

New Models of Collaborations with Academia to foster Translational Clinical Research, the Key to Personalised Healthcare in Practice

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Key Technologies that have increased the Body of Knowledge for Drug Discovery

Genes

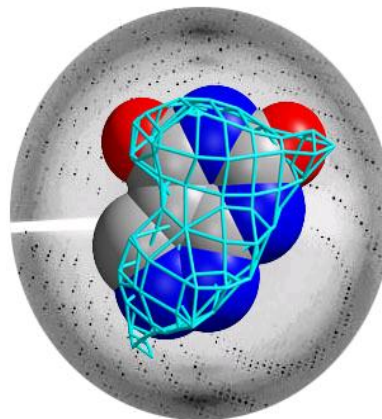


Key technology

Gene Sequencing

- Understanding of genetic basis of disease, and impact of genetic variation

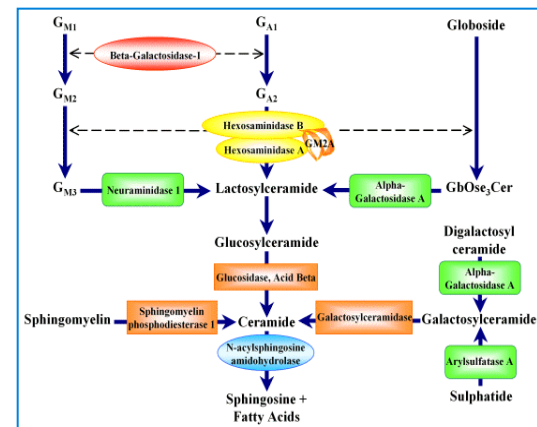
Protein structure



X-ray Crystallography and Nuclear Magnetic Resonance

- Understanding of function from structure
- Enabler of rational drug design

Disease pathway



System Biology Proteomics / Metabolomics

- Understanding of biological pathways and intervention points that impact disease states

The advent of Personalised Healthcare (PHC)

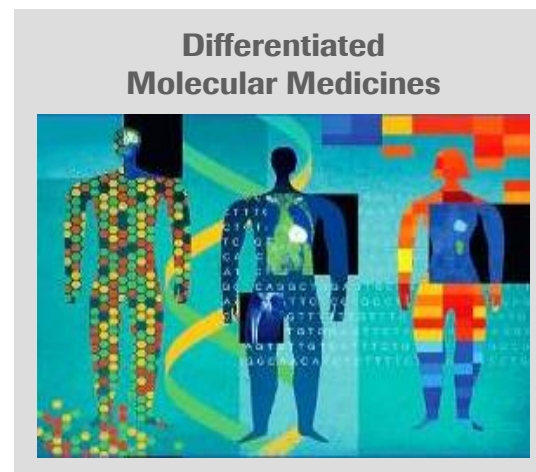
- **Translational Research** is at the core to enable PHC
- **New technologies** open new opportunities to translate the progress in basic science into the clinical setting
- **Innovation** is driven by a diversity of approaches
- **New models of industry/academia collaborations** catalyze the translation of basic science progress into the clinical setting

Better
Understanding
of Disease
Mechanisms

New &
Established
Technologies



New
Plausible
and
“Druggable”
Targets



Fitting Treatments to Patients: Personalized Healthcare

Key steps to bringing new value for better, more predictable medicines



- 1 Understand heterogeneity of diseases
- 2 Discover and develop relevant biomarkers
- 3 Stratify patients with diagnostic tests
- 4 Build evidence for better benefit-risk ratio



Agenda



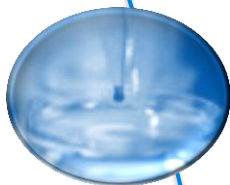
PHC in practice – the Zelboraf® story



The future - Integration of molecular diagnostics with targeted therapies

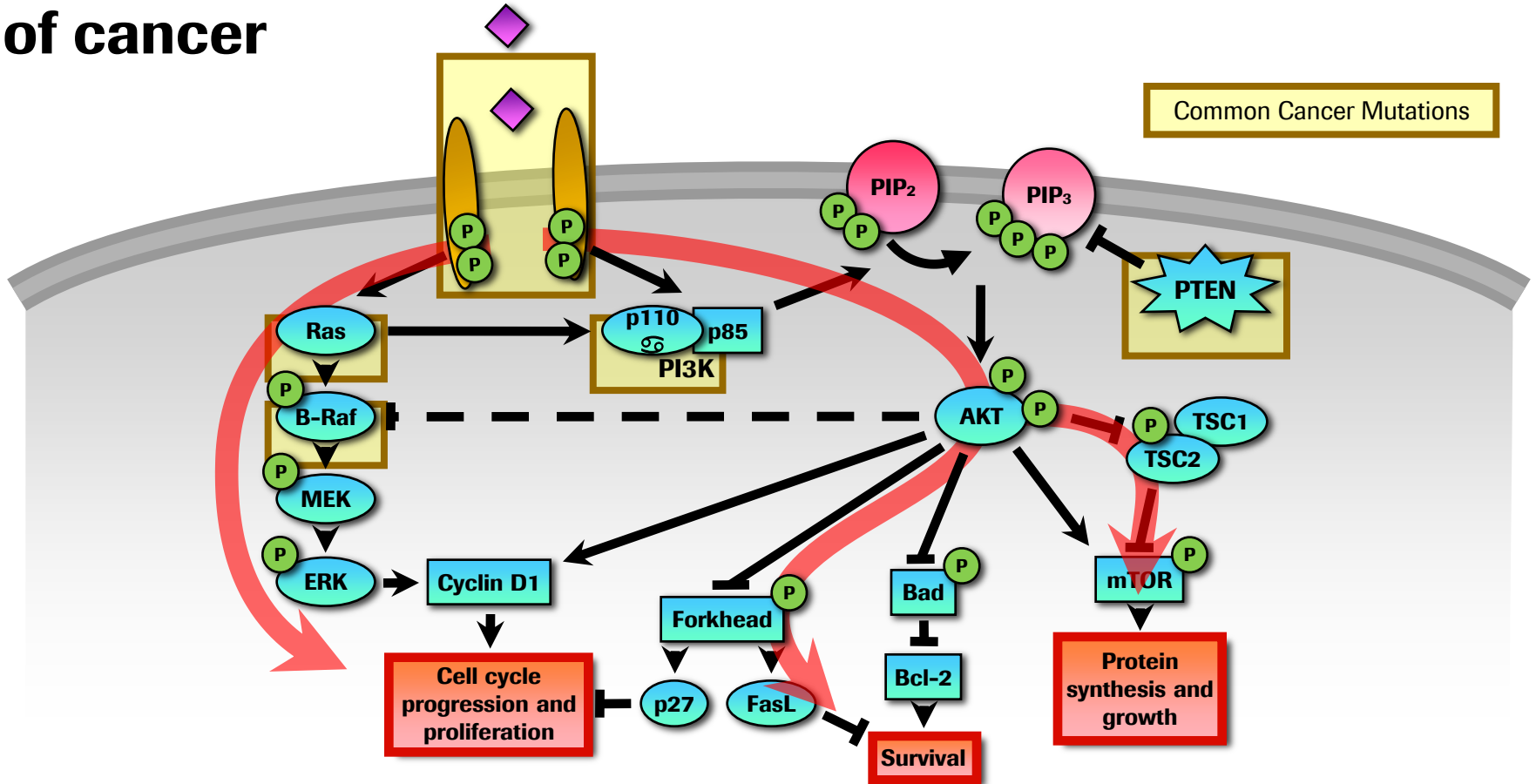


Innovate R&D - New models of partnership with academia



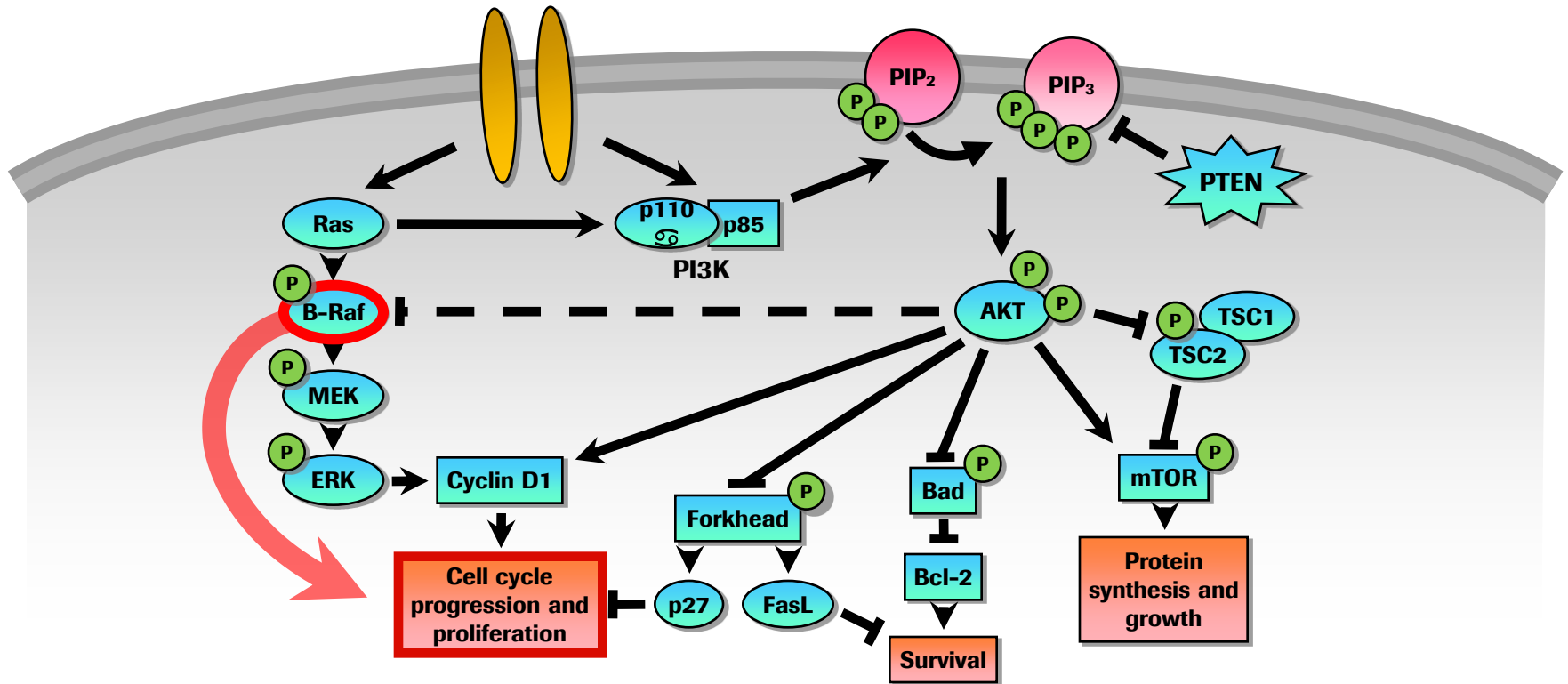
Conclusions

Understanding the molecular mechanisms of disease: Growth factor pathways in the heartland of cancer

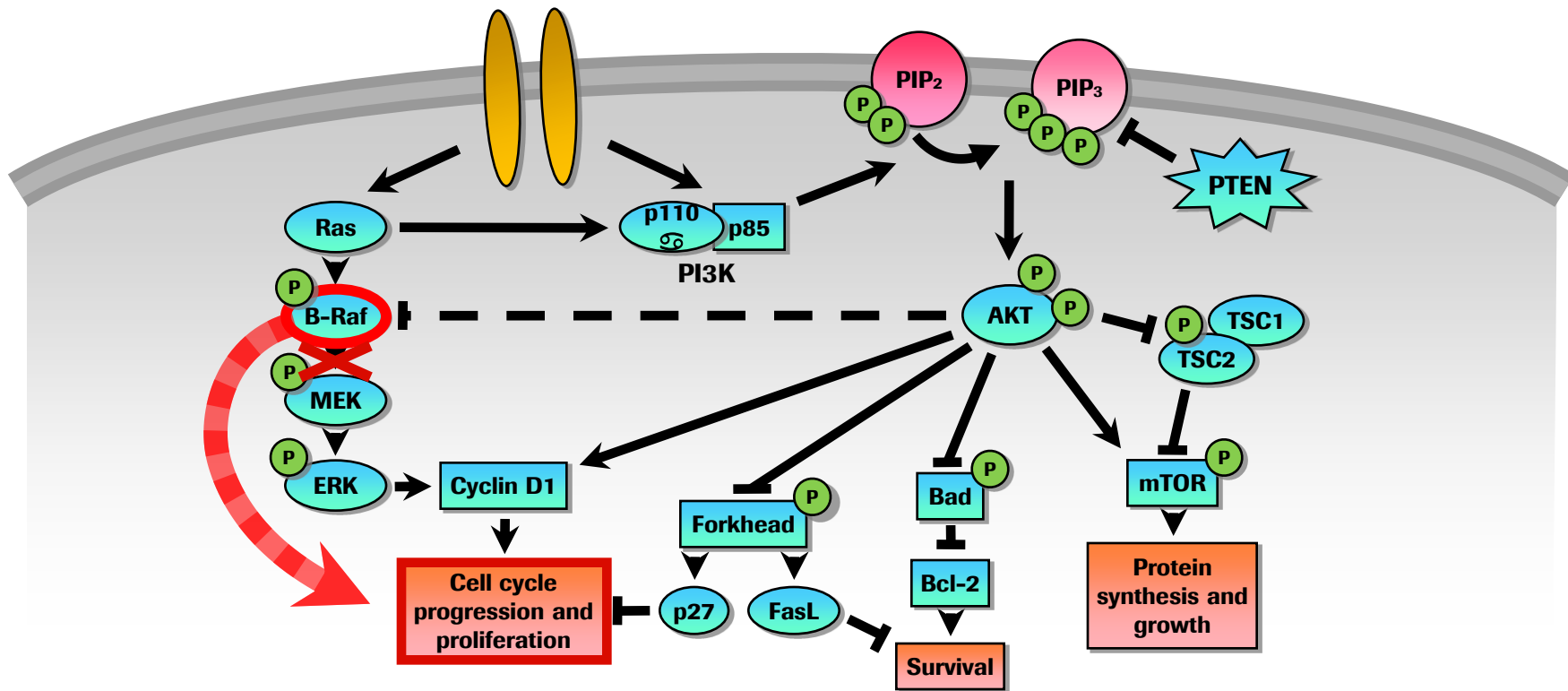


B-Raf mutations stimulate cell growth

40-60% of melanoma patients have V600 mutation



Zelboraf[®] (Vemurafenib) inhibits mutant B-Raf signaling

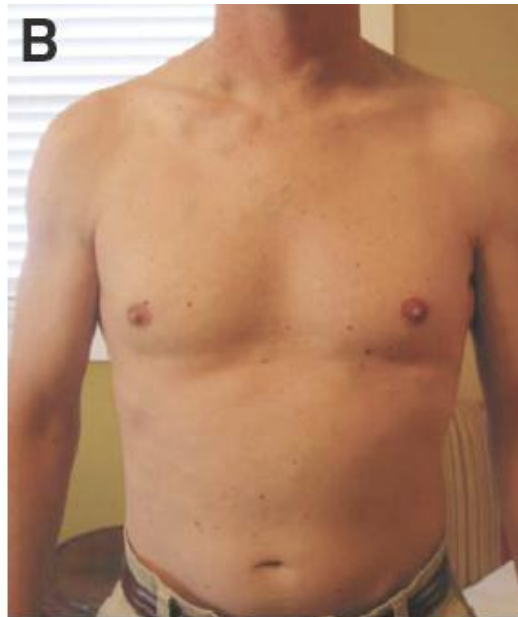


About 50% of BRAF V600 mutated patients respond to vemurafenib...

Before initiation of vemurafenib

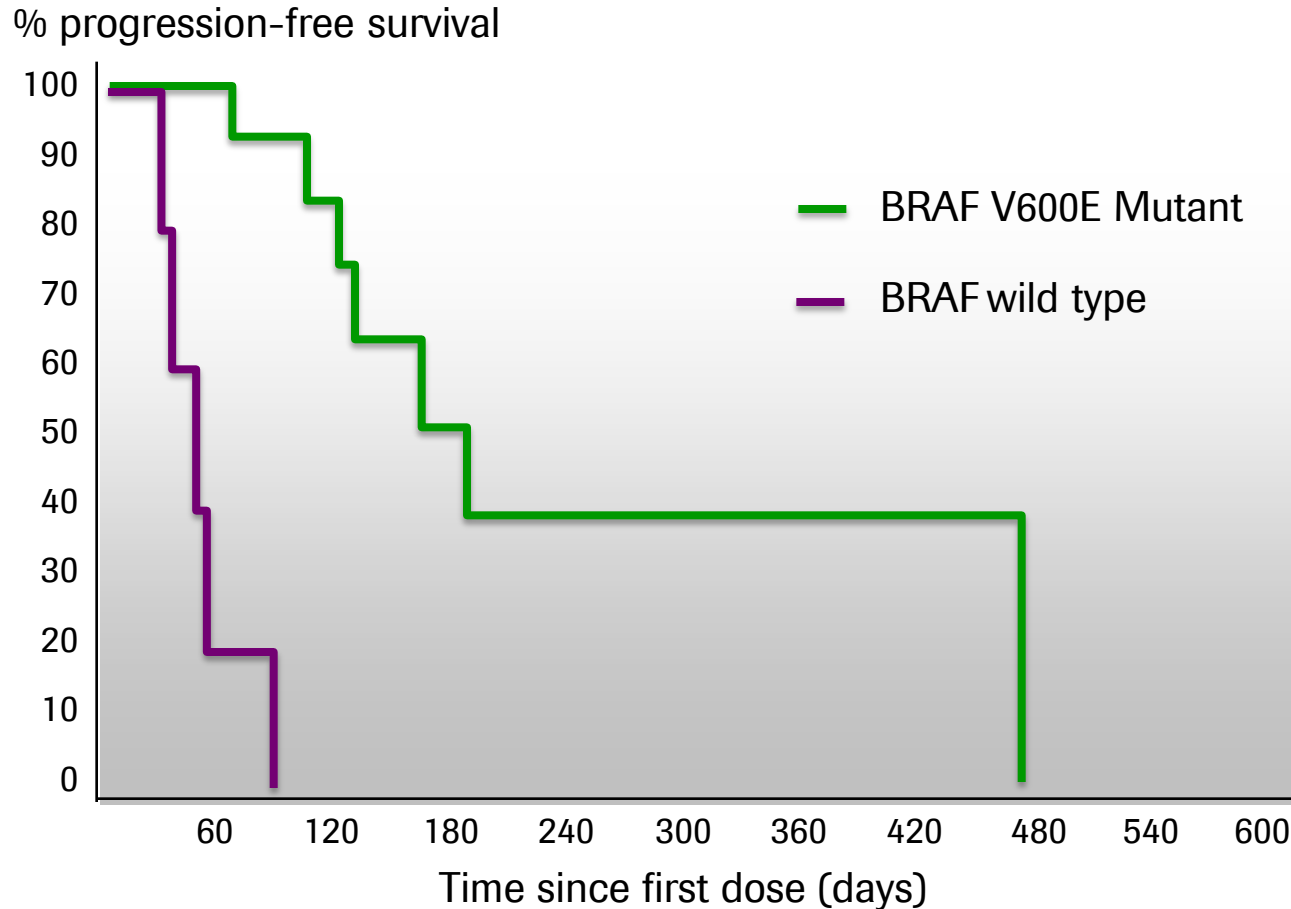


15 weeks on vemurafenib



Vemurafenib in metastatic melanoma patients

Mutated BRAF vs non- mutated BRAF patients



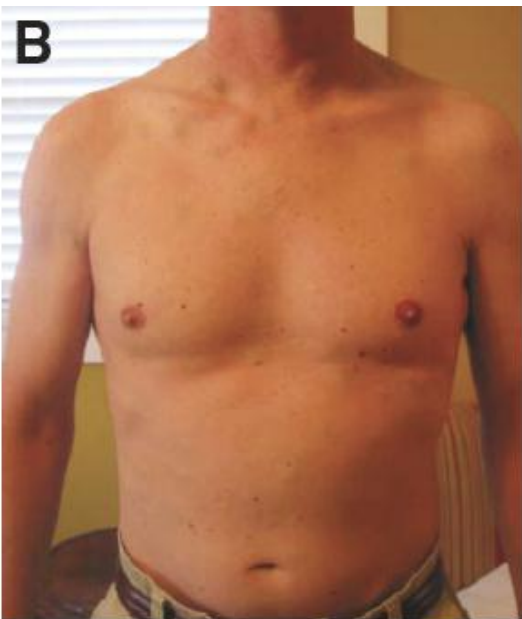
...Relapse occurs

Case study

Before initiation of vemurafenib



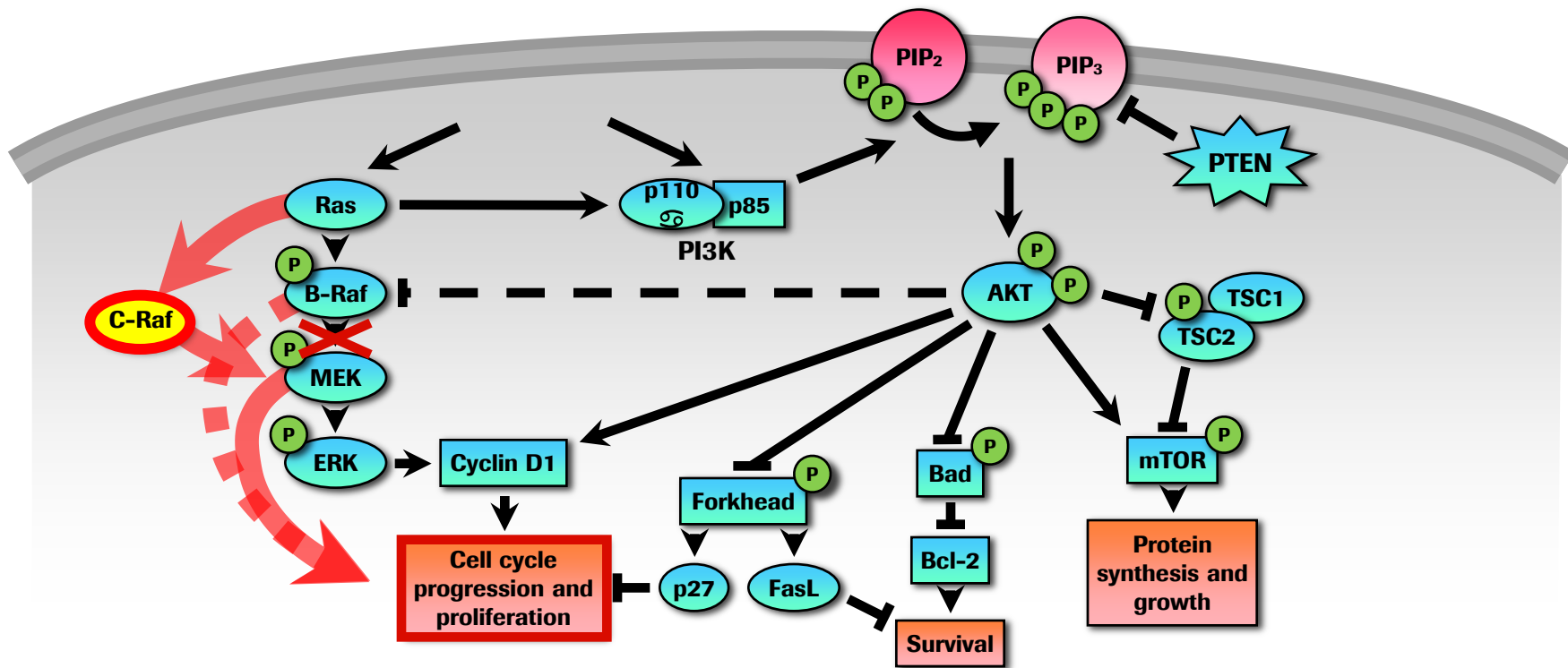
15 weeks on vemurafenib



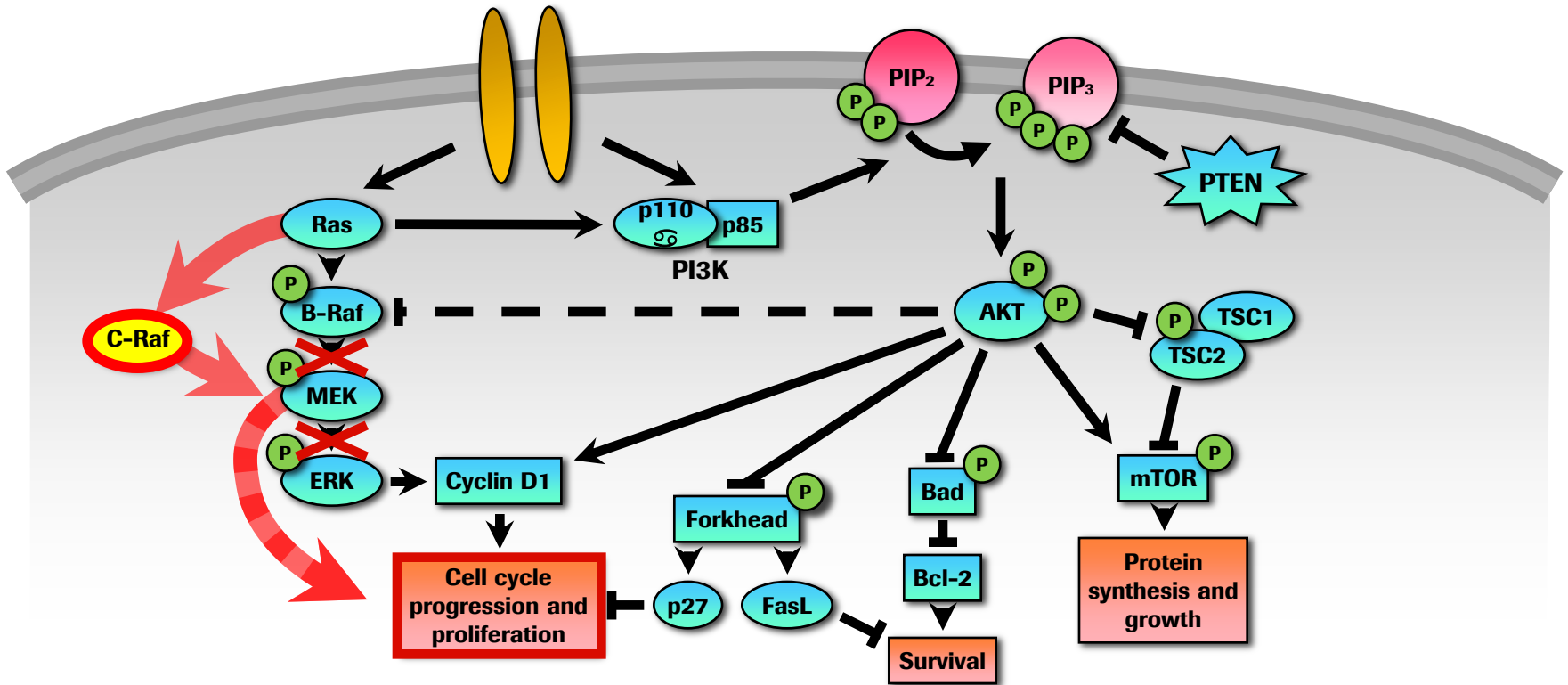
23 weeks after therapy



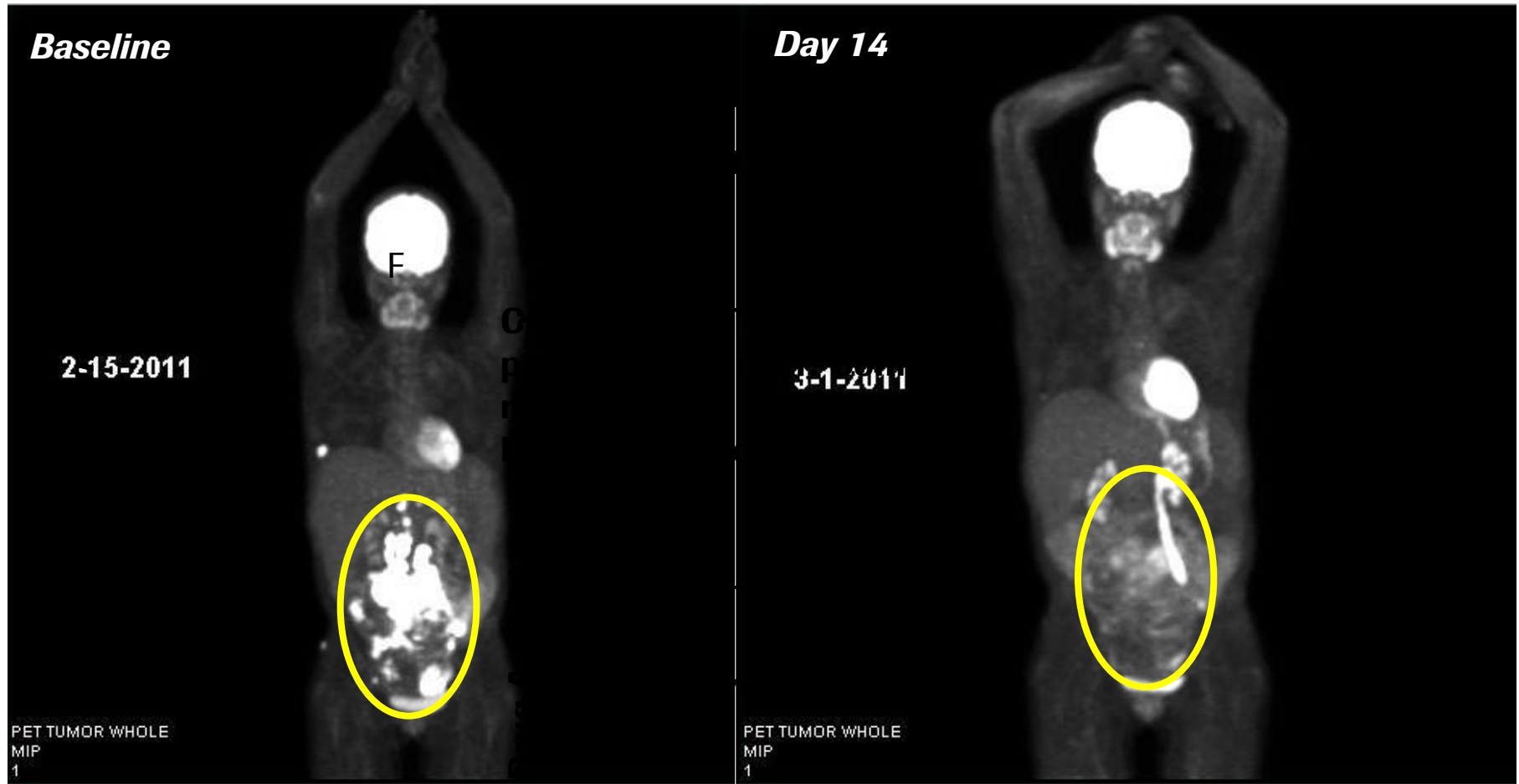
Escape from B-Raf inhibition may be through activating C-Raf



MEK inhibition may be useful in B-Raf escape tumors



Efficacy of MEK inhibitor in Combination with Vemurafenib B-Raf kinase Inhibition in relapsing Patients



Agenda



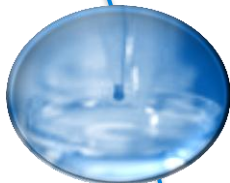
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**The future - Integration of molecular diagnostics
with targeted therapies**



Innovate R&D - New models of partnership with
academia

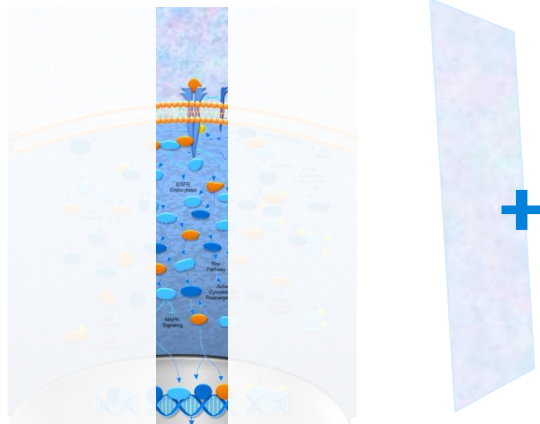


Conclusions

Where our science is taking us in oncology

Understand the patient and their disease to effect cure

Dysregulated cell signaling

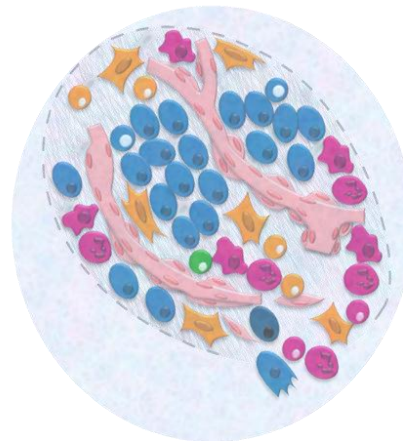


Paradigm 1

Cancer cell directed targets

- e.g. Zelboraf
- Relapse highly probable, requires combinations, e.g. Zelboraf plus MEKi

Tumour-stroma interaction

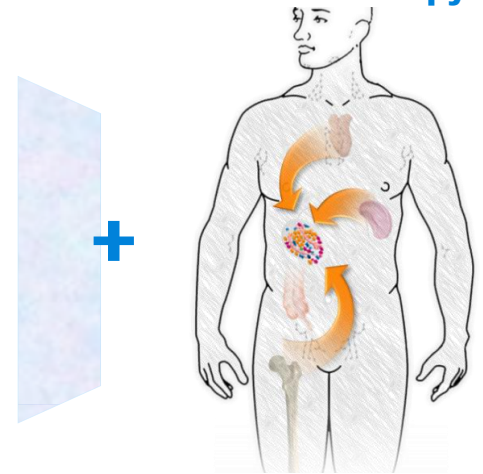


Paradigm 2

Microenvironment modulation

- Antiangiogenesis

Targeted Immunotherapy



Paradigm 3

Engage host immune response

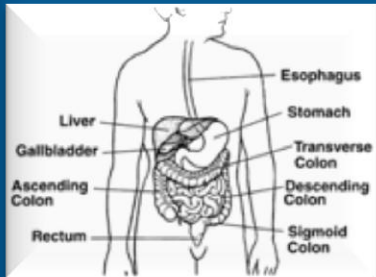
- Antibody engineering, activation of NK cells

Cure requires a multi-paradigm approach

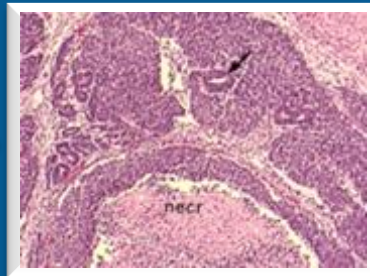
Changing paradigms in healthcare

Example in cancer therapy

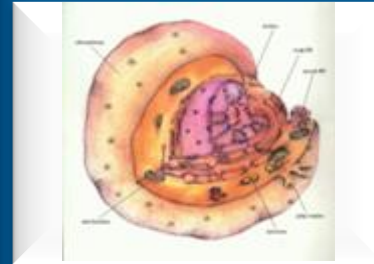
Tumor site



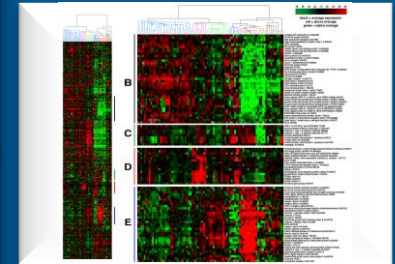
Tumor histology



Molecular biology



Molecular profile



Old paradigm

Toxic, non-selective, chemotherapy drugs

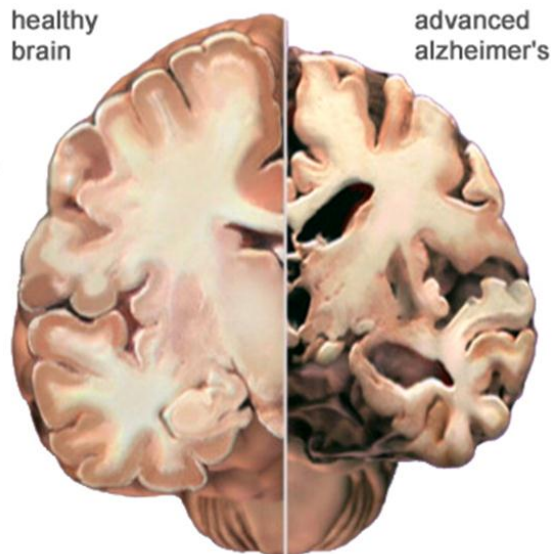
Targeted therapies

Wider therapeutic index, derived from molecular biology discoveries of the '80s

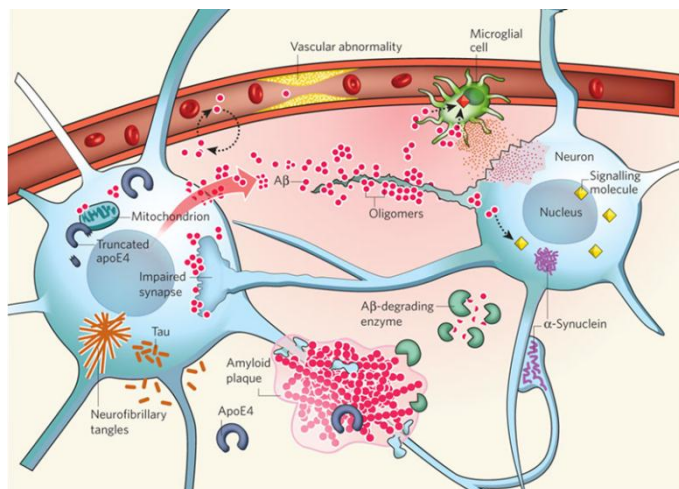
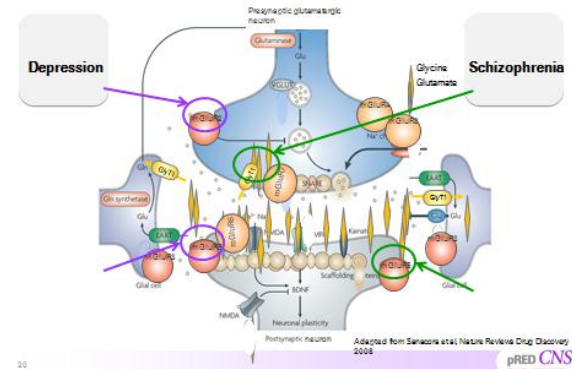
Future paradigm

Integration of molecular diagnostics with targeted therapies for integrated cancer care

Neuroscience – the next frontier to deliver new tailored medicines to patients



The glutamate synapse

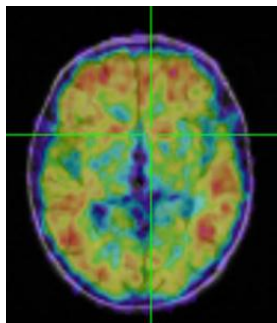
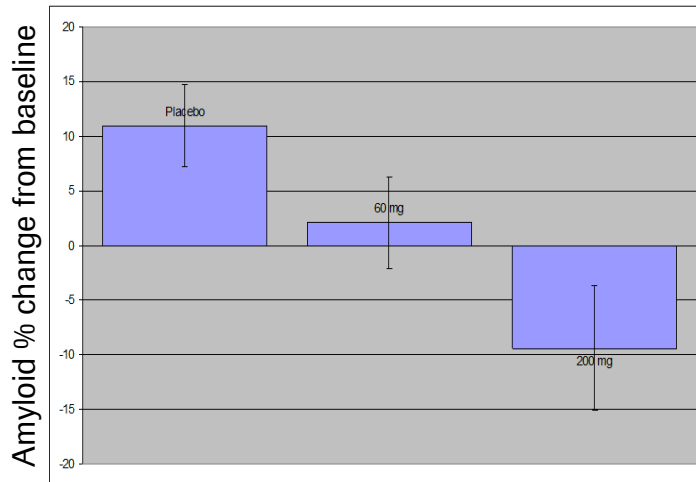


Gantenerumab – Alzheimer’s disease

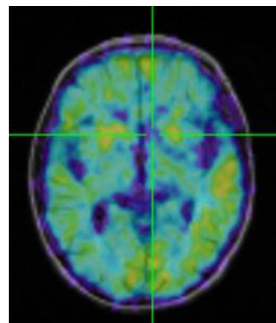
Opportunity to be first in disease for prodromal AD with Phase 2/3

Demonstrated plaque clearance in human brain

Treatment before conversion to dementia



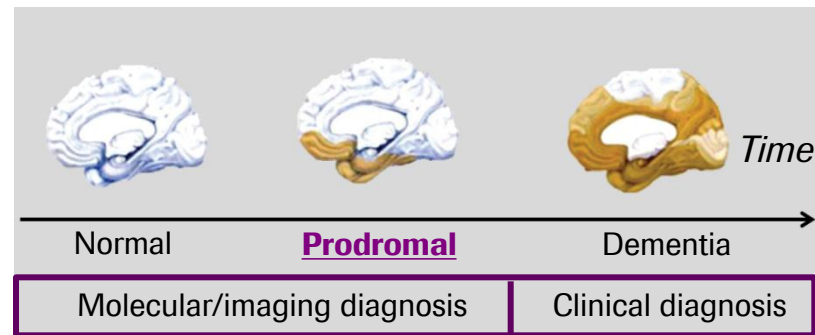
Baseline PET



6 month PET

Gantenerumab data from Alzheimer’s patients

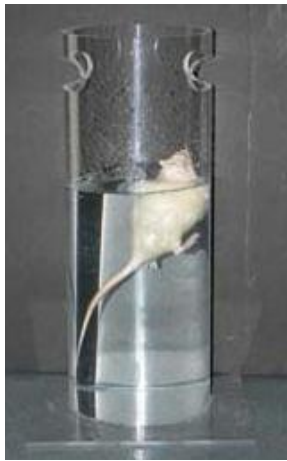
Alzheimer’s starts 20 years before clinical symptoms



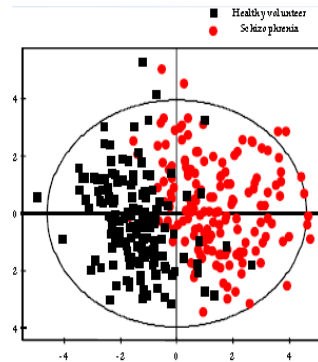
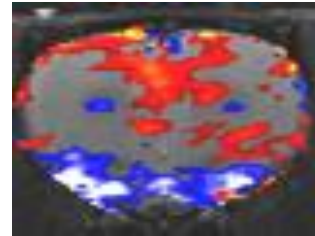
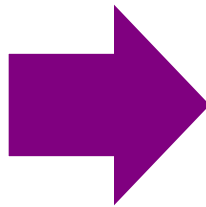
- **Molecular BMs (CSF A β and Tau) enable early diagnosis and treatment**
- **Dosing based on ApoE4 phenotype**

Evolution of R&D methodology in Psychiatry

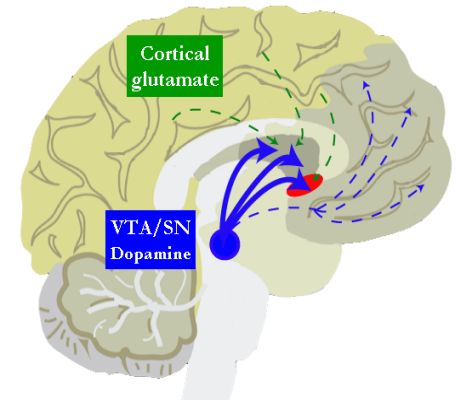
Targeting brain circuits to treat specific symptom domains



Past



Controls
Schizophrenia

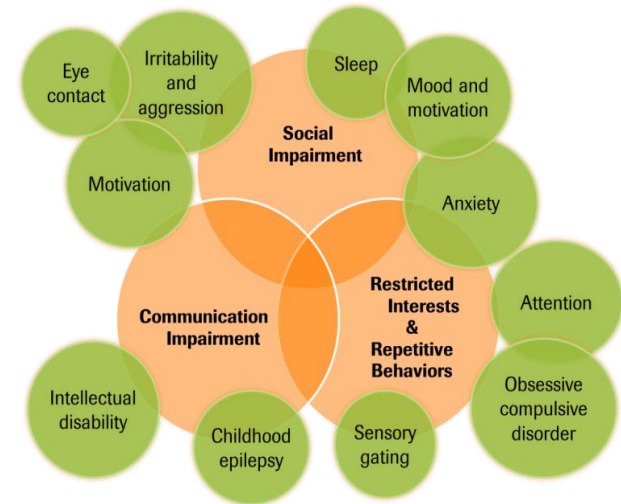
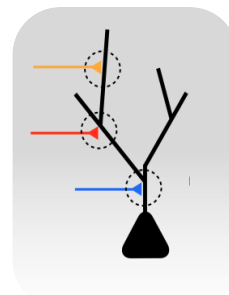
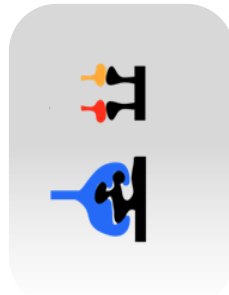
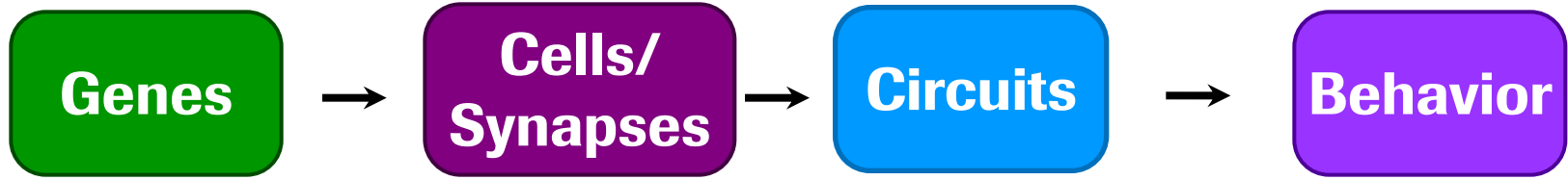


Future

- Focus on disease understanding at the level of **neural circuitry** instead of pure phenomenology/behavior, leveraging understanding of genetics, biomarkers and imaging modalities

Targeting synapses and circuits for therapeutics

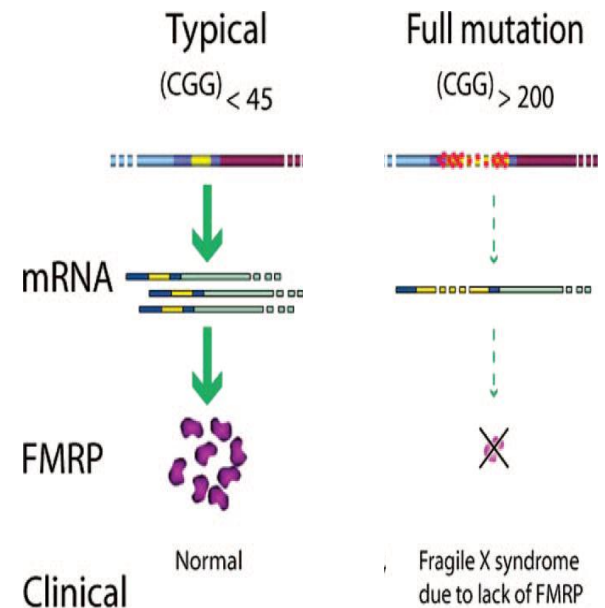
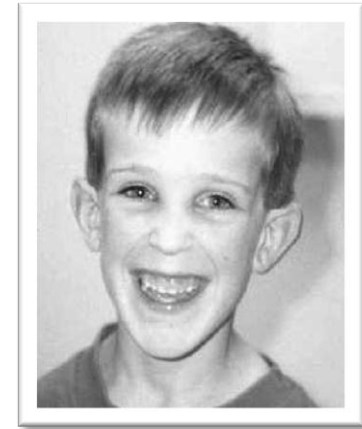
The bridge between genes and behavior



The example of Fragile X Syndrome

A genetic condition of Autism

- **Most common genetic cause of autism**
 - 1:4000 males, 1:8000 females
 - Striking psychiatric phenotype, additional physical abnormalities
 - Caused by triplet repeat expansion in 5'UTR of FMR1 gene (leads to methylation and silencing)
- **No approved pharmacotherapy – high medical need**
- **Established molecular pathophysiology** with a key modulatory role of mGlu5 receptors
- **PHC program** with diagnostic and response prediction BMs



Agenda



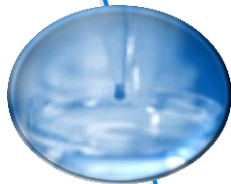
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Conclusions

Roche is committed to foster new models for academic collaboration

- Innovation comes from diversity of approach and from bringing different disciplines together to progress science through translational medicine.
 - In today's leading academic centers, different groups are working together – often across multiple academic institutions.

- There are new opportunities and dynamics in the area of translational clinical research and PHC.
 - Opportunities for innovation in area with shared research interest and research focus that benefits the academic and the Pharma partner
 - Different models ranging from single center collaboration to multi-institute network to industry/academia translational research “hub”



pRED External Innovation Network

Complementing our capabilities and amplifying our ability to innovate

Technology Partnerships

Harvard

- iPSC (Stem Cells)



PTC Therapeutics

- Advanced treatment options for Spinal Muscular Atrophy



Baylor

- Therapeutic vaccines



Geneva University

- Proteomics and pathway analysis



Yissum

- Novel pathways, β -cell Stem Cells discovery, CV risk biomarkers



Mt Sinai

- Novel screening approaches in Virology

Translational Hubs

Singapore

- Network of 26 academic partner institutes, several programs e.g. angiogenesis
- Virtual R&D unit with financial reimbursements



Netherlands Imaging Hub

- Collaborative Hub of 3 world-class academic imaging sites



French R&D Institute

- Access to academic innovation network with positive impact on key European affiliate



Montreal Heart Institute

- Cardiovascular centre of excellence



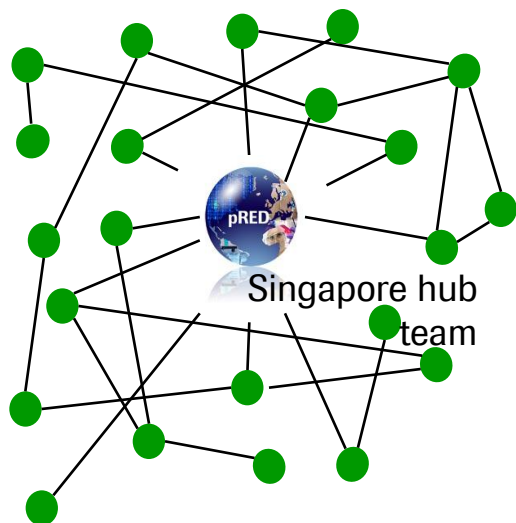
Swiss University Network

- Basel, neuroscience cognition research & ETH Zurich, joint Rx/Dx hub



Singapore Translational Medicine (TM) Hub

Proof of Concept of a new collaborative model has been achieved



What we set out to do:

- Provide a platform to interact and collaborate sustainably with academic partners
- Synergise on infrastructure & capabilities
- Broaden portfolio
- Enhance flexibility
- Remove hurdles for Roche scientists to work with academia and vice versa and reap benefits
- Create and deliver mutual benefits to collaborative scientific innovation

Summary and Conclusions

- Translational clinical research is essential to implement Personalized Healthcare (PHC) for better and more predictable medicines
- New technologies are available and enable the translation of the progress in basic science into the clinic
- PHC is reality and opens great opportunities for better medicines for patients suffering from diseases with no tailored effective treatments
- Roche fosters new models for innovation and collaborations with Academic partner in areas of joint research interest and expertise

**“If it were not for the great
variability among
individuals, medicine might
be a science, not an art.”**

Sir William Osler

*The Principles and Practice of
Medicine, 1892*





We Innovate Healthcare