regional, to systemic – it evolves

Main reason why curing cancer has been tricky!

Evolutionary parallels

All are designed to eliminate growing cells
Many toxicities and side-effects
Can’t we apply our molecular knowledge and evolve further?

Design a drug that addresses the root of the problem and minimizes side-effects:
Attack the mutation and its associated behavioral change

From research to clinical practice

BASIC
- Laboratory-based
- Lots of small grants in academic labs

TRANSLATIONAL
- Links lab and clinic
- In academia or industry
- Very hard to find funding

CLINICAL
- Clinical trials
- Led by academics
- Supported by industry
- Phase I
- Phase II
- Phase III
Targeted cancer therapy

- Her2/neu → Herceptin
- EGF Receptor → Iressa & Tarceva
- Abl → Gleevec

Personalized Cancer Therapy

Test for specific mutation → Targeted therapies
One size doesn’t fit all: personalized medicine

Successes in changing the standard of care

• **Chronic Myelogenous Leukemia**
  Patients with the Philadelphia chromosome (99%) treated with imatinib increased 5-year survival from 30% to 89%

• **Breast**
  Patients with overexpressed HER-2 (20%) have a 37% improvement in overall survival if treated with trastuzumab

• **Lung**
  Patients with an EML4-ALK fusion (5%) treated with crizotinib have improved survival from 8 to 20 months

• **Melanoma**
  Patients with a V600E BRAF mutation (40%) have a 48% response rate to venurafenib or dabrafenib/trametinib

• **Lung**
  Patients with EGFR mutations (8 to 30%) have improved progression free survival from 4.6 to 13 months when treated with erlotinib

There have been minimal attempts at personalized medicine in pancreatic cancer

• There are no clinically meaningful targeted treatments for pancreatic cancer

• 5 – 15% of current pancreatic cancer clinical trials are using a personalized medicine approach
Know Your Tumor™
As of November 1, 2016

>900 patients enrolled
>400 reports completed
91% successful biopsies
35% from community physicians
41 states
Know Your Tumor results Oct 2016

NGS

Highly actionable 27%
Not actionable 51%
Modifies Options (in pathway, WNT, MEK, MET, etc)

Highly Actionable
- BRCA1/2
- PALB2
- ATM
- CHEK1/2
- FANCA/C
- STK11
- AKT1/2/3
- TSC12
- CDK4/6
- FGFR1/4
- ERBB2
- RET
- NTRK1/3
- TOP2A
- BRAF
- ALK
- ROS1

PARP inhibitor
mTOR/AKT inhibitor
CDK inhibitor
FGFR inhibitor
HER2 inhibitor
TRK inhibitor
Anthracycline
BRAF inhibitor
ALK inhibitor
ROS inhibitor

Pishvaian et al, manuscript in preparation

Action: 61 patients initiated treatment with report-based therapy

Clinical Trial (N=15)
- IMTX/Vaccine
- Ruxolitinib
- PARP
- Other

Off Label (N=11)
- PARP
- Trastuzumab
- Ceritinib
- Sunitinib
- Everolimus
- Crizotinib
- Immunotherapy

FDA approved (N=36)
- Standard of care CHX
- Erlotinib

Pishvaian et al, manuscript in preparation
Clinical Trials

Increase clinical trial enrollment rate

Promote running “smart” clinical trials

PRECISION PROMISE

Revolutionizing treatment for every pancreatic cancer patient.
**Precision Promise Clinical Trial Consortium**

**Initial Precision Promise trial**

**Master Protocol**
- Initial biopsy, at progression
- DNA panel, WGS/WES
- RNA seq
- IHC: HA, IO

**Stromal disruption**
- HA Hi to PEGPH20, 4 mos
- With platinum OR Gem/Abx
- Determine persistence

**DNA Damage Repair**
- Platinum 4 mos
- PARPi if platinum responsive
- PARPi if BrCa mutant
- Determine biomarkers of response

**Immuno-oncology**
- Gem/Abx backbone
- FAKi or CCR2i plus anti PD-1
- Determine response & biomarkers
- CD40 agonist 2 mos in some
- Biomarker hypothesis

**Supportive Care**
- Standardize throughout sites
- Learn and modify

**COMING:** Spring 2017

**Initial 3 Sub-studies**
Benefits of Precision Promise

*Precision Medicine is an opportunity to dramatically improve outcomes for pancreatic cancer patients*

For the patients in the trial

- Biomarker-driven
- Rapidly move through options
- Best practice supportive care

For future patients

- Learn which biomarkers predict response
- Signal seeking: guide subsequent trials
- Refine supportive care

Our goal

**Double SURVIVAL by 2020**