Karen and Kevin Capel
(Parents and Research Funders)
Christopher's Smile

European Parliament Workshop

"Paediatric Regulation: are children still missing out on potentially life-saving treatments?"

16th June 2015

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Christopher

- Diagnosed with medulloblastoma at $4^{1}/_{4}$
- Treated with chemotherapy/high dose chemotherapy with stem cell rescue
- Immediate post therapy prognosis good
- Relapse 4 months post therapy
- Died 21 months after diagnosis

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Paediatric Oncology Current Treatments

First line treatment options: surgery, and/or cytotoxic chemotherapy and/or radiotherapy

- Surgery: Neurosurgery – high risk, amputated limbs do not grow back
- Chemotherapy: vast majority is used 'off label' and often leaves a legacy of issues
- Radiotherapy: devastates a developing brain

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Commonly used drugs to treat children with cancer:

- include known carcinogens
- are not approved for use on children and have an average age of 40-50 years

Is this the best that is available in 2015 after 8 years of the Paediatric Regulation?

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Current Treatments – Legacy of Issues

- Survival plateaued in last 10 years
- Children still dying from decades old toxic treatments
- Unacceptable side effects
- Ongoing late effects
- Cost burden of survival
- 7 years since Christopher's death, 8 years of the Paediatric Regulation – **what has changed**?

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What parents want

New safe and effective treatments - ***NOW***

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New treatments for children - Challenges

- Pharma focus their R&D on adult conditions
- Too easy for Pharma to obtain a waiver for potential new life saving treatments for children
- Years may pass between initial adult trial and agent availability for paediatric pre clinical testing

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Current Implementation of the Paediatric Regulation - Oncology

- More waivers are issued for oncology drugs than any other clinical area despite cancer being the principal cause of death by disease in children in Europe
- In the implementation of Article 43 for Oncology drugs, the EMA have drawn up an inventory which includes highly cytotoxic agents decades old and drugs for which the EMA have granted waivers

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Can anyone explain this?

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SCIENCE MEDICINES HEALTH

25 September 2014
EMA/PDCO/381728/2014
Human Medicines Research & Development Support Division

Draft inventory of paediatric therapeutic needs
Paediatric oncology

Contains the following drugs that **ALL** have a waiver

Axitinib
Bortezomib
Cabazitaxel
Crizotinib
Ruxolinitib
Sorafenib

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VI Discussion on the applicability of class waiver

Active substance	Proposed indication	Condition	Outcome	Potential paediatric interest of this medicine suggested by PDCO
^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate	Treatment of metastatic or unresectable, well differentiated, midgut neuroendocrine tumours, which overexpress somatostatin receptors	Treatment of gastroentero-pancreatic neuroendocrine tumours (excluding neuroblastoma, neuroganglio-blastoma, phaeochromocytoma)	Positive	Neuroblastomas, Medulloblastomas and Ewing sarcomas
Ramucirumab	• Cyramza in combination with paclitaxel is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy; • Cyramza monotherapy is indicated for the	• Treatment of lung carcinoma (small and non-small cell carcinoma); • Treatment of liver and intrahepatic bile duct carcinoma (excluding hepatoblastoma); • Treatment of gastric adenocarcinoma; • Treatment of adenocarcinoma of the colon and rectum; • Treatment of ureter and bladder carcinoma.	Positive	Paediatric solid tumours

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5 March 2015
EMA/PDCO/17136/2015
Procedure Management and Business Support Division

Paediatric Committee (PDCO)
Minutes of the 14-16 January 2015 meeting

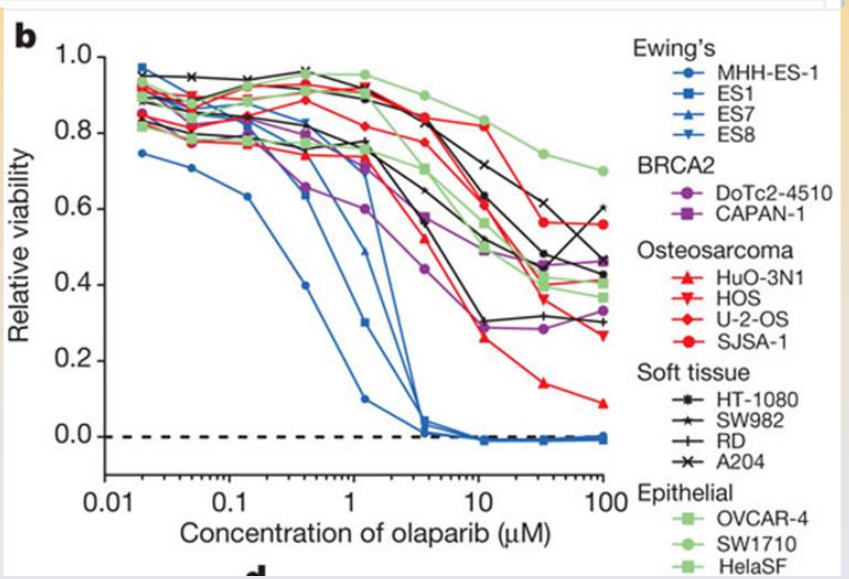
Figure 4: **Ewing's sarcoma cell lines are sensitive to PARP inhibition.**

From

Systematic identification of genomic markers of drug sensitivity in cancer cells

Mathew J. Garnett, Elena J. Edelman, Sonja J. Heidorn, Chris D. Greenman, Anahita Dastur, King Wai Lau, Patricia Greninger, I. Richard Thompson, Xi Luo, Jorge Soares, Qingsong Liu, Francesco Iorio, Didier Surdez, Li Chen, Randy J. Milano, Graham R. Bignell, Ah T. Tam, Helen Davies, Jesse A. Stevenson, Syd Barthorpe, Stephen R. Lutz, Fiona Kogera, Karl Lawrence, Anne McLaren-Douglas, Xeni Mitropoulos + *et al.*

Nature **483**, 570–575 (29 March 2012) | doi:10.1038/nature11005



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

09 January 2012
EMA/638304/2008
Human Medicines Development and Evaluation

Paediatric Committee (PDCO)

Minutes of the 05-07 December 2012 meeting

Class waiver number	Active substance	Proposed indication	Condition	Outcome (confirmed / not confirmed)
EMEA-62-2012	Olaparib (AZD2281, KU-0059436)	Maintenance monotherapy for the treatment of patients with gBRCA mutation positive Platinum Sensitive Relapse (PSR) ovarian cancer who have responded (complete response or partial response) to platinum-based chemotherapy Maintenance monotherapy for the treatment of patients with gBRCA mutation positive first line ovarian cancer who have responded (complete response or partial response) to first-line platinum-based chemotherapy.	Treatment of ovarian carcinoma	Confirmed

Paediatric Regulation Chapter 2 Article 11

1. Production of the information referred to in point (a) of Article 7(1) shall be waived for specific medicinal products or for classes of medicinal products, if there is evidence showing any of the following:
   (a) that the specific medicinal product or class of medicinal products is likely to be ineffective or unsafe in part or all of the paediatric population;
   (b) that the disease or condition for which the specific medicinal product or class is intended occurs only in adult populations;
   (c) that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

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What needs to change

- The original objectives of the Paediatric Regulation need to be implemented for the area of oncology.
- The current implementation of Article 11(b) for oncology drugs is failing children with cancer (MedDRA HLT vs PT)

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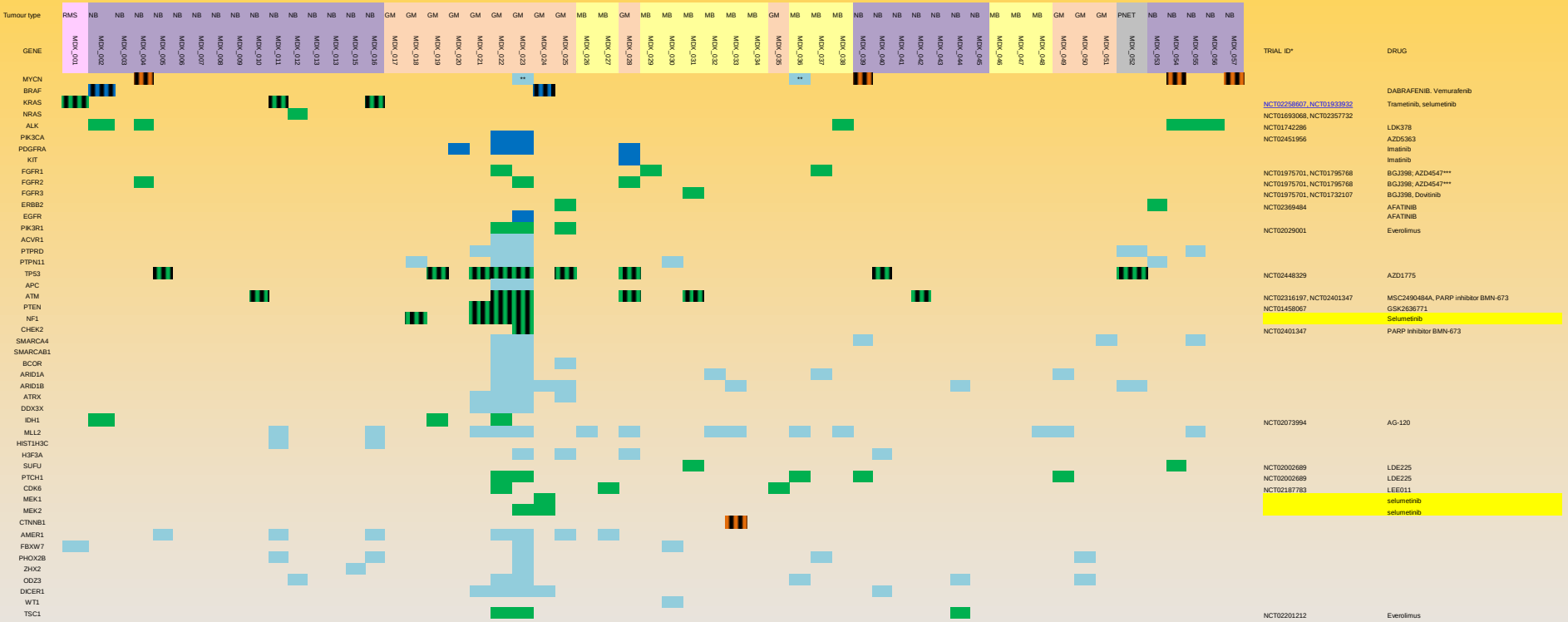
Genetic Characterisation by Next Generation Sequencing



- Predictive biomarker with drug approved in adult indications
- Predictive biomarker with drug approved in adult indications and Prognostic biomarker
- Predictive biomarker with multitrial open in adult indications
- Predictive biomarker with multitrial open in adult indications and Prognostic biomarker
- Prognostic biomarker
- Unknown

NB	Neuroblastoma
GM	Glioma
MB	Medulloblastoma
RMS	Rhabomyosarcoma

Data supplied by ICR The Institute of Cancer Research

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Genetic Characterisation by Next Generation Sequencing

From 57 patients 35 (~60%) could potentially be eligible for novel trials using target specific therapies, either as predictive biomarkers into clinical practice or prognostic biomarkers for treatment decision.

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Genetic mutations “talked about” in the media

DIE WELT

DIE WELT Jetzt testen

Politik Wirtschaft Geld Sport Wissen Panorama Feuilleton ICON Reise PS WELT Regional Meinung Vid

› Brustamputation: Jolie ging radikal vor – doch gab es Alternativen

WISSEN BRUSTAMPUTATION 14.05.13

Jolie ging radikal vor – doch gab es Alternativen

Hollywood-Star Angelina Jolie trägt ein defektes Gen namens BRCA1. Das bringt ihr ein Lebenszeitrisiko von bis zu 80 Prozent, an Brustkrebs zu erkranken. Doch es gibt Alternativen zur Amputation.

The Telegraph

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The conversation about cancer Angelina Jolie will dread

Adele Sewell has a BRCA gene mutation like Angelina Jolie. She can only hope it is not passed on to the next generation

Women like Angelina Jolie who carry the BRCA1 gene are less likely to die from breast cancer if they have their OVARIES removed

- Carriers of BRCA1 gene mutation who are diagnosed with breast cancer are less likely to die if they have their ovaries removed, study found
- But the theory does not apply for those with BRCA2 gene mutation
- Having the BRCA1 or BRCA2 genes increase risk of breast cancer by 70%

Ovarian cancer drug row: 'Breakthrough' treatment won't be available on the NHS because it's deemed too expensive

- Olaparib is designed for women who carry the BRCA gene
- HER2-positive is responsible for 13,000 new cases in the UK each year

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Paediatric Regulation Recital (13)

(13) In order to ensure that research in the paediatric population is only conducted to meet their therapeutic needs, there is a need to establish procedures for the Agency to waive the requirement referred to in Recital (11) for specific products or for classes or part of classes of medicinal products, these waivers being then made public by the Agency. As knowledge of science and medicine evolves over time, provision should be made for the lists of waivers to be amended. However, if a waiver is revoked, that requirement should not apply for a given period in order to allow time for at least a paediatric investigation plan to be agreed and studies in the paediatric population to be initiated before an application for marketing authorisation is submitted.

Actions – not just talk

- What & Who
  - EC to instruct EMA Paediatric Committee to implement Article 11(b) to issue waivers based upon 'Condition' where 'Condition' is defined by a biological or genetic abnormality (change to MedDRA PT-level)
  - For oncology, EMA should review class list and remove all diseases where biological or genetic mutation occurs in the paediatric population.
  - MEPs to work with the Commission to ensure necessary changes are implemented with all speed.
- When
  - Agree timescales *at this meeting*

Children with cancer do not have time on their side

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