Butterfly effect vs. homeostasis: implications in miRNA-guided repression and other gene regulation events

Hervé Seitz

IGH (UMR9002, CNRS and university of Montpellier)

October 19, 2018

Gene expression regulation

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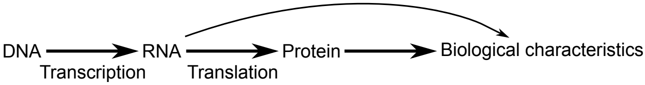
DNA → Biological characteristics

Gene expression regulation



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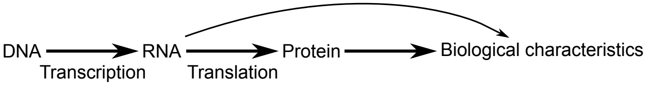

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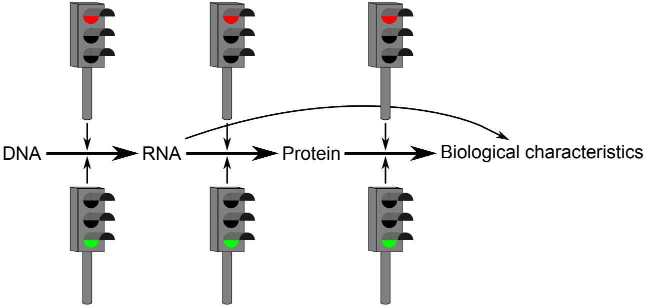

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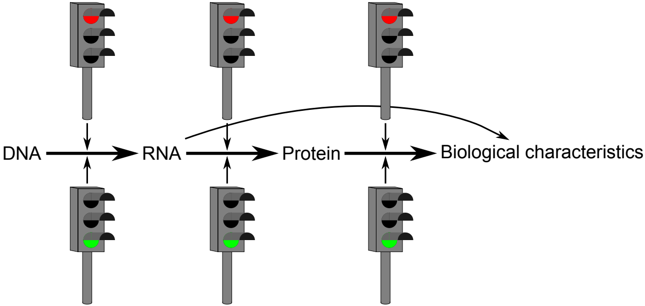

Paradox: in a pluricellular organism, every cell has (almost) the same DNA, yet various characteristics.

Mechanisms of “gene expression regulation” turn genes on or off in each cell type.

microRNAs

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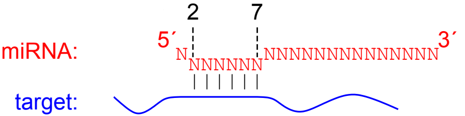

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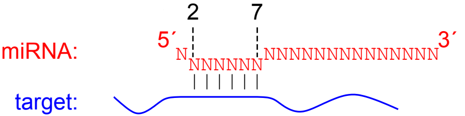

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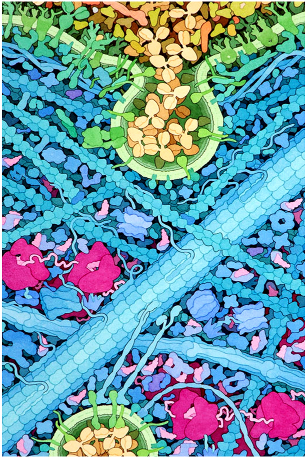
High throughput experimental methods identify thousands of targets per microRNA.

The concept of “biological relevance”



(illustration by D. Goodsell, Scripps Research Institute and Rutgers University)

How to make sense of big data?

Problem #1: processing and comparing large experimental datasets.

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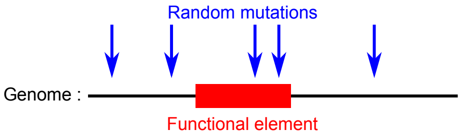

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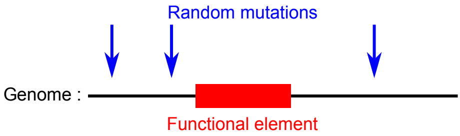

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The availability of genome sequences profoundly changed the practice of biology:

- use *grep* instead of Southern blotting;
- compare genomic sequences to find phylogenetically conserved elements.

Comparative genomics

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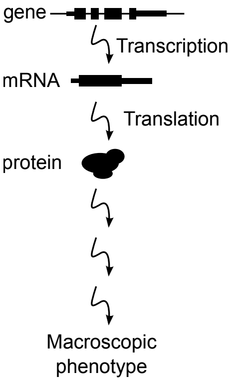

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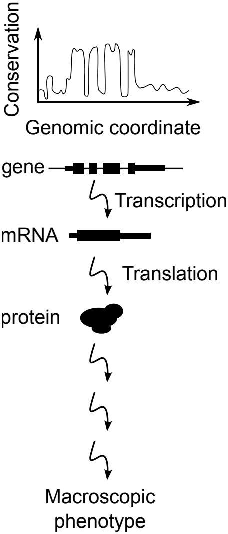

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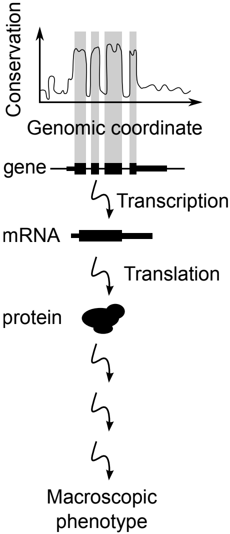

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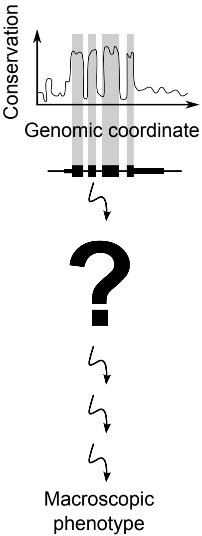

microRNA target prediction

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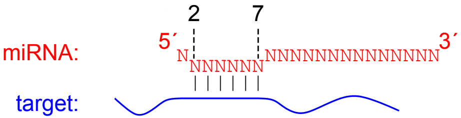

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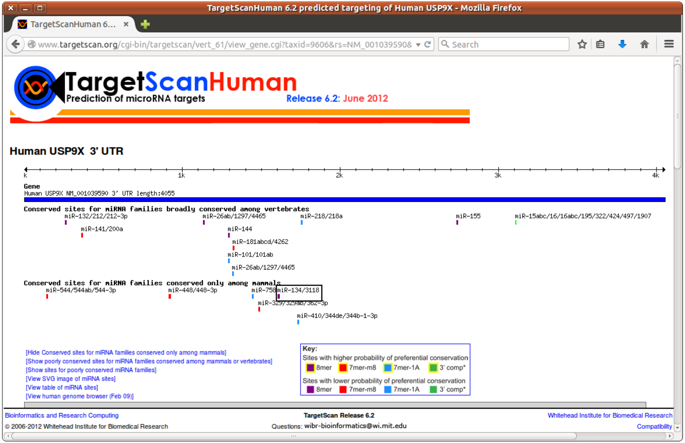
Computational programs for target prediction: look for seed matches in 3´ UTRs, select the ones that were conserved in evolution.

microRNA target prediction



Human USP9X 3' UTR

Gene
Human USP9X NM_001039590 3′ UTR length:4055

Conserved sites for miRNA families broadly conserved among vertebrates

miR-132/212/212-3p
miR-26ab/1297/4465
miR-218/218a
miR-155
miR-15abc/16/16abc/195/322/424/497/1907
miR-141/200a
miR-144
miR-181abcd/4262
miR-101/101ab
miR-26ab/1297/4465

Conserved sites for miRNA families conserved only among mammals

miR-544/544ab/544-3p
miR-448/448-3p
miR-758
miR-134/3118
miR-329/329ab/362-3p
miR-410/344de/344b-1-3p

[Hide Conserved sites for miRNA families conserved only among mammals]
[Show poorly conserved sites for miRNA families conserved among mammals or vertebrates]
[Show sites for poorly conserved miRNA families]
[View SVG image of miRNA sites]
[View table of miRNA sites]
[View human genome browser (Feb 09)]

Key:
Sites with higher probability of preferential conservation
🟪 8mer 🟥 7mer-m8 🟦 7mer-1A 🟩 3' comp*
Sites with lower probability of preferential conservation
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Bioinformatics and Research Computing
TargetScan Release 6.2
Whitehead Institute for Biomedical Research
© 2006-2012 Whitehead Institute for Biomedical Research
Questions: wibr-bioinformatics@wi.mit.edu
Compatibility

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Such short matches are very frequent (60 % of human coding genes seem to be targeted: Friedman *et al.*, 2009).

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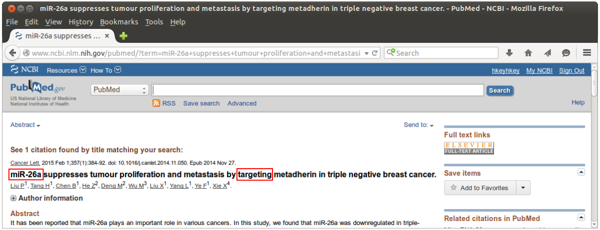

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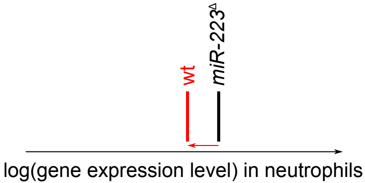
$\Longrightarrow$ miRNAs are implicated in every physiological process in animals.

miRNA-mediated repression is very modest (usually $<$ 2-fold): lower than well tolerated fluctuations in gene expression (*e.g.*, haplosufficiency). Why have these sites been conserved if they are not functional?

Robustness of predicted targets

miR-223 in mouse neutrophils.



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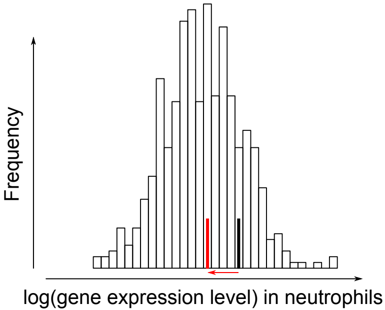

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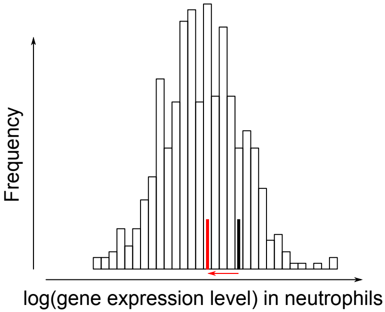

For 150 predicted targets out of 192: inter-individual variability among 5 wild-type mice is larger than miRNA-mediated repression.

Comparative genomics yield false positives

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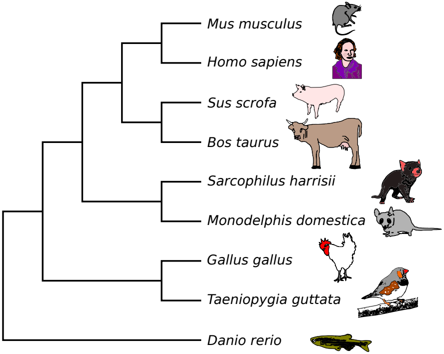

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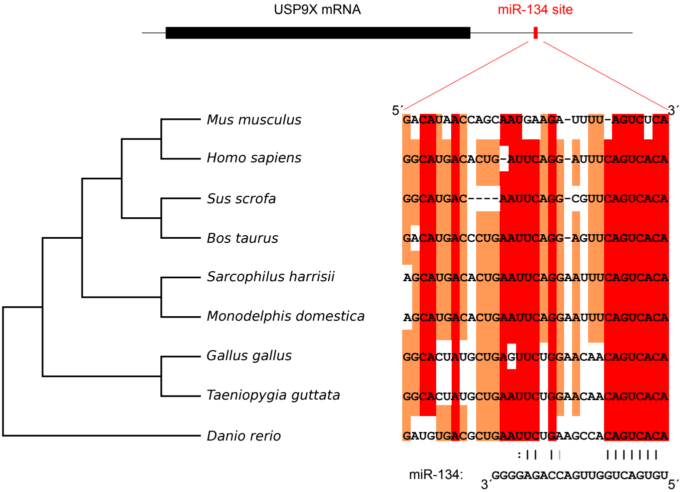

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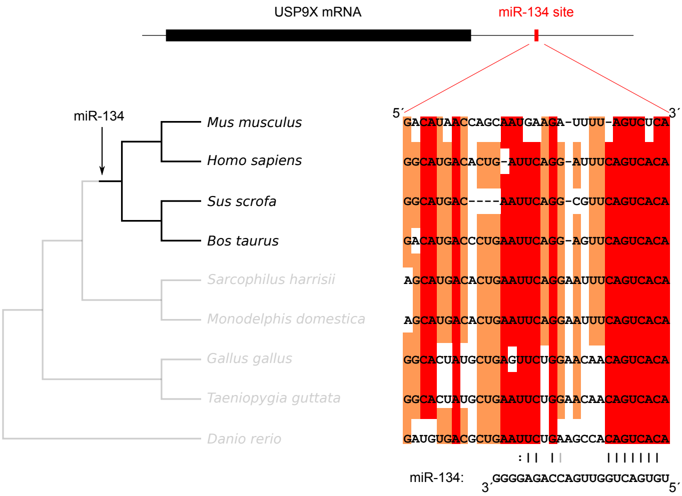

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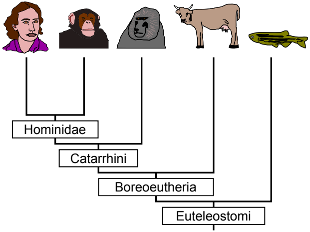

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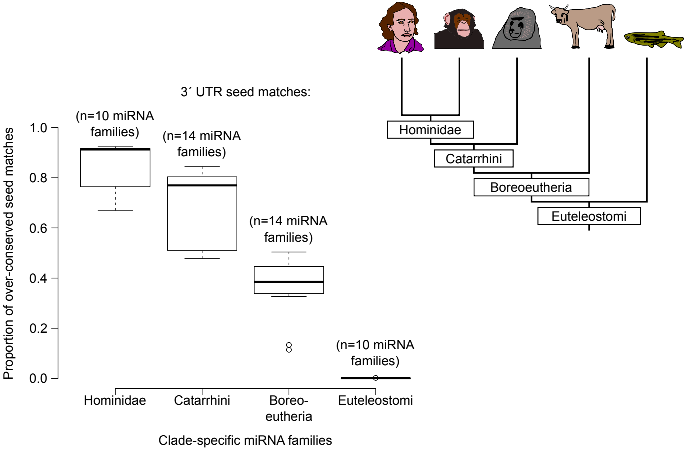

▸ Comparison to prediction programs

▸ Effect of tree architecture

Conclusion: revisiting microRNA target definition

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Every measurable change in gene expression does not translate into a macroscopic, evolutionarily selectable phenotype.

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Among the (many !) predicted targets: finding those that are responsible for visible phenotypes.

Conclusion: revisiting "gene regulation" definition

High-throughput identification of transcription factor or RNA-binding protein targets: thousands of genes are bound, many of them are not under selective pressure to keep these binding sites. ▸ Supplementary data

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Microscopic events which are neutral in evolutionary terms.

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Microscopic events which are neutral in evolutionary terms.

A central feature of biological systems: their robustness to external insults. Hard to reconcile with the extreme sensitivity required for fine-tuning (the “butterfly effect” has probably been counter-selected).

Acknowledgements

Anna Sergeeva:

Laura Martinez:

Blaise Li:

Natalia Pinzón:

Isabelle Busseau:

Sophie Mockly:

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Supplementary data

Introduction:

- ▸ Mechanism of target repression

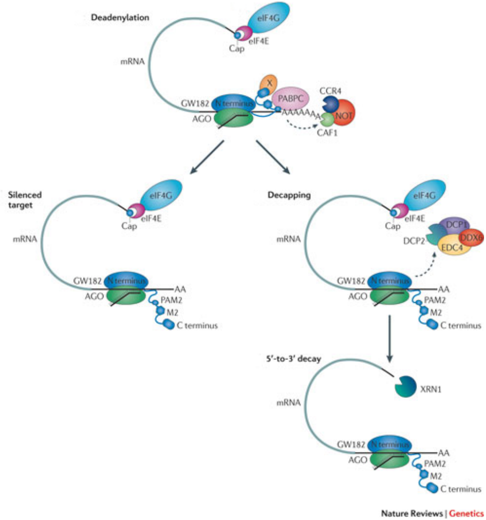
Results:

- ▸ Robustness of biological pathways
- ▸ Over-conserved sites in prediction programs

Conclusion:

- ▸ Pseudo-targets for other regulators?
- ▸ Propagation of gene expression perturbation

miRNA target repression

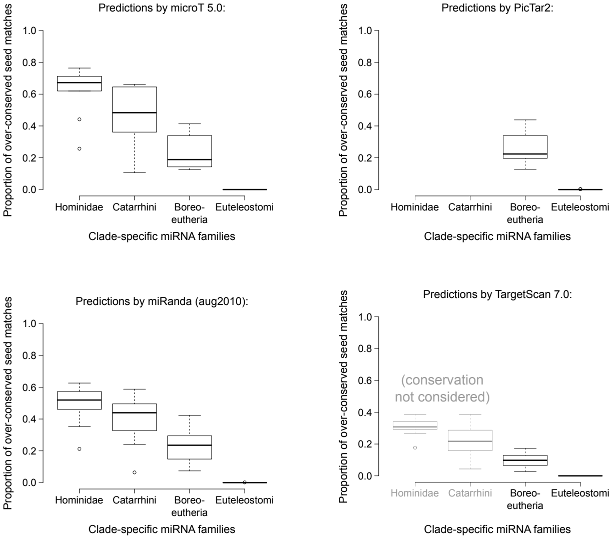


(adapted from Huntzinger and Izaurralde, 2011)

Biological robustness

$$\text{Substrate} \xrightarrow{\text{enzyme 1}} \text{Product 1} \xrightarrow{\text{enzyme 2}} \text{Product 2} \xrightarrow{\text{enzyme 3}} \text{Product 3}$$

Over-conservation in prediction programs



Predictions by microT 5.0:

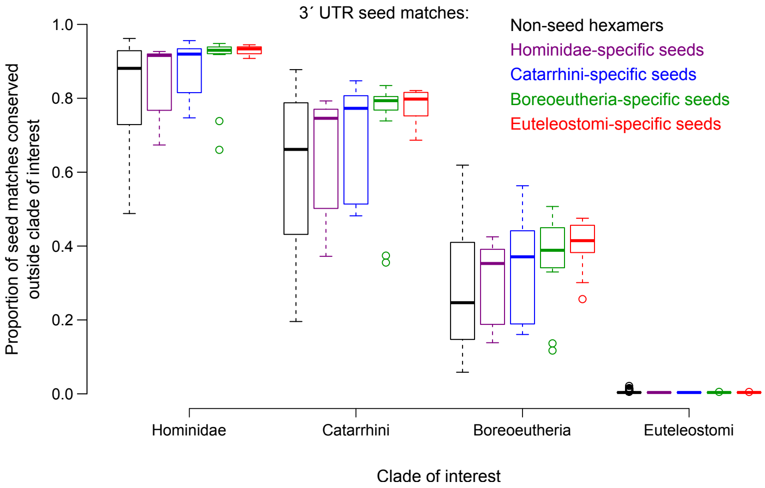
Predictions by PicTar2:

Predictions by miRanda (aug2010):

Predictions by TargetScan 7.0:

Return

Effect of tree architecture



◂ Return

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Real molecular events, which are neutral in evolutionary terms?

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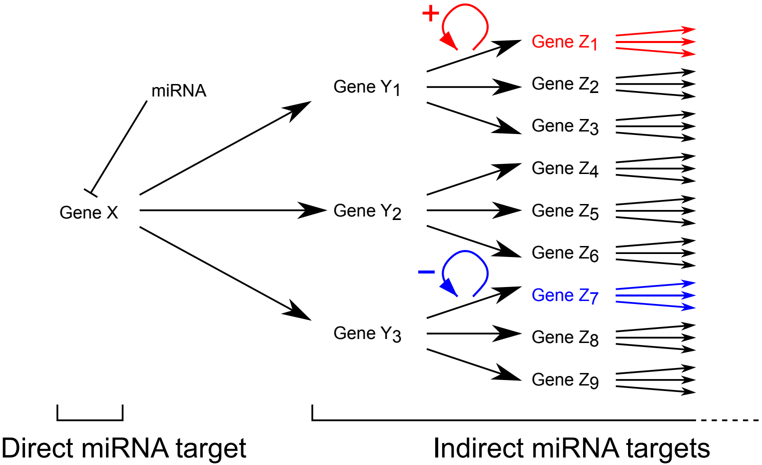
Propagation of gene expression perturbation



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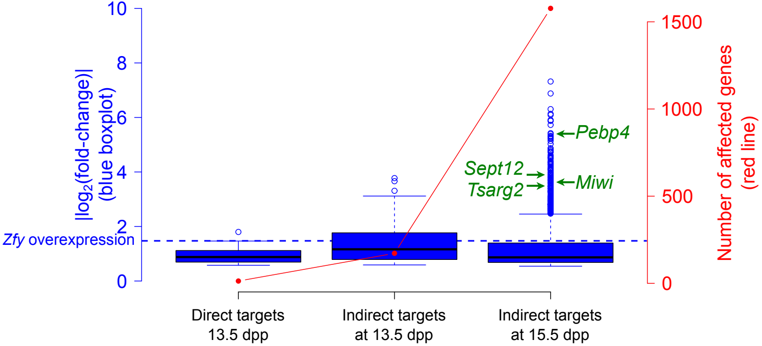

(in collaboration with H. Royo and J. Turner, MRC, London)