


Target identification and therapy validation by post genomic technologies

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Genomics

- 
- 1990 Human genome project – estimated \$3bn 15 years
 - 1995 First full genome published (bacteria)
 - 2000 1st draft Human Genome
 - 2003 Full human genome (92% at 99.99% accuracy)
 - 2008 1000 genomes project – estimated 5 years \$30-50M
 - 2012 Genetic variation map 1092 genomes
UK Government - £100M for 100,000 genomes

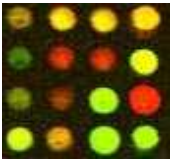
Post Genomics

Genome: the complete set of genetic material.



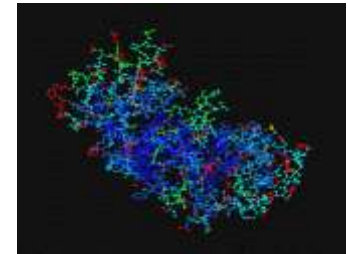
Transcription

Transcriptome: the set of expressed genes (mRNA)



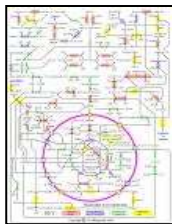
Translation

Proteome: the set of expressed proteins



Function

Metabolome: the set of small chemical molecules



Proteomics



1990 Human Genome Project starts

1995 Term proteomics first used

2000

2003

2008

“Considering the hundreds of billions of dollars poured into proteomics research in the past decade, it is striking that not a single commercial molecule has emerged from it.”

Mitchell P., *Nature Biotech.*, 2010, 28, 665

2012 Initiation of the Human Proteome Project

“Billions of dollars spent and proteomics has delivered nothing!”

Genome:
~ 20,000 genes

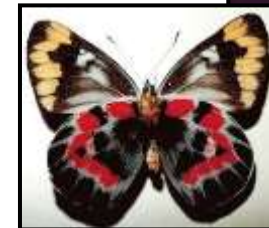


Transcriptome:
~ 60,000 mRNA transcripts



Proteome:
~ 800,000
functional entities

Same
genome ...



If we can't do Proteomics, what can we do?



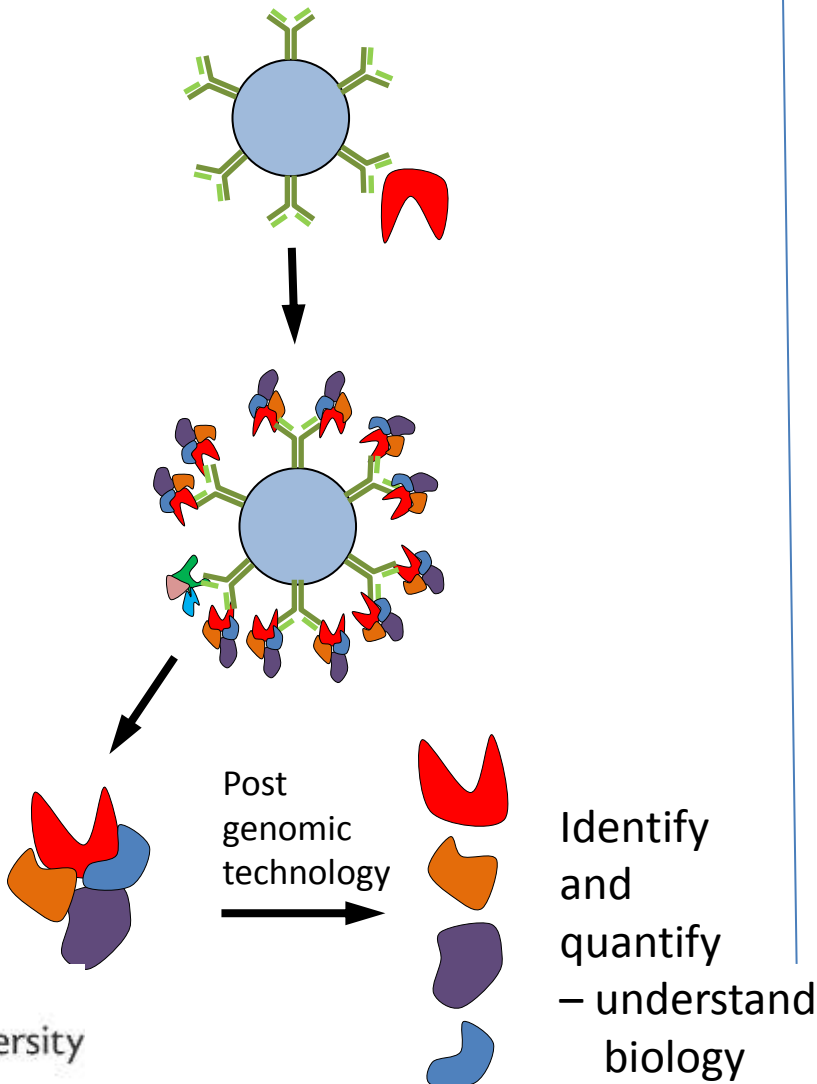
Targeted proteomics can do just about everything else!

Post-genomic technologies allow us to ask questions of biology that we could not address before.

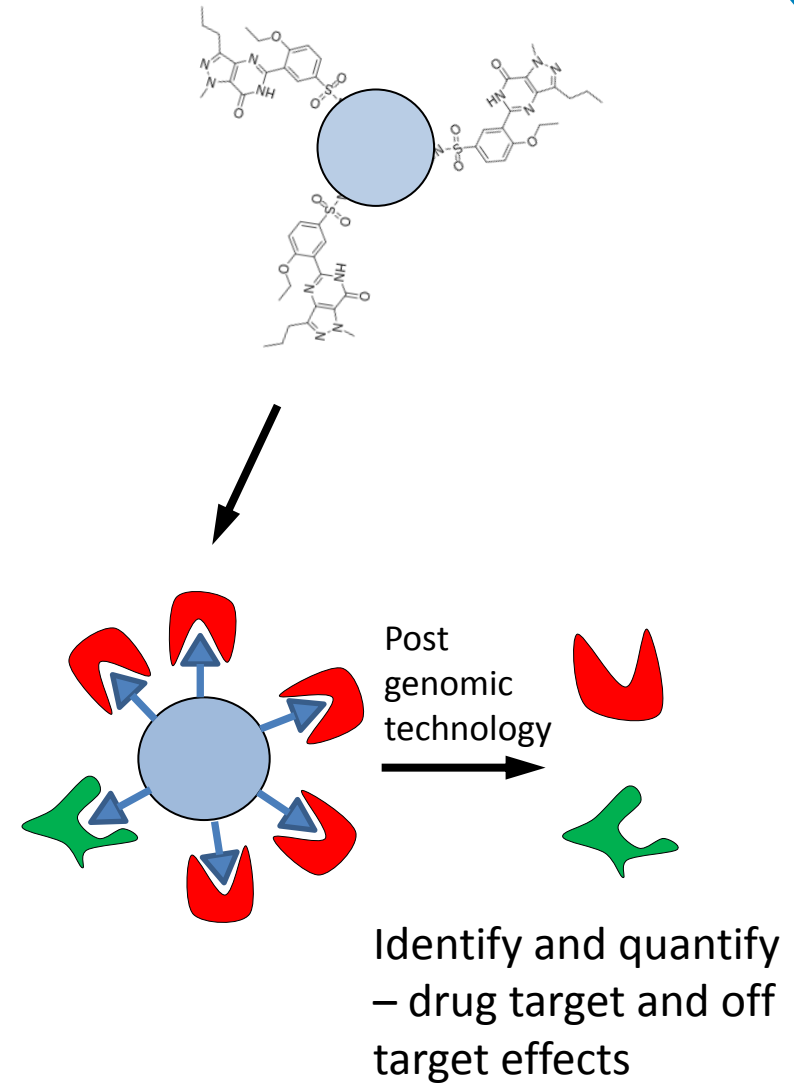
- 1) Affinity proteomics**
- 2) Biomarkers**

Affinity Proteomics

Antibody/protein - interactome

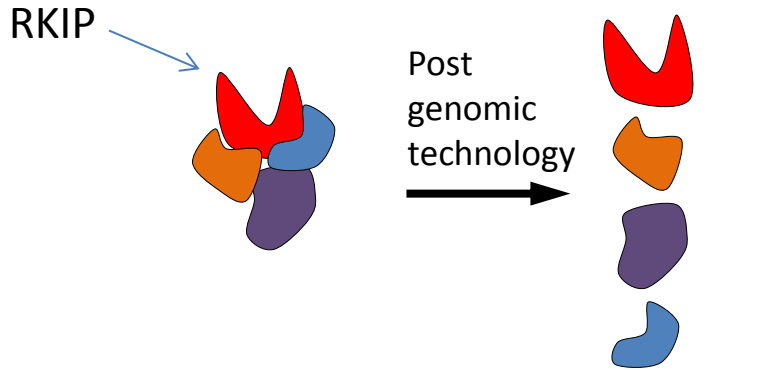


Drug molecule



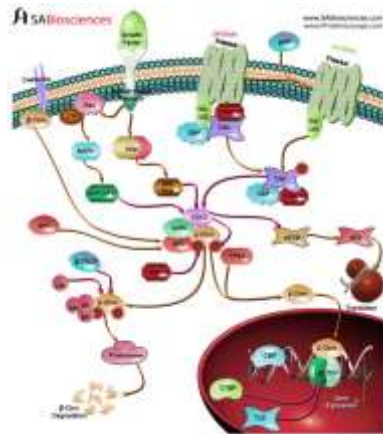
Affinity Proteomics

Antibody/protein - interactome

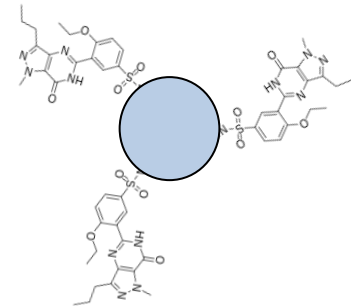


Identify and quantify – understand biology

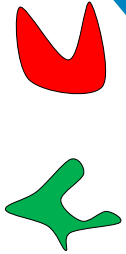
- casein kinase 1, epsilon (CSNK1E), transcript variant 2
- Similar to Nedd-4-like ubiquitin-protein ligase**
- feline sarcoma oncogene (FES)
- cell division cycle 2, G1 to S and G2 to M (CDC2)
- TANK-binding kinase 1 (TBK1)**
- B lymphoid tyrosine kinase (BLK)
- hypothetical protein FLJ31795
- tec protein tyrosine kinase (TEC)**
- Coilin (COIL)
- NIMA (never in mitosis gene a)-related kinase 2 (NEK2)
- feline sarcoma oncogene (FES),
- homer homolog 2 (Drosophila)
- ALL1 fused gene from 5q31
- mitogen-activated protein kinase-activated protein kinase 5 (MAPKAPK5)
- mitogen-activated protein kinase-activated protein kinase 5 (MAPKAPK5)
- p21(CDKN1A)-activated kinase 6 (PAK6)
- serine/threonine kinase 40 (STK40)
- NUAK family, SNF1-like kinase, 1 (NUAK1)**
- ribosomal protein S6 kinase, 90kDa, polypeptide 1 (RPS6KA1)
- neurotrophic tyrosine kinase, receptor, type 3 (NTRK3)
- PAI-1 mRNA-binding protein (PAI-RBP1)
- megakaryocyte-associated tyrosine kinase (MATK)**
- serine/threonine kinase 6, transcript variant 6



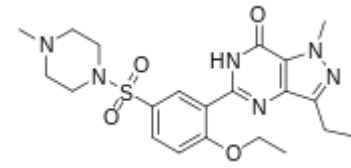
Drug molecule



Post genomic technology



Identify and quantify – drug target and off target effects

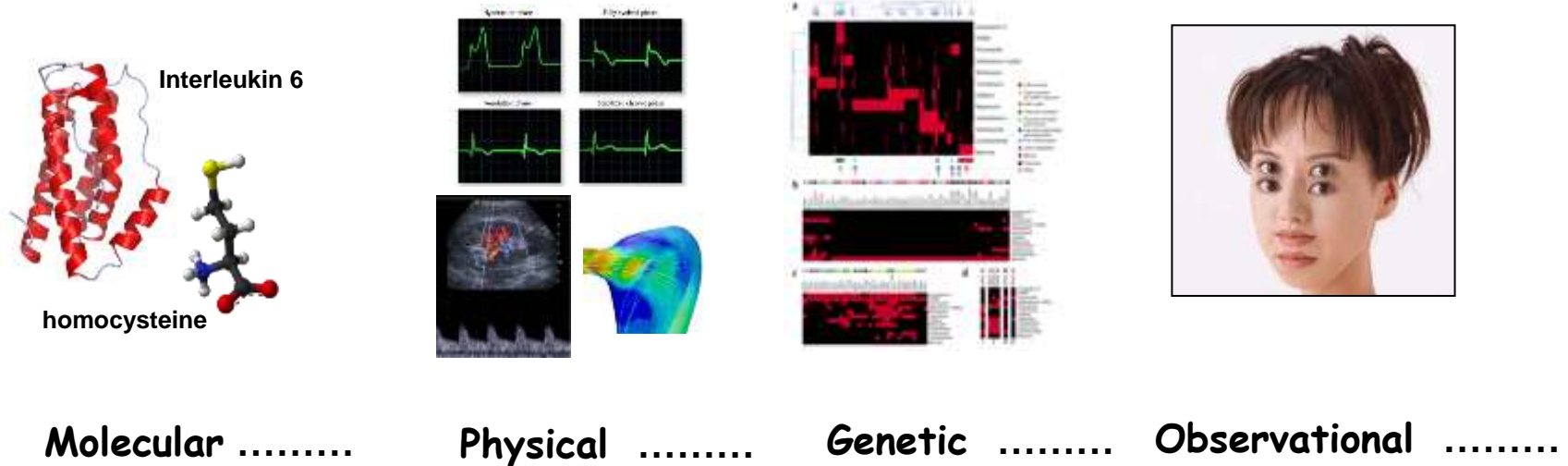


Sildenafil:

PDE5
other PDEs
RKIP

Biomarkers

a measurable indicator of a biological state

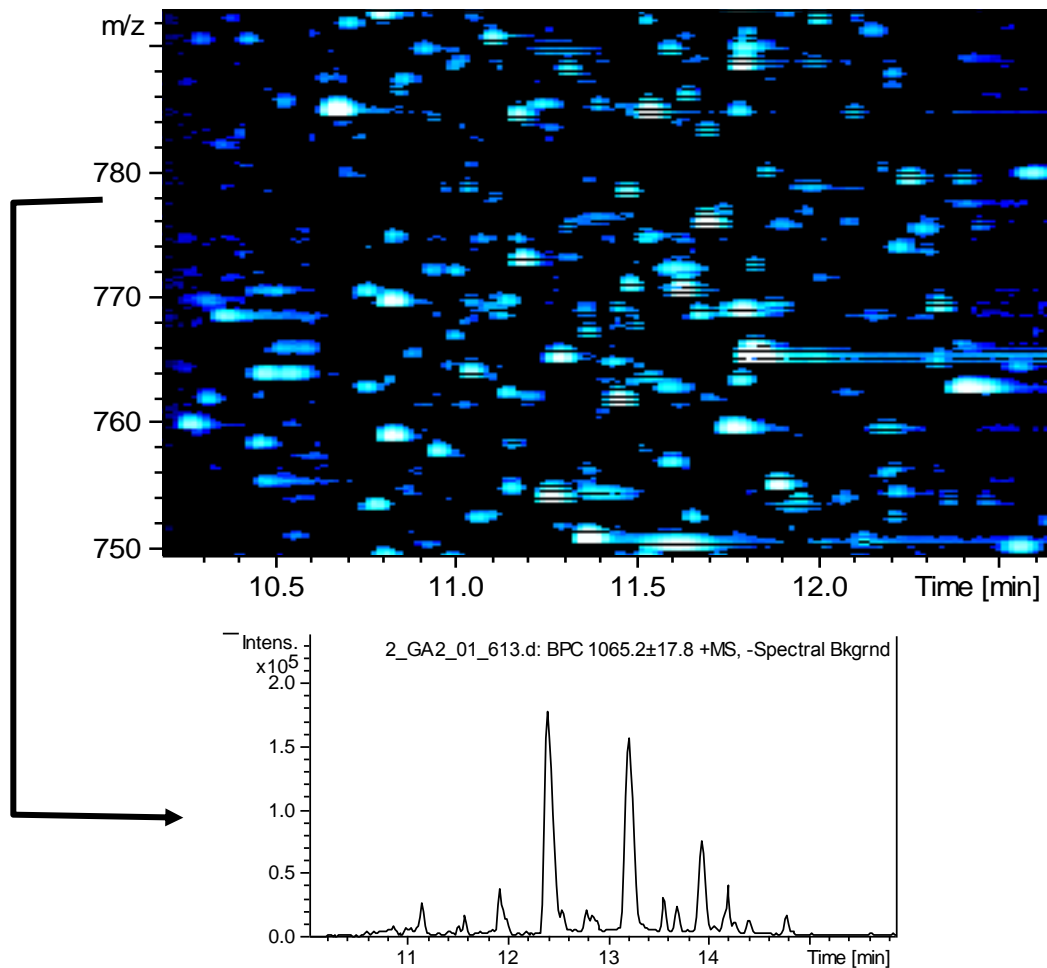


Molecular biomarkers can be used to characterize:

- normal biological processes
- pathogenic processes
- pharmacologic responses to a therapeutic intervention

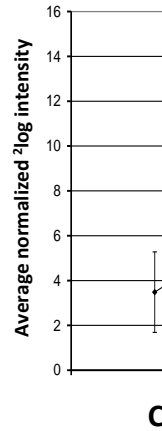
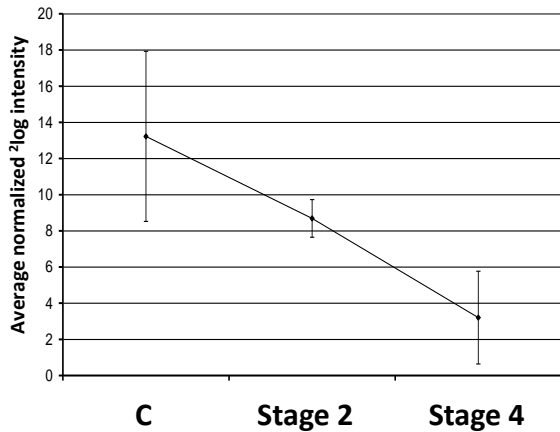
Application of Post-Genomic Technologies

Urine from cancer study



High quality separation interfaced with mass spectrometry

Quantification and Identification of Markers

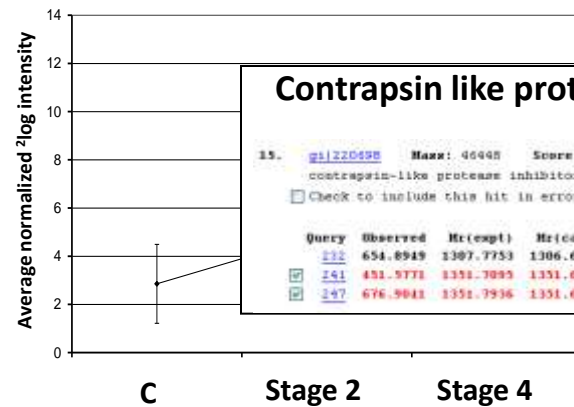
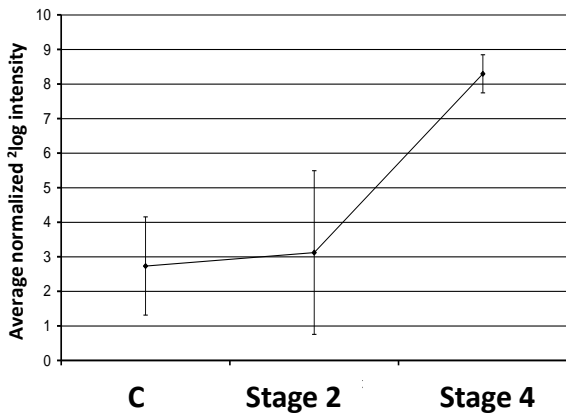


Fibrinogen alpha chain isoform 1

1. [M1593272](#) Name: 06003 Score: 137 Queries matched: 20 mpAI: 0.10
Fibrinogen alpha chain isoform 1 [Bos taurus]

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Query	Observed	Mr(esp1)	Mr(calc)	Delta Miss Score	Expect	Rank	Peptide
13	366.2054	732.3963	731.3013	0.0148	0	35	R.LKELSK-N
14	366.2054	732.3963	731.3013	0.0148	0	35	R.LKELSK-N
15	409.7548	815.3943	815.3773	0.0178	0	12	R.GRLPGRSE-G
16	469.7553	937.5091	937.5091	0.0200	0	10	R.KZHELR-G
17	571.2845	942.5545	940.5281	0.0281	0	43	R.ELLEARRK-G
18	688.7592	967.4036	967.4036	0.0281	0	15	R.TVLSRQGR-E
19	688.7592	967.4036	967.4036	0.0281	0	15	R.TVLSRQGR-E
20	689.9281	1397.0892	1397.0892	0.0288	0	36	R.SYQDFPFR-A
21	689.9281	1397.0892	1397.0892	0.0288	0	36	R.SYQDFPFR-A
22	689.9281	1397.0892	1397.0892	0.0288	0	36	R.SYQDFPFR-A
23	689.9281	1397.0892	1397.0892	0.0288	0	36	R.SYQDFPFR-A
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50	689.9281	1397.0892	1397.0892	0.0288	0	36	R.SYQDFPFR-A



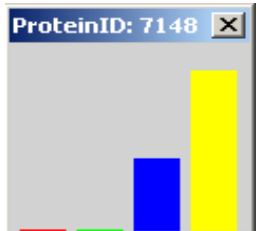
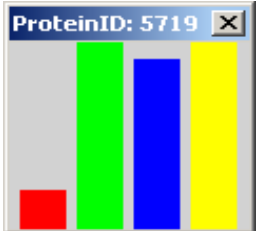
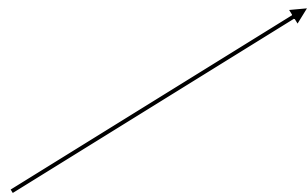
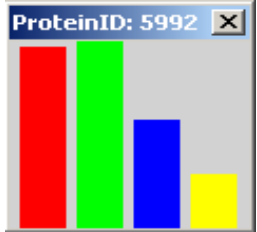
Contrapsin like protease inhibitor (CPI-21)

15. [M1220688](#) Name: 46445 Score: 69 Queries matched: 3 mpAI: 0.15
contrapsin-like protease inhibitor [CPI-21] [Bos taurus]

Check to include this hit in error tolerant search or archive report

Query	Observed	Mr(esp1)	Mr(calc)	Delta Miss Score	Expect	Rank	Peptide
232	654.8949	1307.7753	1306.6405	1.1348	0	11	R.LAELFSDLDER-I
241	481.5771	1351.7095	1351.6400	0.0619	1	(34)	R.DTLPHEDQGR-R
247	676.9041	1351.7936	1351.6400	0.1456	1	44	R.DTLPHEDQGR-R

Protein ID	Migration Time (min)	Frequency (%)			
		Control	Bladder Cancer		
			grade T2	grade T3	grade T4
8027	41,6	100	40	38	14
5992	39,8	97	100	57	29
6370	39,5	97	100	57	14
4877	44,6	90	80	24	14
8022	41,3	90	40	24	0
5445	36	86	80	57	14
6622	39,1	86	80	38	14
8017	40,8	86	40	19	0
1721	42,3	83	20	19	14
2730	45,5	83	0	0	0
4545	43	83	40	29	14
2095	38,7	79	0	14	14
3967	43,7	79	20	10	14
6105	48,7	79	60	48	14
4182	47,7	76	80	43	14
6989	39,5	76	80	38	14
1435	48,2	72	0	5	0
3605	46,7	72	80	57	14
5719	38,9	21	100	90	100
6264	35,9	21	60	81	86
6809	36,8	17	40	57	86
7776	33,8	14	20	52	86
153	35	3	20	24	71
734	33,1	3	20	29	71
1228	37,4	3	20	43	71
5633	36,4	3	40	52	71
7148	46,2	0	0	38	86



Post Genomic Technologies

Post-genomic technologies are:

- Unlocking our understanding of complex biological processes
- Helping us to identify the action of drugs and other bioactive molecules
- Helping us to diagnose disease and monitor effects of drugs

Science

~~“Life is a journey, not a destination”~~