OPS-O

WELCOME!

The BEST is YET to COME....

THINK TANK
- PHYSICAL SCIENCES-ONCOLOGY
- PREVIOUS THINK TANK PARTICIPANTS
- NEW PARTICIPANTS

→ ASSESS, TUNE + TWEAK
→ NEW RESEARCH

TRANSFORMATIVE PERSPECTIVES
- BASIC RESEARCH
- TRANSLATIONAL
- CLINICAL

OPEN and ACTIVE DISCUSSIONS
- SINGLE-CELL ANALYSIS
- INTERACTIONS IN MICRO-ENVIRONMT.

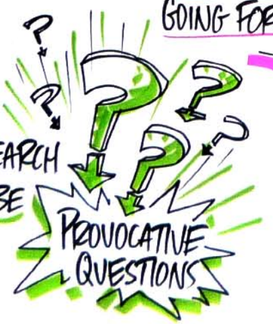
A RANGE of QUESTIONS

PAIRING PHY. SCI. INVESTIGATORS and SENIOR INVESTIGATORS

ONCOLOGY CENTERS ORG.
- SHARING INFORMATION
- NETWORK
- BI-DIRECTIONAL

MODELS GOING FORWARD → LEARNINGS from OTHER DOMAINS

PHYS. SCI. and CANCER RESEARCH SHOULD NOT BE LIMITED



PROVOCATIVE QUESTIONS

Jim Nuttle / ROBERT MITTMAN

- REDUCE PAIN + SUFFERING
- NEW TREATMT'S + THERAPIES

- THIS is NOT a CONVENTIONAL NIH GRANT

- ONCOGENESIS is an EVOLUTIONARY PROBLEM
  - TARGETS
  - THERAPY
  - PREVENTION

- WHAT is the EXTENT of DIVERSITY?
- HOW DOES a SINGLE CELL INTEGRATE INTO a COMMUNITY of CELLS?

- EVOLUTION
- STRESS
- DIFFERENTIATION
- ORGANIZATION

- ISSUES to IMPROVE the PROGRAM
  - PHY. SCI. DOESN'T FULLY ADDRESS the PROBLEM
- PHYSICAL PROXIMITY of RESEARCHERS

- MULTI-SCALE PROBLEM
  - YOU DON'T NEED ALL of the DETAILS

- TOOL DEVELOPMENT
  - NEW WAYS of THINKING ABOUT the DATA

OPENING ROUNDTABLE

- PHYS. SCI.
- ENGINEERING
- ONCOLOGY
- CANCER RESEARCH

- NEW TOOLS, IMAGING, THEORETICAL MODELS and FRAMEWORKS
- GROUPS WORKING TOGETHER

- NEW QUESTIONS
- MATHEMATICAL MODELING

- IMPACT of the NETWORK
  - the "PERSISTENT HANDSHAKE"
  - CONNECT PATIENTS

- 5-D ORGANIZATION of CHROMATIN
  - UNDERSTANDING CANCER PROGRESSION
- UNDERSTAND FACTORS IN CANCER MICRO ENVIRONMT.
- COLLABORATION

- DRUG TREATMENT is FAILING - NEED to WORK ON THERAPY

KEYNOTE: APPLYING PHYSICAL SCIENCES PRINCIPLES to CANCER RESEARCH

HON. STEVEN CHU, PhD
- SEC'Y, US. DEPT of ENERGY

PHYSICAL SCIENCES 2nd MEDICINE

THERE HAS BEEN a LONG HISTORY

X-RAY

MRI

DETECTING or IMAGING

ELECTRON MICRO-SCOPE

IMPROVEMENTS IN OPTICAL MICROSCOPY

SUB WAVELENGTH IMAGING

BLUR

LIGHT "BLOBS"

RADIUS

250 NM

BETTER SIGNAL to NOISE

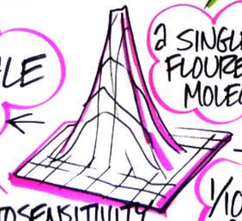
WHERE is the CENTER?

SEQUENTIAL PHOTO-BLEACHING

FILTERS

10 NM

VISUALIZING MOLECULAR-SCALE STRUCTURES



a SINGLE FLOURESCENT MOLECULE

PHOTOSENSITIVITY of PIXELS
THEY VARY

1/100th of ONE PIXEL

BETTER THAN BEADS

MOVE the MOLECULE to MAP the SHIFT
- PLOT the DEVIATION

6NM

PLEXXIKON

ACCELERATES OTHER TUMORS

DOWNSTREAM SIGNALLING PROTEINS

INCREASE BY DIMERIZATION

RAS/RAF SIGNALLING PATHWAYS

GT-ACTIVATED

SMALL MOLECULE ATTACHS to RAF

- DRUG STOPS SOME TUMOR GROWTH

DNA

STRETCH BY OPTICAL TWEEZER

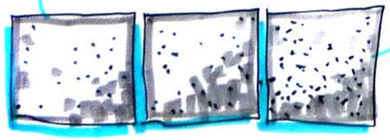
DISTANCE RES. of 5 ANGSTROMS

VISUALISE RAS

~600 GOLD PARTICLES

TETRACYCLIN ON 2nd OFF

1-2 ng/ml DOX SHOWS DOWNSTREAM SIGNALLING - DIMERS



VARIABLE EXPRESSION of DOX

Y. BERRA

"YOU CAN OBSERVE ALOT BY JUST WATCHING"

PAmCherry1 ARTIFICIAL DIMER

BHK2 CELLS

DIRECT VISUALISATION of PROTEIN DIMERS IN CELLS w/ PALM

DBSCAN • SIZE DISTRIBUTION

cRAF IS MONOMERIC IN CYTOPLASM

DOES IT ACTIVATE the MEK/ERK SIGNALLING?

RAF INHIBITOR EXPERIMENTS

PLX 2nd GDC

LESS ↑ DIMERIZATION

BRAF WT + V600E RESPOND DIFFERENTLY to RAFi

NEW PLEXXIKON "PARADOX BREAKER" to BE TRIED NEXT

BIOFILM IMAGING

SCANNING CONFOCAL MICROSCOPE

• STAIN the CELLS

• STAIN the PROTEINS

LIVE CELL IMAGING

UP to 3 COLOR FILTERS

3-D IMAGING

SUB-WAVELENGTH

MUNC 18-SNAP 25

NON-DESTRUCTIVE

Jim Nuttle / ROBERT MITMAN

PANEL: 3-D STRUCTURE of the GENOME and CELLS OVER TIME

FRANZISKA MICHOR

HIGHER ORDER ORGANIZATION of the GENOME

- STRUCTURE

HIGHER ORDER PROCESSES
- REPLICATION
- TRANSCRIPTION
- GENERATION of BREAK-POINTS IN CANCER

BOUNDARIES of ALTERATIONS REMAIN IN CLOSE SPATIAL PROXIMITY

- PREDICTION of MUTATIONAL LANDSCAPE (TRANSCRIPTION ROLE)
- BREAKPOINTS COINCIDE w/ G-QUADRUPLEXES

METHYLATION
HYPOMETHYLATION

LEONID MIRNY

MUTATIONS
- CHROMOSOMAL ARCHITECTURE ↓
- SPATIAL PROXIMITY ↓
- SCNA EVENTS ↓
- SCNA IN CANCER

SELECTION

GENOME IN 3D

PROXIMITY of REGIONS
- FRACTAL GLOBULE

- Hi-C

PURIFYING SELECTIONS (IMPORTANT)

UNIFORM | HiC | FG

LANDSCAPE

3000 SAMPLES

NEED RANGE of TECHNIQUES in the SPECTRUM

- DELETIONS
- AMPLIFICATIONS

COPY-NUMBER ALTERATIONS

PASSENGER ALTERATIONS are DELETERIOUS

DATA MAPPING and MODELLING

TOM MISTELLI

HIGHER-ORDER GENOME OPERATION 3D

WHAT'S the RELEVANCE?

NEED: SINGLE-CELL HiC EXPERIMT.

WE KNOW VERY LITTLE ABOUT STRUCTURE

CHANGE CHROMATIN STRUCTURE – CHANGE ALTERATION

YOU CAN AFFECT the PROTEIN LANDSCAPE

LAMINS
LONG FILAMENT PROTEINS in the CELL – NUCLEAR STRUCTURE IS IMPORTANT

WE CAN MAP the 3-D STRUCTURE
- WHAT SHOULD WE BE LOOKING at? (NUCLEAR STRUCTURE)
- WHAT DOES ALL of THIS MEAN for STRUCTURE?
- HOW CAN WE USE THIS INFORMATION?

WHY DO THESE GENES CHANGE POSITION?

ALEXANDER VAN OUDENAARDEN

WHAT ABOUT CANCER STEM CELLS?

TEMPORAL ORDER
STEM CELLS
- UNLIMITED PRO-LIFERATION CAPACITY

INTESTINE

GENERAL PRINCIPLES
- INFINITE POSSIBIL-ITIES for PROLIFERATION
- MINIMIZE the TIME

MATURE CRYPT IN MINIMAL TIME

SYMMETRIC DIVISION

ASYMMETRIC DIVISION

STEM and NON-STEM CELLS

"BANG-BANG" CONTROL is the OPTIMAL SOLUTION

LINEAGE TRACING

The NUMBER of STEM CELLS CAN BE ESTIMATED BY COUNTING Lgr5

LIN CHEN

PROTEINS

DNA BRIDGING BY TRANSCRIPTION FACTORS

MEASURING the 3-D STRUCTURE of the GENOMES

TETHERED CONFORMATION CAPTURE

POPULATION-BASED MODELING of the HUMAN GENOME

NEED: NEW TECHNIQUE to VIEW and ANALYZE the GENOME STRUCTURE + SEQUENCING DATA

STEVEN CHU

WE HAVE a LOT of PIECES that HAVE NOT YET BEEN DEFINED

IN-VITRO ASSAY

WHAT is DRIVING the COLLAPSED GLOBULAR FORM?

IS THERE a MARKER?
- PROTEIN INTERACTING w/ NUCLEO-SOME?
- IDENTIFY TUMOR STEM CELLS?
- WHAT KIND of TUMOR?
- STRUCTURE?

- GENOME REORGANIZATION – TAGGED IN REAL TIME

"INAPPROPRIATE EXPRESSION" of GENES IN TUMOR CELLS
- SILENCING

PHYSICAL CHALLENGES

30 NM AND SMALLER

CHROMATIN STRUCTURE

WE DON'T HAVE the TOOL to STUDY IT

- HOW FAST DO the MOLECULES MOVE?
- STRUCTURE and DYNAMIC BEHAVIOR
- HETEROGENEITY of the POPULATION
- WE CAN WATCH the CHROMATIN IN REAL-TIME
  - WHAT GENE are WE LOOKING at?

WHOLE GENOME

WE NEED to LOOK HERE

ONE GENE

WHAT HAPPENS WHEN YOU BREAK the CHROMOSOMES? → CAN WE DO Hi-C RECONSTRUCTION of CANCER CELLS?

IF WE DON'T HAVE the INFORMATION

STEM CELL

HOW WILL a CANCER STEM CELL BEHAVE?
- WE DON'T KNOW

- UNCONTROLLED PROLIFERATION

Jim Nuttle / ROBERT MITTMAN

CHARACTERIZING the PHYSICAL SCIENCES PERSPECTIVE

"PSOC-NESS"
- MEASURING MULTIPLE THINGS SIMULTANEOUSLY
- UNDERLYING PRINCIPLES
  - ENTROPY
  - NON-EQUILIBRIUM
  - SYMMETRY
  - COMPLEX-ADAPTIVE SYSTEMS
  - DIFFUSION
  - VISCOSITY

THERMO-DYNAMICS

UNDERSTAND the PHYSICAL ACTIVITIES that are GOING ON

PROTEINS
- LARGER SYSTEMS
- ENERGY DRIVEN STRUCTURES

IT'S a DIFFERENT PHYSICS...

YOU HAVE to TAKE COMPLEXITY INTO ACCOUNT

and DIVERSITY

PROBLEM-DRIVEN

PHYS. SCI. as a MEANS to an END

"The POINT of PHYSICS is to MAKE THINGS SIMPLE..."

YOU NEED JUST ENOUGH COMPLEXITY...

5-20 PARAMETERS

SWEET SPOT

MODELS

as YOU GET HIGHER IN SCALE, YOU NEED LESS DETAIL

BUT WE DO NEED DATA ACROSS NUMEROUS LEVELS

ADJUSTABLE PARAMETERS

WHAT DO WE TURN the KNOBS TOO?

MAPPING to the RIGHT LEVEL

WHAT PARAMETERS DO WE NEED?

TISSUE

CELLULAR

MOLECULAR

SELF-ASSEMBLY

TOOLS and MEASUREMENTS

ARE WE DATA-LIMITED?

HOW MANY PATIENTS?

BIO-MOLECULAR TRAFFIC WITHIN CELLS

"The CELLULAR OPERATING SYSTEM"

- CONTEXT
- PATHWAYS

MODELS

YOU HAVE to EXCITE the EXPERIMENTALIST

DO WE HAVE the RIGHT ONES?

ARE WE ASKING the RIGHT QUESTIONS?

OUR PRESENT WAY of TREATING CANCER is a FAILURE

CHEMOTHERAPY - EXOTIC

WHY?

THIS is the QUESTION WE NEED to ANSWER

NEW WAYS of LOOKING at IT?

SO WHAT?

HOW WILL WE IMPACT PATIENT CARE?
- DIAGNOSIS
- TREATMENT

PHYSICAL: STRUCTURE LEADS FUNCTION

WHAT are WE MISSING?

STOCHASTICITY

YOU'LL NEVER HAVE FULL CONTROL

The PATIENTS

The MORE INFORMATION WE HAVE, the BETTER

- PHENOTYPE

500K PER YEAR

WHAT are WE DOING for the PATIENT?

WE'RE VERY GOOD at LOOKING at CELLS in 2-D

WE NEED to BE LOOKING at THEM in 3-D

SELF-ORGANIZATION vs CONTEXT

THEORETICAL vs. PRACTICAL

BIOLOGY ONLY MAKES SENSE in the LIGHT of EVOLUTION

SINCE 1932

WE DON'T UNDERSTAND THIS

...ONLY MAKES SENSE IN the LIGHT of BIOLOGY

STRESS

WE are LOOKING at the "EVOLUTIONARY DRIFT" of the CELL POPULATIONS

- BIOPSY
- IMAGING

ENGINEERING

THERE are CHEMICAL TREATMENTS that WORK

Jim Nuttle / ROBERT MITTMAN

KEYNOTE: PHYSICAL MECHANISMS of TUMOR METASTASIS

DAVID TARIN, MD PhD
UNIV. of CALIFORNIA SAN DIEGO

The "MESSY REALITY" of the TUMOR ENVIRONMENT

CELLS EXITING the TUMOR

WE CAN MAKE SOME GUESSES...

SOME TUMORS LOOK "INDOLENT" (BUT AREN'T)

SOME TUMORS LOOK AGGRESSIVE (BUT AREN'T)

WE DON'T KNOW WHAT THEY'RE GOING to DO

METASTASIS: EXPONENTIAL GEOMETRIC GROWTH

LIKE the TIDE

LYMPHATIC SYSTEM

FLOW DRIVEN BY MUSCULAR FORCE

VASCULAR SYSTEM

"JET" FLOW

FLOW DRIVEN BY the HEART

TURBULENT ENVIRONMENT IN the HEART

HIGH ATTRITION of CELLS

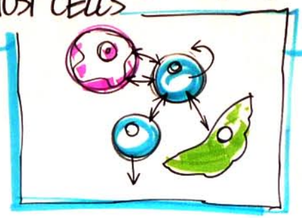
BUT WIDE DISTRIBUTION UNIVERSALLY

DYNAMIC FLOW PATTERNS

FLOW of PERITONAIC FLUID

THERE are PHYSICAL SIGNALS ("SEDUCTION" or "COERCION") to ATTRACT HOST CELLS

WE NEED DRUGS to INTERFERE WITH the CELL INTERACTIONS and ARREST METASTASIS of the TUMOR



IT TAKES TWO to TANGO

STUDIES IN MICE

DISSEMINATION THROUGH CAPILLARIES

NO METASTASIS w/o HOST CELL

WILL GROW TUMORS WHEN LOCATED IN NEW HOST MATERIALS

DIFFICULT to STUDY

- ACCESS to AUTOPSY
- SCALE
- ETHICS
- DISTRIBUTION

ABDOMINAL MALIGNANCY

ABLE to STUDY THROUGH TREATMENT for FLUID BUILD-UP

USE of a SHUNT to RECIRCULATE the FLUID

TUMORIGENIC CELLS

BILLIONS of TUMOR CELLS are CIRCULATED

The HOST ORGAN is NOT PASSIVE

NO METASTASIS IN LUNGS

METASTASIS IN LIVER

The TUMOR CANNOT SURVIVE ANYWHERE w/o the STROMAL SUPPORT of the HOST CELL

CAPILLARIES

IT DOESN'T MATTER WHAT GOES ON IN The TUMOR CELL if IT CAN'T FIND a HOST

DRUGS that ATTACK the TUMOR HAVE TOO MANY DELETERIOUS SIDE EFFECTS

Jim Nuttle / ROBERT MITMAN

PANEL — The MOVEMENT of CANCER "STUFF" THROUGH the PHYSIOLOGY

PETER KUHN — "HODGE PODGE"

- HEMATOGENOUS SPREAD
- CTC's (SINCE 1869) — SEEING is BELIEVING
- PRIMARY CANCERS — DISSEMINATE to DISTINCT SECONDARY METASTATIC SITES

7% WHO DON'T RESPOND to INITIAL TREATMT.

CURRENTLY CURABLE → INCURABLE

DRUG DISCOVERY 2nd DEVELOPMENT (2009, 2010, 12)

WE DO a GOOD JOB... BUT WE DON'T KNOW WHICH ONE to GIVE

SPREADERS 2nd SPONGES →

WE NEED to STUDY why DRUGS FAIL

TIME is the MISSING DIMENSION

LARRY NORTON

BE CAREFUL of STUFF EVERYONE KNOWS — EARLY DIAGNOSIS is NOT the ANSWER to ALL CANCERS

WHAT DON'T WE KNOW?

"A UNITARY THEORY" — WE NEED → MATHEMATICAL UNDERSTANDING of TUMOR GROWTH

NEWTON'S THEORY of GRAVITATION VS OUR "KNOWLEDGE" (CIRCA 1500)

WE KNOW EVERY-THING!

"The UNKNOWN is VASTLY GREATER THAN the KNOWN"

BASIC UNDER-STANDINGS — LESSONS from the CLINIC

NO TWO PATIENTS LOOK the SAME

WHY aren't THERE MORE MATHEMITICIANS INVOLVED?

SELF-SEEDING

IT'S NOT CHAOTIC + UNPREDICTABLE ... WE JUST DON'T KNOW the RULES

WE NEED an EMPIRICAL WAY of WORKING

WE DON'T GET PAID to THINK

WHAT IDEAS DON'T REACH the SURFACE?

DAVID R. PARKINSON

WE NEED TOOLS

WE'RE GOOD at CREATING MOLECULES ... BUT IT'S NOT SUFFICIENT

- RELEVANCE

SEQUENCING to LEARN the NATURAL HISTORY of TUMORS

- SINGLE CELL TECHNOLOGIES
- RATE

15-20 PATHWAYS

CIRCULATING TUMOR CELLS — "LIQUID BIOPSIES" — WHAT are THEY TELLING US?

HIGHER DOSAGE CHEMOTHERAPY RESISTANCE — IT'S the WHITE CELLS

WE NEED to SPEND MORE TIME STUDYING the PATIENT

- ENVIRONMENT
- STUDY HEALTHY PHYSIOLOGIES
- PATIENT PROFILING
- SCREENING MOLECULES at PHENOTYPIC LEVEL

CHARACTERIZE SIGNALLING PATHWAYS — NORMAL + ABNORMAL

BRING EFFICIENCY to WHAT WE DO

CREATING ENABLING TOOLS to LOOK at COMPLEX CELL POPULATIONS to SEE HOW DRUGS WORK w/ ENABLING METHODOLOGY

SEE the BIOLOGY, NOT the TECHNOLOGY

THERE'S a LOT WE DON'T UNDERSTAND

IT'S NOT ENOUGH to HAVE the TOOLS

FUNCTIONAL IMAGING ANALYSIS

REMOVE the BOUNDARIES of the KNOWN — EXPECT the UNKNOWN

RAKESH JAIN — TUMOR MICROENVIRONMENT

The TUMOR as an ORGAN

The CATALYST

INCREASED PRESSURE IN TUMORS

BLOOD VESSEL | MATRIX | CANCER CELLS | HOST CELLS | LYMPHATIC VESSEL

The TUMOR DOES THIS → HYPOXIC REGIONS PUT PRESSURE ON TUMOR CELLS

SHUTTING DOWN BLOOD VESSELS → INVASIVE PHENOTYPES

HOW DO WE REGULATE the MICRO-ENVIRONMENT and NORMALIZE PRESSURE?

ANTI-ANGIOGENIC THERAPY INCREASES LONGEVITY

CLINIC — ENABLERS — BENCH

REPURPOSE OLD DRUGS

ANIMAL MODELS FUNCTIONAL + MOLECULAR

Jim Nuttle / ROBERT MITMAN

PANEL

MECHANICAL FORCES/PROPERTIES IN TISSUE and the CANCER MICROENVIRONMENT

"NO MAN IS AN ISLAND"

JAN LIPHARDT

WHAT'S INSIDE? WHAT'S OUTSIDE?

CANCER MECHANICS

- MECHANICS + CELL REPROGRAMMING - CELLS are RESPONSIVE
- MATRIX STIFFNESS
- SIGNALLING and MECHANOSENSING

DEVELOPMENTAL BIOLOGY?

TARGETS?

HOW DO YOU SHOOT BULLETS at an ARCHITECTURE?

CONTEXT DEPENDENCE

ALL SCALES are CONNECTED to ALL OTHER SCALES

PERSONALIZATION:

SIGNALLING CAN BE REPROGRAMED

VEGF SIGNALLING IS NOT JUST CHEMISTRY

COLLECTIVE COMMUNICATION + PROPAGATION

LONG RANGE CONSTRUCTION

COLLAGEN FIBERS

TWO CAN ACCOMPLISH WHAT ONE CANNOT

DORMANCY of CELLS?

MINA BISSELL

HOW DO 10 TRILLION CELLS COORDINATE to MAKE YOU?

CANCER is a TISSUE-SPECIFIC DISEASE

CAN WE REVERT to NORMAL?

ARCHITECTURE

GROWTH and MALIGNANT BEHAVIOR are REGULATED at the TISSUE LEVEL

REVERSION is REVERSIBLE

CHIN-LIN GUO

BIO-MECHANICS at SINGLE-MULTI-CELL ENVIRONMENTS

- GEOMETRY-DEPENDENT IN CELL SHAPE PATTERNING
- LONG-RANGE MECHANICAL INTERACTIONS

CTCs → SEEDING → COLONIZATION → DEATH

NORMAL CELLS

MICRO ENVIRONMENT

ADAPTATION → SURVIVAL

DEGENERATION?

HOW FAST and HOW FAR?

SCOTT MANALIS

MEASURING SINGLE CELL PROPERTIES

MICRO ENVIRONMT ⟷ ARTIFICIAL ENVIRONMT

MICRO CHANNEL RESONATOR

LAMIN A/C - MORE DEFORMABLE

ENTRY and TRANSIT of CELL THROUGH a CONSTRICTION

DISTINGUISHING TWO CELL TYPES

BOUYANT MASS

THROUGHPUT ~10,000 CELLS/SEC.

IN VITRO → EX VIVO?

LAB CONDITIONS AWAY from the MICRO-ENVIRONMT.

WHICH PROCESSES WOULD BE VALUABLE for MAPPING?

INNOVATION and THINKING DIFFERENTLY

WHAT IF WE HAD... a FUNDAMENTAL PRINCIPLE → THEORIES LEADING to HYPOTHESIS → TESTED IN PEOPLE

LIKE the GERM THEORY of DISEASE

CALCULATION of AN OBJECT

REMEMBER

DARK MATTER

UNIFIED THEORY of GRAVITATION — ASKS MORE QUESTIONS THAN IT ANSWERS

PATHOLOGY RELIES ON:

SHAPE of the CELL

STIFFNESS — MEASURED OVER TIME

FIBROSIS

TRENDS IN UNDERSTANDING THESE PROPERTIES

YOU CAN USE SINGLE CELLS to UNDERSTAND THESE ASPECTS

SEVERAL THEORIES

- CANCER is a WOUND?

ANALOGIES to OTHER PHYSIOLOGIES?

MODELS w/ a SMALL NUMBER of PARAMETERS

EXTERNAL MECHANICAL and FLUID FORCES

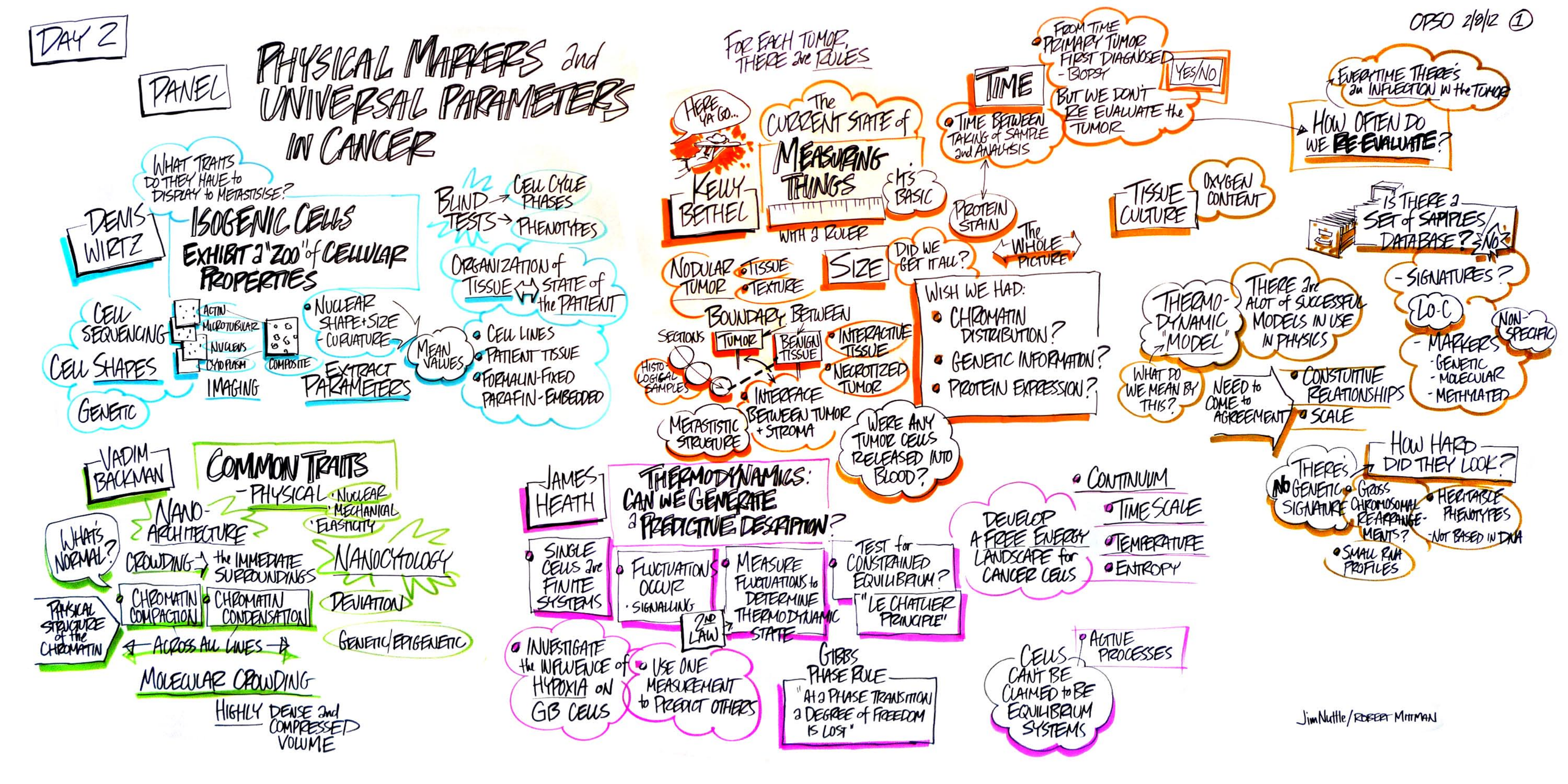
CELLS CAN SENSE and INTEGRATE MECHANICAL SIGNALS

DEVELOPMENTAL BIOLOGY

LIVER CELLS

PHYSICAL FORCES + ENVIRONMENT

Jim Nuttle / ROBERT MITMAN


DAY 2
OPSO 2/8/12 ①
PANEL
PHYSICAL MARKERS and UNIVERSAL PARAMETERS IN CANCER
DENIS WIRTZ
WHAT TRAITS DO THEY HAVE to DISPLAY to METASTISISE?
ISOGENIC CELLS EXHIBIT a "ZOO" of CELLULAR PROPERTIES
CELL SEQUENCING
CELL SHAPES
GENETIC
ACTIN
MICROTUBULAR
NUCLEUS
CYTOPLASM
COMPOSITE
IMAGING
NUCLEAR SHAPE + SIZE
CURVATURE
EXTRACT PARAMETERS
MEAN VALUES
BLIND TESTS
CELL CYCLE PHASES
PHENOTYPES
ORGANIZATION of TISSUE
STATE of the PATIENT
CELL LINES
PATIENT TISSUE
FORMALIN-FIXED PARAFIN-EMBEDDED
VADIM BACKMAN
COMMON TRAITS
PHYSICAL
NUCLEAR
MECHANICAL
ELASTICITY
NANO-ARCHITECTURE
WHAT'S NORMAL?
CROWDING
the IMMEDIATE SURROUNDINGS
NANOCYTOLOGY
DEVIATION
GENETIC/EPIGENETIC
PHYSICAL STRUCTURE of the CHROMATIN
CHROMATIN COMPACTION
CHROMATIN CONDENSATION
ACROSS ALL LINES
MOLECULAR CROWDING
HIGHLY DENSE and COMPRESSED VOLUME
FOR EACH TUMOR, THERE are RULES
HERE YA GO...
KELLY BETHEL
The CURRENT STATE of MEASURING THINGS
WITH a RULER
IT'S BASIC
TIME
FROM TIME PRIMARY TUMOR FIRST DIAGNOSED - BIOPSY
YES/NO
BUT WE DON'T RE EVALUATE the TUMOR
TIME BETWEEN TAKING of SAMPLE and ANALYSIS
PROTEIN STAIN
The WHOLE PICTURE
HOW OFTEN DO WE RE-EVALUATE?
EVERYTIME THERE'S an INFLECTION in the TUMOR
TISSUE CULTURE
OXYGEN CONTENT
IS THERE a SET of SAMPLES/DATABASE?
NO
NODULAR TUMOR
TISSUE
TEXTURE
SIZE
DID WE GET IT ALL?
BOUNDARY BETWEEN
SECTIONS
TUMOR
BENIGN TISSUE
HISTOLOGICAL SAMPLES
INTERACTIVE TISSUE
NECROTIZED TUMOR
INTERFACE BETWEEN TUMOR + STROMA
METASTISTIC STRUCTURE
WISH WE HAD:
CHROMATIN DISTRIBUTION?
GENETIC INFORMATION?
PROTEIN EXPRESSION?
WERE ANY TUMOR CELLS RELEASED INTO BLOOD?
THERMO-DYNAMIC "MODEL"
THERE are ALOT of SUCCESSFUL MODELS IN USE IN PHYSICS
WHAT DO WE MEAN BY THIS?
NEED to COME to AGREEMENT
CONSTUITIVE RELATIONSHIPS
SCALE
- SIGNATURES?
LO-C
NON-SPECIFIC
- MARKERS
- GENETIC
- MOLECULAR
- METHYLATED
HOW HARD DID THEY LOOK?
THERE'S NO GENETIC SIGNATURE
GROSS CHROMOSOMAL REARRANGEMENTS?
HERITABLE PHENOTYPES
- NOT BASED IN DNA
SMALL RNA PROFILES
JAMES HEATH
THERMODYNAMICS: CAN WE GENERATE a PREDICTIVE DESCRIPTION?
SINGLE CELLS are FINITE SYSTEMS
FLUCTUATIONS OCCUR
SIGNALLING
2ND LAW
MEASURE FLUCTUATIONS to DETERMINE THERMODYNAMIC STATE
TEST for CONSTRAINED EQUILIBRIUM?
"LE CHATLIER PRINCIPLE"
DEVELOP A FREE ENERGY LANDSCAPE for CANCER CELLS
CONTINUUM
TIME SCALE
TEMPERATURE
ENTROPY
INVESTIGATE the INFLUENCE of HYPOXIA on GB CELLS
USE ONE MEASUREMENT to PREDICT OTHERS
GIBBS PHASE RULE
"At a PHASE TRANSITION a DEGREE of FREEDOM IS LOST"
CELLS CAN'T BE CLAIMED to BE EQUILIBRIUM SYSTEMS
ACTIVE PROCESSES
Jim Nuttle/ROBERT MITTMAN

PANEL

LARGE-SCALE MODELING of CANCER

"WE'RE DOOMED to FAILURE"

LET'S AGREE on the BIG QUESTIONS.

WE DON'T KNOW ALL of the ELEMENTS of the SYSTEM

"STORED INFORMATION" IMPACT ON PHYSICAL PROCESSES

KIRK JORDAN

OTHER AREAS WHERE WE CAN LOOK at MODELS

GEOGRAPHY

SEISMIC REFLECTION

SONOGRAM

MODELS → MACHINES → SIMULATIONS → PREDICTIONS

WEATHER PREDICTION
- HEAT
- STORMS
- ICE SHEETS

LOCALLY:
- HUNDREDS of SENSORS
- DETAILED ACCURATE PICTURE

FUTURE FORESIGHT and RIGHT ACTION

DATA → INFO. → KNOWLEDGE → WISDOM

WHOLE ORGAN SIMULATION - from the CELLULAR LEVEL

AGENT BASED MODEL PLUS CONTINUUM MODEL

MULTI-SCALE

EASY ACCESS DELIVERED ANYWHERE w/ ELASTIC RESOURCES

COMPUTATION

MOBILE

BILLIONS of UNITS

INSTRUMENTATION
- USE of MULTIPLE SENSORS to GATHER DATA

WHAT KIND of INPUT DO WE NEED?

"COARSE GRAINING"

MORE DATA CAN CHANGE the MODEL

CLINICAL DECISION POINTS

Jim Nuttle / ROBERT MITMAN

HERBERT LEVINE

COMPUTATIONAL MODELS for CANCER RESEARCH

YOU'RE SOLVING the WRONG PROBLEM...

BASIC PHYSICS UNDERLYING MOTION

THEORY → MODELS - REALIZATION
- STATIC
- DYNAMIC

SCALING
- MOLECULAR
- SINGLE CELL

DEFORMING CELLS

IT TAKES a LOT of COMPUTATION POWER

NEED to USE THEORETICAL CONCEPTS

CLIMATE CHANGE

PHENOMOLOGICAL "BLACK BOX" - WE DON'T NEED to MODEL EVERY PROCESS

DYNAMICAL RESPONSE

IT COSTS MONEY

IT'S EASIER to MODEL PHYSICS THAN BIOLOGY

KAISER

LARGE-SCALE DISEASE MODELS to MAKE TREATMENT DECISIONS

MODELING NUCLEAR WARHEADS

SPACE SHUTTLE MODELING ASSUMPTIONS

MODERN CHEMICAL PLANT

SYSTEM MODEL

"TURBULENT FLOW"

IDENTIFY KEY PARAMETERS and DECISION POINTS
- HELPS US UNDERSTAND WHAT WE NEED to KNOW

TIM KAXIRAS

CHALLENGES for COMPUTATIONAL PHYSICAL SCIENCES

MULTI-SCALE APPROACHES

PREDICT from FIRST PRINCIPLES?
- RELEVANT STRUCTURES, FUNCTIONS of COMPLEX SYSTEMS

ACUTE MYOCARDIAL INFARCTION

FLOW

STRUCTURE of DNA

HISTONS

QUANTUM MECHANICS

STRESS CORROSION CRACKING

SIMULATION

0 PARAMETERS

SHEER STRESS

1 PARAMETER

TURBULENCE

"RELIABLE PREDICTIVE METHODOLOGY"

BLOOD CELLS

3 TYPES of MOTION

TUMBLE

TANK TREADING

DEFORMATION

LIFT OFF the WALL

AFFECTS of OTHER CELLS

MULTI-SCALE MODELING

NEEDS a SEPARATION of SCALES

TIME SCALE

RARE "BLACK SWAN" EVENTS

HOW DO YOU INCORPORATE THIS IN YOUR MODEL?

STOCK MARKET

- DYNAMICAL AVENUES
- MODELS CAN HELP YOU FIND POTENTIAL "BLACK SWANS"
- NEW PHENOMENONS

HIGHER RESOLUTION