Drug Development for COVID-19 – Repurposed Drugs & Plant Based Drugs: An Update

Presentation to
PMO constituted Task Force for Focused Research on Corona Vaccine and other S&T
By TFORD-COVID19-India, 30 June 2020

Outline

- About TFORD in brief
- TFORD output so far
- Strategy for Therapy & CTs
- Insights: Drug repurposing
- Insights: Medicinal herb
- Insights: CTs in India
- Suggestions
- Extra slides

About TFORD

(23 March – Present)

Task Force on Repurposing of Drugs (TFORD) for COVID-19

S&T Core Group on COVID19 constituted by PSA to GoI

सत्यमेव जयते
Office of Principal Scientific Adviser to the Government of India

Goal: To compile and disseminate high quality information to support decisions on repurposing of drugs for COVID-19; To provide structure frameworks for better decisions; To facilitate stakeholders.

https://nclinnovations.org/covid19/

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Advisory Group:

- 26 Senior Professionals
- Clinicians, Drug Developers, Medicinal Chemists, Pharmacologists, Virologists, Disease Biology, Immunologists, Clinical Research Specialists, Pharma Industry, Intellectual Property

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Nerve Center:

- 9 PhDs + 1 MPharm
- Drug discovery, Biology, Pharmacology, Health Sciences, Chemical Engineering

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Support: DSIR, CSIR-NCL, BIRAC

Initiative of

TFORD-COVID19 INDIA

Supported by

Under DSIR-A2K+ Program

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DSIR
DEPARTMENT OF SCIENTIFIC AND INDUSTRIAL RESEARCH

Research & Analysis Support for Advisory Group

TechEx.in
Tech Transfer Hub at Venture Center
Supported by NBM - BIRAC

CBA
CENTER FOR BIOPHARMA ANALYSIS AT VENTURE CENTER
Supported by National Biopharma Mission, BIRAC

NCL INNOVATIONS
Solutions from CSIR India

GNA'N'Lex Hermeneutics Pvt. Ltd.

VENTURE CENTER

Support for TRAC Study

PERSISTENT FOUNDATION

TFORD Output

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Molecule Briefs – 30
(Scientific Evidence, CTs, IP)

Heat Maps –
Drug Potential, Patent Barriers

Medicinal Herb Briefs - 9

Manufacturers Status

Opinion on Patent Barriers

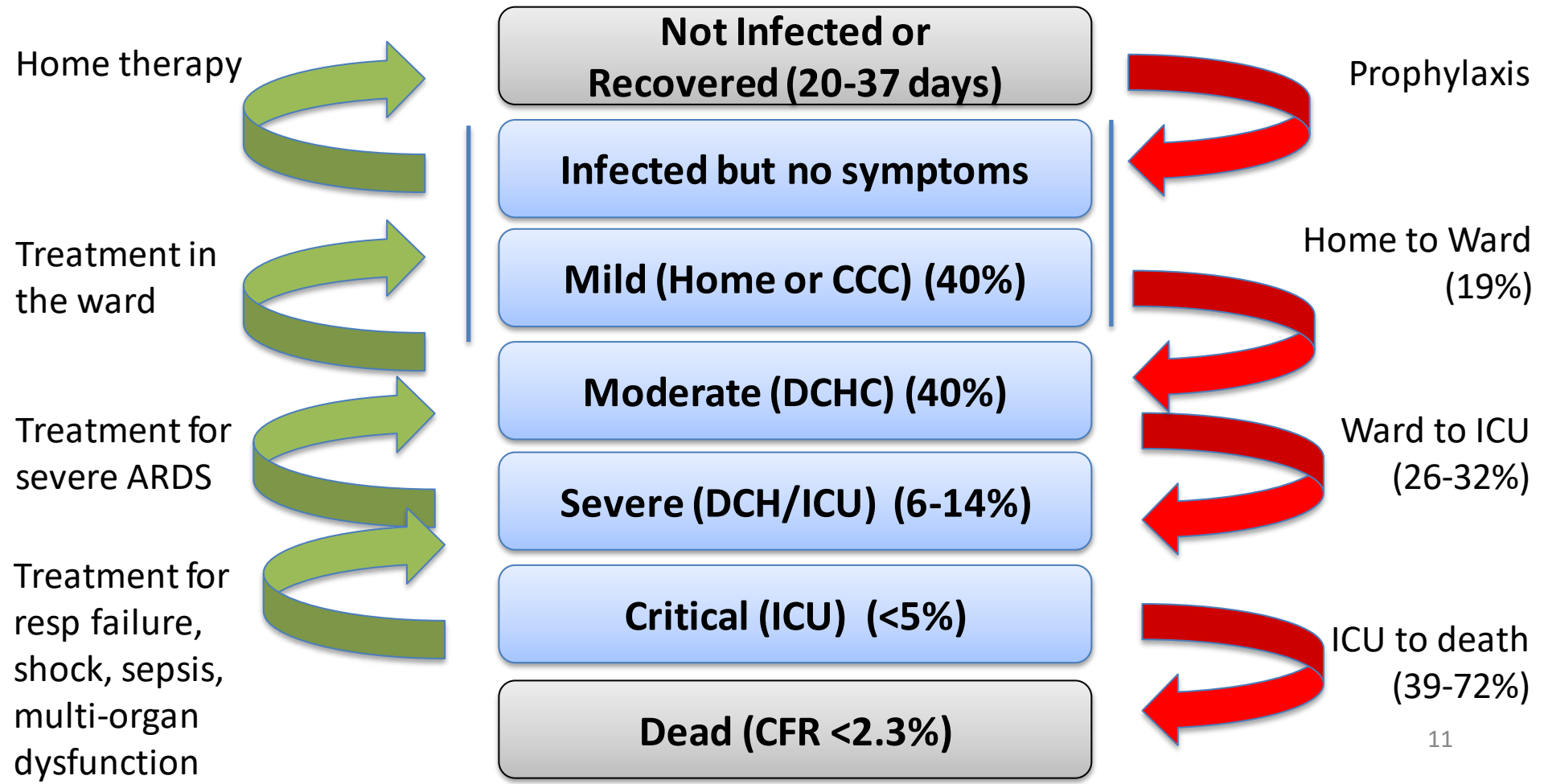
TRAC Study
(Retrospective Study)

Clinical Trials in India

Others: Assessment/ Decision Frameworks; Translation Network; Requests to PSA

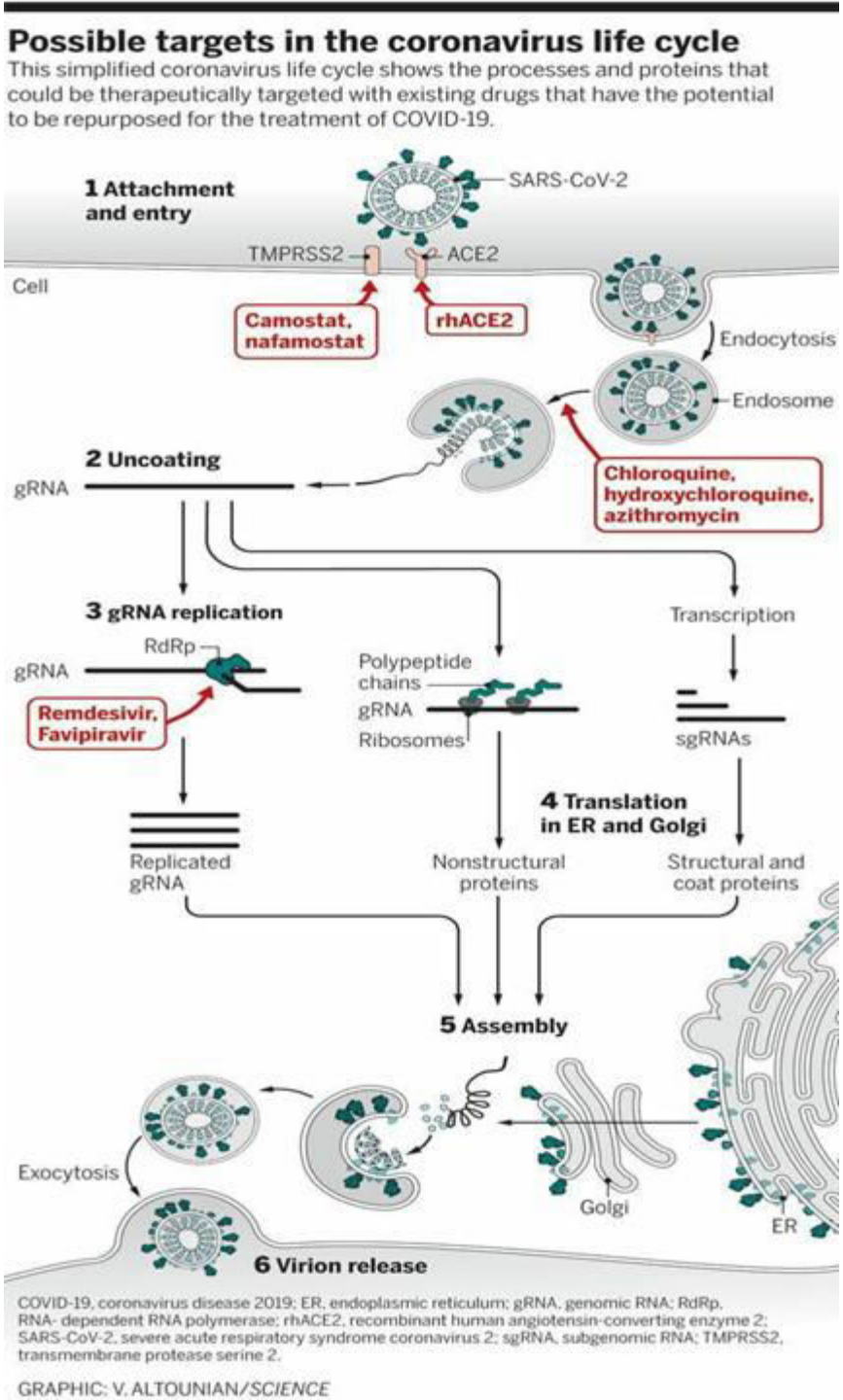
Strategy for Therapy and CTs

Therapeutic Strategy (Data: WHO/CN/US)



Priority Goals

- (Goal 1) Reduce mortality and ICU load; CFR: From 2.3% to 0.1%
  - Dexamethazone? Enoxaparin?
  - Remdesivir? Tocilizumab?
  - Sepsivac? Itolizumab? Plasma?
- (Goal 2) Reduce hospital load
  - Oxygen therapy
  - HCQ? Methylprednisolone? Enoxaparin?
  - Favipiravir? Medicinal herbs?
- (Goal 3) Reduce infection and early disease progression
  - HCQ?
  - Medicinal herbs? Umifenovir?
  - Vaccine?



Approaches

- Viral entry (ACE2, TMPRSS2, FP, Endosomal pH)
- Viral replication (RdRp, 3CLPro/ Main Protease)
- Immuno-modulation and anti-inflammatory
- Anti-coagulants
- Others

Insights:
Drug Repurposing

Drugs studied

Anti-virals

RdRp Inhibitors	Remdesivir
	Favipiravir
	Baloxavir Marboxil
	Ribavirin
	Galidesivir
3CLpro inhibitors	Lopinavir/ Ritonavir
	Darunavir
Viral entry/Fusion inhibitors	Chloroquine
	Hydroxychloroquine
	Umifenovir
Other mechanism	Oseltamivir
	Nitazoxanide
	Ivermectin

Immunomodulatory & Others

Human protease inhibitors	Camostat Mesylate
	Ulinastatin
IL-6 Pathway inhibitors	Tocilizumab
	Sarilumab
JAK inhibitors	Ruxolitinib
	Tofacitinib
	Baricitinib
Immuno-modulators	IFN- β
	Sepsivac

Antibiotics	Nigericin
	Teicoplanin
hACE	hR ACE Protein
IL-12/23 Inhibitor	Ustekinumab
Cortico-steroid	Dexamethasone
Anti-coagulant	Enaxoparin
Others	Famotidine
	ACEi/ARB

Patent Protected APIs

Anti-virals

RdRp Inhibitors	Remdesivir (2035)
	Favipiravir
	Baloxavir M (2031)
	Ribavirin
	Galidesivir
3CLpro inhibitors	Lopinavir/ Ritonavir
	Darunavir
Viral entry/Fusion inhibitors	Chloroquine
	Hydroxychloroquine
	Umifenovir
Other mechanism	Oseltamivir
	Nitazoxanide
	Ivermectin

Immunomodulatory & Others

Human protease inhibitors	Camostat Mesylate
	Ulinastatin
IL-6 Pathway inhibitors	Tocilizumab
	Sarilumab (2027)
JAK inhibitors	Ruxolitinib (2026)
	Tofacitinib (2022)
	Baricitinib (2029)
Immuno-modulators	IFN- β
	Sepsivac

Antibiotics	Nigericin
	Teicoplanin
hACE	hr ACE Protein
IL-12/23 Inhibitor	Ustekinumab (2021)
Cortico-steroid	Dexamethasone
Anti-coagulant	Enaxoparin
Others	Famotidine
	ACEi/ARB

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Key Drugs: Summary
(Approved for COVID-19/mentioned in clinical management guidelines)

Drug	Type	Approved for COVID-19		Clinical Trial Results for COVID-19 *(only interventional trials)*		Clinical Trials in progress^		Indian Mfrs
		India	Others	Randomized	Others	India	Others	
Hydroxy-chloroquine	AV	Yes (P)	No	4 (T) – 3 Negative/1 Inconclusive 2 (P) – 1 Negative, 1 Inconclusive	1 (T) - Positive	8 (T & P)	100+ (T & P)	10+
Remdesivir	AV	Yes (T)	Yes (T)	2 (T) – Positive 2 (T) – Negative	2 (T) – Positive	1 (T)	15+ (T)	5
Favipiravir	AV	Yes (T)	Yes (T)	2 (T) – Negative (Pre-prints) 1 (T) – Positive (News article)	1 (T) – Positive	3 (T)	30+ (T)	5
Tocilizumab	AI	No; CM	No; CM	Data not available	4 (T) – Positive	1 (T)	50+ (T)	None
Dexamethasone	AI	No; CM	Yes (T)	1 (T) – Positive (Preprint)	Data not available	0	10+ (T)	10+
Enoxaparin	AC	No; CM	No; CM	Data not available	Data not available	0	15+ (T)	40+

Oral Injectable

AV- Anti-viral; AI – Anti-inflammatory; AC – Anti-coagulant; T - Therapeutic; P - Prophylactic; CM - Used for clinical management (according to clinical management guidelines); ^ - Only includes interventional trials

Drugs in CM Guidelines > Patent Barriers

Drug	Innovator/ patentee	Patent status	Rough price	Indian Mfrs
Hydroxy-chloroquine	Generic	Generic	10 day regime Total cost: ₹ 190	10+
Remdesivir	Gilead	API: Markush: Valid: 22/04/2029 API Form: Valid: 22/07/2031 API & Dosage form: Valid 29/10/2035	5 day regime Total cost: ₹ 33,000	5
Favipiravir	Toyama Chemical	API -- expired Product composition: 14/02/2028 Intermediate process patent: 25/09/2028	14 day regime Total cost: ₹ 12,566	5
Tocilizumab	Chugai Seiyaku Kabushiki Kaisha/ Hoffman Roche	Injection formulation: 14/02/2023 Product composition+ Derivative forms: 25/09/2029	1 day dose Total cost: ₹ 40,000	None
Dexamethasone	Generic	Generic	10 day regime Total cost: Approx: ₹ 80	10+
Enoxaparin	Generic	Generic	Dose as per need Total cost: Approx: ₹ 500	40+

Oral **Injectable**

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Drugs with Potential for Controlled CTs: Summary

Drug	Type/ MoA	Disease Stage	Clinical Trial Results for COVID-19 *(only interventional trials)*		Clinical Trials in Progress^		Indian Mfrs
		(where drug could be effective)	**Randomized**	**Others**	**India**	**Others**	
Umifenovir	AV; Viral fusion inhibitor	Prophylaxis, Mild Disease	2 (T) – Negative (Preprints)	Data not available	1 (T)	5 (T & P)	0
Baricitinib	AI; JAK Inhibitor	Moderate/ Severe/Critical	Data not available	1 (T) - Positive	0	10+ (T)	1
Ulinastatin	AI; Protease Inhibitor	Severe/Critical	Data not available		1 (T)	2 (T)	2
Sepsivac*	Immunomodulator	Prophylaxis/Mild/ Moderate/Severe /Critical	Data not available		4 (T & P)	0	1
Ivermectin	AV; MoA not proven	Prophylaxis/ Mild/ Moderate	Data not available		7 (T & P)	30+ (T & P)	10+
Itolizumab*	AI; Anti-CD6	Severe/Critical	Data not available		1 (T)	1 (T)	1
IFN-β	Immunomodulator (Adjunct therapy)	Moderate/Severe	1 (T) – Positive	1 (T) – Positive	1 (T)	10+ (T)	2

Oral **Injectable**

AV- Anti-viral; AI – Anti-inflammatory; AC – Anti-coagulant; T - Therapeutic; P - Prophylactic; ^ - Only includes interventional trials; * - Indian Innovator Drugs

Drugs with Potential for Controlled CTs: Patent Barriers

Drug	Innovator/ patentee	Patent status	Rough price	Indian Mfrs
Umifenovir	Generic	Generic	Price not available	0
Baricitinib	Incyte Corporation	API: Valid: 10/03/2029	2 mg/once daily ₹17900/strip of 7 tablets	1
Ulinastatin	Generic	Generic	5 day regime Total cost: ₹ 33750	2
Sepsivac*	Cadilla	Process: Valid: 19/02/2030	3 day regime (sepsis) Total cost: ₹ 15909	1
Ivermectin	Generic	Generic	Single dose Total cost: Approx ₹ 70	10+
Itolizumab*	Biocon	Product: Valid: 14/03/2028	Single dose 25mg Total Cost: Approx ₹ 7500	1
IFN-β	Generic	Generic	Single dose 30mcg Total cost: Approx ₹ 6000	2

Oral **Injectable** *** - Indian Innovator Drugs**

The need:

- Need strong candidates for Goal 1, Goal 2, Goal 3
- Need national, coordinated and well-designed CTs for candidates
- CTs for Small Molecules (RoA-Oral) vs Biologics (Injectables)
- Need for CTs with drug combinations (Anti-virals, Anti-virals + Immunomodulators etc.)
- Navigating patent barriers: Alernative tech/ alternative mfrs/ price control/ use Patent Law, if required
- Help support and expedite biosimilars, ex of Tocilizumab
- Encourage Indian innovators, ex – Sepsivac, Itolizumab

Insights:
Medicinal Herbs

MEDICINAL HERBS BRIEFS

First list features

Tinospora cordifolia
(Guduchi, Giloy)

Glycyrrhiza glabra
(Yashtimadhu, Liquorice)

Withania somnifera
(Indian Ginseng)

Zingiber officinale
(Ginger)

Andrographis paniculata
(Kalmegh)

Artemisia annua
(Sweet Wormwood)

Cissampelos pareira
(Patha)

Vitis vinifera
(Grapevine)

Myrica cerifera
(Bayberry)

Medicinal Herbs studied

1. Tinospora cordifolia
2. Glycyrrhiza glabra
3. Withania somnifera
4. Zingiber officinale
5. Andrographis paniculata
6. Artemisia annua
7. Cissampelos pareira
8. Vitis vinifera
9. Myrica cerifera

Note: AQCH not studied yet by TFORD. Sun Pharma and CSIR are pursuing this.

Name of Herb	Pharmacological activity (in context of COVID-19)				Reported conditions relevant to repurposing									Clinical Trials ongoing for COVID-19 Prophylaxis (P) Treatment (T)		Availability in India	
	Anti-viral	Anti-inflammatory	Anti-coagulation	Immune boosting	Rheumatoid Arthritis	HIV	Herpes Simplex	Dengue	SARS viruses	Other viral infections	Influenza	Bronchitis/asthma	Fever	Global	India	Herb	OTC products
Tinospora cordifolia															P(12) T(08)		
Glycyrrhiza glabra														T(03)	P(01) T (02)		
Withania somnifera															P(07) T (03)		
Zingiber officinale															P(03) T(02)		
Andrographis paniculata														T(01)			
Artemisia annua														T(05)			#
Cissampelos pareira																	
Vitis vinifera																	
Myrica cerifera																	#

YES NO # Prescription drugs

Indian herbal drugs industry is ready!

Name of Herb	Companies that use these herbs in their products										
	Dabur	Himalaya	Baidyanath	Zandu	Patanjali	Ayush	Hamdard	Sandu Pharmaceuticals	Charak Pharma	(SBL) [Homeopathic medicine]	TOTAL
Tinospora cordifolia	■	■	■	■	■	■	■	■	■		9
Glycyrrhiza glabra	■	■	■	■	■	■	■		■		8
Withania somnifera	■	■	■	■	■	■		■			7
Zingiber officinale		■	■	■	■	■	■	■	■		8
Andrographis paniculata			■	■	■	■	■	■			6
*Artemisia annua**											0
Cissampelos pareira			■	■							2
Vitis vinifera	■		■	■	■			■			5
Myrica cerifera										■	1

Herbs used in Ayurvedic Products

Herbs used to obtain semisynthetic drug Products

Herbs used in Homeopathic Products

* Artemisia annua OTC products not available in India. Semisynthetic derivatives of its bioactive Artemisinin are commonly used. Ex: Artesunate and its formulations are mfrd by pharma companies like IPCA, Intas & Zydus Cadila.

The need:

- Standardization of herbs and herbal products; Testing standards; Build industry credibility; Efficient processes to obtain the product with consistent quality.
- High-quality, well-designed Clinical Trials

Insights:
CTs in India

Update (29 June 2020): Too many sub-critical trials

- Total number of interventional CTs: **163** (recruiting ~ 3.3 lakh people)
  - Prophylactic: 52
  - Treatment: 71
  - Mixed: 40
- Type of therapeutic intervention:
  - Modern medicine: 60 trials (Drugs, Convalescent Plasma, Others)
  - Phytochemicals/ herbs: 103 trials (Ayurvedic, Homeopathy, Others)

Suggestions

Suggestions (Slide 1)

- National coordinated CTs and data
  - Different strategies for different stages/ goals
  - Take help of CT & biostat industry experts
  - Rapid deployment, adaptive?
  - GoI/ ICMR backed
  - PPP models like ACTIV of USA
- Indigenous products with potential for technology leadership for India/ Indian innovators
  - Sepsivac (Cadilla + CSIR)
  - Itolizumab (Biocon)

Suggestions (Slide 2)

- Adequate availability and pricing
  - Create threat of alternate technology/vendors (CSIR)
  - Price control ? (NPPA)
  - Use IP Law provisions (CGPDTM/ DPITT)
- Indigenous manufacturing
  - Small molecules – Tech development (CSIR), support indian manufacturers (DPITT; CDSCO)
    - Ex: CTAP (Accelerator Program) of US-FDA
  - Biosimilars – support and accelerate (DBT, CSIR)
  - Herbs – standardization, testing, quality (CSIR, DBT)

Suggestions (Slide 3)

- R&D programs (DST, DBT, CSIR, ICMR)
  - High-throughput screening (10,000 X)
  - Animal models (with leading companies)
  - Alternative routes for drug delivery
  - Antibody libraries (post-infection; post-recovery)
  - Analysis of active patient plasma
  - Biobanks
- *In vitro* anti-viral testing facilities
  - More locations – speed, volume, other cell lines (ICMR, CSIR, DBT)
  - Allow selected private labs with capabililty (ex: FNDR)

Suggestions (Slide 4)

- Longer range strategic R&D programs
  - Major thrust needed in biologicals. India does not have enough options. Both innovator products and biosimilars (DBT/NBM, CSIR)
    - See example: JAK inhibitors/ IL-6 inhibitors
  - Screening natural resources to get 'lead' molecules for drug design. Identify bio-actives and the molecular mechanism (CSIR, DBT, DST, AYUSH)
- Longer range systems
  - Electronic medical record; Clinical case records (ICMR/DHR)
  - Automated data analytics/ insights/ dashboard on CTRI website (ICMR)

Contact:

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http://www.nclinnovations.org/covid19/
https://twitter.com/TFORDCOVID19
https://www.linkedin.com/in/tford-covid19/

Extra Slide

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TRAC: *Retrospective Study in Pune*

Title : TFORD Retrospective Assessment of Treatments of Hospitalized Covid-19 Patients

Objective

- To collect clinical management information for COVID-19 patients
- To evaluate efficacy and safety of currently used treatments
- Use of this information to design CTs and chose CT candidates effectively

Principal Investigator: Dr Sundeep Salvi, Advisory Group, TFORD
Clinical Research Lead: Dr Ravindra Ghooi, Advisory Group, TFORD

CTRI Registration Number : CTRI/2020/05/025371
Study has been approved by DCGI approved Ethics Committee