INVESTIGATING THE MECHANISMS OF TOXICITY OF CURRENT FLAME RETARDANTS

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INFLAME

Who am I?

- Boris Krivoshiev
- 25
- Born: Sofia, Bulgaria
- Home: Cape Town, South Africa
- Interests: Economics, current world events, innovation and discovery, sports, surfing, surfing, and surfing

Introduction

What do we know?

- Previously used FRs toxic and have thus been tightly regulated
- Studies showed toxicity ranging from carcinogenesis to endocrine disruption

What is lacking?

- Toxicological data for current FRs
- Mechanistic insight into how these compounds exert their toxic phenotypes

What now?

Aim

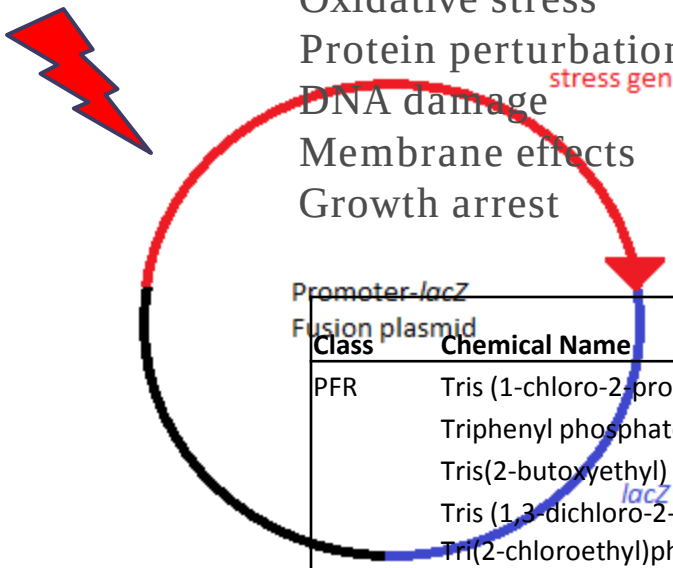
- **Establish potential toxicological and mechanistic profiles of current FRs**

How?

- Monitoring toxicological endpoints
  - Prokaryotic stress gene profiling
  - Eukaryotic stress gene profiling
  - Endocrine disruption
- Develop an unbiased mechanistic overview
  - Differential proteomics

Prokaryotic Stress Gene Profiling

Stressor



Stress Response	*Stress Promoters*
Oxidative stress	KatG, Zwf, Soi28, Nfo
Protein perturbation	ClpB
DNA damage	Nfo, RecA, UmuDC, Ada, sfiA, DinD
Membrane effects	MicF, OsmY
Growth arrest	UspA

B-Galactosidase

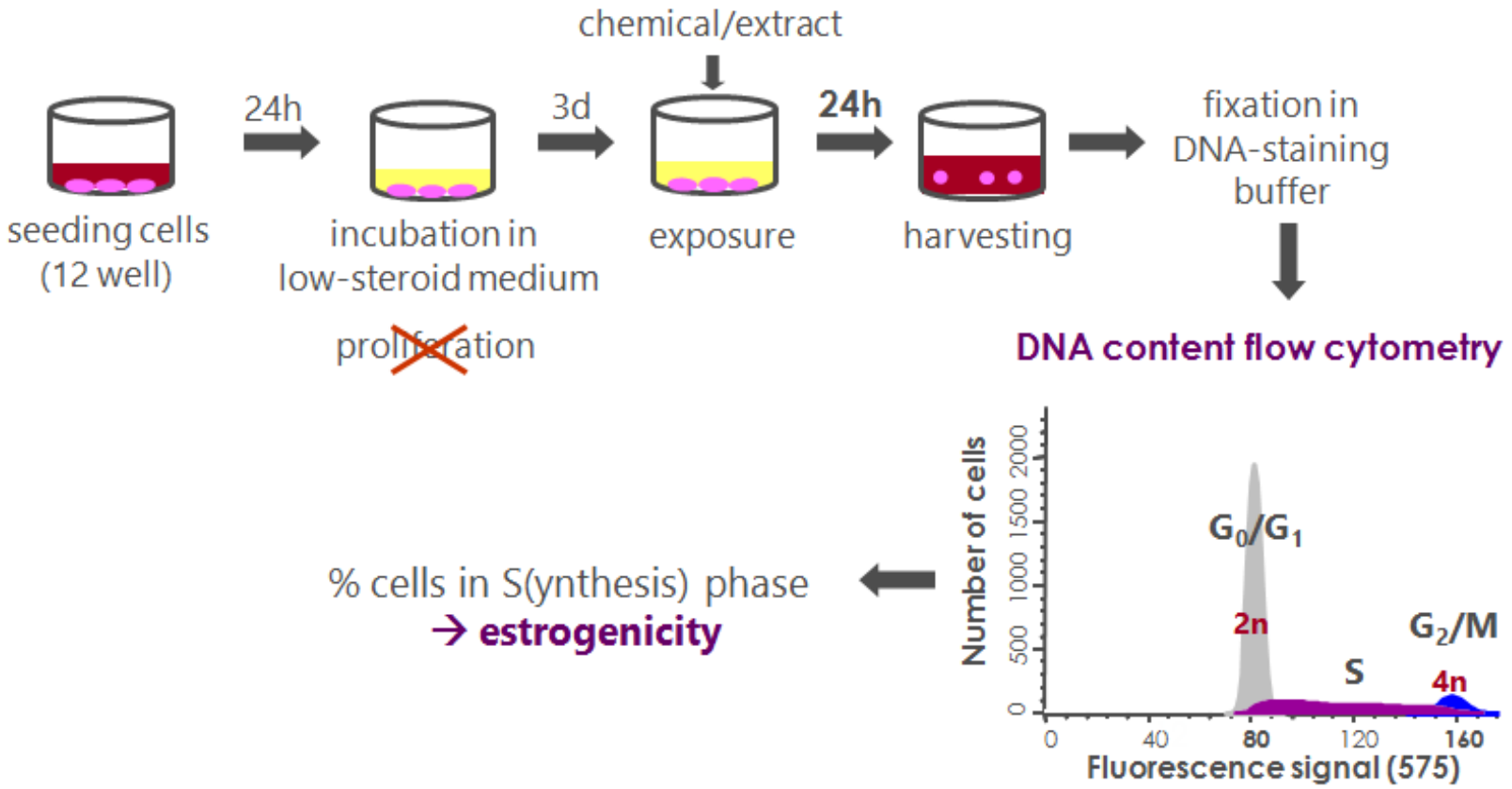
+ ONPG

Class	Chemical Name	Abbreviation
PFR	Tris (1-chloro-2-propyl) phosphate	TCPP
	Triphenyl phosphate	TPP
	Tris(2-butoxyethyl) phosphate	TBEP
	Tris (1,3-dichloro-2-propyl) phosphate	TDCPP
	Tri(2-chloroethyl)phosphate	TCEP
	Tris(butyl) phosphate	TNBP
NBFR	Hexabromocyclododecane	HBCD
	Tetrabromobisphenol A	TBBPA
	2-Ethylhexyl tetrabromobenzoate	TBB
	Decabromodiphenyl ethane	DBDPE
	Bis(2-ethylhexyl) tetrabromophthalate	TBPH
	1,2-bis(2,4,6-tribromophenoxy)ethane	BTBPE

ONP

Absorbance @ 418nm

Endocrine Disruption

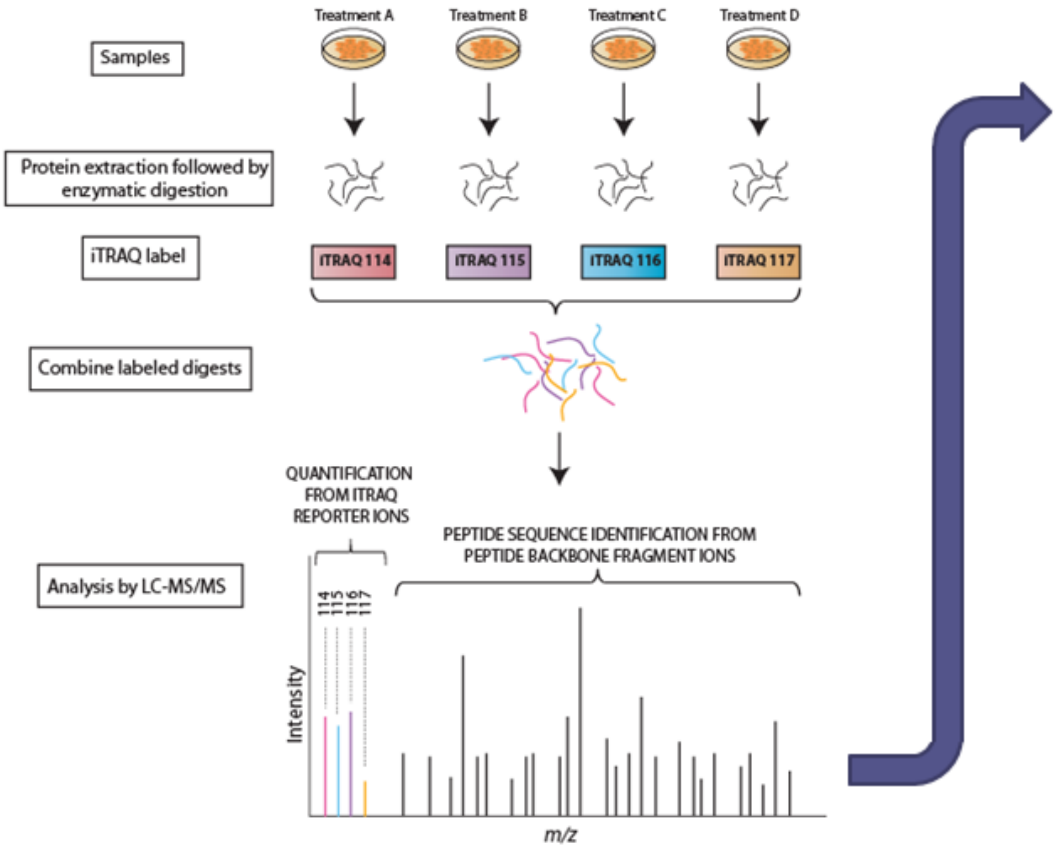


Differential Proteomics

- So far, monitoring toxicological endpoints for indication of toxicity. However, not much mechanistic information including in literature
- Need to develop an understanding of the modes-of-action of these FRs to exert their toxic phenotypes
- Differential proteomics approach
  - Result in understanding what the compounds do *in vitro*, elucidate other toxicological effects that could not be investigated when monitoring endpoints, identification of effect biomarkers

- Additionally, will develop structure-based profiles according to compound structure
  - Halgenated vs non-halogenated
  - Organophosphorus vs non-organophosphorus
  - Organic vs non-organic

Differential Proteomics



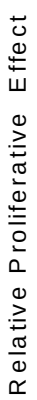
- Construction of effected pathways
- Identification of other potential toxicological effects
- Identification of key proteins/other effector biomarkers

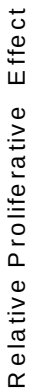
Preliminary results- Protox

- 2-5 fold induction across the majority of stress response promoters

	Ox. stress				protein dmg	DNA dmg			membr. dmg		Growth arrest
	katG	zwf	soi28	nfo	clpB	recA	umuDC	ada	micF	osmY	uspA
BDE209	2.5E-05										
TBBPA	2.5E-06	3.13E-07			2.5E-06	2.5E-06			1.25E-06		
TBEP			3E-06								
TnBP											
TCEP	1.25E-03	1.56E-04				1.56E-04	6.25E-05	1.25E-03	1.25E-03	1.56E-04	6.25E-04
TPP	1.56E-06	6.25E-06							1.25E-05		6.25E-06

Preliminary results- Estrogenicity





- TPP and TBBPA shows signs of estrogenic activity


Sheila, we need more flame retardants.